

Supporting Information

Synthesis of *gem*-Difluoroalkenes via Nickel-Catalyzed Allylic Defluorinative Reductive Cross-Coupling

Yun Lan, Feiyan Yang and Chuan Wang*

^a Department of Chemistry, Center for Excellence in Molecular Synthesis, Hefei National Laboratory for Physical Science at the Microscale, University of Science and Technology of China, Hefei, Anhui, 230026 (China). E-mail: chuanw@ustc.edu.cn

Table of Contents

I. General Information.	S2
II. Preparation of Substrates.	S3
III. Optimization of Reaction Conditions.	S37
IV. Nickel-Catalyzed Allylic Defluorinative Reductive Cross-Couplings.	S39
V. Control Experiments.	S119
VI. References.	S123

I. General Information.

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 400M NMR spectrometers at ambient temperature in CDCl_3 at 400 and 101 MHz. ^{19}F NMR were reported as ^{19}F exp. comp. pulse decoupling (F19CPD) unless otherwise noted. The chemical shifts are given in ppm relative to tetramethylsilane [^1H : δ (SiMe₄) = 0.00 ppm] as an internal standard or relative to the resonance of the solvent [^1H : δ (CDCl_3) = 7.26, ^{13}C : δ (CDCl_3) = 77.16 ppm]. Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); dt (doublet of triplets); m (multiplets), etc. Coupling constants are reported as J values in Hz. High resolution mass spectral analysis (HRMS) was performed on Waters XEVO G2 Q-TOF. HPLC was performed on Thermo UltiMate 3000. Flash chromatography was performed using 200-300 mesh silica gel with the indicated solvent system.

Unless otherwise stated, all reactions were set up on 25 mL Schlenk tube and carried out under nitrogen. $\text{NiBr}_2 \cdot \text{glyme}$ was purchased from Strem and used as received. 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine was purchased from Sigma-Aldrich. Iodocyclohexane was purchased from TCI China. All solvents were purchased from Adamas-beta China and used as received. Other commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, TCI, Strem, Acros, and Energy Chemical and were used as received.

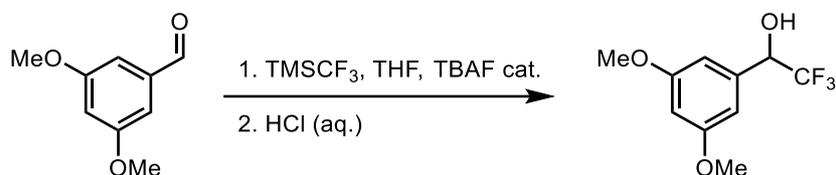
Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Other visualization methods include staining with a basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating.

II. Preparation of Substrates.

1b, 1d, 1f-1g, 1k-1l, 1n, 1q were synthesized following reported methods.^{1,2}

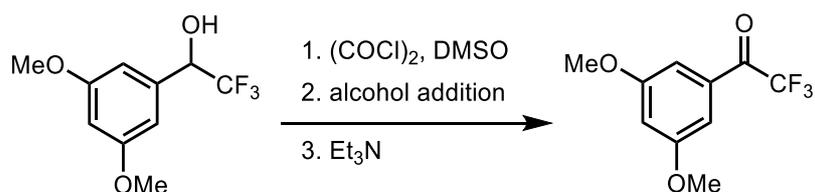
Procedure for the preparation of 1,3-Dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene 1a:¹

Step 1:



To a stirred solution of 3,5-dimethoxy benzaldehyde (8.3 g, 50 mmol, 1 equiv.) in THF (150 mL) was added TMSCF₃ (15.65 g, 110 mmol, 2.2 equiv.) followed by the dropwise addition of TBAF (1M in THF, 2.5 mL, 5 mol%) at 0 °C. The reaction was allowed to warm slowly to room temperature and stirred overnight. Then the reaction was quenched with aqueous 2N HCl (50 mL). The biphasic mixture was stirred vigorously until the full conversion of the silyl ether was observed according to TLC. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was used in next step without further purification.

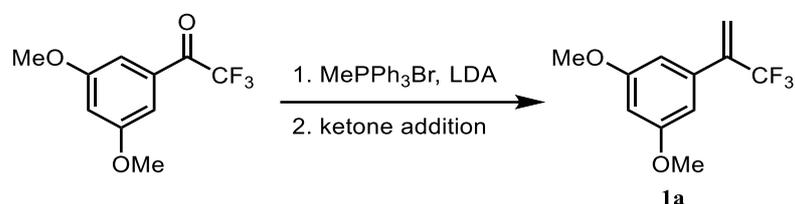
Step 2:



To a stirred solution of DMSO (11.72 g, 150 mmol, 3 equiv.) in CH₂Cl₂ (200 mL) was added dropwise oxalyl chloride (9.53 g, 75 mmol, 1.5 equiv.) at -78 °C. The resulting mixture was stirred for an additional 10 minutes and a solution of the previously prepared alcohol (1 equiv) in CH₂Cl₂ (50 mL) was added. The resulting solution was stirred for 30 minutes and Et₃N (34.85 mL, 250 mmol, 5 equiv.) was added. The reaction mixture was then stirred for 30 minutes at -78 °C, before the cold bath was removed. After an additional 60 minutes, the reaction mixture was quenched with aq. NH₄Cl (sat.). The organic layer was separated and the aqueous layer was extracted

with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄, filtered through a pad of Celite, and concentrated under reduced pressure. The residue was used in next step without further purification.

Step 3:

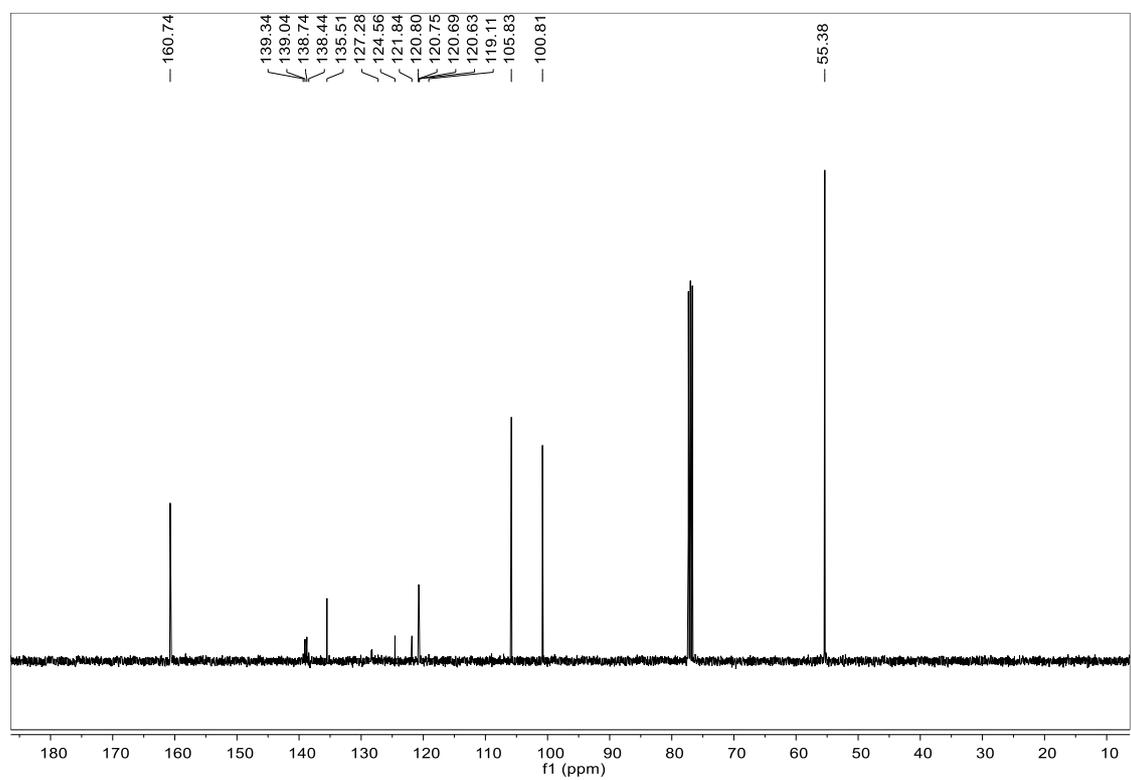
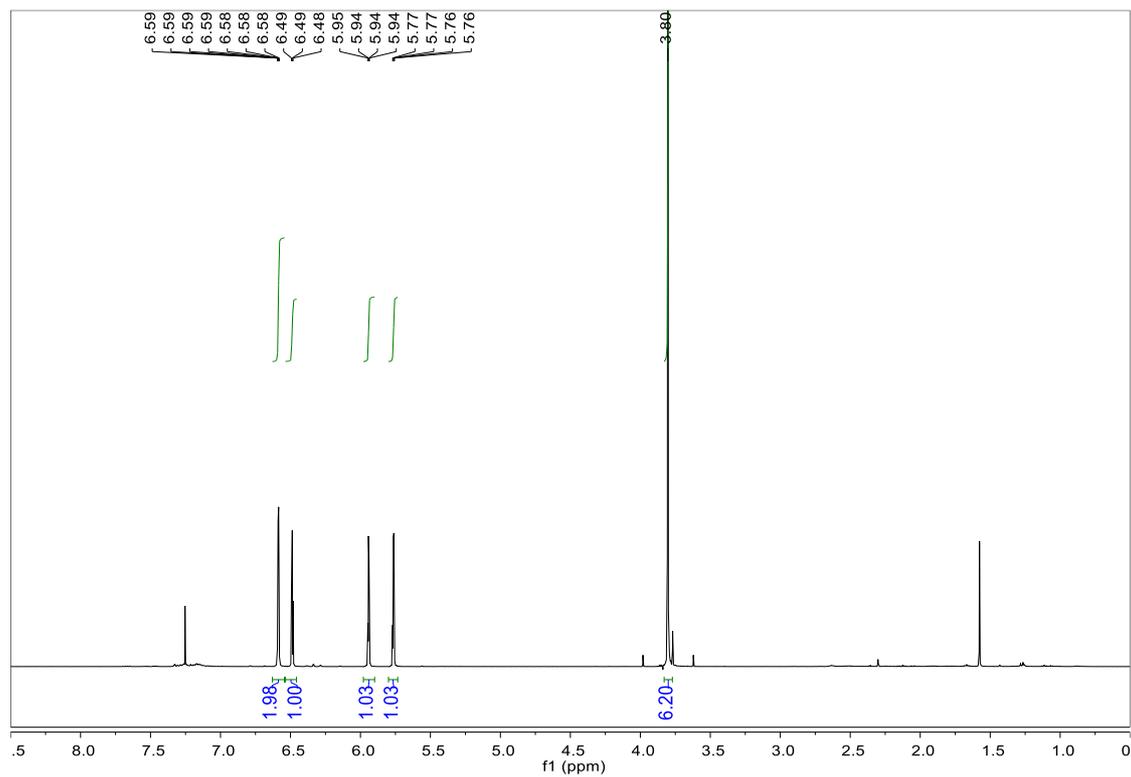


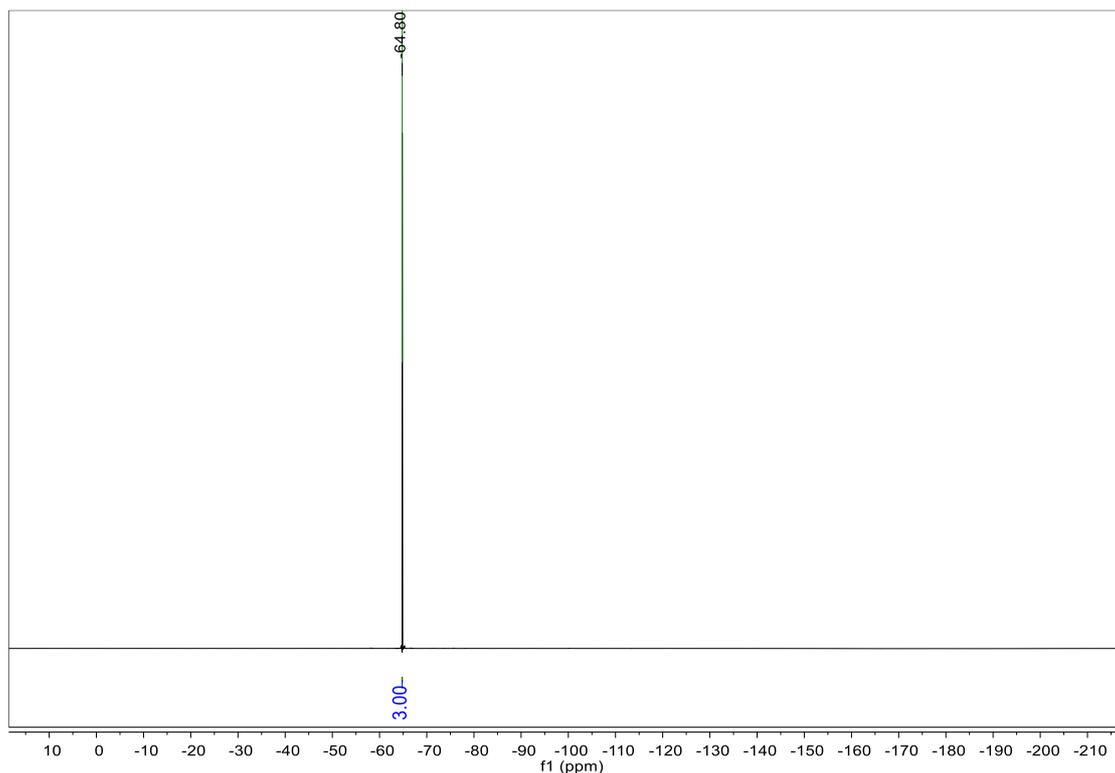
A flame dried flask was charged with methyl triphenylphosphonium bromide (62.5 mmol, 1.25 equiv) and THF (60 mL) was added under an argon atmosphere. The resulting suspension was cooled to 0 °C and LDA (60 mmol, 1.2 equiv.) was added dropwise. After the resulting orange solution was stirred for 10 minutes and cooled to -78 °C, a solution of trifluoromethyl ketones (1 equiv.) in THF (50 mL) was added to the reaction mixture. The cooling bath was removed and the solution was allowed to warm to room temperature and stirred overnight. Then the reaction was quenched with aq. NH₄Cl (sat.). The organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (10% EtOAc in petroleum ether) to give the desired styrene **1a** as a pale yellow oil in 65% yield (7.55 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 6.60 – 6.57 (m, 2H), 6.49 (t, *J* = 2.3 Hz, 1H), 5.94 (q, *J* = 1.4 Hz, 1H), 5.76 (q, *J* = 1.7 Hz, 1H), 3.80 (s, 6H).

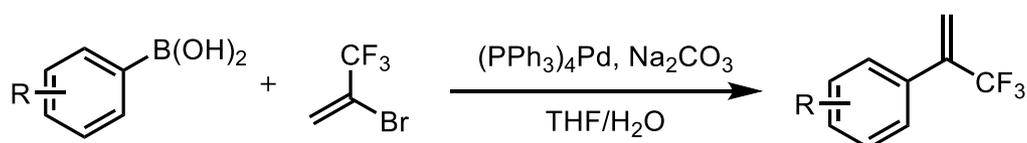
¹³C NMR (101 MHz, Chloroform-*d*) δ 160.74, 138.89 (q, *J* = 30.7, 30.3 Hz), 135.51, 123.20 (q, *J* = 273.9 Hz), 120.72 (q, *J* = 5.8 Hz), 105.83, 100.81, 55.38.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -64.70 (s, 3F).



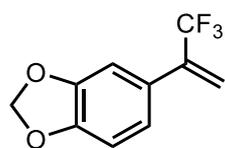


General procedure (A) for the preparation of trifluoromethyl-substituted alkenes:³



Boronic acids (10 mmol, 1 equiv.), Na₂CO₃ (20 mmol, 2 equiv.) and Pd(PPh₃)₄ (0.5 mmol, 0.05 equiv.) were mixed and degassed. To this mixture was added THF (40 mL, pre-degassed), H₂O (40 mL, pre-degassed) and vinyl bromide (2.1 mL, 20 mmol, 2 equiv.) respectively. The reaction tube was sealed and the reaction mixture was stirred at room temperature for one hour and then 60 °C overnight. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate) to give the desired styrenes **1** (Note: the products might be volatile under high vacuum).

5-(3,3,3-Trifluoroprop-1-en-2-yl)benzo[d][1,3]dioxole (1c).

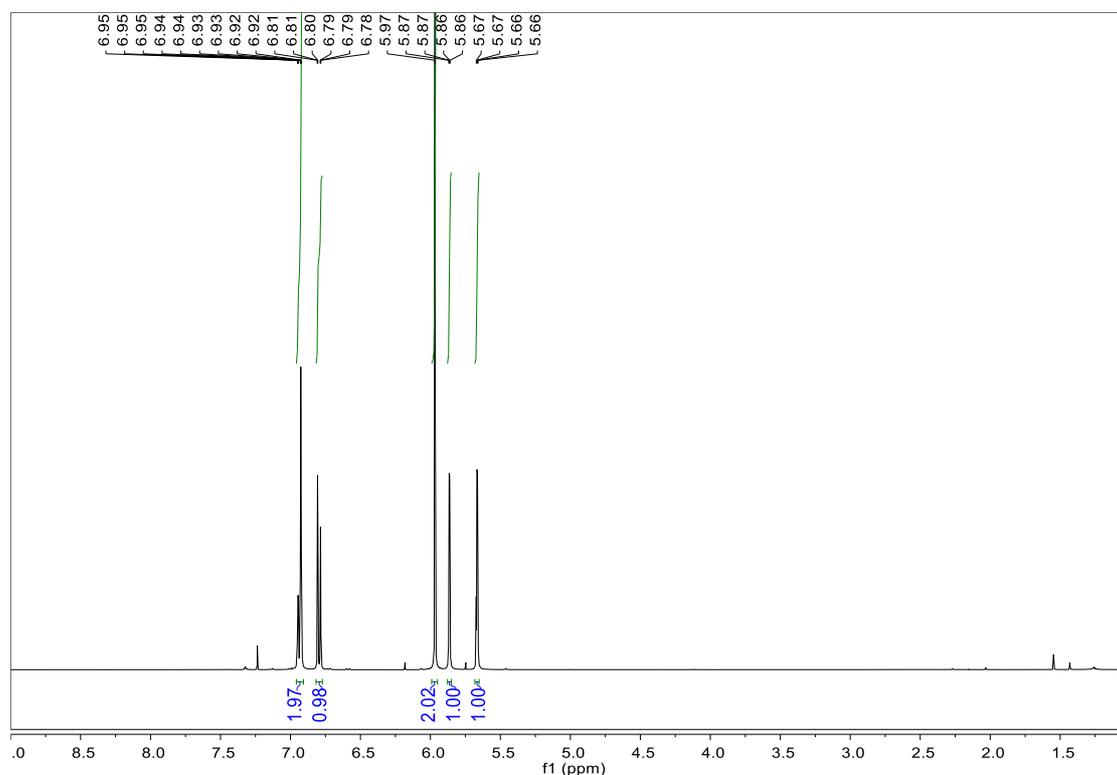


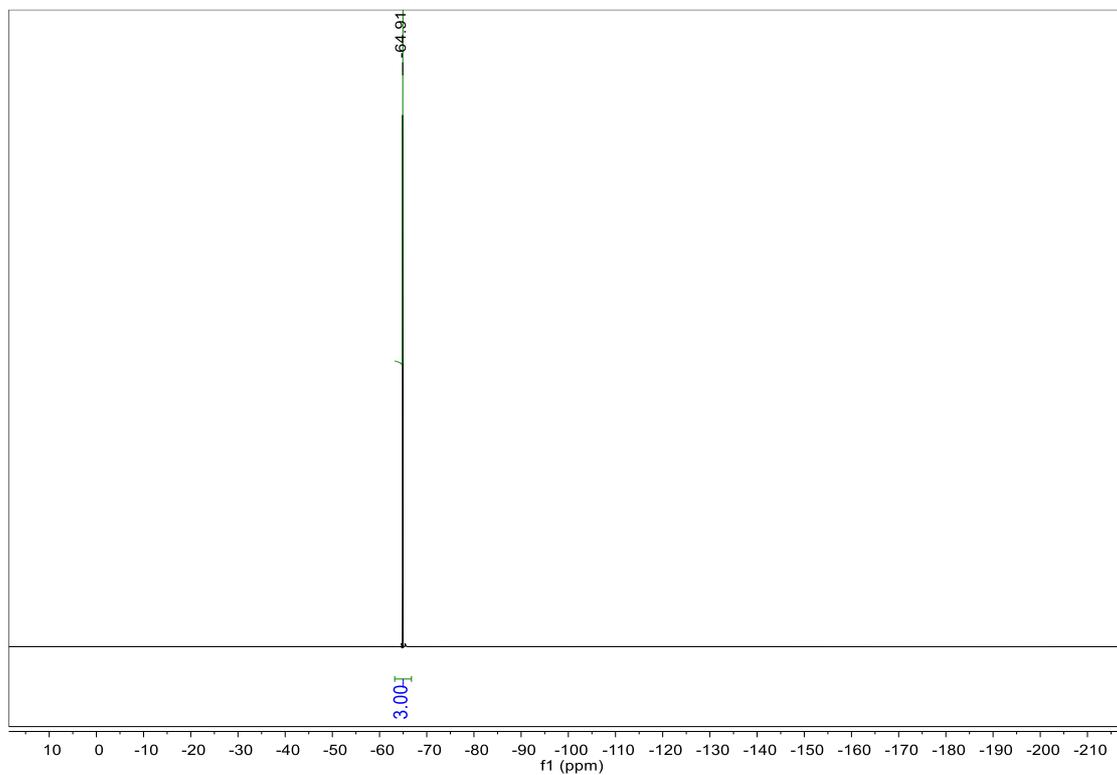
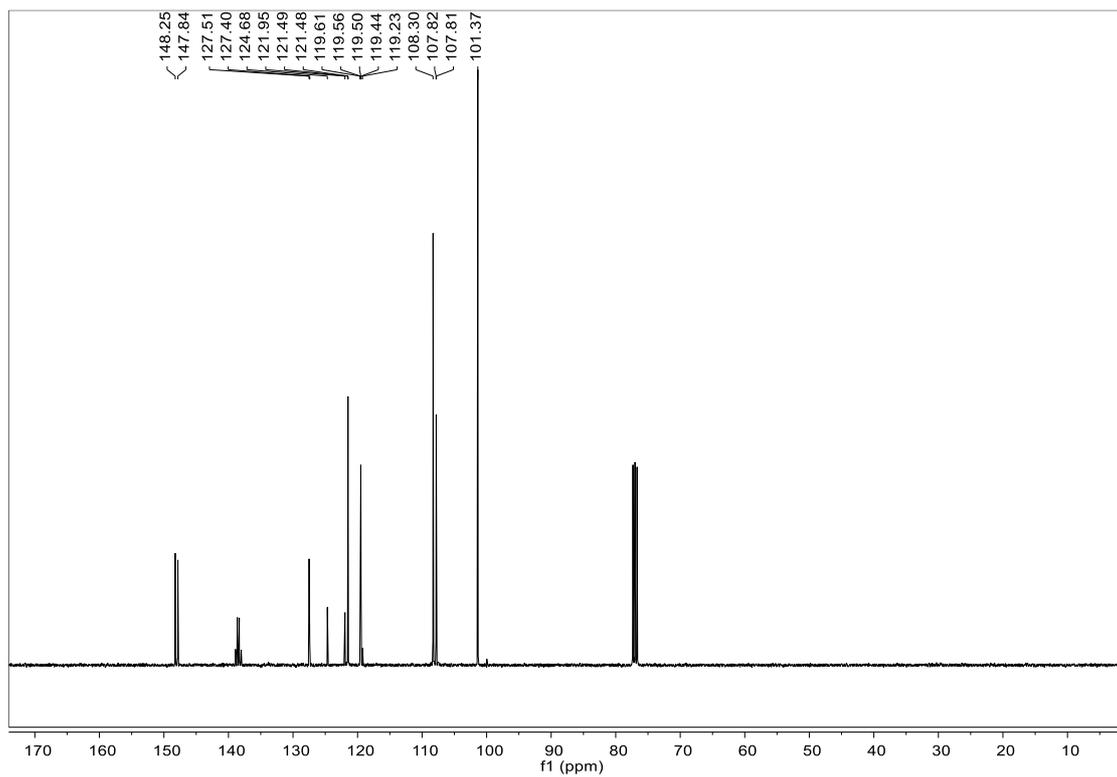
Prepared following general procedure A. The residue was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 64% yield (1.38 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 6.94 (dq, $J = 8.4, 0.8$ Hz, 2H), 6.82 – 6.77 (m, 1H), 5.97 (s, 2H), 5.86 (dd, $J = 2.6, 1.3$ Hz, 1H), 5.67 (dd, $J = 3.5, 1.6$ Hz, 1H)..

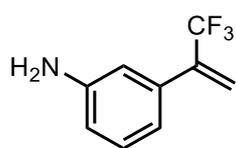
¹³C NMR (101 MHz, Chloroform-*d*) δ 148.25, 147.84, 138.47 (q, $J = 30.0$ Hz), 127.51, 123.32 (q, $J = 274.0$ Hz), 121.48 (d, $J = 0.9$ Hz), 119.53 (q, $J = 5.7$ Hz), 108.30, 107.81 (d, $J = 1.1$ Hz), 101.37.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -64.91 (s, 3F).





3-(3,3,3-Trifluoroprop-1-en-2-yl)aniline (1e).

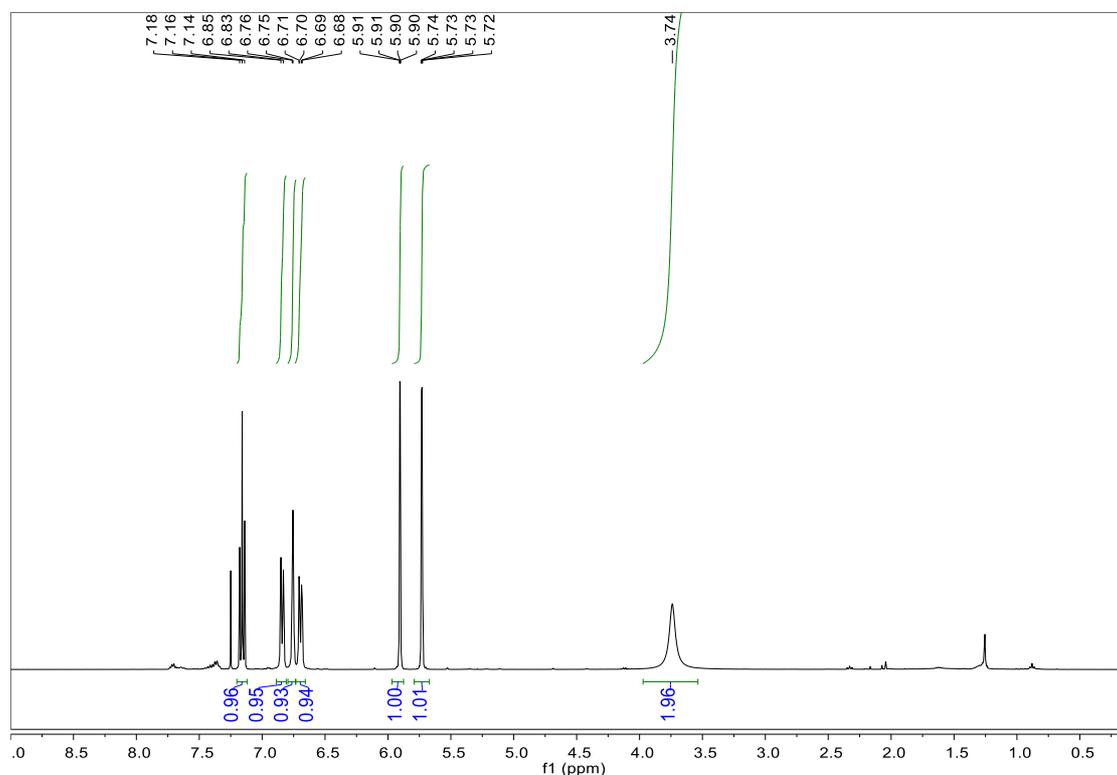


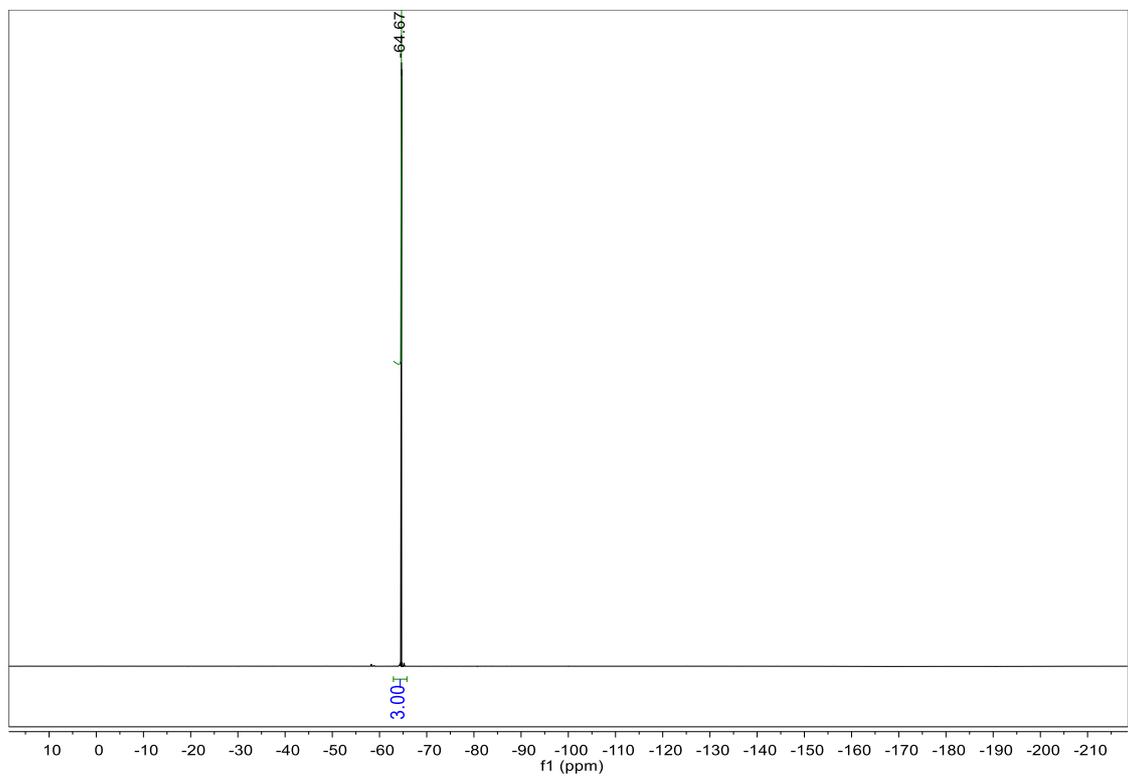
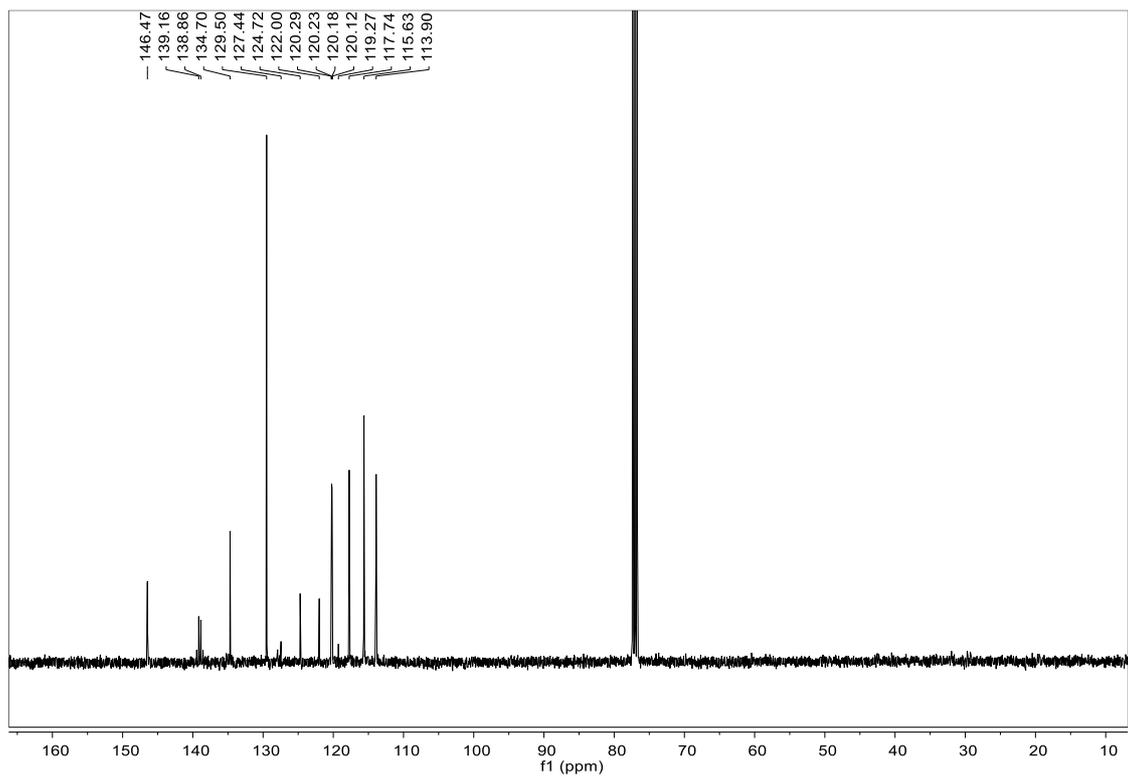
Prepared following general procedure A. The residue was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to provide the title compound as a brown oil in 45% yield (0.84 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.16 (t, $J = 7.8$ Hz, 1H), 6.84 (d, $J = 7.7$ Hz, 1H), 6.76 (d, $J = 2.5$ Hz, 1H), 6.69 (dd, $J = 8.1, 2.3$ Hz, 1H), 5.90 (dd, $J = 2.6, 1.3$ Hz, 1H), 5.73 (dd, $J = 3.2, 1.6$ Hz, 1H), 3.74 (s, 2H)..

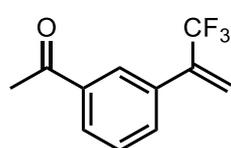
¹³C NMR (101 MHz, Chloroform-*d*) δ 146.47, 139.01 (d, $J = 29.9$ Hz), 134.70, 129.50, 123.36 (q, $J = 274.0$ Hz), 120.21 (q, $J = 5.9$ Hz), 117.74, 115.63, 113.90.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -64.67 (s, 3F).





1-(3-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)ethan-1-one (1h).

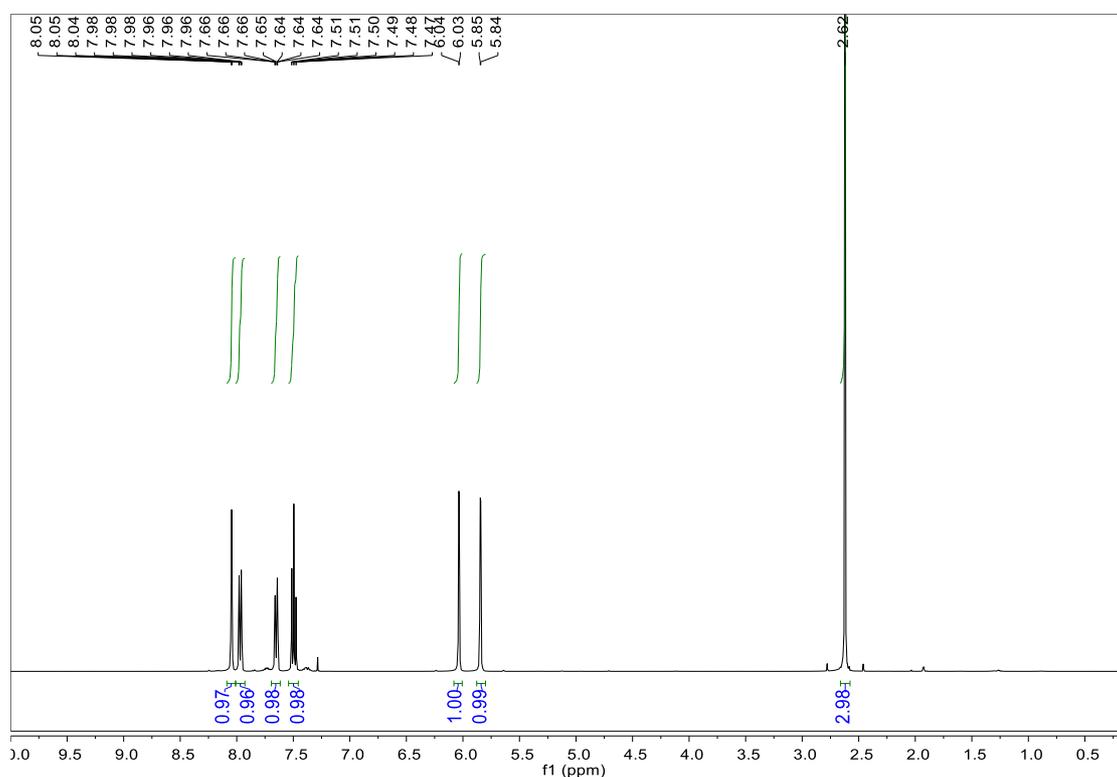


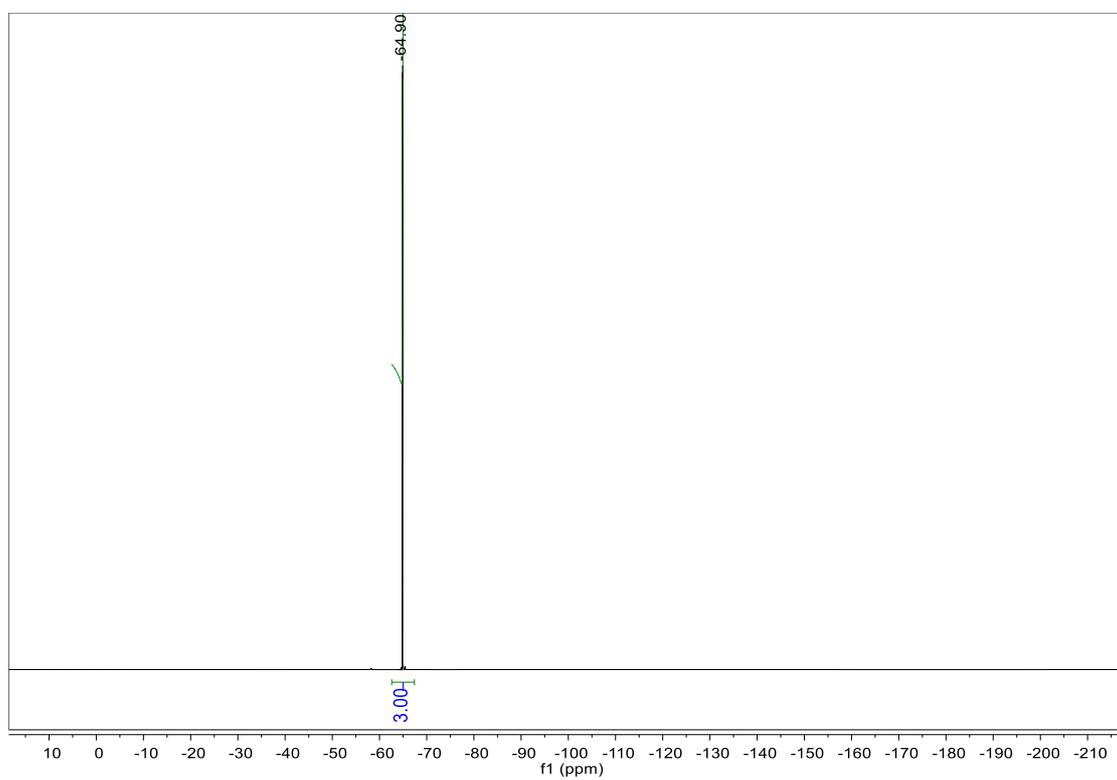
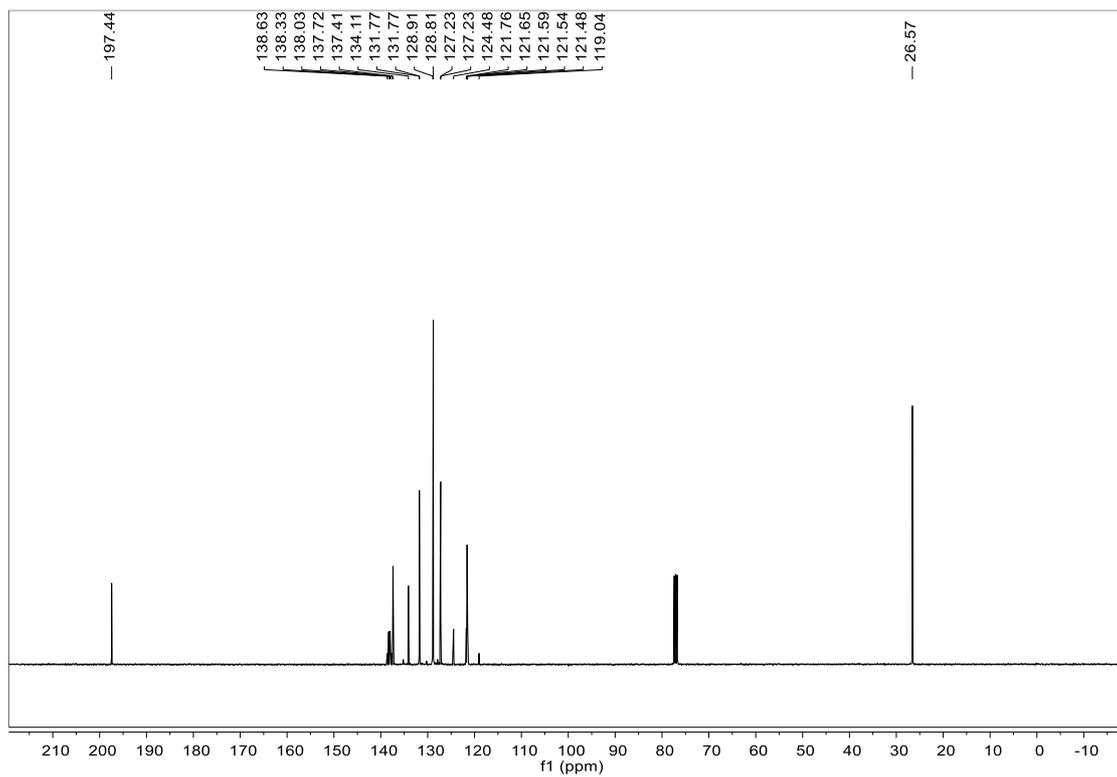
Prepared following general procedure A. The residue was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 78% yield (1.67 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, J = 1.8 Hz, 1H), 7.97 (dt, J = 7.8, 1.4 Hz, 1H), 7.65 (ddt, J = 7.8, 2.0, 1.0 Hz, 1H), 7.49 (td, J = 7.8, 0.7 Hz, 1H), 6.04 (dd, J = 2.5, 1.2 Hz, 1H), 5.84 (dd, J = 3.1, 1.5 Hz, 1H), 2.62 (s, 3H).

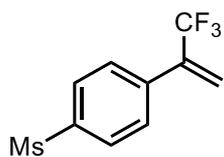
¹³C NMR (101 MHz, Chloroform-*d*) δ 197.44, 138.18 (q, J = 30.4 Hz), 137.41, 134.11, 131.77 (d, J = 0.8 Hz), 128.91, 128.81, 127.23 (d, J = 0.7 Hz), 123.12 (q, J = 273.9 Hz), 121.57 (q, J = 5.7 Hz), 26.57.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -64.90 (s, 3F).





1-(Methylsulfonyl)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (1i).

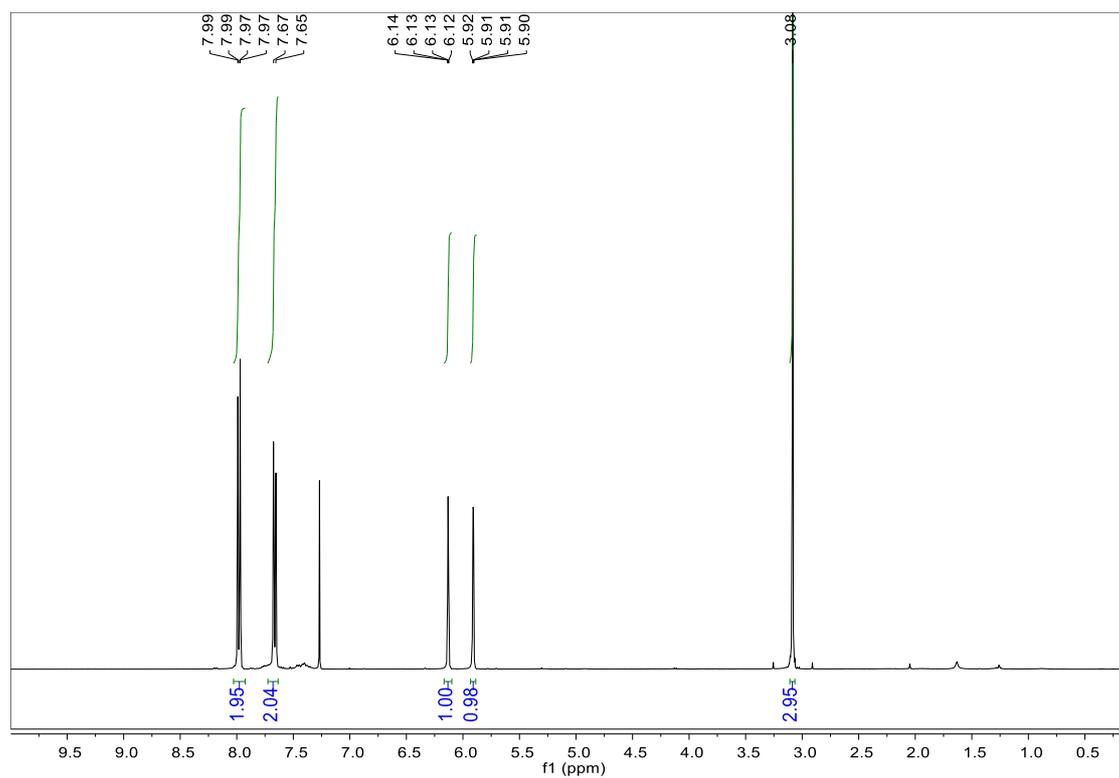


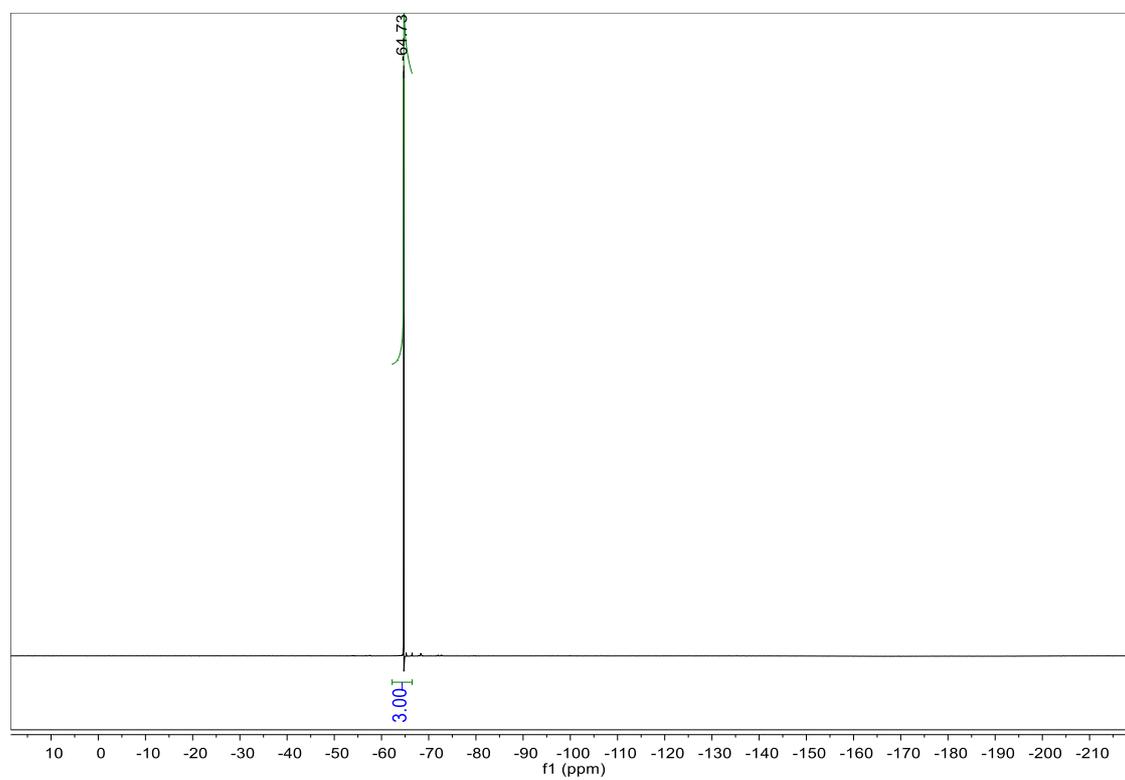
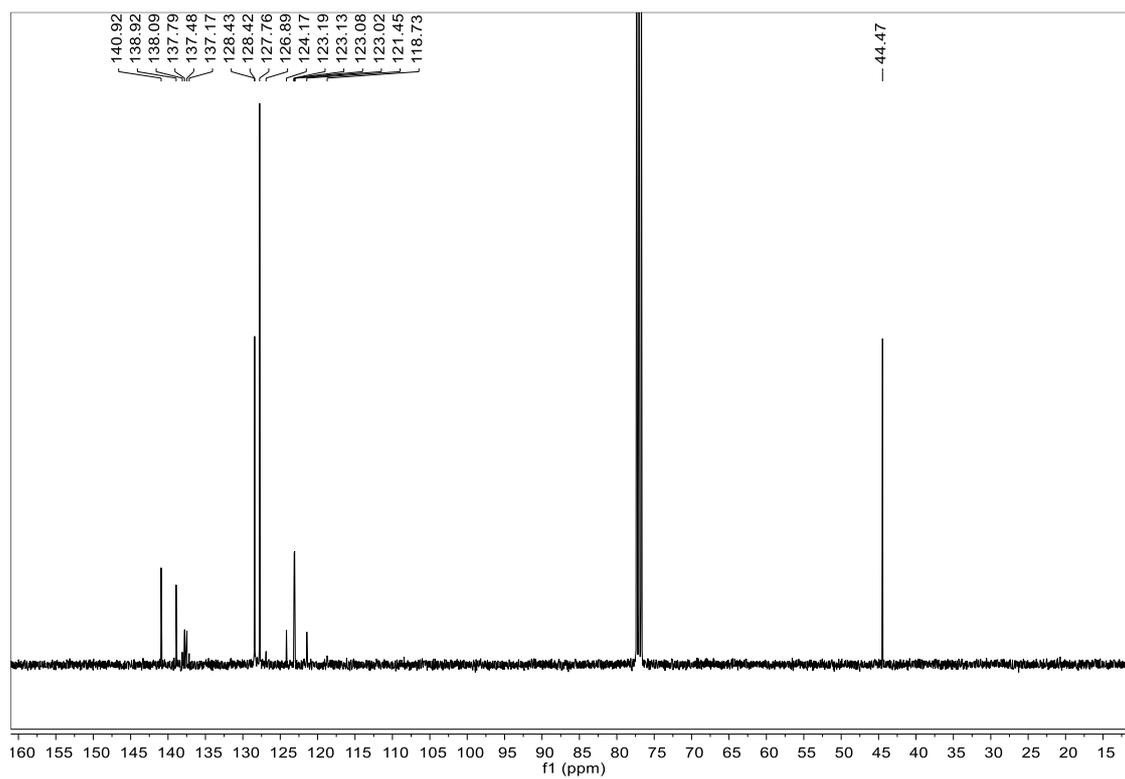
Prepared following general procedure A. The residue was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 92% yield (2.30 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.03 – 7.93 (m, 2H), 7.66 (d, $J = 8.2$ Hz, 2H), 6.13 (dd, $J = 2.6, 1.3$ Hz, 1H), 5.91 (dd, $J = 3.1, 1.5$ Hz, 1H), 3.08 (s, 3H).

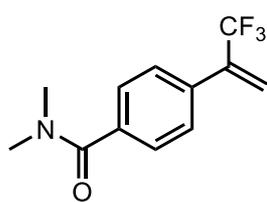
¹³C NMR (101 MHz, Chloroform-*d*) δ 140.92, 138.92, 137.63 (q, $J = 30.8$ Hz), 128.43 (d, $J = 1.1$ Hz), 127.76, 123.10 (q, $J = 5.7$ Hz), 122.81 (q, $J = 273.9$ Hz), 44.47.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -64.73 (s, 3F).





***N,N*-Dimethyl-4-(3,3,3-trifluoroprop-1-en-2-yl)benzamide (1j).**

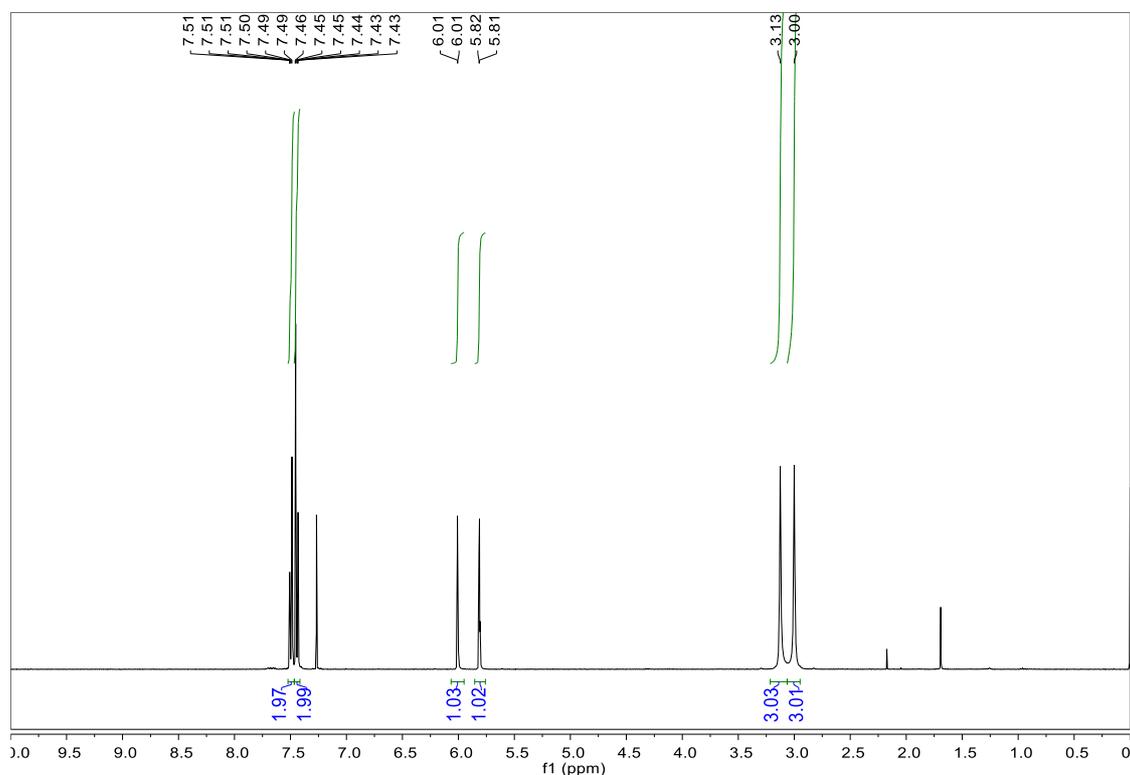


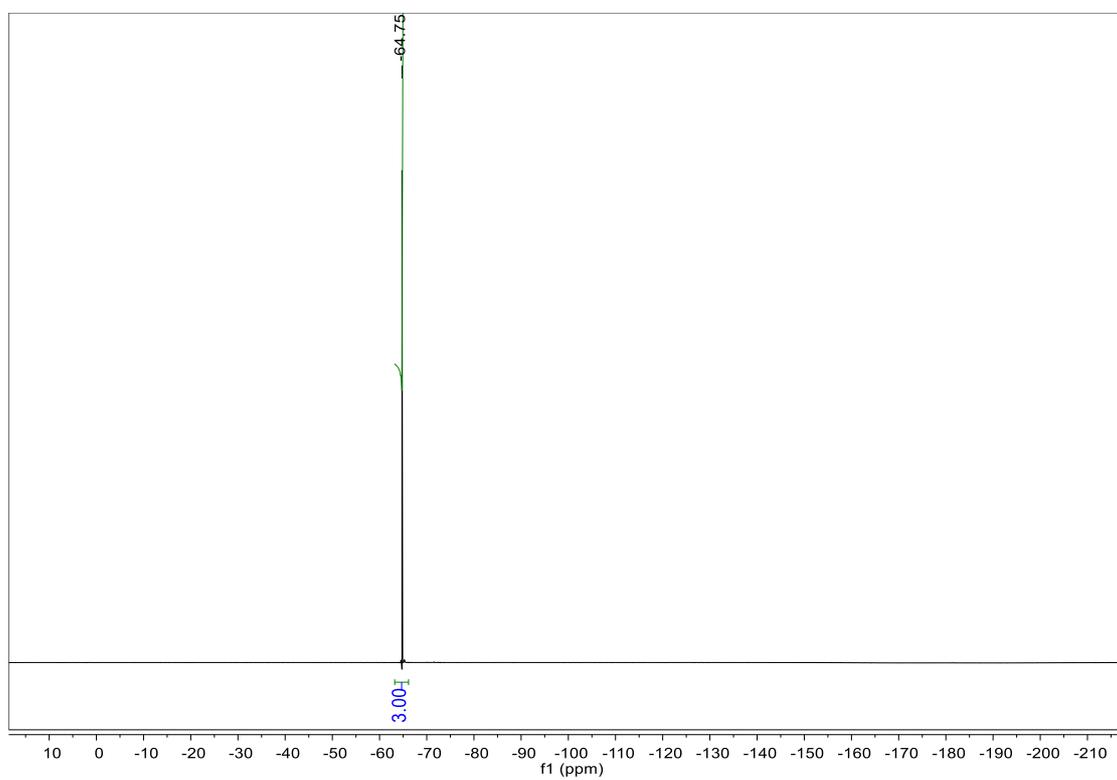
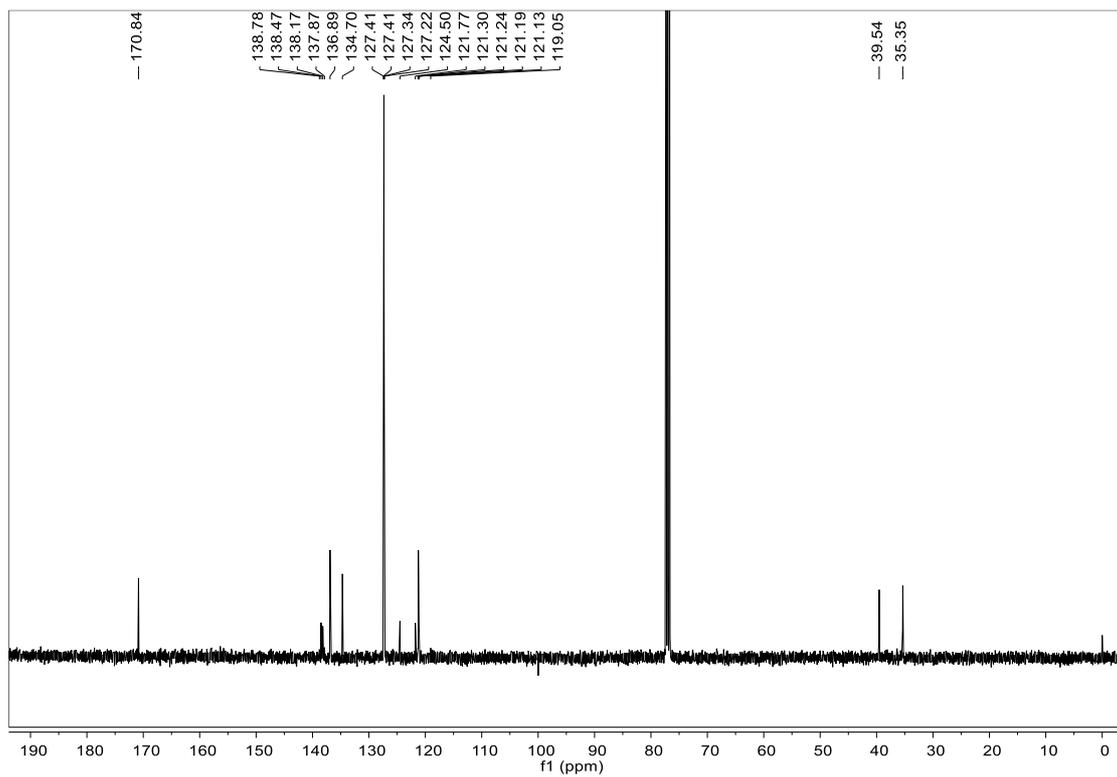
Prepared following general procedure A. The residue was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to provide the title compound as a pale yellow solid in 67% yield (1.63 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.46 (m, 2H), 7.47 – 7.42 (m, 2H), 6.01 (dd, $J = 2.7, 1.3$ Hz, 1H), 5.81 (dd, $J = 3.3, 1.7$ Hz, 1H), 3.13 (s, 3H), 3.00 (s, 3H).

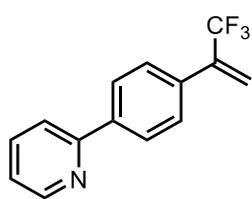
¹³C NMR (101 MHz, Chloroform-*d*) δ 170.84, 138.32 (q, $J = 30.4$ Hz), 136.89, 134.70, 127.41 (d, $J = 0.7$ Hz), 127.34, 123.13 (q, $J = 274.0$ Hz), 121.21 (q, $J = 5.8$ Hz), 39.54, 35.35.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -64.75 (s, 3F).





2-(4-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl)pyridine (1m).

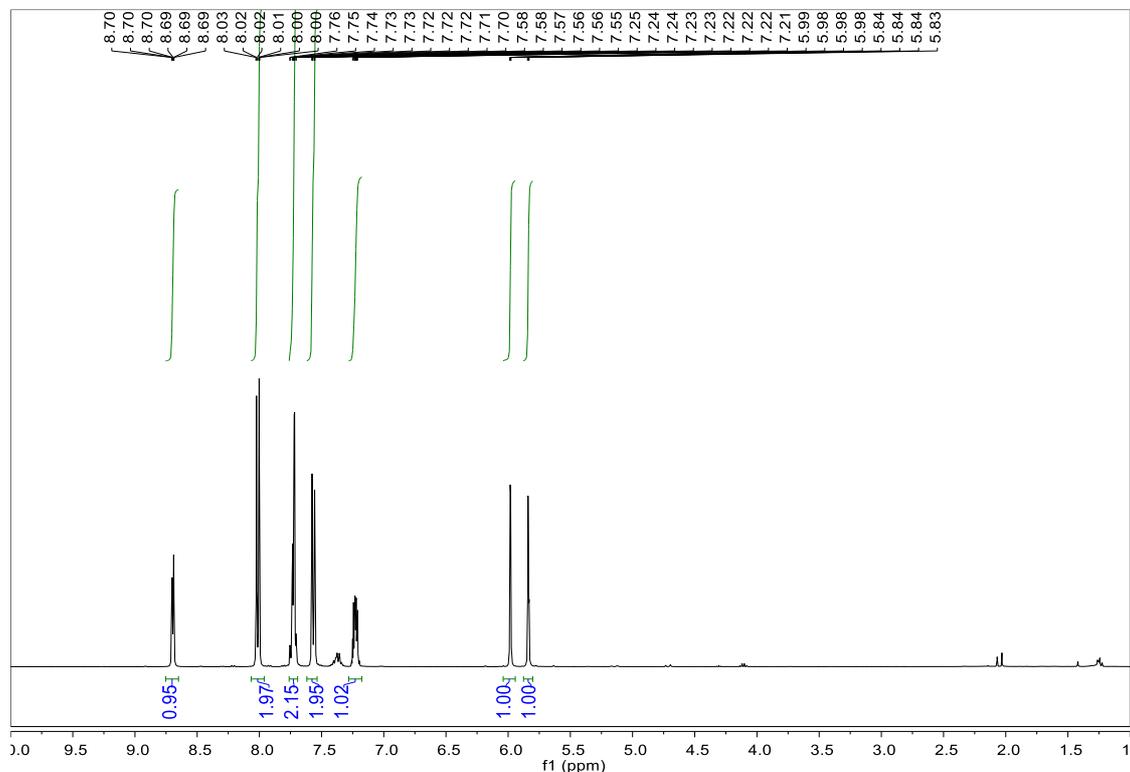


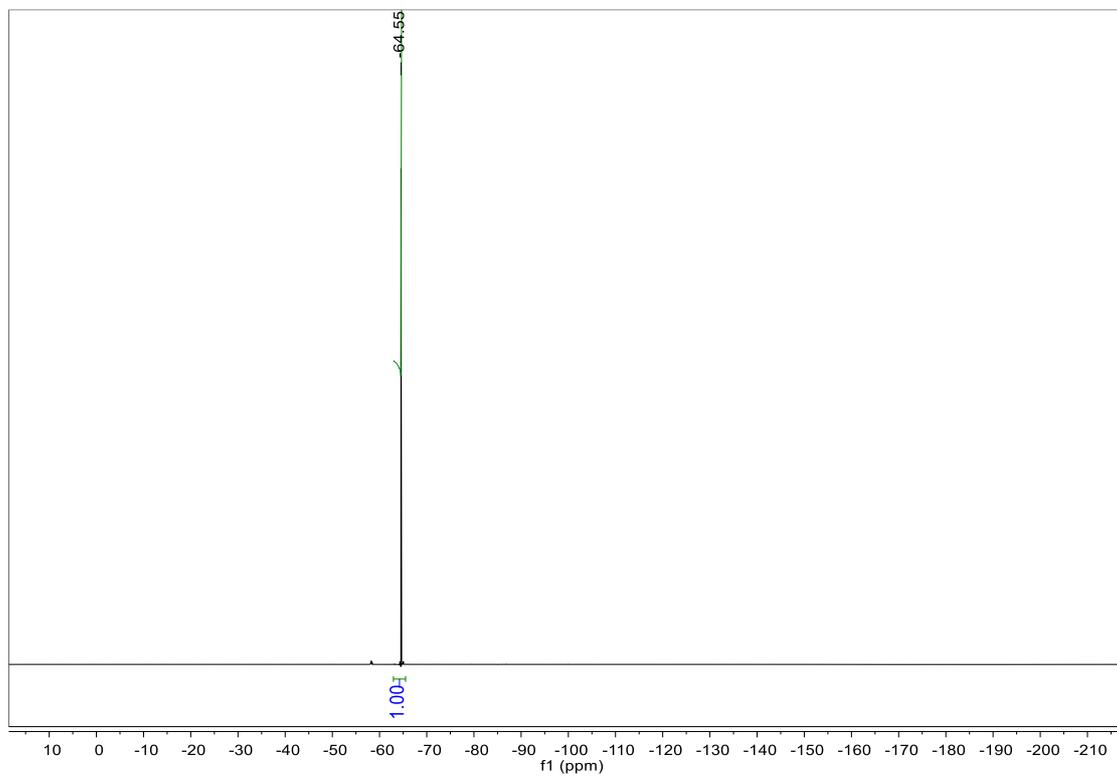
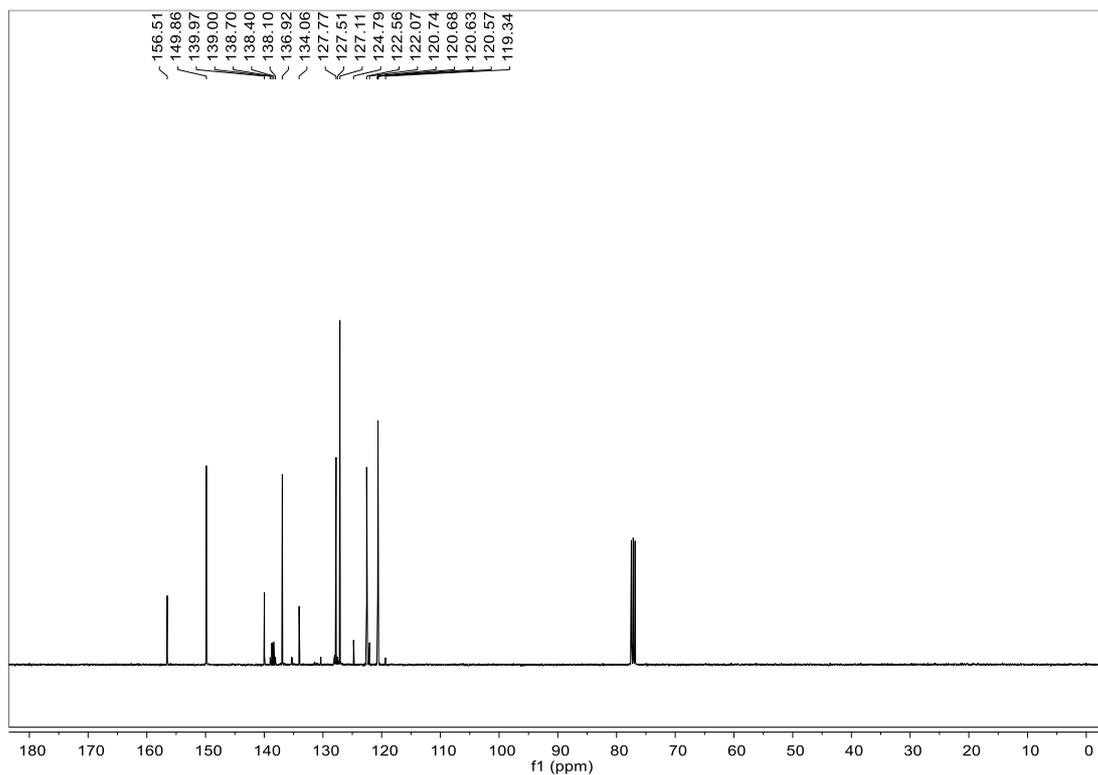
Prepared following the general procedure A. The residue was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to provide the title compound as a pale yellow solid in 70% yield (1.74 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.70 (dt, $J = 4.8, 1.4$ Hz, 1H), 8.07 – 7.96 (m, 2H), 7.76 – 7.69 (m, 2H), 7.62 – 7.54 (m, 2H), 7.28 – 7.18 (m, 1H), 5.98 (dd, $J = 2.6, 1.2$ Hz, 1H), 5.84 (dd, $J = 3.3, 1.6$ Hz, 1H).

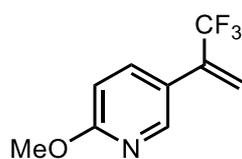
¹³C NMR (101 MHz, Chloroform-*d*) δ 156.51, 149.86, 139.97, 138.55 (q, $J = 30.1$ Hz), 136.92, 134.06, 127.77, 127.11, 123.43 (q, $J = 274.1$ Hz), 122.56, 120.66 (q, $J = 5.8$ Hz), 120.63.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -64.55 (s, 3F).





2-Methoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyridine (1o).

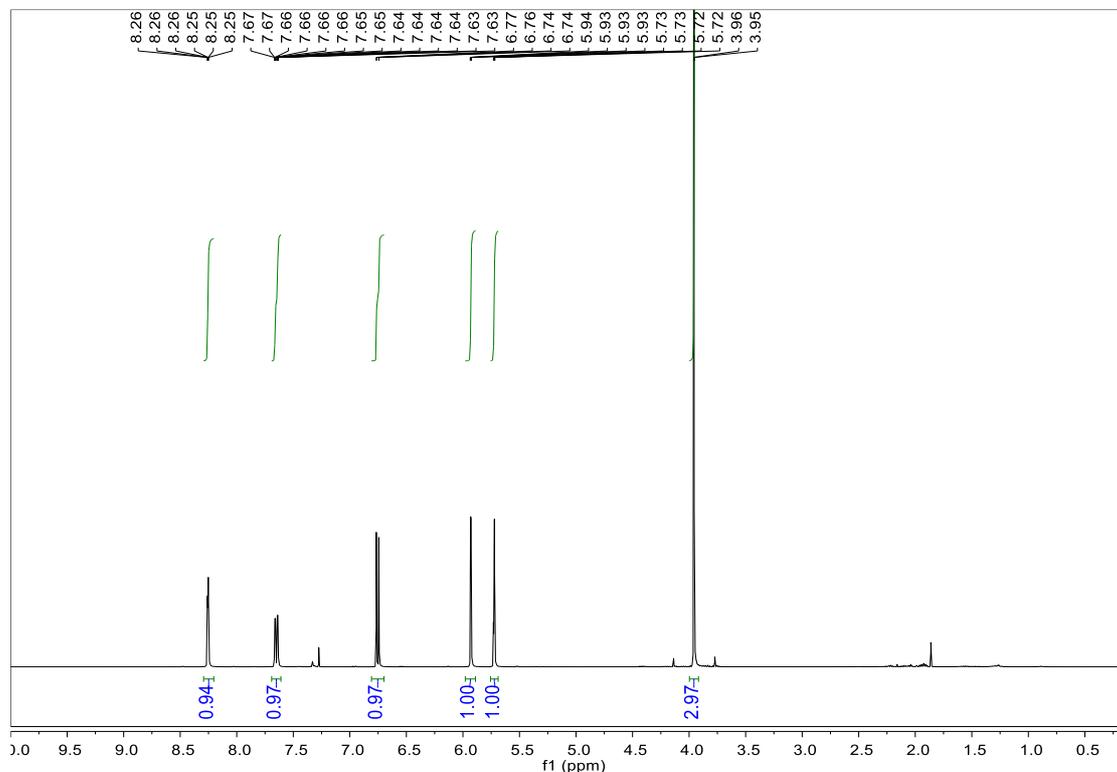


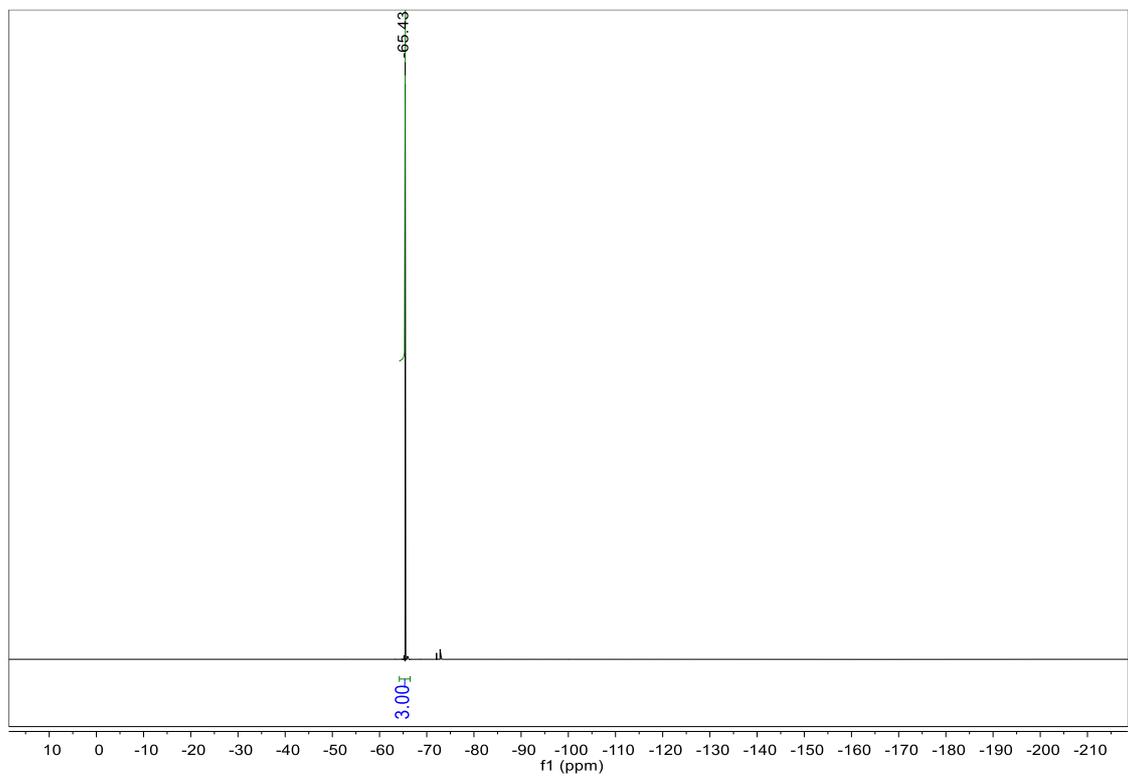
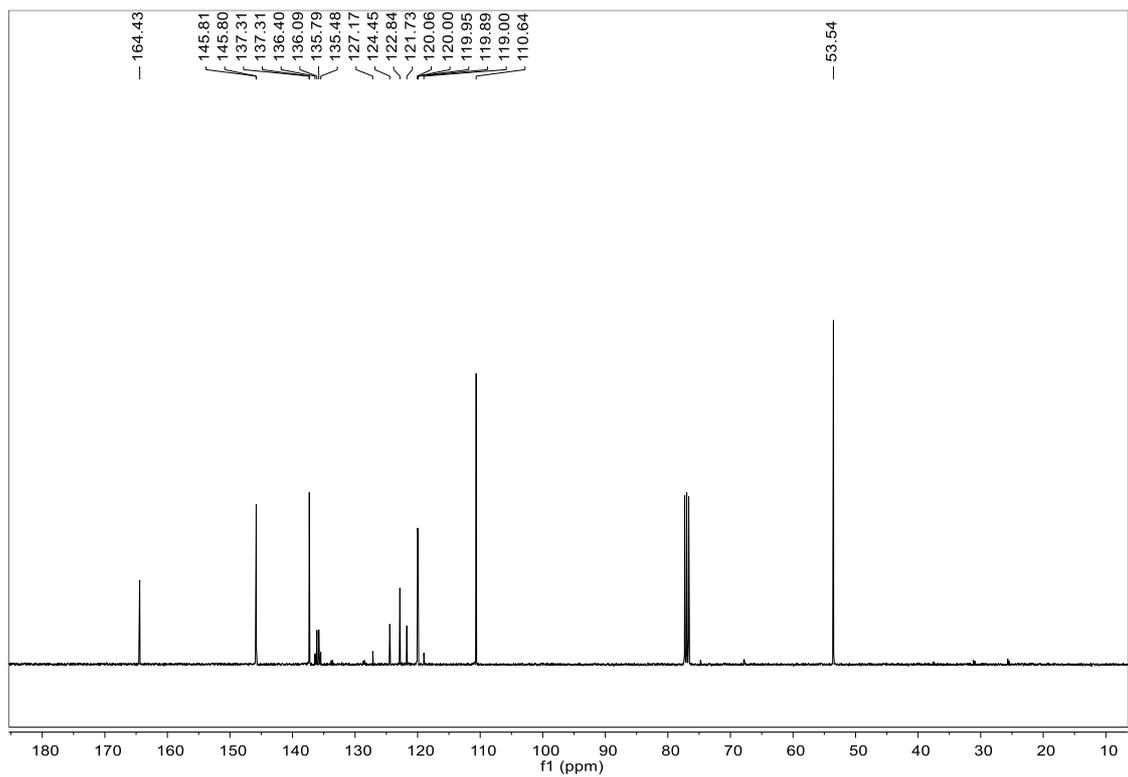
Prepared following general procedure A. The residue was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 74% yield (1.50 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.26 (dt, $J = 2.6, 0.6$ Hz, 1H), 7.65 (ddq, $J = 8.7, 2.5, 0.8$ Hz, 1H), 6.75 (dd, $J = 8.7, 0.8$ Hz, 1H), 5.93 (q, $J = 2.7, 1.3$ Hz, 1H), 5.72 (q, $J = 3.3, 1.6$ Hz, 1H), 3.96 (s, 3H).

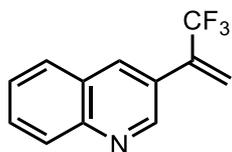
¹³C NMR (101 MHz, Chloroform-*d*) δ 164.43, 145.81 (d, $J = 1.3$ Hz), 137.31 (d, $J = 0.8$ Hz), 135.94 (q, $J = 30.8$ Hz), 123.09 (q, $J = 273.9$ Hz), 122.84, 119.97 (q, $J = 5.7$ Hz), 110.64, 53.54.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -65.43 (s, 3F).





3-(3,3,3-Trifluoroprop-1-en-2-yl)quinoline (1p).

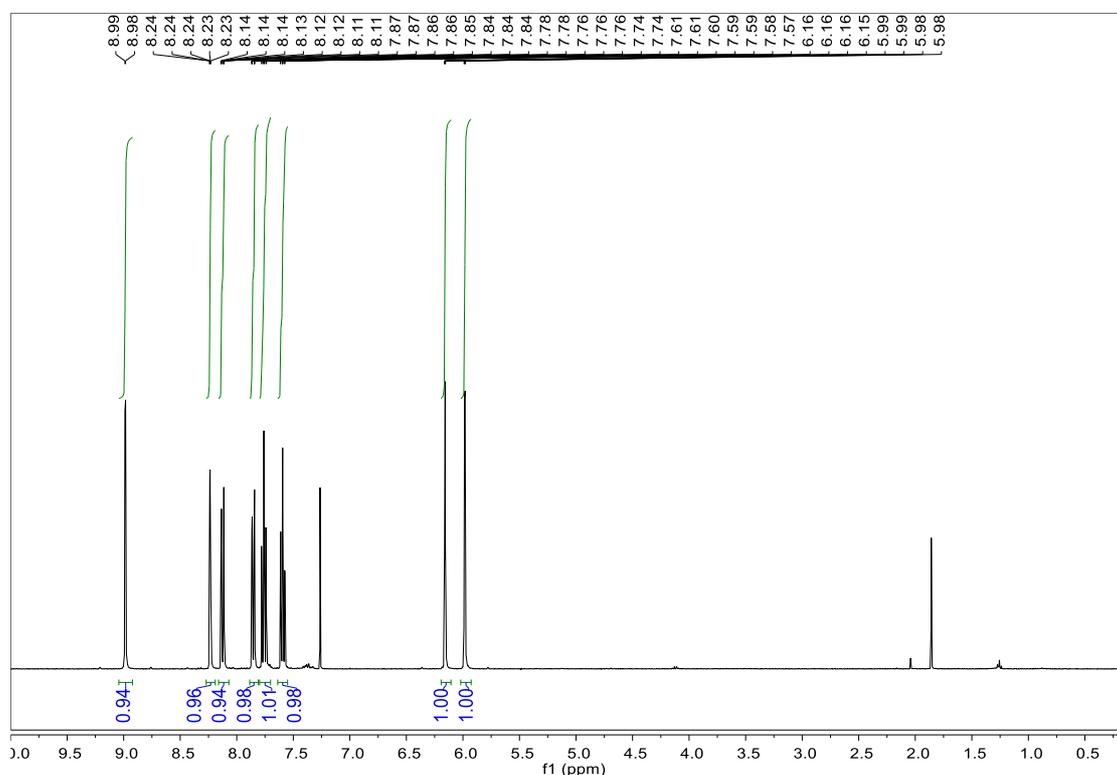


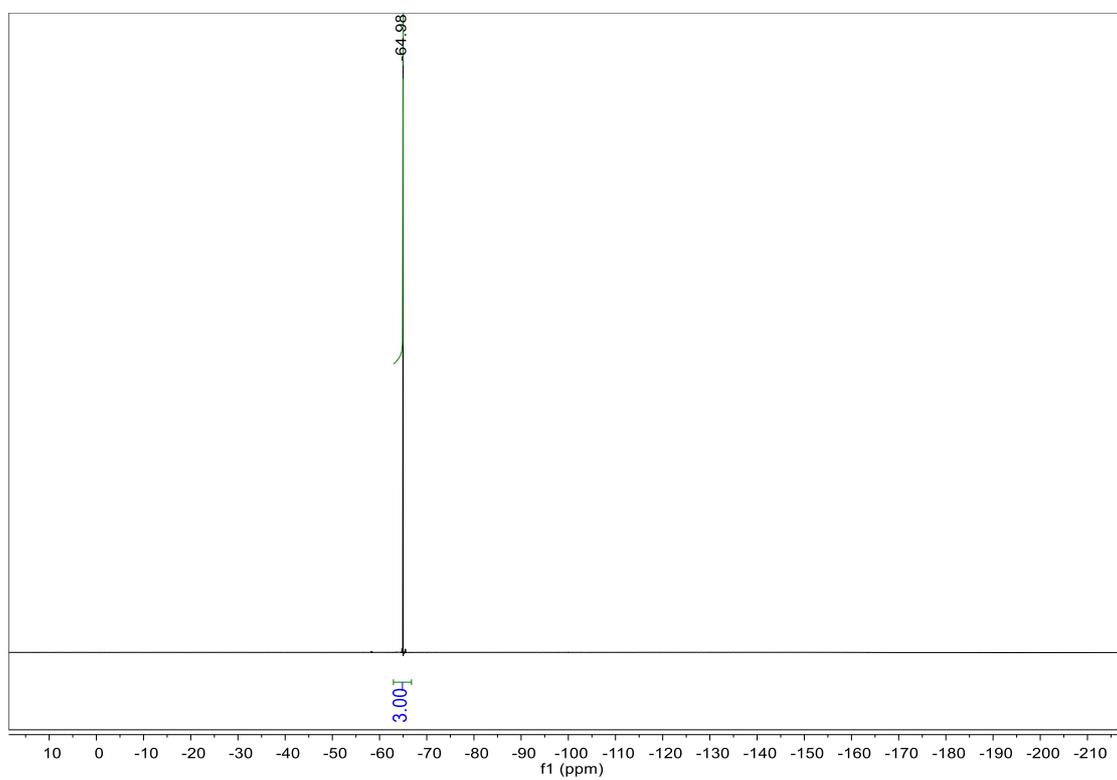
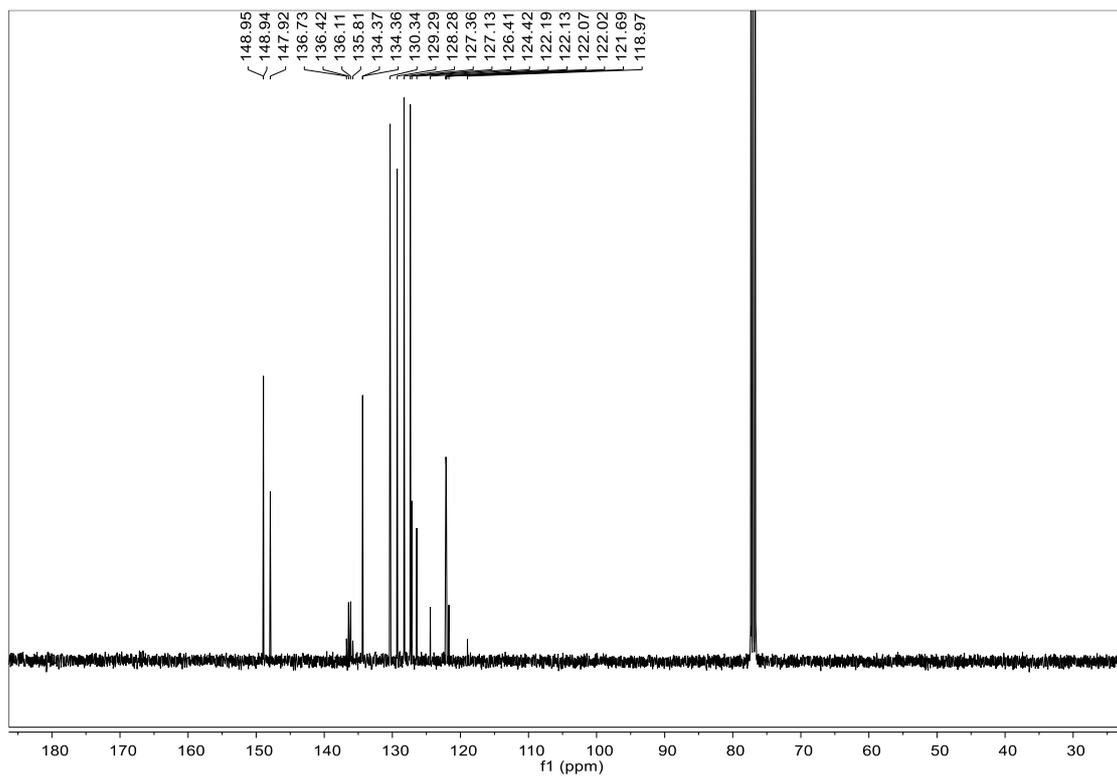
Prepared following general procedure A. The residue was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 72% yield (1.61 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.99 (d, $J = 2.3$ Hz, 1H), 8.24 (dt, $J = 2.2, 1.0$ Hz, 1H), 8.13 (dq, $J = 8.5, 0.9$ Hz, 1H), 7.85 (ddd, $J = 8.7, 1.2, 0.5$ Hz, 1H), 7.76 (ddd, $J = 8.4, 6.9, 1.5$ Hz, 1H), 7.59 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 6.16 (dd, $J = 2.6, 1.2$ Hz, 1H), 5.98 (dd, $J = 3.1, 1.5$ Hz, 1H).

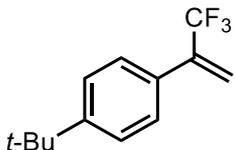
¹³C NMR (101 MHz, Chloroform-*d*) δ 148.94 (d, $J = 1.1$ Hz), 147.92, 136.27 (q, $J = 31.0$ Hz), 134.36 (q, $J = 1.1$ Hz), 130.34, 129.29, 128.28, 127.36, 127.13, 126.41, 122.10 (q, $J = 5.7$ Hz), 123.06 (q, $J = 273.4$ Hz).

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -64.98 (s, 3F).





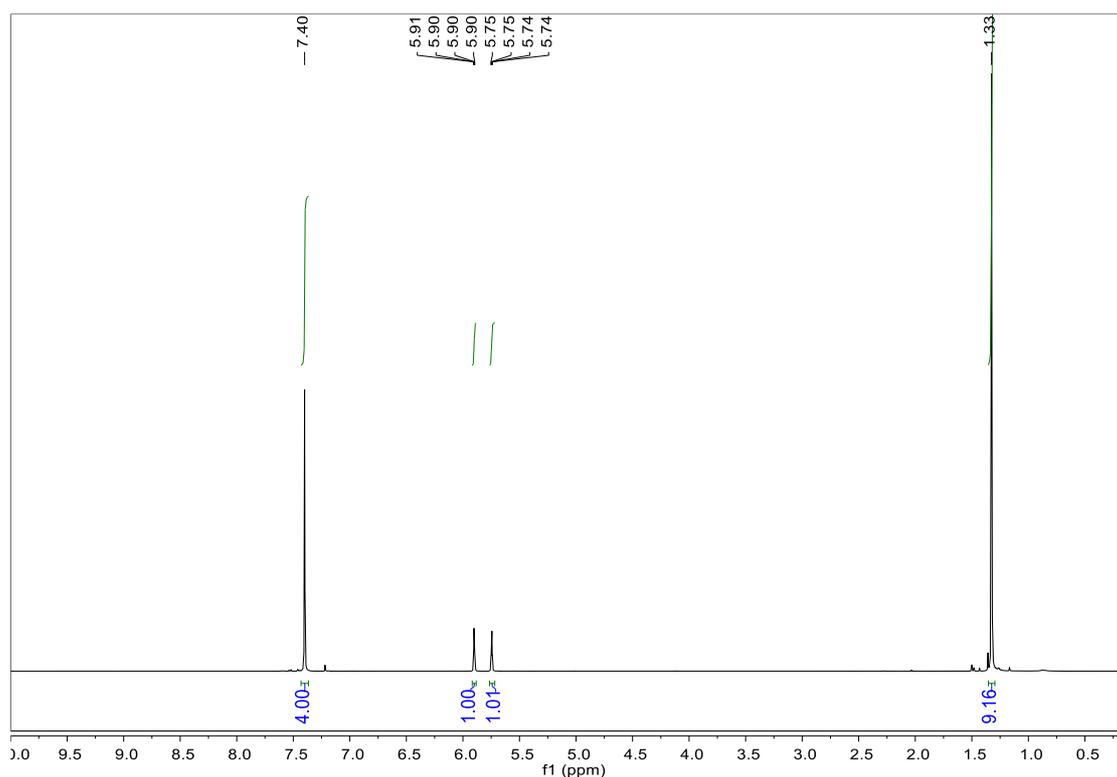
1-(*Tert*-butyl)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (1r).

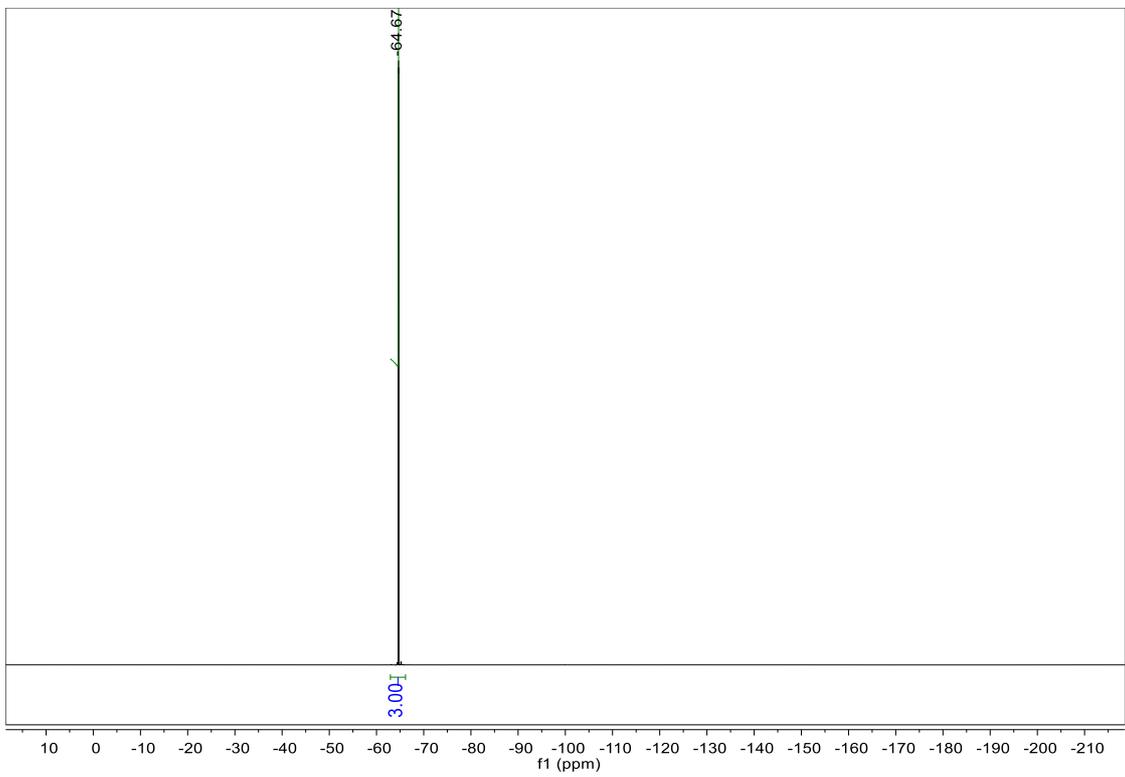
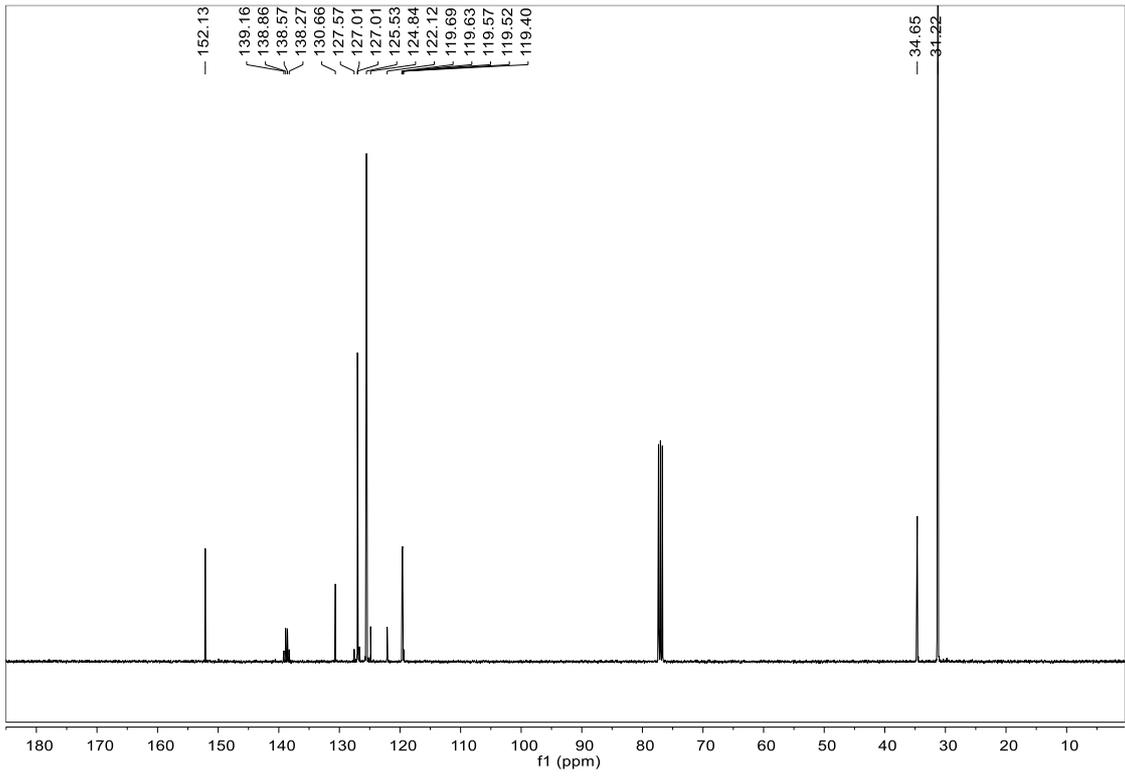
 Prepared following general procedure A. The residue was purified by silica gel column chromatography (petroleum ether) to provide the title compound as a colorless oil in 68% yield (1.55 g).

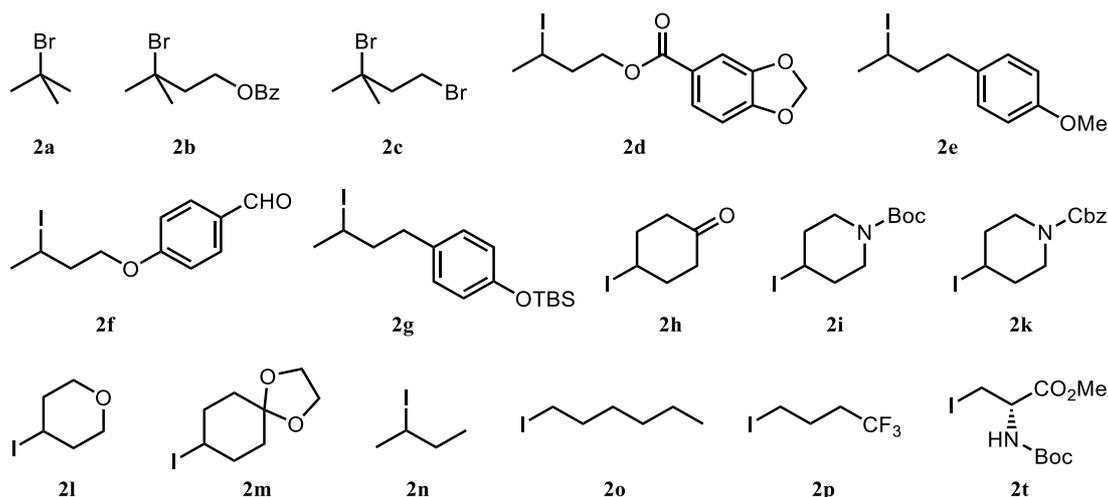
^1H NMR (400 MHz, Chloroform-*d*) δ 7.40 (s, 4H), 5.90 (dd, $J = 2.4, 1.3$ Hz, 1H), 5.75 (dd, $J = 3.2, 1.5$ Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 152.13, 138.72 (q, $J = 29.9$ Hz), 130.66, 127.01 (d, $J = 0.9$ Hz), 125.53, 123.48 (q, $J = 274.0$ Hz), 119.60 (q, $J = 5.9$ Hz), 34.65, 31.22.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -64.67 (s, 3F).



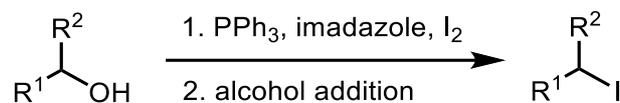




2a, 2c, 2l, 2n-2t were commercial available.

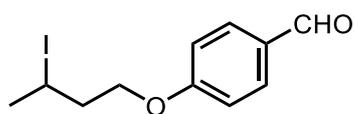
2d, 2e, 2h-2k, 2m were synthesized following the reported method.⁴

General procedure (B) for the preparation of alkyl iodides.⁴



To a stirred solution of PPh₃ (3.15 g, 12 mmol, 1.2 equiv.), imidazole (0.82 g, 12 mmol, 1.2 equiv.) and I₂ (3.05 g, 12 mmol, 1.2 equiv.) in CH₂Cl₂ (50 mL) was added a solution of alcohols (10 mmol, 1.0 equiv.) in CH₂Cl₂ (10 mL) at 0 °C. After stirring overnight at room temperature, the mixture was quenched with aqueous solution of Na₂S₂O₃ (sat.) The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (petroleum ether/ethyl acetate) to give the corresponding iodides.

4-(3-Iodobutoxy)benzaldehyde (2f).

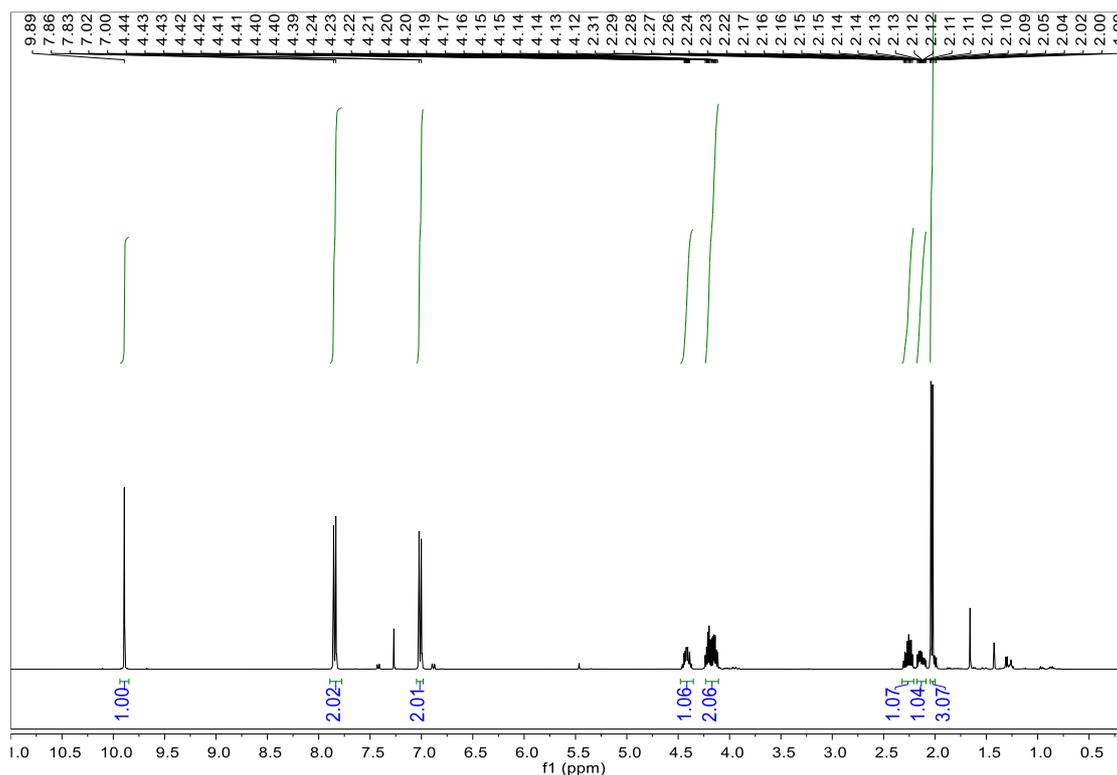


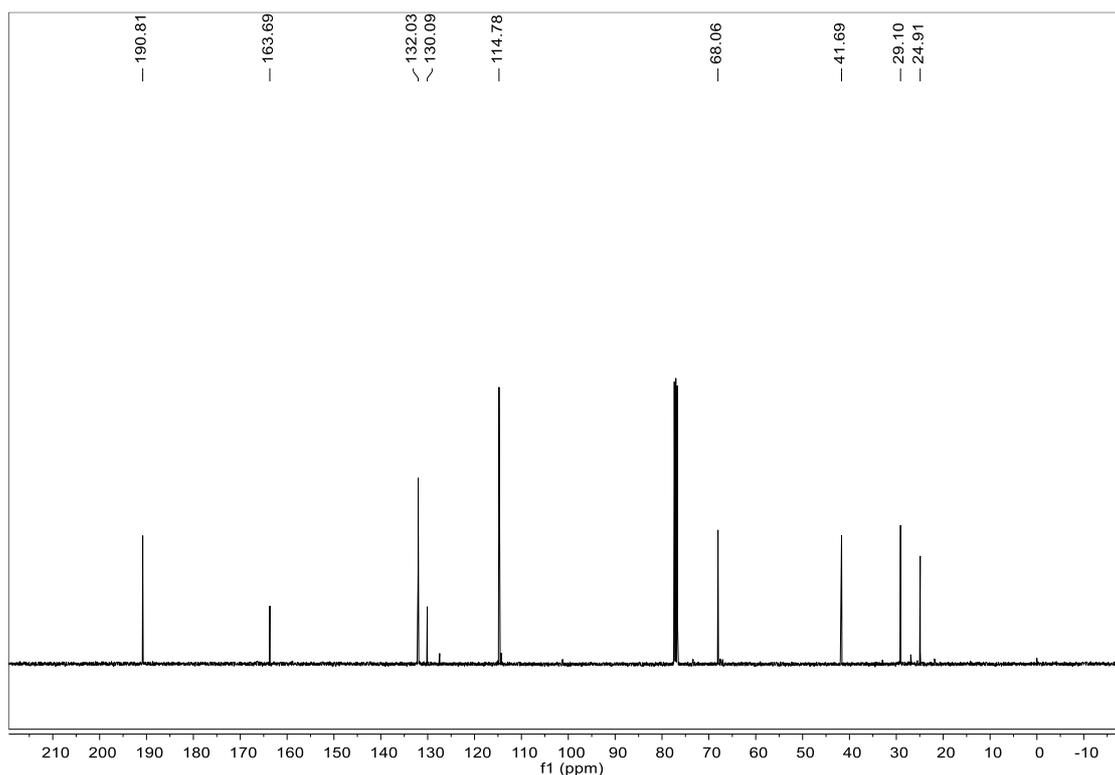
Prepared following general procedure **B** using 4-(3-hydroxybutoxy)benzaldehyde (1.94 g, 10 mmol). The residue was purified by silica gel column chromatography

(10% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 44% yield (1.34 g).

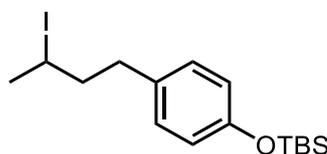
¹H NMR (400 MHz, Chloroform-*d*) δ 9.89 (s, 1H), 7.84 (d, $J = 8.7$ Hz, 2H), 7.01 (d, $J = 8.7$ Hz, 2H), 4.47 – 4.35 (m, 1H), 4.23 – 4.11 (m, 2H), 2.32 – 2.20 (m, 1H), 2.18 – 2.08 (m, 1H), 2.03 (d, $J = 6.9$ Hz, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 190.81, 163.69, 132.03, 130.09, 114.78, 68.06, 41.69, 29.10, 24.91.





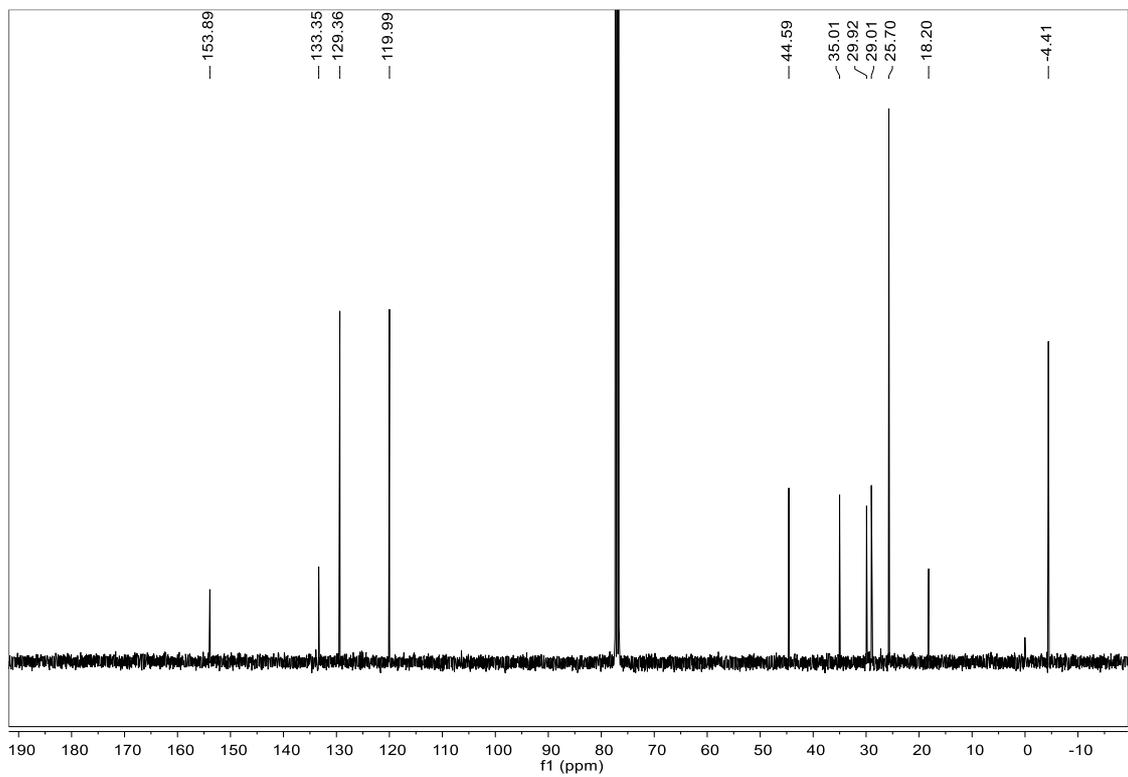
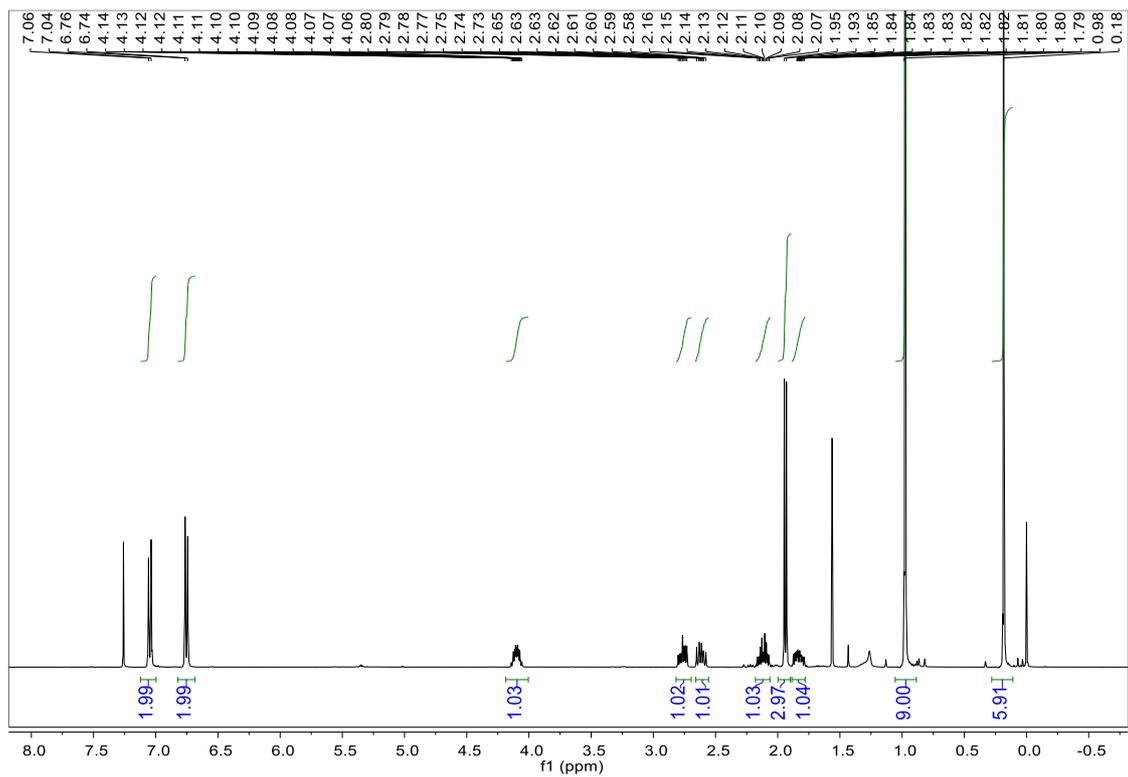
***Tert*-butyl(4-(3-iodobutyl)phenoxy)dimethylsilane (2g).**



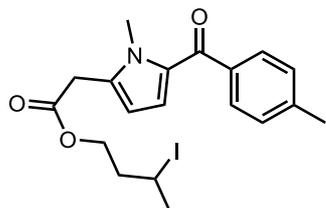
Prepared following general procedure **B** using 4-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)butan-2-ol (2.80 g, 10 mmol). The residue was purified by silica gel column chromatography (petroleum ether) to provide the title compound as a colorless oil in 71% yield (2.77 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 7.05 (d, $J = 8.4$ Hz, 2H), 6.75 (d, $J = 8.4$ Hz, 2H), 4.15 – 4.04 (m, 1H), 2.82 – 2.72 (m, 1H), 2.67 – 2.56 (m, 1H), 2.18 – 2.06 (m, 1H), 1.94 (d, $J = 6.8$ Hz, 3H), 1.89 – 1.78 (m, 1H), 0.98 (s, 9H), 0.18 (s, 6H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 153.89, 133.35, 129.36, 119.99, 44.59, 35.01, 29.92, 29.01, 25.70, 18.20, -4.41.



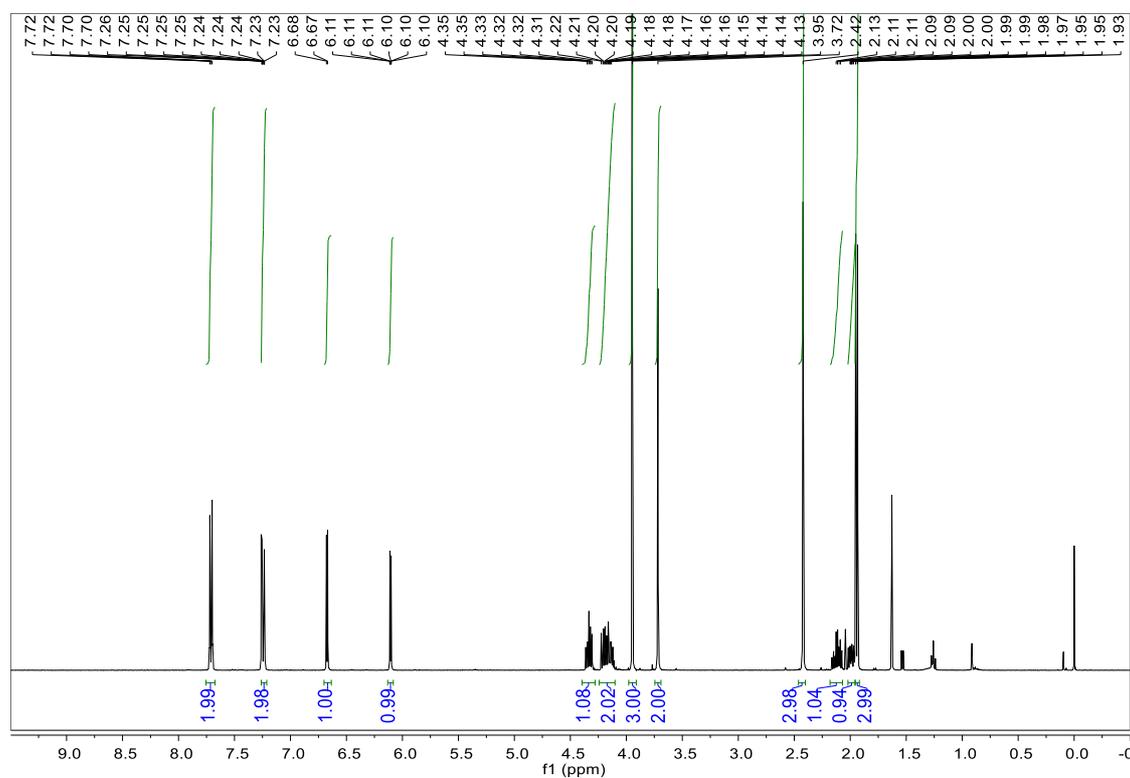
3-Iodobutyl 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetate (2q).

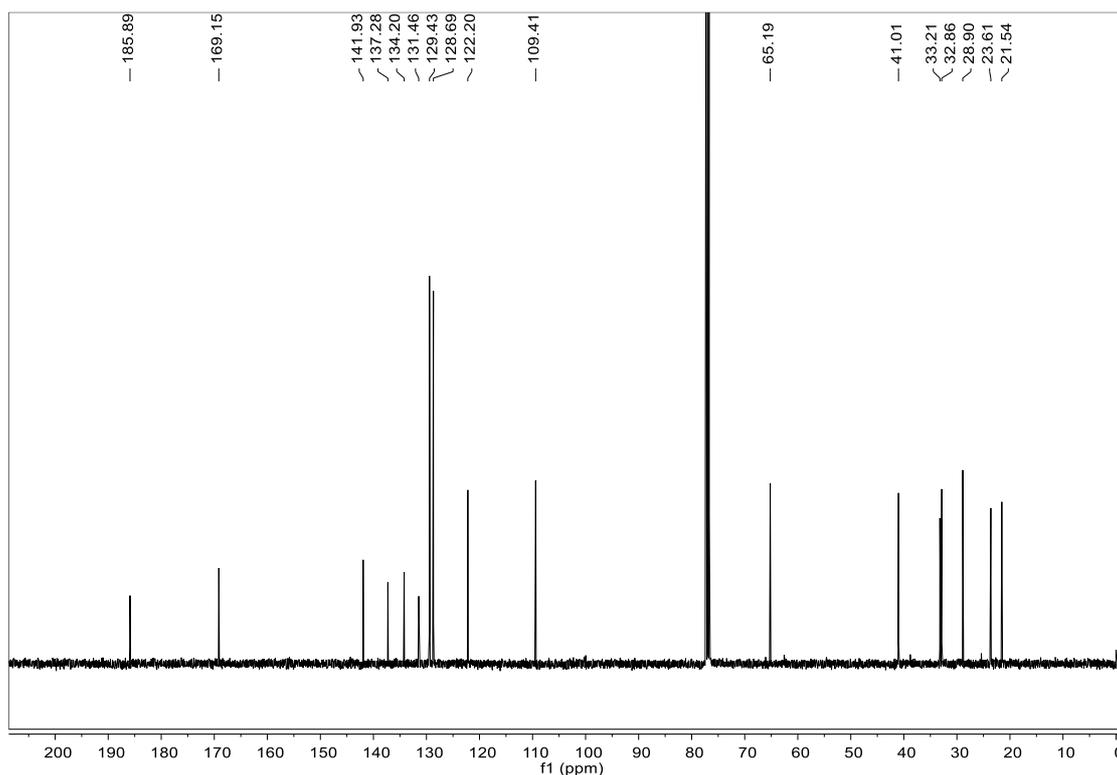


Prepared following general procedure **B** using 3-hydroxybutyl 2-(1-methyl-5-(4-methyl benzoyl)-1H-pyrrol-2-yl)acetate (3.29 g, 10 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a yellow oil in 68% yield (3.00 g).

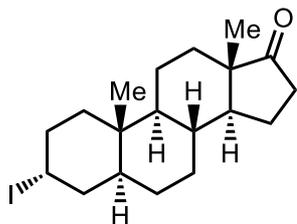
¹H NMR (400 MHz, Chloroform-*d*) δ 7.76 – 7.67 (m, 2H), 7.26 – 7.21 (m, 2H), 6.67 (d, $J = 4.1$ Hz, 1H), 6.11 (dd, $J = 4.0, 0.5$ Hz, 1H), 4.37 – 4.29 (m, 1H), 4.24 – 4.10 (m, 2H), 3.95 (s, 3H), 3.72 (s, 2H), 2.42 (s, 3H), 2.17 – 2.07 (m, 1H), 2.02 – 1.96 (m, 1H), 1.94 (d, $J = 6.9$ Hz, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 185.89, 169.15, 141.93, 137.28, 134.20, 131.46, 129.43, 128.69, 122.20, 109.41, 65.19, 41.01, 33.21, 32.86, 28.90, 23.61, 21.54.





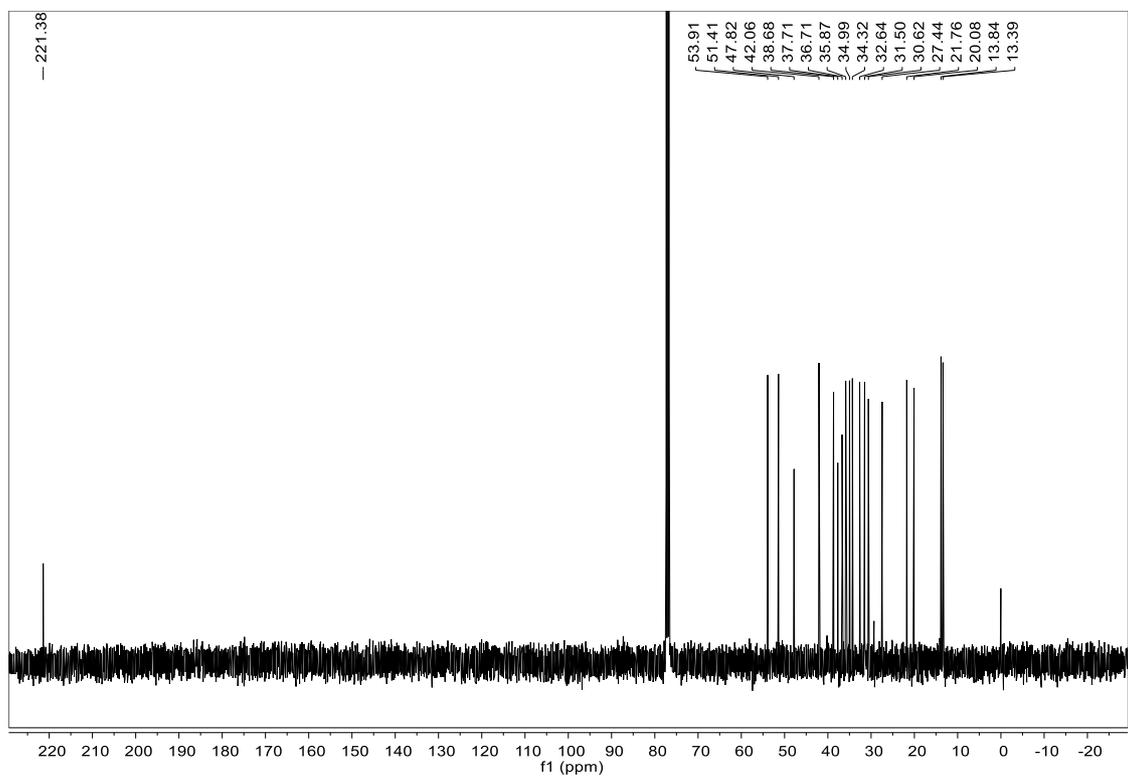
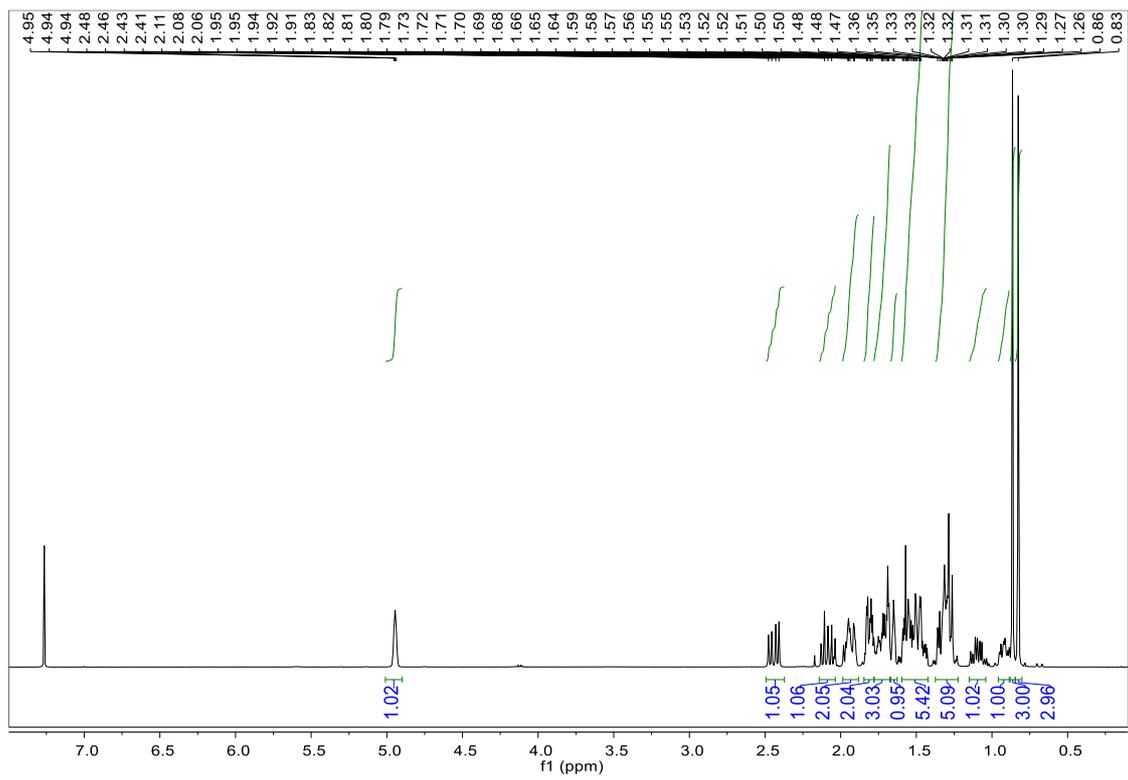
(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-3-Iodo-10,13-dimethylhexadecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (2r).



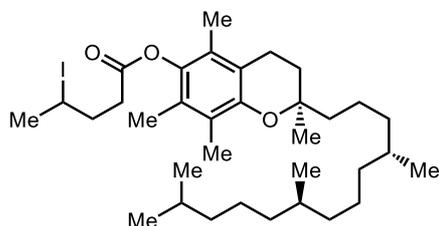
Prepared following general procedure **B** using Epiandrosterone (2.90 g, 10 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a white solid in 77% yield (3.08 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 4.94 (p, $J = 3.1$ Hz, 1H), 2.44 (dd, $J = 19.2, 8.8$ Hz, 1H), 2.14 – 2.04 (m, 1H), 1.99 – 1.88 (m, 2H), 1.85 – 1.78 (m, 2H), 1.72 (ddd, $J = 15.8, 7.6, 3.4$ Hz, 3H), 1.65 (t, $J = 2.8$ Hz, 1H), 1.60 – 1.42 (m, 5H), 1.37 – 1.22 (m, 5H), 1.16 – 1.04 (m, 1H), 0.96 – 0.89 (m, 1H), 0.86 (s, 3H), 0.83 (s, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 221.38, 53.91, 51.41, 47.82, 42.06, 38.68, 37.71, 36.71, 35.87, 34.99, 34.32, 32.64, 31.50, 30.62, 27.44, 21.76, 20.08, 13.84, 13.39.



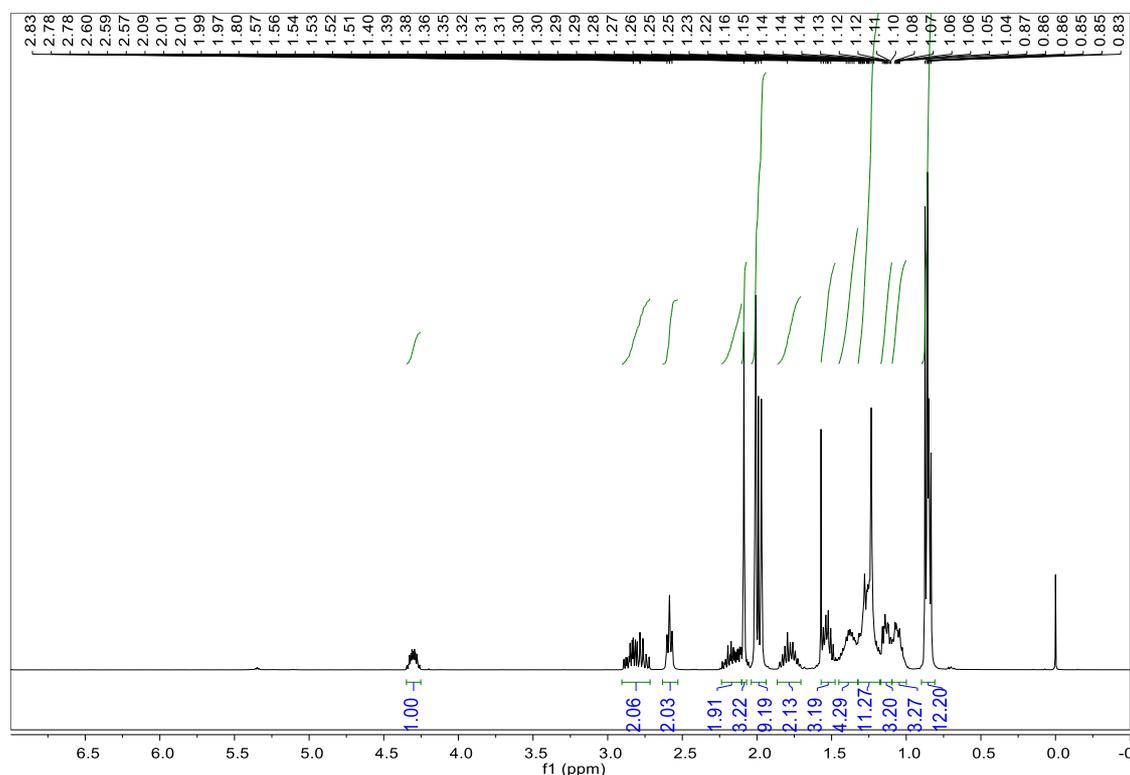
(R)-2,5,7,8-Tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl 4-iodopentanoate (2s).

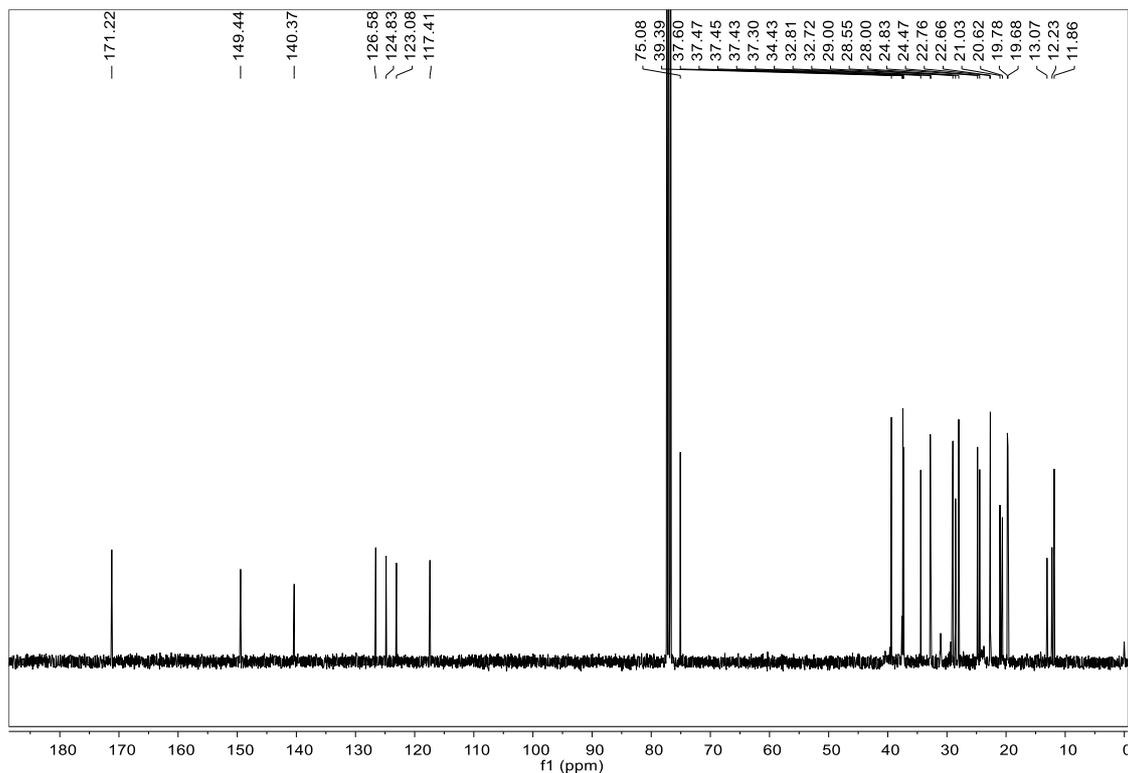


Prepared following general procedure **B** using (R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl 4-hydroxypentanoate (5.31 g, 10 mmol). The residue was purified by silica gel column chromatography (3% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 42% yield (2.69 g).

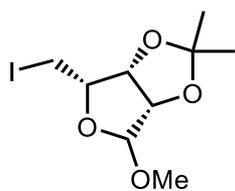
¹H NMR (400 MHz, Chloroform-*d*) δ 4.35 – 4.25 (m, 1H), 2.90 – 2.72 (m, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.24 – 2.10 (m, 2H), 2.09 (s, 3H), 2.04 – 1.94 (m, 9H), 1.86 – 1.70 (m, 2H), 1.57 – 1.48 (m, 3H), 1.45 – 1.32 (m, 4H), 1.32 – 1.18 (m, 11H), 1.17 – 1.10 (m, 3H), 1.10 – 1.00 (m, 3H), 0.90 – 0.81 (m, 12H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 171.22, 149.44, 140.37, 126.58, 124.83, 123.08, 117.41, 75.08, 39.39, 37.60, 37.47, 37.45, 37.43, 37.30, 34.43, 32.81, 32.72, 29.00, 28.55, 28.00, 24.83, 24.47, 22.76, 22.66, 21.03, 20.62, 19.78, 19.68, 13.07, 12.23, 11.86.





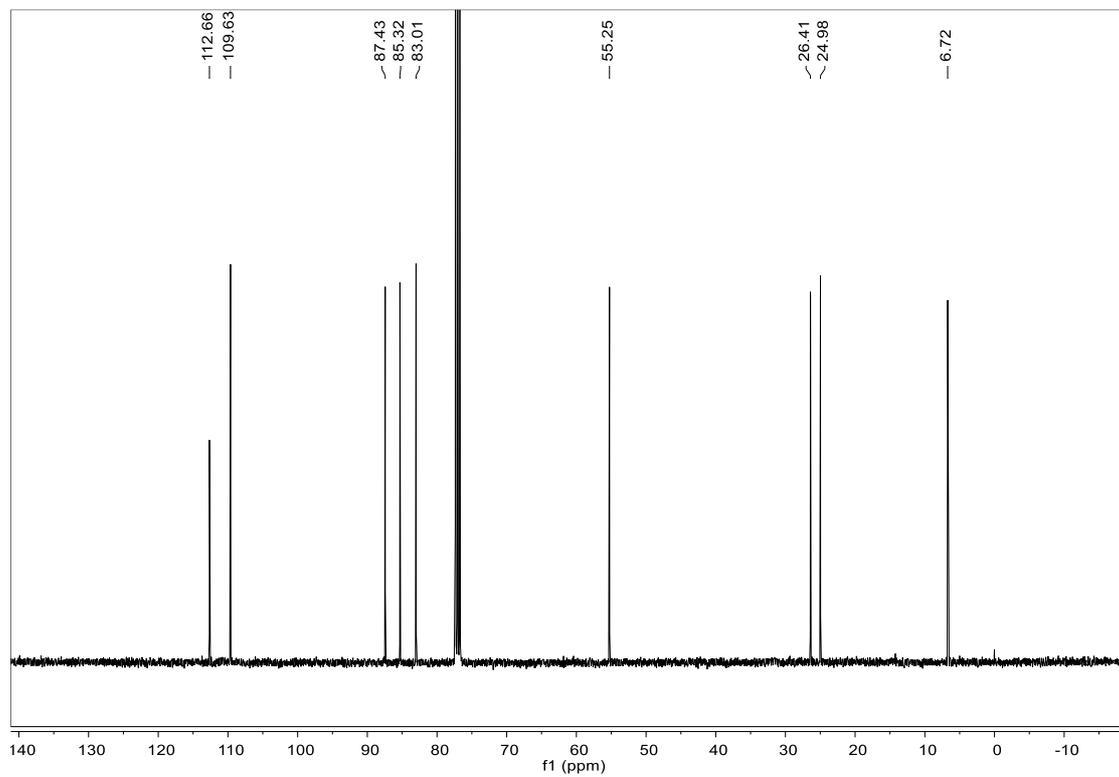
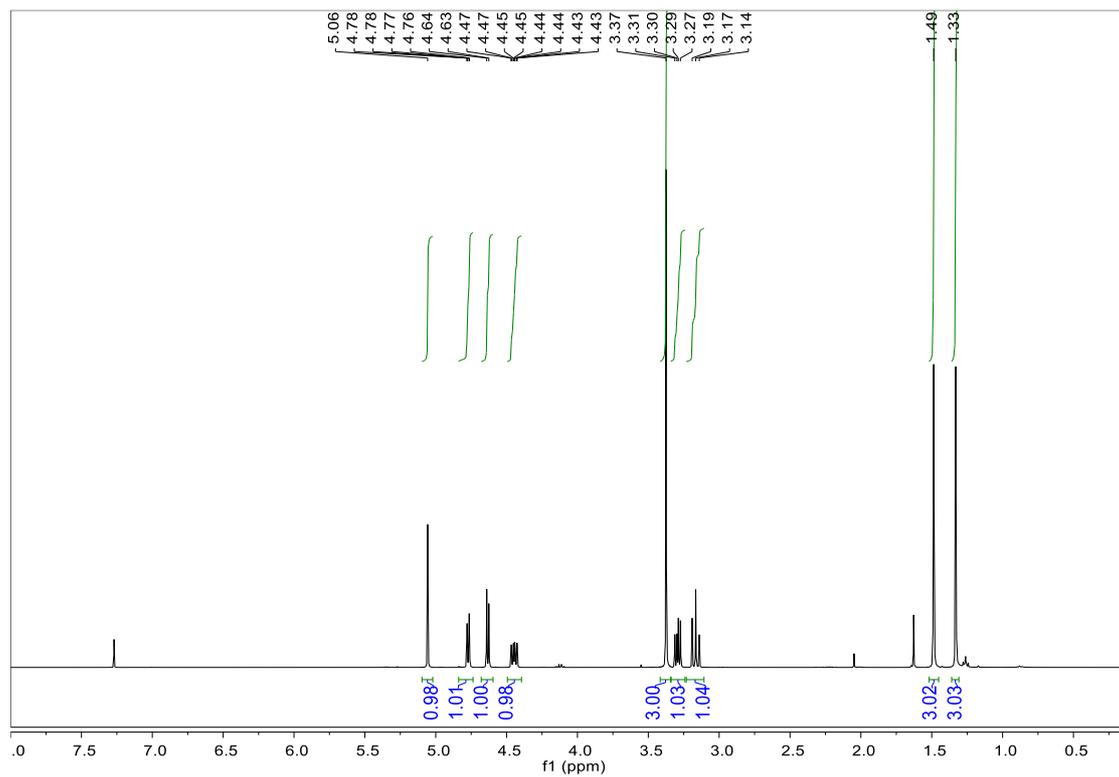
(3a*R*,4*S*,6*R*,6a*S*)-4-(Iodomethyl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole (2u).



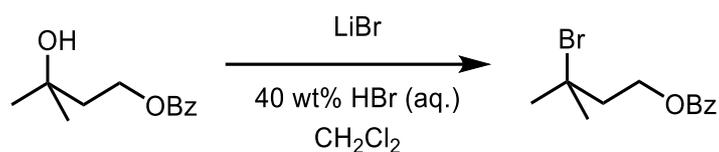
Prepared following general procedure **B** using ((3a*S*,4*R*,6*S*,6a*S*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (2.04 g, 10 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 54% yield (1.70 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 5.06 (s, 1H), 4.77 (dd, *J* = 6.0, 1.0 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 1H), 4.45 (ddd, *J* = 10.1, 6.0, 1.0 Hz, 1H), 3.37 (s, 3H), 3.29 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.17 (t, *J* = 10.0 Hz, 1H), 1.49 (s, 3H), 1.33 (s, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 112.66, 109.63, 87.43, 85.32, 83.01, 55.25, 26.41, 24.98, 6.72.



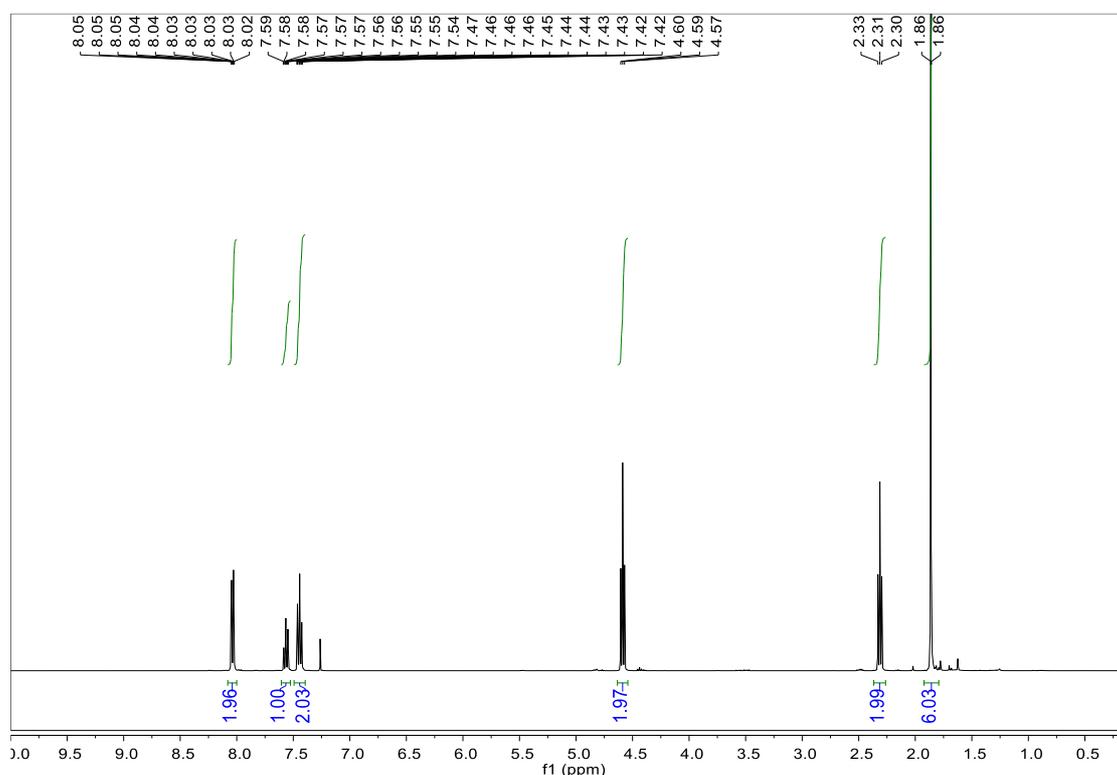
Procedure for the preparation of 3-Bromo-3-methylbutyl benzoate.⁴

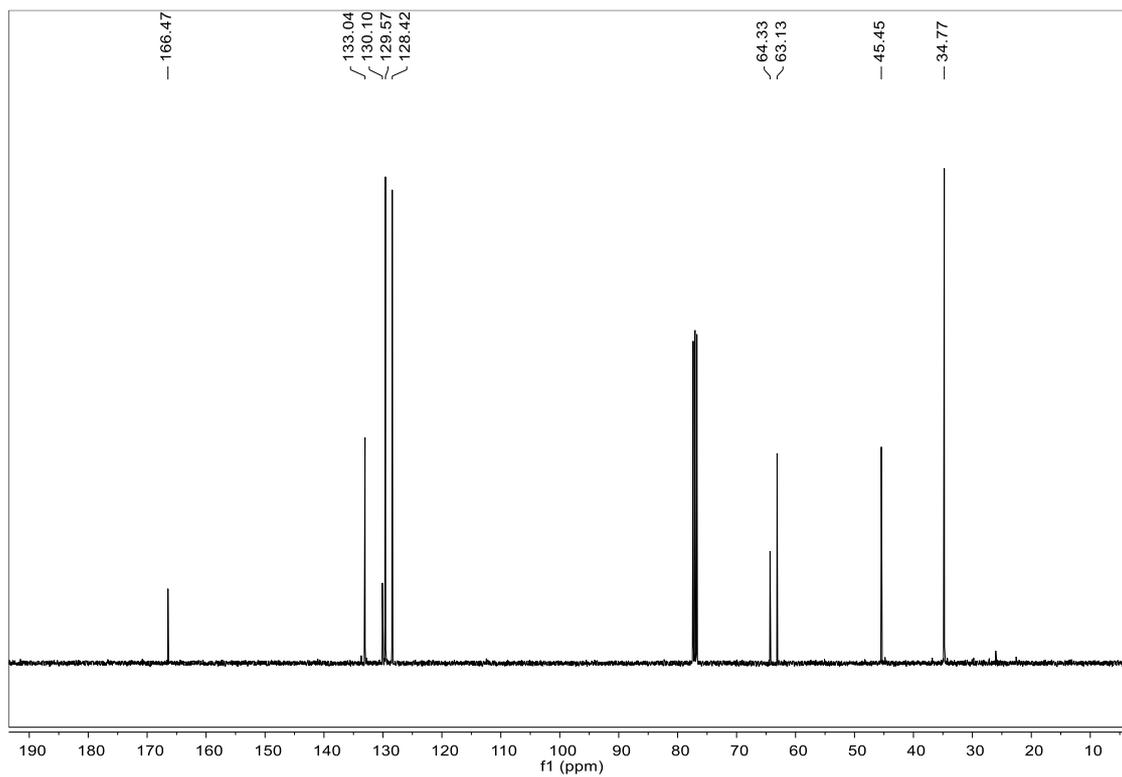


To a solution of 3-hydroxy-3-methylbutyl benzoate (2.08 g, 10 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) was added LiBr (1.74 g, 20 mmol, 2.0 equiv.) in 40 wt% HBr aqueous solution (20 mL) at 0 °C. The mixture was allowed to warm to r.t. and stirred for 16 hours, before it was diluted with H_2O . The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica (petroleum ether/ethyl acetate) gel to give the title bromide as a colorless oil in 83% yield (2.25 g).

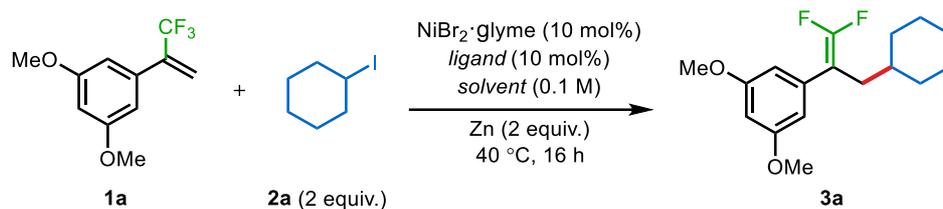
^1H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 8.00 (m, 2H), 7.61 – 7.53 (m, 1H), 7.49 – 7.39 (m, 2H), 4.59 (t, $J = 6.7$ Hz, 2H), 2.31 (t, $J = 6.7$ Hz, 2H), 1.86 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.47, 133.04, 130.10, 129.57, 128.42, 64.33, 63.13, 45.45, 34.77.

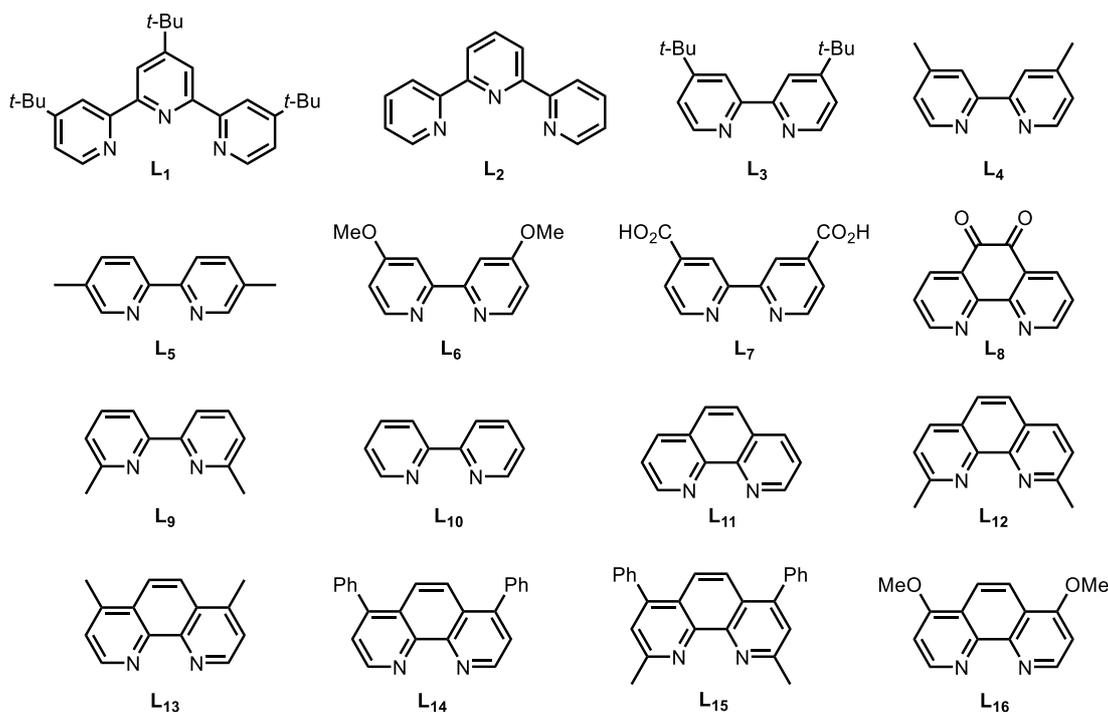




III. Optimization of Reaction Conditions.



$\text{NiBr}_2 \cdot \text{DME}$ (6 mg, 0.02 mmol, 10 mol%), ligand (0.02 mmol, 10 mol%), additive (0.2 mmol, 1.0 equiv.) and Zn (26 mg, 0.4 mmol, 2.0 equiv.) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and filled with nitrogen (three cycles). To these solids, 2 mL solvent was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 60 seconds. Next, iodocyclohexane (84mg, 0.4 mmol, 2.0 equiv.) was added under a positive flow of argon and stirred at room temperature for another 60 seconds. Then 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (0.2 mmol, 1.0 equiv.) was added under nitrogen atmosphere. The reaction mixture was stirred at 40 °C for 16 hours, before it was quenched with H_2O . The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The yield was determined by ^{19}F NMR spectroscopy using 4-fluoroanisole as an internal standard.

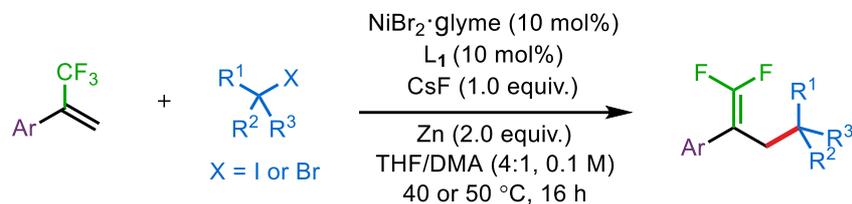


entry	ligand	solvent	Yield (%)
1	L ₁	THF	49
2	L ₂	THF	37
3	L ₃	THF	10
4	L ₄	THF	8
5	L ₅	THF	trace
6	L ₆	THF	13
7	L ₇	THF	trace
8	L ₈	THF	0
9	L ₉	THF	trace
10	L ₁₀	THF	49
11	L ₁₁	THF	42
12	L ₁₂	THF	30
13	L ₁₃	THF	33
14	L ₁₄	THF	23
15	L ₁₅	THF	0
16	L ₁₆	THF	26
17	L ₁	DMF	63
18	L ₁	DMA	68
19	L ₁	DCE	0
20	L ₁	DME	13
21	L ₁	HFIP	25
22	L ₁	MeOH	41
23	L ₁	1,4-dioxane	19
24	L ₁	MeCN	45
25	L ₁	THF/DMA (v/v = 1:1)	83
26	L ₁	THF/DMA (v/v = 4:1)	93
27^a	L₁	THF/DMA (v/v = 4:1)	99 (97^{b,c})

^aCsF (30 mg, 0.2 mmol, 1.0 equiv.) was added as additive. ^bPerformed on 0.5 mmol scale. ^cIsolated yield.

IV. General procedure for the synthesis of *gem*-difluoroalkenes.

General procedure (C) for secondary and tertiary alkyl halide substrates.

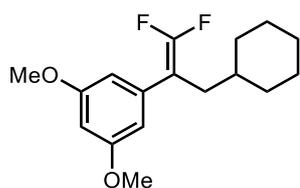


NiBr₂·DME (10 mol%), 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (**L1**) (10 mol%), alkyl halide (if solid, 2.0 equiv), trifluoromethyl-substituted alkene (if solid, 1.0 equiv.), CsF (1.0 equiv.) and Zn (2.0 equiv.) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and filled with nitrogen (three cycles). To these solids, THF (0.125 mmol/mL) and DMA (0.5 mmol/mL) were added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 60 seconds. Next, alkyl halide (if liquid, 2.0 equiv) was added under a positive flow of argon and stirred at room temperature for another 60 seconds. Then trifluoromethyl-substituted alkene (if liquid, 1.0 equiv.) was added. The reaction mixture was stirred at 40 or 50 °C for 16 hours^b, before it was quenched with H₂O. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to give the corresponding *gem*-difluoroalkenes.^a

^a**3f, 3i, 3j, 3p, 4b, 4d, 4f, 4g, 4i-4k, 5a-5c** were synthesized at 50 °C, the others were synthesized at 40 °C.

^a24 hours for **5a**.

1-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)-3,5-dimethoxybenzene (3a).



Prepared following general procedure C using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol).

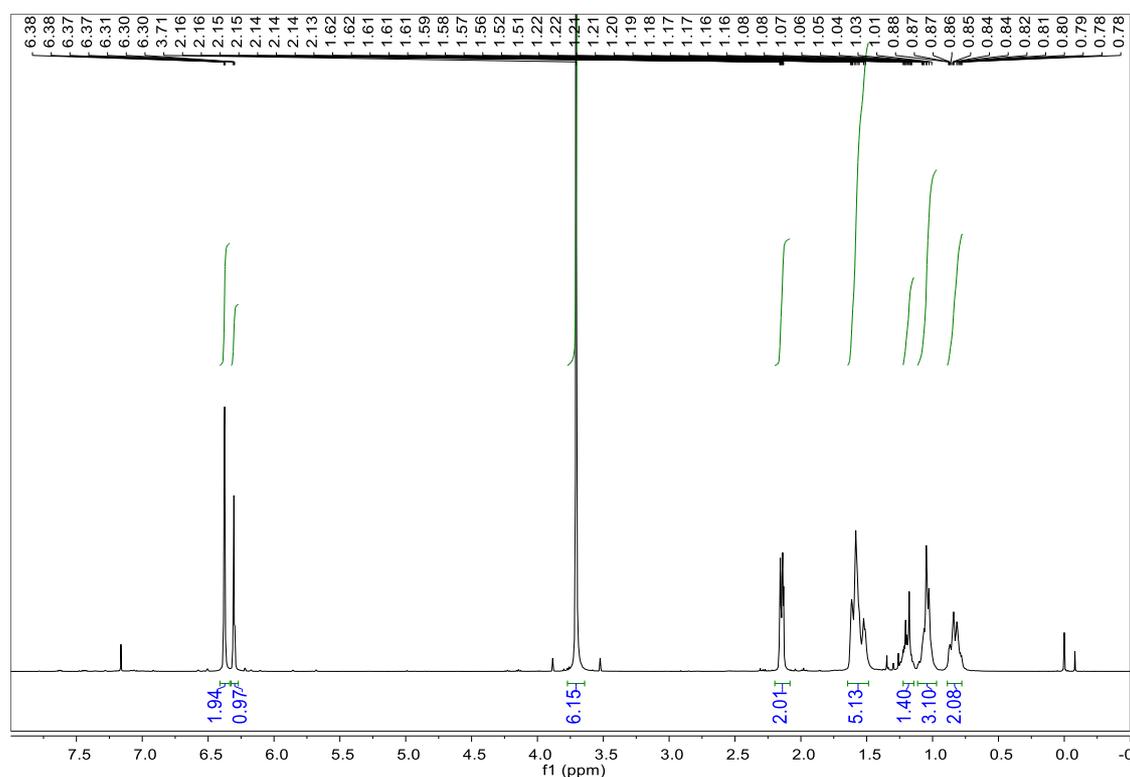
The residue was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 97% yield (144 mg).

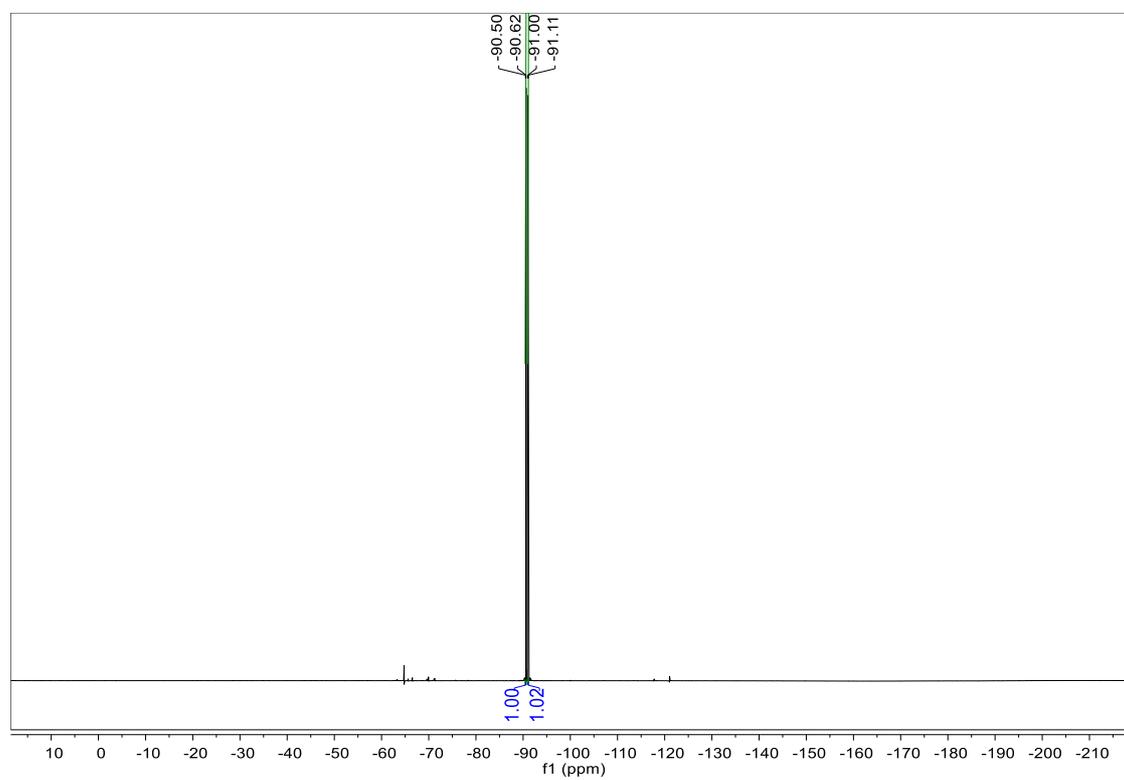
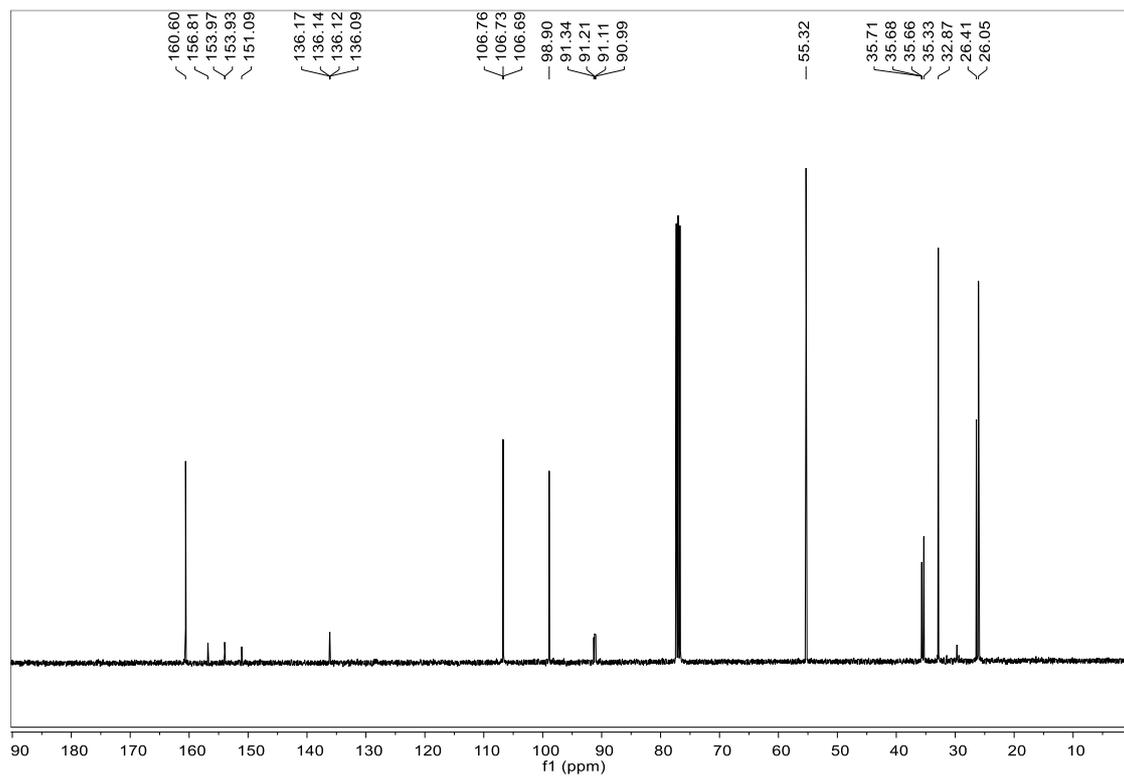
¹H NMR (400 MHz, Chloroform-*d*) δ 6.38 (dd, $J = 2.3, 1.1$ Hz, 2H), 6.30 (t, $J = 2.3$ Hz, 1H), 3.71 (s, 6H), 2.15 (ddd, $J = 7.3, 2.9, 2.0$ Hz, 2H), 1.64 – 1.49 (m, 5H), 1.22 – 1.14 (m, 1H), 1.11 – 0.97 (m, 3H), 0.89 – 0.78 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.60, 153.95 (dd, $J = 290.4, 285.8$ Hz), 136.13 (dd, $J = 4.9, 3.0$ Hz), 106.73 (t, $J = 3.3$ Hz), 98.90, 91.16 (dd, $J = 22.4, 12.3$ Hz), 55.32, 35.68 (t, $J = 2.4$ Hz), 35.33, 32.87, 26.41, 26.05.

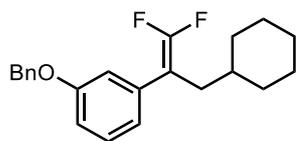
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.56 (d, $J = 43.4$ Hz, 1F), -91.06 (d, $J = 43.2$ Hz, 1F).

HRMS (ESI) calcd for $C_{17}H_{23}F_2O_2^+$ [(M+H)⁺] 297.1661, found 297.1657.





1-(Benzyloxy)-3-(3-cyclohexyl-1,1-difluoroprop-1-en-2-yl)benzene (3b).



Prepared following general procedure C using 1-(benzyloxy)-3-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1b**) (139 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (1% EtOAc

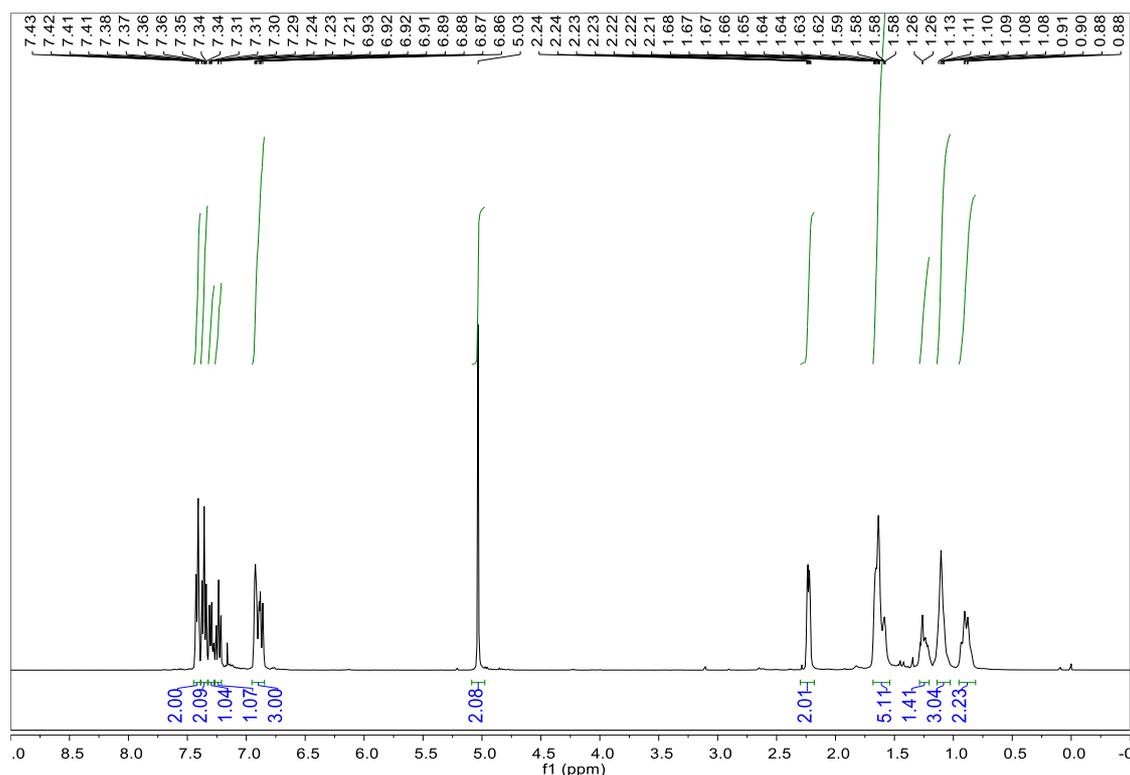
in petroleum ether) to provide the title compound as a colorless oil in 86% yield (147 mg).

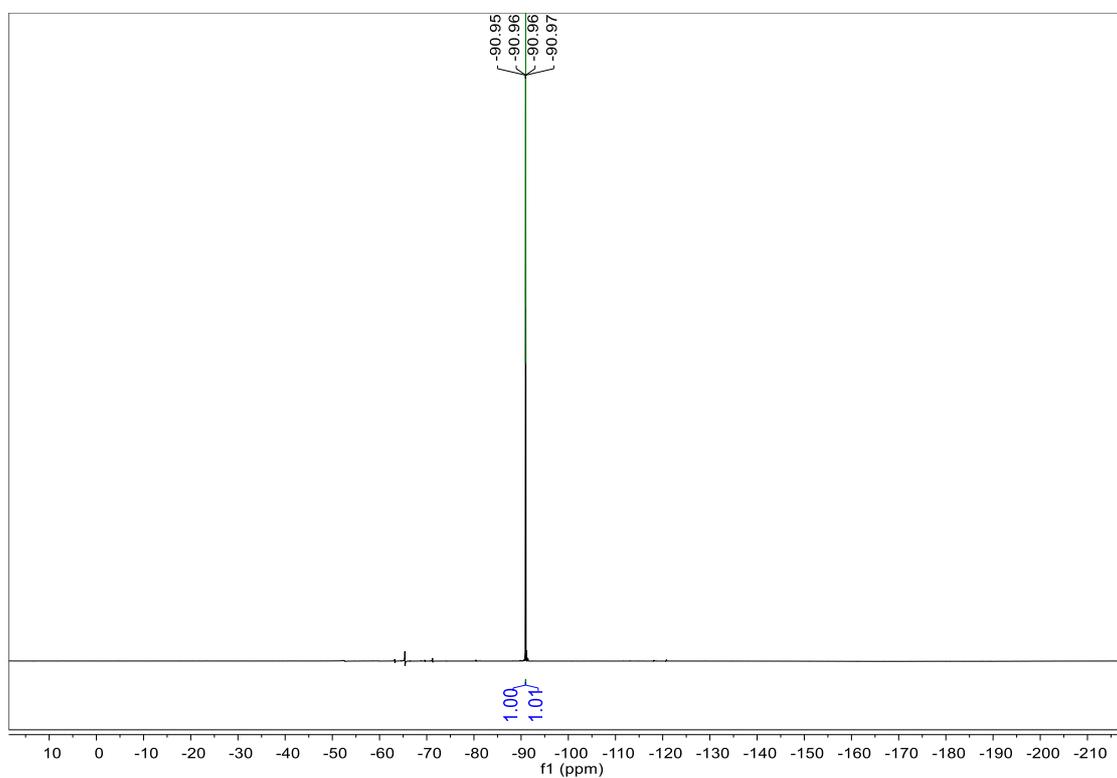
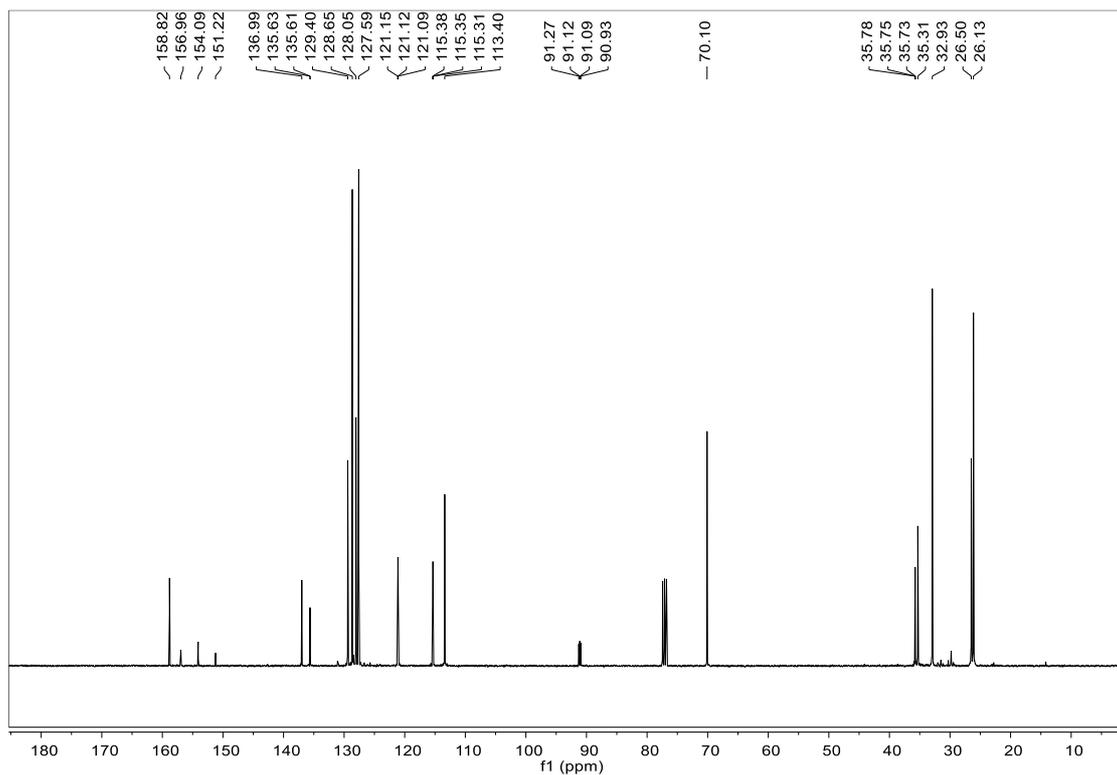
¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 (dd, $J = 7.1, 2.0$ Hz, 2H), 7.36 (ddd, $J = 7.8, 6.5, 1.8$ Hz, 2H), 7.32 – 7.27 (m, 1H), 7.24 (td, $J = 8.1, 1.9$ Hz, 1H), 6.95 – 6.85 (m, 3H), 5.03 (s, 2H), 2.27 – 2.18 (m, 2H), 1.68 – 1.54 (m, 5H), 1.29 – 1.21 (m, 1H), 1.16 – 1.03 (m, 3H), 0.95 – 0.81 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 158.82, 154.09 (t, $J = 287.9$ Hz), 136.99, 135.62 (d, $J = 1.9$ Hz), 129.40, 128.65, 128.05, 127.59, 121.12 (t, $J = 3.3$ Hz), 115.35 (t, $J = 3.3$ Hz), 113.40, 91.10 (dd, $J = 18.7, 15.9$ Hz), 70.10, 35.74 (t, $J = 2.5$ Hz), 35.31, 32.93, 26.50, 26.13.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.96 (d, $J = 2.9$ Hz, 1F), -90.97 (d, $J = 2.4$ Hz, 1F).

HRMS (ESI) calcd for $C_{22}H_{25}F_2O^+$ [(M+H)⁺] 343.1868, found 343.1884.





5-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)benzo[d][1,3]dioxole (3c).



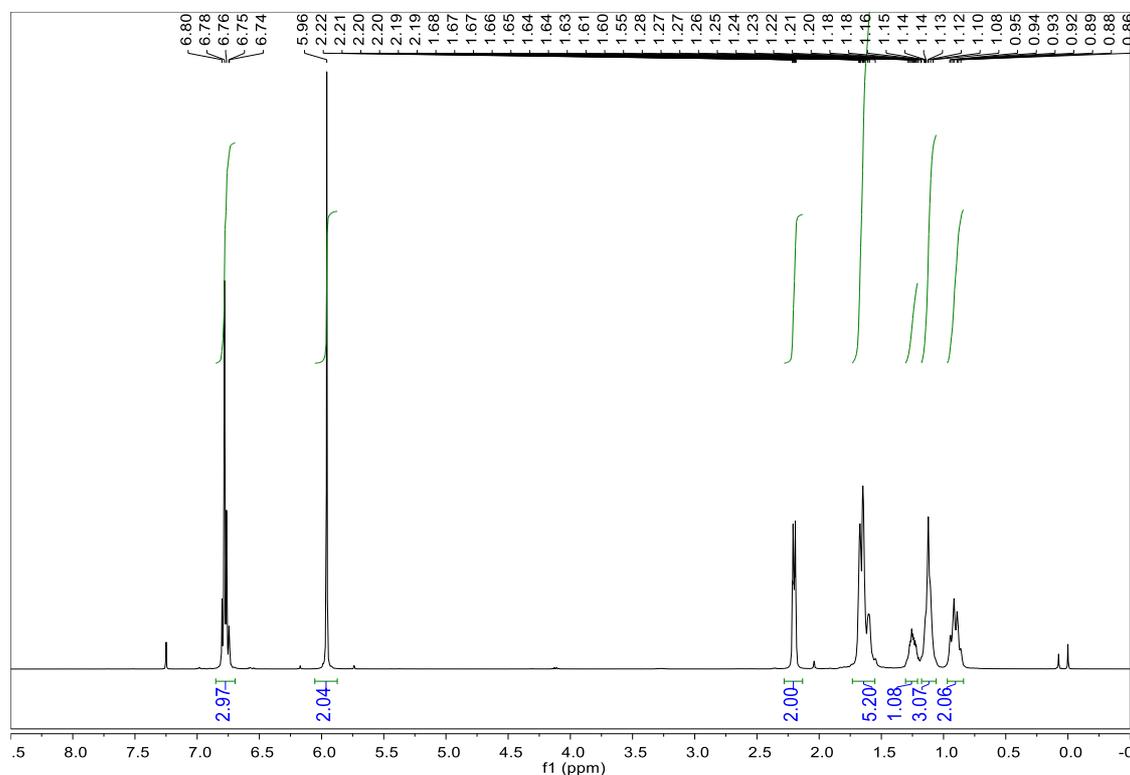
Prepared following general procedure C using 5-(3,3,3-trifluoroprop-1-en-2-yl)benzo[d][1,3]dioxole (**1c**) (108 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 96% yield (135 mg).

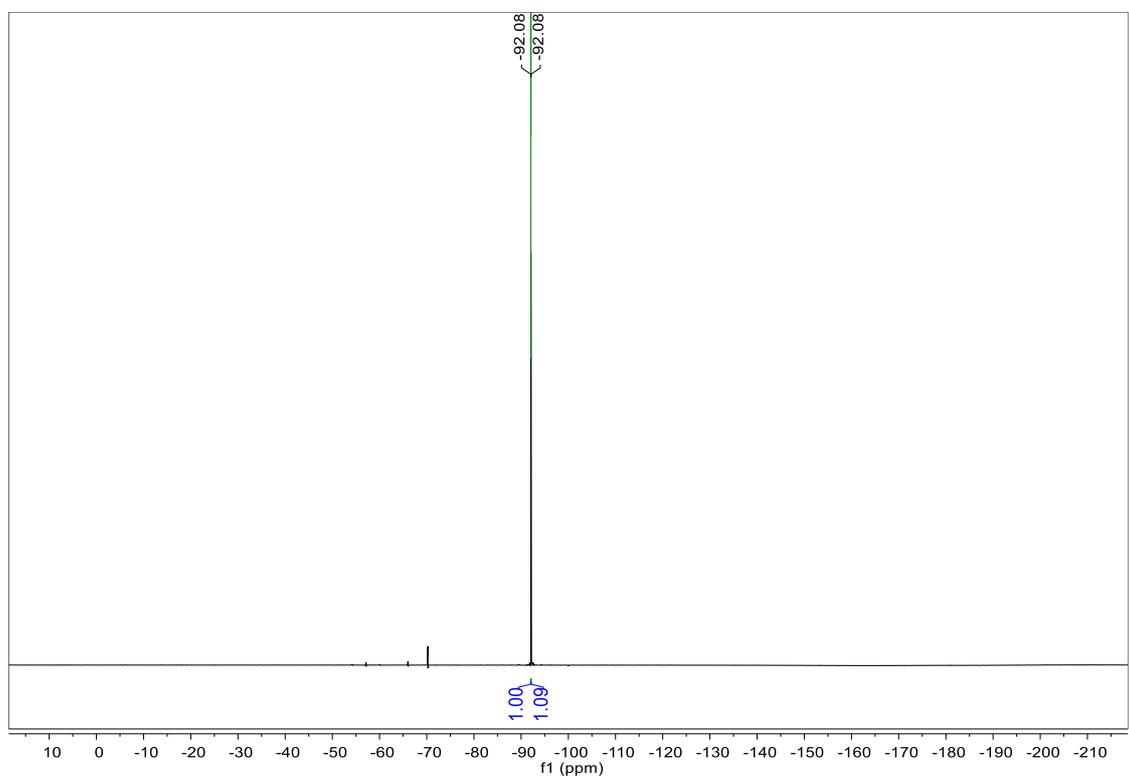
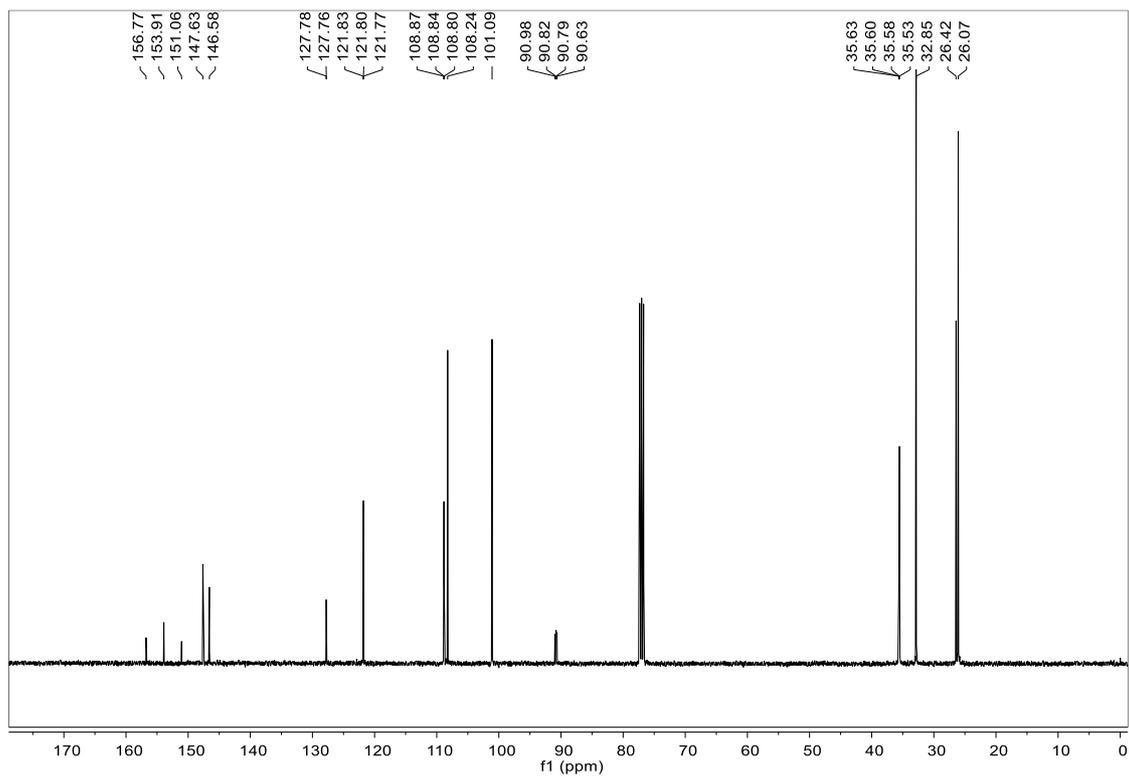
¹H NMR (400 MHz, Chloroform-*d*) δ 6.85 – 6.71 (m, 3H), 5.96 (s, 2H), 2.20 (dt, $J = 7.2, 2.5$ Hz, 2H), 1.73 – 1.55 (m, 5H), 1.31 – 1.21 (m, 1H), 1.18 – 1.06 (m, 3H), 0.97 – 0.84 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 153.91 (t, $J = 287.4$ Hz), 147.63, 146.58, 127.77 (d, $J = 1.8$ Hz), 121.80 (t, $J = 3.2$ Hz), 108.84 (t, $J = 3.4$ Hz), 108.24, 101.09, 90.80 (dd, $J = 18.9, 16.6$ Hz), 35.60 (t, $J = 2.4$ Hz), 35.53, 32.85, 26.42, 26.07.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -92.08 (d, $J = 0.2$ Hz, 1F), -92.08 (d, $J = 0.2$ Hz, 1F).

HRMS (ESI) calcd for C₁₆H₁₈F₂O₂Na⁺ [(M+Na)⁺] 303.1167, found 303.1136.





1-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)-4-(trifluoromethoxy)benzene (3d).



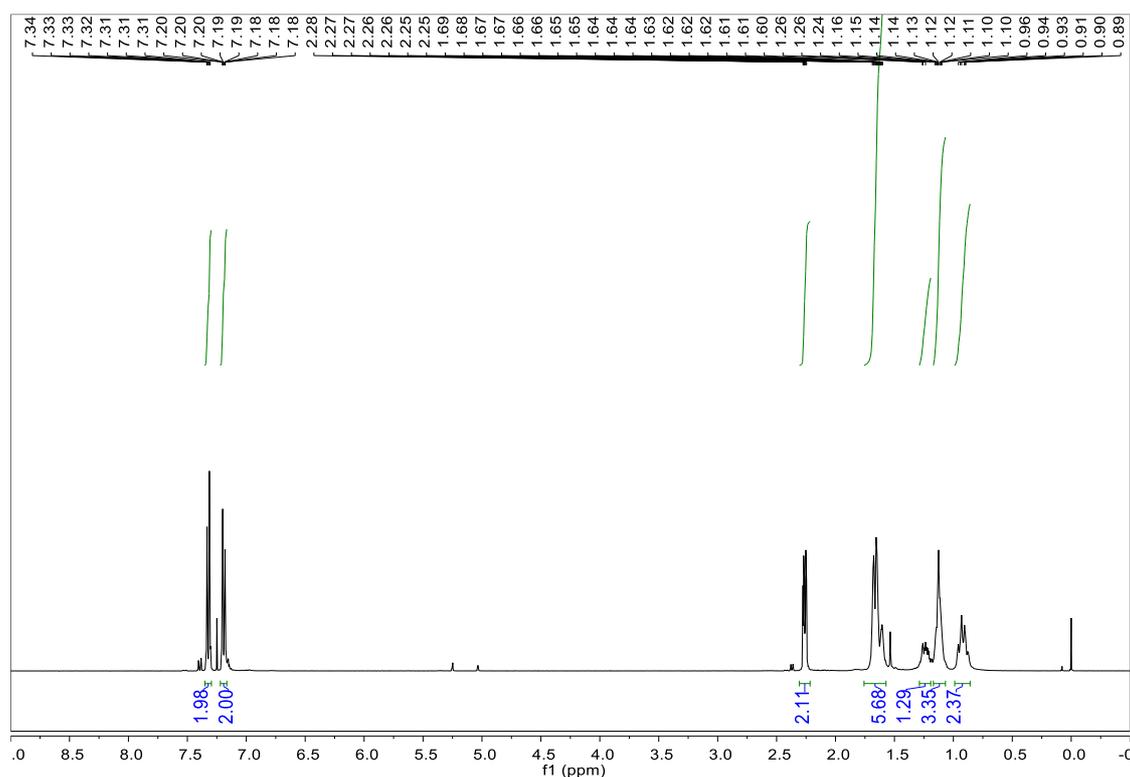
Prepared following general procedure C using 1-(trifluoromethoxy)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1f**) (128 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (petroleum ether) to provide the title compound as a colorless oil in 87% yield (140 mg).

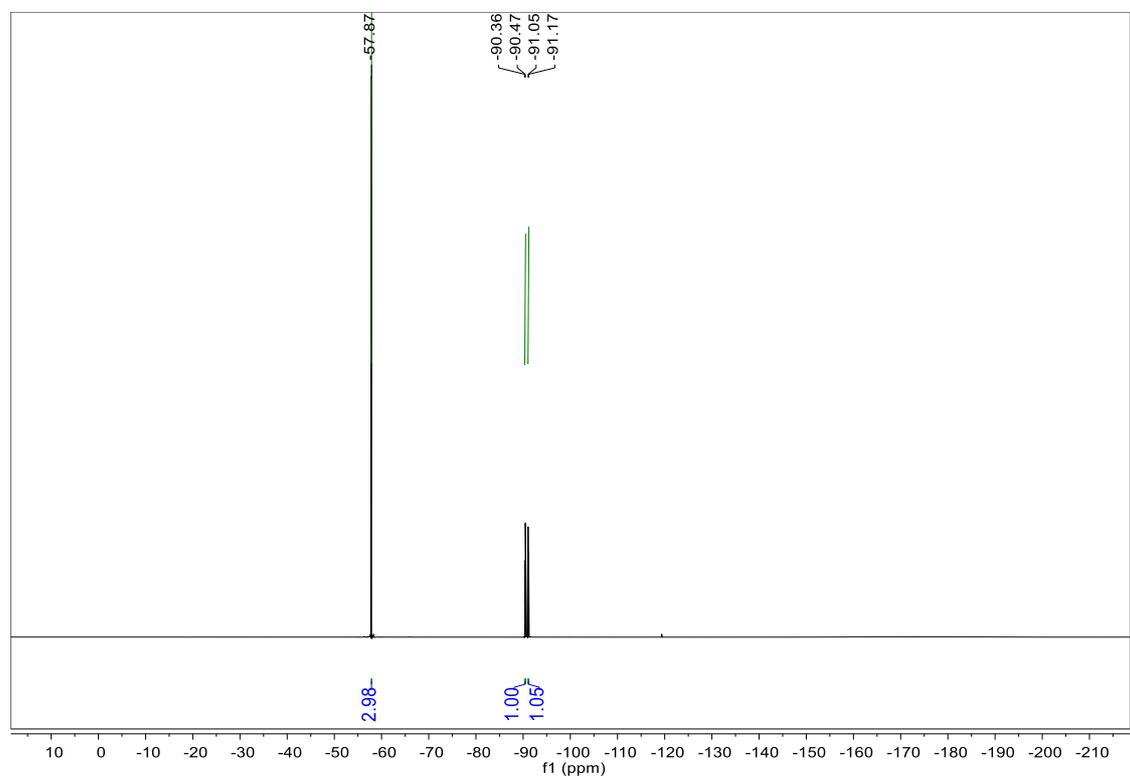
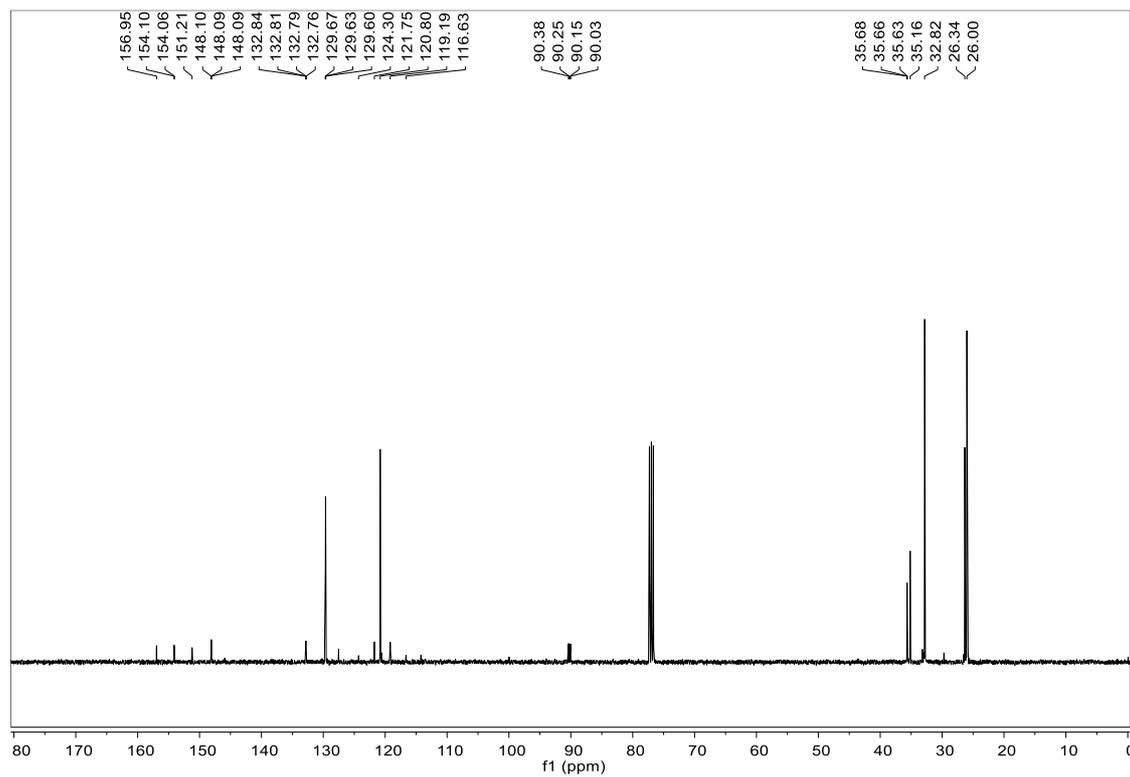
¹H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.30 (m, 2H), 7.22 – 7.16 (m, 2H), 2.31 – 2.22 (m, 2H), 1.76 – 1.57 (m, 6H), 1.29 – 1.19 (m, 1H), 1.17 – 1.07 (m, 3H), 0.99 – 0.86 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 154.08 (dd, $J = 290.7, 286.7$ Hz), 148.09 (t, $J = 0.7$ Hz), 132.80 (dd, $J = 4.9, 3.2$ Hz), 129.63 (t, $J = 3.3$ Hz), 120.80, 120.47 (q, $J = 257.2$ Hz), 90.20 (dd, $J = 23.0, 12.3$ Hz), 35.66 (t, $J = 2.5$ Hz), 35.16, 32.82, 26.34, 26.00.

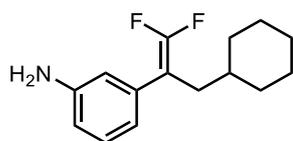
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -57.87 (s, 1F), -90.42 (d, $J = 42.4$ Hz, 1F), -91.11 (d, $J = 42.4$ Hz, 1F).

HRMS (ESI) calcd for C₁₆H₁₇F₅ONa⁺ [(M+Na)⁺] 343.1092, found 343.1085.





3-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)aniline (3e).



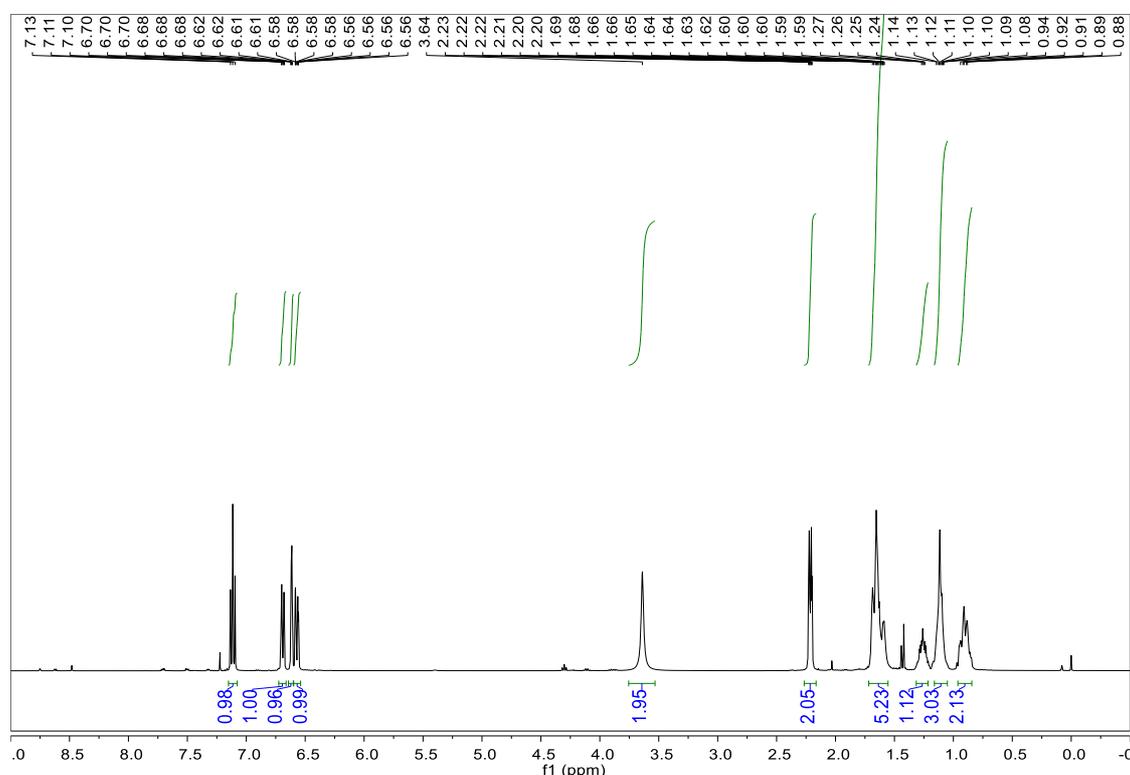
Prepared following general procedure C using 3-(3,3,3-trifluoroprop-1-en-2-yl)aniline (**1e**) (94 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to provide the title compound as a pale yellow oil in 91% yield (114 mg).

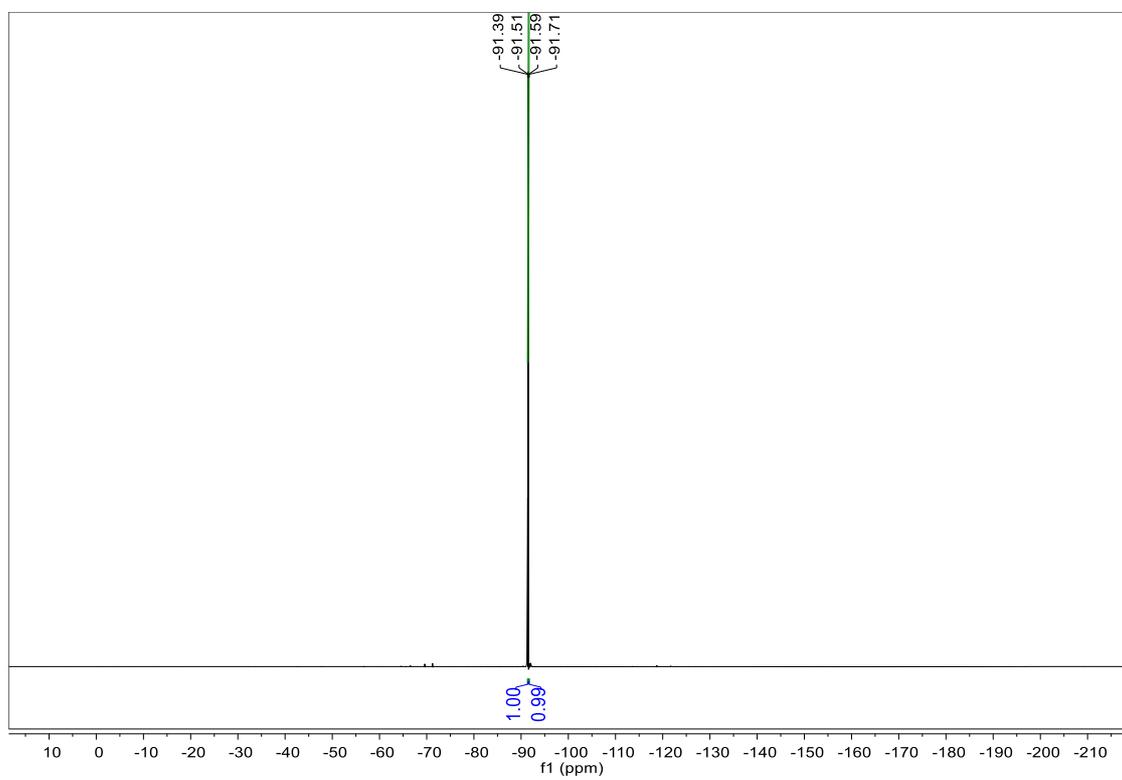
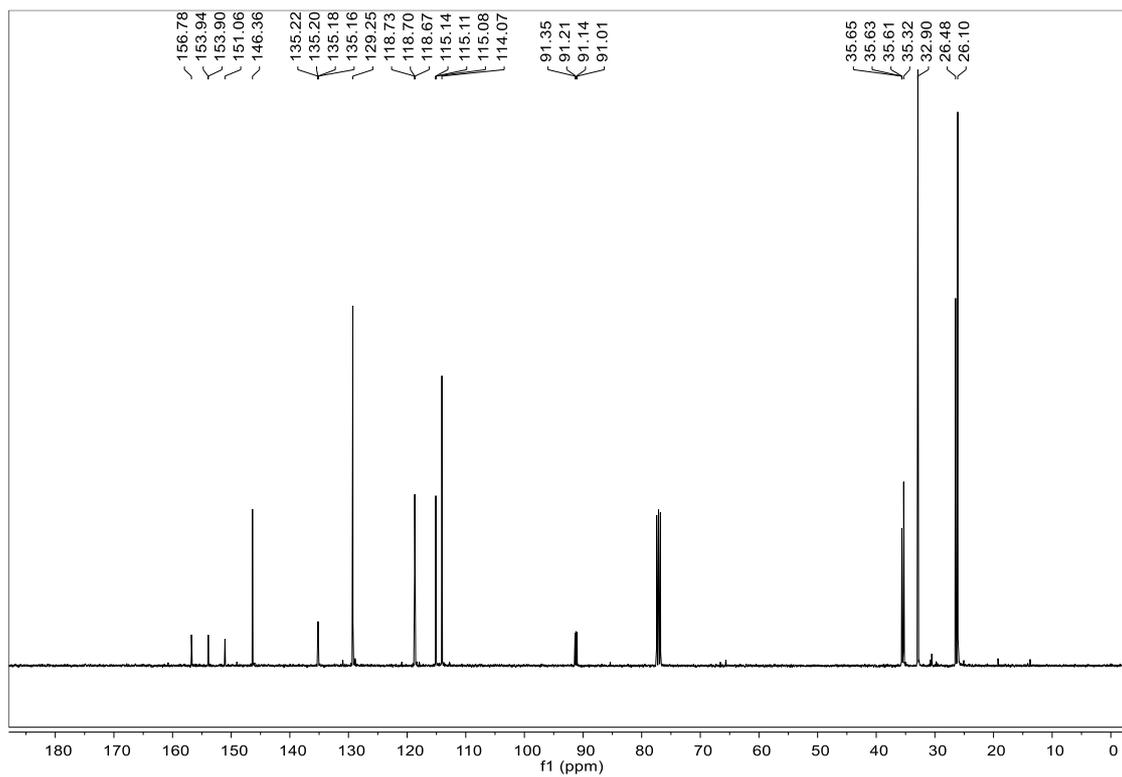
¹H NMR (400 MHz, Chloroform-*d*) δ 7.11 (t, $J = 7.8$ Hz, 1H), 6.72 – 6.66 (m, 1H), 6.64 – 6.60 (m, 1H), 6.60 – 6.55 (m, 1H), 3.64 (s, 2H), 2.21 (dt, $J = 7.2, 2.5$ Hz, 2H), 1.72 – 1.55 (m, 5H), 1.31 – 1.22 (m, 1H), 1.16 – 1.05 (m, 3H), 0.96 – 0.84 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 153.92 (dd, $J = 289.4, 285.8$ Hz), 146.36, 135.19 (dd, $J = 3.9, 2.2$ Hz), 129.25, 118.70 (t, $J = 3.1$ Hz), 115.11 (t, $J = 3.3$ Hz), 114.07, 91.18 (dd, $J = 21.0, 13.4$ Hz), 35.63 (t, $J = 2.4$ Hz), 35.32, 32.90, 26.48, 26.10.

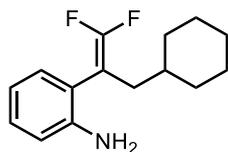
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -91.45 (d, $J = 44.5$ Hz, 1F), -91.65 (d, $J = 44.6$ Hz, 1F).

HRMS (ESI) calcd for C₁₅H₂₀F₂N⁺ [(M+H)⁺] 252.1558, found 252.1573.





2-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)aniline (3f).



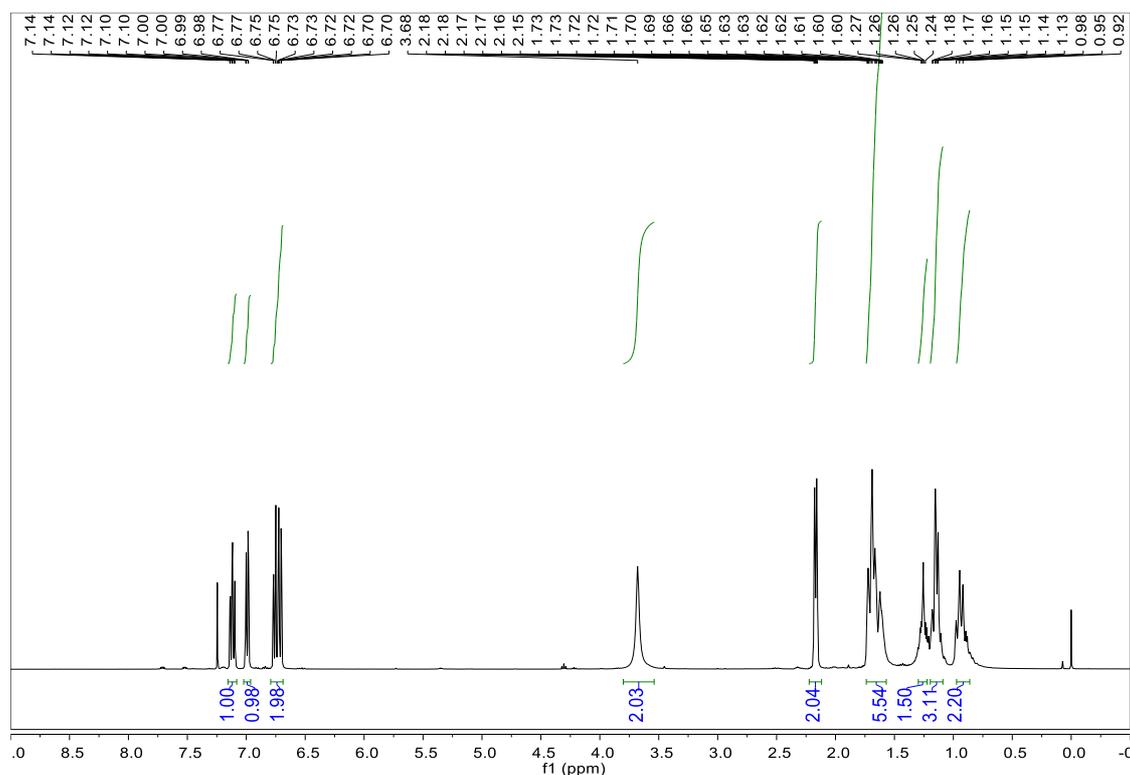
Prepared following general procedure C using 2-(3,3,3-trifluoroprop-1-en-2-yl)aniline (**1f**) (94 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a pale yellow oil in 66% yield (83 mg).

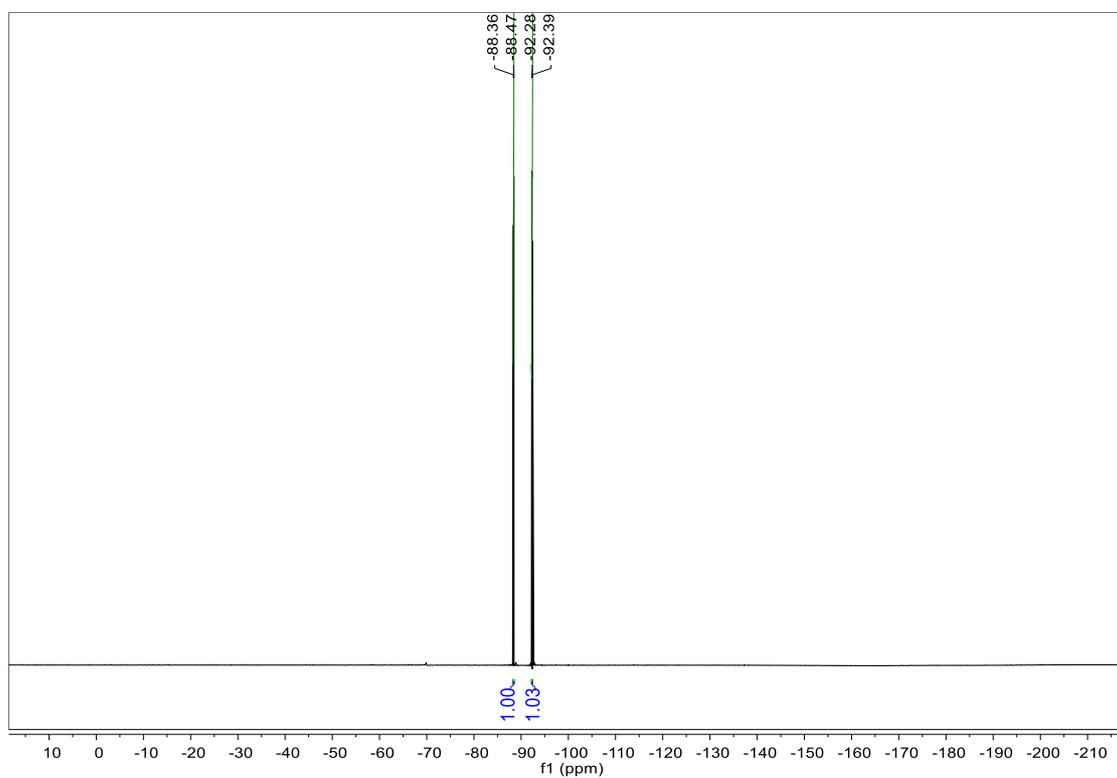
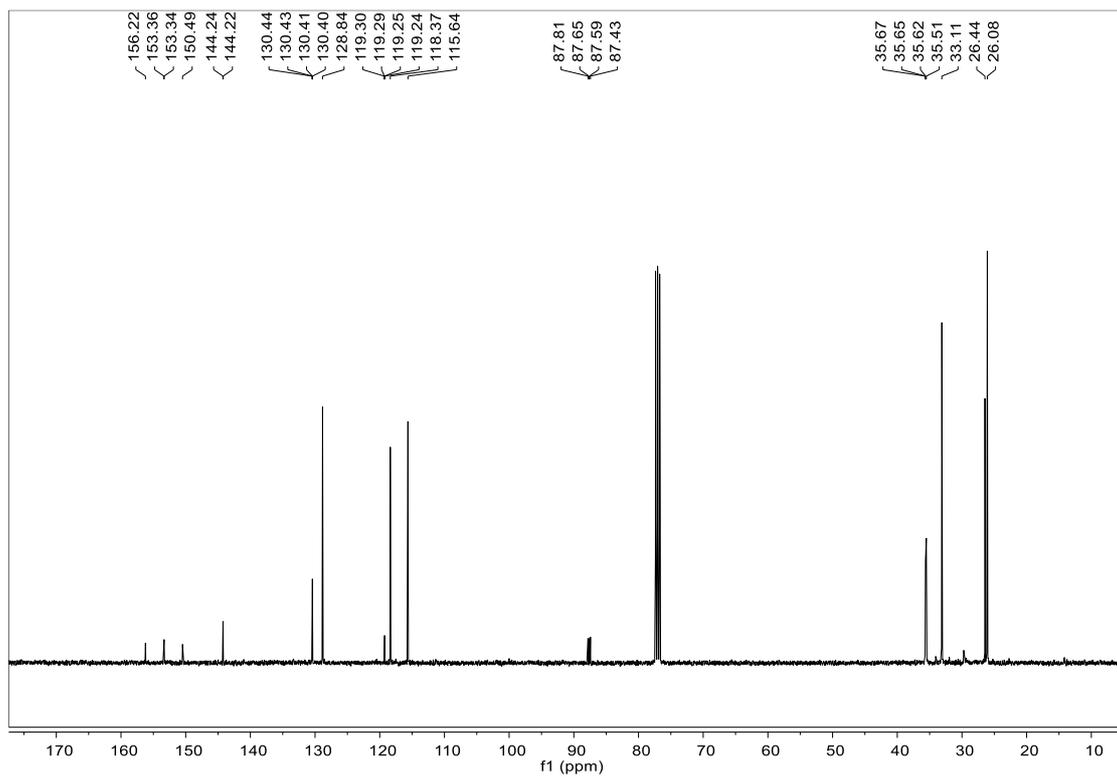
¹H NMR (400 MHz, Chloroform-*d*) δ 7.12 (td, $J = 7.7, 1.6$ Hz, 1H), 6.99 (dd, $J = 7.6, 1.6$ Hz, 1H), 6.79 – 6.69 (m, 2H), 3.68 (s, 2H), 2.17 (dt, $J = 7.1, 2.3$ Hz, 2H), 1.74 – 1.57 (m, 5H), 1.30 – 1.22 (m, 1H), 1.20 – 1.19 (m, 3H), 0.97 – 0.86 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 153.35 (dd, $J = 289.4, 287.2$ Hz), 144.23 (d, $J = 2.3$ Hz), 130.42 (dd, $J = 3.3, 1.5$ Hz), 128.84, 119.27 (dd, $J = 4.6, 1.3$ Hz), 118.37, 115.64, 87.62 (dd, $J = 21.9, 16.4$ Hz), 35.64 (t, $J = 2.6$ Hz), 35.51, 33.11, 26.44, 26.08.

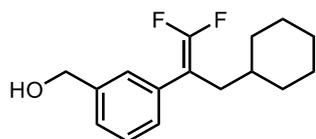
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -88.41 (d, $J = 42.3$ Hz, 1F), -92.34 (d, $J = 42.4$ Hz, 1F).

HRMS (ESI) calcd for C₁₅H₂₀F₂N⁺ [(M+H)⁺] 252.1558, found 252.1568.





(3-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)phenyl)methanol (3g).



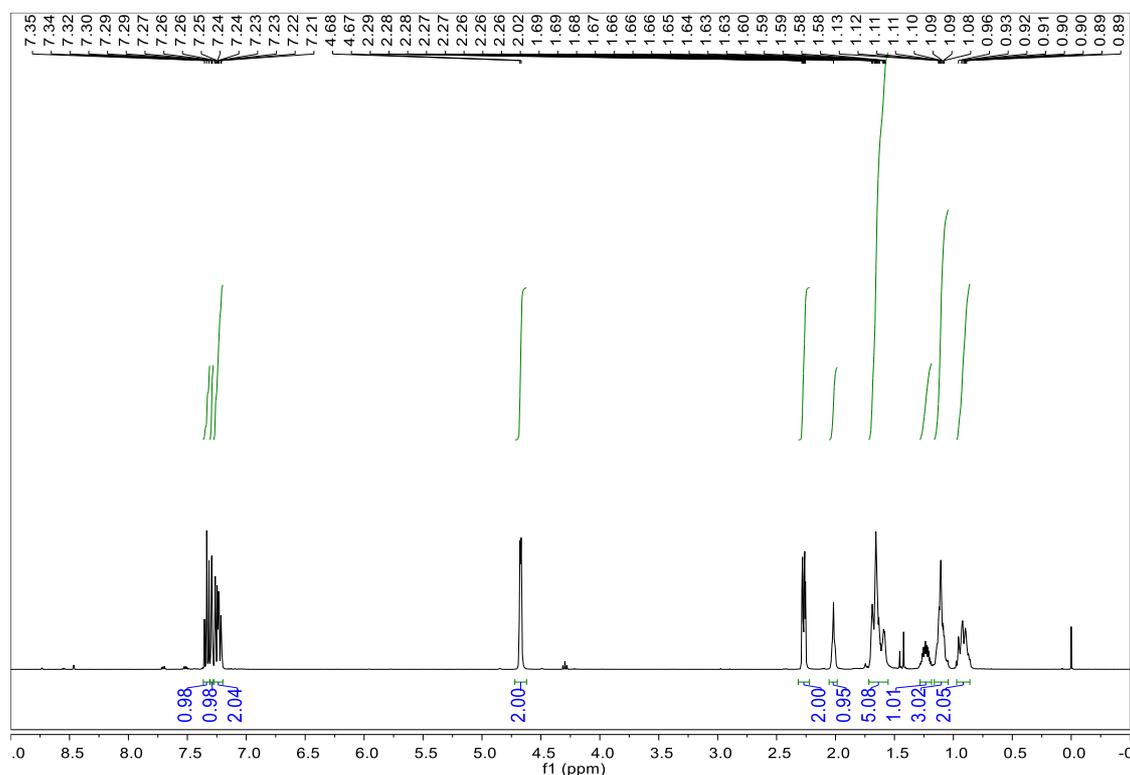
Prepared following general procedure **C** using (3-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)methanol (**1g**) (101 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to provide the title compound as a pale yellow oil in 68% yield (91 mg).

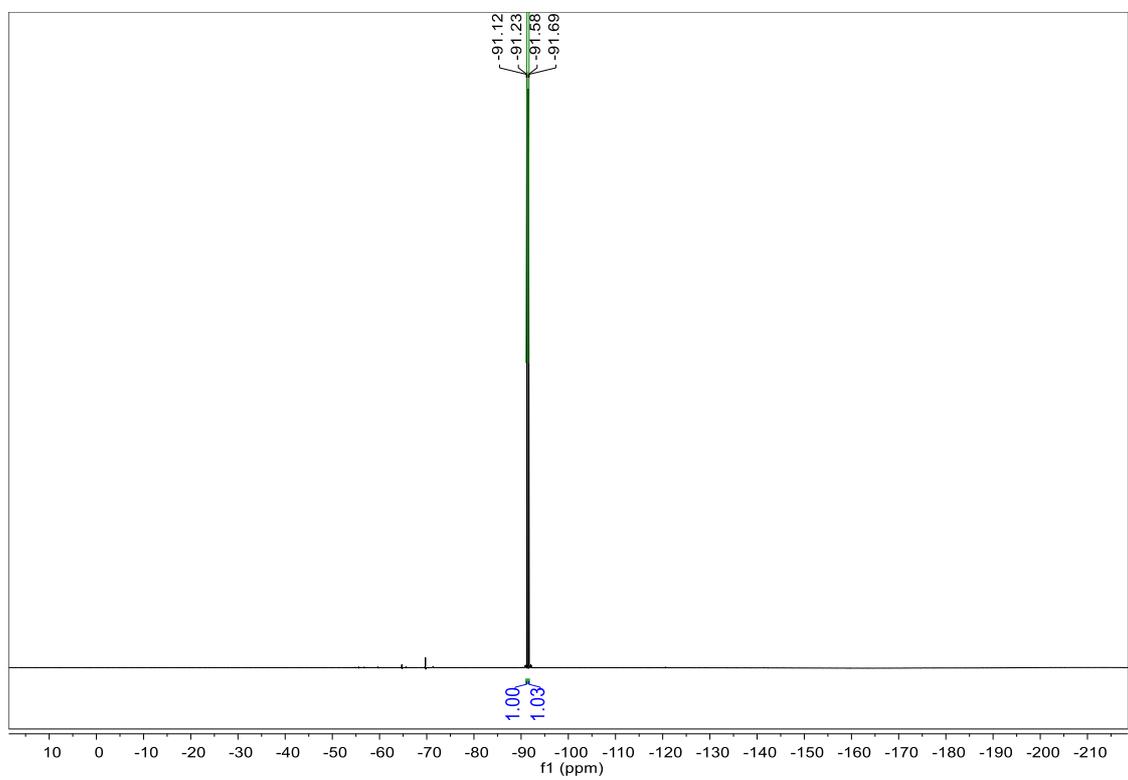
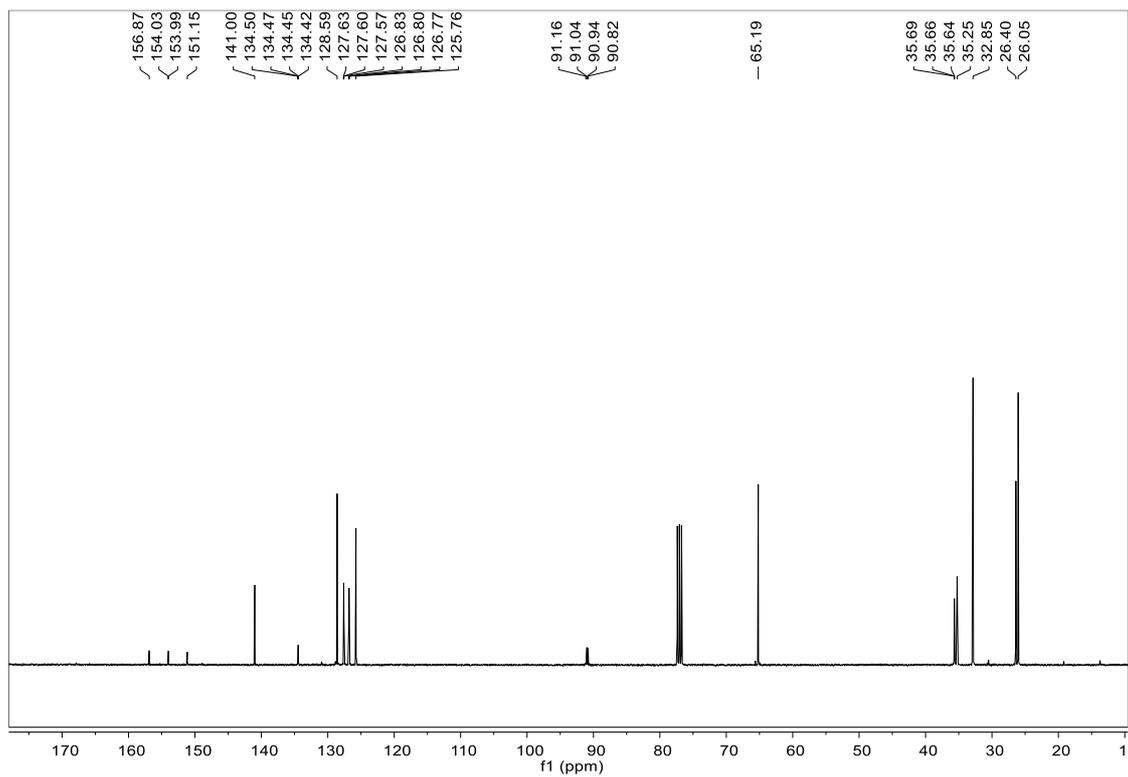
¹H NMR (400 MHz, Chloroform-*d*) δ 7.34 (t, $J = 7.6$ Hz, 1H), 7.29 (d, $J = 1.7$ Hz, 1H), 7.28 – 7.20 (m, 2H), 4.67 (d, $J = 4.2$ Hz, 2H), 2.30 – 2.24 (m, 2H), 2.05 – 1.99 (m, 1H), 1.72 – 1.55 (m, 5H), 1.28 – 1.19 (m, 1H), 1.16 – 1.04 (m, 3H), 0.97 – 0.86 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 154.01 (dd, $J = 290.1, 286.1$ Hz), 141.00, 134.46 (dd, $J = 4.6, 3.0$ Hz), 128.59, 127.60 (t, $J = 3.1$ Hz), 126.80 (t, $J = 3.2$ Hz), 125.76, 90.99 (dd, $J = 22.1, 12.6$ Hz), 65.19, 35.66 (t, $J = 2.4$ Hz), 35.25, 32.85, 26.40, 26.05.

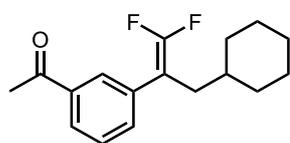
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -91.17 (d, $J = 43.7$ Hz, 1F), -91.63 (d, $J = 43.7$ Hz, 1F).

HRMS (ESI) calcd for C₁₆H₂₀F₂ONa⁺ [(M+Na)⁺] 289.1374, found 289.1385.





1-(3-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)phenyl)ethan-1-one (3h).



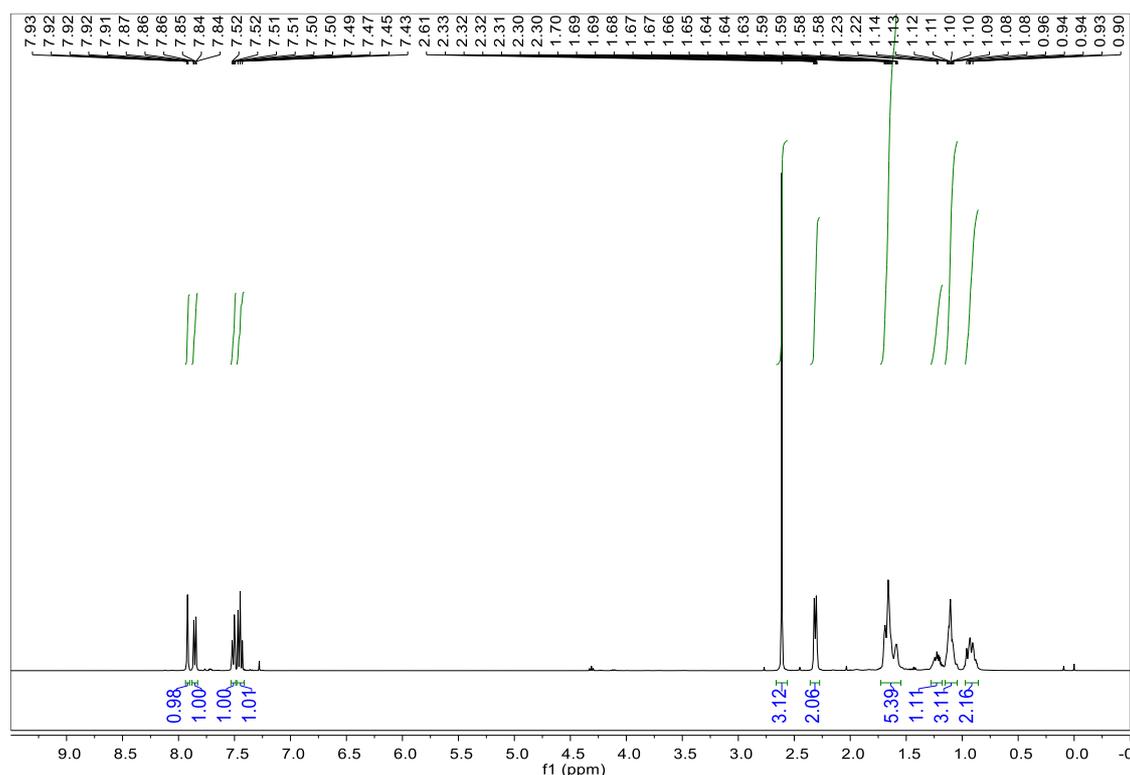
Prepared following general procedure **C** using 1-(3-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)ethan-1-one (**1h**) (107 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (3% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 95% yield (132 mg).

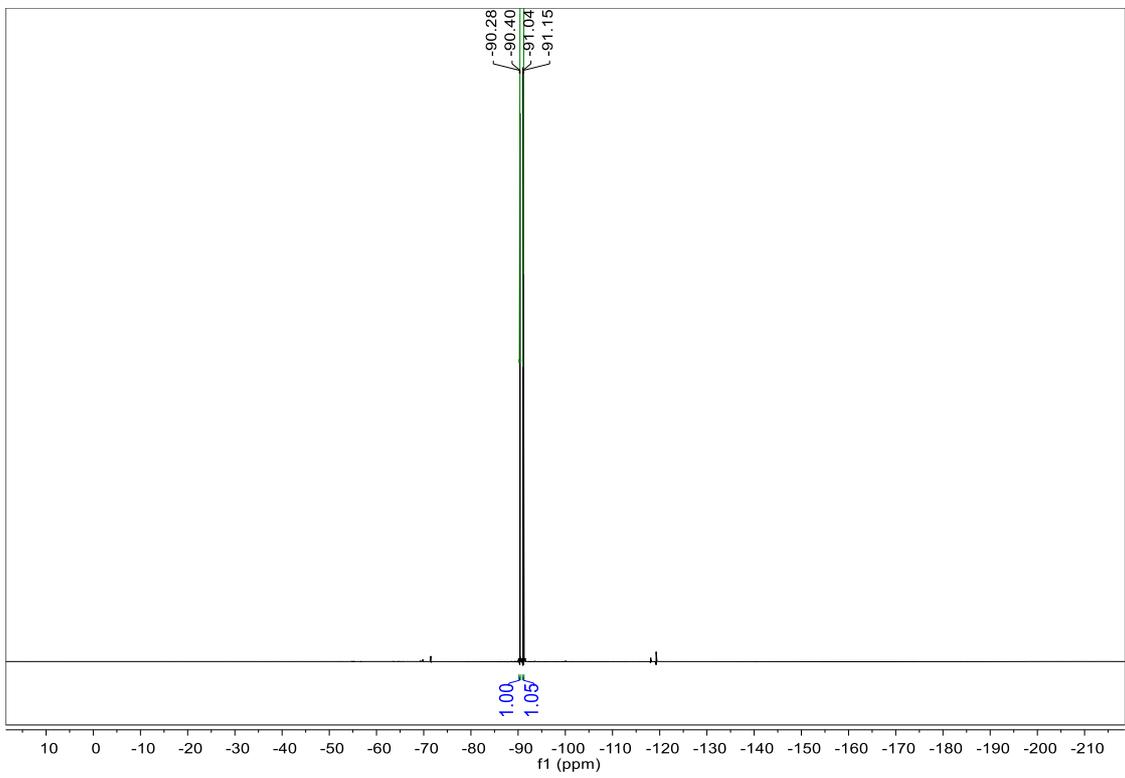
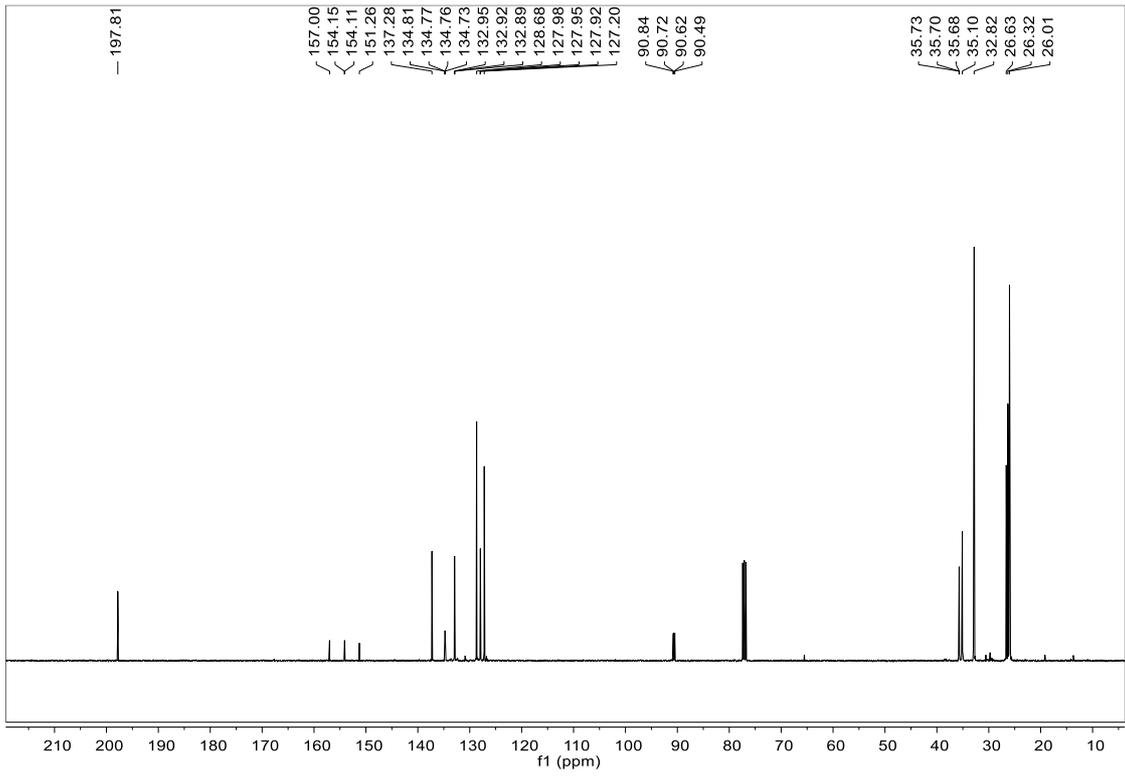
¹H NMR (400 MHz, Chloroform-*d*) δ 7.92 (dd, $J = 2.0, 1.1$ Hz, 1H), 7.85 (dt, $J = 7.6, 1.6$ Hz, 1H), 7.51 (dq, $J = 7.8, 1.5$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 1H), 2.61 (s, 3H), 2.31 (dt, $J = 7.2, 2.4$ Hz, 2H), 1.73 – 1.55 (m, 5H), 1.28 – 1.18 (m, 1H), 1.15 – 1.05 (m, 3H), 0.97 – 0.86 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 197.81, 154.13 (dd, $J = 290.8, 286.9$ Hz), 137.28, 134.77 (dd, $J = 4.9, 3.1$ Hz), 132.92 (t, $J = 3.2$ Hz), 128.68, 127.95 (t, $J = 3.2$ Hz), 127.20, 90.67 (dd, $J = 22.8, 12.3$ Hz), 35.70 (t, $J = 2.4$ Hz), 35.10, 32.82, 26.63, 26.32, 26.01.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.34 (d, $J = 42.1$ Hz, 1F), -91.09 (d, $J = 42.0$ Hz, 1F).

HRMS (ESI) calcd for $C_{17}H_{21}F_2O^+$ [(M+H)⁺] 279.1555, found 279.1565.





1-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)-4-(methylsulfonyl)benzene (3i).



Prepared following general procedure **C** using 1-(methylsulfonyl)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1i**) (125 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol).

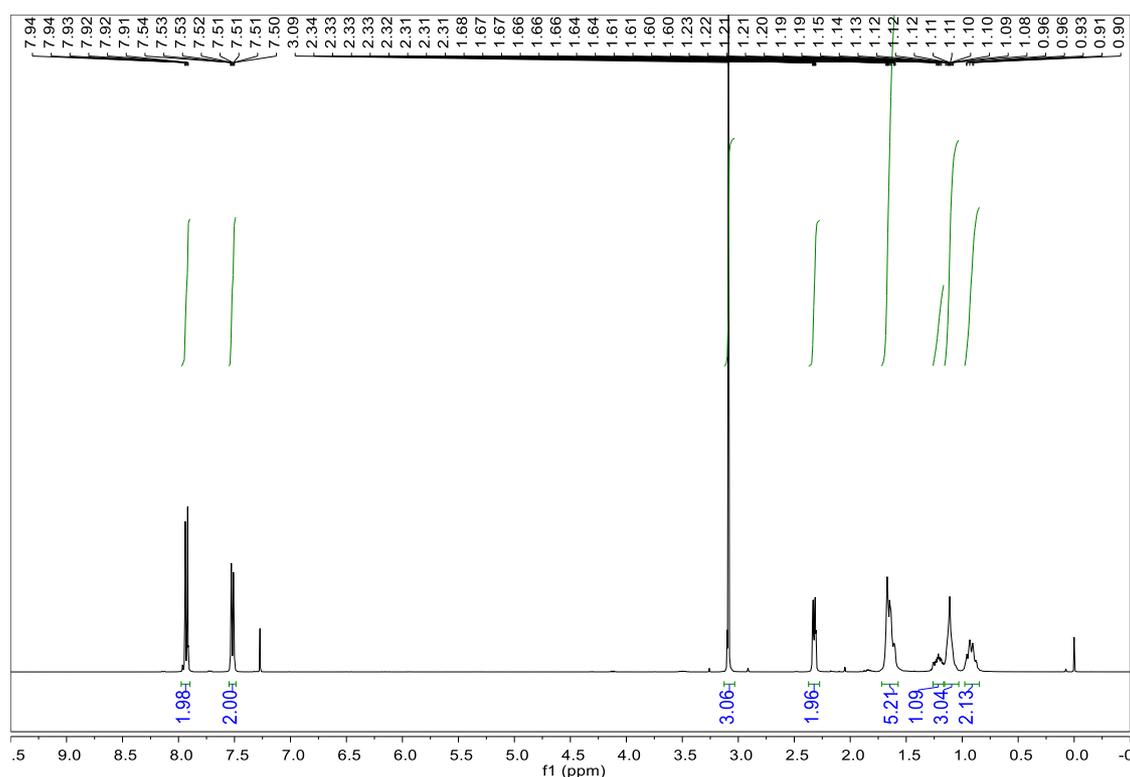
The residue was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 89% yield (140 mg).

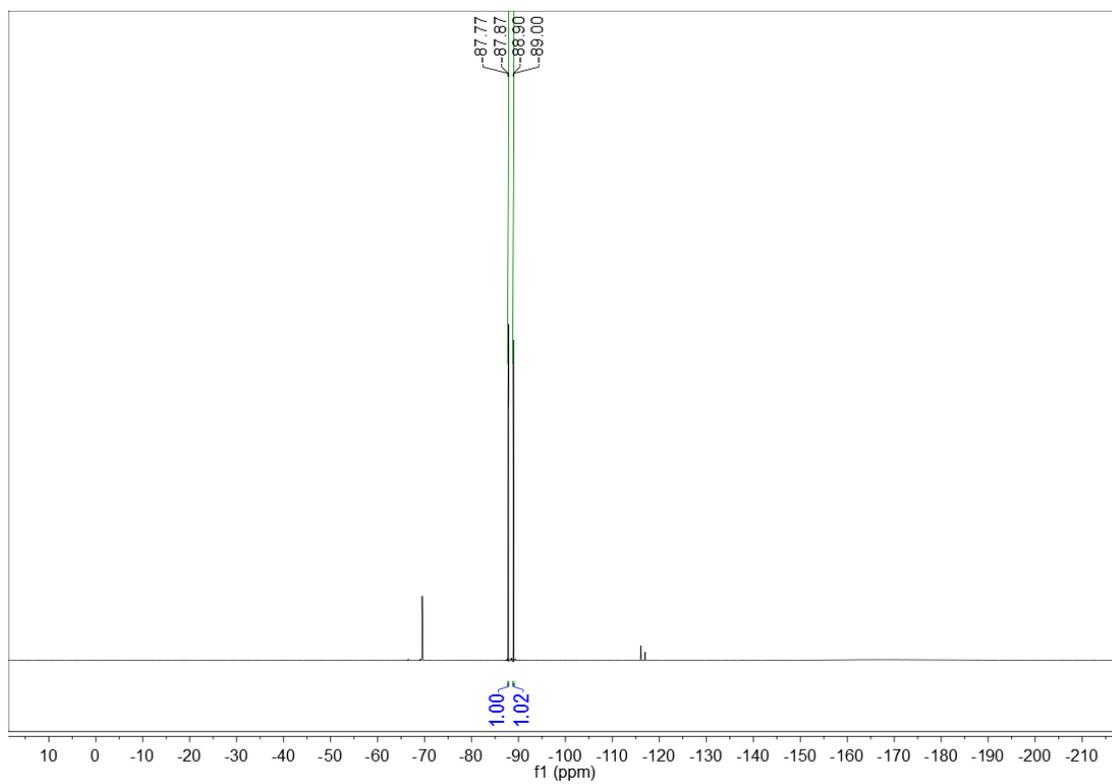
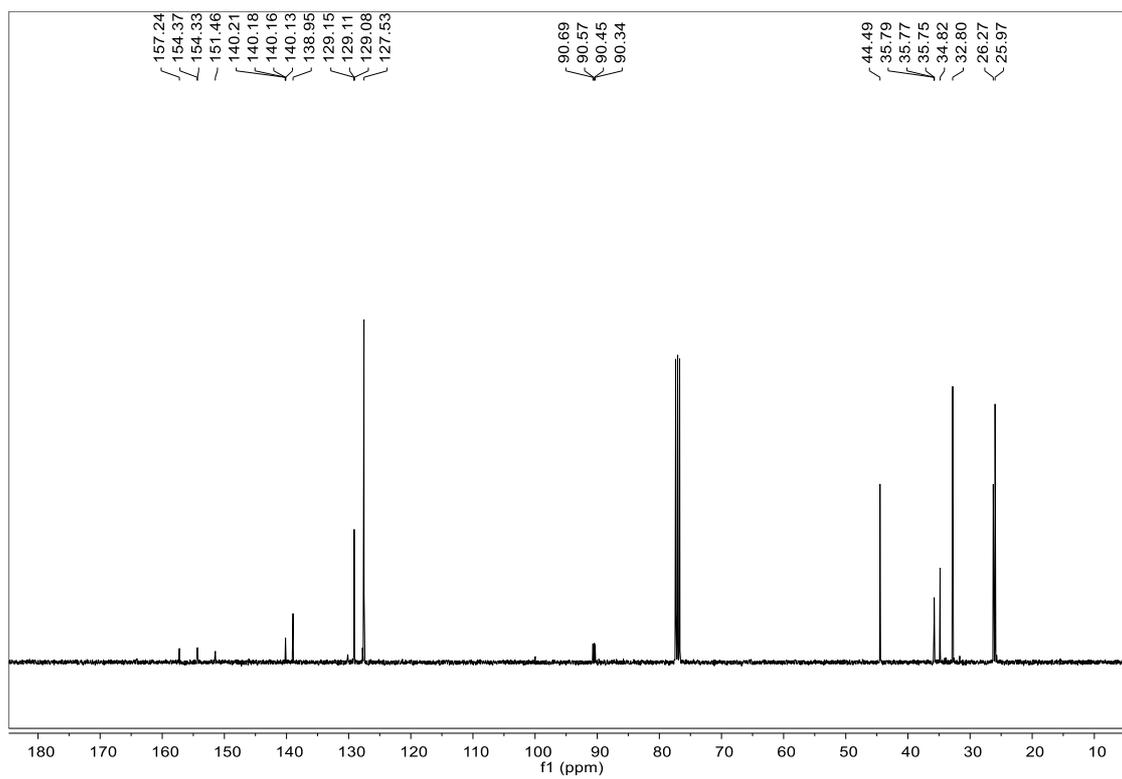
¹H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.90 (m, 2H), 7.55 – 7.49 (m, 2H), 3.09 (s, 3H), 2.37 – 2.27 (m, 2H), 1.72 – 1.57 (m, 5H), 1.26 – 1.16 (m, 1H), 1.15 – 1.04 (m, 3H), 0.98 – 0.85 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 154.35 (dd, $J = 293.1, 288.6$ Hz), 140.17 (dd, $J = 5.2, 3.6$ Hz), 138.95, 129.11 (t, $J = 3.5$ Hz), 127.53, 90.51 (dd, $J = 23.6, 11.5$ Hz), 44.49, 35.77 (t, $J = 2.3$ Hz), 34.82, 32.80, 26.27, 25.97.

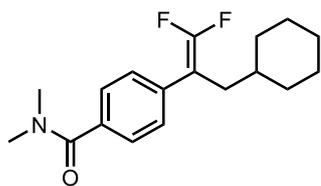
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -87.78 (d, $J = 36.8$ Hz, 1F), -88.93 (d, $J = 36.8$ Hz, 1F).

HRMS (ESI) calcd for C₁₆H₂₁F₂O₂S⁺ [(M+H)⁺] 315.1225, found 315.1238.





4-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)-*N,N*-dimethylbenzamide (3j).



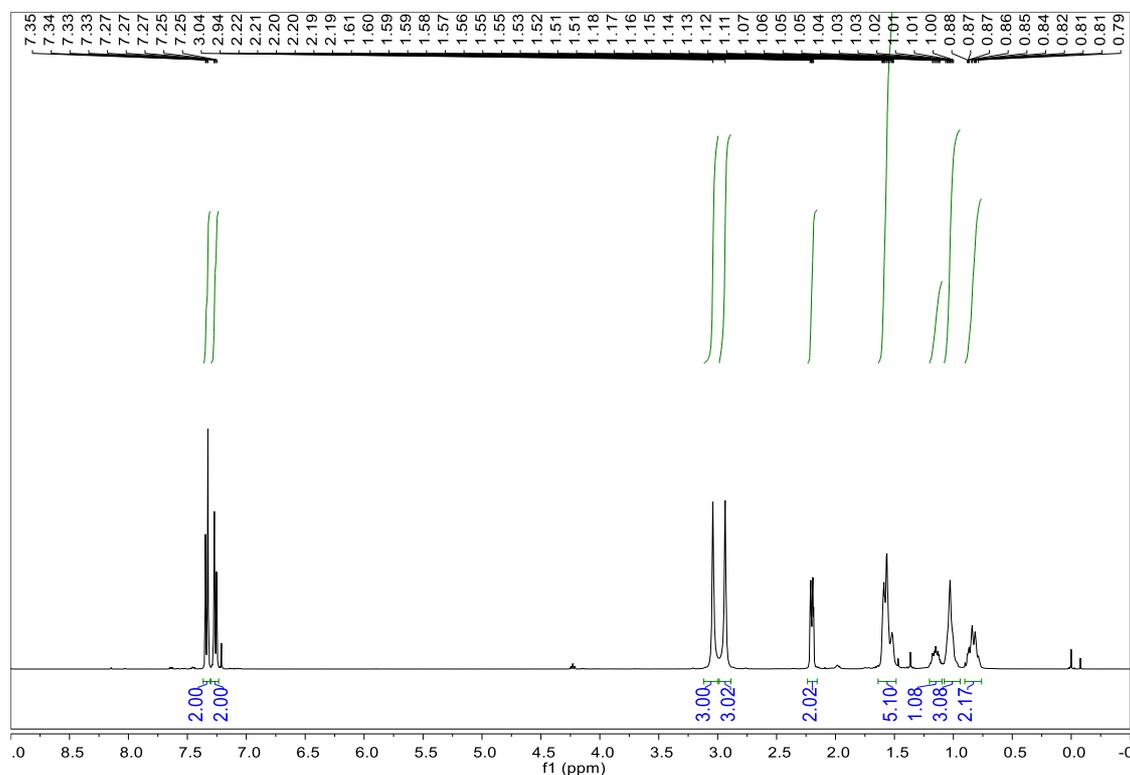
Prepared following general procedure **C** using *N,N*-dimethyl-4-(3,3,3-trifluoroprop-1-en-2-yl)benzamide (**1j**) (122 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 94% yield (144 mg).

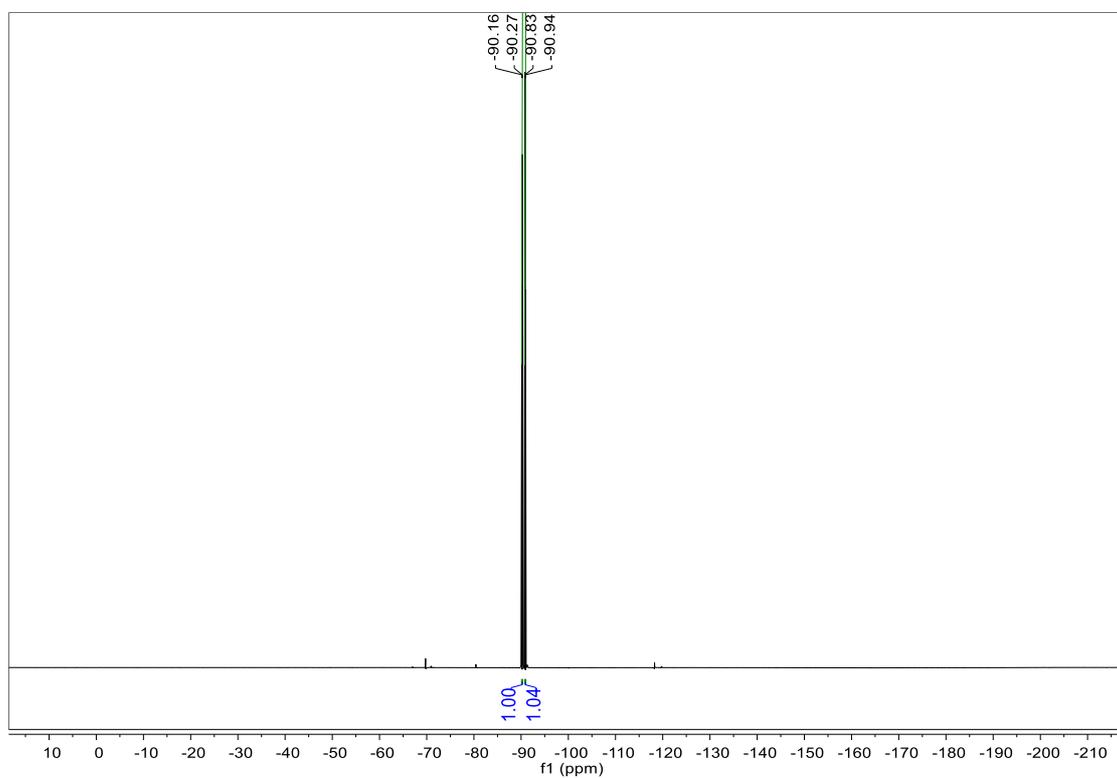
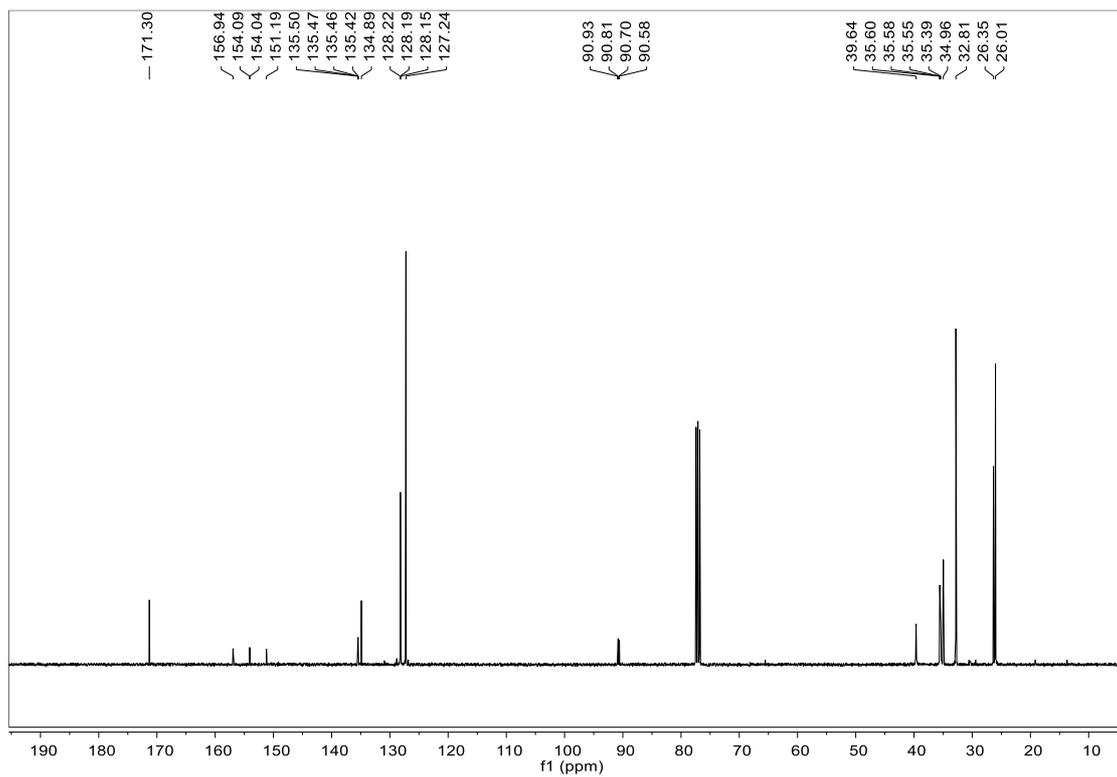
¹H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, $J = 8.3$ Hz, 2H), 7.26 (dd, $J = 8.3, 1.3$ Hz, 2H), 3.04 (s, 3H), 2.94 (s, 3H), 2.20 (dt, $J = 7.3, 2.5$ Hz, 2H), 1.64 – 1.49 (m, 5H), 1.20 – 1.10 (m, 1H), 1.08 – 0.94 (m, 3H), 0.90 – 0.76 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 171.30, 154.07 (dd, $J = 291.2, 286.8$ Hz), 135.46 (dd, $J = 4.7, 3.3$ Hz), 134.89, 128.19 (t, $J = 3.3$ Hz), 127.24, 90.75 (dd, $J = 22.6, 12.1$ Hz), 39.64, 35.58 (t, $J = 2.4$ Hz), 35.39, 34.96, 32.81, 26.35, 26.01.

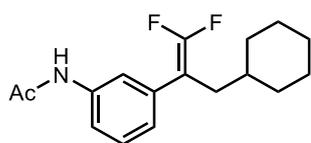
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.21 (d, $J = 41.8$ Hz, 1F), -90.88 (d, $J = 41.8$ Hz, 1F).

HRMS (ESI) calcd for C₁₈H₂₃F₂NONa⁺ [(M+Na)⁺] 330.1640, found 330.1644.





***N*-(3-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)phenyl)acetamide (3k).**



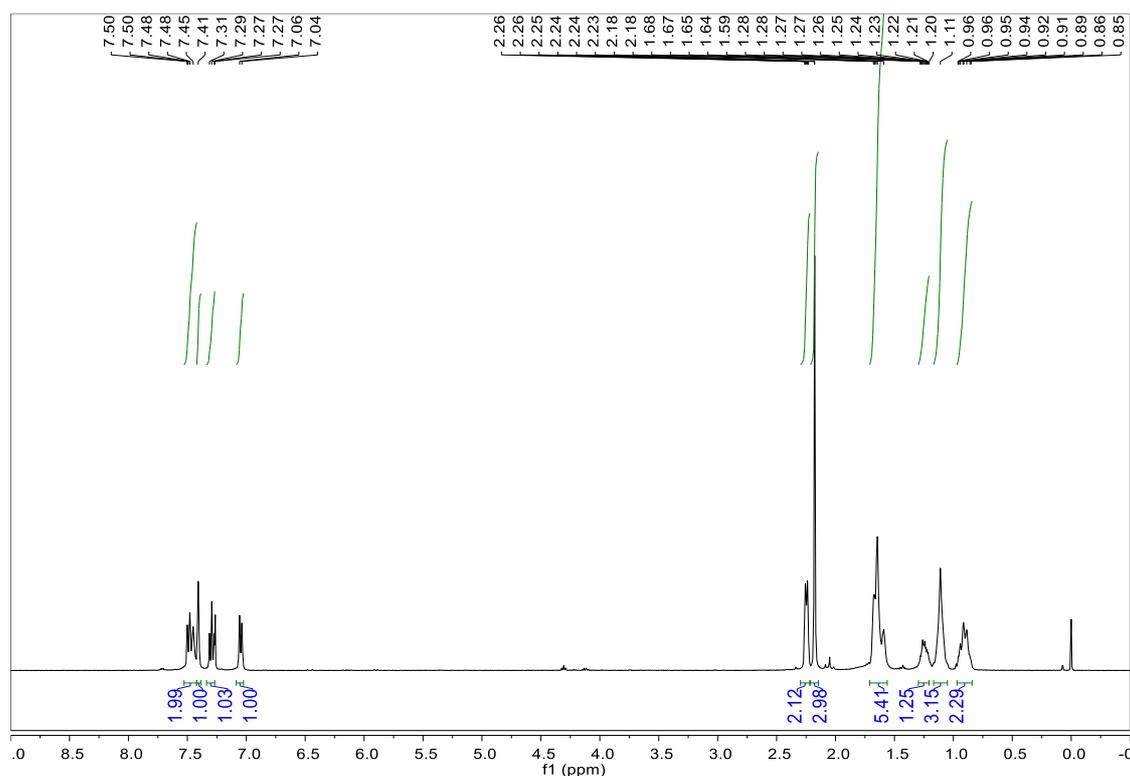
Prepared following general procedure **C** using *N*-(3-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)acetamide (**1k**) (115 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (40% EtOAc in petroleum ether) to provide the title compound as a pale yellow oil in 97% yield (142 mg).

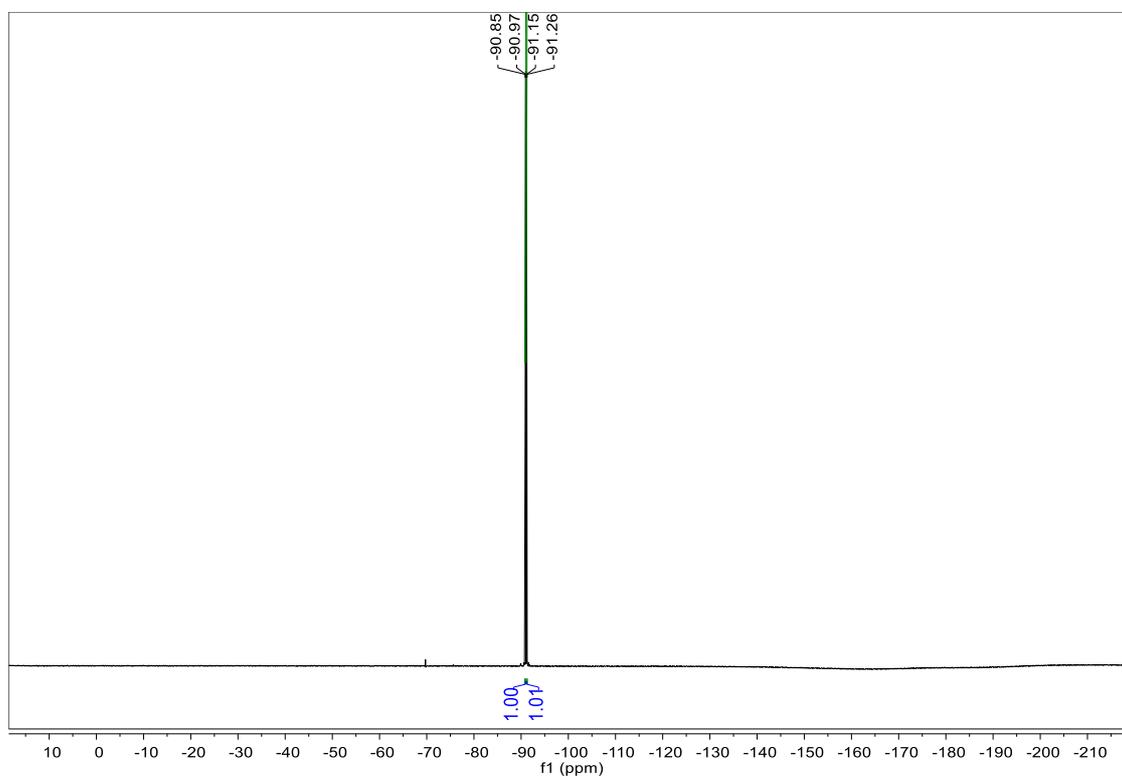
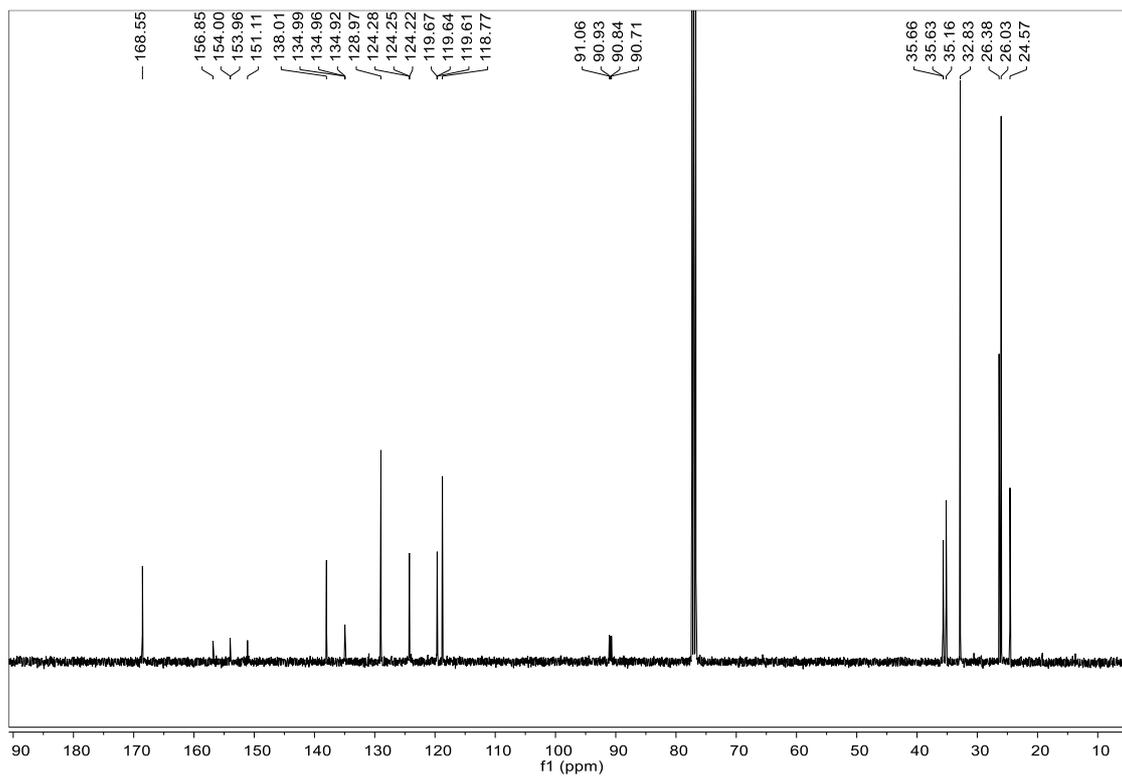
¹H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.42 (m, 2H), 7.41 (s, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 2.25 (dt, *J* = 7.4, 2.4 Hz, 2H), 2.18 (s, 3H), 1.71 – 1.56 (m, 5H), 1.30 – 1.21 (m, 1H), 1.17 – 1.05 (m, 2H), 0.97 – 0.84 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 168.55, 153.98 (dd, *J* = 290.3, 286.3 Hz), 138.01, 134.95 (dd, *J* = 4.0, 3.3 Hz), 128.97, 124.25 (t, *J* = 3.2 Hz), 119.64 (t, *J* = 3.3 Hz), 118.77, 90.89 (dd, *J* = 22.2, 12.7 Hz), 35.66 (t, *J* = 2.6 Hz), 35.16, 32.83, 26.38, 26.03, 24.57.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.91 (d, *J* = 43.2 Hz, 1F), -91.21 (d, *J* = 43.2 Hz, 1F).

HRMS (ESI) calcd for C₁₇H₂₂F₂NO⁺ [(M+H)⁺] 294.1664, found 294.1663.





2-Bromo-4-(3-cyclohexyl-1,1-difluoroprop-1-en-2-yl)-1-methoxybenzene (3l).



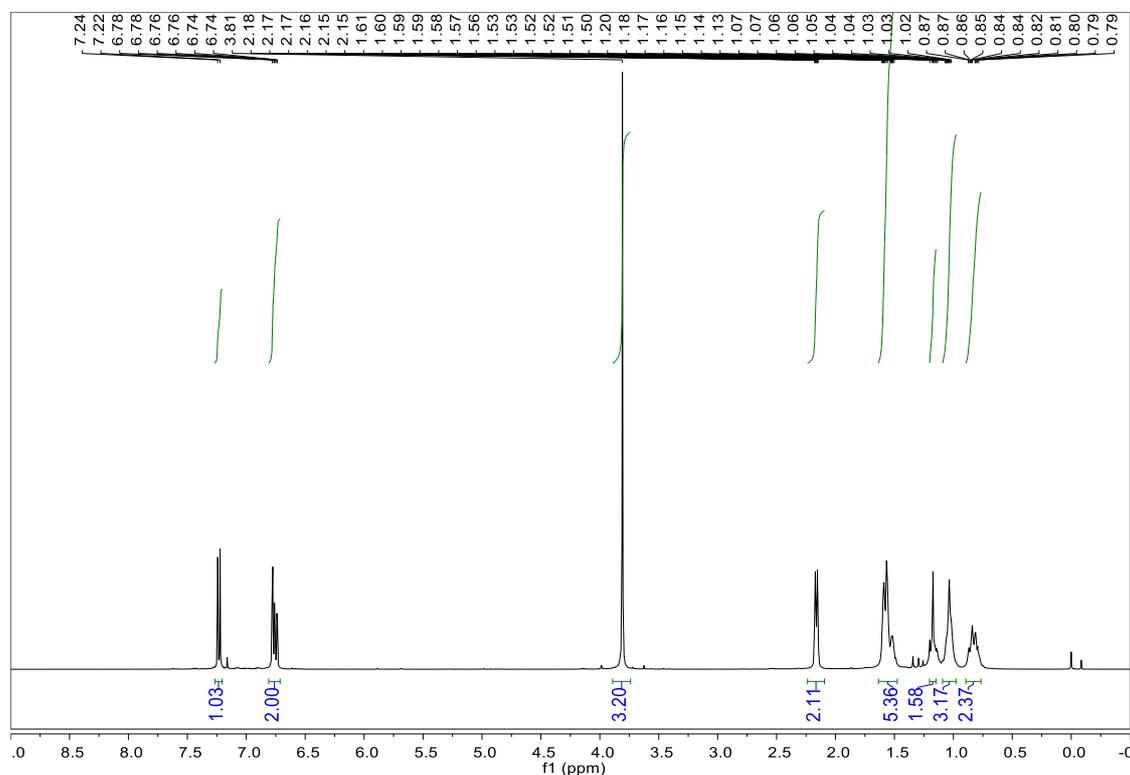
Prepared following general procedure **C** using 2-bromo-1-methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**11**) (141 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 89% yield (154 mg).

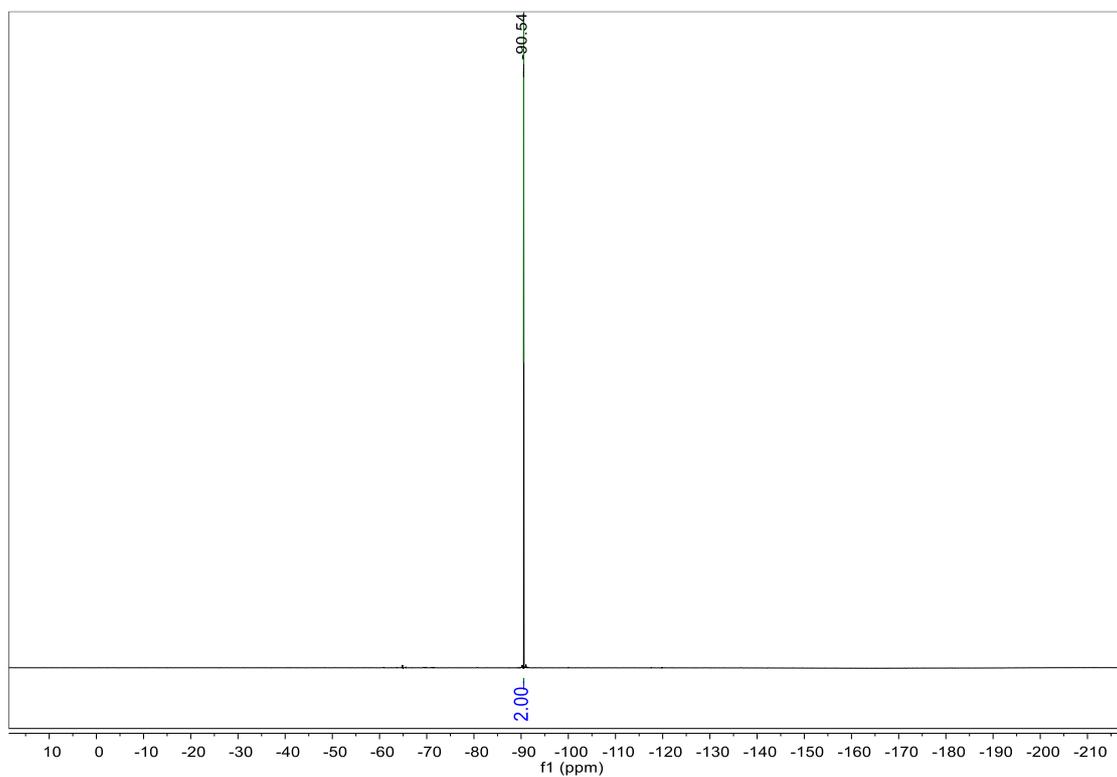
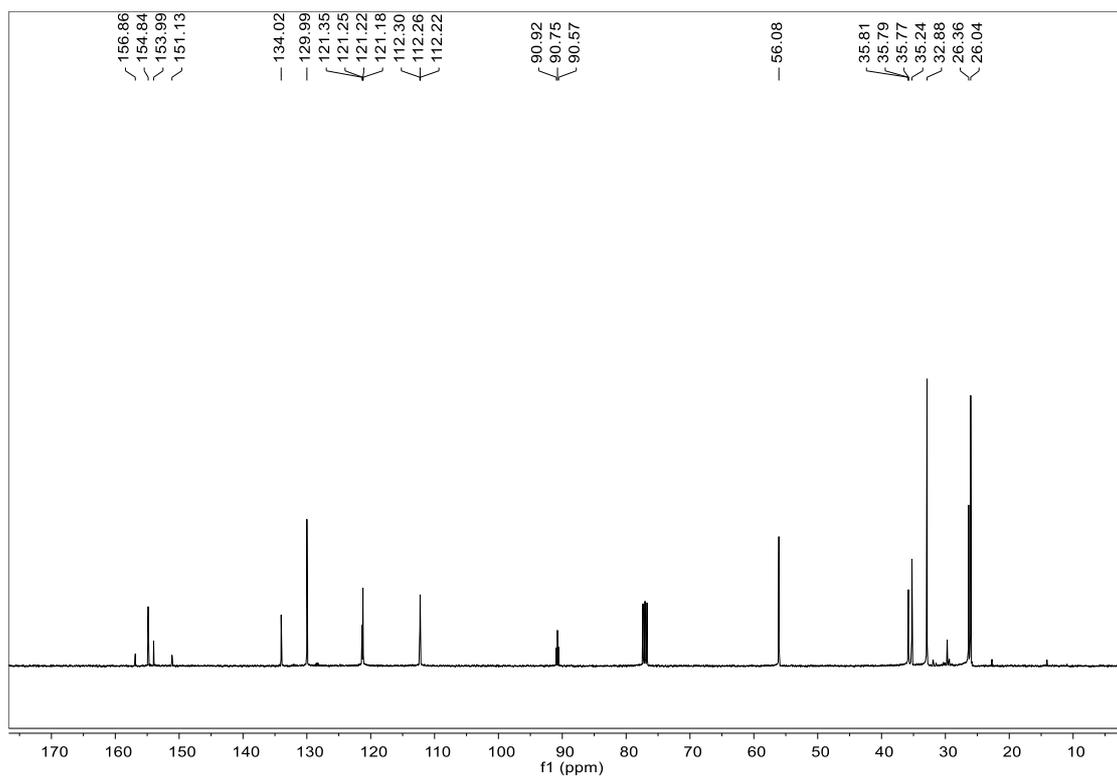
¹H NMR (400 MHz, Chloroform-*d*) δ 7.23 (d, $J = 8.1$ Hz, 1H), 6.81 – 6.71 (m, 2H), 3.81 (s, 3H), 2.16 (dt, $J = 7.3, 2.5$ Hz, 2H), 1.64 – 1.48 (m, 5H), 1.20 – 1.15 (m, 1H), 1.09 – 0.98 (m, 3H), 0.89 – 0.77 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 154.84, 153.99 (t, $J = 288.6$ Hz), 134.02, 129.99, 121.35, 121.22 (t, $J = 3.3$ Hz), 112.26 (t, $J = 3.6$ Hz), 90.75 (t, $J = 17.6$ Hz), 56.08, 35.80 (t, $J = 2.4$ Hz), 35.24, 32.88, 26.36, 26.04.

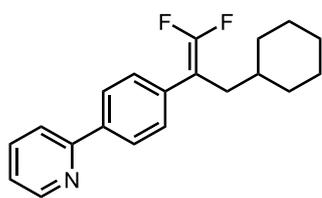
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.54 (s, 2F).

HRMS (ESI) calcd for C₁₆H₁₉BrF₂ONa⁺ [(M+Na)⁺] 367.0480, found 367.0482.





2-(4-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)phenyl)pyridine (**3m**).



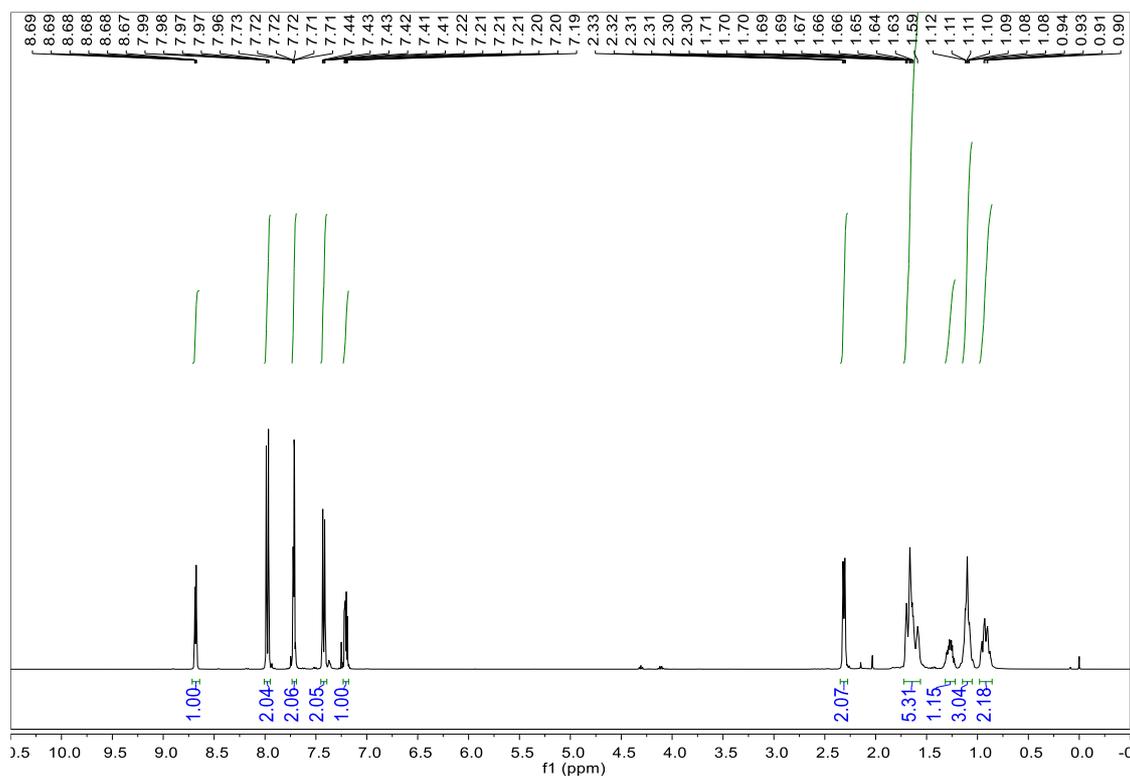
Prepared following general procedure **C** using 2-(4-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)pyridine (**1m**) (125 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 90% yield (141 mg).

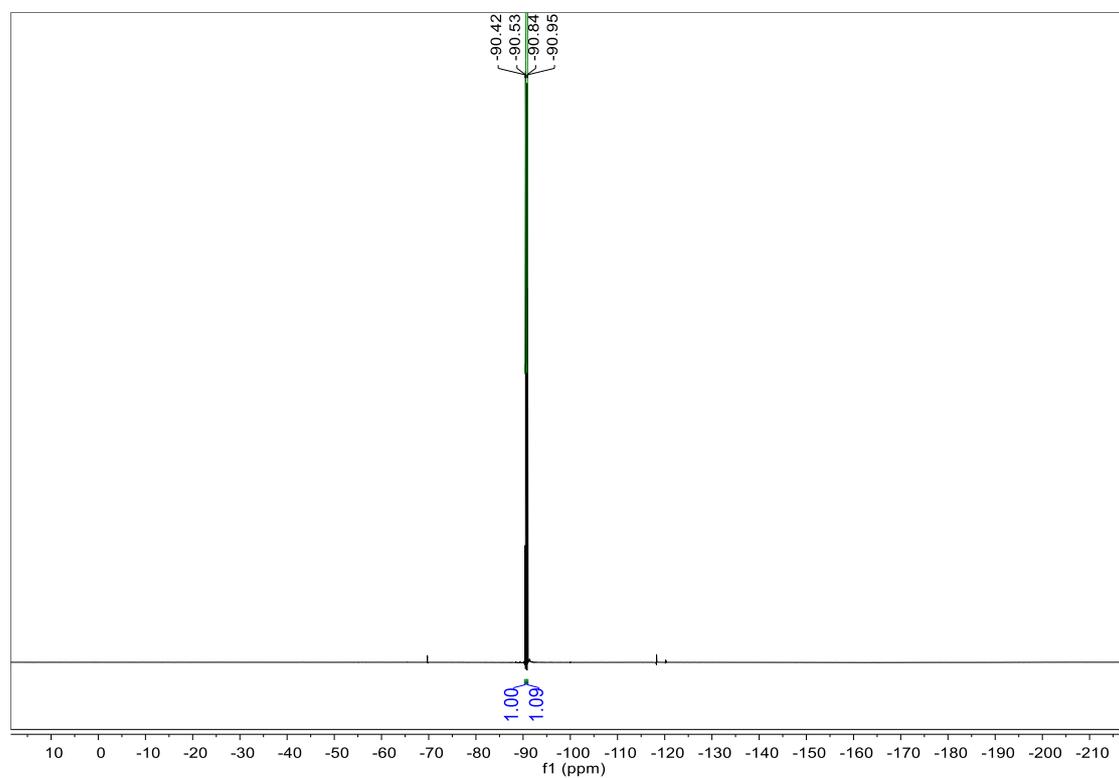
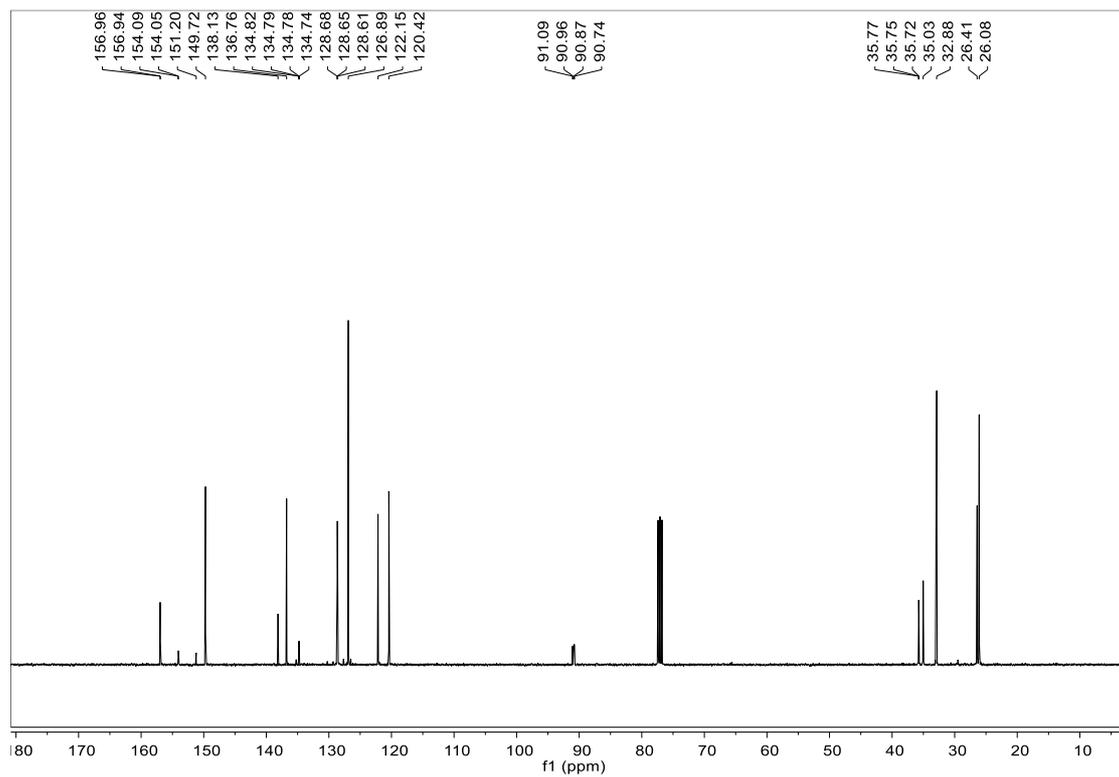
¹H NMR (400 MHz, Chloroform-*d*) δ 8.68 (dt, $J = 4.8, 1.4$ Hz, 1H), 8.01 – 7.95 (m, 2H), 7.73 – 7.69 (m, 2H), 7.45 – 7.39 (m, 2H), 7.23 – 7.18 (m, 1H), 2.31 (dt, $J = 7.2, 2.4$ Hz, 2H), 1.72 – 1.56 (m, 5H), 1.32 – 1.22 (m, 1H), 1.15 – 1.05 (m, 3H), 0.98 – 0.86 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 156.96, 154.07 (dd, $J = 291.0, 286.6$ Hz), 149.72, 138.13, 136.76, 134.78 (dd, $J = 4.4, 3.4$ Hz), 128.65 (t, $J = 3.3$ Hz), 126.89, 122.15, 120.42, 90.92 (dd, $J = 22.2, 12.3$ Hz), 35.75 (t, $J = 2.3$ Hz), 35.03, 32.88, 26.41, 26.08.

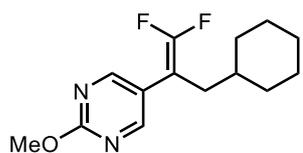
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.47 (d, $J = 42.2$ Hz, 1F), -90.89 (d, $J = 42.5$ Hz, 1F).

HRMS (ESI) calcd for $C_{20}H_{22}F_2N^+$ [(M+H)⁺] 314.1715, found 314.1727.





5-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)-2-methoxypyrimidine (3n).



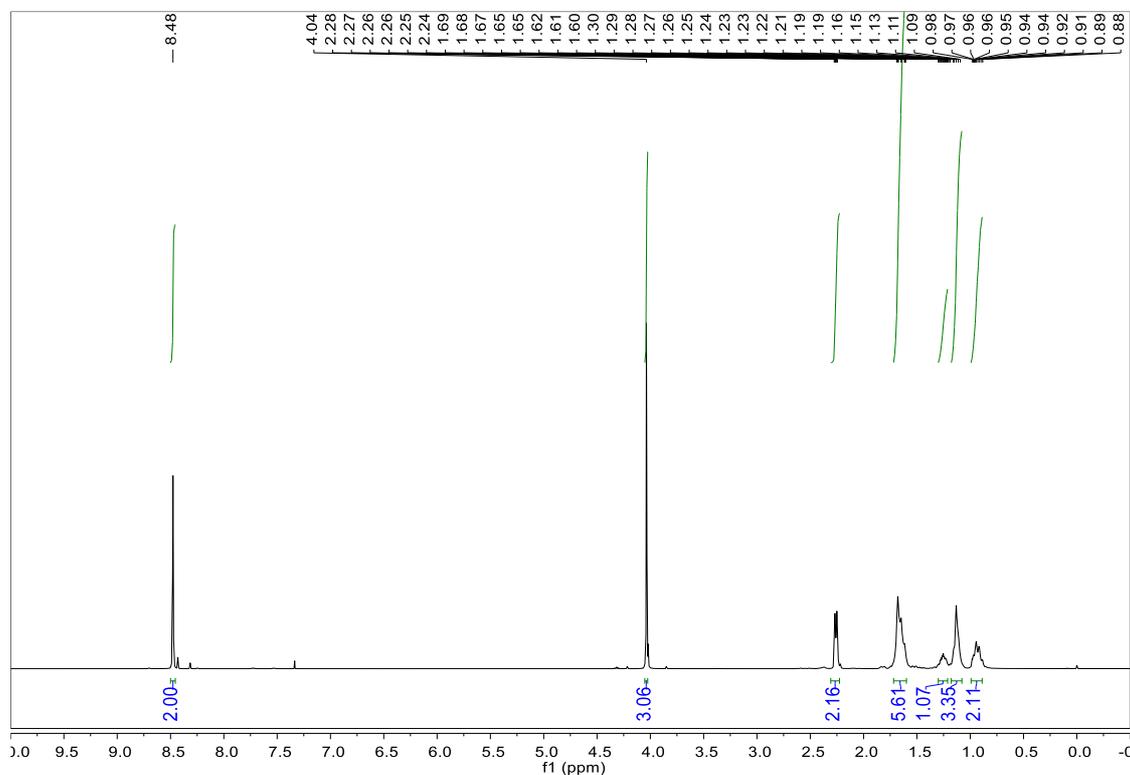
Prepared following general procedure C using 2-methoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyrimidine (**1n**) (102 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 96% yield (129 mg).

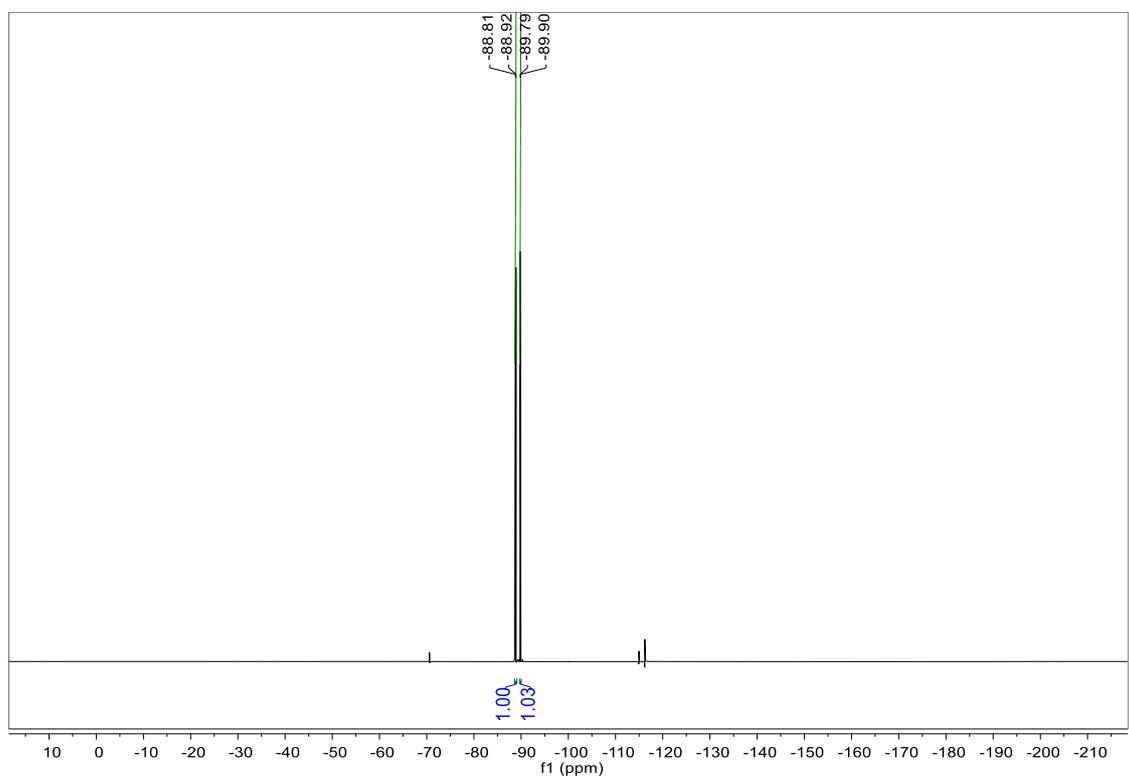
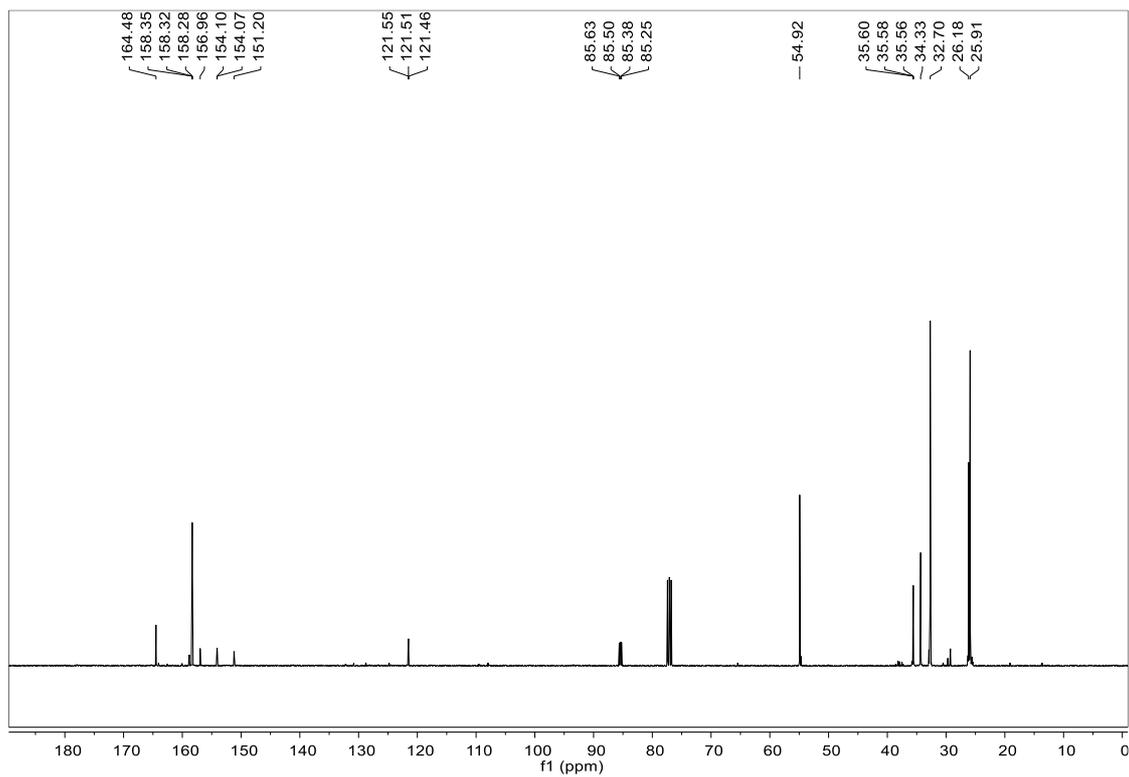
¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 2H), 4.04 (s, 3H), 2.26 (dt, $J = 7.4, 2.4$ Hz, 2H), 1.72 – 1.60 (m, 5H), 1.30 – 1.21 (m, 1H), 1.18 – 1.08 (m, 3H), 0.99 – 0.89 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 164.48, 158.31 (t, $J = 3.7$ Hz), 154.08 (dd, $J = 291.3, 288.3$ Hz), 121.51 (t, $J = 4.4$ Hz), 85.44 (dd, $J = 25.3, 12.9$ Hz), 54.92, 35.58 (t, $J = 2.3$ Hz), 34.33, 32.70, 26.18, 25.91.

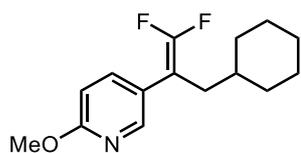
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -88.86 (d, $J = 40.2$ Hz, 1F), -89.84 (d, $J = 40.2$ Hz, 1F).

HRMS (ESI) calcd for C₁₄H₁₉F₂N₂O⁺ [(M+H)⁺] 269.1460, found 269.1471.





5-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)-2-methoxypyridine (3o).



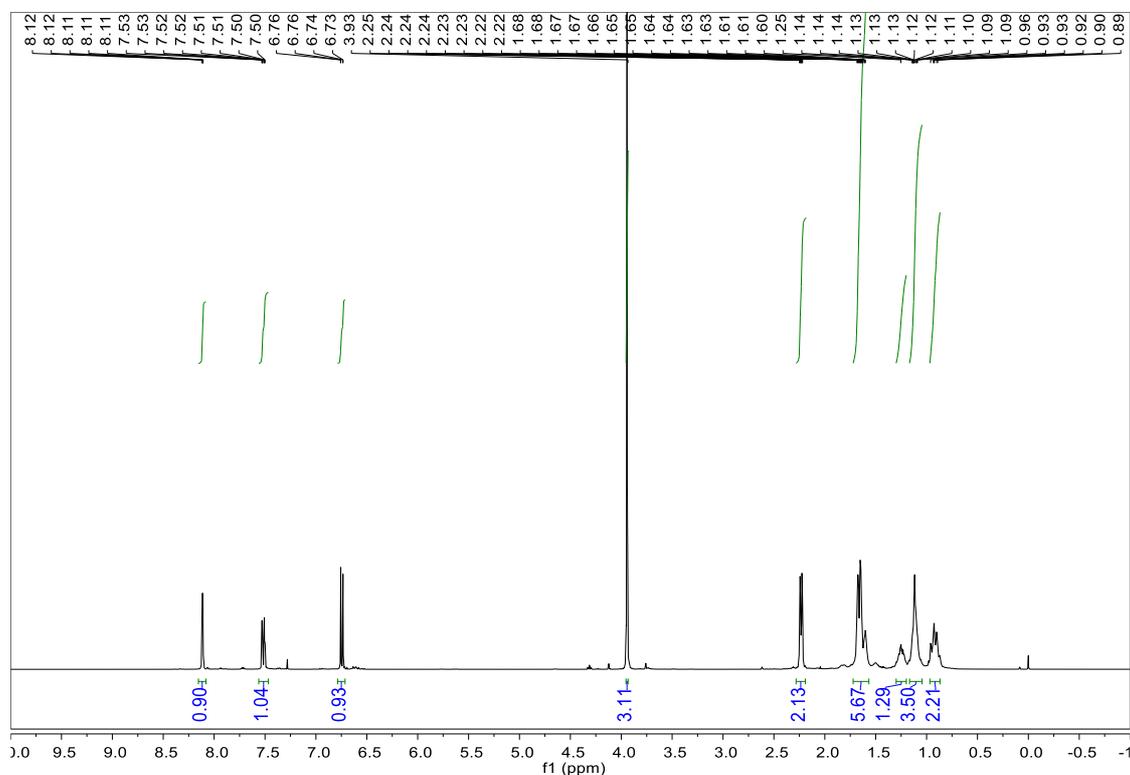
Prepared following general procedure C using 2-methoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyridine (**1o**) (102 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 98% yield (131 mg).

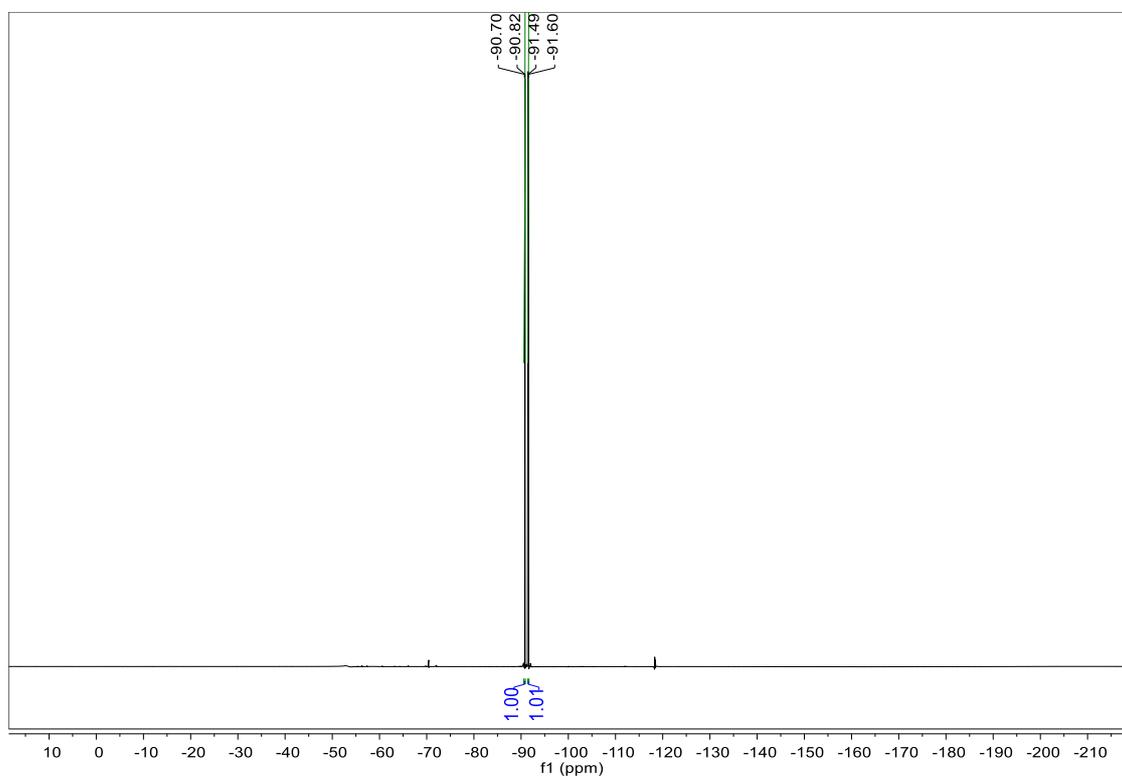
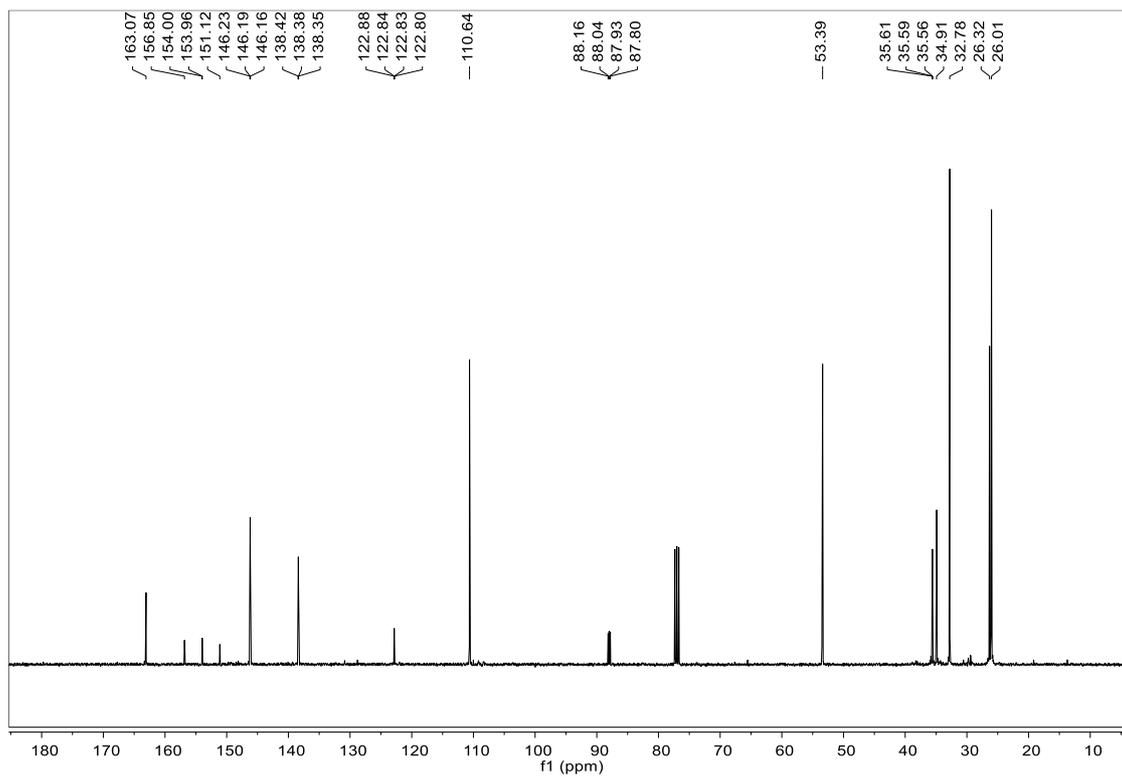
¹H NMR (400 MHz, Chloroform-*d*) δ 8.15 – 8.09 (m, 1H), 7.52 (ddd, $J = 8.6, 2.5, 1.1$ Hz, 1H), 6.75 (dd, $J = 8.6, 0.7$ Hz, 1H), 3.93 (s, 3H), 2.23 (dt, $J = 7.2, 2.4$ Hz, 2H), 1.72 – 1.57 (m, 5H), 1.30 – 1.20 (m, 1H), 1.17 – 1.04 (m, 3H), 0.97 – 0.87 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 163.07, 153.98 (dd, $J = 290.0, 286.6$ Hz), 146.19 (t, $J = 3.7$ Hz), 138.38 (t, $J = 3.3$ Hz), 122.84 (dd, $J = 4.7, 3.4$ Hz), 110.64, 87.98 (dd, $J = 23.6, 12.9$ Hz), 53.39, 35.59 (t, $J = 2.5$ Hz), 34.91, 32.78, 26.32, 26.01.

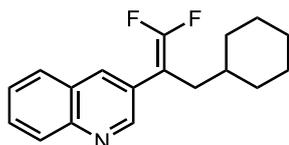
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.76 (d, $J = 44.0$ Hz, 1F), -91.55 (d, $J = 44.1$ Hz, 1F).

HRMS (ESI) calcd for C₁₅H₂₀F₂NO⁺ [(M+H)⁺] 268.1507, found 268.1515.





3-(3-Cyclohexyl-1,1-difluoroprop-1-en-2-yl)quinoline (3p).



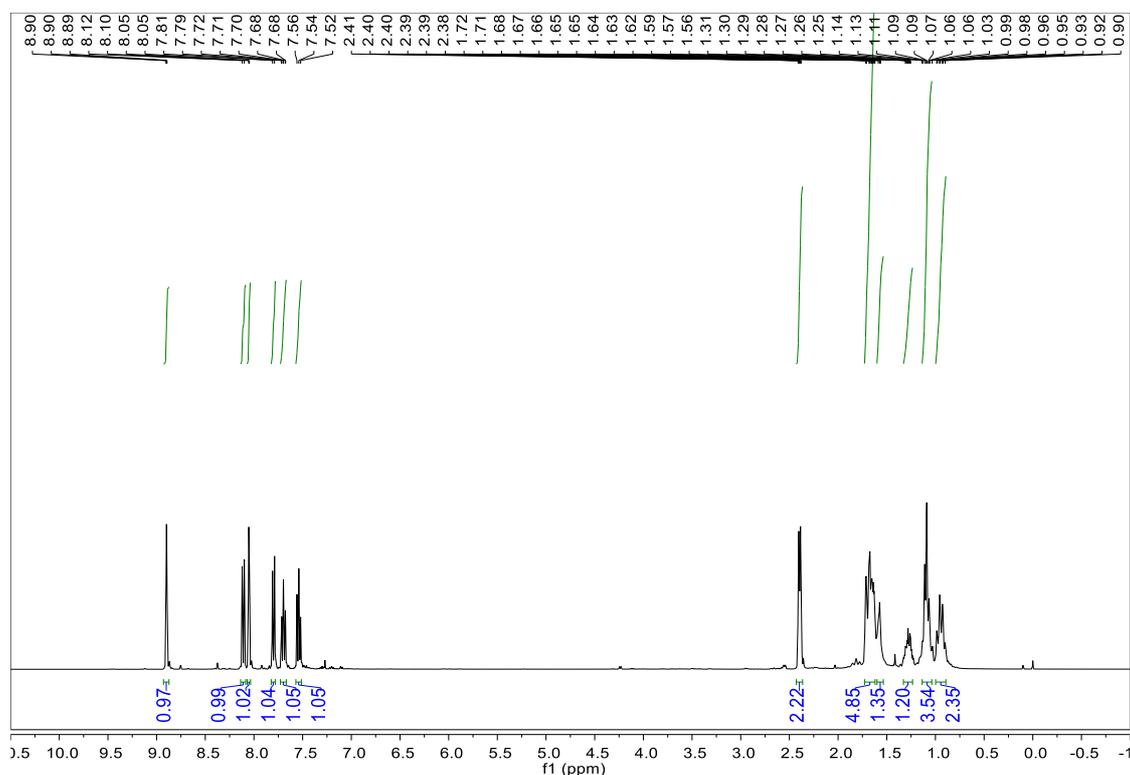
Prepared following general procedure **C** using 3-(3,3,3-trifluoroprop-1-en-2-yl)quinoline (**1p**) (112 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a pale yellow oil in 92% yield (132 mg).

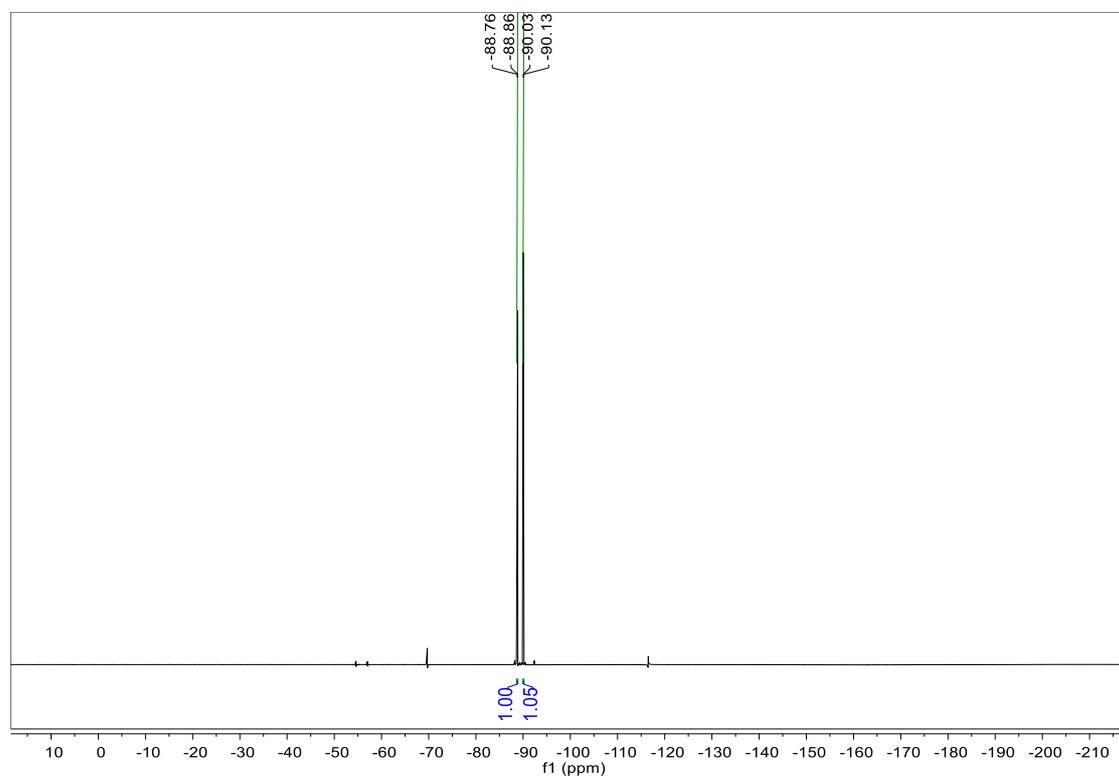
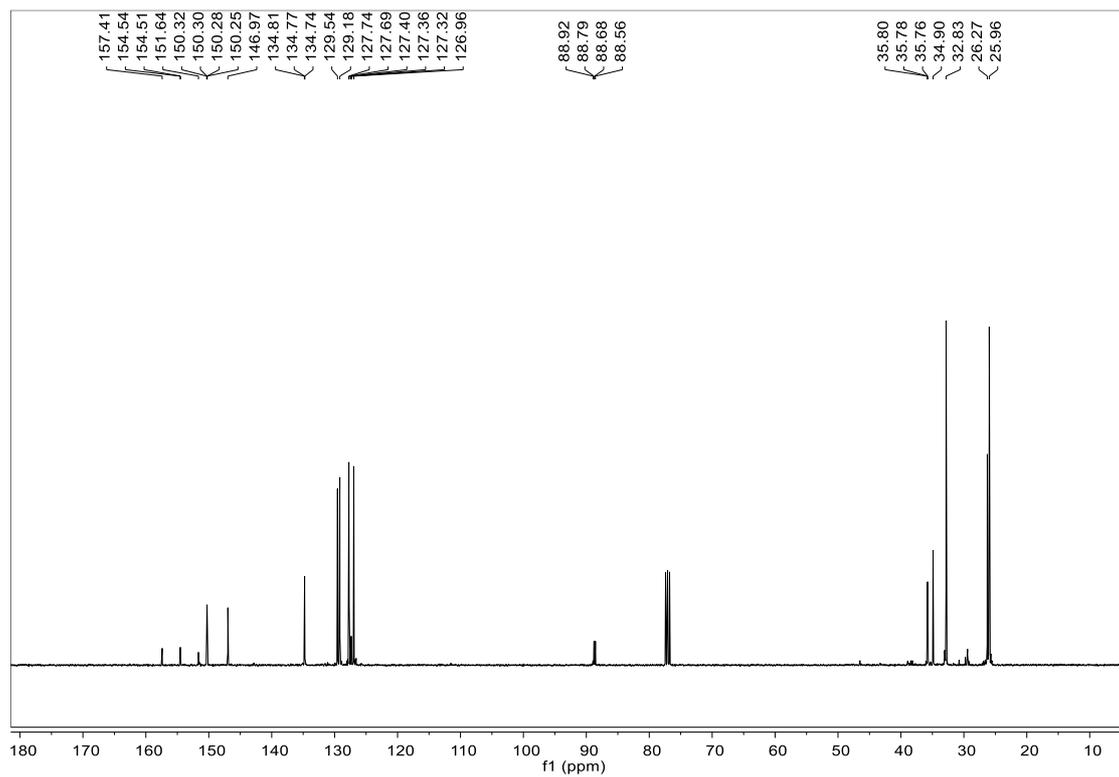
¹H NMR (400 MHz, Chloroform-*d*) δ 8.90 (d, $J = 2.1$ Hz, 1H), 8.11 (d, $J = 8.5$ Hz, 1H), 8.05 (d, $J = 2.2$ Hz, 1H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.73 – 7.67 (m, 1H), 7.54 (t, $J = 7.5$ Hz, 1H), 2.40 (dt, $J = 7.3, 2.5$ Hz, 2H), 1.73 – 1.62 (m, 4H), 1.60 – 1.54 (m, 1H), 1.33 – 1.24 (m, 1H), 1.14 – 1.04 (m, 3H), 1.00 – 0.89 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 154.52 (dd, $J = 291.8, 288.4$ Hz), 150.29 (dd, $J = 4.3, 2.7$ Hz), 146.97, 134.77 (t, $J = 3.5$ Hz), 129.54, 129.18, 127.74, 127.69, 127.36 (t, $J = 4.2$ Hz), 126.96, 88.74 (dd, $J = 23.8, 12.6$ Hz), 35.78 (t, $J = 2.4$ Hz), 34.90, 32.83, 26.27, 25.96.

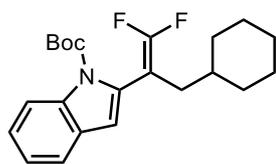
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -88.81 (d, $J = 39.6$ Hz, 1F), -90.08 (d, $J = 39.6$ Hz, 1F).

HRMS (ESI) calcd for $C_{18}H_{20}F_2N^+$ [(M+H)⁺] 288.1558, found 288.1570.





***Tert*-butyl 2-(3-cyclohexyl-1,1-difluoroprop-1-en-2-yl)-1*H*-indole-1-carboxylate (3q).**



Prepared following general procedure **C** using *tert*-butyl 2-(3,3,3-trifluoroprop-1-en-2-yl)-1*H*-indole-1-carboxylate (**1q**) (156 mg, 0.5 mmol) and iodocyclohexane (210 mg, 1.0 mmol).

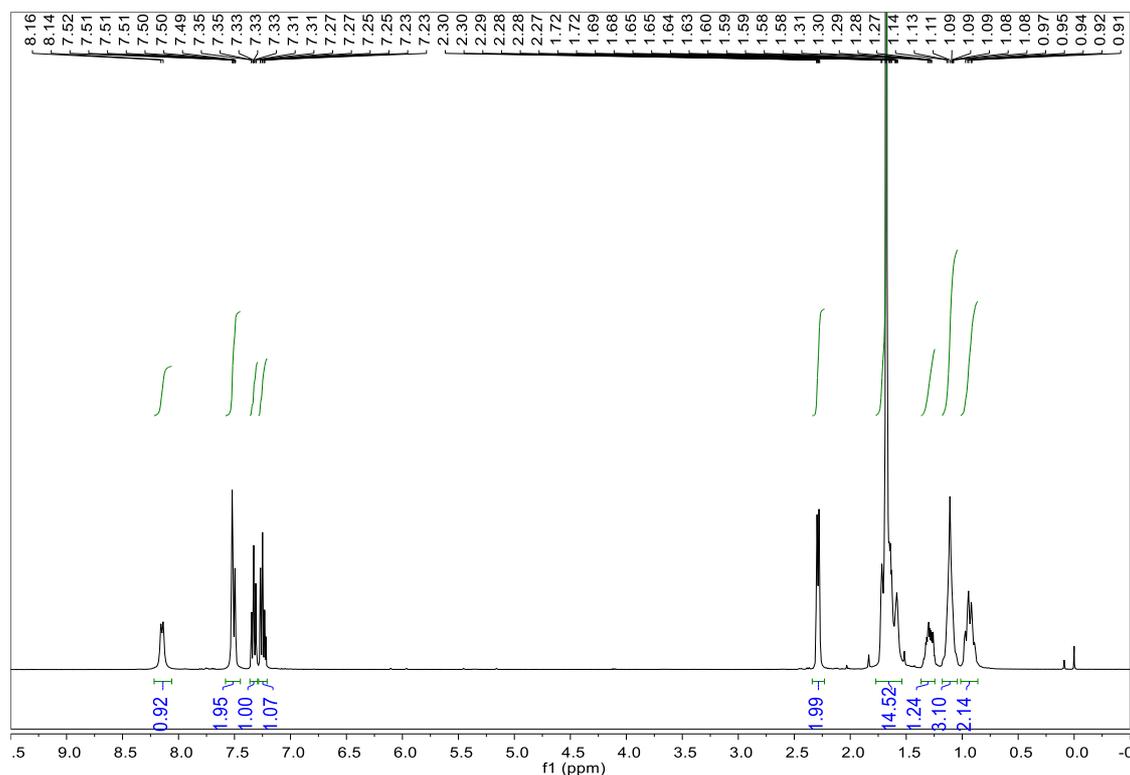
The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 64% yield (120 mg).

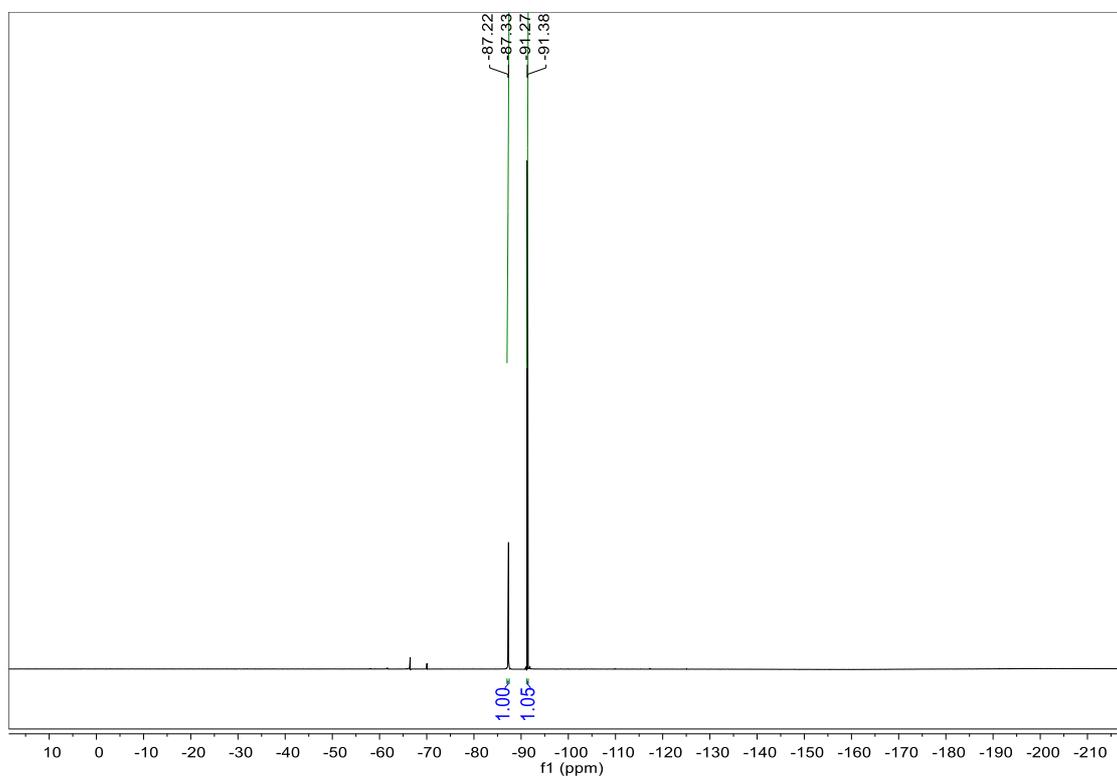
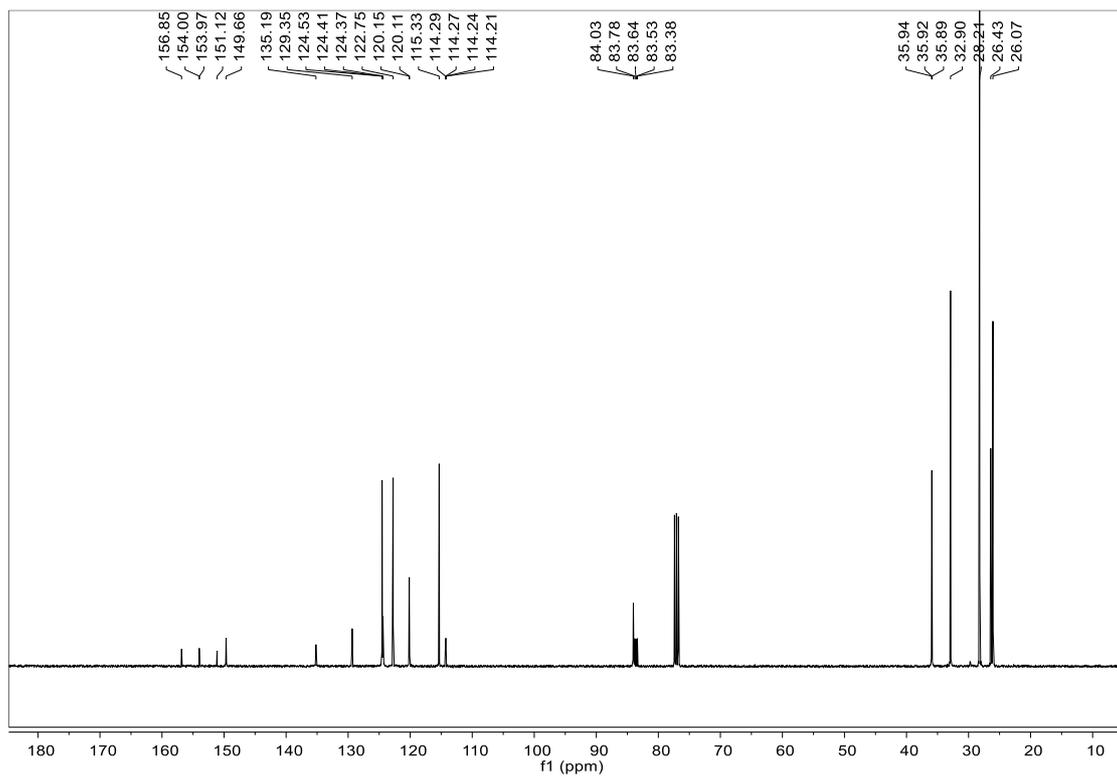
¹H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, $J = 8.3$ Hz, 1H), 7.58 – 7.45 (m, 2H), 7.33 (ddd, $J = 8.4, 7.2, 1.3$ Hz, 1H), 7.29 – 7.21 (m, 1H), 2.29 (dt, $J = 7.4, 2.3$ Hz, 2H), 1.77 – 1.54 (m, 5H), 1.68 (s, 9H), 1.37 – 1.24 (m, 1H), 1.18 – 1.04 (m, 3H), 1.01 – 0.86 (m, 2H),.

¹³C NMR (101 MHz, Chloroform-*d*) δ 153.98 (dd, $J = 289.6, 286.7$ Hz), 149.66, 135.19, 129.35, 124.53, 124.39 (d, $J = 3.5$ Hz), 122.75, 120.13 (d, $J = 3.5$ Hz), 115.33, 114.25 (dd, $J = 5.2, 2.2$ Hz), 84.03, 83.58 (dd, $J = 25.8, 14.8$ Hz), 35.92 (t, $J = 1.8$ Hz), 35.89, 32.90, 28.21, 26.43, 26.07.

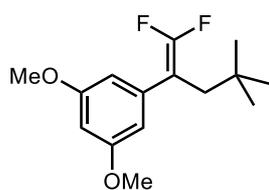
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -87.28 (d, $J = 41.6$ Hz, 1F), -91.33 (d, $J = 41.6$ Hz, 1F).

HRMS (ESI) calcd for C₂₂H₂₈F₂NO₂⁺ [(M+H)⁺] 276.2083, found 276.2086.





1-(1,1-Difluoro-4,4-dimethylpent-1-en-2-yl)-3,5-dimethoxybenzene (4a).



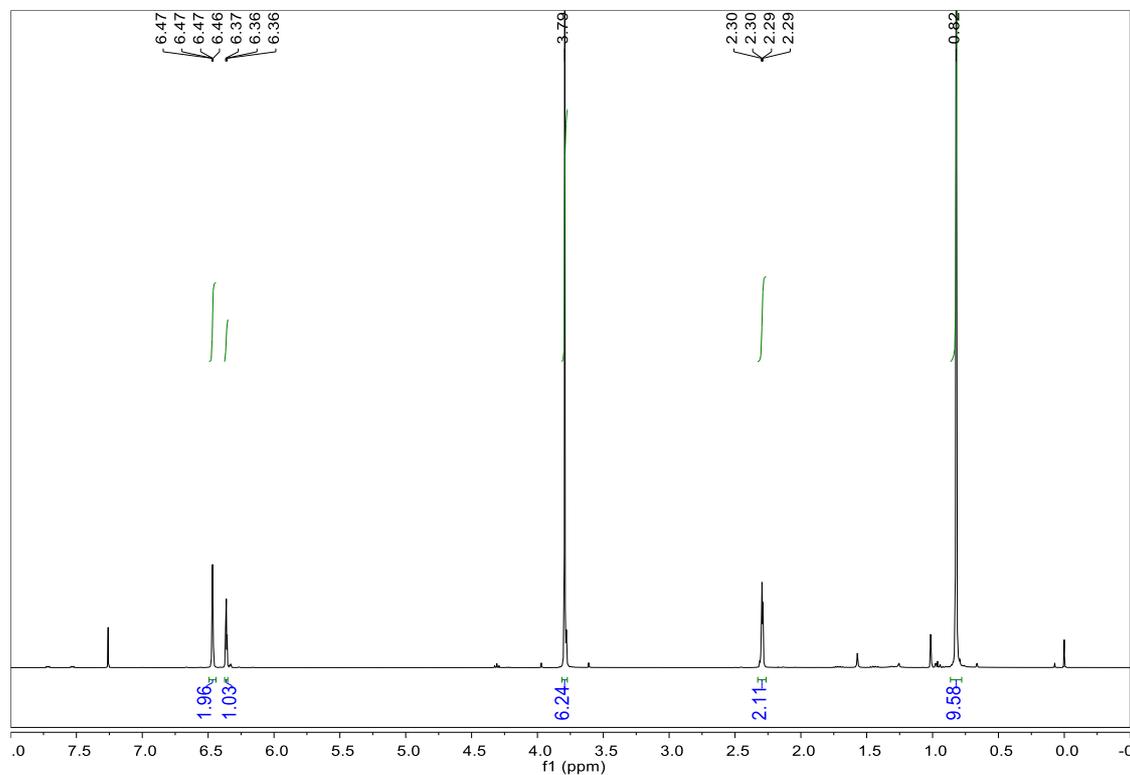
Prepared following general procedure **C** using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and 2-bromo-2-methylpropane (137 mg, 1.0 mmol). The reaction mixture was stirred at 40 °C. The residue was purified by silica gel column chromatography (3% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 95% yield (128 mg).

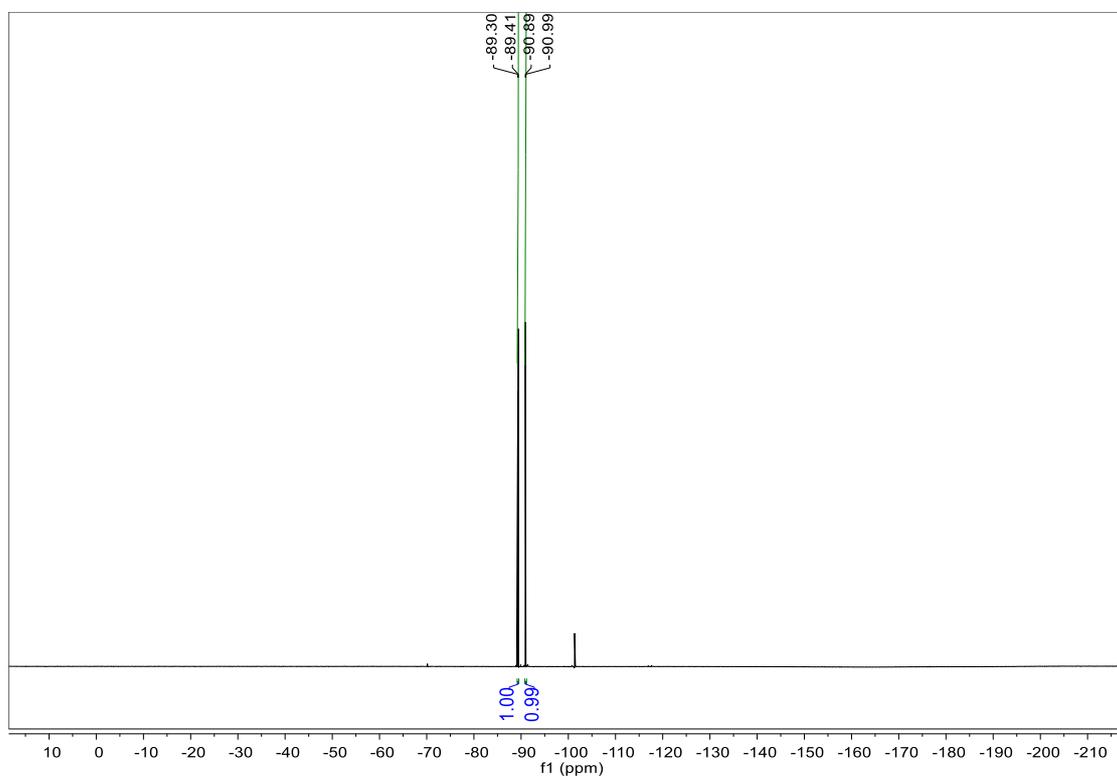
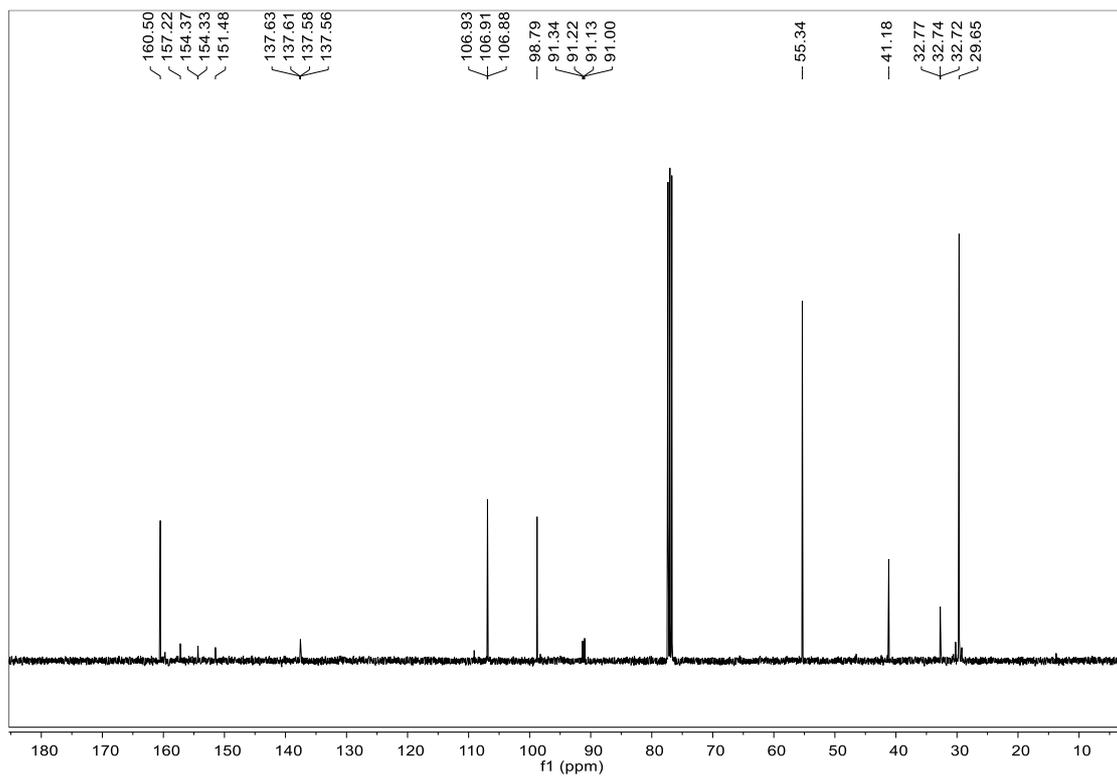
¹H NMR (400 MHz, Chloroform-*d*) δ 6.47 (dd, $J = 2.3, 1.4$ Hz, 2H), 6.36 (t, $J = 2.3$ Hz, 1H), 3.79 (s, 6H), 2.29 (dd, $J = 2.9, 2.0$ Hz, 2H), 0.82 (s, 9H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.50, 154.35 (dd, $J = 290.5, 286.8$ Hz), 137.59 (dd, $J = 5.0, 2.7$ Hz), 106.91 (t, $J = 2.9$ Hz), 98.79, 91.17 (dd, $J = 22.0, 12.5$ Hz), 55.34, 41.18, 32.74 (t, $J = 2.5$ Hz), 29.65.

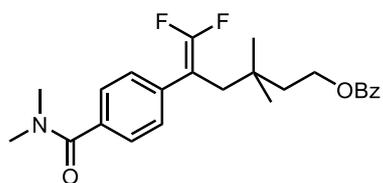
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.36 (d, $J = 40.0$ Hz, 1F), -90.94 (d, $J = 39.8$ Hz, 1F).

HRMS (ESI) calcd for C₁₅H₂₁F₂O₂⁺ [(M+H)⁺] 271.1504, found 271.1506.





5-(4-(Dimethylcarbamoyl)phenyl)-6,6-difluoro-3,3-dimethylhex-5-en-1-yl benzoate (4b).



Prepared following general procedure C using *N,N*-dimethyl-4-(3,3,3-trifluoroprop-1-en-2-yl)benzamide (**1j**) (122 mg, 0.5 mmol) and 3-bromo-3-methylbutyl benzoate (271 mg, 1.0 mmol). The residue was purified

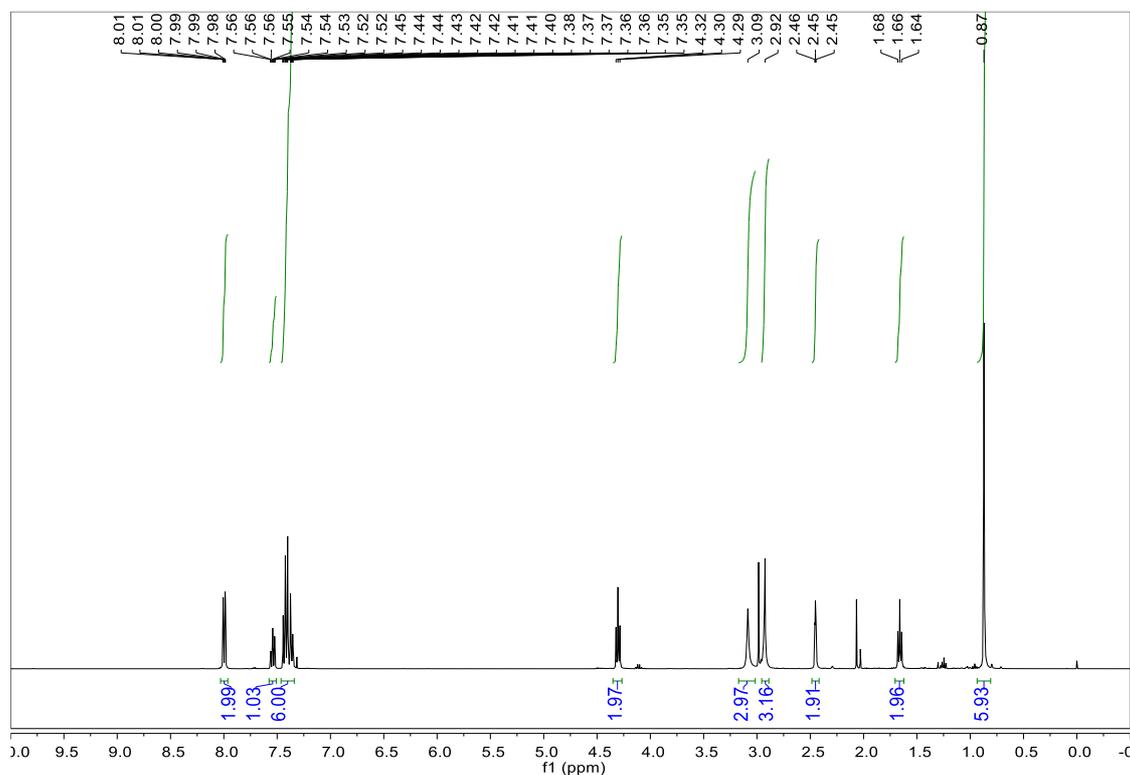
by silica gel column chromatography (40% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 94% yield (195 mg).

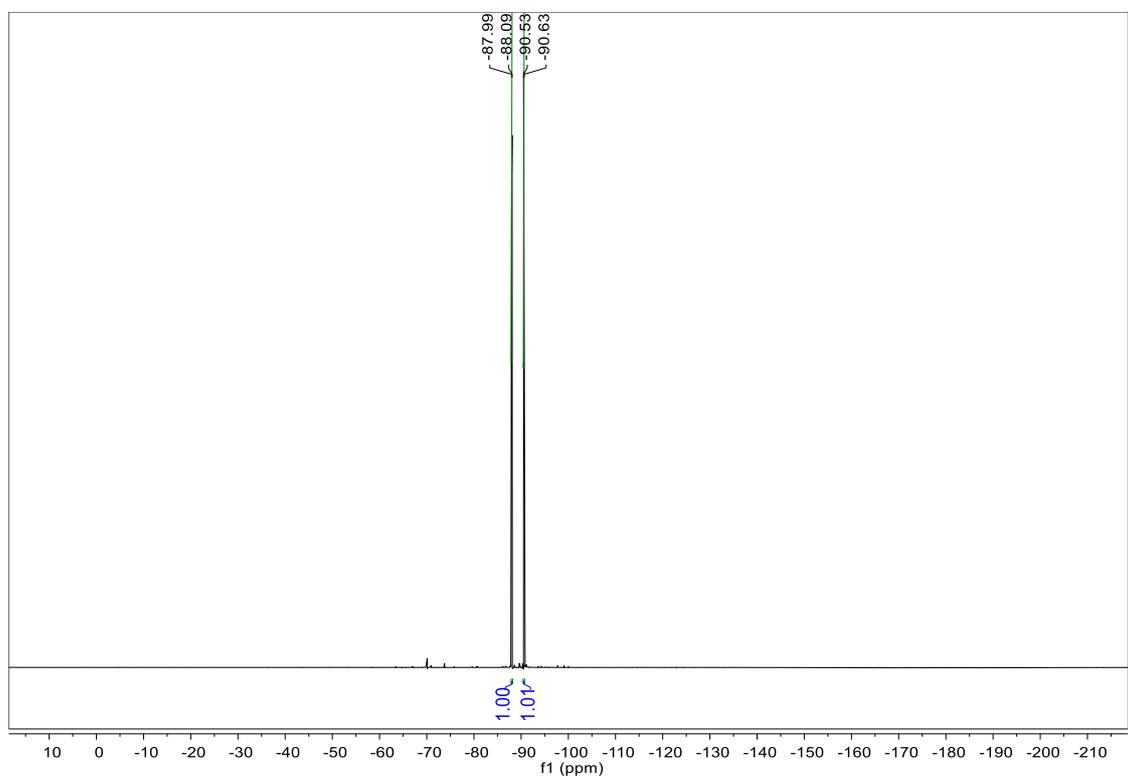
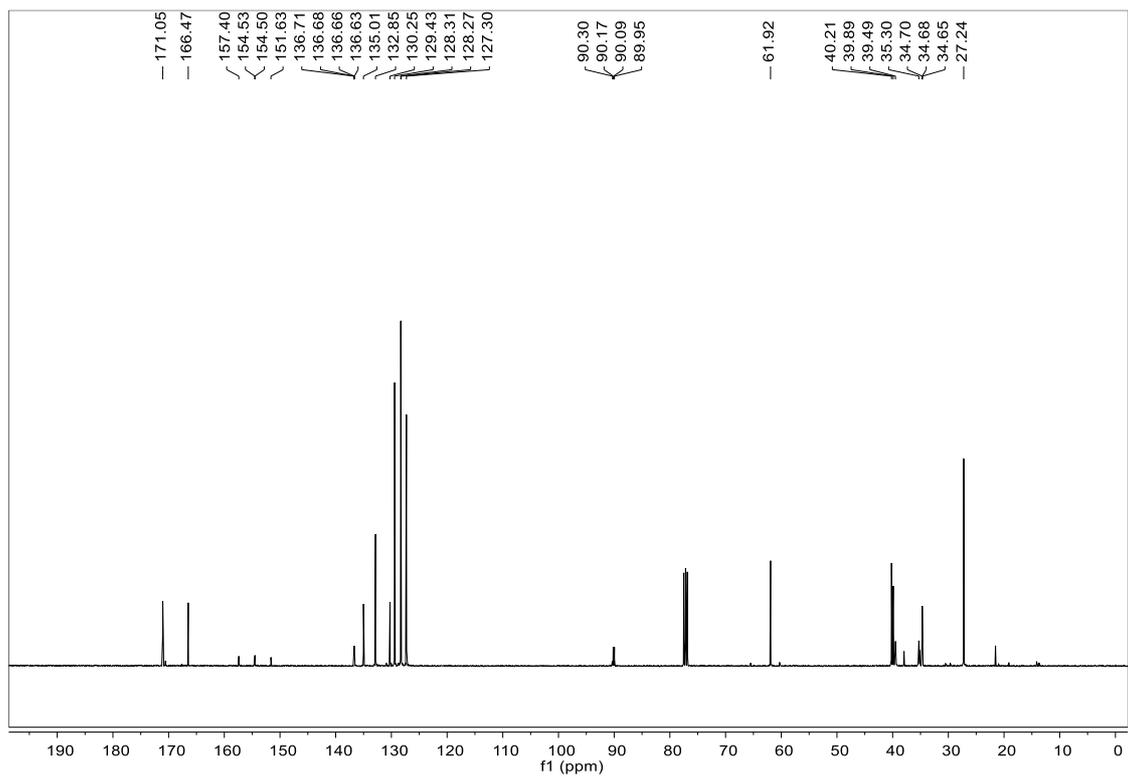
¹H NMR (400 MHz, Chloroform-*d*) δ 8.03 – 7.96 (m, 2H), 7.58 – 7.51 (m, 1H), 7.46 – 7.34 (m, 6H), 4.30 (t, *J* = 7.2 Hz, 2H), 3.09 (s, 3H), 2.92 (s, 3H), 2.45 (t, *J* = 2.4 Hz, 2H), 1.66 (t, *J* = 7.2 Hz, 2H), 0.87 (s, 6H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 171.05, 166.47, 154.51 (dd, *J* = 291.5, 288.6 Hz), 136.67 (dd, *J* = 4.8, 2.7 Hz), 135.01, 132.85, 130.25, 129.43, 128.31, 128.27, 127.30, 90.13 (dd, *J* = 21.9, 13.2 Hz), 61.92, 40.21, 39.89, 39.49, 35.30, 34.68 (t, *J* = 2.6 Hz), 27.24.

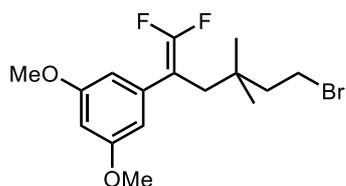
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -88.04 (d, *J* = 37.6 Hz, 1F), -90.58 (d, *J* = 37.5 Hz, 1F).

HRMS (ESI) calcd for C₂₄H₂₈F₂NO₃⁺ [(M+H)⁺] 416.2032, found 416.2038.





1-(6-Bromo-1,1-difluoro-4,4-dimethylhex-1-en-2-yl)-3,5-dimethoxybenzene (4c).



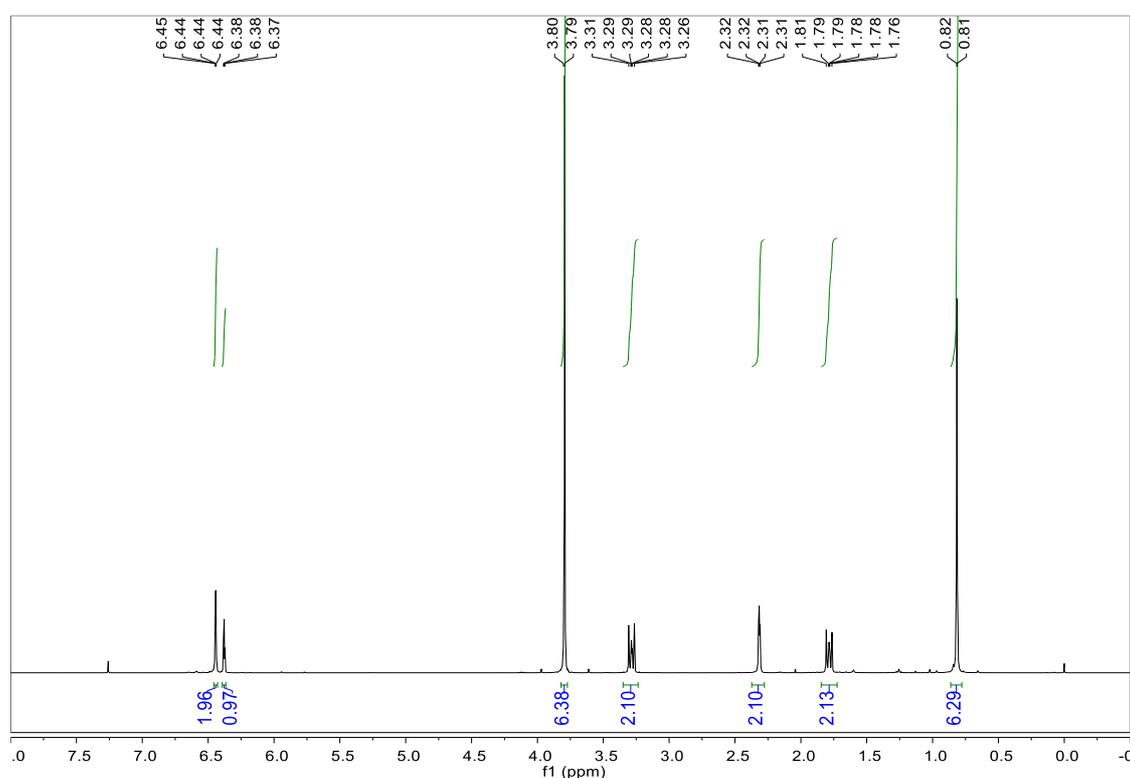
Prepared following general procedure **C** using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and 1,3-dibromo-3-methylbutane (230 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (3% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 90% yield (163 mg).

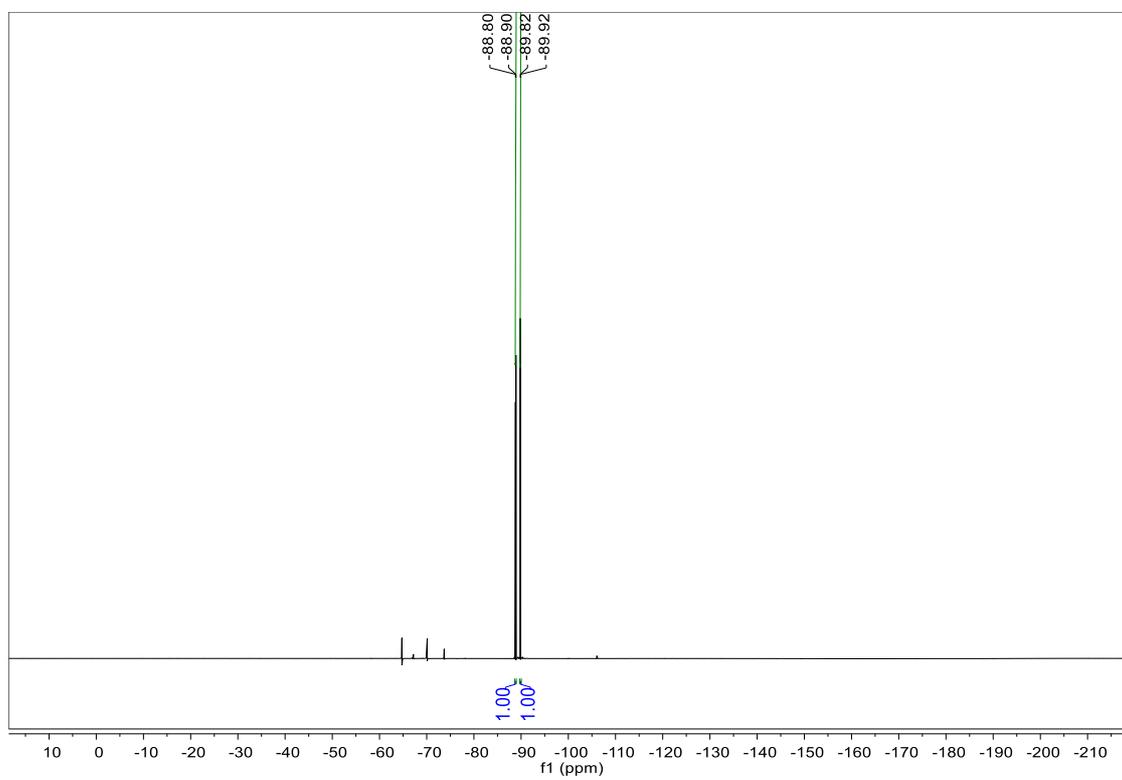
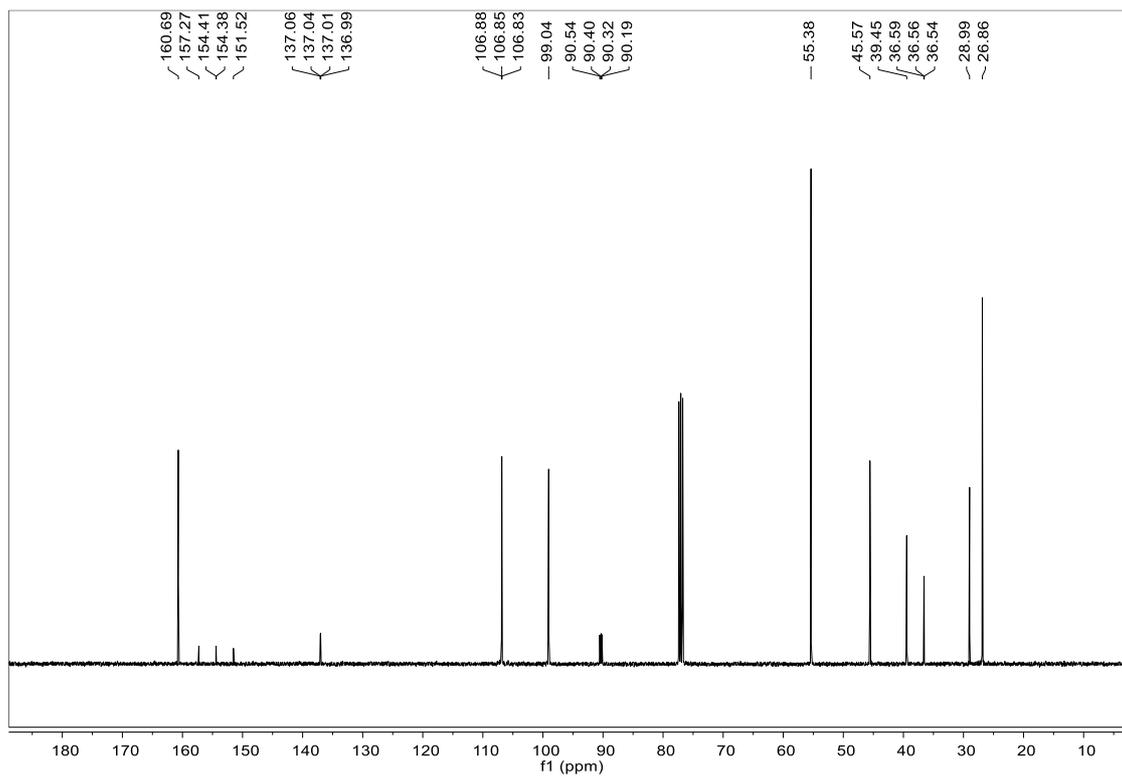
¹H NMR (400 MHz, Chloroform-*d*) δ 6.44 (dd, $J = 2.3, 1.3$ Hz, 2H), 6.38 (t, $J = 2.3$ Hz, 1H), 3.79 (s, 6H), 3.35 – 3.24 (m, 2H), 2.32 (dd, $J = 2.9, 1.9$ Hz, 2H), 1.85 – 1.72 (m, 2H), 0.86 – 0.78 (m, 6H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.69, 154.39 (dd, $J = 291.0, 287.7$ Hz), 137.02 (dd, $J = 4.8, 2.5$ Hz), 106.85 (t, $J = 2.8$ Hz), 99.04, 90.36 (dd, $J = 21.6, 13.6$ Hz), 55.38, 45.57, 39.45, 36.56 (t, $J = 2.6$ Hz), 28.99, 26.86.

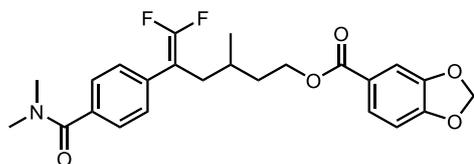
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -88.85 (d, $J = 38.7$ Hz, 1F), -89.87 (d, $J = 38.8$ Hz, 1F).

HRMS (ESI) calcd for $C_{16}H_{22}BrF_2O_2^+$ [(M+H)⁺] 363.0766, found 363.0762.





5-(4-(Dimethylcarbamoyl)phenyl)-6,6-difluoro-3-methylhex-5-en-1-yl benzo[d][1,3]dioxole-5-carboxylate (4d).



Prepared following general procedure C using *N,N*-dimethyl-4-(3,3,3-trifluoroprop-1-en-2-yl)benzamide (**1j**) (122 mg, 0.5 mmol) and 3-iodobutyl benzo[d][1,3]dioxole-5-carboxylate (348 mg, 1.0 mmol). The reaction mixture was

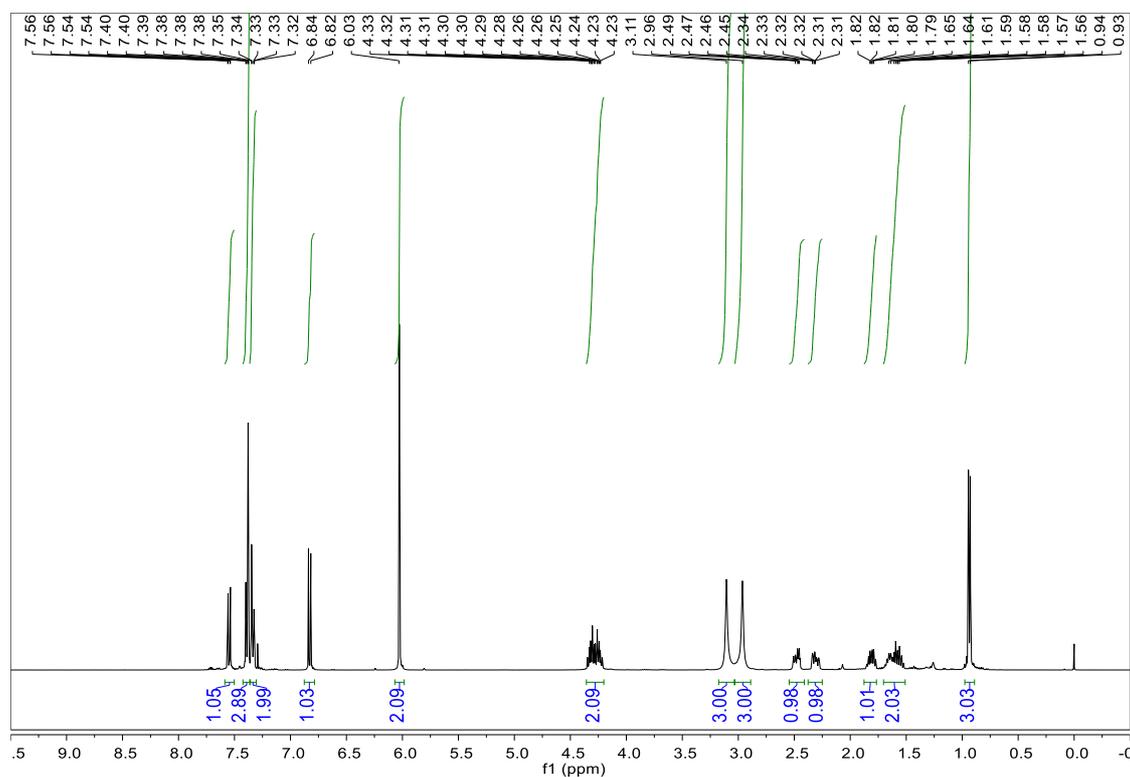
stirred at 50 °C. The residue was purified by silica gel column chromatography (50% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 70% yield (156 mg).

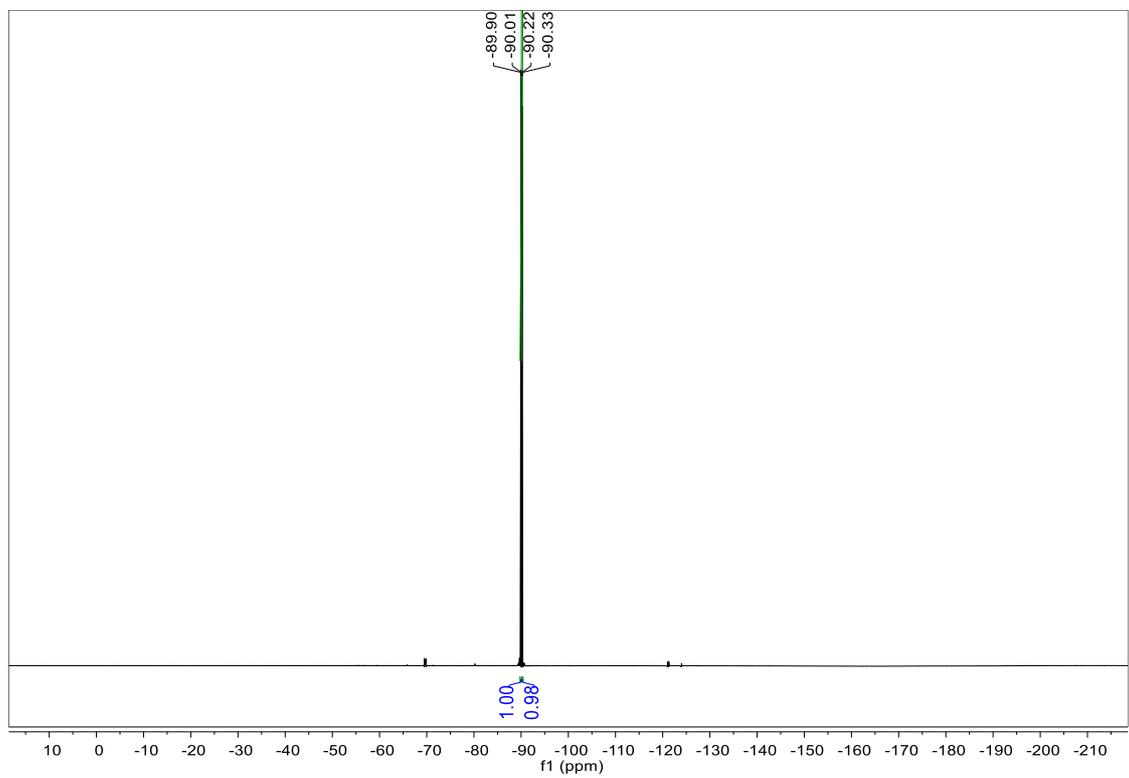
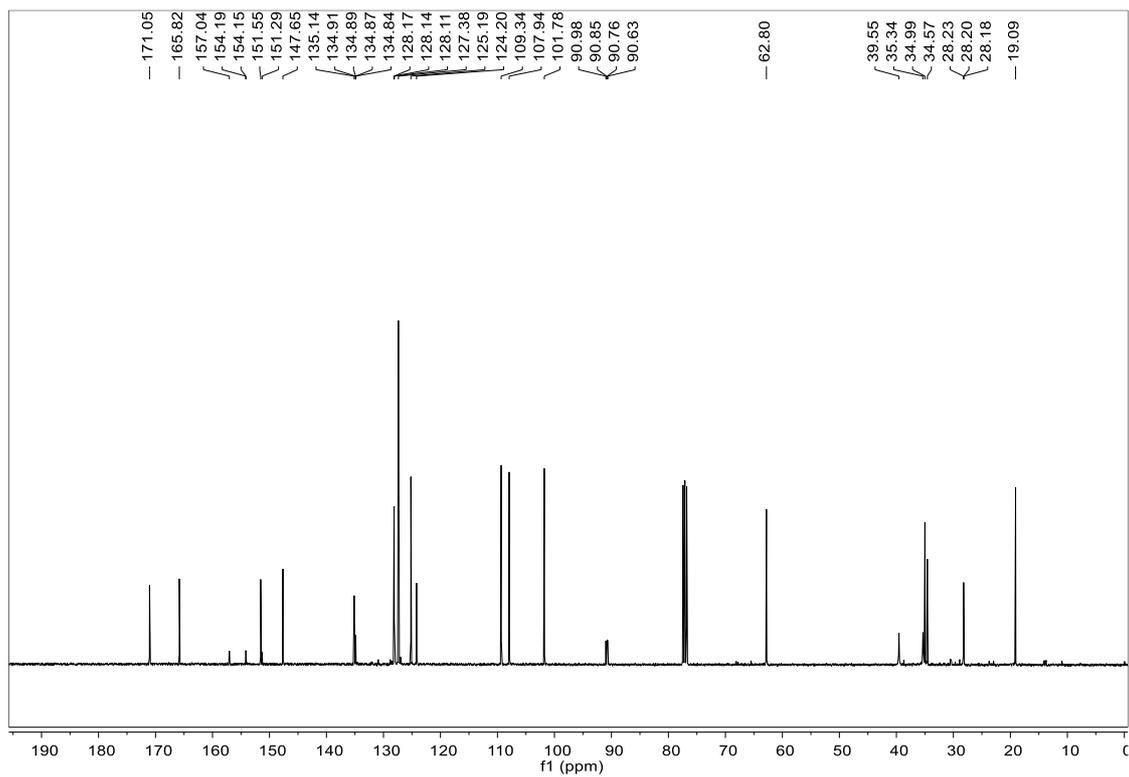
¹H NMR (400 MHz, Chloroform-*d*) δ 7.55 (dd, $J = 8.2, 1.7$ Hz, 1H), 7.42 – 7.36 (m, 3H), 7.34 (dd, $J = 8.7, 1.1$ Hz, 2H), 6.83 (d, $J = 8.2$ Hz, 1H), 6.03 (s, 2H), 4.36 – 4.20 (m, 2H), 3.11 (s, 3H), 2.96 (s, 3H), 2.53 – 2.43 (m, 1H), 2.38 – 2.25 (m, 1H), 1.87 – 1.76 (m, 1H), 1.70 – 1.51 (m, 2H), 0.94 (d, $J = 6.5$ Hz, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 171.05, 165.82, 154.17 (dd, $J = 291.4, 287.3$ Hz), 151.55, 147.65, 135.14, 134.88 (dd, $J = 4.4, 3.0$ Hz), 128.14 (t, $J = 3.2$ Hz), 127.38, 125.19, 124.20, 109.34, 107.94, 101.78, 90.80 (dd, $J = 22.0, 13.0$ Hz), 62.80, 39.55, 35.34, 34.99, 34.57, 28.20 (t, $J = 2.4$ Hz), 19.09.

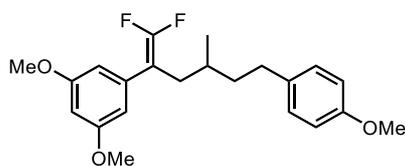
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.96 (d, $J = 40.8$ Hz, 1F), -90.28 (d, $J = 40.8$ Hz, 1F).

HRMS (ESI) calcd for C₂₄H₂₆F₂NO₅⁺ [(M+H)⁺] 446.1774, found 446.1767.





1-(1,1-Difluoro-6-(4-methoxyphenyl)-4-methylhex-1-en-2-yl)-3,5-dimethoxybenzene (4e).



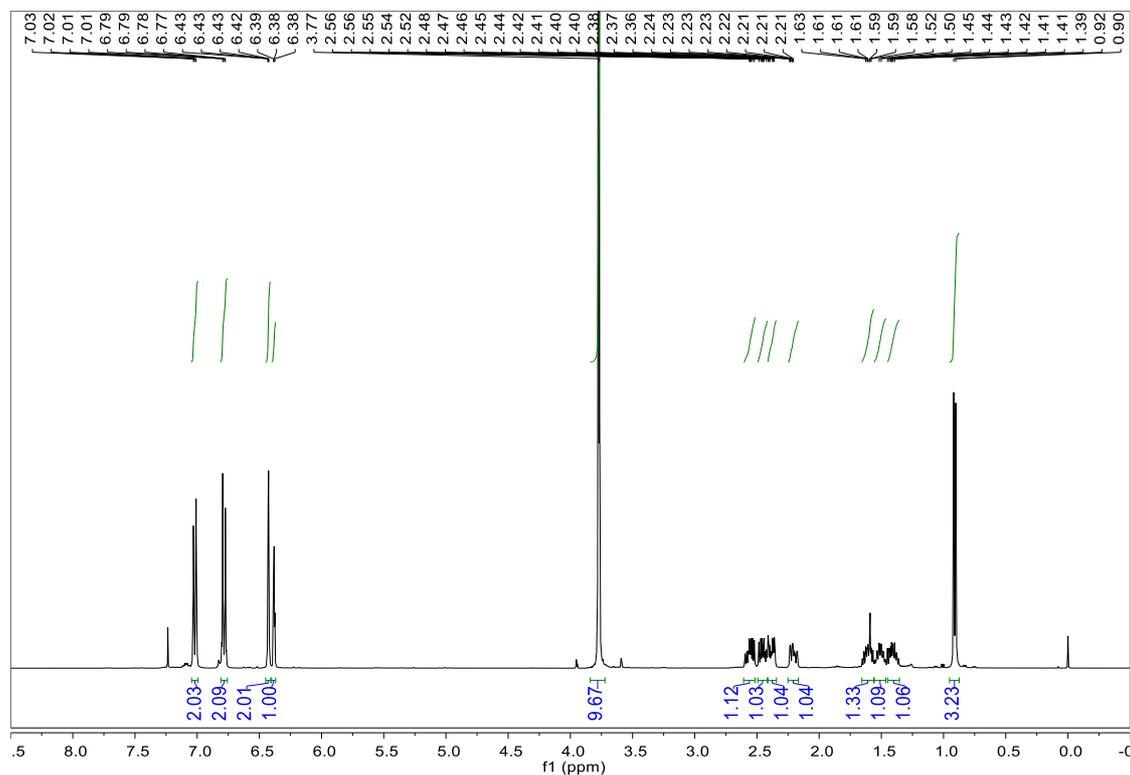
Prepared following general procedure C using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and 1-(3-iodobutyl)-4-methoxybenzene (290 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (3% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 93% yield (175 mg).

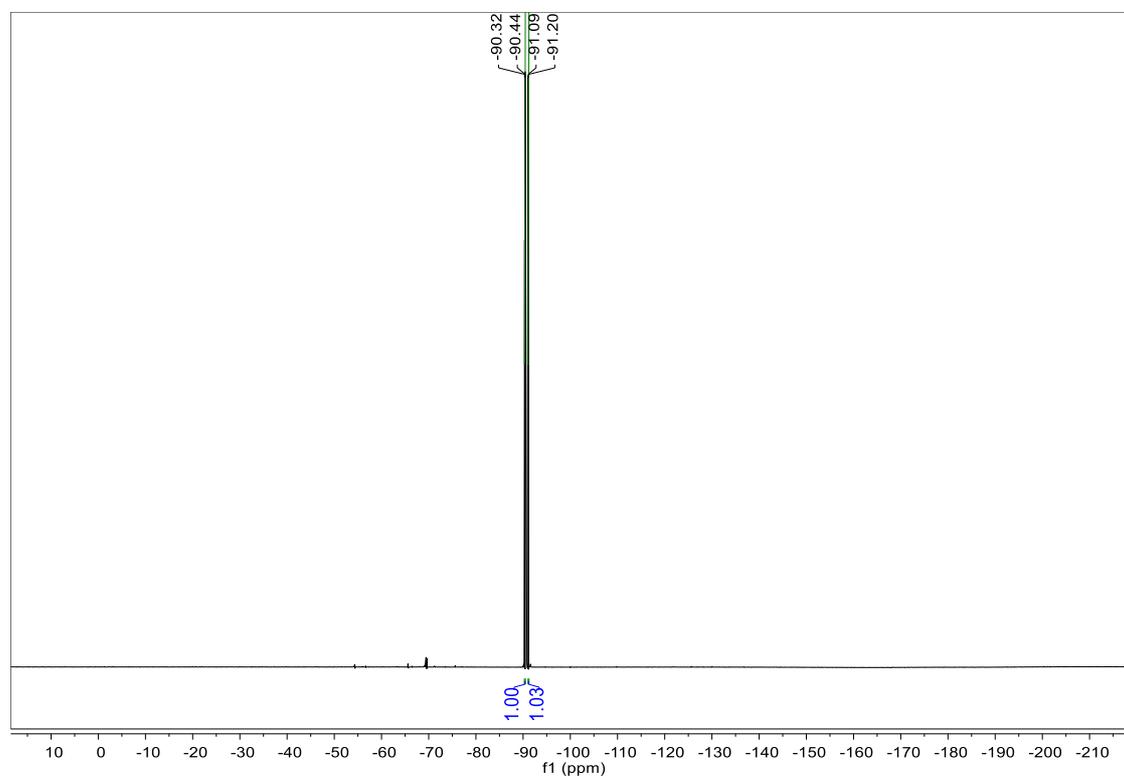
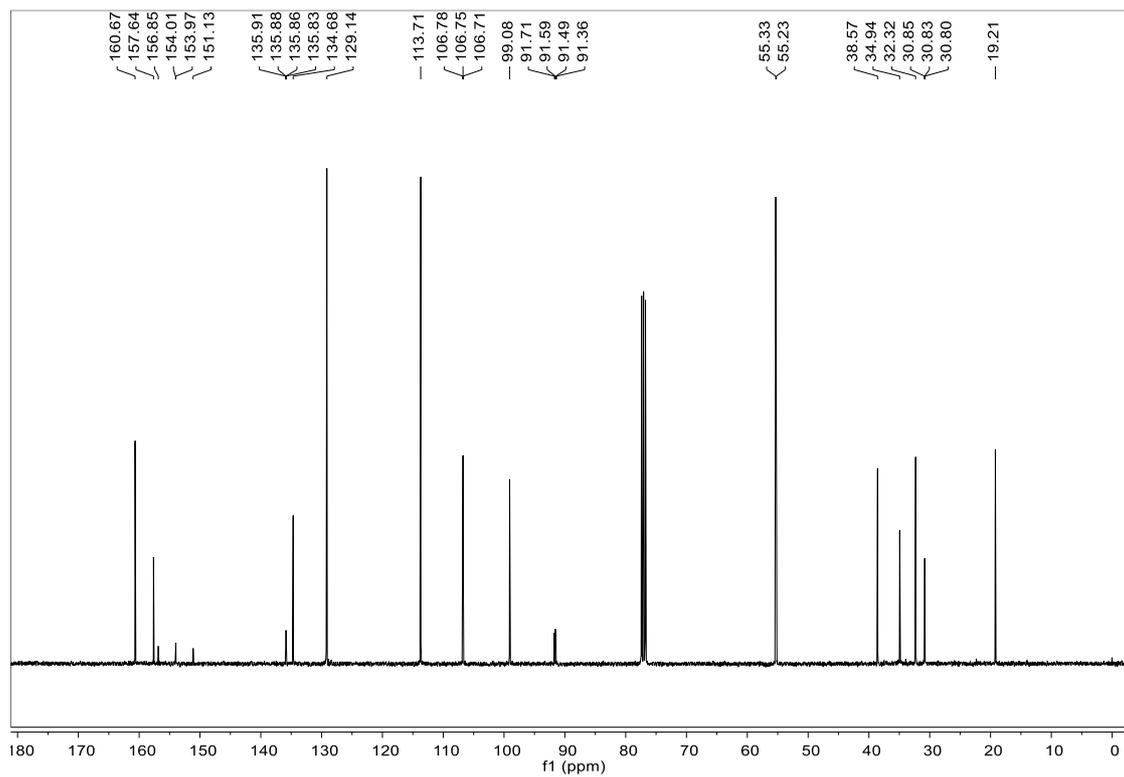
¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 (dd, $J = 7.1, 2.0$ Hz, 2H), 7.36 (ddd, $J = 7.8, 6.5, 1.8$ Hz, 2H), 7.32 – 7.27 (m, 1H), 7.24 (td, $J = 8.1, 1.9$ Hz, 1H), 6.95 – 6.85 (m, 3H), 5.03 (s, 2H), 2.27 – 2.18 (m, 2H), 1.68 – 1.54 (m, 5H), 1.29 – 1.21 (m, 1H), 1.16 – 1.03 (m, 3H), 0.95 – 0.81 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 158.82, 154.09 (t, $J = 287.9$ Hz), 136.99, 135.62 (d, $J = 1.9$ Hz), 129.40, 128.65, 128.05, 127.59, 121.12 (t, $J = 3.3$ Hz), 115.35 (t, $J = 3.3$ Hz), 113.40, 91.10 (dd, $J = 18.7, 15.9$ Hz), 70.10, 35.74 (t, $J = 2.5$ Hz), 35.31, 32.93, 26.50, 26.13.

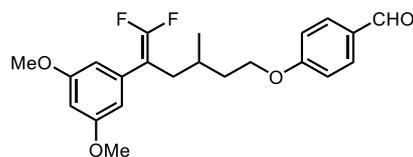
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.96 (d, $J = 2.9$ Hz), -90.97 (d, $J = 2.4$ Hz).

HRMS (ESI) calcd for C₂₂H₂₇F₂O₃⁺ [(M+H)⁺] 377.1923, found 377.1919.





4-((5-(3,5-Dimethoxyphenyl)-6,6-difluoro-3-methylhex-5-en-1-yl)oxy)benzaldehyde (4f)



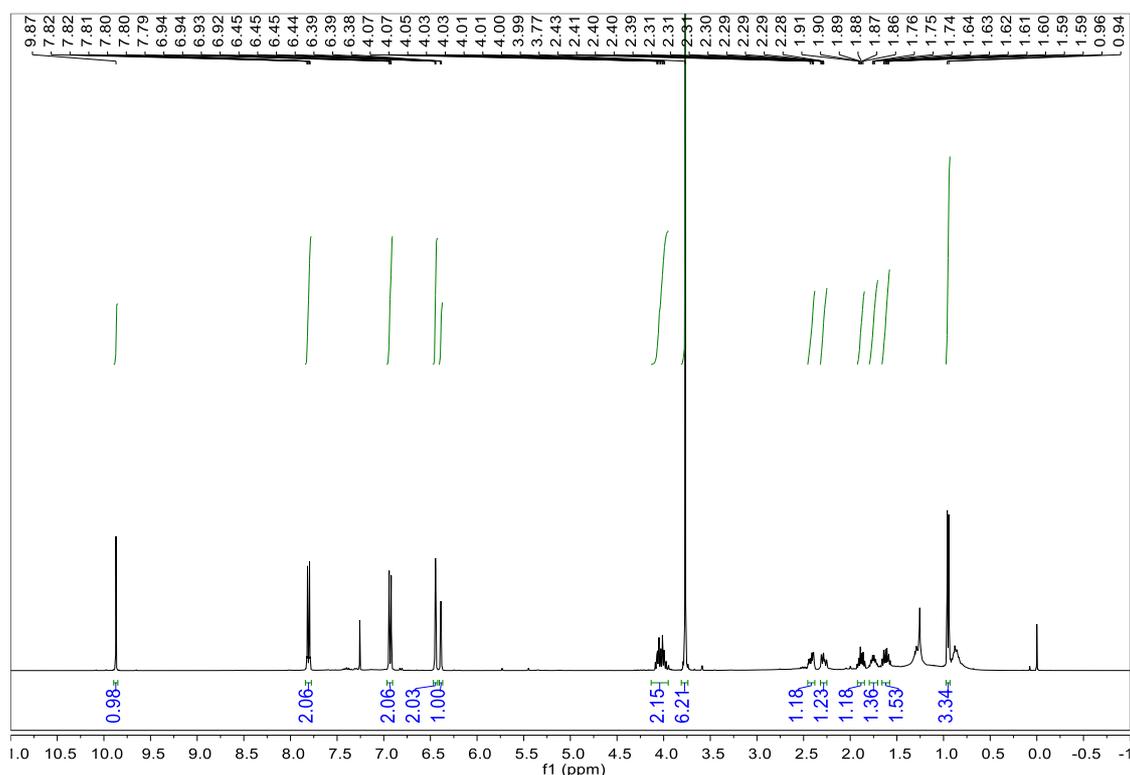
Prepared following general procedure **C** using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and 4-(3-iodobutoxy)benzaldehyde (304 mg, 1.0 mmol). The residue was purified by column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a pale yellow oil in 84% yield (164 mg).

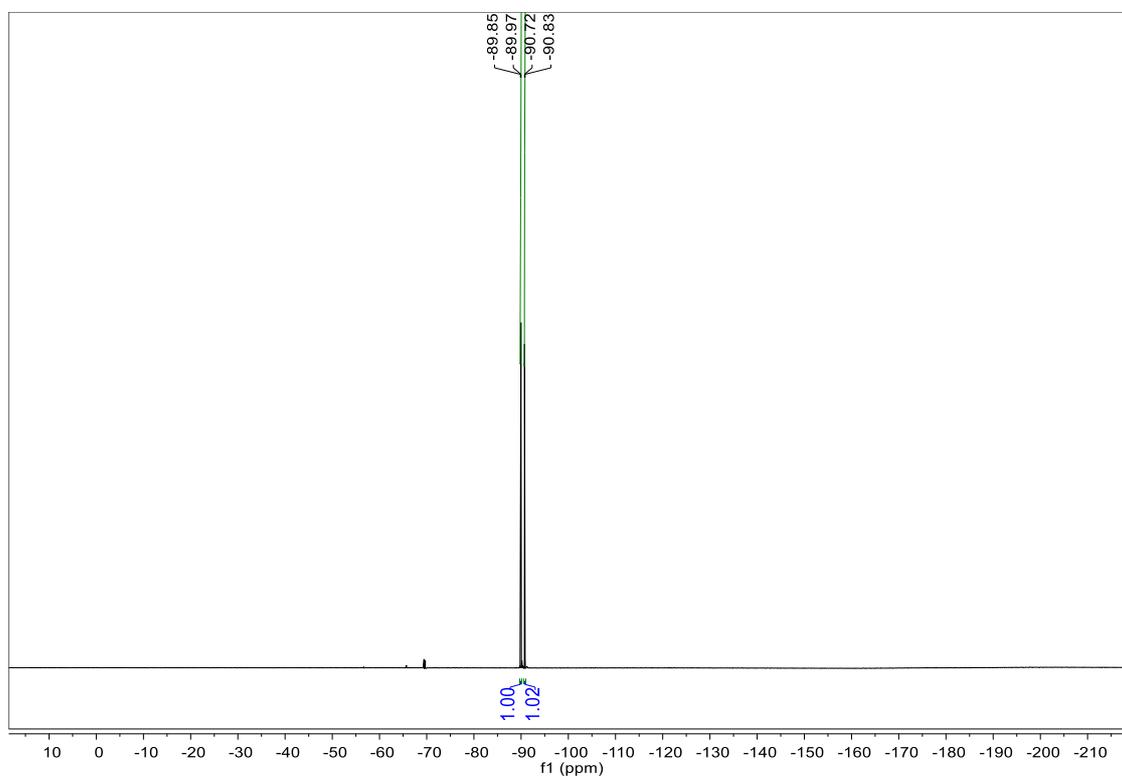
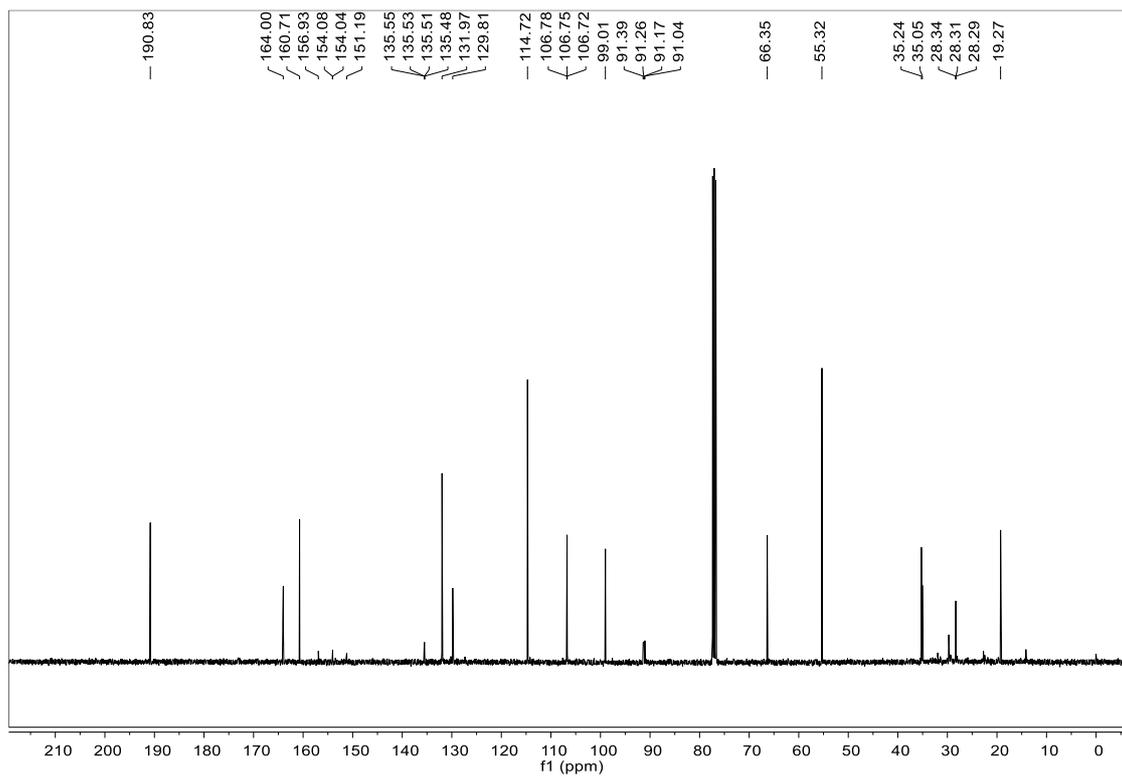
¹H NMR (400 MHz, Chloroform-*d*) δ 9.87 (s, 1H), 7.84 – 7.78 (m, 2H), 6.97 – 6.91 (m, 2H), 6.45 (dd, $J = 2.3, 1.1$ Hz, 2H), 6.39 (t, $J = 2.2$ Hz, 1H), 4.13 – 3.95 (m, 2H), 3.77 (s, 6H), 2.46 – 2.38 (m, 1H), 2.32 – 2.25 (m, 1H), 1.92 – 1.85 (m, 1H), 1.80 – 1.71 (m, 1H), 1.66 – 1.58 (m, 1H), 0.95 (d, $J = 6.6$ Hz, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 190.83, 164.00, 160.71, 154.06 (dd, $J = 290.7, 286.2$ Hz), 135.52 (dd, $J = 4.7, 2.9$ Hz), 131.97, 129.81, 114.72, 106.75 (t, $J = 3.2$ Hz), 99.01, 91.22 (dd, $J = 22.2, 13.0$ Hz), 66.35, 55.32, 35.24, 35.05, 28.31 (t, $J = 2.4$ Hz), 19.27.

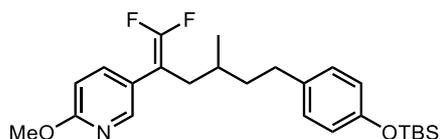
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.91 (d, $J = 42.2$ Hz, 1F), -90.78 (d, $J = 42.2$ Hz, 1F).

HRMS (ESI) calcd for $C_{22}H_{25}F_2O_4^+$ [(M+H)⁺] 391.1715, found 391.1713.





5-(6-(4-((*Tert*-butyldimethylsilyl)oxy)phenyl)-1,1-difluoro-4-methylhex-1-en-2-yl)-2-methoxypyridine (4g).



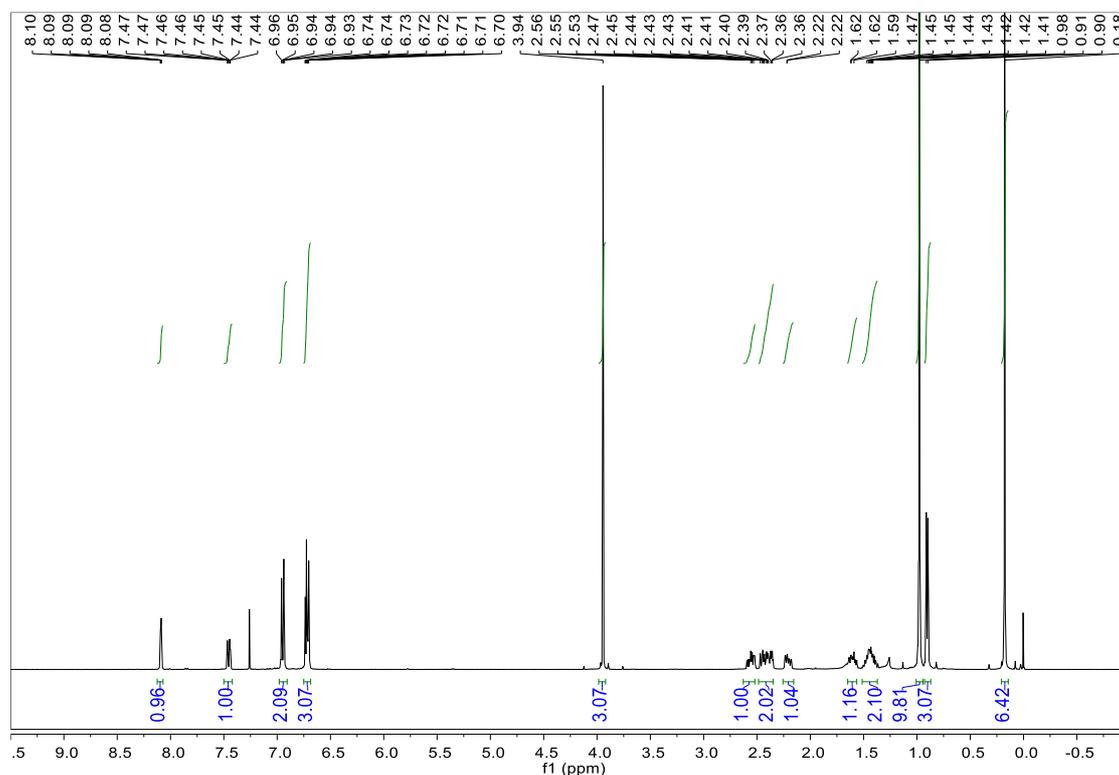
Prepared following general procedure **C** using 2-methoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyridine (**1o**) (102 mg, 0.5 mmol) and *tert*-butyl(4-(3-iodobutyl)phenoxy)dimethylsilane (390 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to provide the title compound as a pale yellow oil in 74% yield (166 mg).

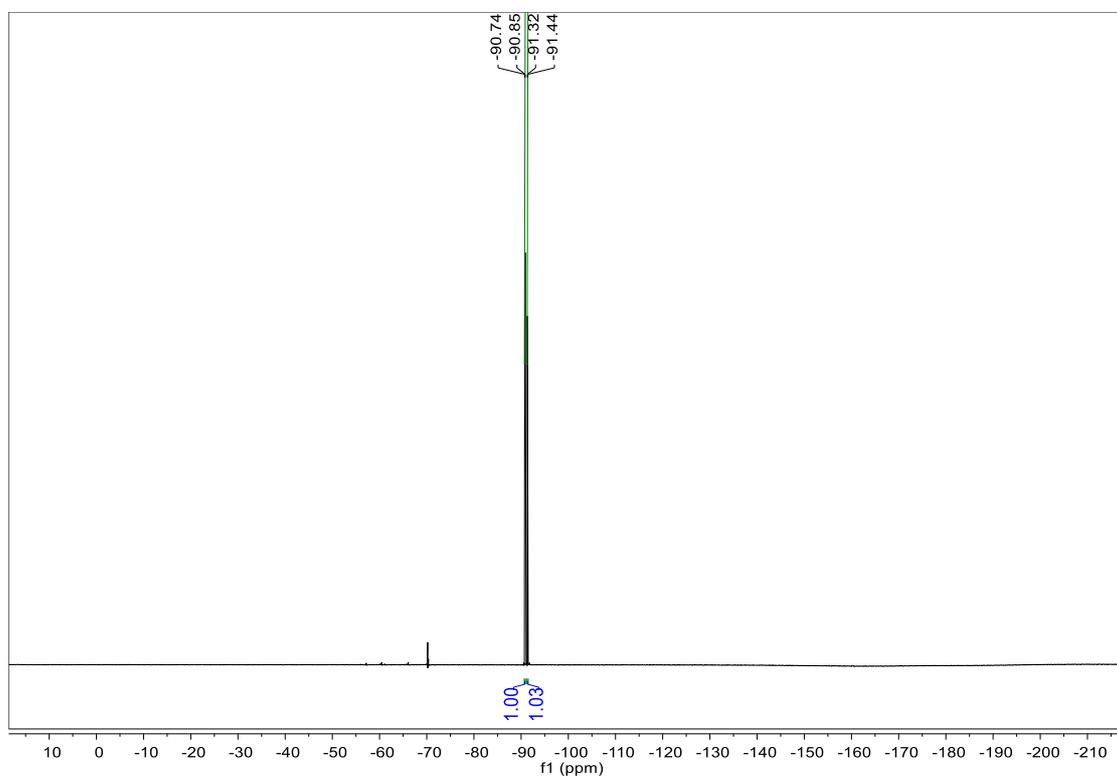
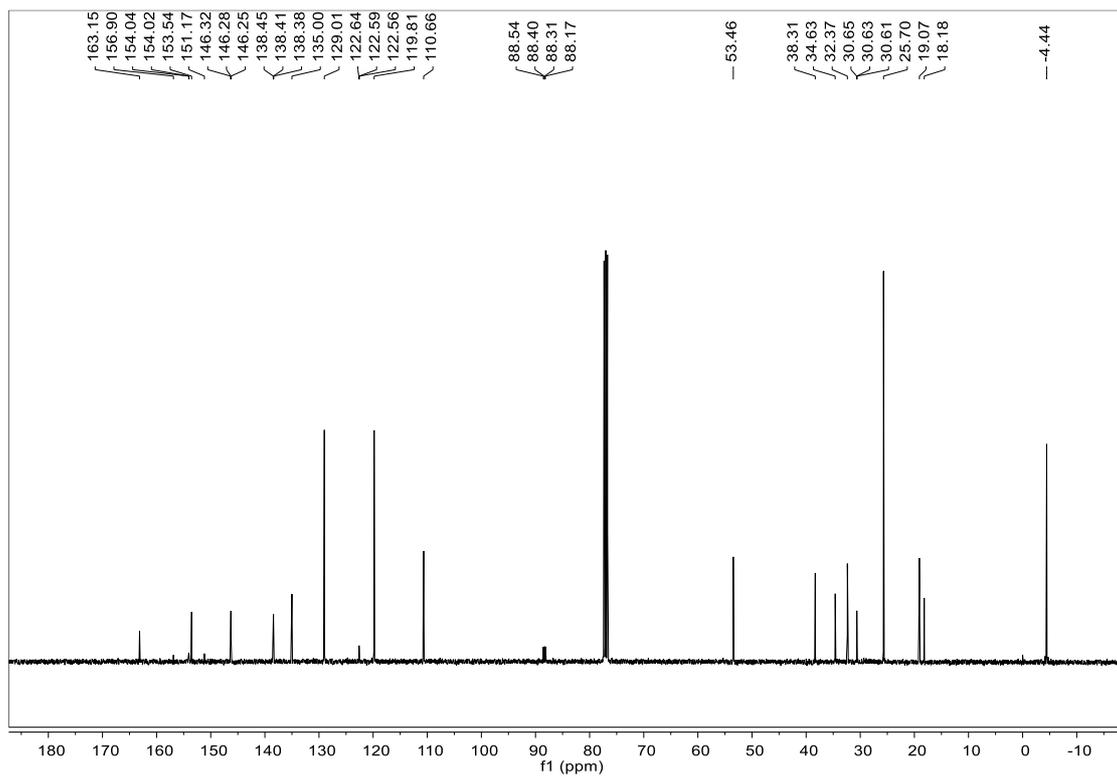
¹H NMR (400 MHz, Chloroform-*d*) δ 8.09 (dt, $J = 2.1, 1.0$ Hz, 1H), 7.45 (ddd, $J = 8.6, 2.5, 1.0$ Hz, 1H), 6.98 – 6.91 (m, 2H), 6.75 – 6.69 (m, 3H), 3.94 (s, 3H), 2.62 – 2.51 (m, 1H), 2.48 – 2.35 (m, 2H), 2.26 – 2.16 (m, 1H), 1.65 – 1.56 (m, 1H), 1.51 – 1.37 (m, 2H), 0.98 (s, 9H), 0.90 (d, $J = 6.3$ Hz, 3H), 0.18 (s, 6H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 163.15, 138.41 (dd, $J = 290.1, 286.9$ Hz), 153.54, 146.28 (t, $J = 3.5$ Hz), 138.41 (t, $J = 3.2$ Hz), 135.00, 129.01, 122.59 (dd, $J = 4.5, 3.2$ Hz), 119.81, 110.66, 88.36 (dd, $J = 23.3, 13.3$ Hz), 53.46, 38.31, 34.63, 32.37, 30.63 (t, $J = 2.4$ Hz), 25.70, 19.07, 18.18, -4.44.

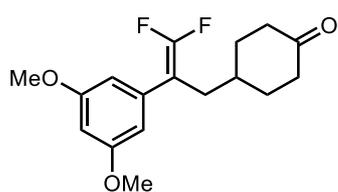
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.80 (d, $J = 43.8$ Hz, 1F), -91.38 (d, $J = 43.8$ Hz, 1F).

HRMS (ESI) calcd for C₂₅H₃₆F₂NO₂Si⁺ [(M+H)⁺] 448.2478, found 448.2483.





4-(2-(3,5-Dimethoxyphenyl)-3,3-difluoroallyl)cyclohexan-1-one (4h).



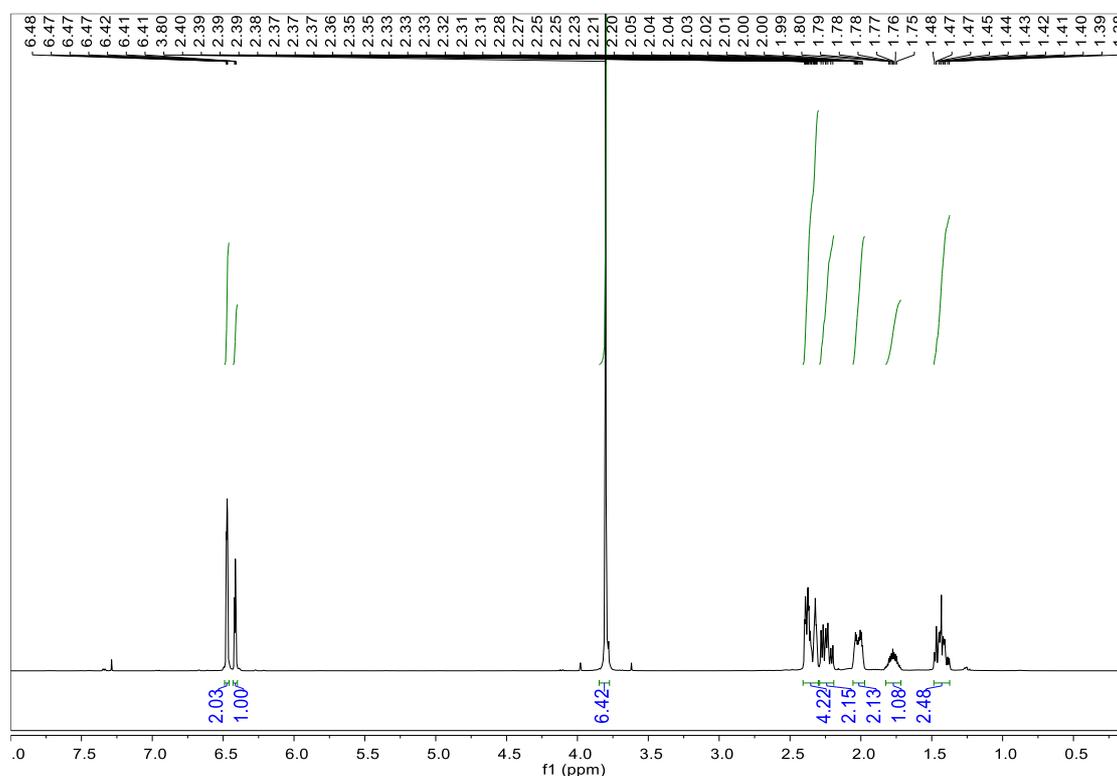
Prepared following general procedure **C** using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and 4-iodocyclohexan-1-one (224 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 76% yield (118 mg).

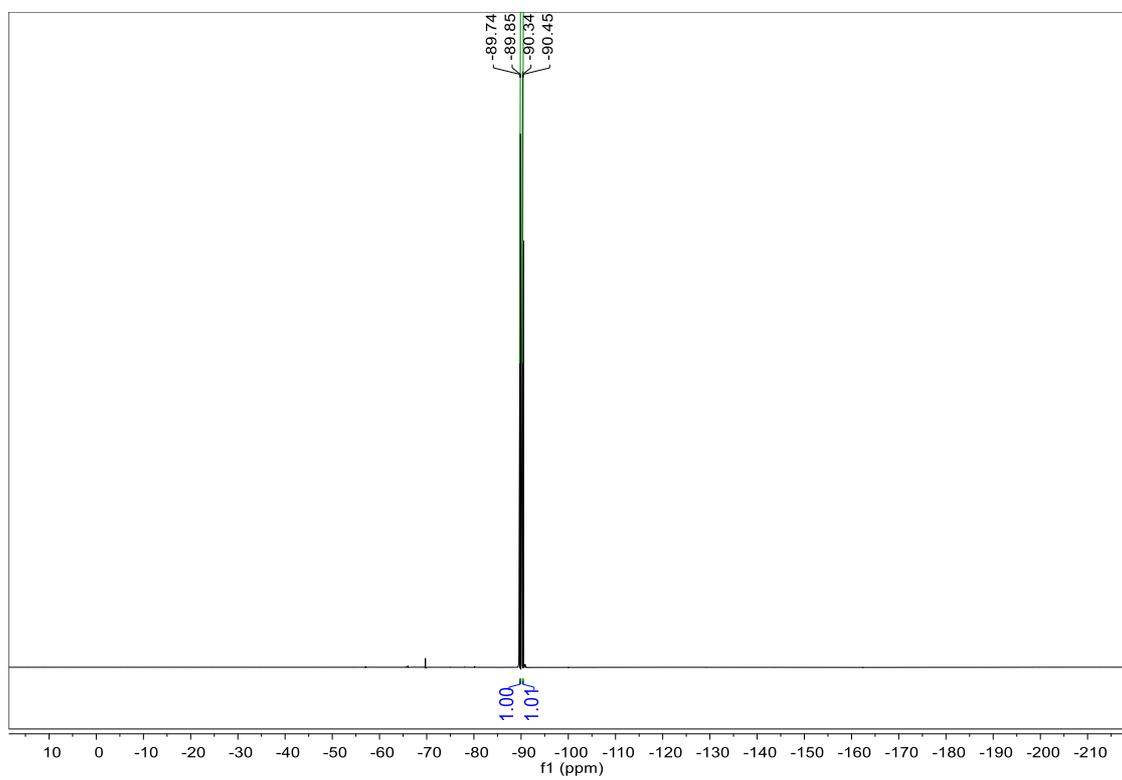
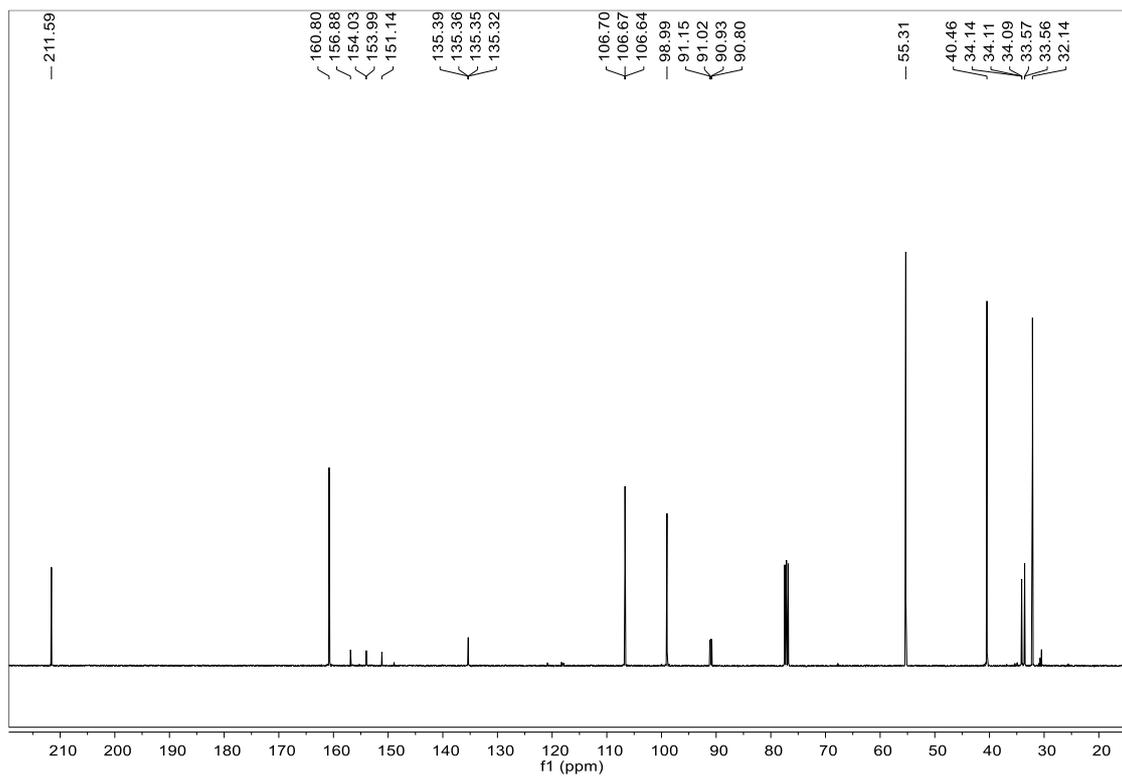
¹H NMR (400 MHz, Chloroform-*d*) δ 6.47 (dd, $J = 2.3, 1.2$ Hz, 2H), 6.41 (t, $J = 2.3$ Hz, 1H), 3.80 (s, 6H), 2.41 – 2.30 (m, 4H), 2.29 – 2.19 (m, 2H), 2.06 – 1.97 (m, 2H), 1.82 – 1.72 (m, 1H), 1.49 – 1.37 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 211.59, 160.80, 154.01 (dd, $J = 291.3, 286.5$ Hz), 135.36 (dd, $J = 4.7, 3.0$ Hz), 106.67 (t, $J = 3.2$ Hz), 98.99, 90.97 (dd, $J = 22.1, 13.2$ Hz), 55.31, 40.46, 34.11 (t, $J = 2.5$ Hz), 33.57, 33.56, 32.14.

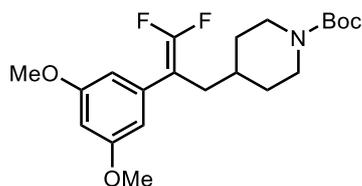
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.80 (d, $J = 41.6$ Hz, 1F), -90.39 (d, $J = 41.6$ Hz, 1F).

HRMS (ESI) calcd for $C_{17}H_{21}F_2O_3^+$ [(M+H)⁺] 311.1453, found 311.1459.





***Tert*-butyl 4-(2-(3,5-dimethoxyphenyl)-3,3-difluoroallyl)piperidine-1-carboxylate (4i).**



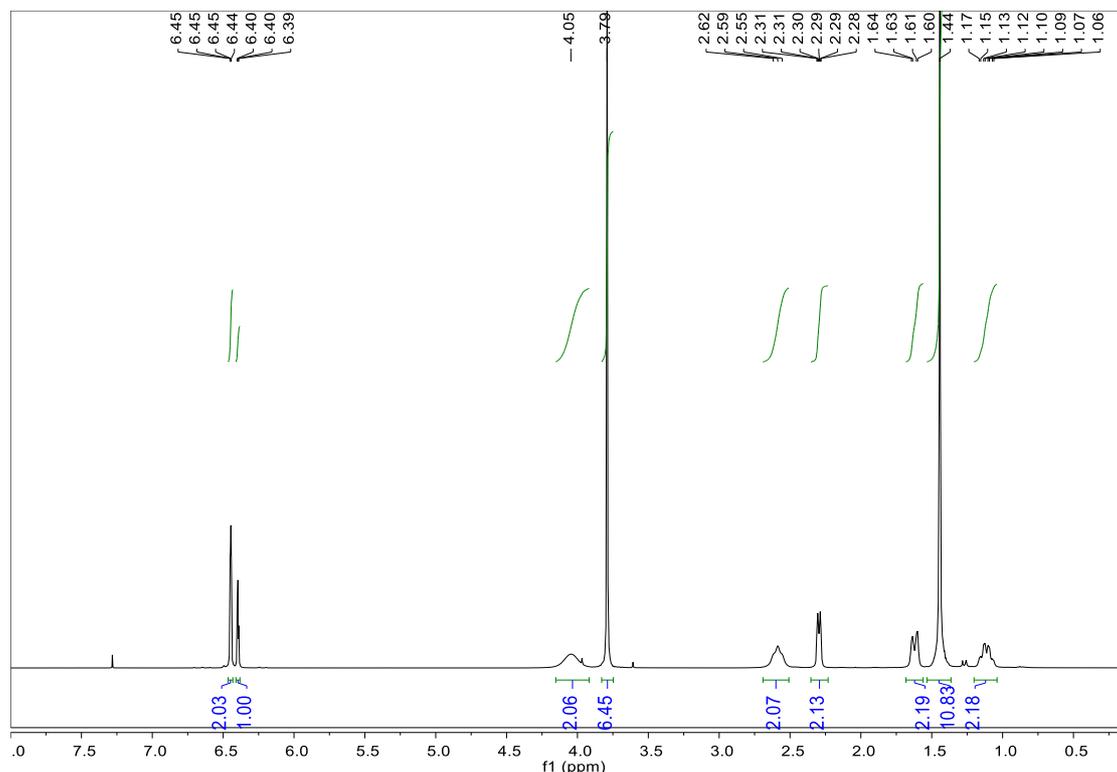
Prepared following general procedure **C** using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and *tert*-butyl 4-iodopiperidine-1-carboxylate (311 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 93% yield (185 mg).

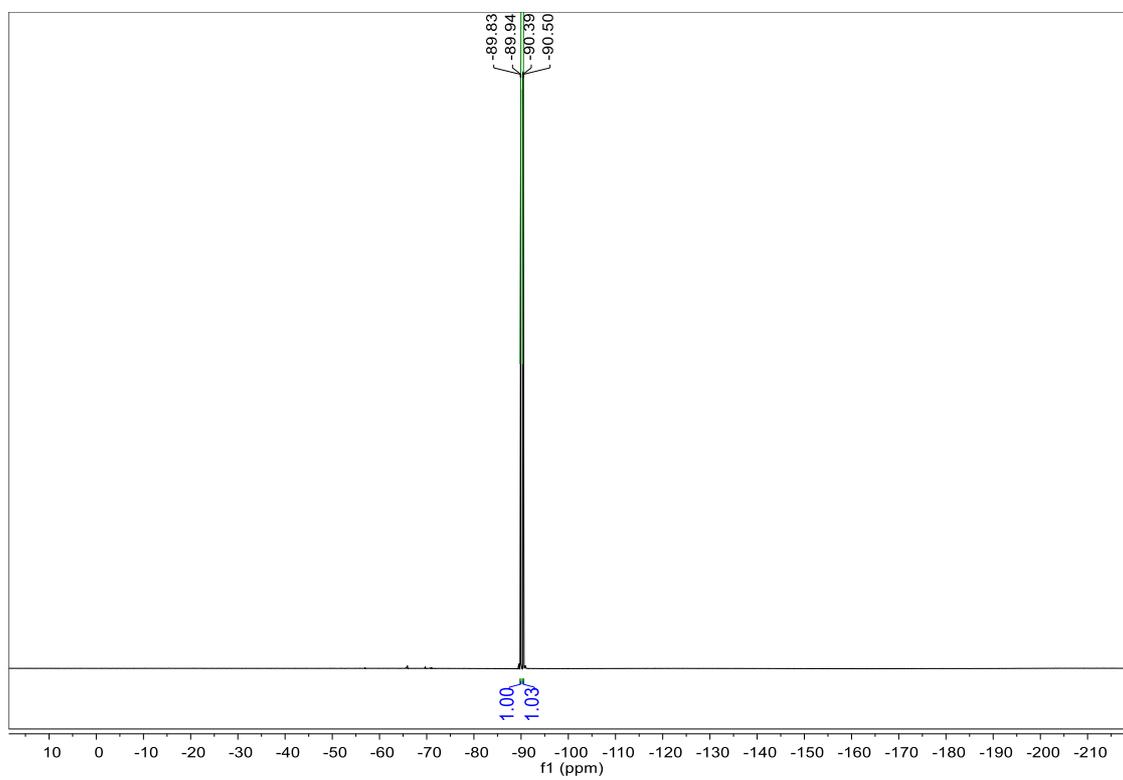
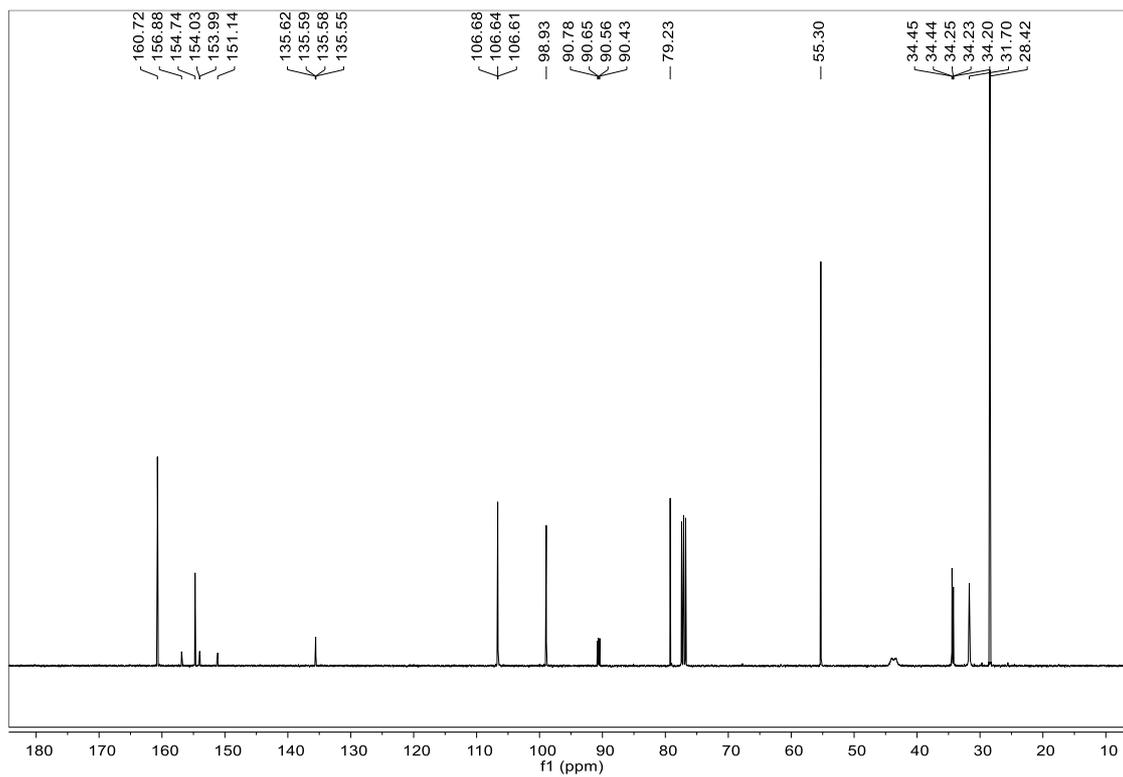
¹H NMR (400 MHz, Chloroform-*d*) δ 6.45 (dd, $J = 2.3, 1.1$ Hz, 2H), 6.40 (t, $J = 2.3$ Hz, 1H), 4.17 – 3.92 (m, 2H), 3.79 (s, 6H), 2.69 – 2.50 (m, 2H), 2.30 (dt, $J = 7.7, 2.3$ Hz, 2H), 1.68 – 1.56 (m, 2H), 1.44 (s, 10H), 1.11 (qd, $J = 12.5, 4.3$ Hz, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.72, 154.74, 154.01 (dd, $J = 291.2, 286.5$ Hz), 135.59 (dd, $J = 4.7, 3.0$ Hz), 106.64 (t, $J = 3.2$ Hz), 98.93, 90.61 (dd, $J = 22.2, 12.9$ Hz), 79.23, 55.30, 34.45, 34.44, 34.23 (t, $J = 2.4$ Hz), 31.70, 28.42.

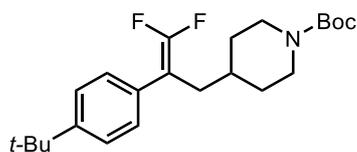
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.89 (d, $J = 41.8$ Hz, 1F), -90.45 (d, $J = 41.9$ Hz, 1F).

HRMS (ESI) calcd for C₂₁H₂₉F₂NO₄Na⁺ [(M+Na)⁺] 420.1957, found 420.1957.





***Tert*-butyl 4-(2-(4-(*tert*-butyl)phenyl)-3,3-difluoroallyl)piperidine-1-carboxylate (4j).**



Prepared following general procedure **C** using 1-(*tert*-butyl)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1r**) (114 mg, 0.5 mmol) and *tert*-butyl 4-iodopiperidine-1-carboxylate (311 mg, 1.0 mmol). The residue was purified

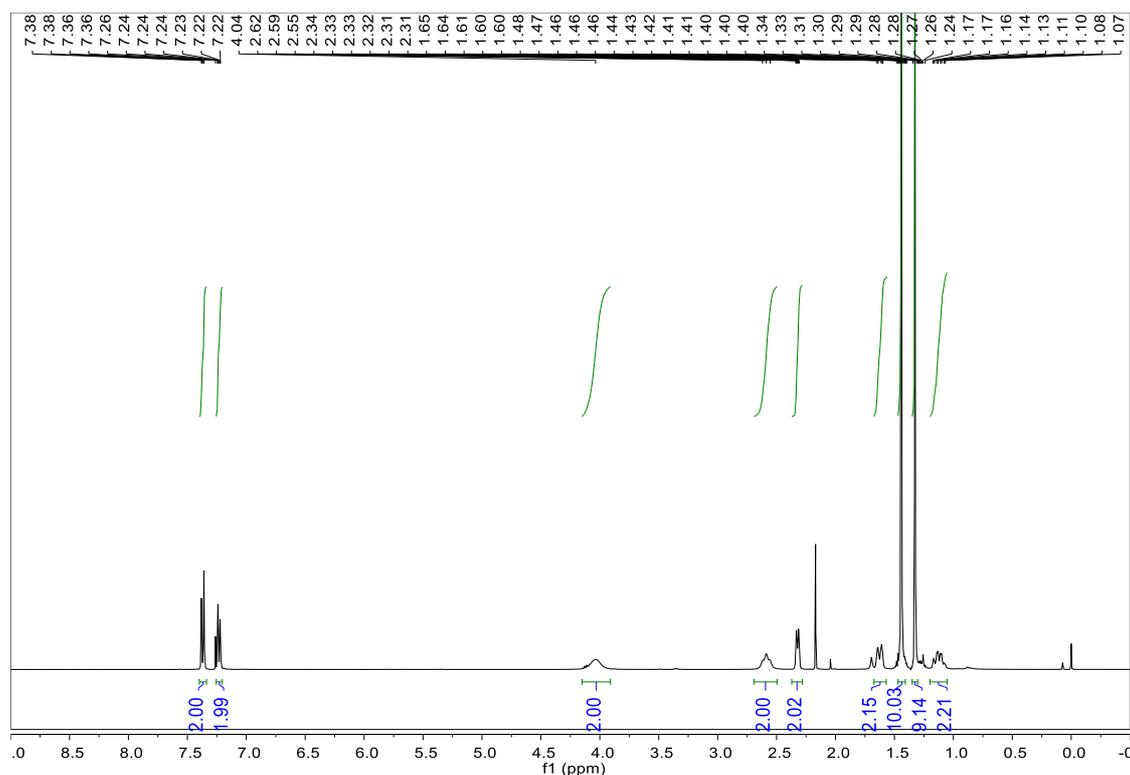
by silica gel column chromatography (5% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 87% yield (171 mg).

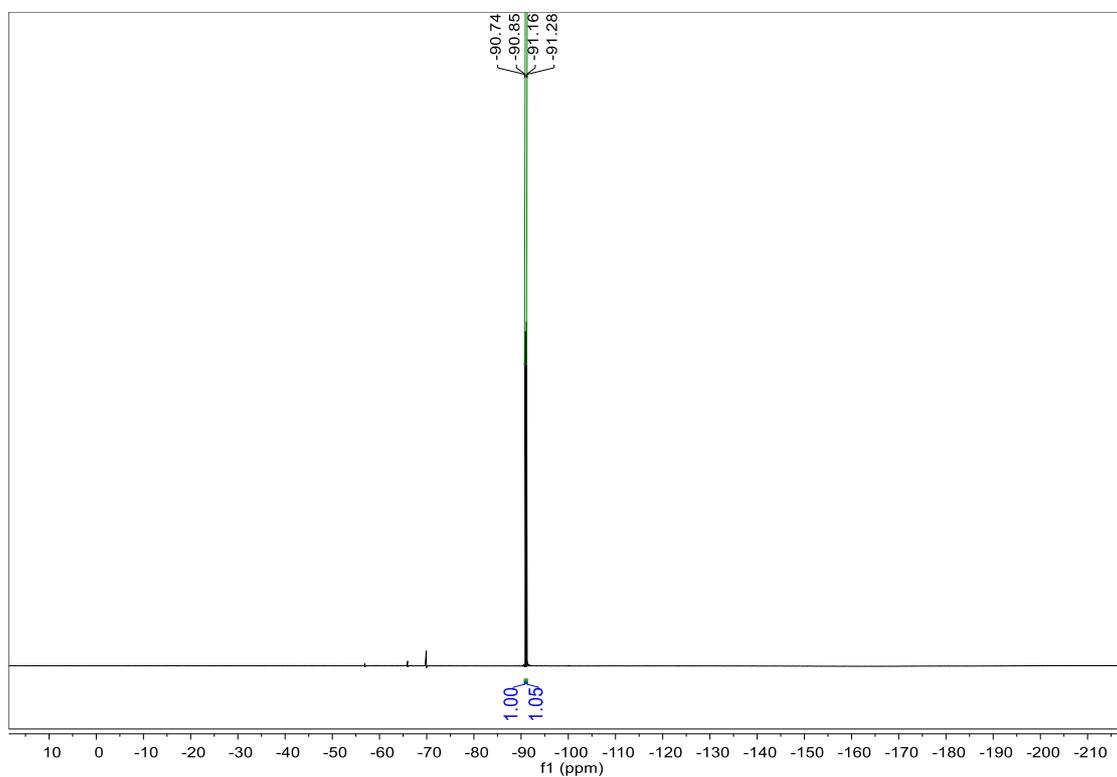
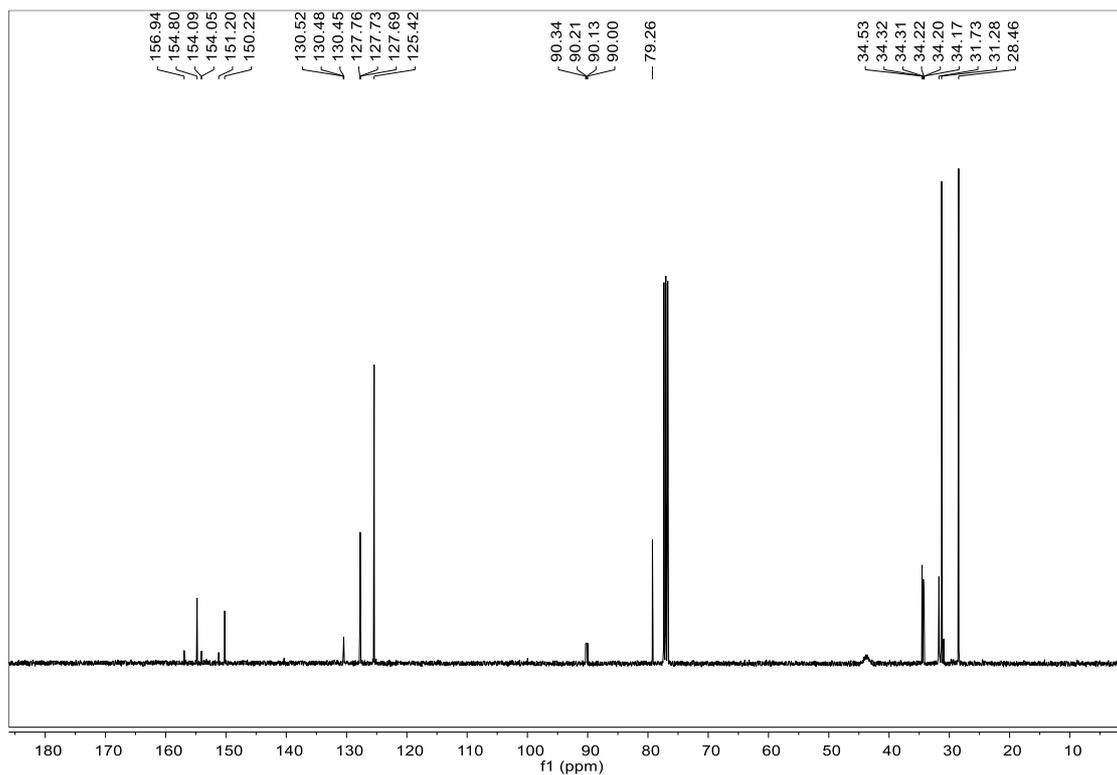
¹H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.34 (m, 2H), 7.26 – 7.20 (m, 2H), 4.15 – 3.91 (m, 2H), 2.59 (t, $J = 13.1$ Hz, 2H), 2.32 (dt, $J = 7.3, 2.4$ Hz, 2H), 1.67 – 1.57 (m, 2H), 1.44 (s, 10H), 1.33 (s, 9H), 1.20 – 1.05 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 154.80, 154.07 (dd, $J = 290.8, 286.2$ Hz), 150.22, 130.48 (t, $J = 3.7$ Hz), 127.73 (t, $J = 3.3$ Hz), 125.42, 90.17 (dd, $J = 21.6, 13.1$ Hz), 79.26, 34.53, 34.32, 34.31, 34.20 (t, $J = 2.5$ Hz), 31.73, 31.28, 28.46.

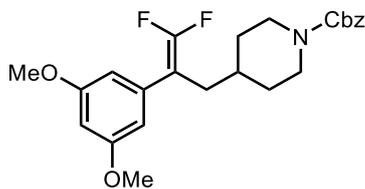
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.80 (d, $J = 43.6$ Hz, 1F), -91.22 (d, $J = 43.6$ Hz, 1F).

HRMS (ESI) calcd for C₂₃H₃₃F₂NO₂Na⁺ [(M+Na)⁺] 416.2372, found 416.2375.





Benzyl 4-(2-(3,5-dimethoxyphenyl)-3,3-difluoroallyl)piperidine-1-carboxylate (4k).



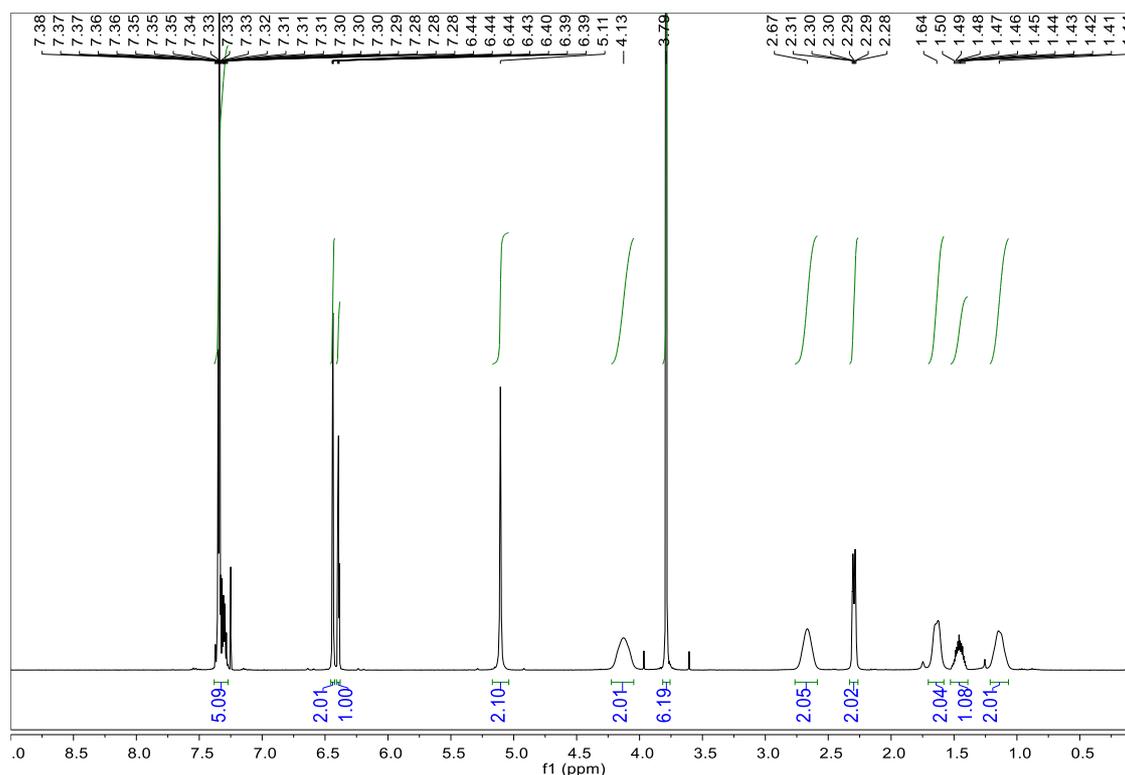
Prepared following general procedure **C** using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and benzyl 4-iodopiperidine-1-carboxylate (345 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 88% yield (190 mg).

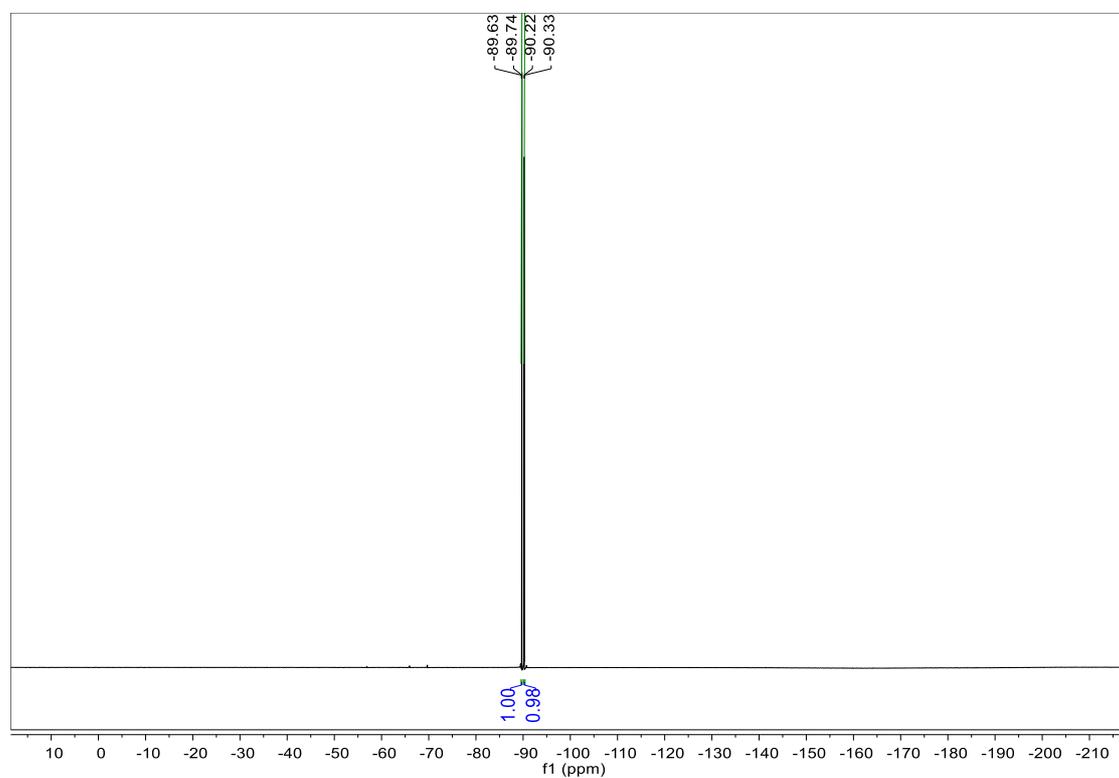
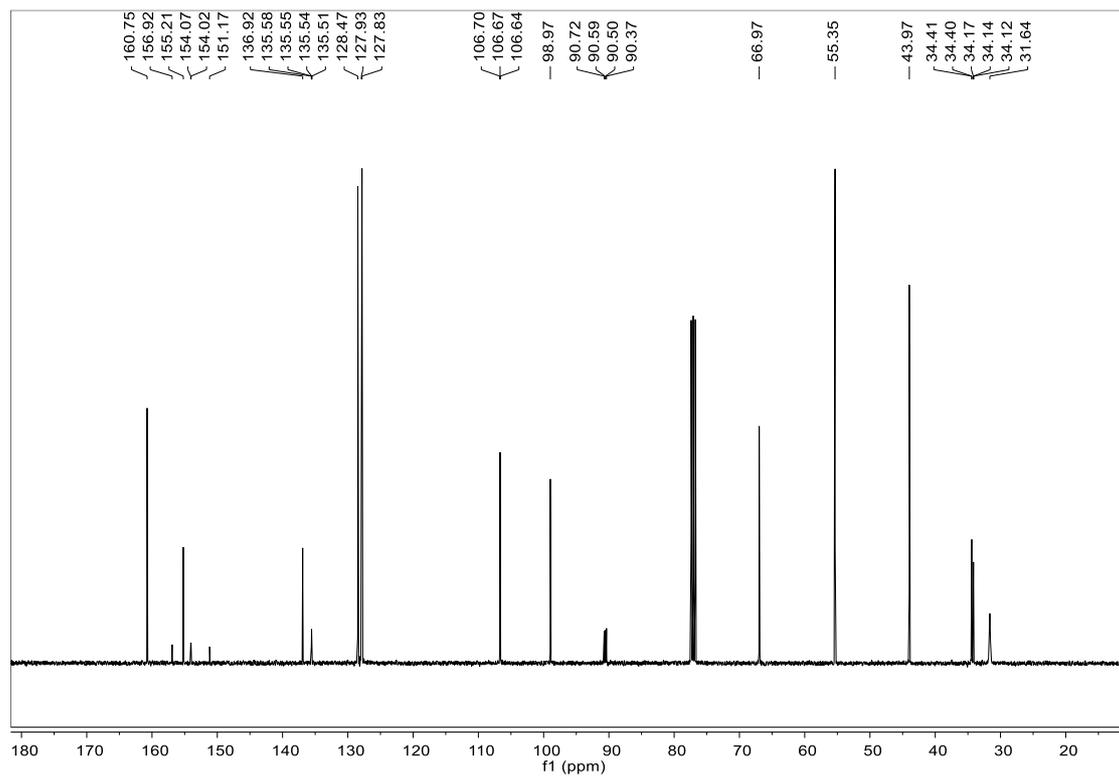
¹H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.27 (m, 5H), 6.44 (dd, $J = 2.3, 1.1$ Hz, 2H), 6.39 (t, $J = 2.2$ Hz, 1H), 5.11 (s, 2H), 4.22 – 4.04 (m, 2H), 3.79 (s, 6H), 2.76 – 2.59 (m, 2H), 2.29 (dt, $J = 7.3, 2.4$ Hz, 2H), 1.70 – 1.58 (m, 2H), 1.53 – 1.39 (m, 1H), 1.22 – 1.07 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.75, 155.21, 154.04 (dd, $J = 291.3, 286.6$ Hz), 136.92, 135.54 (dd, $J = 4.7, 3.0$ Hz), 128.47, 127.93, 127.83, 106.67 (t, $J = 3.2$ Hz), 98.97, 90.54 (dd, $J = 22.2, 13.0$ Hz), 66.97, 55.35, 43.97, 34.41, 34.40, 34.14 (t, $J = 2.5$ Hz), 31.64.

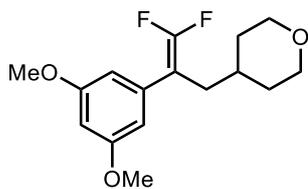
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.69 (d, $J = 41.5$ Hz, 1F), -90.27 (d, $J = 41.5$ Hz, 1F).

HRMS (ESI) calcd for $C_{24}H_{27}F_2NO_4Na^+$ [(M+Na)⁺] 454.1800, found 454.1796.





4-(2-(3,5-Dimethoxyphenyl)-3,3-difluoroallyl)tetrahydro-2H-pyran (4l).



Prepared following general procedure C using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and 4-iodotetrahydro-2H-pyran (212 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to provide

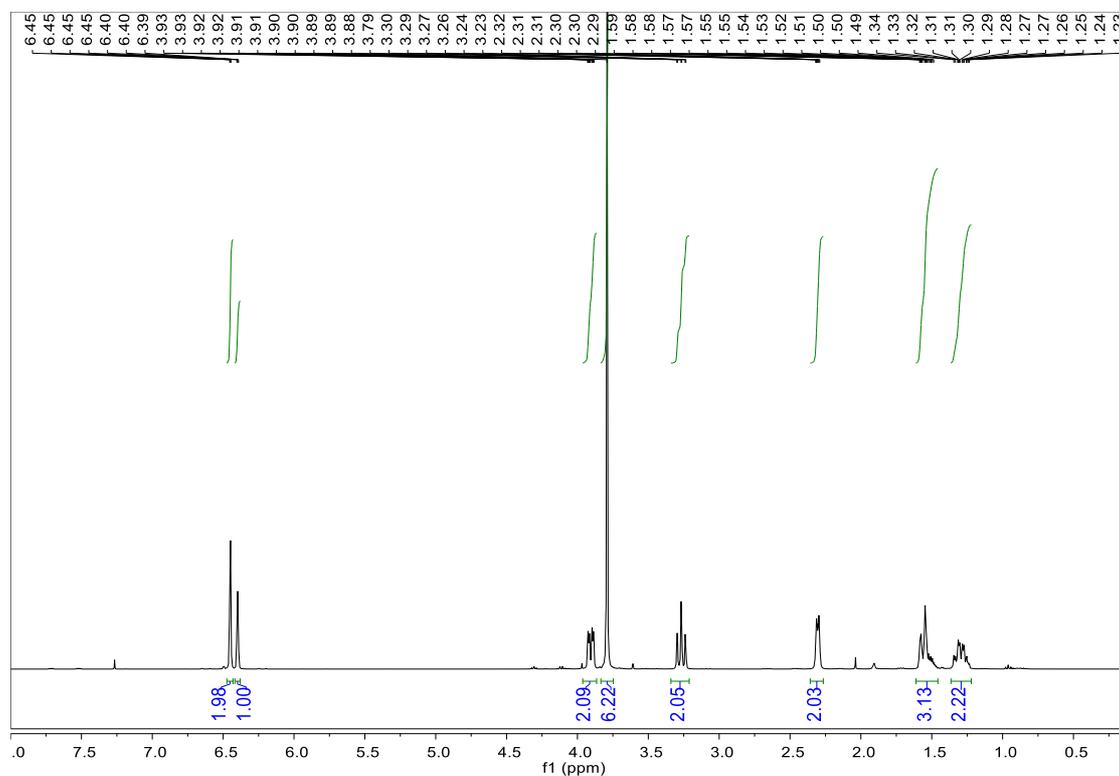
the title compound as a colorless oil in 78% yield (116 mg).

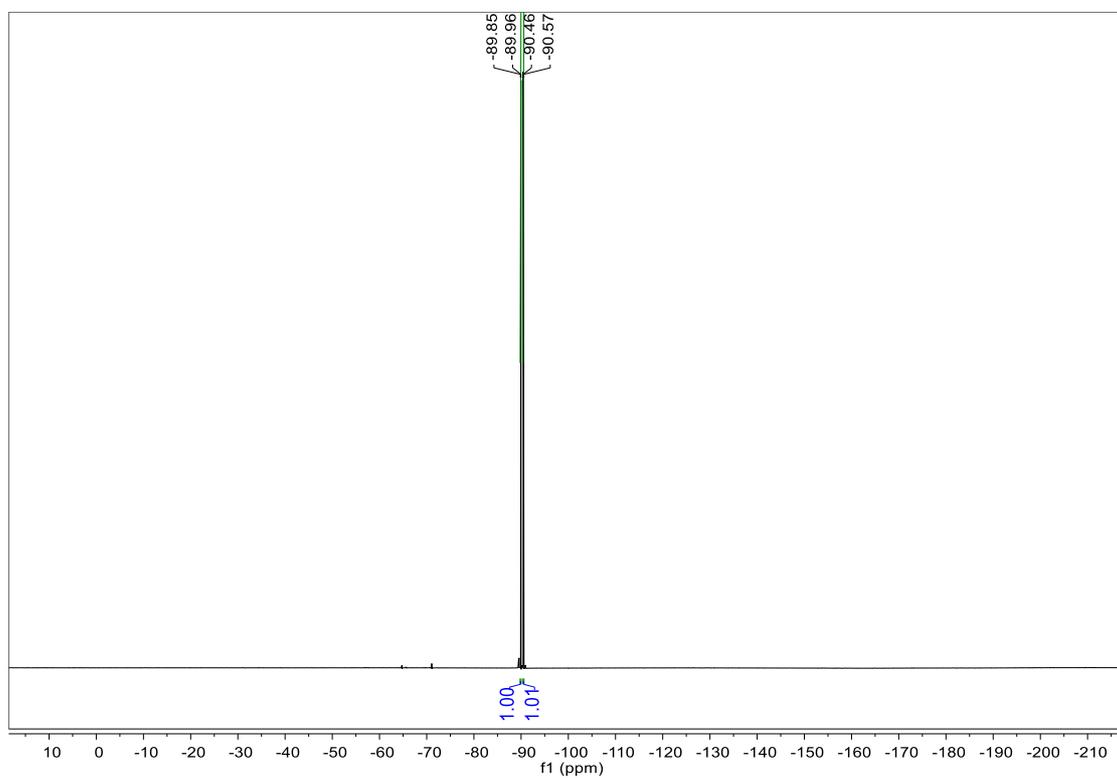
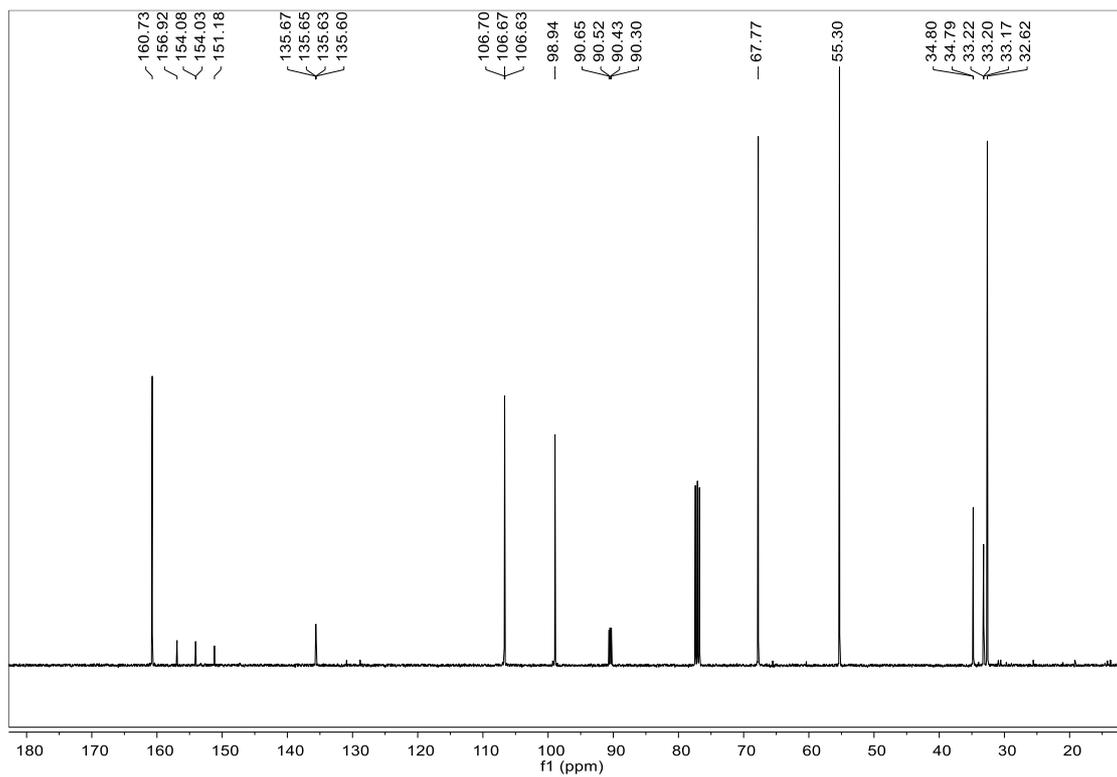
¹H NMR (400 MHz, Chloroform-*d*) δ 6.45 (dd, $J = 2.3, 1.1$ Hz, 2H), 6.40 (t, $J = 2.3$ Hz, 1H), 3.96 – 3.86 (m, 2H), 3.79 (s, 6H), 3.27 (td, $J = 11.8, 2.0$ Hz, 2H), 2.30 (dt, $J = 6.9, 2.3$ Hz, 2H), 1.61 – 1.46 (m, 3H), 1.36 – 1.22 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.73, 154.05 (dd, $J = 291.1, 286.4$ Hz), 135.64 (dd, $J = 4.8, 3.0$ Hz), 106.67 (t, $J = 3.3$ Hz), 98.94, 90.47 (dd, $J = 22.3, 12.9$ Hz), 67.77, 55.30, 34.80, 34.79, 33.20 (t, $J = 2.5$ Hz), 32.62.

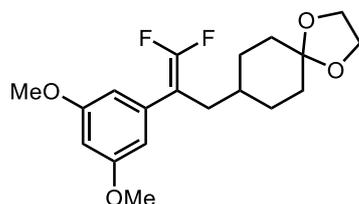
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.90 (d, $J = 41.9$ Hz, 1F), -90.51 (d, $J = 41.9$ Hz, 1F).

HRMS (ESI) calcd for C₁₆H₂₁F₂O₃⁺ [(M+H)⁺] 299.1453, found 299.1458.





8-(2-(3,5-Dimethoxyphenyl)-3,3-difluoroallyl)-1,4-dioxaspiro[4.5]decane (4m).



Prepared following general procedure C using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and 8-iodo-1,4-dioxaspiro[4.5]decane (268 mg, 1.0 mmol). The residue

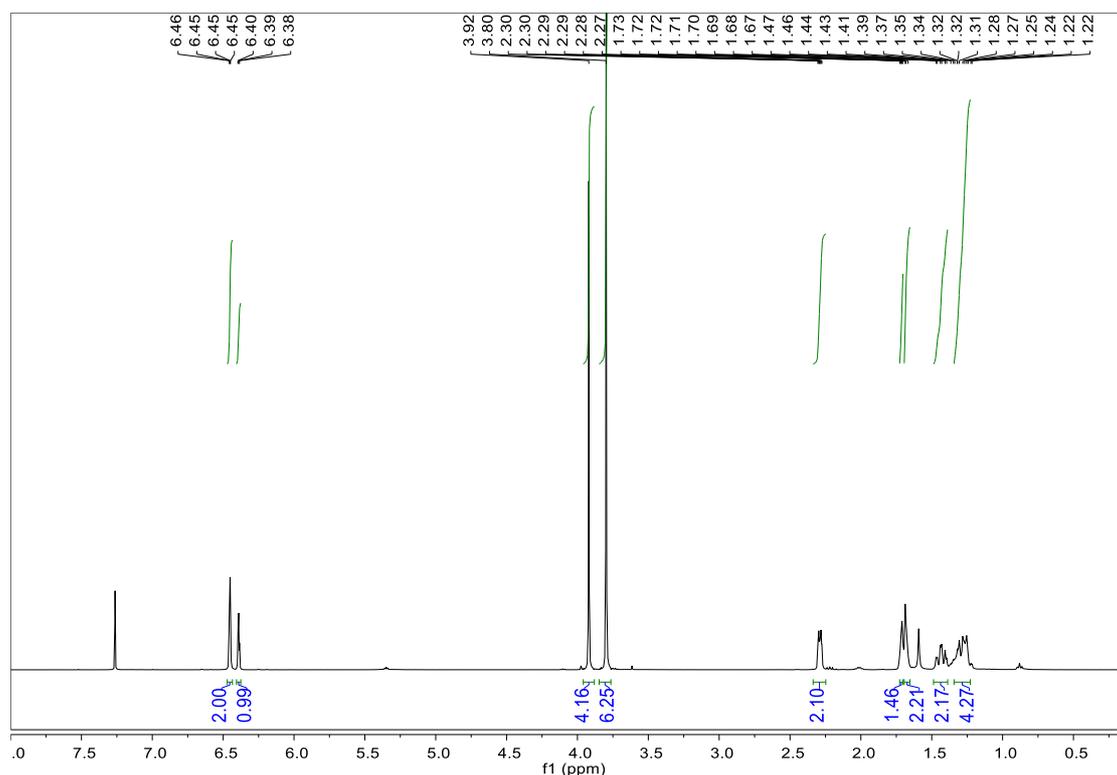
was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 95% yield (168 mg).

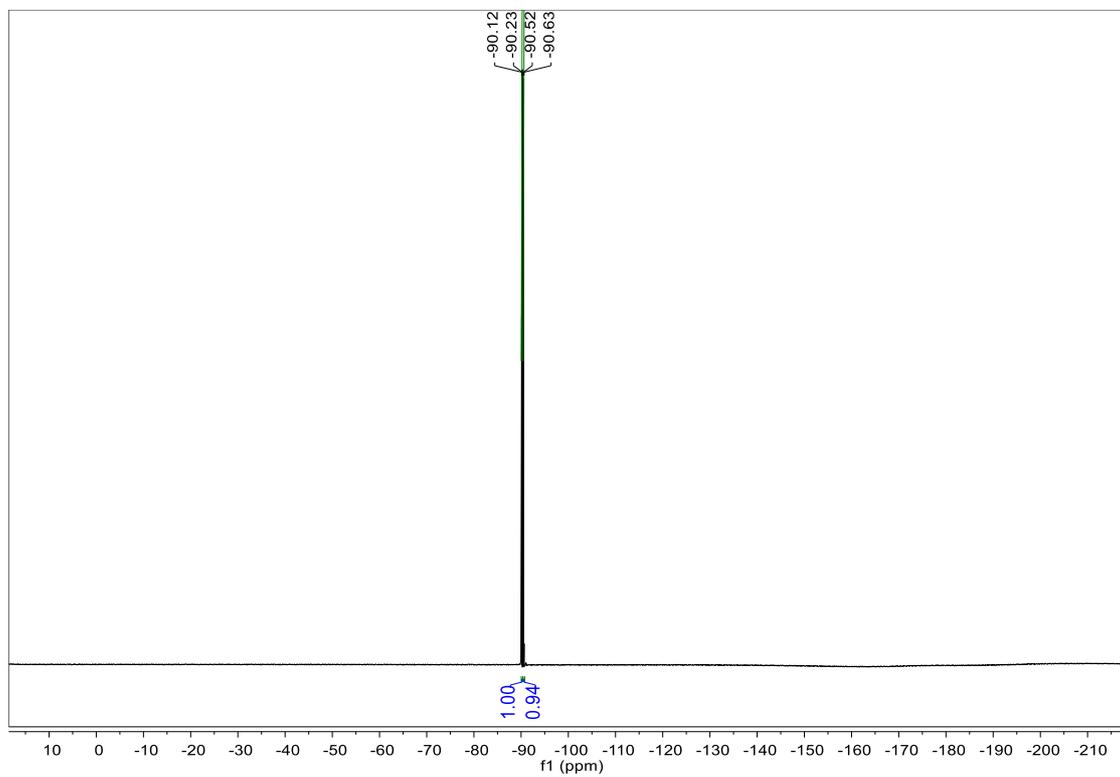
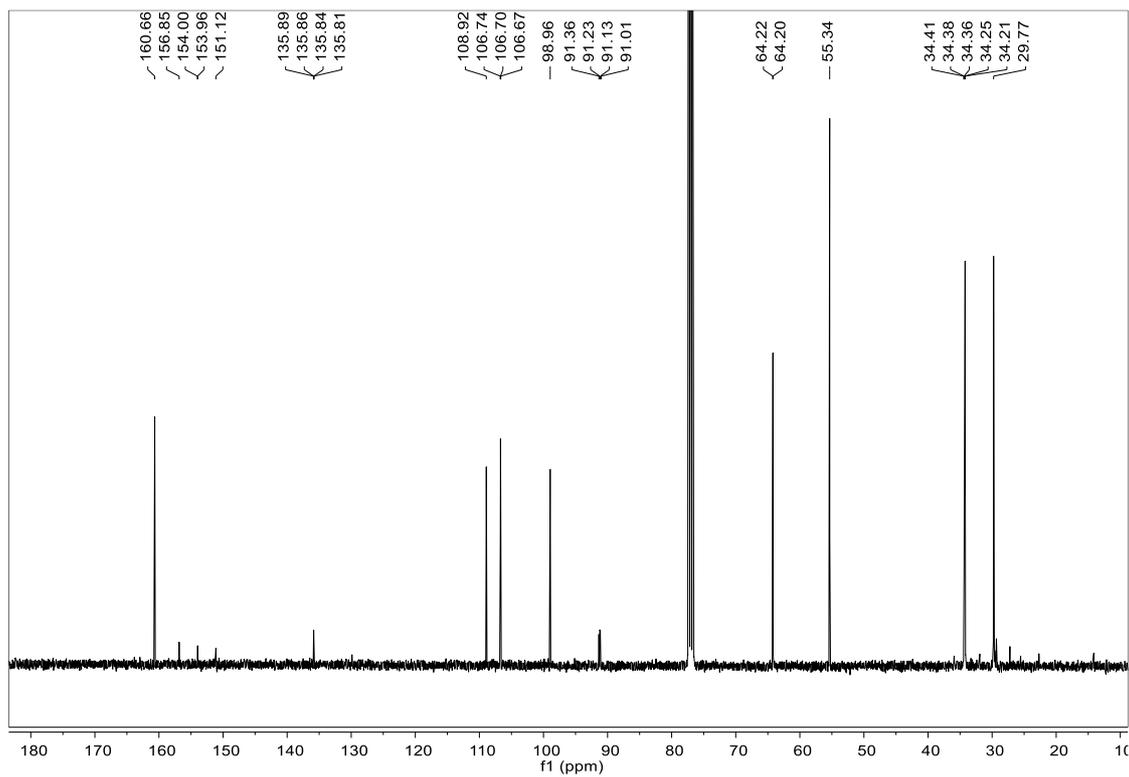
¹H NMR (400 MHz, Chloroform-*d*) δ 6.45 (dd, $J = 2.3, 1.1$ Hz, 2H), 6.39 (t, $J = 2.3$ Hz, 1H), 3.92 (s, 4H), 3.80 (s, 6H), 2.29 (dt, $J = 6.8, 2.4$ Hz, 2H), 1.73 – 1.70 (m, 1H), 1.70 – 1.65 (m, 2H), 1.49 – 1.39 (m, 2H), 1.34 – 1.23 (m, 4H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.66, 153.98 (dd, $J = 290.7, 286.4$ Hz), 135.85 (dd, $J = 4.7, 2.9$ Hz), 108.92, 106.70 (t, $J = 3.3$ Hz), 98.96, 91.18 (dd, $J = 22.2, 12.7$ Hz), 64.22, 64.20, 55.34, 34.39 (d, $J = 2.6$ Hz), 34.25, 34.21, 29.77.

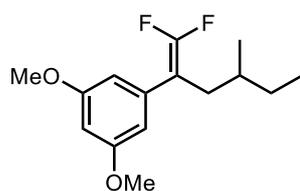
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.18 (d, $J = 42.1$ Hz, 1F), -90.57 (d, $J = 42.1$ Hz, 1F).

HRMS (ESI) calcd for C₁₉H₂₅F₂O₄⁺ [(M+H)⁺] 355.1715, found 355.1726.





1-(1,1-Difluoro-4-methylhex-1-en-2-yl)-3,5-dimethoxybenzene (4n).



Prepared following general procedure **C** using 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol) and 2-iodobutane (184 mg, 1.0 mmol).

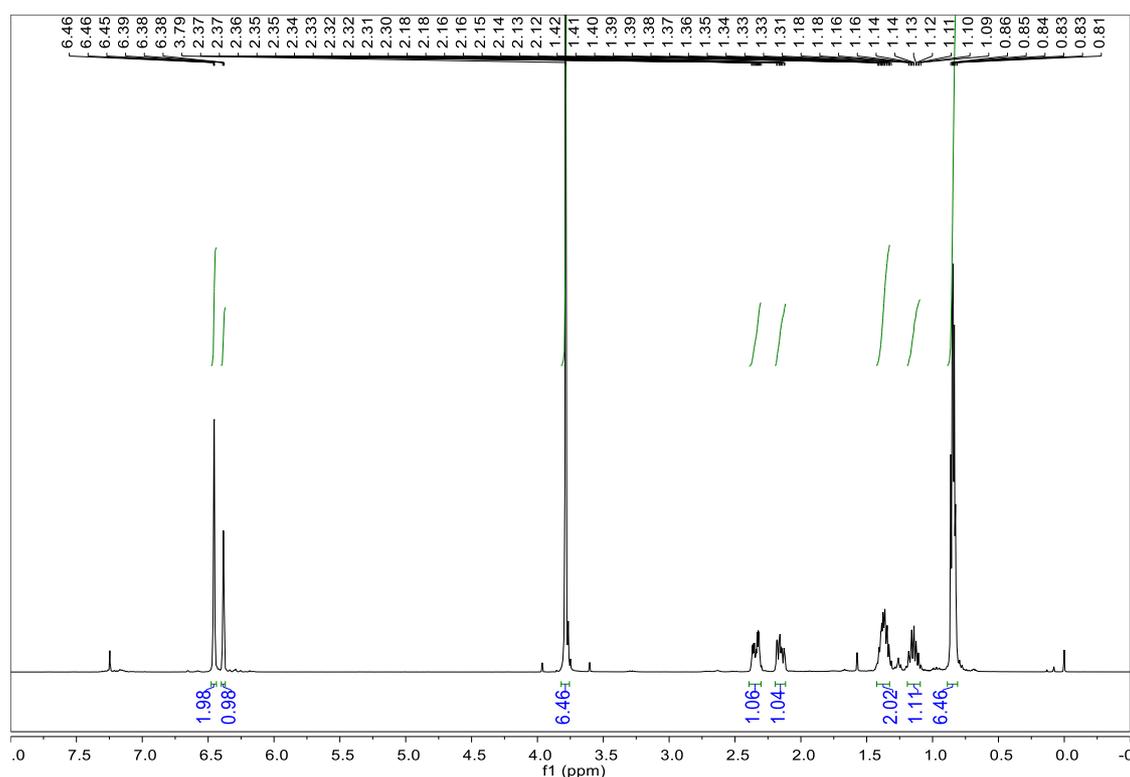
The residue was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 97% yield (131 mg).

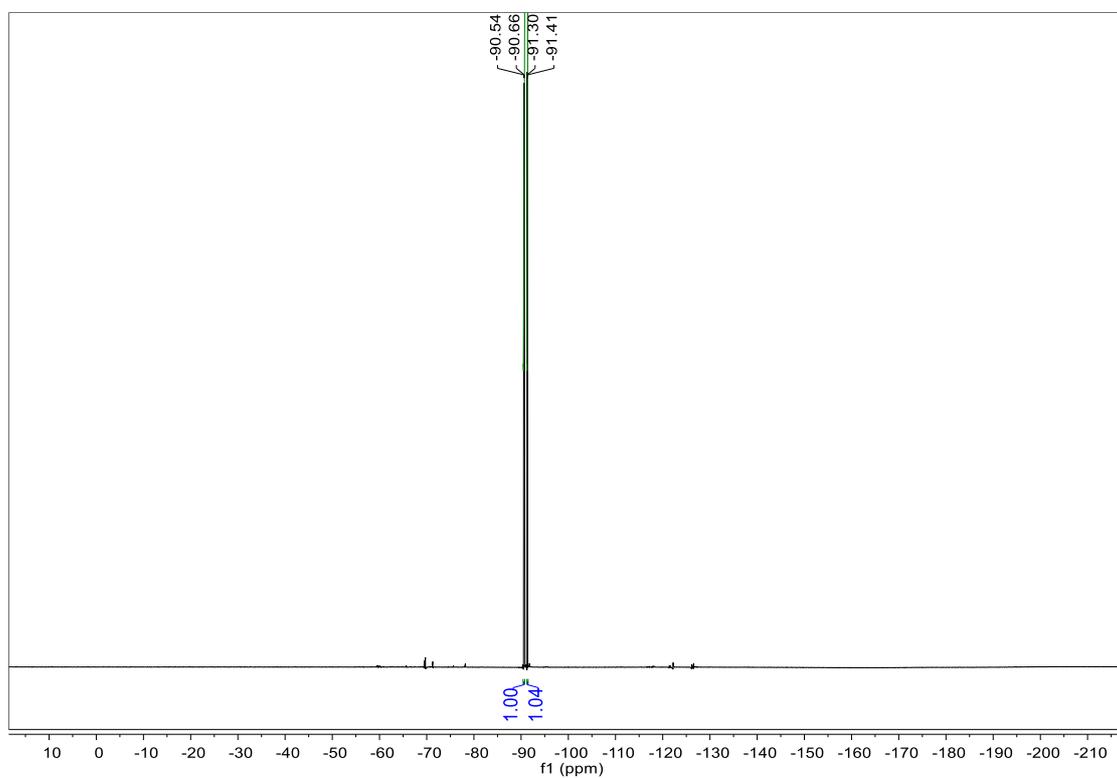
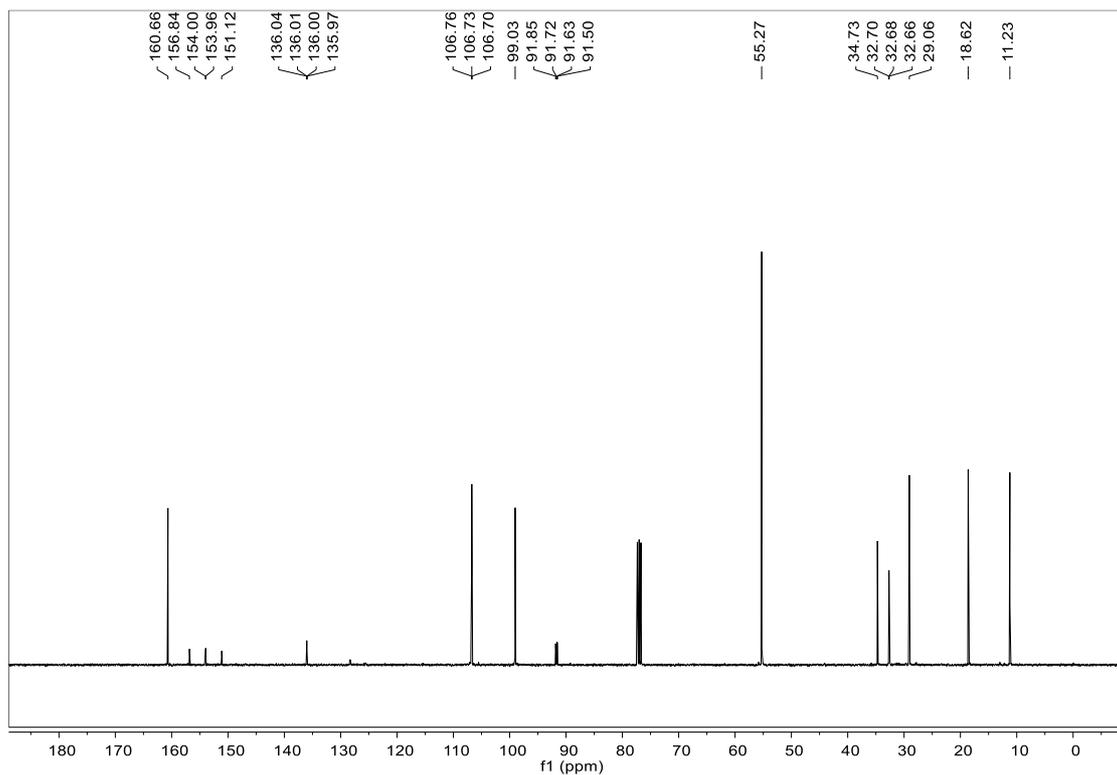
¹H NMR (400 MHz, Chloroform-*d*) δ 6.48 – 6.44 (m, 2H), 6.38 (t, $J = 2.3$ Hz, 1H), 3.79 (s, 6H), 2.34 (ddt, $J = 14.3, 5.9, 2.9$ Hz, 1H), 2.15 (ddd, $J = 14.5, 8.0, 2.7$ Hz, 1H), 1.42 – 1.33 (m, 2H), 1.19 – 1.09 (m, 1H), 0.89 – 0.81 (m, 6H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.66, 153.98 (dd, $J = 290.4, 286.1$ Hz) 136.01 (dd, $J = 4.8, 2.9$ Hz), 106.73 (t, $J = 3.2$ Hz), 99.03, 91.68 (dd, $J = 22.4, 12.5$ Hz), 55.27, 34.73, 32.68 (t, $J = 2.4$ Hz), 29.06, 18.62, 11.23.

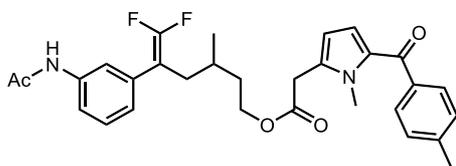
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.60 (d, $J = 43.5$ Hz, 1F), -91.36 (d, $J = 43.5$ Hz, 1F).

HRMS (ESI) calcd for C₁₅H₂₁F₂O₂⁺ [(M+H)⁺] 271.1504, found 271.1508.





5-(3-Acetamidophenyl)-6,6-difluoro-3-methylhex-5-en-1-yl 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetate (5a).



Prepared following general procedure C using *N*-(3-(3,3,3-trifluoroprop-1-en-2-yl)phenyl) acetamide (**1k**) (46 mg, 0.2 mmol) and 3-iodobutyl 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-

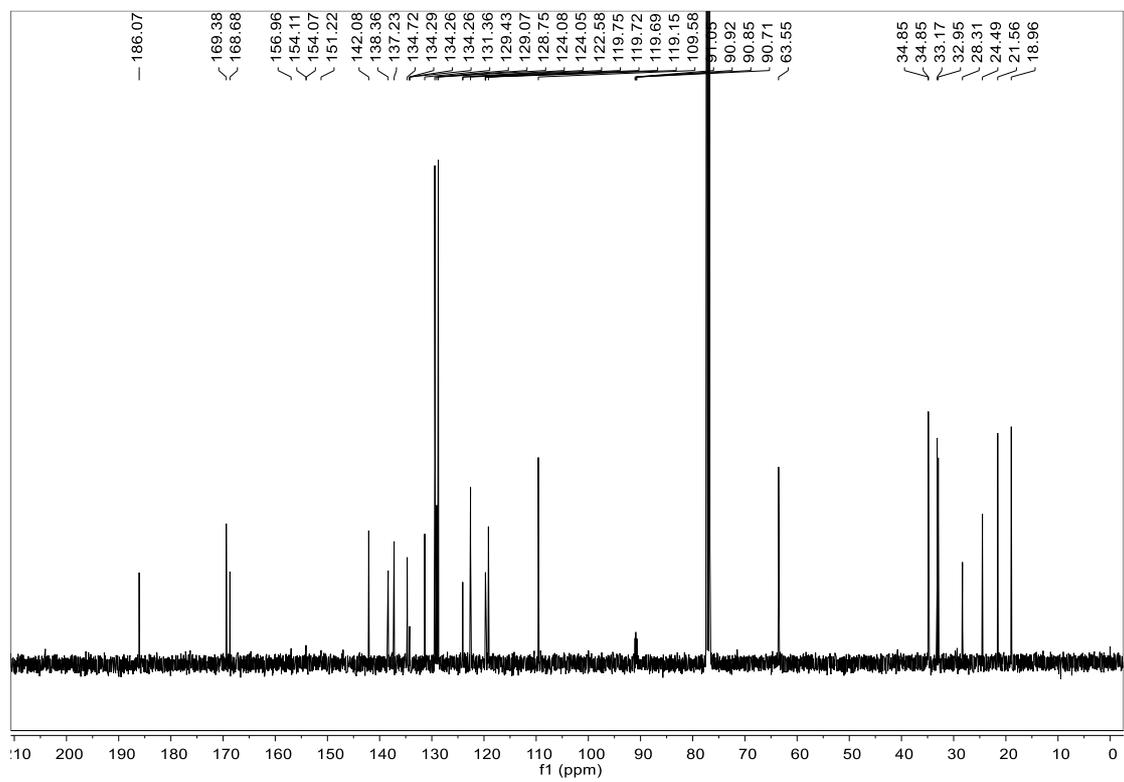
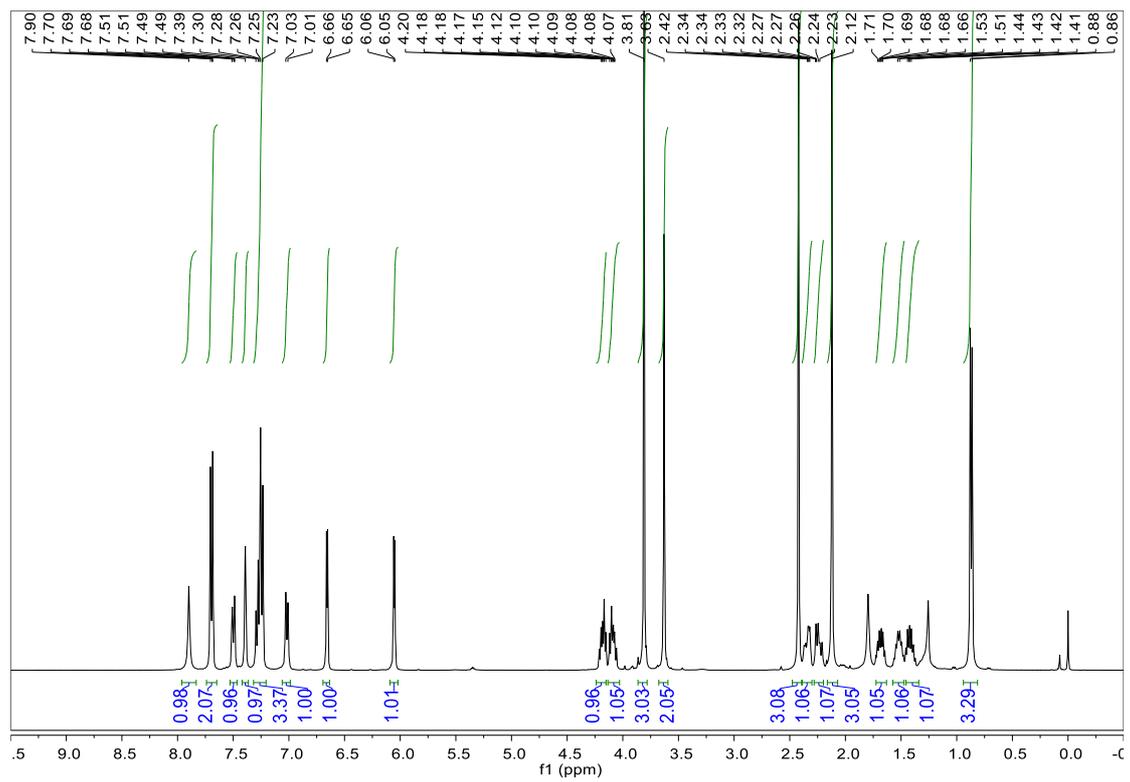
yl)acetate (176 mg, 0.4 mmol). The residue was purified by silica gel column chromatography (35% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 84% yield (88 mg).

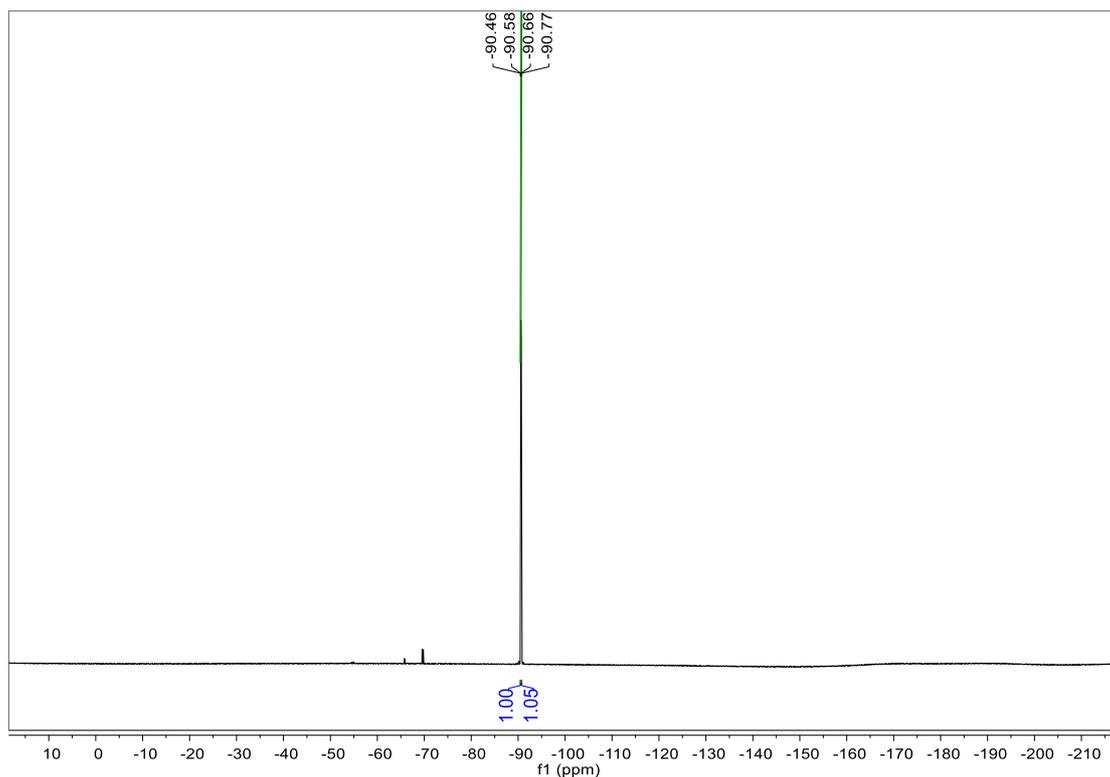
¹H NMR (400 MHz, Chloroform-*d*) δ 7.90 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.50 (dd, *J* = 8.0, 2.2 Hz, 1H), 7.39 (s, 1H), 7.32 – 7.20 (m, 3H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 4.0 Hz, 1H), 6.05 (d, *J* = 4.1 Hz, 1H), 4.18 (dt, *J* = 11.1, 6.3 Hz, 1H), 4.13 – 4.03 (m, 1H), 3.81 (s, 3H), 3.63 (s, 2H), 2.42 (s, 3H), 2.39 – 2.30 (m, 1H), 2.28 – 2.20 (m, 1H), 2.12 (s, 3H), 1.74 – 1.63 (m, 1H), 1.57 – 1.47 (m, 1H), 1.46 – 1.35 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 186.07, 169.38, 168.68, 154.09 (dd, *J* = 290.5, 287.1 Hz), 142.08, 138.36, 137.23, 134.72, 134.26 (dd, *J* = 4.1, 2.6 Hz), 131.36, 129.43, 129.07, 128.75, 124.08 (t, *J* = 3.1 Hz), 122.58, 119.72 (t, *J* = 2.9 Hz), 119.15, 109.58, 90.88 (dd, *J* = 21.3, 13.7 Hz), 63.55, 34.85 (t, *J* = 1.8 Hz), 33.17, 32.95, 28.31, 24.49, 21.56, 18.96.

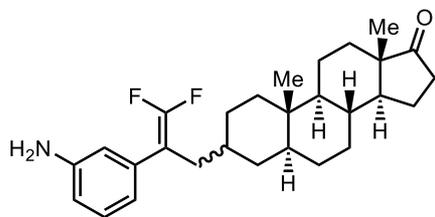
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.52 (d, *J* = 42.0 Hz, 1F), -91.36 (d, *J* = 42.0 Hz, 1F).

HRMS (ESI) calcd for C₃₀H₃₂F₂N₂O₄Na⁺ [(M+Na)⁺] 545.2222, found 545.2232.





(5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-3-(2-(3-Aminophenyl)-3,3-difluoroallyl)-10,13-dimethylhexadecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (5b).



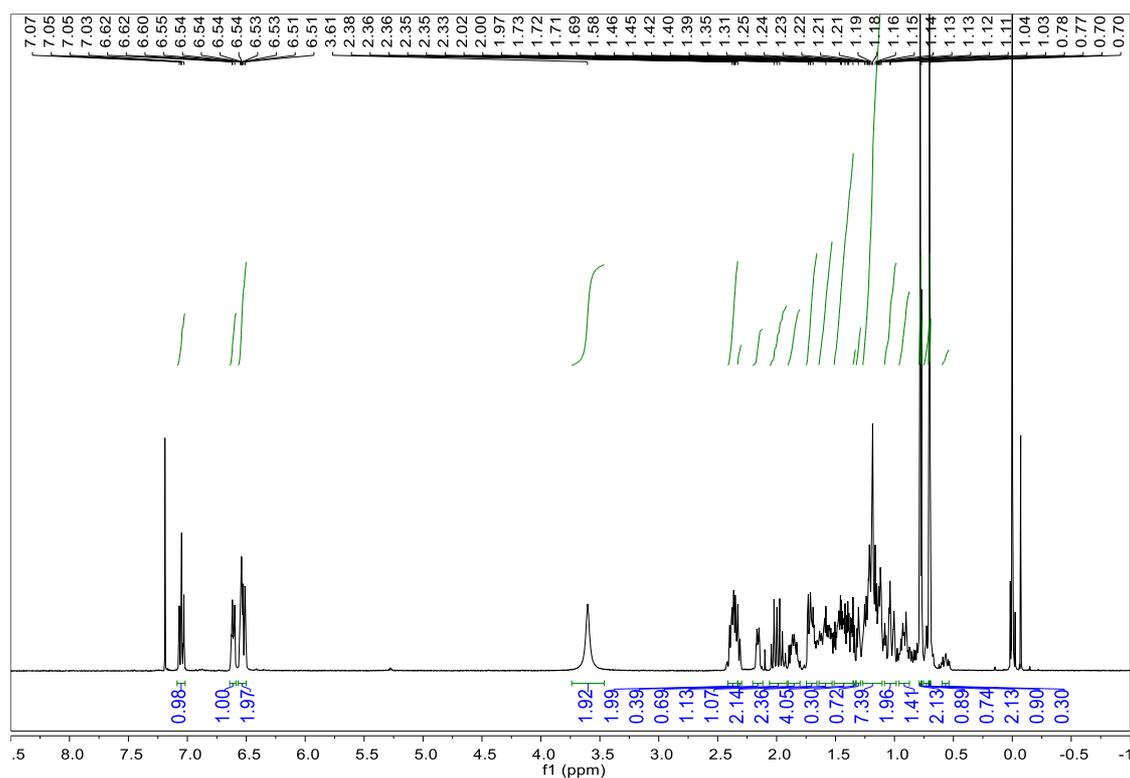
Prepared following general procedure C using 3-(3,3,3-trifluoroprop-1-en-2-yl)aniline (**1e**) (94 mg, 0.5 mmol) and (5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-3-iodo-10,13-dimethylhexadecahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (400 mg, 1.0 mmol). The residue was purified by column chromatography (30% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 89% yield (197 mg).

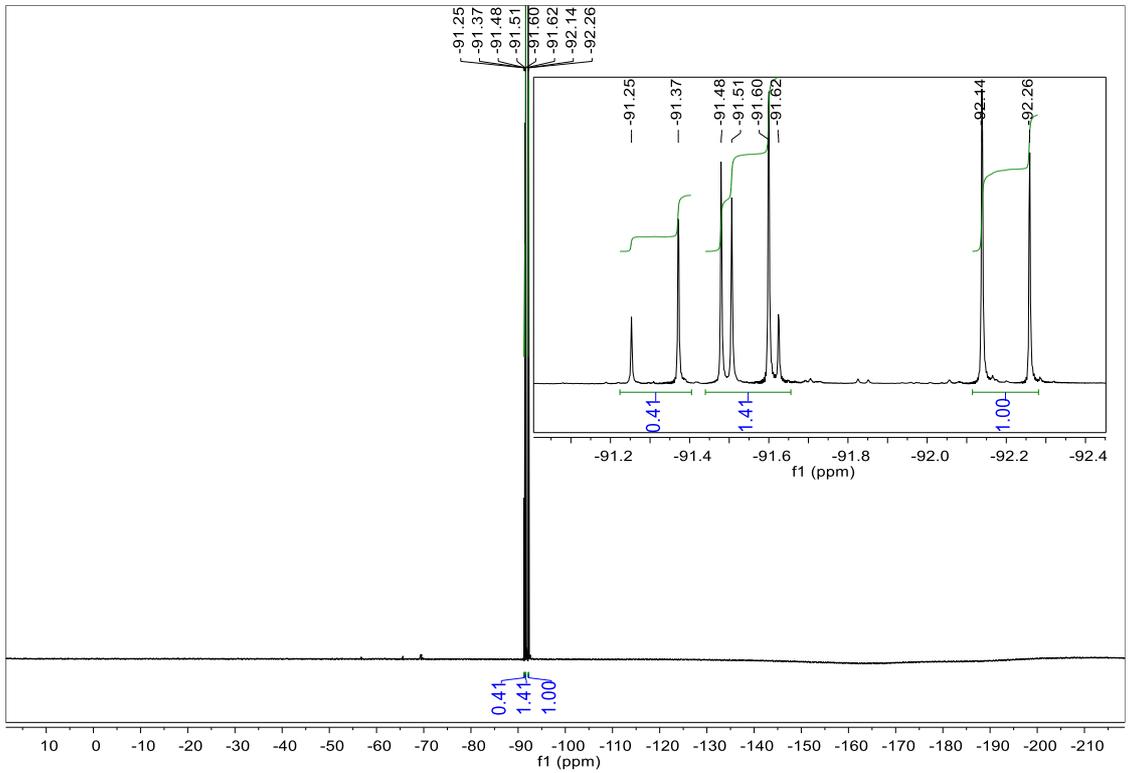
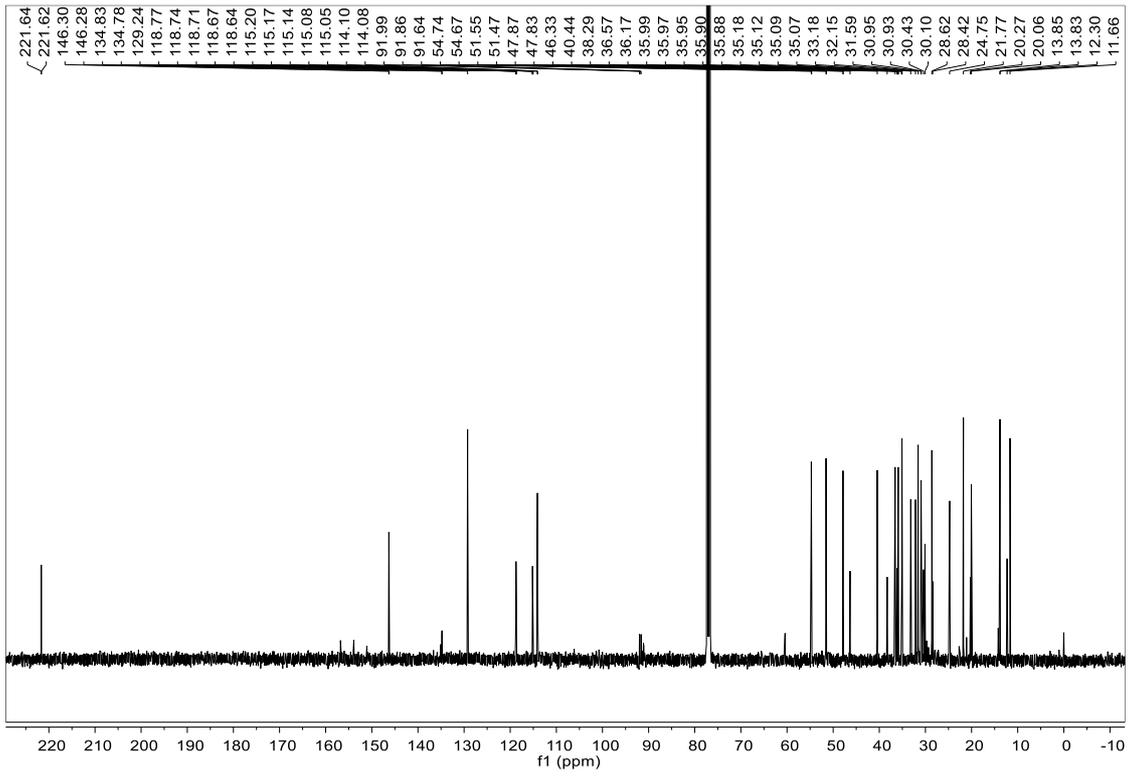
¹H NMR (400 MHz, Chloroform-*d*) δ 7.08 – 7.02 (m, 1H), 6.64 – 6.57 (m, 1H), 6.57 – 6.50 (m, 2H), 3.61 (s, 2H), 2.41 – 2.33 (m, 2H), 2.33 – 2.29 (m, 1H, 1 diastereomer), 2.19 – 2.13 (m, 1H, 1 diastereomer), 2.06 – 1.91 (m, 1H), 1.90 – 1.80 (m, 1H), 1.75 – 1.66 (m, 2H), 1.64 – 1.53 (m, 2H), 1.51 – 1.35 (m, 4H), 1.35 – 1.33 (m, 1H, 1 diastereomer), 1.33 – 1.28 (m, 1H, 1 diastereomer), 1.27 – 1.11 (m, 7H), 1.08 – 0.98 (m, 2H), 0.97 – 0.87 (m, 1H), 0.78 (s, 3H, 1 diastereomer), 0.77 (s, 3H, 1 diastereomer), 0.75 – 0.71 (m, 1H, 1 diastereomer), 0.70 (s, 3H, 1 diastereomer), 0.70 (s, 3H, 1 diastereomer), 0.59 – 0.54 (m, 1H, 1 diastereomer).

¹³C NMR (101 MHz, Chloroform-*d*) δ 221.64 (1 diastereomer), 221.62 (1 diastereomer), 153.93 (dd, *J* = 290.0, 285.3 Hz, 1 diastereomer), 153.85 (dd, *J* = 290.2, 285.3 Hz, 1 diastereomer), 146.30 (1 diastereomer), 146.28 (1 diastereomer), 135.08 (dd, *J* = 4.0, 1.7 Hz, 1 diastereomer), 134.82 (dd, *J* = 4.5, 2.8 Hz, 1 diastereomer), 129.24, 118.74 (t, *J* = 3.0 Hz, 1 diastereomer), 118.67 (d, *J* = 3.1 Hz, 1 diastereomer), 115.17 (t, *J* = 3.1 Hz, 1 diastereomer), 115.05 (t, *J* = 3.2 Hz, 1 diastereomer), 114.10 (1 diastereomer), 114.08 (1 diastereomer), 91.81 (dd, *J* = 21.9, 12.8 Hz, 1 diastereomer), 91.07 (dd, *J* = 21.9, 12.8 Hz, 1 diastereomer), 54.74 (1 diastereomer), 54.67 (1 diastereomer), 51.55 (1 diastereomer), 51.47 (1 diastereomer), 47.87 (1 diastereomer), 47.83 (1 diastereomer), 46.33, 40.44 (1 diastereomer), 38.29 (1 diastereomer), 36.57 (1 diastereomer), 36.17 (1 diastereomer), 35.97 (t, *J* = 3.1 Hz, 1 diastereomer), 35.90 (1 diastereomer), 35.88 (1 diastereomer), 35.18, 35.09 (t, *J* = 2.5 Hz, 1 diastereomer), 33.18, 32.15 (1 diastereomer), 31.59 (1 diastereomer), 30.95 (1 diastereomer), 30.93 (1 diastereomer), 30.43 (1 diastereomer), 30.10 (1 diastereomer), 28.62 (1 diastereomer), 28.42 (1 diastereomer), 24.75, 21.77, 20.27 (1 diastereomer), 20.06 (1 diastereomer), 13.85 (1 diastereomer), 13.83 (1 diastereomer), 12.30 (1 diastereomer), 11.66 (1 diastereomer).

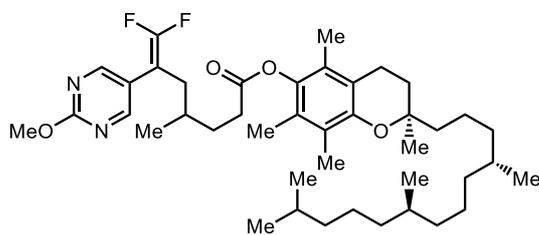
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -91.31 (d, *J* = 44.5 Hz, 1F, 1 diastereomer), -91.54 (d, *J* = 45.3 Hz, 1F, 1 diastereomer), -91.57 (d, *J* = 44.5 Hz, 1F, 1 diastereomer), -92.20 (d, *J* = 45.3 Hz, 1F, 1 diastereomer).

HRMS (ESI) calcd for C₂₈H₃₈F₂NO⁺ [(M+H)⁺] 442.2916, found 442.2917.





(R)-2,5,7,8-Tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl 7,7-difluoro-6-(2-methoxypyrimidin-5-yl)-4-methylhept-6-enoate (5c).



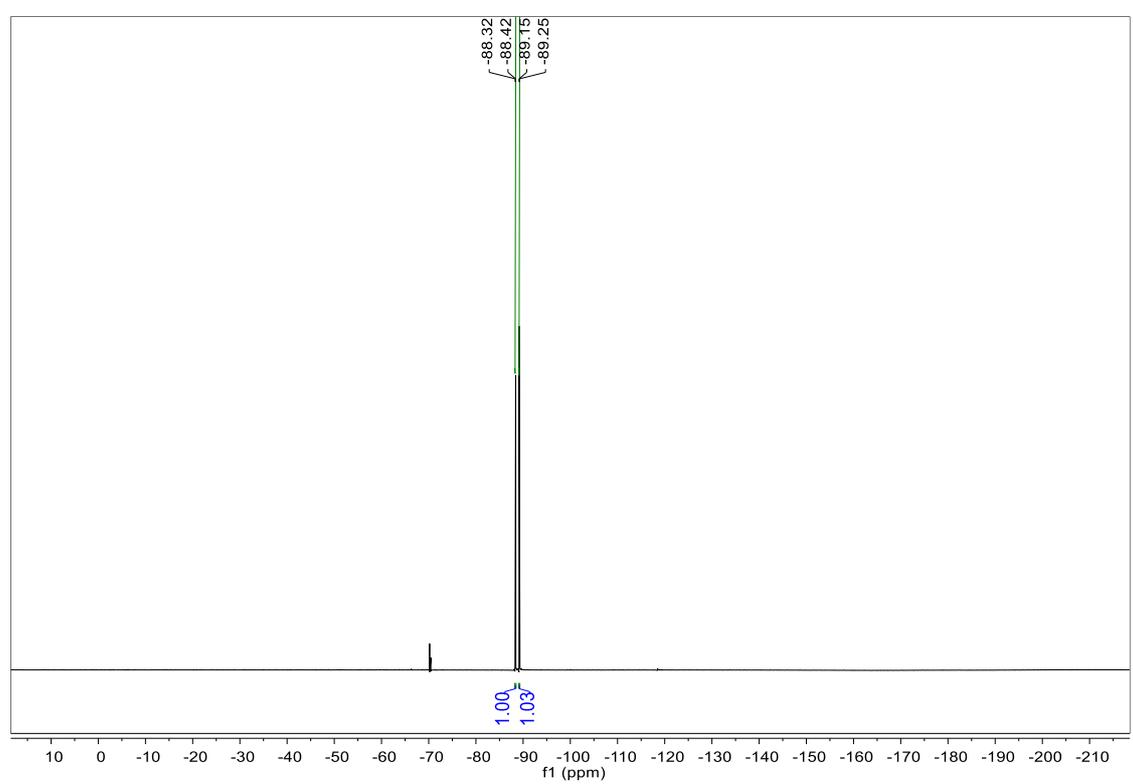
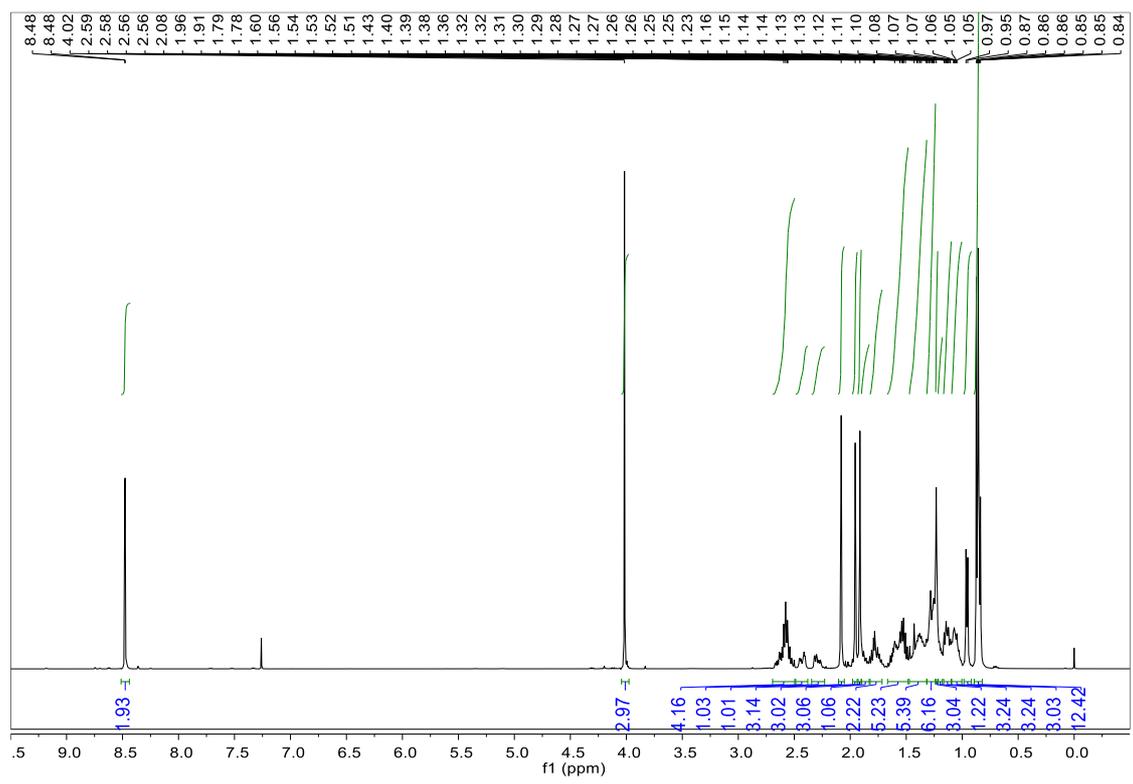
Prepared following general procedure **C** using 2-methoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyrimidine (**1n**) (41 mg, 0.2 mmol) and (*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl 4-iodopentanoate (256 mg, 0.4 mmol). The residue was purified by column chromatography (10% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 83% yield (116 mg).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, $J = 1.0$ Hz, 2H), 4.02 (s, 3H), 2.69 – 2.50 (m, 4H), 2.43 (ddt, $J = 14.4, 5.8, 2.9$ Hz, 1H), 2.34 – 2.23 (m, 1H), 2.08 (s, 3H), 1.96 (s, 3H), 1.91 (s, 3H), 1.90 – 1.83 (m, 1H), 1.82 – 1.72 (m, 2H), 1.67 – 1.48 (m, 5H), 1.47 – 1.32 (m, 5H), 1.32 – 1.24 (m, 6H), 1.23 (s, 3H), 1.22 – 1.18 (m, 1H), 1.17 – 1.10 (m, 3H), 1.09 – 1.00 (m, 3H), 0.96 (d, $J = 6.1$ Hz, 3H), 0.89 – 0.82 (m, 12H).

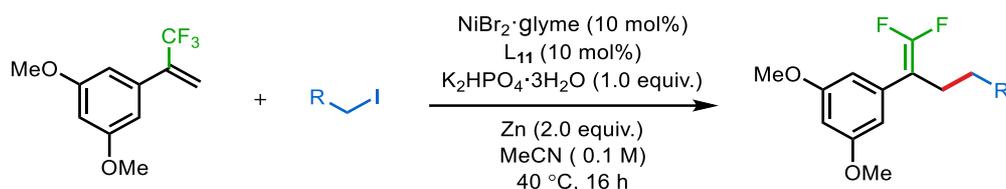
¹³C NMR (101 MHz, Chloroform-*d*) δ 190.83, 164.00, 160.71, 154.06 (dd, $J = 290.7, 286.2$ Hz), 135.52 (dd, $J = 4.7, 2.9$ Hz), 131.97, 129.81, 114.72, 106.75 (t, $J = 3.2$ Hz), 99.01, 91.22 (dd, $J = 22.2, 13.0$ Hz), 66.35, 55.32, 35.24, 35.05, 28.31 (t, $J = 2.4$ Hz), 19.27.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -88.37 (d, $J = 39.1$ Hz, 1F), -89.20 (d, $J = 39.1$ Hz, 1F).

HRMS (ESI) calcd for C₄₂H₆₅F₂N₂O₄⁺ [(M+H)⁺] 699.4907, found 699.4915.

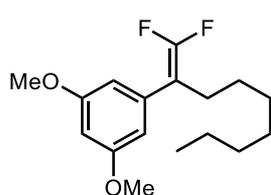


General procedure (D) for primary alkyl halides as substrates.



NiBr₂·DME (15 mg, 0.05 mmol, 10 mol%), 1,10-phenanthroline (**L**₁₁) (9 mg, 0.05 mmol, 10 mol%), alkyl halide (if solid, 1.0 mmol, 2.0 equiv), K₂HPO₄·3H₂O (114 mg, 0.5 mmol, 1.0 equiv.) and Zn (65 mg, 1.0 mmol, 2.0 equiv.) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and filled with nitrogen (three cycles). To these solids, MeCN (5 mL) was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 60 seconds. Next, alkyl halide (if liquid, 1.0 mmol, 2.0 equiv) was added under a positive flow of argon and stirred at room temperature for another 60 seconds. Then 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (116 mg, 0.5 mmol, 1.0 equiv.) was added. The reaction mixture was stirred at 40 °C for 16 hours, before it was quenched with H₂O. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by preparative TLC (petroleum ether/ethyl acetate) to give the corresponding *gem*-difluoroalkenes.

1-(1,1-Difluoronon-1-en-2-yl)-3,5-dimethoxybenzene (**4o**).



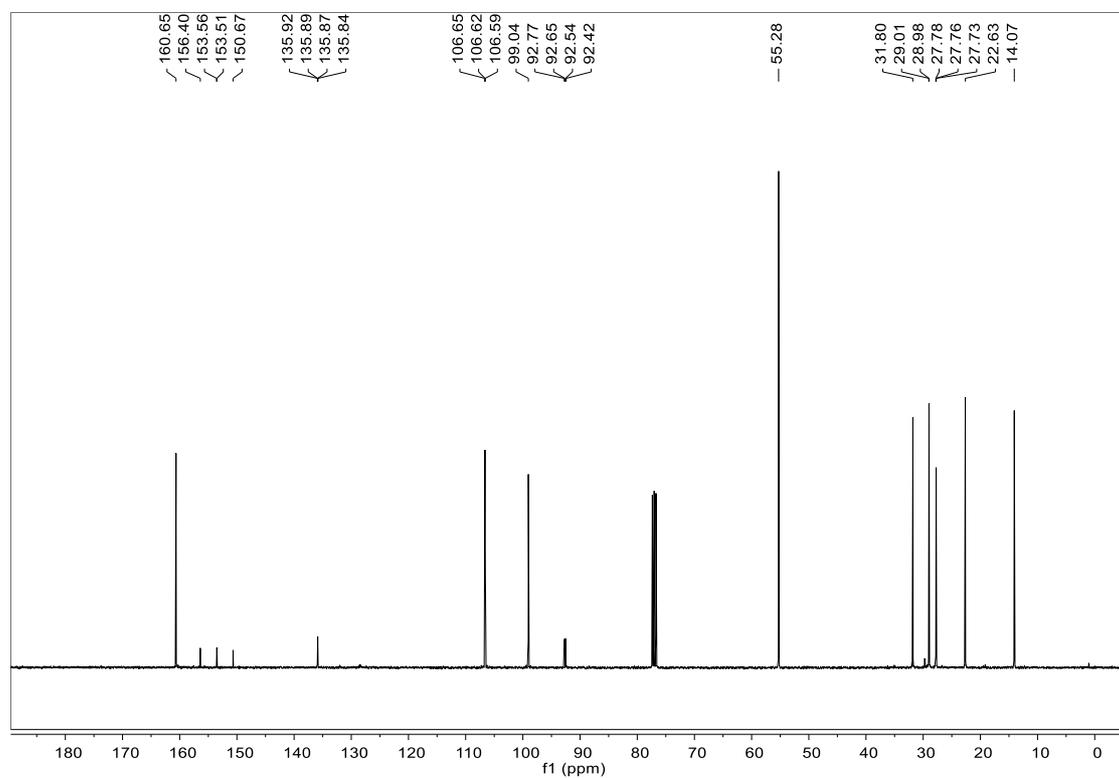
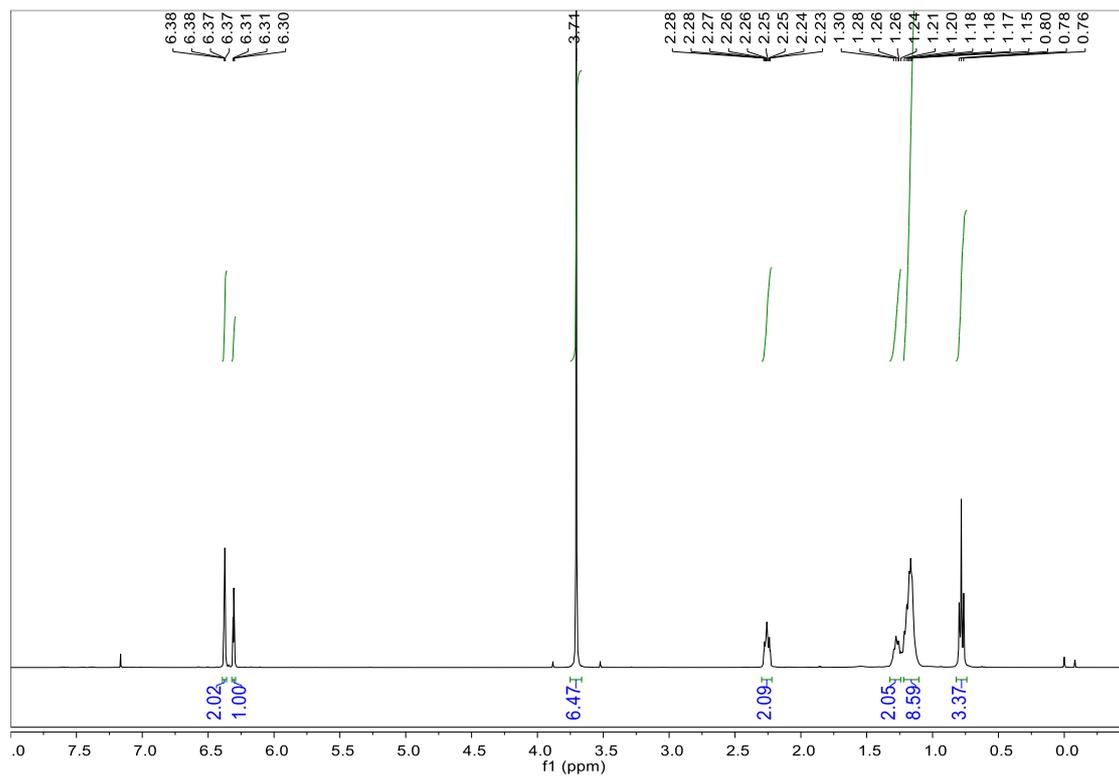
Prepared following general procedure **D** using 1-iodohexane (212 mg, 1.0 mmol). The residue was purified by preparative TLC (2% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 55% yield (82 mg).

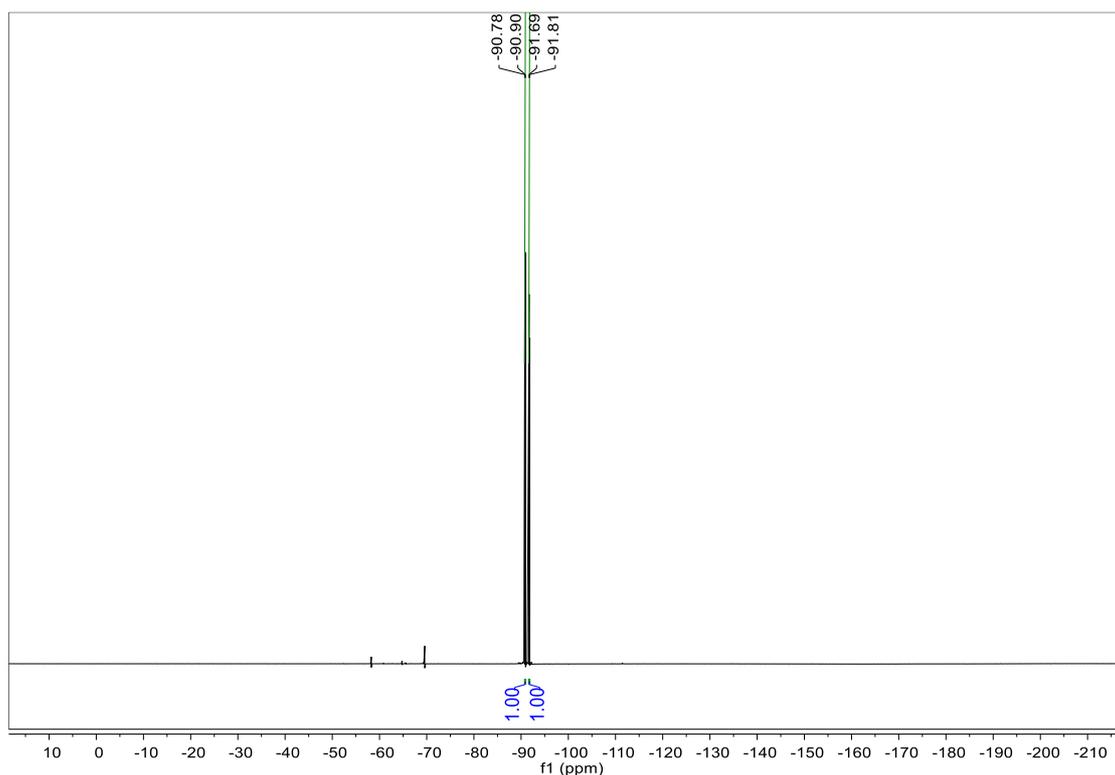
¹H NMR (400 MHz, Chloroform-*d*) δ 6.37 (dd, *J* = 2.3, 1.1 Hz, 2H), 6.31 (t, *J* = 2.3 Hz, 1H), 3.71 (s, 6H), 2.30 – 2.22 (m, 2H), 1.33 – 1.24 (m, 2H), 1.22 – 1.10 (m, 8H), 0.78 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.65, 153.53 (dd, *J* = 290.4, 285.9 Hz), 135.88 (dd, *J* = 5.0, 3.0 Hz), 106.62 (t, *J* = 3.4 Hz), 99.04, 92.59 (dd, *J* = 22.4, 12.2 Hz), 55.28, 31.80, 29.01, 28.98, 27.76 (t, *J* = 2.5 Hz), 27.73, 22.63, 14.07.

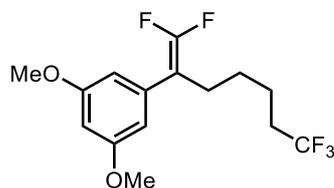
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -90.84 (d, *J* = 44.0 Hz, 1F), -91.75 (d, *J* = 44.0 Hz, 1F).

HRMS (ESI) calcd for C₁₇H₂₅F₂O₂⁺ [(M+H)⁺] 299.1817, found 299.1821.





1,3-Dimethoxy-5-(1,1,7,7,7-pentafluorohept-1-en-2-yl)benzene (4p).



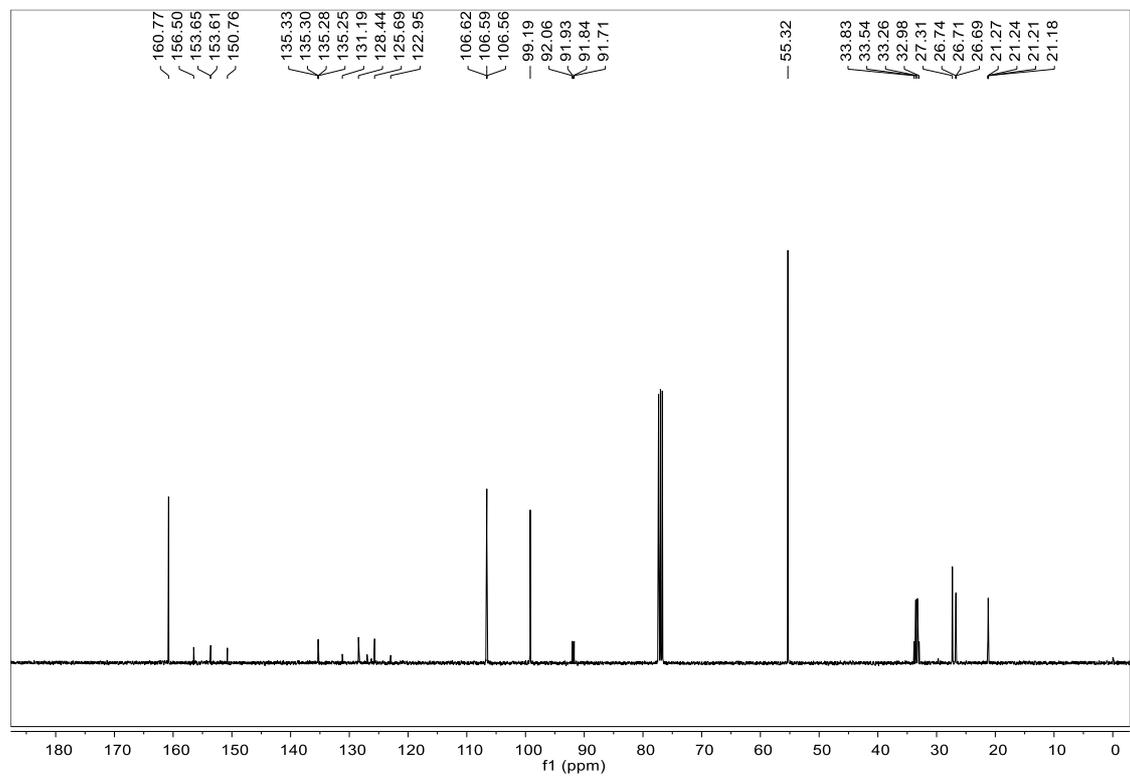
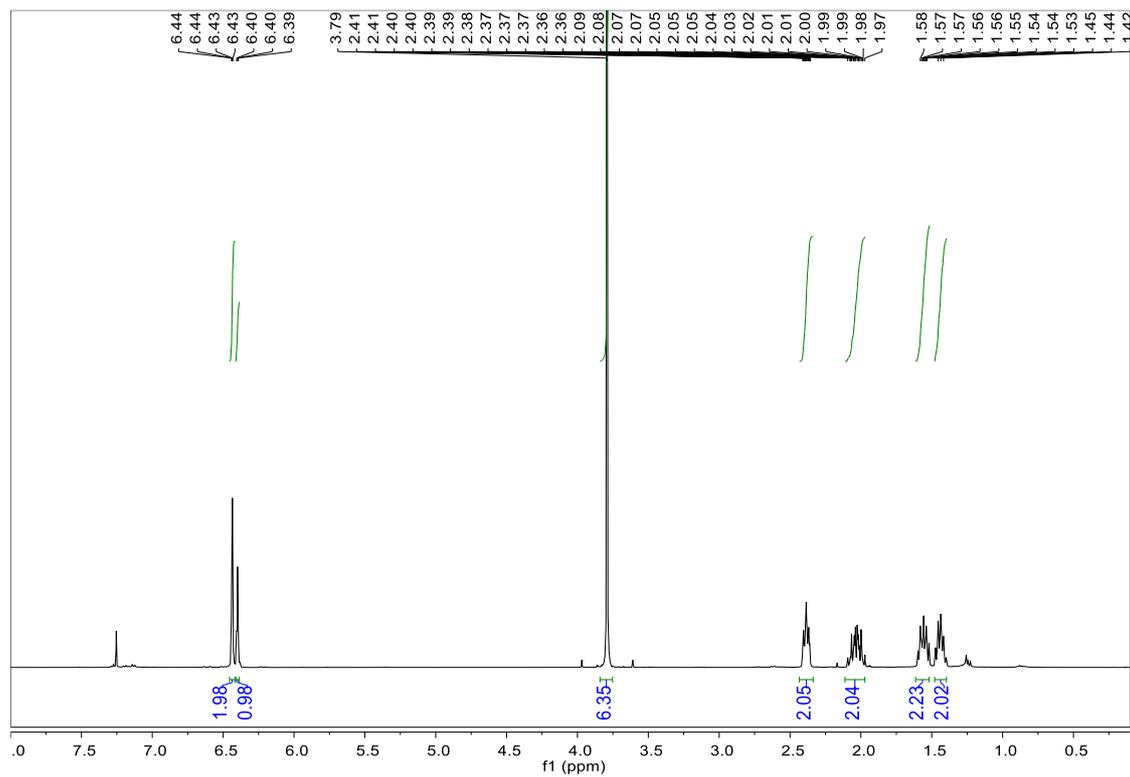
Prepared following general procedure **D** using 1,1,1-trifluoro-4-iodobutane (238 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (3% EtOAc in petroleum ether) to provide the title compound as a colorless oil in 47% yield (76 mg).

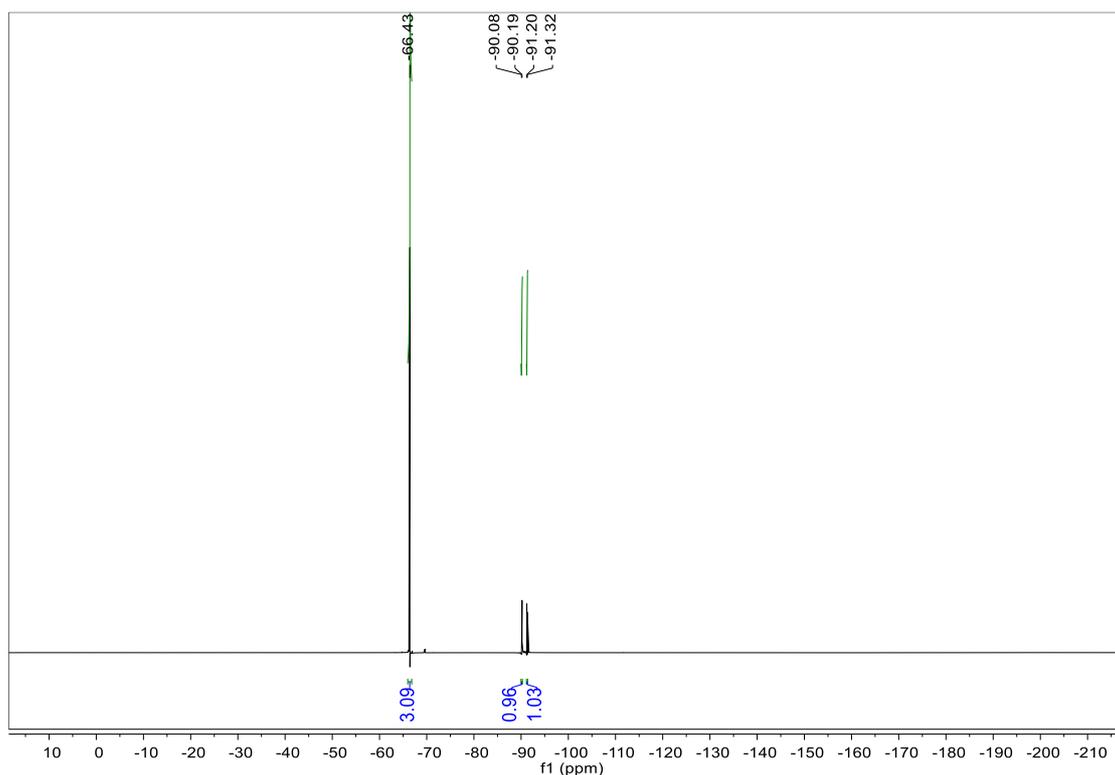
¹H NMR (400 MHz, Chloroform-*d*) δ 6.44 (dd, $J = 2.3, 1.1$ Hz, 2H), 6.40 (t, $J = 2.3$ Hz, 1H), 3.79 (s, 6H), 2.39 (ddt, $J = 9.6, 7.3, 2.3$ Hz, 2H), 2.11 – 1.97 (m, 2H), 1.61 – 1.52 (m, 2H), 1.48 – 1.39 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.77, 153.63 (dd, $J = 290.9, 286.4$ Hz), 135.29 (dd, $J = 4.8, 3.1$ Hz), 127.07 (q, $J = 276.3$ Hz), 106.59 (t, $J = 3.3$ Hz), 99.19, 91.89 (dd, $J = 22.2, 13.1$ Hz), 55.32, 33.40 (q, $J = 28.5$ Hz), 27.31, 26.71 (t, $J = 2.6$ Hz), 21.23 (q, $J = 2.9$ Hz).

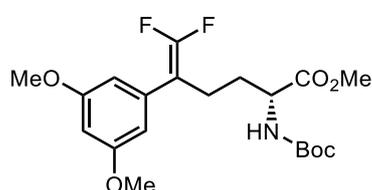
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -66.43 (s, 3F), -90.14 (d, $J = 42.9$ Hz, 1F), -91.26 (d, $J = 42.8$ Hz, 1F).

HRMS (ESI) calcd for C₁₅H₁₈F₅O₂⁺ [(M+H)⁺] 325.1221, found 325.1223.





Methyl (R)-2-((tert-butoxycarbonyl)amino)-5-(3,5-dimethoxyphenyl)-6,6-difluorohex-5-enoate (5d).



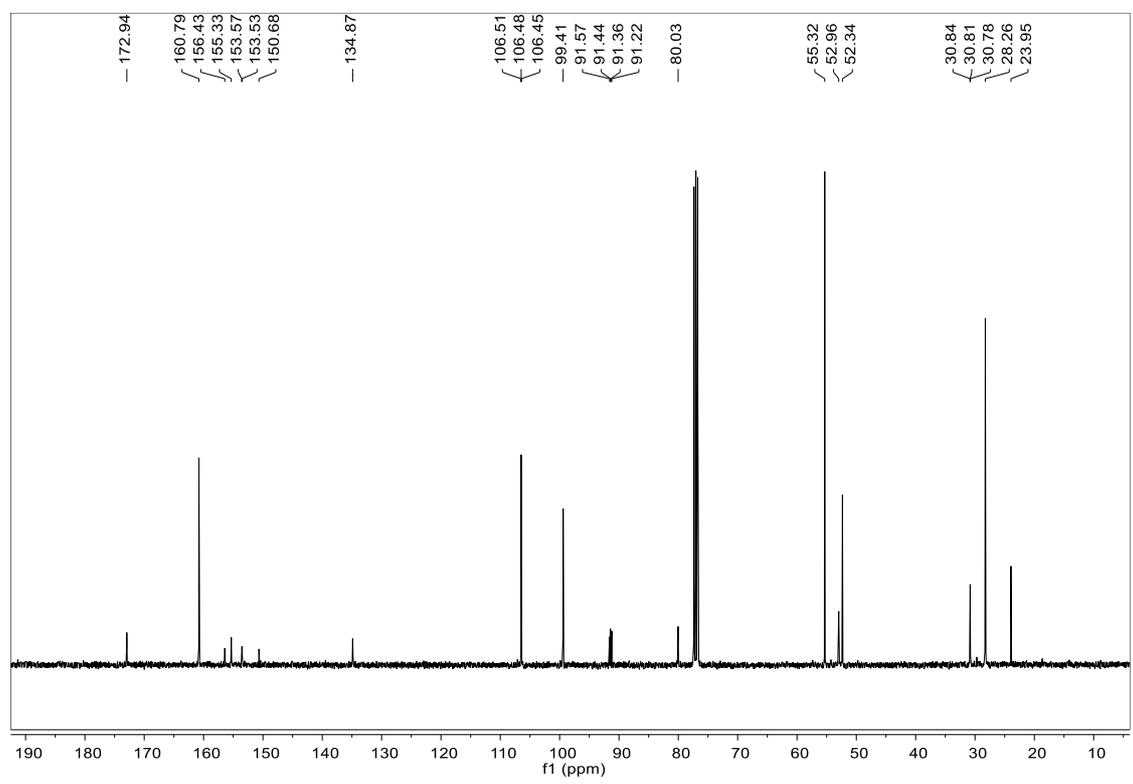
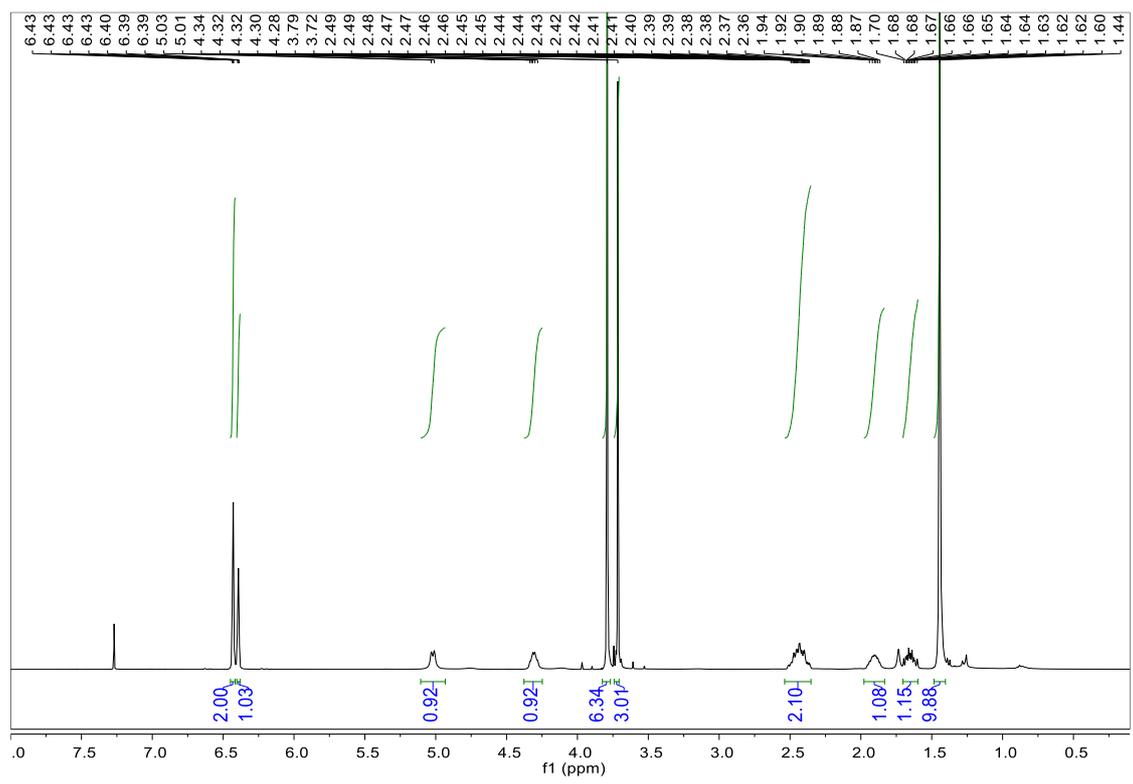
Prepared following general procedure **D** using methyl (S)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate (329 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to provide the title compound as a colorless oil (93 mg, 45% yield, 97% ee).

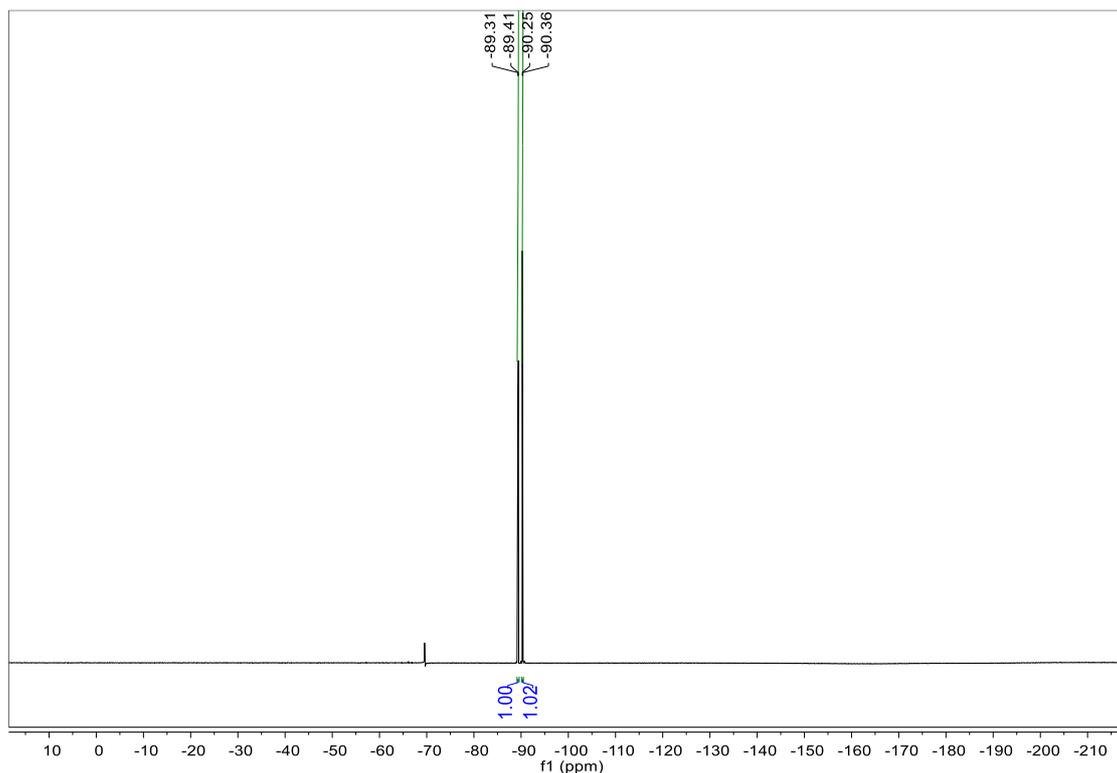
¹H NMR (400 MHz, Chloroform-*d*) δ 6.43 (dd, $J = 2.3, 1.0$ Hz, 2H), 6.39 (t, $J = 2.3$ Hz, 1H), 5.02 (d, $J = 8.7$ Hz, 1H), 4.31 (dt, $J = 13.8, 6.3$ Hz, 1H), 3.79 (s, 6H), 3.72 (s, 3H), 2.54 – 2.35 (m, 2H), 1.98 – 1.83 (m, 1H), 1.70 – 1.60 (m, 1H), 1.44 (s, 9H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 172.94, 160.79, 155.33, 153.55 (dd, $J = 291.3, 287.3$ Hz), 134.87, 106.48 (t, $J = 3.3$ Hz), 99.41, 91.40 (dd, $J = 21.9, 13.9$ Hz), 80.03, 55.32, 52.96, 52.34, 30.81 (t, $J = 2.7$ Hz), 28.26, 23.95.

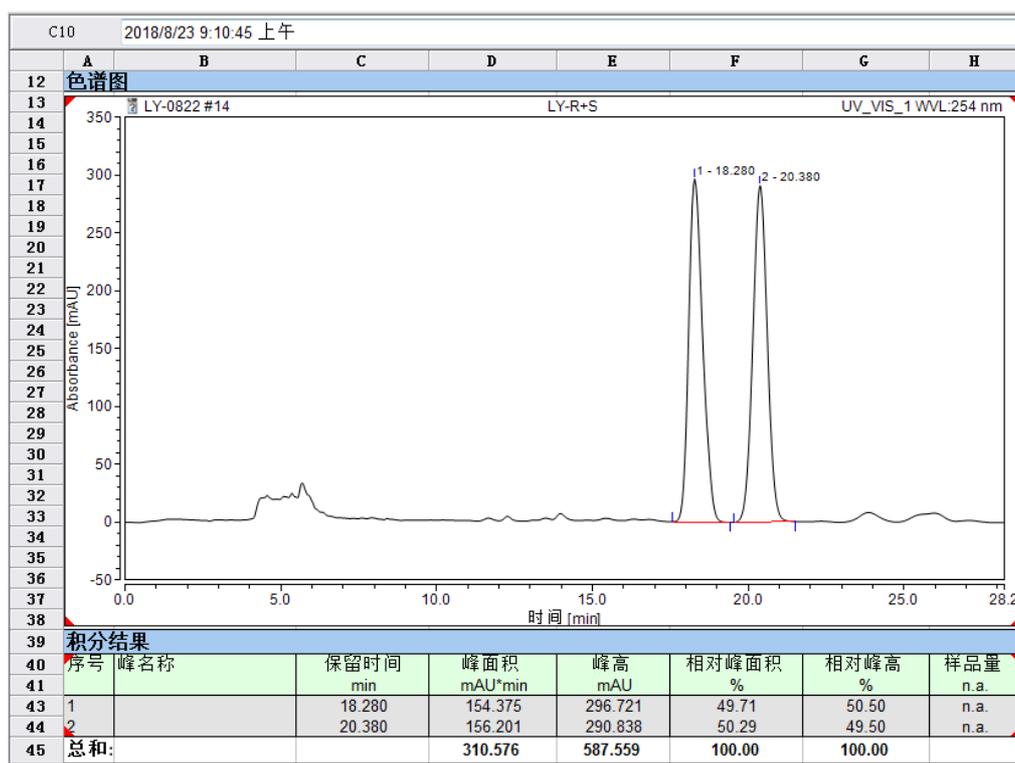
¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.36 (d, $J = 40.8$ Hz, 1F), -90.30 (d, $J = 40.8$ Hz, 1F).

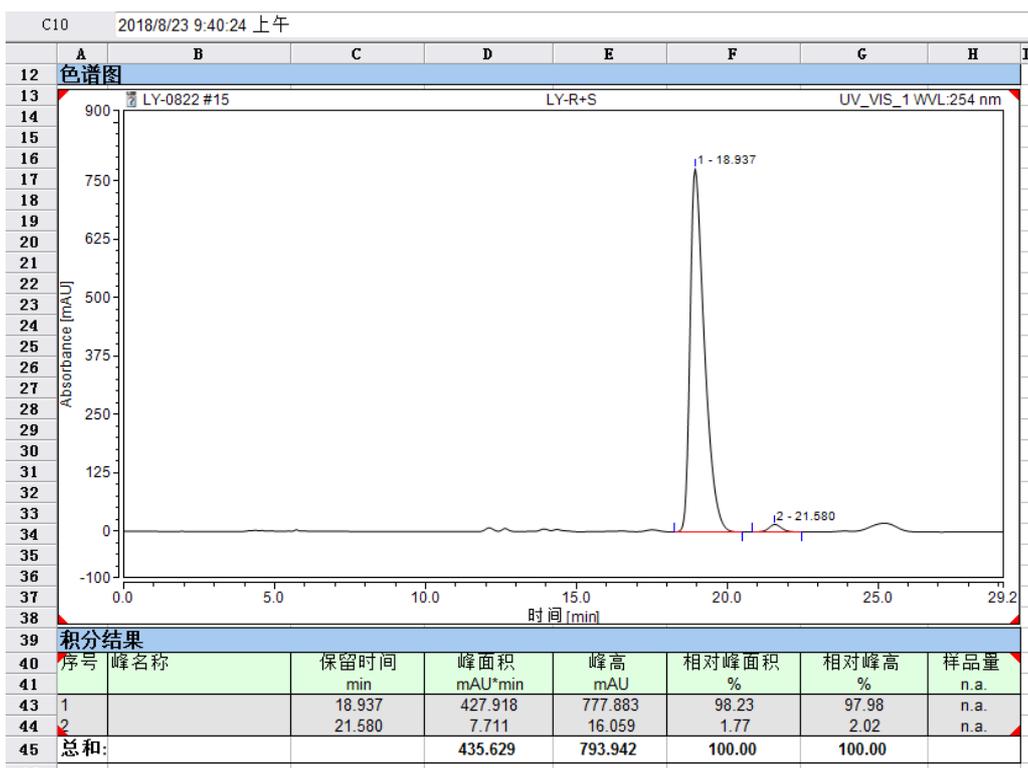
HRMS (ESI) calcd for $C_{20}H_{27}F_2NO_6Na^+$ [(M+Na)⁺] 438.1699, found 438.1700.



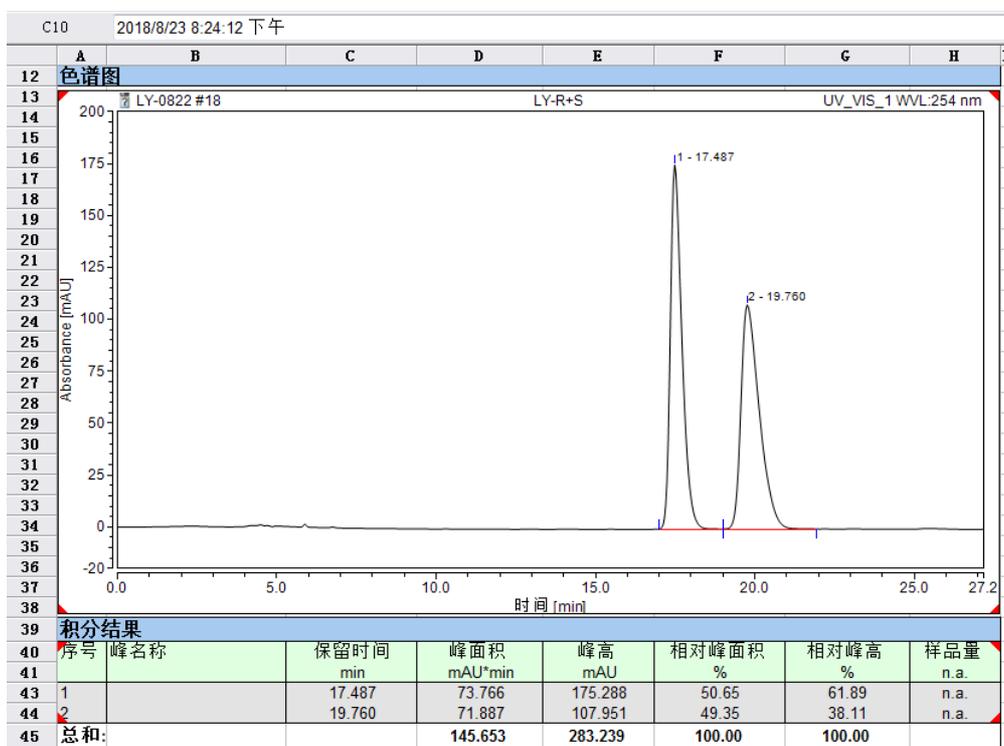


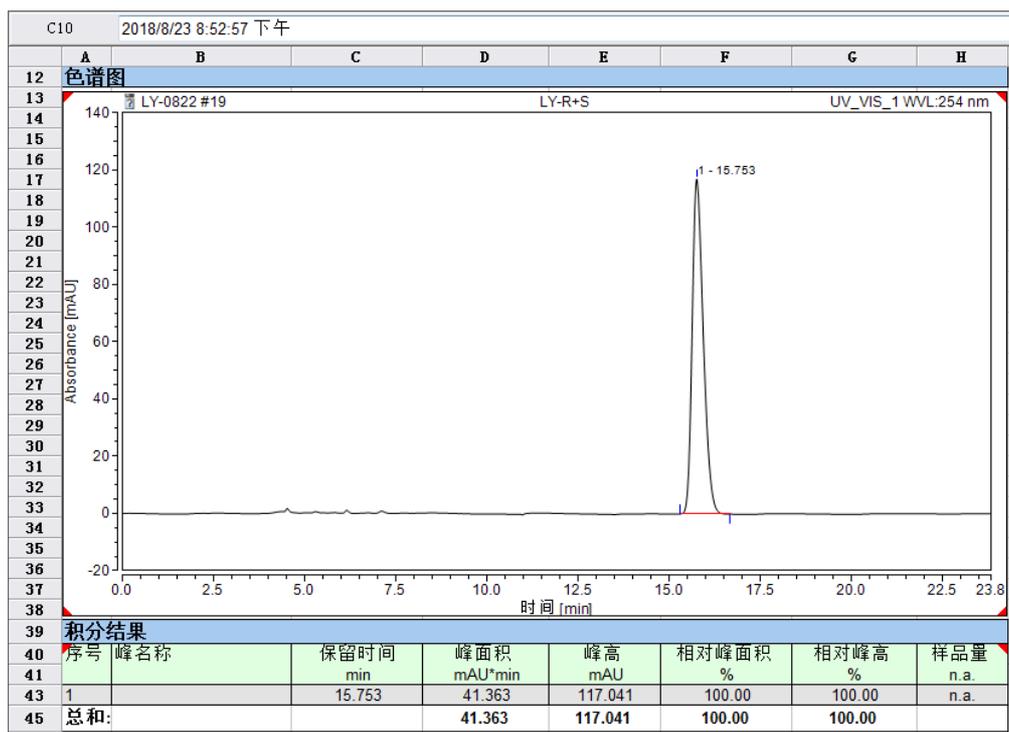
The enantiomeric excess of **5d** was determined by chiral HPLC analysis on Chiralpak AD-H column. Conditions: hexane/isopropanol = 91/9, flow rate = 0.7 mL/min, column temperature = 25 °C, uv-vis detection at $\lambda = 254$ nm, $t_{R1} = 18.94$ min (major), $t_{R2} = 21.58$ min (minor).



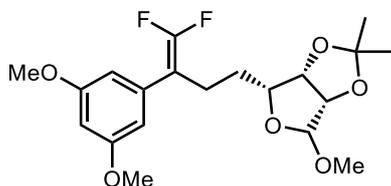


The enantiomeric excess of **2t** (> 99% ee) was determined by chiral HPLC analysis on Chiralpak AD-H column. Conditions: hexane/isopropanol = 95/5, flow rate = 0.7 mL/min, column temperature = 25 °C, uv-vis detection at $\lambda = 254$ nm, $t_R = 15.73$ min.





(3a*S*,4*R*,6*S*,6a*S*)-4-(3-(3,5-Dimethoxyphenyl)-4,4-difluorobut-3-en-1-yl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole (5e).



Prepared following general procedure **D** using (3a*R*,4*S*,6*S*,6a*S*)-4-(iodomethyl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole (314 mg, 1.0 mmol). The residue was purified by silica gel column chromatography (10% EtOAc in petroleum

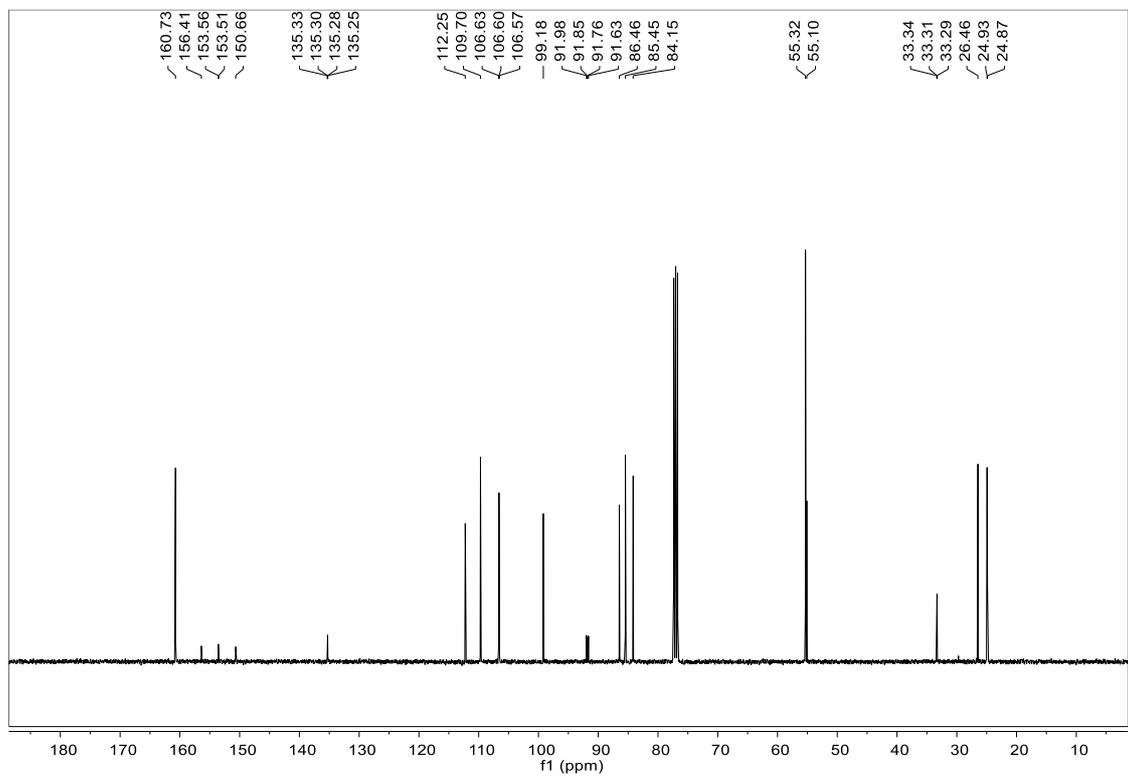
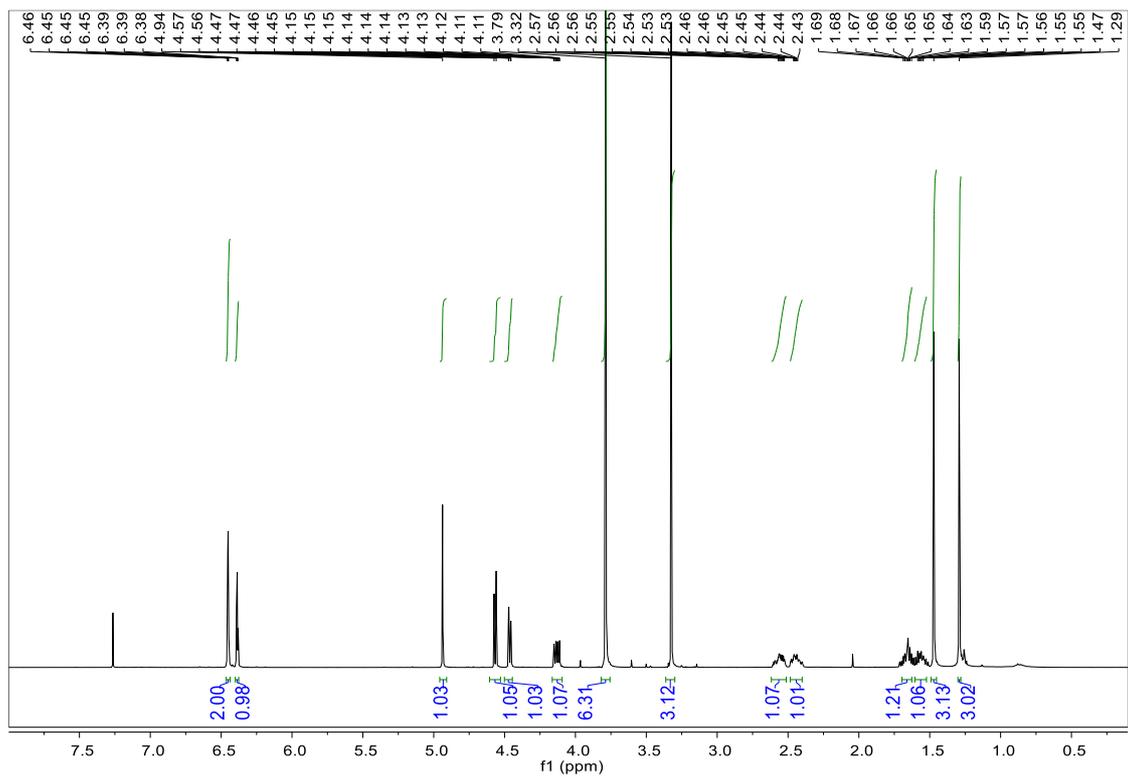
ether) to provide the title compound as a pale yellow oil in 48% yield (96 mg).

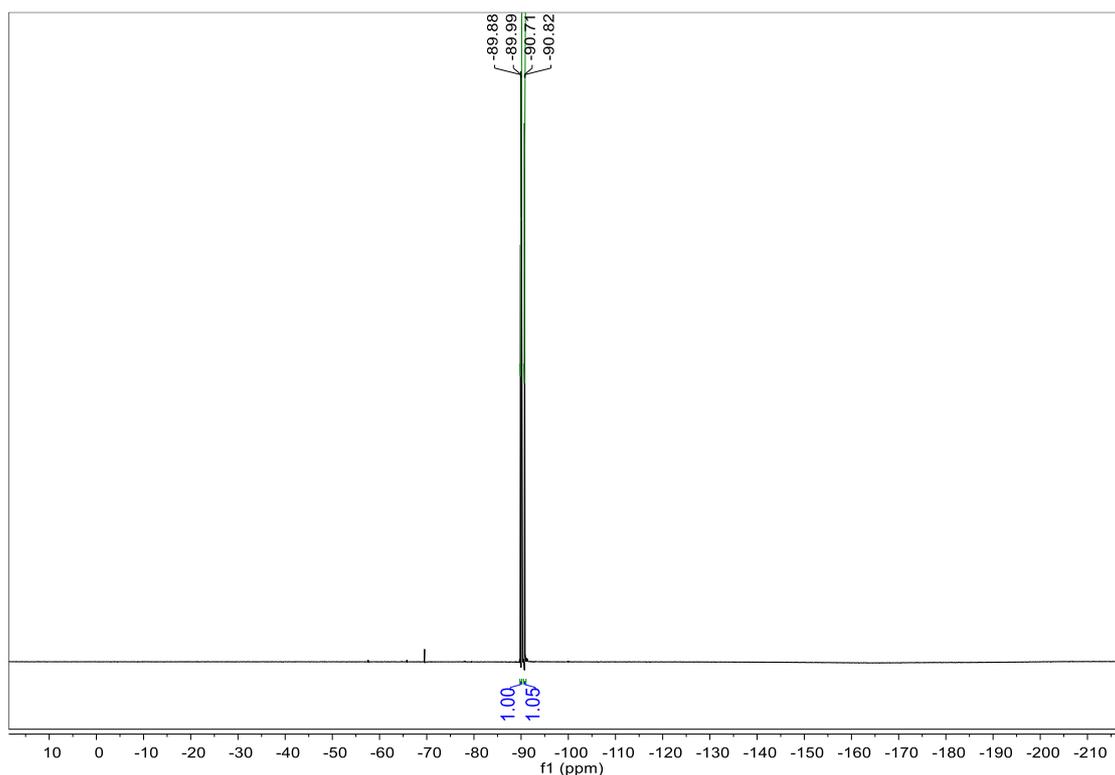
¹H NMR (400 MHz, Chloroform-*d*) δ 6.45 (dd, *J* = 2.3, 1.1 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 4.94 (s, 1H), 4.57 (d, *J* = 5.9 Hz, 1H), 4.46 (dd, *J* = 6.0, 1.0 Hz, 1H), 4.16 – 4.09 (m, 1H), 3.79 (s, 6H), 3.32 (s, 3H), 2.62 – 2.51 (m, 1H), 2.48 – 2.40 (m, 1H), 1.70 – 1.63 (m, 1H), 1.60 – 1.52 (m, 1H), 1.47 (s, 3H), 1.29 (s, 3H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 160.73, 153.53 (dd, *J* = 290.9, 286.8 Hz), 135.29 (dd, *J* = 4.8, 3.1 Hz), 112.25, 109.70, 106.60 (t, *J* = 3.3 Hz), 99.18, 91.80 (dd, *J* = 22.1, 13.2 Hz), 86.46, 85.45, 84.15, 55.32, 55.10, 33.31 (t, *J* = 2.6 Hz), 26.46, 24.93, 24.87.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -89.94 (d, *J* = 42.0 Hz, 1F), -90.77 (d, *J* = 41.8 Hz, 1F).

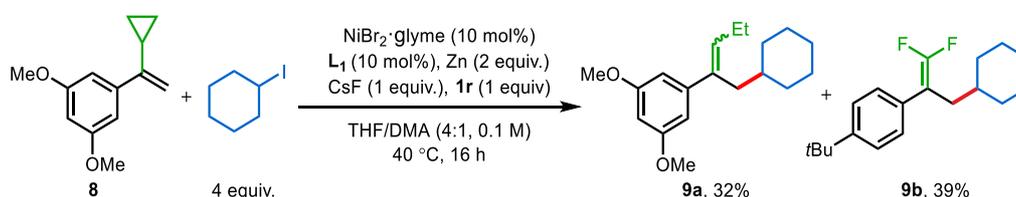
HRMS (ESI) calcd for C₂₀H₂₆F₂O₆Na⁺ [(M+Na)⁺] 423.1590, found 423.1604.





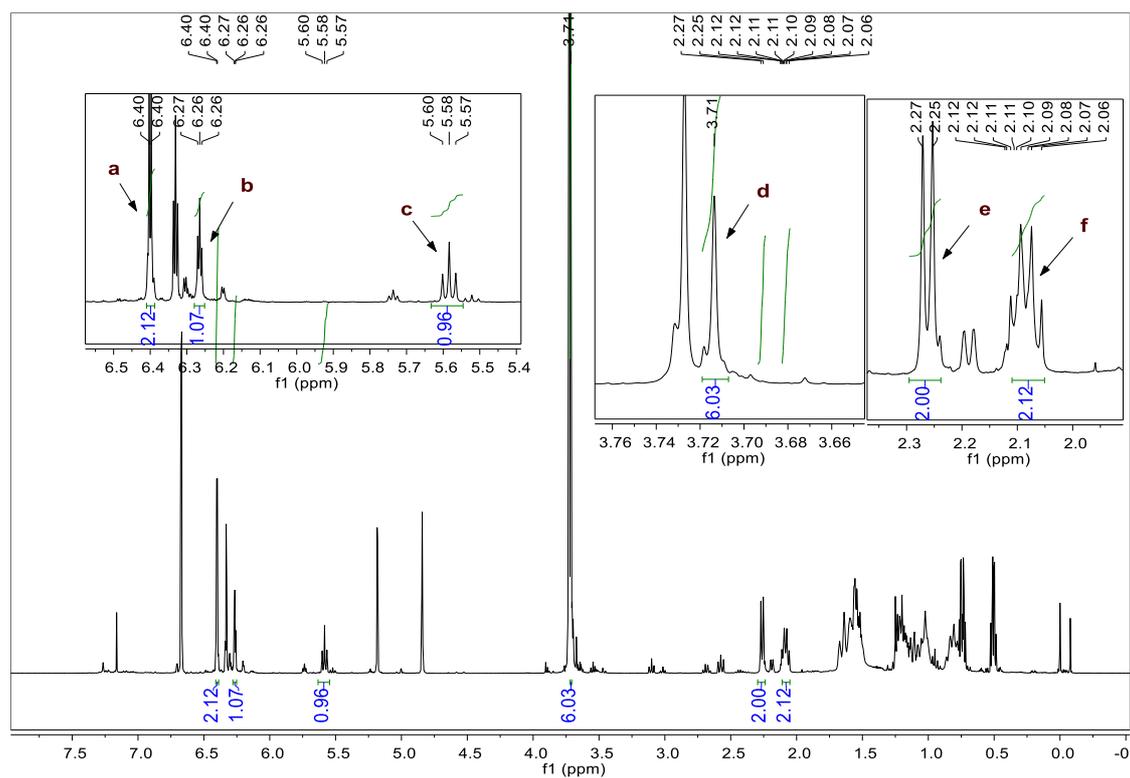
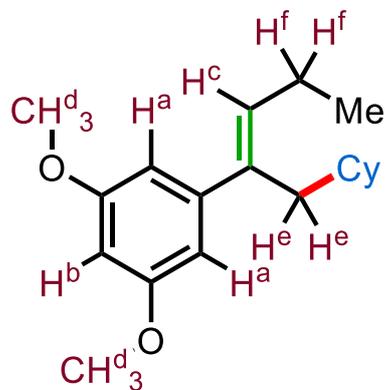
V. Control Experiments.

a. Radical Clock Experiment.

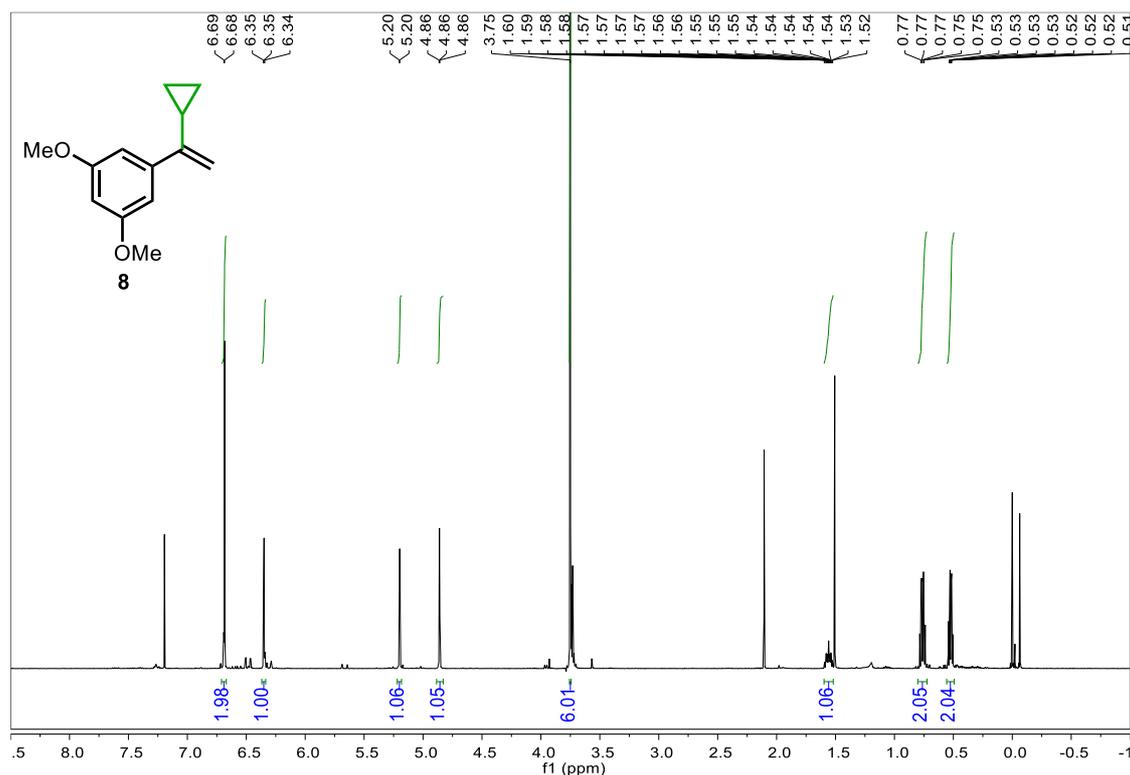


Experimental procedure: $\text{NiBr}_2 \cdot \text{DME}$ (15 mg, 0.05 mmol, 10 mol%), 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (**L**₁) (20 mg, 0.05 mmol, 10 mol%), CsF (76 mg, 0.5 mmol, 1.0 equiv.) and Zn (65 mg, 1.0 mmol, 2.0 equiv.) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and filled with nitrogen (three cycles). To these solids, THF (4 mL) and DMA (1 mL) were added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 60 seconds. Next, iodocyclohexane (210 mg, 1.0 mmol, 2.0 equiv) was added under a positive flow of argon and stirred at room temperature for another 60 seconds. Then 1-(1-cyclopropylvinyl)-3,5-dimethoxybenzene (**8**) (102 mg, 0.5 mmol, 1.0 equiv.) and 1-(*tert*-butyl)-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1r**) (114 mg, 0.5 mmol, 1.0 equiv.) were added. The reaction mixture was stirred at 40 °C for 16 hours, before it

was quenched with H₂O. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The yield was determined by ¹⁹F NMR and ¹H NMR spectroscopy.



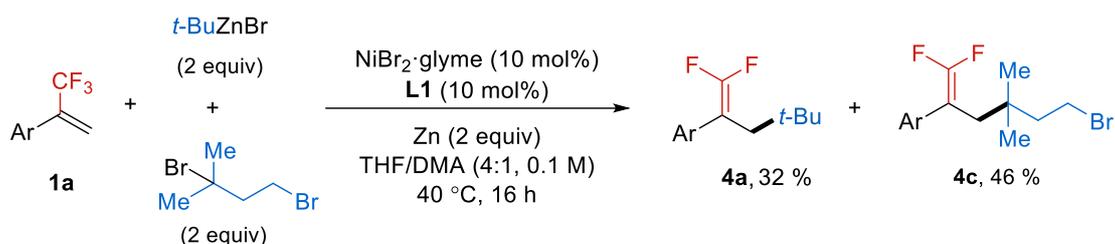
Crude ¹H NMR Spectroscopy of 8 and 9a



¹H NMR Spectroscopy of 8

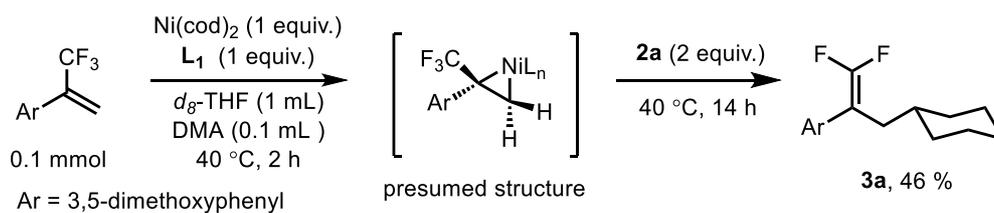
HRMS of 9a (ESI) calcd for C₁₉H₂₉O₂⁺ [(M+H)⁺] 289.2162, found 289.2162.

b. Competitive Reaction using an Organozinc and an Alkyl Halide as Reactants

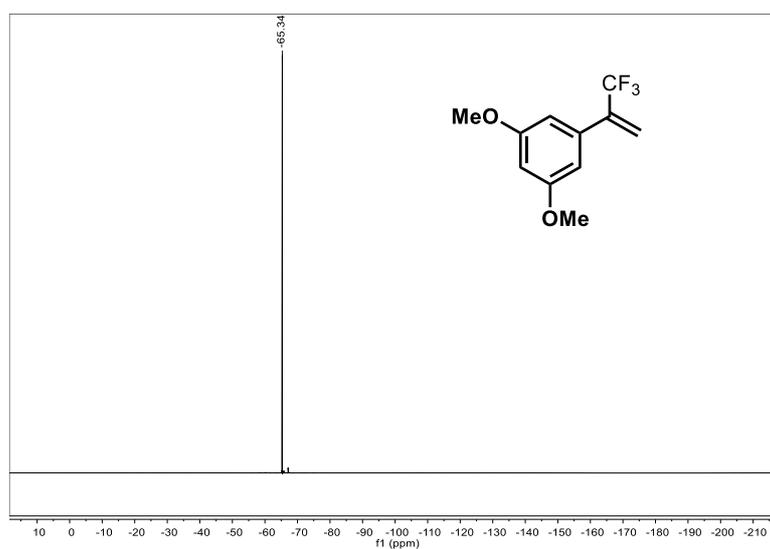


Ar = 3,5-(MeO)₂C₆H₃

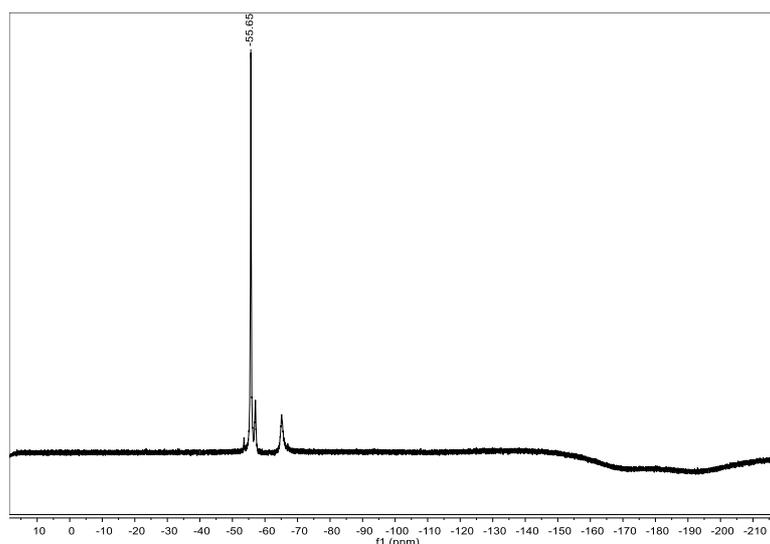
c. Preparation and Reaction of Nickelacyclopropane.



Ni(cod)₂ (28 mg, 0.1 mmol, 1 equiv) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (**L1**) (40 mg, 0.1 mmol, 1 equiv) were added to a Schlenk tube equipped with a stir bar. The Schlenk tube was evacuated and filled with nitrogen (three cycles). To these solids, THF-D₈ (1 mL) and DMA (0.05 mL) were added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 60 seconds. Next, 1,3-dimethoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)benzene (**1a**) (23 mg, 0.1 mmol, 1 equiv) was added. The reaction mixture was stirred at 40 °C for 2 hours. Subsequently, iodocyclohexane (42 mg, 0.2 mmol, 2 equiv) was added under nitrogen atmosphere, the reaction mixture was stirred at 40 °C for 16 hours, before it was quenched with H₂O. The reaction mixture was filtered through a pad of Celite, and concentrated under reduced pressure.



¹⁹F NMR spectroscopy of 1a (in THF-D₈)



¹⁹F NMR spectroscopy of the new F-species (in THF-D₈)

VII. References

- [1] Trost, B. M.; Debien, L. Palladium-Catalyzed Trimethylenemethane Cycloaddition of Olefins Activated by the σ -Electron-Withdrawing Trifluoromethyl Group. *J. Am. Chem. Soc.* **2015**, *137*, 11606-11609.
- [2] Lang, S. B.; Wiles, R. J.; Kelly, C. B.; Molander, G. A. Photoredox Generation of Carbon-Centered Radicals Enables the Construction of 1,1-Difluoroalkene Carbonyl Mimics. *Angew. Chem. Int. Ed.* **2017**, *56*, 15073-15707.
- [3] Wan, Z.-K.; Chenail, E.; Li, H.-Q.; Kendall, C.; Wang, Y.; Gingras, S.; Xiang, J.; Masefski, W. W.; Tarek, Mansour, S.; Saiah, E. Synthesis of Potent and Orally Efficacious 11 β -Hydroxysteroid Dehydrogenase Type 1 Inhibitor HSD-016. *J. Org. Chem.* **2011**, *76*, 7048-7055.
- [4] Lu, X.; Wang, Y.; Zhang, B.; Pi, J.-J.; Wang, X.-X.; Gong, T.-J.; Xiao, B.; Fu, Y. Nickel-Catalyzed Defluorinative Reductive Cross-Coupling of *gem*-Difluoroalkenes with Unactivated Secondary and Tertiary Alkyl Halide. *J. Am. Chem. Soc.* **2017**, *139*, 12632-12637.