Fluorinated cyclopropanes: Synthesis and chemistry of the aryl α,β,β-trifluorocyclopropane motif

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Contents

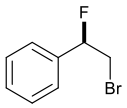
General information

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware or PTFE flask under an atmosphere of argon. Styrenes **8c** and **8d** were prepared by Wittig olefination of benzaldehydes.[1] THF, DCM, Et_2O and toluene were dried and deoxygenated using a MBraun SPS-800 solvent system. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker AV 300, Bruker AV 400, Bruker AVII 400, Bruker AVIII-HD 500 or Bruker AVIII 500 instrument. $CDCl_3$, MeOD, DMSO-d_6 or toluene-d_8 were used as solvents. Chemical shifts are reported in parts per million (ppm). Tetramethylsilane (δ 0 ppm) functioned as an external standard for ^{1}H and ^{13}C NMR experiments. $CFCl_3$ was used as an external standard for ^{19}F NMR experiments. Where appropriate, solvent signals were used as internal standard for calibration. Coupling constants (*J*) are reported in Hertz (Hz). High resolution mass spectra were recorded on a Waters Micromass GCT time of flight mass spectrometer or on a Thermo Scientific Exactive orbitrap mass spectrometer by internal mass spectroscopy service or on a Waters Xevo G2-S by the EPSRC UK National Mass Spectrometry Facility at Swansea University, UK.

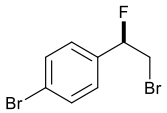
General Synthetic Procedures and Analytical Data

General procedure A for fluorobromination of styrenes **9a**-**9f**[2]

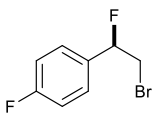
A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with NBS (1.50 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous CH_2Cl_2 and the appropriate styrene (1.00 equiv) were added sequentially via syringe. The resulting suspension was cooled to 0 ^oC and stirred for 30 minutes, followed by addition of $NEt_3.3HF$ via syringe. The reaction mixture was warmed to RT, and then stirred for 18 h. After completion, the reaction was quenched with a 28% aqueous solution of NH_3 and stirred for 10 minutes. The resulting solution was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were washed sequentially with aqueous dilute HCl (0.1 M, 50 mL) and a saturated aqueous solution of $NaHCO_3$ (50 mL), followed by drying over Na_2SO_4. After filtration, solvent was removed *in vacuo*. Purification by flash column chromatography (petroleum ether/CH_2Cl_2) afforded the appropriate (2-bromo-1-fluoroethyl)benzenes (**9a**-**9f**).



(2-Bromo-1-fluoroethyl)benzene (9a) was prepared following general procedure A, using styrene (**8a**) (5.00 g, 48.0 mmol, 1.0 equiv), *N*-bromosuccinimide (9.56 g, 52.8 mmol, 1.5 equiv), and $NEt_3.HF$ (11.76 mL, 72.00 mmol, 1.5 equiv) in CH_2Cl_2 (80 mL). The product was obtained by flash column chromatography (silica gel, 100% petroleum ether) as a colourless oil (7.209 g, 74%). ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.45-7.36 (5H, m, Ar-C<u>H</u>), 5.64 (1H, ddd, $^2J_{HF}$ = 46.8, $^3J_{HH}$ 7.9, 4.1 Hz, C<u>H</u>F), 3.74-3.57 (2H, m, C<u>H</u>$_2$Br); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 137.1 (d, $^2J_{CF}$ = 20.3 Hz, Ar-<u>C</u>), 129.3 (d, $^5J_{CF}$ = 1.4 Hz, Ar-<u>C</u>H), 128.8 (2 x Ar-<u>C</u>H), 125.7 (d, $^3J_{CF}$ = 6.6 Hz, 2 x Ar-<u>C</u>H), 92.8 (d, *J* = 177.9 Hz, <u>C</u>HF,), 34.3 (d, *J* = 28.4 Hz, <u>C</u>HBr); ^{19}F NMR (400 MHz, $CDCl_3$) δ_F -174.9 (ddd, $^2J_{HF}$ = 46.8 Hz, $^3J_{HF}$ = 25.2, 15.9 Hz, CH<u>F</u>).

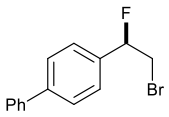


1-Bromo-4-(2-bromo-1-fluoroethyl)benzene (9b) was prepared following general procedure A, using 1-bromo-4-vinylbenzene (**8b**) (6.00 g, 32.78 mmol, 1.00 equiv), *N*-bromosuccinimide (8.90 g, 49.17 mmol, 1.50 equiv), and $NEt_3.HF$ (8.02 mL, 49.17 mmol, 1.50 equiv) in CH_2Cl_2 (40 mL). The product was obtained by flash column chromatography (silica gel, 95% petroleum ether/5% CH_2Cl_2) as a colourless oil (6.15 g, 67%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.89 (2H, d, *J* = 8.4 Hz, Ar-C<u>H</u>), 7.58 (2H, d, *J* = 8.4 Hz, Ar-C<u>H</u>), 5.93 (1H, ddd, $^2J_{HF}$ = 46.6, $^2J_{HH}$ = 7.4, 4.5 Hz, C<u>H</u>F), 4.03-3.89 (2H, m, C<u>H</u>$_2$Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 137.2 (d, $^2J_{CF}$ = 20.3 Hz, Ar-<u>C</u>), 131.92 (2 x Ar-<u>C</u>H), 127.4 (d, $^3J_{CF}$ = 6.7 Hz, 2 x Ar-<u>C</u>H), 123.6 (Ar-<u>C</u>), 92.0 (d, $^1J_{CF}$ = 178.8 Hz, <u>C</u>HF), 33.8 (d, $^2J_{CF}$ = 28.7 Hz, <u>C</u>HBr,); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -174.1 (ddd, $^2J_{HF}$ = 46.6 Hz, $^3J_{HF}$ = 24.1, 16.5 Hz, CH<u>F</u>); HRMS (ASAP$^+$) 281.8875 $[M]^+$, $C_8H_7{}^{79}Br^{81}BrF$ requires 281.8878.

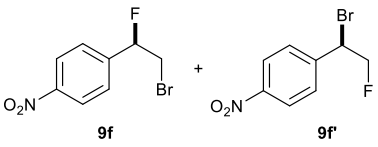


1-(2-Bromo-1-fluoroethyl)-4-fluorobenzene (9c) was prepared following general procedure A, using 1-fluoro-4-vinylbenzene (**8c**) (1.00 g, 8.19 mmol, 1.00 equiv), *N*-bromosuccinimide (2.22 g, 12.29 mmol, 1.50 equiv), and $NEt_3.HF$ (2.00 mL, 12.29 mmol, 1.50 equiv) in CH_2Cl_2 (20 mL). The product was obtained by flash column chromatography (silica gel, 90% petroleum ether/10% CH_2Cl_2) as a colourless oil (1.279 g, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.31 (2H, m, Ar-C<u>H</u>), 7.17 – 7.06 (2H, m, Ar-C<u>H</u>), 5.61 (1H, ddd, $^2J_{HF}$ = 46.4, $^3J_{HH}$ 7.6, 4.4 Hz, C<u>H</u>F), 3.87 – 3.41 (2H, m, C<u>H</u>$_2$Br); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C

163.1 (d, $^{1}J_{CF}$ = 248.2 Hz, Ar-CF), 133.0 (dd, $^{2}J_{CF}$ = 20.8 Hz, $^{3}J_{CF}$ = 3.4 Hz, Ar-C), 127.8 (dd, $^{3}J_{CF}$ = 6.9, 7.8 Hz, 2 x Ar-CH), 115.8 (d, $^{2}J_{CF}$ = 21.8 Hz, 2 x Ar-CH), 92.1 (d, $^{1}J_{CF}$ = 178.0 Hz, CHF), 34.1 (d, $^{2}J_{CF}$ = 29.0 Hz, CHBr); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -111.9 to -111.9 (m, Ar-F), -171.6 (ddd, $^{2}J_{HF}$ = 46.4 Hz, $^{3}J_{HF}$ = 24.5, 15.0 Hz, CHF).



4-(2-Bromo-1-fluoroethyl)-1,1'-biphenyl (9d) was prepared following general procedure A, using 1-vinyl-1,1'-biphenyl (**8d**) (1.00 g, 5.55 mmol, 1.00 equiv), *N*-bromosuccinimide (1.51 g, 8.32 mmol, 1.50 equiv), and NEt_3.HF (1.36 mL, 8.32 mmol, 1.50 equiv) in CH_2Cl_2 (10 mL). The product was obtained by flash column chromatography (silica gel, 95% petroleum ether/5% CH_2Cl_2 as a colourless solid (1.23 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.64-7.37 (9H, m, Ar-CH), 5.68 (1H, ddd, $^{2}J_{HF}$ = 46.5 Hz, $^{3}J_{HH}$ 7.9, 4.1 Hz, CHF), 4.77-3.61 (2H, m, CH_2Br); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 142.2 (Ar-C), 140.3 (Ar-C), 136.0 (Ar-C, d, $^{2}J_{CF}$ = 20.3 Hz), 128.9 (2 x Ar-CH), 127.7 (Ar-CH), 127.5 (2 x Ar-CH), 127.1 (2 x Ar-CH), 126.2 (d, $^{3}J_{CF}$ = 6.5 Hz, 2 x Ar-CH), 92.6 (d, $^{1}J_{CF}$ = 177.9 Hz, CHF), 34.2 (d, $^{2}J_{CF}$ = 28.6 Hz, CHBr); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -176.6 (ddd, $^{2}J_{HF}$ = 46.5 Hz, $^{3}J_{HF}$ = 25.8, 15.3 Hz, CHF), HRMS (ASAP$^+$) 261.0102 $[M\text{-}F]^+$, $C_{14}H_{12}{}^{81}$Br requires 261.0102.



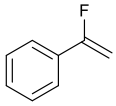
1-(2-Bromo-1-fluoroethyl)-4-nitrobenzene (9f) and 1-(1-bromo-2-fluoroethyl)-4-nitrobenzene (9f') were prepared following general procedure A (except for the use of HF-pyridine), using 1-nitro-4-vinylbenzene (**8f**) (0.25 g, 1.83 mmol, 1.00 equiv), *N*-bromosuccinimide (0.495 g, 2.78 mmol, 1.50 equiv), and HF-pyridine (0.050 mL, 2.78 mmol, 1.50 equiv) in CH_2Cl_2 (7 mL). The crude product was purified by flash column chromatography (silica gel, 70% petroleum ether/30% CH_2Cl_2) to afford the title compounds **9f** and **9f'** as a light yellow oil (0.483 g) and a light yellow oil (0.046 g), respectively (overall 39%).

9f: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.28 (2H, d, $^{3}J_{HH}$ = 8.6 Hz, Ar-CH), 7.56 (2H, d, $^{3}J_{HH}$ = 8.6 Hz, Ar-CH), 5.76 (1H, dt, $^{2}J_{HF}$ = 46.6 Hz, $^{3}J_{HH}$ = 5.6 Hz, CHF), 3.72-3.65 (2H, m, CH_2Br); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 148.3 (Ar-C), 143.9 (d, $^{2}J_{CF}$ = 20.8 Hz, Ar-C), 126.7 (d, $^{3}J_{CF}$ = 7.4 Hz, 2 x Ar-CH), 124.0 (2 x Ar-CH), 91.2 (d, $^{1}J_{CF}$ = 180.9 Hz, CHF), 33.4 (d, $^{2}J_{CF}$ = 27.4 Hz, CHBr,). ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -176.94 (dt, $^{2}J_{HF}$ = 46.6 Hz, $^{3}J_{HF}$ = 19.7 Hz, CHF). **9f'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.26-8.20 (2H, m, Ar-CH), 7.62-7.59 (2H, m, Ar-CH), 5.07 (1H, m, CHBr), 3.60-3.49 (2H, m, CH_2F); ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -150.8 to -150.9 (m, CH_2F). HRMS (EI$^+$) 248.9624 $[M]^+$, $C_8H_7NO_2F^{81}$Br requires 248.9624.

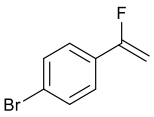
General Procedure B for Synthesis of Vinyl Fluorides **10a**-**10f**.[2]

A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with potassium *tert*-butoxide (1.15-3.00 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous THF was added via syringe before cooling the resulting suspension to 0^{o}C. After stirring at this temperature for 15 minutes, the appropriate fluorobromoethane **9a-9f** (1.00 equiv) was added via syringe. The resulting suspension was allowed to warm to RT, and then stirred for 18 h. After completion, the reaction mixture was filtered and solvent removed *in vacuo*. Purification by flash column chromatography (petroleum

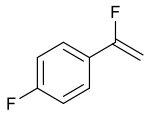
ether/CH_2Cl_2) afforded the appropriate vinyl fluoride.



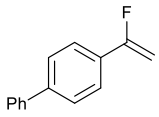
(1-Fluorovinyl)benzene (10a) was prepared following general procedure B, using (2-bromo-1-fluoroethyl)benzene (**9a**) (5.00 g, 24.60 mmol, 1.00 eq), potassium *tert*-butoxide (4.12 g, 36.19 mmol, 1.50 eq) and THF (30 mL). The product was obtained by flash column chromatography (silica gel, 100% petroleum ether) as a colourless oil (1.506 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61-6.54 (2H, m, Ar-C<u>H</u>), 7.41-7.34 (3H, m, Ar-C<u>H</u>), 5.04 (1H, dd, $^3J_{HF}$ = 49.8 Hz, $^2J_{HH}$ = 3.5 Hz, C<u>H</u>$_{trans}$H$_{cis}$), 4.86 (1H, dd, $^3J_{HF(cis)}$ = 17.3 Hz, $^2J_{HH}$ = 3.5 Hz, CH$_{trans}$<u>H</u>$_{cis}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.9 (d, $^1J_{CF}$ = 250.5 Hz, <u>C</u>F), 132.0 (d, $^1J_{CF}$ = 29.2 Hz, Ar-C), 129.4 (Ar-<u>C</u>H), 128.5 (2 x Ar-<u>C</u>H), 124.6 (d, $^3J_{CF}$ = 7.1 Hz, 2 x Ar-<u>C</u>H), 89.6 (d, $^2J_{CF}$ = 22.6 Hz, <u>C</u>H$_2$); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -107.9 (dd, $^3J_{HF\ (trans)}$ = 49.8 Hz, $^3J_{HF\ (cis)}$ = 17.3 Hz, C<u>F</u>).



1-Bromo-4-(1-fluorovinyl)benzene (10b) was prepared following general procedure B, using 1-bromo-4-(2-bromo-1-fluoroethyl)benzene (**9b**) (2.70 g, 9.65 mmol, 1.00 equiv), potassium *tert*-butoxide (1.25 g, 11.10 mmol, 1.15 equiv) and THF (25 mL). The product was obtained by flash column chromatography (silica gel, 95% petroleum ether/5% CH_2Cl_2) as a colourless oil (0.459 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54-7.49 (2H, m, Ar-C<u>H</u>), 7.43-7.40 (2H, m, Ar-C<u>H</u>), 5.04 (1H, dd, $^3J_{HF\ (trans)}$ = 49.4 Hz, $^2J_{HH}$ = 3.7 Hz, CH$_{cis}$<u>H</u>$_{trans}$), 4.88 (1H, dd, $^3J_{HF\ (cis)}$ = 17.7 Hz, $^2J_{HH}$ = 3.7 Hz, C<u>H</u>$_{cis}$H$_{trans}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.0 (d, $^1J_{CF}$ = 250.3 Hz, <u>C</u>F), 131.9 (Ar-<u>C</u>) 130.9 (d, $^2J_{CF}$ = 29.9 Hz, Ar-<u>C</u>), 131.7 (2 x Ar-<u>C</u>H), 126.2 (d, $^3J_{CF}$ = 7.1 Hz, 2 x Ar-<u>C</u>H), 90.5 (d, $^2J_{CF}$ = 22.1 Hz, <u>C</u>H$_2$); **^{19}**F NMR (471 MHz, $CDCl_3$) δ_F -108.0 (dd, $^3J_{HF\ (trans)}$ = 49.4 Hz, $^3J_{HF\ (cis)}$ = 17.7 Hz, C<u>F</u>).

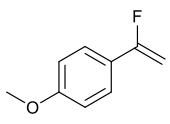


Fluoro-4-(1-fluorovinyl)benzene (10c) was prepared following general procedure B, using 1-(2-bromo-1-fluoroethyl)-4-fluorobenzene (**9c**) (3.00 g, 13.59 mmol, 1.00 equiv), potassium *tert*-butoxide (1.91 g, 16.98 mmol, 1.25 equiv) and THF (50 mL). The product was obtained by flash column chromatography (silica gel, 90% petroleum ether/10% CH_2Cl_2) to afford the title compound (**10c**) as a colourless solid (1.408 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.59-7.51 (2H, m, Ar-C<u>H</u>), 7.10-7.03 (2H, m, Ar-C<u>H</u>), 4.96 (1H, dd, $^3J_{HF\ (trans)}$ = 49.7 Hz, $^2J_{HH}$ = 3.6 Hz, CH$_{cis}$<u>H</u>$_{trans}$), 5.10 (1H, dd, $^3J_{HF\ (cis)}$ = 17.9 Hz, $^2J_{HH}$ = 3.6 Hz, C<u>H</u>$_{cis}$H$_{trans}$); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -107.03 (dd, $^3J_{HF\ (trans)}$ = 49.7 Hz, $^3J_{H,F\ (cis)}$ = 17.9 Hz, C<u>F</u>), -111.5 (m, Ar-<u>F</u>).

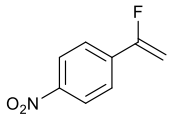


4-(1-Fluorovinyl)-1,1'-biphenyl (10d) was prepared following general procedure B, using 4-(2-bromo-1-fluoroethyl)-1,1'-biphenyl (**9d**) (0.80 g, 2.87 mmol, 1.00 equiv), potassium *tert*-butoxide (0.371 g, 3.31 mmol, 1.15 equiv) and THF (10 mL). The product was obtained by flash column chromatography (silica gel, 95% petroleum ether/5% CH_2Cl_2) as a colourless solid (0.387 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H7.67–7.62 (6H, m, Ar-CH), 7.46–7.50 (2H, m, Ar-CH), 7.38–7.41 (1H, m, Ar-CH), 5.08 (1H, dd, $^3J_{HF\ (trans)}$ = 49.7 Hz, $^2J_{HH}$ = 3.5 Hz, CH$_{cis}$<u>H</u>$_{trans}$), 4.89 (1H, dd, $^3J_{HF\ (cis)}$ = 17.9 Hz, $^2J_{HH}$ = 3.5 Hz, C<u>H</u>$_{cis}$H$_{trans}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.8 (d, $^1J_{CF}$ = 250.0 Hz, <u>C</u>F), 142.1 (Ar-<u>C</u>), 140.3 (Ar-<u>C</u>), 130.9 (d, $^2J_{CF}$ = 29.5 Hz, Ar-<u>C</u>), 128.9 (2 x Ar-<u>C</u>H), 127.7 (Ar-<u>C</u>H), 127.2 (2 x Ar-<u>C</u>H), 127.1 (2 x Ar-<u>C</u>H), 125.1 (d, $^3J_{CF}$ = 6.9 Hz, 2 x Ar-<u>C</u>H), 89.6

(d, $^{2}J_{CF}$ = 22.5 Hz, CH_2); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -108.0 (dd, $^{3}J_{H,F\ (trans)}$ = 49.7 Hz, $^{3}J_{H,F\ (cis)}$ = 17.9 Hz, CF).



1-(1-fluorovinyl)-4-methoxybenzene (10e) was prepared by a one pot sequential reaction of HF addition and HBr elimination. A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with N-bromosuccinimide (4.99 g, 27.54 mmol, 1.50 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous CH_2Cl_2 (25 mL) and 1-methoxy-4-vinylbenzene (**8e**) (2.50 g, 18.631 mmol, 1.00 equiv) were added sequentially via syringe. The resulting suspension was cooled to 0 °C and stirred for 30 minutes, followed by addition of NEt_3.3HF (4.49 mL, 27.54 mmol, 1.50 equiv) via syringe. The reaction mixture was warmed to RT, and then stirred for 4 h before cooling to 0 °C. Potassium *tert*-butoxide (16.72 g, 14.9 mmol, 8.00 equiv) was added and the resulting suspension was allowed to warm to RT. After 16 h, the reaction mixture was filtered and solvent was removed *in vacuo*. Purification by flash column chromatography (95% petroleum ether/5% CH_2Cl_2) afforded the product as a colourless oil (2.32 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.51-7.46 (2H, m, Ar-CH), 6.92-6.86 (2H, m, Ar-CH), 5.88 (1H, dd, $^{3}J_{H,F\ (trans)}$ = 50.2 Hz, $^{2}J_{HH}$ = 3.2 Hz, $CH_{cis}H_{trans}$), 4.86 (1H, dd, $^{3}J_{H,F\ (cis)}$ = 18.4 Hz, $^{2}J_{HH}$ = 3.5 Hz, $CH_{cis}H_{trans}$), 3.85 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.9 (d, $^{1}J_{CF}$ = 248.9 Hz, CF), 160.5 (Ar-C), 124.6 (d, $^{2}J_{CF}$ = 29.9 Hz, Ar-C), 126.1 (d, $^{3}J_{CF}$ = 7.2 Hz, 2 x Ar-CH), 113.8 (2 x Ar-CH), 87.6 (d, $^{2}J_{CF}$ = 23.2 Hz, CH_2), 55.3 (CH_3); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -107.1 (dd, $^{3}J_{H,F\ (trans)}$ = 50.3 Hz, $^{3}J_{H,F\ (cis)}$ = 18.1 Hz, CF).

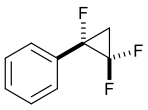


1-(1-Fluorovinyl)-4-nitrobenzene (10f) was prepared following general procedure B, using 1-(2-bromo-1-fluoroethyl)-4-nitrobenzene (**9f**) (1.50 g, 6.07 mmol, 1.00 equiv), potassium *tert*-butoxide (1.02 g, 9.11 mmol, 1.50 equiv) and THF (50 mL). The product was obtained by flash column chromatography (silica gel, 80% petroleum ether/20% CH_2Cl_2) as a colourless solid (0.790 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.25 (2H, d, *J* = 8.8 Hz, Ar-CH), 7.72 (2H, d, *J* = 8.8 Hz, Ar-CH), 5.26 (1H, dd, $^{3}J_{HF\ (trans)}$ = 48.3 Hz, $^{2}J_{HH}$ = 4.0 Hz, $CH_{cis}H_{trans}$), 5.10 (1H, dd, $^{3}J_{HF\ (cis)}$ = 17.5 Hz, $^{2}J_{HH}$ = 4.0 Hz, $CH_{cis}H_{trans}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.8 (d, $^{1}J_{CF}$ = 250.8 Hz, CF), 148.2 (C-NO_2), 137.8 (d, $^{2}J_{CF}$ = 29.9 Hz, Ar-C), 125.4 (d, $^{3}J_{CF}$ = 7.2 Hz, 2 x Ar-CH), 124.6 (d, $^{4}J_{CF}$ = 1.9 Hz, 2 x Ar-CH), 93.8 (d, $^{2}J_{CF}$ = 21.9 Hz, CH_2); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -108.16 (dd, $^{3}J_{HF\ (trans)}$ = 48.3 Hz, $^{3}J_{HF\ (cis)}$ = 17.5 Hz, CF).

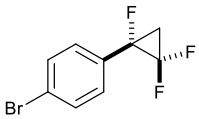
General Procedure C for Cyclopropanation of Vinyl Fluorides **11a**-**11f**.

A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with NaI (2.50-5.00 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous THF, the appropriate vinyl fluoride **10a-10f** (1.00 equiv) and trifluoromethyltrimethylsilane (2.50-5.00 equiv) were added sequentially via syringe. The resulting suspension was stirred at 75 °C for 20 h. After completion, the reaction mixture was allowed to cool to RT and solvent was removed *in vacuo*. The crude residue was diluted with diethyl ether (50 mL) and washed with distilled water (50 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed sequentially with saturated aqueous solutions of Na_2SO_3 and $NaHCO_3$, followed by drying over Na_2SO_4, filtration and evaporation of solvent *in vacuo.* Purification by flash column chromatography (petroleum ether/CH_2Cl_2)

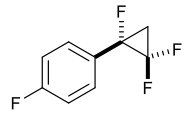
afforded the appropriate 1,2,2-trifluorocyclopropane.



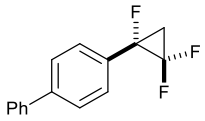
(1,2,2-Trifluorocyclopropyl)benzene (11a) was prepared following general procedure C, using (1-fluorovinyl)benzene (**10a**) (2.00 g, 16.38 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (6.05 mL, 40.94 mmol, 2.50 equiv), and NaI (6.14 g, 40.94 mmol, 2.50 equiv) in THF (60 mL). The product was obtained by flash column chromatography (silica gel, 100% petroleum ether) as a colourless oil (1.506 g, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44 (5H, s, Ar-C<u>H</u>), 2.21-2.01 (2H, m, C<u>H</u>$_2$); ^{13}C NMR (125 MHz, $CDCl_3$**)** δ_C 131.1 (d, $^{2}J_{CF}$ = 21.0 Hz, Ar-<u>C</u>), 129.5 (d, $^{5}J_{CF}$ = 2.3 Hz, Ar-<u>C</u>H,), 128.7 (2 x Ar-<u>C</u>H), 126.9 (d, $^{3}J_{CF}$ = 5.0 Hz, 2 x Ar-<u>C</u>H), 109.3 (ddd, $^{1}J_{CF}$ = 294.4, 294.1 Hz, $^{2}J_{CF}$ = 12.0 Hz, <u>C</u>F$_2$), 78.8 (ddd, $^{1}J_{CF}$ = 233.5 Hz, $^{2}J_{CF}$ = 13.0, 10.2 Hz, <u>C</u>F), 22.2 (dt, $^{2}J_{CF}$ = 12.9, 10.0 Hz, <u>C</u>H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F -136.8 (dd, $^{2}J_{FF}$ = 167.3 Hz, $^{3}J_{FF}$ 9.6 = Hz, C<u>F</u>F), -141.8 (dd, $^{2}J_{FF}$ = 167.3 Hz, $^{3}J_{FF}$ = 3.9 Hz, CF<u>F</u>), -180.9 (dd, $^{3}J_{FF}$ = 9.6 Hz, $^{3}J_{FF}$ = 3.9 Hz, C<u>F</u>); HRMS (ASAP^{+}) 173.0583 $[M+H]^{+}$, $C_9H_8F_3$ requires 173.0578.



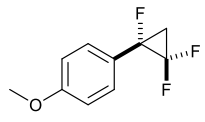
1-Bromo-4-(1,2,2-trifluorocyclopropyl)benzene (11b) was prepared following general procedure C, using 1-(1-fluorovinyl)-4-bromobenzene (**10b**) (0.500 g, 2.50 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (0.924 mL, 6.25 mmol, 2.50 equiv), and NaI (0.937 g, 6.25 mmol, 2.50 equiv) in THF (25 mL). The product was obtained by flash column chromatography (silica gel, 90% petroleum ether/10% CH_2Cl_2) as a light yellow oil (0.128 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58-7.56 (2H, d, *J* = 8.4 Hz, Ar-C<u>H</u>), 7.31-7.28 (2H, d, *J* = 8.4 Hz, Ar-C<u>H</u>), 2.22-1.98 (2H, m, C<u>H</u>$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 131.9 (2 x Ar-<u>C</u>H), 130.1 (d, $^{2}J_{CF}$ = 19.9 Hz, Ar-<u>C</u>), 128.4 (d, $^{3}J_{CF}$ = 5.1 Hz, 2 x Ar-<u>C</u>H), 123.8 (Ar-<u>C</u>), 108.9 (ddd, $^{1}J_{CF}$ = 294.8, 294.8 Hz, $^{2}J_{CF}$ = 4.1 Hz, <u>C</u>F$_2$), 79.2 (ddd, $^{1}J_{CF}$ = 235.6 Hz, $^{2}J_{CF}$ = 10.6, 2.1 Hz, <u>C</u>F), 22.4 (dt, $^{2}J_{CF}$ = 12.9, 10.0 Hz, <u>C</u>H$_2$); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -136.9 (dddd, $^{2}J_{FF}$ = 167.8 Hz, $^{3}J_{FF}$ = 8.3 Hz, $^{3}J_{FH}$ 15.2 = Hz, $^{3}J_{FH}$ = 5.6 Hz, C<u>F</u>F), -141.9 (dddd, $^{2}J_{FF}$ = 167.8 Hz, $^{3}J_{FF}$ = 3.7 Hz, $^{3}J_{FH}$ = 7.1 Hz, $^{3}J_{FH}$ = 16.6 Hz, CF<u>F</u>), -181.5 – -182.7 (m, C<u>F</u>). HRMS (ASAP^{+}): 232.9596 $[M-F]^{+}$, $C_9H_6{}^{81}BrF_2$ requires 232.9600.



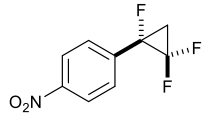
1-Fluoro-4-(1,2,2-trifluorocyclopropyl)benzene (11c) was prepared following general procedure C, using 1-(1-fluorovinyl)-4-fluorobenzene (**10c**) (0.300 g, 1.76 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (0.792 mL, 5.36 mmol, 2.50 equiv), and NaI (0.804 g, 5.36 mmol, 2.50 equiv) in THF (20 mL The product was obtained by flash column chromatography (silica gel, 90% petroleum ether/10% CH_2Cl_2) as a colourless oil (0.224 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.52-7.37 (2H, br s, Ar-C<u>H</u>), 7.17-7.06 (2H, m, Ar-C<u>H</u>), 2.21-1.96 (2H, m, C<u>H</u>$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 163.4 (d, $^{1}J_{CF}$ = 249.8 Hz, Ar-C), 129.4 (dd, $^{3}J_{CF}$ = 8.8, 4.6 Hz, 2 x Ar-<u>C</u>H), 126.9 (d, $^{3}J_{CF}$ =20.4 Hz, Ar-<u>C</u>), 115.9 (d, $^{2}J_{CF}$ = 21.9 Hz, 2 x Ar-<u>C</u>H), 108.7 (ddd, $^{1}J_{CF}$ = 295.0, 297.1 Hz, $^{2}J_{CF}$ = 12.6 Hz, <u>C</u>F$_2$), 78.7 (ddd, $^{1}J_{CF}$ = 233.3 Hz, $^{2}J_{CF}$ = 9.8, 2.2 Hz, <u>C</u>F), 22.3 (dt, $^{2}J_{CF}$ = 14.0, 10.2 Hz, <u>C</u>H$_2$); ^{19}F NMR (471 MHz, $CDCl_3$**)** δ_F -111.1 – -111.2 (m, Ar-<u>F</u>), -136.3 (dddd, $^{2}J_{FF}$ = 167.4 Hz, $^{3}J_{FF}$ = 9.3 Hz, $^{3}J_{FH}$ = 15.2 Hz, $^{3}J_{FH}$ = 5.5 Hz, C<u>F</u>F), -142.31 (dddd, $^{2}J_{FF}$ = 167.4 Hz, $^{3}J_{FF}$ = 3.8 Hz, $^{3}J_{FH}$ = 6.7 Hz, $^{3}J_{FH}$ = 16.2 Hz, CF<u>F</u>), -178.5 to -178.6 (m, C<u>F</u>). HRMS (ASAP^{+}): 189.0326 $[M-H]^{+}$, $C_9H_5F_4$ requires 189.0327.



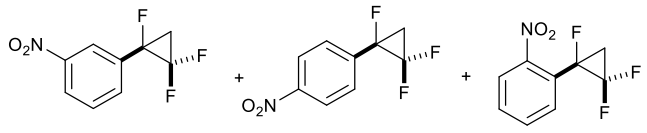
4-(1,2,2-Trifluorocyclopropyl)-1,1'-biphenyl (11d) was prepared following general procedure C, using 4-(1-fluorovinyl)-1,1'-biphenyl (**10d**) (0.180 g, 0.908 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (0.335 mL, 2.27 mmol, 2.50 equiv), and NaI (0.340 g, 2.27 mmol, 2.50 equiv) in THF (10 mL). The product was obtained by flash column chromatography (silica gel, 95% petroleum ether/5% CH_2Cl_2) as a pale yellow solid (0.209 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.67-7.59 (4H, m, Ar-C<u>H</u>), 7.51-7.44 (4H, m, Ar-C<u>H</u>), 7.40-7.36 (1H, m, Ar-C<u>H</u>), 2.24-2.05 (2H, m, C<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 130.0 (d, $^2J_{CF}$ = 19.7 Hz, Ar-<u>C</u>), 128.9 (2 x Ar-<u>C</u>H) , 127.8 (Ar-<u>C</u>H) , 127.4 (2 x Ar-<u>C</u>H) , 127.3 (2 x Ar-<u>C</u>H) , 127.2 (2 x Ar-<u>C</u>H), 126.9 (Ar-<u>C</u>), 126.5 (Ar-<u>C</u>), 108.9 (ddd, $^1J_{CF}$ = 294.5, 294.5 Hz, $^2J_{CF}$ 2.5 Hz, <u>C</u>F$_2$), 80.0-77.4 (m, <u>C</u>F), 22.4 (dt, $^2J_{CF}$ = 13.5, 10.1 Hz, <u>C</u>H$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F -136.6 (dddd, $^2J_{FF}$ = 166.0 Hz, $^3J_{FF}$ = 8.3 Hz, $^3J_{FH}$ 14.9 = Hz, $^3J_{FH}$ = 5.9 Hz, C<u>F</u>F), -141.7 (dddd, $^2J_{FF}$ = 166.0 Hz, $^3J_{FF}$ = 4.0 Hz, $^3J_{FH}$ = 7.8 Hz, $^3J_{FH}$ = 15.6 Hz, CF<u>F</u>), -180.8 – -181.0 (m, C<u>F</u>). HRMS (ASAP$^+$) 248.0809 $[M]^+$, $C_{15}H_{11}F_3$ requires 248.0813.



1-Methoxy-4-(1,2,2-trifluorocyclopropyl)benzene (11e) was prepared following general procedure C, using 1-(1-fluorovinyl)-4-methoxybenzene (**10e**) (0.150 g, 0.990 mmol, 1.00 equiv), trifluoromethyltrimethylsilane (0.365 mL, 2.47 mmol, 2.50 equiv), and NaI (0.369 g, 2.47 mmol, 2.50 equiv) in THF (8 mL). The product was obtained by flash column chromatography (silica gel, 80% petroleum ether/20% CH_2Cl_2) as a light yellow oil (0.128 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.42-7.38 (2H, m, Ar-C<u>H</u>), 6.97-6.92 (2H, m, Ar-C<u>H</u>), 3.84 (3H, s, CH_3), 2.16-1.91 (2H, m, C<u>H</u>$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.7 (Ar-<u>C</u>), 129.5 (d, $^3J_{CF}$ = 3.7 Hz, 2 x Ar-<u>C</u>H), 122.8 (d, $^2J_{CF}$ = 20.0 Hz, Ar-<u>C</u>), 114.1 (2 x Ar-<u>C</u>H), 109.5 (ddd, $^1J_{CF}$ = 295.3, 293.9 Hz, $^2J_{CF}$ = 13.4 Hz, <u>C</u>F$_2$), 78.6 (ddd, $^1J_{CF}$ = 233.5 Hz, $^2J_{CF}$ = 12.8, 9.9 Hz, <u>C</u>F), 55.4 (CH_3), 22.2 (dt, $^2J_{CF}$ = 14.4, 10.1 Hz, <u>C</u>H$_2$); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -135.7 (dddd, $^2J_{FF}$ = 166.4 Hz, $^3J_{FF}$ 9.7 Hz, $^3J_{FH}$ 15.6 Hz, $^3J_{FH}$ 5.5 Hz, C<u>F</u>F), -142.5 (dddd, $^2J_{FF}$ = 166.4 Hz, $^3J_{FF}$ 5.2 Hz, $^3J_{FH}$ 7.1 Hz, $^3J_{FH}$ 16.7 Hz, CF<u>F</u>), -175.0 – -175.2 (m, C<u>F</u>). HRMS (ASAP$^+$) 183.0625 $[M-F]^+$, $C_{10}H_{10}F_2O$ requires 183.0621.



1-Nitro-4-(1,2,2-trifluorocyclopropyl)benzene (11f) was prepared following general procedure C, using 1-(1-fluorovinyl)-4-nitrobenzene (**10f**) (0.500 g, 2.994 mmol, 1.0 equiv), trifluoromethyltrimethylsilane (2.21 mL, 14.97 mmol, 5.00 equiv), and NaI (2.24 g, 14.97 mmol, 5.00 equiv) in THF (10 mL). The product was obtained by flash column chromatography (silica gel, 80% petroleum ether/20% CH_2Cl_2) as a pale yellow oil (0.480 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.29 (2H, d, *J* = 9.0 Hz, Ar-C<u>H</u>), 7.55 (2H, d, *J* = 9.0 Hz, Ar-C<u>H</u>), 2.40-2.11 (2H, m, C<u>H</u>$_2$); ^{13}C NMR (125 MHz**,** $CDCl_3$) δ_C 148.1 (Ar-C), 138.5 (d, *J* = 19.3 Hz, Ar-<u>C</u>), 126.6 (d, *J* = 5.1 Hz, 2 x Ar-<u>C</u>H), 123.8 (2 x Ar-<u>C</u>H), 108.7 (ddd, $^1J_{CF}$ = 299.0, 294.5 Hz, $^2J_{CF}$ 11.0 Hz, <u>C</u>F$_2$), 77.4 (ddd, $^1J_{CF}$ = 234.5 Hz, $^2J_{CF}$ = 12.6, 2.2 Hz, <u>C</u>F), 23.5 (dt, $^2J_{CF}$ = 13.4, 9.7 Hz, <u>C</u>H$_2$); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -137.8 (dddd, $^2J_{FF}$ = 167.8 Hz, $^3J_{FF}$ = 8.5 Hz, $^3J_{FH}$ = 15.3 Hz, $^3J_{FH}$ = 6.8 Hz, C<u>F</u>F), -140.4 (dddd, $^2J_{FF}$ = 167.8 Hz, $^3J_{FF}$ = 2.9 Hz, $^3J_{FH}$ = 6.9 Hz, $^3J_{FH}$ = 16.3 Hz, CF<u>F</u>), -187.3 – -187.4 (m, C<u>F</u>); HRMS (ASAP$^+$) 218.0431 $[M+H]^+$, $C_9H_7F_3NO_2$ requires 218.0429.

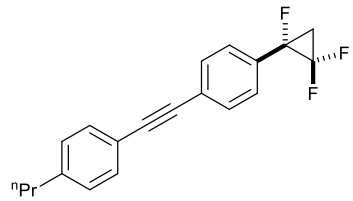


11f' **11f** **11f''**

Nitration of 11a. A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with ammonium nitrate (0.174 g, 2.56 mmol, 1.10 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. **11a** (0.400 g, 2.32 mmol, 1.00 equiv), acetonitrile (25 mL) and trifluoroacetic anhydride (1.147 mL, 8.12 mmol, 3.50 equiv) were added via syringe. The resulting solution was stirred at 60 ^{o}C for 24 h before quenching with 1M aqueous HCl solution and washing sequentially with saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (25 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness *in vacuo*. Purification of the crude residue by flash column chromatography (silica gel, 70% petroleum ether/30% CH_2Cl_2) afforded the *meta*-isomer **11f'** (0.087 g) as a pure material and the *para* - and *ortho* -isomers **11f** and **11f"** as a 3.85:1.00 mixture (0.172 g) (overall 48%).

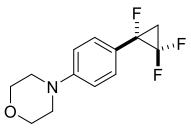
1-Nitro-3-(1,2,2-trifluorocyclopropyl) benzene (11f') ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.25-8.14 (1H, m, Ar-C<u>H</u>), 7.81 – 7.66 (3H, m, Ar-C<u>H</u>), 2.12-1.93 (2H, m, C<u>H</u>$_2$); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ_F -133.5 (dd, $^{2}J_{FF}$ = 171.9 Hz, $^{3}J_{FF}$ 7.1 = Hz, C<u>F</u>F), -142.6 (dd, $^{2}J_{FF}$ = 171.9 Hz, $^{3}J_{FF}$ = 2.6 Hz, CF<u>F</u>), -187.4 (dd, $^{3}J_{FF}$ = 7.2 Hz, $^{3}J_{FF}$ = 2.6 Hz, C<u>F</u>); HRMS (EI^{+}) 217.0340 $[M]^{+}$, $C_9H_6F_3NO_2$ requires 217.0345.

11f and **1-nitro-2-(1,2,2-trifluorocyclopropyl)benzene (11f")** (approx. 4:1 isolated). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.31 (2H, d, *J* = 8.8 Hz, **11f** Ar-C<u>H</u>), 7.83 – 7.62 (1H, m, **11f"** Ar-C<u>H</u>), 7.58 (2H, d, *J* = 8.8 Hz, **11f** Ar-C<u>H</u>), 2.48-2.12 (2.5 H, m, **11f** and **11f"** C<u>H</u>$_2$); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ_F -137.3 (dd, $^{2}J_{FF}$ = 168.5 Hz, $^{3}J_{FF}$ = 8.8 Hz, **11f"** -C<u>F</u>F), -137.6 (dd, $^{2}J_{FF}$ = 168.1 Hz, $^{3}J_{FF}$ 9.0 = Hz, **11f**-C<u>F</u>F), -140.7 (dd, $^{2}J_{FF}$ = 168.1 Hz, $^{3}J_{FF}$ = 3.0 Hz, **11f** -CF<u>F</u>), -141.4 (dd, $^{2}J_{FF}$ = 168.5 Hz, $^{3}J_{FF}$ = 3.5 Hz, **11f"** -CF<u>F</u>), -185.1 (dd, $^{3}J_{FF}$ = 9.0 Hz, $^{3}J_{FF}$ = 3.5 Hz, **11f"**-C<u>F</u>), -187.4 (dd, $^{3}J_{FF}$ = 9.4 Hz, $^{3}J_{FF}$ = 2.9 Hz, **11f**-C<u>F</u>). HRMS (ASAP^{+}) 218.0423 $[M+H]^{+}$, $C_9H_6F_3NO_2$ requires 218.0429.

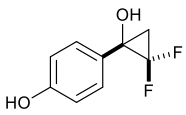


1-Propyl-4-((4-(1,2,2trifluorocyclopropyl)-phenyl)ethynyl)- benzene (13).[3] A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with PPh_3 (0.058 g, 0.220 mmol, 0.825 equiv), CuI (0.010 g, 0.058 mmol, 0.21 equiv) and $Pd(PPh_3)Cl_2$ (0.010 g, 0.014 mmol, 0.05 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous DMF (5.4 mL), Et_3N (5.4 mL), 1-ethynyl-4-propylbenzene (0.078 g, 0.540 mmol, 0.825 equiv) and **11a** (0.070 g, 0.270 mmol, 1.00 equiv) were added via syringe. The resulting suspension was stirred at 80^{o}C for 24 h before quenching with EtOAc and washing sequentially with an aqueous 1M solution of HCl (25 mL), a saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (25 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness *in vacuo*. The titled compound was obtained by flash column chromatography (silica gel, 75% petroleum ether/25% CH_2Cl_2) as a light yellow oil (0.064 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 – 7.55 (2H, m, Ar-C<u>H</u>), 7.49 – 7.42 (2H, m, Ar-C<u>H</u>), 7.39 (2H, m, Ar-C<u>H</u>), 7.20 – 7.14 (2H, m, Ar-C<u>H</u>), 2.60 (2H, t, *J* = 7.2 Hz, C<u>H</u>$_2$), 2.28 – 1.97 (2H, m, CF-C<u>H</u>$_2$-CF$_2$), 1.74 – 1.57 (2H, m, C<u>H</u>$_2$-CH$_3$), 0.94 (3H, t, *J* = 7.3 Hz, C<u>H</u>$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 143.6 (Ar-<u>C</u>), 131.7 (2 x Ar-<u>C</u>H), 131.6 (2 x Ar-<u>C</u>H), 130.7 (d, $^{2}J_{CF}$ = 19.8 Hz, Ar-<u>C</u>), 128.6 (2 x Ar-<u>C</u>H) , 126.6 (d, $^{3}J_{CF}$ = 5.5 Hz, 2 x Ar-<u>C</u>H), 124.7 (Ar-<u>C</u>), 120.0 (Ar-<u>C</u>), 109.1 (ddd, $^{1}J_{CF}$ = 295.1, 294.2 Hz, $^{2}J_{CF}$ = 11.3 Hz, <u>C</u>F$_2$), 91.0 (<u>C</u>≡C), 87.9 (C≡<u>C</u>), 79.6-77.4 (m, <u>C</u>F), 38.0 (<u>C</u>H$_2$), 24.4 (<u>C</u>H$_2$), 23.5

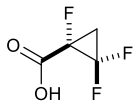
– 21.8 (m, cyclopropyl $\underline{C}H_2$), 13.8 ($\underline{C}H_3$); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -136.9 (dddd, $^2J_{FF}$ = 166.9 Hz, $^3J_{FF}$ = 15.2 Hz, $^3J_{FH}$ 8.8 = Hz, $^3J_{FH}$ = 5.7 Hz, C$\underline{F}$F), -141.5 (dddd, $^2J_{FF}$ = 167.1 Hz, $^3J_{FF}$ = 16.2 Hz, $^3J_{FH}$ = 6.6 Hz, $^3J_{FH}$ = 3.8 Hz, CF$\underline{F}$), -182.5 – -185.7 (m, C$\underline{F}$); HRMS (ASAP$^+$) 315.136 $[M+H]^+$, $C_{20}H_{18}F_3$ requires 315.1361.



4-(4-(1,2,2-trifluorocyclopropyl)phenyl)-morpholine (14). A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with BINAP (0.037 g, 0.060 mmol, 0.15 equiv), Cs_2CO_3 (0.267 g, 0.637 mmol, 1.60 equiv) and $Pd_2(dba)_3$ (0.018 g, 0.020 mmol, 0.05 equiv). The reaction vessel was sealed, then evacuated and backfilled with nitrogen. Anhydrous toluene (6.0 mL), morpholine (0.055 g, 0.637 mmol, 1.60 equiv) and **11a** (0.100 g, 0.398 mmol, 1.00 equiv) were added via syringe. The resulting suspension was stirred at 70^{o}C for 24 h before quenching with EtOAc and washing sequentially with an aqueous 1 M solution of HCl (25 mL), a saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (25 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness *in vacuo*. Purification of the crude residue by flash column chromatography (70% petroleum ether/30% CH_2Cl_2) afforded the title compound as a light yellow oil (0.095 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.32 (2H, m, Ar-C$\underline{H}$), 6.99 – 6.87 (2H, m, Ar-C$\underline{H}$), 3.96 – 3.80 (4H, m, 2 x C$\underline{H}_2$), 3.31 – 3.12 (4H, m, 2 x C$\underline{H}_2$), 2.13 – 1.89 (2H, m, CF-C$\underline{H}_2$-CF$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 152.2 (Ar-$\underline{C}$), 129.1 (2 x Ar-$\underline{C}$H), 121.3 (d, $^2J_{CF}$ = 20.0, Ar-$\underline{C}$), 115.0 (2 x Ar-$\underline{C}$H), 108.6 (ddd, $^1J_{CF}$ = 294.7, 294.9 Hz, $^2J_{CF}$ =10.8 Hz, $\underline{C}F_2$), 79.1-77.9 (m, $\underline{C}$F), 66.8 (2 x O$\underline{C}H_2$), 48.5 (2 x N$\underline{C}H_2$), 22.0 (dt, $^2J_{CF}$ = 14.8, 10.3 Hz, CH_2); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -135.7 (dddd, $^2J_{FF}$ = 166.3 Hz, $^3J_{FF}$ = 14.5 Hz, $^3J_{FH}$ 8.7, 5.3 Hz, C$\underline{F}$F), -142.6 (dddd, $^2J_{FF}$ = 166.4 Hz, $^3J_{FF}$ = 16.2 Hz, $^3J_{FH}$ = 11.4, 6.2 Hz, CF$\underline{F}$), -178.5 – -178.6 (m, C$\underline{F}$). HRMS (ESI$^+$) 258.1100 $[M+H]^+$, $C_{13}H_{15}F_3NO$ requires 258.1100.

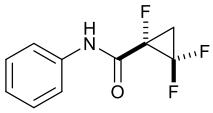


4-(2,2-Difluoro-1-hydroxycyclopropyl)phenol (17). A flame-dried round-bottomed flask equipped with a magnetic stir bar was sealed, then evacuated and backfilled with nitrogen. **11e** (0.100 g, 0.546 mmol, 1.00 equiv) and CH_2Cl_2 (18 mL) were added and the solution cooled to 0 ^{o}C. Boron tribromide (0.520 mL, 5.46 mmol, 10.00 equiv) was added dropwise over 5 minutes and the reaction mixture was stirred at 0 ^{o}C for 1 h. After completion, the reaction mixture was warmed to RT, quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness *in vacuo* to afford the title compound as colourless oil (0.091 g, 90%).^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.35 (2H, d, *J* = 8.6 Hz, Ar-C$\underline{H}$), 6.83 (2H, d, *J* = 8.6 Hz, Ar-C$\underline{H}$), 2.19 (1H, ddd, $^3J_{FH}$ = 4.7, 13.7 Hz, $^3J_{HH}$ = 9.4 Hz, CH$\underline{H}$), 2.05 (1H, ddd, 1H, ddd, $^3J_{FH}$ 4.7, 13.7 Hz, $^3J_{HH}$ = 9.3 Hz, C$\underline{H}$H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 156.3 (Ar-$\underline{C}$), 131.0 (2 x Ar-$\underline{C}$H), 128.4 (Ar-$\underline{C}$), 115.8 (2 x Ar-$\underline{C}$H), 109.6 (t, $^1J_{CF}$ = 290.8 Hz, $\underline{C}F_2$), 27.3 (t, $^2J_{CF}$ = 10.5 Hz, $\underline{C}H_2$); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F -126.9 (ddd, $^2J_{FF}$ = 149.2 Hz, $^3J_{FH}$ = 11.5 Hz, $^3J_{FH}$ 4.8 = Hz, C$\underline{F}$F), -132.3 (ddd, $^2J_{FF}$ = 148.5 Hz, $^3J_{FH}$ = 13.1 Hz, $^3J_{FH}$ = 4.7 Hz, CF$\underline{F}$); HRMS(EI$^+$) 186.0484 $[M]^+$, $C_9H_8F_2O_2$ requires 186.0492.

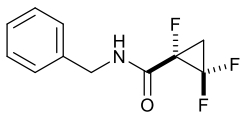


1,2,2-Trifluorocyclopropane-1-carboxylic acid (18). Ruthenium chloride (0.4 g, 0.73 mmol, 0.1 equiv) and sodium periodate (12.5 g, 58.4 mmol, 7.9 equiv) were added to a solution of **11a** (1.25 g, 7.3 mmol, 1.0 equiv) in mixed solvents of carbon tetrachloride/acetonitrile/water (70

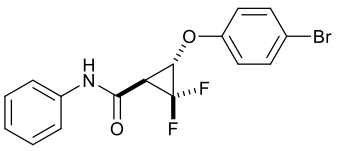
mL, v/v/v 2/2/3). The mixture was stirred at 90°C for 3 days until all starting material is consumed as monitored by ^{19}F NMR. The reaction mixture was diluted with water (100 mL). The organic layer was isolated. The aqueous layer was extracted with ethyl acetate (6 x 50 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed under vacuum to give a brown gum which gradually solidified into colourless needle crystals (0.6 g, 60%). ^{1}H NMR (500 MHz, MeOD) δ_H 2.56-2.44 (1H, m, CHH), 2.34-2.20(1H, m, CHH); ^{13}C NMR (125 MHz, MeOD) δ_C 165.6 (d, $^2J_{CF}$ 23.1 Hz, C=O), 108.6 (ddd, $^1J_{CF}$ 298.4, 288.0, $^2J_{CF}$ 9.6 Hz, CF_2), 74.6 (ddd, $^1J_{CF}$ 245.5 Hz, $^2J_{CF}$ 10.5, 13.2 Hz, CF), 22.2-21.9 (m, CH_2); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F -137.0 (dd, $^2J_{FF}$ = 163.8 Hz, $^3J_{FF}$ = 11.2 Hz, CFF), -139.0 (d, $^2J_{FF}$ = 163.8 Hz, CFF), -202.6 (*d*, $^3J_{FF}$ = 11.2 Hz, CF); HRMS (ESI$^-$) 139.0007 $[M-H]^-$, $C_4H_2F_3O_2$ requires 139.0007.



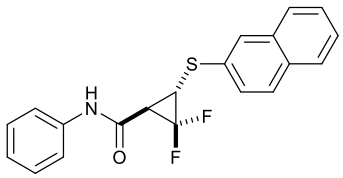
1,2,2-Trifluoro-N-phenylcyclopropane-1-carboxamide (19a). HOBt (153 mg, 1.13 mmol, 2 equiv), EDC (218 mg, 1.13 mmol, 2 equiv) were added to a solution of 1,2,2-trifluorocyclopropane-1-carboxylic acid (**18**) (80 mg, 0.57 mmol, 1 equiv), aniline (105 mg, 1.13 mmol, 2 equiv) and triethylamine (0.3 mL, 2.15 mmol, 3.8 equiv) in dichloromethane (10 mL) at 0°C. The mixture was stirred at this temperature for 1 h and then at rt overnight. After solvent removal, the residue was separated by flash column chromatography (80% petroleum ether/20% EtOAc) to afford the titled compound as light brown solid (98 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.09 (br s, 1H, NH), 7.61-7.54 (2H, m, Ar-CH), 7.41-7.36 (2H, m, Ar-CH), 7.21 (1H, tt, *J* = 7.4, 1.1 Hz, Ar-H), 2.76-2.64 (1H, m, CHH), 2.22-2.07 (m, 1H, CHH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.5 (d, $^2J_{CF}$ = 17.2 Hz, CO), 136.4 (Ar-C), 129.2 (2 x Ar-CH), 125.4 (Ar-CH), 120.4 (2 x Ar-CH), 107.6 (td, $^1J_{CF}$ = 291.7 Hz, $^2J_{CF}$ = 9.4 Hz, CF_2), 77.7 (dt, $^1J_{CF}$ = 256.3 Hz, $^2J_{CF}$ = 11.1 Hz, CF), 22.9 (q, $^2J_{CF}$ = 11.1 Hz, CH_2); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F -138.7 (dd, $^3J_{FF}$ = 3.2, $^2J_{FF}$ = 164.1 Hz, CFF), -139.2 (dd, $^3J_{FF}$ = 11.1 Hz, $^2J_{FF}$ = 164.1 Hz, CFF), -200.5 (*d*, $^3J_{FF}$ = 11.2, 2.5 Hz, CF); HRMS (ESI$^+$) 216.0628 $[M+H]^+$, $C_{10}H_9F_3NO$ requires 216.0636.



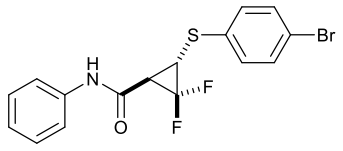
1,2,2-Trifluoro-N-benzylcyclopropane-1-carboxamide (19b). HOBt (52 mg, 0.38 mmol, 2 equiv), EDC (84 mg, 0.38 mmol, 2 equiv) and triethylamine (0.1 ml, 0.72 mmol, 3.8 equiv) was added to a solution of 1,2,2-trifluorocyclopropane-1-carboxylic acid (27 mg, 0.19 mmol, 1 equiv) and benzylamine (41 mg, 0.38 mmol, 2 equiv) in DCM (5 mL). The mixture was stirred at rt overnight. After solvent removal, the residue was purified by column chromatography (silica gel, 80% petroleum ether/20% EtOAc) to give the product as colourless solid (36 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43-7.33 (m, 5H, Ar-H), 6.68 (br s, 1H, NH), 4.62-4.53 (2H, m, CH_2NH), 2.71-2.59 (1H, m, CHH), 2.06 (1H, m, CHH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.5 (d, $^2J_{CF}$ 18.8 Hz, CO), 137.0 (Ar-C), 128.9 (2 x Ar-CH), 120.0 (3 x Ar-CH), 107.0 (dt, $^2J_{CF}$ = 9.1, $^1J_{CF}$ 295.6 Hz, CF_2), 77.8 (dt, $^1J_{CF}$ = 255.0 Hz, $^2J_{CF}$ = 11.0 Hz, CF), 43.8 (CH_2), 22.9 (dt, $^2J_{CF}$ = 10.1 Hz); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F -139.2 (m, CF_2), -202.2 (*dd*, $^3J_{FF}$ = 5.8, 8.1Hz, CF); HRMS (ESI$^+$) 230.0788 $[M+H]^+$, $C_{11}H_{11}F_3NO$ requires 230.0793.



3-(4-Bromophenyoxy)-N-phenylclopropane-1-2,2-difluoro-1-carboxamide (22). 4-Bromophenol (32 mg, 0.185 mmol, 5 equiv) and potassium carbonate (26 mg, 0.188 mmol, 5 equiv) were added to a solution of 1,2,2-trifluoro-*N*-phenylcyclopropane-1-carboxamide **19a** (8.0 mg, 0.037 mmol, 1 equiv) in acetonitrile (2 mL). The mixture was heated at 60°C for 3 days. The solvent was removed under reduced pressure. The residue was purified by preparative TLC (to give the product as white solid (4.3 mg, 32%). δ_H 7.55 (2H, d, *J* = 7.4 Hz, 2 x Ar-CH), 7.46 (2H, d, *J* = 8.9 Hz, 2 x Ar-CH), 7.40 (2H, *J* = 7.4 Hz, 2 x Ar-CH), 7.37 (s, 1H, NH), 7.20 (1H, t, *J* = 7.4 Hz, Ar-CH), 6.95 (2H, d, *J* = 8.9 Hz, 2 x Ar-CH), 4.79 (1H, ddd, $^3J_{HF}$ = 1.0, 9.9 Hz, $^3J_{HH}$ = 4.7 Hz, CHCO), 2.64 (ddd, 1H, $^3J_{HF}$ = 1.0, 15.8 Hz, $^3J_{HH}$ = 4.7 Hz, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.4 (C=O), 155.9 (Ar-C), 137.0 (Ar-C), 132.8 (2 x ArCH), 129.2 (2 x ArCH), 125.3 (Ar-CH), 120.0 (2 x Ar-CH), 116.7 (2 x Ar-CH), 115.2 (Ar-C), 108.9 (t, $^1J_{CF}$ = 296.2 Hz, CF_2), 58.1 (dd, $^2J_{CF}$ = 15.6, 7.7 Hz, C-3), 35.5 (dd, $^2J_{CF}$ = 12.3, 9.4 Hz, C-1); ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -131.8 (dd, $^3J_{HF}$ 10.2 Hz, $^2J_{FF}$ 165.0 Hz, CFF), -133.7 (ddd, $^3J_{HF}$ 13.0, 1.5 Hz, $^2J_{CF}$ = 165.0 Hz, CFF); HRMS (ESI^+) 368.0087 $[M+H]^+$, $C_{16}H_{13}{}^{79}BrF_2NO_2$ requires 389.0092.

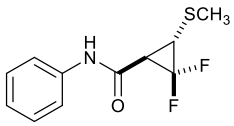


2,2-Difluoro-3-(naphthalen-2-ylthio)-N-Phenylcyclopropane-1-carboxamide (23a). Sodium hydride (6 mg, 60% in mineral oil, 0.15 mmol, 3 equiv) was added to a solution of 1,2,2-trifluoro-*N*-phenylcyclopropane-1-carboxamide (11 mg, 0.05 mmol) **19a** and naphthalene-2-thiol (18.9 mg, 0.1 mmol, 2 equiv) in THF (1 mL) at °C. The mixture was stirred at this temperature until the starting material was completely consumed (ca 4h). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (silica gel, 80% petroleum ether/20% EtOAc) to give the product as brownish solid (12 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83-7.77 (4H, m, 4 x Ar-CH), 7.53-7.48 (4H, m, 4 x Ar-CH), 7.47-7.43 (1H, m, Ar-CH), 7.42 (br s, 1H, NH), 7.38-7.34 (2H, m, 2 x Ar-CH), 7.12 (1H, t, *J* = 7.5 Hz, Ar-CH), 3.89 (dd, 1H, $^3J_{HH}$ = 6.8 Hz, $^3J_{HF}$ = 13.3 Hz, CHCO), 2.54 (dd, 1H, $^3J_{HH}$ = 6.8 Hz, $^3J_{HF}$ 12.5 Hz, CHS); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 161.0 (CO), 137.1 (Ar-C), 133.7 (Ar-C), 132.0 (Ar-C), 131.4 (Ar-C), 129.2 (2 x Ar-CH), 129.0 (Ar-CH), 127.8 (Ar-CH), 127.3 (Ar-CH), 126.9 (Ar-CH), 126.7 (Ar-CH), 126.2 (Ar-CH), 126.1 (Ar-CH), 125.1 (Ar-CH), 120.1 (2 x Ar-CH), 111.1 (t, $^1J_{CF}$ = 294.7 Hz, CF_2), 36.7 (t, $^2J_{CF}$ 10.1 Hz, CH), 28.4 (t, $^2J_{CF}$ = 11.5 Hz, CH); ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -130.5 (dd, $^3J_{HF}$ = 2.1 Hz, $^2J_{FF}$ = 150.5 Hz, CFF), -132.8 (dd, $^3J_{HF}$ 13.2 Hz， $^2J_{FF}$ = 150.5 Hz, CFF); HRMS (ESI^+) 378.0726 $[M+Na]^+$, $C_{20}H_{15}F_2NOSNa$ requires 378.0740.

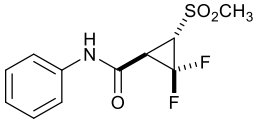


3-((4-Bromophenyl)thio)-2,2-difluoro-N-phenylcyclopropane-1-carboxamide (23b). Sodium hydride (4.5 mg, 60% in mineral oil, 0.11 mmol, 3 equiv) was added to a solution of 1,2,2-trifluoro-*N*-phenylcyclopropane-1-carboxamide **19a** (7.8 mg, 0.036 mmol, 1 equiv) and 4-bromothiophenol (13.6 mg, 0.072 mmol, 2 equiv) in THF (1 mL) at °C under argon atmosphere. The mixture was stirred at this temperature until the starting material was completely consumed (ca 4 h). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (silica gel, 80% petroleum ether/20% EtOAc) to give the product as white solid (9.0 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.53 (2H, d, *J* = 7.7 Hz, 2 x Ar-

H), 7.48 (2H, d, *J* = 8.4 Hz, 2 x ArH), 7.48 (2H, d, *J* = 7.7 Hz, 2 x ArH), 7.36 (1H, br s, NH), 7.25 (2H, d, *J* = 8.4 Hz, 2 x ArH), 7.19 (1H, t, *J* = 8.4 Hz, Ar-H), 3.77 (dd, 1H, $^3J_{HH}$ = 6.8 Hz, $^3J_{HF}$ = 12.9 Hz, CHCO), 2.51 (dd, 1H, $^3J_{HH}$ = 6.8 Hz, $^3J_{HF}$ = 12.1 Hz, CHS); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.6 (C=O), 137.1 (Ar-C), 133.2 (Ar-C), 132.8 (Ar-C), 132.4 (2 x Ar-CH), 129.8 (2 x Ar-CH), 129.2 (2 x Ar-CH), 125.2 (Ar-CH), 119.9.1 (2 x Ar-CH), 110.8 (t, $^1J_{CF}$ = 278.3 Hz, CF_2), 36.6 (t, $^2J_{CF}$ = 10.0 Hz, CH), 28.0 (t, $^2J_{CF}$ = 11.0 Hz, CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F -130.5 (d, $^2J_{FF}$ 151.0 Hz, CFF), -132.9 (d, $^2J_{CF}$ = 151.0 Hz, CFF); ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -130.5 (dd, $^2J_{HF}$ = 12.1 Hz, $^2J_{FF}$ = 151.0 Hz, CFF), -132.9 (d, $^2J_{FF}$ = 13.1 Hz, $^2J_{CF}$ = 151.0 Hz, CFF); HRMS (ESI$^+$) 405.9679 $[M+Na]^+$, $C_{16}H_{12}F_2NOBrSNa$ requires 405.9683.



2,2-difluoro-3-(methylthio)-N-phenylcyclopropane-1-carboxamide (23c). Sodium thiomethoxide (15.6 mg, 0.22 mmol, 4.8 eq) was added to a solution of 1,2,2-trifluoro-*N*-phenylcyclopropane-1-carboxamide (**19a**) (10.0 mg, 0.046 mmol, 1 eq) in acetonitrile (3 mL). The mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The residue was purified by preparative TLC to give the product as white solid (8.1 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.53 (2H, d, *J* = 7.9 Hz, 2 x Ar-CH), 7.38 (1H, s, NH), 7.35 (2H, t, *J* = 7.9 Hz, 2 x Ar-CH), 7.17 (1H, t, *J* = 7.3 Hz, Ar-CH), 3.43 (ddd, 1H, $^3J_{HH}$ = 6.6 Hz, $^3J_{HF}$ = 1.9, 11.5 Hz, CHC=O), 2.42 (ddd, 1H, $^3J_{HH}$ = 6.6 Hz, $^3J_{HF}$ = 1.7, 10.5 Hz, CHS), 2.29 (s, 3H, SMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 161.4 (C=O), 137.2 (ArC), 129.2 (2 x Ar-CH), 125.0 (Ar-CH), 119.9 (2 x Ar-CH), 111.6 (dd, $^1J_{CF}$ = 288.3, 292.8 Hz, CF_2), 36.6 (t, $^2J_{CF}$ = 10.3 Hz, CHCO), 29.4 (t, $^2J_{CF}$ = 11.3 Hz, CHS), 16.1 (s, SCH_3; ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F -132.6 (d, $^2J_{FF}$ 151.2 Hz, CFF), -133.2 (d, $^2J_{CF}$ = 151.2 Hz, CFF); ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -132.6 (ddd, $^3J_{HF}$ 11.0, 2.0 Hz, $^2J_{FF}$ 151.2 Hz, CFF), -133.2 (dd, $^3J_{HF}$ 12.2 Hz, $^2J_{CF}$ = 151.2 Hz, CFF); HRMS (ESI$^+$) 266.0416 $[M+Na]^+$, $C_{11}H_{11}F_2NOSNa$ requires 266.0422.



2,2-Difluoro-3-(methylsulfonyl)-N-phenylcyclopropane-1-carboxamide (25). *meta*-Chloroperoxybenzoic acid (48.6 mg (70%), 197 μmol, 4.0 equiv) was added to a solution of **23c** (12.1 mg, 49 μmol, 1.0 equiv) in DCM (5 mL). The mixture was stirred at rt for 4 hours before being quenched with saturated sodium metabisulfite. The mixture was diluted with DCM (5 mL) and the layers were isolated. The organic layer was washed with water, aqueous sodium bicarbonate and brine. After dryness ($MgSO_4$), the solvent was removed under reduced pressure. The residue was purified by preparative TLC (silica gel, 70% petroleum ether/30% EtOAc), to give the product as white solid (10.9 mg, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.60 (br s, 1H, NH), 7.53 (2H, d, *J* = 7.7 Hz, 2 x Ar-H), 7.38 (2H, t, *J* = 7.7 Hz, 2 x Ar-H), 7.21 (1H, t, *J* = 7.7 Hz, Ar-H), 3.98 (ddd, 1H, $^3J_{HH}$ = 7.0 Hz, $^3J_{HF}$ = 1.5, 11.5 Hz, CHCO), 3.41 (ddd, 1H, $^3J_{HH}$ = 7.0 Hz, J_{HF} = 1.2, 13.1 Hz, CHS), 3.18 (s, 3H, SCH_3); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 10.69 (s, 1H, NH), 7.58 (d, 2H, *J* = 7.8 Hz, 2 x Ar-CH), 7.38 (t, 1H, *J* = 7.8 Hz, Ar-CH), 7.12 (t, *J* = 7.4 Hz, Ar-CH), 4.45 (d, 1H, $^3J_{HH}$ = 7.9 Hz, $^3J_{HF}$ = 12.7 Hz, CHCO), 3.64 (dd, 1H, $^3J_{HH}$ = 7.9 Hz, $^3J_{HF}$ = 14.5 Hz, CHS), 3.31 (3H, s, CH_3); ^{1}H NMR (400 MHz, MeOD) δ_H 7.60-7.57 (2H, m, 2 x Ar-CH), 7.37-7.32 (2H, m, 2 x Ar-CH), 7.14 (1H, tt, *J* = 7.4, 1.1 Hz, Ar-CH), (CHCO at around 3.98 in $CDCl_3$ was not observed as it was exchanged to CDCO), 3.59 (1H, d, $^3J_{HF}$ = 14.0 Hz, CHS, over weekend, this signal disappeared as it was exchanged by deuterated MeOD), 3.22 (3H, s, SCH_3); ^{13}C NMR (125 MHz, MeOD) δ_C 159.6 (C=O), 138.0 (Ar-C), 128.6 (2 x Ar-CH), 124.3 (Ar-CH), 119.6 (2 x Ar-

CH), 107.2 (t, $^{1}J_{CF}$ = 291.0 Hz, CF_2), signals for CDCO and CDCS too weak to be observed, 41.4 (SCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C 159.7 (C=O), 138.8 (Ar-C), 129.5 (2 x Ar-CH), 124.6 (Ar-CH), 119.6 (2 x Ar-CH), 108.0 (t, $^{1}J_{CF}$ = 291.0 Hz, CF_2), 42.8 (SCH_3), 42.6 (t, $^{2}J_{CF}$ = 9.6 Hz, CHCO), 32.2 (t, $^{2}J_{CF}$ = 9.0 Hz, CHS; ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F -131.8 (d, $^{2}J_{FF}$ 160.1 Hz, CFF), -133.7 (d, $^{2}J_{CF}$ = 160.1 Hz, CFF); ^{19}F NMR (470 MHz, $CDCl_3$) δ_F -131.8 (ddd, $^{3}J_{HF}$ 11.0, 1.0 Hz, $^{2}J_{FF}$ 160.1 Hz, CFF), -133.7 (ddd, $^{3}J_{HF}$ 13.0, 1.5 Hz, $^{2}J_{CF}$ = 160.1 Hz, CFF); ^{19}F{^{1}H} NMR (470 MHz, DMSO-d_6) δ_F -131.2 (d, $^{2}J_{FF}$ 157.1 Hz, CFF), -133.8 (d, $^{2}J_{CF}$ = 157.1 Hz, CFF); ^{19}F NMR (470 MHz, DMSO-d_6) δ_F -131.2 (dd, $^{3}J_{HF}$ 12.8 Hz, $^{2}J_{FF}$ 157.1 Hz, ½ CF_2), -133.8 (dd, $^{3}J_{HF}$ 14.7 Hz, $^{2}J_{CF}$ = 160.1 Hz, ½CF_2); HRMS (ESI$^+$) 276.0496 $[M+H]^+$, $C_{11}H_{11}F_2NO_3S$ requires 276.0500, for the deuterated version HRMS (ESI$^+$) 3010503 $[M+Na]^+$, $C_{11}H_8D_3F_2NO_3SNa$ requires 301.0514.

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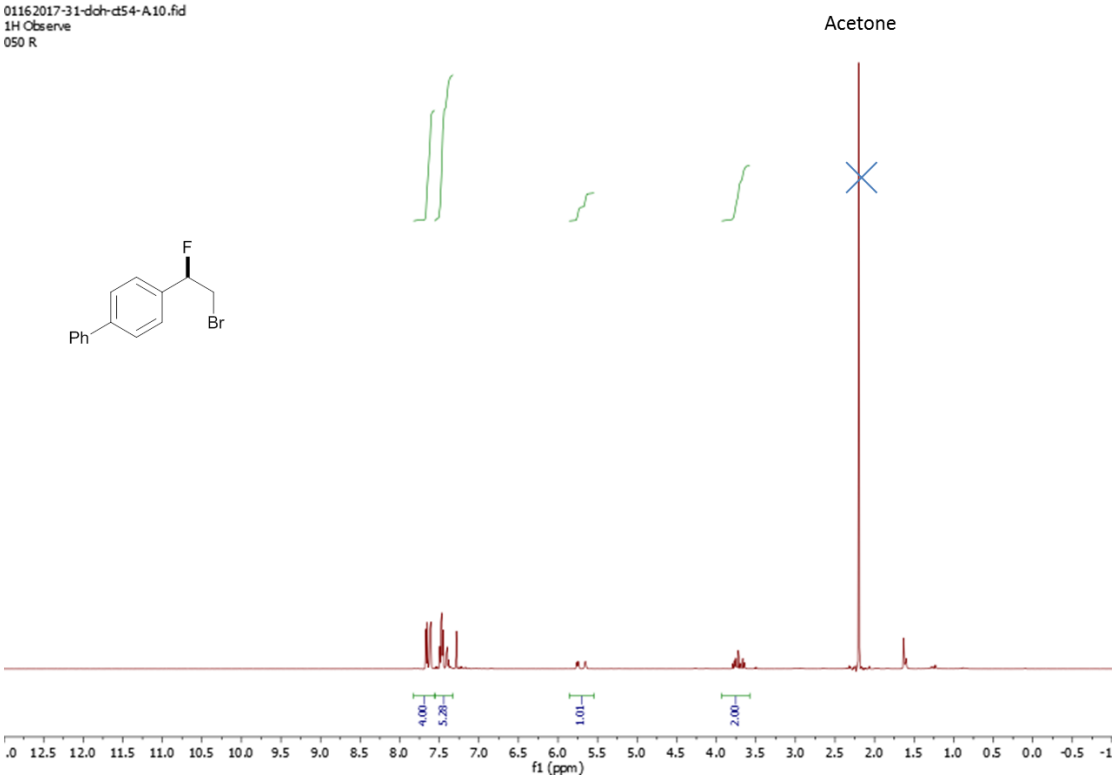
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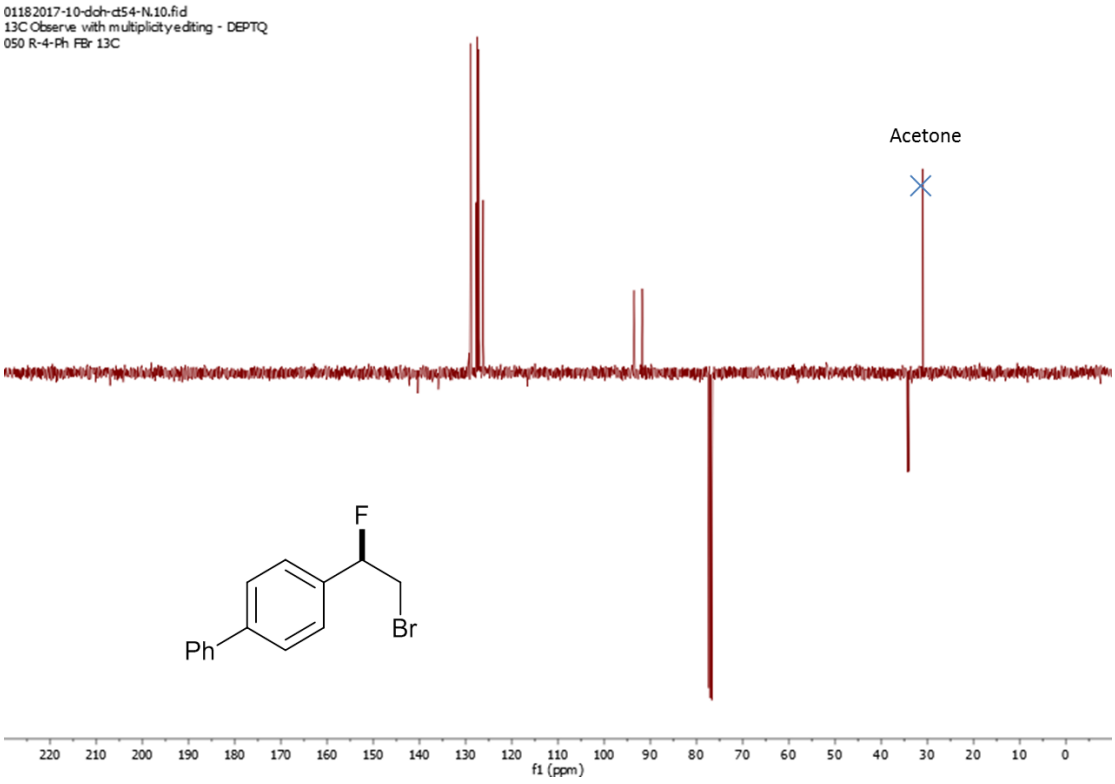
1H Observe
050 R
Acetone
F
Ph
Br
4.00
5.28
1.01
2.00
f1 (ppm)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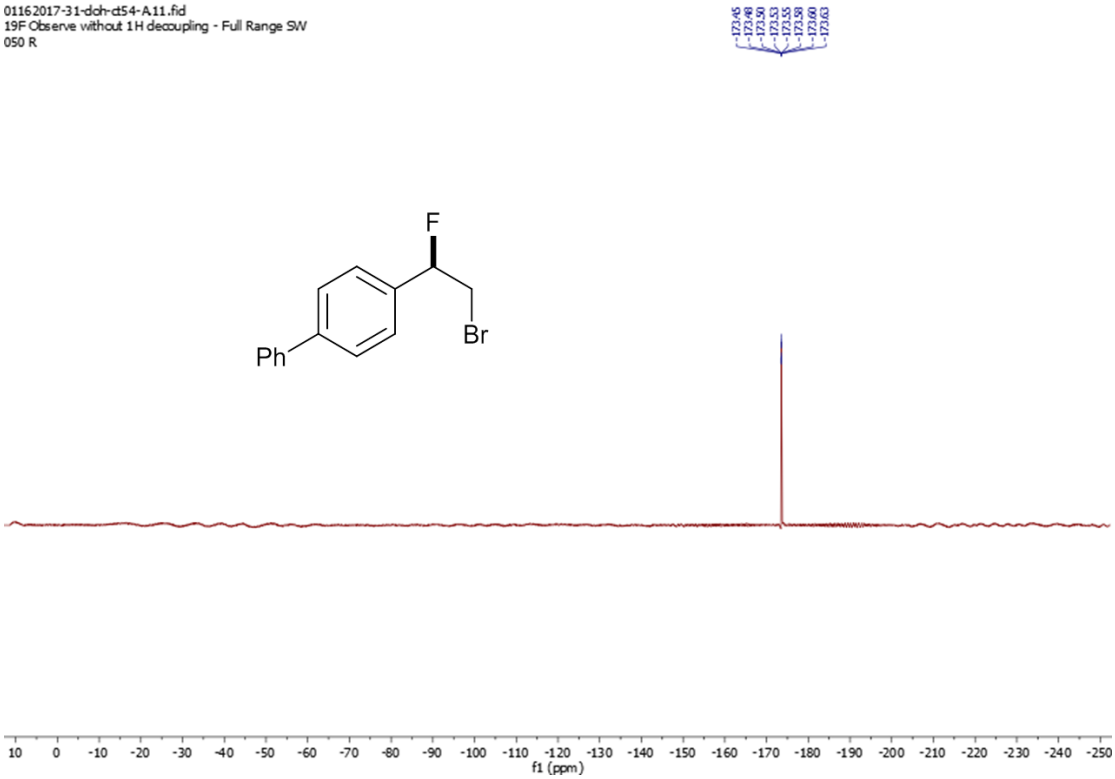
13C Observe with multiplicity editing - DEPTQ
050 R-4-Ph FBr 13C
Acetone
F
Ph
Br
f1 (ppm)

01162017-31-doh-ct54-A11.fid
19F Observe without 1H decoupling - Full Range SW
050 R



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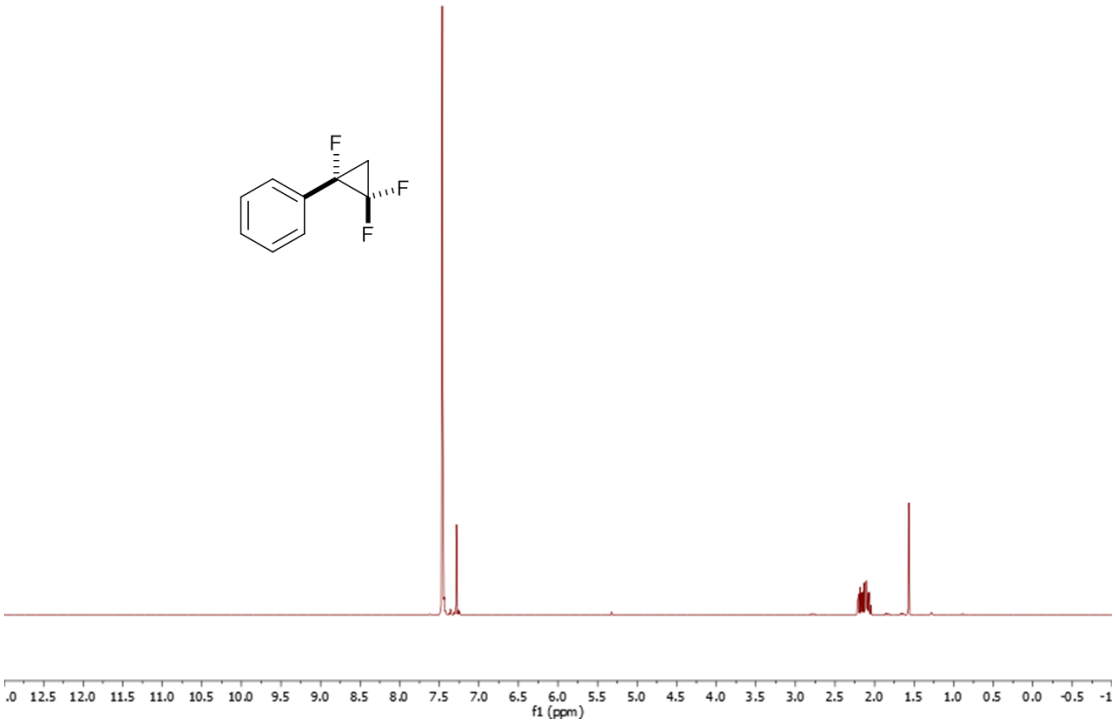
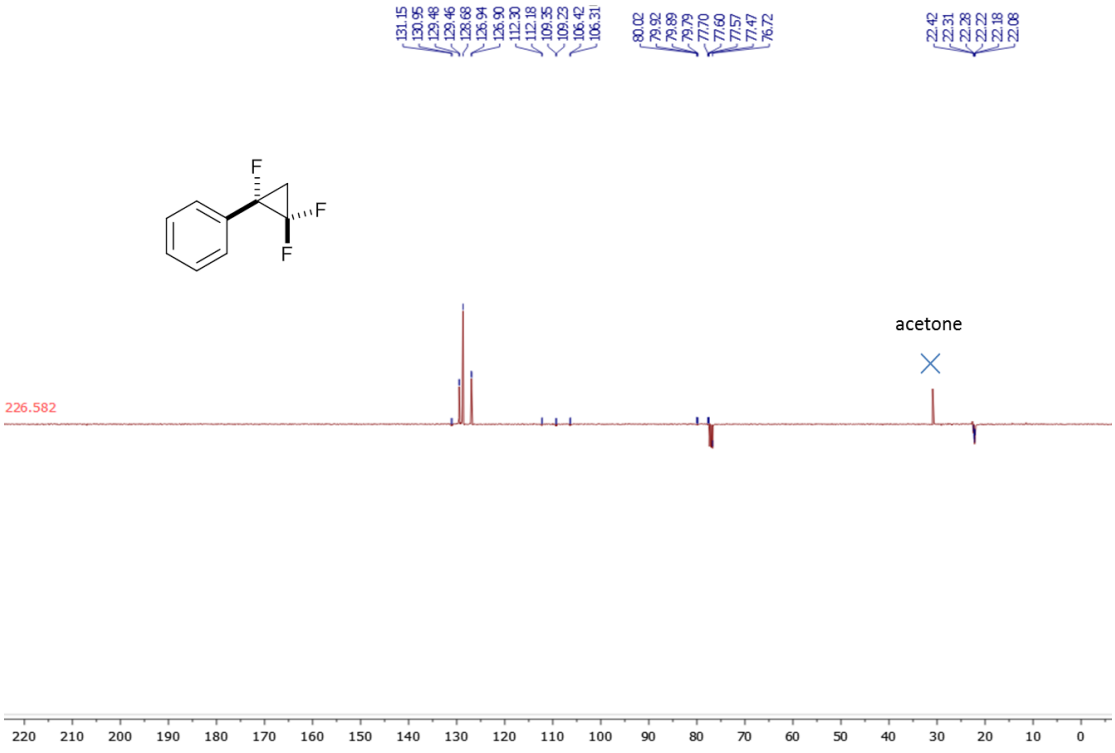
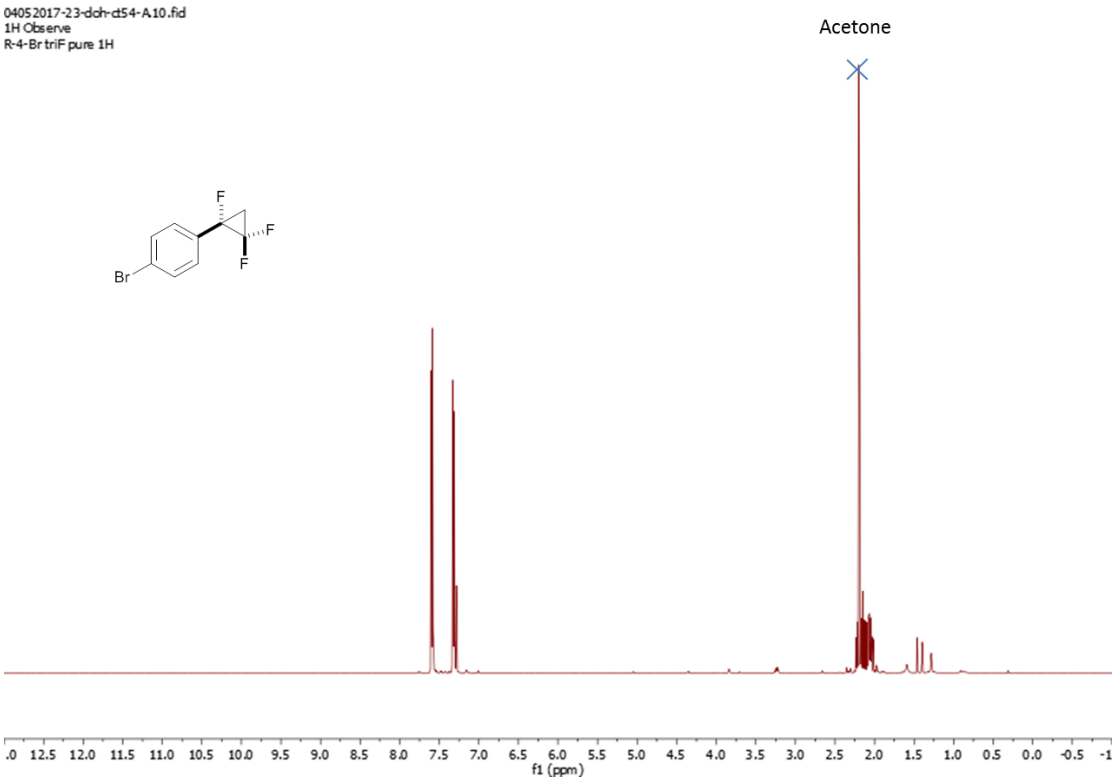
1H Observe
PhtriF CDCl3 1H




131.15
130.95
129.48
129.46
128.88
126.94
126.90
112.30
112.18
109.35
109.23
106.42
106.31
80.02
79.92
79.89
79.79
77.70
77.60
77.57
77.47
76.72
22.42
22.31
22.28
22.22
22.18
22.08
F
F
F
acetone
226.582
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
0814 2017-26-doh-qz-N.10.fid
19F Observe with 1H decoupling - Full Range SW
QZDH338 big scale
F
F
F
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)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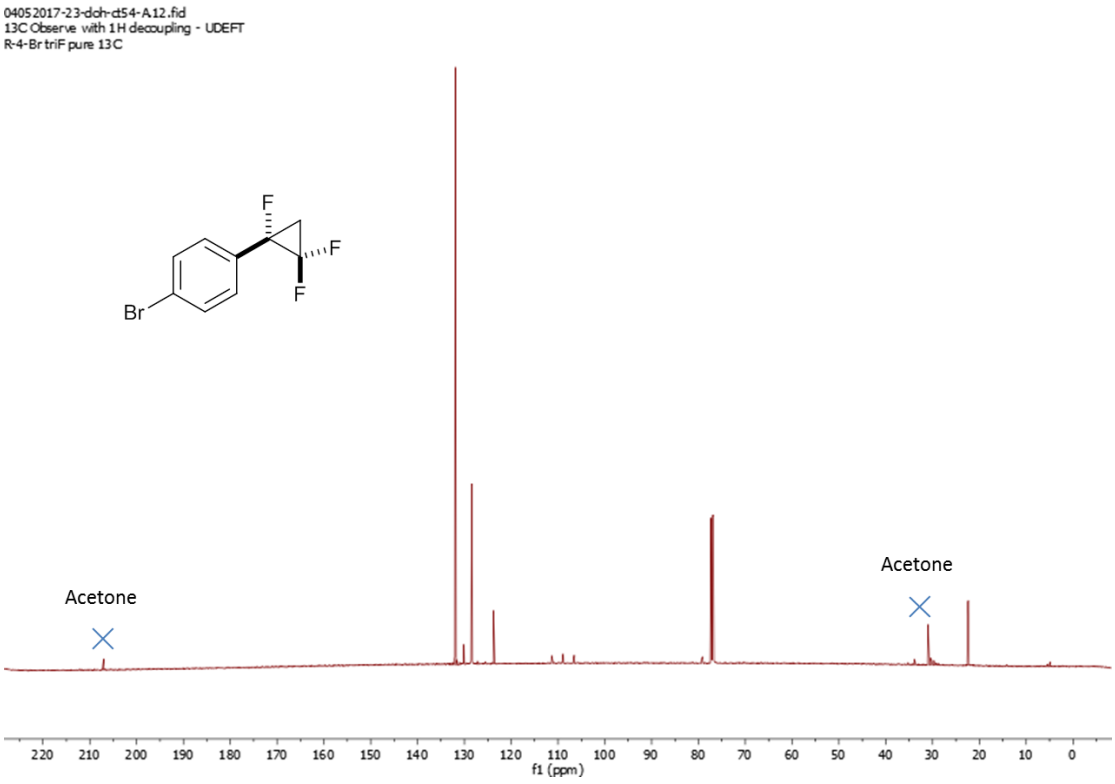
1H Observe
R-4-Br triF pure 1H
Acetone
F
F
F
Br
.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)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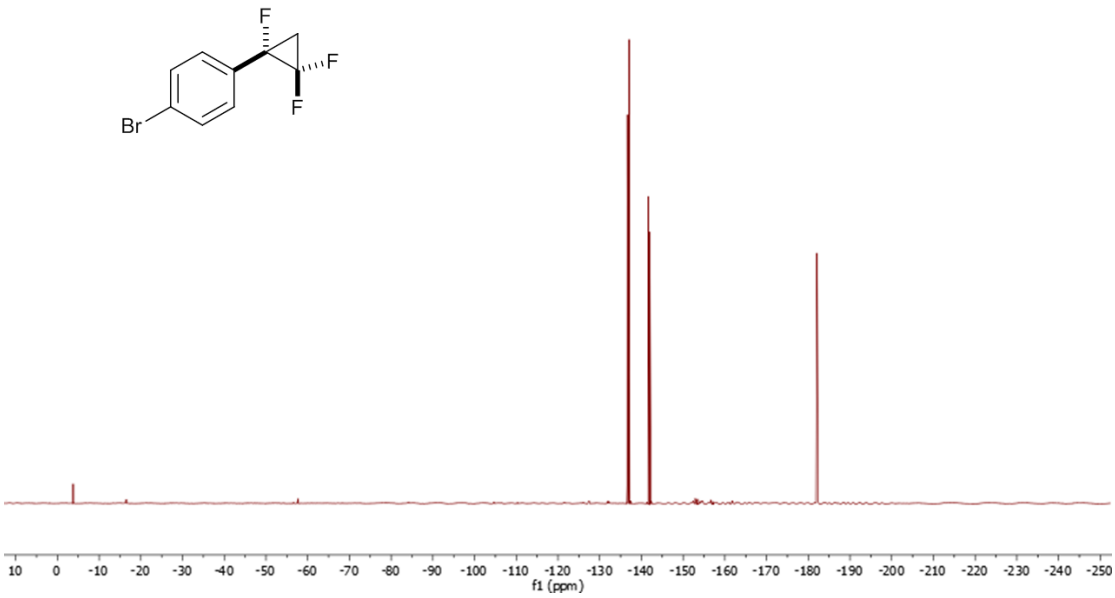
13C Observe with 1H decoupling - UDEFT
R-4-Br triF pure 13C
F
F
F
Br
Acetone
Acetone
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

04052017-23-doh-ct54-A.11.fid
19F Observe without 1H decoupling - Full Range SW
R-4-Br triF pure 19Fcp



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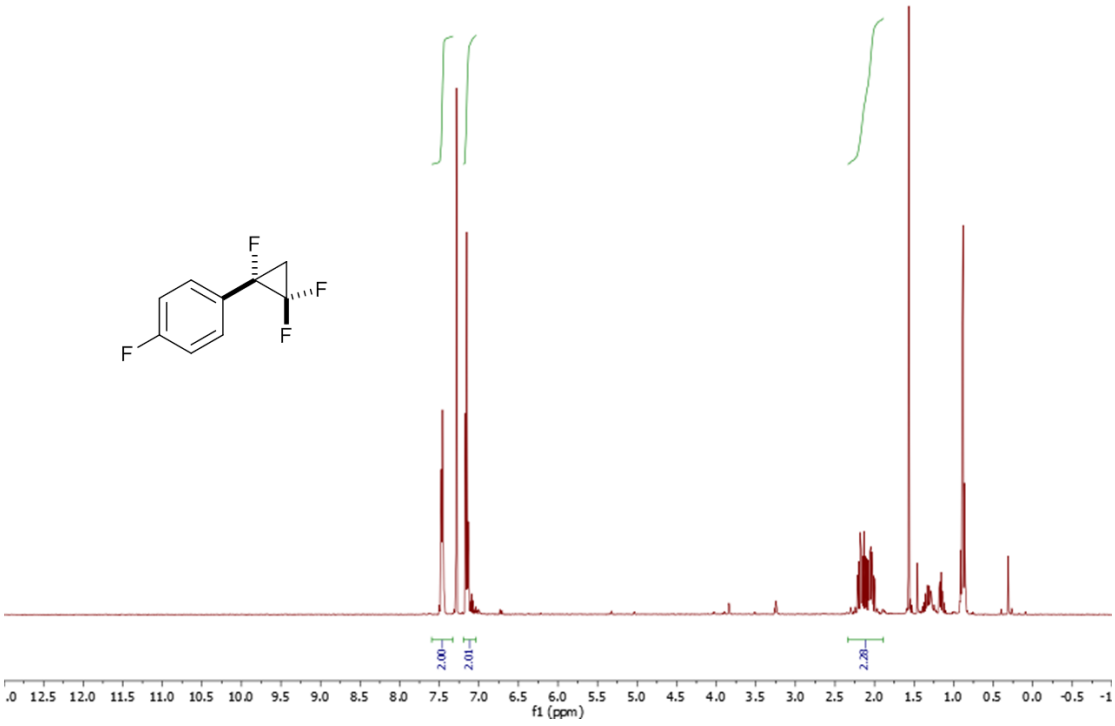
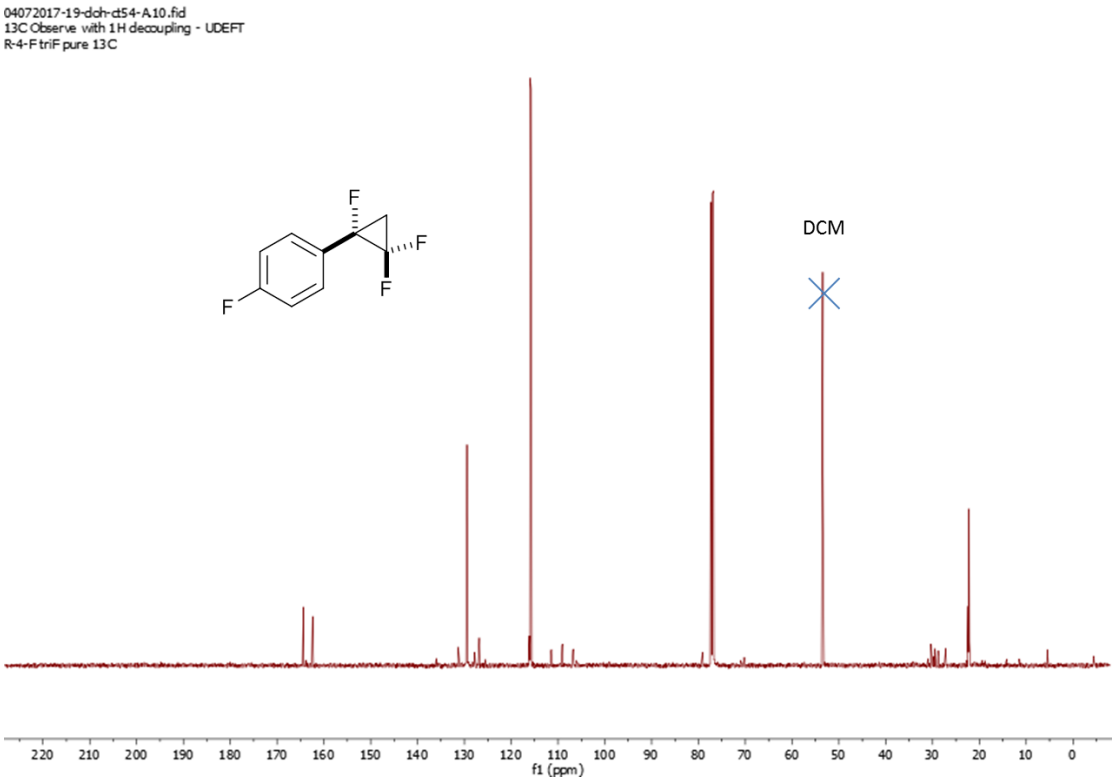
1H Observe
R-4-F triF top spot 1H

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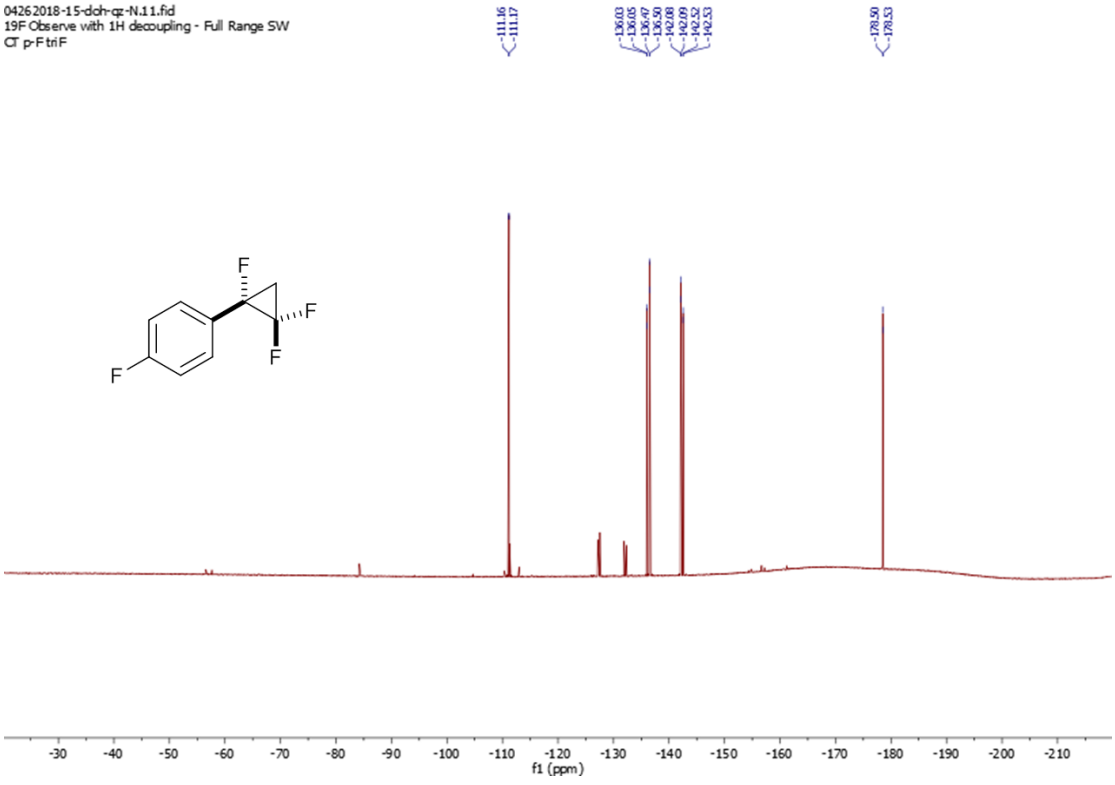
13C Observe with 1H decoupling - UDEFT
R-4-F triF pure 13C
F
F
F
DCM
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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CF p-F triF
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-111.17
-136.03
-136.05
-136.47
-136.50
-142.08
-142.09
-142.52
-142.53
-178.50
-178.53
F
F
F
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

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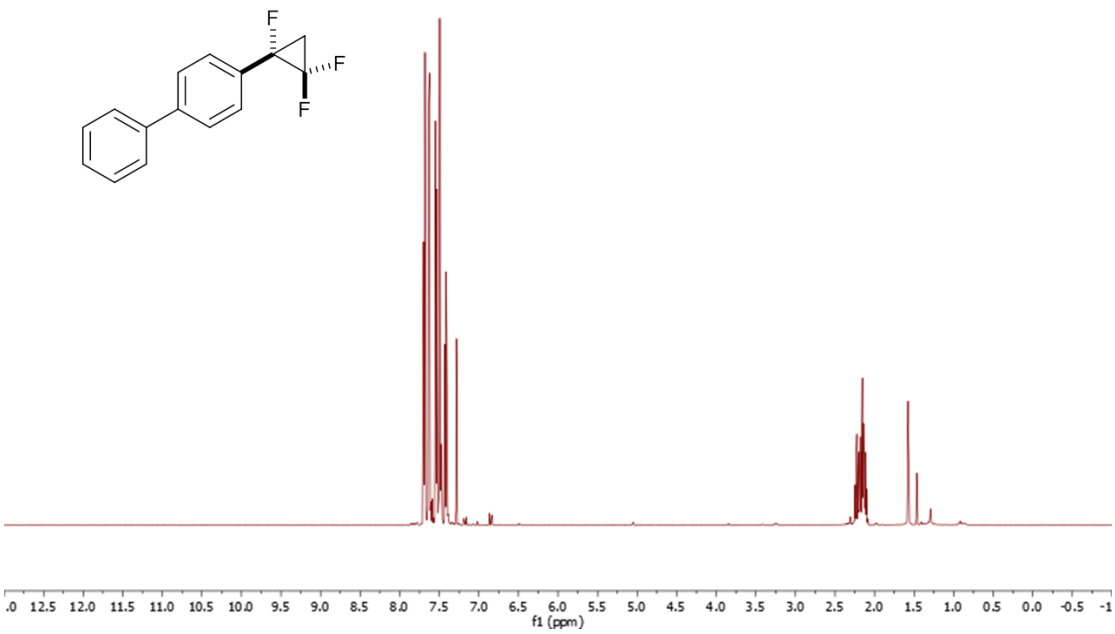
1H Observe
PhPhtriF 1H



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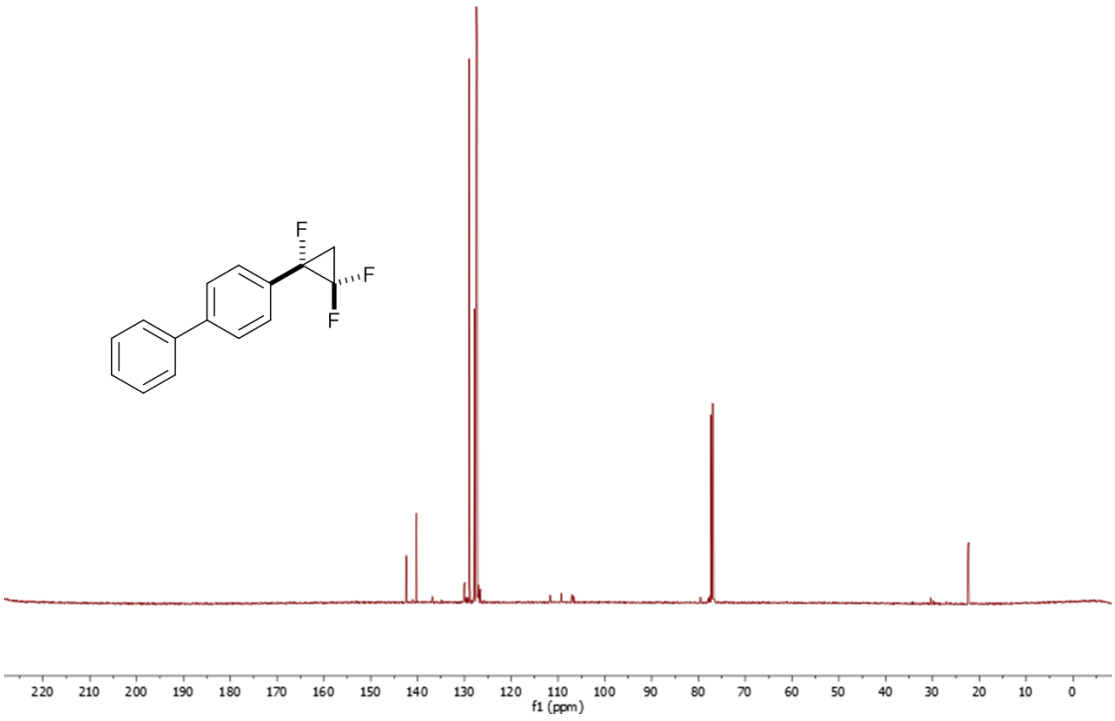
PhPhtriF 13C



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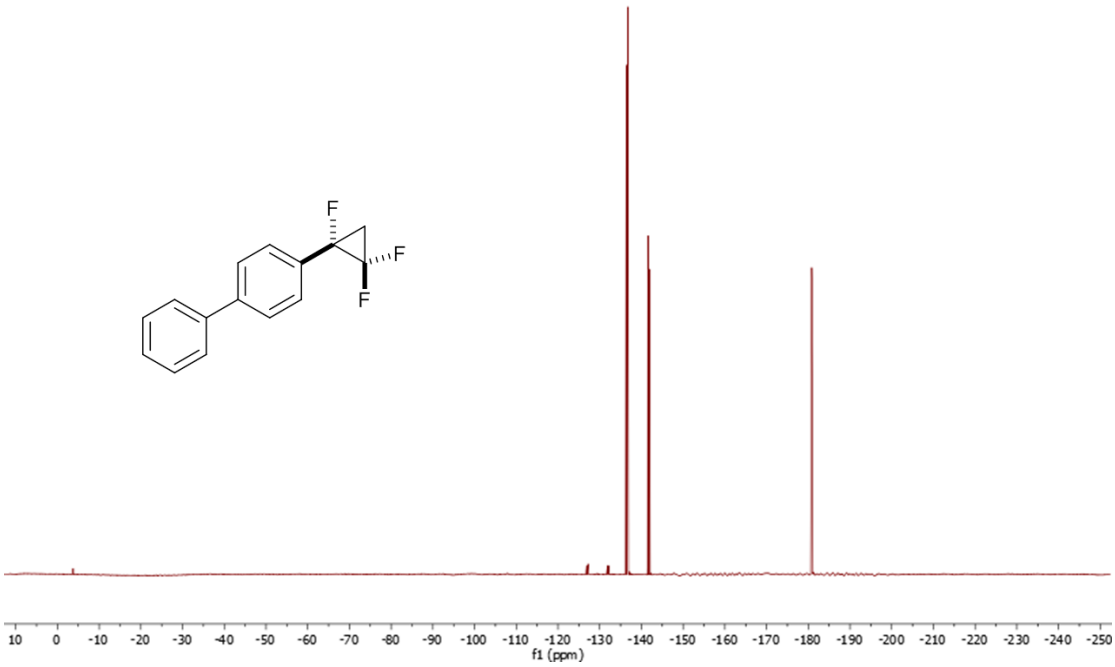
19F Observe without 1H decoupling - Full Range SW
PhPhtriF 19cp



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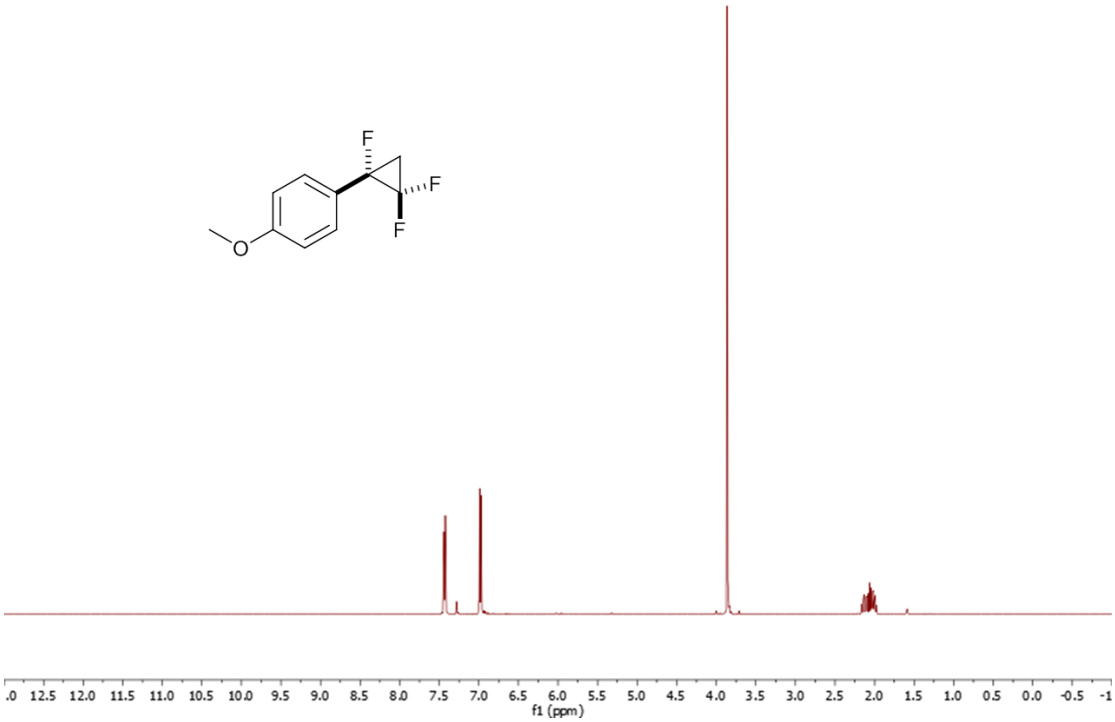
1H Observe
R-4-OMe triF 1H



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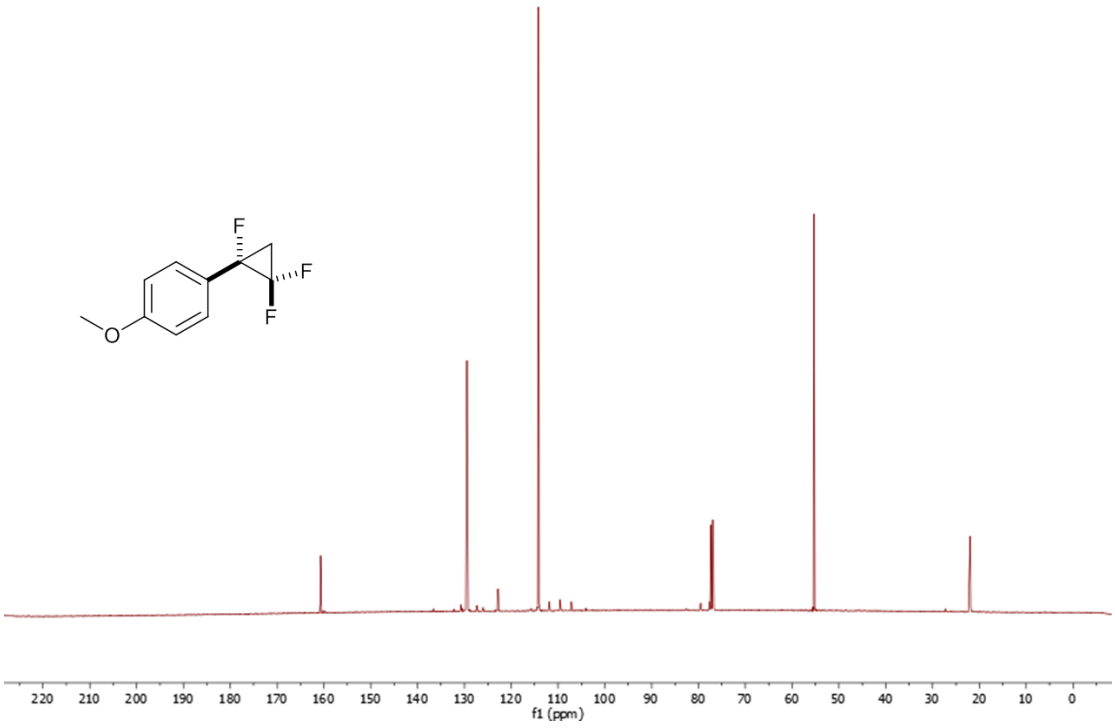
13C Observe with 1H decoupling - UDEFT
R-4-OMe triF 13C



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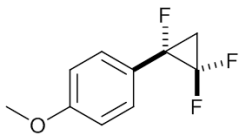
19F Observe without 1H decoupling - Full Range SW
R-4-OMe triF 19F



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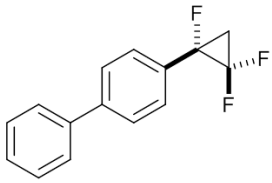
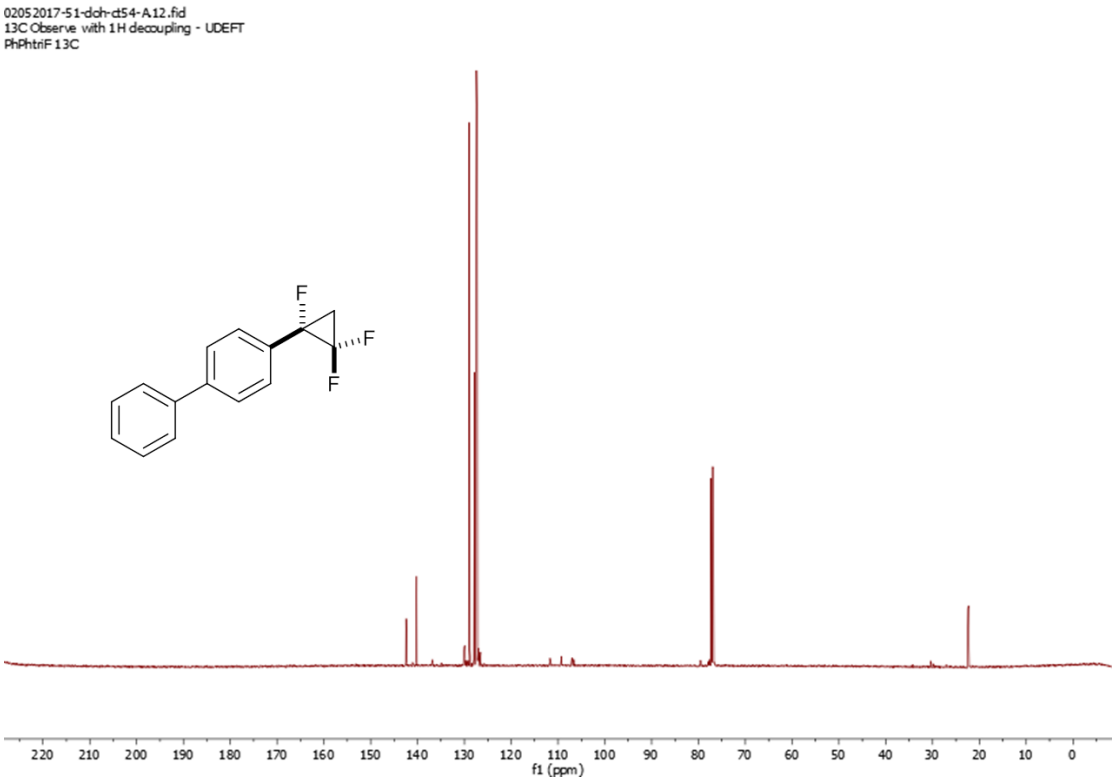
1H Observe
PhPhtriF 1H

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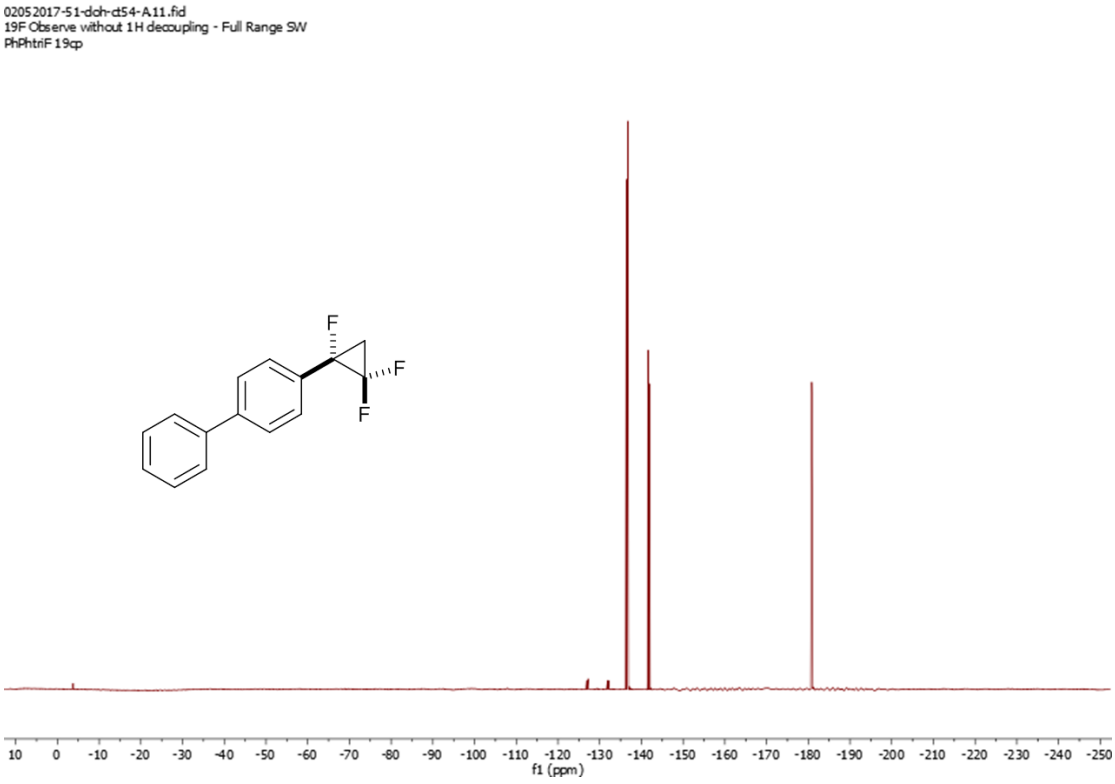
13C Observe with 1H decoupling - UDEFT
PhPhtriF 13C
F
F
F
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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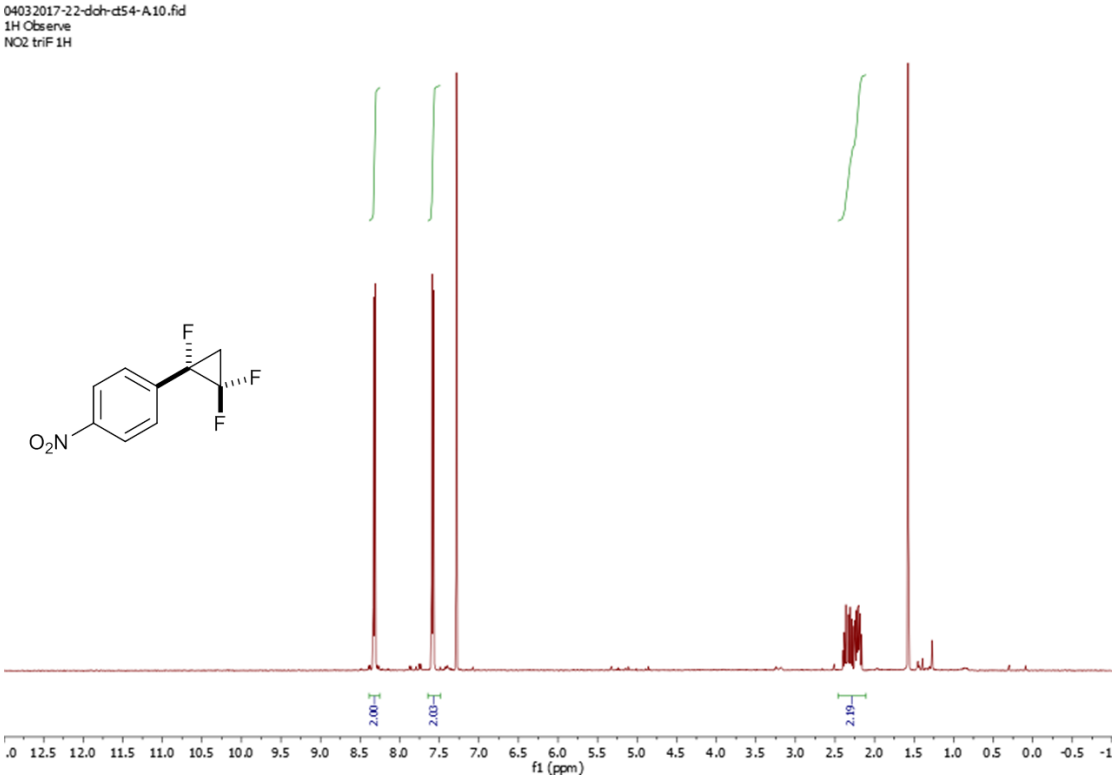
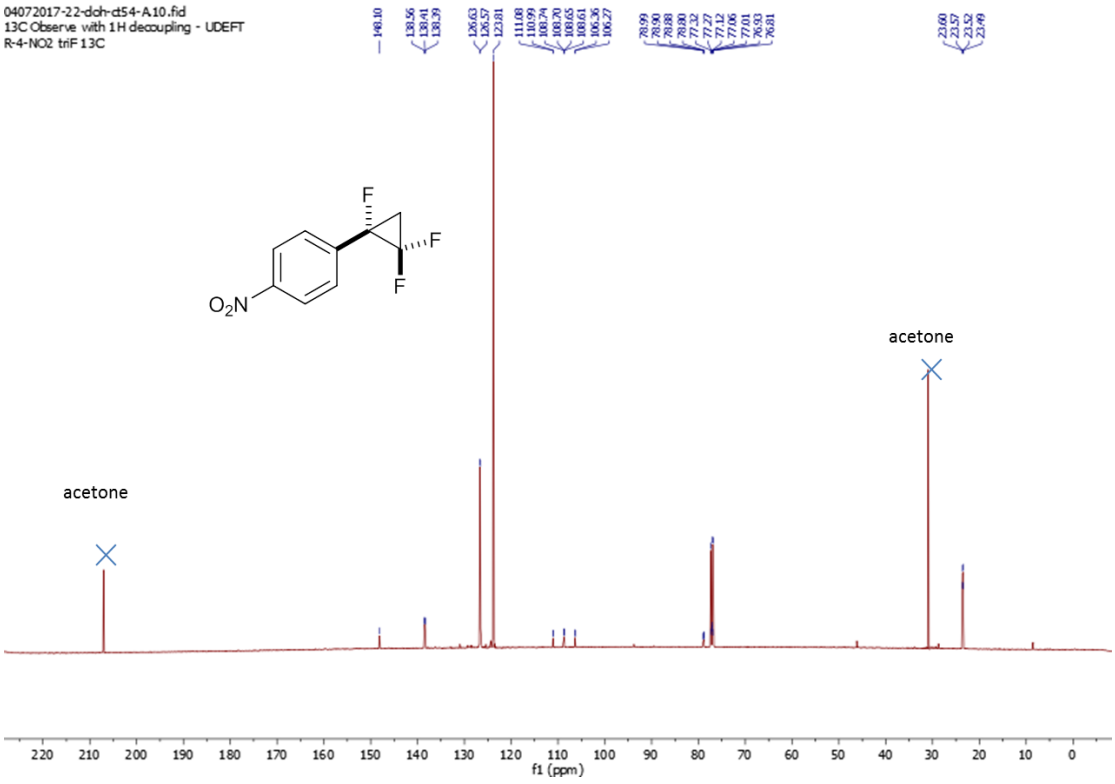
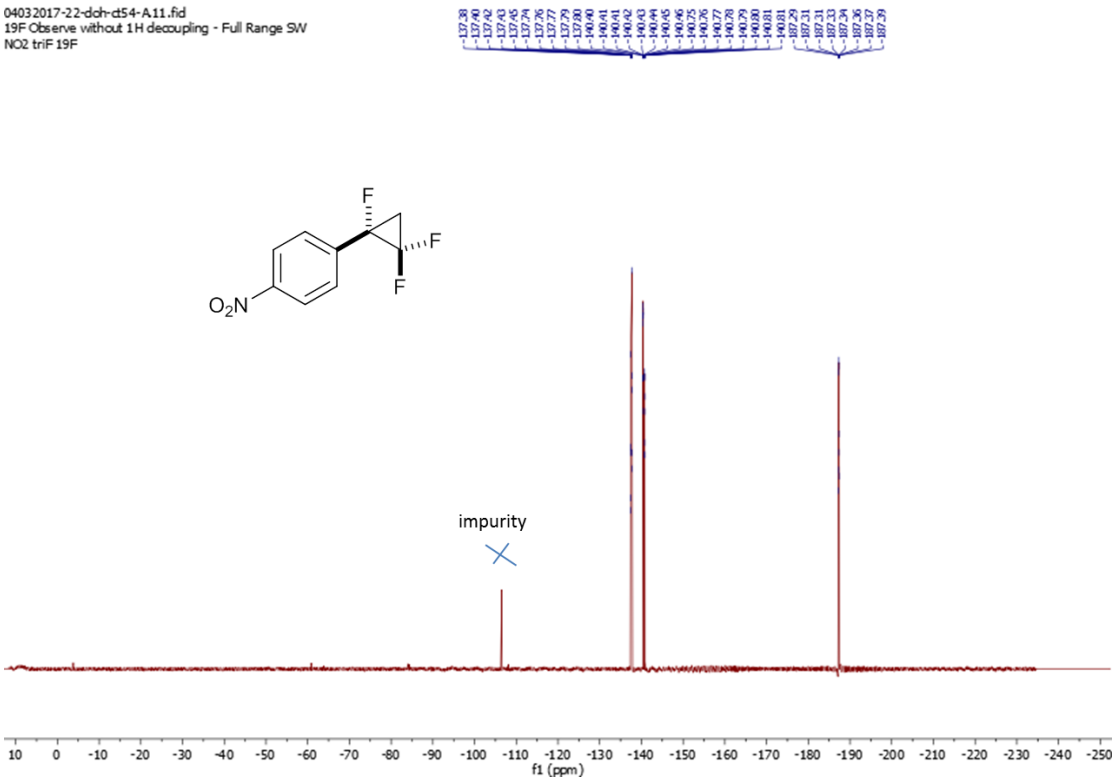
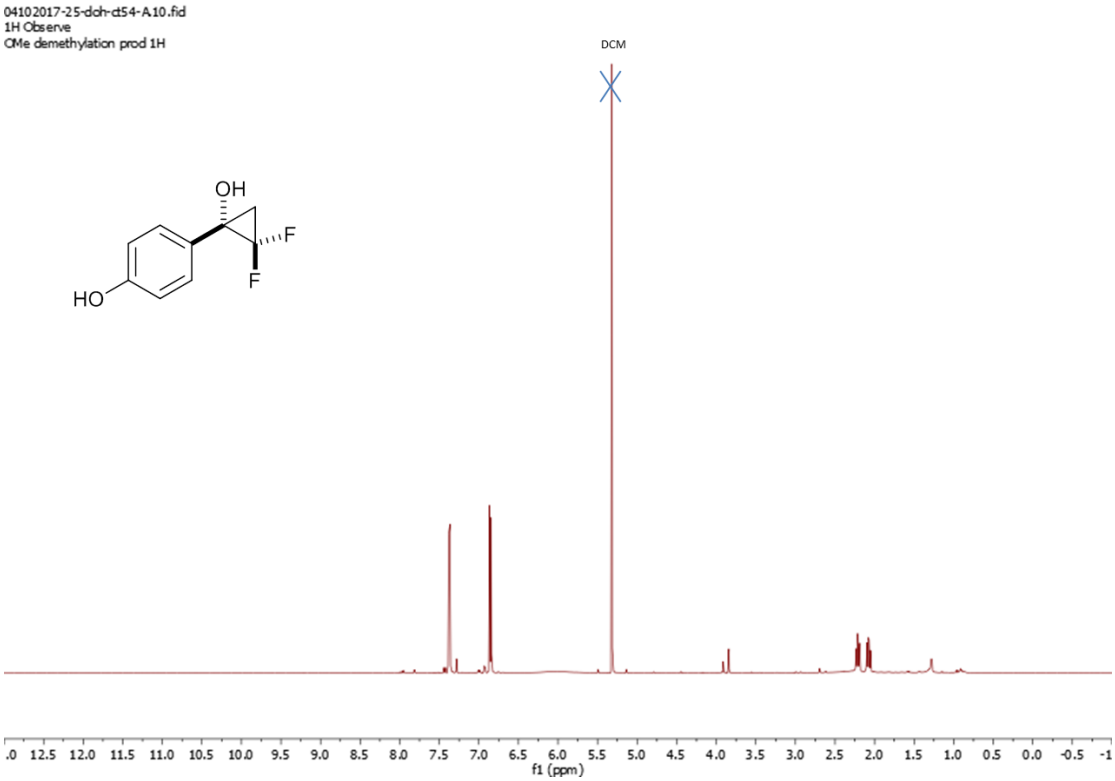
19F Observe without 1H decoupling - Full Range SW
PhPhtriF 19cp
F
F
F
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

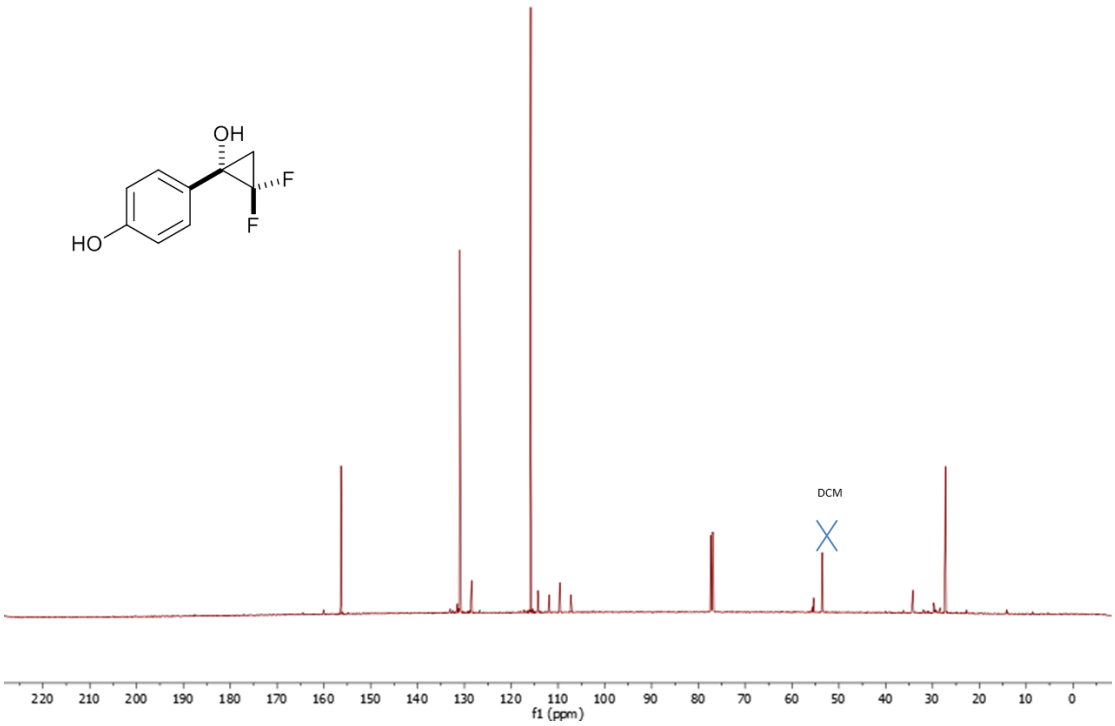

04032017-22-doh-ct54-A10.fid
1H Observe
NO2 triF 1H
F
F
F
O2N
2.00
2.03
2.19
f1 (ppm)


04072017-22-doh-ct54-A10.fid
13C Observe with 1H decoupling - UDEFT
R-4-NO2 triF 13C
F
F
F
O2N
acetone
acetone
f1 (ppm)

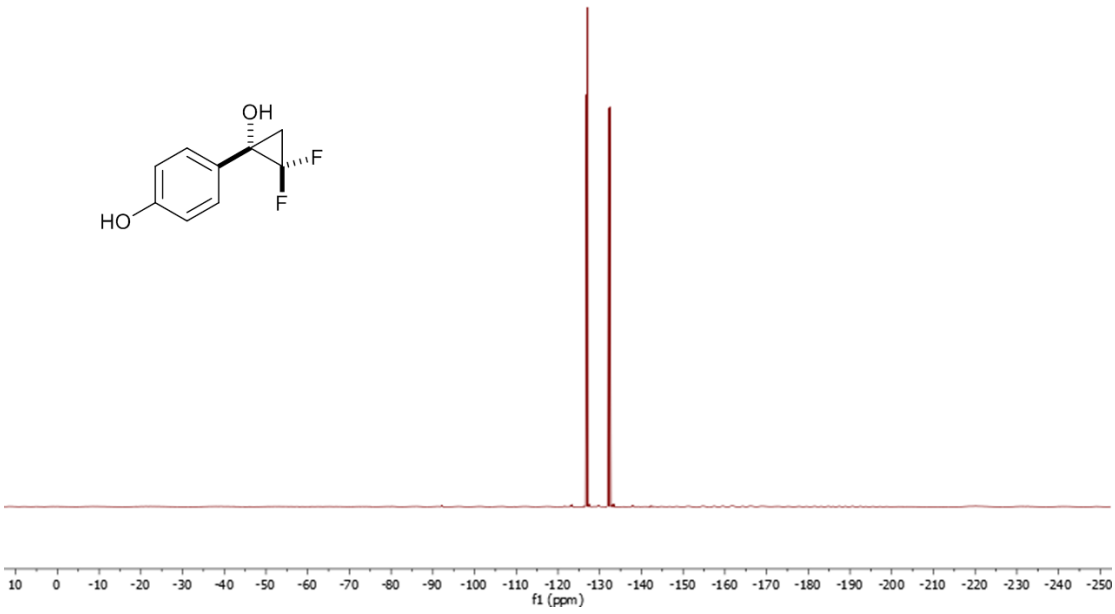

04032017-22-doh-ct54-A11.fid
19F Observe without 1H decoupling - Full Range SW
NO2 triF 19F
F
F
F
O2N
impurity
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

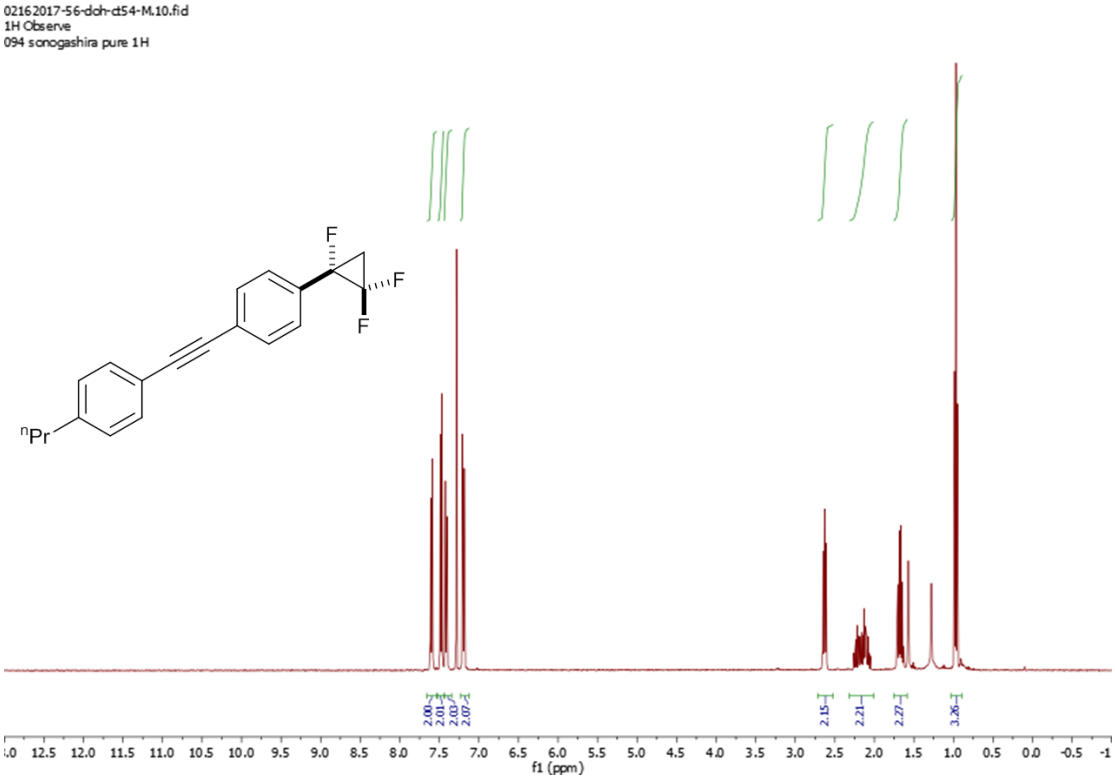

04102017-25-doh-ct54-A10.fid
1H Observe
OMe demethylation prod 1H
DCM
OH
F
F
HO
.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

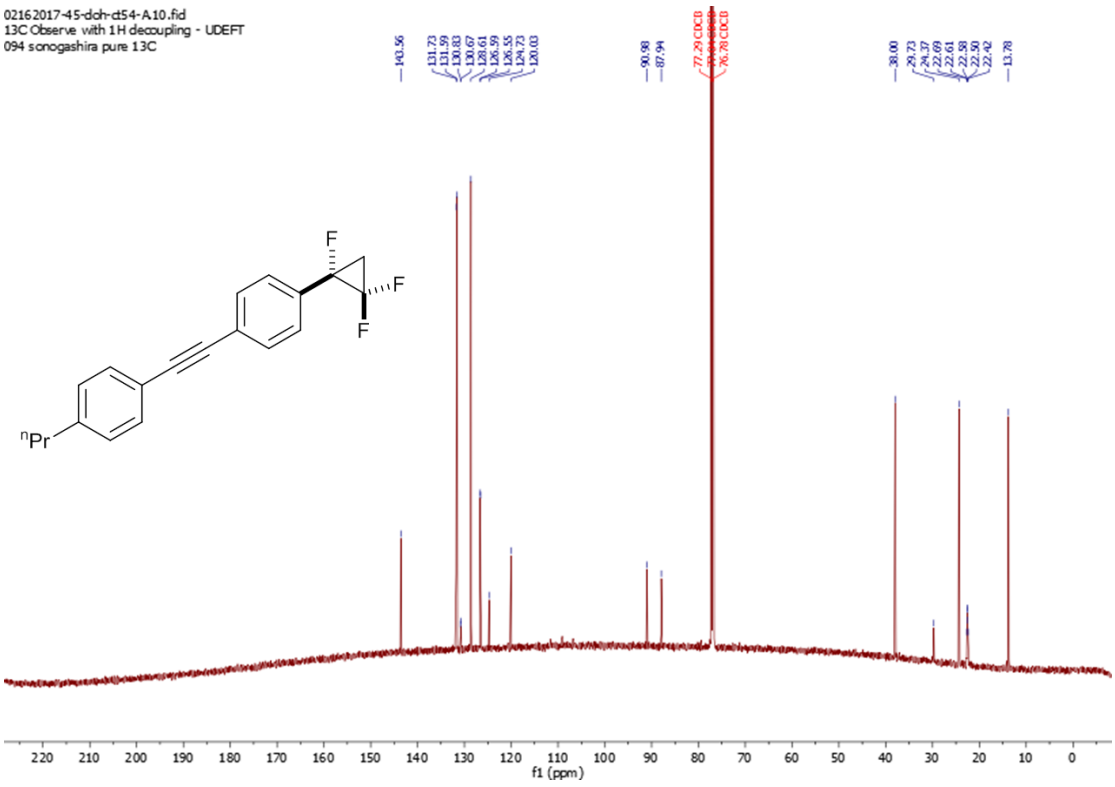
04102017-26-doh-ct54-A10.fid
13C Observe with 1H decoupling - UDEFT
diOH pure 13C



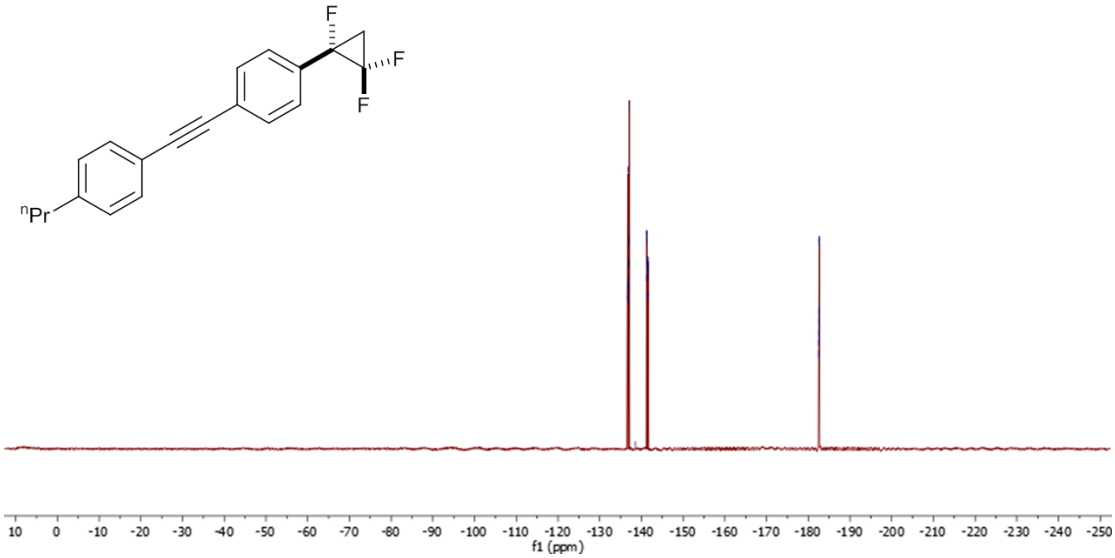
04102017-25-doh-ct54-A11.fid
19F Observe without 1H decoupling - Full Range SW
OMe demethylation prod 19F



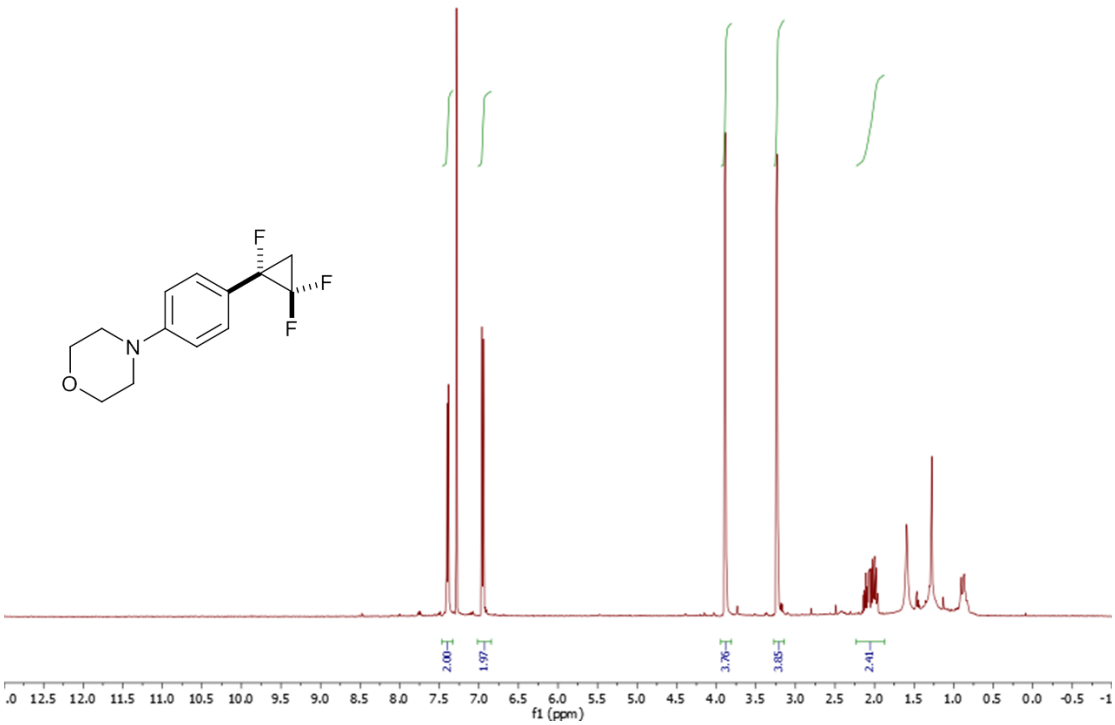

02162017-56-doh-ct54-M.10.fid
1H Observe
094 sonogashira pure 1H
F
F
F
nPr
2.00
2.01
2.03
2.07
2.15
2.21
2.27
3.26
f1 (ppm)

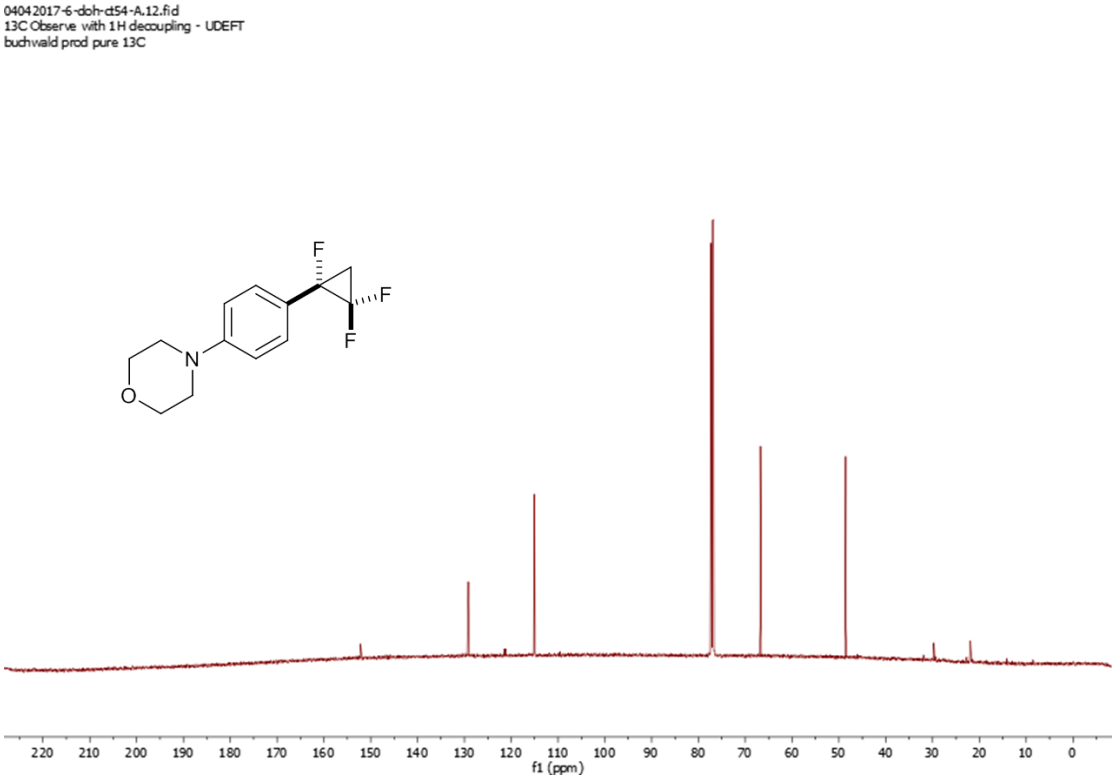

02162017-45-doh-ct54-A10.fid
13C Observe with 1H decoupling - UDEFT
094 sonogashira pure 13C
143.56
131.73
131.59
130.83
130.67
128.61
126.59
126.55
124.73
120.03
90.98
87.94
77.29 CDCl3
76.78 CDCl3
38.00
29.73
24.37
22.69
22.61
22.58
22.50
22.42
13.78
F
F
F
nPr
f1 (ppm)

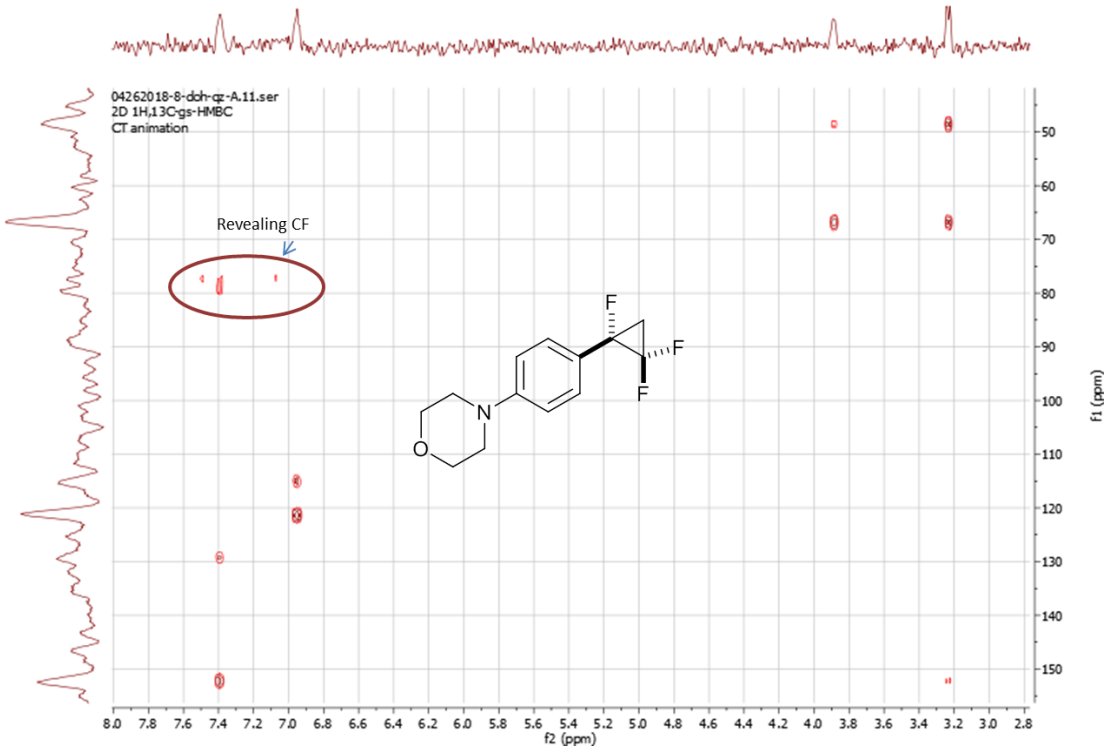
02162017-45-doh-ct54-A11.fid
19F Observe without 1H decoupling - Full Range SW
094 sonogashira pure 19Fcp



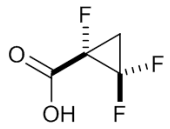
04042017-6-doh-ct54-A.10.fid
1H Observe
buchwald prod pure 1H




04042017-6-doh-ct54-A.12.fid
13C Observe with 1H decoupling - UDEFT
buchwald prod pure 13C
F
F
F
N
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

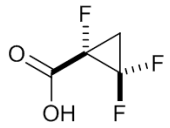

04262018-8-doh-qz-A.11.ser
2D 1H,13C-gs-HMBC
CT animation
Revealing CF
F
F
F
N
O
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8
f2 (ppm)
50 60 70 80 90 100 110 120 130 140 150
f1 (ppm)

08172017-24-doh-qz-N.10.fid
1H Observe
QZDH339 MeOD



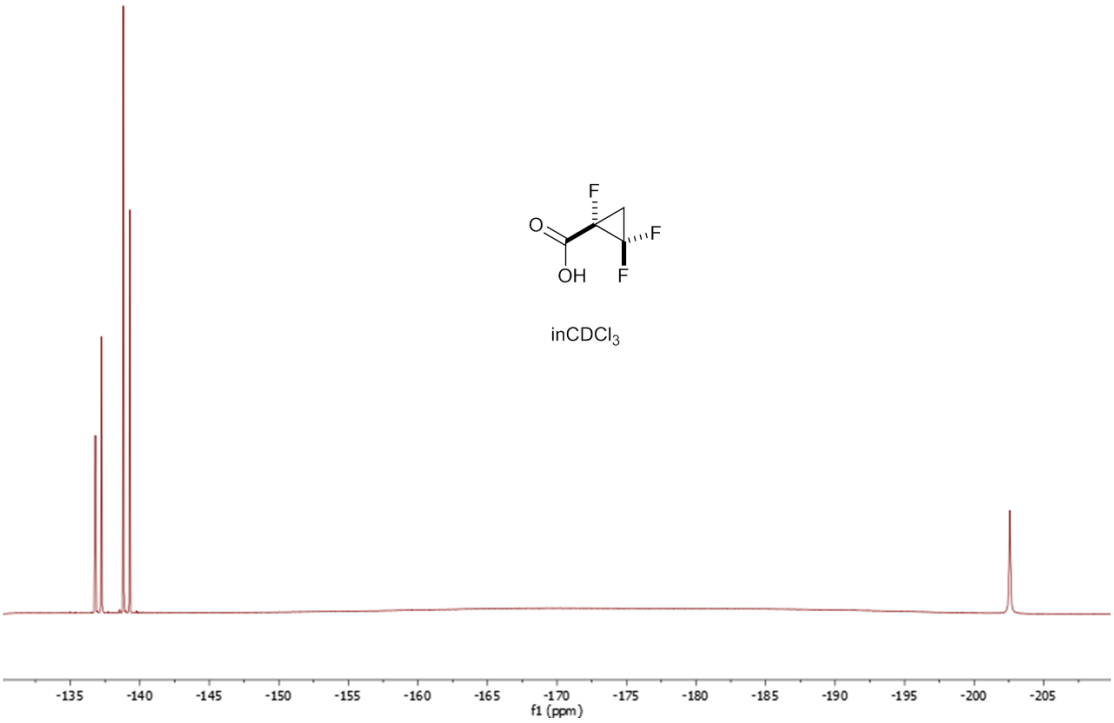
in MeOD

03142018-7-doh-qz-A.10.fid
13C Observe with multiplicity editing - DEPTQ
Trifluorocyclopropanyl carboxylic acid



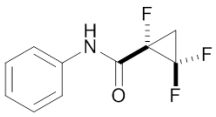
in MeOD

08172017-10-doh-qz-M.11.fid
19F Observe with 1H decoupling - SW 80 ppm
QZDH339 after column



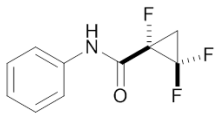
in$CDCl_3$

08292017-28-doh-qz-N.11.fid
1H Observe
QZDH342pure



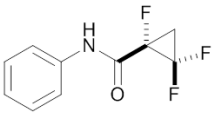
in $CDCl_3$

08292017-31-doh-qz-N.10.fid
13C Observe with multiplicity editing - DEPTQ
QZDH341 pure



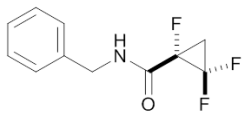
in $CDCl_3$

08292017-28-doh-qz-N.10.fid
19F Observe with 1H decoupling - Full Range SW
QZDH342pure



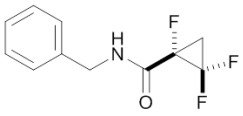
in $CDCl_3$

09132017-2-doh-qz-N.10.fid
1H Observe
QZDH343F1



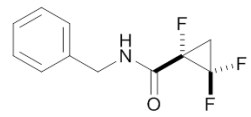
in $CDCl_3$

09132017-18-doh-qz-A.10.fid
13C Observe with multiplicity editing - DEPTQ
QZDH347



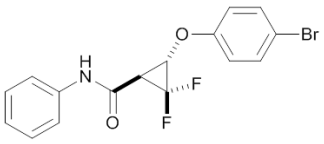
in $CDCl_3$

09112017-6-doh-qz-N.10.fid
19F Observe with 1H decoupling - Full Range SW
QZDH344F1



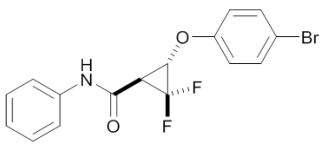
in $CDCl_3$

11012017-12-doh-qz-N.10.fid
1H Observe
QZDH359 purified



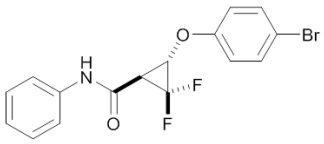
in $CDCl_3$

11012017-5-doh-qz-A.10.fid
13C Observe with 1H decoupling - D1 = 2s
QZDH359



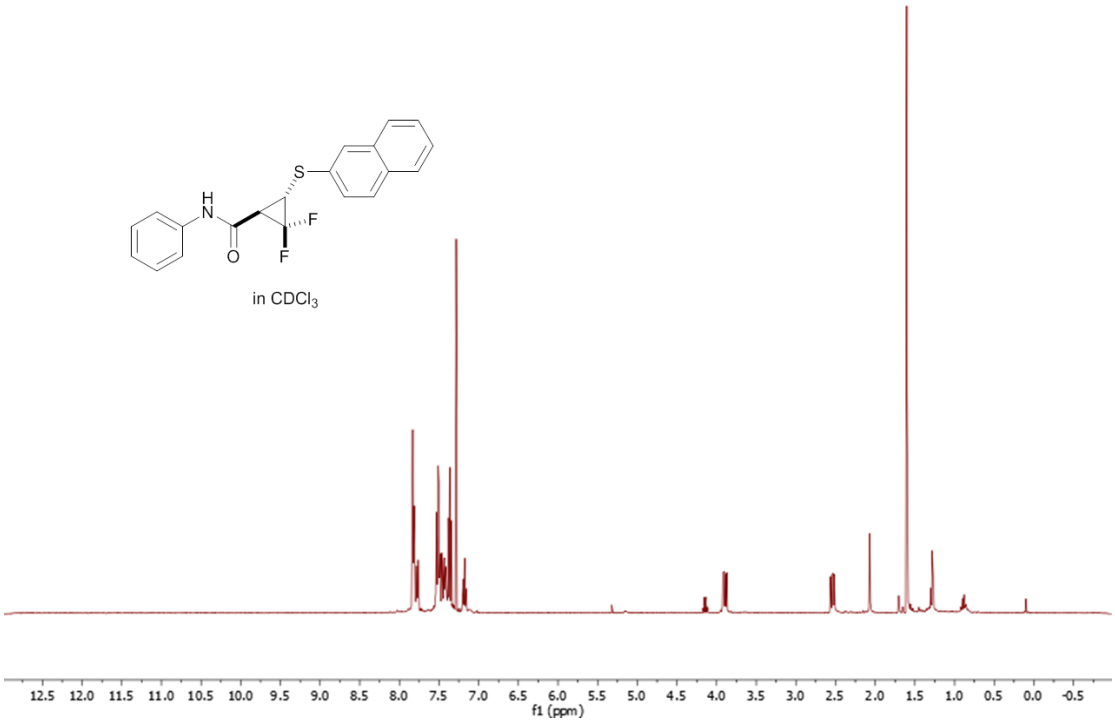
in $CDCl_3$

11012017-12-doh-qz-N.11.fid
19F Observe with 1H decoupling - Full Range SW
QZDH359 purified

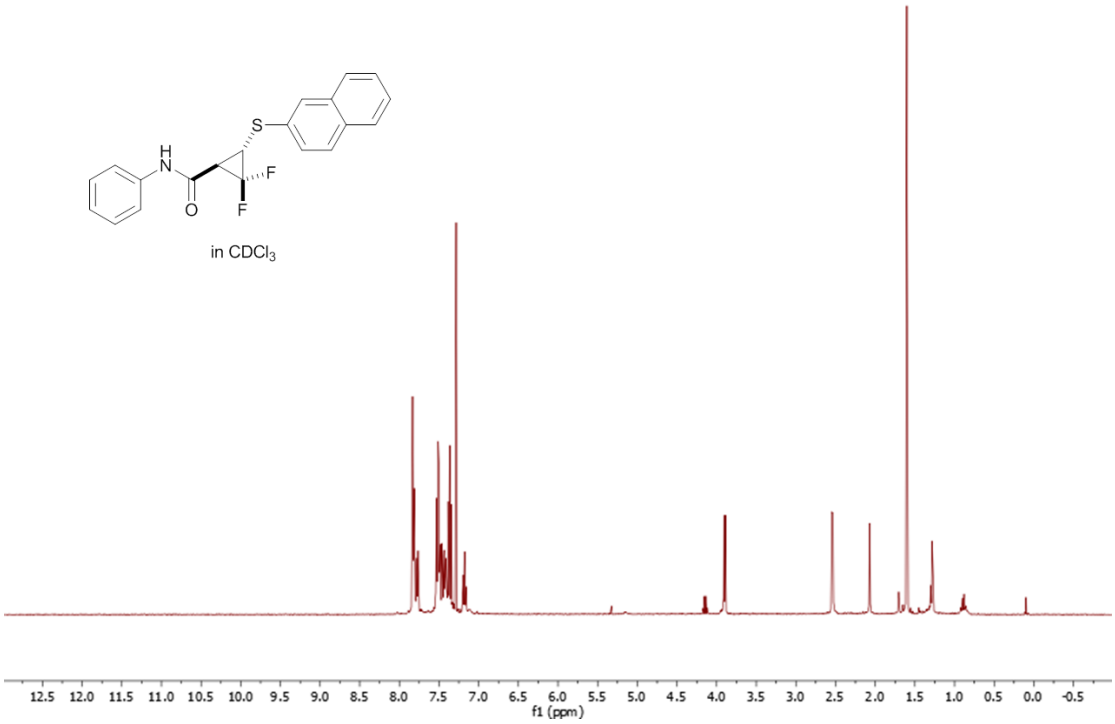


in $CDCl_3$

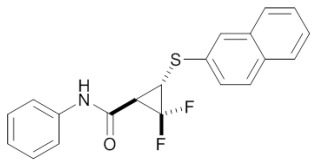
09182017-18-doh-qz-N.10.fid
1H Observe
QZDH348



09182017-18-doh-qz-N.11.fid
1H Observe with 19F Decoupling
QZDH348

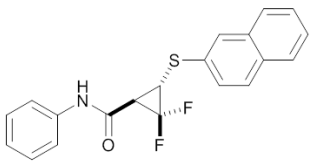


09182017-2-doh-qz-N.11.fid
13C Observe with multiplicity editing - DEPTQ
QZDH348

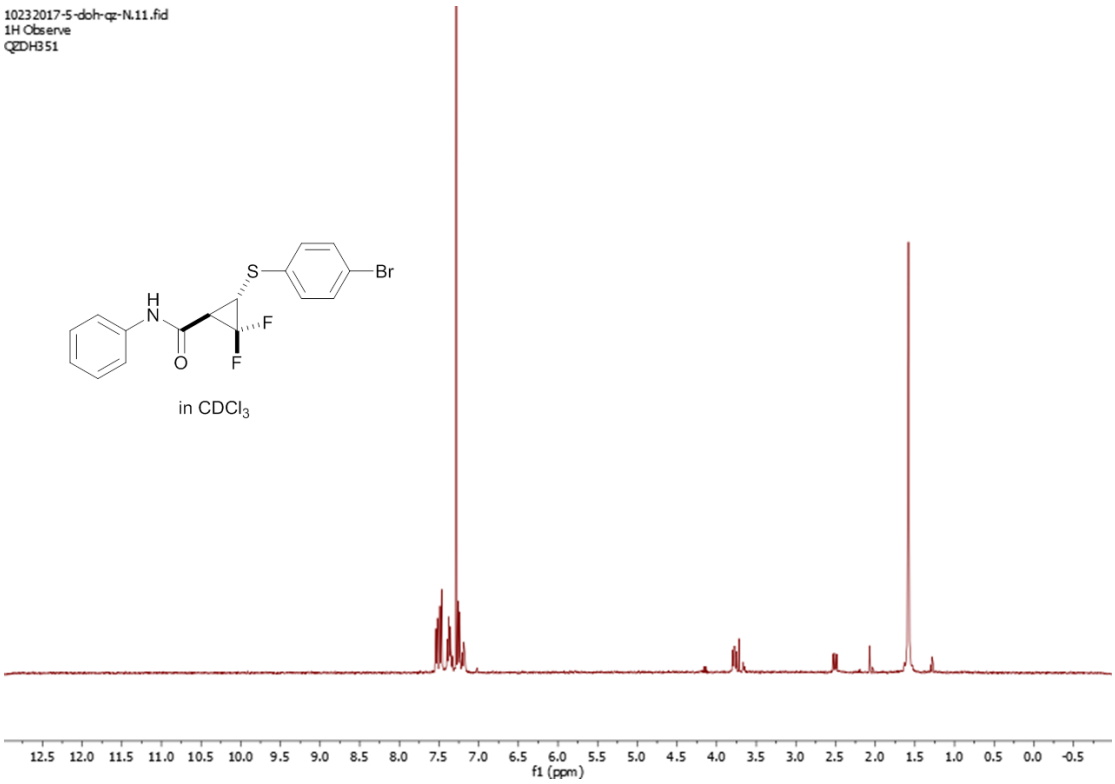


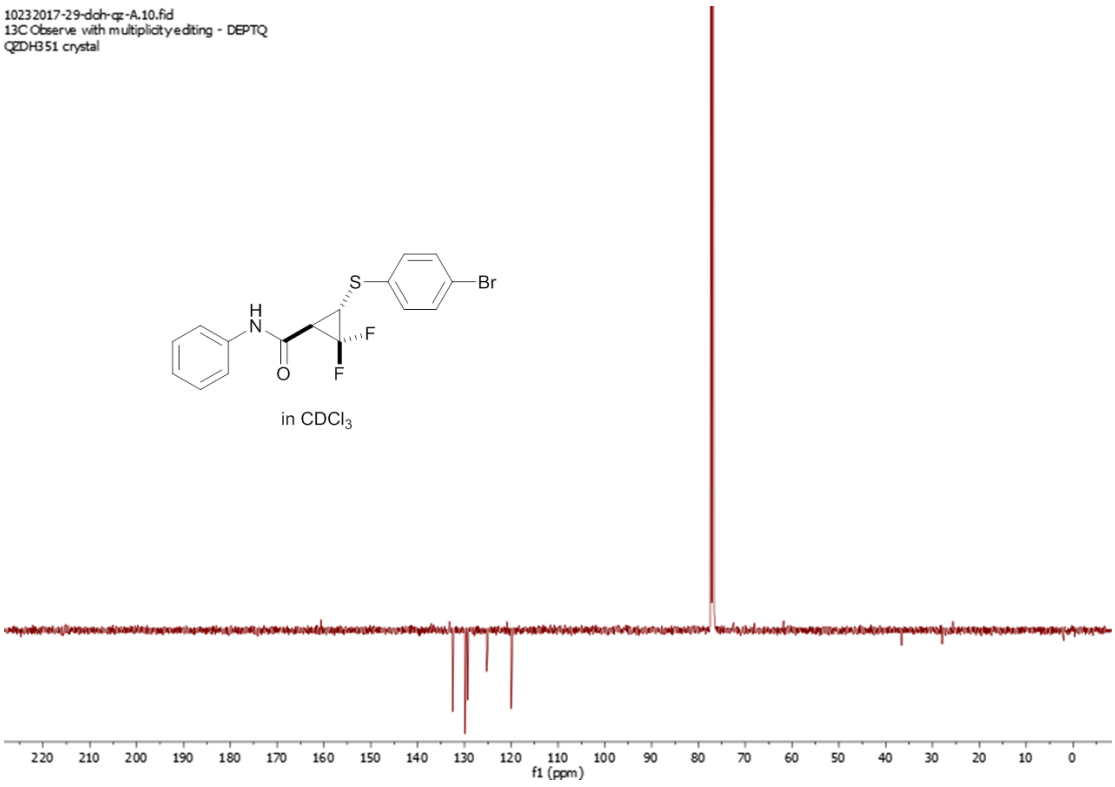
in $CDCl_3$

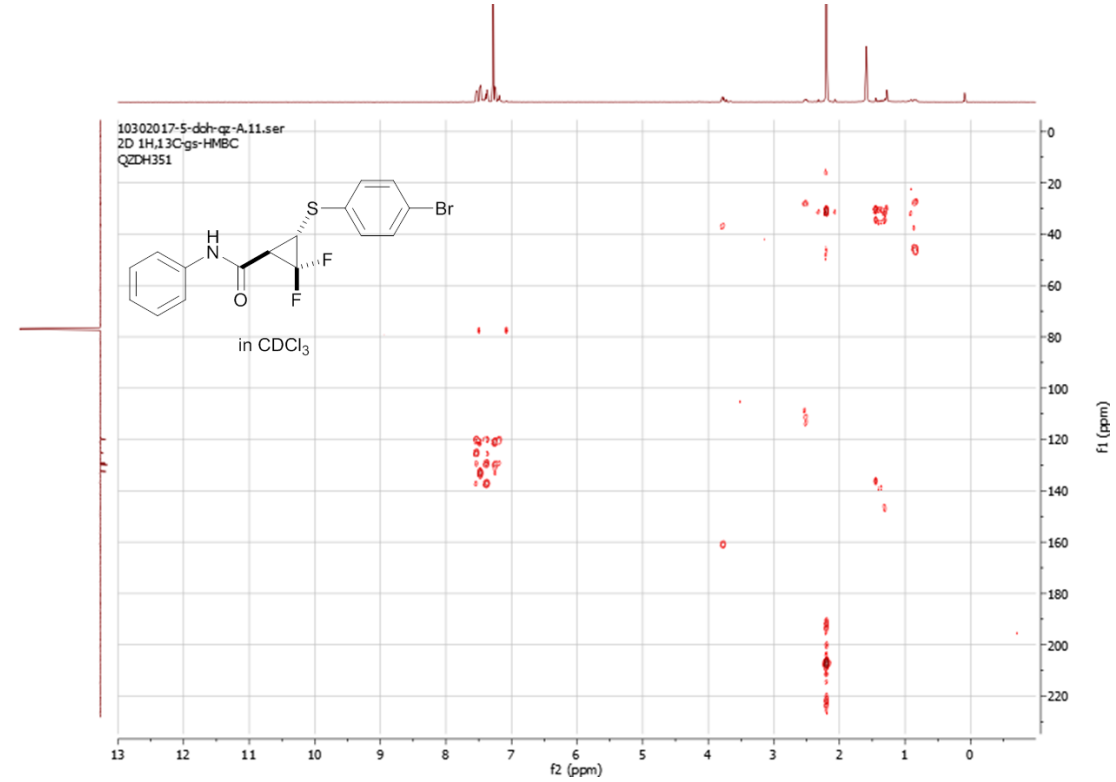
09182017-16-doh-qz-N.10.fid
19F Observe with 1H decoupling - Full Range SW
QZDH348



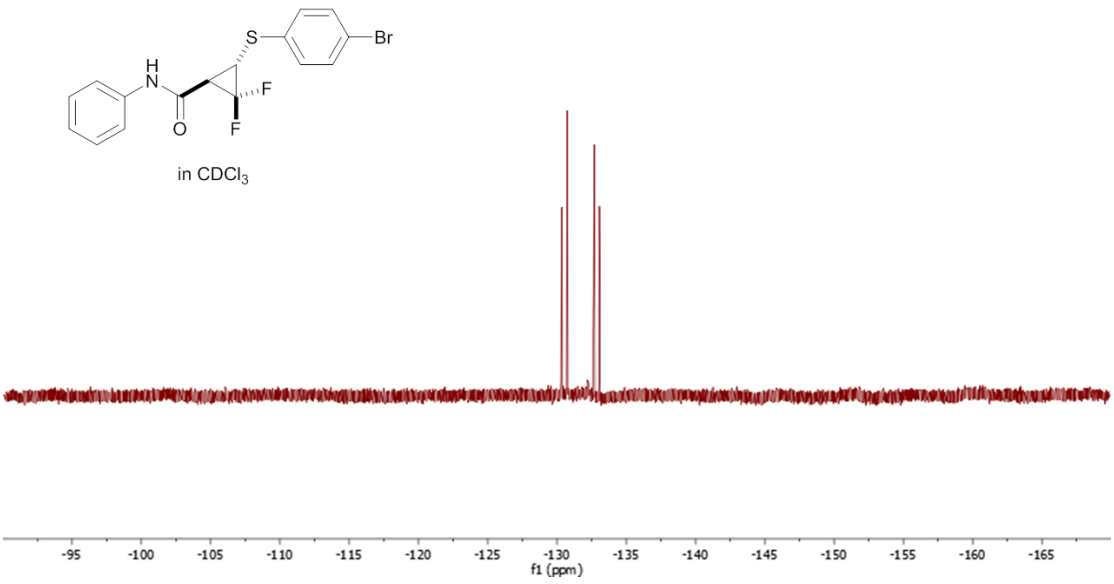
in $CDCl_3$


10232017-5-doh-qz-N.11.fid
1H Observe
QZDH351
S
Br
H
N
O
F
F
in CDCl3
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

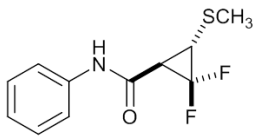

10232017-29-doh-qz-A.10.fid
13C Observe with multiplicity editing - DEPTQ
QZDH351 crystal
S
Br
H
N
O
F
F
in CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



11022017-2-doh-qz-N.11.fid
19F Observe without 1H decoupling - SW 80 ppm
QZDH351

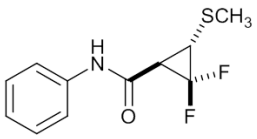


12042017-1-doh-qz-N.10.fid
1H Observe
QZDH376 washed with hexane



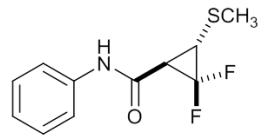
in $CDCl_3$

12042017-8-doh-qz-A.10.fid
13C Observe with 1H decoupling - D1 = 2s
QZDH376



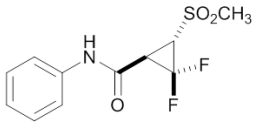
in $CDCl_3$

12042017-1-doh-qz-N.11.fid
19F Observe with 1H decoupling - SW 80 ppm
QZDH376 washed with hexane



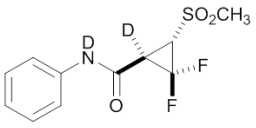
in $CDCl_3$

10312017-25-doh-qz-N.10.fid
1H Observe
QZDH362 washed with DCM



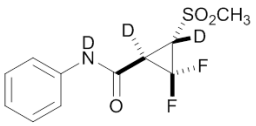
in $CDCl_3$

11032017-15-doh-qz-N.11.fid
1H Observe with 19F Decoupling
QZDH362



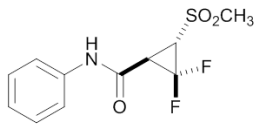
in MeOD 2 h

11062017-22-doh-qz-N.10.fid
1H Observe
QZDH362 in MeOD



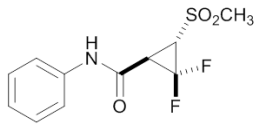
in MeOD in 3 days

1214 2017-6-doh-qz-A.10.fid
1H Observe
QZDH380 mCPBA oxidation

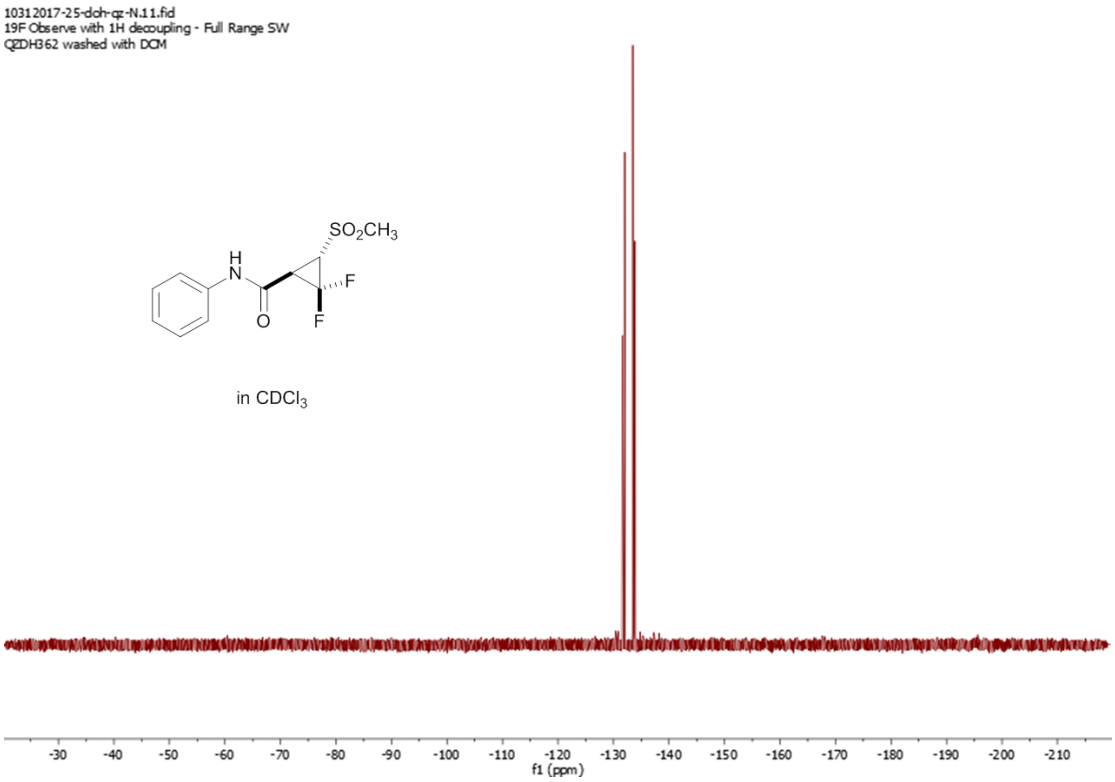


iin DMSO-d_6

1214 2017-6-doh-qz-A.11.fid
13C Observe with multiplicity editing - DEPTQ
QZDH380 mCPBA oxidation



iin DMSO-d_6


10312017-25-doh-qz-N.11.fid
19F Observe with 1H decoupling - Full Range SW
QZDH362 washed with DCM
SO2CH3
H
N
F
O
F
in CDCl3
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

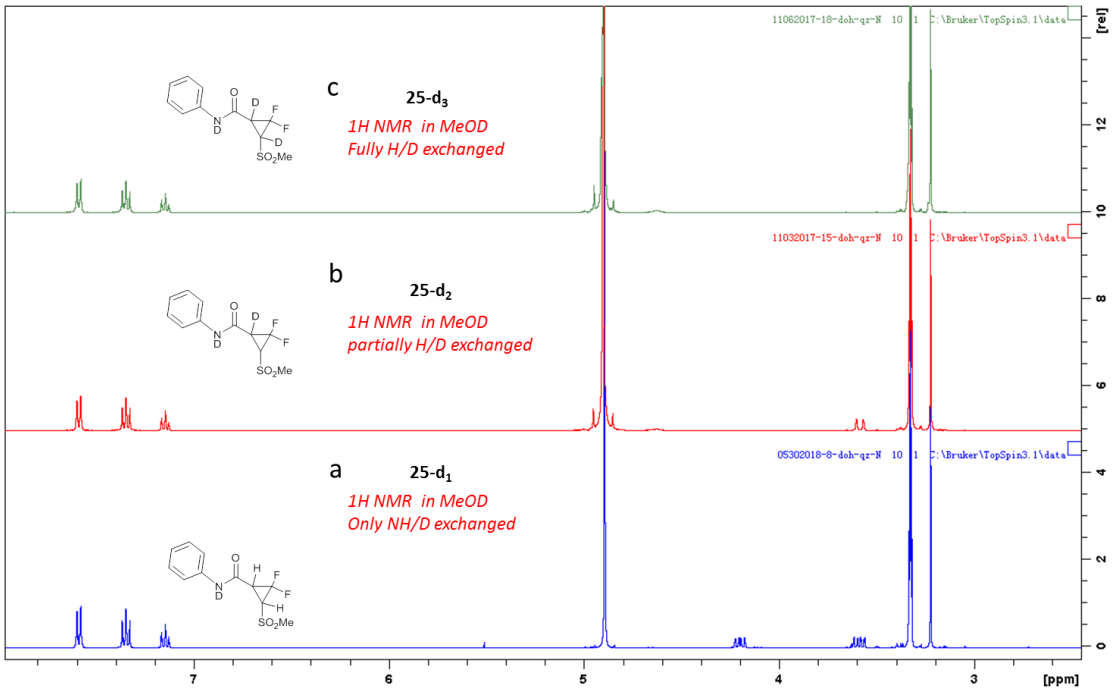


Figure S1.[1]H NMR of **25** in MeOD. a) in several minutes, the NH was exchanged; b) in 3 h, the CH alpha to amide exchanged; c) in 3 days, the CH adjacent to sulfonyl group also exchanged

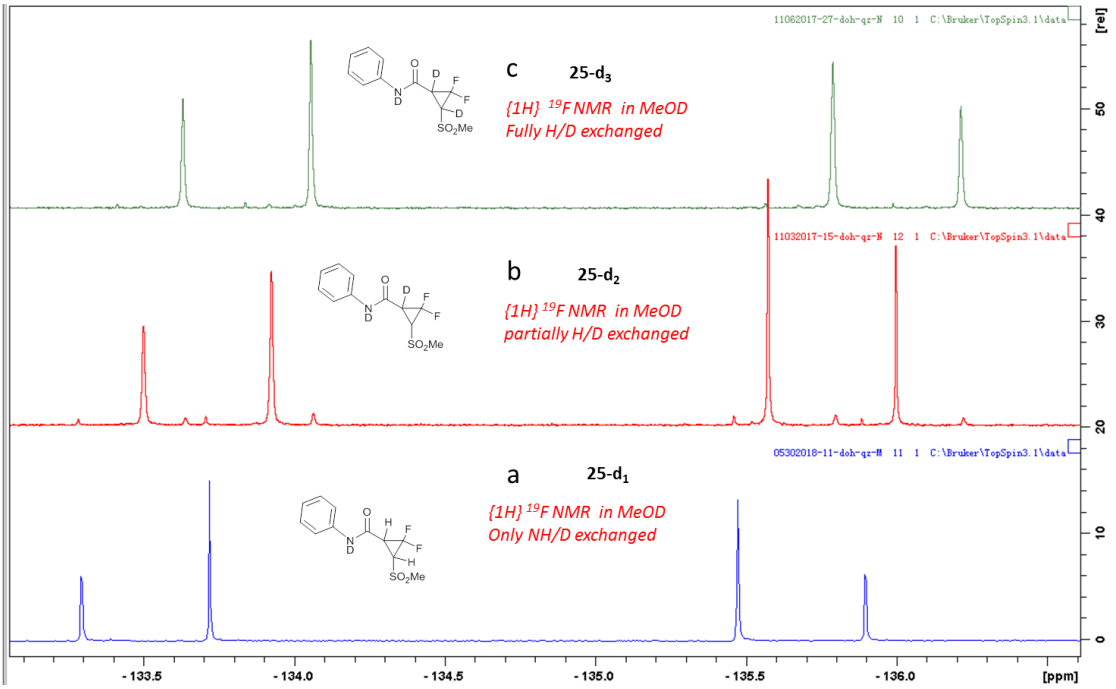
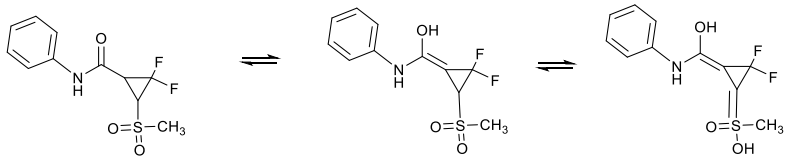


Figure S2. [19]F NMR of **25** in MeOD: a) in several minutes the NH was exchanged; b) in 3 h the CH alpha to amide exchanged, both F signals up-shifted slightly; c) in 3 days, the CH adjacent to sulfonyl group also exchanged, both F signals slightly further up-shifted.



Scheme S1. Enolisation responsible for proton exchange of **25** in MeOD

DFT Computations for 11a

A conformational analysis was performed[4] for (1,2,2-trifluorocyclopropyl)benzene **11a** by scanning an F-C-C=C dihedral angle (B2LYP[5]/6-311+G** level of density functional theory, **Figure** S3). Due to the symmetry of the Ph substituent, only a rotation of 180° has to be considered. The rotational profile is very flat, with a maximum barrier of little more than 2 kcal mol^{-1}. Two minima are found in gas phase, one with the Ph ring approximately bisected with respect to the adjacent CF bond (**bis**, dihedral -77°), and one where both are eclipsed (**ecl**, dihedral -9)°. After full optimization, rotamer **bis** is more stable than **ecl** by 0.3 Kcal mol^{-1}. Rotamer **bis** has the slightly higher dipole moment (3.0 D, as opposed to 2.7 D for **ecl**). In the plarisable continuum the higher lyring minimum disappears, leaving bis as the sole stable minimum.

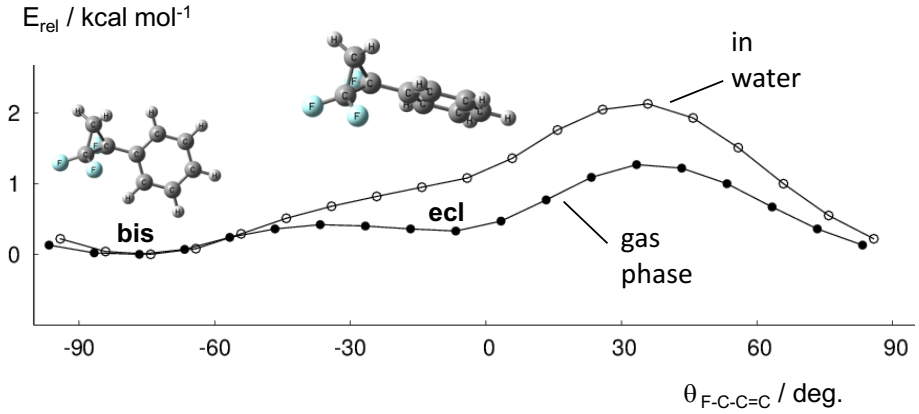


Figure S3: Rotational profiles about the C(F)-C(=C) bond in **11a** (B3LYP/6-311+G** level), energies given in kcal mol^{-1} relative to the most stable conformer (**bis**); full circles: gas phase, open circles: in a polarizable continuum (CPCM). The electrostatic potential (ESP) for **bis** is shown in Figure 2 and Figure S4. Rather than a facial polarity characteristic for all-cis fluorinated rings, an "in-plane polarity" is obtained, pointing from the CH_2 group with positive ESP to the C_2F_3 moiety with negative ESP. The direction of the overall dipole moment vector, however, is rather dominated by the Ph ring with its notably positive ESP.

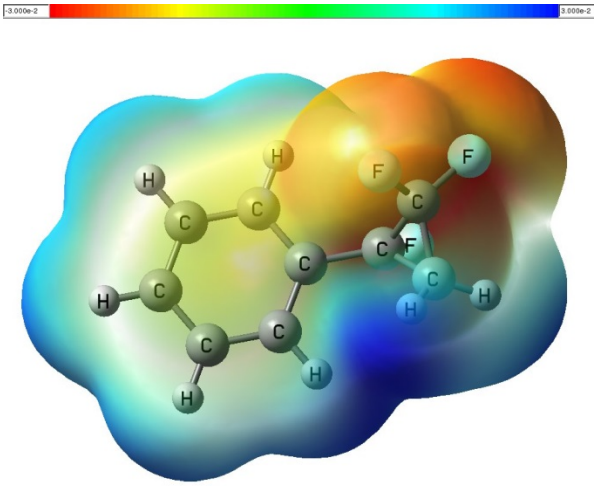


Figure S4: Electrostatic potential of rotamer bis of **11a** at the B3LYP/6-311+G** level, plotted on a colour scale from -0.003 a.u. (red) to +0.003 a.u. (blue) and mapped onto an isodensity surface (= $4 \cdot 10^{-4}$ a.u.).

Coordinates of the DFT-optimised structures for 11a

Cartesian coordinates in Å, B3LYP/6-311+G** optimised (xyz format)

11a minimum **bis**

F,0,-2.5835629041,0.2484324986,-0.6317291223
F,0,-0.2880882679,1.6446698128,-0.1459826912
F,0,-1.6186436169,-1.6903853101,-0.1897502404
C,0,-1.3114659487,0.102381317,1.4599971748
H,0,-1.064976162,-0.642021169,2.2071664781
H,0,-1.8542649868,0.9755208819,1.8026595156
C,0,-0.3170256263,0.336959455,0.3165567232
C,0,-1.6148390825,-0.3631046887,0.0810068336
C,0,1.0096832728,-0.3376907313,0.232482776
C,0,1.8176176292,-0.4682283372,1.3640260062
C,0,1.475760906,-0.7969347276,-1.0039656161
C,0,3.077968473,-1.0534500424,1.2641230638
H,0,1.4615230899,-0.1079879186,2.322817639
C,0,2.7355443265,-1.3797128947,-1.1039313142
H,0,0.8502087042,-0.6971905984,-1.883737676
C,0,3.5373394451,-1.5098141629,0.0300557769
H,0,3.6998461843,-1.1511792643,2.1465647455
H,0,3.0900832315,-1.7366380644,-2.0640319154
H,0,4.5170654328,-1.9673647858,-0.0484344368

11a minimum **ecl**

F,0,-2.493338562,0.5546605005,-0.681351615
F,0,-0.2287574157,1.7244886739,0.2363750316
F,0,-1.6241218745,-1.4729256437,-0.5834070117
C,0,-1.3880845554,-0.0674677519,1.4127635658
H,0,-1.2055706882,-0.9495964329,2.0146812103
H,0,-1.919249844,0.7459249554,1.8928339569
C,0,-0.2986806266,0.3586595517,0.4141903416
C,0,-1.6030449783,-0.2315808518,-0.0445966988
C,0,1.0265708767,-0.3160320379,0.2876305912
C,0,2.1239536947,0.4187319425,-0.1748231989
C,0,1.2016725833,-1.6657769787,0.616226468
C,0,3.3727371207,-0.1862385721,-0.3004459882
H,0,1.9995246321,1.4632091053,-0.427682097

C,0,2.4505442159,-2.2656423246,0.4852334234

H,0,0.3669068599,-2.2616301147,0.9634237036

C,0,3.5417021167,-1.5288188726,0.0277234832

H,0,4.2143436763,0.3973915156,-0.6558534525

H,0,2.5689995235,-3.3124036231,0.7408105565

H,0,4.5136987147,-1.9980622708,-0.0716184201

DFT Computations for 19b through a truncated model 20

The same conformational analysis was performed[4] for a model amide at the same level as in our previous study on related tetrafluorocyclohexyl amides[6] (B3LYP[5]/6-311+G** level of density functional theory). Starting from the X-ray derived coordinates for the *N*-benzyl derivative **19b**, a truncated model **20** was built by replacing the benzyl substituent with a methyl group. After initial optimisation to the minimum **A**, a full rotational profile was constructed through a relaxed scan of the F-C-C=O dihedral angle (θ). To model a polar environment, the same procedure was repeated using a simple solvent model, namely the polarizable conductor variant of the polarizable continuum model (CPCM),[7] employing the parameters of water and the default options in Gaussian 09. The resulting profiles are displayed in Figure 5. In both environments, the conformation observed in the solid state of benzyl amide **19b** with a 1,5-NH...F interaction is the lowest minimum (denoted **A**). Two higher lying minima are apparent, namely rotamers **B** with a 1,6-NH...F interaction and **C** with a more bisected orientation of amide and cyclopropane moieties. These structures were subjected to full energy minimisation; relative energies and salient geometrical parameters of all minima are collected in Table S1. Because minima **B** and **C** have the adjacent CO and CF bonds in *syn* orientation, these forms are characterized by higher dipole moments than the global minimum **A**, where these groups are oriented in an *anti* fashion. Conformers minima **B** and **C** are therefore somewhat stabilized in a polar environment, but not to an extent that would make them competitive with the global minima **A**, which remains at least 3 kcal mol^{-1} more stable.

Table S1: Computed properties (energies ΔE_{rel} relative to **A**, dipole moments μ, selected angles and distances) of model amide compound **20** (truncated version of **19b**) at the B3LYP/6-311+G** level (gas phase values, unless otherwise noted)

Conformer Property	**A**	**B**	**C**
ΔE_{rel} [kcal mol^{-1}] gas phase ΔE_{rel} [kcal mol^{-1}] in water) [a]	0.0 (0.0)	4.6 (3.1)	6.5 (3.4)
$\theta_{F\text{-}C\text{-}C=O}$ calc [°] *X-ray*	164.3 *165.2*[b]	26.3 *n.a.*	-54.4 *n.a.*
nearest $d_{F\ldots H(N)}$ [Å] [c]	2.198	2.062	3.558
μ [D]	3.0	4.2	6.0

[a]CPCM method. [b]N-benzyl derivative **19b**, this work. [c]Distance between NH proton and nearest F atom.

Coordinates of the DFT-optimised structures for amide 20 (the truncated model of 19b)

Cartesian coordinates in Å, B3LYP/6-311+G** optimised (xyz format)

20 (the truncated amide model of **19b**) minimum **A**

F,0,-0.3989555077,-1.1970330135,5.7136555527
F,0,-0.1166581105,-1.5332333253,3.0446203049
F,0,1.1881860237,0.3290104501,5.8193047771
O,0,2.061407013,1.2590272111,3.044924964
N,0,2.2484624293,-0.8033656344,2.0722638819
H,0,1.7935378778,-1.6977503221,1.9696386337
C,0,-0.5805969095,0.6485057558,4.1337144408
H,0,-0.2786412259,1.682196602,4.0132179115
H,0,-1.6324638238,0.4088132683,4.0343080759
C,0,1.6586786915,0.1218900115,2.8664131366
C,0,0.4118862851,-0.3706920825,3.5710187543
C,0,0.2161025885,-0.1938143023,5.0514288774
C,0,3.4509887489,-0.5224796104,1.3016394161
H,0,3.8618274135,0.4248113203,1.6459341248
H,0,3.2278554815,-0.4441093362,0.2336545654
H,0,4.1895110246,-1.3120209927,1.4556365829

20 (the truncated amide model of **19b**) minimum **B**

F,0,-2.6031270106,-0.3010999425,-0.6080590301
F,0,-0.907867296,1.8024545685,-0.4631580854
F,0,-1.0196741261,-1.7758637026,-0.1776671888
O,0,1.7305476122,1.5689813052,-0.0881488484
N,0,1.6194167478,-0.7006173035,-0.0289924334
H,0,1.023611681,-1.4999024314,-0.1783444614
C,0,-1.1843345453,0.160172217,1.3294855145
H,0,-0.602565025,-0.3767480335,2.0693122808
H,0,-1.9522275569,0.8284786623,1.7016273599
C,0,1.0777323841,0.5450245106,-0.0468401282
C,0,-0.4429141303,0.6335450246,0.0616848353
C,0,-1.4351365327,-0.4902912196,0.0263150351
C,0,3.064842773,-0.8818845934,-0.0996850552
H,0,3.4492094454,-0.6771057894,-1.1031879621
H,0,3.3024239786,-1.9097130338,0.1742849324
H,0,3.5535216009,-0.2008202386,0.596760235

20 (the truncated amide model of **19b**) minimum C

F,0,-2.7005867728,0.0291086277,-0.4368586566
F,0,-0.798466853,1.7938021509,0.4581381589
F,0,-1.1731473983,-1.5033563857,-0.8941486659
O,0,1.2987110181,0.9376109649,-1.255463099
N,0,1.8630487171,-0.3719228829,0.518968845
H,0,1.5853831435,-0.6572617092,1.4438730893
C,0,-1.0751173612,-0.4804498729,1.3258849828
H,0,-0.5237734131,-1.3467800523,1.6720697057
H,0,-1.7510461499,-0.0225678848,2.0387044076
C,0,1.0041859578,0.3776312279,-0.2184126444
C,0,-0.416894324,0.4850109469,0.3265333709
C,0,-1.493028126,-0.4557430682,-0.1011873478
C,0,3.2538639017,-0.5455035283,0.1198476568
H,0,3.2990605424,-0.6716301204,-0.9612909924
H,0,3.6562427289,-1.4350409173,0.6049158745
H,0,3.8630683891,0.3223395038,0.3897703147