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

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Contents

| Constal information | 1 |
|--|----|
| | T |
| General synthetic procedures and analytical data | 2 |
| References | 13 |
| NMR spectra of new compounds | 14 |
| Figure S1: Comparison of ¹ H NMR of 25 in CDCl ₃ and MeOD | 46 |
| Figure S2: Comparison of ¹⁹ F NMR of 25 in CDCl ₃ and MeOD | 46 |
| Scheme S1: Enolisation responsible for H/D exchange of 25 in MeOD | 47 |
| DFP computations for 11a | 48 |
| Figure S3: Rotational profiles about the C(F)-C(=C) bond in 11a (B3LYP/6-311+G** level) | |
| Figure S4: Electrostatic potential of rotamer bis of 11a at the B3LYP/6-311+G** level) | |
| Coordinates of the DFT-optimised structures for 11a | 49 |
| DFT Computations for 19b through a truncated model 20 | 50 |
| Table S1: Computed properties of the model amide 20 (the truncated model of 19b) | |
| Coordinates of the DFT-optimised structures for amide 20 (the truncated model of 19b) | |

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, Et₂O and toluene were dried and deoxygenated using a MBraun SPS-800 solvent system. ¹H NMR, ¹³C NMR and ¹⁹F NMR spectra were recorded on a Bruker AV 300, Bruker AV 400, Bruker AVII 400, Bruker AVIII-HD 500 or Bruker AVIII 500 instrument. CDCl₃, MeOD, DMSO-d₆ or toluene-d₈ were used as solvents. Chemical shifts are reported in parts per million (ppm). Tetramethylsilane (δ 0 ppm) functioned as an external standard for ¹H and ¹³C NMR experiments. CFCl₃ was used as an external standard for ¹⁹F 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 °C and stirred for 30 minutes, followed by addition of NEt₃.3HF 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 NH₃ 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 NaHCO₃ (50 mL), followed by drying over Na₂SO₄. After filtration, solvent was removed *in vacuo*. Purification by flash column chromatography (petroleum ether/CH₂Cl₂) 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 NEt₃.HF (11.76 mL, 72.00 mmol, 1.5 equiv) in CH₂Cl₂ (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, CDCl₃) $\delta_{\rm H}$ 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>₂Br); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 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, CHF,), 34.3 (d, J = 28.4 Hz, CHBr); ¹⁹F NMR (400 MHz, CDCl₃) $\delta_{\rm F}$ -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 NEt₃.HF (8.02 mL, 49.17 mmol, 1.50 equiv) in CH₂Cl₂ (40 mL). The product was obtained by flash column chromatography (silica gel, 95% petroleum ether/5% CH₂Cl₂) as a colourless oil (6.15 g, 67%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 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>₂Br); ¹³C NMR (101 MHz, CDCl₃) $\delta_{\rm C}$ 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,); ¹⁹F NMR (471 MHz, CDCl₃) $\delta_{\rm F}$ -174.1 (ddd, ²J_{HF} = 46.6 Hz, ³J_{HF} = 24.1, 16.5 Hz, CH<u>F</u>); HRMS (ASAP⁺) 281.8875 [M]⁺, C₈H₇⁷⁹Br⁸¹BrF 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 NEt₃.HF (2.00 mL, 12.29 mmol, 1.50 equiv) in CH₂Cl₂ (20

mL). The product was obtained by flash column chromatography (silica gel, 90% petroleum ether/10% CH₂Cl₂) as a colourless oil (1.279 g, 71%). ¹H NMR (400 MHz, CDCl₃) 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>₂Br); ¹³C NMR (126 MHz, CDCl₃)

 $δ_{C}$ 163.1 (d, ${}^{1}J_{CF}$ = 248.2 Hz, Ar-<u>C</u>F), 133.0 (dd, ${}^{2}J_{CF}$ = 20.8 Hz, ${}^{3}J_{CF}$ = 3.4 Hz, Ar-<u>C</u>), 127.8 (dd, ${}^{3}J_{CF}$ = 6.9, 7.8 Hz, 2 x Ar-<u>C</u>H), 115.8 (d, ${}^{2}J_{CF}$ = 21.8 Hz, 2 x Ar-<u>C</u>H), 92.1 (d, ${}^{1}J_{CF}$ = 178.0 Hz, <u>C</u>HF), 34.1 (d, ${}^{2}J_{CF}$ = 29.0 Hz, <u>C</u>HBr); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} -111.9 to -111.9 (m, Ar-<u>F</u>), -171.6 (ddd, ${}^{2}J_{HF}$ = 46.4 Hz, ${}^{3}J_{HF}$ = 24.5, 15.0 Hz, CH<u>F</u>).

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 NEt₃.HF (1.36 mL, 8.32 mmol, 1.50 equiv) in CH₂Cl₂ (10 mL). The product was obtained by flash column chromatography (silica gel, 95% petroleum ether/5% CH₂Cl₂ as a colourless solid (1.23 g, 80%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 7.64-7.37 (9H, m, Ar-C<u>H</u>), 5.68 (1H, ddd, ²J_{HF} = 46.5 Hz, ³J_{HH} 7.9, 4.1 Hz, C<u>H</u>F), 4.77-3.61 (2H, m, C<u>H</u>₂Br); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 142.2 (Ar-<u>C</u>), 140.3 (Ar-<u>C</u>), 136.0 (Ar-<u>C</u>, d, ²J_{CF} = 20.3 Hz), 128.9 (2 x Ar-<u>C</u>H), 127.7 (Ar-<u>C</u>H), 127.5 (2 x Ar-<u>C</u>H), 127.1 (2 x Ar-<u>C</u>H), 126.2 (d, ³J_{CF} = 6.5 Hz, 2 x Ar-<u>C</u>H), 92.6 (d, ¹J_{CF} = 177.9 Hz, <u>C</u>HF), 34.2 (d, ²J_{CF} = 28.6 Hz, <u>C</u>HBr); ¹⁹F NMR (471 MHz, CDCl₃) $\delta_{\rm F}$ -176.6 (ddd, ²J_{HF} = 46.5 Hz, ³J_{HF} = 25.8, 15.3 Hz, CH<u>F</u>), HRMS (ASAP⁺) 261.0102 [M-F]⁺, C₁₄H₁₂⁸¹Br 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_2CI_2 (7 mL). The crude product was purified by flash column chromatography (silica gel, 70% petroleum ether/30% CH_2CI_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: ¹H NMR (400 MHz, CDCl₃) δ_{H} 8.28 (2H, d, ³J_{HH} = 8.6 Hz, Ar-C<u>H</u>), 7.56 (2H, d, ³J_{HH} = 8.6 Hz, Ar-C<u>H</u>), 5.76 (1H, dt, ²J_{HF} = 46.6 Hz, ³J_{HH} = 5.6 Hz, C<u>H</u>F), 3.72-3.65 (2H, m, C<u>H</u>₂Br); ¹³C NMR (125 MHz, CDCl₃) δ_{C} : 148.3 (Ar-C), 143.9 (d, ²J_{CF} = 20.8 Hz, Ar-C), 126.7 (d, ³J_{CF} = 7.4 Hz, 2 x Ar-CH), 124.0 (2 x Ar-CH), 91.2 (d, ¹J_{CF} = 180.9 Hz, CHF), 33.4 (d, ²J_{CF} = 27.4 Hz, CHBr,). ¹⁹F NMR (470 MHz, CDCl₃) δ_{F} -176.94 (dt, ²J_{HF} = 46.6 Hz, ³J_{HF} = 19.7 Hz, CH<u>F</u>). **9f**': ¹H NMR (400 MHz, CDCl₃) δ_{H} : 8.26-8.20 (2H, m, Ar-C<u>H</u>), 7.62-7.59 (2H, m, Ar-C<u>H</u>), 5.07 (1H, m, C<u>H</u>Br), 3.60-3.49 (2H, m, C<u>H</u>₂F); ¹⁹F NMR (470 MHz, CDCl₃) δ_{F} -150.8 to -150.9 (m, CH₂<u>F</u>). HRMS (EI⁺) 248.9624 [M]⁺, C₈H₇NO₂F⁸¹Br 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°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/CH₂Cl₂) afforded the appropriate vinyl fluoride.



(1-Fluorovinyl)benzene (10a) was prepared following general procedure B, using (2-bromo-1fluoroethyl)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%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 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_{trans}H_{cis}</u>), 4.86 (1H, dd, ${}^{3}J_{HF(cis)} = 17.3 \text{ Hz}, {}^{2}J_{HH} = 3.5 \text{ Hz}, \text{ CH}_{trans}\underline{H}_{cis}$; ${}^{13}\text{C} \text{ NMR} (125 \text{ MHz}, \text{CDCl}_{3}) \delta_{C} 162.9 (d, {}^{1}J_{CF} = 250.5 \text{ Hz}, \underline{CF}), 132.0 (d, {}^{1}J_{CF} = 250.5 \text{ Hz}, \underline{CF})$ ¹*J*_{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, ³*J*_{CF} = 7.1 Hz, 2 x Ar-<u>C</u>H), 89.6 (d, ²*J*_{CF} = 22.6 Hz, <u>CH2</u>); ¹⁹F NMR (471 MHz, CDCl₃) 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%). ¹H NMR (400 MHz, CDCl₃) 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}H_{trans}), 4.88 (1H, dd, ³J_{HF (cis)} = 17.7 Hz, ²J_{HH} = 3.7 Hz, CH_{cis}H_{trans}); ¹³C NMR (125 MHz, CDCl₃) δ_{C} 162.0 (d, ${}^{1}J_{CF}$ = 250.3 Hz, <u>C</u>F), 131.9 (Ar-<u>C</u>) 130.9 (d, ${}^{2}J_{CF}$ = 29.9 Hz, Ar-<u>C</u>), 131.7 (2 x Ar-<u>C</u>H), 126.2 (d, ${}^{3}J_{CF}$ = 7.1 Hz, 2 x Ar-<u>C</u>H), 90.5 (d, ²J_{CF} = 22.1 Hz, <u>C</u>H₂); ¹⁹F NMR (471 MHz, CDCl₃) δ_F -108.0 (dd, ³J_{HF (trans)} = 49.4 Hz, ³J_{HF} $_{(cis)} = 17.7 \text{ Hz}, CF$).

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% CH₂Cl₂) to afford the title compound (**10c**) as a colourless solid (1.408 g, 74%). ¹H NMR (500 MHz, CDCl₃) 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}H_{trans}), 5.10 (1H, dd, ³J_{HF (cis)} = 17.9 Hz, ²J_{HH} = 3.6 Hz, $CH_{cis}H_{trans}$); ¹⁹F NMR (471 MHz, CDCl₃) 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-(2bromo-1-fluoroethyl)-1,1'-biphenyl (9d) (0.80 g, 2.87 mmol, 1.00 equiv), potassium tertbutoxide (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% CH₂Cl₂) as a colourless solid (0.387 g, 68%). ¹H NMR (400 MHz, CDCl₃) 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 $(1H, dd, {}^{3}J_{HF (trans)} = 49.7 Hz, {}^{2}J_{HH} = 3.5 Hz, CH_{cis}H_{trans}), 4.89 (1H, dd, {}^{3}J_{HF (cis)} = 17.9 Hz, {}^{2}J_{HH} = 3.5 Hz, CH_{cis}H_{trans}); {}^{13}C$ NMR (125 MHz, CDCl₃) 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, <u>C</u>H₂); ${}^{19}F$ NMR (471 MHz, CDCl₃) δ_{F} -108.0 (dd, ${}^{3}J_{H,F(trans)}$ = 49.7 Hz, ${}^{3}J_{H,F(cis)}$ = 17.9 Hz, C<u>F</u>).

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 CH₂Cl₂ (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 NEt₃.3HF (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% CH₂Cl₂) afforded the product as a colourless oil (2.32 g, 82%). ¹H NMR (400 MHz, CDCl₃) δ_{H} : 7.51-7.46 (2H, m, Ar-C<u>H</u>), 6.92-6.86 (2H, m, Ar-C<u>H</u>), 5.88 (1H, dd, ³J_{H,F (trans}) = 50.2 Hz, ²J_{HH} = 3.2 Hz, CH_{cis}H_{trans}), 4.86 (1H, dd, ³J_{H,F (cis)} = 18.4 Hz, ²J_{HH} = 3.5 Hz, C<u>H_{cis}H_{trans}), 3.85 (3H, s, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ_{C} 162.9 (d, ¹J_{CF} = 248.9 Hz, <u>C</u>F), 160.5 (Ar-<u>C</u>), 124.6 (d, ²J_{CF} = 29.9 Hz, Ar-C), 126.1 (d, ³J_{CF} = 7.2 Hz, 2 x Ar-<u>C</u>H), 113.8 (2 x Ar-<u>C</u>H), 87.6 (d, ²J_{CF} = 23.2 Hz, <u>C</u>H₂), 55.3 (<u>C</u>H₃); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} -107.1 (dd, ³J_{H,F (trans}) = 50.3 Hz, ³J_{H,F (cis)} = 18.1 Hz, C<u>F</u>].</u>

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% CH₂Cl₂) as a colourless solid (0.790 g, 79%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 8.25 (2H, d, *J* = 8.8 Hz, Ar-C<u>H</u>), 7.72 (2H, d, *J* = 8.8 Hz, Ar-C<u>H</u>), 5.26 (1H, dd, ³*J*_{HF (trans)} = 48.3 Hz, ²*J*_{HH} = 4.0 Hz, CH_{cis}<u>H</u>_{trans}), 5.10 (1H, dd, ³*J*_{HF (cis)} = 17.5 Hz, ²*J*_{HH} = 4.0 Hz, C<u>H</u>_{cis}H_{trans}); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 160.8 (d, ¹*J*_{CF} = 250.8 Hz, <u>C</u>F), 148.2 (<u>C</u>-NO₂), 137.8 (d, ²*J*_{CF} = 29.9 Hz, Ar-C), 125.4 (d, ³*J*_{CF} = 7.2 Hz, 2 x Ar-<u>C</u>H), 124.6 (d, ⁴*J*_{CF} = 1.9 Hz, 2 x Ar-<u>C</u>H), 93.8 (d, ²*J*_{CF} = 21.9 Hz, <u>C</u>H₂); ¹⁹F NMR (471 MHz, CDCl₃) $\delta_{\rm F}$ -108.16 (dd, ³*J*_{HF (trans)} = 48.3 Hz, ³*J*_{HF (cis)} = 17.5 Hz, <u>CF</u>).

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 Na₂SO₃ and NaHCO₃, followed by drying over Na₂SO₄,

filtration and evaporation of solvent *in vacuo*. Purification by flash column chromatography (petroleum ether/CH₂Cl₂) 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 Nal (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%). ¹H NMR (500 MHz, CDCl₃) δ_{H} 7.44 (5H, s, Ar-C<u>H</u>), 2.21-2.01 (2H, m, C<u>H</u>₂); ¹³C NMR (125 MHz, CDCl₃) 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, CF₂), 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>H₂); ¹⁹F{¹H} NMR (376 MHz, CDCl₃) 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]⁺, C₉H₈F₃ 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,

Br 1.00 equiv), trifluoromethyltrimethylsilane (0.924 mL, 6.25 mmol, 2.50 equiv), and Nal (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% CH₂Cl₂) as a light yellow oil (0.128 g, 66%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 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>H₂</u>); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 131.9 (2 x Ar-C<u>H</u>), 130.1 (d, ²*J*_{CF} = 19.9 Hz, Ar-C<u>C</u>), 128.4 (d, ³*J*_{CF} = 5.1 Hz, 2 x Ar-C<u>H</u>), 123.8 (Ar-C<u>C</u>), 108.9 (ddd, ¹*J*_{CF} = 294.8, 294.8 Hz, ²*J*_{CF} = 4.1 Hz, CF₂), 79.2 (ddd, ¹*J*_{CF} = 235.6 Hz, ²*J*_{CF} = 10.6, 2.1 Hz, CF), 22.4 (dt, ²*J*_{CF} = 12.9, 10.0 Hz, CH₂); ¹⁹F NMR (471 MHz, CDCl₃) $\delta_{\rm F}$ -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>), -141.9 (dddd, ²*J*_{FF} = 167.8 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]⁺, C₉H₆⁸¹BrF₂ 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 Nal (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% CH₂Cl₂) as a colourless oil (0.224 g, 67%). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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-C<u>C</u>H), 126.9 (d, ³*J*_{CF} = 20.4 Hz, Ar-C<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>F₂), 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>H₂); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} -111.1 - -111.2 (m, Ar-<u>F</u>), -136.3 (dddd, ²*J*_{FF} = 167.4 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]⁺, C₉H₅F₄ 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 Nal (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% CH₂Cl₂) as a pale yellow solid (0.209 g, 93%). ¹H NMR (500 MHz, CDCl₃) $\delta_{\rm H}$ 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>H₂</u>); ¹³C NMR (101 MHz, CDCl₃) $\delta_{\rm C}$ 130.0 (d, ²*J*_{CF} = 19.7 Hz, Ar-C), 128.9 (2 x Ar-CH), 127.8 (Ar-CH), 127.4 (2 x Ar-CH), 127.3 (2 x Ar-CH), 127.2 (2 x Ar-CH), 126.9 (Ar-C), 108.9 (ddd, ¹*J*_{CF} = 294.5, 294.5 Hz, ²*J*_{CF} 2.5 Hz, CF₂), 80.0-77.4 (m, CF), 22.4 (dt, ²*J*_{CF} = 13.5, 10.1 Hz, CH₂); ¹⁹F NMR (377 MHz, CDCl₃) $\delta_{\rm F}$ -136.6 (dddd, ²*J*_{FF} = 166.0 Hz, ³*J*_{FF} = 8.3 Hz, ³*J*_{FH} 14.9 = Hz, ³*J*_{FH} = 5.9 Hz, CFF), -141.7 (dddd, ²*J*_{FF} = 166.0 Hz, ³*J*_{FF} = 4.0 Hz, ³*J*_{FH} = 7.8 Hz, ³*J*_{FH} = 15.6 Hz, CFF), -180.8 - -181.0 (m, CF). HRMS (ASAP⁺) 248.0809 [M]⁺, C₁₅H₁₁F₃ 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), trifluoromethyltrimethylailane (0.205 ml -2.47 mmol -2.50 equiv), and Nal

1.00 equiv), trifluoromethyltrimethylsilane (0.365 mL, 2.47 mmol, 2.50 equiv), and Nal (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% CH₂Cl₂) as a light yellow oil (0.128 g, 64%). ¹H NMR (500 MHz, CDCl₃) $\delta_{\rm H}$ 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, CH₃), 2.16-1.91 (2H, m, C<u>H₂</u>); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 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>F₂), 78.6 (ddd, ¹J_{CF} = 233.5 Hz, ²J_{CF} = 12.8, 9.9 Hz, <u>C</u>F), 55.4 (CH₃), 22.2 (dt, ²J_{CF} = 14.4, 10.1 Hz, <u>C</u>H₂); ¹⁹F NMR (471 MHz, CDCl₃) $\delta_{\rm F}$ -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]⁺, C₁₀H₁₀F₂O 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 Nal (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% CH₂Cl₂) as a pale yellow oil (0.480 g, 74%). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ_{C} 148.1 (Ar-C), 138.5 (d, *J* = 19.3 Hz, Ar-C), 126.6 (d, *J* = 5.1 Hz, 2 x Ar-CH), 123.8 (2 x Ar-CH), 108.7 (ddd, ¹*J*_{CF} = 299.0, 294.5 Hz, ²*J*_{CF} 11.0 Hz, CF₂), 77.4 (ddd, ¹*J*_{CF} = 234.5 Hz, ²*J*_{CF} = 12.6, 2.2 Hz, CF), 23.5 (dt, ²*J*_{CF} = 13.4, 9.7 Hz, CH₂); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} -137.8 (dddd, ²*J*_{FF} = 167.8 Hz, ³*J*_{FH} = 8.5 Hz, ³*J*_{FH} = 15.3 Hz, ³*J*_{FH} = 6.8 Hz, CFF), -140.4 (dddd, ²*J*_{FF} = 167.8 Hz, ³*J*_{FH} = 6.9 Hz, ³*J*_{FH} = 16.3 Hz, CFF), -187.3 - -187.4 (m, CF); HRMS (ASAP⁺) 218.0431 [M+H]⁺, C₉H₇F₃NO₂ requires 218.0429.



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 °C for 24 h before quenching with 1M aqueous HCl solution and washing sequentially with saturated aqueous solution of NaHCO₃ (25 mL) and brine (25 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness *in vacuo*. Purification of the crude residue by flash column chromatography (silica gel, 70% petroleum ether/30% CH₂Cl₂) afforded the *meta*-isomer **11f**¹ (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') ¹H NMR (300 MHz, CDCl₃) 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); ¹⁹F{¹H} NMR (282 MHz, CDCl₃) δ_{F} -133.5 (dd, ²*J*_{FF} = 171.9 Hz, ³*J*_{FF} 7.1 = Hz, C<u>F</u>), -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]⁺, C₉H₆F₃NO₂ requires 217.0345.

11f and **1-nitro-2-(1,2,2-trifluorocyclopropyl)benzene (11f")** (approx. 4:1 isolated). ¹H NMR (300 MHz, CDCl₃) $\delta_{H} 8.31 (2H, d, J = 8.8 Hz,$ **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"** $C<u>H</u>₂); ¹⁹F{¹H} NMR (282 MHz, CDCl₃) <math>\delta_{F}$ -137.3 (dd, ²J_{FF} = 168.5 Hz, ³J_{FF} = 8.8 Hz, **11f"** -C<u>F</u>F), -137.6 (dd, ²J_{FF} = 168.1 Hz, ³J_{FF} 9.0 = Hz, **11f**-C<u>F</u>F), -140.7 (dd, ²J_{FF} = 168.1 Hz, ³J_{FF} = 3.0 Hz, **11f** -CF<u>F</u>), -141.4 (dd, ²J_{FF} = 168.5 Hz, ³J_{FF} = 3.5 Hz, **11f"** -CF<u>F</u>), -185.1 (dd, ³J_{FF} = 9.0 Hz, ³J_{FF} = 3.5 Hz, **11f"**-C<u>F</u>), -187.4 (dd, ³J_{FF} = 9.4 Hz, ³J_{FF} = 2.9 Hz, **11f**-C<u>F</u>). HRMS (ASAP⁺) 218.0423 [M+H]⁺, C₉H₆F₃NO₂ 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 PPh₃ (0.058 g, 0.220 mmol, 0.825 equiv), Cul (0.010 g, 0.058 mmol, 0.21 equiv) and Pd(PPh₃)Cl₂ (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), Et₃N (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°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 NaHCO₃ (25 mL) and brine (25 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness *in vacuo*. The titled compound was obtained by flash column chromatography (silica gel, 75% petroleum ether/25% CH₂Cl₂) as a light yellow oil (0.064 g, 76%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 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-CF₂), 1.74 – 1.57 (2H, m, C<u>H</u>₂-CH₃), 0.94 (3H, t, *J* = 7.3 Hz, C<u>H</u>₃); ¹³C NMR (126 MHz, CDCl₃) $\delta_{\rm C}$ 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, C<u>F</u>₂), 91.0 (C=C), 87.9 (C=C), 79.6-77.4 (m, CF), 38.0 (CH₂), 24.4 (CH₂), 23.5 – 21.8 (m, cyclopropyl <u>CH₂)</u>, 13.8 (<u>CH₃</u>); ¹⁹F NMR (471 MHz, CDCl₃) $\delta_{\rm F}$ -136.9 (ddd, ²*J*_{FF} = 166.9 Hz, ³*J*_{FF} = 15.2 Hz, ³*J*_{FH} 8.8 = Hz, ³*J*_{FH} = 5.7 Hz, C<u>F</u>), -141.5 (dddd, ²*J*_{FF} = 167.1 Hz, ³*J*_{FF} = 16.2 Hz, ³*J*_{FH} = 6.6 Hz, ³*J*_{FH} = 3.8 Hz,

CF<u>F</u>), -182.5 – -185.7 (m, C<u>F</u>); HRMS (ASAP⁺) 315.136 [M+H]⁺, C₂₀H₁₈F₃ 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°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 NaHCO₃ (25 mL) and brine (25 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness *in vacuo*. Purification of the crude residue by flash column chromatography (70% petroleum ether/30% CH₂Cl₂) afforded the title compound as a light yellow oil (0.095 g, 93%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 7.44 – 7.32 (2H, m, Ar-C<u>H</u>), 6.99 – 6.87 (2H, m, Ar-C<u>H</u>), 3.96 – 3.80 (4H, m, 2 x C<u>H₂), 3.31 – 3.12 (4H, m, 2 x CH₂), 2.13 – 1.89 (2H, m, CF-CH₂-CF₂); ¹³C NMR (126 MHz, CDCl₃) $\delta_{\rm C}$ 152.2 (Ar-<u>C</u>), 129.1 (2 x Ar-<u>C</u>H), 121.3 (d, ²*J*_{CF} = 20.0, Ar-<u>C</u>), 115.0 (2 x Ar-<u>C</u>H), 108.6 (ddd, ¹*J*_{CF} = 294.7, 294.9 Hz, ²*J*_{CF} =10.8 Hz, <u>C</u>F₂), 79.1-77.9 (m, <u>C</u>F), 66.8 (2 x O<u>C</u>H₂), 48.5 (2 x N<u>C</u>H₂), 22.0 (dt, ²*J*_{CF} = 14.8, 10.3 Hz, CH₂); ¹⁹F NMR (471 MHz, CDCl₃) $\delta_{\rm F}$ - 135.7 (dddd, ²*J*_{FF} = 166.3 Hz, ³*J*_{FF} = 14.5 Hz, ³*J*_{FH} 8.7, 5.3 Hz, C<u>F</u>F), -142.6 (dddd, ²*J*_{FF} = 166.4 Hz, ³*J*_{FF} = 16.2 Hz, ³*J*_{FH} = 11.4, 6.2 Hz, CF<u>F</u>), -178.5 – -178.6 (m, C<u>F</u>). HRMS (ESI⁺) 258.1100 [M+H]⁺, C₁₃H₁₅F₃NO requires 258.1100.</u>



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 CH₂Cl₂ (18 mL) were added and the solution

cooled to 0 °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 °C for 1 h. After completion, the reaction mixture was warmed to RT, quenched with H₂O (20 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated to dryness *in vacuo* to afford the title compound as colourless oil (0.091 g, 90%).¹H NMR (500 MHz, CDCl₃) $\delta_{\rm H}$ 7.35 (2H, d, *J* = 8.6 Hz, Ar-C<u>H</u>), 6.83 (2H, d, *J* = 8.6 Hz, Ar-C<u>H</u>), 2.19 (1H, ddd, ³*J*_{FH} = 4.7, 13.7 Hz, ³*J*_{HH} = 9.4 Hz, CH<u>H</u>), 2.05 (1H, ddd, 1H, ddd, ³*J*_{FH} 4.7, 13.7 Hz, ³*J*_{HH} = 9.3 Hz, C<u>H</u>H); ¹³C NMR (126 MHz, CDCl₃) $\delta_{\rm C}$ 156.3 (Ar-<u>C</u>), 131.0 (2 x Ar-<u>C</u>H), 128.4 (Ar-<u>C</u>), 115.8 (2 x Ar-<u>C</u>H), 109.6 (t, ¹*J*_{CF} = 290.8 Hz, <u>CF₂), 27.3 (t, ²*J*_{CF} = 10.5 Hz, <u>CH₂); ¹⁹F NMR (471 MHz, CDCl₃) $\delta_{\rm F}$ -126.9 (ddd, ²*J*_{FF} = 149.2 Hz, ³*J*_{FH} = 11.5 Hz, ³*J*_{FH} 4.8 = Hz, C<u>F</u>F), -132.3 (ddd, ²*J*_{FF} = 148.5 Hz, ³*J*_{FH} = 13.1 Hz, ³*J*_{FH} = 4.7 Hz, CF<u>F</u>); HRMS(EI⁺) 186.0484 [M]⁺, C₉H₈F₂O₂ requires 186.0492.</u></u>

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 ¹⁹F 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 (Na₂SO₄) and the solvent was removed under vacuum to give a brown gum which gradually solidified into colourless needle crystals (0.6 g, 60%). ¹H NMR (500 MHz, MeOD) δ_{H} 2.56-2.44 (1H, m, C<u>H</u>H), 2.34-2.20(1H, m, CH<u>H</u>); ¹³C NMR (125 MHz, MeOD) δ_{C} 165.6 (d, ²*J*_{CF} 23.1 Hz, <u>C</u>=O), 108.6 (ddd, ¹*J*_{CF} 298.4, 288.0, ²*J*_{CF} 9.6 Hz, <u>C</u>F₂), 74.6 (ddd, ¹*J*_{CF} 245.5 Hz, ²*J*_{CF} 10.5, 13.2 Hz, <u>C</u>F), 22.2-21.9 (m, <u>C</u>H₂); ¹⁹F{¹H} NMR (470 MHz, CDCl₃) δ_{F} -137.0 (dd, ²*J*_{FF} = 163.8 Hz, ³*J*_{FF} = 11.2 Hz, C<u>F</u>), -139.0 (d, ²*J*_{FF} = 163.8 Hz, CF<u>F</u>), -202.6 (*d*, ³*J*_{FF} = 11.2 Hz, C<u>F</u>); HRMS (ESI⁻) 139.0007 [M-H]⁻, C₄H₂F₃O₂ 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%). ¹H NMR (400 MHz, CDCl₃) δ_{H} 8.09 (br s, 1H, NH), 7.61-7.54 (2H, m, Ar-C<u>H</u>), 7.41-7.36 (2H, m, Ar-C<u>H</u>), 7.21 (1H, tt, *J* = 7.4, 1.1 Hz, Ar-<u>H</u>), 2.76-2.64 (1H, m, C<u>H</u>H), 2.22-2.07 (m, 1H, CH<u>H</u>); ¹³C NMR (125 MHz, CDCl₃) δ_{C} 160.5 (d, ²*J*_{CF} = 17.2 Hz, <u>C</u>O), 136.4 (Ar-<u>C</u>), 129.2 (2 x Ar-<u>C</u>H), 125.4 (Ar-<u>C</u>H), 120.4 (2 x Ar-<u>C</u>H), 107.6 (td, ¹*J*_{CF} = 291.7 Hz, ²*J*_{CF} = 9.4 Hz, CF₂), 77.7 (dt, ¹*J*_{CF} = 256.3 Hz, ²*J*_{CF} = 11.1 Hz, CF_F), 22.9 (q, ²*J*_{CF} = 11.1 Hz, CH₂); ¹⁹F¹H} NMR (470 MHz, CDCl₃) δ_{F} -138.7 (dd, ³*J*_{FF} = 3.2, ²*J*_{FF} = 164.1 Hz, C<u>F</u>F), -139.2 (dd, ³*J*_{FF} = 11.1 Hz, ²*J*_{FF} = 164.1 Hz, CF<u>F</u>), -200.5 (*d*, ³*J*_{FF} = 11.2, 2.5 Hz, CF); HRMS (ESI⁺) 216.0628 [M+H]⁺, C₁₀H₉F₃NO 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%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 7.43-7.33 (m, 5H, Ar-<u>H</u>), 6.68 (br s, 1H, NH), 4.62-4.53 (2H, m, C<u>H</u>₂NH), 2.71-2.59 (1H, m, C<u>H</u>H), 2.06 (1H, m, CH<u>H</u>); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 162.5 (d, ²J_{CF} 18.8 Hz, <u>C</u>O), 137.0 (Ar-<u>C</u>), 128.9 (2 x Ar-<u>C</u>H), 120.0 (3 x Ar-<u>C</u>H), 107.0 (dt, ²J_{CF} = 9.1, ¹J_{CF} 295.6 Hz, CF₂), 77.8 (dt, ¹J_{CF} = 255.0 Hz, ²J_{CF} = 11.0 Hz, CF), 43.8 (CH₂), 22.9 (dt, ²J_{CF} = 10.1 Hz); ¹⁹F{¹H} NMR (470 MHz, CDCl₃) $\delta_{\rm F}$ -139.2 (m, C<u>F</u>₂), -202.2 (dd, ³J_{FF} = 5.8, 8.1Hz, CF); HRMS (ESI⁺) 230.0788 [M+H]⁺, C₁₁H₁₁F₃NO 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%). $\delta_{\rm H}$ 7.55 (2H, d, *J* = 7.4 Hz, 2 x Ar-C<u>H</u>), 7.46 (2H, d, *J* = 8.9 Hz, 2 x Ar-C<u>H</u>), 7.40 (2H, *J* = 7.4 Hz, 2 x Ar-C<u>H</u>), 7.37 (s, 1H, NH), 7.20 (1H, t, *J* = 7.4 Hz, Ar-C<u>H</u>), 6.95 (2H, d, *J* = 8.9 Hz, 2 x Ar-CH), 4.79 (1H, ddd, ${}^{3}J_{\rm HF}$ = 1.0, 9.9 Hz, ${}^{3}J_{\rm HH}$ = 4.7 Hz, C<u>H</u>CO), 2.64 (ddd, 1H, ${}^{3}J_{\rm HF}$ = 1.0, 15.8 Hz, ${}^{3}J_{\rm HH}$ = 4.7 Hz, C<u>H</u>O); 13 C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 160.4 (<u>C</u>=O), 155.9 (Ar-<u>C</u>), 137.0 (Ar-<u>C</u>), 132.8 (2 x Ar<u>C</u>H), 129.2 (2 x Ar<u>C</u>H), 125.3 (Ar-<u>C</u>H), 120.0 (2 x Ar-<u>C</u>H), 116.7 (2 x Ar-<u>C</u>H), 115.2 (Ar-<u>C</u>), 108.9 (t, ${}^{1}J_{\rm CF}$ = 296.2 Hz, <u>C</u>F₂), 58.1 (dd, ${}^{2}J_{\rm CF}$ = 15.6, 7.7 Hz, C-3), 35.5 (dd, ${}^{2}J_{\rm CF}$ = 12.3, 9.4 Hz, C-1); ¹⁹F NMR (470 MHz, CDCl₃) $\delta_{\rm F}$ -131.8 (dd, ${}^{3}J_{\rm HF}$ 10.2 Hz, ${}^{2}J_{\rm FF}$ 165.0 Hz, C<u>F</u>F), -133.7 (ddd, ${}^{3}J_{\rm HF}$ 13.0, 1.5 Hz, ${}^{2}J_{\rm CF}$ = 165.0 Hz, CF<u>F</u>); HRMS (ESI⁺) 368.0087 [M+H]⁺, C₁₆H₁₃⁷⁹BrF₂NO₂ 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%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 7.83-7.77 (4H, m, 4 x Ar-C<u>H</u>), 7.53-7.48 (4H, m, 4 x Ar-C<u>H</u>), 7.47-7.43 (1H, m, Ar-C<u>H</u>), 7.42 (br s, 1H, N<u>H</u>), 7.38-7.34 (2H, m, 2 x Ar-C<u>H</u>), 7.12 (1H, t, *J* = 7.5 Hz, Ar-C<u>H</u>), 3.89 (dd, 1H, ³*J*_{HH} = 6.8 Hz, ³*J*_{HF} = 13.3 Hz, C<u>H</u>CO), 2.54 (dd, 1H, ³*J*_{HH} = 6.8 Hz, ³*J*_{HF} 12.5 Hz, C<u>H</u>S); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 161.0 (<u>C</u>O), 137.1 (Ar-<u>C</u>), 133.7 (Ar-<u>C</u>), 132.0 (Ar-<u>C</u>), 131.4 (Ar-<u>C</u>), 129.2 (2 x Ar-<u>C</u>H), 129.0 (Ar-<u>C</u>H), 127.8 (Ar-<u>C</u>H), 127.3 (Ar-<u>C</u>H), 126.9 (Ar-<u>C</u>H), 126.7 (Ar-<u>C</u>H), 126.2 (Ar-<u>C</u>H), 126.1 (Ar-<u>C</u>H), 125.1 (Ar-<u>C</u>H), 120.1 (2 x Ar-<u>C</u>H), 111.1 (t, ¹*J*_{CF} = 294.7 Hz, <u>C</u>F₂), 36.7 (t, ²*J*_{CF} 10.1 Hz, <u>C</u>H), 28.4 (t, ²*J*_{CF} = 11.5 Hz, <u>C</u>H); ¹⁹F NMR (470 MHz, CDCl₃) $\delta_{\rm F}$ -130.5 (dd, ³*J*_{HF} = 2.1 Hz, ²*J*_{FF} = 150.5 Hz, C<u>F</u>F), -132.8 (dd, ³*J*_{HF} 13.2 Hz, ²*J*_{FF} = 150.5 Hz, CF<u>F</u>); HRMS (ESI⁺) 378.0726 [M+Na]⁺, C₂₀H₁₅F₂NOSNa 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%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 7.53 (2H, d, *J* = 7.7 Hz, 2 x Ar-<u>H</u>), 7.48 (2H, d, *J* = 8.4 Hz, 2 x Ar<u>H</u>), 7.48 (2H, d, *J* = 7.7 Hz, 2 x Ar<u>H</u>), 7.36 (1H, br s, N<u>H</u>), 7.25 (2H, d, *J* = 8.4 Hz, 2 x Ar<u>H</u>), 7.19 (1H, t, *J* = 8.4 Hz, Ar-<u>H</u>), 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, C<u>H</u>S); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 160.6 (<u>C</u>=O), 137.1 (Ar-<u>C</u>), 133.2 (Ar-<u>C</u>), 132.8 (Ar-<u>C</u>), 132.4 (2 x Ar-<u>C</u>H), 129.8 (2 x Ar-<u>C</u>H), 129.2 (2 x Ar-<u>C</u>H), 125.2 (Ar-<u>C</u>H), 119.9.1 (2 x Ar-<u>C</u>H), 110.8 (t, ¹J_{CF})

= 278.3 Hz, $\underline{C}F_2$), 36.6 (t, ${}^{2}J_{CF}$ = 10.0 Hz, $\underline{C}H$), 28.0 (t, ${}^{2}J_{CF}$ = 11.0 Hz, $\underline{C}H$); ${}^{19}F{}^{1}H$ NMR (470 MHz, CDCl₃) δ_F -130.5 (d, ${}^{2}J_{FF}$ 151.0 Hz, C<u>F</u>F), -132.9 (d, ${}^{2}J_{CF}$ = 151.0 Hz, CF<u>F</u>); ${}^{19}F$ NMR (470 MHz, CDCl₃) δ_F -130.5 (dd, ${}^{2}J_{HF}$ = 12.1 Hz, ${}^{2}J_{FF}$ = 151.0 Hz, C<u>F</u>F), -132.9 (d, ${}^{2}J_{FF}$ = 13.1 Hz, ${}^{2}J_{CF}$ = 151.0 Hz, CF<u>F</u>); HRMS (ESI⁺) 405.9679 [M+Na]⁺, C₁₆H₁₂F₂NOBrSNa 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%). ¹H NMR (400 MHz, CDCl₃) $\delta_{\rm H}$ 7.53 (2H, d, *J* = 7.9 Hz, 2 x Ar-C<u>H</u>), 7.38 (1H, s, N<u>H</u>), 7.35 (2H, t, *J* = 7.9 Hz, 2 x Ar-C<u>H</u>), 7.17 (1H, t, *J* = 7.3 Hz, Ar-C<u>H</u>), 3.43 (ddd, 1H, ³*J*_{HF} = 6.6 Hz, ³*J*_{HF} = 1.9, 11.5 Hz, C<u>H</u>C=O), 2.42 (ddd, 1H, ³*J*_{HF} = 6.6 Hz, ³*J*_{HF} = 1.7, 10.5 Hz, C<u>H</u>S), 2.29 (s, 3H, SMe); ¹³C NMR (125 MHz, CDCl₃) $\delta_{\rm C}$ 161.4 (C=O), 137.2 (ArC), 129.2 (2 x Ar-<u>C</u>H), 125.0 (Ar-<u>C</u>H), 119.9 (2 x Ar-<u>C</u>H), 111.6 (dd, ¹*J*_{CF} = 288.3, 292.8 Hz, <u>C</u>F₂), 36.6 (t, ²*J*_{CF} = 10.3 Hz, <u>C</u>HCO), 29.4 (t, ²*J*_{CF} = 11.3 Hz, <u>C</u>HS), 16.1 (s, SCH₃; ¹⁹F¹H} NMR (470 MHz, CDCl₃) $\delta_{\rm F}$ -132.6 (ddd, ³*J*_{HF} 11.0, 2.0 Hz, ²*J*_{FF} 151.2 Hz, C<u>F</u>F), -133.2 (dd, ³*J*_{HF} 12.2 Hz, ²*J*_{CF} = 151.2 Hz, CF<u>F</u>); HRMS (ESI⁺) 266.0416 [M+Na]⁺, C₁₁H₁₁F₂NOSNa requires 266.0422.

SO₂CH₃

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 (MgSO₄), 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, CDCl₃) $\delta_{\rm H}$ 7.60 (br s, 1H, NH), 7.53 (2H, d, J = 7.7 Hz, 2 x Ar-<u>H</u>), 7.38 (2H, t, J = 7.7 Hz, 2 x Ar-<u>H</u>), 7.21 (1H, t, J = 7.7 Hz, Ar-<u>H</u>), 3.98 (ddd, 1H, ³J_{HH} = 7.0 Hz, ³J_{HF} = 1.5, 11.5 Hz, C<u>H</u>CO), 3.41 (ddd, 1H, ${}^{3}J_{HH}$ = 7.0 Hz, J_{HF} = 1.2, 13.1 Hz, C<u>H</u>S), 3.18 (s, 3H, SC<u>H</u>₃); ¹H NMR (400 MHz, DMSO-d₆) 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, CH₃); ¹H NMR (400 MHz, MeOD) $\delta_{\rm H}$ 7.60-7.57 (2H, m, 2 x Ar-C<u>H</u>), 7.37-7.32 (2H, m, 2 x Ar-C<u>H</u>), 7.14 (1H, tt, J = 7.4, 1.1 Hz, Ar-C<u>H</u>), (C<u>H</u>CO at around 3.98 in CDCl₃ was not observed as it was exchanged to CDCO), 3.59 (1H, d, ${}^{3}J_{HF}$ = 14.0 Hz, CHS, over weekend, this signal disappeared as it was exchanged by deuterated MeOD), 3.22 (3H, s, SCH₃); ¹³C 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-<u>C</u>H), 107.2 (t, ${}^{1}J_{CF}$ = 291.0 Hz, CF₂), signals for <u>C</u>DCO and <u>C</u>DCS too weak to be observed, 41.4 (S<u>C</u>H₃); ${}^{13}C$ NMR (125 MHz, DMSO-d₆) 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, ¹J_{CF} = 291.0 Hz, <u>CF</u>₂), 42.8 (S<u>C</u>H₃), 42.6 (t, ²J_{CF} = 9.6 Hz, <u>C</u>HCO), 32.2 (t, ²J_{CF} = 9.0 Hz, <u>C</u>HS; ¹⁹F{¹H} NMR (470 MHz, CDCl₃) $\delta_{\rm F}$ -131.8 (d, ²J_{FF} 160.1 Hz, C<u>F</u>F), -133.7 (d, ²J_{CF} = 160.1 Hz, CF<u>F</u>); ¹⁹F NMR (470 MHz, CDCl₃) $\delta_{\rm F}$

-131.8 (ddd, ${}^{3}J_{HF}$ 11.0, 1.0 Hz, ${}^{2}J_{FF}$ 160.1 Hz, C<u>F</u>F), -133.7 (ddd, ${}^{3}J_{HF}$ 13.0, 1.5 Hz, ${}^{2}J_{CF}$ = 160.1 Hz, CF<u>F</u>); ${}^{19}F{}^{1}H$ } NMR (470 MHz, DMSO-d₆) δ_{F} -131.2 (d, ${}^{2}J_{FF}$ 157.1 Hz, C<u>F</u>F), -133.8 (d, ${}^{2}J_{CF}$ = 157.1 Hz, CF<u>F</u>); ${}^{19}F$ NMR (470 MHz, DMSO-d₆) δ_{F} -131.2 (dd, ${}^{3}J_{HF}$ 12.8 Hz, ${}^{2}J_{FF}$ 157.1 Hz, ${}^{4}CF_{2}$), -133.8 (dd, ${}^{3}J_{HF}$ 14.7 Hz, ${}^{2}J_{CF}$ = 160.1 Hz, ${}^{4}CF_{2}$); HRMS (ESI⁺) 276.0496 [M+H]⁺, C₁₁H₁₁F₂NO₃S requires 276.0500, for the deuterated version HRMS (ESI⁺) 3010503 [M+Na]⁺, C₁₁H₈D₃F₂NO₃SNa requires 301.0514.

References

- 1. S. Movahhed, J. Westphal, M. Dindaroglu, A. Falk and H.-G. Schmalz, Chem. Eur. J. 2016, 22, 7381-7384.
- 2. O. G. J. Meyer, R. Fröhlich and G. Haufe, *Synthesis*, **2000**, *10*, 1479-1490.
- 3. A. J. Durie, T. Fujiwara, R. Cormanich, M. Bühl, A. M. Z Slawin and D. O'Hagan, *Chem. Eur. J.*, **2014**, *20*, 6259-6263
- M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. Montgomery, J. A. J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, Rev. A.02, Wallingford CT, **2009**
- (a) A. D. Becke, J. Chem. Phys. 1993, 98, 5648-5642; (b) C. Lee, W. Yang, R. G. Parr, Phys. Rev. B 1988, 37, 785-789.
- 6. T. Bykova, N. Al-Maharik, M. Bühl, A. M. Z. Slawin, T. Lebl, D. O' Hagan, Chem. Eur. J., in press (ref 4b in the main paper).
- (a) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. J. Comp. Chem., 2003, 24, 669-681; (b) review: Tomasi, J.; Mennucci, B.; Cammi, R. Chem. Rev. 2005, 105, 2999-3093.





.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)

131.15 132.85



-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 f1 (ppm)



04052017-23-doh-d54-A11.fid 19F Observe without 1H decoupling - Full Range SW R-4-Br triF pure 19Fcp







02052017-51-doh-ct54-A10.fid 1H Observe PhPhtriF1H



02052017-51-doh-ct54-A11.fid 19F Observe without 1H decoupling - Full Range SW PhPhtriF 19cp







04072017-24-doh-ct54-A11.fid 19F Observe without 1H decoupling - Full Range SW R-4-OMe triF 19F







04032017-22-doh-ct54-A.11.fid 19F Observe vithout 1H decoupling - Full Range SW NO2 triF 19F

852/11-262/11-272



.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)







04042017-6-doh-dt54-A.12.fid 13C Observe with 1 H decoupling - UDEFT buchwald prod pure 13C













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





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)







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)







1102 2017-2-doh-qz-N.11.fid 19F Observe without 1H decoupling - SW 80 ppm QZDH351







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)

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



12142017-6-doh-qz-A.10.fid 1H Observe Q2DH380 mCPBA oxidation





-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 f1 (ppm)



Figure S1.¹H 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. ¹⁹F 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 performed⁴ for (1,2,2-trifluorocyclopropyl)benzene **11a** by scanning an F-C-C=C dihedral angle (B2LYP⁵/6-311+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[.]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 performed⁴ for a model amide at the same level as in our previous study on related tetrafluorocyclohexyl amides⁶ (B3LYP⁵/6-311+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 | А | В | С |
|---|--------------------|-------|-------|
| Property | | | |
| ΔE_{rel} [kcal mol ⁻¹] gas phase | 0.0 | 4.6 | 6.5 |
| ΔE_{rel} [kcal mol ⁻¹] in water) ^a | (0.0) | (3.1) | (3.4) |
| $\theta_{\text{F-C-C=O}}$ calc [°] | 164.3 | 26.3 | -54.4 |
| X-ray | 165.2 ^b | n.a. | n.a. |
| nearest d _{FH(N)} [Å] ^c | 2.198 | 2.062 | 3.558 |
| μ[D] | 3.0 | 4.2 | 6.0 |

^aCPCM method. ^bN-benzyl derivative **19b**, this work. ^cDistance 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 0,0,2.061407013,1.2590272111,3.044924964 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 0,0,1.7305476122,1.5689813052,-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 0,0,1.2987110181,0.9376109649,-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