A simple, rapid procedure for nucleophilic radiosynthesis of aliphatic 1-[^18]Ftrifluoromethyl groups

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General: All solvents and reagents where obtained from Alfa-Aesar (Alfa Aesar UK Ltd, Heysham, Morecambe, UK), Sigma-Aldrich (Sigma-Aldrich Co. Ltd, Poole, UK) and Fisher Scientific (Fisher Scientific UK Ltd, Loughborough, UK). Solid phase extraction cartridges were obtained from Waters (Waters Ltd, Elstree, UK). Analytical HPLC was performed on an Agilent 1100 series HPLC-system (Agilent Technologies UK Ltd, Wokingham, UK), consisting of a G1312 A binary pump and a G1314 variable wavelength UV-detector. A Bioscan (Bioscan Inc., Washington DC, USA) dual BGO metabolite detector system with Flow-Count B-FC-4000 analogue/digital interface and a Bioscan 1” NaI(Tl) detector with Flow-Count B-FC-4000 analogue/digital interface were used for radioactivity detection. Lablogic Laura 3 and Laura 4 software (Lablogic Systems Ltd, Sheffield, UK) was used for data acquisition and evaluation. For screening of reaction conditions, a Chromolith RP18e (5μm) 0.4 mm x 100 mm column (Merck KGaA, Darmstadt, Germany) at a flow rate of 2 mL/min (7 mM NH₄OH-Acetonitril gradient), a Phenomenex Primesphere RP-18 (5 μm) 0.46 x 250 mm column at a flow rate of 1 mL/min (70-80% MeCN in 0.05 M Ammonium formate pH 6.8) and a Phenomenex Gemini RP-18 (5 μm) 0.46 x 250 mm column at a flow rate of 1 mL/min (70-80% MeCN in 0.05 M Ammonium formate pH 6.8) were used as stationary phase. A GE Healthcare BAS-IP MS storage phosphor screen 35cm x 43cm was used for radio TLC (Fisher Scientific UK Ltd, Loughborough, UK). Detection and evaluation was performed using a Duerr CR 35 NDT (raytest Isotopenmessgeraete GmbH, Straubenhardt, Germany) and raytest AIDA QWBA software. NMR spectra were recorded on Bruker Avance III 400 QNP Ultrashield Plus Cryo or a Bruker Bruker Avance 500 Cryo Ultrashield (Bruker UK Ltd, Coventry, UK). Chemical shifts are reported downfield from TMS, relative to the solvent residual signal. Melting points were determined using a Kofler melting point apparatus. Low resolution mass spectrometry was conducted using a Bruker Esquire (Bruker UK Ltd, Coventry, UK) electron spray ion source and detector. Accurate high resolution mass spectra were recorded on an Orbitrap spectrometer using electron spray ionisation. Flash chromatography was conducted using a Gilson PLC 2020 chromatography system and normal phase silica gel cartridges.

General procedure for radiolabelling:[^18]FFluoride ion was produced using the ^18O(p,n)^18F nuclear reaction via proton bombardment (16→3MeV) of an H₂¹⁸O liquid target on a GE PETtrace cyclotron at a beam current of 30-40 μA for 5 to 10 minutes. The radionuclide was extracted from the enriched target water by solid phase extraction on a waters accell plus light QMA strong anion exchanger cartridge (CO₂⁻-form). Reactive[^18]F was obtained by elution of the trapped radioactivity using a mixture of appropriate bases (20μmol) in acetonitrile (300 μl) and water (300 μl). Six aliquots of the eluate (100 ml) were transferred to 5 ml conical bottom reaction tubes and the mixtures were concentrated in a stream of nitrogen. Remaining free water was removed by azeotropic co-evaporation with 3 portions of anhydrous acetonitrile (3x1 ml). Labelling precursor dissolved in the appropriate solvent was added to the residue and heated to the desired temperature. Aliquots were withdrawn from the reaction mixture (100 ml) at multiple timepoints and transferred into water (0.5 ml). The resultant sample was directly injected into radioHPLC or used for radioTLC (1 ml, CHCl₃).

Determination of the influence of trace water in the solvent on radiolabelling: Anhydrous DMSO was used as obtained from Sigma-Aldrich for the 0ppm condition. In all other cases 10 ml portions of DMSO where prepared and kept in separate septum vials. 10 μl of sterile filtered de-ionised water was added to 10 ml of DMSO using a microliter syringe to obtain a 10³ ppm stock solution. 1 ml of this solution was diluted with 9 ml of DMSO to prepare a 10² ppm stock solution. This step was repeated in order to obtain 10 ppm and 1 ppm mixtures. A mixture containing 5 ppm was obtained from 2 ml of 10 ppm stock solution and 2 ml of DMSO. These mixtures were used as described in the general labelling procedures to quantify the RCY.
Figure S1: Dependency of the radiochemical yield from the water content. X-axis denotes amounts of water being added to the solvent.

Figure S2: Time-dependent radiochemical yield as a function of temperature.

Figure S3: Time-dependent radiochemical yield as a function of solvent.
Table S1: Two step labelling yields

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<th>RCY / %</th>
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<td>4-CNC₆H₄OCH₂CF₂[¹⁸F]F (11b)</td>
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<td>2-ClC₆H₄CO₂H</td>
<td>2-ClC₆H₄CO₂CH₂CF₂[¹⁸F]F (12b)</td>
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<tr>
<td>13a</td>
<td>HN(CH₂C₆H₅) (C₆H₅CH₂)₂CH₂CF₂[¹⁸F]F (13b)</td>
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2,2,2-trifluoroethyl 4-methylbenzenesulfonate (7b): 2,2,2-trifluoroethanol (10g, 100 mmol) and triethylamine (14.3g, 140 mmol) are dissolved in anhydrous diethylether (120 ml). Toluene sulfonfonyl chloride (17.2g, 90 mmol) are added in portions at room temperature. The mixture was stirred for approximately 48 hours, until the toluenesulfonyl chloride had been consumed. The solids were filtered off and the filter cake is washed with diethyl ether (2 x 30 ml). The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (Hexane-diethyl ether: 1:9). Product 6a was obtained as colourless crystals in 89% (20.3g) yield. MP = ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.46 (s, 3H, ArCH₃), 4.38 (q, J = 8 Hz, 2 H, CH₂), 7.38 (d, J = 9 Hz, 2 H, ArH), 7.81 (d, J = 9 Hz, 2 H, ArH). ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 21.7, 64.5 (q, JCF = 37.8 Hz, 120.5, 123.2, 128.1, 130.1, 131.8, 145.9. ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -74.06. MS (ESI) = 254.0, C₉H₉F₃O₃S requires 254.0224.

1,1,1-trifluoropropan-2-yl 4-methylbenzenesulfonate (8b): Synthesised as described for 7b, from 5.7 g (50 mmol) 1,1,1-trifluoropropan-2-ol. Product 6b was obtained as colourless oil in 84% (10.1 g)
yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 1.45 (d, $J = 7$ Hz, 3 H, CH$_3$), 2.44 (s, 3H, ArCH$_3$), 4.82 (p, $J = 6$ Hz, 1 H, CH), 7.35 (d, $J = 9$ Hz, 2 H, ArH), 7.79 (d, $J = 9$ Hz, 2 H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 14.7, 21.7, 73.2 (q, $J_{CF} = 34.2$ Hz, 118.7, 121.5, 124.3, 127.9, 132.9, 145.6. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -78.66. MS (ESI) = 267.0, C$_{10}$H$_{10}$F$_3$O$_3$S requires 267.0297, HRMS C$_{10}$H$_{10}$F$_3$O$_3$S requires 267.0297, found: 267.0303; C$_{10}$H$_{11}$F$_3$O$_3$S requires C, 44.77; H, 4.13; F, 21.25; O, 17.89; S, 11.95; found C, 45.07 H, 4.07.

$^{((2,2,2\text{-trifluoroethoxy})\text{methyl})\text{benzene (9b):}}$ Sodium hydride (504 mg, 20 mmol) was suspended in anhydrous DMF (25 ml) and 2,2,2-trifluoroethanol (2 g, 20 mmol) was added dropwise at room temperature. When effervescence ceased, benzyl bromide (2.8 g, 0.8 equiv, 16 mmol) was added and the reaction mixture was refluxed for 3 h. The reaction mixture was distilled in vacuo to yield 9b as a colourless oil, BP (40 mbar) = 80-83°C (2.83g, 93%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 3.81 (q, $J = 9$ Hz, 2 H, CH$_2$), 4.67 (s, 2H, CH$_2$), 7.30 – 7.39 (m, 5 H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 67.2 (q, $J_{CF} = 33.7$ Hz), 74.1, 127.9, 128.3, 128.6, 136.5. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -74.1. MS C$_9$H$_9$F$_3$O requires 190.0605, found: 190.1

$^{N,N\text{-dibenzyl}\text{-2,2,2\text{-trifluoroethanamine (10b):}}}$ 2,2,2-trifluoroethyl amine (1.1g, 11mmol) was dissolved in acetonitrile (12 ml), N,N-diisopropyl-N-ethyl amine (1.45g, 11 mmol) and benzyl bromide (3.75g, 22 mmol) were added and the reaction mixture was stirred at 70°C over night. The mixture was concentrated and the residue was purified by flash chromatography on silica gel (1% triethylamine in pentane) to afford 10b as a colourless oil (2.01g, 72%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 3.11 (q, $J = 18.9$ Hz, 2 H, CH$_2$), 3.80 (s, 2H, CH$_2$), 7.28 – 7.41 (m, 5 H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 53.0 (q, $J_{CF} = 29.9$ Hz), 58.2, 127.4, 128.4, 128.9, 138.3. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -68.1. MS (ESI) = 280.2, C$_{16}$H$_{17}$F$_3$N requires 280.1308, HRMS C$_{16}$H$_{17}$F$_3$N requires 280.1308, found: 280.1291; C$_{16}$H$_{16}$F$_3$N requires C, 69.50; H, 5.77; F, 20.41; N, 5.01; found C, 69.20; H, 5.86; N, 5.25.

$^{1\text{-methoxy-4-(2,2,2\text{-trifluoroethyl})benzene (11b):}}$ Obtained as a byproduct from 11a (7%). bp (30 mbar) = 94°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 3.11 (q, $J = 8$ Hz, 2 H, CH$_2$), 3.87 (s, 3H, CH$_2$), 6.90 (d, $J = 7$ Hz, 2 H, ArH), 7.19 (d, $J = 7$ Hz, 2 H, ArH), $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -71.1. MS (ESI) = 190.1, C$_9$H$_9$F$_3$O requires 190.0605.
1-dimethylamino-4-(2,2,2-trifluoroethyl)benzene (12b): Obtained as a byproduct from 12a (4%). 
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 3.05 (s, 6 H, N(CH$_3$)$_2$), 4.18 (q, $J = 11$ Hz, 2 H, CH$_2$), 6.70 (d, $J = 8$ Hz, 2 H, ArH), 7.10 (d, $J = 8$ Hz, 2 H, ArH), $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -73.1. MS (ESI) = 204.0. C$_{10}$H$_{12}$F$_3$N requires 203.0922.

1-fluoro-4-(2,2,2-trifluoroethyl)benzene (13b): Obtained as a byproduct from 13a (10%). bp (45 mbar) = 57-59°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 3.06 (q, $J = 8$ Hz, 2 H, CH$_2$), 7.17 (d, $J = 8$ Hz, 2 H, ArH), 7.31 (d, $J = 8$ Hz, 2 H, ArH), $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -75.3. MS (ESI) = 178.0, C$_8$H$_6$F$_4$ requires 178.0406.

1-nitro-4-(2,2,2-trifluoroethyl)benzene (14b): Obtained as a byproduct from 14b (22%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 3.46 (q, $J = 10.5$ Hz, 2H, CH$_2$), 7.52 (d, $J = 8.5$ Hz, 2 H, ArH), 8.21 (d, $J = 9$ Hz, 2 H, ArH), $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -69.9. MS (ESI) = 178.0, C$_8$H$_6$NO$_2$F$_3$ requires 205.0351.

2-methoxy-6-(1,1,1-trifluoropropan-2-yl)naphthalene (15b): Obtained as a byproduct from 15a (8%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 1.33 (d, $J = 7$ Hz, 3H, CH$_3$), 7.11 (s, 1H), 3.93 (s, 3H), 3.92 (p, $J = 6$ Hz, 1 H, CH), 7.15 (dd, $J = 9$ Hz, $J = 2.0$ Hz, 1H), 7.45 (d, $J = 8.5$ Hz, 1H), 7.72-7.69 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 31, 44.8, 55.5, 105.8, 119.0, 123.7, 126.0, 126.6, 127.0, 129.0, 129.4, 133.1, 144.0, 157.0. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -73.2 (ESI) = 254.1, C$_{14}$H$_{13}$F$_3$O requires 254.0918, HRMS C$_{14}$H$_{13}$F$_3$O requires 254.0918, found: C$_{14}$H$_{13}$F$_3$O requires C, 66.14; H, 5.15; F, 22.42; O, 6.29; found C, 65.96 H, 4.94.
4-((2,2,2-trifluoroethoxy)methyl)benzonitrile (16b): 2,2,2-trifluoroethanol (110 mg, 1.1 mmol) dissolved in 2 ml of DMF was added dropwise to a suspension of sodium hydride (26 mg, 1 mmol) in DMF (2 ml). When gas evolution ceased, 4-fluorobenzonitrile (121 mg, 1 mmol) was added and the obtained mixture was refluxed for 3 h. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (hexane-diethyl ether; 9:1). 94% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 4.74 (q, $J = 8$ Hz, 2 H, CH$_2$), 7.01 (d, $J = 9$ Hz, 2 H, ArH), 7.59 (d, $J = 9$ Hz, 2 H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 62.3 (q, $J_{CF} = 33.0$ Hz), 105.2, 116.4, 118.6, 122.7, 125.5, 134.2, 160.1. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -74.77. MS (ESI) = 201.1, C$_9$H$_6$F$_3$NO requires 201.0401, HRMS C$_9$H$_6$F$_3$NO requires 201.0401, found: 201.0410; C$_9$H$_6$F$_3$NO requires, C, 53.74; H, 3.01; F, 28.34; N, 7.28.

2,2,2-trifluoroethyl 2-chlorobenzoate (17b): 2-chlorobenzoyl chloride (175 mg, 1 mmol) and triethylamine (102 mg, 1 mmol) were dissolved in diethyl ether (5 ml). 2,2,2-trifluoroethanol (100 mg, 1 mmol) was added dropwise and the mixture was stirred overnight at r.t.. The solids were filtered off and the filter cake was washed with two portions of diethyl ether (2 x 5 ml). The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel using a gradient of pentane-diethyl ether for elution. 87%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 4.70 (q, $J = 8.5$ Hz, 2 H, CH$_2$), 7.31 – 7.38 (m, 2 H, ArH), 7.44-7.51 (m, 1 H, ArH), 7.89 (d, $J = 6$ Hz, 1 H, ArH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 60.0 (q, $J_{CF} = 36.6$ Hz), 126.7, 131.4, 131.9, 133.5, 163.7. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -73.69. MS (ESI) = 238.0, C$_9$H$_6$F$_3$ClO$_2$ requires 238.0008, HRMS C$_9$H$_6$F$_3$ClO$_2$ requires 238.0008, found: 238.0010 C$_9$H$_6$F$_3$ClO$_2$.

1-(4-fluorobenzyl)-N-(1-(4-(2,2,2-trifluoroethoxy)phenethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (19b): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 1.38 (q, $J = 10$ Hz, 2H), 1.85 (t, $J = 11$ Hz, 2H), 2.02 (d, $J = 11$ Hz, 2 H), 2.37 (t, $J = 8$ Hz, 1H), 2.39 (d, $J = 6$ Hz, 1H), 2.62 (d, $J = 6$ Hz, 1H), 2.64 (t, $J = 8$ Hz, 1H), 2.79 (d, $J = 8$ Hz, 2 H), 3.79-3.95 (m, 2 H), 5.03 (s, 2H), 6.82 (d, $J = 9$ Hz, 2H), 6.94- 7.14 (m, 8 H), 7.52 (d, $J = 8$ Hz, 2 H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 163.7, 161.3, 155.7, 153.1, 141.5, 134.2, 130.8, 130.7, 130.6, 129.6, 129.5, 128.3, 128.2, 121.9, 120.2, 116.4, 116.3, 116.1, 113.9, 107.3, 61.4, 52.2, 50.0, 45.1, 32.7, 32.5, 30.9. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ (ppm): -77.7, -113.6. MS (ESI) = 526.2, C$_{29}$H$_{30}$F$_4$N$_4$O requires 526.2356, HRMS C$_{29}$H$_{30}$F$_4$N$_4$O requires, C, 52.49; H, 4.61; N, 14.39; O, 16.81; found C, 52.54; H, 4.63; N, 14.40; O, 16.83.
C_{29}H_{30}F_{4}N_{4}O requires 526.2356, found: 527.2360 [M+H], C_{29}H_{30}F_{4}N_{4}O requires C, 66.15; H, 5.74; F, 14.43; N, 10.64; found C, 66.09; H, 5.72, N, 10.86.

(1R,2S,3S,5S)-methyl 3-p-tolyl-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (20b): \(^1^H \text{NMR} (400 MHz, CDCl}_3) \delta (ppm): 1.60 – 1.75 (m, 2H), 1.77 - 1.85 (m, 3H), 1.87 – 1.95 (m, 2H), 1.96 – 2.09 (m, 2.29 (s, 3H, CH3), 2.75 (td, J = 2.8, J = 12.5 Hz, 1H, CH), 2.78 (q, J = 9Hz, 2H, CH2), 2.85 – 2.99 (m, 2 H), 3.45 (bros, 1 H, CH), 3.48 (s, 3H, OCH3), 3.75 (bros, 1H, CH), 7.11 (d, J = 8 Hz, 2H, ArCH), 7.19 (d, J = 8 Hz, 2H, ArCH). \(^1^C \text{NMR} (100 MHz, CDCl}_3) \delta (ppm): 21.1, 26.1 (d, JCF = 22.1 Hz), 33.5 (d, J = 43.4 Hz), 51, 52.6, 55.9 (q, J = 30.8 Hz), 63.2, 65.2, 127.2, 128.7, 135.3, 139.5, 171.5. \(^1^F \text{NMR} (376 MHz, CDCl}_3) \delta (ppm): -72.01. MS (ESI) = 341.2, C_{18}H_{22}F_{3}NO_{2} requires 341.1603, HRMS: C_{18}H_{22}F_{3}NO_{2} requires 341.1603, found: C_{18}H_{22}F_{3}NO_{2} requires C, 63.33; H, 6.50; F, 16.70; N, 4.10; O, 9.37; found C, 63.03; H, 6.58; N, 4.05.

2,2-difluorovinyl 4-methylbenzenesulfonate (7a): 2,2,2-trifluoroethyl tosylate (2.57g, 10 mmol) was dissolved in anhydrous THF (15 ml) and cooled to -78°C. n-Butyl lithium (1.6 M in hexanes, 12.5 ml, 20 mmol) was added dropwise and the resultant mixture was stirred at -78°C for 40 minutes. A mixture of water (4.5g, 25 mmol) and THF (10 ml) was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether and the phases were separated. The aqueous phase was extracted with diethyl ether (20 ml) and discarded. The organic phases were combined, dried over MgSO\(_4\) and concentrated. The residue was purified by flash chromatography on silica gel (pentane-diethyl ether, 19:1). Compound 7a was obtained as a colourless oil in 79% (1.86g) yield. \(^1^H \text{NMR} (500 MHz, CDCl}_3) \delta (ppm): 2.46 (s, 3H, ArCH3), 6.08 (dd, J =14 Hz, J = 4 Hz, 1H, CH), 7.38 (d, J = 9 Hz, 2H, ArH), 7.80 (d, J = 9 Hz, 2H, ArH). \(^1^C \text{NMR} (100 MHz, CDCl}_3) \delta (ppm): 21.8, 109.6 (dd, J_{CF} = 59.5 Hz, J_{CF} = 15.5 Hz), 128.8, 130.7, 131.8, 146.1, 157.4 (dd, J_{CF} = 293.5 Hz, J_{CF} = 283 Hz). \(^1^F \text{NMR} (376 MHz, CDCl}_3) \delta (ppm): -91.0 (ddd, J = 13 Hz, J = 22.5 Hz, J = 52 Hz), -109.6 (d, 52 Hz). MS (ESI) = 234.0, C_{9}H_{8}F_{2}O_{3}S requires: 234.0162.

1,1-difluoroprop-1-en-2-ylation of benzene-4-sulfonate (8a): Synthesised from 6b (2.7g, 10 mmol) as described for 7a. Compound 7b was obtained as a colourless oil in 83% (2.05g) yield. \(^1^H \text{NMR} (400 MHz, CDCl}_3) \delta (ppm): 1.91 (t, J = 3 Hz, 3H, CH3), 2.46 (s, 3H, ArCH3), 7.31 (d, J = 8.5 Hz, 2H, ArH), 7.81 (d, J = 9 Hz, 2H, ArH). \(^1^C \text{NMR} (100 MHz, CDCl}_3) \delta (ppm): 13.1, 21.7, 109.6 (dd, J_{CF} =
15.5 Hz, J_{CF} = 49.5 Hz), 128.3, 129.9, 132.5, 145.7. 19F NMR (376 MHz, CDCl3) δ (ppm): -94.99 (d, J = 55.6 Hz), -108.5 (d, J = 55.6 Hz). MS (ESI) = 247.0, C_{10}H_{10}F_{2}O_{3}S requires: 247.0235. HRMS C_{10}H_{9}F_{2}O_{3}S requires: 247.0235, found: 247.0241; C_{10}H_{10}F_{2}O_{3}S requires C, 48.38; H, 4.06; F, 15.31; O, 19.33; S, 19.33, found C, 48.41; H, 3.93.

((2,2-difluorovinyl(oxy)methyl)benzene (9a): benzyl 2,2,2-trifluoroethyl ether (0.95 g, 5 mmol) was dissolved in THF (5 ml) and cooled to -100°C. n-Butyl lithium (1.6 M in hexanes, 6.6 ml, 10 mmol) was added dropwise and the resultant mixture was stirred at -78°C for 1 h. A mixture of water (3.6g, 20 mmol) and THF (10 ml) was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether and the phases were separated. The aqueous phase was extracted with diethyl ether (20 ml) and discarded. The organic phases were combined, dried over MgSO4, concentrated and distilled in vacuo. BP (30 mbar) = 82-84°C. Yield 59%. 1H NMR (400 MHz, CDCl3) δ (ppm): 4.69 (s, 2H, ArCH2), 5.63 (dd, J = 3 Hz, J = 16.2 Hz, 1H), 7.39-7.28 (m, 5H, ArH). 13C NMR (100 MHz, CDCl3) δ (ppm): 74.9, 107.6 (dd, J_{CF} = 15.5 Hz, J_{CF} = 49.5 Hz), 127.9, 128.3, 128.9, 136.5 (d, J = 271 Hz), 155.7. 19F NMR (376 MHz, CDCl3) δ (ppm): -101.10 (dd, J = 16 Hz and 77.7 Hz), -101.8 (d, J = 53.9 Hz). MS (ESI) = 170.0, C_{9}H_{8}F_{2}O requires: 170.0539.

N,N-dibenzyl-2,2-difluoroethenamine (10a): Synthesised from 6d (700mg, 2.5 mmol) as described for 7c. Compound 7d was obtained (85%) as a colourless oil after purification by flash chromatography on silica gel (NEt3-pentane; 1:99). 1H NMR (400 MHz, CDCl3) δ (ppm): 4.26 (s, 2H, ArCH2), 5.56 (dd, J = 1.8 Hz, J = 21.4 Hz, 1H, CH), 7.31 – 7.44 (m, 5 H, ArH). 13C NMR (100 MHz, CDCl3) δ (ppm): 51.3, 83.0 (dd, J_{CF} = 13.2 Hz, J_{CF} = 51.8), 127.3, 127.9, 128.5, 140.7, 154.5 (dd, J_{CF} = 292.3, 282.1 Hz). 19F NMR (376 MHz, CDCl3) δ (ppm): -87.9 (dd, J = 54.1, 21.0 Hz), -101.8 (d, J = 53.9 Hz). MS (ESI) = 259.1, C_{16}H_{15}F_{2}N requires: 259.1173. HRMS C_{16}H_{15}F_{2}N requires: 259.1173, found: 259.1164; C_{16}H_{15}F_{2}N requires C, 74.11; H, 5.83; F, 14.65; N, 5.40, found C, 74.5; H, 6.20; N, 5.80.

General procedure for the conversion of aldehydes into 2',2'-difluorostyrenes: Aldehyde (1 equiv.), triphenyl phosphine (2 equiv) and sodium 2-chloro-2,2-difluoroacetate (2 equiv) were dissolved in DMF (1 ml per mmol) and slowly heated to 80-100°C until gas evolution became apparent. The reaction mixture was stirred at this temperature until no further evolution of CO2 was observed. Water was added from a dropping funnel and the product was co-distilled with water at 100 mbar. The crude products were distilled in vacuo to obtain compounds 6e-6g and 7e-7g.

1-(2,2-difluorovinyl)-4-methoxybenzene (11a): From anisaldehyde (2.72g, 20 mmol), triphenylphosphine (10.48g, 40mmol), sodium 2-chloro-2,2-difluoroacetate (6.1g, 40 mmol) in 20 ml DMF. Products 7e was isolated from the distillate by phase separation, dried over MgSO4 and distilled...
in vacuo (BP (30 mbar) = 95-98°C) to afford a colourless liquid in 39% (1.33g) yield. \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm): 3.80 (s, 3H, OCH\(_3\)), 5.21 (dd, \( J_{HF} = 4 \) Hz, \( J_{HF} = 26.4 \) Hz, 1H, CH), 6.87 (d, \( J = 9 \) Hz, 2H, ArH), 7.25 (d, \( J = 9 \) Hz, 2H, ArH). \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm): 55.2, 81.5 (dd, \( J_{CF} = 14 \) Hz, \( J_{CF} = 29 \) Hz), 114.2, 122.7, 128.8, 152.9, 155.8, 158.5. \(^{19} \)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) (ppm): -84.89 (d, \( J = 39.2 \) Hz), -86.69 (d, \( J = 39.2 \) Hz). MS(ESI) = 170.1, C\(_9\)H\(_8\)F\(_2\)O requires 170.0543.

4-(2,2-difluorovinyl)-N,N-dimethylaniline (12a): From 4-dimethylaminobenzaldehyde (2.98g, 20 mmol), triphenylphosphine (10.48g, 40mmol), sodium 2-chloro-2,2-difluoroacetate (6.1g, 40 mmol) in 20 ml DMF. Crude \( 7f \) was extracted from the distillate using diethyl ether (3 x 75 ml). The combined organic extracts were dried over MgSO\(_4\), concentrated and the residue was distilled in vacuo (BP (30 mbar) = 107-110°C) to obtain a yield of 58% (2.1g) of a yellowish liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm): 2.94 (s, 6 H, NCH\(_3\)), 5.16 (dd, \( J_{HF} = 4 \) Hz, \( J_{HF} = 25.8 \) Hz, 1H, CH), 6.70 (d, \( J = 8 \) Hz, 2H, ArH), 7.20 (d, \( J = 8 \) Hz, 2H, ArH). \(^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm): 14.1, 22.9, 29.7, 40.4, 58.2, 81.7 (d, \( J_{CF} = 4.2 \) Hz, \( J_{CF} = 28.5 \) Hz), 112.6, 128.4, 128.8, 149.4, 155.5, 158.2. \(^{19} \)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) (ppm): -86.09 (d, \( J = 42.8 \) Hz), -88.24 (d, \( J = 42.8 \) Hz). MS(ESI) = 183.1, C\(_{10}\)H\(_{11}\)F\(_2\)N requires 183.0860.

1-(2,2-difluorovinyl)-4-fluorobenzene (13a): From 4-fluorobenzaldehyde (6.2g, 50 mmol), triphenylphosphine (26.2g, 100mmol), sodium 2-chloro-2,2-difluoroacetate (15.1g, 100 mmol) in 100 ml DMF. Products \( 7g \) was isolated from the distillate by phase separation, dried over MgSO\(_4\) and distilled in vacuo (BP (30 mbar) = 55-57°C) to afford a colourless liquid in 79% (6.2g) yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm): 5.24 (dd, \( J_{HF} = 4 \) Hz, \( J_{HF} = 25.9 \) Hz, 1H, CH), 7.02 (d, \( J = 8 \) Hz, 2H, ArH), 7.29 (d, \( J = 8 \) Hz, 2H, ArH). \(^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm): 81.3 (dd, \( J_{CF} = 14 \) Hz, \( J_{CF} = 29.7 \) Hz), 115.6, 126.3, 129.2, 153.2, 156.1 (d, \( J_{CF} = 36.1 \) Hz), 159.0, 160.4, 162.9. \(^{19} \)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) (ppm): -83.65 (d, \( J = 35.2 \) Hz), -85.1 (d, \( J = 4 \) Hz, \( J = 35.2 \) Hz). MS(ESI) = 185.1, C\(_8\)H\(_5\)F\(_3\) requires 185.0343.

1-(2,2-difluorovinyl)-4-nitrobenzene (14a): From 4-nitrobenzaldehyde (7.55g, 50 mmol), triphenylphosphine (26.2g, 100mmol), sodium 2-chloro-2,2-difluoroacetate (15.1g, 100 mmol) in 100 ml DMF. Product \( 14a \) was isolated from the reaction mixture diluted with water (100 ml) by extraction with diethyl ether (3 x 50 ml). The organic extract was dried over MgSO\(_4\) and purified by column chromatography to afford a yellow solid in 19% (1.76g) yield. M.p. = 35°C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm): 5.4 (dd, \( J = 3 \) Hz, \( J = 25.5 \) Hz, 1H, CH), 7.5 (d, \( J = 8.9 \) Hz, 2H, ArH), 7.92 (d, \( J = 8.9 \) Hz, 2H, ArH), 7.94 (d, \( J = 8.9 \) Hz, 2H, ArH). \(^{19} \)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) (ppm): -77.9 (d, \( J = 25.4 \) Hz, \( J = 18.7 \) Hz), -79.1 (d, \( J = 18.2 \) Hz). MS(ESI) = 185.1, C\(_8\)H\(_2\)F\(_2\)NO\(_2\) requires 185.0288.
2-(1,1-difluoroprop-1-en-2-yl)-6-methoxynaphthalene (15a): Product 7h was extracted from the quenched reaction mixture using diethylether (3 x 75 ml) the combined organic extracts were dried over MgSO4, concentrated and the residue was purified by flash chromatography on silica gel (pentane-diethyl ether; 19:1). Product 15a was extracted from the quenched reaction mixture using diethylether (3 x 75 ml) the combined organic extracts were dried over MgSO4, concentrated and the residue was purified by flash chromatography on silica gel (pentane-diethyl ether; 19:1). Compound 7i was obtained as a colorless solid. mp 88-90°C.

1H NMR (400 MHz, CDCl3) δ (ppm) 7.72-7.64 (m, 3H), 7.54-7.39 (m, 2H), 7.16-7.08 (m, 2 H), 3.91 (s, 3H), 2.15 (s, 3H). HRMS C14H13F2O requires: 235.0929, found: 235.0915