Electronic Supplementary Material (ESI) for Chemical Communications

A simple, rapid procedure for nucleophilic radiosynthesis of aliphatic 1-[^{18}F]trifluoromethyl 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 NH_4OH-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 radioTLC (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}F]Fluoride ion was produced using the $^{18}O(p,n)^{18}F$ nuclear reaction via proton bombardment (16→3MeV) of an $H_2{}^{18}O$ 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 via solid phase extraction on a waters accell plus light QMA strong anion exchanger cartridge (CO_2^{2-}-form). Reactive [^{18}F]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, $CHCl_3$)

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 10^3 ppm stock solution. 1 ml of this solution was diluted with 9 ml of DMSO to prepare a 10^2 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.

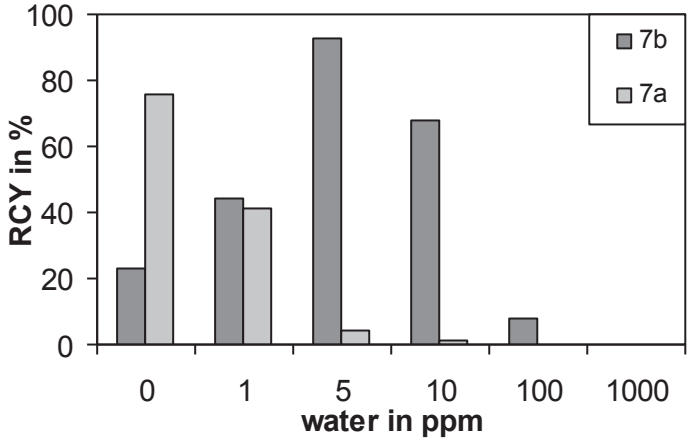


Figure S1: Dependency of the radiochemical yield from the water content. X-axis denotes amounts of water being added to the solvent.

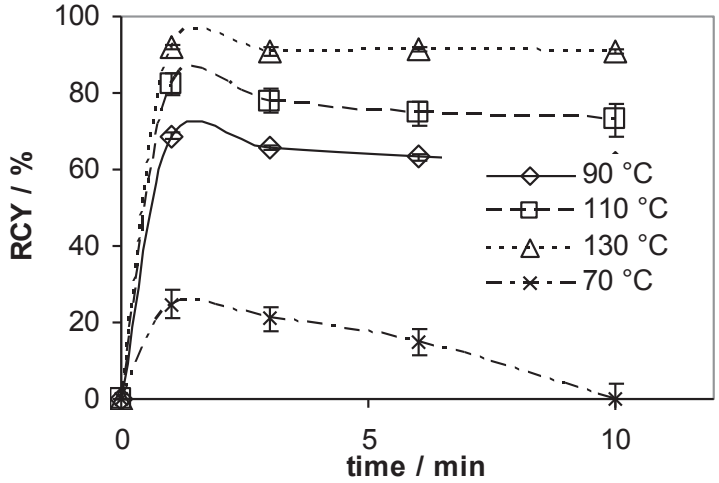


Figure S2 Time-dependent radiochemical yield as a function of temperature

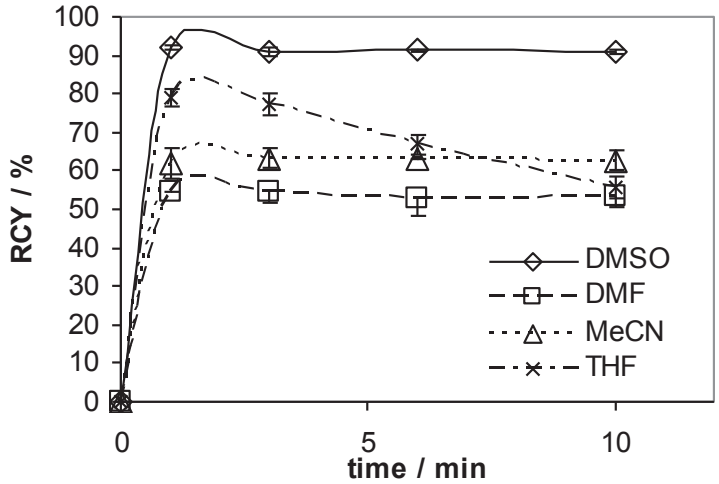


Figure S3 Time-dependent radiochemical yield as a function of solvent

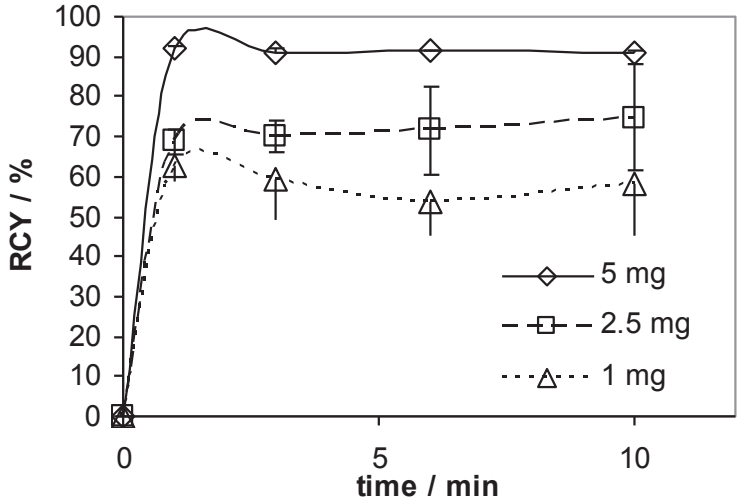
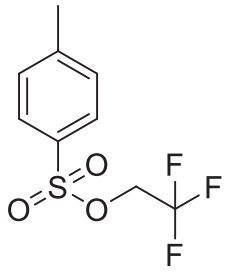


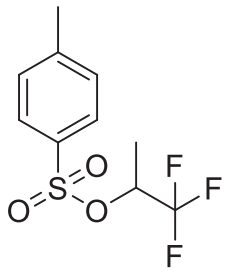
Figure S4 Time-dependent radiochemical yield as a function of labelling precursor mass.

Table s1: Two step labelling yields

entry	precursor	product	RCY / %
11a	4-CNC_6H_4OH	4-$CNC_6H_4OCH_2CF_2[^{18}F]F$ (**11b**)	93
12a	2-$ClC_6H_4CO_2H$	2-$ClC_6H_4CO_2CH_2CF_2[^{18}F]F$ (**12b**)	82
13a	$HN(CH_2C_6H_5)$	$(C_6H_5CH_2)_2CH_2CF_2[^{18}F]F$ (**13b**)	77

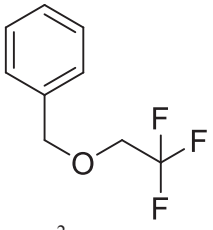


2,2,2-trifluoroethyl 4-methylbenzenesulfonate (7b):[1] 2,2,2-trifluoroethanol (10g, 100 mmol) and triethylamine (14.3g, 140 mmol) are dissolved in anhydrous diethylether (120 ml). Toluenesulfonyl chloride (17.2g, 90 mmol) are added in portions at room temperature. The mixture was stirred for approximately 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 = ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.46 (s, 3H, $ArCH_3$), 4.38 (q, J = 8 Hz, 2 H, CH_2), 7.38 (d, J = 9 Hz, 2 H, ArH), 7.81 (d, J = 9 Hz, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.7, 64.5 (q, J_{CF} = 37.8 Hz, 120.5, 123.2, 128.1, 130.1, 131.8, 145.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -74.06. MS (ESI) = 254.0, $C_9H_9F_3O_3S$ requires 254.0224.

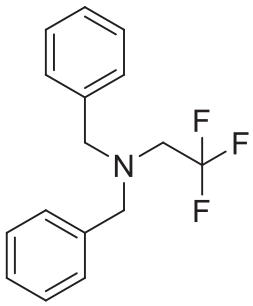


1,1,1-trifluoropropan-2-yl 4-methylbenzenesulfonate (8b): Synthesised as described for **7b**, from 5.7 g (50 mmol) 1,1,1-trifluoropropan-2-ol. Product **6b** was obtained as colourless oil in 84% (10.1 g)

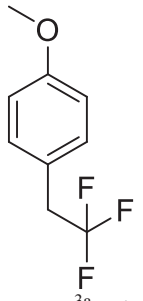
yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.45 (d, J = 7 Hz, 3 H, CH_3), 2.44 (s, 3H, $ArCH_3$), 4.82 (p, J = 6 Hz, 1 H, CH), 7.35 (d, J = 9 Hz, 2 H, ArH), 7.79 (d, J = 9 Hz, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.7, 21.7, 73.2 (q, J_{CF} = 34.2 Hz, 118.7, 121.5, 124.3, 127.9, 132.9, 145.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -78.66. MS (ESI) = 267.0, $C_{10}H_{10}F_3O_3S$ requires 267.0297, HRMS $C_{10}H_{10}F_3O_3S$ requires 267.0297, found: 267.0303; $C_{10}H_{11}F_3O_3S$ requires C, 44.77; H, 4.13; F, 21.25; O, 17.89; S, 11.95; found C, 45.07 H, 4.07.



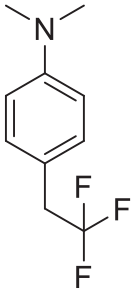
((2,2,2-trifluoroethoxy)methyl)benzene (9b):[2] Sodium hydride (504 mg, 20 mmol) was suspended in anhydrous DMF (25 ml) and 2,2,2-trifluoroethanol (2 g, 20 mmol) was added dropwise at room temperature. When effervescence ceased, benzyl bromide (2.8 g, 0.8 equiv, 16 mmol) was added and the reaction mixture 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, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm): 67.2 (q, J_{CF} = 33.7 Hz), 74.1, 127.9, 128.3, 128.6, 136.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -74.1. MS $C_9H_9F_3O$ requires 190.0605, found: 190.1



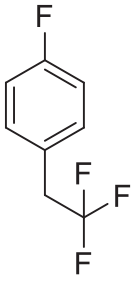
N,N-dibenzyl-2,2,2-trifluoroethanamine (10b): 2,2,2-trifluoroethyl amine (1.1g, 11mmol) was dissolved in acetonitrile (12 ml), N,N-diisopropyl-N-ethyl amine (1.45g, 11 mmol) and benzyl bromide (3.75g, 22 mmol) were added and the reaction mixture was stirred at 70°C over night. The mixture was concentrated 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, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm): 53.0 (q, J_{CF} = 29.9 Hz), 58.2, 127.4, 128.4, 128.9, 138.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -68.1. MS (ESI) = 280.2, $C_{16}H_{17}F_3N$ requires 280.1308, HRMS $C_{16}H_{17}F_3N$ requires 280.1308, found: 280.1291; $C_{16}H_{16}F_3N$ requires C, 68.80; H, 5.77; F, 20.41; N, 5.01; found C, 69.20; H, 5.86; N, 5.25.



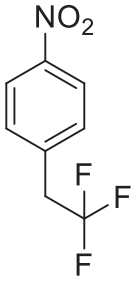
1-methoxy-4-(2,2,2-trifluoroethyl)benzene (11b):[3a] Obtained as a byproduct from **11a** (7%). bp (30 mbar) = 94°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.11 (q, J = 8 Hz, 2 H, CH_2), 3.87 (s, 3H, CH2), 6.90 (d, J = 7 Hz, 2 H, ArH), 7.19 (d, J = 7 Hz, 2 H, ArH), ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -71.1. MS (ESI) = 190.1, $C_9H_9F_3O$ requires 190.0605.



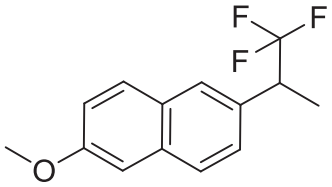
1-dimethylamino-4-(2,2,2-trifluoroethyl)benzene (12b): Obtained as a byproduct from **12a** (4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.05 (s, 6 H, $N(CH_3)_2$), 4.18 (q, J = 11 Hz, 2 H, CH_2), 6.70 (d, J = 8 Hz, 2 H, ArH), 7.10 (d, J = 8 Hz, 2 H, ArH), ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -73.1. MS (ESI) = 204.0, $C_{10}H_{12}F_3N$ requires 203.0922.



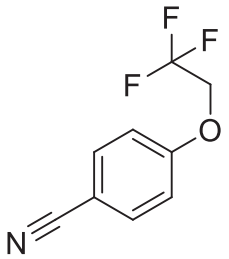
1-fluoro-4-(2,2,2-trifluoroethyl)benzene (13b):[5] Obtained as a byproduct from **13a** (10%). bp (45 mbar) = 57-59°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.06 (q, J = 8 Hz, 2 H, CH_2), 7.17 (d, J = 8 Hz, 2 H, ArH), 7.31 (d, J = 8 Hz, 2 H, ArH), ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -75.3. MS (ESI) = 178.0, $C_8H_6F_4$ requires 178.0406.



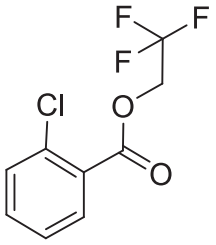
1-nitro-4-(2,2,2-trifluoroethyl)benzene (14b):[3,5] Obtained as a byproduct from **14b** (22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.46 (q, J = 10.5 Hz, 2H, CH_2), 7.52 (d, J = 8.5 Hz, 2 H, ArH), 8.21 (d, J = 9 Hz, 2 H, ArH), ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -69.9. MS (ESI) = 178.0, $C_8H_6NO_2F_3$ requires 205.0351.



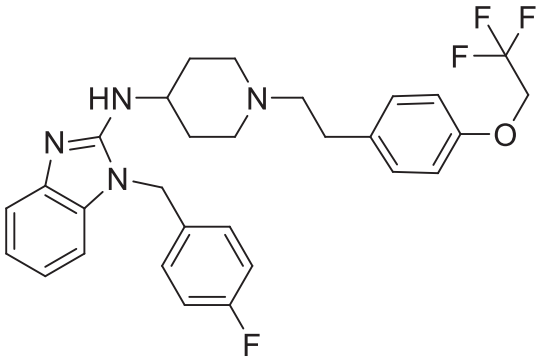
2-methoxy-6-(1,1,1-trifluoropropan-2-yl)naphthalene (15b): Obtained as a byproduct from **15a** (8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (d, J = 7 Hz, 3H, CH3), 7.11(s, 1H), 3.93 (s, 3H), 3.92 (p, J = 6 Hz, 1 H, CH), 7.15 (dd, *J* = 9 Hz, J = 2.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.72-7.69 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 3.1, 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, $CDCl_3$) δ (ppm): -73.2 (ESI) = 254.1, $C_{14}H_{13}F_3O$ requires 254.0918, HRMS $C_{14}H_{13}F_3O$ requires 254.0918, found: $C_{14}H_{13}F_3O$ 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, $CDCl_3$) δ (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, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm): -74.77. MS (ESI) = 201.1, $C_9H_6F_3NO$ requires 201.0401, HRMS $C_9H_6F_3NO$ requires 201.0401, found: 201.0410; $C_9H_6F_3NO$ requires, C, 53.74; H, 3.01; F, 28.34; N, 6.96; O, 7.95; found C, 53.86; H, 2.98; N, 7.28.

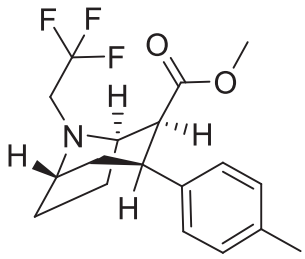


2,2,2-trifluoroethyl 2-chlorobenzoate (17b)[8]: 2-chlorobenzoyl chloride (175 mg, 1 mmol) and triethylamine (102 mg, 1 mmol) were dissolved in diethylether (5 ml). 2,2,2-trifluoroethanol (100 mg, 1 mmol)was added dropwise and the mixture was stirred over night at r.t.. The solids were filtered off and 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-diethylether for elution. 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm): 60.0 (q, J_{CF} = 36.6 Hz), 126.7, 131.4, 131.9, 133.5, 163.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -73.69. MS (ESI) = 238.0, $C_9H_6F_3ClO_2$ requires 238.0008, HRMS $C_9H_6F_3ClO_2$ requires 238.0008, found: 238.0010 $C_9H_6F_3ClO_2$

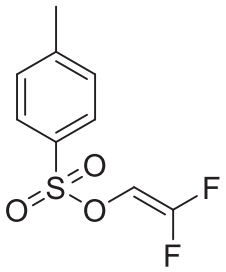


1-(4-fluorobenzyl)-N-(1-(4-(2,2,2-trifluoroethoxy)phenethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2-amine (19b): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.38 (q, J = 10 Hz, 2H), 1.85 (t, J = 11 Hz, 2H), 2.02 (d, J = 11 Hz, 2 H), 2.37 (t, J = 8 Hz, 1H), 2.39 (d, J = 6 Hz, 1H), 2.62 (d, J = 6 Hz, 1 H), 2.64 (t, J = 8 Hz, 1H), 2.79 (d, J = 11 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, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm): -77.7, -113.6. MS (ESI) = 526.2, $C_{29}H_{30}F_4N_4O$ requires 526. 2356, HRMS

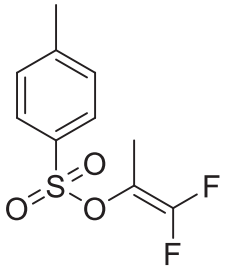
$C_{29}H_{30}F_4N_4O$ requires 526. 2356, found: 527.2360 [M+H], $C_{29}H_{30}F_4N_4O$ requires C, 66.15; H, 5.74; F, 14.43; N, 10.64; found C, 66.09; H, 5.72, N, 10.86.



(1R,2S,3S,5S)-methyl 3-p-tolyl-8-(2,2,2-trifluoroethyl)-8-azabicyclo[3.2.1]octane-2-carboxylate (20b): ^{1}H NMR (400 MHz, $CDCl_3$) δ (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 (brs, 1 H, CH), 3.48 (s, 3H, OCH3), 3.75 (brs, 1H, CH), 7.11 (d, J = 8 Hz, 2H, ArCH), 7.19 (d, J = 8 Hz, 2H, ArCH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (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. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -72.01. MS (ESI) = 341.2, $C_{18}H_{22}F_3NO_2$ requires 341.1603, HRMS: $C_{18}H_{22}F_3NO_2$ requires 341.1603, found: $C_{18}H_{22}F_3NO_2$ 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.

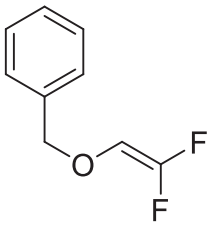


2,2-difluorovinyl 4-methylbenzenesulfonate (7a): 2,2,2-trifluoroethyl tosylate (2.57g, 10 mmol) was dissolved in anhydrous THF (15 ml) and cooled to -78°C. n-Butyl lithium (1.6 M in hexanes, 12.5 ml, 20 mmol) was added dropwise and the resultant mixture was stirred at -78°C for 40 minutes. A mixture 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 NMR (500 MHz, $CDCl_3$) δ (ppm): 2.46 (s, 3H, $ArCH_3$), 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.8, 100.9 (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). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -91.0 (ddd, J = 13 Hz, J = 22.5 Hz, J = 52 Hz), -109.6 (d, 52 Hz). MS (ESI) = 234.0, $C_9H_8F_2O_3S$ requires: 234.0162.

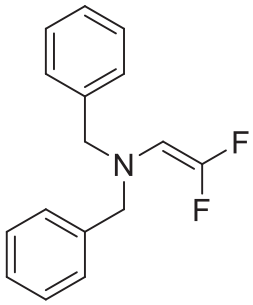


1,1-difluoroprop-1-en-2-yl 4-methylbenzenesulfonate (8a): Synthesised from **6b** (2.7g, 10 mmol) as described for **7a**. Compound **7b** was obtained as a colourless oil in 83% (2.05g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.91 (t, J = 3 Hz, 3H, CH_3), 2.46 (s, 3H, $ArCH_3$), 7.31 (d, J = 8.5 Hz, 2H, ArH), 7.81 (d, J = 9 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (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. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -94.99 (d, J = 55.6 Hz), -108.5 (d, J = 55.6 Hz). MS (ESI) = 247.0, $C_{10}H_{10}F_2O_3S$ requires: 247.0235. HRMS $C_{10}H_9F_2O_3S$ requires: 247.0235, found: 247.0241; $C_{10}H_{10}F_2O_3S$ requires C, 48.38; H, 4.06; F, 15.31; O, 19.33; S, 12.92, found C, 48.41; H, 3.93.

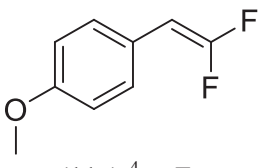


((2,2-difluorovinyloxy)methyl)benzene (9a):[2] benzyl 2,2,2-trifluoroethyl ether (0.95 g, 5 mmol) was dissolved in THF (5 ml) and cooled to -100°C. n-Butyl lithium (1.6 M in hexanes, 6.6 ml, 10 mmol) was added dropwise and the resultant mixture was stirred at -78°C for 1 h. A mixture of water (3.6g, 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 $MgSO_4$, concentrated and distilled in vacuo. BP(30 mbar) = 82-84°C. Yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.69 (s, 2H, $ArCH_2$), 5.63 (dd, *J* = 3 Hz, J = 16.2 Hz, 1H) 7.39-7.28 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) 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. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -101.10 (dd, *J* = 16 Hz and 77.7 Hz), -121.71 (d, *J* = 77.5 Hz). MS (ESI) = 170.0, $C_9H_8F_2O$ requires: 170.0539.



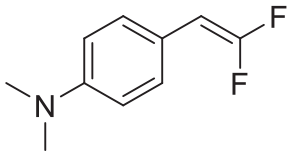
N,N-dibenzyl-2,2-difluoroethenamine (10a): Synthesised from **6d** (700mg, 2.5 mmol) as described for **7c**. Compound **7d** was obtained (85%,) as a colourless oil after purification by flash chromatography on silica gel (NEt_3-pentane; 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.26 (s, 2H, $ArCH_2$), 5.56 (dd, J = 1.8 Hz, J = 21.4 Hz, 1H, CH), 7.31 – 7.44 (m, 5 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) 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). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -87.9 (dd, J = 54.1, 21.0 Hz), -101.8 (d, J = 53.9 Hz). MS (ESI) = 259.1, $C_{16}H_{15}F_2N$ requires: 259.1173. HRMS $C_{16}H_{15}F_2N$ requires: 259.1173, found: 259.1164; $C_{16}H_{15}F_2N$ 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:[5b] 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% until gas evolution became apparent. The reaction mixture was stirred at this temperature until no further evolution of CO_2 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**.

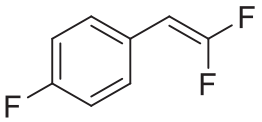


1-(2,2-difluorovinyl)-4-methoxybenzene (11a):[4] From anisaldehyde (2.72g, 20 mmol), triphenylphosphine (10.48g, 40mmol), sodium 2-chloro-2,2-difluoroacetate (6.1g, 40 mmol) in 20 ml DMF. Products **7e** was isolated from the distillate by phase separation, dried over MgSO4 and distilled

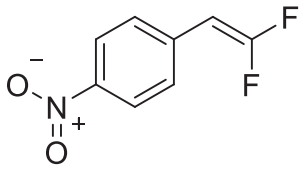
in vacuo (BP (30 mbar) = 95-98°C) to afford a colourless liquid in 39% (1.33g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.80 (s, 3H, OCH_3), 5.21 (dd, J_{HF} = 4 Hz, J_{HF} = 26.4 Hz, 1H, CH), 6.87 (d, J = 9 Hz, 2H, ArH), 7.25 (d, J = 9 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 55.2, 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, $CDCl_3$) δ (ppm): -84.89 (d, J = 39.2 Hz), -86.69 (d, J = 39.2 Hz). MS(ESI) = 170.1, $C_9H_8F_2O$ requires 170.0543.



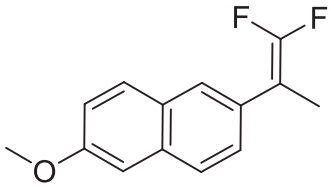
4-(2,2-difluorovinyl)-N,N-dimethylaniline (12a):[4] From 4-dimethylaminobenzaldehyde (2.98g, 20 mmol), triphenylphosphine (10.48g, 40mmol), sodium 2-chloro-2,2-difluoroacetate (6.1g, 40 mmol) in 20 ml DMF. Crude **7f** was extracted from the distillate using diethyl ether (3 x 75 ml). The combined organic 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, $CDCl_3$) δ (ppm): 2.94 (s, 6 H, NCH_3) 5.16 (dd, J_{HF} = 4 Hz, J_{HF} = 26.8 Hz, 1H, CH), 6.70 (d, J = 8 Hz, 2H, ArH), 7.20 (d, J = 8 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.1, 22.9, 29.7, 40.4, 58.2, 81.7 (dd, 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, $CDCl_3$) δ (ppm): -86.09 (d, J = 42.8 Hz), -88.24 (d, J = 42.8 Hz). MS(ESI) = 183.1, $C_{10}H_{11}F_2N$ requires 183.0860.



1-(2,2-difluorovinyl)-4-fluorobenzene (13a):[5] 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, $CDCl_3$) δ (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 (dd, J = 8 Hz, J = 6 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm): -83.65 (d, J = 35.2 Hz), -85.1 (dd, J = 4 Hz, J = 35.2 Hz). MS(ESI) = 158.1, $C_8H_5F_3$ requires 158.0343.



1-(2,2-difluorovinyl)-4-nitrobenzene (14a):[5,6] 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, $CDCl_3$) δ (ppm): 5.4 (dd, J = 3 Hz, J = 25.5 Hz, 1H), 7.5 (d, J = 8.9 Hz, 2H), 8.2 (d, J = 8.9 Hz, 2H), ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -77.9 (dd, *J* = 25.4 Hz, J = 18.7 Hz), -79.1 (d, *J* = 18.2 Hz). MS(ESI) = 185.1, $C_8H_5F_2NO_2$ requires 185.0288.



2-(1,1-difluoroprop-1-en-2-yl)-6-methoxynaphthalene (15a)[1]: 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.
^{1}H NMR (400 MHz, $CDCl_3$) 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 $C_{14}H_{13}F_2O$ requires: 235.0929, found: 235.0915

1 T. M. Gøgsig, L. S. Søbjerg, A. T. Lindhardt (neé Hansen), K. L. Jensen, T. Skrydstrup. J. Org. Chem. 2008, 73, 3404
2 P. V. Ramachandran, A. Chatterjee. *Org. Lett.*, 2008, 10, 1195

3 a) C.-C.Lee, A.T. Lin, J. Chem. Res. Synopses 2000, 3, 142; b) M. M. Kremlev; A. I. Mushta; Y. L. Yagupolskii, W. Tyrra, D. Naumann. J Fluorine Chem 2010, 131, 212

4 a) Y. Zhao, W. Huang, L. Zhu, J. Hu, Org. Lett., 2010, 12, 1444; b) M. Obayashi, E. Ito, K. Matsui, K. Kondo, Tetrahedron Lett. 1982, 23, 2323; c) F. Tellier, R. Sauvetre, J.F. Normant, Y. Dromzee, Y. Jeannin. J. Organomet. Chem. 1987, 331, 281

5 a) W. F. Reynolds, V. G. Gibb, N. Plavac, Can. J. Chem. 1980, 58, 839; b) H. F. Koch, J. G. Koch, N. H. Koch, A. S. Koch, J. Am. Chem. Soc. 1983, 105, 2388

6 B. V. Nguyen, D. J. Burton, J Org. Chem. 1997, 62, 7758

7 J. P. Idoux, M. L. Madenwald, B. S. Garcia, D. L. Chu, J. T. Gupton, J. Org. Chem. 1985, 50, 1876
8 a) K.L. Koller, H. C. Dorn, Anal. Chem. 1982, 54, 529; b) S. Kumai, O. Yokokouji, Eur. Pat. Appl. (1990), EP 355774 A2 19900228