Electronic Supplementary Material (ESI) for Chemical Communications
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Electronic supplementary information for:

Efficient synthesis of [^{18}F]trifluoromethane and its application in the synthesis of PET tracers.

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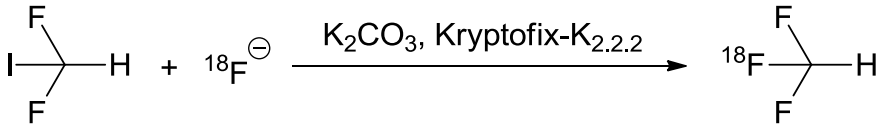
General methods and materials

All chemicals, including reference compounds 2,2,2-trifluoro-1-diphenylethanol **2a**, 1,1,1-trifluoro-2-phenylpropan-2-ol **4b** and 2,2,2-trifluoro-1-phenylethanol and all precursors were obtained from commercial suppliers and were used without further purification, except for the precursors 4-nitrobenzaldehyde, 4-fluorobenzaldehyde and 4-(trifluoromethyl)-benzaldehyde, which were further purified by distillation or sublimation. THF was distilled from lithium aluminium hydride, all other solvents were dried on 3Å molecular sieves. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 250 (^{1}H = 250.13 MHz, ^{13}C = 60.90 MHz, ^{19}F = 235.33 MHz) instrument, where spectra were recorded at a temperature of 25 °C. Chemical shifts (δ) are given in ppm, internally referenced to residual solvent resonances (^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.0 ppm). Thin Layer Chromatography was performed using TLC plates from Merck (SiO_2, neutral kieselgel 60 on alumina with a 254 nm fluorescence indicator). Compounds on the TLC plate were visualised by 254 nm UV light. Flash column chromatography was performed with Screening Devices 60Å silica gel. Analytical HPLC was done on a HPLC system consisting of a Jasco PU-1580 pump, a Jasco UV-2075 Plus UV/Vis detector set at a wavelenght of 254 nm, a Scionex 51BP 51/2 NaI radioactivity detector, a Raytest Gina data acquisition and control interface and a Grace Alltima^{TM} C18 5u 250mm x 4.6mm column using a 70:30:0.2 MeCN/H_2O/TFA eluent at a flow of 1 mL/min. Radioactivity was quantified with a Veenstra VDC-304 dose calibrator.

Synthesis of [^{18}F]trifluoromethane



Scheme S1 Synthesis of [^{18}F]trifluoromethane

[^{18}F]fluoride was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction using an IBA 18/9 cyclotron. After irradiation, [^{18}F]fluoride was trapped on a Chromafix® 30-PS-HCO_3 ^{18}F separation cartridge and eluted to a reaction vessel using a solution of Kryptofix $K_{2.2.2}$ (13 mg) and K_2CO_3 (2 mg) in MeCN/H_2O (1 mL, ratio 9:1). The solution was dried under a stream of Helium and reduced pressure at 90 °C. Residual water was removed by azeotropic co-evaporation using three portions of anhydrous MeCN (3 times 1 mL). Difluoroiodomethane (8 mg, 7.1 µmol) dissolved in MeCN (1 mL) was added to the dry [^{18}F]fluoride and was allowed to stand at room temperature for 10 minutes. Using a helium flow of 10 mL/min, the formed

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[^{18}F]trifluoromethane (60% ± 15% yield) was purged out of the reaction mixture, through a Waters Sep-Pak® Plus Silica cartridge and trapped in DMF (1 mL, -60 °C) or THF (1 mL, -100 °C) in an efficiency of 88 ± 8% and 96% ± 3% respectively in 3 minutes.

Detailed analysis of separation of [^{18}F]trifluoromethane from difluoroiodomethane

To purify gaseous [^{18}F]trifluoromethane from any gaseous difluoroiodomethane precursor, a stream of helium (10 mL/min) was led through a Waters Sep-Pak® Plus Silica cartridge as described in the previous paragraph. The boiling points of [^{18}F]trifluoromethane (-82.1 °C) and difluoroiodomethane (21.6 °C) are far enough apart that the silica column can separate the gasses (silica column acts as a small room temperature gas chromatograph).

To demonstrate the efficiency of the Waters Sep-Pak® Plus Silica cartridge, Helium was bubbled (10 mL/min) through a vessel containing 1 mL of a 0.04M difluoroiodomethane solution in MeCN and trapped in a second vessel containing 1 mL THF at -60 °C for 3 minutes or for 6 minutes. For entry 1 (3 minutes from start) and 3 (6 minutes from start) of table S1, a Waters Sep-Pak® Plus Silica cartridge was placed before the second vessel and for entry 2 (3 minutes from start) and 4 (6 minutes from start) of table S1 no Waters Sep-Pak® Plus Silica cartridge was placed before the second vessel. The distillate was analysed using UV-HPLC, which can detect difluoroiodomethane at 250 nm with a detection limit of 10 µM. All experiments were performed in triplicate. The results are shown in Table S1.

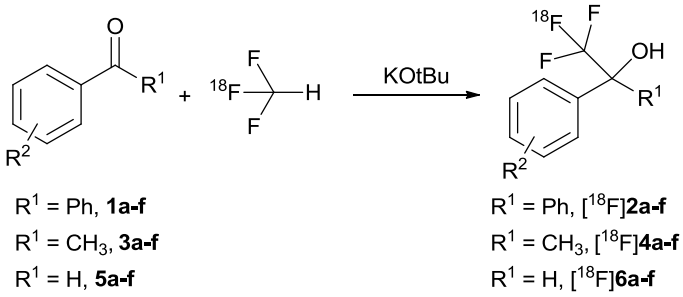
Table S1 Efficacy of a Waters Sep-Pak® Plus Silica cartridge

Entry	Time (min)	Silica Sep-Pak	CHF_2I (µM)	CHF_2I (%)
1	3.0	YES	<10	<0.03
2	3.0	NO	267 ± 42	0.67
3	6.0	YES	31 ± 20	0.08
4	6.0	NO	461 ± 215	1.15

The concentration of difluoroiodomethane, when using a Silica Sep-Pak, is under the HPLC detection limit of 10 µM for the 3.0 minutes distillation and is 31 µM for the 6.0 minutes distallation. Fortunately, 3.0 minutes is sufficient to transport al the [^{18}F]trifluoromethane and therefore the [^{18}F]trifluoromethane stock solution will contain less than 10 nanomol of difluoroiodomethane using 1 mL THF to trap [^{18}F]trifluoromethane. These amounts will not interfere in the labelling reactions. When no Silica Sep-Pak is used (entry 2 & 4), the difluor-

oiodomethane concentration is 267 µM after 3.0 minutes and 461 µM 6.0 minutes of distillation, showing that the silica Sep-Pak is actually effectively separating [^{18}F]trifluoromethane from its precursor difluoroiodomethane.

General procedure for the synthesis of [^{18}F]trifluoromethylcarbinols



R^1 = Ph, **1a-f**
R^1 = CH_3, **3a-f**
R^1 = H, **5a-f**

R^1 = Ph, [^{18}F]**2a-f**
R^1 = CH_3, [^{18}F]**4a-f**
R^1 = H, [^{18}F]**6a-f**

Scheme S2 Synthesis of [^{18}F]trifluoromethylcarbinols

To a reaction vessel was added either benzophenone **1a-f**, acetophenone **3a-f**, or benzaldehyde **5a-f**, followed by DMF, [^{18}F]CHF_3 in DMF and 0.2M KO*t*Bu in DMF up to a total volume of 1 mL. The reaction was stirred for 5 minutes at 20 °C for benzophenones **1** and benzaldehydes **3**, or at 80 °C for acetophenones **5**. The reaction mixture was analyzed by injecting 1 µL reaction mixture directly on analytical HPLC.

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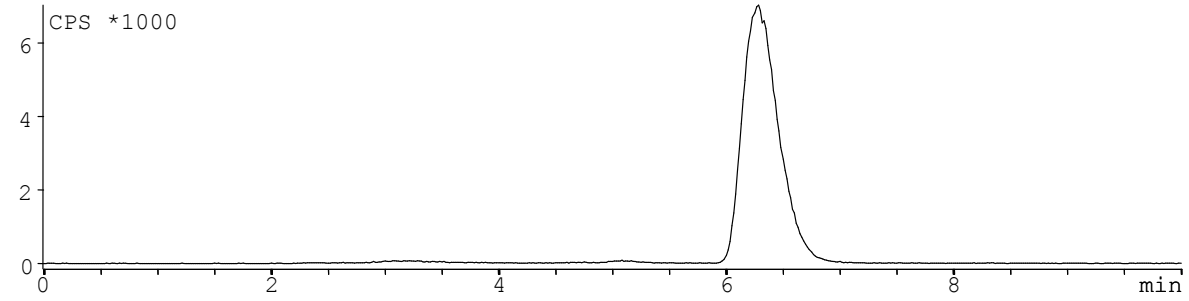
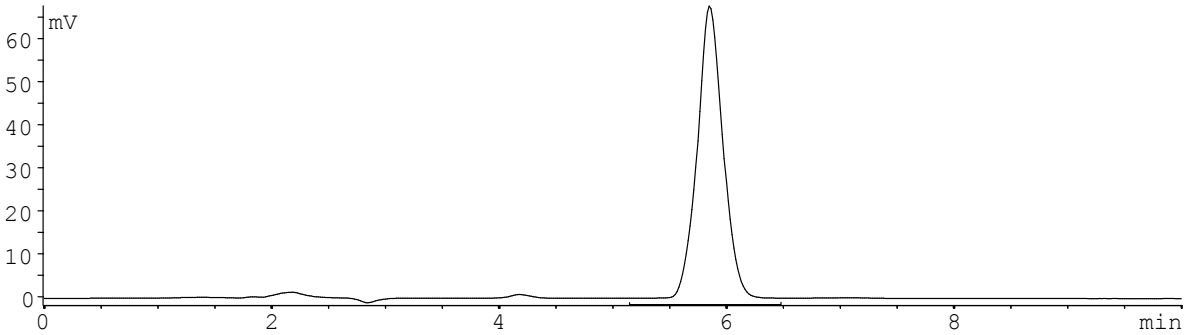


Graph S1 radioHPLC of the synthesis of [^{18}F]2,2,2-trifluoro-1-phenylethanol



Graph S2 HPLC-UV (254 nm) chromatogram of cold reference 2,2,2-trifluoro-1-phenylethanol

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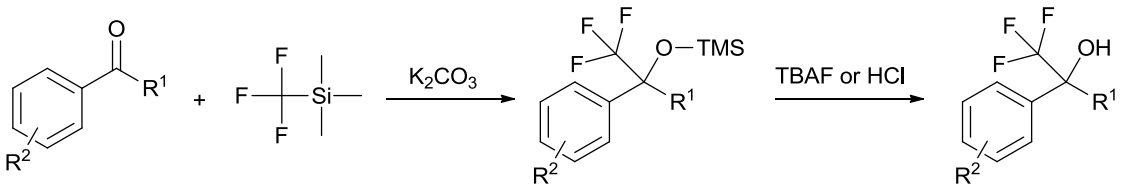
The radioHPLC chromatograph in Graph S1 shows the result of the reaction of [^{18}F]trifluoromethane with benzaldehyde. The peak of radioactive [^{18}F]trifluoromethane at 4.23 min has disappeared and a new radioactivity peak has formed at 6.27 min. To identify this peak as [^{18}F]2,2,2-trifluoro-1-phenylethanol, the cold reference compound was injected on HPLC under the same HPLC conditions. Graph S2 shows that the reference compound forms a peak at 5.90 minutes. There is a time difference between detection on the UV detector and the radioactivity detector of 0.37 minutes. The radioactive product thus has the same retention on the HPLC column as the 2,2,2-trifluoro-1-phenylethanol reference and can be positively identified to be [^{18}F]2,2,2-trifluoro-1-phenylethanol.

Formation and identification of [^{18}F]fluoral hydrate

After addition of KOtBu (100 µmol) to a solution of [^{18}F]CHF_3 in DMF (1 mL), HPLC analysis showed conversion of [^{18}F]CHF_3 (R_t: 4.27 min) towards a new radioactive peak (R_t: 3.38 min), most probably [^{18}F]fluoral hydrate, formed from the intermediate *gem*-aminoalcoholate II upon quenching in the HPLC eluent. To identify the radioactive peak as [^{18}F]fluoral hydrate, the reaction mixture was co-injected on HPLC with 30 µmol non-radioactive fluoral hydrate and the radioactive peak with Rt 3.38 min was collected. ^{19}F-NMR analysis of the collected peak positively identified the radioactive peak to be [^{18}F]fluoral hydrate.

Synthesis of the reference compounds



R^1 = Ph, **1a-f**
R^1 = CH_3, **3a-f**
R^1 = H, **5a-f**

R^1 = Ph, **2a-f**
R^1 = CH_3, **4a-f**
R^1 = H, **6a-f**

Scheme S3 Synthesis of reference trifluorocarbinols

All reference compounds were synthesised by following the method published by Prakash *et al.*[1] The TMS-ether trifluorocarbinol derivatives are synthesised first, followed by hydrolysis by either 1M TBAF in THF or 1M HCl in 1:1 H_2O / THF. Further experimental details for every reference compound are described on the following pages.

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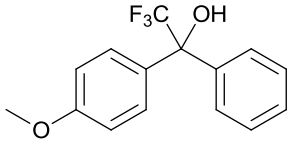
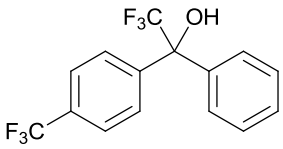
*2,2,2-trifluoro-1-(4-methoxyphenyl)-1-phenylethanol (**2b**):*



To a solution of 4-methoxybenzophenone (250 mg, 1.18 mmol) in DMF (3 mL) was added $TMSCF_3$ (517 µL, 3.50 mmol) and K_2CO_3 (50.0 mg, 0.36 mmol). After stirring at room temperature for 42 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:99) and hydrolysed by adding THF (3 mL) and TBAF (3 mL, 1M in THF, 3 mmol). After stirring at room temperature for 3 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:9) to yield **2b** as a colorless oil (37 mg, 11%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.53 - 7.46 (m, 2H), 7.44 - 7.31 (m, 5H), 6.92 - 6.82 (m, 2H), 3.81 (s, 3H), 2.77 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -74.5 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 159.8, 139.7, 131.7, 129.0, 128.7, 128.3, 127.6, 125.5 (q, $^1J_{CF}$ = 286.3 Hz), 113.7, 79.4 (q, $^1J_{CF}$ = 29.0 Hz), 55.4, HPLC retention time: 11.32 min. Synthesis and analysis of this compound is described previously by White *et al*.[2]

*2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)-1-phenylethanol (**2c**):*



To a solution of 4-(trifluoromethyl)benzophenone (212 mg, 0.85 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 72 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 3 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:9) to yield **2c** as a pale yellow oil (171 mg, 63%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.63 (br. s, 4H), 7.54 - 7.43 (m, 2H), 7.43 - 7.34 (m, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -62.8 (s, 3F), -74.3 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 143.1, 139.0, 131.0 (q, $^2J_{CF}$ = 32.6 Hz), 129.2, 128.8, 128.2, 127.4, 125.3 (q, $^3J_{CF}$ = 3.4 Hz), 125.2 (q, $^1J_{CF}$ = 286.3 Hz), 124.1 (q, $^1J_{CF}$ =

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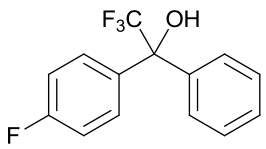
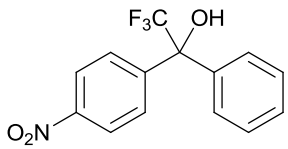
272.1 Hz), 79.5 (q, $^{2}J_{CF}$ = 29.0 Hz), HPLC retention time: 21.32 min. Synthesis of this compound is described previously by Liu *et al*.[3]

*2,2,2-trifluoro-1-(4-fluorophenyl)-1-phenylethanol (**2d**):*



To a solution of 4-fluorobenzophenone (212 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 96 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 3 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:9) to yield **2d** as a pale yellow oil (134 mg, 50%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.55 - 7.42 (m, 4H), 7.41 - 7.32 (m, 3H), 7.11 - 6.97 (m, 2H), 2.83 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -74.5 (s, 3F), -113.1 (s, 1F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 162.9 (d, $^{1}J_{CF}$ = 248.2 Hz), 139.4, 135.2 (d, $^{4}J_{CF}$ = 3.2 Hz), 129.7 (d, $^{3}J_{CF}$ = 7.4 Hz), 129.0, 128.6, 127.4, 125.4 (q, $^{1}J_{CF}$ = 286.8 Hz), 115.3 (d, $^{2}J_{CF}$ = 21.6 Hz), 79.3 (q, $^{2}J_{CF}$ = 29.0 Hz), HPLC retention time: 12.72 min. Synthesis of this compound and ^{19}F-NMR analysis is described previously by Dayal *et al*.[4]

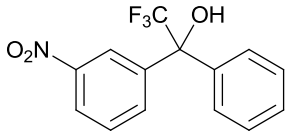
*2,2,2-trifluoro-1-(4-nitrophenyl)-1-phenylethanol (**2e**):*



To a solution of 4-nitrobenzophenone (227 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 3 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 15 minutes, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was two times purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:4) to yield **2e** as a pale yellow crystals (99 mg, 33%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.28 - 8.14 (m, 2H), 7.70 (d, ^{3}J = 8.5 Hz, 2H), 7.53 - 7.35 (m, 5H), 2.98 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -74.2 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.0, 145.9, 138.6, 129.4, 128.9, 128.8, 127.2, 123.4, 125.0 (q, $^{1}J_{CF}$ = 286.3 Hz), 79.4 (q, $^{2}J_{CF}$ = 29.0 Hz), HPLC retention

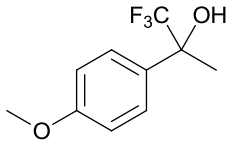
time: 12.18 min. Synthesis and analysis of this compound is described previously by Prakash *et al.*[5]

*2,2,2-trifluoro-1-(3-nitrophenyl)-1-phenylethanol (**2f**):*



To a solution of 3-nitrobenzophenone (227 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 72 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 3 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:4) to yield **2f** as a pale yellow crystals (196 mg, 66%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.43 (s, 1H), 8.25 - 8.20 (m, 1H), 7.84 - 7.76 (m, 1H), 7.54 (t, ^3J = 8.1 Hz, 1H), 7.50 - 7.37 (m, 5H), 3.00 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -74.3 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.2, 141.3, 138.5, 133.8, 129.4, 129.3, 128.9, 127.2, 123.7, 122.7, 125.0 (q, $^1J_{CF}$ = 282.7 Hz), 79.1 (q, $^2J_{CF}$ = 29.4 Hz), HPLC retention time: 11.87 min.

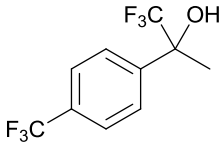
*1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol (**4b**):*



To a solution of 4'-methoxyacetophenone (150 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (500 µL, 3.38 mmol) and K_2CO_3 (50.0 mg, 0.36 mmol). After stirring at room temperature for 24 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:99) and hydrolysed by adding TBAF (3 mL, 1M in THF, 3 mmol). After stirring at room temperature for 19 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 15:85) to yield **4b** as a yellow oil (20 mg, 9%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.55 - 7.44 (m, 2H), 6.96 - 6.87 (m, 2H), 3.82 (s, 3H), 2.41 (s, 1H), 1.77 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -81.2 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 159.9, 130.7, 127.6, 125.8 (q, $^1J_{CF}$ = 285.0 Hz), 113.8,

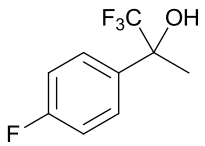
74.7 (q, $^2J_{CF}$ = 29.4 Hz), 55.4, 24.0, HPLC retention time: 6.32 min. Synthesis and analysis of this compound is described previously by Amyes *et al.*[6]

*1,1,1-trifluoro-2-(4-(trifluoromethyl)phenyl)propan-2-ol (**4c**):*



To a solution of 4'-(trifluoromethyl)acetophenone (564 mg, 3.00 mmol) in DMF (10 mL) was added $TMSCF_3$ (665 µL, 4.50 mmol) and K_2CO_3 (41 mg, 0.1 mmol). After stirring at room temperature for 22 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (10 mL) and 1M HCl (10 mL). After stirring at room temperature for 24 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 15:85) to yield **4c** as a yellow oil (312 mg, 40%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.83 - 7.57 (m, 4H), 2.43 (s, 1H), 1.81 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -62.8 (s, 3F), -80.9 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 142.6, 131.1 (q, $^2J_{CF}$ = 32.6 Hz), 126.9, 125.6 (q, $^1J_{CF}$ = 285.0 Hz), 125.4 (q, $^3J_{CF}$ = 3.7 Hz), 124.2 (q, $^1J_{CF}$ = 272.5 Hz), 75.0 (q, $^2J_{CF}$ = 29.4 Hz), 23.8, HPLC retention time: 11.07 min. Synthesis and analysis of this compound is described previously by Liu *et al.*[3]

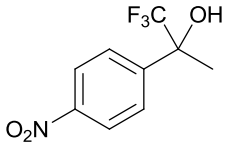
*1,1,1-trifluoro-2-(4-fluorophenyl)propan-2-ol (**4d**):*



To a solution of 4'-fluoroacetophenone (414 mg, 3.00 mmol) in DMF (10 mL) was added $TMSCF_3$ (665 µL, 4.50 mmol) and K_2CO_3 (41 mg, 0.1 mmol). After stirring at room temperature for 96 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (10 mL) and 1M HCl (10 mL). After stirring at room temperature for 72 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:9) to yield **4d** as a yellow oil (122 mg, 20%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.61 - 7.51 (m, 2H), 7.14 - 7.01 (m,

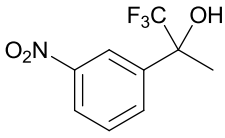
2H), 2.38 (s, 1H), 1.78 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -81.2 (s, 3F), -113.7 (s, 1F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 162.9 (d, $^1J_{CF}$ = 248.2 Hz), 134.2 (d, $^4J_{CF}$ = 3.2 Hz), 128.1 (d, $^3J_{CF}$ = 7.8 Hz), 125.5 (q, $^1J_{CF}$ = 285.4 Hz), 115.2 (d, $^2J_{CF}$ = 22.1 Hz), 74.6 (q, $^2J_{CF}$ = 29.9 Hz), 23.9, HPLC retention time: 7.05 min. Synthesis and analysis of this compound is described previously by Mizuta *et al*.[7]

*1,1,1-trifluoro-2-(4-nitrophenyl)propan-2-ol (**4e**):*



To a solution of 4'-nitroacetophenone (165 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.10 mmol). After stirring at room temperature for 17 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 4 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:4) to yield **4e** as white crystals (129 mg, 55%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.32 - 8.19 (m, 2H), 7.86 - 7.72 (m, 2H), 2.57 (s, 1H), 1.83 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -80.8 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.1, 145.4, 127.6, 123.5, 125.2 (q, $^1J_{CF}$ = 285.4 Hz), 74.9 (q, $^2J_{CF}$ = 30.1 Hz), 24.1, HPLC retention time: 7.02 min. Synthesis and analysis of this compound is described previously by Song *et al*.[8]

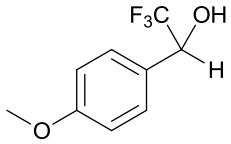
*1,1,1-trifluoro-2-(3- nitrophenyl)propan-2-ol (**4f**):*



To a solution of 3'-nitroacetophenone (165 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (443 µL, 3.00 mmol) and K_2CO_3 (28 mg, 0.20 mmol). After stirring at room temperature for 21 hours, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 1 hour, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:4) to yield **4f** as a yellow oil (138 mg, 59%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.49 (s, 1H), 8.34 - 8.19 (m, 1H), 8.03 - 7.87 (m, 1H), 7.60 (t, ^3J = 7.8 Hz), 2.53 (s, 1H), 1,85 (s, 3H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -81.0 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.3, 140.8, 132.6, 129.5, 123.7, 121.7, 125.2

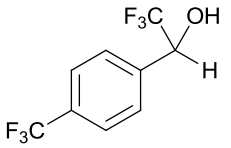
(q, $^1J_{CF}$ = 285.9 Hz), 74.6 (q, $^1J_{CF}$ = 29.9 Hz), 23.9, HPLC retention time: 6.93 min. Synthesis and analysis of this compound is described previously by Mizuta *et al*.[7]

*2,2,2-trifluoro-1-(4-methoxyphenyl)ethanol (**6b**):*



To a solution of 4-methoxybenzaldehyde (136 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.10 mmol). After stirring at room temperature for 1 hour, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 16 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:4) to yield **6b** as a yellow oil (90 mg, 44%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.45 - 7.35 (m, 2H), 6.98 - 6.89 (m, 2H), 5.04 - 4.90 (m, 1H), 3.38 (s, 3H), 2.42 (d, ^3J = 4.5 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.5 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 160.6, 128.9, 126.4, 124.5 (q, $^1J_{CF}$ = 281.7 Hz), 114.2, 72.6 (q, $^2J_{CF}$ = 32.2 Hz), 55.4, HPLC retention time: 5.53 min. Synthesis and analysis of this compound is described previously by Shi *et al*.[9]

*2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethanol (**6c**):*

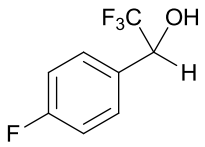


To a solution of 4-(trifluoromethyl)benzaldehyde (174 mg, 1.00 mmol) in DMF (10 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 5 hours, H_2O was added (20 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (3 mL) and 1M HCl (3 mL). After stirring at room temperature for 21 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 15:85) to yield **6c** as a colorless oil (33 mg, 13%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.73 - 7.57 (m, 4H), 5.11 (q, J = 6.6 Hz, 1H), 2.79 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -62.9 (s, 3F), -78.4 (d, J = 6.9 Hz, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 137.6, 131.8 (q, $^2J_{CF}$ = 32.6 Hz), 127.9, 125.6 (q, $^3J_{CF}$ = 3.7 Hz),

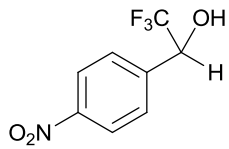
123.9 (q, ^{1}J = 282.2 Hz) 123.8 (q, $^{1}J_{CF}$ = 282.2 Hz), 72.2 (q, $^{2}J_{CF}$ = 32.2 Hz), HPLC retention time: 8.80 min. Synthesis and analysis of this compound is described previously by Miyake *et al.*[10]

*2,2,2-trifluoro-1-(4-fluorophenyl)ethanol (**6d**):*



To a solution of 4-fluorobenzaldehyde (745 mg, 6 mmol) in DMF (20 mL) was added $TMSCF_3$ (1330 µL, 9.00 mmol) and K_2CO_3 (83 mg, 0.6 mmol). After stirring at room temperature for 48 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (20 mL) and 1M HCl (20 mL). After stirring at room temperature for 18 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 15:85) to yield **6d** as a yellow oil (751 mg, 65%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.52 - 7.41 (m, 2H), 7.16 - 7.05 (m, 2H), 5.09 - 4.96 (m, 1H), 2.55 (d, ^{3}J = 4.0 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.6 (s, 3F), -111.8 (s, 1F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 163.6 (d, $^{1}J_{CF}$ = 248.2 Hz), 129.9, 129.5 (d, $^{3}J_{CF}$ = 8.3 Hz), 124.3 (q, $^{1}J_{CF}$ = 282.2 Hz), 115.8 (d, $^{2}J_{CF}$ = 21.6 Hz), 72.3 (q, $^{2}J_{CF}$ = 32.6 Hz), HPLC retention time: 6.02 min. Synthesis and analysis of this compound is described previously by Xu *et al.*[11]

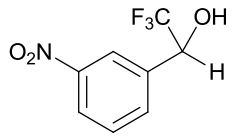
*2,2,2-trifluoro-1-(4-nitrophenyl)ethanol (**6e**):*



To a solution of 4-nitrobenzaldehyde (453 mg, 3 mmol) in DMF (3 mL) was added $TMSCF_3$ (665 µL, 4.50 mmol) and K_2CO_3 (41 mg, 0.3 mmol). After stirring at room temperature for 4 hours, H_2O was added (40 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (3 mL) and 1M HCl (3 mL). After stirring at room temperature for 2 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 15:85) to yield **6e** as a yellow oil (313 mg,

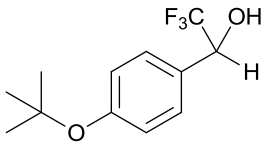
47%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.38 - 8.27 (m, 2H), 7.75 (d, J=8.8 Hz), 5.23 (q, J = 6.4 Hz); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.2 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.8, 140.5, 128.6, 123.9 (q, $^{1}J_{CF}$ = 282.2 Hz), 123.8, 72.0 (q, $^{2}J_{CF}$ = 32.6 Hz), HPLC retention time: 5.95 min. Synthesis and analysis of this compound is described previously by Xu *et al.*[11]

*2,2,2-trifluoro-1-(3-nitrophenyl)ethanol (**6f**):*



To a solution of 3-nitrobenzaldehyde (151 mg, 1.00 mmol) in DMF (3 mL) was added $TMSCF_3$ (222 µL, 1.50 mmol) and K_2CO_3 (14 mg, 0.10 mmol). After stirring at room temperature for 1 hour, TBAF (3 mL, 1M in THF, 3 mmol) was added to hydrolyse the intermediate TMS ether. After stirring at room temperature for 25 minutes, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:4) to yield **6f** as a yellow oil (103 mg, 47%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.39 (s, 1H), 8.33 - 8.22 (m, 1H), 7.89 - 7.80 (m, 1H), 7.62 (t, J = 8.1 Hz, 1H), 5.19 (q, J = 6.4 Hz, 1H), 2.83 (s, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.4 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 148.4, 136.2, 133.7, 129.8, 124.5, 124.0 (q, $^{1}J_{CF}$ = 282.7 Hz), 122.7, 71.8 (q, $^{2}J_{CF}$ = 32.2 Hz), HPLC retention time: 6.02 min. Synthesis and analysis of this compound is described previously by Prakash *et al.*[12]

*2,2,2-trifluoro-1-(4-(tert-butoxy)phenyl)ethanol (**8**):*



To a solution of 4-(*tert*-butoxy)benzaldehyde (178 mg, 1 mmol) in DMF (3 mL) was added $TMSCF_3$ (443 µL, 3.00 mmol) and K_2CO_3 (28 mg, 0.2 mmol). After stirring at room temperature for 22 hours, H_2O was added (20 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude TMS ether was hydrolysed by adding THF (3 mL) and 1M HCl (3 mL). After stirring at room temperature for 18 hours, H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with H_2O (2 x 60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (silicagel, EtOAc / *n*-Hexane 1:9) to yield **8** as white crystals (75 mg, 30%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.40 - 7.31 (m, 2H), 7.10 -

6.92 (m, 2H), 5.04 - 4.91 (m, 1H), 2.57 (d, ^{3}J = 4.4 Hz, 1H), 1.36 (s, 9H); ^{19}F NMR (235 MHz, $CDCl_3$) δ (ppm): -78.4 (s, 3F); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 156.3, 129.0, 128.2, 124.0, 124.4 (q, $^{1}J_{CF}$ = 281.7 Hz), 79.2, 72.5 (q, $^{2}J_{CF}$ = 31.7 Hz), 28.8, HPLC retention time: 8.73 min.

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