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Fluorine-18 labelled Ruppert-Prakash reagent ([^{18}F]Me_3SiCF_3) for the synthesis of ^{18}F-trifluoromethylated compounds

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1 General methods and materials

The research described in this article has been carried out at two different locations, Amsterdam UMC (The Netherlands) and the Center for Addiction and Mental Health (CAMH) in Toronto, Canada.

Unless otherwise stated all chemicals and solvents were obtained from commercially available sources and used without further purification.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 (^{1}H = 500 MHz, ^{19}F = 471 MHz) instrument at 20°C. Chemical shifts (δ) are given in ppm, internally referenced to residual solvent resonances (^{1}H: δ = 7.26 ppm ($CDCl_3$)). Coupling constants (*J*) are reported in Hertz (Hz).

Analysis of radioactive reactions and products was carried out with high-performance liquid chromatography (HPLC). Analysis of the [^{18}F]$MeCF_3$ formation and purification was carried out on a Jasco system, consisting of a Jasco PU-1580 pump, a Jasco UV-2075 Plus UV/VIS detector set at a wavelength of 254 nm, a Jasco RI-2031 Plus Intelligent RI detector, a Scionex 51BP 51/2 NaI radioactivity detector and a Raytest Gina data acquisition and control interface (Amsterdam UMC). For the analysis of the subsequent [^{18}F]trifluoromethylation reactions, a Shimadzu SPD-20A system using LabSolutions 5.85 software (Amsterdam UMC) or an Agilent 1260 Infinity II system with a Ludlum 177 radiodetector (CAMH) was used. On all systems, analysis was performed using an Alltima C18 column (5µ 4.6x250mm) (VWR), MeCN/water/TFA 60:40:0.1 as eluent and a flow of 1 $mL \cdot min^{-1}$. Radioactive products were identified by comparison with the unlabelled reference compounds.

2 Radiochemistry

2.1 [^{18}F]Fluoroform synthesis

Research carried out at Amsterdam UMC

[^{18}F]fluoroform was obtained according to our previously published procedure[1]:

[^{18}F]Fluoride was produced by irradiation of an oxygen-18 enriched water target and was trapped on a Chromafix® 30-PS-HCO_3 cartridge. It was eluted using 500 µL 0.1 M potassium sulfate solution in water. The eluate was collected in a vessel containing 850 µL DMF. 150 µL 0.1 M *N,N*-bis(trifluoromethylsulfonyl)aniline was added and the vessel was heated to 40 °C. The gaseous [^{18}F]triflyl fluoride was purged out of the reaction mixture for 5 min with a helium flow of 10 mL/min and was trapped in a solution of 0.15 µmol K_2CO_3 and 0.35 µmol K_{222} in 899 µL MeCN and 1 µL water at -40 °C. Subsequently, the trapping vial was heated to 80 °C and 100 µL 0.01 M (1 µmol) $CHIF_2$ in MeCN was added. After 5 minutes, [^{18}F]fluoroform was distilled out of the solution with a helium flow of 10 mL/min in 3 minutes.

Research carried out at CAMH, Toronto

The literature procedure[1] was slightly modified to reduce the need for heating and cooling during the synthesis:

[^{18}F]Fluoride was produced by irradiation of an oxygen-18 enriched water target and was trapped on a Chromafix® 30-PS-HCO_3 cartridge. It was eluted using 300 µL 0.1 M potassium sulfate solution in water. The eluate was collected in a vessel containing 1050 µL DMF and 150 µL 0.1 M *N,N*-bis(trifluoromethylsulfonyl)aniline at room temperature and the formed gaseous [^{18}F]triflyl fluoride was immediately purged out of the reaction mixture with a nitrogen flow of 20 mL/min. It was trapped in a solution of 0.15 µmol K_2CO_3 and 0.35 µmol K_{222} in 899 µL MeCN and 1 µL water at room temperature. Subsequently, the trapping vial was heated to 70 °C and 100 µL 0.01 M (1 µmol) $CHIF_2$ in MeCN was added. After 5 minutes, [^{18}F]fluoroform was distilled out of the solution with a nitrogen flow of 10 mL/min in 5 minutes.

2.2 [^{18}F]Me_3SiCF_3

2.2.1 [^{18}F]Me_3SiCF_3 synthesis under optimal conditions

[^{18}F]Fluoroform was synthesized as described above and distilled into a vial containing 150 µL (1182 µmol) chlorotrimethylsilane and 1000 µL 0.5M (500 µmol) potassium hexamethyldisilazide in toluene cooled to -80 °C. After complete distillation (~3 min), all needles were removed and the vial was warmed up to room temperature (either 2 min with active heating or 5 min standing at rt). Then, the vial was heated to 70 °C and [^{18}F]Me_3SiCF_3 was distilled for 5 min with a flow of 30 mL/min into a vial containing 2 mL THF at -80 °C.

2.2.2 Optimization of reaction conditions

[^{18}F]Me_3SiCF_3 was synthesized as described under 2.2.1. The following parameters were varied: chlorotrimethylsilane (amount, concentration) and potassium hexamethyldisilazide (amount), trapping temperature, warm up method and stirring. Furthermore, It was investigated if it was necessary to pre-stirr chlorotrimethylsilane and potassium hexamethyldisilazide in toluene before the trapping, as described for the organic synthesis.[2]

Table S1 Optimization of the reaction conditions of [^{18}F]Me_3SiCF_3 formation; RCY and RCP are given in average±SD, dc, RCY [^{18}F]CHF_3 = yield of the isolated building block after distillation, RCP Me_3SiCF_3 = yield of the product determined by analysis of the crude mixture by HPLC; *added after trapping.

	Me_3SiCl µmol	KHMDS µmol	Toluene µL	Trapping temp. °C	Pre-stirr. min	warmup		Stirr.	RCY CHF_3 %	RCP Me_3SiCF_3 %	n
						Type	Time min				
1	394	325	650	-80 °C	15	Leave at rt	5	n	37	0	1
2	394	325	650	-80 °C	15	Leave at rt	10	n	"	81	1
3	394	325	650	-80 °C	15	Leave at rt	15	n	"	94	1
4	394	325	650	-80 °C	15	Heat to 20 °C	2.5	y	43	92	1
5	394	325	650	-80 °C	15	Heat to 20 °C	5	y	"	89	1
6	788	325	650	-80 °C	15	Heat to 20 °C	2.5	n	38	97	1
7	788	325	650	-80 °C	10	Heat to 20 °C	2.5	n	38	96	1
8	788	325	650	-80 °C	5	Heat to 20 °C	2.5	n	35	96	1
9	788	325	650	-80 °C	-	Heat to 20 °C	2.5	n	37	97	1
10	788	325	650	-41 °C	-	Leave at rt	5	n	34	68	1
11	788*	325	650	-80 °C	-	Leave at rt	5	n	6	63	1
12	788	325	650	-80 °C	-	Leave at rt	5	n	28±1	74±28	3
13	788	650	1300	-80 °C	-	Leave at rt	5	n	25±1	89±9	3
14	1576	650	1300	-80 °C	-	Leave at rt	5	n	39±0	95±4	3
15	1182	487.5	975	-80 °C	-	Leave at rt	5	n	44±0	98±2	3
16	1182	500	1000	-80 °C	-	Leave at rt	5	n	43±3	97±3	3

2.2.3 Optimization of the [^{18}F]Me_3SiCF_3 distillation

[^{18}F]Me_3SiCF_3 was synthesized as described under 2.2.1. The following parameters were varied: chlorotrimethylsilane (amount, concentration) and potassium hexamethyldisilazide (amount),

distillation temperature, flow (see Table 2). Furthermore, [^{18}F]Me_3SiCF_3 was distilled over various seppak cartridges to improve the UV purity (see Table S3).

Table S2 Optimization of the [^{18}F]Me_3SiCF_3 distillation; RCY is given in average±SD, dc; *needle blocked in 2 out of 3 distillations.

	Me_3SiCl µmol	KHMDS µmol	Toluene µL	Flow mL/min	Temp. °C	RCY Me_3SiCF_3 %	n
1	788	650	1300	10	70	62±0	3
2	1576	650	1300	10	70	27±2	3
3	1182	487.5	925	10	70	49±3	2
4	1182	487.5	925	20	70	86±6	3
5	1182	500	1000	5	70	52±6	3
6	1182	500	1000	10	70	69±3	3
7	1182	500	1000	20	70	86±3	3
8	1182	500	1000	30	70	93±1	3
9	1182	500	1000	40	70	94±1	3
10	1182	500	1000	50	70	95±1	3
11	1182	500	1000	70	70	95±1	3
12	1182	500	1000	50	50	75±21*	3
13	1182	500	1000	50	60	88±6	3
14	1182	500	1000	50	80	95±1	3

Table S3 Distillation of [^{18}F]Me_3SiCF_3 over various seppak cartridges; n=3, RCY and area is given in average±SD, dc.

seppak	distillation yield ([^{18}F] Me_3SiCF_3) %	detected area (Me_3SiCl) at 20 µL inj
none	88±6	2490±1273
alumina N light	69±7	40±53
silica light	81±6	637±69
2 silica light	83±4	222±25
3 silica light	79±4	11±12
silica long 10 min	86±1	0±0

2.3 [^{18}F]Trifluoromethylation of aldehydes and ketones

2.3.1 Optimization of reaction parameters for the reaction with 4-nitrobenzaldehyde using TBAF

[^{18}F]Me_3SiCF_3 was synthesized as described under 2.2.1 and trapped in 2 mL THF at -80 °C. An aliquot (75-400 µL) of this solution was combined with 20-400 µmol 4-nitrobenzaldehyde. 50-400 µL 1M TBAF solution in THF was added and the mixture was reacted for 2.5 to 20 min at 0 to 80 °C. After the specified reaction time, the solution was immediately analysed by HPLC.

Detailed reaction conditions and results can be found in the tables below.

Table S4 Variation of the amount of TBAF; reaction conditions: 100 µmol 4-nitrobenzaldehyde, 5 min, 20 °C; total reaction volume: 0.5 mL THF (1M TBAF solution + [^{18}F]Me_3SiCF_3 aliquot); * dc, determined by HPLC; n=3.

Entry	TBAF µmol/µL	[^{18}F]Me_3SiCF_3 aliquot µL	RCY* %
1	400	100	6±10
2	300	200	26±9
3	200	300	39±4
4	100	400	25±4

Table S5 Variation of reaction time and temperature; reaction conditions: 100 µmol 4-nitrobenzaldehyde, 200 µmol TBAF; total reaction volume: 0.5 mL THF (200 µL1M TBAF solution + 300 µL [^{18}F]Me_3SiCF_3 aliquot) ; * dc, determined by HPLC; n=3.

Entry	Temperature °C	Time min	RCY* %
1	0	5	40±9
2	80	5	42±8
3	20	2.5	33±2
4	20	10	37±8
5	20	20	35±6

Table S6 Variation of precursor amount and reaction scale; reaction conditions: 5 min, rt; total reaction volume = TBAF solution + [^{18}F]Me_3SiCF_3 aliquot; * dc, determined by HPLC; n=3.

Entry	Precursor µmol	[^{18}F]Me_3SiCF_3 aliquot µL	TBAF µmol (= µL)	RCY* %
1	20	300	200	20±1
2	50	300	200	33±2
3	100	300	200	39±4
4	200	300	200	45±4
5	400	300	200	64±5
6	100	150	100	61±3
7	200	150	100	76±6
8	400	150	100	66±10
9	100	75	50	77±6
10	200	75	50	77±2

2.3.2 Screening of different initiators

[^{18}F]Me_3SiCF_3 was synthesized as described under 2.2.1 and trapped in 2 mL THF at -80 °C. A 250 µL aliquot of this solution was added to 200 µmol aldehyde or ketone and 100 µmol TBAT (54 mg) or KOPh (13.2 mg). The mixture was reacted for 5 minutes at rt and analysed by HPLC.

Table S7 RCYs* (%) of the [^{18}F]trifluoromethylation of various substrates using different initiators; reaction conditions: 200 µmol substrate, 100 µmol initiator, 250 µL [^{18}F]Me_3SiCF_3 stock solution, 5 min, rt; * dc, determined by HPLC; n=2.

Substrate	KOPh	TBAT
4-Nitrobenzaldehyde	10±8	n.d.
4-Nitroacetophenone	2±1	n.d.
4-Nitrobenzophenone	1±1	64±6

2.3.3 Investigation of the reaction scope - TBAF

[^{18}F]Me_3SiCF_3 was synthesized as described under 2.2.1 and trapped in 2 mL THF at -80 °C. A 150 µL aliquot of this solution was added to 200 µmol aldehyde or ketone. After addition of 100 µL 1M TBAF solution in THF the mixture was reacted for 5 minutes at rt, quenched with 250 µL 2M HCl and analysed by HPLC. The results are presented in the main manuscript.

2.3.4 Investigation of the reaction scope - TBAT

[^{18}F]Me_3SiCF_3 was synthesized as described under 2.2.1 and trapped in 2 mL THF at -80 °C. A 50 µL aliquot of this solution was added to 200 µmol aldehyde or ketone. After addition of 200 µL 0.4M TBAT solution in THF the mixture was reacted for 5 minutes at rt, quenched with 250 µL 2M HCl and analysed by HPLC. The results are presented in the main manuscript.

Remark: The chosen TBAT concentration and the added volumes of TBAT solution and [^{18}F]Me_3SiCF_3 stock were resulting from the limited solubility of TBAT in THF. However, 80 µmol instead of the 100 µmol initiator used in previous experiments proved to be sufficient for optimal yields in this experiment.

2.3.5 Full batch reaction and molar activity determination

[^{18}F]Me_3SiCF_3 was synthesized as described under 2.2.1 and trapped at -80°C in 1 mL THF containing 30 mg (200 µmol) 4-nitrobenzaldehyde and 300 mg (556 µmol) TBAT. After complete trapping the reaction vessel was actively warmed up to rt and the mixture was reacted for 5 minutes. Then, it was diluted with 1 mL H_2O, passed over a LCR PTFE filter, diluted with 2 mL mobile phase and purified by semi-preparative HPLC (Luna 10u C18(2) 100A 250x10 mm,

MeCN/H_2O/TFA 40/60/0.1, 4 mL/min). The product fraction was collected and a known aliquot (1 mL) was taken from the fraction and measured for radioactivity. 20 µL of this aliquot were analysed by HPLC (Alltima C18 5µ 4.6x250mm, MeCN/water/TFA 40:60:0.1, 1 mL/min, UV: 254 nm). Molar activity was determined based on a calibration curve of the reference compound.
The calibration curve was obtained by measuring samples of different concentrations of 2,2,2-trifluoro-1-(4-nitrophenyl)ethanol by HPLC (Alltima C18 5µ 4.6x250mm, water/MeCN/TFA 40:60:0.1, 1 mL/min, UV: 254 nm) and determining the peak area. The amount of 2,2,2-trifluoro-1-(4-nitrophenyl)ethanol was plotted against the peak area (see Figure 1) to obtain the following equation:

Amount of reference compound [nmol] = (0.0000021868 * area + 0.0032449133) [nmol]

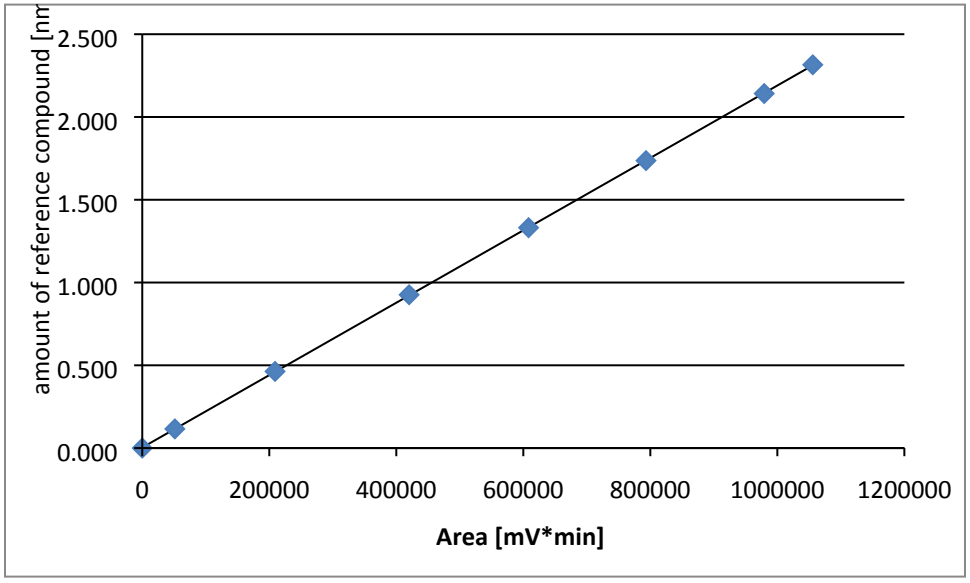

Figure S1 Calibration curve of 2,2,2-trifluoro-1-(4-nitrophenyl)ethanol; HPLC conditions: column: Alltima C18 5µ 4.6x250mm, water/MeCN/TFA 40:60:0.1, 1 mL/min, UV: 254 nm.

The injected amount of 2,2,2-trifluoro-1-(4-nitrophenyl)ethanol was calculated by filling in the peak area of the sample into the equation above. The molar activity then was calculated according to

Molar activity [GBq/µmol] = amount of radioactivity [GBq] / amount of compound [µmol]

while the amount of radioactivity was determined by dividing the activity of the aliquot by a factor of 50 (20 µL of a total volume of 1 mL were injected).

2.3.6 One-pot reaction on the Neptis perform module

[^{18}F]Me_3SiCF_3 was synthesized on the Neptis perform module according to our published procedure for the [^{18}F]fluoroform synthesis.[1] The setup was identical to the one previously described, the synthesis was adapted to the formation of Me_3SiCF_3:

[^{18}F]Fluoride was loaded onto the Chromafix® 30-PS-HCO_3 cartridge and the cartridge was dried with N_2 (10 mL/min, 30 sec). [^{18}F]Fluoride was eluted with 100 µL 0.1 M K_2SO_4, followed by 400 µL 0.011M bistriflate solution in DMF into RV1. [^{18}F]Triflyl fluoride was distilled for 7.5 min at room temperature with a N_2 flow of 10 mL/min from RV1 to RV2, where it was trapped in a solution of 0.15 µmol K_2CO_3 and 0.35 µmol K_{222} in 899 µL MeCN and 1 µL water. After the distillation (7.5 min), RV2 was heated to 80 °C. When the temperature was reached (~90 sec of heating), 100 µL 0.01 M $CHIF_2$ solution in MeCN was added and the mixture was reacted for 5 min at 80 °C. After cooling down RV2 to 60 °C with the help of pressurized air [^{18}F]fluoroform was distilled from RV2 to RV3 with a N_2 flow of 10 mL/min (4 min). [^{18}F]Fluoroform was trapped in RV3 in 150 µL (1182 µmol) chlorotrimethylsilane and 1000 µL 0.5M (500 µmol) potassium hexamethyldisilazide in toluene cooled to -80 °C with an ethyl acetate/liquid N_2 cooling bath. After the distillation, RV3 was removed from the cooling bath and was left at room temperature for 5 minutes to form [^{18}F]Me_3SiCF_3. The overall RCY up until this step was 16±2% (dc, with regard to the amount of aqueous [^{18}F]fluoride loaded onto the module).

For the trifluoromethylation reaction, a solution of 30 mg (200 µmol) 4-nitrobenzaldehyde and 300 mg (556 µmol) TBAT in 1 mL THF was manually added to RV3. After 5 minutes, a sample was taken and analysed by HPLC.

3 Organic chemistry

3.1 2,2,2-Trifluoro-1-(4-nitrophenyl)ethanol 6g[3]

A solution of 1.5 g 4-nitrobenzaldehyde (10 mmol) and 1.7 g trimethylsilylchloride (12 mmol, 1.2 eq.) in 25 mL THF was cooled to 0 °C. 77 µL 1M tetrabutylammonium fluoride in THF was added and the solution was stirred for 1 hour while slowly warming up to room temperature. Then, 25 mL 1M HCl in water was added and the solution was stirred for another 5 hours at room temperature. The reaction mixture was extracted twice with diethyl ether. The combined organic phases were washed with water and brine, were dried over magnesium sulfate and concentrated *in vacuo*. The resulting crystals were washed with cold hexane and dried to obtain 1.2 g (5.5 mmol, 55 %) pale yellow crystals.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.16-8.31 (m, 2 H), 7.68 (d, *J*=8.85 Hz, 2 H), 5.84 (d, *J*=5.19 Hz, 1 H), 5.02 - 5.17 (m, 1 H); ^{19}F-NMR (377 MHz, $CDCl_3$): δ (ppm) = -77.81 (d, *J*=6.8 Hz, 3 F).

3.2 2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol 6d[4]

122 µL 4-methoxybenzaldehyde (136 mg, 1.0 mmol) was dissolved in 3 mL DMF. 222 µL $TMSCF_3$ (1.5 mmol) and 14 mg K_2CO_3 (0.1 mmol) were added and the reaction mixture was stirred at room temperature. After 2 h, the formed TMS ether was hydrolysed by adding 3 mL 1M TBAF (3 mmol) in THF and stirring at room temperature for 16 h. Subsequently, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the product was purified by column chromatography (silica, hexane/ethyl acetate 4:1). The product was obtained as light yellow oil. Yield: 87 mg (0.42 mmol, 42%), ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.38-7.44 (m, 2 H), 6.92 - 6.97 (m, 2 H), 4.95-5.01 (m, 1 H), 3.84 (s, 3 H), 2.50 (d, *J*=4.27 Hz, 1 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ (ppm) = -78.56 (d, *J*=6.93 Hz, 3 F).

3.3 2,2,2-Trifluoro-1-(3-nitrophenyl)ethanol 6j[4]

151 mg 3-nitrobenzaldehyde (1.0 mmol) was dissolved in 3 mL DMF. 222 µL $TMSCF_3$ (1.5 mmol) and 14 mg K_2CO_3 (0.1 mmol) were added and the reaction mixture was stirred at room temperature. After 1 h, the formed TMS ether was hydrolysed by adding 3 mL 1M TBAF (3 mmol) in THF and stirring at room temperature for 1 h. Subsequently, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the

product was purified by column chromatography (silica, hexane/ethyl acetate 4:1). The product was obtained as light yellow solid. Yield: 174 mg (0.79 mmol, 79%), ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.40 (s, 1 H), 8.29 (ddd, J=8.24, 2.29, 1.07 Hz, 1 H), 7.82 - 7.88 (m, 1 H), 7.63 (t, *J*=7.93 Hz, 1 H), 5.16 - 5.23 (m, 1 H), 2.91 (d, *J*=4.58 Hz, 1 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ (ppm) = -78.43 (d, *J*=6.93 Hz, 3 F).

3.4 1,1,1-Trifluoro-2-(4-nitrophenyl)propan-2-ol 6h[4]

165 mg 4'-nitroacetophenone (1.0 mmol) was dissolved in 3 mL DMF. 222 µL $TMSCF_3$ (1.5 mmol) and 14 mg (0.1 mmol) K_2CO_3 were added and the reaction mixture was stirred at room temperature. After 21 h, the formed TMS ether was hydrolysed by adding 3 mL 1M TBAF (3 mmol) in THF and stirring at room temperature for 4 h. Subsequently, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the product was purified by column chromatography (silica, hexane/ethyl acetate 4:1). The product was obtained as light yellow crystals. Yield: 210 mg (0.89 mmol, 89%), ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.24-8.29 (m, 2 H), 7.80 (d, *J*=8.50 Hz, 2 H), 2.54 (s, 1 H), 1.83-1.85 (m, 3 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ (ppm) = -78.43 (d, *J*=6.93 Hz, 3 F).

3.5 1,1,1-Trifluoro-2-(4-methoxyphenyl)propan-2-ol 6e[4]

150 mg 4'-methoxyacetophenone (1.0 mmol) was dissolved in 3 mL DMF. 500 µL $TMSCF_3$ (3.4 mmol) and 50 mg K_2CO_3 (0.4 mmol) were added and the reaction mixture was stirred at room temperature. After 24 h, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the TMS ether was purified by column chromatography (silica, hexane/ethyl acetate 99:1). The purified TMS ether was hydrolysed by adding 3 mL 1M TBAF (3 mmol) in THF and stirring at room temperature for 23 h. Subsequently, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the product was purified by column chromatography (silica, hexane/ethyl acetate 85:15). The product was obtained as a colourless oil. Yield: 88 mg (0.4 mmol, 40%), ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.40-7.45 (m, 2 H), 6.82-6.87 (m, 2 H), 3.75 (s, 3 H), 2.28 (s, 1 H), 1.68-1.70 (m, 3 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ (ppm) = -81.23 (s, 3 F).

3.6 1,1,1-Trifluoro-2-(3-nitrophenyl)propan-2-ol 6k[4]

165 mg 3'-nitroacetophenone (1.0 mmol) was dissolved in 3 mL DMF. 443 µL $TMSCF_3$ (3.0 mmol) and 28 mg K_2CO_3 (0.2 mmol) were added and the reaction mixture was stirred at room temperature. After 16 h, the formed TMS ether was hydrolysed by adding 3 mL 1M TBAF (3 mmol) in THF and stirring at room temperature for 4 h. Subsequently, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the product was purified by column chromatography (silica, hexane/ethyl acetate 4:1). The product was obtained as a yellow oil. Yield: 201 mg (0.86 mmol, 86%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.49-8.51 (m, 1 H), 8.26 (ddd, *J*=8.16, 2.37, 1.07 Hz, 1 H), 7.93-7.97 (m, 1 H), 7.61 (t, *J*=8.09 Hz, 1 H), 2.64 (s, 1 H), 1.86 (d, *J*=0.92 Hz, 3 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ (ppm) = -81.06 (s, 3 F).

3.7 2,2,2-Trifluoro-1-(4-nitrophenyl)-1-phenylethanol 6i[4]

227 mg 4-nitrobenzophenone (1.0 mmol) was dissolved in 3 mL DMF. 222 µL $TMSCF_3$ (1.5 mmol) and 14 mg K_2CO_3 (0.1 mmol) were added and the reaction mixture was stirred at room temperature. After 3 h, the formed TMS ether was hydrolysed by adding 3 mL 1M TBAF (3 mmol) in THF and stirring at room temperature for 1 h. Subsequently, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the product was purified by column chromatography (silica, hexane/ethyl acetate 4:1). The product was obtained as yellow oil. Yield: 276 mg (0.93 mmol, 93%), ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.20 - 8.24 (m, 2 H), 7.71 (d, *J*=8.54 Hz, 2 H), 7.46 - 7.51 (m, 2 H), 7.40 - 7.44 (m, 3 H), 3.02 (s, 1 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ (ppm) = -74.17 (s, 3 F).

3.8 2,2,2-Trifluoro-1-(4-methoxyphenyl)-1-phenylethanol 6f[4]

250 mg 4-methoxybenzophenone (1.2 mmol) was dissolved in 3 mL DMF. 517 µL $TMSCF_3$ (3.5 mmol) and 50 mg K_2CO_3 (0.4 mmol) were added and the reaction mixture was stirred at room temperature. After 72 h, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the TMS ether was purified by column chromatography (silica, hexane/ethyl acetate 99:1). The purified TMS ether was hydrolysed by adding 3 mL 1M TBAF (3 mmol) in THF and stirring at room temperature for 24 h. Subsequently, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined

organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the product was purified by column chromatography (silica, hexane/ethyl acetate 9:1). The product was obtained as a colourless oil. Yield: 103 mg (0.36 mmol, 31%), ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.48 - 7.53 (m, 2 H), 7.34 - 7.43 (m, 5 H), 6.86 - 6.91 (m, 2 H), 3.82 (s, 3 H), 2.82 (s, 1 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ (ppm) = -74.45 (s, 3 F).

3.9 2,2,2-Trifluoro-1-(3-nitrophenyl)-1-phenylethanol 6l[4]

227 mg 3-nitrobenzophenone (1.0 mmol) was dissolved in 3 mL DMF. 222 µL $TMSCF_3$ (1.5 mmol) and 14 mg K_2CO_3 (0.1 mmol) were added and the reaction mixture was stirred at room temperature. After 40 h, the formed TMS ether was hydrolysed by adding 3 mL 1M TBAF (3 mmol) in THF and stirring at room temperature for 1 h. Subsequently, the mixture was quenched with 40 mL water and extracted with Et_2O (3x20 mL). The combined organic layers were washed with water (2x30 mL), dried over Na_2SO_4 and filtered. After removal of the solvent *in vacuo*, the product was purified by column chromatography (silica, hexane/ethyl acetate 4:1). The product was obtained as yellow oil. Yield: 260 mg (0.88 mmol, 88%), ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 8.44 (s, 1 H), 8.21 - 8.25 (m, 1 H), 7.70 - 7.88 (m, 1 H), 7.55 (t, *J*=7.93 Hz, 1 H), 7.47 - 7.53 (m, 2 H), 7.39 - 7.44 (m, 3 H), 3.04 (s, 1 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ (ppm) = -74.36 (s, 3 F).

4 HPLC analysis

4.1 Me_3SiCF_3 synthesis

Table S8 Overview of HPLC retention times; HPLC conditions: Alltima C18 5µ 4.6x250mm, MeCN/water/TFA 60:40:0.1, 1 mL/min.

Compound	t_R [min]	
	UV	Radioact.
Me_3SiCl	2'20	-
Me_3SiF	9'44	10'37
Me_3SiCF_3	14'32	15'41
THF	4'14	-
toluene	11'26	-
$[^{18}F]CHF_3$	-	5'10

Me_3SiCF_3

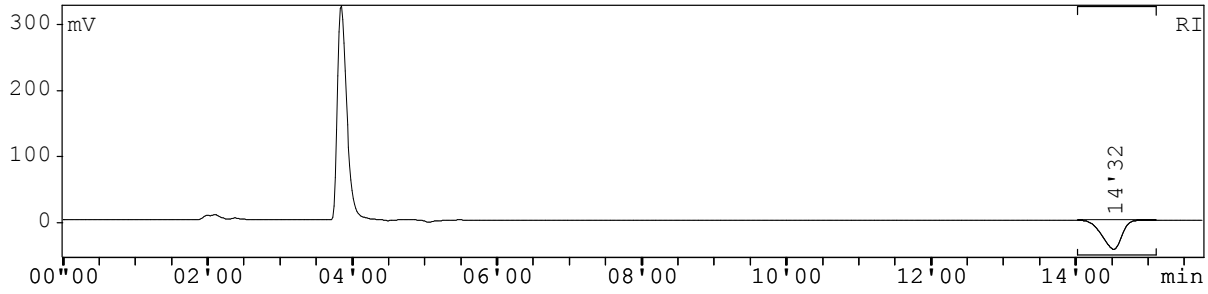

Figure S1 HPLC chromatogram of trimethyl(trifluoromethyl)silane (t_R=14'32); Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

Me_3SiF

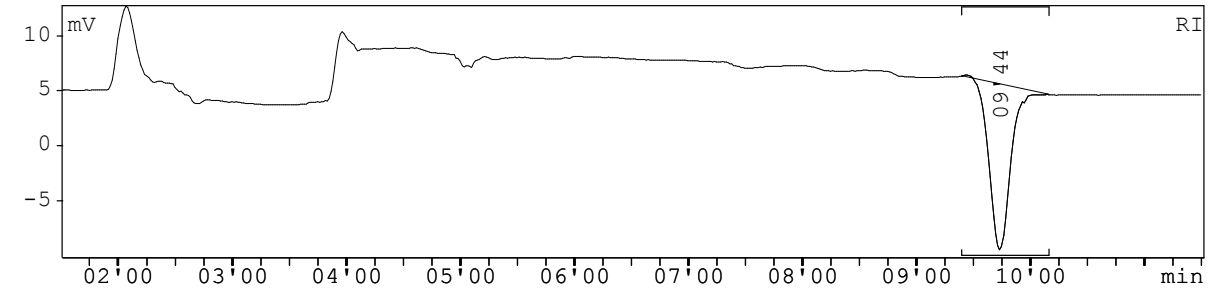

Figure S2 HPLC chromatogram of trimethylsilyl fluoride (t_R=9'44); Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

Me_3SiCl

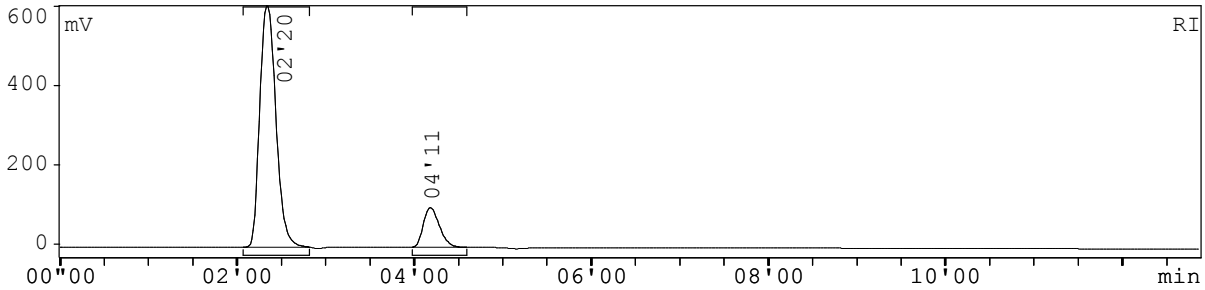

Figure S3 HPLC chromatogram of Me_3SiCl (t_R=2'20) in THF (t_R=4'11); Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

Toluene

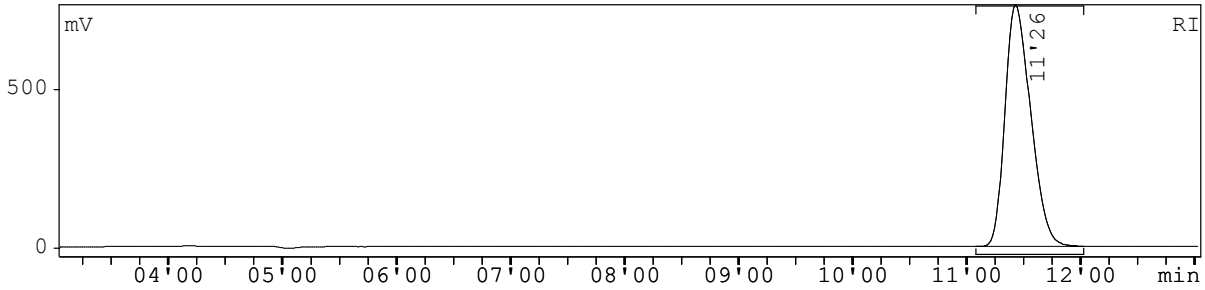

Figure S4 HPLC chromatogram of toluene (t_R=11'26); Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

THF

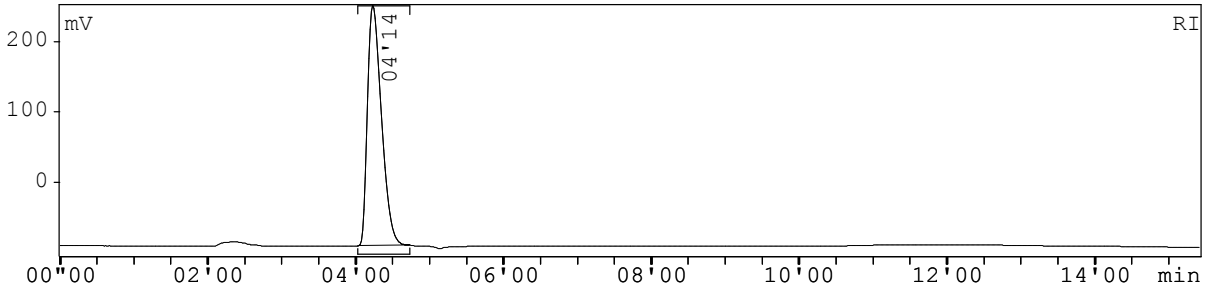

Figure S5 HPLC chromatogram of THF (t_R=4'14); Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

[^{18}F]CHF_3

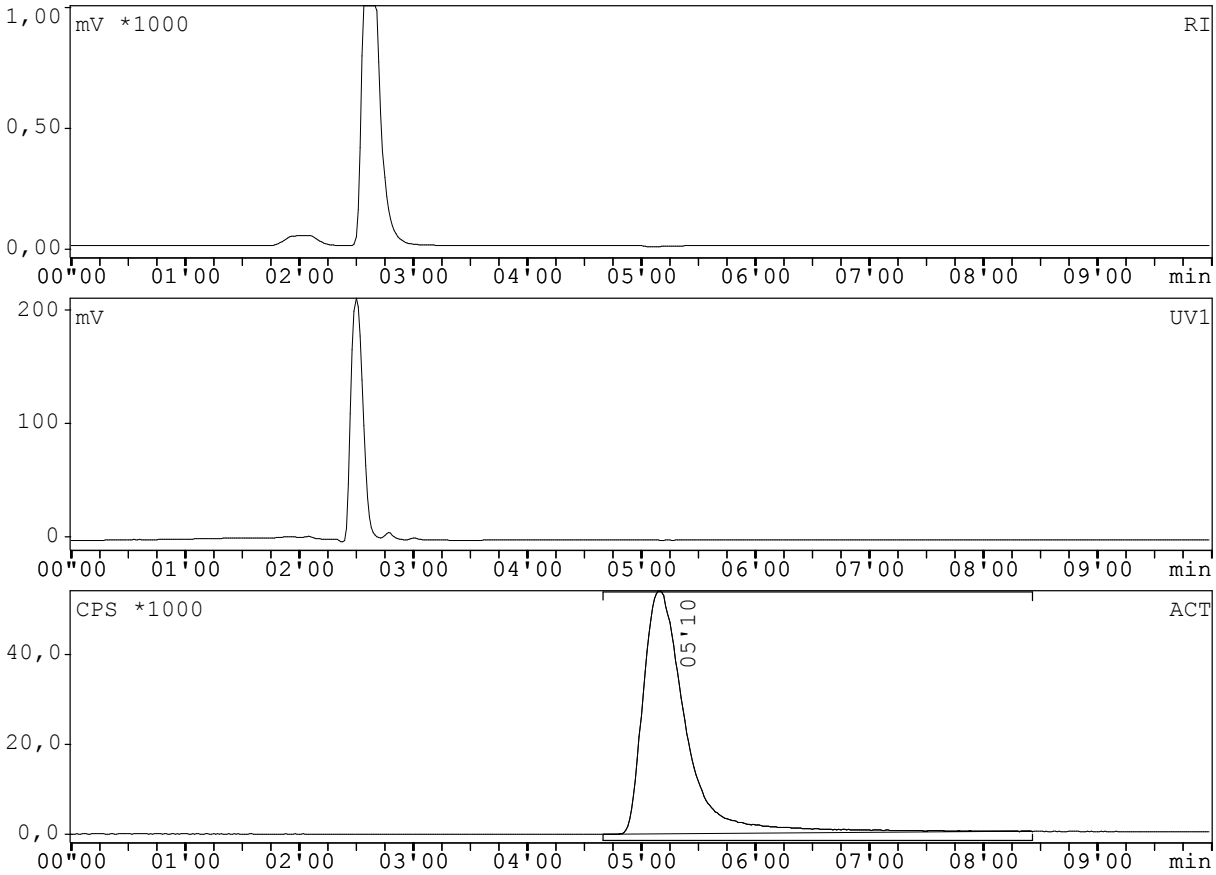

Figure S6 HPLC chromatogram of [^{18}F]CHF_3 (t_R=5'10); Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

[^{18}F]Me_3SiCF_3

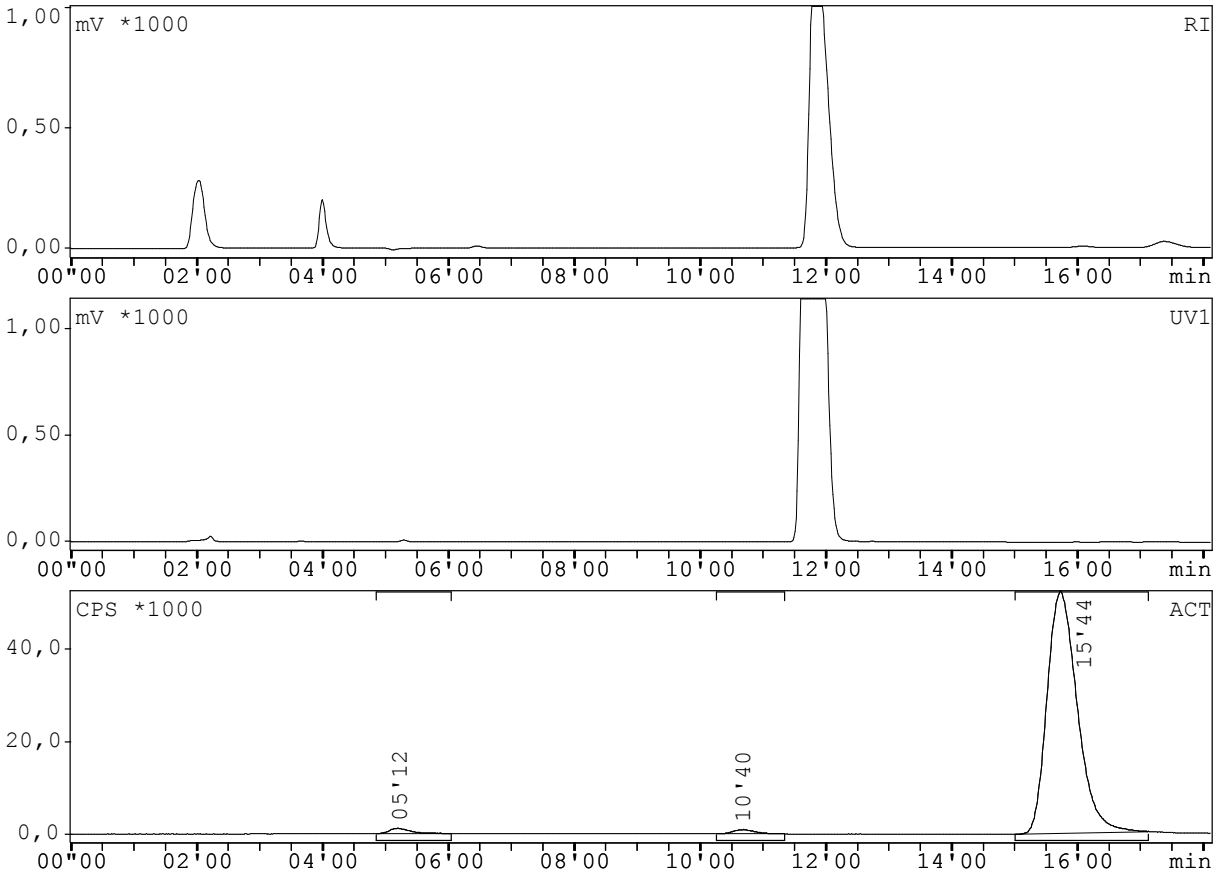

Figure S7 HPLC chromatogram of the **optimized** [^{18}F]Me_3SiCF_3 synthesis (crude); t_R([^{18}F]Me_3SiCF_3)=15'44; Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

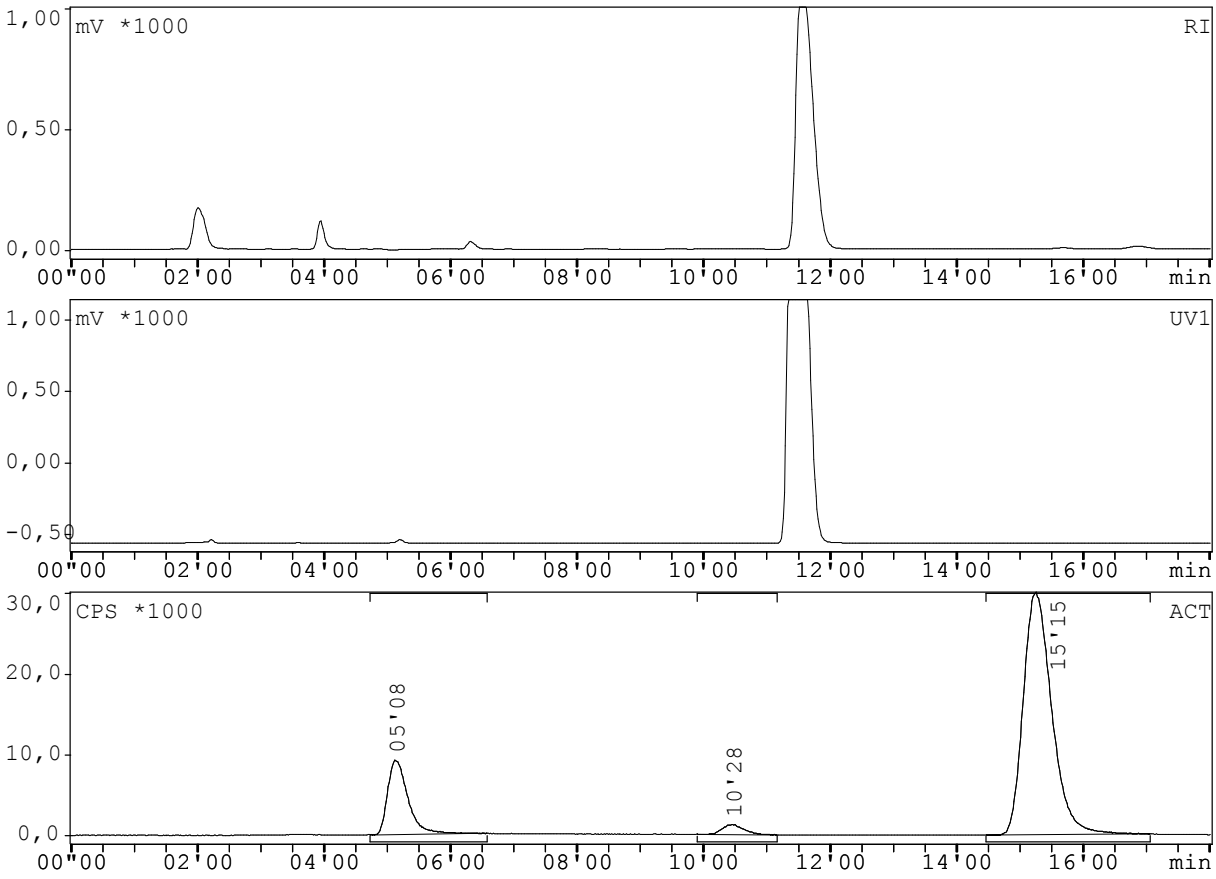

Figure S8 HPLC chromatogram of the **unoptimized** [^{18}F]Me_3SiCF_3 synthesis (crude); t_R([^{18}F]Me_3SiCF_3)=15'15; Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

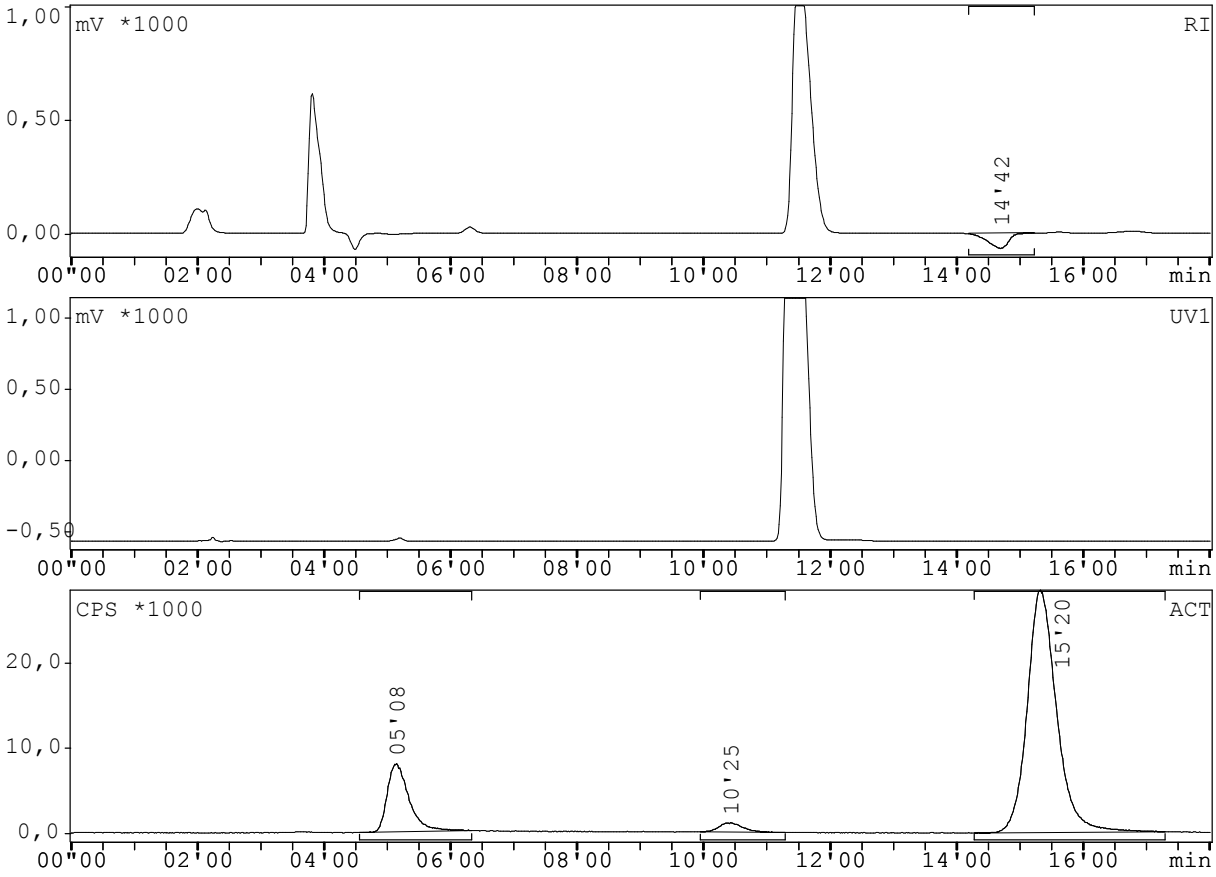

Figure S9 HPLC chromatogram of the unoptimized [^{18}F]Me_3SiCF_3 synthesis (crude) + **spike with reference**; t_R([^{19}F]Me_3SiCF_3)=14'42, t_R([^{18}F]Me_3SiCF_3)=15'20; Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

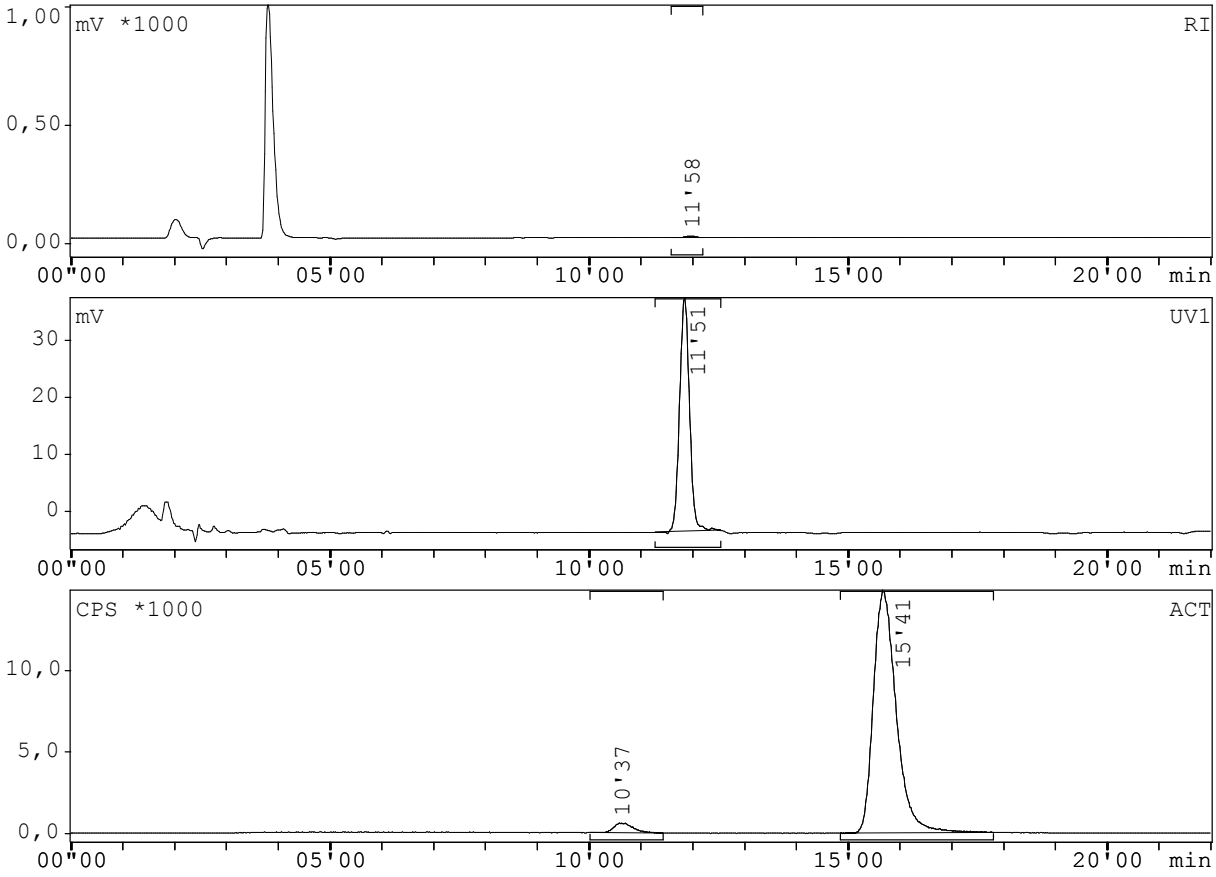

Figure S10 HPLC chromatogram of $^{18}F]Me_3SiCF_3$ **after distillation**; $t_R([^{18}F]Me_3SiCF_3)$=15'41; Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

4.2 [^{18}F]Trifluoromethylation of aldehydes and ketones

Precursors, reference compounds and reaction mixtures were analysed on a Alltima C18 5µ 4.6x250mm column with MeCN/H2O/TFA 60:40:0.1 as eluent. Retention times of precursors, references and radiolabelled products are shown in the tables below.

Table S8 Overview of HPLC retention times; HPLC conditions: Alltima C18 5µ 4.6x250mm, MeCN/water/TFA 60:40:0.1, 1 mL/min.

precursors	t_R UV [min]
benzophenone	11.473
acetophenone	5.47
benzaldehyde	5.346
4-methoxybenzophenone	10.917
4´-methoxyacetophenone	5.305
4-methoxybenzaldehyde	5.192
4-nitrobenzophenone	11.46
4´-nitroacetophenone	5.66
4-nitrobenzaldehyde	5.281
3-nitrobenzophenone	10.883
3'-nitroacetophenone	5.536
3-nitrobenzaldehyde	5.171
2,2,2-trifluoroacetophenone	4.15

Products	t_R [min]	
	UV	Radioact.
2,2,2-trifluoro-1,1-(diphenyl)ethanol	11.88	11.944
1,1,1-trifluoro-2-phenylpropan-2-ol	6.732	6.762
2,2,2-trifluoro-1-phenylethanol	5.769	5.776
2,2,2-trifluoro-1-(4-methoxyphenyl)-1-phenylethanol	11.549	11.6
1,1,1-trifluoro-2-(4-methoxyphenyl)propan-2-ol	6.365	6.454
2,2,2-trifluoro-1-(4-methoxyphenyl)ethanol	5.52	5.631
2,2,2-trifluoro-1-(4-nitrophenyl)-1-phenylethanol	12.017	12.027
1,1,1-trifluoro-2-(4-nitrophenyl)propan-2-ol	6.729	6.783
2,2,2-trifluoro-1-(4-nitrophenyl)ethanol	5.946	6.023
2,2,2-trifluoro-1-(3-nitrophenyl)-1-phenylethanol	11.394	11.534
1,1,1-trifluoro-2-(3- nitrophenyl)propan-2-ol	6.644	6.74
2,2,2-trifluoro-1-(3-nitrophenyl)ethanol	5.834	5.948
1,1,1,3,3,3-hexafluoro-2-phenylpropan-2-ol	9.242	9.388

Example chromatograms: 1-(4-Nitrophenyl)-2,2,2-trifluoroethanol

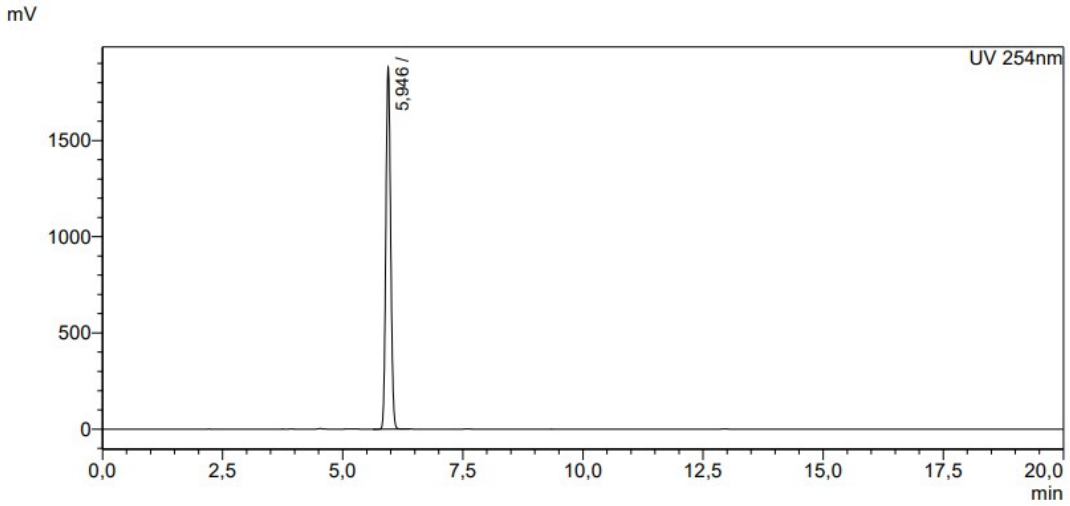

Figure S11 HPLC chromatogram of 1-(4-nitrophenyl)-2,2,2-trifluoroethanol (t_R=5.946 min); Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

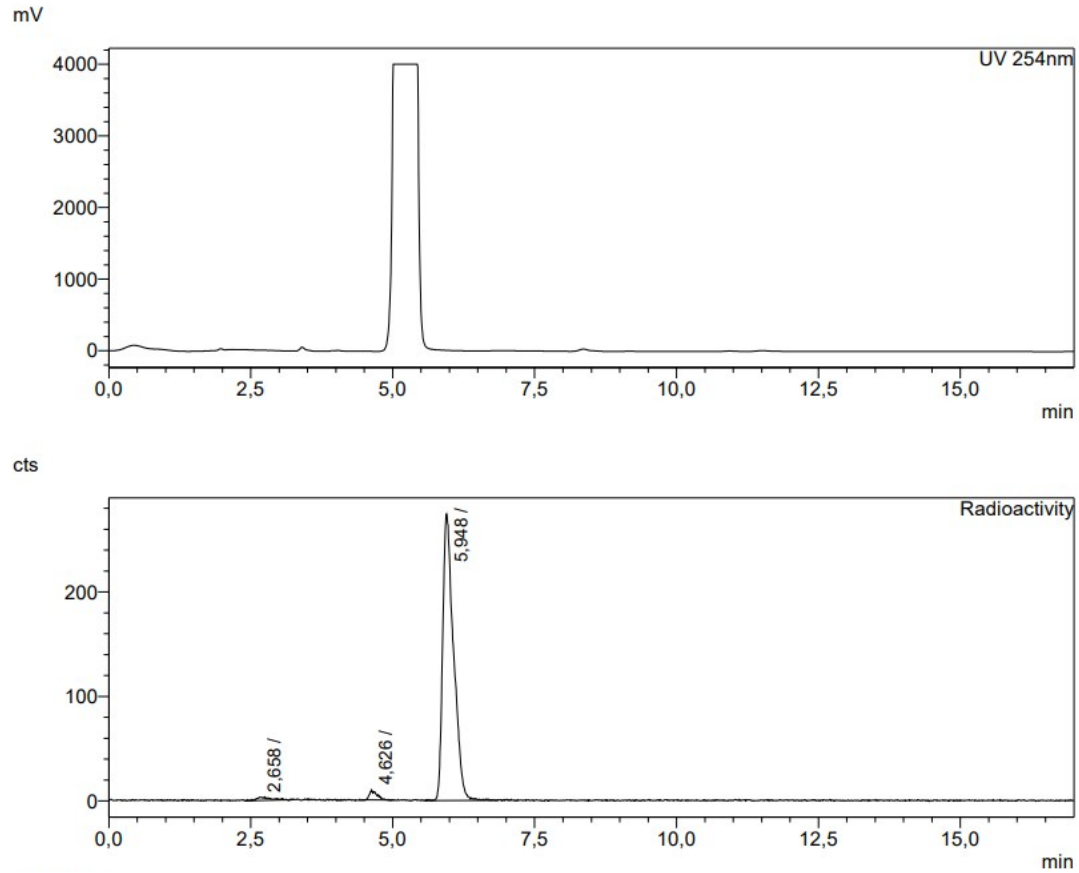

Figure S12 HPLC analysis of the [^{18}F]trifluoromethylation reaction of 4-nitrobenzaldehyde; top panel: UV at 254 nm; bottom panel: radioactivity signal, t_R(1-(4-nitrophenyl)-2,2,2-[^{18}F]trifluoroethanol)=5.948 min; Column: Alltima C18 5µ 4.6x250mm, Eluent: 60:40:0.1 MeCN/H_2O/TFA.

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