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Use of perfluoro groups in nucleophilic ^{18}F-fluorination

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Substrates with leaving groups that contained perfluoro moieties were investigated in labelling chemistry in order to exploit their properties to improve reactivity and purification. [^{18}F](Fluoromethyl)benzene was used as the model target compound. Precursors containing perfluoroalkyl and perfluoroaryl sulfonate moieties were subjected to nucleophilic ^{18}F-fluorination, and the impact of perfluoro groups on the substitution reaction and product purification was investigated. [^{18}F]Fluoride interacted with perfluoroalkyl chains, precluding nucleophilic substitution. When perfluoroaryl groups were used, the substitution proceeded, and the separation of product was explored. The radiolabelled product was obtained in 32% analytical yield and the radiochemical purity was increased to approximately 77% using fluorous solid phase extraction purification.

Keywords: perfluoro; nucleophilic ^{18}F-fluorination; F-SPE; chemical reactivity; purification

Introduction

Owing to the short half-lives of the radionuclides used in positron emission tomography (PET), the technique requires tracers with high specific radioactivity that can be purified quickly. A high specific radioactivity makes it possible to use a very small amount of the tracer in the biological system, thereby decreasing the risk of saturation or perturbation. ^{18}F is a radionuclide used in PET, and has interesting synthetic[1,2] and physical properties[1]. In this work, perfluorinated moieties have been used as leaving groups in nucleophilic ^{18}F-labelling. This may both increase the reactivity of the leaving group and simplify separation. The high electronegativity of the fluorine atom means that a fluorous leaving group has significantly different electronic properties, and consequently reactivity, from a non-fluorinated group.[3] Additionally, a fluorous starting material can be removed using a fluorous separation technique[4] like fluorous solid phase extraction (F-SPE), which allows faster purification than the commonly used high-performance liquid chromatography (HPLC) method. As time is an important parameter in labelling chemistry, it would be advantageous to improve the reactivity of the leaving group and/or the ease of purification of a nucleophilic substitution reaction.[5]

Fluorous-labelling strategies have previously been used in radiolabelling with ^{18}F, using perfluoro chains with two-carbon spacers,[6] as well as with other nuclides. A perfluoro leaving group has been used in the synthesis of [^{18}F]FDG,[7] and an iodo-demetalation ^{125}I-labelling reaction was achieved using a fluorine-rich tin support.[8] F-SPE was used in combination with fluorous scavengers in a ^{35}S-labelling.[9]

Fluorous separation techniques are methods for separating fluorous or fluorous-labelled molecules from other types of molecules, or from each other, based primarily on the structure of their fluorous domain(s).[4] These techniques are based on the interaction between a fluorous medium and a fluorous portion of a molecule, and include liquid–liquid extraction with organic and fluorous solvents,[10] F-SPE and fluorous HPLC.[11,12] In the current labelling strategy, we explored the use of F-SPE to separate a non-perfluorinated ^{18}F-labelled product from the perfluorinated starting material. This technique uses fluorous silica gel for the separation of fluorous from non-fluorous compounds.[13] Perfluoroalkyl and perfluoroaryl sulfonate groups were used as leaving groups.

Results and discussion

Labelling

The effects of a perfluoro structure on chemical reactivity and purification were explored in two model reactions, the syntheses of [^{18}F](fluoromethyl)benzene (**8**) and [^{18}F](4-fluorobutyl)benzene (**10**) by nucleophilic substitution (Schemes 1 and 2). As a control, the tosyl compound **1** was used as a precursor for the ^{18}F-labelling to give **8,** which was obtained in 90% analytical radiochemical yield. The radiolabelled products **8** and **10** were identified using co-elution HPLC analysis (UV and radiodetectors) with their unlabelled fluorinated counterparts, (fluoromethyl)benzene and (4-fluorobutyl)benzene, respectively. The reference compounds were prepared from the corresponding bromide compounds and tetrabutylammonium fluoride.

A number of perfluoro-containing precursors were investigated. All attempts to label **2** (Scheme 1), which bore a perfluorooctyl chain on the sulfonate, with [^{18}F]fluoride at 150°C in acetonitrile failed. Neither additional heating to 180°C nor the

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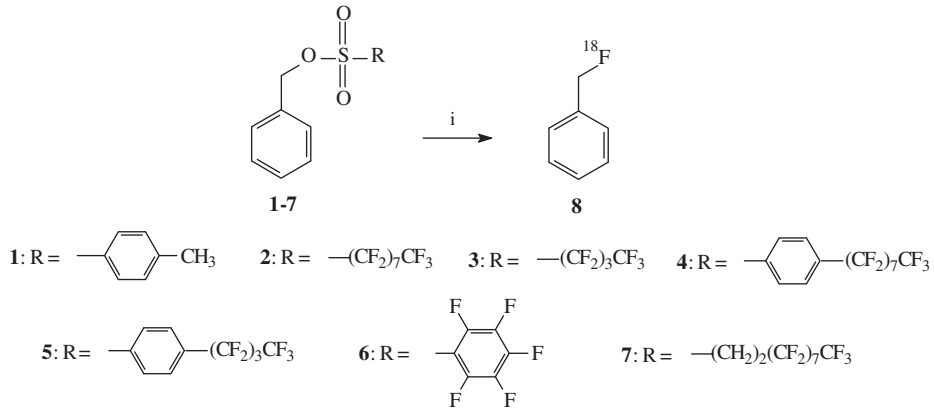
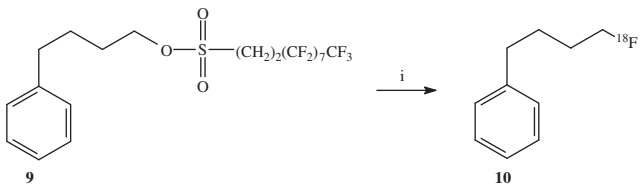


Scheme 1. General reaction of sulfonyl compounds **1–7** with [^{18}F]fluoride to form [^{18}F](fluoromethyl)benzene. (i): [K/K2.2.2.]$^{+}$^{18}F^{-}, acetonitrile/DMF, 15 min, 110–180°C, 0–32% yield.



Scheme 2. ^{18}F-Labelling of compound **9**. Reaction conditions (i): [K/K2.2.2.]$^{+}$^{18}F^{-}, acetonitrile, 15 min, 110°C, 50% yield.

addition of water or methanol to influence solvation improved the result. When tetrabutylammonium fluoride was added and the reaction mixture was further heated for 1 h, a trace amount of unlabelled (fluoromethyl)benzene was formed. The substitution that occurred at the sulfonyl group upon addition of excess ^{19}Ffluoride could indicate that the perfluoroalkyl part of the precursor interacts with the [^{18}F]fluoride, preventing it from taking part in the substitution reaction, since the addition of an excess of fluoride ions seemed to release [^{18}F]fluoride for replacing the sulfonyl group. It has previously been observed that perfluoro chains can leach fluoride ions, so the ^{19}F-fluoride likely comes from solvolysis, rather than $^{18/19}$F exchange.[13] The high reactivity of the perfluoroalkyl sulfonate group has been reported to lead to the problematic formation of ammonium sulfonate salts.[14,15] To see whether this unwanted incorporation of ^{19}F could be reduced, a precursor with a four-carbon perfluoroalkyl chain (**3**) was used. The outcome of this labelling reaction was, however, the same as for the reaction of compound **2**. The next two precursors had modified tosyl groups, with perfluoroalkyl chains of different lengths attached to benzene rings (**4** and **5**). A benzene ring has previously been used to insulate a perfluoroalkyl group from an active site.[16] Using these modified precursors in the labelling reaction gave the same result as for compounds **2** and **3**, though trace amounts of products were also obtained in these cases when fluoride ions were added. Acetonitrile, dimethyl sulfoxide (DMSO) and dichloromethane were also used as solvents in the labelling reaction, but did not improve the formation of radiolabelled product. When the leaving group was perfluorophenyl sulfonate (**6**), the labelled product **8** was obtained in 32% analytical yield in a mixture of acetonitrile and *N,N*-dimethylformamide (DMF). Apparently the [^{18}F]fluoride does not interact with the perfluorinated benzene ring as it does with the perfluoroalkyl groups. The radiochemical yield of this reaction was moderate compared with the control reaction with **1**. This could be due to some incorporation of the [^{18}F]fluoride into the perfluoroaromatic ring structure,[17] or to differences in reactivity. Despite this lower radiochemical yield, using compound **6** as the precursor not only makes the labelling reaction feasible, but also makes the purification by F-SPE possible. The radiochemical purity was increased to 77% after purification of the reaction mixture by F-SPE using a silica gel modified with pentafluorophenyl groups (Figure 1). The non-perfluoro product was eluted in four fractions with a fluorophobic solvent system (0.5 mL methanol/water (40:60)), with the purest product obtained in the third fraction. The specific radioactivity was 120 ± 30 ($n = 2$) GBq/μmol after the purification. Using FluoroFlash® silica, which features perfluorinated alkyl chains, increased the radiochemical purity to approximately 40%. In this case the product was eluted with 2 mL methanol/water (80:20). The perfluoro molecules can be eluted using a fluorophilic solvent like methanol, acetone, acetonitrile or tetrahydrofuran (THF).[18]

As a comparison, published labelling experiments that used a chain containing a two-carbon spacer between the fluorous chain and the sulfonyl group were repeated.[6] Compound **7**, was labelled in 10% analytical radiochemical yield in acetonitrile at 110°C after 15 min. Compound **9**,[6] Scheme 2, was labelled in 50% yield, compared with the previously published 88% radiochemical yield.[6] This indicates that the reactivity of the perfluoroalkyl chains and their possible interactions with [^{18}F]fluoride are clearly impacted by the hydrocarbon spacer.

Precursor synthesis

Precursors **1**–**3** were prepared from the corresponding sulfonyl chloride and phenylmethanol by combining with sodium hydride in THF[19] (Scheme 3), in 9–50% yield.

Compounds **4** and **5** were prepared by coupling the corresponding perfluoro iodides **11**–**12** to benzene rings using the Grignard reaction[20] (Scheme 4). Sulfonyl acid was attached and converted to sulfonyl chlorides **19–20** before coupling with phenylmethanol according to the procedure described above. The precursors **4–5** were obtained in 5–6% overall yield.

Precursor **6** was prepared starting from pentafluorobenzenesulfonyl chloride, which was heated in water to form the sulfonic acid **21**, and subsequently combined with silver carbonate to give the corresponding silver salt **22**[21] (Scheme 5). This, in turn, was coupled to (chloromethyl)benzene to give compound **6** in 10% yield.

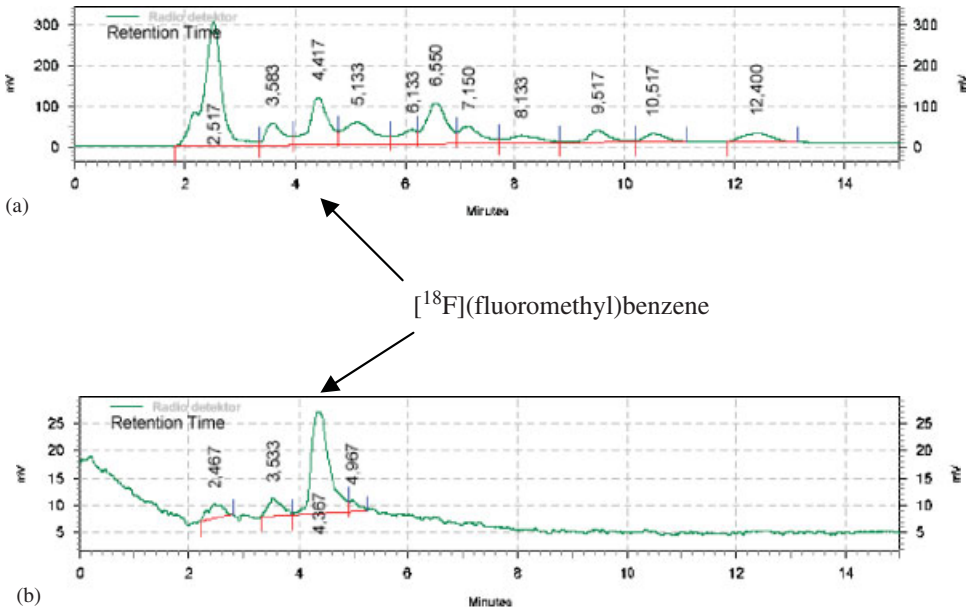
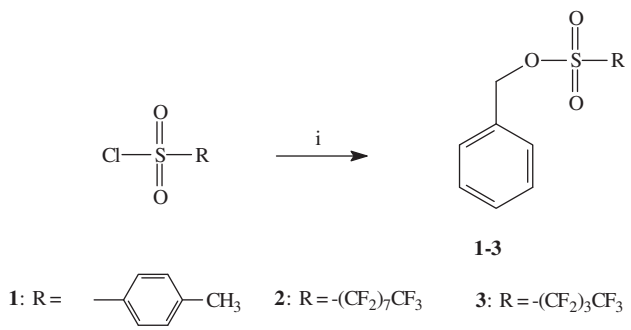


Figure 1. Radiochromatogram of (a) crude reaction mixture from labelling of compound **6**, (b) after purification by F-SPE.



Scheme 3. Synthesis of precursors **1**-**3**. Reaction conditions (i): phenylmethanol, NaH, THF, 16–94 h, room temperature (r.t.), 9–50% yield.

Compounds **7** and **9** (Scheme 6) were prepared using the published procedure.[6] 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoro-10-iododecane was converted to (diaminomethylene)(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)sulfonium iodide (**23**) by reaction with thiourea in ethanol. This was further transformed into the sulfonyl chloride **24** and combined with phenylmethanol or 4-phenylbutan-1-ol to give the respective compound **7** or **9**.

Only precursors **1** and **6** could be purified by column chromatography on silica; the rest were purified by recrystallization from $CHCl_3$/petroleum ether.

Experimental section

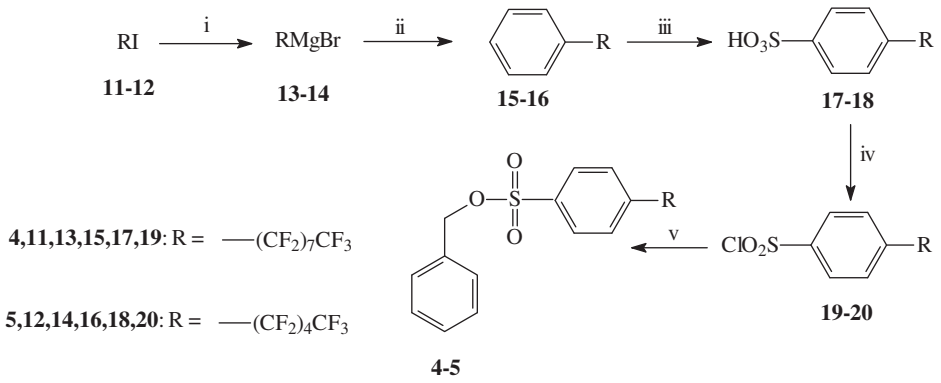
Radiosynthesis

General

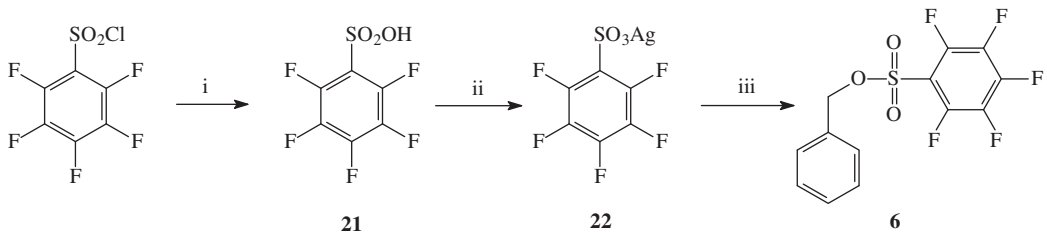
No-carrier-added [^{18}F]fluoride was produced from water 95% enriched in ^{18}O (Rotem Industries Ltd., Israel or Taiyo Nippon Sanso Corporation) by the nuclear reaction ^{18}O(p,n)^{18}F using a Scanditronix MC-17 cyclotron at Uppsala Imanet. The produced [^{18}F]fluoride in water was transferred from the cyclotron target by HPLC pump and trapped on a QMA filter (ABX, advanced biochemical compounds, Pre-conditioned Sep-PAK®, Light QMA Cartridge with CO_3^{2-} as counter ions, Radeberg). The QMA filter was purged with helium for 3 min and thereafter the [^{18}F]fluoride was released with a 2 mL solution of 96:4 (by volume, total volume 12 mL) acetonitrile–water mixture containing 55.9 mg of Kryptofix 2.2.2 (K2.2.2) and 12.7 mg K_2CO_3. After the eluted ^{18}F-Kryptofix/K_2CO_3 solution was dried under N_2 (g) at 110°C, it was further dried with 2 × 1 mL dry acetonitrile. Synthia,[22] an automated synthesis system, was used. Liquid chromatographic analysis (LC) was performed with a VWR Hitachi Pump L-2130 and a VWR Hitachi UV Detector L-2400 UV detector in series with a β^+-flow detector. A Discovery® C18, Supelco, 25 cm × 4.6 mm, 5 μm HPLC column was used. The following mobile phases were used: 25 mM KH_2PO_4 in water (A) and acetonitrile/water 50:7 (B). Program: 60–90% (B) on 5 min, then 90% for 10 min. In the analysis of the ^{18}F-labelled compounds, isotopically unmodified reference substances were used for identification in all LC runs. Radioactivity was measured in an ion chamber, Veenstra Instrumenten BV, VDC-202. F-SPE columns FluoroFlash® containing $Si(CH_2)_2C_8F_{17}$ and Silica gel, functionalized, pentafluorophenylpropyl silicate, 1 mmol/g, particle size: 40–3 μm, Acros Organics were used as bonded phases. All chemicals were obtained from commercial suppliers and used without further purification.

General labelling procedure

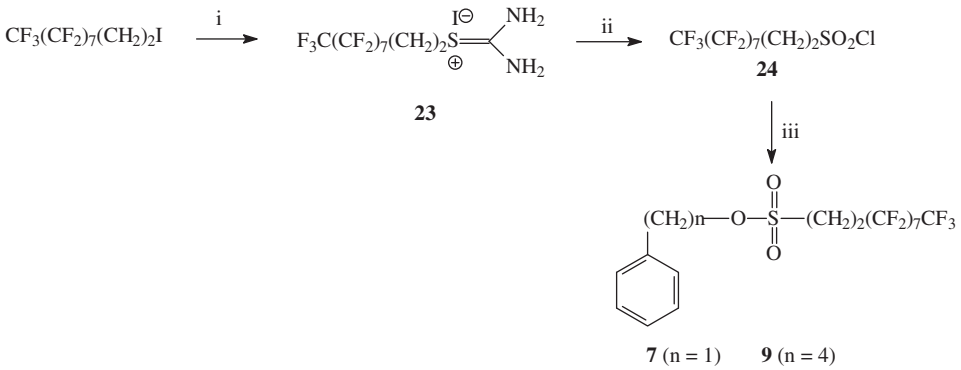
The precursors **1**-**5**, **7** and **9** (8–15 μmol) were dissolved in 200 μL acetonitrile, DMSO, DMF or dichloromethane. Compound **6** was dissolved in 200 μL DMF. The dissolved precursors were added to a solution of the dried [K/K2.2.2.]$^+$^{18}F$^-$ in 200 μL one of the mentioned solvents. The reaction mixtures containing only acetonitrile or dichloromethane were heated at 110°C for 15 min, whereas the one containing a mixture of acetonitrile and DMF were heated at 150°C in a closed vessel. In some cases (compounds **25**) tetrabutylammonium fluoride (0.5 mL, 1 M in THF) was also added and the reaction mixture heated at 100°C for 1 h extra.



Scheme 4. Synthesis of precursors **4**-**5**. Reaction conditions: (i) Mg, EtBr, Et_2O, 4 h, −40 to 35°C, (ii) chlorobenzene, $NiCl_2$(dppp), 20–48 h, 35°C, (iii) $ClSO_3H$, 1,2-dichloroethane, 20–22 h, r.t., (iv) thionyl chloride, DMF, 5–9 h, 80°C, (v) phenylmethanol, NaH, THF, 5–18 h, r.t., 45–69% yield.



Scheme 5. Synthesis of precursor **6**. Reaction conditions: (i) H_2O, 22 h, 100°C, (ii) Ag_2CO_3, H_2O, 25 h, r.t., (iii) (chloromethyl)benzene, CH_3CN, 18 h, 85°C, 10% yield.



Scheme 6. Synthesis of precursors **7** and **9**. Reaction conditions: (i) thiourea, ethanol, 20 h, 78°C, (ii) $KMnO_4$, HCl, acetic acid, H_2O, 2 h, 0–10°C, 50% yield, (iii) phenylmethanol or 4-phenylbutan-1-ol, triethylamine, CH_2Cl_2, 20 h, r.t., 30–40% yield.

SPE conditions

Silica gel, functionalized, pentafluorophenylpropyl silicate, 1 mmol/g, particle size: 40–63 μm, Acros Organics, 80 mg.

(1) The cartridge was washed with 1 mL DMF.
(2) Preconditioning with 1 mL methanol/water (40:60).
(3) Reaction mixture loaded.
(4) Elution: 0.5 mL methanol/water (40:60) × 4.

F-SPE conditions[23]

2 g SPE-column (FluoroFlash®, ($Si(CH_2)_2C_8F_{17}$))

(1) The cartridge was washed with 1 mL DMF.
(2) Preconditioning with 2 mL methanol/water (80:20).
(3) Reaction mixture loaded.
(4) Fluorophobic elution: 2 mL methanol/water (80:20) × 2.

Chemical synthesis

General

^{1}H NMR, ^{13}C NMR and ^{19}F spectra were recorded on a Varian Unity (^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) or Varian Mercury (^{1}H at 300 MHz, ^{13}C at 75 MHz, ^{19}F at 282 MHz) spectrometer using $CDCl_3$ or CD_3OD as deuterated solvent (solvent peaks were used as the reference, $CDCl_3$: ^{1}H 7.26 ppm, ^{13}C 77.0 ppm; CD_3OD: ^{1}H 3.31 ppm, ^{13}C 49.00 ppm). In the case of ^{19}F NMR, $CFCl_3$ was used as the reference. Chemical shifts are reported in ppm. All NMR experiments were conducted at 25°C. Mass spectrometric analyses were performed using a Finnigan MAT GCQ mass spectrometer in EI mode. Thin-layer chromatography (TLC) was performed on Merck silica gel F-254 aluminum plates using CH_2Cl_2 as eluent.

Silica gel 60, particle size 0.040–0.063 mm, Merck, was used for column chromatography.

*(Fluoromethyl)benzene (unlabelled reference for **8**).*[24] Tetrabutylammonium fluoride (1.5 mL, 1.5 mmol, 1 M in THF) was added to (bromomethyl)benzene (0.144 g, 0.84 mmol). The reaction mixture was heated at 90°C for 45 min and then extracted with pentane (3 × 50 mL) and water (100 mL). The organic phase was evaporated by a flow of nitrogen to yield (fluoromethyl)benzene as a colorless liquid (0.046 g, 50%) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.20 (m, 5H, ArH), 5.32 (d, $^2J_{H,F}$ = 48.9 Hz, 2H, –C$\underline{H_2}$F). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.5 (d, $^2J_{C,F}$ = 16.5 Hz, *ipso*-C), 128.8 (d, $^4J_{C,F}$ = 4.1 Hz, *m*-C), 128.5 (*p*-C), 127.7 (d, $^3J_{C,F}$ = 5.0 Hz, *o*-C), 84.5 (d, $^1J_{C,F}$ = 165.0 Hz, –$\underline{C}H_2$F). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –204.1 (m). EI–MS: *m/z* 110 $[M]^{\bullet+}$, 91 $[C_6H_5CH_2]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. R_f = 0.49.

*(4-Fluorobutyl)benzene (unlabelled reference for **10**).* Tetrabutylammonium fluoride (1.5 mL, 1.5 mmol, 1 M in THF) was added to (4-bromobutyl)benzene (0.179 g, 0.84 mmol). The reaction mixture was heated at 90°C for 45 min and then extracted with pentane (3 × 50 mL) and water (100 mL). The organic phase was concentrated under reduced pressure to yield (4-fluorobutyl)-benzene as a colorless liquid (0.079 g, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16–7.07 (m, 3H, ArH), 6.97–6.92 (m, 2H, ArH), 4.32–4.17 (m, 2H, –C$\underline{H_2}$F), 2.72 (m, 2H, –C$\underline{H_2}$–C_6H_5), 1.80 (m, 4H, –$\underline{CH_2CH_2}$–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.3 (*ipso*-C), 129.6 (*m*-C), 125.8 (*o*-C), 125.6 (*p*-C), 83.5 (d, $^1J_{C,F}$ = 160.0 Hz, –$\underline{C}H_2$F), 33.4 (–$\underline{C}H_2$–C_6H_5), 31.5 (d, $^2J_{C,F}$ = 20.5 Hz, –$\underline{C}H_2CH_2$F), 24.6 –$\underline{CH_2CH_2}CH_2$F. ^{19}F NMR ($CDCl_3$, 376 MHz) δ −210.8 (m). EI–MS: *m/z* 152 $[M]^{\bullet+}$, 91 $[C_6H_5CH_2]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. R_f = 0.55.

*Benzyl 4-methylbenzenesulfonate (**1**)*[19]. A solution of phenylmethanol (0.082, 0.76 mmol) in 2 mL dry THF was added to sodium hydride (95%, 0.019 g, 0.76 mmol) in 5 mL dry THF. A solution of 4-methylbenzenesulfonyl chloride (0.145 g, 0.76 mmol) in 3 mL dry THF was added. The reaction mixture was stirred at room temperature (r.t.) for 16 h and then extracted with ethyl acetate (50 mL) and water (100 mL). The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2) to yield **1** as a white solid (0.018 g, 9%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (AA′BB′, 2H, ArH), 7.34–7.30 (m, 5H, ArH), 7.25–7.23 (AA′BB′, 2H, ArH), 5.05 (s, 2H, –C$\underline{H_2}$–), 2.44 (s, 3H, –C$\underline{H_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8 (Ar$\underline{C}$–CH_3), 133.3, 129.8, 129.0, 128.6, 128.5, 127.9, 71.9 (–$\underline{C}H_2$–), 21.6 (–$\underline{C}H_3$). EI–MS: *m/z* 262 $[M]^{\bullet+}$, 91 $[C_6H_5CH_2]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. Mp 58–59°C. R_f = 0.50.

*Benzyl 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane-1-sulfonate (**2**).* A solution of sodium hydride (95%, 0.058 g, 2.31 mmol) in 6 mL dry THF was added to a solution of phenylmethanol (0.250 g, 2.31 mmol) in 1 mL dry THF. 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptadecafluorooctane-1-sulfonyl chloride (0.599 g, 1.16 mmol) was added.[19] The reaction mixture was stirred at r.t. for 24 h and then extracted with diethyl ether (50 mL) and water (100 mL). The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$/petroleum ether to yield **2** as white crystals (0.420 g, 31%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.35–7.29 (m, 5H, ArH), 4.54 (s, 2H, –C$\underline{H_2}$–). ^{13}C NMR (CD_3OD, 100 MHz) δ 139.5 (*ipso*-C), 129.4 (*m*-C), 128.9 (*o*-C), 128.6 (*p*-C), 125.4–99.5 (m, –$\underline{C}_8F_{17}$), 73.1 (–$\underline{C}H_2$–). ^{19}F NMR (CD_3OD, 376 MHz) δ –82.7 (t, $^3J_{F,F}$ = 10.1 Hz, 3F), −116.0 (m, 2F), −118.9 (m, 2F), −122.0 (m, 2F), −123.0 (m, 2F), −123.3 (m, 4F), −124.1 (m, 2F), −127.7 (m, 2F). EI–MS: *m/z* 590 $[M]^{\bullet+}$, 91 $[C_6H_5CH_2]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. Mp 79–80°C. R_f = 0.78.

*Benzyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**3**).* A solution of phenylmethanol (0.110 g, 1.02 mmol) in 2 mL dry THF was added to sodium hydride (95%, 0.019 g, 0.76 mmol) in 5 mL dry THF. A solution of 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl chloride (0.163 g, 0.51 mmol) in 3 mL dry THF was added. The reaction mixture was stirred at r.t. for 94 h and then extracted with ethyl acetate (50 mL) and water (100 mL). The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure.[19] The residue was recrystallized from $CHCl_3$/petroleum ether to yield **3** as white crystals (0.100 g, 50%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.34–7.22 (m, 5H, ArH), 4.50 (s, 2H, –C$\underline{H_2}$–). ^{13}C NMR (CD_3OD, 100 MHz) δ 139.3 (*ipso*-C), 129.3 (*m*-C), 128.7 (*o*-C), 127.8 (*p*-C), 126.0-101.1 (m, –$\underline{C}_4F_{11}$), 72.9 (–$\underline{C}H_2$–). ^{19}F NMR (CD_3OD, 376 MHz) δ −82.5 (t, $^3J_{F,F}$ = 9.9 Hz, 3F), −115.9 (m, 2F), −122.7 (m, 2F), −127.3 (m, 2F). EI–MS: *m/z* 390 $[M]^{\bullet+}$, 91 $[C_6H_5CH_2]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. Mp 70–71°C. R_f = 0.72.

*Benzyl 4-(heptadecafluorooctyl)benzenesulfonate (**4**).* Magnesium (0.057 g, 2.33 mmol) was dried and 5 mL dry diethylether and bromoethane (0.246 g, 2.26 mmol) were added. The reaction mixture was heated at 35°C for 4 h under a nitrogen atmosphere. After cooling to −40°C, 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluoro-8-iodooctane **11** (1.000 g, 1.84 mmol) was added. The temperature was raised to −20°C and chlorobenzene (0.209 g, 1.65 mmol) and $NiCl_2$(dppp) (0.002 g, 3.7 μmol) were added. The mixture was heated at 35°C for 48 h under a nitrogen atmosphere. After cooling to 0°C, the mixture was hydrolyzed by adding 2 M HCl (*aq*) and extracted with ether and H_2O. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure.[20] The resulting (heptadecafluorooctyl)-benzene **15**[25] was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.32 (m, 2H, ArH), 7.31–7.24 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 129.7 (m, (*ipso*-C)), 128.6 (m, *m*-C), 126.4 (m, *o*-C), 125.5 (*p*-C), 122.4–99.0 (m, –$\underline{C}_8F_{17}$). ^{19}F NMR ($CDCl_3$, 282 MHz) δ −81.3 (m, 3F), −117.4 (m, 2F), −118.6 (m, 2F), −120.2 (m, 2F), −122.7 (m, 2F), −123.2 (m, 2F), −124.3 (m, 2F), −126.6 (m, 2F). EI–MS: *m/z* 496 $[M]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. R_f = 0.84.

Compound **15** (0.100 g, 0.20 mmol) was dissolved in 2 mL 1,2-dichloroethane and a solution of chlorosulfonic acid (0.023 g, 0.47 mmol) in 1 mL 1,2-dichloroethane was added dropwise.[20] After stirring at r.t. for 22 h, the solvent was evaporated. The resulting 4-(heptadecafluorooctyl)benzenesulfonic acid **17** was used in the next step without purification.^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.61 (AA′BB′, 2H, ArH), 7.87 (AA′BB′, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.9 (Ar$\underline{C}$-SO_3H), 129.5 (m, *o*-C or *m*-C), 128.0 (m, *o*-C or *m*-C), 125.8 (m, Ar$\underline{C}$-C_8F_{17}), 120.9-97.9 (m, –$\underline{C}_8F_{17}$). ^{19}F NMR ($CDCl_3$, 282 MHz) δ −81.2 (t, $^3J_{F,F}$ = 8.8 Hz, 3F), −118.5 (m, 2F), −119.6 (m, 2F), −120.6 (m, 2F), −122.5 (m, 2F), −123.1 (m, 2F), −124.1 (m, 2F), −126.5 (m, 2F). EI–MS: *m/z* 576 $[M]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. R_f = 0.10.

Compound **17** (0.100 g, 0.17 mmol) was dissolved in 3 mL dry DMF and thionyl chloride (0.01 mL, 0.17 mmol) was added dropwise. After heating the reaction mixture at 80°C for 9 h, the solvent was evaporated. The resulting 4-(heptadecafluorooctyl)-benzenesulfonyl chloride **19** was analyzed by TLC and used in the next step without purification. R_f = 0.80.

A solution of phenylmethanol (0.017 g, 0.16 mmol) in 3 mL dry THF was added to a solution of sodium hydride (95%, 0.004 g,

0.16 mmol) in 3 mL dry THF. A solution of **19** (0.100 g, 0.16 mmol) in 5 mL dry THF was added.[19] The reaction mixture was stirred at r.t. for 5 h and then extracted with ethyl acetate (50 mL) and water (100 mL). The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$/petroleum ether, to yield **4** as white crystals (0.074 g, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.30 (m, 8H, ArH), 7.25–7.23 (m, 1H, ArH), 3.01 (m, 2H, –C$\underline{H_2}$–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 130.8, 128.8 (m), 128.6, 128.5, 128.3, 128.1, 127.6 (m), 127.0, 122.4–100.1 (m, –$\underline{C_8}F_{17}$), 73.2 (–$\underline{C}H_2$–). ^{19}F NMR ($CDCl_3$, 282 MHz) δ −81.1 (m, 3F), −118.0 (m, 2H), −119.2 (m, 2F), −120.3 (m, 2F), −122.3 (m, 2F), −123.4 (m, 2F), −124.3 (m, 2F), −126.0 (m, 2F). EI–MS: *m/z* 666 $[M]^{\bullet}$ 91 $[C_6H_5CH_2]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. Mp 86–87°C. R_f = 0.81.

Benzyl 4-(nonafluorobutyl)benzenesulfonate (***5***). Magnesium (0.178 g, 7.32 mmol) was dried and 5 mL dry diethylether and bromoethane (0.774 g, 7.10 mmol) were added. The reaction mixture was heated at 35°C for 4 h under nitrogen atmosphere. After cooling to −40°C, 1,1,1,2,2,3,3,4,4-nonafluoro-4-iodobutane **12** (2.000 g, 5.78 mmol) was added. The temperature was raised to −20°C and chlorobenzene (0.519 g, 4.10 mmol) and $NiCl_2$(dppp) (0.006 g, 11.6 μmol) were added. Thereafter, the mixture was heated at 35°C for 20 h under a nitrogen atmosphere. After cooling to 0°C, the mixture was hydrolyzed by adding 2 M HCl (*aq*) and extracted with ether (50 mL) and H_2O (10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure.[21] The resulting (nonafluorobutyl)benzene **16**[26] was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.28 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.3 (m, *ipso*-C), 129.7 (m, *m*-C), 128.6 (m, *o*-C), 126.4 (*p*-C), 125.5–104.3 (m, –$\underline{C_4}F_{11}$). ^{19}F NMR ($CDCl_3$, 282 MHz) δ −85.9 (m, 3F), −111.2 (m, 2F), −120.3 (m, 2F), −125.5 (m, 2F). EI–MS: *m/z* 296 $[M]^{\bullet}$ 77 $[C_6H_5]^{\bullet+}$. R_f = 0.73.

(Nonafluorobutyl)benzene **16** (0.140 g, 0.47 mmol) was dissolved in 4 mL 1,2-dichloroethane and chlorosulfonic acid (0.03 mL, 0.47 mmol) was added dropwise.[20] After stirring at r.t. for 20 h, the solvent was evaporated. The resulting 4-(nonafluorobutyl)benzenesulfonic acid **18** was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.28 (AA′BB′, 4H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.3 (Ar$\underline{C}$-SO_3H), 129.7 (m, *o*-C or *m*-C), 128.6 (m, *o*-C or *m*-C), 126.4 (m, Ar$\underline{C}$-$(CF_2)_7CF_3$), 126.0–105.0 (m, –$\underline{C_4}F_{11}$). ^{19}F NMR ($CDCl_3$, 282 MHz) δ −85.1 (m, 3F), −110.0 (m, 2F), −120.9 (m, 2F), −126.0 (m, 2F). EI–MS: *m/z* 376 $[M]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. R_f = 0.12.

18 (0.100 g, 0.27 mmol) was dissolved in 4 mL dry DMF and thionyl chloride (0.02 mL, 0.27 mmol) was added dropwise. The reaction mixture was heated at 80°C for 5 h and then the solvent was evaporated. The resulting 4-(nonafluorobutyl)benzenesulfonyl chloride **20** was analyzed by TLC and used in the next step without purification. R_f = 0.70.

A solution of sodium hydride (95%, 0.003 g, 0.12 mmol) in 3 mL dry THF was added to a solution of phenylmethanol (0.013 g, 0.12 mmol) in 2 mL dry THF A solution of **20** (0.050 g, 0.12 mmol) in 4 mL dry THF was added next.[19] The reaction mixture was stirred at r.t. for 18 h and then extracted with ethyl acetate (50 mL) and water (100 mL). The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$/petroleum ether to yield **5** as white crystals (0.025 g, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.27 (m, 9H, ArH), 4.69 (s, 2H, –C$\underline{H_2}$–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.8, 135.4, 133.4, 130.2, 129.1, 128.5, 127.6, 127.0 (m), 126.0–105.9 (m, –$\underline{C_4}F_{11}$), 65.3 (–$\underline{C}H_2$–). ^{19}F NMR ($CDCl_3$, 282 MHz) δ −83.8 (m, 3F), −111.5 (m, 2F), −120.0 (m, 2F), −125.1 (m, 2F). EI–MS: *m/z* 466 $[M]^{\bullet+}$, 91 $[C_6H_5CH_2]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. Mp 70–71°C. R_f = 0.75.

Benzyl pentafluorobenzenesulfonate (***6***). Pentafluorobenzenesulfonyl chloride (3.030 g, 11.37 mmol) was added to 8 mL H_2O. The reaction mixture was heated at 100°C for 22 h and then concentrated under reduced pressure. The resulting pentafluorobenzenesulfonic acid **21**[21] was redissolved in 10 mL H_2O, and silver carbonate (3.125 g, 11.33 mmol) was added. The reaction mixture was stirred for 25 h at r.t. in darkness, and excess silver carbonate was filtered off. The filtrate was concentrated under reduced pressure. The resulting silver salt **22**[21] was dissolved in 9 mL dry acetonitrile and (chloromethyl)benzene (1.301 g, 10.28 mmol) was added. The mixture was stirred at 85°C in darkness for 17 h and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2) to yield **6** as yellow crystals (0.350 g, 10%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.15–6.80 (m, 5H, ArH), 3.97–3.80 (m, 2H, –C$\underline{H_2}$–C_6H_5). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 144.9–133.8 (m, Ar$\underline{C}$-F), 138.8 (m, *ipso*-C), 130.5 (*o*-C or *m*-C), 128.9 (*o*-C or *m*-C), 126.5 (*p*-C), 71.6 (–$\underline{C}H_2$–C_6H_5). ^{19}F NMR (DMSO-d_6, 376 MHz) δ −140.5 (m, 2F, *o*-F), −148.2 (m, 2F, *m*-F), −158.7 (m, 1F, *p*-F). EI–MS: *m/z* 338 $[M]^{21\cdot+}$, 91 $[C_6H_5CH_2]^{\cdot+}$, 77 $[C_6H_5]^{\cdot+}$. Mp 77–78°C. R_f = 0.65.

Benzyl 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecane-1-sulfonate (***7***). Thiourea (0.161 g, 2.11 mmol) was added to a solution of 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluoro-10-iododecane (1.211 g, 2.11 mmol) in 20 mL ethanol. The reaction mixture was heated at 78°C for 20 h under an atmosphere of nitrogen before the solvent was removed under reduced pressure to yield (diaminomethylene)(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)sulfonium iodide **23**,[6] as a white solid. The product was used in the next step without purification. ^{1}H NMR (CD_3OD, 400 MHz) δ 3.47 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, –C$\underline{H_2}$–S–), 2.70 (m, 2H, –C$\underline{H_2}$–C_8F_{17}). ^{13}C NMR (CD_3OD, 100 MHz) δ 127.5 (m, =$\underline{C}$–$(NH_2)_2$), 120.0–108.1 (m, –$\underline{C_8}F_{17}$), 30.5 (m, –$\underline{C}H_2$–S–), 22.1 (m, –$\underline{C}H_2$–C_8F_{17}). ^{19}F NMR (CD_3OD, 376 MHz) δ −82.8 (t, $^3J_{F,F}$ = 10.0 Hz, 3F), −115.6 (m, 2F), −122.7 (m, 2F), −123.0 (m, 2F), −123.3 (m, 2F), −124.3 (m, 2F), −124.8 (m, 2F), −127.7 (m, 2F). R_f = 0.73.

(Diaminomethylene)(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)sulfonium iodide (1.184 g, 1.82 mmol) was dissolved in a mixture of 10 mL acetic acid and 2 mL H_2O, then cooled to 10°C. In another flask, which was cooled to 0°C, HCl (9.6 mL) was added dropwise to $KMnO_4$ (3.635 g, 23.0 mmol) to give Cl_2 (*g*). The Cl_2 gas was bubbled through water and into the reaction mixture for 2 h at 10°C. The mixture was stirred for one additional hour, under a nitrogen flow, and then cooled to 0°C. This caused the product 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecane-1-sulfonyl chloride **24**[6] to fall out as white crystals, which were removed by filtration and dried under reduced pressure (0.497 g, 50%). The product was used in the next step without purification. ^{1}H NMR ($CDCl_3$/CD_3OD, 400 MHz) δ 3.43–3.40 (m, 2H, –CH_2–SO_2–), 2.58–2.36 (m, 2H, –C$\underline{H_2}$–C_8F_{17}). ^{13}C NMR ($CDCl_3$/CD_3OD, 100 MHz) δ 121.5–105.0 (m, –$\underline{C_8}F_{17}$), 49.4 (m, –$\underline{C}H_2$–SO_2–), 30.4 (m, –$\underline{C}H_2$–C_8F_{17}). ^{19}F NMR ($CDCl_3$/CD_3OD, 376 MHz) δ −81.2 (t, $^3J_{F,F}$ = 9.6 Hz, 3F), −114.6 (m, 2F), −122.3 (m, 2F), −122.6 (m, 2F), −122.9 (m, 2F), −123.3 (m, 2F), −123.7 (m, 2F), −126.6 (m, 2F). R_f = 0.63.

Triethylamine (0.312 mL, 0.24 mmol) and **24** (0.612 g, 1.12mmol) were added to a solution of phenylmethanol (0.242 g, 2.24 mmol) in 5 mL dry CH_2Cl_2. The reaction mixture was stirred at r.t. for 20 h. H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$/petroleum ether to yield **7** as white crystals (0.296 g, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.30 (m, 5H, ArH), 5.20 (s, 2H, –C<u>H</u>$_2$–C_6H_5), 2.93–2.89 (m, 2H, –C<u>H</u>$_2$–SO_2–), 2.63–2.50 (m, 2H, –C<u>H</u>$_2$–C_8F_{17}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2 (*ipso*-C), 128.7 (*o*-C or *m*-C), 126.7 (*o*-C or *m*-C), 125.6 (*p*-C), 124.1–100.5 (m, –<u>C</u>$_8F_{17}$), 70.7 (m, –<u>C</u>H_2–O–), 48.0 (–<u>C</u>H_2–SO_2–), 25.0 (m, –<u>C</u>H_2–C_8F_{17}). ^{19}F NMR ($CDCl_3$, 376 MHz) δ −80.1 (t, $^3J_{F,F}$ = 9.8 Hz, 3F), −113.5 (m, 2F), −121.1 (m, 2F), −121.9 (m, 2F), −122.0 (m, 2F), −122.4 (m, 2F), −123.1 (m, 2F), −125.3 (m, 2F). EI–MS: *m/z* 660 $[M]^{\bullet+}$, 91 $[C_6H_5CH_2]^{\bullet+}$, 77 $[C_6H_5]^{\bullet+}$. Mp 51–52°C. R_f = 0.75.

*4-Phenylbutyl 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecane-1-sulfonate (**9**)*[6]. Triethylamine (0.043 mL, 0.31 mmol) and **24** (0.085 g, 0.16 mmol) were added to a solution of 4-phenylbutan-1-ol (0.047 g, 0.31 mmol) in 5 mL dry CH_2Cl_2. The reaction mixture was stirred at r.t. for 20 h. H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$/petroleum ether to yield **9** as white crystals (0.027 g, 30%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.25 (m, 5H, ArH), 4.17 (t, $^3J_{H,H}$ = 6.5 Hz, 2H, –C<u>H</u>$_2$–O–), 3.44 (tt, $^3J_{H,H}$ = 7.1, $^4J_{H,F}$ = 1.0 Hz, 2H, –C<u>H</u>$_2$$SO_2$–), 2.62 (m, 2H, –C<u>H</u>$_2$–C_6H_5), 1.86–1.77 (m, 2H, –C<u>H</u>$_2$–C_8F_{17}), 1.74–1.68 (m, 4H, –C<u>H</u>$_2$–$(CH_2)_2$–CH_2–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.9 (*ipso*-C), 128.4 (*o*-C or *m*-C), 125.9 (*o*-C or *m*-C), 125.1 (*p*-C), 124.1–98.9 (m, –<u>C</u>$_8F_{17}$), 70.6 (–CH_2-SO_2–), 42.7 (m, –<u>C</u>H_2–O–), 35.1 (–<u>C</u>H_2–C_6H_5), 28.6 (–<u>C</u>H_2-CH_2–O–), 27.9 (–<u>C</u>H_2–CH_2–C_6H_5), 24.7 (m, –<u>C</u>H_2–C_8F_{17}). ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.3 (t, $^3J_{F,F}$ = 9.9 Hz, 3F), −114.4 (m, 2F), −122.3 (m, 2F), −122.7 (m, 2F), −123.1 (m, 2F), −123.4 (m, 2F), −123.9 (m, 2F), −126.1 (m, 2F). EI–MS: *m/z* 560 $[M]^{\bullet+}$ 133 $[C_6H_5(CH_2)_4]^{\bullet+}$, 91 $[C_6H_5CH_2]^{\bullet+}$. Mp 55–56°C. R_f = 0.82.

Conclusion

The model target compound [^{18}F](fluoromethyl)benzene was obtained from the perfluorinated precursor benzyl pentafluorobenzenesulfonate in 32% analytical radiochemical yield, but was not obtained from the perfluoroalkyl containing precursors. The radiochemical purity was increased to 77% after application to an F-SPE column with a perfluorinated benzene stationary phase. Even though the radiochemical yield is moderate, the results suggest that further exploration of perfluoro compounds in labelling is worthwhile, especially as it may enable the use of an automatic system for labelling and fast separation.

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