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Research Article

One-step reductive etherification of 4-[^{18}F]fluoro-benzaldehyde with decaborane

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Summary

Reductive coupling reactions between 4-[^{18}F]fluoro-benzaldehyde ([^{18}F]**1**) and different alcohols by use of decaborane ($B_{10}H_{14}$) as reducing agent have the potential to synthesize 4-[^{18}F]fluoro-benzylethers in one step. [^{18}F]**1** was synthesized from 4-trimethylammonium benzaldehyde (triflate salt) via a standard fluorination procedure (K[^{18}F]F/Kryptofix® 222) in dimethylformamide at 90°C for 25 min and purified by solid-phase extraction. Subsequently, reductive etherifications of [^{18}F]**1** were performed as one-step reactions with primary and secondary alcohols, mediated by $B_{10}H_{14}$ in acetonitrile at 60°C. Various 4-[^{18}F]fluorobenzyl ethers (6 examples are shown) were obtained within 1–2 h reaction time in decay-corrected radiochemical yields of 12–45%. Copyright © 2006 John Wiley & Sons, Ltd.

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Key Words: 4-[^{18}F]fluoro-benzylether; fluorine-18; reductive etherification; decaborane; labelling

Introduction

Tailor-made radiotracers are the key for molecular imaging by means of positron emission tomography (PET). Radiosyntheses utilizing the short-lived

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radionuclide ^{18}F (half-life 109.8 min) have an increased relevance in research and radiopharmaceutical application. Because of the short half-life of ^{18}F, it is essential to keep the time for radiotracer production, including all radiosynthetic and separation steps, as short as possible. A convenient access to a variety of ^{18}F-labelled compounds is still limited, e.g. in the case of ether compounds. Despite the inherent benefit of a good stability regarding metabolic defluorination, only one ^{18}F-labelled aralkyl ether (4-[^{18}F]fluoroproxyfan) has been described until now. This 4-[^{18}F]fluoro-benzyl ether has been prepared from 4-[^{18}F]fluoro-benzaldehyde via a three-step procedure.[1]

Recently, a series of studies has been published on the application of decaborane ($B_{10}H_{14}$) as a mild and quite stable reducing agent in methanol.[2–11] The reductive etherification of aromatic aldehydes with $B_{10}H_{14}$ in methanol or ethanol has been reported to be an efficient way to synthesize the corresponding ethers.[2] This suggests the possibility to synthesize ^{18}F-labelled fluoro-benzylethers from 4-[^{18}F]fluoro-benzaldehyde in one step. However, until now the method mentioned above has only been used to synthesize simple compounds (ROR': R = methyl, ethyl; R′ = aralkyl). It had to be performed in neat alcohols acting as reactant and solvent as well, which may be disadvantageous in some cases. Furthermore, reductive etherification of 4-fluoro-benzaldehyde has not been reported until now.

Since the reaction seems to run via an oxonium ion intermediate,[2,10,12] it would also be interesting to explore whether the electron withdrawing fluorine substitute hampers the formation of such an oxonium ion.

Results and discussion

Non-radioactive syntheses

In order to broaden the application of this reaction for its preparative use as well as for the subsequent ^{18}F-labelling, non-radioactive experiments were initially carried out. For practical reasons, a 10:1 molar ratio of alcohol to 4-fluoro-benzaldehyde was used. The demand of a solvent is evident, if we take into account that for a common ^{18}F-radiosynthesis the molar ratio of the respective alcohol to 4–[^{18}F]fluoro-benzaldehyde is expected to be higher than 1.000:1. 4-Fluoro-benzaldehyde (**1**) was reacted in the presence of decaborane in acetonitrile (MeCN) at 50–60°C with a series of primary and secondary alcohols and one tertiary alcohol (**2a–g**), respectively (Scheme 1, Table 1).

The consumption of 4-fluoro-benzaldehyde was monitored by thin-layer chromatography (TLC). At the end of the synthesis, acetone was added to the solution in order to decompose unreacted decaborane. The product was separated by extraction with hexane and washed with 1 M NaOH solution. Further purification by column chromatography (hexane–ethyl acetate) gave respective ethers as colourless liquids in moderate to good yields (Table 1).

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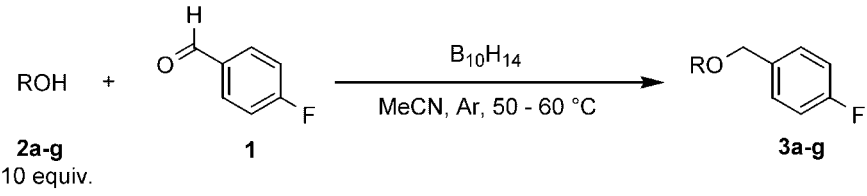
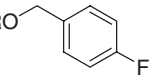
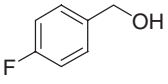
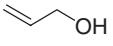
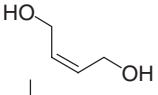
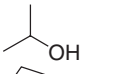
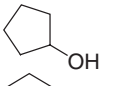
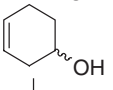
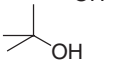


Scheme 1. Reductive etherification of 4-fluoro-benzaldehyde (1) with alcohols (2a–g) in the presence of decaborane in acetonitrile

Table 1. Reductive etherification of 4-fluoro-benzaldehyde with alcohols in acetonitrile in the presence of decaborane

Entry	Alcohols R–OH		Reaction time (h)	Products[a,c] 	Yield (%)[b]
1		**2a**	4	**3a**[c]	75
2		**2b**	6	**3b**[c]	46
3		**2c**	6	**3c**[d]	59
4		**2d**	6	**3d**	64
5		**2e**	15	**3e**	75
6		**2f**	15	**3f**	44
7		**2g**	8	**3g**[c]	50

[a] All products were fully characterized by spectroscopic methods. Spectral data are consistent with the assigned structures and data from literature as well.
[b] Yields of isolated products.
[c] **3a**,[13] **3b**,[14] and **3g**[15] have been previously described.
[d] **3c**: Partially etherified diol (*cis*-4-(4-fluoro-benzyloxy)-but-2-en-1-ol).

As shown in Table 1, not only primary (**2a–c**), but also secondary alcohols (**2d–f**) and one tertiary alcohol (**2g**) can be used for the reductive etherification of 4-fluoro-benzaldehyde. Derivatives of carboxylic acids,[2–5,11] such as esters or cyano groups have been reported to remain intact under the reaction conditions, whereas nitro groups[3,5,11] or alkenes[6] can only be reduced in the presence of palladium catalysts. The smooth conversion of the olefinic alcohols **2b**, **2c** and **2f** (Table 1, entries 2, 3 and 6) confirms the qualified stability of double bonds in the presence of decaborane.

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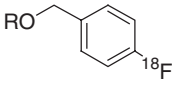
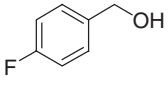
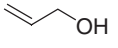
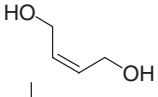
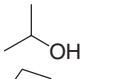
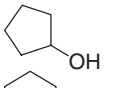
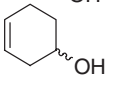
In conclusion, the reductive coupling of 4-fluoro-benzaldehyde with different alcohols by means of $B_{10}H_{14}$ could readily proceed in acetonitrile. The synthetic potential of this type of reaction could be broadened to prepare 4-fluoro-benzylethers with a range of variable functional groups.

Radiosyntheses

The results of the non-radioactive syntheses encouraged us to synthesize 4-[^{18}F]fluoro-benzylethers (Table 2) from 4-[^{18}F]fluoro-benzaldehyde in one step.

The labelling precursor for 4-[^{18}F]fluoro-benzaldehyde ([^{18}F]**1**), trimethylammonium benzaldehyde triflate (**5**, TMABA), was obtained from *N*,*N*-dimethylamino benzaldehyde (**4**) via quaternization.[16] In radiotracer experiments, the preparation of [^{18}F]**1** was achieved by the nucleophilic aromatic substitution of TMABA by [^{18}F]fluoride ion in dry DMF instead of DMSO[16] at 90°C, as shown in Scheme 2. After purification by solid-phase extraction on reversed phase (RP-SPE), the resulting solution of [^{18}F]**1** in

Table 2. Reductive etherification of 4-[^{18}F]fluoro-benzaldehyde with alcohols in acetonitrile in the presence of decaborane

Entry	Alcohols R–OH		Products 	Decay-corrected radiochemical yield [% (SD)][a,b]	TLC R_f (C_6H_{12}/EtOAc: 5/1 v/v)[c]
1		**2a**	[^{18}F]**3a**	18.2 (3.4)	0.68
2		**2b**	[^{18}F]**3b**	14.9 (0.4)	0.66
3		**2c**	[^{18}F]**3c**	31.9 ($n = 2$)[d]	0.43[e]
4		**2d**	[^{18}F]**3d**	25.5 (5.8)	0.76
5		**2e**	[^{18}F]**3e**	9.6 (3.5)	0.76
6		**2f**	[^{18}F]**3f**	11.3 (4.0)	0.75

[a] Reaction conditions: Solution of [^{18}F]**1** (approx. 0.7 ml, 5–215 MBq) in MeCN, corresponding alcohol (0.5–9.5 mmol) and $B_{10}H_{14}$ (0.01–0.07 mmol), 60°C, argon, 60–120 min. For further details see experimental part.

[b] Number of reactions: $n = 3-7$ unless otherwise stated. SD = Standard deviation.

[c] Values are corresponding to the results of the non-radioactive substances.

[d] Individual numbers: 17.9, 45.8.

[e] R_f in cyclohexane (C_6H_{12})/ethyl acetate (EtOAc): 1/1 v/v.

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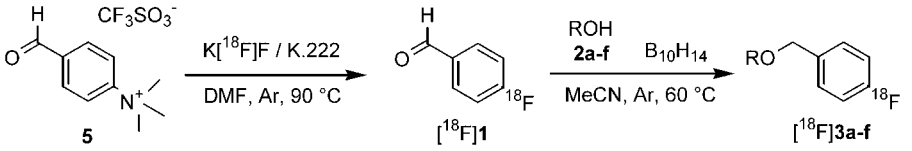

Scheme 2. Preparation of 4-[^{18}F]fluoro-benzaldehyde and reductive etherification with alcohols in the presence of decaborane in acetonitrile

acetonitrile was applied directly to synthesize the 4-[^{18}F]fluoro-benzylethers ([^{18}F]**3a–f**, Scheme 2, Table 2).

In a first series of experiments we adapted the conditions of the non-radioactive coupling reactions for radiosynthesis by adding 0.05–0.06 mmol solid $B_{10}H_{14}$ and 0.5–0.6 mmol of the respective alcohol to a solution of no-carrier-added (n.c.a.) 4-[^{18}F]fluoro-benzaldehyde ([^{18}F]**1**) in MeCN. [^{18}F]**1** was consumed within 30 min yielding only minor amounts of the desired radiofluorinated ethers. The rapid reduction of [^{18}F]**1** to 4-[^{18}F]fluoro-benzyl alcohol ([^{18}F]**2a**) by decaborane caused this unexpected result.

Thus, we increased the amount of alcohol and used a stock solution of decaborane in acetonitrile to lower the concentration of $B_{10}H_{14}$, and consequently the reductive power. The results of selected experiments with different proportions of **2d** and $B_{10}H_{14}$ are shown in Figure 1.

A large excess of alcohol and a minor amount of decaborane result in a pseudo-first-order reaction, so the undesired reduction of 4-[^{18}F]fluoro-benzaldehyde to [^{18}F]**2a** could be diminished. Although reaction times, necessary for the reductive etherification of [^{18}F]**1**, increased to 60–120 min,

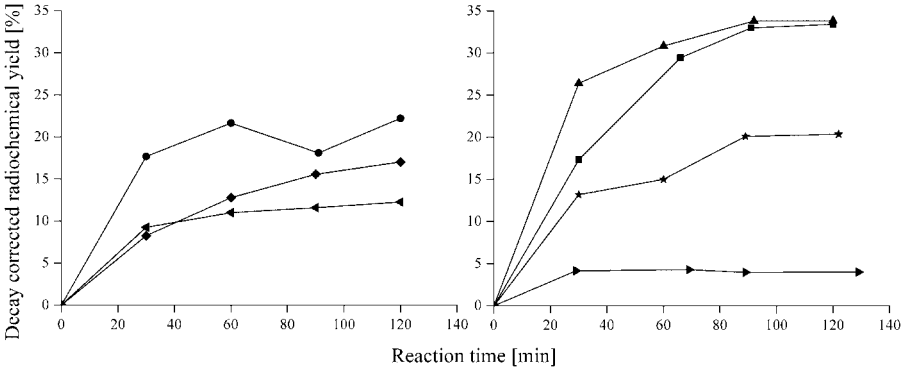

Figure 1. Radiochemical yields of 4-[^{18}F]fluoro-benzyl-*iso*-propylether ([^{18}F]3d) as quantified by Radio-TLC: Influence of reaction time and mass ratio of alcohol and $B_{10}H_{14}$ (*iso*-propanol [mmol] / $B_{10}H_{14}$ [mmol]: ◄ 1.3 / 0.005; ◆ 1.3 / 0.01; ● 1.3 / 0.015; ► 3.3 / 0.01; ★ 3.3 / 0.02; ■ 6.5 / 0.01; ▲ 6.5 / 0.02)

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the radiochemical yield of [^{18}F]**3d** could be improved up to 33% (decay-corrected, Figure 1). In the course of high-performance liquid chromatography (HPLC) analysis, 4-[^{18}F]fluoro-benzoic acid ([^{18}F]**6**) was observed as radioactive by-product and identified by co-elution with an authentic sample of **6**. The radiochemical yields of 4-[^{18}F]fluoro-benzylethers were not further increased at an elevated reaction temperature of 70°C.

In addition, we tried to perform one-pot synthesis, starting from TMABA/n.c.a. [^{18}F]fluoride, i.e. we omitted the purification of [^{18}F]**1** by RP-SPE. Attempts in mixtures of acetonitrile/DMF with 50–100 µl of alcohol (**2b**, **2e**) for 1 h at 60°C (starting from [^{18}F]**1**) did not succeed. However, a selected one-pot synthesis using a large excess of alcohol **2a** (1 ml) resulted in 22% radiochemical yield (decay-corrected) of [^{18}F]**3a**.

Further attempts to simplify the procedure and diminish the reaction volume were carried out by elution of [^{18}F]**1** from the RP-cartridge directly with the corresponding alcohol instead of MeCN. Thus, applying **2a** as an eluent for RP-SPE as well as reactant gave a 14% radiochemical yield of [^{18}F]**3a**.

Identification and quantification of the ^{18}F-labelled ethers were accomplished by radio-TLC and radio-HPLC in comparison with their non-radioactive analogues. Aqueous ammonium acetate solutions with MeCN ratios of 40–60% were proven as suitable eluents for HPLC analysis, except in the case of the more hydrophilic ether **3c** ([^{18}F]**3c**) as depicted in Figure 2.

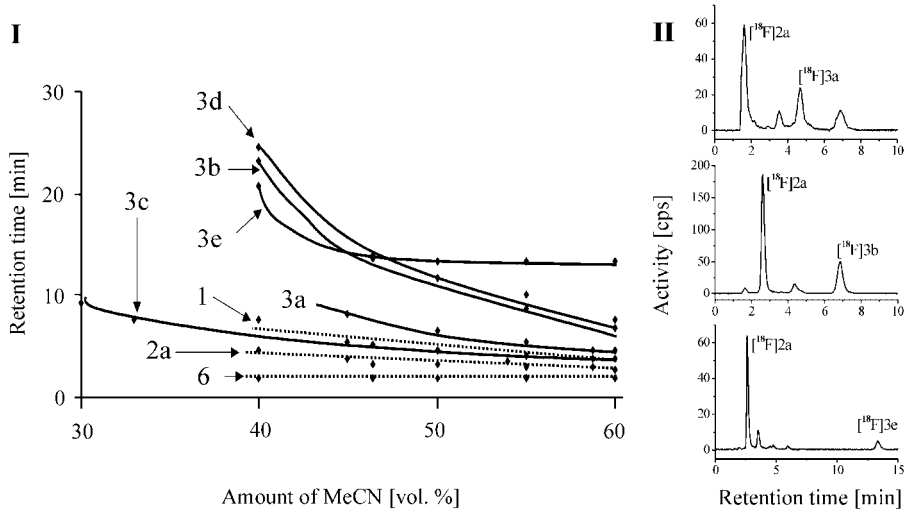

Figure 2. (I) Retention times of reference compounds in dependence on the percentage of MeCN in eluent and (II) Radiochromatograms of selected 4-[^{18}F]fluoro-benzylethers

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Experimental

Material and methods

Cyclohex-3-enol (**2f**, Table 1) was prepared from *cis*/*trans*-cyclohexane-1,4-diol.[17] All other reagents and substrates were purchased from commercial sources and were used without further purification. N.c.a. aqueous [^{18}F]fluoride was generated by the $^{18}O(p,n)^{18}F$ nuclear reaction at a GE PETtrace 16.5 MeV cyclotron.

^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Varian Gemini VXR200 or Gemini 300BB in $CDCl_3$ or $(CD_3)_2SO$ (DMSO), at frequencies as indicated. Chemical shifts are reported in δ units (ppm) relative to the signal of the given solvents as internal reference ($CHCl_3$: $\delta_H = 7.27$ ppm, $\delta_C = 77$ ppm; DMSO: $\delta_H = 2.49$ ppm, $\delta_C = 39.5$ ppm). Coupling constants are given in Hz. Low-resolution mass spectra (LRMS) were recorded on an Applied Biosystems Mariner Biospectrometry Workstation (MS-TOF) using direct inlet system and electron spray ionization (ESI). High-resolution mass spectra (HRMS) were recorded on a 7 T APEX II Fourier transform ion cyclotron resonance mass analyser (FT-ICR-MS) with ESI or on a Finnigan MAT 8230 with electron impact (EI).

Thin-layer chromatography (TLC) was performed on Macherey-Nagel silica gel $60F_{254}$ plates (0.2 mm on aluminium) in cyclohexane/ethyl acetate mixtures (C_6H_{12}/EtOAc: 5/1 v/v) and *n*-pentane/chloroform mixtures (nP/$CHCl_3$: 3/1 v/v) as eluents. For calculation of the retention factors (R_f) compounds were localized by irradiation with an UV lamp (254 and 366 nm). Autoradiograms on Fuji imaging plates were scanned with a Fuji BAS 1800 II phosphor imager, applying BASReader 2.26 software. Amounts of radiolabelled products were calculated with AIDA 2.31 program. Merck Silica gel 60 and Waters SepPack C18 cartridges were used for column chromatography. High-performance liquid chromatography (HPLC, Figure 2) was performed on a Merck-Hitachi LaChrom system with D-7000 interface, L-7100 pump and a CS Nucleosil 100-5C18 AB column (250 × 4 mm) by elution with acetonitrile/aqueous ammonium acetate buffer solutions (MeCN/NH_4AcO: 60/40 and 50/50 v/v, C_{buffer} = 20 mmol/l, flow rate 1 ml/min). Retention times (t_R, means not adjusted) were determined by UV detector L7400 at 220 nm and by Raytest 2″ Socket 81030043 and NaI 2 × 2″ Pinhole radioflow detectors.

Representative procedure for reductive etherification with 4-fluoro-benzaldehyde (entry 6, Table 1)

$B_{10}H_{14}$ (62 mg, 0.50 mmol) was added to a solution of 4-fluoro-benzaldehyde (**1**, 124 mg, 1.0 mmol) and cyclohex-3-enol (**2f**, 980 mg, 10.0 mmol) in acetonitrile (5 ml) at room temperature (RT) under inert atmosphere. The resulting mixture was stirred at 50°C for 15 h. Acetone (2 ml) was added and

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the mixture was stirred for 2 h. The solvent was evaporated and the residue was extracted with hexane (20 ml). The hexane solution was washed with 1 M NaOH (2 ml) and evaporated. The crude ether was purified by column chromatography (*n*-hexane/EtOAc: 5/1 v/v) to yield **3f** (44%, 91 mg) of a colourless liquid.

*Bis-(4-fluoro-benzyl)-ether (***3a***)*.[13] TLC $R_f = 0.68$, 0.46 (C_6H_{12}/EtOAc, nP/$CHCl_3$); HPLC $t_R = 4.73$, 6.49 min (MeCN/NH_4AcO: 60/40, 50/50). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 4 H, ArH), 7.04 (m, 4 H, ArH), 4.52 (s, 4 H, $(ArCH_2)_2O$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 71.7, 115.6 (d, $J = 21.6$ Hz), 129.8 (d, $J = 8.0$ Hz), 134.1 (d, $J = 3.5$ Hz), 162.7 (d, $J = 244.2$ Hz); LRMS (ESI) m/z 257.1 ($M + Na^+$).

*1-Allyloxymethyl-4-fluoro-benzene (***3b***)*.[14] TLC $R_f = 0.66$, 0.37 (C_6H_{12}/EtOAc, nP/$CHCl_3$); HPLC $t_R = 6.86$, 11.65 min (MeCN/NH_4AcO: 60/40, 50/50). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.33 (m, 2 H, ArH), 7.04 (m, 2 H, ArH), 5.94 (ddt, $J^3 = 16.9$ Hz, $J^3 = 10.3$ Hz, $J^3 = 5.9$ Hz, 1 H, OCH_2CHCH_2), 5.32 (dq-like, $J^3 = 17.2$ Hz, $J^{2,4} = 1.7$ Hz, 1 H, $OCH_2CHCH\mathit{H}^{cis}$), 5.23 (dq-like, $J^3 = 10.3$ Hz, $J^{2,4} = 1.5$ Hz, 1 H, $OCH_2CHCH\mathit{H}^{trans}$), 4.50 (s, 2 H, $ArCH_2O$), 4.04 (dt, $J^3 = 5.6$ Hz, $J^4 = 1.4$ Hz, 2 H, OCH_2CHCH_2); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 71.3, 71.5, 115.4 (d, $J = 21.2$ Hz), 117.4, 129.6 (d, $J = 8.1$ Hz), 134.2 (d, $J = 3.4$ Hz), 134.8, 162.5 (d, $J = 244.3$ Hz); LRMS (ESI) m/z 189.1 ($M + Na^+$).

*cis-4-(4-Fluoro-benzyloxy)-but-2-en-1-ol (***3c***)*. TLC $R_f = 0.16$, 0.43 (C_6H_{12}/EtOAc: 5/1, 1/1 v/v); HPLC $t_R = 2.75$, 3.21 min (MeCN/NH_4AcO: 60/40, 50/50). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.32 (m, 2 H, ArH), 7.03 (m, 2 H, ArH), 5.68–5.87 (m, 2 H, $CH{=}CHCH_2OH$), 4.47 (s, 2 H, $ArCH_2O$), 4.15 (d, $J^3 = 5.5$ Hz, 2 H, $ArCH_2OCH_2CH{=}CH$), 4.07 (d, $J^3 = 5.4$ Hz, 2 H, $CH{=}CHCH_2OH$), 2.30 (m, 1 H, OH). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 58.7, 65.8, 71.8, 115.4 (d, $J = 21.3$ Hz), 128.1, 129.6 (d, $J = 8.1$ Hz), 132.6, 133.8 (d, $J = 3.1$ Hz), 162.5 (d, $J = 244.4$ Hz); LRMS (ESI) m/z 219.1 ($M + Na^+$); HRMS (ESI) m/z $C_{11}H_{13}FO_2 \cdot Na$ ($M + Na^+$) calculated 219.07918; found: 219.07920.

*1-Fluoro-4-iso-propoxymethyl-benzene (***3d***)*. TLC $R_f = 0.76$, 0.41 (C_6H_{12}/EtOAc, nP/$CHCl_3$); HPLC $t_R = 7.70$, 13.34 min (MeCN/NH_4AcO: 60/40, 50/50). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.35 (m, 2 H, ArH), 7.05 (m, 2 H, ArH), 4.49 (s, 2 H, $ArCH_2O$), 3.70 (sept, $J^3 = 6.2$ Hz, 1 H, $OCH(CH_3)_2$), 1.24 (d, $J^3 = 6.2$ Hz, 6 H, $OCH(CH_3)_2$). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 22.2, 69.5, 71.2, 115.2 (d, $J = 21.1$ Hz), 129.3 (d, $J = 8.0$ Hz), 135.0 (d, $J = 2.9$ Hz), 162.3 (d, $J = 243.7$ Hz); LRMS (ESI) m/z 191.1 ($M + Na^+$); HRMS (EI) m/z $C_{10}H_{13}FO_2$ (M^+) calculated 168.09504; found: 168.09509.

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1-Cyclopentyloxymethyl-4-fluoro-benzene (**3e**). TLC $R_f = 0.76$, 0.28 (C_6H_{12}/EtOAc, nP/$CHCl_3$); HPLC $t_R = 13.16$, 20.64 min (MeCN/NH_4AcO: 60/40, 50/50). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.31 (m, 2 H, ArH), 7.01 (m, 2 H, ArH), 4.42 (s, 2 H, ArCH_2O), 3.95–4.05 (m, 1 H, *c*-pentyl: C*H*-O), 1.50–1.80 (2 m, 8 H, *c*-pentyl: 4CH_2). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 23.8, 32.5, 70.2, 81.2, 115.3 (d, $J = 21.3$ Hz), 129.5 (d, $J = 8.0$ Hz), 135.0 (d, $J = 3.5$ Hz), 162.4 (d, $J = 243.4$ Hz); LRMS (ESI) m/z 217.1 ($M + Na^+$); HRMS (ESI) m/z $C_{12}H_{15}FO_2 \cdot Na$ ($M + Na^+$) calculated 217.09991; found: 217.10000.

1-(Cyclohex-3-enyloxymethyl)-4-fluoro-benzene (**3f**). TLC $R_f = 0.75$, 0.38 (C_6H_{12}/EtOAc, nP/$CHCl_3$); HPLC $t_R = 12.42$, 20.72 min (MeCN/NH_4AcO: 60/40, 50/50). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.32 (m, 2 H, ArH), 7.03 (m, 2 H, ArH), 5.60–5.65 (m, 2 H, *c*-hexenyl: –CH=CH–), 4.50–4.55 (AB, 2 H, ArCH_2O), 3.65–3.68 (m, 1 H, *c*-hexenyl: C*H*-O), 2.35–2.40, 1.94–2.22, 1.62–1.80 (3 m, 6 H, *c*-hexenyl: 3CH_2). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 24.3, 28.1, 32.0, 69.5, 74.2, 115.4 (d, $J = 21.6$ Hz), 124.5, 127.1, 129.5 (d, $J = 8.0$ Hz), 135.1, 162.5 (d, $J = 243.6$ Hz); LRMS (ESI) m/z 229.2 ($M + Na^+$); HRMS (ESI) m/z $C_{13}H_{15}FO_2 \cdot Na$ ($M + Na^+$) calculated 229.09991; found: 229.09997.

1-tert-Butoxymethyl-4-fluoro-benzene (**3g**).[15] TLC $R_f = 0.77$, 0.37 (C_6H_{12}/EtOAc, nP/$CHCl_3$). ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.31 (m, 2 H, ArH), 7.02 (m, 2 H, ArH), 4.42 (s, 2 H, ArCH_2O), 1.31 (s, 9 H, -C(CH_3)$_3$). ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 27.9, 63.6, 73.6, 115.2 (d, $J = 21.4$ Hz), 129.1 (d, $J = 7.9$ Hz), 135.8, 162.2 (d, $J = 242.9$ Hz); LRMS (ESI) m/z 205.1 ($M + Na^+$).

(4-Formyl-phenyl)-trimethyl-ammonium trifluoro-methanesulfonate (TMABA, **5**).[16] Methyl trifluoro-methanesulfonate (1.1 ml, 10 mmol) was added to a solution of *N*,*N*-dimethylamino benzaldehyde (**4**, 1.64 g, 11 mmol) in dichloromethane (20 ml) at RT under argon. The dark green reaction mixture was stirred at RT for 48 h. The resulting green solid was filtrated, washed, recrystallized and again filtrated from hot dichloromethane to yield **5** (21%, 664 mg) of a white powdery solid. mp (*Boetius*): 110°C (sublimation at 100–103°C). ^{1}H-NMR (DMSO, 200 MHz): δ 3.38 (s, CH_3), 3.65 (s, CH_3), 8.12, 8.17, 8.19, 8.24 (dd, 4 H, CH_{arom}, $J = 8.79$ Hz), 10.11 (s, 1 H, CHO). ^{13}C-NMR (DMSO, 50 MHz) δ 56.43 (CH_3), 121.73 (CH_{arom}, *ortho* to –N(CH_3)$_3^+$), 130.92 (CH_{arom},), 136.81 (C_{quart}, C-CHO), 151.07 (C_{quart}, C-N(CH_3)$_3^+$), 192.17 (CHO); LRMS (ESI) m/z 164.13 (M^+).

4-[^{18}F]Fluoro-benzaldehyde ([^{18}F]**1**). An aqueous [^{18}F]F^- solution of 278–1384 MBq was transferred in a 2–3 ml reaction vial with septum. About 100–200 µl of a solution of Kryptofix®222 (K.222) in acetonitrile (100 mg/ml,

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0.027–0.053 mmol), 100–200 µl of an aqueous solution of potassium carbonate (20 mg/ml, 0.015–0.029 mmol) and 300–500 µl of MeCN (p.a.) were added. The reaction mixture was stirred under argon stream/vacuum and heated in a conventional glycol bath up to 90°C for 15–20 min, while 2–3 times 300–500 µl MeCN (p.a., in proportion to the quantity of water) and one time MeCN (puriss., absolute) were added for co-evaporation to give n.c.a. K[^{18}F]F-K.222-carbonate complex as a white semi-solid residue.

After addition of 6-12 mg (0.02–0.04 mmol) precursor **5**, dissolved in 300–400 µl DMF, to the K[^{18}F]F-K.222-carbonate complex, the dark green to brown reaction mixture was stirred in a closed vial under argon at 90°C for 25 min. After monitoring the reaction with HPLC and TLC, it was quenched by addition of 10 ml 0.1 M HCl. The resulting yellowish aqueous solution was passed through a C18 cartridge, methanol/water conditioned. Rinsing with 3 ml water, drying with air and elution of the product with 2 ml MeCN (puriss., absolute) into a Na_2SO_4-filled vial (1 g) resulted in 36–59% ($n = 9$) decay-corrected radiochemical yield of [^{18}F]1. *4-[^{18}F]Fluoro-benzaldehyde* ([^{18}F]**1**): TLC $R_f = 0.50$, 0.20 (C_6H_{12}/EtOAc, nP/$CHCl_3$); HPLC $t_R = 3.71$, 4.54 min (MeCN/NH_4AcO: 60/40, 50/50).

Representative procedure for reductive etherification with 4-fluoro-benzaldehyde to obtain 4-[^{18}F]fluoro-benzylethers [^{18}F]**3a**–**f** *(entry 3, Table 2)*. A solution of [^{18}F]**1** (0.7 ml, 41 MBq) in MeCN was retained from Na_2SO_4 by syringe. Then, 500 µl of *cis*-but-2-ene-1,4-diol (**2c**, 6 mmol) and 150 µl of a decaborane solution in MeCN (0.2 mol/l, 0.03 mmol) were added. The reaction mixture was heated in a conventional glycol bath up to 60°C and stirred in a closed vial under argon. For 2 h, the reaction was controlled by TLC every 30 min. After 100 min reaction time, a decay-corrected radiochemical yield of 45.8% of *cis-4-(4-[^{18}F]fluoro-benzyloxy)-but-2-en-1-ol* ([^{18}F]**3c**) was obtained. The product was identified and the yield was determined by TLC and HPLC in comparison to the non-radioactive compound **3c**.

Analytical data of radioactive by-products. 4-[^{18}F]Fluoro-benzyl alcohol ([^{18}F]**2a**). TLC $R_f = 0.18$, 0.05 (CH/EtOAc, nP/$CHCl_3$); HPLC $t_R = 2.79$, 3.22 min (MeCN/NH_4AcO: 60/40, 50/50). *4-[^{18}F]Fluoro-benzoic acid* ([^{18}F]**6**). TLC $R_f = 0.07$ (C_6H_{12}/EtOAc); HPLC $t_R = 1.86$, 1.90 min (MeCN/NH_4AcO: 60/40, 50/50).

Conclusion

4-[^{18}F]Fluoro-benzylethers were obtained from 4-[^{18}F]fluoro-benzaldehyde and primary and secondary alcohols via a one-step reductive coupling in MeCN mediated by $B_{10}H_{14}$. This procedure could serve as a new and easy access to ^{18}F-labelled benzylethers. However, radiochemical yields are dependent on the conditions applied and need to be optimized individually.

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