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Synthesis of ^{18}F-difluoromethylarenes using aryl boronic acids, ethyl bromofluoroacetate and [^{18}F]fluoride†

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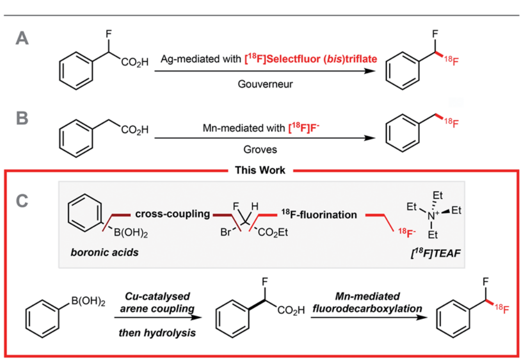
Herein, we report the radiosynthesis of ^{18}F-difluoromethylarenes *via* the assembly of three components, a boron reagent, ethyl bromofluoroacetate, and cyclotron-produced non-carrier added [^{18}F]fluoride. The two key steps are a copper-catalysed cross-coupling reaction, and a Mn-mediated ^{18}F-fluorodecarboxylation.

Introduction

Positron emission tomography (PET) is a molecular imaging technique that requires molecules labelled with a positron-emitting radionuclide. Fluorine-18 is a widely used positron emitting radionuclide in part due to its favourable decay properties, and the numerous clinical applications of 2-deoxy-2-[^{18}F]fluoro-D-glucose, a radiopharmaceutical prepared from [^{18}F]fluoride.[1] While radiochemists have in recent years focused their efforts on methods enabling ^{18}F-fluorination[2] and ^{18}F-trifluoromethylation of (hetero)arenes,[2,3] ^{18}F-difluoromethylation reactions have been less studied despite the importance of the CF_2H motif[4] in radioligand design for drug discovery programmes. In 2013, we reported a Ag(I)-mediated ^{18}F-fluorodecarboxylation of 2-fluoro-2-arylacetic acids with [^{18}F]Selectfluor (bis)triflate leading to [^{18}F]$ArCF_2H$.[5] Subsequently, we disclosed a Ag(I)-mediated halogen exchange reaction using [^{18}F]fluoride.[6] In 2016, a multi-step method to label [^{18}F]$ArCF_2H$ from aryl (pseudo)halides was disclosed by Ritter and co-workers.[7] Later, Liang and co-workers demonstrated that halogen exchange of benzyl (pseudo)halides with [^{18}F]fluoride followed by oxidative benzylic C–H fluorination with Selectfluor afforded [^{18}F]$ArCF_2H$ with improved molar activity.[8] Despite these advances, ^{18}F-difluoromethylation remains a challenging problem, especially for structurally complex targets. We initially considered adapting difluoromethylation reactions operating *via* C–H functionalisation.[9] Whilst this strategy is ideal for (hetero)arenes with innate reactivity leading to site-selective ^{18}F-difluoromethylation, substrates that are not reactive or too reactive would be unsuitable, thereby limiting applicability for radioligand synthesis. We therefore opted to develop a method using pre-functionalised aryl boron reagents; these are amenable to ^{18}F-fluorination and ^{18}F-trifluoromethylation,[10] so extension to ^{18}F-difluoromethylation was viewed as a valuable development. Building on our Ag(I)-mediated ^{18}F-fluorodecarboxylation towards [^{18}F]$ArCF_2H$,[5] a reaction requiring [^{18}F]Selectfluor (bis)triflate (Scheme 1A),[11] and on the Mn-mediated fluorodecarboxylation reported by Groves and co-workers, a reaction using [^{18}F]fluoride (Scheme 1B),[12,13] we envisaged that the ^{18}F-fluorodecarboxylation of 2-fluoro-2-arylacetic acids with [^{18}F]fluoride could afford [^{18}F]$ArCF_2H$. The beneficial effect of fluorine substitution on radical stabilisation would be favorable for this process.[5,14] This approach would require a robust method to cross-couple the aryl boron reagent with ethyl bromofluoroacetate followed by hydrolysis to



Scheme 1 (A) Ag(I)-mediated ^{18}F-fluorodecarboxylation with [^{18}F]Selectfluor (bis)triflate. (B) Mn(III)-mediated ^{18}F-fluorodecarboxylation with [^{18}F]fluoride towards [^{18}F]$ArCH_2F$. (C) Synthetic plan towards [^{18}F]$ArCF_2H$ from boron reagents and [^{18}F]fluoride.

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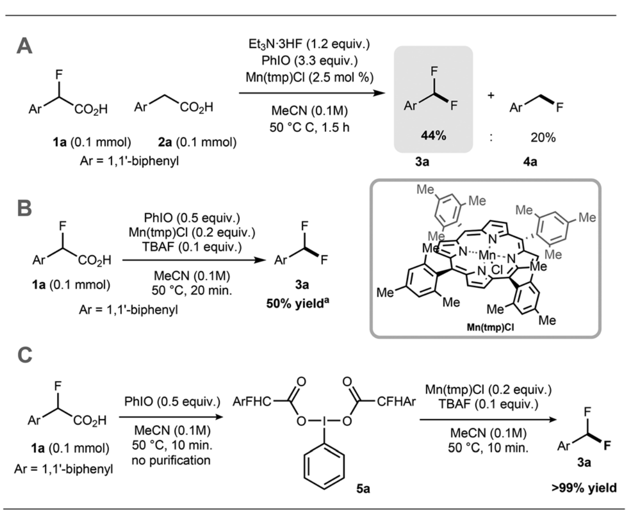
access the carboxylic acid precursor; we gave preference to a coupling methodology applying Cu-catalysis instead of Pd or Ni, a decision driven by guidelines for residual metals in (radio) pharmaceuticals.[15] The proposed strategy therefore relies on three readily available components, the boron reagent, ethyl bromofluoroacetate, and [^{18}F]fluoride (Scheme 1C).[16]

Results and discussion

Preliminary experiments demonstrated that the model fluoro-substituted carboxylic acid **1a** is amenable to fluorodecarboxylation with fluoride. When an equimolar mixture of **1a** and **2a** was treated with Mn(tmp)Cl (2.5 mol%), $Et_3N\cdot3HF$ (1.2 equiv.) and PhIO (3.3 equiv.) in MeCN at 50 °C, **3a** and **4a** were obtained in 44% and 20% yield, respectively. This result indicates that the fluorine-substituted precursor **1a** is more reactive than non-fluorinated **2a** towards fluorodecarboxylation (Scheme 2A). We verified that product **4a** did not undergo fluorination *via* C–H functionalisation under these conditions.[17] When an excess of **1a** (1 equiv.) was treated with TBAF (0.1 equiv.), PhIO (0.5 equiv.) and Mn(tmp)Cl (0.2 equiv.) in MeCN, **3a** was obtained in 50% yield (determined by ^{19}F NMR based on TBAF consumption) (Scheme 2B). Notably, quantitative fluoride incorporation was observed applying similar reaction conditions to the preformed hypervalent iodine complex **5a** (Scheme 2C). These preliminary data boded well for ^{18}F-labeling with [^{18}F]fluoride as the limiting reagent, and prompted the development of a robust protocol to convert aryl boron reagents into 2-fluoro-2-arylacetic acids.

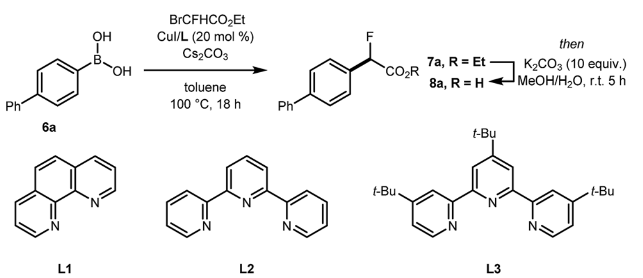
The cross-coupling of arylboronic acids and ethyl bromofluoroacetate has been reported using an excess of boron reagent under Ni or Pd catalysis, but has not been accomplished under Cu catalysis.[18–22] Initial studies reacting [1,1′-biphenyl]-4-ylboronic acid **6a** (2 equiv.) with ethyl bromofluoroacetate (1 equiv.) in the presence of 1,10-phenanthroline (**L1**, 20 mol%), CuI (20 mol%) and Cs_2CO_3 (2 equiv.) in dioxane (0.2 M) under N_2 at 100 °C afforded **7a** in 7% yield (Table 1, entry 1). When 2,2′:6′,2″-terpyridine (**L2**) was used as the ligand, the yield was significantly improved to 58% yield (Table 1, entry 2). When the stoichiometry was altered to 1 equivalent of **6a** and 2 equivalents of ethyl bromofluoroacetate in the presence of 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (**L3**) in toluene instead of dioxane **7a** was obtained in 63% yield (Table 1, entry 3). Further optimisation increasing the concentration led to the optimal protocol consisting of treating **6a** (0.1 mmol) with ethyl bromofluoroacetate (0.2 mmol), Cs_2CO_3 (0.2 mmol), CuI (20 mol%) and **L3** (20 mol%) in toluene (0.4 M) at 100 °C. Under these reaction conditions, **7a** was isolated in 82% yield (Table 1, entry 4). A one-pot sequence involving cross-coupling followed by hydrolysis with MeOH and aqueous K_2CO_3 afforded **8a** isolated in 75% yield (Table 1, entry 5). In the absence of ligand and/or copper source (Table 1, entries 6, 7), no product formation was observed. Furthermore, no reaction was observed with $CuCl_2$ (Table 1, entry 8), or when the reaction solvent was DMF or DMSO (Table 1, entry 9).

These optimised conditions gave access to a range of 2-fluoro-2-arylacetic acids (Scheme 3). The reaction is broad in scope and tolerates various functional groups, for example alkyl **8c–8e** and **8s–8u**, alkoxy **8f**, **8g**, trifluoromethyl **8h**, bromo **8p**, **8q**, iodo **8r**, and aldehyde **8i** all performed well. Substrates featuring heterocycles such as dibenzofuran **8j**, pyridine **8k**,



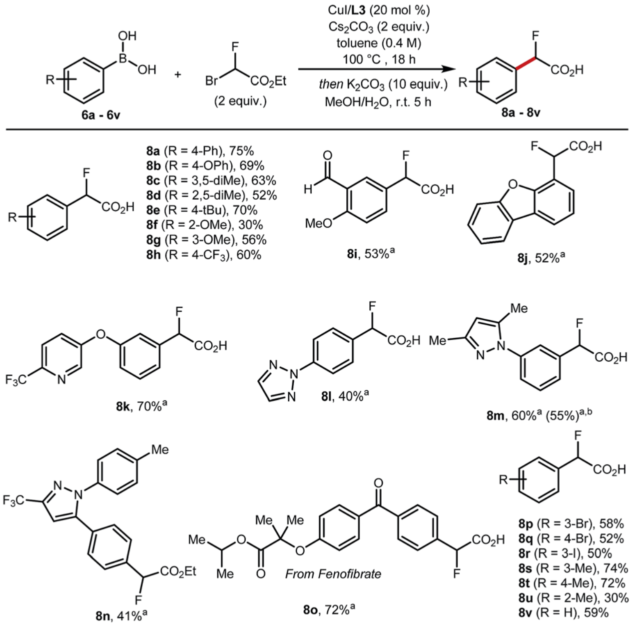
Scheme 2 (A) Competition studies evaluating the effect of fluorine substitution on fluorodecarboxylation. (B) Reaction with sub-stoichiometric fluoride. (C) Reaction of iodine(III) complex **5a** with sub-stoichiometric fluoride. Yields of isolated products. Mn(tmp)Cl = Mn(III) *meso*-tetra(2,4,6-trimethylphenyl)porphyrin chloride. [a]Yield determined by ^{19}F NMR using α,α,α-trifluorotoluene as internal standard.

Table 1 Optimisation of the Cu-catalysed cross-coupling of aryl boronic acid **6a** with ethyl bromofluoroacetate towards ester **7a** and the corresponding carboxylic acid **8a**[a]

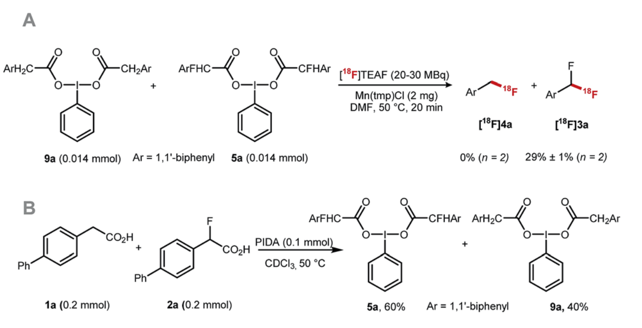


Entry	Solvent	Cu-source	Ligand	Product	Yield[b]
1[c]	Dioxane (0.2 M)	CuI	**L1**	**7a**	7%
2[c]	Dioxane (0.2 M)	CuI	**L2**	**7a**	58%
3	Toluene (0.2 M)	CuI	**L3**	**7a**	63%
4[d]	Toluene (0.4 M)	CuI	**L3**	**7a**	82%[e]
5[d]	Toluene (0.4 M)	CuI	**L3**	**8a**	75%[e,f]
6[d]	Toluene (0.4 M)	CuI	—	**7a**	0%
7[d]	Toluene (0.4 M)	—	—	**7a**	0%
8[d]	Toluene (0.4 M)	$CuCl_2$	**L2**	**7a**	0%
9[d]	DMF or DMSO (0.2 M)	CuI	**L3**	**7a**	0%

[a] Screening reactions performed on 0.1 mmol scale. [b] Yield determined by ^{19}F-NMR using α,α,α-trifluorotoluene as internal standard. [c] 2 equiv. of **6a** and 1 equiv. of ethyl bromofluoroacetate. [d] 1 equiv. of **6a**, and 2 equiv. of ethyl bromofluoroacetate. [e] Yield of isolated product. [f] One-pot procedure towards **8a**.



Scheme 3 Scope of Cu-catalysed cross-coupling. The reactions were performed on a 0.3 mmol scale. Conditions: CuI (20 mol%), L3 (20 mol%), aryl boronic acid (1 equiv.), ethyl bromofluoroacetate (2 equiv.), Cs_2CO_3 (2 equiv.), toluene (0.4 M) at 100 °C for 18 h then one-pot hydrolysis with K_2CO_3 (10 equiv.), $MeOH/H_2O$ (1 : 1), 5 h. [a]Hydrolysis performed as a subsequent step with K_2CO_3 (5 equiv.). [b]Reaction run on 5 mmol scale. All yields are of isolated products.

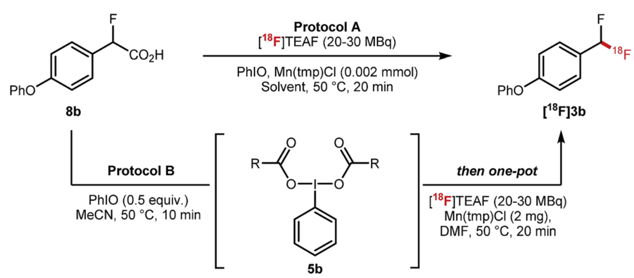


Scheme 4 (A) Competition experiment subjecting equimolar amount of **9a** and **5a** to [^{18}F]fluorodecarboxylation. (B) Competition experiment reacting equimolar amount of **1a** and **3a** with PIDA.

triazole **8l**, and pyrazoles **8m**, **8n** are also suitable coupling partners applying our optimised protocol affording the desired products in 40% to 70% yield. Additionally, this cross-coupling chemistry afforded **8o**, a derivative of fenofibrate, in 72% yield. Finally, the reaction was amenable to scale-up to 5 mmol (Scheme 3, **8m**).

The key ^{18}F-fluorodecarboxylation step was studied next (Table 2). We started our investigation applying protocol A that consists of reacting in one-pot **8b** (0.11 mmol) with PhIO (0.33 mmol), Mn(tmp)Cl (2 mg) and [^{18}F]TEAF (20–30 MBq) in MeCN (600 μL) at 50 °C; this protocol led to only traces of **[^{18}F]3b** (Table 2, entry 1). When the loading of PhIO (0.02 mmol) and MeCN (300 μL) was reduced, **[^{18}F]3b** was obtained in 6% ± 1% radiochemical conversion (RCC) (Table 2, entry 2). Similar results were obtained in DMF (Table 2, entry 3). Reducing the stoichiometry of **8b** led to a significant increase in RCC (22% ± 7%) (Table 2, entry 4). When applying protocol B which consists of mixing **8b** with PhIO, a process generating complex **5b**, prior to the addition of Mn(tmp)Cl (2 mg) and [^{18}F]TEAF (20–30 MBq)

Table 2 Optimisation studies for the [^{18}F]fluorodecarboxylation of **8b**

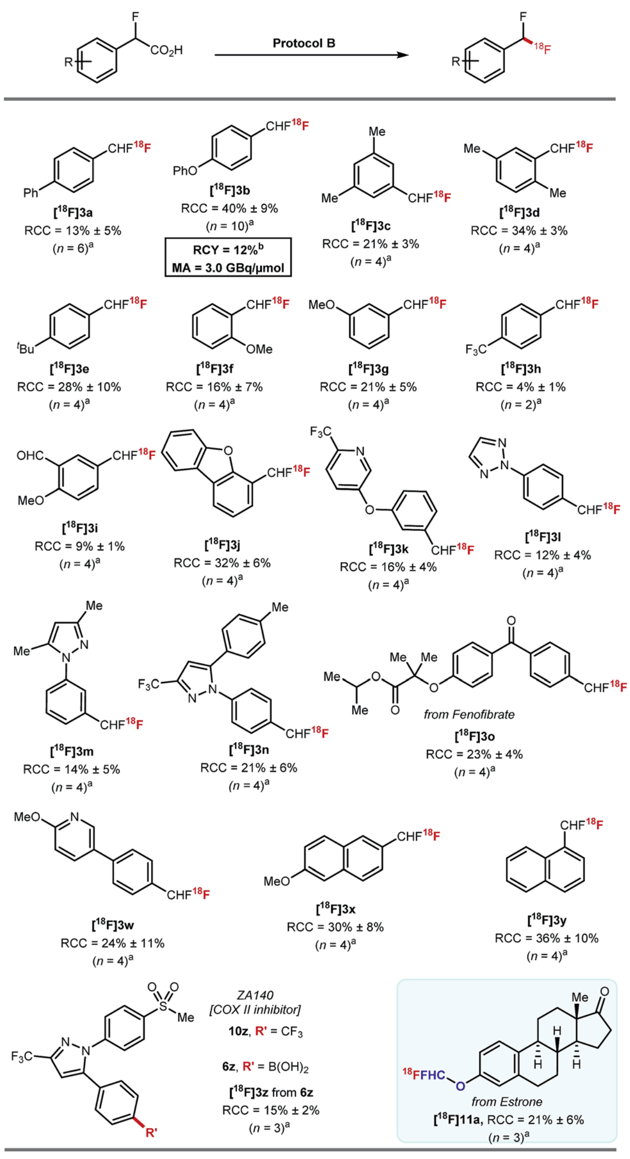


Entry	Starting material (mmol)	Protocol	Solvent	PhIO (mmol)	RCC[a,b] ($n = 2$)
1	**8b** (0.11)	A	MeCN[c]	0.33	3% ± 1%
2	**8b** (0.11)	A	MeCN[d]	0.02	6% ± 1%
3	**8b** (0.11)	A	DMF[d]	0.02	7% ± 2%
4	**8b** (0.055)	A	DMF[d,e]	0.02	22% ± 7%
5	**5b (0.014)**	**B**	**DMF**[d,e]	—	**40% ± 10%**[f]
6	**5b** (0.014)	B	DMF[d,e]	—	0% ± 0%[g]
7	**8b** (0.014)	A	MeCN[d]	0.02	0% ± 0%[h]
8	**5b** (0.014)	B	DMF[d,e]	—	0% ± 0%[i]

[a] Radiochemical conversion. [b] n = number of reactions. [c] 600 μL of MeCN. [d] 300 μL of MeCN. [e] MeCN removed at 100 °C after dispensing [^{18}F]TEAF. [f] ($n = 10$). [g] Reaction temperature = 100 °C. [h] Catalyst is Mn(tmp)OTs. [i] No Mn Catalyst.

and DMF (300 μL), a drastic improvement was observed, and **[^{18}F]3b** was obtained in 40% ± 10% RCC ($n = 10$) (Table 2, entry 5). When the reaction was run at 100 °C, the formation of **[^{18}F]3b** was not observed (Table 2, entry 6). No ^{18}F-labelled product was obtained when Mn(tmp)OTs was used as catalyst, or in the absence of Mn(tmp)Cl (Table 2, entries 7 and 8).

The fluorine substituent is advantageous for ^{18}F-fluorodecarboxylation as demonstrated with a competition experiment subjecting equimolar amount of pre-formed hypervalent iodine(III) complexes **9a** and **5a** to ^{18}F-fluorination with [^{18}F]TEAF, Mn(tmp)Cl at 50 °C in DMF. Difluoromethylarene **[^{18}F]3a** was the only product observed in the crude reaction mixture (Scheme 4A). Furthermore, an additional competition experiment



Scheme 5 Scope of [^{18}F]fluorodecarboxylation applying protocol B: [a]$ArCHFCO_2H$ (0.028 mmol), PhIO (0.5 equiv.), MeCN (1 mL), 50 °C, 10 min then addition of [^{18}F]TEAF (20–30 MBq) Mn(tmp)Cl (2 mg), DMF (300 μL), 50 °C, 20 min. [b]$ArCHFCO_2H$ (0.014 mmol), PhIO (0.5 equiv.), MeCN (1 mL), 50 °C, 10 min then addition of [^{18}F]Mn(tmp)F (841 MBq) DCE (300 μL), 60 °C, 20 min.

showed that the iodine(III) complex **5a** is formed preferentially to **9a** (Scheme 4B). Fluorine substitution therefore facilitates the two steps of the process leading to fluorodecarboxylation.

Protocol B was applied to a selection of arenes using 20–30 MBq of [^{18}F]fluoride (Scheme 5). Ether, alkyl, aldehyde, ketone, pyridine, triazole, pyrazole, dibenzofuran motifs were all tolerated. The highest RCCs were obtained for electron rich arenes. **[^{18}F]3o** derived from a boronic acid analogue of fenofibrate was successfully labelled in 23% ± 4% ($n = 4$). The boronic acid derivative of the COX-II inhibitor ZA140 **6z** was transformed into the labelled difluoromethylated product **[^{18}F]3z** in 15% ± 2% RCC ($n = 3$).

The ^{18}F-fluorodecarboxylation of **5b** performed with 841 MBq of [^{18}F]fluoride required further optimisation. For this experiment, [^{18}F]fluoride was captured on an anion exchange cartridge then eluted using a solution of Mn(tmp)Cl in methanol, resulting in 85% ^{18}F-recovery. Lowering the starting material stoichiometry to 0.007 mmol of **5b** and changing the solvent from DMF to DCE afforded the cartridge-purified **[^{18}F]3b** in a decay corrected RCY of 12% and a molar activity of 3.0 GBq μmol^{-1} in a total synthesis time of 30 minutes.[23]

Pleasingly, ^{18}F-fluorodecarboxylation also enabled access to the [^{18}F]$ArOCF_2H$ motif. The only known route to label this motif was reported by our group, and required a multi-step synthesis of the ArOCHFCl precursors which were themselves prepared from $ArOCHFCO_2H$.[24] The reaction of estrone (1.0 equiv.) with ethyl bromofluoroacetate (1.5 equiv.) and K_2CO_3 (2.5 equiv.) in DMF (2 mL) at room temperature followed by a subsequent hydrolysis with aqueous NaOH (2.5 equiv.) in 1 : 1 H_2O/Et_2O afforded the precursor required for fluorodecarboxylation. ^{18}F-labelling applying protocol B afforded **[^{18}F]11a** in 21% ± 6% RCC ($n = 3$).

Conclusions

In summary, a novel method was developed to transform aryl boronic acids to [^{18}F]$ArCF_2H$. Prior to labelling, the cross-coupling with ethyl bromofluoroacetate was accomplished under Cu catalysis followed by *in situ* hydrolysis. The radioisotope ^{18}F is then introduced in the last step applying a Mn-mediated fluorodecarboxylation with readily available [^{18}F]fluoride. This study has unveiled three key features for this last transformation. Firstly, the fluorine substituent on the carboxylic acid precursor is advantageous for fluorodecarboxylation; secondly, the benefit of preforming the hypervalent iodine complex prior to ^{18}F-fluorination; and thirdly, we have established that Mn-mediated fluorodecarboxylation enables access to [^{18}F]$ArOCF_2H$ in addition to [^{18}F]$ArCF_2H$.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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17 See the ESI.†

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