EDGE ARTICLE

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

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Herein, we report the radiosynthesis of 18F-difluoromethylarenes *via* the assembly of three components, a boron reagent, ethyl bromofluoroacetate, and cyclotron-produced non-carrier added [18F]fluoride. The two key steps are a copper-catalysed cross-coupling reaction, and a Mn-mediated 18F-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-[18F] fluoro-D-glucose, a radiopharmaceutical prepared from [18F]fluoride.[1] While radiochemists have in recent years focused their efforts on methods enabling 18F-fluorination[2] and 18F-trifluoromethylation of (hetero)arenes,[2,3] 18F-difluoromethylation reactions have been less studied despite the importance of the CF2H motif[4] in radioligand design for drug discovery programmes. In 2013, we reported a Ag(I)-mediated 18F-fluorodecarboxylation of 2-fluoro-2-arylacetic acids with [18F] Selectfluor (bis)triflate leading to [18F]ArCF2H.[5] Subsequently, we disclosed a Ag(I)-mediated halogen exchange reaction using [18F]fluoride.[6] In 2016, a multi-step method to label [18F]ArCF2H 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 [18F]fluoride followed by oxidative benzylic C–H fluorination with Selectfluor afforded [18F]ArCF2H with improved molar activity.[8] Despite these advances, 18F-difluoromethylation remains a challenging problem, especially for structurally complex targets. We initially considered adapting difluoromethylation reactions operating *via* C–H

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functionalisation.[9] Whilst this strategy is ideal for (hetero)arenes with innate reactivity leading to site-selective 18F-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 18F-fluorination and 18F-trifluoromethylation,[10] so extension to 18F-difluoromethylation was viewed as a valuable development. Building on our Ag(I)-mediated 18F-fluorodecarboxylation towards [18F]ArCF2H,[5] a reaction requiring [18F]Selectfluor (bis)triflate (Scheme 1A),[11] and on the Mn-mediated fluorodecarboxylation reported by Groves and co-workers, a reaction using [18F]fluoride (Scheme 1B),[12,13] we envisaged that the 18F-fluorodecarboxylation of 2-fluoro-2-arylacetic acids with [18F]fluoride could afford [18F] ArCF2H. 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
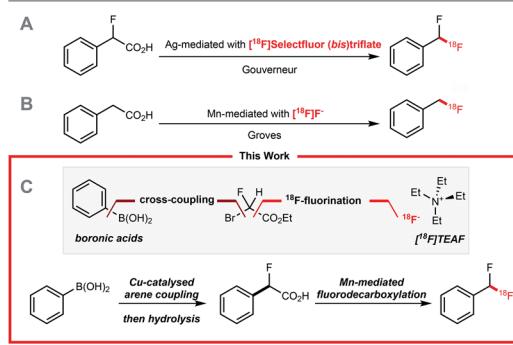
Scheme 1 (A) Ag(I)-mediated 18F-fluorodecarboxylation with [18F] Selectfluor (bis)triflate. (B) Mn(III)-mediated 18F-fluorodecarboxylation with [18F]fluoride towards [18F]ArCH2F. (C) Synthetic plan towards [18F] ArCF2H from boron reagents and [18F]fluoride.
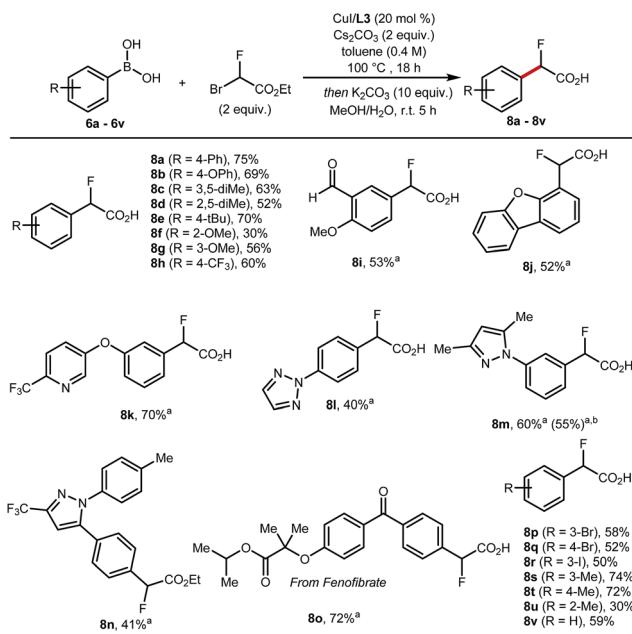
Scheme 3 Scope of Cu-catalysed cross-coupling. The reactions were performed on a 0.3 mmol scale. Conditions: CuI (20 mol%), L3 (20 mol%), aryl boronic acid (1 equiv.), ethyl bromofluoroacetate (2 equiv.), Cs$_2$CO$_3$ (2 equiv.), toluene (0.4 M) at 100 °C for 18 h then one-pot hydrolysis with K$_2$CO$_3$ (10 equiv.), MeOH/H$_2$O (1 : 1), 5 h. [a]Hydrolysis performed as a subsequent step with K$_2$CO$_3$ (5 equiv.). [b]Reaction run on 5 mmol scale. All yields are of isolated products.

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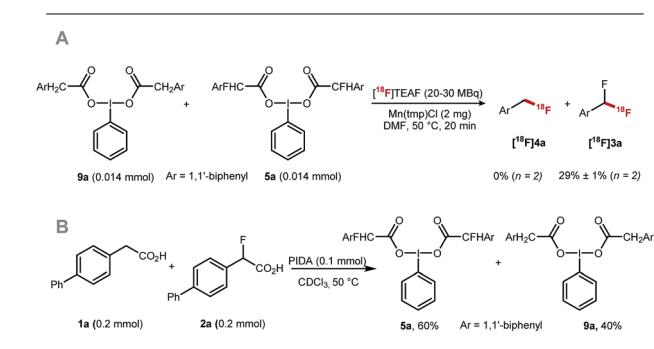
Scheme 4 (A) Competition experiment subjecting equimolar amount of **9a** and **5a** to [18F]fluorodecarboxylation. (B) Competition experiment reacting equimolar amount of **1a** and **3a** with PIDA.

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 [18F]-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 [18F]TEAF (20–30 MBq) in MeCN (600 μL) at 50 °C; this protocol led to only traces of [18F]3b (Table 2, entry 1). When the loading of PhIO (0.02 mmol) and MeCN (300 μL) was reduced, [18F]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 [18F]TEAF (20–30 MBq)

Table 2 Optimisation studies for the [18F]fluorodecarboxylation of **8b**
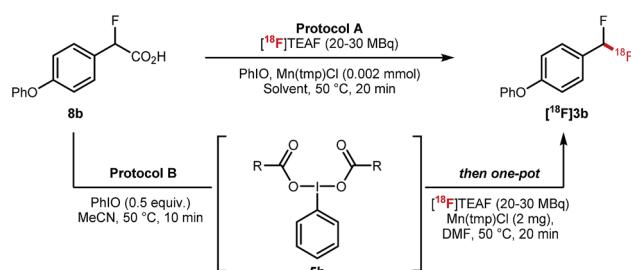
Entry	Starting material (mmol)	Protocol	Solvent	PhIO (mmol)	RCC[a,b] ($n = 2$)
1	**8b** (0.11)	A	MeCN[c]	0.33	3% ± 1%
2	**8b** (0.11)	A	MeCN[d]	0.02	6% ± 1%
3	**8b** (0.11)	A	DMF[d]	0.02	7% ± 2%
4	**8b** (0.055)	A	DMF[d,e]	0.02	22% ± 7%
5	**5b** (0.014)	B	DMF[d,e]	—	**40% ± 10%**[f]
6	**5b** (0.014)	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 [18F]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. Difluoromethylarylene [^{18}F]3a was the only product observed in the crude reaction mixture (Scheme 4A). Furthermore, an additional competition experiment

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$_2$H 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$_2$H.[24] The reaction of estrone (1.0 equiv.) with ethyl bromofluoroacetate (1.5 equiv.) and K$_2$CO$_3$ (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$_2$O/Et$_2$O 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$_2$H. Prior to labelling, the cross-coupling with ethyl bromofluoroacetate was accomplished under Cu catalysis followed by in situ hydrolysis. The radio-isotope ^{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$_2$H in addition to [^{18}F]ArCF$_2$H.

Conflicts of interest

There are no conflicts to declare.
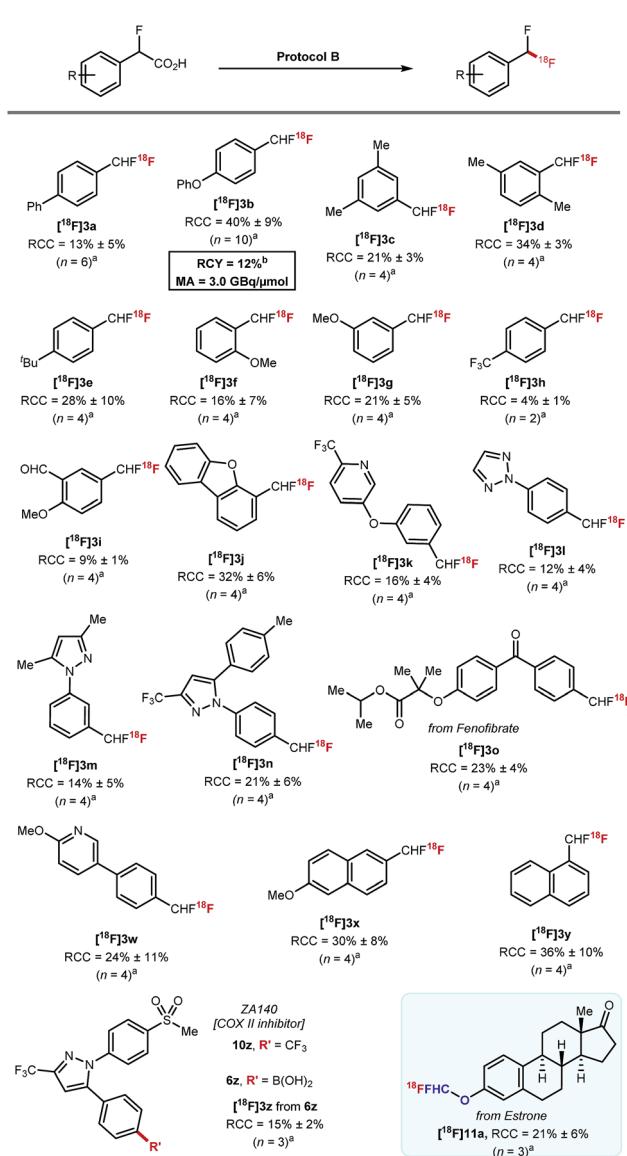
Scheme 5 Scope of [^{18}F]fluorodecarboxylation applying protocol B: [a]ArCHFCO$_2$H (0.028 mmol), PhIO (0.5 equiv.), MeCN (1 mL), 50 °C, 10 min then addition of [^{18}F]TEAF (20–30 MBq) Mn(tmp)Cl (2 mg), DMF (300 μL), 50 °C, 20 min. [b]ArCHFCO$_2$H (0.014 mmol), PhIO (0.5 equiv.), MeCN (1 mL), 50 °C, 10 min then addition of [^{18}F]Mn(tmp)F (841 MBq) DCE (300 μL), 60 °C, 20 min.

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