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Synthesis of ^{18}F -difluoromethylarenes using aryl boronic acids, ethyl bromofluoroacetate and $[^{18}\text{F}]$ 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 $[^{18}\text{F}]$ 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- $[^{18}\text{F}]$ fluoro-D-glucose, a radiopharmaceutical prepared from $[^{18}\text{F}]$ fluoride.¹ While radiochemists have in recent years focused their efforts on methods enabling ^{18}F -fluorination² and ^{18}F -trifluoromethylation of (hetero)arenes,^{2,3} ^{18}F -difluoromethylation reactions have been less studied despite the importance of the CF_2H motif⁴ 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 $[^{18}\text{F}]$ Selectfluor (bis)triflate leading to $[^{18}\text{F}]\text{ArCF}_2\text{H}$.⁵ Subsequently, we disclosed a Ag(I)-mediated halogen exchange reaction using $[^{18}\text{F}]$ fluoride.⁶ In 2016, a multi-step method to label $[^{18}\text{F}]\text{ArCF}_2\text{H}$ 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 $[^{18}\text{F}]$ fluoride followed by oxidative benzylic C–H fluorination with Selectfluor afforded $[^{18}\text{F}]\text{ArCF}_2\text{H}$ 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 $[^{18}\text{F}]\text{ArCF}_2\text{H}$,⁵ a reaction requiring $[^{18}\text{F}]$ Selectfluor (bis)triflate (Scheme 1A),¹¹ and on the Mn-mediated fluorodecarboxylation reported by Groves and co-workers, a reaction using $[^{18}\text{F}]$ fluoride (Scheme 1B),^{12,13} we envisaged that the ^{18}F -fluorodecarboxylation of 2-fluoro-2-arylacetic acids with $[^{18}\text{F}]$ fluoride could afford $[^{18}\text{F}]\text{ArCF}_2\text{H}$. 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 $[^{18}\text{F}]$ Selectfluor (bis)triflate. (B) Mn(III)-mediated ^{18}F -fluorodecarboxylation with $[^{18}\text{F}]$ fluoride towards $[^{18}\text{F}]\text{ArCH}_2\text{F}$. (C) Synthetic plan towards $[^{18}\text{F}]\text{ArCF}_2\text{H}$ from boron reagents and $[^{18}\text{F}]$ 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 [¹⁸F]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%), Et₃N·3HF (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 ¹⁹F 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 ¹⁸F-labeling with [¹⁸F]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 Cs₂CO₃ (2 equiv.) in dioxane (0.2 M) under N₂ 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''-tr-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), Cs₂CO₃ (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 K₂CO₃ 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 CuCl₂ (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**,

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 ¹⁹F-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**.



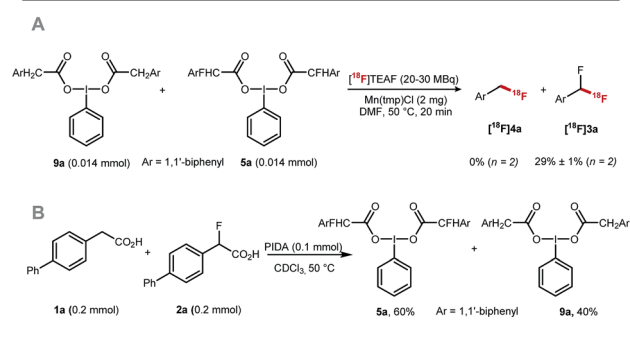
Scheme 2 (A) Competition studies evaluating the effect of fluorine substitution on fluorodecarboxylation. (B) Reaction with sub-stoichiometric fluoride. (C) Reaction of iodine(III) complex **5a** with sub-stoichiometric fluoride. Yields of isolated products. Mn(tmp)Cl = Mn(III) meso-tetra(2,4,6-trimethylphenyl)porphyrin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





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.), Cs₂CO₃ (2 equiv.), toluene (0.4 M) at 100 °C for 18 h then one-pot hydrolysis with K₂CO₃ (10 equiv.), MeOH/H₂O (1 : 1), 5 h. ^aHydrolysis performed as a subsequent step with K₂CO₃ (5 equiv.). ^bReaction 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 μ L), a drastic improvement was observed, and [^{18}F]**3b** was obtained in $40\% \pm 10\%$ 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)OTf 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

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 $23\% \pm 4\%$ ($n = 4$). The boronic acid derivative of the COX-II inhibitor ZA140 **6z** was transformed into the labelled difluoromethylated product [^{18}F]**3z** in $15\% \pm 2\%$ 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 $3.0\text{ GBq } \mu\text{mol}^{-1}$ in a total synthesis time of 30 minutes.²³

Pleasingly, ^{18}F -fluorodecarboxylation also enabled access to the [^{18}F]ArOCF₂H 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 ArOCHFCl precursors which were themselves prepared from ArOCHFCl precursors.²⁴ The reaction of estrone (1.0 equiv.) with ethyl bromofluoroacetate (1.5 equiv.) and K₂CO₃ (2.5 equiv.) in DMF (2 mL) at room temperature followed by a subsequent hydrolysis with aqueous NaOH (2.5 equiv.) in 1 : 1 H₂O/Et₂O afforded the precursor required for fluorodecarboxylation. ^{18}F -labelling applying protocol B afforded [^{18}F]**11a** in $21\% \pm 6\%$ RCC ($n = 3$).

Conclusions

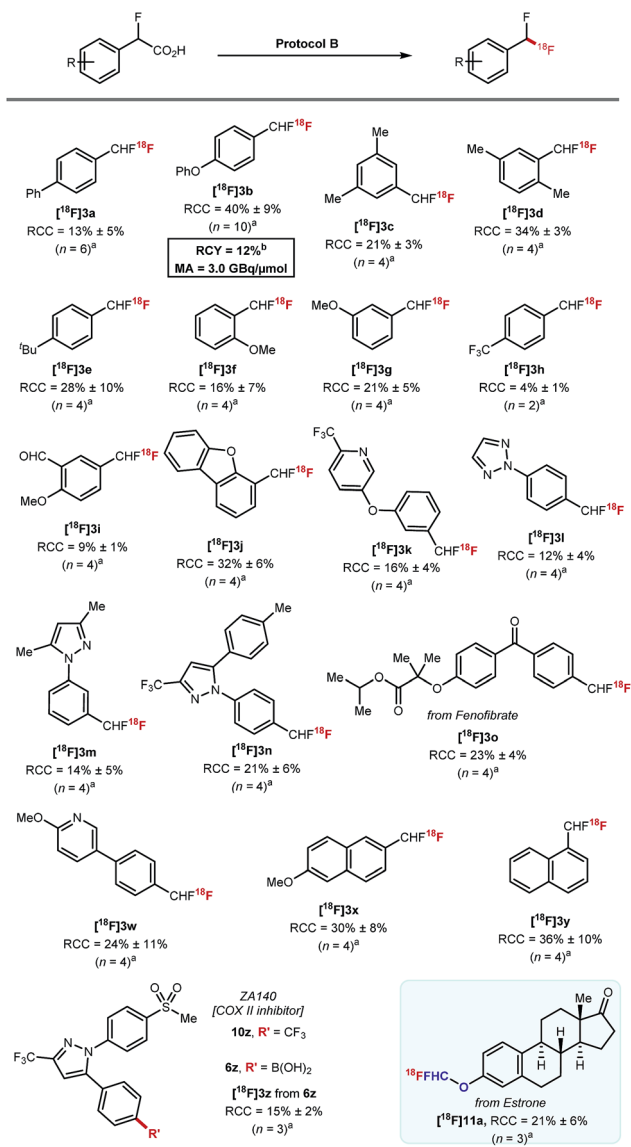
In summary, a novel method was developed to transform aryl boronic acids to [^{18}F]ArCF₂H. Prior to labelling, the cross-coupling with ethyl bromofluoroacetate was accomplished under Cu catalysis followed by *in situ* hydrolysis. The radioisotope ^{18}F is then introduced in the last step applying a 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 performing the hypervalent iodine complex prior to ^{18}F -fluorination; and thirdly, we have established that Mn-mediated fluorodecarboxylation enables access to [^{18}F]ArOCF₂H in addition to [^{18}F]ArCF₂H.

Conflicts of interest

There are no conflicts to declare.

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Scheme 5 Scope of [^{18}F]fluorodecarboxylation applying protocol B: ^aArCHFCO₂H (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 μ L), 50°C , 20 min. ^bArCHFCO₂H (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 μ L), 60°C , 20 min.



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