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

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Herein, we report the radiosynthesis of  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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.<sup>1</sup> While radiochemists have in recent years focused their efforts on methods enabling  $^{18}\text{F}$ -fluorination<sup>2</sup> and  $^{18}\text{F}$ -trifluoromethylation of (hetero)arenes,<sup>2,3</sup>  $^{18}\text{F}$ -difluoromethylation reactions have been less studied despite the importance of the  $\text{CF}_2\text{H}$  motif<sup>4</sup> in radioligand design for drug discovery programmes. In 2013, we reported a Ag(I)-mediated  $^{18}\text{F}$ -fluorodecarboxylation of 2-fluoro-2-arylacetic acids with  $[^{18}\text{F}]$  Selectfluor (bis)triflate leading to  $[^{18}\text{F}]\text{ArCF}_2\text{H}$ .<sup>5</sup> Subsequently, we disclosed a Ag(I)-mediated halogen exchange reaction using  $[^{18}\text{F}]$  fluoride.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup> Despite these advances,  $^{18}\text{F}$ -difluoromethylation remains a challenging problem, especially for structurally complex targets. We initially considered adapting difluoromethylation reactions operating *via* C–H

functionalisation.<sup>9</sup> Whilst this strategy is ideal for (hetero)arenes with innate reactivity leading to site-selective  $^{18}\text{F}$ -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  $^{18}\text{F}$ -fluorination and  $^{18}\text{F}$ -trifluoromethylation,<sup>10</sup> so extension to  $^{18}\text{F}$ -difluoromethylation was viewed as a valuable development. Building on our Ag(I)-mediated  $^{18}\text{F}$ -fluorodecarboxylation towards  $[^{18}\text{F}]\text{ArCF}_2\text{H}$ ,<sup>5</sup> a reaction requiring  $[^{18}\text{F}]$  Selectfluor (bis)triflate (Scheme 1A),<sup>11</sup> and on the Mn-mediated fluorodecarboxylation reported by Groves and co-workers, a reaction using  $[^{18}\text{F}]$  fluoride (Scheme 1B),<sup>12,13</sup> we envisaged that the  $^{18}\text{F}$ -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.<sup>5,14</sup> 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  $^{18}\text{F}$ -fluorodecarboxylation with  $[^{18}\text{F}]$  Selectfluor (bis)triflate. (B) Mn(III)-mediated  $^{18}\text{F}$ -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.<sup>15</sup> The proposed strategy therefore relies on three readily available components, the boron reagent, ethyl bromofluoroacetate, and [<sup>18</sup>F]fluoride (Scheme 1C).<sup>16</sup>

## 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<sub>3</sub>N·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.<sup>17</sup> 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 <sup>19</sup>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 <sup>18</sup>F-labeling with [<sup>18</sup>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.<sup>18–22</sup> 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<sub>2</sub>CO<sub>3</sub> (2 equiv.) in dioxane (0.2 M) under N<sub>2</sub> 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''-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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>CO<sub>3</sub> 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<sub>2</sub> (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**<sup>a</sup>



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. <sup>d</sup>Yield determined by <sup>19</sup>F NMR using  $\alpha,\alpha,\alpha$ -trifluorotoluene as internal standard.



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

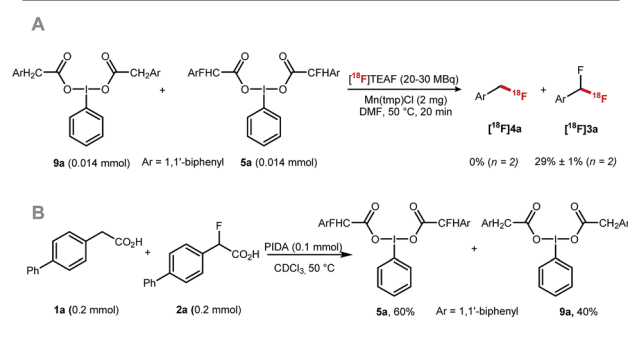
<sup>a</sup> Screening reactions performed on 0.1 mmol scale. <sup>b</sup> Yield determined by <sup>19</sup>F-NMR using  $\alpha,\alpha,\alpha$ -trifluorotoluene as internal standard. <sup>c</sup> 2 equiv. of **6a** and 1 equiv. of ethyl bromofluoroacetate. <sup>d</sup> 1 equiv. of **6a**, and 2 equiv. of ethyl bromofluoroacetate. <sup>e</sup> Yield of isolated product. <sup>f</sup> 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<sub>2</sub>CO<sub>3</sub> (2 equiv.), toluene (0.4 M) at 100 °C for 18 h then one-pot hydrolysis with K<sub>2</sub>CO<sub>3</sub> (10 equiv.), MeOH/H<sub>2</sub>O (1 : 1), 5 h. <sup>a</sup>Hydrolysis performed as a subsequent step with K<sub>2</sub>CO<sub>3</sub> (5 equiv.). <sup>b</sup>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 [<sup>18</sup>F]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 <sup>18</sup>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 [<sup>18</sup>F]TEAF (20–30 MBq) in MeCN (600 μL) at 50 °C; this protocol led to only traces of [<sup>18</sup>F]**3b** (Table 2, entry 1). When the loading of PhIO (0.02 mmol) and MeCN (300 μL) was reduced, [<sup>18</sup>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 [<sup>18</sup>F]TEAF (20–30 MBq)

**Table 2** Optimisation studies for the [<sup>18</sup>F]fluorodecarboxylation of **8b**

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

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







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