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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 -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}F Selectfluor (bis)triflate leading to ^{18}F ArCF₂H.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 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 ^{18}F fluoride followed by oxidative benzylic C–H fluorination with Selectfluor afforded ^{18}F ArCF₂H 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 ArCF₂H,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 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 ^{18}F -fluorodecarboxylation with ^{18}F Selectfluor (bis)triflate. (B) Mn(III)-mediated ^{18}F -fluorodecarboxylation with ^{18}F fluoride towards ^{18}F ArCH₂F. (C) Synthetic plan towards ^{18}F ArCF₂H 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 [¹⁸F]fluoride (Scheme 1C).¹⁶

Results and discussion

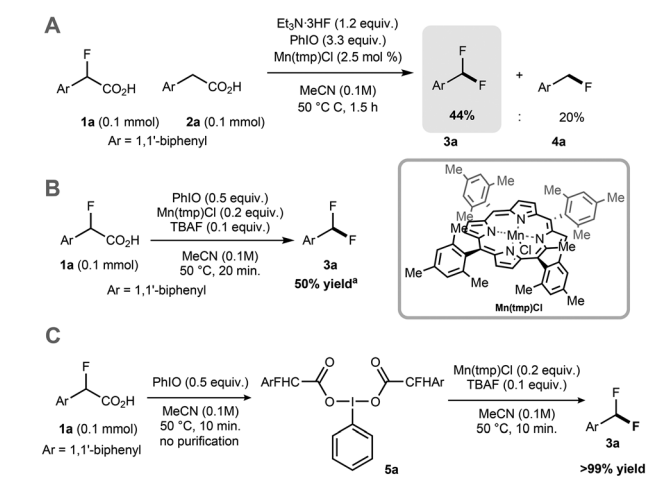
Preliminary experiments demonstrated that the model fluoro-substituted carboxylic acid **1a** is amenable to fluorodecarboxylation with fluoride. When an equimolar mixture of **1a** and **2a** was treated with Mn(tmp)Cl (2.5 mol%), Et₃N·3HF (1.2 equiv.) and PhIO (3.3 equiv.) in MeCN at 50 °C, **3a** 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''-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



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.

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%

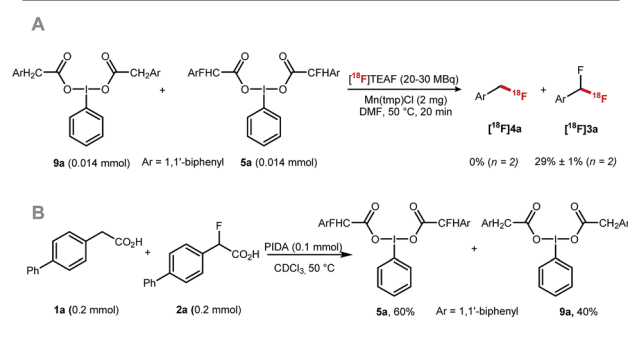
^a Screening reactions performed on 0.1 mmol scale. ^b Yield determined by ¹⁹F-NMR using α,α,α -trifluorotoluene as internal standard. ^c 2 equiv. of **6a** and 1 equiv. of ethyl bromofluoroacetate. ^d 1 equiv. of **6a**, and 2 equiv. of ethyl bromofluoroacetate. ^e Yield of isolated product. ^f One-pot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





Scheme 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.), $\text{MeOH}/\text{H}_2\text{O}$ (1 : 1), 5 h. ^aHydrolysis performed as a subsequent step with K_2CO_3 (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 $[\text{F}^{18}]\text{fluorodecarboxylation}$. (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 ^{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), $[\text{F}^{18}]\text{TEAF}$ (20–30 MBq) and $\text{Mn}(\text{tmp})\text{Cl}$ (2 mg) in MeCN (600 μL) at 50°C ; this protocol led to only traces of $[\text{F}^{18}]\text{3b}$ (Table 2, entry 1). When the loading of PhIO (0.02 mmol) and MeCN (300 μL) was reduced, $[\text{F}^{18}]\text{3b}$ 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 $\text{Mn}(\text{tmp})\text{Cl}$ (2 mg) and $[\text{F}^{18}]\text{TEAF}$ (20–30 MBq)

Table 2 Optimisation studies for the $[\text{F}^{18}]\text{fluorodecarboxylation}$ 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 $[\text{F}^{18}]\text{TEAF}$. ^f (n = 10). ^g Reaction temperature = 100°C . ^h Catalyst is $\text{Mn}(\text{tmp})\text{OTf}$. ⁱ No Mn Catalyst.



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References

- (a) S. M. Ametamey, M. Honer and P. A. Schubiger, *Chem. Rev.*, 2008, **108**, 1501; (b) P. M. Matthews, E. A. Rabiner, J. Passchier and R. N. Gunn, *Br. J. Clin. Pharmacol.*, 2012, **73**, 175.
- (a) P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem., Int. Ed.*, 2008, **47**, 8998; (b) Z. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, M. Hopkinson, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2012, **51**, 6733; (c) B. H. Rotstein, N. A. Stephenson, N. Vasdev and S. H. Liang, *Nat. Commun.*, 2014, **5**, 4365; (d) E. L. Cole, M. N. Stewart, R. Littich, R. Hoareau and P. J. H. Scott, *Curr. Top. Med. Chem.*, 2014, **14**, 875; (e) M. Tredwell, S. M. Preshlock, N. J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Genicot and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2014, **53**, 7751; (f) A. V. Mossine, A. F. Brooks, K. J. Makaravage, J. M. Miller, N. Ichiishi, M. S. Sanford and P. J. H. Scott, *Org. Lett.*, 2015, **17**, 5780; (g) C. N. Neumann, J. M. Hooker and T. Ritter, *Nature*, 2016, **534**, 369; (h) S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719; (i) M. K. Narayanam, G. Ma, P. A. Champagne, K. N. Houk and J. M. Murphy, *Angew. Chem., Int. Ed.*, 2017, **56**, 13006; (j) X. Deng, J. Rong, L. Wang, N. Vasdev, L. Zhang, L. Josephson and S. Liang, *Angew. Chem., Int. Ed.*, 2018, DOI: 10.1002/anie.201805501.
- (a) M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nat. Chem.*, 2013, **5**, 941; (b) D. van der Born, C. Sewing, J. D. M. Herscheid, A. D. Windhorst, R. V. Orru and D. J. Vugts, *Angew. Chem., Int. Ed.*, 2014, **53**, 11046; (c) T. Rühl, W. Raffique, V. T. Lien and P. J. Riss, *Chem. Commun.*, 2014, **50**, 6056.
- (a) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (b) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2017, **60**, 797; (c) C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang and S. J. Lippard, *J. Am. Chem. Soc.*, 2017, **139**, 9325; (d) N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822; (e) D. Rageot, T. Bohnacker, A. Melone, J. B. Langlois, C. Borsari, P. Hillmann, A. M. Sele, F. Beaufile, M. Zvelebil, P. Hebeisen, W. Löscher, J. Burke, D. Fabbro and M. P. Wymann, *J. Med. Chem.*, 2018, **61**, 10084; (f) G. W. Rewcastle, S. A. Gamage, J. U. Flanagan, R. Frederick, W. A. Denny, B. C. Baguley, P. Kestell, R. Singh, J. D. Kendall, E. S. Marshall, C. L. Lill, W.-J. Lee, S. Kolekar, C. M. Buchanan, S. M. F. Jamieson and P. R. Shepherd, *J. Med. Chem.*, 2011, **54**, 7105; (g) F. Jeppsson, S. Eketjäll, J. Janson, S. Karlström, S. Gustavsson, L. L. Olsson, A. C. Radesäter, B. Ploeger, G. Cebers, K. Kolmodin, B. M. Swahn, S. von Berg, T. Bueters and J. Fäلتing, *J. Biol. Chem.*, 2012, **287**, 41245.
- S. Mizuta, I. S. Stenhagen, M. O'Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin and V. Gouverneur, *Org. Lett.*, 2013, **15**, 2648.
- S. Verhoog, L. Pfeifer, T. Khotavivattana, S. Calderwood, T. L. Collier, K. Wheelhouse, M. Tredwell and V. Gouverneur, *Synlett*, 2016, **27**, 25.
- H. Shi, A. Braun, L. Wang, S. H. Liang, N. Vasdev and T. Ritter, *Angew. Chem., Int. Ed.*, 2016, **55**, 10786.
- G. Yuan, F. Wang, N. A. Stephenson, L. Wang, B. H. Rotstein, N. Vasdev, P. Tang and S. H. Liang, *Chem. Commun.*, 2017, **53**, 126.
- (a) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 1494; (b) T. T. Tung, S. B. Christensen and J. Nielsen, *Chem.-Eur. J.*, 2017, **23**, 18125; (c) R. Sakamoto, H. Kashiwagi and K. Maruoka, *Org. Lett.*, 2017, **19**, 5126.
- T. C. Wilson, T. Cailly and V. Gouverneur, *Chem. Soc. Rev.*, 2018, **47**, 6990.
- H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2010, **49**, 6821.
- X. Huang, W. Liu, J. M. Hooker and J. T. Groves, *Angew. Chem., Int. Ed.*, 2015, **54**, 5241.
- X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker and J. T. Groves, *J. Am. Chem. Soc.*, 2014, **136**, 6842.
- W. R. Dolbier, *Chem. Rev.*, 1996, **96**, 1557.
- Source: <http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>, accessed on 20/09/18.
- Our attempts to assemble one-pot the aryl boron reagent, ethyl bromofluoroacetate and [¹⁸F]fluoride were not fruitful. Details in ESI.†
- See the ESI.†
- Y. Wu, H.-R. Zhang, Y.-X. Cao, Q. Lan and X.-S. Wang, *Org. Lett.*, 2016, **18**, 5564.
- C. Guo, X. Yue and F. L. Qing, *Synthesis*, 2010, **11**, 1837.
- Y. M. Su, G. S. Feng, Z. Y. Wang, Q. Lan and X. S. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 6003.
- T. Xia, L. He, Y. A. Liu, J. F. Hartwig and X. Liao, *Org. Lett.*, 2017, **19**, 2610.
- A. Fahandj-Sadi and R. J. Lundgren, *Synlett*, 2017, **28**, 2886.
- All radiochemical yields (RCYs) are decay corrected.
- T. Khotavivattana, S. Verhoog, M. Tredwell, L. Pfeifer, S. Calderwood, K. Wheelhouse, T. L. Collier and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2015, **54**, 9991.

