Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Open Access Article. Published on 29 Qunxa Garablu 2019. Downloaded on 19/07/2025 1:02:11 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Check for updates

Cite this: *Chem. Sci.*, 2019, **10**, 3237

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 15th November 2018
Accepted 28th January 2019

DOI: 10.1039/c8sc05096a

rsc.li/chemical-science

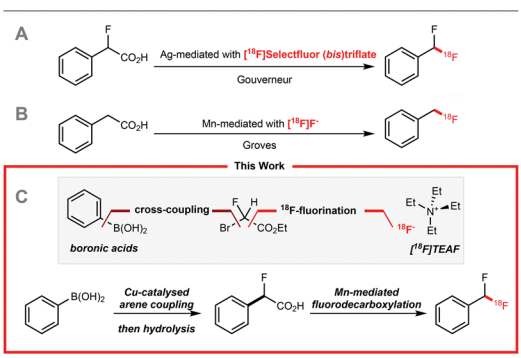
Synthesis of ^{18}F-difluoromethylarenes using aryl boronic acids, ethyl bromofluoroacetate and [^{18}F]fluoride†

Jeroen B. I. Sap,[a] Thomas C. Wilson,[a] Choon Wee Kee,[a] Natan J. W. Straathof,[a] Christopher W. am Ende,[b] Paramita Mukherjee,[b] Lei Zhang,[b] Christophe Genicot[c] and Véronique Gouverneur *[a]

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.

[a]Chemistry Research Laboratory, Department of Chemistry, Oxford University, OX1 3TA Oxford, UK. E-mail: veronique.gouverneur@chem.ox.ac.uk; Tel: +44 (0)1865 285002

[b]Pfizer Inc., Medicine Design, Eastern Point Road, Groton, Connecticut 06340, and 1 Portland Street, Cambridge, Massachusetts 02139, USA

[c]Global Chemistry, UCB New Medicines, UCB Biopharma Sprl, 1420 Braine-L'Alleud, Belgium

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8sc05096a

Open Access Article. Published on 29 Qunxa Garablu 2019. Downloaded on 19/07/2025 1:02:11 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

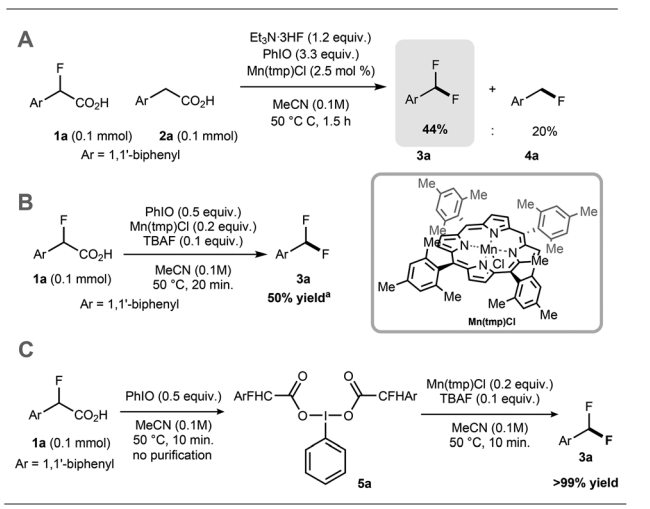
access the carboxylic acid precursor; we gave preference to a coupling methodology applying Cu-catalysis instead of Pd or Ni, a decision driven by guidelines for residual metals in (radio) pharmaceuticals.[15] The proposed strategy therefore relies on three readily available components, the boron reagent, 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%), $Et_3N\cdot 3HF$ (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 ^{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.

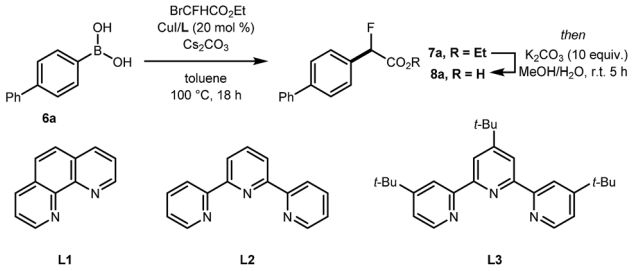
The cross-coupling of arylboronic acids and ethyl bromofluoroacetate has been reported using an excess of boron reagent under Ni or Pd catalysis, but has not been accomplished under Cu catalysis.[18–22] Initial studies reacting [1,1′-biphenyl]-4-ylboronic acid **6a** (2 equiv.) with ethyl bromofluoroacetate (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.

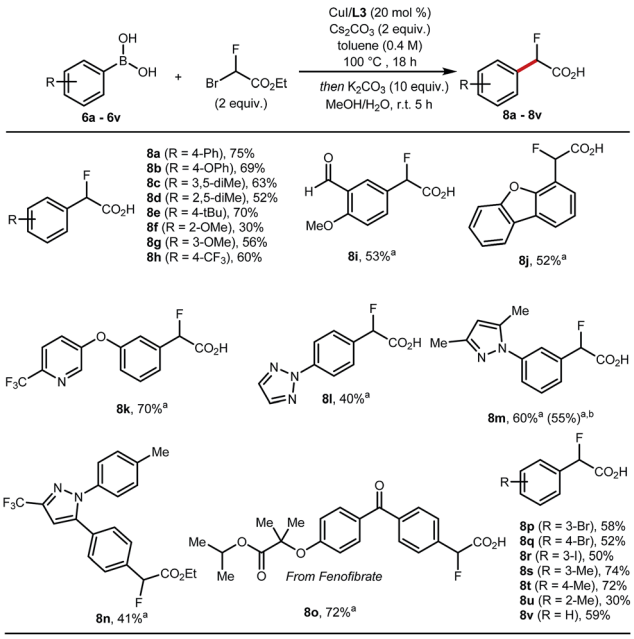
Table 1 Optimisation of the Cu-catalysed cross-coupling of aryl boronic acid **6a** with ethyl bromofluoroacetate towards ester **7a** and the corresponding carboxylic acid **8a**[a]



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%

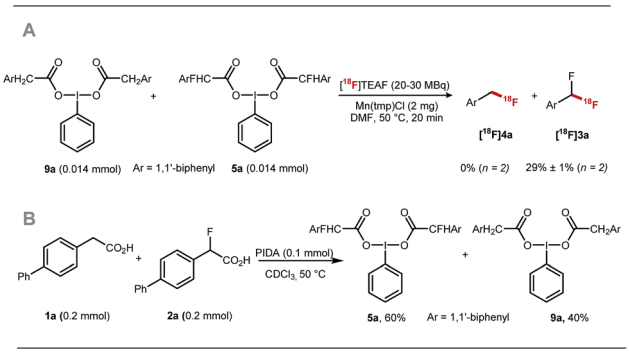
[a] Screening reactions performed on 0.1 mmol scale. [b] Yield determined by ^{19}F-NMR using α,α,α-trifluorotoluene as internal standard. [c] 2 equiv. of **6a** and 1 equiv. of ethyl bromofluoroacetate. [d] 1 equiv. of **6a**, and 2 equiv. of ethyl bromofluoroacetate. [e] Yield of isolated product.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

Open Access Article. Published on 29 Qunxa Garablu 2019. Downloaded on 19/07/2025 1:02:11 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



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.

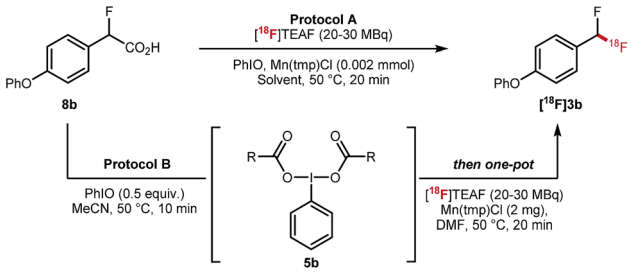
triazole **8l**, and pyrazoles **8m**, **8n** are also suitable coupling partners applying our optimised protocol affording the desired products in 40% to 70% yield. Additionally, this cross-coupling chemistry afforded **8o**, a derivative of fenofibrate, in 72% yield. Finally, the reaction was amenable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



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.

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**



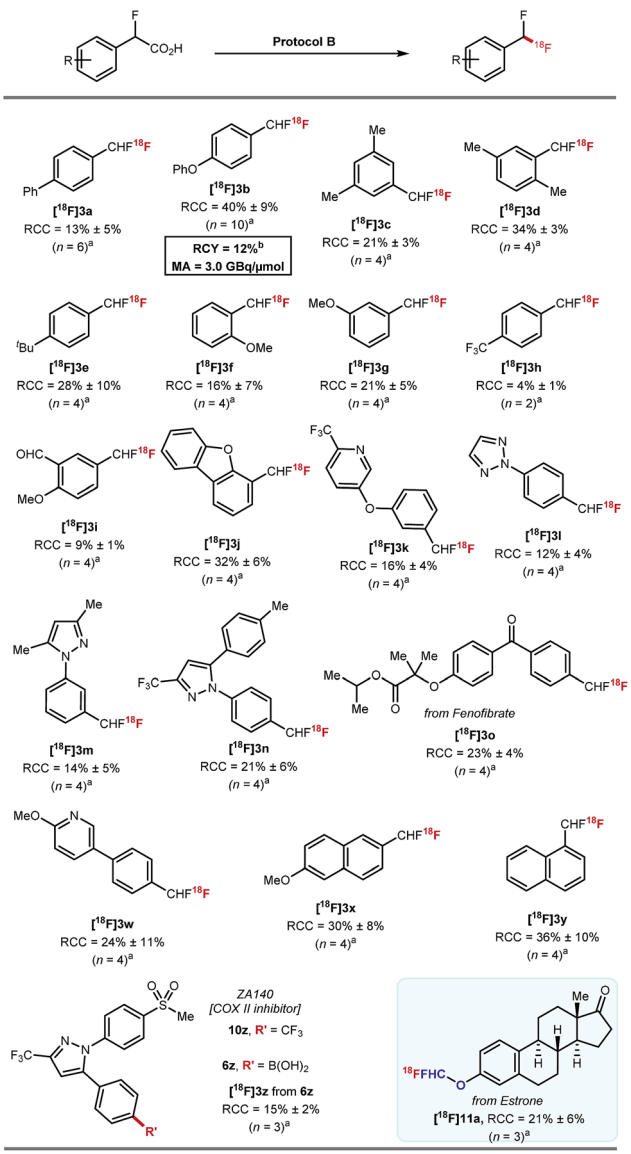
Entry	Starting material (mmol)	Protocol	Solvent	PhIO (mmol)	RCC^{a,b} ($n = 2$)
1	**8b** (0.11)	A	MeCN^c	0.33	3% ± 1%
2	**8b** (0.11)	A	MeCN^d	0.02	6% ± 1%
3	**8b** (0.11)	A	DMF^d	0.02	7% ± 2%
4	**8b** (0.055)	A	DMF^{d,e}	0.02	22% ± 7%
5	**5b (0.014)**	**B**	**DMF**^{d,e}	—	**40% ± 10%**^{f}
6	**5b**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

Open Access Article. Published on 29 Qunxa Garablu 2019. Downloaded on 19/07/2025 1:02:11 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

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 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.



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.

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 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$_2$H in addition to [^{18}F]ArCF$_2$H.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Pfizer, and the Engineering and Physical Sciences Research Council (EP/N509711/1) (studentship

Open Access Article. Published on 29 Qunxa Garablu 2019. Downloaded on 19/07/2025 1:02:11 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

to J. B. I. S.). We also acknowledge the financial support from the Cancer Research UK (C5255/A16466) (T. C. W.), The Agency for Science, Technology and Research (A*STAR, Singapore) (fellowship to C. W. K.), and UCB (N. J. W. S).

References

1 (*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.

2 (*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.

3 (*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. Rafique, V. T. Lien and P. J. Riss, *Chem. Commun.*, 2014, **50**, 6056.

4 (*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. Beaufils, 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. Eketjall, 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. Fälting, *J. Biol. Chem.*, 2012, **287**, 41245.

5 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.

6 S. Verhoog, L. Pfeifer, T. Khotavivattana, S. Calderwood, T. L. Collier, K. Wheelhouse, M. Tredwell and V. Gouverneur, *Synlett*, 2016, **27**, 25.

7 H. Shi, A. Braun, L. Wang, S. H. Liang, N. Vasdev and T. Ritter, *Angew. Chem., Int. Ed.*, 2016, **55**, 10786.

8 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.

9 (*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.

10 T. C. Wilson, T. Cailly and V. Gouverneur, *Chem. Soc. Rev.*, 2018, **47**, 6990.

11 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.

12 X. Huang, W. Liu, J. M. Hooker and J. T. Groves, *Angew. Chem., Int. Ed.*, 2015, **54**, 5241.

13 X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker and J. T. Groves, *J. Am. Chem. Soc.*, 2014, **136**, 6842.

14 W. R. Dolbier, *Chem. Rev.*, 1996, **96**, 1557.

15 Source: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html, accessed on 20/09/18.

16 Our attempts to assemble one-pot the aryl boron reagent, ethyl bromofluoroacetate and [^{18}F]fluoride were not fruitful. Details in ESI.†

17 See the ESI.†

18 Y. Wu, H.-R. Zhang, Y.-X. Cao, Q. Lan and X.-S. Wang, *Org. Lett.*, 2016, **18**, 5564.

19 C. Guo, X. Yue and F. L. Qing, *Synthesis*, 2010, **11**, 1837.

20 Y. M. Su, G. S. Feng, Z. Y. Wang, Q. Lan and X. S. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 6003.

21 T. Xia, L. He, Y. A. Liu, J. F. Hartwig and X. Liao, *Org. Lett.*, 2017, **19**, 2610.

22 A. Fahandej-Sadi and R. J. Lundgren, *Synlett*, 2017, **28**, 2886.

23 All radiochemical yields (RCYs) are decay corrected.

24 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.