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One-pot synthesis of high molar activity 6- ^{18}F fluoro-L-DOPA by Cu-mediated fluorination of a BPin precursor†

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A one-pot two-step synthesis of 6- ^{18}F fluoro-L-DOPA (^{18}F FDOPA) has been developed involving Cu-mediated radiofluorination of a pinacol boronate ester precursor. The method is fully automated, provides ^{18}F FDOPA in good activity yield (104 ± 16 mCi, $6 \pm 1\%$), excellent radiochemical purity ($>99\%$) and high molar activity (3799 ± 2087 Ci mmol^{-1}), $n = 3$, and has been validated to produce the radiotracer for human use.

6- ^{18}F Fluoro-L-DOPA (^{18}F FDOPA, **3**) is a diagnostic radiopharmaceutical for positron emission tomography (PET) imaging.¹ The first ^{18}F FDOPA PET study of the human brain was reported in 1983² and, since its introduction, ^{18}F FDOPA PET imaging has been used to image Parkinson's disease,³ brain tumors,⁴ and focal hyperinsulinism of infancy.⁵

Despite the numerous important applications in molecular imaging, ^{18}F FDOPA PET remains underutilized because of synthetic challenges associated with accessing the radiotracer for clinical use.^{1b} Chief amongst these is the need to radiofluorinate a highly electron rich catechol ring in the presence of an amino acid. Historically this has been accomplished with an organostannane or organomercury precursor *via* electrophilic aromatic substitution ($\text{S}_{\text{E}}\text{Ar}$) with ^{18}F F₂ or ^{18}F acetyl hypofluorite (Fig. 1a).⁶ However, the production and handling of these reagents requires specialized equipment that is not

widely accessible. Furthermore, the site- and chemoselectivities of $\text{S}_{\text{E}}\text{Ar}$ reactions are typically modest, and the ^{18}F FDOPA produced using electrophilic methods generally has low molar activity.^{1b}

Due to the inherent limitations of electrophilic radiofluorination reactions, a synthesis of ^{18}F FDOPA that uses nucleophilic ^{18}F fluoride has long been in demand. In contrast to the electrophilic reagents described above, ^{18}F fluoride is readily available in high molar activity and is routinely handled in radiochemistry production facilities. However, the electronic mismatch between the nucleophilic $^{18}\text{F}^-$ and the electron rich catechol ring has hampered efforts to develop an operationally simple nucleophilic synthesis of high molar activity ^{18}F FDOPA. The typical approach involves nucleophilic radiofluorination of a benzaldehyde precursor with an appropriate leaving group (*e.g.* $-\text{F}$, $-\text{NO}_2$, $-\text{N}^+\text{Me}_3$).^{1b,7} The ^{18}F -labelled aldehyde intermediate is then converted to the ester *via* a Dakin oxidation. Finally, hydrolysis of the ester with concentrated HI or HBr generates ^{18}F FDOPA (Fig. 1b). While this approach yields ^{18}F FDOPA in good yields and molar activity, it is confined to certain synthesis modules (or manual syntheses) because of the requirements for automation of multiple steps after the introduction of ^{18}F and the use of corrosive reagents during the deprotection step. Finally, the complexity of this process results in multiple potential fail points (both chemical and mechanical) during automated radiosynthesis.

There thus remains a need for a one-pot, two-step (fluorination + deprotection) synthesis of ^{18}F FDOPA from nucleophilic ^{18}F fluoride that is high yielding, uses milder reagents, and is easily automated. While such a method has eluded radiochemists to date, fluorine-18 radiochemistry has undergone a renaissance in recent years.⁸ For instance, hypervalent iodine reagents,⁹ organoborons,¹⁰ organostannanes,¹¹ Ni/Pd complexes,¹² and phenols¹³ have recently been introduced as precursors for nucleophilic radiofluorination of electron rich arenes. While we and others have used a number of these approaches to synthesize ^{18}F FDOPA in proof-of-concept

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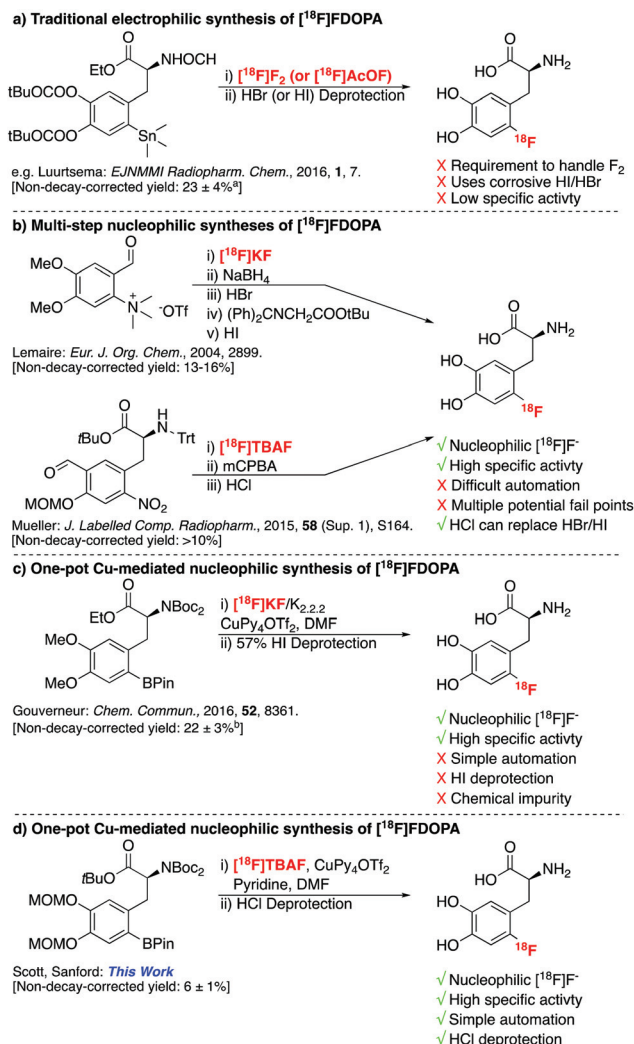


Fig. 1 Radiosyntheses of [¹⁸F]FDOPA and motivation for this work.

^aBased on [¹⁸F]F₂ in reactor; ^bdoses not reformulated for clinical use.

studies,^{9,10d,11,12b,14} a method that is compliant with current Good Manufacturing Practice (cGMP) and validated for production of human doses has yet to be reported. For example, the full-scale automated synthesis of a number of radiotracers from BPin precursors, including [¹⁸F]FDOPA, was reported by Gouverneur (Fig. 1c).^{10d} However, since [¹⁸F]FDOPA was not the main focus of that paper, extensive development work was not done and in its published form the method gives doses of [¹⁸F]FDOPA contaminated with a chemical impurity that disqualify it from clinical use at the University of Michigan. Moreover, the requirement to introduce air into the radiofluorination reaction is difficult to automate given that radiochemistry synthesis modules are typically kept under an inert atmosphere and closed to the environment. The use of 57% HI in the deprotection step is also problematic as it is highly corrosive to the valves and lines employed in automated synthesis modules.

To address the outstanding need in the PET radiochemistry community for ready access to [¹⁸F]FDOPA, in this communi-

cation we describe a new one-pot, two-step synthesis of the radiotracer from a BPin precursor, and validate it for production of clinical doses (Fig. 1d). Precursor **1** was selected because it is commercially available (ABX Advanced Biochemicals), and has MOM and Boc protecting groups that enable mild deprotection with HCl. Our radiofluorination methodology does not require the introduction of air,^{10b} simplifying automation. Lastly, we have also developed a new approach for purification and reformulation of [¹⁸F]FDOPA that utilizes hydrophilic interaction liquid chromatography (HILIC). HILIC is an alternative technique to HPLC for separating particularly polar compounds (for an overview of the method, see:¹⁵). HILIC employs traditional polar stationary phases (e.g. silica, amino or cyano), but mobile phases used are similar to reversed-phase HPLC and, in this case, it provided [¹⁸F]FDOPA in high chemical, radiochemical and enantiomeric purity.

To develop a synthesis of [¹⁸F]FDOPA (**3**), we elected to use our recently developed Cu-mediated radiofluorination of organoboron precursors,^{10b} which was expected to simplify automation as, unlike the method described above it does not require air, and began by conducting the automated radiofluorination of BPin **1** using a TRACERLab FX_{FN} synthesis module (Table 1). [¹⁸F]Fluoride from the cyclotron was trapped on a bicarbonate-preconditioned QMA cartridge, eluted into the reactor with an aqueous solution of 10 mg mL⁻¹ KOTf/0.1 mg mL⁻¹ K₂CO₃ (0.5 mL) and azeotropically dried with MeCN (1 mL). For initial proof-of-concept, manual radiofluorination was conducted using our standard labelling protocol (**1** (4 μmol), Cu(OTf)₂ (20 μmol) and pyridine (500 μmol) in 1 mL DMF for 20 min at 110 °C). This provided protected [¹⁸F]FDOPA (**2**) in 49 ± 7% radiochemical yield (RCY_s) (entry 1). This process was readily translated to an automated process on the synthesis module to provide **2** in 38 ± 4% RCY (entry 2).

We next focused on optimizing the radiofluorination step. Our prior work has shown that both the ¹⁸F⁻ processing technique and the order/temperature of reagent addition were both key to reaction outcome in related systems.^{10ef} Thus, we used these as starting points for optimizing the [¹⁸F]FDOPA

Table 1 Optimization of the Labeling of **1**

Entry ^a	[¹⁸ F]XF	RCY _s [§]
1 ^b	[¹⁸ F]KF	49 ± 7%
2 ^c	[¹⁸ F]KF	38 ± 4%
3 ^c	[¹⁸ F]TBAF	55 ± 13%

^a Conditions: **1BPin** (4 μmol), Cu(OTf)₂ (20 μmol), and pyridine (500 μmol) in DMF at 4 mM concentration of the BPin precursor in DMF, [¹⁸F]XF, 110 °C, 20 min. ^b Manual syntheses. ^c Automated syntheses.

synthesis. In our previous work, the dissolution of $^{18}\text{F}^-$ before heating the fluorination reaction proved critical to avoid competing reactions (e.g. protodeborylation and/or hydroxydeborylation) that competitively consume **1**.^{10e,f} To address this issue, we developed an alternate eluent in order to facilitate rapid dissolution of $^{18}\text{F}^-$. Given the greater solubility of tetrabutylammonium (TBA^+) and Cs^+ cations relative to K^+ in DMF, without loss of anion exchange properties, we settled on an aqueous eluent consisting of 15 mg mL^{-1} tetrabutylammonium triflate (TBAOTf) and 0.2 mg mL^{-1} Cs_2CO_3 (0.5 mL), as a replacement for KOTf and K_2CO_3 , respectively. This eluent gave good recovery of $^{18}\text{F}^-$ from the QMA, and improved the RCY of **2** to $55 \pm 13\%$ (entry 3).

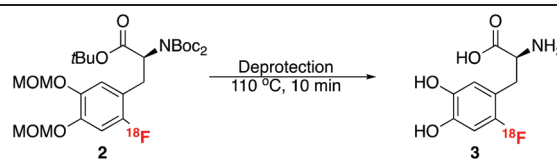
With an optimized fluorination in hand, we next investigated the deprotection step. Historically, deprotection steps to generate ^{18}F FDOPA have most commonly utilized concentrated HI or HBr to remove methoxy protecting groups.^{1b} While such reagents can be used with automated synthesis modules, they are highly corrosive and greatly reduce the lifetime of lines and valves in the synthesis module. We therefore sought to employ a milder acid for deprotection, and reasoned that HCl should be both compatible with our synthesis module and adequate to deprotect the methoxymethyl ether (MOM) and *tert*-butyl ester groups of **2** (Table 2). Initial attempts to treat **2** in the fluorination reaction mixture with 12 N HCl resulted in significant decomposition and minimal ($<1\%$) ^{18}F FDOPA (**3**) (entry 1). We hypothesized that the decomposition could be due to the presence of Cu(II) salts, which could promote numerous potential side reactions.¹⁶ As such, we examined the addition of ascorbic acid during the deprotection, as this is known to reduce the Cu(II) to Cu(I) . Gratifyingly, this resulted in a dramatic enhancement in the yield of the deprotection step, providing ^{18}F FDOPA in $84 \pm 8\%$ RCY (entry 2). Intermediate **2** could also be purified by SPE prior to deprotection using a modified synthesis module. This resulted in an even cleaner deprotection that proceeded in $>99\%$ RCY (entry 3).

We next sought to develop a robust semi-preparative chromatography system that would enable purification of ^{18}F FDOPA from reactants and potential by-products (e.g. OH-DOPA and

H-DOPA). Prior reports utilized reverse-phase HPLC with C18 columns, but we have found these to be unsatisfactory due to the close retention times of ^{18}F FDOPA and both OH-DOPA and H-DOPA by-products which result from competing hydroxy- and proto-deborylation, respectively. We therefore switched to HILIC purification and evaluated several different columns (see ESI†). The best results were achieved using a Phenomenex Luna NH_2 $5 \mu\text{m}$ column and an eluent with a high organic content: $75\% \text{ MeCN}$ incl. 10 mM KOAc buffered with acetic acid to $\text{pH}: 5.0\text{--}5.5$ (near the hypothetical isoelectric point of FDOPA).[¶] This system enables adequate separation of FDOPA, OH-DOPA and H-DOPA using both semi-preparative and analytical columns (see ESI†). PET radiotracers purified using MeCN -based HILIC eluents require reformulation into an injectable vehicle such as ethanolic saline. Reverse phase SPE is typically used for reformulation of small molecule radiopharmaceuticals using, for example, C18 or Oasis HLB cartridges, but this is not possible with ^{18}F FDOPA due to its hydrophilicity. We thus employed a HILIC Strata NH_2 cartridge for reformulation. We found trapping/release efficiency for ^{18}F FDOPA of 70% and 75% for the 100 mg and 200 mg cartridges, respectively, and selected the 200 mg cartridges for routine use.

Finally, we automated the one-pot, two-step synthesis of ^{18}F FDOPA using a TRACERLab FX_{FN} synthesis module and validated the synthesis for cGMP production of doses for clinical use. To simplify routine automation, we changed the Cu source from Cu(OTf)_2 to the less hygroscopic $\text{Cu(pyridine)}_4(\text{OTf})_2$. This Cu source has been used to radiofluorinate BPin esters by Gouverneur but, as stated above, that method requires the introduction of air into the radiofluorination reaction which is difficult to automate.^{10a,d} To negate this issue, we adapted $\text{Cu(Py)}_4(\text{OTf})_2$ for use in our chemistry, which is compatible with the inert atmosphere of the TRACERLab synthesis module,^{10b} by maintaining the same relative ratio of substrate: copper: pyridine (**1BPin** ($4 \mu\text{mol}$), Cu ($20 \mu\text{mol}$), and pyridine ($420 \mu\text{mol}$)). Radiofluorination and deprotection then proceeded as described above. The reaction mixture was diluted with MeCN (3 mL) and purified by semi-preparative HILIC. The peak corresponding to ^{18}F FDOPA ($t_{\text{R}} \sim 22\text{--}23 \text{ min}$, see Fig. S2† in ESI for a typical trace) was collected in 100 mL MeCN and this solution was passed through the HILIC Strata NH_2 cartridge to trap the radiotracer. Following trapping and rinsing with US Pharmacopeia (USP) grade ethanol ($2\text{--}3 \text{ mL}$) to remove residual MeCN , ^{18}F FDOPA was eluted from the cartridge with 0.9% saline, USP (10 mL) to produce doses formulated for injection. The final drug product was dispensed into a septum-sealed, sterile, pyrogen-free glass vial through a $0.22 \mu\text{m}$ sterile filter (Millex GV) to afford formulated doses of ^{18}F FDOPA ($104 \pm 16 \text{ mCi}$, $n = 3$). The total synthesis time was approximately 110 min from end-of-bombardment, and the activity yield (AY) was $6 \pm 1\%$, based upon 1.8 Ci of ^{18}F fluoride. Radiochemical purity (RCP) was $>99\%$ and molar activity was $3799 \pm 2087 \text{ Ci mmol}^{-1}$. Doses were submitted for full quality control (QC) testing to validate the method, and all doses met or exceeded release criteria for

Table 2 Optimization of the deprotection of ^{18}F **2**

		
Entry ^a	Deprotection	RCY ^{b§}
1	12 M HCl	Decomp.
2	$12 \text{ M HCl} + 0.25 \text{ M ascorbic acid}$	$84 \pm 8\%$
3 ^c	$12 \text{ M HCl} + 0.25 \text{ M ascorbic acid}$	$>99\%$

^a Conditions: $\text{HCl} \pm$ ascorbic acid, $110 \text{ }^\circ\text{C}$, 10 min . ^b RCY represents transformation of **2** $\rightarrow$ **3**. ^c **2** purified by SPE prior to deprotection.

Table 3 Validation data for cGMP synthesis of [^{18}F]FDOPA (**3**)

QC test	Specifications	Result ($n = 3$)
Radioactivity conc.	≥ 10 mCi per batch	104 ± 16 mCi
FDOPA conc.	≤ 5 $\mu\text{g mL}^{-1}$	0.69 ± 0.47 $\mu\text{g mL}^{-1}$
Molar activity	≥ 500 Ci mmol^{-1}	3799 ± 2087 Ci mmol^{-1}
Radiochemical purity	$> 90\%$	99.7 ± 0.3
Radiochemical identity	$\text{RRT}^a = 0.9\text{--}1.1$	1.02 ± 0.002
Enantiomeric purity	$\geq 95\%$ L-FDOPA	$> 99\%$
Visual inspection	Clear, colorless, no ppt	Pass
pH	4.5–7.5	5.5 ± 0
Radionuclidic identity	$T_{1/2} = 105\text{--}115$ min	112 ± 2 min
Residual TBA $^+$	≤ 260 $\mu\text{g mL}^{-1}$ by Dragendorff reagent	< 260 $\mu\text{g mL}^{-1}$
Residual DMF	≤ 880 ppm	106 ± 56 ppm
Residual MeCN	≤ 410 ppm	179 ± 78 ppm
Residual Cu	≤ 34 ppm	0.11 ± 0.02 ppm
Filter membrane integrity	≥ 50 psi	56 ± 1 psi
Bacterial endotoxins	≤ 2.00 EU b mL^{-1}	< 2.00 EU b mL^{-1}
Sterility	No microbial growth	Pass

a Relative retention time (RRT) = [HPLC retention time of [^{18}F]FDOPA/HPLC retention time of FDOPA reference standard]. b EU = endotoxin units.

clinical application at the University of Michigan, including purity, sterility, residual TBA levels, and residual solvent analysis (Table 3). Notably, enantiomeric purity was found to be $> 99\%$ using chiral HPLC, confirming that the stereochemistry of the precursor was retained throughout the entire manufacturing process. Doses produced using Cu-mediated reactions also need to be free of residual Cu if they are to be applied in the clinic, since the permitted daily exposure limit for Cu is ≤ 340 $\mu\text{g day}^{-1}$ for parenteral administration.¹⁷ Samples from each of the qualification runs were submitted for inductively coupled plasma mass spectrometry (ICP-MS) analysis and were found to contain residual Cu below the limit of quantification (0.11 ± 0.02 ppm), well under the established limit for Cu.

In summary, we report the validation of our Cu-mediated radiofluorination of BPIn esters for the cGMP synthesis of [^{18}F]FDOPA for clinical use. The synthesis was fully automated using a commercial radiochemistry synthesis module, and doses met all QC criteria for human use. We expect to initiate clinical imaging studies with [^{18}F]FDOPA in the near future.

All hazardous laboratory chemicals were used by trained personnel under the supervision of University of Michigan (UM) Environmental Health and Safety. Radioactivity was used by trained personnel under the approval of the UM Radiation Policy Committee (Protocol 12-029) and supervision of the UM Radiation Safety Service.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

§ Radiochemical yields (RCY) are non-isolated and were calculated by % integrated area of the appropriate ^{18}F product peak *versus* total $^{18}\text{F}^-$ peaks in a radio-TLC trace.

¶ The HPLC employs a dual eluent (0–13 min: 90% MeCN (10 mM KOAc pH: 7.0–7.5); 13–30 min: 75% MeCN (10 mM KOAc pH: 5.0–5.5) to separate FDOPA from ascorbic acid used during deprotection).

- For reviews and perspectives on the synthesis and application of [^{18}F]F-DOPA, see: (a) D. Taïeb, A. Imperiale and K. Pacak, *Eur. J. Nucl. Med. Mol. Imaging*, 2016, **43**, 1187; (b) M. Pretze, C. Wängler and B. Wängler, *BioMed. Res. Int.*, 2014, 674063.
- E. S. Garnett, G. Firnau and C. Nahmias, *Nature*, 1983, **305**, 137.
- J. Darcourt, A. Schiavza, N. Sapin, M. Dufour, M. J. Ouvrier, D. Benisvy, X. Fontana and P. M. Koulibaly, *Q. J. Nucl. Med. Mol. Imaging*, 2014, **58**, 355.
- F. Calabria and G. L. Cascini, *Hell. J. Nucl. Med.*, 2015, **18**, 152.
- P. Shah, H. Demirbilek and K. Hussain, *Semin. Pediatr. Surg.*, 2014, **23**, 76.
- (a) A. Luxen, M. Perlmutter, G. T. Bida, G. Van Moffaert, J. S. Cook, N. Satyamurthy, M. E. Phelps and J. R. Barrio, *Appl. Radiat. Isot.*, 1990, **41**, 275; (b) F. Füchtner, J. Zessin, P. Mäding and F. Wüst, *Nuklearmedizin*, 2008, **47**, 62;

- (c) G. Luurtsema, H. H. Boersma, M. Schepers, A. M. T. de Vries, B. Maas, R. Zijlma, E. F. J. de Vries and P. H. Elsinga, *EJNMMI Radiopharm. Chem.*, 2017, **1**, 7.
- 7 (a) T. Tierling, K. Hamacher and H. H. Coenen, *J. Labelled Compd. Radiopharm.*, 2001, **44**(Suppl. 1), S146; (b) F. M. Wagner, J. Ermert and H. H. Coenen, *J. Nucl. Med.*, 2009, **50**, 1724; (c) C. Lemaire, S. Gillet, S. Guillouet, A. Plenevaux, J. Aerts and A. Luxen, *Eur. J. Org. Chem.*, 2004, 2899; (d) B. Shen, W. Ehrlichmann, M. Uebele, H.-J. Machulla and G. Reischl, *Appl. Radiat. Isot.*, 2009, **67**, 1650; (e) C. Lemaire, L. Libert, X. Franci, J.-L. Genon, S. Kuci, F. Giacomelli and A. Luxen, *J. Labelled Compd. Radiopharm.*, 2015, **58**, 281; (f) C. Sauvage, N. Lazarova, M. Mueller and D. Goblet, *J. Labelled Compd. Radiopharm.*, 2015, **58**(Suppl. 1), S164.
- 8 For reviews of new late-stage fluorination approaches, see: (a) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford and P. J. H. Scott, *Chem. Sci.*, 2014, **5**, 4545–4553; (b) M. G. Campbell and T. Ritter, *Chem. Rev.*, 2015, **115**, 612–633; (c) S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719–766; (d) X. Deng, J. Rong, L. Wang, N. Vasdev, L. Zhang, L. Josephson and S. H. Liang, *Angew. Chem., Int. Ed.*, 2019, **58**, 2580–2605.
- 9 (a) N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford and P. J. H. Scott, *Org. Lett.*, 2014, **16**, 3224; (b) B. H. Rotstein, N. A. Stephenson, N. Vasdev and S. H. Liang, *Nat. Commun.*, 2014, **5**, 4365.
- 10 (a) M. Tredwell, S. M. Preshlock, N. J. Taylor, S. Gruber, M. Huiban, J. Passchier, J. Mercier, C. Génicot and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2014, **53**, 7751; (b) 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; (c) B. D. Zlatopolskiy, J. Zischler, P. Krapf, F. Zarrad, E. A. Urusova, E. Kordys, H. Endepols and B. Neumaier, *Chem. – Eur. J.*, 2015, **21**, 5972; (d) S. Preshlock, S. Calderwood, S. Verhoog, M. Tredwell, M. Huiban, A. Hienzsch, S. Gruber, T. C. Wilson, N. J. Taylor, T. Cailly, M. Schedler, T. L. Collier, J. Passchier, R. Smits, J. Mollitor, A. Hoepping, M. Mueller, C. Génicot, J. Mercier and V. Gouverneur, *Chem. Commun.*, 2016, **52**, 8361; (e) A. V. Mossine, A. F. Brooks, N. Ichiishi, K. J. Makaravage, M. S. Sanford and P. J. H. Scott, *Sci. Rep.*, 2017, **7**, 233; (f) A. V. Mossine, A. F. Brooks, V. Bernard-Gauthier, J. J. Bailey, N. Ichiishi, R. Schirrmacher, M. S. Sanford and P. J. H. Scott, *J. Labelled Compd. Radiopharm.*, 2018, **61**, 228; (g) N. J. Taylor, E. Emer, S. Preshlock, M. Schedler, M. Tredwell, S. Verhoog, J. Mercier, C. Génicot and V. Gouverneur, *J. Am. Chem. Soc.*, 2018, **139**, 8267; (h) Y. Zhang, F. Basuli and R. E. Swenson, *J. Labelled Compd. Radiopharm.*, 2019, **62**, 139.
- 11 (a) K. J. Makaravage, A. F. Brooks, A. V. Mossine, M. S. Sanford and P. J. H. Scott, *Org. Lett.*, 2016, **18**, 5440; (b) R. F. Gamache, C. Waldmann and J. M. Murphy, *Org. Lett.*, 2016, **18**, 4522; (c) F. Zarrad, B. D. Zlatopolskiy, P. Krapf, J. Zischler and B. Neumaier, *Molecules*, 2017, **22**, 2231; (d) G. D. Bowden, B. J. Pichler and A. Maurer, *Sci. Rep.*, 2019, **9**, 11370.
- 12 (a) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker and T. Ritter, *Science*, 2011, **334**, 639; (b) E. Lee, J. M. Hooker and T. Ritter, *J. Am. Chem. Soc.*, 2012, **134**, 17456; (c) A. J. Hoover, M. Lazari, H. Ren, M. K. Narayanam, J. M. Murphy, R. M. van Dam, J. M. Hooker and T. Ritter, *Organometallics*, 2016, **35**, 1008.
- 13 (a) C. N. Neumann, J. M. Hooker and T. Ritter, *Nature*, 2016, **534**, 369; (b) M. H. Beyzavi, D. Mandal, M. G. Strebl, C. N. Neumann, E. M. D'Amato, J. Chen, J. M. Hooker and T. Ritter, *ACS Cent. Sci.*, 2017, **3**, 944.
- 14 A. Maisonia-Besset, A. Serre, A. Ouadi, S. Schmitt, D. Canitrot, F. Léal, E. Miot-Noirault, D. Brasse, P. Marchand and J.-M. Chezal, *Eur. J. Org. Chem.*, 2018, 7058.
- 15 B. Buszewski and S. Noga, *Anal. Bioanal. Chem.*, 2012, **402**, 231.
- 16 (a) S. D. McCann and S. S. Stahl, *Acc. Chem. Res.*, 2015, **48**, 1756; (b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234.
- 17 Guidelines for Elemental Impurities. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3D/Q3D_Step_4.pdf; accessed 17-May-2019.