Radiochemistry Hot Paper

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A General Copper-Mediated Nucleophilic ^{18}F Fluorination of Arenes**

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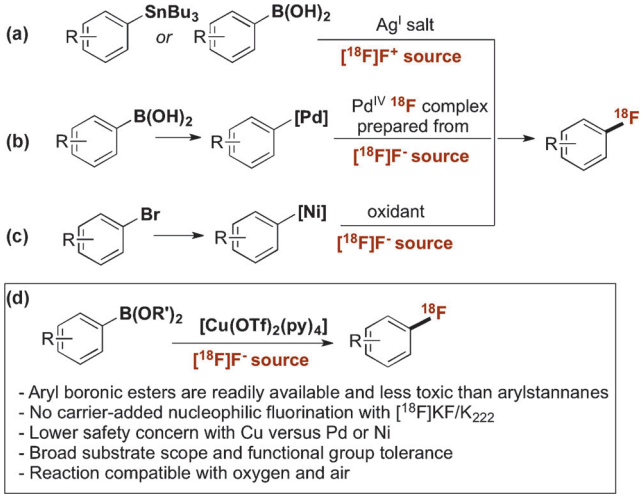
Abstract: *Molecules labeled with fluorine-18 are used as radiotracers for positron emission tomography. An important challenge is the labeling of arenes not amenable to aromatic nucleophilic substitution (S_NAr) with $[^{18}F]F^-$. In the ideal case, the ^{18}F fluorination of these substrates would be performed through reaction of $[^{18}F]KF$ with shelf-stable readily available precursors using a broadly applicable method suitable for automation. Herein, we describe the realization of these requirements with the production of ^{18}F arenes from pinacol-derived aryl boronic esters (arylBPin) upon treatment with $[^{18}F]KF/K_{222}$ and $[Cu(OTf)_2(py)_4]$ (OTf = trifluoromethanesulfonate, py = pyridine). This method tolerates electron-poor and electron-rich arenes and various functional groups, and allows access to 6-$[^{18}F]$fluoro-L-DOPA, 6-$[^{18}F]$fluoro-m-tyrosine, and the translocator protein (TSPO) PET ligand $[^{18}F]$DAA1106.*

The first application of positron annihilation radiation for medical imaging,[1] followed by the development of the first human positron emission tomography (PET) scanner, were milestones in the deployment of PET imaging as we know it today.[2] Further technological developments coupled with the appearance of radiopharmaceuticals, perhaps most famously 2-[^{18}F]fluoro-2-deoxy-D-glucose,[3] firmly established PET as a non-invasive imaging modality for in vivo measurement and quantification of biochemical processes. Today PET is used routinely in the clinic to diagnose cancers,[4] neurological disorders, and cardiovascular diseases,[5] and has become a useful tool to facilitate drug discovery and development.[6] These applications have created a demand for new radiochemistry with a focus on ^{18}F fluorination,[7] a choice driven by the favorable properties of ^{18}F as a positron emitter and the prevalence of fluorine in drug design.[8]

In the past decade, the number of methods available to incorporate fluorine into (hetero)arenes has increased as these structural motifs are commonly found in pharmaceutical drugs to impart metabolic robustness.[9] In contrast, the preparation of ^{18}F-labeled (hetero)arenes that are not accessible by aromatic nucleophilic substitution (S_NAr) with [^{18}F]fluoride remains challenging.[10] Metal-mediated processes have recently emerged for the direct ^{18}F fluorination of arenes not suitable for S_NAr (Scheme 1). The [^{18}F]NF reagent



Scheme 1. Metal-mediated ^{18}F fluorination of arenes.

[^{18}F]Selectfluor bis(triflate) prepared from $[^{18}F]F_2$ allowed for the silver(I)-mediated ^{18}F fluorination of arylstannanes[11] and arylboronic acids[12] within the time constraint imposed by the short half-life ^{18}F isotope ($t_{1/2} = 109.6$ min). This chemistry is not widely used as few PET centers are equipped to produce $[^{18}F]F_2$, and tracers derived from $[^{18}F]F_2$ are of lower specific activity than those produced from [^{18}F]fluoride.[13] A purpose-built $[^{18}F]Pd^{IV}F$ complex prepared from $[^{18}F]F^-$ but acting as a source of $[^{18}F]F^+$, converted palladium(II) aryl complexes into [^{18}F]fluoroarenes (Scheme 1b).[14] Nickel(II) aryl complexes derived from aryl bromides were also found amenable to nucleophilic ^{18}F fluorination in the presence of an oxidant.[15] These organometallic Pd- and Ni-based precursors

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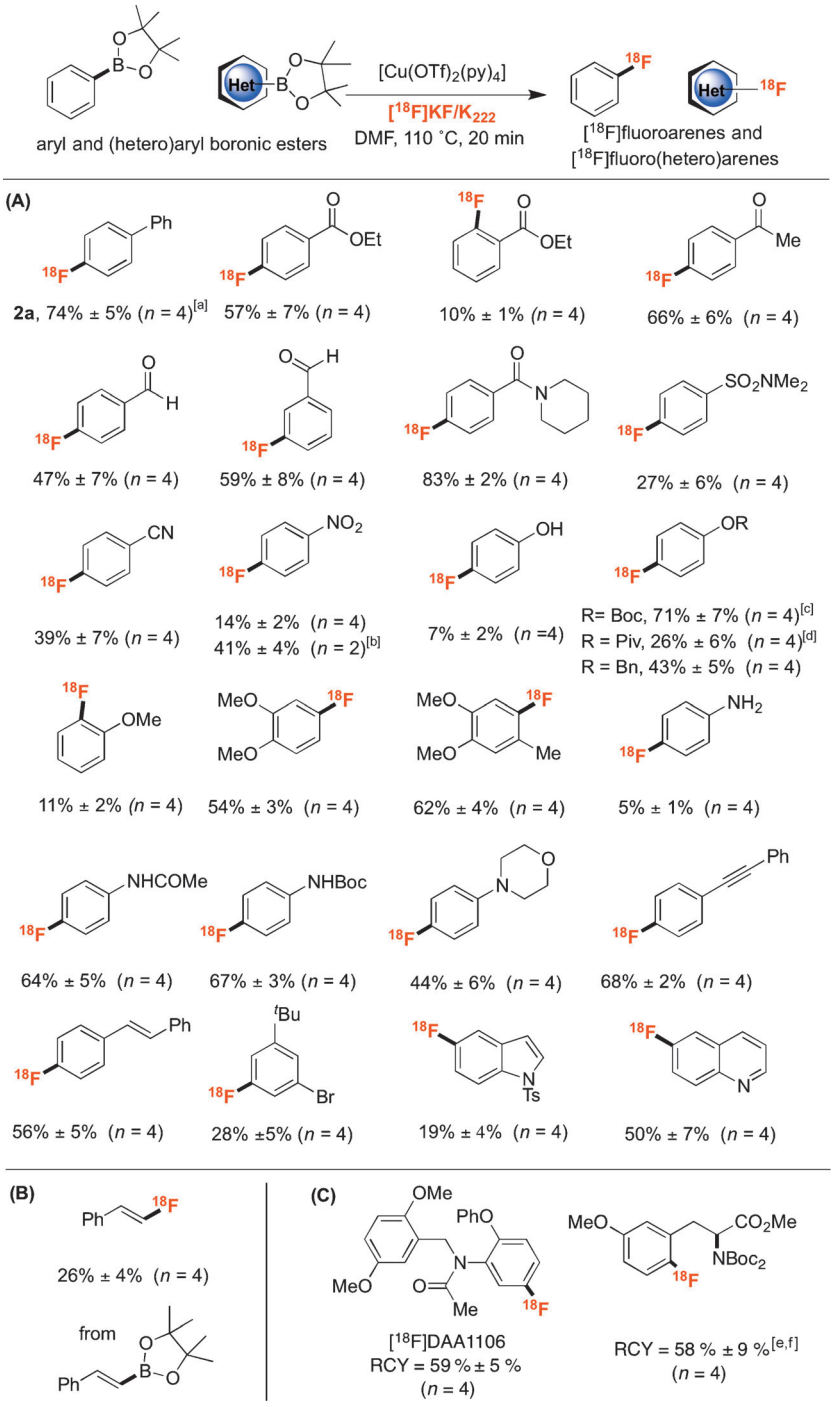
are not commercially available and not trivial to prepare by non-chemist professionals performing (pre)clinical PET studies. These characteristics, coupled with the necessity to develop automated procedures in compliance with good manufacturing practice (GMP) requirements, encourage the development of simpler and readily applicable solutions for the direct nucleophilic ^{18}F fluorination of (hetero)arenes from easy to prepare, shelf-stable materials. Herein, we report the unprecedented nucleophilic ^{18}F fluorination of a broad range of pinacol-derived aryl boronate esters with [^{18}F]KF/K_{222} in the presence of the commercially available copper complex [$Cu(OTf)_2(py)_4$] (OTf = trifluoromethanesulfonate, py = pyridine). This transformative method is characterized by its broad substrate scope and its direct application to the synthesis of radiotracers currently prepared in the clinic from [^{18}F]F^+ sources (Scheme 1).

We have recently exploited the value of copper complexes for ^{18}F-labeling with the [^{18}F]trifluoromethylation of (hetero)aryl iodides from [^{18}F]$CuCF_3$.[16] Our next objective was the development of a copper-mediated nucleophilic ^{18}F fluorination of readily available and stable precursors with the aim to provide a general and direct method to access ^{18}F-labeled arenes. The remarkable scope of the copper(II)-promoted Chan–Lam coupling reaction of boronic acids and derivatives with heteronucleophiles provided a focus,[17] and the ability of aryltrifluoroborates and arylboronate esters to undergo fluorination with KF and $Cu(OTf)_2$ served as a starting point for ^{18}F-radiochemical development.[18] Translation to no-carrier-added ^{18}F radiochemistry presents distinctive challenges since only minute quantities of ^{18}F are available for labeling (10^{-7}–10^{-9} M), and complications could arise from sequestration of [^{18}F]fluoride onto the boron-containing substrates which are used in excess.[19] We discarded aryltrifluoroborates for ^{18}F-labeling as these substrates could undergo $^{19}F/^{18}F$ isotopic exchange, a process resulting in decreased specific activity (SA).

2-([1,1′-Biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) served as the model substrate for validation and optimization studies.[20] All reactions were conducted without deliberate addition of ^{19}F-fluoride (no-carrier added). When the reaction was performed in acetonitrile at 60 °C for 20 minutes using [^{18}F]KF/K_{222} with a **1a**:[$Cu(OTf)_2$] ratio of 1:4, the formation of compound 4-[^{18}F]fluoro-1,1′-biphenyl [^{18}F]**2a** was not detected. This result prompted an exploration of key parameters to induce ^{18}F incorporation. ^{18}F Fluorination of **1a** was observed at 150 °C using [^{18}F]KF/K_{222} in dimethylformamide (DMF) or in *N*-methylpyrrolidone affording [^{18}F]**2a** in low radiochemical yield (RCY < 5 %); higher RCYs averaging 15 % were obtained in DMF at 110 °C. The RCYs were affected by the **1a**:[$Cu(OTf)_2$] ratio. The best results were obtained by reducing the amount of Cu complex relative to **1a** (ratio **1a**:[$Cu(OTf)_2$] = 10:1). During the optimization studies, we observed the formation of 1,1′-biphenyl and (1,1′-biphenyl)-4-ol, resulting from competitive protodeboronation and oxidation, respectively. These products are not ^{18}F-labeled contaminants but the similar polarities of 1,1′-biphenyl and 4-[^{18}F]fluoro-1,1′-biphenyl cause complications with purification. Both ^{18}F fluorination and protodeboronation were affected by the procedure applied to evaporate the solution of [^{18}F]KF/K_{222} in acetonitrile. Evaporation under N_2 led to decreased RCYs and encouraged the formation of 1,1′-biphenyl, an observation indicating that the presence of O_2 is beneficial for the reaction. Consequently, the reaction vial was purged with air after drying [^{18}F]fluoride. These modifications led to the formation of [^{18}F]**2a** in up to 43 % RCY ([**1a**] 0.26 M in DMF). We then focused on the nature of the copper complex itself and the effect of any ligand on reaction efficiency. All ligands tested had a detrimental effect on the RCY with the exception of pyridine.[20] These experiments prompted the use of the pyridine copper complex [$Cu(OTf)_2(py)_4$] for further optimization. To our delight, this complex proved optimal, affording [^{18}F]**2a** in 73 % RCY. When samples of [$Cu(OTf)_2(py)_4$] were left open to air for two weeks and subsequently employed in radiofluorination, no adverse effect on RCY was observed. The screening of various additives did not lead to further improvements in RCY, so the reaction requires only the copper complex, in addition to the substrate and [^{18}F]KF/K_{222}. Applying the optimized reaction conditions, [^{18}F]4-fluoro-1,1′-biphenyl (**2a**) was obtained in 74 % RCY ($n = 4$, number of repeats).

To evaluate the utility of the Cu-mediated ^{18}F fluorination, a series of pinacol-derived (hetero)aryl boronic esters was tested (Scheme 2). Numerous functional groups, such as alkyl, aryl, aldehyde, ketone, nitro, cyano, amido, sulfonamido, ether, ester, alkene, alkyne, bromo, piperidino, morpholino, Boc-protected amines (Boc = *tert*-butoxycarbonyl), and alcohols, are compatible with this new ^{18}F fluorination with RCYs reaching up to 83 %. Precursors with unprotected alcohol or amine functionalities give only trace amounts of the desired ^{18}F-product (RCY < 10 %), a result possibly owing to competitive C–O or C–N coupling.[17] The reaction of arylBPin with *ortho*-, *para*-, and *meta*-positioned electron-withdrawing groups proceeds efficiently, and the presence of electron-donating groups on the arylBPin precursor is very well tolerated. *Ortho*-substituted [^{18}F]fluoroarenes are also accessible by application of our standard method. [^{18}F]6-Fluoroquinoline and [^{18}F]5-fluoro-1-tosyl-1*H*-indole were obtained in 50 % and 19 % RCY, respectively. The reaction can also be extended to an alkenylBpin precursor as demonstrated by the preparation of the [^{18}F]fluoroalkene derived from (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane. The successful application of our method to electron-rich arenes such as phenol, aniline, and veratrole derivatives offers tantalizing opportunities in PET ligands and radiopharmaceuticals development. Ultimately, a major benefit of our method is its amenability to late-stage ^{18}F fluorination of radiotracers notoriously difficult to access from [^{18}F]fluoride. Our methodology provided easy access to known radiotracers without the need for further optimization. The translocator protein (TSPO) PET ligand [^{18}F]DAA1106 was readily labeled in 59 % RCY by applying our method.[21] TSPO is up-regulated in activated microglia and can serve as a biomarker for many applications, for example, in the early stages of neuroinflammation associated with brain tumors. 6-[^{18}F]Fluoro-L-tyrosine[22] could be prepared from the *N*,*N*-diBoc-protected arylBPin precursor. The ^{18}F fluorination step delivered protected 6-[^{18}F]fluoro-*m*-D,L-tyrosine in 58 %

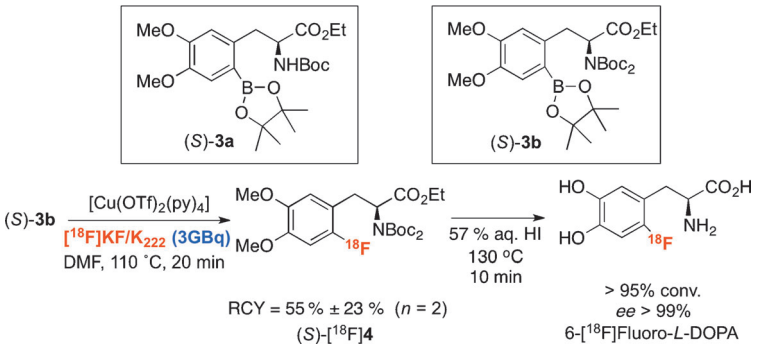


Scheme 2. Cu^{II}-mediated ^{18}F fluorination of (hetero)aryl pinacol-derived boronic esters with [^{18}F]fluoride. All reactions were performed in 300 µL of DMF with 0.06 mmol of arylBPin and 0.0053 mmol of Cu complex and were repeated *n* times. Piv = pivaloyl, Bn = benzyl, Ts = *p*-toluenesulfonyl. [a] The precursor for this reaction is 2-([1,1′-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**). [b] Reaction time 40 min. [c] RCY includes 5% of 4-[^{18}F]fluorophenol. [d] RCY includes 1% of 4-[^{18}F]fluorophenol. [e] RCY includes 16% of partially *N*-Boc protected 6-[^{18}F]fluorotyrosine. [f] Quantitative deprotection leading to 6-[^{18}F]fluoro-*m*-D,L-tyrosine was accomplished with 57% aq. HI at 130°C. All RCYs are decay corrected.

RCY, from which 6-[^{18}F]fluoro-*m*-D,L-tyrosine was quantitatively released upon treatment with aqueous HI at 130 °C.[12]

The remarkable scope of this reaction prompted us to test this reaction using a large dose of [^{18}F]fluoride. Starting from 12 GBq of [^{18}F]fluoride, a dose of 1.38 GBq of [^{18}F]4-fluoro-1,1′-biphenyl (**2a**) was isolated,[20] which corresponds to a decay-corrected radiochemical yield of 21%. Specific activity (SA) is an important consideration for new radiochemistry as the mass dose of the tool compound defines the extent of application and dictates the level of toxicology required to support human use. The SA on the dose of [^{18}F]**2a** was found to be 112 GBq µmol^{-1} at the end of the synthesis, which suggests that radiotracers obtained with this method can be used for a broad range of (pre)clinical applications. For translational studies, the copper content of ^{18}F radiotracers prepared with our method was considered, although such copper contamination concerns are very different for PET imaging because of the small amount of radiotracer that is required. Inductively coupled plasma mass spectrometry (ICP-MS) analysis was performed on [^{18}F]**2a** purified by a conventional HPLC technique. This analysis indicated that $[Cu(OTf)_2(py)_4]$ can be removed effectively since the labeled material contained 2.07 ppm Cu–63 residue ($n = 4$), well below any levels of concern as defined in the draft guidance ICH Q3D.[23]

To further demonstrate the high translational potential of the nucleophilic ^{18}F fluorination of arylBPin precursors, we focused on accessing 6-[^{18}F]fluoro-L-dihydroxy-phenylalanine ([^{18}F]FDOPA). [^{18}F]FDOPA is an iconic radiotracer broadly used in neurology for detecting the loss of functional dopaminergic neuron terminals in the striatum, and has found applications in oncology where enhanced intracellular transport and decarboxylation of the amino acid dihydroxyphenylalanine serve as the diagnostic target. This radiotracer is prepared in the clinic from [^{18}F]F_2.[24] Alternative radiosynthetic procedures have been developed, for example based on multistep syntheses,[25] the late-stage ^{18}F fluorination of nickel(II) aryl complexes,[15] or iodyl precursors[26–28] with [^{18}F]fluoride, but these methods require substrates which are not shelf-stable or not easily accessible. We were delighted that the copper-mediated ^{18}F fluorination gave direct access to [^{18}F]FDOPA from [^{18}F]fluoride using the aryl boronic esters **3a** or **3b** (Scheme 3). The *N*-Boc precursor (*S*)-**3a** gave a low radiochemical yield of 5% possibly as a result of the occurrence of



Scheme 3. Radiosynthesis of 6-[^{18}F]fluoro-L-DOPA from [^{18}F]fluoride.

Chan–Lam cross coupling, which leads to aryl–N bond formation in preference to ^{18}F fluorination; the *N*,*N*-diBoc precursor (*S*)-**3b** was a superior substrate and delivered (*S*)-[^{18}F]**4** in 83 % RCY. Starting from 3 GBq of [^{18}F]KF/K_{222}, it was necessary to refine the reaction conditions altering the quantity of copper complex relative to the substrate (ratio (*S*)-**3b**: $[Cu(OTf)_2(py)_4]$ = 3:1). Applying these conditions, (*S*)-[^{18}F]**4** was obtained in 55 % RCY. Deprotection of (*S*)-[^{18}F]**4** was performed with HI for 10 minutes at 130 °C to afford [^{18}F]FDOPA as a single enantiomer with complete conversion (> 95 %). The identity of [^{18}F]FDOPA was unambiguously confirmed by HPLC analysis.

This new radiosynthetic route is suitable for the production of clinical dose of [^{18}F]FDOPA (ca. 4 MBq kg^{-1} of body mass). In an initial approach aiming at full automation and starting with 13 GBq of [^{18}F]fluoride, a dose of 609 MBq of [^{18}F]FDOPA was isolated, which corresponds to a 12 % decay-corrected RCY.[20] The product met the European Pharmacopoeial quality demands with radiochemical and enantiomeric purities in excess of 98 %, confirming the exclusive preparation of 6-[^{18}F]fluoro-L-DOPA. In comparison, clinical doses ranging from 300 to 1200 MBq are routinely produced by applying the current optimized process for the manufacture of [^{18}F]FDOPA through electrophilic ^{18}F fluorodestannylation.[24]

In this work, we have introduced an efficient no-carrier-added procedure that allows for the nucleophilic ^{18}F fluorination of aromatic systems with [^{18}F]KF/K_{222} from (hetero)aryl boronic esters derived from pinacol in high radiochemical yields. ArylBPin reagents are ideal precursors for ^{18}F fluorination as they are stable to air and moisture, and are readily accessible. This procedure relying on $[Cu(OTf)_2(py)_4]$ to mediate [^{18}F]F–aryl bond formation tolerates a large range of electron-neutral, -rich, and -poor arenes as well as numerous functional groups. The method is readily applicable to the radiosynthesis of the TSPO PET ligand [^{18}F]DAA106 and 6-[^{18}F]fluorotyrosine, and is also suitable for the preparation of a clinical dose of 6-[^{18}F]fluoro-L-DOPA. This radiopharmaceutical is immediately accessible from the corresponding protected arylBpin precursor using a commercially available Cu complex and cyclotron produced [^{18}F]fluoride. The process could be applied in all PET centers having the capacity to produce 2-[^{18}F]fluoro-L-deoxyglucose. This ^{18}F radiochemistry may find ample applications in drug development, and previously unavailable [^{18}F]PET tracers for clinical studies may come within reach. The process does not necessitate the preparation of complex starting materials or reagents, and can be performed in a reaction vessel exposed to air. The suitability of this method for automated synthesizers and microfluidic development is under investigation.

Experimental Section

General procedure for the ^{18}F-labeling of arylBPin: the optimized method started with the preparation of a V-vial containing a magnetic stirrer, $[Cu(OTf)_2(py)_4]$ (0.0053 mmol), and arylBPin (0.06 mmol) followed by the addition of [^{18}F]KF/K_{222} (ca. 30 MBq) in MeCN (ca. 30 μL). DMF (300 μL) was added by syringe and the sealed vial heated at 110 °C and allowed to stir for 20 min. The reaction was quenched by addition of water (200 μL). An aliquot was removed for analysis by radioactive thin-layer chromatography (radioTLC) and radioactive high-performance liquid chromatography (radioHPLC) to calculate the RCY and identify the product, respectively.

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