Synthesis of [18F]Arenes via the Copper-Mediated [18F]Fluorination of Boronic Acids

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Supporting Information

ABSTRACT: A copper-mediated radiofluorination of aryl- and vinylboronic acids with K[18F] is described. This method exhibits high functional group tolerance and is effective for the radiofluorination of a range of electron-deficient, neutral, and -rich aryl-, heteroaryl-, and vinylboronic acids. This method has been applied to the synthesis of [18F]FPEB, a PET radiotracer for quantifying metabotropic glutamate 5 receptors.

There are over 1.5 million positron emission tomography (PET) scans performed annually in the US, in which patients are injected with a PET tracer (a bioactive molecule tagged with a positron-emitting radionuclide). The functional information obtained from these studies can be used to diagnose and stage disease as well as to predict and/or monitor response to therapy. The most common PET radionuclide is 18F, due to its convenient half-life (110 min), excellent imaging properties, and ready availability of large amounts of no-carrier-added [18F]. The growing prevalence of fluorine in pharmaceutical scaffolds also offers rich opportunities for the simultaneous development of PET radiotracers as companion diagnostics. However, despite these benefits, the development of new 18F radiotracers is complicated by the limited number of reactions available for the introduction of 18F into bioactive molecules, particularly on electron-rich aromatic rings.

18F-labeled aromatics are most commonly prepared using SnAr reactions. These reactions typically require high temperatures (often >150 °C) and are restricted to electron-deficient substrates. Recent advances have expanded the scope of nuclophilic aromatic radiofluorination using triaryl sulfonium, diaryl sulfoxide, and iodonium ylide precursors. Complementary studies from our group and others have focused on the transition-metal-mediated nuclophilic radiofluorination of aromatic substrates. However, despite these advances, there are still very few operationally simple nuclophilic radiofluorination reactions that are effective for electron-rich aromatic substrates and use stable, commercially available precursors.

In 2013, the Sanford group disclosed the Cu-mediated fluorination of aryl trifluoroborates, arylboronate esters, and aryloboronic acids with KF (Scheme 1a), and we immediately sought to translate this discovery to a radiofluorination of aryloboronic compounds with K[18F]. Our initial studies focused on conditions similar to those used for nonradioactive 19F fluorination, and we found that both potassium trifluoroborate salts and boronate esters undergo Cu-mediated radiofluorination. Preliminary optimization focused on arylpinacol ester 1-BPin (a substrate of particular interest in connection with a program developing radiotracers for glycogen synthase kinase-3). These studies uncovered conditions for the radiofluorination of 1-BPin with K[18F] to afford 2 in ~5% radiochemical conversion (RCC; % integrated area corresponding to product versus 18F in a radio-HPLC or -TLC trace) (Scheme 1b and Scheme 2).

Concomitant with our initial studies, Gouverneur reported a closely related radiofluorination of pinacol boronate esters and demonstrated its application to the synthesis of a range of [18F]arenes, including 2 in 66 ± 6% radiochemical yield. However, in our hands, exposing 1-BPin to Gouverneur’s conditions provided 2 in just 31 ± 13% RCC (n = 7, Scheme 2).

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Scheme 1. Nucleophilic Fluorination of Aryl Boron Reagents
In addition to the modest yield and reproducibility, we noted several other limitations of Gouverneur’s method. These include (1) the requirement for an expensive copper salt [Cu(OTf)2](py)4,15 (2) incompatibility with more abundant organoboron precursors such as boronic acids, and (3) incompatibility with automation using a commercial radiochemistry synthesis module.16 The latter point is particularly critical given that all modern radiopharmaceuticals in routine clinical use are prepared according to current good manufacturing practice (cGMP) via automated synthesis.

We report herein that these limitations have all been addressed through the development of a copper-mediated radiofluorination of boronic acids (Scheme 1c). These starting materials are particularly practical given their ready availability17 and stability (most boronic acids are white crystalline solids that can be handled in air without special precautions and typically possess long shelf lives).18 While the central theme of this paper is the radiofluorination reaction using a commercial radio-TLC and radio-HPLC confirmed the formation of 2 in 48 ± 2% (n = 3) RCC (entry 4).

We next optimized the reaction with respect to copper source. These studies revealed that copper is essential for the reaction (entry 6 and Table S1) and that CuI complexes do not promote radiofluorination (Table S2). A screen of different solvents showed that radiofluorination proceeds in DMF but not MeCN (Tables S3 and S4). Finally, an evaluation of different pyridine additives showed that pyridine is essential for reactivity (entry 7 and Table S1) and that many substituted pyridines afford yields comparable to that of pyridine (Table S5). As such, pyridine was utilized moving forward due to its low cost and ready availability.19 Reagent concentrations and ratios were also optimized, as well as reaction temperature (Tables S6–10), leading to optimal conditions as follows: a 1:5:125 ratio of boronic acid in DMF at 110 °C for 20 min, providing 61 ± 8% RCC to 2 (n = 7; entry 8). Notably, the analogous reaction with Cu(OTf)2(py)4 proceeded in 51 ± 7% RCC (n = 3, entry 9), confirming that the readily available and inexpensive combination of Cu(OTf)2 and pyridine promotes this reaction as effectively as the more costly Cu(OTf)2(py)4. The process was fully automated in one pot (entry 10), resulting in high specific activity 2 ( ~2000 Ci/mmol), albeit in lower RCC of 10 ± 2% (n = 2).

We next tested the compatibility of this radiofluorination method with water and strong bases. The reaction showed water tolerance, with water/boronic acid ratios of 16:1 resulting in only minor decreases in RCC (Table S11). Despite being tolerant of pyridine, the reaction was highly sensitive to stronger bases. For

### Table 1. Optimization of Radiofluorination of 1-B(OH)2 To Form [18F]-4-Fluoroacetophenone 2

| entry | QMA eluent | [Cu] | RCC (%) |
|-------|------------|------|---------|
| 1     | K2CO3      | Cu(OTf)2 | 0      |
| 2     | K2CO3      | Cu(OTf)2(py)4 | 0      |
| 3     | K2CO3      | (MeCN),Cu(OTf)2 | 0      |
| 4     | PPTS       | Cu(OTf)2 | 48 ± 2 |
| 5     | KOTf/K2CO3 | Cu(OTf)2 | 51 ± 5a |
| 6     | KOTf/K2CO3 | none     | <1     |
| 7     | KOTf/K2CO3 | Cu(OTf)2 | <4a    |
| 8     | KOTf/K2CO3 | Cu(OTf)2 | 61 ± 8 |
| 9     | KOTf/K2CO3 | Cu(OTf)2(py)4 | 51 ± 7 |
| 10    | KOTf/K2CO3 | Cu(OTf)2 | 10 ± 2a |

aConditions: 1:5:125 1-B(OH)2/Cu(OTf)2/py at 4 mM concentration of the boronic acid precursor in DMF, K18F, 110 °C, 20 min. RCC was determined by radio-TLC (n ≥ 2). Other Cu sources were tested as well. See the SI. bBest conditions 1:5:125:0.1 1-B(OH)2/Cu(OTf)2/py/PPTS. cPyridine omitted. dReaction automated using a GE TRACERLab FXFN.
The formation of organoboron compounds with K\(^{18}F\). This method represents the first high-yielding nucleophilic fluorination of boronic acids (using \(^{18}F\) or \(^{19}F\)), is compatible with aryl, heteroaryl, and vinyl boronic acids, and thus fills an important gap in the late-stage fluorination space. The method is also suitable for the radiofluorination of boronate esters and potassium trifluoroborates. Finally, this process can be automated on a commercial radiochemistry synthesis module and applied to clinically relevant radiotracers, such as \([^{18}F]\)FPEB. Validation of the method for cGMP clinical production of \([^{18}F]\)FPEB and other PET tracers is currently under investigation.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02875.

Experimental procedures, optimization details, radio-HPLC/TLC traces, and spectral data for all new compounds (PDF)

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#### Notes

The authors declare no competing financial interest.

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K2CO3 requires backflushing of the QMA cartridge. As such, this process is challenging to automate and can lead to the introduction of cyclotron byproducts to the reaction mixture. 