DOI: 10.1002/anie.200802164

Fluorination

# Palladium-Mediated Fluorination of Arylboronic Acids**

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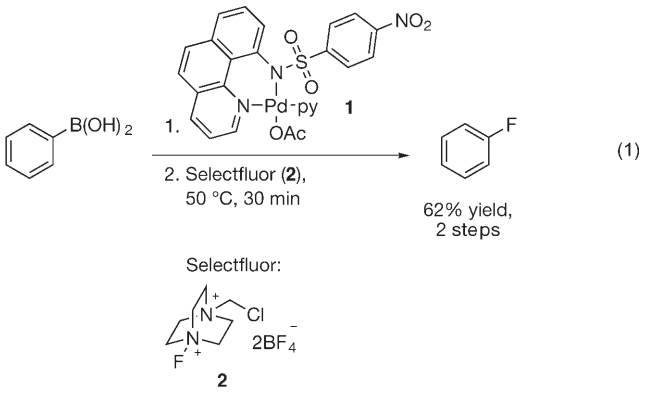
Fluorinated organic molecules have become increasingly important as pharmaceuticals[1] and tracers for positron-emission tomography (PET), a powerful technology for noninvasive molecular imaging.[2] The nucleus of choice for PET is fluorine-18 ($^{18}F$), which is typically introduced into PET tracers through the formation of carbon–fluorine bonds using nucleophilic fluoride ($^{18}F^-$) under harsh reaction conditions.[3] The short half-life of $^{18}F$ (109 minutes) requires that carbon-fluorine bond formation occurs at a late stage in the PET tracer synthesis, ideally as the last step. Many promising PET tracers for imaging are currently inaccessible owing to the lack of suitable chemistry for the general, late-stage introduction of fluorine into complex, functionalized molecules.[3,4] Herein, we present a new strategy for carbon–fluorine bond formation that relies on the fluorination of arylboronic acids using palladium complexes [Eq. (1)]. The




(1)

reaction permits a general, regiospecific late-stage formation of carbon–fluorine bonds in the presence of a large variety of functional groups found in biologically active molecules. Ultimately, we anticipate our new fluorination reaction will provide a chemical solution for the synthesis of currently inaccessible PET tracers to increase both knowledge and understanding of basic, biomedical, and pharmaceutical research through molecular imaging.[5–8]

Carbon–fluorine bond formation is a challenging chemical transformation, and no general, functional-group-tolerant fluorination reaction of arenes is currently available for the synthesis of complex molecules. Simple fluoroarenes are typically synthesized by pyrolysis of diazonium tetrafluoroborates,[9] direct fluorination using highly reactive elemental fluorine,[10] or nucleophilic aromatic substitution reactions of electron-poor aromatic molecules.[11,12] Common aromatic organometallic compounds, such as aryl lithium and aryl Grignard reagents, can afford arylfluorides if using electrophilic fluorine sources; however, neither aryl lithium nor aryl Grignard reagents can be used for the late-stage fluorination of arenes bearing electrophiles, such as aldehydes, or protic functionalities, such as alcohols, limiting their general utility.[13] Organometallic compounds with lower basicity, such as aryl zinc halides, aryl silanes, aryl stannanes, and aryl boronic acids, afford fluorobenzenes in less than 10% yield (see the Supporting Information). The electrophilic fluorination of specific carbon–hydrogen bonds of phenylpyridine derivatives and related structures was reported in 2006 by Sanford et al., and uses catalytic palladium (II) acetate and *N*-fluoropyridinium salts.[14] The reaction takes advantage of a covalently attached pyridine directing group and affords fluorinated aryl pyridine derivatives using microwave irradiation (100–150 °C, 1–4 h, 33–75% yield). A different approach, the reductive elimination of aryl fluorides from palladium(II) fluoride complexes, would obviate the use of directing groups, and has been investigated over the past decade by Grushin and Yandulov.[15,16] Carbon–fluorine bond formation to form aryl fluorides by reductive elimination from a palladium(II) fluoride complex has not yet been substantiated.[16,17] In general, all methods mentioned above cannot be employed for late-stage fluorination of structurally complex molecules owing to either harsh reaction conditions or limited substrate scope.

We have sought a new regiospecific, late-stage fluorination reaction of arenes that encompasses a larger substrate scope than is currently accessible, tolerates the presence of a variety of functional groups, is not limited to a particular class of arenes, and is not dependent on a directing group. Our strategy is illustrated in Equation (1), and consists of the synthesis of new aryl palladium complexes that react with the electrophilic fluorination reagent selectfluor[18] to afford fluoroarenes.

Our initial investigations for the design of transition-metal complexes that afford efficient fluorination was guided by the observation that palladium has been successfully employed in several carbon–heteroatom bond formations,[19,20] including carbon–fluorine bonds for specific substrates.[14,21] Additionally, the development of our methodology was directed by the

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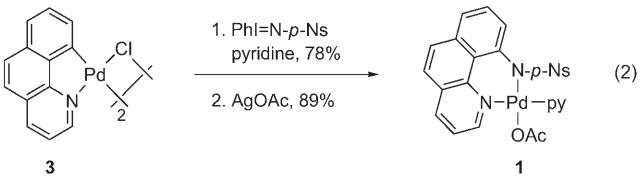
[**] We thank Merck & Co. and Amgen Inc. for unrestricted support, Eli Lilly & Co. for a Graduate Fellowship for T.F., and the Degussa Foundation for a fellowship for H.M.K. We thank Dr. Douglas M. Ho for X-ray crystallographic analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802164.

necessity to predict and control the exact location of fluorination and the need to introduce fluorine at any desired aromatic position. Therefore, the target molecules for fluorination are pre-functionalized with boronic acids at the position at which fluorine is desired. Boronic acids are readily accessible, compatible with a variety of functional groups present in PET tracers, competent nucleophiles for transmetallation to palladium, and can be introduced into complex molecules.[22]

Several aryl palladium complexes based on ligands that are commonly used for palladium chemistry did not lead to carbon–fluorine bond formation when evaluated for fluorination. We therefore designed new aryl palladium complexes that are derived from a bidentate ligand that contains a neutral and an anionic nitrogen donor atom for coordination to palladium. Our design was based on the assumptions that nitrogenous ligands resist oxidation by electrophilic fluorination reagents, can support high-valent aryl palladium fluorides for subsequent carbon–fluorine reductive elimination, and do not induce competing nitrogen–fluorine reductive elimination. We prepared the new palladium acetate complex **1** by known sulfonamide insertion[23] into the palladium–carbon bond of benzoquinoline-derived palladacycle **3**,[24] followed by chloride–acetate ligand exchange [Eq. (2)]. The

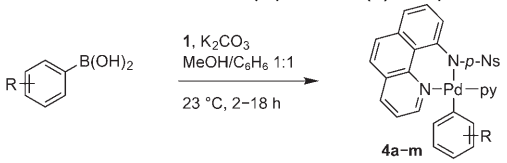



3 1 (2)

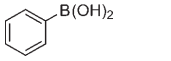
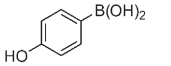
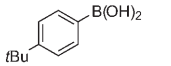
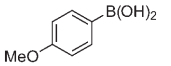
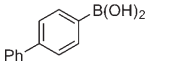
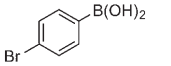
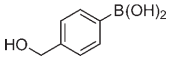
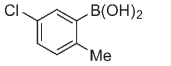
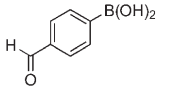
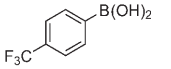
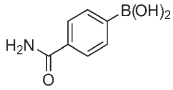
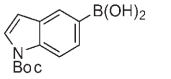
aryl palladium complexes **4a–m** were prepared by transmetallation using twelve different arylboronic acids (Table 1). Transmetallation proceeded at 23 °C in a basic methanol/benzene solution and afforded the palladium complexes as moisture- and air-stable yellow solids in 65–91 % yield on a 400 mg scale after purification by chromatography on silica gel. The aryl palladium complexes derived from **1** are tolerant toward the presence of a variety of functional groups found in biologically active compounds, including alcohols, an indole, and a primary amide. The phenyl palladium sulfonamide **4a** (R = H) crystallized in a square-planar geometry with the aryl group *trans* to the $\kappa^1$-sulfonamide ligand (Figure 1). The *trans* relationship may be crucial to prevent undesired carbon–nitrogen bond formation through reductive elimination of the aryl and sulfonamide substituents.[25]

Fluorination of the aryl palladium complexes **4a–m** using the electrophilic reagent selectfluor (**2**) afforded the arylfluorides **5a–m** regiospecifically in 31–82 % isolated yield (Table 2). The fluorination reaction tolerates the presence of a variety of functional groups, most notably protic functionalities that are not typically compatible with nucleophilic aromatic substitution methods owing to the high basicity of fluoride ion in anhydrous solvents suitable for nucleophilic displacement.[10] Additionally, electron-rich fluoroarenes (**5b**, **5g**, **5h**), which cannot be synthesized through late-stage fluorination using nucleophilic displacement, are accessible

***Table 1:*** Transmetallation to form aryl palladium(II) complexes.




**4a–m**

| Boronic acid | | Yield [%] | Boronic acid | | Yield [%] |
|---|---|---|---|---|---|
|  | **4a** | 76 |  | **4g** | 70 |
|  | **4b** | 85 |  | **4h** | 79 |
|  | **4c** | 91 |  | **4i** | 65 |
|  | **4d** | 80 |  | **4k** | 90 |
|  | **4e** | 71 |  | **4l** | 88 |
|  | **4f** | 73 |  | **4m**[a] | 76 |

[a] Boc = *tert*-butyloxycarbonyl.

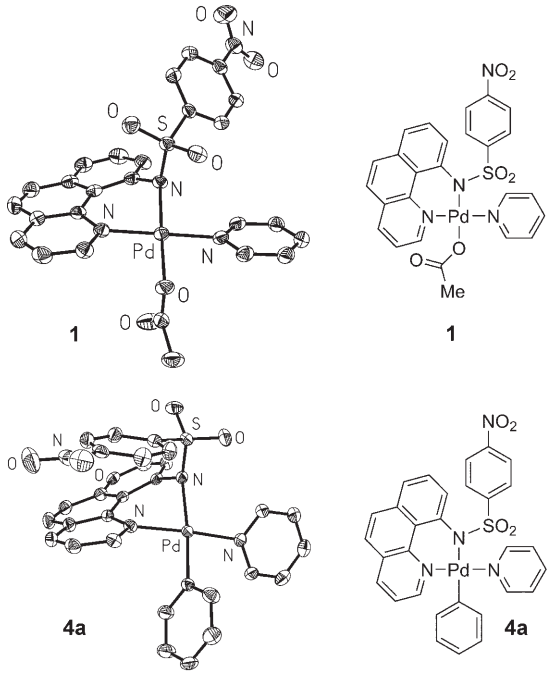
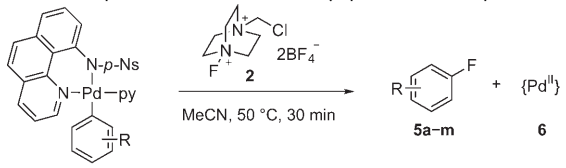


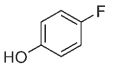
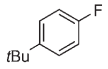
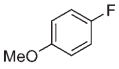
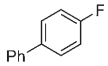
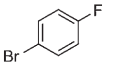
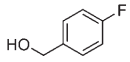
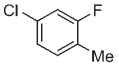
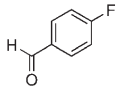
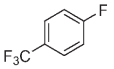
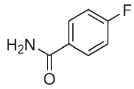
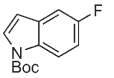

***Figure 1.*** ORTEP diagrams of **1** and **4a**, with thermal ellipsoids set at 50% probability, showing the *trans* relationship of the sulfonamide nitrogen atom to the acetate and to the aryl ligands.

regiospecifically. The scope of the reaction was further extended to electron-poor (**5e**, **5l**), heterocyclic (**5m**), and *ortho*-substituted arenes (**5k**). Fluorination proceeds in 30 minutes when performed in acetonitrile or acetone at 50 °C. Although fluorination was observed at 23 °C, the highest

***Table 2:*** Electrophilic fluorination with aryl palladium complexes.

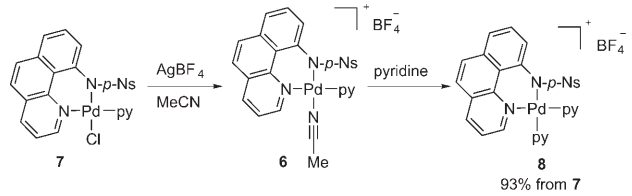



| 4 | Product | Yield [%] | 4 | Product | Yield [%] |
|---|---|---|---|---|---|
| **4a** |  | **5a**[a] 81 | **4g** |  | **5g**[b] 31 |
| **4b** |  | **5b**[a] 79 | **4h** |  | **5h**[b] 46 |
| **4c** |  | **5c** 72 | **4i** |  | **5i** 73 |
| **4d** |  | **5d** 70 | **4k** |  | **5k** 82 |
| **4e** |  | **5e** 61 | **4l** |  | **5l**[a] 54 |
| **4f** |  | **5f** 74 | **4m** |  | **5m**[b] 60 |

[a] Yield for this entry determined by $^{19}$F NMR analysis because of low boiling point of product. [b] Acetone used as solvent.

yields were obtained at a reaction temperature of 50 °C. Yields of isolated products were identical when the fluorination reactions were performed under rigorous exclusion of air and moisture or open to the atmosphere.

The fate of the palladium moiety after fluorination was determined to be cationic palladium complex **6**, which was independently synthesized by treatment of palladium chloride **7** with silver tetrafluoroborate in acetonitrile (Scheme 1). Subsequent reaction of **6** with one equivalent of pyridine afforded the stable palladium tetrafluoroborate salt **8**, which was isolated and characterized. Addition of pyridine after termination of the reaction shown in Table 2 also afforded **8**, which suggests that the pyridyl sulfonamide ligand remained coordinated to palladium throughout the reaction. The stability of the ligand–metal complex is advantageous for a prospective catalytic version of the presented fluorination reaction.




***Scheme 1.*** Independent synthesis of palladium byproduct **6**. *p*-Ns = *para*-nitrobenzenesulfonyl.

Transition-metal catalysis for carbon–fluorine bond formations is a valuable goal in itself. However, for the synthesis of PET tracers, a fluorination reaction using stoichiometric amounts of transition metal is advantageous, as stoichiometric reactions are faster than the corresponding catalyzed reactions, and time is the most important factor for the efficient preparation of PET tracers owing to the short half-life of $^{18}$F. Moreover, price and toxicity of palladium are of lesser importance for applications in molecular imaging because PET tracers are used in picomolar quantities and are purified by HPLC before injection in vivo.

Two possible mechanisms for the fluorination reaction presented herein are electrophilic palladium–carbon bond cleavage and carbon–fluorine reductive elimination from a discrete, high-valent palladium fluoride.[21] The redox activity of palladium (II) may play a crucial role for fluorination, which suggests a high-valent, discrete palladium fluoride complex as an intermediate before carbon–fluorine reductive elimination.[26]

In conclusion, we report a fluorination reaction of aryl boronic acids mediated by palladium, in which carbon–fluorine bond formation is the final synthetic step. The functional group tolerance, broad substrate scope, and regiospecificity of the reaction provide a general method for the late-stage fluorination of functionalized arenes. This new chemistry may become the basis for the development of a general solution for the synthesis of PET tracers for biomedical applications. Electrophilic $^{18}$F sources are available, but from a biomedical perspective nucleophilic $^{18}F^-$ is the preferred source of fluorine for PET imaging because it can be prepared in high specific activity.[3] A subsequent goal is therefore the development of an electrophilic fluorine source originating from nucleophilic fluoride ($^{18}F^-$). Further development of the transformation presented herein, in combination with known or new electrophilic fluorine sources, may deliver promising PET tracers to impact biomedical research in the fields of cancer, neurodegenerative diseases, gene therapy, and drug development.

## *Experimental Section*

Representative fluorination (4-fluorobiphenyl, **5c**): Aryl palladium complex **4c** was added as a solid (143 mg, 0.200 mmol, 1.00 equiv) in 10 portions over 10 min to a solution of selectfluor (**2**; 85.0 mg, 0.240 mmol, 1.20 equiv) in acetonitrile (6.0 mL) at 50 °C. The reaction mixture was subsequently stirred at 50 °C for 20 min. After cooling to 23 °C, pyridine was added to the reaction mixture (8.1 μL, 0.10 mmol, 1.0 equiv), and the reaction mixture filtered through a plug of celite. The filtrate was concentrated in vacuo and the residue purified by chromatography on silica gel, eluting with hexane/ethyl acetate 99:1 (v/v) to afford 24.8 mg of **5c** as a white solid (72% yield).

CCDC-675999 (**1**) and CCDC-676000 (**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: May 8, 2008
Published online: July 4, 2008

**Keywords:** boronic acids · fluorination · palladium · synthetic methods · tomography

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