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Palladium(III)-Catalyzed Fluorination of Arylboronic Acid Derivatives

Anthony R. Mazzotti,‡ Michael G. Campbell,‡ Pingping Tang, Jennifer M. Murphy, and Tobias Ritter*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

Supporting Information

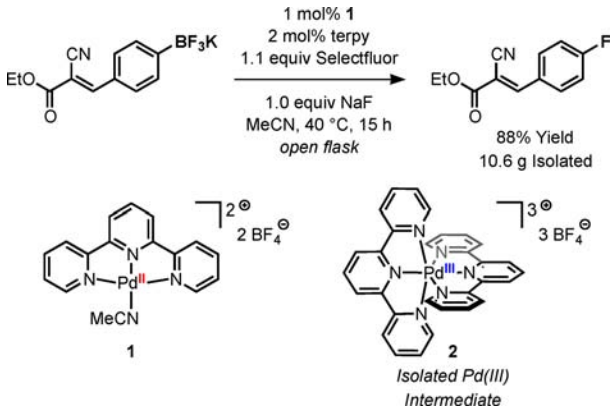
ABSTRACT: A practical, palladium-catalyzed synthesis of aryl fluorides from arylboronic acid derivatives is presented. The reaction is operationally simple and amenable to multigram-scale synthesis. Evaluation of the reaction mechanism suggests a single-electron-transfer pathway, involving a Pd(III) intermediate that has been isolated and characterized.

In the past decade there has been an increase in the number of available methods for the installation of fluorine and fluorine-containing functional groups into organic molecules.[1] However, the development of practical carbon−fluorine bond-forming reactions to provide aryl fluorides still remains as one of the most challenging transformations in the field of fluorination.[1] In this Communication, we report a palladium-catalyzed fluorination of arylboronic acid derivatives, which allows for an operationally simple, multigram-scale synthesis of functionalized aryl fluorides. A metal-catalyzed fluorination of arylboronic acid derivatives has not previously been reported. Kinetic studies suggest a mechanism distinct from other known arene fluorination reactions, which proceeds through a single-electron-transfer (SET) pathway without the formation of organopalladium species, and involving an unusual Pd(III) intermediate (**2**) that has been isolated and characterized (Scheme 1).

To date, only two catalytic reactions have been reported that provide a general route to functionalized aryl fluorides: Buchwald's palladium-catalyzed fluorination of aryl triflates,[2] and our group's silver-catalyzed fluorination of aryl stannanes.[3] Our silver-catalyzed reaction requires the preparation and use of toxic aryl stannanes. The palladium-catalyzed nucleophilic fluorination uses more readily available aryl triflates; it currently requires dried fluoride salts and can give mixtures of constitutional isomers for some substrates due to competing pathways in addition to C−F reductive elimination. Work toward catalytic C−H fluorination has been reported by the groups of Groves,[4a] Sanford,[4b,c] and Yu.[4d,e] Direct C−H fluorination is ideal from a perspective of step- and atom-economy, but the development of catalysts that provide selectivity for a broad range of substrates remains challenging.

There are a handful of modern stoichiometric arene fluorination reactions. On gram and smaller scales, deoxyfluorination with PhenoFluor[5] is in our opinion currently the most practical method to obtain a large variety of aryl fluorides, but it requires stoichiometric amounts of PhenoFluor. Metal-mediated procedures have been developed for a variety of arene precursors, but frequently require superstoichiometric amounts of transition metal. A copper-mediated fluorination of aryl iodides was reported by Hartwig,[6] and silver-mediated fluorination reactions have been developed for aryl stannanes, aryl silanes, and arylboronic acids.[7] There are several other metal-mediated fluorination reactions of arylboronic acid derivatives, using either palladium[8a] or copper.[8b,c] Further development of the reported metal-mediated reactions to use only catalytic quantities of the transition metal has remained difficult. For arylboronic acid derivatives, slow transmetalation of the arene from boron to the transition metal complex is frequently a hurdle to achieving C−F bond-forming catalysis.[7c,8a]

Scheme 1. Catalytic Fluorination of Aryl Trifluoroborates and Isolated Pd(III) Intermediate 2[a]



[a]terpy = 2,2′:6′,2″-terpyridine.

Herein we describe a palladium-catalyzed fluorination of arylboronic acid derivatives, using terpyridyl Pd(II) complex **1** as a precatalyst (Scheme 1). We propose a mechanism that proceeds without the formation of organopalladium intermediates, which circumvents the problem of transmetalation from the arylboron reagent. Complex **1** has been prepared in one step from $Pd(OAc)_2$, terpyridine (terpy), and HBF_4 on decagram scale, and all reagents used in the catalytic fluorination reaction including **1** are stable to air and moisture. The reaction can be performed in an open flask, and is effective for milligram to at least multigram-scale synthesis of aryl fluorides, which are readily isolated. Inseparable side products from protodeborylation were not observed for the majority of substrates, which may also be due in part to a mechanism that does not involve organopalladium intermediates. Protodeborylation is a common problem for fluorination reactions of arylboronic acid derivatives.[8b,c]

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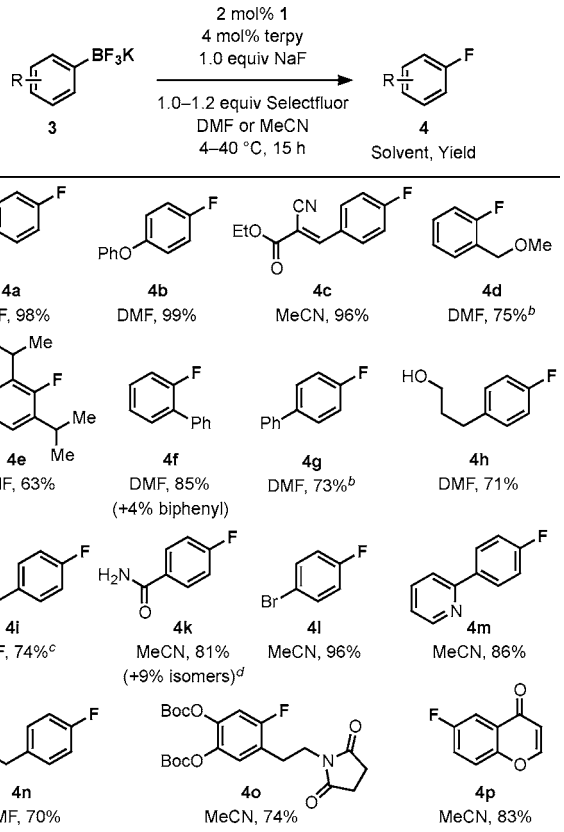
Table 1. Fluorination of Aryl Trifluoroborates[a]



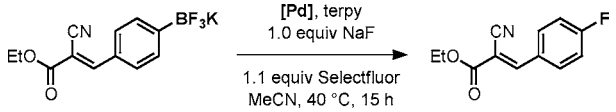
[a]Yields refer to isolated material of ≥98% purity unless otherwise noted. [b]No NaF was used. [c]5 mol% **1** and 10 mol% terpy were used. [d]9% of a mixture of constitutional isomers (*ortho*- and *meta*-fluorobenzamide).

As shown in Table 1, a wide variety of aryl trifluoroborates can be fluorinated, including both electron-rich and electron-poor arenes. DMF was found to be the optimal solvent for most electron-rich and electron-neutral arenes, while acetonitrile typically provided higher yields for arenes with electron-withdrawing substituents. Ketones, primary amides, carboxylic acids, esters, alcohols, basic heterocycles, aryl bromides, and *ortho,ortho′*-disubstitution are tolerated in the reaction.

Competing formation of constitutional isomers is a challenge for metal-catalyzed fluorination reactions.[2] Such impurities are usually difficult to separate from the desired aryl fluoride product. The majority of the aryl fluorides shown in Table 1 were isolated cleanly, with ≥98% purity. In particular, electron-rich aryl trifluoroborates generally did not react to form inseparable side products. Substrates with electron-withdrawing substituents are more likely to give constitutional isomers and difluorinated products along with the expected aryl fluoride product (typically ≤10%): substrate **3k** is a representative example, which reacts to form **4k** along with 9% of *ortho*- and *meta*-fluorobenzamide. Other electron-poor substrates such as **3c** provided clean isolated product. The Pd-catalyzed fluorination reaction is ineffective for fluorination of heterocycles, and arenes bearing methoxy substituents gave significant amounts of side products resulting from demethylation.

A variety of commercially available Pd(II) salts can be used in the fluorination reaction, as shown in Table 2. In general, palladium salts with less coordinating anions gave the highest yields. Anion metathesis using $NaBF_4$ as an additive resulted in higher yields for precatalysts with coordinating anions such as acetate. Palladium salts with halide anions were not suitable precatalysts for the fluorination reaction. Ultimately, we found **1** to be the most convenient precatalyst because no additive was needed, and due to its robust stability toward air and moisture as compared to $[Pd(MeCN)_4][BF_4]_2$. Complex **1** can be stored on the benchtop under ambient conditions without observable decomposition or decrease in catalytic reactivity for at least 6 months.

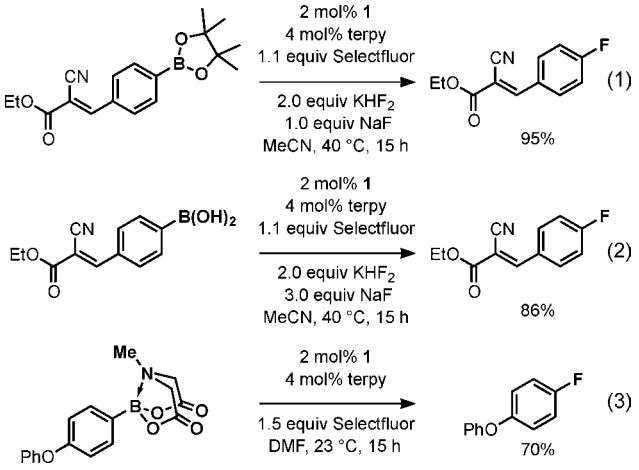
Table 2. Effectiveness of Other Palladium Precatalysts[a]



[Pd]	additive	yield (%)
1	none	96
2	none	95
$[Pd(MeCN)_4][BF_4]_2$	none	95
$Pd(OAc)_2$	$NaBF_4$ (2.0 equiv)	91[b]
$Pd(O_2CCF_3)_2$	$NaBF_4$ (1.0 equiv)	91

[a]2 mol% [Pd] and 4 mol% terpy were used. Yields refer to isolated, purified material. [b]5 mol% $Pd(OAc)_2$ and 10 mol% terpy were used.

To highlight the reaction's practical utility, we have demonstrated that other common arylboron reagents are viable substrates. *In situ* formation of aryl trifluoroborates via addition of a mixture of NaF and KHF_2 allowed for efficient fluorination of pinacol boronic esters and arylboronic acids (eqs 1 and 2). The ability to directly use a variety of arylboronic acid derivatives, without the need for prior isolation of the aryl trifluoroborate, allows for fluorination of a greater range of starting materials.



We observed that MIDA esters of electron-rich arylboronic acids can also undergo Pd-catalyzed fluorination, albeit in lower yield and requiring a larger amount of Selectfluor reagent (Air Products and Chemicals, Inc.) (eq 3). No aryl fluoride product was obtained when either NaF or KHF_2 was added, suggesting that fluorination proceeds without formation of the aryl trifluoroborate. MIDA esters of electron-poor arylboronic acids did not afford product. The direct fluorination of MIDA boronates, in the absence of exogenous fluoride anion, indicates a mechanism in which the fluorine atom involved in C–F bond formation is derived from Selectfluor, rather than added fluoride anion.

We propose that the Pd-catalyzed fluorination reaction proceeds via an outer-sphere pathway, involving an unusual

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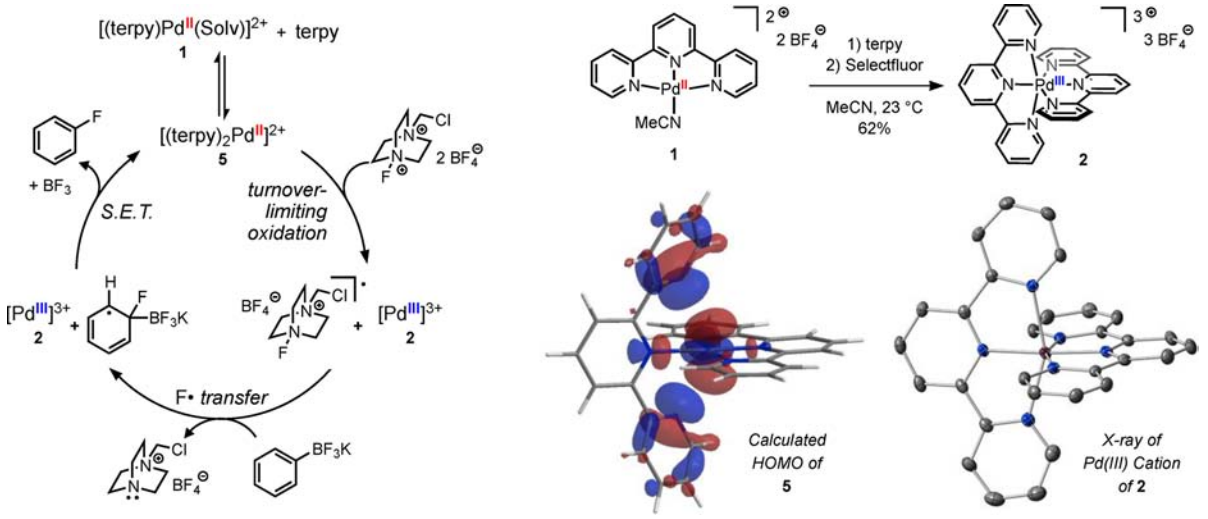
Scheme 2. Proposed Mechanism for Pd-Catalyzed Fluorination, Synthesis and X-ray Structure of Pd(III) Intermediate 2, and DFT Calculated Structure of Pd(II) Intermediate 5[a]



[a]terpy = 2,2′:6′,2″-terpyridine; Solv = solvent (DMF or MeCN). See Supporting Information for details of DFT calculations. X-ray structure of **2** is shown with 50% probability ellipsoids; H-atoms, counteranions, and solvent molecules omitted for clarity.

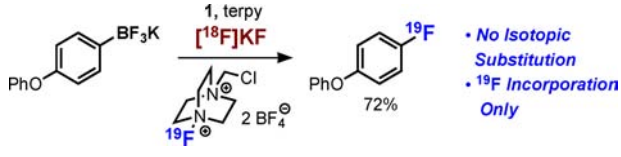
mononuclear Pd(III) intermediate. A mechanism that is consistent with the experimental data, as described below, is shown in Scheme 2: first, turnover-limiting oxidation of a bis-terpyridyl Pd(II) complex (**5**) by Selectfluor affords Pd(III) **2** and a Selectfluor radical cation; F$^{\bullet}$ transfer from the Selectfluor radical cation to an aryl trifluoroborate forms the C−F bond and generates a delocalized radical; finally, SET from the radical to **2** regenerates **5**, and provides a delocalized cation, which converts to the aryl fluoride with loss of BF_3. The generated BF_3 can react with fluoride anion or adventitious water, which may be why the addition of one equivalent of NaF typically increases the yield of aryl fluoride. Complexes of palladium in the +III oxidation state are uncommon, and have only recently been identified as relevant intermediates in organic and organometallic reactions.[9]

Aryl fluoride formation displayed a well-behaved kinetic profile throughout the course of the catalytic reaction, and no induction period was observed. Therefore, we were able to experimentally determine the rate law using initial rate kinetics, by monitoring aryl fluoride formation via ^{19}F NMR spectroscopy. The reaction displays first-order kinetic dependence on the palladium catalyst, saturation kinetics with respect to terpyridine, zero-order dependence on aryl trifluoroborate, and a non-integer kinetic order of 1.4 with respect to Selectfluor. The saturation behavior observed for terpyridine, along with *in situ* ^{1}H NMR spectroscopy of the reaction mixture, indicates a catalyst resting state consisting of an off-cycle equilibrium between bis-terpyridyl Pd(II) complex **5** and a terpyridyl Pd(II) solvento complex (e.g., **1**). In DMF, the equilibrium of **5** with **1** and free terpyridine is rapid, with a measured binding constant $K_a = 3 \times 10^3$. The non-integer kinetic order experimentally determined for Selectfluor suggests that Selectfluor also participates in a rapid equilibrium with **5**, prior to turnover-limiting oxidation (*vide infra*).

No reaction was observed between precatalyst **1** and aryl trifluoroborates in the presence or absence of exogenous terpyridine ligand, and less than 5% background reaction was observed between Selectfluor and the evaluated aryl trifluoroborates. When **1** was treated with one equivalent of terpyridine, followed by one equivalent of Selectfluor, a color change from orange to deep red occurred. The color persisted in MeCN, and crystallization afforded red needles of Pd(III) complex **2** in 62% yield. The structure of **2** was determined by X-ray crystallography (Scheme 2) and exhibits a Jahn−Teller distorted octahedral geometry. The identity of **2** in MeCN solutions was confirmed by EPR spectroscopy ($g = 2.09$ at 77 K), magnetic susceptibility, and UV−vis/NIR spectroscopy. The Jahn−Teller distorted octahedral geometry and the metric parameters of the terpyridine ligands are consistent with a d^7 configuration at Pd with an unpaired electron in a d_{z^2}-based orbital, rather than a ligand-centered radical, which is also supported by the UV−vis/NIR data and DFT calculations. In the solid state, **2** is stable for months under ambient conditions. Pd(III) complex **2** is a chemically competent catalyst in the fluorination reaction, and was not observed to react with aryl trifluoroborates in the absence of Selectfluor, consistent with the mechanism shown in Scheme 2. Additionally, **2** was not observed to react further when treated with additional Selectfluor, suggesting that a Pd(IV) intermediate is not accessible under the reaction conditions.

The structure of the initial complex formed by **1** and terpyridine, Pd(II) **5**, is predicted to have a pseudo-octahedral geometry, which is supported by DFT calculations. The calculated HOMO of **5**, shown in Scheme 2, is primarily of d_{z^2} parentage with respect to palladium and antibonding between palladium and the apical pyridyl ligands. Removal of one electron from the HOMO results in the Jahn−Teller distorted structure displayed by **2**. Selectfluor's ability to act as a single-electron oxidant has been supported through a combination of experimental and theoretical studies.[10] Electrochemical measurements show that oxidation of Pd(II) **5** to Pd(III) **2** does not proceed by outer-sphere SET, which suggests the formation of an intermediate adduct between **5** and Selectfluor. The formation of

Scheme 3. Isotopic Labeling Experiment



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such an adduct is also consistent with the non-integer kinetic order measured for Selectfluor (1.4). The specific mode of interaction between the palladium catalyst and Selectfluor is unclear at this point, but is likely critical to the success of the fluorination reaction; we speculate that the fluxional binding of terpyridine in **5** is important to the observed reactivity (see Supporting Information).

The observation of turnover-limiting oxidation during catalysis prevents us from studying the C−F bond-forming step via kinetic analysis. We postulate that C−F bond formation occurs via one of two pathways after initial oxidation of **5** by Selectfluor: (1) direct $F^{\bullet}$ transfer to the aryl trifluoroborate or (2) SET from the aryl trifluoroborate to the Selectfluor radical cation, to afford a radical cation, followed by nucleophilic attack of fluoride. In both cases, one-electron oxidation of the resulting radical by Pd(III) **2**, as shown in Scheme 2, would afford product and regenerate Pd(II) **5**. We carried out an isotopic labeling experiment to distinguish between the two pathways, in which the fluorination reaction was performed in the presence of exogenous [^{18}F]fluoride. Aryl fluoride formation proceeded in 72% yield, but no incorporation of the ^{18}F label was observed (Scheme 3). While the SET/fluoride attack pathway via a tight solvent cage mechanism cannot be rigorously excluded, the absence of ^{18}F incorporation suggests the $F^{\bullet}$ transfer pathway for C−F bond formation.

In previously reported metal-mediated or -catalyzed arene fluorination reactions, including our group's palladium- and silver-mediated fluorination of arylboronic acids, carbon−fluorine bond formation is proposed to occur via reductive elimination from an aryl−metal fluoride complex.[11] The palladium-catalyzed fluorination reaction presented here is unusual in that it seems to proceed without the formation of organopalladium intermediates, yet provides high levels of selectivity.

In conclusion, we have reported the first metal-catalyzed fluorination of arylboronic acid derivatives. The reaction proceeds under mild conditions, is tolerant toward moisture and air, and is amenable to multigram-scale synthesis of functionalized aryl fluorides. We propose a single-electron-transfer mechanism involving a well-defined Pd(III) intermediate. This reaction provides a level of practicality and operational simplicity not previously achieved by metal-catalyzed or -mediated arene fluorination reactions, and does not generally afford side products from protodemetalation, a common problem for the synthesis of aryl fluorides. Drawbacks of the reaction include the inability to fluorinate heterocycles and the formation of constitutional isomers for some electron-poor substrates.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectroscopic data for all new compounds, details of DFT calculations, and crystallographic data for **1**, **2**, **S1**, and **S2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ritter@chemistry.harvard.edu

Author Contributions

‡A.R.M. and M.G.C. contributed equally.

Notes

The authors declare no competing financial interest.

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