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Pd-Catalyzed Nucleophilic Fluorination of Aryl Bromides

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S Supporting Information

ABSTRACT: On the basis of mechanism-driven reaction design, a Pd-catalyzed nucleophilic fluorination of aryl bromides and iodides has been developed. The method exhibits a broad substrate scope, especially with respect to nitrogen-containing heteroaryl bromides, and proceeds with minimal formation of the corresponding reduction products. A facilitated ligand modification process was shown to be critical to the success of the reaction.

In recent years, the synthesis of fluorinated arenes has attracted much attention from the community of synthetic organic chemists as a result of the importance of these compounds in pharmaceutical¹ and radiological² applications. Among the various strategies for their preparation,³ nucleophilic fluorination of aryl (pseudo)halides with a metal fluoride salt (MF) is ideal because of the wide availability of substrates and easy access to the fluoride source.⁴ In 2009, we reported a method for the nucleophilic fluorination of aryl triflates, and to a lesser extent aryl bromides, using Pd catalysts based on bulky biarylphosphine ligands.⁵ However, only highly activated (i.e., ortho-substituted and electron-deficient) aryl bromides could be successfully fluorinated. More recently, we described an improved system for the fluorination of aryl triflates using AdBrettPhos (**1**)-based Pd precatalyst **2** (Figure 1).⁶

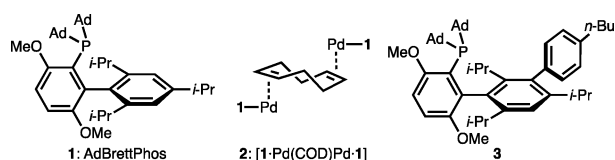


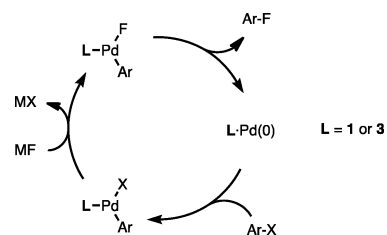
Figure 1. Structure of ligands **1** and **3** and precatalyst **2**.

Since our initial report, however, only a single method that converts unactivated aryl halides to the corresponding aryl fluorides (a Cu-mediated fluorination of aryl iodides) has been described.⁷ However, this reaction, like many other transition-metal-mediated fluorination methods, is hampered by the formation of reduction products that are usually difficult to separate from the desired aryl fluoride. Herein we report a practical method for the Pd-catalyzed nucleophilic fluorination of (hetero)aryl bromides that are not activated toward direct nucleophilic substitutions or transition-metal-mediated reactions.^{3b} Our system is applicable to the fluorination of widely available aryl bromides,⁸ and the process does not result in significant reduction of the aryl halide. Reduction products were not observed for a majority of the examples. In those cases for which reduction products were formed, the amount of Ar–H

ranged from 0.10% to 1.6% with an average of 0.5%. In only one case was the reduction product formed in greater than 1% yield (see the Supporting Information).⁹

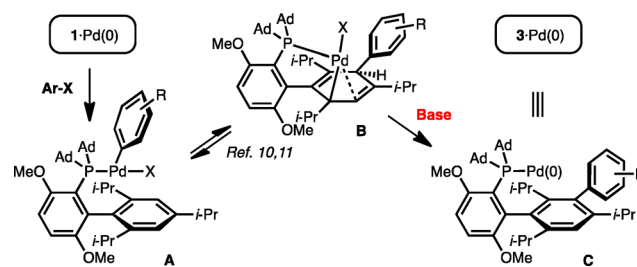
To expand our previously reported strategy (X = OTf, M = Cs; Scheme 1) to the reaction of aryl bromides, we hypothesized that

Scheme 1. Catalytic Cycle of Pd-Catalyzed Fluorination



two modifications would be required. First, a more reactive metal fluoride might be necessary to facilitate transmetalation, since the Pd(II) center of an aryl bromide oxidative addition complex is less readily substituted than that of a cationic triflate complex. We postulated that AgF, containing the bromophilic Ag(I) counterion, might drive the transmetalation by irreversible formation of AgBr. Second, a substoichiometric amount of base might be required to facilitate ligand activation. In our recent report, we showed that base induces an in situ ligand modification during the catalytic fluorination of aryl triflates (Scheme 2, A to B to C, X

Scheme 2. Ligand Modification during the Catalytic Fluorination



= OTf) and that the catalyst is effective only when it is supported by the modified ligand.¹⁰ In addition, this event was shown to be more pronounced in the case of aryl halide oxidative addition complexes (Scheme 2, A to B, X = Cl or Br),¹¹ suggesting that the process is important in the catalytic fluorination of aryl bromides. We reasoned that AgF might not be basic enough to induce the elimination of HX (Scheme 2, B to C), rendering the ligand

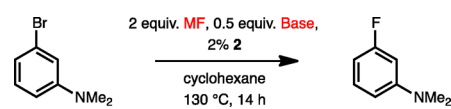
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modification inefficient. Therefore, it was initially hypothesized that the introduction of a substoichiometric amount of base would promote the formation of C [3·Pd(0)].

To test this hypothesis, the fluorination of 3-bromo-*N,N*-dimethylaniline was attempted using precatalyst **2** as the Pd source (Table 1).¹² As expected, a metal fluoride alone was not

Table 1. Effect of Base in the Pd-Catalyzed Fluorination of an Aryl Bromide Using Precatalyst **2^a**



entry	MF	base	yield (%) ^b
1	KF	—	0
2	CsF	—	0
3	AgF	—	0
4	AgF	NaHCO ₃	0
5	AgF	K ₂ CO ₃	11
6	AgF	K ₃ PO ₄	21
7	AgF	NaF	0
8	AgF	KF	71
9	AgF	CsF	65

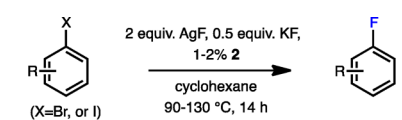
^aReaction conditions: 3-bromo-*N,N*-dimethylaniline (0.10 mmol), MF (0.20 mmol), base (0.050 mmol), **2** (0.0020 mmol), cyclohexane (1 mL), 130 °C, 14 h. ^bDetermined by ¹⁹F NMR analysis.

effective in promoting the transformation (entries 1–3). However, when AgF was used in combination with 0.5 equiv.¹³ of K₂CO₃ (entry 5) or K₃PO₄ (entry 6), the desired aryl fluoride product was formed in modest yield, while the use of NaHCO₃ was ineffective (entry 4). Ultimately, fluoride bases (except NaF) were shown to be the most effective for promoting the reaction in high yield (entries 7–9). Even though KF and CsF are equally competent, inexpensive and less hygroscopic KF was chosen as the base for reasons of cost and practicality.

The optimized reaction conditions were applied to the fluorination of a variety of aryl bromides and iodides (Table 2).¹⁴ Substrates with ortho (**4** and **5**), meta (**6–13**), and para (**14–19**) substituents were fluorinated with comparable efficiencies regardless of the electronic nature of the substituents. Importantly, base-sensitive functional groups such as methyl sulfone (**6**), fluorene (**10**), and ketone (**14** and **15**) groups were tolerated, as were nitrile (**7**), ester (**8**), and amide (**16**) groups, which are common in pharmaceutical compounds. In addition, substrates that are not amenable to electrophilic fluorination because of potential oxidation, such as alkyl sulfides (**9**) and electron-rich amines (**12** and **13**), were also fluorinated in good yields.¹⁵ Unactivated aryl iodides were also viable substrates for this reaction (**10**, **14**, and **17**). Analogous to our fluorination of aryl triflates, 4-bromoanisole, which is electron-rich and lacks ortho substituents, provided a mixture of regioisomers (**19**).^{5,6}

We next tried to extend this methodology to the fluorination of heteroaryl bromides using 3-bromo-5-cyanopyridine as a representative substrate. Even though the addition of KF significantly improved the reaction, the conditions failed to provide the fluorinated heteroarene in a satisfactory yield (Table 3, entries 1 and 2). To remedy this situation, we decided to use a precatalyst with a new ligand that had been modified *ex situ*. We postulated that with heteroaryl substrates, either the ligand modification process is not facile or the resulting modified ligand (analogous to **3**) is not effective for the fluorination reaction.

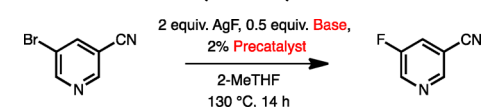
Table 2. Pd-Catalyzed Fluorination of Aryl Halides Using Precatalyst **2^a**



4^b X=Br: 94% (2.0% 2 , 90 °C)	5^c X=Br: 73% (2.0% 2 , 130 °C)	6^b X=Br: 75% (1.0% 2 , 110 °C)	7^c X=Br: 73% (1.5% 2 , 110 °C)	8^c X=Br: 93% (1.0% 2 , 110 °C)
9^c X=Br: 69% (2.0% 2 , 110 °C)	10 X=I: 76% α:β = 17:1 (2.0% 2 , 130 °C)	11 X=Br: 88% m:p > 50:1 (1.5% 2 , 110 °C)	12 X=Br: 86% (1.5% 2 , 120 °C)	13 X=Br: 86% m:p > 50:1 (1.0% 2 , 120 °C)
14^c X=I: 86% (1.0% 2 , 90 °C)	15 X=Br: 87% (1.0% 2 , 110 °C)	16 X=Br: 92% (1.5% 2 , 90 °C)	17 X=Br: 90% p:m = 33:1 (1.5% 2 , 90 °C)	18 X=I: 92% p:m = 24:1 (2.0% 2 , 90 °C)
				19^c X=Br: 70% p:m = 1:2.7 (2.0% 2 , 130 °C)

^aIsolated yields (averages of two runs) are shown. Reaction conditions: aryl halide (1.0 mmol), AgF (2.0 mmol), KF (0.50 mmol), **2** (0.010–0.020 mmol), cyclohexane (10 mL), 14 h. ^bToluene was used as the solvent. ^c0.50 mmol scale; yield was determined by ¹⁹F NMR analysis.

Table 3. Effects of Precatalyst and KF in the Pd-Catalyzed Fluorination of a Heterocyclic Aryl Bromide^a

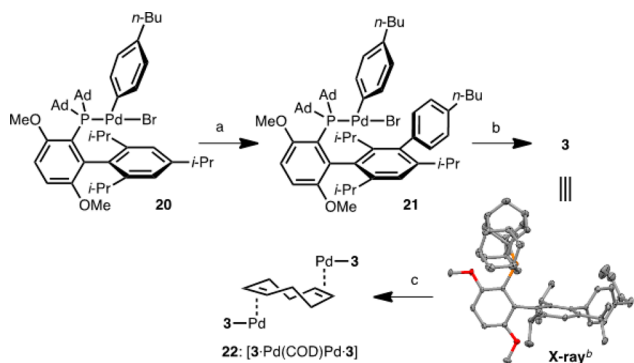


entry	precatalyst	base	yield (%) ^b
1	2	—	11
2	2	KF	48
3	22	—	21
4	22	KF	72

^aReaction conditions: 3-bromo-5-cyanopyridine (0.10 mmol), AgF (0.20 mmol), KF (0.050 mmol), **2** or **22** (0.0020 mmol), 2-MeTHF (1 mL), 130 °C, 14 h. ^bDetermined by ¹⁹F NMR analysis.

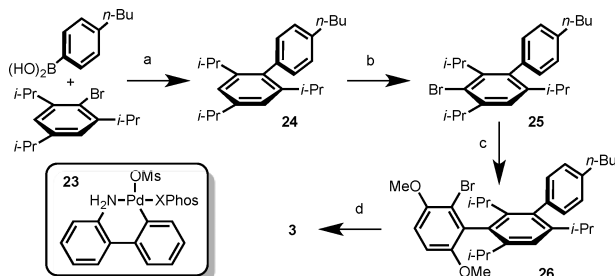
Therefore, by using a premodified ligand such as **3**, we could circumvent the modification process altogether, allowing us to take full advantage of the established system.

A synthetic route to ligand **3** is described in Scheme 3.¹⁶ The known oxidative addition complex **20**¹¹ underwent the desired rearrangement, elimination, and oxidative addition cascade in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1-bromo-4-*n*-butylbenzene.¹⁰ The new complex **21** with the modified ligand was treated with excess propane-1,2-diamine to provide free phosphine **3** in 49% overall yield from **20**. Ligand **3** was successfully converted to the corresponding cyclooctadiene-ligated Pd(0) precatalyst **22** using our reported conditions.^{6,17}

Scheme 3. First Synthesis of Ligand 3 and Precatalyst 22^a

^aReagents and conditions: (a) DBU, 1-bromo-4-*n*-butylbenzene, THF, 23 °C, 12 h, 81%. (b) Propane-1,2-diamine, THF, 23 °C, 12 h, 61%. (c) [(COD)Pd(CH₂TMS)₂], pentane, 23 °C, 48 h, 79%. ^bEllipsoids are shown at 50% probability.

Alternatively, a more robust and scalable synthesis was also developed for access to 3 on a gram scale (Scheme 4). The 4-*n*-

Scheme 4. Scalable Synthesis of Ligand 3^a

^aReagents and conditions: (a) 23 (1.0 mol %), K₃PO₄, THF/H₂O, 80 °C, 12 h, 99%. (b) Br₂, DMF/CH₂Cl₂, 0 °C, 30 min, 76%. (c) *t*-BuLi, THF, −78 °C, 1 h; added to 2-fluoro-1,4-dimethoxybenzene and *n*-BuLi in THF, −78 to 0 °C, 2 h; Br₂, 0 °C, 30 min, 65%. (d) *t*-BuLi, THF, −78 °C, 1 h; CuCl; Ad₂PdCl, toluene, 140 °C, 48 h, 54%.

butylphenyl moiety was installed by Suzuki–Miyaura cross-coupling of commercially available 4-*n*-butylphenylboronic acid in the presence of XPhos-based precatalyst 23.¹⁸ The resulting biaryl 24 was monobrominated to furnish 25, which was converted to the desired product via triaryl 26 using our previously reported protocol.¹⁹

The new precatalyst 22 (Table 3, entry 3) showed improved reactivity compared to 2 (entry 1). Unexpectedly, the use of 22 alone with AgF (entry 3) was not as effective as the combined use of 2 with KF and AgF (entry 2). Only when a combination of KF and AgF was used with 22 was the product obtained in high yield (entry 4). This result suggests that KF plays a role beyond simply assisting the modification of 1.²⁰

Employing 22 enabled the successful preparation of fluorinated heteroarenes that are not accessible through traditional S_NAr reactions (Table 4). Importantly, the use of 22 rather than 2 for the fluorination of heteroaryl bromides provided superior results in almost all instances (the yields obtained using 2 under identical conditions are shown in parentheses for selected cases).²¹ In addition, reduction products were not observed (by GC) in the purified samples in any case, with the exception of 30, for which 0.10% Ar–H was observed. 3-Fluoropyridine derivatives with varying electronic properties

Table 4. Pd-Catalyzed Fluorination of Heterocyclic Aryl Bromides Using Precatalyst 22^a

2 equiv. AgF, 0.5 equiv. KF, 1–3% 22		2-MeTHF 90–150 °C, 14 h		
HetAr–Br		HetAr–F		
27 76% (2.0% 22, 110 °C)	28 89% (18% ^{b, c}) (1.0% 22, 90 °C)	29 71% (3.0% 22, 150 °C)	30 ^d 86% (19% ^{b, c}) (2.0% 22, 110 °C)	31 75% (46% ^{b, c}) (2.0% 22, 130 °C)
32 84% (73% ^{b, c}) (1.5% 22, 90 °C)	33 ^e 96% (1.5% 22, 90 °C)	34 ^d 90% (75% ^{b, c}) (1.5% 22, 110 °C)	35 88% (1.0% 22, 110 °C)	36 ^f 51% ^g (9% ^{b, c}) (3.0% 22, 150 °C)
37 ^d 90% (1.0% 22, 110 °C)	38 73% (68% ^{b, c}) (1.5% 22, 110 °C)	39 ^f 69% (2.0% 22, 130 °C)		

^aIsolated yields (averages of two runs) are shown. Reaction conditions: aryl halide (1.0 mmol), AgF (2.0 mmol), KF (0.50 mmol), 22 (0.010–0.030 mmol), 2-MeTHF (10 mL), 14 h. ^b0.10 mmol scale. ^cDetermined by ¹⁹F NMR analysis. ^dTBME was used as the solvent. ^eCyclohexane was used as the solvent. ^f0.50 mmol scale.

were prepared from the corresponding bromides (27–29), although 3-bromopyridine itself furnished a 1:1 para/meta mixture of aryl fluoride regioisomers (not shown). In line with our previous observations, forcing conditions were required to synthesize electron-rich fluoropyridine 29.⁶ Indole (30), quinoline (31–33), and isoquinoline (34 and 35) derivatives were also prepared in high yields. Heteroaryl bromides with more than one nitrogen atom, such as pyrimidine (36), indazole (37), and quinoxaline (38), were also suitable substrates. Finally, the vascular disorder drug Nicergoline (Sermion)²² was fluorinated to provide analogue 39. This result suggests that our methodology should be viable for the late-stage fluorination of advanced intermediates where pharmaceutically relevant functional groups are present. Notably, five-membered heteroaryl halides remain challenging substrates for this methodology.

In conclusion, we have developed a new Pd-catalyzed method for converting unactivated (hetero)aryl bromides and iodides to the corresponding fluorides. The reaction proceeds without significant formation of reduction byproducts, which are difficult to separate from the desired product. The success of the reaction stems from the use of AgF with added KF to promote the reaction and from control of the ligand modification process we previously observed. Future efforts will be focused on identifying the exact role of KF during the reaction and applying this methodology to the synthesis of ¹⁸F-containing radiotracers.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare the following competing financial interest(s): MIT has obtained or has filed patents on some of the ligands/precatalysts that are described in the paper from which S.L.B. and former/current coworkers receive royalty payments.

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- (12) Other sources of Pd were also evaluated; we found that precatalyst **2** is the most effective Pd source. See the Supporting Information for details.
- (13) The optimal loading of KF was found to be 0.5 equiv. See the Supporting Information for details.
- (14) To date, this reaction is not effective for unactivated aryl chlorides and substrates with bulky ortho substituents, likely because of slower

transmetalation with AgF in these cases. Unprotected amino/hydroxyl groups are also not tolerated.

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- (16) Preliminary unpublished results suggest that **3** containing 4-*n*-butylphenyl gives the highest yield compared with ligands modified with other aryl groups.
- (17) Similar to **2**, precatalyst **22** is insoluble in most organic solvents. Therefore, spectroscopic characterization was not possible. However, it readily forms the oxidative addition complex **21** and 1,5-COD upon exposure to 1-bromo-4-*n*-butylbenzene. See the Supporting Information for details.
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