Pd-Catalyzed Nucleophilic Fluorination of Aryl Bromides
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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.8 Our system is applicable to the fluorination of widely available aryl bromides,4 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 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 = 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). As expected, a metal fluoride alone was not effective in promoting the transformation (entries 1–3). However, when AgF was used in combination with 0.5 equiv of K$_2$CO$_3$ (entry 5) or K$_3$PO$_4$ (entry 6), the desired aryl fluoride product was formed in modest yield, while the use of NaHCO$_3$ 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. Unactivated aryl iodides were also viable substrates for this reaction (10, 14, and 17). Analogous to our fluorination of aryl triflates, 4-bromomethanesulfonate, which is electron-rich and lacks ortho substituents, provided a mixture of regioisomers (19). $^{3,6}$

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.

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. The known oxidative addition complex 20 underwents 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. 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. $^{21}$

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           |

$^a$Reaction 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. $^b$Determined by $^{19}$F NMR analysis.

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

| entry | precatalyst | base  | yield (%)$^b$ |
|-------|-------------|-------|--------------|
| 1     | 2           | –     | 11           |
| 2     | 2           | KF    | 48           |
| 3     | 2           | –     | 21           |
| 4     | 2           | KF    | 72           |

$^a$Reaction 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. $^b$Determined by $^{19}$F 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     | 2           | –     | 21           |
| 4     | 2           | KF    | 72           |

$^a$Reaction 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. $^b$Determined by $^{19}$F NMR analysis.

$^c$Determined by $^{19}$F NMR analysis.
Reagents and conditions: (a) DBU, 1-bromo-4-n-buty1benzene, 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%. Ellipsoids 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-butylphenyl moiety was installed by Suzuki coupling of commercially available 4-iodoacetophenone with 3-bromopyridine and 2-MeTHF (0.010 mmol), 2-MeTHF (10 mL), 14 h. 0.10 mmol scale. Determined by 19F NMR analysis. TBME was used as the solvent. Cyclohexane was used as the solvent. 0.50 mmol scale.

Butylphenyl moiety was installed by Suzuki–Miyaura cross-coupling of commercially available 4-n-buty1phenylboronic 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 coupling of commercially available 4-iodoacetophenone with 3-bromopyridine and 2-MeTHF (0.010 mmol), 2-MeTHF (10 mL), 14 h. 0.10 mmol scale. Determined by 19F NMR analysis. TBME was used as the solvent. Cyclohexane was used as the solvent. 0.50 mmol scale.

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.
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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**REFERENCES**

1. For reviews, see: (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Angew. Chem., Int. Ed. 2012, 51, 11426. (b) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. Angew. Chem., Int. Ed. 2008, 47, 8998. For recent examples, see: (a) Lee, E.; Hooker, J. M.; Ritter, T. J. Am. Chem. Soc. 2012, 134, 17456. (b) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. Science 2011, 334, 639.

2. For a review, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. Angew. Chem., Int. Ed. 2013, 52, 8214. Also see: (b) Mu, X.; Zhang, H.; Chen, P.; Liu, G. Chem. Sci. 2014, 5, 275. (c) Fier, P. S.; Hartwig, J. F. Science 2013, 342, 956. (d) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. J. Am. Chem. Soc. 2013, 135, 16292. (e) Ichishii, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. Org. Lett. 2013, 15, 5134. (f) Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. J. Am. Chem. Soc. 2013, 135, 14012. (g) Tran, T.; Klimovic, K.; Daugulis, O. J. Am. Chem. Soc. 2013, 135, 9342. (h) Ye, Y.; Sanford, M. S. J. Am. Chem. Soc. 2013, 135, 4648. (i) Fier, P. S.; Luo, J.; Hartwig, J. F. J. Am. Chem. Soc. 2013, 135, 2552.

3. (a) Hollingworth, C.; Gouverneur, V. Chem. Commun. 2012, 48, 2929. (b) Grushin, V. V. Acc. Chem. Res. 2010, 43, 160.

4. (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. Science 2009, 325, 1661. (b) Lee, H. G.; Milner, P. J.; Buchwald, S. L. Org. Lett. 2013, 15, 5602.

5. (a) Fier, P. S.; Hartwig, J. F. J. Am. Chem. Soc. 2012, 134, 10795.

6. (b) Related fluoride effects have been documented. See: (a) Su, W.; Radler, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. Angew. Chem., Int. Ed. 2006, 45, 5852. (b) Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S. L. Org. Lett. 2011, 13, 4974.

7. (1) For reviews, see: (a) Tredwell, M.; Gouverneur, V. Acc. Chem. Res. 2012, 45, 135, 342. (b) Fors, B. P.; Doolweerd, K.; Zeng, Q.; Buchwald, S. L. Tetrahedron 2009, 65, 6576.

8. Other sources of Pd were also evaluated; we found that precatalyst 2 is the most effective Pd source. See the Supporting Information for details.

9. Related fluoride effects have been documented. See: (a) Su, W.; Radler, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. Angew. Chem., Int. Ed. 2006, 45, 5852. (b) Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S. L. Org. Lett. 2011, 13, 4974.

10. The starting materials corresponding to 4-n-butyphenyl were contaminated with 0.85% and 0.3% Ar·H, respectively. See the Supporting Information for details.

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12. Related fluoride effects have been documented. See: (a) Su, W.; Radler, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. Angew. Chem., Int. Ed. 2006, 45, 5852. (b) Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S. L. Org. Lett. 2011, 13, 4974.

13. It was discovered that 22 is not as effective as 2 for certain non-heterocyclic substrates. This result suggests that 4-n-butyphenyl may not be the best modifying group for the fluorination of non-heterocyclic substrates. The origin of this effect is under investigation in our lab. However, ligand 3 was chosen for study because of its ease of synthesis and generality.

14. For details.