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An Improved Catalyst System for the Pd-Catalyzed Fluorination of (Hetero)Aryl Triflates

Hong Geun Lee,† Phillip J. Milner,† and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

sbuchwal@mit.edu

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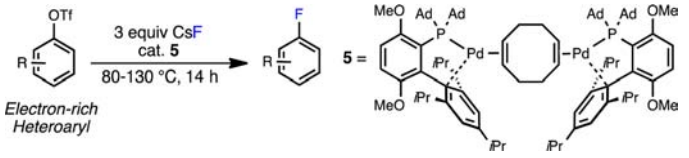
ABSTRACT



The stable Pd(0) species [(1,5-cyclooctadiene)(L·Pd)$_2$] (L = AdBrettPhos) has been prepared and successfully evaluated as a precatalyst for the fluorination of aryl triflates derived from biologically active and heteroaryl phenols, challenging substrates for our previously reported catalyst system. Additionally, this precatalyst activates at room temperature under neutral conditions, generates 1,5-cyclooctadiene as the only byproduct, and leads to overall cleaner reaction profiles.

Fluorination of aromatic rings is a widely used strategy for modifying the biological activities of potential pharmaceutical and agrochemical agents.[1] In addition, ^{18}F-substituted compounds are important radiotracers for positron emission tomography (PET).[2] Aryl fluorides are typically installed early in a target molecule's synthesis using the harsh Balz–Schiemann reaction, making the synthesis of ^{18}F-radiotracers and highly functionalized fluorinated materials difficult. Although a number of methods for electrophilic aryl fluorination with Ag,[3] Pd,[4] and Cu[5] catalysts, and without added transition metals,[6] have been developed to address this need, these reactions typically do not tolerate easily oxidizable functional groups such as tertiary amines and electron-rich heterocycles, result in 5–50% reduction of the starting material, and/or require the synthesis of unstable or toxic organometallic reagents. The direct transformation of aryl (pseudo)halides to aryl fluorides using a metal fluoride salt is a promising alternative to electrophilic fluorination in terms of generality and practicality[7] that has received less attention than electrophilic fluorination methods.[8] To this end, we reported the successful coupling of aryl triflates with CsF using a Pd catalyst based on the bulkyl biaryl phosphine ligand *t*BuBrettPhos (**1**) (Figure 1).[9,10]

† These authors contributed equally.

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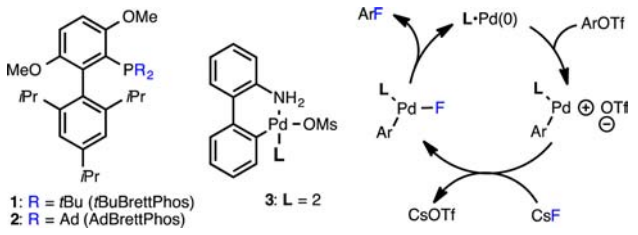
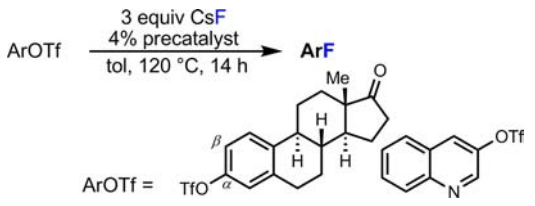


Figure 1. Ligands and precatalysts for the Pd-catalyzed fluorination of aryl triflates.

However, there remains a strong need for the further development of simple methods for aryl fluorination that demonstrate a broad substrate scope and clean reaction profiles.

Table 1. Fluorination with Catalysts Based on **1** or **2**[a]



entry	Pd source	ligand (L:Pd = 1.5:1)	ArF yield	ArF yield
1	[(cinnamyl)PdCl]$_2$	**1**	< 20%	30%[b]
2	[(cinnamyl)PdCl]$_2$	**2**	75% (α:β = 8:1)[b]	70%[b]
3	Pd(OAc)$_2$	**2**	0%	0%
4	Pd$_2$(dba)$_3$	**2**	58% (α:β = 7:1)	0%
5	Pd(dba)$_2$	**2**	73% (α:β = 5:1)	47%
6	**3**	-	35%	50%
7	**2**•Pd(4-*n*BuPh)OTf	-	63% (α:β = 8:1)	66%
8	**5**	-	72% (α:β = 13:1)	70%

[a] Reaction conditions: Aryl triflate (0.1 mmol), CsF (0.3 mmol), 4% "Pd", tol (0.1 M), 120 °C, 12 h. ^{19}F NMR yields. [b] Corresponding ArCl detected by GC analysis.

Our original catalyst system of [(cinnamyl)PdCl]$_2$/**1** facilitates the catalytic fluorination of a variety of aryl triflates with minimal formation (< 5%) of the corresponding reduction product.[9b] However, this method suffers from poor reactivity with highly electron-rich and heteroaryl substrates, such as estrone and 3-quinolinyl triflates (Table 1, entry 1). After extensive investigation, a catalyst system based on the related ligand AdBrettPhos (**2**)[11] (Figure 1) was found to be more capable in the fluorination of these substrates (Table 1, entry 2), though formation of two regioisomeric aryl fluorides was observed in the case of estrone triflate.[9b] The effectiveness of a catalyst based on **2** is likely due to the faster rate of reductive elimination from Pd−F intermediates bearing **2** compared to those bearing **1**.[11] However, the use of [(cinnamyl)PdCl]$_2$ as the source of active Pd requires 1.5 equiv of **2** relative to Pd to be added and results in generation of 1 equiv of "Cl$^-$", which participates in a competitive cross-coupling process to produce the corresponding aryl chloride. In some cases, this side product can be difficult to separate from the desired aryl fluoride product. Thus, we evaluated alternative Pd sources in conjunction with **2**. However, other Pd sources, such as Pd(OAc)$_2$ (Table 1, entry 3), Pd$_2$(dba)$_3$ (Table 1, entry 4), and Pd(dba)$_2$ (Table 1, entry 5), did not prove as effective as [(cinnamyl)PdCl]$_2$ for one or both of these substrates.[12] In contrast to the use of separate sources of Pd and ligand, we have found that precatalysts are superior in terms of convenience, efficiency of catalyst generation, and the use of only 1 equiv of ligand relative to Pd.[13] However, when our third generation palladacycle precatalyst **3**[14] (Figure 1) was employed in the fluorination of estrone and 3-quinolinyl triflates, low yields of the desired products were obtained (Table 1, entry 6). The low yields result from arylation of the carbazole generated as the byproduct of catalyst activation, resulting in an overall formation of 2 equiv of HF, which is also detrimental to the reaction yield.[15] Only when **2**·Pd(4-*n*BuPh)OTf (**4**) was employed as catalyst could high yields of these aryl fluoride products be obtained without formation of the aryl chloride side product or the need for excess **2** relative to Pd (Table 1, entry 7). Based on these results, a precatalyst bearing **2** that activates without producing reactive and/or inhibitory byproducts, such as chloride, dba, carbazole, or HF, would be ideal for this transformation.

In pursuit of such a species, we found that simply combining equimolar quantities of **2** and [(1,5-COD)Pd(CH$_2$TMS)$_2$] (COD = cyclooctadiene) together in pentane resulted in precipitation of a pale yellow solid (**5**) (Figure 2); due to the lack of oxidant present in this reaction, we anticipated that **5** was an isolable Pd(0) species. The filtrate of this reaction mixture contained 53% of the starting amount of COD[16] and minimal quantities of **2**, suggesting that **5** possesses a 2:2:1 ratio of **2**/Pd/1,5-COD. However, assessing the structure of **5** by solution-state NMR proved difficult due to its insolubility or instability in all tested organic solvents (see Supporting Information).

(10) Notably, Ritter has recently disclosed a straightforward method for transition-metal-free direct deoxyfluorination of phenols, but this methodology requires anhydrous reaction conditions and stochoimetric quantities of Phenofluor, which is expensive and moisture sensitive. See: Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.

(11) Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 4710.

(12) When 0.1 equiv of dba was added to the reactions in Table 1, entry 1, an identical yield of fluorodeoxyestrone (66%, α:β = 5:1), but a diminished yield of 3-fluoroquinoline (40%), was observed. Thus, in the case of fluorination of heteroaryl triflates, dba likely inhibits the desired transformation. See: Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176.

(13) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916and the references cited therein.

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(15) In reactions conducted with **1**, HF is also generated as a result of 3′-arylation of the ligand. Our results suggest that HF is detrimental to the yield; see: Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.

(16) GC analysis of the filtrate showed 11% of 1,3-COD, 33% 1,5-COD, and 9% of what is likely 1,4-COD to be present (determined by assuming an identical response factor that of 1,5-COD). Although isomerization of alkenes in the presence of Pd(0) has not been reported, isomerization in the presence of Pd(II) has been thoroughly studied.

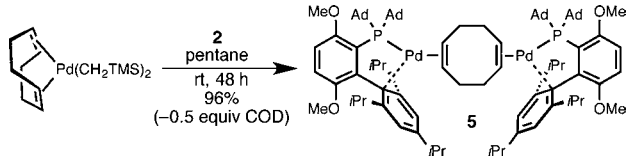
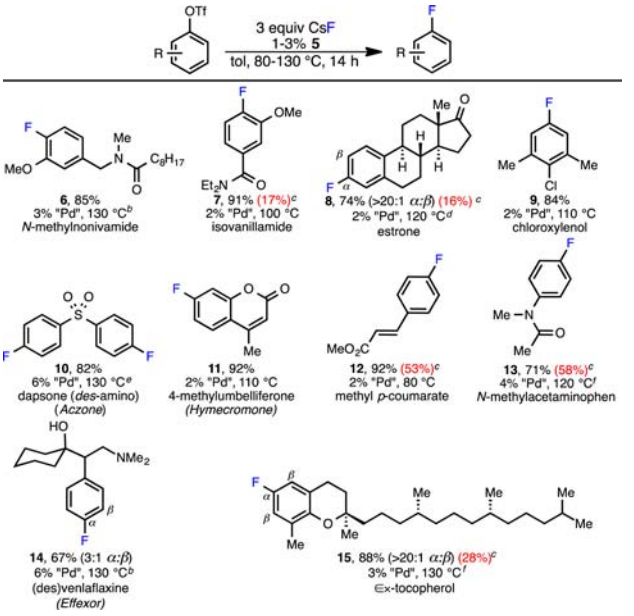


Figure 2. Synthesis of Pd(0) species **5** from **2** and [(1,5-COD)-$Pd(CH_2TMS)_2$].

Nonetheless, when exposed to 4-*n*BuPhOTf in toluene-d_8, **5** quantitatively converts to **2**·(4-*n*BuPh)PdOTf (**4**) in less than 10 min at room temperature under neutral conditions, generating 0.5 equiv of 1,5-COD relative to Pd in the process. Significantly, when this experiment was repeated using **5** that had been exposed to air for 24 h on the benchtop, the ^{1}H NMR yield of **4** produced was only diminished to 83%, suggesting that the half-life of **5** in air is on the order of days. Based on the available structural information, we propose a C_2-symmetric structure for **5** wherein two trigonal-planar Pd(0) centers, each ligated by a molecule of **2**, are coordinated to a double bond of the 1,5-COD ligand (Figure 2); a similar structure has been proposed for the complex [(1,5-COD)(dippe·Pd)$_2$] (dippe = 1,2-bis(diisopropylphosphino)ethane).[17] Despite containing two reactive tricoordinate Pd(0) centers, **5** is indefinitely stable at rt in a glovebox or when stored under N_2 in a benchtop desiccator. Collectively, these results suggest that dissociation of the 1,5-COD ligand from **5** is very facile at rt, even though **5** itself is relatively stable and easy to handle. Most importantly, **5** is also an excellent precatalyst for the fluorination of estrone and 3-quinolinyl triflates (Table 1, entry 8), providing yields comparable to those obtained with [(cinnamyl)PdCl]$_2$/**2** without generation of aryl chloride byproducts.[18] By GC analysis, the only side products observed were trace amounts (< 5%) of the reduction product and the corresponding biaryl ethers.[9b] In light of these results, the ability of **5** to function as a precatalyst for the fluorination of aryl triflates derived from heterocyclic and biologically active phenols, the substrates for which incorporation of fluorine centers is most important, was further investigated (Schemes 1 and 2).

Fluorination could be cleanly carried out on the triflate derivatives of various naturally occurring phenols (Scheme 1). These include the *N*-methyl derivative of nonivamide (pseudocapsaicin, **6**), the diethyl amide of isovanillin (**7**), estrone (**8**), the plant-derived antioxidant methyl *p*-coumarate (**12**), and *δ*-tocopherol (**15**). In addition, the fluorinated derivatives of a number of phenol-containing

Scheme 1. Fluorination of Aryl Triflates Derived from Biologically Active Phenols[a]



[a] Isolated yields, average of two runs. Reaction conditions unless otherwise noted: Aryl triflate (1 mmol), CsF (3 mmol), **5** (1–3%), tol (0.1 M). [b] Aryl triflate (0.5 mmol), CsF (1.5 mmol), **5** (1.5–3%), tol (0.1 M). [c] Yield when conducted under same reaction conditions using [(cinnamyl)PdCl]$_2$/**1** (Pd/**1** = 1:1.5) instead of **5**. Aryl triflate (0.1 mmol), CsF (0.3 mmol), ^{19}F NMR yield. [d] Aryl triflate (0.5 mmol), CsF (1.5 mmol), **5** (1%), cy (0.1 M). [e] Aryl triflate (0.5 mmol), CsF (3 mmol), **5** (3%), tol (0.1 M). [f] Aryl triflate (1 mmol), **5** (1.5–2%), cy (0.1 M).

pharmaceuticals could be accessed, including the antimicrobrial chloroxylenol (**9**),[19] the chloretic 4-methylumbelliferone (Hymecromone, **11**),[20] the *N*-methyl derivative of the analgesic acetaminophen (**13**), the antidepressant (des)venlaflaxine (**14**),[21] and *N*-methylnonivamide, whose relative, capsaicin, has a number of promising medicinal uses (Scheme 1).[22] The des-aminofluorinated analog of the antibacterial dapsone (Aczone)[23] could also be prepared (**10**). Additionally, the aryl nonaflate of 4-methylumbelliferone could be used in place of the triflate to access **11** in comparable yield (89%). Regiosiomeric mixtures of products were observed for the fluorinations leading to electron-rich aryl fluorides **8**, **13**, **14**, and **15** when the reactions were conducted in toluene. As we have previously reported,[9b] switching the solvent to cyclohexane in these cases led to an increase in regioselectivity for the desired product. Substrates containing free NH or OH groups are not tolerated because they undergo competitive cross-coupling processes,

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(18) Unlike with dba, when 1,5-COD was added to the reactions in Table 1, entry 1, comparable yields of both fluorodeoxyestrone (67%, α:β = 5:1) and 3-fluoroquinoline (73%) to reactions conducted in the absence of 1,5-COD were observed. Thus, 1,5-COD does not show an inhibitory effect on these reactions.

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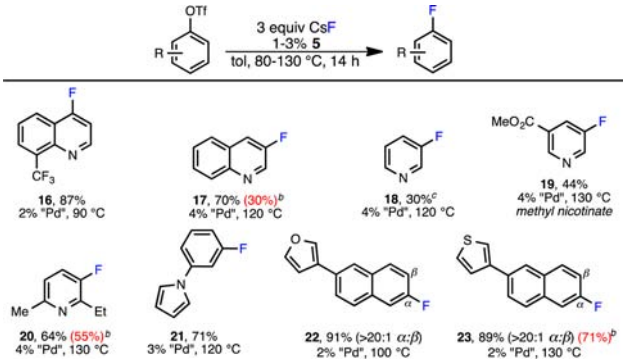
(23) Osborne, D. W.. Compositions and methods for topical application of therapeutic agents. U.S. Patent 5863560A, Jan 26, 1999.

Scheme 2. Fluorination of Heteroaryl and Heterocycle-Containing Triflates[a]



[a] Isolated yields, average of two runs. Reaction conditions unless otherwise noted: Aryl triflate (1 mmol), **6** (1−2%), CsF (3 mmol), tol (0.1 M). [b] Yield when conducted under same reaction conditions using [(cinnamyl)PdCl]$_2$/**1** (Pd/**1** = 1:1.5) instead of **5**. Aryl triflate (0.1 mmol), CsF (0.3 mmol), ^{19}F NMR yield. [c] 3-Pyridyl triflate (0.1 mmol), CsF (0.3 mmol), **5** (2%), tol (0.1 M), ^{19}F NMR yield.

although the hindered tertiary carbinol present in (des)venlaflaxine (**14**) did not need to be protected. In every case < 5% of the reduction product was observed; the major side product of these couplings is the corresponding biaryl ethers.[9b] Notably, when the preparations of electron-rich aryl fluorides **7**, **8**, **13**, and **15** were attempted using our previous catalyst system of [(cinnamyl)PdCl]$_2$/**1**, lower yields of the desired products were observed in each case (Scheme 1), demonstrating the superiority of our new catalyst system. Even in the case of electron-deficient **12**, an improved yield was observed when using **5** in place of [(cinnamyl)PdCl]$_2$/**1** (Scheme 1).

We also examined the application of **5** to the synthesis of heteroaryl fluorides, which are typically more difficult to access using transition-metal-mediated fluorination methods (Scheme 2). Precatalyst **5** is competent for the synthesis of 4- and 3-quinolinyl fluorides alike (**16**−**17**). Although fluorination of 3-pyridyl triflate to **18** proceeded in low yield, electron-deficient 3-pyridyl triflates, such as that corresponding to methyl nicotinate (**19**), provided somewhat higher yields of the desired aryl fluoride. In addition, 2,6-disubstituted 3-pyridyl fluorides can be accessed in good yield using this reaction (**20**). Lastly, substrates containing the five-membered heterocycles pyrrole (**21**), furan (**22**), and thiophene (**23**) could also be fluorinated, confirming that decomposition of these electron-rich aromatic systems does not occur under the reaction conditions. As before, when the fluorinations of **17**, **20**, and **23** were carried out using [(cinnamyl)PdCl]$_2$/**1**, lower yields of the desired products were observed in every case (Scheme 2), although the improvements when switching to **5** were not dramatic. Other nitrogen-containing heteroaryl triflates, such as those derived from 5- membered heteroaryl phenols, could not be fluorinated under these conditions. An inhibition study[24] of the conversion of δ-tocopherol triflate to **15** in the presence of various sp^2-hybridized nitrogen-containing additives suggests that these species inhibit this transformation to some degree, which may explain why such heteroaryl triflates remain challenging substrates for this reaction (see Supporting Information for details).

In conclusion, Pd(0) precatalyst **5** activates to provide the active catalytic species **2**·Pd(0) without generation of reactive byproducts, such as "Cl$^-$", dba, carbazole, or HF, that accompany the activation of other Pd sources and represents a significant improvement for this reaction. As such, **5** is an efficient precatalyst for the fluorination of electron-rich substrates, as well as heterocycle-containing aryl triflates, providing the corresponding aryl fluorides in synthetically useful yields and contaminated only with easily separated side products. Further investigation of the structure and reactivity of **5** is currently underway. Future efforts will also focus on preventing the formation of regioisomeric aryl fluoride products for electron-rich substrates, improving the scope with respect to heteroaryl triflates, and finding nonhygroscopic fluoride sources to carry out this reaction.[25]

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Supporting Information Available. Procedural and spectroscopic data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597.

(25) In their recently reported one-pot nonaflation/fluorination of phenols methodology based on our reaction, Larhed and coworkers found that their reactions could be set up on the benchtop using CsF dried in a vacuum oven with the reaction carried out at 180 °C in a microwave reactor. However, in our hands this procedure could not be replicated when using catalyst systems based on **2**. See: Wannberg, J.; Wallinder, C.; Unlüsoy, M.; Sköld, C.; Larhed, M. *J. Org. Chem.* **2013**, *78*, 4184.

The authors declare the following competing financial interest(s): MIT has patents on the ligands and precatalysts used in this work from which S.L.B. receives royalty payments.