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Versatile $Pd(OTf)_2 \cdot 2H_2O$-Catalyzed *ortho*-Fluorination Using NMP as a Promoter

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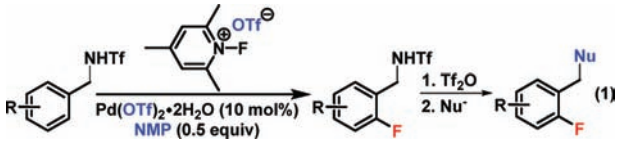
Aryl fluoride (ArF) moieties have long been recognized as privileged pharmacophores; they not only are isosteric to parent arenes but also exhibit improved lipophilicity as well as inertness to metabolic transformations.[1] Therefore, development of new methods for the introduction of fluorines into arenes is a significant task.[2,3] The *ortho*-lithiation/fluorination protocol with F^+ reported by Snieckus and Davis represents an important approach for regioselective fluorination of arenes.[4] In light of the remarkable success of the Pd(0)-catalyzed carbon heteroatom formation processes, especially the Buchwald−Hartwig amination reaction,[5] Pd(0) catalyzed displacement of halides by fluoride would appear to be the most viable approach. However, reductive elimination of fluoride from Pd(II) species is notoriously sluggish owing to the high strength of the Pd−F bond and has been a formidable problem to overcome.[6] In contrast to this approach, two years ago in a pioneering study, Sanford and co-workers reported the first example of Pd(II)-catalyzed *ortho*-fluorination of C−H bonds in 2-phenylpyridine substrates using a F^+ source (*N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate) under microwave conditions.[7a] Further mechanistic investigations into the reductive elimination of fluoride from the Pd(IV) center provided structural evidence for the involvement of a Pd(II)/Pd(IV) cycle.[7−9]

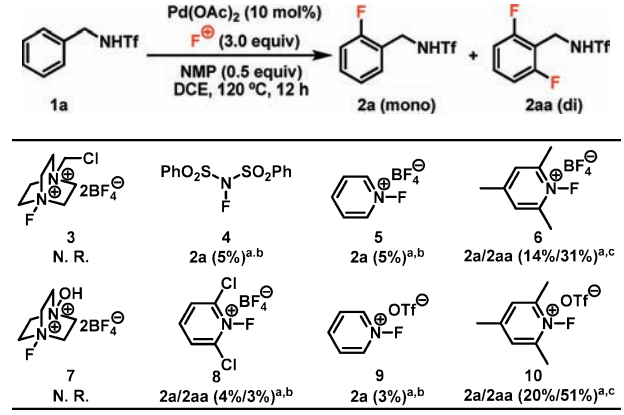
Although Pd(II)-catalyzed iodination of C−H bonds using an I^+ source has been successfully extended to simple substrates, such as benzoic acids and amine derivatives,[10] attempts to establish Pd(II)-catalyzed fluorination of C−H bonds with such substrates using F^+ sources have met with great difficulty in our early efforts.[11] It is possible that the pyridyl group in the electrophilic fluorinating reagents compete with substrates in binding to Pd(II) and hence severely inhibit C−H activation. Furthermore, the oxidation of Pd(II) to Pd(IV) by F^+ appears to require electron-donating ligands.[7−9]

Herein we report a new protocol for expedient *ortho*-fluorination of triflamide-protected benzylamines (eq 1). The use of a new fluorinating reagent (*N*-fluoro-2,4,6-trimethylpyridinium triflate), $Pd(OTf)_2 \cdot 2H_2O$, and 0.5 equiv of NMP is crucial for the fluorination to proceed in synthetically useful yields. Notably, the aryl fluoride reductive elimination occurs at a satisfactory rate without microwave heating. In addition to the *ortho*-fluorobenzylamines being pharmacophores of elagolix and other clinical compounds,[12] the facile displacement of the corresponding di-triflamide group by a variety of carbon and heteroatom nucleophiles renders this fluorination reaction broadly useful in medicinal chemistry and synthesis.



Triflamide directed *ortho*-palladation has previously been established in our iodination and olefination reactions.[10b] The use of either a mixture of DCE/DMF (20:1) or DCE in the presence of Cs_2CO_3 as the reaction media was found to be crucial for palladation to occur. However, reaction of **1a** with 10 mol % $Pd(OAc)_2$ and various F^+ sources previously used by Sanford (**3**−**6**)[7] and other fluorinating reagents **7** and **8** under similar conditions (various solvents in the presence of mild bases such as DMF and Cs_2CO_3) gave only less than 5% of the desired fluorinated products. We found through extensive screening that the presence of 0.5 equiv of NMP (*N*-methylpyrrolidinone)[13] in DCE increased the yield to 45% using *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**6**), while other F^+ sources **3**−**8** were ineffective (Table 1).

Table 1. NMP-Promoted Fluorination with F^+ Source



[a] The ratio of **2a/2aa** was determined by ^1H NMR. [b] ^1H NMR yield. [c] Isolated yield.

To investigate whether other counteranions could have beneficial effects on this reaction, we tested other F^+ sources and found that **10** greatly increased the yield to give a mixture of **2a** (20%) and **2aa** (51%) as products (Table 1). The best results were obtained in DCE, $PhCF_3$. This improvement by replacing BF_4^- with OTf^- prompted us to revisit this reaction in the absence of acetate anions by using $Pd(CH_3CN)_4(OTs)_2$,[14] $Pd(CH_3CN)_4(OTf)_2$, $Pd(NTf_2)_2$, or $Pd(OTf)_2 \cdot 2H_2O$.[15] We found that the use of any of these catalysts improves the reaction to some extent (see Supporting Information, SI). The best results were obtained with $Pd(OTf)_2 \cdot 2H_2O$ to give mainly difluorinated product **2aa** in 68% yield respectively within 4 h. Notably, two competing side pathways, acetoxylation and carbonylative lactamization (the carbonyl source likely comes from the decomposition of acetate) are also avoided by removing acetate from the system. The reaction is also sensitive to the quantity of NMP, with 0.5 equiv being optimal. The use of 0.1 or 5 equiv of NMP reduced the yield to 30% (see SI).

With this newly established fluorination protocol, *ortho*-substituted substrates were fluorinated to give the corresponding products in 60−88% yields (see Table 2). Both electron-donating (OMe) and -withdrawing groups (CF_3, F, Cl, Br) were tolerated (**2aa**, **2b**−**h**). The

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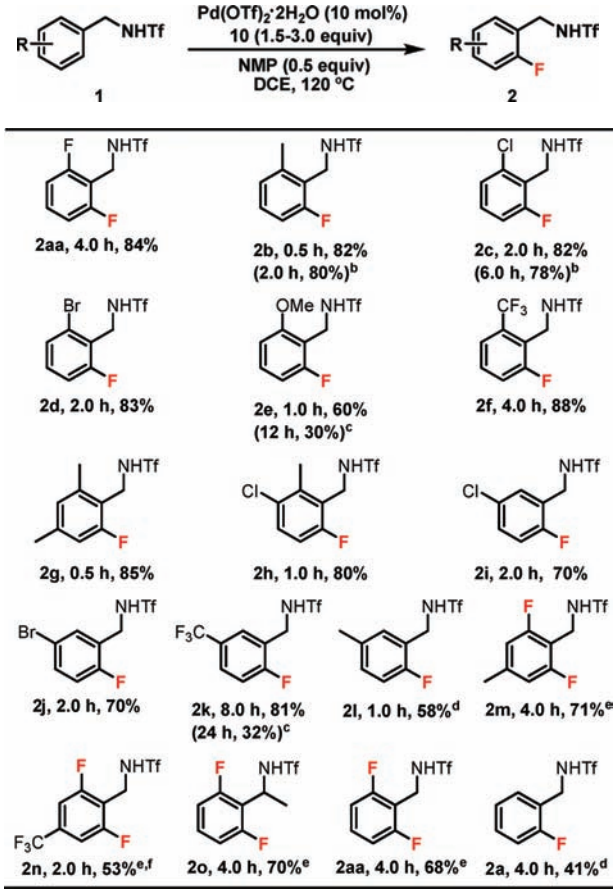
Table 2. Pd(OTf)$_2$·2H$_2$O-Catalyzed *ortho*-Fluorination[a]



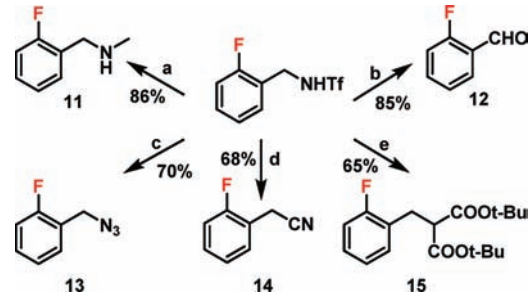
[a] Isolated yield. [b] 5 mol % Pd(OTf)$_2$·2H$_2$O. [c] Pd(OAc)$_2$ was used instead of Pd(OTf)$_2$·2H$_2$O. [d] DMF (0.5 equiv) was used instead of NMP. [e] PhCF$_3$ was used as solvent. [f] 20 mol % Pd(OTf)$_2$·2H$_2$O, and the reaction was performed at 150 °C under microwave heating.

use of 5 mol % Pd catalyst is sufficient, albeit requiring longer reaction times (**2b** and **2c**). The presence of Cl and Br in the products is very useful for further synthetic elaborations. Fluorination of *meta*-substituted arenes gives monofluorinated products predominantly (**2i-l**). To avoid the difficult separation of the mono- and difluorinated products, we attempted to achieve monoselectivity with benzylamine triflamide **1a**. While difluorinated product **2aa** is obtained in 68% yield (~4% **2a**), the best yield of monofluorinated product **2a** was 41% (~7% **2aa**) when the reaction was performed using 0.5 equiv of DMF instead of NMP.

To minimize the restriction that the fluorine is introduced onto *ortho* positions to a particular directing group, triflamides are converted to a broad range of synthetically useful functional groups exploiting known reactivities (Scheme 1).[16] These transformations allowed access to five major classes of *ortho*-fluorinated synthons, namely, benzaldehyde, benzylamine, benzylazide, phenylacetonitrile, and phenylpropanoate, thus greatly expanding the scope of ArF synthesis. The *ortho*-fluorinated phenylpropionic acids are especially valuable as they cannot be accessed by either *ortho*-lithiation[4] or by palladation using previously reported directing groups.

Finally, the detailed role of NMP remains to be elucidated. Investigations have led Vigalok to propose that oxidation of L$_2$PdArI by the F$^+$ source via an S$_N$2-type mechanism gives a cationic pentacoordinated L$_2$Pd(IV)ArIF complex.[8] Structural evidence has also been obtained by Ritter[9] and Sanford[7b] in support of Pd(IV) intermediates. The combination of the triflamide and catalytic amount of NMP as a promoter appears to be crucial for the formation of such an intermediate.

Scheme 1. Transformations of Triflamides[a]



[a] Reaction conditions: (a) (i) MeI (3 equiv), K_2CO_3 (1.5 equiv), acetone, reflux, 8 h; (ii) $LiAlH_4$ (2 equiv), THF, reflux, 10 h; (b) (i) ibid.; (ii) NaH (3 equiv), DMF, 100 °C, 10 h; (iii) HCl (2 N)/THF (1/2), reflux, 2 h; (c−e) (i) NaH (1.0 equiv), Tf_2O (1.0 equiv), CH_2Cl_2, −78−0 °C, 2 h; (ii) NaN_3, NaCN or NaCH(COO*t*-Bu)$_2$ (1.5 equiv), HMPT, 24 °C, 8 h.

In summary, we have developed a new protocol for efficient *ortho*-fluorination using Pd(OTf)$_2$·2H$_2$O as the catalyst, *N*-fluoro-2,4,6-trimethylpyridinium triflate as the F$^+$ source, and NMP as the crucial promoter. The triflamide directing group can be readily displaced by a wide range of heteroatom and carbon nucleophiles, thereby affording this fluorination protocol excellent versatility for synthetic applications.

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Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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