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Pd-Catalyzed C−H Fluorination with Nucleophilic Fluoride

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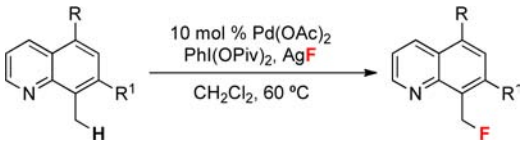
ABSTRACT



The palladium-catalyzed C−H fluorination of 8-methylquinoline derivatives with nucleophilic fluoride is reported. This transformation involves the use of AgF as the fluoride source in combination with a hypervalent iodine oxidant. Both the scope and mechanism of the reaction are discussed.

The substitution of hydrogen with fluorine can have a dramatic impact on the lipophilicity, metabolism, and overall biological activity of organic molecules.[1] As a result, carbon−fluorine bonds feature prominently in pharmaceuticals, agrochemicals, and PET imaging reagents. However, despite the prevalence and great utility of this functional group, synthetic methods for forming C−F bonds under mild conditions remain limited.[2] Transition-metal-catalyzed C−F coupling reactions are particularly rare and constitute powerful synthetic tools to complement more conventional methods. In particular, efficient catalytic fluorination via either cross-coupling[3−6] or C−H functionalization[7,8] can facilitate the late stage introduction of fluorine into biologically active molecules. This is of great value for both SAR studies and for radiolabeling applications (since $t_{1/2}$ for ^{18}F is approximately 110 min).[2]

We and others have previously reported the Pd-catalyzed conversion of C−H bonds to C−F bonds using electrophilic fluorinating reagents (abbreviated F^+ reagents or Oxidant−F throughout this manuscript).[7,8] These reactions are believed to proceed via a catalytic cycle such as that shown in Scheme 1, where C−F bond-forming reductive elimination from $Pd^{IV}(R)(F)$ (**D**)[9,10] serves as a key step. Thus the role of the F^+ reagent is twofold: (1) it oxidizes the Pd^{II} to Pd^{IV} (step *ii*), and (2) it serves as the source of fluorine that ends up in the final product (step *iii*).

While this first-generation approach to C−H fluorination was successful, these reactions suffer from the distinct disadvantage that they require electrophilic fluorinating reagents. Even though a number of F^+ sources are commercially available, they are often much more expensive

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(3) (a) Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106. (b) Noel, T.; Maimone, T. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8900. (c) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *321*, 1661.

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(5) Casitas, A.; Canta, M.; Sola, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386.

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(7) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.

(8) (a) Chan, C. S. L.; Wasa, M.; Wang, X.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081. (b) Wang, X.; Mei, T. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.

(9) For examples of C−F bond formation from $Pd^{IV}(R)(F)$ species, see: (a) Racowski, J. M.; Kampf, J. W.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3414. (b) Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 2878. (c) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793.

(10) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177.

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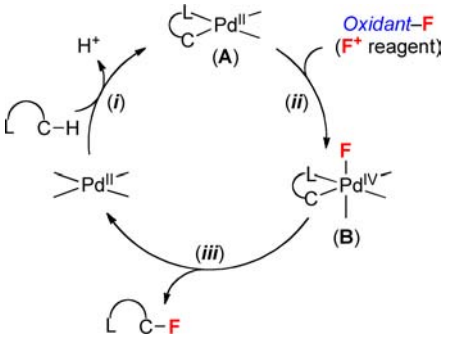
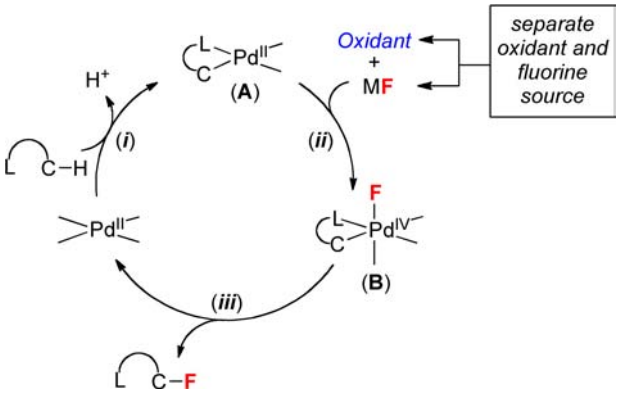
Scheme 1. Pd-Catalyzed C−H Fluorination with F^+ Reagents



Scheme 2. Proposed Sequence



than fluoride reagents. For example, the Sigma-Aldrich prices for *N*-fluoropyridinium salts (NFPs) and Selectfluor (both F^+ reagents) are several orders of magnitude more expensive than CsF and KF (Figure 1). In addition, commonly used F^+ reagents such as NFPs and Selectfluor generate large quantities of organic waste and exhibit modest tolerance to nucleophilic functional groups. Finally, electrophilic fluorinating reagents are much less desirable than fluoride for PET imaging applications, because $^{18}F^-$ has significantly higher specific activity than $^{18}F^+$ precursors.[2]

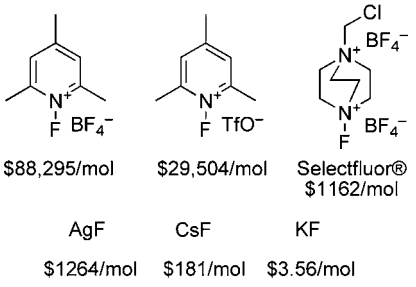
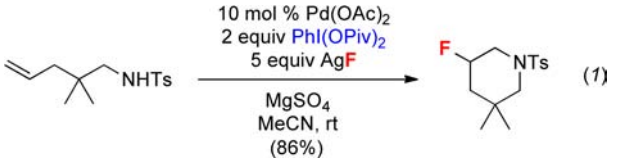


Figure 1. Prices for commercial fluorine sources (based on largest quantity available from Sigma Aldrich in >95% purity).

We hypothesized that Pd-catalyzed C−H fluorination with nucleophilic fluoride could be accomplished by separating the two roles played by the F^+ reagent in these transformations.[11] As shown in Scheme 2, an external oxidant could be used to convert Pd^{II} to Pd^{IV} (step *ii*) while a fluoride source could provide a ligand to Pd^{IV} that would ultimately participate in C−F bond-forming reductive elimination (step *iii*).

A recent report on Pd-catalyzed alkene aminofluorination provided preliminary support for the viability of this approach. As shown in eq 1, Liu and co-workers demonstrated this transformation using $PhI(OPiv)_2$ as an oxidant in conjunction with AgF as a nucleophilic fluoride source.[12] We describe herein the use of a similar strategy to achieve the Pd-catalyzed ligand-directed C−H fluorination of 8-methylquinoline derivatives using the combination of hypervalent iodine reagents and fluoride salts.



Our initial studies focused on the C−H fluorination of 8-methylquinoline, since this is an excellent substrate for Pd-catalyzed fluorination with F^+ reagents.[7] The use of 10 mol % of $Pd(OAc)_2$ along with $PhI(OAc)_2$ and AgF in MeCN at 25 °C for 24 h provided a modest yield of the desired fluorinated product **1a** (14%), along with the corresponding C−H oxygenation product **2a** (17%) and recovered starting material (61%).[13,14] Increasing the temperature to 60 °C resulted in nearly complete conversion of 8-methylquinoline; however, the yield of the desired fluorinated product remained low (14%) (Table 1, entry 1). Changing the oxidant from $PhI(OAc)_2$ to $PhI(OPiv)_2$ and the solvent from MeCN to CH_2Cl_2 resulted in quantitative conversion of 8-methylquinoline and provided a 58% yield of **1a** (entry 3).

The major side product in this transformation (**2a**) derives from C−H oxygenation of the 8-methylquinoline.[15] While products **1a** and **2a** are easily separable by column chromatography on silica gel, it would clearly be desirable to obtain higher yields of **1a** in these transformations. We initially hypothesized that the electronic/steric properties

(11) For related "umpolung" strategies to achieve fluorination with F^- reagents, see: (a) Gao, Z.; Lim, Y. H.; Tredwell, M.; Li, L.; Verhoog, S.; Hopkinson, M.; Kaluza, W.; Collier, T. L.; Passchier, J.; Huiban, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 6733. (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.

(12) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354.

(13) Importantly, control reactions show that **1a** and **2a** do not interconvert under the reaction conditions, indicating that they are not formed from one another in this transformation (see p S8 of the Supporting Information for details).

(14) By analogy to Liu's work, $MgSO_4$ was also added. The role of this additive is likely to remove water.

(15) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *124*, 2300.

of R in the hypervalent iodine reagent could be tuned to enhance the yield of **1a**. However, examination of 19 different R substituents revealed that $PhI(OPiv)_2$ provides the best results (see Table S4 for complete details). Significant additional experimentation led to the discovery that the yield of **1a** could be enhanced by modification of the reaction conditions. Specifically, prestirring the $PhI(OPiv)_2$ and AgF in CH_2Cl_2 for 1 h at 60 °C before adding the Pd catalyst, substrate, and $MgSO_4$ resulted in a modest boost in the yield of **1a** as well as an improved ratio of **1a**/**2a** (entry 4). Importantly, all of these reactions were set up on the benchtop using commercially available reagents without any drying or prepurification. This is relatively rare for a nucleophilic fluorination reaction.[2]

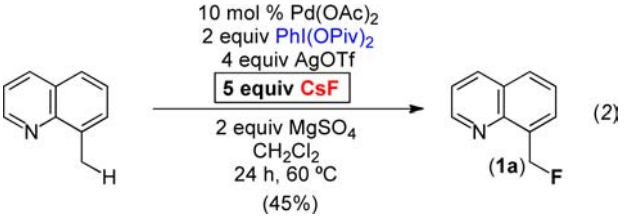
Table 1. Optimization of C−H Fluorination with $PhI(O_2CR)_2$/MF

entry	solvent	R	M	conversion (%)	yield (%)[a] 1a	2a
1	MeCN	Me	Ag	87	14	64
2	MeCN	^{t}Bu	Ag	32	8	14
3	CH_2Cl_2	^{t}Bu	Ag	100	58	25
4[b]	CH_2Cl_2	^{t}Bu	Ag	100	62	18
5[b]	CH_2Cl_2	^{t}Bu	Cs	9	<1	6
6[b]	CH_2Cl_2	^{t}Bu	Rb	15	<1	14
7[b]	CH_2Cl_2	^{t}Bu	K	19	<1	15
8[b]	CH_2Cl_2	^{t}Bu	NBu_4	25	<1	11

[a] Yields determined by GC based on an average of at least two runs. [b] AgF and $PhI(OPiv)_2$ were prestirred at 60 °C for 1 h in CH_2Cl_2 prior to addition of the rest of the reagents.

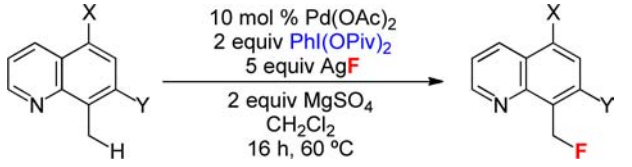
The optimal conditions in Table 1 require 24 h to achieve maximum yield. Such long reaction times are undesirable for PET imaging applications because the half-life of ^{18}F is short (~110 min). Thus, we also examined a variety of approaches to accelerate this transformation. Gratifyingly, when the temperature was increased to 80 °C, a 40% yield of product **1a** could be obtained after just 15 min under the $PhI(OPiv)_2$/AgF conditions.

It would also be attractive to replace AgF with an alternative fluoride source. This would be particularly useful in the context of PET imaging applications, where the most readily available $^{18}F^-$ starting materials are CsF, RbF, NBu_4F, and KF-Kryptofix.[16] However, as shown in Table 1, entries 5−8, the substitution of AgF with CsF, RbF, NBu_4F, or KF under our optimized reaction conditions led to <1% yield of the fluorinated product. These results suggest that the presence of Ag(I) is important for the success of the desired fluorination reaction. As such, we examined the use of an exogenous Ag(I) salt in conjunction with CsF.[17] Gratifyingly, the Pd-catalyzed C−H fluorination proceeded to afford **1a** in 45% yield under these conditions (eq 2).



The scope of Pd-catalyzed nucleophilic C−H fluorination was evaluated with a variety of 8-methylquinoline derivatives. As shown in Table 2, diverse substituents at positions X and Y were tolerated. Most notably, a variety of halogens were compatible with the reaction conditions (entries 5−8), providing sites for further elaboration of the products. In general, the best results were obtained when X and Y were electron-withdrawing groups (entries 2−8). Significantly lower yields of the fluorinated product were observed when X = phenyl or methyl (entries 9, 10); furthermore, the substrate with X = methoxy afforded <1% of **1k**. Notably, in all cases, the C−H oxygenation product (analogue of **2a**) was the major side product.

Table 2. Substrate Scope of C−H Fluorination of 8-Methylquinoline Derivatives



entry	X	Y	product	GC yield (%)	isolated yield (%)
1	H	H	**1a**	67	49
2[a]	NO_2	H	**1b**	62	41
3	CN	H	**1c**	67	70
4[a]	CO_2CH_3	H	**1d**	59	59
5	F	H	**1e**	44	30
6	Br	H	**1f**	53	44
7	H	Br	**1g**	49	42
8[a]	I	H	**1h**	67	55
9[b,c]	Ph	H	**1i**	43	39
10[c]	Me	H	**1j**	41	39
11[a]	MeO	H	**1k**	<1	nd

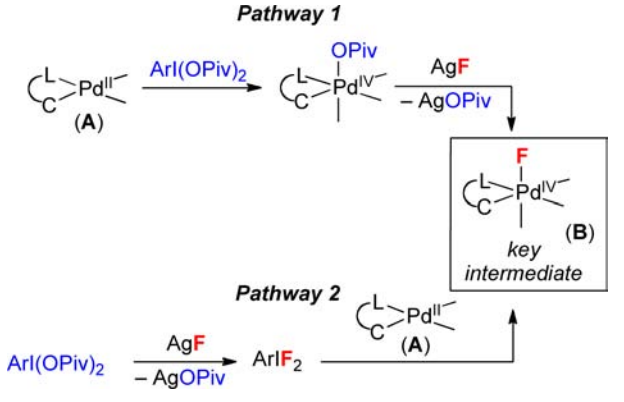
[a] The reaction was run for 24 h. [b] The reaction was run for 28 h. [c] PhF was used as a solvent in place of CH_2Cl_2.

We hypothesize that high valent Pd-alkyl fluorides of general structure **B** are key intermediates in this process. There are at least two possible pathways for accessing such

(16) Schlyer, D. J. *Ann. Acad. Med. Singapore* **2004**, *33*, 146.

(17) Low yields were obtained when CsF was replaced with other fluoride salts (NaF, TBAF, or KF).

Scheme 3. Two Possible Routes to **B** from **A**, AgF, and ArI(OPiv)$_2$



species under the current reaction conditions. A first would involve the oxidation of cyclometalated Pd^{II} complex **A** by PhI(OPiv)$_2$ followed by ligand substitution of pivalate for fluoride at the resultant Pd^{IV} intermediate (Scheme 3, *pathway 1*). A second pathway would proceed via initial substitution of pivalate for fluoride at the iodine(III) center followed by oxidation of **A** with PhIF$_2$ (Scheme 3, *pathway 2*). Notably, a recent report by DiMagno demonstrated that the treatment of PhI(OAc)$_2$ with rigorously dry TBAF affords PhIF$_2$ in high yield.[18] This precedent suggests the potential plausibility of pathway 2.

To gain preliminary insights into the mechanism, we monitored the reaction by ^{19}F NMR spectroscopy using iodotoluene dipivalate [*p*-MeC$_6$H$_4$I(OPiv)$_2$] as the oxidant.[19] Analysis of the crude reaction mixture after prestirring 1 equiv of *p*-MeC$_6$H$_4$I(OPiv)$_2$ with 2.5 equiv of AgF for 30 min at 60 °C in CD_2Cl_2 showed a new resonance at −176 ppm.[20] This signal corresponds to the literature value[18] as well as to that obtained for an authentic sample of *p*-MeC$_6$H$_4$IF$_2$, providing strong evidence that this iodine(III) reagent is formed under the reaction conditions.

We next independently synthesized a pure sample of *p*-MeC$_6$H$_4$IF$_2$[21] to establish whether it is effective at promoting C−H fluorination in the absence of *p*-MeC$_6$H$_4$I(OPiv)$_2$/AgF. Intriguingly, the use of 2 equiv of *p*-MeC$_6$H$_4$IF$_2$ in place of *p*-MeC$_6$H$_4$I(OPiv)$_2$/AgF under otherwise analogous conditions afforded only a 7% yield of **1a** along with 42% recovered starting material.[22] Finally, the combination of 2 equiv of *p*-MeC$_6$H$_4$IF$_2$ and 3 equiv of AgF did not enhance the yield, instead providing 6% of **1a** and 27% starting material. *Collectively, these results suggest that, while ArIF$_2$ is present under these reaction conditions, it is not the primary active fluorinating reagent in this transformation.* More detailed investigations will be required to establish a comprehensive mechanistic understanding of this transformation.[23]

In conclusion, we have demonstrated a transformation that is, to our knowledge, the first example of palladium-catalyzed C−H fluorination using nucleophilic fluoride. The fluoride source can be either AgF or CsF (the latter in combination with AgOTf). The reactions typically proceed in modest to good yield over 24 h, and the use of a higher reaction temperature leads to the formation of significant quantities of fluorinated product in just 15 min. Ongoing work in our laboratory will probe the mechanism and expand the scope of this transformation to diverse C−H substrates.

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Supporting Information Available. Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Sun, H.; Wang, B.; DiMagno, S. G. *Org. Lett.* **2008**, *10*, 4413.

(19) Under our standard reaction conditions *p*-MeC$_6$H$_4$I(OPiv)$_2$ performs nearly identically to PhI(OPiv)$_2$, providing **1a** and **2a** in 63% and 19% yield, respectively, in the Pd-catalyzed C−H fluorination of 8-methylquinoline.

(20) A second resonance at 129.6 ppm is also visible in the ^{19}F NMR spectrum of the prestirred reaction mixture. The identity of this species has not yet been definitively established.

(21) Shreeve, J. M.; Ye, C.; Twamley, B. *Org. Lett.* **2005**, *7*, 3961.

(22) Batchwise addition of *p*-MeC$_6$H$_4$IF$_2$ (three batches over 1 h in CH_2Cl_2) afforded very similar results.

(23) One possibility to be investigated is that the compound showing the ^{19}F NMR resonance at 129.6 ppm [ref 20] is serving as the active fluorinating reagent in this transformation.

The authors declare no competing financial interest.