J|A|C|S
COMMUNICATIONS

Published on Web 05/10/2006

Palladium-Catalyzed Fluorination of Carbon−Hydrogen Bonds

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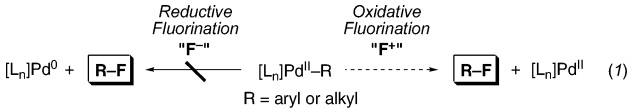
The substitution of hydrogen for fluorine can have a profound effect on the biological activity, metabolism, solubility, hydrophobicity, and bulk properties of organic substances.[1] As a result, molecules containing carbon−fluorine bonds are extremely important as pharmaceuticals, imaging agents, fine chemicals, and materials.[1] However, despite the great utility of this functional group, relatively few synthetic approaches for the formation of C−F bonds are currently available, and transition metal catalyzed methods for C−F bond construction are particularly rare.[1,2]

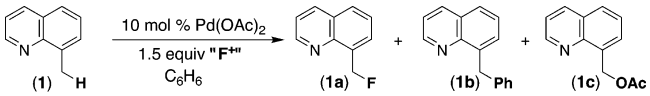
Previous efforts in this area have aimed to develop palladium-based catalysts for C−F bond formation[3] since Pd catalysts have found widespread application in a variety of related carbon−heteroatom cross-coupling reactions.[4] This prior work has predominantly focused on potential $Pd^{0/II}$ catalytic cycles, involving oxidative addition of an aryl or alkyl halide (R−X) to Pd^0, metathesis of X^- with F^- at the resulting σ-alkyl/aryl Pd^{II} complex, and, finally, C−F bond-forming reductive elimination to release the fluorinated product. While the first two reactions in this sequence are well-precedented,[3] the final C−F coupling step (C = aryl, alkyl) has not yet been achieved at Pd^{II} (or, to our knowledge, at any other transition metal center) in either a stoichiometric or a catalytic reaction manifold.[5,6]

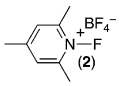
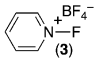
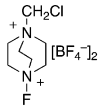
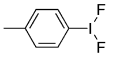
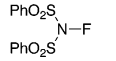


We reasoned that an alternative approach to this key C−F coupling step would be to react a Pd^{II} alkyl/aryl intermediate with an electrophilic fluorinating reagent (F^+ source) to effect the oxidative transformation of the Pd−C bond to a C−F bond (eq 1). Carbon−fluorine bond formation in these systems could proceed by direct electrophilic attack of F^+ on the Pd^{II}−C bond or via oxidation to Pd^{IV} followed by C−F bond-forming reductive elimination. Importantly, we have recently demonstrated that related oxidizing conditions promote other challenging Pd-catalyzed C−X coupling reactions (e.g., formation of C−Cl and C−Br bonds[7a] and coupling between weakly nucleophilic acetate and electron-rich arenes[7a,d]) that are not typically possible via conventional $Pd^{0/II}$ catalytic cycles.[8,9] We describe herein the application of this new approach to the development of the first Pd-catalyzed C−H activation/C−F bond-forming reaction.

Initial investigations focused on the $Pd(OAc)_2$-catalyzed benzylic fluorination of 8-methylquinoline (**1**). This substrate was selected because it undergoes facile quinoline-directed C−H activation at Pd^{II} to generate a σ-benzyl Pd species and, as such, has been shown to serve as an excellent substrate for related Pd-catalyzed C−H activation/oxidative functionalization reactions.[7a−c] As summarized in Table 1, column 3, an initial screen of F^+ reagents under thermal reaction conditions (10 mol % of $Pd(OAc)_2$, 110 °C, 13 h, benzene) revealed that several effected the desired benzylic C−H bond fluorination reaction, providing **1a** in modest 9−36% yields along with several other products (vide infra). The long reaction times

Table 1. Palladium-Catalyzed Fluorination of 8-Methylquinoline



entry	"F⁺" source	yield of **1a**+**1b**+**1c** (yield **1a**) Thermal[a]	yield of **1a**+**1b**+**1c** (yield **1a**) μwave[b]
1	 (**2**)	82% (36%)	**97% (75%)**
2	 (**3**)	25% (0%)	37% (15%)
3		24 % (22%)	19% (16%)
4		25% (12%)	8% (3%)
5		19% (9%)	15% (9%)

[a] Conditions: 110 °C, 18 h. [b] Conditions: 110 °C, 1 h, 200 W; yields of **1a**, **1b**, and **1c** were determined by GC using naphthalene as an internal standard.

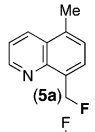
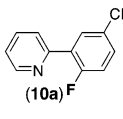
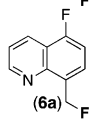
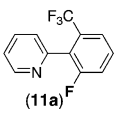
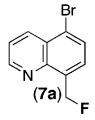
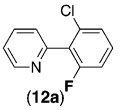
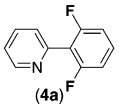
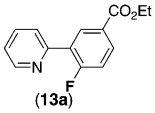
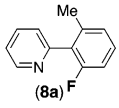
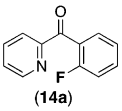
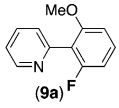
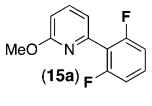
associated with the thermal conditions led us to examine microwave irradiation as a potentially faster way to assay a variety of catalysts, solvents, and fluorinating oxidants.[10] Gratifyingly, microwave heating greatly accelerated the Pd-catalyzed fluorination of **1**, and the reactions generally proceeded within 1 h at 110 °C. Interestingly, *p*-$MeC_6H_4I(F)_2$ afforded only traces of the fluorinated product **1a** under both thermal and microwave conditions (Table 1, entry 4), in contrast to the success of analogous iodine(III) oxidants in related C−H bond acetoxylation[7a,b,d] and arylation reactions.[7c] However, we were pleased to discover that *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**2**) served as a highly effective F^+ source upon microwave irradiation, affording **1a** in a dramatically improved 75% GC (59% isolated) yield. Importantly, control reactions in the absence of Pd catalyst showed none of the fluorinated product **1a**.

The moderate 75% GC yield of **1a** is due to incomplete conversion (3% of **1** remained at the end of the reaction), as well as the formation of two minor side products—phenylated product **1b** (18%) and acetoxylated product **1c** (4%).[11] We initially hypothesized that phenylated product **1b** was formed by Pd-catalyzed oxidative coupling between 8-methylquinoline (**1**) and the benzene solvent—another transformation of significant potential importance and utility.[12] However, control experiments revealed that **1b** is actually generated by reaction of 8-fluoromethylquinoline (**1a**) with C_6H_6 in the presence of oxidant **2**. This reaction does not appear to be Pd-catalyzed, as it proceeds with comparable rates in the presence and absence of $Pd(OAc)_2$. While the detailed mechanism for formation of **1b** remains under investigation, preliminary results suggest that it takes place via an electrophilic pathway.[13]

10.1021/ja061943k CCC: $33.50

We next aimed to expand the scope of these reactions to the fluorination of aromatic C−H bonds in substrates, such as phenylpyridine **4** (eq 2). After some experimentation (see Table S1), we determined that *N*-fluoropyridinium tetrafluoroborate (**3**) was the optimal F^+ source for this reaction, and that microwave irradiation under similar conditions to those described for substrate **1** (10 mol % of $Pd(OAc)_2$, 150 °C, 1.5 h, 0.5 mL of CH_3CN in trifluorotoluene) afforded the *ortho*-fluorinated product **4a** in 69% isolated yield. Notably, neither arylated side products analogous to **1b** nor acetoxylated side products analogous to **1c** were observed in reactions of substrate **4**.[14]

Table 2. Substrate Scope of Pd-Catalyzed C−H Bond Fluorination

entry	oxidant	product	isolated yield	entry	oxidant	product	isolated yield
1	**2**	 (**5a**)	57%[a]	7	**3**	 (**10a**)	75%[b]
2	**2**	 (**6a**)	49%[a]	8	**3**	 (**11a**)	59%[b]
3	**2**	 (**7a**)	53%[a]	9	**3**	 (**12a**)	50%[b]
4	**3**	 (**4a**)	62%[b]	10	**3**	 (**13a**)	54%[b]
5	**3**	 (**8a**)	52%[b]	11	**3**	 (**14a**)	52%[b]
6	**3**	 (**9a**)	33%[b]	12	**3**	 (**15a**)	60%[b]

[a] Conditions: 7−10 mol % of $Pd(OAc)_2$, 1.5−2 equiv of **2**, C_6H_6, microwave (1−4 h, 100−110 °C, 200−250 W). [b] Conditions: 10 mol % of $Pd(OAc)_2$, 2.5−4.5 equiv of **3**, 0.12−0.5 mL of CH_3CN, $CF_3C_6H_5$, microwave (1.5−2 h, 150 °C, 300 W).

With these preliminary results in hand, we next surveyed the substrate scope of quinoline/pyridine-directed benzylic and aromatic fluorination. As summarized in Table 2, these reactions can be utilized for the preparation of diverse fluorinated products and are tolerant of many common functional groups, including aryl halides, nonenolizable ketones and esters, trifluoromethyl substituents, and methyl ethers. The compatibility with aryl bromides is both synthetically useful (as these are readily elaborated further) and mechanistically interesting (as these are often not tolerated under $Pd^{0/II}$ catalysis). Benzylic C−H bonds that are remote from the pyridine or quinoline directing group (e.g., in substrate **5**, entry 1) are also well-tolerated. Furthermore, with substrate **8**, which contains both benzylic and aromatic C−H bonds adjacent to the pyridine directing group, the aromatic fluorination product was obtained exclusively. Notably, the same selectivity is observed in Pd-catalyzed C−H activation/acetoxylation reactions of related substrates[7e] and likely is derived from a preference for the formation of five-membered (versus six-membered) palladacyclic intermediates.[7] However, it is interesting to note that arene C−H activation/fluorination via six-membered palladacycles can be achieved if a five-membered intermediate is not accessible (substrate **14**, entry 11).

In conclusion, this paper describes the first example of a Pd-catalyzed method for the formation of aromatic and benzylic C−F bonds. In contrast to previous unsuccessful efforts in this area, these reactions were achieved under oxidizing conditions, using electrophilic (rather than nucleophilic) fluorinating reagents. The success of these C−H activation/oxidative fluorination reactions suggests a potentially general strategy for the fluorination of organometallic Pd intermediates. Ongoing efforts in our labs seek to expand the scope and to probe the mechanism of the current transformation, as well as to exploit this approach for the development of new metal-catalyzed C−F coupling reactions.

Acknowledgment. We thank the NIH NIGMS (RO1-GM-073836), the Camille and Henry Dreyfus Foundation, the Arnold and Mabel Beckman Foundation, Amgen, Boehringer Ingelheim, Merck, and Eli Lilly for support of this work. We are also grateful to Novartis (graduate fellowship to K.L.H.) and the Margaret and Henry Sokol Fund (summer fellowship to W.Q.A.).

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.

References

(1) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214−231 and references therein.
(2) For metal-catalyzed α-fluorination of carbonyl compounds, see: (a) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147−1155. (b) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164−10165 and references therein.
(3) Grushin, V. V. *Chem.—Eur. J.* **2002**, *8*, 1006−1014 and references therein.
(4) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002.
(5) A single example of stoichiometric C−F coupling at Pd^{II}, where C = acyl, has been reported. Fraser, S. L.; Antipin, V. N.; Khroustalyov, V. N.; Grushin, V. V. *J. Am. Chem. Soc.* **1997**, *119*, 4769−4770.
(6) In contrast, the microscopic reverse of this process—C−F bond oxidative addition—is well-known. For reviews, see: (a) Burdeniuc, J.; Jedlicka, B.; Crabtree, R. H. *Chem. Ber. Recl.* **1997**, *130*, 145−154. (b) Richmond, T. G. *Top. Organomet. Chem.* **1999**, *3*, 243−269. (c) Braun, T.; Perutz, R. N. *Chem. Commun.* **2002**, 2749−2757. For an example at Pd^0, see: (d) Jasim, N. A.; Perutz, R. N.; Whitwood, A. C.; Braun, T.; Izundu, J.; Neumann, B.; Rothfeld, S.; Stammler, H. G. *Organometallics* **2004**, *23*, 6140−6149.
(7) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543. (c) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330−7331. (d) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149−4152. (e) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141−1144.
(8) C−O coupling at Pd^{II} has strict electronic requirements: Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504−6511.
(9) C−Cl and C−Br couplings at Pd^{II} typically have unfavorable values of K_{eq}: Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533−1541.
(10) For C−H activation/functionalization reactions accelerated by microwave heating, see: Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2005**, *45*, 1589−1591.
(11) The OAc of **1c** is derived from the $Pd(OAc)_2$ catalyst, and this product could be generated by either Pd-catalyzed or non-Pd-mediated reactions. See the Supporting Information for a full discussion of these possibilities.
(12) For a review that discusses Pd-catalyzed oxidative coupling reactions, see: Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420.
(13) Several results are consistent with an electrophilic mechanism for the formation of **1b**. For example, when the reaction was conducted in anisole, both *o*- and *p*-substituted arylated products were obtained in a ~1:1.1 ratio. Additionally, when the reaction was run in the presence a 1:1 mixture of 1,4-dimethoxybenzene and C_6H_6, incorporation of the electron-rich (*p*-$MeO)_2C_6H_3$ group was favored (with a product ratio of 29:1). Ongoing work seeks to more fully elucidate the mechanism of this unusual arylation reaction.
(14) Additionally, **4a** also does not react with aromatic solvents in the presence of oxidants **2** or **3** to afford arylated side products analogous to **1b**. These data are consistent with the hypothesis that **1b** is formed by an electrophilic mechanism, possibly involving a transient benzylic cation.

JA061943K