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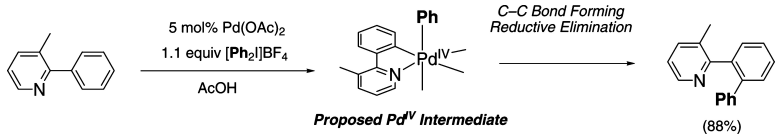

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Oxidative C−H Activation/C−C Bond Forming Reactions: Synthetic Scope and Mechanistic Insights

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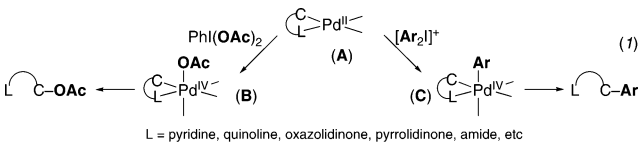
Palladium-catalyzed reactions for the formation of $C-C_{Ar}$ bonds are widely used in organic synthesis. The vast majority of these transformations (e.g., Stille, Suzuki−Miyaura, Sonogashira, Hiyama, and Negishi reactions) involve coupling of an aryl halide with an organometallic fragment.[1] The disadvantage of this approach is that it requires the use of two functionalized starting materials, which can be challenging and/or expensive to access in the context of complex molecule synthesis. An alternative strategy for $C-C_{Ar}$ bond construction would involve Pd-mediated C−H activation followed by functionalization of the resulting Pd−aryl/alkyl species with an appropriate arylating reagent. The development of such C−H activation/arylation reactions, particularly with broad scope, high functional group tolerance, and mild reaction conditions, represents an area of significant current interest,[2−5] as such transformations promise to facilitate selective construction of carbon−carbon bonds at late stages in the synthesis of drug molecules and/or natural products.

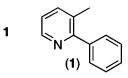
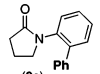
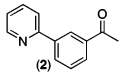
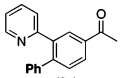
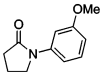
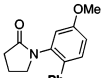
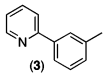
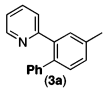
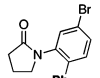
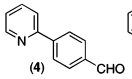
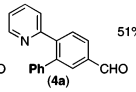
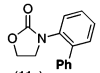
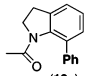
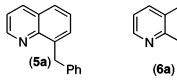
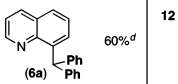
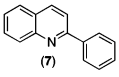
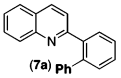


(1)

We recently reported Pd-catalyzed ligand-directed C−H activation/oxygenation reactions[6] and proposed that they proceed via C−O bond forming reductive elimination from Pd(IV) acetate intermediates of general structure **B** (eq 1). We reasoned that C−H activation/$C-C_{Ar}$ bond forming processes could be available via an analogous mechanistic pathway involving Pd(IV) aryl intermediate **C** (eq 1).[7] We further hypothesized that, by analogy to the oxygenation reactions (which use $PhI(OAc)_2$ as a stoichiometric oxidant), iodine(III) arylating agents might be used to access **C**.[7,8] The resulting C−H activation/arylation reactions would be of significant synthetic utility; furthermore, they would be highly mechanistically unusual, as Pd-catalyzed $C-C_{Ar}$ bond forming processes almost universally proceed via Pd(0)/(II) catalytic cycles.[1,9,10]

Our initial investigations focused on the Pd-catalyzed C−H activation/arylation of 2-phenyl-3-methylpyridine (**1**) with iodine(III) reagent $[Ph_2I]BF_4$. We were pleased to find that 5 mol % $Pd(OAc)_2$ catalyzes the formation of monophenylated product **1a** in a variety of common organic solvents, including AcOH, CH_2Cl_2, and C_6H_6, and under optimized conditions (5 mol % $Pd(OAc)_2$, 1.1 equiv of $[Ph_2I]BF_4$, AcOH, 100 °C), **1a** is obtained in 88% isolated yield (Table 1, entry 1).[4] Importantly, this transformation is very practical; it does not require the use of strong bases or expensive ligands and is conducted in the presence of ambient air/moisture. Directed C−H activation/phenylation also proceeds in good yield with a variety of alternative arene (entries 2−4, 7−13) and benzylic (entries 5 and 6) substrates. Diverse heterocycles, including pyridines, quinolines, pyrrolidinones, and oxazolidinones, are effective directing groups, and a wide variety of functionalities, including ethers, amides, enolizable ketones, aldehydes, aryl halides, and benzylic hydrogens, are well tolerated. Activated arenes are not required for efficient catalysis, and both electron-rich and electron-poor aromatic rings (e.g., entries 9 and 2) are phenylated in excellent yields. Notably, substrates containing *meta* arene substituents (X) (entries 2, 3, 9, 10, and 13) react to form a single detectable regioisomeric product (with the new C−C bond installed *para* to X) regardless of the electronic nature of the substituent. These results are particularly remarkable in substrates with *m*-OMe, *m*-halide, and *m*-acetyl groups, where dual point chelation of Pd to the primary directing group and to X might be expected to afford the opposite isomer,[11] and suggest that the regioselectivity of C−H activation is predominantly controlled by sterics in these systems.[5d,12] The observed regioselectivity makes this reaction a potentially valuable complement to more traditional arene functionalization methods such as directed ortho-metalation.[13]

Table 1. Palladium-Catalyzed Phenylation of C−H Bonds[a]

Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1	 (1)	 (1a)	88%	8	 (8)	 (8a)	75%[c]
2	 (2)	 (2a)	91%	9	 (9)	 (9a)	84%[c]
3	 (3)	 (3a)	74%	10	 (10)	 (10a)	78%
4	 (4)	 (4a)	51%[e]	11	 (11)	 (11a)	83%[c]
5	 (5)	 (5a)	72%[b]	12	 (12)	 (12a)	49%[e]
6	 (5a) Ph	 (6a) Ph	60%[d]	13	 (13)	 (13a)	67%
7	 (7)	 (7a) Ph	58%[e]				

[a] Conditions: 1 equiv of substrate, 1.1−2.5 equiv of $[Ph_2I]BF_4$, 5 mol % $Pd(OAc)_2$ in AcOH, $AcOH/Ac_2O$, C_6H_6, or toluene, 100 °C, 8−24 h. [b] With 2 equiv of substrate, 1.0 equiv of $[Ph_2I]BF_4$. [c] $NaHCO_3$ (1.5−2.0 equiv) added. [d] Approximately 16% of **6a** was formed in the absence of $Pd(OAc)_2$. [e] The balance of material was starting material (**12**) and/or starting material and diarylated product (**4** and **7**).

We next sought to expand these transformations to the transfer of diverse aryl groups, and initial studies toward this goal focused on the $Pd(OAc)_2$-catalyzed reaction of **1** with the mixed iodine(III) reagents $[Ph-I-Ar]BF_4$ (eq 2a). These reactions were found to afford the desired arylated products (**1b−g**), but only as mixtures with the analogous phenylated compound **1a** [in ratios ranging from 2.6:1 to 0.31:1 (**1b−g**: **1a**); see Table S1]. We reasoned that a sub-

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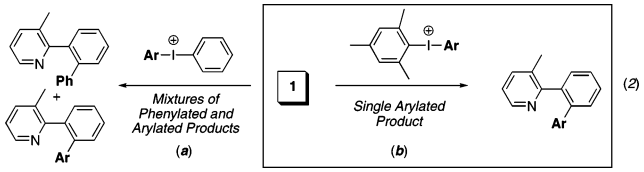
Table 2. Functionalization of **1** with Diverse Aryl Substituents Using $[Mes-I-Ar]BF_4$[a]

Entry	Ar (Product)	Yield	Entry	Ar (Product)	Yield
1	(**1a**)	85%	5	CH_3 (**1e**)	84%
2	CF_3 (**1b**)	87%	6	H_3C (**1f**)	72%
3	F (**1c**)	88%	7	OCH_3 (**1g**)	81%[b]
4	Cl (**1d**)	83%			

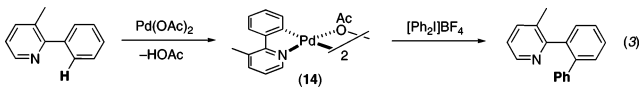
[a] Conditions: substrate **1** (0.12 M), $[Mes-I-Ar]BF_4$ (1.1−1.3 equiv), $Pd(OAc)_2$ (5 mol %), AcOH, 12 h, 100 °C. [b] Reaction carried out at 120 °C.

stantial steric differentiation between the two aryl groups at iodine(III) might allow for the selective transfer of the smaller substituent; as such, reactions between **1** and $[Mes-I-Ar]BF_4$ were examined.[14] Gratifyingly, these transformations proceeded cleanly to provide a single arylated product in good to excellent isolated yield (eq 2b). As summarized in Table 2, both electron-poor (entries 2−4) and electron-rich (entries 5−7) Ar groups were coupled efficiently, and benzylic C−H bonds as well as aryl ethers and halides were well tolerated on the arene component. Furthermore, even sterically hindered aryl substituents, such as *ortho*-tolyl (entry 6), could be transferred with good selectivity and yield using this approach.



(2)

Our efforts next turned to investigation of the mechanism of these C−H activation/arylation reactions. Specifically, we sought to probe the possible intermediacy of cyclopalladated complex **A** and Pd(IV) species **C** (eq 1) in the catalytic cycle. First, we replaced $[Ph_2I]BF_4$ with Ph−I or Ph−OTf, electrophiles that are well-known to undergo rapid oxidative addition to Pd(0), and found that <1% of phenylated product **1a** is formed under our catalytic conditions. Next, we prepared cyclopalladated complex **14** (eq 3) and found that it catalyzes the phenylation of **1** at a rate approximately identical to that of $Pd(OAc)_2$. In addition, **14** undergoes stoichiometric reaction with $[Ph_2I]BF_4$ to afford phenylated product **1a** (eq 3);[7,15] in contrast, <1% of **1a** is formed in analogous reactions between **14** and Ph−I or Ph−OTf.



(3)

Further studies revealed that the reaction of **1** with $[Ph_2I]BF_4$/5 mol % $Pd(OAc)_2$ is unaffected by the addition of ∼500 equiv of metallic Hg (a potent poison for heterogeneous catalysis)[10] or 25 mol % MEHQ or galvinoxyl (well-known free radical inhibitors), suggesting that neither Pd nanoparticles nor free radicals are participants in the reaction pathway.[10] In sum, these experiments provide compelling evidence against a traditional Pd(0)/(II) catalytic cycle and are consistent with C−H activation to form a cyclometalated Pd(II) intermediate followed by either (i) oxidation of Pd(II) to Pd(IV) by $[Ph_2I]BF_4$ and subsequent C−C bond forming reductive elimination (eq 1) or (ii) direct electrophilic cleavage of the Pd(II)−carbon bond by $[Ph_2I]BF_4$ (without a change of oxidation state at the metal). Both mechanisms are highly unusual in Pd-catalyzed C−C bond forming reactions,[9,10] and neither can be definitively excluded based on the current data. However, a recent report by Canty,[7] which demonstrates the direct stoichiometric oxidation of electron-rich Pd(II) complexes to Pd(IV) phenyl adducts with $[Ph_2I]OTf$, provides additional support in favor of the former.

In summary, we have described a new Pd-catalyzed method for C−H activation/C−C bond formation and have demonstrated its high functional group tolerance, regioselectivity, and scope under relatively mild conditions. Preliminary mechanistic experiments have provided evidence in support of a rare Pd(II)/(IV) catalytic cycle for this transformation. Current efforts are aimed at further elucidating the mechanism and exploring the scope of these transformations.

Acknowledgment. We thank the University of Michigan, the Camille and Henry Dreyfus Foundation, and the Arnold and Mabel Beckman Foundation for financial support.

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

References

(1) *Metal-Catalyzed Cross-Coupling Reactions*; Dieterich, F., Stang, P. J., Eds; Wiley-VCH: New York, 1998.
(2) For recent examples of Pd(0)/(II)-catalyzed C−H activation/arylation of activated arenes/heterocycles, see: (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (c) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301.
(3) For recent examples of Pd(0)/Pd(II)-catalyzed C−H activation/arylation of unactivated arenes/alkanes, see: (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658 and references therein. (c) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (d) Sezen, B.; Franz, R.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 13372.
(4) For related Ru-catalyzed imine and pyridine-directed C−H activation/arylation reactions, see: (a) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (b) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.
(5) For other examples of C−H activation/C−C bond forming reactions, see: (a) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (b) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192. (c) Davies, H. M. L.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862. (d) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguschi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (e) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (f) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.
(6) (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
(7) Canty, A. J.; Patel, J.; Rodemann, T.; Ryan, J. H.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 3466.
(8) For the use of iodine(III) arylating agents in Pd(II)/(0) C−C bond forming reactions, see: Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523.
(9) For rare examples of Pd-catalyzed $C-C_{Ar}$ bond forming reactions in which evidence supports the intermediacy of Pd(IV), see: (a) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem.* Soc. **2004**, *126*, 78 and references therein. (b) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. For a related stoichiometric reaction, see: (c) Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687.
(10) Palladacycle-catalyzed Heck reactions were originally proposed to proceed via a Pd(II)/(IV) cycle; however, more recent experiments (e.g., Hg poisoning studies) suggest that most of these reactions are actually catalyzed by Pd(0) nanoparticles. Eberhard, M. R.; Wang, Z. *Org. Lett.* **2004**, *6*, 2125 and references therein. For some potential exceptions, see: van der Boom, M.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759.
(11) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117.
(12) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R., III. *J. Am. Chem. Soc.* **2003**, *125*, 7792.
(13) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(14) Similar steric effects have been observed in Cr-catalyzed aldehyde arylation. Chen, D.; Ochiai, M. *J. Org. Chem.* **1999**, *64*, 6804.
(15) The stoichiometric reaction between **14** and $[Ph_2I]BF_4$ produces **1a** in quantitative yield in the presence of 2.5 equiv of a free arylpyridine substrate, such as **3**. Without the addition of **3**, **1a** is produced in modest (∼20%) yield along with a complex mixture of high MW organic products (see Supporting Information for more details). The role of the external ligand **3** is not entirely clear (and is currently under investigation), but it may serve as a trap for highly reactive cationic Pd species generated after C−C bond forming reductive elimination.

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