J|A|C|S
COMMUNICATIONS

Published on Web 02/03/2004

A Highly Selective Catalytic Method for the Oxidative Functionalization of C−H Bonds

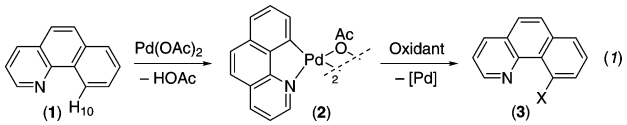
Allison R. Dick, Kami L. Hull, and Melanie S. Sanford*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055

Received December 5, 2003; E-mail: mssanfor@umich.edu

The development of metal-catalyzed methods for the regio- and chemoselective oxidative functionalization of arene and alkane carbon−hydrogen bonds remains a tremendous challenge in organic and organometallic chemistry.[1,2] Rare examples of such transformations have been described; however, their application to the elaboration of complex organic structures is generally limited by the harsh reaction conditions, low TON, low functional group tolerance, significant formation of byproducts, and large excesses of substrate relative to oxidant typically required in such reactions.[1,2] Additionally, most oxidation catalysts have been developed for substrates containing a single type of C−H bond (e.g., C_6H_6 or CH_4), and low levels of regioselectivity are typically observed in the presence of multiple C−H bonds.[1,2] Recent elegant work[3−5] has begun to successfully address some of these challenges, but a general solution, particularly for arene/alkane oxygenation, has thus far remained elusive.

Our approach to regioselective C−H bond oxidation involves the use of substrates containing coordinating functional groups that can bind to a metal catalyst and direct oxidation to a specific C−H bond within the molecule. We felt that recent progress in related C−H activation/C−C bond-forming reactions provided good precedent that such transformations could proceed with high levels of efficiency and selectivity.[6,7] We report herein a new and operationally simple Pd-catalyzed reaction for the chelate-directed oxidative functionalization of sp^2 and sp^3 C−H bonds.



Our first studies in this area focused on the Pd(II)-catalyzed oxidation of benzo[*h*]quinoline (**1**). This substrate was selected for initial investigation because it presents a single bond [C−H(10)] for directed C−H activation and is well-known to undergo cyclopalladation under mild conditions (eq 1).[8] Iodobenzene diacetate was chosen as the oxidant on the basis of its commercial availability, ease of handling, and utility in a related Pd-catalyzed arene oxidation reaction.[2c] The combination of 1 equiv of benzo[*h*]quinoline with $PhI(OAc)_2$ (2 equiv) and 2 mol % $Pd(OAc)_2$ in CH_3CN at 75 °C for 12 h produces an 11:1 ratio of the monoacetoxylated product **3a** and the analogous phenol **3b** in 86% isolated yield.[9] Oxidation also proceeds in comparable yield and efficiency when cyclopalladated complex **2** is used as the catalyst. This reaction exhibits extraordinarily high selectivity for oxidation at C_{10}, and regioisomeric oxidized products are not observed by GC or ^{1}H NMR spectroscopy.

We have found that simple modification of the reaction conditions allows the selective installation of a variety of different functional groups at C_{10} (Table 1). For example, reaction of **1** with $PhI(OAc)_2$/catalytic Pd(II) in alcohol solvents produces a range of

Table 1. Regioselective Oxidation of Benzo[*h*]quinoline[a]

entry	oxidant	solvent	X (product)	yield[b] (%)
1[c]	$PhI(OAc)_2$	CH_3CN	OAc (**3a**): OH (**3b**)	86[d]
2[c]	$PhI(OAc)_2$	MeOH	OMe (**3c**)	95
3[c]	$PhI(OAc)_2$	EtOH	OEt (**3d**)	80
4[c]	$PhI(OAc)_2$	*i*-PrOH/HOAc	O*i*Pr (**3d**)	72
5[c]	$PhI(OAc)_2$	CF_3CH_2OH	OCH_2CF_3 (**3f**)	71
6[e]	NCS	CH_2CN	Cl (**3g**)	95
7[e]	NBS	CH_3CN	Br (**3h**)	93

[a] 1 equiv of **1** (0.12 M), 1−2 equiv of oxidant, 1−5 mol % $Pd(OAc)_2$ or **2**, 75−100 °C. [b] Isolated yields. [c] 12 h. [d] 11:1 mixture of **3a**:**3b**. [e] 1−3 days.

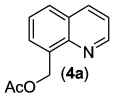
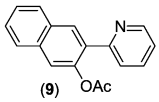
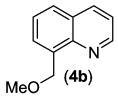
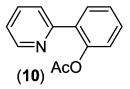
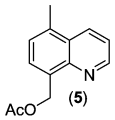
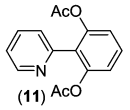
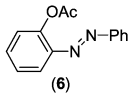
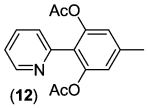
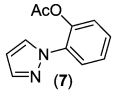
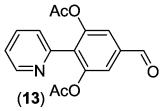
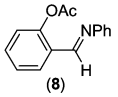
sterically and electronically diverse alkyl−aryl ethers [e.g., X = OMe (**3c**), OEt (**3d**), O*i*-Pr (**3e**), and OCH_2CF_3 (**3f**)] in good yields. Alternatively, when oxidation is carried out in the presence of excess LiX (X = Cl, Br) in CH_3CN, traces of mono-halogenated **3g** and **3h** are formed. The yields of these products can be optimized by the use of *N*-chloro- or *N*-bromosuccinimide (NCS or NBS) in place of $PhI(OAc)_2$ as the stoichiometric oxidant. Importantly, the rigorous exclusion of air/moisture is not required in any of these transformations, and comparable results are obtained in the presence and absence of air, as well as in freshly distilled versus commercial solvents. As such, this represents an exceedingly practical method for functional group-directed oxidation of arene C−H bonds and offers an attractive alternative to more traditional ortho-lithiation/electrophilic addition procedures.[10]

As summarized in Table 2, chelate-directed oxidation can be extended to a wide variety of substrates. For example, the sp^3 C−H bond of 8-methylquinoline reacts readily with 1.1 equiv of $PhI(OAc)_2$/1−2 mol % $Pd(OAc)_2$ in AcOH or MeOH to afford benzyl ester **4a** or benzyl ether **4b** in good yield (entries 1 and 2). Although these products contain additional benzylic hydrogens, essentially no over-oxidation is observed under our reaction conditions. Further C−H activation/oxidation of the product is likely inhibited due to steric hindrance at the more substituted benzylic position. Importantly, an appropriate directing group is absolutely required to achieve high yields and selectivities for benzylic oxidation. For instance, under our reaction conditions, 5,8-dimethylquinoline is oxidized exclusively at the 8-position to afford **5** (entry 3),[11] while 1-methylnaphthalene affords low yields of a complex mixture of benzylic and ring oxidation products.

Other functional groups, including azobenzene (entry 4), pyrazole (entry 5), imine (entry 6), and pyridine (entries 7−11) derivatives can also be utilized to direct arene C−H bond oxidation. In substrates that present two *o*-C−H bonds, modest to good yields of the mono-oxidized products **6**−**10** are obtained upon addition of 1.1−1.6 equiv of $PhI(OAc)_2$ relative to substrate (entries 4−8). Furthermore, the use of 2.3−2.5 equiv of $PhI(OAc)_2$ results in clean formation of the dioxidized adducts **11**−**13** (entries 9−11). This reaction is tolerant of a variety of readily oxidizable functional groups including benzylic hydrogens and aromatic aldehydes (entries 10, 11). Notably, the oxidation of 4-(2-pyridyl)benzaldehyde

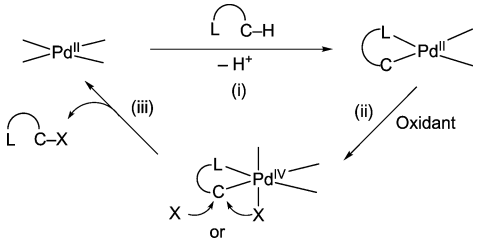
10.1021/ja031543m CCC: $27.50

Table 2. Chelate-Directed Oxidation of sp^2 and sp^3 C−H Bonds[a,b]

Entry	Major Product	Yield[c]	Entry	Major Product	Yield[c]
1	 (**4a**)	88%	7	 (**9**)	72%
2	 (**4b**)	77%	8	 (**10**)	52%
3	 (**5**)	80%	9	 (**11**)	83%
4	 (**6**)	62%	10	 (**12**)	78%
5	 (**7**)	54%	11	 (**13**)	58%
6	 (**8**)	47%[d]			

[a] For mono-oxidation: 1 equiv of substrate [0.12 M in AcOH (entries 1, 3, 5), MeOH (entry 2), or CH_3CN (entries 4−8)], 1.1−1.6 equiv of $PhI(OAc)_2$, 1−6 mol % $Pd(OAc)_2$, 100 °C, 12−20 h. [b] For dioxidation: 1 equiv substrate (0.12 M in CH_3CN), 2.3−2.5 equiv of $PhI(OAc)_2$, 6−8 mol % $Pd(OAc)_2$, 100 °C, 12 h. [c] Isolated yields. [d] Yield determined by GC.

Scheme 1. Proposed Catalytic Cycle



(entry 11) is directed by the pyridine rather than the aldehyde moiety,[11] presumably because the former is a better ligand for Pd(II).

A possible mechanism for this new transformation is outlined in Scheme 1. Step (i) involves chelate-directed C−H activation of the substrate to afford a cyclopalladated intermediate. The extraordinarily high regioselectivity of these reactions (particularly in substrates such as 5,8-dimethylquinoline that present two otherwise identical functional groups) as well as the high catalytic activity of the isolated cyclopalladated complex **2** provides strong evidence in support of this step. Step (ii) of the proposed catalytic cycle involves oxidation of Pd(II) to Pd(IV). While the Pd(0)/Pd(II) couple is more common in catalysis,[12b,13] Pd(II)/Pd(IV) cycles have been implicated in related benzene acetoxylation reactions.[1f,2c] Furthermore, no product is formed in the presence of benzoquinone or $Cu(OAc)_2$ (oxidants that typically mediate Pd(0)/Pd(II) catalysis)[13] or when the putative intermediate **2** is subjected to the reaction conditions in the absence of oxidant. The final step (iii) involves carbon−heteroatom bond-forming reductive elimination to afford the product. Such reactions have significant precedent[1,2,12] and typically proceed either by intramolecular C−X bond elimination from the metal center[12b,c] or by attack of an external nucleophile (X) in an S_N2-like reaction.[12a,d]

In conclusion, this report describes a new, highly regio- and chemoselective Pd-catalyzed procedure for the conversion of sp^2 and sp^3 C−H bonds to esters, ethers, and aryl-halides. A wide variety of substrates are readily oxidized under mild and operationally simple reaction conditions. Current studies are focused on further exploration of the substrate scope and synthetic utility of this methodology as well as on probing the mechanism of this transformation.

Acknowledgment. We thank the University of Michigan for generous support of this research. We also thank Professors J. P. Wolfe and E. Vedejs for helpful discussions.

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

References

(1) (a) Fekl, U.; Goldberg, K. I. *Adv. Inorg. Chem.* **2003**, *54*, 259. (b) Groves, J. T. *J. Porphyrins Phthalocyanines* **2000**, *4*, 350. (c) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2181. (d) Sen, A. *Acc. Chem. Res.* **1998**, *31*, 550. (e) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (f) Henry, P. M. *Catalysis by Metal Complexes*; Palladium Catalyzed Oxidation of Hydrocarbons, Vol. 2; Reidel: Dordrecht, 1980.

(2) Selected recent examples: (a) Mukhopadhyay, S.; Bell, A. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2990. (b) Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560. (c) Yoneyama, T.; Crabtree R. H. *J. Mol. Catal. A* **1996**, *108*, 35.

(3) (a) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390.

(4) (a) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.

(5) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149.

(6) (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.

(7) Related *stoichiometric* cyclopalladation/oxidation reactions have also been reported. For example, see: (a) Valk, J.-M.; Boersma, J.; van Koten, G. *Organometallics* **1996**, *15*, 4366. (b) Carr, K.; Saxton, H. M.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans 1* **1988**, 1599.

(8) Hartwell, G. E.; Lawrence, R. V.; Smas, M. J. *J. Chem. Soc., Chem. Commun.* **1970**, 912.

(9) Traces of **3b** are observed in crude GC traces of the reaction, but this product forms predominantly via ester hydrolysis during purification on silica gel. The ratio of **3a**:**3b** was determined by ^1H NMR spectroscopy.

(10) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(11) The regioselectivity of oxidation was confirmed by nOe experiments (see Supporting Information for details).

(12) (a) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Han, R. Y.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135. (d) Backvall, J. E. *Acc. Chem. Res.* **1983**, *16*, 335.

(13) For example, see: Jonasson, C.; Horvath, A.; Backvall, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9600.

JA031543M