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Oxone as an Inexpensive, Safe, and Environmentally Benign Oxidant for C–H Bond Oxygenation

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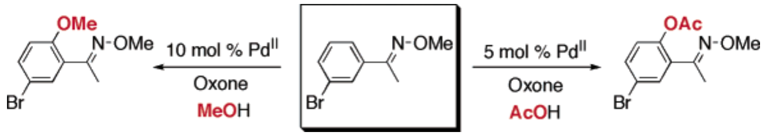
ABSTRACT



This paper describes the application of peroxide-based oxidants in the Pd(OAc)$_2$-catalyzed acetoxylation and etherification of arene and alkane C–H bonds. Oxone in acetic acid and/or methanol proved particularly effective, and these transformations were applied to a wide variety of substrates.

The development of selective and efficient catalytic methods for the oxidation of organic molecules remains a significant challenge in synthetic chemistry. In particular, oxidation reactions that utilize environmentally benign and inexpensive peroxides[1−4] and/or O$_2$[5] as stoichiometric oxidants are extremely attractive, as they render the resulting transformations "greener" and more practical for large-scale synthesis. We have recently described a new method for the Pd-catalyzed oxygenation of arene[6b,c] and alkane[6a] C−H bonds using PhI(OAc)$_2$ as a terminal oxidant. These ligand-directed reactions typically proceed in good yields and with high levels of regioselectivity; however, they suffer from significant disadvantages: the iodine(III) oxidant is expensive (~$1/g)[7] and forms stoichiometric quantities of toxic PhI with each catalytic turnover. As such, an ongoing goal in our group has been the development of C−H bond oxygenation reactions that utilize more desirable organic or inorganic peroxides as terminal oxidants.[8]

Our approach to this challenge began with a careful consideration of the mechanism of the Pd-catalyzed C−H bond oxidation. Our previous work suggested that the key carbon−oxygen coupling step involves C−O bond-forming reductive elimination from a Pd^{IV} acetoxy intermediate of general structure **1** (Scheme 1).[6,9] When PhI(OAc)$_2$ is used as the oxidant in an organic solvent, the OAc ligand of **1**

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[1] For reviews on hydrogen peroxide as a terminal oxidant in catalysis, see: (a) Noyori, R.; Aoki, M.; Sato, K. *Chem. Commun.* **2003**, 1977. (b) Jones, C. W. *Applications of Hydrogen Peroxide and Derivatives*; Royal Society of Chemistry: Cambridge, 1999. (c) *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Strukul, G., Ed.; Kluwer Academic: Dordrecht, 1992.

[2] For recent examples of the use of peracetic acid as an oxidant in catalysis, see: Murphy, A.; Pace, A.; Stack, T. D. P. *Org. Lett.* **2004**, *6*, 3119 and references therein.

[3] For recent examples of the use of Oxone as a stoichiometric oxidant in catalytic reactions, see: (a) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497 and references therein. (b) Schomaker, J. M.; Travis, B. R.; Borhan, B. *Org. Lett.* **2003**, *5*, 3089 and references therein. (c) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824.

[4] For examples of the use of $K_2S_2O_8$ in the Pd-catalyzed C−H activation/oxygenation of methane, see: (a) Muehlhofer, M.; Strassner, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1745. (b) Gretz, E.; Oliver, T. F.; Sen, A. *J. Am. Chem. Soc.* **1987**, *109*, 8109.

[5] For recent reviews on the use of O$_2$ as a stoichiometric oxidant in catalysis, see: (a) Stahl, S. S. *Science* **2005**, *309*, 1824. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400.

[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. (c) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35.

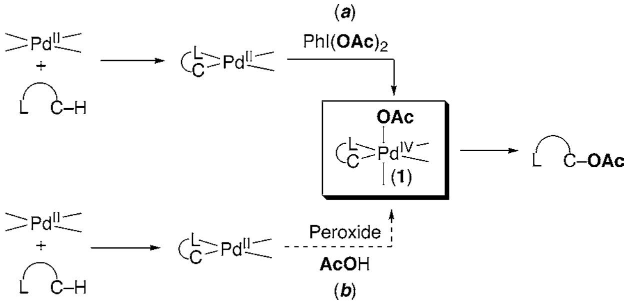
[7] Aldrich Chemical Catalog, 2005.

[8] While the current manuscript was in preparation, the use of organic peroxyesters as oxidants for Pd-catalyzed oxygenation reactions was reported. Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420.

[9] Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

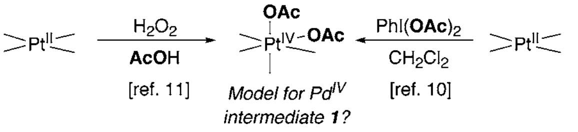
10.1021/ol0530272 CCC: $33.50

Scheme 1. C−H Bond Oxygenation Using $PhI(OAc)_2$ or Peroxides as Terminal Oxidants



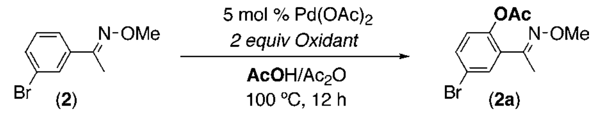
(which ultimately ends up in the product) is derived from the iodine(III) oxidant (Scheme 1a).[9]

However, we reasoned that the key Pd^{IV} intermediate **1** might be accessed using alternative peroxide-based oxidants if the reactions were conducted in the presence of an external acetate source such as acetic acid (Scheme 1b). This hypothesis was predicated on the fact that platinum(IV) analogues of **1** can be prepared by treatment of Pt^{II} complexes with either $PhI(OAc)_2$ in CH_2Cl_2[10] or with hydrogen peroxide in AcOH (eq 1).[11] Importantly, such Pt^{IV} adducts are frequently considered to be stable model complexes for transient Pd^{IV} catalytic intermediates,[12] suggesting that analogous conditions (peroxides in AcOH) might be used to generate the key intermediate **1** in Pd-catalyzed transformations.



(1)

Table 1. Use of Peroxide-Based Oxidants in the $Pd(OAc)_2$-Catalyzed C−H Bond Oxygenation

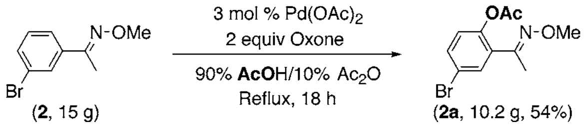


entry	oxidant	isolated yield (%) of **2a**[a]	entry	oxidant	isolated yield (%) of **2a**[a]
1	H_2O_2·urea	10	5	CH_3CO_3H	34
2	50% aq H_2O_2	11	6	Oxone	68
3	*m*-CPBA	14	7	$K_2S_2O_8$	76[b]
4	70% aq *t*-BuOOH	18	8	$PhI(OAc)_2$	81[b]

[a] Conditions: 5 mol % $Pd(OAc)_2$, 2 equiv of oxidant, 0.12 M **2** in AcOH/Ac_2O (50:50), 100 °C, 12 h; **2a** isolated as a 5:1 mixture of oxime *E*/*Z* isomers and as a >20:1 mixture of regioisomers. [b] Between 10 and 15% of the di-*o*-acetoxylated product was also isolated.

Our initial investigations to test this hypothesis focused on the $Pd(OAc)_2$-catalyzed acetoxylation of oxime ether **2** with a variety of peroxide oxidants in AcOH/Ac_2O (Table 1).[13] We were delighted to discover that all of the peroxides examined (including hydrogen peroxide,[14] peracetic acid, $K_2S_2O_8$, and Oxone) produced significant quantities of the *o*-acetoxylated product **2a**. Under standard reaction conditions (0.12 M **2** in AcOH/Ac_2O,[13] 2 equiv of oxidant, 5 mol % of $Pd(OAc)_2$, 100 °C, 12 h), Oxone and $K_2S_2O_8$ performed best, providing **2a** in 68% and 76% isolated yield, respectively. These yields were only slightly lower than those obtained with $PhI(OAc)_2$ under otherwise identical reaction conditions.

Carbon−hydrogen bond oxygenation reactions with Oxone are particularly attractive because they can be easily, safely, and inexpensively scaled. For example, the acetoxylation of **2** proceeds cleanly and efficiently when carried out with 15 g of substrate—an approximately 100-fold increase in scale from the initially optimized reaction conditions (eq 2). Product **2a** was readily isolated via Kugelrohr distillation in 54% yield. Notably, the large-scale reaction was conducted using just 3 mol % of $Pd(OAc)_2$, and the catalyst loading could potentially be reduced even further, albeit with longer reaction times.



(2)

The scope of the $Pd(OAc)_2$-catalyzed C−H bond acetoxylation with Oxone and/or $K_2S_2O_8$[15] in AcOH was next examined with a diverse array of organic substrates. As summarized in Table 2, these transformations could be applied to compounds containing a variety of different directing groups, including oxime ethers of both ketones (entries 1−7, 12, 13) and aldehydes (entries 8, 9), amides (entry 10), and isoxazolines (entry 11).[16] The reactions generally proceeded in comparable or moderately lower yields than with $PhI(OAc)_2$ under otherwise identical reaction conditions. The acetoxylation of aromatic C−H bonds with these inorganic peroxides proceeded efficiently in arene

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(10) Barnard, C. F. J.; Vollano, J. F.; Chaloner, P. A.; Dewa, S. Z. *Inorg. Chem.* **1996**, *35*, 3280.

(11) For example, see: Lee, Y.-A.; Yoo, K. H.; Jung, O.-S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 107.

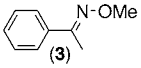
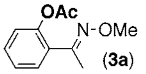
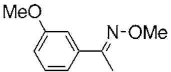
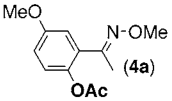
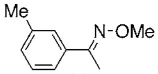
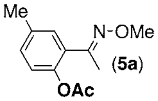
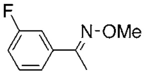
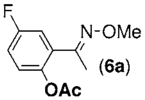
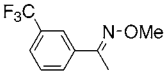
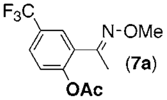
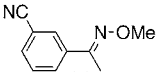
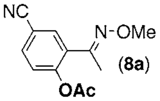
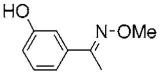
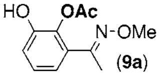
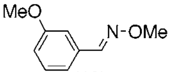
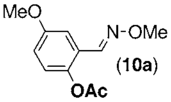
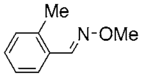
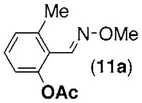
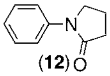
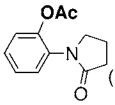
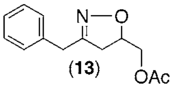
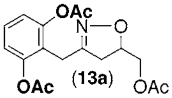
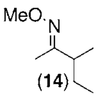
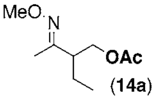
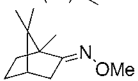
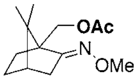
(12) For recent examples of the use of Pt compounds as models for Pd catalytic intermediates, see: (a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2005**, *24*, 482. (b) Canty, A. J.; Denney, M. C.; van Koten, G.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 5432. (c) Canty, A. J.; Patel, J.; Rodemann, T.; Ryan, J. H.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 3466.

(13) In general, comparable yields of oxygenated products were obtained with or without added acetic anhydride. However, without this additive, some hydrolysis of the OAc group of the product was often observed under the reaction conditions.

(14) The modest reactivity of H_2O_2 in the catalytic reactions (despite its ability to stoichiometrically oxidize Pt^{II} complexes) may be due to the tendency for H_2O_2 to undergo disproportionation in the presence of Pd^{II} salts. For a detailed discussion of such disproportionation reactions, see: Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766.

(15) For most substrates, Oxone and $K_2S_2O_8$ afforded similar results; however, in some cases (e.g., the sp^3 substrates) significantly better yields were obtained with $K_2S_2O_8$. The reasons for this difference in reactivity are unclear at this time and are currently under investigation.

Table 2. Pd(OAc)$_2$-Catalyzed Acetoxylation of C−H Bonds

entry	starting material	major product	yield (Peroxide)[a]	yield (PhI(OAc)$_2$)[b]
1	 (3)	 (3a)	53%	73%
2	 (4)	 (4a)	69%	78%
3	 (5)	 (5a)	71%	72%
4	 (6)	 (6a)	63%	57%
5	 (7)	 (7a)	75%[c]	95%
6	 (8)	 (8a)	57%[c]	66%
7	 (9)	 (9a)	37%	<5%
8	 (10)	 (10a)	53%	40%
9	 (11)	 (11a)	53%	69%
10	 (12)	 (12a)	75%[c]	77%
11	 (13)	 (13a)	53%[c,d]	72%[d]
12	 (14)	 (14a)	45%[c]	75%
13	 (15)	 (15a)	63%[c]	75%

[a] Conditions: 5 mol % Pd(OAc)$_2$, 1−2 equiv of Oxone, 0.12 M in AcOH or AcOH/Ac$_2$O, 100 °C, 12 h. Major regioisomer and oxime *E*/*Z* isomer of product is shown where relevant. [b] Conditions: 5 mol % Pd(OAc)$_2$, 1.1−1.3 equiv of PhI(OAc)$_2$, 0.12 M in AcOH or AcOH/Ac$_2$O. [c] $K_2S_2O_8$ used as the oxidant. [d] 3 equiv of oxidant.

substrates containing both electron-withdrawing (entries 4−6) and electron-donating (entries 2, 3, 7−9) substituents. Furthermore, a wide variety of functional groups, including aryl halides, nitriles, ethers, enolizable oxime ethers and amides, and benzylic C−H bonds were tolerated under the oxidizing reaction conditions. In fact, in some cases, Oxone showed substantially improved functional group tolerance relative to PhI(OAc)$_2$. For example, a modest (37%) yield was obtained in the acetoxylation of phenol substrate **9** with Oxone as a terminal oxidant, while the analogous reaction with PhI(OAc)$_2$ afforded <5% of the product **9a**.

In most substrates containing a meta substituent on the aromatic ring (Table 2, entries 2−8), modest to high selectivity was observed for acetoxylation of the less sterically hindered *o*-C−H bond.[17] The levels of regioselectivity in these transformations ranged from ~1.6:1 for a *m*-F substituent to >20:1 for the *m*-Br and *m*-CF$_3$ groups. Importantly, nearly identical selectivities were obtained with PhI(OAc)$_2$ under the same conditions, consistent with a mechanism in which the selectivity is determined by the initial C−H activation step and is therefore unaffected by the nature of the terminal oxidant. A notable exception to the observed trends was the *m*-hydroxyl-substituted oxime ether **9**, which underwent Pd(OAc)$_2$-catalyzed reaction with Oxone to afford the 1,2,3-trisubstituted arene **9a** as the sole observed regioisomeric product. While the origin of this unusual selectivity remains under investigation, it might result from a combination of the relatively small size and the strong coordinating ability of the OH substituent.

The activation and subsequent oxidative functionalization of unactivated sp^3 C−H bonds typically represents a significantly greater challenge than the analogous reactions of arene derivatives.[4,6a,8] Therefore, it is particularly notable that alkane substrates **14** and **15** also underwent Pd(OAc)$_2$-catalyzed acetoxylation with inorganic peroxides in AcOH (Table 2, entries 12 and 13). Both Oxone and $K_2S_2O_8$ could be utilized as terminal oxidants for these transformations, although better isolated yields were obtained with $K_2S_2O_8$.[15] Substrate **14** is particularly noteworthy, as it contains 6 diverse types of sp^3 carbon−hydrogen bonds. Similar to reactions with PhI(OAc)$_2$,[6a] a single acetoxylated product **14a** was obtained in which a primary *β*-C−H bond was functionalized, despite the presence of both weaker (secondary and tertiary) as well as more acidic (enolic) C−H bonds. This result indicates that competing free radical pathways (which are well-precedented with $K_2S_2O_8$)[18] are negligible under our reaction conditions.

We next turned our attention to expanding the use of peroxide-based oxidants to other Pd(OAc)$_2$-catalyzed C−H

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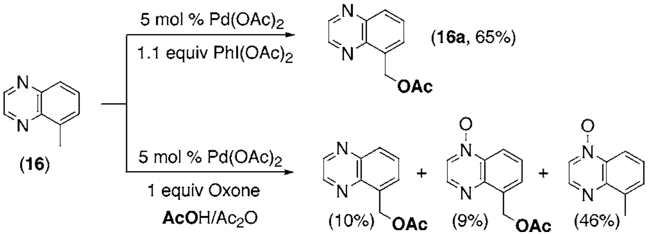
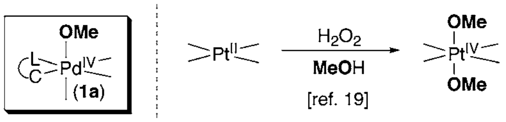
[16] One limitation of peroxide-based oxidants with respect to substrate scope is their tendency to promote competitive *N*-oxidation of some basic nitrogen-based directing groups. This is exemplified by the reaction of 8-methylquinoxoline shown below.



[17] For a detailed investigation of regioselectivity in Pd(OAc)$_2$-catalyzed C−H bond acetoxylation with PhI(OAc)$_2$, see: Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.

[18] For examples of C−H bond functionalization reactions initiated by $K_2S_2O_8$ that proceed through free radical mechanisms, see: (a) Lobree, L. J.; Bell, A. T. *Ind. Eng. Chem. Res.* **2001**, *40*, 736. (b) Asadullah, M.; Kitamura, T.; Fujiwara, Y. *Appl. Organomet. Chem.* **1999**, *13*, 539. (c) Basickes, N.; Hogan, T. E.; Sen, A. *J. Am. Chem. Soc.* **1996**, *118*, 13111.

bond functionalization reactions. Based on the mechanistic discussions above (Scheme 1 and eq 1), we reasoned that changing the reaction solvent from AcOH to MeOH might result in the formation of Pd^{IV} alkoxide intermediates analogous to **1** (e.g., complex **1a**, eq 3), which could undergo C−O bond-forming reductive elimination to afford ether products.[6b] Again, this hypothesis was supported by the known chemistry of inorganic platinum(IV) complexes, which serve as potential models for highly reactive Pd^{IV} intermediates.[12a,19] For example, as summarized in eq 3, Pt^{II} starting materials are well-known to react with H_2O_2 in methanol to afford stable Pt^{IV} dialkoxides in good yields.[19]

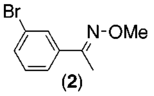
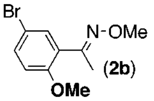
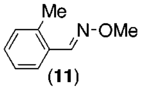
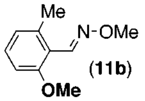
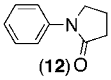
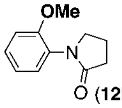
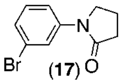
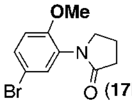
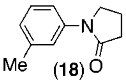
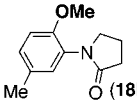
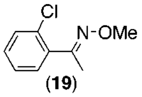
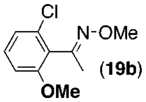


(3)

Our initial attempts to form ether products focused on the Pd-catalyzed reaction of oxime ether **2** with Oxone in methanol. Gratifyingly, this transformation cleanly afforded aryl methyl ether **2b** in 70% isolated yield (Table 3, entry 1). Notably, this and related ether-forming reactions required careful temperature regulation (with a gradual ramp from room temperature to between 40 and 80 °C) to avoid irreversible formation of palladium black (presumably via reduction of Pd^{II} by the alcohol solvent). However, under these carefully controlled conditions, $Pd(OAc)_2$-catalyzed C−H bond methoxylation with Oxone or $K_2S_2O_8$ could be applied to several different unsubstituted, ortho-substituted, and meta-substituted arene substrates. Furthermore, as summarized in Table 3, these reactions exhibited comparable functional group tolerance and reaction yields to the peroxide-mediated acetoxylation reactions described above.

In conclusion, we have demonstrated that mechanistic considerations in conjunction with platinum(IV) model complexes have led to the development of new $Pd(OAc)_2$-catalyzed C−H bond oxygenation reactions that utilize peroxides as stoichiometric oxidants. Inexpensive, safe, and environmentally benign Oxone was found to be a particularly effective terminal oxidant in these transformations and exhibited functional group tolerance and substrate scope that was comparable (and, in some cases, complementary) to $PhI(OAc)_2$. Our ongoing work in this area seeks to further expand the scope and functional group tolerance as well as to gain further insights into the mechanisms of these peroxide-mediated reactions.

Table 3. $Pd(OAc)_2$-Catalyzed Formation of Aryl Ethers with Oxone or $K_2S_2O_8$ in Methanol

entry	starting material	major product	yield[a]
1	 (2)	 (2b)	70%
2	 (11)	 (11b)	59%
3	 (12)	 (12b)	72%[b]
4	 (17)	 (17b)	61%[b]
5	 (18)	 (18b)	57%[b]
6	 (19)	 (19b)	60%

[a] Conditions: 5−10 mol % $Pd(OAc)_2$, 2−3 equiv of Oxone, 0.12 M in MeOH, 25 °C to between 40 and 80 °C over 48 h. Major regioisomer and oxime *E*/*Z* isomer is shown (where relevant). [b] $K_2S_2O_8$ used as the oxidant.

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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.

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(19) For example, see: Lee, Y.-A.; Jung, O.-S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1533.