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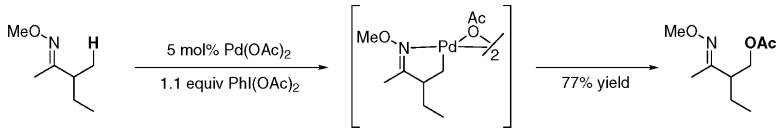

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Palladium-Catalyzed Oxygenation of Unactivated sp³ C−H Bonds

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General catalytic methods for the oxidation of unactivated sp³ C−H bonds would find widespread application in synthetic chemistry.[1] The development of such reactions remains challenging as a result of the strength of these bonds, the susceptibility of the products toward over-oxidation, and the difficulty of achieving regioselective functionalization in the context of complex organic molecules.[1] A number of reports have described stoichiometric chelate-directed alkane activation/oxidation mediated by group 10 metals,[2,3] and these reactions have been applied to the functionalization of steroids[3c−e] and to the synthesis of several other natural products.[3a,b] More recently, transition-metal-catalyzed procedures for the oxidation of methane[4] and of some more complex alkane substrates[5,6] have been reported; however, these transformations generally remain limited as a result of their modest substrate scope and/or harsh reaction conditions.

We have recently described a new Pd-catalyzed approach to the selective oxidation of arene and benzylic C−H bonds.[7] *We report herein that unactivated sp³ C−H bonds of both oxime and pyridine substrates undergo highly regio- and chemoselective Pd(II)-catalyzed oxygenation with PhI(OAc)₂ as a stoichiometric oxidant.* The reactivity and selectivity observed in these transformations are the result of (i) the use of substrates containing chelating functional groups (which both direct and accelerate unactivated sp³ C−H activation) and (ii) the exquisite sensitivity of directed C−H activation to the steric and electronic properties of the alkane substrate.

Our initial investigations of alkane oxidation focused on the β-functionalization of pinacalone *O*-methyl oxime **1** (Scheme 1). This substrate was selected on the basis of its ready availability from the parent ketone, as well as on precedent that related molecules undergo stoichiometric C−H activation at Pd(II).[2b] In addition, the expected β-oxygenated products (**3a**−**c**) can be converted to carbonyls[8] or amines,[9] providing an attractive route to valuable β-hydroxy ketones and β-amino alcohols, respectively. Gratifyingly, the reaction of **1** with 1.1 equiv of $PhI(OAc)_2$ and 5 mol % $Pd(OAc)_2$ at 100 °C for 5.5 h resulted in sp³ C−H bond oxidation to afford a mixture of the mono-, di-, and tri-acetoxylated products **3a**−**c**.[10,11] When the stoichiometry of the oxidant was increased to 4.5 equiv, **3c** was obtained as the major product in 59% isolated yield. Notably, α-oxidation was not observed despite the higher acidity of the α-C−H bonds (which generally increases reactivity toward electrophilic C−H activation).[2a]

A series of substituted *O*-methyl oxime substrates were next examined to probe the regioselectivity of these transformations.[12,13] As summarized in Table 1, substrates **4**−**6** reacted with 1.1 equiv of $PhI(OAc)_2$ and 5 mol % $Pd(OAc)_2$ to afford mono-β-oxygenated products **9**−**11** in modest to good yields (entries 1−3). Interestingly, no β-hydride elimination was observed in any of these systems, presumably due to the rigidity of the palladacyclic intermediates.[14] Reactions of substrate **5** (entry 2), which contains multiple possible sites for directed C−H activation, showed extremely high selectivity (i) for functionalization of 1° β-C−H bonds in lieu of those at 2°

Scheme 1. Chelate-Directed Oxidation of Pinacalone *O*-Methyl Oxime

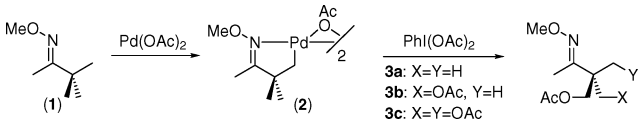
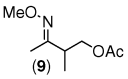
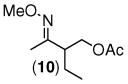
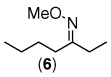
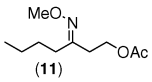
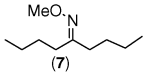
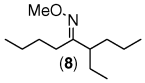


Table 1. Selectivity of Unactivated sp³ C−H Bond Oxidation[a]

Entry	Substrate	Major Product	Yield[b]
1	 (4)	 (9)	74%[c]
2	 (5)	 (10)	78%[c]
3	 (6)	 (11)	39%[c]
4	 (7)	No Reaction	0%
5	 (8)	No Reaction	0%

[a] 1 equiv of substrate (0.12 M), 1.1 equiv of $PhI(OAc)_2$, 5 mol % $Pd(OAc)_2$, 50% AcOH/50% Ac_2O, 100 °C, 1.5−3.5 h. [b] Isolated yields. [c] Isolated as a mixture of oxime *E*/*Z* isomers.

carbon centers and (ii) for oxidation at the β- rather than at the γ-position. Substrates **7** and **8**, which contain only 2° β- and/or 1° γ-C−H bonds, provided further confirmation of the high selectivity of these transformations, as they did not undergo detectable oxidation under our standard conditions (entries 4 and 5). Notably, reactivity toward oxidation was also significantly enhanced by α-branching, as exemplified by the dramatically higher yield obtained in the reaction of branched substrate **4** versus linear **6** (entries 1 and 3).

The observed regioselectivities can be rationalized on the basis of the requirements of C−H activation at Pd(II).[2,13] For example, selective oxidation at 1° versus 2° carbon centers likely results from a strong steric preference for the formation of less hindered 1° Pd alkyls.[2a] The high reactivity of β (versus α or γ) C−H bonds reflects the advantage of forming five-membered palladacycles.[2a] Finally, selectivity for oxygenation at α-branched sites is believed to result from the requirement for a coplanar relationship between the oxime and the target C−H bond,[2] a conformation that is more readily accessed with increasing α-substitution.

As summarized in Table 2, Pd-catalyzed oxidation of sp³ C−H bonds was applied to a variety of additional substrates. For example, the *O*-methyl oximes of both 2,2-dimethylcyclopentanone and camphor were efficiently oxygenated to afford **22** and **23** in good yields (entries 1 and 2). Interestingly, both of these substrates were

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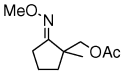
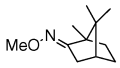
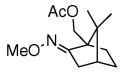
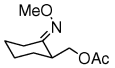
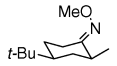
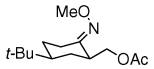
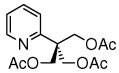
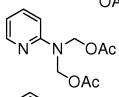
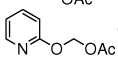
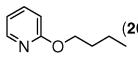
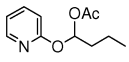
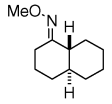
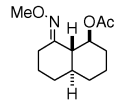
Table 2. Substrate Scope of sp^3 C−H Bond Oxygenation[a]

Entry	Substrate	Product	Yield[b]
1	 (**12**)	 (**22**)	61%
2	 (**13**)	 (**23**)	75%
3	 (**14**)	 (**24**)	81%[c]
4	 (**15**)	 (**25**)	86%[c]
5	 (**16**)	 (**26**)	63%
6	 (**17**)	 (**27**)	42%
7	 (**18**)	 (**28**)	70%
8	 (**19**)	 (**29**)	66%
9	 (**20**)	 (**30**)	44%
10	 (**21**)	 (**31**)	81%

[a] 1 equiv of substrate (0.12 M), 1.1−3.2 equiv of $PhI(OAc)_2$, 5 mol % $Pd(OAc)_2$, in AcOH, 50% AcOH/50% Ac_2O, or CH_2Cl_2, 80−100 °C, 5 min−12 h. [b] Isolated yields. [c] Isolated as a mixture of oxime E/Z isomers.

previously deemed unreactive in stoichiometric cyclopalladation reactions.[3e] Oximes of 2-methyl cyclohexanone derivatives were also good substrates for β-oxygenation (entries 3 and 4), and the rates of these transformations were extremely sensitive to conformational effects. For example, while the reaction of **14** took 1.5 h at 100 °C, **15** (whose *tert*-butyl substituent locks the 2-methyl group into coplanarity with the oxime) was completely oxidized within 5 *min* under analogous conditions. Pyridine was also an effective directing group (entries 5−9), and both the 2-*tert*-butyl and 2-*i*-propyl derivatives underwent oxidation to afford tri- and mono-oxidized products, respectively (entries 5 and 6). Pyridine-directed oxidation of alkyl groups adjacent to heteroatoms also proved facile, and 2-methoxy- and 2-(dimethylamino)pyridine were converted to **28** and **29** in good yields. Notably, these transformations offer a mild and selective approach to the dealkylation of ethers/amines, as the acetoxy-substituted acetal (**28**) and aminal (**29**) products are susceptible to acid-catalyzed cleavage to unmask free OH or NH_2 functionality.[8]

Oxidation at 2° carbon centers was also achieved in these systems after appropriate electronic or steric modification of the substrate. For example, when a 2° C−H bond was placed α to an activating ether substituent, Pd-catalyzed oxygenation proceeded in moderate yield (entry 9). Additionally, the use of structurally rigid *trans*-decalone *O*-methyl oxime (**21**) enabled functionalization of an unactivated 2° sp^3 C−H bond (entry 10). Interestingly, the product **31** was formed as a single diastereomer, with the OAc substituent in the equatorial position.[15] This result provides strong evidence that C−H activation (to form a palladacyclic intermediate) and subsequent oxidative cleavage (via oxidation to Pd(IV) followed by C−O bond forming reductive elimination)[7,16] both proceed with high levels of stereoselectivity.[17]

In conclusion, we have demonstrated an efficient method for Pd-catalyzed oxygenation of unactivated sp^3 C−H bonds using $PhI(OAc)_2$ as a stoichiometric oxidant. These reactions have significant potential synthetic utility, particularly as a result of their high selectivities. Current work is aimed at more fully elucidating the scope of potential substrates and oxidants as well as gaining further insights into the mechanisms of these transformations.

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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.

References

(1) For recent reviews, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.
(2) (a) Dunina, V. V.; Zalevskaya, O. A.; Potapov, V. M. *Russ. Chem. Rev.* **1988**, *57*, 250. (b) Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1980**, 1992.
(3) (a) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (b) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (c) Bore, L.; Honda, T.; Gribble, G. W. *J. Org. Chem.* **2000**, *65*, 6278. (d) Carr, K.; Saxton, H. M.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1599. (e) Baldwin, J. E.; Jones, R. H.; Najera, C.; Yus, M. *Tetrahedron* **1985**, *41*, 699.
(4) Recent examples: (a) Periana, R. A.; Mironov, O.; Taube, D.; Bhalla, G.; Jones, C. J. *Science* **2003**, *301*, 814. (b) Mukhopadhyay, S.; Bell, A. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2990. (c) Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560.
(5) (a) Sezen, B.; Franz, R.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 13372. (b) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (c) Kao, L. C.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1242.
(6) Other approaches to alkane functionalization: (a) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (c) Renkema, K. B.; Kissin, Y. V.; Goldman, A. S. *J. Am. Chem. Soc.* **2003**, *125*, 7770. (d) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig J. F. *Science* **2000**, *287*, 1995.
(7) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
(8) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999.
(9) Umino, N.; Iwakuma, T.; Ikezaki, M.; Itoh, N. *Chem. Pharm. Bull.* **1978**, *26*, 2897.
(10) Other Pd(II) salts afforded comparable or lower yields in catalytic sp^3 C−H acetoxylation (see Supporting Information, Table S1).
(11) Notably, the analogous OH oxime underwent oxidative cleavage to the ketone under the reaction conditions, and the ketone showed no reactivity towards Pd(II)-catalyzed acetoxylation.
(12) Oxime starting materials were typically used as a mixture of *E*/*Z* isomers and were found to equilibrate rapidly under the reaction conditions.
(13) Stoichimetric directed C−H activation at Pd(II) has been reported to require fully α-alkylated (e.g., *tert*-Bu-substituted) substrates, while substrates analogous to **4**−**6** have typically been considered unreactive in such transformations (refs 2 and 3).
(14) Clique, B.; Fabritius, C. H.; Couturier, C.; Monteiro, N.; Balme, G. *Chem. Commun.* **2003**, 272.
(15) Stereochemistry was assigned by standard analysis of the coupling constants of the hydrogen α to the acetate (see Supporting Information).
(16) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35.
(17) The observed stereochemistry is consistent with either (i) initial C−H activation at the axial position followed by reductive elimination with inversion of configuration or (ii) equatorial C−H activation followed by reductive elimination with retention. Experiments aimed at distinguishing these mechanistic possibilities are currently underway.

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