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Ligand-Modulated Palladium Oxidation Catalysis: Mechanistic Insights into Aerobic Alcohol Oxidation with the $Pd(OAc)_2$/Pyridine Catalyst System

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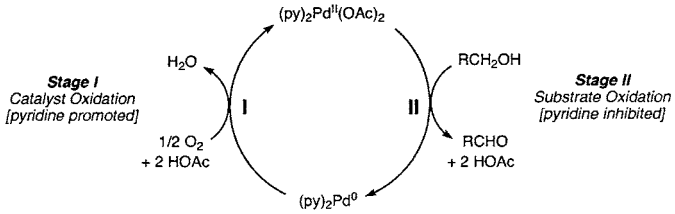
ABSTRACT



$Pd(OAc)_2$:pyridine (1:4) is an efficient catalyst system for the oxidation of alcohols with molecular oxygen. A mechanistic study of this reaction reveals that pyridine promotes the aerobic oxidation of palladium(0) but inhibits the oxidation of alcohol by palladium(II). Kinetic results reveal that turnover-limiting substrate oxidation consists of (i) formation of a palladium(II)–alkoxide, (ii) pyridine dissociation, and (iii) β-hydride elimination. These results provide a framework for the design and/or screening of more effective aerobic oxidation catalysts.

Selective alcohol oxidation is a prominent reaction in laboratory and industrial synthetic chemistry, and dioxygen-coupled strategies have attracted substantial recent effort.[1] Our attention has centered on a growing class of palladium-catalyzed oxidation reactions that do not require copper chloride or other traditional cocatalysts to achieve dioxygen-coupled turnover.[2−4] We anticipate that mechanistic insights into these reactions will facilitate catalyst design and screening efforts. Recent characterization of the $Pd(OAc)_2$/dimethyl sulfoxide (DMSO) catalyst system[4b] revealed that the solvent, DMSO, participates in ligand-promoted oxidation of palladium(0) by molecular oxygen. This insight prompted us to investigate other reactions that employ ligands instead of cocatalysts in dioxygen-coupled palladium oxidation catalysis. Uemura's $Pd(OAc)_2$/pyridine catalyst system for alcohol oxidation[2,5] is particularly attractive because of its operational simplicity, its use of catalytic quantities of ligand, and its enhanced activity relative to the $Pd(OAc)_2$/DMSO system. We highlight herein key kinetic and mechanistic features of $Pd(OAc)_2$/pyridine-catalyzed aerobic alcohol oxidation that reveal both beneficial and detrimental effects

(1) For leading references, see: Sheldon, R. A.; Arends, I. W. C. E.; Dijksman, A. *Catal. Today* **2000**, *57*, 157−166.

(2) (a) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **1998**, *39*, 6011−6014. (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750−6755.

(3) (a) Blackburn, T. F.; Schwartz, J. *J. Chem. Soc., Chem. Commun.* **1977**, 157−158. (b) Gómez-Bengoa, E.; Noheda, P.; Echavarren, A. M. *Tetrahedron Lett.* **1994**, *35*, 7097−7098. (c) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185−3189. (d) Bortolo, R.; Bianchi, D.; D'Aloisio, R.; Querci, C.; Ricci, M. *J. Mol. Catal. A* **2000**, *153*, 25−29. (e) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636−1639. (f) Hallman, K.; Moberg, C. *Adv. Synth. Catal.* **2001**, *343*, 260−263. (g) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475−7476. (h) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725−7726.

(4) (a) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188−7189. (b) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766−767.

(5) Similar catalyst systems have been employed in other oxidative transformations. (a) Oxidative ring opening of *tert*-cyclobutanols: Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2001**, *66*, 1455−1465. (b) Intramolecular oxidative amination of olefins: Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164−166.

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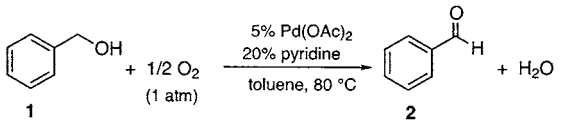
of pyridine in the reaction. Important differences between the $Pd(OAc)_2$/pyridine- and $Pd(OAc)_2$/DMSO-catalyzed alcohol oxidation are evident.[6]

Benzyl alcohol undergoes quantitative oxidation to benzaldehyde in 2 h under catalytic conditions (eq 1).[2] The



(1)

catalyst is generally prepared in situ from $Pd(OAc)_2$ and 4 equiv of pyridine; however, the use of crystalline *trans*-$(py)_2Pd(OAc)_2$[7] and 2 equiv of pyridine yields identical results. Each of the individual reaction components was investigated for its influence on the catalytic rate (Figure 1).[8] The rate exhibits no dependence on oxygen pressure,

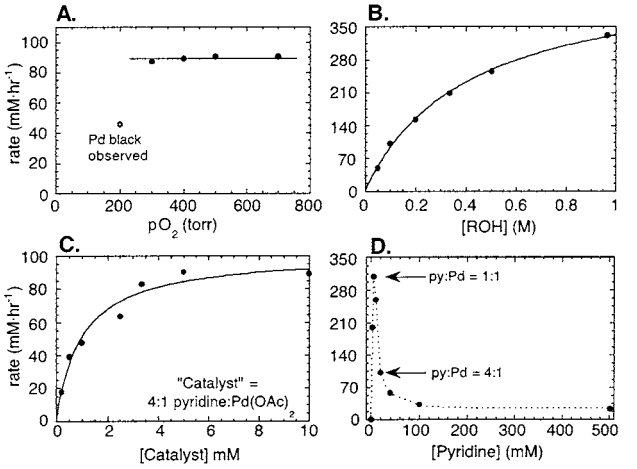
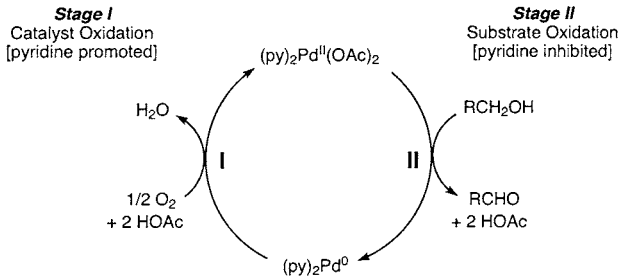


Figure 1. Initial rate dependence on oxygen pressure (A) and alcohol (B), catalyst (C), and pyridine (D) concentrations. Reaction conditions: (A) $[Pd(OAc)_2] = 5.0$ mM, [py] = 20 mM, $[PhCH_2OH] = 100$ mM, $pO_2 = 200-700$ Torr, 10 mL of toluene, 80 °C; (B) $[Pd(OAc)_2] = 5.0$ mM, [py] = 20 mM, $[PhCH_2OH] = 50-970$ mM, $pO_2 = 700$ Torr, 10 mL of toluene, 80 °C; (C) $[Pd(OAc)_2]$: [py] = 1:4 (0.20−10 mM:0.80−40 mM), $[PhCH_2OH] = 100$ mM, $pO_2 = 700$ Torr, 10 mL of toluene, 80 °C; (D) $[Pd(OAc)_2] = 5.0$ mM, [py] = 0−500 mM, $[PhCH_2OH] = 100$ mM, $pO_2 = 700$ Torr, 10 mL of toluene, 80 °C. The trendlines in (B) and (C) reflect nonlinear least-squares fits to eq 2 (see text).

except at low pressures, i.e., ≤200 Torr, where the reduced rate correlates with the formation of palladium black (Figure 1A). The rate does increase with increasing [alcohol], displaying saturation behavior (Figure 1B). Moreover, the use of deuterated substrate, $PhCD_2OH$, reveals a kinetic isotope effect on the catalytic rate. The magnitude of this effect increases with increasing substrate concentration: $k_H/k_D = 1.3(2)$ and 1.8(1) at [alcohol] = 0.10 and 1.0 M respectively. These values approach the intramolecular isotope effect of 2.6(2) obtained in the oxidation of PhCHDOH under both catalytic and stoichiometric conditions.[9] These results support turnover-limiting substrate oxidation by palladium(II) (Stage II, Scheme 1), in contrast to the

Scheme 1. Catalytic Cycle



$Pd(OAc)_2$/DMSO system, which features turnover-limiting oxidation of palladium(0).[4b]

The rate dependence on catalyst loading displays saturation behavior (Figure 1C), with the maximum rate nearly achieved at 5% $Pd(OAc)_2$. This result indicates that *higher catalytic efficiency is obtained at lower catalyst loading* (see further discussion below).

Pyridine has a dramatic influence on both half-reactions in the catalytic cycle (Figure 1D and Scheme 1). Oxidation of palladium(0) by molecular oxygen (Stage 1) requires pyridine. In its absence, only stoichiometric alcohol oxidation is observed with concomitant formation of palladium black. Inclusion of pyridine, however, results in rapid catalytic turnover, with a maximum initial rate arising at 1:1 pyridine:palladium (62 turnovers·h^{-1}). Comparison with the $Pd(OAc)_2$/DMSO system reveals that 1 equiv of pyridine is more effective than neat DMSO in promoting the oxidation of palladium(0). Kinetic insights into this step are limited because the catalytic turnover rate is dictated by substrate oxidation. Increasing [pyridine] beyond 1 equiv with respect to palladium results in substantial diminution of the catalytic rate, reflecting inhibition of alcohol oxidation by palladium(II) (Figure 1D).[10]

Our present hypothesis for the mechanism of palladium(II)-mediated alcohol oxidation involves a three-step

(6) During the preparation of this paper, two groups independently reported mechanistic studies of alcohol oxidation with related catalyst systems. (a) [(−)-sparteine]$PdCl_2$: Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202−8203. (b) (PhenS*)$Pd(OAc)_2$: ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355−369.

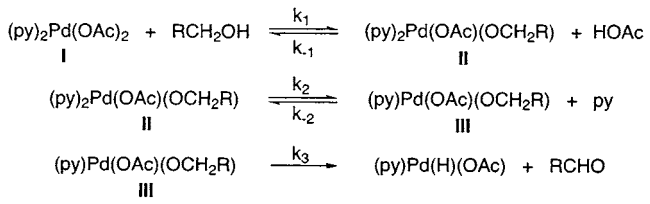
(7) Kravtsova, S. V.; Romm, I. P.; Stash, A. I.; Belsky, V. K. *Acta Crystallogr. Sect. C* **1996**, *52*, 2201−2204.

(8) Kinetics data were obtained by monitoring the initial rates of dioxygen consumption during the catalytic reaction with a computer-interfaced, gas-uptake kinetics apparatus. The product was quantified by GC after each reaction (internal standard = hexadecane), and a dioxygen:product ratio of 0.50(1) was observed in each case. Rate data obtained in units of Torr/s were converted into mM alcohol·h^{-1} for display in Figure 1. Reaction parameters are included in the figure caption.

(9) The stoichiometric reaction was carried out at 80 °C with a 1:1 substrate:palladium ratio.

(10) The catalyst appears to have enhanced stability at higher pyridine:palladium ratios based on the absence of palladium black at longer reaction times. The synthetically optimized ratio of 4:1 probably reflects a balance between optimal turnover rates and catalyst lifetime.

Scheme 2. Proposed Mechanism for Alcohol Oxidation by Palladium(II)



sequence (Scheme 2) initiated by preequilibrium formation of a palladium(II)−alkoxide, **II**. Reversible pyridine dissociation from **II** generates a three-coordinate palladium(II) species, **III**, from which β-hydride elimination yields the product aldehyde. The rate law for this mechanism (eq 2) readily accommodates the kinetic data in Figure 1. Rate inhibition by acetic acid, as predicted by this mechanism, has been confirmed experimentally. Furthermore, substantial precedent exists for three-coordinate intermediates in β-hydride elimination from d^8-transition-metal alkyl and alkoxide complexes,[11−13] and in one case, inhibition of β-hydride elimination by pyridine was reported.[11b] The kinetic isotope effects observed in these reported reactions are similar to those above.[11b,12]

$$\frac{d[RCHO]}{dt} = \frac{k_1 k_2 k_3 [Pd]_t [RCH_2OH]}{(k_1[RCH_2OH] + k_{-1}[AcOH])\cdot(k_{-2}[py] + k_3) + k_2 k_3} \quad (2)$$

Rates for both $Pd(OAc)_2$/DMSO- and $Pd(OAc)_2$/pyridine-catalyzed alcohol oxidation plateau with increasing [catalyst]. In DMSO, this behavior arises from competition between oxidation versus aggregation of the palladium(0) resting state. Because aggregation exhibits a bimolecular [Pd]-dependence, it experiences a kinetic advantage over oxidation at higher [catalyst]. In the $Pd(OAc)_2$/pyridine system, however, there is no evidence for catalyst decomposition to palladium black, except at low oxygen pressures. Instead, the saturation dependence on [catalyst] arises from the corresponding increase in [pyridine], which inhibits the formation of reactive intermediate **III** (Scheme 2).[14] This behavior accounts for the unprecedented catalytic activity at low catalyst loading (0.2 mol %) in the $Pd(OAc)_2$/pyridine-catalyzed oxidative amination of olefins.[5b]

This study reveals several features of the $Pd(OAc)_2$/pyridine catalyst system that account for its comparatively high catalytic activity. The >10-fold rate enhancement over the $Pd(OAc)_2$/DMSO system can be traced to the ability of pyridine to promote the dioxygen-coupled oxidation of palladium(0). Significantly, the presence of a palladium(II) catalyst resting state minimizes palladium(0) aggregation, which represents a persistent problem in palladium catalysis.[15] Meanwhile, substrate oxidation by palladium(II) benefits from a kinetically labile catalyst coordination sphere. The fact that bipyridine significantly inhibits catalytic turnover[2b] supports this notion. Altogether, these insights provide a mechanistic framework that should facilitate future catalyst screening and development efforts.

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Supporting Information Available: Derivation of eq 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For metal−alkyl β-hydride elimination reactions, see: (a) Whitesides, G. M.; Gaasch, J. F.; Stedronsky, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 5258−5270. (b) Romeo, R.; Alibrandi, G.; Scolaro, L. M. *Inorg. Chem.* **1993**, *32*, 4688−4694. (c) Goj, L. A.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11133−11147. (d) Shultz, L. H.; Brookhart, M. *Organometallics* **2001**, *20*, 3975−3982.

(12) For an iridium(I)−alkoxide β-hydride elimination reaction, see: Zhao, J.; Hesslink, H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 7220−7227.

(13) β-Hydride elimination from four-coordinate, d^8-complexes has also been observed. See: (a) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457−6463. (b) Bryndza, H. E.; Calabrese, J. C.; Marsi, M.; Roe, D. C.; Tam, W.; Bercaw, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 4805−4813. (c) Alibrandi, G.; Cusumano, M.; Minniti, D.; Scolaro, L. M.; Romeo, R. *Inorg. Chem.* **1989**, *28*, 342−347.

(14) The [Pd]-dependence under conditions of constant (excess) [py] also reveals a nonlinear dependence, although the curvature is substantially less than that in Figure 1C. The precise origin of this effect is presently being investigated; it may reflect slow palladium decomposition during the reaction or the presence of a multinuclear (i.e., ≥2) catalyst resting state. The results of these studies will be reported in a forthcoming full report.

(15) van Leeuwen, P. W. N. M. *Appl. Catal. A-Gen.* **2001**, *212*, 61−81.