Aerobic Oxidation of Alcohols

A Well-Defined Complex for Palladium-Catalyzed Aerobic Oxidation of Alcohols: Design, Synthesis, and Mechanistic Considerations**

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The Pd^{II}-catalyzed oxidation of an alcohol using molecular oxygen as the terminal oxidant is potentially a powerful transformation for organic synthesis.[1–3] Of the reported oxidations, monodentate nitrogenous ligands in combination with $Pd(OAc)_2$ have generally provided active catalyst mixtures, yet many of these oxidations suffer from relatively high catalyst loadings, an excess of ligand or base, and/or high oxygen pressures. Mechanistic explanations for these trends have recently been sought in several studies.[4] Key findings include: 1) base is necessary for catalysis,[4a,b] 2) an excess of ligand is needed to prevent catalyst decomposition,[2a,4c] and 3) a ligand must dissociate to allow alcohol binding and/or β-hydride elimination.[2a,4,5] Unfortunately, the need for excess ligand to prevent decomposition of the catalyst leads to less-efficient oxidation as a result of inhibition of either alcohol binding or β-hydride elimination. Herein, we report the design, use, and preliminary mechanistic studies of a well-defined Pd complex for alcohol oxidation that circumvents

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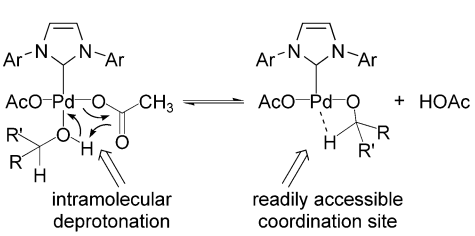
[**] This work was supported by the National Institutes of Health (NIGMS no. RO1 GM63540). D.R.J. is supported by an ACS Division of Organic Chemistry Graduate Fellowship sponsored by the Schering–Plough Research Institute. Pd salts were provided by Johnson Matthey. The crystal-structure analysis was performed by Atta Arif.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/anie.200351997

this conflict and is consequently suitable for oxidation using lower catalyst loadings and an ambient air atmosphere.

Based on the above discussion, a highly effective Pd^{II}-catalyzed alcohol oxidation might be achieved using a well-defined complex that does not require excess ligand to prevent decomposition of the catalyst. Directed by our previous studies, we considered using a palladium(II) acetate complex with a single N-heterocyclic carbene (NHC) ligand, since the NHC should act as a strong ligand to stabilize Pd^{II} and Pd^0 intermediates without the need for excess ligand.[6] Furthermore, Pd^{II}–NHC complexes have been shown to facilitate alcohol oxidation with the tertiary diamine (−)-sparteine as base.[3c] The acetate ligands were envisioned to serve two purposes: as a ligand for the Pd^{II} center and as a base to deprotonate the Pd-bound alcohol.[7] Since the acetate base would be masked as an anionic ligand, an intriguing possibility is that the acetate group could facilitate an intramolecular deprotonation (Scheme 1). Not only should this enhance the rate of deprotonation, but the resulting Pd–alkoxide should also have a readily accessible coordination site for β-hydride elimination.



Scheme 1. Proposed intramolecular deprotonation.

To test these ideas complex **1** (Figure 1) was generated in situ from AgOAc and the requisite $PdCl_2$–NHC dimer and used for the oxidation of alcohol **2a.** The oxidation proved effective with 5 mol% of catalyst and gave > 99% conversion in less than 2 h. [Pd(I*i*Pr)$(OAc)_2(H_2O)$] (**1**) was characterized by X-ray crystallography.[8] Our initial experiments were aimed at producing a reliable procedure at low catalyst loading, and, surprisingly, lowering the catalyst loading from 5 mol% to 0.5 mol% was found to give inconsistent results. However, the addition of a small amount of acetic acid to the reaction eliminated these inconsistencies and gave a reliable procedure under the following conditions: 0.5 M alcohol in toluene, 0.5 mol% **1**, 2.0 mol% HOAc, activated 3-Å molecular sieves, and a balloon of oxygen.

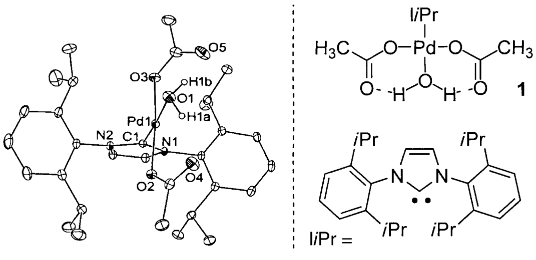
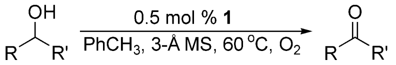


Figure 1. ORTEP and ChemDraw views of [Pd(I*i*Pr)$(OAc)_2(H_2O)$] (**1**). Hydrogen bond lengths [Å]: O(1)-H(1a) = 0.89(4), O(1)-H(1b) = 0.85(4), O(4)-H(1a) = 1.73(4), O(5)-H(1b) = 1.82(4), O(1)-O(4) = 2.571(3), O(1)-O(4) = 2.627 (3), and hydrogen bond angles [°]: O(1)-H(1A)···O(4) = 156(3), O(1)-H(1B)···O(5) = 159(3).

A variety of benzylic and allylic alcohols were cleanly oxidized to the corresponding aldehyde or ketone under these conditions, and high yields of the isolated products could be obtained by simple filtration through a plug of silica (Table 1, entries 1, 3, 5, and 7). The catalyst is capable of up to 1000 turnovers with the activated substrate **2b** (Table 1, entry 4). For synthetic simplicity, the catalyst can be pregenerated in the same reaction pot using $Pd(OAc)_2$, the I*i*Pr–HBF_4 salt, and KO*t*Bu, and applied successfully to the transformation (Table 1, entry 2). The sterically encumbered alcohol **2d** reacted slower but underwent good conversion by increasing the catalyst loading to 1.0 mol% (Table 1, entry 6). Only 1.0 mol% of acetic acid was needed for the clean oxidation of less reactive aliphatic alcohols to their corresponding ketones (Table 1, entries 8 and 10). Oxidation of non-benzylic, primary alcohols was accompanied by degradation of the aldehyde product which hindered catalysis. Several changes to the reaction conditions were required since auto-oxidation of aldehydes is possible under slightly acidic conditions. Removing the HOAc, adding Bu_4NOAc, and diluting the substrate to 0.125 M resulted in good yields of the aldehydic product (Table 1, entries 11–13).

Table 1: Oxidation of alcohols using pure O_2.

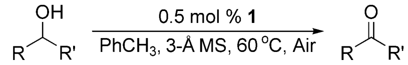


Entry[a]	Substrate	R	R′	*t* [h]	Yield [%][b,c]
1[d]	**2a**	Ph	CH_3	5	> 99 (98)
2[e]	**2a**			13	> 99
3[d]	**2b**	4-$MeOC_6H_4$	H	3.5	> 99 (99)
4[d],[f]	**2b**			20	> 99
5[d]	**2c**	3-$CF_3C_6H_4$	CH_3	12	> 99 (99)
6[d],[g]	**2d**	Ph	*t*Bu	14	91
7[d]	**2e**	1-cyclohexenyl	CH_3	12	91 (84)
8[h]	**2f**	$CH_3(CH_2)_7$	CH_3	13	99 (93)
9[d]	**2g**	3-Me-cyclohexenol		12	92
10[h]	**2h**	*cis*-4-Me-cyclohexanol		13	> 99
11[i]	**2i**	myrtenol		20	97
12[i],[j]	**2j**	$CH_3(CH_2)_{10}$	H	10	85 (76)
13[i],[j]	**2k**	$CH_3(CH_2)_{16}$	H	10	(85)

[a] See Supporting Information for details. [b] GC conversion. [c] Yield of isolated compound in parenthesis. [d] 2 mol% HOAc. [e] Catalyst prepared in situ using 0.5 mol% $Pd(OAc)_2$, 0.65 mol% I*i*Pr–HBF_4, 0.7 mol% KO*t*Bu. [f] 0.1 mol% **1**. [g] 1 mol% **1**. [h] 1 mol% HOAc. [i] 5.0 mol% Bu_4NOAc. [j] 0.75 mol% **1**. MS = molecular sieves.

A substantial practical improvement for aerobic oxidations is to replace the pure O_2 with air. Increasing the amount of acetic acid used enabled the oxygen balloon to be removed and the reaction carried out under the ambient atmosphere (no balloon necessary), with only slightly extended reaction times (Table 2). Increasing the amount of acetic acid to 5 mol% allowed the reaction to be scaled up to one gram in air, and gave > 99% conversion in 14 h with the product isolated in a yield of 97% (Table 2, entry 1). Replacement of O_2 with air at ambient pressure usually leads to decomposi-

Table 2: Oxidation of alcohols using air.



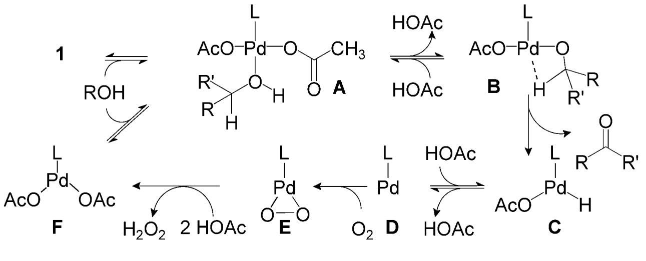
Entry[a]	Substrate	R	R′	*t* [h]	Yield [%][b,c]
1[d,e]	**2a**	Ph	CH_3	14	> 99 (97)
2[f]	**2l**	4-$MeOC_6H_4$	CH_3	14	> 99 (93)
3[f]	**2c**	3-$CF_3C_6H_4$	CH_3	20	> 99
4[f]	**2m**	4-$CH_3C_6H_4$	H	14	> 99
5[g]	**2f**	$CH_3(CH_2)_7$	CH_3	14	99 (91)
6[f]	**2n**	1-indanol		14	> 99
7[f]	**2h**	*cis*-4-Me-cyclohexanol		14	96

[a] See Supporting Information for details. [b] GC conversion. [c] Yield of isolated product in parenthesis. [d] 5 mol% HOAc. [e] 1.0 g scale. [f] 4 mol% HOAc. [g] 2 mol% HOAc.

tion of the catalyst in Pd-catalyzed aerobic oxidation of alcohols, thus the use of air in the current reactions is notable and can be considered a tribute to the robustness of this catalyst system.[9]

The crystal structure lends credence to our initial hypothesis of the acetate group acting as an intramolecular base (Figure 1): when the complex forms, a molecule of water is captured by the complex, with formation of a dative bond to the Pd and a hydrogen bond to each acetate ligand.[10,11] The presence of the hydrogen bonds between the water and the acetate oxygen atoms is quite remarkable as they suggest that an acetate ligand could indeed facilitate an intramolecular deprotonation. With evidence to suggest that the acetate ligand could function as an intramolecular base, several mechanistic experiments were undertaken to determine what effect(s) this might have on catalysis. After determining a first-order dependence on both [alcohol] and [**1**], the kinetic isotope effect (KIE) for the β-hydride (deuteride) of **2a** was measured. In contrast to the typically small KIE (1.3–2.5) for rate-limiting elimination of a β-hydride from a Pd–alkoxide complex,[12] an unusually large primary KIE of 6.8 ± 0.7 was determined. The magnitude of this KIE is similar to the calculated value for a transition state with no C–H(D) bond vibration and is consistent with a readily accessible coordination site for β-hydride elimination. The lower KIEs measured in other systems may be attributed to agostic interactions needed to displace a relatively strong ligand (for example, pyridine or chloride).

A reasonable catalytic cycle can be proposed (Scheme 2) from the structural and mechanistic data. The catalytic cycle begins with the binding of the alcohol to **1** and concomitant loss of water. Intramolecular deprotonation of the Pd-bound alcohol **A** gives a Pd–alkoxide **B**. Rate-limiting transfer of a β-hydride to a readily accessible coordination site gives the carbonyl product and the Pd–hydride **C**. Reductive elimination of acetic acid from **C** gives a Pd^0–NHC complex **D**, which can be oxidized by molecular oxygen to give a Pd^{II}–NHC peroxo complex **E**.[4f] Protonation with two equivalents of acetic acid regenerates the $Pd(OAc)_2$–NHC complex **F** and completes the catalytic cycle. While the precise role(s) of added acetic acid is not defined, added acetic acid could affect the turnover of the Pd^0–NHC peroxo intermediate **E**, reprotonation of Pd–alkoxide **B**, or an equilibrium between Pd–hydride **C** and Pd^0 species **D**.[13]



Scheme 2. Proposed mechanism.

In conclusion, a robust and effective Pd catalyst for aerobic alcohol oxidation that is effective for a variety of alcohols with turnover numbers of up to 1000 has been discovered and studied. Using a slightly higher concentration of acetic acid and extending the reaction times, the oxidations can be carried out under an ambient atmosphere of air, as showcased by the oxidation of alcohol **2a** on a one-gram scale. Mechanistic and structural data support proposals of intramolecular deprotonation and transfer of a β-hydride to a readily accessible coordination site. Future directions for this project include identifying chiral NHC ligands and/or carboxylates for an asymmetric variant and applying this catalyst system to other Pd-catalyzed reactions. A full study of the mechanism will be reported in due course and should elucidate the role(s) of acetic acid in the current oxidation as well as an evolved understanding of β-hydride elimination from Pd complexes.

Received: May 28, 2003 [Z51997]

Keywords: alcohols · oxidation · oxygen · palladium · reaction mechanisms

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2002, *344*, 355; f) S. S. Stahl, J. L. Thorman, R. C. Nelson, M. A. Kozee, *J. Am. Chem. Soc.* **2001**, *123*, 7188.

[5] A notable exception is the phenathrolene-based catalyst.[2d] In this catalyst, a bidentate ligand is used. Since the solvent is H_2O at 100 °C and 30 atm, the oxidation precedes by dissociation of anionic ligands.

[6] For a review of NHC ligands, see W. A. Hermann, *Angew. Chem.* **2002**, *114*, 1342; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290.

[7] For evidence of acetate acting as a base, see ref. [4b].

[8] CCDC-213715 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk). A yellow prism-shaped crystal $0.30 \times 0.23 \times 0.18$ mm in size was mounted on a glass fiber with traces of viscous oil and then transferred to a Nonius KappaCCD diffractometer equipped with $\mathrm{Mo}_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Ten frames of data were collected at 150(1) K with an oscillation range of 1 deg/frame and an exposure time of 20 s/frame. Indexing and unit-cell refinement based on all observed reflection from those ten frames indicated a monoclinic *P* lattice. A total of 12906 reflections ($\lambda_{max} = 27.5°$) were indexed, integrated, and corrected for Lorentz, polarization, and absorption effects using DENZO-SMN and SCALEPAC. Post refinement of the unit cell gave $a = 9.59400(10)$, $b = 19.1341(3)$, $c = 17.1480(3)$ Å, $\beta = 92.3451(5)°$, and $V = 3145.27(8)$ Å^3. Axial photographs and systematic absences were consistent with the compound having crystallized in the monoclinic space group $P2_1/a$. The structure was solved by a combination of direct methods and heavy atom using SIR 97. All of the non-hydrogen atoms were refined with anisotropic displacement coefficients. Hydrogen atoms were located and refined isotropically except those on the C31 atom which were assigned isotropic displacement coefficients $U(H) = 1.5\,U(\text{C methyl})$, and their coordinates were allowed to ride on their respective carbon atoms using SHELXL97. The weighting scheme employed was $w = 1/[\sigma^2(F_o^2) + (0.0257\,P)^2 + 2.171\,P]$ where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to $R1 = 0.0303$, $wR2 = 0.0726$, and $S = 1.027$ for 6402 reflections with $I > 2\sigma(I)$, and $R1 = 0.0353$, $wR2 = 0.0758$, and $S = 1.027$ for 7162 unique reflections and 517 parameters. The maximum Δ/σ value in the final cycle of the least-squares was 0.001, and the residual peaks on the final difference-Fourier map ranged from −0.594 to 0.869 e Å^{-3}.

[9] For a homogeneous Pd catalyst using air, see ref. [2c]. For a heterogeneous Pd catalyst using air, see ref. [2b].

[10] The H_2O molecule binds when the complex is formed and not during recrystallization, as evidenced by identical ^{1}H NMR spectra for the complex formed in situ and after recrystallization.

[11] The hydrogen atoms of the water molecule were located and found to be within the van der Waal radii of the acetate and the water. See Supporting Information for details.

[12] See ref. [4b,c,e] and G. Noronha, P. M. Henry, *J. Mol. Catal. A* **1997**, *120*, 75.

[13] For the reversible formation of Pd^{II}–hydride species under acidic conditions, see C. Amatore, A. Jutand, G. Meyer, I. Carelli, I. Chiarotto, *Eur. J. Inorg. Chem.* **2000**, 1855.