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$Pd(OAc)_2$-Catalyzed Oxidation of Alcohols to Aldehydes and Ketones by Molecular Oxygen

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Abstract: *A novel combination of $Pd(OAc)_2$/pyridine/MS3A catalyzes the aerobic oxidation of various benzylic alcohols into corresponding aldehydes and ketones in good yield. Primary and secondary aliphatic alcohols also are smoothly oxidized to aldehydes and ketones, respectively, under the same conditions.* © 1998 Elsevier Science Ltd. All rights reserved.

The transformation of alcohols into aldehydes and ketones is a fundamental reaction in organic synthesis.[1] So far, some stoichiometric oxidants such as manganese and chromium salts have been widely used for this purpose,[1c, d] but they are toxic and the use of these reagents induces hazardous problems. To overcome these problems the development of catalytic process using aerobic conditions is of great value.[2] Recently, Markó *et al.* found an effective catalytic system using CuCl/phenanthroline/K_2CO_3/$DBADH_2$ and TPAP/MS4A employing molecular oxygen or air as co-oxidant.[3] Kaneda *et al.* also reported, quite recently, that Ru-Al-Mg hydrotalcites work as reusable heterogeneous catalysts for the aerobic oxidation of allylic and benzylic alcohols.[4]

With regard to aerobic oxidation of alcohols into aldehydes and ketones palladium complexes were well investigated, but most of them required the combined use of molecular oxygen and re-oxidants such as copper salts.[5] In 1977, palladium-catalyzed aerobic oxidation without re-oxidants was reported by Schwartz *et al.*, who found that a combination of $PdCl_2$ and NaOAc was effective for oxidation of *secondary* alcohols into ketones at 38 °C in ethylene carbonate as solvent.[6] In 1996 and 1997, Kaneda *et al.* reported selective dehydrogenative oxidation of allylic alcohols to α,β-unsaturated aldehydes catalyzed by Pd clusters in the presence of molecular oxygen without re-oxidants.[7] These studies are quite interesting, but these systems are not yet applicable to a wide range of alcohols. Henry *et al.* reported a similar type of catalytic aerobic oxidation of various alcohols using palladium salts supported on a polyphenylene polymer.[8]

We have been investigating homogeneous and heterogeneous catalytic systems for oxidation of various organic compounds.[9] During the course of these studies, we have now found that the aerobic oxidation of alcohols to carbonyl compounds smoothly proceeds in the presence of a catalytic amount of $Pd(OAc)_2$, pyridine and MS3A. We report herein a novel procedure for simple, practical, clean and selective oxidation of various alcohols into corresponding aldehydes and ketones.[10]

In the search for the catalyst in aerobic oxidation of alcohols, we found that $Pd(OAc)_2$ was a good catalyst to promote the oxidation of benzyl alcohol in the presence of base under O_2 atmosphere (Scheme 1, Table 1). Among organic bases examined, pyridine was revealed to be most effective (entries 1-5). Interestingly, when MS3A was added to the reaction mixture, the oxidation proceeded more efficiently to give a quantitative yield of benzaldehyde (entry 6). The reaction also proceeded using air instead of O_2, but continuous bubbling of air was required as well as longer reaction time.[11] The complete conversion of alcohols was attained at 80 °C, but at lower temperature the rate of oxidation was slow. Other palladium(II) reagents, *i.e.* $PdCl_2$, $PdCl_2(CH_3CN)_2$, were ineffective for this oxidation.

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Scheme 1

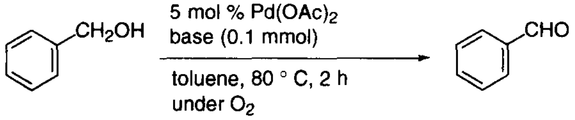


Table 1. Pd(OAc)$_2$-Catalyzed Oxidation of Benzyl Alcohol by Molecular Oxygen [a]

entry	base	conversion(%)	GLC yield(%) [b]
1	—	5	5
2	pyridine	86	86
3	2,6-lutidine	82	81
4	triethylamine	78	76
5	2,2'-bipyridine	5	5
6[c]	pyridine	~100	quantitative

a) Reaction conditions; Pd(OAc)$_2$ (0.05 mmol), benzyl alcohol (1.0 mmol), base (0.1 mmol), toluene (10 mL), under atmospheric O_2 at 80 °C for 2 h.

b) Bibenzyl was used as an internal standard.

c) In the presence of MS3A (500 mg).

Next, we carried out oxidation of various alcohols under the optimum conditions, the results of which being listed in Table 2.[12] *Primary* and *secondary* benzylic alcohols were converted to corresponding aldehydes and ketones in 89-100% yield within 2 h (entries 1-7). The amount of Pd(OAc)$_2$ can be reduced to 1 mol%, but longer reaction time was required to attain the quantitative conversion (12 h, entry 3). Surprisingly, *primary* aliphatic alcohols were smoothly oxidized to aldehydes in high yields (entries 8 and 10). *Secondary* aliphatic alcohols also were converted into ketones in high yields under the same conditions (entries 11 and 12). For practical purpose, the large scale oxidation of *p*-methoxybenzyl alcohol (1.38 g, 10.0 mmol) was carried out to give *p*-methoxybenzaldehyde (1.29 g, 9.50 mmol, entry 4). In general, an effective catalyst for oxidation of benzylic alcohols is also applicable to that of allylic alcohols. However, oxidation of cinnamyl alcohol by this system was sluggish and only 65% of cinnamaldehyde was obtained even by prolonging the reaction time (12 h) under the identical conditions. Although the details are not yet known, we suppose that the reaction proceeds *via* formation of a Pd(II)-alkoxide species[6, 8] from alcohol and Pd(II)-pyridine complex[13] followed by β-elimination of a Pd(II)-hydride species from the alkoxide species. The Pd(II)-hydride species can be converted again to an active Pd(II) species by molecular oxygen,[14] the divalent palladium complex working as an active species throughout the reaction.

In conclusion, a system of simple combination of commercially available reagents, Pd(OAc)$_2$/pyridine/MS3A, has shown a high catalytic activity for aerobic oxidation of benzylic and aliphatic alcohols. Scope and limitations of this oxidation as well as mechanistic work will be reported in due course.

Scheme 2

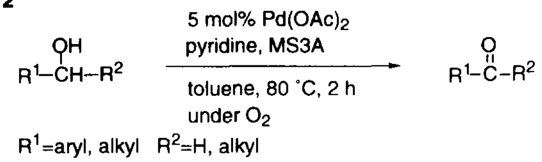
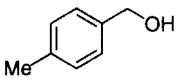
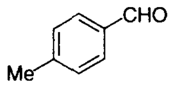
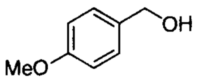
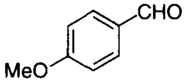
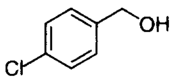
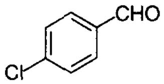
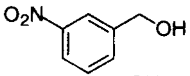
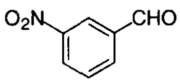
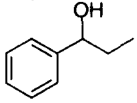
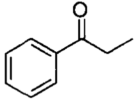
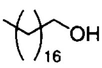
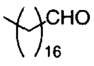
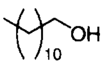
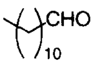
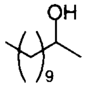
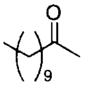
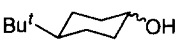
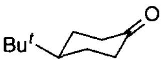


Table 2. $Pd(OAc)_2$-Catalyzed Oxidation of Alcohols by Molecular Oxygen[a]

entry	substrate	product	conversion(%)	isolated yield(%)
1			97	95
2			~100	96
3[b]			~100	96
4[c]			~100	95
5			92	89
6			94	92
7			95	94
8			96	95
9[d]			61	58
10			97	93
11			98	97
12			~100	93
13[d]			89	80

a) Reaction conditions; $Pd(OAc)_2$ (0.05 mmol), alcohol (1.0 mmol), pyridine (0.2 mmol), MS3A (500 mg), toluene (10 mL), under atomospheric O_2 at 80 °C for 2 h.

b) 1 mol% $Pd(OAc)_2$, for 12 h.

c) 10-Fold scale reaction using 1 mol% $Pd(OAc)_2$ and 1.00 g of MS3A for 12 h.

d) In the absence of MS3A.

References and Notes

1. For example, a) Sheldon, R. A.; Kochi, J. K. In *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press; New York, 1994. b) Hudlucky, M. In *Oxidations in Organic Chemistry*; ACS Monograph; Washington, DC, 1990. c) Procter, G. In *Comprehensive Organic Synthesis*; Ley, S. V., Ed.; Pergamon; Oxford, 1991; Vol. 7, 305. d) Ley, S. V. In *Comprehensive Organic Synthesis*; Trost, B.M., Ley, S. V., Eds.; Pergamon; Oxford, 1991; Vol. 7, 251.
2. For example, Mukaiyama, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17 and references therein.
3. DBADH$_2$=di-*tert*-butoxycarbonyl hydrazine; TPAP=tetra-*iso*-propylammonium perruthenate

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4. Kaneda, K.; Yamashita, T.; Matsushita, T.; Ebitani, K. *J. Org. Chem.* **1998**, *63*, 1750.
5. For example, a) Tsuji, J. In *Palladium Reagents and Catalysis*; John Wiley; New York, 1995. b) Lloyd, W. G. *J. Org. Chem.* **1967**, *32*, 2816. c) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286. d) Wilson, N. S.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2918 and references therein.
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7. a) Kaneda, K.; Fujii, M.; Morioka, K. *J. Org. Chem.* **1996**, *61*, 4502. b) Kaneda, K.; Fujie, Y.; Ebitani, K. *Tetrahedron Lett.* **1997**, *38*, 9023.
8. a) Noronha, G.; Henry, P. M. *J. Mol. Catal. A: Chemical* **1997**, *120*, 75. Other examples of palladium-catalyzed aerobic oxidation without re-oxidants: b) Hronec, M.; Cvengrosová, Z.; Kizlink, J. *J. Mol. Catal.* **1993**, *83*, 75. c) Gomez-Bengoa, E.; Noheda, P.; Echavarren, A. M. *Tetrahedron Lett.* **1994**, 35, 7097.
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10. After submission of this paper, similar palladium-catalyzed oxidation of alcohols was reported: Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185.
11. Benzaldehyde (74 %) was obtained using air (2 h).
12. Typical procedure: To a mixture of Pd(OAc)$_2$ (0.05 mmol) and toluene (4 mL) in a 20-mL two-necked flask were added pyridine (0.2 mmol) and MS3A (500 mg) activated by calcination. The orange suspension turned to yellow-white suspension when pyridine was added. Oxygen was introduced into the flask and the mixture was heated to 80 °C for 10 min. Then, alcohol (1 mmol) in toluene (4 mL) was added dropwise for 10 min using syringe pump. After additional toluene (2 mL) was added by the syringe used, the mixture was stirred for 2 h at 80 °C under atmospheric O$_2$. Products were determined by ^{1}H-, ^{13}C-NMR and GC/MS.
13. Kravtsova, S. V.; Romm, I. P.; Stash, A. I.; Belsky, V. K. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1996**, *C52*, 2201.
14. In one experiment we confirmed the absorption of O$_2$ (*ca.* 0.65 mmol) in the oxidation of benzyl alcohol (1 mmol) under this catalytic condition.