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A convenient palladium-catalyzed aerobic oxidation of alcohols at room temperature†

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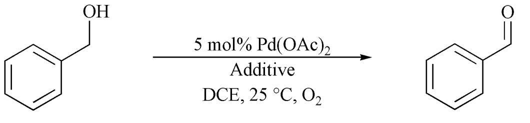
A simple Pd-catalyzed aerobic oxidation of benzylic and aliphatic alcohols to the corresponding aldehydes and ketones at room temperature is described.

The use of palladium catalysts for the oxidation of alcohols to aldehydes and ketones is well-precedented.[1] Recently, the use of molecular oxygen as a reoxidant in Pd-catalyzed oxidations of alcohols has been reported.[2,3] The use of molecular oxygen as the stoichiometric oxidant is ideal because it is readily available, soluble in common organic solvents,[4] and generates environmentally benign by-products. However, Pd-catalyzed aerobic oxidations are often limited by the use of high temperatures, pressures, and/or catalyst loadings. Therefore, the development of more active Pd-catalysts is desirable for improving the utility of these oxidations. Described herein is the first example of a Pd-catalyzed aerobic oxidation of alcohols at room temperature.

We recently reported a Pd-catalyzed aerobic oxidative kinetic resolution of secondary alcohols.[5,6] In this study, monodentate, nitrogen-based additives in combination with $Pd(OAc)_2$ at 70 °C provided the most active catalyst systems. Of those evaluted, Tröger's base displayed the highest reactivity. Therefore, we set out to evaluate monodentate, nitrogen-based additives for the oxidation of benzyl alcohol at room temperature. In an initial screen, it was found that both Tröger's base and triethylamine (TEA) were effective at room temperature (Table 1, entries 6 and 7). Interestingly, pyridine (Table 1, entry 1), which is more active then TEA at elevated temperatures, was a poor additive for the oxidation.[7]

The catalyst system was optimized for the oxidation of benzyl alcohol using TEA.‡ Optimal conditions were found as 0.3 M alcohol in 15% THF/toluene using 3 mol% $Pd(OAc)_2$, 6 mol% TEA and activated 3Å molecular sieves under a balloon pressure of oxygen.[8] The somewhat unusual solvent system was identified after observing the best initial rates in toluene and the highest conversions in THF.[9] The role of THF could be to stabilize any putative Pd(0) intermediates and prevent decomposition to palladium metal.[10]

Table 1 Additive screen



Entry	Additive[a]	Conversion[b] (%)
1[c]	Pyridine	< 5
2[c]	Pyrimidine	< 5
3[c]	4-Dimethylaminopyridine	< 5
4[c]	1,8-Diazabicyclo[5.4.0]undec-7-ene	< 5
5[c]	Triethylene Diamine	< 5
6[c]	Tröger's Base	59
7[d]	NEt_3	84
8[d]	i-Pr_2NEt	25

[a] $Pd(OAc)_2$ is not a viable catalyst. [b] Conversion of benzyl alcohol measured by GC analysis using undecane as the internal standard. [c] 0 mol% additive for 6 h. [d] 10 mol% additive for 12 h.

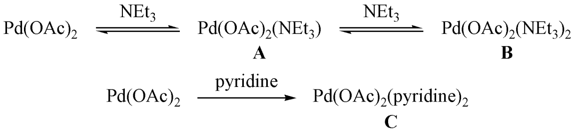
The substrate scope of the optimized system was evaluated. Both electron rich and electron deficient benzylic alcohols are found to oxidize efficiently and are isolated by simple filtration through silica gel in excellent yields (Table 1, entries 1–8). A secondary alcohol with two large substituents (entry 5) was oxidized cleanly to the ketone, albeit in lower yield with a longer reaction time (36 h). A benzylic alcohol with an *ortho*-methoxy substituent oxidized poorly (entry 9). A possible explanation for this result is the ability of the alcohol substrate or the ketone product to chelate the palladium thus inhibiting the oxidation (*vide infra*).

Aliphatic alcohols are also viable substrates (Table 1, entries 10–14). Both primary and secondary aliphatic alcohols oxidize cleanly with secondary alcohols giving slightly higher isolated yields. An aliphatic diol oxidized cleanly to the corresponding lactone in good yield (entry 14).

Not surprisingly, the oxidation of allylic alcohols proved challenging (Table 1, entries 15–17). A cyclic allylic alcohol (entry 15) was oxidized successfully under slightly modified conditions to yield the ketone (5 mol% $Pd(OAc)_2$ and 50 mol% TEA). Cinnamyl alcohol was a poor substrate for the oxidation causing the precipitation of palladium metal (entries 15 and 16). The addition of 3 equivalents of TEA allowed for a slight improvement in the isolated yield. Since the product of this oxidation is an α,β-unsaturated carbonyl compound, a well-known ligand for Pd(0), it is possible that the product is acting as an inhibitor in the reaction. To test this possibility, the oxidation of 2-decanol was carried out and cinnamaldehyde was added after 30 min. In the presence of cinnamaldehyde, the oxidation of 2-decanol was completely inhibited while a control oxidation without added cinnamaldehyde remained competent.[9] This is consistent with cinnamaldehyde inhibiting the oxidation reaction.

To help elucidate the role of TEA, the dependence of [TEA] on the initial rate of benzyl alcohol oxidation was evaluated. Initially increasing [TEA] leads to enhanced rates, but increasing [TEA] beyond 8 mol% reduced the observed oxidation rate.[9] While TEA is necessary for oxidation at room temperature, these results indicate that high concentrations of TEA inhibit the reaction.

To further understand the active catalyst, ^1H NMR analysis of the catalyst mixture was undertaken. An equilibrium between three Pd species was observed and includes free $Pd(OAc)_2$ along with both **A** and **B** (Scheme 1). As the concentration of TEA is increased, the equilibrium favors **B**. This observation provides for a potential explanation for the inhibitory role of



$$Pd(OAc)_2 \underset{}{\overset{NEt_3}{\rightleftharpoons}} \underset{\mathbf{A}}{Pd(OAc)_2(NEt_3)} \overset{NEt_3}{\rightleftharpoons} \underset{\mathbf{B}}{Pd(OAc)_2(NEt_3)_2}$$

$$Pd(OAc)_2 \xrightarrow{\text{pyridine}} \underset{\mathbf{C}}{Pd(OAc)_2(pyridine)_2}$$

Scheme 1 NMR experiments.

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† Electronic supplementary information (ESI) available: screening procedures and optimization tables. See http://www.rsc.org/suppdata/cc/b2/b209344h/

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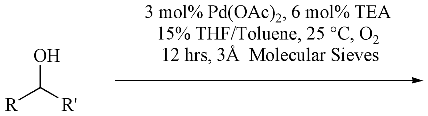
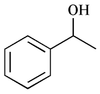
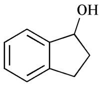
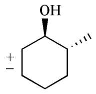
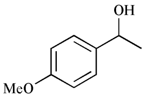
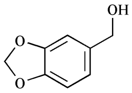
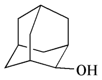
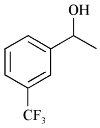
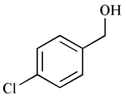
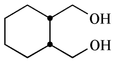
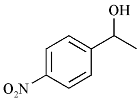
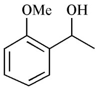
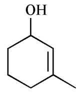
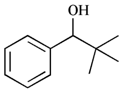
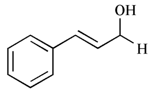
Table 2 Substrate scope[a]



Entry	Substrate	Yield[b] (%)	Entry	Substrate	Yield[b] (%)	Entry	Substrate	Yield[b] (%)
1		93	6		95	12		98
2		96	7		97	13		81
3		95	8		93	14		90[e]
4		85	9		0	15		93
5		50[c]	10	2-Decanol	97	16		30[f]
			11	1-Dodecanol	88[d]	17		39[g]

[a] All products have been previously reported in the literature. [b] Average of two experiments. [c] 36 h. [d] 0.1 M alcohol. [e] Product is the corresponding lactone. [f] 5 mol% Pd(OAc)$_2$ and 50 mol% TEA. [g] 5 mol% Pd(OAc)$_2$ and 300 mol% TEA.

excess TEA, where **A** is the catalytically active species at room temperature.

Since the reactivity of catalysts derived from pyridine and TEA are dramatically different at room temperature, we examined Uemura's catalyst using Pd(OAc)$_2$ and pyridine[3] by ^{1}H NMR. In contrast to the use of TEA, the use of pyridine results in a single Pd-species, **C**, at room temperature and 80 °C. From these results, it is apparent that the nature and number of nitrogen-based ligands on Pd play a vital role in catalyst activity.[11]

In conclusion, a convenient aerobic alcohol oxidation, which is effective at room temperature, has been developed. To the best of our knowledge, this is the first example of a Pd-catalyzed aerobic oxidation of an alcohol at room temperature. All reagents are commercially available. Using a catalyst loading of 3 mol% Pd(OAc)$_2$, both benzylic and aliphatic alcohols can be oxidized. Initial mechanistic studies provide evidence that the active catalyst may be a Pd-complex containing a single TEA ligand. The development of more active catalysts, and elucidating the exact role of TEA are currently being investigated.

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Notes and references

‡ *Typical procedure* for alcohol oxidation: Pd(OAc)$_2$ (8.1 mg, 0.036 mmol, 0.03 equiv., 3 mol%), toluene (3.4 ml), THF (0.6 ml), triethylamine (0.01 ml, 0.072 mmol, 0.06 equiv., 6 mol%), 3Å molecular sieves (200 mg), and a magnetic stir bar were placed in a 25 ml schlenk flask. A balloon attached to a three-way valve was placed on the flask and the vessel evacuated then filled with oxygen. The purge was repeated three times using a water aspirator. The mixture was allowed to stir at room temperature under an oxygen atmosphere for 30 min. At this time, the *sec*-phenethyl alcohol (0.145 ml, 1.2 mmol, 1.0 equiv.) was syringed into the flask. Upon addition of the alcohol, the mixture changed from yellow to orange. The reaction mixture was allowed to stir for 12 h. A 0.03 ml aliquot was syringed out of the vessel and GC analysis performed. Upon completion of reaction, the reaction mixture was loaded directly on a small pad of silica. The plug was then flushed with hexanes to remove the toluene and the product eluted with dichloromethane. The solvent was removed *in vacuo* to yield acetophenone (137 mg, 95% yield). Purity confirmed by GC and ^{1}H NMR.

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8 On small scale (< 0.3 mmol), oxygen could be replaced with a balloon of air and MS 3Å were not required. However, reactions on larger scale required MS 3Å for reactions to proceed without decomposition of palladium. For details on the use of MS 3Å, see ref. 3.
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