

## Efficient and Practical Catalytic Oxidation of Alcohols Using Molecular Oxygen†

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The oxidation of alcohols into aldehydes and ketones is a ubiquitous functional group transformation in organic chemistry.<sup>1</sup> However, despite its obvious commercial importance and the detrimental ecological impact of the usual oxidants, few efficient and mild catalytic oxidation procedures have been reported that utilize dioxygen (or air) as the stoichiometric oxidant.<sup>2</sup> Recently, we have disclosed two catalytic aerobic oxidation protocols<sup>3</sup> that allow the transformation of alcohols **1** into carbonyl derivatives **2** in high yield and which release water as the only byproduct (Figure 1).

Both of these systems are compatible with a variety of sensitive functionalities and protecting groups. However, the ruthenium-based aerobic oxidation procedure requires 5 mol % of the rather expensive tetrapropylammonium perruthenate (TPAP) and is thus unsuitable for large-scale operations. Moreover, the much cheaper copper chloride/phenanthroline protocol necessitates the use of 2 equiv of  $K_2CO_3$ . The stringent requirement for such a large amount of  $K_2CO_3$  was puzzling, and we initiated some studies in order to understand the role(s) of this heterogeneous base. In particular, we wished to find suitable reaction conditions

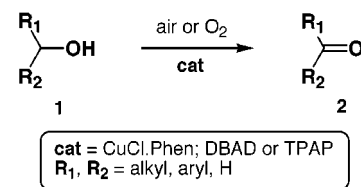


Figure 1.

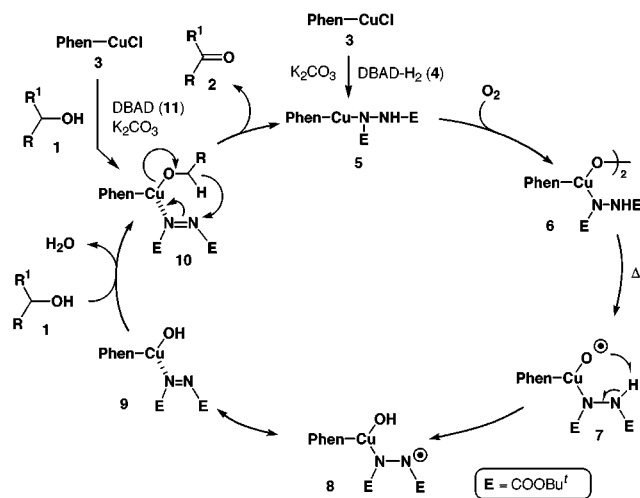


Figure 2.

in which smaller amounts of base could be employed in order to transform our original system into a more ecologically friendly protocol.

Therefore, a variety of other bases ( $Na_2CO_3$ ,  $Li_2CO_3$ ,  $Na_2HPO_4$ ,  $NaH_2PO_4$ ,  $Al_2O_3$ ,  $NaOAc$ ,  $KOAc$ ,  $KOH$ , and  $CuCO_3$ ) were initially tested in this aerobic oxidation system. Surprisingly, none proved to be as efficient as  $K_2CO_3$ .<sup>4</sup> Examination of the postulated mechanism of this transformation (Figure 2) suggested a number of possible roles for  $K_2CO_3$ .<sup>5</sup> First,  $K_2CO_3$  should act as a base and react with the HCl formed during the initial replacement of the chloride ligand by the alcohol. However, if this was the sole purpose of  $K_2CO_3$ , then only 5 mol % should actually be necessary in the reaction to fulfill the requirement of catalyst formation.

Second, examination of the oxidation in toluene revealed its heterogeneous nature. Filtration of the dark-brown suspension gave a filtrate devoid of oxidizing activity and a solid material that, once resuspended in toluene, smoothly oxidized alcohols to the corresponding ketones and aldehydes. It thus appears that  $K_2CO_3$  may also serve as a solid support on which the copper catalyst can be anchored. Finally, since water is released during the oxidation process,  $K_2CO_3$  might also be acting as a water scavenger.

The importance of the dehydrating properties of  $K_2CO_3$  was clearly revealed by performing the oxidation reaction using only 10 mol % of  $K_2CO_3$  in the presence of an excess of 4 Å MS. Although 4 Å MS proved to be less efficient than  $K_2CO_3$  in trapping the released water (larger loading and

(4) One rare exception appears to be  $KOBu'$ . For example, the aerobic oxidation of 2-undecanol (5 mol %  $CuCl·Phen$ , 5 mol %  $KOBu'$ , toluene, 80–90 °C) afforded 2-undecanone in almost quantitative yields. However, this system appears, so far, to be limited to secondary alcohol oxidations.

(5) For a discussion of the possible mechanism of this reaction, see: Markó, I. E.; Tsukazaki, M.; Giles, P. R.; Brown, S. M.; Urch, C. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2208.

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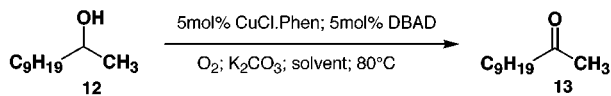
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**Table 1. Solvent and Base Effects in the Aerobic Oxidation of 2-Undecanol**

Entry	Solvent	K <sub>2</sub> CO <sub>3</sub>	Conversion <sup>(a)</sup>	Yields <sup>(b)</sup>
1	CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	2eqs	90%	88%
2	CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	1eq	70%	61% <sup>(c)</sup>
3	CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	0.5eq	<20%	11%
4	FC <sub>6</sub> H <sub>5</sub>	2eqs	50%	44% <sup>(d)</sup>
5	FC <sub>6</sub> H <sub>5</sub>	1eq	100%	94%
6	FC <sub>6</sub> H <sub>5</sub>	0.5eq	100%	>99%
7	FC <sub>6</sub> H <sub>5</sub>	0.25eq	100%	>99%
8	FC <sub>6</sub> H <sub>5</sub>	0.1eq	60%	58% <sup>(e)</sup>

<sup>a</sup> The % conversion was measured by <sup>1</sup>H NMR spectroscopy and by capillary GC analysis. <sup>b</sup> All yields are for pure, isolated compounds. <sup>c</sup> The reaction was stopped after 5 h. <sup>d</sup> The reaction was stopped after 3 h. <sup>e</sup> The reaction was stopped after 8 h.

longer reaction time are required), the oxidation went smoothly to completion.

A major breakthrough was accomplished during the study of the influence of the solvent on the amount of K<sub>2</sub>CO<sub>3</sub> required for the aerobic oxidation of 2-undecanol into 2-undecanone (Table 1).<sup>6</sup>

Whereas in toluene 2 equiv of K<sub>2</sub>CO<sub>3</sub> is necessary to achieve complete conversion of alcohol **12** into ketone **13** (Table 1, entries 1–3), we were quite surprised to find that only a mediocre yield of the desired ketone was obtained in fluorobenzene (Table 1, entry 4) under comparable conditions.<sup>7</sup> Unexpectedly, **lowering the amount of K<sub>2</sub>CO<sub>3</sub> dramatically increased the conversion of 12 into 13, reaching a 100% conversion even when only 25 mol % of the base was employed** (Table 1, entry 7). Under these conditions, 2-undecanone **13** could be isolated in up to 99% yield. These optimized conditions were then applied to the aerobic oxidation of a variety of structurally representative alcohols. The results are summarized in Table 2.

It is quite remarkable that essentially every type of alcohol is smoothly oxidized into the corresponding carbonyl derivative in high yield and with good to complete conversion. Under these conditions, primary aliphatic, allylic, and benzylic alcohols afford the expected aldehydes and secondary alcohols are smoothly transformed into ketones. Geraniol affords geranial and nerol gives neral with no detectable loss of the geometric integrity of the C–C double bond (Table 2, entries 5 and 6). The catalyst tolerates both sulfur and nitrogen substituents (Table 2, entries 2, 4, and 8). Protected  $\beta$ -amino alcohols are smoothly converted into the corresponding aldehydes without detectable racemization (Table 2, entries 4 and 8). It is also noteworthy that the reaction conditions are sufficiently mild as to be compatible with the Boc protecting group (Table 2, entry 8).

Remarkably, steric hindrance does not seem to play a major role in determining the outcome of this oxidation.

(6) It is interesting to note that other solvents gave repeatedly poorer conversions (benzene, xylenes) or destroyed the catalyst activity (CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, ClCH<sub>2</sub>CH<sub>2</sub>Cl, DMF, and MeCN).

(7) It is interesting to note that fluorobenzene was also used successfully by Mukaiyama and co-workers as a solvent in their Mn(salen)-catalyzed epoxidation of alkenes using the O<sub>2</sub>/aldehyde protocol: Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Chem. Lett.* **1992**, *11*, 2231.

**Table 2. Aerobic, Catalytic Oxidation of Alcohols**

Entry	Substrate	Product	Yield <sup>(a)</sup>
1	C <sub>9</sub> H <sub>19</sub> CH <sub>2</sub> OH	C <sub>9</sub> H <sub>19</sub> CHO	65% <sup>(b)</sup>
2			85%
3			87%
4			85% <sup>(c)</sup>
5			86% <sup>(d)</sup>
6			80% <sup>(d)</sup>
7			75%
8			80% <sup>(e)</sup>
9			93%
10			90%

<sup>a</sup> All yields are for pure, isolated compounds. Complete conversions were achieved unless specified. <sup>b</sup> In this case, the reaction was stopped after 70% conversion. The recovered alcohol amounted to ~30%. <sup>c</sup> No racemization was observed in this oxidation reaction. The aldehyde was reduced to the alcohol (LiAlH<sub>4</sub> in THF), and the ee of the resulting amino alcohol was measured by HPLC analysis: Daicel chiralpak column; 2% <sup>t</sup>PrOH in hexane; 1 mL/min; T = 20 °C;  $\lambda$  = 254 nm; (*R*)-Bn<sub>2</sub>valinol, 11.16 min; (*S*)-Bn<sub>2</sub>valinol, 12.70 min; ee > 99%. <sup>d</sup> No double-bond isomerization took place under these conditions. <sup>e</sup> No racemization was observed in this oxidation reaction. The ee was measured by chiral GC (CP-Chiral-Dex CB, 25 m;  $\phi$  = 0.25 mm, DF = 0.25  $\mu$ m, 130 °C for 12 min then 1 °C per min) of the derived bis-Boc-prolinol obtained by LiAlH<sub>4</sub> reduction of Boc-prolinol followed by derivatization with Boc<sub>2</sub>O (*t<sub>R</sub>* (*R*)-enantiomer, 43.1 min; *t<sub>R</sub>* (*S*)-enantiomer, 43.6 min).

Indeed, both *endo*- and *exo*-borneol are oxidized to camphor at the same rate, despite the tremendous difference in the steric environment of these two alcohols (Table 2, entries 9 and 10).

In summary, we have discovered an efficient, aerobic, catalytic oxidation procedure that allows the transformation of alcohols into aldehydes and ketones in high yield and under mild conditions. The property of fluorobenzene that is responsible for its unequalled behavior is not known at present. The new conditions described in this paper represent a significant step toward a highly efficient and truly ecologically friendly oxidation protocol for alcohols.

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**Supporting Information Available:** Fluorobenzene data and a typical experimental procedure (1 page).