



Practical Cu(OAc)₂/TEMPO-catalyzed selective aerobic alcohol oxidation under ambient conditions in aqueous acetonitrile



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ABSTRACT

We reported a ligand- and additive-free Cu(OAc)₂/TEMPO catalyst system that enables efficient and selective aerobic oxidation of a broad range of primary and secondary benzylic alcohols, primary and secondary 1-heteroaryl alcohols, cinnamyl alcohols, and aliphatic alcohols to the corresponding aldehydes and ketones. This ambient temperature oxidation protocol is of practical features like aqueous acetonitrile as solvent, ambient air as the terminal oxidant, and low catalyst loading, presenting a potential value in terms of both economical and environmental considerations. Based on the experimental observations, a plausible reaction mechanism was proposed.

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Selective oxidation of alcohols to the corresponding aldehydes or ketones is a ubiquitous transformation in organic chemistry since aldehydes/ketones have served as significant chemical feedstocks for pharmaceutical, perfume, dye, and agrochemical industries, as well as for fundamental research.^{1,2} Traditionally, numerous stoichiometric oxidants are necessary to effect this key conversion with uncontrollable explosive danger, meantime producing almost the same amount of oxidant-derived waste during manufacturing.¹ For this reason, over the past decades, it has been a focus of considerable attention to implement eco-friendly aerobic alcohol oxidation with the aid of transition metal catalysts such as Pd,³ Ru,⁴ Co,⁵ Mo-Co,⁶ Pt,⁷ Os,⁸ Ni,⁹ Fe,¹⁰ Cu,¹¹ and others,¹² or a metal-free catalyst system.¹³ More significantly, the combinations of transition metals and nitroxyl radical 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) have been feasible to this oxidation using oxygen as terminal oxidant with water as only by-product, and intensive research efforts have kept this field in the limelight.¹⁴ However, the daily practice of the known aerobic oxidation protocols has been severely restricted by the use of complex metal–ligand-coordinated catalysts, pure O₂ as oxidant, and non-standard solvents like fluorinated arenes^{10c,14b} and ionic liquids.^{14f,h} In reality, from a standpoint of sustainable development, it is still highly desirable to develop cleaner, safer, cheaper, and more practical catalyst systems for the aerobic alcohol oxidation under ambient conditions. Especially, the mild reaction conditions are

demanding for tolerating sensitive functional groups, for example, C=C bond, aldehyde group, and heteroatoms. Hence, further research in this field should be warranted.

Herein, we described a practical ligand- and additive-free Cu(OAc)₂/TEMPO catalyst system for aerobic oxidation of a broad range of alcohols, including primary and secondary benzylic alcohols, primary and secondary 1-heteroaryl alcohols, cinnamyl alcohols, and aliphatic alcohols to the corresponding aldehydes and ketones at room temperature with ambient air as terminal oxidant. Our work was inspired by recently elegant reports of Mase¹¹ and Stahl¹¹ on copper/TEMPO-catalyzed aerobic oxidation of primary alcohols with 2,2'-bipyridine (bpy) as a ligand and MeONa¹¹ or *N*-methylimidazole (NMI)¹¹ as a basic additive. The use of ligand and additive in their protocols, however, albeit with catalytic amount, was less desirable in view of practical considerations. Regrettably, Mase's protocol only gave a narrow scope of primary alcohols and Stahl's catalyst system was found to be ineffective for oxidizing phenolic alcohols. We were intrigued as to whether a ligand- and additive-free copper/TEMPO catalyst system could attain the efficient aerobic alcohol oxidation under ambient conditions. But, our tests demonstrated that CuCl, CuCl₂, CuOTf, or Cu(OTf)₂ in combination with TEMPO showed marginally catalytic activities. Based on the understanding of powerful renovation of Cu(OAc)₂ by ambient air¹⁵ as well as good performance of Cu(OAc)₂/TEMPO oxidation systems,¹⁶ we envisioned that Cu(OAc)₂ might activate TEMPO for aerobic alcohol oxidation.

Our studies commenced with the oxidation of benzyl alcohol with 5 mol % Cu(OAc)₂ and 5 mol % TEMPO in acetonitrile under

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ambient air (open system) at room temperature (Table 1, entry 1). An exciting yield of 92% suggested that the initial assumption was sufficiently feasible (entry 1). Next, the other experiments showed that the oxidation was excluded in the absence of any component of the catalyst system (entries 2–4). Notably, the same outcome was achieved in aqueous acetonitrile ($\text{CH}_3\text{CN}/\text{H}_2\text{O}$, v/v, 1/2, entry 5). It was safer and more feasible to conduct a reaction with oxygen in aqueous solvent instead of neat organic solvent. To survey the viability of the new catalyst system, we further carried out the reaction with less $\text{Cu}(\text{OAc})_2/\text{TEMPO}$. It was observed that the reaction still gave 92% yield even using 1 mol % $\text{Cu}(\text{OAc})_2/1$ mol % TEMPO (entries 6 and 7). But, the outcome sharply reduced to 76% or 79% when using the combination of 1 mol % $\text{Cu}(\text{OAc})_2/0.5$ mol % TEMPO or 0.5 mol % $\text{Cu}(\text{OAc})_2/1$ mol % TEMPO (entries 8 and 9). It was noteworthy that there was no any benzoic acid detected. Thus, a practical protocol was acquired for the formation of benzaldehyde in an excellent yield of 92% (entry 7).

With the optimized $\text{Cu}(\text{OAc})_2/\text{TEMPO}$ catalyst system in hand, the initial substrate generality studies focused on the most common primary and secondary benzylic alcohols (Table 2, entries 1–18).¹⁷ We were pleased to observe that this simple protocol easily converted 5 mmol of differently substituted primary and secondary benzylic alcohols into the corresponding benzaldehydes and phenones bearing various functionalities. The results showed that the electronic nature of functional groups on the aromatic ring did not apparently affect the oxidation efficiency in terms of the yields (entries 1–18). The benzylic alcohols bearing electron-donating substituent(s) such as 4-methyl, 4-methoxy, 4-phenoxy, 3,4-dimethoxy, 3,4-dimethoxy, and 3,4,5-trimethoxy group(s) were readily transformed into the corresponding aldehydes in excellent yields of 90–96% (entries 1–6). On the other hand, the electron-withdrawing group(s) substituted benzylic alcohols gave marginally decreased yields of 82–90% (entries 7–13). With respect to 1,4-phenylenedimethanol, terephthalaldehyde was obtained in good yield of 83% (entry 14). Similar to primary benzylic alcohols, secondary benzylic alcohols delivered the desired phenones in excellent yields of 91–93% (entries 15–18).

In addition, this concise $\text{Cu}(\text{OAc})_2/\text{TEMPO}$ system was compatible with the oxidation of congeneric primary and secondary 1-heteroaryl alcohols into their respective aldehydes and ketones. The experiments indicated that the aerobic oxidation of these pseudo-benzylic alcohols smoothly achieved the desired heteroaryl aldehydes and ketones in good yields of 82–89% (entries 19–24).

In order to further expand the practical utility of this protocol, we investigated the oxidation of the challenging benzylic alcohols

Table 1
Optimization for $\text{Cu}(\text{OAc})_2/\text{TEMPO}$ -catalyzed aerobic oxidation of benzyl alcohol^a

Entry	$\text{Cu}(\text{OAc})_2$	TEMPO	Solvent	Yield ^b (%)
1	5 mol %	5 mol %	CH_3CN	92
2	None	None	CH_3CN	0
3	None	5 mol %	CH_3CN	Trace
4	5 mol %	None	CH_3CN	0
5 ^c	5 mol %	5 mol %	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	92
6 ^c	3 mol %	3 mol %	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	92
7 ^c	1 mol %	1 mol %	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	92
8 ^c	1 mol %	0.5 mol %	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	76
9 ^c	0.5 mol %	1 mol %	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	79

^a The reaction performed with benzyl alcohol (0.54 g, 5.0 mmol), $\text{Cu}(\text{OAc})_2$ (n_1 mol %), and TEMPO (n_2 mol %) in specified solvent (15 mL) at room temperature for 3 h.

^b Isolated yield via column chromatography.

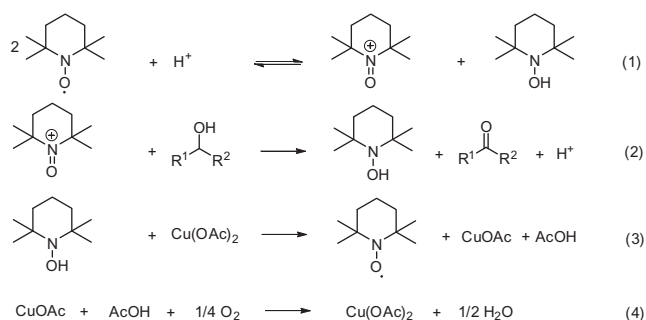
^c Solvents: $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (5 mL/10 mL).

containing the phenolic hydroxyl group. As mentioned, Stahl's catalyst system failed to oxidize the phenolic alcohols.¹¹ In contrast, our protocol was capable of selectively oxidizing the phenolic alcohols into the corresponding phenolic aldehydes with high yields of 85–91% (entries 25–31), without overoxidation to carboxylic acids¹⁸ or quinones¹⁹ being observed. This selectivity is of great interest for the elaboration of the difunctional molecules (containing both alcoholic and phenolic hydroxyl groups) in organic synthesis, verifying the potential of $\text{Cu}(\text{OAc})_2/\text{TEMPO}$ catalyst system again. Moreover, the protocol was well tolerated to oxidize cinnamyl alcohol and 2-methoxycinnamyl alcohol in excellent yields of 93% and 94%, respectively (entries 32 and 33), as well as 3-chlorocinnamyl alcohol with a slightly low yield of 89% (entry 34) into the corresponding cinnamyl aldehydes. Furthermore, primary and secondary aliphatic alcohols also underwent this facile oxidation to access the corresponding aldehydes and ketones in good yields of 81–88% (entries 35–38), unambiguously demonstrating the synthetic value of the protocol. The mildness of the reaction conditions was evident with no aliphatic acids being detected (entries 35 and 36).

The results shown in Table 2 highlights the advantages of the catalyst system: (i) broad substrate scope including primary and secondary benzylic alcohols, primary and secondary 1-heteroaryl alcohols, cinnamyl alcohols, and aliphatic alcohols; (ii) clean reaction giving high yields; (iii) impressive functional group tolerance covering Me, OMe, PhO, NO_2 , CF_3 , Br, Cl, F, phenolic OH, C=C bond, heteroaryl ring, etc.; (iv) simple catalyst system and mild reaction conditions avoiding overoxidation; (v) safe aqueous acetonitrile as solvent to moderate flammability of neat organic solvent.²⁰

To understand the role of each catalytic component and probe the oxidation mechanism, we initially surveyed the catalytic activities of different copper salts (Table 3, entries 1–5). Relative to the excellent performance of $\text{Cu}(\text{OAc})_2$, other counterparts CuCl , CuCl_2 , CuOTf , and $\text{Cu}(\text{OTf})_2$ all gave low yields for the model oxidation in the analogous conditions. It was interesting that acidic additive had no influence on this oxidation (entry 6), but stoichiometric basic additive Na_2CO_3 almost completely prohibited the reaction (entry 7). Moreover, no reaction occurred with sole $\text{Cu}(\text{OAc})_2$ using 200 mol % loading, implying that $\text{Cu}(\text{OAc})_2$ did not serve as a direct oxidant (entry 8). In contrast, 200 mol % loading of TEMPO could efficiently achieve the desired benzaldehyde in an excellent yield of 92% (entry 9), indicating the essential importance of TEMPO in the current oxidation reaction. Under argon atmosphere, the control experiments demonstrably revealed that $\text{Cu}(\text{OAc})_2$ regenerated active TEMPO (entry 10), meantime, $\text{Cu}(\text{OAc})_2$, comparing to other copper salts, could be more efficiently renovated via the air-sensitive CuOAc (entry 11).¹⁵

Based on the above experiments and the reported TEMPO catalytic systems,^{14a,c,e,g} a catalytic sequence for the oxidation was proposed in Scheme 1. Initially, TEMPO is disproportionated into TEMPOH and the oxo-ammonium ion in our reaction conditions



Scheme 1. A proposed mechanism.

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