Biomimetic Catalysis

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# A TEMPO-Free Copper-Catalyzed Aerobic Oxidation of Alcohols**

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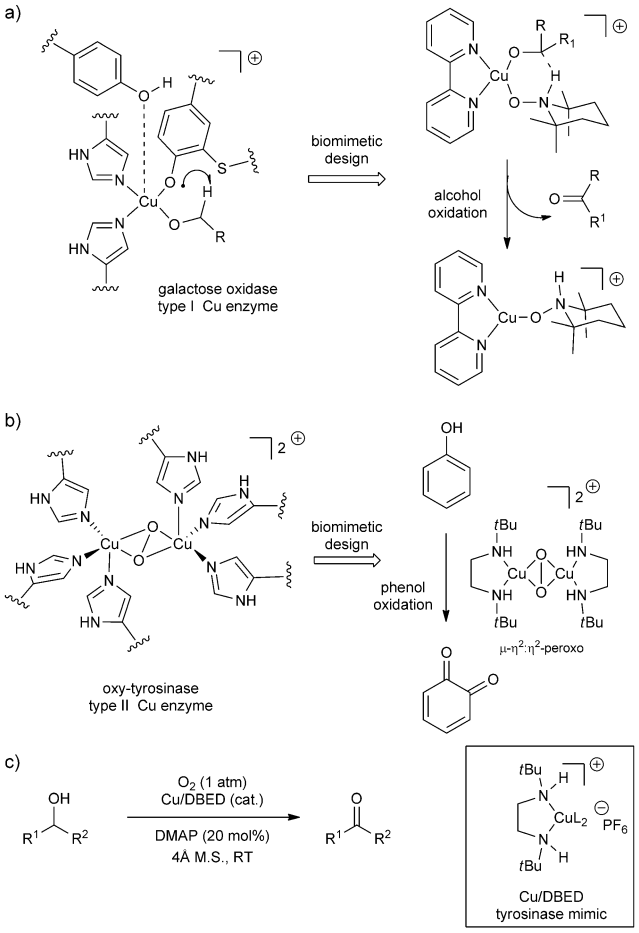
***Abstract:*** *The copper-catalyzed aerobic oxidation of primary and secondary alcohols without an external N-oxide co-oxidant is described. The catalyst system is composed of a Cu/diamine complex inspired by the enzyme tyrosinase, along with dimethylaminopyridine (DMAP) or N-methylimidazole (NMI). The Cu catalyst system works without 2,2,6,6-tetramethyl-l-piperidinoxyl (TEMPO) at ambient pressure and temperature, and displays activity for un-activated secondary alcohols, which remain a challenging substrate for catalytic aerobic systems. Our work underscores the importance of finding alternative mechanistic pathways for alcohol oxidation, which complement Cu/TEMPO systems, and demonstrate, in this case, a preference for the oxidation of activated secondary over primary alcohols.*

The development of synthetic catalysts that mimic metalloenzymes provides an important means of improving synthetic efficiency.[1] This has been particularly true in the development of catalytic aerobic oxidations, which have relied heavily on biomimetic approaches to activate $O_2$.[2] Significant interest has been placed on the development simplified mimics of galactose oxidase for the ubiquitous oxidation of alcohols to aldehydes (Scheme 1 a), leading to catalytic aerobic replacements of stoichiometric oxidations.[3,4] Consistent with the enzymatic mechanism, these systems employ a radical *N*-oxide co-catalyst, which is a surrogate for the tyrosyl radical in the active site of the enzyme.[5] Mechanistic studies on Cu/TEMPO-based catalysts have identified steric interactions between the *N*-oxide and the substrate as key factors that affect catalytic reactivity, chemo- and regioselectivity.[6] In order to tolerate increasingly encumbered substrates, catalytic systems have been developed with sterically less demanding *N*-oxide radicals.[7] While the resulting systems provide improved efficiency, their reliance upon *N*-oxides imposes certain limitations, as it is frequently the most expensive component of the catalyst system, which becomes a significant concern for industrial-scale applications.[8] Moreover, TEMPO and related *N*-oxide-based oxidations are selective for primary over secondary alcohols, which is only reinforced by more active, and sterically less encumbered *N*-oxides. This represents an important limitation of current catalytic aerobic methods, as the chemoselective oxidation of secondary alcohols is a fundamentally important tool for chemical synthesis.[9] One alternative to *N*-oxide-based oxidations are Cu catalysts capable of directly oxidizing alcohols without radical transfer agents.[10–12] While such systems have been described, they are not widely employed in synthesis, as they are generally limited to activated alcohols, and require elevated temperatures and high pressures of $O_2$.[4]

The type II Cu enzyme tyrosinase is an alternative Cu-based enzyme that has been extensively investigated for its ability to activate $O_2$ as a characteristic $\mu$-$\eta^2$,$\eta^2$ peroxo dicopper reactive oxygen species (Scheme 1 b).[13,14] While tyrosinase has evolved to oxygenate phenols to *ortho*-quinones,[15] simplified mimics of its peroxo core have




***Scheme 1.*** Biomimetic approaches to copper-catalyzed oxidation of alcohols. a) Alcohol oxidation inspired by galactose oxidase. b) Activation of $O_2$ by tyrosinase. c) TEMPO-free alcohol oxidation with complementary selectivity.

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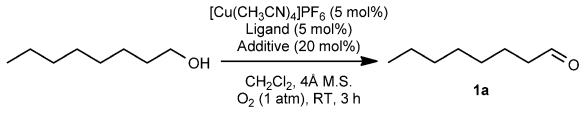
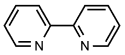
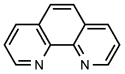
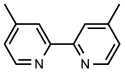
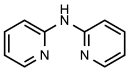
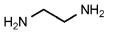
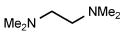
demonstrated reactivity for the oxidation of benzyl alcohol without an *N*-oxide, albeit under stoichiometric conditions.[16] Recent success in mimicking the catalytic reactivity of tyrosinase with *N*,*N*′-di-*tert*-butyl-ethylenediamine (DBED) and $[Cu(CH_3CN)_4]PF_6$,[17] prompted us to consider the aerobic oxidation of alcohols without an *N*-oxide co-catalyst, with the potential to achieve complementary selectivity over existing methods by employing a dramatically different mechanism for $O_2$ activation and substrate oxidation. Here we report the successful investigation of this approach, which led to a practical Cu catalyst for the aerobic oxidation of a diverse range of activated and unactivated alcohols. This system also shows complementary selectivity to TEMPO-based oxidations, with preferential oxidation of activated secondary over primary alcohols.

As a starting point, we examined the aerobic oxidation of 1-octanol under previously optimized conditions for the oxygenation of phenols,[17a] but no significant reaction was observed in the presence of 4 mol% $[Cu(CH_3CN)_4]PF_6$ and 5 mol% DBED (Table 1, entry 1). The addition of nitrogen bases had different effects. While strong Brønsted bases, such as DBU, DABCO, or N*i*Pr$_2$Et, were ineffective, (Table 1, entries 2–4), aromatic amines, such as pyridine, NMI, or DMAP, had beneficial effects (entries 5–7). Of these, DMAP-based systems showed the highest reactivity, providing 1-octanal in 92% yield after 3 h.[18,19] While optimized conditions employ one atmosphere of $O_2$, the reaction can also be conducted in air, albeit with longer reaction times (Table 1, entry 8). DBED is a unique diamine ligand, as evidenced by the lack of reactivity with 2,2′-bipyridine or 1,10-phenanthroline, which are commonly employed in Cu/TEMPO-catalyzed aerobic oxidations (Table 1, entries 8–14). Furthermore, no aldehyde was observed when DMAP was used in the absence of DBED (Table 1, entry 16). These results demonstrate the high reactivity of the $Cu_2/O_2$ adducts that were formed with this ligand,[10a,13a] and underscores the unique ability of the Cu/DBED catalyst system to affect the rapid oxidation of unactivated alcohols without the use of any external radical co-oxidant.

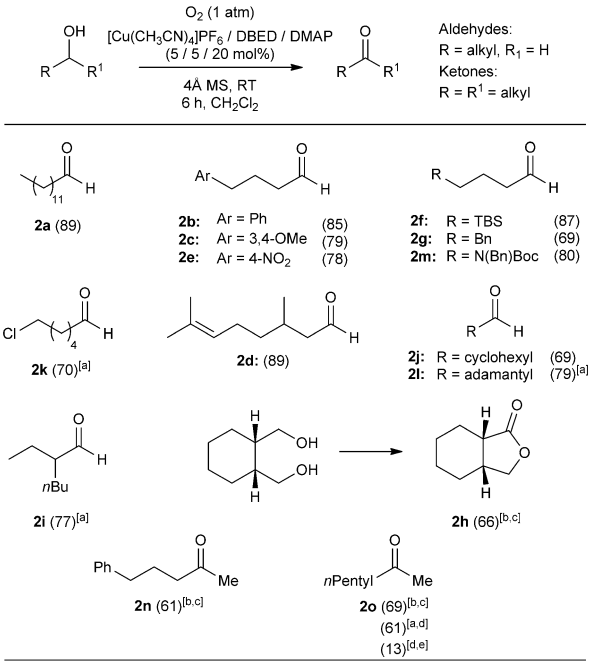
Our optimized conditions proved to be efficient for the oxidation of linear non-activated alcohols bearing common functional groups to the corresponding aldehydes or ketones (Scheme 2). The functional groups that were tolerated by the reaction include alkenes (**2d**), alkyl halides (**2k**), nitro groups (**2e**), aryl and alkyl ethers (**2c**,**g**), protected alcohols (**2f**), and protected amines (**2m**). We observed a decreased reactivity for sterically encumbered substrates with β-alkyl branches, but some activity could be regained by increasing the reaction

***Table 1:*** Optimization of reaction conditions for the oxidation of 1-octanol.



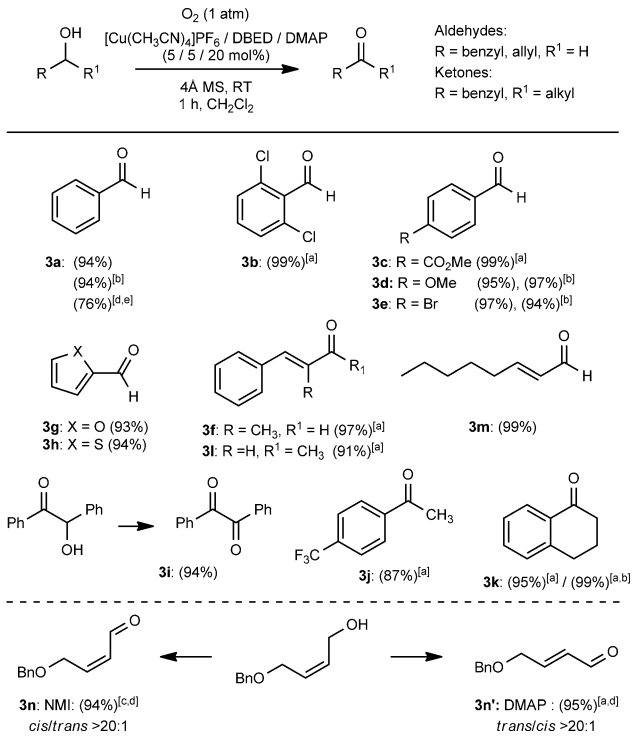

| Entry | Ligand | Additive | Yield [%] |
|---|---|---|---|
| 1[a] | DBED | – | 2 |
| 2 | DBED | DBU | – |
| 3 | DBED | DABCO | – |
| 4 | DBED | N*i*Pr$_2$Et | 8 |
| 5 | DBED | pyridine | 17 |
| 6 | DBED | NMI | 62 |
| 7 | DBED | DMAP | 92 |
| 8[b] | DBED | DMAP | 84 |
| 9 |  | DMAP | 4 |
| 10 |  | DMAP | 6 |
| 11 |  | DMAP | 6 |
| 12 |  | DMAP | – |
| 13 |  | DMAP | – |
| 14 |  | DMAP | – |
| 15 |  | DMAP | 18 |
| 16 | – | DMAP | – |

Reaction conditions: alcohol (0.5 mmol), $[Cu(CH_3CN)_4]PF_6$ (0.025 mmol), ligand (0.025 mmol), additive (0.1 mmol), 4 Å molecular sieves (100 mg), $CH_2Cl_2$ (4 mL), $O_2$ (1 atm), 3 h. Yield determined by $^1$H NMR spectroscopy with benzyl benzoate as internal standard. [a] No molecular sieves added, $[Cu(CH_3CN)_4]PF_6$ (0.02 mmol). [b] Conducted under air for 20 h.




***Scheme 2.*** Oxidation of primary and secondary unactivated alcohols. For standard reaction conditions, see Table 1, entry 7, 6 h. [a] 20 h. [b] $[Cu(CH_3CN)_4]PF_6$ (0.05 mmol), DBED (0.05 mmol), 0.20 mmol DMAP. [c] 40 h. [d] Yield determined by NMR analysis with benzyl benzoate as internal standard. [e] Catalyst reported in Ref. [5e]: $[Cu(CH_3CN)_4]OTf$ (0.025 mmol), 2,2′bipyridine (0.025 mmol), NMI (0.05 mmol), TEMPO (0.025 mmol), $CH_3CN$ (4 mL), 20 h, $O_2$ (1 atm).

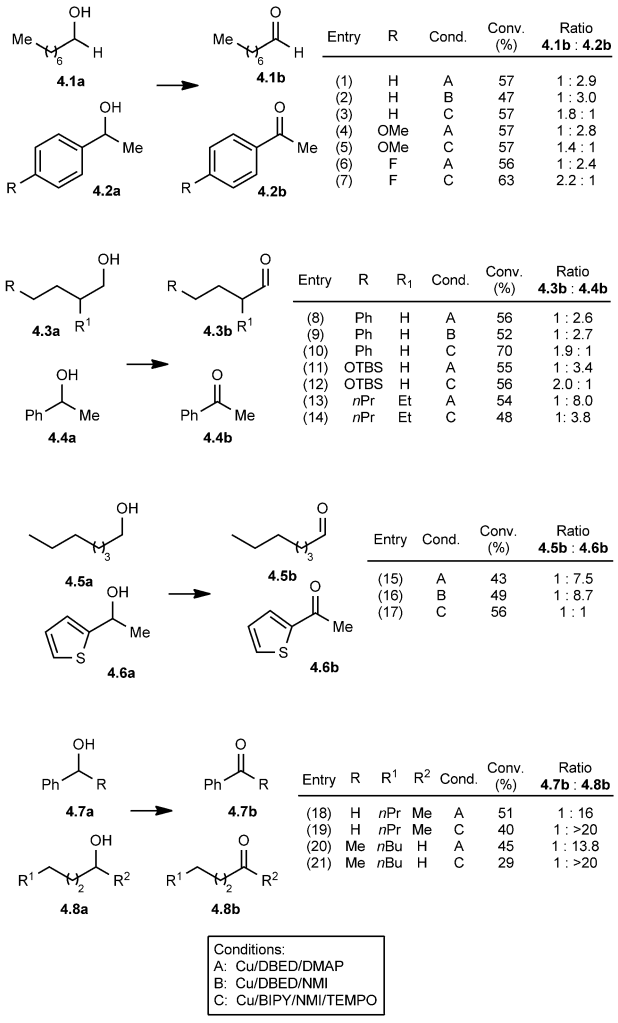



***Scheme 3.*** Oxidation of activated alcohols. For standard reaction conditions, see Table 1, entry 7, 1 h. [a] 3 h. [b] NMI (0.10 mmol). [c] $[Cu(CH_3CN)_4]PF_6$ (0.05 mmol), NMI (0.05 mmol), 2 h. [d] Product ratio and yields determined by $^1$H NMR analysis with benzyl benzoate as internal standard standard. [e] No molecular sieves used, 16 h.

time and/or the catalyst loading (**2i** and **2l**). The oxidation of a 1,4 diol cleanly afforded the five-membered lactone **2h**, thus demonstrating the compatibility of the reaction conditions with the presumed lactol intermediate. Most importantly, secondary aliphatic alcohols could be oxidized to the analogous ketones in good yields under surprisingly mild conditions (**2n**,**o**). In this context, the Cu/DBED catalyst system displays a unique reactivity for the synthesis of aliphatic ketones from non-activated, secondary alcohols, reactions that otherwise require modified *N*-oxide co-catalysts when Cu is used.[7b,20] By comparison, the analogous TEMPO-based oxidation of 2-heptanol (**2o**) proceeded in low yield under previously reported conditions (13% yield).[5b]

While non-activated aliphatic alcohols require the use of DMAP, certain activated alcohols are converted to the desired aldehydes and ketones equally well with NMI (Scheme 3). For example, the prototypical oxidation of benzyl alcohol to benzaldehyde is comparably efficient with both amine additives, and displays reasonable reactivity, even in the absence of molecular sieves (**3a**).[21] This trend is consistent for benzylic alcohols with electron-donating and electron-withdrawing substituents on the aromatic ring (**3b**–**3e**). Reactivity is maintained for activated alcohols of furan and thiophene heterocycles, as well as secondary benzylic (**3j**–**3k**) and allylic alcohols (**3m**). The use of NMI is beneficial for base-sensitive substrates, as we demonstrated by the selective oxidation of a *cis*-allylic alcohol to the corresponding *cis*-α,β-unsaturated aldehyde **3n** without significant isomerization of the alkene double bond, which is otherwise observed with the use of DMAP to afford **3n′** selectively.[22]

The Cu/DBED-catalyzed oxidations offer important complementary selectivity to TEMPO-based systems, and favor the oxidation of activated secondary over primary alcohols (Scheme 4). Competition experiments between 1-octanol (**4.1**) and 1-phenylethanol (**4.2**) under our standard oxidation conditions led to a 2.9:1 ratio in favor of the oxidation of the secondary benzylic alcohol (entry 1). By comparison, the TEMPO-based oxidation shows the opposite selectivity (1.8:1 ratio) in favor of the primary alcohol (entry 3). This trend is observed for secondary benzylic alcohols possessing either electron-rich or electron-poor aromatic rings (entries 4–7) or linear primary alcohols (entries 8–11), and is maximized when the aromatic ring is




| Entry | R | Cond. | Conv. (%) | Ratio **4.1b** : **4.2b** |
|---|---|---|---|---|
| (1) | H | A | 57 | 1 : 2.9 |
| (2) | H | B | 47 | 1 : 3.0 |
| (3) | H | C | 57 | 1.8 : 1 |
| (4) | OMe | A | 57 | 1 : 2.8 |
| (5) | OMe | C | 57 | 1.4 : 1 |
| (6) | F | A | 56 | 1 : 2.4 |
| (7) | F | C | 63 | 2.2 : 1 |

| Entry | R | $R_1$ | Cond. | Conv. (%) | Ratio **4.3b** : **4.4b** |
|---|---|---|---|---|---|
| (8) | Ph | H | A | 56 | 1 : 2.6 |
| (9) | Ph | H | B | 52 | 1 : 2.7 |
| (10) | Ph | H | C | 70 | 1.9 : 1 |
| (11) | OTBS | H | A | 55 | 1 : 3.4 |
| (12) | OTBS | H | C | 56 | 2.0 : 1 |
| (13) | *n*Pr | Et | A | 54 | 1 : 8.0 |
| (14) | *n*Pr | Et | C | 48 | 1: 3.8 |

| Entry | Cond. | Conv. (%) | Ratio **4.5b** : **4.6b** |
|---|---|---|---|
| (15) | A | 43 | 1 : 7.5 |
| (16) | B | 49 | 1 : 8.7 |
| (17) | C | 56 | 1 : 1 |

| Entry | R | $R^1$ | $R^2$ | Cond. | Conv. (%) | Ratio **4.7b** : **4.8b** |
|---|---|---|---|---|---|---|
| (18) | H | *n*Pr | Me | A | 51 | 1 : 16 |
| (19) | H | *n*Pr | Me | C | 40 | 1 : >20 |
| (20) | Me | *n*Bu | H | A | 45 | 1 : 13.8 |
| (21) | Me | *n*Bu | H | C | 29 | 1 : >20 |

***Scheme 4.*** Selectivity competition experiments. Reaction conditions: 0.25 mmol of each alcohol. Catalyst A: $[Cu(CH_3CN)_4]PF_6$ (0.025 mmol), DBED (0.025 mmol), DMAP (0.10 mmol), 4 Å molecular sieves (25 mg), $CH_2Cl_2$ (4 mL), $O_2$ (1 atm), 30 min. Catalyst B: NMI replacing DMAP, 3 h. Catalyst C: $[Cu(CH_3CN)_4]PF_6$ (0.025 mmol) 2,2-bipyridine (0.025 mmol), NMI (0.05 mmol), TEMPO (0.025 mmol), $CH_3CN$ (4 mL), 1 h, air. Conversions and ratios determined by $^1$H NMR analysis with benzyl benzoate as internal standard.

a thiophene (entries 15–17).[23] As the steric environment of the primary alcohol becomes more crowded, the TEMPO-based oxidation begins to favor the oxidation of the secondary benzylic alcohol, but selectivity is significantly higher for the DBED-based oxidation (entries 13 and 14). When substrates bearing substituents of similar steric demands are used (i.e. primary benzylic vs. primary aliphatic or secondary benzylic vs. secondary aliphatic, entries 18–21), similar selectivities were observed for both systems. These data suggest that the Cu/DBED catalyst system is less sensitive to steric influences in the substrate than TEMPO-based systems, which provides an important complement for synthesis when the chemoselective oxidation of an activated alcohol is desired.

In summary, we have developed a Cu-catalyzed, aerobic oxidation of alcohols that displays complementary selectivity to existing Cu/TEMPO-based systems and high catalytic activity with both activated and unactivated, sterically encumbered substrates. Our conditions do not employ an *N*-oxide co-catalyst and thus result in a new mechanistic pathway. This work constitutes an important extension of biomimetic studies relating to tyrosinase, and sets the stage for a variety of synthetic applications beyond the native substrates of the enzyme.

**Keywords:** aerobic oxidation · alcohols · biomimetic catalysis · copper · tyrosinase

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*Angew. Chem.* **2015**, *127*, 4282–4285

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[18] We noted only a slight decrease in yield (80%), when the reaction was performed without the use of a nitrogen glovebox or dried solvents, see the Supporting Information for details.
[19] We observed only minimal catalytic turnover when we used $Cu(OTf)_2$ as the catalyst (14% yield). In addition no oxidation product was produced when $Cu(OTf)_2$ was used stoichiometrically under anaerobic ($N_2$) conditions.
[20] For the use of non-Cu-based systems in the oxidation of secondary aliphatic alcohols, see Ref. [3c].
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[23] We noted that NMI provided similar selectivity to that achieved with DMAP (entries 1 vs. 2 and 8 vs. 9).

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