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Copper/TEMPO-Catalyzed Aerobic Alcohol Oxidation: Mechanistic Assessment of Different Catalyst Systems

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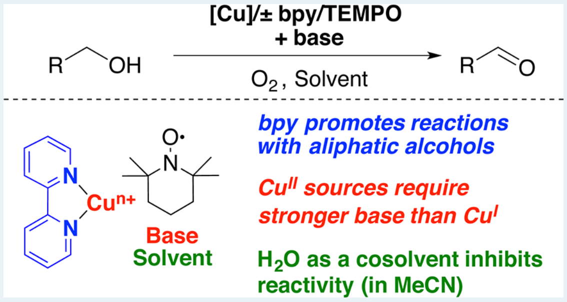
Supporting Information

ABSTRACT: Combinations of homogeneous Cu salts and 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) have emerged as practical and efficient catalysts for the aerobic oxidation of alcohols. Several closely related catalyst systems have been reported, which differ in the identity of the solvent, the presence of 2,2′-bipyridine as a ligand, the identity of basic additives, and the oxidation state of the Cu source. These changes have a significant influence on the reaction rates, yields, and substrate scope. In this report, we probe the mechanistic basis for differences among four different Cu/TEMPO catalyst systems and elucidate the features that contribute to efficient oxidation of aliphatic alcohols.



KEYWORDS: *alcohol oxidation, aerobic, kinetics, copper, TEMPO, mechanism*

INTRODUCTION

Oxidations of alcohols to aldehydes or ketones are widely used transformations in synthetic organic chemistry,[1] and extensive recent efforts have focused on the development of aerobic oxidation methods.[2] Homogeneous catalysts containing a copper salt in combination with TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) are among the most versatile catalysts for the aerobic oxidation of primary alcohols to aldehydes, and numerous variants have been reported.[3−7] The first of these was reported by Semmelhack in 1984 and consists of $Cu^{I}Cl$/TEMPO in DMF (*N*,*N*-dimethylformamide).[3] In 2003, Sheldon reported a $Cu^{II}Br_2$/TEMPO catalyst that employed bpy (2,2′-bipyridine) as an ancillary ligand and $KO^{t}Bu$ as a base in an acetonitrile/water (2:1) solvent mixture.[4] More recently, Koskinen reported a $Cu^{II}(OTf)_2$/TEMPO catalyst (OTf, trifluoromethanesulfonate) that differs from the Sheldon catalyst by the replacement of $KO^{t}Bu$ with NMI (*N*-methylimidazole) and/or DBU (1,8-diazabicycloundec-7-ene) and the use of nonaqueous MeCN as the solvent.[5] Finally, our group has described a $Cu^{I}OTf$/bpy/NMI catalyst in which the use of a Cu^{I} source improved the performance of the catalyst and substrate scope.[6] Each of these catalyst systems, designated **A**−**D** (Table 1), promotes aerobic oxidation of activated alcohols, such as benzyl alcohol. The latter two exhibit broad utility in the oxidation of aliphatic primary alcohols, including those with diverse functional groups.

We recently investigated the mechanism of aerobic alcohol oxidation catalyzed by $Cu^{I}OTf$/bpy/NMI/TEMPO (catalyst **D**).[8] Gas uptake and *in situ* infrared spectroscopic studies of the reaction kinetics, together with electron paramagnetic resonance and UV−visible spectroscopic analysis of the reaction mixture, provided evidence for the catalytic mechanism illustrated in Scheme 1. The reduced catalyst, consisting of L_nCu^{I} and TEMPOH, is oxidized by O_2 in steps i and ii to afford L_nCu^{II}-OH and TEMPO. Oxidation of the alcohol is initiated by formation of a Cu^{II}-alkoxide (step iii), followed by TEMPO-mediated H-atom abstraction to produce the aldehyde and regenerate Cu^{I} (step iv). To gain a more thorough understanding of the contributions of the solvent, ligand, base, and Cu oxidation state to catalytic activity, we undertook a comparative mechanistic study of the four catalyst systems in Table 1. The results of this investigation are described below.

RESULTS

Effect of Solvent and Ligand on Redox Potential and Reactivity. Our initial mechanistic studies focused on probing mechanistic differences between CuCl/TEMPO/DMF (catalyst **A**) and the three other catalyst systems, which employ bpy as an ancillary ligand and acetonitrile as the solvent. Catalyst **A** promotes efficient oxidation of primary benzylic and allylic alcohols; however, reactions of aliphatic alcohols result in low yields of the corresponding aldehydes (∼10%) unless stoichiometric quantities of Cu and TEMPO are employed.

Electrochemical data demonstrate the influence of the bpy ligand and solvent on the Cu redox properties (Figure 1). Cyclic voltammograms of TEMPO and CuCl in the presence or absence of bpy were acquired under N_2 with 0.1 M $LiClO_4$ as the electrolyte in both MeCN (solid red line) and DMF (dashed blue line). In the absence of bpy, switching from MeCN to DMF results in a significant decrease in the Cu^{II}/Cu^{I} reduction potential ($\Delta E_{mp} \sim 0.28$ V) (Figure 1A). Inclusion of the bpy ligand further lowers the Cu^{II}/Cu^{I} potential and results

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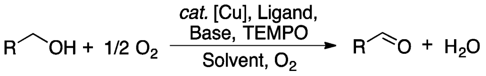
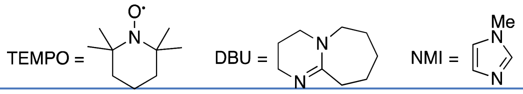
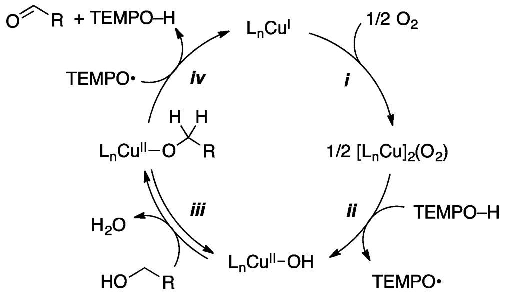
Table 1. Representative Cu/TEMPO-Based Catalyst Systems for the Aerobic Oxidation of Primary Alcohols



catalyst system	[Cu]	ligand	base	solvent
A (Semmelhack)[3]	$Cu^{I}Cl$	–	–	DMF
B (Sheldon)[4]	$Cu^{II}Br_2$	bpy	KO^tBu	2:1 $MeCN/H_2O$
C (Koskinen)[5]	$Cu^{II}(OTf)_2$	bpy	DBU (+NMI)	MeCN
D (Stahl)[6]	$Cu^{I}OTf$	bpy	NMI	MeCN



Scheme 1. Simplified Catalytic Cycle for $Cu^{I}OTf$/bpy/NMI/TEMPO-Catalyzed Aerobic Alcohol Oxidation



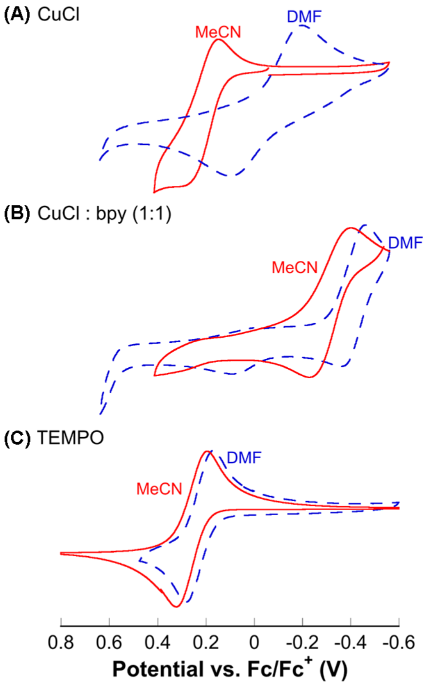


Figure 1. Cyclic voltammograms of CuCl (with or without bpy) and TEMPO in DMF (dashed blue line) and MeCN (solid red line). See the Supporting Information for details.

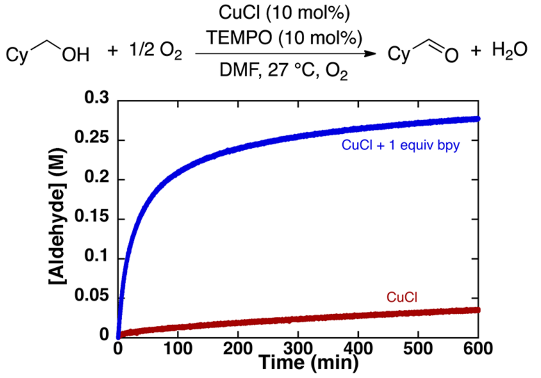
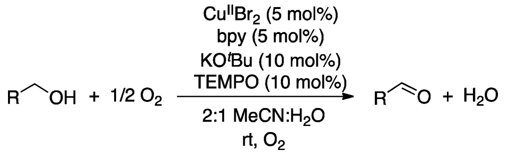


Figure 2. Oxidation of $CyCH_2OH$ by CuCl with (blue) and without (red) bpy in DMF. Standard conditions: 0.4 M $CyCH_2OH$, 0.04 M TEMPO, 0.04 M CuCl, 0.04 M bpy, 600 Torr of O_2, and 27 °C.

in a smaller solvent effect ($\Delta E_{mp} \sim 0.10$ V) (Figure 1B). The solvent has a minimal effect on the potential of the TEMPO/$TEMPO^+$ redox couple (Figure 1C).

Attempts to oxidize cyclohexylmethanol, $CyCH_2OH$, with catalyst **A** led to poor conversion (Figure 2, red trace), consistent with the low reactivity of aliphatic alcohols noted in the original report.[3] Addition of bpy to otherwise identical reaction conditions, however, resulted in rapid formation of the corresponding aldehyde CyCHO (Figure 2, blue trace).

Effect of Water on Catalyst Deactivation. Catalyst **B** is composed of $Cu^{II}Br_2$ with a bpy ligand and employs a 2:1 $MeCN/H_2O$ solvent mixture (eq 1). Water is used to enhance the solubility of the KO^tBu base. This system was one of the first to allow oxidation of aliphatic alcohols (such as 1-octanol);[9] however, elevated temperatures and an increased catalyst loading were required to achieve high yields with these substrates. In contrast, catalysts **C** and **D** mediate efficient oxidation of aliphatic alcohols at room temperature. The origin of these differences appears to be associated with the influence of water on the reactions.



(1)

Use of catalyst **B** in the oxidation of $CyCH_2OH$ at room temperature exhibits a slow initial reaction rate, proceeds to only a low level of conversion (7% yield after 12 h), and forms a green precipitate. Longer reaction times did not lead to higher levels of conversion.

To probe the potential influence of water on Cu/TEMPO-mediated alcohol oxidation, we investigated the oxidation of $PhCH_2OH$ by catalyst **D** with varying amounts of water. We observe minimal rate inhibition at ≤ 2 M H_2O (2 M = 10 equiv relative to $PhCH_2OH$); however, higher concentrations of water inhibit the reaction (Figure 3 and Figure S2 of the Supporting Information). Catalyst **B** with the 2:1 $MeCN/H_2O$

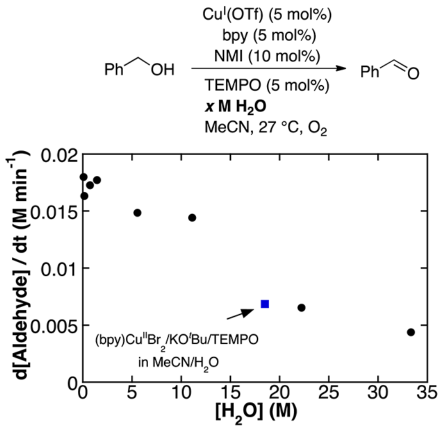


Figure 3. Rates of oxidation of $PhCH_2OH$ by Cu^IOTf/bpy/NMI/TEMPO with the addition of H_2O. Standard conditions: 0.2 M $PhCH_2OH$ (0.5 mmol), 10 mM Cu^IOTf, 10 mM bpy, 10 mM TEMPO, 20 mM NMI, 600 Torr of O_2, and 27 °C. Oxidation of $PhCH_2OH$ by $Cu^{II}Br_2$/bpy/KO^tBu/TEMPO in a MeCN/H_2O mixture (blue square) included for comparison.

solvent mixture (18.5 M H_2O) exhibits a rate consistent with the trend shown in Figure 3 (blue square in Figure 3). These data suggest that the water cosolvent, rather than the identity of the Cu source or base, is the origin of the decreased reaction rates with catalyst **B**.

Copper(II)−hydroxide species have been proposed as products of catalyst deactivation in Cu/TEMPO catalyst systems,[5] and their formation is supported by the appearance of precipitates during the reaction, as noted above. After prolonged reaction times, a blue precipitate forms in reaction mixtures with the Cu^IOTf/bpy/NMI/TEMPO catalyst system. Dark blue crystals were isolated from a reaction mixture that was left open to the air for 16 h and submitted for X-ray diffraction analysis. Structural analysis identified this species as the bis-μ-hydroxide dimer $[(bpy)Cu(OH)]_2(OTf)_2$ (Figure 4A; for details, see the Supporting Information).[10] This Cu^{II} dimer may be used as a catalyst in the presence of added TEMPO and NMI. The oxidation of $PhCH_2OH$ exhibits an induction period but then achieves a rate similar to that of parent catalyst **D** (Figure S3 of the Supporting Information), while the oxidation of $CyCH_2OH$ with this complex is somewhat slower than with catalyst **D** (Figure 4B).

These data indicate that the use of water as a cosolvent leads to both decreased reaction rates and catalyst deactivation. The formation of the dimeric copper(II)−hydroxide complex and potentially other Cu−hydroxide species as precipitates is promoted by the presence of high concentrations of water and makes the efficient oxidation of aliphatic alcohols difficult in the MeCN/H_2O solvent mixture.

Effect of the Base (DBU vs NMI) and Cu Oxidation State. Catalysts **C** and **D** employ $Cu^{II}(OTf)_2$ or Cu^IOTf in combination with an organic base (DBU and/or NMI) and do not employ water as a cosolvent.[11] In the work described below, DBU and NMI are investigated independently to understand the role of the copper oxidation state and base. The kinetic dependencies of the oxidation of $PhCH_2OH$ on the major reaction components (O_2, Cu/bpy, alcohol, and TEMPO) were measured with $Cu^{II}(OTf)_2$ and either NMI or DBU as the base (eq 2). The results are compared to the previously reported kinetic data with Cu^IOTf and NMI. The reactions were analyzed by monitoring the change in oxygen pressure within a sealed, temperature-controlled reaction vessel using a computer-interfaced gas uptake apparatus. These data are shown in Figure 5.

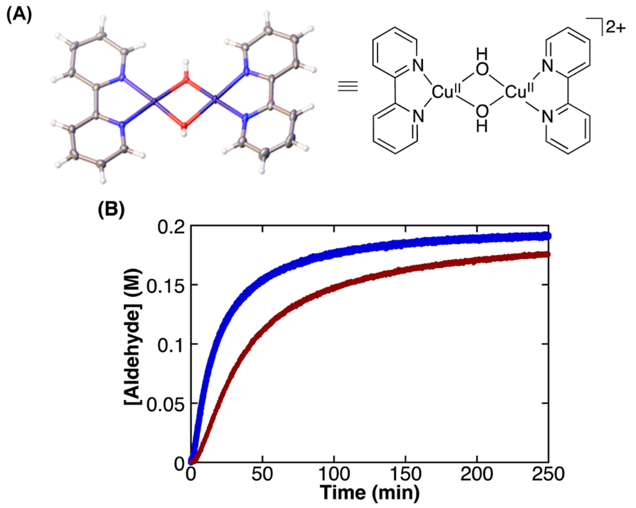
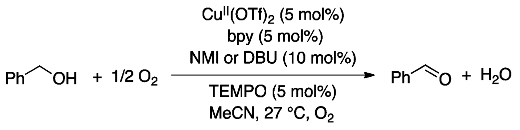


Figure 4. (A) X-ray structure of $[(bpy)Cu(OH)]_2(OTf)_2$, which crystallizes as a dimer of dimers (see the Supporting Information for details). The triflate counterions have been omitted for the sake of clarity. (B) Oxidation of $CyCH_2OH$ by Cu^IOTf (blue) and $[(bpy)Cu(OH)]_2(OTf)_2$ (red). Data were obtained by monitoring pressure changes during catalytic turnover. Reaction conditions: 10 mM (bpy)Cu, 10 mM TEMPO, 20 mM NMI, 0.2 M $CyCH_2OH$, 1 atm of O_2, 2.5 mL of MeCN, and 27 °C.



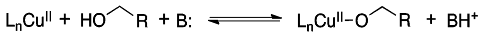
$$\text{Ph}\diagup\!\!\diagdown\text{OH} + 1/2\ O_2 \xrightarrow[\text{TEMPO (5 mol\%), MeCN, 27 °C, } O_2]{Cu^{II}(OTf)_2\text{ (5 mol\%), bpy (5 mol\%), NMI or DBU (10 mol\%)}} \text{Ph}\diagup\!\!\diagdown\text{O} + H_2O \qquad (2)$$

The influence of the base and copper oxidation state is evident from a comparison of kinetic data acquired for the three different catalytic conditions. As we reported previously, Cu^IOTf/bpy/NMI/TEMPO-catalyzed oxidation of $PhCH_2OH$ revealed a zero-order dependence on substrate and TEMPO, a first-order dependence on pO_2, and a mixed first- and second-order dependence on Cu^IOTf/bpy (Figure 5, column I).

The $Cu^{II}(OTf)_2$/DBU conditions show kinetic dependencies that are similar to those obtained with Cu^IOTf/NMI, with one notable exception (Figure 5, column II, and Figures S4−S11 of the Supporting Information). $Cu^{II}(OTf)_2$/DBU exhibits a saturation dependence on alcohol concentration, rather than the zero-order dependence observed with Cu^IOTf/NMI.

The $Cu^{II}(OTf)_2$/NMI conditions exhibit much slower rates and very different kinetic dependencies. In this case, the oxidation of $PhCH_2OH$ is independent of the oxygen pressure, exhibits a first-order dependence on $Cu^{II}(OTf)_2$/bpy and TEMPO concentrations, and a saturation dependence on alcohol concentration (Figure 5, column III).

We speculated that the change in reaction rate and kinetic dependencies associated with the use of NMI as the basic additive could be associated with the formation of the conjugate acid, $NMIH^+OTf^-$, under the reaction conditions. (For example, NMI could serve as a Brønsted base in the formation of a Cu^{II}−alkoxide species, as shown in eq 3.) To probe this



$$L_nCu^{II} + \text{HO}\diagup\!\!\diagdown\text{R} + \text{B:} \rightleftharpoons L_nCu^{II}\text{–O}\diagup\!\!\diagdown\text{R} + \text{BH}^+ \qquad (3)$$

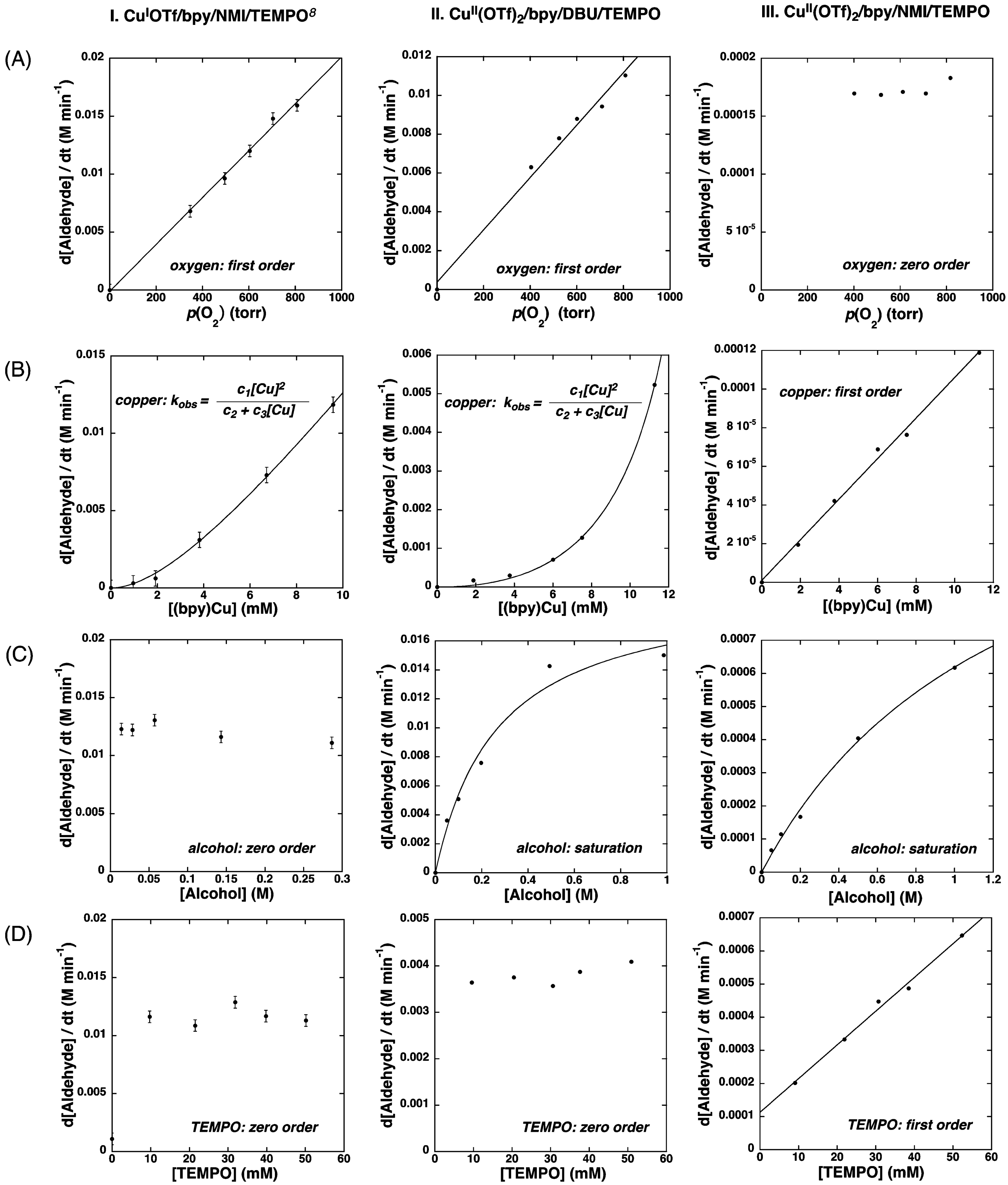


Figure 5. Dependence of (I) Cu^IOTf/bpy/TEMPO/NMI-catalyzed (data adapted from ref 8), (II) $Cu^{II}(OTf)_2$/bpy/TEMPO/DBU-catalyzed, and (III) $Cu^{II}(OTf)_2$/bpy/TEMPO/NMI-catalyzed alcohol oxidation on initial (A) dioxygen pressure, (B) Cu/bpy concentration, (C) $PhCH_2OH$ concentration, and (D) TEMPO concentration. The curves in row B are derived from a fit of the data to the following equation: rate = $c_1[Cu]^2/(c_2 + c_3[Cu])$. The curves in row C are derived from a nonlinear least-squares fit of the data to the following equation: rate = $c_1[\text{alcohol}]/(c_2 + c_3[\text{alcohol}])$. Standard reaction conditions: 0.2 M $PhCH_2OH$, 10 mM Cu, 10 mM bpy, 20 mM NMI or DBU, 10 mM TEMPO, 600 Torr of O_2, 2.5 mL of MeCN, and 27 °C.

hypothesis, $NMIH^+OTf^-$ was synthesized and added at varying concentrations to catalytic reaction mixtures employing Cu^IOTf/bpy/NMI/TEMPO as the catalyst. The inclusion of $NMIH^+OTf^-$ led to significant inhibition of the reaction rate (Figure 6A). Addition of 1 equiv of $NMIH^+OTf^-$ produces a rate that is almost identical to that obtained with $Cu^{II}(OTf)_2$/bpy/NMI/TEMPO (blue square in Figure 6A). In contrast, the addition of $DBUH^+OTf^-$ has no significant effect on the catalytic rate of oxidation of $PhCH_2OH$ by Cu^IOTf/bpy/NMI/TEMPO (Figure 6B).

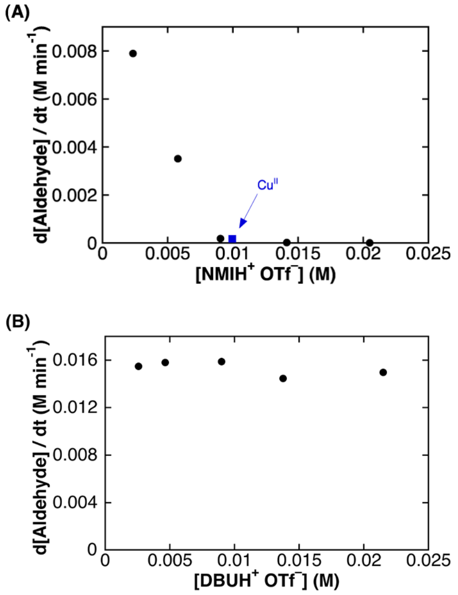


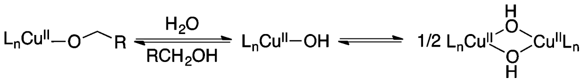
Figure 6. Dependence of Cu^IOTf/bpy/TEMPO/NMI-catalyzed benzyl alcohol oxidation on added (A) $NMIH^+OTf^-$ and (B) $DBUH^+OTf^-$. The reaction catalyzed by $Cu^{II}(OTf)_2$/bpy/TEMPO/NMI (blue square) is included in panel A for the sake of comparison. Rates were obtained by monitoring pressure changes during catalytic turnover. Standard reaction conditions: 10 mM Cu^IOTf, 10 mM bpy, 20 mM NMI, 10 mM TEMPO, and 0.2 M alcohol.

■ DISCUSSION

The data presented above provide valuable insights into the roles of the solvent (DMF, CH_3CN, or H_2O), the ancillary bpy ligand, the oxidation state of the Cu source, and identity of the basic additive (KO^tBu, NMI, or DBU). Addition of bpy to the CuCl/TEMPO catalyst system in DMF enables the catalytic oxidation of aliphatic alcohols (Figure 2). Bipyridine lowers the Cu^{II}/Cu^I reduction potential in DMF (cf. panels A and B of Figure 1), so the effect of bpy cannot be attributed to the formation of a more oxidizing catalyst capable of reacting with the more challenging aliphatic alcohol. We speculate that the bpy ligand could play at least two roles: (1) enhancing the rate of Cu^I oxidation by O_2 and (2) altering the Cu speciation to maximize the number of catalytically active Cu sites (e.g., by preventing aggregation).

The reactions tolerate substantial quantities of water before being inhibited (Figure 3). This observation is significant because water is a byproduct of the catalytic reaction, but stoichiometric amounts of water are well below the threshold of water inhibition (approximately 2 M). Use of water as a cosolvent, however, leads to significant inhibition of the rate. Excess water will disfavor formation of the Cu^{II}–alkoxide intermediate in favor of a Cu^{II}–hydroxide species (Scheme 2). Increased concentrations of monomeric or dimeric Cu^{II}–hydroxide species can lead to catalyst deactivation via formation of off-cycle intermediates or precipitation of Cu species from the reaction mixture. For example, the isolated $[bpyCu(OH)]_2^{2+}$ can enter the catalytic cycle, but it is sparingly soluble and reacts more slowly than the parent catalyst under normal reaction conditions.

Scheme 2. Formation of a Bis-μ-hydroxo Cu^{II} Dimer



The kinetic studies of benzyl alcohol oxidation provide valuable insights into the influence of the base and Cu oxidation state effects, summarized in Scheme 3. The kinetic data for the three different catalyst systems are summarized in Table 2. The only difference among the three catalyst systems is the oxidation state of the Cu source, Cu^IOTf or $Cu^{II}(OTf)_2$, and/or the organic base, NMI or DBU. Our previous mechanistic studies of catalyst **D** provide a framework for understanding these results. For example, the mixed second- and first-order dependence on Cu/bpy concentration and the first-order dependence on pO_2 with the first two catalyst systems are rationalized by a two-step aerobic Cu oxidation pathway that involves two metal centers (Scheme 4).

Scheme 3. Proposed Mechanism for the (bpy)Cu^{II}/TEMPO-Catalyzed Aerobic Oxidation of Alcohols

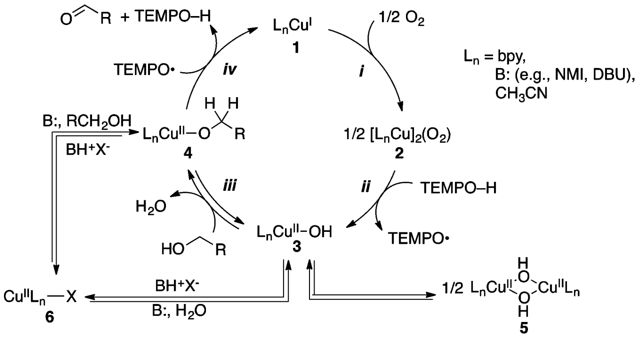
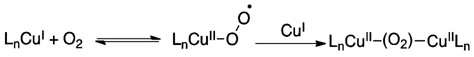


Table 2. Kinetic Dependencies for Cu/bpy Systems with $PhCH_2OH$

	Cu^I/NMI	Cu^{II}/DBU	Cu^{II}/NMI
pO_2	first-order	first-order	zero-order
[Cu]	mixed second- and first-order	mixed second- and first-order	first-order
[$PhCH_2OH$]	zero-order	saturation	saturation
[TEMPO]	zero-order	zero-order	first-order

When a Cu^{II} source is used, the identity of the base plays a key role in the rate of the reaction: DBU promotes fast rates,

Scheme 4. Catalyst Oxidation Sequence Accounting for a Mixed First- and Second-Order Cu Dependence



while NMI leads to slow rates. The saturation dependence on $PhCH_2OH$ concentration, observed with both Cu^{II} systems in Figure 5, suggests a substrate binding step contributes to the overall reaction rate. This step is attributed to the formation of a L_nCu^{II}−alkoxide intermediate from Cu^{II}/base and $PhCH_2OH$ (eq 3).[12] The strong base DBU allows the formation of the Cu^{II}−alkoxide species, while the weaker base, NMI, is less effective in this step.

The formation of a Cu^{II}−alkoxide complex generates 1 equiv of acid, which persists throughout the reaction. In the case of Cu^{II}/NMI, the resulting acid is $NMIH^+OTf^-$. This acid has a pK_a of 14.3 in MeCN,[13] which is sufficiently strong to favor protonolysis of a Cu^{II}−OH or Cu^{II}−OR group. The resulting Cu^{II} species (**6**) lies off the catalytic cycle and must access the active Cu^{II}−alkoxide intermediate via reaction with alcohol and the weak base, NMI. In the case of Cu^{II}/DBU, the acid is $DBUH^+OTf^-$, which is substantially less acidic (pK_a = 24 in MeCN[14]). These considerations account for the data shown in Figure 6, which show that $NMIH^+$ strongly inhibits the reaction while $DBUH^+$ lacks this inhibitory effect.

We propose that under the Cu^{II}/NMI conditions, an unfavorable equilibrium to form the Cu^{II}−alkoxide species (i.e., eq 3) leads to a change in the turnover-limiting step. Aerobic oxidation of the Cu^I catalyst (step i) is no longer turnover-limiting. Instead, substrate oxidation by Cu^{II}/TEMPO is rate-controlling (step iv). The first-order dependencies on Cu^{II}/bpy concentration and TEMPO concentration and the lack of a dependence on pO_2 support this interpretation.

The Cu^I/NMI catalyst system is the most active of the three catalysts evaluated in Figure 5. This result can be rationalized by formation of a Cu^{II}−OH species in steps i and ii of the catalytic mechanism. This species can react directly with the alcohol to afford the Cu^{II}−alkoxide intermediate, without requiring the involvement of the organic base. According to this proposal, the beneficial effect of NMI could arise from its role as a ligand for Cu (e.g., promoting aerobic oxidation of Cu^I), rather than its use as a Brønsted base. The similar efficacies of the Cu^I/NMI and Cu^{II}/DBU catalyst systems (i.e., **C** and **D**, respectively, in Table 1) highlight the importance of properly matching the Cu oxidation state and the identity of the basic additive. Perhaps most significantly, the use of Cu^I permits the reaction to proceed efficiently even in the absence of a strong exogenous base. This result has important synthetic implications. For example, strong bases could lead to epimerization of stereocenters adjacent to the aldehyde in the product or isomerization of (*Z*)-enals to the thermodynamically favored (*E*) product.[15] The mildly basic conditions associated with the Cu^IOTf/NMI catalyst system prevent these complications. Electrochemical data[8] show that NMI serves as a ligand for Cu^I and thus contributes to the aerobic oxidation step (step i of Scheme 3). In addition, NMI could hinder formation and/or facilitate dissociation of dimer **5**.

The reactivity of $[(bpy)Cu(OH)]_2(OTf)_2$ is consistent with the proposed mechanism. This Cu^{II}−hydroxide dimer is a more efficient catalyst precursor than other Cu^{II} sources because the Brønsted base (hydroxide) is present within the complex. This species enters the catalytic cycle after dissociation of the dimer into monomeric $(bpy)Cu^{II}(OH)(OTf)$. Only 1 equiv of water is formed upon entering the catalytic cycle, so the oxidation of aliphatic alcohols is efficient. The slower rates observed with this Cu^{II} dimer, relative to those with Cu^IOTf, probably reflect its slow dissociation into the active monomeric form and/or its poor solubility.

■ SUMMARY AND CONCLUSION

The number of Cu/TEMPO catalyst systems extends well beyond those considered in this investigation.[7,16] In most of these cases, the catalysts are limited in scope to the oxidation of activated alcohols (e.g., benzylic and allylic). The results of this investigation provide a framework for understanding key factors that contribute to the activity and/or limitations of these catalyst systems. Specifically, we have found that seemingly minor changes in the solvent, the oxidation state of the Cu source, and the identity of basic additives can have a significant effect on the kinetic profile and substrate scope of the catalyst. Use of a ligand, such as bpy, can lead to catalytic activity with substrates such as aliphatic alcohols that are otherwise unreactive. Water can significantly inhibit catalytic turnover when it is present at high concentrations. Kinetic studies of several different Cu/TEMPO catalyst systems reveal that rate acceleration observed with the use of a Cu^I source arises from *in situ* formation of a hydroxide base that promotes formation of the key L_nCu^{II}−alkoxide intermediate. When Cu^{II} sources are employed, a suitably strong base must be used to deprotonate the alcohol to form the Cu^{II}−alkoxide species. The insights gained here have important implications for other emerging classes of Cu/TEMPO-mediated aerobic oxidation reactions, such as amine dehydrogenation.[17]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, kinetic time course traces, and CIF data for $[(bpy)Cu(OH)]_2(OTf)_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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