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

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Abstract

Combinations of homogeneous Cu salts and 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 (TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl) are among the most versatile catalysts for 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 (DMF = *N,N*-dimethylformamide).[3] In 2003, Sheldon reported a Cu^{II}Br$_2$/TEMPO catalyst that employed bpy as an ancillary ligand (bpy = 2,2′-bipyridine) 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 and/or DBU (NMI = *N*-methylimidazole, DBU = 1,8-diazabicycloundec-7-ene) and the use of non-aqueous MeCN as the solvent.[5] Finally, our group recently described a Cu^{I}OTf/bpy/NMI catalyst in which the use of a Cu^I source improved the catalyst performance and substrate scope.[6] Each of these catalyst systems, designated **A**, **B**, **C**, and **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.

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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 IR spectroscopic studies of the reaction kinetics, together with EPR and UV-visible spectroscopic analysis of the reaction mixture, provided evidence for the catalytic mechanism illustrated in Scheme 1. The reduced catalyst, consisting of $L_n Cu^I$ and TEMPOH, is oxidized by O_2 in steps *i* and *ii* to afford $L_n Cu^{II}$–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*). In order to gain a more thorough understanding of the contributions of solvent, ligand, base, and Cu oxidation state to the catalytic activity, we undertook a comparative mechanistic study of the four catalyst systems in Table 1. The results of this investigation are described below.

$$R\frown OH + 1/2\ O_2 \xrightarrow[\text{Solvent, } O_2]{\substack{\textit{cat.} [\text{Cu}], \text{Ligand,} \\ \text{Base, TEMPO}}} R\diagdown O + H_2O$$
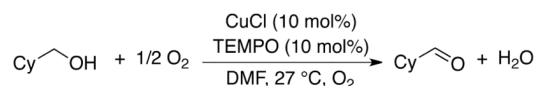
Results

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 other three 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.
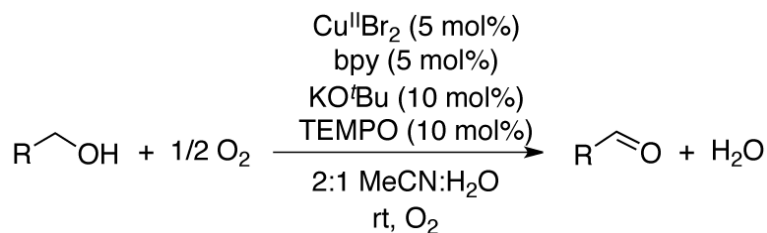
Electrochemical data demonstrate the influence of the bpy ligand and solvent on the Cu redox properties (Figure 1). Cyclic voltammograms of TEMPO and CuCl in the presence or absence of bpy were acquired under N_2 with 0.1 M $LiClO_4$ as the electrolyte in both MeCN (solid red line) and DMF (dashed blue line). In the absence of bpy, switching from MeCN to DMF results in a significant decrease of the Cu^{II}/Cu^I reduction potential (ΔE_{mp} ~0.28 V) (Figure 1a). Inclusion of the bpy ligand further lowers the Cu^{II}/Cu^I potential and results in a smaller solvent effect (ΔE_{mp} ~0.10 V) (Figure 1b). The solvent has 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).

$$Cy\frown OH + 1/2\ O_2 \xrightarrow[\text{DMF, 27 °C, } O_2]{\substack{\text{CuCl (10 mol\%)} \\ \text{TEMPO (10 mol\%)}}} Cy\diagdown O + H_2O$$

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^{t}Bu base. This system was one of the first to enable oxidation of aliphatic alcohols (such as 1-octanol);[9] however, elevated temperatures and 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.

$$R\diagup OH + 1/2\ O_2 \xrightarrow[\substack{\text{2:1 MeCN:H}_2\text{O} \\ \text{rt, O}_2}]{\substack{\text{Cu}^{II}\text{Br}_2\ (5\ \text{mol\%}) \\ \text{bpy}\ (5\ \text{mol\%}) \\ \text{KO}^t\text{Bu}\ (10\ \text{mol\%}) \\ \text{TEMPO}\ (10\ \text{mol\%})}} R\diagup O + H_2O$$

(1)

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

In order 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 $[H_2O]$ 2 M (2 M = 10 equiv relative to $PhCH_2OH$); however, higher concentrations of water inhibit the reaction (Figures 3 and S2). Catalyst **B** with the 2:1 $MeCN/H_2O$ solvent mixture ($[H_2O]$ = 18.5 M) exhibits a rate consistent with 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**.
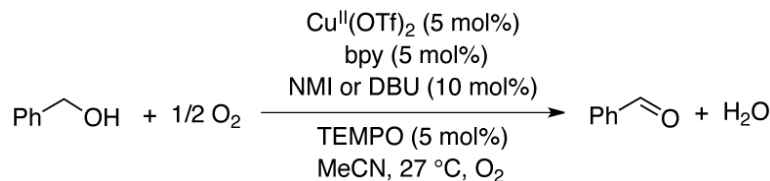
Copper(II) hydroxides have been proposed as products of catalyst deactivation in Cu/ TEMPO catalyst systems[5] and their formation is supported by the appearance of precipitates during the reaction, as noted above. After prolonged reaction times, a blue precipitate forms in reaction mixtures with the $Cu^{I}OTf/bpy/NMI/TEMPO$ catalyst system. Dark blue crystals were isolated from a reaction mixture that was left open to 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 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 the parent catalyst **D** (Figure S3), while the oxidation of $CyCH_2OH$ with this complex is somewhat slower than with catalyst **D** (Figure 4B).

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

Effect of base (DBU vs. NMI) and Cu oxidation state

Catalysts **C** and **D** employ $Cu^{II}(OTf)_2$ or $Cu^{I}OTf$ 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 role of 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 $Cu^{I}OTf$ and NMI. The reactions were analyzed by monitoring the change in oxygen pressure of a sealed, temperature-controlled reaction vessel using a computer interfaced gas uptake apparatus. These data are shown in Figure 5.

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

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

(2)

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

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

$$L_nCu^{II} \;+\; HO\diagup\!\!\!\diagdown R \;+\; B: \quad\rightleftharpoons\quad L_nCu^{II}\!-\!O\diagup\!\!\!\diagdown R \;+\; BH^+$$
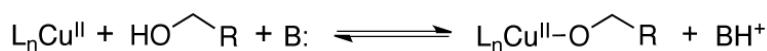
(3)

Discussion

The data presented above provide valuable insights into the roles of solvent (DMF, CH_3CN, H_2O), the ancillary bpy ligand, the oxidation state of the Cu source, and identity of basic additive ($KO^{t}Bu$, NMI, DBU). Addition of bpy to the CuCl/TEMPO catalyst system in DMF enables catalytic oxidation of aliphatic alcohols (Figure 2). Bipyridine lowers the Cu^{II}/Cu^{I} reduction potential in DMF (cf. Figures 1A and 1B), 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) enhance the rate of Cu^I oxidation by O_2 and (2) alter 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 experiencing inhibition (Figure 3). This observation is significant because water is a byproduct of the catalytic reaction, but stoichiometric amounts of water is well below the threshold of water inhibition (approx. 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}-hydroxides 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.

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 2nd/1st-order dependence on the [Cu/bpy] and 1st-order dependence on pO_2 with the first two catalyst systems is rationalized by a two-step aerobic Cu oxidation pathway that involves two metal centers (Scheme 4).

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, 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 formation of a L_nCu^{II}–alkoxide intermediate from Cu^{II}/base and $PhCH_2OH$ (eq 3).[12] The strong base DBU enables formation of the Cu^{II}-alkoxide, while the weaker base NMI is less effective in this step.

Formation of a Cu^{II}–alkoxide generates an equivalent 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 (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] and [TEMPO] 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 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

efficacy of the Cu^I/NMI and Cu^{II}/DBU catalyst systems (i.e., **C** and **D**, Table 1) highlight the important of proper matching of the Cu oxidation state and 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 avoids 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*, Scheme 3). In addition, NMI could hinder formation and/or facilitate dissociation of the 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, and so the oxidation of aliphatic alcohols is efficient. The slower rates observed with this Cu^{II} dimer, relative to Cu^IOTf, probably reflects it slow dissociation into the active monomeric form and/or its poor solubility.

Summary and Conclusion

The number of Cu/TEMPO catalyst systems extend 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/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 solvent, oxidation state of the Cu source, and 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 aliphatic alcohols that are otherwise unreactive. Water can significantly inhibit catalytic turnover when it is present in high concentration. Kinetic sutdies of several different Cu/TEMPO catalyst systems reveals 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]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(11). With $Cu^{II}(OTf)_2$, use of both DBU and NMI was shown to afford higher yields with aliphatic alcohols (see ref. 5). For example, applying the mixed DBU/NMI catalyst system to the oxidation of $CyCH_2OH$ provided higher yields of the corresponding aldehyde than a reaction with DBU alone (94% vs. 85% ^1H NMR spectroscopy). The initial rates for the two systems were similar suggesting that employing NMI in addition to DBU helps mitigate the catalyst deactivation observed when DBU is the only base present.

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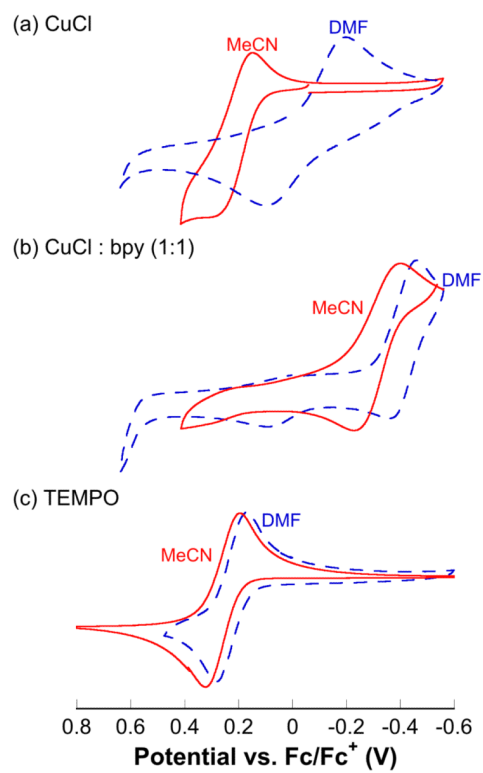
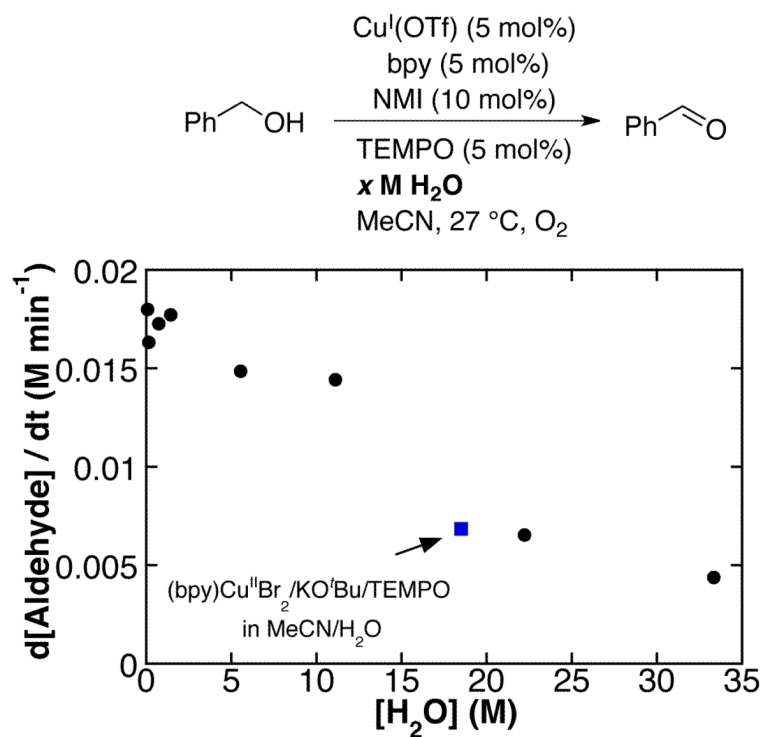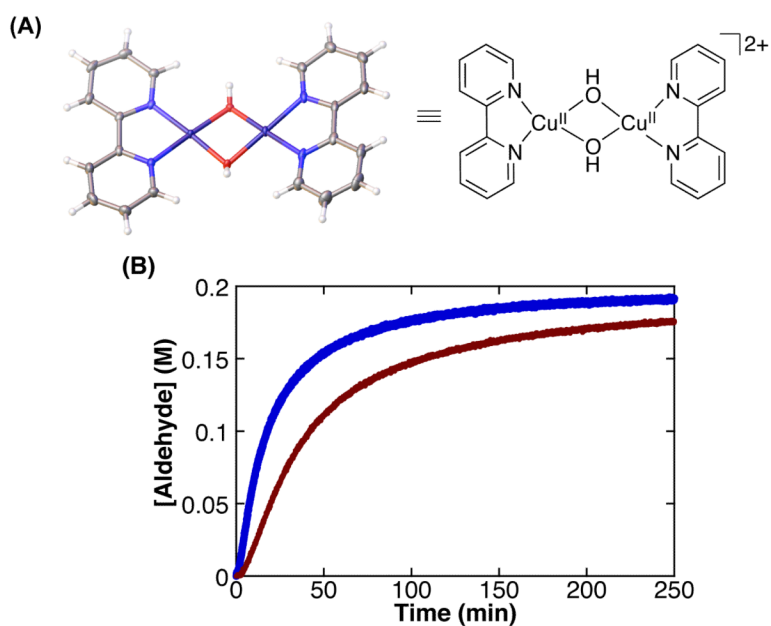**Figure 1.**
Cyclic voltammograms of CuCl (± bpy) and TEMPO in DMF (dashed blue line) and MeCN (solid red line). See Supporting Information for details.
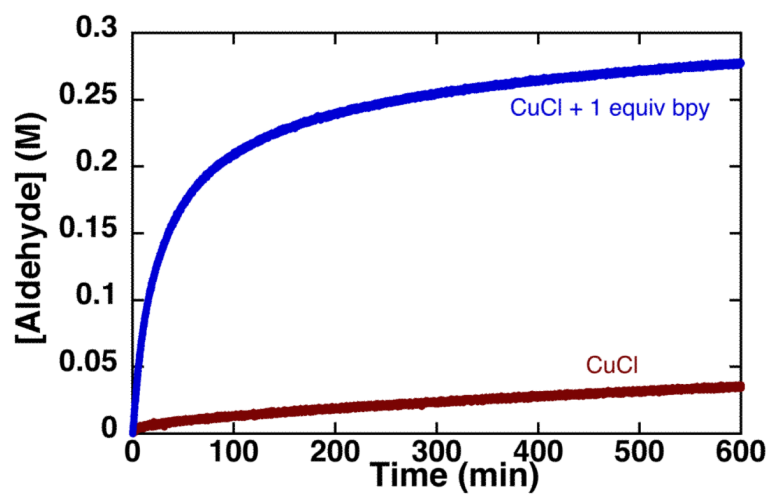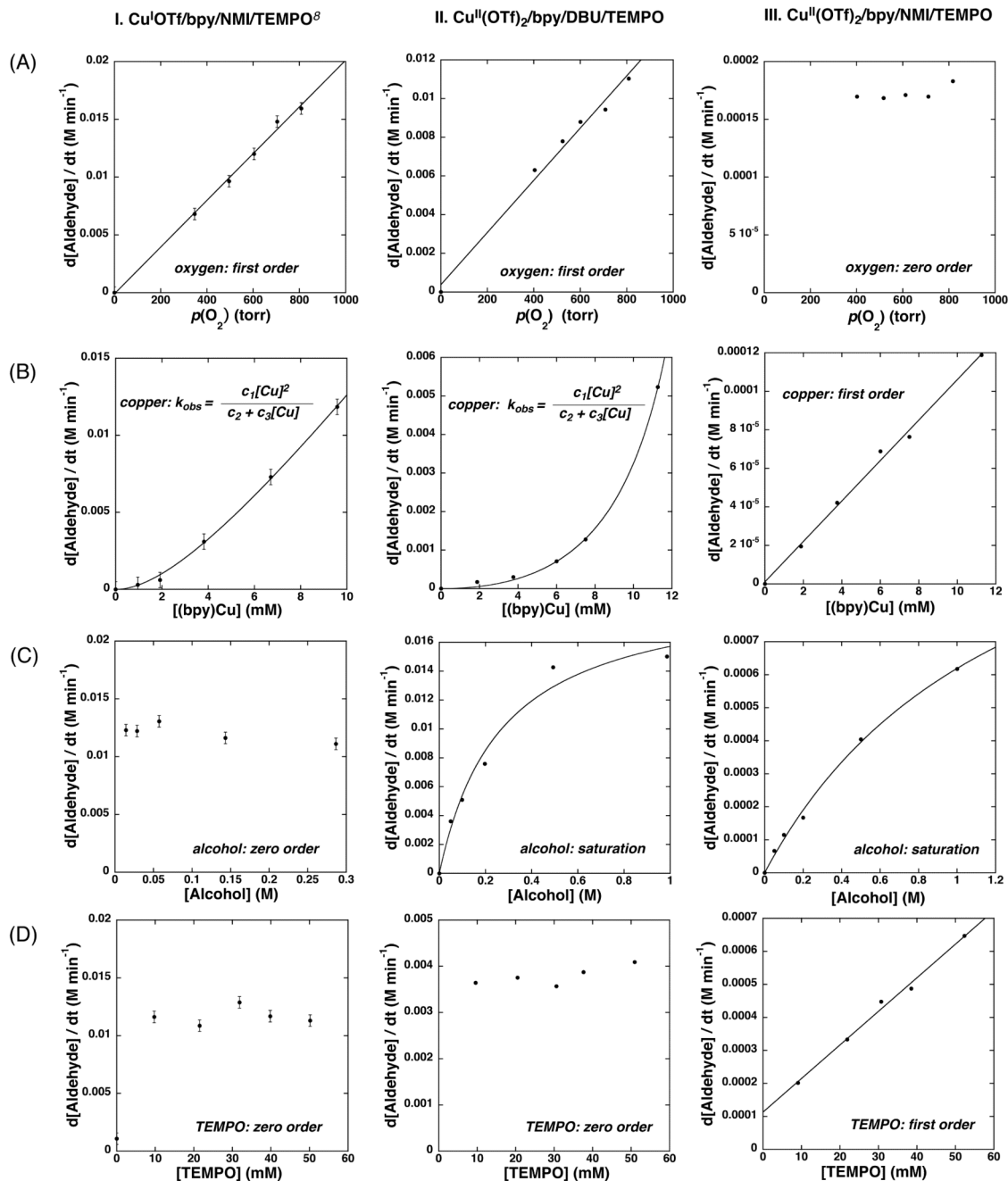
Figure 2.
The oxidation of CyCH$_2$OH by CuCl with (●) and without (●) bpy in DMF. Standard conditions: 0.4 M CyCH$_2$OH, 0.04 M TEMPO, 0.04 M CuCl, 0.04 M bpy, 600 torr O$_2$, 27 °C.

Figure 3.
Rates of oxidation of PhCH$_2$OH by Cu^{I}OTf/bpy/NMI/TEMPO with the addition of H$_2$O. Standard conditions: 0.2 M PhCH$_2$OH (0.5 mmol), 10 mM Cu^I(OTf), 10 mM bpy, 10 mM TEMPO, 20 mM NMI, 600 torr O$_2$, 27 °C. Oxidation of PhCH$_2$OH by Cu^{II}Br$_2$/bpy/KO^{t}Bu/ TEMPO in MeCN/H$_2$O (■) included for comparison.

Figure 4.
(A) X-ray structure of [(bpy)Cu(OH)]$_2$(OTf)$_2$, which crystallizes as a dimer of dimers (see Supporting Information for details). The triflate counterions are omitted for clarity. (B) The oxidation of CyCH$_2$OH by Cu^{I}OTf (●) and [(bpy)Cu(OH)]$_2$(OTf)$_2$. (●). 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$_2$ OH, 1 atm O$_2$, 2.5 mL MeCN, 27 °C.

I. Cu^{I}OTf/bpy/NMI/TEMPO^8   **II. Cu^{II}(OTf)$_2$/bpy/DBU/TEMPO**   **III. Cu^{II}(OTf)$_2$/bpy/NMI/TEMPO**

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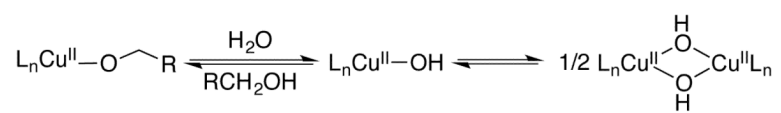
(A)

(B)
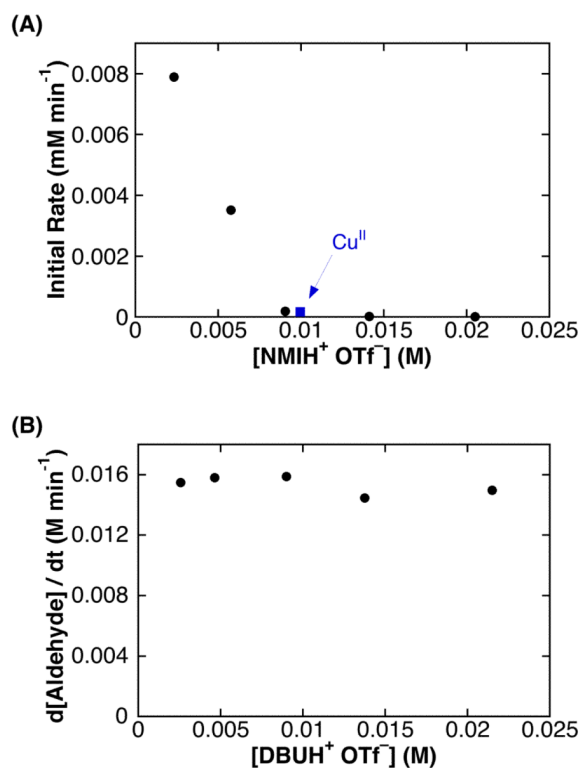
Figure 6.
Dependence of Cu^{I}OTf/bpy/TEMPO/NMI catalyzed benzyl alcohol oxidation on added (A) NMIH$^+$ OTf$^-$ and (B) DBUH$^+$ OTf$^-$. The reaction catalyzed by Cu^{II}(OTf)$_2$/bpy/-TEMPO/ NMI (■) is included in A for comparison. Rates were obtained by monitoring pressure changes during catalytic turnover. Standard reaction conditions: 10 mM Cu^I(OTf), 10 mM bpy, 20 mM NMI, 10 mM TEMPO, 0.2 M alcohol.
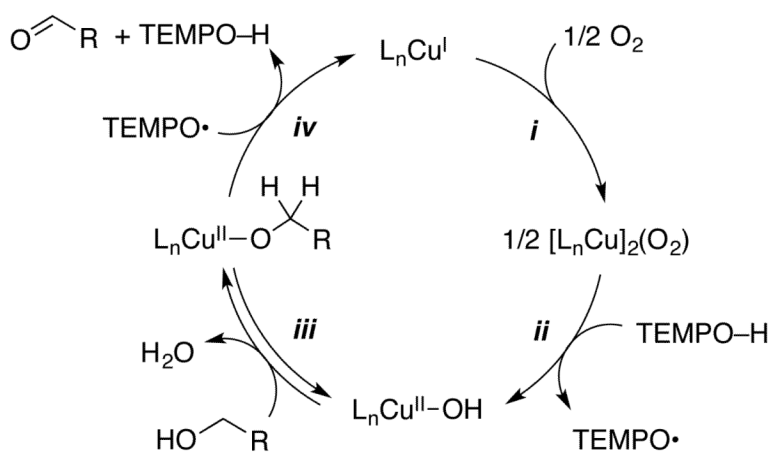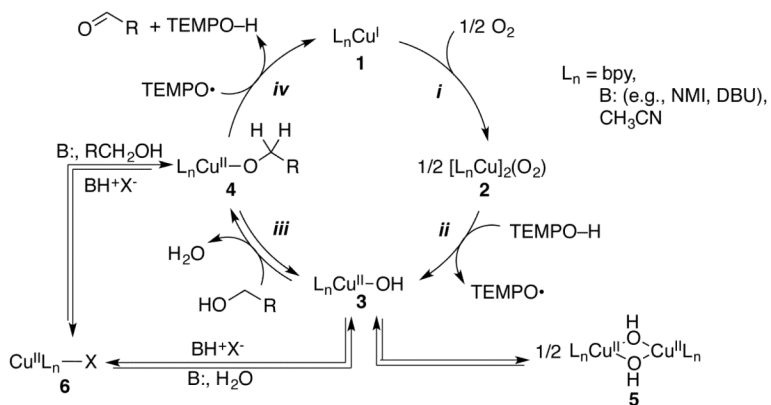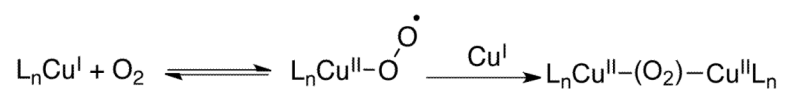
Scheme 1. Simplified Catalytic Cycle for Cu^{I}OTf/bpy/NMI/TEMPO Catalyzed Aerobic Alcohol Oxidation

$$L_nCu^{II}-O-R \underset{RCH_2OH}{\overset{H_2O}{\rightleftharpoons}} L_nCu^{II}-OH \rightleftharpoons 1/2\ L_nCu^{II}\begin{smallmatrix}H\\O\\O\\H\end{smallmatrix}Cu^{II}L_n$$

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

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

$$L_nCu^I + O_2 \rightleftharpoons L_nCu^{II}-O{\overset{\bullet}{O}} \xrightarrow{Cu^I} L_nCu^{II}-(O_2)-Cu^{II}L_n$$

Scheme 4. Catalyst Oxidation Sequence Accounting for a Mixed 1st /2nd Order Cu Dependence

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^ICl	–	–	DMF
B (Sheldon)[4]	$Cu^{II}Br_2$	bpy	KO^{t}Bu	2:1 MeCN/H_2O
C (Koskinen)[5]	$Cu^{II}(OTf)_2$	bpy	DBU (+ NMI)	MeCN
D (Stahl)[6]	Cu^IOTf	bpy	NMI	MeCN

TEMPO =   DBU =   NMI =
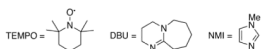
Table 2
Kinetic Dependences for Cu/bpy Systems with PhCH$_2$OH

	Cu^I/NMI	Cu^{II}/DBU	Cu^{II}/NMI
pO$_2$	1st order	1st order	0th order
[Cu]	mixed 2nd/1storder	mixed 2nd/1st order	1st order
[PhCH$_2$OH]	0th order	saturation	saturation
[TEMPO]	0th order	0th order	1st order