

Nitroxyl Surprise: A Simple Amine Additive Revealed as Copper's Co-Catalyst in the Aerobic Oxidation of Alcohols

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Even the best mechanistic hypotheses can be refined. Unexpected details discovered by careful analysis can promote useful reactions.

In the search for new catalytic activity, chemists rely on working hypotheses and their intuition. All new transformations involve a combination of design and fortuitous discovery, whether they are discovered in a high-throughput platform, or by more traditional flask-by-flask experimentation. Particular additives or ligands are typically chosen based on a mechanistic hypothesis. The beauty of true discovery occurs when careful experimentalists, in fully developing and analyzing their reactions, are surprised to find that the added reagent facilitates catalysis by an unexpected pathway.¹ Such happenstances exemplify the best of the scientific method, as the scientist must remain impartial, breaking allegiance with the original working hypothesis and generates new ones. The highlighted paper provides a new example of serendipitous discovery that may guide development of related oxidation reactions and inform bioinorganic chemistry. While developing environmentally friendly copper-catalyzed oxidation reactions, it was determined that the diamine originally added as a ligand for copper actually acts as a co-catalyst upon oxidation in situ to a nitroxyl radical (Scheme 1).² Furthermore, this mechanism provides an example of a catalyst performing two roles: the copper complex must first oxidize the diamine to the nitroxyl radical, and then it must catalyze the oxidation of the alcohol to the carbonyl.

Oxidation reactions are among the most prevalent transformations in chemical synthesis, used by both biological systems and synthetic chemists. Enzymatic oxidases, such as galactose oxidase, use molecular oxygen as the terminal oxidant for alcohol oxidation, whereas most common synthetic methods require toxic and/or atom-inefficient stoichiometric oxidants.³ Development of sustainable catalytic oxidation reactions that employ molecular oxygen and non-precious transition metals has been an active field of study.⁴

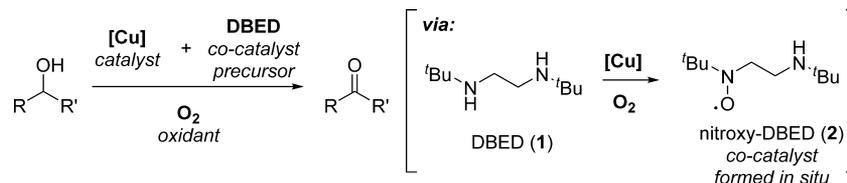
To address this challenge, a number of copper-catalyzed oxidations have been developed.⁵ Most of these transformations require the use of a redox active co-catalyst that lowers the kinetic barrier for hydrogen-atom transfer from a copper alkoxide species.⁶ The mechanisms of these transformations often mirror those of enzymatic oxidations, as the co-catalyst serves a similar function to cofactors present in the active site. In 2015 Lumb and Arndtsen reported an efficient oxidation of alcohols that did not require a redox-active co-catalyst (Scheme 1).⁷ Stahl, Lumb, and Arndtsen have now collaborated to provide an in-depth mechanistic investigation of this reaction, discovering the mechanistic parallels to enzymatic activity are more pronounced than expected.

In a first catalytic cycle, a copper complex oxidizes the diamine ligand to its corresponding nitroxyl radical (cycle 1), resembling oxygenase activity. In a second catalytic cycle, a copper complex and nitroxyl radical are co-catalysts for alcohol oxidation (cycle 2), mimicking oxidase activity.

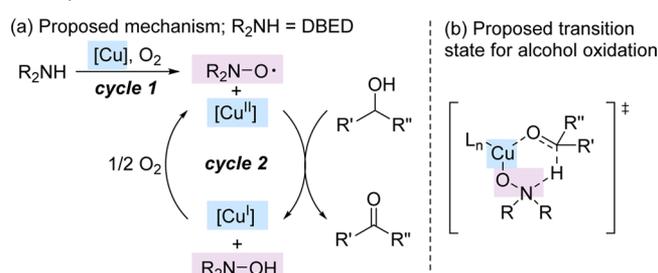
Stahl, Lumb, and Arndtsen propose a mechanism that is outlined in Scheme 2. In a first catalytic cycle, a copper complex oxidizes the diamine ligand to its corresponding nitroxyl radical (cycle 1), resembling oxygenase activity. In a second catalytic cycle, a copper complex and nitroxyl radical are co-catalysts for alcohol oxidation (cycle 2), mimicking oxidase activity. The evidence for this mechanism arises from the results of several experiments. First, the reaction was shown to exhibit an induction period, consistent with formation of a new catalytic species in the reaction mixture. Second, more than one equivalent of O₂ was consumed

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Scheme 1. Copper/Diamine Catalyzed Oxidations of Alcohols



Scheme 2. Proposed Mechanism for the Copper/Diamine Catalyzed Oxidation of Alcohols



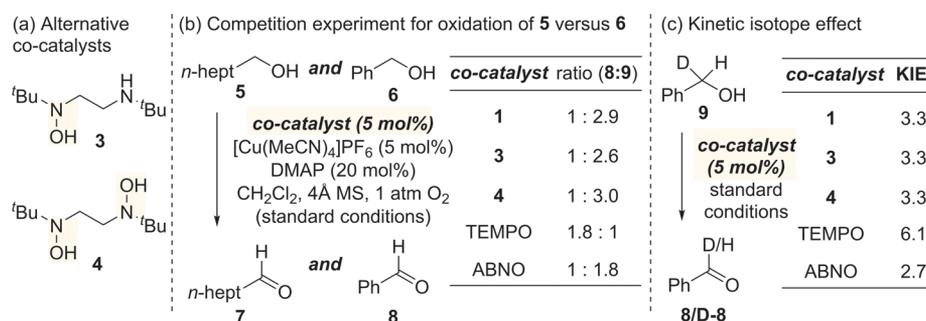
over the course of the reaction, consistent with oxygen requirement for formation of the new catalytic species. Third, electron paramagnetic resonance (EPR) spectra of the reaction mixtures showed the presence of an organic radical with spectral data similar to those previously reported for nitroxyl radicals. All of these data are consistent with copper-catalyzed oxidation of the diamine to a nitroxyl radical, which then serves as a co-catalyst for alcohol oxidation. The second catalytic cycle is one that was previously proposed by Stahl and co-workers for TEMPO-mediated copper oxidations.⁸ In the previous work, they performed a series of experiments including density functional theory calculations which supported a concerted two-electron oxidation pathway for deprotonation, according to a cyclic transition state (Scheme 2b).

If these mechanisms were valid, a hydroxylamine should directly enter the second catalytic cycle and serve as a competent catalyst. Thus, hydroxylamines **3** and **4** were prepared and validated as co-catalysts (Scheme 3). When employing either **3** or **4** in place of DBED, the reactions occurred with no induction period and with rates similar to those previously measured for Cu/TEMPO systems.

Therefore, the induction period in reactions employing DBED was attributed to required oxidation of the amine (Scheme 2, cycle 1) prior to initiation of alcohol oxidation (cycle 2). To confirm that diamine **1** and hydroxylamine **3** generate the same co-catalyst species in situ, substrate selectivity and kinetic isotope effects were measured. It is known that the substrate selectivity in these oxidation reactions is strongly dependent on the steric properties of the nitroxyl radical and competition experiments for oxidation of two substrates can be used as a sensitive probe for catalyst structure. For example, TEMPO and ABNO, traditional nitroxyl radical co-catalysts, give significantly different product distributions in competition experiments for oxidation of octanol and benzyl alcohol (Scheme 3b). Diamine **1** and hydroxylamines **3** and **4** provided similar product distributions, consistent with formation of the same active species in situ. Similarly, DBED and hydroxylamines **3** and **4** displayed the same kinetic isotope effects, whereas the use of TEMPO and ABNO provided different kinetic isotope effects (Scheme 3c). These data are consistent with a common co-catalyst for reactions employing DBED, **3**, and **4**, which is distinct from those in systems that employ the nitroxyl co-catalyst additives TEMPO and ABNO. These experiments

These findings present a significant practical advantage that simple amines can be employed as co-catalyst precursors in lieu of the corresponding hydroxylamines or nitroxyl radicals.

Scheme 3. Competition Experiments and Determination of Kinetic Isotope Effects



strongly support the in situ oxidation of DBED to the corresponding nitroxyl radical **2** as the active co-catalyst.

In summary, Stahl, Lumb, and Arndtsen have demonstrated that a copper/diamine catalyst system generates a nitroxyl radical as a co-catalyst in situ. The copper catalyst plays two roles: first to oxidize the amine to the corresponding nitroxyl radical and then to oxidize the alcohol to the ketone or aldehyde. These findings present a significant practical advantage that simple amines can be employed as co-catalyst precursors in lieu of the corresponding hydroxylamines or nitroxyl radicals. This flexibility could lower the cost of related oxidation reactions that employ TEMPO or ABNO. More importantly, many nitroxyl co-catalysts have not been previously evaluated, due to their instability. These co-catalyst architectures can now be evaluated by using the corresponding amine precursor. Given that substrate selectivity is strongly dependent on the co-catalyst's steric and electronic features, new catalysts are anticipated to allow for site-selective alcohol oxidation. This reaction provides a new minimal enzyme model for bioinorganic and biomimetic chemistry, since a simple copper complex provides both oxygenase and oxidase-like activity. The results also remind us that reasonable hypotheses are often found not to be valid and that rigorous experimentation can open new pathways for discovery.

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