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Copper-Catalyzed Aerobic Oxidations of Organic Molecules: Pathways for Two-Electron Oxidation with a Four-Electron Oxidant and a One-Electron Redox-Active Catalyst

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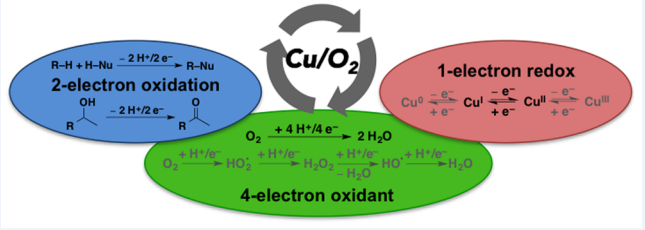
CONSPECTUS: Selective oxidation reactions have extraordinary value in organic chemistry, ranging from the conversion of petrochemical feedstocks into industrial chemicals and polymer precursors to the introduction of heteroatom functional groups into pharmaceutical and agrochemical intermediates. Molecular oxygen (O_2) would be the ideal oxidant for these transformations. Whereas many commodity-scale oxidations of simple hydrocarbon feedstocks employ O_2 as an oxidant, methods for selective oxidation of more complex molecules bearing diverse functional groups are often incompatible with existing aerobic oxidation methods. The latter limitation provides the basis for our interest in the development of new catalytic transformations and the elucidation of mechanistic principles that underlie selective aerobic oxidation reactions. One challenge inherent in such methods is the incommensurate redox stoichiometry associated with the use of O_2, a four-electron oxidant, in reactions that achieve two-electron oxidation of organic molecules. This issue is further complicated by the use of first-row transition-metal catalysts, which tend to undergo facile one-electron redox steps. In recent years, we have been investigating Cu-catalyzed aerobic oxidation reactions wherein the complexities just noted are clearly evident. This Account surveys our work in this area, which has emphasized three general classes of reactions: (1) single-electron-transfer reactions for oxidative functionalization of electron-rich substrates, such as arenes and heterocycles; (2) oxidative carbon−heteroatom bond-forming reactions, including C−H oxidations, that proceed via organocopper(III) intermediates; and (3) methods for aerobic oxidation of alcohols and amines that use Cu^{II} in combination with an organic redox-active cocatalyst to dehydrogenate the carbon−heteroatom bond. These reaction classes demonstrate three different pathways to achieve two-electron oxidation of organic molecules via the cooperative involvement of two one-electron oxidants, either two Cu^{II} species or Cu^{II} and a nitroxyl cocatalyst. They show the ability of Cu to participate in traditional organometallic steps commonly associated with precious-metal catalysts, such as C−H activation and reductive elimination, but also demonstrate the accessibility of reaction steps not typically associated with precious-metal catalysts, such as single-electron transfer. Many of the Cu-catalyzed reactions offer advantages over analogous two-electron oxidation reactions mediated by palladium or other noble metals. For example, carbon−heteroatom oxidative coupling reactions in the first two reaction classes noted above are capable of using O_2 as the terminal oxidant, while analogous reactions with Pd commonly require less desirable oxidants, such as hypervalent iodine or electrophilic halogen sources. In addition, the alcohol and amine oxidations in the third reaction class are significantly more efficient and show much broader scope and functional group tolerance than related Pd-catalyzed reactions. The mechanistic basis for these differences are described herein.



1. INTRODUCTION

The selective oxidation of organic molecules is a formidable challenge in synthetic chemistry. Molecular oxygen is the most abundant and least expensive oxidant available, but its use is largely confined to commodity-scale oxidation reactions where economic and environmental considerations dictate that O_2 is the only viable oxidant.[1] Safety concerns and limitations in reaction scope and/or selectivity have inhibited the use of aerobic oxidation reactions in the fine chemical, pharmaceutical, and related industries.[2] On the other hand, aerobic oxidations are widespread in nature, and biological aerobic oxidation reactions provide valuable insights into catalytic mechanisms that are compatible with selective liquid-phase oxidation of organic molecules. Two different classes of these enzymes exist, *oxygenases* and *oxidases*, which differ in the role of O_2 in the reaction. Oxygenases directly incorporate oxygen atoms into the organic molecule (Scheme 1A), while oxidases couple diverse oxidation reactions to the reduction of O_2 to water or hydrogen peroxide (Scheme 1B).

Synthetic modeling of binuclear Cu oxygenases has been the subject of extensive investigation.[3] Recent progress includes, for

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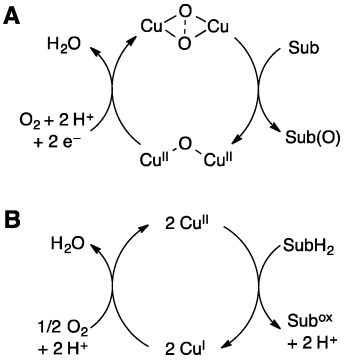
Scheme 1. Catalytic Cycles for Copper-Based (A) "Oxygenase" and (B) "Oxidase" Pathways for Aerobic Oxidation of Organic Molecules



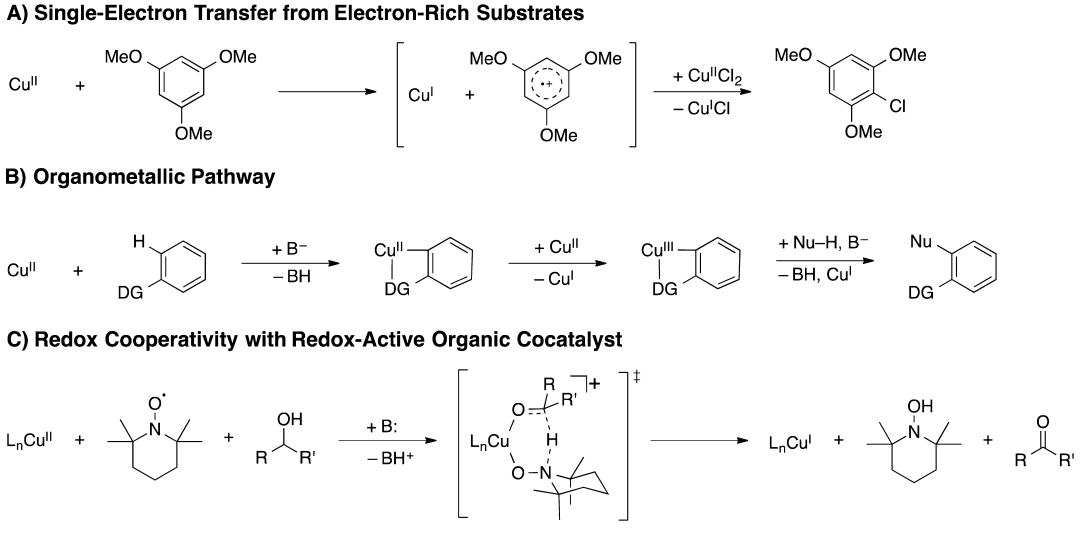
example, selective catalytic *ortho* oxygenation of phenols, resembling tyrosinase activity.[4] Our efforts toward the development of synthetically useful aerobic oxidation reactions have taken inspiration from the "oxidase" class of enzymes because they do not require a sacrificial reductant to activate molecular oxygen (e.g., NAD(P)H is a common reductant used in enzymatic oxygenase reactions). Such methods formally enable any oxidation reaction to be coupled to O_2 as the stoichiometric oxidant. Historically, much of our effort has focused on palladium-catalyzed reactions[5] involving a $Pd^{II/0}$ cycle in which Pd^{II}-mediated oxidation of alcohols, alkenes, or C−H bonds is coupled to aerobic oxidation of Pd^0 to Pd^{II}. The use of a noble metal, such as palladium, promotes selective oxidation of the organic molecules because of its tendency to undergo two-electron redox reactions.

Copper catalysts represent an appealing alternative to palladium. Not only is copper much less expensive and less toxic than palladium, but also, Cu-containing oxidases mediate a wide range of important oxidation reactions in nature, ranging from outer-sphere electron transfer (e.g., laccases) to dehydrogenation (e.g., galactose oxidase).[6] Extensive efforts by numerous groups have been directed toward the development of nonenzymatic copper catalysts for aerobic oxidation.[7] One particular challenge in these reactions, however, is the tendency of copper to undergo one-electron redox transformations. Whereas Cu^I/Cu^{III} is isoelectronic with Pd^0/Pd^{II}, Cu^{II} is the most stable redox state under aerobic conditions. Therefore, Cu-catalyzed aerobic oxidation reactions must successfully manage one-electron redox steps to achieve selective two-electron oxidation of organic molecules.

Numerous successful Cu-catalyzed aerobic oxidation reactions have been developed,[7] but the mechanisms of these reactions are not as well understood as aerobic oxidation reactions catalyzed by palladium and other noble metals. The present Account summarizes our contributions to the development and/or mechanistic characterization of a series of different Cu-catalyzed aerobic oxidation reactions. The reactions fit into three general mechanistic pathways (Scheme 2). The first is initiated by single-electron transfer (SET) from electron-rich substrates to Cu^{II}, as observed in the oxyhalogenation of arenes and heterocycles (Scheme 2A).[8] The second involves an organometallic mechanism that features disproportionation of two Cu^{II} species into Cu^I and Cu^{III} species (Scheme 2B). Our work in this area provided the first direct evidence for an organocopper intermediate in an aerobic oxidation reaction and revealed factors that contribute to SET versus organometallic reaction pathways.[7c] The third pathway involves redox cooperativity between Cu^{II} and a redox-active nitroxyl cocatalyst (Scheme 2C), which enables highly versatile and efficient alcohol and amine oxidation reactions.[9]

The results of our studies have important implications for the relationship between precious-metal and nonprecious-metal catalysis. Cu-catalyzed reactions are often more complex mechanistically than reactions catalyzed by palladium and other precious metals, but they can offer important advantages. For example, organo-Cu^{III} species undergo more facile reductive elimination than isoelectronic Pd^{II} species. This feature explains why organometallic Cu-catalyzed oxidations (cf. Scheme 2B) can form carbon−heteroatom bonds under aerobic conditions, while Pd-catalyzed reactions require hypervalent iodine or other stoichiometric oxidants in related transformations.[5d,10] In addition, Cu/nitroxyl-catalyzed aerobic alcohol oxidations exhibit much faster rates and broader functional group compatibility than analogous Pd-catalyzed reactions. It is hoped that catalyst development and mechanistic studies of the type elaborated here will continue to expand the

Scheme 2. Mechanistic Pathways for Copper-Catalyzed Oxidation of Organic Substrates



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scope and utility of aerobic oxidation reactions capable of using nonprecious-metal catalysts.

2. SINGLE-ELECTRON-TRANSFER AND ORGANOMETALLIC OXIDATIONS: CATALYTIC METHODS

The tendency of Cu^{II} to participate in one-electron redox reactions is often manifested in oxidation reactions of electron-rich substrates initiated by single-electron transfer. An advantage of using Cu^{II} as a SET reagent over other reagents such as Ce^{IV}, ferrocenium, or high-potential quinones (e.g., DDQ) is that it can be regenerated by aerobic oxidation of the Cu^{I} byproduct.[7] In an early effort to explore Cu-catalyzed oxidative functionalization of arenes, we discovered a new method for regioselective bromination and chlorination of electron-rich arenes and heterocycles under aerobic conditions (Figure 1).[11,12] Cu-catalyzed aerobic oxyhalogenation of

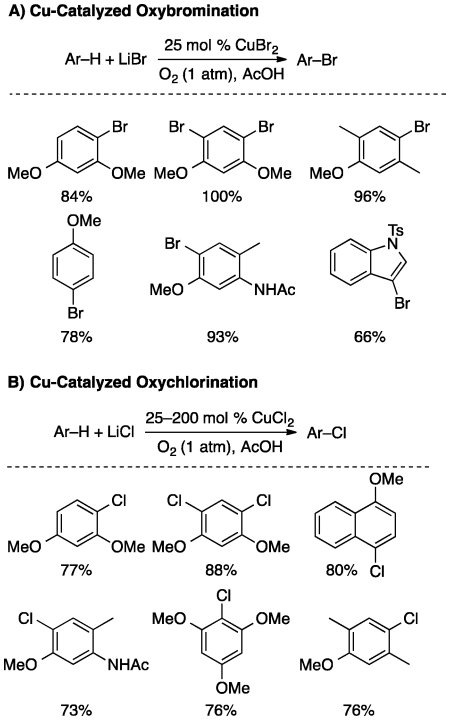


Figure 1. Aerobic oxidative halogenation of electron-rich arenes catalyzed by CuX_2 sources (X = Br, Cl).[11]

electron-rich aromatic molecules provides access to aryl halides, which are important industrial chemicals and useful intermediates in organic synthesis. The ability to use lithium halide salts as the source of halogen offers practical advantages over classical electrophilic halogenation methods that utilize Cl_2, Br_2, or other electrophilic halogenation reagents. The results complement previously reported oxyhalogenation reactions of phenols and anilines.[12c] The strong dependence of the reaction on the electronic richness of the arene was interpreted as support for an SET mechanism involving arene radical-cation intermediates, at least in the case of the oxychlorination reaction. For example, electron-deficient and electronically neutral arenes, such as benzene, are unreactive under these conditions. An electrophilic bromination pathway was also considered for the oxybromination reactions, which could arise from in situ aerobic oxidation of bromide to Br_2.[11]

In the course of these studies, our attention was drawn to Chan–Evans–Lam coupling reactions, which are versatile Cu-catalyzed methods for oxidative coupling of arylboron reagents and diverse *N*- and *O*-based nucleophiles (Figure 2).[13] Many of

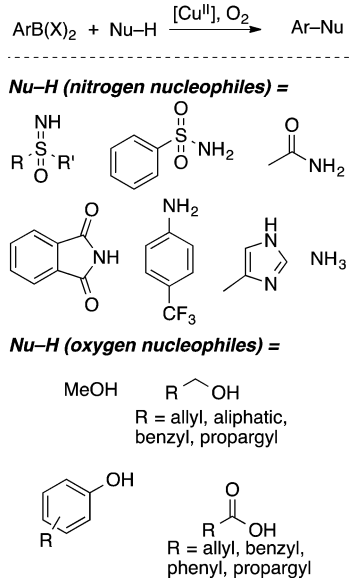
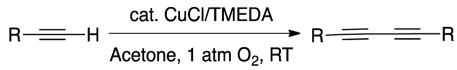


Figure 2. Chan–Evans–Lam reaction and scope of heteroatom nucleophiles.[13]

these reactions undergo catalytic turnover in the presence of O_2, but they do not display the reactivity trends expected from SET reactivity. Instead, it seemed likely that these reactions represented an unusual example of "organometallic" Cu-catalyzed aerobic oxidation reactions. The lack of precedent for organo-Cu intermediates in aerobic oxidation reactions prompted us to undertake a mechanistic study of these reactions, which is presented in the next section.

The Glaser–Hay oxidative homocoupling of alkynes (eq 1) traces its origin to the 19th century. While the mechanism of



(1)

these reactions remains the subject of debate,[14] the electronic trends observed in these reactions (i.e., they are not limited to electron-rich alkynes), the facile activation of the acidic alkyne C–H bond by copper salts, and the stoichiometric coupling reactions observed with copper acetylides support the involvement of an organometallic mechanism. Taking inspiration from the Chan–Evans–Lam and Glaser–Hay oxidative coupling reactions, we developed a Cu-catalyzed method for aerobic oxidative amidation of terminal alkynes that combines features from the two coupling reactions (Figure 3).[15] After this report, a number of related reactions involving selective cross-coupling between terminal alkynes and diverse nucleophiles have been published by others.[7,16]

In an effort to extend Cu-mediated C–H oxidation from alkynes to alkenes, we developed a method for the preparation of oxazoles (Figure 4) via oxidative cyclization of enamides.[17] The mechanism of these reactions was not studied in detail, but the electron-rich nature of the enamide substrate leads us to believe that an SET mechanism rather than an organometallic mechanism may be involved. These methods resemble earlier Cu-catalyzed methods reported by Nagasawa[18] and Buchwald[19]

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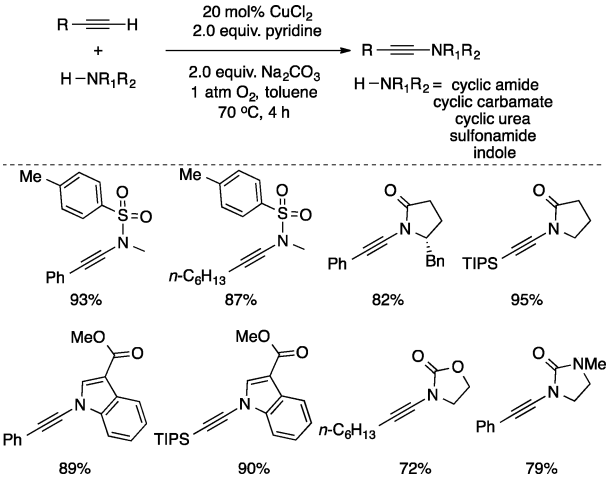


Figure 3. Aerobic Cu-catalyzed amidation of terminal alkynes.[15]

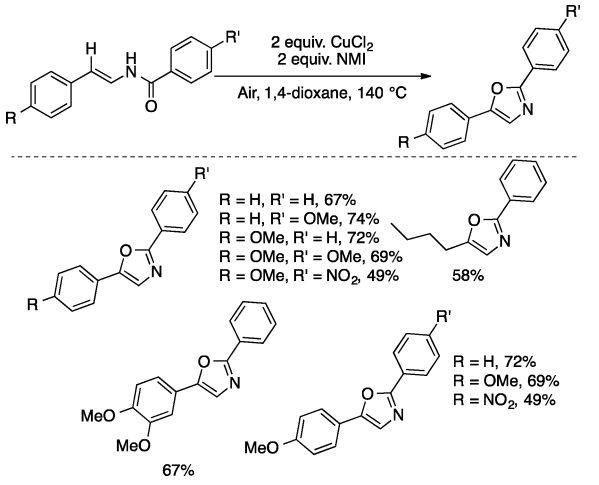


Figure 4. Substrate scope of Cu-mediated enamide cyclization.[17]

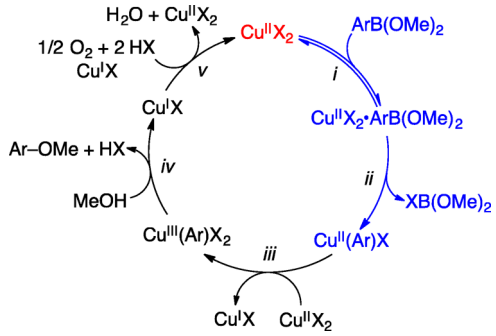
for the oxidative synthesis of benzoxazoles and benzimidazoles from *N*-aryl amides and amidines.

The small subset of reactions surveyed above highlights distinctions commonly observed in Cu-catalyzed C–H oxidation reactions. Different electronic trends in substrate reactivity provide qualitative evidence that at least two different pathways could be involved. Nevertheless, a mechanistic framework for understanding these distinctions was lacking at the time we began our work, particularly for the "organometallic" reactions.

3. SINGLE-ELECTRON-TRANSFER AND ORGANOMETALLIC OXIDATIONS: CATALYTIC MECHANISMS

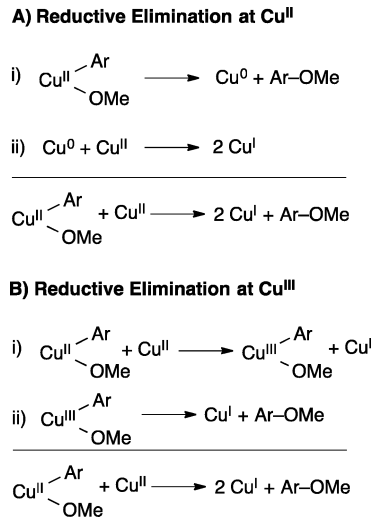
Our initial foray into the mechanistic investigation of Cu-catalyzed oxidative coupling reactions focused on the Chan–Evans–Lam reactions, specifically $Cu(OAc)_2$-catalyzed methoxylation of *p*-tolylboronic dimethyl ester.[20] The overall reaction stoichiometry is consistent with a two-stage oxidase-style mechanism (cf. Scheme 1A), in which two equivalents of Cu^{II} promote oxidative coupling of the arylboron reagent and methanol in the first stage, followed by aerobic oxidation of Cu^{I} to Cu^{II} in the second stage. A more detailed mechanism is provided in Scheme 3. EPR analysis of the catalytic reaction mixture showed that the catalyst resting state consists of Cu^{II}

Scheme 3. Proposed Catalytic Mechanism for Chan–Evans–Lam Reactions[20]



species with acetate, methanol, and boronic ester-based methoxide ligands. Kinetic studies showed that the turnover-limiting step involves transmetalation of the aryl group from boron to copper (step *ii*). Steps beyond formation of the aryl-Cu^{II} intermediate (i.e., steps *iii*–*v*) are kinetically invisible, and two mechanistic pathways were considered to account for the 2:1 Cu:$ArB(OMe)_2$ stoichiometry of the reaction (Scheme 4).

Scheme 4. Possible Pathways for C–O Bond Formation from an Aryl-Cu^{II} Species[20]



The first involved C–O reductive elimination from Cu^{II} followed by comproportionation of Cu^{0} and a second equivalent of Cu^{II} (Scheme 4A), and the second involved oxidation of the aryl-Cu^{II} intermediate by a second equivalent of Cu^{II} followed by C–O reductive elimination from an aryl-Cu^{III} species (Scheme 4B). The latter mechanism was strongly favored on two grounds: (1) comproportionation of Cu^{0} and Cu^{II} was shown to be thermodynamically unfavorable under the reactions conditions (instead, Cu^{I} undergoes disproportionation to Cu^{0} and Cu^{II}), and (2) the aryl-Cu^{II}/Cu^{II} "disproportionation" reactions had direct precedent in a well-defined stoichiometric reaction, as described further below.[21] An alternate mechanism in which O_2 oxidizes the aryl-Cu^{II} intermediate to aryl-Cu^{III} was excluded on the basis of the ability of $Cu(OAc)_2$ to mediate kinetically competent stoichiometric oxidative coupling of the boronic ester and methanol under anaerobic conditions. The role of O_2 is simply to promote oxidation of Cu^{I} to Cu^{II} in the final step of the cycle (step *v*).

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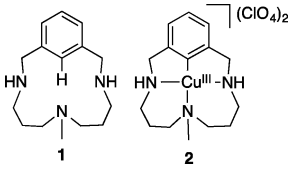
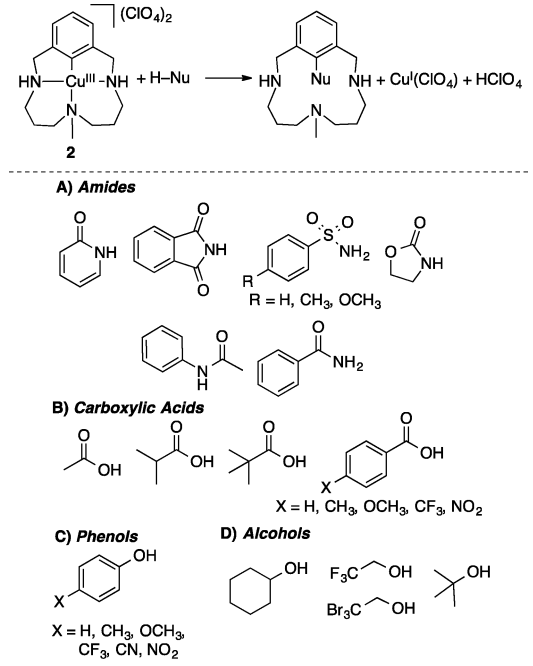
Our studies of the Chan–Evans–Lam reactions highlighted the potential involvement of organo-Cu^{II} and/or -Cu^{III} intermediates in Cu-catalyzed aerobic oxidation reactions. At the time, very little was known about the organometallic chemistry of Cu^{II} and Cu^{III};[22] however, Ribas, Llobet, Stack, and co-workers had previously reported a unique stoichiometric C–H activation reaction in which the macrocyclic arene **1** reacted with Cu^{II} salts to form the aryl-Cu^{III} complex **2**.[21] The



aryl-Cu^{III} species **2** was appealing as a model for the proposed Cu^{III} intermediate in Chan–Evans–Lam chemistry because it features a Cu–C_{aryl} bond within a square-planar coordination environment similar to that expected to be present in the cross-coupling reactions (cf. Scheme 3). The reactivity of aryl-Cu^{III} species **2** was assessed by combining it in acetonitrile solution with nitrogen nucleophiles commonly encountered in Chan–Evans–Lam coupling reactions (Scheme 5A).[23] More acidic

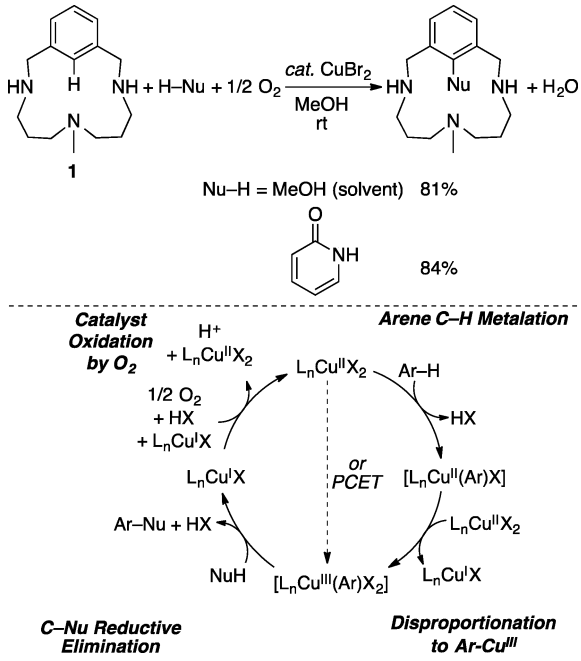
Scheme 5. C–N and C–O Bond-Forming Reductive Elimination Reactions Observed with the Aryl-Cu^{III} Species 2[23,24]



(less nucleophilic) amides reacted more rapidly; however, facile C–N bond formation was observed with a wide range of nucleophiles, even in the absence of a Brønsted base. Subsequent work in collaboration with Ribas demonstrated analogous C–O bond-forming reactions with phenol and carboxylic acid nucleophiles (Scheme 5B–D).[24,25]

The first direct evidence for the involvement of organo-Cu^{III} intermediates in aerobic C–H oxidation reactions was obtained from further studies of arene **1**.[26] The macrocyclic arene was combined with a catalytic Cu^{II} source, $Cu(ClO_4)_2$ or $CuBr_2$ (10 mol %), in methanol under an atmosphere of O_2, and the reaction led to the formation of the corresponding Ar–OMe

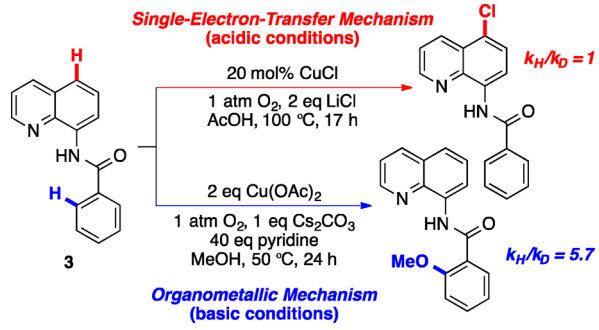
Scheme 6. Catalytic Mechanism of Aerobic C–H Oxidation of Macrocyclic Arene 1[26a]



product in 81% yield (Scheme 6). A C–N oxidative-coupling product was obtained in 84% yield when pyridone was included in the reaction mixture. Direct evidence for the formation and disappearance of the aryl-Cu^{III} intermediate in the reaction was obtained by monitoring the reaction by UV–vis spectroscopy. While the macrocyclic nature of the arene substrate **1** undoubtedly influences the relative stability of the corresponding aryl-Cu intermediate(s), the catalytic mechanism arising from this work (Scheme 6) directly aligns with the mechanism proposed previously for the Chan–Evans–Lam coupling reactions (cf. Scheme 3).

In order to probe Cu^{II}-catalyzed C–H oxidation reactions of less biased substrates, we turned our attention to the reactivity of *N*-benzoyl-8-aminoquinoline (**3**).[27] The amidoquinoline directing group was pioneered by Daugulis in Pd-catalyzed C–H functionalization reactions[28] and has been used more recently by a number of researchers in Cu-catalyzed C–H functionalization reactions.[29,30] Cu^{II}-mediated reactions of amidoquinoline substrate **3** led to different products depending on the identity of the Cu^{II} source and the reaction conditions (Scheme 7). The use of CuCl/LiCl in AcOH led to

Scheme 7. Divergent Reactivity in Cu^{II}-Mediated C–H Oxidation of 3[27]



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chlorination of the quinoline ring, whereas use of $Cu(OAc)_2$/Cs_2CO_3/pyridine in methanol led to *ortho* methoxylation of the *N*-benzoyl aromatic ring. These observations and subsequent studies provided unique insights into mechanisms of Cu^{II}-mediated C−H oxidation reactions.

The two reactions show very different kinetic isotope effects (KIEs). An intermolecular competition KIE of 1.04 ± 0.05 was determined for chlorination of the quinoline ring. This observation resembles a KIE of 1.0 noted by Yu and coworkers in the aerobic Cu-catalyzed halogenation of 2-phenylpyridine, for which a SET mechanism was proposed.[12a] In contrast, a KIE of 5.7 ± 0.8 was obtained from a comparison of independent rates of methoxylation of the *N*-benzoyl-h_5 versus -d_5 substrates. This observation was interpreted as evidence for organometallic C−H activation as the rate-determining step of the reaction. Hammett analysis of 4-substituted benzoyl groups provided further support for the organometallic mechanism (Figure 5). The data revealed that

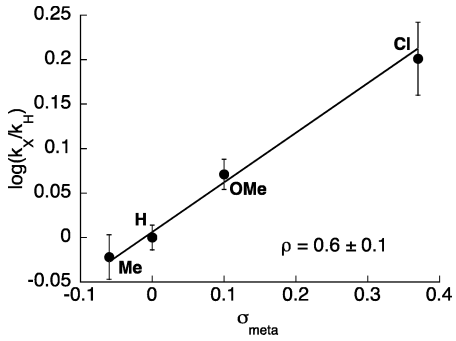
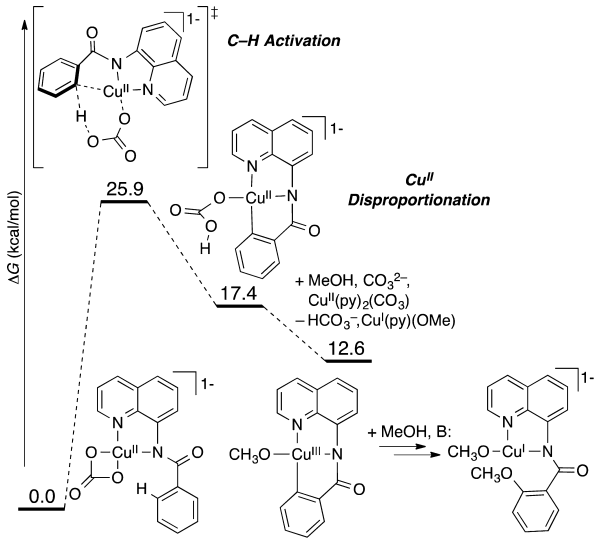


Figure 5. Hammett plot for methoxylation of the benzoyl moiety. Reproduced from ref 27. Copyright 2013 American Chemical Society.

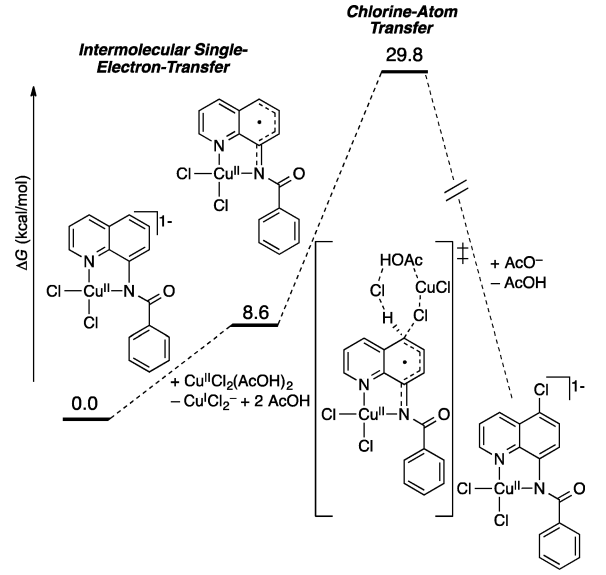
C−H bonds of less electron-rich aryl rings (i.e., more acidic C−H bonds) react more rapidly, reflecting an electronic trend opposite to that expected as expected from an SET-based mechanism. DFT calculations, performed in collaboration with Ertem and Cramer,[27] provided support for a concerted metalation−deprotonation mechanism in which formation of the aryl-Cu^{II} intermediate proceeds via carbonate-assisted cleavage of the arene C−H bond (Scheme 8). Subsequent formation of an aryl-Cu^{III} species arises from a quasi-disproportionation step involving oxidation of the aryl-Cu^{II} species by a different Cu^{II} species. The functionalized product is then formed via C−O reductive elimination from a downstream five-coordinate aryl-Cu^{III} intermediate.[27]

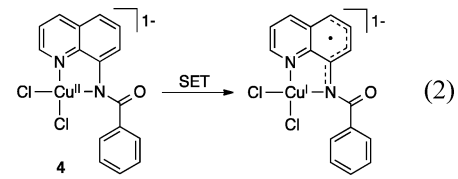
DFT studies of the chlorination reaction show that the SET step involves oxidation of the (8-amidoquinoline)-Cu^{II} species by a second Cu^{II} species, analogous to the Cu^{II} disproportionation step in the organometallic mechanism (cf. Scheme 8). In the chlorination reaction, however, this step favors oxidation of the amidoquinoline fragment rather than the Cu^{II} center (Scheme 9). The intermolecular SET (free energy of +8.6 kcal/mol) is calculated to be significantly favored over intramolecular SET from the amidoquinoline to the Cu^{II} center to which it is coordinated (+31.4 kcal/mol; eq 2). The strongly donating amidate ligand stabilizes Cu^{II} and significantly lowers the reduction potential of the Cu^{II} center, thereby disfavoring the intramolecular SET process in eq 2. Chlorination of the arene radical (or radical cation, if represented in a zwitterionic formulation) resulting from intermolecular SET was found to proceed via chlorine-atom transfer from another equivalent of

Scheme 8. Key Steps in the Simplified Calculated Mechanism of the Cu^{II}-Mediated Benzamide C−H Methoxylation Reaction[27]



Scheme 9. Key Steps in the Mechanism of the Cu^{II}-Mediated Quinoline C−H Chlorination Reaction[27]





(2)

$CuCl_2$, assisted by chloride and an equivalent of acetic acid (Scheme 9).

The results of this study are noteworthy for the insights they provide into the switch between the SET and organometallic C−H activation pathways. DFT studies showed that the reduction potentials of Cu^{II} species present under the acidic chlorination conditions are nearly 1 V higher than those of Cu^{II} species under the basic methoxylation conditions (Scheme 10). Thus, the basic carbonate ligand not only participates in the organometallic arene C−H activation step (cf. Scheme 8) but

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Scheme 10. Computed Reduction Potentials for the Lowest-Energy Species in the Cu^{II}-Mediated Chlorination and Methoxylation Reactions in Scheme 7[27]

A) Chlorination Reaction

$Cu^{II}Cl_2(AcOH)_2 \xrightarrow{+\ e^-} Cu^{I}Cl_2^- + 2\ AcOH$

E(V) vs. NHE = **+ 0.18**

High Cu^{II} Reduction Potential
Favors ***SET Mechanism***

B) Methoxylation Reaction

$Cu^{II}(py)_2CO_3 + CH_3OH \xrightarrow{+\ e^-} Cu^{I}(py)(OCH_3) + py + HCO_3^-$

E(V) vs. NHE = **– 0.80**

Low Cu^{II} Reduction Potential + Basic Ligand
Favors ***Organometallic Mechanism***

also stabilizes Cu^{II} and Cu^{III}, reducing the tendency of Cu^{II} to initiate SET reactivity and facilitating access to the aryl-Cu^{III} intermediate. In contrast, weak ligands (Cl^-, AcOH) and acidic reaction conditions destabilize Cu^{II} and promote SET reactivity.

Collectively, the studies outlined in this and the previous section highlight the accessibility of both SET and organometallic reaction pathways in aerobic Cu^{II}-catalyzed C–H oxidation reactions. The two mechanisms exhibit obvious differences, but they also share a number of common features. In both cases, two Cu^{II} species participate in the two-electron oxidation reaction, and the role of O_2 is to regenerate Cu^{II} via oxidation of Cu^{I}. In the examples described in this section, the first Cu^{II} center activates the substrate via formation of a Cu^{II}–substrate adduct, and the second Cu^{II} center oxidizes this intermediate. In the SET pathway, the oxidation step removes an electron from the electron-rich aromatic ring, while in the organometallic pathway, the oxidation step removes an electron from the metal center, converting an organo-Cu^{II} species to an organo-Cu^{III} species. The oxidized intermediates in both pathways are then susceptible to carbon–heteroatom bond formation, via either atom transfer (SET) or reductive elimination (organometallic). The nature of the substrate as well as the catalyst and reaction conditions dictate the favored reaction pathway.

5. CU/NITROXYL-CATALYZED ALCOHOL OXIDATION REACTIONS

The oxidation of alcohols to carbonyl compounds is one of the most widely used oxidation reactions in organic chemistry, and Cu-catalyzed aerobic alcohol oxidation reactions have emerged as some of the most practical methods for effecting these transformations.[9] The acidic nature of the O–H bond in alcohols enables relatively facile formation of a Cu^{II}–alkoxide, but pathways for two-electron oxidation of the bound alkoxide are not especially clear. The most versatile methods reported to date employ nitroxyl radicals as redox-active organic cocatalysts to facilitate the 1 H^+/2 e^- process associated with conversion of an alkoxide ligand to a carbonyl compound. In this section, we summarize our recent contributions to development and mechanistic characterization of Cu/nitroxyl catalysts of this type.

Earlier work in our lab had been focused on homogeneous Pd-catalyzed aerobic alcohol oxidation reactions. A collaborative effort with Eli Lilly to develop scalable methods for this chemistry revealed several limitations of these methods, including catalyst instability, relatively low rates, and limited functional group tolerance.[31] A subsequent literature search suggested that Cu/2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) catalyst systems had the potential to address these limitations,[32] and initial empirical studies led to the discovery of a highly practical method for chemoselective aerobic oxidation of primary alcohols to aldehydes (Figure 6).[33] The catalyst

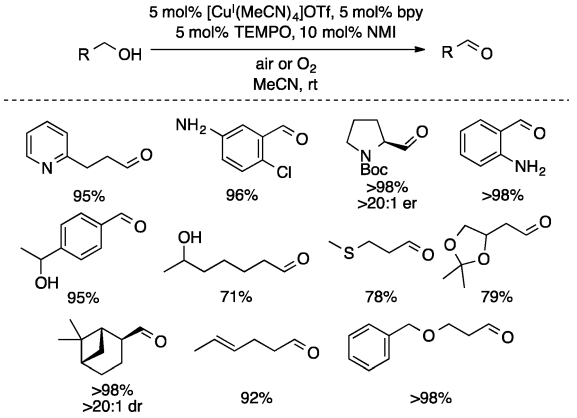
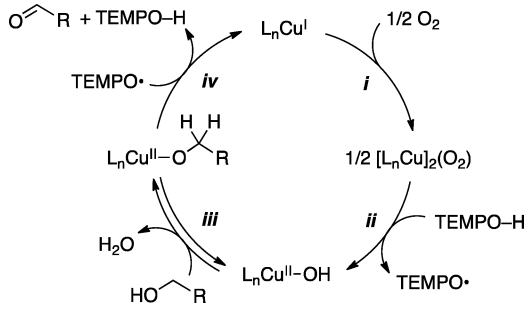


Figure 6. Aerobic oxidation of primary alcohols with bpy/Cu^{I}/NMI/TEMPO.[33]

consisted of an inexpensive copper(I) salt, [Cu(MeCN)$_4$]OTf, and TEMPO. Use of a Cu^{I} source, especially with non-coordinating anions, leads to significantly faster rates than use of a Cu^{II} source. Efficient reactivity was observed with a wide range of primary alcohols bearing diverse functional groups, in many cases at room temperature using ambient air as the source of oxidant.

The unique reactivity and practical utility of this new Cu/TEMPO catalyst system prompted us to explore the mechanism of the catalytic reaction.[34,35] Stoichiometric reactivity studies showed that both Cu^{II} and TEMPO participate in the alcohol oxidation step, and aerobic oxidation of Cu^{I} and TEMPO–H affords Cu^{II} and TEMPO. The origin of the superior reactivity of Cu^{I} relative to Cu^{II} catalyst sources can be attributed to the formation of a Cu^{II}–OH species in the aerobic oxidation step. The basic hydroxide ligand can react with the alcohol to afford the Cu^{II}–alkoxide intermediate in the substrate oxidation half-reaction (Scheme 11). Benzylic and other activated alcohols react more rapidly and show no kinetic dependence on [alcohol] or [TEMPO]. A kinetic dependence on [Cu] and [O_2] in these reactions suggests that aerobic oxidation of the Cu catalyst (step *i*) is the turnover-limiting

Scheme 11. Mechanism of (bpy)Cu/TEMPO-Catalyzed Alcohol Oxidation[34]



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step of the reaction. Aliphatic alcohols react more slowly than activated alcohols, and they exhibit a saturation dependence on [alcohol] and a first-order dependence on [TEMPO]. These data are consistent with pre-equilibrium formation of a Cu^{II}–alkoxide species followed by turnover-limiting hydrogen transfer to TEMPO (steps *iii* and *iv*).

The insights from these mechanistic studies provided a foundation to address two limitations of the (bpy)Cu/TEMPO/NMI catalyst system: (1) oxidations of unactivated aliphatic alcohols are significantly slower than those of activated alcohols, and (2) secondary alcohols are unreactive. While the latter feature can lead to highly chemoselective oxidation of primary alcohols even in the presence of unprotected secondary alcohols, it limits the reaction scope.[33] Both limitations were overcome by replacing TEMPO with a less hindered bicyclic nitroxyl such as 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) or ketoABNO. This change significantly enhances the rate of aliphatic alcohol oxidation and also enables efficient oxidation of secondary alcohols.[36,37] The optimized Cu/ABNO catalyst system shows excellent reactivity with a broad range of activated and aliphatic primary and secondary alcohols, including those bearing diverse functional groups and stereocenters adjacent to the product aldehyde group (Figure 7).

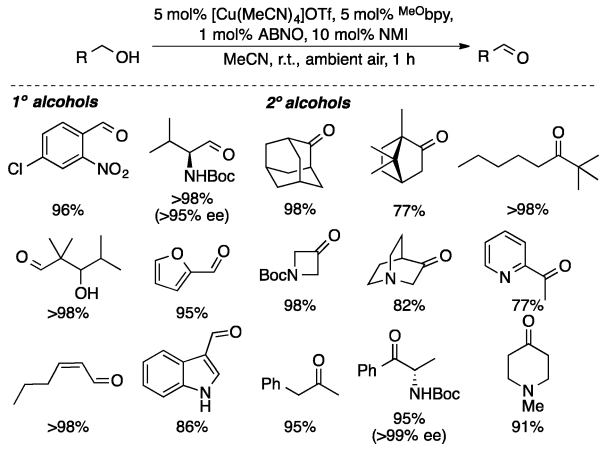


Figure 7. Cu/ABNO catalyst system that is effective with diverse primary and secondary alcohols under ambient conditions.[36]

Whereas the Cu/TEMPO catalyst system shows significantly different rates for different classes of alcohols (i.e., 1° benzylic > 1° aliphatic/2° benzylic ≫ 2° aliphatic and/or sterically hindered 2° benzylic), the Cu/ABNO catalyst system exhibits nearly identical rates with all classes of alcohols (Figure 8).

These catalysts bear a resemblance to the active site of galactose oxidase, which features a Cu^{II} center and phenoxyl radical ligand (Figure 9).[6] In a recent mechanistic study, however, we showed that the mechanisms of Cu/nitroxyl- and galactose oxidase-catalyzed alcohol oxidations are different.[38] For example, a series of radical-clock substrates undergo alcohol oxidation to the corresponding carbonyl compounds with no evidence for radical intermediates, which have been implicated in galactose oxidase. DFT studies provided numerous additional insights, including the basis for the substantially different reactivities with the TEMPO and ABNO cocatalysts.

Three different mechanisms for oxidation of the alkoxide ligand were evaluated in our DFT studies (Scheme 12): bimolecular H-atom transfer, H-atom transfer to an η^2-nitroxyl ligand, and hydrogen transfer to an η^1-nitroxyl ligand. The last

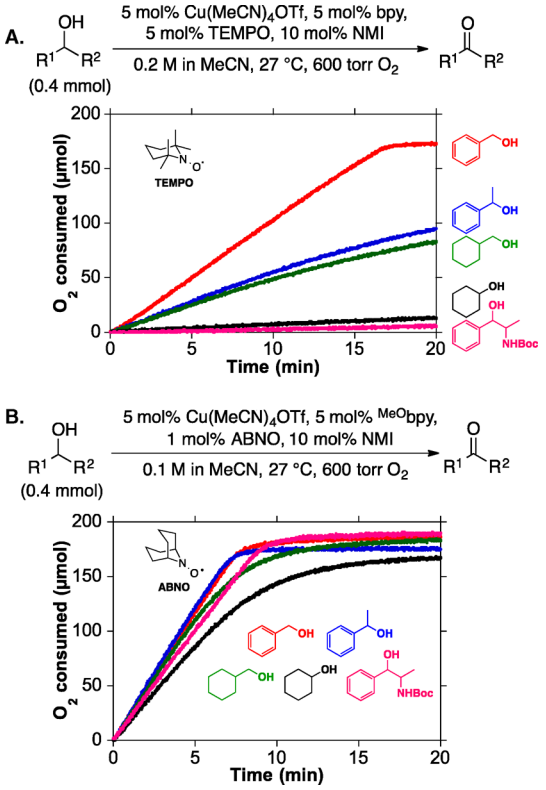


Figure 8. Rate comparison of five different alcohols with the Cu^{I}/TEMPO and Cu^{I}/ABNO alcohol oxidation systems. Adapted from ref 36. Copyright 2013 American Chemical Society.

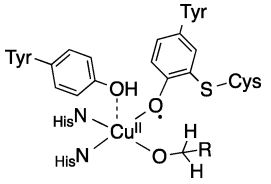
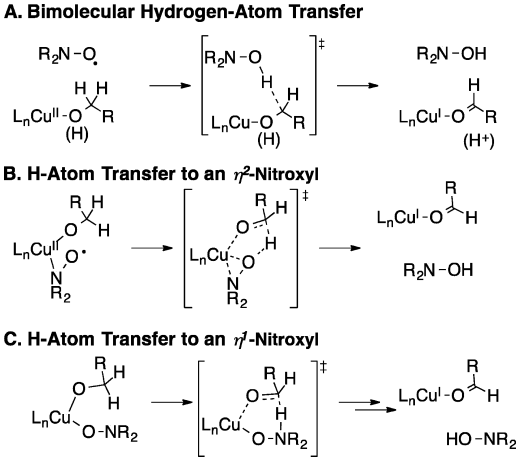


Figure 9. Active-site structure of galactose oxidase.

Scheme 12. Mechanistic Proposals for Cu^{II}/Nitroxyl-Mediated Alcohol Oxidation



mechanism (Scheme 12C) exhibits the lowest-energy pathway for alcohol oxidation, rationalizes the observed selectivity for primary over secondary alcohol oxidation, and accounts for the bimolecular [Cu]·[TEMPO] kinetic dependence of the

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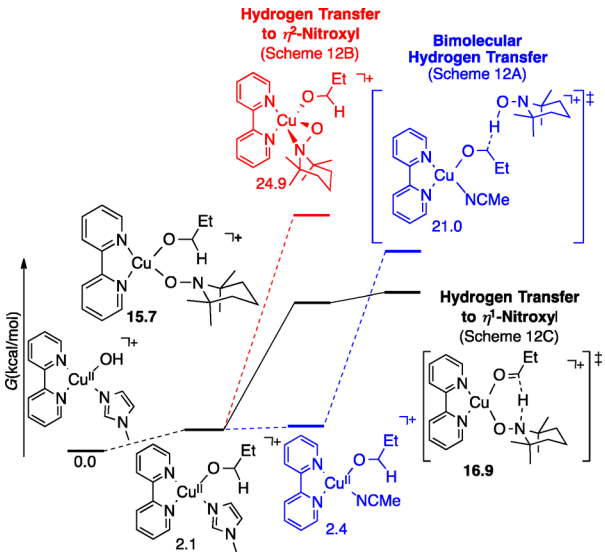
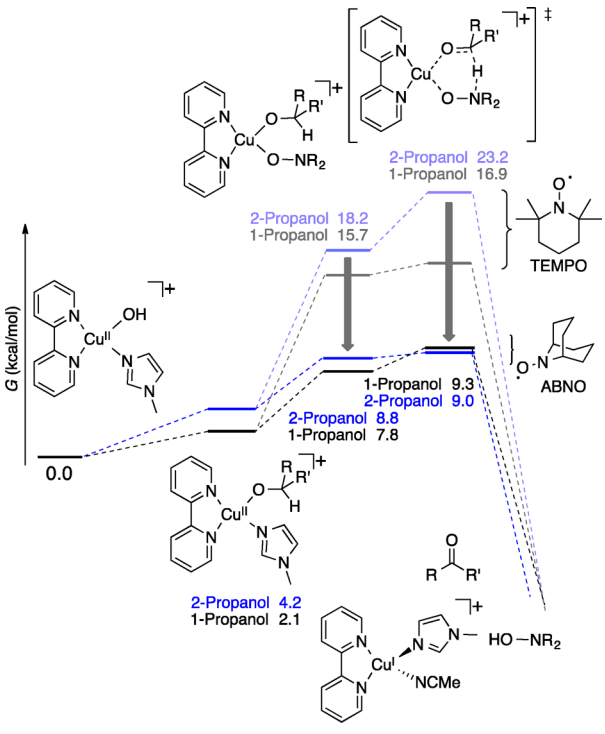
Scheme 13. Potential Energy Surface for Cu/TEMPO-Mediated Alcohol Oxidation[38]



reaction (Scheme 13, black pathway). Hydrogen transfer from the alkoxide to the η^1-nitroxyl is the highest point on the energy surface (i.e., the rate-limiting step), but formation of the η^1-nitroxyl–Cu adduct is the most significant contribution to the overall energy barrier (Scheme 13).

A comparison of the energy profiles for Cu/TEMPO- and Cu/ABNO-mediated alcohol oxidation provides clear insights into the enhanced activity and broader scope observed with the Cu/ABNO catalyst system (Scheme 14). The η^1-nitroxyl–Cu adduct with ABNO is stabilized by ~8 kcal/mol relative to the analogous TEMPO adduct. The C–H bond-cleavage transition state is also much lower in energy for ABNO relative to TEMPO, and the ABNO transition-state energies exhibit virtually no distinction between primary and secondary alcohols, as observed experimentally (cf. Figure 8B). In contrast, the difference between the TEMPO transition-state energies for the oxidations of 1- and 2-propanol is >6 kcal/mol (Scheme 14).

Scheme 14. Comparison of Computed Reaction Pathways for Cu/TEMPO- and Cu/ABNO-Mediated Oxidation of 1-Propanol and 2-Propanol[38]



Recently we have exploited insights gained from these studies to develop four-electron oxidation reactions, including oxidative lactonization of diols via sequential oxidation of a primary alcohol followed by oxidation of an intermediate hemiacetal,[39] sequential dehydrogenation of primary amines to nitriles,[40] and oxidative coupling of primary alcohols and ammonia to nitriles (Figure 10).[40] These results complement numerous recent contributions by other groups in this area.[41]

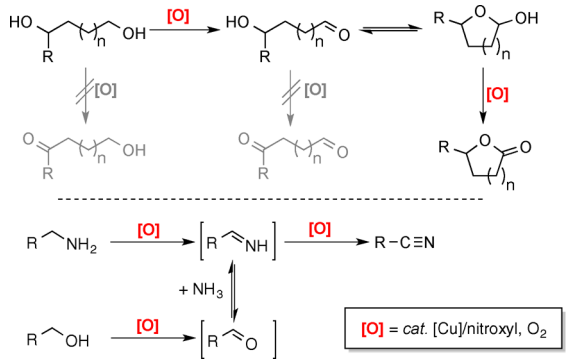


Figure 10. Cu/nitroxyl-catalyzed four-electron aerobic oxidation reactions for the preparation of lactones and nitriles.[39,40]

6. CONCLUSION

Cu-catalyzed aerobic oxidation reactions exhibit significant potential for the selective oxidation of organic substrates. These reactions not only avoid the use of precious metals but also exhibit a number of advantages over aerobic oxidation reactions catalyzed by precious metals. For example, the C–H oxidations and boronic acid oxidative coupling reactions described above can use O_2 as the stoichiometric oxidant, while many analogous Pd-catalyzed reactions require oxidants other than O_2 (e.g., $PhI(OAc)_2$, Ag^I salts, etc.). The Cu/nitroxyl-catalyzed aerobic alcohol oxidations show much higher activity and functional group compatibility than analogous reactions catalyzed by precious-metal catalysts. These characteristics are undoubtedly linked to the weaker metal–ligand bonds and increased kinetic lability of first-row transition metals relative to second- and third-row transition metals. Continued mechanistic characterization of Cu-catalyzed aerobic oxidation reactions should provide a foundation for the development of new chemical transformations that exploit the unique reactivity patterns evident in these systems, wherein coupled one-electron redox partners (Cu^{II}/Cu^{II} or Cu^{II}/organic cocatalyst) combine to achieve efficient and selective two-electron oxidation of organic molecules.

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Notes

The authors declare no competing financial interest.

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Shannon S. Stahl is a a Professor of Chemistry at the University of Wisconsin-Madison. He was an undergraduate at the University of Illinois at Urbana–Champaign and subsequently attended Caltech (Ph.D., 1997), where he was an NSF Predoctoral Fellow with Prof. John E. Bercaw. From 1997 to 1999, he was an NSF Postdoctoral Fellow with Prof. Stephen J. Lippard at MIT.

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