Published in final edited form as:

J Am Chem Soc. 2018 December 05; 140(48): 16625–16634. doi:10.1021/jacs.8b08748.

Catalytic Aerobic Oxidation of Alcohols by Copper Complexes Bearing Redox-Active Ligands with Tunable H-Bonding Groups

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Abstract

In this research article, we describe the structure, spectroscopy, and reactivity of a family of copper complexes bearing bidentate redox-active ligands that contain H-bonding donor groups. Single-crystal X-ray crystallography shows that these tetracoordinate complexes are stabilized by intramolecular H-bonding interactions between the two ligand scaffolds. Interestingly, the Cu complexes undergo multiple reversible oxidation—reduction processes associated with the metal ion (Cu^I, Cu^{II}, Cu^{III}) and/or the *o*-phenyldiamido ligand (L²⁻, L^{•-}, L). Moreover, some of the Cu^{II} complexes catalyze the aerobic oxidation of alcohols to aldehydes (or ketones) at room temperature. Our extensive mechanistic analysis suggests that the dehydrogenation of alcohols occurs via an unusual reaction pathway for galactose oxidase model systems, in which O₂ reduction occurs concurrently with substrate oxidation.

Graphical Abstract

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b08748.

Synthetic, experimental and computational details, Figures S1—S50, Schemes S1—S2, and Tables S1—S59 (PDF)

CIF file for 5_Me2_Ph_CuII_DMA (CIF)

CIF file for 5_Me2_Ph_CuII_DMF (CIF)

CIF file for PhEt_CuII (CIF)

CIF file for PhPh_CuII_DMA (CIF)

CIF file for PhPh_CuII_DMF (CIF)

CIF file for S_MeBz_PhPh_CuII (CIF)

CIF file for 5_Me2_Ph_CuII (CIF)

CIF file for tBuEt_CuII (CIF)

CIF file for tBuPh_CuII_DMA (CIF)

CIF file for tBuPh_CuII_DMF (CIF)

The authors declare no competing financial interest.

1. INTRODUCTION

Enzymatic machinery carries out important chemical transformations. The active sites of these enzymes usually combine bioavailable metal ions (Fe, Cu, Mn, Zn) with natural ligands (N, O, and S donors) that sometimes are able to accept and/or supply electrons during catalysis (e.g., porphyrin π -cation radical in Cmpd-I in Cyt. P450).^{1,2} In most cases, the primary and secondary coordination spheres surrounding the metal center are highly structured due to the presence of H-bonding interactions that provide unique properties to these metal complexes such as fast e^- transfer rates (e.g., entatic state of blue Cu proteins) and control of the reductive reactivity of $M-O_2$ species (e.g., heterolytic O—O cleavage in Cyt P450).^{3–5} In this research paper, we combined these three features (i.e., first row metal, redox-active ligands, and H-bonds) to synthesize a family of complexes with unusual structure and reactivity (Figure 1).

The ligand scaffolds used in this article are based on pioneering research by Holm, Gray, and Wieghardt, where it was established that metal complexes bearing α -phenyl-enediamido derivative ligands (L^{2-}) can undergo multiple oxidation—reduction processes.⁶ These redox transformations can be metal-centered (e.g., $Cu^I/Cu^{II}/Cu^{III}$) and/or ligand-centered, in which the diamido scaffold (L^{2-}) can be oxidized to the α -benzosemiquinonediiminato radical ($L^{\bullet-}$) and α -benzoquinonediimine (L) forms (see Figure 1).⁷ Metal complexes bearing redox-active ligands catalyze a wide variety of important chemical transformations including H_2O oxidation,⁸ C—C coupling reactions,⁹ $[2 + 2]$ cycloaddition reactions,¹⁰ and H_2 formation,¹¹ among others.^{12–14}

We functionalized the 1,2-phenylenediamido moiety with ureanyl groups (see $tBuPhL^{2-}$ in Figure 1), a strategy developed by Borovik and co-workers to stabilize metal-oxo and metal-hydroxo complexes via intramolecular H-bonding interactions.^{15,16} Systematic variations of

the ureanyl system allowed us to tune the properties of these H bonds. The tetracoordinate metal complexes derived from these bidentate scaffolds are stabilized by H-bonding interactions between the two ligands (ureanyl H and N) and between the ureanyl H and the metal center, which have been described as intramolecular multicenter hydrogen bonds (or bifurcated hydrogen bonds; see Figure 3).^{17–19}

Interestingly, some of the copper complexes catalyze the oxidation of alcohols to aldehydes at room temperature (galactose oxidase-like reactivity²⁰) using O₂ as sole oxidant and without using additives (most Cu-based catalytic systems require the use of base and/or nitroxyl cocatalysts).^{21,22} The mechanism by which the Cu complexes perform this oxidation is studied in detail, and our findings point toward a mechanistic scenario that is unprecedented for galactose oxidase model systems.²³

2. RESULTS AND DISCUSSION

2.1. Synthesis and Characterization of Ligand Scaffolds and Metal Complexes.

The bidentate diamido-ureanyl ligands (LH₂) were synthesized in one step by reacting commercially available diamines with isocyanates (Figure 2).¹⁷ The ligands were isolated as white powders in good yields (see Supporting Information, SI, for details on synthesis and characterization).

In the glovebox, deprotonation of the ligand scaffolds (LH₂) with 2 equiv of KH in DMA (DMA: dimethylacetamide) followed by addition of 0.5 equiv of Cu^{II}(OAc)₂ led to the formation of complexes formulated as [Cu^{II}(L²⁻)₂](K)₂(DMA)₄ (Figure 2B, see SI for details).¹⁷ The metal complexes were characterized by different spectrometric and spectroscopic means including elemental analysis, single-crystal X-ray crystallography, NMR (i.e., ¹H NMR for diamagnetic complexes), EPR, UV–vis, and FT-IR spectroscopy (see SI). It is worth mentioning that metal complexes bearing the reduced form of *o*-phenylenediamino ligands are scarce.²⁴

Crystalline samples of the Cu compounds were analyzed by single-crystal X-ray crystallography (Figure 3A, see also SI). The molecular structure of the copper complexes was dependent on the ligand and solvent used in crystallization, adopting square-planar (*D*_{4h}) or twisted pseudotetrahedral (*D*_{2d}) geometries.¹ We observed that some of the Cu complexes can adopt both geometries, *D*_{4h} and *D*_{2d}, by changing the solvent of crystallization (Figure 3A): *D*_{4h} in DMF (*t*BuPhCu^{II}_{DMF}, orange crystals) and *D*_{2d} in DMA (*t*BuPhCu^{II}_{DMA} purple crystals). On the other hand, Ph-4,5-Me₂-Ph-Cu^{II} adopted the *D*_{2d} geometry in both solvents (see SI).

From the structural analysis of this family of meta complexes (Cu complexes included in this paper, unpublished crystal structures²⁵ and the *t*BuEtFe^{II}, *t*BuEtNi^{II}, *t*BuEtCo^{II}, and *t*BuEtZn^{II} structures previously reported by Borovik¹⁷) we can extract some general trends. We observed H-bonding interactions between the ureanyl H α' and the Na atoms of the other ligand and some weak interactions between the ureanyl H α' and the metal center, an intramolecular multicenter fashion (Figure 3B).^{18,26,27} We found that these H-bonding interactions are dependent on the geometry of the complex: for square-planar complexes

(twist-angle, $\alpha_{TW} = 0$) short $Na...Ha'$ ($\sim 2.1\text{--}2.3$ Å) and long $M...Ha'$ distance; ($\sim 2.3\text{--}2.9$ Å) are observed, which systematically varied upon increase of α_{TW} to generally longer $Na-Ha'$ ($\sim 2.3\text{--}2.8$ Å) and shorter $M...Ha'$ ($\sim 2.6\text{--}2.9$ Å) distances (Figure 3B).

Our current efforts are focused on having a deeper understanding of the effect of the ligand (diamine and ureany group), metal, and crystallization solvent that will eventually allow us to predict the geometry and H-bonding interaction upon modification of the metal complex systems. To the best of our knowledge, this is one of the first reports in which changes in the H-bonding interactions led to a deep impact on the geometry and chemical properties (vide infra) of the derived copper complexes.²⁸

2.2. Redox Chemistry of Copper Complexes.

2.2.1. Cyclic Voltammetry.—Electrochemical characterization of the copper(II) complexes was carried out in CH_3CN (Figure 4, see also SI). We observed that the copper(II) systems underwent multiple redox processes at relatively low potentials (see table in Figure 4). For example, **tBuPhCu^{II}** was reversibly oxidized at -0.58 V, -0.34 V, and -0.20 V (red cyclic voltammogram in Figure 4). These redox processes are assigned as the formation of three high-valent oxidation states that are associated with the oxidation of the metal center and/or the oxidation of the ligand scaffold (**tBuPhCu^{II}** is described as **tBuPhCu^{O.S.2}**, and its high-valent oxidation states are **tBuPh-Cu^{O.S.3}**, **tBuPhCu^{O.S.4}** and **tBuPhCu^{O.S.5}**, in which an electron is successively removed from the system with each increase in n , O.S. n).

The redox chemistry of **PhPhCu^{II}** was also analyzed by CV measurements (Figure 4, blue cyclic voltammogram). When compared with **tBuPhCu^{II}**, the electron-withdrawing properties of the phenyl ureanyl substituents shifted the oxidation of the **PhPhCu^{II}** to **PhPhCu^{O.S.3}** to higher potentials (-0.58 V for **tBuPhCu** and -0.19 V for **PhPhCu**) but also allowed for observing the reduction of **PhPhCu^{II}** ($E_{1/2}^{O.S.1/O.S.2} = -1.58$ V). The redox processes associated with the formation of **PhPhCu^{O.S.4}** and **PhPhCu^{O.S.5}** were found to be irreversible. We speculate that this irreversibility might be associated with the increased acidity of the Ha' in **PhPhCu**, which might trigger an intramolecular proton transfer (from the Ha' to the Na) with concomitant release of the Cu ion during the generation of **PhPhCu** high-valent species.²⁹

The electrochemistry of the **(S)-MeBzPhCu^{II}** complex was similar to the **PhPhCu^{II}** and **tBuPhCu^{II}** analogues, with four redox processes (one reduction and three oxidations) at higher potentials than the ones found for **tBuPhCu^{II}** but lower than the ones observed for **PhPhCu^{II}**, which is consistent with the donating ability of the methyl-benzyl ureanyl group (i.e., less donating than **tBu** but more donating than **Ph**). We also obtained the CV data for the Cu complexes bearing the 4,5-dimethyl-1,2-phenyldiamido ligands (**tBu-4,5-Me2-PhCu^{II}** and **Ph-4,5-Me2-PhCu^{II}**). The electrochemical behavior of these systems is analogous to the corresponding 1,2-phenyldiamido systems with the redox couples shifted to lower potentials ($E_{1,2} \approx -0.1$ V), which accounts for the stronger donating ability of the 4,5-dimethyl-1,2-phenyldiamido backbone (see SI).

With all the electrochemical data in hand, we conclude that the strong donating ability of the ligands used (dianionic ligands) leads to very low reduction potentials (i.e., Cu^I oxidation state is highly destabilized) and relatively low oxidation potentials. The capacity of the ligand scaffolds to stabilize the square-planar geometries might suggest that the first oxidation process is metal centered (i.e., formation of [(L²⁻)₂Cu^{III}]⁻ with d⁸ electronic configuration stabilized for D_{4h} geometries), but the formulation of the O.S.3 species as a Cu^{II} center bound by an *o*-benzosemiquinonediminato radical ligand ([L²⁻](L^{•-})Cu^{II})]⁻ should not be discarded. Similarly, O.S.4 and O.S.5 could be formulated as square-planar Cu^{III} species bound by one and two oxidized ligand-radical scaffolds, respectively, or as Cu^{II} complexes with two radical-ligand scaffolds for O.S.4 ([L^{•-})₂Cu^{II})] and a cupric center coordinated to a ligand-radical and an *o*-benzoquinonedimine ligand for O.S.5 ([L^{•-})(L)Cu^{II}]⁺). Based on the spectroscopic characterization of some of the high-valent species and DFT calculations (see sections below), we favor the former formulations (i.e., ligand-based oxidations and D_{2d} geometry).³⁰ Interestingly, we observed that changes in the ureanyl substituent for complexes with the same backbone like in **tBuPhCu^{II}** and **PhPhCu^{II}** led to remarkable changes in the *E*_{1/2} (*E*_{1/2}^{O.S.3/O.S.2} ~ 0.4 V!) compared to the ones found when the 1,2-phenyldiamido backbone is substituted by the 4,5-dimethyl-1,2-phenyldiamido (**tBuPhCu^{II}** vs **tBu-4,5-Me₂-PhCu^{II}**,

$$E_{1/2}^{\text{O.S.3/O.S.2}} \sim -0.1 \text{ V}).$$

2.2.2. Generation and Characterization of High-Valent Oxidation States Using

1e⁻ Oxidants.—Reaction of **tBuPhCu^{II}** ([Cu] = 0.25 mM) with ferrocenium (FcPF₆, Fc⁺) was followed by UV-vis in DMF at -55 °C (Figure 5). Titration experiments showed that 1 equiv of Fc⁺ was required to convert **tBuPhCu^{O.S.2}** (purple spectrum, λ_{max}: 511 nm, ε = 1500 M⁻¹ cm⁻¹) to **tBuPhCu^{O.S.3}** (blue spectrum, λ_{max}: 535 nm, ε = 6000 M⁻¹ cm⁻¹). The **tBuPhCu^{O.S.3}** species could also be oxidized to **tBuPhCu^{O.S.4}** (red spectrum, λ_{max}: 707 nm, ε = 9200 M⁻¹ cm⁻¹) by addition of 1 equiv of Fc⁺. Further oxidation to **tBuPhCu^{O.S.5}** (black spectrum, λ_{max}: 657 nm, ε = 9600 M⁻¹ cm⁻¹) was observed by addition of another equiv of Fc⁺. Further addition of Fc⁺ decomposed **tBuPhCu^{O.S.5}** to produce a species at 375 nm (yellow spectrum), which we believe is an oxidation product derived from an unknown process. To our surprise, the generation of **tBuPhCu^{O.S.3}**, **tBuPhCu^{O.S.4}**, and **tBuPhCu^{O.S.5}** was reversible. After generation of **tBuPhCu^{O.S.5}** by addition of 3 equiv of Fc⁺, stepwise addition of 3 equiv of CoCp₂ cleanly regenerated **tBuPhCu^{O.S.4}**, **tBuPhCu^{O.S.3}**, and **tBuPhCu^{O.S.2}** consecutively. The data obtained in these oxidation/reduction experiments using 1e⁻ reactants (i.e., FcPF₆, CoCp₂) are in agreement with the cyclic voltammetry experiments for **tBuPhCu^{II}** (described above) in which three reversible oxidation processes were observed at -0.58 V, -0.34 V, and -0.20 V. These reversibility experiments using external 1e⁻ reactants are unusual for complexes with redox-active ligands, and it highlights the unique stereoelectronic structure of the compounds described in this research article.³¹

The high-valent oxidation states for **tBuPhCu** were also characterized by EPR spectroscopy (Figure 5, bottom right). Addition of 1 equiv of FcPF₆ to **tBuPhCu^{II}** (DMF, -55 °C) led to the disappearance of the EPR features of the cupric complex (*g*_⊥ = 2.05, *g*_{||} = 2.21, *A*_{||} = 154 G), in agreement with the formation of **tBuPhCu^{O.S.3}** (silent in perpendicular mode EPR and

consistent with the formation of a species in a singlet or triplet state). Addition of a second equivalent of Fc^+ produced $\text{tBuPhCu}^{\text{O.S.4}}$ with concomitant appearance of an EPR signal at $g = 1.99$ (red EPR spectrum in Figure 5). These results are consistent with the formulation of $\text{tBuPhCu}^{\text{O.S.4}}$ as a copper(II) complex bound by two α -benzosemiquinonediminato radical ligands, in which the metal ion and the ligand radicals are antiferromagnetically coupled ($S = 1/2$ ground state, $\uparrow/\downarrow/\uparrow$) due to the nonplanar geometry (i.e., D_{2d} geometry).^{24,32} Addition of 1 equiv of Fc^+ to $\text{tBuPhCu}^{\text{O.S.4}}$ quenched the EPR signal, suggesting the formation of $\text{tBuPhCu}^{\text{O.S.5}}$ (silent in perpendicular mode EPR, species with $S = 0$ or $S = 1$ ground state).

2.3. Galactose-Oxidase-Like Catalytic $2\text{H}^+/2\text{e}^-$ Oxidation of Alcohols with O_2 at Room Temperature.

2.3.1. Catalytic Oxidation of Alcohols: Performance and Scope.—We envisioned that the ability of the Cu complexes to stabilize various oxidation states via oxidation of the metal and/or the ligand scaffold would allow for galactose-oxidase-like catalytic oxidation of alcohols (Figure 6, see SI for details). All the Cu complexes were tested for the catalytic oxidation of benzyl alcohol to benzaldehyde using O_2 as oxidant (entries 1–10 in Figure 6). We observed that the complexes able to generate high-oxidation states (see CV experiments above) at lower potentials (e.g., tBuPhCu) performed the catalytic oxidation with very good reaction yields (90–96%). On the other hand, the Cu complexes that were oxidized at higher potentials and that led to irreversible oxidations (e.g., PhPhCu) did not catalyze the oxidation of benzyl alcohol very efficiently (reaction yields between 0 and 30%). Interestingly, $\text{tBuPhCu}^{\text{II}}$ performed the dehydrogenation of benzyl alcohol under low catalyst loadings (down to 0.1 mol %, see entries 1–4 in Figure 6) and reached remarkable turnover numbers (TNs up to 184).

The oxidation of other alcohol substrates with O_2 was also conducted using $\text{tBuPhCu}^{\text{II}}$ as catalyst (entries 11–17 in Figure 6). We obtained excellent yields in the oxidation of substrates with weak C—H bonds and acidic O—H bonds such as diphenylmethanol (PhBzOH , 85%), benzoin (99%), and cinnamyl alcohol (CinnOH , 85%). In contrast, substrates with stronger C—H bonds (e.g., cyclohexanol, CyOH) and slightly more basic O—H bonds (e.g., 1-phenyl ethanol, MeBzOH) were not oxidized, or poor reaction yields were observed.

2.3.2. Catalytic Oxidation of Alcohols: Mechanistic Studies.—In order to determine the reaction mechanism by which the copper complexes perform the catalytic oxidation of alcohols, we studied the kinetics of the reaction under different catalyst, benzyl alcohol, and dioxygen concentrations (Figure 7). The reaction rates for the formation of benzaldehyde were first-order dependent on the concentration of catalyst and first-order dependent on the concentration of BzOH . On the other hand, we observed that the reaction rates were independent of the concentration of O_2 (i.e., zero-order dependence). We also studied the rates for the oxidation of benzyl alcohol- d_7 (deuterated in the benzylic and phenyl positions with a nondeuterated O—H moiety), which were compared with the rates obtained for the nondeuterated substrate to obtain a kinetic isotope effect (KIE) of 6.5.

With these kinetic results (and the computational studies described below), we propose the reaction mechanism depicted in Figure 7. Reaction between the Cu^{II} complex and O₂ forms a Cu^{II}—superoxide intermediate (species B in Figure 7) in which one of the ligand scaffolds provides the electron required to reduce dioxygen to superoxide. The substrate then coordinates (species C in Figure 7) before undergoing oxidation in the rate-determining step (r.d.s.) via intramolecular H atom transfer. We propose that this first 1H⁺/1e[−] oxidation event generates a Cu—peroxide intermediate (i.e., Cu—superoxide is reduced to Cu—peroxide) in which one of the ligands has accepted a proton from the substrate (species D in Figure 7). A second 1H⁺/1e[−] transfer forms the dehydrogenation product with concomitant generation of a Cu—hydroperoxide complex (species E in Figure 7). We suggest that in this second process the oxidized ligand scaffold accepts the electron from the substrate, and the proton is transferred to the peroxide. After product release, the Cu—hydroperoxide would deprotonate the ligand scaffold to form H₂O₂ and regenerate the active catalyst. The kinetic first-order dependence on the concentration of Cu complex and substrate is consistent with the proposed bimolecular process.³³ Our mechanism is also in agreement with the primary KIE observed, which implies that C–H bond cleavage occurs in the r.d.s. (H atom abstraction in species C). The zero-order dependence on O₂ concentration suggests that the coordination of O₂ to the Cu catalyst is not rate-limiting and that it probably occurs before the r.d.s.³⁴

According to the proposed mechanism, O₂ is reduced to H₂O₂ in the oxidation of alcohols. We quantified the H₂O₂ formed in the oxidation of BzOH using the Ti^{IV}/H₂SO₄ spectrophotometric titration method (see SI for experimental details).³⁵ We observed that H₂O₂ was not detected at any point of the reaction, which suggests that the Cu catalyst is able to perform the disproportionation of hydrogen peroxide. In fact, addition of H₂O₂ to a solution of **tBuPhCu** led to very fast decomposition of H₂O₂. When compared with the reaction yields obtained in the aerobic oxidation of benzyl alcohol under the same reaction conditions, the Cu-catalyzed decomposition of H₂O₂ was 3 orders of magnitude faster than the oxidation of the alcohol. Hence, detection of H₂O₂ in the Cu-catalyzed oxidation of benzyl alcohol was precluded.

Our mechanistic scenario also predicts that the Cu complexes can catalyze the reduction of O₂ to H₂O₂ and ultimately to H₂O, using external H⁺ and e[−] sources (i.e., external protons and electrons could be used to reduce O₂ to H₂O₂ instead of the alcohol substrate). In fact, addition of trifluoroacetic acid ([CF₃CO₂OH] = 2 mM), decamethylferrocene ([Me₁₀Fc] = 2 mM), and **tBuPhCu^{II}** to O₂-saturated DMF produced decamethyl ferrocenium, which was quantified by UV–vis (see SI). Interestingly, we observed quantitative oxidation of the e[−] source (yields up to 95%) in a short period of time using small amounts of catalyst ([**tBuPhCu^{II}**] = 0.02 mM). It is worth noting that Cu complexes able to catalyze the reduction of O₂ using relatively mild acids such as CF₃CO₂H are scarce.^{36,37}

We also compared the reaction rates obtained for three different substrates (benzyl alcohol, 1-phenyl ethanol, and dibenzyl methanol). We observed that the reaction rates for benzyl alcohol and dibenzyl methanol were similar (slightly faster for dibenzyl methanol), but the rate for 1-phenyl ethanol was an order of magnitude slower. This is in agreement with the proposed mechanism in which the C–H bond cleavage is rate-determining (dibenzyl

methanol has the weakest C–H bond). The slower reaction rates observed for 1-phenyl ethanol might be contradictory with our mechanistic proposal (i.e., benzylic C–H bond in 1-phenyl ethanol weaker than in benzyl alcohol), but other factors such as the greater steric hindrance and higher pK_a for 1-phenyl ethanol might also affect the kinetics of the reaction (e.g., substrate coordination step).³⁸

Lastly, we compared the reaction rates for the different Cu complexes using benzyl alcohol as substrate (Figure 8C, (iv)). We found that the Cu compounds capable of stabilizing high-oxidation states at lower redox potentials (e.g., **tBu-4,5-Me2-phCu**) performed the oxidation of the alcohol at higher catalytic rates. This is consistent with the proposed reaction mechanism since Cu complexes bearing strong donor ligands should favor the formation of high-valent copper species (e.g., species B–D in Figure 7), which would accelerate the overall catalytic rate.

2.4. Computational Studies.

2.4.1. Geometry and Electronic Structure of the **tBuPhCu** in the Different Oxidation States.

DFT calculations were conducted to gather insight into the structure and electronics of the **tBuPhCu** in the different oxidation states (Figure 8). For **tBuPhCu^{O.S.2}**, DFT predicted that the D_{2d} geometry is more stable than the D_{4h} , in agreement with experimental data obtained for **tBuPhCu^{II}** (e.g., UV–vis and EPR spectroscopy, see SI). When compared with the structures obtained by single-crystal X-ray crystallography (**tBuPhCu^{II}DMF**, **tBuPhCu^{II}DMA**), similar Cu...N_α, C_{Ar}...C_{Ar}, and N...C_{Ar} distances were obtained computationally. We observed a slight increase in the twist angle (α_{TW}) for the DFT structure of **tBuPhCu^{O.S.2}_{D2d}** and shorter intramolecular multicenter H-bonding interactions (N_α...H α' , Cu...H α') for both D_{4h} and D_{2d} geometries, which might account for the constraints imposed by the crystal lattice in the solid state. Like in the crystal structures, we computed shorter N_α...H α' distances for the square-planar geometry (~0.2 Å) and shorter Cu...H α' distances for the distorted tetrahedral geometry (~0.1 Å).

Like in **tBuPhCu^{O.S.2}**, all the high-valent species (**tBuPhCu^{O.S.3}**, **tBuPhCu^{O.S.4}**, and **tBuPhCu^{O.S.5}**) favored the D_{2d} geometry over the D_{4h} geometry ($E(D_{2d} - D_{4h}) = -4.9, -18.6, \text{ and } -29.4 \text{ kcal/mol}$). We observed that oxidation of **tBuPhCu^{O.S.2}_{D2d}** to **tBuPhCu^{O.S.3}_{D2d}** and **tBuPhCu^{O.S.4}_{D2d}** entailed elongation of the C_{Ar}...C_{Ar} distance (from 1.44 to 1.45 Å and 1.47 Å) and decrease of the N_α...C_{Ar} distances (from 1.39 to 1.37 Å and 1.35 Å), which is consistent with oxidation of the diamido scaffold (L^{2-}) to the *o*-benzosemiquinonediiminato radical form ($L^{\bullet-}$).^{6,24} The spin density plots (Figure 8, bottom) provide insight into the electronic structures of **tBuPhCu** in the different oxidation states. We observed that oxidation of **tBuPhCu^{O.S.2}** to **tBuPhCu^{O.S.3}** and **tBuPhCu^{O.S.4}** caused the delocalization of the spin density from the Cu and Na to the aromatic backbones (Figure 8, bottom). The spin state calculated for **tBuPhCu^{O.S.4}_{D2d}** is in agreement with the EPR measurements (see above), which suggested that this species is a Cu^{II} center bound by two *o*-benzosemiquinonediiminato radicals that are antiferromagnetically coupled with the Cu^{II} ion ($S = 1/2, \uparrow/\downarrow/\uparrow$).^{24,32}

We also computed the structural changes upon conversion of ${}^{\text{tBuPh}}\text{Cu}^{\text{O.S.4}}_{D_{2d}}$ to ${}^{\text{tBuPh}}\text{Cu}^{\text{O.S.5}}_{D_{2d}}$. After oxidation, spin density plots indicated no density in the ligand scaffolds or in the metal center. We also observed a significant increase in the $\text{C}_{\text{Ar}}\dots\text{C}_{\text{Ar}}$ distances for both ligand scaffolds, which suggested the formation of two diimine ligands (L). Analysis of the occupation of the d orbitals is consistent with a Cu^{I} metal ion. Thus, we tentatively formulate ${}^{\text{tBuPh}}\text{Cu}^{\text{O.S.5}}_{D_{2d}}$ as a copper(I) center bound by two diimine ligands $[\text{Cu}^{\text{I}}(\text{L})_2]^+$. However, other formulations such as $[\text{Cu}^{\text{II}}(\text{L}^{\bullet-})(\text{L})]^+$ or $[\text{Cu}^{\text{II}}(\text{L}^{\bullet-})_2]^+$ are also possible, and additional spectroscopic and computational analysis is required to establish the formulation of ${}^{\text{tBuPh}}\text{Cu}^{\text{O.S.5}}_{D_{2d}}$.

2.4.2. Catalytic Oxidation of Alcohols: Computational Analysis.—The mechanism by which ${}^{\text{tBuPh}}\text{Cu}^{\text{II}}$ performs the aerobic dehydrogenation of benzyl alcohol was also studied computationally (Figure 9). We calculated that the reaction between ${}^{\text{tBuPh}}\text{Cu}^{\text{II}}$ and O_2 generates a Cu-superoxide species (${}^{\text{tBuPh}}\text{Cu}^{\text{O.S.3}}\text{-O}_2^{\bullet-}$) in which one of the ligand scaffolds is oxidized to a ligand radical (elongation of $\text{C}_{\text{Ar}}\dots\text{C}_{\text{Ar}}$ and decrease of $\text{Na}\dots\text{C}_{\text{Ar}}$ in only one of the ligands; see SI). The computed O—O distance is also characteristic of an end-on Cu—superoxide core (O...O: 1.33 Å). We observed that this Cu— O_2 adduct was stabilized via a H-bonding interaction between the Ha' and the proximal oxygen of the superoxide.

We found that the addition of BzOH to the computed ${}^{\text{tBuPh}}\text{Cu}^{\text{O.S.3}}\text{-O}_2^{\bullet-}$ structure stabilized a Cu-superoxide substrate adduct (${}^{\text{tBuPh}}\text{Cu}^{\text{O.S.3}}\text{-O}_2^{\bullet-}\text{-PhCH}_2\text{OH}$), in which the substrate interacts with the Cu— O_2 core via H-bonding between the H of the alcohol moiety and the proximal oxygen of the superoxide. This arrangement is critical for substrate oxidation since it directs the benzylic H atom of the substrate toward the Na that will accept the proton from the substrate. During the transition state (TS1), the benzylic H atom is transferred from the substrate to the Cu-superoxide complex in which the proton is transferred to the Na and the electron is transferred to the superoxide moiety. The energy of TS1 is the highest along the calculated reaction pathway, in agreement with our experimental kinetic data, which indicates that H atom abstraction occurs during the r.d.s. (i.e., primary KIE and first-order kinetics for substrate and catalyst concentration).

The intermediate derived from this first oxidation event is formulated as a substrate—radical Cu^{II} —peroxide complex bound by a protonated ligand (LH^-) and α -benzosemiquinonediiminato radical ($\text{L}^{\bullet-}$). This is supported by the calculated $\text{C}_{\text{Ar}}\dots\text{C}_{\text{Ar}}$ and $\text{Na}\dots\text{C}_{\text{Ar}}$ distances (longer $\text{C}_{\text{Ar}}\dots\text{C}_{\text{Ar}}$ and shorter $\text{Na}\dots\text{C}_{\text{Ar}}$ for $\text{L}^{\bullet-}$) as well as an increase in the O—O distance, indicative of reduction of the superoxide to peroxide (from 1.33 to 1.46 Å). We calculated that a second one-step H^+/e^- transfer event generates the benzaldehyde product with concomitant reduction of the α -benzosemiquinonediiminato radical and protonation of the Cu-peroxide core. The resulting ${}^{\text{tBuPh}}\text{Cu}^{\text{OS3-H}^+}\text{-O}_2\text{H-PhCHO}$ intermediate releases H_2O_2 via deprotonation of the ligand scaffold, which entails rotation of the Cu— O_2H (via formation of ${}^{\text{tBuPh}}\text{Cu}^{\text{O.S.3-H}^+}\text{-O}_2\text{H-PhCHO-(2)}$). The activation energies for both reaction steps (rotation and H_2O_2 formation) are very small ($G^\ddagger \sim 1$ kcal/mol).

2.5. Mechanistic Discussion.

Like in the proposed catalytic cycle for galactose oxidase, most mechanisms of GAO model systems separate the reduction of O₂ (to generate H₂O₂) and the oxidation of the substrate in a so-called ping-pong mechanism (Figure 10A).^{39,40} In the Cu/bpy/NMI/TEMPO catalytic system reported by Stahl, the data suggested that O₂ reduction led to the formation of a Cu^{II}—alkoxide species before intramolecular H atom abstraction of the substrate via generation of a Cu—alkoxide—TEMPO complex.^{22,41} Stack and co-workers reported that a Cu complex bearing a tetradentate redox-active ligand (^{N2O2}LCu) was oxidized by O₂ to generate an (^{N2O2}L)Cu^{II}—OOH intermediate which reacted with benzyl alcohol to release H₂O₂ and to produce an (^{N2O2}L)Cu^{II}—alkoxide species before intramolecular H atom abstraction of the substrate (Figure 10B).²⁰ In contrast, in our system, we propose that the reduction of O₂ and the oxidation of the substrate occur simultaneously, in which both O₂ and redox-active ligands cooperatively accept the H⁺ and e[−] derived from substrate oxidation (Figure 10B, bottom). We initially considered a mechanistic scenario similar to those in previous reports in which our Cu complexes reached high-valent oxidation states, for example, **tBuPhCu^{O.S.2}** to **tBuPhCu^{O.S.4}**, by reducing O₂ and releasing H₂O₂ via deprotonation of the alcohol to produce a **tBuPhCu^{O.S.4}**—alkoxide intermediate before substrate oxidation. To test this hypothesis, we generated **tBuPhCu^{O.S.4}** (by reacting **tBuPhCu^{II}** with 2 equiv of FcPF₆ at −55 °C in DMF, see Figure 5), and we added 10 equiv of deprotonated benzyl alcohol (PhCH₂O[−]) under anaerobic conditions (see SI for details). The spectral features of **tBuPhCu^{O.S.4}** decayed very fast (5–10 s), but no benzaldehyde product was observed when the crude reaction was analyzed. Similar reactivity was observed in the reaction between **tBuPhCu^{O.S.3}** or **tBuPhCu^{O.S.5}** and PhCH₂O[−] (i.e., fast decay but no substrate oxidation). This differs with the results described by Stack and co-workers in which anaerobic oxidation of the copper complexes using 1e[−] oxidants led to the catalytic oxidation of PhCH₂OLi to benzaldehyde and implies that in our Cu systems both O₂ and redox-active ligands are required for alcohol oxidation.⁴²

3. CONCLUSIONS AND PERSPECTIVES

In this article, we described one of the first literature examples in which intramolecular H-bonding interactions in Cu complexes could be finely tuned.^{28,43} We showed that modification of these H-bonds led to variations in the geometry of the Cu complexes and in the capacity of these compounds to reach multiple oxidation states. Interestingly, one of the copper complexes (**tBuPhCu^{II}**) could be reversibly oxidized to three higher oxidation states using external 1e[−] reagents. The unique stereoelectronic structure of the Cu complexes, able to provide electrons during catalysis via oxidation of the ligand scaffold and to stabilize Cu—O₂ species via H-bonding interactions, is key to explaining their distinct reactivity in the catalytic dehydrogenation of alcohols. We envision that the synergy between the redox-active ligand and the intramolecular H-bonds might also lead to unexpected reactivity in other Cu-catalyzed biologically relevant transformations (e.g., catalytic reduction of O₂, oxygenation of C—H bonds, phenol oxidation, etc.) but also in oxidative functionalization reactions beyond metalloenzymatic activity (e.g., organometallic cross-coupling reactions, C—H functionalization, etc.). These kinds of reactivity are currently under investigation in our lab.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank the Robert A. Welch Foundation (grant N-1900 to I.G.B.) and the National Institutes of Health (NIH award number R15GM128078 to I.G.B.) for financial support. Prof. Swart thanks MINECO (CTQ2017-87392-P and CTQ2015-70851-ERC to M.S.), Gen-Cat (2014SGR1202 to M.S.), and FEDER (UNGI10-4 $\times 10^{-801}$ to M.S.). We thank Prof. Pia Vogel (Dept. of Biology at Southern Methodist University) for help with the EPR measurements.

REFERENCES

- (1). Solomon EI; Heppner DE; Johnston EM; Ginsbach JW; Cirera J; Qayyum M; Kieber-Emmons MT; Kjaergaard CH; Hadt RG; Tian L Copper Active Sites in Biology. *Chem. Rev.* 2014, 114, 3659. [PubMed: 24588098]
- (2). Costas M; Mehn MP; Jensen MP; Que L Dioxygen activation at mononuclear nonheme iron active sites: Enzymes, models, and intermediates. *Chem. Rev.* 2004, 104, 939. [PubMed: 14871146]
- (3). Shaik S; Cohen S; Wang Y; Chen H; Kumar D; Thiel W P450 Enzymes: Their Structure, Reactivity, and Selectivity — Modeled by QM/MM Calculations. *Chem. Rev.* 2010, 110, 949. [PubMed: 19813749]
- (4). Rittle J; Green MT Cytochrome P450 Compound I: Capture, Characterization, and C-H Bond Activation Kinetics. *Science* 2010, 330, 933. [PubMed: 21071661]
- (5). Borovik AS Bioinspired Hydrogen Bond Motifs in Ligand Design: The Role of Noncovalent Interactions in Metal Ion Mediated Activation of Dioxygen. *Acc. Chem. Res.* 2005, 38, 54. [PubMed: 15654737]
- (6). Ray K; Petrenko T; Wieghardt K; Neese F Joint spectroscopic and theoretical investigations of transition metal complexes involving non-innocent ligands. *Dalton Trans* 2007, 1552. [PubMed: 17426855]
- (7). Broere DLJ; Plessius R; van der Vlugt JI New avenues for ligand-mediated processes — expanding metal reactivity by the use of redox-active catechol, o-aminophenol and o-phenylenediamine ligands. *Chem. Soc. Rev.* 2015, 44, 6886. [PubMed: 26148803]
- (8). Garrido-Barros P; Funes-Ardoiz I; Drouet S; Benet-Buchholz J; Maseras F; Llobet A Redox Non-innocent Ligand Controls Water Oxidation Overpotential in a New Family of Mononuclear Cu-Based Efficient Catalysts. *J. Am. Chem. Soc.* 2015, 137, 6758.
- (9). van der Meer M; Rechkemmer Y; Peremykin I; Hohloch S; van Slageren J; Sarkar B (Electro)catalytic C-C bond formation reaction with a redox-active cobalt complex. *Chem. Commun.* 2014, 50, 11104.
- (10). Chirik PJ; Wieghardt K Radical Ligands Confer Nobility on Base-Metal Catalysts. *Science* 2010, 327, 794. [PubMed: 20150476]
- (11). Matsumoto T; Chang H-C; Wakizaka M; Ueno S; Kobayashi A; Nakayama A; Taketsugu T; Kato M Nonprecious- Metal-Assisted Photochemical Hydrogen Production from ortho-Phenylenediamine. *J. Am. Chem. Soc.* 2013, 135, 8646. [PubMed: 23544498]
- (12). Lyaskovskyy V; de Bruin B Redox Non-Innocent Ligands: Versatile New Tools to Control Catalytic Reactions. *ACS Catal* 2012, 2, 270.
- (13). Kaim W Manifestations of Noninnocent Ligand Behavior. *Inorg. Chem.* 2011, 50, 9752. [PubMed: 21744793]
- (14). Luca OR; Crabtree RH Redox-active ligands in catalysis. *Chem. Soc. Rev.* 2013, 42, 1440. [PubMed: 22975722]
- (15). Cook SA; Borovik AS Molecular Designs for Controlling the Local Environments around Metal Ions. *Acc. Chem. Res.* 2015, 48, 2407. [PubMed: 26181849]
- (16). Borovik AS Role of metal-oxo complexes in the cleavage of C-H bonds. *Chem. Soc. Rev.* 2011, 40, 1870. [PubMed: 21365079]

- (17). MacBeth CE; Larsen PL; Sorrell TN; Powell D; Borovik AS A bidentate ligand with appended hydrogen bond donors:: synthesis and structure of four-coordinate metal complexes with bis[(tert-butyl)aminocarbonyl]-1,2-diaminoethane. *Inorg. Chim. Acta* 2002, 341, 77.
- (18). Braga D; Grepioni F; Tedesco E; Biradha K; Desiraju GR Hydrogen Bonding in Organometallic Crystals. 6. X—H—M Hydrogen Bonds and M—(H—X) Pseudo-Agostic Bonds. *Organometallics* 1997, 16, 1846.
- (19). Steiner T The Hydrogen Bond in the Solid State. *Angew. Chem., Int. Ed.* 2002, 41, 48.
- (20). Wang Y; DuBois JL; Hedman B; Hodgson KO; Stack TDP Catalytic Galactose Oxidase Models: Biomimetic Cu(II)-Phenoxyl-Radical Reactivity. *Science* 1998, 279, 537. [PubMed: 9438841]
- (21). Marko IE; Giles PR; Tsukazaki M; Brown SM; Urch CJ Copper-Catalyzed Oxidation of Alcohols to Aldehydes and Ketones: An Efficient, Aerobic Alternative. *Science* 1996, 274, 2044. [PubMed: 8953027]
- (22). Hoover JM; Ryland BL; Stahl SS Mechanism of Copper(I)/TEMPO-Catalyzed Aerobic Alcohol Oxidation. *J. Am. Chem. Soc.* 2013, 135, 2357. [PubMed: 23317450]
- (23). Jazdzewski BA; Tolman WB Understanding the copper- phenoxyl radical array in galactose oxidase: contributions from synthetic modeling studies. *Coord. Chem. Rev.* 2000, 200–202, 633.
- (24). Khushniyarov MM; Harms K; Burghaus O; Sundermeyer J; Sarkar B; Kaim W; van Slageren J; Duboc C; Fiedler J A series of metal complexes with the non-innocent N,N'-bis(pentafluorophenyl)- o-phenylenediamido ligand: twisted geometry for tuning the electronic structure. *Dalton Trans* 2008, 1355. [PubMed: 18305848]
- (25). Note: A detailed analysis of 30 X-ray structures of Fe, Co, Ni, Cu, and Zn complexes bearing tunable bidentate ureanyl ligand scaffolds will be published elsewhere.
- (26). Jeffrey GA; Maluszynska H; Mitra J Hydrogen bonding in nucleosides and nucleotides. *Int. J. Biol. Macromol* 1985, 7, 336.
- (27). Natale D; Mareque-Rivas JC The combination of transition metal ions and hydrogen-bonding interactions. *Chem. Commun.* 2008, 425.
- (28). Dahl EW; Kiernicki JJ; Zeller M; Szymczak NK Hydrogen Bonds Dictate O₂ Capture and Release within a Zinc Tripod. *J. Am. Chem. Soc.* 2018, 140, 10075. [PubMed: 30074788]
- (29). Note: The irreversibility observed in the electrochemistry of PhPhCu could also be due to other structural changes in the ligand scaffold upon oxidation/protonation such as ureanyl rearrangement. See: Hill EA; Weitz AC; Onderko E; Romero-Rivera A; Guo Y; Swart M; Bominaar EL; Green MT; Hendrich MP; Lacy DC; Borovik AS Reactivity of an FeIV-Oxo Complex with Protons and Oxidants. *J. Am. Chem. Soc.* 2016, 138, 13143. [PubMed: 27647293]
- (30). Note: Kaim and co-workers observed a similar redox behavior, in which a Cu bissemiquinonato complex reached 5 oxidation states via oxidation/reduction of the ligand scaffolds. See ref 32.
- (31). Chaudhuri P; Verani CN; Bill E; Bothe E; Weyhermueller T; Wieghardt K Electronic Structure of Bis(o- iminobenzosemiquinonato)metal Complexes (Cu, Ni, Pd). The Art of Establishing Physical Oxidation States in Transition-Metal Complexes Containing Radical Ligands. *J. Am. Chem. Soc.* 2001, 123, 2213. [PubMed: 11456867]
- (32). Ye S; Sarkar B; Lissner F; Schleid T; van Slageren J; Fiedler J; Kaim W Three-Spin System with a Twist: A Bis(semiquinonato)copper Complex with a Nonplanar Configuration at the Copper(II) Center. *Angew. Chem., Int. Ed.* 2005, 44, 2103.
- (33). Note: use of higher amounts of substrate might lead to Michaelis-Menten saturation kinetics, which was not observed under our experimental conditions ([BzOH] = 1 mM–50 mM).
- (34). Hoover JM; Ryland BL; Stahl SS Copper/TEMPO-Catalyzed Aerobic Alcohol Oxidation: Mechanistic Assessment of Different Catalyst Systems. *ACS Catal.* 2013, 3, 2599. [PubMed: 24558634]
- (35). Garcia-Bosch I; Company A; Frisch JR; Torrent-Sucarrat M; Cardellach M; Gamba I; Gell M; Casella L; Que L Jr.; Ribas X; Luis JM; Costas M O₂ Activation and Selective Phenolate ortho Hydroxylation by an Unsymmetric Dicopper μ -[1,1'-bis(2,2,6,6-tetramethyl-3,5-pyridinediyl)]²⁺- Peroxido Complex. *Angew. Chem., Int. Ed.* 2010, 49, 2406.
- (36). Fukuzumi S; Kotani H; Lucas HR; Doi K; Suenobu T; Peterson RL; Karlin KD Mononuclear Copper Complex- Catalyzed Four-Electron Reduction of Oxygen. *J. Am. Chem. Soc.* 2010, 132, 6874. [PubMed: 20443560]

- (37). Kakuda S; Rolle CJ; Ohkubo K; Siegler MA; Karlin KD; Fukuzumi S Lewis Acid-Induced Change from Four- to Two- Electron Reduction of Dioxygen Catalyzed by Copper Complexes Using Scandium Triflate. *J. Am. Chem. Soc.* 2015, 137, 3330. [PubMed: 25659416]
- (38). Ryland BL; McCann SD; Brunold TC; Stahl SS Mechanism of Alcohol Oxidation Mediated by Copper(II) and Nitroxyl Radicals. *J. Am. Chem. Soc.* 2014, 136, 12166. [PubMed: 25090238]
- (39). Whittaker JW Free radical catalysis by galactose oxidase. *Chem. Rev.* 2003, 103, 2347. [PubMed: 12797833]
- (40). Whittaker MM; Ballou DP; Whittaker JW Kinetic Isotope Effects as Probes of the Mechanism of Galactose Oxidase. *Biochemistry* 1998, 37, 8426. [PubMed: 9622494]
- (41). Walroth RC; Miles KC; Lukens JT; MacMillan SN; Stahl SS; Lancaster KM Electronic Structural Analysis of Copper(II)-TEMPO/ABNO Complexes Provides Evidence for Copper(I)-Oxoammonium Character. *J. Am. Chem. Soc.* 2017, 139, 13507. [PubMed: 28921958]
- (42). Wang Y; Stack TDP Galactose Oxidase Model Complexes: Catalytic Reactivities. *J. Am. Chem. Soc.* 1996, 118, 13097.
- (43). Bhadra M; Lee JYC; Cowley RE; Kim S; Siegler MA; Solomon EI; Karlin KD Intramolecular Hydrogen Bonding Enhances Stability and Reactivity of Mononuclear Cupric Superoxide Complexes. *J. Am. Chem. Soc.* 2018, 140, 9042. [PubMed: 29957998]

Figure 1.
Copper complexes with redox-active ligands and H-bonding interactions.

A. Ligands systems. **B. Synthesis of Cu complexes.** **Figure 2.**

Ligand systems included in this work (A) and synthesis of metal complexes (B). See SI for further details. Note: tBuEtCu^{II} was previously synthesized by Borovik and co-workers.¹⁷

A. X-Ray diffraction analysis. **B. Intramolecular multicenter hydrogen bonds.** **Figure 3.**

Single-crystal X-ray diffraction analyses of ^tBuPhCu^{II} (A) featuring intramolecular multicenter H bonds (B) (see also SI).

Figure 4.

Cyclic voltammetry experiments depicting the oxidation/reduction processes undergone by the copper complexes. Note: In the formation of O.S.3, O.S.4, and O.S.5 depicted in this figure, we only considered the oxidation of the ligand scaffold (see text for detailed explanations).

Notes:^a E in V vs. $Fc^{0/+}$. In parentheses, separation between anodic and cathodic peaks (in V).^b Measurements carried out in CH_3CN using $TBAPF_6$ as electrolyte with 1mM complex concentration and scan rate of 100 mV/s.

Figure 5.

Reversible oxidation/reduction of $\text{tBuPhCu}^{\text{II}}$ using ferrocenium hexafluorophosphate ($1e^-$ oxidant) and cobaltocene ($1e^-$ reductant). The formation of the high-valent oxidation species was carried out in DMF at -55°C and followed by UV-vis (including titration experiments) and EPR spectroscopy. Note: In titrations, $[\text{Cu}] = 0.25$ mM. In reversibility experiments, $[\text{Cu}] = 0.2$ mM.

Entry	Complex ^a	Substrate	Yield (%)	TN
1	tBuPhCu^{II}	BzOH	94	19
2	tBuPhCu^{II} (2%)	BzOH	99	50
3	tBuPhCu^{II} (1%)	BzOH	83	83
4	tBuPhCu^{II} (0.1%)	BzOH	18	184
5	PhPhCu ^{II}	BzOH	1	0
6	(S)-MeBzPhCu ^{II}	BzOH	41	8
7	tBu-4,5-Me2-PhCu^{II}	BzOH	99	20
8	Ph-4,5-Me2-PhCu ^{II}	BzOH	28	6
9	tBuEtCu ^{II}	BzOH	20	4
10	PhEtCu ^{II}	BzOH	39	8
11	tBuPhCu^{II}	MeBzOH	21	4
12	tBuPhCu^{II}	PhBzOH	85	17
13	tBuPhCu^{II}	Benzoin	99	20
14	tBuPhCu ^{II}	CyOH	6	1
15	tBuPhCu ^{II}	1-C ₆ OH	2	0
16	tBuPhCu^{II}	CinnOH	85	17
17	tBuPhCu ^{II}	2-Me-1-C ₅ OH	0	0

^a 5 mol% unless stated. ^b BzOH: benzyl alcohol; MeBzOH: 1-phenyl-ethanol; PhBzOH: diphenylmethanol; CyOH: cyclohexanol; CinnOH: cinnamyl alcohol; 1-C₆OH: 1-hexanol; 2-Me-1-C₅OH: 2-methyl-1-pentanol

Figure 6.

Catalytic dehydrogenation of alcohols catalyzed by the copper complexes. See SI for further details.

Figure 7.
Proposed mechanism for the Cu-catalyzed aerobic oxidation of alcohols based on mechanistic evidence.

	tBuPhCu ^{II} (X-ray)	tBuPhCu ^{0.S.2}	tBuPhCu ^{0.S.3}	tBuPhCu ^{0.S.4}	tBuPhCu ^{0.S.5}
	<i>D</i> _{2d} (<i>D</i> _{4h})	<i>D</i> _{2d} (<i>D</i> _{4h}) ^a	<i>D</i> _{2d} (<i>D</i> _{4h}) ^a	<i>D</i> _{2d} (<i>D</i> _{4h}) ^a	<i>D</i> _{2d} (<i>D</i> _{4h}) ^a
d(Cu...Nα) (Å) ^b	1.99 (1.99)	1.97 (2.01)	1.96 (1.93)	1.94 (1.94)
	d(Nα...Hα') (Å) ^b	2.23 (2.18)	2.11 (1.94)	2.19 (1.89)	2.46 (2.18)
	d(Cu...Hα') (Å) ^b	2.64 (2.76)	2.44 (2.58)	2.36 (2.61)	2.64 (2.57 ^c)
	d(Nα...C _{Ar}) (Å) ^b	1.40 (1.42)	1.39 (1.40)	1.38 (1.42)	1.35 (1.40 ^c)
	d(C _{Ar} ...C _{Ar}) (Å) ^b	1.42 (1.41)	1.44 (1.42)	1.45 (1.40)	1.47 (1.43)
	α _{TW} (°)	46 (0)	63 (0)	76 (0)	85 (10)
	ΔE (<i>D</i> _{2d} - <i>D</i> _{4h}) (Kcal/mol)	-	- 2.7	- 4.9	- 18.6
	S-2 (unpaired e ⁻)	-	0.75 (0.75)	2.00 (0.00)	0.00 (0.00)

Notes: ^aOptimized DFT structures. See S.I. for further details. ^bAverage distances. ^cUnsymmetric system with substantial differences in the distances (see S.I.).

Spin density plots:

Figure 8.

DFT calculations on the structure and electronics of the tBuPhCu system in the different oxidation states.

Figure 9. DFT calculations (Gibbs energy profile and optimized stationary points) for the aerobic oxidation of benzyl alcohol catalyzed by, $\text{tBuPhCu}^{\text{II}}$

A. Oxidation of alcohols by Galactose Oxidase (GAO). **B. Oxidation of alcohols by copper complexes***Stack and coworkers* *This work* **Figure 10.**

GAO catalytic cycle (A) and proposed mechanisms for the dehydrogenation of alcohols by selected synthetic Cu complexes (B).