

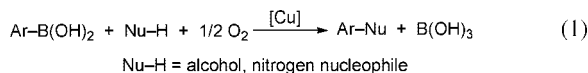
Mechanistic Study of Copper-Catalyzed Aerobic Oxidative Coupling of Arylboronic Esters and Methanol: Insights into an Organometallic Oxidase Reaction

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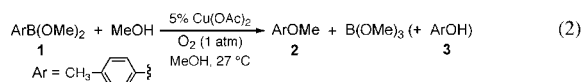
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Copper-catalyzed oxidative and nonoxidative coupling reactions have been known for more than a century. Prominent early examples include the Glaser coupling of terminal alkynes¹ and Ullmann–Goldberg cross-coupling reactions of aryl halides.² Among a wide range of new copper-catalyzed coupling reactions reported in recent years,³ one class with growing importance is the Cu-catalyzed oxidative coupling of boronic acids and heteroatom nucleophiles (eq 1), first reported by Chan, Evans, and Lam in 1998.⁴ These reactions typically employ milder reaction conditions than the analogous Ullmann–Goldberg reactions, and their applications have expanded significantly since the initial reports.^{3,5} Despite this utility, the reaction mechanism is not known and has never been the focus of systematic investigation. Insights into these reactions could have broad implications for Cu-catalyzed coupling reactions, including methods for aerobic oxidative functionalization of C–H bonds.⁶ In the present study, we elucidate key mechanistic features of these reactions, including the identity of the catalyst resting state and turnover-limiting step, and identify principles that underlie the ability of copper, a metal that tends to undergo one-electron redox changes, to mediate a two-electron oxidative coupling reaction with a four-electron oxidant (O₂).



The Chan–Evans–Lam (CEL) coupling reactions are compatible with a wide range of heteroatom nucleophiles, including amines, amides, nitrogen heterocycles, alcohols, and phenols. The Cu-catalyzed methoxylation of tolylboronic ester **1** (eq 2), performed under conditions inspired by those reported by Xie et al.,⁷ provided the basis for the studies described here. This reaction affords *p*-methylanisole (**2**) in 88% yield after 6 h; *p*-cresol (**3**) is obtained as a byproduct (12% yield).⁸ Mechanistic studies were carried out by performing the reaction in a sealed reaction vessel under an O₂ atmosphere, which enabled the reaction progress to be monitored by gas-uptake methods.⁹ Gas chromatography was used to monitor the organic reactants and products during the reaction.



Our initial studies focused on establishing features of the reaction stoichiometry. O₂ can serve as a two- or four-electron oxidant in Cu-catalyzed oxidation reactions. H₂O₂ is typically obtained as a byproduct in the former case.¹⁰ The quantities of O₂ consumed and product formed reflect a 1:2 stoichiometry (Figure 1A), demonstrating that O₂ serves as a four-electron oxidant.

Many of the early CEL oxidative coupling reactions employed Cu^{II} as a stoichiometric oxidant. These studies, however, did not establish whether Cu^{II} served as a one- or two-electron oxidant: the two-electron oxidative coupling reaction could involve a single Cu^{II} center that

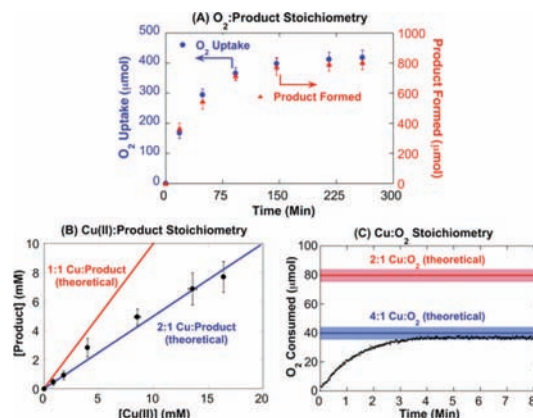
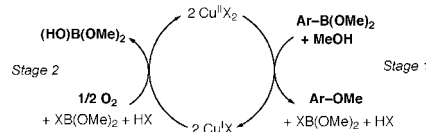


Figure 1. Analysis of reaction stoichiometry in Cu-catalyzed aerobic oxidative coupling of ArB(OMe)₂ and MeOH. See Supporting Information for details.

undergoes reduction to Cu⁰ or two Cu^{II} centers that are reduced to Cu^I. To address this issue, the methoxylation reaction was performed under rigorously anaerobic conditions, and the amount of product formed with respect to the initial [Cu^{II}] was quantified (Figure 1B). These experiments established that the Cu^{II}/product stoichiometry is 2:1, indicating that Cu^{II} serves as a one-electron oxidant. The Cu^I-containing solutions obtained from these experiments were then exposed to O₂, and gas-uptake measurements established that Cu^I reacts with O₂ in a 4:1 stoichiometry (Figure 1C).

The experiments outlined above, summarized in Figure 1, are consistent with an “oxidase”-style catalytic mechanism (Scheme 1)¹¹ that features two key stages: (1) oxidative coupling of the boronic ester and methanol mediated by 2 equiv of Cu^{II} and (2) oxidation of Cu^I to Cu^{II} by O₂. This mechanistic framework accommodates the experimentally observed 2:1 product/O₂, 2:1 Cu^{II}/product, and 4:1 Cu/O₂ stoichiometries.

Scheme 1. Oxidase-Style Mechanism for Cu-Catalyzed Aerobic Oxidative Coupling of Arylboronic Esters and Methanol



Kinetic data, acquired by monitoring initial rates of O₂-uptake, reveal a first-order dependence on [Cu(OAc)₂], a saturation dependence on [ArB(OMe)₂], and a zero-order dependence on [O₂] (Figure S1). These results indicate that reoxidation of Cu^I by O₂ (Scheme 1, Stage 1) is fast relative to the substrate oxidation sequence, and the kinetic dependence on [Cu(OAc)₂] and [ArB(OMe)₂] suggests that transmetalation of the aryl group to the copper center is the turnover-limiting step.

Additional insights into the catalytic mechanism were obtained from spectroscopic analysis of the reaction mixture. Aliquots of the solution

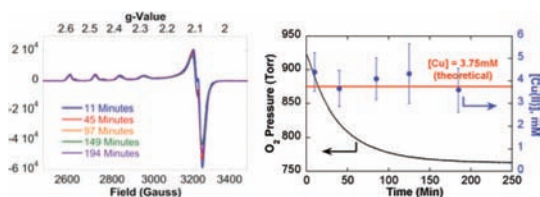
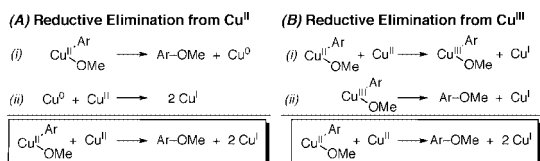


Figure 2. EPR spectra acquired during the reaction time course and analysis of the concentration of EPR-active Cu^{II} species present during the reaction.

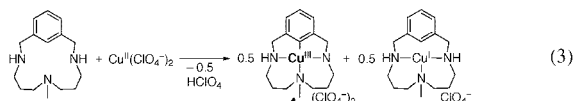
were analyzed by EPR spectroscopy (77 K), and the spectra exhibit a nearly axial EPR signal ($g_x = 2.09$, $g_y = 2.08$, $g_z = 2.40$, and $A_z = 375$ MHz). Integration of the signal indicates that essentially all of the copper in the reaction exists as EPR-active Cu^{II} (Figure 2).¹² These data suggest that the catalyst resting state consists of a Cu^{II} species with weak donor ligands. The lack of a strong-field aryl ligand is consistent with kinetic studies, which suggest that formation of an arylcopper(II) intermediate is the turnover-limiting step.

C–O bond formation occurs *after* the turnover-limiting step and, therefore, cannot be probed directly under the catalytic conditions. One mechanism proposed in the literature for C–O bond formation features direct reductive elimination of a C–O bond from Cu^{II} (Scheme 2A).¹³ For this mechanism to be consistent with the observed Cu^{II} /product stoichiometry (Figure 1B), the resulting Cu^0 would need to undergo comproportionation with Cu^{II} to produce 2 equiv of Cu^{I} (Scheme 2A, step *ii*). This mechanism is problematic, however, because the relative thermodynamic stabilities of Cu^0 , Cu^{I} , and Cu^{II} in methanol favor *disproportionation* of Cu^{I} into Cu^0 and Cu^{II} ,¹⁴ a phenomenon confirmed under catalytically relevant conditions.⁹

Scheme 2. Possible Carbon–Oxygen Bond Forming Pathways



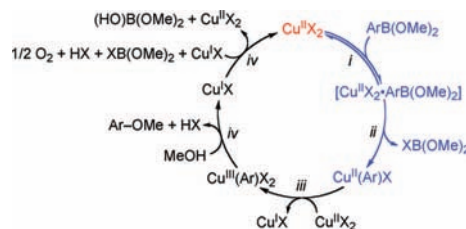
An alternative C–O bond-forming pathway features an identical reaction stoichiometry but proceeds via Cu^{III} (Scheme 2B). The arylcopper(II) intermediate is oxidized by another equivalent of Cu^{II} , forming an arylcopper(III) species that undergoes C–O reductive elimination. This mechanism finds a compelling analogy in recent studies by Ribas, Llobet, Stack et al., who reported a Cu^{II} -mediated C–H activation that results in formation of 0.5 equiv of an arylcopper(III) species (**4**) and 0.5 equiv of a Cu^{I} complex (eq 3).¹⁵ The arylcopper(III) species was proposed to form via oxidation of an arylcopper(II) intermediate by another equivalent of Cu^{II} , analogous to step *i* in Scheme 2B. The arylcopper(III) complex **4** has been shown to undergo facile carbon–heteroatom bond formation in the presence of O and N nucleophiles,¹⁶ including methanol,¹⁷ analogous to step *ii* in Scheme 2B.



The data and mechanistic considerations described above lead to the following proposed mechanism for Cu-catalyzed aerobic oxidative coupling of arylboronic esters and heteroatom nucleophiles (Scheme 3). The reaction is initiated by transmetalation of the aryl group from B to Cu^{II} (steps *i* and *ii*). The resulting arylcopper(II) species is oxidized by another equivalent of Cu^{II} to yield an arylcopper(III) intermediate (step *iii*) that can undergo facile C–O bond formation (step *iv*). Finally, rapid aerobic oxidation of Cu^{I} regenerates Cu^{II} , the resting state of the catalyst. This mechanism differs from Pd-oxidase mechanisms¹¹ in that it features both *one- and two-electron* redox steps. Additionally,

this mechanism provides a valuable framework for the consideration of other Cu-catalyzed aerobic oxidation reactions, including methods for the oxidative functionalization of C–H bonds.⁶ These “organometallic oxidase” reactions are mechanistically distinct from biomimetic oxygen-atom transfer (“oxygenase”) reactions, and they point toward significant opportunities for the development of synthetically useful methods for selective aerobic oxidation of organic molecules.

Scheme 3. Proposed Catalytic Mechanism



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Supporting Information Available: Experimental procedures, plots of kinetic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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