

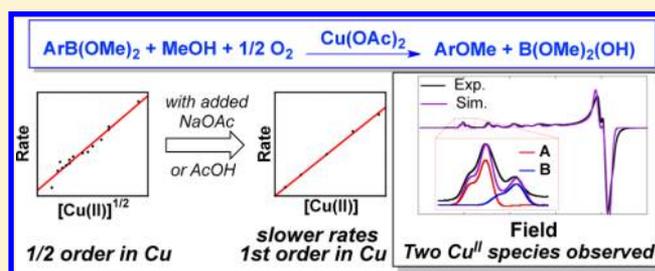
Kinetic and Spectroscopic Studies of Aerobic Copper(II)-Catalyzed Methoxylation of Arylboronic Esters and Insights into Aryl Transmetalation to Copper(II)

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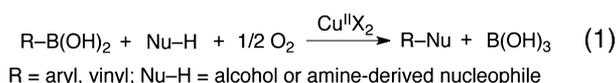
Supporting Information

ABSTRACT: We previously reported a preliminary mechanistic study of aerobic Cu(OAc)₂-catalyzed methoxylation of 4-tolylboronic ester (King et al. *J. Am. Chem. Soc.*, **2009**, *131*, 5044–5045), which revealed that aryl transmetalation from the boronic ester to Cu^{II} is the turnover-limiting step. In the present study, more thorough kinetic and spectroscopic studies provide additional insights into the transmetalation pathway and identity of the Cu^{II} catalyst resting state(s). EPR spectroscopic studies show that at least two copper(II) species are present under catalytic conditions, and their relative populations vary as a function of reaction time and acidity of the arylboronic ester and are influenced by addition of acetic acid or acetate to the reaction mixture. Analysis of kinetic data and ¹¹B NMR and EPR spectra under diverse reaction conditions suggests that aryl transmetalation occurs from a tetracoordinate, anionic boronate to a cationic Cu^{II} species, mediated by a methoxide bridge.



INTRODUCTION

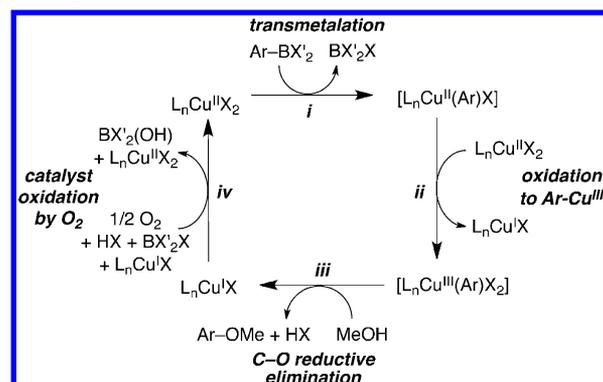
Methods for the copper(II)-mediated oxidative coupling of arylboronic acids and heteroatom nucleophiles (eq 1) were



introduced in 1998 in three sequential publications by the groups of Chan, Evans, and Lam.^{1,2} Since these original reports, work by these and a number of other groups has significantly expanded the substrate scope with respect to both the boronic acid and heteroatom-nucleophile reaction partners and established reaction conditions compatible with the use of catalytic quantities of copper(II) and O₂ as the stoichiometric oxidant. The reactions have emerged as a versatile approach to the synthesis of heterofunctionalized arenes, with utility that complements other synthetic methods, such as the Ullmann–Goldberg and Buchwald–Hartwig coupling reactions.

Most of the improvements in scope and utility of these methods have been achieved through empirical reaction-development efforts, while comparatively little effort has been directed toward mechanistic investigations.³ Our interest was drawn to these reactions because they represent an important example of Cu-catalyzed aerobic oxidation, and insights into these reactions could have implications for a wide range of analogous transformations, including C–H oxidation methods.⁴ We recently reported a preliminary mechanistic investigation of Cu(OAc)₂-catalyzed aerobic oxidative methoxylation of 4-tolylboronic acid, conducted in methanol as the solvent, employing

Scheme 1. Simplified Catalytic Mechanism for Cu^{II}-Catalyzed Oxidative Coupling of 4-Tolylboronic Acid Derivatives (Ar-BX'₂) and Methanol (X, X' = OAc, OMe, OH)



a series of kinetic studies, EPR spectroscopic analysis of the catalytic reaction mixture, and investigation of stoichiometric reactions between Cu and substrates under aerobic and anaerobic conditions.^{3a} The results of this study provided the basis for the catalytic mechanism shown in Scheme 1, the key features of which may be summarized as follows. EPR-active Cu^{II} species represent the catalyst resting state, and transmetalation of the aryl group from boron to Cu^{II} is the turnover-limiting step

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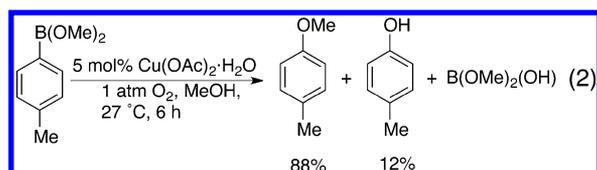
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(step *i*, Scheme 1). Copper(II) mediates the oxidative coupling reaction, even in the absence of O₂, and this process features a 2:1 Cu^{II}/Ar-BX₂ stoichiometry (steps *i*–*iii*, Scheme 1). Oxidation of the resulting Cu^I catalytic intermediates by molecular oxygen takes place with a 4:1 Cu^I/O₂ stoichiometry (step *iv*, Scheme 1). The aryl-Cu^{II} and aryl-Cu^{III} intermediates proposed in Scheme 1 are not directly observed under catalytic conditions; however, well-defined examples of aryl-Cu^{III} species have been shown previously to form via analogous Cu^{II} disproportionation pathways.⁵

In this report, we present additional kinetic and spectroscopic data associated with Cu(OAc)₂-catalyzed aerobic oxidative methoxylation of 4-tolylboronic dimethyl ester (hereafter, tolylboronic ester). The results provide valuable insights into the nature of the catalyst resting state and the reaction steps that precede rate-limiting transmetalation of the aryl group from boron to copper(II), and they establish a solid foundation for future characterization of reactions that employ other heteroatom nucleophiles.

RESULTS

Overview of Reactions Investigated. The oxidative methoxylation of tolylboronic ester in methanol was selected as a prototypical example of the Chan–Evans–Lam coupling reaction. The standard reaction conditions for this study employed commercially available Cu(OAc)₂·H₂O as the catalyst (7.5 mM) and tolylboronic ester (150 mM) under 1 atm of O₂ in methanol. The reaction was conducted slightly above room temperature (27 °C) to enable maintenance of a constant temperature. “Tolylboronic ester” refers to the mixture of tolylboron species obtained upon dissolution of the well-defined trimeric tolylboronic anhydride (boroxine) in anhydrous methanol.⁶ The precise speciation of this mixture (e.g., boronic acid, ester, and mixed species) varies as a function of the reaction conditions.⁷ The reaction of the tolylboronic ester, prepared in this way, under the standard reaction conditions affords an 88% yield of 4-methylanisole, together with a 12% yield of 4-methylphenol (*p*-cresol) (eq 2). The latter product has been shown previously to arise from the oxidative coupling of boronic acid derivatives and water.⁸



Modification of the reaction conditions led to a number of observations that have implications for the reaction mechanism. These observations, summarized in Table 1, provide the basis for the kinetic and spectroscopic studies described herein. Addition of acetate or acetic acid inhibits the catalytic reaction (entries 2 and 3). Replacing Cu(OAc)₂ with a copper(II) salt with a non-coordinating anion [Cu(ClO₄)₂·6H₂O] leads to almost complete loss of catalytic activity (entry 4); however, reactivity is recovered upon addition of a base to this mixture. Use of 1 equiv of NaOAc in combination with Cu(ClO₄)₂ (i.e., Cu^{II}:OAc = 1:1) results in catalytic activity even higher than that observed under the standard conditions (entry 5). Use of 1 equiv of NaOMe with Cu(ClO₄)₂ also results in rapid catalytic turnover (entry 6).

Table 1. Qualitative Effect of Different Reaction Conditions on the Oxidative Coupling of Tolyboronic Ester and Methanol

entry	deviation from standard conditions ^a	effect on reactivity
1	–	(see eq 2)
2	added acetate	inhibition
3	added acetic acid	inhibition
4	Cu(ClO ₄) ₂ instead of Cu(OAc) ₂	negligible reactivity
5	Cu(ClO ₄) ₂ + 1 equiv NaOAc	acceleration
6	Cu(ClO ₄) ₂ + 1 equiv NaOMe	acceleration

^aStandard conditions: 7.5 mM Cu(OAc)₂, 150 mM tolylboronic ester, 1 atm O₂, 27 °C, 6 h.

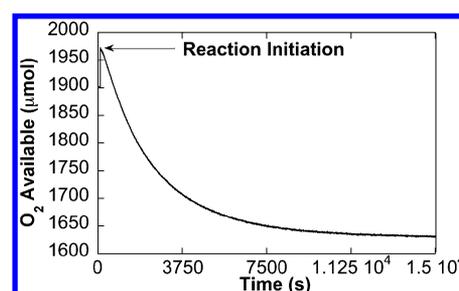


Figure 1. Gas-uptake trace for methoxylation of tolylboronic ester (eq 2). Conditions: 7.5 mM Cu(OAc)₂, 150 mM tolylboronic ester, 1 atm O₂, 27 °C, 5 mL of MeOH.

Kinetic Studies. *Kinetic Studies under Standard Conditions.* The consumption of O₂ during the catalytic reaction in eq 2 enables gas-uptake methods to be used to monitor the reaction kinetics (Figure 1). The reaction was conducted within a computer-interfaced manometry apparatus to monitor changes in O₂ pressure during the course of the reaction.⁹ The monotonic kinetic profile (Figure 1) enabled the kinetics to be analyzed by the method of initial rates.

Under standard conditions, copper-catalyzed oxidative coupling of tolylboronic ester and methanol (eq 2) exhibits saturation dependence on [tolylboronic ester], a half-order dependence on [Cu(OAc)₂], and a zero-order dependence on O₂ pressure (Figure 2).¹⁰ As we concluded previously,^{3a} the dependence of the rate on [Cu] and [ArBX₂] and the lack of a dependence on *p*O₂ are consistent with transmetalation as the turnover-limiting step and oxidation of the reduced catalyst by O₂ being comparatively rapid (cf. Scheme 1).

Kinetic Studies in the Presence of Added AcOH or Acetate. Addition of NBu₄OAc (or NaOAc; data not shown) or acetic acid to the reaction mixture inhibits catalytic turnover (Figure 3). The effect is slightly stronger with acetic acid. In order to probe the effect of [acetate] at concentrations below [Cu^{II}], we employed Cu(ClO₄)₂ as the copper source in combination with variable quantities of NaOAc. As shown in Figure 4, the reaction rate was very slow in the absence of acetate, and it reached a maximum at a Cu^{II}:OAc ratio of 1:1. The rate decreased steadily with increasing concentrations of acetate. The rate observed at a 1:2 Cu^{II}:OAc ratio agreed well with the rate observed when Cu(OAc)₂ was employed as the Cu^{II} source.

Systematic kinetic studies were then carried out using reaction mixtures containing 4 equiv of NaOAc relative to Cu(ClO₄)₂ and mixtures containing 4 equiv of AcOH relative to Cu(OAc)₂ (Figure 5). The results show that under these conditions

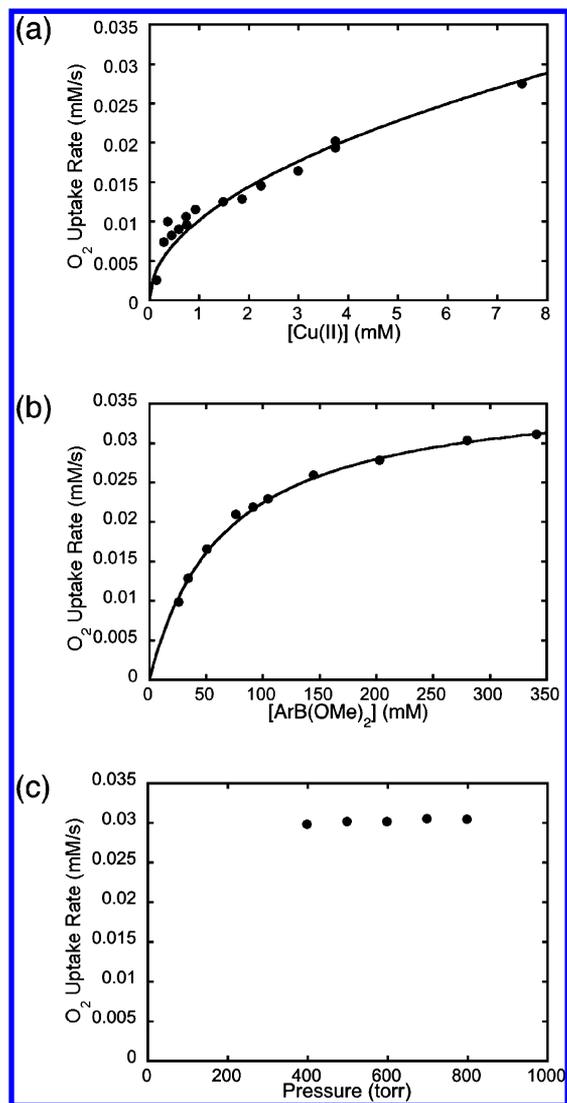


Figure 2. Kinetic data for Cu(OAc)₂-catalyzed aerobic oxidative coupling of tolylboronic ester and methanol. Conditions: (a) 0.75–7.5 mM Cu(OAc)₂, 150 mM tolylboronic ester, 900 Torr O₂, 5 mL of MeOH, 27 °C. The solid line reflects a nonlinear least-squares fit to [Cu^{II}]^{1/2}. (b) 7.5 mM Cu(OAc)₂, 25–341 mM tolylboronic ester, 900 Torr O₂, 5 mL of MeOH, 27 °C. The solid line reflects a nonlinear least-squares fit to a generic hyperbolic function of [tolylboronic ester]. (c) 7.5 mM Cu(OAc)₂, 300 mM tolylboronic ester, 400–900 Torr O₂, 5 mL of MeOH, 27 °C.

saturation dependence on [tolylboronic ester] is retained, but the dependence on [Cu^{II}] becomes first-order. Possible explanations for the shift in [Cu^{II}] dependence from half- to first-order (cf. Figures 2 and 5) will be discussed below. At a fixed 1:1 Cu^{II}:OAc ratio, the kinetic orders of the components were identical to those observed with Cu(OAc)₂: zero-order in *p*O₂, saturation in [tolylboronic ester], and half-order in [Cu^{II}] (Figure S2).

Hammett Study. Modifying the organic group on the boronic ester has a significant effect on the reaction rate. Alkylboronic esters such as methyl and isobutyl boronic esters do not react under the standard conditions; however, various 4-substituted phenylboronic acid derivatives undergo reaction at room temperature. A Hammett plot (Figure 6) indicates that, in general, more electron-rich arylboronic acids undergo faster catalyst turnover.¹¹ This observation is consistent with the pro-

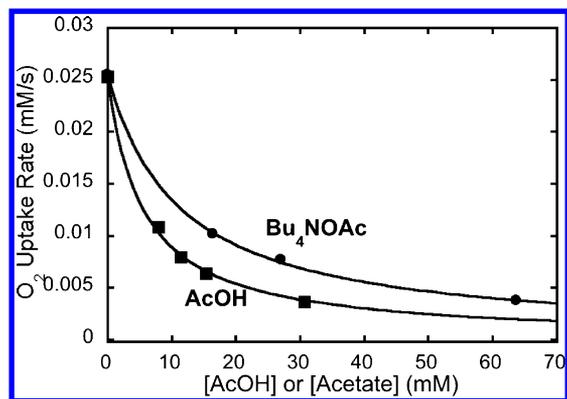


Figure 3. Effect of [AcOH] and [acetate] on the reaction rate. Conditions: 7.5 mM Cu(OAc)₂, 150 mM tolylboronic ester, 900 Torr O₂, 27 °C, 5 mL of MeOH.

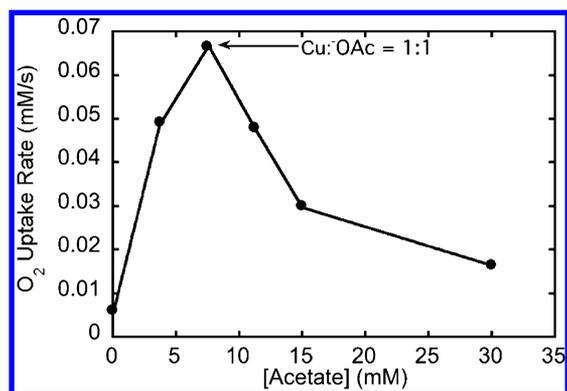


Figure 4. Effect of acetate on the reaction rate, using Cu(ClO₄)₂ as the Cu^{II} source to probe the effect of [acetate] lower than the [Cu^{II}]. Conditions: 7.5 mM Cu(ClO₄)₂, 150 mM tolylboronic ester, 0–30 mM NaOAc, 700 Torr O₂, 27 °C, 5 mL of MeOH.

posal in our preliminary mechanistic study that transmetalation is the turnover-limiting step of the catalytic reaction.^{3a} The ability of electron-donating groups to promote transmetalation from boronic acids has been documented previously.¹²

Studies in the Presence of Sodium Methoxide. The apparent requirement for a basic ligand prompted us to explore the use of methoxide instead of acetate (cf. Table 1). A copper(II)/methoxide catalyst was generated in situ by adding variable quantities of NaOMe to a solution of Cu(OTf)₂ in methanol. Use of ≥2 equiv of methoxide with respect to Cu^{II} resulted in the formation of a light blue precipitate, probably corresponding to insoluble oligomeric [Cu(OMe)₂]_n species.¹³ Solutions containing a Cu^{II}:NaOMe ratio of 0.5 to 1.5 remained homogeneous and light green in color; all showed catalytic activity significantly higher (5–7-fold increase) than Cu(OAc)₂ and produced a mixture of the hydroxylated and methoxylated products (cf. eq 2 and Table S1).⁷

Spectroscopic Studies. ¹¹B NMR Spectroscopic Analysis of Tolyboronic Ester in Methanol. Use of ¹¹B NMR spectroscopy provided insights into potential interactions between tolylboronic ester and solvent, acetate, and methoxide in the absence of Cu^{II}. The boronic ester obtained upon dissolving 4-tolyboroxine in CD₃OD exhibits a peak in the ¹¹B NMR spectrum at 30.9 ppm (Figure 7, trace a). Addition of 0.1 equiv of sodium acetate led to a slight upfield shift of this peak to 30.5 ppm (trace b). In the presence of 1.0 equiv of sodium

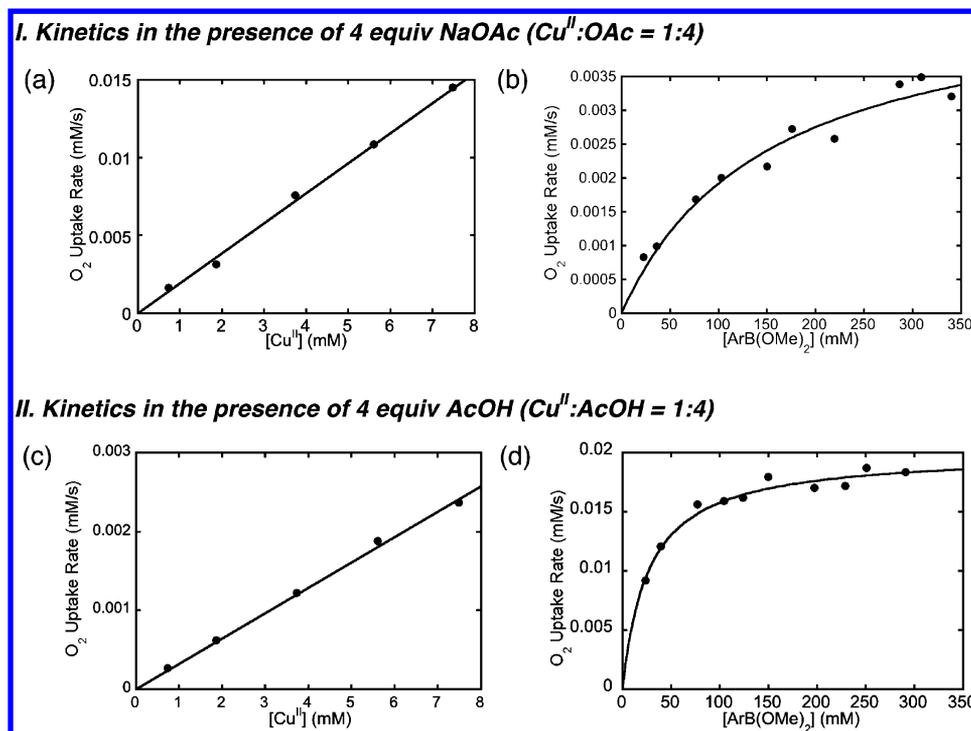


Figure 5. Kinetic data for Cu-catalyzed aerobic oxidative coupling of tolylboronic ester and methanol with a constant concentration of NaOAc (I) or AcOH (II). Conditions: (a) 0.75–7.5 mM $\text{Cu}(\text{ClO}_4)_2$, 150 mM tolylboronic ester, 30 mM NaOAc, 900 Torr O_2 , 27 °C, 5 mL of MeOH. The solid line reflects a linear least-squares fit to a function of $[\text{Cu}^{\text{II}}]$. (b) 7.5 mM $\text{Cu}(\text{ClO}_4)_2$, 25–341 mM tolylboronic ester, 30 mM NaOAc, 900 Torr O_2 , 27 °C, 5 mL of MeOH. (c) 0.75–7.5 mM $\text{Cu}(\text{OAc})_2$, 150 mM tolylboronic ester, 30 mM AcOH, 900 Torr O_2 , 27 °C, 5 mL of MeOH. The solid line reflects a linear least-squares fit to a function of $[\text{Cu}^{\text{II}}]$. (d) 7.5 mM $\text{Cu}(\text{OAc})_2$, 25–341 mM tolylboronic ester, 30 mM AcOH, 900 Torr O_2 , 27 °C, 5 mL of MeOH. The solid line reflects a nonlinear least-squares fit to a generic hyperbolic function of [tolylboronic ester].

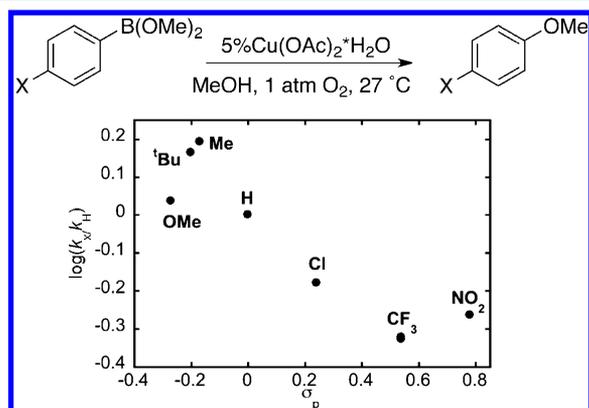


Figure 6. Hammett plot for Cu-catalyzed oxidative coupling with electronically modified arylboronic acid derivatives, based on initial reaction rates determined by gas uptake kinetics. Conditions: 7.5 mM $\text{Cu}(\text{OAc})_2$, 150 mM tolylboronic ester, 760 Torr O_2 , 27 °C, 5 mL of MeOH.

acetate, the peak shifted further upfield to 29.2 ppm and became significantly broader (trace c). Acetic acid had little effect on the spectrum (trace d). More significant spectral changes were observed with NaOMe. Addition of 0.1 equiv of NaOMe resulted in a spectrum that exhibits two broad peaks, one at 30.6 ppm and the other at 27.1 ppm (trace e). The spectrum obtained upon addition of a full equivalent of NaOMe exhibits a single peak at 6.4 ppm (trace f). The significant upfield shift and sharpening of the peak is consistent with formation of a tetracoordinate boronate species, $[\text{ArB}(\text{OMe})_3]^-$,

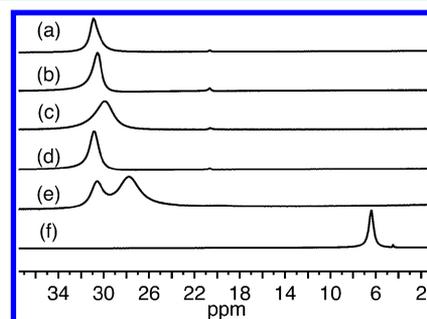
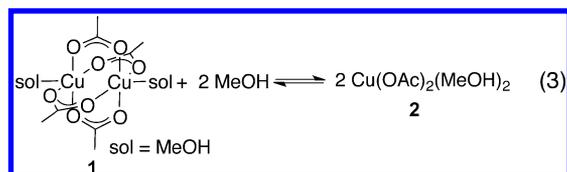


Figure 7. ^{11}B NMR spectra of 4-tolylboroxine with (a) no additives, (b) 0.1 equiv of NaOAc, (c) 1.0 equiv of NaOAc, (d) 1.0 equiv of AcOH, (e) 0.1 equiv of NaOMe, and (f) 1.0 equiv of NaOMe.

under these conditions.¹⁴ Spectra (a)–(e) suggest that tri-coordinate boron species predominate under all of the other conditions.

Effects of Additives on Concentration of EPR-Active Cu^{II} . EPR spectroscopy was used to probe the Cu^{II} species present under catalytic conditions. During the catalytic reactions, 0.5 mL aliquots were removed from reaction mixtures and rapidly frozen in liquid nitrogen, and EPR spectra were acquired at 77 K. $\text{Cu}(\text{OAc})_2$ in methanol exhibits a very weak EPR signal, accounting for <10% of the total Cu in solution. This observation is consistent with $\text{Cu}(\text{OAc})_2$ being present in the form of the EPR-silent paddlewheel dimer (1). In alcohol solvents, only a small portion of this dimer dissociates into the corresponding mononuclear species (2) (eq 3).^{15,16}



Upon addition of tolylboronic ester to a solution of $\text{Cu}(\text{OAc})_2$ in methanol, strong Cu^{II} EPR signals become evident. The concentration of total EPR-active Cu^{II} displays a saturation dependence on [tolylboronic ester] (Figure 8a); a similar effect is observed upon addition of $\text{B}(\text{OMe})_3$ (Figure 8b). This saturation dependence is similar to the kinetic dependence on tolylboronic ester and likely has a common origin (see discussion below). When 10 equiv of acetic acid or sodium acetate is present in the solution, addition of tolylboronic acid is less effective in inducing formation of the Cu^{II} EPR signal (Figure 8c and d), probably indicating that the EPR-silent paddlewheel dimer **1** is more stable in the presence of these additives. The stability of dimer **1** under these conditions may provide an explanation for the inhibitory effect of acetate and acetic acid (see further discussion below).

The EPR spectra contain contributions from two EPR-active Cu^{II} species present in solution (Figure 9), hereafter referred to as species A and B. The presence of two species was established from a fit of the EPR spectra in the lowest field g_z region (Figure 8, inset). The shoulder evident on the low-field side of the signal was attributed to the ^{65}Cu satellite of species A, and this feature was reproduced in the simulation.¹⁷ The g and hyperfine A values obtained upon fitting the experimental spectra (Table 2) are consistent with both copper species possessing nearly axial symmetry and weak-field oxygen ligands, such as methanol or acetate. The EPR parameters indicate that an aryl- Cu^{II} resting state is unlikely, as a strong-field ligand such as an aryl group should give rise to a significantly smaller g_z value.¹⁸

When oxidative methoxylation of the tolylboronic ester is initiated, species A and B are present in a 3:1 ratio. Species A increases in concentration at the expense of B during the course of the reaction (Figure 10). The depletion of B as the reaction progresses is attributed to the formation of trimethylborate as a product of the reaction (eq 2). An independently prepared solution of $\text{B}(\text{OMe})_3$ (150 mM) and $\text{Cu}(\text{OAc})_2$ (7.5 mM) in methanol exhibits the EPR spectral signatures of only species A (Figure S5). The relative concentrations of A and B are also influenced by the acetate concentration. When the reaction is performed with a catalyst consisting of only 1 equiv of acetate

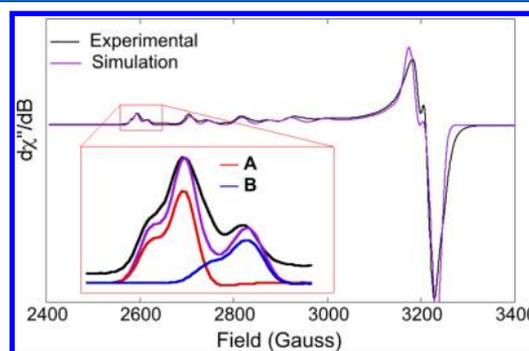


Figure 9. EPR spectrum acquired immediately after mixing of $\text{Cu}(\text{OAc})_2$ and tolylboronic and fit assuming contributions from two species. Inset: Lowest field signal, with deconvolution of spectral fit. For g and A values see Table 2.

Table 2. Fitted EPR Parameters for Species Observed during Catalytic Turnover^a

species	g_x	g_y	g_z	A_x, A_y	A_z
A	2.099	2.073	2.421	20	360
B	2.100	2.073	2.381	20	410

^aHyperfine coupling constants reported in MHz.

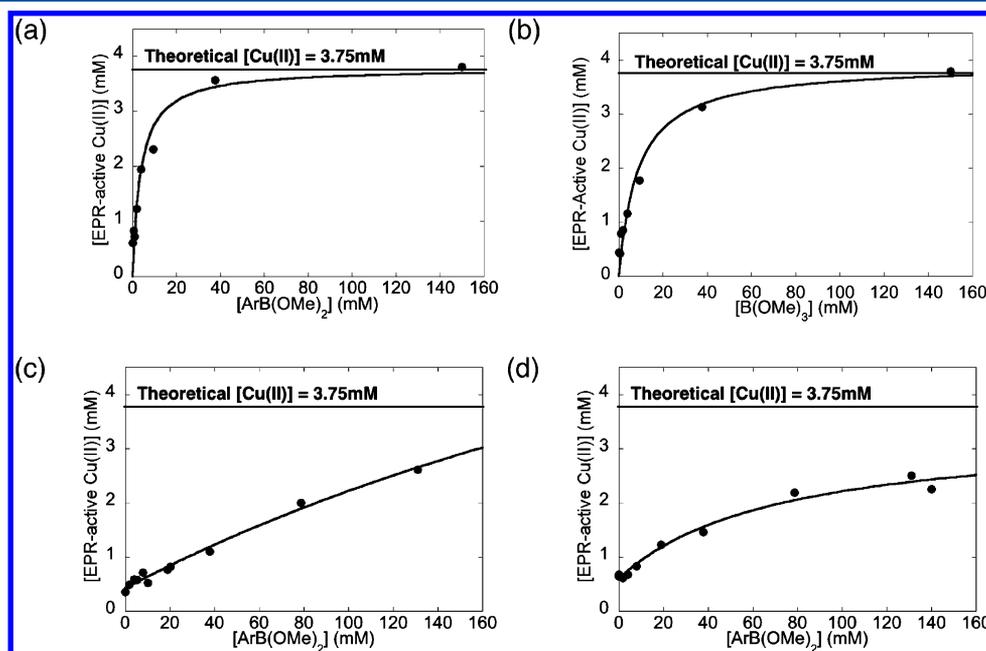


Figure 8. Quantitation of EPR-active Cu^{II} based on double integration of spectra upon titration of (a) tolylboronic ester in the presence of no additives, (b) trimethyl borate, (c) tolylboronic ester and 10 equiv of acetic acid, (d) tolylboronic ester and 10 equiv of sodium acetate. Conditions: 3.75 mM $\text{Cu}(\text{OAc})_2$ in MeOH.

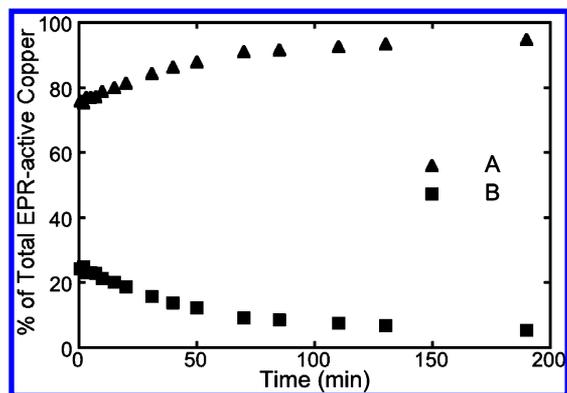


Figure 10. Change in speciation of EPR-active Cu^{II} species during the reaction time course. Conditions: 7.5 mM $\text{Cu}(\text{OAc})_2$, 150 mM tolylboronic ester, 25 mL of MeOH, O_2 , 25 °C.

relative to Cu^{II} , lower concentrations of **B** are observed. The initial **A**:**B** ratio is approximately 9:1 (see Figure S6).

The presence of acetate is required to reproduce the EPR signals identified from the catalytic mixtures. Solutions of either $\text{Cu}(\text{ClO}_4)_2$ or $\text{Cu}(\text{OTf})_2$ containing tolylboronic ester exhibit axial EPR spectra consistent with a Jahn–Teller-distorted solvent-ligated Cu^{II} complex ($g_z = 2.430$, $g_{x,y} = 2.085$, $A_z = 365$ MHz).^{7,19} Species **A** and **B** are observed in these solutions only upon addition of ≥ 1 equiv of acetate. With a Cu^{II} :OAc ratio of less than 1:2, several new species are observed, probably corresponding to the solvent-ligated complex and other unidentified complexes. The necessity of acetate to reproduce the EPR spectral signatures of the catalytic reaction mixtures implies that the Cu^{II} species corresponding

to the catalyst resting state had at least one coordinated acetate ligand.

Addition of acetic acid or sodium acetate to the catalytic reaction mixtures under standard conditions leads to minor changes in the concentration of **B**; however, **A** decreases significantly in concentration, and the total concentration of EPR-active Cu^{II} also decreases, most likely reflecting formation of the EPR-silent paddlewheel dimer **1** (Figure 11).

Use of electron-deficient arylboronic acids as coupling partners led to similar EPR spectra, containing contributions from two species, **A'** and **B'**, with parameters similar to those of **A** and **B** (Figure 12). Furthermore, the relative concentration of these

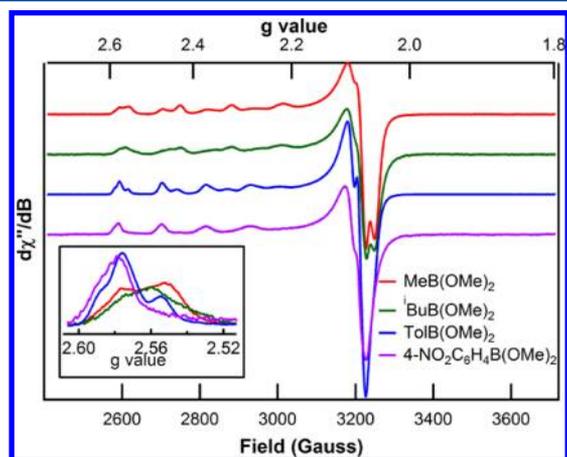


Figure 12. EPR spectra of $\text{Cu}(\text{OAc})_2$ in the presence of boron-based Lewis acid additives that display multiple species in MeOH. Conditions: 7.5 mM $\text{Cu}(\text{OAc})_2$, 150 mM $\text{RB}(\text{OMe})_2$.

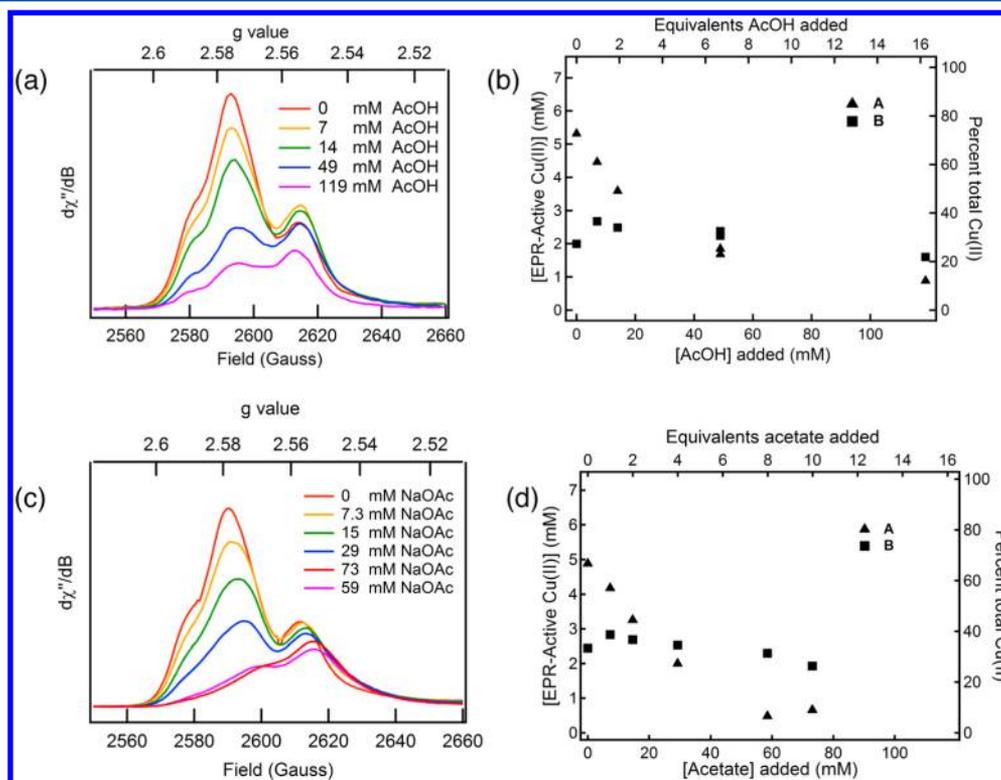
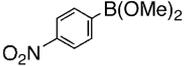
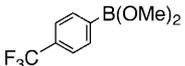
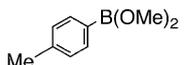


Figure 11. Effect of acetic acid and sodium acetate on the EPR signal associated with the Cu^{II} species: (a) lowest field region after addition of acetic acid; (b) quantitation of spectra; (c) lowest field region after addition of sodium acetate; (d) quantitation of spectra. Conditions: 7.5 mM $\text{Cu}(\text{OAc})_2$, 150 mM tolylboronic ester.

two species appears to correlate with the relative Lewis acidity of the boronic acids, with species **A** being favored in the presence of stronger Lewis acids (Table 3). The relative Lewis acid

Table 3. Relative Concentration of Observable Species by EPR and Relation to Acidity.^a

Entry	Additive	pK _a ^b	A:B Observed by EPR
1	B(OMe) ₃	9.0 ^c	100:0
2		7.1 ^c	89:11
3		7.39 ^d	78:22
4		9.3 ^c	75:25
5	MeB(OMe) ₂	10.4 ^c	47:53
6	ⁱ BuB(OMe) ₂	10.6 ^e	42:58

^aConditions: 7.5 mM Cu(OAc)₂, 150 mM boron additive, MeOH, under air; spectra acquired at 77 K. ^bpK_a value of a water molecule coordinated to the corresponding three-coordinate boronic acid (ref 20). ^cref 20. ^dRef 22. ^eRef 23.

strength is estimated from the pK_a values of water molecules coordinated to the three-coordinate boronic acid.²⁰ The single species observed in the presence of trimethylborate corresponds to **A**.²¹

The EPR spectra obtained upon addition of NaOMe to a solution of Cu(OTf)₂ and tolylboronic ester in methanol provide further insights into the identity of the copper species observed during catalytic turnover. The EPR spectrum of a catalyst system consisting of 1:1 Cu(OTf)₂:NaOMe in the presence of tolylboronic ester (Figure 13a) is consistent with a

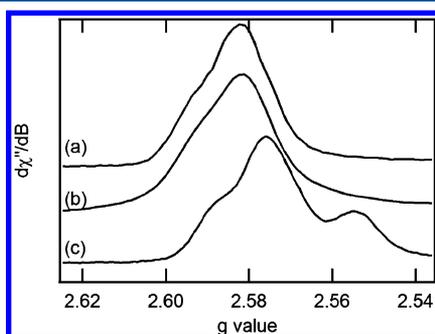


Figure 13. Comparison of the low-field signals in the EPR spectra observed under conditions with different additives: (a) 7.5 mM Cu(OTf)₂, 7.5 mM NaOMe, 150 mM tolylboronic ester; (b) 7.5 mM Cu(OTf)₂; (c) 7.5 mM Cu(OAc)₂, 150 mM tolylboronic ester. Spectra from reaction mixtures (b) and (c) were obtained from aliquots from reactions under 1 atm O₂, room temperature after 5 min reaction initiation; spectra acquired at 77 K. See Figure S9 for full spectra.

single species, and the speciation does not change during the course of the catalytic reaction. The EPR spectra associated with this catalyst system are fit well using EPR spectral parameters associated with Cu(OTf)₂ in methanol (Figure 13b; see above for parameters), and they differ somewhat from species **A**

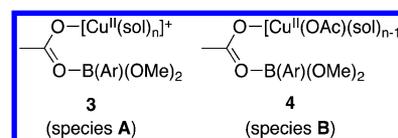
and **B**, present under catalytic conditions that contain acetate (Figure 13c). These data suggest that the coordination sphere of Cu^{II} in species **A** and **B** probably includes one or more acetate ligands (see further discussion below).

DISCUSSION

The data described above support the conclusions and expand upon our preliminary mechanistic investigation of Cu(OAc)₂-catalyzed oxidative methoxylation of tolylboronic ester.^{3a} In the previous report, we concluded that transmetalation of the aryl group from boron to Cu^{II} is the turnover-limiting step of the overall cycle. The additional EPR spectroscopic studies and kinetic data described here provide further insights into the nature of the Cu^{II} resting state(s) during catalytic turnover and elaborate upon the mechanism of the reaction of these species with the tolylboronic ester substrate. The inhibitory effect of acetate and acetic acid on the catalytic rate and the shift of the rate law from a half-order to a first-order dependence on [Cu] have important implications for the mechanism of the transmetalation step.

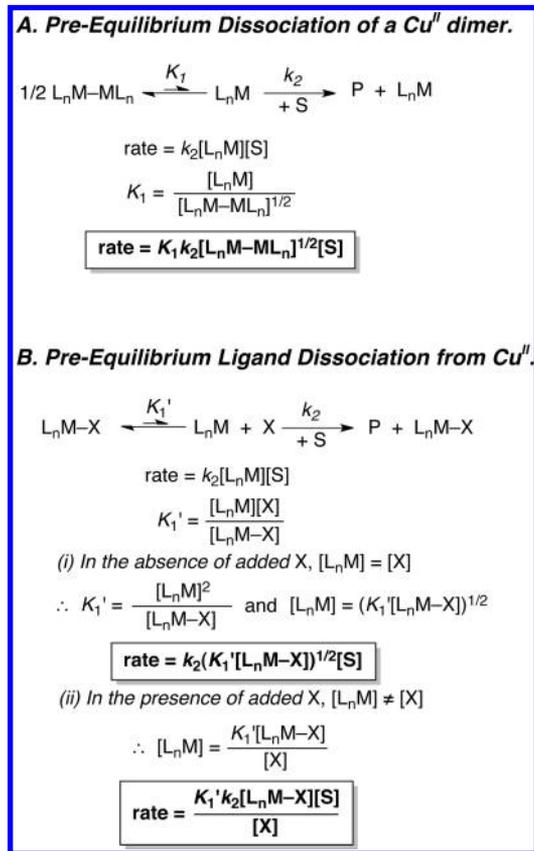
The appearance of a strong EPR signal upon addition of tolylboronic ester to Cu(OAc)₂ in methanol reveals that a reaction takes place between these two components. The saturation dependence of the EPR signal intensity on [ArB(OMe)₂] (0–40 equiv with respect to [Cu]) closely resembles the kinetic saturation dependence of the catalytic rate on [ArB(OMe)₂] (cf. Figures 2 and 8). These observations suggest that the catalyst resting state consists of an EPR-active adduct between Cu^{II} and the tolylboronic ester.

The EPR data do not permit definitive structural assignment of species **A** and **B**. However, as these species arise from the reaction of tolylboronic ester with the EPR-silent [Cu(OAc)₂]₂ dimer **1**, it seems plausible that they consist of acetate-bridged heterobimetallic Cu^{II}/boron structures, such as **3** and **4**, with one or two acetate ligands coordinated to the Cu^{II} center. Carboxylate-bridged heterobimetallic M/boron complexes, in which M = Pt^{II} or Ni^{II}, have been structurally characterized.²⁴ One or more additional bridging ligands, such as methoxide, may be present in the structures of **3** and **4**. Also, we cannot exclude the possibility of higher order Cu^{II}/boron aggregates, in which **A** and **B** correspond to ensembles of electronically similar binuclear and polynuclear aggregates of Cu^{II} and boron that give rise to the observed EPR spectra. The significant decrease in the EPR signal associated with **A** upon addition of acetic acid or acetate to the Cu(OAc)₂/tolylboronic ester solution, but comparatively little effect on **B** (Figures 11 and S4), is consistent with the presence of one (bridging) acetate ligand in **3** and two acetate ligands (one bridging, one nonbridging) in **4**. This assignment is also consistent with the higher ratio of A:B observed when the reaction is carried out with 1:1 Cu(ClO₄)₂/NaOAc as the catalyst.



An interesting kinetic phenomenon, evident from the data in Figures 2a and 5a and 5c, is the shift from a half- to first-order dependence of the catalytic rate on [Cu^{II}] when excess acetate or acetic acid is included in the reaction mixture. The half-order dependence could be explained by the presence of

Scheme 2. Mechanistic Scenarios That Account for a Half-Order Kinetic Dependence on [Catalyst] (S = Substrate, P = Product)



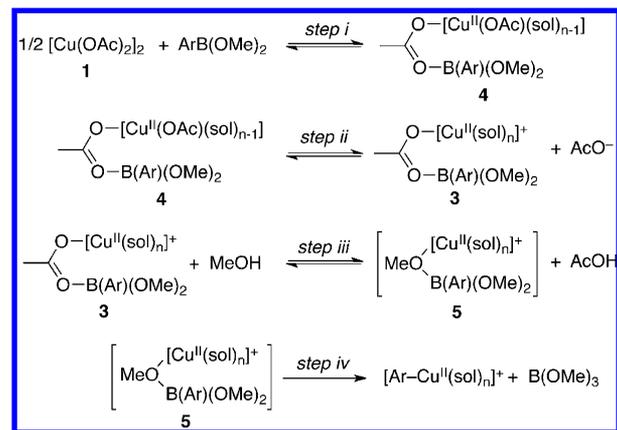
a dimeric Cu^{II} resting state that is in equilibrium with a catalytically active monomer (Scheme 2A).²⁵ The presence of EPR-active (presumably monomeric) Cu^{II} species, which form via reaction of the EPR-silent dimer, [Cu(OAc)₂]₂ (**1**), with the boronic ester substrate under the catalytic conditions, suggests a Cu^{II} dimer–monomer equilibrium does not account for the half-order kinetic behavior. Moreover, EPR spectroscopic data suggest that EPR-silent **1** is more prevalent in the presence of added acetate or acetic acid, conditions that lead to a first-order dependence on [Cu^{II}]. These considerations suggest the half-order dependence on [Cu^{II}] under standard catalytic conditions has a different origin.

Pre-equilibrium ligand dissociation from a catalyst resting state represents another mechanistic scenario that can give rise to a half-order kinetic dependence on [catalyst] (Scheme 2B). The simplest rate law (Scheme 2B, i) associated with such a mechanism features a half-order dependence on [L_nM–X], arising from equal concentrations of [L_nM] and [X] formed in the pre-equilibrium step. If X is added to the reaction mixture, the concentrations of [L_nM] and [X] will no longer be equal and the rate (Scheme 2B, ii) exhibits a first-order dependence on [L_nM–X] and an inverse first-order dependence on [X]. The rate law can become significantly more complex, depending on the specific kinetic characteristics of the reaction (e.g., if significant concentrations of L_nM accumulate in the pre-equilibrium step, if additional pre-equilibrium or steady-state steps are present in the mechanism, etc.); however, the shift

from half- to first-order dependence on [L_nM–X] and an inhibitory effect of X are retained.²⁶

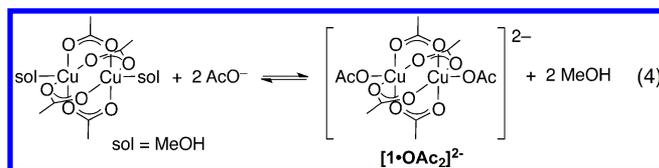
The rate laws in Scheme 2 do not directly correspond to the kinetic behavior of the Cu-catalyzed oxidative coupling reactions described here, but they provide a qualitative framework for understanding the experimental observations. Rigorous interpretation of the kinetic data is complicated by, and will be avoided because of, the uncertain identities of the Cu^{II} intermediates observed under the catalytic conditions and the diversity of chemical steps that could contribute to the transmetalation mechanism. Nevertheless, possible chemical steps involved in transmetalation of the tolyl group from the boronic ester to Cu^{II} are depicted in Scheme 3. Steps *i* and *ii* involve the

Scheme 3. Possible Chemical Steps Involved in Boron-to-Cu^{II} Transmetalation



reaction of tolylboronic ester with [Cu(OAc)₂]₂ (**1**) to afford the EPR-active Cu^{II} species **3** and **4**. The rate-limiting transmetalation (step *iv*) is proposed to proceed from a methoxide-bridged intermediate, **5**, formed via loss of acetic acid from an intermediate, such as **3**, in a (steady-state) pre-equilibrium reaction (step *iii*).

The mechanistic steps in Scheme 3 account for several experimental observations. Evidence for the formation of intermediates **3** and **4** and their assignment as species **A** and **B**, detected by EPR spectroscopy, was presented above. These species represent the Cu^{II} resting state under catalytic conditions. Pre-equilibrium, methanol-induced displacement of AcOH from **3** in step *iii* accounts for the inhibitory effect of acetic acid. In accordance with the simplified kinetic analysis in Scheme 2, this step also accounts for the shift from a half- to first-order kinetic dependence on [Cu^{II}] when acetic acid is added to the reaction mixture. A step similar to step *iii*, involving loss of acetate, could account for the rate inhibition and change from half- to first-order kinetic dependence on [Cu^{II}] upon addition of sodium acetate to the catalytic reaction mixture. At least some of the rate inhibition that occurs upon addition of acetic acid or acetate to the reaction mixture appears to reflect sequestration of Cu^{II} as the dimeric [Cu(OAc)₂]₂ (**1**) species (or another EPR-silent species), evident from the decreased EPR signal intensity under these conditions (Figures 7c, d and 10). The basis for these observations is not clear, but stabilization of **1** via coordination of acetate or acetic acid to the apical sites of the EPR-silent paddlewheel dimer (e.g., eq 4) may account for this result and has precedent in the literature.²⁷



The oxidative coupling reaction employing $\text{Cu}(\text{OTf})_2/\text{NaOMe}$ as the catalyst system provides insights relevant to the mechanism in Scheme 3. EPR and ^{11}B NMR spectroscopic data (Figures 7 and 13) suggest that methoxide binds preferentially to the boronic ester, rather than the Cu^{II} center. Specifically, the EPR spectrum of $\text{Cu}(\text{OTf})_2$ in the presence of tolylboronic ester and NaOMe is indistinguishable from that of $\text{Cu}(\text{OTf})_2$ alone. These observations suggest that the anionic tetracoordinate tolylboronate species is not a strong ligand for Cu^{II} . Thus, the methoxide-bridged intermediate 5 (cf. steps *iii* and *iv* in Scheme 3) is not expected to be a stable species under the catalytic conditions. Circumstantial evidence for such an intermediate, however, includes the enhanced turnover rate observed with the $\text{Cu}(\text{OTf})_2/\text{NaOMe}$ catalyst system relative to the use of $\text{Cu}(\text{OAc})_2$ as a catalyst and the negligible catalytic activity observed when $\text{Cu}(\text{OTf})_2$ or $\text{Cu}(\text{ClO}_4)_2$ is used as the catalyst in the absence of an added base (i.e., acetate or methoxide). The proposed involvement of tetracoordinate boronates in transmetalation reactions involving transition-metal centers other than Cu^{II} has extensive precedent,^{28,29} and preformed triol-derived, anionic boronates have been shown to be very effective reagents in Cu^{II} -catalyzed oxidative coupling reactions.³⁰

CONCLUSION

The results described herein expand upon the mechanistic insights into $\text{Cu}(\text{OAc})_2$ -catalyzed oxidative methoxylation of boronic esters. The EPR spectroscopic studies show that $\text{Cu}(\text{OAc})_2$ does not retain its paddlewheel, dimeric structure and likely forms a heterobimetallic adduct with the boronic ester under the reaction conditions. The Cu^{II} resting state of the catalyst consists of at least two different EPR-active species, which appear to be differentiated by the number of acetate ligands coordinated to the Cu^{II} center. Kinetic data suggest that transmetalation requires the loss of an acetate ligand (potentially in the form of acetic acid). These results, together with ^{11}B NMR spectroscopic data and kinetic studies carried out with a $\text{Cu}^{\text{II}}/\text{NaOMe}$ catalyst system (in the absence of acetate), suggest that rate-limiting aryl transmetalation proceeds from an anionic boronate species to Cu^{II} , probably mediated by a methoxide bridge. These results provide a foundation for future studies focused on Cu^{II} -catalyzed aerobic oxidative coupling reactions between arylboronic esters and other heteroatom nucleophiles, such as azoles, amides, and related important coupling partners.

EXPERIMENTAL SECTION

General Considerations. 4-Tolylboroxine was formed by dehydration of the corresponding acid at 125 °C for at least 3 days. The resulting mixture consisted of at least 95% boroxine ($\leq 5\%$ acid) by ^1H NMR spectroscopy in CDCl_3 . Dissolution of the boroxine in anhydrous methanol from a SureSeal bottle forms primarily tolylboronic ester as the major arylboron species and was used without further purification. Copper acetate and perchlorate were used as the monohydrate and hexahydrate, respectively. Methanol solutions of sodium methoxide were made by dissolving sodium metal in anhydrous methanol and titrating the solution (~ 2 M) with an HCl solution of known concentration. Gas chromatographic analyses of the reactions were conducted with a Shimadzu GC-17A gas chromatograph, using

tri-*tert*-butylbenzene or trimethoxybenzene as an internal standard. X-band EPR data were collected using a Bruker EleXsys E500 spectrometer; all spectra were acquired at 77 K using a $\text{N}_2(l)$ dewar. EPR quantitation was performed using a solution of known CuBr_2 concentration with a 100-fold excess of imidazole as an external standard. All spectra were acquired under nonsaturating conditions. ^{11}B and ^1H NMR spectra were acquired on a Varian UNITY 500 spectrometer (^{11}B resonance frequency of 160.4 MHz) and referenced to corresponding ^1H NMR spectra.

Gas-Uptake Kinetic Studies. A typical kinetic run was conducted as follows. A volume-calibrated round-bottom flask equipped with a stir bar was attached to a computer-interfaced manometry apparatus. The flask was evacuated to 50 Torr and backfilled with O_2 to 900 Torr; this cycle was repeated 10 times, and the final pressure prior to substrate addition was set to 500 Torr. The arylboronic ester stock solution (260 mM in methanol, 3 mL, 0.78 mmol) was injected into the reaction vessel via syringe through a septum, and the pressure was allowed to equilibrate at 27 °C for several hours. Subsequently, the reaction was initiated by adding a solution of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (18.75 mM in methanol, 2 mL, 0.038 mmol) via a syringe through a septum, leading to a final concentration of 150 mM arylboronic ester and 7.5 mM copper acetate. Data were acquired using a custom LabVIEW (National Instruments) software program. Rates were obtained by using the method of initial rates, and data fitting was performed by using Microsoft Excel. See Supporting Information for kinetics runs in the presence of additives.

EPR Spectroscopic Studies. EPR samples were made by flash-freezing samples of interest in quartz EPR tubes at 77 K, and spectra were acquired as described under General Considerations. Spectra were fit using the W95EPR program³¹ using the fewest number of species to satisfactorily reproduce observed spectra. For determining relative concentrations of species, fitting of the species' lowest field signals in the g_z region was used to guide the fitting process.

^{11}B NMR Spectroscopic Studies. Quartz NMR tubes were used for all samples, and the remaining broad background signal from borosilicate glass in the probe was removed via background subtraction. Separate 0.75 mL samples were prepared in CD_3OD . All contained 13.3 mg (0.0374 mmol, 50 mM) of 4-tolylboroxine (150 mM tolylboronic ester); 4.8 and 48 μL of a stock solution of 2.3 M NaOMe in CH_3OH were used for samples containing 0.1 and 1.0 equiv of methoxide, respectively. Sodium acetate (9.2 mg, 0.11 mmol, 150 mM) was used for the experiment with 0.1 equiv of acetate, and a 150 mM stock solution was used for the experiment with 0.1 equiv of NaOAc . Glacial acetic acid (6.3 μL , 0.11 mmol, 150 mM) was used for the sample containing 1.0 equiv of AcOH .

ASSOCIATED CONTENT

Supporting Information

Full experimental details and additional experiments with figures are available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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