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Cross-coupling by a noncanonical mechanism involving the addition of aryl halide to Cu(II)

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Abstract

Copper complexes are widely used in the synthesis of fine chemicals and materials to catalyze couplings of heteroatom nucleophiles with aryl halides. We show that cross-couplings catalyzed by some of the most active catalysts occur by a mechanism not previously considered. Copper(II) [Cu(II)] complexes of oxalamide ligands catalyze Ullmann coupling to form the C–O bond in aryl ethers by concerted oxidative addition of an aryl halide to Cu(II) to form a high-valent species that is stabilized by radical character on the oxalamide ligand. This mechanism diverges from those involving Cu(I) and Cu(III) intermediates that have been posited for other Ullmann-type couplings. The stability of the Cu(II) state leads to high turnover numbers, >1000 for the coupling of phenoxide with aryl chloride electrophiles, as well as an ability to run the reactions in air.

Metal-catalyzed cross-coupling reactions between aryl halide electrophiles and heteroatom nucleophiles are among the most widely used reactions for the discovery and production of fine chemicals and materials (1, 2). Although copper catalysts were first used for such couplings more than a century ago (3, 4), palladium catalysts led to the first mild couplings over 80 years later (5). Only recently, with the advent of new ligands, have couplings with catalysts based on the less expensive, earth-abundant metal copper become competitive with the counterparts catalyzed by palladium (6). However, much less is known about the mechanism of copper-catalyzed couplings than of palladium-catalyzed couplings, in part because copper complexes are often paramagnetic and, therefore, more difficult to

identify spectroscopically; in addition, ligand-exchange processes are typically faster than the elementary steps of the catalytic cycle (7). Thus, most copper catalysts have been identified by trial and error.

Both the oxidation state of the active catalyst and the identity of the elementary steps on the catalytic cycle have been the source of much speculation (8). After initial mechanistic proposals that included σ-bond metathesis, activation of the carbon-halogen bond by π-coordination of the arene, or electron transfer to form aryl radicals (Fig. 1A) (8), careful studies have supported mechanisms in which a Cu(I) complex bound by commonly used neutral (9–12) or anionic (12, 13) bidentate ligands undergoes concerted oxidative addition of an aryl halide (Fig. 1B). However, a variety of ligands proposed to bind as dianions also have been reported recently to generate catalysts for cross-coupling reactions that are challenging to achieve (Fig. 1C) (14–16). In particular, catalysts containing diamides derived from oxalic acid (oxalamide ligands), reported by Dawei Ma (17–23), are more active than any previous copper catalysts and enable reactions of unactivated, electron-rich aryl bromides and of aryl chlorides (6), but no mechanistic explanation of the high activity of the catalyst has been reported.

We show that complexes of oxalamide ligands catalyze the cross-coupling of aryl halides with phenols, and likely other nucleophiles, by a mechanism that is distinct from prior mechanisms considered for copper-catalyzed coupling. Our data imply that the mechanism involves a catalytically active, Cu(II) resting state and that a Cu(II) complex undergoes a concerted, rate-determining insertion of copper into the carbon-halogen bond of the aryl halide (Fig. 1D). Computations imply that radical character on the oxalamide ligand accommodates what would be an abnormally high valence at copper from a typical oxidative addition. The recognition of Cu(II) as the resting state led us to synthesize a preformed Cu(II) oxalamide complex, and this complex catalyzes couplings under air and coupling of an unactivated aryl chloride with turnover numbers exceeding 1000.

Synthesis of Cu(I) phenoxide complexes and reactions with aryl halides

Our mechanistic studies focused on reactions between aryl bromides and phenols to form biaryl ethers (24). The model coupling reaction of 1-bromo-4-fluorobenzene (**1**) with potassium phenoxide (**2**) formed 4-fluorobiphenyl ether (**3**) catalyzed by copper(I) iodide and bis-(2-phenylphenyl)oxalamide (H$_2$-BPPO, **4**) in 98% yield after heating at 100°C for 16 hours in dimethyl sulfoxide (DMSO) (Fig. 2A). Because studies with monoanionic ligands showed that couplings of phenols occur by turnover-limiting oxidative addition of aryl halides to a Cu(I) phenoxide complex (13), we first sought to generate a Cu(I) phenoxide complex bound by a mono- or dianionic form of the oxalamide ligand and to test the reactivity of such complexes with aryl halides.

Cu(I) complex **5** containing a dianionic oxalamide ligand was prepared from a 1:1 ratio of K,H-BPPO (**6**) and mesitylcopper(I). Single-crystal x-ray diffraction showed that complex **5** adopts a dimeric structure with two dianionic oxalamides bridging two copper atoms (supplementary materials section S2.4). The propensity of complex **5** to form a phenoxy-copper complex (**8**) was assessed by progressive addition of potassium 3-*tert*-butylphenoxide

to **5** in DMSO. Diagnostic ^{1}H nuclear magnetic resonance (NMR) signals of **5** shifted monotonically downfield, implying that phenoxide binds rapidly and reversibly to this complex.

The reaction of 1-bromo-4-fluorobenzene (**1**) with the mixture of **5** and potassium phenoxide at room temperature formed little aryl ether (Fig. 2B). Instead, the ^{1}H NMR resonances corresponding to the Cu complex **5** disappeared, along with 25% of **1**. No new ^{19}F NMR signals were observed, implying that the arene was transformed into a paramagnetic or insoluble species. The absence of ligand resonances suggests that the Cu(I) complex was oxidized to a new, paramagnetic, Cu(II) complex, and this hypothesis was confirmed by electron paramagnetic resonance (EPR) spectroscopy (supplementary materials section S4.7). Heating the sample at 100°C for 20 min formed biaryl ether **3** in 75% yield, along with fluorobenzene (**11**) in 18% yield, even though a Cu(II) species, rather than a Cu(I) phenoxide complex, was present in solution.

To determine whether an alternative cuprate **12** that bears one monoanionic oxalamide ligand, rather than a dianionic oxalamide, and one phenoxide ligand, was a catalytic intermediate, we prepared **12** by combining **5** with one equiv of 4-fluorophenol (**13**) (Fig. 2C). NMR spectroscopy and mass spectrometry suggest that heteroleptic cuprate **12** forms but equilibrates with the two homoleptic cuprates **14** and **15**. Addition of bromoarene 1 to this equilibrating mixture, again, caused the loss of ^{1}H NMR resonances of the ligand, presumably due to oxidation of Cu(I) to Cu(II). In this case, ^{19}F NMR spectroscopy showed that 0.20 equiv of **1** were consumed, and 0.10 equiv of fluorobenzene (**11**) formed. After heating at 100°C for 23 hours, 0.30 equiv of fluorobenzene (**11**) had formed, along with 0.20 equiv of biphenyl ether **16**; 0.33 equiv of **1** remained. Thus, the product distributions from the reaction of phenoxycuprates in the +1 oxidation state are far from the >95% yield from the catalytic coupling of the phenoxide with the same aryl halide, indicating that these Cu(I) species are not intermediates in the catalytic process.

Identification and reactions of Cu(II) complexes to assess their intermediacy in the catalytic reactions

To probe for Cu(II) complexes in the catalytic reaction, we obtained EPR spectra (Fig. 3 A). The EPR signals of a frozen reaction mixture generated from heating the aryl halide **1**, phenoxide **2**, copper iodide, and oxalamide **4** in DMSO at 100°C for 20 min corresponded to one Cu(II) species. The hyperfine pattern with- in the $g_∥$ signal at g = 2.210 (Fig. 3A, inset) indicates that the electron is coupled to four magnetically equivalent $I = 1$ nuclei. Copper(II) dioxalamide complex **17** bound by four nitrogen atoms is the most reasonable structure that matches the EPR data (25–28). Complex **17** was independently synthesized from CuBr$_2$, ligand, and base (Fig. 3C) and was fully characterized, including single-crystal x-ray diffraction (Fig. 3B). The EPR spectrum of this material matched that of the catalytic reaction (supplementary materials section S4.1 to S4.5).

Because a Cu(II) complex can initiate reactions catalyzed by a Cu(I)/Cu(III) couple (29), we assessed whether the Cu(II) complex **17** is a true catalyst or a precatalyst that is reduced to Cu(I) (Fig. 4A). To do so, complex **17** and one of the two organic reactants were combined

in an equimolar ratio, along with a 10-fold excess of the coupling partner. If complex **17** were a precatalyst and transforms to the active catalyst more rapidly than the coupling reaction, then the reagent in equimolar amounts with copper would be consumed in the catalyst activation step, leading to a low yield of biaryl ether. If complex **17** transforms to the active catalyst more slowly than the coupling reaction, then an induction period would be observed. However, if the observed Cu(II) species were a true intermediate, then the reaction would form a nearly quantitative yield of biaryl ether without an induction period and with a reaction progress curve that would reflect the order of the limiting reagent.

In the event, the reaction of Cu(II) **17** with one equiv of phenoxide **18** and excess of aryl halide **1** gave a 97% yield of biaryl ether **16** with a pseudo–zero order reaction profile through 70% conversion. The reaction of Cu(II) **17** with one equiv of aryl halide **1** and excess of phenoxide **18** gave a 99% yield of biaryl ether **16** with a pseudo–first order reaction profile. These results are inconsistent with the conversion of the Cu(II) complex to an active Cu(I) species and are consistent with the intermediacy of **17** or a species formed reversibly from **17**.

Kinetic studies were performed to establish the relative stoichiometry of the resting state and the turnover-limiting transition state (Fig. 4B). The reaction was zero order in potassium 4-chlorophenoxide (**19**), indicating that the phenoxide is either present in the resting state or that it enters the catalytic cycle after the turnover-limiting step. The reaction was nearly first order in aryl halide **1**, indicating that it associates prior to the transition state of the catalytic process. Added dianionic ligand K_2-BPPO (**20**) inhibited the reaction but had no measurable effect on the rate at concentrations higher than 0.50 mM. Because added **20** does not coordinate to **17** in solution (supplementary materials section S4.6), these data are consistent with a combination of reaction pathways involving dissociative and associative displacement of a ligand by the aryl halide. Finally, the reaction occurred with a linear dependence on the concentration of catalyst, albeit with an apparent nonzero intercept. These kinetic data are discussed in further detail in the supplementary materials.

Our experiments rule out reduction of **17** by phenoxide to form Cu(I), but we also conducted cyclic voltammetry (CV) experiments to address whether two equivalents of Cu(II) could disproportionate to form a catalytically active Cu(I) species and a corresponding Cu(III) species. CV was conducted in DMSO containing 0.20 M tetrabutylammonium hexafluorophosphate as electrolyte (Fig. 4C). The oxidation of **17** to a Cu(III) species and the corresponding reduction of **17** to a Cu(I) species are both reversible and separated by 1.81 V. This separation shows that disproportionation of two equiv of **17** into a Cu(I) and Cu(III) species is uphill by more than 41 kcal/mol, providing strong evidence against the generation of the active catalyst by disproportionation of the Cu(II) species.

Distinguishing between four potential mechanisms

Four mechanisms that have been proposed previously for Ullmann couplings and that are consistent with the kinetic data are shown in Fig. 5A. These experiments include a sigma-bond metathesis process by which a nucleophile-bound copper complex reacts directly with the aryl halide in a redox-neutral step; a nucleophilic aromatic substitution reaction that

is also redox neutral and is facilitated by formation of an arene complex to Cu; electron transfer from Cu to the aryl halide to form a Cu(III) intermediate and an aryl radical, which combines with bound phenoxide; and oxidative addition by a concerted pathway resulting in a high-valent copper intermediate. A series of further experiments were conducted to distinguish these mechanisms.

The sigma-bond metathesis mechanism would be consistent with our kinetic data only if the phenoxide were bound to copper in the resting state and remained bound through the turnover-limiting step. To assess whether a copper phenoxide complex reacts with the aryl halide, we measured the rate as a function of the identity of the phenoxide. If phenoxide were bound when the copper species reacts with the aryl halide, then the electronic properties of the phenoxide would change the identity of the complex and influence the rate of the reaction. However, no influence of the identity of the phenoxide on the rate of the reaction was detected (Fig. 5B). Further studies that show an effect of phenoxide electronic properties on the steps after the rate-determining step, thereby corroborating a lack of binding of phenoxide derivatives to Cu(II) complex **17**, are described in the supplementary materials.

The S_NAr pathway involving rate-determining attack of phenoxide on a bound aryl halide is inconsistent with the zeroth reaction order in phenoxide, but a version of this mechanism involving rate-limiting coordination of arene before nucleophilic attack is consistent with the data presented so far. To determine if coordination of the arene or cleavage of the C-X bond occurs during the rate-limiting reaction between Cu(II) and the aryl halide, we measured the ^{13}C kinetic isotope effect (KIE) (Fig. 5C). No ^{13}C KIE at the ipso carbon would be expected for reaction by the mechanism involving irreversible coordination of the aryl halide, whereas a primary ^{13}C KIE at this carbon would be expected for a mechanism involving irreversible cleavage of the aryl halide by copper. ^{13}C KIE values were measured by both intermolecular competition (30) and intramolecular competition (31) (1.011 ± 0.0003 and 1.014 ± 0.004, respectively). These normal, primary ^{13}C KIE values are comparable to those observed previously for oxidative additions of aryl iodides to Cu(I) complexes (13) and rule out irreversible binding of the aryl halide prior to nucleophilic aromatic substitution by the phenoxide.

The third pathway involving electron transfer to form an aryl halide radical anion that generates halide and an aryl radical was assessed by conducting the coupling of phenoxide with aryl halide **22** catalyzed by Cu(II) complex **17** (Fig. 5D). An aryl radical formed from **22** is known to cyclize rapidly ($k > 10^7 \ s^{-1}$) (32) with the *ortho*-butenyl substituent. However, the reaction of phenoxide **2** with aryl halide **22** formed no cyclized products, as determined by gas chromatography–mass spectrometry and NMR spectroscopy. This result, in concert with the low reducing power of complex **17** (Fig. 4C), rules out reduction of the aryl halide to generate an aryl radical intermediate and subsequent outer-sphere reductive elimination with a copper(III) phenoxide complex, and it is consistent with the previously reported lack of cyclization during the reaction between 2-butenyl-chlorobenzene and *p*-cresol catalyzed by copper and a different oxalamide ligand (18). Instead, all our data are consistent with the fourth mechanism involving concerted, rate-determining reaction of

the aryl halide with a Cu(II) complex of the oxalamide ligand to cleave the carbon-halogen bond.

DFT study of the oxidative addition of aryl halides to Cu(II).

We assessed by density functional theory (DFT) calculations the mechanism by which a Cu(II) species could react with an aryl halide to cleave the carbon-halogen bond. Because large differences in energy result from modeling of charged species with different degrees of explicit solvation, we did not compute the energetics for dissociation of the anionic ligand from the cuprate to form a neutral Cu(II) species. Instead, we studied the energetics for binding of the aryl bromide to (BPPO)Cu (**29**) and the feasibility of an insertion of the Cu intermediate into the carbon-halogen bond of the bound aryl halide by a step akin to a concerted oxidative addition. Analysis by the fractional orbital density (FOD) method published by Grimme (33) demonstrated that most structures on the reaction coordinate possess appreciable multireference character (N_FOD = 1.4 to 2.0). Because the inclusion of HF-exchange energy causes high errors in the relative calculated energies for structures with multireference character (33), we used the meta-GGA functional TPSS-D3(BJ) for all calculations. Geometry optimization and frequency calculations were conducted with the def2-TZVP basis set on copper and the def2-SVP basis set on all other atoms, and single-point energies were calculated with the def2-TZVP basis set on all atoms. The computed profile begins with a copper(II) complex ligated by an *N,N*-bound oxalamide ligand (**29**) (Fig. 6A). Association of the aryl halide to yield **30** was calculated to be endergonic by 12.4 kcal/mol, and the product from oxidative addition of the bound arene (**31**) was found to be 21.0kcal/mol higher in free energy than the starting complex. The transition state to form this complex (**32**) was computed to lie 23.1 kcal/mol above the starting complex. These energies are consistent with our conclusion from experimental studies that the Cu(II) species cleaves the carbon-halogen bond in the rate-determining step and suggest that this bond cleavage can occur by oxidative addition. A full account of our DFT studies is included in the supplementary materials.

To reveal the electronic structure of the complexes involved in this oxidative addition, we conducted natural population analysis on each species. Arylcopper halide complex **31** lacked spin density on copper. Instead, >98% of the spin density was located on the ligands bound to copper, with 86% located on the oxalamide. This ligand redox non-innocence (34) enables the Cu(II) resting state to undergo oxidative addition of the aryl halide to form complex **31** containing both an aryl ligand and a halide ligand without a nearly unprecedented oxidation state at Cu. Indeed, natural population analysis of this complex suggests that the copper in it possesses 10 d-electrons, and this electron count implies that intermediate **31**, although formally Cu(III) by the presence of three formally anionic ligands and an overall neutral charge, is best described as a Cu(I) complex with an inverted ligand field, as discussed for many formally Cu(III) complexes (35, 36), and with radical character on the ligand to accommodate the large number of X-type ligands.

Reaction improvements with a preformed Cu(II) catalyst

A Cu(II) resting state is stable to air and disproportionation. Thus, a purposeful synthesis of a Cu(II) catalyst should create a system that is stable to air and that reacts with high turnover numbers. Indeed, the cross-coupling reaction between 4-fluorobromobenzene (**1**) and 3-*tert*-butyl phenol (**33**) catalyzed by just 1.0 mol % of **17** in DMSO on a 1-mmol scale without any effort to exclude air or water gave the coupled product **34** in 97% yield after 36 hours at 100°C. Moreover, the coupling of 2-chloronaphthalene (**35**) with potassium 3-*tert*-butylphenoxide (**7**) with just 500 parts per million of pure **17** as the catalyst for 72 hours at 130°C gave 59% yield of biaryl ether **36**, corresponding to >1000 turnovers. We propose that the high stability of these catalysts at the temperatures required for the activation of carbon-chlorine bonds makes them more long-lived for this transformation than electron-rich, Cu(I) complexes that are more prone to degradation.

These results highlight the potential of well-defined copper(II) catalysts to increase catalyst activity, turnover numbers, and reproducibility of copper-catalyzed coupling reactions with this and related classes of ligands. In addition, the discovery of this reaction mechanism could facilitate the development of next-generation ligands for catalysts containing copper or other first-row metals to minimize single-electron reactivity and allow such metals to fill roles that are currently realized by noble metal catalysts in a variety of reactions important for organic synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data and materials availability:

All other data are available in the main text or the supplementary materials. X-ray data are available in the Cambridge Crystallographic Data Center under CCDC numbers 2265761 and 2265762.

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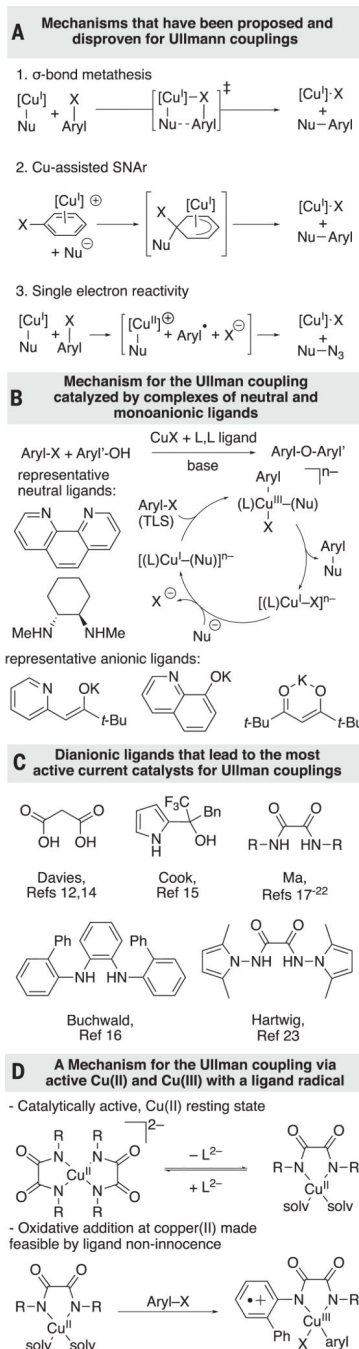36. Hoffmann R et al., Chem. Rev 116, 8173–8192 (2016). [PubMed: 27398715]

Fig. 1. Current understanding of reaction mechanisms for Cu-catalyzed C–O coupling reactions.
(**A**) Proposed mechanisms for the reaction between copper complexes and aryl halides that have been ruled out by prior studies. (**B**) General reaction mechanism determined for C–O cross-coupling catalyzed by copper complexes of neutral or anionic bidentate ligands. (**C**) Recently discovered ligands that are highly active and can bind as dianionic ligands. (**D**) This work: Discovery of a mechanism with a copper(II) resting state and oxidative addition to a copper(II) complex.
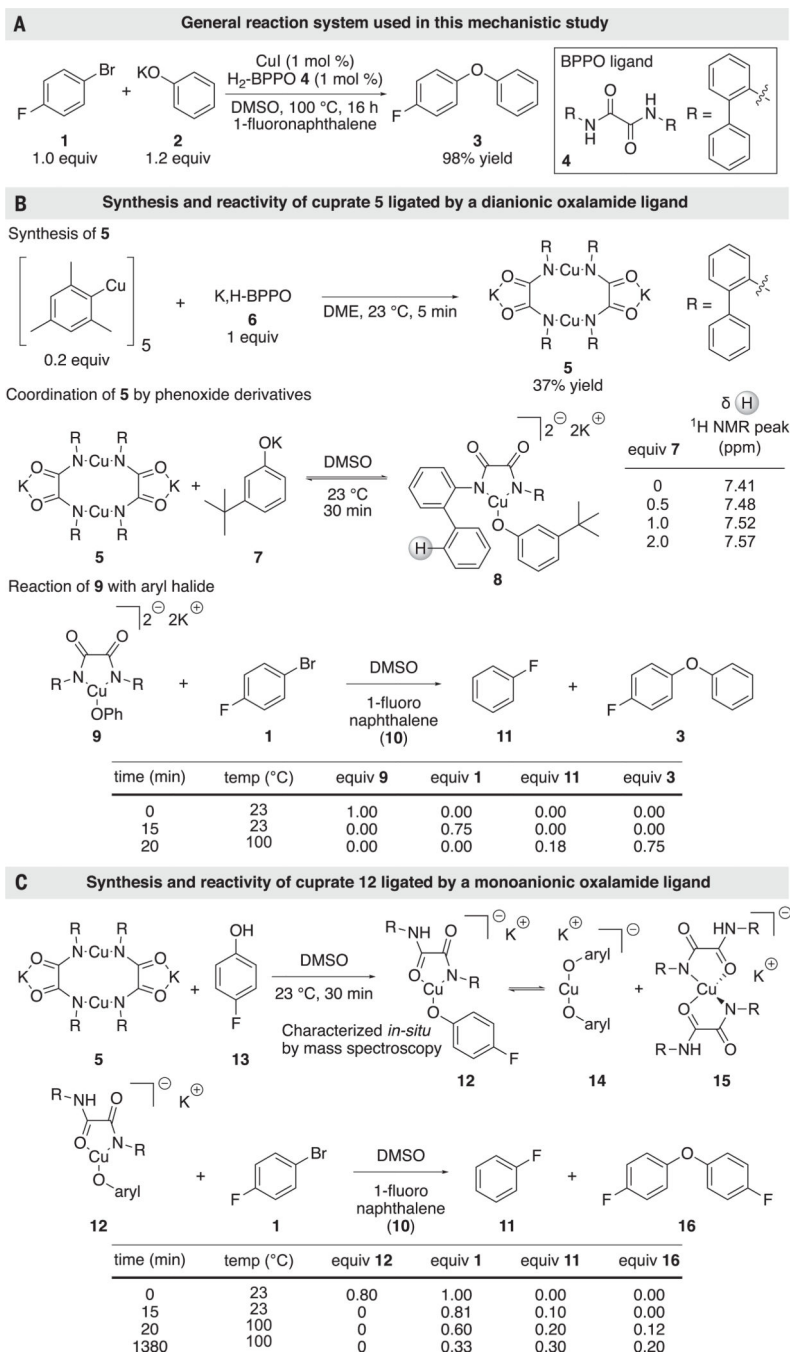
Fig. 2. Synthesis and reactivity of Cu(I) complexes of oxalamide ligands.
(**A**) General conditions for the reaction under study, adapted from (21). (**B**) Synthesis of dianion-bound cuprate **5** and reactivity with aryl halides and potassium phenoxide derivatives. (**C**) Synthesis of monoanion-bound cuprate **12** and reactivity with aryl halide electrophiles.
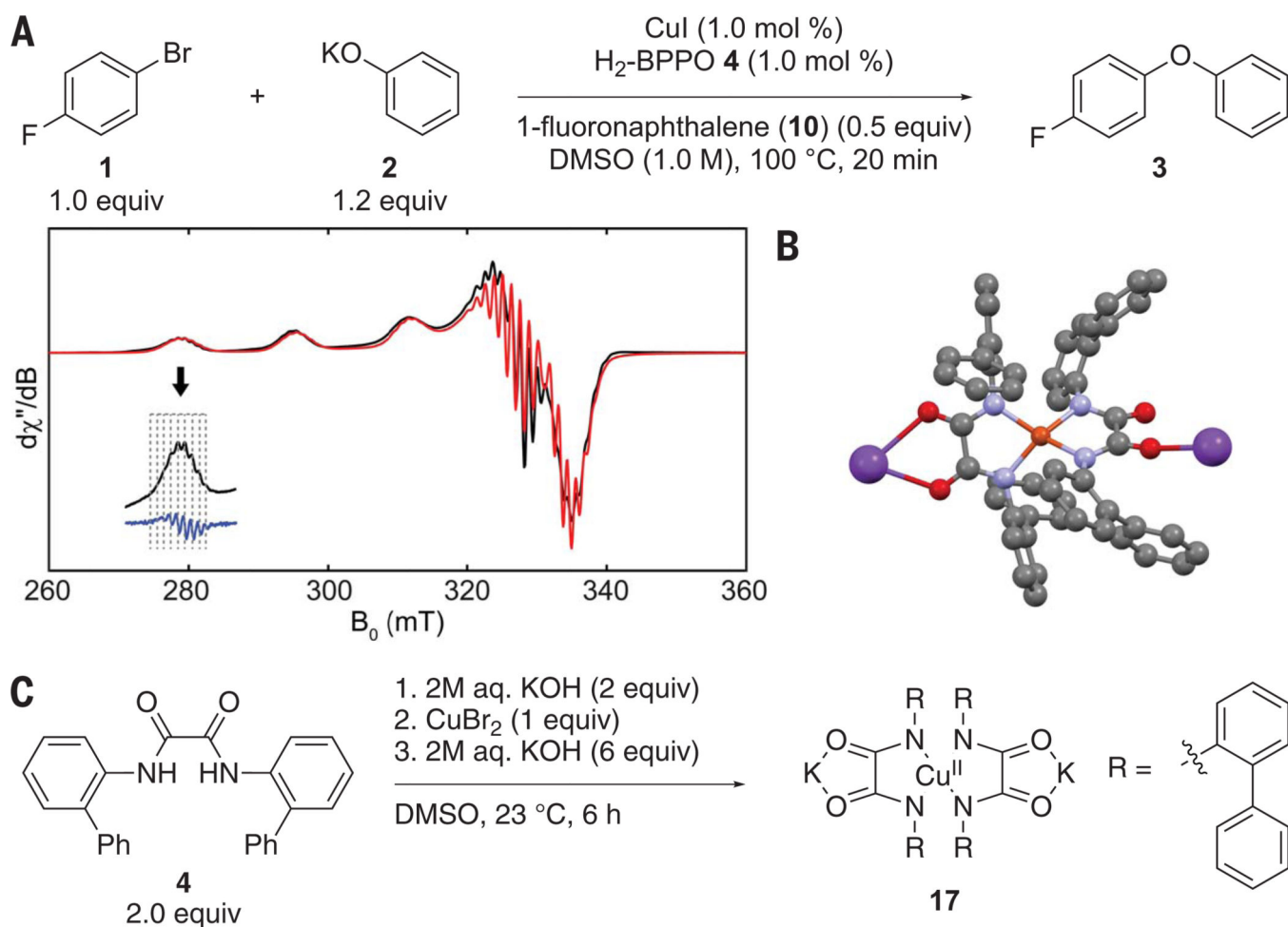
Fig. 3. Synthesis and key characterization of Cu(II) complex 17.
(**A**) X-band EPR spectrum of a reaction mixture set up with CuI, H₂-BPPO, 4-fluorobromobenzene, potassium phenoxide, and 1-fluoronapthalene in DMSO, heated at 100°C for 30 min then flash frozen in liquid nitrogen. Black trace: Experimentally obtained spectrum. Red trace: Simulated spectrum. (Inset) The hyperfine splitting pattern within the g∥ signal, along with the second-derivative spectrum in that region. (**B**) Structure of **17** determined by single-crystal x-ray diffraction; five DMSO molecules that cocrystallized and crystallographic disorder were removed for clarity. (**C**) Synthetic route to **17**.
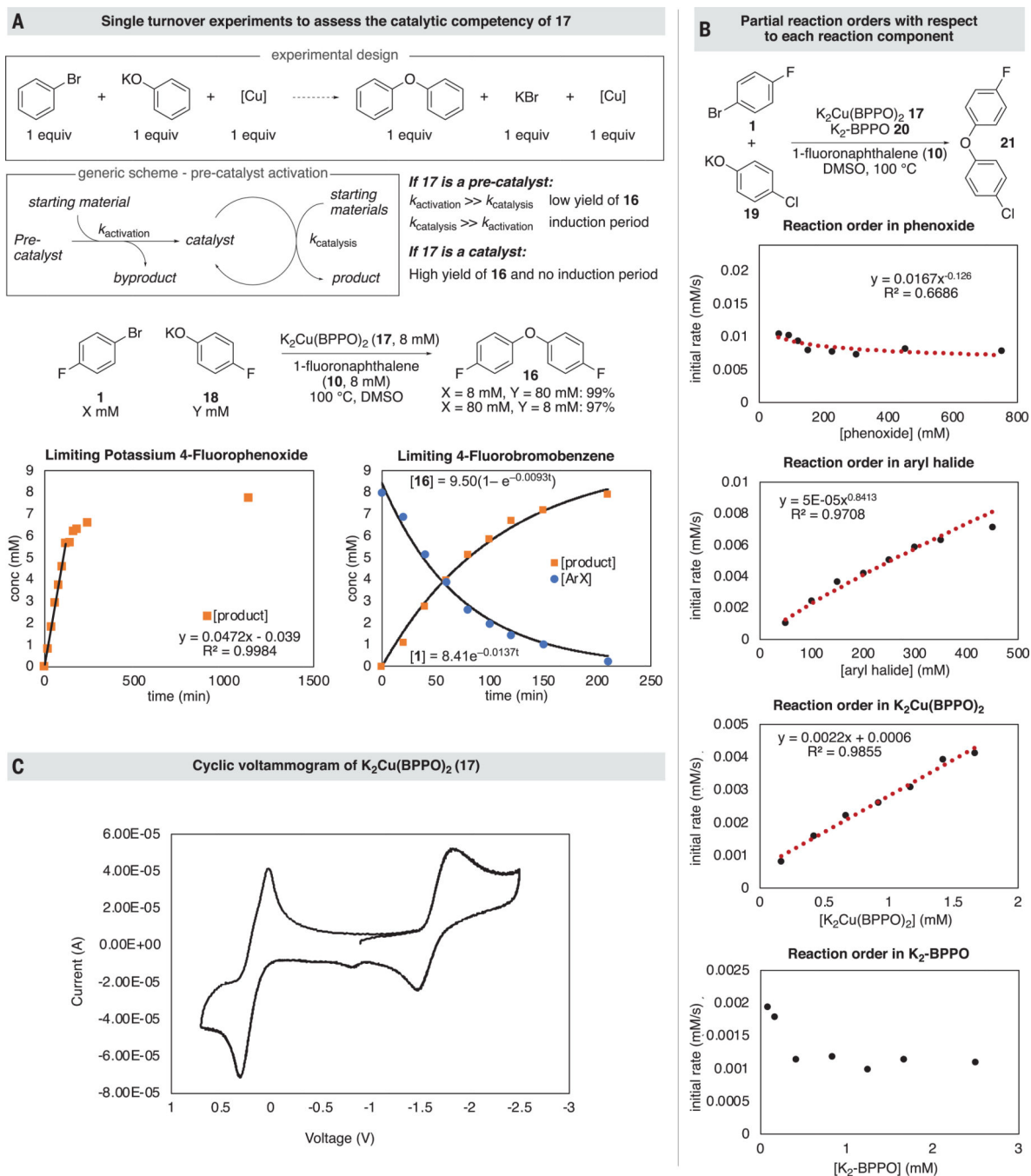
Fig. 4. Mechanistic experiments to establish the resting state, turnover-limiting step, and pre-equilibria.

(**A**) Single-turnover experiment that determines whether **17** must be activated by either coupling partner before entering the catalytic cycle. (**B**) Reaction orders in phenoxide (zero order), aryl halide (first order), catalyst (first order), and ligand dipotassium salt (inverse order). (**C**) Cyclic voltammogram of $K_2Cu(BPPO)_2$ in a 0.20 M DMSO solution of tetrabutylammonium hexafluorophosphate.
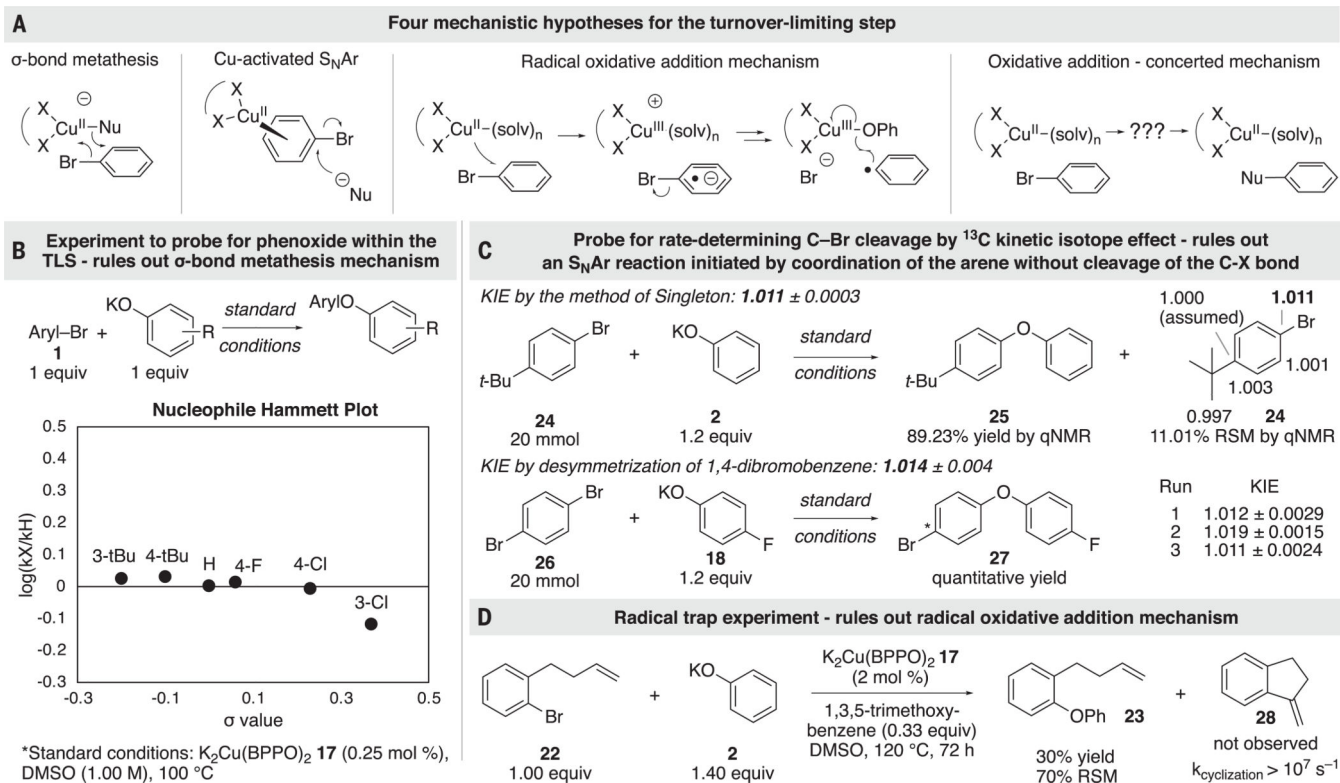
Fig. 5. Mechanistic studies to probe the nature of the resting state and turnover-limiting step.
(**A**) Four mechanistic hypotheses for the turnover-limiting reaction between Cu and the aryl halide. (**B**) Hammett plot demonstrating that phenoxide is not bound to copper in the turnover-limiting step. (**C**) Natural abundance ^{13}C kinetic isotope experiments conducted by the methods of Singleton and Vetticatt. (**D**) Reactions conducted with an aryl bromide containing a pendant alkene that probes the intermediacy of aryl radical species.
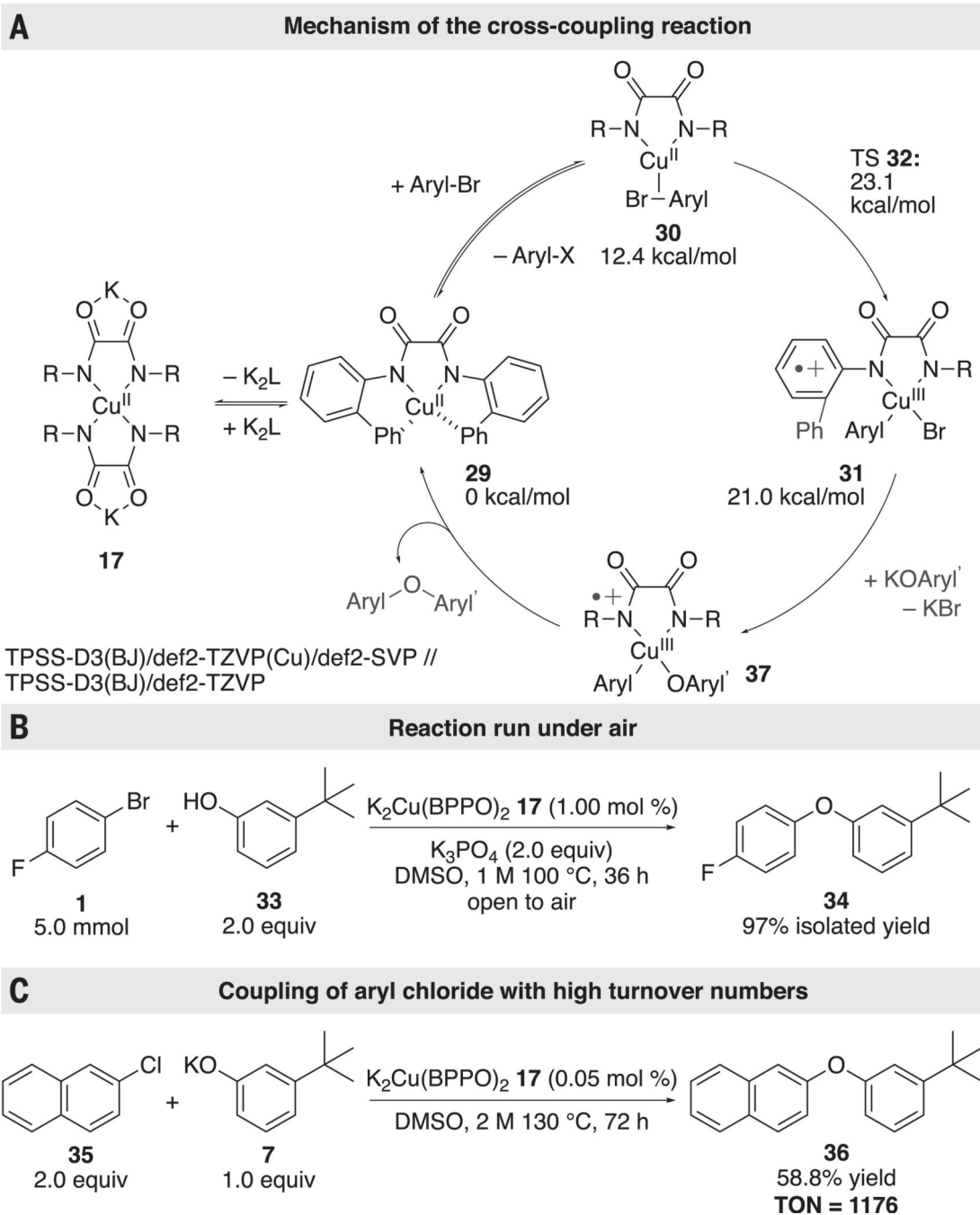
Fig. 6. Mechanism of the cross-coupling reaction and synthetic applications.
(**A**) Catalytic cycle representing our mechanistic conclusions. (**B** and **C**) Applications of the Cu(II) complex in preparative, cross-coupling reactions.