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Three-Coordinate Copper(II) Alkynyl Complex in C−C Bond Formation: The Sesquicentennial of the Glaser Coupling

Abolghasem Bakhoda,[‡] Otome E. Okoromoba,[‡] Christine Greene, Mahdi Raghibi Boroujeni, Jeffery A. Bertke, and Timothy H. Warren*

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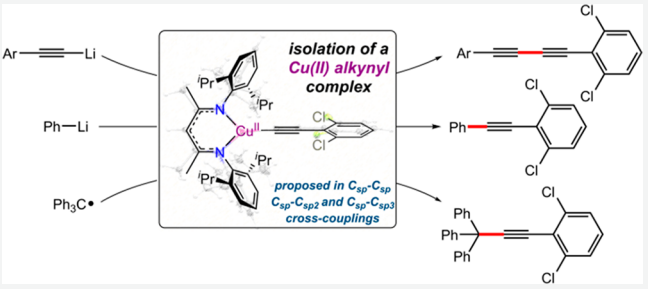
ABSTRACT: Copper(II) alkynyl species are proposed as key intermediates in numerous Cu-catalyzed C−C coupling reactions. Supported by a β-diketiminate ligand, the three-coordinate copper(II) alkynyl [Cu^{II}]−C≡CAr (Ar = 2,6-$Cl_2C_6H_3$) forms upon reaction of the alkyne H−C≡CAr with the copper(II) *tert*-butoxide complex [Cu^{II}]−O^{t}Bu. In solution, this [Cu^{II}]−C≡CAr species cleanly transforms to the Glaser coupling product ArC≡C−C≡CAr and [Cu^{I}](solvent). Addition of nucleophiles R′C≡C−Li (R′ = aryl, silyl) and Ph−Li to [Cu^{II}]−C≡CAr affords the corresponding C_{sp}−C_{sp} and C_{sp}−C_{sp2} coupled products RC≡C−C≡CAr and Ph−C≡CAr with concomitant generation of [Cu^{I}](solvent) and {[Cu^{I}]−C≡CAr}$^-$, respectively. Supported by density functional theory (DFT) calculations, redox disproportionation forms [Cu^{III}](C≡CAr)(R) species that reductively eliminate R−C≡CAr products. [Cu^{II}]−C≡CAr also captures the trityl radical Ph_3C· to give Ph_3C−C≡CAr. Radical capture represents the key C_{sp}−C_{sp3} bond-forming step in the copper-catalyzed C−H functionalization of benzylic substrates R−H with alkynes H−C≡CR′ (R′ = (hetero)aryl, silyl) that provide C_{sp}−C_{sp3} coupled products R−C≡CR via radical relay with ^{t}BuOO^{t}Bu as oxidant.



INTRODUCTION

Transition metal-mediated carbon−carbon bond formation represents one of the most fundamental transformations in chemical and material synthesis.[1] Carl Glaser developed the first copper-mediated oxidative coupling of terminal alkynes 150 years ago, suggesting copper organometallic intermediates in the C_{sp}−C_{sp} coupling of phenylacetylene (H−C≡C−Ph) to give the diyne Ph−C≡C−C≡C−Ph via reaction of ammoniacal cuprous chloride with oxygen as the oxidant (Figure 1a).[2] Glaser suggested that copper(I) acetylide dimer forms and undergoes oxidation by O_2 to ultimately release Ph−C≡C−C≡C−Ph.[2]

A number of mechanistic proposals have evolved to explain the Glaser C_{sp}−C_{sp} coupling (Figure 1a). Salkind and Fundyler offered an early proposition that involved alkyne deprotonation followed by oxidation via copper(II) to form an alkynyl radical that dimerizes to give the 1,3-diyne product (Figure 2a).[3] On the basis of a combination of kinetic studies and the prevalence of selective homocoupling in mixtures of alkynes, Bohlman discounted a radical mechanism and put forth dimeric copper(II) acetylides as key species in C−C coupling (Figure 2b).[4] As part of a detailed mechanistic study of the Glaser−Hay reaction, which enables catalytic dimerization of terminal alkynes with O_2 as a terminal oxidant, Vilhelmsen, Nielsen, and co-workers suggested a new role for a discrete copper(II) acetylide complex (Figure 2c).[5,6] They proposed that a

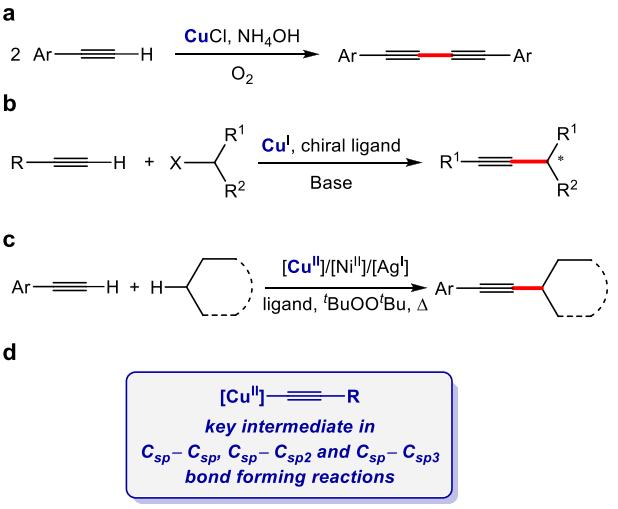


Figure 1. Proposed Cu alkynyl intermediates in C_{sp}−C_{sp}, C_{sp}−C_{sp2}, and C_{sp}−C_{sp3} bond-forming reactions.

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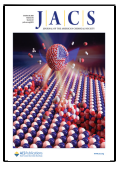

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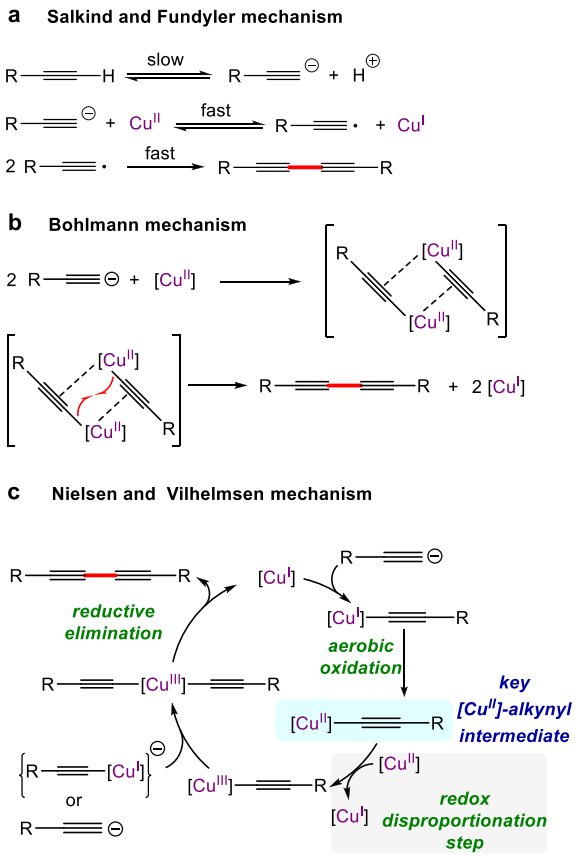

Figure 2. Mechanistic proposals for copper(II)-promoted C_{sp}–C_{sp} coupling. (a) Homocoupling of alkynyl radicals (Salkind and Fundyler). (b) Dimerization of Cu^{II} alkynyl intermediates (Bohlmann). (c) Redox disproportionation of Cu^{II} acetylide to $[Cu^{III}](C{\equiv}CR)_2$ intermediate that undergoes C–C reductive coupling (Nielsen and Vilhelmsen).

copper(I) acetylide (formed upon deprotonation of the alkyne in the presence of a copper(I) source)[7] is aerobically oxidized to the corresponding copper(II) acetylide.[5] Redox disproportionation of this copper(II) acetylide generates a cationic copper(III) acetylide and a nucleophilic copper(I) acetylide that can combine to give a copper(III) bis(acetylide) species that is susceptible to reductive elimination to give the C–C coupled 1,3-diyne product.

Such copper(II) alkynyl intermediates are also envisioned in several copper-catalyzed organic transformations such as oxidative C_{sp}–C_{sp3} couplings (Figure 1b), trifluoromethylalkynylation of alkenes, [3 + 2] cycloaddition with azides, oxidative C_{sp3}–H/C_{sp}–H cross-couplings (Figure 1c), oxidative coupling of terminal alkynes, deacetylative coupling of ynones, and oxidative amidation of terminal alkynes.[8−19] For instance, recent Pd-free Sonogashira-type reactions that form C_{sp}–C_{sp3} or C_{sp}–C_{sp2} bonds have been proposed to proceed through the intermediacy of a copper(II) alkynyl species.[8,20,21] Such cupric acetylides were also proposed by Liu and co-workers as intermediates in the enantioselective trifluoromethylalkynylation of alkenes under particularly mild conditions.[9] Recently, Lei and co-workers reported the cross-dehydrogenative coupling of terminal alkynes with unactivated alkanes using a multimetal-catalyzed reaction strategy to prepare internal alkynes (Figure 1c) that was also proposed to proceed via copper(II) alkynyl intermediates.[11−14] Most recently, Liu and his team reported an elegant methodology for the enantioselective alkynylation of benzylic C–H bonds via a radical relay mechanism. Employing *N*-fluorodi(benzenesulfonyl)amine (NFSI) as an oxidant, they proposed chiral (bisoxazoline)Cu^{II} alkynyl species as key intermediates that enantioselectively capture benzylic radicals.[19]

Despite numerous examples of well-characterized copper(I) acetylide complexes,[22] copper(II) alkynyls, and in general any structurally well-defined organocopper(II) complexes, are extremely rare.[23] In 2017, Tilley and co-workers described the mixed-valent Cu(I)Cu(II) μ-alkynyl complex $\{[DPFN]\text{-}Cu_2(\mu\text{-}\eta^1{:}\eta^1\text{-}C{\equiv}CArp\text{-}Me)\}^{2+}$ (DPFN = 2,7-bis[fluorodi(2-pyridyl)methyl]-1,8-naphthyridine; Arp-Me = 4-MeC_6H_4) as stable toward diyne formation (Figure 3a).[24] Inspired by a β-diketiminato mononuclear copper(II) aryl complex isolated in our laboratory (Figure 3b),[25] we targeted a discrete, mononuclear copper(II) alkynyl $[Cu^{II}]$–C≡CAr.

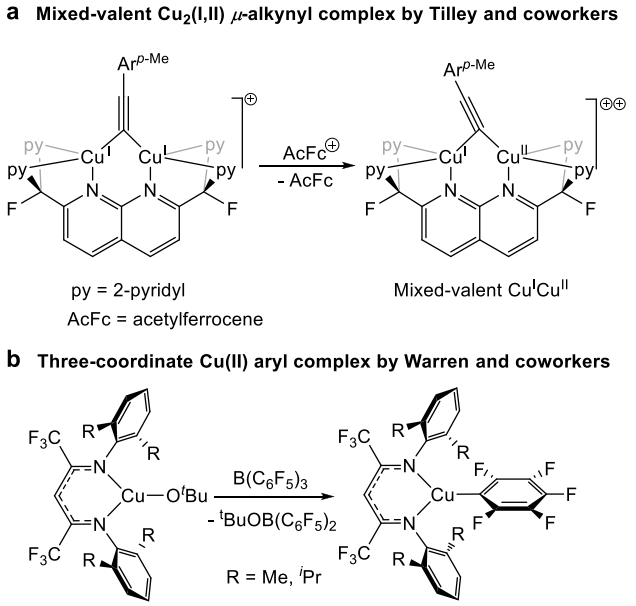

Figure 3. Structurally well-defined organocopper(II) compounds.

RESULTS AND DISCUSSION

Synthesis, Characterization, and Reactivity of a Copper(II) Alkynyl Complex. Reaction of the copper(I) β-diketiminate complex $[^iPr_2NN]Cu(NCMe)$[26] (**1-MeCN**) with ^{t}BuOO^{t}Bu at room temperature (RT) gives $[^iPr_2NN]Cu^{II}$–O^{t}Bu (**2**). This three-coordinate Cu(II) alkoxide is similar in structure to several related $[Cu^{II}]$–O^{t}Bu species (Figure S20) and possesses closely related spectroscopic parameters.[27−29] Addition of H–C≡CAr^{Cl2} (Ar^{Cl2} = 2,6-$Cl_2C_6H_3$) to **2** in *n*-pentane at RT results in a color change from brown to dark violet. The choice of the terminal alkyne was crucial in order to successfully synthesize and isolate the terminal, three-coordinate copper(II) alkynyl complex. While the reaction of a range of alkyl- and arylacetylenes H–C≡CR and H–C≡CAr were examined with $[^iPr_2NN]Cu^{II}$–O^{t}Bu (**2**), ultimately 2,6-dichlorophenylacetylene H–C≡CAr^{Cl2} possessed an appropriate combination of steric protection and C–H acidity to cleanly furnish the terminal Cu(II) alkynyl **3**. Crystallization from *n*-pentane affords dark violet crystals of $[^iPr_2NN]Cu$–C≡CAr^{Cl2} (**3**) in 41% isolated yield (Figure 4a). The X-ray

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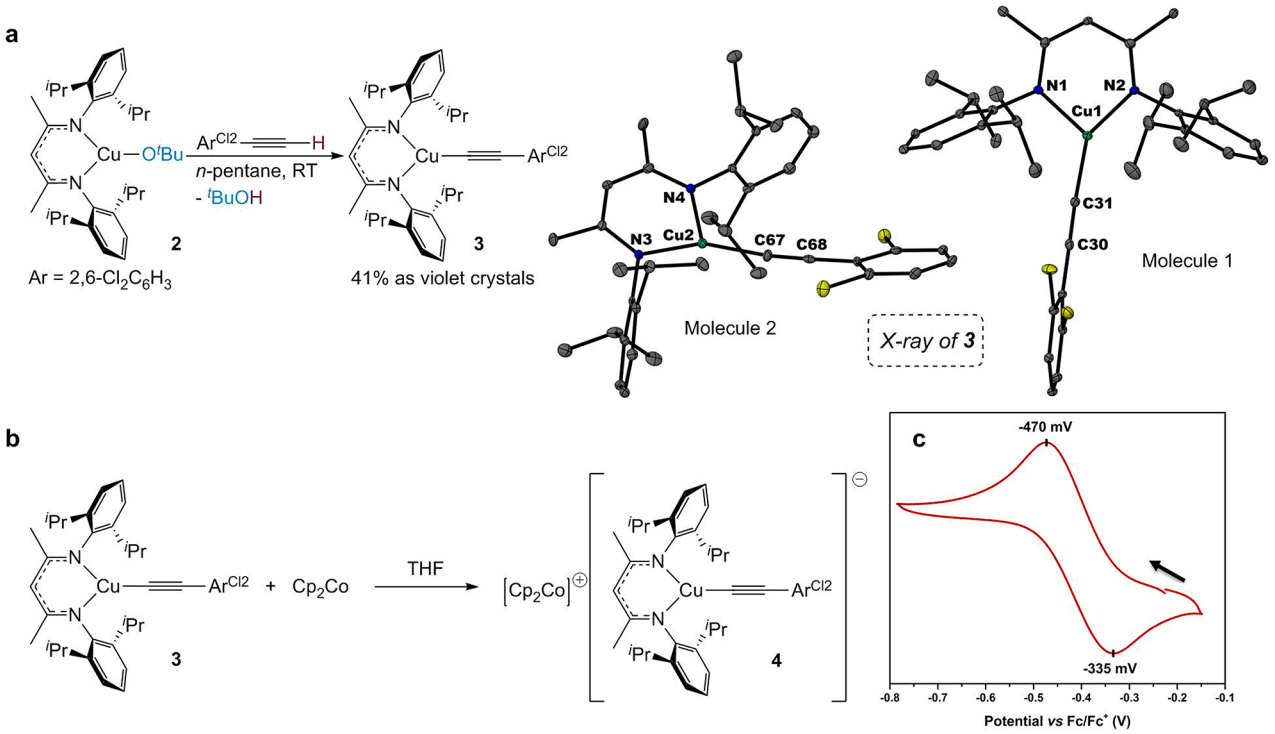

Figure 4. Synthesis and isolation of the three-coordinate Cu(II) alkynyl **3**. (a) Synthesis and X-ray crystal structure of [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2} (**3**). (b) One-electron reduction of **3** with cobaltocene to generate [Cp$_2$Co]$^+${[^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2}}$^-$ (**Cp$_2$Co$^+$-4**). (c) Cyclic voltammogram at 20 mV/s of **3** in fluorobenzene (1.8 mM) at 23 °C with 0.1 M NaBAr$^F_4$ (Ar^F = 3,5-(CF$_3$)$_2$C$_6$H$_3$) as a supporting electrolyte.

structure of **3** reveals two nearly identical, yet crystallographically independent, molecules featuring trigonal planar coordination at the Cu centers (Σ(angles about Cu) = 359.72(7) and 359.60(8)°). The Cu−C$_{alkynyl}$ distances of 1.887(5) and 1.872(6) Å are on the low end of those reported for Cu(I) acetylide complexes (1.87−1.98 Å).[22] The large disparity of the two N−Cu−C angles in **3** (molecule 1, 142.5(2) and 122.0(2)°; molecule 2, 150.6(2) and 112.9(2)°) and the shortened Cu−N distance distal to the Cu−C unit (Cu−N distances: molecule 1, 1.907(4) and 1.859(4) Å; molecule 2, 1.903(4) and 1.861(4) Å) result in a Y-shaped geometry around the Cu atom. In the solid state there is a π-stacking interaction between an electron-rich *N*-aryl ring of molecule 1 and an electron-deficient alkynyl dichlorophenyl ring of molecule 2 (Figure 4a).

The isotropic X-band electron paramagnetic resonance (EPR) spectrum of **3** in toluene at 200 K shows a four-line signal characteristic of a mononuclear Cu(II) center (Figure S5). Simulation of the isotropic EPR spectrum provides g_{iso} = 2.097 with A_{iso}(Cu) = 210 and A_{iso}(N) = 40 MHz. The frozen glass EPR spectrum of **3** in toluene at 80 K is axially biased with g_1 = 2.178, g_2 = 2.040, and g_3 = 2.050 with A_1(Cu) = 130, A_2(Cu) = 290, and A_3(Cu) = 130 MHz, respectively (Figure S6). These data are in good agreement with previously reported axially biased three-coordinate [Cu^{II}]−X species (X = amide, alkoxide, thiolate, and halide) with $g_1 \approx 2.20$ and $g_{2,3} \approx 2.05$.[27−32] The IR spectrum of **3** exhibits $\nu_{C\equiv C}$ at 2187 cm^{-1} (Figure S7), while the optical spectrum of **3** in toluene shows a strong band at λ_{max} = 580 nm (4300 M^{-1} cm^{-1}) (Figure S4).

Cyclic voltammetry of [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2} (**3**) in fluorobenzene (PhF) at RT exhibits a quasi-reversible reduction wave centered at −470 mV vs Fc$^+$/Fc (Figure 4c). Encouraged by this observation, reduction of **3** by cobaltocene (Cp$_2$Co) in C$_6$D$_6$ at RT allows for in situ formation of the corresponding copper(I) acetylide [Cp$_2$Co]$^+${[^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2}}$^-$ (**Cp$_2$Co$^+$-4**) as shown in Figure 4b. Unfortunately, this species decays in solution over a matter of minutes to form an insoluble yellow solid preventing characterization by X-ray crystallography. Nonetheless, ^{1}H NMR analysis of the reaction mixture in THF-d_8 (tetrahydrofuran) fully supports the diamagnetic nature of anionic **Cp$_2$Co$^+$-4**. These spectroscopic signatures include a sharp, distinct doublet at δ 6.60 ppm and a triplet at δ 6.17 ppm that represents *meta*-H and *para*-H resonances of the Ar^{Cl2} ring on the acetylide ligand, respectively, along with a diagnostic signal for the β-diketiminate backbone C−H methine at δ 4.75 ppm (Figure S9).

Mechanism for C$_{sp}$−C$_{sp}$ and C$_{sp}$−C$_{sp2}$ Coupling via [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2}: Experiment and Theory. The copper(II) alkynyl [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2} (**3**) is unstable in solution at RT, transforming to ^{Cl2}ArC≡C−C≡CAr^{Cl2} (**5**) and [^{i}Pr$_2$NN]Cu(solvent) over hours to minutes, depending on the solvent (Figure 5a). Surprisingly, the use of polar solvents such as MeCN accelerates diyne formation from [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2} (**3**) to form ^{Cl2}ArC≡C−C≡CAr^{Cl2} and [Cu^I]−NCMe (**1-MeCN**) in 88% and 98% yields, respectively, within 5 min (Figure 5a). These observations run counter to the Bohlmann mechanism[4] (Figure 2b), which requires a bimolecular interaction between [Cu^{II}]−C≡CR species to form a less-polar dimer {[Cu^{II}]$_2$(μ-C≡CR)$_2$}. Moreover, a spontaneous loss of the ·C≡CAr^{Cl2} radical from [Cu^{II}]−C≡CAr^{Cl2} (**3**) connected to the Salkind and Fundyler mechanism[3] (Figure 2a) is unlikely due to the high bond-dissociation free energy (BDFE) of the copper(II) acetylide bond calculated at 73.1 kcal/mol (BP86+GD$_3$BJ/6-311++G(d,p)/SMD-acetonitrile//BP86/6-311+G(d)/gas).

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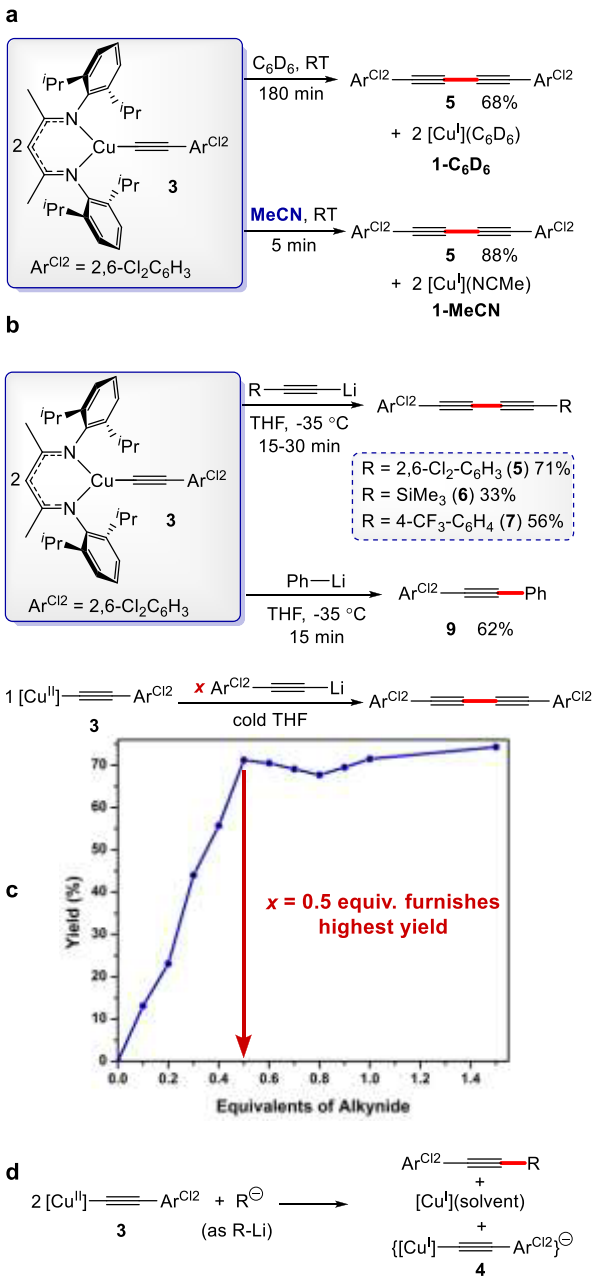

Figure 5. Mechanistic studies of Cu(II) alkynyl-mediated C−C coupling reactions. (a) C_{sp}−C_{sp} and C_{sp}−C_{sp2} coupling promoted by polar solvents (MeCN) or (b) organolithium nucleophiles (R−Li) mediated by Cu(II) alkynyl complex **3**. (c) Yield of diyne **5** vs equivalents of Li−C≡CAr^{Cl2} added to **3**, reaching a maximum yield with a 2[Cu^{II}]−C≡CAr^{Cl2}:1Li−C≡CAr^{Cl2} stoichiometry.

On the other hand, the addition of alkynide and phenyl nucleophiles R^- (as Li−R reagents) to [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2} (**3**) spontaneously leads to R−C≡CAr^{Cl2} products according to the stoichiometry 2[Cu^{II}]−C≡CAr^{Cl2}:1Li−R (Figure 5b). Addition of 1 equiv of Li−C≡CAr^{Cl2} (Ar^{Cl2} = 2,6-$Cl_2C_6H_3$) to 2 equiv of **3** in THF at −35 °C provides the symmetric diyne ^{Cl2}ArC≡C−C≡CAr^{Cl2} (**5**) in 71% yield (Figure 5b). Interestingly, the addition of 1 equiv of Li−C≡CTMS (TMS = trimethylsilyl) or Li−C≡CAr^{CF3} (Ar^{CF3} = 4-$CF_3C_6H_4$) to 2 equiv of **3** in cold THF results in an immediate color change from violet to bright orange and formation of the corresponding unsymmetric 1,3-diynes TMS−C≡C−C≡CAr^{Cl2} (**6**) or ^{CF3}ArC≡C−C≡CAr^{Cl2} (**7**) in 33% and 56% yields, respectively (Figure 5b). In each case, the homocoupled 1,3-diyne ^{Cl2}ArC≡C−C≡CAr^{Cl2} (**5**) also forms in 36% and 13% yields, respectively.

This coupling reaction of the copper(II) acetylide with incoming nucleophiles may be general. For instance, the reaction of Ph−Li (1 equiv) with **3** (2 equiv) in cold THF afforded PhC−C≡CAr^{Cl2} (**9**) in 62% yield. Carrying out the reaction in a mixture of THF and benzene-d_6, we observed the formation of both [^{i}Pr$_2$NN]Cu(benzene) and {[^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2}}$^-$ by ^{1}H NMR analysis (Figures 5d and S13). Considering the 2:1 [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2}:Li−R stoichiometry, a balanced reaction can be drawn (Figure 5d). This reactivity parallels the addition of a PhO^- nucleophile to the β-diketiminato-supported copper(II) aryl [Cu^{II}]−C_6F_5 (Figure 3) that results in the formation of the coupled organic product PhO−C_6F_5 along with a reduced copper species [Cu^I](solvent) and {[Cu^I]−C_6F_5}$^-$.[25]

DFT studies support reaction pathways that proceed through redox disproportionation of the copper(II) acetylide into copper(III) and copper(I) acetylide complexes (Figure 6). In the absence of an added nucleophile, [^{i}Pr$_2$NN]Cu^{II}−C≡CAr^{Cl2} disproportionates to {[^{i}Pr$_2$NN]Cu^{III}−C≡CAr^{Cl2}}$^+$ (**8**) and {[^{i}Pr$_2$NN]Cu^I−C≡CAr^{Cl2}}$^-$ (**4**), facilitated by a polar solvent such as MeCN that stabilizes these charged species (Figure 6a). This accounts for the dramatic rate acceleration in MeCN vs benzene (Figure 5a). In the next step, anionic acetylide **4** attacks cationic acetylide **8** to form [^{i}Pr$_2$NN]-Cu^{III}(C≡CAr^{Cl2})$_2$ followed by reductive elimination that furnishes the homocoupled product ^{Cl2}ArC≡C−C≡CAr^{Cl2} (**5**).

The addition of a nucleophile R^- stimulates redox disproportionation by stabilizing the higher oxidation state copper(III) intermediate. [Cu^{II}]−C≡CAr^{Cl2} (**3**) binds the nucleophile R^-, modeled as either ^{Cl2}ArC≡C^- or Ph^-, to form the four-coordinate {[Cu^{II}](C≡CAr^{Cl2})R}$^-$ species (Figure 6b). Owing to their negative charge, electron-rich {[Cu^{II}](C≡CAr^{Cl2})R}$^-$ complexes are especially unstable toward redox disproportionation in the presence of [Cu^{II}]−C≡CAr^{Cl2} (**3**) to give [Cu^{III}](C≡CAr^{Cl2})R along with the anionic acetylide {[Cu^I]−C≡CAr^{Cl2}}$^-$ (**4**). Facile reductive elimination from [Cu^{III}](C≡CAr^{Cl2})R provides the corresponding C−C coupled products R−C≡CAr^{Cl2} (Figure 5b). As noted earlier, this mechanism is related to the Cu-mediated C_{sp2}−O bond formation via a [Cu^{II}]−C_6F_5 intermediate (Figure 3b) that undergoes attack by a phenolate nucleophile PhO^- that triggers redox disproportionation between {[Cu^{II}](C_6F_5)-(OPh)}$^-$ and [Cu^{II}]−C_6F_5 to give [Cu^{III}](C_6F_5)(OPh), which rapidly reductively eliminates the diaryl ether PhO−C_6F_5.[25]

C_{sp}−C_{sp3} Coupling Mediated by [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2} (3) and Catalytic C−H Alkynylation. The copper(II) alkynyl [^{i}Pr$_2$NN]Cu−C≡CAr^{Cl2} (**3**) captures the radical Ph_3C· (formed in the equilibrium dissociation of Gomberg's dimer {Ph_3C}$_2$)[33] to form Ph_3C−C≡CAr^{Cl2} (**10**) within 5 min at RT in 69% yield along with [^{i}Pr$_2$NN]Cu(C_6D_6) in 78% yield (Figure 7a). Because capture of radicals R· by [Cu^{II}]−FG (FG = amide, anilide, alkoxides, phenoxide) to give R−FG is the key C−FG bond-forming step in radical relay mechanisms for C_{sp3}−H functionalization (Figure 7b, step (iv)),[27,29,31,32,34−36] we explored the possibility of C_{sp3}−H alkynylation mediated by copper(II) alkynyls [Cu^{II}]−C≡CR

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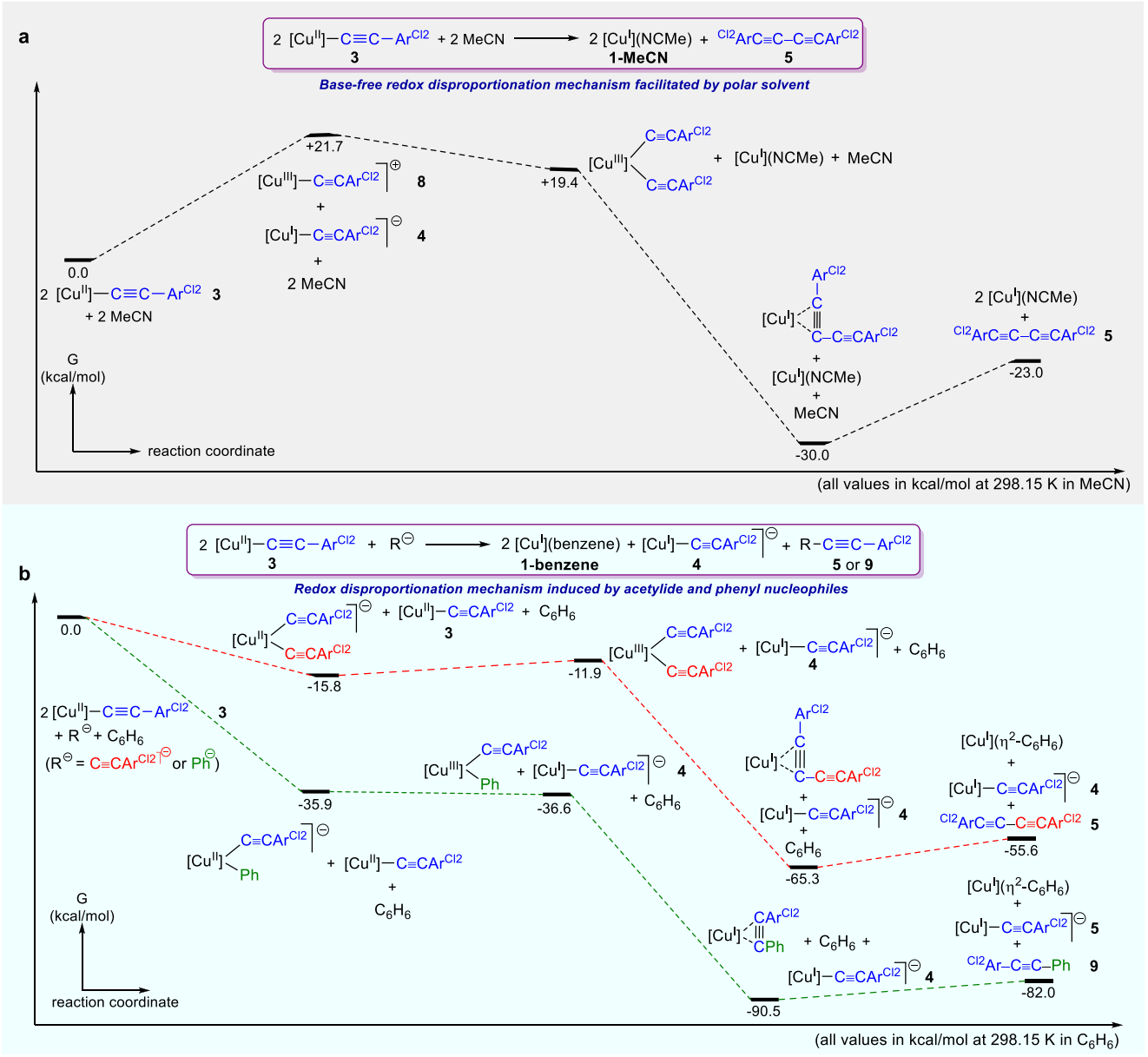

Figure 6. (a) DFT-calculated thermodynamic values for C_{sp}–C_{sp} via redox disproportionation in polar solvents such as MeCN. (b) C_{sp}–C_{sp} and C_{sp}–C_{sp2} coupling reactions mediated by **3** that involve redox disproportionation/nucleophile transmetalation pathways. All computed free energies are reported at the BP86+GD$_3$BJ/6-311++G(d,p)/SMD-acetonitrile//BP68/6-311+G(d)/gas level of theory in kcal/mol at 25 °C.

generated by acid–base reaction of terminal alkynes H–C≡CR with [Cu^{II}]–O^{t}Bu intermediates readily formed upon reaction of β-diketiminato catalysts [Cu^I] with ^{t}BuOO^{t}Bu (Figure 4b).[32]

We embarked on catalytic C_{sp}–C_{sp3} coupling[11−13,19] by examining a model reaction of ethylbenzene (PhCH$_2$Me) with H–C≡CAr^{CF3} (Ar^{CF3} = 4-CF$_3$–C$_6$H$_4$) to form PhCH(C≡CAr^{CF3})Me under various conditions (Tables S3–S6). Several types of Cu(I) β-diketiminate catalysts were extensively screened in combination with various catalyst loadings, different oxidants, and different solvents (Tables S3–S6). The desired C–H alkynylation product PhCH(C≡CAr^{CF3})-Me forms along with ^{CF3}ArC≡C–C≡CAr^{CF3} and an alkene byproduct (Table S3).[37] While the [^{i}Pr$_2$NN]Cu(NCMe) (**1-MeCN**) catalyst provides a moderate yield of PhCH(C≡CAr^{CF3})Me, the closely related [Cl$_2$NN]Cu catalyst enhances the C_{sp3}–H alkynylation yield, especially when the catalyst loading is reduced from 5% to 1%, which effectively suppresses the Glaser homocoupled product ^{CF3}ArC≡C–C≡CAr^{CF3} (Table S4).

We next surveyed a range of C_{sp3}–H substrates that undergo C–H alkynylation with 1-chloro-2-ethynylbenzene (**11**). While a range of alkylbenzenes with benzylic C–H bonds provide good yields (Table 1), we observed little success with substrates that possess only stronger, unactivated C_{sp3}–H bonds such as cyclohexane or linear alkanes. Slower generation of R· radicals anticipated from stronger C_{sp3}–H bonds in substrates R–H may allow ArC≡C–C≡CAr formation from [Cu^{II}]–C≡CAr intermediates to compete with radical capture by R· to give the desired C–H alkynylation products R–C≡CAr.

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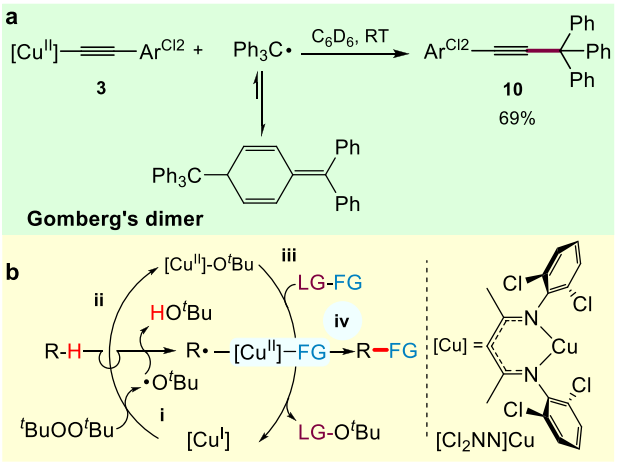
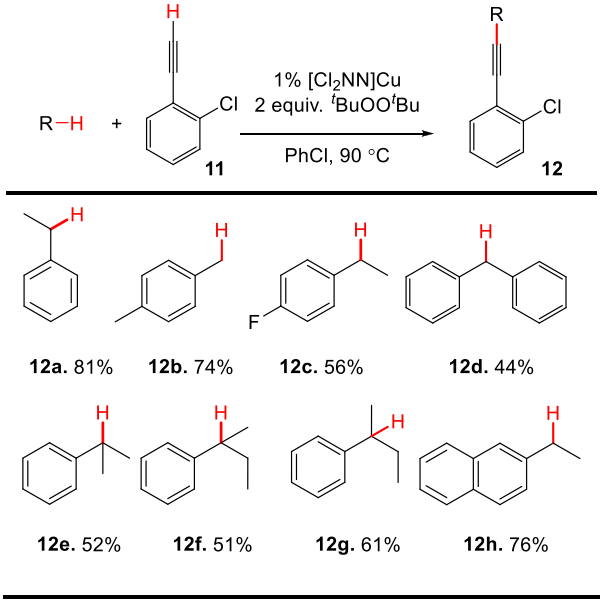


Figure 7. (a) Capture of the trityl radical $Ph_3C\cdot$ (via Gomberg's dimer) by **3** to form $Ph_3C{-}C{\equiv}CAr^{Cl2}$ (**10**). (b) Radical relay mechanism for catalytic C−N, C−O, and C−C bond formation.

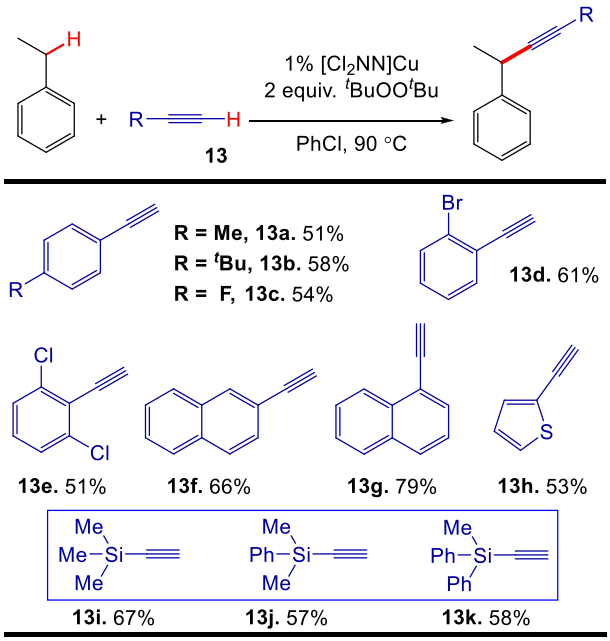
Table 1. Substrate Scope for Alkylation of 1-Chloro-2-ethynylbenzene Catalyzed by $[Cl_2NN]Cu$[a]



[a]Conditions: 0.5 equiv of 1-chloro-2-ethynylbenzene, 10 equiv of ethylbenzene, 2 equiv of $^tBuOO^tBu$, 90 °C in PhCl, 24 h. Isolated yields.

A range of terminal alkynes participate in the C_{sp3}−H alkynylation of ethylbenzene (Table 2). Commercially available electron-rich (**13a**−**13b**) or electron-poor (**13c**−**13e**) aryl alkynes afforded good yields (51−66%). 1- and 2-Ethynylnaphthalene also participate in this C_{sp3}−H alkynylation methodology to give the corresponding alkylated products **13g** and **13f** in 79% and 66% isolated yields, respectively. Gratifyingly, this methodology could also be applied in the alkylation of silyl-protected alkynes (**13h**−**13j**). For instance, the use of TMS−C≡CH (TMS = $SiMe_3$) affords trimethyl(3-phenylbut-1-yn-1-yl)silane (**13h**) in 65% yield. Silyl-protected alkyne products $R'{-}C{\equiv}C{-}SiR_3$ are broadly useful as they can be directly deployed in cross-coupling reactions or easily deprotected to synthetically versatile terminal alkynes $R'{-}C{\equiv}C{-}H$.[38]

Table 2. C−H Alkynylation of Ethylbenzene with Various Terminal Alkynes, Including Silyl-Protected Alkynes 13h−13j[a]



[a]Conditions: 0.5 equiv of terminal alkyne, 10 equiv of ethylbenzene, 2 equiv of $^tBuOO^tBu$, 90 °C in PhCl, 24 h. Isolated yields.

CONCLUSIONS

$[^iPr_2NN]Cu{-}C{\equiv}CAr^{Cl2}$ (**3**) represents the first crystallographically characterized mononuclear copper(II) alkynyl complex, representing a key intermediate in the valuable $C_{sp}{-}C_{sp}$ Glaser coupling reaction. Mechanistic studies reveal that such coupling is assisted by polar solvents such as MeCN, supporting a redox disproportionation pathway via charged $\{[Cu^{III}]{-}C{\equiv}CR\}^+$ and $\{[Cu^{I}]{-}C{\equiv}CR\}^-$ intermediates. Furthermore, the addition of 1/2 equiv of nucleophiles R^- such as $ArC{\equiv}C{-}Li$ or Ph−Li to $[^iPr_2NN]Cu{-}C{\equiv}CAr^{Cl2}$ results in the immediate formation of $^{Cl2}ArC{\equiv}C{-}R$ with concomitant reduction to Cu(I) as both $[Cu^I]$(solvent) and the Cu(I) alkynylate $\{[Cu^I]{-}C{\equiv}CAr^{Cl2}\}^-$. These observations shed light on other $C_{sp}{-}C_{sp2}$ bond-forming reactions such as the Pd-free Sonogashira reactions.[8,20,21] Additionally, $[Cu^{II}]{-}C{\equiv}CAr^{Cl2}$ cleanly reacts with Gomberg's dimer to provide $Ph_3C{-}C{\equiv}CAr^{Cl2}$ (**10**), indicating the ability of $[Cu^{II}]{-}C{\equiv}CAr^{Cl2}$ to capture alkyl radicals ·R. On the basis of this key finding, we developed a Cu-catalyzed C−H alkynylation protocol featuring Cu(II) alkynyls.

This report underscores the diverse roles that copper(II) organometallic intermediates play in cross coupling and C−H functionalization catalysis. Such $[Cu^{II}]{-}R'$ (R′ = aryl or alkynyl) species undergo homocoupling reactions to form new $C_{sp2}{-}C_{sp2}$ or $C_{sp}{-}C_{sp}$ bonds in $R'{-}R'$ homocoupling products connected to the Ullman (R′ = aryl)[39] or Glaser (R′ = alkynyl) couplings (Figure 8a).[40] Importantly, these $R'{-}R'$ bond-forming reactions do not appear to be simple bimolecular couplings of $[Cu^{II}]{-}R'$ intermediates. Rather, they proceed via redox disproportionation to $\{[Cu^{III}]{-}R'\}^+$ and $\{[Cu^{I}]{-}R'\}^-$ species that can generate $[Cu^{III}](R')_2$ intermediates that are susceptible to facile reductive elimination of $R'{-}R'$. Addition of a nucleophile Nu^- to such $[Cu^{II}]{-}R'$ species stimulates this redox disproportionation by facilitating the formation of more

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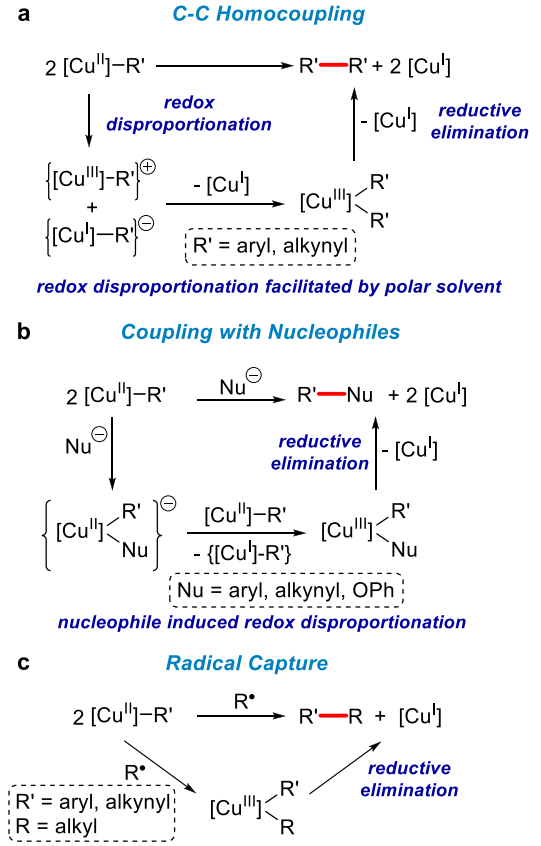

Figure 8. Organocopper(II) intermediates in (a) Ullman- or Glaser-type homocoupling reactions, (b) C–C and C–O bond formation with nucleophiles, and (c) C–C bond formation via the capture of alkyl radicals.

electron-rich $[Cu^{III}](R')(Nu)$ species that reductively eliminate Nu–R′ products (Figure 8b). On the other hand, the addition of a Lewis base that is resistant to cross-coupling L to copper(II) alkynyl **3** such as the pyridine derivative 2,4-lutidine accelerates homocoupling, perhaps by stabilizing cationic copper(III) intermediates $\{[Cu^{III}](R)(L)\}^+$. The addition of a nucleophile Nu^- that can engage in cross-coupling, however, is connected to the Chan–Lam–Evans coupling that commonly employs boronate esters $(R''O)_2B–R'$ with O- and N-based nucleophiles under copper catalysis.[41,42] Lastly, such $[Cu^{II}]–R'$ species are rather reactive toward incoming radicals R· generated under catalytic C–H functionalization conditions employed in radical relay catalysis. R–R′ coupled products form, perhaps via $[Cu^{III}](R)(R')$ intermediates that are unstable toward reductive elimination (Figure 8c).[43] Copper(II) organometallic species $[Cu^{II}]–R'$ thus enable facile coupling of $C–C_{sp}$, $C–C_{sp2}$, and $C–C_{sp3}$ bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c07137.

General instrumentation and physical methods, materials, synthesis and characterization data, crystallographic details and additional structures, references for synthetic and crystallographic details, computational details, and spectral data (PDF)

X-ray crystallographic data for **2** (CIF)

X-ray crystallographic data for **3** (CIF)

X-ray crystallographic data for **10** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Timothy H. Warren – *Department of Chemistry, Georgetown University, Washington, District of Columbia 20057, United States;* orcid.org/0000-0001-9217-8890; Email: thw@georgetown.edu

Authors

Abolghasem Bakhoda – *Department of Chemistry, Georgetown University, Washington, District of Columbia 20057, United States;* orcid.org/0000-0002-3222-8873

Otome E. Okoromoba – *Department of Chemistry, Georgetown University, Washington, District of Columbia 20057, United States;* orcid.org/0000-0001-8963-8390

Christine Greene – *Department of Chemistry, Georgetown University, Washington, District of Columbia 20057, United States*

Mahdi Raghibi Boroujeni – *Department of Chemistry, Georgetown University, Washington, District of Columbia 20057, United States;* orcid.org/0000-0001-8146-5878

Jeffery A. Bertke – *Department of Chemistry, Georgetown University, Washington, District of Columbia 20057, United States;* orcid.org/0000-0002-3419-5163

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c07137

Author Contributions

‡A.B. and O.E.O. contributed equally.

Notes

The authors declare no competing financial interest.

The X-ray crystallographic data for **2**, **3**, and **10** have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number CCDC 1938189–1938191, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/data_request/cif).

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