Angewandte
International Edition Chemie

C–C and C–N Coupling

DOI: 10.1002/anie.201301843

Ambient-Light-Mediated Copper-Catalyzed C–C and C–N Bond Formation

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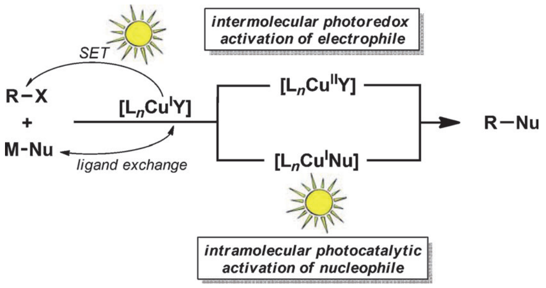
amination · copper · cross-coupling · photochemistry · radical reactions

Over the past decade, metal-catalyzed cross-coupling reactions have matured to high levels of efficiency, utility, and versatility. The early copper catalysts[1] have largely been outshone by highly effective palladium and nickel catalysts for C–C and C–X bond formation. With the rediscovery of visible light as an abundant energy source for organic reactions in which (sensitized) photo-excitation can facilitate metal-catalyzed elemental steps or trigger free radical reactions,[2] the venerable copper-catalyzed coupling reactions have returned to the limelight. Several reports on photocatalytic reactions have recently revitalized the field of C–C and C–N coupling reactions and prompted the rethinking of activation modes and reaction mechanisms (Scheme 1).



Scheme 1. Modes of substrate activation in visible-light-mediated copper-catalyzed coupling reactions.

Visible-light-mediated photoredox catalysis is currently emerging as a powerful alternative to metal-catalyzed "dark" reactions.[3] However, the prevalent use of expensive ruthenium and iridium photocatalysts is still a severe limitation in terms of sustainability and scalability. There is a persistent effort to introduce cheaper dyes to drive photocatalytic reactions. Some success has already been achieved by applying organic dyes.[4] Recently, photoactive copper(I) complexes have shaped up as inexpensive catalysts. Initial efforts were directed at photoredox catalysis where $[Cu(dap)_2]Cl$ (dap = 2,9-bis(4-anisyl)-1,10-phenanthroline), a complex originally reported by Sauvage and Kern,[5,6] acts as catalytic single-electron-transfer reagent in dehalogenation, allylic substitution, and atom-transfer radical addition (ATRA) reactions.[7] Very recently, this activation mode was complemented by two examples where direct excitation of a covalently bonded copper–substrate complex by ambient light triggers coupling reactions. This new reaction paradigm combines the best of two worlds: an inexpensive base metal complex as catalytic platform for the construction of new bonds in its coordination sphere and the use of the most abundant energy source for electronic activation, ambient visible light.

Anilines constitute one of the most ubiquitous structural motifs and find diverse synthetic applications as fine chemicals, agrochemicals, active pharmaceutical ingredients (API), and materials. Copper-catalyzed aminations of aryl halides, first described by Ullmann and Goldberg more than 100 years ago, have recently emerged as highly effective tools in modern organic synthesis.[8] While the mechanistic minutiae are still not fully understood, two pathways have been discussed: one resembling a cross-coupling reaction through the oxidative addition of aryl halide to form a Cu^{III} species; the other involving an initial single-electron transfer (SET) and radical intermediates. There is already some experimental proof that the former mechanism is operative in certain cases.[9] Theoretical studies have also supported the SET pathway, but solid experimental evidence has remained scarce.[10] Now, a report by Creutz et al. provides conclusive evidence that an SET pathway is operating under ambient-light irradiation in the presence of a photoluminescent copper catalyst.[11] The C–N bond formation is based on the effective luminescence quenching of carbazolide complex **1** by aryl halides. The energy transfer between **1** and the aryl halide iodobenzene ultimately results in the formation of the arylamine in 77% yield when the reaction solution is irradiated with a 13 W compact fluorescent lamp (CFL) at room temperature (Scheme 2).

Bromo- and chlorobenzene fared poorer (40% and 5%, respectively) and required irradiation with a 100 W Hg lamp to ensure similar turnovers. This suggests the operation of an SET mechanism with the initial electron transfer from electron-rich copper(I) complex **1** being limited by the oxidation potential of the acceptor ($E_{ox}(PhI) = -1.91$ V; $E_{ox}(PhBr) = -2.43$ V; $E_{ox}(PhCl) = -2.76$ V). Two reaction pathways are conceivable, both involving the intermediacy

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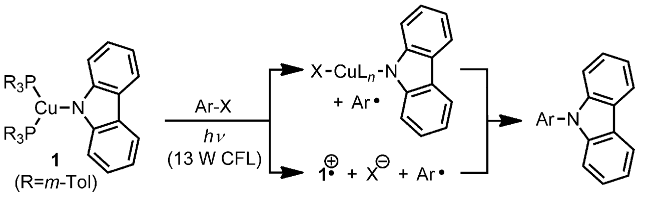
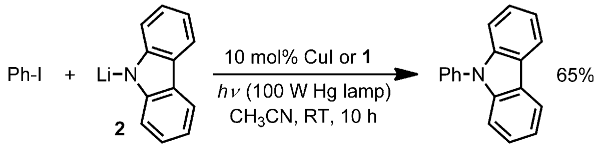


Scheme 2. UV/Vis-mediated Ullmann amination.

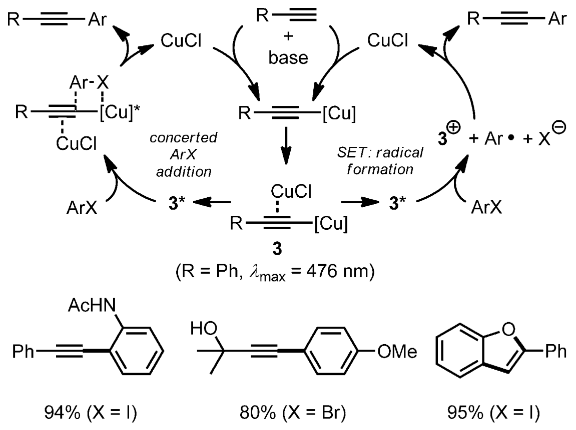
of a copper(II) complex and a free aryl radical (Scheme 2). Electron paramagnetic resonance (EPR) spectra of the frozen reaction mixture indicated the presence of the radical cation [**1**•]$^{+}$; the intermediacy of a free phenyl radical was proven by isotope labeling. Further evidence in favor of a SET mechanism was deduced fromradical-trapping experiments. The authors also developed a catalytic procedure (Scheme 3). In the presence of 10 mol% of CuI, lithium carbazolide **2** underwent phenylation in 65% yield. The mild conditions of this light-mediated amination (RT) will certainly fuel endeavors into new synthetic applications.



Scheme 3. Catalytic light-mediated Ullmann amination.

The palladium-catalyzed Sonogashira coupling is one of the prime methods for the construction of substituted alkynes by virtue of its high operational simplicity and functional-group tolerance. Recent examples of palladium-free protocols were highly controversial, as ppb levels of Pd contamination in inorganic additives (e.g. K_2CO_3) were present.[12] Early attempts to effect Pd-free Sonogashira reactions by near-UV irradiation were met with limited success due to competitive photolytic decomposition.[13] Sagadevan and Hwang recently reported that copper-catalyzed alkynylations of aryl halides aided by visible light cleanly proceed at room temperature.[14] Initial studies revealed identical catalytic activity of inorganic Cu$^{\text{I}}$ salts and copper(I) phenylacetylide. The rate acceleration observed upon addition of 0.1 mol% CuCl to copper(I) phenylacetylide was indicative of the key role of strongly absorbing copper acetylide complexes of type **3** ($\lambda_{max} = 425$–485 nm; Scheme 4) as catalytic photosensitizers, while decreased yields were obtained at other wavelengths. Excitation of **3** to **3*** by blue light (40 mW cm^{-2} at 460 nm) is believed to trigger a ligand-to-metal charge transfer (LMCT).[15]

The authors claim that the triple bond within **3*** experiences enhanced polarization and transfer of the aryl halide in a concerted fashion (Scheme 4). Alternatively, ArX can undergo SET reduction with **3*** and set the stage for attack of an aryl radical onto the copper acetylide. It is likely that this mechanism operates if **3** undergoes intersystem crossing from singlet to triplet state. Indeed, copper(I) phenylacetylides were shown to undergo facile intersystem crossing,[16] so that the latter pathway cannot be ruled out without further experimental data. The authors have shown that Pd is not catalytically active, but rather inhibits turnover due to the high opacity of reaction mixtures containing as little as 1‰ $PdCl_2$. The general protocol exhibits wide substrate scope (aryl bromides and iodides) and high functional-group tolerance (aldehyde, ester, nitro, amino groups). Domino reactions with 2-iodophenols afforded substituted benzofurans.



Scheme 4. Possible mechanisms of light-mediated alkynylations.

The similar reactivity patterns of light-mediated electron-transfer processes and conventional copper-catalyzed coupling reactions have recently prompted the merging of the two activation concepts for efficient C–C and C–N coupling reactions. Irradiation of copper complexes with visible light has been shown to a) trigger copper-centered SET processes and b) assist copper-catalyzed elemental steps in which the substrate is covalently bonded. The quest for cooperative copper photocatalysis should certainly extend beyond coupling reactions between activated substrates. Successful applications of this new activation paradigm to selective reactions of nonactivated substrates that are unknown under conventional (thermal) conditions will undoubtedly become an indispensable part of the organic chemists' toolbox.

Received: March 4, 2013

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