

REVIEW SUMMARY

ORGANIC CHEMISTRY

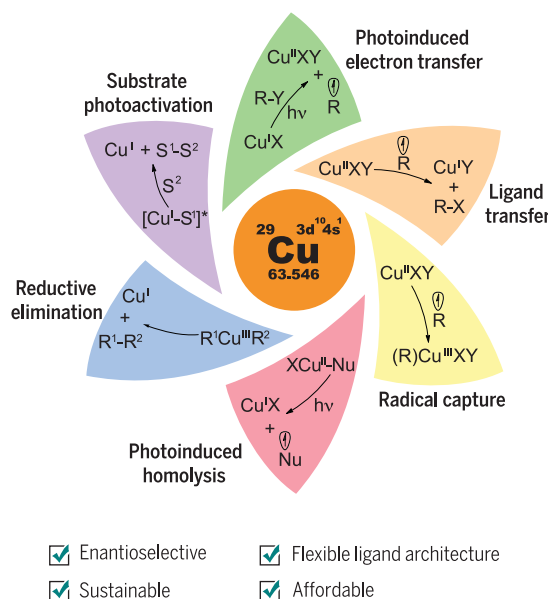
Copper's rapid ascent in visible-light photoredox catalysis

Asik Hossain*, Aditya Bhattacharyya*, Oliver Reiser†

BACKGROUND: The recent resurgence and dramatic evolution of visible-light photoredox catalysis has led to a paradigm shift in organic synthesis that encompasses activation of small molecules, unconventional modes of bond formation, and access to heretofore elusive reaction pathways. Exogenous photocatalysts undergo single-electron or energy transfer from their excited states to generate open-shell intermediates that can participate in nontraditional, low-energy reaction pathways complementary to more conventional thermal, high-energy, two-electron processes. These mechanisms undergird elegant synthetic methodologies for the rapid yet controlled construction of value-added products with desired molecular complexity. Ru(II) or Ir(III)-polypyridyl complexes and organic dye sensitizers have been the chromophores of choice owing to strong absorption, long excited-state lifetimes, and high redox potentials. However, the cost and adverse environmental impact of these compounds, as well as their restrictive conformational constraints (both with respect to inner-sphere substrate interactions and chiral ligand design for asymmetric transformations), limit their applications. Given the imperative need to develop ecologically benign, cost-effective, multipurpose, and flexible catalytic systems, copper has emerged as an appealing complement. Copper-based photocatalysts display highly tunable redox properties in their excited states, accommodate flexible ligand architecture, allow stereoinduction, and offer multiple accessible oxidation states to achieve rapid radical capture or facile reductive elimination, exerting exquisite control over the photoredox processes occurring in their inner coordination sphere.

ADVANCES: Conspicuous features of Cu(I) photocatalysts include the generation of radical species through the reduction of organic substrates upon photoexcitation and capture of the incipient radical and/or anionic

species in a rebound process. The resulting transitory Cu(III) intermediate can undergo reductive elimination to furnish cross-coupled products. Alternatively, the Cu(II) intermediate can exchange ligands with the radical to form cross-coupled products. Following this paradigm, the monoalkylation of primary amines with sterically hindered electrophiles becomes possible, an elusive process by



Applications of copper in photoredox catalysis.

way of the classical nucleophilic substitution approach. Alternatively, nucleophiles such as chlorosulfonyl anion or fluoride can be delivered to carbon-centered radicals. The redox potential of copper photocatalysts is highly tunable with ligand variation in a broad array of synthetically accessible homoleptic or heteroleptic complexes. Sauvage's complex $\{[\text{Cu}(\text{dap})_2]\text{Cl}\}$ and other copper-based complexes have found widespread applications in photo-induced transformations, such as bifunctionalization of olefins and various C-C and C-N cross-coupling reactions. In

other mechanistic paradigms, Cu(I) and Cu(II) substrate complexes can be directly excited with visible light to instigate cross-coupling reactions and homolytic cleavage, respectively. Recently, the oxoazidation of vinyl arenes has been developed in which a Cu(II) complex simultaneously acts as electron-transfer and

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aerobic oxygen-transfer agent, obviating the requirement of any exogenous oxidants. An enantioselective alkylation of imines has also been achieved, showcasing the capacity of chiral photoactive copper complexes to act as asymmetric/photoredox bifunctional catalysts. Various copper salts have also been used as cocatalysts alongside iridium or ruthenium photocatalysts. Owing to the persistent radical effect (PRE) demonstrated by copper, organic radical intermediates generated by the visible light-induced photocatalytic cycles are efficiently trapped at the metal center and get stabilized. Many photochemical cross-coupling reactions that forge C-C, C-N, C-O, and C-S bonds have been developed. Copper can also be used as a Lewis acid to activate C-C multiple bond functionalities. Enantioselective transformations such as cyanoalkylation of styrenes, decarboxylative cyanation of alkyl carboxylic acids, and C(sp³)-H arylation and alkynylation of tetrahydroisoquinolines have been developed by exploiting copper's innate capacity to form chiral tetrahedral complexes with polydentate N,O/P-ligands.

OUTLOOK: Although copper is currently enjoying signal success in photoredox catalysis, a number of challenges remain to be addressed that warrant exploration of the oxidizing potential of copper photocatalysts involving Cu(II)* to Cu(I) or Cu(I)* to Cu(0) transitions, further prolongation of the excited-state lifetime through sophisticated ligand design, and enhancement of scale-up efficiency. Broader use of copper photocatalysts in asymmetric transformations will enhance their value for the synthesis of drugs and natural products. The prospects are limited only by the ingenuity underlying the design of catalytic reaction prototypes. ■

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Copper's rapid ascent in visible-light photoredox catalysis

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Visible-light photoredox catalysis offers a distinct activation mode complementary to thermal transition metal catalyzed reactions. The vast majority of photoredox processes capitalizes on precious metal ruthenium(II) or iridium(III) complexes that serve as single-electron reductants or oxidants in their photoexcited states. As a low-cost alternative, organic dyes are also frequently used but in general suffer from lower photostability. Copper-based photocatalysts are rapidly emerging, offering not only economic and ecological advantages but also otherwise inaccessible inner-sphere mechanisms, which have been successfully applied to challenging transformations. Moreover, the combination of conventional photocatalysts with copper(I) or copper(II) salts has emerged as an efficient dual catalytic system for cross-coupling reactions.

The recent resurgence and dramatic evolution of visible-light photoredox catalysis has led to a paradigm shift in organic synthesis (1–3). The inventive yet intricate design principles, accompanied by practical technological developments for ease of implementation, have allowed chemists to activate small molecules, to contrive unconventional modes of bond formation, and to access heretofore elusive reaction pathways by efficiently converting photonic energy into chemical energy. In order to circumvent the incapacity of small organic molecules to absorb in the visible-light region of the electromagnetic spectrum, various external chromophores have been induced to undergo single-electron transfer (SET) or energy transfer processes from their photoexcited states, generating radical species upon reduction or oxidation of organic substrates. In turn, these intermediates participate in nontraditional reaction pathways complementary to common thermal two-electron processes (4, 5). For this purpose, appropriately ligated heavy transition-metal catalysts such as Ru(II) or Ir(III)-polypyridyl complexes or metal-free organic dye sensitizers have been most commonly used, owing to their favorable characteristics such as long excited-state lifetimes, strong absorption in the visible region, and high reduction or oxidation potentials of the corresponding excited states (3). However, organic dyes generally suffer from lower photostability, and heavy transition metal-based complexes are expensive as well as environmentally unfriendly. Moreover, the high oxidation states of conventional Ir- or Ru-based photocatalysts and the inflexibility of their ligand

orientation hinder their capacity to undergo oxidative addition with organic substrates. In addition, although stereoselective transformations have been elegantly developed through the use of Ir- or Ru-based photocatalysts with prefunctionalized substrates (6), synthesizing the appropriate chiral octahedral complexes with

labile ligands remains a substantial challenge. Catalysts that can straightforwardly direct photoredox processes in their inner sphere, and thereby control reactions through their ligand environment, are desirable in this context. First-row transition metal complexes hold the promise to meet this requirement (7). Consequently, considerable advancements have been attained by merging conventional Ir- or Ru-based photocatalysts with various nickel(II) salts or complexes that are capable of effecting oxidative addition to aryl, vinyl, and alkyl halides, leading to C- or N-arylation, -olefination, and -alkylation (8). However, with very recent discoveries copper has now come to the fore in the arena of photocatalysis (9), owing to its versatile redox characteristics that make it capable both of initiating a reaction by means of single electron transfer as well as directly interacting with substrates in its coordination sphere. Moreover, copper complexes are highly dynamic; various heteroleptic complexes with N- and P-based multidentate ligands (Fig. 1) can be readily synthesized to tune redox properties and enhance excited-state lifetime (10–12). Here, we chronicle the inception and evolution of copper as a visible-light photoredox catalyst.

Cu(I) complexes as standalone photocatalysts

In 1977, McMillin *et al.* synthesized $[\text{Cu}(\text{dmp})_2]\text{BF}_4$ (dmp = 2,9-dimethyl-1,10-phenanthroline), which

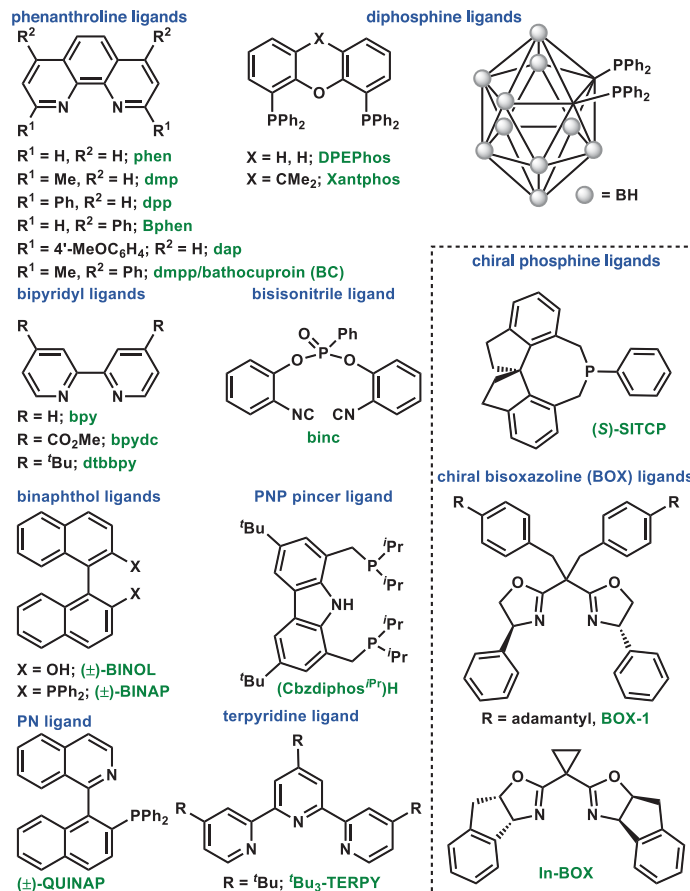


Fig. 1. Representative varieties of commonly employed racemic and chiral ligands for copper-based photocatalysts.

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can be excited at 454 nm; the resulting metal-to-ligand charge transfer (MLCT) state can reduce Co(III) in $K[*cis*-Co(IDA)_2] \cdot 1.5H_2O$ to the corresponding Co(II) complex (13). A decade later, Sauvage introduced an ingeniously designed Cu(I) complex that rigidly confined the copper ion within the concave portions of two crescent-shaped phenanthroline ligands, considerably enhancing the lifetime of its MLCT excited state (≤ 270 ns) (14). The complex, $[Cu(dap)_2]Cl$ [dap =

2,9-bis(*p*-anisyl)-1,10-phenanthroline; $E_{red} = -1.43$ V versus saturated calomel electrode (SCE) in CH_3CN], was shown to induce reductive coupling of nitrobenzyl bromide to the corresponding bibenzyl coupling product. Surprisingly, this catalyst went into hibernation until it was resuscitated in 2012 for a C-C bond-forming atom transfer radical addition (ATRA) transformation (15). That study, along with concurrent reports on electrocyclic 6π -reactions catalyzed by

heteroleptic Cu(I)-phenanthroline-bisphosphine complexes (16) and palladium-free Sonogashira couplings by means of light-activated copper(I)-alkyne complexes (17), set in motion the recent proliferation of studies involving Cu(I)- and Cu(II)-complexes as effective visible-light photocatalysts.

The general mechanistic paradigm of $Cu(I)_n$ complexes as standalone photocatalysts is depicted in Fig. 2A. Upon excitation with visible light, an appropriately ligated $Cu(I)_n$ complex

A Cu(I)-complexes as standalone photocatalysts: Mechanistic paradigms

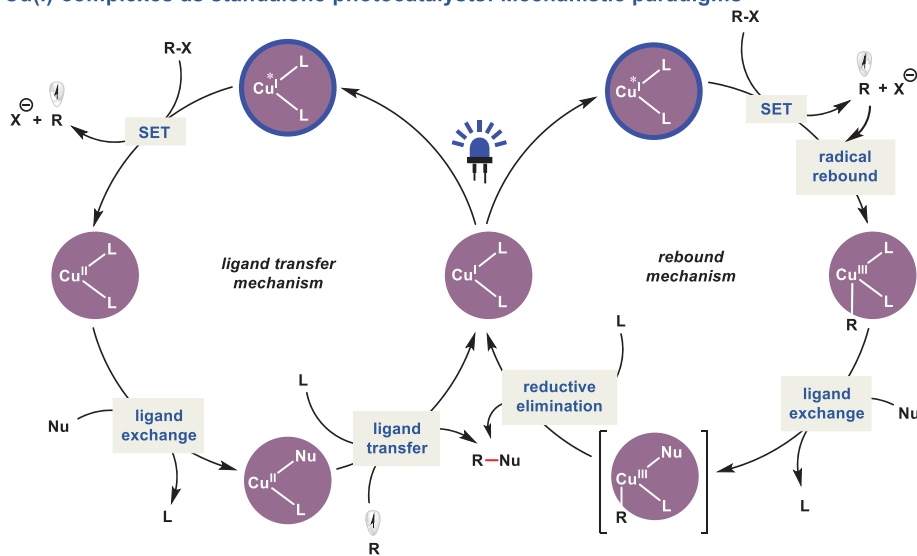


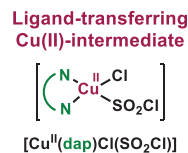
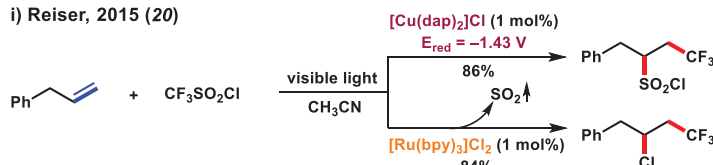
Fig. 2. Cu(I) complexes as standalone photocatalysts.

(A) The mechanistic paradigm of Cu(I) photocatalysts for cross-coupling reactions is depicted. The transformation can proceed either by means of a Cu(I)/Cu(II) catalytic cycle involving sequential elementary steps—namely, SET, ligand exchange, and ligand transfer—or a Cu(I)/Cu(II)/Cu(III) catalytic cycle involving SET-radical rebound, ligand exchange, and reductive elimination steps to yield the cross-coupled product. L, ligand; R-X, electron-accepting substrate (X = leaving group); Nu, nucleophile; and LED, light-emitting diode. (B and C) Mechanistically distinct copper-photocatalyzed olefin-bifunctionalization processes. OTf, Triflate.

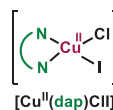
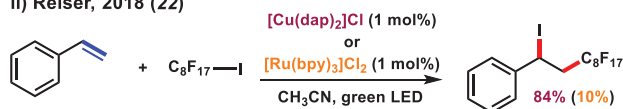
^aIn the presence of 10 mole % $[Ru(bpy)_3](PF_6)_2$ photocatalyst (yield in parenthesis).

B Cu(I)-based photocatalysts in bifunctionalization of olefins

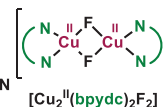
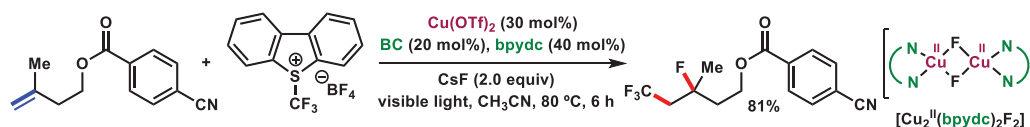
i) Reiser, 2015 (20)



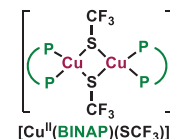
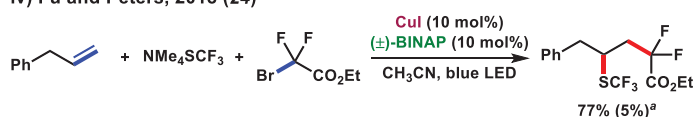
ii) Reiser, 2018 (22)



iii) Yu and Li, 2018 (23)

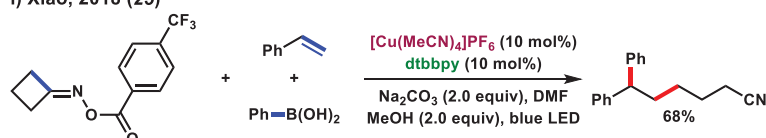


iv) Fu and Peters, 2018 (24)

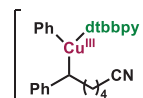


C Cu(I)-based photocatalysts in $C(sp^2)$ - $C(sp^3)$ cross-coupling

i) Xiao, 2018 (25)



Cu(III)-intermediate for cross-coupling



transfers a single electron to an electron-accepting substrate, producing a radical species (R^\bullet) [which can further be intercepted by an alkene or alkyne, resulting in a more nucleophilic radical species (R'^\bullet)] and a transient $Cu(II)L_n$ intermediate. At this stage, two possibilities emerge: (i) The $Cu(II)L_n$ intermediate can exchange a ligand (L) with an incoming nucleophilic cross-coupling partner (Nu) to generate a $Nu-Cu(II)L_{(n-1)}$ intermediate

that transfers the newly coordinated nucleophile to R^\bullet to furnish the cross-coupled product ($R-Nu$) and reverts to the initial $Cu(I)L_n$ complex by reuniting with the previously departed ligand (L); and (ii) the incipient radical (R^\bullet) can rebound to the $Cu(II)L_n$ intermediate to generate a high-valent $R-Cu(III)-L_n$ intermediate (**18**) that exchanges a ligand with Nu to form $R-Cu(III)L_{(n-1)}-Nu$, which undergoes facile reductive elimination

to deliver the desired cross-coupled product ($R-Nu$) and regenerate the initial $Cu(I)L_n$ complex with L .

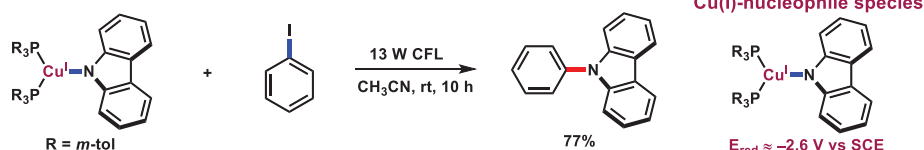
Bifunctionalization of olefins

A wide range of functionalities can coordinate to the $Cu(II)$ -intermediate generated by means of SET from the photoexcited $Cu(I)^*$, and consequently, the process of ligand transfer to the intermediate radicals gets accelerated in various ATRA reactions. The first such example was demonstrated in 2015 with the development of vicinal trifluoromethylation/chlorosulfonylation of olefins (Fig. 2B, i). Cognizant of the importance of fluorinated and trifluoromethylated organic compounds in the pharmaceutical sector (**19**), when unactivated olefins were exposed to triflyl chloride (CF_3SO_2Cl) in the presence of 1 mole % $[Cu(dap)_2]Cl$, the corresponding trifluoromethyl-chlorosulfonylated products were obtained in high yields (**20**), contrasting with $[Ru(bpy)_3]Cl_2$, which yielded trifluoromethyl-chlorinated products (**21**). The formation of the unexpected sulfonylchloride was attributed to coordination between the chlorosulfonyl anion, which is generated upon mesolysis of triflyl chloride after single-electron reduction by excited-state $[Cu(dap)_2]Cl$ and the concurrently formed $Cu(II)$ -center. In a similar vein, the iodoperfluoroalkylation of styrenes fails with common ruthenium or iridium-based photocatalysts but proceeds efficiently with $[Cu(dap)_2]Cl$, suggesting the intermediacy of an iodine-transferring $[Cu^{II}(dap)ClI]$ species (Fig. 2B, ii) (**22**). Along these lines, Yu, Li, and co-workers have recently demonstrated a remarkable fluorine atom-transfer (FAT) capability of an innovative $Cu(II)-F$ complex to efficiently promote carbofluorination of unactivated olefins (Fig. 2B, iii) (**23**). The reaction proceeds in the presence of CsF as the F-source, Umemoto's reagent, 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate, as the CF_3 -source, and $Cu(OTf)_2$ as the catalyst, with the assistance of two ligands: bathocuproine (BC) to reduce $Cu(II)$ to $Cu(I)$ and electron-deficient 4,4'-di(methoxycarbonyl)-2,2'-bipyridine (bpydc) to accelerate FAT from the $LCu(II)-F$ complex. A similar dicopper complex has been synthesized by Fu, Peters, and co-workers to effect the transfer of a thiotrifluoromethyl (SCF_3) group in a three-component reaction between electrophiles, olefins, and trifluoromethylthiolate (Fig. 2B, iv) (**24**). The process is initiated with the photoexcitation of a $Cu^I(BINAP)(SCF_3)$ complex that reduces the electrophile, which is intercepted by an olefin to generate a more nucleophilic alkyl radical. Meanwhile, the newly formed $[Cu^{II}(BINAP)(SCF_3)_2]$ complex effectively transfers an SCF_3 group to this radical species to furnish the targeted trifluoromethyl thioether with concurrent regeneration of the initial Cu^I -complex with the SCF_3 source.

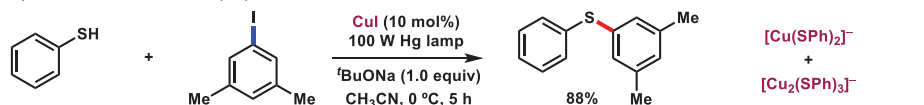
Whereas all previously discussed examples can be explained either by ligand transfer or rebound/reductive elimination of $Cu(II)$ species with a SET-generated radical, the three-component cross-coupling protocol reported by Xiao and co-workers involving redox-active

A $C(sp^2)$ -heteroatom cross-coupling: UV-light-mediated transformations

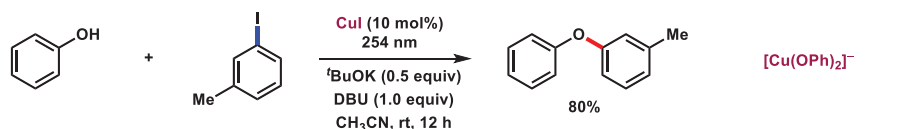
i) Fu and Peters, 2012 (26)



ii) Fu and Peters, 2013 (28)

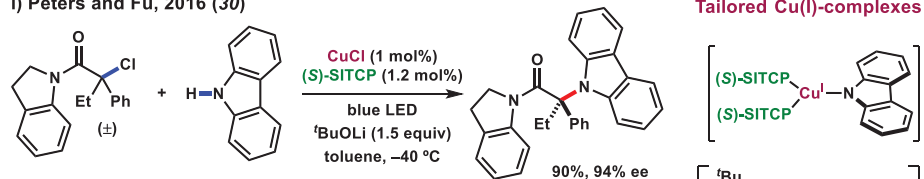


iii) Fu and Peters, 2014 (29)

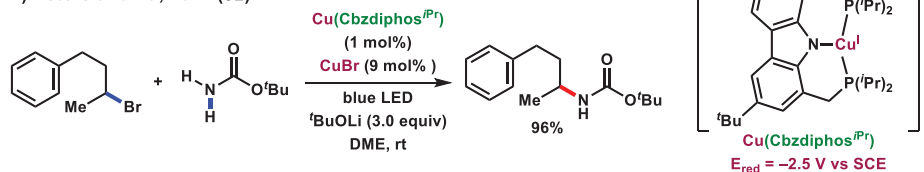


B $C(sp^3)-N(sp^3)$ cross-coupling: Visible-light-mediated transformations

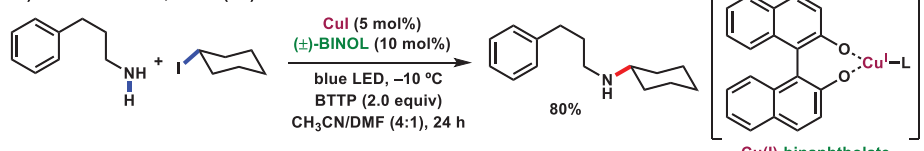
i) Peters and Fu, 2016 (30)



ii) Peters and Fu, 2017 (32)



iii) Peters and Fu, 2017 (33)



iv) Peters and Fu, 2017 (35)

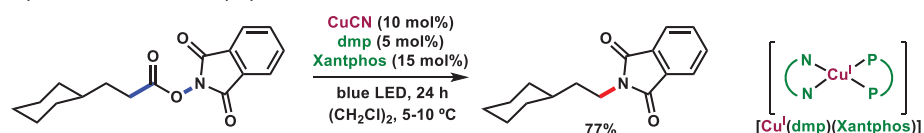


Fig. 3. $Cu(I)$ complexes as standalone photocatalysts: Synthetic applications in carbon-heteroatom cross-coupling reactions. The mechanistic paradigms are similar to Fig. 2A. (A) Evolution of copper in UV light-mediated photoreactions by means of a radical pathway. (B) Visible light-mediated reactions. W, watt; CFL, compact fluorescent light bulb; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; BTPP, *tert*-butylimino-tri(pyrrolidino)phosphorane.

cycloketone oxime esters, styrenes, and aryl boronic acids provides a strong case for the intermediacy of Cu(III) species by means of a rebound pathway (Fig. 2C, i) (25). The proposed mechanism involves photoexcited Cu(I)(dtbbpy)-catalyzed SET-assisted formation of a cyanoalkyl radical that reacts with an olefin to generate another intermediate radical. Simultaneously, the newly formed Cu(II) species undergoes transmetalation with aryl boronic acid to form an aryl-Cu(II) intermediate; it subsequently captures the intermediate radical to form a new aryl-Cu(III)(alkyl) species that undergoes reductive elimination to yield the cross-coupled product.

C(sp³/sp²)-heteroatom cross-coupling

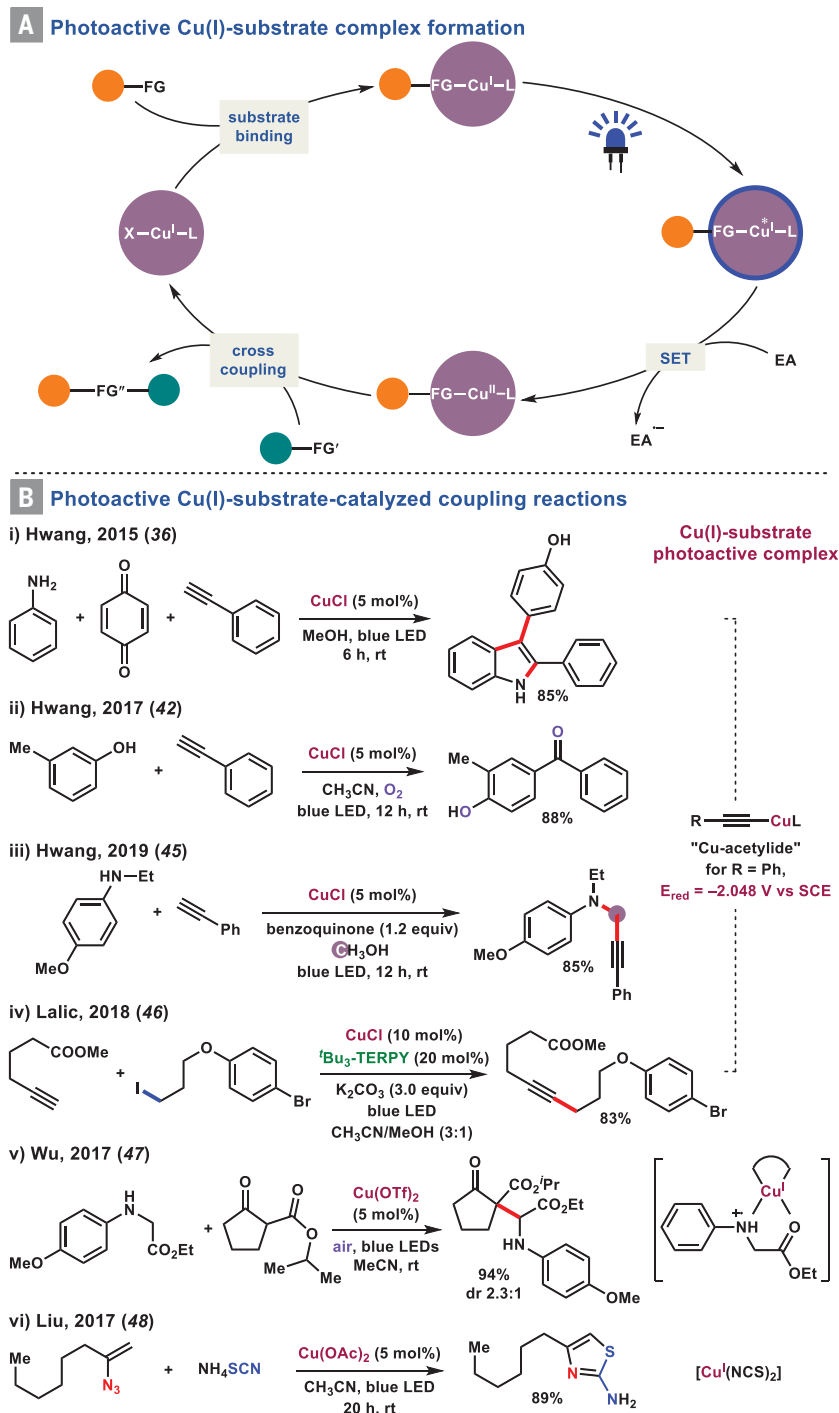
A seminal report by Fu and Peters (26) in 2012 disclosing an ultraviolet (UV) light-mediated radical variant of the Ullmann C-N cross-coupling protocol between a copper-carbazolide complex and aryl halides and a succeeding report describing the extension of the chemistry to alkyl electrophiles (27) paved the way for developing various other UV light-induced copper-catalyzed carbon-heteroatom coupling reactions (Fig. 3A, i). The authors have subsequently demonstrated that other heteroatomic nucleophiles such as thiophenols (Fig. 3A, ii) (28) and phenols (Fig. 3A, iii) (29) can also be viable coupling partners in C(sp²)-S and C(sp²)-O cross-coupling reactions advancing by means of the intermediacy of UV light-absorbing Cu(I)-nucleophile species such as [Cu(SPh)₂], [Cu₂(SPh)₃], and [Cu(OPh)₂], respectively.

Shifting the classical pathway of nucleophilic substitution to a radical regime under visible-light irradiation conditions provides remarkable solutions to longstanding challenges for the (asymmetric) synthesis of amines, as progressively addressed by the pioneering contributions from the groups of Peters and Fu. An enantioconvergent cross-coupling of racemic tertiary α -chloroamides with carbazoles and indoles could be achieved in the presence of a Cu(I)/Nu/(S)-SITCP complex (Nu = carbazole or indole) that acts both as a photocatalyst and as the source of enantioinduction (Fig. 3B, i) (30, 31). The commercially available chiral phosphine ligand (S)-SITCP controls the absolute configuration of the products regardless of the initial stereochemistry of the electrophiles. A mechanistic inquest indicated toward the plausible intermediacy of a photoactive {Cu(I)-[(S)-SITCP]₂-carbazolide} complex. Hence, with a view to generalizing the protocol, a novel tridentate bisphosphine/carbazolide ligand-containing [Cu(CbzdiPhos^{SP})] photocatalyst was later prepared and used in combination with CuBr to accomplish C-N cross-coupling between unactivated secondary alkyl iodides and carbamates in an "out-of-cage" process (Fig. 3B, ii) (32). The use of Ru- or Ir-based photocatalysts instead of the aforementioned Cu(I) photocatalyst led to <1% formation of the desired product.

The scope of nitrogen-containing cross-coupling counterpart could be further extended to pri-

mary aliphatic amines circumventing usual synthetic problems such as overalkylation and steric encumbrance. The same groups used a photoactive Cu(I)-binaphtholate complex to mediate the desired cross-coupling between the primary

amines with unactivated secondary alkyl iodides for the exclusive synthesis of the corresponding mono-alkylated amine derivatives under mild reaction conditions (Fig. 3B, iii) (33). The *rac*-BINOL ligand was found to be essential in this



reaction. According to the proposed reaction mechanism, the photoexcited Cu(I)/BINOL complex undergoes SET to generate an alkyl radical and a Cu(II)/BINOL species that, upon ligand exchange with an amine, forms the key Cu(II)-amine species. Then, the alkyl radical combines

with the Cu(II)-amine species, and subsequent cross coupling furnishes the desired product.

From the perspective of sustainability, carboxylic acids are a more abundant, stable, and less toxic chemical feedstock in comparison with alkyl halides. *N*-(hydroxy)phthalimide (NHPI)

esters are being widely exploited as superior sources of alkyl radicals through a SET-reduction-decarboxylation process, leading to the development of a wide variety of decarboxylative cross-coupling methodologies (34). This principle was exploited for a decarboxylative C-N

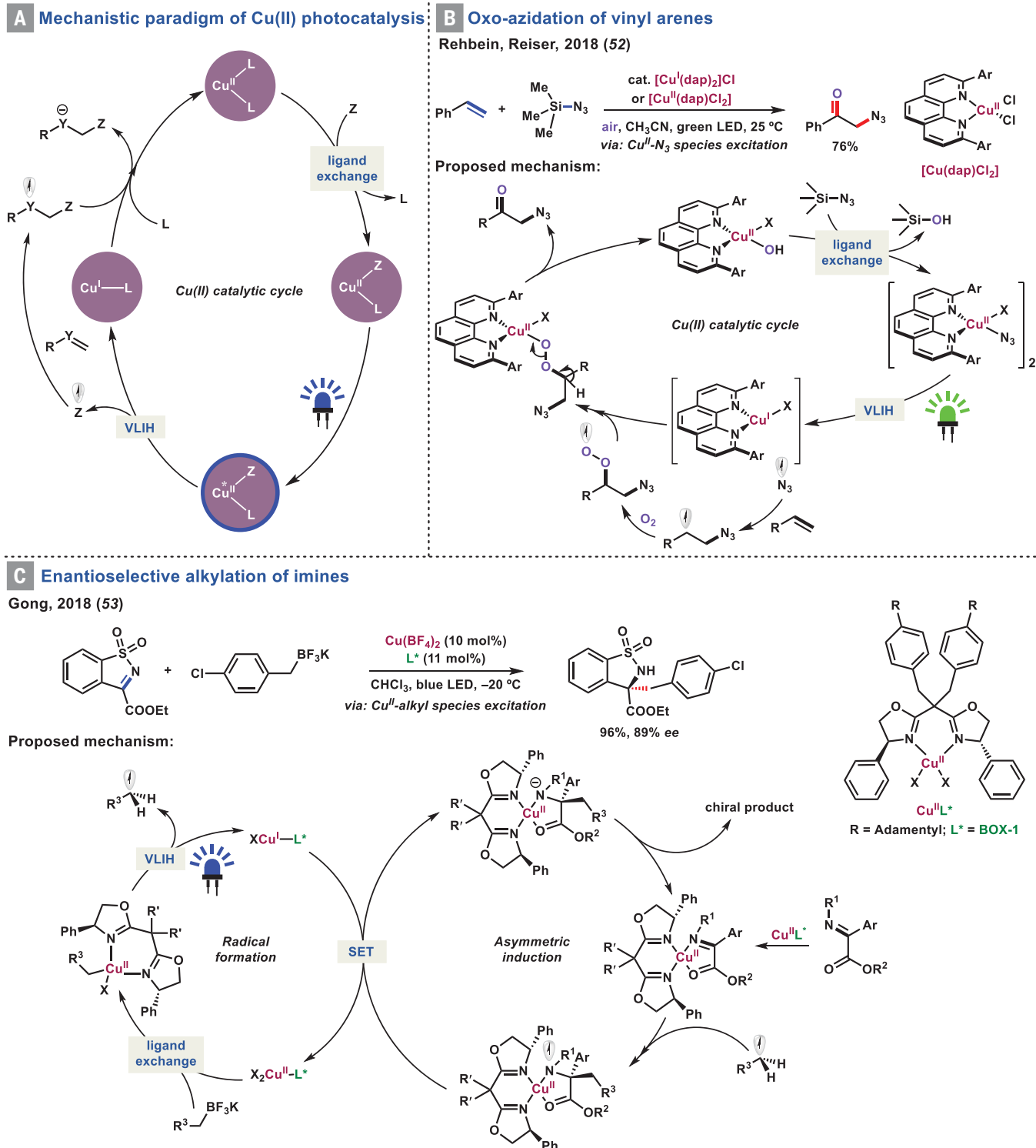
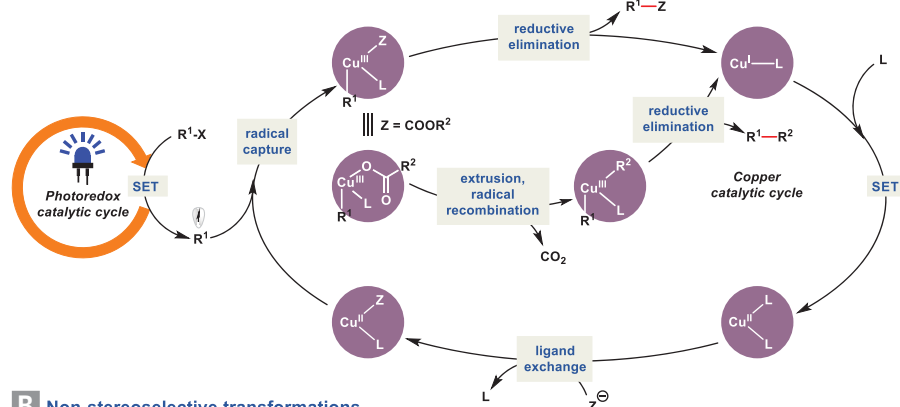


Fig. 5. Photocatalysis with Cu(II) complexes (LMCT excitation). (A) Z, nucleophile; Y, heteroatom. Key steps are (B) [Cu(II)-N₃]-species excitation. (C) [Cu(II)-alkyl]-species excitation. Ar, 4-(OMe)C₆H₄; X, counter anion.

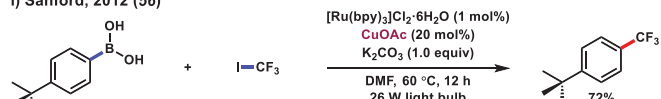
A Co-operative photoredox-copper catalysis: Capturing radicals with copper



B Non-stereoselective transformations

C(sp²)-C(sp³) cross-coupling

i) Sanford, 2012 (56)

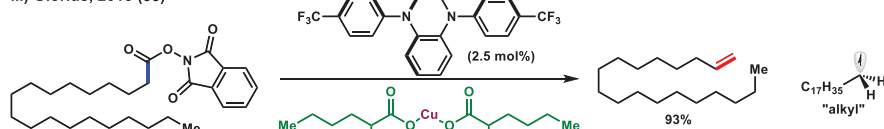


ii) MacMillan, 2018 (57)



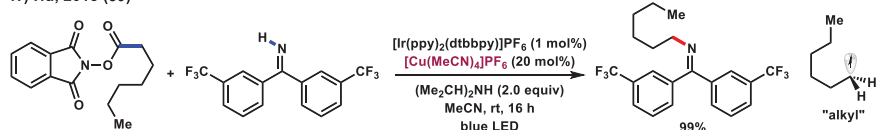
Decarboxylative olefination

iii) Glorius, 2018 (58)



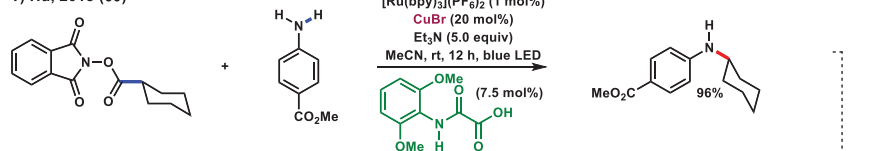
Decarboxylative C(sp³)-N(sp²) cross-coupling

iv) Hu, 2018 (59)

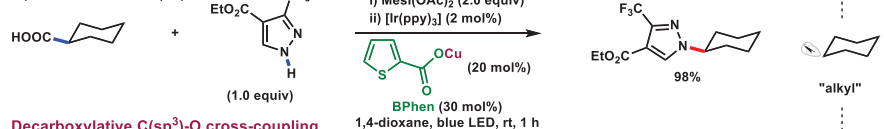


Decarboxylative C(sp³)-N(sp³) cross-coupling

v) Hu, 2018 (60)



vi) MacMillan, 2018 (62)



Decarboxylative C(sp³)-O cross-coupling

vii) Hu, 2018 (61)

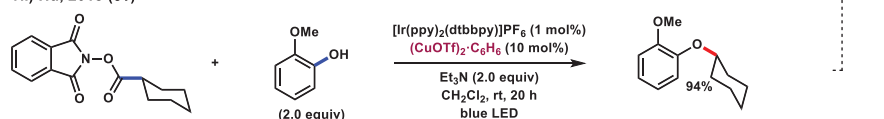


Fig. 6. Cooperative photoredox dual catalysis. (A) The general mechanistic pathways are shown. The radical capture by Cu(II) species gives rise to a high-valent Cu(III) intermediate that undergoes facile reductive elimination to furnish the cross-coupled product. (B) A series of nonstereoselective transformations involving C–C and C–N bond formations are shown. The wide variety of organic radicals captured by Cu(II) intermediates is highlighted.

coupling as an azide-free alternative to the Curtius rearrangement (Fig. 3B, iv) (35). NHPI-esters in the presence of a Cu(I) photocatalyst offered a route to protected amines by means of initial SET from a photoexcited Cu(I)/dmp/xantphos complex to form a Cu(II) species and the radical anion of the NHPI ester. Fragmentation produces an alkyl radical, CO₂, and the phthalimide anion, which binds to Cu(II). The recombination of the alkyl radical with this Cu(II)-phthalimide species and subsequent cross coupling affords the desired product, with regeneration of the Cu(I) catalytic species.

Photoexcitation of in situ-generated Cu(I) substrate complexes

A mechanistically distinct class of reaction manifolds specific to copper has emerged in which suitable substrates can form visible light-absorbing complexes by coordinating to Cu(I), obviating the use of exogenous ligands. The excited Cu(I) substrate complex reduces an electrophile by means of a SET process, and the resulting Cu(II) substrate complex then participates in a diverse range of synthetic transformations, including cross-coupling reactions and functional group modifications (Fig. 4A). By capitalizing on this concept, Hwang and co-workers developed a visible light-mediated, high-yielding Sonogashira cross-coupling reaction between aryl halides and alkyl- or aryl-substituted terminal alkynes in the presence of catalytic amounts of CuCl (17).

This group has also applied this concept to a three-component coupling of anilines, terminal alkynes, and benzoquinones to regioselectively synthesize functionalized indoles (Fig. 4B, i) (36). The transformation advances with the in situ formation of a Cu(I)-phenylacetylide species that, upon excitation by blue LEDs, reduces benzoquinone through SET (−2.048 V versus SCE in CH₃CN) to enable further reactions with aniline. The visible light-absorbing properties of Cu-acetylide species have also been applied to denitrogenative oxidative C(sp²)-C(sp) coupling between hydrazinylpyridines and terminal alkynes (37), oxidative C–N coupling of anilines with terminal alkynes to synthesize α-ketoamides (38), oxidative C–N coupling of 2-aminopyridine with terminal alkynes via C–C triple bond cleavage (39), and oxidative C(sp)-C(sp) homo and cross-coupling of terminal alkynes (40, 41). An intriguing example of this strategy entailed the coupling of phenols and terminal alkynes in the presence of molecular oxygen to produce aryl and alkyl ketones. According to the proposed mechanism, the excited state of the in situ-generated Cu(I)-acetylide species reduces molecular oxygen through SET to generate a Cu(II)-acetylide species and a superoxide radical anion. Simultaneously, phenol is also converted to benzoquinone by the Cu(II)-superoxo intermediate. Sequential Paterno-Buchi-type [2+2] cycloaddition of Cu(II)-phenylacetylide and benzoquinone, oxetane ring-opening, fragmentation, formation of a peracid species, CO₂ extrusion, and keto-enol tautomerism furnish the aryl ketone product (Fig. 4B, ii) (42, 43). By contrast, the coupling between phenylacetylene

and aliphatic alcohols in the presence of oxygen, stoichiometric 2-picolinic acid, and catalytic copper(I) iodide furnished α -keto esters in high yields (44). Very recently, a CuCl-catalyzed three-component reaction between *N*-alkylanilines, terminal alkynes, and primary alcohols in the presence of stoichiometric benzoquinone as an oxidant to furnish propargylamines is reported by the same group (Fig. 4B, iii) (45). The photoexcited Cu(I)-phenylacetylide reduces benzoquinone, and then the corresponding radical anion species triggers a hydrogen atom transfer process with a primary alcohol to generate an α -oxy radical. It undergoes a radical-radical cross-coupling with aminyl radical cation previously generated upon ligand-to-metal charge transfer (LMCT) excitation of a Cu(II)-amine species. Subsequent intramolecular proton-transfer followed by elimination of water molecule results in the formation

of an iminium species, which gets trapped by Cu(I)-phenylacetylide to produce the desired product. Lalic and co-workers found that catalytic amounts of CuCl in combination with a substituted terpyridine ligand can modulate the reactivity of the photoexcited Cu(I)-acetylide complex to achieve the coupling of unactivated alkyl iodides and terminal alkynes (Fig. 4B, iv) (46). Wu and co-workers have reported a C-H functionalization protocol in which Cu(II) salts can bind 2-arylaminoacetates for the in situ formation of Cu(I) intermediates that can be excited with visible light to promote the alkylation of enolates (Fig. 4B, v) (47). In situ-generated Cu(NCS)₂⁻ can play the dual role of a photocatalyst and a Lewis acid, as exploited by Liu and co-workers (Fig. 4B vi) (48). Energy transfer from photoexcited Cu(NCS)₂^{-*} to a vinyl azide effects rearrangement to an azirine intermediate that, upon coordina-

tion by ground state Cu(NCS)₂⁻, is activated for the subsequent coupling with thiocyanide to give rise to 2-aminothiazole derivatives.

Cu(II) complexes as standalone photocatalysts

Very recently, the successful applications of Cu(II) complexes as visible light photoredox catalysts have been reported. Following the seminal work of Kochi and co-workers, who demonstrated that CuCl₂ undergoes homolysis to Cu(I)Cl and Cl• upon UV irradiation (49), the activation of Cu(II)X₂ complexes endowed with suitable ligands to redshift absorption into the visible region can produce radicals X• that initiate productive organic transformations (Fig. 5A). Thus, rather than MLCT states fundamental to photoexcitation of Cu(I) complexes, Cu(II) complexes react from LMCT states (50, 51), which oxidize the anionic nucleophile.

Following this concept, the synthesis of azido ketones from vinyl arenes, TMSN₃, and oxygen was developed by use of the copper(II) complex [Cu(dap)Cl₂] as photoredox catalyst (Fig. 5B) (52). The Cu(II) complex undergoes ligand exchange with azide to give rise to a new LCu(II)azide-bridged dimer. Upon visible light-induced homolysis (VLIH), LCu(I) and an azido radical are formed, and the latter can be intercepted by an alkene followed by molecular oxygen. Rebound of the *O*-centered radical with LCu(I) regenerates the LCu(II) species, which upon elimination releases the product and closes the catalytic cycle.

A second, notable example was reported shortly after by Gong and co-workers (Fig. 5C) (53). In this case, a chiral Cu(II)-bisoxazoline complex is alkylated through transmetalation from the corresponding trifluoroborate salt, and once again, VLIH generates an alkyl radical and a Cu(I) intermediate. In a second catalytic cycle, this alkyl radical adds to the substrate—here, a protected imine that is activated by the same chiral Cu(II)-bisoxazoline complex. The newly generated *N*-centered radical is reduced by the previously formed Cu(I) species in the first cycle to release the alkylated imine with high enantioselectivity.

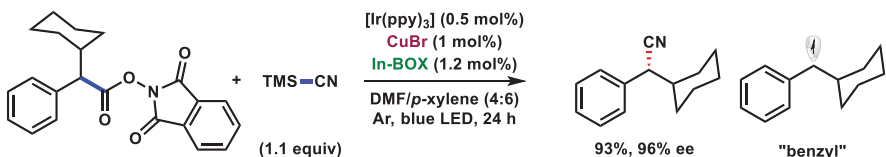
Very recently, [Cu(dap)Cl₂] has been successfully used in a photochemical ATRA reaction between sulfonyl chloride and olefins (54). In line with Kochi's proposal, VLIH of LCu(II)-Cl bond generates LCu(I) species for reduction of sulfonyl chlorides. The presence of stoichiometric amount Na₂CO₃ is necessary when unactivated olefins (such as allylbenzene) are subjected to the aforementioned reaction, in contrast to activated olefins (such as styrene), for which no additive is required. The role of Na₂CO₃ is proven to prevent the catalyst poisoning during the reaction in case of a less efficient radical trapping through the unactivated alkene substrate.

Another report by Yuan and co-workers (55) discloses the ability of CuCl₂ salt to form photoactive species with solvents (namely, acetonitrile or acetone), which can efficiently convert benzyl alcohol to benzaldehyde in the presence of molecular oxygen. Detailed mechanistic studies suggest that molecular oxygen helps only in the

A Stereoselective transformations with chiral Cu complexes

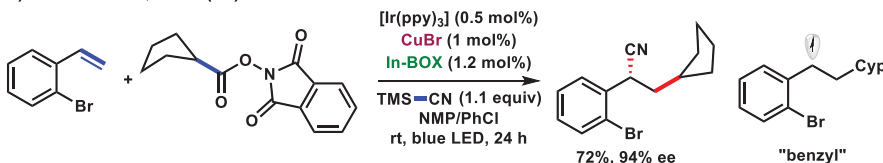
C(sp³)-CN bond formation

i) Lin and Liu, 2017 (63)



Bifunctionalization of olefins

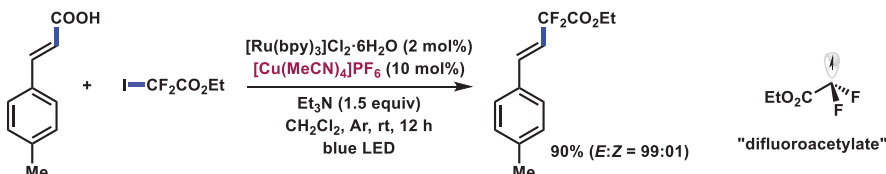
ii) Mei and Han, 2018 (64)



B Decarboxylative cross-coupling transformations

C(sp²)-C(sp³) cross-coupling

i) Liu, 2016 (65)



C(sp³)-C(sp³) cross-coupling

ii) MacMillan, 2018 (66)

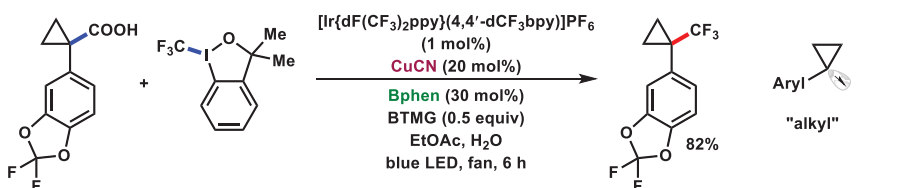
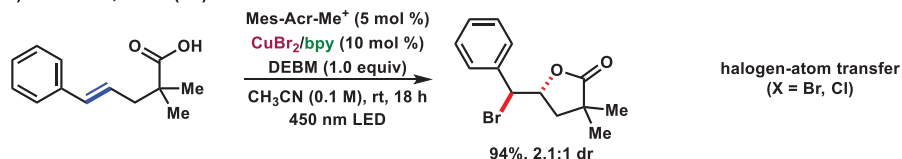


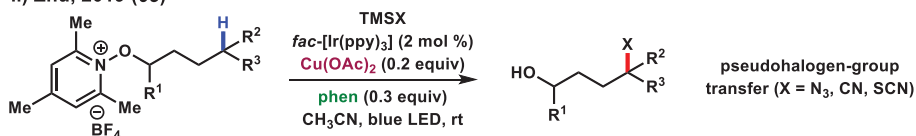
Fig. 7. Mechanistic paradigms are similar to Fig. 6A. (A) Efficient mergers of radical-capture and asymmetric induction by chiral Cu-complexes have been demonstrated. (B) Cross-coupling through decarboxylation from Cu(II)-carboxylate intermediates has been demonstrated. BTMG, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine.

A Functionalization of C-centered radicals

i) Nicewicz, 2017 (67)

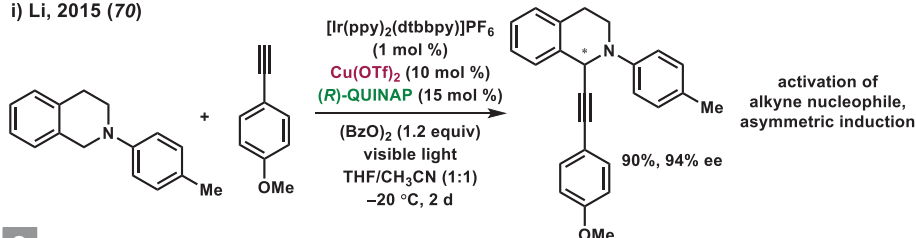


ii) Zhu, 2019 (68)



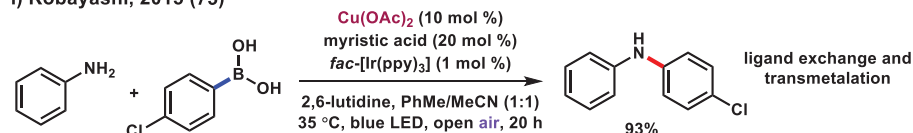
B Cross-dehydrogenative coupling

i) Li, 2015 (70)



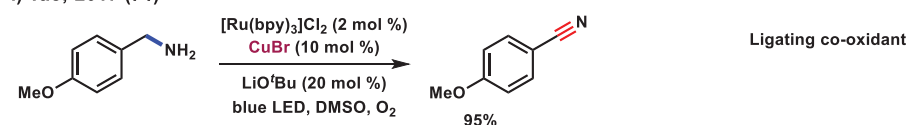
C Oxidative cross-coupling reaction

i) Kobayashi, 2015 (73)



D Activation of substrates by Lewis acidity

i) Tao, 2017 (74)



ii) Guo, 2016 (76)

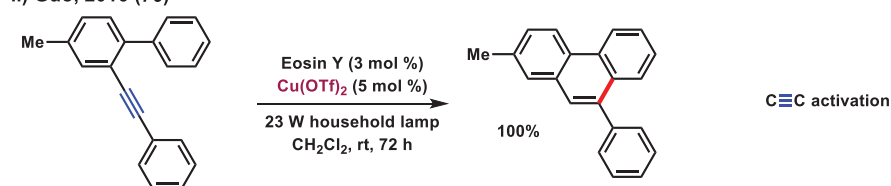


Fig. 8. Miscellaneous roles of copper in photoredox catalysis. DEBM, diethyl bromomalonate; QUINAP, 1-(2-diphenylphosphino-1-naphthyl)isoquinoline.

regeneration of the catalyst but does not act as a source of oxygen in benzaldehyde.

Cooperative photoredox-copper dual catalysis

Cu(I) and Cu(II) salts have also recently been applied in conjunction with traditional Ir- or Ru-based photocatalysts. Owing to the persistent radical effect (PRE) demonstrated by copper, organic radical intermediates generated by the visible light-induced photocatalytic cycles are efficiently trapped and thus stabilized by the metal center. The resulting organocopper inter-

mediates display a wealth of prospective follow-up chemistry. The mechanistic paradigm involves the following generic steps (irrespective of order): (i) exogenous excited-state photocatalyst-assisted generation of a radical species by means of single-electron reduction of an electrophile; (ii) simultaneous single-electron oxidation of the initial Cu(I) species to the ligated Cu(II)_{L_n} species by the oxidized state of the photocatalyst; (iii) anionic ligand (Z) substitution from one of the reaction counterparts and formation of Cu(II)_{L_{n-1}}Z (or in some cases transmetalation); (iv) capture of the incipient radical (R[•]) emanating from the

photocatalytic cycle by Cu(II)_{L_{n-1}}Z and formation of the high-valent transient Cu(III)R[•]L_{n-1}Z species; and (v) collapse of Cu(III)R[•]L_{n-1}Z through reductive elimination to generate the cross-coupled product and to regenerate the initial Cu(I) species to close the copper-catalytic cycle (Fig. 6A). The carbophilic nature of copper allows access to various Cu-C species, such as Cu-aryl and Cu-alkyl, that in turn translate to several cross-coupling strategies with the formation of a wide variety of vital bonds, such as C(sp²)-C(sp³), C(sp²)-C(sp²), C(sp³)-N(sp²), C(sp³)-N(sp³), C(sp³)-O, C(sp³)-C(sp), and C(sp³)-C(sp³).

In a pioneering study published in 2012, Sanford and co-workers revealed a mild synthetic method for the preparation of perfluoroalkylated (hetero) aromatic compounds by the cross coupling of (hetero)aryl boronic acids and perfluoroalkyl iodides in the presence of [Ru(bpy)₃]Cl₂·6H₂O as the photocatalyst and copper(I) acetate as the C(sp²)-C(sp³) bond-forming catalyst (Fig. 6B, i) (56).

Although high-valent Cu(III) species undergo facile reductive elimination, oxidative addition of carbon-halogen bonds to low-valent Cu(I) species was a longstanding problem in copper chemistry that had barred the widespread use of Cu as an efficient cross-coupling catalyst. MacMillan and co-workers have provided an excellent work-around by developing an efficient cross-coupling strategy between aryl bromides and a trifluoromethylating agent in the presence of an Ir-based photocatalyst and copper cocatalyst (57). The transformation proceeds through the initial formation of a reactive silyl radical from tris(trimethylsilyl)silanol that abstracts bromine from aryl bromide to generate an aryl radical. Meanwhile, the Cu(I) complex combines with the CF₃ radical generated from the trifluoromethylating agent during the closure of the Ir-photocatalytic cycle and forms a Cu(II)CF₃ complex, which captures the aryl radical to subsequently reductively eliminate the trifluoromethylated arenes in excellent yields (Fig. 6B, ii).

A different mechanistic manifestation of reductive elimination from Cu(III) species has been reported by Glorius and co-workers, entailing decarboxylative olefination of primary carboxylic acids to produce terminal alkenes (58). Redox-active esters were reduced by the excited photocatalyst, and after the extrusion of carbon dioxide, the corresponding alkyl radical was generated and subsequently captured by the Cu(II) complex. The newly formed Cu(III)alkyl species underwent β-hydride elimination to generate the desired terminal olefin in high yields concurrent with regeneration of the Cu(I) complex, which was subsequently oxidized to the initial Cu(II) species to close the photocatalytic cycle (Fig. 6B, iii).

Cognizant of the challenges associated with amine synthesis from readily available chemical feedstocks, Hu and co-workers have recently developed an efficient cross-coupling method between activated carboxylic acids and nitrogen nucleophiles for the synthesis of a wide range of alkyl amines (59). In the initial step, benzophenone imine coordinates Cu(I), and subsequent

deprotonation generates a Cu(I) amido complex. Efficient capture of the alkyl radical generated from the alkyl NHPI ester with the help of the photocatalyst forms the alkyl Cu(II) species. The oxidized photocatalyst oxidizes this Cu(II) complex to a corresponding Cu(III) complex that subsequently collapses through reductive elimination to give the cross-coupled product, with concurrent regeneration of the initial Cu(I) complex. The benzophenone imine group can be subsequently hydrolyzed or transaminated to give the corresponding primary amines (Fig. 6B, iv). Hu's group has further expanded the scope of the C–N bond-formation to anilines (Fig. 6B, v) (60) as well as to C–O bond-forming reactions with phenols (Fig. 6B, vi) (61).

MacMillan and co-workers further extended the scope of the strategy by using a wide range of primary, secondary, and tertiary alkyl carboxylic acids through in situ iodonium activation with a broad range of nitrogen nucleophiles, such as heteroaromatics, amides, sulfonamides, and anilines (Fig. 6B, vi) (62). The synthetic transformation proceeds by means of the initial formation of the Cu(I)-amido species through sequential binding of amine with Cu(I) and deprotonation. The excited Ir(III)* complex oxidizes this Cu(I)-amido species to the corresponding Cu(II)-amido species, and the resultant Ir(II) reduces the iodomesitylene dicarboxylate to generate the carboxyl radical and ultimately the alkyl radical (after CO₂ extrusion). In contrast to Hu's protocol, the Cu(II)-amido species captures the alkyl radical to form the corresponding alkyl-Cu(III)-amido species that collapses by means of reductive elimination to furnish the desired alkyl amine product and regenerate the Cu(I) catalyst.

Ligand modularity of the Cu complexes can again greatly vary the chemistry and redox properties in Cu/photocatalyst cooperative systems, as reflected in the decarboxylative cyanation reaction developed by Lin, Liu, and co-workers. Secondary benzylic NHPI esters were used along with trimethylsilyl cyanide (TMSCN) in the presence of [Ir(ppy)₃], CuBr, and the chiral pyBOX ligand to produce benzyl nitriles (Fig. 7A, i) (63). The key step is the combination of the radical obtained through photoreduction of the NHPI ester with the chiral L*Cu(II)CN complex, the latter stemming from oxidation of the initially formed L*Cu(I)CN by the oxidized photocatalyst. Reductive elimination from the resulting Cu(III) species provided the products in good yields with excellent enantioselectivities. Enantioselective bifunctionalization—cyanoalkylation of olefins—has been accomplished as well with this strategy (Fig. 7A, ii) (64).

The aforementioned studies invariably required activation of the carboxylic acids either as their NHPI esters or through in situ iodonium formation. This potential drawback has recently been addressed in photoredox catalysis by using copper as the cocatalyst to enable the direct decarboxylation of the free carboxylic acids through formation of Cu(II)-carboxylate complexes, which can capture the photochemically generated radical to form Cu(III)(alkyl)-carboxylates. These can

then undergo decarboxylation, radical recombination, and reductive elimination to furnish the cross-coupled product (Fig. 6A). In one such study, Liu and co-workers achieved difluoroacetylation of α,β -unsaturated carboxylic acids with ethyl iododifluoroacetate (Fig. 7B, i) (65). The transformation proceeds by the Ru(II)*-catalyzed initial oxidation of the Cu(I) cocatalyst to Cu(II), which accommodates two coordinated carboxylates. In turn, upon reoxidation of Ru(I) to Ru(II), difluoroacetyl radical is generated and adds to the α -position of the olefinic double bonds of the Cu(II)-carboxylate species, which subsequently undergoes simultaneous elimination of Cu(I) and CO₂ to produce the desired difluoroacetylated olefin derivatives in good yields.

Along the same lines, MacMillan and co-workers have recently reported the decarboxylative trifluoromethylation of aliphatic carboxylic acids (Fig. 7B, ii) (66). Initially, the free carboxylic acid coordinates the Cu(II) cocatalyst, which is oxidized by photoexcited Ir(III)* to the corresponding Cu(III)-carboxylate complex. Then, subsequent extrusion of carbon dioxide and recombination of the incipient alkyl radical generates the alkyl-Cu(III) intermediate, which oxidizes Ir(II) to ground-state Ir(III) to close the photocatalytic cycle and generate an alkyl-Cu(II) intermediate. This intermediate engages with Togni's reagent, 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, to furnish the targeted alkyl-CF₃ product in good yields and regenerates the Cu(II) cocatalyst to reenter the catalytic cycle.

Miscellaneous examples

Apart from the aforementioned studies, copper has enriched the field of photoredox catalysis by adopting various other roles in a wide panoply of synthetic applications. A regioselective halofunctionalization of unsaturated carboxylic acids has been accomplished by Nicewicz and co-workers (Fig. 8A, i). The transformation proceeds by means of the initial oxidation of the alkene by an acridinium photocatalyst followed by the nucleophilic addition of the internal carboxylate to the radical cation intermediate. Then, Cu(II) cocatalyst transfers the halide from an external halide source to newly generated C-centered radical to furnish the corresponding product (67). Zhu and co-workers have recently achieved remote C(sp³)-H functionalization of *N*-alkoxyppyridinium salts with silyl reagents through photoredox/copper dual catalysis (Fig. 8A, ii). The transformation takes place through the reductive generation of an alkoxy radical with Ir(III) photocatalyst and 1,5-hydrogen atom-transfer followed by functionalization of the C-centered radical with Cu(II)-catalyzed transfer of pseudohalide groups such as azido, cyano, and isothiocyanato from their corresponding trimethylsilylated precursors to furnish various δ -functionalized alcohols (68).

In 2012, Rueping *et al.* developed a photocatalytic oxidative alkylation reaction of tetrahydroisoquinolines using [Ru(bpy)₃](PF₆)₂ as a photocatalyst and a catalytic amount of [Cu(MeCN)₄]PF₆ to generate copper acetylide as the active nucleophile from terminal alkyne (69).

Later, Li and co-workers substantially advanced the strategy with the development of its asymmetric variant by using a chiral Cu-QUINAP complex. It activates the terminal alkyne and forms a chiral Cu-QUINAP-acetylide species that acts as the active nucleophile toward the iminium intermediate and furnishes the corresponding 1-alkynyl tetrahydroisoquinoline derivatives with excellent enantioselectivity (Fig. 8B) (70). The strategy has also been successfully extended to the functionalization of isochromans with β -keto esters in which a catalytic amount of Cu(OTf)₂ has been used to activate the nucleophiles for their addition to oxonium intermediates (71). A photocatalyzed decarboxylative alkylation with terminal alkynes has been achieved by Fu and co-workers, in which a catalytic amount of CuI was necessary to generate the active nucleophile in the form of copper acetylide (72).

An improved Chan-Lam coupling reaction between electron-deficient aryl boronic acids and anilines has been developed by Kobayashi and co-workers (Fig. 8C) by means of a combined copper/photocatalyst system. The reaction takes off with Cu(II) undergoing ligand exchange with aromatic amine and transmetalation with aryl boronic acid to form an organo-Cu(II)-amide species. It subsequently gets oxidized by Ir(IV) to form a Cu(III) intermediate that, upon reductive elimination, generates the desired cross-coupled product (73). Aerobic oxidation of a wide range of primary amines to the corresponding nitriles (Fig. 8D, i) could be accomplished by Tao's group by use of a [Ru(bpy)₃]Cl₂/CuBr dual catalytic system. The mechanistic pathway involves an initial ligand exchange of Cu(I) with amine to form a copper amide intermediate that undergoes single-electron oxidation by a photoexcited Ru(II) catalyst and subsequent hydrogen abstraction and neutralization by a superoxide radical anion and hydrogen peroxide anion, respectively, to form a copper amido intermediate. Then, another similar catalytic cycle furnishes the desired nitrile derivative (74). In another study, photoredox catalyzed C4–H sulfonylation of 1-naphthylamides could be achieved by using Cu(OAc)₂ catalyst, which aided in single-electron oxidation of the substrate in the presence of an oxidant (75).

Copper's Lewis acidity has also been leveraged in activation of C=C triple bonds through the formation of a π -complex between an internal alkyne and Cu(II) to form a three-center two-electron (3c-2e) system conducive to single-electron oxidation by an exogenous photocatalyst, as shown by Guo and co-workers (Fig. 8D, ii). The newly formed 3c-1e system could then undergo an arene-cyclization reaction to produce phenanthrene derivatives (76).

Apart from the aforementioned studies, Cu(II) salts have been used in an intramolecular oxidative cyclization/oxygen insertion of aromatic enamines to furnish polysubstituted quinolines under mild reaction conditions (77). Bode and co-workers have used stoichiometric Cu(OTf)₂ as the Lewis acid to lower oxidation potentials of demanding imine substrates that can then

participate in photocatalytic syntheses of various aza-heterocycles by using the silicon amine protocol (SLAP) (78). Stoichiometric Cu(II) salts have also found other uses in photocatalyzed synthetic applications, such as additives in *O*-sialylation (79) and as terminal oxidants, as recently shown by Yoon and co-workers in a study involving oxyamination of olefins (80).

Conclusion and outlook

Although copper-based photocatalysts have predominantly been used for single-electron reduction from photoexcited states involving transition from Cu(I)* to Cu(II), there have been tangible successes that exploit the photo-oxidizing potential of transitions from Cu(I)* to Cu(0) (81, 82) or from Cu(II)* to Cu(I) (83). The high degree of tunability in the coordination sphere and ligand-coordination mode renders copper complexes conducive to further optimization of redox properties and excited-state lifetimes in the development of more sophisticated catalytic systems (10). Likewise, a structurally predistorted bis(chelated) Cu(I) complex with a guanidine-quinoline ligand system has been prepared that sustains its constrained geometry in both the +1 and +2 oxidation states to instigate photochemical reactions by facilitating faster MLCT transition (84). In the coming years, copper complexes with such augmented potential will almost certainly have extensive impact in organic synthesis, materials science, and pharmaceutical chemistry.

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Copper's rapid ascent in visible-light photoredox catalysis

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Spotlight on copper

Photoredox catalysis relies on visible-light excitation to accelerate a burgeoning number of chemical reactions. Initially, the technique relied primarily on complexes of precious metals, such as ruthenium or iridium, to absorb the light. Hossain *et al.* review recent progress in the use of copper complexes as an alternative. In addition to its Earth abundance, copper opens up a variety of distinct mechanisms involving electron transfer within the coordination sphere. *Science*, this issue p. eaav9713

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