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Photoinduced copper-catalyzed enantioselective coupling reactions

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Copper-catalyzed enantioselective coupling has been widely investigated, which allows rapid construction of various chiral molecules. Despite important advances *via* polar and radical mechanisms, exploring general and practical strategies for the regio-, enantio- and diastereoselective assembly of stereogenic centers is of significant value but remains highly problematic. The integration of photocatalysis with asymmetric copper catalysis could provide appealing access to the development of new reaction pathways and structurally diverse chiral compounds, and extend the boundaries of radical chemistry. This review summarizes recent advances in photoinduced copper-catalyzed enantioselective coupling reactions, and discusses the mechanistic aspects.

1. Introduction

The construction of carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds *via* cross-coupling reactions is treated as one of the most common and useful protocols in synthetic organic chemistry. Copper is the first transition metal employed in the catalytical formation of C–C and C–X bonds.[1,2] The first C–C cross-coupling reaction by copper catalysis was reported by Ullman in 1901. Following extension to C–X cross-coupling reactions was developed by Ullman and Goldberg from 1903 to 1906. The sequential Cadiot-Chodkiewicz coupling reaction in 1957, Castro–Stephens coupling reaction in 1963, and

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Corey–House synthesis in 1967, accelerated the progress of C–C bond formation. By introducing noble metal palladium in the cross-coupling reactions, important advances have been achieved,[3,4] by *e.g.* Heck (1972), Sonogashira (1975), Negishi (1977), Stille (1978), Suzuki (1979), Hiyama (1988), Buchwald-Hartwig (1994), and Liebeskind–Srogl (2000). Despite the powerful role of palladium in cross-coupling reactions, copper is still widely treated as one of the important catalysts, due to its high abundance, low cost and less toxicity.

In addition to the above copper-catalyzed cross-coupling reactions involving polar mechanisms, copper could serve as single electron transfer (SET) reagent to commence the radical redox reaction,[5–8] due to four oxidation states (0, +1, +2, +3), such as Kharasch–Sosnovsky oxidation. For instance, low-valent copper facilely reduces oxidative species into radicals. Cu^{II}, a useful one-electron oxidant, could oxidize alkyl radicals into carbocations. Cu^{II} is able to reversibly trap an alkyl radical to generate high-valent Cu^{III} species *via* an inner-sphere process. This process could isolate the highly reactive alkyl radical through the formation of relatively stable Cu^{III} species, inhibiting the facile homodimerization, improving the desired radical cross-coupling. Also, the interaction of Cu^{II} with an alkyl radical could furnish the desired product *via* an outer-sphere radical substitution pathway.[9] Besides, copper could provide good Lewis acid activation, increasing the reactivity of radical acceptors.

Compared to traditional copper-catalyzed $C(sp^2)$–C/X cross-coupling of aryl/alkenyl (pseudo)halides, the cross-coupling of alkyl (pseudo)halides for the generation of $C(sp^3)$–C/X bonds could provide an efficient complementarity.[10] Especially, the development of enantioconvergent radical cross-coupling of racemic alkyl (pseudo)halides for the construction of chiral $C(sp^3)$–C/X bonds would potentially open up a new window in organic synthesis.[11] However, it remains less investigated due to the difficult oxidative addition of alkyl (pseudo)halides and facile β-H elimination of alkyl copper complexes. At the early stage, enantioconvergent radical $C(sp^3)$–C cross-coupling of racemic alkyl halides has been developed by Fu and others by using chiral nickel, cobalt, and iron catalysts.[12] Despite major advances, this strategy still faces some problems, such as the utilization of moisture- and/or oxygen-sensitive organometallic reagents and limited alkyl halides as radical precursors. Moreover, copper-catalyzed enantioconvergent radical cross-coupling of racemic alkyl halides has been less explored, mainly due to the weaker reducing capability of copper in contrast with nickel, cobalt and iron at the ground state.[11] Recently, Liu has strategically designed chiral anionic ligands to enhance the reducing capability of the Cu^I complex and initiate the radical process under thermal conditions.[6,11] Additionally, the introduction of visible light would provide new ideas for relieving this challenge. Visible light-triggered energy or single-electron transfer usually result in the formation of a highly reactive radical intermediate,[13–15] which would extend the scope of copper-catalyzed $C(sp^2)$–C/X cross-coupling and enhance the possibility of copper-catalyzed $C(sp^3)$–C/X cross-coupling.[16–18] Molander, Doyle and MacMillan, and others have pioneered this field by merging photoredox catalysis and nickel catalysis *via* the single-electron transmetalation to achieve a series of radical $C(sp^3)$–$C(sp^2)$ cross-coupling.[19] Peters and Fu, and others have demonstrated that the visible light-excited copper complex could act as the photocatalyst to reduce alkyl halides to radical species, achieving an array of achiral $C(sp^3)$–C/N cross-coupling.[17] By using proper chiral ligands and counterparts, visible light-induced copper-catalyzed asymmetric cross-coupling would be possible.[20–23] In contrast with conventional asymmetric copper catalysis, the introduction of visible light provides milder and greener reaction conditions,

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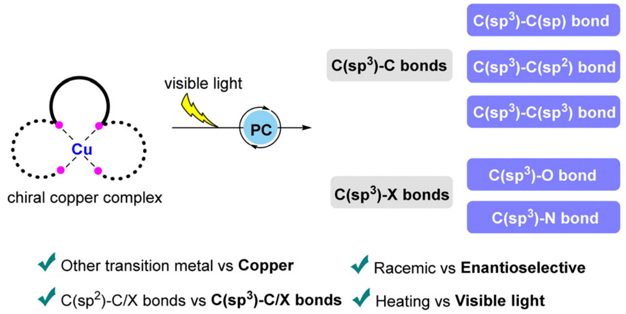


Fig. 1 Photoinduced copper-catalyzed enantioselective coupling reactions.

and enhances the reactivity of radicals. Photoinduced asymmetric copper catalysis consists of dual photoredox/copper catalysis and bifunctional copper catalysis. Dual catalysis *via* a chiral copper catalyst and an additional photocatalyst, is the common one and has been widely investigated. An impressive pioneering work by Li disclosed a photoinduced copper-catalyzed enantioselective C(sp^3)–C(sp) cross-coupling using Ir^{III} photocatalyst and chiral phosphine ligand.[24] While bifunctional catalysis *via* a single chiral copper catalyst is highly challenging due to relatively weaker visible-light absorption, shorter excited-state lifetimes and lower reduction potentials. An attractive pioneering work by Peters and Fu presented a photoinduced enantioselective C(sp^3)–N cross-coupling by using a copper(I) catalyst containing a chiral phosphine ligand as bifunctional catalyst.[25] Recently, a variety of photoinduced asymmetric copper-catalyzed reactions have been developed by using versatile chiral ligands, such as bisoxazoline (BOX) ligands, monodentate or bidentate phosphine ligands, NHC ligands and diamine ligands, giving an attractive approach to synthesizing diverse types of chiral organic molecules. This review highlights recent advances in photoinduced copper-catalyzed enantioselective coupling reactions according to the classification of bond formation (Fig. 1). Generally, for dual catalysis (Fig. 2), the Ir^{III} photocatalyst is excited by the visible light to give Ir^{III}*, which undergoes SET with an alkyl (pseudo)halide to form an alkyl radical and Ir^{IV}. The chiral copper catalyst L*Cu^I reacts with a nucleophile to generate L*Cu^{I}Nu, which is oxidized into L*Cu^{II}Nu by Ir^{IV} with the regeneration of Ir^{III}. Subsequently, the alkyl radical is captured by L*Cu^{II}Nu to produce L*Cu^{III} species *via* an inner-sphere process, followed by reductive elimination to deliver the chiral product and regenerate L*Cu^I. Alternatively, the interaction of L*Cu^{II}Nu with the alkyl radical could furnish the chiral product *via* an outer-sphere radical substitution pathway. For bifunctional catalysis (Fig. 2), the chiral copper catalyst L*Cu^I reacts with a nucleophile to generate L*Cu^{I}Nu, which is excited by the visible light to give [L*Cu^{I}Nu]*. The SET between [L*Cu^{I}Nu]* and an alkyl (pseudo)halide forms an alkyl radical and L*Cu^{II}Nu, which could afford the chiral product and regenerate L*Cu^I *via* either an inner-sphere L*Cu^{III} complex or an outer-sphere radical substitution pathway.

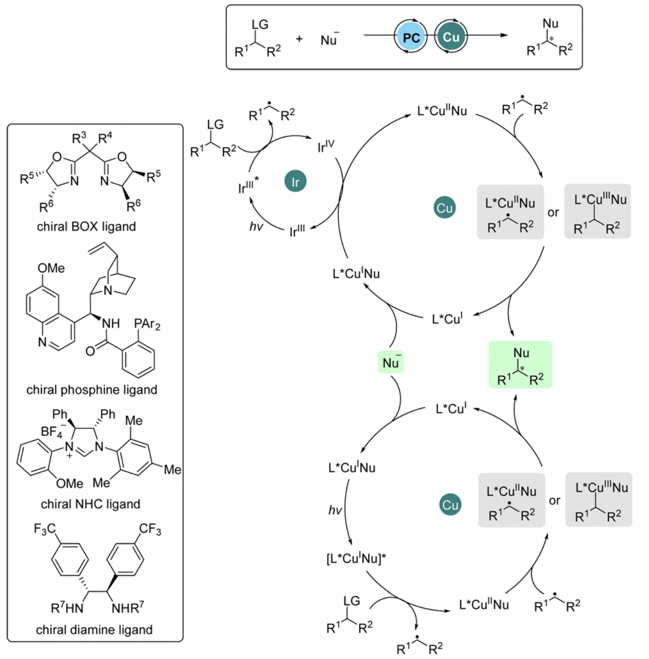
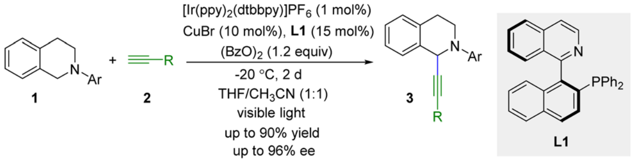


Fig. 2 General pathways for photoinduced asymmetric copper catalysis.

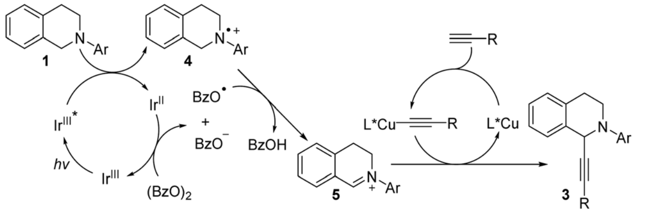
2. Carbon–carbon bond formation

2.1. C(sp^3)–C(sp) bond formation

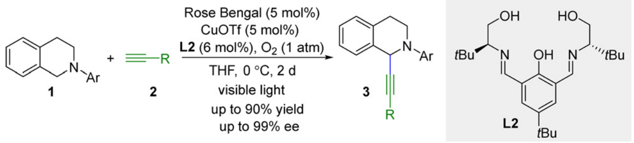
C-1 substituted tetrahydroisoquinoline derivatives possess diverse bioactivities and are important motifs in anticancer and antitubulin agents.[26] In 2015, Li and co-workers described efficient enantioselective cross-dehydrogenative-coupling (CDC) reactions of tertiary amines **1** and terminal alkynes **2** (Scheme 1).[24] By using $(BzO)_2$ as oxidant and chiral phosphine ligand **L1**, dual photoredox/copper catalysis delivered 1-alkynyl tetrahydroisoquinolines **3** in good yields and excellent enantioselectivities under mild conditions. Without copper salt, the reaction could not proceed. In the absence of photosensitizer or performing the reaction in the dark, much lower conversion was observed. As proposed (Scheme 2), photoexcited state Ir^{III}* undergoes SET with *N*-aryl-tetrahydroisoquinoline **1** to give Ir^{II} and a cation radical intermediate **4**. Through SET reduction of $(BzO)_2$ to BzO^- anion and $BzO^\bullet$ radical, Ir^{II} is reoxidized into Ir^{III}. The $BzO^\bullet$ radical abstracts a hydrogen of **4** to generate iminium ion intermediate **5**, which undergoes nucleophilic addition with chiral copper acetylide to afford optically active 1-alkynyl tetrahydroisoquinoline **3**.



Scheme 1 Photoinduced copper-catalyzed enantioselective CDC reactions using Ir^{III} photocatalyst.



Scheme 2 Proposed mechanism for the photoinduced copper-catalyzed enantioselective CDC reactions.

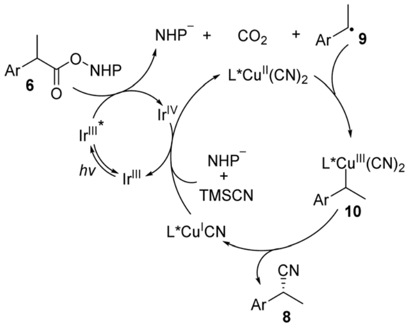


Scheme 3 Photoinduced copper-catalyzed enantioselective CDC reactions using Rose Bengal photocatalyst.

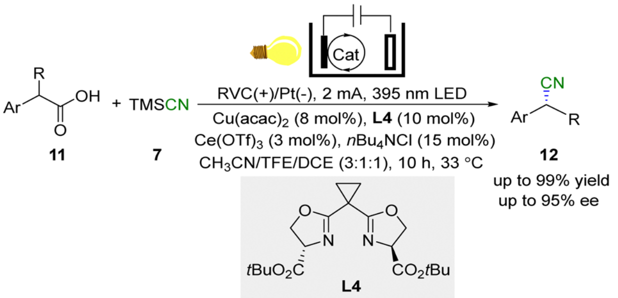
Later on, Khan and co-workers developed a similar asymmetric CDC reaction using oxygen as oxidant, Rose Bengal as photocatalyst and chiral amino alcohol-derived Schiff base **L2** as ligand under mild reaction conditions (Scheme 3).[27]

N-Hydroxyphthalimide (NHP) esters obtained from carboxylic acids have been approved to be important alkyl radical precursors, and have been employed in a variety of cross-coupling reactions.[28] In 2017, Liu and Lin reported an enantioselective decarboxylative cyanation between NHP esters **6** and TMSCN through cooperative photoredox/copper catalysis (Scheme 4).[29] By employing chiral BOX ligand **L3**, achiral NHP esters were converted into chiral alkyl nitriles **8** with high yields and enantioselectivities. Control experiments indicated that conjugate NHP esters could absorb an incoming electron more easily than unconjugated ones, resulting in higher yields and better enantioselectivies. The scope of alkyl radical precursors could be extended to NHP esters derived from anti-inflammatory drugs, while limited to substrates derived from secondary aliphatic carboxylic acids involving benzylic carbon radicals. Mechanistically (Scheme 5), under the irradiation of blue LEDs, NHP ester **6** undergoes SET and sequential decarboxylation to give benzylic radical **9** and Ir^{IV}, which could oxidize $L^*Cu^{I}CN$ into $L^*Cu^{II}(CN)_2$ with regeneration of Ir^{III}. Benzylic radical **9** is captured by $L^*Cu^{II}(CN)_2$ to form L^*Cu^{III} species **10**, followed by reductive elimination to give the final product **8** and regenerate $L^*Cu^{I}CN$.

Scheme 4 Photoinduced copper-catalyzed enantioselective decarboxylative cyanation of NHP esters.

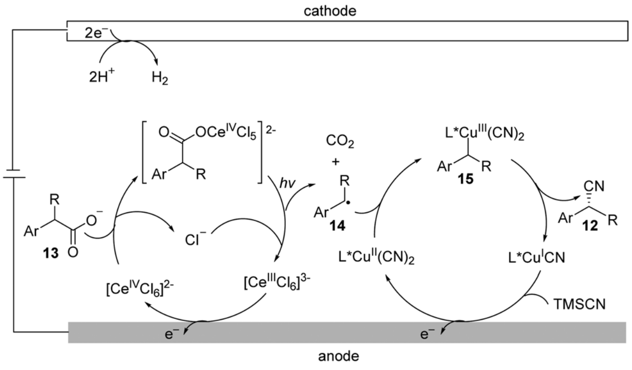


Scheme 5 Proposed mechanism for the photoinduced copper-catalyzed enantioselective decarboxylative cyanation.

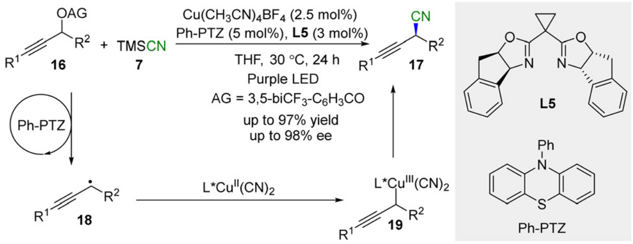


Scheme 6 Enantioselective decarboxylative cyanation through the combination of photoelectrocatalysis and asymmetric copper catalysis.

Instead of using NHP esters, achiral carboxylic acids could be directly treated as alkyl radical precursors. Recently, Xu and Song combined photoelectrocatalysis and asymmetric copper catalysis, achieving the enantioselective decarboxylative cyanation from carboxylic acids **11** (Scheme 6).[30] By using cerium/copper relay catalysis, diverse chiral nitriles **12** were delivered in high yields and enantioselectivities. In this reaction, cerium salt served as photocatalyst for the decarboxylation of the carboxylic acid to provide a benzylic radical, while a chiral copper complex was employed for the stereoselective C–CN formation. According to the mechanism (Scheme 7), $Ce(OTf)_3$ reacts with nBu_4NCl to give $CeCl_6^{3-}$, which is followed by oxidation at the anode to generate $CeCl_6^{2-}$. Sequential interaction with carboxylate **13** and photoinduced ligand-to-metal



Scheme 7 Proposed mechanism for the enantioselective cyanation through photoelectrocatalysis.

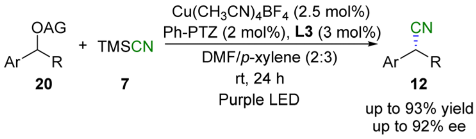


Scheme 8 Photoinduced copper-catalyzed asymmetric propargylic radical cyanation.

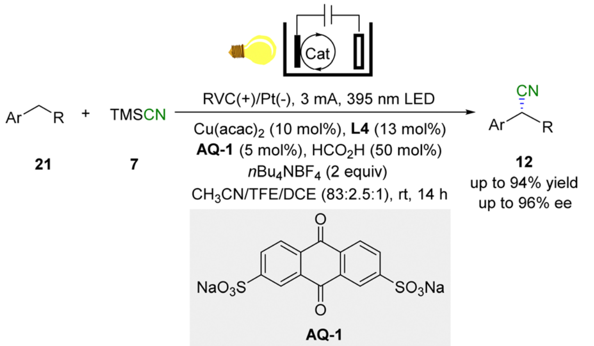
charge transfer (LMCT) afford benzylic radical **14** and regenerate $CeCl_6^{3-}$. $L^*Cu^{II}(CN)_2$ reacts with benzylic radical **14** to deliver the L^*Cu^{III} species **15**, which is followed by reductive elimination to produce the chiral nitrile **12** and $L^*Cu^{I}CN$, which would be oxidized into $L^*Cu^{II}(CN)_2$ at the anode.

Besides transition metal photocatalysts, organic photocatalysts could also be employed in photoinduced copper-catalyzed enantioselective coupling reactions. In 2019, Xiao, Lu and Lan reported an asymmetric propargylic radical cyanation *via* dual photoredox and copper catalysis (Scheme 8).[31] Various optically pure propargyl cyanides **17** were obtained with high yields and enantioselectivities. Notably, other propargyl esters bearing AG = AcO, BocO, BzO or *p*-MeO-BzO failed to give the desired product due to lacking sufficiently oxidative potentials. The organic photocatalyst Ph-PTZ not only promoted the formation of the propargyl radical, but also oxidized Cu^{I} species into Cu^{II} species. For this reaction, propargyl ester **16** firstly undergoes SET to give propargyl radical **18** under photoredox induction. Sequential reaction with $L^*Cu^{II}(CN)_2$ delivers Cu^{III} species **19**, followed by reductive elimination to produce the final product **17**.

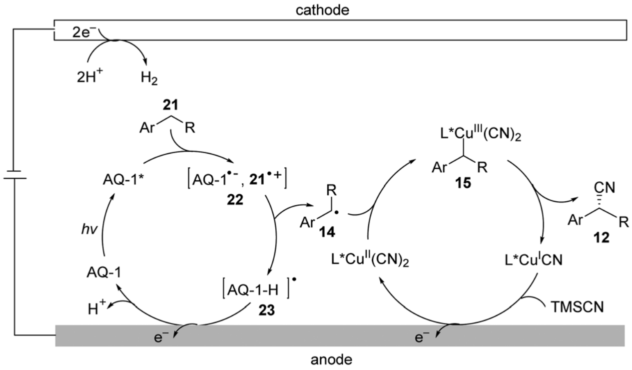
Following this line, the same group described an asymmetric deoxygenative cyanation of benzyl esters **20** through synergistic photoredox and copper catalysis (Scheme 9).[32] By using the organic photosensitizer Ph-PTZ, various chiral benzyl nitriles **12** were synthesized in good yields and high enantioselectivities.



Scheme 9 Photoinduced copper-catalyzed asymmetric deoxygenative cyanation of benzyl esters.



Scheme 10 Direct enantioselective cyanation of alkylarenes *via* photoelectrocatalysis.

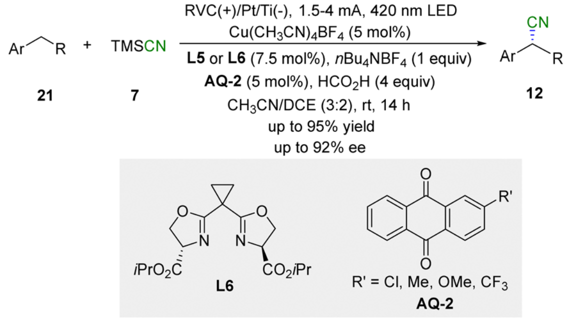


Scheme 11 Proposed mechanism for the enantioselective cyanation of alkylarenes.

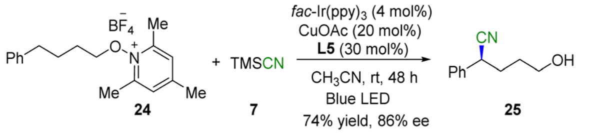
Without using activated precursor to produce alkyl radical, Xu's group actualized the direct enantioselective cyanation from alkylarenes as benzylic radical precursors (Scheme 10).[33] By using AQ-1 as photocatalyst and chiral BOX ligand **L4**, various chiral nitriles **12** were obtained in high yields and enantioselectivities. Photoelectrocatalysis is the key to this success of highly site-selective cyanation of multiple benzylic sites. This method did not require any chemical oxidant and could be extended to the late-stage diversification of complex bioactive molecules and natural products. As proposed (Scheme 11), photoexcitation of AQ-1 gives AQ-1*. This is followed by SET with alkylarene **21** to generate ion-radical pair **22**. Sequential proton transfer forms benzylic radical **14** and semiquinone radical **23**, which is oxidized to regenerate AQ-1 at the anode. Benzylic radical **14** reacts with $L^*Cu^{II}(CN)_2$ to offer L^*Cu^{III} species **15**. This is followed by reductive elimination to generate the chiral nitrile **12** and $L^*Cu^{I}CN$, which could be oxidized to regenate $L^*Cu^{II}(CN)_2$ at the anode.

In concurrence to the above report, Liu and Wang reported a similar enantioselective cyanation (Scheme 12).[34] Through dual photoelectrocatalysis/copper catalysis, highly efficient benzylic C–H functionalization was achieved with excellent stereocontrol.

In 2019, Zhu's group reported a dual photoredox/copper catalysis for the remote $C(sp^3)$–H functionalization between *N*-alkoxypyridinium salts and silyl reagents ($TMSN_3$, TMSCN, TMSNCS) employing 1,10-Phen as ligand, affording various δ-azido, δ-cyano, δ-thiocyanato alcohols in high yields.[35] By using chiral BOX ligand **L5** instead of 1,10-Phen, an enantioselective example of δ-$C(sp^3)$–H cyanation was shown (Scheme 13). Subsequently, Liu and co-workers utilized *N*-alkoxyphthalimides **26** as alkoxy radical precursors, achieving similar asymmetric cyanation of remote $C(sp^3)$–H bonds (Scheme 14).[36] In the asymmetric cyanation reaction, *N*-alkoxyphthalimide **26** firstly undergoes SET to give alkoxyl radical **28** under photoredox induction,



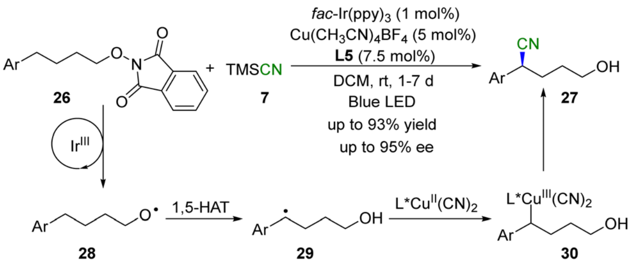
Scheme 12 Efficient benzylic C–H functionalization.



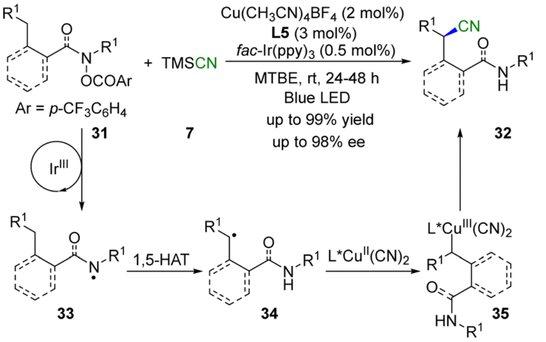
Scheme 13 Photoinduced copper-catalyzed asymmetric cyanation of remote C(sp^3)–H bonds from *N*-alkoxypyridinium salts.

followed by 1,5-hydrogen atom transfer (HAT) to generate alkyl radical **29.** Subsequent reaction with $L^*Cu^{II}(CN)_2$ forms Cu^{III} species **30,** followed by reductive elimination to give the final product **27.**

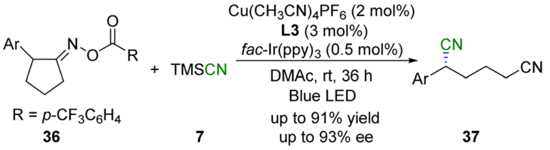
In 2020, Yu and co-workers developed a site-selective and enantiocontrolled remote C(sp^3)–H cyanation of *O*-acyl hydroxamides **31** *via* dual photoredox and copper catalysis (Scheme 15).[37] The reaction involved nitrogen radical-mediated intramolecular HAT. Control experiments indicated that blue light, photocatalyst, copper catalyst, chiral BOX ligand **L5** and nitrogen atmosphere are all essential for the reaction. Notably, nonbenzylic *O*-acyl hydroxamides could conduct the remote C(sp^3)–H cyanation, affording good yields but very low enantioselectivities. For this reaction, SET between *O*-acyl hydroxamide **31** and photoexcited Ir^{III}* generates amidyl radical **33,** followed by 1,5-HAT to give benzylic radical **34.** Subsequent reaction with $L^*Cu^{II}(CN)_2$ delivers Cu^{III} species **35,** followed by reductive elimination to produce the final product **32.**



Scheme 14 Photoinduced copper-catalyzed asymmetric cyanation of remote C(sp^3)–H bonds from *N*-alkoxyphthalimides.



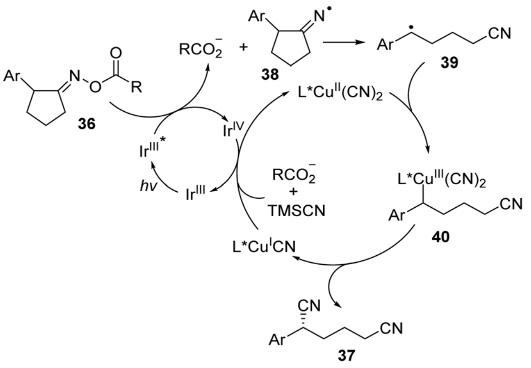
Scheme 15 Photoinduced copper-catalyzed asymmetric cyanation of remote C(sp^3)–H bonds from *O*-acyl hydroxamides.



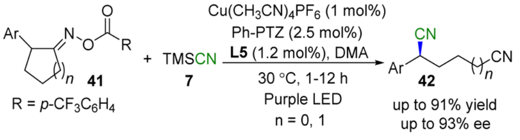
Scheme 16 Photoinduced copper-catalyzed enantioselective cyanation of oxime esters.

Besides NHP esters, propargyl esters and benzyl esters, oxime esters could also serve as alkyl radical precursors *via* sequential N–O bond cleavage and β-C scission. In 2019, Wang and co-workers described an enantioselective cyanation of five-membered cycloketone oxime esters **36** *via* radical-mediated C–C single bond cleavage for the construction of chiral 1,6-dinitriles **37** (Scheme 16).[38] Dual photoredox/copper catalysis was necessary for the asymmetric ring-opening cyanation. This reaction featured mild conditions, low catalyst loading, broad substrate scope, high yields and good enantioselectivities. As proposed (Scheme 17), under irradiation of blue LEDs, oxime ester **36** undergoes SET to give iminyl radical **38** and Ir^{IV}, which could oxidize L^*Cu^ICN into $L^*Cu^{II}(CN)_2$. Benzylic radical **39** generated from ring-opening of iminyl radical **38,** is trapped by $L^*Cu^{II}(CN)_2$ to afford the Cu^{III} species **40.** Final reductive elimination forms the final product **37** and regenerates L^*Cu^ICN.

At the same year, Chen and Xiao reported a similar enantioselective radical ring-opening cyanation of oxime esters **41**



Scheme 17 Proposed mechanism for the photoinduced copper-catalyzed enantioselective cyanation of oxime esters.

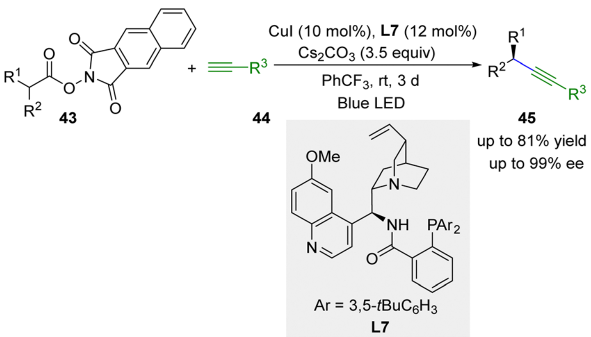


Scheme 18 Photoinduced copper-catalyzed enantioselective radical ring-opening cyanation of oxime esters.

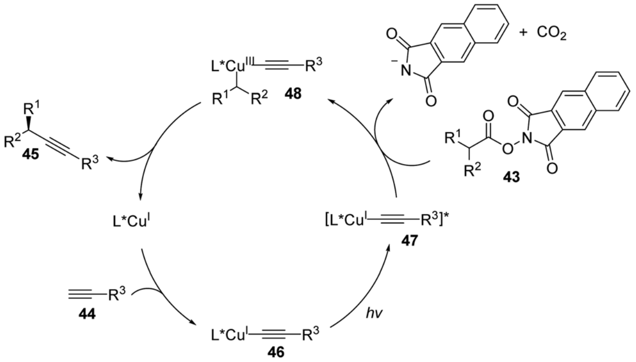
using organic photocatalyst Ph-PTZ (Scheme 18).[39] This mild reaction displayed good functional group tolerance, broad substrate scope, high yields and excellent enantioselectivities.

In contrast with dual catalysis through the combination of a chiral copper catalyst and an additional photocatalyst, chiral ligand–copper–nucleophile complexes own the ability to absorb visible light and act as bifunctional catalysts in the photoinduced enantioselective coupling reactions. In 2020, Liu's group reported a photoinduced copper-catalyzed asymmetric radical decarboxylative alkynylation between NHP-type esters **43** and terminal alkynes **44**, offering a flexible platform for the construction of chiral C(sp^3)–C(sp) bonds (Scheme 19).[40] The *in situ*-generated chiral copper acetylide served as a dual photo/cross-coupling catalyst. Tuning of NHP-type esters could inhibit the homodimerization of terminal alkyne and alkyl radical. Control experiments indicated that copper catalyst, blue light, cinchona alkaloid-derived N,N,P-ligand **L7** and base are necessary for the asymmetric alkynylation. Compared to reactions using alkyl halides, this reaction employing NHP-type esters featured broader substrate scope, providing a good complement to the reported methods. Benzylic, allylic and α-aminocarbonyl NHP-type esters were all tolerated in this transformation, while homobenzylic NHP-type esters could only produce racemic products, and tertiary NHP-type esters were not compatible with this reaction. According to the mechanism (Scheme 20), chiral copper acetylide **46** is firstly generated from L*Cu^I and terminal alkynes **44** in the presence of Cs_2CO_3, which is directly excited to give intermediate **47**. Subsequently, NHP-type ester **43** undergoes SET with intermediate **47** to give Cu^{III} species **48**. Final reductive elimination provides chiral alkyne **45** and regenerates L*Cu^I for the next catalytic cycle.

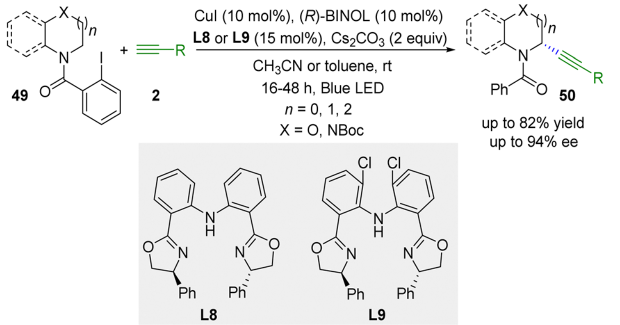
Later on, Zhang, Qi and Guo described a photoinduced copper-catalyzed asymmetric C(sp^3)–H alkynylation of unactivated cyclic 2-iodo-benzamides **49** (Scheme 21).[41] Through intramolecular 1,5-HAT and the employment of chiral bisoxazoline diphenylamine (BOPA) ligand, various chiral propargyl amines were delivered in good yields and enantioselectivities. The key to the success of this reaction is the formation of BOPA-copper acetylide-BINOL complex, which serves as photoredox and coupling catalyst. Mechanistic and computational studies indicated that intramolecular 1,5-HAT process is involved in the rate-limiting step. As proposed (Scheme 22), the BOPA-copper acetylide species **52** interacts with BINOL to give intermediate **53**, which undergoes photoexcitation to afford Cu^I species **54**. SET between cyclic 2-iodo-benzamide **49** and intermediate **54** delivers phenyl radical **55** and Cu^{II} species **57**. Intramolecular 1,5-HAT results in alkyl radical **56**, which reacts with **57** to produce the final product **50** and regenerates BOPA-copper complex **51**.



Scheme 19 Photoinduced copper-catalyzed enantioselective radical decarboxylative alkynylation.

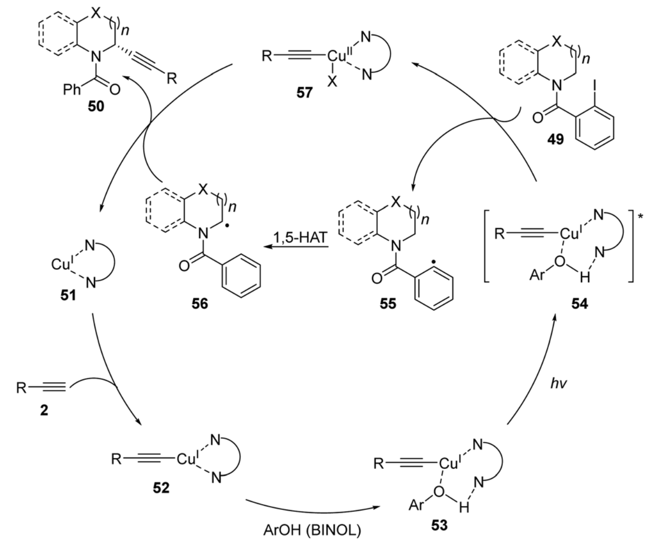


Scheme 20 Proposed mechanism for the photoinduced copper-catalyzed enantioselective radical decarboxylative alkynylation.

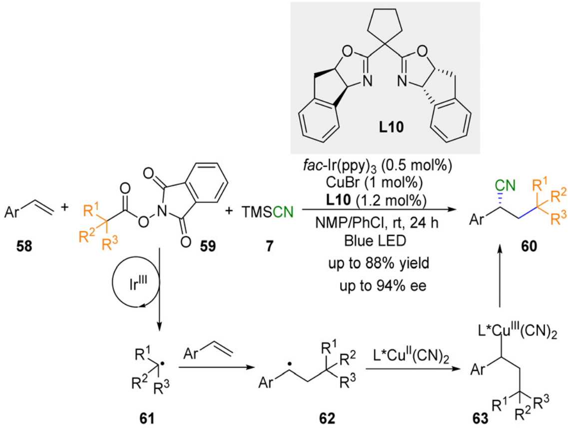


Scheme 21 Photoinduced copper-catalyzed asymmetric C(sp^3)–H alkynylation.

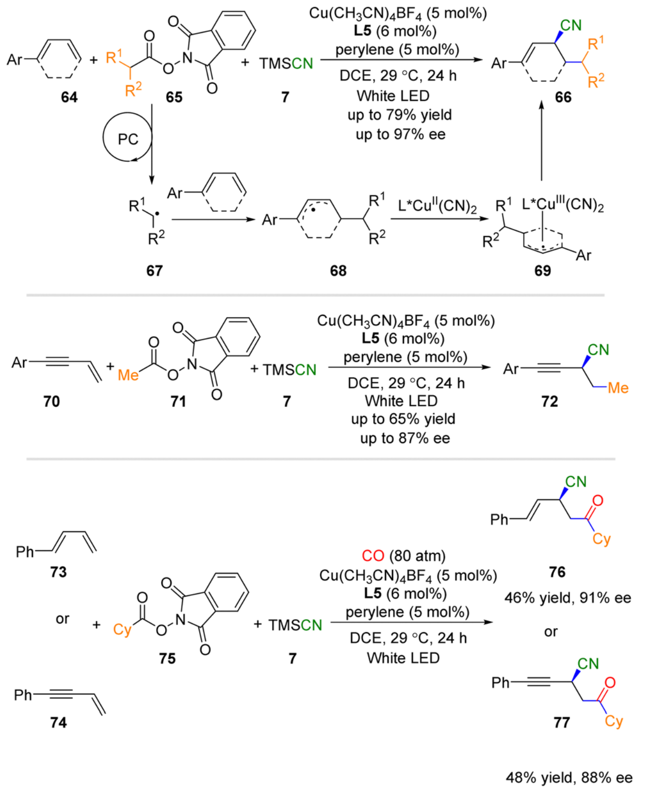
1,2-Difunctionalization of alkenes has emerged as an extensive research topic in organic synthesis, due to the ability to simultaneously construct two sequential chemical bonds and extend molecular complexity in a single reaction from commercially available starting materials.[42] NHP esters have also been treated as alkyl radical precursors under light irradiation in 1,2-difunctionalization of alkenes, providing promising, mild and green approaches to complex molecules. In 2018, Han and Mei developed a three-component reaction, by merging photoredox and copper catalysis for the asymmetric cyanoalkylation



Scheme 22 Proposed mechanism for the photoinduced copper-catalyzed asymmetric C(sp^3)–H alkynylation.



Scheme 23 Photoinduced copper-catalyzed asymmetric cyanoalkylation of alkenes using NHP esters as alkylation reagents.

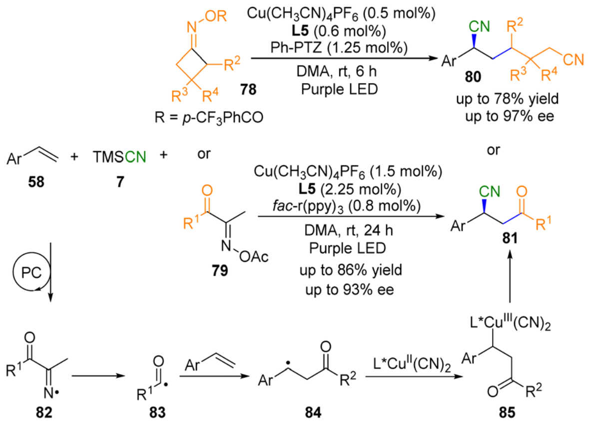


Scheme 24 Photoinduced copper-catalyzed asymmetric enantioselective carbocyanation of 1,3-dienes or 1,3-enynes.

of alkenes **58** using NHP esters **59** as alkylation reagents (Scheme 23).[43] This reaction featured high yields and enantioselectivities, broad substrate scope including primary, secondary and tertiary alkyl substituted NHP esters, while being limited to aryl alkenes. This reaction starts with SET between NHP esters **58** and photoexcited Ir^{III}* to deliver alkyl radical **61**, followed by addition to the alkene to form benzylic radical **62**. This would couple with L*Cu^{II}(CN)$_2$ to give Cu^{III} species **63**, which undergoes reductive elimination to deliver the final product **60**.

Recently, Xiao and co-workers presented a visible light-induced enantioselective carbocyanation of 1,3-dienes **64** (Scheme 24).[44] By employing NHP esters **65**, TMSCN and organic photocatalyst perylene, various chiral allyl cyanides **66** were afforded in good yields and high enantioselectivities under mild conditions. Notably, a Cu^{I} catalyst was necessary for this reaction. This transformation featured broad substrate scope including primary and secondary alkyl substituted NHP esters, while it was limited to aryl dienes, probably because the aryl group could stabilize the formed allyl radical and promote the yield and enantioselectivity. Additionally, this strategy could be extended to 1,3-enynes and four-component carbonylative carbocyanation of 1,3-dienes or 1,3-enynes. For this carbocyanation, NHP ester **65** firstly undergoes SET to give alkyl radical **67** under photoredox induction, followed by addition to 1,3-diene to generate allyl radical **68**. Subsequent interaction with L*Cu^{II}(CN)$_2$ affords Cu^{III} species **69**, followed by reductive elimination generates the final product **66**.

Oxime esters also exhibit the potential to be alkyl radical precursors under photo-induction in 1,2-difunctionalization of alkenes, offering a suitable complement to NHP esters. In 2021, Xiao and Chen described an intermolecular enantioselective three-component 1,2-dicarbofunctionalization of alkenes enabled by merger of photoredox and copper catalysis (Scheme 25).[45] By using redox-active oxime esters **78** and **79** under mild conditions, a variety of alkyldinitriles **80** and β-cyano ketones **81** were obtained in good yields and high enantioselectivities. Notably, fine adjustment of catalyst loading could control the concentration of the reactive radical species, restraining the competing two-component cross-coupling and dimerization. Other light sources such as blue LEDs and CFL lamp were also examined, giving high enantioselectivities, but only moderate yields. The scope of alkenes could be expanded to styrene analogs derived from bioactive compounds, while it was limited to aromatic olefins. This reaction commences with

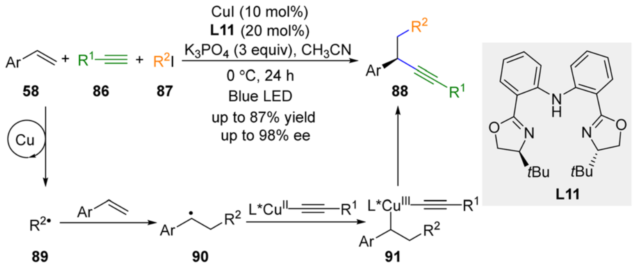


Scheme 25 Photoinduced copper-catalyzed enantioselective three-component 1,2-dicarbofunctionalization of alkenes.

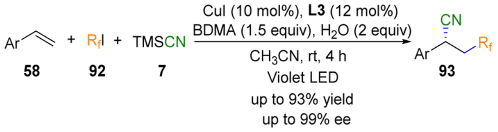
SET between oxime ester **79** and photoexcited Ir^{III}* to give iminyl radical **82**. This is followed by C–C bond cleavage to generate acyl radical **83**. This is trapped by styrene to form benzylic radical **84**, which reacts with L*Cu^{II}(CN)$_2$ to form Cu^{III} species **85**. Final reductive elimination affords the desired product **81**.

Chiral copper acetylide could serve as bifunctional catalyst in photoinduced 1,2-difunctionalization of alkenes. Recently, Zhang's group reported a photoinduced copper-catalyzed enantioselective 1,2-dicarbofunctionalization of alkenes (Scheme 26).[46] By using single chiral copper acetylide for photoredox catalysis and enantioselective cross-coupling, the dual alkylation/arylation and alkynylation of alkenes **58** were achieved to form diverse chiral propargylic compounds **88** using *t*Bu-BOPA (**L11**) as chiral ligand under mild reaction conditions. Unactivated alkenes and disubstituted styrenes were not compatible with this reaction. For this cross-coupling, alkyl iodide **87** firstly undergoes SET to give alkyl radical **89** under photoredox induction. Subsequent trapping by styrene generates benzylic radical **90**, which reacts with Cu^{II} to form Cu^{III} species **91**. Final reductive elimination delivers the final product **88**.

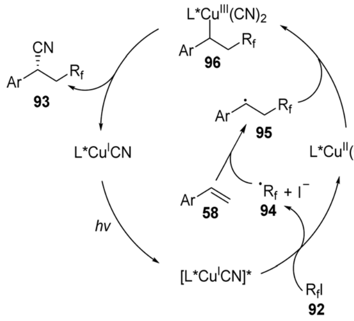
Besides chiral copper acetylide, chiral copper cyanide could also be used as a bifunctional catalyst in photoinduced enantioselective coupling reactions. In 2019, Wang and Xu described a visible-light-induced copper-catalyzed three-component reaction (Scheme 27).[47] In the enantioselective cyanofluoroalkylation of alkenes, the bifunctional chiral copper cyanide served not only as the photoredox catalyst for electron transfer, but also as the asymmetric cross-coupling catalyst for enantioselective C(sp^3)–C(sp) bond formation. This reaction featured mild conditions, high yields and enantioselectivities, and broad scope including diverse fluoroalkyl iodides, while nonconjugated alkenes and conjugated dienes were not tolerated. As proposed in Scheme 28, L*Cu^{I}CN is excited to [L*Cu^{I}CN]* under violet LED irradiation. Oxidative quenching of R$_f$I forms radical **94** and L*Cu^{II}(CN)$_2$. The following radical addition to alkene generates radical intermediate **95**, which subsequently reacts with L*Cu^{II}(CN)$_2$ to deliver Cu^{III} species **96**. Reductive elimination gives the final product **93** and regenerates L*Cu^{I}CN.



Scheme 26 Photoinduced copper-catalyzed enantioselective 1,2-dicarbofunctionalization of alkenes using terminal alkynes.



Scheme 27 Photoinduced copper-catalyzed enantioselective cyanofluoroalkylation of alkenes.

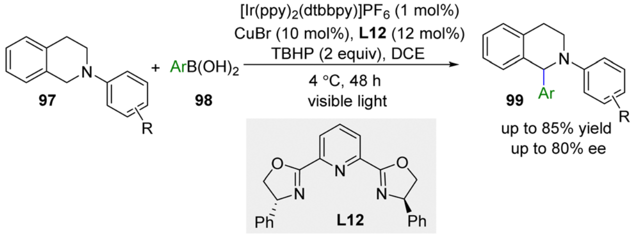


Scheme 28 Proposed mechanism for the photoinduced copper-catalyzed enantioselective cyanofluoroalkylation of alkenes.

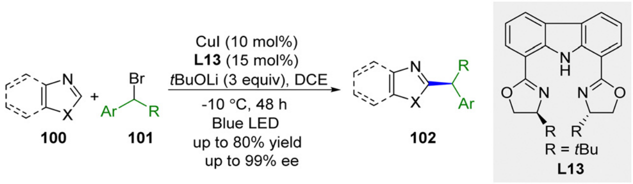
2.2. C(sp^3)–C(sp^2) bond formation

Based on their previous work,[24] Li and co-workers reported an efficient asymmetric C(sp^3)–H arylation between *N*-arylated tetrahydroisoquinolines **97** and arylboronic acids **98** (Scheme 29).[48] The combination of photoredox catalyst, copper salt, oxidant TBHP and chiral ligand PhPyBOX (**L12**) produced arylated products **99** with good yields and enantioselectivities.

Besides chiral copper acetylide and copper cyanide, the *t*BuCbzBOX-copper-azole complex has proved to be an efficient

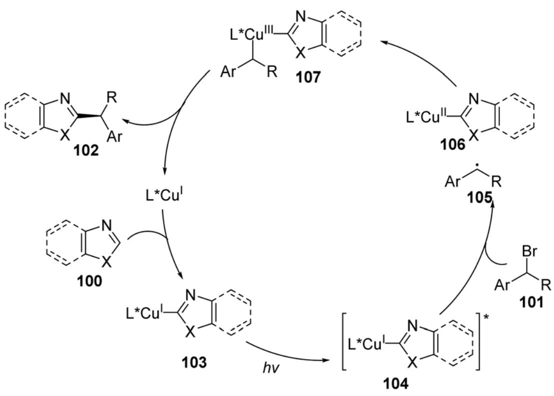


Scheme 29 Photoinduced copper-catalyzed asymmetric C(sp^3)–H arylation using arylboronic acids.

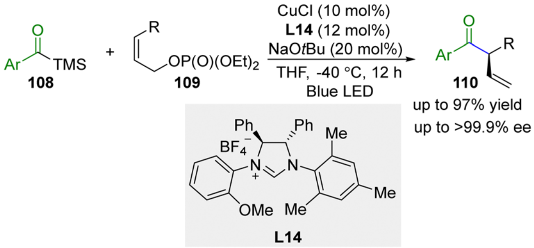


Scheme 30 Photoinduced copper-catalyzed enantioselective alkylation using azoles.

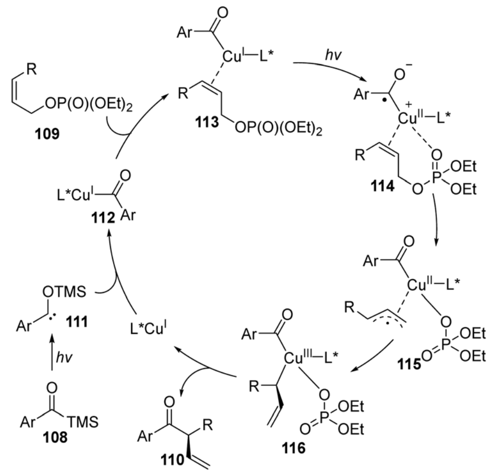
bifunctional catalyst in the photoinduced enantioselective coupling reactions. In 2021, Zhang and co-workers developed an enantioselective alkylation between azoles **100** and secondary 1-arylalkyl bromides **101** (Scheme 30).[49] By employing blue-light photoexcitation and chiral ligand *t*BuCbzBOX (**L13**), the copper-catalyzed direct C–H functionalization afforded diverse chiral alkyl azoles **102** in good yields and high enantioselectivities. In the absence of copper salt, ligand or base, no desired product was formed. Without light, the yield decreased significantly, but enantioselectivity remained unchanged. However, unactivated alkyl bromides, α-bromoketone and pseudohalide such as OMs, failed to provide the desired products. As proposed (Scheme 31), azole **100** firstly undergoes transmetallation with L*Cu^I to give intermediate **103**, which is directly excited to form intermediate **104**. Subsequently, alkyl bromide **101** undergoes SET to deliver alkyl radical **105** and Cu^{II} complex **106**, which would rapidly transform into Cu^{III} species **107**. Final reductive elimination results in the desired product **102** and regenerates L*Cu^I for the next catalytic cycle.



Scheme 31 Proposed mechanism for the photoinduced copper-catalyzed enantioselective alkylation.



Scheme 32 Photoinduced copper-catalyzed asymmetric umpolung allylic acylation.

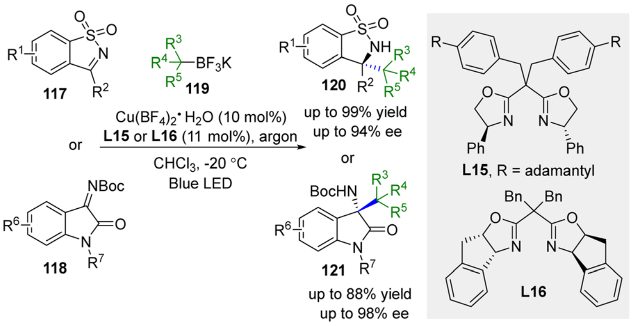


Scheme 33 Proposed mechanism for the photoinduced copper-catalyzed asymmetric umpolung allylic acylation.

Acylsilane has proved to be an acyl anion equivalent through sequential photoexcitation and isomerization.[50] In 2022, Hasegawa and Sawamura presented a photoinduced copper-catalyzed asymmetric umpolung allylic acylation between allylic acylsilanes **108** and phosphates **109** (Scheme 32).[51] Employing acylsilanes **108** as acyl anion equivalents facilitated this transformation under blue-light irradiation, delivering α-stereogenic β,γ-unsaturated ketones **110** with good yields and excellent enantioselectivities. The key to this success is the employment of a chiral NHC-acylcopper-alkene complex as both photocatalyst and chiral catalyst. Notably, in the absence of blue LED irradiation, no reaction occurred. When alkene with *E* configuration was used, a lower yield and enantioselectivity were observed. Moreover, this approach was not compatible with alkanoylsilanes. Triplet-quenching experiments and DFT calculations suggested that the reaction mechanism involves copper-to-acyl metal-to-ligand charge transfer (MLCT) photoexcitation, which produces a charge-separated triplet state as a highly reactive intermediate. According to the mechanism (Scheme 33), acylsilane **108** firstly undergoes photoexcitation to give singlet siloxycarbene species **111**, which reacts with L*Cu^I to produce intermediate **112**. Allylic phosphate **109** coordinates with intermediate **112** to afford intermediate **113**, which undergoes second photoexcitation in an MLCT fashion to form the charge-separated triplet excited state **114**. Sequential molecular activation and electron shift generate L*Cu^{II} complex **115**, which undergoes regio- and stereocontrolled formation of the ground state L*Cu^{III} complex **116**. Final stereoretentive reductive elimination delivers the desired product **110** and regenerates L*Cu^I for the next catalytic cycle.

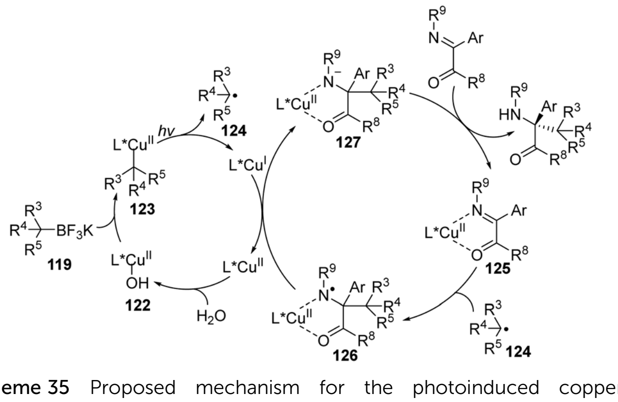
2.3. C(sp^3)–C(sp^3) bond formation

Besides bifunctional catalysts depicted above, the chiral BOX-alkylcopper complex is also an appropriate bifunctional catalyst in photoinduced enantioselective coupling reactions. In 2018, Gong and co-workers reported a visible light-induced copper-catalyzed

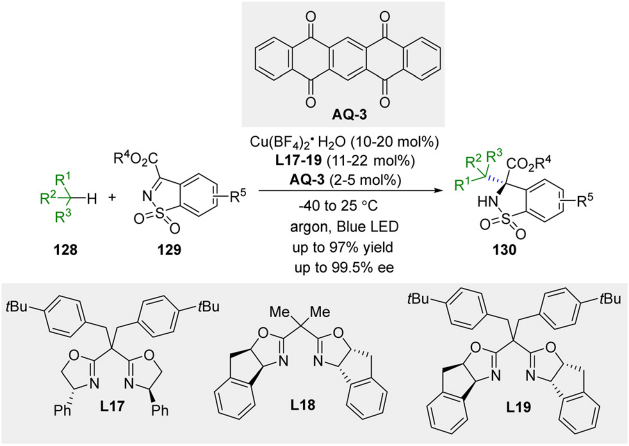


Scheme 34 Photoinduced copper-catalyzed enantioselective alkylation of imines using trifluoroborates.

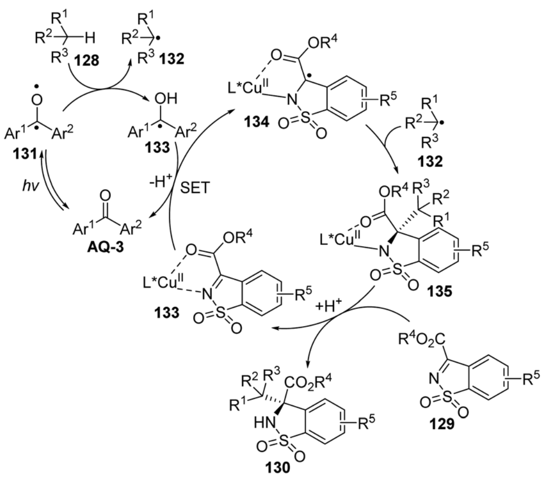
enantioselective alkylation of sulfonylimines **117** and isatin-derived ketimines **118** (Scheme 34).[52] By using trifluoroborates **119** as alkyl radical precursors, various chiral amines **120** and **121** bearing a tetrasubstituted carbon stereocenter were constructed in good yields and enantioselectivities under mild conditions. The key to this success is the photo-induced homolysis of the copper–carbon bond to generate an alkyl radical *via* LMCT. In the absence of blue light, ligand, or copper catalyst, no desired product was generated. Notably, secondary and tertiary trifluoroborates were tolerated, leading to good yields, but lower enantioselectivities. As proposed (Scheme 35), L^*Cu^{II} complex firstly reacts with H_2O to form hydroxide intermediate **122**, which undergoes ligand exchange with alkyl trifluoroborate **119** to generate intermediate **123.** Intermediate **123** is excited by visible light, followed by LMCT and homolysis to offer L^*Cu^{I} species and alkyl radical **124**. Meanwhile, the imine coordinates with L^*Cu^{II} to afford intermediate **125.** Radical addition to intermediate **125** affords nitrogen radical **126**, which undergoes SET to regenerate L^*Cu^{II} and give intermediate **127.** Sequential protonation and ligand exchange afford final product and regenerate intermediate **125.**



Scheme 35 Proposed mechanism for the photoinduced copper-catalyzed enantioselective alkylation of imines using trifluoroborates.



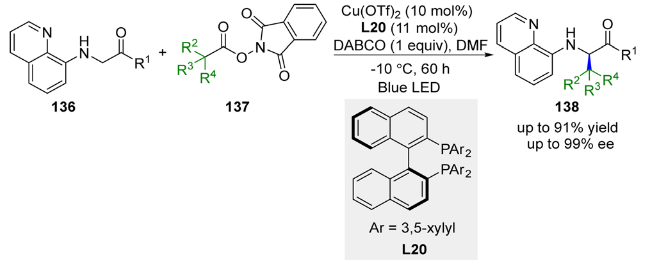
Scheme 36 Photoinduced copper-catalyzed enantioselective alkylation between sulfonylimines and alkanes.



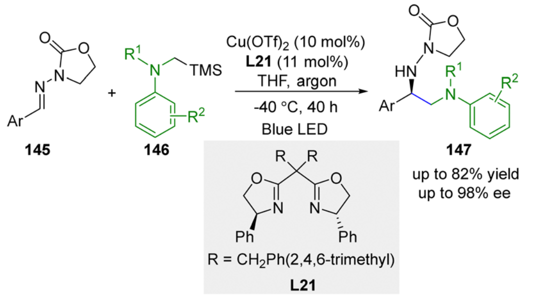
Scheme 37 Proposed mechanism for the photoinduced copper-catalyzed enantioselective alkylation between sulfonylimines and alkanes.

Different with the above described process employing trifluoroborates as alkyl radical precursors, the same group recently successfully developed a dual photoredox/copper catalysis system, directly using benzylic or allylic hydrocarbons, and even unactivated alkanes as alkyl radical precursors (Scheme 36).[53] By using 5,7,12,14-pentacenetetrone (AQ-3) as organophotocatalyst, a number of benzylic or allylic hydrocarbons, and unactivated alkanes reacted with sulfonylimines **129** to give functionalized chiral products **130.** Copper catalysts with readily tunable chiral BOX ligands **L17–L19** displayed excellent regio- and stereoselectivity for inert $C(sp^3)$–H bonds. However, secondary C–H bonds in unactivated acyclic alkanes and cyloalkanes delivered much lower yields and enantioselectivities. According to the mechanism (Scheme 37), the photocatalyst AQ-3 is excited by blue light to give the biradical species **131**, which undergoes HAT with alkane **128** to afford radical intermediate **133** and alkyl radical **132.** On the other hand, imine **129** coordinates with L^*Cu^{II} to form intermediate **133**, which undergoes SET to regenerate photocatalyst AQ-3 and give carbon radical **134.** The cross-coupling of radical **132** and radical **134** provides intermediate **135.** This is followed by protonation and ligand exchange to offer the final product **130** and regenerate intermediate **133.**

In 2021, Wang and Xu reported a visible light-induced copper-catalyzed enantioselective $C(sp^3)$–H alkylation using



Scheme 38 Photoinduced copper-catalyzed enantioselective C(sp^3)–H alkylation of unnatural α-amino acids.

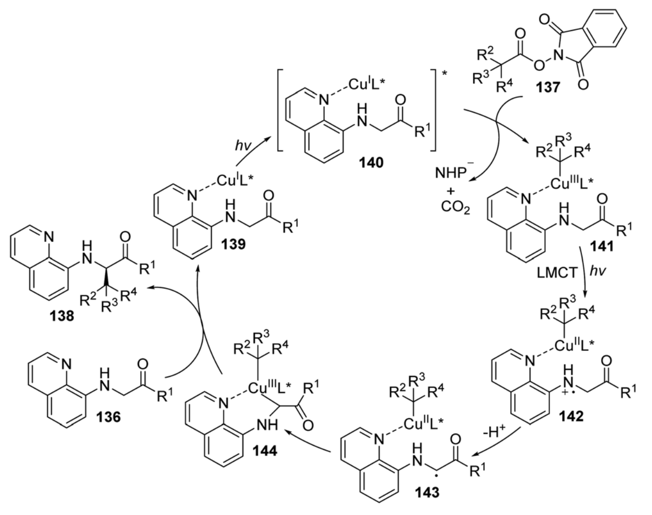


Scheme 40 Photoinduced copper-catalyzed enantioselective α-aminomethylation of acyclic imines using α-silylamines.

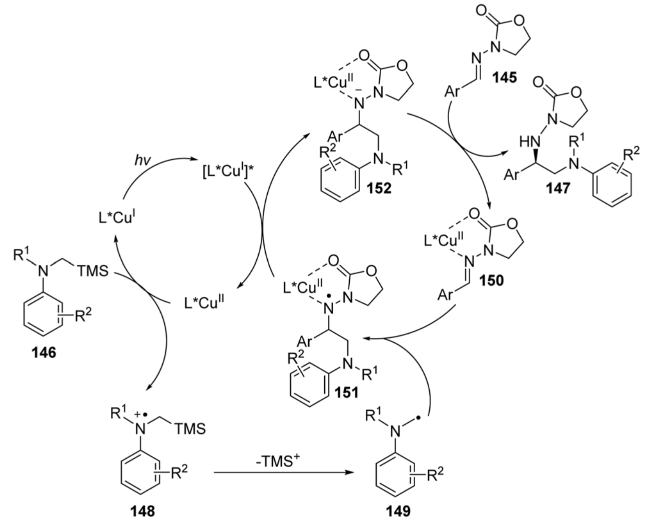
chiral bisphosphine ligand **L20**, providing unnatural α-amino acids **138** bearing primary, secondary and tertiary alkyl fragments in good yields and high enantioselectivities (Scheme 38).[54] This reaction could be also employed for the late-stage functionalization of bioactive compounds. Quinoline auxiliary was crucial for this reaction through coordination with chiral copper complex to form a new chiral photocatalyst, controlling the stereochemistry and suppressing the competing racemic background reaction. As proposed (Scheme 39), quinolinyl-8-glycinate ester **136** coordinates with L*Cu^{I} to form intermediate **139**, which is then excited by blue light to give intermediate **140**. SET between NHP ester **137** and intermediate **140** generates the alkyl radical, which subsequently recombines to deliver intermediate **141**. Intramolecular LMCT of intermediate **141** generates radical cation **142**, which undergoes deprotonation to produce alkyl radical **143**. Sequential intramolecular recombination affords Cu^{III} species **144**, followed by reductive elimination to afford the desired product **138**.

In contrast with aforementioned examples using chiral ligand–copper–nucleophile complexes as bifunctional catalysts in the photoinduced asymmetric couplings, simple chiral ligand–copper complexes could also be excited by visible light and act as bifunctional catalysts. In 2019, Gong and co-workers reported a photoinduced enantioselective α-aminomethylation of acyclic imine derivatives **146** employing α-silylamines **146** as the α-aminomethyl radical precursors (Scheme 40).[55] By employing chiral BOX copper for photoredox catalysis, Lewis acid activation and asymmetric induction, diverse chiral vicinal diamines **147** were constructed in high yields and enantioselectivities. Alkyl-substituted imine was not reactive enough, affording much lower yield and enantioselectivity. α-Silylamines bearing bulky substituents on nitrogen gave good yields, but lower enantioselectivities. As proposed (Scheme 41), SET between α-silylamine **146** and L*Cu^{II} gives L*Cu^{I} species and radical cation **148**, which undergoes the removal of the TMS cation to afford radical **149**. L*Cu^{I} species is then excited by visible light to form [L*Cu^{I}]*. Meanwhile, imine **146** coordinates with L*Cu^{II} to form intermediate **150**, followed by addition of radical **149** to give nitrogen radical **151**. Sequential SET between intermediate [L*Cu^{I}]* and radical **151** regenerates L*Cu^{II} and delivers complex **152**. This is followed by protonation and ligand exchange to produce the final product **147** and regenerate intermediate **150**.

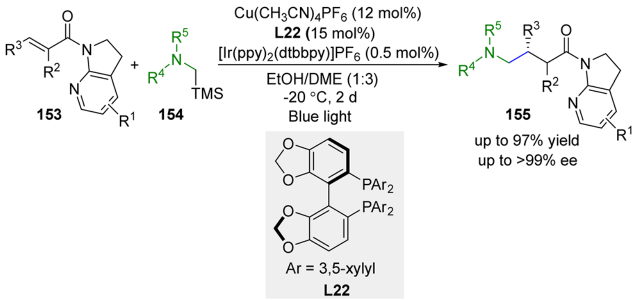
Different with the above described reaction, Shibasaki and Kumagai developed a cooperative system involving a chiral Cu(I) complex and Ir(III) photocatalyst using α,β-unsaturated



Scheme 39 Proposed mechanism for the photoinduced copper-catalyzed enantioselective C(sp^3)–H alkylation of unnatural α-amino acids.



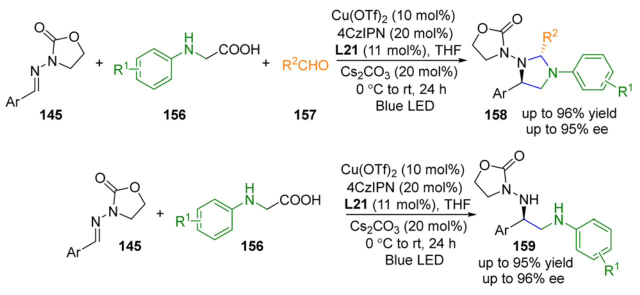
Scheme 41 Proposed mechanism for the photoinduced copper-catalyzed enantioselective α-aminomethylation of acyclic imines using α-silylamines.



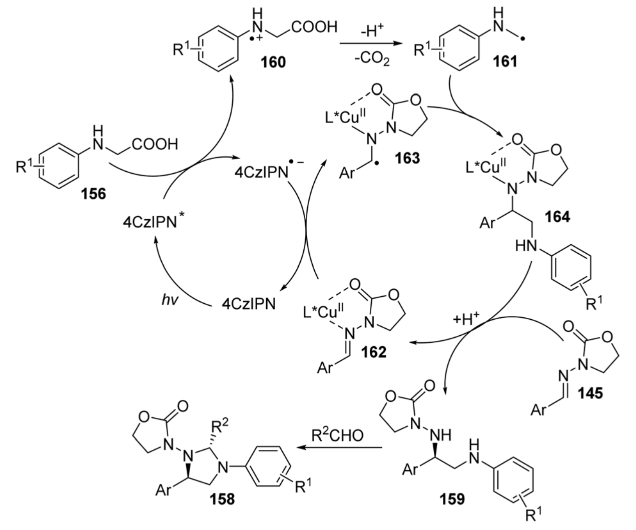
Scheme 42 Photoinduced copper-catalyzed enantioselective α-aminomethylation of α,β-unsaturated amides.

amides **153** as efficient radical acceptors, achieving enantioselective α-aminomethylation (Scheme 42).[56] 7-Azaindoline auxiliary on the amide moiety was essential to suppress the undesired reactions. A variety of γ-aminobutyramides **155** were generated in good yields and excellent enantioselectivities. Notably, the 7-azaindoline auxiliary could be readily recovered, providing diverse transformations.

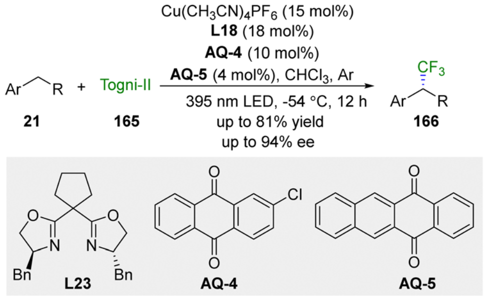
In 2022, Zeng and Han developed an effective strategy for the asymmetric synthesis of chiral imidazolidines **158** and vicinal diamines **159**, employing glycine derivatives **156** as the α-aminomethyl radical precursors (Scheme 43).[57] By merging copper catalysis and photoredox catalysis, the decarboxylative radical coupling of glycine derivatives **156** and imines **145** with or without aldehydes **157** was achieved in high efficiency and enantioselectivity. Without adding photocatalyst, no reaction occurred. In the absence of copper catalyst, a high yield was observed, but only giving racemic product. According to the mechanism (Scheme 44), *N*-phenylglycine **156** firstly undergoes SET to give radical cation **160**, followed by the removal of CO$_2$ to form alkyl radical **161**. On the other hand, imine **145** coordinates with L*Cu^{II} to afford intermediate **162**, which then undergoes SET to give intermediate **163** and to regenerate the photocatalyst. Radical–radical coupling between radical **161** and intermediate **163** produces intermediate **164**. This is followed by protonation and ligand exchange to regenerate intermediate **162** and deliver the diamine product **159**. Sequential cyclization with aldehyde forms imidazolidine product **158**.



Scheme 43 Photoinduced copper-catalyzed enantioselective α-aminomethylation using glycine derivatives.

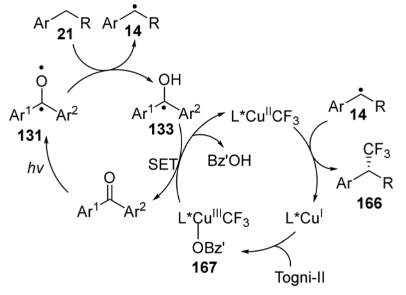


Scheme 44 Proposed mechanism for the photoinduced copper-catalyzed enantioselective α-aminomethylation using glycine derivatives.

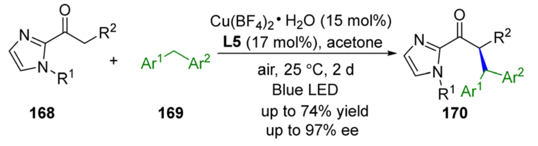


Scheme 45 Photoinduced copper-catalyzed asymmetric trifluoromethylation of benzylic C–H bonds.

Recently, Liu's group directly employed alkylarenes **21** as benzylic radical precursors, achieving the asymmetric trifluoromethylation of benzylic C–H bonds (Scheme 45).[58] Through cooperative photoredox/copper catalysis, various chiral trifluoromethylated products **166** were obtained in good yields and excellent enantioselectivities under mild conditions. The photocatalyst was responsible for the formation of benzylic radicals from alkylarenes *via* a HAT process, and the chiral copper complex was the key for the enantioselective trifluoromethylation. As proposed (Scheme 46), photoexcitation of the photosensitizer generates diradical **131**, which absorbs a hydrogen atom from alkylarene **21** to form benzylic radical **14** and radical **133**. L*Cu^{I}



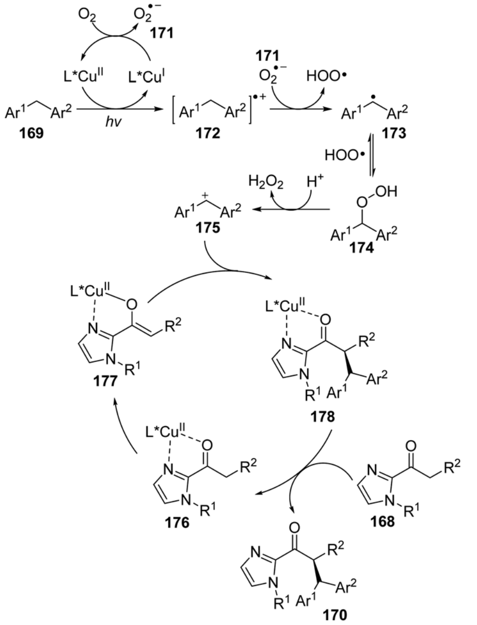
Scheme 46 Proposed mechanism for the asymmetric trifluoromethylation of benzylic C–H bonds.



Scheme 47 Photoinduced copper-catalyzed aerobic asymmetric CDC reactions between 2-acyl imidazoles and xanthene derivatives.

undergoes oxidative addition with Togni-II reagent to produce L*Cu^{III} species **167**, which could oxidize radical **133** to give L*Cu^{II}CF$_3$ and to regenerate photosensitizer. Benzylic radical **14** could be trapped by L*Cu^{II}CF$_3$ to deliver the final product **166** and regenerate L*Cu^{I}.

Based on their previous work using chiral BOX copper complex as bifunctional catalyst,[55] Gong and co-workers applied the same catalytic strategy to aerobic asymmetric CDC reactions between 2-acyl imidazoles **168** and xanthene derivatives **169** using oxygen as oxidant (Scheme 47).[59] The chiral BOX copper showed good performance on both photoactivation and asymmetric induction, affording a variety of chiral products **170** in high yields and enantioselectivities. N-*t*Bu imidazole failed to give the desired product, probably due to steric hindrance. Asymmetrical xanthenes produced reasonable yields and high enantioselectivities, but low diastereoselectivities. According to the mechanism (Scheme 48), SET between xanthene **169** and L*Cu^{II} produces radical cation **172** and L*Cu^{I} species, which would be oxidized by O$_2$ to regenerate L*Cu^{II} and afford superoxide radical anion **171**. The superoxide radical anion **171** reacts with radical cation **172** to give benzyl radical **173** and HOO$^•$. This is followed by radical–radical coupling to generate peroxide **174**. Protonation of peroxide **174** results in benzyl cation **175** and H$_2$O$_2$. Meanwhile, imidazole **168** coordinates with L*Cu^{II} to form intermediate **176**, which is deprotonated to generate intermediate **177**. Benzyl cation **175** undergoes electrophilic addition to deliver intermediate **178**. This is followed by ligand exchange with imidazole substrate **168** to produce the final product **170** and regenerate intermediate **176**.



Scheme 48 Proposed mechanism for the photoinduced copper-catalyzed aerobic asymmetric CDC reactions.

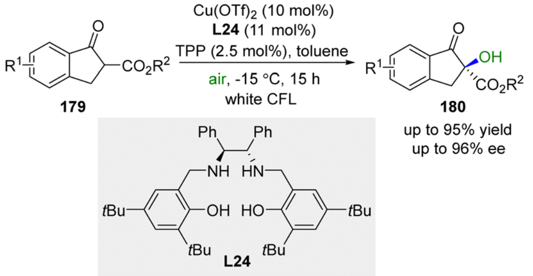
3. Carbon–heteroatom bond formation

3.1. C(sp^3)–O bond formation

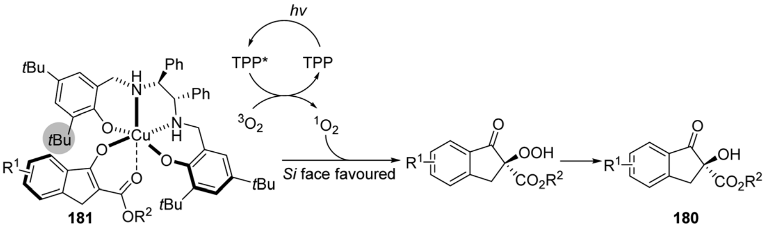
Dual photoredox/copper catalysis has also been employed in the enantioselective construction of C(sp^3)–O bonds. In 2019, Meng and co-workers developed an enantioselective aerobic α-hydroxylation of β-keto esters **179** using chiral salan ligand **L24**, proving that the energy-transfer process is tolerated with photoinduced asymmetric copper catalysis (Scheme 49).[60] By using air as the oxidant and tetraphenylporphyrin (TPP) as the photosensitizer, a number of α-hydroxyl β-keto esters **180** were constructed in high yields and enantioselectivities. Notably, this protocol could be employed as the key step to achieve the formal total synthesis of (*S*)-indoxacarb. For this transformation (Scheme 50), TPP is firstly excited by white light to give TPP*, which subsequently produces singlet ^{1}O$_2$ from unreactive triplet ^{3}O$_2$. Meanwhile, the Re face of the enolate intermediate **181** is efficiently blocked by the back *t*Bu group. Therefore, singlet ^{1}O$_2$ could only attack the Si face of enolate intermediate **181**, leading to the desired product **180** with *S* configuration.

In 2021, Chen and Xiao developed an asymmetric three-component Kharasch–Sosnovsky reaction between 1,3-dienes **183**, oxime esters **182** and carboxylic acids **184** employing photoinduced copper catalysis (Scheme 51).[61] This reaction featured mild conditions, broad scope and applications in the late-stage diversification of drugs and natural products. In this asymmetric three-component coupling, oxime ester **182** firstly undergoes SET to give iminyl radical under photoredox induction, which is followed by ring-opening to generate alkyl radical **186**. Then alkyl radical **186** is trapped by the 1,3-diene to form allylic radical **187**, which reacts with L*Cu^{II} complex **188** to form L*Cu^{III} species **189**. Final reductive elimination affords the desired product **185**.

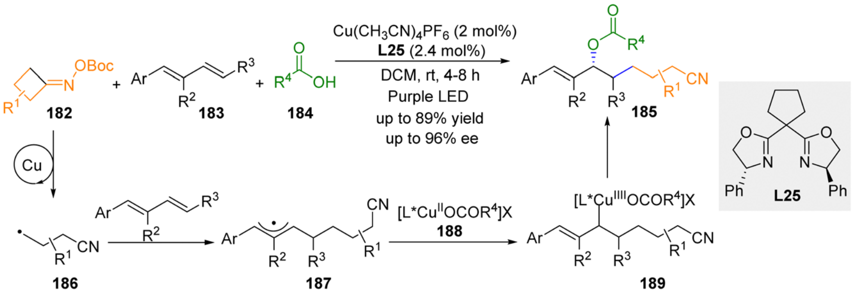
Subsequently, the same group employed styrenes as radical acceptors, achieving the visible light-induced copper-catalyzed



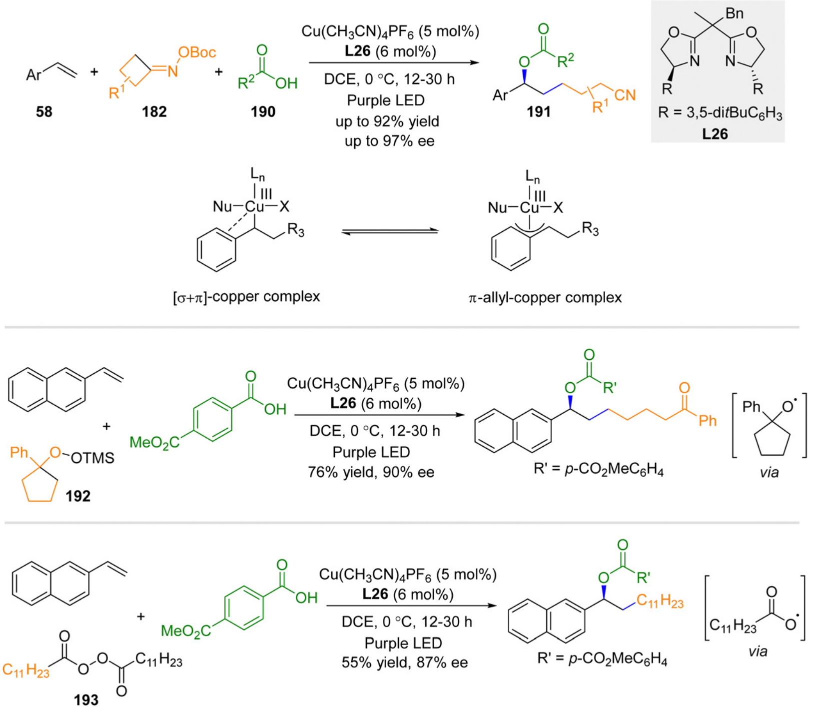
Scheme 49 Photoinduced copper-catalyzed enantioselective aerobic α-hydroxylation of β-keto esters.



Scheme 50 Proposed mechanism for the photoinduced copper-catalyzed enantioselective aerobic α-hydroxylation.



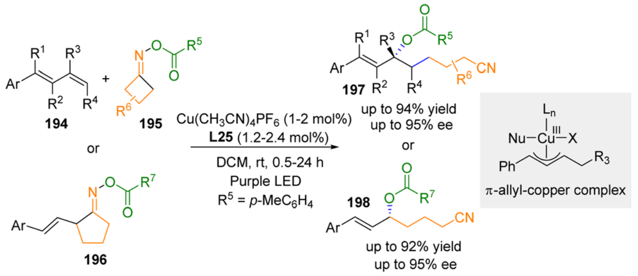
Scheme 51 Photoinduced copper-catalyzed asymmetric three-component Kharasch–Sosnovsky reaction.



Scheme 52 Photoinduced copper-catalyzed asymmetric three-component reaction using styrenes.

asymmetric intermolecular C(sp^3)–O cross-coupling (Scheme 52).[62] With the aid of newly identified chiral BOX ligand **L26** and the formation of aryl π-bond-engaged [σ + π]-copper complex, the enantioselective three-component reaction showed broad substrate scope, high yields and enantioselectivites. Besides cycloketone-derived oxime esters **182**, alkylsilyl peroxide **192** and lauroyl peroxide **193** could also act as alkyl radical precursors in this transformation, affording good yields and high enantioselectivites.

By making use of the cleavage fragment of oxime esters, Chen, Guan and Xiao presented a photoinduced copper-catalyzed asymmetric two-component oxyalkylation between oxime esters **195** and 1,3-dienes **194** to produce diversely substituted allylic esters **197** with high yields as well as excellent regio- and

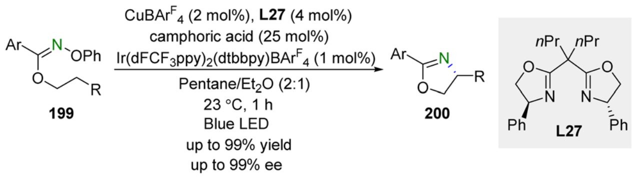


Scheme 53 Photoinduced copper-catalyzed asymmetric two-component oxyalkylation.

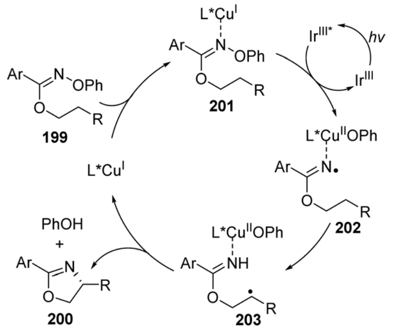
enantioselectivities (Scheme 53).[63] By using a single chiral copper catalyst as both photoredox catalyst for radical formation and the source of asymmetric induction, the reaction could be performed under mild conditions through the excitation by purple LED. Notably, 2-styrenyl-substituted cycloketoxime esters **196** were well tolerated to give allylic esters **198** in high yields and excellent enantioselectivities. Experimental results and DFT calculations indicated the generation of π-allylcopper species from oxime esters serving as bifunctional reagents and 1,3-dienes *via* radical-polar crossover process.

3.2. C(sp^3)–N bond formation

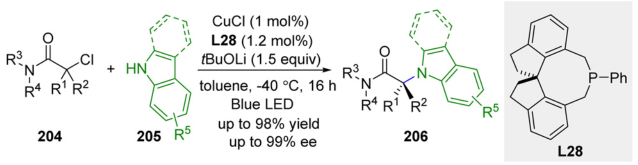
In 2020, Nagib and co-workers applied energy-transfer catalysis in the photo-induced enantioselective radical C(sp^3)–H amination (Scheme 54).[64] By means of blue light and chiral copper catalyst, a variety of optically pure oxazolines **200** were obtained in high yields and enantioselectivities. The Ir photosensitizer and chiral BOX ligand **L27** were necessary for this reaction, providing broad scope including oxime imidates derived from alkyl, allyl, benzyl and propargyl alcohols. Compared to other counterions, the BAr$^F{}_4$ counterion gave better enantioselectivity. Moreover, the bulky chiral acid played an important role in controlling yield and enantioselectivity. Notably, the chiral oxazoline products **200** could be transformed into diverse chiral β-amino alcohols *via* acidic hydrolysis. According to the mechanism (Scheme 55), oxime imidate **199** firstly coordinates with L*Cu^I to generate intermediate **201**. By energy transfer from excited Ir^{III}*, a net photoinduced oxidative addition occurs to form nitrogen radical **202** through triplet sensitization of the N–O bond. Intramolecular HAT of radical **202** affords alkyl radical **203**, which undergoes either metalation and sequential reductive elimination of the ensuing L*Cu^{III} intermediate, or coupling of the radical within the L*Cu^{II} complex, to afford the final product **200** and regenerate L*Cu^I.



Scheme 54 Photoinduced copper-catalyzed enantioselective radical C(sp^3)–H amination.

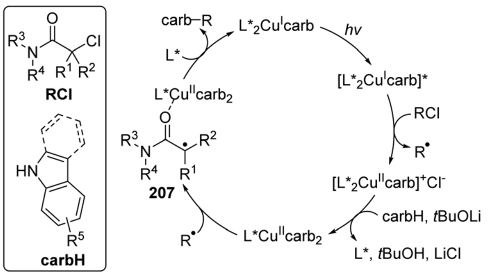


Scheme 55 Proposed mechanism for the photoinduced copper-catalyzed enantioselective radical C(sp^3)–H amination.

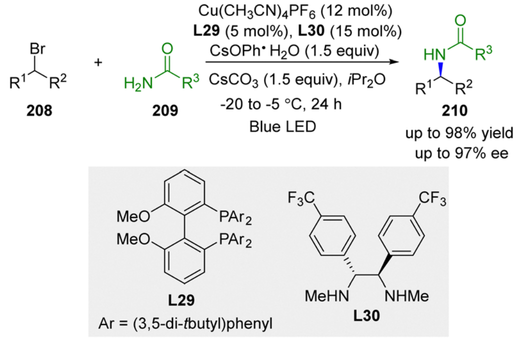


Scheme 56 Photoinduced copper-catalyzed enantioselective formation of C–N bonds.

Chiral ligand–copper–nucleophile complexes could also be used as bifunctional catalyst in the photoinduced enantioselective formation of C(sp^3)–N bonds. In 2016, Peters and Fu reported a photoinduced copper-catalyzed cross-coupling reaction between available racemic tertiary alkyl chlorides **204** and amines **205** to generate chiral C(sp^3)–N bonds (Scheme 56).[25] By using alkyl chlorides **204** as alkyl radical precursors and chiral phosphine ligand **L28**, diverse chiral products **206** bearing quaternary carbon stereocenter were produced in high yields and enantioselectivities. Decreasing the loading of copper catalyst to 0.25 mol% could still give the desired product in good yield and excellent enantioselectivity with 300 turnovers. As proposed (Scheme 57),[65] L*$_2$Cu^{I}Cl reacts with nucleophile to generate complex L*$_2$Cu^{I}carb, which undergoes irradiation to form excited-state adduct [L*$_2$Cu^{I}carb]*. Sequential SET delivers an alkyl radical and [L*$_2$Cu^{II}carb]$^+$Cl$^-$ complex, reacting with another nucleophile to give L*Cu^{II}carb$_2$. The following interaction with alkyl radical affords intermediate **207**, which undergoes cross-coupling to produce the desired product and regenerate L$_2$*Cu^{I}carb.



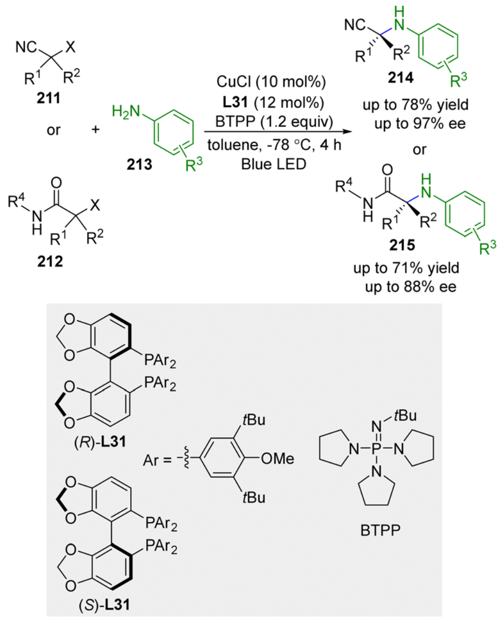
Scheme 57 Proposed mechanism for photoinduced copper-catalyzed enantioselective formation of C–N bonds.



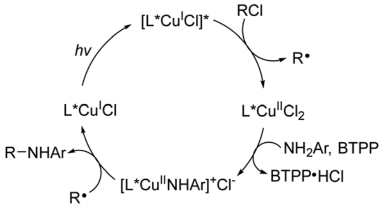
Scheme 58 Photoinduced copper-catalyzed asymmetric amidation using primary amides.

Sequentially, the same group employed this strategy in a photoinduced copper-catalyzed asymmetric amidation between unactivated alkyl bromides **208** and primary amides **209**, leading to diverse chiral secondary amides **210** in high yields and enantioselectivities (Scheme 58).[66] This asymmetric amidation was supported by three distinct kinds of ligands—a bisphosphine, a phenoxide and a chiral diamine, which were assembled with copper salt *in situ* to provide two cooperative catalysts: a copper/bisphosphine/phenoxide complex serving as a photocatalyst, and a chiral copper/diamine complex catalyzing enantioselective amidation. In the absence of a copper catalyst, blue light, chiral diamine or bisphosphine ligand, very worse results were obtained. Under standard conditions, alkyl iodide was well tolerated, giving similar yield and enantioselectivity. Notably, this transformation was not highly air- and moisture-sensitive.

Recently, Fu and Peters described a photoinduced copper-catalyzed enantioselective coupling between racemic tertiary alkyl halides **211** or **212** and anilines **213** to construct new C(sp^3)–N bonds (Scheme 59).[67] By performing the reaction at -78 °C, a variety of secondary amines **214** and **215** bearing a chiral quaternary carbon center were obtained in good yields and high enantioselectivities. The key to the success is the formation of chiral ligand–copper complex, which acts as not only a photoredox catalyst to give alkyl radicals from alkyl halides *via* SET, but also a chiral catalyst for enantioselective C–N bond formation. As proposed (Scheme 60), L*Cu^{I}Cl undergoes irradiation to form excited-state intermediate [L*Cu^{I}Cl]*, followed by SET to generate L*Cu^{II}Cl$_2$ and an alkyl radical. Sequential reaction between aniline and L*Cu^{II}Cl$_2$ affords intermediate [L*Cu^{II}NHAr]$^+$Cl$^-$, which combines with the alkyl radical to give the final product and regenerate L*Cu^{I}Cl.



Scheme 59 Photoinduced copper-catalyzed enantioselective coupling using anilines.



Scheme 60 Proposed mechanism for the photoinduced copper-catalyzed enantioselective coupling using anilines.

4. Conclusion and outlook

Visible light is renewable, readily available and abundant, and has been employed in numerous organic reactions. Through energy or single electron transfer, visible light could give reactive species, usually radicals, resulting in novel chemical transformations as well as new and unusual products. Visible light-mediated photoredox catalysis has become a powerful tool for the construction of C–C/X bonds, accelerating the development of organic synthesis and enlarging the scope of radical chemistry. Through the combination with asymmetric catalysis strategy, visible light-induced asymmetric catalysis has emerged as a promising tool for the construction of chiral molecules under mild and green conditions, providing new directions and opportunities for asymmetric catalysis. Consequently, the integration of photocatalysis with asymmetric copper catalysis has been developed to explore the construction of chiral C(sp^3)–C/X bonds, providing an efficient complementarity and new life of traditional C(sp^2)–C/X cross-coupling, such as Ullmann coupling, Sonogashira coupling, Goldberg amination and Buchwald–Hartwig coupling.

This review highlights the progress in photoinduced copper-catalyzed enantioselective coupling reactions. By choosing proper light sources and chiral ligands, diverse chiral C(sp^3)–C/X bonds are forged in an efficient way. Two kinds of chiral ligands are mainly utilized to produce high enantioselectivities: chiral BOX ligands and phosphine ligands, the former being dominant. In the presence of external oxidants, enantioselective CDC reactions are performed to asymmetrically construct C(sp^3)–C(sp) and C(sp^3)–C(sp^3) bonds. By employing alkyl radical precursors, such as NHP esters, propargyl esters, benzyl esters, oxime esters and alkyl iodides, asymmetric cyanation is achieved from benzyl/propargyl/allyl radical intermediates to form chiral C(sp^3)–C(sp) bonds. With the aid of photoelectrocatalysis, asymmetric cyanation could be directly performed from achiral carboxylic acids, even unactivated alkylarenes. The 1,5-HAT strategy could also asymmetrically install the cyano group with a variety of secondary benzylic C(sp^3)–H. Copper acetylide is the key intermediate to finish asymmetric alkynylation for the construction of chiral C(sp^3)–C(sp) bonds. Alkyl radical precursors, such as trifluoroborates, α-silylamines, glycine derivatives, even unactivated alkanes, enhance the enantioselective formation of C(sp^3)–C(sp^3) bonds *via* Mannich reaction or Michael addition. NHP esters and Togni-II reagent could initiate the installation of alkyl and trifluoromethyl groups in α-aminomethyl and benzylic C(sp^3)–H bonds, respectively. In contrast, the enantioselective construction of C(sp^3)–C(sp^2) bonds is less developed, probably due to the lack of an efficient strategy to form a relatively stable Cu^{III} complex. Photoexcited energy-transfer provides an efficient platform to asymmetrically construct C(sp^3)–O and C(sp^3)–N bonds. π-Allyl- and [σ + π]-copper complexes facilitate the asymmetric oxyalkylation of alkenes. Racemic tertiary alkyl halides prove to be suitable alkyl radical precursors, resulting in the effective formation of chiral C(sp^3)–N bonds.

Despite significant progress in photoinduced asymmetric copper catalysis, some limitations remain. Firstly, the transformations are mainly limited to the process involving a stabilized carbon radical such as benzyl, propargyl and allyl radicals, to promote the yields and enantioselectivities. General strategies for the asymmetric capture of unstabilized carbon radicals are required in photoinduced asymmetric copper catalysis. Secondly, most of alkyl radicals are generated from activated precursors, such as NHP esters, propargyl esters, benzyl esters, oxime esters, alkyl iodides, carboxylic acids, trifluoroborates, α-silylamines and glycine derivatives, hampering broad applications in synthetic chemistry. It is highly desirable to explore new methods to form alkyl radicals from general alkanes. Thirdly, the reactions involving chiral C(sp^3)–C(sp^2) bond formation are limited. It is necessary to develop new approaches to form diverse chiral C(sp^3)–C(sp^2) bonds, which are widely present in important natural products and bioactive molecules. Fourthly, the employed ligands are mainly restricted to chiral BOX ligands and phosphine ligands. Other novel chiral ligands should be developed to switch the steric and electronic properties of copper catalysts to solve the remained problems, expanding the scope of photoinduced asymmetric copper catalysis. Finally, the use of the simple catalytic system bearing low loading copper catalyst to achieve high efficiency and high enantioselectivity with broad substrate scope would be one of the major future objectives in this area. We hope that this review would help researchers to better understand the chemistry behind photoinduced asymmetric copper catalysis, and stimulate the future developments in this field.

Author contributions

Writing (original draft): LS and LC. writing (reviewing and editing): LG and EVVdE. funding acquisition: LS, LC, LG and EVVdE. the final manuscript has been read and approved by all authors.

Conflicts of interest

There are no conflicts to declare.

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