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Copper-catalyzed radical relay in C(sp^3)–H functionalization

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Radical-involved transition metal (TM) catalysis has greatly enabled new reactivities in recent decades. Copper-catalyzed radical relay offers enormous potential in C(sp^3)–H functionalization which combines the unique regioselectivity of hydrogen atom transfer (HAT) and the versatility of copper-catalyzed cross-coupling. More importantly, significant progress has been achieved in asymmetric C–H functionalization through judicious ligand design. This tutorial review will highlight the recent advances in this rapidly growing area, and we hope this survey will inspire future strategic developments for selective C(sp^3)–H functionalization.

1. Introduction

C–H bonds are arguably the most abundant functional groups in organic compounds. Direct C–H functionalization arguably represents the most straightforward and atom economic transformations in organic synthesis. Instead of focusing on manipulating functional groups, the new logic relies on the controllable functionalization of specific C–H bonds, even in the presence of supposedly more reactive functional groups.[1–4] For a general comparison, direct C–H functionalization could substantially streamline target molecule synthesis *via* a better step and atom economy than canonical strategies.[5,6] The key challenge is achieving good selectivity under the forcing conditions that would be required to activate inert C–H bonds. Numerous strategies have been developed to achieve this target over recent decades.[7,8] Of these, radical C–H functionalization *via* hydrogen atom transfer (HAT) represents one of the most powerful approaches and allows a unique profile of reactivity and selectivity that is complementary to ionic chemistry in which electrons move in pairs. In fact, this process is prevalent in the metabolization of organisms. For instance, enzymatic oxygenases, such as cytochrome P450, operate through selective abstraction of an H atom from C(sp^3)–H bonds with the reactive metal-oxo species to generate a radical intermediate, followed

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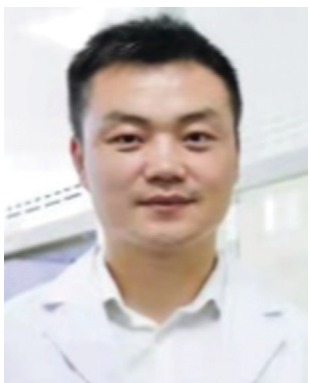

Zuxiao Zhang

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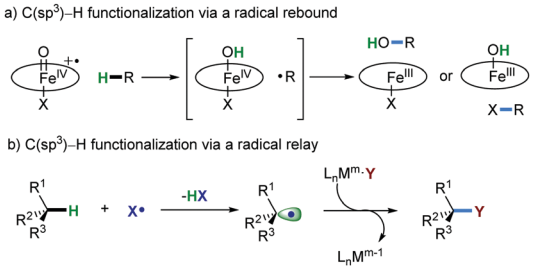

Scheme 1 (1a) Radical rebound mechanism for enzymatic and biominetic C–H hydroxylation and halogenation. (1b) C–H functionalization *via* a radical relay.

by its direct rebound to the metal-bound hydroxide group (Scheme 1a).[9,10] Plenty of elegant methods of C(sp^3)–H oxidation have been developed using small-molecules as catalysts to mimic the modes of C–H functionalization in enzyme catalysis.[11–14] However, the rapid radical rebound process limits its further application in installing other functional groups and enantioselectivity control.[15] Alternatively, a diffusible carbon radical species formed through HAT could be trapped by a second species/catalysts to afford the C(sp^3)–H functionalized product, known as a radical relay pathway (Scheme 1b).[16] Meanwhile, TM catalysis has displayed impressive controllability and reactivity in radical-mediated cross-coupling reactions.[17,18] Thus, TM-catalyzed radical relay offers substantial opportunities to expand the regime of radical-mediated C(sp^3)–H bond functionalization, and significant progress has been achieved in recent decades.[19–21] More importantly, the asymmetrical version of radical C–H functionalization could be achieved by introducing appropriate chiral ligands.

The term "radical relay" initially appeared in Breslow's article on C(sp^3)–H functionalization published in 1974 (Scheme 2a).[22] In this transformation, an iodine-centered radical (**II**), generated from chlorine atom transfer from the PhICl radical to steroid

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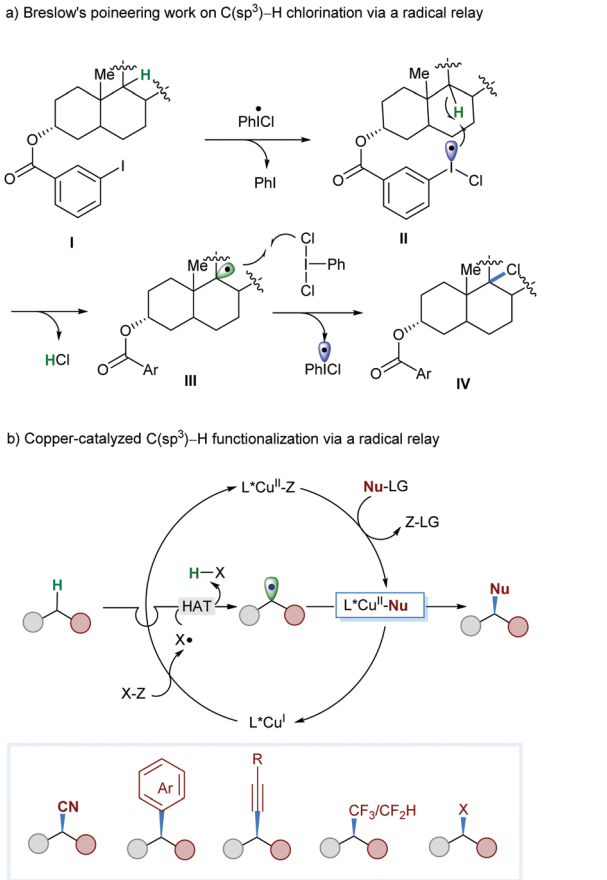


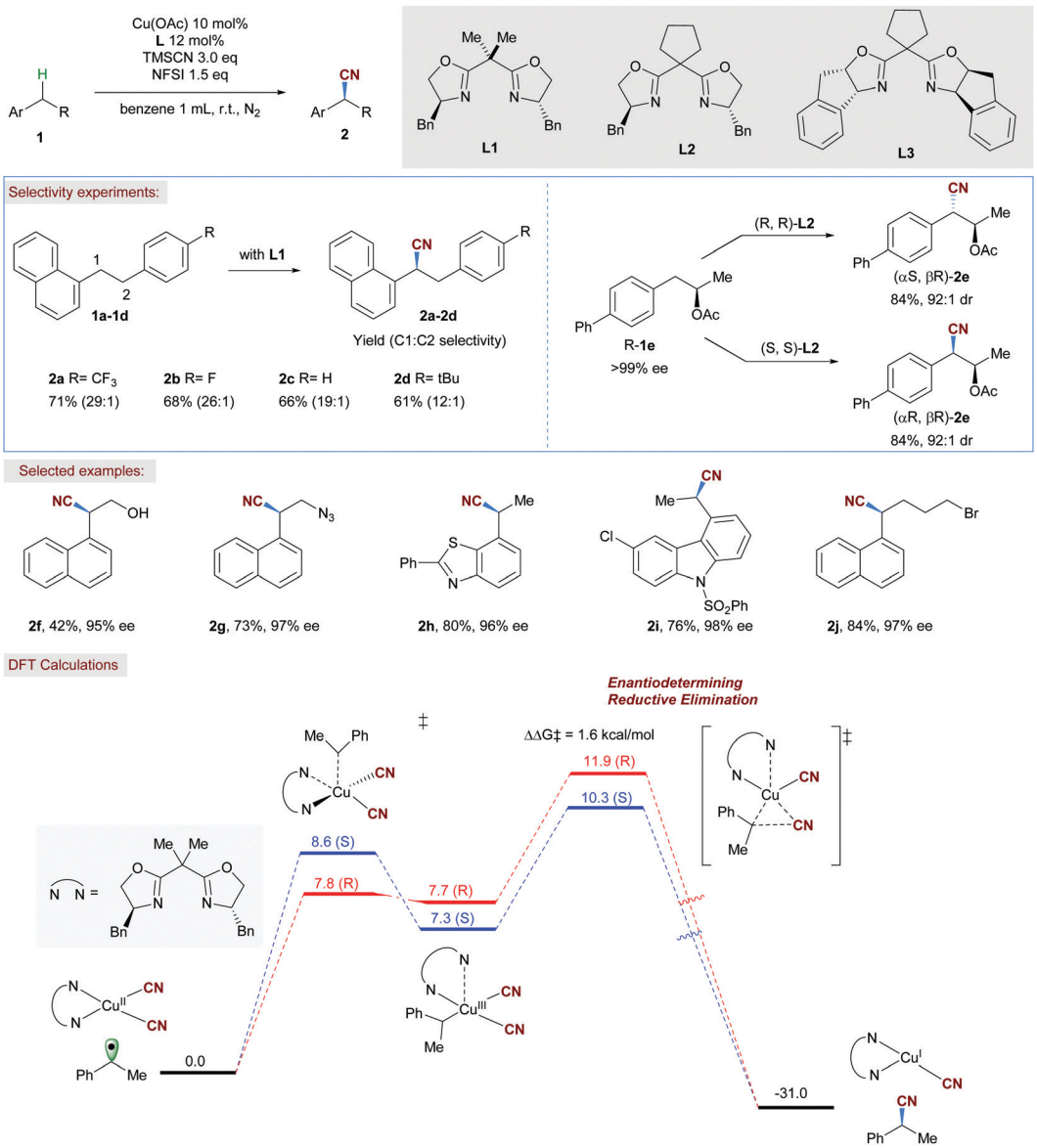
Scheme 2 (2a) Breslow's pioneer work on C(sp^3)–H chlorination *via* a radical relay. (2b) Copper-catalyzed C–H functionalization *via* a radical relay.

tethered iodobenzene, could undergo intramolecular HAT to form a C-centered radical (**III**). The carbon radical then reacted with $PhICl_2$ to afford a C–H chlorination product (**IV**) and PhICl radical. Although the concept of "radical relay" for C(sp^3)–H bond functionalization was introduced in 1974, this type of reactivity has a much longer history. For example, the Hofmann–Löffler–Freytag reaction involving a 1,5-HAT and radical relocation thereof, represents one of the pioneering examples in the radical relay domain, which has been developed into a powerful tool for pyrrolidine synthesis. A myriad of related reactions has also been extensively developed as well as the original aminations.[23,24] In addition, transition metals (TMs) involved in the radical reaction is suspected to considerably expand the scope of radical-mediated C(sp^3)–H functionalization by interrupting the conventional radical trap with TM-catalysed cross coupling. The pioneering example is the Kharasch–Sosnovsky reaction, copper-catalyzed allylic C–H oxidations,[25] where the allylic radical is formed *via* a HAT process by a *tert*-butoxyl radical, and then trapped by copper(II) benzoate efficiently to build up C–O bonds.[26] Later, the asymmetric Kharasch–Sosnovsky reaction was achieved by introducing chiral ligands, however, it still suffers from significant limitations, such as a narrow substrate scope, a large excess amount of alkenes and very limited chemical bond formations.[27–29] Notably, over the 60 years of development, these limitations are still unconquered.[30]

Conspicuously, with the first introduced asymmetric copper-catalyzed radical relay strategy, the enantioselective benzylic C(sp^3)–H cyanation featuring excellent regio- and enantioselectivity, and broad substrate scope was accomplished by Liu and Stahl in 2016.[31] Further study on the allylic C–H cyanation revealed that the incorporation of copper catalysts plays an important role, not only in the asymmetric radical control step, but also in the initially site-selective HAT step *via* an unprecedented Cu-bound N-centered radical.[32] Subsequently, the copper-catalyzed radical relay has proliferated to accomplish various enantioselective transformations and its scope has gone far beyond C–H functionalization.[33] Since enantioselective difunctionalization of alkenes *via* a copper-catalyzed radical relay has been well documented,[34] this review focuses on the recent advances in C(sp^3)–H functionalization (Scheme 2b), which is categorized by the functional groups being installed and the patterns of C(sp^3)–H cleavage. The choice of ligands to achieve excellent enantioselectivity and various functional group installation *via* a radical interception will be highlighted.

2. Copper-catalyzed radical relay in C(sp^3)–H functionalization

Copper-catalyzed enantioselective C(sp^3)–H functionalization *via* a radical relay has emerged as a powerful tool in organic synthesis. A variety of functional groups such as cyano, aryl, and alkynyl could be installed in an enantioselective manner directly from C–H bonds. Recently, numerous elegant asymmetrical C–H functionalizations involving a copper-catalyzed radical relay have been reported.

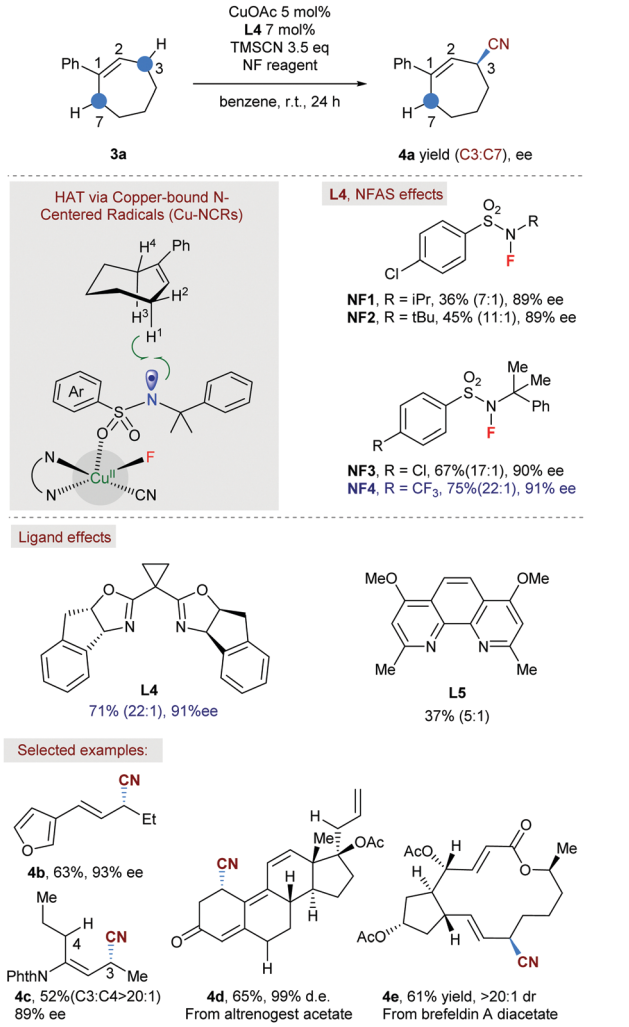


Scheme 3 Enantioselective benzylic C–H cyanation (Liu, 2016).[31]

2.1. C(sp^3)–H cyanation

In 2016, the Liu and Stahl groups established an innovative approach to enantioselective cyanation of benzylic C–H bonds *via* a copper-catalyzed radical relay (Scheme 3).[31] This transformation selectively converted benzylic C–H bonds into chiral nitriles using C–H substrates as the limiting reagents. The reaction featured mild conditions, broad functional-group tolerance, and exceptional regioselectivity. The site-selectivity of HAT prefers to take place at the benzylic position adjacent to the naphthalene with the substrates bearing two benzylic positions (**1a–1d**). When changing the para substituents from electron-donating to electron-deficient groups, the site selectivity increases from 12 : 1 to 29 : 1 (**2a–2d**). The reaction of enantiomerically pure homobenzylic acetate (*R*)-**1e** with each of the enantiomers of ligand **L2** could lead to products with excellent diastereoselectivity which reflected high levels of catalyst-rather than substrate-controlled stereoselectivity. A variety of 1-alkyl-substituted (hetero)arenes as well as the precursor to a CCR1 receptor antagonist could be converted into chiral nitriles (**2f–2j**) in both good yield and enantioselectivity. A preliminary mechanism study was performed using density functional theory (DFT) calculations (Scheme 3). A benzylic radical reacts with (**L1**)$Cu^{II}(CN)_2$ species to afford the benzyl-Cu^{III} species with a low barrier. In contrast, the subsequent C(sp^3)–CN reductive elimination Cu^{III} species generates the benzylic nitrile products with a higher barrier. This calculation suggested that the formation of the alkyl-Cu^{III} species is reversible, and the reductive elimination step accounted for the enantioselectivity control. This seminal work represents one of the most efficient methods for the synthesis of chiral nitriles *via* C–H functionalization.

The site-selectivity of HAT mainly relies on the C–H bond's environment, including bond dissociation energies, polarities, steric and electronic factors.[35] With further investigation of regioselective C–H cyanation, the Liu and Lin groups found that the site-selectivity could be controlled by a tuneable Cu(II)-bound N-centred radical (NCR) acting as an HAT species. Taking advantage of this discovery, a regio-, stereo- and enantioselective allylic C–H cyanation *via* a copper-catalyzed radical relay was realized (Scheme 4).[32] The effect on the site-selective HAT of *N*-fluoroalkylsulfonamide (NFAS) and ligands was carefully examined with the substrate bearing two sets of allylic hydrogens. Modification of NFAS exhibited a great effect on the site-selectivity and efficiency of this reaction. For example, a bulkier alkyl group on the nitrogen atom could lead to both better selectivity and yield (from **NF1** at 36% yield, C3 : C7 = 7 : 1 to **NF3** at 67% yield, C3 : C7 = 17 : 1). The introduction of an electron-withdrawing aryl group could further improve the site-selectivity (**NF4**, C3 : C7 = 22 : 1). DFT calculations indicated that the site-selectivity is amplified with a Cu(II)-bound NCR compared to a free NCR. Similar enantiomeric excess values (89–91%) were obtained with different NCR precursors, **NF1** to **NF4**, indicating that NCR precursors are not involved in the enantioselective radical trapping process by the Cu species. Notably, while changing the ligand from **L4** to **L5**, the regioselectivity remarkably dropped from 22 : 1 to 5 : 1. The regioselectivity influenced by both an N-centered radical and chiral copper



Scheme 4 Regio-, stereo- and enantioselective allylic C–H cyanation *via* a copper-catalyzed radical relay (Liu, 2019).[32]

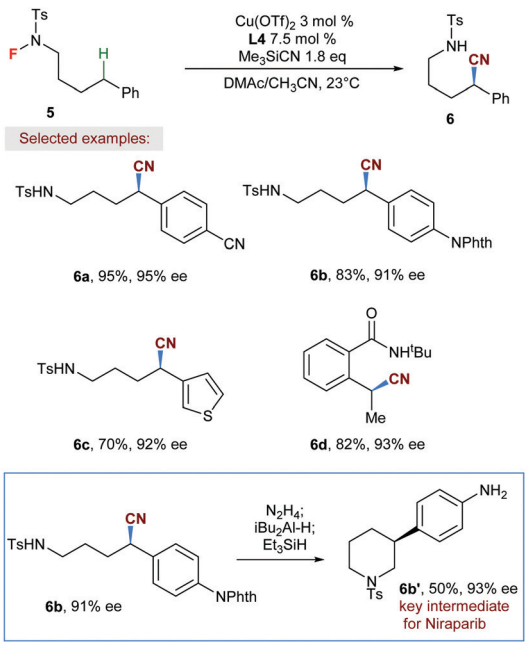
complex suggested that the HAT process is not simply controlled by a free NCR, while a Cu(II)-bound NCR is proposed for the high regioselectivity, which was supported by experiments and computational studies as well. This transformation exhibited excellent site selectivity in the presence of multiple allylic C–H bonds and showcased the utility of late-stage functionalization of complex alkene-containing molecules, including drug derivatives (**4d–4e**). The strategy of tuning Cu(II)-bound NCRs to achieve excellent regioselective HAT offers an alternative solution to site-specific and enantioselective C–H oxidation reactions, including those with allylic and other types of C–H bonds.

The regioselectivity could be governed by an intramolecular 1,5-HAT, such as the Hofmann–Löffler–Freytag reaction, which has a long history in the use for selective generation of δ C-centered radicals from N–X substrates. However, asymmetric interruption of the Hofmann–Löffler–Freytag reaction is highly limited due to the rapid process of chain propagation or radical–radical combination. Recently, several groups have developed enantioselective remote cyanation.

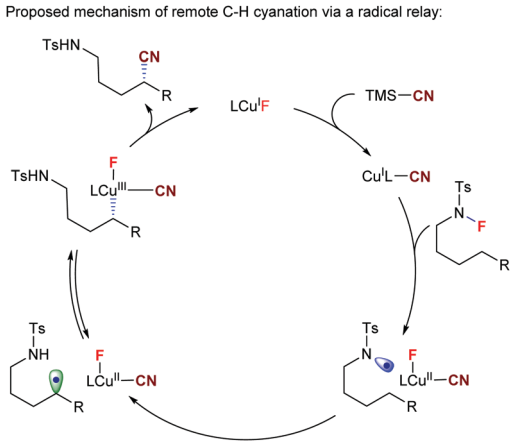
The Nagib group intercepted a remote carbon radical using a chiral copper complex and realized a copper-catalyzed enantioselective C–H cyanation (Scheme 5).[36] The enantioenriched products could be further converted into valuable chiral piperidines. Notably, the ratio of copper and ligand played a crucial role in suppressing the background reaction and enhancing the reaction efficiency. More importantly, formal synthesis of the anticancer drug, niraparib, *via* enantioselective cyanation further demonstrated the synthetic utility. Shortly after, the Wang group reported a similar protocol of enantioselective remote C–H cyanation independently.[37] These reactions take advantage of 1,5-HAT from a N-centered radical generated by single electron reduction of N–F substrates to achieve excellent regioselectivity even in the presence of multiple benzylic C–H bonds. The generated C-centered radicals are trapped by a chiral copper cyanide complex to afford enantioenriched δ-amino nitriles (Scheme 6).

Instead of cleaving N–F bonds, N–O bonds can be reduced to generate hetero atom radicals as well by merging photoredox catalysis and copper catalysis. Inspired by the successful cooperative copper and photocatalysis on the asymmetric decarboxylative cyanation reactions,[38] Liu and co-workers developed an enantioselective cyanation of remote C–H bonds of alcohols by merging photoredox catalysis with copper catalysis (Scheme 7a).[39] In this reaction, *N*-hydroxyphthalimide ether 7 was reduced by a photoredox catalyst to generate an O centred radical which could undergo 1,5-HAT to generate a δ carbon radical. The formed carbon radical could be trapped by a copper catalyst to install a cyanide group enantioselectively. In 2020, the Yu group applied a similar strategy and realized enantioselective remote C–H cyanation of amides (Scheme 7b).[40]

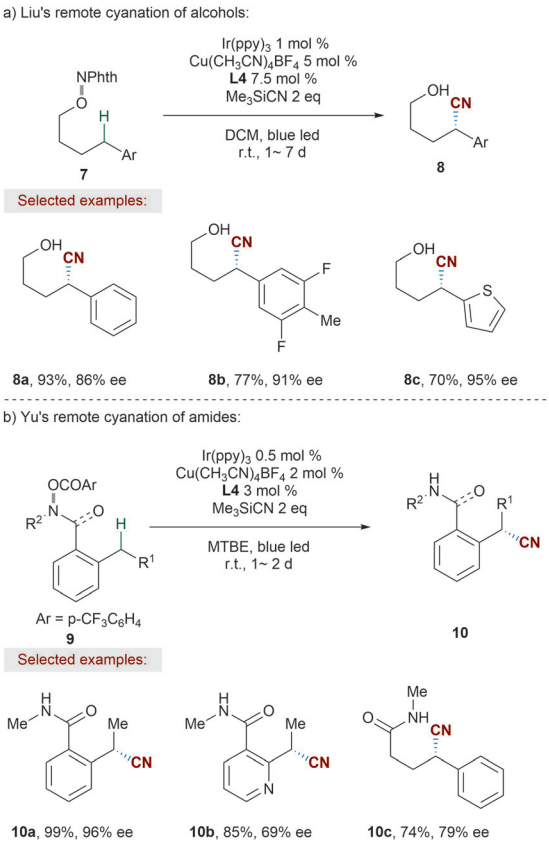
The proposed mechanism of the copper-catalyzed radical relay merging with photoredox chemistry is depicted in Scheme 8. Moreover, the copper-catalyzed radical relay not only exhibited



Scheme 5 Enantioselective remote δ C–H cyanation (Nagib, 2019).[36]



Scheme 6 Proposed mechanism of enantioselective δ C–H cyanation.

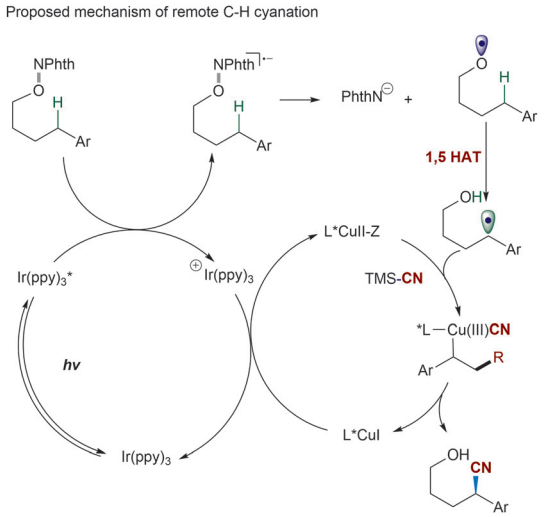


Scheme 7 Enantioselective remote C–H cyanation *via* merging photoredox and copper catalysis.[39,40]

good compatibility with photoredox chemistry but has also been well adapted with electrochemistry by the Lin group recently, which provides an opportunity to achieve greener asymmetric transformations by avoiding the use of stoichiometric amounts of oxidants/reductants.[41,42]

2.2. C–H arylation

Transition-metal-catalyzed cross-coupling reactions represent one of the most important methods to construct C(sp^2)–C(sp^3)

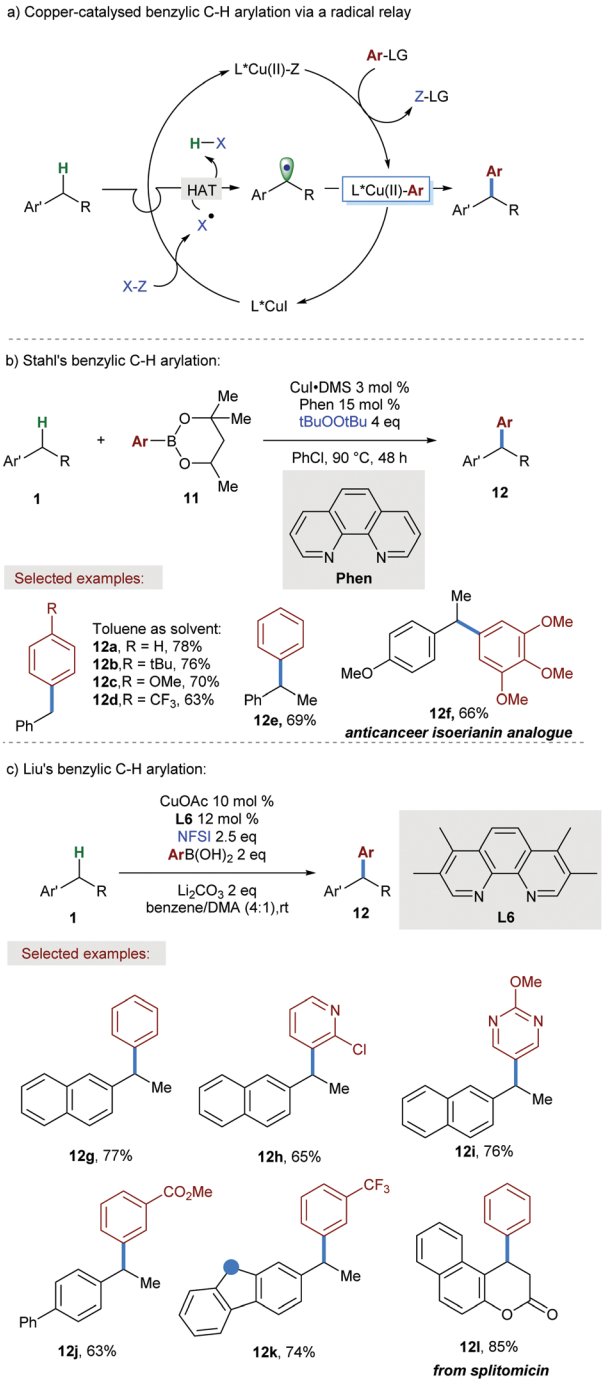


Scheme 8 Proposed mechanism of enantioselective remote C–H cyanation of alcohols by merging photoredox and copper catalysis.

bonds. Using C(sp^3)–H substrates as a cross-coupling partner draws increasing attention due to the better atom- and step-economy.

In 2017, the Liu group and Stahl group independently reported a copper-catalyzed benzylic C–H arylation.[43,44] Both reactions underwent a radical relay mechanism as follows: a heteroatom radical was generated in the presence of a copper catalyst, which could abstract an H atom at the benzylic position to form a carbon radical, and the formed carbon radical could then be trapped by Cu(II)Aryl species to afford the desired product. Inspired by the Kharasch–Sosnovsky reaction, which uses a Cu catalyst in combination with a peroxide-based oxidant to achieve allylic oxygenation, ^{t}BuOO^{t}Bu was used as the oxidant and HAT reagent in Stahl's benzylic C–H arylation (Scheme 9b).[43] The 4,4,6-trimethyl-1,3,2-dioxaborinane ester **11** which was readily accessed in one step from 2-methyl-2,4-pentanediol and the corresponding commercially available arylboronic acid could give better yields than other aryl boronic acid derivatives. The excess loading of the ligand played a crucial role in supressing the unproductive biphenyl formation by slowing the rate of aryl transmetalation from boron to Cu. The reaction exhibited a broad substrate scope of the boronic ester: both electron-rich and electron-deficient boronic esters undergo effective coupling in similar good yields (**12a–12d**). However, the reaction needed access to an amount of alkylarenes to achieve medium to good yields. Competition studies revealed that the relative reactivity of alkylarenes follows the order 2° (ethyl) > 1° (methyl) ≫ 3° (isopropyl) and tertiary diarylalkanes do not react under the catalytic conditions.

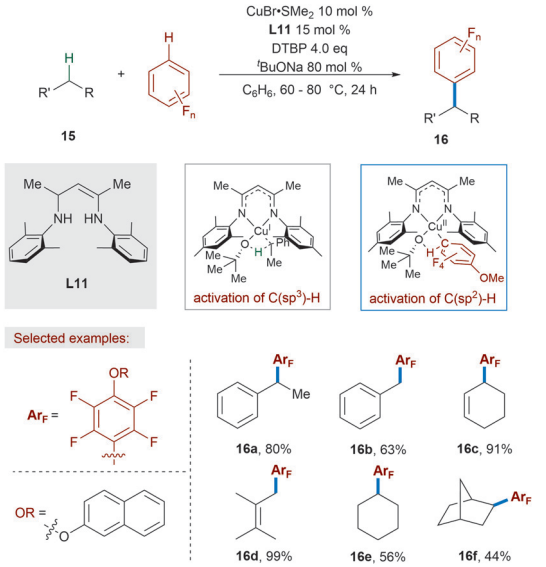
In comparison, under Liu's arylation of benzylic C–H conditions,[44] NFSI was used as an HAT reagent and commercially available arylboronic acids as aryl sources (Scheme 9c). Impressively, the alkylarenes could be used as limiting reagents which made this reaction suitable for the late-stage functionalization of valuable and complex substrates. Due to the slow rate of transmetalation to form ArCu(II), Li_2CO_3 was needed to promote the transmetalation and a less sterically bulky ligand, TMPhen (tetramethyl phenanthroline) **L6**, was essential to promote the efficiency of this reaction. The reaction features a broad substrate scope, and a variety of naphthalenes and heteroarenes could be installed efficiently (**12g–12k**). The late-stage arylation of bioactive compound **12l** was investigated which further demonstrated the utility of this transformation. However, electron-rich arylboronic acids and the simple alkylbenzenes exhibited poor reactivity toward C–H arylation under the reaction conditions.



Scheme 9 Arylation of benzylic C–H bonds (Stahl and Liu, 2017).[43,44]

On the other hand, copper-catalyzed enantioselective C–H arylation *via* a radical relay was less developed, and Liu's previous work showed that arylcopper(II) species can trap a benzylic radical to install aryl groups enantioselectively in the reactions of alkene difunctionalization.[45] In 2019, Liu and co-workers developed an asymmetric arylation of benzylic C–H bonds *via* a radical relay which provided an attractive protocol for the synthesis of enantiomerically enriched 1,1-diarylalkanes (Scheme 10).[46,47] The steric hinderance of the bulky chiral copper complex that is required to control enantioselectivity undermines the efficiency of transmetalation between the $(L^*)Cu^{II}$ species and $PhB(OH)_2$. As a result, the active benzylic radicals could not be captured efficiently using a low concentration of the $(L^*)Cu^{II}Ar$ species. To solve this dilemma, a directing group was introduced onto the chiral ligands (**L***) to accelerate the transmetalation step, therefore leading to a higher concentration of $(\mathbf{L^*})Cu^{II}Ar$ and prohibiting side reactions. With this concept, a Box ligand bearing a carbonyl ester group **L10** was developed which could promote both yield and enantioselectivity. This reaction demonstrated impressive chemo- and enantioselectivity, notwithstanding the fact that the C–H substrate scope was limited to alkyl naphthalene.

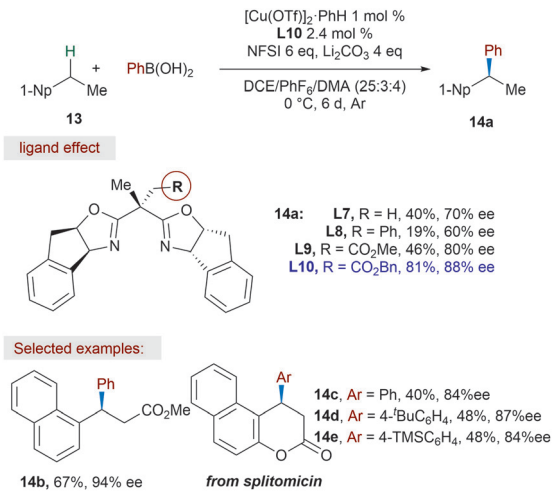
Besides using arylboronic acids as nucleophiles, the Chang group developed a copper-catalyzed $C(sp^3)$–H polyfluoroarylation using polyfluoroarenes as nucleophiles (Scheme 11).[48] The aryl copper species were directly generated from C–H activation of polyfluoroarenes. Di-*tert*-butyl peroxide (DTBP) was identified as the most efficient oxidant in presence of ^{t}BuONa as a basic additive. The β-diketimine ligand **L11** played a crucial role in the transformation to achieve the desired chemoselectivity. The different HAT behaviour observed in this transformation with free alkoxy radicals, which prefer to activate tertiary C–H bonds, suggests that the copper catalyst was involved in the HAT step. And the copper catalyst also took part in activating the $C(sp^2)$–H bonds of polyfluoroarene. Moreover, the noncovalent π–π interaction and weak hydrogen bonds between the ligand and aryl substrates were also vital for this coupling reaction. Impressively,



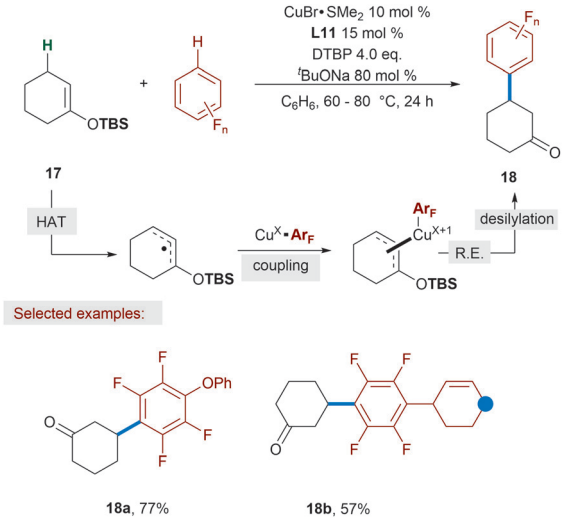
Scheme 11 Copper-catalyzed $C(sp^3)$–H polyfluoroarylation (Chang, 2020).[48]

the reaction exhibited a broad substrate scope, a variety of $C(sp^3)$–H bonds including relatively weak $C(sp^3)$–H bonds at the benzylic or allylic positions, and nonactivated hydrocarbons could be alkylated under the standard conditions. Various C–H bonds were compatible with the reaction conditions, affording the coupling products in moderate to excellent site selectivity, including gaseous feedstocks and complex molecules (**16a–16f**).

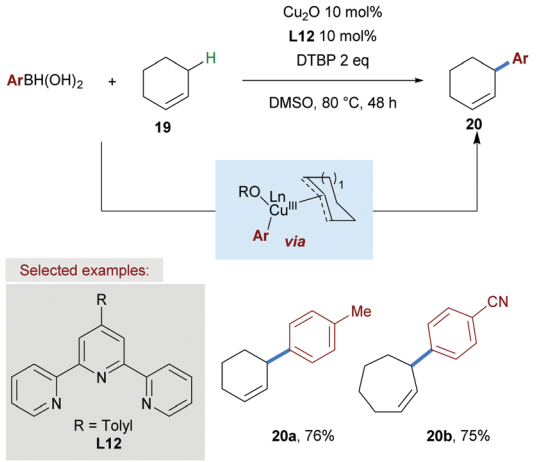
Shortly after, the same group realized a copper-catalyzed radical β-arylation of carbonyls *via* allylic C–H arylation of *O*-silyl enol ethers (Scheme 12).[49] In this process, the carbon radical formed from the HAT of **17** could react with a copper catalyst to afford a high valent copper intermediate which underwent reductive elimination to generate the desired β-aryl ketones **18**. The combination of the ^{t}BuONa base with the



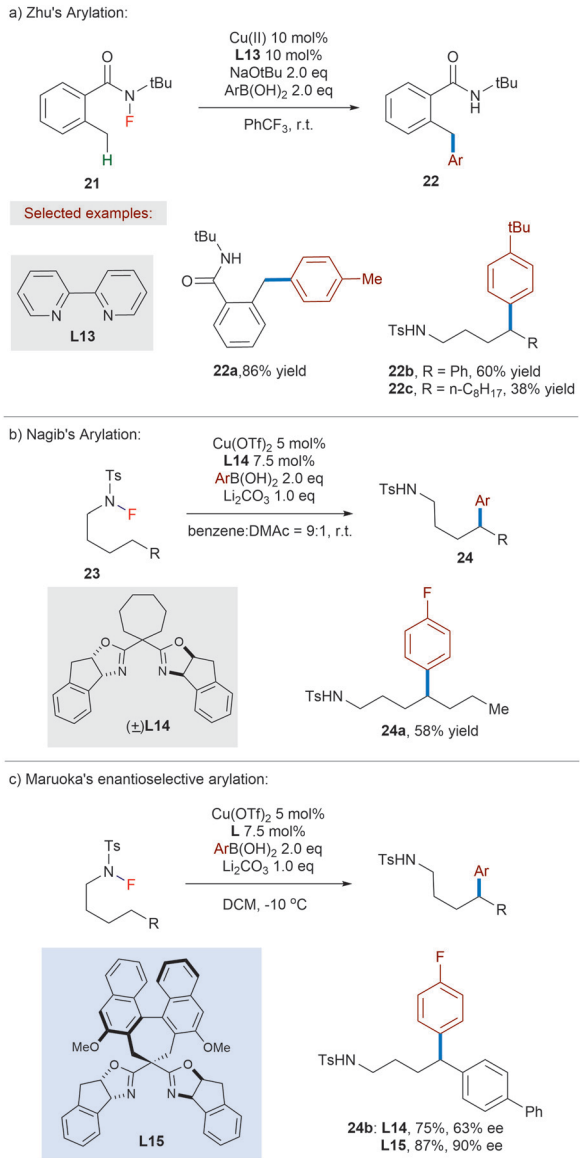
Scheme 10 Asymmetric arylation of benzylic C–H bonds (Liu, 2019).[46]



Scheme 12 Copper-catalyzed β-arylation of carbonyls (Chang, 2020).[49]



Scheme 13 Allylic C–H arylation (Schneider, 2021).[50]



Scheme 14 Copper-catalyzed remote C–H arylation *via* a radical relay.[51–53]

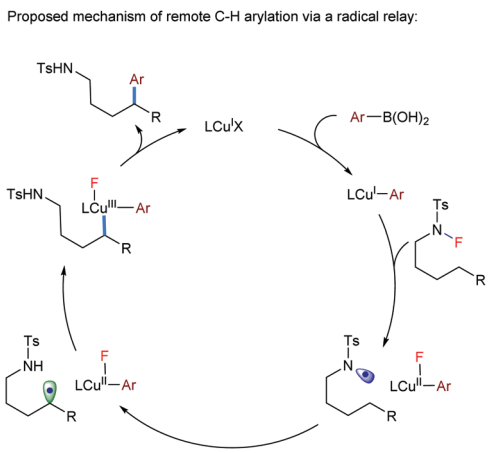
di-*tert*-butyl peroxide oxidant could promote the reaction to achieve a high efficiency.

The *O*-silyl group was found to be critical to the coupling performance and $BuSiMe_2$ was identified as the optimal one. The transformation also showed a very good broad substrate scope, as cyclic and linear ketones, aldehydes, and esters were all compatible with the reaction conditions.

In 2021, the Schneider group achieved allylic C–H arylation *via* a copper-catalyzed radical relay using a broad range of heteroaryl boronic acids with both terminal and internal alkenes (Scheme 13).[50] In this transformation, the oxidant DTBP and solvent DMSO played a crucial role to achieve a high yield. The formation of a homocoupling by-product could be circumvented by using tert-pyridine **L12** as the ligand. However, the reaction still needs an excess amount of alkenes, and the substrate scope is mainly limited to cycloalkenes (**20a–20b**). In addition, the related asymmetrical investigation was not involved in all the above studies.

As for C–H arylation *via* intramolecular HAT, the Zhu group and Nagib group independently reported a copper-catalyzed remote C–H arylation of amides or *N*-fluorosulfonamides and *N*-fluorocarboxamides.[51,52]

In Zhu's paper,[51] the reaction was catalyzed by copper(II) trifluoroacetylacetonate with 2,2′-bipyridine as the ligand, in the presence of sodium *tert*-butoxide as the base to afford the δ-C–H arylated products (Scheme 14a). The reaction exhibited a very broad substrate scope, and both carboxamides substrates and linear sufonylamides were compatible with the reaction conditions, affording the corresponding remote arylated products (**22a–22c**) in moderate to good yields. In contrast, the Nagib group developed a different condition which used $Cu(OTf)_2$ and box ligand as the catalyst and Li_2CO_3 as the base (Scheme 14b).[52] The reaction could convert various linear sulfonylamide substrates into the corresponding remote arylated product **24a** in good yield. An enantioselective version of remote C–H arylation was also presented for the first time. Later, the Maruoka group developed a chiral BN–BOX hybrid ligand **L15** which could further promote the enantioselectivity of δ-C–H arylation of *N*-fluorotosylamide of over 90% ee (Scheme 14c).[53]



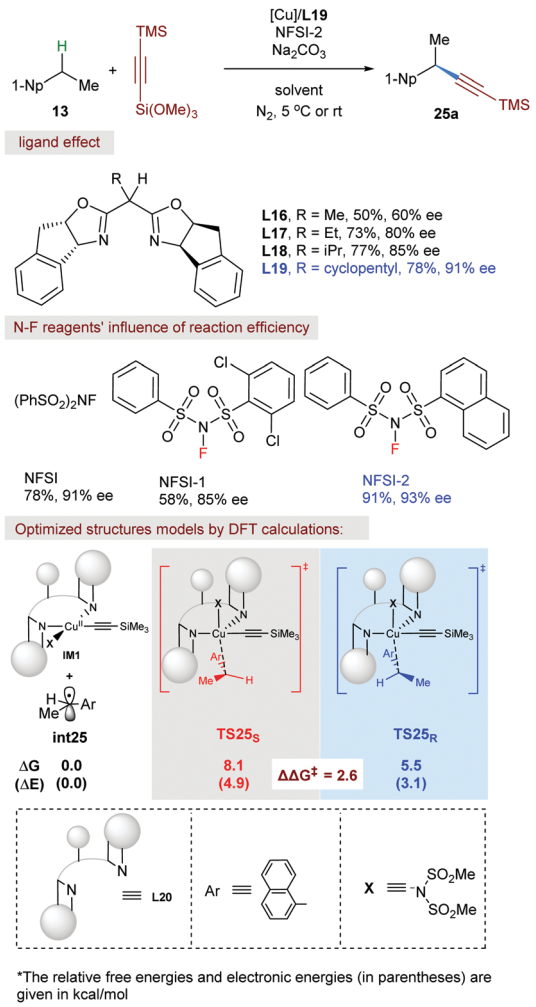
Scheme 15 Proposed mechanism of remote C–H arylation *via* a radical relay.

Nevertheless, a general method to achieve enantioselective C–H arylation *via* a copper-catalyzed radical relay still needs to be developed. Both transformations involved using a copper catalyst to reduce the NF bond to generate an amidyl radical which goes through 1,5-HAT to form a remote carbon radical. The formed carbon radical could be trapped by the copper catalyst and undergo the cross-coupling with arylboronic acids to install aryl groups (Scheme 15).

2.3. C–H alkynylation

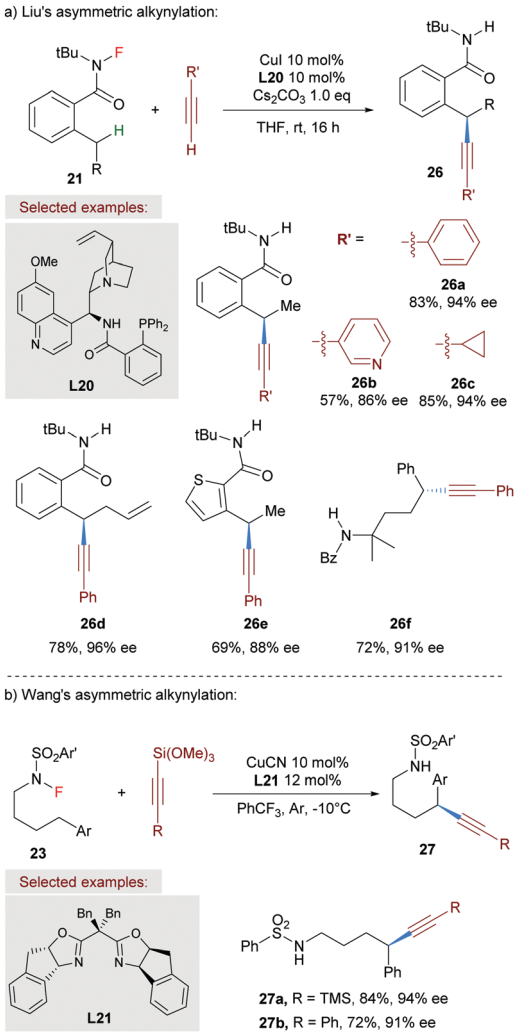
Alkynes have been widely used as pivotal intermediates for the synthesis of complex biologically active or functional molecules due to their electronic properties and various methods for further transformations. The expansion of copper-catalyzed C–H functionalization *via* a radical relay to alkynylation offered an efficient method to install an alkynyl group selectively from inert C–H bonds.

The first enantioselective benzylic C–H alkynylation of simple alkyl arenes *via* a copper-catalyzed radical relay was established by the Liu group (Scheme 16).[54] Based on their previous work on the asymmetric trifluoromethylalkynylation of alkenes,[55] alkynylsilanes were chosen as nucleophiles. The reaction efficiency could be promoted by using Na_2CO_3 as the base and 1,2,4,5-tetrafluorobenzene as the solvent. The screening of ligands (**L16–L19**) revealed that the steric hindrance of Box ligands had a significant effect on the enantioselectivity. For example, using ligand **L16** with a methyl group to **L18** with an isopropyl group led to increasing enantioselectivities (60% ee to 85% ee). Finally, using **L19** bearing a cyclopentyl group could further improve the enantioselectivity to 91% ee of **25a** without loss of the reaction efficiency. In addition, the N–F reagents which were used as N-centered radical precursors also exhibited a remarkable effect on the yield and enantioselectivity (NFSI to NFSI-2), indicating that the generated bisarenesulfonimide should be involved in the enantioselective capture of benzylic radicals by chiral L*Cu(II)-alkynyl species, presumably due to coordination of the bisarenesulfonimide to a Cu(II) centre. The reaction also featured a very broad substrate scope, as a variety of alkyl arenes and heteroarenes were compatible with the reaction conditions. Impressively, alkylbenzenes which exhibited poor reactivity and low enantioselectivity in the asymmetric benzylic C–H arylation could be employed as substrates for the asymmetric alkynylation to afford the corresponding products in moderate to good yields with excellent enantioselectivities. Control experiments and DFT calculations were performed and supported the fact that the C–C bond formation stemmed from a Cu(III) intermediate rather than an outer sphere radical addition–elimination pathway. An examination of the structures of the two enantiomeric-control transition states ($\mathbf{TS25_S}$ and $\mathbf{TS25_R}$) suggested that the different repulsive interactions of the two transition states from the H and Me substituents at the benzylic position with the alkynyl ligand and the substituents on an oxazoline ring was the key to achieving high enantioselectivity. Later, the Kramer group demonstrated that using alkynylboronic esters as nucleophilic coupling partners instead of alkynylsilanes could also achieve benzylic C–H alkynylation *via* a copper-catalyzed radical relay.[56]



Scheme 16 Enantioselective alkynylation of benzylic C–H (Liu, 2020).[54]

The variants of the Hofmann–Löffler–Freytag reaction in remote C–H alkynylation was investigated by several groups. In 2019, the Liu group developed a general stereoconvergent Sonogashira C(sp^3)–C(sp) cross-coupling of a broad range of terminal alkynes and racemic alkyl halides *via* copper-catalyzed radical-involved alkynylation using a chiral cinchona alkaloid-based P,N-ligand.[57] Later, they expanded this system and realized a copper-catalyzed asymmetric oxidative cross-coupling of C(sp^3)–H bonds with terminal alkynes (Scheme 17a).[58] In this transformation, *N*-fluoroamides **21** were used as the substrates. An N-Centered radical was generated *via* single electron reduction and fluoride releasing, which proceeded through 1,5-HAT to form a carbon radical. The chiral alkynylated products **26** were delivered from trapping the carbon radical by the copper(I)/cinchona alkaloid-based *N*,*N*,*P*-ligand catalyst. It was believed that both the *N*-fluoroamide and base played a crucial role to suppress the side reactions to achieve good efficiency. Shortly after, the Wang group realized copper-catalyzed enantioselective C–H alkynylation of sulfonamides (Scheme 17b).[59] The chiral box-copper

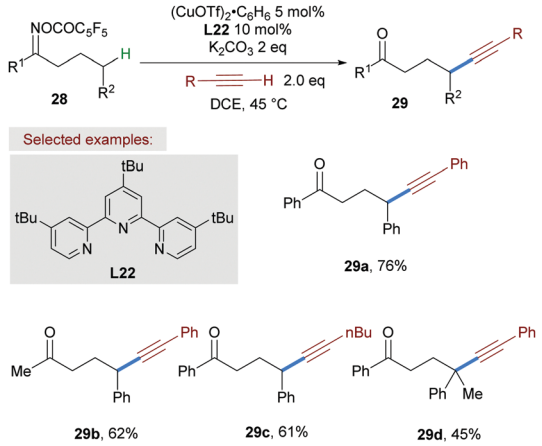


Scheme 17 Copper-catalyzed asymmetric alkynylation of unactivated C(sp^3)–H bonds *via* 1,5-HAT (Liu and Wang).[58,59]

complex is used to reduce the N–F bond to generate an N-centered radical, and to capture the carbon radical which is formed *via* 1,5-HAT. Alkynylsilanes were the only successful alkylating reagents in this reaction.

Instead of reducing the N–F bond to generate an N centred radical, the Zhu group disclosed a racemic version of γ-C(sp^3)–H alkynylation of linear oxime esters *via* a copper-catalyzed radical relay (Scheme 18).[60] In this reaction, a more nucleophilic alkynyl copper complex generated from the reaction of copper with a terminal alkyne could reduce the N–O bond in oxime ester **28** to form an iminyl radical, which undergoes 1,5-HAT to generate a benzylic radical. Trapping the benzylic radical by the Cu(II) species generates a Cu(III) intermediate, which subsequently undergoes reductive elimination to afford the remote alkynylated ketones **29** and the Cu(I) species. (*t*-Bu)$_3$-TERPY was found to be the effective ligand in this reaction.

Except to take advantage of 1,5-HAT to control regioselectivity, the Zhang group merged copper catalysis with a silicon tethered carbon radical initiating 1,*n*-HAT and realized remote radical C–H alkynylation and amination of diverse aliphatic alcohols

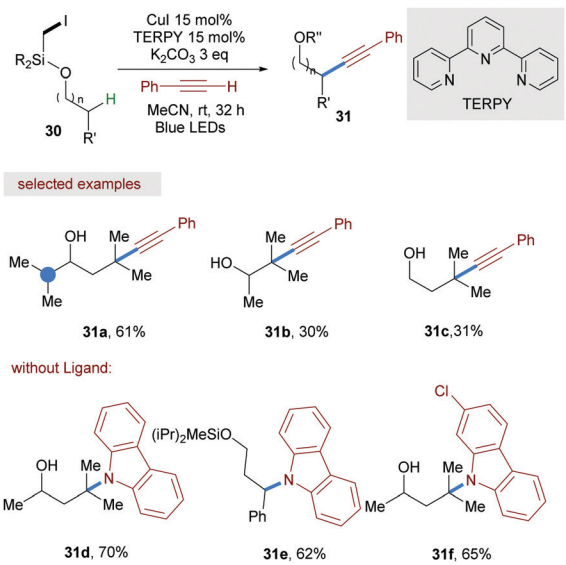


Scheme 18 Copper-catalyzed alkynylation of γ-C(sp^3)–H alkynylation of linear oxime esters (Zhu, 2020).[60]

(Scheme 19).[61] In the reaction, a photoactive copper nucleophile complex was formed *in situ*, which could reduce the silicon-tethered aliphatic iodide **30** after being exited by visible light to an alkyl radical to initiate 1,*n*-HAT. The formed carbon radical could be trapped by the Cu(II) complex to give the desired products **31**. Various mono-substituted alkynes and carbazoles could be used as nucleophiles. Tertiary and benzylic C–H bonds at the γ-position showed exclusive regioselectivity due to the preference of 1,6-HAT to 1,5-HAT in the Si-tethered alcohol **30**. However, with no weaker C–H bonds at the γ-position, the 1,5-HAT products **31b** and **31c** could be formed albeit in lower yields.

2.4. C–H fluoroalkylation

Fluorinated groups such as CF_3, SCF_3, $SeCF_3$, and CF_2H, are drawing increasing attention due to their important roles in pharmaceuticals and agrochemicals. Therefore, tremendous

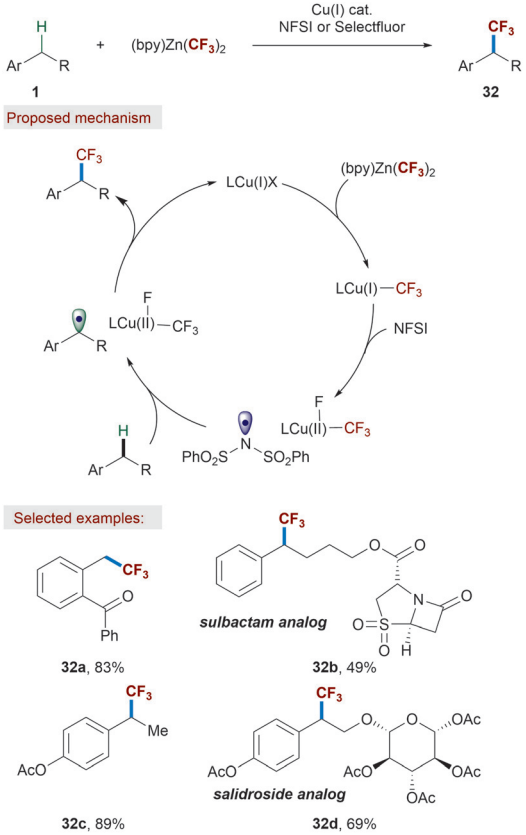


Scheme 19 Copper-catalyzed remote C–H functionalization of alcohols (Zhang, 2021).[61]

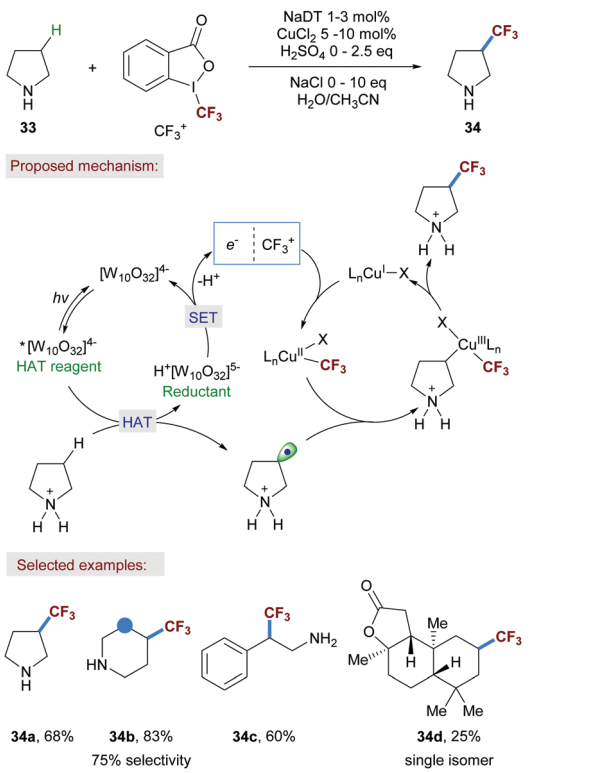
effort has been devoted to developing novel methodologies to introduce fluorinated groups *via* C–H functionalization.

Direct C(sp^3)–H trifluoromethylation *via* a radical relay was underdeveloped due to the lack of methods for trifluoromethylation of alkyl radicals. In 2017, the Li group demonstrated the trifluoromethylation of alkyl halides which underwent the mechanism of CF_3 transfer to alkyl radicals from Cu(II)–CF_3 intermediates.[62] Later, they successfully developed a general copper-catalyzed protocol for benzylic C(sp^3)–H trifluoromethylation (Scheme 20).[63] The reaction mechanism was proposed as follows: the Cu(I)–CF_3 generated from ligand exchange between Cu(I)X with a trifluoromethyl anion could reduce *N*-fluorobis(benzenesulfonyl)imide (NFSI) *via* a single electron transfer to generate a Cu(II)–CF_3 intermediate and N-centered radical. The HAT of substrate (**1**) by the N-centered radical generates the corresponding benzyl radical which could be trapped by Cu(II)–CF_3 to afford the desired products (**32**). The more stabilized CF_3^- source (bpy)Zn(CF_3)$_2$ was the key to avoiding the oxidation of CF_3^- to the CF_3 radical. The reaction also features mild conditions and a broad substrate scope. In addition, late-stage functionalization of a variety of organic molecules and known drugs was showcased to indicate its utility.

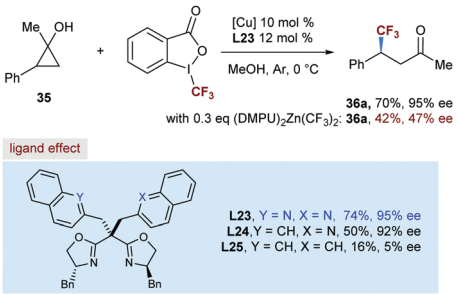
MacMillan and coworkers developed an elegant procedure of general C(sp^3)–H trifluoromethylation using Togni reagent II *via* the merging of decatungstate photocatalysis with copper catalysis (Scheme 21).[64] In this reaction, substrate **33** was used as a limiting reagent and the substrate scope was not limited to activated C–H bonds. The photoexcited decatungstate has remarkable efficiency in cleaving strong C–H bonds, and it is prone to abstract the most sterically accessible, electron-rich C(sp^3)–H bond due to its highly electrophilic ligand-to-metal charge transfer excited state. This reaction was suggested to undergo the following pathway. The decatungstate was excited upon photo irradiation to afford the oxometallate excited state. While using protonated amine substrates such as pyrrolidine (**33a**), the adjacent hydrogen atoms become stronger and less hydridic. As a result, the traditionally less reactive distal carbon radical could be formed *via* HAT due to the polarity-match effect. The ground-state polyoxometallate would reduce the Togni reagent in the presence of a Cu(I) catalyst to afford a Cu(II)–CF_3 intermediate and regenerate the decatungstate anion. The carbon-centered radical would be intercepted by the Cu(II)–CF_3 species at near-diffusion rates to afford the desired product through an alkyl–Cu(III)–CF_3 intermediate while regenerating the Cu(I) catalyst. The radical capture and reductive elimination steps were also supported by computational studies. This transformation features exceptional functional group tolerance such as unprotected amines and carboxylic acids. Late-stage C–H functionalization of complex and medicinally relevant molecules further demonstrated its utility. Moreover, the obvious enantioenrichment was observed while tuning the copper ligand environment which supported the bond-forming event being mediated by copper.



Scheme 20 Copper-catalyzed benzylic C–H trifluoromethylation (Li, 2019).[63]



Scheme 21 Aliphatic C(sp^3)–H trifluoromethylation (MacMillan, 2020).[64]



Scheme 22 Enantioselective copper-catalyzed trifluoromethylation of benzylic radicals (Liu, 2020).[65]

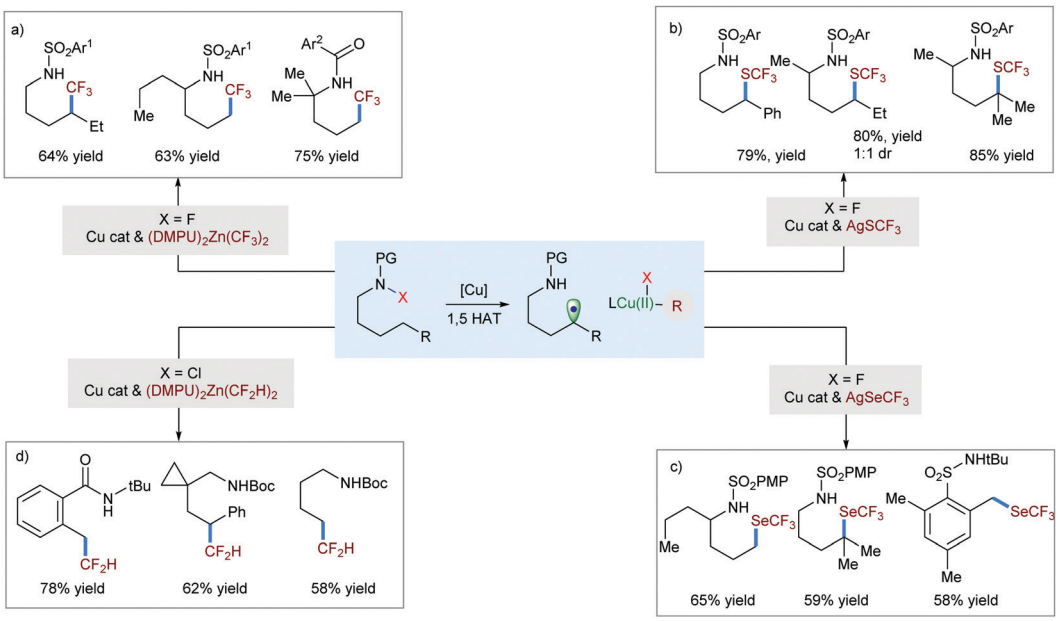
Despite the great progress in C–H trifluoromethylation, the asymmetrical version of C–H trifluoromethylation *via* a radical relay has not been realized yet. Recently, the first enantioselective trifluoromethylation of an alkyl radical was accomplished by the Liu group (Scheme 22).[65] Adding extra $(DMPU)_2Zn(CF_3)_2$ to the reaction caused a great decrease in enantioselectivity from 95% ee to 45% ee which could be attributed to ligand dissociation from copper promoted by an extra CF_3 anion. Alternatively, Togni reagent II was used as the oxidant and CF_3 source. In addition, a novel quinolinyl-containing bisoxazoline ligand was developed to provide an extra coordination site. Therefore, a weak interaction between quinoline and the copper center made the copper center adopt a more crowded geometry, which is crucial to achieving higher enantioselectivities in the benzylic radical-trapping step. As a result, the enantioselectivity was increased from 5% ee to 95% ee while introducing two extra coordination sites (**L25** *vs.* **L23**). Mechanistic understanding gained from this work will have important implications for the development of asymmetric radical C–H trifluoromethylation.

Taking advantage of regioselective intramolecular HAT, the Li group developed a protocol for the remote C–H trifluoromethylation of *N*-fluorosubstituted carboxamides (or sulfonamides) *via* an intramolecular 1,5-HAT (Scheme 23a). In this reaction, $(DMPU)_2Zn(CF_3)_2$ was used as a CF_3 source in the presence of $Cu(OTf)_2$ as the catalyst to afford the corresponding δ-trifluoromethylated carboxamides (or sulfonamides) in moderate to good yields.[66] A similar radical mechanism was proposed in which the 1,5-HAT of N-radicals generates the alkyl radical, which reacts with Cu^{II}–CF_3 species to form C–H trifluoromethylation products. Additionally, the Cook group realized copper-catalyzed directed Csp^3–H trifluoromethylthiolation ($-SCF_3$) and trifluoromethyl-selenation ($-SeCF_3$) using $AgSCF_3$ or $AgSeCF_3$ as transmetallation reagents (Scheme 23b and c).[67] During this time, Liu and coworkers developed a copper-catalyzed remote C–H difluoromethylation of *N*-chloroamides using $(DMPU)_2Zn(CF_2H)_2$ as a nucleophilic difluoromethyl source (Scheme 23d).[68]

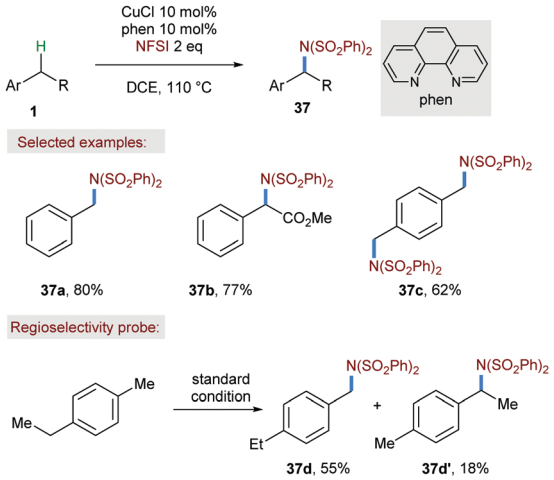
2.5. C–X bond formation

Direct oxidation of ubiquitous $C(sp^3)$–H bonds to install carbon–heteroatom bonds is of great significance to avoid tedious functional group manipulations which is required for the synthesis of target functional molecules. The classic Kharasch–Sosnovsky reaction with copper catalysis has been expanded to incorporate heteroatom units *via* a radical relay.[69] We summarized very recent advances of copper-catalyzed radical relay to convert C–H bonds into carbon–heteroatom bonds as well.

In 2011, the Zhang group developed an efficient copper-catalyzed benzylic C–H amination (Scheme 24).[70] Alkyl arenes were used as the limiting reagents, and NFSI was employed as an HAT reagent and a nitrogen source. The amination products could be obtained in similar yields under a nitrogen or air atmosphere.



Scheme 23 Copper-catalyzed remote C–H fluoroalkylation *via* 1,5-HAT.[66–68]

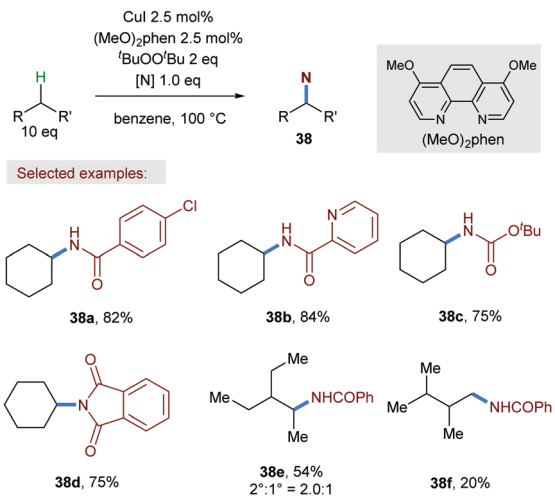


Scheme 24 Copper-catalyzed benzylic C–H amination (Zhang, 2011).[70]

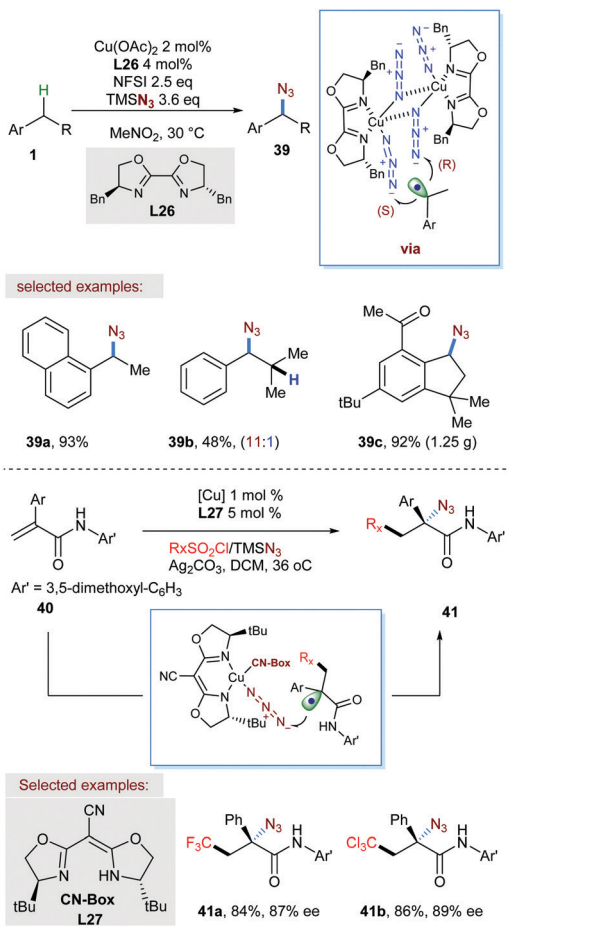
A broad range of toluene derivatives were compatible with this reaction. In addition, the corresponding diamination products could be formed in moderate yields with *p*-xylene using excess amounts of NFSI (5 equiv.). Impressively, this transformation exhibited remarkable preference for primary over secondary C–H bonds.

Later, the Hartwig group realized copper-catalyzed imidation of sp^3 C–H bonds of unactivated alkanes which could assemble alkanes with simple amides, sulfonamides, and imides to form the corresponding *N*-alkyl products (Scheme 25).[71] Both copper and tBuOOtBu were required to afford the desired products in catalytic and stoichiometric reactions. Radical trap experiments supported the intermediary of a *tert*-butoxy radical, which formed an alkyl radical intermediate. Additionally, the amination products were preferentially formed at secondary sites and primary C–H bonds over tertiary sites. A mechanistic study revealed that the C–H cleavage of cyclohexane by a *tert*-butoxy radical was the turnover-limiting step in this transformation. Overall, the mechanistic study indicated that the radical relay pathway is initiated by the *tert*-butoxy radical rather than a copper–nitrene insertion mechanism. Warren and co-workers also developed a copper-catalyzed sp^3 C–H amination of alkanes which were used as solvents.[72] A detailed mechanistic study was performed by the same group as well which supported the C–H amination undergoing a copper-catalyzed radical relay pathway.[73] In 2020, the König group achieved a similar C–H amination under milder conditions through photoinduced copper catalysis.[74]

In 2020, the Stahl group developed a copper-catalyzed benzylic C–H azidation *via* a radical relay (Scheme 26, top).[75] In this reaction, a Cu^I complex could reduce NFSI to generate an imidyl radical which promotes the HAT of benzylic C–H bonds. The formed benzylic radical could be trapped by a Cu^{II}-azide species to afford the benzyl azide **39**. This method exhibited diverse functional group compatibility and high benzylic site selectivity which made it well-suited for the late-stage functionalization of pharmaceutical and agrochemical building blocks, intermediates, and existing bioactive molecules. Notably, the reaction of CuOAc, **L26**, NFSI, and $TMSN_3$ could generate a dimeric Cu^{II}-azide complex, which could react with an alkyl radical to install an azide group efficiently. When the



Scheme 25 Copper-catalyzed imidation of sp^3 C–H bonds of unactivated alkanes (Hartwig, 2014).[71]



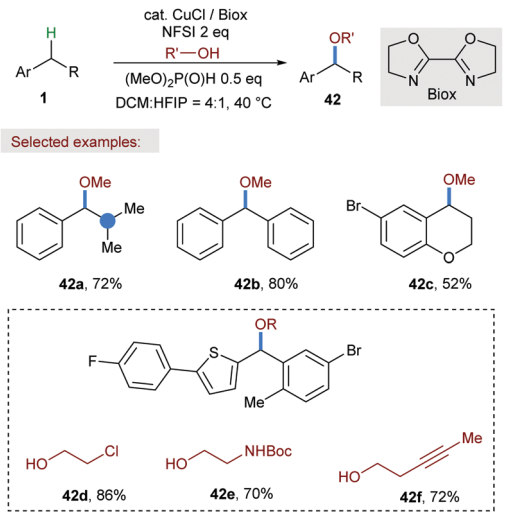
Scheme 26 Copper-catalyzed azidation *via* a radical relay (Stahl and Liu).[75,77]

benzylic radical reacted with the (Box)Cu complex dimmer bearing bridging and terminal azide, both azides on the copper can be transferred to a benzylic radical, leading to a pair of azidation enantiomers. Besides, computational data indicated that a benzylic carbon cation more likely governed the C–N bond formation step. These mechanism probes explained the reason for the low enantioselectivity when using chiral ligands.

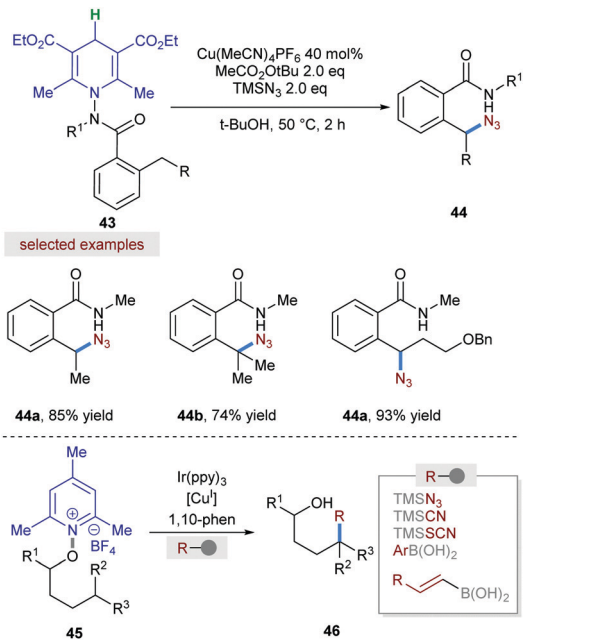
In addition, transition metal catalyzed radical azidation reactions usually underwent a radical group transfer (outer sphere) pathway.[76] As a result, the asymmetrical version of radical C–H azidation still remains elusive. The Liu group demonstrated that an alkyl radical could be trapped by a chiral copper complex installing azide in an enantioselective manner (Scheme 26, bottom).[77] An excess amount of anionic cyanobisoxazoline (CN-Box) ligand **L27** was used to prevent the formation of dimeric Cu(II) azide species and reduced the oxidation ability of the Cu(II) azide species. As a result, a highly enantioselective radical trifluoromethyl azidation of acrylamides was achieved which shed light on the development of asymmetric C–H azidation *via* a radical relay.

In the same year, the Stahl group also demonstrated that alcohols could be used as nucleophiles to afford benzyl ethers *via* copper-catalyzed radical benzylic C–H bond oxygenation (Scheme 27).[78] NFSI was used as both the oxidant and HAT reagent to abstract an H atom from the benzylic position. As a mechanistic study, stoichiometric experiments were performed and revealed that both trimethylsilyl cyanide and arylboronic acid induced rapid reduction of Cu^{II} to Cu^{I}, resulting in the formation of cyanogen and biaryl. In contrast, MeOH does not reduce Cu^{II} under these conditions. Therefore, the Cu catalyst would accumulate as a Cu^{II} species which would lead the reaction to stall due to the inability of Cu^{II} to react with NFSI. To solve this problem, a variety of reductants were examined and dialkylphosphites were identified to be effective which could convert Cu^{II} into catalytically active Cu^{I} in the reaction. Inclusion of hexafluoroisopropanol (HFIP) as a co-solvent could promote the yield due to the activation of the •NSI radical by HFIP. The transformation uses alkylarenes as the limiting reagents, and has a broad substrate scope. Based on the computational and experimental results, a catalytic pathway involving radical-polar crossover initiated by the HAT from the benzylic C–H site was more likely instead of the HAT followed by reductive elimination from a Cu(III) intermediate. The possible mechanism also explained the observation of no enantioselectivity while chiral ligand derivatives were used. While using $MeB(OH)_2$ as a redox buffer and Li_2CO_3 as a Brønsted base, the same group also realized benzylic C–H fluorination *via* a Cu/NFSI-based catalyst system.[79] Moreover, the formed benzyl fluorides could be used without isolation as coupling partners to access products with new C(sp^3)–O, –N, and –C bonds.

For C–H functionalization *via* intramolecular HAT, Zhu and coworkers designed a Cu-catalyzed γ-C(sp^3)–H azidation of benzohydrazides (Scheme 28).[80] Mechanistically, the process is initiated by the polarity-matched abstraction of the Hantzsch ester's C-4 hydrogen by the electrophilic ^{t}BuO radical to afford the amidyl radical and pyridine after fragmentation. In the presence of gamma C–H bonds, the alkyl radical was formed *via* 1,5HAT. The high bond strength of ^{t}BuO-H prevented the chain propagation, which allowed the carbon radical to be trapped by a copper catalyst. In the presence of $TMSN_3$, the azide group could be installed efficiently. In the same year, the Zhu group also developed a dual photoredox/copper catalytic system to convert *N*-alkoxypyridium salts into δ-functionalized alcohols in moderate to good yields (Scheme 28).[81,82] An oxygen centered radical and Ir^{IV} were generated *via* single electron reduction of *N*-alkoxypyridium **45** by an excited Ir^{III}* complex. Reduction of the latter by $Cu^{I}X$ would regenerate the Ir^{III} and Cu^{II} species which, upon transmetalation with nucleophiles, would afford



Scheme 27 Copper-catalyzed benzylic C–H coupling with alcohols *via* a radical relay (Stahl, 2020).[78]



Scheme 28 Remote C–H functionalization *via* a copper-catalyzed radical relay (Zhu, 2019).[80–82]

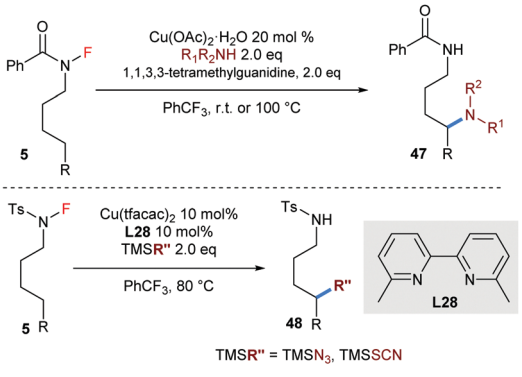
$RCu^{II}X$. On the other hand, 1,5-HAT from an alkoxyl radical was used to generate a carbon radical which could be trapped by $RCu^{II}X$ to afford the Cu^{III} species. Subsequent reductive elimination would then deliver the δ-functionalized alcohol **46** with the concurrent regeneration of Cu^{I} salt. A variety of nucleophiles such as $TMSN_3$, TMSCN, TMSSCN and aryl/vinyl boronic acids were compatible with the reaction conditions and could afford the desired product in medium to good yield.

Liu and coworkers merged C–N bond cross-coupling with the Hofmann–Löffler–Freytag reaction and realized intermolecular C(sp^3)–H amination of carboxamides (Scheme 29).[83] This transformation utilized copper as a catalyst to convert *N*-fluorocarboxamides into a wide range of distal aminated carboxamides with various nucleophiles such as aryl/aliphatic amines, indoles, and imines. The reaction was initiated by an *in situ* generated Cu(I)–N complex which reduced the N–F substrates to generate amidyl radicals, triggering 1,5-HAT. The formed alkyl radical was then trapped by the Cu(II)–N complex and C–N bond reductive elimination afforded the desired products. Later, they also expanded this system to remote azidation and thiocyanation of unactivated C(sp^3)–H bonds distal to the amine moiety using $TMSN_3$ and TMSSCN as nucleophiles.[84]

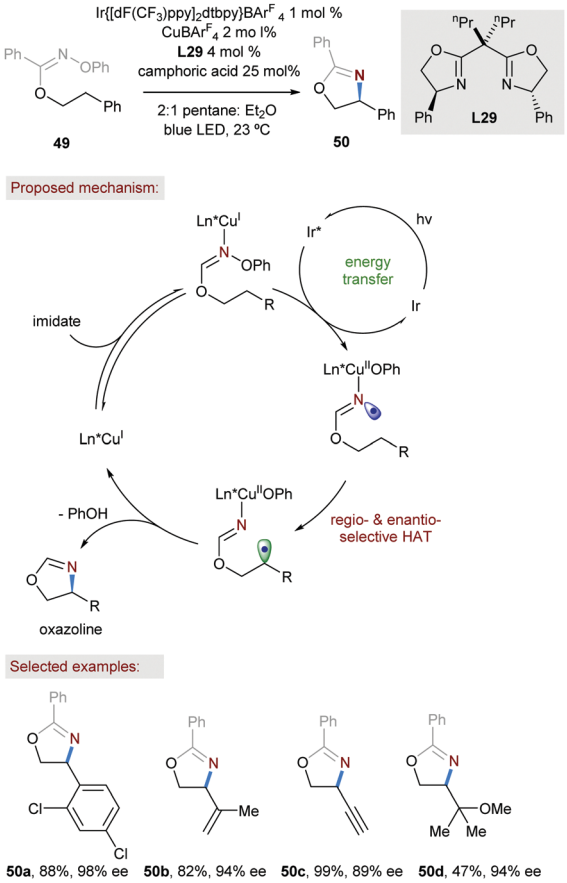
The transformations of C–H functionalization to install C–X bonds asymmetrically are rare. In 2020, Nagib and coworkers designed an elegant strategy of regio- and enantio-selective C–H amination of alcohol which merged a radical chaperone, energy transfer and asymmetric copper catalysis (Scheme 30).[85] In this transformation, an oxime imidate generated from an alcohol is transiently converted to an imidate radical that undergoes intramolecular HAT. Notably, the 1,5-HAT was also rendered enantioselective by a chiral copper catalyst. Success of this multi-catalytic, asymmetric radical relay has enabled a unified synthesis of chiral β amino alcohols *via* selective C–H amination of a variety of alcohols containing alkyl, benzyl, allyl, and propargyl C–H bonds (**50a–50d**). Both experimental and computational studies supported the proposed mechanism elaborated in Scheme 30. In addition, examples of the synthetic utility of this enantioselective radical C–H amination approach were also showcased in the original paper.

In the same year, the Liu group developed a Cu^{I}/CPA-catalyzed asymmetric intramolecular radical-involved C–H amination of allylic and benzylic substrates *via* an intermolecular HAT (Scheme 31).[86] In this transformation, 4-OMe-PINO was used as a stable and chemoselective HAT mediator which is crucial for the fulfillment of this transformation to selectively abstract the hydrogen atom at the allylic and benzylic positions. The formed carbon radical could then be trapped in the presence of a chiral Cu^{II} phosphate complex and zinc phosphate complex to construct a C–N bond asymmetrically. Various chiral α-alkenyl and α-aryl pyrrolidines could be synthesized by this transformation with excellent enantioselectivity and moderate to high yields. This novel method to control enantioselectivity also provided useful insight for enantioselective C(sp^3)–H bond functionalization *via* a radical relay.

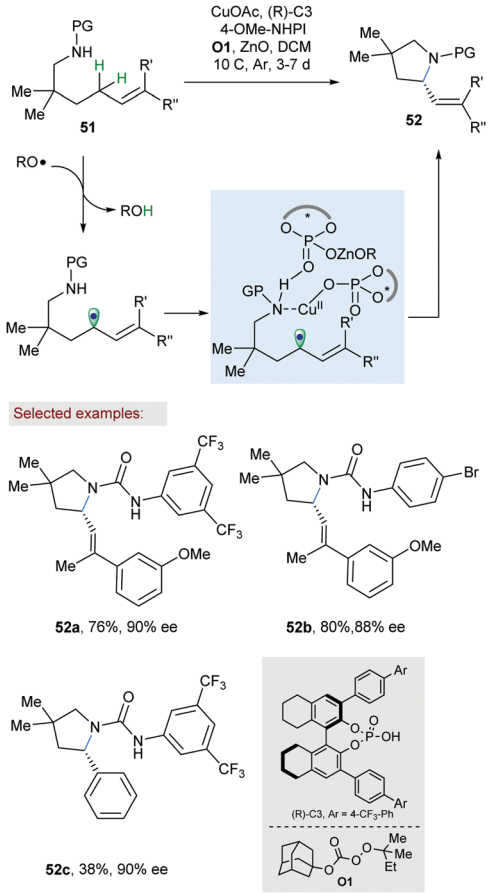
The asymmetric tertiary C(sp^3)–H bond functionalization *via* a copper catalyst is extremely rare due to steric sensitivity of the bulky copper complex which is required for enantioselective control. In 2020, the Liu group developed an elegant strategy for direct radical enantioconvergent tertiary C(sp^3)–H amination with dual Cu/CPA catalysis (Scheme 32).[87] This transformation could convert readily β-C(sp^3)–H of racemic ketones into enantioenriched quaternary stereocentres. The reaction involved a HAT which allowed for chirality loss of the generated tertiary C-radical, followed by asymmetric radical functionalization to afford the desired products. This reaction features a broad substate scope. Moreover, this transformation offered a



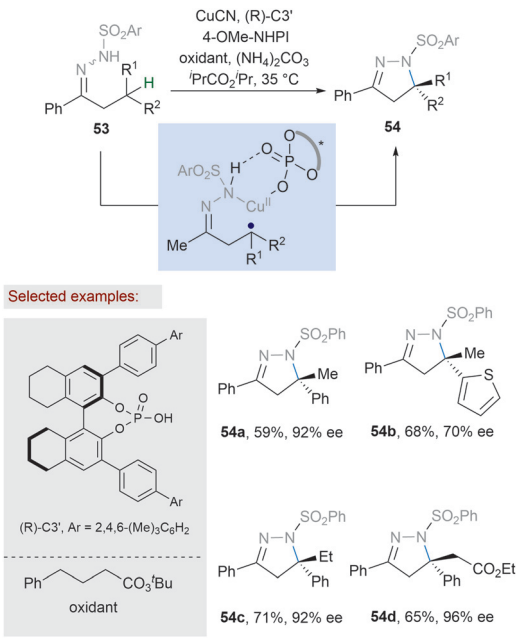
Scheme 29 Remote C–H functionalization of carboxamides and sulfonamides *via* a radical relay.[83,84]



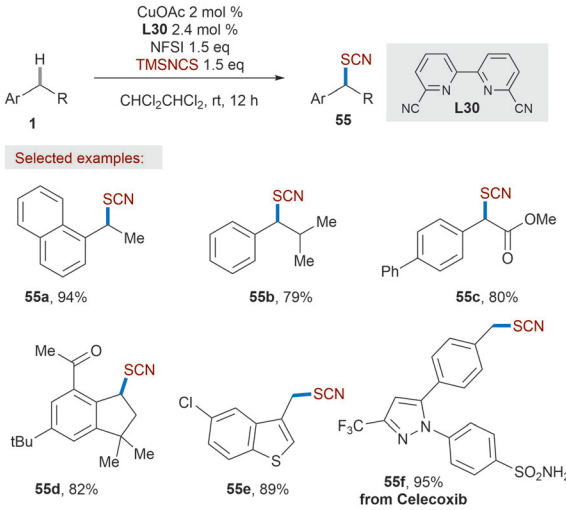
Scheme 30 Asymmetric intramolecular C–H amination (Nagib, 2020).[85]



Scheme 31 Enantioselective amination of allylic and benzylic C–H bonds (Liu, 2020).[86]



Scheme 32 Enantioselective amination of allylic and benzylic C–H bonds (Liu, 2020).[87]

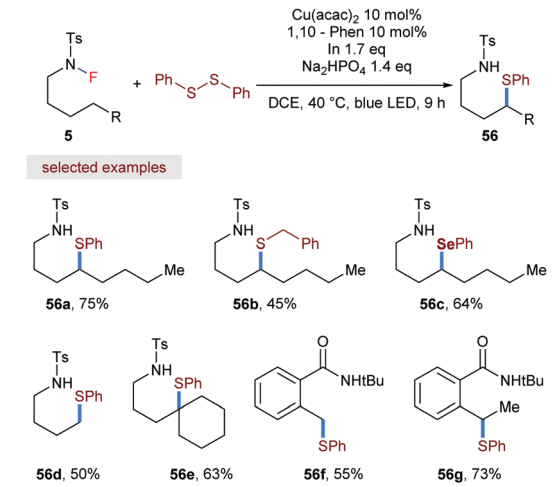


Scheme 33 Thiocyanation of benzylic C–H bonds *via* a copper-catalyzed radical relay (Liu, 2020).[88]

new solution to achieve stereo-convergent tertiary C–H functionalization.

Copper-catalyzed radical relay has been expanded to construct a C–S bond as well, and the Liu group demonstrated an efficient method for thiocyanation of benzylic C–H bonds in 2020 (Scheme 33).[88] The reaction exhibited broad substrate scope and exquisite benzylic selectivity with C–H substrates as limiting reagents. This method provided a distinctive route to incorporate various medicinally and synthetically important functionalities, including thiocyanate, isothiocyanate, thiourea, SCF_3, and SCF_2H, among others. Moreover, the transformation also features a broad substrate scope, diverse functional group tolerance, one-pot derivatization, and applicability to late-stage functionalization.

The Yang group realized thiolation of C(sp^3)–H bonds on aliphatic amines *via* the merger of visible light and copper catalysis (Scheme 34).[89] Mechanistically, an excited copper



Scheme 34 Remote C–S bond formation *via* a copper-catalyzed radical relay (Yang, 2020).[89]

disulfide complex generated from ligand exchange between an *in situ* generated Cu(I) catalyst and disulfide *via* photoexcitation allowed for the reduction of the N–F bond of the aliphatic amine. After release the F-SR moiety *via* a metathesis process, a Cu(II)-SR complex was formed and later trapped the alkyl radical forming the key Cu(III) intermediate. Subsequent reductive elimination of the Cu(III) intermediate allowed for the generation of the thiolation products. This transformation is notably highlighted for showcasing broad substrate compatibility with various C–H bonds, broad amine scope, good functional compatibility, and late-stage modification of biologically active intermediates.

3. Conclusions and outlook

Copper has four oxidation states (Cu^0, Cu^I, Cu^{II}, Cu^{III}) attributed to its valence electron configuration ($3d^{10}4s^1$). Thus, a copper catalyst could act as a good single electron transfer reagent to initiate a radical redox reaction. In addition, the open shell species of Cu^{II} could react with a carbon radical to promote the formation of new chemical bonds. More importantly, the judicious choice of chiral ligands and nucleophiles makes the asymmetric cross coupling *via* copper catalysis possible. As a result, copper displayed a remarkable capacity for catalysing transformations *via* a radical relay as a cheap and robust catalyst. Consequently, a copper-catalyzed asymmetrical radical relay strategy has been developed to explore the novel C–H functionalization, which has been recognized as an important tool in organic synthesis. This review surveyed the recent advances in C–H functionalization *via* a copper-catalyzed radical relay with the emphasis on enantioselective conversions. An attempt has also been made to summarize the rationale of the choice and design of ligands to achieve good enantioselectivity. There are mainly two classes of chiral ligands that have been used, including chiral box ligands and cinchona alkaloid-based P,N-ligands, the former were used as the predominate ligands at the current stage. So far, cyanide, alkynyl, and aryl groups can be asymmetrically installed *via* a copper-catalyzed radical relay strategy from C(sp^3)–H bonds as well as C–N bonds. The secondary benzylic and allylic C(sp^3)–H could be converted into chiral nitriles *via* enantioselective C–H cyanation. In contrast, the asymmetric arylation was more challenging which may be due to the slow transmetalation between a copper catalyst and arylboronic acids. As a result, the scope of asymmetric arylation is limited in alkyl naphthalene. Enantioselective C(sp^3)–H alkynylation could install alkynyl groups asymmetrically within a broader scope of secondary benzylic C(sp^3)–H. In contrast, copper catalyzed asymmetric C–H alkenylation *via* a radical relay has not been successful so far. This challenge may be due to the rapid competitive process of radical addition toward carbon–carbon double bonds consumed the reactive radical species which is required for the HAT step. Recently, asymmetrical radical benzylic C–H alkenylation was achieved *via* photoredox/nickel dual catalysis.[90] The asymmetrical carbon–heteroatom bonds are less developed which may be due to the electronegative nature of the heteroatom that altered the pathway of the Cu(III) intermediate to a carbon cation mechanism. Besides, an outer sphere mechanism is more favorable to transfer azide, chloride, and sulfur from a copper center to carbon radicals. Therefore, only intramolecular asymmetrical amination of C(sp^3)–H bonds have been achieved so far. On the other hand, most of the transformations involved a stabilized carbon radical such as benzylic, allylic, and propargyl radicals to achieve good enantioselective control. Very recently, interesting enantioselective propargylic (aryl) C–H cyanations were reported to deliver various enantiomerically enriched allenylnitriles efficiently, but there was no observation of chiral propoarylic nitriles.[91] Although an unactivated C(sp^3)–H bond could be converted into carbon radicals *via* HAT, there is still no general method to intercept unstabilized carbon radicals asymmetrically *via* copper catalysis. In addition, due to the bulky chiral ligands which are required for enantioselective control, asymmetric tertiary C(sp^3)–H bond functionalization *via* a copper catalyst is less developed.

To solve the forementioned problems in this area, the future relies on the development of new ligands to alter the electronic and steric properties of a copper catalyst to trap regular secondary carbon radicals and tertiary radicals efficiently and broaden the asymmetrically installed functional groups. The development of new catalytic system using other transition metals instead of copper is crucial to conquer the unsolved problems as well. In addition, a novel catalytic system is needed to achieve regioselective H atom abstraction on unbiased C–H bonds. We hope that the concept introduced in this review will inspire future developments in the area.

Author contributions

Z. Z. and G. L. summarized and wrote the review. P. C. and G. L. proofed the manuscript.

Conflicts of interest

There are no conflicts to declare.

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