

Ligand-Enabled Copper(I)-Catalyzed Asymmetric Radical C(sp³)-C Cross-Coupling Reactions

Huan Zhou,[§] Zhong-Liang Li,[§] Qiang-Shuai Gu, and Xin-Yuan Liu*



Cite This: *ACS Catal.* 2021, 11, 7978–7986



Read Online

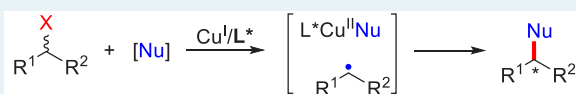
ACCESS |

Metrics & More

Article Recommendations

ABSTRACT: The first-row transition-metal-catalyzed asymmetric C(sp³)-C cross-coupling represents a powerful approach in the expedient synthesis of enantioenriched molecules. Recently, a series of chiral copper catalysts have been designed to promote a variety of asymmetric radical C(sp³)-C cross-coupling reactions with high efficiency and enantioselectivity. The key to success is the design of chiral ligands to initiate the reaction and achieve enantiocontrol over the highly reactive prochiral alkyl radical species. This Perspective will discuss the impressive advances and provide an outlook on the direction of further development.

KEYWORDS: ligand design, asymmetric transformation, radical reaction, racemic alkyl halides, copper catalysis



ligand design:

- enhancing reducing capability of copper for reaction initiation
- enantiocontrol over the highly reactive prochiral alkyl radical

1. INTRODUCTION

Transition-metal-catalyzed C-C cross-coupling reactions have revolutionized the way chemists constructed complex molecules and found great application in all aspects of chemistry.^{1–5} In particular, the asymmetric C(sp³)-C cross-coupling of racemic alkyl electrophiles will further expand its synthetic utility in the synthesis of three-dimensional enantioenriched molecules. In this scenario, the earth-abundant first-row transition metals (Fe, Co, Ni, and Cu) engage more easily in a single-electron-transfer (SET) process due to their high-spin electronic configurations.⁶ Therefore, these transition metals can convert racemic alkyl electrophiles to the same prochiral radical intermediate, thus providing a suitable mechanism for their enantioconvergent transformation.^{7–9} In this context, Fu and others have pioneered this field by using chiral nickel catalysis for the achievement of a range of asymmetric radical C(sp³)-C cross-couplings of racemic alkyl halides with organometallic reagents dating from 2005.^{7–10} To demonstrate the feasibility of other first-row transition metals in such transformations, Zhong, Bian, and Nakamura have designed chiral cobalt^{11,12} and iron^{13,14} catalysts to accomplish the asymmetric radical C(sp³)-C cross-coupling, respectively.

Since copper is a good redox catalyst and the Cu^{II} species can react efficiently with the alkyl radical, it should be a potential first-row transition-metal catalyst for the achievement of asymmetric radical C(sp³)-C cross-coupling.^{15–17} As such, it has been utilized in the past several years in the asymmetric radical oxidative cross-coupling of C(sp³)-H bonds through a hydrogen atom abstraction (HAA) and the subsequent interaction of Cu^{II}Nu with the prochiral alkyl radical species.^{18,19} However, it has been less applied to the asymmetric radical C(sp³)-C cross-coupling of racemic alkyl

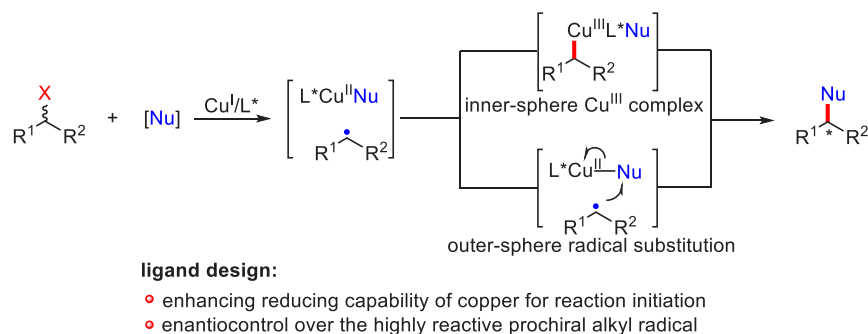
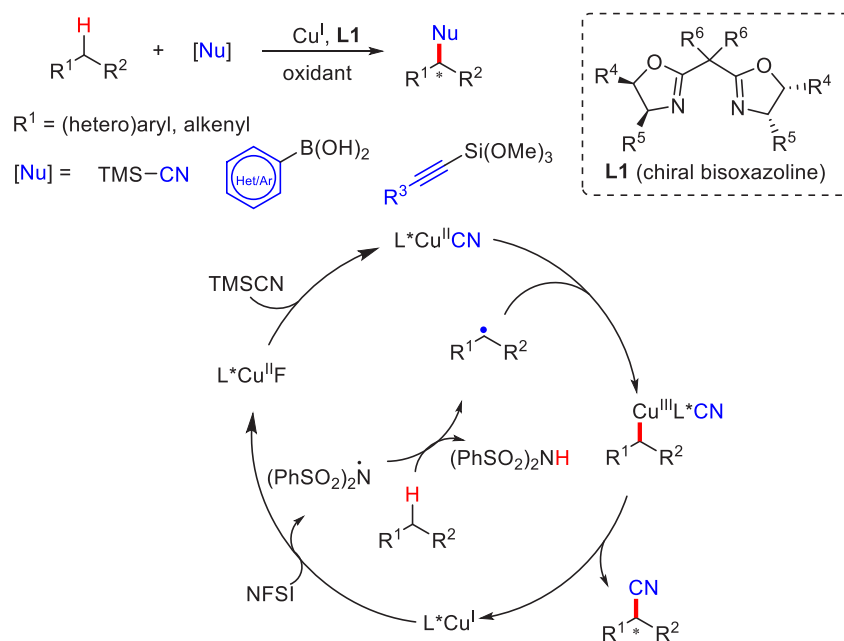
electrophiles due to its relatively low reducing capability at the ground state of the copper catalyst to initiate the reaction via an SET process with alkyl electrophiles.^{15,20} Only until very recently has the copper-catalyzed asymmetric radical C(sp³)-C cross-coupling of racemic alkyl electrophiles been described with the development of new chiral anionic ligands. The purpose of this Perspective is to conceptually summarize the copper-catalyzed asymmetric radical oxidative C(sp³)-C cross-coupling of C(sp³)-H bonds and move further to the coupling of racemic alkyl electrophiles with an emphasis on endeavors to initiate the latter process (Scheme 1). In this Perspective, we will discuss the reaction initiation, the scope of coupling partners, and specifically the chiral ligand design. Finally, we will discuss the existing challenges and prospects in order to encourage more efforts in this emerging field.

2. ASYMMETRIC RADICAL OXIDATIVE CROSS-COUPLING

The straightforward copper-catalyzed asymmetric C(sp³)-H functionalization to forge chiral C(sp³)-C bonds via a hydrogen atom abstraction (HAA) strategy is one of the most promising approaches due to the high atom and step economy.²¹ Although cross dehydrogenative coupling (CDC) was developed by Li and others early in 2004, an ionic pathway is generally proposed for the enantiodetermining step.²² In

Received: April 30, 2021

Revised: June 3, 2021

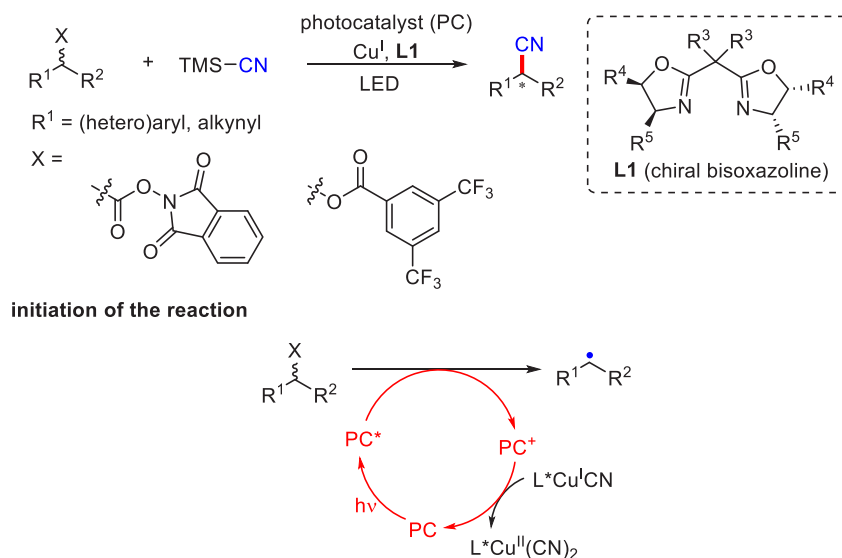
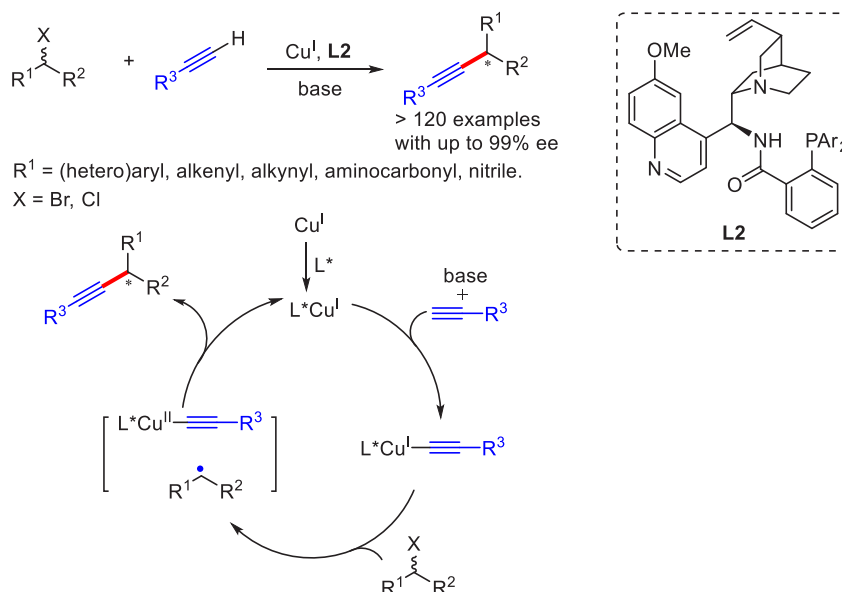
Scheme 1. General Strategy for Copper-Catalyzed Asymmetric Radical C(sp³)-C Cross-Coupling ReactionsScheme 2. Asymmetric Radical Oxidative C(sp³)-C Cross-Coupling via the HAA Strategy

comparison, the direct enantiocontrol over the prochiral alkyl radical to achieve asymmetric C(sp³)-C cross-coupling has been less developed, possibly due to the lack of a suitable chiral copper catalyst to trap the highly reactive radical. Only until 2016 did Liu and Stahl make a significant breakthrough in this area by using a Cu^I/chiral bisoxazoline catalyst to realize the asymmetric cyanation of benzylic C(sp³)-H bonds via the first-coined copper-catalyzed radical relay process.²³ The reaction is initiated by the SET process between L*Cu^I and the oxidant NFSI, affording L*Cu^{II}F and a highly reactive bisulfonimidyl radical (Scheme 2). The L*Cu^{II}F complex undergoes a transmetalation process with TMSCN to afford the L*Cu^{II}CN complex, and the bisulfonimidyl radical undergoes a HAA process with C(sp³)-H to produce a benzylic radical, which is trapped by L*Cu^{II}CN to form a Cu^{III} intermediate. The reductive elimination of this Cu^{III} complex affords the desired coupling product and releases L*Cu^I for the next catalytic cycle. DFT calculations demonstrate that the trapping of the benzylic radical by L*Cu^{II}CN is reversible and the enantioselectivity is determined by the reductive elimination step. In addition to the excellent enantioselectivity, interestingly, the reaction also exhibited excellent site selectivity on the activation of benzylic C-H bonds. A subsequent investigation of the asymmetric allylic C(sp³)-H cyanation revealed that an unprecedented Cu(II)-bonded N-

centered radical is involved as a key intermediate to abstract C(sp³)-H bonds precisely, leading to an excellent site- and enantioselective allylic C-H cyanation.²⁴ In addition, they have achieved the asymmetric C(sp³)-H arylation²⁵ and alkylation,²⁶ extending the scope of nucleophiles to aryl boronic acid and silylated alkyne. Inspired by this success, Nagib,^{27,28} Zhu,²⁹ Liu,³⁰ Wang,^{31,32} and Yu³³ have reported a remote intramolecular asymmetric radical C(sp³)-H functionalization under a similar copper/chiral bisoxazoline catalysis. Generally, these intramolecular strategies depend on the design of a substrate with a preinstalled oxidative radical precursor, which is reduced by L*Cu^I to generate the highly reactive N-/O-centered radical and further triggers an intramolecular HAA process, providing a prochiral alkyl radical species for the enantiocontrol. These remarkable advances showcase the powerful application of chiral bisoxazoline in the oxidative radical C(sp³)-C cross-coupling of C(sp³)-H bonds.

Despite the well-established oxidative asymmetric radical cross-coupling of C(sp³)-H bonds, the Cu^I/chiral bisoxazoline catalyst has rarely been used in the cross-coupling of racemic alkyl electrophiles due to the weak reducing capability of such a copper catalyst at the ground state. To solve this problem, Liu³⁴ and Xiao^{35,36} have merged a photocatalyst with the copper catalyst and developed the asymmetric radical cross-coupling of benzyl and propargyl electrophiles with

Scheme 3. Asymmetric Radical Cyanation by Merging Photocatalysis and Copper Catalysis

Scheme 4. Ligand-Enabled Asymmetric Radical C(sp³)-C(sp) Cross-Coupling of Racemic Alkyl Halides with Alkynes

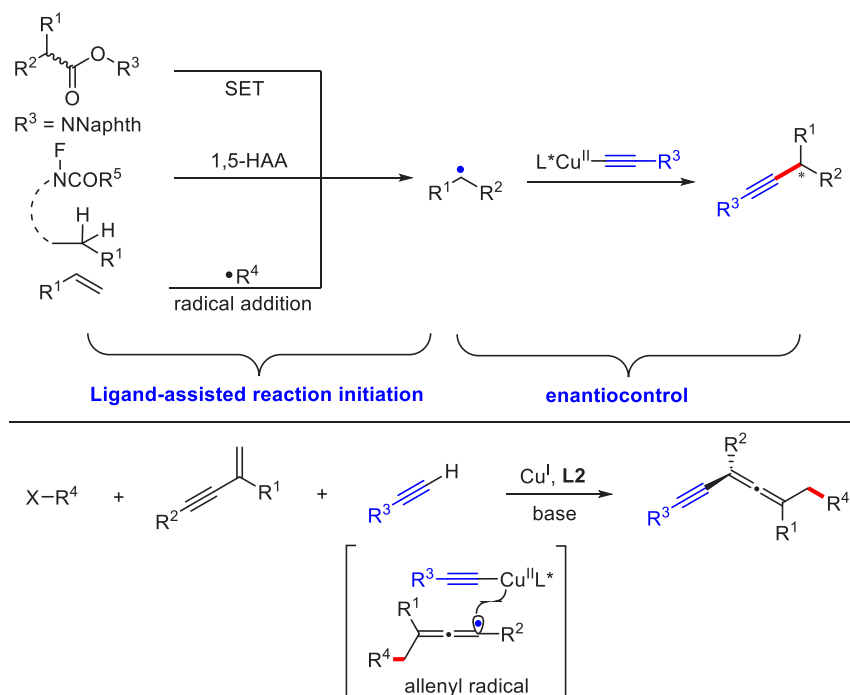
TMSCN, respectively (Scheme 3). The excited state of the photocatalyst is used to reduce the racemic alkyl electrophiles via a SET process to initiate the reaction. The SET process between the oxidized state of the photocatalyst and L^{*}Cu^ICN is the key to enclose the two catalytic cycles.

3. CHIRAL ANIONIC LIGAND ENABLED ASYMMETRIC RADICAL CROSS-COUPLING OF RACEMIC ALKYL ELECTROPHILES

Although Liu and Xiao realized the enantioconvergent radical C(sp³)-C cross-coupling with chiral copper/bisoxazoline catalysts, the weak reducing capability of this catalyst at the ground state prompted them to use an extra photocatalyst to facilitate the reaction initiation.^{34–36} The merger of photoredox with copper catalysis might complicate the reaction optimization process and raise compatibility issues in the further development of C(sp³)-C cross-coupling reactions with more racemic alkyl electrophiles. Theoretically, there

exists a solution for the enantioconvergent transformation of alkyl electrophiles with copper as the sole catalyst at the ground state via a rational design of chiral ligands. In this scenario, the ligand design must meet two criteria: (1) it should be an electron-rich chiral ligand (more electron rich than bisoxazoline) that could greatly enhance the reducing capability of the copper catalyst to initiate the reaction via the SET process between the copper catalyst and alkyl electrophiles at the ground state; (2) the chiral ligand must coordinate tightly with copper and provide a suitable chiral environment for the enantiocontrol over the highly reactive prochiral alkyl radical species.

As part of our continuous interest in designing chiral anionic ligands to realize copper-catalyzed asymmetric radical reactions,^{37–40} we have designed a chiral cinchona alkaloid derived anionic N,N-ligand that could not only enhance the reducing capability of the copper catalyst but also achieve enantiocontrol over the prochiral alkyl radical species.⁴⁰ On the basis of this concept, we worked toward the development of the

Scheme 5. Ligand-Enabled Asymmetric Radical C(sp³)–C(sp) Coupling of Diverse Radical Precursors with Alkynes

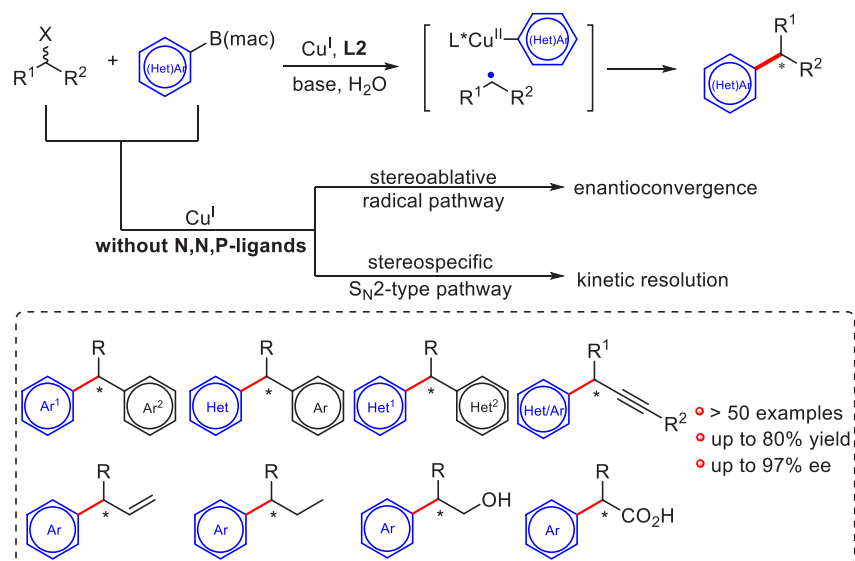
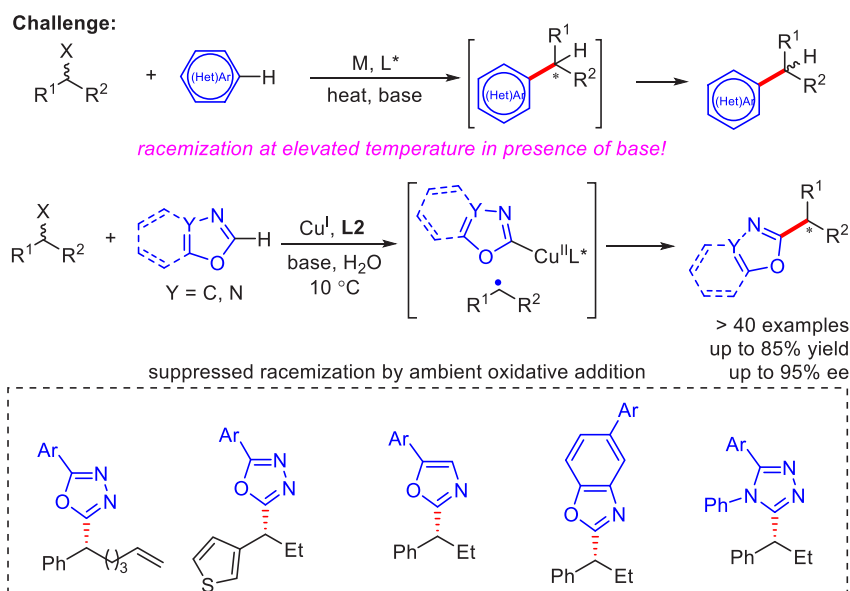
asymmetric radical C(sp³)–C(sp) cross-coupling of readily available racemic alkyl halides with terminal alkynes, which is very important in the synthesis of chiral alkynes and other building blocks. However, the anionic N,N-ligand⁴⁰ proved to be ineffective in initiating this reaction and only the Glaser homocoupling of terminal alkyne was observed. As such, we speculated that a more electron donating multidentate chiral ligand should be designed to further enhance the reducing capability of the copper catalyst at the ground state as well as suppress the easily occurring Glaser homocoupling. As such, we switched our attention to Dixon's cinchona alkaloid based tridentate ligand, which possesses an electron-rich phosphine coordination site and is easily accessible just by coupling the cinchona alkaloid derived amine and the corresponding carboxylic acid.⁴¹ Thus, we have designed a chiral cinchona alkaloid derived anionic multidentate N,N,P-ligand to realize the asymmetric radical C(sp³)–C(sp) cross-coupling of racemic alkyl halides with terminal alkynes with high efficiency and enantioselectivity (Scheme 4).⁴²

This anionic multidentate N,N,P-ligand L2 meets all the criteria for the enantioconvergent C(sp³)–C cross-coupling of alkyl electrophiles. A subsequent cyclic voltammogram (CV) study showed a quasi-reversible couple at –0.1 V for the L*Cu^I complex, suggesting that the reducing capability of L*Cu^I is stronger than that of the Cu^I catalyst itself (+0.6 V).⁴³ More significantly, it could also coordinate with copper tightly to suppress the easily occurring Glaser homocoupling.⁴⁴ This reaction exhibits a remarkably wide scope (more than 120 examples) covering diverse racemic alkyl halides, such as benzyl, allyl, and propargyl halides, α -bromo amides, and α -bromo nitrile as well as (hetero)aryl, alkyl, alkenyl, and silyl alkynes. Even the industrially relevant acetylene and propyne are successfully incorporated, laying the foundation for industrial applications. The reaction possibly proceeds via the following pathway: in the presence of base, Cu^I, L*, and alkyne form the complex L*Cu^INu. The multidentate ligand could

greatly enhance the reducing capability of the copper catalyst, and therefore the complex L*Cu^INu easily undergoes a SET process with the racemic alkyl halides to afford a prochiral alkyl radical species and a L*Cu^{II}Nu complex. The subsequent coupling of L*Cu^{II}Nu with the prochiral alkyl radical species delivers the desired coupling product and releases the L*Cu^I catalyst for the next catalytic cycle. For the C(sp³)–C bond formation, an inner-sphere Cu^{III} complex or an outer-sphere radical substitution are both possible (Scheme 1).

We further demonstrated the design of the anionic chiral multidentate N,N,P-ligand in the enantiocontrol over the prochiral alkyl radical through the asymmetric radical C(sp³)–C(sp) cross-coupling of diverse radical precursors with alkynes. As such, we have realized the decarboxylative C(sp³)–C(sp) cross-coupling reactions of racemic carboxylic N-hydroxyphthalimide(NHP)-type esters with terminal alkynes using the copper/chiral anionic ligand catalyst as a dual photo and coupling catalyst.⁴⁵ Intriguingly, this strategy exhibits unique features in terms of electrophiles that are challenging or even inapplicable in our previous coupling of alkyl halides, rendering it a valuable alternative to the previous approach (Scheme 5, top).⁴² Meanwhile, we have also discovered an oxidative C(sp³)–C(sp) cross-coupling of C(sp³)–H bonds with terminal alkynes via an intramolecular HAA process under the same chiral copper catalysis (Scheme 5, top).⁴⁶

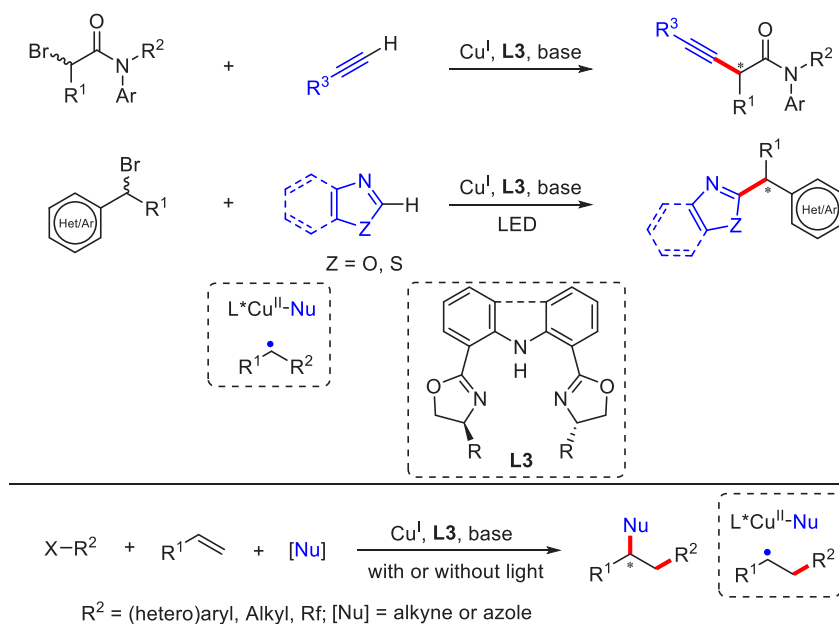
Radicals generally have a high propensity to react with alkenes because the singly occupied molecular orbital (SOMO) of most radical species could efficiently interact with the highest occupied molecular orbital (HOMO) or lowest unoccupied molecular orbital (LUMO) of alkenes.⁴⁷ This feature renders the radical alkene difunctionalization a promising strategy in the synthesis of complex molecules from an alkene feedstock.⁴⁸ In this scenario, we have successfully merged the radical-initiated alkene functionalization with the cross-coupling step to achieve a three-component asymmetric radical 1,2-carboalkynylation of alkenes from alkyl halides and

Scheme 6. Ligand-Enabled Asymmetric Suzuki-Miyaura Radical $C(sp^3)-C(sp^2)$ CouplingScheme 7. Ligand-Enabled Asymmetric Radical $C(sp^3)-C(sp^2)$ Coupling with Azoles

alkynes under the copper/chiral N,N,P-ligand catalysis (Scheme 5, top).⁴³ Mechanistically, the generated alkyl radical prefers to react with alkenes instead of $L^*Cu^{II}Nu$, which is crucial for the success of the reaction. This strategy may find potential application, since the 1,2-difunctionalization of alkenes is a powerful tool for the synthesis of complex molecules from easily available feedstocks with a step economy. In contrast to the sp^2 -hybridized alkyl radical, the sp -hybridized allenyl radical features a unique elongated linear configuration with two flanking substituents far away from the radical reaction sites. Thus, the enantiocontrol over such a radical is difficult and has been less developed. To this end, we have achieved the asymmetric radical 1,4-carboalkynylation of 1,3-enynes to afford tetrasubstituted chiral allenes with a similar catalysts, demonstrating the powerfulness of the chiral copper catalyst in the enantiocontrol over the prochiral allenyl radical (Scheme 5, bottom).^{49,50} The reaction features a broad substrate scope, covering a variety of (hetero)aryl and alkyl

alkynes, and 1,3-enynes, as well as radical precursors, with excellent functional group tolerance.

The success of the anionic chiral multidentate N,N,P-ligand in enabling the enantioconvergent radical $C(sp^3)-C(sp)$ cross-coupling encouraged us to develop more $C(sp^3)-C$ coupling of racemic alkyl electrophiles by expanding the scope of nucleophiles. We switched our attention to the easily available aryl boronate esters. However, the reported copper-catalyzed racemic $C(sp^3)-C$ coupling of alkyl halides with organoboronate esters proceeds via promiscuous mechanisms: a stereoablative radical process or a stereospecific S_N2 -type pathway with different stereochemical outcomes.^{51–53} As such, due to the electron-donating feature of the anionic chiral N,N,P-ligand, it is able to significantly enhance the reducing capability of the copper catalyst and tune the reaction toward a radical process, thus making it possible to achieve the enantioconvergent transformation. After systematically modifying the ligand structure, we have achieved the asymmetric

Scheme 8. Chiral Bisoxazoline-Derived N,N,N-Ligands in Asymmetric Radical C(sp³)-C Cross-Coupling and Alkene 1,2-Dicarbofunctionalization


radical Suzuki–Miyaura C(sp³)-C(sp²) cross-coupling of racemic alkyl halides with aryl boronate esters (Scheme 6).⁵⁴ More than 50 examples have been shown with up to 80% yield and 97% ee, demonstrating the generality of the reaction. The choice of the methylated acenaphthoquinone-derived boronate (B(mac)) esters and addition of H₂O are crucial to the success, possibly due to the enhancement of a transmetalation process. Both (hetero)benzyl and propargyl bromides and chlorides are applicable to the reaction, delivering enantioenriched 1,1-diaryllkanes, alkynes, and other chiral building blocks via a straightforward manipulation (Scheme 6). Mechanistically, a Cu^{III} complex or an outer-sphere radical substitution are both possible in the C(sp³)-C bond formation step (Scheme 1). Although the scope of aryl boronate esters is broad, the heteroaryl boronate esters provide a lower yield and ee.

The shortcoming of the Suzuki–Miyaura reaction in constructing the chiral heteroarenes forced us to look for more heteroarene-type nucleophiles, since this class of products has a common structural motif with many bioactive molecules and natural products. We then focused on the direct use of many azoles via their C–H functionalization, which represents a high atom and step economy. However, the use of a base at elevated temperature is generally inevitable in the racemic coupling of alkyl electrophiles with azole C(sp²)-H bonds,⁵⁵ which makes the asymmetric transformation challenging due to the easily occurring racemization of an α proton of the formed chiral alkylated azoles. To this end, we identified that the newly designed anionic chiral N,N,P-ligand could significantly reduce the reaction temperature of the coupling reaction by accelerating the oxidative addition step between Cu^I and alkyl halides. Therefore, we have developed a mild asymmetric radical C(sp³)-C(sp²) cross-coupling of racemic alkyl bromides with azole C(sp²)-H bonds under such chiral copper catalysis (Scheme 7).⁵⁶ Although the alkyl electrophiles are limited to benzyl bromides, the scope of azoles is quite broad and provides a range of enantioenriched α -chiral alkylated azoles, such as 1,3,4-oxadiazoles, oxazoles, and benzo[*d*]oxazoles as well as 1,3,4-triazoles with up to 85%

yield and 95% ee. Similar to the Suzuki–Miyaura reaction, the addition of H₂O also enhances the reaction efficiency, possibly due to the enhanced deprotonation of azoles and subsequent formation of a C–Cu bond.

Following the concept of anionic chiral ligand design, Zhang has recently demonstrated an asymmetric radical C(sp³)-C(sp) coupling of α -bromoamides with alkynes under a copper/chiral bisoxazoline diphenylalanine catalysis, delivering β,γ -alkynyl amides with high enantioselectivity (Scheme 8, top).⁵⁷ This type of chiral ligand, containing a central anionic nitrogen σ donor and two pendant lone-pair donors from nitrogen atoms in oxazoline, was first reported by Nakada in the chromium-catalyzed asymmetric Nozaki–Hiyama allylation-type reactions.^{58,59} The simple chiral bisoxazoline ligands are not effective for the cross-coupling reaction, showcasing the unique advantage of the chiral bisoxazoline-derived N,N,N-ligands. Two possible pathways involving either an inner-sphere Cu^{III} complex or an outer-sphere bond formation are proposed in the process. Despite the success, this copper/chiral N,N,N-ligand catalyst is only applicable to the coupling with the α -bromoamides, possibly due to the weaker reducing capability. In order to apply the catalytic system to more alkyl electrophiles, the same group has disclosed a copper-catalyzed asymmetric alkylation of azoles with secondary (hetero)benzyl bromides, wherein a visible light irradiation strategy is employed to initiate the reaction (Scheme 8, up).⁶⁰ In this strategy, they disclosed the dual role of the copper catalyst as both a photo and coupling catalyst, and thus no extra photocatalyst is necessary, illustrating the robustness of such a copper catalyst in the photoinduced C(sp³)-C coupling of alkyl electrophiles. The success of bisoxazoline-derived N,N,N-ligands in the enantiocontrol over the prochiral alkyl radical species also inspired Zhang to develop the three-component asymmetric radical 1,2-dicarbofunctionalization of alkenes. Using their chiral copper catalyst, they have accomplished several transformations, such as the 1,2-carboalkynylation and 1,2-carboazolation of alkenes (Scheme 8, below).^{61–63}

4. CONCLUSION AND PERSPECTIVES

Great efforts have been made in developing the chiral copper catalysis to accomplish asymmetric radical $C(sp^3)-C$ cross-coupling, providing a powerful tool in the synthesis of enantioenriched molecules in the past several years. Crucial to the success is the interaction of the *in situ* generated prochiral alkyl radical with $L^*Cu^{II}Nu$ to achieve enantiocontrol over the highly reactive radical species. In this Perspective, we have summarized the recent development of neutral chiral bisoxazoline ligands in the oxidative $C(sp^3)-C$ cross-coupling of $C(sp^3)-H$ bonds and the designed anionic chiral ligands in initiating the coupling of racemic alkyl electrophiles. It is noteworthy that the copper/chiral anionic ligand catalyst possesses a stronger reducing capability at the ground state and offers a suitable radical pathway in the copper-catalyzed enantioconvergent transformation of racemic alkyl electrophiles.

Despite significant progress in this rapidly developing research area, several challenges and opportunities remain in this area. (1) For the radical precursors, the chiral $C(sp^3)-C$ bond formation in copper-catalyzed radical reactions is still confined to certain positions, such as benzyl, allyl, propargyl, α -position of the carbonyl group, etc. More efforts are still needed to realize stereocontrol over the common prochiral alkyl radicals, such as the pure aliphatic radicals through the rational design of chiral ligands. (2) In most cases, only secondary alkyl electrophiles have been demonstrated and the application of tertiary substrates to forge the quaternary carbon centers has seldom been reported due to the steric crowdedness and the difficult enantiodifferentiation of three distinct carbon substituents of the prochiral tertiary radicals.^{64–66} The rational design of a chiral ligand possessing small substituents on the coordinating site to allow the formation of a quaternary carbon center might be a solution to this challenge.

With regard to the scope of nucleophiles, more efforts are still needed to expand many other organometallic reagents, such as organolithium⁶⁷ and organomagnesium,^{11,13,68} as well as the more promising organozinc,⁶⁹ organozirconium,^{70,71} and organosilicon reagents,⁷² given the functionality tolerance of the latter reagents. Moreover, the $C(sp^3)-C(sp^2)$ and $C(sp^3)-C(sp^3)$ cross-coupling with alkenyl and alkyl nucleophiles should also be addressed. The successful achievement of these cross-coupling reactions will constitute a powerful toolkit of copper catalysis in the assembly of enantioenriched molecules.

Finally, the mechanism is still unclear in many enantioconvergent $C(sp^3)-C$ cross-couplings of alkyl electrophiles, even though high levels of stereoselectivity has been achieved. A further in-depth mechanistic study by a combination of the control experiments and DFT calculations is necessary to fully understand the transformation and might open up new avenues in the chiral ligand design for asymmetric radical $C(sp^3)-C$ cross-coupling reactions. In addition, more structural information on copper intermediates and the stoichiometric transformations with these transient species are also awaited to reveal the mechanism and stereocontrol mode. Depending on the possible reductive elimination of the Cu^{III} complex and the outer-sphere radical substitution pathway,³⁷ the concept for ligand design might be different.

We believe that the concept introduced in this Perspective will inspire the design of more novel chiral ligands to address these challenges and realize more copper-catalyzed asymmetric

radical $C(sp^3)-C$ cross-coupling reactions. While the neutral bisoxazoline ligands have played an important role in copper-catalyzed oxidative $C(sp^3)-C$ cross-coupling, we have confidence that anionic chiral multidentate ligands would be more promising in the whole field on the basis of the following facts. (1) The enrichment of coordinating atoms (N, O, P, S) in the multidentate anionic ligands would easily tune the reducing capability of the copper catalyst for the initiation of reactions. (2) The abundance of privileged chiral skeletons (such as diamine, amino alcohol, cinchona, amino acid, axial skeleton, etc.) would provide more options in tuning the chiral environment of the copper catalyst. (3) The unique anionic moiety (amide, sulfonamide, amine, etc.) of these types of ligands could coordinate tightly with the copper center, forming a stable L^*Cu complex. Furthermore, this different anionic moiety may be beneficial to both the tuning of the reducing capability of copper and the chiral environment.

AUTHOR INFORMATION

Corresponding Author

Xin-Yuan Liu – Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, People's Republic of China; orcid.org/0000-0002-6978-6465; Email: liuxy3@sustech.edu.cn

Authors

Huan Zhou – Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, People's Republic of China

Zhong-Liang Li – Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, People's Republic of China

Qiang-Shuai Gu – Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, People's Republic of China; orcid.org/0000-0002-3840-425X

Complete contact information is available at:
<https://pubs.acs.org/10.1021/acscatal.1c01970>

Author Contributions

[§]H.Z. and Z.-L.L. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (Nos. 21831002 and 22025103), the Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), the Guangdong Innovative Program (No. 2019BT02Y335), the Shenzhen Special Funds (No. JCYJ20200109141001789), and the SUSTech Special Fund for the Construction of High-Level Universities (No. G02216303) is acknowledged.

REFERENCES

- (1) *Transition Metal Catalyzed Oxidative Cross-Coupling Reactions*; Lei, A., Ed.; Springer: Berlin, Germany, 2019; pp 1–192.
- (2) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review. *Chem. Rev.* **2018**, *118*, 2249–2295.

- (3) *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A., Bräse, S., Oestreich, M., Eds.; Wiley-VCH: Weinheim, Germany, 2014; pp 1–1066.
- (4) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.
- (5) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111*, 1417–1492.
- (6) Bullock, R. M.; Chen, J. G.; Gagliardi, L.; Chirik, P. J.; Farha, O. K.; Hendon, C. H.; Jones, C. W.; Keith, J. A.; Klosin, J.; Minter, S. D.; Morris, R. H.; Radosevich, A. T.; Rauchfuss, T. B.; Strotman, N. A.; Vojvodic, A.; Ward, T. R.; Yang, J. Y.; Surendranath, Y. Using Nature's Blueprint to Expand Catalysis with Earth-Abundant Metals. *Science* **2020**, *369*, eabc3183.
- (7) Choi, J.; Fu, G. C. Transition Metal–Catalyzed Alkyl-Alkyl Bond Formation: Another Dimension in Cross-Coupling Chemistry. *Science* **2017**, *356*, eaaf7230.
- (8) Fu, G. C. Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to S_N1 and S_N2 Processes. *ACS Cent. Sci.* **2017**, *3*, 692–700.
- (9) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents To Construct C–C Bonds. *Chem. Rev.* **2015**, *115*, 9587–9652.
- (10) Fischer, C.; Fu, G. C. Asymmetric Nickel-Catalyzed Negishi Cross-Couplings of Secondary α -Bromo Amides with Organozinc Reagents. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595.
- (11) Mao, J.; Liu, F.; Wang, M.; Wu, L.; Zheng, B.; Liu, S.; Zhong, J.; Bian, Q.; Walsh, P. J. Cobalt–Bisoxazoline-Catalyzed Asymmetric Kumada Cross-Coupling of Racemic α -Bromo Esters with Aryl Grignard Reagents. *J. Am. Chem. Soc.* **2014**, *136*, 17662–17668.
- (12) Huang, W.; Wan, X.; Shen, Q. Cobalt-Catalyzed Asymmetric Cross-Coupling Reaction of Fluorinated Secondary Benzyl Bromides with Lithium Aryl Boronates/ZnBr₂. *Org. Lett.* **2020**, *22*, 4327–4332.
- (13) Jin, M.; Adak, L.; Nakamura, M. Iron-Catalyzed Enantioselective Cross-Coupling Reactions of α -Chloroesters with Aryl Grignard Reagents. *J. Am. Chem. Soc.* **2015**, *137*, 7128–7134.
- (14) Tyrol, C. C.; Yone, N. S.; Gallin, C. F.; Byers, J. A. Iron-catalyzed enantioconvergent Suzuki–Miyaura cross-coupling to afford enantioenriched 1,1-diaryllalkanes. *Chem. Commun.* **2020**, *56*, 14661–14664.
- (15) Patten, T. E.; Matyjaszewski, K. Copper(I)-Catalyzed Atom Transfer Radical Polymerization. *Acc. Chem. Res.* **1999**, *32*, 895–903.
- (16) *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; Wiley: Hoboken, New Jersey, 2013; pp 1–840.
- (17) Trammell, R.; Rajabimoghadam, K.; Garcia-Bosch, I. Copper-Promoted Functionalization of Organic Molecules: from Biologically Relevant Cu/O₂ Model Systems to Organometallic Transformations. *Chem. Rev.* **2019**, *119*, 2954–3031.
- (18) Andrus, M. B.; Lashley, J. C. Copper Catalyzed Allylic Oxidation with Peresters. *Tetrahedron* **2002**, *58*, 845–866.
- (19) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036–2046.
- (20) Boyer, C.; Corrigan, N. A.; Jung, K.; Nguyen, D.; Nguyen, T.-K.; Adnan, N. N. M.; Oliver, S.; Shanmugam, S.; Yeow, J. Copper-Mediated Living Radical Polymerization (Atom Transfer Radical Polymerization and Copper(0) Mediated Polymerization): From Fundamentals to Bioapplications. *Chem. Rev.* **2016**, *116*, 1803–1949.
- (21) Zhang, C.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Catalytic Enantioselective C(sp³)-H Functionalization Involving Radical Intermediates. *Nat. Commun.* **2021**, *12*, 475.
- (22) Li, C.-J. Cross-Dehydrogenative Coupling (CDC): Exploring C–C Bond Formations beyond Functional Group Transformations. *Acc. Chem. Res.* **2009**, *42*, 335–344.
- (23) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Enantioselective Cyanation of Benzylic C–H Bonds via Copper-Catalyzed Radical Relay. *Science* **2016**, *353*, 1014–1018.
- (24) Li, J.; Zhang, Z.; Wu, L.; Zhang, W.; Chen, P.; Lin, Z.; Liu, G. Site-Specific Allylic C–H Bond Functionalization with a Copper-Bound N-Centred Radical. *Nature* **2019**, *574*, 516–521.
- (25) Zhang, W.; Wu, L.; Chen, P.; Liu, G. Enantioselective Arylation of Benzylic C–H Bonds by Copper-Catalyzed Radical Relay. *Angew. Chem., Int. Ed.* **2019**, *58*, 6425–6429.
- (26) Fu, L.; Chen, P.; Lin, Z.; Liu, G. Enantioselective Copper-Catalyzed Alkynylation of Benzylic C–H Bonds via Radical Relay. *J. Am. Chem. Soc.* **2020**, *142*, 12493–12500.
- (27) Zhang, Z.; Zhang, X.; Nagib, D. A. Chiral Piperidines from Acyclic Amines via Enantioselective, Radical-Mediated δ C–H Cyanation. *Chem.* **2019**, *5*, 3127–3134.
- (28) Zhang, Z.; Stateman, L. M.; Nagib, D. A. δ C–H (hetero)-Arylation via Cu-Catalyzed Radical Relay. *Chem. Sci.* **2019**, *10*, 1207–1211.
- (29) Bao, X.; Wang, Q.; Zhu, J. Dual Photoredox/Copper Catalysis for the Remote C(sp³)-H Functionalization of Alcohols and Alkyl Halides by N-Alkoxyppyridinium Salts. *Angew. Chem., Int. Ed.* **2019**, *58*, 2139–2143.
- (30) Cheng, Z.; Chen, P.; Liu, G. Enantioselective Cyanation of Remote C–H Bonds via Cooperative Photoredox and Copper Catalysis. *Acta Chim. Sin.* **2019**, *77*, 856–860.
- (31) Wang, C. Y.; Qin, Z. Y.; Huang, Y. L.; Hou, Y. M.; Jin, R. X.; Li, C.; Wang, X. S. Enantioselective Copper-Catalyzed Remote C(sp³)-H Alkynylation of Linear Primary Sulfonamides. *Org. Lett.* **2020**, *22*, 4006–4009.
- (32) Wang, C. Y.; Qin, Z. Y.; Huang, Y. L.; Jin, R. X.; Lan, Q.; Wang, X. S. Enantioselective Copper-Catalyzed Cyanation of Remote C(sp³)-H Bonds Enabled by 1,5-Hydrogen Atom Transfer. *iScience* **2019**, *21*, 490–498.
- (33) Chen, H.; Jin, W.; Yu, S. Enantioselective Remote C(sp³)-H Cyanation via Dual Photoredox and Copper Catalysis. *Org. Lett.* **2020**, *22*, 5910–5914.
- (34) Wang, D.; Zhu, N.; Chen, P.; Lin, Z.; Liu, G. Enantioselective Decarboxylative Cyanation Employing Cooperative Photoredox Catalysis and Copper Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 15632–15635.
- (35) Lu, F. D.; Liu, D.; Zhu, L.; Lu, L. Q.; Yang, Q.; Zhou, Q. Q.; Wei, Y.; Lan, Y.; Xiao, W. J. Asymmetric Propargylic Radical Cyanation Enabled by Dual Organophotoredox and Copper Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 6167–6172.
- (36) Chen, H.-W.; Lu, F.-D.; Cheng, Y.; Jia, Y.; Lu, L.-Q.; Xiao, W.-J. Asymmetric Deoxygenative Cyanation of Benzyl Alcohols Enabled by Synergistic Photoredox and Copper Catalysis. *Chin. J. Chem.* **2020**, *38*, 1671–1675.
- (37) Gu, Q.-S.; Li, Z.-L.; Liu, X.-Y. Copper(I)-Catalyzed Asymmetric Reactions Involving Radicals. *Acc. Chem. Res.* **2020**, *53*, 170–181.
- (38) Lin, J.-S.; Dong, X.-Y.; Li, T.-T.; Jiang, N.-C.; Tan, B.; Liu, X.-Y. A Dual-Catalytic Strategy To Direct Asymmetric Radical Amino-trifluoromethylation of Alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 9357–9360.
- (39) Cheng, Y.-F.; Dong, X.-Y.; Gu, Q.-S.; Yu, Z.-L.; Liu, X.-Y. Achiral Pyridine Ligand-Enabled Enantioselective Radical Oxytrifluoromethylation of Alkenes with Alcohols. *Angew. Chem., Int. Ed.* **2017**, *56*, 8883–8886.
- (40) Li, X.-T.; Gu, Q.-S.; Dong, X.-Y.; Meng, X.; Liu, X.-Y. A Copper Catalyst with a Cinchona-Alkaloid-Based Sulfonamide Ligand for Asymmetric Radical Oxytrifluoromethylation of Alkenyl Oximes. *Angew. Chem., Int. Ed.* **2018**, *57*, 7668–7672.
- (41) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. A New Family of Cinchona-Derived Amino Phosphine Precatalysts: Application to the Highly Enantio- and Diastereoselective Silver-Catalyzed Isocyanacetate Aldol Reaction. *J. Am. Chem. Soc.* **2011**, *133*, 1710–1713.

- (42) Dong, X.-Y.; Zhang, Y.-F.; Ma, C.-L.; Gu, Q.-S.; Wang, F.-L.; Li, Z.-L.; Jiang, S.-P.; Liu, X.-Y. A General Asymmetric Copper-Catalyzed Sonogashira C(sp³)-C(sp) Coupling. *Nat. Chem.* **2019**, *11*, 1158–1166.
- (43) Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalyzed Asymmetric Radical 1,2-Carboalkynylation of Alkenes with Alkyl Halides and Terminal Alkynes. *J. Am. Chem. Soc.* **2020**, *142*, 9501–9509.
- (44) Leophairatana, P.; Samanta, S.; De Silva, C. C.; Koberstein, J. T. Preventing Alkyne–Alkyne (i.e., Glaser) Coupling Associated with the ATRP Synthesis of Alkyne-Functional Polymers/Macromonomers and for Alkynes under Click (i.e., CuAAC) Reaction Conditions. *J. Am. Chem. Soc.* **2017**, *139*, 3756–3766.
- (45) Xia, H.-D.; Li, Z.-L.; Gu, Q.-S.; Dong, X.-Y.; Fang, J.-H.; Du, X.-Y.; Wang, L.-L.; Liu, X.-Y. Photoinduced Copper-Catalyzed Asymmetric Decarboxylative Alkynylation with Terminal Alkynes. *Angew. Chem., Int. Ed.* **2020**, *59*, 16926–16932.
- (46) Zhang, Z.-H.; Dong, X.-Y.; Du, X.-Y.; Gu, Q.-S.; Li, Z.-L.; Liu, X.-Y. Copper-Catalyzed Enantioselective Sonogashira-Type Oxidative Cross-Coupling of Unactivated C(sp³)-H Bonds with Alkynes. *Nat. Commun.* **2019**, *10*, 5689.
- (47) Giese, B. Formation of CC Bonds by Addition of Free Radicals to Alkenes. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753–764.
- (48) Li, Z.-L.; Fang, G.-C.; Gu, Q.-S.; Liu, X.-Y. Recent Advances in Copper-Catalyzed Radical-Involved Asymmetric 1,2-Difunctionalization of Alkenes. *Chem. Soc. Rev.* **2020**, *49*, 32–48.
- (49) Dong, X.-Y.; Zhan, T.-Y.; Jiang, S.-P.; Liu, X.-D.; Ye, L.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalyzed Asymmetric Coupling of Allenyl Radicals with Terminal Alkynes to Access Tetrasubstituted Allenes. *Angew. Chem., Int. Ed.* **2021**, *60*, 2160–2164.
- (50) Almost at the same time, Bao and Zhang reported similar work with a chiral copper/bisoxazoline ligand: Zeng, Y.; Chiou, M.; Zhu, X.; Cao, J.; Lv, D.; Jian, W.; Li, Y.; Zhang, X.; Bao, H. Copper-Catalyzed Enantioselective Radical 1,4-Difunctionalization of 1,3-Enynes. *J. Am. Chem. Soc.* **2020**, *142*, 18014–18021.
- (51) Wang, G.-Z.; Jiang, J.; Bu, X.-S.; Dai, J.-J.; Xu, J.; Fu, Y.; Xu, H.-J. Copper-Catalyzed Cross-Coupling Reaction of Allyl Boron Ester with 1°/2°/3°-Halogenated Alkanes. *Org. Lett.* **2015**, *17*, 3682–3685.
- (52) Sun, Y.-Y.; Yi, J.; Lu, X.; Zhang, Z.-Q.; Xiao, B.; Fu, Y. Cu-Catalyzed Suzuki–Miyaura reactions of primary and secondary benzyl halides with arylboronates. *Chem. Commun.* **2014**, *50*, 11060–11062.
- (53) Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. Copper-Catalyzed Cross-Coupling Reaction of Organoboron Compounds with Primary Alkyl Halides and Pseudohalides. *Angew. Chem., Int. Ed.* **2011**, *50*, 3904–3907.
- (54) Jiang, S.-P.; Dong, X.-Y.; Gu, Q.-S.; Ye, L.; Li, Z.-L.; Liu, X.-Y. Copper-Catalyzed Enantioconvergent Radical Suzuki–Miyaura C(sp³)-C(sp²) Cross-Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 19652–19659.
- (55) Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. Copper-Catalyzed Alkylation of Benzoxazoles with Secondary Alkyl Halides. *Org. Lett.* **2012**, *14*, 1748–1751.
- (56) Su, X.-L.; Ye, L.; Chen, J.-J.; Liu, X.-D.; Jiang, S.-P.; Wang, F.-L.; Liu, L.; Yang, C.-J.; Chang, X.-Y.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalyzed Enantioconvergent Cross-Coupling of Racemic Alkyl Bromides with Azole C(sp²)-H Bonds. *Angew. Chem., Int. Ed.* **2021**, *60*, 380–384.
- (57) Mo, X.; Chen, B.; Zhang, G. Copper-Catalyzed Enantioselective Sonogashira Type Coupling of Alkynes with α -Bromoamides. *Angew. Chem., Int. Ed.* **2020**, *59*, 13998–14002.
- (58) Inoue, M.; Suzuki, T.; Nakada, M. Asymmetric Catalysis of Nozaki–Hiyama Allylation and Methallylation with a New Tridentate Bis(oxazolonyl)carbazole Ligand. *J. Am. Chem. Soc.* **2003**, *125*, 1140–1141.
- (59) Deng, Q.-H.; Melen, R. L.; Gade, L. H. Anionic Chiral Tridentate N–Donor Pincer Ligands in Asymmetric Catalysis. *Acc. Chem. Res.* **2014**, *47*, 3162–3173.
- (60) Li, C.; Chen, B.; Ma, X.; Mo, X.; Zhang, G. Light-Promoted Copper-Catalyzed Enantioselective Alkylation of Azoles. *Angew. Chem., Int. Ed.* **2021**, *60*, 2130–2134.
- (61) Lei, G.; Zhang, H.; Chen, B.; Xu, M.; Zhang, G. Copper-Catalyzed Enantioselective Arylalkynylation of Alkenes. *Chem. Sci.* **2020**, *11*, 1623–1628.
- (62) Zhang, Y.; Sun, Y.; Chen, B.; Xu, M.; Li, C.; Zhang, D.; Zhang, G. Copper-Catalyzed Photoinduced Enantioselective Dual Carbofunctionalization of Alkenes. *Org. Lett.* **2020**, *22*, 1490–1494.
- (63) Ma, X.; Zhang, G. Asymmetric Alkyl and Aryl/Azolation of Alkenes via a Single Cu(I) Complex. *ACS Catal.* **2021**, *11*, 5108–5118.
- (64) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C–N Cross-Couplings Induced by Visible Light. *Science* **2016**, *351*, 681–684.
- (65) Wu, L.; Wang, F.; Chen, P.; Liu, G. Enantioselective Construction of Quaternary All-Carbon Centers via Copper-Catalyzed Arylation of Tertiary Carbon-Centered Radicals. *J. Am. Chem. Soc.* **2019**, *141*, 1887–1892.
- (66) Wu, L.; Zhang, Z.; Wu, D.; Wang, F.; Chen, P.; Lin, Z.; Liu, G. Anionic Bisoxazoline Ligands Enable Copper-Catalyzed Asymmetric Radical Azidation of Acrylamides. *Angew. Chem., Int. Ed.* **2021**, *60*, 6997–7001.
- (67) Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. Catalytic Asymmetric Carbon–Carbon Bond Formation via Allylic Alkylations with Organolithium Compounds. *Nat. Chem.* **2011**, *3*, 377–381.
- (68) Lou, S.; Fu, G. C. Nickel/Bis(oxazoline)-Catalyzed Asymmetric Kumada Reactions of Alkyl Electrophiles: Cross-Couplings of Racemic α -Bromoketones. *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266.
- (69) Fischer, C.; Fu, G. C. Asymmetric Nickel-Catalyzed Negishi Cross-Couplings of Secondary α -Bromo Amides with Organozinc Reagents. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595.
- (70) Lou, S.; Fu, G. C. Enantioselective Alkenylation via Nickel-Catalyzed Cross-Coupling with Organozirconium Reagents. *J. Am. Chem. Soc.* **2010**, *132*, 5010–5011.
- (71) You, H.; Rideau, E.; Sidera, M.; Fletcher, S. P. Non-Stabilized Nucleophiles in Cu-Catalyzed Dynamic Kinetic Asymmetric Allylic Alkylation. *Nature* **2015**, *517*, 351–355.
- (72) Dai, X.; Strotman, N. A.; Fu, G. C. Catalytic Asymmetric Hiyama Cross-Couplings of Racemic α -Bromo Esters. *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303.