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Perspective

Ligand Development for Copper-Catalyzed Enantioconvergent Radical Cross-Coupling of Racemic Alkyl Halides

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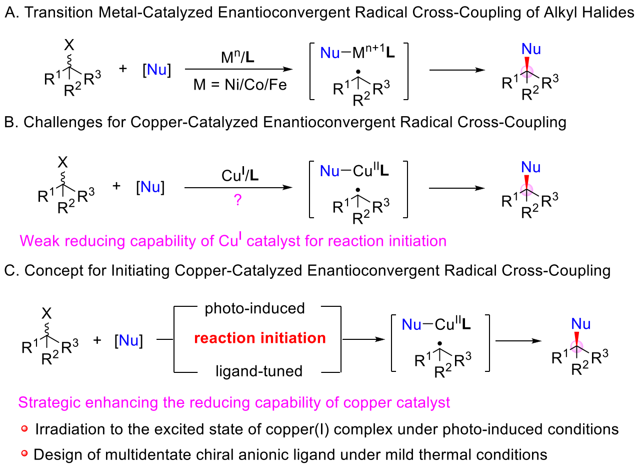
ABSTRACT: The enantioconvergent cross-coupling of racemic alkyl halides represents a powerful tool for the synthesis of enantioenriched molecules. In this regard, the first-row transition metal catalysis provides a suitable mechanism for stereoconvergence by converting racemic alkyl halides to prochiral radical intermediates owing to their good single-electron transfer ability. In contrast to the noble development of chiral nickel catalyst, copper-catalyzed enantioconvergent radical cross-coupling of alkyl halides is less studied. Besides the enantiocontrol issue, the major challenge arises from the weak reducing capability of copper that slows the reaction initiation. Recently, significant efforts have been dedicated to basic research aimed at developing chiral ligands for copper-catalyzed enantioconvergent radical cross-coupling of racemic alkyl halides. This perspective will discuss the advances in this burgeoning area with particular emphasis on the strategic chiral anionic ligand design to tune the reducing capability of copper for the reaction initiation under thermal conditions from our research group.

1. INTRODUCTION

Transition metal-catalyzed cross-coupling serves as a prevailing and modular toolkit for the construction of target molecules and plays a pivotal role in synthetic chemistry, drug discovery, and material sciences.[1,2] As such, tremendous progress has been made in the past several decades in the cross-coupling of aryl/alkenyl (pseudo)halides for the construction of $C(sp^2)-C/X$ bonds.[3] As an analogy, the $C(sp^3)-C/X$ cross-coupling of alkyl (pseudo)halides could offer an important complementary approach to classic nucleophilic substitutions in the construction of sp^3-hybridized carbon centers. Particularly, the development of enantioconvergent $C(sp^3)-C/X$ cross-coupling of racemic alkyl halides would provide enantioenriched three-dimensional molecular frameworks and further expand its utilities in organic synthesis.[4]

However, several daunting challenges exist: (i) the difficult oxidative addition of alkyl halides compared with aryl/alkenyl halides; (ii) the lack of strategic enantioconvergent transformations of diverse racemic alkyl halides since the classic oxidative addition with palladium, the most frequently used transition metal, is generally accepted as a concerted insertion process.[5] In this context, first-row transition metals (Fe, Co, Ni, and Cu) possess good single-electron transfer (SET) ability and easily convert a pair of racemic alkyl electrophiles to the same prochiral alkyl radical intermediate.[6] Thus, they offer an ideal solution for the above-mentioned challenges from two aspects. First, the thus forming transition metals easily combined with the generated alkyl radicals to smoothly achieve the oxidative addition of alkyl halides.[6] Second, the interaction of a chiral transition metal catalyst with the prochiral alkyl radicals could afford a single enantiomer of the coupling product, thus providing a uniform mechanism for the enantioconvergent transformations (Scheme 1A).[7] Fu and others have pioneered this field by designing chiral nickel, cobalt, and iron catalysts to achieve an array of efficient enantioconvergent radical $C(sp^3)-C$ cross-coupling of readily available alkyl halides dating from 2005.[6,8] Notably, the nucleophiles are mainly focused on carbon-based organometallics (B, Mg, Si, Zn, Zr, etc.) reagents and most of the alkyl halides are secondary ones with activating or directing groups.[8] The utilization of heteroatom-based nucleophiles or

Scheme 1. Strategic Design of Copper-Catalyzed Enantioconvergent Radical Cross-Coupling of Alkyl Halides



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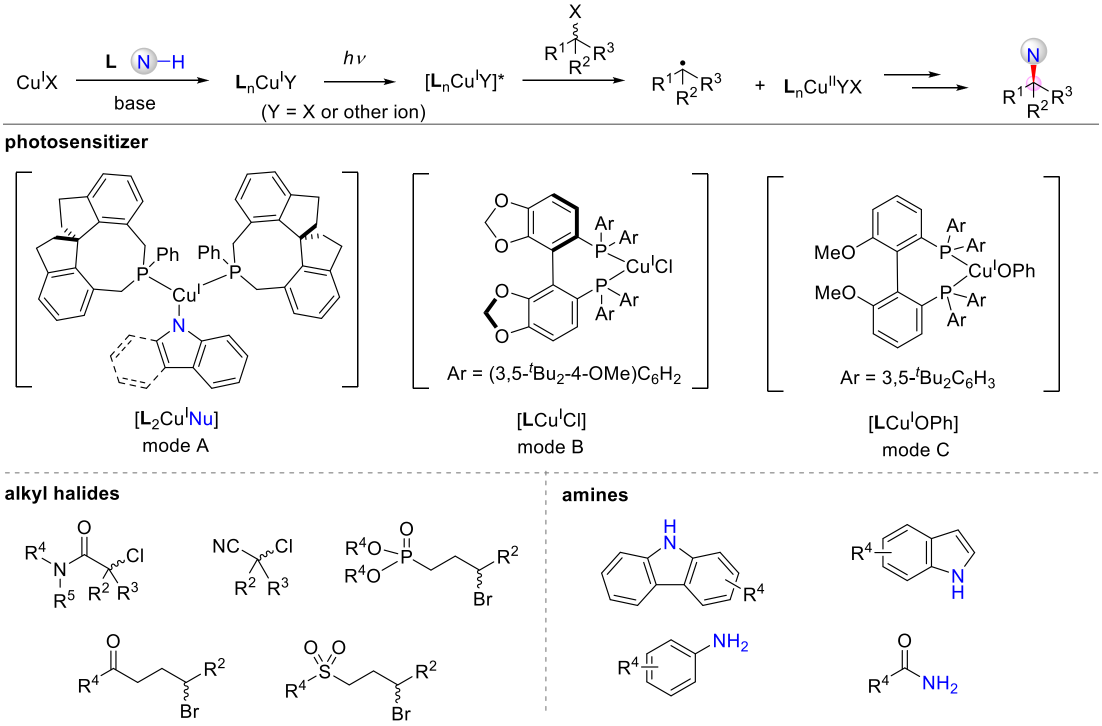
Scheme 2. Initiation Modes of Photoinduced Enantioconvergent Radical Cross-Coupling



sterically bulky tertiary alkyl halides[9] is less explored at the early stage. Therefore, it is necessary to develop more chiral first-row transition metal catalysis to expand the scope of the enantioconvergent radical cross-coupling.

Copper is an earth-abundant first-row transition metal,[10] and the metalloradical Cu^{II} complex could easily interact with alkyl radicals to forge new chemical bonds.[11] Moreover, a series of copper-catalyzed radical asymmetric reactions of alkanes and alkenes have been developed to form chiral $C(sp^3)-C/X$ bonds through the addition of chiral ligands, such as chiral bisoxazolines, phosphoric acids, etc.[12] In comparison, the enantioconvergent cross-coupling of racemic alkyl halides has been less developed. The major challenge lies in the weaker reducing capability of copper compared with that of nickel/cobalt/iron catalysts at the ground state (Scheme 1B).[13] This factor renders the reaction initiation quite difficult, thus impeding the development of copper-catalyzed enantioconvergent radical $C(sp^3)-C/X$ cross-coupling under mild thermal conditions. To surmount the challenging reaction initiation, Fu, Peters, and our research group have conceptually designed different strategies to enhance the reducing capability of copper catalyst for gentle initiation of the enantioconvergent process, respectively (Scheme 1C). The purpose of this Perspective is to briefly summarize the enantioconvergent transformation under photoinduced conditions from the groups of Fu and Peters. More importantly, chiral anionic ligands provide an inherently enhanced reducing capacity for copper under thermal conditions, making it possible to cover many types of nucleophiles in the cross-coupling. Consequently, we will introduce the strategic development of multidentate chiral anionic ligands from our group to initiate the enantioconvergent transformations under thermal conditions. At last, a summary and outlook would be given for the emerging field.

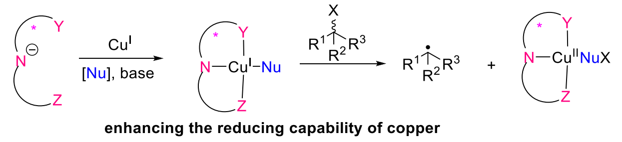
2. PHOTOINDUCED ENANTIOCONVERGENT RADICAL CROSS-COUPLING

Due to the weak reducing capability of copper catalyst, it can hardly activate the strong C−X bond of racemic alkyl halides and generate prochiral alkyl radicals under mild thermal conditions.[14] In the past decades, photocatalysis has found broad application in organic synthesis since it easily delivers the radical intermediate *via* an SET process between a photocatalyst of a long excited-state lifetime and relatively redox-inert substrates.[15] As such, Fu and Peters have reported several photoinduced copper-catalyzed achiral C−C/X cross-coupling,[16] wherein the excited state of the copper complex was demonstrated to act as the photocatalyst to reduce organohalides to radical species.[17] They further accomplished the enantioconvergent C−N cross-coupling of racemic tertiary alkyl halides with carbazoles and indoles under photoinduced conditions in 2016.[18] Mechanistically, it is the nucleophile-sequestered copper(I) complex $(\mathbf{L})_2Cu^INu$ that is irradiated to its excited state with the aid of visible light, featuring a highly reducing capability. This excited photocatalyst reduces racemic alkyl halides to prochiral alkyl radicals (Scheme 2, mode A). As for the C−N formation step, they recently proposed that it is through the interaction of the *in situ* generated $\mathbf{L}Cu^{II}Nu_2$ (*via* ligand exchange with an additional carbazole or indole) with tertiary alkyl radicals adjacent to the carbonyl group.[19] Afterward, they found that DTBM-SEGPHOS-chelated copper(I) complex $\mathbf{L}Cu^ICl$ could act as a photocatalyst to accomplish an enantioconvergent radical alkylation of anilines with racemic tertiary alkyl halides (Scheme 2, mode B).[20] Meanwhile, Fu and Peters accomplished a general enantioconvergent amidation of unactivated secondary alkyl bromides.[21] It is important to mention that two catalytic cycles are merged in this reaction: while $\mathbf{L}Cu^IOPh$ served as the photocatalyst (Scheme 2, mode C), the enantioselective C−N formation step was mediated by a chiral diamine ligandchelated copper complex. Employing the photoinduced strategy, Zhang et al. also reported a copper-catalyzed enantioconvergent radical C(sp^3)−C(sp^2) cross-coupling of secondary (hetero)benzyl bromides with azoles.[22] Their mechanistic study showed that the nucleophile-sequestered copper complex serves as the photoactive species for the reaction initiation.

3. CHIRAL ANIONIC LIGANDS-TUNED ENANTIOCONVERGENT RADICAL CROSS-COUPLING UNDER MILD THERMAL CONDITIONS

Owing to the weak reducing capability of copper catalyst, Fu and Peters have elegantly designed the photoactive copper catalyst to smoothly initiate the reaction under UV light irridation.[16,17] Several enantioconvergent radical C(sp^3)−C/N cross-coupling reactions of alkyl halides have been further realized under visible light irridation.[18−21] It should be noted that the association of suitable nucleophiles to $\mathbf{L}_n$Cu^I is necessary for the catalyst to be photoactive in some cases.[18] Under this circumstance, the photoactive property of a $\mathbf{L}_n$Cu^{I}Nu complex depended greatly on the nucleophiles, which may raise compatibility issues in the further exploration of more nucleophiles. Theoretically, the proper design of an electron-rich chiral ligand to enhance the reducing capability of copper would provide an alternative solution for the enantioconvergent transformation of alkyl halides *via* a halogen atom transfer process under mild thermal conditions.[23] As such, we think a multidentate anionic chiral ligand would be helpful in that it not only significantly enhances the reducing capability of copper catalyst for reaction initiation but also provides a rigid chiral environment for enantiocontrol. Moreover, the multidentate architecture of the ligand may also help to suppress the easily occurring oxidative homocoupling of nucleophiles by coordinatively saturating the copper catalyst (Scheme 3).[24] In this section, we will mainly introduce our conceptual design in developing the enantioconvergent radical cross-coupling under thermal conditions.

Scheme 3. Initiation Modes of Chiral Anionic Ligands-Tuned Enantioconvergent Transformations



Chiral Anionic Tridentate *N,N,P*-Ligands. Dating from 2019, we have designed a library of cinchona alkaloid-derived tridentate anionic *N,N,P*-ligands[25] with different steric and electronic properties on the *P*-substituents based on the above-mentioned conceptual ligand design. A subsequent study showed that the bridgehead tertiary amine, anionic amide as well as the electron-rich phosphine coordination motif would coordinate with copper to form the tridentate copper complex **I** (Figure 1).[26] The redox potential of **L1**CuBr (−0.1 V) is lower than that of CuBr (+0.6 V) according to the cyclic voltammogram study, demonstrating that this coordination mode significantly enhanced the reducing capability of copper catalyst (Figure 1).[26] Moreover, the redox potential of **L1**CuBr is also lower than that of the commonly used copper/chiral bisoxazoline catalyst (+0.2 V),[12a,27] and this is supposed to be beneficial to the reaction initiation process.

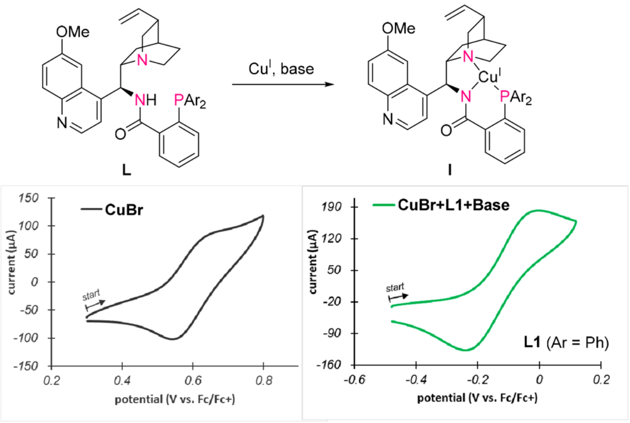
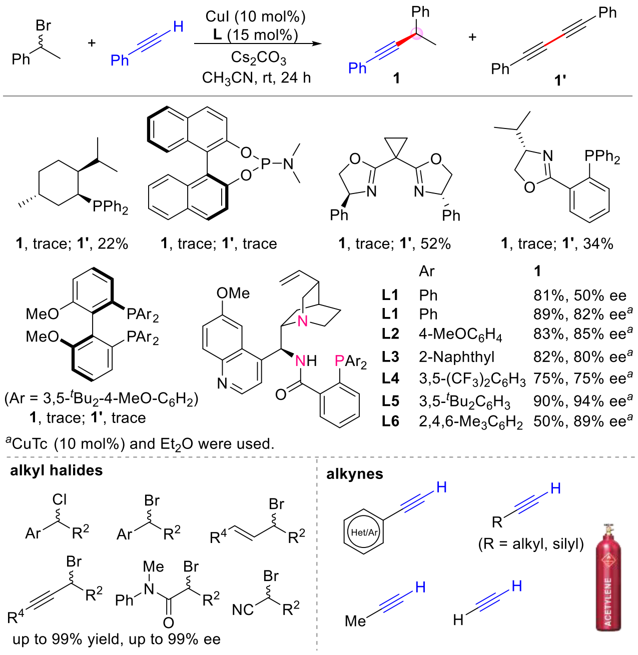


Figure 1. Coordination mode and cyclic voltammogram study.

With this copper/chiral ligand in hand, we first investigated the enantioconvergent radical C(sp^3)−C(sp) cross-coupling of racemic secondary alkyl halides with alkynes, which would provide chiral alkyne motifs of interest in organic synthesis and medicinal chemistry. Before our discovery, a general enantioconvergent transformation of racemic alkyl halides other than allylic ones has been rarely presented. As for copper-catalyzed transformation, the major challenges arise from the weakly reducing capability for the reaction initiation and the easily occurring Glaser homocoupling. This could be seen from our investigation of the commercially available chiral ligands: the mono- and bidentate chiral ligands afforded a trace amount of the coupling product **1** together with the Glaser homocoupling product **1′** in some cases (Scheme 4).[28] Only the tridentate *N,N,P*-ligand **L1** promoted the coupling process with no generation of the Glaser homocoupling product. The subsequent ligand investigation revealed that steric bulkiness

Scheme 4. Ligand Effect and Scope of Enantioconvergent Radical C(sp^3)−C(sp) Cross-Coupling



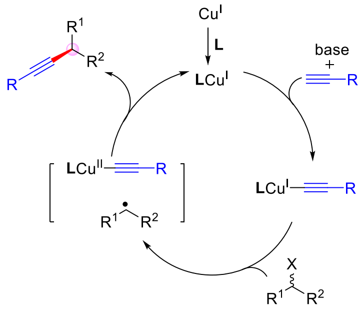
	Ar	1
L1	Ph	81%, 50% ee
L1	Ph	89%, 82% ee[a]
L2	4-MeOC$_6$H$_4$	83%, 85% ee[a]
L3	2-Naphthyl	82%, 80% ee[a]
L4	3,5-(CF$_3$)$_2$C$_6$H$_3$	75%, 75% ee[a]
L5	3,5-^{t}Bu$_2$C$_6$H$_3$	90%, 94% ee[a]
L6	2,4,6-Me$_3$C$_6$H$_2$	50%, 89% ee[a]

[a] CuTc (10 mol%) and Et$_2$O were used.

on the *meta* (**L5**, 3,5-di-*tert*-butyl substituents) or *ortho* (**L6**, 2,4,6-trimethyl substituents) positions of *P*-aryl rings is beneficial for the enantioselectivity and **L5** provided the best result (Scheme 4). The scope of alkyl halides is very broad, covering benzyl chlorides and bromides, allyl bromides, propargyl bromides, α-bromo amides, and α-bromo nitrile, to afford the coupling products with up to 99% ee. As for the scope of alkynes, the industrially relevant acetylene and propyne are suitable for the reactions in addition to (hetero)aryl and alkyl alkynes, showing the potential industrial application (Scheme 4).[28]

Based on the mechanistic study, we postulated a possible pathway: Cu$^{\rm I}$, **L**, and alkyne first reacted to afford a complex **L**Cu$^{\rm I}$Nu, which possessed a high reducing capability (Scheme 5). This complex easily reduced the racemic alkyl halides to afford a prochiral alkyl radical species and a **L**Cu$^{\rm II}$Nu complex probably *via* a halogen atom transfer process. Finally, the interaction of **L**Cu$^{\rm II}$Nu with the prochiral alkyl radical would furnish the chiral C(sp^3)−C(sp) bond and releases the **L**Cu$^{\rm I}$Nu species *via* either an inner-sphere Cu$^{\rm III}$ complex or an outer-sphere radical substitution pathway, which is still under investigation in our laboratory. As the enantiodetermining process is probably *via* the interaction of **L**Cu$^{\rm II}$Nu with the prochiral alkyl radicals, it inspired us to apply the enantiocontrol model to other related radical reactions.

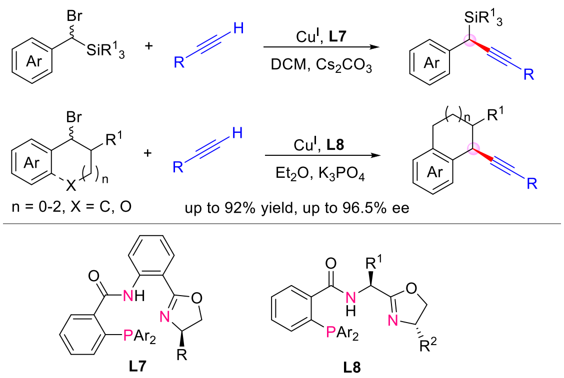
Scheme 5. Possible Mechanism for the Enantioconvergent Cross-Coupling



Utilizing the anionic chiral ligand effect, Zhang et al. recently reported an enantioconvergent radical cross-coupling of racemic alkyl halides with alkynes.[29] An oxazoline-derived ligand (**L7**) similar to that reported by our group[30] was employed to realize the enantioconvergent transformation of α-silyl benzyl halides (Scheme 6). More significantly, an extra chiral center was strategically introduced into the bridge of chiral anionic *N,N,P*-ligands connecting the 2-diphenylphosphinobenzamide and oxazoline moieties (**L8**). This type of ligands was successfully applied to the coupling of benzo-fused cyclic α-halides that proved to be challenging in previous works.[28] They also demonstrated the role of this type of anionic chiral *N,N,P*-ligand on both enhancing the reducing capability of copper and achieving the enantiocontrol.

Utilizing the same copper/*N,N,P*-ligand catalyst, we have achieved a series of asymmetric radical alkynylation, such as decarboxylative alkynylation,[31] 1,2-carboalkynylation of alkenes,[26] 1,4-carboalkynylation of 1,3-enyens,[32] C(sp^3)−H alkynylation *via* an intramolecular 1,5(6)-hydrogen atom abstraction (HAA),[33] etc. More recently, we have realized an intermolecular C(sp^3)−H alkynylation through the design of a new type of oxazoline-derived *N,N,P*(*O*)-ligands that tolerate strong oxidative conditions required for an intermolecular HAA.[30] In all these transformations, the key enantiodetermining step is the interaction of **L**Cu$^{\rm II}$Nu with an *in situ* generated prochiral alkyl radicals (Scheme 5). It should be emphasized that the pathway also serves as an important mechanistic guidance for our development of enantioconvergent cross-coupling with other nucleophiles.

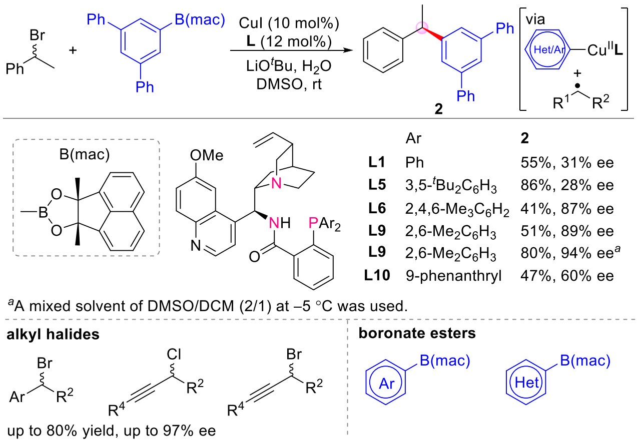
Scheme 6. Zhang's Enantioconvergent Radical C(sp^3)−C(sp) Cross-Coupling



The Suzuki−Miyaura cross-coupling is one of the most widely used strategies for the construction of C−C bonds owing to the stability, availability, and low toxicity of organoboron reagents. As such, we next switched our attention to the enantioconvergent radical C(sp^3)−C(sp^2) cross-coupling. As reported in the literature, two possible mechanisms are involved in the achiral copper-catalyzed C(sp^3)−C coupling of alkyl halides with organoboronate esters: a radical pathway and an S$_{\rm N}$2-type pathway.[34] While the former provides a solution for the enantioconvergent transformation, the latter can only lead to a kinetic resolution outcome in case that the alkyl halide racemates are hard to epimerize.[4a] Theoretically, the employment of electron-rich chiral *N,N,P*-ligands would tune the reaction into a radical pathway by enhancing the reducing capability of the copper catalyst, paving the way for enantioconvergent transformation. Our initial study showed that the chiral *N,N,P*-ligand **L1** is effective for the C(sp^3)−C(sp^2) cross-coupling of benzyl bromide with arylboronate ester after carefully choosing the suitable base and solvent (Scheme 7).[35] In contrast to the coupling with alkynes, the ligand investigation suggested a slightly different trend for enantioselectivity. While **L1** provided a low enantioselectivity, the steric bulkiness on the *ortho* positions (**L6**, **L9**, **L10**) rather than the *meta* positions (**L5**) had a remarkably positive influence on the enantioselectivity (Scheme 7). Mechanistic studies illustrated the enantioconvergent radical nature of the reaction, showcasing the powerfulness of the copper/chiral *N,N,P*-ligand system. The scope of alkyl halides includes (hetero)benzyl bromides and propargyl chlorides and bromides. As for the scope of organoboronate esters, arylboronate esters afford excellent enantioselectivities (up to 97% ee).[35] The heteroarylboronate esters only result in moderate enantioselectivities, which prompted us to put more endeavors into this field.

Azoles are a class of heteroaryl structural motifs in many bioactive molecules and possess an acidic C(sp^2)−H bond that easily undergoes transmetalation with the copper catalyst in the presence of a base. This property renders the enantioconvergent cross-coupling with azoles possible, which

Scheme 7. Enantioconvergent Radical Suzuki–Miyaura $C(sp^3)-C(sp^2)$ Cross-Coupling

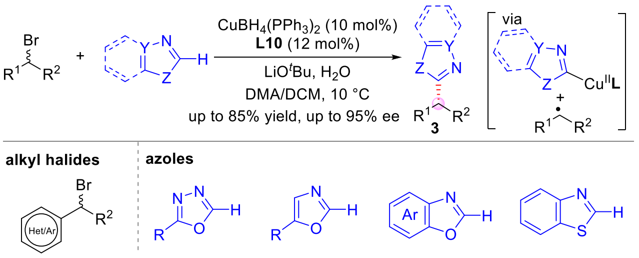


	Ar	2
L1	Ph	55%, 31% ee
L5	3,5-^{t}Bu$_2$C$_6$H$_3$	86%, 28% ee
L6	2,4,6-Me$_3$C$_6$H$_2$	41%, 87% ee
L9	2,6-Me$_2$C$_6$H$_3$	51%, 89% ee
L9	2,6-Me$_2$C$_6$H$_3$	80%, 94% ee[a]
L10	9-phenanthryl	47%, 60% ee

[a] A mixed solvent of DMSO/DCM (2/1) at −5 °C was used.

is also necessary considering the moderate enantioselectivity of the corresponding coupling with heteroarylboronate esters.[35] Notably, the literature reported cross-coupling of alkyl halides with azoles generally proceeds at a high temperature and the use of base at this circumstance easily leads to racemization of the α proton of the formed chiral alkylated azoles.[36] The strong reducing capability of the copper/chiral *N,N,P*-ligand catalyst could enable the transformation under mild conditions, thus suppressing the racemization process. As such, we have successfully applied the catalyst to the enantioconvergent radical $C(sp^3)-C(sp^2)$ cross-coupling of benzyl bromides with azoles under similar conditions as that of Suzuki–Miyaura coupling to provide a wide array of chiral azoles (Scheme 8).[37]

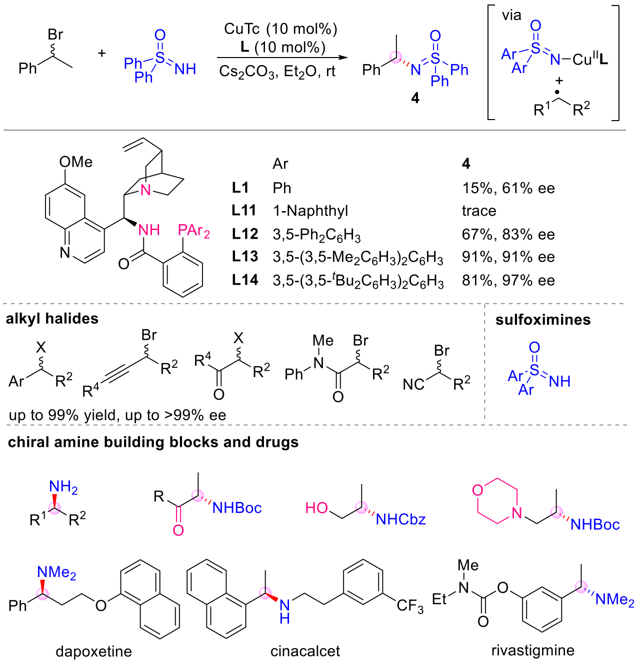
Scheme 8. Enantioconvergent Radical $C(sp^3)-C(sp^2)$ Cross-Coupling with Azoles



The reaction covers a lot of azoles, such as 1,3,4-oxadiazoles, oxazoles, and benzo[*d*]oxazoles as well as 1,3,4-triazoles with up to 95% ee. Nonetheless, the scope of alkyl halides is restricted to (hetero)benzyl bromides.

Chiral amines are important structural motifs in organic synthesis, pharmaceuticals as well as many other disciplines. As such, we were intrigued to apply our developed copper/chiral *N,N,P*-ligand catalytic system to the enantioconvergent radical $C(sp^3)-N$ cross-coupling of alkyl halides for expedient assembly of chiral amines. The choosing of amine sources is crucial to the transformation: (i) the deprotonated form and its complex with copper(I) should be free of S_N2 alkylation with secondary alkyl halides; (ii) the chiral environment of amine-sequestered $LCu^{II}Nu$ complex should be compatible with the prochiral alkyl radicals for good enantiocontrol. We finally identified diaryl sulfoximines[38] as the amine sources and achieved an enantioconvergent radical $C(sp^3)-N$ cross-coupling with diverse secondary alkyl halides under thermal conditions (Scheme 9).[39] Notably, both the reaction efficiency and enantioselectivity were strongly affected by the electronic and steric properties of the *meta* substituents on the *P*-aryl rings of *N,N,P*-ligands. The steric crowded ligand **L13** and **L14** gave rise to the coupling product with satisfactory yields and ee. Our investigation of a wide array of secondary alkyl halides, such as (hetero)benzyl halides, propargyl bromides, α-bromo ketones, α-bromo nitriles as well as α-bromo amides is suitable for the coupling reaction to afford diverse α-chiral sulfoximines. A general trend was also identified for these two ligands: the bulkier ligand **L14** proved to be effective for less steric crowded alkyl halides and the less bulky one **L13** worked well for sterically crowded substrates. Further follow-up transformations of the products have led to a range of common chiral N-containing building blocks, such as simple amines, α-amino ketones, 1,2-amino alcohols, 1,2-diamines, etc. The strategy also provides an expedient tool for the synthesis of N-containing chiral drugs, such as dapoxetine, cinacalcet as well as rivastigmine (Scheme 9).

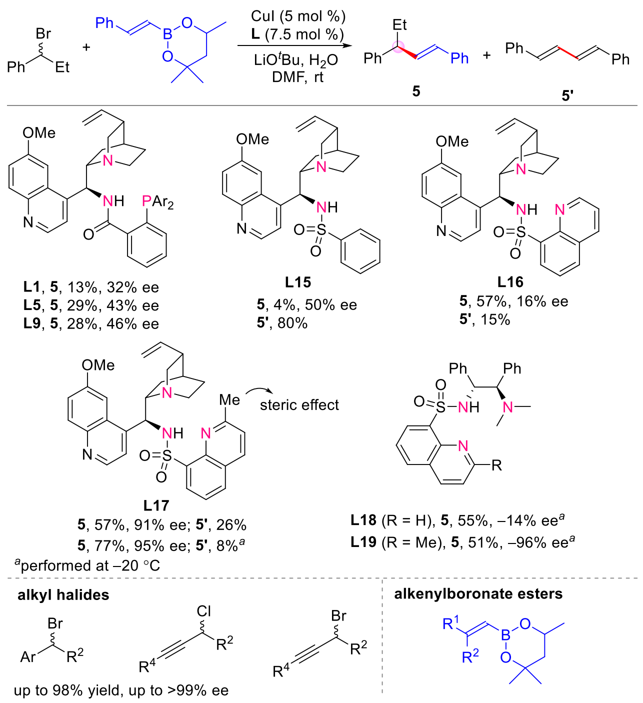
Scheme 9. Enantioconvergent Radical $C(sp^3)-N$ Cross-Coupling



	Ar	4
L1	Ph	15%, 61% ee
L11	1-Naphthyl	trace
L12	3,5-Ph$_2$C$_6$H$_3$	67%, 83% ee
L13	3,5-(3,5-Me$_2$C$_6$H$_3$)$_2$C$_6$H$_3$	91%, 91% ee
L14	3,5-(3,5-^{t}Bu$_2$C$_6$H$_3$)$_2$C$_6$H$_3$	81%, 97% ee

Hemilabile Chiral Anionic *N,N,N*-Ligands. The powerfulness of chiral *N,N,P*-ligands enabled us to develop a series of enantioconvergent $C(sp^3)-C$ cross-coupling with alkynes, arylboronate esters as well as azoles, etc. Notably, this catalytic system proved to be less effective for the enantioconvergent coupling with alkenylboronate esters due to the different enantiocontrol model between alkenylcopper and that of alkynyl- or (hetero)arylcopper complexes (Scheme 10). Therefore, a new type of chiral ligand scaffolds should be developed for such a transformation. Recently, we have identified a type of hemilabile *N,N,N*-ligands for realizing the challenging reactions, and the ligand exhibits unique features: (i) it enhances the reducing capability of copper catalyst in the tridentate form and initiates the radical cross-coupling process; (ii) it delivers an excellent enantiocontrol in the $C(sp^3)-$

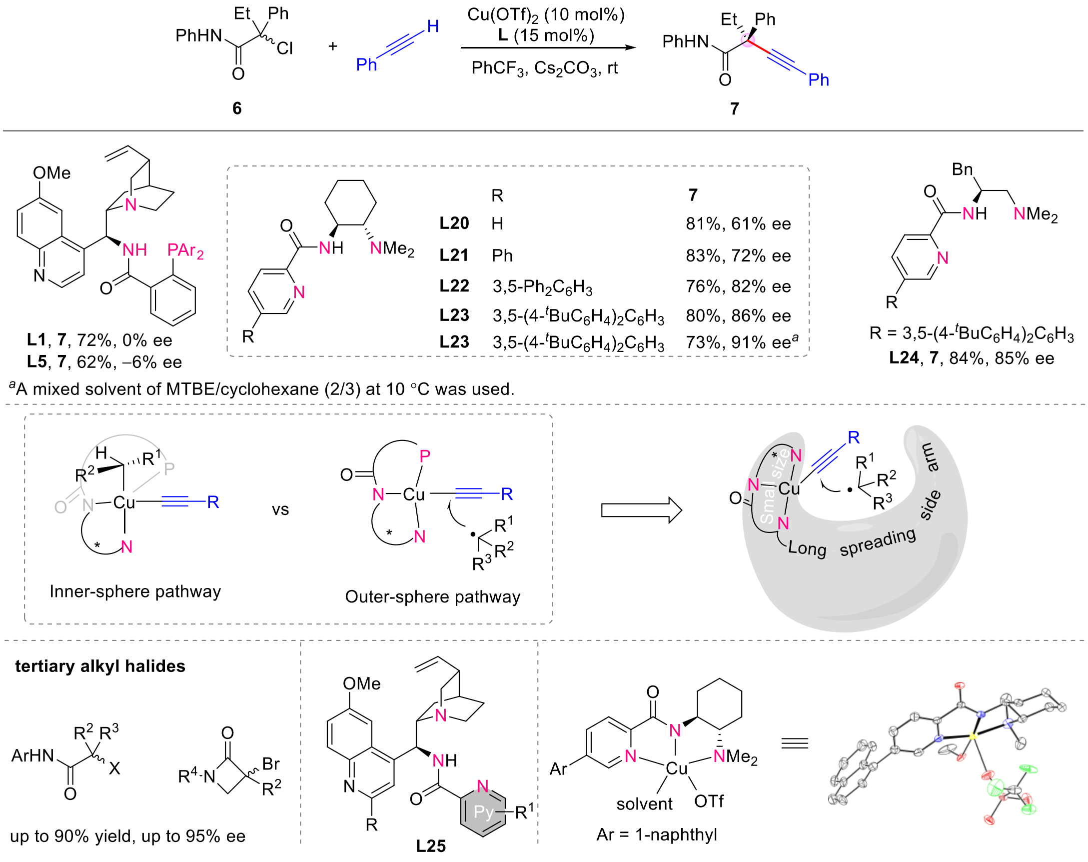
Scheme 10. Hemilabile Ligand Design in Enantioconvergent Radical C(sp^3)−C(sp^2) Cross-Coupling with Alkenylboronates



C(sp^2) formation between the prochiral alkyl radicals and the chiral alkenylcopper complex in the bidentate form.[39] The ligand design was based on a preliminary ligand screening result: we found that the bidentate *N,N*-ligand **L15** is good for the enantiocontrol and the tridentate *N,N,N*-ligand **L16** is good for the reaction efficiency (Scheme 10).[40] Collectively, we have mounted steric hindrance at the *ortho* position of one coordinating quinoline ring of **L16** to weaken the adjacent coordinating C−N bond and provide a hemilabile ligand architecture (**L17**) for the success of the coupling. The concept was further supported by changing the chiral skeleton from quinine to 1,2-diphenylethane-1,2-diamine: the reaction with **L18** and **L19** afforded an enantiomer of **5** with similar yields but totally different enantioselectivities (Scheme 10). The scope of the coupling reaction is nice and affords chiral alkenes with up to >99% ee.

Chiral Anionic *N,N,N*-Ligands with a Long Spreading Side Arm. In contrast to the well-established coupling of secondary alkyl halides,[8b] the enantioconvergent radical coupling of tertiary alkyl halides to forge enantioenriched all-carbon quaternary stereocenters is less recognized. The major challenges lie in the steric hindrance and the difficult enantio-differentiation of three distinct carbon substituents adjacent to prochiral tertiary radicals.[9] Until recently, Fu and co-workers have successfully disclosed several reports on enantioconvergent radical C(sp^3)−C coupling of tertiary alkyl halides with chiral nickel catalysis.[9] Our developed copper/chiral *N,N,P*-ligand catalyst provides a powerful tool in the establishment of enantioconvergent radical C(sp^3)−C cross-coupling of secondary alkyl halides with diverse nucleophiles. Given the

Scheme 11. New Chiral Anionic *N,N,N*-Ligands for the Coupling of Tertiary Alkyl Halides



	R	7
L20	H	81%, 61% ee
L21	Ph	83%, 72% ee
L22	3,5-Ph$_2$C$_6$H$_3$	76%, 82% ee
L23	3,5-(4-^{t}BuC$_6$H$_4$)$_2$C$_6$H$_3$	80%, 86% ee
L23	3,5-(4-^{t}BuC$_6$H$_4$)$_2$C$_6$H$_3$	73%, 91% ee^a

^{a}A mixed solvent of MTBE/cyclohexane (2/3) at 10 °C was used.

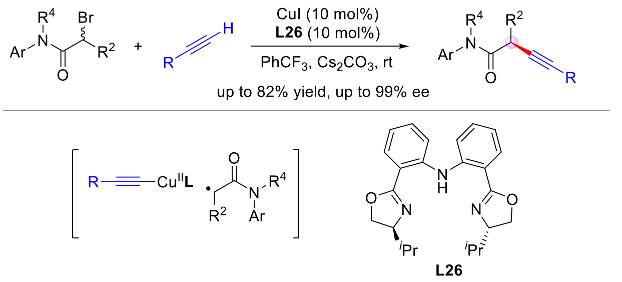
importance of quaternary carbons in natural products and bioactive molecules, we then switched our attention to the development of the enantioconvergent radical coupling of tertiary alkyl halides. We are further encouraged to disclose a clear mechanism for the $C(sp^3)-C$ bond formation process to guide the development of more coupling reactions.

The initial ligand tests for the reaction of a racemic *α*-aminocarbonyl-*α*-phenyl alkyl chloride **6** with phenylacetylene showed that the copper/*N,N,P*-ligand catalyst only afforded the coupling product **7** with a poor ee (Scheme 11, top).[41] The collaboration with Hong's group showed the preference for an out-sphere radical substitution-type C−C formation pathway between the tertiary alkyl radical and copper(II) complex.[41] The mechanistic scenario is different from the coupling of secondary alkyl radicals with our copper/*N,N,P*-ligand catalyst, but resembles the pathway suggested by the groups of Fu and Peters (Scheme 11).[19] As such, the enantio-determining transition state in the outer-sphere C−C formation pathway is more loosely organized compared with that of an inner-sphere process. It may indicate that the enantio-discriminating interaction probably occurs far away from the first coordination spheres around the copper centers. Based on the mechanistic guidance, we designed a new type of multidentate anionic chiral ligands that meets the following criteria: (i) low steric congestion around the first coordination sphere and (ii) a long spreading side arm (Scheme 11, middle). Therefore, it not only allows for easy accommodation of sterically bulky tertiary alkyl radicals but also effectively interacts with the substrates in the outer side of the second coordination sphere for stereodiscrimination.[41] In a systematic ligand investigation experiment, we proved this concept by identifying that the long side arm of diamine-derived chiral *N,N,N*-ligand (**L20**−**L24**) is beneficial to the enantioselectivity. An array of tertiary alkyl halides and alkynes are applied to the transformation to afford the coupling products with up to 95% ee. As for the coupling of cyclic tertiary alkyl bromides, the quinine-derived *N,N,N*-ligands (**L25**) provided the best result owing to the possible different transition state with that of the acyclic substrates. For the first time, we have proven an anionic nature of the copper/*N,N,N*-ligand catalyst *via* the X-ray structural analysis of the copper-ligand complex from the newly designed *N,N,N*-ligands (Scheme 11, bottom).[41] Under the guidance of this work, the enantioconvergent radical cross-coupling of tertiary alkyl halides with other nucleophiles has also been realized in our research group and will be disclosed soon.

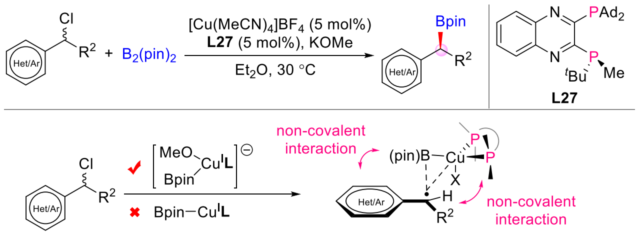
Other Ligands for Enantioconvergent Radical Cross-Coupling Reactions. In 2020, Zhang and co-workers developed a copper/chiral bisoxazoline diphenylanaline (BOPA) catalyst for the enantioconvergent radical $C(sp^3)-C(sp)$ cross-coupling of *α*-bromoamides and alkynes to afford chiral *β*,*γ*-alkynyl amides with up to 99% ee (Scheme 12).[42a] According to their mechanistic consideration, the chiral ligand **L26** also serves as an anionic form to enhance the reducing capability of copper catalyst and achieve the enantiocontrol. Either a Cu^{III} complex intermediate or an out-of-cage pathway was postulated in the $C(sp^3)-C(sp)$ formation step. More recently, Zhang accomplished the $C(sp^3)-C(sp)$ cross-coupling of tertiary alkyl bromides with alkynes using the similar copper/chiral BOPA catalyst.[42b]

Shortly after Fu's pioneering discovery on enantioconvergent $C(sp^3)-B$ coupling using the nickel catalyst,[43] Ito and co-workers reported a copper/chiral bisphosphine ligand-catalyzed enantioconvergent $C(sp^3)-B$ cross-coupling of racemic benzyl chlorides in 2019 (Scheme 13).[44] This approach provided the corresponding chiral benzylboronates with up to 92% ee. The key to the success is the design of chiral quinoxaline-based bisphosphine ligands based on quadrant-by-quadrant structure modulation (**L27**), which engaged in noncovalent interactions of the favored transition state with the benzyl radical to achieve a high ee. Based on their mechanistic study, they proposed that the catalytic active species for the enantioconvergent radical transformation is the alkoxide-coordinated LCu^IBpin complex, as shown in Scheme 13.

Scheme 12. Zhang's BOPA-Ligand for Enantioconvergent $C(sp^3)-C(sp)$ Cross-Coupling



Scheme 13. Ito's Enantioconvergent $C(sp^3)-B$ Cross-Coupling



4. SUMMARY AND OUTLOOK

The first-row transition metal-catalyzed enantioconvergent radical cross-coupling of racemic alkyl halides represents a powerful tool for the synthesis of enantioenriched molecules. Compared with the noble development of chiral nickel catalysis, copper-catalyzed transformation is a challenging task owing to the weak reducing capability of copper that impedes the reaction initiation. In this perspective, we have summarized the recent progress in copper-catalyzed enantioconvergent radical cross-coupling from the point of view of the initiation strategy. Two strategies are generally developed to accomplish the transformations. In the first part, Fu and Peters utilize photochemistry to irradiate the copper(I) complex to an excited state, which possesses a much higher reducing capability to reduce the alkyl halides to alkyl radicals *via* an SET process for reaction initiation. In the second part, chiral anionic ligands were strategically designed to enhance the reducing capability of copper(I) complex and initiate the radical process *via* a halogen atom abstraction process under thermal conditions, a concept mainly developed by our group. We have also discussed more details on the ligand design concept for the enantiocontrol from our group. It should be emphasized that the advantage of copper chemistry is apparent: it provides a feasible and general pathway for the construction of chiral carbon-heteroatom bonds, while almost all of the coupling under Ni/Co/Fe catalyst deals with the carbon−carbon bond formation.[43] The copper catalyst could also realize the enantioconvergent radical cross-coupling of tertiary alkyl halides, of which the mechanistic understanding is clearly disclosed. The outer-sphere pathway in the bond formation step is impressively instructive for the proper design of alkyl halide substrates and ligand architecture in the future.

Despite the notable development in this burgeoning field, there are still many challenging tasks to be addressed. As for the scope of nucleophiles, the sp^3-hybridzied nucleophiles have not been achieved with the copper catalyst. Although the successful coupling with alkynes and alkenylboronate esters provided an alternative pathway, the direct coupling with sp^3-hybridzied nucleophiles should be more appealing. Given the importance of chiral amines in many fields, the $C(sp^3)$−N coupling with more readily available N-based nucleophiles (amine, amide, etc.) is still desirable. The cross-coupling with other heteroatom-based nucleophiles to forge chiral C−Si, C−P, C−O, C−S, and C−F bonds is still in a great shortage. As for the electrophiles, most of the alkyl halides are those generating the π-stabilized alkyl radicals. Unactivated alkyl halides are scarcely used and only one recent example was reported using the unactivated alkyl halides with directing groups.[21] The coupling with purely aliphatic alkyl halides should be focused on in the future but seems difficult due to the lack of stabilized or directing effect. The mechanism for the whole pathway, especially for the enantio-determining bond formation has also lagged the reaction development.

More efforts are required to expand the scope of nucleophiles and alkyl halides to render the copper-catalyzed enantioconvergent cross-coupling more general and powerful. We tentatively conclude that the design of more multidentate anionic chiral ligands would give a promising direction for not only enhancing the reducing capability but also providing a suitable chiral environment for enantiocontrol by offering covalent and/or noncovalent interactions. The implementation of collaborative experimental tools is still encouraged to unravel detailed mechanistic insights, such as the isolation of intermediates, cyclic voltammogram experiment, electron paramagnetic resonance spectroscopy, X-ray analysis as well as DFT calculations.

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The manuscript was written through contributions of all authors.

Notes

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