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

Xiao-Yang Dong, Zhong-Liang Li, Qiang-Shuai Gu, and Xin-Yuan Liu*

Cite This: J. Am. Ch	em. Soc. 2022, 144, 17319–17329	Read 0	Online	
ACCESS	III Metrics & More		E Article Recommendations	

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 crosscoupling 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 sp³-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,

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

A. Transition Metal-Catalyzed Enantioconvergent Radical Cross-Coupling of Alkyl Halides

$$\begin{array}{c} X \\ X^{1} \stackrel{}{ \bigwedge}_{R^{2}} R^{3} \end{array} + [Nu] \xrightarrow{M^{n}/L} \left[\begin{array}{c} Nu - M^{n+1}L \\ R^{1} \stackrel{}{ \bigwedge}_{R^{2}} R^{3} \end{array} \right] \longrightarrow R^{1} \stackrel{Nu}{R^{2}} R^{2} \end{array}$$

B. Challenges for Copper-Catalyzed Enantioconvergent Radical Cross-Coupling

$$\begin{array}{c} X \\ R^{1} \stackrel{\wedge}{\underset{R^{2}}{\overset{\wedge}{\underset{R^{2}}{\overset{\wedge}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\overset{\vee}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\underset{R^{2}}{\atopR}}{\underset{R^{2}}{\underset{R}}}{\underset{R^{2}}{\underset{R^{2}}{\atopR^{1}}$$

Weak reducing capability of Cu^I catalyst for reaction initiation

C. Concept for Initiating Copper-Catalyzed Enantioconvergent Radical Cross-Coupling



Strategic enhancing the reducing capability of copper catalyst • Irradiation to the excited state of copper(I) complex under photo-induced conditions • Design of multidentate chiral anionic ligand under mild thermal conditions

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

Published: September 1, 2022





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



sterically bulky tertiary alkyl halides⁹ 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 crosscoupling,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 nucleophilesequestered copper(I) complex $(L)_2Cu^INu$ 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 LCu^{II}Nu₂ (*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 LCu^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 LCu^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(sp³)–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 L_nCu^I is necessary for the catalyst to be photoactive in some cases.¹ Under this circumstance, the photoactive property of a L_nCu^INu 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 synthesized a library of cinchona alkaloidderived tridentate anionic *N,N,P*-ligands²⁵ with different steric and electronic properties on the *P*-substituents based on Dixon's ligand²⁵ and 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 L1CuBr (-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 L1CuBr is also lower than that of the



Figure 1. Coordination mode and cyclic voltammogram study.

commonly used copper/chiral bisoxazoline catalyst (+0.2 V), 12a,27 and this is supposed to be beneficial to the reaction initiation process.

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 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^{I} , L, and alkyne first reacted to afford a complex LCu^INu, which possessed a high reducing capability (Scheme 5). This complex easily reduced the racemic alkyl halides to

Scheme 5. Possible Mechanism for the Enantioconvergent Cross-Coupling



afford a prochiral alkyl radical species and a LCu^{II}Nu complex probably *via* a halogen atom transfer process. Finally, the interaction of LCu^{II}Nu with the prochiral alkyl radical would furnish the chiral $C(sp^3)-C(sp)$ bond and releases the LCu^INu species *via* either an inner-sphere Cu^{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 LCu^{II}Nu with the prochiral alkyl radicals, it inspired us to apply the enantiocontrol model to other related radical reactions.

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 group³⁰ 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-diphenylphos-phinobenzamide 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

Scheme 6. Zhang's Enantioconvergent Radical C(sp³)-C(sp) Cross-Coupling



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 LCu^{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.

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 $C(sp^3)-C(sp^2)$ crosscoupling. 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_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 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(sp³)–C(sp²) 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 $S_N 2$ 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 sulfoximines³⁸ as the amine sources and

achieved an enantioconvergent radical $C(sp^3)$ –N crosscoupling with diverse secondary alkyl halides under thermal conditions (Scheme 9).³⁹ Notably, both the reaction efficiency

Scheme 9. Enantioconvergent Radical C(sp³)–N Cross-Coupling



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).

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



(ii) it delivers an excellent enantiocontrol in the $C(sp^3)$ - $C(sp^2)$ 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 allcarbon quaternary stereocenters is less recognized. The major challenges lie in the steric hindrance and the difficult enantiodifferentiation 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 secon-

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



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.⁴ 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 innersphere 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,Nligands (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 $\beta_i\gamma$ -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) crosscoupling 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 coworkers reported a copper/chiral bisphosphine ligand-





catalyzed enantioconvergent $C(sp^3)$ -B cross-coupling of racemic benzyl chlorides in 2019 (Scheme 13).⁴⁴ This

Scheme 13. Ito's Enantioconvergent C(sp³)-B Cross-Coupling



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.

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 sp³-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 sp³hybridzied 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.

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, China; orcid.org/0000-0002-6978-6465; Email: liuxy3@sustech.edu.cn

Authors

- Xiao-Yang Dong Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China; Orcid.org/0000-0002-0663-1482
- Zhong-Liang Li Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China
- **Qiang-Shuai Gu** Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of

Science and Technology, Shenzhen 518055, China; orcid.org/0000-0002-3840-425X

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c06718

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from National Key R&D Program of China (Nos. 2021YFF0701604 and 2021YFF0701704), the National Natural Science Foundation of China (Nos. 22025103 and 21831002), Guangdong Innovative Program (No. 2019BT02Y335), Guangdong Provincial Key Laboratory of Catalysis (No. 2020B121201002), and Shenzhen Special Funds (No. JCYJ20200109141001789) was appreciated.

REFERENCES

(1) Miyaura, N.; Buchwald, S. L.Cross-coupling reactions: a practical guide; Springer: Germany, 2002; Vol. 219.

(2) (a) Buskes, M. J.; Blanco, M. J. Impact of Cross-Coupling Reactions in Drug Discovery and Development. *Molecules* 2020, 25, 3493. (b) Brown, D. G.; Bostrom, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* 2016, 59, 4443–4458. (c) Yasuda, N. Application of cross-coupling reactions in Merck. *J. Organomet. Chem.* 2002, 253 (1-2), 279–287.

(3) (a) Johansson Seechurn, 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. (b) De Meijere, A.; Bräse, S.; Oestreich, M.*Metal catalyzed cross-coupling reactions and more*; Wiley-VCH: Weinheim, Germany, 2014. (c) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564–12649.

(4) For selected reviews on enantioconvergent transformation of allyl electrophiles, see: (a) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. Advances in Stereoconvergent Catalysis from 2005 to 2015: Transition-Metal-Mediated Stereoablative Reactions, Dynamic Kinetic Resolutions, and Dynamic Kinetic Asymmetric Transformations. Chem. Rev. 2017, 117, 4528-4561. (b) Rössler, S. L.; Petrone, D. A.; Carreira, E. M. Iridium-Catalyzed Asymmetric Synthesis of Functionally Rich Molecules Enabled by (Phosphoramidite,Olefin) Ligands. Acc. Chem. Res. 2019, 52, 2657-2672. For selected examples on enantioconvergent transformation of alkyl electrophiles with noble transition metal- or organo-catalysts, see: (c) Sidera, M.; Fletcher, S. P. Rhodium-Catalysed Asymmetric Allylic Arylation of Racemic Halides with Arylboronic Acids. Nat. Chem. 2015, 7, 935-939. (d) Li, B.; Li, T.; Aliyu, M. A.; Li, Z. H.; Tang, W. Enantioselective Palladium-Catalyzed Cross-Coupling of *a*-Bromo Carboxamides and Aryl Boronic Acids. Angew. Chem., Int. Ed. 2019, 58, 11355-11359. (e) Wendlandt, A. E.; Vangal, P.; Jacobsen, E. N. Quaternary Stereocentres via An Enantioconvergent Catalytic S_N1 Reaction. Nature 2018, 556, 447-451. (f) Zhang, X.; Ren, J.; Tan, S. M.; Tan, D.; Lee, R.; Tan, C.-H. An Enantioconvergent Halogenophilic Nucleophilic Substitution (S_N2X) Reaction. Science 2019, 363, 400-404.

(5) (a) Netherton, M. R.; Fu, G. C. Nickel-Catalyzed Cross-Couplings of Unactivated Alkyl Halides and Pseudohalides with Organometallic Compounds. *Adv. Synth. Catal.* **2004**, *346*, 1525– 1532. (b) Frisch, A. C.; Beller, M. Catalysts for Cross-Coupling Reactions with Non-Activated Alkyl Halides. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (c) Rudolph, A.; Lautens, M. Secondary Alkyl Halides in Transition-Metal-Catalyzed Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670. (d) Kambe, N.; Iwasaki, T.; Terao, J. Pd-Catalyzed Cross-Coupling Reactions of Alkyl Halides. *Chem. Soc. Rev.* **2011**, *40*, 4937–4947.

(6) 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.

(7) (a) Mondal, S.; Dumur, F.; Gigmes, D.; Sibi, M. P.; Bertrand, M. P.; Nechab, M. Enantioselective Radical Reactions Using Chiral Catalysts. *Chem. Rev.* 2022, *122*, 5842–5976. (b) Wang, X.; Zhang, X. P.Catalytic Radical Approach for Selective Carbene Transfers via Cobalt(II)-Based Metalloradical Catalysis. In *Transition Metal-Catalyzed Carbene Transformations*; Wang, J., Che, C.-M., Doyle, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2022; Chapter 2, pp 25–66.

(8) For selected reviews, see: (a) 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. (b) Choi, J.; Fu, G. C. Transition Metal-Catalyzed Alkyl-Alkyl Bond Formation: Another Dimension in Cross-Coupling Chemistry. Science 2017, 356 (6334), eaaf7230. (c) Lipp, A.; Badir, S. O.; Molander, G. A. Stereoinduction in Metallaphotoredox Catalysis. Angew. Chem., Int. Ed. 2021, 60, 1714-1726. (d) Fischer, C.; Fu, G. C. Asymmetric Nickel-Catalyzed Negishi Cross-Couplings of Secondary a-Bromo Amides with Organozinc Reagents. J. Am. Chem. Soc. 2005, 127, 4594-4595. (e) 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 a-Bromo Esters with Aryl Grignard Reagents. J. Am. Chem. Soc. 2014, 136, 17662-17668. (f) Jin, M.; Adak, L.; Nakamura, M. Iron-Catalyzed Enantioselective Cross-Coupling Reactions of a-Chloroesters with Aryl Grignard Reagents. J. Am. Chem. Soc. 2015, 137, 7128-7134.

(9) For sporadic reports with the nickel catalyst, see: (a) Wang, Z.; Yin, H.; Fu, G. C. Catalytic Enantioconvergent Coupling of Secondary and Tertiary Electrophiles with Olefins. *Nature* 2018, 563, 379–383. (b) Wang, Z.; Yang, Z. P.; Fu, G. C. Quaternary Stereocentres via Catalytic Enantioconvergent Nucleophilic Substitution Reactions of Tertiary Alkyl Halides. *Nat. Chem.* 2021, 13, 236–242.

(10) (a) Kochi, J. K. Electron-Transfer Mechanisms for Organometallic Intermediates in Catalytic Reactions. Acc. Chem. Res. 1974, 7, 351-360. (b) McCann, S. D.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidations of Organic Molecules: Pathways for Two-Electron Oxidation with a Four-Electron Oxidant and a One-Electron Redox-Active Catalyst. Acc. Chem. Res. 2015, 48, 1756-1766. (c) Adachi, S.; Moorthy, R.; Sibi, M. P.Chiral Copper Lewis Acids in Asymmetric Transformations. In Copper-Catalyzed Asymmetric Synthesis; Alexakis, A., Krause, N., Woodward, S., Eds.; Wiley-VCH: Weinheim, Germany, 2014; Chapter 11, pp 283-324. (d) Stanley, L. M.; Sibi, M. P. Enantioselective Copper-Catalyzed 1,3-Dipolar Cycloadditions. Chem. Rev. 2008, 108 (8), 2887-2902. (e) Alexandre, A.; Norbert, K.; Simon, W.Copper-Catalyzed Asymmetric Synthesis; Wiley-VCH: Weinheim, Germany, 2014. (f) Evano, G.; Blanchard, N.Copper-Mediated Cross-Coupling Reactions; John Wiley & Sons: Hoboken, NJ, 2014. (g) Gopinathan, A.; Salim, S.Copper Catalysis in Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2020. (h) Chemler, S. R. Copper's Contribution to Amination Catalysis. Science 2013, 341, 624-626. (i) Yang, Q.; Zhao, Y.; Ma, D. Cu-Mediated Ullmann-Type Cross-Coupling and Industrial Applications in Route Design, Process Development, and Scale-up of Pharmaceutical and Agrochemical Processes. Org. Process Res. Dev. 2022, 26, 1690-1750.

(11) Ribelli, T. G.; Matyjaszewski, K.; Poli, R. The Interaction of Carbon-Centered Radicals with Copper(I) and Copper(II) Complexes*. *J. Coord. Chem.* **2018**, *71*, 1641–1668.

(12) For selected reviews, see: (a) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* 2018, *51*, 2036–2046. (b) Gu, Q.-S.; Li, Z.-L.; Liu, X.-Y. Copper(I)-Catalyzed Asymmetric Reactions Involv-

ing Radicals. Acc. Chem. Res. 2020, 53, 170-181. (c) Li, Z.-L.; Fang, G.-C.; Gu, Q.-S.; Liu, X.-Y. Recent Advances in Copper-Catalysed Radical-Involved Asymmetric 1,2-Difunctionalization of Alkenes. Chem. Soc. Rev. 2020, 49, 32-48. For selected examples, see: (d) Zhu, R.; Buchwald, S. L. Enantioselective Functionalization of Radical Intermediates in Redox Catalysis: Copper-Catalyzed Asymmetric Oxytrifluoromethylation of Alkenes. Angew. Chem., Int. Ed. 2013, 52, 12655-12658. (e) 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 Aminotrifluoromethylation of Alkenes. J. Am. Chem. Soc. 2016, 138, 9357-9360. (f) Cheng, Y.-F.; Liu, J.-R.; Gu, Q.-S.; Yu, Z.-L.; Wang, J.; Li, Z.-L.; Bian, J.-Q.; Wen, H.-T.; Wang, X.-J.; Hong, X.; Liu, X.-Y. Catalytic Enantioselective Desymmetrizing Functionalization of Alkyl Radicals via Cu(I)/CPA Cooperative Catalysis. Nat. Catal. 2020, 3, 401-410. (g) Yang, C.-J.; Zhang, C.; Gu, Q.-S.; Fang, J.-H.; Su, X.-L.; Ye, L.; Sun, Y.; Tian, Y.; Li, Z.-L.; Liu, X.-Y. Cu-Catalysed Intramolecular Radical Enantioconvergent Tertiary β -C(sp³)-H Amination of Racemic Ketones. Nat. Catal. 2020, 3, 539-546.

(13) For a rough comparison, the standard electrode potentials $E^0(M^{II}/M^0)$ are -0.26, -0.28, -0.44, and +0.34 V for Ni, Co, Fe, and Cu, respectively. For data sources, see: (a) Bard, A. J.; Parsons, R.; Jordan, J.Standard Potentials in Aqueous Solution; CRC Press, 1985. (b) Standard Electrode Potentials. http://www.benjamin-mills.com/ chemistry/ecells.htm (accessed 2022-08-18).

(14) (a) Hossain, A.; Bhattacharyya, A.; Reiser, O. Copper's Rapid Ascent in Visible-Light Photoredox Catalysis. *Science* **2019**, *364* (6439), eaav9713. (b) Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C. A Radical Approach to The Copper Oxidative Addition Problem: Trifluoromethylation of Bromoarenes. *Science* **2018**, *360*, 1010–1014. (c) Zhang, L.; Israel, E. M.; Yan, J.; Ritter, T. Copper-Mediated Etherification via Aryl Radicals Generated from Triplet States. *Nat. Syn.* **2022**, *1*, 376–381.

(15) (a) Huang, X.; Meggers, E. Asymmetric Photocatalysis with Bis-cyclometalated Rhodium Complexes. Acc. Chem. Res. 2019, 52, 833-847. (b) Yao, W.; Bazan-Bergamino, E. A.; Ngai, M. Y. Asymmetric Photocatalysis Enabled by Chiral Organocatalysts. ChemCatChem. 2021, 14 (1), e202101292. (c) Yu, X. Y.; Chen, J. R.; Xiao, W. J. Visible Light-Driven Radical-Mediated C-C Bond Cleavage/Functionalization in Organic Synthesis. Chem. Rev. 2021, 121, 506-561. (d) Genzink, M. J.; Kidd, J. B.; Swords, W. B.; Yoon, T. P. Chiral Photocatalyst Structures in Asymmetric Photochemical Synthesis. Chem. Rev. 2022, 122, 1654-1716. (e) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. Chem. Rev. 2013, 113, 5322-5363. (f) Paria, S.; Reiser, O. Copper in Photocatalysis. ChemCatChem. 2014, 6, 2477-2483.

(16) (a) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. Photoinduced Ullmann C-N Coupling: Demonstrating the Viability of a Radical Pathway. Science 2012, 338, 647-650. (b) Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. A New Family of Nucleophiles for Photoinduced, Copper-Catalyzed Cross-Couplings via Single-Electron Transfer: Reactions of Thiols with Aryl Halides Under Mild Conditions (0 °C). J. Am. Chem. Soc. 2013, 135, 9548-9552. (c) Ziegler, D. T.; Choi, J.; Munoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. A Versatile Approach to Ullmann C-N Couplings at Room Temperature: New Families of Nucleophiles and Electrophiles for Photoinduced, Copper-Catalyzed Processes. J. Am. Chem. Soc. 2013, 135, 13107-13112. (d) Tan, Y.; Muñoz-Molina, J. M.; Fu, G. C.; Peters, J. C. Oxygen Nucleophiles as Reaction Partners in Photoinduced, Copper-Catalyzed Cross-Couplings: O-Arylations of Phenols at Room Temperature. Chem. Sci. 2014, 5, 2831-2835. (e) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. Transition-Metal-Catalyzed Alkylations of Amines with Alkyl halides: Photoinduced, Copper-Catalyzed Couplings of Carbazoles. Angew. Chem., Int. Ed. 2013, 52, 5129-5133. (f) Do, H. Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Alkylation of Amides with Unactivated Secondary Alkyl Halides at Room Temperature. J. Am. Chem. Soc. 2014, 136, 21622167. (g) Ratani, T. S.; Bachman, S.; Fu, G. C.; Peters, J. C. Photoinduced, Copper-Catalyzed Carbon–Carbon Bond Formation with Alkyl Electrophiles: Cyanation of Unactivated Secondary Alkyl Chlorides at Room Temperature. *J. Am. Chem. Soc.* **2015**, *137*, 13902–13907.

(17) (a) Johnson, M. W.; Hannoun, K. I.; Tan, Y.; Fu, G. C.; Peters, J. C. A Mechanistic Investigation of The Photoinduced, Copper-Mediated Cross-Coupling of An Aryl Thiol with An Aryl Halide. *Chem. Sci.* **2016**, *7*, 4091–4100. (b) Ahn, J. M.; Peters, J. C.; Fu, G. C. Design of a Photoredox Catalyst that Enables the Direct Synthesis of Carbamate-Protected Primary Amines via Photoinduced, Copper-Catalyzed N-Alkylation Reactions of Unactivated Secondary Halides. *J. Am. Chem. Soc.* **2017**, *139*, 18101–18106. (c) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. Photoinduced, Copper-Catalyzed Alkylation of Amines: A Mechanistic Study of the Cross-Coupling of Carbazole with Alkyl Bromides. *J. Am. Chem. Soc.* **2017**, *139*, 12716–12723.

(18) 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.

(19) Lee, H.; Ahn, J. M.; Oyala, P. H.; Citek, C.; Yin, H.; Fu, G. C.; Peters, J. C. Investigation of the C-N Bond-Forming Step in a Photoinduced, Copper-Catalyzed Enantioconvergent N-Alkylation: Characterization and Application of a Stabilized Organic Radical as a Mechanistic Probe. J. Am. Chem. Soc. **2022**, 144, 4114-4123.

(20) Cho, H.; Suematsu, H.; Oyala, P. H.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Enantioconvergent Alkylations of Anilines by Racemic Tertiary Electrophiles: Synthesis and Mechanism. J. Am. Chem. Soc. **2022**, 144, 4550–4558.

(21) Chen, C.; Peters, J. C.; Fu, G. C. Photoinduced Copper-Catalysed Asymmetric Amidation via Ligand Cooperativity. *Nature* **2021**, *596*, 250–256.

(22) 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.

(23) (a) Patten, T. E.; Matyjaszewski, K. Copper(I)-Catalyzed Atom Transfer Radical Polymerization. *Acc. Chem. Res.* 1999, 32, 895–903.
(b) Ribelli, T. G.; Lorandi, F.; Fantin, M.; Matyjaszewski, K. Atom Transfer Radical Polymerization: Billion Times More Active Catalysts and New Initiation Systems. *Macromol. Rapid Commun.* 2019, 40, 1800616.

(24) 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.

(25) (a) 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 Isocyanoacetate Aldol Reaction. J. Am. Chem. Soc. 2011, 133, 1710–1713. (b) Ortín, I.; Dixon, D. J. Direct Catalytic Enantioand Diastereoselective Mannich Reaction of Isocyanoacetates and Ketimines. Angew. Chem., Int. Ed. 2014, 53, 3462–3465. (c) de la Campa, R.; Ortín, I.; Dixon, D. J. Direct Catalytic Enantioand Diastereoselective Ketone Aldol Reactions of Isocyanoacetates. Angew. Chem., Int. Ed. 2015, 54, 4895–4898. (d) Manzano, R.; Datta, S.; Paton, R. S.; Dixon, D. J. Enantioselective Silver and Amine Co-catalyzed Desymmetrizing Cycloisomerization of Alkyne-Linked Cyclohexanones. Angew. Chem., Int. Ed. 2017, 56, 5834–5838.

(26) 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.

(27) Chen, Z.-H.; Wang, X.-Y.; Sun, X.-L.; Li, J.-F.; Zhu, B.-H.; Tang, Y. Highly Efficient Atom Transfer Radical Polymerization System Based on the SaBOX/Copper Catalyst. *Macromolecules* **2019**, *52*, 9792–9798. (28) 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-Catalysed Sonogashira $C(sp^3)-C(sp)$ Coupling. *Nat. Chem.* **2019**, *11*, 1158–1166.

(29) Guo, R.; Sang, J.; Xiao, H.; Li, J.; Zhang, G. Development of Novel Phosphino-Oxazoline Ligands and Their Application in Asymmetric Alkynlylation of Benzylic Halides. *Chin. J. Chem.* **2022**, 40, 1337–1345.

(30) Liu, L.; Guo, K.-X.; Tian, Y.; Yang, C.-J.; Gu, Q.-S.; Li, Z.-L.; Ye, L.; Liu, X.-Y. Copper-Catalyzed Intermolecular Enantioselective Radical Oxidative $C(sp^3)$ -H/C(sp)-H Cross-Coupling with Rationally Designed Oxazoline-Derived N,N,P(O)-Ligands. *Angew. Chem., Int. Ed.* **2021**, 60, 26710–26717.

(31) 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.

(32) 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.

(33) 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 $C(sp^3)$ -H Bonds with Alkynes. *Nat. Commun.* **2019**, *10* (1), 5689.

(34) (a) 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. (b) 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 $1^{\circ}/2^{\circ}/3^{\circ}$ -Halogenated Alkanes. *Org. Lett.* **2015**, *17*, 3682–3685.

(35) Jiang, S.-P.; Dong, X.-Y.; Gu, Q.-S.; Ye, L.; Li, Z.-L.; Liu, X.-Y. Copper-Catalyzed Enantioconvergent Radical Suzuki-Miyaura C- $(sp^3)-C(sp^2)$ Cross-Coupling. J. Am. Chem. Soc. **2020**, 142, 19652–19659.

(36) Ren, P.; Salihu, I.; Scopelliti, R.; Hu, X. Copper-Catalyzed Alkylation of Benzoxazoles with Secondary Alkyl Halides. *Org. Lett.* **2012**, *14*, 1748–1751.

(37) 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 $C(sp^2)$ -H Bonds. *Angew. Chem., Int. Ed.* **2021**, *60*, 380–384.

(38) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. Sulfoximines from a Medicinal Chemist's Perspective: Physicochemical and in vitro Parameters Relevant for Drug Discovery. *Eur. J. Med. Chem.* **2017**, *126*, 225–245.

(39) Zhang, Y.-F.; Dong, X.-Y.; Cheng, J.-T.; Yang, N.-Y.; Wang, L.-L.; Wang, F.-L.; Luan, C.; Liu, J.; Li, Z.-L.; Gu, Q.-S.; Liu, X.-Y. Enantioconvergent Cu-Catalyzed Radical C–N Coupling of Racemic Secondary Alkyl Halides to Access α -Chiral Primary Amines. J. Am. Chem. Soc. **2021**, 143, 15413–15419.

(40) Wang, P.-F.; Yu, J.; Guo, K.-X.; Jiang, S.-P.; Chen, J.-J.; Gu, Q.-S.; Liu, J.-R.; Hong, X.; Li, Z.-L.; Liu, X.-Y. Design of Hemilabile N,N,N-Ligands in Copper-Catalyzed Enantioconvergent Radical Cross-Coupling of Benzyl/Propargyl Halides with Alkenylboronate Esters. J. Am. Chem. Soc. 2022, 144, 6442–6452.

(41) Wang, F.-L.; Yang, C.-J.; Liu, J.-R.; Yang, N.-Y.; Dong, X.-Y.; Jiang, R.-Q.; Chang, X.-Y.; Li, Z.-L.; Xu, G.-X.; Yuan, D.-L.; Zhang, Y.-S.; Gu, Q.-S.; Hong, X.; Liu, X.-Y. Mechanism-Based Ligand Design for Copper-Catalysed Enantioconvergent $C(sp^3)-C(sp)$ Cross-Coupling of Tertiary Electrophiles with Alkynes. *Nat. Chem.* 2022, 14, 949–957.

(42) (a) 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. (b) Mo, X.; Huang, H.; Zhang, G. Tetrasubstituted Carbon Stereocenters via Copper-Catalyzed Asymmetric Sonogashira Cou-

pling Reactions with Cyclic gem-Dihaloketones and Tertiary α -Carbonyl Bromides. ACS Catal. **2022**, 12, 9944–9952.

(43) Wang, Z.; Bachman, S.; Dudnik, A. S.; Fu, G. C. Nickel-Catalyzed Enantioconvergent Borylation of Racemic Secondary Benzylic Electrophiles. *Angew. Chem., Int. Ed.* **2018**, *57*, 14529–14532.

(44) Iwamoto, H.; Endo, K.; Ozawa, Y.; Watanabe, Y.; Kubota, K.; Imamoto, T.; Ito, H. Copper(I)-Catalyzed Enantioconvergent Borylation of Racemic Benzyl Chlorides Enabled by Quadrant-by-Quadrant Structure Modification of Chiral Bisphosphine Ligands. *Angew. Chem., Int. Ed.* **2019**, *58*, 11112–11117.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on September 1, 2022. Additonal citations have been added to Reference 25. The paper was reposted on September 14, 2022.

Recommended by ACS

Copper Hydride-Catalyzed Enantioselective Olefin Hydromethylation

Yuyang Dong, Stephen L. Buchwald, *et al.* AUGUST 31, 2022 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

READ 🗹

READ 🗹

Photoexcited Chiral Copper Complex-Mediated Alkene $E \rightarrow Z$ Isomerization Enables Kinetic Resolution

Iao Zhang, Shouyun Yu, et al.	
UNE 08, 2022	
OURNAL OF THE AMERICAN CHEMICAL SOCIETY	READ 🗹

Cobalt-Catalyzed Enantioselective C-H Arylation of Indoles

Nicolas Jacob, Joanna Wencel-Delord, et al.	
JANUARY 10, 2022	
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY	READ 🗹

A Unified and Desymmetric Approach to Chiral Tertiary Alkyl Halides

Yin Zheng, Zhongxing Huang, et al. JANUARY 25, 2022 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Get More Suggestions >

H