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Copper-catalyzed asymmetric radical C(sp³)—C(sp²) bond formation with organoboron reagents

XU Dantong¹, LIANG Simou^{1,2}, YANG Changjiang^{1,2}, LI Zhongliang^{1,2}, GU Qiangshuai³,
LIU Lin^{*1,2}, LIU Xinyuan^{*1}

1. Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China;

2. Department of Chemistry and Dongguan Key Laboratory for Data Science and Intelligent Medicine, Great Bay University, Dongguan 523000, China;

3. Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China

Abstract: Organoboron reagents are widely applied in the C—C bond formation due to the advantages of easy synthesis, stability, and low toxicity. Among them, copper-catalyzed asymmetric radical (hetero)aryl/alkenylation of organoboron reagents is an important approach to efficiently construct chiral C(sp³)—C(sp²) bonds. The key to the success is the use of copper/rationally designed chiral ligand catalytic system for not only efficiently initiating the reaction, but also achieving the challenging enantiocontrol over the highly reactive radical species. In this perspective, we have summarized the impact of the development of two types of chiral ligands and anticipate further development in the research field.

Keywords: copper catalyst; radical; asymmetric; organoboron reagents; chiral ligand

1 Introduction

Organoboron reagents have always been important synthetic blocks in organic chemistry due to the advantages of easy synthesis, stability, and low toxicity. For example, the classic palladium-catalyzed Suzuki-Miyaura C(sp²)—C(sp²) coupling of organoboron reagents with aryl/alkenyl halides is one of the most widely applied reactions in the fields of organic chemistry and pharmaceuticals^[1-2]. By contrast, the precious metal-catalyzed Suzuki-Miyaura C(sp³)—C(sp²) coupling of organoboron reagents with alkyl halides has been less studied^[3-5] due to the difficult oxidative addition and the facile β-H elimination of alkyl metal species^[6-7]. In recent years, with the rapid development of first-row transition metal catalysts, the chiral nickel^[8-12], iron^[13-14], and cobalt^[15] catalysts were utilized to realize the enantioconvergent radical Suzuki-Miyaura C(sp³)—C(sp²) couplings of racemic alkyl halides.

Copper is a cheap and low-toxicity transition metal, which would be a great potential metal catalyst for such a reaction^[16]. However, compared with chiral nickel, iron, and cobalt catalysts, chiral copper catalyst has weaker reducing capability, which slows the reaction initiation to generate the corresponding radicals. Thus, the copper-catalyzed radical asymmetric Suzuki-Miyaura C(sp³)—C(sp²) coupling of alkyl halides has been less de-

veloped^[17-19]. To compensate for the weak reduction ability of copper, Liu and others have developed a copper/chiral neutral bisoxazoline ligand (BOX) catalyst to achieve the asymmetric arylation of alkenes and C(sp³)—H bonds with the use of strong electrophilic radical precursors or strong oxidants^[20-23]. Xiao and co-workers have disclosed a photoinduced copper-catalyzed enantioconvergent deaminative arylation couplings^[24]. Liu has designed a class of electron-rich tridentate anionic ligands to enhance the single-electron reducing capability of copper, which could convert mild electrophiles (such as alkyl halides) to the corresponding radicals, and further to realize the enantioconvergent radical Suzuki-Miyaura C(sp³)—C(sp²) coupling^[25-27] (See Figure 1). In summary, the key to the success is the rational design of chiral ligands to both efficiently initiate the reaction and realize

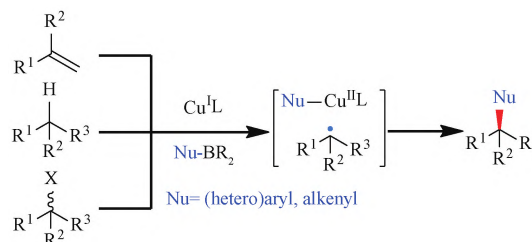


Figure 1 Copper-catalyzed asymmetric radical C(sp³)—C(sp²) bond formation with organoboron reagents

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*Corresponding author.

E-mail address: liul@gbu.edu.cn (LIU Lin); liuxy3@sustech.edu.cn (LIU Xinyuan)

the stereoselective control of highly active alkyl radicals. This perspective will summarize and categorize these reactions into two parts based on the different ligand skeleton structures used: first, the asymmetric radical arylation catalyzed by copper/neutral BOX ligands; second, the enantioconvergent radical Suzuki-Miyaura C(sp³)-C(sp²) coupling catalyzed by copper/tridentate anionic ligands.

2 The asymmetric radical arylation catalyzed by copper/neutral BOX ligands

2.1 The asymmetric radical arylation of alkenes catalyzed by copper/neutral BOX ligands

In 2017, Liu has developed a copper/neutral BOX ligand catalyst to achieve an asymmetric radical trifluoromethylarylation of styrenes using the highly active Togni-I reagent as the trifluoromethyl radical precursor, and afford a variety of chiral CF₃-containing 1,1-diarylethane compounds with excellent yields and enantioselectivities (See Figure 2a). This reaction has a broad substrate scope, covering various styrenes and aryl boronic acids. A plausible mechanism was proposed as shown in Figure 2b. Firstly, the reaction of an *in-situ* [CF₃[•]-BAr²] reagent and Cu^IL1 generated a trifluoromethyl radical and Cu^{II}L1 *via* a single elec-

tron transfer (SET) process. Afterward, the radical attacked the styrene to generate a benzylic radical. Meanwhile, Cu^{II}L1 underwent a transmetalation process with the activated aryl boronic acid to give Ar²-Cu^{II}L1 species, which was interacted with benzylic radical to construct the final C(sp³)-C(sp²) bond^[20].

Based on such catalytic system, Liu and co-workers have developed an enantioselective aminoarylation of styrenes with the use of a strong oxidative *N*-fluoro-*N*-alkylsulfonamide (NFAS) as the amino radical precursor. The key to the success of this reaction lies in benzylic radical formation to match the turnover-limiting transmetalation of (hetero)aryl boronic acid. During the optimization of reaction conditions, the authors found that steric hindrance and the electronic nature of the NFAS reagents could significantly impact the efficiency of the reaction. Subsequently, a detailed screening of these factors discovered that the use of NFAS-7 gave the best results (See Figure 3). Further investigations of other parameters (such as temperature, additives) allowed the reaction to achieve the target products with good to excellent yields and excellent enantioselectivities^[21].

In 2020, Maruoka developed a copper-catalyzed enantioselective alkylation of styrenes

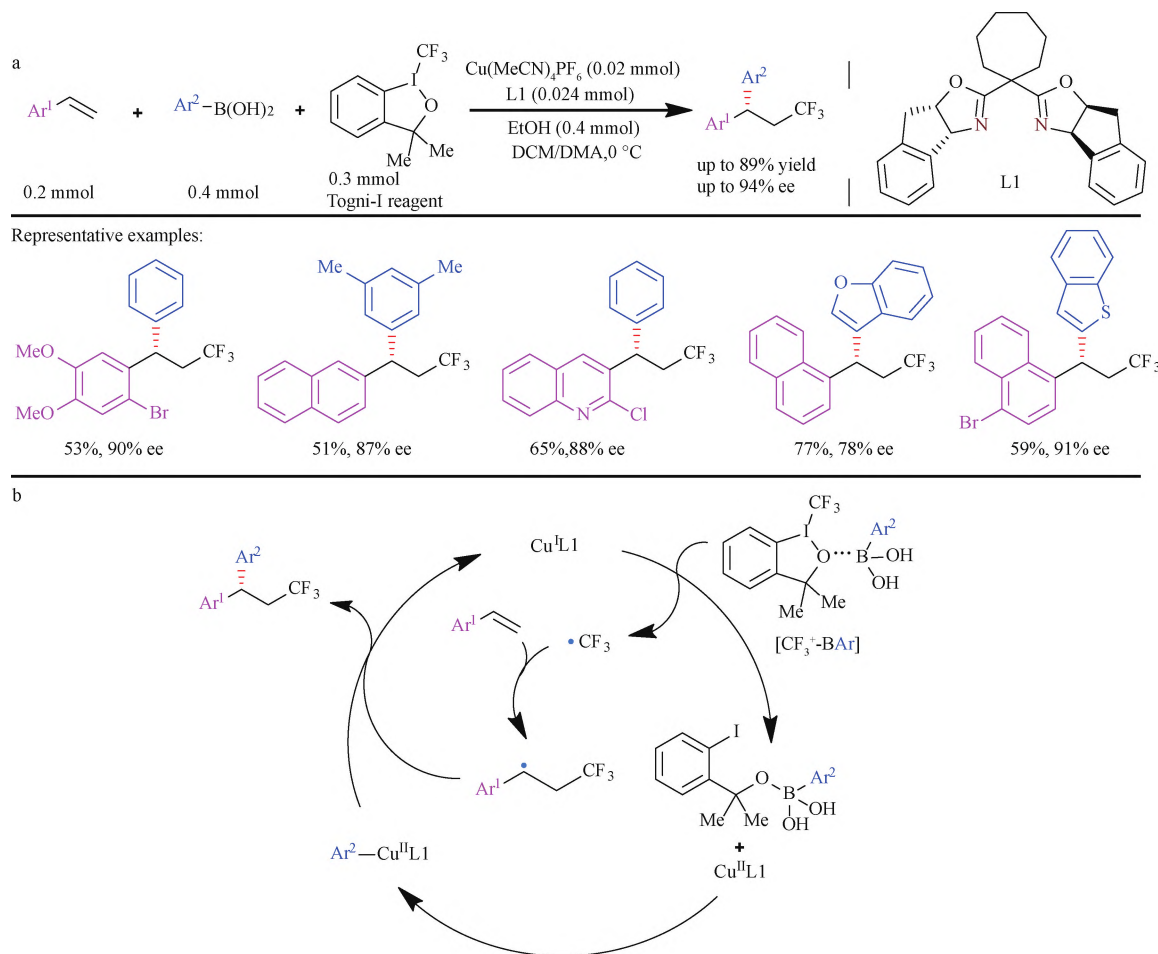


Figure 2 The asymmetric radical trifluoromethylarylation of styrenes catalyzed by copper/neutral BOX ligand

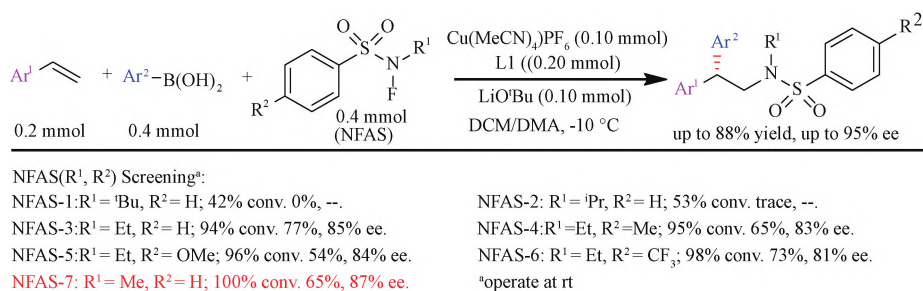


Figure 3 The asymmetric radical aminoarylation of styrenes catalyzed by copper/neutral BOX ligand

using alkylsilyl peroxides as alkyl radical precursors (See Figure 4). Notably, a class of novel chiral binaphthyl-derived neutral BOX ligands (L2–L4) were rationally designed in this reaction to give the target products with excellent yields and enantioselectivities^[28].

The above reports are limited in secondary alkyl radical involved asymmetric arylation reactions of alkenes. Up to now, there is only one reported example of such reaction involving tertiary alkyl

radicals to construct chiral quaternary carbon centers. In this reaction, the trifluoromethyl radical attacked an electron-deficient 1,1-disubstituted alkene to generate a tertiary alkyl radical, which was trapped by Ar-Cu^{II}L5 species to construct the sterically congested quaternary stereocenter. During the initial substrate screening, the authors found that the introduction of the secondary amide substituent (CONHPh) in the alkene could significantly improve the yield and enantioselectivity (See Figure 5)^[22].

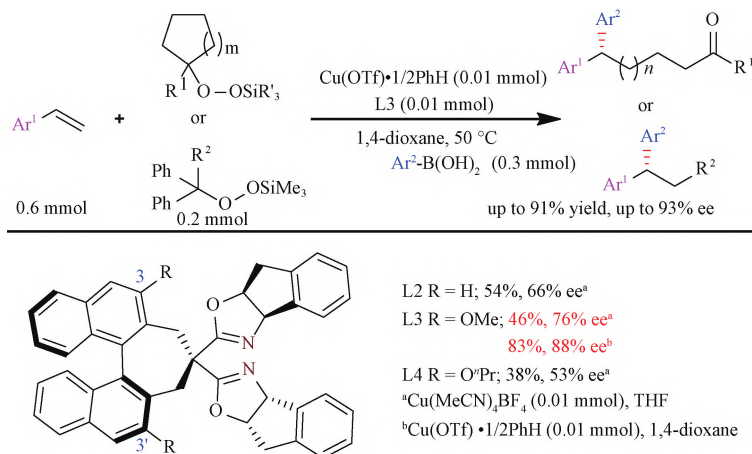


Figure 4 The enantioselective alkylarylation of styrenes catalyzed by copper/binaphthyl-derived neutral BOX ligand

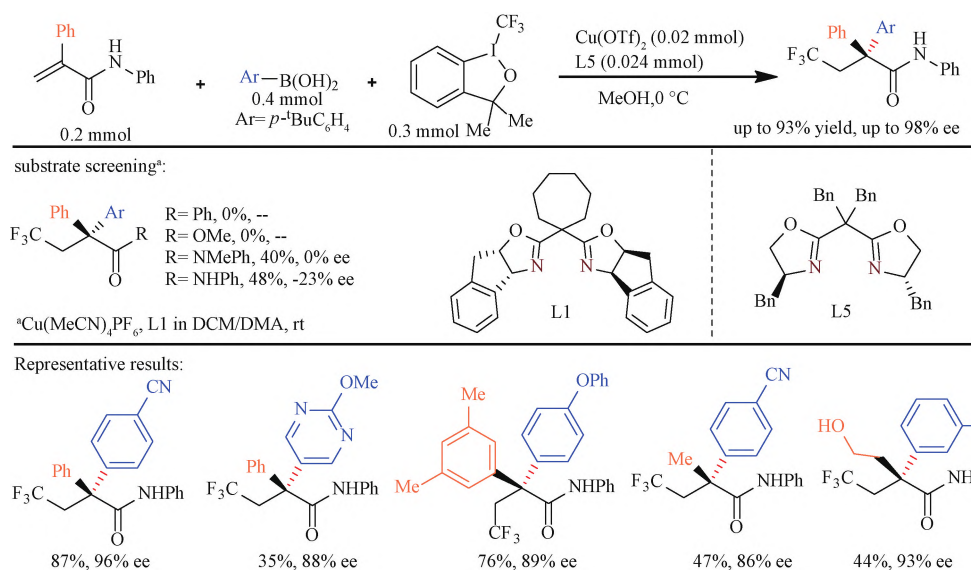


Figure 5 The enantioselective arylation of tertiary alkyl radicals catalyzed by copper/neutral BOX ligand

2.2 Enantioselective radical arylation of benzylic C—H bonds catalyzed by copper/neutral BOX ligands

In 2019, Liu has achieved an enantioselective arylation of benzylic C—H bonds through intermolecular hydrogen atom abstraction (HAA) process based on the developed catalytic system and radical relay strategy^[29-30]. Notably, the introduction of an ester group on the side arm of the chiral BOX ligand can increase the reaction yield and suppress side reactions. This may be due to the effective enhancement of the interaction of the chiral copper/ligand species with arylboronic acids, thereby accelerating the transmetalation process. A plausible mechanism was proposed as shown in Figure 6. Firstly, the reaction of highly oxidative NFSI^[31] and Cu^IL6 generated a highly active N-centered radical and Cu^{II}L6 via a SET process. Afterward, the N-centered radical abstracted a benzylic hydrogen atom to produce the corresponding benzylic radical. Meanwhile, Cu^{II}L6 underwent a transmetalation process with aryl boronic acid to give Ar²-Cu^{II}L6 species, which interacted with the benzylic radical to provide chiral 1,1-diarylkane compounds^[23].

In 2021, Wang developed an enantioselective arylation to give chiral ω,ω -diaryl alkyl nitriles using above catalytic system. In this reaction, the N—O bond cleavage of cyclic ketoximes produced N-center iminyl radicals, followed by ring-opening process to generate a prochiral benzylic radical species, which was enantioselectively trapped by Ar²-Cu^{II}L7 species to forge the chiral C(sp³)—C(sp²) bond^[32] (See Figure 7).

In 2019, Nagib assembled the highly active N—F reagents into C—H bond substrates and developed an enantioselective radical δ C—H arylation

of sulfonamides *via* intramolecular hydrogen atom transfer (HAT) by an N-centered radical. Unfortunately, this corresponding product could be only afforded in moderate enantioselectivity catalyzed by Cu/chiral BOX ligand^[33] (See Figure 8a). With the same strategy, Maruoka afforded such a similar product with the use of the chiral binaphthyl-derived BOX ligand in excellent yield and enantioselectivity^[28] (See Figure 8b).

2.3 Visible light induced enantioconvergent deaminative arylations catalyzed by Cu/chiral BOX ligand

The above studies typically require the addition of strong oxidative radical precursors for reaction initiation. Recently, Xiao and co-workers utilized a mild oxidative arylpyridinium salt as an electrophile and developed a copper-catalyzed asymmetric deaminative arylation reaction under visible-light irradiation (See Figure 9). Mechanistic investigation indicates that phenol play a crucial role in this reaction: firstly, its combination with chiral Cu^IL5 generates an in-situ photocatalyst that significantly enhances the reductive capability of Cu(I) under blue light excitation, thereby reducing arylpyridinium salts to prochiral secondary alkyl radicals; secondly, the phenoxy anion promotes transmetalation process of arylboronic acid; additionally, the weak intermolecular hydrogen bonding interaction between phenol and the substrate could slightly enhance the enantioselectivity of the products^[24].

3 Enantioconvergent Suzuki-Miyaura C(sp³)—C(sp²) coupling reactions catalyzed by copper/chiral tridentate anionic ligands

To address the challenge of copper's weak reducibility, we speculated that a rationally designed

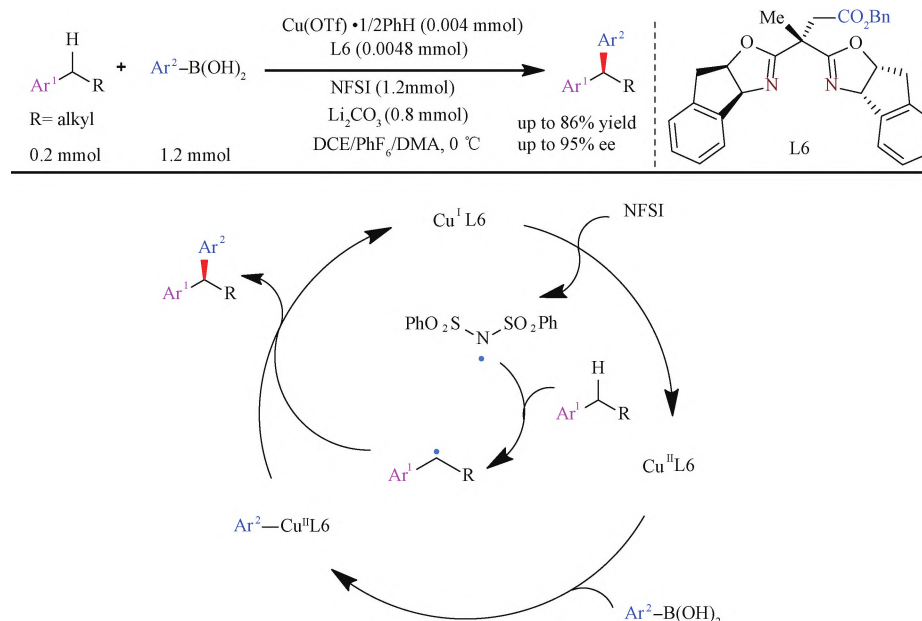


Figure 6 Enantioselective radical arylation of benzylic C—H bonds catalyzed by copper/neutral BOX ligand

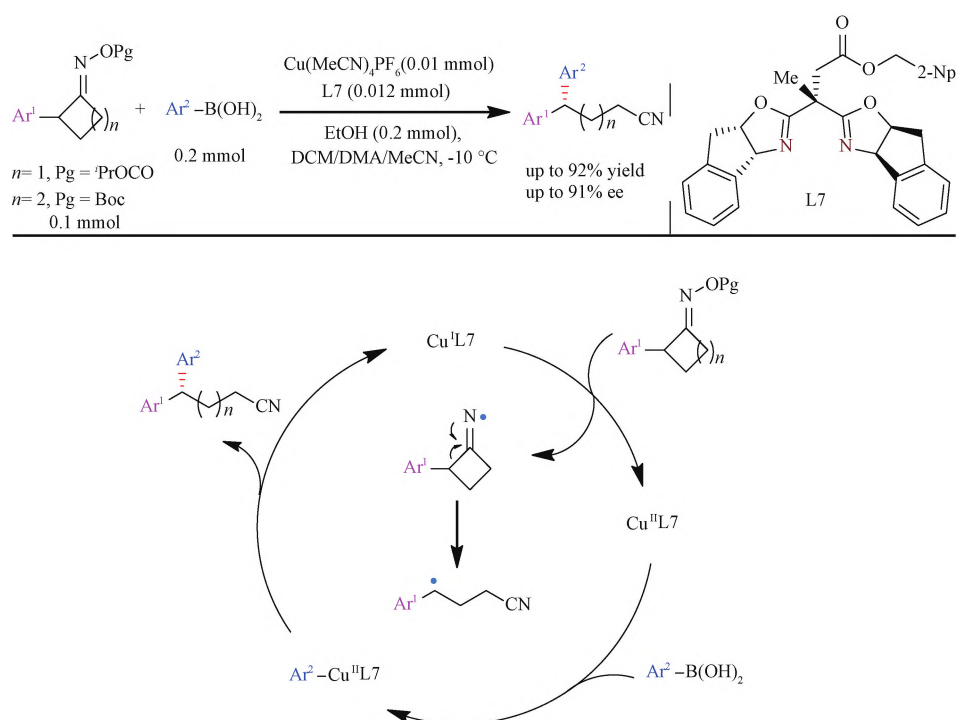


Figure 7 Enantioselective radical arylation via radical-mediated C—C bond cleavage catalyzed by copper/neutral BOX ligand

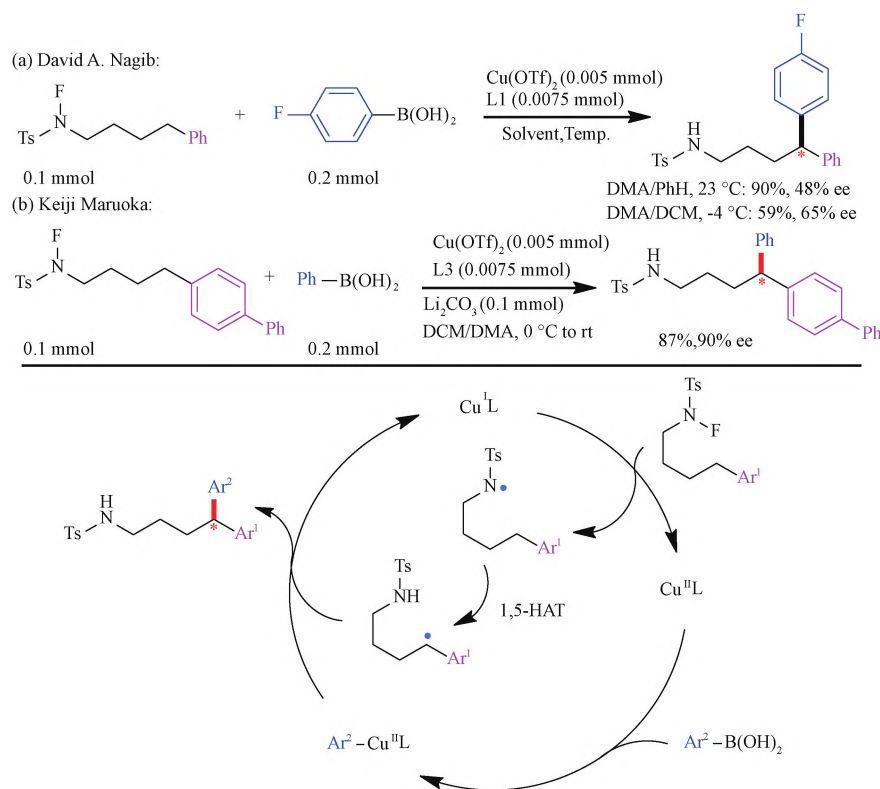


Figure 8 Enantioselective radical δ C—H arylation of sulfonamides catalyzed by copper/neutral BOX ligand

electron-rich chiral ligands could potentially enhance the reducing ability of copper, which may promote the reduction of mild electrophiles to generate radicals. Based on this concept, Liu have developed a copper(I)/cinchona alkaloid-derived *N*,

N,P-ligand catalytic system for enantioconvergent Sonogashira C(sp³)—C(sp) coupling of alkyl halides with terminal alkynes^[34-35]. The key to the success of this reaction lies in the catalytic system not only efficiently generates alkyl radicals from

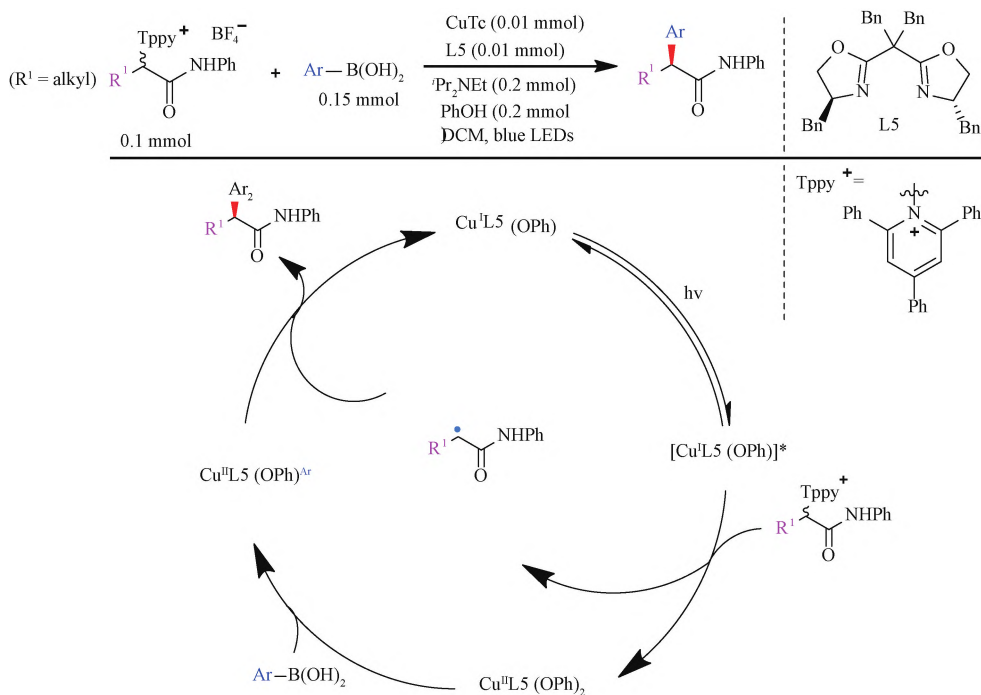


Figure 9 Visible light induced enantioconvergent deaminative arylations catalyzed by Cu/chiral BOX ligand

alkyl halides, but also provides an excellent chiral environment for the reaction. Following the same strategy, we further developed an asymmetric Suzuki-Miyaura C(sp³)-C(sp²) coupling reaction of the secondary benzylic and propargylic halides with (hetero)arylboronate esters (See Figure 10). During the initial optimization of the conditions, we discovered that the choice of arylboron reagents is crucial for the transmetalation step and further affects the reaction efficiency. Notably, less reactive propargylic chloride is also suitable substrate, which could afford the desired product with moderate yield and excellent enantioselectivity. A plausible mechanism was proposed as shown in Figure 10, Cu^IL underwent a transmetalation process with aryl boronic ester to give (hetero) Ar-Cu^IL species. Afterward, this species can interact with alkyl halide to generate a prochiral alkyl radical and the (hetero) aryl-Cu^{II}L species via a SET process. The alkyl radical could react efficiently with the (hetero) aryl-Cu^{II}L species to construct the chiral C(sp³)-C(sp²) bond^[25].

Based on the enantioconvergent (hetero)arylation of racemic halides with (hetero)arylboronate esters, our focus transferred to the more significant enantioconvergent Suzuki-Miyaura alkenylation of racemic halides with alkenylboronate esters. Through a careful investigation of chiral ligands, it was found that the originally superior *N,N,P* ligand in the (hetero)arylation reaction could only provide the target product with lower than 30% yield and moderate enantiomeric excess (ee). Subsequently, screening of other skeleton-type ligands discovered that the use of a chiral *N,N,N*-tridentate

anionic ligand provided the best yield with excellent enantioselectivity for the reaction (See Figure 11). The optimization of the reaction conditions shown that the rational designed ligand not only significantly enhanced the reductive capability of copper but also suppressed the undesired self-coupling of alkenylboronic esters. Preliminary density functional theory (DFT) calculations indicated that the novel hemilabile *N,N,N*-anionic ligand promoted the radical coupling process in a tridentate form and controlled the enantioselectivity of the alkyl radical in a bidentate form^[26].

The above reports have just achieved the enantioconvergent Suzuki-Miyaura couplings of secondary alkyl radicals. The study of tertiary alkyl radicals involved asymmetric Suzuki-Miyaura coupling has been less reported due to the difficult construction of sterically congested quaternary stereocenters. In 2023, Liu utilized a copper/hemilabile *N,N,N* ligand catalytic system to develop an enantioselective Suzuki-Miyaura C(sp³)-C(sp²) coupling reactions of tertiary α -bromo- β -lactams with (hetero) aryl/alkenylboronate esters. In contrast to our previous studies^[25-26], Cu^IL reduced the slightly more reactive tertiary alkyl halide to generate a tertiary alkyl radical and Cu^{II}L, followed by transmetalation to generate a new aryl/alkenyl-Cu^{II}L species. The combination of this species with the tertiary alkyl radical led to the construction of α -quaternary β -lactam^[36] (See Figure 12). Notably, this reaction has broad substrate scope, including tertiary bromides as well as (hetero) aryl/alkenylboronate esters with different steric and electrical functional groups^[27].

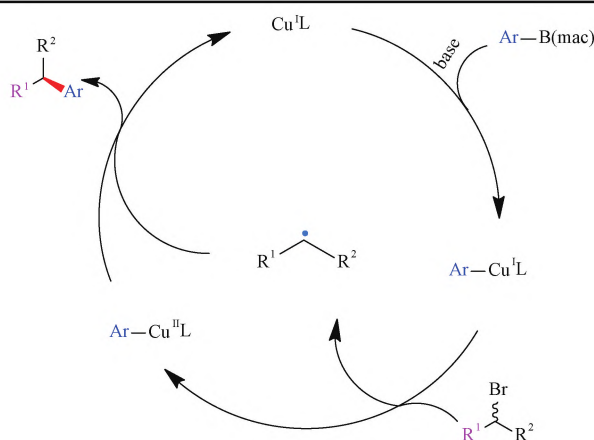
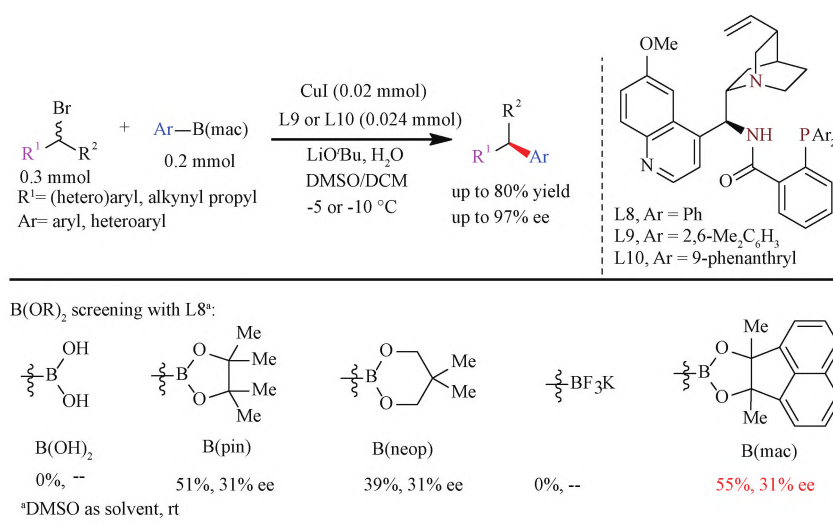


Figure 10 Enantioconvergent radical Suzuki-Miyaura C(sp³)-C(sp²) coupling of (hetero)arylboronate esters catalyzed by copper/chiral tridentate anionic ligand

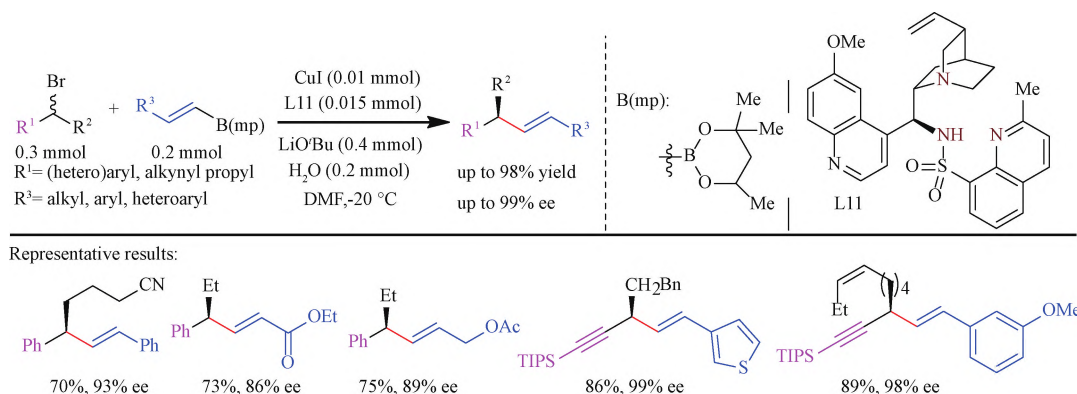


Figure 11 Enantioconvergent radical Suzuki-Miyaura C(sp³)-C(sp²) coupling of alkenylboronate esters catalyzed by copper/chiral tridentate anionic ligand

4 Summary and outlook

Considerable progress has been made in the copper-catalyzed asymmetric radical C(sp³)-C(sp²) bond formation of organoboron reagents. To address the challenge of the weak reductive capability of copper slowing the initiation of the reaction, three different strategies were developed; first, the addition of strong electrophiles or ox-

dants as radical precursors could compensate the challenge; second, the introduction of a light source enhanced the reducing ability of the copper catalyst in the excited state; third, the rational design of chiral tridentate anionic ligands improved the single-electron reducing ability of the copper catalyst, enabling mild electrophiles to be reduced to radicals. In summary, these three strategies complement each other, providing an effective syn-

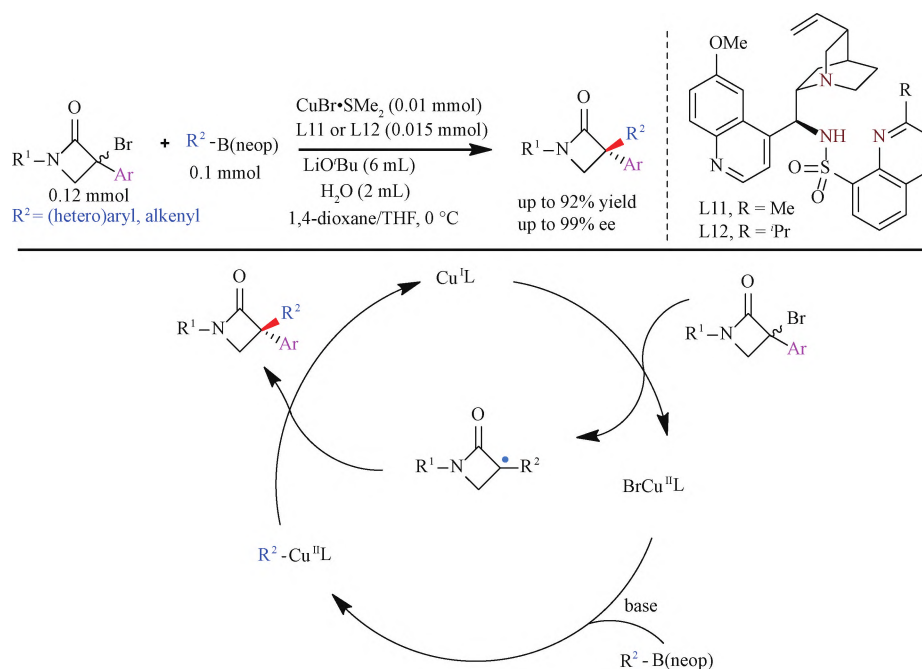


Figure 12 Enantioconvergent radical Suzuki-Miyaura C(sp³)—C(sp²) coupling of tertiary α -bromo- β -lactams catalyzed by copper/chiral tridentate anionic ligand

thetic tool for the construction of chiral C(sp³)—C(sp²) bonds. Despite the significant development in this field, there are still many challenges to be addressed. Firstly, as for the scope of nucleophiles, copper-catalyzed enantioselective C(sp³)—C(sp³) bond construction reaction of alkyl boron reagents has not been reported, alkenyl boron reagents have just been applied in cross-coupling reactions and urgently need to be applied to more types of asymmetric radical reactions. Secondly, as for the scope of electrophiles, the types of reported radical precursors are limited, and more radical precursors (such as carbon electrophiles, heteroatom electrophiles, and fluorine-containing electrophiles) urgently need to be explored to provide more structurally diverse chiral products. Furthermore, the design of novel chiral ligands and the development of new catalytic systems to achieve a wider range of enantioselective radical reactions are necessary. Finally, the in-depth research into the reaction mechanism is needed, especially the discovery of the key enantio-determining step, combination with detailed mechanistic experiments and DFT calculations to further deeply understand of the reaction process.

Acknowledgement

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铜催化有机硼试剂参与的自由基不对称 C(sp³)—C(sp²)键构建反应

徐丹彤¹, 梁思谋^{1,2}, 杨昌江^{1,2}, 李忠良^{1,2}, 顾强帅³, 刘霖^{*,1,2}, 刘心元^{*,1}

1. 南方科技大学化学系深圳市格拉布斯研究院, 广东 深圳 518055;
2. 大湾区大学(筹)化学系东莞市数据科学与智能医学重点实验室, 广东 东莞 523000;
3. 南方科技大学前沿与交叉科学研究院, 广东 深圳 518055

[摘要] 有机硼试剂具有易于合成、稳定以及低毒的优势, 被广泛地应用于C—C键的构建中。其中, 铜催化有机硼试剂参与的自由基不对称(杂)芳基/烯基化反应是构建手性C(sp³)—C(sp²)键的重要方式之一, 该类型反应成功的关键在于手性配体的合理设计, 其与铜组成的手性协同催化体系既要保证反应的高效启动, 还要实现高活性烷基自由基的立体控制。本文综述了两种类型手性配体的发展对这个领域研究进展的影响, 并对该领域做出展望。

[关键词] 铜催化剂; 自由基; 不对称; 有机硼试剂; 手性配体