



Cite this: DOI: 10.1039/d3gc02793g

The first-row transition metal-catalysed enantioconvergent radical Suzuki–Miyaura C(sp³)–C coupling of racemic alkyl halides

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The enantioconvergent radical Suzuki–Miyaura cross-coupling of racemic alkyl halides represents a powerful approach for the construction of valuable C(sp³)–C bonds. In this regard, the earth-abundant first-row transition metal (Ni, Fe, Co, and Cu) catalyst possesses a good single-electron transfer ability and can easily convert racemic alkyl halides to the prochiral alkyl radicals, providing an ideal solution for enantioconvergence. The utilization of chiral ligands would further facilitate the realization of enantioselective control over the prochiral alkyl radicals. This Perspective will discuss the advances and anticipate further development in this burgeoning field.

 Received 28th July 2023,
Accepted 17th January 2024

DOI: 10.1039/d3gc02793g

rsc.li/greenchem

1. Introduction

Transition metal-catalysed Suzuki–Miyaura coupling serves as one of the most applied cross-coupling reactions to construct

synthetically valuable C–C bonds owing to the use of stable, easily available, and low-toxic organoboron reagents.¹ As such, tremendous development has been achieved in the past several decades in the classic Suzuki–Miyaura C(sp²)–C coupling of (hetero)aryl/alkenyl (pseudo)halides.² As an analogy, the C(sp³)–C coupling of alkyl (pseudo)halides has been less developed, which stems from difficult oxidative addition and facile β-H elimination of alkyl-metal complexes compared with the (hetero)aryl/alkenyl-metal counterparts.³ Notably, the achievement of asymmetric Suzuki–Miyaura C(sp³)–C coupling can construct synthetically valuable enantioenriched three-dimensional molecules of great interest in organic chemistry and drug synthesis.⁴ In this respect, the stereospecific coup-

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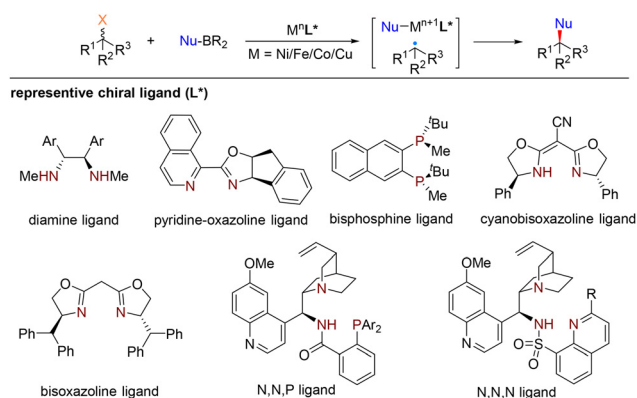
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ling of chiral alkyl electrophiles with organoboron nucleophiles using an achiral catalyst has provided an important approach for constructing the chiral C(sp³)-C bonds.⁵ The development of enantioconvergent C(sp³)-C cross-coupling of racemic alkyl halides using chiral catalysts represents a more attractive approach since no chiral substrates are needed.⁶ In this regard, the precious transition metal (Rh, Pd) catalyst has been utilized in several examples of enantioconvergent C(sp³)-C(sp²) coupling *via* a dynamic kinetic asymmetric transformation by Fletcher and Tang, respectively.^{7,8}

Compared with the precious transition metal catalyst *via* a two-electron insertion process,^{7,8} the earth-abundant first-row transition metal (Ni, Fe, Co, and Cu) catalyst possesses a good single-electron transfer (SET) ability.⁹ Thus, the chiral first-row transition metal complexes can easily reduce racemic alkyl halides to smoothly generate the corresponding prochiral alkyl radicals and the oxidized transition metal complexes *via* an SET process. Subsequently, the interaction of the thus-oxidized transition metal complexes with the alkyl radicals could afford a single enantiomer of the coupling product. The whole process provides a good solution for the enantioconvergent radical Suzuki-Miyaura C(sp³)-C coupling of racemic alkyl halides with organoboron reagents, as pioneered by Fu and others (Scheme 1).¹⁰ For a comparison of the first-row transition metal at the ground state, the standard electrode potentials $E^\circ(\text{M}^{\text{II}}/\text{M}^0)$ are -0.44, -0.28, -0.26, and +0.34 V for Fe, Co, Ni, and Cu, respectively.¹¹ So, the SET ability follows this trend: Fe > Co ~ Ni > Cu. Notably, the addition of diverse chiral ligands could greatly tune the redox potential of the first-row transition metal. This Perspective summarizes these enantioconvergent radical Suzuki-Miyaura C(sp³)-C cross-coupling, which is categorized on the basis of different transition metals. In this Perspective, we will introduce the substrate scope of organoboron reagents and racemic alkyl halides, and discuss the chiral ligand development to achieve



Scheme 1 The first-row transition metal-catalysed enantioconvergent radical Suzuki-Miyaura coupling of racemic alkyl halides.

the enantioselective control. At last, we will discuss the existing challenges and anticipate continuous efforts in this emerging field.

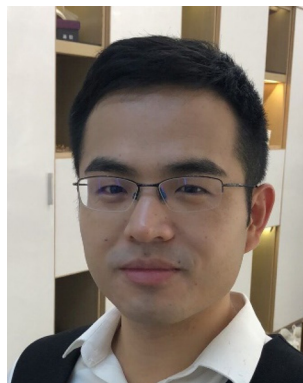
2. Ni-catalysed enantioconvergent radical Suzuki-Miyaura cross-coupling of racemic secondary alkyl halides

Compared with its congeners (palladium or platinum), nickel possesses a greater propensity to access an array of oxidation states (such as Ni⁰, Ni^I, Ni^{II}, and Ni^{III}), which made nickel an appealing catalyst for the development of enantioconvergent radical coupling of racemic alkyl electrophiles with organoboron nucleophiles.⁹ The pioneering work on Ni-catalysed enantioconvergent Suzuki-Miyaura coupling has been reported by Fu's group in 2008,^{12a} showcasing C(sp³)-C(sp³)



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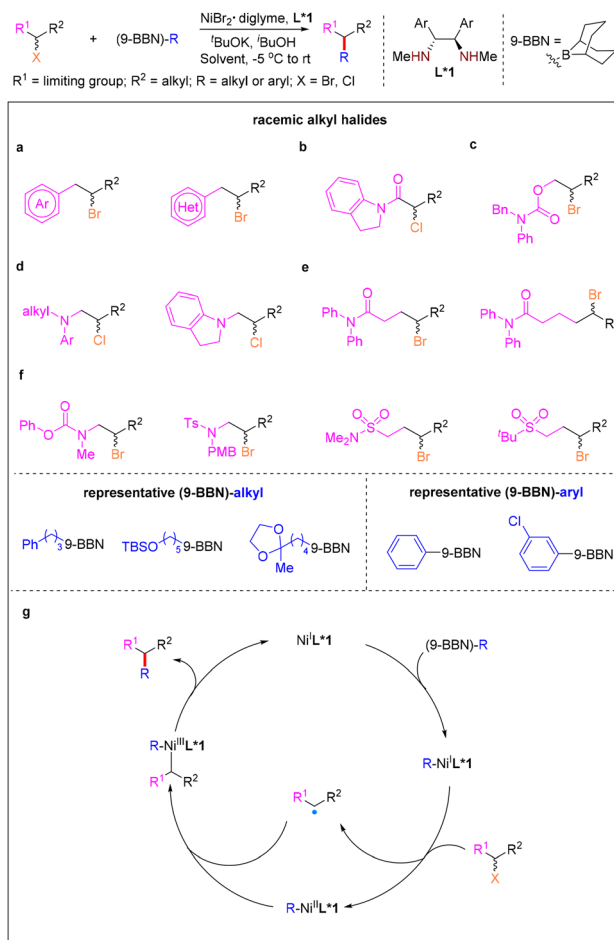
coupling by the use of easily accessible chiral diamine ligands **L*1**. In this paper, Fu and co-workers described this enantioconvergent coupling of secondary homobenzylic bromides with alkyl-(9-borabicyclo[3.3.1]nonane) (alkyl-(9-BBN)) to afford new C(sp³)-C(sp³) bonds with good yields and enantioselectivity (Scheme 2a).^{12a} Notably, rather than the use of aryl boronic acids in the racemic transformations from the same group,^{12b-d} the authors employ the highly reactive 9-BBN-derived organoboron reagents as the coupling partners in the enantioconvergent transformations. After demonstrating the potential of Ni-catalysed enantioconvergent C(sp³)-C(sp³) coupling, the same group has developed an enantioconvergent arylations of secondary α -chloroamides with aryl-(9-BBN) for the formation of new C(sp³)-C(sp²) bonds (Scheme 2b).¹³ Besides, secondary alkyl bromides bearing carbamate group or alkyl chlorides bearing proximal amine moiety could also undergo Ni-catalysed enantioconvergent C(sp³)-C(sp³) coupling to provide the desired chiral products bearing carbamate or amine group with excellent enantioselectivity, respectively (Scheme 2c and d).¹⁴ Interestingly, such a catalytic system could also be smoothly accomplished with the use of directing group (including amides, carbamates, sulfonamides, and sulfones) on secondary alkyl halides to provide the C(sp³)-C(sp³) coupled product with good to excellent enantioselectivity (Scheme 2e and f).¹⁵ On the basis of these reported results, the authors subsequently proposed a plausible mechanism as shown in Scheme 2g.^{14b,15} First, the Ni^IL*1 complex undergoes a transmetalation process with R-(9-BBN) and gives the intermediates R-Ni^IL*1. Afterward, the intermediates undergo a single electron reduction with alkyl halides to deliver prochiral alkyl radicals and the complexes R-Ni^{III}L*1 and subsequently proceed oxidative addition to give the Ni^{III} intermediates. Finally, the reductive elimination of the Ni^{III} intermediates delivered the desired products and regenerated Ni^IL*1 complexes for the next catalytic cycle.



Xin-Yuan Liu

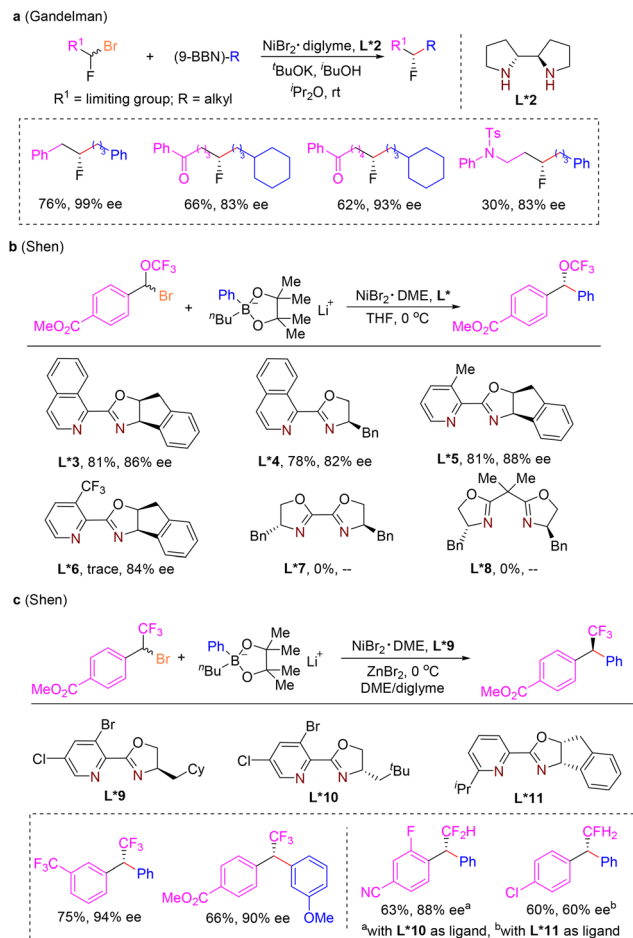
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Scheme 2 Ni-catalysed enantioconvergent radical Suzuki-Miyaura coupling of racemic secondary alkyl halides (Fu).

The fluorine and fluoroalkyl groups, such as fluoro-, trifluoromethoxy-, and trifluoromethyl moieties serve as a valuable “magic effect” in drug discovery of the pharmaceutical and agrochemical industries.¹⁶ Based on the above development, two other groups have achieved the Ni-catalysed enantioconvergent radical Suzuki-Miyaura coupling of fluoro-, trifluoromethoxy-, and trifluoromethyl-substituted secondary alkyl halides, respectively. Gandelman and co-workers have established an attractive method to generate chiral fluoroalkanes with good to excellent enantioselectivity.¹⁷ In this Ni/chiral diamine ligand **L*2** catalytic system, diverse directing groups, including benzylic moieties, ketones, and sulfonamides in the alkyl halides are used in the cross-coupling (Scheme 3a). In 2017, Shen and co-workers developed a Ni-catalysed enantioconvergent Suzuki-Miyaura coupling of readily available α -bromobenzyl trifluoromethyl ethers with arylboronate lithium salts.¹⁸ Notably, the utilization of lithium organoborate is due to its good transmetalation ability compared with the corresponding boronic acids. The ligand investigation suggested that the reaction proceeded smoothly with the use of chiral pyridine-oxazoline ligands (**L*3-L*6**) and **L*5** provided the best result in 81% yield and 88% ee. However, chiral

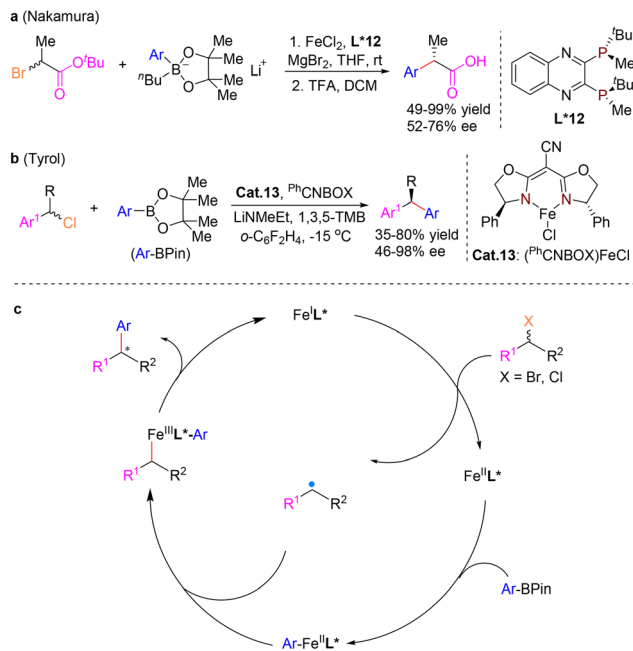


Scheme 3 Ni-catalysed enantioconvergent radical Suzuki–Miyaura coupling to construct fluoro-, trifluoromethoxy-, and fluoroalkyl-substituted chiral centers.

bisoxazoline ligands (**L*7** and **L*8**) were completely ineffective (Scheme 3b). Encouraged by the above success and used similar strategy, the same group further developed an enantioconvergent coupling of racemic fluoroalkyl-substituted benzyl halides with arylzinc reagents (*in situ* generated from arylboronate lithium salts with $ZnBr_2$) to construct trifluoromethyl-, difluoromethyl-, and monofluoromethyl-substituted chiral stereogenic centers with good to excellent enantioselectivity (Scheme 3c).¹⁹ Recently, the Ni/chiral pyridine-oxazoline catalyst was also used in enantioconvergent coupling of racemic 3-bromo-phthalides and arylboronic acids to give chiral 3-aryl-phthalides in moderate to excellent yields with good enantioselectivity.²⁰

3. Fe-catalysed enantioconvergent radical Suzuki–Miyaura cross-coupling of racemic secondary alkyl halides

Iron and cobalt possess good single electron transfer ability as well, and several examples using these transition metals have been disclosed in the enantioconvergent radical cross-coupling.

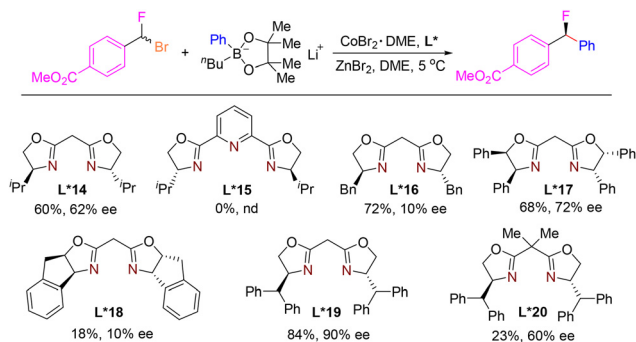


Scheme 4 Fe-catalysed enantioconvergent radical Suzuki–Miyaura coupling of racemic secondary alkyl halides.

ling. Nakamura and co-workers have developed the first iron-catalysed enantioconvergent radical Suzuki–Miyaura coupling of *tert*-butyl α -bromopropionate with arylboronate ester lithium salts to fast access various optically active α -arylpropionic acids using P-stereogenic chiral bisphosphine ligand **L*12** (Scheme 4a).²¹ In 2020, Tyrol and co-workers have accomplished another enantioconvergent radical $C(sp^3)$ – $C(sp^2)$ coupling of the low reactive benzylic chlorides and arylboronic esters to obtain chiral 1,1-diaryllkanes with the use of an iron-based catalyst containing a chiral cyanobisoxazoline ligand framework **Cat.13** (Scheme 4b).²² Although these two examples only gave a moderate to good enantioselectivity, the iron catalyst is still a considerable alternative due to its cost-effectiveness and safe properties, which might apply in pharmaceutical and agrochemical synthesis.²³ The plausible mechanism was proposed as shown in Scheme 4c. First, the $Fe^I L^*$ complex undergoes a single electron reduction with alkyl halides to generate prochiral alkyl radicals and the $Fe^{II} L^*$ intermediate. Afterward, the $Fe^{II} L^*$ intermediate undergoes a transmetalation process with arylboronate esters to give the aryl- $Fe^{III} L^*$ intermediate, which interacts with the alkyl radicals to give the aryl- $Fe^{III} L^*$ intermediate. The final reductive elimination step affords the desired products and regenerates the $Fe^I L^*$ complex.

4. Co-catalysed enantioconvergent radical Suzuki–Miyaura cross-coupling of racemic secondary alkyl halides

Even though Co-catalysed cross-coupling of alkyl halides has been remarkably developed,²⁴ the enantioconvergent $C(sp^3)$ – C



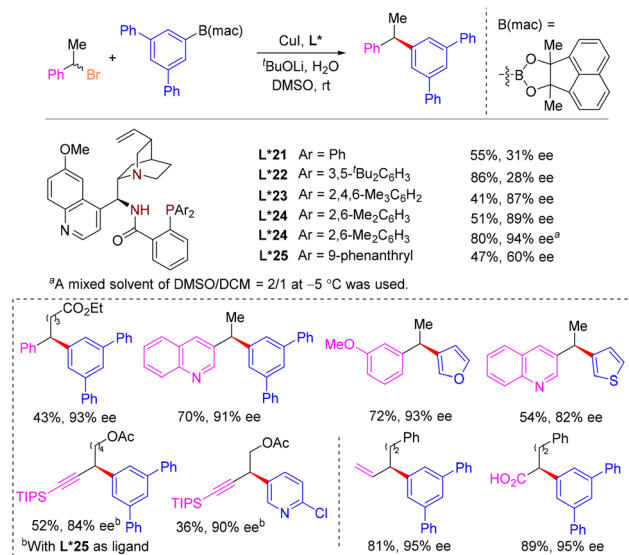
Scheme 5 Co-catalysed enantioconvergent radical Suzuki–Miyaura coupling of racemic secondary fluorinated benzyl bromides (Shen).

cross-coupling reactions using Co catalyst have rarely been reported.²⁵ The major challenges lie in the lack of suitable ligands for the enantioselective control and the significant background reaction in the absence of chiral ligands.²⁴ Until recently, Shen and co-workers have successfully achieved the first Co/chiral bisoxazoline ligand **L*19** catalysed enantioconvergent radical Suzuki–Miyaura C(sp³)–C(sp²) coupling of the easily available secondary fluorinated benzyl bromides with a variety of arylboronate lithium salts in the presence of zinc bromide to give medically valuable α-fluorinated diaryl-methane with good yields and excellent enantioselectivity (Scheme 5).^{25d}

5. Cu-catalysed enantioconvergent radical Suzuki–Miyaura cross-coupling of racemic alkyl halides

Compared with Ni/Fe/Co catalysts, copper possesses a relatively weak reducing capability, which retards the reaction initiation to generate the alkyl radicals from the corresponding alkyl halides. Thus, copper-catalysed C(sp³)–C coupling of alkyl halides with organoboron reagents might undergo two pathways (the stereoablative radical process or stereospecific S_N2-type process).²⁶ To achieve a Cu-catalysed enantioconvergent cross-coupling of racemic alkyl halides with organoboron reagents, the reaction mechanism has to completely proceed through the stereoablative radical process. To solve this challenge, we hypothesized that a rationally designed chiral electron-rich ligand could enhance the reducing capability of copper, which might promote the generation of alkyl radicals *via* a single electron reduction of alkyl halides. As part of our continuous efforts in designing novel ligands for Cu-catalysed asymmetric radical reactions,²⁷ we have developed a Cu/multidentate anionic N,N,P-ligand²⁸ catalyst for enantioconvergent radical Sonogashira C(sp³)–C(sp).^{27c} The utilization of the electron-rich N,N,P-ligand is crucial for the efficient radical generation and the chiral C(sp³)–C(sp) bond formation. To further prove the above hypothesis, a class of experiments on the catalysis's redox potential was conducted, and found that the

reduction potential of Cu/N,N,P-ligand catalyst is lower than that of Cu/chiral bisoxazoline catalyst and CuBr according to the cyclic voltammogram study. The above results demonstrated that N,N,P-ligand can significantly enhance the reducing capability of copper catalyst and further promote the reaction initiation process.^{10c,29} Based on these developments, the novel catalytic system was further applied in enantioconvergent radical C(sp³)–C(sp²) coupling of alkyl bromides with (hetero)arylboron nucleophiles. After systematically modifying the ligand structure (**L*21–L*26**), we have found that the steric bulkiness of the ligand on the *ortho* position of the aryl ring (**L*23** and **L*24**) could obviously improve the enantioselectivity. Notably, the reaction proceeded well with the stable and easily available neutral arylboronate esters, and the addition of ^tBuOLi and H₂O can largely improve the reaction efficiency possibly due to the promotion of the transmetalation process. Furthermore, this reaction has a broad scope, tolerating the (hetero)aromatics either on the alkyl bromides or the boronate esters. Thus, it could quickly deliver pharmaceutically valuable enantioenriched 1,1-di(hetero)arylalkane, 1-aryl-1-heteroarylalkane, (hetero)aryl-benzyl alkynes as well as other chiral building blocks *via* follow-up transformations (Scheme 6). Notably, when using the low reactive propargyl

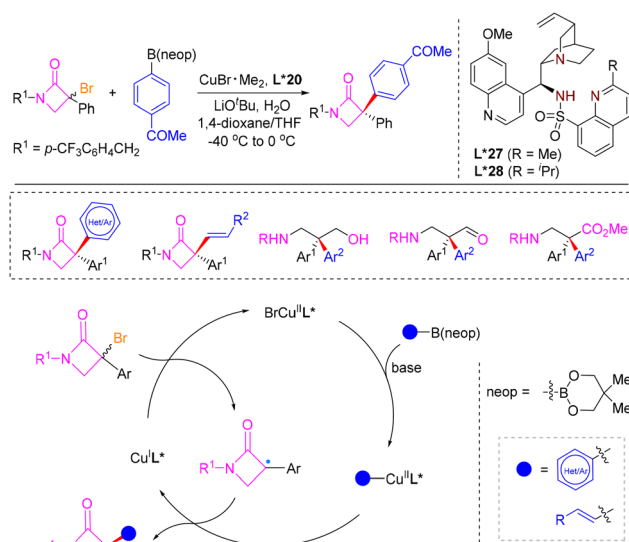


Scheme 6 Cu-catalysed enantioconvergent radical Suzuki–Miyaura coupling of racemic secondary alkyl bromides with (hetero)arylboronate esters (Liu).

chloride as an electrophile, this reaction could also proceed smoothly to afford the desired product with excellent enantioselectivity, but with a moderate yield. It might be due to the low reactivity of alkyl chlorides that led to the low reaction efficiency. Based on the reported results, a plausible mechanism was proposed as shown in Scheme 6. First, $\text{Cu}^{\text{I}}\text{L}^*$ complex undergoes a transmetalation process with B(mac)-derived arylboronate esters to give the (hetero)aryl- $\text{Cu}^{\text{I}}\text{L}^*$ intermediate. Afterward, the intermediate undergoes a single electron reduction with alkyl bromides to generate prochiral alkyl radicals and the (hetero)aryl- $\text{Cu}^{\text{II}}\text{L}^*$ intermediate. Finally, $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ bonds are constructed with excellent enantioselective control *via* the interaction of (hetero)aryl- $\text{Cu}^{\text{II}}\text{L}^*$ intermediate and alkyl radicals.³⁰

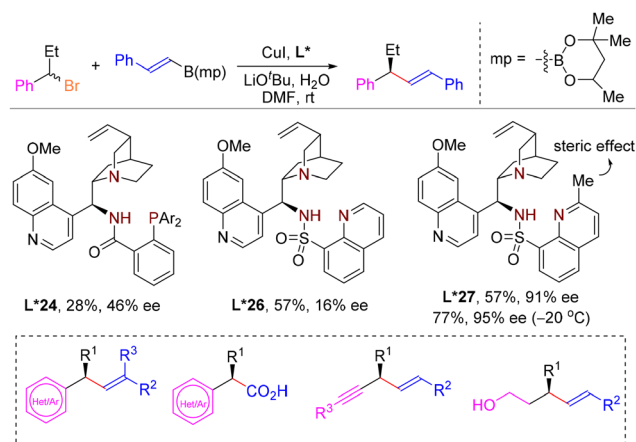
Chiral alkenes are valuable synthons to quickly access diverse chiral building blocks, such as chiral alkanes, alcohols, aldehydes, ketones, carboxylic acids, *etc.*³¹ As such, we next switched our attention to the enantioconvergent radical $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ cross-coupling of alkyl halides with alkenylboronate esters (Scheme 7). Unfortunately, the originally superior N,N,P-ligands **L*24** for (hetero)arylboronate esters showed low yields and moderate enantioselectivity in this reaction. After systematically investigating many ligand scaffolds, we discovered a hemilabile anionic N,N,N-ligand **L*27** to achieve the coupling of the secondary alkyl halides with alkenylboronate esters. The reaction has a broad scope, covering diverse (hetero)benzyl and propargyl bromides as well as vinyl- and mono-/disubstituted alkenylboronate esters with good to excellent yields and excellent enantioselectivity.³² Propargyl chloride was also a suitable coupling partner for the reaction to provide the corresponding product in a diminished yield with similar ee.³²

Encouraged by the above success of Cu-catalysed enantioconvergent $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ coupling of secondary alkyl halides with (hetero)aryl and alkenylboronate esters, we next switched our attention to the enantioconvergent radical coupling of ter-



Scheme 8 Cu-catalysed enantioconvergent radical Suzuki–Miyaura coupling to construct α-quaternary β-lactams (Liu).

tiary alkyl halides with these types of organoboron reagents (Scheme 8).³³ With our originally superior Cu/hemilabile N,N,N-ligand catalytic system,³² we further successfully achieved the asymmetric cross-coupling of α-bromo-β-lactams with (hetero)aryl or alkenylboronate esters to construct the sterically congested quaternary stereocenters. More importantly, when allied with follow-up ring-opening reactions, this strategy could quickly deliver β-quaternary γ-amino alcohols as well as α-quaternary β-amino aldehyde/esters, respectively. Different from the mechanism of our previous work,^{30,32} this reaction may be initiated by the single-electron reduction of tertiary alkyl bromides with $\text{Cu}^{\text{I}}\text{L}^*$. The $\text{Cu}^{\text{I}}\text{L}^*$ complex then undergoes the transmetalation with organoboronate esters with $\text{Cu}^{\text{II}}\text{L}^*$, and subsequently interacts with the newly generated tertiary alkyl radicals to provide the desired chiral α-quaternary β-lactams.³⁴



Scheme 7 Cu-catalysed enantioconvergent radical Suzuki–Miyaura coupling of racemic secondary alkyl bromides with alkenylboronate esters (Liu).

6. Conclusion and perspectives

Great efforts have been made in the development of the first-row transition metal-catalysed enantioconvergent radical Suzuki–Miyaura couplings of racemic alkyl halides with organoboron reagents in the past two decades. Crucial to the enantioselective control is the interaction of *in situ* prochiral alkyl radicals generated from alkyl halides with the chiral Nu- $\text{M}^{\text{II}}\text{L}^*$ complex. In this Perspective, we have summarized the recent development of Ni-catalysed $\text{C}(\text{sp}^3)\text{--C}$ coupling of diverse secondary alkyl halides, Fe-catalysed $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ coupling of secondary α-bromo esters or benzyl halides; Co-catalysed $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ coupling of secondary fluorinated benzyl bromides, and Cu-catalysed $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ coupling of secondary benzyl/propargyl halides and tertiary α-bromo-β-lactams. Notably, when the less reactive alkyl chlorides were

utilized instead of the corresponding bromides as electrophiles in Ni, Fe, and Cu catalysis, the reaction would generally afford the coupling products with diminished yields and similar ee.

Despite the significant progress in this burgeoning field, there are still many challenges to be addressed and tasks to be accomplished. The scope of nucleophiles and electrophiles has to be further expanded to develop the more general and powerful enantioconvergent Suzuki–Miyaura C(sp³)–C coupling. As for the scope of nucleophiles, the enantioconvergent transformation of secondary and tertiary alkyl boron reagents has not been developed probably due to the steric hindrance of these alkyl boron reagents. Despite the enormous challenges, we hope that the development of chiral ligands with low steric effect might be helpful to realize the coupling of the sterically congested alkyl organoboron reagents. As for the scope of electrophiles, most alkyl halides are limited to those generating secondary alkyl radicals with π -stabilized effect or directing group. Tertiary alkyl halides are scarcely used and only one example was reported using tertiary α -bromo- β -lactam.³¹ The coupling of unfunctionalized alkyl halides and more tertiary alkyl halides should attract enough attention in the future. The realization of the challenging substrates calls for the design of a new catalytic cycle and the development of chiral ligands.

To further promote this cross-coupling development, the mechanism for the whole reaction pathway, especially the key enantio-determining step should be clearly disclosed. Thus, a series of mechanistic experiments and DFT calculations are necessary to conduct a deep understanding of the reaction process. In addition, X-ray structure analysis of chiral catalysts, the isolation of different intermediates, *in situ* NMR spectroscopy as well as electron paramagnetic resonance spectroscopy (EPR) analysis also contributed to the discourse of the mechanism. Finally, trace metal impurities^{27c,35} (Pd, Ag, and other 3d transition metals, *etc.*) might be responsible for some catalytic activity in the asymmetric reaction and should be considered and investigated in future research.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Natural Science Foundation of China (no. 22025103, 92256301, 21831002, 22201127, and 22101122), the National Key R&D Program of China (no. 2021YFF0701604 and 2021YFF0701704), Shenzhen Science and Technology Program (KQTD20210811090112004 and JCYJ20220818100604009), Shenzhen Key Laboratory of Cross-Coupling Reactions (ZDSYS20220328104200001), and Great Bay University is gratefully acknowledged. We appreciate the assistance of SUSTech Core Research Facilities.

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