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Enantioselective Borylative Functionalization of Internal Alkenes: A Platform for Constructing Vicinal Stereocenters†

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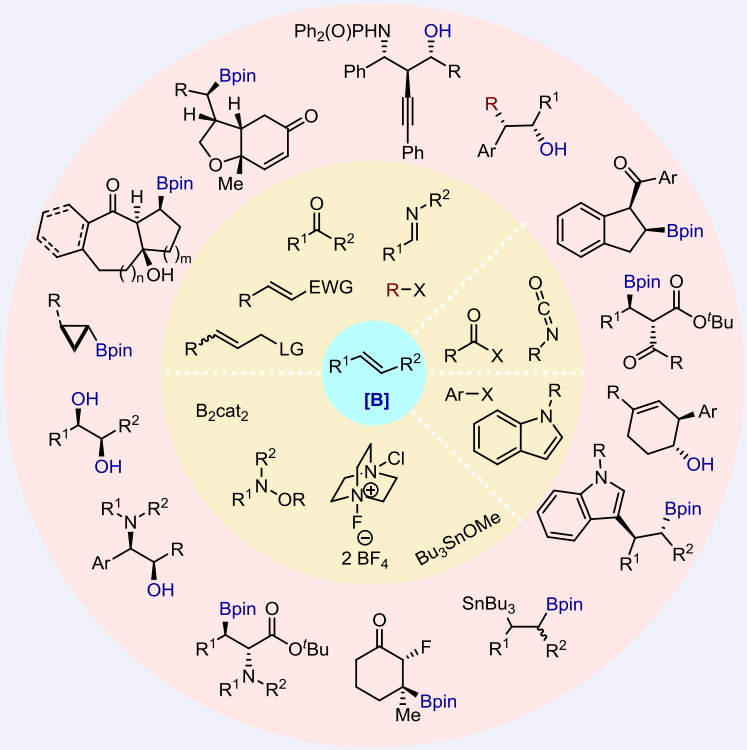
Keywords

Borylative functionalization | Organoboron | Vicinal stereogenic centers | Transition metal catalysis | Asymmetric synthesis

Comprehensive Summary



Vicinal stereogenic centers are ubiquitous structural scaffolds in both natural products and synthetic compounds, yet their enantioselective construction remains a significant challenge in organic synthesis. Organoboron compounds are of paramount importance in synthetic chemistry due to their ability to undergo facile transformations, yielding diverse essential chemical bonds such as carbon-carbon, carbon-oxygen, carbon-nitrogen, and carbon-halogen bonds. Transition-metal-catalyzed asymmetric borylative functionalizations of internal alkenes offer a promising strategy for the enantioselective installation of two adjacent chiral centers across carbon-carbon bonds. By leveraging the versatile transformations of the newly introduced boryl unit, this approach holds great potential for expanding the structural diversity of vicinal stereogenic scaffolds. In this concise review, we aim to highlight recent advancements in transition-metal-catalyzed asymmetric borylative functionalizations of internal alkenes, underscore their utility as a versatile approach for constructing vicinal stereogenic centers, and discuss unsolved challenges and future directions in this field.

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† Dedicated to the Special Issue of Boron Chemistry.

Key Scientists

Contents

1. Introduction

Vicinal stereogenic centers are common structural scaffolds in natural products and synthetic compounds.[1] The biological activity of chiral molecules is often closely related to their stereochemistry. Consequently, their enantioselective construction is of significant importance. Although various reactions have been reported for synthesizing vicinal chiral centers, the development of general and versatile synthetic strategies that enables precise control over both absolute and relative stereochemistry remains challenging.[1-3]

Organoboron compounds are a vital class of organic compounds, playing crucial roles in both synthetic chemistry and drug discovery.[4] Due to the efficiency with which carbon-boron (C-B) bonds can be transformed into various new chemical bonds, such as carbon-carbon, carbon-nitrogen, and carbon-halogen bonds, the development of C-B bond-forming reactions has been extensively pursued.[4a,c-d,5] Enantioenriched alkyl boron compounds, which typically undergo transformations in a stereospecific manner, are thus particularly attractive targets in asymmetric catalysis.

In this context, transition metal-catalyzed asymmetric hydroboration and borylative functionalization of alkenes has emerged as an effective approach to synthesizing these compounds.[6-7]

Internal alkenes are another important class of organic compounds, serving as useful precursors for a wide range of transformations. Although significant progress has been made in the transition metal-catalyzed asymmetric hydroboration and borylative functionalization of activated and terminal alkenes,[5a,c,e,g,8] the counterpart borylative functionalization reactions with internal alkenes remain underdeveloped. Developing such reactions has been challenging due to issues associated with reactivity and chemo-, regio- and enantioselectivity.[5e,g,8c] Nonetheless, these reactions have garnered considerable synthetic interest because they allow for the simultaneous installation of both a boryl group and other functionalities across unsaturated C-C double bonds.[5e,g,8c,9]

In recent years, there has been significant development in the transition metal-catalyzed asymmetric borylative functionalization of internal alkenes.[8-9] By leveraging the versatile transformations of the newly introduced boryl unit, this approach holds great potential for expanding the structural diversity of vicinal stereogenic scaffolds. In this review, we aim to highlight recent advancements in transition-metal-catalyzed asymmetric borylative functionalizations of internal alkenes and underscore their utility as a versatile tool for constructing structurally diverse vicinal stereogenic centers. The contents are categorized based on the type of electrophiles and are divided into four main sections: asymmetric borylative alkylation, borylative acylation, borylative arylation, and borylative heteroatomation.[8-9] Emphasis will be placed on discussing the characteristics of internal alkenes, electrophiles, as well as chiral catalysts. We also discuss unsolved challenges and future directions in this field, aiming to inspire further interest and advancements.

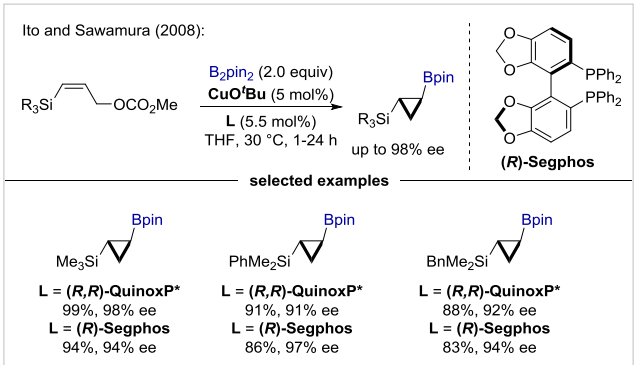
2. Asymmetric Borylative Alkylation of Internal Alkenes

2.1. Intramolecular asymmetric borylative alkylation

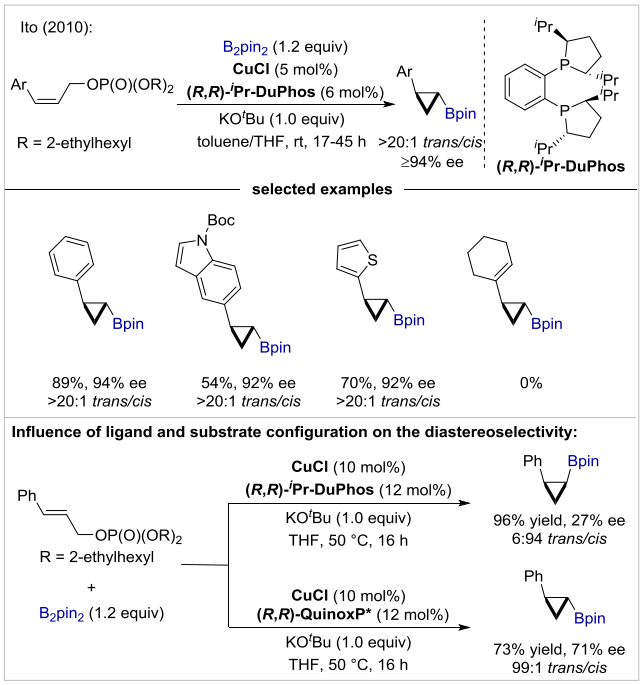
In 2008, Ito and Sawamura reported an intramolecular asymmetric borylative alkylation of silyl-substituted (*Z*)-alkenes, catalyzed by copper complexes bearing chiral Segphos or QuinoxP* ligands (Scheme 1).[10] The reaction exhibited good regio-, enantio-, and diastereoselectivity. The reaction initiated with an enantioselective addition of an *in situ*-generated boryl-copper intermediate (Cu-Bpin), in which the silyl group was crucial for controlling the regioselectivity of the borylcupration, enabling the formation of a stable *α*-silyl alkyl copper intermediate and thereby facilitating the cyclization. It is worth noting that the silyl-substituted (*E*)-alkenes also reacted smoothly but showed lower reactivity, chemoselectivity, and *trans*/*cis* selectivity.

β-Substituted styrenes also reacted regioselectively with boryl-copper species to form *α*-aryl alkyl copper intermediates due to the stabilizing effect of the aryl groups. Subsequently, the same group expanded their intramolecular asymmetric borylative alkylation reaction to 3-aryl allylic phosphate substrates (Scheme 2), yielding enantioenriched *trans*-2-aryl- and heteroaryl-substituted cyclopropyl boronates with high levels of enantio- and diastereoselectivity.[11] Both the chiral ligand and the configuration of the alkene were responsible for achieving high diastereoselectivity: when the reaction of (*E*)-allylic phosphates was conducted with (*R*,*R*)-^{i}Pr-Duphos, *cis*-substituted cyclopropane products formed, whereas *trans*-substituted products dominated when (*R*,*R*)-QuinoxP* was used. The stabilizing effect of aryl group in the substrate was indispensable for the reaction; switching the aryl group to a cyclohexenyl group resulted in no desired product formation.

Scheme 1 Intramolecular enantioselective borylative alkylation of silyl-substituted alkenes



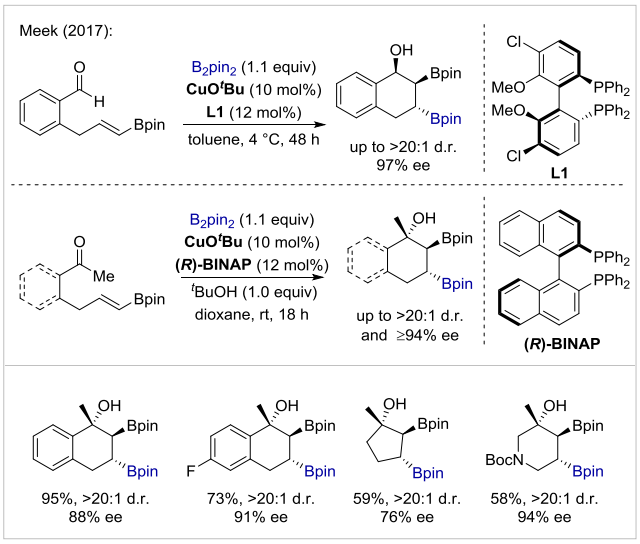
Scheme 2 Intramolecular enantioselective borylative alkylation of aryl-substituted alkenes



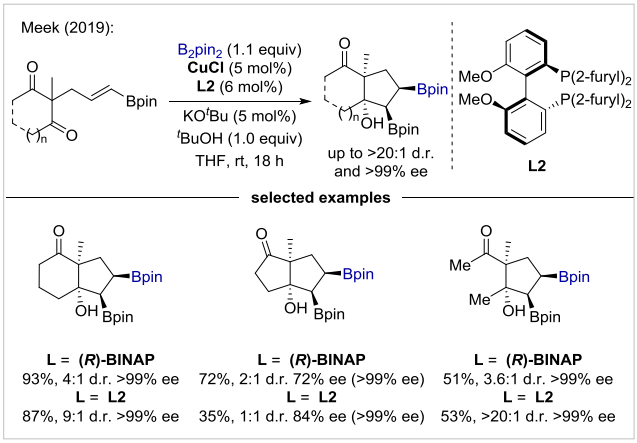
Boryl group exhibits similar *α*-stabilizing effect on the alkyl-copper species.[12] In 2017, Meek and co-workers designed an intramolecular borylative carbonyl-trapping reaction (Scheme 3).[13] 1-Alkenyl-B(pin) substrates bearing a carbonyl moiety underwent regio- and enantioselective borylcupration at the boryl-substituted alkene to afford an *α*-boryl alkyl-copper intermediate, which subsequently attacked the tethered electrophilic carbonyl group in a high diastereoselective fashion. This reaction resulted in the construction of tetralin products with three consecutive chiral centers, achieving high enantio- and diastereoselectivity. It is worth noting that although both ketone and aldehyde substrates could undergo the intramolecular borylative cyclization enantioselectively, the aldehyde substrate gave only moderate yield (49%) due to the severe competitive side reaction of Cu-Bpin with the aldehyde moiety (vs. the alkenyl-Bpin).

Later, the same group expanded the asymmetric intramolecular borylative carbonyl-trapping strategy to synthesize chiral cyclic compounds with four contiguous chiral stereogenic centers through a desymmetrization strategy (Scheme 4).[14] This approach enabled the synthesis of [6,5]- and [5,5]-bicyclic compounds as well as five-membered rings with high levels of enantioselectivity but moderate diastereoselectivity. Notably, the alkenyl-Bpin formation from alkynes and the subsequent borylative cyclization could be achieved using a single copper catalyst, enabling the assembly of these two reactions into a cascade.

Scheme 3 Intramolecular enantioselective borylative cyclization with aldehyde



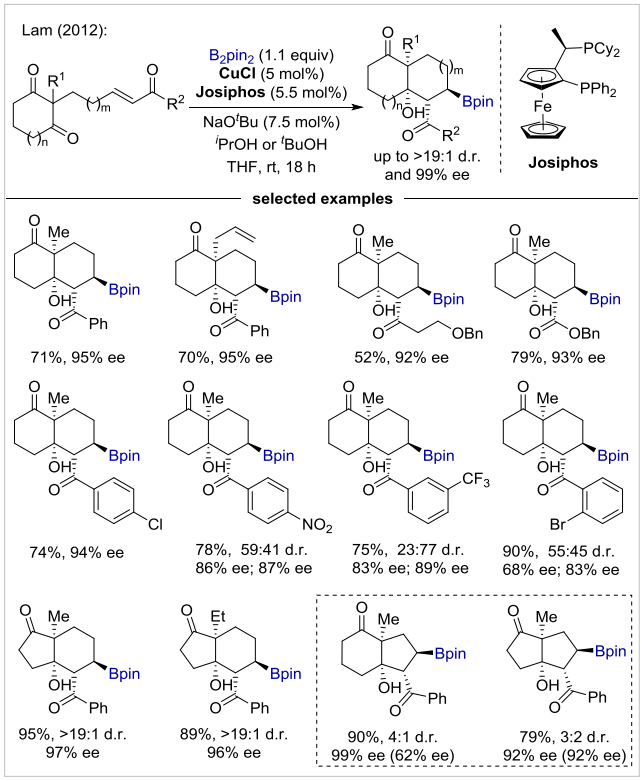
Scheme 4 Intramolecular enantioselective borylative cyclization with ketone



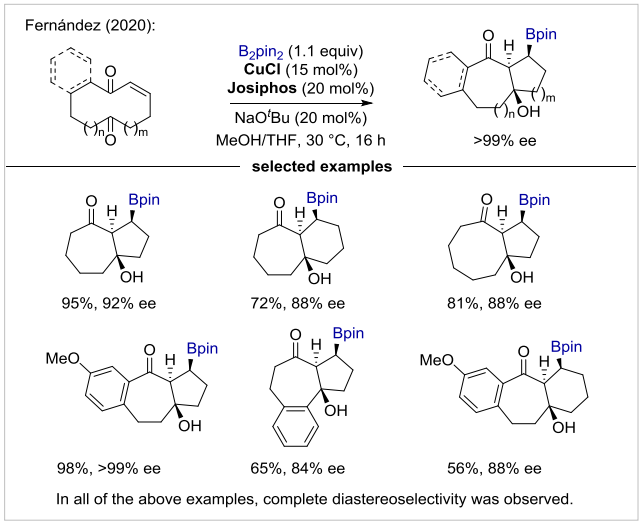
α, β-Unsaturated carbonyl units are also able to serve as acceptors of Cu-Bpin species, resulting in a chiral copper enolate intermediate. In 2012, Lam and co-workers developed a copper-catalyzed asymmetric borylative conjugate addition/aldol cyclization reaction (Scheme 5).[15] This reaction enabled the construction of various cyclic systems, such as [6,6]-, [5,6]-, [6,5]- and [5,5]-bicycles, each bearing four contiguous stereocenters, two of which were quaternary carbons, with high levels of enantioselectivity. However, the diastereoselectivity was found to be very sensitive to the variations in both the electronic and steric properties of the substrates. For example, when *α,β*-unsaturated aromatic ketones bearing electron-withdrawing substituents (*para*-NO_2 and *meta*-CF_3) or *ortho*-substituent (steric effect), the diastereoselectivity decreased significantly. Moreover, although [6,6]- and [5,6]-bicycles were obtained with high diastereoselectivity, [6,5]- and [5,5]-bicycles could only be obtained with low diastereoselectivity (d.r. = 4 : 1 and 3 : 2, respectively).

In 2020, Fernández and Vicario expanded the copper-catalyzed borylative conjugate-addition/carbonyl-trapping strategy to macrocyclic substrates (Scheme 6).[16] They achieved an asymmetric transannular borylative Aldol reaction by identifying a Josiphos-containing copper catalyst, enabling the construction of various bicycles bearing three continuous chiral centers with high levels of enantio- and diastereoselectivity.

Scheme 5 Intramolecular enantioselective borylative conjugate addition/cyclization



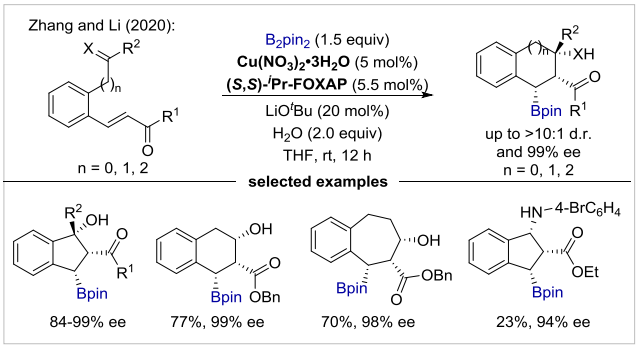
Scheme 6 Intramolecular enantioselective borylative transannular carbonyl addition



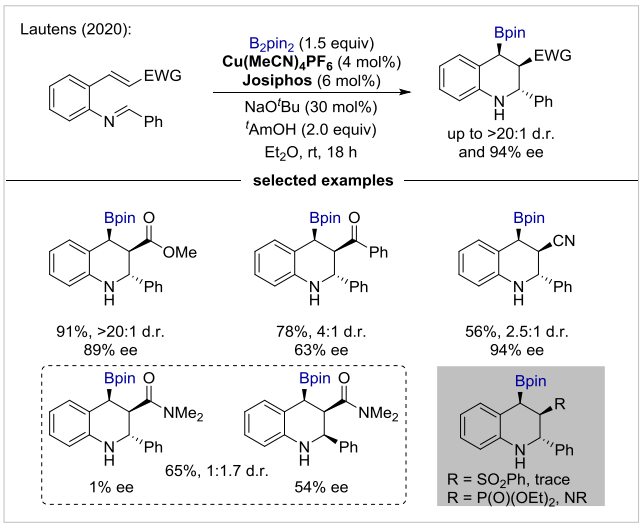
In the same year, Zhang and Li developed a copper-catalyzed tandem conjugate addition/aldol cyclization of electron-deficient olefins, utilizing a pendant aldehyde, ketone, or imine as electrophiles (Scheme 7).[17] The reaction produced benzo-fused five-, six-, and seven-membered ring products with good yields and high enantioselectivities when carbonyl groups were used as electrophiles. When an imine was used as the electrophile, the desired product could also be obtained with high enantioselectivity (94% ee), albeit in a low 23% yield.

Using internal imines as the electrophiles, Lautens and co-workers achieved an asymmetric copper-catalyzed borylative conjugate-addition/Mannich cyclization reaction (Scheme 8).[18] This innovative approach was applicable to various Michael acceptors, including *α,β*-unsaturated esters, ketones, nitrile, and

Scheme 7 Intramolecular enantioselective borylative conjugate addition/aldol cyclization



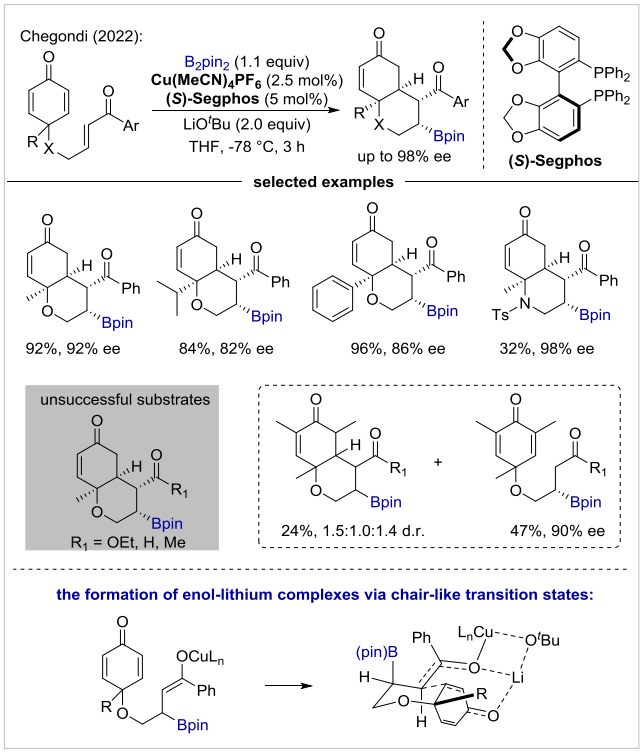
Scheme 8 Intramolecular enantioselective borylative conjugate addition/cyclization



amide, resulting in the formation of multifunctional tetrahydroquinolines with three contiguous stereocenters and moderate to good enantioselectivity. Unfortunately, reactions involving *α,β*-unsaturated sulfones or phosphonate as Michael acceptors did not proceed. Diastereoselectivity was typically high when *α,β*-unsaturated esters were used as Michael acceptors but was low with *α,β*-unsaturated ketones and nitriles. An interesting observation was the reversal of diastereoselectivity when *α,β*-unsaturated amides were employed as substrates, with the all-*cis* diastereomer becoming the major product, but the reasons for this phenomenon remain unknown.

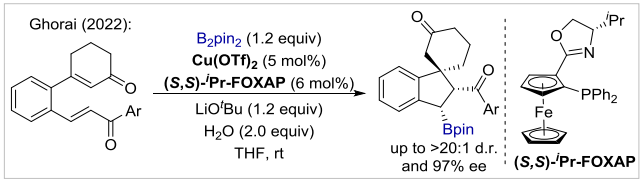
Electron-poor alkenes can serve as acceptors for both Cu-Bpin and alkyl-copper intermediates, but differentiating between these roles is not trivial. In 2022, Chegondi reported a copper-catalyzed asymmetric borylative conjugate addition/intramolecular Michael cascade reaction on enone-tethered 2,5-cyclohexadienones (Scheme 9).[19] This reaction exhibits a broad substrate scope, enabling the synthesis of bicyclic ketones with four contiguous stereocenters, and demonstrating excellent yields, enantioselectivity, and diastereoselectivity. However, using *α,β*-unsaturated ester, aldehyde, and methyl ketone as the acceptors of Cu-Bpin species failed to yield the desired products under standard reaction conditions. This failure was possibly due to the decreased electrophilicity of these *α,β*-unsaturated carbonyl units, resulting in the decomposition of most starting materials. When substrates with a methyl substituent at the *α*-position of cyclohexadienone were used, the target product was obtained with a low yield of 24%, and a significant amount of uncyclized product was also observed, likely due to the decreased electrophilicity of the cyclohexadienone. However, the sterically hindered quaternary carbon center at the γ-position of the cyclohexadienones is crucial for differentiating the reactivity of the enone and the cyclohexadienone scaffolds. DFT calculations were conducted to elucidate the role of the addition of an equimolar base in the reaction: it facilitates the formation of enol-lithium complexes via chair-like transition states, promoting C—C bond formation.

Scheme 9 Intramolecular enantioselective borylative conjugate addition/Michael addition



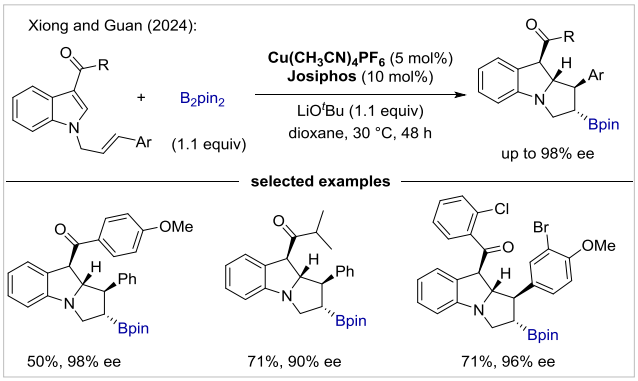
In the same year, the Ghorai group reported a similar copper-catalyzed borylative Michael addition/intramolecular Michael reaction cascade for synthesizing spirocyclic compounds (Scheme 10),[20] using a chiral bidentate phosphine oxazoline ligand. This reaction enabled the installation of three contiguous chiral centers with both good absolute and relative stereochemical control.

Scheme 10 Intramolecular enantioselective borylative conjugate addition/cyclization



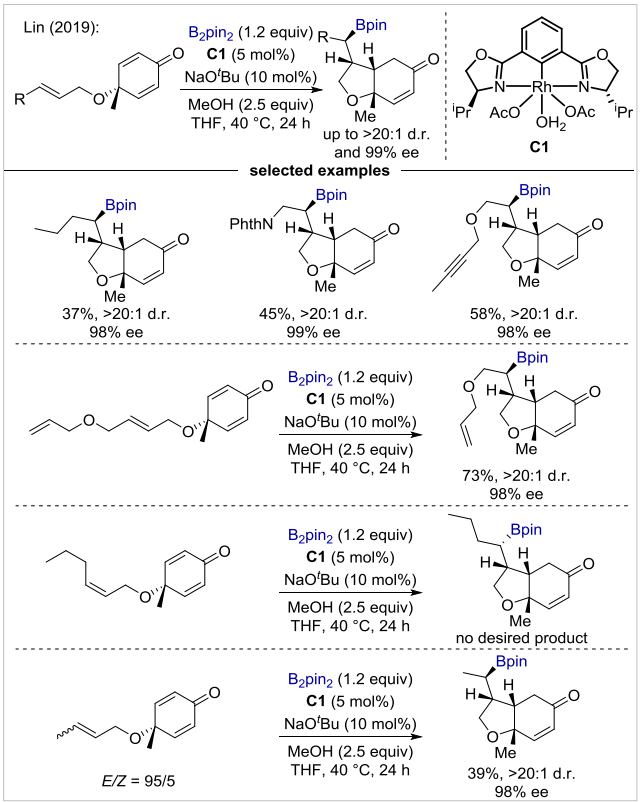
Saturated nitrogen-containing heterocycles, such as polycyclic indoline derivatives with multiple stereogenic centers, are widely found in natural products, agrochemicals, and pharmaceuticals, making them an important structural scaffold. In 2024, the groups of Xiong and Guan reported the enantioselective copper-catalyzed dearomative borylative cyclization of indoles, achieving the desired products with good yield, enantioselectivity, and diastereoselectivity (Scheme 11).[21] The reaction provided a convenient access to densely substituted enantioenriched *N*-heterocycles. DFT calculations indicated that olefin insertion is both the rate- and enantio-determining step of the reaction.

Scheme 11 Intramolecular enantioselective dearomative borylative cyclization of indoles



In previous discussions, copper catalysts have been highlighted as the major players in the borylative cyclization of internal alkenes. Other metal catalysts have also been reported to promote these reactions. In 2019, the Lin group disclosed a rhodium-catalyzed asymmetric borylative cyclization of cyclohexadienone-containing 1,6-dienes (Scheme 12).[22] This reaction notably utilized an internal allyl ether moiety as the acceptor of Rh-Bpin species, and the regioselectivity of the Rh-Bpin addition to the carbon-carbon bond in the allyl ether unit was proposed to result from a noncovalent interaction between the inserting alkene and the tethered cyclohexadienone moiety. To demonstrate their hypothesis, they designed substrates containing an unactivated monosubstituted terminal alkene, an unactivated *trans*-1,2-disubstituted internal alkene, and a cyclohexadienone (Scheme 12). The asymmetric borylative cyclization of these substrates occurred at the internal alkene rather than at the more reactive terminal alkene. It is also noteworthy that the configuration of the alkene

Scheme 12 Intramolecular enantioselective borylative conjugate addition/cyclization with cyclohexadienones



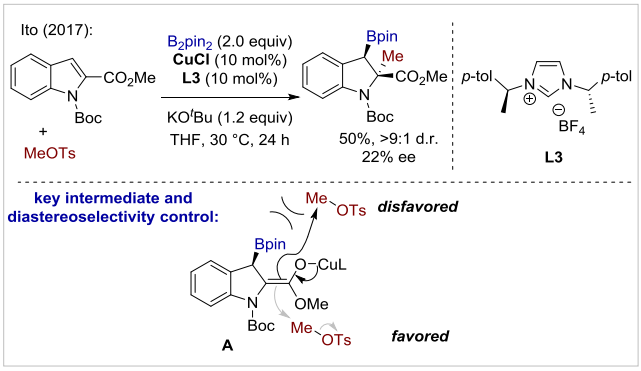
significantly influences the reactivity. While substrates with 1,2-disubstituted *trans*-alkenes proceeded smoothly, no desired borylative cyclization product was formed when the substrate bore a 1,2-disubstituted *cis*-alkene. This work highlights the versatility and potential of rhodium catalysts in asymmetric borylative cyclization reactions, providing a new avenue for the construction of complex chiral bicyclic structures with high regio-, diastereo-, and enantioselectivity.

2.2. Intermolecular asymmetric borylative alkylation of internal alkenes

The C2-C3 double bonds of indole-2-carboxylates exhibit similar reactivity with electron-poor alkenes, especially when an electron-withdrawing group is installed at the nitrogen atom. This unique reactivity allows electron-poor indoles to undergo dearomative functionalization. In 2015, Ito and co-workers developed a copper-catalyzed asymmetric dearomative borylative protonation of indole-2-carboxylates, achieving high levels of both enantioselectivity and diastereoselectivity.[23]

Building on this success, they later achieved the dearomative borylative methylation reaction with good diastereoselectivity (> 9 : 1 d.r.) (Scheme 13).[24] This reaction employed an NHC-containing copper complexes as the catalysts and MeOTs as the methylating reagent. However, attempts to develop an asymmetric version of this reaction were not successful: only 22% ee was obtained when a chiral NHC **L3** was used. To explain the high diastereoselectivity observed, the authors proposed that MeOTs prefers to approach the copper *O*-enolate intermediate **A** from the opposite face of the Bpin group to avoid steric congestion between the bulky B(pin) and MeOTs.

Scheme 13 Intermolecular enantioselective borylative methylation of electron-poor indoles

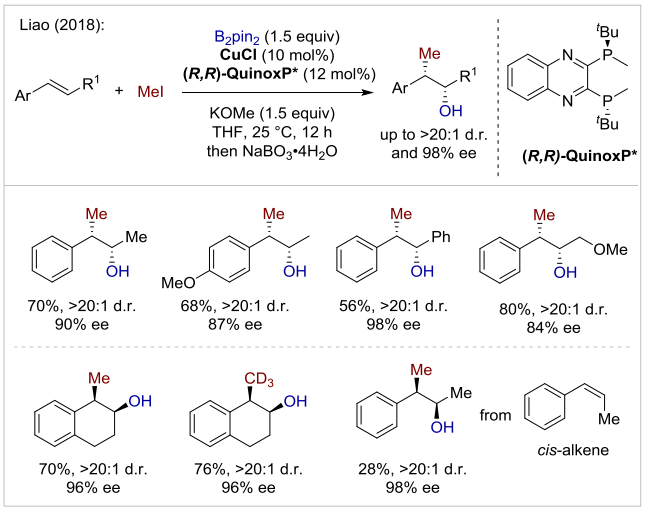


In 2018, Liao and co-workers disclosed an asymmetric borylative methylation of *β*-substituted styrenes using copper complexes ligated with a (*R,R*)-QuinoxP* ligand as the catalysts (Scheme 14).[25] This reaction was compatible with *E*-styrene derivatives bearing methyl, phenyl, or methoxymethyl substituents at the *β*-position, as well as dihydronaphthalene, resulting in the corresponding borylative methylation products with high levels of enantio- and diastereoselectivity. Interestingly, *Z*-*β*-substituted styrene also underwent the borylative methylation smoothly and yielded product with opposite configuration to those obtained from the *E*-substrate.

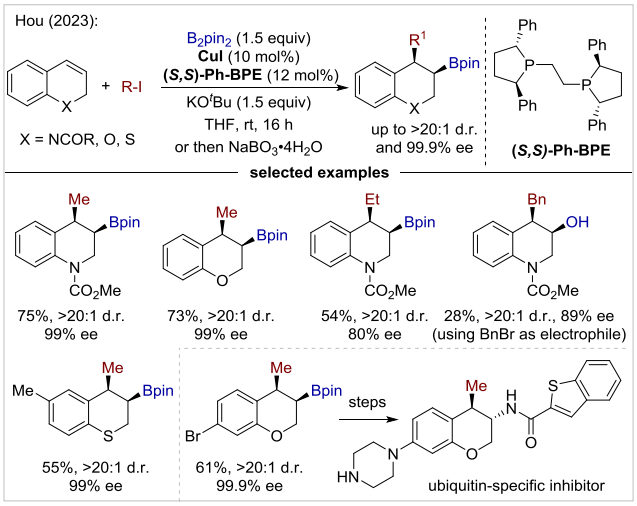
Recently, Hou's group achieved a highly enantio- and diastereoselective borylative methylation of diverse heterocyclic compounds, including 1,2-dihydroquinolines, 2*H*-chromenes and 2*H*-thiochromenes, catalyzed by copper complexes with a chiral bisphosphine (*R,R*)-Ph-BPE ligand (Scheme 15).[26] Besides methyl iodide, ethyl iodide and benzyl bromide could also be used as electrophiles, although these afforded the target products with lower yields. Scaffolds obtained from this reaction are of importance in the synthesis of biologically active molecules and drug

candidates. For instance, using the resulting borylmethylation product as key intermediate, a type of ubiquitin-specific inhibitor could be readily prepared through simple transformations.

Scheme 14 Intermolecular enantioselective borylative methylation of *β*-substituted styrenes

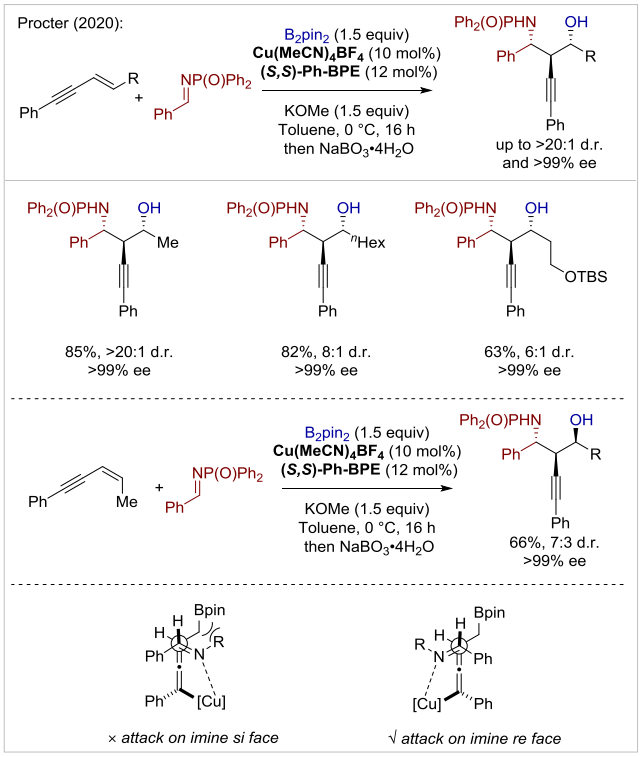


Scheme 15 Intermolecular enantioselective borylative methylation of heterocyclic alkenes



External imines can also serve as electrophiles to react with the alkyl metal intermediates generated *in situ* from borylative metalation of alkenes. In 2020, Procter and co-workers developed a chiral copper-catalyzed chemo-, regio-, and steroselective borylative alkylation of 1,3-enynes (Scheme 16).[27] The use of *N*-phosphinoylimine as electrophile is crucial for achieving high levels of enantio- and diastereoselectivity. Furthermore, the configuration of the enynes also significantly influences the diastereoselectivity: the reaction of *E*-enyne gave the target product with excellent d.r. (> 20 : 1), whereas the *Z*-enyne counterpart formed the product with a much lower diastereomeric ratio (d.r. = 7 : 3). Additionally, this system was applicable to substrates substituted at the terminal position of the alkene, enabling the synthesis of amino alcohols with three contiguous stereocenters and excellent enantioselectivity. When using *E*- or *Z*-enynes, two different diastereoisomers can be obtained. The reaction is proposed to proceed through borylcupration to form a propargyl copper intermediate, which isomerizes to an allenyl-copper intermediate. The latter attacked the *N*-phosphinoylimine from the less sterically demanding *re* face to avoid the unfavorable interactions between the *N*-phosphinoyl group and the CH_2Bpin group, accounting for the observed *anti*-diastereoselectivity.

Scheme 16 Intermolecular enantioselective borylative alkylation of 1,3-enynes with imines as the alkylating reagents

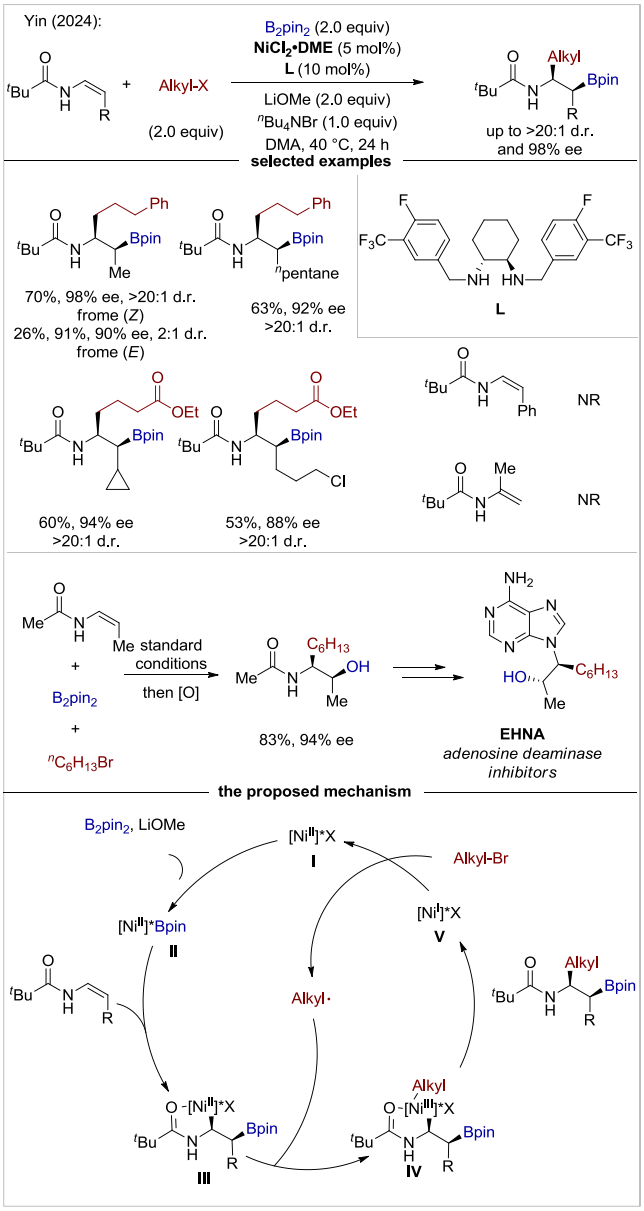


Copper-catalyzed intermolecular asymmetric borylative alkylation reactions forming a single stereocenter are out of the scope of this Review and are not discussed in detail here.[28]

In addition to the copper- and rhodium-catalyzed asymmetric borylative functionalization of internal olefins mentioned above, nickel catalysis has also made significant breakthrough in this field. For example, in 2024, Yin, Zhu, and Li reported a nickel-catalyzed asymmetric borylative alkylation of enamides (Scheme 17).[29] Using (*Z*)-enamides as substrates, the reaction delivered the desired products with good yield, enantioselectivity, and diastereoselectivity. However, when (*E*)-enamines were used, the yield dropped significantly (26%) and the diastereomeric ratio deteriorated to 2.6 : 1. The reaction was also sensitive to substituents on the alkenes. While various 2-alkyl-substitutd enamides underwent smooth borylalkylation, 2-phenyl-substituted or 1,1-disubstituted enamides were incompatible with the reaction. The resulting *β*-aminoboronic acid serves as an essential synthon in organic synthesis, and the authors demonstrated its utility in the synthesis of the adenosine deaminase inhibitor EHNA.

The mechanism of this reaction begins with a chiral nickel catalyst (**I**) and B_2pin_2, forming a [Ni^{II}]-Bpin intermediate (**II**). This intermediate then undergoes a carbonyl-directed regioselective migratory insertion into the enamide, yielding an enantioenriched, five-membered nickelacycle intermediate (**III**), which is the enantioselectivity-controlling step. Intermediate (**III**) subsequently couples with an alkyl radical, followed by reductive elimination to give the desired borylalkylated product, along with the formation of nickel intermediate **V**. Finally, intermediate (**V**) reacts with an alkyl halide through single electron transfer mechanism, generating an alkyl radical species and regenerating the chiral Ni catalyst (**I**).

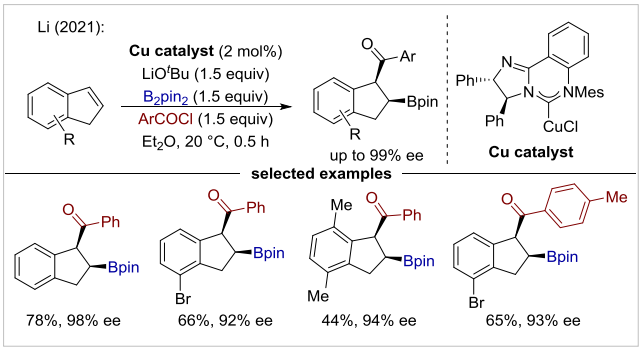
Scheme 17 Intermolecular enantioselective borylative alkylation of enamides



3. Asymmetric Borylative Acylation of Internal Alkenes

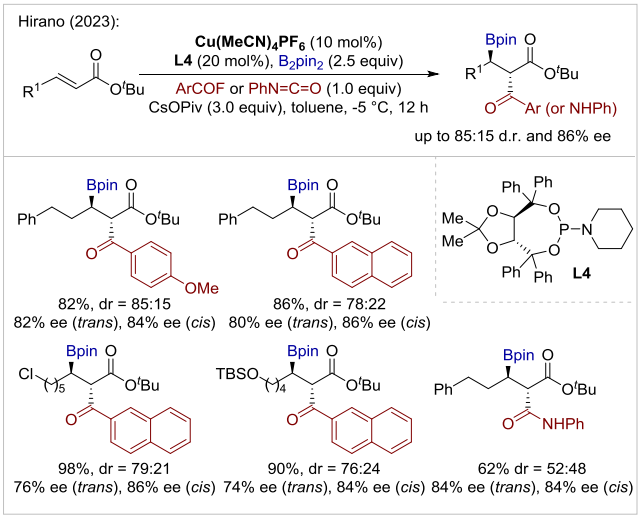
In 2021, Li and co-workers reported a copper-catalyzed borylative acylation of indenes using acyl chlorides as the acylating reagent (Scheme 18).[30] This reaction initiated with *cis* borylcupration of the alkene to form an alkyl copper intermediate, which then reacted with acyl chloride in a stereoretentive fashion, thus yielding *β*-borylated ketone products with complete diastereoselectivity. By employing chiral carbene as ligands, this reaction proceeded in good yields and with high enantioselectivities. Despite significant advancements, the reaction system was not applicable to other cyclic alkenes and acyclic internal alkenes. This limitation highlights the challenge of controlling regio- and stereoselectivity in more flexible, less constrained substrates. Acyclic internal alkenes often present difficulties due to their inherent conformational flexibility, which can lead to competing reaction pathways and lower selectivity. Continued research is necessary to develop new catalytic systems and strategies to overcome these challenges and expand the scope of asymmetric borylative functionalization to include acyclic internal alkenes.

Scheme 18 Enantioselective borylative acylation of indene derivatives



Copper-catalyzed asymmetric borylative protonation of acyclic *α*,*β*-unsaturated carbonyl compounds has been well-established,[5a,c,8c] however, achieving such borylative functionalization of these compounds is still challenging. One significant challenge is the control of diastereoselectivity, arising from the facial epimerization of the copper C-enolate, which is in equilibrium with the copper O-enolate, as well as the products bearing acidic protons at the *α*-position. Recently, Hirano and co-workers achieved a copper-catalyzed enantioselective borylative acylation of *β*-monosubstituted *α*,*β*-unsaturated esters (Scheme 19).[31] This reaction utilized acyl fluorides or isocyanates as the acylating reagents and chiral monodentate phosphoramidite as the ligand, yielding *anti*-borylacylation products with good enantioselectivity but poor diastereoselectivity. The poor diastereoselective control was found to be primarily due to the epimerization of the stereocenter *α* to the carbonyl group.

Scheme 19 Enantioselective borylative acylation of *α*,*β*-unsaturated esters



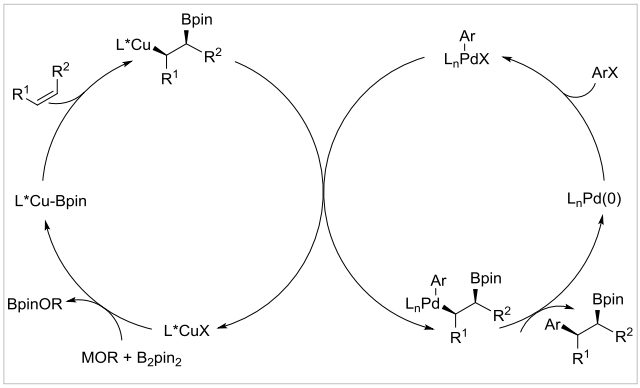
4. Asymmetric Borylative Arylation of Internal Alkenes

4.1. Asymmetric borylative arylation enabled by copper and palladium dual catalysis

Alkyl copper species generated from borylcupration of alkenes are sufficiently nucleophilic to directly react with active electrophiles such as alkyl halides, aldehydes, ketones, imine, and acyl chlorides, thus the aforementioned borylative alkylation and acylation reactions can occur with a single copper catalyst. However, the corresponding copper-catalyzed borylative arylation of alkenes is difficult to proceed due to the poor electrophilicity of common aryl halides, and pre-activation of aryl electrophiles by a

second metal catalyst is required. To address this limitation, the groups of Semba and Nakao,[32] Brown,[33] and Liao[34] developed a copper and palladium dual catalysis strategy,[9a] where palladium catalysts are employed to activate the aryl halide electrophiles.

Scheme 20 General mechanism for Cu/Pd dual-catalyzed borylative arylation



These reactions commonly proceed through two cooperative catalytic cycles involving both copper catalysis and palladium catalysis (Scheme 20). The palladium catalytic cycle is initiated by the oxidative addition of an aryl halide to palladium(0) to form an electrophilic ArPd(II) intermediate. Simultaneously, the copper catalytic cycle begins with the formation of Cu–Bpin (generated *in situ* from B_2pin_2, copper salt, and base), which then adds to an alkene to yield a *β*-boryl alkyl copper intermediate. The resulting nucleophilic alkyl copper intermediate undergoes transmetallation with the electrophilic ArPd(II) species, allowing for the regeneration of the copper catalyst and the formation of an ArPd(II)R intermediate. This intermediate then undergoes reductive elimination to give the borylarylation product and regenerates the palladium catalyst.

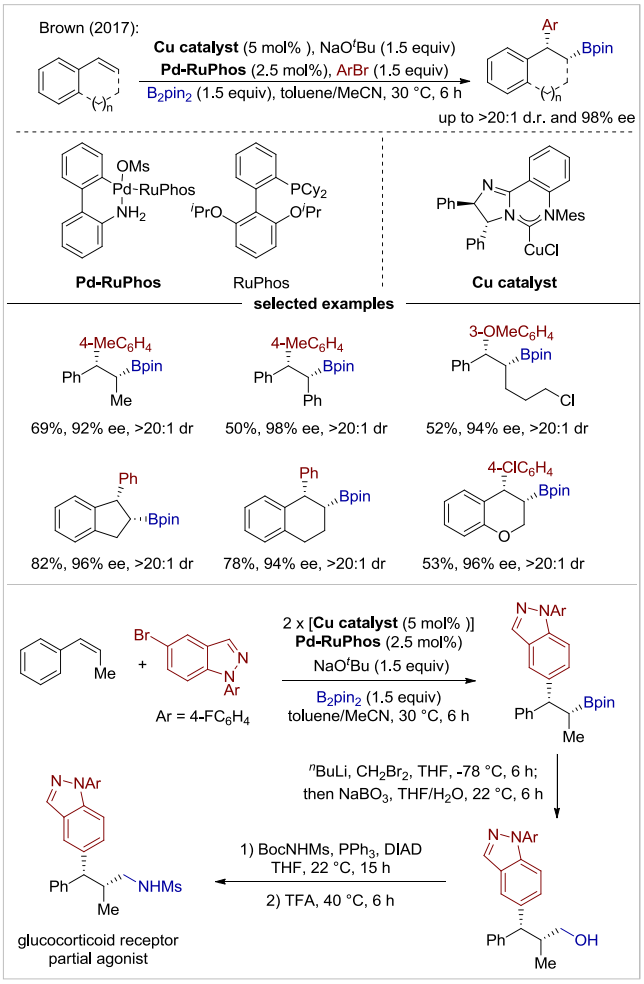
Although copper and palladium dual catalysis enabling borylative arylation of alkenes has been pursued,[9] achieving such asymmetric reactions with internal alkenes is challenging due to the match of reaction kinetics of each metal catalytic cycles and the associated selectivity control, including regio-, diastereo-, and enantioselectivity.[35]

In 2017, Brown and co-workers established an enantioselective borylative arylation of aryl-substituted internal alkenes with high levels of diastereo- and enantioselectivity (Scheme 21).[36] This reaction utilized pre-formed palladium catalysts Pd-RuPhos to activate aryl bromides and pre-formed chiral carbene-containing copper catalysts to incorporate the boryl and the aryl into alkenes. This dual catalysis system is applicable to various both acyclic and cyclic alkenylarenes, providing a straightforward and efficient method for the synthesis of enantioenriched boryl-containing 1,1-diarylalkanes. To demonstrate the utility of this method, the authors prepared a glucocorticoid receptor partial agonist through a short synthetic sequence (Scheme 21).

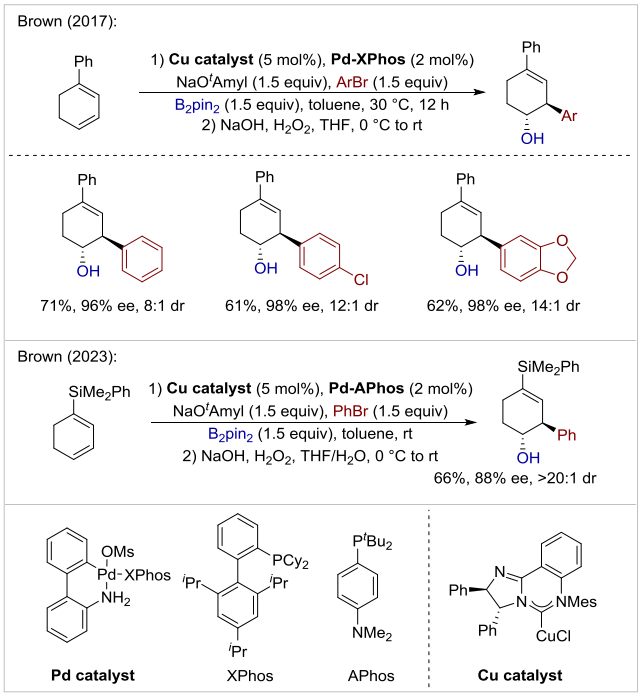
Almost simultaneously, the Liao group also reported a copper and palladium dual-catalyzed asymmetric borylative arylation of styrenes.[37] They employed a chiral sulfoxide-phosphine (SOP) ligand to assist the copper in inducing enantioselectivity. Although styrene derivatives underwent the borylative arylation with high enantioselectivity, aryl-substituted internal alkenes did not react under the same conditions due to their lower reactivity. Only one strained cyclic alkene, norbornadiene, was reported to undergo the borylative arylation, but the enantioselectivity was low (54% ee).

Brown and co-workers also disclosed asymmetric 1,2-borylative arylation of cyclohexadienes (Scheme 22), utilizing a copper and palladium dual catalysis system involving Pd-Xphos and a

Scheme 21 Pd/Cu-catalyzed enantioselective borylative arylation of alkenylarenes



Scheme 22 Pd/Cu-catalyzed enantioselective borylative arylation of cyclic aryl-substituted 1,3-hexadienes



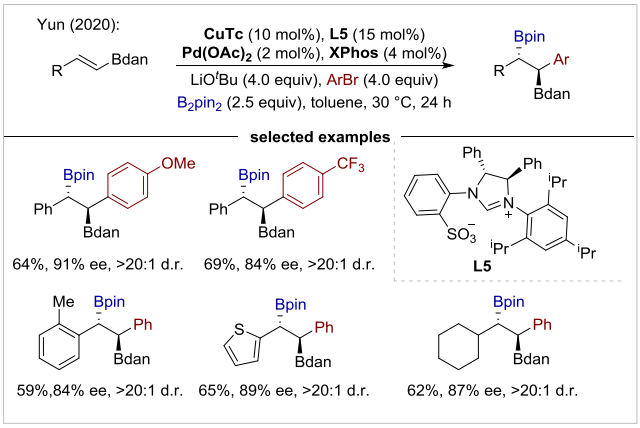
chiral copper complex.[35c] This approach yielded *trans*-1,2-aryl-

boration products with high levels of enantioselectivity and diastereoselectivity. It is worth mentioning that attempts to apply this dual catalysis system to acyclic 1,3-dienes only resulted in the formation of racemic products.

Recently, the same group extended the copper and palladium dual-catalyzed borylative arylation reaction to a 1-silyl-1,3-cyclohexanediene substrate (Scheme 22).[35d] This substrate underwent the *trans*-1,2-borylative arylation smoothly with high diastereo- and enantioselectivity (> 20 : 1 d.r. and 88% ee). The resulting product, which bears versatile silyl, boryl, and alkene moieties, can sever as useful synthetic intermediate for synthesizing multiple substituted cyclohexane derivatives.

Besides aryl-substituted alkenes and cyclohexanedienes, boryl-substituted alkenes are also suitable substrates for copper-catalyzed borylative arylation reactions. In 2020, the Yun group achieved such a reaction using alkenyl-Bdan substrates under copper and palladium dual catalysis (Scheme 23).[38] This reaction yielded a range of *trans*-diborylated products highly enantio- and diastereoselectively. The selection of NHC ligand for the copper catalysts was crucial for achieving the high selectivity.

Scheme 23 Pd/Cu-catalyzed enantioselective borylative arylation of borylalkenes



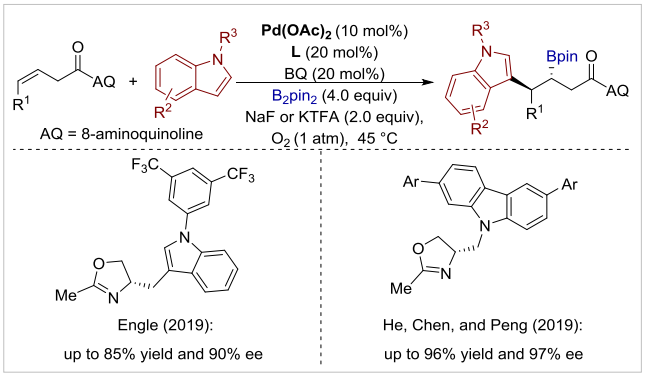
4.2. Asymmetric borylative arylation enabled by palladium catalysis

While the copper and palladium dual catalysis strategy holds great promise for executing borylative arylation on alkenes with high efficiency and selectivity, it also presents significant challenges. These include issues related to catalyst compatibility (especially due to metal-metal interactions and ligand cross-coordination), matching the kinetics of both catalytic cycles, and a limited substrate scope. Consequently, developing borylative arylation of alkenes with a single catalyst has been pursued.

Building on their prior studies[39] on palladium-catalyzed, substrate-directed regioselective hydrocarbonation of internal alkenes, and the discovery[40] by Chen and co-workers that chiral monodentate oxazoline ligand could exert good enantioselective control on such a hydroarylation reaction, Engle and co-workers, in 2019, developed a palladium-catalyzed aminoquinoline (AQ)-directed arylboration of internal alkenes (Scheme 24).[41] This reaction utilized electron-rich *N*-Me indoles as the arylating reagents and B_2pin_2 as the boron reagents, transforming AQ-masked *β,γ*-unsaturated carboxyl compounds into *anti*-arylborylated products with high regio- and enantioselectivity. Although reactions with both *Z*- and *E*-alkenes afforded the arylborylated products, the *Z*-isomers were the reactive ones, and *E*-isomers need to be isomerized to *Z*-isomers under reaction conditions. This reaction initiated with a substrate-directed, regio- and enantioselective Wacker-type nucleopalladation to form a five-membered palladacycle intermediate, which was crucial for controlling enantioselectivity, as demonstrated by the observation that AQ-masked γ,δ-unsaturated carboxyl compounds, proceeding via a six-membered palladacycle intermediate, also reacted but yielded products with significantly lower enantioselectivity (52% ee).

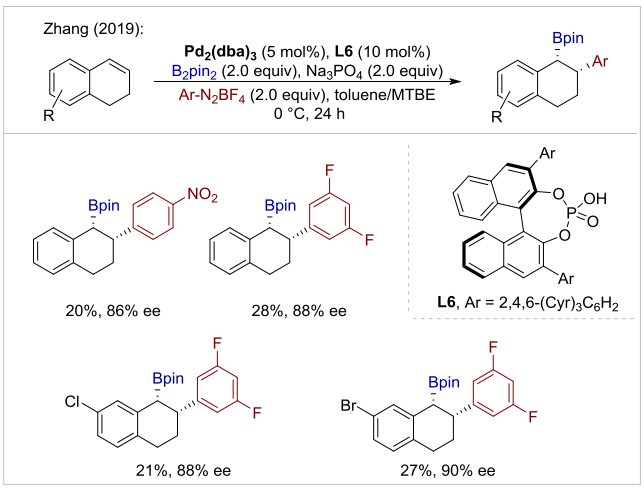
Almost simultaneously, the groups of He, Chen, and Peng disclosed a similar palladium-catalyzed asymmetric carboborylation on related substrates (Scheme 24).[42] In their reaction, they found that the additive potassium trifluoroacetate and the selected solvent trifluoroethanol were crucial for achieving high reactivity, although exact roles of these components remain unknown.

Scheme 24 Pd-catalyzed directed enantioselective arylborylation of unactivated alkenes



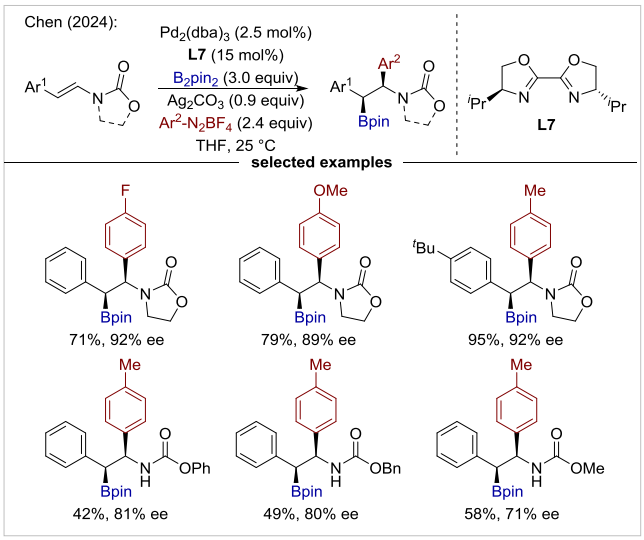
Palladium-catalyzed cascade Heck/Miyaura boration of internal alkenes provides an alternative access to install both an aryl and a boryl across carbon-carbon double bonds. Despite its attractiveness, this strategy has been challenging due to the propensity of the unproductive β-hydride elimination, and only a few examples have been reported. In 2019, Zhang's group developed a palladium-catalyzed 1,2-arylboration of both cyclic and acyclic 1,2-substituted arylalkenes.[43] They utilized aryldiazonium tetrafluoroborates as the arylating electrophiles and B_2pin_2 as the boron reagent. The racemic reaction proceeded with high regioselectivity, affording *cis*-arylborylated products in moderate to high yields. To render the reaction enantioselective, the authors employed chiral anion phase-transfer (CAPT) reagents (Scheme 25), such as chiral phosphoric acids, to induce enantioselectivity. When chiral phosphoric acid **L6** was added, the reaction occurred highly enantioselectively (up to 90% ee), but the yields were typically lower than 30% due to the competitive direct Heck reaction.

Scheme 25 Pd-catalyzed enantioselective arylboration of dihydronaphthenes



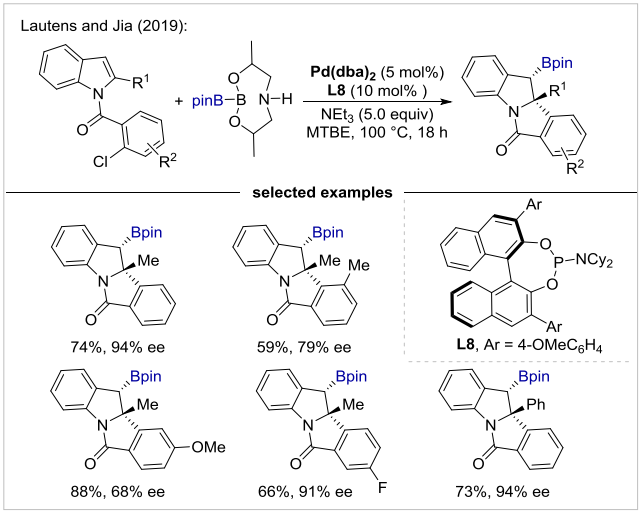
Very recently, the Chen group achieved an enantio- and diastereoselective Heck/Miyaura borylation reaction of unique internal alkenes, specifically alkenylcarbomates, by employing a chiral bisoxazoline-containing palladium catalyst (Scheme 26).[44] The carbamate motifs attached to the alkenes were crucial for the success of the reaction; switching the carbamate to an amide or alkyl group resulted in no desired 1,2-arylborylated product formation. Although the exact role of the carbamate unit remains elusive, the proposed mechanism suggests that it might coordinate with the alkyl palladium species generated from migratory insertion of the aryl palladium species into the alkene, thus favoring its stability.

Scheme 26 Pd-catalyzed enantioselective arylboration of enamides



Palladium-catalyzed asymmetric intramolecular Heck/Miyaura boration has also been disclosed. In 2019, Lautens and Jia achieved an asymmetric dearomative arylboration of indoles catalyzed by palladium complexes ligated with a BINOL-based chiral phosphoramidite (Scheme 27).[45] Indoline products bearing vicinal borylated trisubstituted and tetrasubstituted stereogenic centers were obtained. It should be noted that because the resulting boryl group at the benzylic position of the products was susceptible to inorganic base-promoted protodeboronation, the commonly used boron reagent B_2pin_2 necessitating the use of inorganic base for activation was not applicable to this reaction.

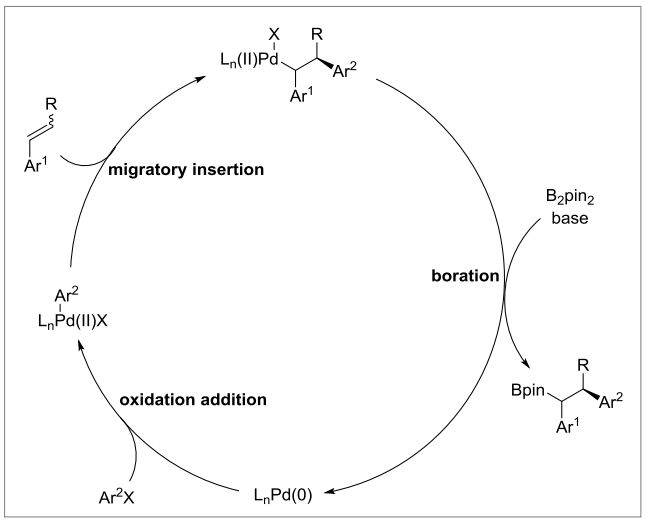
Scheme 27 Pd-catalyzed dearomative enantioselective arylboration of indoles



Instead, an sp^2-sp^3 mixed boron reagent first reported by Santos in copper-catalyzed hydroboration reactions was utilized.[46]

The mechanism of the palladium-catalyzed arylboration of alkenes differs from that of the copper and palladium cooperative catalytic system. In the palladium-catalyzed arylboration of alkenes, the mechanism proceeds depicted as follows (Scheme 28). Initially, aryl halide undergoes oxidative addition to palladium, forming an electrophilic aryl-Pd(II) species. This species then coordinates with alkene substrate, followed by migratory insertion, generating an alkyl palladium intermediate. This alkyl palladium intermediate reacts with B_2pin_2 with the assistance of bases to form the desired arylboration product, which may proceed through a direct σ-bond metathesis pathway or a transmetallation and subsequent reductive elimination pathway.

Scheme 28 General mechanism for Pd-catalyzed borylative arylation



5. Asymmetric Borylative Heteroatomation of Internal Alkenes

In addition to borylative carbonation, borylative heteroatomation of internal alkenes is also appealing. Such a reaction enables the installation of a boryl group and a second heteroatom-based functionalities such as boron and amine across alkenes.

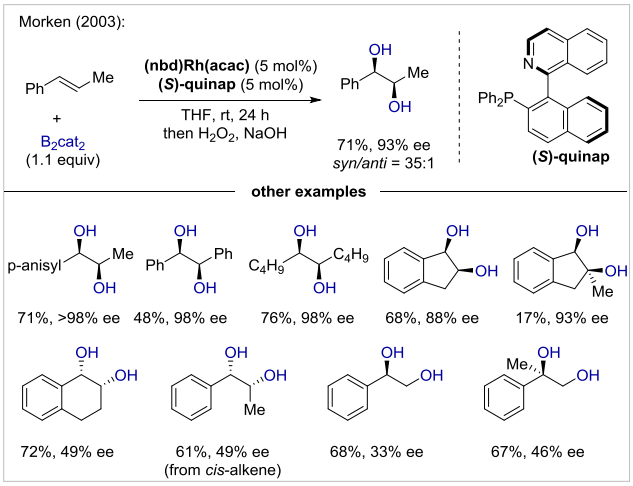
5.1. Asymmetric diboration

In 1995, Westcott, Marder, and Baker discovered that both gold and rhodium complexes could catalyze the addition of the diboron reagent $B_2(Cat)_2$ across vinylarenes.[47] Smith and Miyaura later found that platinum catalyst could promote the diboration of terminal aliphatic alkenes and strained cyclic alkenes.[48] In 1998, Marder achieved the diboration of unstrained internal alkenes such as *β*-methyl-styrene.[49] Moreover, silver-catalyzed diboration of terminal alkenes was also disclosed by Fernandez and Peris, but yield was low with internal alkenes.[50] Despite these significant advances, developing enantioselective diboration of alkenes which forms synthetically valuable enantioenriched vicinal diboron compounds[51] has been not trivial due to the challenges in achieving high reactivity, inhibiting the competitive *β*-hydride elimination, and controlling over regio- and enantioselectivity.

Based on these prior findings, in 2003, the Morken group reported a rhodium-catalyzed asymmetric diboration of internal alkenes (Scheme 29).[52] During the screening of chiral ligands for the diborylation of *trans*-*β*-methyl-substituted styrene, they found that (*S*)-BINAP and (*S*)-Quinap showed comparably high enantioselectivity (84% ee and 88% ee, respectively) but distinct diastereoselectivity. The reaction with (*S*)-Quinap yielded product with exceptionally high diastereoselectivity (*syn* : *anti* = 35 : 1),

whereas the reaction exhibited no significant diasteroselectivity (*syn* : *anti* = 1.5 : 1) with (*S*)-BINAP. Both unsymmetrical and symmetrical internal underwent the diboration with significant level of enantioselectivity. Cyclic alkenes also underwent the reaction smoothly, but the ring size influenced the enantioselectivity; five-membered cycloalkenes (indenes) reacted with high selectivity, while six-membered cycloalkene (1,2-dihydrophenanthrene) reacted with low selectivity. Configuration of the alkene also has a significant influence on the enantioselectivity; reaction with *cis*-*β*-methylstyrene showed poorer enantioselectivity (49% ee vs. 98% ee; *cis* vs. *trans*). Additionally, only moderate enantioselectivity was observed from the reactions with terminal alkenes. This catalyst system was further proven to be suitable for unsymmetrical internal alkenes substrates by the same group.[53]

Scheme 29 Rh-catalyzed enantioselective diboration of internal alkenes

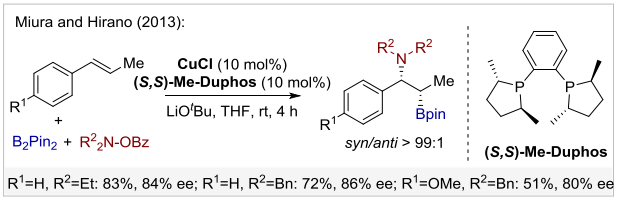


5.2. Asymmetric borylative amination

Amino groups are ubiquitous in natural products and pharmaceuticals. Boryl amine compounds have also been pursued as drug candidates.[54] In this context, the development of reactions enabling the installation of both functionalities across alkenes is particularly attractive. When the processes are enantioselective, structurally diverse chiral amine-containing vicinal stereogenic centers are accessible.

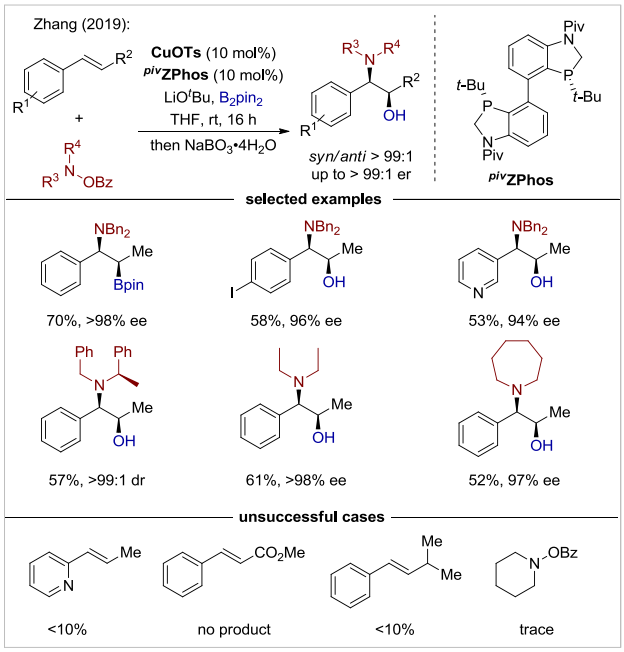
In 2013, Miura and Hirano developed for the first time borylative amination of alkenes catalyzed by copper complexes containing a bisphosphine ligand (dppbz; 1,2-bis(diphenylphosphino)benzene) (Scheme 30).[55] This process initiated with the addition of *in situ*-generated Cu-Bpin to alkenes to result in an alkyl copper intermediate, which then reacted with electrophilic aminating reagent *O*-benzoyl *N*,*N*-dialkylhydroxylamine, producing *cis* 1,2-aminoboration products. This reaction was applicable to various both terminal and internal styrene derivatives, occurring in a regioselective fashion with the amino group at the benzylic position and the boryl group at the homobenzylic position. Building on these important discoveries, the authors also explored asymmetric version of this transformation by examining various chiral ligands. Chiral bisphosphine (*S*,*S*)-MeDuphos was found to be efficient to induce the enantioselectivity, but only three examples were presented in the original paper, with enantioselectivity ranging from 80%—86% ee.

Scheme 30 Cu-catalyzed enantioselective borylative amination of styrene derivatives



In 2019, the Zhang group improved the copper-catalyzed borylative amination of *β*-substituted (*E*)-styrenes to an excellent level of enantioselectivity (up to 99% ee) by employing a biaryls-based bidentate P-chiral bisphosphine ligand ^{piv}ZPhos developed by themselves (Scheme 31).[56] A wide range of styrenes and aminating reagents were well tolerated, and the resulting borylative amination products were highly yielded with excellent regio-, enantio- and diastereoselectivity. For unknown reasons, 2-pyridinyl alkene, sterically hindered styrenes, and electron-poor *α*,*β*-unsaturated ester did not undergo the reaction.

Scheme 31 Cu-catalyzed enantioselective borylative amination of *E*-vinylarenes

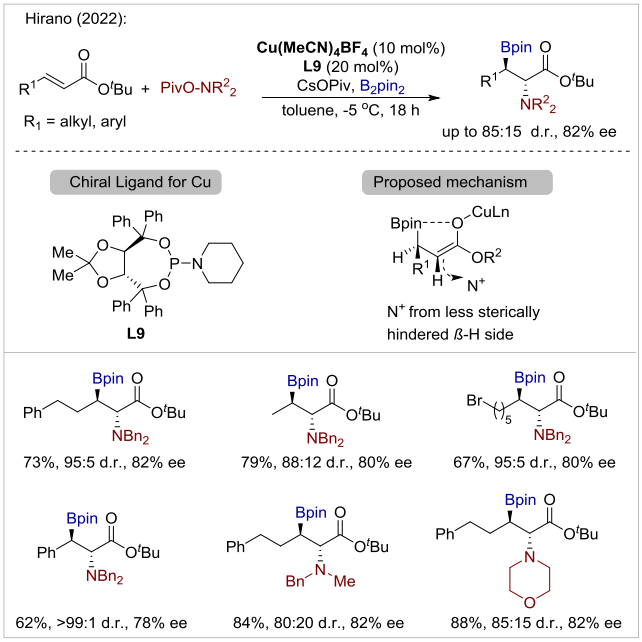


Recently, the Hirano group achieved the asymmetric borylative amination of *α*,*β*-unsaturated esters catalyzed by copper complexes containing a chiral phosphoramidite ligand (Scheme 32).[57] This reaction occurred with moderate to high *anti*-selectivity, and the control of stereochemistry was proposed to be arising from a strong interaction between the newly installed *β*-boron atom and oxygen atom in the *O*-bound copper enolate intermediate. Both aliphatic and aromatic *β*-substituted *α*,*β*-unsaturated esters were suitable substrates, yielding *β*-boryl-*α*-amino acid derivatives with moderate ee values.

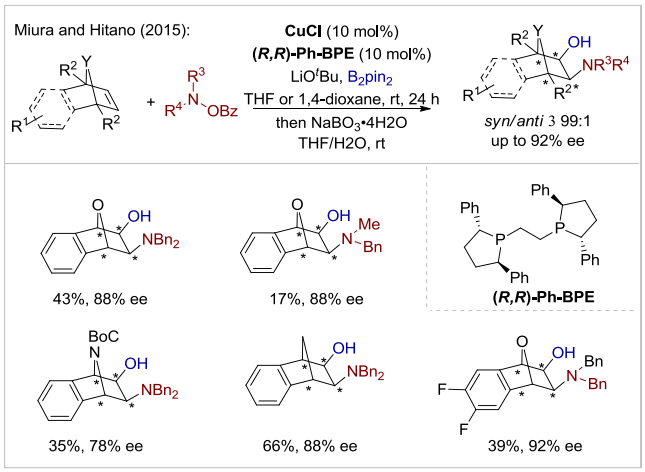
In 2015, Miura and Hirano applied the copper-catalyzed asymmetric borylative amination reaction to bicyclic alkenes, including oxa- and azabenzonorbornadienes (Scheme 33).[58] By employing chiral bisphosphine ligand (*R*,*R*)-Ph-BPE, the desired products were obtained in moderate yields and with exclusive exo-selectivity as well as moderate to good enantioselectivity. Through simple transformations, the resulting enantioenriched cyclic borylated amine products were converted into oxygen- and nitrogen-rich compounds. These scaffolds are common in natural products and pharmaceuticals.

They subsequently examined the performance of (*R*,*R*)-Ph-BPE-containing copper catalysts on the borylative amination of alkenyl-Bdan substrates (Scheme 34).[59] Although borylative amination products could be obtained in moderate to high yields and with high regioselectivity with amino group installed at the *α*-position of the Bdan group, only moderate enantioselectivity was achieved in limited examples.

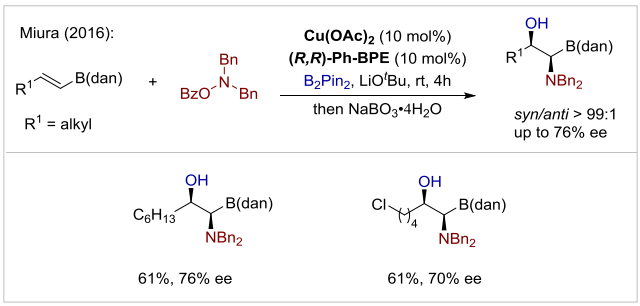
Scheme 32 Cu-catalyzed enantioselective borylative amination of *α,β*-unsaturated esters



Scheme 33 Cu-catalyzed asymmetric aminoboration of bicyclic alkenes



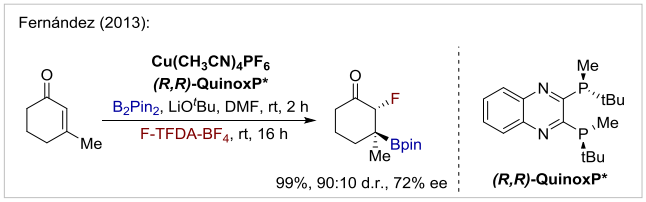
Scheme 34 Cu-catalyzed enantioselective borylative amination of alkenylboronates



5.3. Other borylative heteroatomation

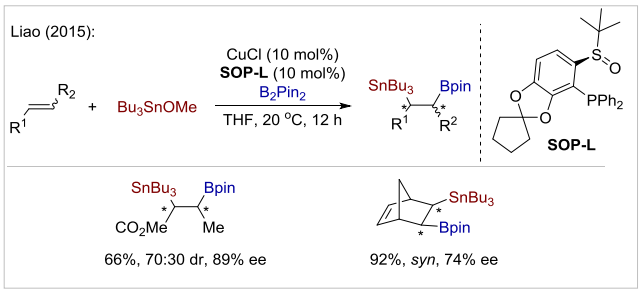
Borylative halogenation has become essential routes for the efficient one-step difunctionalization of unsaturated substrates. In 2013, Fernández group reported the copper-catalyzed borylative fluorination of *α,β*-unsaturated ketones, employing PCy_3 as the ligands and F-TEDA-BF_4 as the fluorinating reagents, but only cyclohexanone derivatives can react with high yields (Scheme 35).[60] They also examined (*R,R*)-QuinoxP for the asymmetric borylative fluorination of *β*-methyl *α,β*-unsaturated cyclohexenone, affording products in a moderate enantio- and diastereoselectivity (72% ee and 90 : 10 d.r.)

Scheme 35 Cu-catalyzed enantioselective borylative fluorination of *α,β*-unsaturated ketones



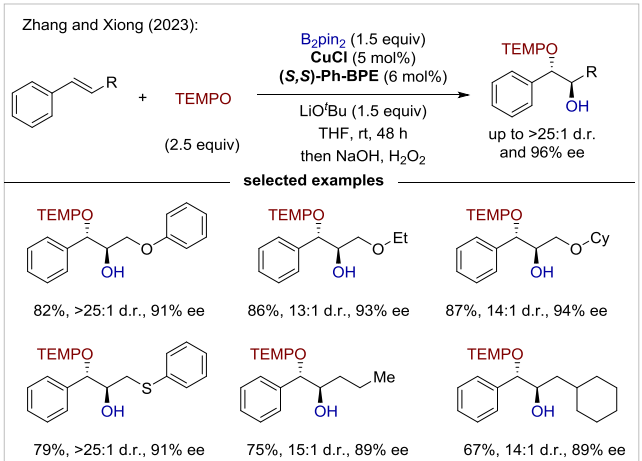
Alkylstannanes are configurationally robust, easily stored, and have been utilized in many asymmetric transformations. However, their catalytic enantioselective synthesis has been less investigated. In 2015, the Liao group explored the copper-catalyzed asymmetric borylative stannation of alkenes, using sulfinylphosphine (SOP) as the chiral ligand. Various styrene derivatives proved to be suitable substrates for this reaction, but the scope of internal alkenes was limited.[61] The reaction with *α,β*-unsaturated ester could give product with a high 89% ee but a low 70 : 30 d.r. Norbornadiene proceeded smoothly, yielding a single *anti*- and *syn*-configuration product in excellent yield (Scheme 36).

Scheme 36 Cu-catalyzed enantioselective borylative stannation of electron-deficient and strained olefins



In addition to the aforementioned borylative heteroatomation reactions, Zhang and Xiong have recently achieved the enantioselective borylative oxygenation of internal olefins (Scheme 37).[62]

Scheme 37 Cu-catalyzed enantioselective borylative oxygenation of *β*-substituted styrenes



This reaction, catalyzed by copper complexes ligated with the chiral bisphosphine ligand (*S*,*S*)-Ph-BPE, used 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) as the oxygenating reagent. A variety of *β*-substituted styrenes were compatible with this reaction, affording the borylative oxygenation products with high enantio- and diastereoselectivity. Interestingly, the reaction initially yielded a mixture of *cis*- and *trans*-boryloxygenated products (21% *trans*-isomer and 71% *cis*-isomer), but over time, the *cis*-isomer was gradually reverted to the starting alkene, which then underwent another round of enantioselective boryloxygenation. This late-stage stereomutation process ultimately contributed to the high diastereoselectivity observed.

6. Conclusions and Perspectives

In this concise Review, we have surveyed recent advances in transition metal-catalyzed asymmetric borylative functionalization reactions of internal alkenes. These reactions enable the incorporation of both a boryl group and various other functionalities across the carbon-carbon double bond of internal alkenes. Facilitated by the versatile transformations of the boryl group, this strategy provides a valuable platform for constructing structurally diverse vicinal stereogenic centers. Typically, these reactions proceed through an enantioselective metal-[B] addition across alkene to form a nucleophilic alkyl metal intermediate. Based on the characteristics of the electrophiles used, this intermediate can then react directly with an active electrophile or with an unreactive electrophile, such as an aryl halide, with the assistance of a second metal catalyst to form the borylative functionalization product. To date, various borylative alkylation, acylation, arylation, and heteroatomation reactions have been developed.

Despite these notable advances, several challenges remain in this area. First, most studies focus on activated internal alkenes, such as styrene derivatives, with fewer examples involving simple, less reactive alkenes. Second, the construction of quaternary carbon-containing vicinal stereocenters, particularly in acyclic systems, using this strategy has been rarely reported. Third, the scope of alkyl electrophiles is largely restricted to primary alkyl halides, with secondary and tertiary alkyl halides seldom employed. Fourth, borylative heteroatomation reactions are still underdeveloped. These challenges are closely tied to the chemo-, regio-, and enantioselectivity of the metal-boryl species. Successful borylative functionalization of internal alkenes requires the metal-boryl species to selectively react with the internal alkenes, undergoing regio- and enantioselective migratory insertion to form a chiral alkyl-metal intermediate. This intermediate must then react with a third component in a stereospecific fashion to maintain high diastereoselectivity throughout the process. Lastly, although copper catalysts dominate this area, the use of alternative metal catalysts remains limited, underscoring the demand for the development of diverse catalytic systems with other metals. Therefore, great attention should be given to developing new catalyst systems and strategies that address these challenges.

With the rapid advancements in transition metal catalysis, we anticipate the continuous growth of borylative functionalization reactions and their applications in creating vicinal stereogenic centers. As more and more transformations are explored, this strategy is poised to evolve into a robust and potent synthetic approach to scaffolds that are difficult to access by traditional methods. We hope that this concise review will inspire further interest from both academia and industry.

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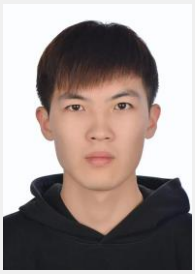

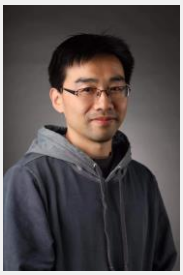

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