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Recent progress in the catalytic enantioselective reactions of 1,1-diborylalkanes

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Organoboron compounds are environmentally benign, have low toxicity and are versatile reagents that are extensively employed in organic synthesis, especially in the realm of asymmetric synthesis. The last several decades have witnessed a tremendous outburst of asymmetric reactions based on various organoboron compounds. Among them, 1,1-diborylalkanes, which contain two boryl groups at the same sp^3-carbon atom, are regarded as some of the most versatile and powerful reagents for their unique structure and unusual reaction mode in organic synthesis. Moreover, owing to the stabilizing effect of the empty p-orbital of the neighboring boron atoms and the inherent good steric-hindrance, 1,1-diborylalkanes often exhibit extraordinary reactivity and stereoselectivity compared to other kinds of organoboron compounds in asymmetric synthesis. Herein, the present highlight summarizes and discusses the recent progress achieved in the catalytic enantioselective reactions of 1,1-diborylalkanes during the past decade.

Introduction

Organoboron compounds are environmentally safer and less toxic than certain other organometallic reagents. They serve as essential plant nutrients, are present in a variety of bioactive natural products, and find broad applications in pharmaceuticals. Besides, they are extensively utilized in a number of organic reactions such as Suzuki–Miyaura cross-coupling, Chan-Lam coupling, and the Petasis borono-Mannich reaction, and have proven to be of great importance in asymmetric synthesis. More importantly, some organoboron compounds, for example boronic acids, are moisture stable and water soluble, thus enabling their reactions to proceed in aqueous solvents. As a consequence, organoboron compounds have emerged as some of the most commonly used reagents in organic synthesis and chemical industry.[1]

Among the various kinds of organoboron compounds, 1,1-diborylalkanes, which contain two boryl groups at the same sp^3-carbon atom, have a unique structure and exhibit an unusual reaction mode in organic synthesis. Specifically, they can serve as an α-borylcarbanion synthon through a base-stimulated monodeborylation of the two boryls, which is facilitated by the stabilizing effect of the empty p-orbital on boron adjacent to the resulting anionic center. After the first reaction, one of the two boryls is kept, which could undergo further

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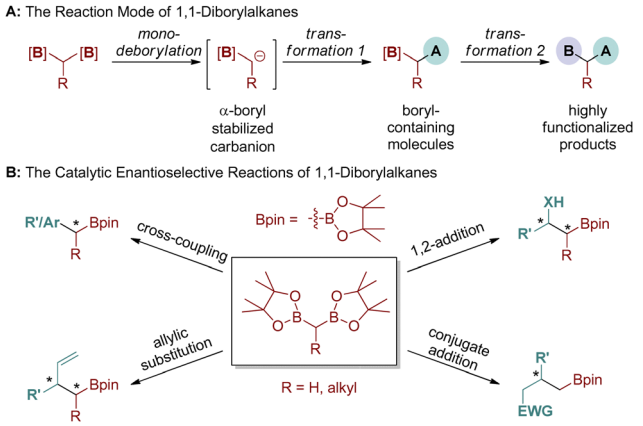

Fig. 1 The reaction mode and catalytic enantioselective reactions of 1,1-diborylalkanes.

transformations to furnish the final highly functionalized products (Fig. 1A). Moreover, owing to the inherent good steric-hindrance, 1,1-diborylalkanes often exhibit extraordinary stereoselectivity compared to other organoboron compounds in asymmetric processes. Therefore, these structurally unique organoboron compounds have become versatile and powerful reagents in asymmetric synthesis and a variety of elegant reactions have been developed since their first report by Endo and Shibata.[2]

This highlight summarizes and discusses the recent advances in the catalytic enantioselective reactions of 1,1-diborylalkanes, which are organized according to the reaction categories including Suzuki–Miyaura cross-coupling, S_N2/S_N2' allylic substitution, 1,2-addition, and conjugate addition (Fig. 1B). Since this highlight only covers the catalytic enantioselective processes, stoichiometric asymmetric synthesis and diastereoselective reactions which generate racemic products will not be discussed in this highlight.

Suzuki–Miyaura cross-coupling

Suzuki–Miyaura cross-coupling is a reliable method for the construction of C–C bonds, especially between sp^2-carbons.

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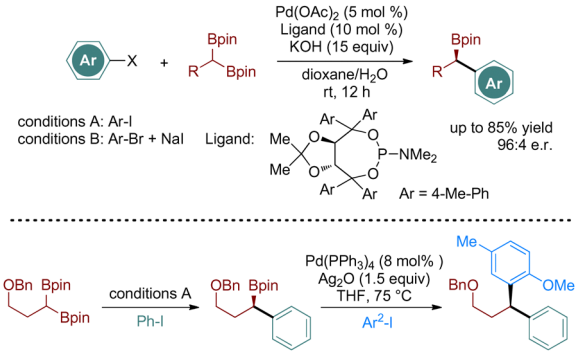


Scheme 1 Pd-catalyzed enantioselective Suzuki–Miyaura cross-coupling of 1,1-diborylalkanes with aryl halides.

However, attributing to β-hydride elimination, regioisomerization, and protodeboronation, the cross-coupling on a sp^3-carbon in organoboron compounds is very challenging. To address this issue, Shibata *et al.* employed 1,1-diborylalkanes as the coupling reagents to react with a series of haloarenes in aqueous solvent at room temperature. The unique structure of 1,1-diborylalkanes gives them extraordinary reactivity in cross-coupling reactions, that is, the assistance of an adjacent B atom in 1,1-diborylalkanes could result in the generation of a monoborate intermediate at room temperature and promote the transmetalation between the borate intermediate and ArPdX, thus facilitating the coupling reaction on a sp^3-carbon under mild conditions. In sharp contrast, other structurally analogous organoboron reagents including 1,1-borylsilylalkane, 1,2-diborylalkane, and mono-borylalkane all failed to afford the coupling products at room temperature.[2a]

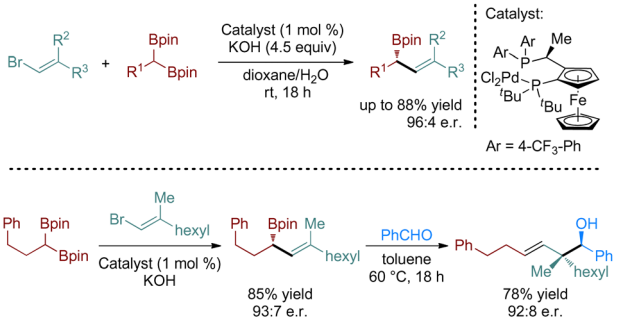
The enantioselective variant of this reaction was developed by Morken *et al.* in 2014. They found that chiral monodentate ligands showed efficient asymmetric induction while bidentate ligands such as BINAP and JosiPhos only promoted nonselective background reactions. Employing aryl iodides as coupling partners and under the catalysis of 5 mol% of $Pd(OAc)_2$ and 10 mol% of TADDOL-derived chiral ligand, a series of nonracemic organoboronates were obtained at room temperature with good enantioselectivities. Mechanism studies revealed that reductive elimination occurs with retention of configuration at carbon, while transmetalation occurs with inversion of configuration at carbon. The unique reaction mode and synthetic utility of 1,1-diborylalkanes were demonstrated by a two-step sequential synthesis of a precursor compound of pharmaceutical molecule (*R*)-tolterodine. Benefitting from the assistance of the adjacent B atom, the 1,1-diborylalkane substrate underwent the first Suzuki–Miyaura cross-coupling at room temperature, while leaving one boryl intact. The resulting mono-borylalkane intermediate subsequently proceeded to the second cross-coupling with another aryl iodide at an elevated temperature of 75 °C, thus affording the target chiral diarylmethane product in very good yield (Scheme 1).[3]

In the same year, Hall *et al.* also reported the enantioselective Suzuki–Miyaura cross-coupling of 1,1-diborylalkanes. In this work, a series of TADDOL-derived phosphoramidite

ligands were synthesized and evaluated in the asymmetric coupling reaction. The authors found that both the size of the aryl groups and the amine groups on the phosphoramidite have significant effect on catalyst activity. Besides, when Morken's reaction conditions were employed to large-scale synthesis, a sharp decrease in both yields and enantioselectivities were observed, while Hall's reaction conditions still worked very well even at 1 gram-scale. Detailed mechanism studies revealed that the doubly hydrolyzed diboronate substrate is the desired coupling partner in this reaction, and the base NaOH and KHF_2 likely serve to hydrolyze the pinacolboronates to the corresponding diboronic acids (Scheme 2).[4]

In 2014, Morken further extended their chemistry to vinyl electrophiles, allowing the rapid access to enantiomerically enriched allylic boronates, which are valuable but structurally challenging intermediates in organic synthesis. Unlike in the cross-coupling of aryl electrophiles, monodentate phosphoramidite ligands failed to promote the reaction. However, Josiphos-type ligands proved to be efficient for this reaction in terms of yield, enantioselectivity, and chemoselectivity. To simplify the experimental setup, an air-stable palladium dichloride complex with a Josiphos-type ligand was prepared and employed as the chiral catalyst. By using only 1 mol% of the catalyst, the desired chiral γ,γ-disubstituted allylic boronate products were obtained in good yields and with high levels of enantioselectivities. In addition, the obtained chiral allylic boronates are quite useful building blocks that can participate in a series of transformations. For example, an asymmetric 1,2-addtion to benzaldehyde furnished a homoallylic alcohol bearing an adjacent all-carbon quaternary center with complete enantiospecificity (Scheme 3).[5]

Besides 1,1-diborylalkanes, other kinds of 1,1-diboron compounds, for example, (diborylmethyl)silanes were also good candidates for Suzuki–Miyaura cross-coupling. In 2019, Cho *et al.* developed a palladium catalytic system for the enantioselective synthesis of a series of chiral benzylic 1,1-silylboronate esters employing readily accessible (diborylmethyl)silanes as coupling reagents. Interestingly, in the screening of chiral ligands, the authors found that while the Josiphos ligand gave poor results towards this coupling, a structurally similar ligand *rev*-Josiphos performed very well in terms of yield and enantioselectivity, which indicated that cyclohexylphosphine (PCy_2) at the cyclopentadienyl ring played an important role in this process. Further structural optimization of the ligands improved the quantitative yield to almost 99% and the ee to 96%. Under the optimized conditions, a wide range of (diborylmethyl)silanes and aryl iodides reacted efficiently, affording the coupling products in excellent yields with high enantioselectivities. Interestingly, the preserved boryl and silyl groups could be further sequentially transformed into other functionalities. For example, after stereospecific vinylation, the chiral allylsilane intermediate could react with pivalaldehyde to afford a homoallylic alcohol in good yield (Scheme 4).[6]

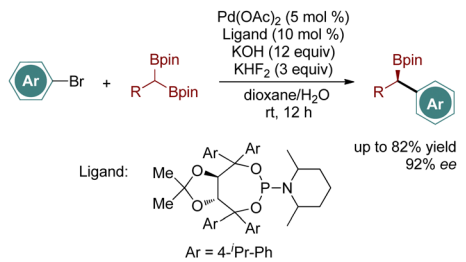


Scheme 3 Pd-catalyzed enantioselective Suzuki–Miyaura cross-coupling of 1,1-diborylalkanes with vinyl bromides.

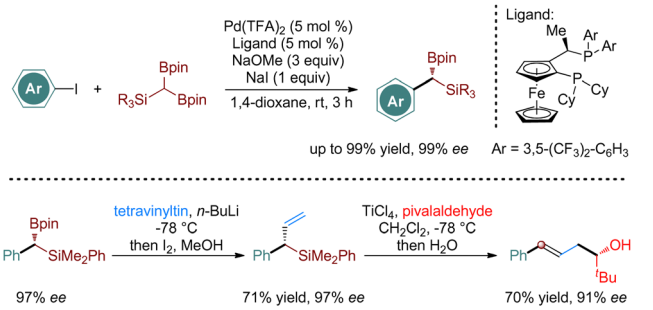
S_N2' and S_N2 allylic substitution

Catalytic enantioselective allylic substitution using 1,1-diborylmethane as the nucleophile was first developed by Hoveyda *et al.* in 2016. After detailed ligand screening, the authors found that a crystalline and air-stable dimeric Ag complex, which could exchange the ligand with the employed copper catalyst, exhibited excellent stereoselectivity, affording the target products in 95 : 5 S_N2'/S_N2 ratio and 97 : 3 e.r. Allylic phosphates were selected as substrates because the Lewis basic phosphate may facilitate the binding to a chiral Cu complex, thereby achieving high S_N2' and/or enantioselectivity. Based on the thoughtfully designed reaction system, a broad range of enantiomerically enriched homo-allylic alcohols were obtained in good yields and with exceptional S_N2' selectivities and enantioselectivities (Scheme 5).[7]

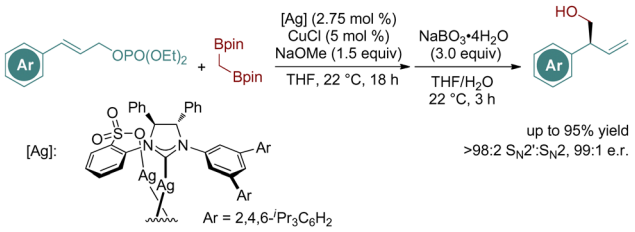
Soon after, Liu, Chen, and Niu also reported an iridium-catalyzed enantioselective allylation of 1,1-diborylmethane. In



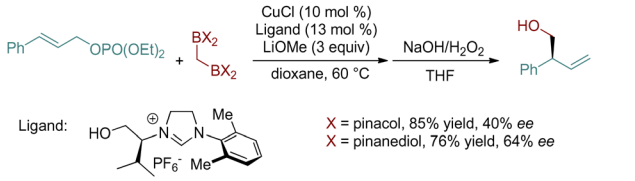
Scheme 2 Pd-catalyzed enantioselective Suzuki–Miyaura cross-coupling of 1,1-diborylalkanes with aryl bromides.



Scheme 4 Pd-catalyzed enantioselective Suzuki–Miyaura cross-coupling of (diborylmethyl)silanes with aryl iodides.



Scheme 5 Cu-catalyzed enantioselective S_N2' allylic substitution of 1,1-diborylmethane.



Scheme 7 NHC-Cu-catalyzed enantioselective S_N2' allylic substitution of 1,1-diborylmethane.

contrast to Hoveyda's reaction system, this work employed less-reactive allylic carbonates as electrophiles, and both linear and branched allylic carbonate substrates could be transformed into the target homoallylic organoboronic esters under different reaction conditions. BINOL-derived phosphoramidite ligands proved to be effective for this reaction. The obtained homoallylic boronic ester products are versatile intermediates that can be transformed into other important classes of compounds, thus demonstrating the synthetic utility of this chemistry. For example, a stereospecific coupling with benzofuran, followed by a hydroboration/oxidation sequence, gave a chiral alcohol product, while treating the boronic ester substrate with butyllithium and $MeONH_2$ yielded an enantiomerically enriched homoallylamine (Scheme 6).[8]

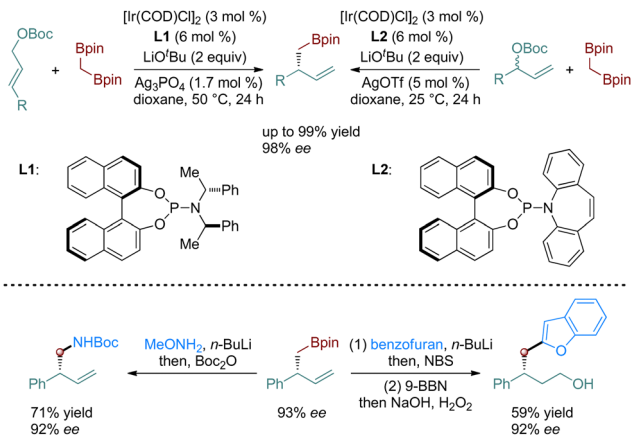
In the same year, Xiao and Fu employed CuCl and chiral *N*-heterocyclic carbene ligands to promote the enantioselective S_N2' substitution of 1,1-diborylmethane. Although moderate enantioselectivities were obtained, the authors found that the ee values were governed by the different skeletons of the diboronates, and pinacol-derived diboronates afforded the target product with 40% ee while pinanediol-derived diboronates gave a 64% ee (Scheme 7).[9]

More challenging catalytic enantioselective allylic substitution of 1,1-diborylalkanes was realized in 2021 by Cho *et al.* After considerable screening of ligands, bases, and various kinds of boronic esters and the leaving groups on electrophiles, the authors found that a combination of CuBr and (*R*)-BINOL-derived phosphoramidite ligands could promote the allylic substitution reaction between 1,1-diborylalkanes and allyl bromides in a highly efficient and enantioselective manner. A broad range of chiral enantioenriched homoallylic boronate esters were obtained in good yields with good to high enantiopurity (Scheme 8).[10] Detailed mechanism studies and DFT calculations revealed that the C–C bond forming process takes place with retention of configuration at the carbon of chiral α-borylalkyl-copper, while the transmetalation between 1,1-diborylalkanes and chiral copper species occurs in a stereoinvertive fashion, which resembled the enantioselective Suzuki–Miyaura cross-coupling event.[3]

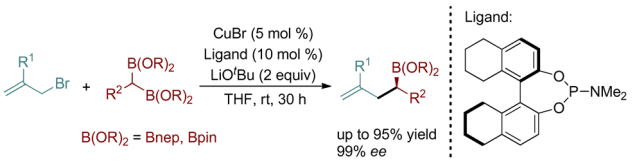
Besides 1,1-diborylalkanes, an isolable (diborylmethyl)-lithium salt, which was first successfully synthesized and isolated in 95% yield with 95% purity by Cho, can also be employed in asymmetric allylic substitution to generate enantiomerically enriched 1,1-diborylalkanes. The authors found that the addition of a zinc salt ZnX_2 was crucial as no target product was formed in the absence of this additive. They considered that a (diborylmethyl)zinc(II) species, which was generated *in situ* from the lithium salt, could serve as a nucleophile under the reaction conditions. By virtue of the established method, a broad range of enantioenriched 1,1-diborylalkanes were obtained in high yields with excellent enantioselectivity (Scheme 9).[11]

1,2-Addition

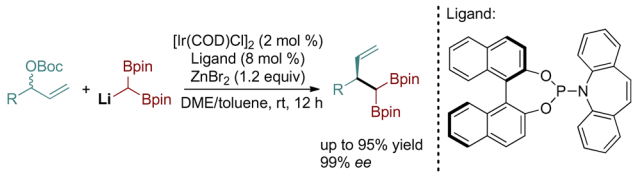
The first catalytic enantio- and diastereoselective 1,2-addition of *gem*-diboronate reagents was developed by Meek *et al.* in 2015. Promoted by a readily available Cu(I) salt and a chiral monodentate phosphine ligand, the highly stereoselective 1,2-addition of methyl 1,1-diboronate to a wide range of aryl and vinyl aldehydes took place under very mild conditions. Of note, only a catalytic amount of alkoxide base LiO*t*-Am was required. By virtue of the high efficiency and good stereocontrol of the reaction, two continuous stereogenic centers were constructed in a single step with up to 91% yield, >98 : 2 d.r., and 98 : 2 e.r.



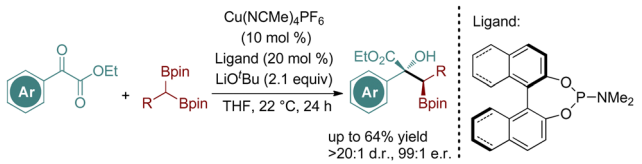
Scheme 6 Ir-catalyzed enantioselective allylic substitution of 1,1-diborylmethane.



Scheme 8 Cu-catalyzed enantioselective allylic substitution of 1,1-diborylalkanes.



Scheme 9 Ir-catalyzed enantioselective allylic substitution of (diboryl-methyl)lithium salt.



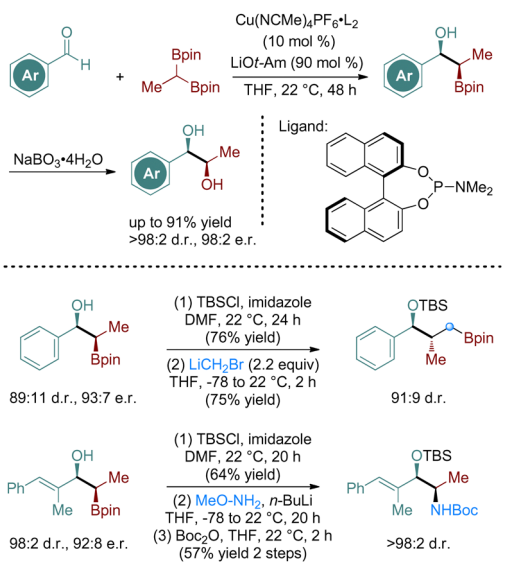
Scheme 11 Cu-catalyzed enantio- and diastereoselective 1,2-addition of 1,1-diborylalkanes to aryl α-ketoesters.

The synthesized chiral *syn*-1,2-hydroxyboronates can be further transformed into many other functionalized molecules. For example, besides oxidizing to *syn*-1,2-diols, homologation reaction and the C–B to C–N conversion both stereospecifically afforded useful functional molecules (Scheme 10).[12]

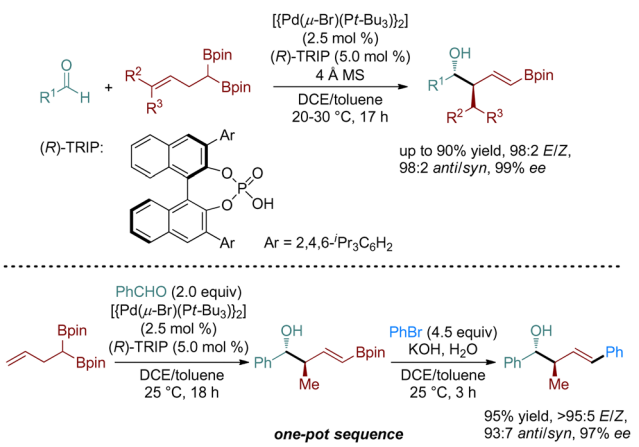
The copper(I)-catalyzed additions of alkyl 1,1-diborons to aldehydes feature high *syn*-selectivity. Soon after, Meek found that *anti*-selectivity could also be realized by employing aryl α-ketoester substrates. Mechanism studies revealed that the key step involved the formation of an enantiomerically enriched α-boryl-copper-alkyl intermediate, which subsequently attacked the α-ketoester with good stereoselectivity. This work represents the first catalytic protocol for the enantio- and diastereoselective synthesis of β-boryl tertiary alcohols bearing two contiguous stereogenic centers (Scheme 11).[13]

The *anti*-selectivity was also observed by Miura and Murakami in their synthesis of *δ*-boryl-substituted homoallylic alcohols. In this reaction, a $[\{Pd(\mu\text{-}Br)(P^tBu_3)\}_2]$ catalyst and a chiral phosphoric acid (*R*)-TRIP worked in relay to form two contiguous stereogenic centers and one double bond with up to 98 : 2 *anti*/*syn* ratio, 98 : 2 *E*/*Z* ratio, and 99% ee. Mechanistically, palladium catalyzed the double bond transposition of homo-allylic 1,1-diboronate substrates to form two isomers of allylic *gem*-diboronates, while chiral phosphoric acid catalyzed the enantioselective allylation of aldehydes followed by a palladium-catalyzed geometrical isomerization. As a result, the configurations of two chiral centers and one double bond are all controlled with high level of stereoselectivities in a single reaction vessel. The synthetic value of this reaction was demonstrated by a one-pot sequential synthesis strategy, *i.e.* after the first asymmetric 1,2-addition, subsequent cross-coupling with bromobenzene was directly conducted without any workup and isolation procedures, thus affording a styrene derivative in good yield with perfect preservation of the chiral centers' configurations and the double-bond's geometry (Scheme 12).[14]

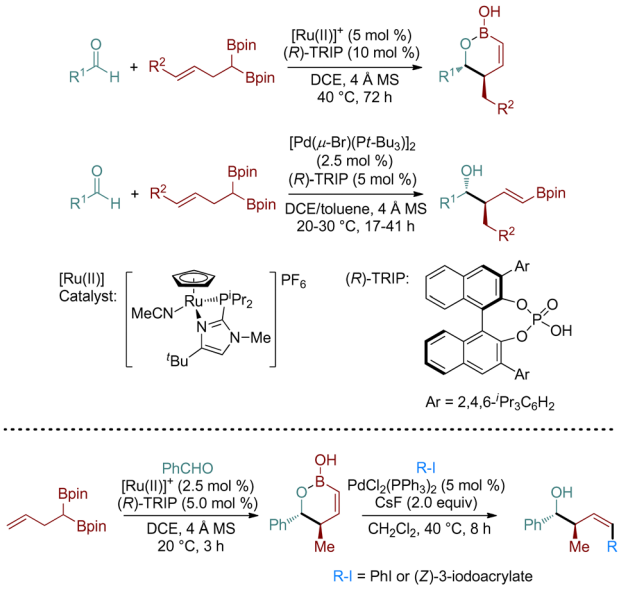
In previous work, the initially produced (*Z*)-vinylboronate was prone to geometrical isomerization to from a more stable (*E*)-vinylboronate under the reaction conditions. To address this problem, the same group then searched for a transition-metal catalyst which is more specifically effective for double-bond transposition of 1,1-diboronate substrates but meantime allows the preservation of the product with (*Z*)-geometry. The authors found that a ruthenium(II) complex performed as specifically as they desired, affording the desired (*Z*)-configured products in good yield with excellent stereoselectivity. However, a six-membered ring structure instead of an acyclic homoallylic alcohol was isolated, and the authors considered that the latter is initially formed but then cyclized during workup/purification. The (*E*)-isomer products, remaining in the acyclic form, could also be obtained by employing the palladium(I) catalyst, hence both of the double-bond geometry of the products can be precisely controlled by simply tuning the transition metal catalysts. The synthetic utility of this chemistry was illustrated by further transformations of the residual boronate moiety. For



Scheme 10 Cu-catalyzed enantio- and diastereoselective 1,2-addition of 1,1-diborylethane to aryl aldehydes.



Scheme 12 Pd-catalyzed enantio- and diastereoselective 1,2-addition of 1,1-diborylalkanes to aldehydes.



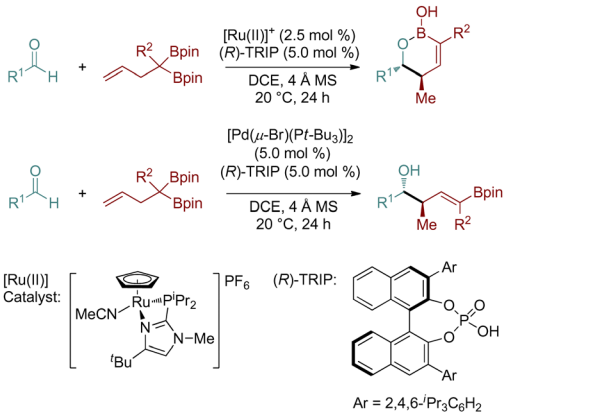
Scheme 13 Ru & Pd-catalyzed enantio- and diastereoselective 1,2-addition of 1,1-diborylalkanes to aldehydes.

example, subsequent Suzuki–Miyaura reactions of the (*Z*)-product using both iodobenzene and ethyl (*Z*)-3-iodoacrylate as coupling partners successfully furnished the target products with retention of the double-bond geometry (Scheme 13).[15]

Propionate-derived motifs are ubiquitous in many natural products; however, the *E*/*Z* stereochemistry of the trisubstituted double bonds is difficult to control. Miura and Murakami found that this challenge could be perfectly solved by using their double-bond transposition/enantioselective allylation cascade. Employing a more structurally complicated α,α-disubstituted *gem*-diboron reagent as a nucleophile to react with aldehydes, both (*E*)- and (*Z*)-isomers of the propionate-derived trisubstituted alkenes can be precisely synthesized by using different transition metal catalysts (Scheme 14).[16]

Prior to this work, the enantioselective 1,2-addition of the more structurally complicated, α,α-disubstituted *gem*-diboron reagent has been disclosed by Chen *et al.* in 2020. This new crotylboronate reagent is highly reactive that it reacts with benzaldehyde in the absence of any catalyst to afford the addition product with a 3 : 1 *E*/*Z* ratio. To enhance the stereoselectivity, the authors added chiral phosphoric acid catalyst into the reaction mixture and gratifyingly found that excellent *E*-selectivity (*E*/*Z* > 20 : 1) and enantioselectivity (97% ee) were both achieved. By virtue of this simple but efficient catalytic system, a wide range of addition products were obtained in good yields with excellent *E*-selectivities and enantioselectivities. Moreover, two non-enantioselective 1,2-additions with opposite *Z*-selectivities were also established by employing $BF_3{\cdot}OEt_2$ as the catalyst (Scheme 15).[17]

In the same year, a structurally analogous crotyl *gem*-diboronate bearing an additional pendent boryl was synthesized by the same group. This new kind of *gem*-diboronate underwent an asymmetric allylation with aldehydes in the presence of a chiral phosphoric acid. A series of 6′-boryl-*anti*-

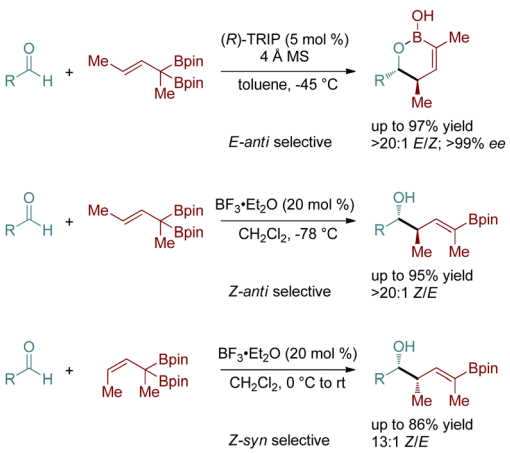


Scheme 14 Ru & Pd-catalyzed enantio- and diastereoselective 1,2-addition of α,α-disubstituted *gem*-diboronates to aldehydes.

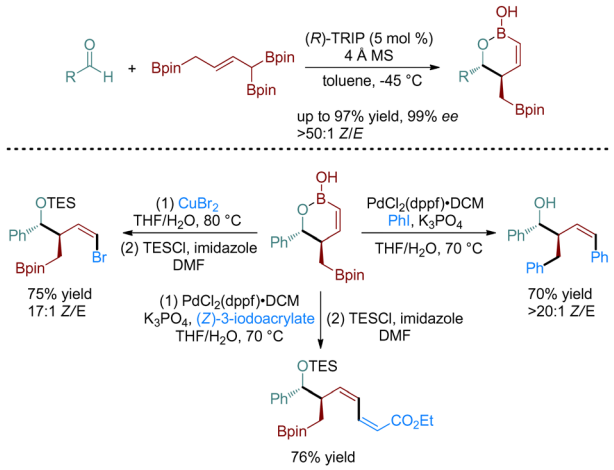
1,2-oxaborinan-3-enes were thereby synthesized with excellent *Z*-, diastereo-, and enantioselectivities. Because the synthesized product contains a vinyl and an alkyl boronate unit, a variety of transformation reactions can be performed with different chemoselectivities (Scheme 16).[18]

The catalytic enantioselective 1,2-addition of 1,1-diborylalkanes to isatins was disclosed by Xiao and Chen in 2022. In the presence of a Cu catalyst and a chiral phosphoramidite ligand, enantiomerically enriched borylated 3-hydroxyoxindoles were obtained with up to > 20 : 1 d.r. and 99% ee (Scheme 17).[19]

The enantio- and diastereo-selective 1,2-addition of 1,1-diborylalkanes to *N*-protected imines was first reported by Cho *et al.* in 2017. In the presence of 5 mol% of CuBr and 10 mol% of (*R*)-BINOL-derived phosphoramidite ligand, a series of cyclic aldimine substrates reacted with 1,1-diborylalkanes in a highly enantio- and diastereo-selective manner, affording the corresponding *syn*-product in up to 99% yields. Acyclic imine substrates, although exhibiting lower *syn*/*anti* selectivity toward the nucleophiles, were still compatible with the conditions and afforded the target 1,2-addtion products in good yields and enantioselectivities (Scheme 18).[20]



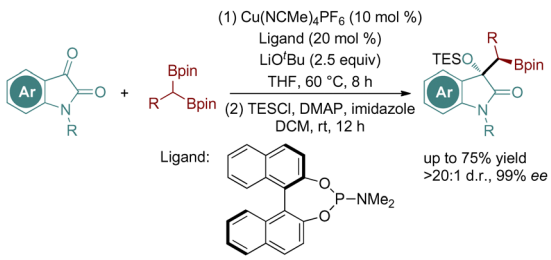
Scheme 15 Chiral phosphoric acid catalyzed enantio- and diastereoselective 1,2-addition of α,α-disubstituted *gem*-diboronates to aldehydes.



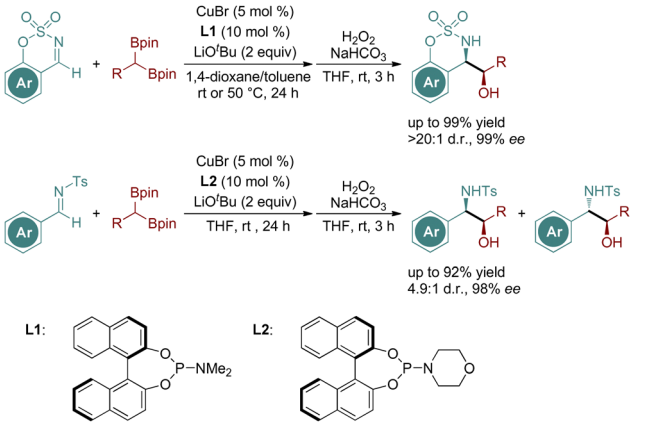
Scheme 16 Chiral phosphoric acid catalyzed enantio- and diastereoselective 1,2-addition of crotyl *gem*-diboronates to aldehydes.

In previous studies, Cho and coworkers found that when acyclic arylaldimines such as *N*-tosyl-protected arylaldimines were employed as substrates, their 1,2-addition with 1,1-diborylalkanes suffered modest diastereoselectivity ($< 5:1$ d.r.). To solve this problem, the authors screened several *N*-protecting groups and found that the *N*,*N*-dimethylsulfamoyl-group could considerably improve the diastereo- and enantio-selectivity. Therefore, under similar reaction conditions reported before, a wide range of β-aminoboronate esters were synthesized in good yields and with good to excellent stereoselectivities (up to 18 : 1 d.r., 99% ee). More importantly, the reaction can be easily scaled up to gram scale without obvious destruction of optical purities. Moreover, the obtained β-aminoboronate esters are versatile building blocks that can be employed in a series of transformations to furnish other important classes of compounds, hence highlighting the practicability of the developed process (Scheme 19).[21]

The first catalytic enantio- and diastereo-selective prenyl addition to aryl imines with allylic *gem*-diboronates was developed by Meek in 2020. Employing a readily prepared (phosphoramidite)–Cu complex as the chiral catalyst, a wide range of enantiomerically enriched homoallylic amines bearing a chiral quaternary carbon and an alkenylboron were obtained in up to 82% yield, $>20:1$ d.r., and $>99:1$ e.r. Of note, CD_3OD was utilized to suppress protonation of the Cu-allyl species by



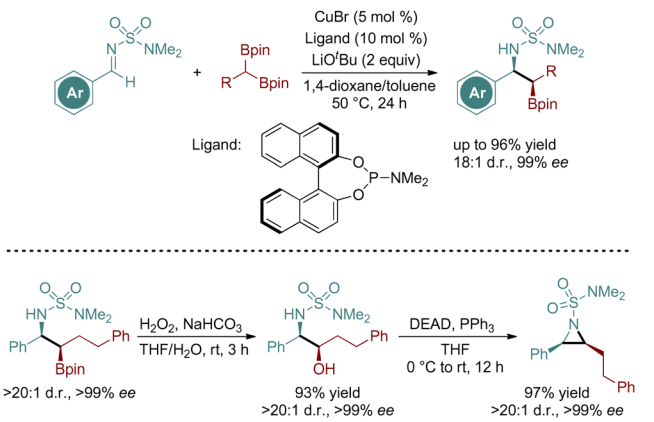
Scheme 17 Cu-catalyzed enantio- and diastereoselective 1,2-addition of 1,1-diborylalkanes to isatins.



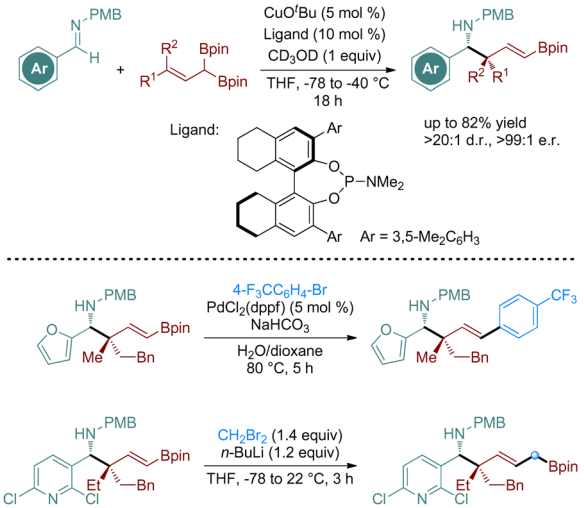
Scheme 18 Cu-catalyzed enantio- and diastereo-selective 1,2-addition of 1,1-diborylalkanes to sulfimides.

virtue of deuterium isotope effect. The reaction proceeded *via* a highly enantioselective transmetalation between the *in situ* generated chiral α-boryl–Cu–allyl nucleophiles and aryl aldimines, thus affording the enantiomerically enriched homoallylic amines with excellent stereoselectivities. Both diastereoisomers can be obtained by simply employing the *E*- and *Z*-isomers of the allyldiboron substrates. The synthesized vinylborate products are versatile building blocks that can undergo a range of functional group transformations to afford various highly functionalized compounds. For example, Suzuki–Miyaura cross-coupling of the vinylborate furnished an alkenylarene derivative while the homologation process afforded an allylborate product (Scheme 20).[22]

Soon after, the same group further extended this chemistry to more challenging aldehyde electrophiles. Under similar reaction conditions, a broad scope of aldehydes, including both aromatic and aliphatic, underwent 1,2-addtion reactions with a series of 1,1-allylic diboronates highly efficiently and enantioselectively, affording the vicinal homoallyl alcohols bearing quaternary carbon stereocenters in good yields and high enantiopurities. Hammett studies revealed that the diastereoselectivity of the reaction is correlated with the electronic



Scheme 19 Cu-catalyzed enantio- and diastereo-selective 1,2-addition of 1,1-diborylalkanes to *N*,*N*-dimethylsulfamoylimides.

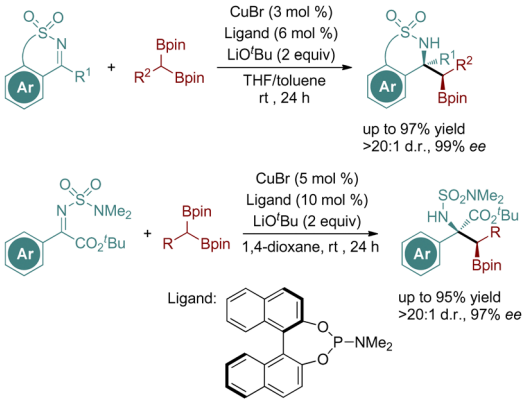


Scheme 20 Cu-catalyzed enantio- and diastereo-selective 1,2-addition of 1,1-diborylalkanes to aryl aldimines.

nature of the aldehyde, with d.r. increasing as the aldehydes become more electron poor (Scheme 21).[23]

In contrast to aldimines, ketimines were intrinsically less reactive and the 1,2-addition of 1,1-diborylalkanes to ketimines is hence more challenging. To address this issue, Cho again employed the CuBr/monodentate phosphine catalytic system to stereoselectively forge a new C–C bond between sterically congested vicinal stereogenic centers. A series of β-aminoboronate esters were thus synthesized with high enantio- and diastereoselectivities. To solve the problem that *N*-protected acyclic substrates often showed poor diastereoselectivities toward 1,2-addition in previous studies, the authors employed α-imino esters as electrophiles. Owing to the better coordination of chiral copper species with nitrogen and oxygen atoms in the imino and ester groups, the transfer of the α-boryl-alkyl moiety to the adjacent C=N double bond could be facilitated, hence affording the target 1,2-addition products in good yields and >20:1 d.r. (Scheme 22).[24]

Ketones, which are less reactive and exhibit poorer face selectivity in contrast to aldehydes and imines, are very challenging substrates in terms of reactivities and stereoselectivities in 1,2-addition reactions. To realize the asymmetric 1,2-addtion of ketones with 1,1-allylic diboronate compounds, Meek employed a more sterically hindered ligand to improve the diastereoselectivity

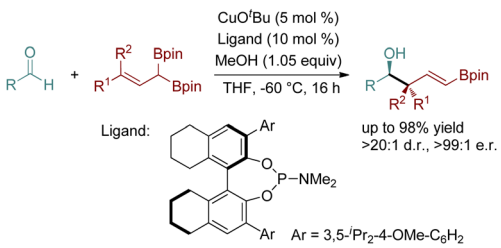


Scheme 22 Cu-catalyzed enantio- and diastereo-selective 1,2-addition of 1,1-diborylalkanes to ketimines.

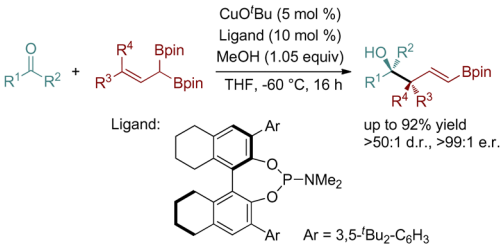
and enantioselectivity. By virtue of this catalytic system, a variety of tertiary homoallylic alcohols bearing vicinal quaternary stereocenters were synthesized with good diastereo- and enantioselectivities. The reaction also showed very good functional group compatibility, and a wide variety of aryl, heteroaryl, alkenyl, alkynyl, and alkyl were all tolerated (Scheme 23).[25]

Conjugate addition

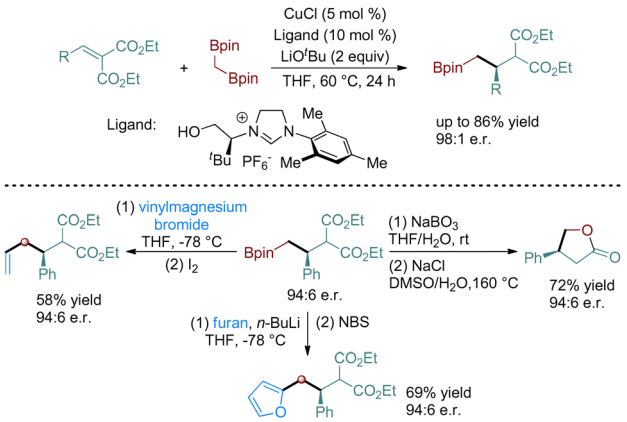
Although enantioselective cross-coupling, S_N2' substitution and 1,2-addition reactions of 1,1-diborylalkanes have been well established, conjugate additions, a powerful tool for C–C bond formation, have rarely been studied in 1,1-diborylalkanes chemistry. In 2019, Yun *et al.* reported the first catalytic enantioselective 1,4-conjugate addition of a borylalkyl copper complex which was generated from 1,1-diborylalkane to α,β-unsaturated carbonyl compounds. In this work, *N*-heterocyclic carbene ligands, which coordinate more tightly to copper, were employed to improve the enantioselectivity of the conjugate addition. A broad range of α,β-unsaturated diethyl diesters bearing different β-substituents reacted with 1,1-diborylmethane in an enantioselective manner to afford the corresponding chiral alkylboronate compounds in good yields. The resulting products can be further transformed into other highly functionalized products with perfect preservation of the chiral centers. For example, a chiral γ-lactone was obtained through oxidation of the boryl followed by a decarboxylation process, while a stereospecific vinylation and a heteroarylation of the alkylboronate



Scheme 21 Cu-catalyzed enantio- and diastereoselective 1,2-addition of 1,1-allylic diboronates to aldehydes.



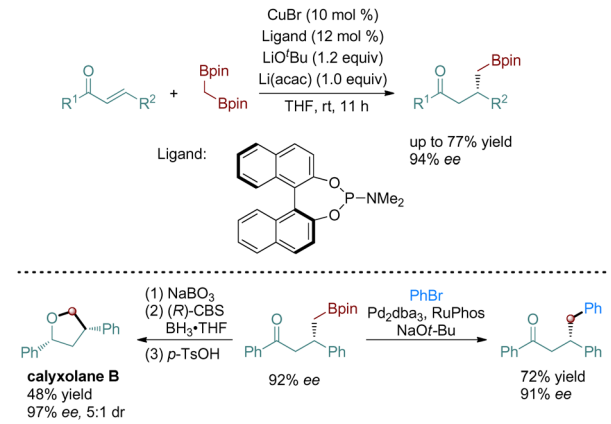
Scheme 23 Cu-catalyzed enantio- and diastereo-selective 1,2-addition of 1,1-diborylalkanes to ketones.



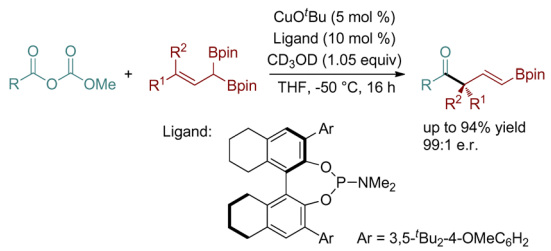
Scheme 24 Cu-catalyzed enantioselective conjugate addition of 1,1-diborylmethane to α,β-unsaturated diethyl diesters.

afforded the corresponding coupling products in moderate yields (Scheme 24).[26]

Although representing the first asymmetric conjugate addition reaction of 1,1-diborylalkanes, the substrate scope of Yun's reaction was limited to highly activated substrates containing multiple electron-withdrawing groups. More general Michael acceptors, such as α,β-unsaturated ketones, are not feasible under this reaction condition. To address this challenge, Lee *et al.* developed a Cu-catalyzed ligand preservation approach to achieve the enantioselective conjugate addition between 1,1-diborylmethane and a series of α,β-unsaturated ketone substrates. Of note, the addition of Li(acac) into the reaction mixture significantly improved both the yield and enantioselectivity. To better understand the important role of Li(acac) in this reaction, detailed mechanism studies were performed and the authors found that the alkoxide base in the reaction mixture could destroy the chiral phosphoramidite ligand, thus resulting in an unproductive catalytic cycle with poor enantioselectivity. In contrast, the addition of Li(acac) could control the extent of the unproductive catalytic cycle and maintain a high catalytic activity by the preservation of ligand's structure, thus improving both the yield and enantioselectivity of this reaction. Further transformations of the residual



Scheme 25 Cu-catalyzed enantioselective conjugate addition of 1,1-diborylmethane to α,β-unsaturated ketones.



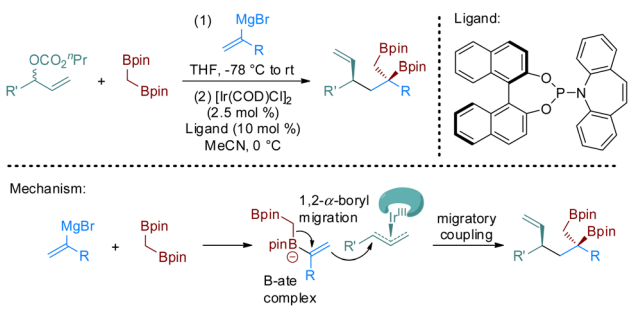
Scheme 26 Cu-catalyzed enantioselective acyl substitution of acyl carbonates with 1,1-allylic diboronates.

boryls could furnish more structurally complicated products without the destruction of enantiomeric purities. For example, Suzuki–Miyaura cross-coupling with bromobenzene afforded the corresponding γ-phenyl ketone product in 72% yield, and an enantioselective reduction of the carbonyl group followed by a stereospecific intramolecular displacement afforded a marine natural product calyxolane B (Scheme 25).[27]

Miscellaneous

Besides those traditional enantioselective reactions, several new reaction modes employing 1,1-diborylalkanes have been disclosed in very recent years, which highlight the importance and versatility of those reagents. For instance, in 2023, Meek reported an enantioselective acyl substitution of readily available acyl electrophiles bearing a suitable leaving group with *in situ* formed chiral allylic nucleophiles. Specifically, the enantioselective transmetalation of 1,1-allylic diboronates and the chiral copper catalyst forms an enantioenriched stereodefined Cu-allyl nucleophile, which subsequently reacts with acyl carbonates through an addition-elimination pathway to afford the chiral α-quaternary ketone products bearing a pendent *E*-alkenyl-B(pin) motif that can be further transformed into other functionalities. Of note, the use of a protic additive CD_3OD is beneficial, for it can facilitate the decomposition of the (L)Cu–O_2COMe species to enhance the catalyst turnover and suppress a competitive but less enantioselective transmetalation (Scheme 26).[28]

In the above-discussed reactions, only one of the two boryls is kept after the reactions. However, in view of the abundant transformations of boryl, an enantioselective reaction which could retain both of the two boryls would be more appealing.



Scheme 27 Ir-catalyzed enantioselective migratory coupling of 1,1-diborylmethanes.

This hypothesis was realized by Gao *et al.* in 2023 through a new activation mode of 1,1-diborylalkanes, *i.e*. no deborylation occurs after forming a vinyldiboron "ate" complex, instead, the latter undergoes a 1,2-α-boryl migration to afford the final diboryl product bearing both a primary and a tertiary boronate unit. Further studies showed that other types of 1,*n*-diborylalkanes (n = 2 and 4), or 1,1-borylsilylalkane all failed to afford the migration products, thus highlighting the unique reaction mode of 1,1-diborylalkanes. Mechanistically, a tetracoordinate B-ate complex is formed by treating the 1,1-diborylalkanes with isopropenylmagnesium bromide, which subsequently undergoes a migratory coupling with chiral Ir-allyl species to furnish the enantiomerically enriched 1,2-diborylalkane products (Scheme 27).[29]

Conclusions

Owing to environmental benignity, low toxicity, good stability, easy availability, and synthetic versatility, organoboron compounds have emerged as some of the most commonly used reagents in organic synthesis and chemical industry. As a structurally unique member of organoboron compounds, 1,1-diborylalkanes often exhibit unusual reactivity and extraordinary stereoselectivity during the reactions. Moreover, the preserved boryl after the reaction could be further converted into many other functionalities through various transformations, thus furnishing a broad range of more structurally complicated compounds. Therefore, since their first report in 2010, the last decade has witnessed a rapid development of 1,1-diborylalkanes, especially in the realm of asymmetric synthesis. A series of catalytic enantioselective reactions, including Suzuki–Miyaura cross-coupling, S_N2/S_N2' allylic substitution, 1,2-addition, and conjugate addition, have been developed. In most cases, the unique structure endows 1,1-diborylalkanes with superior reactivity and stereoselectivity in contrast to other organoboron compounds. Hence it is no doubt that 1,1-diborylalkanes have a promising future and more and more elegant reactions based on these reagents will be disclosed.

However, the present reaction conditions limit the synthetic application of these reagents, for example, the use of these reagents necessitates a strong base (MOH or MOR, M = Li, Na, K) to activate one of the pinacolato boron (Bpin) units of the 1,1-diborylalkanes, leading to a lack of functional group compatibility. Besides, the alkoxide base in the reaction mixture could also destroy the chiral active species, thus resulting in an unproductive catalytic cycle with poor enantioselectivity. Therefore, new activation methods for 1,1-diborylalkanes are still in demand. Moreover, greener synthetic protocols need to be established, and this issue would be addressed by the development of more robust chiral catalysts and ligands that enable the reactions to proceed in aqueous solvents. Based on these ideal breakthroughs, these kinds of 1,1-diborylalkanes-involved asymmetric reactions are expected to increase to a large extent. More challenging reactions such as the enantio- and diastereoselective cross coupling between two sp^3 carbons, and the asymmetric 1,2-difunctionnalization of simple olefins will be developed by employing these unique organoboron compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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