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不对称催化合成手性 1,2-双硼酸酯研究进展

吉崇磊 高得伟*
(上海科技大学物质科学与技术学院 上海 201210)

摘要 手性 1,2-双硼酸酯是合成化学中重要的转化砌块, 其催化不对称合成引起了化学界的广泛关注. 近年来, 过渡金属和手性双醇催化的烯烃不对称双硼化反应已成为合成手性 1,2-双硼酸酯的重要方法, 基于烯基双硼化合物的不对称氢化反应, 可以作为烯烃双硼化反应的补充来合成对应的目标产物. 同时, 烯烃或炔烃的硼化/官能团化也是构建这类化合物的另一种有效方法. 最近, 以偕二硼酸酯为起始物的催化不对称迁移增碳反应, 为手性 1,2-双硼酸酯的合成提供了新的思路. 总结了手性 1,2-双硼酸酯合成的最新研究进展及面临的挑战, 并对未来的研究方向进行了展望.
关键词 手性 1,2-双硼酸酯; 双硼化; 氢硼化; 硼化/官能团化; 偕二硼酸酯; 迁移偶联

Recent Advances in Catalytic Asymmetric Synthesis of Chiral 1,2-Bis(boronic) Esters

Ji, Chonglei Gao, Dewei*
(*School of Physical Science and Technology*, *ShanghaiTech University*, *Shanghai 201210*)

Abstract Chiral 1,2-bis(boronic) esters are essential building blocks in the field of synthetic chemistry, and their catalytic asymmetric synthesis has attracted significant interest of chemists. Recently, asymmetric diboration of olefins, using transition metals and chiral diols, has emerged as the straightforward and atom-economical methods for producing highly valuable chiral 1,2-bis(boronic) esters. Asymmetric hydrogenation of vinyl bis(boronic) esters can be a complementary approach to asymmetric diboration for synthesizing these products. Additionally, borofunctionalization of alkenes or alkynes represents another effective strategy for constructing these highly valuable scaffolds. A recent innovation involves catalytic asymmetric migratory coupling reactions with *gem*-diborylalkanes, offering new avenues for synthesizing chiral 1,2-bis(boronic) esters. The latest developements and challenges in synthesizing these moleculeshis are summarized, and the potential future research directions in this field are prospected.
Keywords chiral 1,2-bis(boronic) esters; diborylation; hydroboration; borofunctionalization; *gem*-diborylalkanes; migratory coupling reactions

1 Introduction

Stereochemical complex molecules in optically pure form are frequently found in many pharmaceutical drugs and biologically active molecules (Figure 1a).[1] Their construction presents a challenge due to the need for highly precise assembly and excellent stereocontrol. Considering that the neighboring functional groups in natural products and pharmaceuticals typically show a high degree of diversity, developing entirely new synthetic strategies for constructing the target molecules, based on differences in functional groups, can be both laborious and time-consuming. However, organoborons, which serve as important building blocks in synthetic and medicinal chemistry, offer a versatile approach for creating various functional groups.[2] Chiral 1,2-bis(boronic) esters are particularly advantageous,[3] enabling selective transformations into various functional groups through cross-coupling, oxidation, radical reactions, *etc.*, which are useful in the synthesis of bioactive molecules (Figure 1b).[4] Recent progress in selective C—B functionalization has facilitated the development of stereospecific cross-coupling reactions,[5] opening new possibilities for precise, stereoselective transformations of 1,2-bis(boronic) esters. Therefore, the efficient synthesis of these compounds could lead to significant advancements in incorporating essential functional

* Corresponding author. E-mail: gaodw@shanghaitech.edu.cn
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units into pharmaceuticals (Figure 1b). This approach provides an efficient and streamlined method for rapid molecular construction.

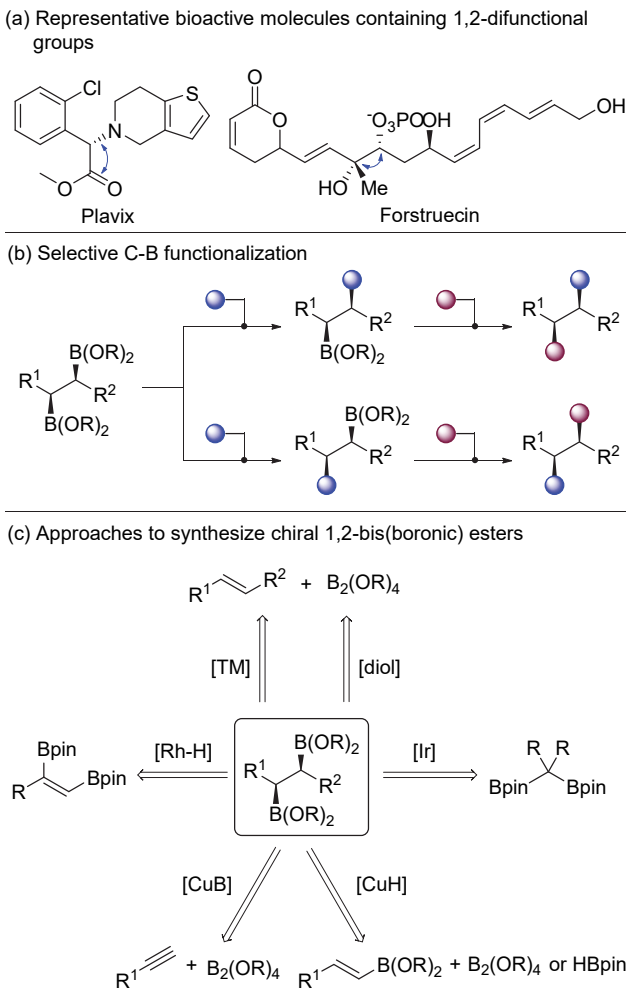

Figure 1 Synthetic potential of 1,2-bis(boronic) esters and the methods used to prepare these privileged scaffolds

Despite their potential, the synthesis of chiral 1,2-diboronates has not been extensively pursued in synthetic chemistry.[6] Current methods for creating these molecules are limited compared to their possible applications. Several factors contribute to the slow progress in this field. One major challenge is the instability of 1,2-bis(boronic) esters during reactions, which can lead to side reactions and difficulty in controlling selectivity. Asymmetric diboration of alkenes, a key method for synthesizing these compounds, is challenging due to the need to regulate the reactivity and stereoselectivity, particularly in non-activated alkenes.[7] Furthermore, achieving control over enantioselectivity is essential for producing chiral molecules, further complicated by the instability of reaction intermediates and complexities of the substrates.

The versatility of these molecules has spurred the exploration of various catalytic approaches to synthesize stereo-defined 1,2-bis(boronic) esters (Figure 1c). Common methods include asymmetric diborylation of alkenes, Cu-catalyzed borylation of unsaturated hydrocarbons, asymmetric hydrogenation, and the recently developed migratory coupling reactions of *gem*-diborylalkanes. While the applications and access to chiral 1,2-bis(boronic) esters have been extensively explored, their synthesis is still in the early stages of development compared to their potential applications. This review aims to provide an overview of the available methods for preparing these esters, hoping to inspire further research in this field. It is organized primarily based on reaction types, as discussed above.

2 Asymmetric diboration of alkenes

Asymmetric diborylation of alkenes provides an efficient and straightforward method for synthesizing chiral 1,2-bis(boronates). Various transition metals, including rhodium (Rh), palladium (Pd), and platinum (Pt), have been effectively utilized in the 1,2-diboration of alkenes, employing chiral ligands. However, these reactions frequently encounter challenges in controlling enantioselectivity, especially in the reactivity and stereoselectivity of non-activated alkenes, likely due to unstable intermediates formed during the reaction. Moreover, 1,1-disubstituted and 1,1,2-trisubstituted olefins present significant challenges due to steric hinderance. Nevertheless, researchers have made significant advances in addressing these issues by developing innovative catalytic systems.

2.1 Rh-catalyzed diboration of alkenes

In 2003, the Morken group[8] achieved a breakthrough by developing the first enantioselective 1,2-diboration of alkenes. This reaction was facilitated by a rhodium catalyst with bis(catecholato)diboron, in the presence of chiral phosphine ligands. The catalytic diboration, followed by oxidation, was applied to *trans*-1,2-disubstituted alkenes (**2a**～**2d**) and terminal alkenes (**2e**～**2f**), including those featuring tertiary alkyl groups (**2f**), yielding optically active 1,2-diols with moderate enantioselectivity. Additionally, *cis*-disubstituted cyclic alkenes and acyclic alkenes afforded relatively modest *ee* values (**2g**～**2h**). The limited availability of 1,2-diborons in the past likely contributed to the scarcity of comprehensive transformations in the literatures. The authors demonstrated that 1,2-bis(catechol) esters produced in the asymmetric diboration reaction could undergo transesterification to form bis(pinacol) ester. This transformation occurs by directly treating the crude reaction mixture with pinacol. Beyond this reaction and simple oxidation to yield the 1,2-diol, it was observed that 1,2-diboron adduct can participate in the Matteson homologation process (Figure 2). Following this seminal research, the same group[9] applied this strategy to tandem one-pot diboration/oxidation or Suzuki coupling reactions. The methodology further expands the types of substrates for asymmetric diborylation, although there are still some challenges with the chiral control of styrene-type substrates. Notably, it facilitated the synthetic transformations of chiral bis(boronic) esters by running oxidation and selective arylation at the terminal C—B bond.

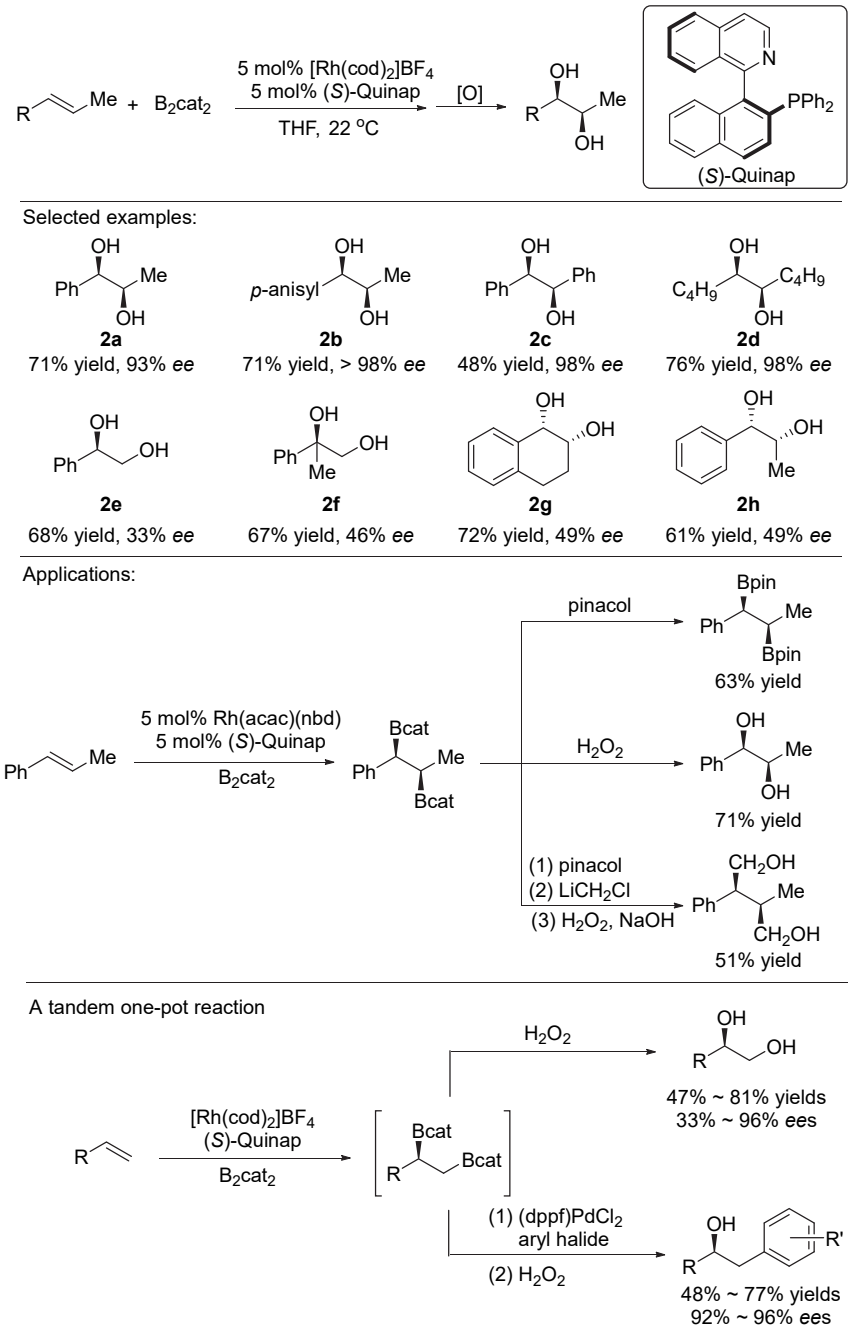

Figure 2 Rhodium-catalyzed enantioselective diboration of alkenes

Based on previous studies, Morken and coworkers[10] further explored rhodium-catalyzed asymmetric diborylation, using bis(catecholato)diboron and simple alkenes. This process leads to the *syn* addition of diboron moieties across the alkenes. The study demonstrates the compatibility with a variety of substrates, including both disubstituted and aliphatic substituted alkenes. They also conducted preliminary tests of the catalytic system on 1,1-disubstituted and trisubstituted alkenes, although these results require further improvement (Figure 3). Nonetheless, this indicates the potential of this reaction in providing a valuable reference for future selective diboration of such challenging substrates. Analysis using both deuterated and non-labeled styrene revealed that most target products exhibited no isotopic disorder, except for a minor amount of the product d^7h^1-**3e** being formed. These findings suggest that the *β*-hydride elimination/hydroboration reaction is likely a minor pathway in this catalytic process.

Addressing the challenge of chiral control in the asymmetric diboration of certain terminal alkenes, especially aryl-substituted ones, Nishiyama group[11] developed another efficient method. In this reaction, chiral [Rh(Phebox)] acetate complexes are crucial as catalysts, effectively overcoming these obstacles. This diboration process offers

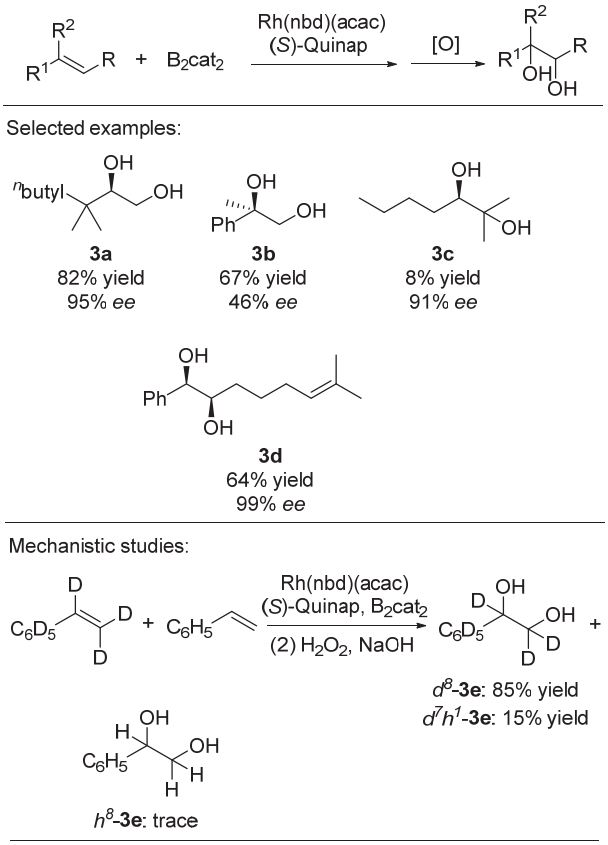

Figure 3 Enantioselective diboration of simple alkenes: reaction development and substrate scope

a synthetic approach for producing optically active 1,2-diols from diverse terminal alkenes, achieving both high yields and exceptional optical purity (**4a**～**4g**). As shown in Figure 4, the formation of a boryl acetate intermediate was confirmed through ^{11}B NMR spectroscopy. This confirmation was achieved by reacting [Rh(Phebox-ip)(OAc)$_2$(H$_2$O)] with B$_2$pin$_2$. The enhancement of the diboration process by the addition of ^{t}BuONa suggests that either σ-bond metathesis or a transmetallation process plays a key role in the catalytic cycle. This likely facilitates the formation of the boryl-Rh(III) species **A**, which then binds to an alkene moiety, initiating the reaction. This is followed by the insertion of the boryl group, leading to the formation of an alkyl-Rh species, labeled as **B**. Subsequently, the reaction proceeds through either σ-bond metathesis or transmetallation, resulting in the production of the diboration product. This step also leads to the regeneration of the active ^{t}BuO-Rh(III) species, or alternatively, it can revert to the original species **A**. Several potential pathways may lead to the formation of species **A**. Hypothetical transition state models have been proposed to further elucidate the reaction mechanism. According to these models, when the boryl group occupies the equatorial position, the *Si*-face attack on the alkene is more hindered compared to the *Re*-face attack. This difference in steric hindrance accounts for the observed selectivity in the catalytic process.

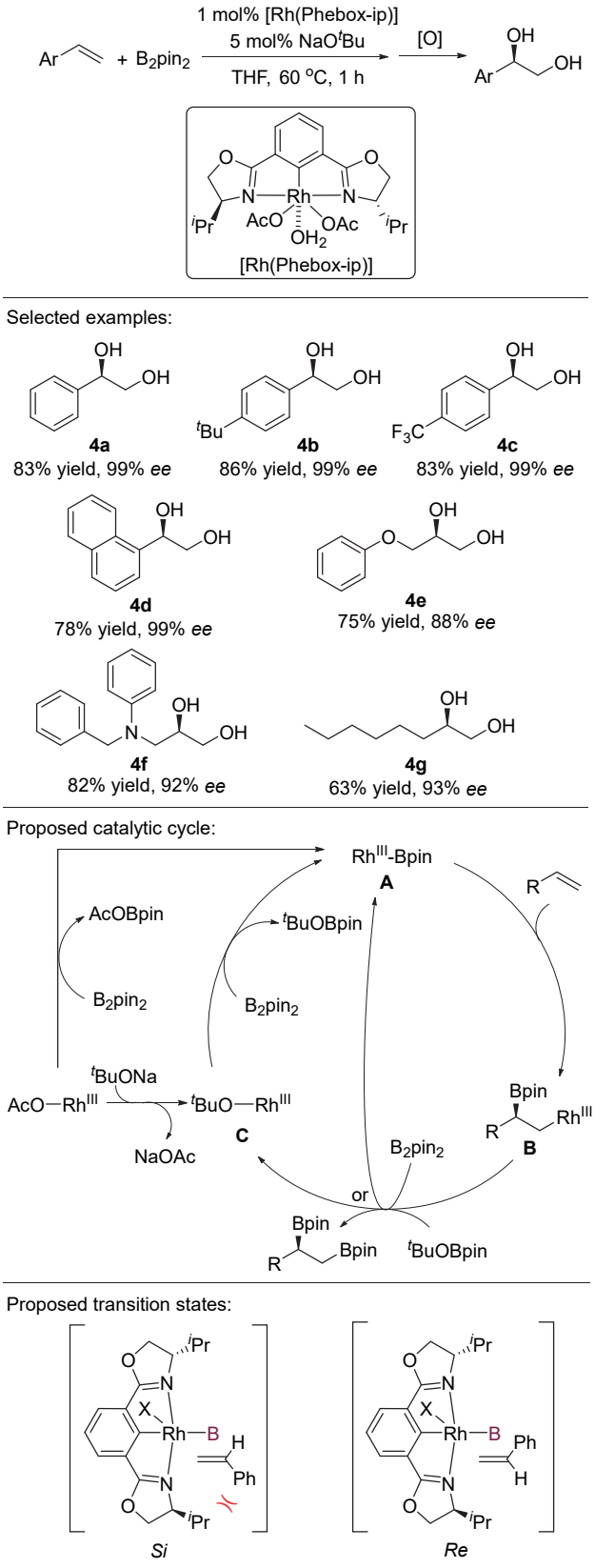

Figure 4 Rhodium-catalyzed enantioselective diboration of terminal alkenes

2.2 Pd-catalyzed diborylation of allenes

The Morken group[12] is at the forefront of advancing

catalytic asymmetric reactions, focusing on creating reactive chiral intermediates for efficient synthesizing complex molecules. Their primary focus is on asymmetric diboration of prochiral allenes, leading to the formation of chiral diboron adducts. These adducts, featuring both allylboronate and vinylboronate groups, are valuable intermediates in asymmetric synthesis. Initial attempts with chiral rhodium-based catalysts resulted in poor regioselectivity, reactivity, and enantioselectivity. Consequently, the group shifted their focus to exploring new transition metal complexes, particularly palladium, due to its lower activation barrier for oxidative addition to diboron reagents. They investigated the use of chiral phosphoramidites in the allene diboration reaction. These ligands are modular, highly tunable, and have been successful in various catalytic asymmetric transformations. Their study discovered that *α*,*α*,*α*′,*α*′-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol (TADDOL)-derived phosphoramidite afforded high levels of asymmetric induction and good yields for various prochiral monosubstituted allenes (**5a**～**5d**). The addition of benzaldehyde followed by oxidation resulted in the formation of *β*-hydroxyketone with high enantiomeric ratios, demonstrating efficient chirality transfer during the allylation of benzaldehyde. The selectivity of this transformation is attributed to the preferred transition state **D** over the less favored (1,2)-interaction in transition state **E** (Figure 5).

Given the significance of chiral amines in synthetic and medicinal chemistry, Morken's group[13] also explored the reactivity of these chiral diborons with imine electrophiles. By using acetic anhydride (Ac_2O) for protection and hydrogen peroxide (H_2O_2) for oxidation, *β*-amidoketones were synthesized with high yields and excellent enantioselectivities . Notably, the allene diboration reaction exhibits remarkable selectivity, and the subsequent allylation frequently achieves chirality transfers nearing 99%. This method enabled a streamlined one-pot synthesis of *β*-amidoketones from allenes, delivering both good yields and excellent enantioselectivities (Figure 6a). Employing a similar strategy, they[14] have demonstrated that the chiral allylboron intermediate is a versatile reagent for the allylation of carbonyls.

Later, Pelz and Morken[15] developed a novel approach for synthesizing chiral diols (Figure 6b). This reaction starts with the catalytic enantioselective diboration of prochiral allenes. It is then followed by an *in-situ* reaction with a hydroboration agent, leading to the formation of a unique triboron intermediate. In this intermediate, the least hindered C—B bond undergoes cross-coupling, facilitated by the same catalyst used in the diboration step. Subsequent oxidation results in the formation of the chiral diols. The method was tested with various allenes and electrophiles, yielding moderate to excellent enantioselectivities in one-step processes. It proved effective for synthesizing both aromatic and alkenyl diols. The single-pot approach not only simplifies the process but also enhances its practical applicability.

2.3 Pt-catalyzed diboration of alkenes

The stereoselective regulation of some terminal alkenes through rhodium catalysis often results in moderate enantioselectivity and depends on the expensive boron source

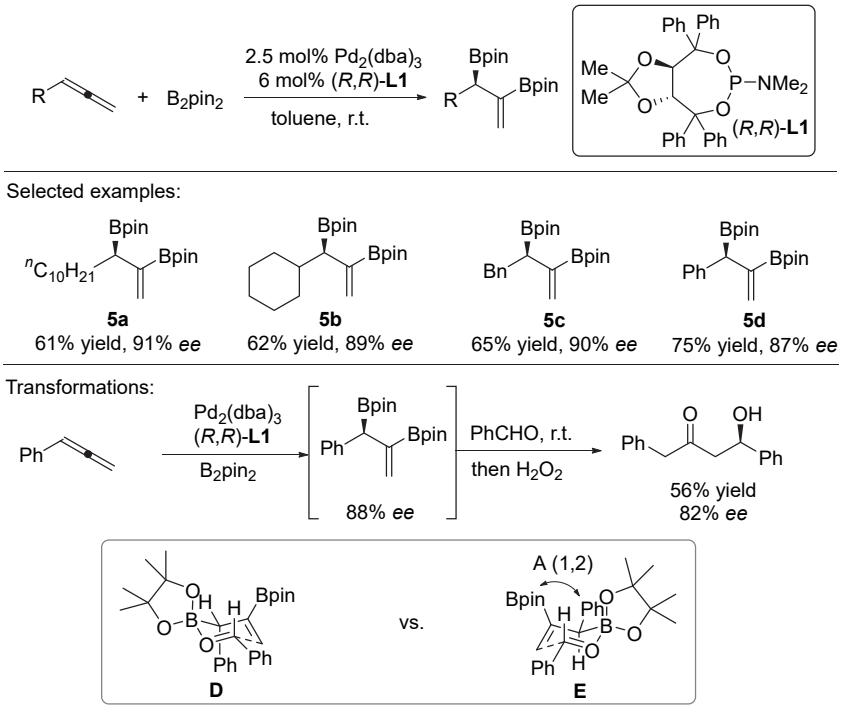

Figure 5 Pd-catalyzed enantioselective diboration of prochiral allenes

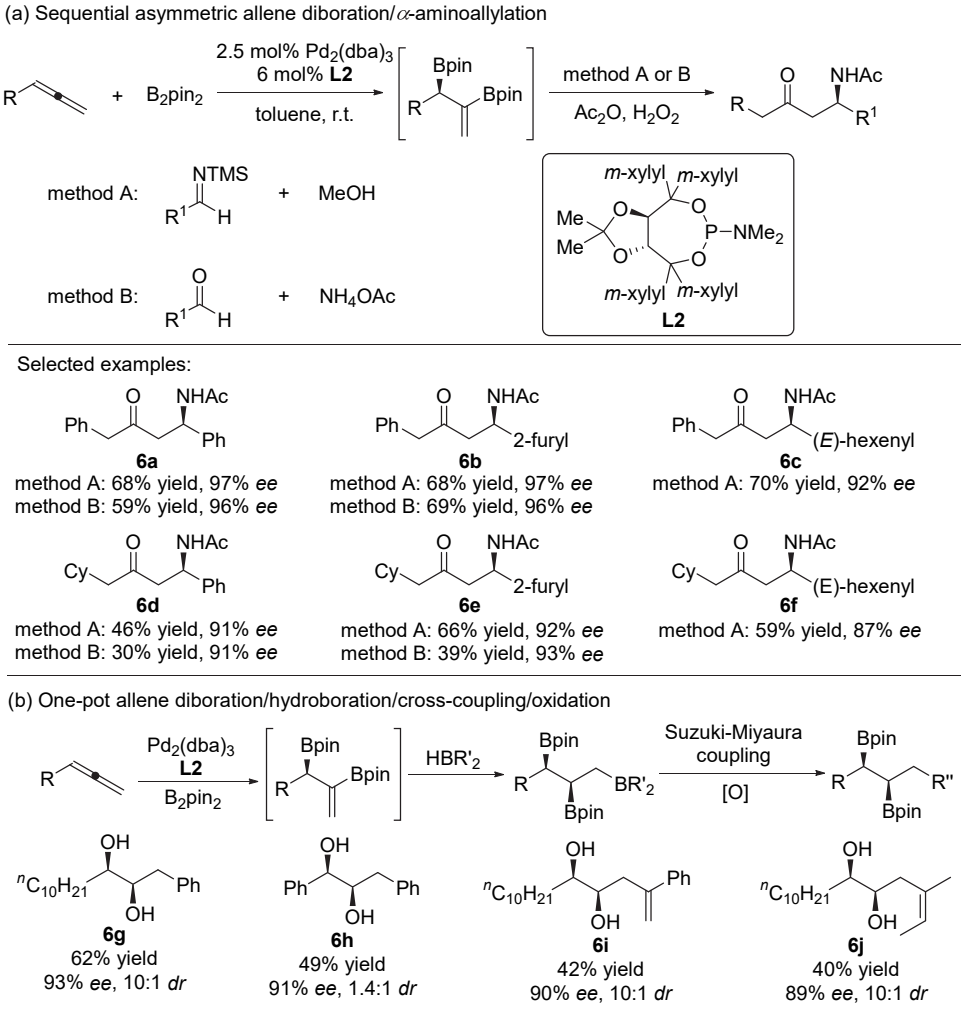

Figure 6 Palladium-catalyzed asymmetric diboration of allenes and subsequent transformations

$B_2(cat)_2$, limiting the practicality of this approach. In 2009, the Morken group[16] developed Pt-catalyzed enantioselective 1,2-diboration of terminal olefins, accommodating both aliphatic and aryl substituents. This reaction achieves high enantioselectivity and good yields using commercially available and cost-effective reagent, bis(pinacolato)-diboron (B_2pin_2). Additionally, this asymmetric diboration reaction allows for single-flask transformations. For example, 1-octene undergoes a streamlined process of Pt-catalyzed diboration, followed by one-carbon homologation and oxidation (Figure 7). This sequence efficiently produces the desired 1,4-diol with 84% overall yield and 91% *ee*, significantly enhancing the process by eliminating the need for intermediate purification in multi-step process.

The Morken group[17a] developed a catalytic, enantioselective 1,2-diboration of 1,3-dienes in 2012, producing allylic 1,2-bis(boronates) that serve as valuable reagents for stereoselective allylation reactions. This method enables efficient access to a variety of functionalized chiral building blocks. The optimal ligand and reaction conditions revealed that all *cis*-dienes, with the exception of the phenyl-substituted diene, showed excellent enantioselectivity using ligand **L3** (Figure 8). For the diboration of 1,1-disubstituted dienes, ligand **L4** was employed to achieve high stereocontrol. Furthermore, allyl boron reagents could be used in the asymmetric allylboration of aldehydes. To suppress bis(allylation), the aldehyde was used in half the equivalent of 1,2-bis(boronate). However, with 1,1-disubstituted dienes, diboration led to the products with all-carbon quaternary centers, reducing the activity of bis(allylation) due to steric hinderance. In these cases, equimolar amounts of diene, B_2pin_2, and aldehyde were used. This process efficiently yields diastereoisomers, as seen in products **8j** and **8k**, using dienes of different stereochemistries. They[17b] have performed mechanism study and confirmed the olefin insertion is rate-determining step through kinetic analysis as well as computational study. Subsequent to this success, the same group explored the asymmetric diboration of alkenes catalyzed by platinum, followed by sequential allylation reactions to construct chiral cyclohexanediols.[18] However, this endeavor, primarily focused on the synthesis of chiral cyclohexane 1,4-diols, is not discussed in detail here due to its limited relevance to the central theme of this review.

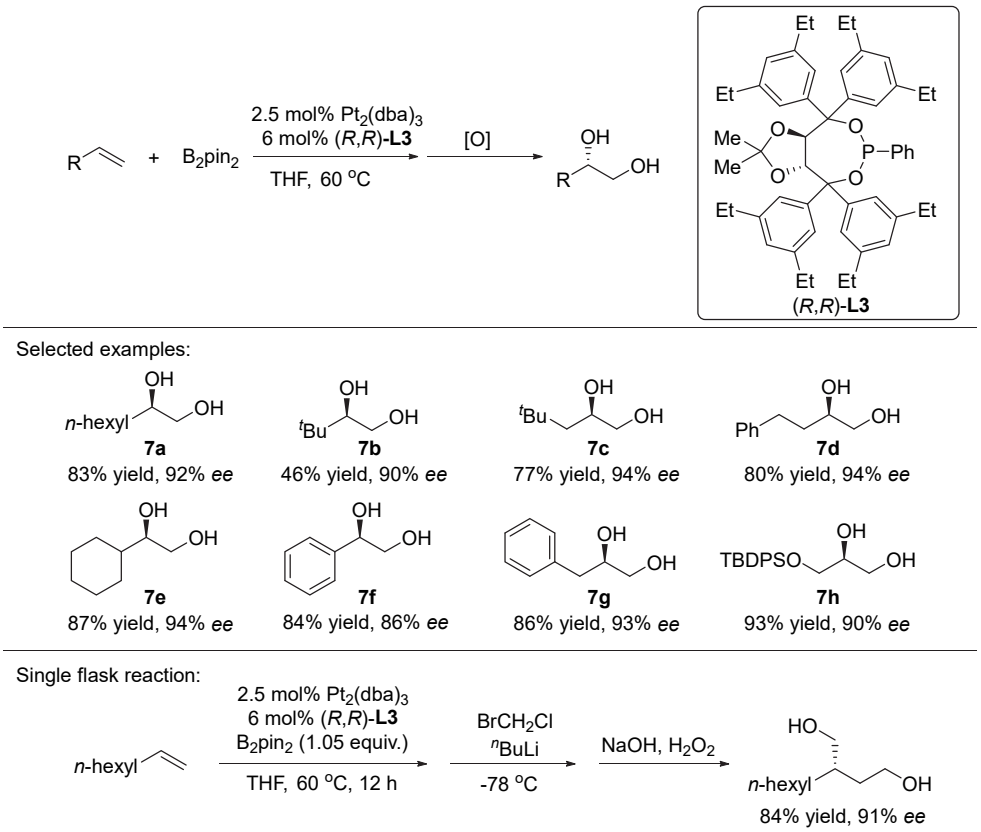

Figure 7 Pt-catalyzed enantioselective diboration of terminal alkenes

In 2014, the Morken group[19] developed an efficient method for synthesizing chiral tris(boronates) through Pt-catalyzed enantioselective diboration of vinyl boronic esters. This method showed broad applicability in the catalytic enantioselective diboration of vinyl boronates, producing products with good yields and enantioselectivities. The desired products could be readily transformed into vicinal bis(boronic) esters through deborylative alkylation of chiral 1,1,2-tris(boronates) with excellent diastereoselectivity. Additionally, 1,1,2-tris(boronates) could undergo intramolecular alkylation followed by oxidation to produce cyclic *anti*-1,2-diols as single stereoisomers. This reaction was highly effective in producing five, six, and seven-membered rings. Besides, *anti*-1,2-bis(hydroxymethyl)-cyclohexane was efficiently prepared through cascades reactions, including deborylative intramolecular alkylation and one-carbon homologation with chloromethyllithium, followed by oxidation. These methods facilitated efficient access to cyclic *anti*-bis(boronates), previously challenging to obtain through alkene diboration. The stereochemical model for deborylative alkylation suggests that the enhanced nucleophilicity of the π bond (carbanion) is likely due to the interaction in intermediate **F** between the electron-rich C—B sigma bond and the neighboring carbon-boron π-type bond. This interaction facilitates the reaction process. The absolute configuration of the products from both intramolecular and intermolecular reactions aligns with the least obstructed pathway for electrophiles towards intermediate **F**. This methodology was applied in the asymmetric formal total synthesis of *exo*-brevicomin (Figure 9). Enantiomerically enriched tris(boronates) were synthesized from a boron-Wittig reaction between bis(boryl)methane and propionaldehyde, followed by asymmetric diboration. Stereoselective intermolecular deborylative alkylation and subsequent oxidation delivered the chiral 1,2-diol in 73% yield and 80% *ee* with 15∶1 *dr*. This method streamlined the synthesis of this intermediate, avoiding the complex steps required in previous approaches due to the highly reactive alkene moiety. This diol was then successfully transformed into *exo*-brevicomin through a precedented Wacker oxidation/cyclization reaction.[20]

The enantio- and diastereoselective diboration of spirocyclobutenes provides a method for rapidly preparing a range of chiral spirocyclic building blocks, which hold significant interest for medicinal chemists. The resulting products, featuring two additional C—B bonds, enable late-stage functionalization to create a diverse array of chiral spirocyclic molecules. Tortosa and coworkers[21] demonstrated the utility of spirocyclobutenes in synthesizing chiral spirocycles through Pt-catalyzed asymmetric diboration process (Figure 10). Spirocyclobutene was selected as a model substrate, and a Taddol-derived phosphonite was chosen as the optimized ligand for the diboration of spirocyclic alkenes. This method proved effective for diborating spirocyclic alkenes possessing nitrogen, sulfone, and fluorine moieties, as well as those with various ring sizes. The enantioselectivity of the resulting products could be further improved through a single recry-

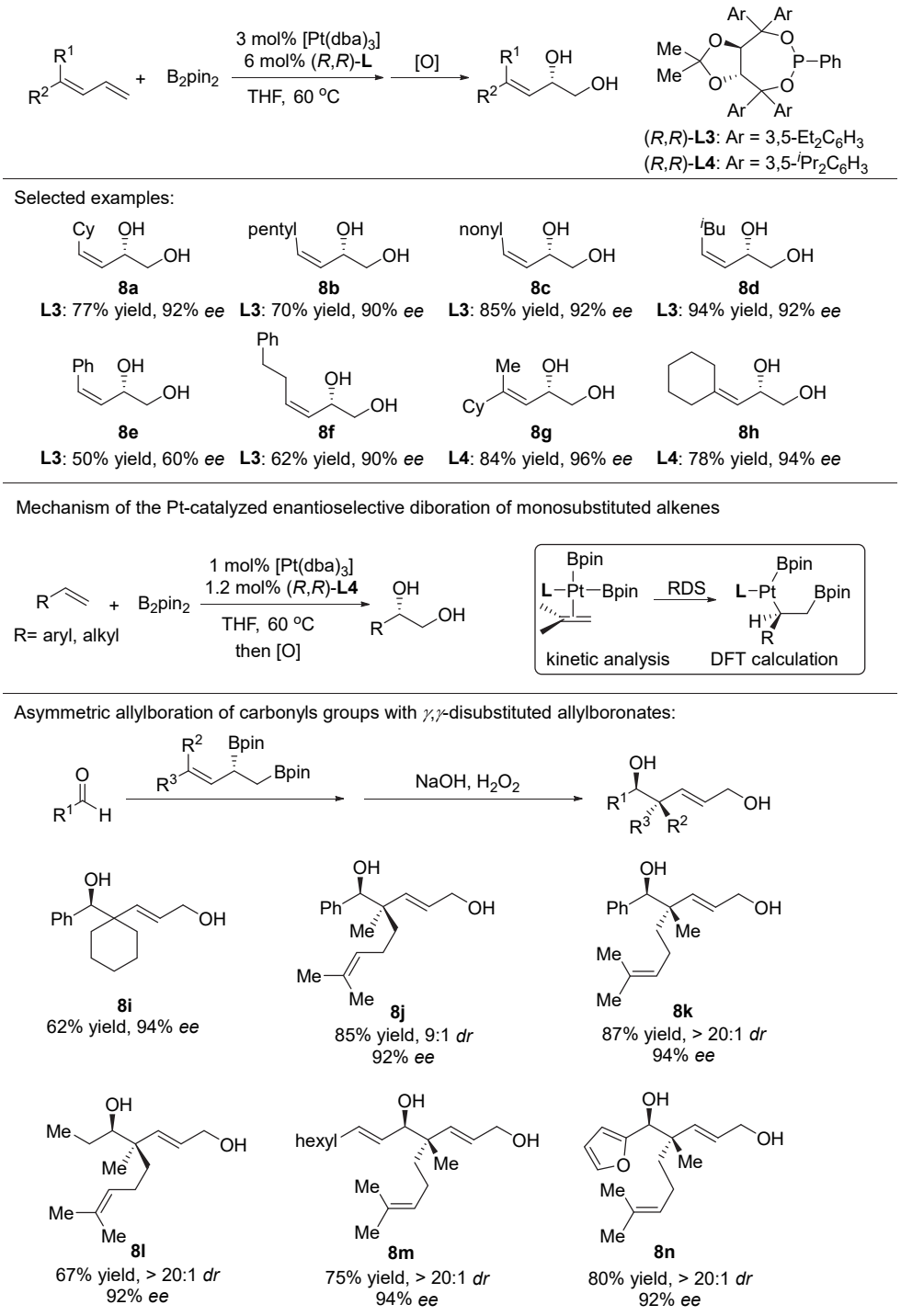

Figure 8 Pt-catalyzed enantioselective diboration of 1,3-dienes

stallization step. Additionally, Suzuki coupling was employed to selectively modify the C—B bond while preserving the enantioselectivity of the product, demonstrating the method of versatility and utility in synthesizing complex chiral molecules.

2.4 Carbohydrate-catalyzed asymmetric diboration of alkenes

Apart from transition-metal catalysis, metal-free strategies offer a feasible approach for synthesizing such compounds, presenting several advantages. Firstly, transition-metal catalysis often struggles to achieve high enantioselectivity without expensive chiral ligands, typically requires harsh conditions, excluding air and moisture. Pioneering research in asymmetric diboration of terminal aliphatic alkene (1-octene), cyclic alkene (indene) and allylbenzene, catalyzed by chiral alcohol, was developed by Fernández, Gulyás and coworkers.[22] Though the chemo- and enatioselectivity of this method need further improvement, it provided valuable insights for future research. In

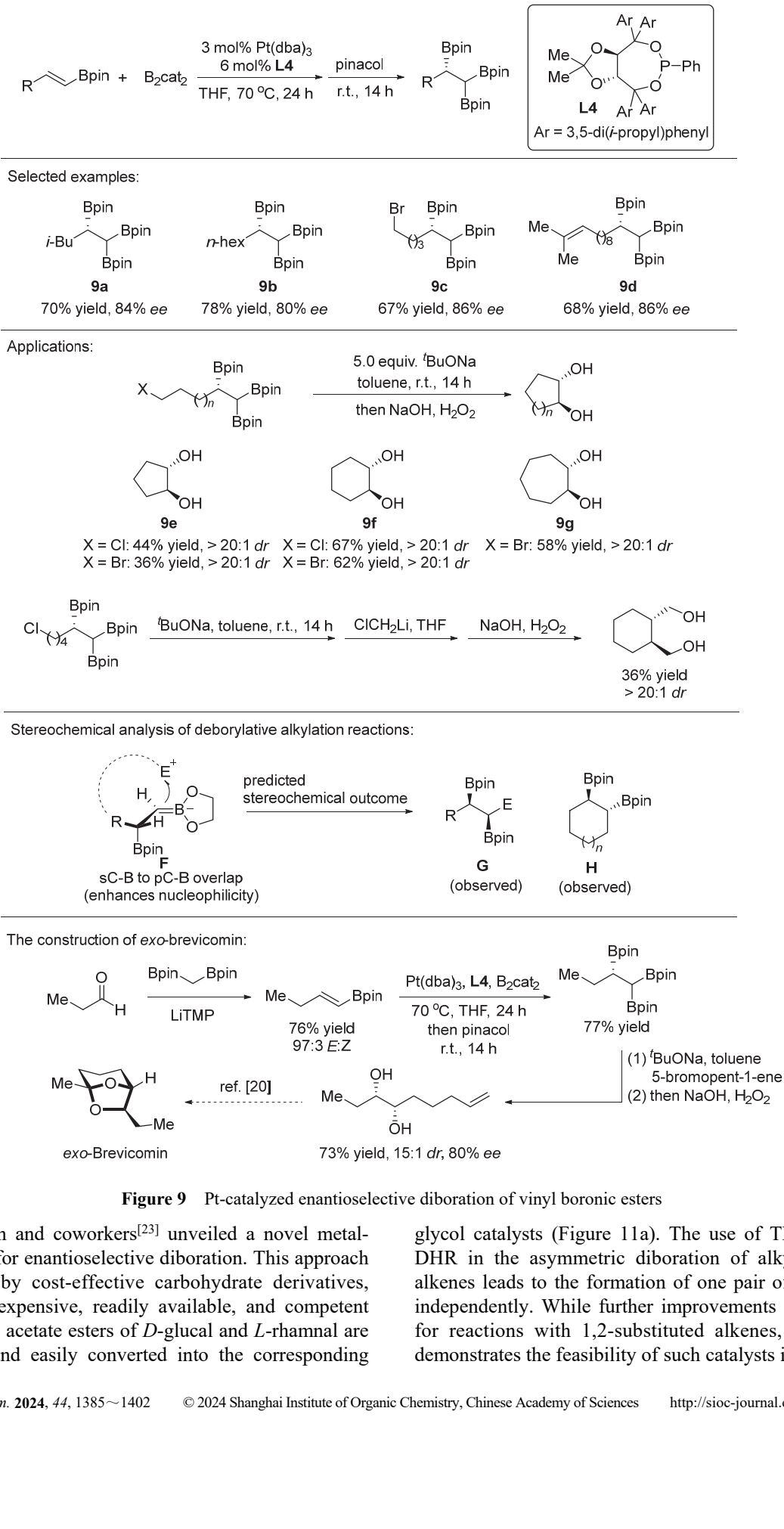

Figure 9 Pt-catalyzed enantioselective diboration of vinyl boronic esters

2016, Morken and coworkers[23] unveiled a novel metal-free strategy for enantioselective diboration. This approach is catalyzed by cost-effective carbohydrate derivatives, which are inexpensive, readily available, and competent catalysts. The acetate esters of *D*-glucal and *L*-rhamnal are economical and easily converted into the corresponding glycol catalysts (Figure 11a). The use of TBS-DHG and DHR in the asymmetric diboration of alkyl-substituted alkenes leads to the formation of one pair of enantiomers independently. While further improvements are necessary for reactions with 1,2-substituted alkenes, this method demonstrates the feasibility of such catalysts in challenging

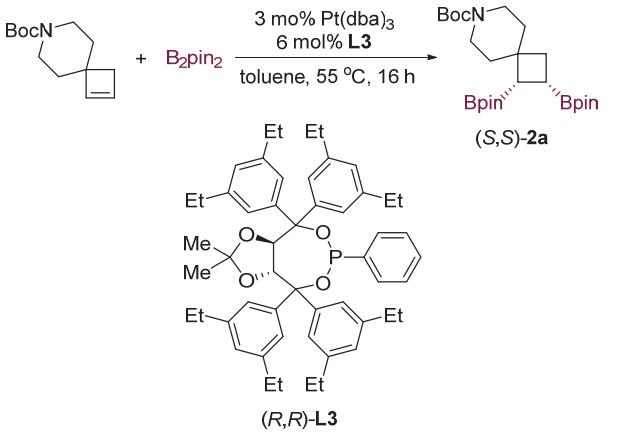

Figure 10 Pt-catalyzed stereoselective diboration of spirocyclobutenes

diboration reactions of olefins (Figure 11b). Subsequent research by Morken and colleagues[24], involving both experimental and computational studies, systematically investigated this reaction mechanism. Mechanistic investigations revealed that the transesterification of the catalytic diol with the stoichiometric achiral diboron reagent generates the 1,2-bonded diboron species **I**. Activation of diboron likely occurs through interaction with an alkoxide, leading to the formation of species **J**. The enantioselective diboration then proceeds through a singlet-carbenoid-like reaction, involving ensemble **K**, followed by internal trapping of the resulting boracyclic ate complex **L** to produce **M**. Subsequent ligand exchange releases both the product and the catalyst (Figure 11c). A more efficient reaction system with an expanded substrate scope was developed (Figure 11d). A variety of internal alkenes were suitable substrates, and the reaction of 1*H*-indene and 1,2-dihydronaphthalene also afforded the desired products in good yields and enantioselectivities, overcoming challenges posed by these substrates in previous approaches. The same research group[25] later accomplished site-selective oxidation of vicinal bis(boronates).

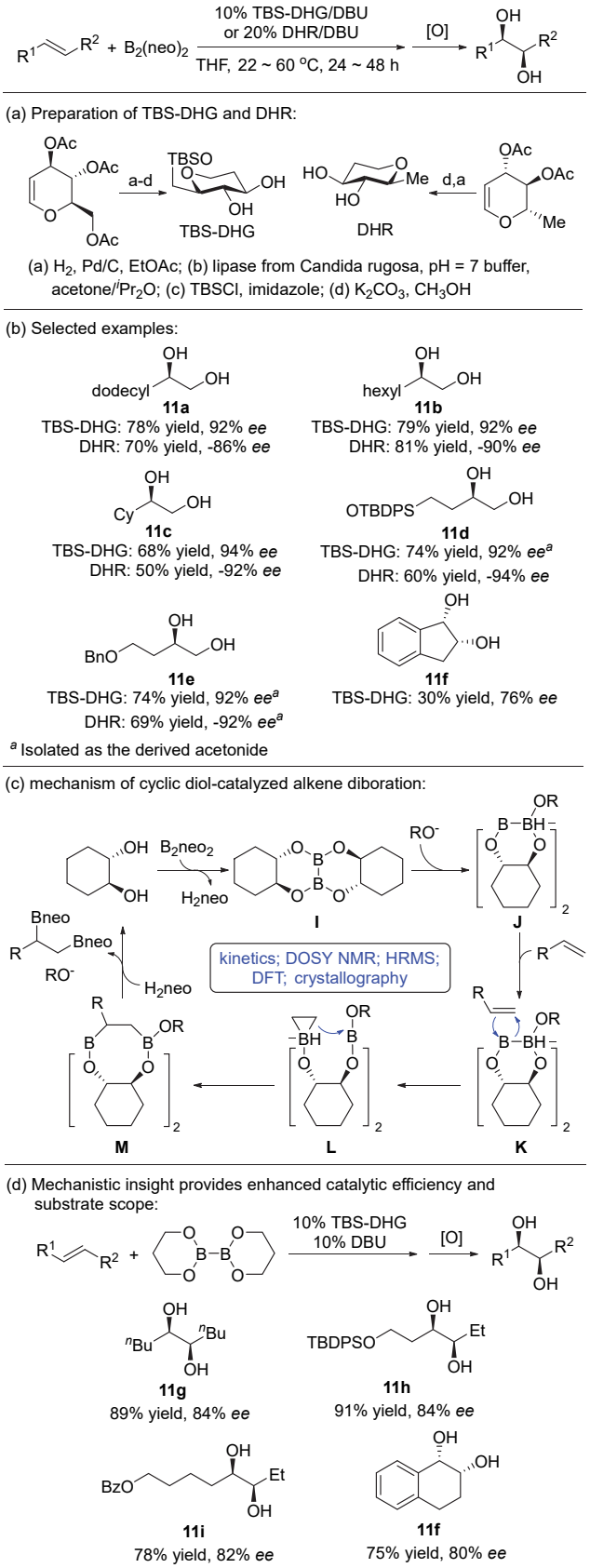

Figure 11 Carbohydrate-catalyzed enantioselective diboration of alkenes

3 Cu-catalyzed borofunctionalization of unsaturated hydrocarbons

CuH and CuBpin catalysis play crucial roles in the synthesis of chiral 1,2-diborons. However, a significant challenge in these reactions is regulating selectivity, particularly in achieving regioselective control for the efficient synthesis of chiral 1,2-diboronic esters. Typically, electronic effects are used to stabilize the copper species and regulate the selectivity of the addition process.

3.1 Cu-catalyzed sequential hydroboration of alkynes

In 2009, a copper-catalyzed asymmetric successive boron/protonation of terminal alkynes was developed by Hoveyda and coworkers[26], producing chiral vicinal diboronates with high enantiomeric purity (Figure 12a). This process was facilitated by a copper catalyst and chiral bidentate *N*-heterocyclic carbene salt, enabling the transformation of a wide range of terminal alkynes into vicinal diboronates. It achieved high regioselectivity with yields

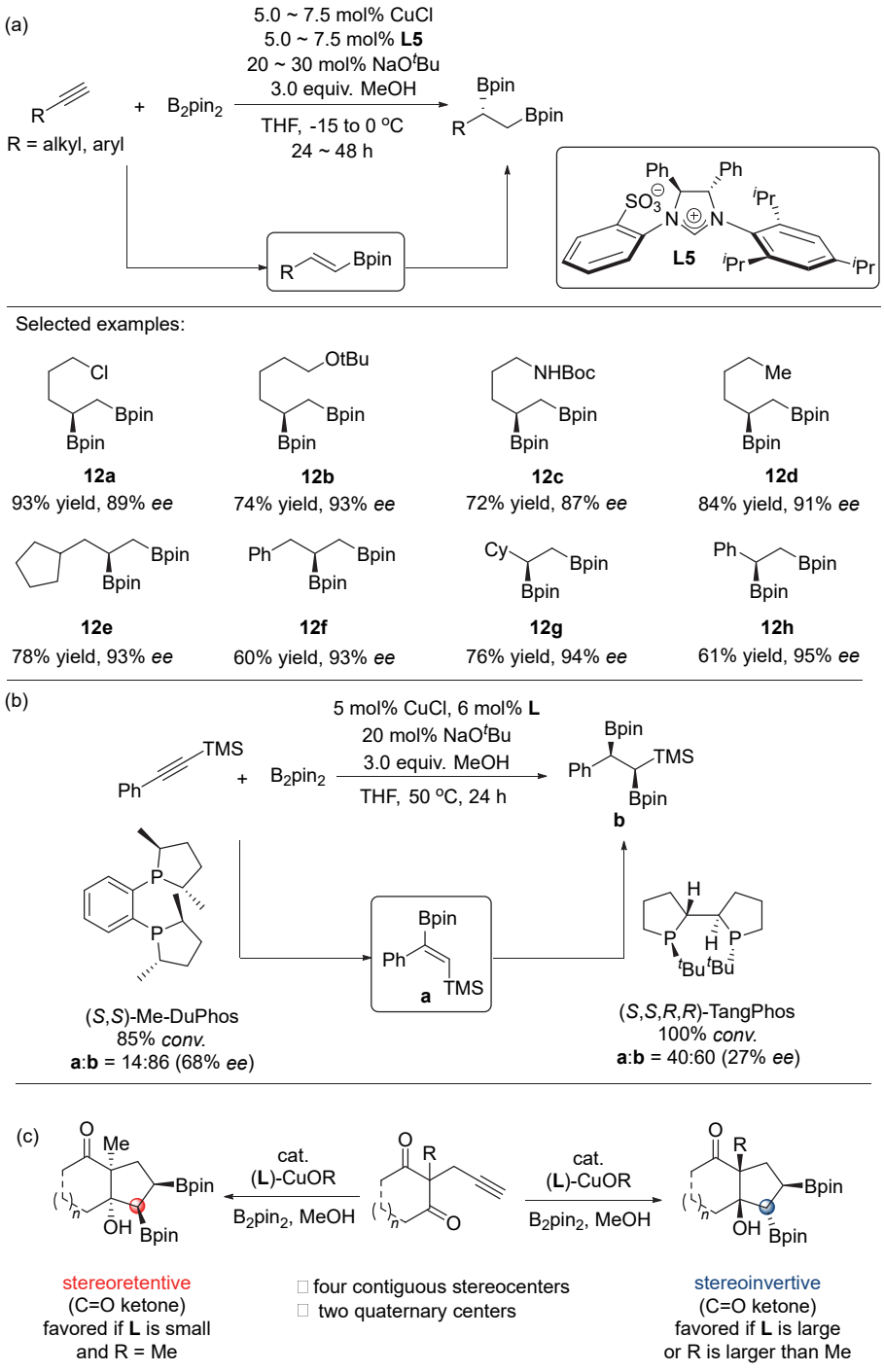

Figure 12 Cu-catalyzed stereoselective diboration of alkenes and alkynes

ranging from 60% to 93% and enantiomeric excess levels between 87% and 95%. Prior to this research, the Hoveyda group[27] had successfully performed asymmetric hydroboration of aromatic internal alkenes using this catalytic system. This study further demonstrated the capability of the copper catalyst in executing regioselective boration/protonation of terminal alkynes, producing (*E*)-*β*-vinylboronates as intermediates, which were then subjected to another cycle of regioselective boration/protonation. Following this seminal research, the Yun group[28] described a phosphite-copper(I) system for the diboration of silylacetylenes with B_2pin_2, bearing internal aryl substituents. In their initial exploration of the asymmetric version, they obtained 68% and 27% enantiomeric excess using chiral Me-Duphos and Tangphos, respectively (Figure 12b).

In 2019, Meek and coworkers[29] developed an enantioselective and diastereoselective tandem hydroboration and borylative cyclization of alkynes with ketones (Figure 12c). This method facilitated the synthesis of [6,5]- and [5,5]-bicycles and cyclopentane product, each featuring four contiguous stereocenters. This reaction demonstrated high tolerance for various cyclic and acyclic 1,3-diketones, achieving yields of up to 78%, with a diastereomeric ratio greater than 20∶1, and an enantiomeric ratio exceeding 99∶1. A key aspect of this method is the catalyst-controlled diastereoselectivity, achieved through the selection of specific bisphosphine ligands. The practical value of the synthesized products is further emphasized by their application in site- and chemoselective transformations, leading to the production of valuable alkenyl and allyl organoborons.

3.2 Cu-catalyzed borofunctionalization of alkenes

During their study of three-component reactions, Hoveyda group[30] investigated asymmetric boron/allylation reactions by leveraging readily accessible alkenyl boronates. A variety of vicinal diboronates, including those with a boron-substituted quaternary carbon center, were synthesized in good yields and promising enantioselectivity (Figure 13a). The method achieves high enantioselectivities (up to 92% *ee*) using commercially available chiral bis-phosphine ligands. These synthesized vicinal diborons are valuable for further chemical transformations.

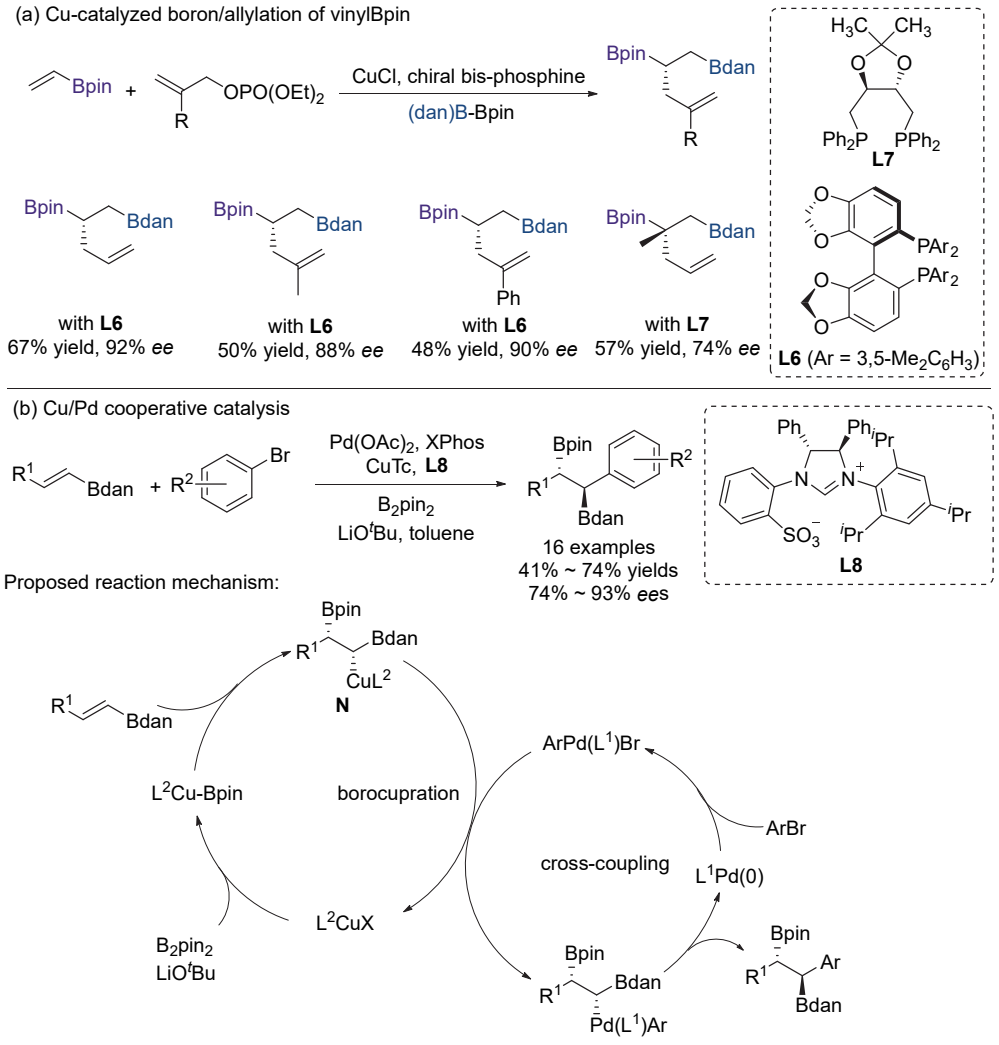

Figure 13 Cu-catalyzed borofunctionalization of alkenes

In 2020, Yun group[31] employed Cu/Pd cooperative strategies for the stereoselective synthesis of 1,2-bis(boronic) esters (Figure 13b). This work demonstrates the use of a palladium catalyst in combination with a copper catalyst and a chiral *N*-heterocyclic carbene (NHC) ligand (**L8**) as an efficient catalytic system. It generates enantioenriched secondary α-borylorganocopper species, followed by cross-coupling reactions with aryl bromides. The reaction catalytic cycle comprises copper and palladium catalytic cycles: the CuBpin catalytic cycle produces intermediate **N**, and the palladium cycle captures this intermediate for subsequent arylation. The substrate scope of this reaction is broad, and diverse aryl bromides as well as aryl and alkyl vinylBdan are well compatible with the reaction conditions, affording the desired targets in good yields and excellent enantioselectivities.

A catalytic enantioselective synthesis of 1-hydroxy-2,3-bis(boronic) esters through a multi-component borylation/1,2-addition process was developed by Meek and coworkers.[32] In this work, an α-boryl-alkyl Cu species was generated through the borocupration of a vinyl boronic ester, a process similar to that described in the previous research.[31] This intermediate then acted as a nucleophile to undergo 1,2-addition with an aldehyde, followed by exchange with B_2pin_2 to generate 1-hydroxy bis(boronic) ester **R**. This process formed LCu-Bpin (**O**), completing the catalytic cycle (Figure 14). The reaction displays a broad substrate scope with both aryl and aliphatic aldehydes, and has potential applications in the synthesis of complex organic molecules. Notably, this strategy can be applied to diastereo- and enantioselective intramolecular cyclization, forming three stereogenic centers.

3.3 Cu-catalyzed diborylation of alkenes

Recently, Song and coworkers[33] developed a method for the enantioselective Cu-catalyzed diborylation of alkenes, producing fluorine-containing chiral 1,2-bis(boronic) esters. This process produces molecules that contains both fluorine and boron, offering more options for complex and diversified structural modifications. The proposed mechanism for this reaction begins with the formation of a copper(I) alkoxide intermediate **R** from $Cu(OTf)_2$, a specific ligand, and ^{t}BuONa (Figure 15). This intermediate then reacts with B_2pin_2 to form a Cu—B complex **S**. This complex inserts into the C=C bond of 1-chloro-1-trifluoromethylalkene, leading to the formation of copper(I) intermediate **T**. Subsequent β-chloro elimination from intermediate **T** leads to the formation of **U**. Alternatively, the Cu(I)—B complex can undergo oxidative addition to the vinyl—Cl bond, yielding intermediate **T'**, which then converts to **U** through reductive elimination. The complex **S** then inserts into the C=C double bond of **U**, forming another copper intermediate **V**. Finally, β-fluoro elimination from **V** produces the desired diborylated product, along with the formation of LCuF (**W**). This fluoride reacts with B_2pin_2 to regenerate the Cu—B complex **S**, completing the catalytic cycle.

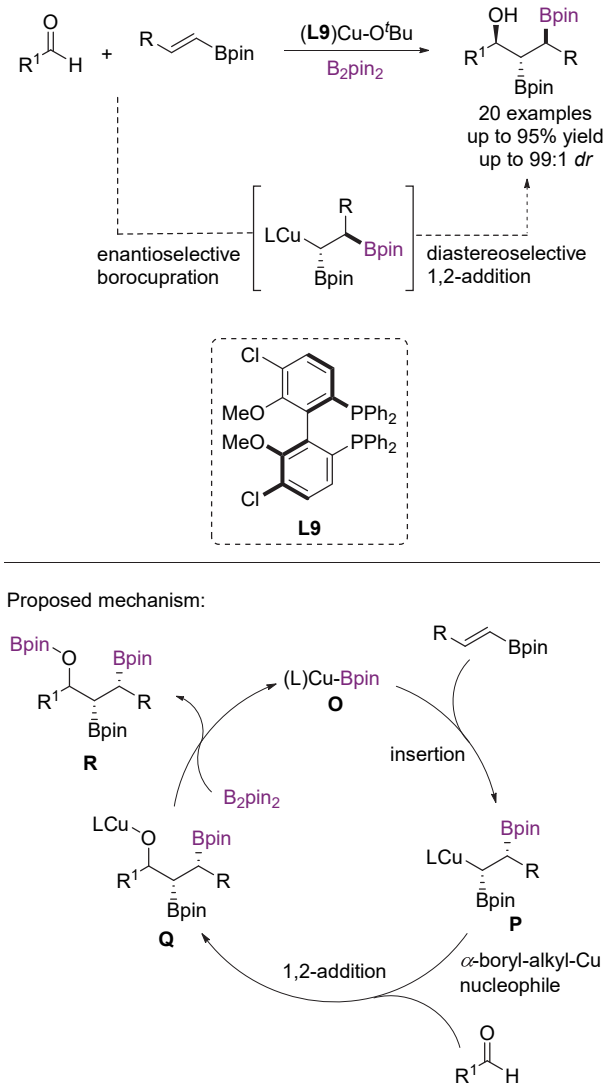

Figure 14 Cu-catalyzed tandem borylation/1,2-addition

4 Asymmetric hydrogenation of vinyl bis(boronates)

The Morken group[34-35] has made significant contributions to the synthesis of chiral 1,2-bis(boronic) esters through asymmetric diboration reactions of alkenes. However, this reaction exhibits low selectivity towards some terminal alkenes, particularly those with aromatic substitutions. Considering the multiple reactive sites and potential applications of these molecules, they developed a new method for synthesizing this type of compounds through asymmetric hydrogenation of vinyl bis(boronates) (Figure 16). After careful examination, a catalytic system employing $(PPh_3)_2Pt$(ethylene) and Walphos was found to be effective for the expedient synthesis of compounds **14a**～**14c** with aryl groups, addressing a challenge encountered in previous reaction systems. Furthermore, this reaction is suitable for synthesizing compounds **14d**～**14e** with alkyl substitutions. The author also prepared chiral diols from inexpensive phenylacetylene using a one-pot synthetic

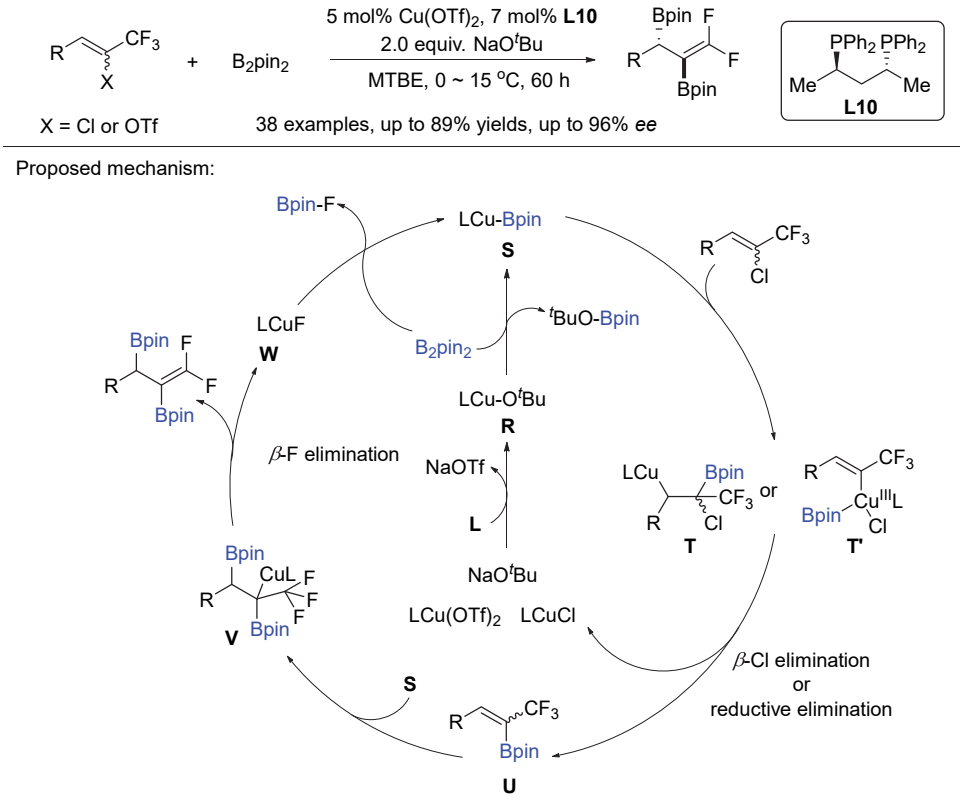

Figure 15 Cu-catalyzed enantioselective diboration of 1-chloro-1-trifluoromethylalkenes

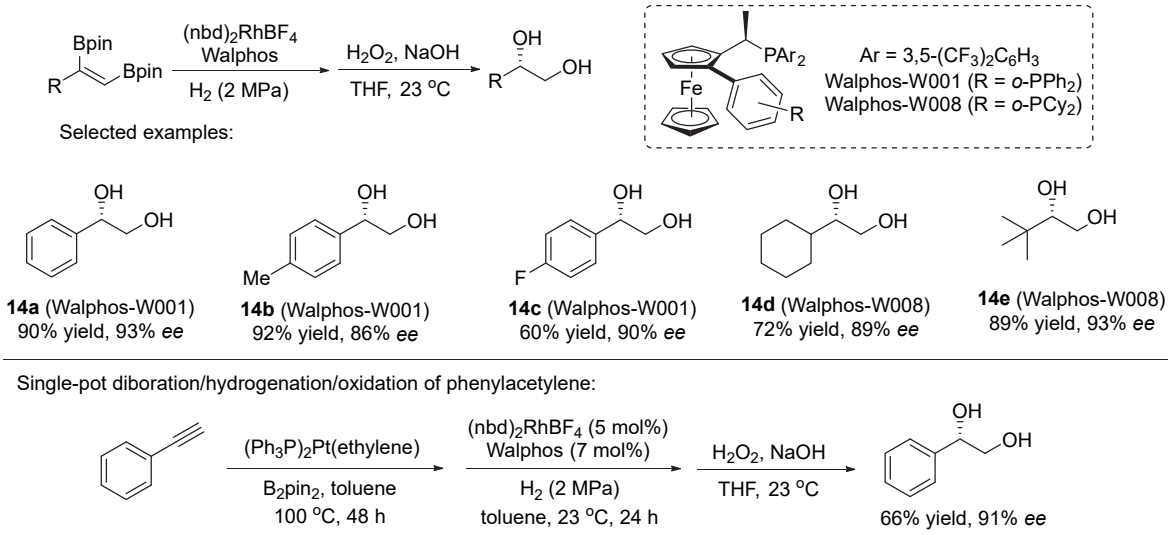

Figure 16 Catalytic enantioselective hydrogenation of vinyl bis(boronates)

method that includes Pt-catalyzed diboration, Rh-catalyzed asymmetric hydrogenation, and subsequent oxidation reactions, further confirming the reaction practicality.

5 Asymmetric synthesis of chiral 1,2-bis(boronic) esters via migratory coupling reactions

1,3-Stereogenic centers are commonly found motifs in natural products and drugs. While some progress has been made in constructing 1,2-adjacent chiral centers through asymmetric catalytic strategies,[36] it is often very challenging to directly construct non-adjacent chiral centers.[37] This challenge may be attributed to the nucleophiles being distant from the chiral environment, making the achievement of enantioselective and diastereoselective control quite difficult. To date, only two activation modes of *gem*-diborylalkanes in asymmetric catalysis have been disclosed.[38] However, based on the research conducted by the Morken[39] and Ready's groups[40], as well as our own work in the field of boron chemistry,[2k,41] we have envisioned the possibility of developing new activation modes

for *gem*-diborylalkanes to enable the rapid construction of chiral 1,2-bis(boronic) esters featuring 1,3-stereocenters through one-carbon homologation reactions (Figure 17).

Very recently, our group[42] has developed an efficient method for the synthesis of chiral 1,2-bis(boronic) esters, which feature acyclic, non-adjacent 1,3-stereocenters with remarkable levels of chemo-, regio-, enantio-, and diastereoselectivity (Figure 18). Significantly, this research introduces a novel activation mode for *gem*-diborylmethane in asymmetric catalysis, effectively avoiding the generation of byproducts typically associated with two classical anion intermediates. We have systematically studied diverse allylic carbonates, dienyl carbonates and vinyl magnesium bromides, generating the corresponding products with good results. Notably, this reaction was found to be compatible with both mono- and disubstituted *gem*-diborylmethanes, which usually suffer from deborative byproducts due to steric hinderance. Due to the presence of one olefin and two C—B bond units in the target product, a wide range of chemical transformations can be carried out based on these units to synthesize various highly valuable target molecules.

6 Conclusions

Chiral 1,2-bis(boronic) esters have gained increasingly recognition for their versatile synthetic utility and broad applicability. Over the past 20 years, catalytic systems have been developed for the direct synthesis of enantiomerically enriched 1,2-bis(boronic) esters from readily available alkenes and alkynes. Various research groups have successfully synthesized a wide array of synthetically valuable building blocks, each featuring different positional arrangements of adjacent chiral boron moieties. The strategies discussed in this review focused on asymmetric diboration, CuH and CuBpin catalysis, asymmetric hydrogenation, and asymmetric migratory coupling reactions, achieving good efficiency and enantioselectivity in the synthesis of various 1,2-bis(boronic) esters. The exploration of inexpensive metal catalysts and novel synthetic methods for 1,2-bis(boronic) esters, particularly based on migratory coupling reactions, deserves further research to construct these valuable scaffolds. It is hoped that these catalytic systems will overcome the limitations in synthesizing multiply substituted 1,2-bis(boronic) esters, which often present more complex stereoenvironments and significant steric hindrance. Additionally, in asymmetric diboration reactions, designing catalytic systems to address the reactivity and selectivity issues of multi-substituted olefins, especially trisubstituted and tetrasubstituted olefins, remains a challenging issue in this field.

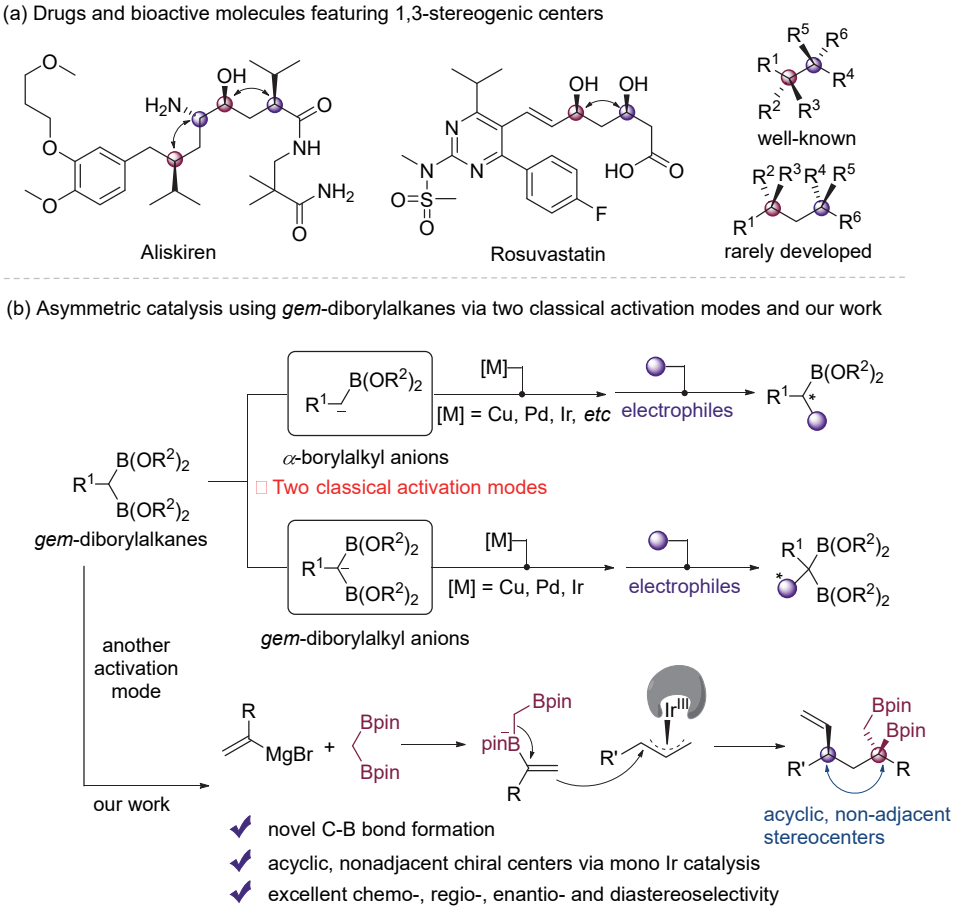

Figure 17 Our idea to construct chiral 1,2-bis(boronic) esters featuring acyclic, 1,3-stereocenters

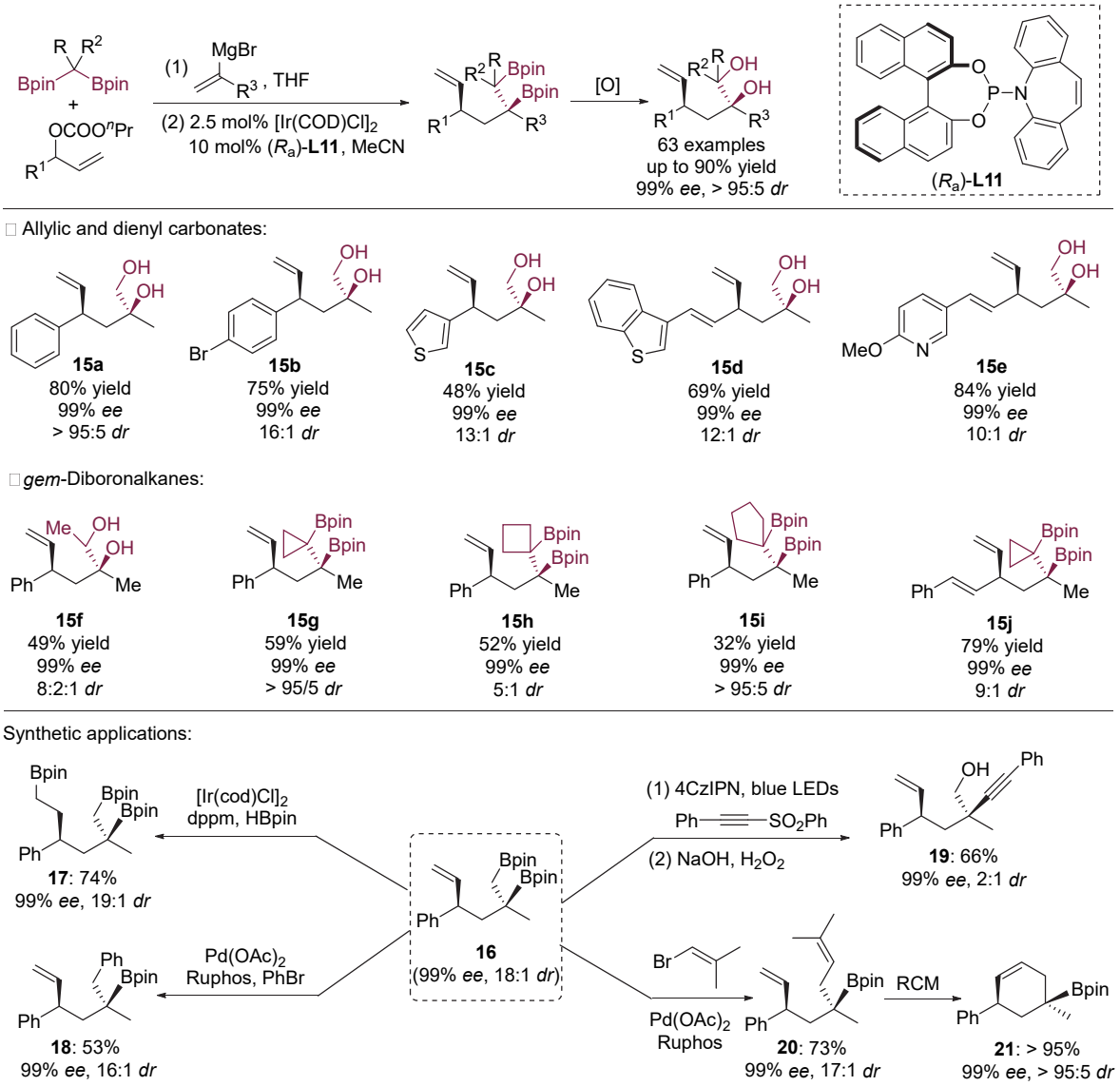

Figure 18 Asymmetric synthesis of chiral 1,2-bis(boronic) esters featuring acyclic, 1,3-stereocenters

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