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Boron-selective reactions as powerful tools for modular synthesis of diverse complex molecules

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Complete List of Authors:	Xu, Liang; Xi'an Jiaotong University, Frontier Institute of Science and Technology Zhang, Shuai; Xi'an Jiaotong University, Frontier Institute of Science and Technology Li, Pengfei; Xi'an Jiaotong University, Frontier Institute of Science and Technology

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Boron-selective reactions as powerful tools for modular synthesis of diverse complex molecules

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Liang Xu,[a] Shuai Zhang[a] and Pengfei Li[a]*

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In the context of modular and rapid construction of molecular diversity and complexity for applications in organic synthesis, biomedical and materials sciences, a generally useful strategy has emerged based on boron-selective chemical transformations. In the last decade, these types of reactions have evolved from proof-of-concept to some advanced applications in the efficient preparation of complex natural products and even automated precise manufacturing on the molecular level. These advances have shown the great potential of boron-selective reactions in simplifying synthetic design and experimental operations, and should inspire new developments in related chemical and technological areas. This tutorial review will highlight the original contributions and representative advances in this emerging field.

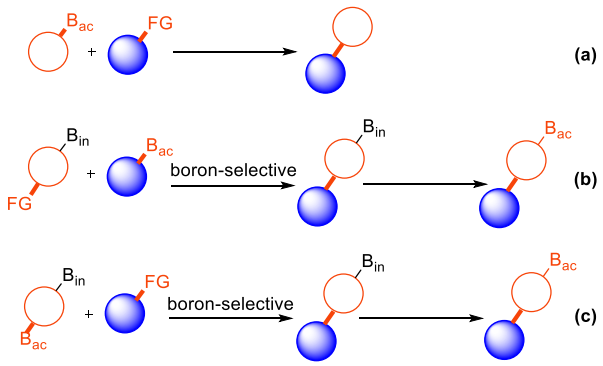
Key learning points

(1) masked organoboronic acids
(2) iterative Suzuki–Miyaura coupling
(3) polyboron compounds
(4) double allylboration reactions
(5) automated synthesis of small molecules

1. Introduction

Nature efficiently produces diverse and complex biological molecules such as polypeptides and carbohydrates by modular assembly of relatively simple di- and/or poly-functionalized building blocks such as amino acids and monosaccharides. To mimic this strategy thus improve our capability in building complex molecules with desired properties, synthetic chemists have unremittingly been developing increasingly more effective building blocks and assembly methodologies. In this context, palladium-catalysed cross-coupling reactions of organohalides and organometallic reagents represent the most reliable approach to constructing new C–C bonds. However, to utilize these reactions in the precise and efficient generation of even more complex molecules, consecutive and chemoselective couplings of suitably functionalized building blocks could be the key to success.

Chemoselective reactions based on the discrimination of electrophiles (i.e. they are electrophile-selective), such as organo(pseudo)halides, are well established. In contrast, the development of nucleophile-selective reactions has seen limited success, largely due to difficulties in the preparation of functionalized organometallic reagents. However, this situation changed after 2007 when Suginome and Burke independently reported their masking group-based nucleophile-selective Suzuki–Miyaura coupling (SMC) of organoboronic acid derivatives. Most organoboron compounds are readily accessible, easy-to-handle and shelf-stable materials, and can be utilized in diverse transformations (Scheme 1, a).[1]



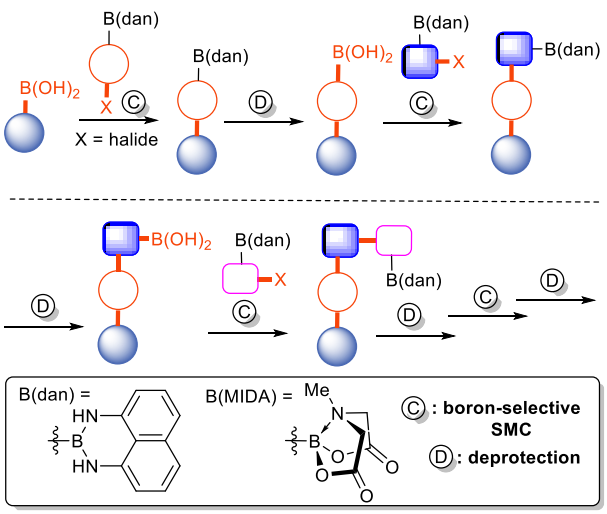
Scheme 1 Boron-selective chemical transformations. B_{ac} = active boronyl group, B_{in} = inactive boronyl group, FG = reactive functional group.

Consequently, developing chemoselective reactions between different boronyl sites has attracted great research interest, and significant progress has been made not only in SMC reactions but also in some other (catalysed) transformations. This tutorial review is intended to present an overview of the original contributions and recent advances in these boron-selective reactions, and their applications in the modular construction of complex molecules.

In this article, boron-selective reactions refer to chemical transformations where two or more boronyl groups are present in the reactants and their reactivity can be distinguished; hence, the more reactive boronyl group can be selectively transformed while the relatively inert boronyl group remains intact. The inert boronyl group can usually be utilized under different reaction conditions and converted to other functional groups, therefore providing consecutive and flexible synthetic approaches to complex molecules (Scheme 1, b and c).

The key for a successful boron-selective reaction is to discriminate between the boronyl groups[2] that are exposed to the same reaction conditions. Generally, two types of reactivity difference have been utilized in the literature. In one type, the carbon atoms bearing the boronyl groups have different steric and/or electronic environments. In the other type, appropriate use of masking groups on the boron atoms plays a critical role in controlling the reactivity. Due to its flexibility, the latter strategy has been developed rapidly in the last decade, especially in the context of iterative coupling[3] and polyboron chemistry.[4]

On the other hand, based on the structural difference of relevant organoboron starting materials, boron-selective reactions may be classified into two types: the reactions involving two competitive organoboron reagents (Scheme 1, b) and the reactions involving a di- or polyboron reagent (Scheme 1, c). The discussion that follows is divided into two major parts (2 and 3, respectively) according to this classification.



Scheme 2 Iterative SMC reactions via repeated boron-selective coupling/deprotection sequence. An example utilizing DAN boronamides. MIDA boronates share the same routes in principle.

2. Boron-selective reactions involving two organoboron reagents

Research into iterative boron-selective SMC reactions was pioneered by Suginome's group[5] and Burke's group[6]. They developed, independently, two efficient masking groups for boronic acids: 1,8-diaminonaphthalene (DAN; Suginome's group, 2007) and *N*-methyliminodiacetic acid (MIDA; Burke's group, 2007). These masking groups were both easily installed, readily removed and stable under certain SMC reaction conditions. When a building block containing both a masked boronic acid group [B(dan) or B(MIDA)] and a halogen (X) was treated with unmasked boronic acids, boron-selective SMC reactions between the C–X bond and free boronic acids occurred, leaving the B(dan) or B(MIDA) moiety temporarily intact. This would then be converted to free boronic acids under deprotection conditions. By iteration of this boron-selective coupling/deprotection (C/D) sequence, precise and modular construction of complex structures could be achieved from readily available bifunctional building blocks (Scheme 2). Such an iterative approach is ideally suited to rapid manual or automated generation of diverse molecules (*vide infra*). Currently, the library of such bifunctional building blocks is still growing, providing innumerable possible combinations for the synthesis of specific intermediates and creation of new molecules.

2.1 Iterative Suzuki–Miyaura coupling enabled by DAN boronamides

In DAN boronamides, the lone pair electrons of two nitrogen atoms may be partially delocalized to the vacant *p*-orbital of boron atoms, thus stabilizing B(dan) moieties significantly. DAN boronamides exhibit superior stability towards hydrolysis and are even intact under aqueous basic conditions. This property makes bifunctional building blocks that contain both B(dan) moieties and halides good substrates for the modular synthesis of oligoarenes[5] (Scheme 3) and oligo(phenylenevinylene)s[7] (Scheme 4) via iterative SMC reactions.

For example, when the bromo-arylboronamide building block **B1** was treated with *p*-tolylboronic acid, the boron-selective SMC reaction occurred, affording biarylboronamide **1** in 99% yield. Facile and clean deprotection of **1** using a mixture of aqueous sulphuric acid (1.0 M) and tetrahydrofuran generated unmasked biarylboronic acid **2**, which went through boron-selective coupling again with **B1** to afford terarylboronamide **3**. After another two-fold iteration of the deprotection/coupling sequence, zigzag oligoarene **5** was synthesized.

Using two different bifunctional building blocks, **B2** and **B3**, the rapid synthesis of functionalized oligo(phenylenevinylene)s was also achieved via iterative SMC reactions (Scheme 4). Since oligo(phenylenevinylene)s have been widely studied as candidates in applications such as light-emitting diodes and photovoltaic devices, this controlled modular synthetic

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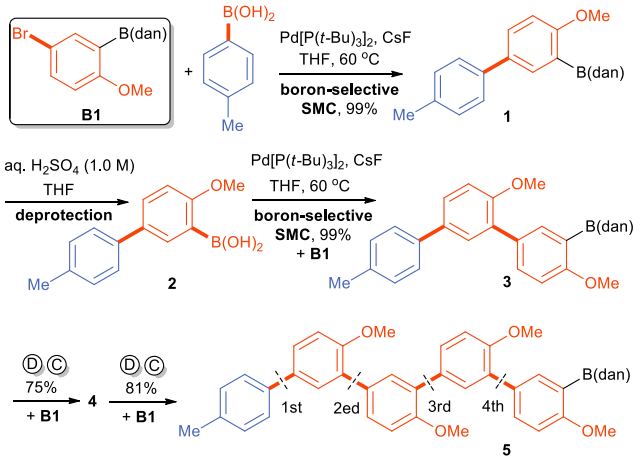
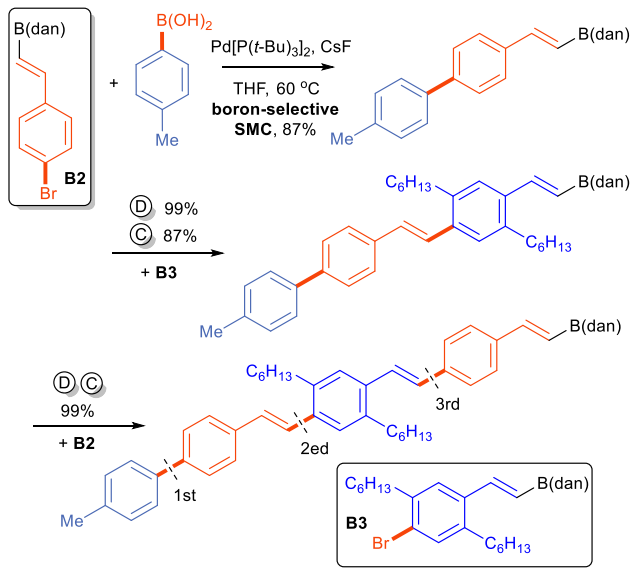
approach would be very useful in precisely modifying the backbone structure to improve properties.



Scheme 3 Iterative SMC reactions for synthesis of oligoarenes.



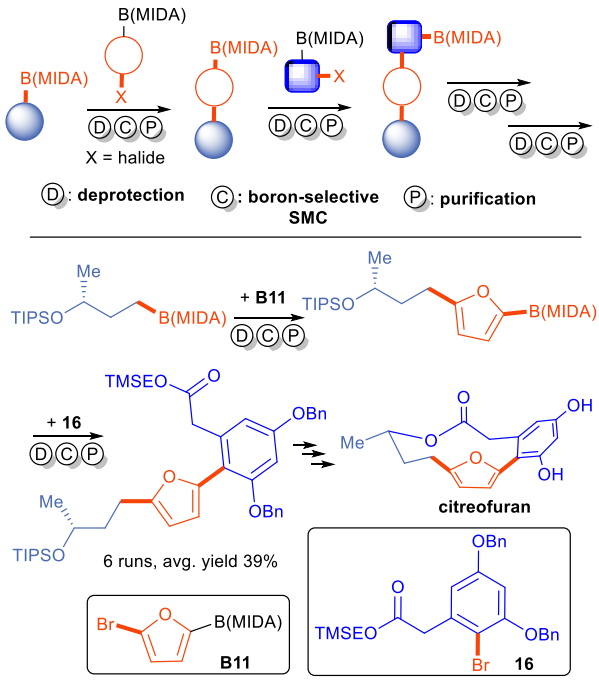
Scheme 4 Iterative SMC reactions for synthesis of oligo(phenylenevinylene)s.

2.2 Iterative Suzuki–Miyaura coupling enabled by MIDA boronates

N to B dative bonds in MIDA boronates can change the hybridisation of the boron atoms from sp^2 to sp^3 and force the boron centres into tetrahedral geometry. Due to lack of a vacant *p*-orbital, which is key to the activation of boronic derivatives, the pyramidalized MIDA boronates are stable towards many types of chemical transformations, including anhydrous SMC reactions.[6] Furthermore, MIDA boronates can be readily deprotected to generate free boronic acids. A more convenient method is to conduct the SMC reaction via a slow-release strategy under mild aqueous basic conditions. The facile switch of reactivity towards SMC conditions is paramount to their successful applications in iterative SMC reactions.

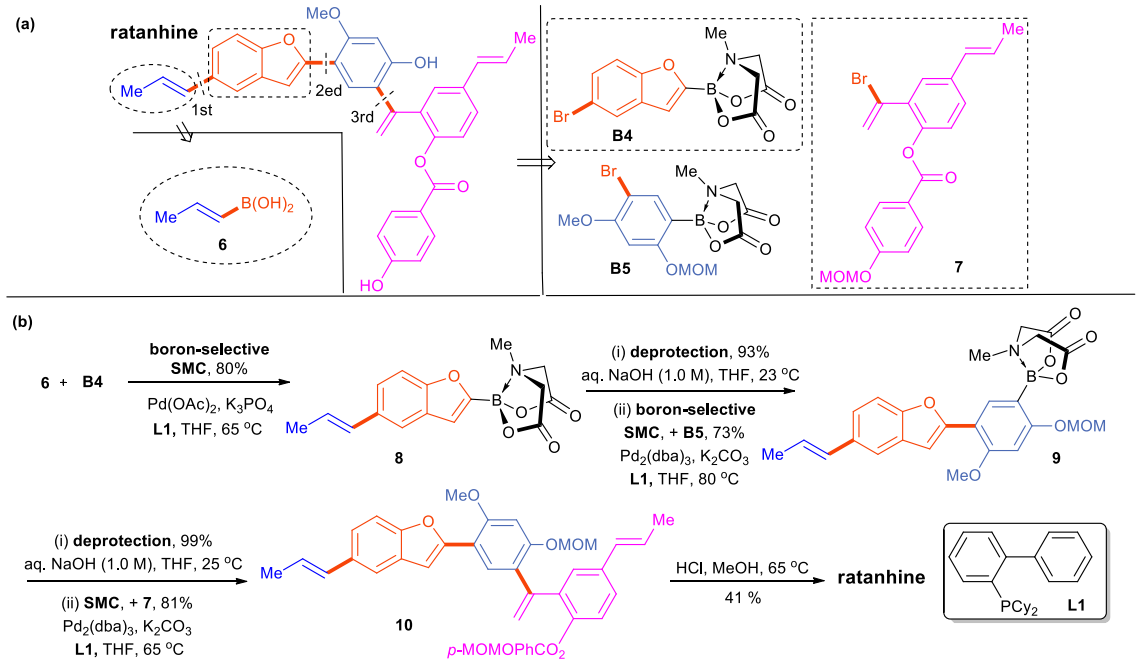
Burke's group first realized the iterative coupling of bifunctional halo-MIDA boronate building blocks and applied this strategy to the total synthesis of ratanhine (Scheme 5).[6] The bromide of **B4** reacted selectively with free alkenyl boronic acid **6** under anhydrous SMC conditions, to afford **8** with an intact B(MIDA) moiety in 80% yield, which would be easily deprotected in aqueous NaOH (1.0 M) to generate the corresponding free boronic acid. Then, another iteration of coupling/deprotection and a following SMC reaction afforded intermediate **10**, with the key structure of ratanhine precisely installed. Final cleavage of the two MOM (methoxymethyl) ethers completed the total synthesis.

Besides the SMC reaction, MIDA boronates also survive Stille and Negishi coupling and Miyaura borylation reactions. This enables the preparation of a series of alkenyl MIDA boronate building blocks with pre-installed stereochemical relationships (Scheme 6, b). These building blocks can be linked together stereospecifically via iterative SMC reactions, to afford polyene motifs in all possible stereoisomeric forms (Scheme 6, a).[8] The key to achieving this iteration is to realize the chemoselective coupling between free alkenyl boronic acids and halides of halo-alkenyl MIDA boronates. For example, in the synthesis of the polyene chain of amphotericin B (**15**),[9] dienyl MIDA boronate **12** was first prepared from bifunctional **B6** and pentenyl boronic acid. The following deprotection/selective SMC process led to polyenyl MIDA boronate **13**, which directly reacted with alkenyl chloride **14** to afford the desired product via a slow-release strategy. This strategy avoided an extra deprotection step and made the iterative SMC process simpler.

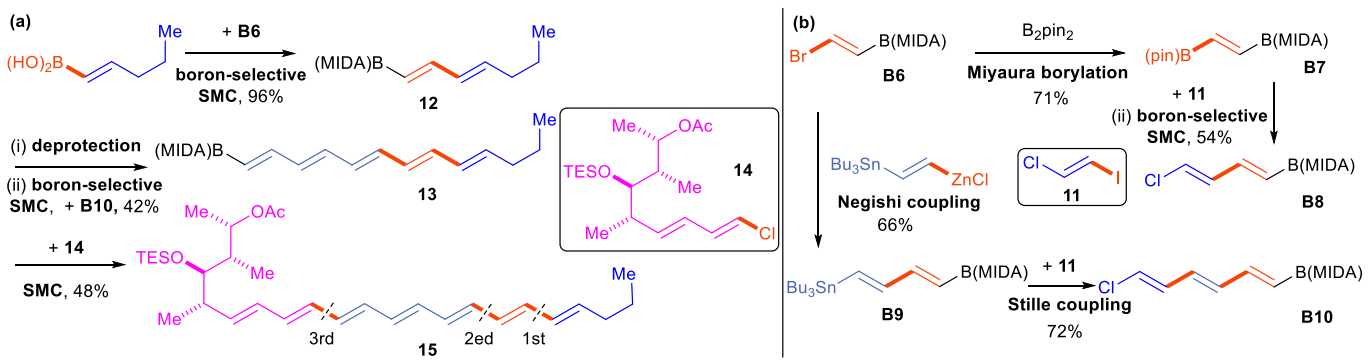


Scheme 7 Schematic and an example of automated synthesis.

A library of MIDA boronates has been developed by Burke's group in order to build a modular platform for iterative synthesis of complex polyene motifs.[9] Many of these boronates are now commercially available.[10] In 2014, using only 12



Scheme 5 (a) Retrosynthetic fragmentation of ratanhine into four simpler building blocks, including two bromo MIDA boronates; (b) Total synthesis of ratanhine via iterative SMC reactions.



Scheme 6 (a) Iterative synthesis of the polyene chain of amphotericin B; (b) Preparation of bifunctional building blocks containing B(MIDA) moieties.

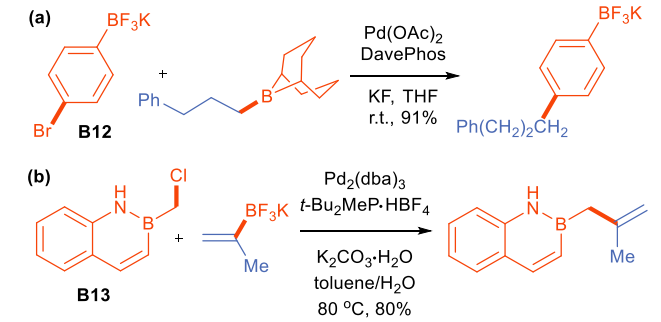
building blocks, through iterative SMC reactions, Burke's group could prepare polyene motifs that are found in >75% of all known polyene natural products.[11]

More recently, this flexible and powerful iterative coupling strategy has evolved into a computer-controlled, fully automated process.[12] Fourteen distinct classes of small molecules, including C(sp^3)-rich cyclic and polycyclic natural product frameworks, can be prepared from readily available building blocks via this synthesis machine (Scheme 7). The key points for the successful automation of such iterative reactions are the above-mentioned boron-selective SMC reactions and a newly developed "catch-and-release" purification strategy that is unique for MIDA boronate intermediates. It was discovered that MIDA boronyl groups can serve as chromatographic purification tags. When a mixture of methanol and diethyl ether is used as the eluting solvent, MIDA boronate compounds, regardless of their appended fragments, uniformly adhere to silica gel. This fact allows the removal of unwanted side products and impurities by simple chromatographic washing. Interestingly, when the eluting solvent is THF, essentially all MIDA boronates are rapidly released from silica gel. Therefore, automated switching of eluting solvents can efficiently purify the intermediates. The entire automation process includes cycles of sequential deprotection, selective coupling and purification steps.

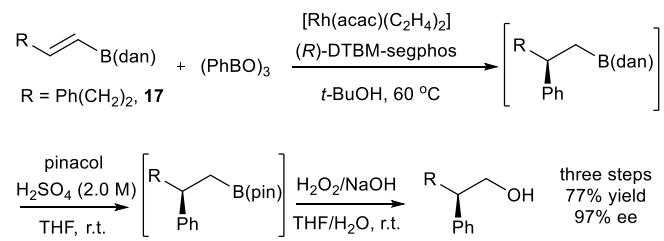
Theoretically, billions of designed organic molecules can be manufactured via this automated process. This building-block-based automated synthetic approach represents a major breakthrough in the unremitting efforts of the chemical community to make organic syntheses simpler and faster. Not only organic chemistry but also relevant disciplines that were previously limited by synthesis bottlenecks might see revolutionary changes with the development and maturity of this new approach.

2.3 Other boron-selective reactions involving two organoboron reagents

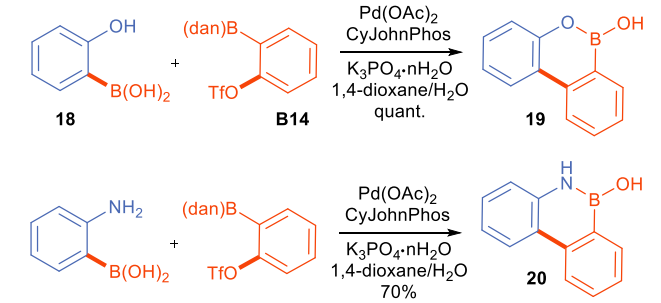
In 2008, Molander's group realized the boron-selective SMC reaction between trialkylboranes and aryl bromides that contained appendant trifluoroborate groups (Scheme 8, a).[13] More recently, the selective cross-coupling between C(sp^3)-Cl of **B13** and aryl- or alkenyltrifluoroborates was developed by the same group, revealing BF_3K to be the more reactive boronyl group(Scheme 8, b).[14] In this case, hydrolysis of the trifluoroborate under aqueous basic conditions afforded the more reactive boronic acid, which is not accessible in anhydrous reactions.



Scheme 8 Trifluoroborate in boron-selective SMC reaction.



Scheme 9 Rh-catalysed asymmetric addition of arylboroxines.

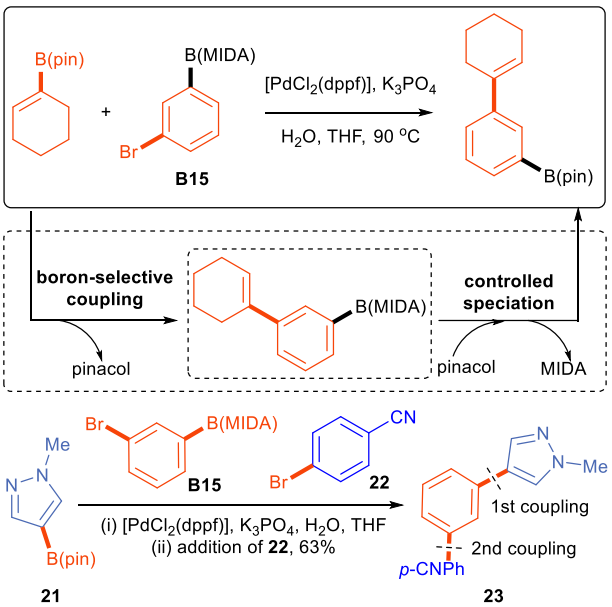


Scheme 10 Synthesis of dibenzoxaborine and dihydrodibenzazaborine.

Hayashi and Sasaki reported that B(dan) group-substituted olefin was a good substrate for Rh-catalysed asymmetric addition of arylboroxines, thus affording chiral β-arylalkylboron compounds with high enantioselectivity.[15] The two boronyl reagents used in this reaction could be well differentiated because of the protective function of DAN. Deprotection was achieved by converting the B(dan) to B(pin) under acidic conditions (Scheme 9).

Boron-selective SMC reactions were also utilized to prepare dibenzoxaborins (Scheme 10).[16] Chemoselective coupling between *ortho*-hydroxyphenylboronic acid **18** and aryl triflate **B14** bearing an *orth*-B(dan) group afforded dibenzoxaborine **19** directly without obtaining the B(dan)-containing intermediate, possibly due to the *in situ* deprotection of the B(dan) moiety, assisted by the adjacent phenolic hydroxyl group. The dihydrodibenzazaborine **20** was similarly prepared.

Chemoselective formal homologation of aryl and alkenyl pinacol boronic esters by reacting with halogenated aryl MIDA boronates was disclosed by Watson and co-workers via an elegant "controlled speciation" process (Scheme 11). Thus, in finely optimized aqueous basic conditions, a series of processes along the reaction time window including fast selective cross coupling of B(pin), slow selective hydrolysis of B(MIDA) and selective re-formation of B(pin) were realized in one step. This reaction required manipulation of multiple equilibria of several boron species and then enabled the chemoselective control of speciation to afford a major product in the same system.[17]



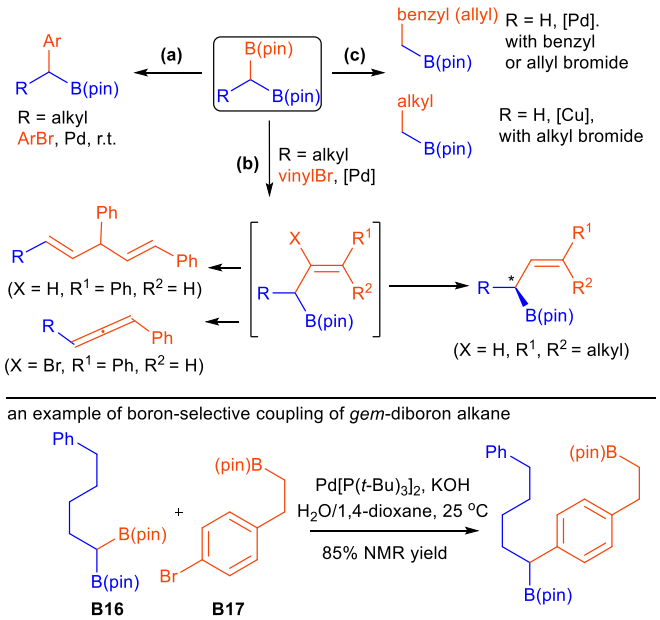
Scheme 11 Formal homologation of aryl and alkenyl pinacol boronic esters.

The successful manipulation of solution equilibrium between pinacol boronic esters and MIDA boronates depended mainly on the stoichiometry of used base and water. This was crucial for effective utilization of B(MIDA) moieties, which remained intact during the coupling process and then hydrolysed to participate in the controlled speciation process, from a microscopic viewpoint. Macroscopically, the homologation of B(pin)-containing starting material led to another B(pin)-containing product, which was ready for the next transformation. As depicted in Scheme 11, after the formal homologation reaction between **21** and **B15**, the second SMC reaction was effected by simply adding **22** in a one-pot fashion, directly affording the final product **23** in good yield.

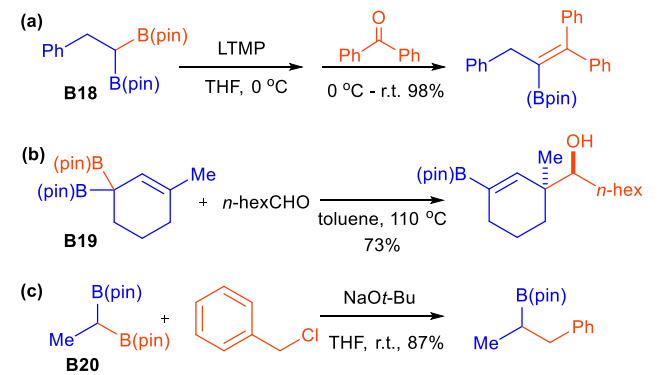
3. Boron-selective reactions of di- and polyboron compounds

Building blocks containing two or more boronyl groups are useful in the synthesis of complex molecules through chemoselective multiple functionalization of the C–B bonds.[18] The reactions in which boronyl groups of di- or polyboron compounds are effectively differentiated are discussed in the following section.

3.1 1,1-Diborylalkanes



Scheme 12 Application of 1,1-diboronates in selective SMC reactions.

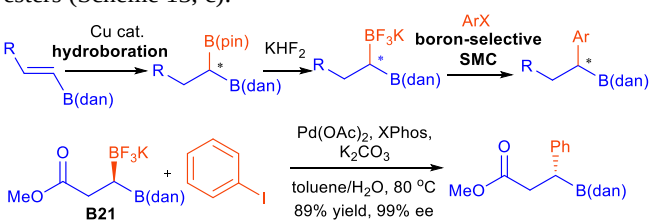


Scheme 13 Selective transformations of 1,1-diboronates.

Chemoselective SMC of 1,1-diborylalkanes was first disclosed by Shibata's group.[19] Usually, alkyl boronates are poor substrates in transmetallation in palladium-catalysed coupling. In contrast, *gem*-bis-B(pin)-substituted alkanes were found to be competent in SMC reactions. This unique reactivity was described as a *gem*-boryl-assisted transmetallation process because a sp^2-boron may stabilize the α-carbanionic and α-organometallic species. Therefore, two pinacol boronic esters on the same C(sp^3) atom could be well differentiated in SMC (Scheme 12, a). This reactivity was nicely exemplified by the competing reaction between **B16** and **B17** shown in Scheme 12. Recently, an asymmetric version of this boron-selective SMC reaction has been developed by Morken's group, enabling the conversion from symmetric 1,1-diborylalkanes to non-racemic organoboronates.[20]

When a vinyl bromide or a 1,1-dibromoalkene was treated with a 1,1-diborylalkane, it was believed that the initial boron-selective coupling between C(sp^3)-B and C(sp^2)-Br bonds led to an allylboron intermediate, which was then transformed to a 1,4-diene by following allyl–vinyl coupling or an allene by 1,2-haloboron elimination depending on the starting material used (Scheme 12, b).[21] When 2,2-disubstituted vinyl bromides were used as the electrophiles, allyl boronic esters could be isolated in moderate yield. This transformation was also realized in asymmetric form with high enantioselectivity to generate chiral γ,γ-disubstituted allyl boronic esters.[22] The selective SMC reactions between diborylmethane and allyl or benzyl halides could also be realized; new C(sp^3)-C(sp^3) bonds could be formed under Pd-catalysed conditions (Scheme 12, c).[23] Recently, nonactivated primary alkyl electrophiles were also utilized in similar transformations under Cu catalysed/promoted conditions. Various secondary or tertiary alkylboronic esters could be obtained in this way (Scheme 12, c).[24]

In addition to boron-selective SMC reactions, 1,1-diborylalkanes could also be converted to tetrasubstituted alkenyl boronic esters chemoselectively and stereoselectively via a lithiation/nucleophilic addition/elimination mechanism when reacted with the carbonyl groups of ketones (Scheme 13, a).[25] In 2014, a new synthetic approach towards 1,1-diborylalkanes was developed by Wang's group, starting from the corresponding *N*-tosylhydrazones under transition-metal-free conditions.[26] This group also revealed the selective allylboration reaction between one 1,1-diborylalkane compound **B19** and *n*-hexaldehyde (Scheme 13, b). More recently, selective deborylative alkylation of 1,1-diborylalkanes was demonstrated by Morken's group through the generation and electrophilic trapping of α-boryl anions by alkyl halides, providing simple and reliable access to various alkylboronic esters (Scheme 13, c).[27]



Scheme 14 The synthesis and application of *gem*-B(pin)/B(dan) compounds.

Enantiomerically enriched *gem*-B(pin)/B(dan) compounds have been prepared by the groups of Hall[28] and Yun,[29] respectively. A process for the highly regio- and enantioselective hydroboration of B(dan)-substituted alkenes was realized by virtue of suitable combinations of copper catalysts and chiral ligands. The B(pin) moieties could be converted to corresponding trifluoroborates (BF_3K) and then applied in boron-selective SMC reactions with aryl halides (Scheme 14).

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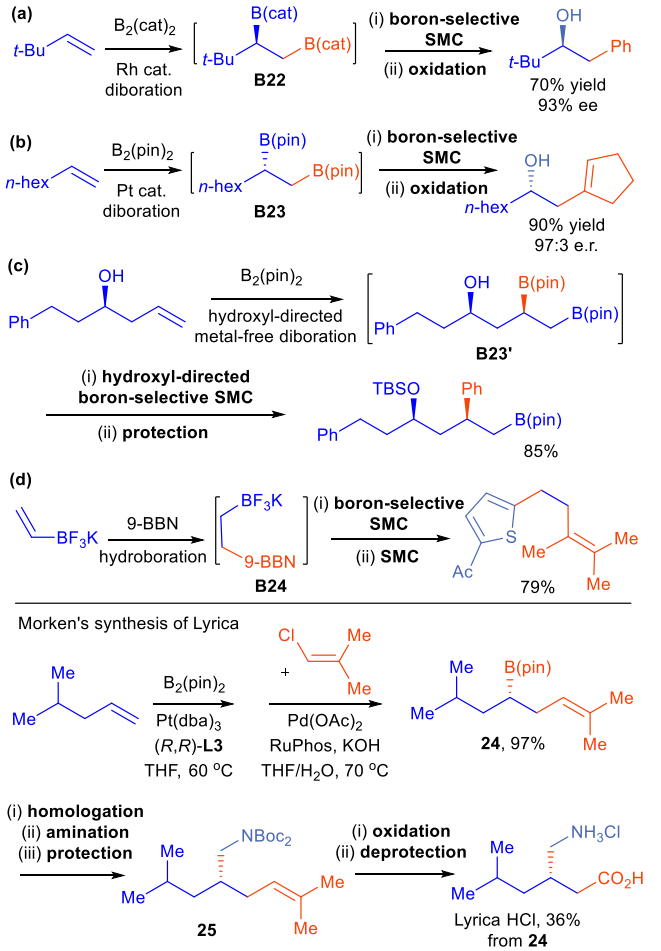
3.2 1,2-Diborylalkanes

Formal asymmetric carbohydroxylation of olefin substrates was realized by Morken's group by virtue of a Rh-catalysed asymmetric diboration/Suzuki–Miyaura coupling/oxidation sequence (Scheme 15, a).[30] In this process, *in situ*-generated 1,2-diborylalkane intermediates underwent boron-selective coupling with aryl halides. The less hindered primary C–B(cat) bond reacted, leaving the secondary C–B(cat) bond intact that was then oxidised to a hydroxyl group.



Scheme 15 Application of 1,2-diborylalkanes in boron-selective SMC reactions.

The same group reported Pt-catalysed asymmetric diboration of terminal alkenes with $B_2(pin)_2$. The following selective SMC reactions of the obtained 1,2-diborylalkanes were also achieved (Scheme 15, b). They also demonstrated that the presence of β-B(pin) groups greatly accelerated transmetallation of the primary B(pin) groups.[31] Taking advantage of boronyl groups as versatile functional group precursors, the further transformations of previously unreacted secondary B(pin) groups afforded a broad array of chiral compounds. These diboration/boron-selective cross-coupling (DCC) reactions plus further conversion of boronyl groups provided a reliable and flexible platform for complex asymmetric synthesis from readily available terminal alkenes. As shown in Scheme 15, for the synthesis of Lyrica (an anticonvulsant drug), the DCC reaction allowed a quick preparation of chiral secondary boronic ester **24** from two simple alkenyl feedstocks in excellent yield. Subsequent stereospecific boronate homologation, amination and protection afforded intermediate **25**. The following oxidation and deprotection completed the synthesis in an overall 36% yield from **24**.[31] To further diversify the downstream transformations, very recently, Morken and Blaisdell reported on the development of β-hydroxyl-directed palladium-catalysed regioselective cross-coupling reactions of 1,2-diborylalkanes, enabling selective transformation of the inherently less reactive secondary boronyl groups (Scheme 15, c).[32] This directing group-assisted approach might inspire more innovative methods to overcome the electronic and/or steric limitations in selective reactions of di- or polyboron compounds.

In 2008, Molander and Sandrock reported that alkenyl-containing organotrifluoroborates underwent hydroboration with 9-BBN to afford diverse diboron products, including 1,2-diborylethane.[13] Selective SMC reactions between the resulting trialkylborane and aryl or alkenyl halides could be efficiently realized. The resulting organotrifluoroborates could be isolated or exposed to other SMC reactions in one-pot version (Scheme 15, d).[33]

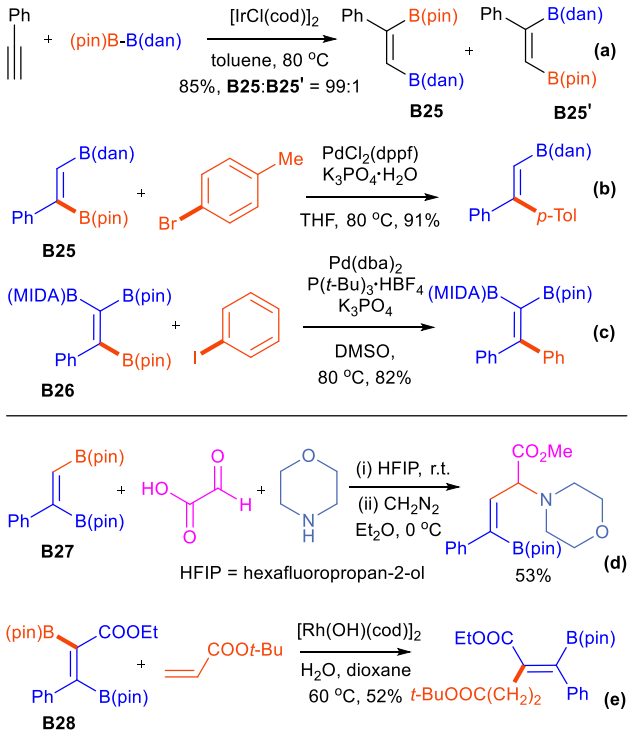
3.3 Di- and polyborylalkenes

The well-documented selective SMC reactions of 1,1-diborylalkenes[34] and 1,2-diborylalkenes[35] with two similar boronyl groups enabled the stereoselective preparation of alkenyl derivatives. Along with the development of boronyl-protecting groups, differentiated di- and polyboron alkenes were also prepared and applied to meet the synthetic needs that could not be solved using previously available building blocks.

In the building block library developed by Burke's group,[10] the bismetalated alkenes, including the diborylalkenes, play important roles as precursors for halo-B(MIDA) building blocks or linchpins for connecting two different fragments by virtue of boron-selective reactions (Scheme 6, b).[9] Diboration of alkynes with an unsymmetrical diboron reagent, B(pin)-B(dan), was disclosed by Suginome's group, affording 1,2-diborylalkenes, such as **B25**, with B(dan) groups incorporated to the terminal carbon atoms regioselectively (Scheme 16, a). Internal selective SMC reactions were then realized as a result of the inertness of B(dan) groups (Scheme 16, b).[36] This was in sharp contrast to the reactivity of 1,2-di(pinacolatoboronic ester)alkenes whose terminal B(pin) moieties generally reacted preferentially. The synthesis of 1,1,2-triborylalkene **B26** containing two different boronyl functionalities was realized by Nishihara's group in 2014 via Pt-catalysed diboration of alkynyl MIDA boronates. These three distinct C–B bonds of the obtained products could be nicely differentiated in the following SMC reactions, affording *gem*-diborylated olefins selectively (Scheme 16, c).[37] This selectivity could be attributed to the inertness of B(MIDA) under anhydrous conditions and the different steric environment for the two B(pin) groups.

In addition to their applications in selective SMC reactions, the diborylalkenes have also recently been applied in other

boron-selective transformations as versatile bifunctional building blocks. Petasis reactions have been realized with the terminal B(pin) moieties of (*Z*)-1,2-diborylalkenes reacted selectively (Scheme 16, d).[38] Sawamura's group found that the α-B(pin) moiety of (*E*)-1,2-diborylacrylate was more reactive, not only in SMC reactions but also in Rh-catalysed conjugate addition (Scheme 16, e), probably due to the electron-withdrawing effect of the ester group.[39]



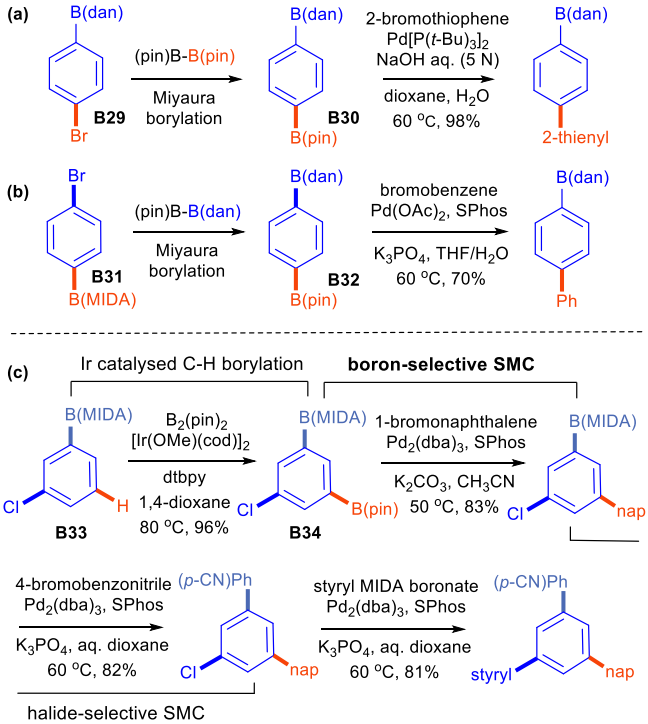
Scheme 16 Application of diborylalkenes in boron-selective transformations.

3.4 Di- and polyborylarenes

Generally, the selective SMC reactions of di- or polyborylarene modules containing two or more identical boronyl groups are difficult to realize. A few cases of these reactions have nonetheless been disclosed; they were achieved by careful control of the reaction conditions.[40] Selective SMC reactions may become more convenient and efficient if reactions commence with differently protected di- or polyborylarenes. Differentiated diborylarenes may function as double nucleophilic linkers to assemble various electrophilic building blocks.

This strategy was first demonstrated to be effective by Suginome's group.[41] They prepared diborylarenes containing both B(dan) and B(pin) such as **B30** by Miyaura borylation of haloaryl-B(dan) compounds. **B30** underwent cross-coupling with aryl or alkenyl halides at the B(pin) moiety exclusively (Scheme 17, a). The intact B(dan) moiety could be further utilized in subsequent SMC reactions.

A more convenient synthetic approach to differentiated diborylarenes would involve starting from simple monoboron compounds. Li and co-workers successfully used iridium-catalysed C–H borylation to introduce B(pin) groups to readily available aryl MIDA boronates and obtained a broad range of di- and triborylarenes. Chemoselective SMC reactions of the newly incorporated B(pin) moieties could be realized in anhydrous acetonitrile in the presence of B(MIDA) groups (Scheme 17, c). The obtained MIDA boronate products could participate directly in the following SMC reactions via the slow-release strategy to provide multi-substituted arenes.[42] More recently, taking advantage of the different stabilities of B(dan) and B(MIDA) groups under aqueous basic conditions, a selective SMC reaction to differentiate these two protected boronyl groups was also realized with the B(dan) moiety intact (Scheme 17, b).[43]



Scheme 17 Selective SMC reactions of differentiated diborylarenes.

3.5 Diboron compounds for selective allylboration

The addition of allyl boronates to polar unsaturated bonds, such as the carbonyl groups in aldehydes, is well known as allylboration reactions. Generally, the reaction can take place via a closed chair-like six-membered transition state, in which the carbonyl is activated by the Lewis acidic boron atom. This transition state enables highly diastereoselective transformation. In combination with chiral boronyl groups or asymmetric catalysts, enantioenriched homoallylic alcohols, an important structural motif in natural product synthesis, may be reliably generated.

Over the past few decades, a series of diboron compounds have been prepared and applied in allylboration of aldehydes. These compounds often contain a reactive boronyl group at the allyl position and another temporarily inert boronyl group at a different position. After the initial allylboration reaction and further transformation of the second boronyl group, a variety of functionalized advanced intermediates are accessible.

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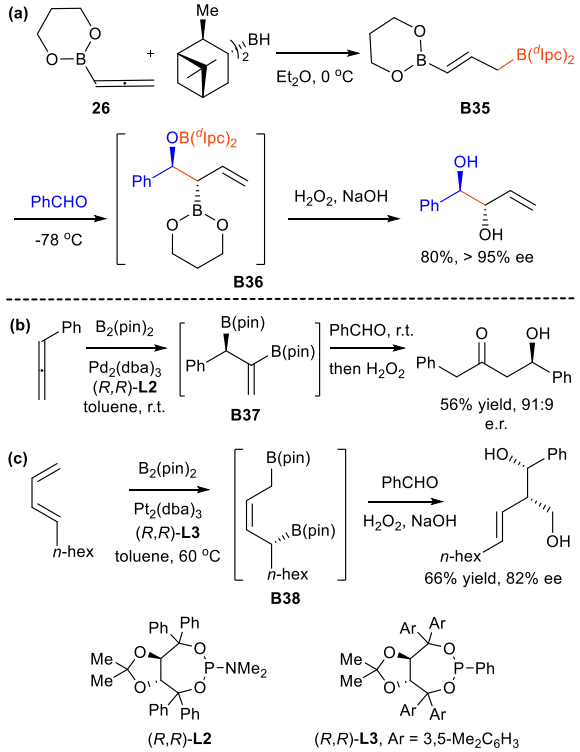
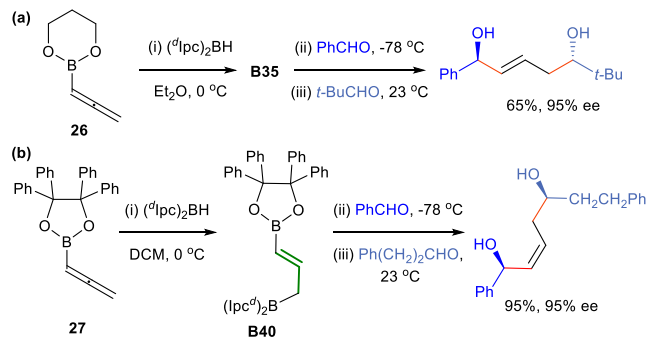
This strategy was explored as early as 1995 and reported by Brown and Narla.[44] They prepared optically active [(*E*)-γ-(boronic ester)allyl] diisopinocampheylborane **B35** via hydroboration of allenyl boronic ester **26** with $^{d}Ipc_2BH$. This diboron reagent could react readily with aldehydes via the more reactive allyl Ipc-borane unit, leading to allylboration products such as **B36** with an allyl boronic ester moiety. Subsequent stereoretentive oxidation afforded *anti*-1,2-diols in high diastereo- and enantioselective fashion (Scheme 18, a).

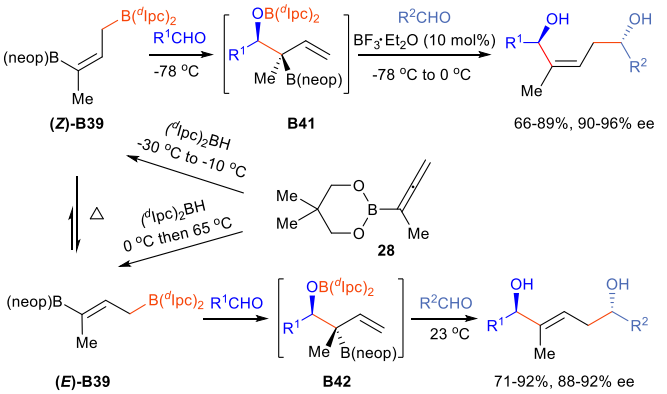


Scheme 18 Boron-selective allylboration.

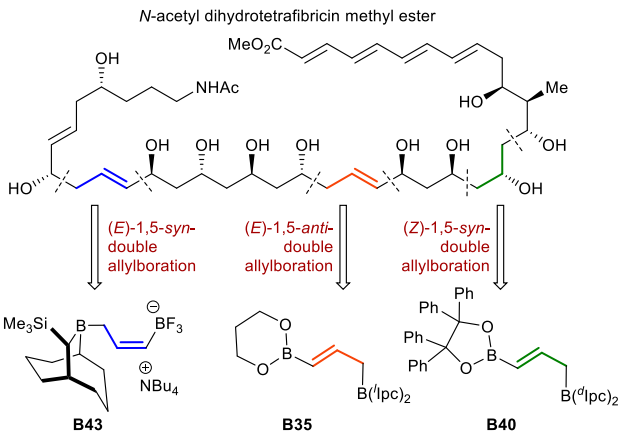


Scheme 19 Double allylboration strategy to construct 1,5-diols.

Using the combination of $Pd_2(dba)_3$ and a chiral phosphoramidite ligand, Morken and co-workers developed a regioselective and enantioselective diboration reaction of allenes using $B_2(pin)_2$ as the borylating reagent. The resulting diboration products contained allyl and alkenyl B(pin) groups. The following tandem allylboration/oxidation sequence made use of these two B(pin) groups and afforded β-hydroxyketones with near-perfect chirality transfer (Scheme 18, b).[45] When a Pt catalyst was used, enantioselective 1,4-diboration (Scheme 18, c)[46] or 1,2-diboration[47] of 1,3-dienes could also be achieved and, in both cases, the generated allyl boronyl groups reacted selectively in the following allylboration steps. After oxidation, synthetically useful enantioenriched 2-buten-1,4-diols or 2-buten-1,5-diols were ultimately obtained.



Scheme 20 Kinetically and thermodynamically controlled stereoselective double allylboration.



Scheme 21 Roush's synthesis of *N*-acetyl dihydrotetrafibricin using three double allylboration reagents.

In 2002, Roush and Flamme reported that the allyl 1,3-propanediol boronate group of **B36**, which was unreactive in the first allylboration step, was further utilized in a second allylboration reaction.[48] This consecutive double allylboration protocol was well controlled by modification of the reaction temperature. Two different aldehydes were formally linked by the carbon chain of the diboron compounds, affording (*E*)-1,5-*anti*-diols in excellent stereoselectivity (Scheme 19, a). When an allenylboronic ester with a bulky diol unit **27** was used as starting material, (*Z*)-*syn*-1,5-diols were obtained in high yield and with a high level of enantioselectivity (Scheme 19, b).

Since then, the double allylboration strategy has evolved to access various diols in a highly stereocontrolled fashion. Recently, Roush's group disclosed an efficient synthetic route towards 2-methyl-1,5-*anti*-pentenediols via sequential kinetically controlled hydroboration of allenylboronate **28** and double allylboration of the resulting diboron compounds

(Scheme 20).[49] Double allylboration of the kinetic allylborane (*Z*)-**B39** afforded (*Z*)-2-methyl-1,5-anti-pentenediols. In the second allylboration step, high enantioselectivity was achieved when $BF_3 \cdot OEt_2$ was used as the catalyst. (*Z*)-**B39** could isomerize to (*E*)-**B39** at 65 °C, which then underwent double allylboration reactions to afford (*E*)-2-methyl-1,5-*anti*-pentenediols in good yield and with high enantioselectivity without the assistance of $BF_3 \cdot OEt_2$.

In a recent synthesis of *N*-acetyl dihydrotetrafibricin methyl ester, a derivative of the potent anti-aggregation natural product tetrafibricin, the double allylboration strategy was utilized triply, for diboron reagents **B35**, **B40** and **B43**, in highly enantioselective and diastereoselective fragment assembly reactions (Scheme 21). This work spectacularly exemplifies how boron-selective double allylboration reactions can be used in the efficient synthesis of complex molecules.[50]

Conclusions

Over the last decade in particular, great strides have been made in the development of boron-selective reactions and their fruitful applications. The prosperity of this type of transformations has been rooted in the extensive research into the preparation and reactivity of organoboron compounds. A variety of bifunctional building blocks have been prepared and utilized in the modular synthesis of complex molecules, such as organic halides containing masked boronyl groups and di- or polyboron compounds. These building blocks, together with related boron-selective transformations, provide an efficient and flexible platform to construct molecular diversity and complexity. A prototypic yet already powerful automated synthesis machine based on this chemistry has recently appeared. The synthetic value of di- and polyboron compounds has also been validated by convergent assemblies of pre-functionalized fragments.

However, compared with the diverse transformations of common organoboronic derivatives, reaction types of the reported boron-selective transformations are relatively limited to Suzuki–Miyaura coupling or the allylboration reaction. It appears that if yet more organoboron-involved reaction types could be realized in boron-selective version then a great number of diverse structures may be readily synthesized from the present building block library. Therefore, further exploration in this area, especially the development of methods and technologies for an automated synthesis platform, might provide new strategies in building small and/or polymer molecules, which may ultimately benefit not only the academic community involved in organic synthesis, biomedical and materials science, but also industrial manufacturing.

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[a] Center for Organic Chemistry, Frontier Institute of Science and Technology (FIST) and Frontier Institute of Chemistry, Xi'an Jiaotong University, 99 Yanxiang Road, Xi'an, Shaanxi, 710054, China. E-mail: lipengfei@mail.xjtu.edu.cn.

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