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Advances in Organoboron Chemistry

Sylvain Roland^a and Stephanie Norsikian^{*b}

^a IPCM - Institut Parisien de Chimie Moléculaire, Sorbonne Université, 4 place Jussieu 75252 Paris Cedex 05, France

^b Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, UPR 2301, Gif-sur-Yvette 91198, France

stephanie.norsikian@cnrs.fr

Abstract

Thanks to the particular properties of boron, organoboron derivatives are excellent tools for substrate- or reagent-controlled asymmetric reactions. In this chapter, we focused on the synthesis of alpha-chiral boron derivatives and their stereospecific transformations, the allylation reaction, the borono-Mannich reaction and stereoselective glycosylations. These synthetic methodologies will be described with their reaction mechanisms or transition states, and their recent applications in the total synthesis of complex natural products and medicinal relevant molecules.

Keywords

Organoboron compounds, α -substituted chiral boronic esters, bioactive molecules, total synthesis, lithiation-borylation, nucleophilic addition, allylation, cross-coupling reactions, carbohydrates, glycosylation

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Key points/objectives box

- ◆ Highlight of the recent synthetic methods using boron reagents
- ◆ Mechanisms and transition states
- ◆ Applications in total synthesis of complex natural products and biologically active molecules.

Introduction

The boron salt $\text{Na}_2\text{B}_4\text{O}_7$, commonly known as borax, has been known and used since antiquity for various applications. Elemental boron was isolated for the first time in 1808 by Gay-Lussac and Thénard¹ and independently by Davy.² Since this work, many chemists have studied boron, notably Moissan, who in 1895 improved the process for preparing pure boron.³ Boron as an element has therefore been known for about two centuries. However, compounds derived from boron have been used in organic chemistry for less than a century. The founding work in this field dates back to 1931 when Schlesinger and Burg prepared diborane and reacted it with an organic compound.⁴ Brown, who collaborated with Schlesinger over the following decades, made an important contribution to the development of boron molecules in synthetic chemistry using these compounds for the reduction of different functional groups.⁵ For the development of these very useful reactions in synthesis, he received the Nobel Prize in Chemistry in 1979 together with Wittig rewarded for his olefination process. Since these discoveries, chemists have continued to be interested in boron and its various uses. The electronic properties of the boron atom and its position adjacent to carbon in the periodic table give organoboron compounds a dual character. With three valence electrons and a ground-state electron configuration of $1s^2 2s^2 2p^1$, boron typically forms trivalent neutral compounds. Thus, the boron atom is

sp^2 hybridized, and has a trigonal planar structure with a vacant p-orbital. It is then analogous to a carbocation while being neutral and behaves like an electrophile. However, when a trigonal boron atom accepts a pair of electrons from a nucleophile, it becomes anionic with a tetrahedral structure (sp^3) and therefore has a nucleophilic character. It is possible to switch from one character to another by various methods. These two forms of boron are relatively stable while being sufficiently reactive to be exploited. These characteristics give borylated molecules multiple and interchangeable chemical properties.⁶

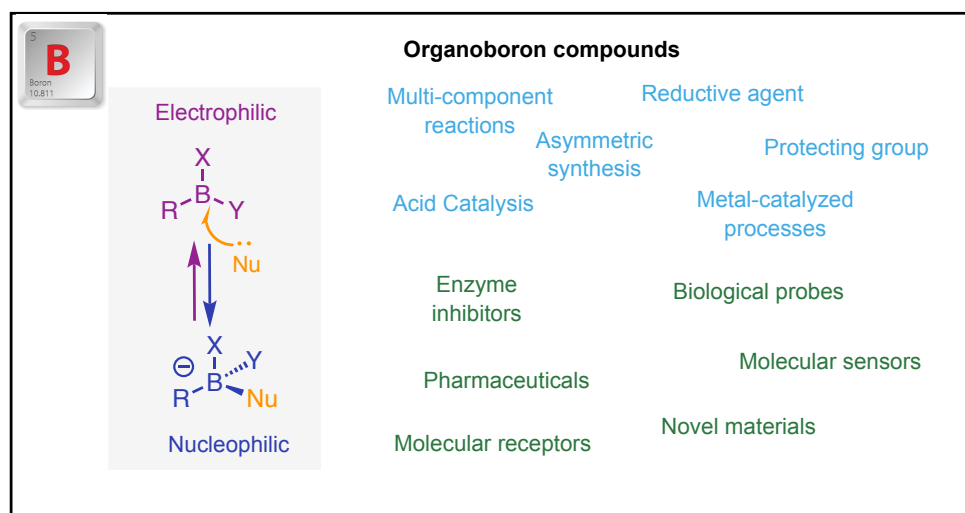


Figure 1 Reactions and applications of organoboron compounds

Thus, organoboron compounds have found many applications in organic chemistry (Figure 1). Indeed, they are used to carry out asymmetric reactions such as hydroborations, aldol reactions, allylboration or reductions. One of the greatest advances made in boron chemistry is the discovery of metal-catalyzed couplings between an organoboron compound and various derivatives. The Suzuki coupling has become an almost essential tool in synthetic and medicinal chemistry and for the synthesis of new organic materials.^{7,8} Several additional metal-catalyzed processes involving organoboron compounds have also been developed in recent years, in particular reactions catalyzed by rhodium, nickel, or even copper. The electrophilic nature of organoboron molecules allows their use in acidic catalysis.⁹ Therefore, small molecules such as boron trifluoride and complex species such as oxazaborolidines¹⁰ can promote various reactions such as aldol reactions, carbonyl reductions, alcohol oxidation, cycloadditions, esterification and amide bond formation.

The development of boron chemistry has also allowed the use of organoboron molecules for applications in medicinal and biological chemistry.^{11,12,13} Indeed, since the discovery of the drug bortezomib,^{14,15} the first-in-class proteasome inhibitor used in the treatment of multiple myeloma, many borylated derivatives (mainly boronic acids) have shown interesting biological activities such as anticancer, antibacterial or antiviral activity. They have also been applied as sensors, delivery systems or bioconjugation warheads thanks to their ability to react reversibly and covalently with 1,2- and 1,3-diols.^{16,17} For example, this property was exploited for monitoring diseases such as diabetes. Upon binding of a sugar, this sensing with boronic acid-based systems generally relies on optical property or conductivity changes. Boronic acids or their esters have been used as “off-on” fluorescent probes for the detection of Reactive Oxygen Species (ROS).^{18,19} In particular, upon reaction with H_2O_2 , these compounds undergo a rapid and selective oxidative conversion into trialkoxyboranes that rapidly hydrolyze into the corresponding fluorescent phenol along with borate esters or boric acid. This chemospecific and biologically compatible reaction method allowed for the development of highly selective fluorescent probes for H_2O_2 imaging in cells and efficient ROS-activated prodrugs.

Additionally, due to the unique characteristics of boron, boron-containing compounds are used as building blocks in supramolecular and inorganic synthesis, as well as in materials science.^{20,21,22} They turned out to have unique physico-chemical properties for potential applications in electronic and energy processes (gas and energy storage, optical data storage, waveguides, multiphoton microscopy, molecular machines, etc.).

The particular combination of properties of boron is ideal for diastereocontrolled organic synthesis and stereospecific reactions. A number of boron-stereodirected reactions are described, and in particular organoboron reagents are excellent tools for selective reduction (hydroboration or stereoselective reactions with boranes and borohydrides),²³ cycloaddition reactions^{24, 25} or aldol reactions.²⁶ In this chapter, we chose to focus on the following five topics: 1) the synthesis of α -chiral boranes and boronic esters; 2) the stereospecific transformations of chiral boron reagent; 3) the allylation reaction; 4) the borono-Mannich reaction (Petasis reaction) and 5) the stereoselective reaction in carbohydrate chemistry. Our aims are to highlight recent synthetic methods using boron reagents with reaction mechanisms or transition states, and their applications in total synthesis of complex natural products and biologically active molecules.

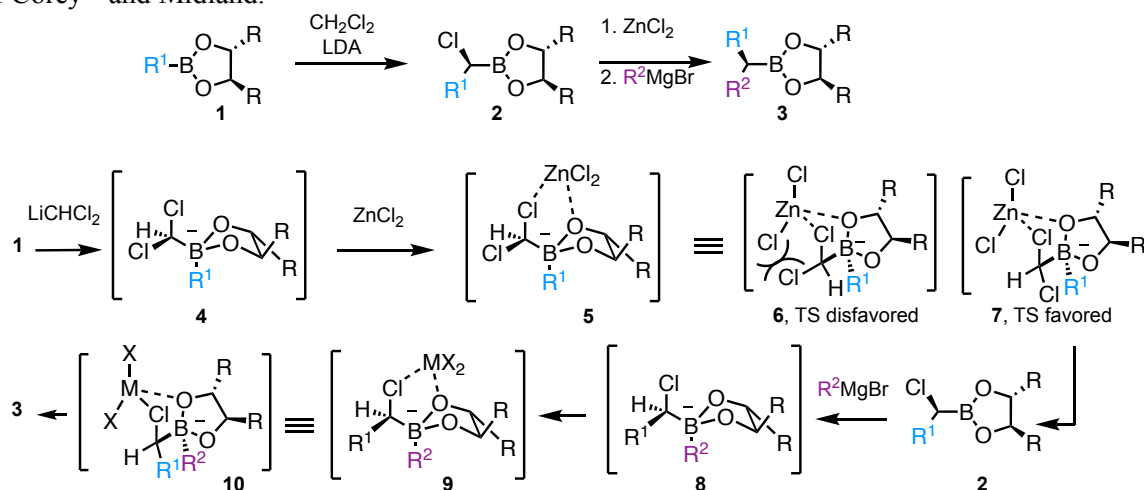
1 Synthesis of α -chiral boranes and boronic esters and applications

Chiral boron-containing compounds are chemically and configurationally stable and thus are important building blocks in organic synthesis. One of the most powerful methods to access these compounds is the 1,2-metallate rearrangement of boronate esters.^{27, 28} In addition, the stereospecific conversion of α -chiral boranes and boronic esters into other useful functional groups is a growing field of research and provides alternative access to drugs or natural molecules.

1.1 1,2-Metallate rearrangement of boronate esters

1.1.1 Substrate control

The Matteson homologation is a highly stereoselective one-carbon extension of an alkyl boronic ester (Scheme 1).^{27, 28} Based on the discovery of metallate rearrangements in the early 1960s,²⁹ the development of this method was investigated by Donald Matteson in the 1980s.³⁰ Typically, an enantiopure electrophilic alkyl boronic ester **1** reacts with a nucleophile to form tetracoordinate borate anions. With deprotonated dichloromethane (performed from *n*-butyllithium and dichloromethane at $-100\text{ }^{\circ}\text{C}$ or generated by *in situ* addition of LDA to a mixture of the boronic ester and dichloromethane), it gives rise on warming to room temperature to an α -chloroboronic ester **2** with high levels of diastereocontrol (often $>99:1$). When a second organometallic reagent (generally a Grignard reagent) is added, it generates a boronate complex, which undergoes a 1,2-shift of the nucleophile and the substitution of the chlorine atom with configuration inversion providing the corresponding alkyl boronic ester **3**. It was later established that the introduction of a sub-stoichiometric amount of zinc chloride accelerated the reaction and significantly improved the observed levels of diastereoselectivity. A model for the observed stereocontrol and the promoter effects of zinc chloride has been proposed by the groups of Corey³¹ and Midland.³²



Scheme 1 Matteson homologation

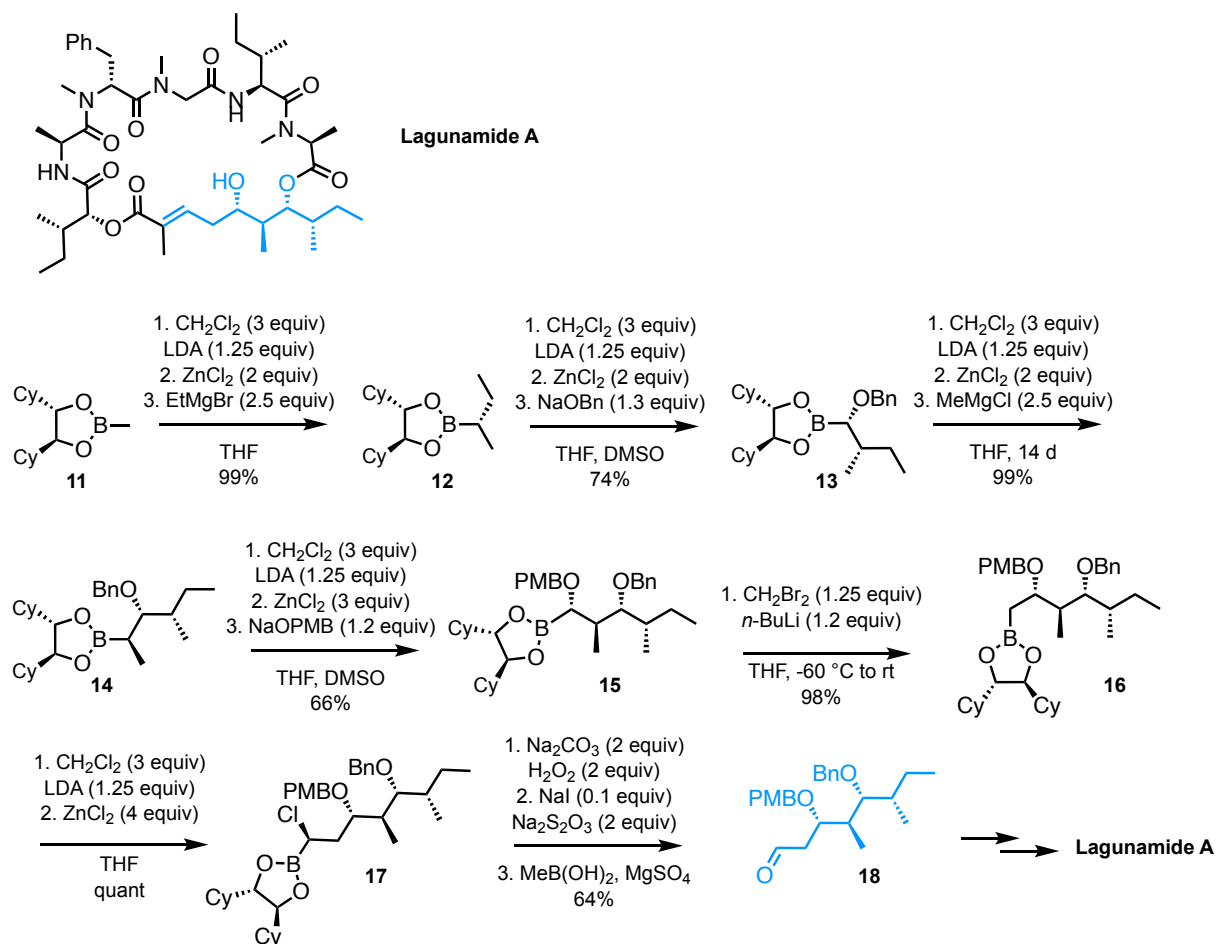
After the initial formation of the tetrahedral (dichloromethyl)borate complex **4**, the zinc chloride coordinates to the most accessible oxygen atoms of the diol ligand. In the preferred TS **7**, the zinc chloride directs the migration of R¹ and assists the departure of the antiperiplanar chlorine atom leading to α -chloroboronic ester **2** with high selectivity. In the alternative TS **6**, there is a destabilizing steric interaction between the two chlorine atoms that disfavored this pathway. The addition of a Grignard or alkyl lithium reagent on this species generates a second boronate complex **8**. Since only one chlorine atom remains, the migration of R² is stereospecific and proceeds through the *anti*-periplanar alignment of the migrating and leaving groups.

Recent DFT calculations showed an additional Cl[⋅]H electrostatic interaction between one chlorine atom of ZnCl₂ and the hydrogen atom of the (dichloromethyl)lithium moiety explaining the origin of the selectivity.³³ This model also rationalizes the different behavior of the ate complex (C-migration vs O-migration) occasionally observed and why substrates lacking the key hydrogen atom involved in such interactions lead to low and unpredictable selectivity.

Concerning the boronic ester, generally C₂-symmetric boronic esters derived from 1,2-diols such as 1,2-diisopropyl ethanediol (DIPED) or 1,2-dicyclohexyl ethanediol (DICHED) give better selectivities than boronic esters derived from pinanediol. It should be noted that the homologation of chiral aryl boronic esters is less selective than with alkyl boronic esters due to epimerization by the released LiCl.³⁴ This reaction was recently reinvestigated by Kinsinger and Kazmaier allowing the Matteson homologation of different aryl boronic esters with higher selectivities.³⁵ Also, functional groups (alkoxy groups, nitrides, halide, carbonyl, thioether, and cyano substituents) on the boronic ester are well tolerated. However, they generally need to be placed at least two carbons away from the boron center to avoid β -elimination.

A wide range of nucleophiles can be employed for the displacement of the α -halide such as lithium or magnesium reagents but also alkoxides, thiolates, nitrogen nucleophiles, azides, lithioacetonitrile, or enolates are suitable. This protocol has proven to be an extremely valuable tool for the selective synthesis of alcohols and building blocks with adjacent stereocenters. Boronic ester intermediates can be converted stereospecifically to primary and secondary amines, including pyrrolidines, via alkyl trifluoroborate salts.³⁶ The Matteson reaction has also been used as a key step in the synthesis of drugs and natural products. In particular, it was applied to the synthesis of a few insect pheromones such as japonilure,³⁷ serricornin,³⁸ stegobinone and stegobiol.³⁹ More recently, six iterative Matteson homologations have been achieved for the preparation of a polyketide fragment of lagunamide A, a cytotoxic and antibiotic peptide natural product (Scheme 2).

To this end, C₂-symmetric chiral methyl boronic ester **11** was first subjected to Matteson homologation with EtMgBr to give the corresponding boronic ester **12** in 99% yield and a single diastereomer. The next homologations were performed successively with benzyl alcoholate, methyl Grignard reagent, and *p*-methoxybenzylate as the nucleophiles affording the desired adduct **15**. The introduction of a methylene group was then performed by reaction with bromomethyl lithium, which was generated *in situ* from dibromomethane and *n*-BuLi at -60 °C. The obtained compound **16** was submitted to a final homologation allowing to give the α -chloro adduct **17**, which was oxidized to the aldehyde **18**. This building block was synthesized with an overall yield of 30% after six iterative Matteson homologation and an oxidation step and could be used for the completion of the total synthesis of lagunamide A. Thanks to this powerful iterative homologation strategy, the total syntheses of the marine cyclodepsipeptides apratoxins A and B⁴⁰ as well as dolicolide⁴¹ were also achieved.



Scheme 2 Preparation of a polyketide fragment of lagunamide A by six iterative Matteson homologations

One of the most significant applications of the Matteson reaction is the formation of α -amino boronic acids by the reaction of (α -haloalkyl)boronic esters with nitrogen-based nucleophiles. These types of compounds have proven to have important biomedical applications since the discovery of bortezomib (VelcadeTM). The latter, approved by the FDA for the treatment of multiple myeloma and mantle cell lymphoma, is the first boron-containing pharmaceutical product and the first successful proteasome inhibitor.^{42, 43, 44} The synthesis of bortezomib relies on the displacement of (α -chloroisopropyl)boronic esters derived from pinandiol with LiHMDS affording the *N*-silylated amino boronic ester **19**, which was further functionalized (Figure 2).

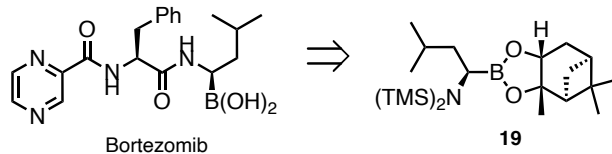
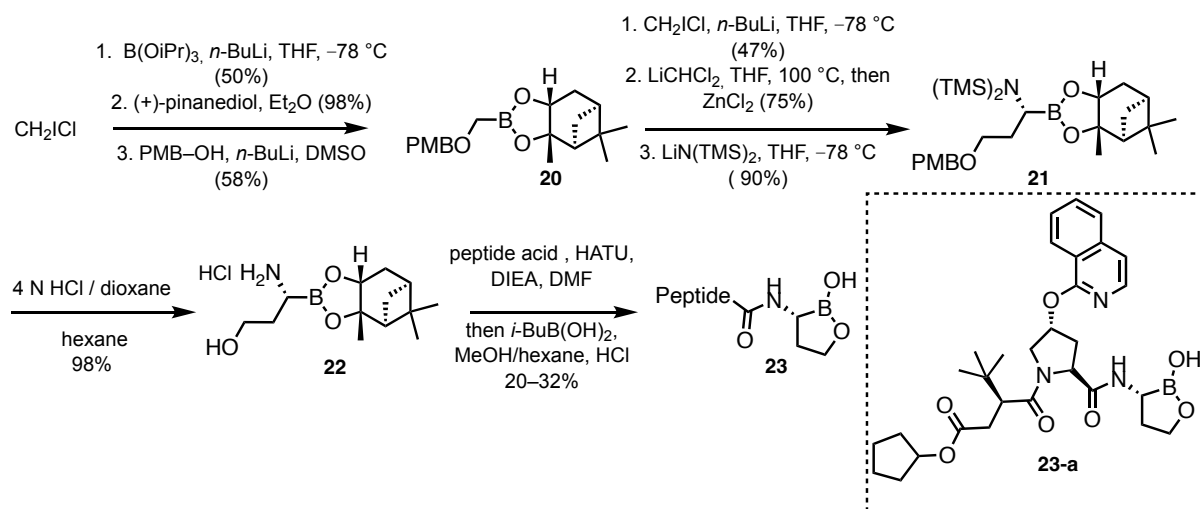


Figure 2 Retrosynthetic pathway to bortezomib

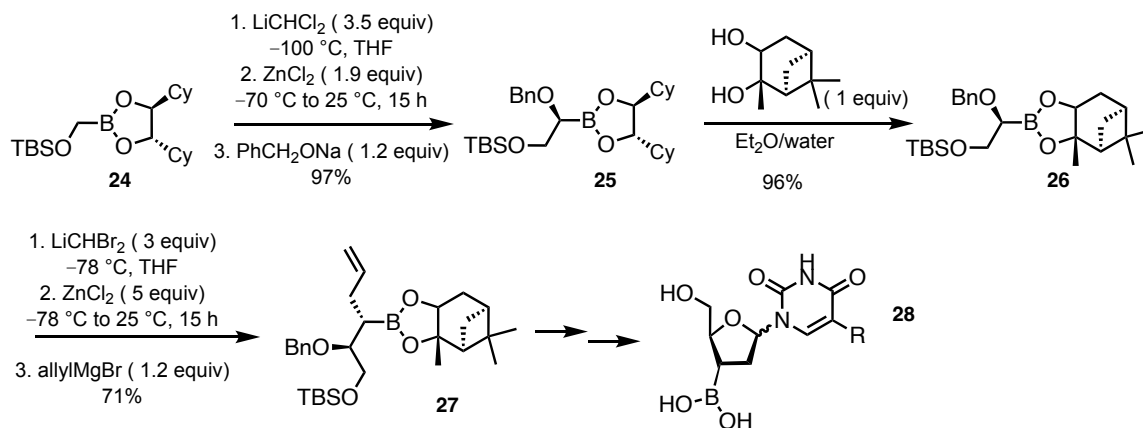
Since then, a number of α -amino boronic acids and peptidyl boronate derivatives have been prepared with this strategy.^{14, 15, 45} The preparation of a series of α -amino cyclic boronates has also been performed as illustrated in Scheme 3.⁴⁶ The synthetic route began with the transmetalation of chloriodomethane with *n*-BuLi in the presence of triisopropyl borate to give diisopropyl chloromethyl boronate that leads after transesterification with (+)-pinandiol the pinandiol ester **20**. The latter was treated with lithium (4-methoxyphenyl)methanolate to yield the PMB-protected alcohol **21**. The introduction of a methylene group was then carried out by reaction with chloromethyl lithium followed by the use of the Matteson procedure for the formation of the α -chloroboronate and nucleophilic

displacement by lithium bis(trimethylsilyl)amide. The TMS-protected α -amino boronate was then treated with HCl to produce α -amino boronate as the chlorhydrate salt **22**. Coupling of **22** with different peptide acids using HATU/DIEA yielded the corresponding carboxamide, which, after treatment with *i*-butyl boronic acid in the presence of HCl afforded the desired products **23**. The SARs included the influence of ring size, chirality, and substitution patterns of these compounds. These products have been evaluated as inhibitors of the HCV NS3 serine protease and the X-ray structure of the boronate inhibitor **23-a** complexed with the protease showed inhibition by trapping the Ser-139 hydroxyl group in the active site.



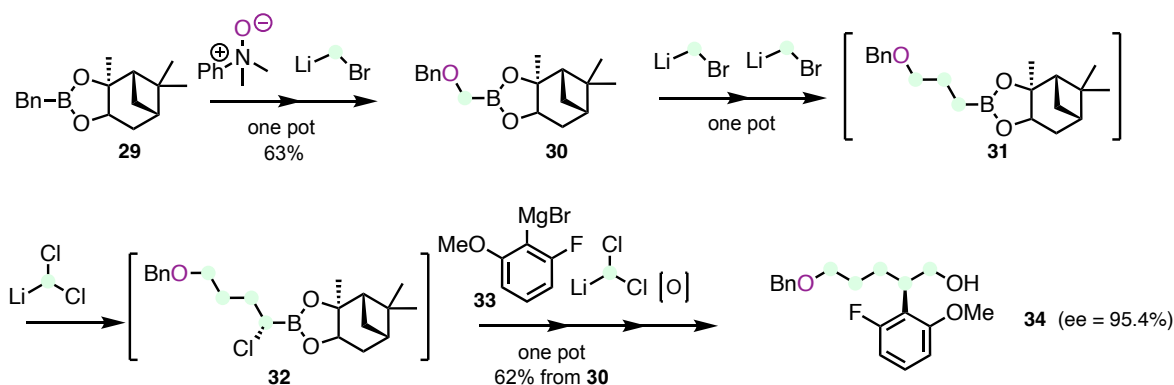
Scheme 3 Preparation of α -amino cyclic boronates compounds as inhibitors of the HCV NS3 serine protease. HATU: hexafluorophosphate de (diméthylamino)-*N,N*-diméthyl(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)méthaniminium; DIEA: *N,N*-diisopropyléthylamine

The Matteson homologation has proven useful in carbohydrate chemistry allowing the preparation of L-ribose⁴⁷ and asymmetrically deuterated glycerol.⁴⁸ In 2012, Kim *et al.* prepared nucleoside analogs having a boronic acid in place of the 3-hydroxyl group of deoxyribose (Scheme 4). The reaction sequence begins with the installation of the first stereocenter via the homologation of a boronate of (*S,S*)-1,2-dicyclohexyl-1,2-ethanediol (DICHEd) **24** with benzyl alcoholate. For the second homologation of the obtained compound **25** with allyl Grignard reagent, the chiral inducer had to be replaced by (+)-(1*S*,2*S*,3*R*,5*S*)-pinanediol given the steric relationship between the two required asymmetric centers. After further functionalizations (oxidation of the terminal vinyl group, catalytic hydrogenolysis, acetylation, Vorbrüggen glycosylation of pyrimidine bases, and deprotections), nucleoside analogs **28** having a boronic acid function at the 3-position has been obtained. Unfortunately, none of the compounds has any significant cytotoxicity toward the Hep G2 cell line.



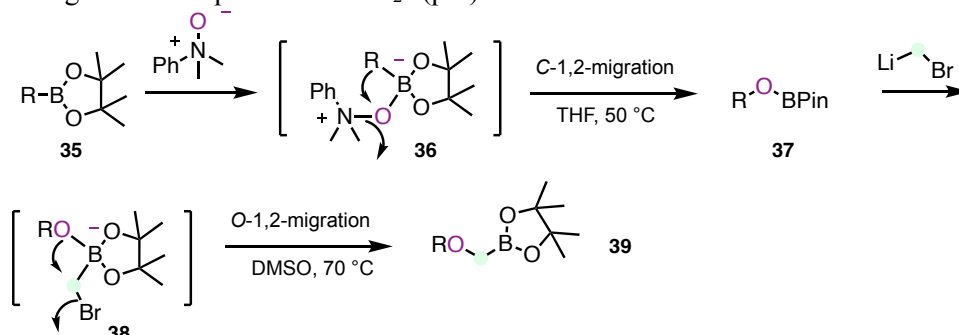
Scheme 4 Preparation of nucleoside analogs with a boronic acid at the 3-position of deoxyribose

Very recently, the oxa-Matteson reaction allowing sequential oxygen and carbenoid insertion into diverse alkyl and aryl boronate esters has been described and produced boron-substituted ethers.⁴⁹ This protocol was exploited for the asymmetric synthesis of benzyl ether **34**, a key intermediate to an acetyl-CoA-carboxylase (AAC) inhibitor (Scheme 5).⁵⁰ Starting with (+)-pinanediol boronate **29**, *O*-insertion into boronate C–B bond was first achieved using *N,N*-dimethylaniline oxide in THF at 50 °C. This was followed by a methylene insertion step using dibromomethane in the presence of *n*-butyllithium that allow the formation of compound **30**. Following two more methylene insertions, the resulting adduct **31** was subjected to the asymmetric Matteson reaction with LiCHCl₂ to produce chiral α -chloroboronic ester **32**. After reaction with the aryl Grignard reagent **33**, a final methylene insertion and oxidation, the desired product **34** was isolated in 37% overall yield and 95.4% ee.



Scheme 5 Application of the oxa-Matteson reaction to the preparation of a key intermediate to a AAC inhibitor

The oxa-Matteson reaction results from the reaction of *N,N*-dimethylaniline oxide with RB(pin) **35** forming the borate anion **36** (Scheme 6). Then the intermediate undergoes C-1,2-migration extruding PhNMe₂ to give the *O*-insertion product ROB(pin) **37**. The latter reacts further with LiCH₂Br at a low temperature to form the ate-complex **38** followed by 1,2-migration of the alkoxy moiety at a higher temperature to generate the product ROCH₂B(pin) **39**.



Scheme 6 Proposed mechanism for the oxa-Matteson reaction

It should also be noted that an enantioselective catalytic version of the 1,2-boronate rearrangement has been described very recently.⁵¹ Thus, thanks to a lithium-isothiourea-boronate complex, the synthesis of enantioenriched α -chloro pinacol boronic esters was possible from easily available boronic esters and dichloromethane.

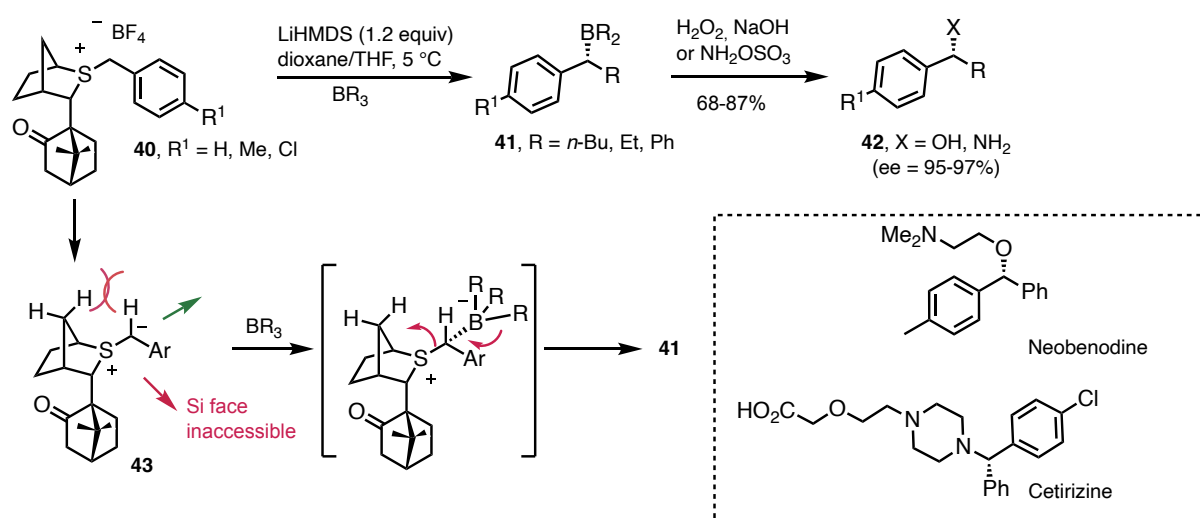
1.1.2 Reagent control

Previously the use of boronic esters derived from chiral diols and their subsequent homologation with achiral organometallic reagents was described where the newly formed stereogenic centers were controlled by the diol architecture (substrate control). Although this methodology is very powerful, some limitations can be encountered. One can cite, for example, a different reactivity of the ate diastereoisomer complexes.⁵² Also, obtaining the opposite stereoisomers simply by changing the order

of addition of the reactants is sometimes not possible and requires a three-step sequence to reverse the stereochemistry of the boronic ester diols. Another drawback relates to the synthesis of tertiary alcohols for which variable levels of selectivity have been obtained with sometimes an unpredictable asymmetric direction of induction.⁵³ To address these issues, complementary approaches to the Matteson reaction have been developed using a chiral carbanion carrying potential leaving groups that reacts with achiral boronic esters.

1.1.2.1 Chiral carbanions derived from sulfur ylides

Aggarwal *et al.* described the reaction of aryl-stabilized sulfur ylides **40**, generated *in situ* by deprotonation of chiral sulfonium salt, with triaryl, or trialkyl boranes (Scheme 7).^{54, 55, 56} This allows to generate the homologated boranes **41**, which give the corresponding alcohols or amines **42** in high yield and high ee after oxidation. The formation of the major enantiomer is explained by the favored conformation of the ylide **43** reacting on the less hindered face and with rearrangement occurring with inversion at the migrating terminus.

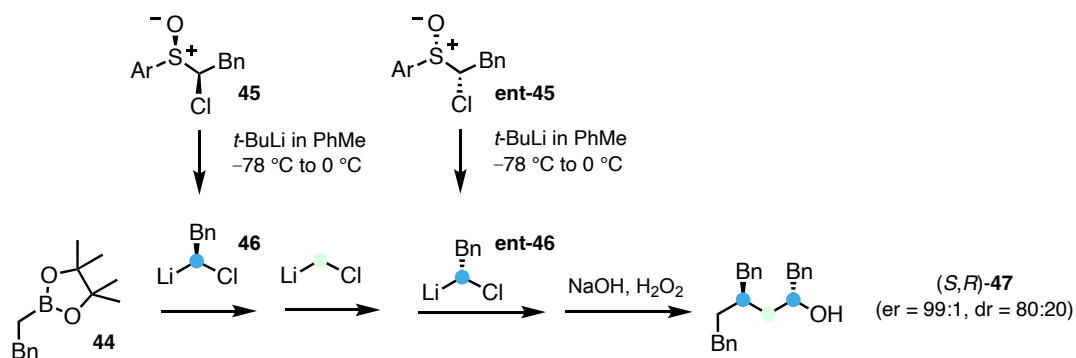


Scheme 7 Reaction of aryl-stabilized sulfur ylides with boranes

This type of compound possessing high enantiomeric excess has proven useful for medicinal chemistry since they could serve as precursors of the anti-inflammatory agents neobenodine and cetirizine. This methodology could also be applied to the synthesis of (+)-iso-agatharesinol thanks to the stereocontrolled synthesis of allyl boranes and their subsequent reactions with aldehydes.⁵⁷

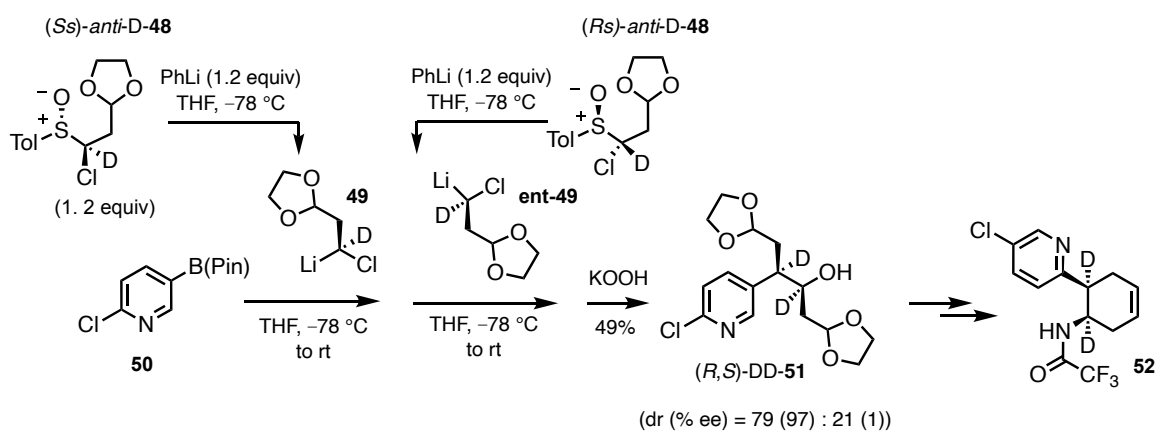
1.1.2.2 Chiral (α -chloroalkyl)lithium reagents

Enantiomerically enriched metal-carbenoid species can be generated by *in situ* sulfoxide ligand exchange. This strategy was employed by Blakemore *et al.* to obtain chiral (α -chloroalkyl)lithium reagents that react with neopentyl glycol or pinacol boronates to afford the desired homologue boronic esters with an excellent stereoselectivity.^{58, 59} As exemplified in Scheme 8, the programmed synthesis of a stereodiad motif could be achieved by iterative stereospecific reagent-controlled homologation. Compound **44** was extended by the treatment of the pinacol boronate with the enantioenriched chiral carbenoid **46**, which was generated from the chlorosulfoxide **45** using *t*-BuLi in toluene. After methylene insertion with chloro-methyl lithium, the resulting pinacol boronate was treated with the enantioenriched chiral carbenoid **ent-46**. Further oxidation yielded the carbinol **47** with a high enantiomeric ratio (99:1). Applying this process with the appropriate carbenoid presentation sequences enabled the programmed assembly of all the possible stereoisomers of this stereodiad system.



Scheme 8 Programmed synthesis of a stereodiad motif by iterative stereospecific reagent-controlled homology

The application of this strategy to the challenging 2-chloropyrid-5-yl pinacol boronic ester allowed the preparation of an isotopomer of Corey's (–)-epibatidine precursor (Scheme 9).^{60, 61} During this study, the use of α -deuterated α -chlorosulfoxides was found beneficial. Indeed, the sulfoxide precursor can be deprotonated reducing the yield of the (α -chloroalkyl)lithium intermediate. This problem is less observed with deuterated sulfoxides by retarding the rate of acid-base chemistry between the carbenoid and its chlorosulfoxide precursor. In this case, the sulfoxide-ligand/lithium exchange was performed with PhLi on α -deuterated α -chlorosulfoxides (*Ss*)-*anti*-D-**48** or (*R**s*)-*anti*-D-**48** to generate the corresponding enantioenriched 1-chloro-2-(1,3-dioxolan-2-yl) ethyl lithium **49** or **ent-49**. One pot sequential double stereospecific reagent-controlled homology of the pinacol boronate **50**, followed by oxidation provides access to **51** having the appropriate contiguous stereodiads for the total synthesis of (–)-epibatidine.

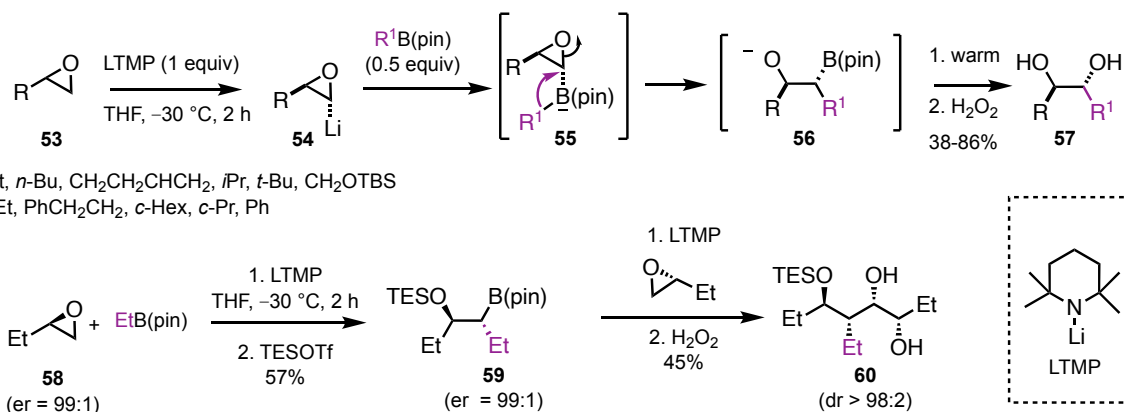


Scheme 9 Preparation of an isotopomer of Corey's (–)-epibatidine precursor from α -deuterated α -chlorosulfoxides

1.1.2.3 Lithiated epoxides and aziridines

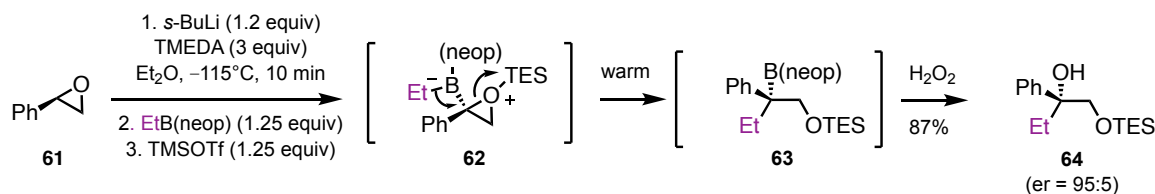
Lithiation of terminal epoxides **53** with lithium 2,2,6,6-tetramethyl piperidine (LTMP) in THF generates the corresponding *trans*-lithiated epoxide **54**, which can be trapped with a boronic ester with configuration retention (Scheme 10).⁶² The formation of the ate complex **55** is followed by 1,2-metalate rearrangement giving a β -alkoxy boronic ester **56** which can be oxidized to the corresponding *syn* diol **57** with complete diastereoselectivity and good yields. The reaction has been applied to a range of alkyl boronic esters and aliphatic epoxides accessible in enantiopure form. A decrease in yield was observed with phenylboronic acid pinacol ester for which competing elimination was observed. The boronic ester intermediate can be further elaborated to triols containing four stereogenic centers. In this case, treatment of (*R*)-**58**, with LTMP in the presence of ethyl boronic acid pinacol ester followed by the addition of triethylsilyl triflate (TESOTf) gave the β -silyloxy-boronic ester **59**. The latter can be engaged

in a second homologation process with lithiated (*S*)-butenoxide **58** leading, after oxidation, to the substituted *anti*-1,3-diol **60** with complete control over stereochemistry.



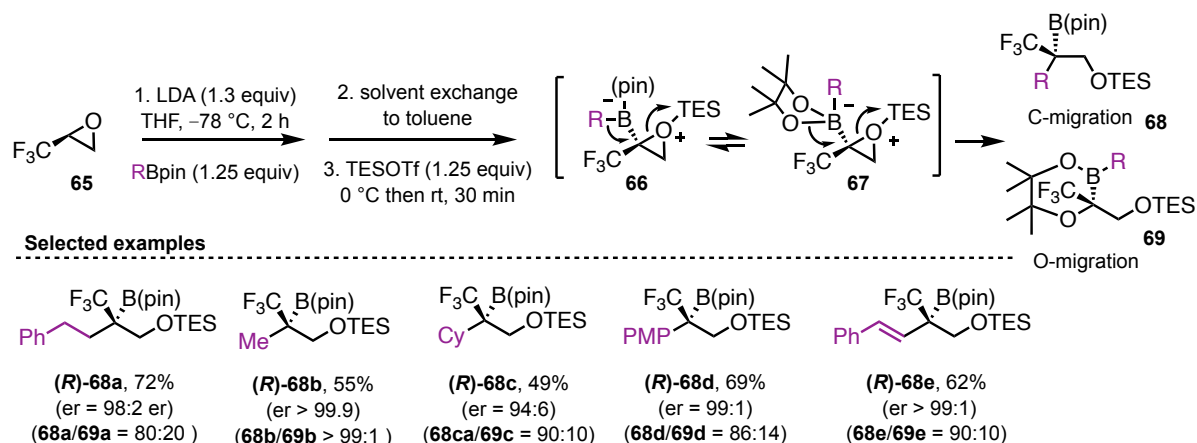
Scheme 10 Trapping of a boronic ester with lithiated epoxide. Application to triols containing four stereogenic centers

With styrene oxide **61**, the deprotonation at $-115\text{ }^{\circ}\text{C}$ in Et₂O, in the presence of *s*-BuLi-TMEDA, occurs adjacent to the phenyl group (Scheme 11). The addition of EtB(neop) is followed by TESOTf which allows the activation of the epoxide towards ring opening and the promotion of the 1,2-metalate rearrangement. Warming to room temperature and subsequent oxidation resulted in the formation of the 1,2-diol **64** bearing quaternary stereogenic centers in 95:5 er.



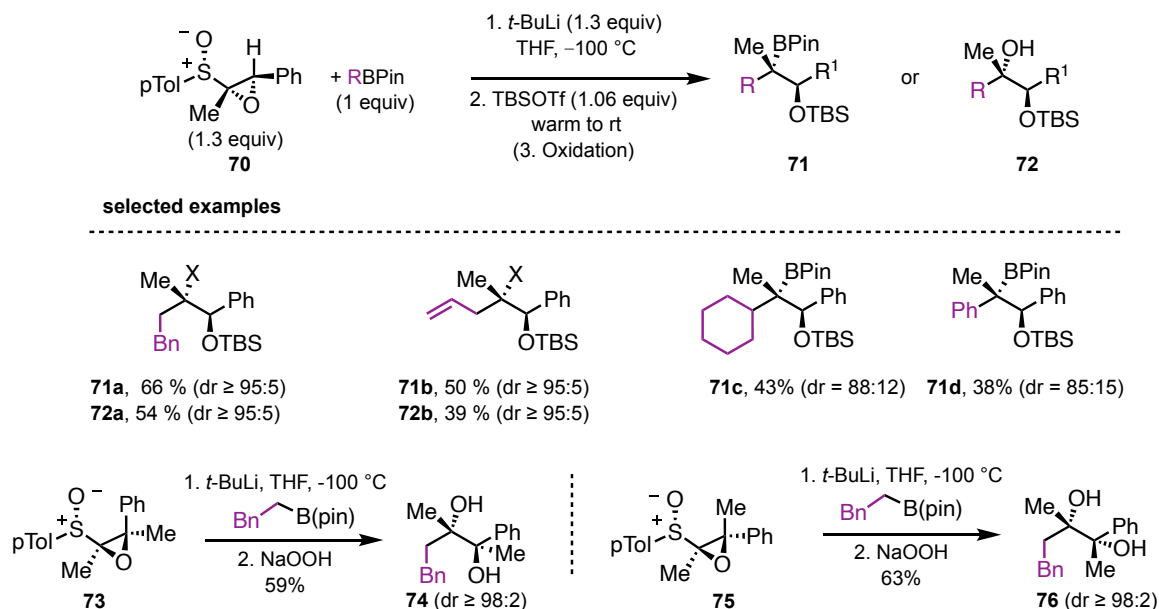
Scheme 11 Trapping of a boronic ester with lithiated styrene oxide

Similarly, functionalized trifluoromethyl-substituted tertiary boronic esters can be obtained by lithiation–borylation reactions of 2-trifluoromethyl oxirane **65** (Scheme 12).⁶³ After deprotonation with LDA at low temperature in the presence of the boronic ester, the intermediate boronate complex **66** undergoes, in the presence of TESOTf, the desired 1,2-rearrangement of the carbon-based group with complete retentive stereospecificity. It should be noted that, before the addition of the Lewis acid, a THF-toluene solvent exchange is carried out after the formation of the boronate. This protocol allows decreasing the proportion of the 1,2-O-migration of one of the pinacol oxygen atoms, which provides the corresponding boronic ester **69**. Starting with (1*S*)-trifluoromethyl oxirane, a range of primary or secondary alkyl, aryl, and heteroaryl boronic esters were transformed into the desired C-migration products **68** with excellent stereospecificity. Further transformations of the α -boryl group have been carried out such as oxidation or Zweifel olefinations which furnish trifluoromethyl-bearing quaternary stereocenters substituted with alkenes, alkynes, and ketones.



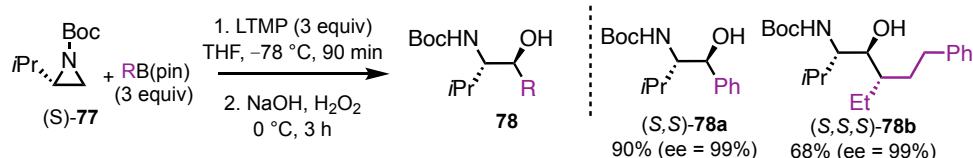
Scheme 12 Trapping of a boronic ester with lithiated 2-trifluoromethyl oxirane

A complementary approach has been developed using *cis*- or *trans*- mono-, di-, and tri-substituted sulfinyl epoxides, which can generate oxiranyl lithium anion by sulfoxide–lithium exchange (PhLi or *t*-BuLi, THF, at or below $-90\text{ }^{\circ}\text{C}$) (Scheme 13).⁶⁴ These carbenoids can be used in the stereospecific reagent-controlled homologation of boronic esters. This led, after the addition of *t*-butyldimethylsilyl triflate (TBSOTf) to the intermediate ate complexes, to the corresponding β -silyloxyboronates **71** which were converted to vicinal diol monosilyl ethers **72** by oxidative treatment. This method has proven useful in providing intermediate tertiary boronates and $2^{\circ}/3^{\circ}$ and $3^{\circ}/3^{\circ}$ vicinal diols with generally obtaining *anti*-like stereodiads **74** from *cis*-sulfinyl epoxides **73**, whereas *syn*-like stereodiads **76** were obtained with *trans*-sulfinyl epoxides **75**. In contrast, with carbenoid precursors bearing α -H-atoms and giving to *cis*- and *trans*-2-substituted-3-lithiooxiranes, low yields of $2^{\circ}/2^{\circ}$ vicinal diols were obtained. This can be explained by deleterious proton transfer between the carbenoid and its precursor.



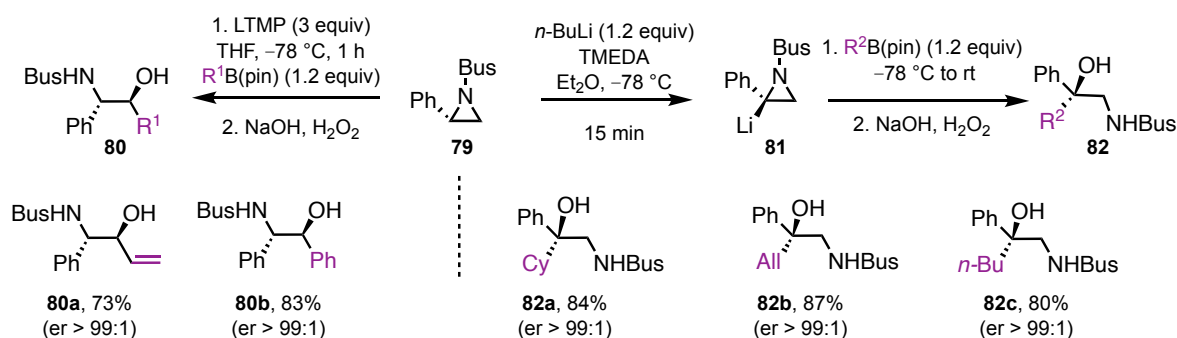
Scheme 13 Generation of the oxiranyl lithium anion by sulfoxide–lithium exchange

Diastereoselective formation of β -amino alcohols can be achieved by an approach similar to terminal epoxides (Scheme 14).⁶⁵ This involves the lithiation of terminal *N*-Boc aziridines with LMTP to the corresponding *trans*-lithiated aziridines which are trapped with boronic esters. 1,2-Metalate rearrangement followed by oxidation gives the corresponding *syn*-amino alcohol with complete selectivity and good yield.



Scheme 14 Formation of β -amino alcohols from terminal *N*-Boc aziridines

With aryl-substituted aziridines, the Boc protecting group has been replaced with a *t*-butylsulfonyl (Bus) group to avoid unwanted migration of the protecting group from nitrogen to carbon. The treatment of *N*-Bus aziridine **79** with LTMP in the presence of various aryl and vinyl boronic esters proceeds in the same way as previously giving *trans*-lithiated aziridines and consequently the formation of the corresponding 1,2-amino alcohols **80** (Scheme 15). On the other hand, with alkyl boronic esters the reaction leads to a mixture of regioisomers which results from a slow equilibration of the terminal lithiated aziridine towards the thermodynamically more stable benzylic lithiated aziridine **81** over time. However, the use of a less hindered base (*n*-BuLi, TMEDA) allows complete regioselective deprotonation at the benzylic position thus reversing the reaction's regioselectivity. In this case, the lithiation had to be carried out before the introduction of the boronic ester. After further addition of alkyl boronic esters, oxidation provided the tertiary alcohols **82** in high yield and full stereocontrol.



Scheme 15 Formation of β -amino alcohols from aryl-substituted aziridines

1.1.2.4-Chiral α -lithioalkyl carbamates and esters

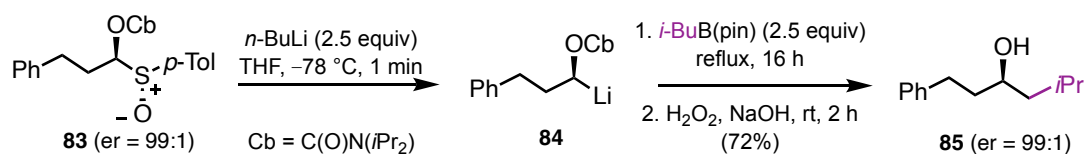
Chiral carbanions, generated from primary or secondary carbamate or benzoate, can also be employed in lithiation–borylation reactions. This methodology proved to be very efficient and has been used in a myriad of applications.⁶⁶

1.1.2.4.1 Primary carbamates or benzoates

Treatment of alkyl carbamates (*N,N*-diisopropyl)carbamate, Ocb) derived from primary alcohols by *s*-BuLi in the presence of (–)-sparteine allows the formation of configurationally stable chiral α -lithioalkyl carbamates.^{67, 68, 69} The intermediate carbenoid can be trapped with boranes or boronic esters that undergo 1,2-migration with inversion at the α -position. After an oxidation step, highly enantiomerically enriched secondary alcohols can be prepared. In the case of boronic esters, the 1,2-metalate rearrangement is much slower than for boranes and requires higher temperature and the addition of MgBr₂ in Et₂O to proceed. This methodology has been successfully applied to the total synthesis of natural products such as (*S*)-(–)-*N*-acetylcolchicol, ⁷⁰ (+)-faranal, ⁷¹ (–)-decastrictine D, ⁷² (+)-giganin and its C10 Epimer.⁷³

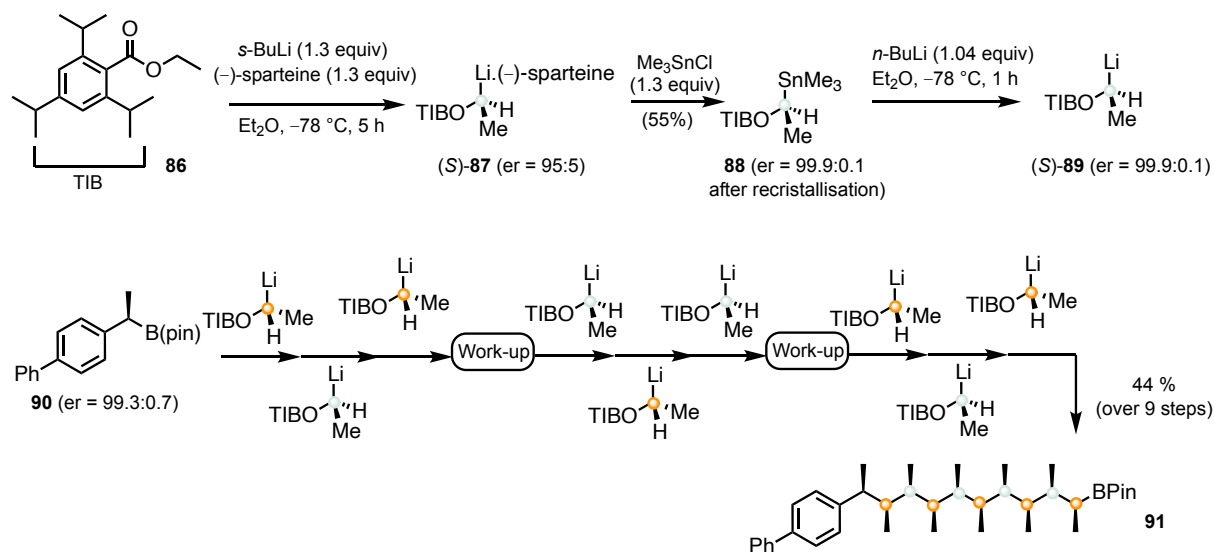
The possibility of obtaining a primary metallated carbamate was also described by O'Brien and involved the conversion of α -sulfinyl benzoates into lithium or magnesium carbenoids through sulfoxide–metal exchange (Scheme 16).⁷⁴ Treatment of **83** with *n*-BuLi (THF, –78 °C, 1 min) followed by reaction with *i*-BuB-pinacolate (reflux, 16 h) gave, after oxidation, the alcohol (*R*)-**85** in 72% yield and 99:1 er. Note

that with the corresponding magnesium carbamate intermediate, the homologation led to a slightly decreased yield (68%) and er (96:4).



Scheme 16 Obtaining and reaction of metallated carbamate from of α -sulfinyl benzoates

With particularly slow migrating groups (Me or (CH₂)₂CN), faster 1,2-metallate rearrangement has been obtained with the hindered 2,4,6-triisopropylbenzoate (TIB) in place of the (*N,N*-diisopropyl)carbamate.⁷⁵ Deprotonation of ethyl tri-isopropylbenzoate **86** was performed with *s*-BuLi/(–)-sparteine (Scheme 17). After treatment with Me₃SnCl, the α -stannyl ethyl benzoate **88** can be obtained in 99.9:0.1 er after recrystallization. The latter is an excellent precursor of enantioenriched α -lithiated benzoate **89** by reaction with *n*-BuLi with retention of stereochemistry. Additionally, both enantiomers are accessible on the multigram scale, using commercially available (+)- or (–)-sparteine. This method has been applied to the preparation of organic molecules that contain ten contiguous, stereochemically defined methyl groups by an iterative homologation process of **90** as exemplified in scheme 17.⁷⁶ Since the reactions are dominated by reagent control, no matched and mismatched effects are observed which allows different stereoisomers to be prepared with equal ease.



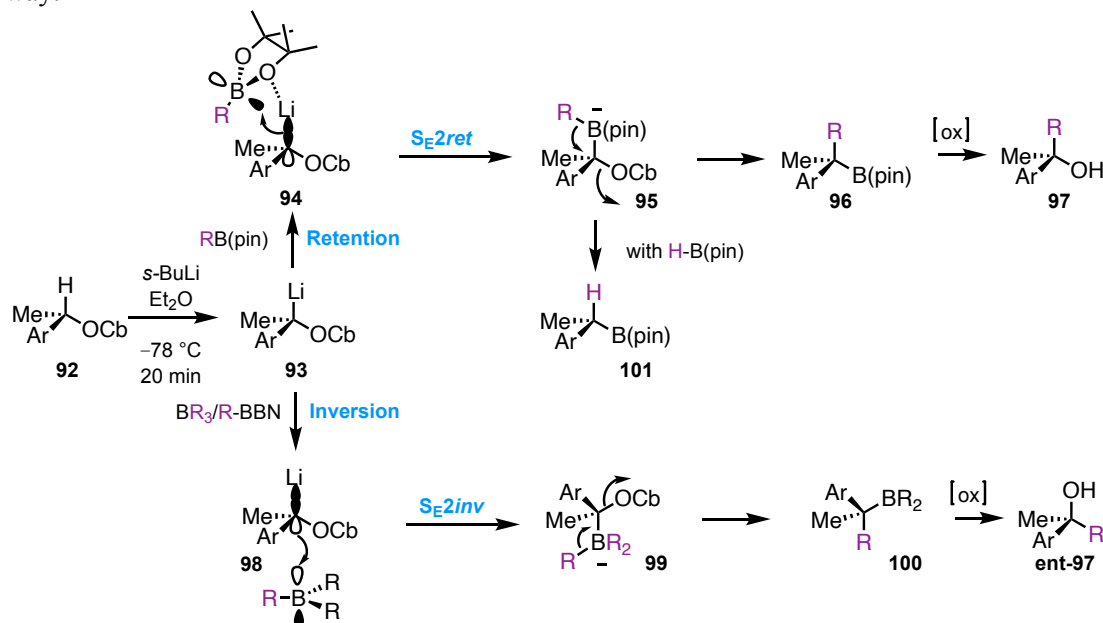
Scheme 17 1,2-metallate rearrangement with 2,4,6-triisopropylbenzoate and iterative homologation process

This type of methodology with enantiomerically enriched α -lithioalkyl benzoate has been exploited in the stereocontrol synthesis of the marine oxylin solandelactone F,⁷⁷ dysoxylactam A,⁷⁸ bastimolide B,⁷⁹ and (–)-rakacidin F.⁸⁰

More recently, the preparation of α -lithioalkyl benzoate has been reported from α -sulfinyl benzoates from sulfoxide–metal exchange.⁸¹ Using Barbier-like reaction conditions, lithium and magnesium carbenoids were prepared and reacted with a wide range of boronic esters allowing efficient and highly stereospecific homologation. With magnesium carbenoids, incorporation of sensitive functional groups (such as alkyl/aryl halides, azides, and esters) was possible while lithium carbenoids allowed reactions with sterically hindered substrates. This kind of strategy has been applied to a 14-step synthesis of the oxopolyene macrolide bahamaolide A with full stereocontrol.⁸²

1.1.2.4.2 Secondary carbamates or benzoates

Unlike primary lithiated benzyl carbamates, secondary lithiated benzyl carbamates are sufficiently configurationally stable at low temperatures to allow their use in lithiation-borylation reactions. Another difference from primary lithiated carbamates is that secondary lithiated benzyl carbamates react with retention with boron esters but inversion with boranes (Scheme 18).⁸³ Thus, boronic esters can complex the lithium atom of the lithiated carbamate **93** and are delivered on the same face as the metal (S_E2ret), while boranes cannot. In the latter case, the borylation occurs on the side opposite to the metal. Indeed, for benzylic substrates, due to mesomeric stabilization, the carbanion **98** is more trigonal, opening the space opposite to the metal and making this face less constrained. In the absence of mesomeric stabilization (non-benzyl carbamates), the anion is tetrahedral and therefore the side opposite the metal is hindered and the reactions almost always occur with retention. This methodology allows the preparation of both enantiomers of chiral tertiary alcohols **97** from the same secondary alcohol simply by changing the nature of the electrophilic boron. This process was applied to a broad range of carbamate and boronic esters including heterocyclic boronic esters. Note that with hindered boronic esters or with carbamates bearing electron-withdrawing substituents on the aromatic ring, an erosion in ee is observed.⁸⁴ This is the result of the dissociation of the intermediate boronate complex giving back the starting lithiated carbamate, a species prone to racemization on heating. However, using $MgBr_2/MeOH$ or neopentyl boronic esters in place of pinacol esters allows the elimination of this pathway.

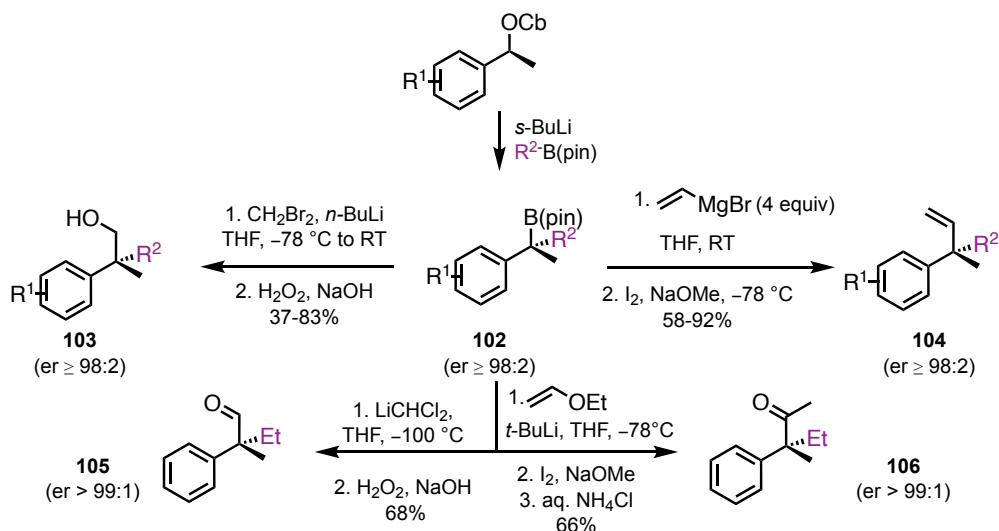


Scheme 18 Reaction of secondary lithiated benzyl carbamates with boron esters and boranes

Starting from primary or secondary carbamate or benzoate and using $H-B(pin)$ as borylated agent, hydride migration from borane–ate complex occurred. This led to the efficient synthesis of various boronic esters **101** with very high levels of enantioselectivity for secondary boronic esters.⁸⁵

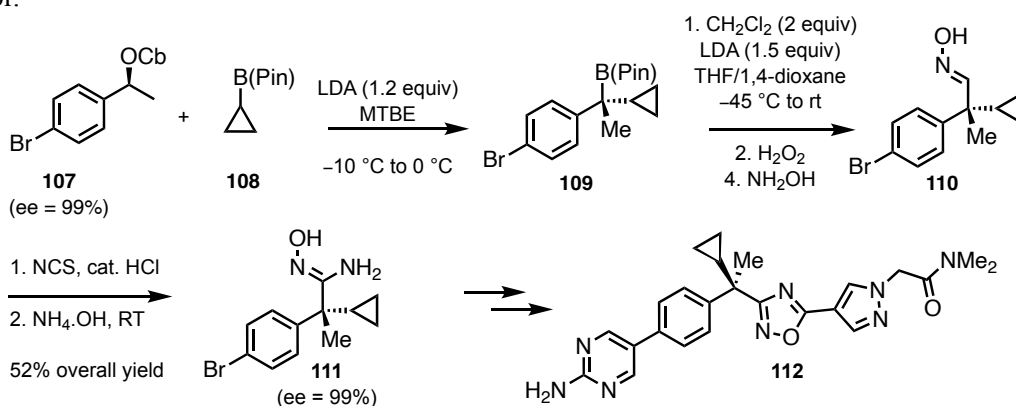
The lithiation-borylation of secondary benzyl carbamates allows the formation of tertiary boronic esters **102** which can further lead to compounds with chiral quaternary centers using C-based homologations (Scheme 19).^{86, 87} Indeed, tertiary boronic esters can be subjected to Matteson homologation using $LiCH_2Br$. With dialkylaryl boronic esters bearing electron-rich or electron-deficient aromatic rings and with substrates bearing an allyl substituent, the reaction was efficient in producing the desired homologated compounds **103** in good yield and high selectivity after the oxidation step. With tertiary boronic ester having a hindered substituent ($R^2 = iPr$), the reaction was more challenging and was carried out with neopentyl glycol boronic ester in place of the pinacol ester to obtain the desired adduct in 37% yield. This can be explained by a steric hindrance of the boronic ester which slows down the bromomethyl lithium addition to the boronic ester leading to the decomposition of the organolithium species.

Quaternary centers bearing a vinyl group are also accessible through Zweifel olefination⁸⁸ conditions with vinylmagnesium bromide followed by the addition of iodine and sodium methoxide. This protocol afforded the vinyolated product **104** with very high er values and good yields. It worth also to notice that enantiospecific alkynylation of boronic esters has also been described.⁸⁹ In addition, the chiral aldehyde **105** or ketone **106** could be obtained by reacting **102** with LiCHCl₂ followed by oxidative treatment or with ethoxy vinylolithium after a brief acid hydrolysis, respectively.



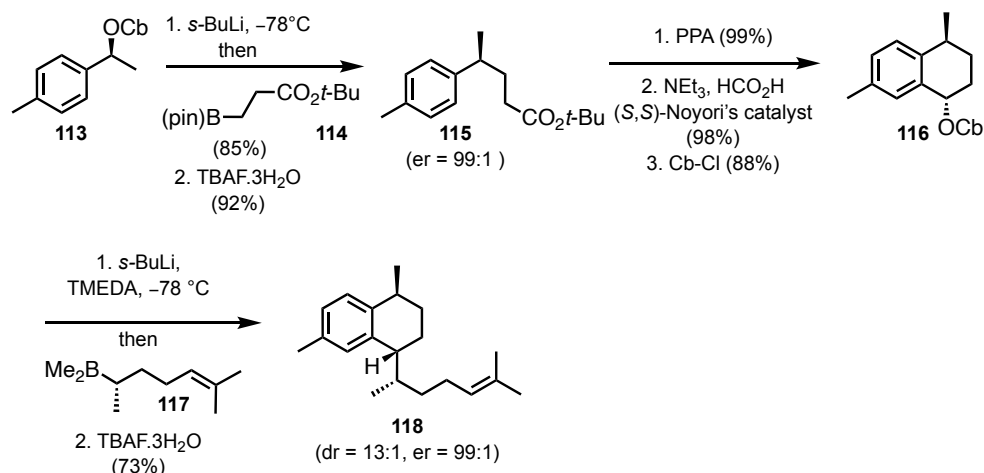
Scheme 19 Formation of chiral quaternary centers using C-based homologations

This powerful borylation-lithiation methodology followed by the stereospecific functionalization of a tertiary boronic ester has also been applied in the syntheses of pharmaceutical compounds such (+)-sertraline, (+)-indatraline,⁹⁰ (+)-igmesine⁹¹, escitalopram⁹², (*R*)-tolterodine⁹³. In 2015, Fandrick *et al.* reported the development of an asymmetric synthesis of a chiral quaternary FLAP inhibitor **112** involving a noncryogenic stereospecific boronate rearrangement (Scheme 20).⁹⁴ This process was made possible thanks to the replacement of *s*-BuLi with LDA as the base and an *in situ* trapping of the unstable lithiated carbamate with the boronic ester **108**. This step, giving the tertiary boronic ester **109**, has been scaled up to 24 kg. For the DCM formylation reaction, a similar procedure was carried out with **109**. The boronate rearrangement of the DCM anion process was temperature-controlled to prevent the overaddition of the DCM anion during the LDA addition at -45 °C in a THF/1,4-dioxane mixture. After oxidation of the crude chloromethylene intermediate with H₂O₂, the oxime **110** was formed in near quantitative yield. *N*-chlorosuccinimide (NCS) oxidation and treatment with NH₄OH led to the formation of the corresponding amido-oxime **111**, which provides access to the chiral quaternary FLAP inhibitor.



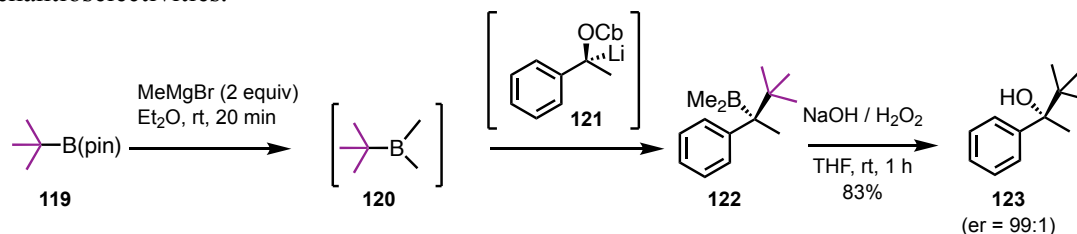
Scheme 20 Synthesis of a chiral quaternary FLAP inhibitor involving noncryogenic boronate rearrangement.

Access to natural products has been also described with the synthesis of a series of sesquiterpenes (bisabolane family,⁹⁵ (-)-aplysin,⁹⁶ (-)-filiformin,⁹⁷), the sesquilignan tatanan A,⁹⁸ (+)-herbertene-1,14-diol⁹⁹ or the marine diterpene (+)-erogorgiaene.¹⁰⁰ In the latter case, a sequence of lithiation–borylation–protodeboration (with TBAF) applied to carbamate **113**, allowed to obtain ester **115** in excellent yield and high enantioselectivity (Scheme 21). Treatment with polyphosphoric acid (PPA) afforded the corresponding ketone, which was reduced by (*S,S*)-Noyori catalyst to obtain the corresponding *trans*-alcohol. After carbamoylation, the substrate **116** was engaged in a lithiation–borylation sequence. Unlike acyclic carbamate derivatives, low enantioselectivity was obtained with **116** in the reaction with boronic esters. However, with the unhindered and more reactive dimethyl borane **117**, the desired homologated borane yields (+)-erogorgiaene **118** (dr = 13:1, 44% overall yield) after *in situ* protodeboration.



Scheme 21 Application to the synthesis of (+)-erogorgiaene

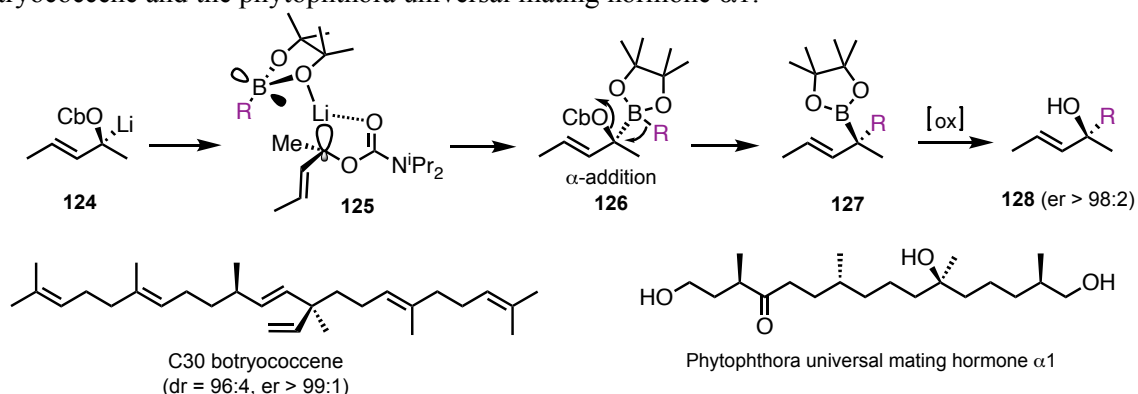
Note that no reaction is observed during the lithiation–borylation with the sterically hindered tertiary boronic ester *t*-BuB(pin) **119**.¹⁰¹ However, with the mixed borane *t*-BuBMe₂ **120** (obtained from the corresponding *t*-BuB(pin)), which is more electrophilic and has a lower barrier to 1,2-migration than boronic esters, the borylation of **121** proceeded well at low temperature with inversion of stereochemistry (Scheme 22). After subsequent warming to rt and oxidation of **122**, the tertiary alcohol **123** was obtained in high yield and very high enantioselectivity. Chemoselectivity for tertiary group migration was found to be very high with no methyl migration observed. The process was also applied to other mixed boranes (such as *i*PrBMe₂) and can be repeated two or three times in one pot leading to carbon chains carrying several contiguous quaternary stereogenic centers. In addition, boranes have been converted into tertiary alcohols or C-tertiary amines using chloramine with excellent diastereo- and enantioselectivities.



Scheme 22 Lithiation–borylation with the mixed borane *t*-BuBMe₂

The lithiation–borylation sequence can also be extended to secondary allylic carbamates since the corresponding lithiated species **124** are configurationally stable (unlike primary allylic carbamates) (Scheme 23). Usually, these species react with electrophiles leading to mixtures of α - and γ -addition products. However, with boronic esters, only high α selectivity was observed. This can be explained by initial coordination between the lithium-ion and the pinacol oxygen atoms, allowing the boron reagent to be delivered to the same site as the metal (α -selectivity) and on the same face (*S_E2ret*).¹⁰² These

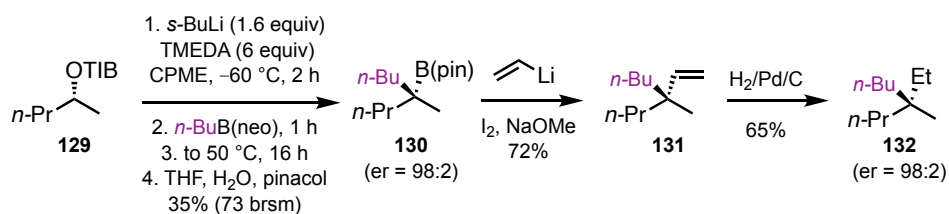
properties have been exploited in the stereoselective syntheses of each of the diastereoisomers of C30 botryococcene and the phytophthora universal mating hormone α 1.¹⁰³



Scheme 23 Lithiation-borylation with secondary allylic carbamates. Application to the synthesis of natural compounds

The scope of this useful method was later applied to propargylic carbamates leading to chiral tertiary propargylic boronic esters.¹⁰⁴ In this case, the reaction must be carried out with the least hindered ethylene glycol boronic ester to obtain a high er.

Secondary lithiated carbamates are usually restricted to substrates having a benzylic or an allylic position enabling deprotonation. However, successful deprotonation of secondary alkyl TIB esters has been reported (Scheme 24).¹⁰⁵ In this case, the lithiation occurred with the combination of *s*-BuLi and TMEDA in cyclopentyl methyl ether (CPME) at $-60\text{ }^{\circ}\text{C}$ and the carbanions were reacted with a range of neopentyl boronic esters. After 1,2-metalate rearrangement and oxidation, the reaction led to tertiary alcohols in high yield and high er. This methodology has been applied to the preparation of the simplest unbranched hydrocarbon bearing a quaternary center, (*R*)-4-ethyl-4-methyloctane **132**, showing the potential of this process. The synthesis started from the enantiomerically enriched TIB ester **129**, which was lithiated followed by a reaction of the intermediate anion with *n*-BuB(neo). After *in situ* transesterification with pinacol, the desired trialkyl-substituted 3 $^{\circ}$ boronic ester **130** has been obtained in 35% yield (73% brsm) and excellent er (98:2). The latter was then subjected to Zweifel olefination^{88, 106} (75%, er = 98:2) and hydrogenation (65%) giving **132** in four steps and thus ensuring the shortest and most selective synthesis of this molecule.



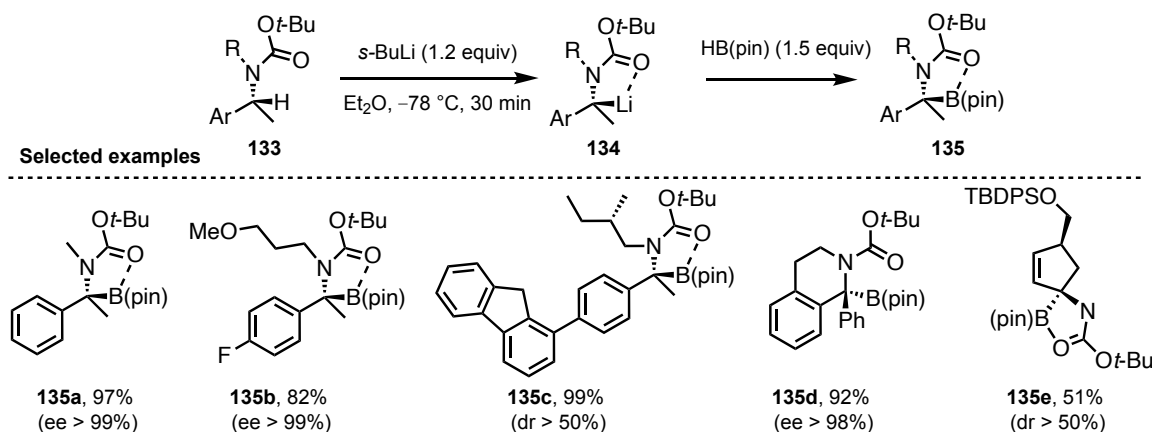
Scheme 24 Reaction of secondary alkyl TIB esters

1.2 Other methods for the preparation of α -chiral boranes and boronic esters

1.2.1 Borylation of configurationally stable *N*-substituted tertiary organolithium species

In 2018, Negishi and coll. reported the preparation of chiral α -amino tertiary boronic esters by a lithiation-borylation process of chiral amines (Scheme 25).¹⁰⁷ Deprotonation with *s*-BuLi in Et_2O at $-78\text{ }^{\circ}\text{C}$ of compound **133** having a *N*-Boc substituted amine, results in the formation of the configurationally stable organolithium species **134**. After trapping with pinacolborane (HB(pin)), enantiospecific borylation allowed the formation of a new stereogenic C-B bond. This reaction has been applied to a

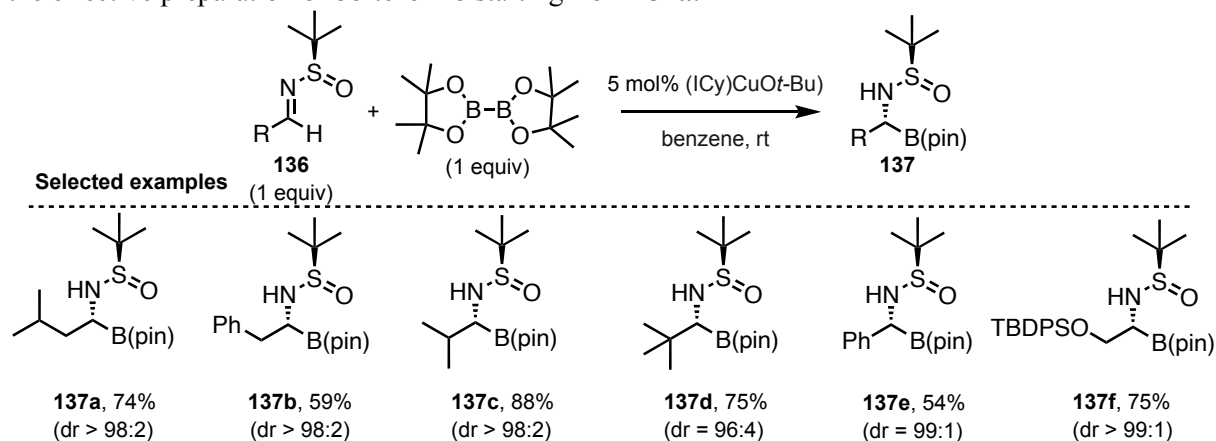
wide range of substrates, enabling the synthesis of various α -amino tertiary boronic esters **135** in excellent yields, excellent enantiospecificity (> 99% es), and complete retention of configuration.



Scheme 25 Preparation of chiral α -amino tertiary boronic esters by a lithiation-borylation process of chiral amines

1.2.2 Diastereoselective borylation of imine

In 2008, Ellman and coll. reported the asymmetric copper-catalyzed synthesis of α -amino boronate esters from *N*-*t*-butanesulfinyl aldimines (**136**) (Scheme 26).¹⁰⁸ The best conditions were found with bis(pinacolato)diboron ($B_2(\text{pin})_2$) using a catalytic amount of (1,3-dicyclohexylimidazol-2-ylidene)copper(I) *t*-butoxide ((ICy)CuOt-Bu) in benzene at room temperature. The reaction has been carried out on a wide range of *N*-*t*-butanesulfinyl aldimines **136** and led to the corresponding adduct **137** in a very high diastereomeric ratio. Moreover, the usefulness of this method has been demonstrated by the effective preparation of bortezomib starting from **137a**.



Scheme 26 Preparation of chiral α -amino boronic esters by diastereoselective borylation of imine

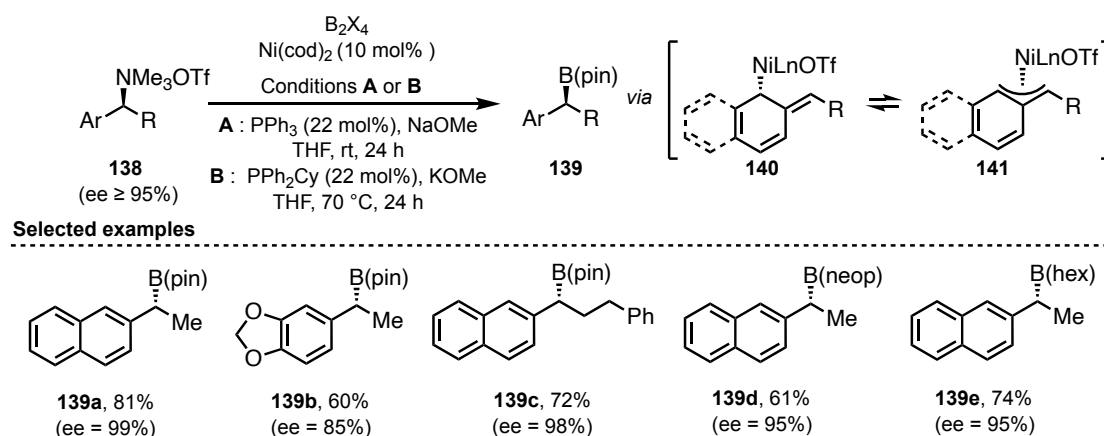
Later, the reaction was improved by modifying the electronic properties of the NHC catalyst.¹⁰⁹ By using benzimidazole-based NHC precursors, a simplified one-pot protocol without the use of a glovebox to isolate the catalytic agent was described and, with aromatic and aliphatic *N*-sulfinyl aldimine substrates, led to the asymmetric synthesis of α -aminoboronic esters with high selectivity. However, with ketimine substrates, the diastereoselectivity ratios dropped to around 70:30.

A further improvement was accomplished through the use of a Cu^{II} catalyst allowing the reaction to be carried with low catalyst loadings (1.2 mol %) on the benchtop in air at room temperature.¹¹⁰ This transformation was applied to the telescoped synthesis of α -sulfinamido trifluoroborates after treatment of the obtained α -amino boronic acid derivatives with KHF_2 in methanol. It should be noted that the

method has proven effective with *N*-*t*-butanesulfinyl ketimines providing access to the corresponding trisubstituted organoboron compounds in good to moderate yield and with good selectivity (dr > 95:5).

1.2.3 Nickel-catalyzed borylation of benzylic ammonium salts

Secondary naphthyl ammonium triflates **138** are able to react with bis(pinacolato)diboron ($B_2(\text{pin})_2$) in the presence of a nickel catalyst ($Ni(\text{cod})_2$) combined with triphenylphosphine as a ligand and with sodium methanolate in THF at room temperature (Scheme 27, conditions A).¹¹¹ Under these conditions, the borylation proceeds with an inversion of the configuration leading to the corresponding boronate products **139** in good yields and excellent ee. Air-stable $Ni(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ can also be used, allowing reaction on the bench and obtaining the product with a slight decrease in yield. The reaction can be performed with a variety of naphthyl ammonium triflates but also with alternative diboranes such as bis(neopentylglycolato)-diboron ($B_2(\text{neop})_2$) and bis(hexylene glycolato)diboron ($B_2(\text{hex})_2$).



Scheme 27 Preparation of chiral boronic esters by nickel-catalyzed borylation of benzylic ammonium salts

On non-naphthyl substrates, the borylation reaction requires the use of a more electron-rich ligand (PPh_2Cy) and a higher temperature ($70\text{ }^\circ\text{C}$) with $KOMe$ as base for the reaction to proceed (Scheme 27, conditions B). In this way, benzylic boronates have been obtained in synthetically useful yields and good ee's (ee = 85-86%). Mechanistically, the reaction can proceed via oxidative addition, which occurs in an S_N2' manner by attack of the nickel catalyst at the ortho carbon to generate nickel species **140** and/or **141**. These intermediates then undergo transmetalation and reductive elimination to provide an enantio-enriched benzyl boronate product.

2 Stereospecific functionalizations and transformations of α -chiral boronic esters

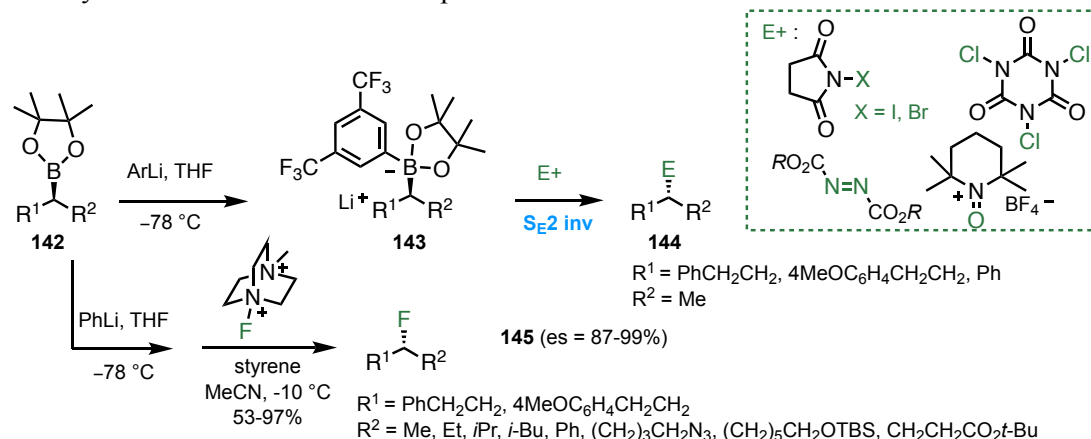
Secondary and tertiary boronic esters and boranes are very useful reagents.¹¹² They can undergo numerous stereospecific transformations such as oxidation, amination, protodeboration,^{113,100,114} non-transition-metal stereospecific arylation with electron-rich aromatic or *N*-heteroaromatic compounds^{115,116,117} or transition-metal-catalyzed couplings.^{118,119,120}

2.1 Carbon-heteroatom bond formation

The stereospecific oxidation of boronic esters, which furnished the corresponding alcohol with complete retention of configuration, is the most widely used functionalization. Stereospecific amination of alkylboronic acid pinacol ester⁹¹ is also possible as well as starting from trifluoroborates salts.¹²¹ In both cases, the configuration retention results from 1,2-metallate rearrangement that involves the migration of the C-B σ -bond into the oxygen or the nitrogen atom.

Another method of functionalization has been developed using boronate complexes as chiral organometallic-type reagents.¹²² Upon addition of an aryl lithium reagent such as 3,5-

difluorophenyllithium to chiral secondary boronic esters **142**, these derivatives lead to a boronate intermediate **143**, which behaves as a chiral nucleophile (Scheme 28). The latter could react with a range of electrophiles with inversion of stereochemistry and allow the conversion of the C-B bond into C-I, C-Br, C-Cl, C-N, C-O, with high levels of stereocontrol. The methodology can also be extended to preparation of fluorine compounds **145** thanks to the reaction of boronic esters with phenyllithium followed by reaction of the boronate complex with selectfluor II.



Scheme 28 Conversion of the C-B bond into C-I, C-Br, C-Cl, C-N, C-O, and C-F bond with inversion of stereochemistry

Using a similar strategy, allylboronate complexes can have increased nucleophilicity and react with a wide range of electrophiles (tropylium, benzodithiolylium, activated pyridines, Eschenmoser's salt, Togni's reagent, Selectfluor, diisopropyl azodicarboxylate, MeSX).¹²³ This method of allylic functionalization with very high γ -selectivity and essentially complete stereospecificity allows access to a broad array of functionalities such as the formation of quaternary stereogenic centers and to fluoro- and trifluoromethyl allylic groups.

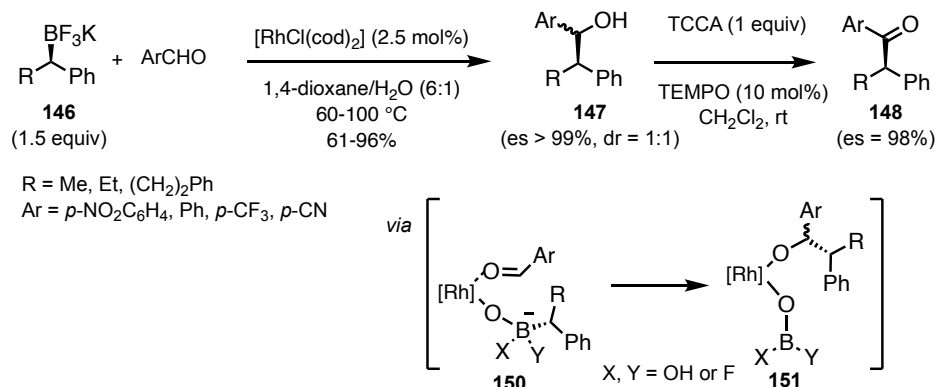
2.2 Carbon-carbon bond formation

As seen in **Section 1**, C-based homologation is one of the greatest methods to functionalize a boronic ester. In addition, boron reagents can react with aldehyde and iminium ions as well as by cross-coupling reaction. The allylation reaction will be covered further in **Section 3**.

2.2.1 Reaction with aldehyde, imine and iminium

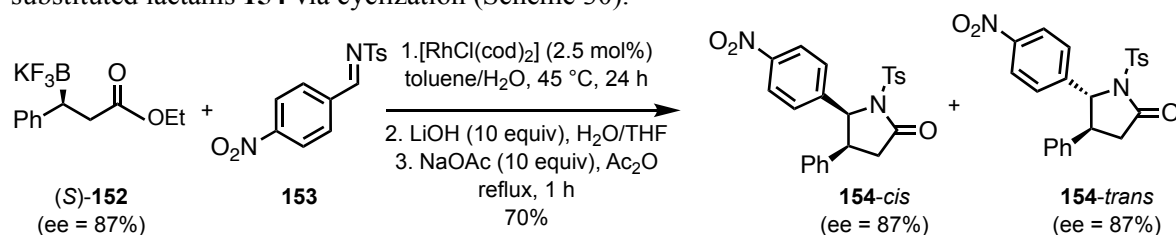
Benzylic boronic esters were found to react with aldehydes in the presence of $[\text{RhCl}(\text{cod})_2]$ or directly with CsF but substantial racemization was observed in both cases.¹²⁴ However, using the parent benzylic trifluoroborate salts **146**, the addition to aldehydes in the presence of a catalytic amount of $[(\text{RhCl}(\text{cod})_2)]$, allows producing the corresponding alcohol **147** in high yield and stereospecificity (Scheme 29). The retention of configuration may be explained by the simultaneous coordination of the rhodium atom to both the aldehyde and the boron atom, which facilitates the carbon-carbon bond formation.

The reaction could be carried out with both secondary and tertiary benzylic trifluoroborate salts and the oxidation of the as-obtained alcohol with TEMPO-TCCA furnished the corresponding ketone **148** without stereocerosion.



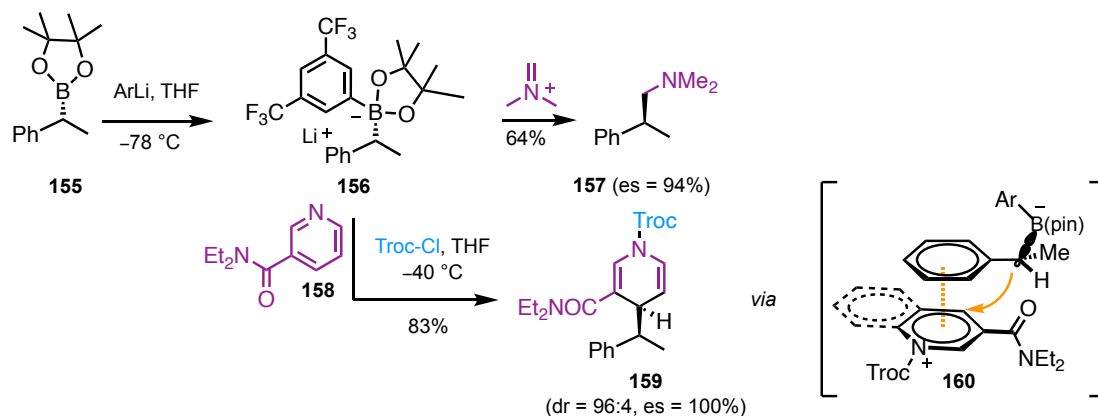
Scheme 29 Reaction of trifluoroborate salts with aldehydes

Later, the methodology was extended to the formation of enantiomerically enriched β,γ -diaryl-substituted γ -butyrolactones starting with β -carbonyl pinacol alkylboronates in the presence of KHF₂ as additive.¹²⁵ Rhodium-catalyzed addition of potassium β -carbonyl alkyltrifluoroborate salts to *N*-tosyl- or nosylimines has been also described as producing the γ -amino ester products in good yields as a mixture of *syn/anti* diastereoisomers.¹²⁶ With the enantiomerically enriched trifluoroborate **152**, the addition to imine **153** proceeded with excellent enantiospecificity and stereoretention without β -hydride elimination. In addition, under mild reaction conditions, the obtained adducts could be converted to β,γ -substituted lactams **154** via cyclization (Scheme 30).



Scheme 30 Reaction of trifluoroborate salts with imines. Application to the synthesis of β,γ -substituted lactams

Chiral boronate complex can also react with iminium ion to form C–C bond without loss of stereochemical integrity (Scheme 31). The reaction of **156** with the Eschenmoser's salt proceeds with inversion of stereochemistry and allows the formation of the corresponding tertiary amine **157** in 64% yield and 94% enantiospecificity (es).¹²⁷ The reaction of **156** is also described with the pyridine **158** activated in the presence of TrocCl (2,2,2-trichloroethoxycarbonyl chloride) to give the enantioenriched heterocyclic structure **159** with very high diastereocontrol over two contiguous stereogenic centers.¹²⁸ The high diastereoselectivity could be explained by from strong cation– π interactions between the cationic heterocycle and the electron rich boronate complex. This leads to the model **160** in which steric interactions between substituents on the ate complex and non-planar substituents on the heterocycle are minimized. Other cyclic iminium ion such as quinolinium, and dihydroisoquinolinium can also be used as electrophiles.

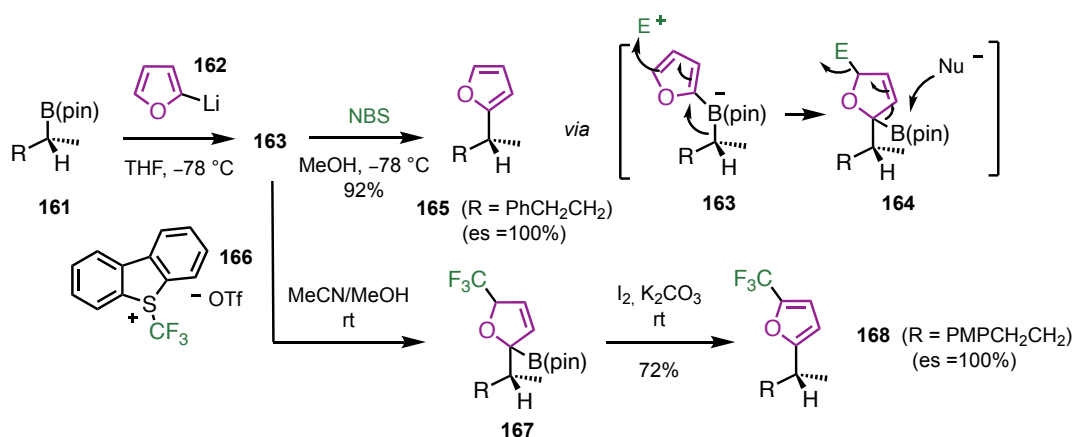


Scheme 31 Reaction of boronate complex with iminium ions

2.2.1 Stereospecific coupling reactions

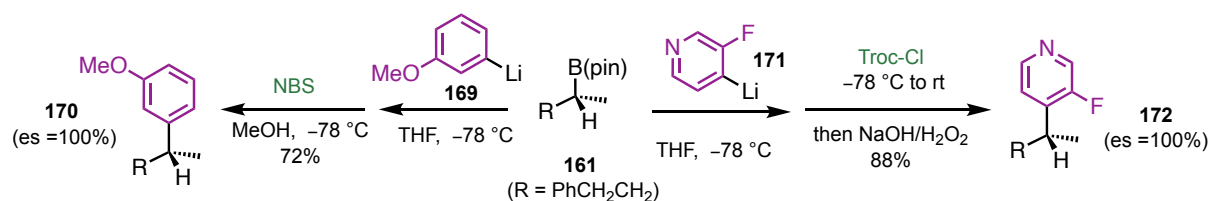
2.2.1.1 Transition-metal-free couplings

It was found that boronate complex **163** derived from boronic ester **161** and 2-furyllithium **162** can react with an electrophile (NBS) to give with retention of configuration the coupling adduct **165** in 92% yield and 100% es (Scheme 32).¹²⁹ The aromatic ring of the boronate complex is activated by the electrophile, which facilitates the desired 1,2-metallate rearrangement and gives **165** after rearomatization of **164**. The reaction was applied to a broad range of secondary and tertiary boronic esters with very different steric demands and bearing a range of functional groups. Other electron-rich heteroaromatics including pyrrole, indole, thiophene, benzofuran, and benzothiophene were also used efficiently. Using trifluoromethylsulfonium reagent such as the trifluoromethyldibenzothiophenium salt **166** (Umemoto's reagent), this methodology was further applied to a three-component coupling giving the corresponding 2,5-disubstituted furans **168**.¹³⁰ The process is believed to proceed via the reaction of the boronate complex **163** with a trifluoromethyl radical, which triggers 1,2-metallate rearrangement upon single-electron oxidation. The rearomatization occurs under oxidative conditions (K_2CO_3 , I_2), and forms the final product **168** with complete enantiospecificity.



Scheme 32 Transition-metal free couplings of boronate complexes with 2-furyllithium

The reaction was also extended to lithiated *m*-methoxybenzene **169** and *N*-heteroaromatic compounds such as **171**, which give respectively the coupling adducts **170** and **172** with high stereospecificity (Scheme 33).¹³¹ In the latter case, the nitrogen atom of the boronate was activated by acylation with Troc-Cl to facilitate the 1,2-metallate rearrangement.



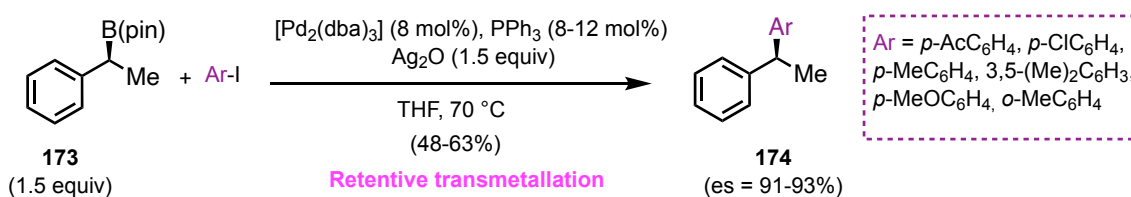
Scheme 33 transition-metal free couplings of boronate complexes with lithiated *m*-methoxybenzene and *N*-heteroaromatic compounds

2.2.1.2 Transition-metal-catalyzed stereospecific couplings of non-racemic boronic esters

Transmetalation of non-racemic organoboron compounds with transition metal complexes generates chiral active organometallic species, which can initiate entirely stereospecific C-C bond formation with retention or inversion.^{118, 132} The first class of chiral secondary boron-containing compounds successfully used in stereospecific Suzuki–Miyaura cross-couplings were the cyclopropyl-based organoborons. Indeed, for these compounds, which have cyclopropyl exocyclic bonds with partial p character, the process of transmetalation is easier. Additionally, these substrates are less prone to undergo β -hydride elimination minimizing the formation of by-products. Initial investigations on optically active substrates were reported by Deng and co-workers in 1998 starting from cyclopropyl boronic acids, which were obtained by substrate-controlled cyclopropanation of a boronic ester tartramide followed by hydrolysis.¹³³ Under palladium catalysis, a wide range of aryl bromides were investigated leading to the formation of the expected coupling adduct in high yield and retention of the absolute configuration. The reaction was also extended to vinyl triflates¹³⁴ and benzylic bromide for which glycol boronic esters must be used to obtain good results.¹³⁵ In 2000 similar results were obtained by Luthle and Pietruzka¹³⁶ and in 2003, Gevorgyan and co-workers reported the first stereospecific coupling of trisubstituted enantioenriched cyclopropyl boronic acids.¹³⁷

2.2.1.2.1 Enantioenriched secondary benzylic boronic esters

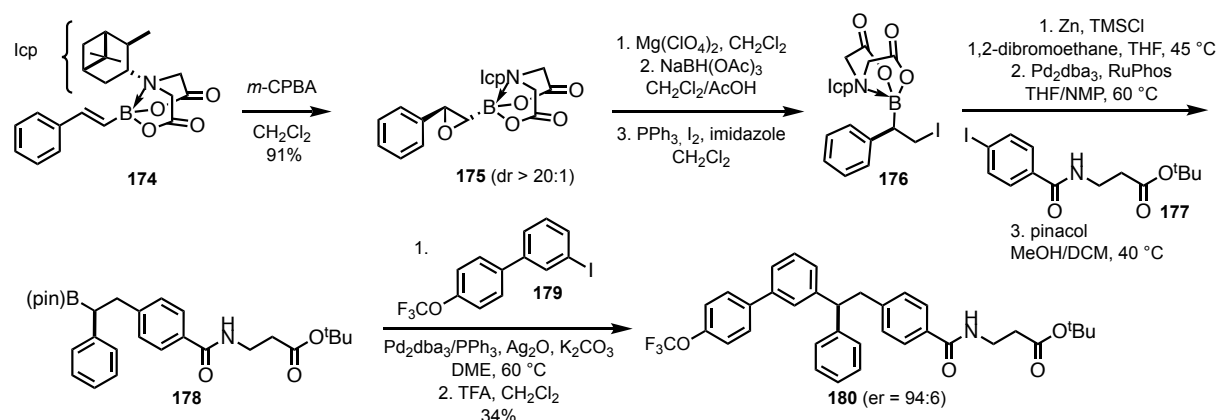
The first stereospecific coupling of enantioenriched secondary benzylic boronic esters with aryl halides was reported by Crudden and coworkers in 2009 (Scheme 34). The reaction was carried out with 1-arylethylboronic pinacol esters **173** and aryl iodides with $[\text{Pd}_2(\text{dba})_3] \cdot \text{PPh}_3$ as the catalyst and Ag_2O as the base. The reaction can be applied to electron-poor or electron-rich aryl iodides yielding the corresponding coupling adduct **174** with high enantioselectivity retention.



Scheme 34 Stereospecific coupling of enantioenriched secondary benzylic boronic esters

Later in 2014, the same group was able to extend the methodology to the preparation of triaryl methanes with almost complete retention of stereochemistry starting from enantiomerically enriched dibenzylic neopentyl boronic esters and a range of aryl iodide.¹³⁸ Moreover, the Crudden procedure could be applied to the preparation of **180**, a glucagon receptor antagonist (Scheme 35).¹³⁹ To this end, the vinyl PIDA boronate **174** was epoxidized with *m*-CPBA giving the corresponding oxiranyl PIDA (pinene-derived iminodiacetic acid) boronate **175** in high yield and diastereoselectivity. After a few steps of functionalization including a Meinwald rearrangement to the α -boryl aldehyde, reduction to the primary alcohol, an iodide exchange provided access to the B-protected haloboronic acid **176**. The latter was then transformed into its organozinc anion to undergo Pd-catalyzed cross-coupling with the aryl iodide **177**. The as-obtained adduct was then trans-esterified to the corresponding pinacol boronic ester **178** with complete stereoretention. Cross-coupling of this chiral boronic ester with aryl iodide **179** under

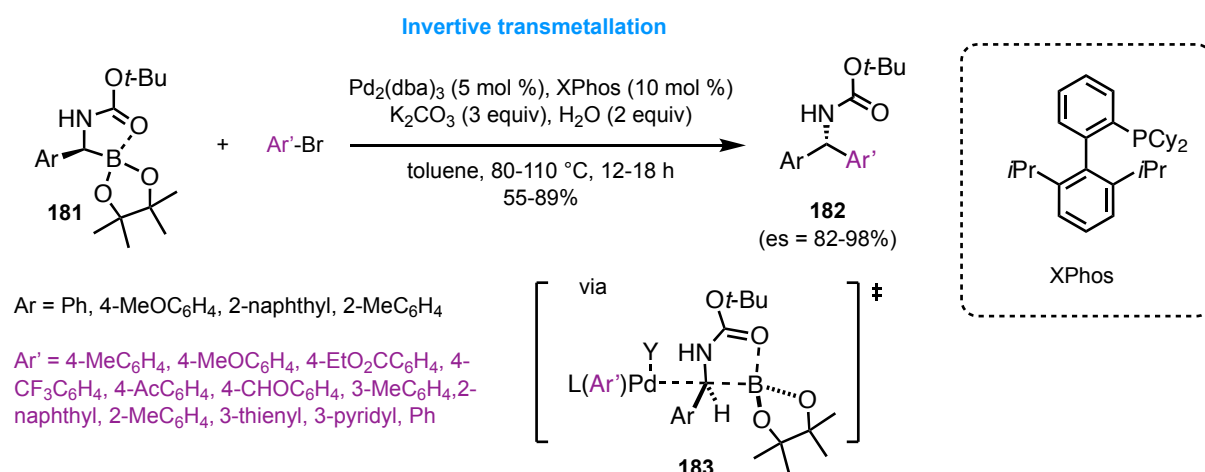
Crudden's conditions provided the corresponding coupling adduct in 94:6 er and the final desired compound **180** after TFA deprotection.



Scheme 35 Application of the Crudden procedure to the preparation a glucagon receptor antagonist

The utility of this methodology was also demonstrated for the enantioselective preparation of pharmaceutically relevant (R)-tolterodine (Detrol LA), used for the treatment of urinary incontinence.¹⁴⁰ In this case, the non-racemic chiral organoboronate precursor was constructed by a catalytic enantiotopic-group-selective cross-couplings of achiral geminal bis(pinacolboronates) in the presence of a chiral monodentate taddol-derived phosphoramidite ligand.

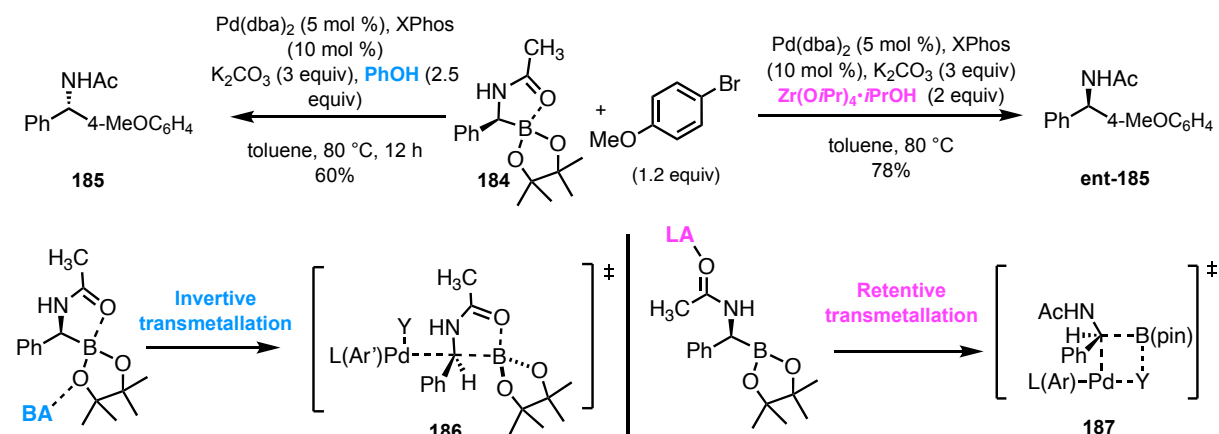
In 2010, the first example of a Suzuki–Miyaura cross-coupling proceeding with inversion of stereochemistry at the boron-bearing carbon atom has been reported (Scheme 36).¹⁴¹ In this case, α -(acylamino)benzyl boronic esters **181** were used as substrates and the selectivity was found to depend on the nature of the *N*-acyl group, the base, and the phosphine. With the use of the sterically demanding pivaloyl (Piv) group in combination with K_2CO_3 as the base and XPhos as the phosphine ligand, excellent yields and nearly perfect enantiopecificities with inversion of configuration have been obtained for **182** with a very wide range of functionalized aryl bromides, and both electron-rich and electron-poor heterocyclic bromides. To rationalize the stereochemical result, a mechanism involving transmetalation via the transition state **183** was proposed. This implies strong intramolecular coordination of the carbonyl group to the boron, which prevents an approach from the boron side by the occupation of the vacant boron p orbital.



Scheme 36 Suzuki–Miyaura cross-coupling of α -(acylamino)benzyl boronic esters with inversion of stereochemistry

Later it was discovered that the stereochemical outcome of this process could be controlled by the addition of Brønsted or Lewis acid additives giving access to invertive or retentive C–C bond formation (Scheme 37).¹⁴² Indeed, with phenol as an additive, very high levels of enantiospecificity with inversion

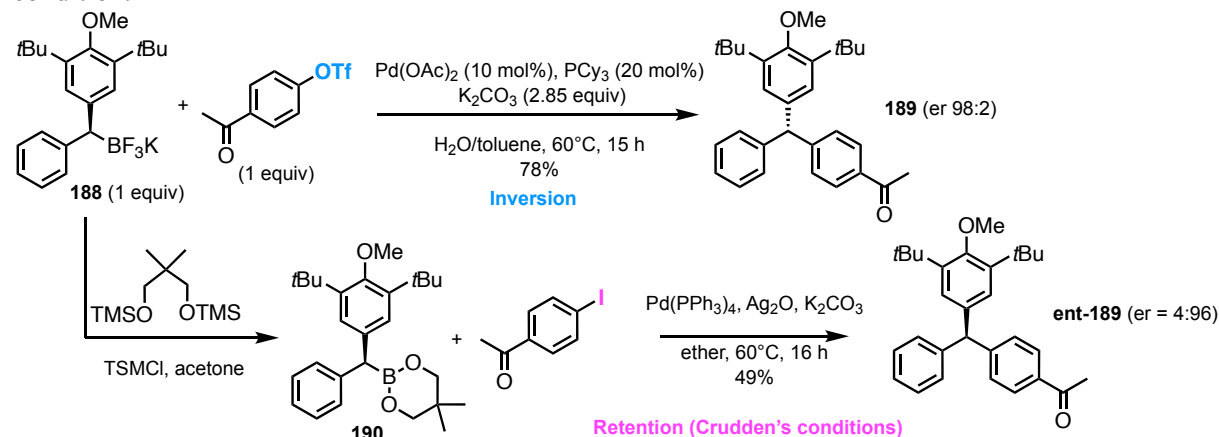
of configuration were obtained. Additionally, the reaction can be carried out with α -(acylamino)benzyl boronic esters **184** having an *N*-acetyl group. On the other hand, in the presence of $\text{Zr}(\text{O}i\text{Pr})_4 \cdot i\text{PrOH}$ as an additive, high enantiospecificity for retention of configuration was achieved.



Scheme 37 Suzuki–Miyaura cross-coupling of α -(acylamino)benzyl boronic esters with inversion or retention of stereochemistry

Phenol, which acts as a Brønsted acid (BA), protonates the pinacol group enhancing the intramolecular coordination of the carbonyl group to the boron. This would lead to the same type of amide-chelated transition state **186** as previously described and an inversion for the transmetalation step. In the case of $\text{Zr}(\text{O}i\text{Pr})_4 \cdot i\text{PrOH}$, the Lewis acid (LA) disrupts the coordination of the carbonyl group to the boron by competitive coordination with the C=O group of acetamide. This would form tricoordinate boron species, which can undergo transmetalation via a four-membered cyclic transition state **187**. In this cyclic transition state, the electrophilic attack of the palladium atom on the same side as the boron atom results in the retention of the configuration at the boron-bonded carbon atom.

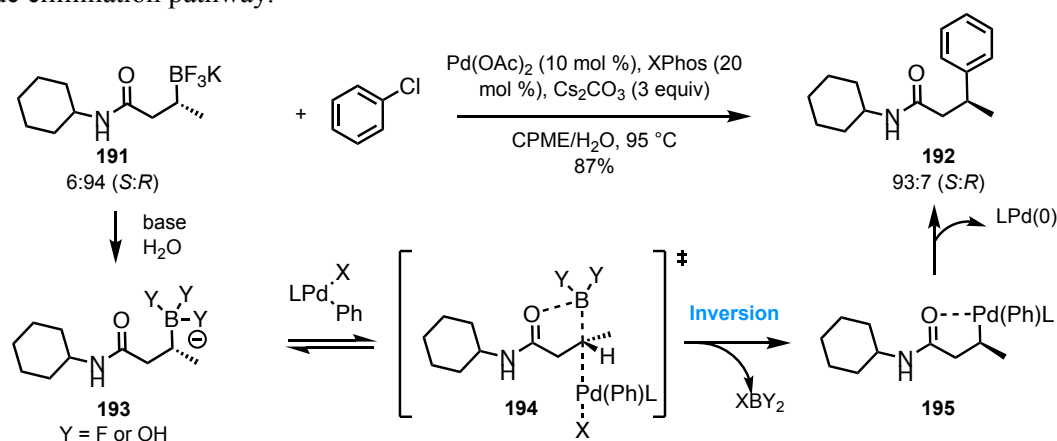
Another example of cross-coupling proceeding with inversion of stereochemistry has been reported by Liao and coworkers in 2015 during the preparation of triarylmethanes (Scheme 38).¹⁴³ In this case, the reaction was carried out on *gem*-diarylmethine trifluoroborates **188**, which were obtained after enantioselective copper-catalyzed 1,6-conjugate addition of bis(pinacolato)diboron to paraquinone methides. The dibenzylic trifluoroborates were able to react with aryltrifluoromethanesulfonates (ArOTf) in the presence of catalytic amounts of $\text{Pd}(\text{OAc})_2$ and PCy_3 under milder reaction conditions giving access to enantioenriched triarylmethanes **189** with high enantiospecificity and inversion of the configuration at the boron-bearing carbon atom. Note that the opposite stereochemistry was observed when coupling the dibenzylic neopentyl glycol boronic ester **190** with aryl iodide under Crudden's condition.



Scheme 38 Preparation of triarylmethanes by Suzuki–Miyaura cross-coupling with inversion or retention of configuration

2.2.1.2.2 Enantioenriched non-benzylic secondary alkyl boron compounds

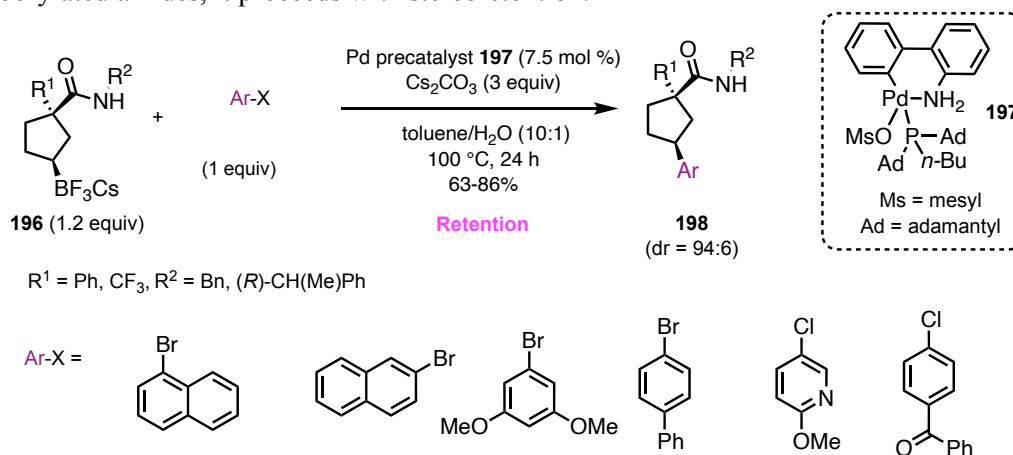
With respect to enantioenriched non-benzylic secondary alkyl boron compounds, which are more challenging than benzylic derivatives, the first stereospecific cross-coupling was reported by Molander and co-workers in 2010 with potassium trifluoroborate salts (Scheme 39).¹⁴⁴ In this case, an ancillary group (β -BF₃ amides) was introduced on the substrate **191** to coordinate the boron atom, assist the transmetalation step, and prevent the undesired β -H elimination pathway. Using the Pd(OAc)₂, XPhos, K₂CO₃ system, **192** has been obtained in good yield and nearly perfect enantiospecificities with inversion of configuration. The stereochemical outcome was rationalized by the ability of the ancillary carbonyl group to coordinate the boron atom, allowing transmetalation with inversion of configuration, presumably through an S_E2 mechanism via an open transition state **194**. In addition, the complexation constrains the conformation of the diorganopalladium intermediate **195** and does not allow the *syn*-coplanar arrangement of palladium and alpha acidic hydrogens to the carbonyl required for the β -hydride elimination pathway.



Scheme 39 Suzuki–Miyaura cross-coupling of enantioenriched non-benzylic secondary alkyl boron compounds

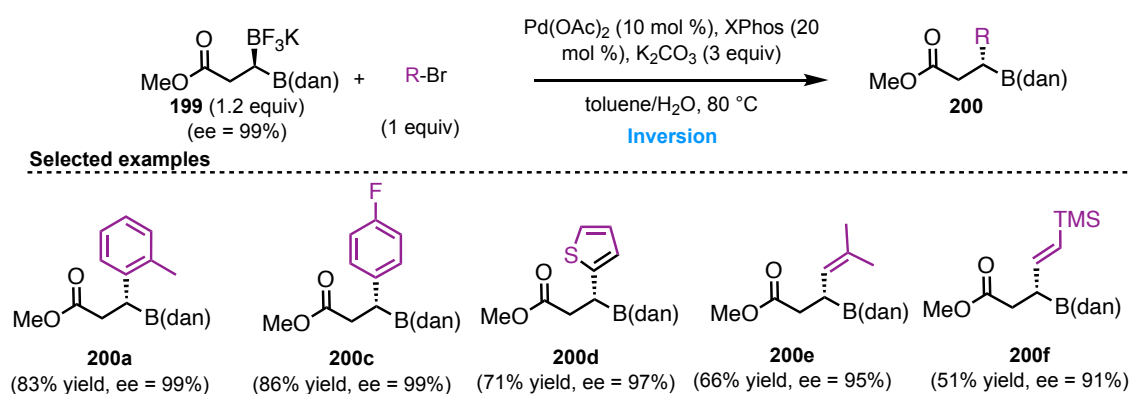
More recently, an efficient catalytic system (Pd/PCy₂Ph) has been described for the reaction of non-benzylic α -(acylamino)alkyl trifluoroborate salt compounds in Suzuki–Miyaura coupling with aryl halides.¹⁴⁵ The coupling proceeds with stereoinvertive transmetalation as proposed previously for the coupling of α -(acylamino)-benzylboronates leading to the expected adduct with high es.

The same type of coupling has been realized on cyclic substrates containing a chiral cesium trifluoroborate salt and a γ -phenethyl amide **196** (Scheme 40).¹⁴⁶ Using Buchwald's palladium-precatalyst **197**, the cross-coupling was found to be highly diastereoselective but unlike to examples with β -borylated amides, it proceeds with stereoretention.



Scheme 40 Suzuki–Miyaura cross-coupling of enantioenriched cyclic substrates having a chiral cesium trifluoroborate salt and a γ -phenethyl amide

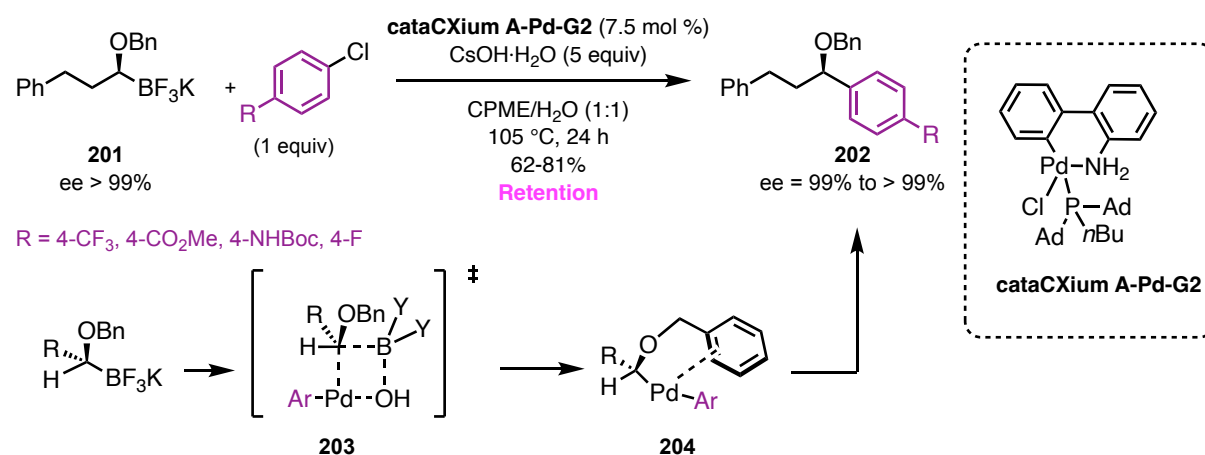
Similar to Molander's work, stereospecific coupling of enantiopure 3,3-diboronyl carboxy-esters compounds has also been reported (Scheme 41).¹⁴⁷ The chemoselective cross-coupling of the trifluoroborate salt **199** under Pd(OAc)₂, XPhos, K₂CO₃ system occurred stereospecifically to produce enantioenriched coupling adduct **200** with inversion of configuration. The reaction could be performed with electron-rich and electron-poor aromatics, heterocycles, and also with vinyl bromides leading respectively to benzylic or allylic boronates. The difficult transmetalation step of the Suzuki-Miyaura reaction is thought to be facilitated both by the internal oxygen coordination of the proximal carboxyester but also by a stabilizing effect of the second B(dan) boronyl unit.



Scheme 41 Stereospecific coupling of enantiopure 3,3-diboronyl carboxy-esters. B(dan): 1,8-naphthalenediaminoboryl

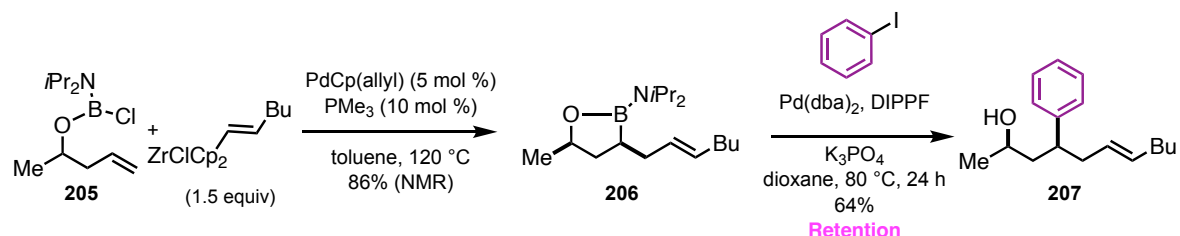
It is worth noticing that 1,1-diboraalkanes carrying a gem BF₃K-B(dan) moiety with no ancillary group can be engaged in Suzuki-Miyaura cross-couplings with retention of configuration.¹⁴⁸ Although the product was obtained in low yield and with a diminished ee value, this result shows the importance of the activating carbonyl group for the transmetalation process.

The chemoselective cross-coupling was extended to enantioenriched potassium 1-(benzyloxy)alkyltrifluoroborates **201** with a broad range of aryl chlorides (Scheme 42).¹⁴⁹ In this case, the reaction was carried out with the very active *cata*CXium A-Pd-G2 palladium source and CsOH·H₂O as the base in a 1:1 CPME/H₂O solvent mixture at 105 °C. In contrast to the previous couplings of β-amido or β-ester trifluoroborate salts, the coupling adducts **202** were formed with retention of configuration, which can be explained by a cyclic four-membered ring TS **203** resulting from the non-coordinating nature of the OBn. In addition, the use of the benzyl protecting group allows to stabilize the diorganopalladium intermediate **204** by coordination of the arene to the metal center and thus prevents the β-hydride elimination pathway.



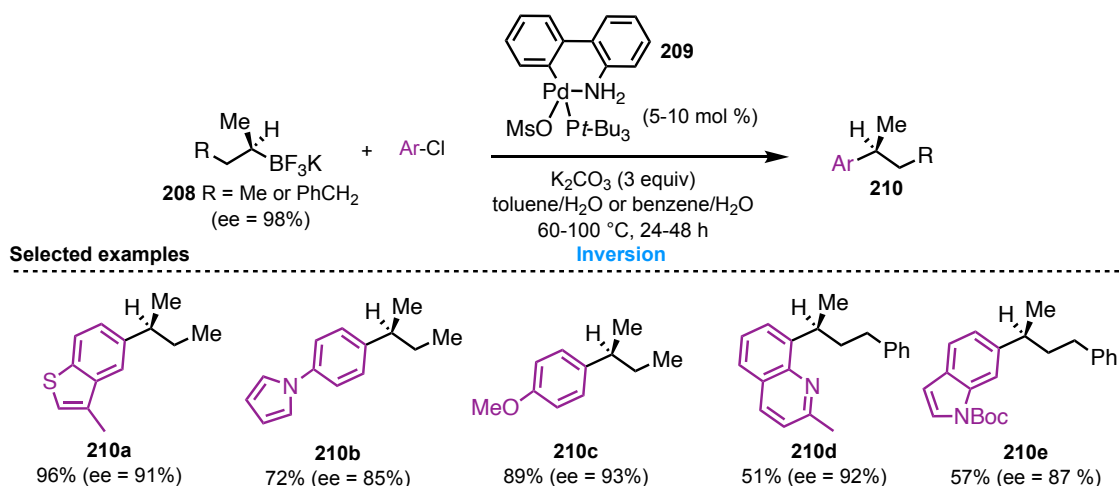
Scheme 42 Stereospecific coupling of enantioenriched potassium 1-(benzyloxy)alkyltrifluoroborates

The Suzuki-Miyaura cross-coupling has been also performed with 1,2-oxaborolane substrate **206**. The latter was obtained by palladium-catalyzed alkenylboration of carbon-carbon double bonds using the reaction of chloro(diisopropylamino)boryl ethers of homoallylic alcohols **205** with alkenylzirconium reagents (Scheme 43).¹⁵⁰ Treatment of the as-obtained adduct with iodobenzene in the presence of a palladium catalyst bearing diisopropylphosphinoferrocene (DIPPF) led to alcohol **207** with complete retention of configuration at secondary carbon atom bonded to boron.



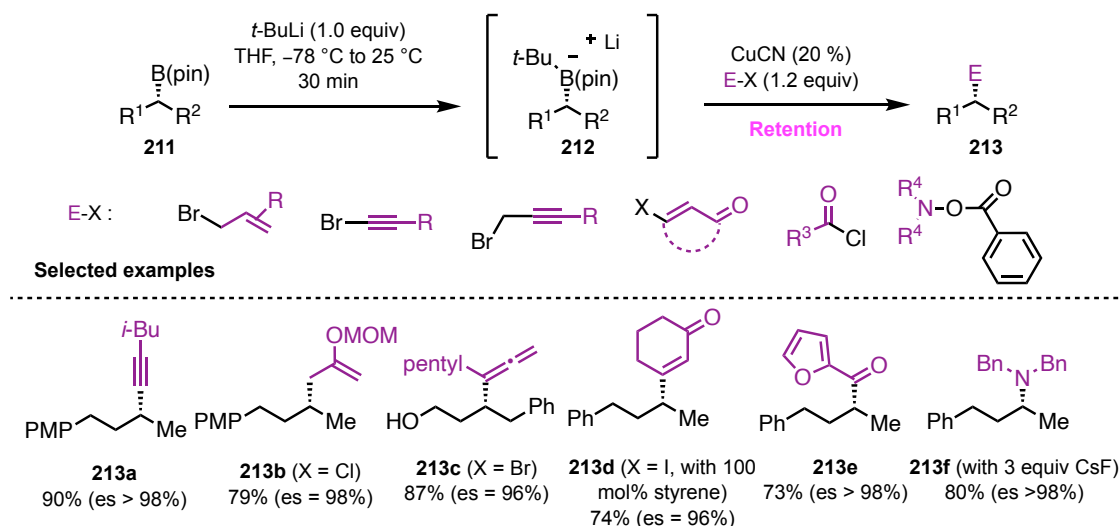
Scheme 43 Stereospecific coupling of 1,2-oxaborolane substrate

In the case of unactivated secondary alkyltrifluoroborates **208**, the transmetalation to Pd^{II} was found to proceed with inversion of the absolute configuration (Scheme 44).¹⁵¹ Employing a preformed *Pt*-Bu₃ palladium precatalyst **209** and K₂CO₃ as the base, the reaction resulted in the formation of the corresponding product **210** with slight erosion of enantiomeric excess.

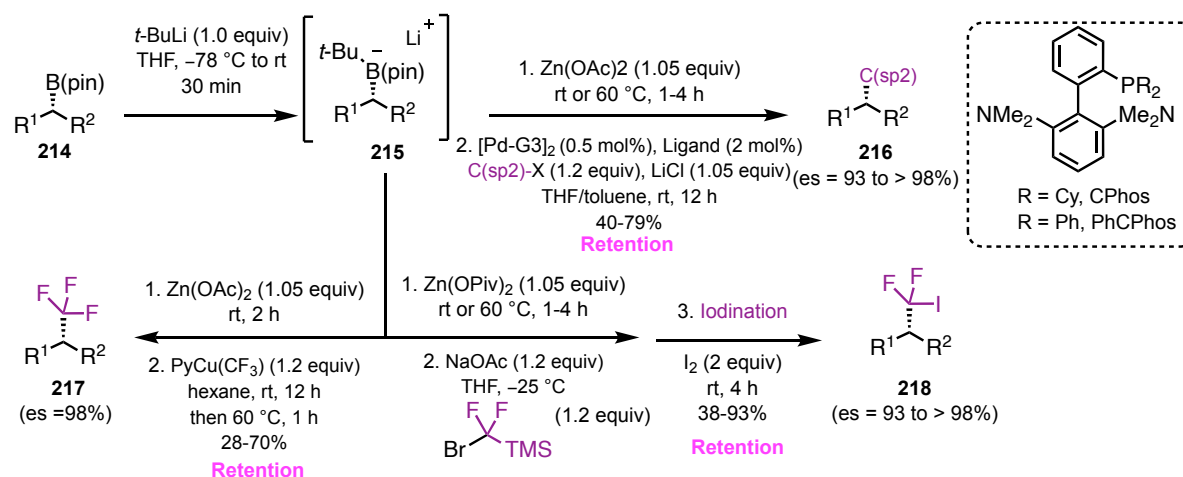


Scheme 44 Stereospecific coupling of unactivated secondary alkyltrifluoroborates

Very recently, a stereospecific cross coupling of boronic esters has been reported using copper catalysis (Scheme 45).¹⁵² After the reaction of pinacol esters **211** with *t*-butyl lithium, the obtained tetracoordinate boronate intermediate **212** can undergo a stereospecific transmetalation with copper cyanide. This was followed by coupling with a wide range of halides such as alkynyl bromides, allyl halides, propargylic halides, β -haloenones, hydroxylamine esters, and acyl chlorides with retention of configuration.



Additionally, treatment of the *t*-butyllithium-activated boronic ester **215** with zinc salts followed by subsequent addition of a palladium catalyst and an aryl halide electrophile provides the Negishi cross-coupling product (Scheme 46).¹⁵³ The enantiospecificity of the reaction proved to be dependent on the zinc salt used with the best results obtained with zinc triflate and zinc acetate. Reaction with zinc pivalate provided high specificity but only when the transmetalation was carried out for short reaction periods. Using Buchwald's [Pd-G3] complex in combination with CPhos or PhCPhos as ligands, efficient coupling reactions were observed with non-heterocyclic arene, alkene coupling partners or heterocyclic electrophiles. Organozinc intermediates have also been found to react with *in situ* generated difluorocarbene. This allowed the delivery of a difluoromethylzinc intermediate, which after iodinolysis produced difluoriodomethyl derivatives **218** with only a slight erosion of enantiomeric purity. Using a copper (III) complex, the trifluoromethylation of the organozinc intermediate also led to **217**.



2.2.1.2.3 Couplings of Secondary Allylic Boronic Esters

The coupling of chiral, non-racemic allylic organoboron species **219** with aryl iodides was first reported in 2013 by Aggarwal, Crudden, and coworkers (Table 1). Using two equivalents of PPh₃ relative to the palladium in the presence of Ag₂O in DME at 90 °C, the reaction proceeds with high retention of chirality giving access to the γ -regioisomer **220** as the major adduct. The geometry of the olefin is connected to the transfer of chirality giving the opposite enantiomer when starting from (*R,E*)-**219b** and (*R,Z*)-**219a**. Note that the (*Z*)-allylic boronates give the γ -products with high *E*-selectivity, while the (*E*)-allylic boronates give the γ -product with lower *E*-selectivity. Since the *E/Z* selectivity is governed by

the A^{1,3} strain between the R¹ and R² substituents during the conversion of **222** to **223** (Figure 3), the high *E*-selectivity is restored with compound **219c** having a more crowded *i*Pr substituent. The electronic effects relative to the aryl halide were also explored showing that all the aryl iodides gave the (*E*)- γ -product as the major adduct with high enantiospecificities but lower yields were obtained with electron-poor coupling partners.

Compound	γ/α	<i>E/Z</i>	Yield (%)	es (%)	Compound	γ/α	<i>E/Z</i>	Yield (%)	es (%)
	83:17	94:6	75	96		94:6	78:22	81	100
	92:8	99:1	71	100		98:2	99:1	78	100

Table 1 Coupling of chiral, non-racemic allylic organoboron species with aryl iodides

The retentive stereochemical outcome of the reaction was rationalized on the basis of a *syn*-S_{E'} transmetallation involving intermediate **222** with the B–O–Pd linkage, which leads to organopalladium intermediate **223** (Figure 3). The latter can subsequently undergo reductive elimination producing the γ -product. Later, unsymmetrical terminally disubstituted allylic boranes have been employed, leading to quaternary centers with high γ -selectivities and excellent enantiospecificities.¹⁵⁴

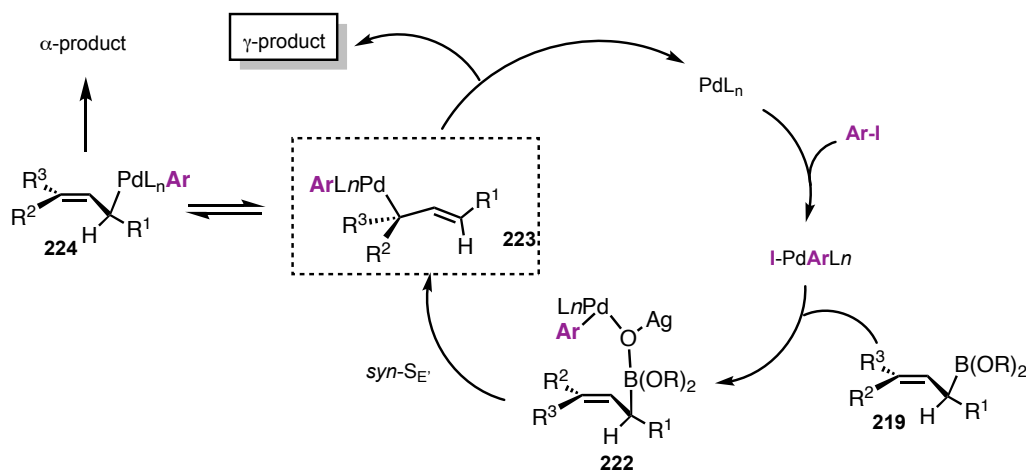
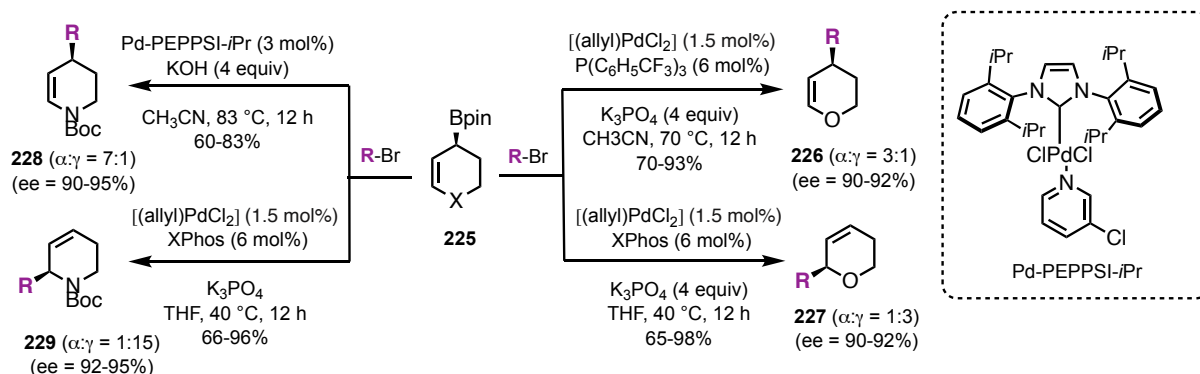


Figure 3 Proposed mechanism for the coupling of secondary allylic boronic esters

The cross-coupling of chiral enantiomerically enriched heterocyclic allylic boronates **225**, prepared by enantioselective borylation of achiral cyclic enol ethers and enamines, has also been reported (Scheme 47).¹⁵⁵ Depending of the ligand used, both regioisomeric 2- and 4-substituted dihydropyrans and dehydropiperidines have been obtained independently in high selectivity with a wide variety of aryl and alkenyl halides. When XPhos was employed as the ligand, high γ -selectivities have been obtained leading to the 2-substituted **227** and **229**. α -Selectivities could be obtained when the cross coupling of **225** (X = O) was carried out with the electron-poor ligand P(C₆H₅CF₃)₃ or with PEPPSI-type catalysts in the amine series.

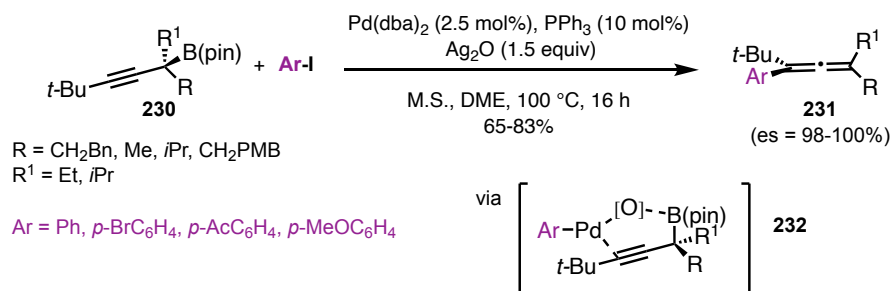


Scheme 47 Stereospecific cross-coupling of enantiomerically enriched heterocyclic allylic boronates

Similarly, this stereoretentive and regiodivergent Suzuki-Miyaura cross-coupling has been applied to a 2-ethoxy dihydropyranyl boronate substrate prepared by an enantioselective oxa[4+2] cycloaddition.¹⁵⁶ As before, the ligand allowed regioselectivity control and the α and γ products could be obtained independently with high optical purity, high regioselectivity and diastereoselectivity. Additionally, from the γ -adduct, a concise synthesis of diospongin B, a diarylheptanoid natural product exhibiting potent antiosteoporotic activity, was performed.

2.2.1.2.3 Coupling of tertiary propargylic boronic esters

Stereospecific cross-coupling reactions of enantioenriched tertiary propargylic boronic esters has also been reported (Scheme 48).¹⁵⁷ The reaction was carried with *t*-butyl-functionalized propargylic substrates **230** and aryl iodides with conditions similar to those developed by Crudden providing the desired tetrasubstituted allene products **231** in good yields and excellent enantiospecificities with retentive transfer of chirality. The palladium(II)-hydroxy-activated boronic ester **232** formed during the process may account for the stereochemical outcome of the reaction. These species can facilitate the transmetalation step through a favorable six-membered transition state structure leading to an allenyl palladium intermediate.



Scheme 48 Stereospecific cross-coupling of enantiomerically enriched tertiary propargylic boronic esters

3 Chiral allyl boron species from the chiral pool and application in synthesis

The asymmetric allylation reaction using allylmetal derivatives is a powerful tool for synthesizing chiral organic molecules.¹⁵⁸ Among the panel of allylmetal species which are available, boron-based reagents exhibit particular properties due to the possibility of controlling 1,3-metallotropic shift by tuning boron substituents and to the configurational stability of stereogenic carbon centers at the α -position of the boron. In addition, bench-stable allyl boron species can be prepared. Although introduced in the late seventies, chiral allylboron species have still been widely studied and used in the last decades. One of their main application resides in the stereoselective addition to carbonyl compounds and imines, but boron-based C–C cross-coupling reactions have also been explored (see part 2.2.1.2). A review on the preparation and application of allylboron species in organic synthesis was published by Szabó and Diner

in 2017,¹⁵⁹ following a book chapter by Ramachandran, Gagare and Nicponski in 2014.¹⁶⁰ A complete chapter untitled "Recent advances in the stereoselective additions of allylic boronates to carbonyl compounds" was also published by Clement and Hall in 2020.¹⁶¹ The main strategies for the synthesis of optically enriched molecules from allylboron species involve (i) the use of chiral allylboronates with chirality transfer, (ii) the reaction of achiral boronates with chiral electrophiles (e.g. carbonyl compounds), and (iii) asymmetric metal-based catalysis or asymmetric organocatalysis involving chiral ligands/catalysts. This present chapter focusses on the application of chiral allylboron species and is divided in two parts dedicated to chiral allylboron species bearing chiral auxiliaries and α -substituted chiral allylboron species. Particular attention is paid to new structures and recent trends/applications in synthesis over the last decade.

3.1 Allylboron species bearing chiral auxiliaries

3.1.1 Chiral allyl borons species with unsubstituted allyl moiety

Asymmetric allylation reactions using chiral allylboron species bearing chiral auxiliaries from the chiral pool on the boron atom, were initially reported by Hoffmann in 1978 using aldehydes as electrophiles.¹⁶² This method, which has been extended to various chiral auxiliaries, allows generating enantioenriched homoallylic alcohols with high enantioselectivity.¹⁶³ A review of boron-containing chiral auxiliaries was published by Pietruszka in 2017.¹⁶⁴ The main families of allylboron species with chiral auxiliaries are based on (+)-camphor, (+)- α -pinene, tartaric acid or amino-acid (norephedrin, valine) derivatives. Some representative examples are depicted in Figure 4.

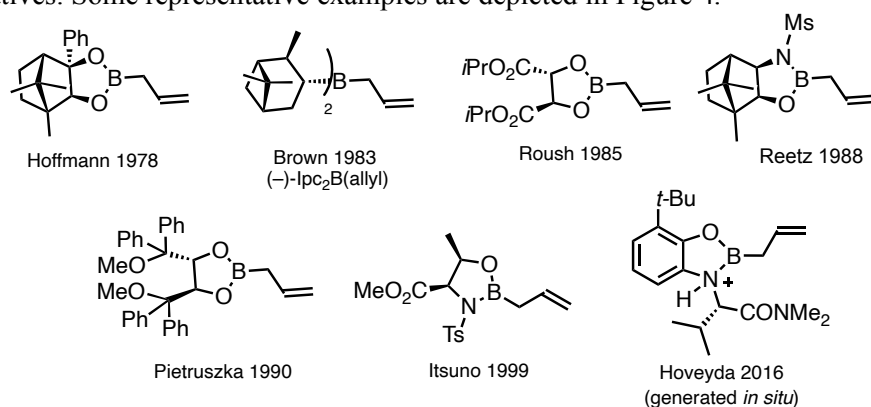
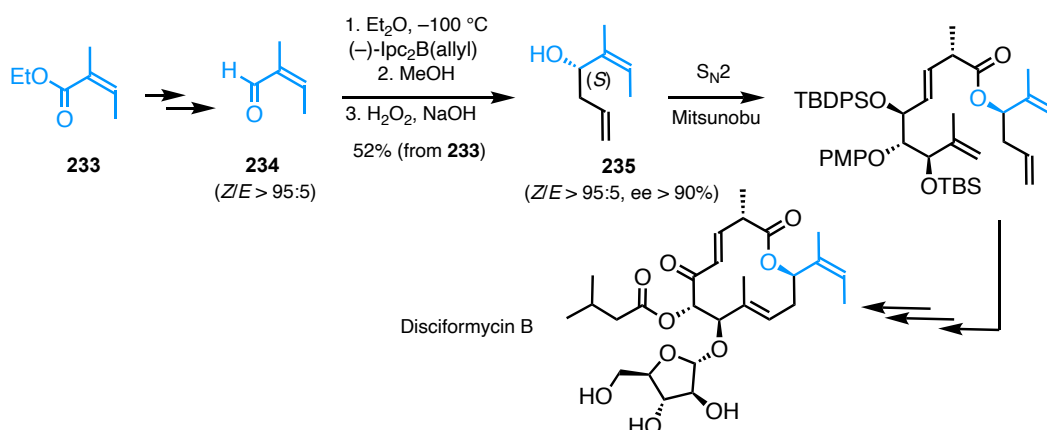


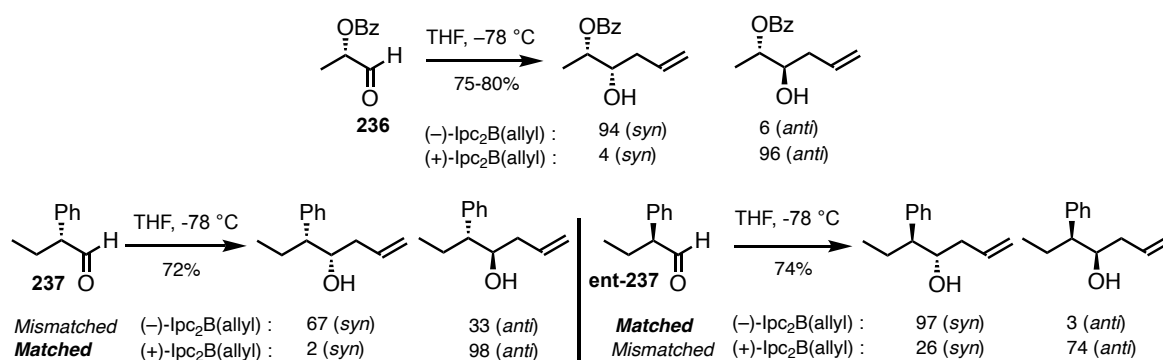
Figure 4 Examples of chiral allylboron species bearing chiral auxiliaries from the chiral pool

The most popular of them is likely the Brown reagent (allyl)diisopinocampheylborane [(Ipc)₂B(allyl)] which was initially reported to give homoallylic alcohols within 83-96% ee from aldehydes.¹⁶⁵ However, the facial selectivity is lower with ketones as electrophiles.¹⁶⁶ Both enantiomers (-)-(Ipc)₂B(allyl) and (+)-(Ipc)₂B(allyl) are commercially available and can be prepared from (Ipc)₂B(OMe), as initially described by Brown.^{166, 167} The Brown allylation reaction with (Ipc)₂B(allyl) has been extensively applied to total synthesis. This topic was reviewed by Passarella in 2021.¹⁶⁸ This review shows that the allylation method, even with a simple allyl fragment, is still widely used in the synthesis of complex molecules, as illustrated in the synthesis of (-)-cryptofolione by Prasad in 2021¹⁶⁹ or the synthesis of disciformycin B reported by Altmann in 2020 (Scheme 49).¹⁷⁰ In the latter case, the treatment of angelic aldehyde **234**, obtained in two steps from ester **233**, with (-)-Ipc₂B(allyl) at -100 °C gave the homoallylic alcohol **235** in 52% overall yield from **233**, with high enantioselectivity (> 90% ee) and without isomerization of the double bond (*Z/E* > 95:5). A more general review on total synthesis with boron species was published by Huang in 2020.¹⁷¹



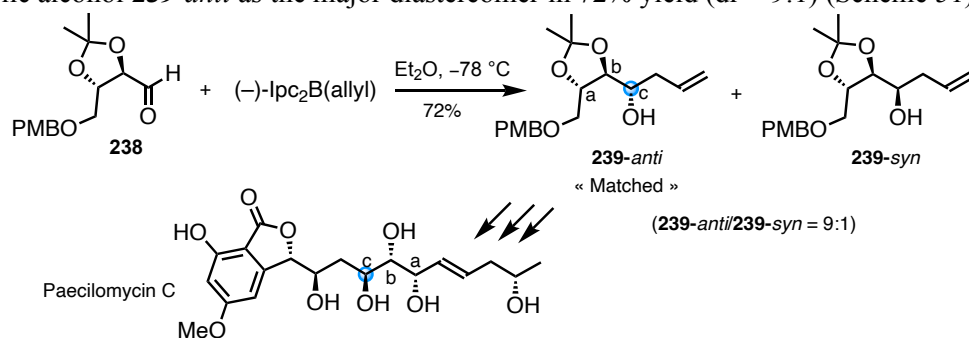
Scheme 49 Brown allylation and synthesis of disciformycin B, reported by Altmann in 2020.

When chiral aldehydes are employed, chiral allylborons species with simple allyl moieties such as Brown reagent (Ipc)₂B(allyl), react through matched or mismatched double asymmetric reactions.^{163, 167, 172, 173, 174} In most cases, the facial selectivity (i.e. the absolute configuration of the homoallylic alcohol) is highly controlled by the chiral allylboron reagent and can be reversed by switching from one enantiomer of Ipc to the other. In the case of α -chiral aldehydes, presenting the most important diastereofacial biases, secondary homoallylic alcohols can be obtained in excellent diastereoselectivities with (Ipc)₂B(allyl) reagents, as shown for aldehyde **236** (Scheme 50).^{163, 172, 174} Even in the case of aldehydes with bulky α -substituents such as α -phenyl aldehyde **237**, reagent control is predominant in the mismatched combination.



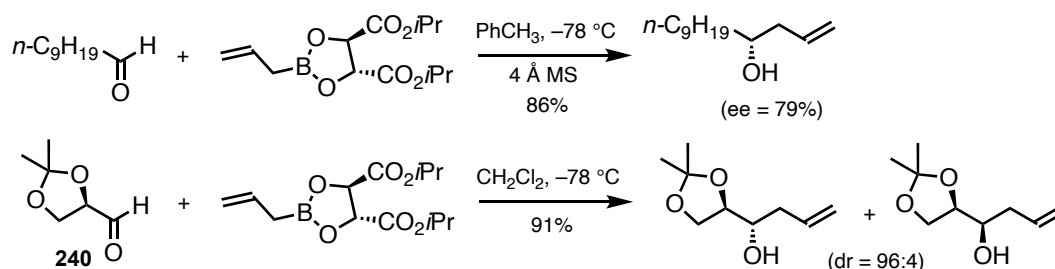
Scheme 50 Examples of selectivity of the Brown allylation with α -chiral aldehydes and matched and mismatched combinations.

Some applications in total synthesis have been recently reported, for instance in the synthesis of dysoxylactam A,¹⁷⁵ penicillinolide A¹⁷⁶ or paecilomycin C.¹⁷⁷ In the latter case, the stereogenic center c is controlled during the addition of the chiral reagent (-)-Ipc₂B(allyl) on aldehyde **238** giving homoallylic alcohol **239-anti** as the major diastereomer in 72% yield (dr = 9:1) (Scheme 51).



Scheme 51 Application of a "matched" combination in the Brown allylation reaction with a chiral aldehyde for the synthesis of paecilomycin C

Other chiral allylboron species which are derived from tartaric acid have been developed by Roush and coworkers.¹⁷² The as-formed allylboronate reagents present the advantage to be more stable than Ipc-based boron reagents and are purified by distillation. These reagents are associated with good facial selectivity,^{178, 179} although ee's are generally lower than with (Ipc)₂B(allyl) reagents. When α -chiral aldehydes such as **240** are used, the facial selectivity is mainly controlled by the chiral auxiliary as shown in Scheme 52.

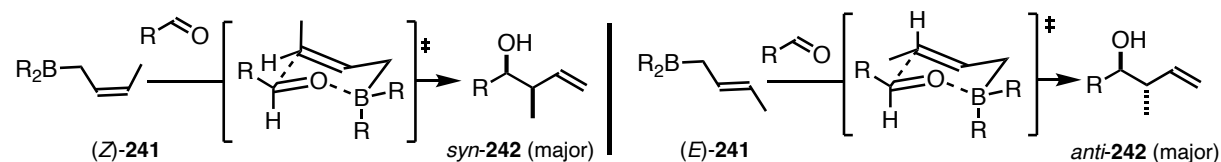


Scheme 52 Roush allylation of aldehydes with tartrate-based allylboronate reagents

3.1.2 Chiral allyl boron species with β - and γ -substituted allyl moieties

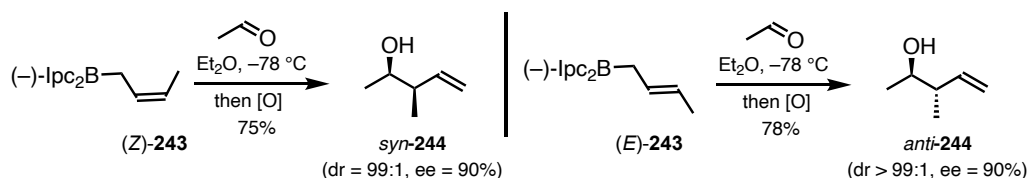
From the earliest studies, substituents have been introduced in the allyl moiety at the β and γ positions of allylboron species and the effect of the substituents on the stereoselectivity of the addition to electrophiles has been investigated. In more recent decades, efforts have been dedicated to the preparation and use of highly substituted and functionalized allylboron species to widen their application in (total) synthesis.¹⁸⁰ In particular, allylboration with γ,γ' -disubstituted allylboron species allows the generation of enantioenriched quaternary centers in organic molecules which is a major challenge in total synthesis. Furthermore, the development and use of chiral diboron species has also attracted significant interest.

Initially, Hoffmann demonstrated the high regio- and diastereoselectivity of the addition of crotylboron species (γ -substituted) to aldehydes.^{181, 182} This high selectivity was found to be predictable and dependent on the double bond configuration yielding the *syn*-adduct **242** as the major isomer from (*Z*)-allylboron reagent **241**, and the *anti*-adduct from (*E*)-**241**, respectively. A closed six-membered chair-like transition state was proposed by Denmark in 1983 to account for the high regio- and stereocontrol of the reaction (Scheme 53).¹⁸³



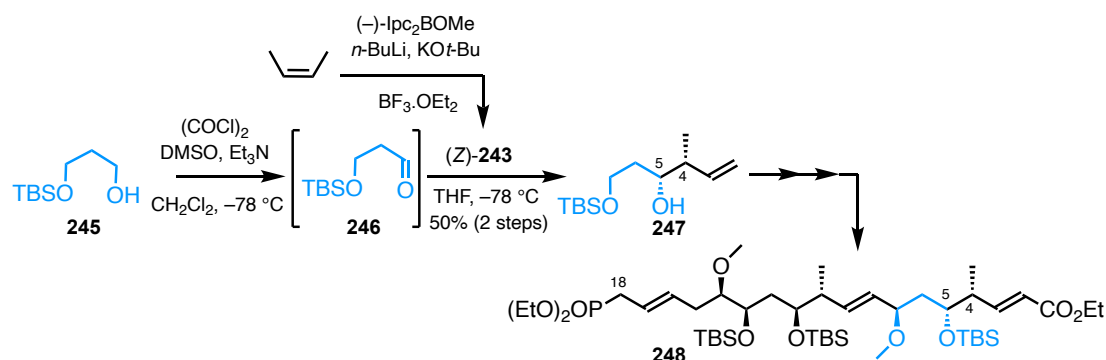
Scheme 53 Diastereoselectivity of the crotylation of aldehydes with crotylboron species

The use of chiral crotylboron species **243** with Ipc ligands was next reported by Brown in 1986. The reaction with *in situ* generated Ipc₂B(crotyl) reagents was found to give the corresponding homoallylic alcohols with high enantio- and diastereoselectivity upon addition to aldehydes. For instance, the reactions with acetaldehyde at low temperature led to allylic alcohols *syn*-**244** or *anti*-**244** with a dr of 99:1 and 90% ee (Scheme 54).¹⁸⁴



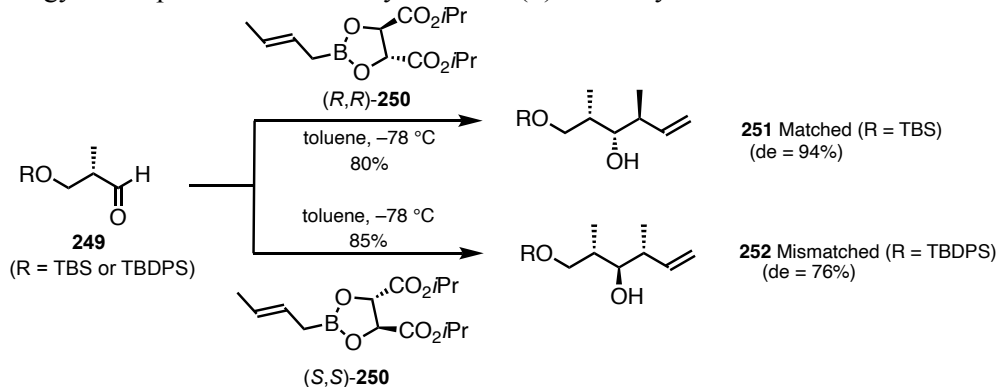
Scheme 54 Facial selectivity of the crotylation of aldehydes reported by Brown

Recent examples of the application of Brown crotylation reaction in total synthesis are found in the synthesis of solomonamide B,¹⁸⁵ dysoxylactam A,¹⁷⁵ or the C1-C18 fragment **248** of neamycin B (Scheme 55).¹⁸⁶ In this case, after a Swern oxidation of the primary alcohol **245**, the resulting aldehyde **246** was subjected to Brown *syn*-crotylation with (*Z*)-**243**, generated in situ from (*Z*)-but-2-ene and (–)-Ipc₂BOMe. This provided the secondary alcohol **247** within 50% yield in two-steps.



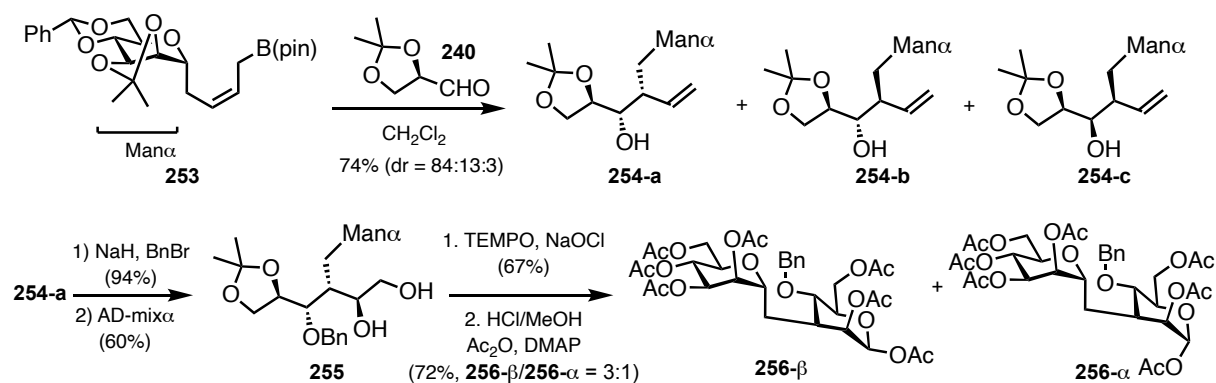
Scheme 55 Brown crotylation in the synthesis of the C1-C18 fragment of neamycin B

Diisopropyltartrate crotylboronate reagents **250** have also been developed by Roush.^{179, 187} The use of matched or mismatched combinations of boronates with chiral aldehydes such as **249** allows to generate stereotriades with control of absolute configurations (Scheme 56). As expected, the stereocontrol is lower in the mismatched combination, but gives a different stereotriade. A representative recent example of this strategy was reported in the total synthesis of (–)-bafilomycin A₁.¹⁸⁸



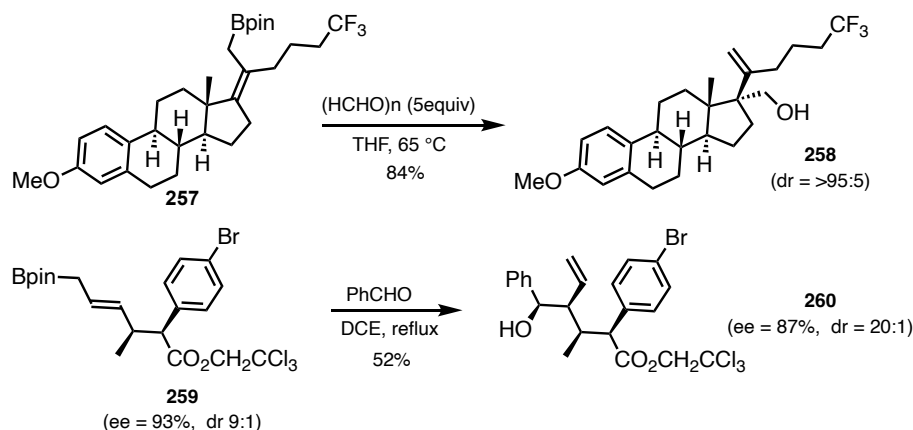
Scheme 56 Roush crotylation with chiral aldehydes

A double asymmetric induction involving an α -substituted chiral aldehyde and a chiral crotyl-type allylboronate **253** derived from α -mannose was reported by Mootoo in 2022.¹⁸⁹ The stereoselectivity of the allylboration of 2,3-*O*-isopropylidene-L-glyceraldehyde **240** which leads to a 83:13:3 ratio of three diastereomers could be increased in the presence of a chiral phosphoric acid catalyst. The reaction was exploited for the synthesis of biologically relevant *C*-manno-disaccharides **256** (Scheme 57).



Scheme 57 Preparation of *C-manno*-disaccharides from *C-glycosylcrotylboronates*

Furthermore, examples of allylation reactions with other types of chiral allylboron species which are structurally more complex, such as **257** and **259**, were reported (Scheme 58).^{190, 191} These reagents bearing chiral substituents at the γ -position led upon reaction with aldehydes to the target molecules **258** and **260** with high diastereoselectivity and controlled formation of quaternary and/or contiguous stereogenic centers.

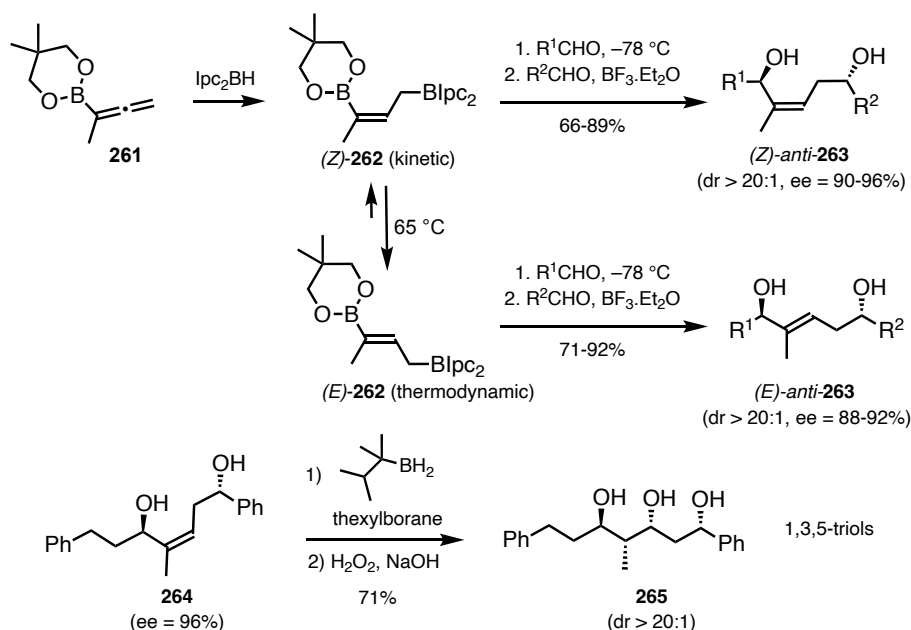


Scheme 58 Allylation of aldehydes with structurally complex chiral allylboron reagents

Note that some recent applications in synthesis described the use of achiral β,γ -functionalized allylboron species in combination with chiral aldehydes.^{192,191} These studies are out of the scope of this chapter.

3.1.3 Ipc-based chiral diboron species

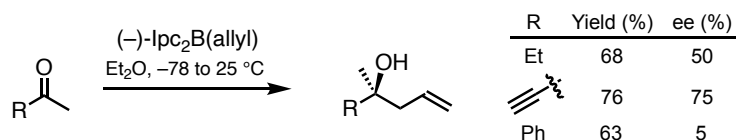
In 2002, Roush and coworkers reported a diastereo- and enantioselective synthesis of *syn* and *anti* 1,5-pentenediols based on the sequential reaction of a bifunctional allyldiborane reagent with two aldehydes.¹⁹³ This strategy was extended to the enantioselective synthesis of 2-methyl-1,5-*anti*-pentenediols via a hydroboration/double-allylboronation reaction sequence from boron-substituted allenes.¹⁹⁴ Upon hydroboration of 2-allenyl-(1,3,2)-dioxaborinane **261**, the selection of kinetic or thermodynamic conditions, allows the formation of either the (*Z*)-**262** or the (*E*)-**262** isomer, which react in double allylation reactions to give isomers (*Z*)-*anti*-**263** or (*E*)-*anti*-**263**, respectively, with excellent diastereoselectivity and enantiomeric excesses (ee = 88-96%) (Scheme 59). The diastereoselective hydroboration/oxydation of the as-obtained 1,5-diol **264** using thexylborane leads to the 1,3,5-triol **265** with excellent diastereoselectivity. These triols are useful structural motifs found in various natural products. In 2013, Roush's group reported the synthesis of *N*-acetyl dihydrotetrafabricin by using this strategy and three different double allylboronation reagents.¹⁹⁵



Scheme 59 Double allylboration reactions for the stereoselective synthesis of 1,5-diols and 1,3,5-triols reported by the group of Roush

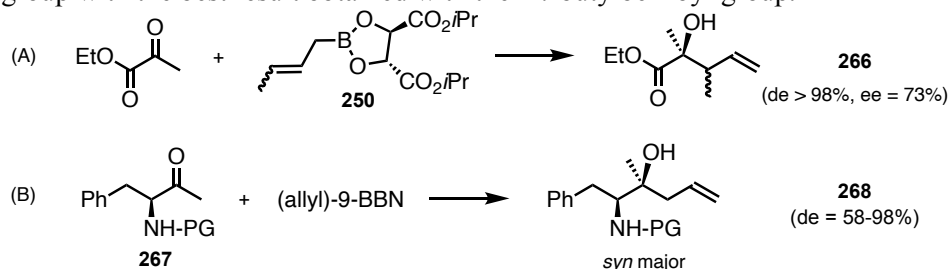
3.1.4 Allylation and crotylation of ketones.

The allylation of ketones is a general route to generate tertiary homoallylic alcohols with contiguous stereocenters, a structure which can be exploited for the total synthesis of various biologically active compounds. Compared to aldehydes, the allylation of ketones is more challenging and remains less developed.^{196, 197, 198} The stoichiometric allylation of ketones with allylboron species was initially shown to require higher temperatures than for aldehydes.¹⁹⁹ Chiral allylboron species from the chiral pool such as $\text{Ipc}_2\text{B}(\text{allyl})$ give lower enantioselectivity upon addition to ketones by comparison with aldehydes, as shown in Brown's study reported in 1986 (Scheme 60).¹⁶⁶



Scheme 60 Brown allylation of ketones and enantioselectivity

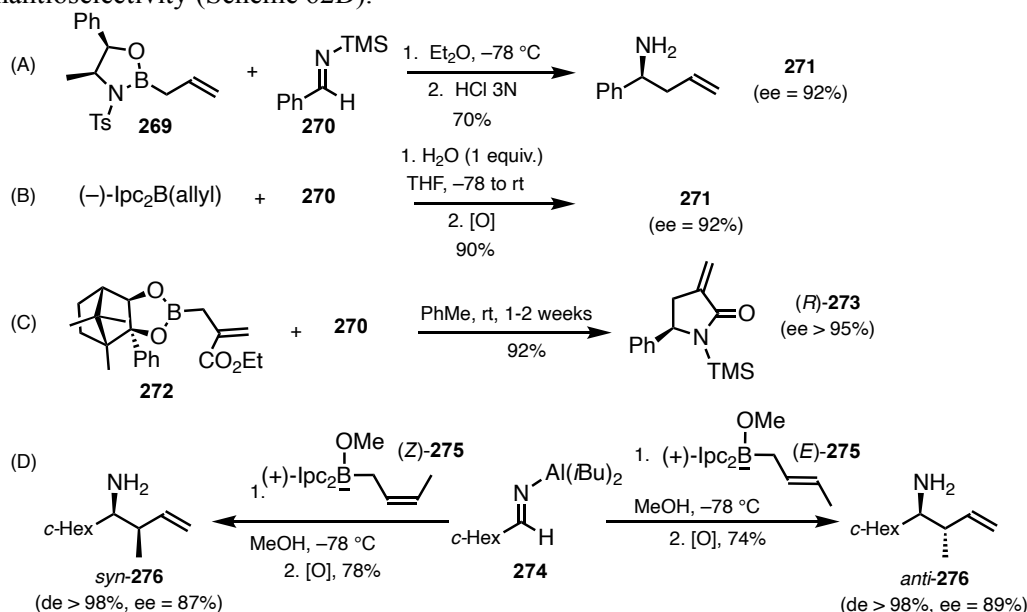
Methods have been developed with activated ketones such as pyruvates,^{200, 201, 202} as electrophiles. In this case, the Roush crotylation gives the corresponding adduct **266** with high diastereoselectivity but still moderate enantioselectivity (Scheme 61A).²⁰³ Good diastereoselectivity could also be achieved in stoichiometric allylboration with non-chiral allylboron species and enantioenriched substrates like α -aminoketones **267**,²⁰⁴ derived from aminoacids, in which a chelating group is present (Scheme 61B). The diastereoselectivity of the reaction was found to be dependent on the steric requirement of the *N*-protecting group with the best result obtained with the 4-*t*-butylbenzoyl group.



Scheme 61 Allylation of pyruvate and α -aminoketones derivatives

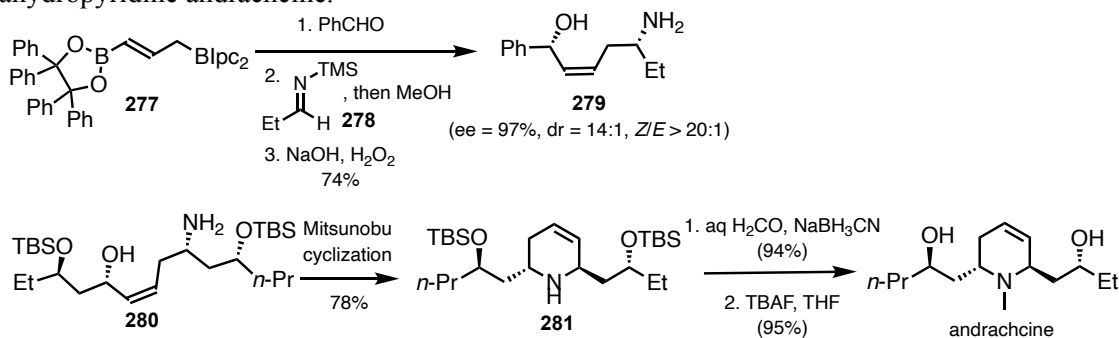
3.1.4 Allylation of imines

The allylation of imines with allylborons species was reviewed by Batey in 2011.²⁰⁵ Stereoselective allylboration of aldimines have been reported but have proven to be more challenging than with aldehydes. Representative examples with chiral allylboron species are depicted in Scheme 62. Itsuno initially explored allylations with camphor and norephedrine-derived chiral auxiliaries. Ee up to 92% were reported in the allylation of *N*-trimethylsilylaldimines **270** with an norephedrine-derived reagent **269** (Scheme 62A) while Brown allylation reagent gave lower enantioselectivity.^{206, 207, 208, 209} Brown and coworkers showed later that *N*-trimethylsilylaldimines required water to react with Ipc₂B(allyl) reagents at low temperature (−78 °C). Under these conditions, the homoallylic amines **271** were obtained with up to 92% ee (Scheme 62B).²¹⁰ Herrmann's type chiral auxiliaries were also found to give good enantioselectivity with β-substituted allylborons species **272** (Scheme 62C).²¹¹ Highly stereoselective crotylation reactions of aldimines, including aliphatic aldimines, were reported by Ramachandran in 2005.²¹² Crotylborane -ate complexes **275** derived from Ipc were shown to react in the presence of methanol with *N*-alumino-aldimines **274**, generated by *in situ* reduction of nitriles with DIBAL, to give homoallylic amines **276** having two stereogenic centers with excellent diastereoselectivity and very good enantioselectivity (Scheme 62D).



Scheme 62 Allylation of aldimines with chiral allylboron species.

A sequential double allylboration reaction of an aldehyde followed by an *in situ*-generated silylimine was reported by Roush in 2017. This strategy uses the chiral allyldiboron species **277** derived from Ipc which induces high facial stereocontrol upon the first addition to benzaldehyde. The second addition of the trimethylsilylaldimine **278**, which is activated by methanol, led to the corresponding aminoalcohols **279** with high diastereo- and enantioselectivity as exemplified in Scheme 63. The double allylation sequence allowed the preparation of **288**, which was applied to the total synthesis of the chiral tetrahydropyridine andrachcine.²¹³



Scheme 63 Sequential double allylboration reaction of aldehydes and imines reported by Roush in 2017 and applied to the total synthesis of andrachine.

Because of lower reactivity of classical ketones/imes in boron-based allylation reactions, various recent strategies have been developed in which the allylboron species is activated through Lewis acid/base or Brønsted acid association.²¹⁴ This approach has led to the development of many stereoselective catalytic methods for the allylboration reaction of aldehydes and ketones,²¹⁵ where chiral Lewis acid/bases are used to both enhance nucleophilicity and stereoselectivity control. For this reason, stoichiometric allylboration of ketones and imines with chiral allylboron reagents from the chiral pool have been less studied. However, note that allylboration of ketones with stoichiometric chiral allylboron species have been developed with other synthetic chiral auxiliaries.^{159, 161, 162, 216} For instance, the asymmetric allylboration of ketones (and aldehydes) using 3,3'-disubstituted binaphthol-modified allylboronates was shown to give up to 91% ee with aromatic ketones.²¹⁷ Furthermore, Hoveyda developed catalytic allylboration reactions of imines and ketones with aminoacid-based catalysts derived from the chiral pool.^{218, 219} In this case, a chiral allylboron reagent is generated *in situ*. Asymmetric catalysis is out of the scope of this chapter. The reaction of allylborons with electrophiles catalyzed by enantioenriched chiral catalysts was described in several reviews and book chapters.^{220, 221, 159, 222, 161} More importantly, a predominant part of the recent research concerning chiral allylboron reagents and their addition to carbonyl compounds has been dedicated to α -chiral allylboron species and related stereoselective reactions which are presented below.

3.2. α -Chiral allylboron species.

As presented before, allylboron-based asymmetric synthesis has been initially developed with chiral auxiliaries. In recent decades, the application of enantioenriched α -chiral allylboron species has attracted increased attention from the synthetic chemist. α -Chiral allylboron species have been shown to provide efficient chirality transfer, with important application in total synthesis. However, this strategy requires the synthesis enantiomerically pure starting materials which has first proven to be challenging. Therefore, the preparation of α -chiral allylboron reagents with high stereocontrol followed by transfer of chirality upon reaction with electrophiles, has represented a major part of recent research in the field of allylboration reactions. Since the first reported preparation of an α -chiral allylboron in 1984,^{223, 224} based on a stepwise Matteson asymmetric homologation of a chiral alkenylboronate, many tools have been developed for stereocontrolled synthesis of α -chiral allylboron reagents,¹⁵⁹ including asymmetric S_N2' reactions, (formal) hydroboration and diboration reactions of 1,3-dienes and allenes, [4+2] cycloadditions, asymmetric homologation of alkenyl boronates, [3.3] sigmatropic rearrangement of chiral vinylboronates,²²⁵ or C–C cross-coupling reactions of bis-boronates with vinyl substrates. Selected structures of α -chiral allylboron species reported before 2017 are depicted in Figure 5. The transition metal-catalyzed preparation of chiral allylboronates was reviewed by Min et al. in 2021,²²⁶ and is not detailed in this chapter.

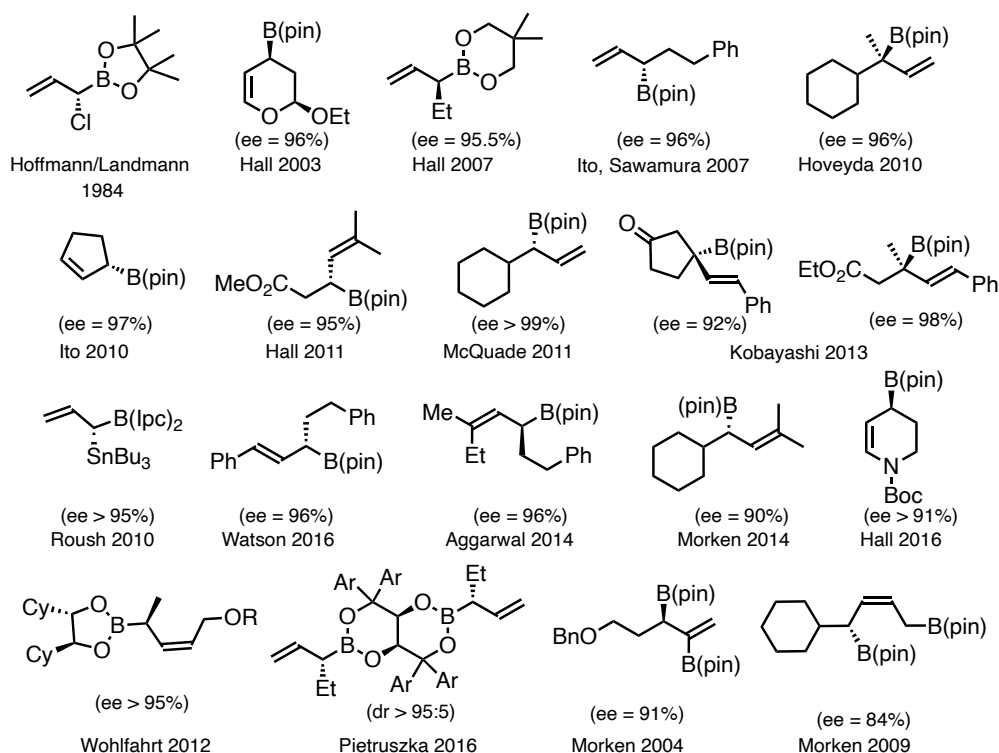


Figure 5 Selected structures of α -chiral allylboron species reported before 2017

In recent years, efforts have been made to widen the scope of the synthetic methods and the available structures. The main challenges have been to increase compatibility with functional groups, to prepare highly substituted α -chiral allylborons, to introduce quaternary centers, to prepare P-, Si-, or F-containing structures, to synthesize heterocycle-based allylboranes, or to control enantioselectivity in the synthesis of both (*E*) and (*Z*) α -chiral allylborons. Selected new structures of α -chiral enantioenriched allylborons species reported since 2017 are shown in Figure 6.^{227, 190, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241} Diastereoselective methods for the preparation of highly substituted racemic α -chiral allylboron species were also reported.^{242, 243}

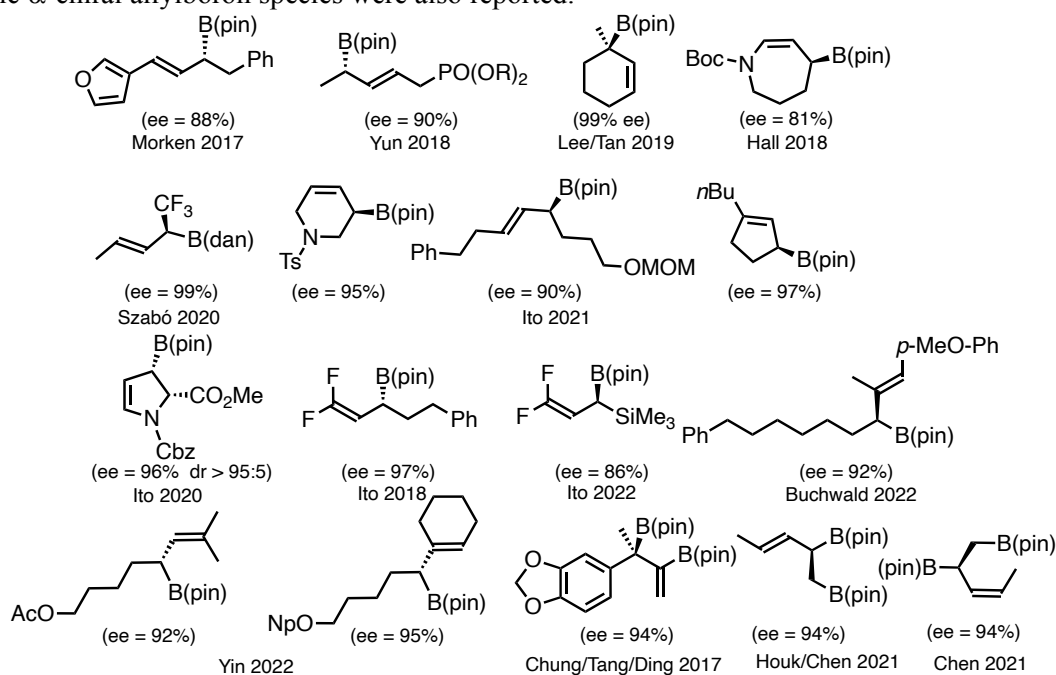
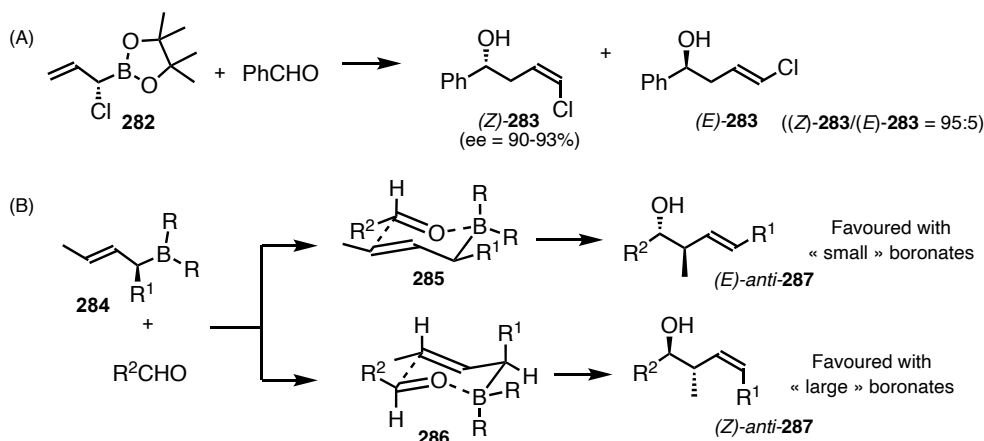


Figure 6 Selected structures of α -chiral allylboron species reported between 2017 and 2023

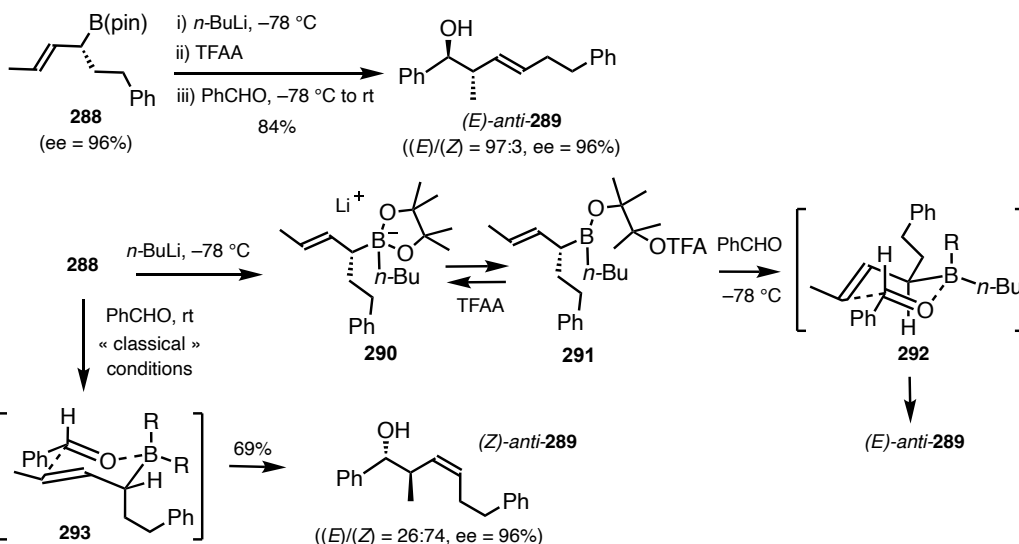
3.2.1 Asymmetric reactions with alpha-chiral allylboron species

Hoffmann reported in 1984,²²³ that the addition of α -chiral (α -chloro)-allylboronates **282** to aldehydes proceeded with excellent transfer of chirality and diastereoselectivity (Scheme 64A). However, it was shown later that the ratio of these two (*E*) or (*Z*) diastereomers which are epimeric, was highly dependent on the nature of the α -substituent R^1 and of the type of boronic ester **284**.^{223, 224} The different steric and dipolar interactions that can occur in the two competing transition structures **285** and **286** are responsible for the different (*Z*)/(*E*) ratio of diastereomeric homoallylic alcohols **287** (Scheme 64B). "Small" boronate groups typically derived from 1,3-propanediol give high diastereoselectivity in favor of the (*E*)-isomer,²⁴⁴ whereas "large" boronate esters, as those derived from tetraphenyl-1,2-diols, give high diastereoselectivity in favor of the (*Z*)-isomer.²⁴⁵ Unfortunately, the commonly used pinacolate boronic esters, which are of intermediate steric hindrance, usually gave modest selectivities under standard conditions (THF, rt), due to competitive steric clash in structures **285/286**.²⁴⁶



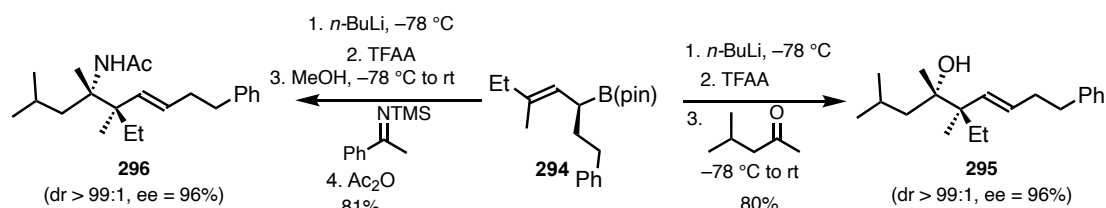
Scheme 64 Transfer of chirality from α -chiral allylboron species: (A) First example reported in 1984 upon addition to benzaldehyde; (B) Competitive transition structures in the allylation of aldehydes with α -chiral allylboronates shown here with crotyl-type reagents.

Since then, and in the last decade, various other modified systems have been reported to give high selectivities with different types of α -chiral allylboronates. In 2013, Aggarwal's group reported an alternative strategy to circumvent steric clash in allylation transition structures involving α -chiral allyl or crotylboronate reagents derived from pinacol.²⁴⁷ The treatment of α -alkyl-substituted α -chiral crotylboronates with *n*-BuLi/TFAA (trifluoroacetic anhydride) was shown to activate allylic pinacol boronic esters toward allylation of aldehydes allowing the reaction to take place at -78 °C to give high diastereoselectivity in favor of the (*E*)-diastereomer and complete transfer of chirality, as depicted in Scheme 65 with allylboron reagent **288**. The (*E*)-*anti* isomer **289** is obtained through a boron-ate complex **290** generated upon addition of *n*-BuLi. This ate complex is in equilibrium with a borinic ester intermediate **291** which is trapped at -78 °C by trifluoroacetic anhydride (TFAA). Addition of the aldehyde leads after work-up to the (*E*)-*anti* diastereomer as the major isomer, through a favoured transition state **292**. By comparison, "classical" conditions in which the aldehyde is directly added at rt to the allylboron reagent, lead to (*Z*)-*anti*-**289** as the major isomer with low diastereoselectivity through transition structure **293**.



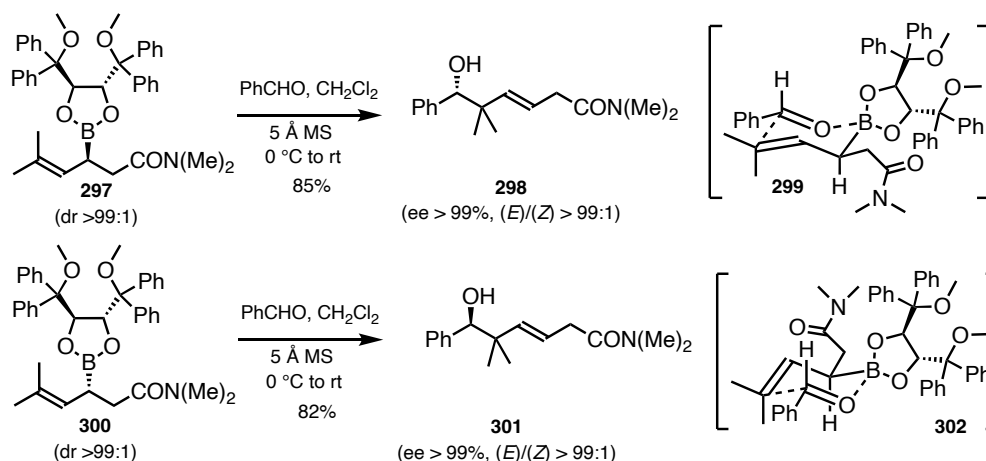
Scheme 65 Crotlylboration of aldehydes with α -alkyl-substituted α -chiral pinacol-based allylboron reagents with *n*-BuLi/TFAA or in classical conditions

This methodology (i.e. Lewis base-mediated allylboration) associated with a Prins cyclization in a tandem reaction, was applied to the construction of substituted tetrahydropyrans and to the total synthesis of (-)-clavosolide B.²⁴⁸ In addition, the scope was further extended to the allylation of both ketones and ketimines with γ,γ' -disubstituted allylic boronic esters **294**, allowing the construction of compounds **295** and **296** having contiguous quaternary stereogenic centers with high stereoselectivity (Scheme 66).²⁴⁹ A similar Lewis-based system was reported in 2017 by the same group for the allylation of electrophiles with pinacol-based allylboronates (see **section 2**).¹²³



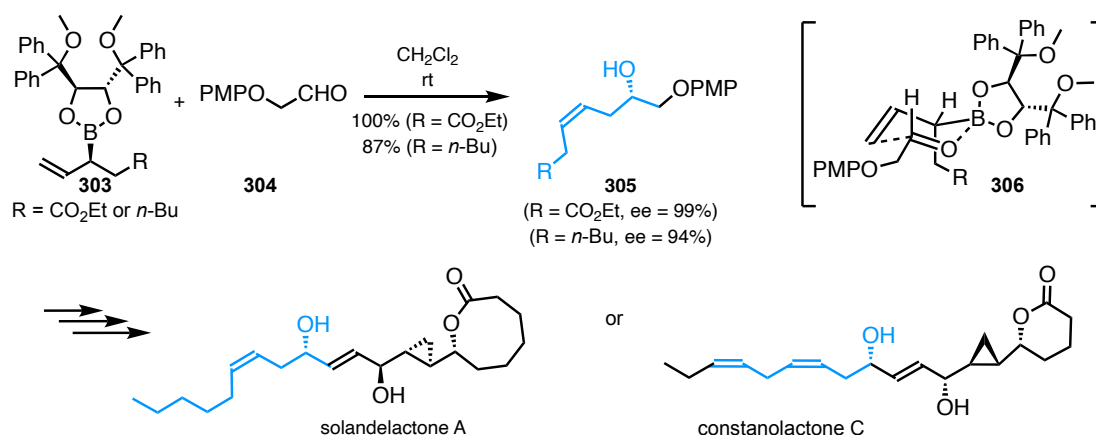
Scheme 66 Allylboration of ketones and ketimines with *n*-BuLi/TFAA system to form contiguous quaternary stereogenic centers

Another highly stereoselective allylboration reaction was reported by Pietruszka in 2013 starting from diastereomerically pure allylboronates **297** and **300** bearing a tartrate derivative which were obtained by sigmatropic rearrangement.²⁵⁰ In contrast to what was expected with large boronates, the reaction was found to give exclusively homoallylic alcohols as the (*E*)-isomers from a broad variety of aldehydes. Furthermore, the enantiofacial selectivity is controlled by the stereogenic center at the α -position of the boron, with no significant effect of the tartrate moiety (Scheme 67). This was attributed to a preference for a pseudo-equatorial orientation of the substituents in the transition structures to minimize allylic 1,3-strain with the axial methyl group at the γ -position of the allyl moiety (TS **299** and **302**). The same (*E*)-selectivity was observed by Yin's group in 2022 with another γ,γ' -dimethyl and α -substituted chiral allylboron reagent under acidic catalytic conditions with TFA.²³³



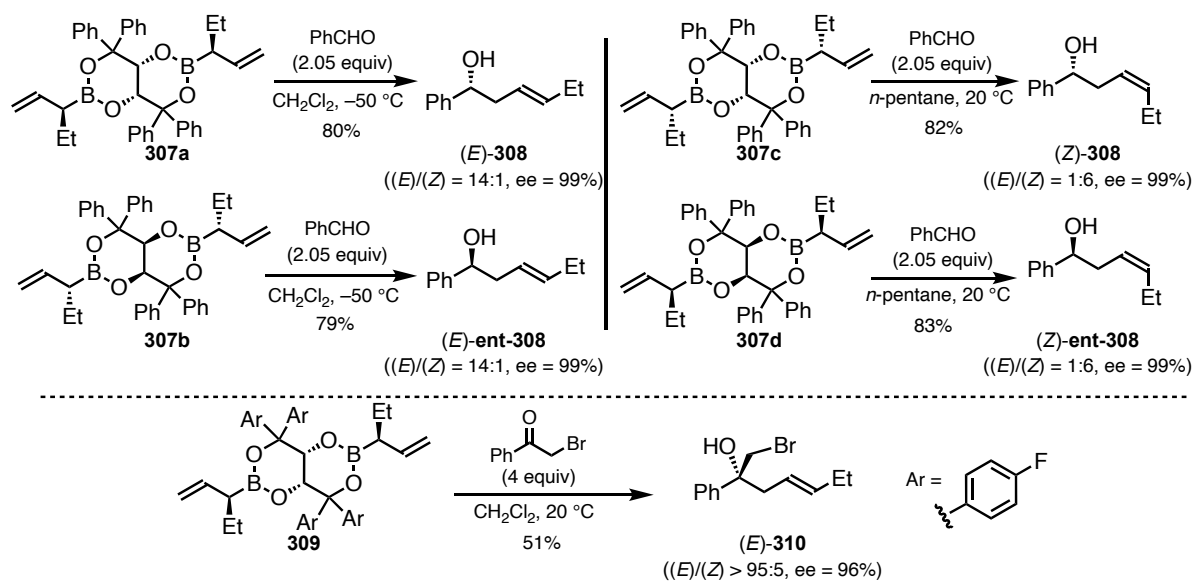
Scheme 67 Allylboration of aldehydes with tartrate-based diastereomerically pure allylboronates

In contrast, in the absence of substituents at the γ -position of the allyl group, (*Z*)-homoallylic alcohols are obtained as the major isomers instead of (*E*)-isomers, as shown with allylboronate **303**, upon reaction with aldehyde **304**. The (*Z*)-isomer **305** is obtained through a favored transition structure **306** in which the alkyl chain is in a pseudo-axial position. The strategy was used in the total synthesis of rugulactone,²⁵¹ constanolactones,²⁵² and solandelactone A and B,^{253, 254} to introduce (*Z*)-homoallylic alcohol units in the molecules (Scheme 68).



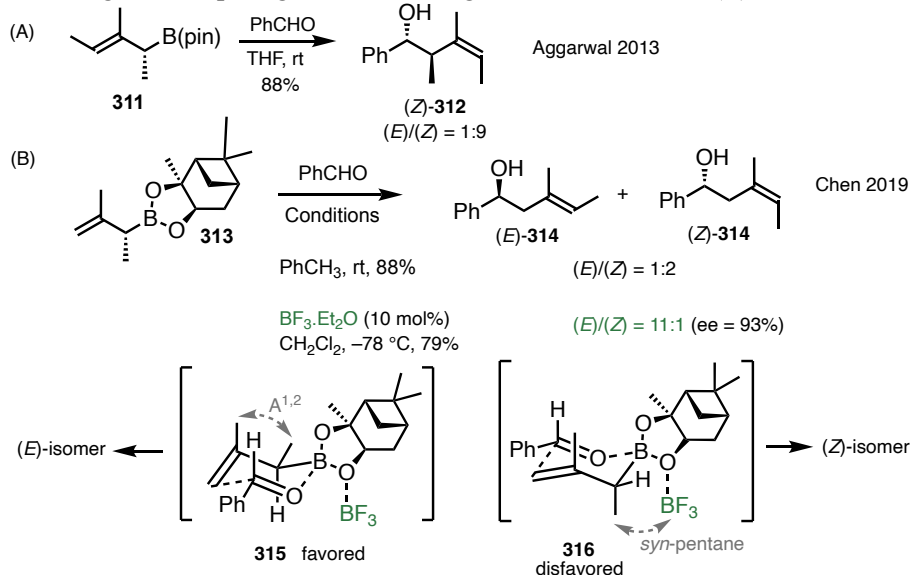
Scheme 68 Application of the allylboration of aldehydes with tartrate-based diastereomerically pure α -alkyl-allylboronates for the total synthesis of solandelactone A and constanolactone C

The same group reported in 2016, the preparation of enantiomerically and diastereomerically pure α -substituted-allylboronates based on dimeric diboron species **307** with one tartrate unit (Scheme 69).²⁵⁵ The separation of the four diastereomers used as starting materials allows highly stereoselective synthesis of all stereoisomeric homoallylic alcohols **308** upon reaction with aldehydes under two different optimized conditions. Note that the stereocontrol to get (*E*)-selectivity is better than for (*Z*)-selectivity. The same strategy was developed with ketones as electrophiles by using an optimized aryl group (*p*-fluorophenyl) on the tartrate derivative **309**, leading to all isomers of quaternary homoallylic alcohols **310** with high enantioselectivities (Scheme 69).²⁵⁶



Scheme 69 Allylboration of aldehydes and ketones with tartrate-based diastereomerically pure α -alkylallylboronates

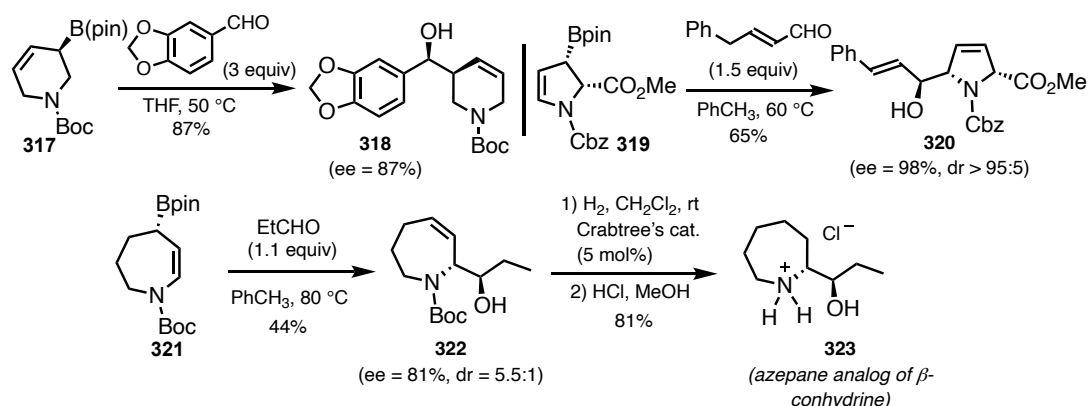
β -Methyl α -substituted allylboronates such as **311** were initially shown by Aggarwal's group in 2013 to give (*Z*)-selectivity upon direct reaction with aldehydes under classical conditions (i.e. THF, rt) (Scheme 70A).²⁴⁷ A similar trend in favor of the (*Z*)-isomer **314** was observed by Chen and coworkers in 2019 upon reaction of benzaldehyde with a β -methyl α -substituted allylboronate **313** bearing a chiral auxiliary (Scheme 70B).²⁵⁷ Looking for a strategy to form (*E*)-isomers, the same group demonstrated that the use of catalytic $\text{BF}_3 \cdot \text{OEt}_2$ induced the formation of homoallylic alcohols **314** with high (*E*)-selectivity and enantioselectivity. This difference in selectivity was attributed to a strong destabilizing *syn*-pentane interaction resulting from the complexation of BF_3 on the oxygen of the boronate, thus disfavoring the transition structure **316** (leading to the (*Z*)-isomer) in which the α -substituent is axially oriented, and favoring the competing TS **315** leading to the formation of (*E*)-isomers.



Scheme 70 Selective allylboration reactions with β -methyl α -alkyl allylboronates

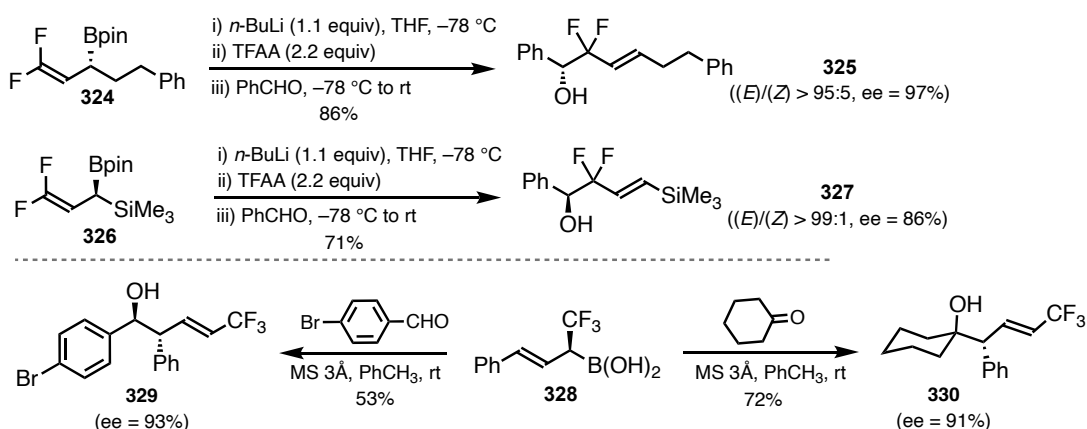
An important part of recent work has been dedicated to the generation of functionalized α -substituted chiral allylboron species. Chiral heterocyclic allyl boron reagents such as **317**, **319** or **321** have been developed by Hall and Ito's groups.^{239, 229, 190} These species react with aldehydes to construct functionalized non-aromatic *N*-heterocycles with high control of stereoselectivity. Such structures are of interest as fragments of a variety of natural products. Selected examples are shown in Scheme 71.

Starting from 7-membered chiral allyl boron reagents **321**, interesting azepane and tetrahydroazepine motifs found in active natural (*e.g.* (-)-balanol) and pharmaceutical molecules can be constructed. An azepane analog **323** of β -conhydrine was synthesized by Hall's group.



Scheme 71 Functionalized non-aromatic *N*-heterocycles obtained by allylboration of aldehydes using α -substituted chiral allylboron species

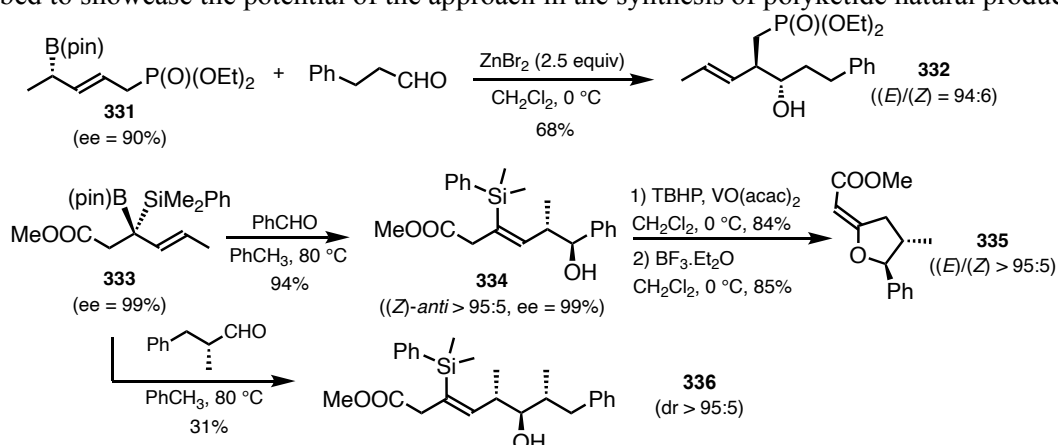
Several groups have also developed efficient synthesis of enantioenriched fluoro-substituted allylboron reagents (Scheme 72). γ,γ' -Difluoro α -substituted allylboron reagents such as **324** have been used by Ito to generate chiral *gem*-difluoro homoallylic alcohols **325** with high enantioselectivity by using Aggarwal's *n*-BuLi/TFAA-based system.²⁴⁰ The strategy was shown to be compatible with α -trimethylsilyl-substituted reagents **326** leading to the synthesis of homoallylic alcohols **327** having a trimethylsilyl-substituted double bond with high (*E*)-selectivity and complete chirality transfer.²³⁴ Szabó and coworkers reported in 2020 an efficient methodology for synthesizing enantioenriched α -CF₃ allylboronic acids by enantioselective 1,2 borotropic migration.²²⁸ The highly reactive allylboronic acids **328** which can be isolated and purified, react with aldehydes, ketones, imines, and indoles at room temperature in the presence of molecular sieves to give the stereoselective formation of homoallylic alcohols in which the double bond is substituted by one CF₃ group. The CF₃ motif is found in many bioactive molecules.



Scheme 72 Examples of chiral fluoro-containing homoallylic alcohols obtained by allylboration reaction using α -substituted chiral allylboron species

Other phosphorus and silicon-containing allylboron reagents were reported (Scheme 73). Phosphonate-substituted species such as **331** were shown to add to various aldehydes in the presence of ZnBr₂ as a Lewis acid to form the corresponding homoallylic alcohols **332** with an (*E*)/(*Z*) ratio ranging from 93:7 to 95:5.²³⁰ Ye and Song reported in 2022 an enantioenriched 3-silyl-3-borylhex-4-enoate reagent **333**. This reagent gives (*Z*)-*anti*-homoallylic alcohols **334** possessing a trisubstituted vinylsilane with excellent stereo- and enantioselectivity upon reaction with various aldehydes through asymmetric

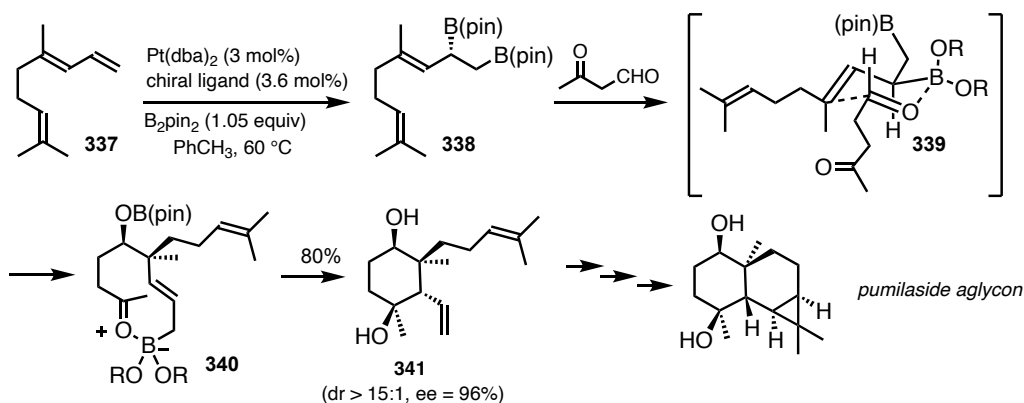
crotylboration. The transformation into functionalized THF rings **335** and stereotriades **336** was described to showcase the potential of the approach in the synthesis of polyketide natural products.²⁵⁸



Scheme 73 Examples of chiral P-containing and Si-containing homoallylic alcohols obtained by allylboration and further transformations

3.2.2 Stereoselective reactions with α -substituted diboron species

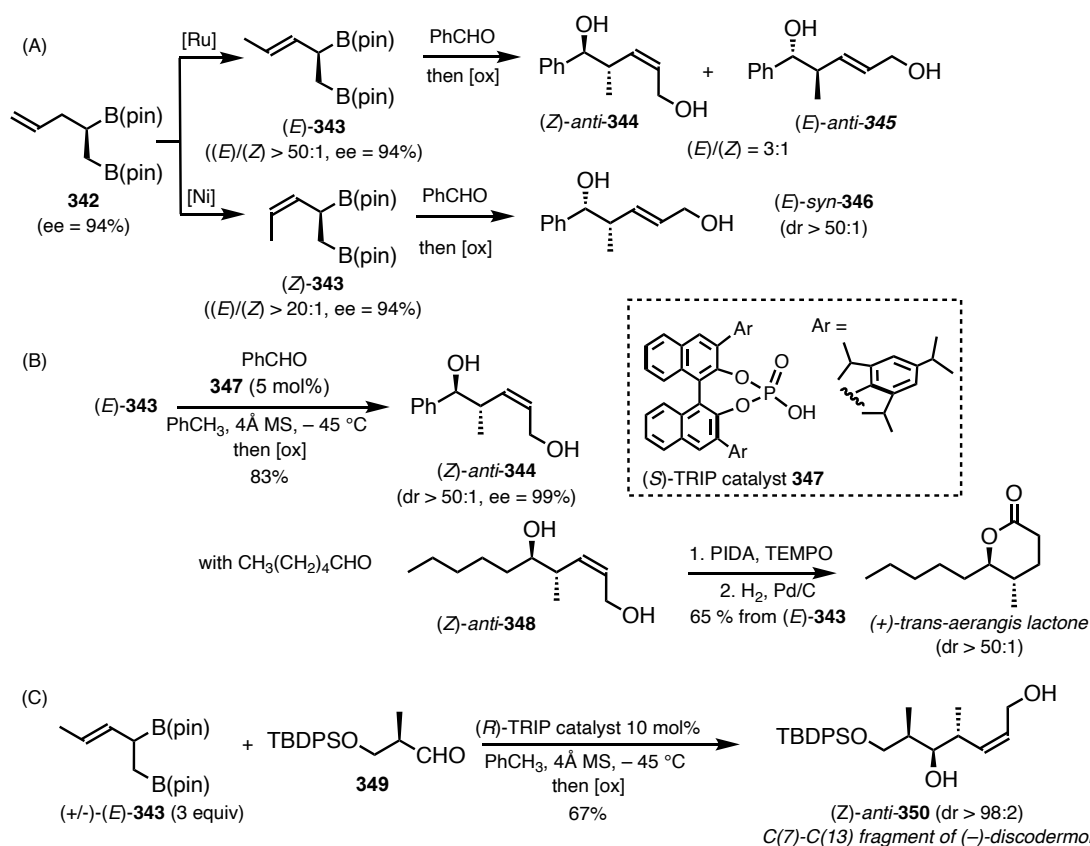
The group of Morken reported in 2013 an enantioselective Pt-catalyzed diboration of 1,3-dienes **337** with a chiral phosphoramidite ligand.²⁵⁹ The double addition of B(pin) provides an enantioenriched allylboron species **338** which was used in cascade allylboration reactions with various dicarbonyl compounds to construct functionalized carbocyclic structures with high stereoselectivity (Scheme 74). The 6-membered cyclic homoallylic alcohols, obtained through the tandem diboration/allylboration reaction, are useful motifs for synthesizing complex molecular targets as demonstrated by the synthesis of pumilaside aglycon. In this case, the reaction of **338** with 4-oxovaleraldehyde led to the *trans*-1,5-diol **341** in good yield and excellent stereoselection through a first transition structure **339** that gives allylboron intermediate **340**, which undergoes intracyclic allylation of the ketone *via* a *trans*-decalin-like transition structure to form **341**.



Scheme 74 Tandem diboration/allylboration reaction and application to the synthesis of pumilaside aglycon

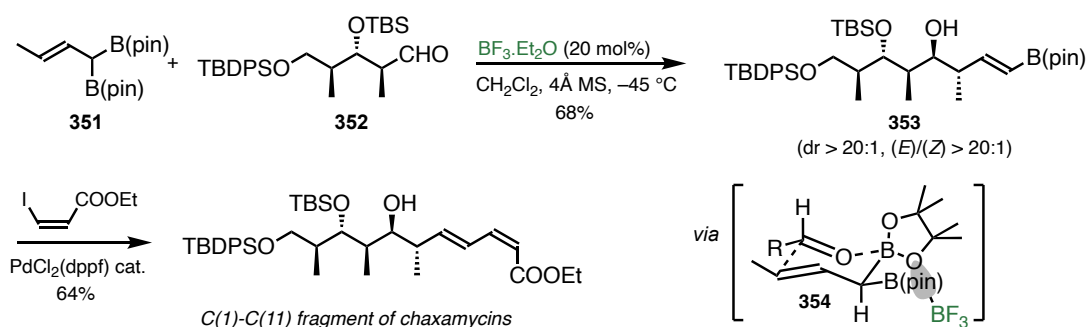
Chen and coworkers developed metal-catalyzed two-steps methodologies to generate either (*E*) or (*Z*) enantioenriched crotyldiborons species **343** (Scheme 75A).²³⁶ These reagents were used to synthesize enantioenriched 1,5-diols through allylboration/oxidation sequences. Upon reaction with aldehydes, it was first observed that the (*E*)-isomer **343** gave low diastereoselectivity. For instance, reaction with benzaldehyde furnishes a 3:1 mixture of the (*Z*)-*anti*-**344** and epimeric (*E*)-*anti*-**345** isomers. In sharp contrast, under similar conditions, the (*Z*)-crotyldiboron reagent was shown to give high diastereoselectivity in favor of the (*E*)-*syn* diol **346**.²¹³ The selectivity issue with (*E*)-crotyldiboron reagents was resolved by the same group by using the chiral phosphoric acid (*S*)-TRIP or (*R*)-TRIP as catalysts. In the example shown in Scheme 75B, the addition of (*S*)-TRIP **347** dramatically enhances

the *Z*-selectivity of the (*Z*)-*anti* diol **344** (>50:1) while slightly increasing the level of enantiopurity (ee > 99% vs 94% ee in the starting reagent).²³⁶ This effect was attributed to a slower reaction rate of the minor enantiomer of the allylboron reagent with benzaldehyde under the reaction conditions. The authors also reported double stereodifferentiation reactions of enantioenriched aldehydes to construct a series stereochemically rich molecules which could serve as useful intermediates for the synthesis of complex molecules. The allylboration/oxidation sequence was applied to the formal synthesis of ACRL toxin IIIB or to the total synthesis of (+)-*trans*-aerangis lactone when starting from hexanal. In further application, the Chen's group described in 2021 catalytic asymmetric transformations of racemic (*E*)-crotylboronate **343** through a kinetic resolution–allylboration/oxidation reaction sequence.²⁶⁰ By using 3 equivalents of racemic (*E*)-crotylboronate reagent, this sequence furnished (*Z*)-*anti*-homoallylic alcohols with high *Z*-selectivities and enantioselectivities. Lee and Jung who reported in 2023 a copper-catalyzed preparation of the same racemic (*E*)-crotyldiboronate and applied this kinetic resolution allylboration sequence with aldehyde **349** to the synthesis of the C(7)-C(13) fragment of (–)-discodermolide (Scheme 75C).²⁴³



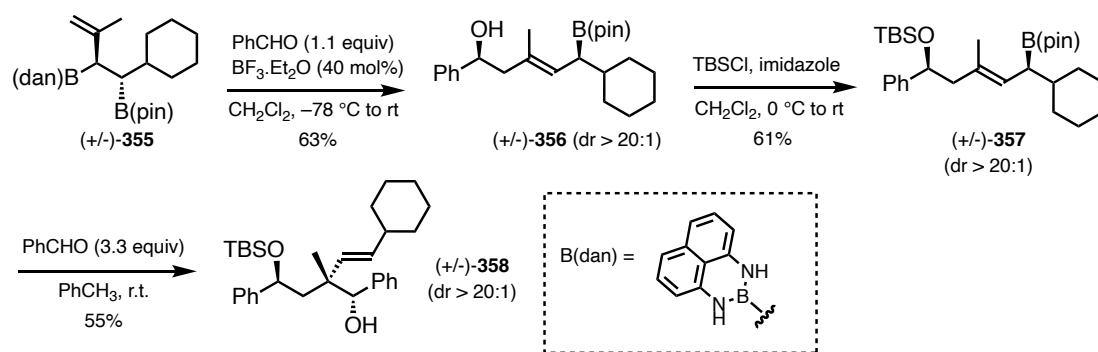
Scheme 75 (A) Reaction of diboron species with benzaldehyde; (B) Diastereoselective allylboration of (*E*)-crotylboronates in the presence of (*S*)-TRIP catalyst and synthetic application; (C) kinetic resolution with a racemic diboron (*E*)-crotyl reagent

The use of BF₃.Et₂O as a catalyst was also found to dramatically improve the stereoselectivity in allylboration reactions starting from (*E*)-crotyldiboron reagent. It was shown that the reaction of achiral gem-diborons crotyl reagents **351** gave high selectivity in favor of the (*E*)-*anti* isomer in the presence of 20% molar of BF₃.Et₂O at low temperature (Scheme 76).²⁶¹ The reaction was applied to various chiral aldehydes to induce stereodifferentiation through the favored transition state **354**. Starting with aldehyde **352**, this strategy allowed a stereoselective synthesis of the C(1)-C(11) fragment of chaxamycins.



Scheme 76 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed allylboration of aldehydes with (*E*)-crotyl-*gem*-diboron reagents

Double-allylation diboron reagents were also developed by Brown to be used in tandem reactions with aldehydes (Scheme 77). Upon reaction with aldehydes and diboron species **355**, the authors used $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to catalyze the first allylboration of the sequence to give (*E*)-homoallylic alcohols **356** with $\text{dr} > 20:1$. The second allylboration takes place at rt without catalyst to give a second homoallylic alcohol **358** having a quaternary stereogenic center with high diastereoselectivity.²⁶²



Scheme 77 Enantioenriched double-allylation diboron reagents developed by Brown

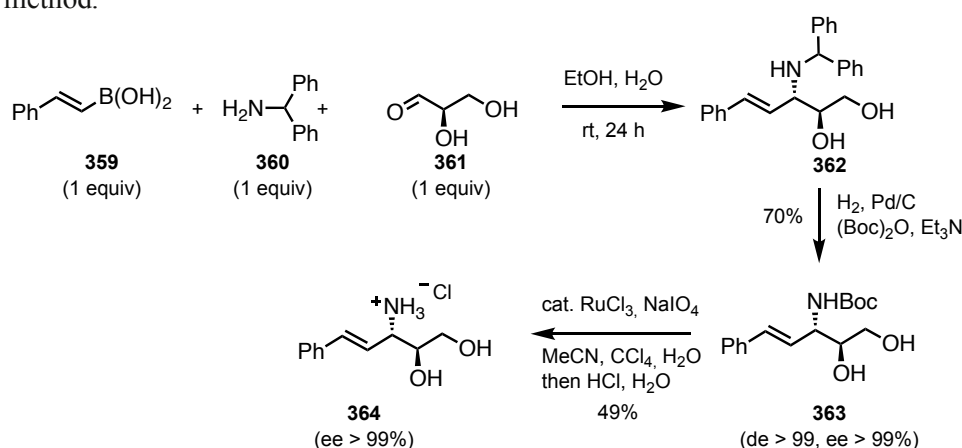
4 Petasis and Petasis-type reaction

An effective way to increase the nucleophilicity of boron reagents is the activation by a Lewis base, which can coordinate with the vacant p orbital of the boron atom. The resulting electronic rearrangement can activate C-B bonds, thereby facilitating substitution reactions^{263, 264} or nucleophilic addition such as in the Petasis reaction.

The Petasis Borono-Mannich (PBM) reactions are multi-component reactions between a carbonyl derivative, an amine and a boronic acid.^{265, 266, 267} First described by Petasis and Akritopoulou in 1993,²⁶⁸ it allows the synthesis of substituted amines with the creation of a C-C bond and a C-N bond. Initially, the reaction was carried out with paraformaldehyde, a secondary amine, and (*E*)-vinyl boronic acid and was applied to the preparation of geometrically pure naphthifine, a potent antifungal agent. Since then the reaction scope has been extended to the use of a wide range of aryl-, vinyl-, propargyl- and allenyl boronic acids or esters as well as trifluoroborates. The reaction can be carried out with primary or secondary amines, hydrazines, hydrazides, or sulfonimides. For carbonyl derivatives, apart from the case of formaldehyde, the reaction is usually restricted to compounds comprising a coordinating group capable of activating boron such as glyoxylic acid, salicylic aldehyde, α -hydroxy- or α -amino aldehydes. Despite this limitation, the PBM reaction proved to be a powerful method providing access to structural diversity, including complex scaffolds, natural compounds, and bioactive derivatives. It is noteworthy that enantioselective catalytic versions of this reaction have been described but are out of the scope of this chapter.^{269, 270, 271, 272, 273, 274}

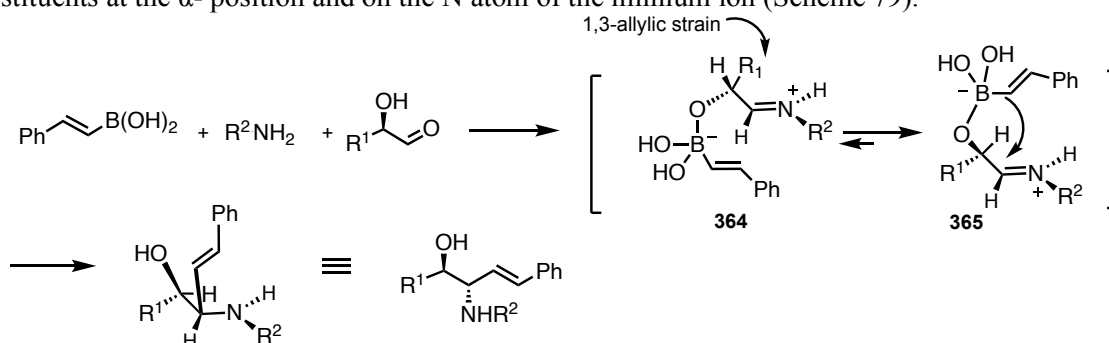
4.1 Diastereoselective reaction starting with α -hydroxy aldehydes/ α -aminoaldehydes and equivalents.

The use of enantiomerically pure α -hydroxy aldehyde was first described by Petasis and Zavialov in 1998 allowing one-step synthesis of enantiopure *anti*- β -amino alcohols.²⁷⁵ For example, the reaction of enantiomerically pure glyceraldehyde **361** with phenylvinyl boronic acid **359** and amino diphenylmethane **360** as the amine component allows the formation of the corresponding amino alcohol **362** under mild conditions (Scheme 78). After hydrogenolysis, conversion to the *N*-Boc derivative **363**, and oxidation, (*S*)-homophenylalanine **364** was obtained as a single enantiomer (>99% ee). A variety of organoboronic acids such as alkenyl, 2-bromoalkenyl, aryl, and heteroaryl were also found to react readily in this multi-component process. The successful stereoselective synthesis of *anti*- α -(difluoromethyl)- β -amino alcohols and *anti*- α -(trifluoromethyl)- β -amino alcohols were also reported using this method.^{276, 277}



Scheme 78 Preparation of enantiopure *anti*- β -amino alcohols by Petasis reaction with enantiomerically pure α -hydroxy aldehyde

The reaction has been proposed to proceed through a transient iminium species followed by an intramolecular transfer of the organyl ligand from the activated 'ate' complex of organoboronic acid.^{278, 279} This hypothesis has been supported by mechanistic studies such as density functional theory (DFT),^{280, 281} nuclear magnetic resonance (NMR),²⁸² mass spectrometry and X-ray diffraction of boronate intermediates.²⁸³ The high diastereoselectivity observed may arise from the reactive intermediate **365** of the tetracoordinate boronate complex with the minimization of the 1,3-allylic strain between the substituents at the α -position and on the N atom of the iminium ion (Scheme 79).²⁸⁴

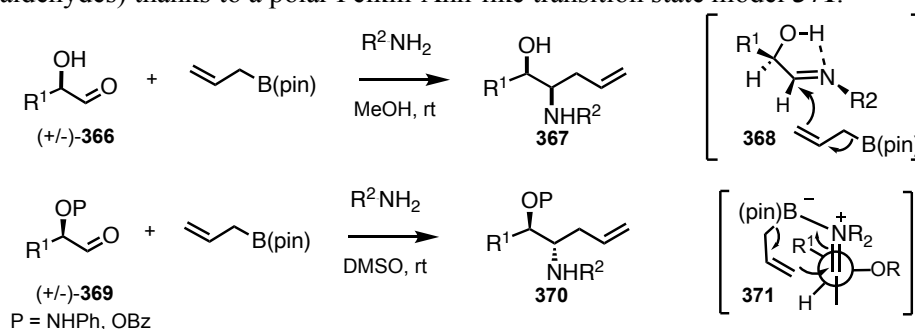


Scheme 79 Formation of the reactive boronate intermediate and explanation of the *anti*-selectivity

Examples of condensation with allenyl boron derivatives have also been described giving access to *anti*- β -amino- β -allenyl alcohols.^{285, 286}

The PBM reaction has been studied with allyl boronate pinacol ester, which is more reactive than aryl or alkenyl boron derivatives and has been shown to lead to the *syn*-amino alcohol **367** with α -hydroxy aldehydes **366** (Scheme 80).^{287, 288} In this case, the stereoselectivity was attributed to the Cram-like H-bonded intermediate **368** with the nucleophilic attack of the allyl group *anti* to R^1 substituent. The *anti*-

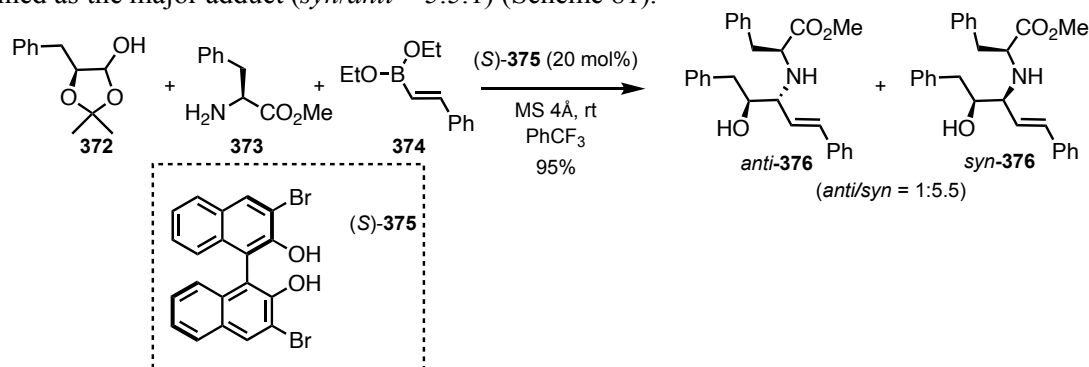
selectivity could be restored using chiral *O*-protected α -hydroxy aldehydes **369** (α -phenylamino or α -benzyloxyaldehydes) thanks to a polar Felkin-Ahn-like transition state model **371**.



Scheme 80 PBM reaction with allyl boronate pinacol ester

It is worth noting that with chiral α -fluoro aldehydes, primary amines, and pinacol allyl boronate, the PBM reaction works efficiently and leads also to α -allyl- β -fluoro amines with excellent *anti*-selectivity.²⁸⁹

Other methods have been developed to override the intrinsic *anti*-diastereoselectivity.²⁹⁰ As example, with (*S*)-5-benzyl-2,2-dimethyl-1,3-dioxolan-4-ol **372**, 1-phenylalanine methyl ester **373**, (*E*)-diethyl styryl boronate **374** and 20 mol% of BINOL-derived catalyst **375**, the *syn* diastereoisomer **376** could be obtained as the major adduct (*syn/anti* = 5.5:1) (Scheme 81).²⁷⁰



Scheme 81 Formation of the *syn*-diastereoisomer using the PBM reaction

Starting with α -hydroxy aldehydes or lactols such as ribose or xylose derivatives, this methodology allowing access to *anti*- β -amino alcohols has been utilized as a key step in the synthesis of bioactive molecules and complex natural products. Thus, during recent years, the preparations of polyfunctionalized pyrrolidines **I** (for example (-)-swainsonine, uniflorine A, hyacinthacines)^{291, 292, 293, 294, 295} or **II** (calystegine B4),²⁹⁶ iminosugars **III**,²⁹⁷ nonulosonic acids (sialic and legionaminic acid) **IV**,^{298, 299} anti-influenza agents **V**³⁰⁰ or conduramines **V**^{301, 302} have been reported (Figure 7).

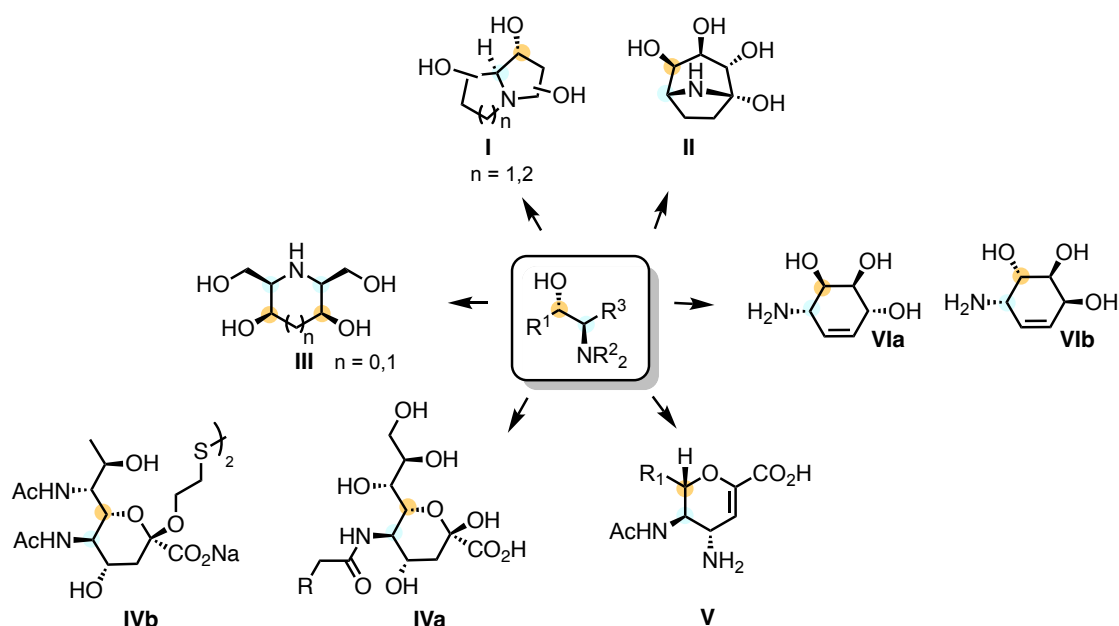
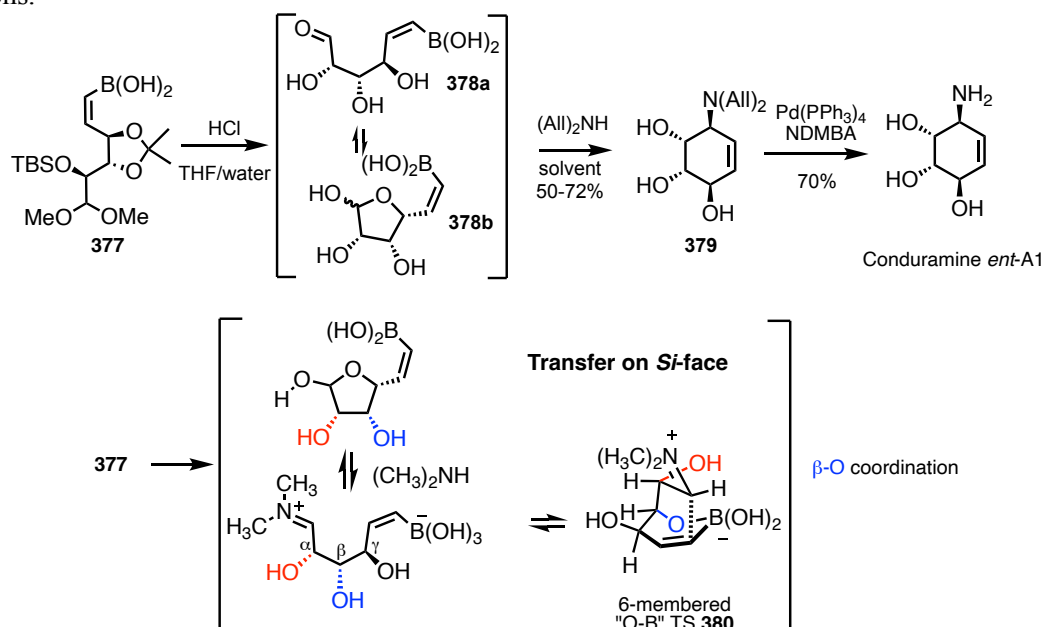


Figure 7 Synthesis of bioactive molecules and complex natural products using PBM reaction with α -hydroxy aldehydes or lactols

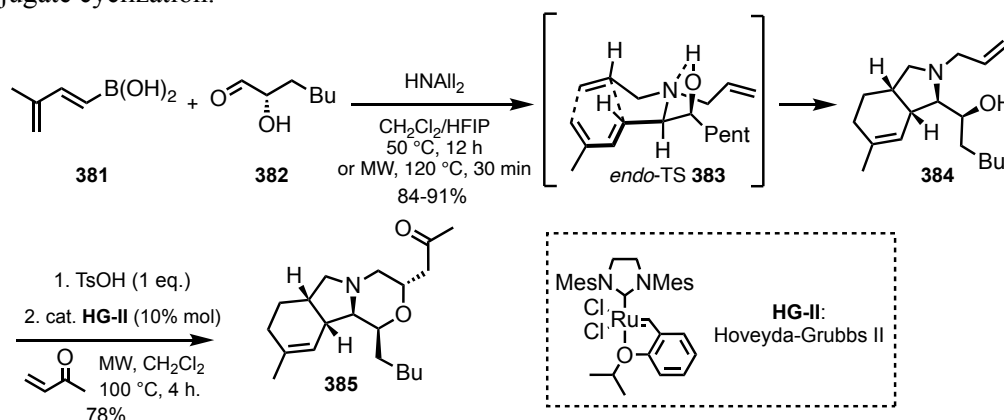
It is worth noting that conduramine **VIa** (conduramine *ent*-A1) was obtained thanks to an unprecedented intramolecular Petasis condensation from the boronic acid **378** (Scheme 82). After removal of all the protected groups on **377**, treatment with an excess of diallyl amine in a 4:1 mixture of ethanol/water at 80 °C allowed the formation of the cyclization product **379** as a unique diastereomer in 72% yield. Conduramine *ent*-A-1 was then obtained after a Pd-catalyzed deallylation reaction. Additionally, the newly created β -amino alcohol motif was found to be *anti* exclusively, which is opposite to that anticipated found in intermolecular PBM reactions. According to DFT calculations on the tetracoordinate borate intermediates, the reaction may proceed through a six-membered TS **380** that involves the β -hydroxyl group of the aldehyde, with the α -OH and the N(allyl)₂ groups in *trans* positions.



Scheme 82 Formation of conduramine *ent*-A1 by intramolecular Petasis condensation

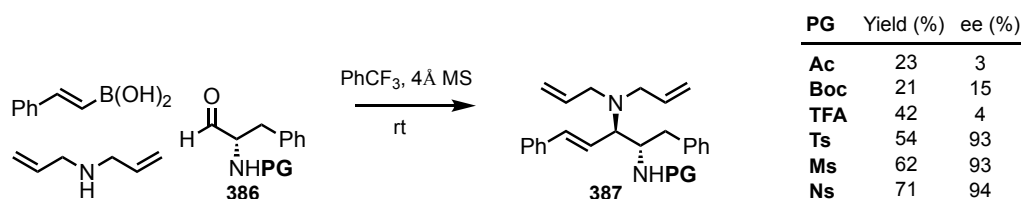
The PBM reaction can also be combined with secondary transformations such as cascade reactions or sequential sequences, allowing the synthesis of complex scaffolds.^{303, 290, 304, 305, 306} As described in Scheme 83, a combination of Petasis borono Mannich, intramolecular Diels-Alder (IMDA) followed by

cross-metathesis and Michael reactions has been developed.^{307, 308} By heating (*E*)-(3-methylbuta-1,3-dien-1-yl)boronic acid **381**, (*S*)-2-hydroxyheptanal **382**, and diallylamine in a 9/1 mixture of CH₂Cl₂/HFIP (50 °C for 12 h or MW at 120 °C for 30 min), the enantiopure hexahydroisindole **384** was obtained in high yields. The IMDA reaction has been shown to proceed with the addition of the diene on the *Re* face of the dienophile through an *endo*-TS **383**. DFT calculations showed the involvement of intramolecular hydrogen bonding displaying an important role in the pre-organization of reactive functional groups in favorable positions during the intramolecular Diels-Alder process. Further treatment of the tosylate ammonium salt of **384** with methyl vinyl ketone and Hoveyda-Grubbs II catalyst (10% mol) in CH₂Cl₂ under MW at 100 °C for 4 h allowed the preparation of the tricyclic 2,6-*trans*-substituted morpholine **385** resulting from the one-pot domino metathesis and intramolecular oxa-conjugate cyclization.



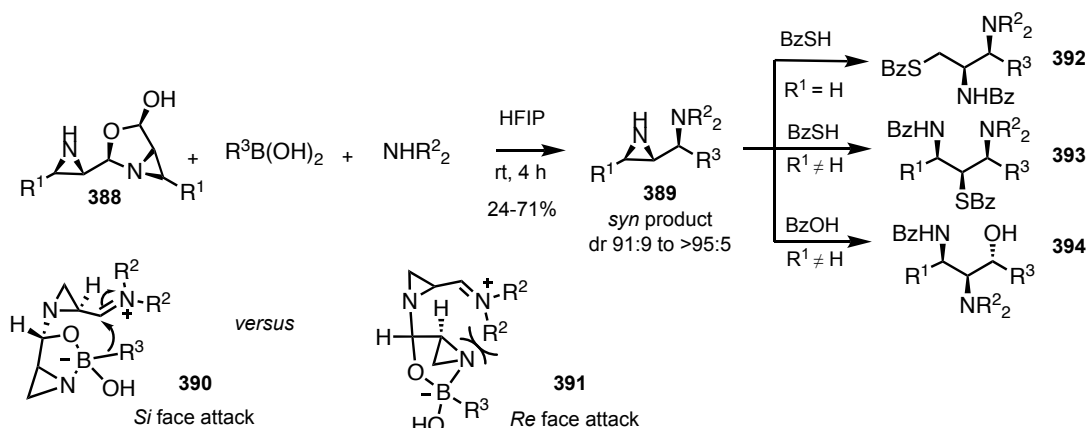
Scheme 83 Association of the PBM condensation to IMDA followed by cross-metathesis and Michael reactions

Recently, thanks to the use of *N*-protected α -aminoaldehydes **386**, the PBM reaction was generalized to the formation of 1,2-*trans*-diamines **387** with an enantiomeric excess of up to 98% (Scheme 84).^{281, 309} The influence of the protecting group on the nitrogen has been demonstrated both on the yield and the enantiomeric purity of the condensation products with the optimal results obtained on *N*-mesylated and *N*-nosylated derivatives. The mechanism of the PBM reaction was investigated using DFT calculations which have shown the importance of the protecting group on the nitrogen atom in coordinating it with boron and forming the transient boronate intermediate. The PBM reaction was found to be favored with sulfonylated substrates, whereas the racemization process became predominant for carbamate and acetamide substrates for which low yields and erosion of ee have been observed.



Scheme 84 PBM condensation with *N*-protected α -aminoaldehydes

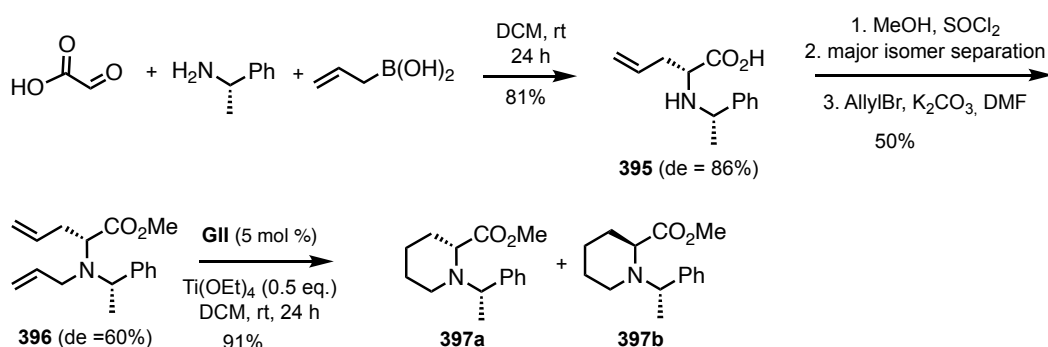
Aziridine aldehyde dimers **388** could also be used in the PBM reaction and with secondary amines and heteroaromatic, styrenyl boronic acids or alkynyl pinacol boronic esters, led to the formation of various vicinal aziridines **389** with high *syn*-stereoselectivity (Scheme 85).³¹⁰ The selectivity obtained was explained thanks to the involvement of the iminium N,O-chelate **390** and alkenyl migration on the *Si* face to provide the *syn* diamine after the dissociation of the complex. Moreover, the aziridine-containing diamines could be further functionalized to obtain 1,2- or 1,3-diamines containing three contiguous stereocenters after nucleophile ring opening.



Scheme 85 PBM condensation with aziridine aldehyde dimers and functionalization of the as-obtained compounds

4.2 Diastereoselective reaction starting with glyoxylic acids

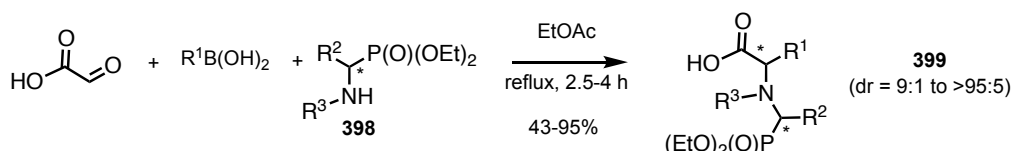
The first examples of diastereoselective reactions with glyoxylic acid were reported by Petasis in 1997. With aryl boronic acids and α -methyl benzyl amine, the preparation of α -aryl glycines in modest diastereoselectivities (de 28-35%) has been described.³¹¹ However, by reaction of an indolyl boronic acid with glyoxylic acid and this amine as the chiral auxiliary, optically active α -indolyl *N*-substituted glycines could be synthesized with high diastereoselectivity (99% de).³¹² With styrenyl boronic acid or boronate esters, the best results in terms of yield and selectivity were obtained for (*S*)-2-phenylglycinol³¹³ or for secondary amines containing only one branched substituent.^{314, 315, 316, 317, 318} Recently the preparation of enantiopure cyclic amino acid derivatives was reported.³¹⁹ Reaction of glyoxylic acid, allyl boronic acid and (*S*)- α -methyl benzylamine afforded the corresponding allylglycine derivative **395** in 81% yield and a diastereoisomeric ratio of 93:7 (Scheme 86). After esterification and *N*-allylation that occurred with partial epimerization, the resulting compound **396** was carbocyclized by Ru-mediated intramolecular ring-closing metathesis in the presence of $\text{Ti}(\text{OEt})_4$ yielding pipercolic acid derivatives **397a-b**.



Scheme 86 Diastereoselective PBM reaction with glyoxylic acid and chiral amine

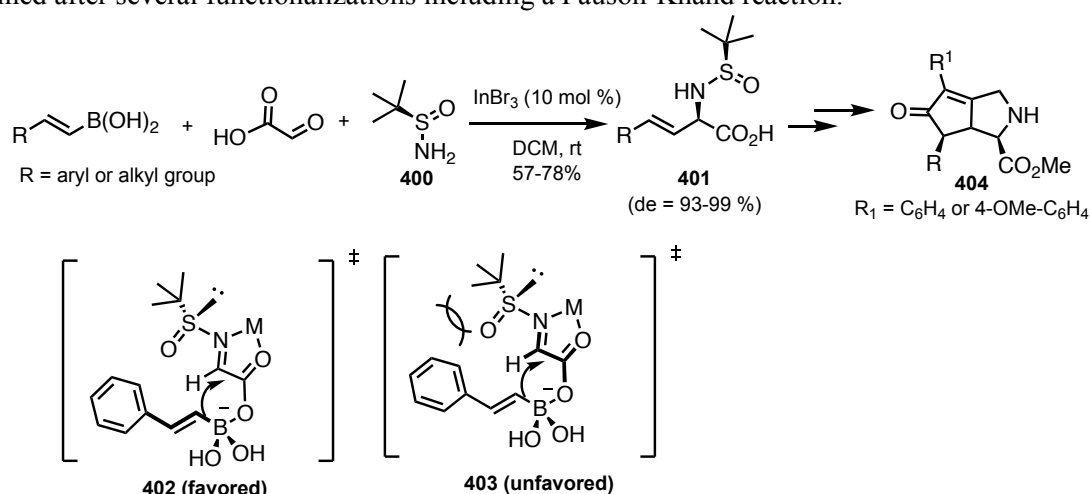
Note that styrenyl boronic acid and benzofuran-2-boronic acid have been put in reaction with glyoxylic acid and a chiral *trans*-1,2-diamino cyclohexane derivative, leading to the corresponding benzopiperazinones with a de of 73 and 40% respectively.³²⁰

The reaction of styryl boronic acid or electron-rich aryl or heteroaryl boronic acids with amino phosphonates **398** was also performed furnishing in refluxing ethyl acetate the corresponding *N*-(phosphonomethyl)-substituted amino acid **399** in high diastereoselectivity (up to >95:5) (Scheme 87).



Scheme 87 Diastereoselective PBM reaction with glyoxylic acid and amino phosphonates

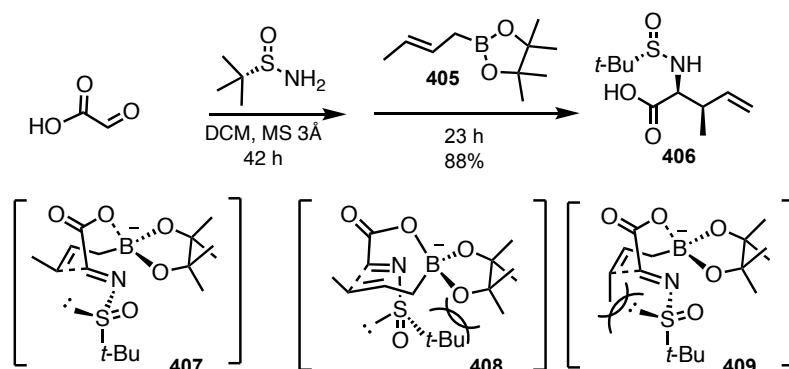
Chiral *t*-butylsulfonamide **400** was used as the amine component with substituted styrenylboronic acids leading to β,γ -dehydrohomoarylalanine derivatives with high stereoselectivity.³²² The reaction has also been described with a wide range of boronic acids and a catalytic amount of indium bromide allowing obtaining the corresponding adducts **401** in excellent diastereoselectivities (de = 93-99%) (Scheme 88).³²³ To explain the selectivity, a possible five-membered ring transition state **402** has been proposed in which the nitrogen of the imine and the carbonyl oxygen of the quaternary boronate complex is coordinated to the metal. In this TS the organyl group migrates from the *Re* face rather than the *Si* face of the imine bond avoiding steric interaction in the latter case. The synthetic usefulness of these compounds has been demonstrated thanks to the construction of cyclopenta[*c*]proline derivatives **404** obtained after several functionalizations including a Pauson-Khand reaction.



Scheme 88 Diastereoselective PBM reaction with glyoxylic acid and chiral *t*-butylsulfonamide

The same method has been carried out with benzofuran or benzothiophene-2-boronic acids toward the stereoselective synthesis of heteroaryl oxadiazine-based gamma-secretase modulators.³²⁴

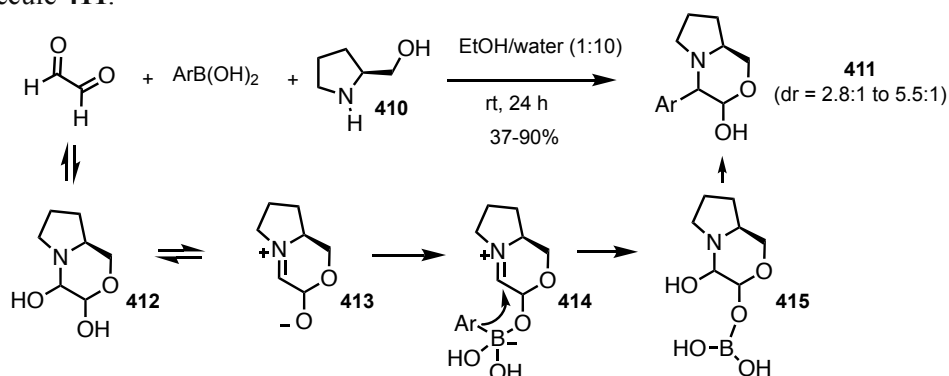
The allylation of the preformed imine of glyoxylic acid with chiral *t*-butylsulfonamide and various allyl boronic acid pinacol esters was reported. This transformation leads to γ,δ -unsaturated amino acids.³²⁵ When the reaction was carried out with (*E*)-crotyl boronic acid pinacol ester **405**, the corresponding acid **406** was obtained with excellent diastereoselectivity (Scheme 89) whereas no reaction occurred with (*Z*)-crotyl boronic acid pinacol ester. After activation of the allyl boronic acid pinacol ester by the carboxylic group, the reaction may proceed via a favored six-membered transition state **407** for which the *trans*-methyl group is located outside. The TS **408** may be disfavored because the *t*-butyl group would interact with the pinacol group and for (*Z*)-crotylboronic acid pinacol ester, the *t*-butylsulfonamide would interfere with the *cis*-methyl group of (*Z*)-crotyl boronic acid pinacol ester resulting in no product (TS **409**).



Scheme 89 Diastereoselective PBM reaction with glyoxylic acid, chiral *tert*-butylsulfinamide and crotyl boronic acid pinacol ester

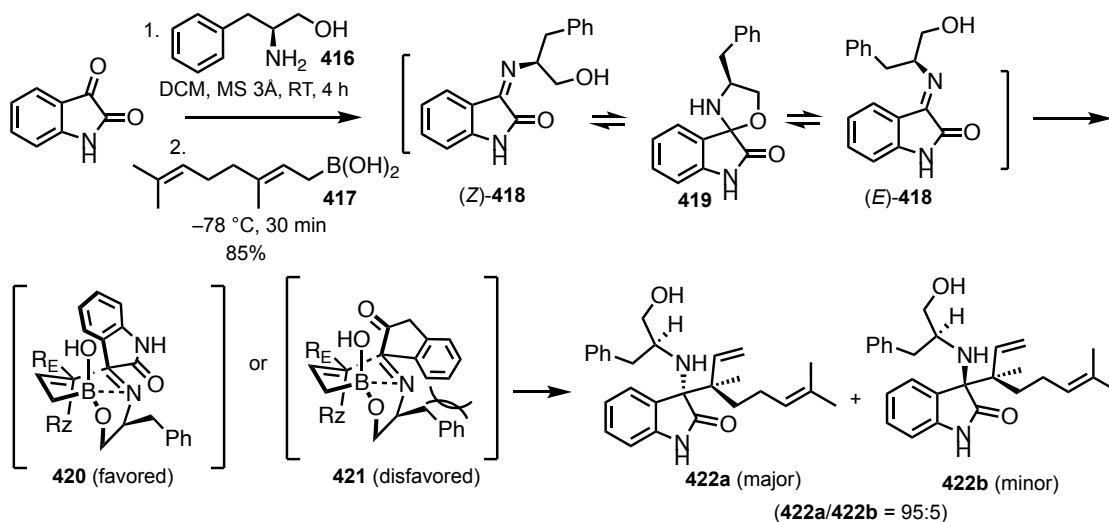
4.3 Case of the use of enantiomerically enriched 1,2-amino alcohols with glyoxal, isatin, or simple aldehydes

Enantiomerically enriched 1,2-amino alcohols have been employed in the PBM reaction allowing the three-component transformation to proceed in a selective manner. A first example was reported with glyoxal, aryl boronic acids, and (*S*)-pyrrolidin-2-ylmethanol **410** to furnish fused morpholine pyrrolidines **411** with potential insecticidal activities (Scheme 90).³²⁶ The reaction proceeded well in a mixture of ethanol-water for 24 h at room temperature allowing the formation of the bicyclic compounds with moderate to good yields and diastereoselectivities ranging from 2.8:1 to 5.5:1. Obtaining the final adduct can be explained by the condensation of the amine with glyoxal to form the hemiacetal **412**. After dehydration, the iminium intermediate **413** is formed and coordinates with the boron atom of aryl boronic acid to give a tetracoordinate boronate intermediate **414**. Next, irreversible intramolecular transfer of the aryl group takes place followed by hydrolysis of the intermediate **415** to produce the target molecule **411**.



Scheme 90 PBM reaction with glyoxylic acid and enantiomerically enriched 1,2-amino alcohol

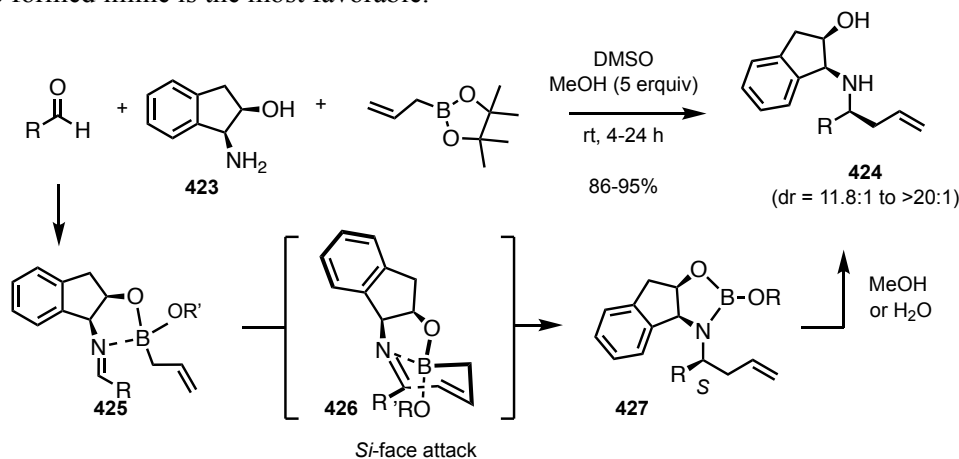
A highly efficient asymmetric allylboration of isatins with a wide range of γ,γ -disubstituted and γ -monosubstituted allyl boronic acids by using chiral amino alcohol as the directing group was described.³²⁷ The best results were obtained with chiral **416** at -78 °C in DCM and led with boronic acid **417** and isatine to the formation of the chiral homoallylic amine **422a** that possesses an adjacent quaternary stereogenic center in 85% yield and a dr of 95:5 (Scheme 91).



Scheme 91 PBM reaction with isatin and an enantiomerically enriched 1,2-amino alcohol

The transition state model **420** was proposed which primarily results from (*E*) to (*Z*) isomerization of imines **418** promoted by the allyl boronic acid. A boronate is then formed by ligand exchange between the allyl boronic acid and the hydroxy group, allowing intramolecular allylation reaction to take place via six-membered fused-chair transition states. Since the phenyl part of isatin is sterically more demanding than the amide group, TS-**420** is favored over TS-**421**, thus leading to the main diastereoisomer observed.

The Petasis allylboration with pinacol allyl boronate using chiral 1,2-amino alcohols has been extended to a wide array of aldehydes including aromatic, heteroaromatic and aliphatic aldehydes.³²⁸ The reaction has been best performed with (1*S*,2*R*)-1-amino-2-indanol **423** in DMSO as the solvent and MeOH (5 equiv.) as an additive at rt producing the corresponding amines **424** with high diastereomeric ratio (from 11.8:1 to >20:1) (Scheme 92). As before, the intramolecular asymmetric allylation of the imine **425** proceeds according to the Zimmerman–Traxler model **426** where the attack of the allyl group on the *Si* face of the formed imine is the most favorable.

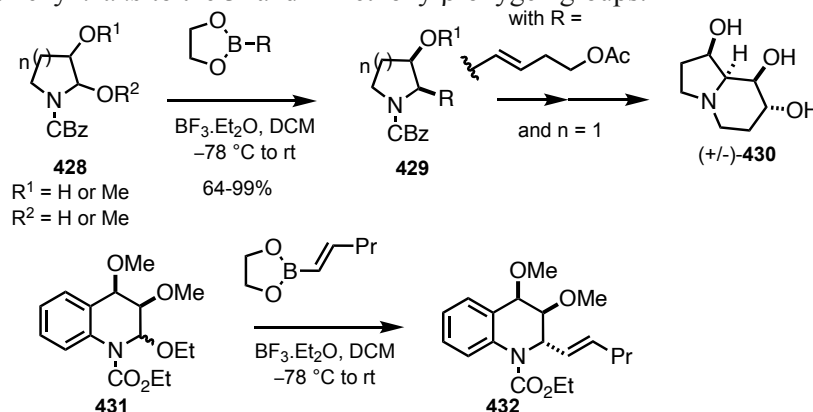


Scheme 92 PBM reaction with simple aldehydes and enantiomerically enriched 1-amino-2-indanol

Chiral *gem*-difluoro homoallyl amines have been prepared through allylation reactions using pinacol *gem*-difluoro allyl boronates, aldehydes or isatin, and β -amino alcohols.³²⁹ Also very recently, the formation of α - and β -butadienyl amines in optically pure forms was described using (1*S*,2*R*)-1-amino-2-indanol as the substrate and activator, with a wide range of aromatic and aliphatic aldehydes and pinacol homoallyl- and isoprenyl boronates, respectively.³³⁰

4.4 The diastereoselective reaction of *N*-acyliminium ions

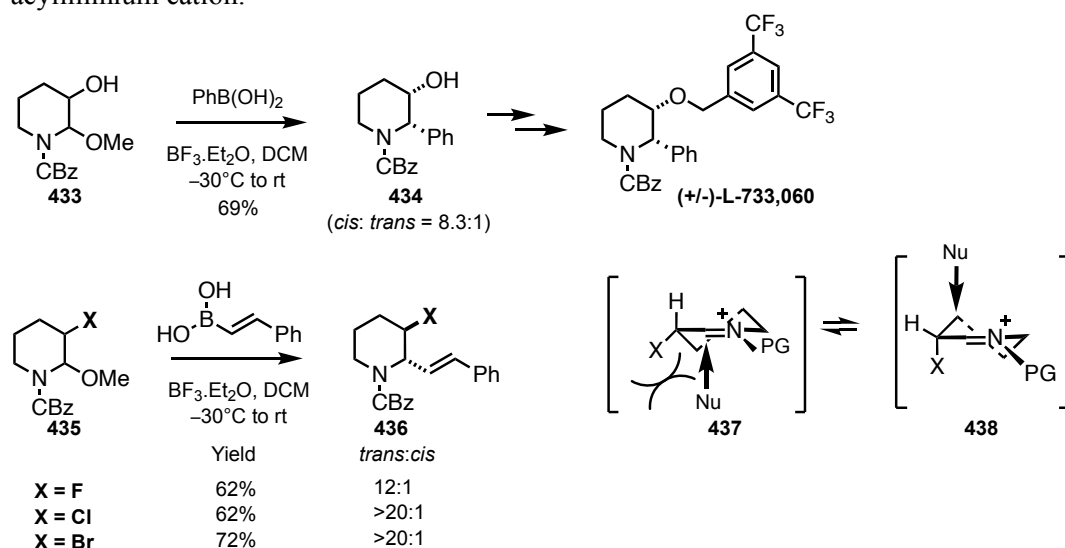
Initially, nucleophilic additions of alkenyl and aryl boronates to *N*-acyliminium ions have been reported by Batey in 1999 (Scheme 93).³³¹ Starting with racemic pyrrolidines or piperidine **428**, the reaction was performed in DCM in the presence of boron trifluoride etherate. The exclusive formation of the *cis*-2,3-substituted products **429** shows that the organyl ligand attacks *N*-acyliminium exclusively from the face bearing the β -oxygen. Interestingly, the reaction works almost as well with the use of *N*-acyliminium ion precursors containing methoxy substituents (R^1 and/or $R^2 = \text{Me}$). On the other hand, when the reaction was carried out with the tetrahydroquinoline **431**, it resulted in the formation of **432** with the addition of the alkenyl *trans* to the 3- and 4-methoxy β -oxygen groups.



Scheme 93 Nucleophilic additions of alkenyl and aryl boronates to *N*-acyliminium ions

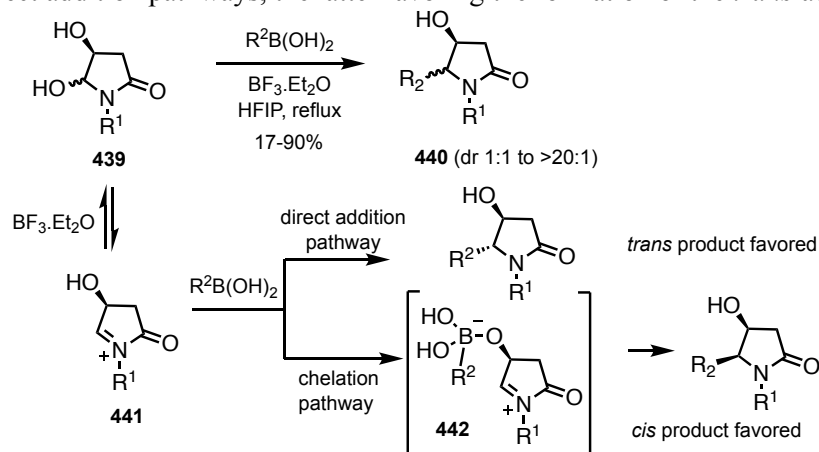
The synthetic usefulness of the reaction has been demonstrated by syntheses of indolizidine and pyrrolizidine alkaloids such as the stereoselective synthesis of 6-deoxy-castanospermine **430**³³² and also, more recently, (+)-loline alkaloid skeleton.³³³

The nucleophilic additions to *N*-acyliminium ions were also studied by Mizuta and Onomura for the diastereoselective preparation of 2,3-disubstituted piperidines.³³⁴ Starting with *N,O*-acetals compound **433**, the reaction carried out in the presence of boron trifluoride etherate in DCM led with aryl- and alkenyl boronic acids to *cis*-substituted derivatives **434** (Scheme 94). By using phenylboronic boronic acid, the resulting compound could be further functionalized for the synthesis of the neurokinin NK1 receptor antagonist (+/-)-L-733,060. It should be noted that, with piperidine **435** having a halogen atom at the β -position, a reversal of stereoselectivity was observed in the nucleophilic reactions of (*E*)-styryl boronic acid. This selectivity can be explained by the preferential nucleophilic attack on the pseudoaxial conformer **438** and not via the pseudoequatorial conformer **437** which might cause a steric repulsion between the halogen (Br or Cl) and the nucleophile. For the organofluorine compound, the pseudoaxial conformer could be favored thanks to the electrostatic interaction between the polarized C-F bond and the *N*-acyliminium cation.



Scheme 94 Preparation of 2,3-disubstituted piperidines by nucleophilic additions to cyclic *N*-acyliminium ions

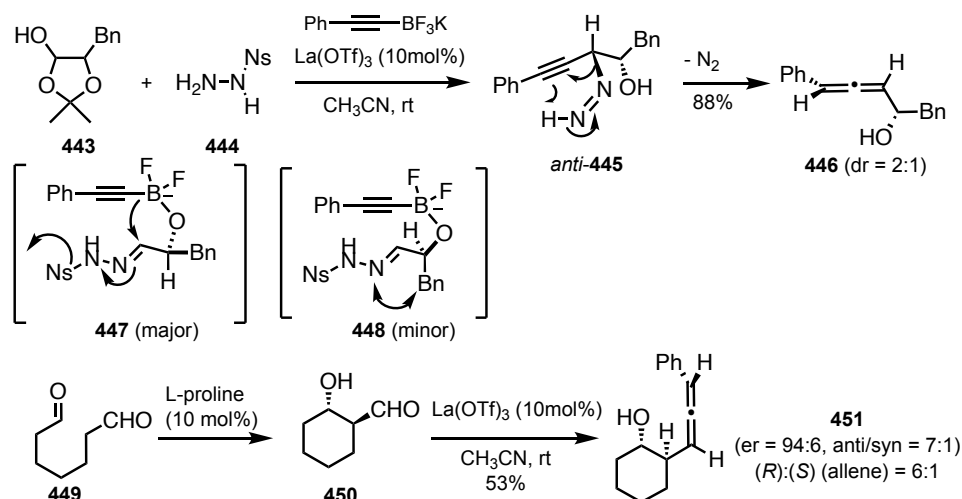
The reaction was extended to enantiomerically enriched cyclic hemiaminals having an endocyclic *N*-acyl group (Scheme 95).^{335, 336} For example, the nucleophilic additions to cyclic *N*-acyliminium ions derived from β,γ -dihydroxy- γ -lactams **439** were described recently by Nielsen and coworkers. Promoted by boron trifluoride–diethyl ether in refluxing HFIP, the reaction works successfully with electron-rich and electron-deficient boronic acids leading to a series of functionalized γ -lactams **440**. When using electron-deficient boronic acids (such as (4-bromophenyl)- and [2-(chloromethyl)vinyl]boronic acids), good *cis* diastereoselectivity was achieved which results from chelation-controlled addition to the *N*-acyliminium **441**. By contrast, more reactive electron-rich boronic acids (such as 2-furyl- and (2-benzo thienyl)boronic acids) resulted in no or poor selectivity. This can be explained by competitive chelation-controlled or direct addition pathways, the latter favoring the formation of the *trans* adducts.



Scheme 95 Nucleophilic additions to cyclic *N*-acyliminium ions derived from β,γ -dihydroxy- γ -lactams

4.5 Traceless Petasis reaction

The production of allenes has been described by coupling α -hydroxy aldehydes with alkynyl trifluoroborate salts and arylsulfonylhydrazine (Scheme 96).³³⁷ This process called “traceless Petasis reaction” is promoted by a catalytic amount of Lewis acid ($La(OTf)_3$), which allows the formation of the corresponding key hydrazone. With aldehyde **443**, (phenylacetylene)trifluoroborate, and 2-nitrobenzenesulfonylhydrazide **444**, the reaction in acetonitrile led to the formation of the allene **446** as a 2:1 mixture of diastereomers and 88% yield. The alkyne is delivered to the intermediate hydrazone intramolecularly via an activated borate species **447** and, after the loss of sulfinic acid to the *anti*-configured diazine **445**, a nitrogen extrusion gives the desired allene. The stereochemical outcome was rationalized by the preference for alkyne addition to the $A^{1,2}$ -minimized hydrazone conformer **447** over conformer **448**.



Scheme 96 Formation of allenes by traceless Petasis reaction

With a cyclic system such as 2-hydroxycyclohexanone, the desired allene product was obtained in 62% yield and a good 20:1 stereoselectivity. Also, with the β -hydroxy aldehyde **450**, obtained after treatment of dialdehyde **449** with (L)-proline, the traceless Petasis reaction led to the corresponding allene **451** in 53% yield and high levels of both enantio- and diastereoselectivity for the three contiguous stereogenic centers formed.

Note that, more recently, asymmetric boronate additions to sulfonyl hydrazones catalyzed by chiral biphenols to access enantioenriched allenes in a traceless Petasis reaction have been reported.^{338, 339}

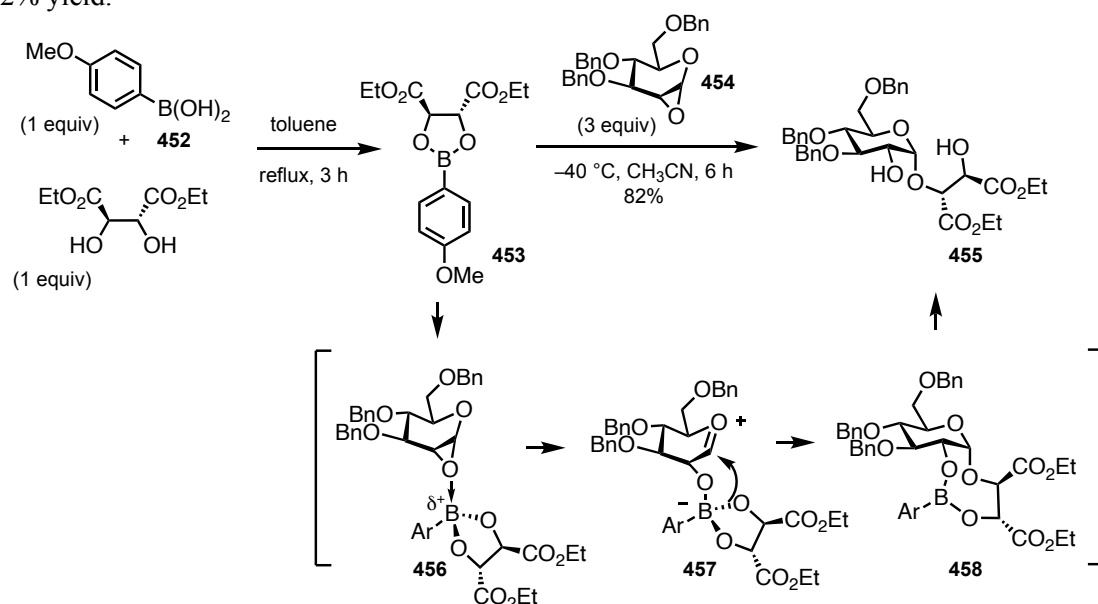
5 Boron-mediated stereoselective glycosylation

Boron compounds play an important role in modern carbohydrate chemistry with many applications as analytical probes, components of chromatographic stationary phases, and tools for chemical synthesis.³⁴⁰ Boronic ester can serve as useful protective group for carbohydrates thanks to the selective formation of cyclic boronates, a property known for more than 60 years. The partial p-character of the B–O bonds attenuates the nucleophilicity of the boron-bonded alkoxy groups and allows performing selective acylation, silylation, sulfation, alkylation, and glycosylation of glycoside substrates.^{341, 342} Usually, organoboron–carbohydrate interactions are sensitive to differences in conformational, steric, and electronic properties of the diol unit with favorable complexation of 1,2- versus 1,3-diol motifs; *cis*- versus *trans*-1,2-diol stereoisomers in cyclic systems; and furanosides versus pyranosides. Organoboron compounds may also be used as activating groups for diol motifs in carbohydrates thanks to the formation of a tetrahedral boronate. The latter can be generated after the complexation of cyclic boronates with a Lewis base or by catalytic protocols employing a borinic acid derivative. These methodologies have been applied to selective functionalization (acylation, sulfonylation, alkylation, and glycosylation) occurring at the less sterically hindered equatorial position of the *cis*-diol.³⁴³ These two properties can be combined with the initial formation of a tri-coordinated boronic ester which serves as a protecting group allowing the functionalization of free OH groups. Then, in a second step, the generation of a tetracoordinate adduct with the addition of a Lewis base serves as an activating group, allowing the functionalization by an electrophile of one of the oxygen atoms bonded to boron.³⁴⁴ This chapter will focus on boron-mediated aglycon delivery for 1,2-*cis*-stereoselective glycosylation and anomeric *O*-alkylation with organoboron catalysis

5.1 Boron-mediated aglycon delivery for 1,2-*cis*-stereoselective glycosylation

Recently, boron derivatives have been used for selective 1,2-*cis* glycosylation reactions.^{345, 346} These types of glycosylations are the most challenging since the formation of the 1,2-*cis* compounds precludes the application of anchimeric assistance from a 2-*O*-acyl functionality in the glycosyl donor. To this end, a new method of 1,2-*cis*- α -stereoselective glycosylation has been proposed using *cis*-1,2- or 1,3-

diol glycosyl-acceptor-derived boronic ester with a 1,2-anhydro glycosyl donor (Scheme 97).³⁴⁷ Initial investigations have been carried out with diethyl L-tartrate as the glycosyl acceptor and 1 α ,2 α -anhydroglucose **454** as the glycosyl donor. The best conditions were obtained with 4-methoxyphenyl boronic acid **452** in MeCN at $-40\text{ }^{\circ}\text{C}$ for 6 hours producing the corresponding 1,2-*cis*- α -glycoside **455** in 82% yield.

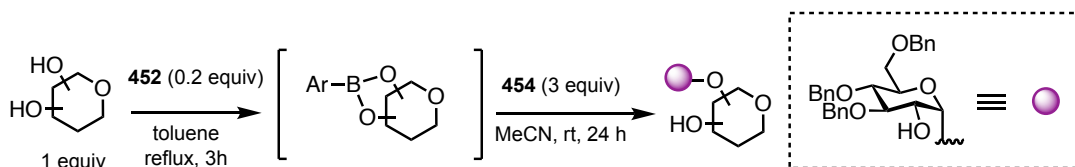


Scheme 97 1,2-*Cis* glycosylation reactions of diethyl L-tartrate with a 1,2-anhydro glycosyl donor

The reaction proceeds thanks to the Lewis acidity of acceptor-derived boronic ester **453**, which activates the 1,2-anhydro glycosyl donor **454** without any further additives. The oxocarbenium intermediate **457**, involving a tetracoordinate boronate ester moiety, increases the nucleophilicity of the boron-bound oxygen atom, and a concomitant S_{NI} (internal nucleophilic substitution)-type glycosylation from the less-hindered B–O moiety in the boronate takes place. The electrostatic effect of the substituents on the benzene ring in the boronic esters has been studied showing that with electron-withdrawing groups, lower yields were obtained. The reaction could also proceed well with a catalytic amount of boronic acid (0.2 equiv).

This glycosylation method was then applied to several 1,3-diol sugar acceptors leading to the corresponding glycoside in excellent α selectivity (Table 2). Except for galactoside **459** which provides the corresponding α -(1,6) glycoside **460**, α -(1,4) glycosides were obtained mainly with other glycosides such as the glucoside **461**, mannoside **463**, glucosaminide **465**. For the galactose derivative, the regioselectivity can be explained by glycosylation from the oxygen atom at the 6-position through the favored TS **472** (Figure 8). The transition state TS **471** is destabilized due to steric hindrance between the anomeric proton of the oxocarbenium and the benzene ring of the boronate ester. For glycosylation with gluco or manno derivatives, similar interaction between the anomeric proton of the oxonium cation and the benzene ring of the boronate ester destabilizes TS **473** and the regioselectivity is obtained through the favored TS **474**.

The glycosylations with **454** of *cis*-1,2-diol sugar acceptors were also examined with the mannoside **467** and galactoside **469** leading respectively to the α -(1,3) glycoside **468** and α -(1,4) glycoside **470** as the main adduct.



Acceptor	Product	Yield (%)	Acceptor	Product	Yield (%)
		70 α -(1,6)			77 α -(1,4) 14 α -(1,6)
		82 α -(1,4)			70 α -(1,3)
		92 α -(1,4)			65 α -(1,4) 7 α -(1,3)

Table 2 1,2-*Cis* glycosylation reactions of 1,3- and 1,2-diol sugar acceptors with a 1,2-anhydro glycosyl donor

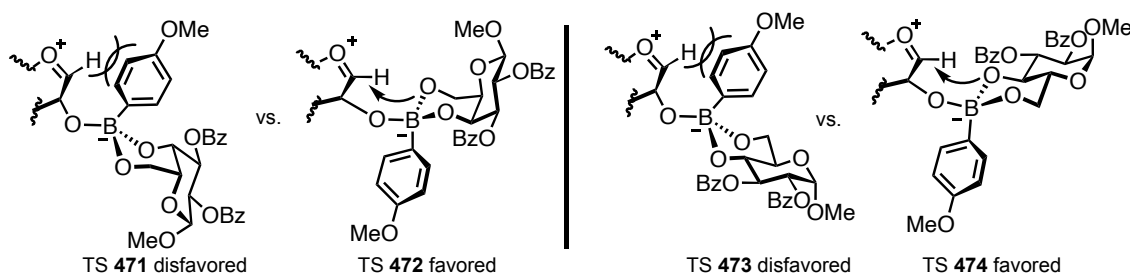
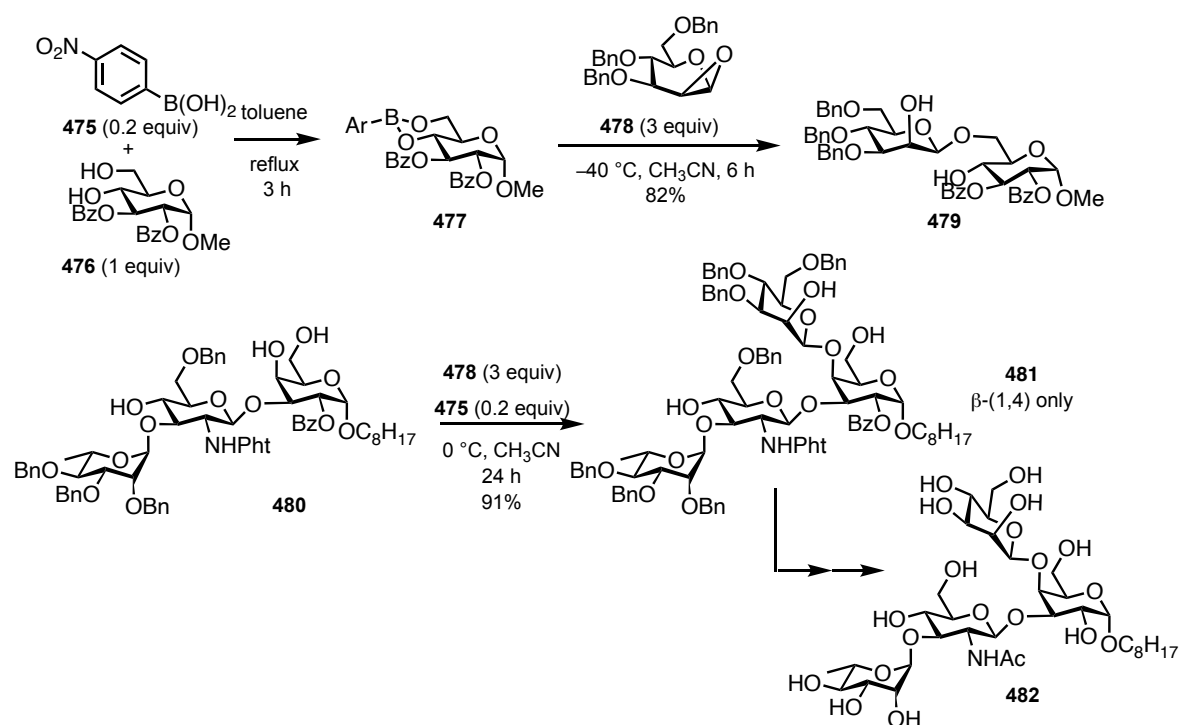


Figure 8 Proposed transition states to explain the regioselectivity of the glycosylation

The glycosylation reaction was described with 1,2-anhydromannose **478** and diol sugar acceptors to give the corresponding β -mannosides with high regio- and β -stereoselectivities (Scheme 98).³⁴⁸ In this case, the reaction required the use of *p*-nitrophenyl boronic acid **475** to obtain high yield and β -selectivity. Thanks to the electron-withdrawing group, the Lewis acidity of the boron atom is increased which allows, after activation of **478** by the boronic ester and formation of the oxonium cation, the intramolecular nucleophilic attack of the S_N1 type of the atom of oxygen bound to boron in the boronate ester from the same β -face of the oxonium cation. For example, reacting glycosyl-acceptor-derived boronic ester **477** and donor **478** in acetonitrile at -20 °C for 6 h produced the corresponding α -1,6-disaccharide **479** in 90% yield and as a unique β -anomer. As previously, the observed regioselectivity is governed by steric factors.

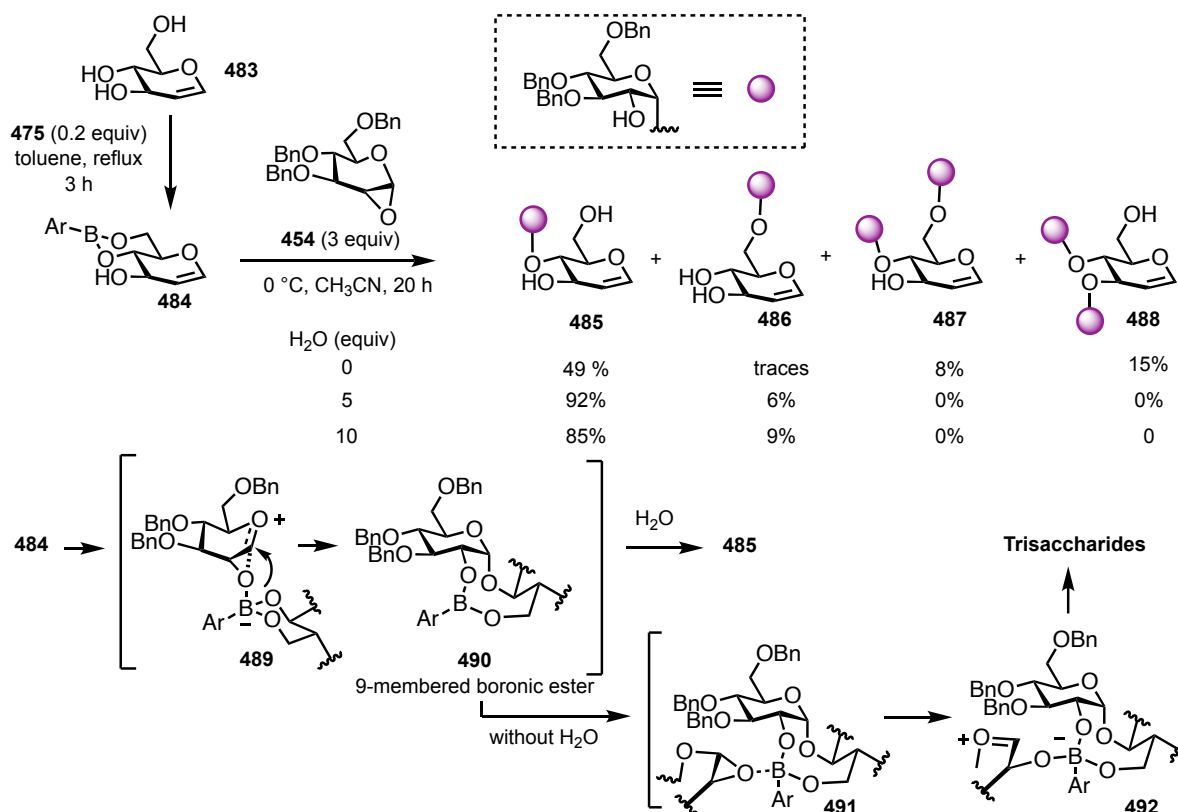
Using this glycosylation method and starting with the trisaccharide **480**, a tetrasaccharide **482** repeating unit of lipopolysaccharide (LPS) derived from *E. coli* O75 was successfully obtained.



Scheme 98 1,2-*Cis* glycosylation reactions with 1,2-anhydromannose. Application to the synthesis of a tetrasaccharide repeating unit of lipopolysaccharide

Stereospecific β -L-rhamnosylation using 1,2-anhydro-L-rhamnose donor and 4,6-diol sugar acceptors has been also developed.³⁴⁹ With a catalytic amount of 4-nitrophenyl boronic acid in CH_3CN , several β -L-Rhap-(1,4) derivatives were produced in high yield and full stereoselectivity. Moreover, the synthesis of a trisaccharide, α -L-Rhap-(1,2)- β -L-Rhap-(1,4)-Glc_p, derived from *Streptococcus pneumoniae* serotypes 7B, 7C, and 7D was completed using this strategy.

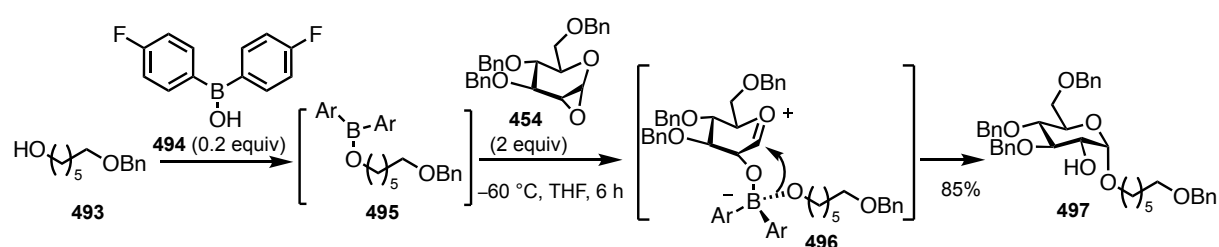
Regio- and 1,2-*cis*-stereoselective glycosylation of unprotected sugar acceptors is also possible (Scheme 99).³⁵⁰ In the reaction of 3,4,6-tri-*O*-benzyl-1,2-anhydroglucose **454** and D-glucal **483** as the glycosyl acceptor, *p*-nitrophenyl boronic acid showed the highest reactivity, producing α -(1,4) glycoside **485** in 49% yield and overreacted trisaccharides **487** and **488** in 8% and 15% yields respectively. This issue can be solved thanks to the addition of water (5-10 equiv) that could induce rapid hydrolysis of 9-membered boronic ester **490**, thus inhibiting the activation of the donor **454** by **490**. This allowed producing the desired disaccharide **485** (85-93% yields) and the relatively stable 6-membered boronic ester catalyst **484** through an equilibrium process.



Scheme 99 1,2-*Cis* glycosylation reactions of unprotected sugar acceptors using boronic acid

The total synthesis of terposide B, a natural pentaglycosylated sphingolipid containing α -L-fucose was achieved thanks to this approach.³⁵¹

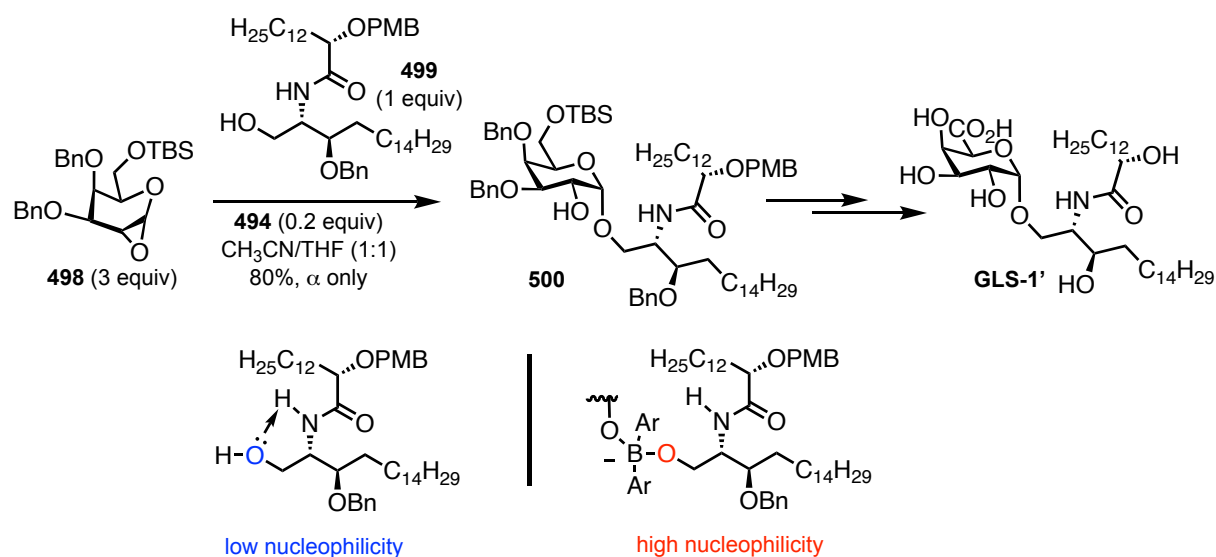
The 1,2-*cis* stereoselective glycosylation has been applied to mono-ol acceptors using a borinic ester (Scheme 100).³⁵² With 1,2-anhydroglucose **454**, the reaction has been optimized on 6-*O*-benzyl-1-hexanol **493**. The best results were obtained with 0.2 equiv of di(4-fluoro) phenylborinic acid **494** in CH₃CN at -60 °C for 6 h, leading to the glycosylated adduct **497** in 85% and a complete α -stereoselectivity.



Scheme 100 1,2-*Cis* glycosylation reactions of mono-ol acceptors using a borinic ester

The scope of the glycosylation has been investigated using several primary or secondary alcohols giving the corresponding α -compounds in high yields. In the case of relatively hindered secondary alcohols, lower yields were obtained due to the low binding affinities of these alcohols to the borinic acid. The problem was partly solved by increasing the amount of borinic acid used (2 equiv instead of 0.2). This glycosylation method was applied to the total synthesis of biologically active natural GSLs that contain the hydrophobic ceramide and the hydrophilic monosaccharide 1,2-*cis*- α -glucuronic (GSL-1) or galacturonic acid (GSL-1') (Scheme 101). This procedure allowed to overcome the problems of the challenging 1,2-*cis*- α -selectivity and the low nucleophilicity of the C1 hydroxyl group in the ceramide acceptor due to hydrogen bond formation between the electron pair on the C1 oxygen and amide hydrogen. Using protected ceramide-derived borinate ester allowed to increase the nucleophilicity of

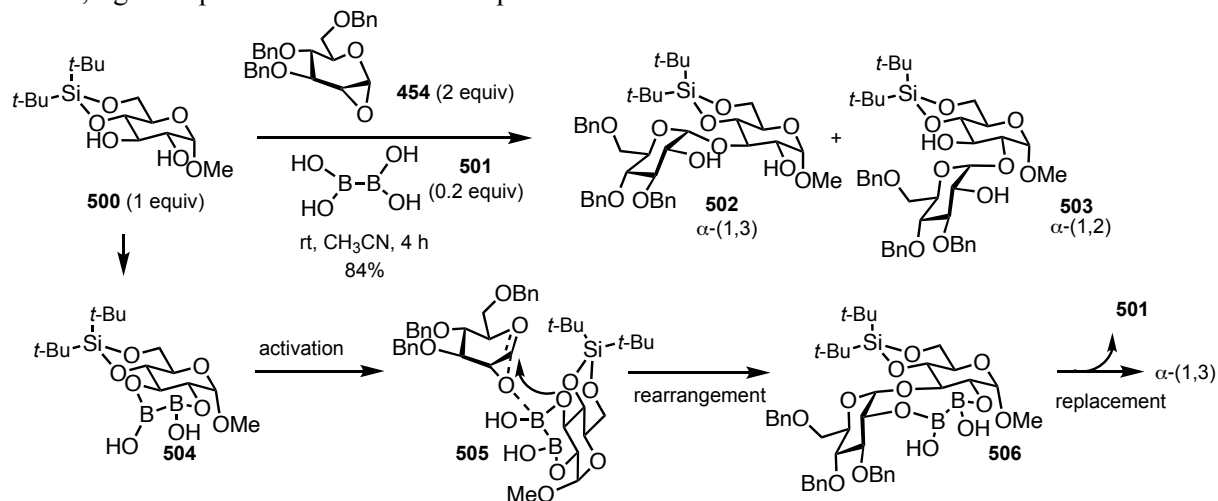
the boron-bound oxygen atom and leads with 1,2-anhydrogalactose **498** and borinic acid **494** to the glycosylated ceramide **499** in 84% yield with excellent α -stereoselectivity. After deprotection of the TBS group, oxidation of the resulting primary hydroxyl group, and removal of the Bn and PMB groups, **GSL-1'** was obtained.



Scheme 101 Total synthesis of natural **GSL-1'** using 1,2-*cis* glycosylation reactions of ceramide acceptor

The glycosylation procedure of mono-ol acceptors with borinic acid was effective for highly β -stereoselective mannosylation of 1,2-anhydromannose and applied successfully to the total synthesis of acremomannolipin **A**³⁵³ and members of mannosyl erythritol lipids (MELs) with different alkyl chain lengths.³⁵⁴

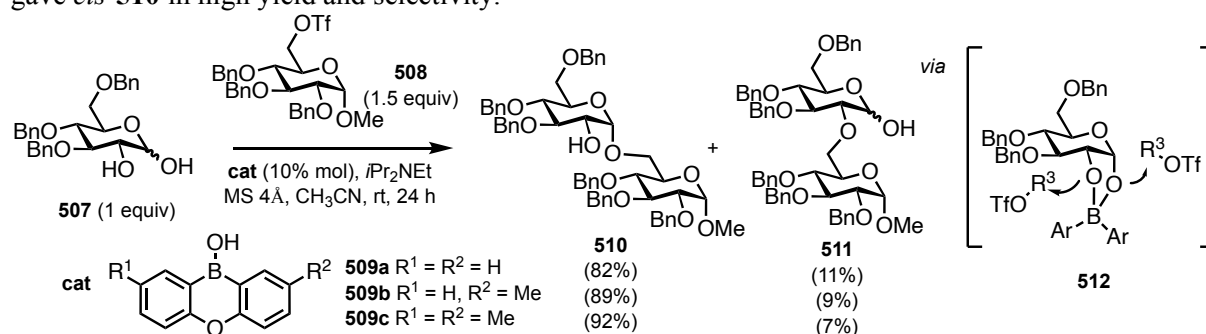
Very recently, the possibility of performing the 1,2-*cis*-stereoselective glycosylation of *trans*-1,2-diol sugar acceptors was demonstrated in the presence of tetrahydroxydiboron **501** (Scheme 102). For example, the reaction of 1,2-anhydroglucose **454** as the glycosyl donor and organoboron catalyst **501** with the diol acceptor **500** containing cyclic di-*t*-butylsilylene protecting group resulted in the formation of the corresponding α -glycosides **502** and **503** in high yields, complete α -stereoselectivity and high α -(1,3)-regioselectivity (**502/503** = 92:8). The reaction outcome was explained by the formation of relatively stable 1,2-bonded diboron **504** which activates the glycosyl donor **454**. After a sequential rearrangement of the B–O moiety in **505** that affords **506**, a diol exchange reaction regenerates tetrahydroxydiboron **501** and provides 1,2-*cis*- α -glycosides. Using this approach, the efficient synthesis of α -1,3-glucan pentasaccharide was completed.



Scheme 102 1,2-*Cis* glycosylation reactions of *trans*-1,2-diol sugar acceptors

5.2 Anomeric *O*-Alkylation with organoboron catalysis

Glycosylations using 1,2-*O*-unprotected sugars have been investigated for preparing 1,2-*cis*-glycosides. Examples of aryl boronic acid-catalyzed dehydrative coupling with 1-hydroxy glycosyl compounds have been reported for which the thermodynamically controlled products are obtained as a mixture of two anomers.³⁵⁵ Alternatively, regio- and stereoselective synthesis of 1,2-*cis*-glycosides has been performed by boron-catalyzed anomeric *O*-alkylation (Scheme 103).^{356,357} Optimization of the reaction conditions has been carried out with **507** and triflate **508**. The best results have been achieved in MeCN with *i*Pr₂NEt, 4 Å molecular sieves in the presence of 10 mol % of the tricyclic boronic acids **509** that gave *cis*-**510** in high yield and selectivity.

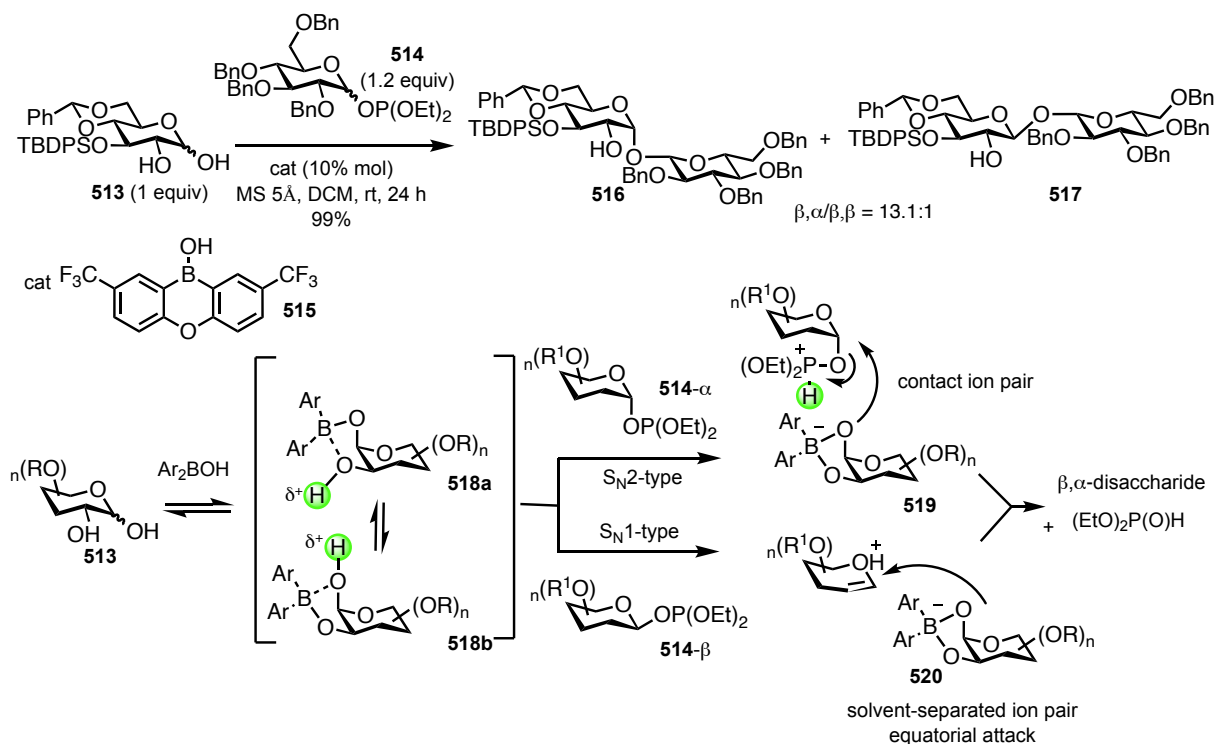


Scheme 103 Boron-catalyzed anomeric *O*-alkylation

The substrate range of glucose-derived diols has been studied with triflate **508** and boronic acid **509** showing broad tolerance to functional-group, including trityl, benzoyl, acetal, and silyl groups. The reaction was also applied to mannose-derived diol and galactose-derived diol, yielding the corresponding *cis* products with excellent regioselectivity in the case of mannose but not in the case of galactose. The reaction scope with triflates showed that the reaction proceeded well with both primary triflates but also secondary triflates. In the latter case, the anomeric *O*-alkylation with diol **507** was carried out in the presence of 20 mol % of boronic acid catalyst, which gave the corresponding α -(1,4)- and α -(1,3)-linked *cis*-products with complete inversion of configuration. Control experiments performed with 2-deoxy and 2-*O*-protected glucoses showed that no alkylation occurred with these substrates demonstrating the need for a 1,2-diol moiety to activate the axially oriented anomeric oxygen.

This strategy with 1,2-dihydroxyglycosyl acceptors and glycosyl donors in the presence of a tricyclic boronic acid catalyst has been applied to the stereoselective synthesis of unsymmetrical 1,1'-disaccharides (Scheme 104).^{358,357} In this case, the complexation of 1,2-diols with boronic acid may generate an "acidic OH group" that can activate glycosyl donors. The reaction was first tested with 1,2-dihydroxy glycosyl acceptor **513** and very good results could be obtained with glycosyl phosphite **514** as a donor in combination with tricyclic boronic acid catalyst **515** (10 mol%). The best conditions were found in DCM at rt for 24 h, giving the corresponding 1,1'-disaccharide in almost quantitative yield, and β , α -isomer **516** was obtained as the major isomer (β , β / β , α = 13.1:1).

After activation of the glycosyl donor by the "acidic OH group" coordinated by the monoborinate ester of the glycosyl 1,2-diol, glycosylation of **519** with the α -phosphite donor **514** can proceed by an S_N2-like pathway via the contact ion pair providing β -disaccharide **516** in high selectivity. In the case of the β -phosphite donor **514**, an S_N1-like pathway can take place via the solvent-separated ion pair with the equatorial attack of the borate anion leading to the same major adduct.



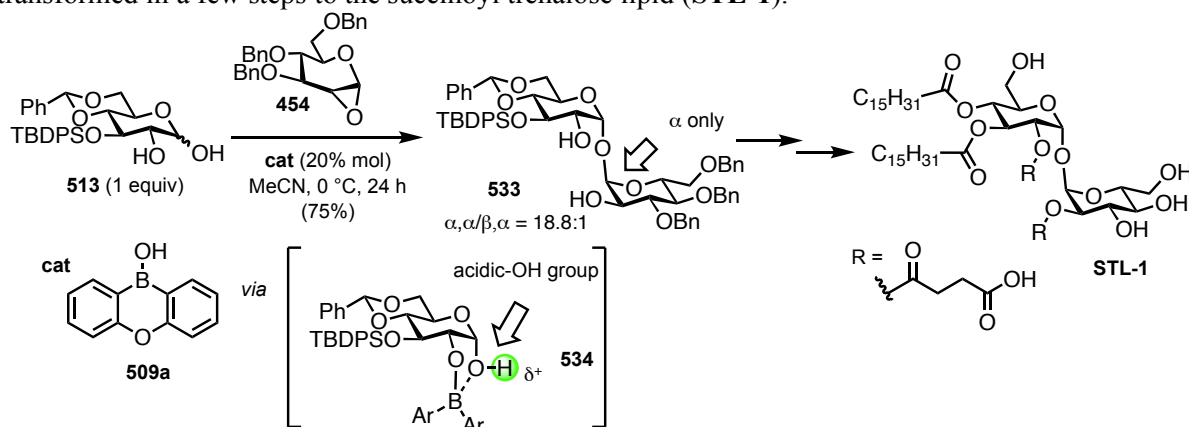
Scheme 104 Boron-catalyzed anomeric *O*-alkylation

By using glycosyl phosphite **514** and boronic acid catalyst **515**, a wide range of glycosyl acceptors could be employed. For example, the glucose derivative **521** having unprotected -OH groups at the 1,2- and 6- positions provided the corresponding adduct **522** in 92 % yield (Table 3). The β,α -selectivity obtained was perfect and no reaction occurred at the C6 position. In contrast, the reaction of 2.4 equivalents of **514** with the glucose compound **523** having four unprotected OH groups at the 1,2,4, and 6 positions led to the corresponding 1,6-diglycosylated adduct **524** in 61% yield. These two results showed again the importance of the complexation of the boronic catalyst with 1,2-diols. With 3,4,6-tri-O-protected galactose **525**, the β,α -disaccharide **526** was obtained exclusively in 86% yield. For D-mannosyl and L-xylosyl acceptors **527** and **529**, excellent yield and high selectivity have been obtained in the favor of the corresponding β,β -disaccharides. The reaction applied to *N*-protected glucosamine such as **531** occurred only with sulfonamides-protecting group and not with acetate or carbamate group (Troc). This is explained by the acidity of the N-H group thus confirming the importance of the coordination of the nitrogen atom with boron to form a borinate intermediate. The reaction could also be applied with success to various glycosyl phosphite donors such as galactosyl phosphites or glycosyl phosphites derived from glucosamine and galactosamine.

Acceptor	Product	Yield (%)	Acceptor	Product	Yield (%)
		92 (β,α)			97 (β,β/α,β = 11.1:1)
		61 (β,α)			92 (β,β)
		86 (β,α)			99 (β,α)

Table 3 Boron-catalyzed anomeric *O*-alkylation

1,1'-Disaccharides could also be obtained from the reaction of the anhydro sugar donor **454** and the "activated OH group" of glycosyl 1,2-diol **513** by the borinic acid catalyst (Scheme 105). In this case, in the presence of catalyst **509a** (20 mol%) and glycosyl 1,2-diol **513**, the donor is activated by the "acidic OH group" and led to the formation of α,α-trehalose **533** as the major isomer. The latter was transformed in a few steps to the succinoyl trehalose lipid (STL-1).



Scheme 105 Boron-catalyzed anomeric *O*-alkylation with anhydro sugar donor

Conclusion

The use of organoboron reagents is one of the most powerful tools in organic synthesis. In particular, the generation of active intermediates is facilitated thanks to the presence of a Lewis acidic boron atom with a vacant p orbital and adjacent Lewis basic oxygen atoms with lone pair of electrons. This may thus allow the performing of asymmetric transformations under the conditions of a chiral environment. The boronate reagent activation strategies have been demonstrated in the 1,2-metallate rearrangement of boronate esters. In this case, the homologation of boronic esters derived from chiral diols with achiral organometallic has been described and allows the formation of new stereogenic centers controlled by the diol architecture (substrate control). The reaction can also proceed via chiral tetravalent boron "ate" complexes formed from a chiral carbanion (mainly lithiated carbamates or benzoate) and achiral boronic esters, which allows asymmetric homologation. The access to the as-formed alpha-chiral boron reagents

provides a very powerful platform for asymmetric synthesis. Indeed, the resulting homologate organoboron can be applied for further transformations and can undergo numerous stereospecific reactions such as oxidation, amination, protodeboronation, non-transition-metal stereospecific arylation with electron-rich aromatic or *N*-heteroaromatic compounds. In addition, transmetallation of chiral organoboron compounds with transition metal complexes generates chiral active organometallic species, which in turn initiate entirely stereospecific C-C bond formation with retention or inversion. The coordination of the Lewis base with the Lewis acid boron atom also facilitates asymmetric nucleophilic addition as in the allylation reaction or in the borono-Mannich reaction (Petasis reaction). For the allylation reaction, the strategy described in this chapter for the preparation of optically enriched molecules involves the use of chirality transfer from chiral allylboron species bearing chiral auxiliaries and α -substituted chiral allylboron species. Usually the electrophilic partner (carbonyls or imines) is coordinated to the boron center, serving to both increase its own electrophilicity and to activate the nucleophilicity of the allyl group by increasing the electron density on the Lewis-acidic boron center. For the Petasis reaction, the cornerstone of the reaction is the presence a directing group near the reacting carbonyl group, which allows the activation of the boronic acid as an 'ate' complex and results in the possible transfer of a organyl group to the transient iminium species. Moreover, in the field of carbohydrate chemistry, the boronate reagent activation strategies have proved to be useful for boron-mediated aglycon delivery for 1,2-*cis*-stereoselective glycosylation and anomeric *O*-alkylation. The power of these methodologies has been demonstrated through countless applications both in total synthesis and for the production of molecules of biological interest.

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