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(2*R*,3*R*)-1,4-Dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol: Valuable reagent in the asymmetric synthesis of organoboronates*,**

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Abstract: Tartrate-derived (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol has found diverse applications in asymmetric organic synthesis. Among these, its utilization as a protecting group for boronic acids has been investigated extensively. Besides being extraordinarily stable and thus allowing a plethora of transformations, it enables access to various diastereo- and enantiomerically pure organoboron reagents and versatile intermediates in asymmetric synthesis.

Keywords: asymmetric synthesis; boron; diastereoselectivity.

INTRODUCTION

While inorganic boron-containing reductants were the first boron-containing reagents applied extensively in organic chemistry [1–4], more sophisticated organoboron reagents were developed to find application in asymmetric reduction reactions [5–7]. Over the last decades, boron-based reagents have also gained a pivotal role as building blocks in efficient C–C bond-forming reactions. For example, the Suzuki–Miyaura cross-coupling reaction belongs to the most valuable and general tools in organic chemistry [8–10], while allylboron reagents are efficient and predictable tools for asymmetric allylation reactions [11–21]. Although boronic acids themselves are convenient and easy-to-handle reagents in general and good substrates for Suzuki–Miyaura cross-coupling reactions [22], in the case of many other reactions and synthetic transformations, protection of the boronic acid moiety **1** is necessary (Fig. 1). Protective groups for boronic acid moiety [23] have to meet general demands as well as special demands depending on the specific application of the protected compound. Generally, a protective reagent should be readily available; introduction of the protective group should proceed in high yield under mild conditions. Additionally, the protected compound has to be sufficiently stable under given conditions, and finally it should be cleavable selectively under defined conditions without substantial loss of substrate [24]. By now, there is a wide range of compounds established for the protection of the boronic acid moiety displaying special properties in each case. Formation of dioxaborolanes and dioxaborinanes is a long-approved way of protection by esterification. Cyclic boronic esters are mostly more stable than acyclic ones, and furthermore the stability of the esters can be improved by selection of substituted diols for boronate formation (**2–7**) [25,26]. Introduction of stereogenic centers to the boronic ester moiety enables application of chiral boronates (**8–12**) in asymmetric synthesis. Several chiral diols have found application as protective groups, acting as chiral auxiliaries at the same time. A number of

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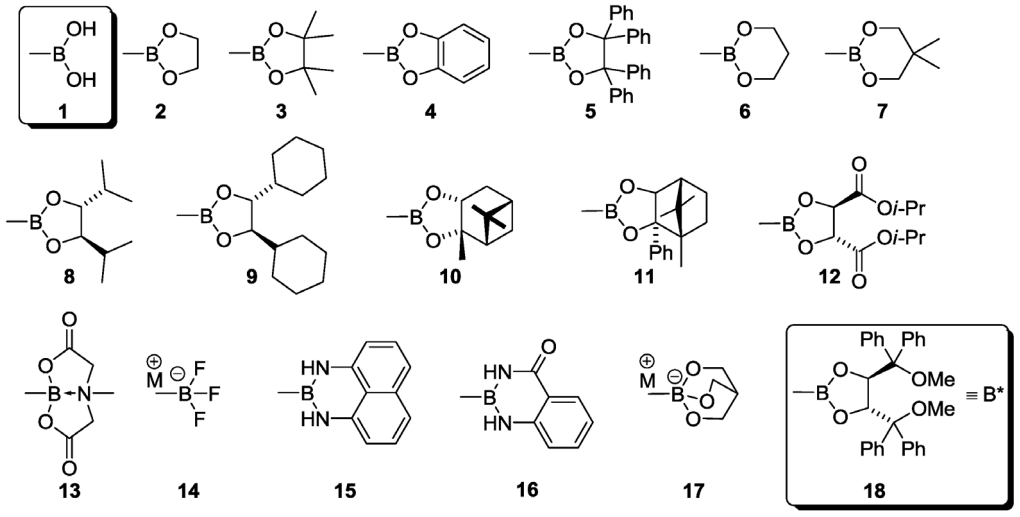


Fig. 1 Protective groups for boronic acids.

applications with very high stereoselectivity of corresponding reagents and reactions have been reported, and in some cases the chiral auxiliaries enable the separation of resulting diastereomeric mixtures [19,27–31]. Trifluoroborates **14** are easy to prepare and purify, and they are exceptionally stable toward air and moisture. They also tolerate many reaction conditions and can be functionalized in many ways [32,33]. Stable triolborates **17** are also ate-complexes insensitive to moisture and air, showing advantageous properties in metal-catalyzed C–C- and C-heteroatom bond-forming reactions [34]. *N*-methyl iminodiacetic acid (MIDA)- and 1,8-diaminonaphthaline (DAN)-protected boronic acid moieties **13** and **15** have gained considerable attention for their ability to enable iterative cross-coupling sequences by efficiently inactivating boronic acid moieties toward cross-coupling conditions and being readily cleavable subsequently [35–42]. The utilization of anthranilamide (AAM) as a modifier for the boronic acid moiety of arenes **16** allows iterative cross-coupling by protection toward cross-coupling reactions, additionally, it serves as a highly efficient *ortho*-directing group for functionalization based on catalytic C–H activation [43].

Diol-protected boronates **18** are extremely stable and can be stored and handled without special precautions. The group tolerates various reaction conditions, acts as a chiral auxiliary and owing to its bulkiness as a steric modifier in specific reactions. It is practically inert towards hydrolysis on silica, and its pronounced absorption in the UV region proved to be beneficial in flash column or medium-pressure liquid chromatography (MPLC). In many cases, diasteromeric mixtures can be separated chromatographically or by selective crystallization.

In this review, we intend to give an overview of the application of diol **26** corresponding to boronic ester **18** in organic synthesis, with a strong focus on its utilization as protective group for the boronic acid moiety. In order to cover all aspects of the issue, we start with a description of its synthesis and improvements made herein during the last few years (second section). Additionally, the role of structurally analogous compounds in asymmetric synthesis is spotlighted briefly in this chapter. In the third section, applications not related to organoboron chemistry are summarized, before the established methods for the preparation of protected (*E*)-alkenyl-, (*Z*)-alkenyl-, and arylboronates are presented. Cyclopropanation, epoxidation, [3.3]-sigmatropic rearrangements, and carbonyl allylation are also covered as methods for the synthesis of dioxaborolanes. Special attention is given to the reactivity and derivatizations of cyclopropylboronates and allylboronates; furthermore, the reported reactions of arylboronates are summed up and finally the recovery of diol **26** from boronates **18** is addressed. The fourth

section is dedicated to applications of cyclopropylboronates and allylboronates in drug and natural product synthesis.

(2*R*,3*R*)-1,4-DIMETHOXY-1,1,4,4-TETRAPHENYLBUTANE-2,3-DIOL

Synthesis

Chiral auxiliaries with C_2-symmetry have attracted considerable attention since it was discovered that they can be utilized in asymmetric processes beneficially [44]. Especially, tartrate-derived compounds of type **19** and **20** are known for their high asymmetric induction, e.g., in catalytic Sharpless epoxidations (**19**) [45–47] nucleophilic addition reactions to carbonyl groups or catalytic Diels–Alder reactions (**20**) (Fig. 2) [48–50]. Inspired by these studies, Nakayama and Rainier designed a new tartrate-derived chiral auxiliary **21** that possesses a variable alkyl group R. In addition, it was intended that the new auxiliaries form five-membered chelate complexes with metal ions applied in organic synthesis [51].

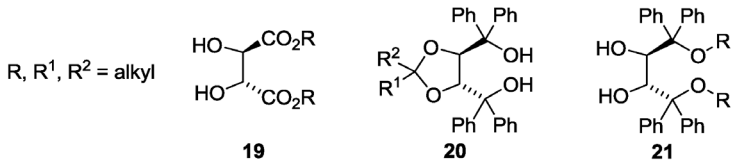
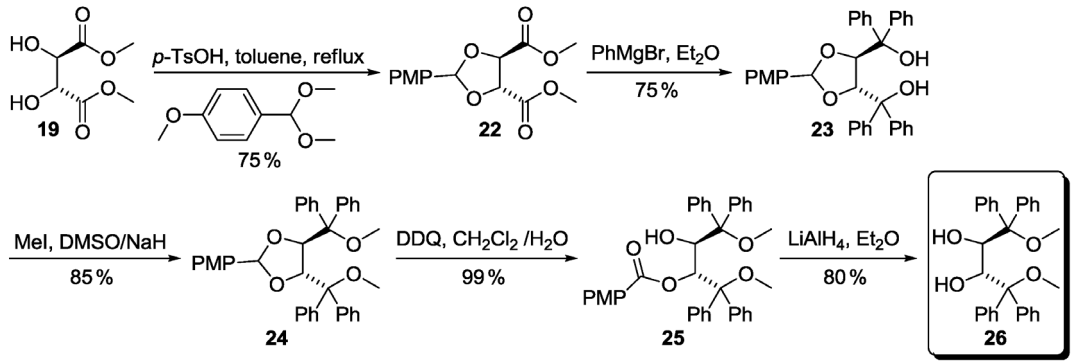


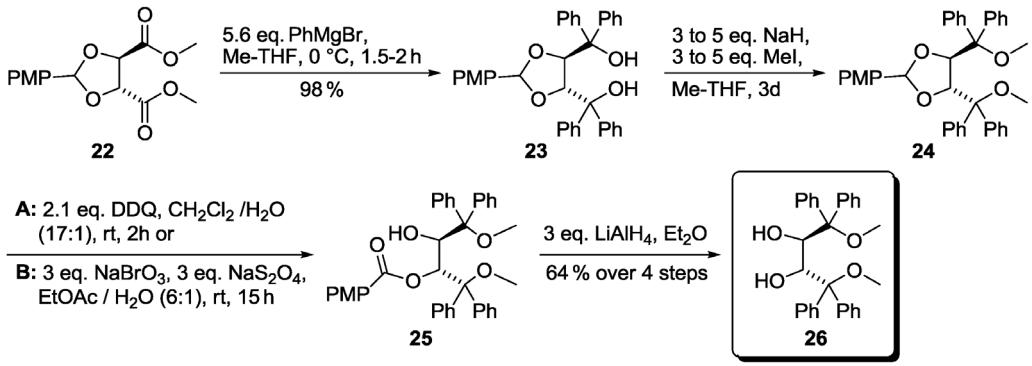
Fig. 2 Tartrate-based auxiliaries.

To form the protected compound **22**, L-tartrate **19** was first treated with α,α-dimethoxy-*p*-methoxybenzaldehyde and a catalytic amount of *p*-toluene sulfonic acid (*p*-TsOH). In the next reaction step, the phenyl groups were introduced via Grignard reaction. Subsequent methylation of **23** with MeI and NaH in dimethylsulfoxide (DMSO) led to compound **24**. The cleavage of the *para*-methoxybenzyl (PMB) group was carried out by oxidation with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) to give the hydroxyester **25**, which was then treated with $LiAlH_4$ to obtain diol **26** (Scheme 1).



Scheme 1 Synthesis of diol **26**.

Although all reactions of the original protocol proceeded in good yields, Pietruszka and co-workers optimized certain steps over the years (Scheme 2). The Grignard reaction for introduction of the phenyl groups was modified several times. Owing to the low solubility of compound **22** in Et_2O and agglutination of the reaction mixture while adding the Grignard reagent, the solvent was changed to tetrahydrofuran (THF) [52,53]. In a study of solvent systems, it was found that using 2-methyl tetra-



Scheme 2 Modified synthesis of diol **26**.

hydrofuran (2-Me-THF) simplifies the work-up procedure by enhancing layer separation during extraction. Furthermore, employing a commercially available solution of PhMgBr in 2-Me-THF facilitated the reaction set-up, and the number of equivalents of PhMgBr needed was reduced from 10 to 5.6 equiv. A lower amount of solvent was required, and the reaction time was shortened as well. The methylation procedure was changed to applying an excess of NaH in THF, followed by addition of MeI [54]. Product **24** was obtained in a higher purity than before changing solvent from DMSO to THF. For the oxidative cleavage of the PMB protection group, an alternative method was found, in which the toxic and expensive DDQ was replaced by the commercially available and inexpensive sodium bromate and sodium dithionite [54,55]. In the final step, ester **25** was reduced with $LiAlH_4$ and diol **26** was obtained. The major advantage of the optimized sequence is that only one final purification step by flash column chromatography has to be performed. Following this procedure on large scale, diol **26** was finally obtained in 64 % yield over 4 steps.

Structurally related compounds in remote-controlled asymmetric synthesis

When reviewing applications of diol **26**, it seems advisable to briefly provide basic information on utilization of structurally analogous compounds of type **27** (Fig. 3). While there is a wide range of α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol (TADDOL)-like structures **20**, which have found a vast number of applications in asymmetric synthesis and have been reviewed [49], applications of compounds **27** having an "inverse-TADDOL"-structure are not as numerous. Not surprisingly, most of these applications are characterized by the use of compounds **27** as protective group having a remote inductive effect in diastereoselective reactions.

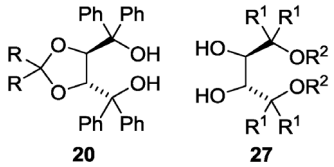
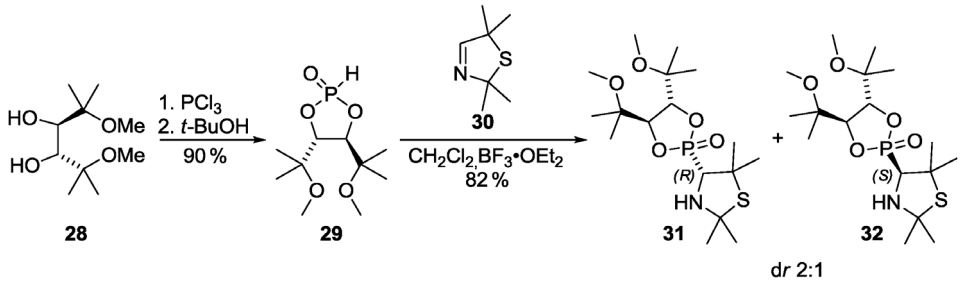


Fig. 3 "TADDOL"- and "inverse-TADDOL"-type compounds.

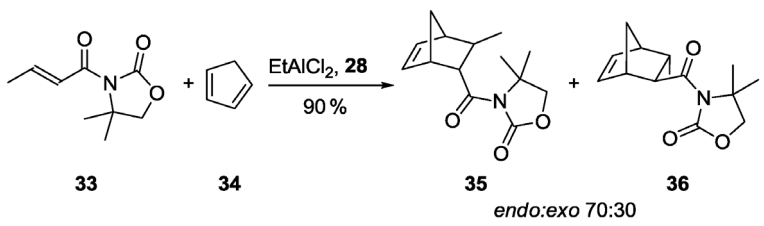
Besides being sufficiently stable to perform the reactions, the protective groups often enable separation of diastereomeric mixtures by chromatography and thereby synthesis of enantiomerically pure compounds. In 1985, Schöllkopf and co-workers reported the formation of enantiomerically pure cyclic phosphite **29** from diol **28** (Scheme 3). Addition to tetramethylthiazole **30** gave a 2:1 mixture of **31** and



Scheme 3 Application of diol **28** in synthesis of enantiomerically pure penicillamine-analogues.

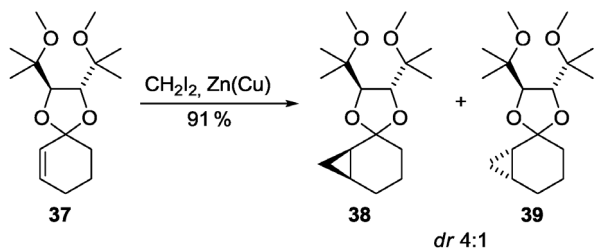
32 in high yield. The diastereomers were separated by chromatography on silica. Enantiomerically pure phosphonic acid analogues of D- and L-penicillamine were obtained upon hydrolysis [56].

Diol **28** was tested as chiral ligand in the Lewis acid-mediated Diels–Alder reaction of cyclopentadiene **34** and 3-crotonoyl-4,4-dimethyl-1,3-oxazolidin-2-one **33** reported by Jurczak and Chapuis (Scheme 4). Although the products were obtained in high yield, an *endo*:*exo* ratio of 70:30, and good diastereoselectivity from the reaction with $EtAlCl_2$ as Lewis acid, other ligands performed comparably or better in described reaction [57].



Scheme 4 Diels–Alder reaction with diol **28** as ligand.

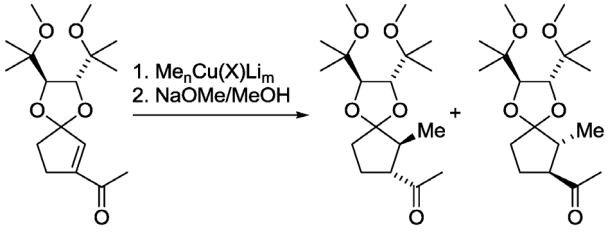
Diastereoselective cyclopropanations of homochiral ketals were investigated by Mash and co-workers. Under Simmons–Smith conditions, substrate **37** was transformed to diastereomers **38** and **39** in a 4:1 ratio in very good yield of 91 % (Scheme 5) [58].



Scheme 5 Diastereoselective cyclopropanation of homochiral ketals.

In diastereoselective organocuprate addition to homochiral cyclopentenone ketal **40** reported by Jung and Lew, products **41** and **42** were obtained in good yields, but with low diastereoselectivity (Table 1) [59]. For a selection of three cuprates, diastereomeric excess in the formation of products **41** and **42** ranged from 12 to 34 %.

Table 1 Diastereoselective organocuprate addition to homochiral ketal **40**.

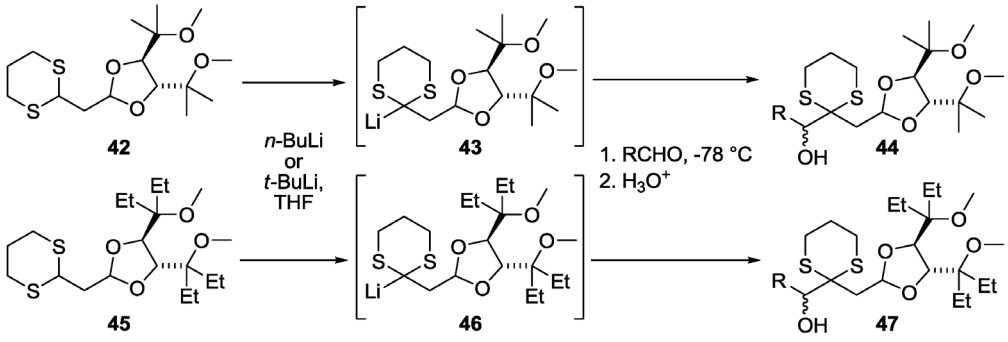


40 **41** **42**

cuprate	*dr* 41:42
Me_2CuLi	67:33
$Me_2Cu(CN)Li_2$	66:34
$(Bu_3P)MeCuLi$	56:44

In 1992, Chikashita and co-workers reported the asymmetric induction-based nucleophilic addition of chiral α-(1,3-dithian-2-yl)acetals **43** and **46** to achiral aldehydes (Table 2) [60]. While the addition of carbanion **44** to several aldehydes gave the expected products in good to excellent yields and diastereomeric ratio of 1.8:1 to 4.6:1, utilization of the tetraethyl-substituted analogue **47** resulted in better diastereoselection (diastereomeric ratio 2.4:1–6.3:1), but only modest yields.

Table 2 Nucleophilic addition of chiral thioketals to aldehydes.



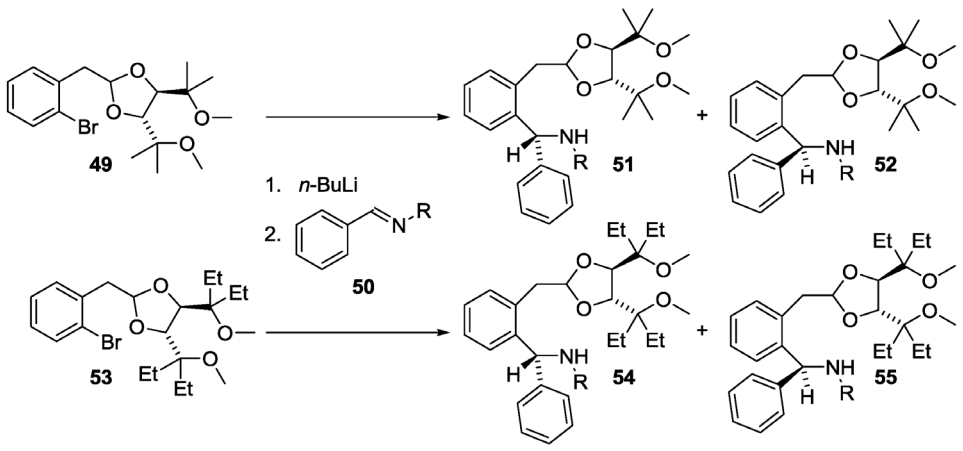
42 **43** **44**

45 **46** **47**

product	aldehyde (RCHO)	yield (%)	diastereomeric ratio
44a	*n*-C_3H_7CHO	74	2.8:1
44b	$(CH_3)_2CHCHO$	72	2.2:1
44c	$(CH_3)_3CCHO$	86	1.8:1
44d	C_6H_5CHO	85	2.6:1
44e	$CH_3CHCHCHO$	92	4.6:1
47a	*n*-C_3H_7CHO	32	4.0:1
47b	$(CH_3)_2CHCHO$	27	3.1:1
47c	$(CH_3)_3CCHO$	31	2.4:1
47d	C_6H_5CHO	26	3.4:1
47e	$CH_3CHCHCHO$	23	6.3:1

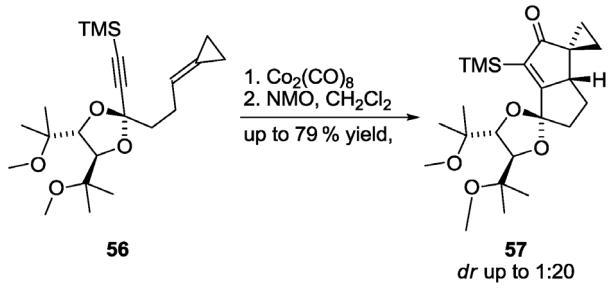
Wünsch and Nerdinger utilized diol **28-**derived 2-(2-bromobenzyl)-1,3-dioxolane **49** for the asymmetric synthesis of 1-aryltetrahydroquinolines (Table 3) [61–63]. Therefore, Li-halide-exchange was performed on acetal **49** before it was added to various imines. Using acylimines **50a** and **50b**, the products were obtained in yield of 63–66 %, but with very low stereoinduction (best result: diastereomeric ratio 55:45). Reaction with tosylimine **50c** resulted in similar yield and only in a slightly enhanced diastereomeric ratio of 61:39. Nearly the same results were obtained with analogous tetraethyl-substituted acetal **53**. Changing the substrate to benzylidene-aniline **50d** or benzylidene-anisidine **50e** improved the diastereomeric ratio to 91:9 for acetal **49**, while no reaction occurred with lithiated acetal **53**.

Table 3 Addition of chiral Li-nucleophiles to imines.



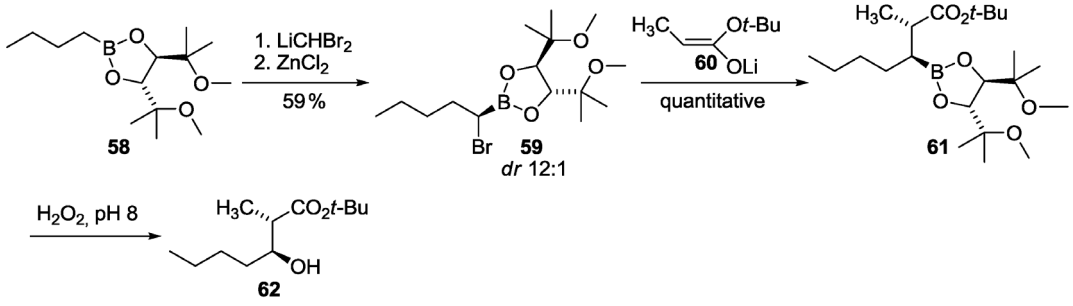
acetal	imine	R	products	*dr*	yield (%)
49	**50a**	CO*t*-Bu	51:52	55:45	66
49	**50b**	COOBn	51:52	51:49	63
49	**50c**	Tos	51:52	61:39	62
53	**50c**	Tos	54:55	62:38	32
49	**50d**	Ph	51:52	91:9	75
53	**50d**	Ph	54:55	-	-
49	**50e**	C_6H_4OMe	51:52	91:9	67
53	**50e**	C_6H_4OMe	54:55	-	-

Krafft and co-workers were able to improve the diastereoselectivity of Pauson–Khand reaction by applying diol **28** for formation of the propargylic acetal moiety of substrate **56** (Scheme 6) [64]. Increase of the steric bulk of the C_2-symmetric acetal group was recognized as one factor enabling a significantly higher level of stereoselection in synthesis of **57** in comparison to studies made earlier [65].



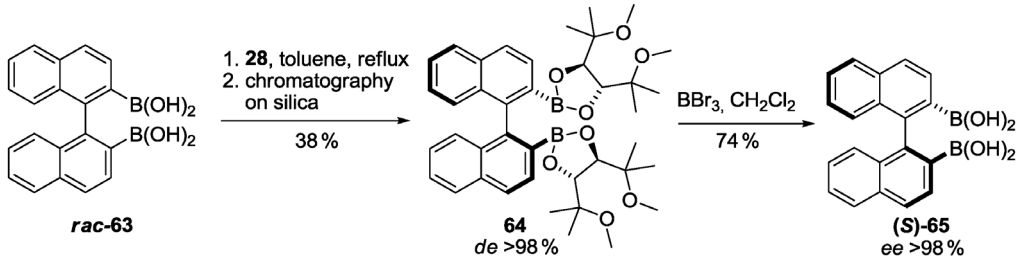
Scheme 6 Stereoselective Pauson–Khand reaction.

Utilization of diol **28** as a stereoinductive protective group for a boron moiety was first reported by Matteson and Michnick in 1990 (Scheme 7) [66]. Starting from butylboronate **58**, chiral α-bromoboronate **59** was synthesized, subsequently reacted with *tert*-butyl-lithiopropionate **60**, and finally deboronated with hydrogen peroxide. Matteson homologation of alkylboronate **61** yielded the product in a diastereomeric ratio of ~12:1. After enolate addition and oxidative deboronation, isolated product **62** contained 8–9 % diastereomeric impurity.



Scheme 7 Diol **28** as chiral boronate protective group.

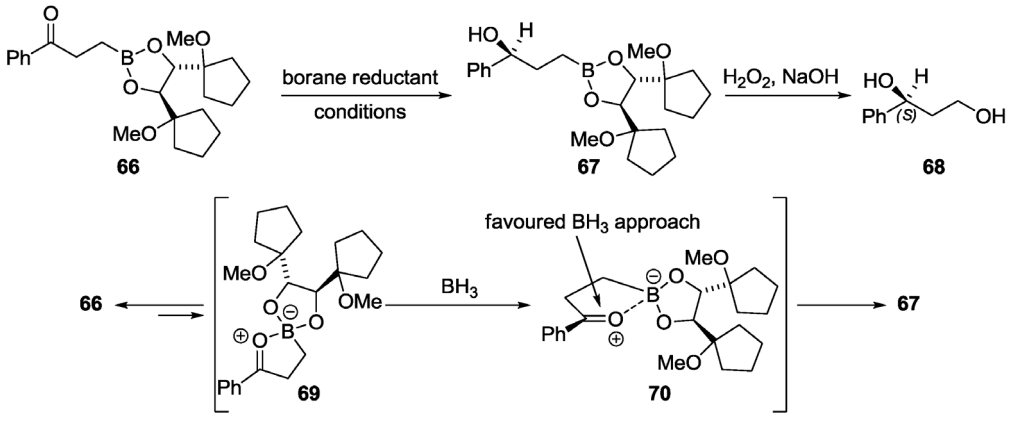
Furthermore, diol **28** was proven to be useful in the resolution of the atropisomers of binaphthyldiboronic acid *rac*-**63** by Kasák and co-workers (Scheme 8) [67]. Ester **64** was separated from its diastereomer by chromatography on silica gel in diastereomeric purity higher than 98 %. Subsequent deesterification yielded (*S*)-**65** with >98 % enantiomeric excess (ee).



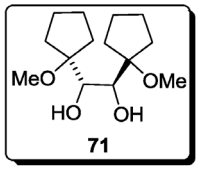
Scheme 8 Resolution of racemic binaphthylboronic acid.

A number of studies on remote asymmetric reaction control by boronates derived from diol **71** have been published by Whiting and co-workers [68–73]. The chiral protective group effected 1,6-asymmetric induction in the reduction of boronate **66** (Table 4). Depending on the reaction conditions, diol **68** was obtained in overall yield of up to 87 and 89 % ee after oxidative deboronation [68]. The efficient asymmetric induction was explained by intramolecular complexation of the carbonyl group by the boronate moiety (**69**), leading to a favored mode for the attack of BH_3 (**70**). This was underlined by the fact that no asymmetric induction was found under identical reaction conditions for the reduction of the analogous dioxolane [69]. The assumption was also reinforced by the results of molecular modeling studies [70].

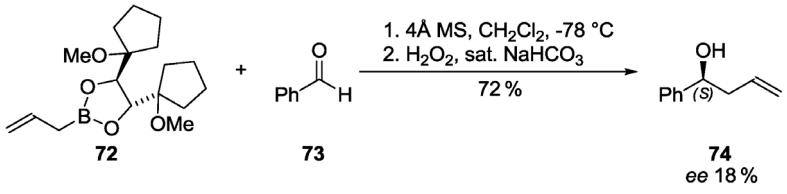
Table 4 Remote-controlled asymmetric induction of carbonyl group.



reductant	conditions	yield (%)	configuration of 68	*ee* (%)
BH_3•SMe_2	THF, -45 °C	81	*S*	55
BH_3•THF	CH_2Cl_2, -45 °C	87	*S*	89
L-Selectride®	THF, -78 °C	76	-	~0

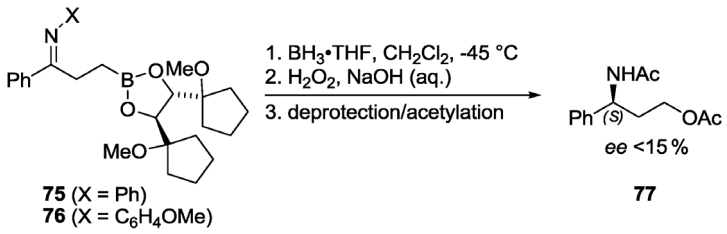


The hindered C_2-symmetric diol **71** was also applied as chiral protective group in allylboronate **72** (Scheme 9). Addition to benzaldehyde **73** gave (*S*)-configured phenylbut-3-en-1-ol **74** in 18 % enantiomeric purity [71].



Scheme 9 Diol **70** as inductor in allylboration.

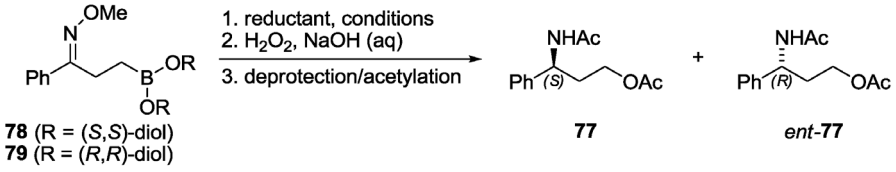
The 1,6-asymmetric reduction of carbonyl groups was extended to the stereoselective reduction of C–N double bonds (Scheme 10). Reduction of benzylidene imines **75** and **76** resulted in poor asymmetric induction (ee below 15 %).



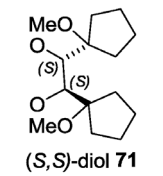
Scheme 10 Remote-controlled asymmetric reaction of imines.

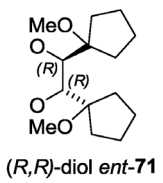
For oxime ethers **78** and **79** as substrates, no asymmetric reduction was effected unless amino-alcohols **80** and **81** were added to the reaction mixture (Table 5). Addition of triethylamine also resulted in the isolation of enantiomerically enriched product *ent*-**77**. Thereby, it was demonstrated that the homochiral boronate functionality in **78** and **79** can influence the stereochemical outcome of C–N double-bond reduction in the presence of a suitable partner reducing agent [72].

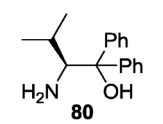
Table 5 Remote-controlled reduction of imines.

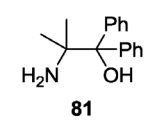


substrate	conditions	yield (%)	*ee* (%)	absolute configuration
79	10 eq. BH_3•SMe_2, THF, -15 °C - rt, 16h	94	0	-
79	10 eq. BH_3•THF, 0 °C - rt, 2d	75	0	-
78	10 eq. BH_3•SMe_2, THF, -15 °C - rt, 16h	73	0	-
79	**80**, 4 eq. BH_3•THF, THF, rt, 20h	71	95	*S*
78	**80**, 4 eq. BH_3•THF, THF, rt, 20h	74	8	*R*
78	**81**, 4 eq. BH_3•THF, THF, rt, 2d	96	13	*S*
78	Et_3N, 5 eq. BH_3•THF, THF, rt, 2d	82	28	*R*

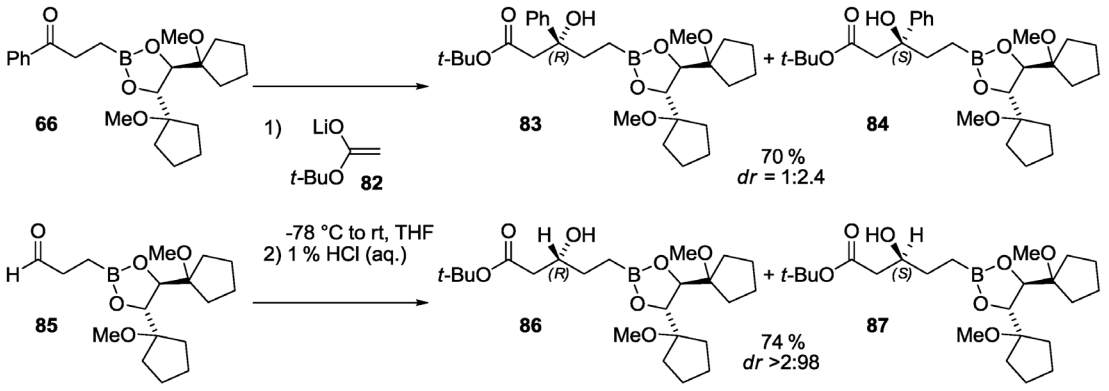

(*S,S*)-diol **71**


(*R,R*)-diol *ent*-**71**


80


81

Furthermore, stereoselective aldol reactions under remote control were also investigated: Diol **71**-derived substrate **66** was treated with lithium *tert*-butyl acetate **82** (Scheme 11), and products **83** and **84** were obtained in good yield and a diastereomeric ratio of 1:2.4. Finally, reaction of aldehyde **85** proceeded in excellent diastereoselectivity, leading to isolation of alcohol **87** as a single diastereomer (as judged by NMR analysis) [73].



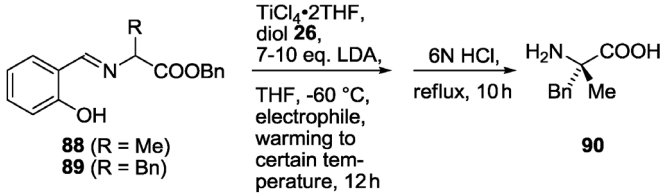
Scheme 11 Remote-controlled aldol reactions.

APPLICATIONS OF DIOL 26 IN SYNTHESIS

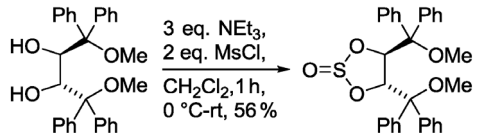
Applications of diol 26 beyond boron

Many of the concepts inherent to the applications of structural analogues **27** presented in the previous section can also be found in the applications of diol **26**. Most reported applications of diol **26** deal with its 1,3,2-dioxaborolane derivatives, but it has also been applied in asymmetric synthesis of α,α-amino acids as a stoichiometric chiral inducer [74]. In this reaction, diol **26** is utilized for chelation of Ti(IV)-cation, forming a chiral nucleophilic intermediate (Table 6). In comparison to other chiral diols tested, it had beneficial effect on the reaction's enantioselectivity. This can be explained by its ability to form a rigid five-membered ring with the Ti ion and the bulkiness of its α-substituents. The reaction of benzyl bromide and alanine-derived substrate **88** failed under conditions shown in Table 6, probably because of the electrophile's bulkiness and steric hindrance provided by diol **26**. In contrast, phenylalanine derivative **89** was successfully methylated to yield product **90** with ee of 55–74 % after refluxing in 6N HCl. Furthermore, Srimurugan and co-workers reported the synthesis of cyclic sulfite **91** from diol **26** (Scheme 12) [55]. Surprisingly, the unusual methanesulfonylation product **91** was formed instead of the expected dimesylate when diol **26** was submitted to standard mesylation conditions. The reaction outcome is attributed to the sterically hindered character of the hydroxyl groups.

Table 6 Application of diol **26** in stereoselective α,α-amino acid synthesis.



substrate	electrophile	temperature (°C)	conversion	*ee* (%)
88	BnBr	-60~0	-	-
89	MeI	-60~0	65 %	55 (*S*)
89	MeI	-60~-15	60 %	74 (*S*)



26 **91**

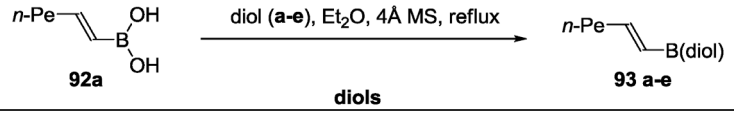
Scheme 12 Attempted dimesylation of diol **26**.

General methods for preparation of 1,3,2-dioxaborolanes

(E)-Alkenylboronates

(*E*)-Alkenylboronic acids and esters are readily available via several well-established routes [75–82]. In 1997, Pietruszka and co-workers investigated the hydroboration [83–86] of heptyne and subsequent transesterification with various diols. In all cases, good yields were obtained, but the stability of the alkenylboronic esters **93a–e** and their properties in the following cyclopropanation step were disappointing (Table 7) [87]. In order to improve results, highly stable alkenylboronic esters **94a–e** were synthesized by the condensation of chiral diol **26** with boronic acids in good yields (Table 8) [87]. Despite the good-to-excellent overall yields of this sequence, it was not only laborious, but also difficult to isolate the boronic acids **92a–d** in analytically pure form due to their tendency to form boroxines. In addition, the formation of boroxines renders the reaction with diol **26** sluggish [88]. To encounter this problem, 1 equiv of water was added to the reaction mixture [52]. A more straightforward sequence was realized via direct hydroboration using the chiral hydroborating reagent **95** (Table 9). Preparation of reagent **95** was performed under mild conditions following a protocol by Knochel and co-workers [81]. In the next step, high temperatures (up to 135 °C) were necessary to obtain the stable alkenylboronic esters **94a–k** [88].

Table 7 Synthesis of various heptenylboronates.



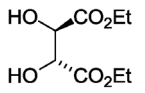
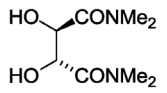
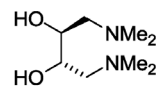
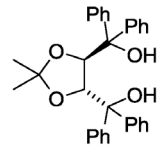
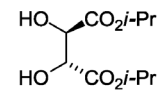
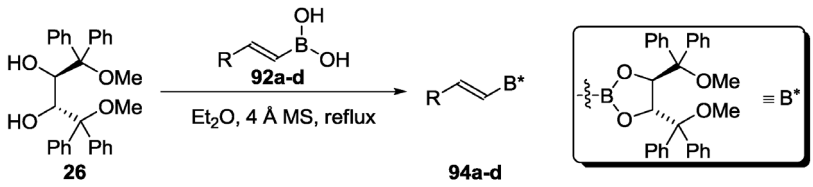
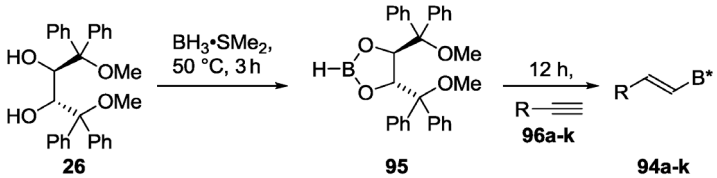
diols				
a	**b**	**c**	**d**	**e**
				

Table 8 Synthesis of diol **26**-protected alkenylboronates.



product	R	Yield (%)
94a	*n*-Pe	92
94b	*n*-Bu	73
94c	*t*-Bu	87
94d	Ph	80

Table 9 Direct hydroboration with diol **26**-based hydroborane.



product	R	T (°C)	Yield (%)
94a	*n*-Pe	90	68
94b	*n*-Bu	90	70
94c	*t*-Bu	40 - 90	-
94d	Ph	120	82
94e	$TPSO(CH_2)_3$	135	83
94f	$TBDPSO(CH_2)_3$	135	83
94g	$TBDPSOCH_2$	120	66
94h	$TBSOCH_2$	120	91
94i	$MOMOCH_2$	100 - 120	-
94j	$BnOCH_2$	120	(31)[a]
94k	$BzOCH_2$	100 - 120	-

[a] unseparable mixture of isomers and undefined sideproducts

When the reaction was carried out at room temperature or under reflux condition with CH_2Cl_2 as solvent, only 2-hydroxy-1,3,2-dioxaborolane **97** was isolated after hydrolysis (Fig. 4). Its structure was determined by X-ray crystallography after recrystallization from MeOH, yielding the corresponding methyl ester **98** [88].

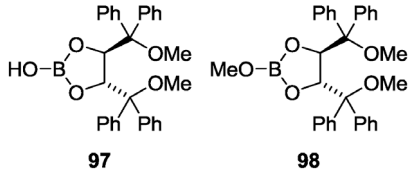
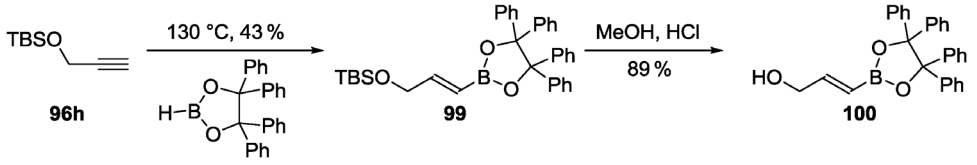


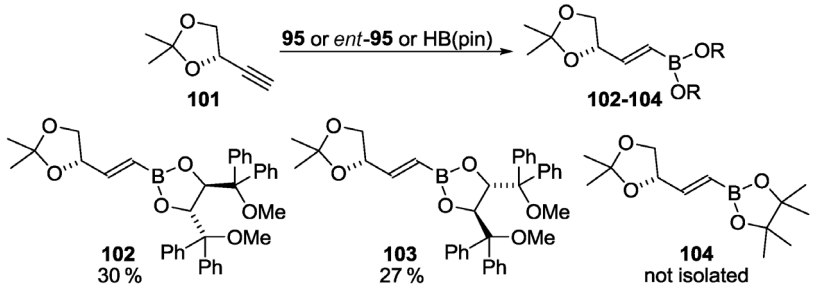
Fig. 4 Solvolysis products of borane **95**.

In the case of alkenylboronic ester **94d**, the product was crystallized directly from the reaction mixture and only traces of a regioisomer (<1 %) were observed. The yields of boronates derived from low-boiling alkynes were improved by using 2 equiv of alkyne (e.g., **96a,b**) and decreasing the reaction temperature. In the case of alkyne **96c**, the reaction failed under the given conditions. For propargyl alcohols **96g–k**, the protecting group plays an important role for the success and yield of the reaction. Only silylethers **96f–h** were compatible with the reaction conditions described, in particular, *tert*-butyldimethylsilyl (TBS)-protected propargyl alcohol **96h** was transformed to the boronic ester in excellent yield [88]. The same reaction using benzpinacolborane as hydroboration reagent gave the stable product **99** in a yield of only 43 %, in contrast to 91 % for the hydroboration with diol **26**-derived borane **95** (Scheme 13). Subsequent deprotection to allylic alcohol **100** proceeded in high yield [89].

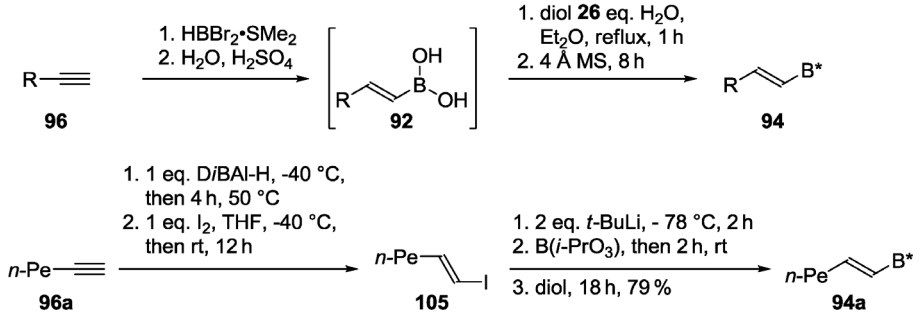


Scheme 13 Direct hydroboration with benzpinacolborane.

Furthermore, compound **101** was synthesized following different approaches and employed as substrate in the hydroboration reaction (Scheme 14) [90–96]. After direct hydroboration of compound **101** with borane **95** and *ent*-**95**, the products **102** and **103** were obtained in modest yields (Scheme 15). Pinacol-derived boronate **104** could not be obtained at all under analogous conditions [97].



Scheme 14 Direct hydroboration of alkyne **101**.

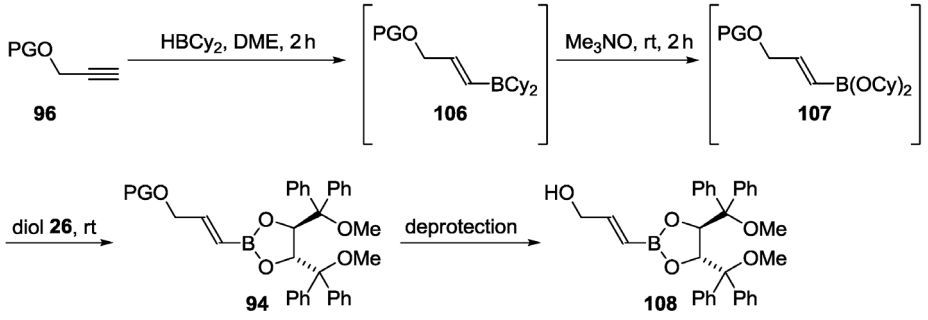


Scheme 15 Alternative routes to stable alkenylboronates.

An alternative route to stable alkenylboronic esters **94** was realized by the hydroboration of alkynes **96** with $HBBr_2{\cdot}SMe_2$, followed by hydrolysis to form the alkenylboronic acids **92** and condensation with diol **26** (Scheme 15). The efficiency of this indirect hydroboration method was only moderate. A further alternative route to alkenylboronic ester **94** starts from alkenyl iodide **105** synthesized via hydroalumination–iodination reaction sequence of the corresponding alkyne **96a**. After Li-halide exchange, an ate-complex was formed with triisopropyl borate. Treatment with diol **26** yielded the alkenylboronic ester **94a** [52].

In order to gain a general access to alkenylboronic esters with various functional groups and protecting groups, another method had to be established. The hydroboration of various protected propargylic alcohols **96h–m** and branched alkynes was successfully performed following Hoffmann's protocol using the more reactive dicyclohexylborane (Cy_2BH) (Table 10) [79].

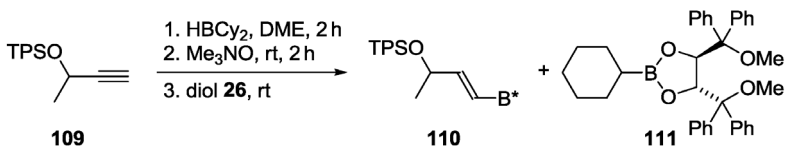
Table 10 Hydroboration/oxidation/transesterification protocol.



compound	PG	Product	Yield (%)
96h	TBS	**94h**	89
96i	MOM	**94i**	38
96j	Bn	**94j**	65
96k	Bz	**94k**	60
96l	TMS	**108**	66
96m	TPS	**94m**	78[a]

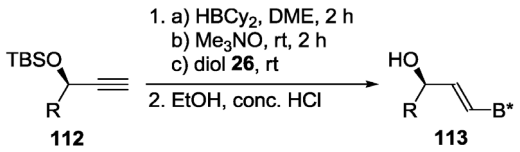
[a] unpublished results

The oxidation of intermediate **106** with anhydrous trimethylamine *N*-oxide and subsequent transesterification of intermediate **107** with diol **26** formed alkenylboronic esters **94h–m** in moderate to very good yields [97,98]. Hydroboration of the branched alkyne **109** was also successful, but the desired boronate **110** could not be separated from side-product **111** (Scheme 16) [97]. Performing the reaction with the branched TBS-protected alkynes **112** and *ent*-**112** gave better results. The products **113** were isolated in pure form after deprotection (Table 11) [99]. For phenyl-substituted alkyne **112c**, the final transesterification step was accomplished with diol **26** and benzpinacol **114** (Scheme 17). The synthesis of benzpinacolboronate **115** under these conditions turned out to be problematic and resulted in isolation of product **115** in low yield.



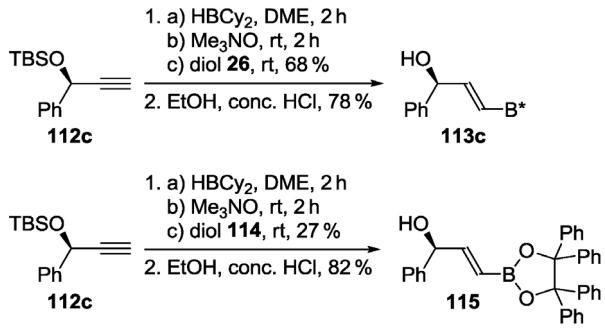
Scheme 16 Hydroboration of branched alkyne **109**.

Table 11 Synthesis of alkenylboronate **113**.



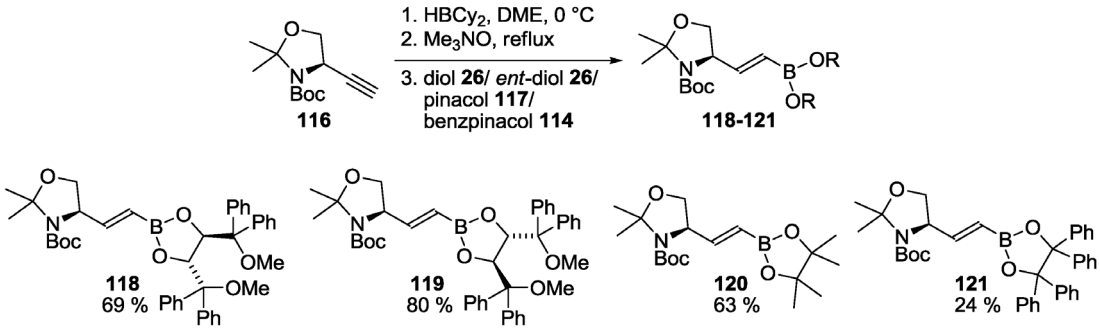
112 **113**

compound	R	product	yield (%)
112a	Me	**113a**	56 %
ent-**112a**	Me	*ent*-**113a**	50 %
112b	*n*-Pe	**113b**	67 %
ent-**112b**	*n*-Pe	*ent*-**113b**	82 %



Scheme 17 Synthesis of boronate-substituted secondary allylic alcohols.

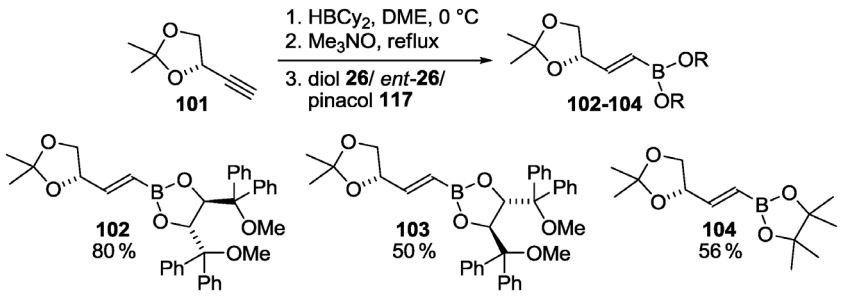
The applicability of diol **26** in this sequence was also demonstrated in the hydroboration of sterically demanding alkynyl substrate **116** (Scheme 18) [92–94,100].



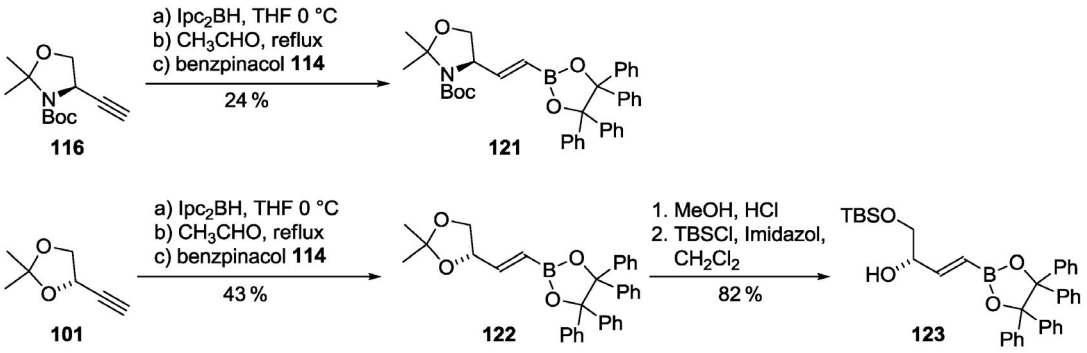
Scheme 18 Hydroboration/oxidation/transesterification of alkyne **116** with various diols.

The hydroboration/oxidation/transesterification sequence was not only performed with diol **26**, but also diol *ent*-**26**, pinacol **117**, and benzpinacol **114** in order to compare the efficiency of the transesterification and stability of the resulting boronates (Scheme 18). Purification of pinacolboronate **120** was problematic because of slow decomposition during chromatographic purification, resulting in decreased yield. The transesterification with benzpinacol **114** proceeded very slowly and resulted in a poor yield, but in contrast to transesterification with pinacol **117**, no problems occurred in the isolation of the boronate **121**. The highest yields were obtained for diol **26** (69 %) and *ent*-diol **26** (80 %) [100].

Compound **101** was also employed in the hydroboration/oxidation/transesterification sequence with diol **26**, *ent*-**26**, and pinacol **117** (Scheme 19). Obviously, the yields could be increased for all reactions in comparison to the previously reported direct hydroboration, which is evidence for the efficiency of this method in the hydroboration of sterically demanding alkynes [97]. Instead of Cy_2BH, the also highly reactive diisopinocampheylborane (Ipc_2BH) was used for the hydroboration of the hindered alkynes **116** and **101** [101,102], followed by transesterification with benzpinacol **114** (Scheme 20). Just as in the previously described reaction, the transesterification process was very slow and both products **121** and **122** were obtained in low yields. This could be explained by the preferentially antiperiplanar conformation of the two hydroxyl groups and thus hindered rotation around the central C–C bond. Acetal cleavage and selective TBS protection of the primary hydroxy group proceeded in high yield to give product **123** [103].



Scheme 19 Hydroboration/oxidation/transesterification of alkyne **104**.

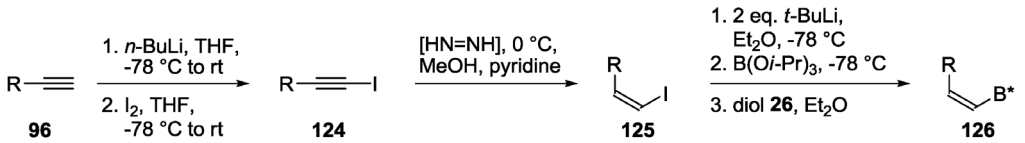


Scheme 20 Hydroboration and derivatization of alkynes **116** and **101**.

(Z)-Alkenylboronates

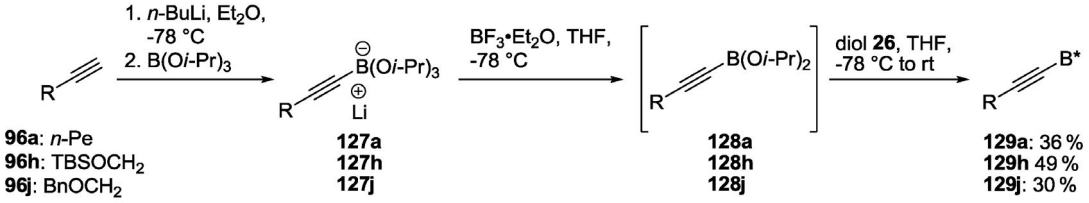
The first reported approach to (*Z*)-configured alkenyl-1,3,2-dioxaborolanes **126** utilized alkynes **96** as starting materials (Table 12). First, (*Z*)-vinyl iodides **125** were prepared from iodoalkynes **124** by diimide reduction. After Li-halide exchange with *t*-butyllithium, the corresponding ate-complexes were formed with triisopropylborate and reacted to yield alkenylboronates **126** by transesterification with diol **26**. In order to obtain (*Z*)-configured products, control of reaction temperature during addition of triisopropylborate is crucial. For substrates bearing bulky residues, this method gave only poor yield or no product at all [104].

Table 12 (*Z*)-Alkenylboronates via imide reduction.



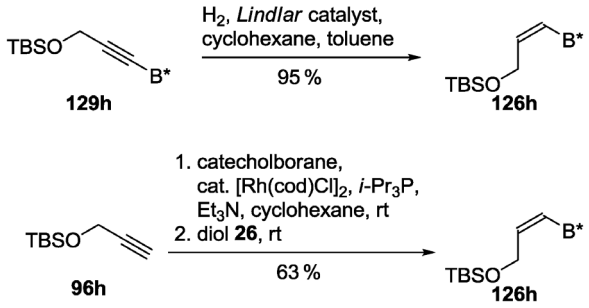
compound	R	yield (%) 124	yield (%) 125	yield (%) 126
96b	*n*-Bu	78	57	68
96d	Ph	80	46	77
96h	$TBSOCH_2$	50	23	-
96i	$MOMOCH_2$	65	50	32

To overcome this restriction, another method was applied: Alkynes **96** were deprotonated with *n*-butyllithium in order to form ate-complexes **127** with triisopropylborate (Scheme 21) [85]. After addition of $BF_3{\cdot}Et_2O$, alkynylboronates **128** were formed and then transesterified with diol **26** [105,106].



Scheme 21 Synthesis of alkynylboronates.

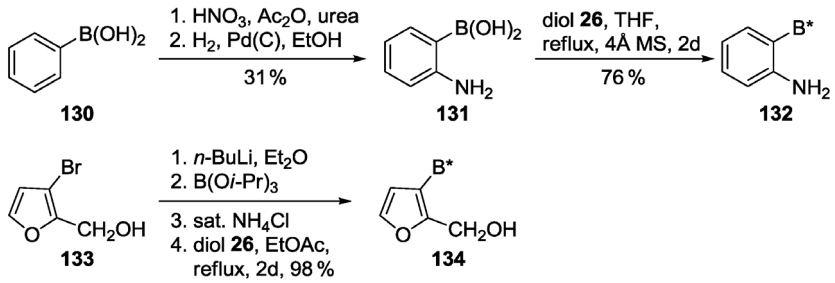
Although (*Z*)-selective reduction with Lindlar catalyst and dihydrogen proceeded with excellent yield for reduction of alkyneboronate **129h** to give compound **126h**, the method suffered from poor overall yield due to the low yield during formation of boronate **129h** from the corresponding ate-complex **127h** (Scheme 22) [86,106]. Finally, a sequence of Rh-catalyzed (*Z*)-selective hydroboration with catecholborane followed by transesterification with diol **26** turned out to be the most practical and high-yielding procedure for the preparation of (*Z*)-alkenylboronate **126h** [107,108].



Scheme 22 Two alternative routes to (*Z*)-alkenylboronate **126h**.

Arylboronates

While various methods for the synthesis of (*E*)- and (*Z*)-alkenylboronates derived from diol **26** have been reported and tested on a plethora of substrates, arylboronates protected with diol **26** are not as numerous. Compound **132** was synthesized by Hall and Kennedy as precursor for a substrate utilized in investigations on remote stereocontrol of Diels–Alder reactions (Scheme 23). After preparation of aniline boronic acid **131** from phenylboronic acid **130**, the corresponding boronate **132** was obtained by condensation of diol **26** and boronic acid moiety in refluxing THF in the presence of molecular sieves [109]. Alcohol **133** was utilized by Wong and Chan in a Li-halide exchange followed by addition of triisopropylborate. The resulting ate-complex was hydrolyzed, and boronate **134** was obtained by condensation with diol **26** in refluxing ethyl acetate [110].

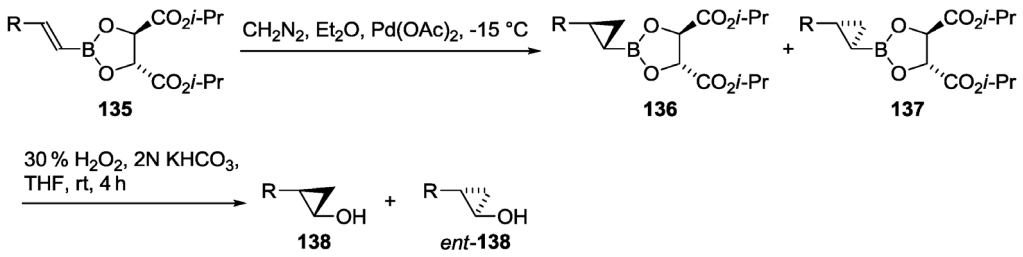


Scheme 23 Preparation of diol **26**-based arylboronates.

Cyclopropanation

Owing to the importance of cyclopropylboronic esters as versatile building blocks in organic synthesis, Pietruszka and co-workers investigated the influence of various boron protective groups on the yield and diastereoselectivity in cyclopropanation reactions of alkenylboronates. The first model compound which was employed in different Simmons–Smith protocols [111–114] and in Pd(II)-catalyzed reactions with diazomethane [115,116] was the diisopropyl L-tartrate-derived boronate **135** (Table 13) [117]. Cyclopropanation using the reported conditions of Imai and co-workers [118] led to the labile diastereomers **136** and **137** in low yield, which could not be purified. The diastereomeric ratio was determined by coupled ^{13}C NMR. Changing the amount of equivalents used and the order of addition of diiodomethane and diethylzinc had only a minor effect on diastereoselectivity and yield. The best yield was obtained by using low temperatures (–15 °C, 70 %), while the best diastereomeric ratio was gained after slow addition of diethylzinc to a mixture of alkenylboronate **135** and diiodomethane. After oxidation of the crude cyclopropylboronates **136** and **137** to the corresponding cyclopropanols **138** and *ent*-**138**, the ee was determined by gas chromatography (GC) on a chiral stationary phase. In contrast to the Simmons–Smith-like methods, the Pd(II)-catalyzed cyclopropanation with diazomethane led to higher yields. For this sequence, the influence of different reaction parameters was also analyzed, in particular in view of the optimization of stereoselectivity. It was proved that high concentrations of boronic ester, slow addition of diazomethane, and lowered reaction temperature (–15 °C) are necessary to obtain the cyclopropanes in moderate-to-good diasteromeric ratio [87,117]. All cyclopropanols synthesized under the optimized conditions were obtained in moderate-to-good ee [117]. In addition, boronates with other protective groups for the boron moiety were applied in the cyclopropanation, which proceeded with lower diastereoselectivity (Table 14).

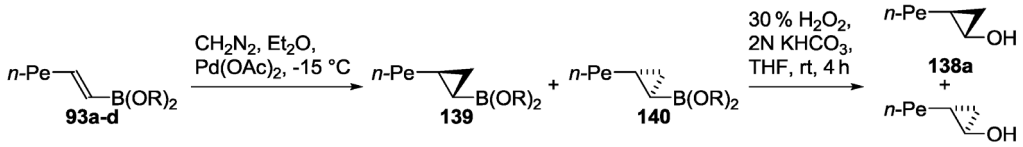
Table 13 Cyclopropanation of tartrate-protected alkenylboronates.



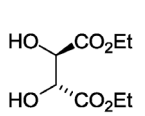
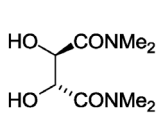
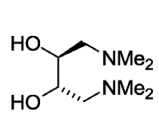
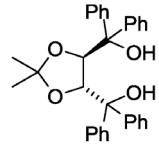
135 136 137 138 *ent*-138

compound	R	yield (%)	*dr* 136:137	*ee* (%) (*ent*-138)
135b	*n*-Bu	94	n.d.	60
135c	*t*-Bu	45	n.d.	85
135d	Ph	78	n.d.	65

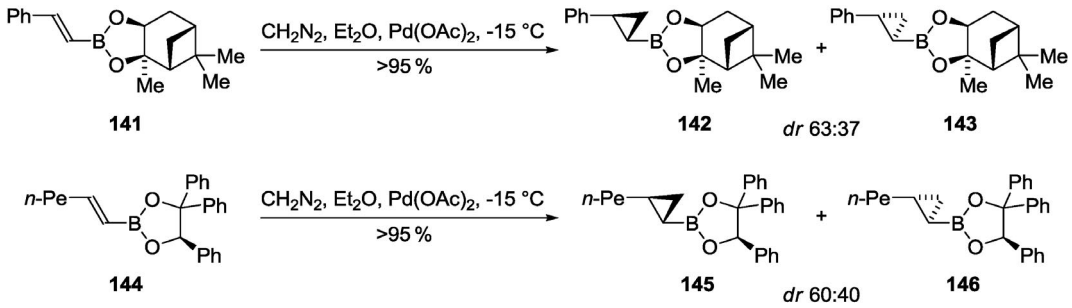
Table 14 Cyclopropanation of alkenylboronates bearing various protective groups.



93a-d 139 140 **138a** *ent*-**138a**

compound	93a	93b	93c	93d
R				
ent-**138a** *ee* (%)	25	42	5	47

The obtained boronic esters **139a–d** and **140a–d** suffered from insufficient stability; additionally, the diastereomers could not be separated and purified. Therefore, pinanediol-derived alkenylboronic ester **141** was employed in a cyclopropanation reaction under the same conditions to give the stable, but inseparable cyclopropanes **142** and **143** in a modest diastereomeric ratio (Scheme 24). The attempted



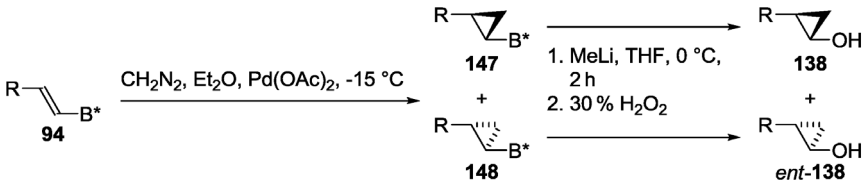
141 142 143 144 145 146

Scheme 24 Cyclopropanation of alkenylboronates **141** and **144**.

separation of the (*R*)-1,1,2-triphenylethane-1,2-diol-protected cyclopropylboronic esters **145** and **146** resulted in hydrolysis on silica gel [52,88].

Repetition of the reactions with diol **26**-protected boronates **94** led to highly stable cyclopropylboronic esters **147** and **148** in good-to-excellent yield and low diastereomeric ratio (Table 15). Except for phenyl-substituted derivative **94d**, the diastereomers were separable by means of MPLC, allowing isolation of the enantiomerically pure cyclopropanes. By determining the absolute configuration after oxidation to the corresponding cyclopropanols **138** and *ent*-**138**, it was proven that (except for the phenyl derivative) opposed stereoselectivity was obtained in comparison to reactions of the substrates bearing other chiral protective groups shown before [87].

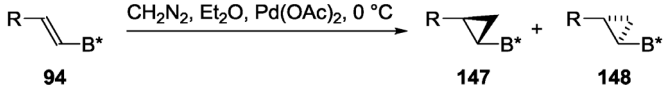
Table 15 Cyclopropanation of diol **26**-protected boronate **94**.



compound	R	yield (%)	*dr* 148:147
94a	*n*-Pe	99	28:72
94b	*n*-Bu	98	31:69
94c	*t*-Bu	95	42:58
94d	Ph	93	59:41

The diastereomeric ratio was improved for cyclopropylboronic esters **147a** (dr 93:7) and **147d** (dr 86:14) by adjusting conditions to reaction temperature of 0 °C, slow addition of diazomethane, and increased catalyst loading (Table 16) [88]. Furthermore, it was found that sonification previous to the addition of diazomethane minimizes the required amount of catalyst and promotes the fine distribution of the catalyst to minimize the formation of the side-product polymethylene, which deactivates the catalyst. The observation of the strong influence of temperature and amount of catalyst on the diastereoselectivity is contrary to the ones made in the study with L-tartrate-derived alkenylboronic esters **93e** and **135** [52]. Cyclopropanations of protected allylic alcohols **94h–m** proceeded only in moderate

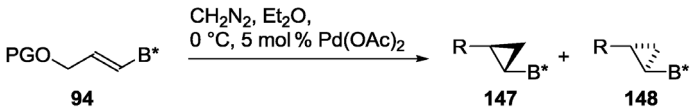
Table 16 Cyclopropanation of alkenylboronates **94** under optimized conditions.



compound	R	yield (%)	*dr* 148:147
94a	*n*-Pe	99	7:93
94b	*n*-Bu	98	11:89
94c	*t*-Bu	95	13:87
94d	Ph	93	14:86
94e	$TPSO(CH_2)_3$	89	5:95

diastereoselectivity (Table 17). To establish the cyclopropanation of functionalized alkenes, various protected allylic alcohols were employed in this reaction [97].

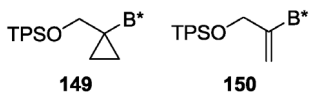
Table 17 Cyclopropanation of protected allylic alcohols.



94 147 148

compound	PG	yield (%)	*dr* 147:148
94h	$TBSOCH_2$	90	70:30
94i	$MOMOCH_2$	98	86:14
94j	$BnOCH_2$	88	80:20
94k	$BzOCH_2$	96	83:17
94m	$TPSOCH_2$	90 (7 % isomer)	66:34

In case of silyl-protected boronates, stereoselectivity was only moderate, while the less bulky protective groups provided the desired products with good diastereomeric ratios and in high yields. Additionally, in the reaction with TPS-protected compound **94m**, not only products **147** and **148** were obtained, but also a small amount of isomer **149** was formed (Fig. 5). This can be explained by incomplete removal of isomer **150** after hydroboration.

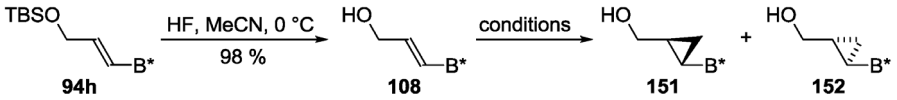


149 150

Fig. 5 By-product isolated from cyclopropanation of protected allylic alcohol and its precursor.

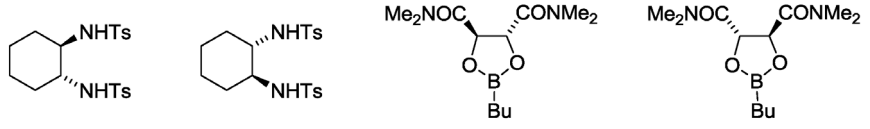
Besides cyclopropanations of protected boronates **94f–m**, the reactivity of the corresponding unprotected allylic alcohols was investigated (Table 18). Therefore, TBS-protected alcohol **94h** was treated with hydrofluoric acid to obtain the corresponding alcohol **108**. For this substrate, various reaction conditions were tested [52]. Reaction of the unprotected alkenylboronic ester **108** with diazomethane led to slightly increased diastereoselectivity in the formation of the products **151** and **152** compared to cyclopropanation of the protected compound **94h**. Under Simmons–Smith conditions, reversed diastereoselectivities were obtained in cyclopropanation reactions. Although the reaction was performed under Denmark conditions applying the chiral ligands **153** and *ent*-**153**, the diastereomeric ratios could not be improved substantially. Incomplete conversion as well as decreased diastereoselectivity were obtained when employing Charette's chiral modifiers **154** and *ent*-**154** in cyclopropanation. The results proved that a free hydroxyl group is a requirement for performing diastereoselective Simmons–Smith reaction successfully, and a matched/mismatched interaction was oberserved using the chiral ligands **153** and *ent*-**153** (entry 3,4; it should be noted that the diastereoselectivty could be improved when performing the reaction on a larger scale [140]) [52]. Besides being risky on large scales, cyclopropanation by Pd-catalyzed decomposition of diazomethane was shown to be impractical for the benzyl-protected boronate **94j**, whereas cyclopropanation under Denmark conditions using racemic chiral ligand *rac*-**153** is easy to handle and enables isolation of the product in a high yield of 92 % (Scheme 25) [98].

Table 18 Cyclopropanation of unprotected allyl alcohol **108** under various conditions.

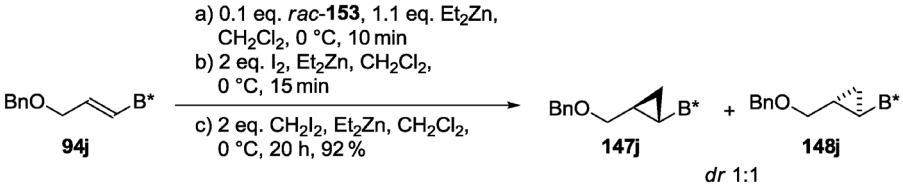


94h **108** **151** **152**

entry	conditions	yield (%)	*dr* 151:152
1	CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C	98	80:20
2	Et_2Zn, CH_2I_2, ZnI_2, CH_2Cl_2, 0 °C	94	36:64
3	Et_2Zn, CH_2I_2, ZnI_2, **153**, CH_2Cl_2, 0 °C	90	20:80
4	Et_2Zn, CH_2I_2, ZnI_2, *ent*-**153**, CH_2Cl_2, 0 °C	91	60:40
5	Et_2Zn, CH_2I_2, **154**, CH_2Cl_2, 0 °C	50 conversion	60:40
6	Et_2Zn, CH_2I_2, *ent*-**154**, CH_2Cl_2, 0 °C	78 conversion	30:70



153 *ent*-**153** **154** *ent*-**154**



94j **147j** **148j**

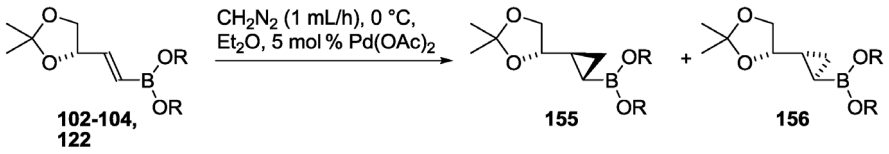
dr 1:1

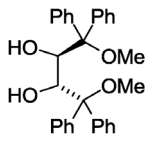
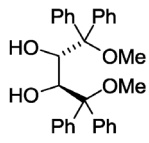
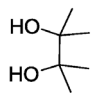
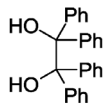
Scheme 25 Cyclopropanation of protected allyl alcohol **94j** under Denmark conditions.

The absolute configuration of the cyclopropylboronic esters **147a** and **148a** was assigned by chemical correlation with known cyclopropanols **138a** and *ent*-**138a** and by the diagnostic NMR signals of the 2'-H and 3'-H_{trans} protons of the cyclopropane moiety. In all spectra, a distinct high-field shift of the 2'-H proton for the major diastereomer relative to the minor diastereomer was observed. On the other hand, the 3'-H_{trans} protons showed a downfield shift. The assignment of absolute configuration was confirmed by X-ray structure analysis of compound **148c**. Furthermore, the stereochemical outcome of the cyclopropanation step can be explained by consideration of the X-ray structures of compounds **94c** and **148c**. In both cases, the conformation of the 1,3,2-dioxaborolane ring with its bulky substituents is very similar, blocking three quadrants efficiently. The same should be true for the reactive confirmation, and in consequence one direction of attack should be favored. The different stereochemical outcome in Simmons–Smith reaction and the Pd-catalyzed decomposition of diazomethane was explained by performing a MM2 calculation. Therefore, the X-ray data of boronate **94c** were used and the *tert*-butyl group was replaced by a hydroxyl group. The result of the calculations revealed that the favored conformation is 8 kJ/mol more stable than energetically less favored conformations bearing the hydroxyalkyl chain [52].

Another investigation was made to elucidate the influence of an additional stereogenic center in the side-chain on the cyclopropanation reaction's outcome. Therefore, several boronates **102–104** and **122** bearing different diols as protective groups were employed in the cyclopropanation reaction with diazomethane, wherein all reactions led to good-to-excellent yields (Table 19). Diastereoselectivity was only moderate, indicating that the reaction is predominantly auxiliary-controlled [97]. The diastereomers of the pinacol-derived cyclopropylboronates could not be separated.

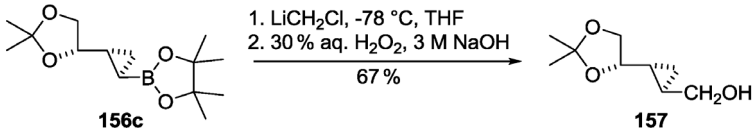
Table 19 Pd-catalyzed cyclopropanation of acetals **102–104** and **122**.



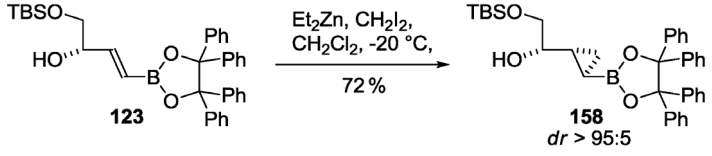
compound	102	103	104	122
R				
yield (%)	93	95	(88)[a]	70
dr 155:156	83:17	50:50	60:40	70:30

[a]diastereomeres could not be separated

Determination of the absolute configuration for products **155a,b** was realized by comparison of the characteristic shifts in ^{1}H NMR and ^{13}C NMR of the cyclopropane moiety (2'-H/C-2' and 3'-H_{trans}/C-3'). However, the absolute configuration of the pinacol-derived compound **156c** had to be assigned via chemical correlation. Cyclopropane **156c** was submitted to the conditions of Matteson homologation and oxidation to give the known enantiomerically pure cyclopropylmethanol **157** (Scheme 26) [97]. Furthermore, cyclopropanation of **123** applying Takemoto's conditions [119] yielded diastereomer **158** as sole product in 72 % yield (Scheme 27) [103].



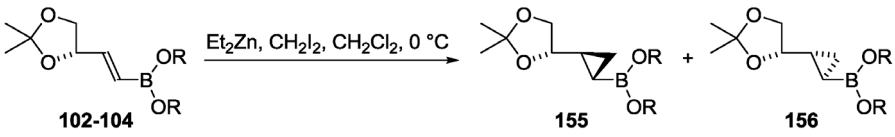
Scheme 26 Matteson homologation/oxidation of cyclopropylboronate **156c**.

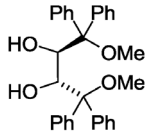
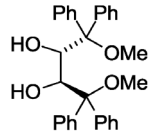


Scheme 27 Derivatization of boronate **123**.

Submitting substrates **102–104** to cyclopropanation under Furukawa conditions led to the products **155a–c** and **156a–c** in moderate-to-good yields with good-to-excellent diastereoselectivities indicating a substrate-controlled reaction (Table 20) [97].

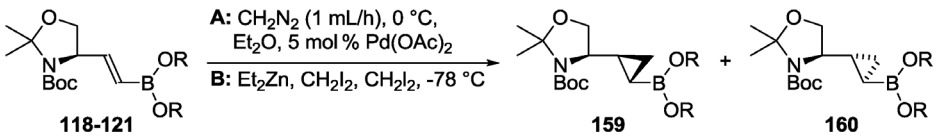
Table 20 Simmons–Smith cyclopropanation of alkenylboronates **102–104**.

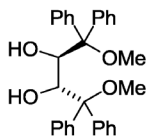
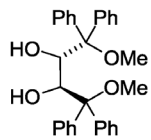
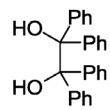


compound	102	103	104
R			
yield (%)	58	72	60
dr **155:156**	11:89	94:6	95:5

Similar investigations were made for boronates **118–121** derived from Garner aldehyde [120,121] to analyze the influence of the boronic acid protecting group in cyclopropanation reactions of this substrate (Table 21).

Table 21 Cyclopropanation of Garner aldehyde-derived alkenylboronates **123–126**.

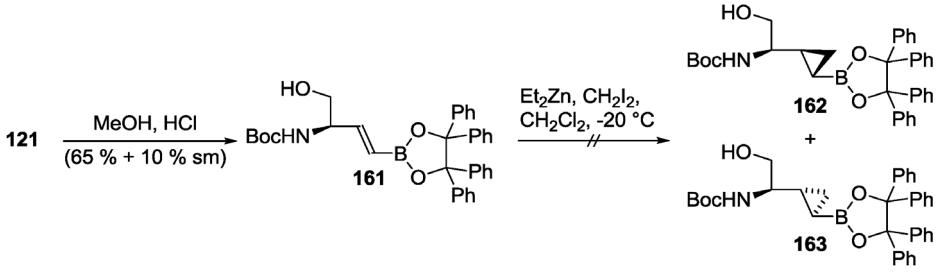


compound	118	119	120	121
R				
yield (%)	79	84	69 [a]48	61
dr **159:160**	84:16	92:8	70:30 [a]22:78	24:76

[a]using conditions **B**

Pd-catalyzed decomposition of diazomethane led to cyclopropanes **159a–d** and **160a–d** in high yields. In almost all cases, the diastereoselectivities for the cyclopropanation were increased in comparison to the glyceraldehyde-derived cyclopropyl boronates **155** and **156**. For boronates **118** and **119**,

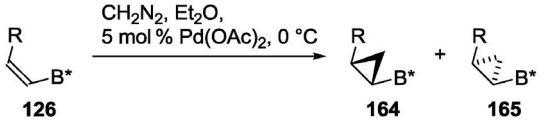
no distinct matched/mismatched interaction was observed, whereas the formation of corresponding products **159** was preferred. The same preference was found for pinacol-protected compound **120**. Unexpectedly, the selectivity was reversed when exchanging pinacol by benzpinacol, possibly due to different preferred reactive conformations for the two protective groups. Additionally, pinacol boronate **120** was employed in cyclopropanation using Simmons–Smith conditions. Only performing the reaction at –78 °C led to products **159** and **160** in a modest yield of 48 % and, compared to cyclopropanation with diazomethane, to reversal of the diastereomeric ratio. Unfortunately, diastereomers **159** and **160** derived from benzpinacolboronate **121** could not be separated completely. The absolute configuration of the products was determined by comparison of NMR data, X-ray analysis, and chemical correlation via GC of the corresponding cyclopropanols [100,103]. Furthermore, boronate **121** was deprotected under acidic conditions, thus allowing the isolation of product **161** in 65 % yield (Scheme 28). In contrast to compound **123**, cyclopropanation using Takemoto conditions was not successful [103].



Scheme 28 Attempted cyclopropanation of alkenylboronate **161**.

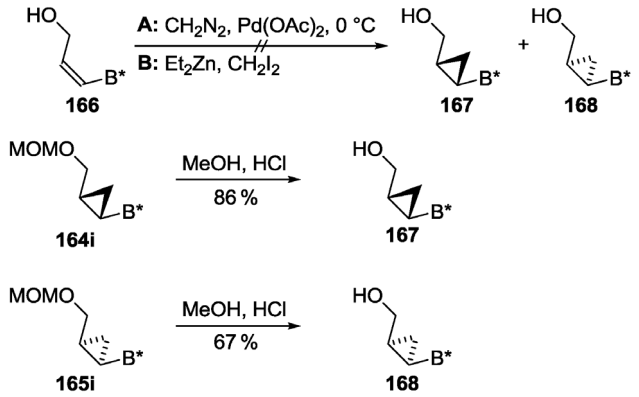
A further challenge was the synthesis of *cis*-configured cyclopropylboronates. The cyclopropanation of compounds **126** was performed by Pd-catalyzed decomposition of diazomethane (Table 22). In all cases, the yields were moderate to excellent and the diastereomers were separable, but the diastereoselectivity was rather poor [104,122].

Table 22 Synthesis of *cis*-configured cyclopropylboronates.



compound	R	yield (%)	*dr* 164:165
126b	*n*-Bu	96	87:13
126d	Ph	90	67:33
126i	$MOMOCH_2$	87	65:35
126k	$BzOCH_2$	62	50:50

In order to submit alkenylboronate **166** to a Simmons–Smith reaction, deprotection of methoxymethyl (MOM)-ether **164i** was necessary (Scheme 29). Unfortunately, the cyclopropanation reaction failed, but the starting material was reisolated. In contrast, the Pd-catalyzed cyclopropanation of **166** with diazomethane led to decomposition and no starting material was recovered. As an alternative approach, cyclopropylboronates **167** and **168** were synthesized by deprotection of compounds **164i** and **165i** [104].

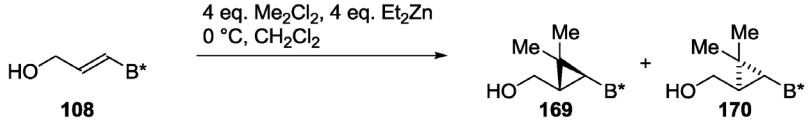


Scheme 29 Attempted cyclopropanation of *cis*-allyl alcohol **166**.

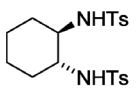
In contrast to the corresponding *trans*-derivatives, it was difficult to assign the absolute configurations of the cyclopropanes directly. Neither X-ray crystal structures were obtained nor were the corresponding cyclopropanols known. For cyclopropylboronic ester **164b**, the determination of the absolute configuration was realized by chemical correlation [104].

After establishment of cyclopropanation conditions for compounds of type **94** and **126**, the synthesis of more highly substituted cyclopropanes was investigated. Starting from allyl alcohol **108** (Table 23), cyclopropanation was performed by using 2,2-diiodopropane and Et_2Zn as cyclopropanation reagent. Low conversions were attributed to the steric bulkiness of diol **26** and decomposition of the highly reactive zinc reagent. In order to increase the yield, the concentration of allyl alcohol **108** was varied in screening experiments. It was shown that the concentration had no influence on the conversion, but a slightly increased diastereomeric ratio was observed for low concentrations of **108**. Addition of chiral ligands (**153** and *ent*-**153**) did not increase the reactions' stereoselectivity. Adding several portions of excess cyclopropanation reagent resulted in higher conversion but also decreased the diastereomeric ratio of **169** and **170**. The absolute configuration of the products was determined via ^{1}H NMR. The proton of the cyclopropane moiety (2'-H) showed similar shifts like other diol **26**-derived boronates mentioned before [89].

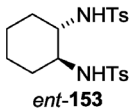
Table 23 Synthesis of tetrasubstituted cyclopropylboronates.



entry	mmol 110/mL CH_2Cl_2	additive	conversion (%)	*dr* 169:170
1	0.025	-	41	88:12
2	0.040	-	45	76:24
3	0.040	**153**	30	80:20
4	0.040	*ent*-**153**	39	81:19
5	0.020	-	90[a]	69:31



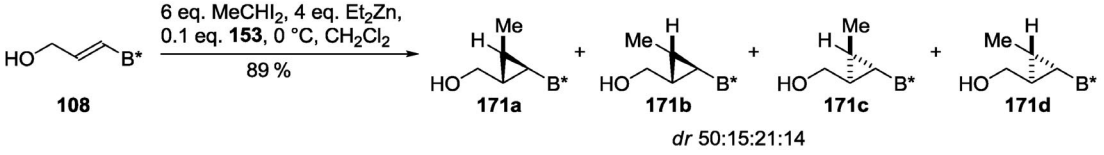
153



ent-**153**

[a]The addition of 4 eq. of the reagents was repeated three times

In addition, 1,2,3-trisubstituted cyclopropylboronic esters **171a–d** were synthesized by reaction of allylic alcohol **108** with bis-sulfonamide **153** and a highly reactive zinc reagent, which was prepared from 1,1-diiodoethane and Et_2Zn (Scheme 30). The product was isolated in 89 % yield and in a diastereomeric ratio of 50:15:21:14 (**a**:**b**:**c**:**d**). Complete separation of the diastereomeric mixture was not possible, but diastereomer **171d** was obtained as pure compound by means of MPLC. The latter compound is a potentially important building block for the synthesis of ambruticin [89]. The absolute configuration was assigned by ^{1}H NMR.

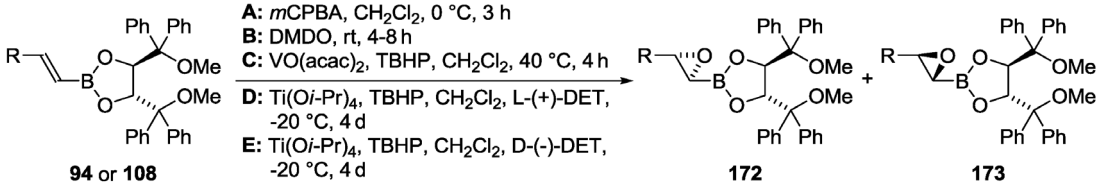


Scheme 30 Synthesis of trisubstituted cyclopropylboronates.

Epoxidation

In organic synthesis, epoxides play a prominent role as useful intermediates and chiral building blocks [123]. Stable epoxides are a special field of interest bearing a boronate group attached directly to the oxirane moiety. Only a few synthetic methods for the preparation of this kind of compounds have been established [37,124–126]. Recent examples are the epoxidation of organotrifluoroborates with dimethyldioxirane (DMDO) by Molander [125] and the epoxidation of alkenyl MIDA and pinene-derived iminodiacetic acid (PIDA) boronates with *meta*-chloroperbenzoic acid (*m*CPBA) [37,126]. The first investigation of air-stable, diol **26**-derived oxiranylboronates **172** and **173** commenced with treatment of alkenylboronic esters **94a,d** and **108** with 1.5 equiv *m*CPBA (Table 24) [127].

Table 24 Epoxidation of alkenylboronates.



compound	R	Method	Yield (%)	Ratio 172:173[a]
94a	*n*-Pe	**A**	40	53:47
94a	*n*-Pe	**B**	>95	54:46
94d	Ph	**A**	35	46:54
94d	Ph	**B**	>95	37:63
108	CH_2OH	**A**	52	43:57
108	CH_2OH	**B**	-	-
108	CH_2OH	**C**	40	43:57
108	CH_2OH	**D**	46	93:7
108	CH_2OH	**E**	65	<1:99

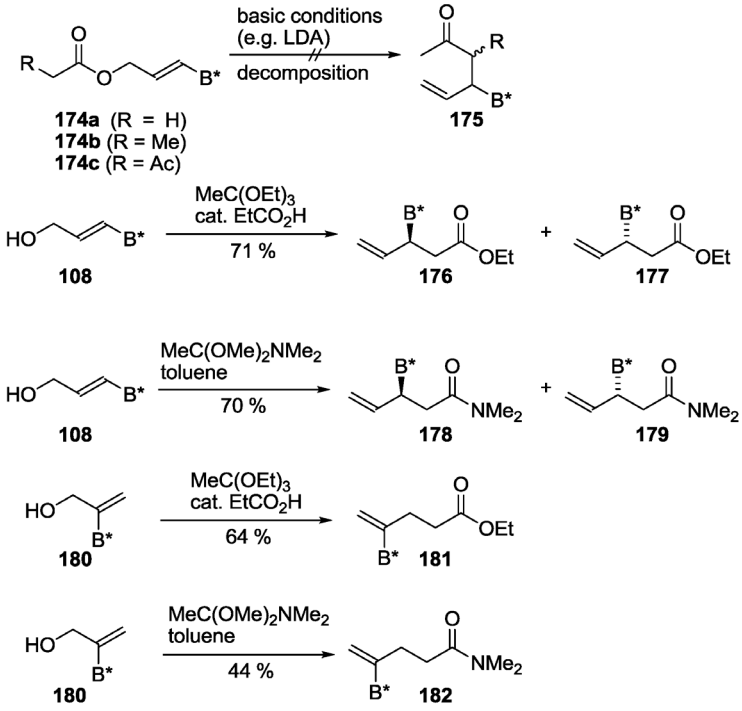
[a] As judged by ^{1}H-NMR of the crude product.

The reactions proceeded with low diastereoselectivity as determined by ^{1}H NMR of the crude products. Only low yields were obtained due to the acidity of benzoic acid, which had caused decomposition of the products via C–B bond cleavage. To avoid decomposition and to improve the yields, the reactions were repeated with DMDO as epoxidation reagent. For alkenylboronic esters, including an alkyl- or aryl moiety, respectively, the products were obtained almost quantitatively, but only low diastereoselectivity was observed. The epoxidation of allyl alcohol **108** was not feasible under these conditions, and only the corresponding aldehyde was recovered. As a consequence, allyl alcohol **108** was treated with 2 mol % of $VO(acac)_2$ and a stoichiometric amount of *tert*-butylhydroperoxide (TBHP) in CH_2Cl_2 at 40 °C. In this reaction, no significant selectivity was observed and the yield was only moderate. An excellent diastereoselectivity was achieved under Sharpless conditions. Use of L-(+)-DET led to the mismatched case product in moderate yield and diastereomeric ratio of 93:7 (**172**:**173**) as a result of an attack from the *si* face. The matched case compound was obtained from *re* face attack induced by D-(–)-DET in good yield and with complete diastereocontrol displayed by diastereomeric ratio of <1:99 (**172**:**173**). Surprisingly, the diastereomer **172** decomposed during column chromatography. In analogy to the related cyclopropyl boronic esters, the diastereomers' configuration was assigned by ^{1}H NMR. This initial assignment based on analysis of the shifts of protons of the epoxide moiety was confirmed by X-ray crystallography [127].

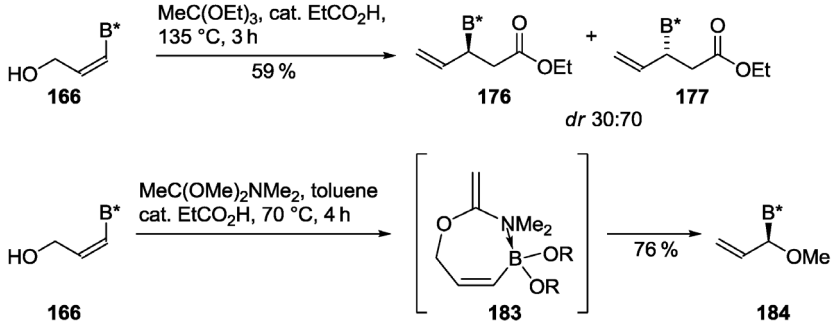
[3.3]-Sigmatropic rearrangements

Taking into account the remarkable stability of boronates containing diol **26** as protective group, the separability of diastereomers as well as the availability of (*E*)- and (*Z*)-configured allylic alcohols **108**, investigations of [3.3]-sigmatropic rearrangement reactions enabling access to chiral α-substituted allylboronates can be considered a stringent step. The best-studied [3.3]-sigmatropic rearrangement is the Johnson rearrangement. In an initial report [108], synthesis of enantiomerically pure allylboronates was addressed as these compounds were expected to be highly stereoselective allylation reagents. Herein, all attempts of performing Claisen–Ireland and Carroll rearrangements of substrates **174** under basic conditions failed. Johnson and Eschenmoser rearrangements were conducted successfully with (*E*)-configured allylic alcohol **108** yielding 50:50 mixtures of products **176–177** and **178–179**, and also with regioisomeric allylic alcohol **180**, which is a minor side-product in the synthesis of **108** (Scheme 31). The resulting diastereomeric mixtures are readily separable by MPLC. The absolute configuration of Johnson rearrangement products was assigned by X-ray crystallography and indirectly by chemical correlation of allylation products.

In contrast to the sigmatropic rearrangements of (*E*)-configured compound **108** with diol **26**-derived boronate-group having no stereoinductive effect, Johnson rearrangement of the (*Z*)-isomer **166** gave products **176** and **177** with a diastereomeric ratio of 30:70 under identical conditions (Scheme 32). Attempted Eschenmoser rearrangement of (*Z*)-configured allylic alcohol **166** furnished homoenolate equivalent **193** as sole diastereomerically stable product. The mechanism of this transformation has not been elucidated, but it seems likely that intramolecular complexation in intermediate **183** prevents proceeding of the rearrangement and allows substitution by previously released methanol instead [108].



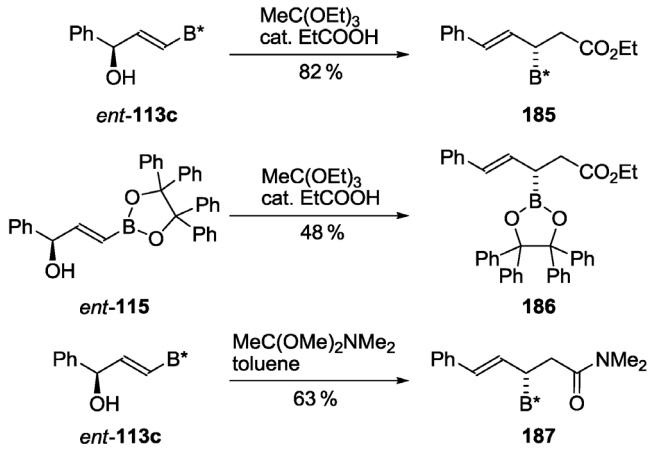
Scheme 31 [3.3]-Sigmatropic rearrangements of alkenylboronates.



Scheme 32 [3.3]-Sigmatropic rearrangements of *cis*-alkenylboronates.

The reaction scope of the Johnson rearrangement was extended to diastereomerically pure secondary B-containing alcohols *ent*-**113c** and *ent*-**115** (Scheme 33). While reaction of phenyl-substituted allylboronate *ent*-**113c** yielded 82 % of the desired product **185**, the benzpinacol-protected analogous substrate *ent*-**115** gave only 48 % of allylboronate **186** under identical conditions [99]. For substrate *ent*-**113c**, Eschenmoser rearrangement gave diastereomerically pure product **187** in good yield of 63 % yield [53].

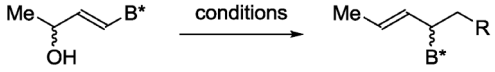
The Johnson rearrangement of both methyl-substituted substrates **113a** and *ent*-**113a** proceeded in a high-yielding and diastereoselective manner. Starting from diastereomerically pure substrates, only diastereomer **188** or **189** was obtained as sole product [99]. For Eschenmoser rearrangement of **113a** and *ent*-**113a**, high yields and complete preservation of stereogenic information was reported as well (Table 25) [53]. Another reported [3.3]-sigmatropic rearrangement is the Overman rearrangement of



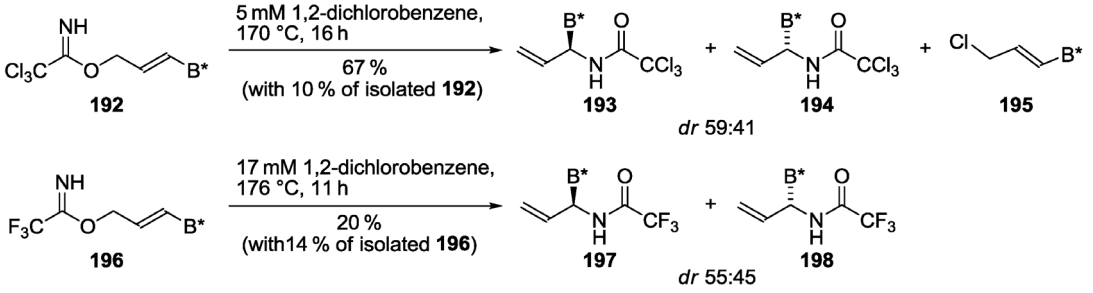
Scheme 33 [3.3]-Sigmatropic rearrangements of phenyl-substituted secondary allylic alcohols.

trichloro- and trifluoroacetimidates **192** and **196**, yielding diastereomeric mixtures **193/194** and **197/198**, respectively (Scheme 34) [106]. Under ligandless conditions, Pd-catalyzed reaction led to the isolation of allylic chloride **195** as unexpected product, only if a phosphine ligand was added, decomposition of the starting material was observed. For this reason, conditions for thermal conversion were optimized in order to obtain desired diastereomers **193** and **194**. In contrast to substrate-controlled rearrangements, low auxiliary induced diastereoselectivity was observed in product formation. Rearrangement of substrate **196** under thermal conditions also gave products **197** and **198** with low diastereomeric excess, while attempts of Pd-catalyzed rearrangement resulted in decomposition of starting material **196**. In both cases, the isolated diastereomeric mixtures could not be separated chromatographically.

Table 25 [3.3]-Sigmatropic rearrangements of methyl-substituted secondary allylic alcohols.



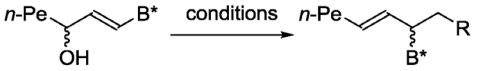
compound	conditions	Yield [%]	product
ent-**113a**	$MeC(OEt)_3$ cat. EtCOOH	78	**188**
113a	$MeC(OEt)_3$ cat. EtCOOH	80	**189**
ent-**113a**	$MeC(OMe)_2NMe_2$ toluene	78	**190**
113a	$MeC(OMe)_2NMe_2$ toluene	86	**191**

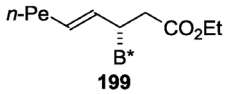
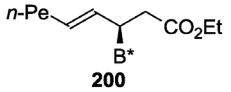
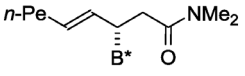
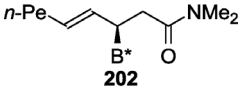


Scheme 34 Overman rearrangement of alkenylboronates.

Performing the Overman rearrangement in a microwave reactor had no positive effect on the reaction outcome [106]. In contrast, microwave heating was applied to the Johnson rearrangement in a useful way (Table 26).

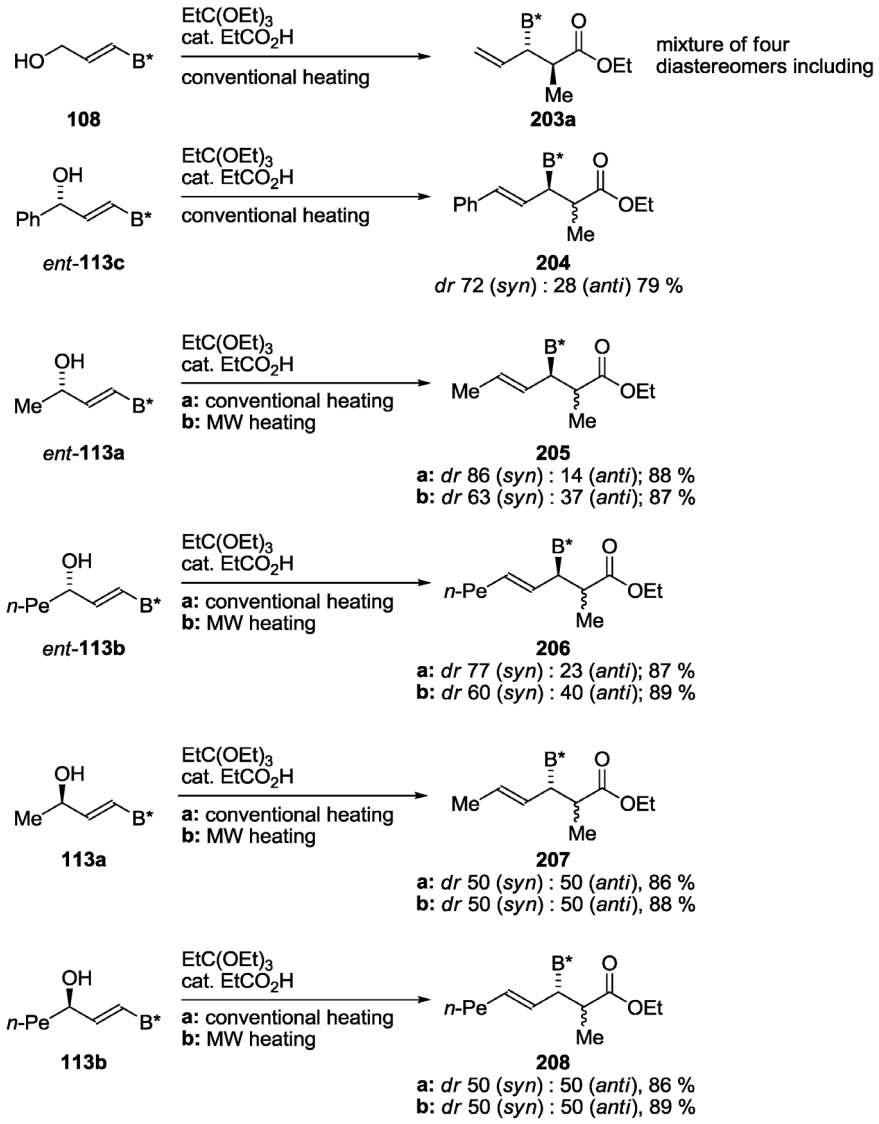
Table 26 Rearrangements of pentyl-substituted secondary allylic alcohols.



compound	conditions	Yield [%]	product
ent-**113b**	$MeC(OEt)_3$, cat. EtCOOH, 200W, 160 °C 9 min, DMF	87	 **199** *dr* >99:1
113b	$MeC(OEt)_3$, cat. EtCOOH, 200W, 160 °C 9 min, DMF	75	 **200** *dr* >99:1
ent-**113b**	$MeC(OMe)_2NMe_2$ toluene, 80 °C, 36 h	79	 **201**
113b	$MeC(OMe)_2NMe_2$ toluene, 80 °C, 36 h	89	 **202**

After optimization of conditions for the microwave-accelerated reaction, the diastereomeric mixture of **176** and **177** was isolated in good yield similar to conventional conditions, albeit within significantly shortened reaction time. Furthermore, microwave conditions were successfully applied to the Johnson rearrangement of substrate **113b** and *ent*-**113b**, while no conversion was achieved in the Eschenmoser rearrangement. For this reason, the Eschenmoser reaction of substrate **113b** and *ent*-**113b** was performed under conventional thermal conditions (Table 26) [53].

Allylic alcohol **108** and secondary alcohols **113a–c** and *ent*-**113a–c** were submitted to reaction conditions with triethyl orthopropionate in order to introduce an additional methyl group (Scheme 35). For all substrates, the reaction was high-yielding under microwave conditions as well as under conventional heating conditions, but a decrease in stereoselectivity was observed in the microwave-accelerated reaction of substrates *ent*-**113a,b**. Substrates **113a,b** gave the corresponding allylboronates **207–208** in high yield, but as chromatographically inseparable 50:50 mixture of diastereomers [53].



Scheme 35 Johnson rearrangements with triethyl orthopropionate.

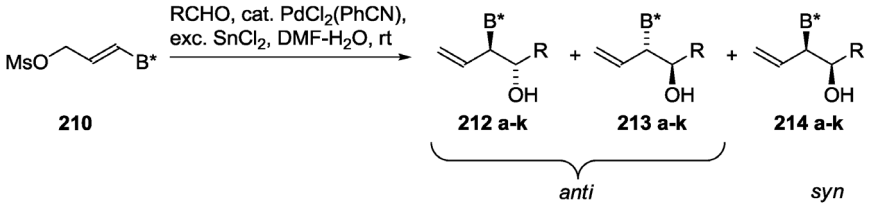
Carbonyl allylation

Besides [3.3]-sigmatropic rearrangements, Pd-catalyzed carbonyl allylation of aldehydes in the presence of $SnCl_2$ was reported as a convenient and reliable way for the preparation of α-substituted *anti*-configured allylboronates **212** and **213** (Table 27) [128,129]. Starting from substrate **108** and following an established protocol for carbonyl allylation reaction [130], the complete starting material **108** was reisolated unreacted. In order to enhance reactivity, allylic alcohols **108** and **166** were mesylated to yield compounds **210** and **211** quantitatively (Scheme 36) [128].

When submitting compound **210** to optimized reaction conditions, the desired products **212**, **213**, and **214** were obtained in good to very good yields after 2–3 h (Table 27). The scope of the reaction comprises various functionalized aldehydes, and the desired allylboronates were formed with mostly excellent *anti*-selectivity. Furthermore, formation of one of the *anti*-diastereomers is strongly favored: With benzaldehyde, diastereomer **212** was isolated as the sole product, for other residues the diastereo-

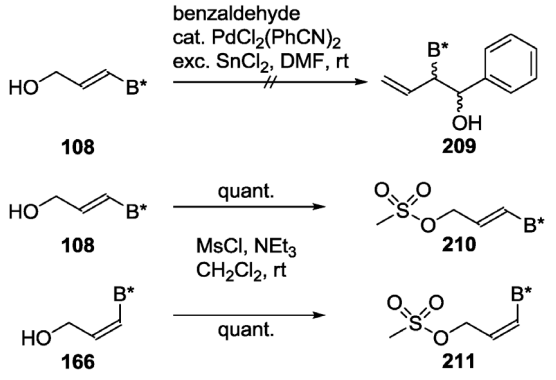
meric ratio of the formed *anti*-products **212** and **213** ranged from 96:4 for 3,4-difluorobenzaldehyde to 75:18 for 3-phenylpropionaldehyde.

Table 27 Carbonyl allylation reactions of mesylate **210**.



entry	R	yield[a] (%)	*dr*[b] 212:213:214
a	Ph	79	100:0:0
b	3,4-$C_6H_3F_2$	86	96:4:0
c	C_6F_5	82	94:6:0
d	furyl	73	93:7:0
e	CO_2Et	79	91:9:0
f	PhCHCH	75	89:11:0
g	$PhCH_2CH_2$	80	75:18:7
h	$(CH_3)_2CH$	70	78:22:0
i	$(CH_3)_2CHCH_2$	71	77:14:9
j	Cy	79	78:18:4
k	H	85	50:50:0

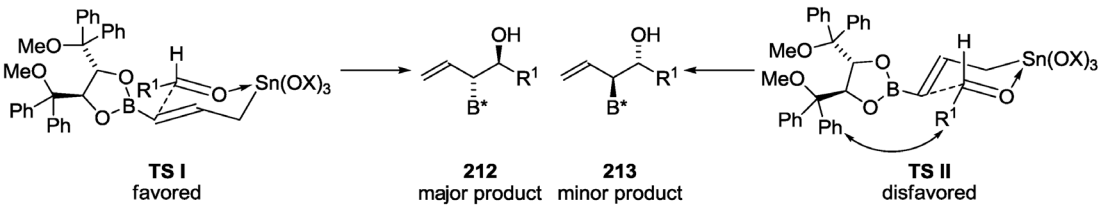
[a]Isolated mixture of diastereomers. [b]As judged by ^{1}H NMR spectrometry



Scheme 36 Synthesis of substrates for carbonyl allylation.

(*Z*)-Configured mesylate **211** gave results similar to the (*E*)-analogue **210**, which can be rationalized by the proposed mechanism of the carbonyl allylation reaction [129].

The high facial selectivity of the process can be explained by steric interactions. Formation of the minor product **213** results from transition state II, in which the aldehyde residue R^1 and the bulky substituent of the dioxaborolane moiety are forced to be in close proximity (Scheme 37). In transition state I, steric interaction between the two groups is minimized leading to the favored products **212**.



Scheme 37 Mechanistical consideration on facial selectivity.

Like the related allylboronates obtained from [3.3]-sigmatropic rearrangements, allylboronates **212–214** synthesized by this method are moisture-stable and can be stored for a long period under ambient conditions. The product mixtures of diastereomers were isolated by column chromatography, the diastereomerically pure products **212–214** were obtained by means of MPLC [129].

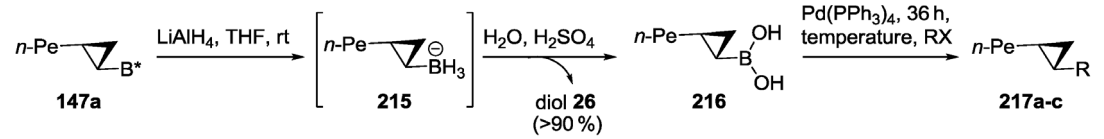
Reactivity and derivatization of 1,3,2-dioxaborolanes

Cyclopropanes

The high stability of cyclopropylboronic esters **146** and **147** makes these compounds valuable substrates for a variety of transformations in the side-chain in the presence of the boron group. On the other hand, transformations on the boron moiety also enable synthesis of attractive compounds.

Suzuki-Miyaura coupling

Highly stable cyclopropylboronic esters **146** and **147** are suitable for further transformations like Matteson homologation and Suzuki–Miyaura coupling, in which alkenyl-, aryl- or cyclopropyl halides are coupled with organoboron compounds [52]. Utilizing cyclopropylboronate **146a** in Suzuki–Miyaura couplings under various conditions failed, apparently because formation of an ate complex is prerequisite for successful reaction. Therefore, cyclopropane **146a** was treated with MeLi or $LiAlH_4$ to form ate complex **215**, and subsequent hydrolysis with diluted sulfuric acid gave boronic acid **216** (Scheme 38).



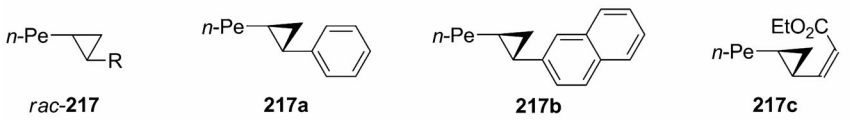
Scheme 38 Activation of cyclopropylboronate and Suzuki–Miyaura coupling.

Diol **26** was recovered almost quantitatively, and crude compound **216** was applied in a Suzuki–Miyaura coupling under conditions reported by Deng and Wang [131] in a moderate yield, whereby side-product formation was observed (Table 28, entry 1). Reaction conditions were optimized with *rac*-**217** first, but conditions described by Marsden and Hildebrand [132] turned out to be the most convenient ones. With enantiomerically pure cyclopropane **216**, a yield of 74 % of product **217a** was obtained (entry 6). The formation of a side-product was observed at reaction temperatures of 70 °C or above, and only moderate yields of the product were obtained (entries 2–6). Employing 1-naphthylbromide in Suzuki–Miyaura cross-coupling under conditions reported by Marsden and Hildebrand, product **217b** was formed in 77 % yield (entry 9). Additionally, naphthalene was isolated as side-product in 10–30 % yield, which explains the moderate yield obtained before. For labile olefins like compound **217c**, the use of potassium phosphate as base was found to be superior [52].

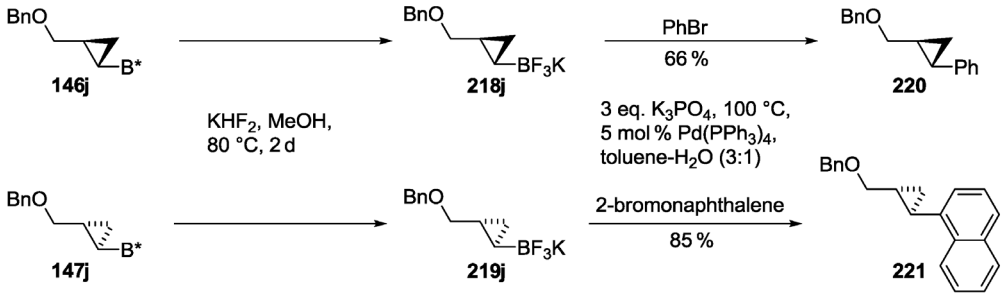
Table 28 Suzuki–Miyaura cross-coupling of **147a**.

entry	product	halide RX	solvent	base	temp (°C)	yield (%)
1	**217a**[a]	PhBr	toluene	3 eq. K_3PO_4	100	65
2	**217a**	PhI	THF	10 % KOH	50	-
3	**217a**	PhI	THF	10 % KOH	70	51
4	**217a**	PhI	hexane	10 % KOH	50	-
5	**217a**	PhI	toluene	10 % KOH	100	71
6	**217a**	PhBr	DME	2 eq. KO*t*-Bu	80	74
7	**217b**	1-naphthyl bromide	THF	10 % KOH	70	66
8	**217b**	1-naphthyl bromide	toluene	3 eq. K_3PO_4	100	48
9	**217b**	1-naphthyl bromide	DME	2 eq. KO*t*-Bu	80	77
10	**217c**	ethyl (*Z*)-3-bromo acrylate	toluene	3 eq. K_3PO_4	100	65

[a] The mixture was left for 14 h at the given temperature

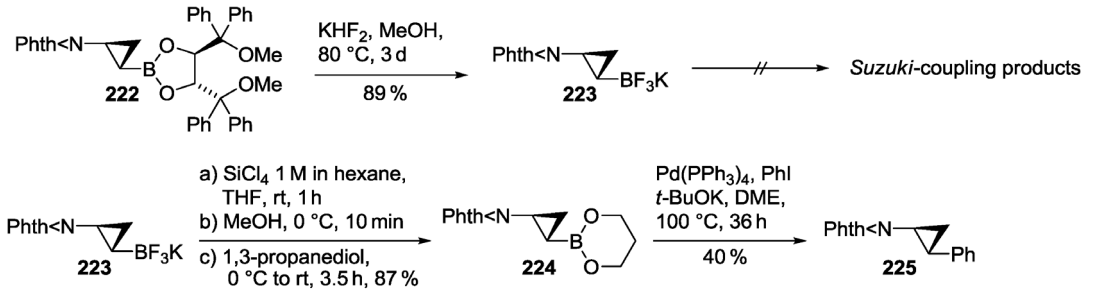


After transformation of boronate **146j** to the corresponding trifluoroborate **218j**, Suzuki–Miyaura cross-coupling was also accomplished with phenylbromide, $Pd(PPh_3)_4$, and potassium phosphate (Scheme 39). Using the conditions of Deng and co-workers [133] led to cyclopropane **220** in moderate yield. In comparison, a better yield of **221** was obtained when employing 2-naphthalenebromide in the cross-coupling with trifluoroborate **219j** [98].



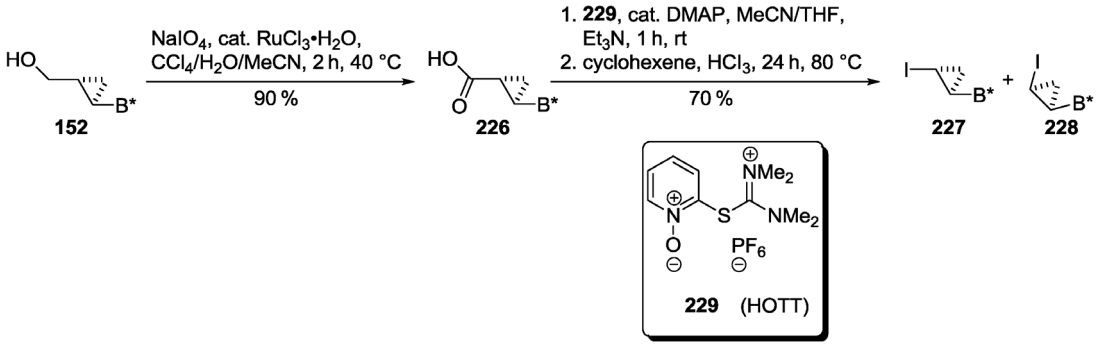
Scheme 39 Trifluoroborates for cross-coupling.

In contrast to the reaction discussed before, Suzuki–Miyaura cross-coupling failed for amino compound **222** under these conditions (Scheme 40). The combination of decreased reactivity of trifluoroborates and the deactivating amine group proved to be preventive to transmetallation. For this reason, trifluoroborate **223** was converted to the more reactive 1,3,2-dioxaborinane **224** in high yield under conditions reported by Matteson and Kim [134,135]. Subsequent cross-coupling with phenyliodide yielded 40 % of cyclopropane **225** [98,122].



Scheme 40 Derivatization and cross-coupling of cyclopropylamine **222**.

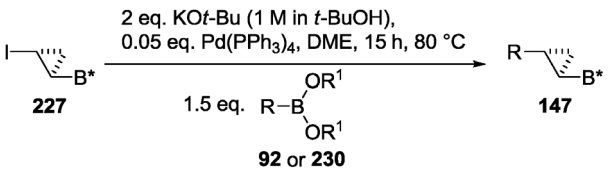
However, the synthetic potential of stable cyclopropanes of types **151** and **152** was not completely exhausted and further cross-coupling reactions were performed in the side-chain (Scheme 41). The boron moiety was left untouched when submitting halocyclopropane **227** to Suzuki–Miyaura coupling: Boronate **152** was first oxidized to the corresponding carboxylic acid **226** by a Ru-catalyzed reaction in high yield. Cyclopropyliodide **227** was obtained from thermal/radical decarboxylation of the corresponding thiohydroxamic ester, which was formed by treating carboxylic acid **226** with the *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT) reagent **229** [136] in the presence of iodoform. A mixture of the separable isomers **227** and **228** (6:1) was obtained in 70 % yield [137].



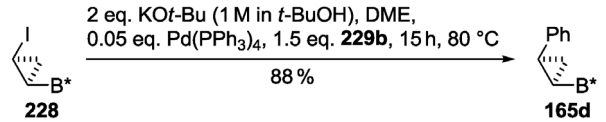
Scheme 41 Synthesis of iodocyclopropylboronates.

Suzuki–Miyaura cross-couplings were performed with pure cyclopropyliodide **227** under various conditions proving conditions by Marsden and Hildebrand to be most efficient (Table 29) [132], yielding the products in moderate to very good yields. The absence of oxygen during the reaction, purity of all reagents, and the use of 1.5 equiv of boronate compounds **92** and **230** were important for good results and allowed cross-couplings with arylboronic acids **230b,c**, alkenylboronic acid **92a**, and especially cyclopropyl derivative **230e** [137,138]. Cross-coupling reactions with alkylboronic acid **230a** and arylboronic acid **230d** containing a halide substituent on the aromatic ring were problematic, and no product formation was observed. *Cis*-isomer **228** was also successfully applied in the Suzuki–Miyaura coupling with phenylboronic acid **230b**, furnishing product **165d** in 88 % yield (Scheme 42) [138].

Table 29 Cross-coupling of iodocyclopropylboronate **227**.

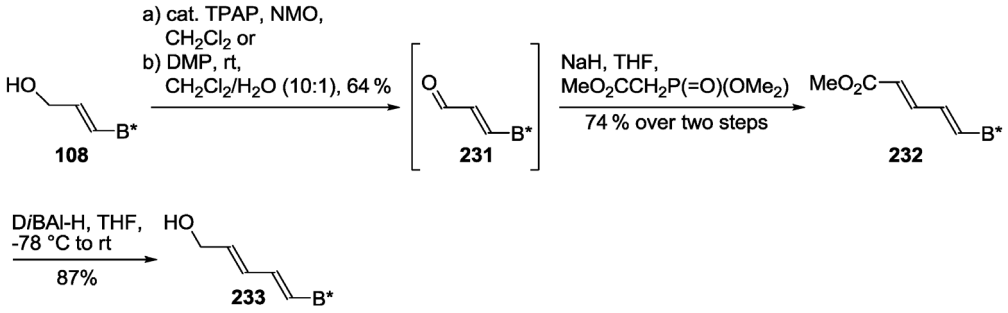


compound	R	product	R^1	yield (%)
230a	*n*-Pr	**147b**	H,H	-
230b		**147d**	H,H	87
92a	*n*-Pe	**147n**	H,H	65
230c		**147o**	H,H	79
230d	Br	**147p**	H,H	-
230e	Ph	**147q**	$-(CH_2)_3-$	67



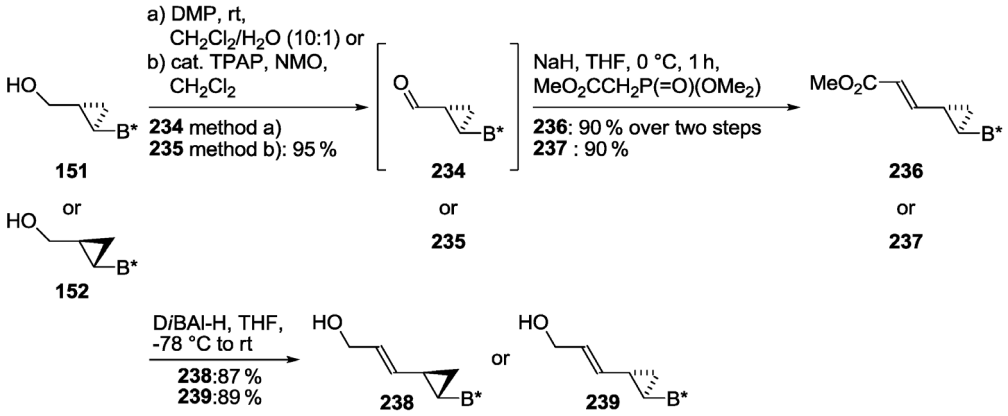
Scheme 42 Cross-coupling of *cis*-cyclopropane **228**.

Having established the Suzuki–Miyaura coupling for *trans*- and *cis*-cyclopropyliodides **227** and **228**, the synthesis of bicyclopropanes and methods for derivatization were investigated (Scheme 43). Vinylcyclopropanes are useful compounds for the synthesis of natural products containing oligocyclopropanes like the antifungal FR-900848 or the cholesterylester transfer-protein-inhibitor U-106305 [139]. The synthesis of allyl alcohol **233** was straightforward, starting with high-yielding oxidation of boronate **108** using Dess–Martin periodinane (DMP) and Ley oxidation, respectively, whereby the latter was found to be more convenient. In a subsequent Horner–Wadsworth–Emmons (HWE) reaction, aldehyde **231** was converted to ester **232** in good yield, followed by a reduction using diisobutylaluminium hydride (D*i*BAl-H) yielding 87 % of the desired alcohol **233** [140]. Unfortunately, the selective mono-cyclopropanation of dienylboronate **233** under Denmark conditions suffered from overreaction and only an inseparable mixture of mono- and dicyclopropanes was obtained [137].



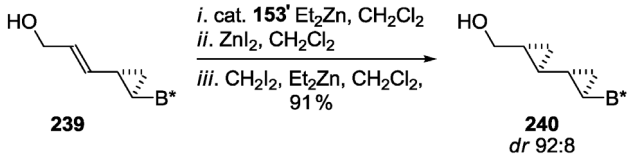
Scheme 43 Synthesis of dienylalcohol **233**.

To circumvent this problem, the same reaction sequence was applied to cyclopropylboronates **151** and **152** (Scheme 44). Oxidation of alcohol **152** was performed under the conditions reported by Ley [141] and subsequent HWE reaction to ester **237** proceeded in a high overall yield of 90 %. Diastereomer **151** was oxidized with Dess–Martin reagent yielding 95 % of the desired aldehyde **234**, and subsequent HWE reaction furnished ester **236** in 90 % yield [137]. After reduction of compounds **236** and **237** with D*i*BAl-H, the corresponding allyl alcohols **238** and **239** were obtained in 87 % (**238**) and 89 % (**239**) yield.



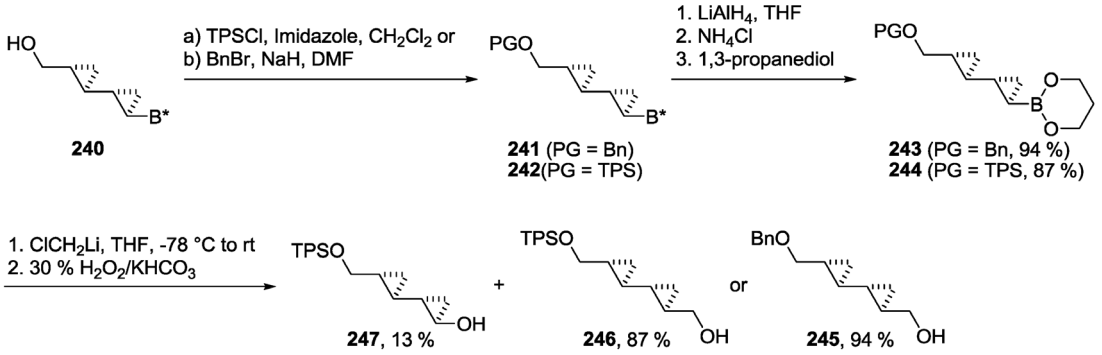
Scheme 44 Chain elongation of cyclopropylboronates **151** and **152**.

Cyclopropanation of allyl alcohol **239** under Denmark conditions was performed using bis-sulfonamide **153** as chiral ligand and bicyclopropane **240** was obtained in high yield and high selectivity (Scheme 45). In contrast, when employing ligand *ent*-**153** in the reaction, only a low selectivity was observed for the mismatched case [140].



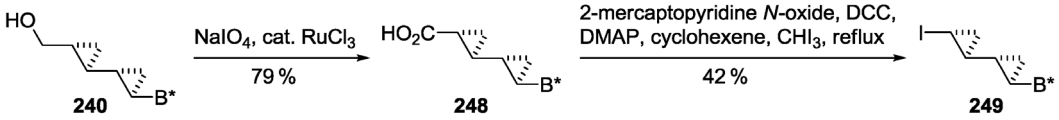
Scheme 45 Cyclopropanation of allylic alcohol **249**.

The absolute configuration of the second cyclopropyl moiety was assigned by chemical correlation after synthesizing the optically pure bicyclopropane **246** via Matteson homologation (Scheme 46). Therefore, the introduction of a benzyl- or a silyl-protecting group to compound **240** was necessary. The following transesterification of the protected compounds **241** and **242** to the dioxaborinanes **243** and **244** was straightforward, and in both cases the product was obtained in high yield. In the last step, the homologation and subsequent oxidation provided the desired products **245** and **246** in a good overall yield. Additionally, side-product **245** was isolated in 13 % yield from the reaction of silyl-protected alcohol **247** [140].

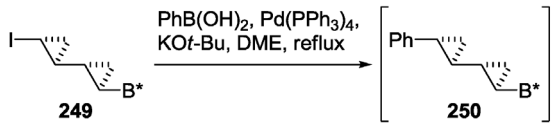


Scheme 46 Derivatization of bicyclopropylalcohol **240**.

In order to perform a Suzuki–Miyaura cross-coupling, boronate **240** had to be transformed to the corresponding iodide **249** (Scheme 47). Therefore, Ru-catalyzed oxidation of cyclopropane **240** was performed yielding 79 % of carboxylic acid **248**. Afterwards, thermal decarboxylation of the corresponding Barton thiohydroxamic ester in the presence of iodoform led to a mixture of *trans*:*cis* isomers (10:1) of iodocyclopropane **249** in low yield. Unfortunately, employing compound **249** in Suzuki–Miyaura cross-coupling with phenylboronic acid gave an inseparable mixture of starting material, deiodinated starting material, and the desired product **250** (Scheme 48) [140].



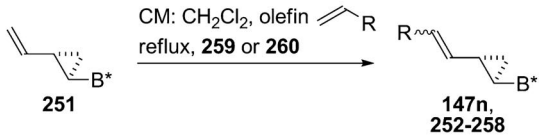
Scheme 47 Preparation of iodobicyclopropane **249**.



Scheme 48 Attempted Suzuki–Miyaura cross-coupling of iodobicyclopropane **249**.

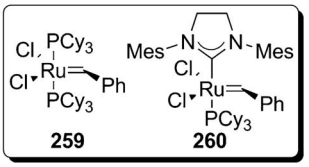
Furthermore, the application of vinylcyclopropane **251** in cross-metathesis was investigated (Table 30). Compound **251** was synthesized by performing Wittig or Peterson reaction starting from aldehyde **234**. Both reactions furnished product **251** in high yield (Scheme 49) [89,137,142].

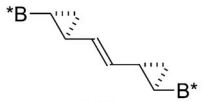
Table 30 Cross-metathesis reactions of cyclopropylboronate **251**.



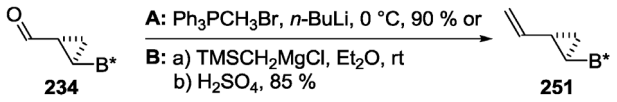
		using **259**		using **260**	
product	**R**	**yield (%)**	**(*E*):(*Z*)**	**yield (%)**	**(*E*):(*Z*)**
147n	*n*-Pe	n.p.	-	81	85:15
252	CO_2Me	52[a]	>95:5	91	>95:5
253	Ph	95	>95:5	96	>98:2
254	*n*-Bu	n.p.	-	83	85:15
255	$TMSCH_2$	n.p.	-	70	50:50
256	CH_2OTES	n.p.	-	90	85:15
257	CH_2OAc	n.p.	-	-	-
258	CH_2OH	n.p.	-	-	-

[a] + 14 % **261**
n.p. = not performed





261
81 % with **259**;
95 % with **260**

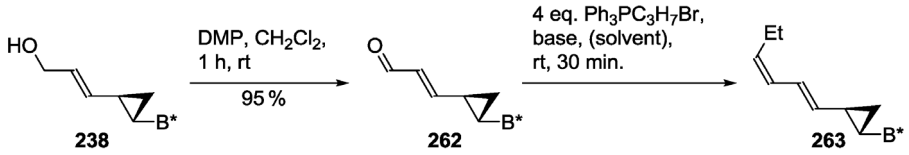


Scheme 49 Olefinations of cyclopropylcarbaldehyde **234**.

Cross-metathesis was performed by treatment of vinylcyclopropane **251** with the commercially available Grubbs catalysts **259** and **260** and various olefins, wherein catalyst **260** turned out to be superior with respect to yield and selectivity in formation of the desired products (Table 30). Performing cross-metathesis with methyl acrylate and Grubbs catalyst **259**, the reaction proceeded sluggishly, yielding product **252** only in moderate yield along with 14 % dimer **261**. When using catalyst **260** for the same substrate, no side-product formation was observed and 91 % of product **252** was obtained. Several substrates have been successfully applied under these conditions, the products were obtained in good-to-high yields and in most cases with good selectivities, exceptions being allylic acetate and unprotected allyl alcohol. Nevertheless, separation of the diastereomers by chromatography failed and only in the cases of product **253** and **254** the selective crystallization of the diastereomers was successful. Performing the reactions without another olefin as cross-metathesis partner gave dimerization product **261** in high yield with both metathesis catalysts [137].

Vinylcyclopropane **262**, which was synthesized by oxidation of alcohol **238** with DMP in 95 % yield, was also utilized in a Wittig reaction (Table 31). It was proven that the high (*Z*)-selectivity of the reaction depends on the solvent and the counterion of the base used. The best result was achieved using THF and potassium hexamethyldisilazide (KHMDS) yielding 96 % of product **263** in an excellent diastereomeric ratio (entry 4), whereby the major (*Z*)-isomer was purified by selective crystallization [137].

Table 31 Wittig olefination of α,β-unsaturated aldehyde **262**.

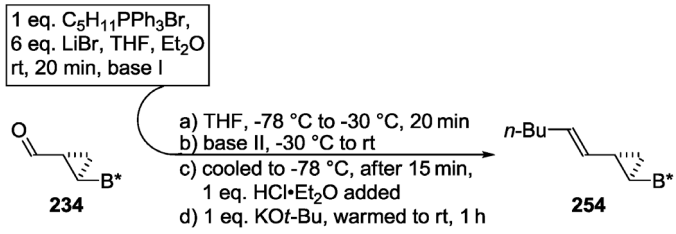


entry	solvent	base (4 eq.)	olefin 264 (*Z*):(*E*)	yield (%)
1	THF	NaHMDS (1M in THF)	91:9	76
2	CH_2Cl_2	NaHMDS (1M in THF)	86:14	75
3	THF	LiHMDS (1M in THF)	81:19	87
4	THF	KHMDS (neat)	97:3[a]	96
5	DME	KHMDS (neat)	97:3	89

[a]the minor diastereoisomer was removed by crystallization.

In order to gain access to the natural product dictyopterene A, considerable efforts were made to synthesize the corresponding (*E*)-isomers (especially the *n*-butyl derivative **254**). For the synthesis of olefin **254** from aldehyde **234** by Schlosser modification of the Wittig reaction, various bases and conditions were screened (Table 32). The best yield (70 %) and diastereomeric ratio (80:20), respectively, were obtained using 1 equiv of *n*-BuLi (entry 4) [137].

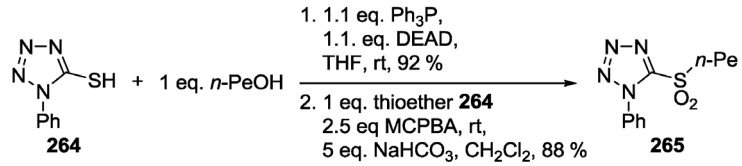
Table 32 Optimization of conditions for (*E*)-selective olefination of aldehyde **234**.

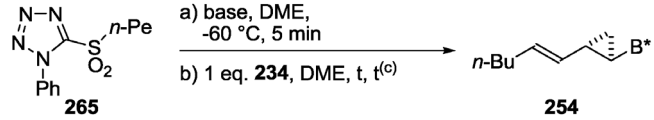


entry	base I	base II	olefin 254 (*E*):(*Z*)	yield (%)
1	2 eq. PhLi	2 eq. PhLi	64:36	30
2	1 eq. PhLi	1 eq. PhLi	59:41	44
3	1 eq. PhLi	1 eq. *n*-BuLi	70:30	53
4	1 eq. *n*-BuLi	1 eq. *n*-BuLi	80:20	70
5	1 eq. *n*-BuLi	2 eq. *n*-BuLi	67:33	23

Furthermore, aldehyde **234** was submitted to Julia–Kocienski reaction using sulfone **265**, which was synthesized from *n*-pentanol and thiol **264** by Mitsunobu reaction and subsequent oxidation (Table 33). In all reactions performed during a screening high *E*/*Z*-selectivity was obtained, but the isolated yield was strongly dependent on the reaction conditions applied. The best result was obtained by

Table 33 Optimization of Julia–Kocienski reaction of **234**.





entry	t (°C)	$t^{(c)}$	sulfone 265 (equivalents)	base	olefin 254 (*E*):(*Z*)	yield (%)
1	-78	15h	1.2	1.2 eq. KHMDS (0.5 M in toluene)	>99:1	20
2	-78	15h	1.2	3 eq. KHMDS (0.5 M in toluene)	98:2	36
3	-78	15h	1.2	1.2 eq. NaHMDS (1 M in toluene)	97:3	43
4	-60	15h	1.2	1.2 eq. KHMDS (neat)	>99:1	46
5	-60	15h	1.2	1.4 eq. KHMDS (neat)	>99:1	54
6	-60	15min	1.3	1.8 eq. KHMDS (neat)	>99:1	73
7	-78	1min	1.3	1.8 eq. KHMDS (neat)	>99:1	71
8	-60	10 min	1.5	1.8 eq. KHMDS (neat)	>99:1	93

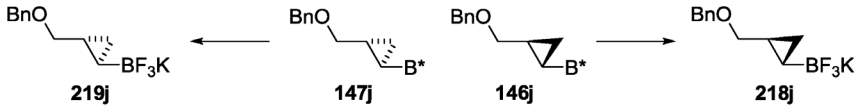
using 1.8 equiv of neat KHMDS, a temperature of –60 °C, 10 min reaction time and 1.5 equiv of sulfone **265** (entry 8) [137].

Trifluoroborates

Since Pietruszka and co-workers successfully established the synthesis of stable enantiomerically pure cyclopropylboronates, derivatizations of the boron moiety have been investigated. First, studies employing cyclopropylboronic ester **146a** in Suzuki–Miyaura reactions failed, and it was shown that these derivatives had to be converted to more active species. Activation of the boronate moiety was first realized by reaction with MeLi or $LiAlH_4$ and subsequent hydrolysis to obtain the corresponding boronic acid [52]. Although diol **26** was recovered almost quantitatively, the harsh conditions are incompatible with many functional groups and therefore alternative ways for the activation of the boronate moiety were necessary.

In recent years, the application of potassium organotrifluoroborates in Suzuki–Miyaura cross-coupling has been extensively studied, not least because these stable boronic acid derivatives tolerate many functional groups [32,33]. Transformation of cyclopropylboronic esters to trifluoroborates using KHF_2 as reagent was first reported by Deng and co-workers [133] utilizing a modified procedure by Genêt and co-workers [143]. In a first investigation applying the original procedure of Vedejs [144] by treating cyclopropylboronates **146j** and **147j** with KHF_2 at room temperature no product was isolated (Table 34). Product formation within 5 days was observed using a reaction temperature of 80 °C and 14 equiv of KHF_2. Further increase of the number of equivalents of KHF_2 (50 equiv) resulted in short-

Table 34 Conversion of cyclopropylboronates **146j** and **147j** to trifluoroborates.

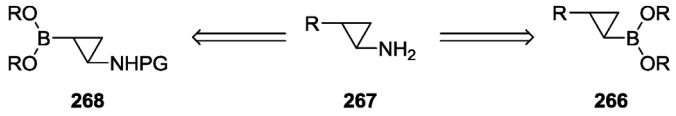


KHF_2 (equivalents)	solvent	time (d)	temp (°C)	turnover	yield (%)
7	MeOH-H_2O	4	rt	-	-
14	MeOH-H_2O	5	80	90 %	~70
50	MeOH-H_2O	2	80	quant.	91
50	MeOH	2	80	quant.	93

ened reaction time and higher yield. Omitting aqueous conditions simplified the procedure, yielding 93 % of trifluoroborates **218j** and **219j** in crystalline form [98,137,142].

Cyclopropylamines

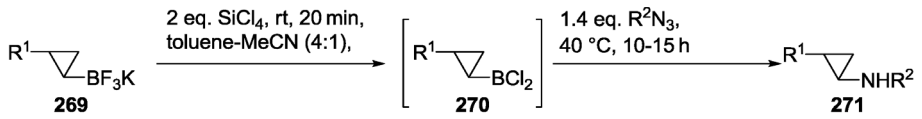
Cyclopropylamines have attracted considerable interest as versatile intermediates in organic synthesis. Besides being key elements of natural products including belactosin A and coronatine [145,146], this structural motif can be found in a number of drugs such as tranylcypromine and trovafloxacin [147,148]. Several methods for the synthesis of these compounds are known, but diastereo- and enantioselective variants have attracted special interest [149–157]. Amination of diol **26**-derived cyclopropyl boronic ester was envisaged to be carried out by two different methods. In the first approach, boronic esters **266** were utilized in C–B to C–N conversion to obtain cyclopropylamines **267** (Scheme 50). Alternatively, Curtius rearrangement in the presence of diol **26**-derived boronate moiety lead to products **268**, which are precursors for cyclopropylamines **267** [122].



Scheme 50 Two approaches to cyclopropylamines.

For amination reactions via C–B to C–N conversion, it was necessary to transform highly stable diol **26**-derived boronates to the corresponding trifluoroborates **269** first and subsequently to a more electrophilic group (Table 35). Utilizing conditions reported by Matteson and co-workers [134,135], racemic cyclopropyltrifluoroborates **269** were treated with $SiCl_4$ to prepare the highly reactive dichloroboranes **270** in situ. Amination of intermediate **270** was then performed with benzyl azide, wherein various reaction conditions were tested. It was found that addition of MeCN increased the solubility of the trifluoroborate and thus higher yields were obtained. Best yields were obtained at a reaction temperature of 40 °C, a solvent mixture of toluene and MeCN (4:1), and reaction times of 15 h. The optimized conditions were successfully applied to various readily available trifluoroborates **269** and azides. Except benzylether **269j**, which was too labile to withstand Lewis-acidic conditions at elevated temperature, all products were obtained in very good yield. Amination with allyl azide had to be carried out at room temperature to avoid evaporation of the starting material, while the reaction with benzoyl-protected trifluoroborate **269e** was stopped after 5 h because of side-product formation [158].

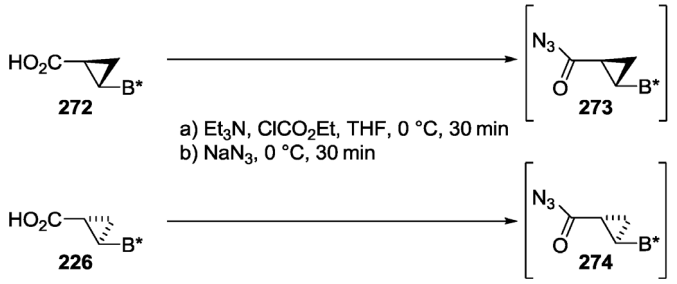
Table 35 C–B to C–N transformation of cyclopropyltrifluoroborates.



product	R^1	R^2	yield (%)
271b	*n*-Bu	Bn	81
271d	Ph	Bn	86
271d	Ph	PMB	80
271d	Ph	Allyl	85[a]
271e	$BzOCH_2$	Bn	73[b]
271j	$BnOCH_2$	Bn	-

[a] The reaction mixture was stirred at r.t.
[b] The reaction mixture was stirred for 5 h.

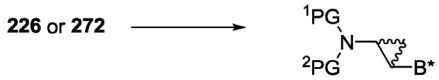
In addition, Curtius rearrangement was performed to synthesize cyclopropylamines, and therefore the corresponding acyl azides **273** and **274** were required (Scheme 51). Oxidation of diastereomerically pure cyclopropylboronates **151** and **152** provided the corresponding carboxylic acids **226** and **272** under established conditions in good yield. Treatment with ethyl chloroformate led to activation by anhydride formation. Subsequent addition of sodium azide furnished the corresponding azides **273** and **274** [98].



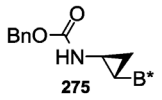
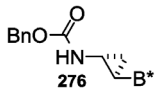
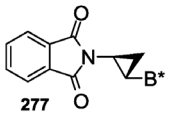
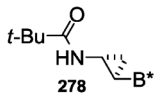
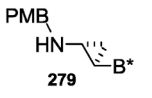
Scheme 51 Preparation of acyl azide cyclopropylboronates.

Then acyl azides **273** and **274** were applied in the Curtius rearrangement, introducing various protective groups (Table 36). Benzylcarbamates **275** and **276** were obtained in high yields for both diastereomers, and the configuration of diastereomer **276** was assigned by X-ray crystal structure analysis [98]. When the azide **274** was treated with *t*-BuOH, high excess (55 equiv) of the nucleophile was required to obtain product **278** in good yields. Compound **277** was synthesized via free amine formation. It was not isolated but treated with phthalic anhydride directly after neutralization with triethylamine. Compound **277** was only obtained in moderate yield from purification by column chromatography. Later it was shown that crude product **277** can also be employed in further transformations without hampering the reaction outcome. Product **279** was synthesized in 66 % yield over three steps by treating free amine formed from compound **226** with anisaldehyde under Dean–Stark conditions, followed by reduction of the crude imine with $NaBH_4$ [122].

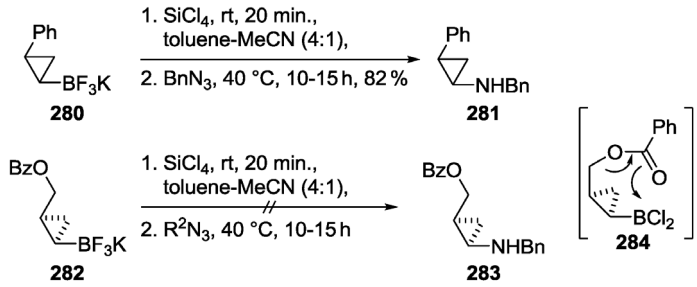
Table 36 Curtius rearrangement of cyclopropylboronates **226** and **272**.



275-279

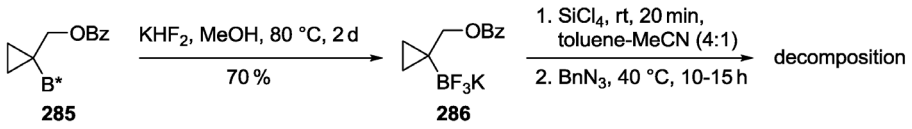
compound	conditions	yield (%)	Product
272	1.0 eq. BnOH, toluene, 100 °C, 4 h	90	 **275**
226	1.0 eq. BnOH, toluene, 100 °C, 4 h	90	 **276**
272	*i* toluene, 100 °C, 30 min *ii* 1.2 eq. HCl 37 %, 2 h *iii* Et_3N, pH > 7 *iv* 5.7 eq. phtalic anhydride, 70 °C, 12 h	67	 **277**
226	55 eq. *t*-BuOH, 90 °C, 2 d	84	 **278**
226	a) *i* toluene, 100 °C, 2 h *ii* 1.3 eq. HCl 37 %, 30 min *iii* 1.3 eq. anisaldehyde, reflux, 15 h b) 2 eq. $NaBH_4$, MeOH/ Et_2O, -20 °C, 40 min	66	 **279**

In addition, the synthesis of the corresponding *cis*-derivatives was investigated using both methods (Scheme 52). The corresponding 2-substituted *cis*-cyclopropyltrifluoroborates were submitted to amination reactions. Reaction of phenyl derivative **280** yielded 82 % of amine **281**, while benzoyl-protected compound **282** did not give the desired product **283**. This observation could be explained that the reaction of the benzoyl group with the dichloride resulted in hydrolysis, followed by decomposition. The same observation was made for compound **286** synthesized from cyclopropane **285** (Scheme 53). Attempted amination by the discussed method led to decomposition [158].



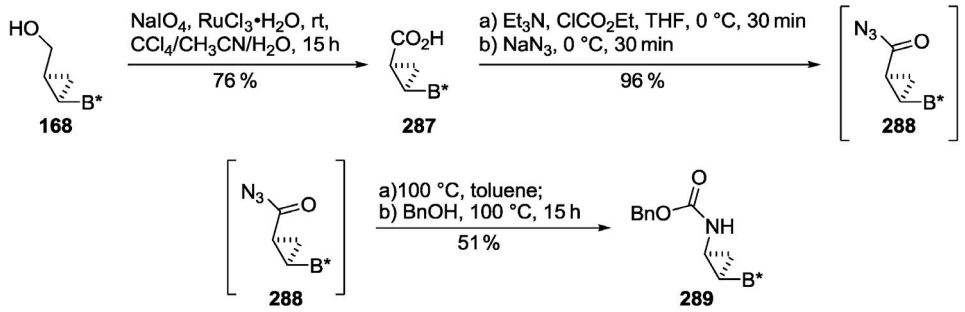
280 **281** **282** **283** **284**

Scheme 52 Synthesis of protected *cis*-cyclopropylamines.



Scheme 53 Attempted amination of trifluoroborate **286**.

The preparation of the corresponding *cis*-azides for the Curtius rearrangement was accomplished under same conditions as for the *trans*-substituted analogues, starting from diastereomerically pure cyclopropylboronate **152** (Scheme 54). Oxidation of boronate **152** to carboxylic acid yielded compound **287** in good yield, and transformation to azide **288** was straightforward, yielding the product in 96 % yield. Performing Curtius rearrangement turned out to be problematic, and only treating azide **288** with rather reactive nucleophile BnOH gave the desired carbamate **289** in moderate yield [122].



Scheme 54 Curtius rearrangement of *cis*-cyclopropylboronate **168**.

Allylboronates: Derivatization and reactivity

Generally, two methods for the generation of chiral α-substituted allylboronates have been applied, [3.3]-sigmatropic rearrangement and Pd-catalyzed carbonyl allylation of aldehydes. Due to the high stability of the boronate moiety **18** under various reaction conditions, further derivatization preceding allyl additions is a considerable option besides direct utilization in allylation reactions. Diastereomerically pure compounds **176** and **177** obtained by separation via MPLC following Johnson rearrangement were submitted to a plethora of transformations.

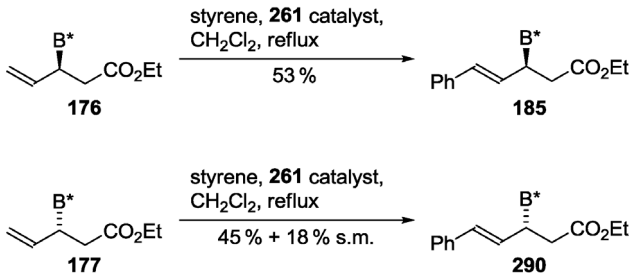
Derivatization of allylboronates

The first reported derivatization of **176** and **177** was cross-metathesis with styrene, yielding products **185** and **290** in moderate yields (Scheme 55). The resulting products were helpful in the assignment of configuration of the same products obtained from Johnson rearrangement of secondary allylic alcohols **113c** and *ent*-**113c** [99].

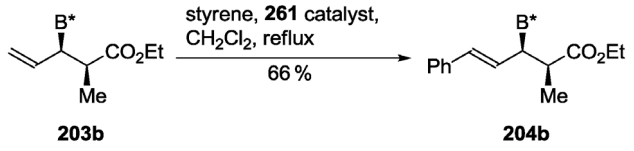
In analogy, cross-metathesis was proven to be useful in the elucidation of the absolute configuration of compound **203b** (Scheme 56). The reaction was utilized to obtain phenyl-substituted allylboronate **204b**, thus enabling determination of absolute configuration by X-ray crystal structure analysis [53].

D*i*BAl-H reduction of **176** and **177** gave the corresponding allylboronates **291** and **294** in excellent yields (Scheme 57). Ethyl-substituted allylboronates **293** and **296** were obtained by submitting alcohols **291** and **294** to mesylation followed by hydrodesulfonylation utilizing superhydride reduction in good yield [159].

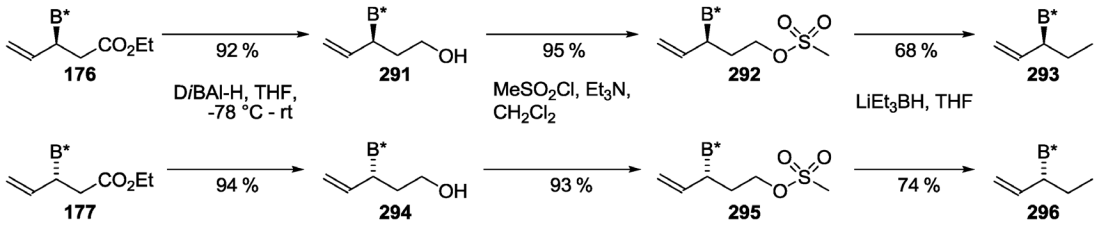
Besides mesylation, alcohols **291** and **294** were submitted to TBS protection with TBSCl/imidazole, which proceeded in excellent yields (Scheme 58) [106]. In order to investigate the properties of



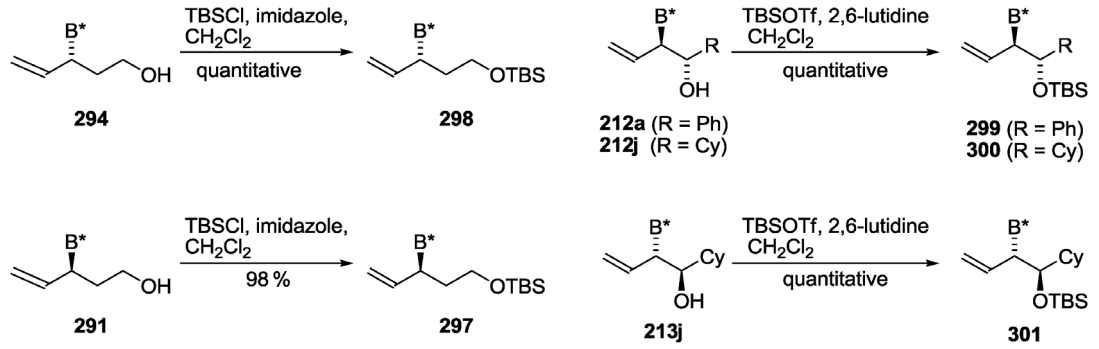
Scheme 55 Cross-metathesis of allylboronates.



Scheme 56 Cross-metathesis for determination of absolute configuration.



Scheme 57 Derivatization of allylboronates by reduction.

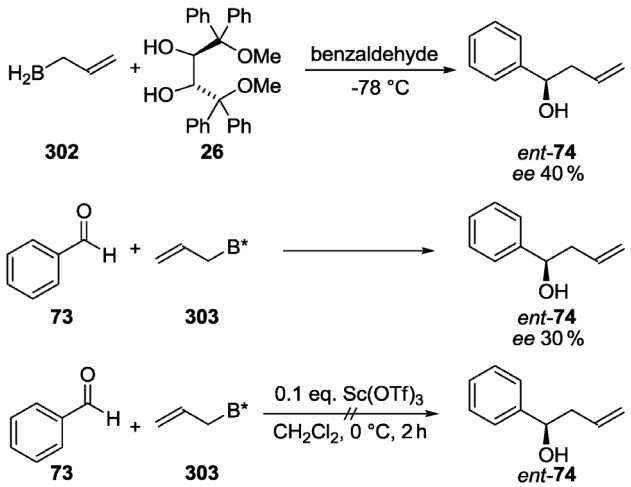


Scheme 58 TBS protection of allylboronates.

TBS-protected products **299–301** in allyl addition reactions, they were prepared from carbonyl allylation products **212a**, **212j**, and **213j** in quantitative yield using TBS-triflate/2,6-lutidine as silylating agent [129]. Thus, synthesized compounds are potentially valuable reagents for application in orthogonal protective group strategies.

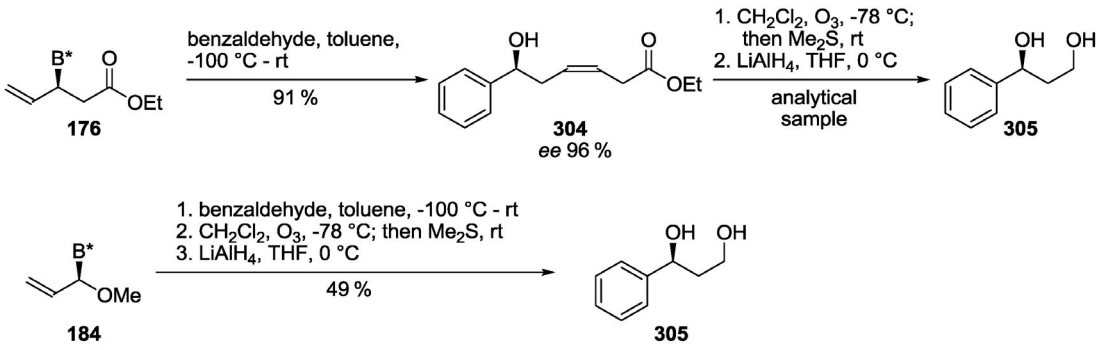
Reactivity of allylboronates: Allyl additions

The allylation of carbonyl groups is one of the most versatile C–C bond-forming reactions in organic chemistry [160]. Among the commonly used allylating reagents, chiral α-substituted boronates belong to the most valuable reagents, as their reactions are mostly characterized by a high degree of stereoselectivity as well as reliability and predictability concerning their stereochemical outcome based on mechanistical considerations [12,13,161]. As mentioned earlier, allylboronates bearing diol **26** as protective group are extraordinarily stable under various conditions and easy to handle. The first reported diol **26**-derived allylboronate was α-unsubstituted allylboronate **303** (Scheme 59) [51]. Allylic addition of allylboronate **303** formed from allylborane **302** and diol **26** to benzaldehyde **73** gave the product *ent*-**74** only in modest ee of 40 %, which can be rationalized by the fact that chiral protective group diol **26** is the reagent's only stereoinductive element. When the allylation reaction of benzaldehyde **73** was performed by Wilhelm, allylboronate **303** was prepared and isolated beforehand [162]. Under these conditions, product *ent*-**74** was isolated with 30 % ee, thereby generally confirming the finding reported by Nakayama and Rainier [51]. When Hall and co-workers investigated the scandium(III)triflate-catalyzed allylboration of aldehydes, allylboronate **303** did not show any conversion after 2 h at 0 °C in the presence of benzaldehyde [163]. Generally, the steric hindrance provided by diol **26** renders the reaction times of corresponding allylboronates long in comparison to allylboronates bearing less bulky groups. Referring to the reports mentioned previously [51,162], in this case some rate-lowering effect has to be attributed to the presence of scandium(III)triflate.



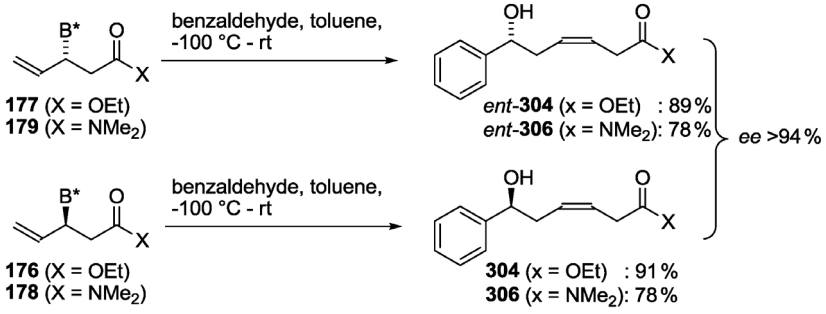
Scheme 59 Allyl addition reaction of diol **26**-derived allylboronate.

While the stereoselectivity of the reaction of allylboronate **303** is merely controlled by the stereogenic information provided by the chiral protective group, in the addition of chiral α-substituted allylboronates to electrophilic acceptors, the configuration of the C-atom in α-position to boron is the decisive factor for the stereochemical outcome. In initial experiments on allylation of aldehydes with chiral α-substituted allylboronates, the compounds **176** and **184** obtained from [3.3]-sigmatropic rearrangement reactions were added to benzaldehyde (Scheme 60). The reaction of **176** proceeded with nearly quantitative yield and excellent enantioselectivity. The configuration of product **304** and the allylboronate **184**-derived allylation product was assigned by chemical correlation utilizing chemical degradation to diol **305**. Later on, X-ray structure analysis of allylboronate **176** indirectly confirmed the assignment [108].



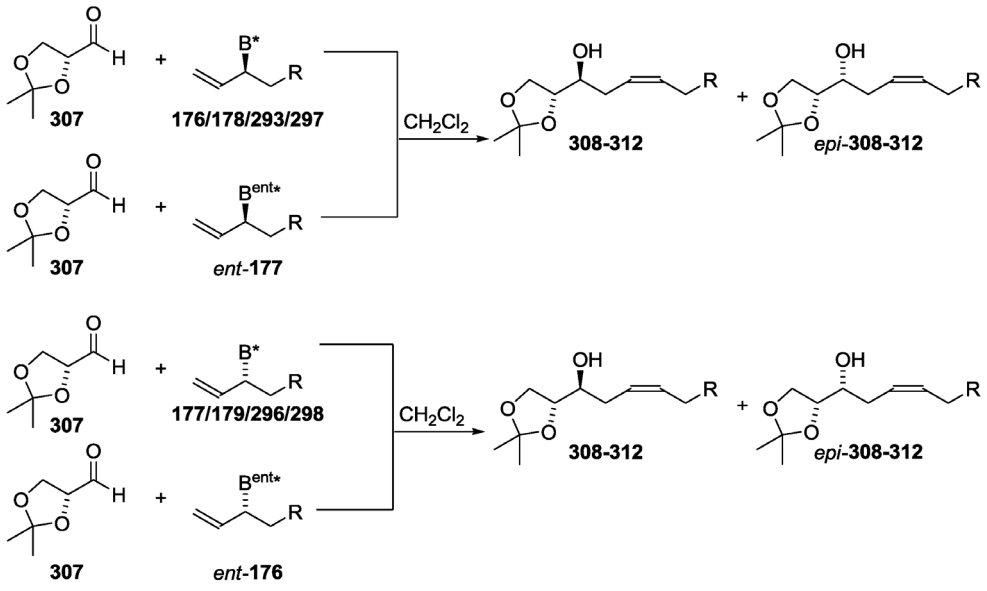
Scheme 60 Initial experiments with diol **26**-derived chiral α-substituted allylboronates.

For the reaction of diastereomers **176** and **177** as well as **178** and **179** with benzaldehyde, the desired products were obtained in good-to-excellent yields and ee's >94 % (Scheme 61). The allylation reactions proceeded with high (*Z*)-selectivity. Attempted kinetic resolution by reacting 2 equiv of a 50:50 mixture of allylboronates **176** and **177** with 1 equiv of substrate yielded racemic product and starting material with the diastereomeric ratio of **176** and **177** being unchanged. The influence of reagent configuration vs. substrate-induced stereocontrol [164–167] was examined by reacting various diastereomerically pure reagents with 2,3-*O*-isopropylidene-glyceraldehyde **307** as a substrate with an additional stereogenic center (Table 37). Herein, isopropylidene-protected glyceraldehyde **307** was considered to have a relatively strong directing effect on nucleophilic attacks to its carbonyl group. Generally, in this case substrate control favors formation of the *anti* addition products. Reagent control of allylboronates **176**, **178**, **293**, and **297** [(*R*)-series] also favors *anti*-products **308–312**, while **177**, **179**, **296**, and **298** [(*S*)-series] favor the configuration of the new-formed stereogenic center belonging to the *syn*-isomers *epi*-**308–312**. In additions of allylboronates **176** and **177**, it was found that substrate control cannot be completely overruled by the reagents' selectivity. As expected, in the matched case of **176** as allylation reagent product **311** was formed with a diastereomeric ratio of 97:3. In mismatched case of allylboronate **177**, product formation was also reagent-controlled, but diastereomeric ratio of 30:70 revealed that substrate control has a certain influence on the reaction outcome. Addition reactions of further allylboronates belonging to the two series confirmed this trend. Diastereomeric mixtures were formed with reagent-controlled formation of the major isomers, but obviously with underlying influence of the substrate, especially in the mismatched cases.



Scheme 61 Enantioselective reaction of chiral α-substituted allylboronates.

Table 37 Experiments on substrate- and reagent-control in allylation reactions.



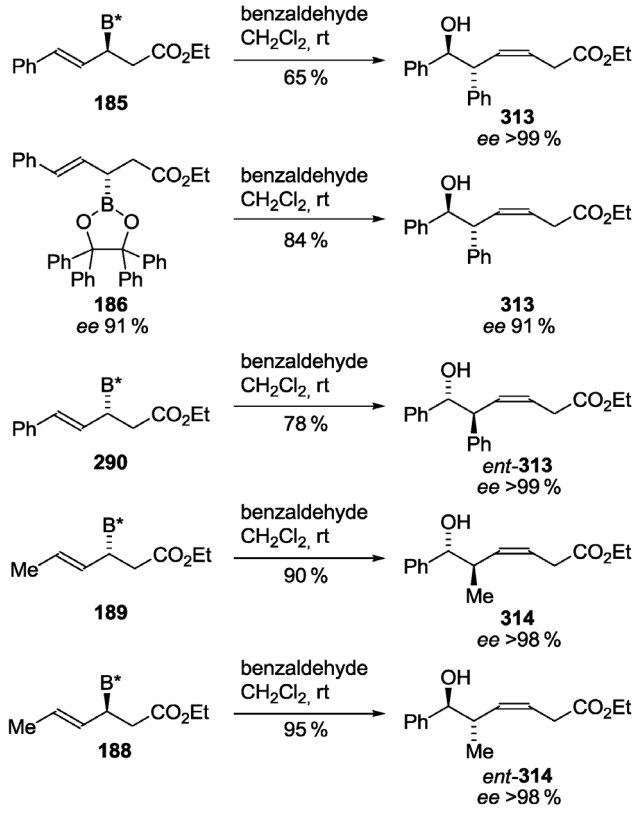
reagent	R	yield (%)	product	*dr*[a]
178	$CONMe_2$	63	**308**/*epi*-**308**	>99:1
179	$CONMe_2$	75	**308**/*epi*-**308**	27:73
297	CH_2OTBS	69	**309**/*epi*-**309**	89:11
298	CH_2OTBS	90	**309**/*epi*-**309**	29:71
293	CH_3	81	**310**/*epi*-**310**	95:5
296	CH_3	91	**310**/*epi*-**310**	30:70
176	$COOCH_2CH_3$	86	**311**/*epi*-**311**	97:3
177	$COOCH_2CH_3$	89	**311**/*epi*-**311**	30:70
ent-**176**	$COOCH_2CH_3$	92	**312**/*epi*-**312**	35:65
ent-**177**	$COOCH_2CH_3$	91	**312**/*epi*-**312**	>99:1

[a]As judged by ^1H NMR spectroscopy of crude reaction mixture

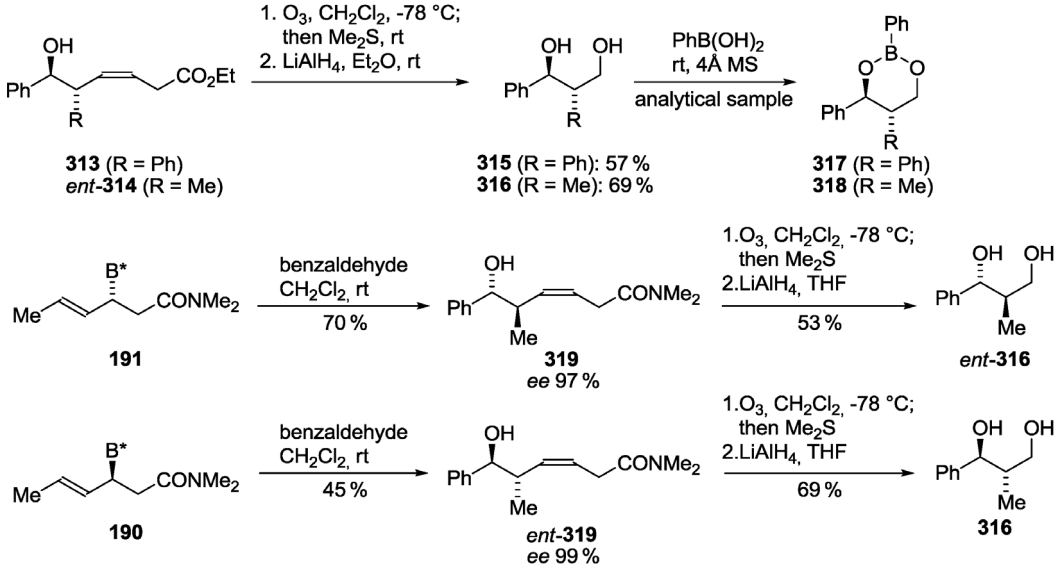
It was also desirable to obtain some information on the influence of the auxiliary's configuration on stereoselectivity. The auxiliary was assumed to have a minor matched/mismatched effect. By addition of allylboronates *ent*-**176** and *ent*-**177** to substrate **307**, this issue was elucidated. The effect was found to be small but distinct: In the "matched/matched" case of *ent*-**177**, formation of *anti*-diastereomer **312** as the only product was found, while addition of *ent*-**176** yielded the products **312** and *epi*-**312** in an *anti*:*syn* ratio of 65:35. This can be seen as "mismatched" relation between reagent and auxiliary or as a "matched" relation between auxiliary and substrate as well [106].

The scope of allylboronates applied was extended to phenyl-substituted allylboronates **185** and **290** and methyl-substituted analogues **188** and **189** (Scheme 62). Addition of the diastereomerically pure reagents to benzaldehyde gave the expected products in good to very good yields and excellent enantioselectivity. Furthermore, the benzpinacol-protected analogue **186** of allylboronate **185** was submitted to allyl addition under identical reaction conditions. While the product **313** was isolated in slightly higher yield of 84 %, the ee dropped from >99 to 91 % [99].

The products' relative and absolute configuration was confirmed by chemical correlation with known diols **315** and **316** and NMR-spectroscopical investigation of dioxaborinanes **317** and **318** (Scheme 63). The same method was used to confirm the expected configuration of the homoallylic alco-



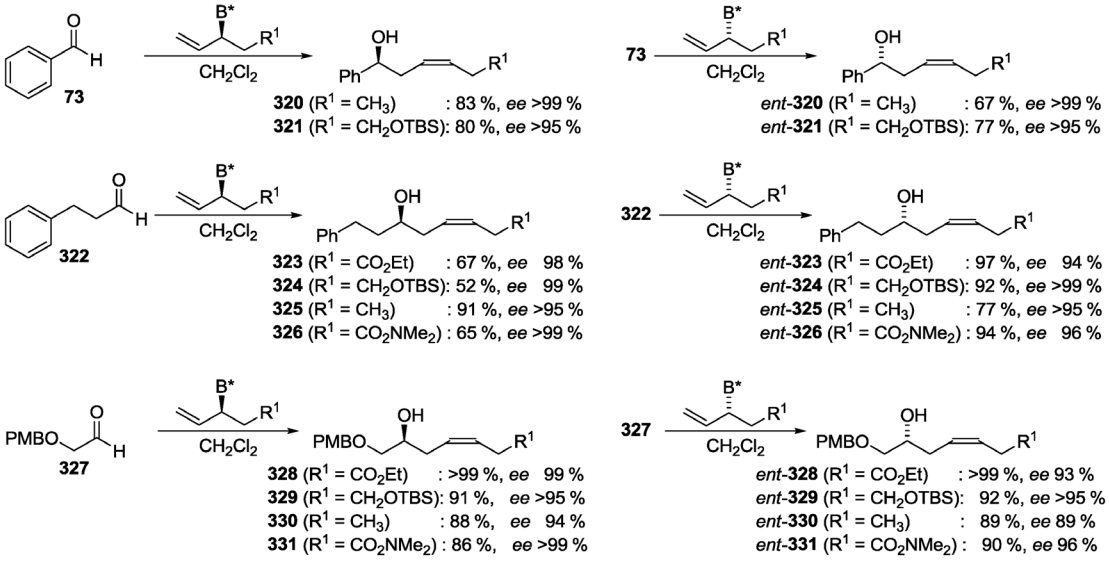
Scheme 62 Addition reactions of chiral α-substituted allylboronates bearing an additional substituent.



Scheme 63 Assignment of configuration of allylation products.

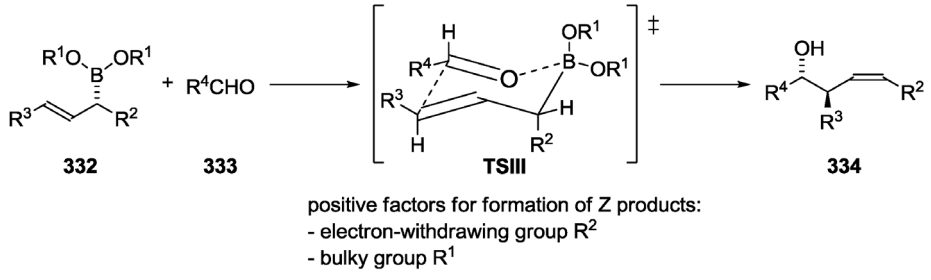
hols **319** and *ent*-**319** obtained from the addition of the amides **190** and **191** to benzaldehyde. The reaction gave the expected nearly enantiomerically pure products in moderate to good yield [53,99].

The scope of substrates was broadened to 3-phenylpropionaldehyde **322** and PMB-protected glycolaldehyde **327** as further acceptors for addition of allylboronates **176–179**, **293/296**, and **297/298**, which were obtained as products from [3.3]-sigmatropic rearrangements or as derivatives of these products (Scheme 64). In the reaction with benzaldehyde, the expected products were obtained in very good to excellent enantioselectivity and mostly good to quantitative yield [106].



Scheme 64 Allyl additions of enantiomerically pure allylboronates to various aldehydes.

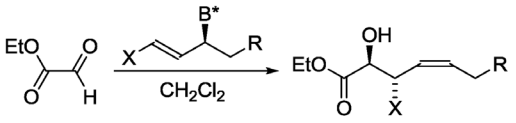
The stereoselectivity and *E*/*Z*-selectivity of favoring the (*Z*)-isomer can be explained by a six-membered transition state assumed for the addition reaction (Scheme 65). In reactions of α-substituted allylboronates the stereogenic center in α-position to boron is a decisive constituent of the transition state, outplaying the stereoinductive effect of the remote auxiliary by far. The influence of the boronic ester's bulkiness in allylic additions was studied by Hoffmann and co-workers who proved that increasing the bulk of the protective group favors formation of the (*Z*)-olefinic products. Furthermore, it was found that electron-withdrawing substituents α to boron promote the formation of (*Z*)-configured products. The relative configuration of the residues R^3 and R^4 in the product is mainly determined by the double-bond configuration in allylboronate **332** and the equatorial positioning of the aldehyde's residue, which depends on its bulkiness [106,161,168,169].



Scheme 65 Six-membered transition state of allyl addition to aldehydes.

In order to synthesize (*Z*)-configured homoallylic α-hydroxyesters, several allylboronates were tested regarding their reactivity with ethyl glyoxalate **335** (Table 38). Besides allylboronates **297** and **298**, which had already been tested on other substrates, derivatives **291** and **294** having an unprotected hydroxyl group were successfully applied, allowing the isolation of diols **337** and *ent*-**337** in good yields of 84 and 77 %, respectively, and nearly complete enantiomeric purity [53].

Table 38 Allyl addition reactions to ethyl glyoxalate.

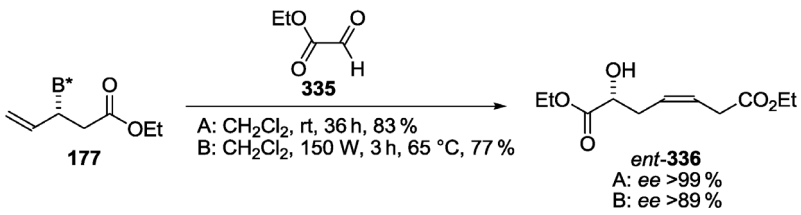


335 **336-339** **335** ***ent*-336-339**

reagent	X	R	*ee* (%)	yield (%)/ product
176	H	CO_2Et	>99	85 (**336**)
291	H	CH_2OH	98	84 (**337**)
297	H	CH_2OTBS	97	42 (**338**)
190	Me	$CONMe_2$	>99	56 (**339**)

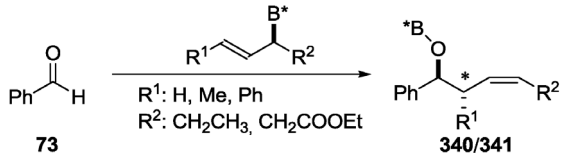
reagent	X	R	*ee* (%)	yield (%)/ product
177	H	CO_2Et	>99	83 (*ent*-**336**)
294	H	CH_2OH	>99	77 (*ent*-**337**)
298	H	CH_2OTBS	92	59 (*ent*-**338**)
191	Me	$CONMe_2$	>99	58 (*ent*-**339**)

The addition of allylboronate **177** to ethyl glyoxylate **335** was studied regarding the influence of conventional and microwave heating on the reaction outcome (Scheme 66). It was found that heating in a microwave reactor increases reaction rate considerably, but has a negative effect on the addition's selectivity. Along with decreasing the reaction time from 36 to 3 h by changing conditions from room temperature to 65 °C in a microwave reactor, the ee was lowered from at least 99 to 89 % while the isolated yield slightly dropped from 83 to 77 %. Performing the reaction at a temperature of 65 °C with conventional heating furnished product *ent*-**335** with an ee of 99 % albeit a certain amount of starting material remained unreacted [53].



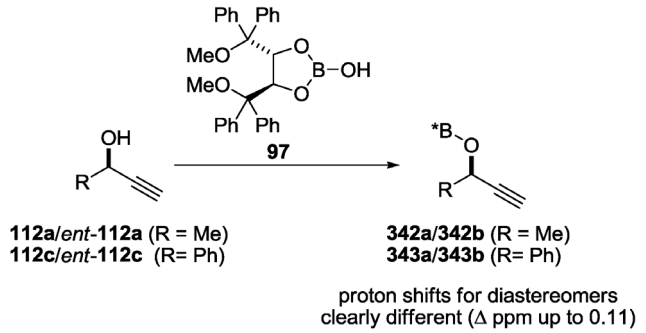
Scheme 66 Influence of microwave heating on reaction rate and stereoselectivity.

Special attention was drawn to the determination of the ee of the homoallylic alcohols obtained from allylic additions. Often the corresponding Mosher ester was formed in order to determine the products' optical purity from the diastereomeric ratio of Mosher ester, especially when direct methods failed. A problem immanent to the Mosher method is that diastereomeric discrimination of the ester formation has to be ruled out as well as differences in hydrolysis rate of boric esters **340** and **341**. To provide a solution to this problem, the NMR data obtained from product mixtures of **340** and **341** were investigated intensively before work-up. It was found that not only the signals of the protons adjacent to and nearby the newly formed stereogenic center but also signals of remote protons found in the R^2 residue show a clear difference in chemical shifts for the two diastereomers **340** and **341** (Scheme 67).



Scheme 67 Formation of boric ester diastereomers in allylic addition.

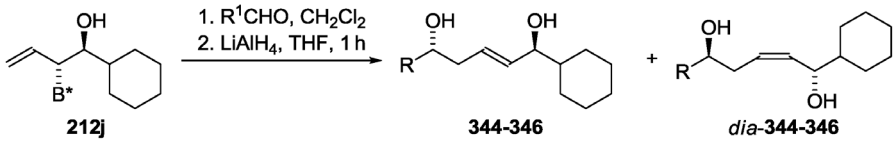
This observation was found to be general; changes in the specific substitution of allylation reagents utilized in the reaction only had minor effects. This implies that in almost all cases, enantio- or diastereoselectivity of allyl additions can be evaluated by NMR analysis of the crude product. Finally, the scope of the approach was extended to determination of the ee of secondary alcohols (Scheme 68). Application of the method to commercially available pure propargylic alcohols **112a**, **112c**, and their enantiomers *ent*-**112a** and **112c** proved the potential of the hydroxydioxaborolane **97** for indirect determination of the ee of secondary alcohols. NMR analysis of boric esters was thereby found to impose a valuable alternative in case direct methods of ee determination fail [159].



Scheme 68 Application of hydroxydioxaborolane **97** as shift reagent for secondary alcohols.

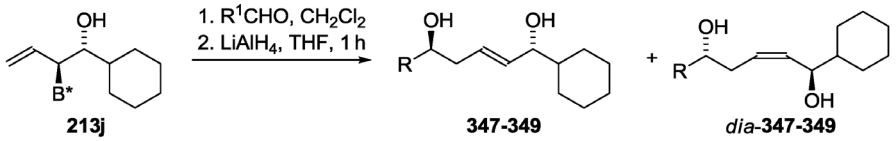
Complementing the scope of chiral α-substituted allylboronates of type **293/296** presented until here, the addition reaction of the *anti*-substituted allylboronates of type **212/213** enables stereocontrolled access to manifold 2-ene-1,5-diols. In an initial report, the reaction of allylboronates **212j** and **213j** derived from cyclohexanecarbaldehyde with a selection of three aldehydes was described. When the reactions had been completed, the diastereomeric mixtures of products were obtained after treatment with $LiAlH_4$ (Table 39). All of these reactions proceeded with very good yield and excellent enantioselectivity. Surprisingly, starting materials **212j** formed predominantly (*E*)-configured homoallylic alcohols **344–346**, while the reactions of compounds **213j** yielded the (*Z*)-isomers *dia*-**347–349** as major products [128].

Table 39 Addition reactions of allylboronates obtained from carbonyl allylation.



212j **344-346** *dia*-**344-346**

products	R	yield (%)	*dr* (*E*):(*Z*)	*ee* (%)
344/*dia*-**344**	Cy	87	84:16	>99
345/*dia*-**345**	Ph	91	50:50	>99
346/*dia*-**346**	$Ph(CH_2)_2$	92	74:26	>99



213j **347-349** *dia*-**347-349**

products	R	yield (%)	*dr* (*E*):(*Z*)	*ee* (%)
347/*dia*-**347**	Cy	89	16:84	>99
348/*dia*-**348**	Ph	83	33:67	>99
349/*dia*-**349**	$Ph(CH_2)_2$	85	24:76	>99

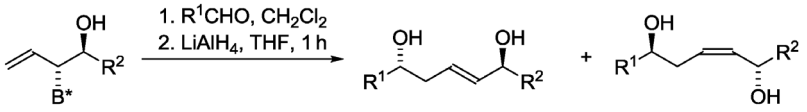
When the scope of the reaction was extended regarding both allylboronates **212**/**213** and aldehyde substrates **333**, this observation appeared to be a general trend related to the configuration of the utilized allylboronates (Table 40). Depending on the configuration of the *anti* diastereomers (**212** and **213**), matched/mismatched interaction with the auxiliary **26** in the boronate moiety renders attack to the aldehyde with the α-substituent being in a pseudo-equatorial (**212**) or pseudo-axial position (**213**) more favorable in comparison to the other diastereomer. Additions of boronate **212** with R^2 = H yielded exclusively (*Z*)-isomers *dia*-**350** and *dia*-**351** in excellent yield and enantioselectivity. For R ≠ H (*Z*)-selectivity was decreased and even turned to (*E*)-selectivity for some substituents. In contrast, all reactions of allylboronates **213** were (*Z*)-selective [129].

Irrespective of the different diastereoselectivities found, all additions proceeded with very good enantioselectivity, providing nearly all products with ee's higher than 95 % [106,129].

To complete the study on the relationship between configuration of allylboronates and corresponding products, addition of *syn*-allylboronate **214j** to benzaldehyde **73** was performed, yielding the *syn*-configured 2-ene-1,5-diols **361** and **362** in a diastereomeric ratio of 17:83 in favor of the (*Z*)-isomer (Scheme 69). An explanation for this reaction outcome was found by comparison of the transition states **TS IV** and **TS V** assumed for the formation of products **361** and **362**. Hydrogen bond interactions may be explanatory for additional stabilization of the favored transition state [129].

TBS-protected *anti*-substituted allylboronates **299**, **300**, and **301** were also submitted to allylic addition reactions (Scheme 70). The resulting monoprotected 2-ene-1,5-diols were isolated in moderate to very good yields and ee over 95 %. In comparison to the unprotected analogues, the reaction of the silylethers resulted in lowered yields and increased formation of (*Z*)-products. The most significant effect of silylation was observed in addition of allylboronate **301** to benzaldehyde **73**: While addition of unprotected compound **213j** led to formation of (*E*)-and (*Z*)-isomers **348**/*dia*-**348** in a ratio of 33:67 in 83 % yield, reaction of **301** resulted in the isolation of *ent*-**365** as sole diastereomer in 86 % yield [129].

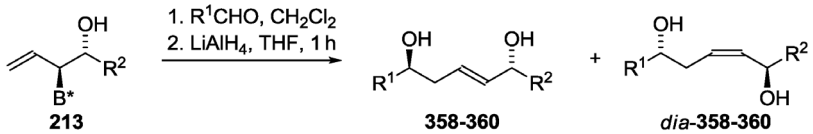
Table 40 Results of addition reactions of *anti*-hydroxy-substituted allylboronates.



212 **350-357** *dia*-**350-357**

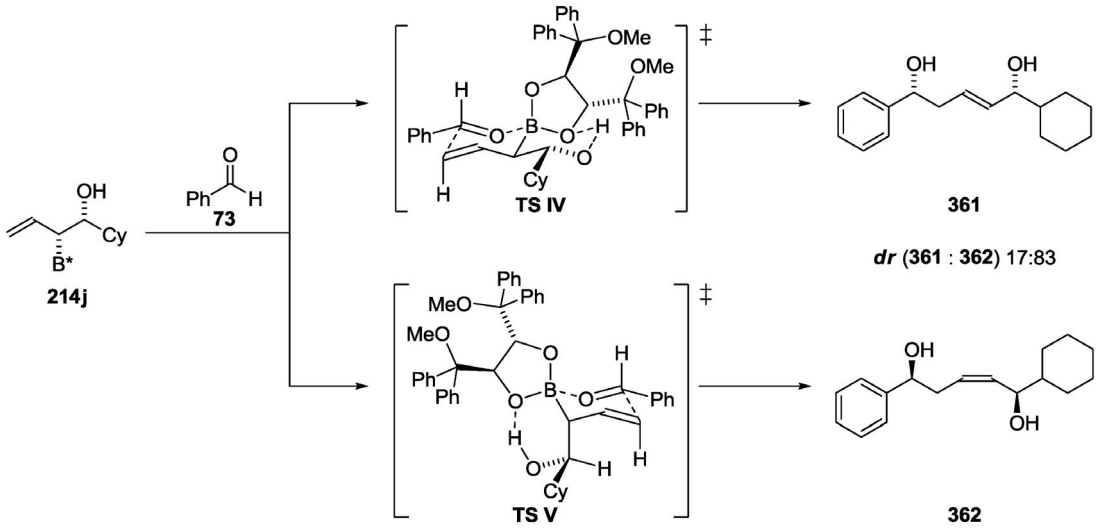
products	R^1	R^2	yield (%)	*dr* (*E*):(*Z*)	*ee* [(*E*)-product; %]	*ee* [(*Z*)-product; %]
350/*dia*-**350**	Ph	H	95	0:100		96/97[a]
351/*dia*-**351**	$PhCH_2CH_2$	H	89	0:100		95/93[a]
352/*dia*-**352**	C_6F_5	C_6F_5	90	33:67	>95	>95
353/*dia*-**353**	3,4-$C_6H_3F_2$	3,4-$C_6H_3F_2$	quant.	40:60	>95	>95
354/*dia*-**354**	H	$PhCH_2CH_2$	71	46:54	>95	>95
355/*dia*-**355**	Ph	Ph	99	59:41	>95	>95
356/*dia*-**356**	$PhCH_2CH_2$	$PhCH_2CH_2$	98	59:41	>95	>95
357/*dia*-**357**	$(CH_3)_2CH$	$(CH_3)_2CH$	66	82:18	>95	>95

[a]Determined by chiral HPLC analysis

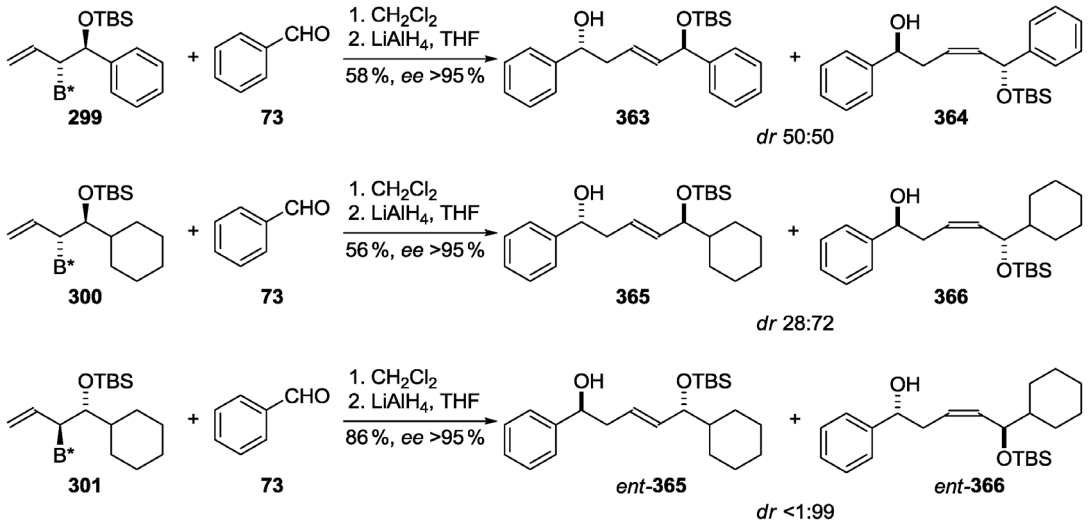


213 **358-360** *dia*-**358-360**

products	R^1	R^2	yield (%)	*dr* (*E*):(*Z*)	*ee* [(*E*)-product; %]	*ee* [(*Z*)-product; %]
358/*dia*-**358**	Ph	H	94	0:100		95
359/*dia*-**359**	$PhCH_2CH_2$	H	88	0:100		92
360/*dia*-**360**	$(CH_3)_2CH$	$(CH_3)_2CH$	60	27:73	>95	>95



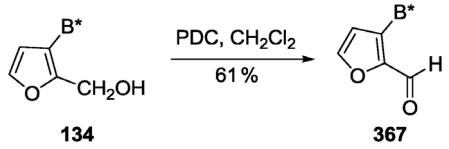
Scheme 69 Transition states in formation of *syn*-1,5-diols from *syn*-hydroxy-substituted allylboronate **214j**.



Scheme 70 Addition reactions of TBS-protected allylboronates.

Reactions of arylboronates

The utilization of diol **26** as an efficient chiral auxiliary in the synthesis of optically active 2,3-disubstituted furylalcohols has been reported by Wong and co-workers (Scheme 71) [110,170,171]. The initially reported reaction sequence started from furylaldehyde **367**, which was prepared by oxidation of the corresponding alcohol **134** [110].



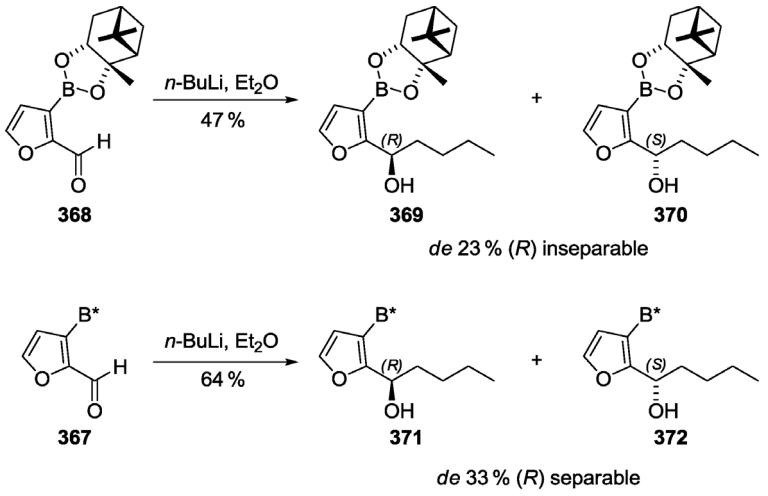
Scheme 71 Oxidation of hydroxymethyl arylboronate.

Addition of *n*-BuLi to pinanediol-containing analogue **368** gave the expected products in moderate yield and low selectivity as an inseparable diastereomeric mixture (Scheme 72). In contrast, the nucleophilic addition of *n*-BuLi to compound **367** gave a separable diastereomeric mixture in good yield and moderate diastereoselectivity [110].

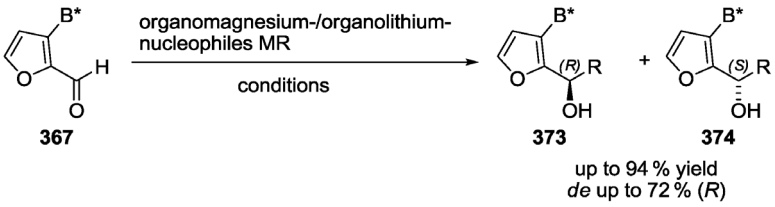
The diastereoselectivity of Grignard reactions of substrate **367** was found to be strongly dependent on the solvent used, namely, on the solvatization ability for organometallic reagents (Scheme 73). Depending on solvent and nucleophile added, products were obtained in a yield up to 94 % and diastereomeric excess of 72 % [110].

Implementing the idea that the first added equivalent of nucleophilic reagent is likely to attack the boronate group before alkylation of the carbonyl group takes place, a tetrahedral borate species in which the chiral director is located closer to the carbonyl moiety was formed by addition of lithium alkoxides. Indeed, subsequent additions proceeded with increased diastereoselectivity which was further improved by selecting alkoxides with bulky alkyl chains (Scheme 74) [110].

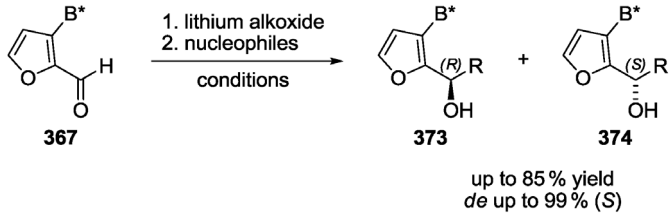
It was also observed that treatment of the substrate with alkoxides before adding the nucleophile inverted the stereoselectivity of the reaction (Scheme 75). This was explained by a transition state in



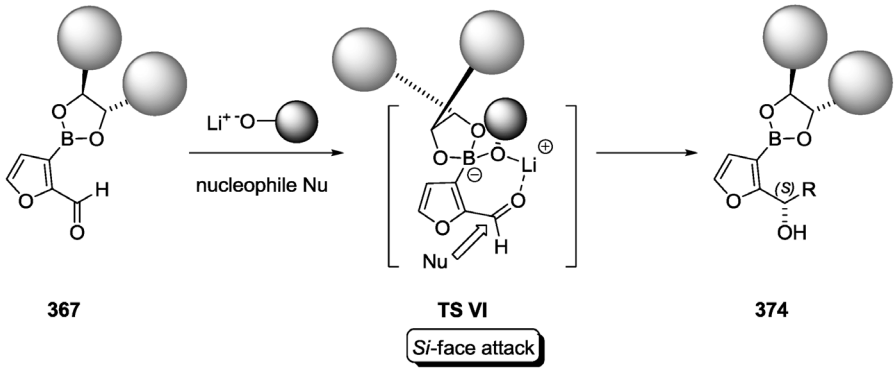
Scheme 72 Nucleophilic addition of *n*-BuLi to furylaldehyde boronates.



Scheme 73 Addition of organometallic nucleophiles to furylaldehyde boronate.



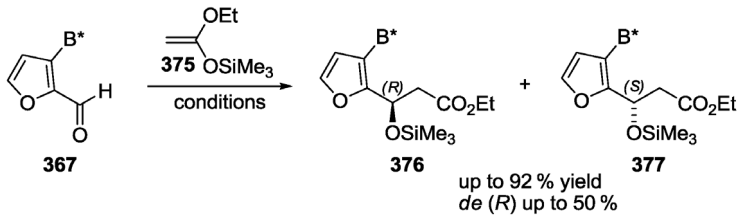
Scheme 74 Enhancement of diastereoselectivity in addition reactions by formation of ate complex.



Scheme 75 Effect of ate complex formation on transition state of nucleophilic attack.

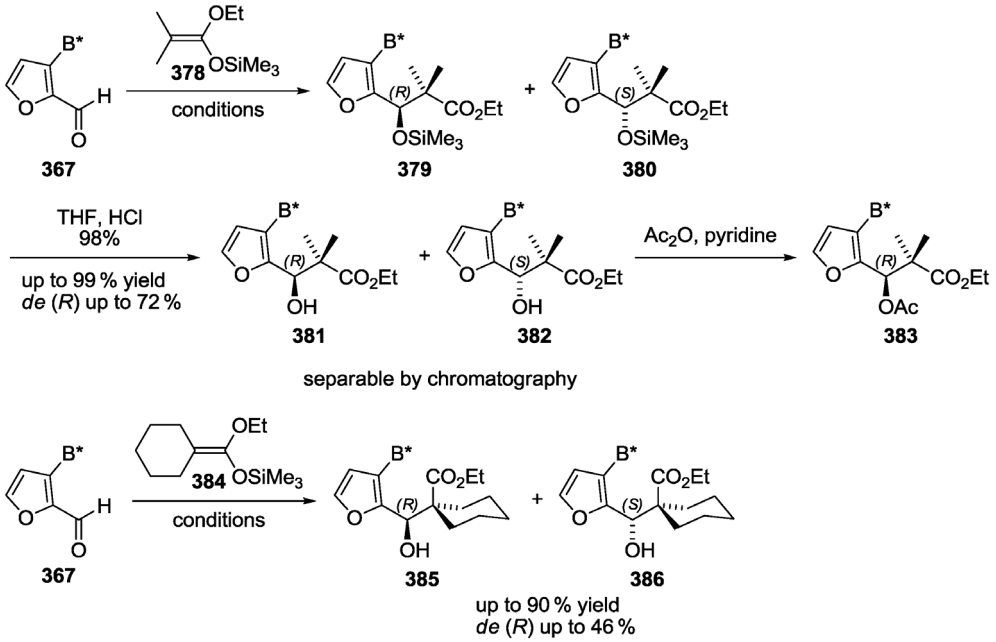
which a seven-membered ring hinders nucleophilic attack by blocking the *re*-face of the carbonyl group [110].

In addition, Lewis acid-catalyzed reactions of furaldehyde **367** with various ketene silyl acetals were investigated (Scheme 76). Under optimized conditions using $La(OTf)_3$ as catalyst, Mukaiyama aldol reaction of **367** and silyl acetal **375** gave the desired silylethers **376** and **377** in good yields and modest diastereoselectivities, wherein the diastereomeric mixtures were separable by column chromatography. The best example yielded 92 % of **376** and **377** with diastereomeric excess of 50 % [170].



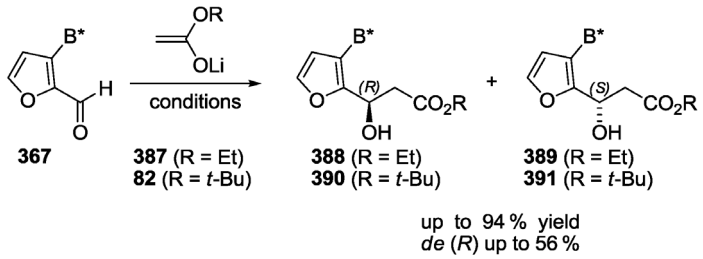
Scheme 76 Mukaiyama aldol reaction of furylaldehyde **367**.

Changing the silylacetal to **378** gave the product mixture of **379** and **380** in good to quantitative yield and with generally increased diastereomeric excesses of up to 72 % (Scheme 77). After silylether cleavage, the diastereomeric mixture was separated and the absolute configuration of **381** was confirmed by crystallization of the corresponding acetate **383**. Further increase of the ketene acetal's bulkiness did not improve diastereoselectivity. The products **385** and **386** from aldol reaction with silylacetal **384** were isolated in good to very good yields and moderate diastereomeric excess [170].

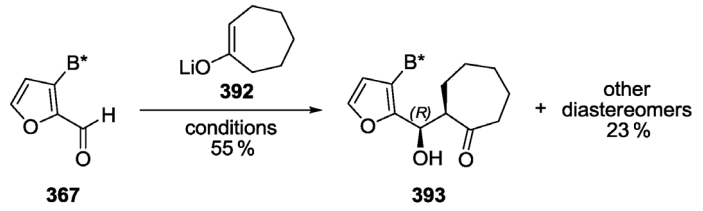


Scheme 77 Further aldol reactions of furylaldehyde **367** and silyl acetals.

The aldol reaction with lithium enolates **387** and **82** gave furyl alcohols **388/389** and **390/391** respectively in good-to-excellent yields, albeit mostly with low diastereoselectivity (Scheme 78). Although the diastereomeric mixtures of the products were not separable by chromatography, the configuration of the products was confirmed after derivatization or selective crystallization from the diastereomeric mixture. Addition of cyclic lithium enolate **392** resulted in isolation of a single diastereomer **393** in 55 % yield and a mixture of other diastereomers in 23 % yield (Scheme 79) [170].

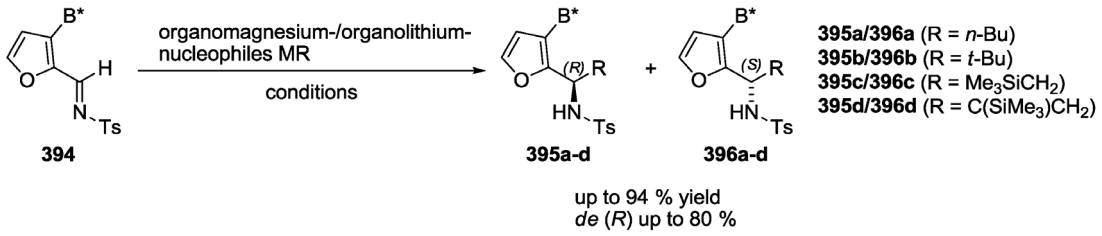


Scheme 78 Reactions of furylaldehyde **367** with lithium enolates.



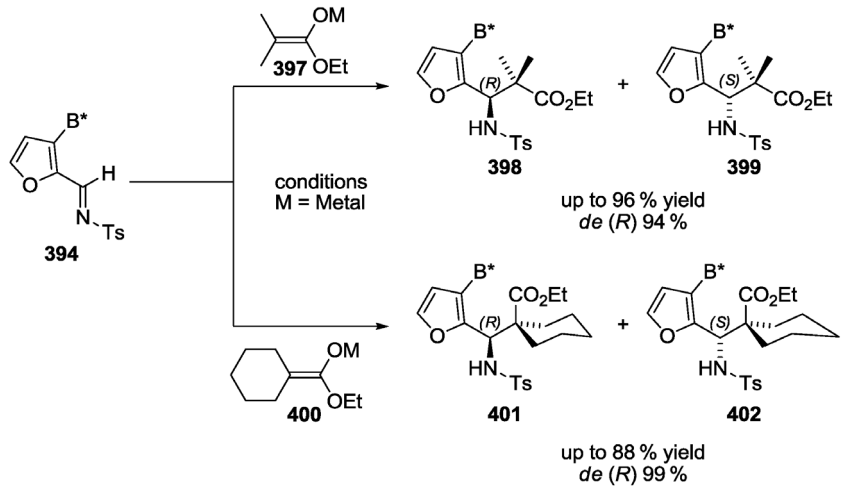
Scheme 79 Aldol reaction of furylaldehyde **367** with cyclic lithium enolate **392**.

Besides furylaldehyde **367**, the corresponding furyl sulfonylimine **394** was also subjected to investigations on the addition of nucleophilic reagents (Scheme 80) [171,172]. The reaction of **394** with various organolithium and Grignard nucleophiles gave diastereomeric mixtures of **395** and **396** in good yields and diastereoselectivities. In analogy to the nucleophilic addition to furylaldehyde **367**, the choice of solvent was crucial in optimization of yield and diastereoselectivity. The diastereomers **395** and **396** obtained were separable by column chromatography and configurations were confirmed by X-ray crystallographic analysis [172].



Scheme 80 Addition of organometallic nucleophiles to furyl sulfonylimine **394**.

The scope of nucleophiles was extended to asymmetric Mannich reaction with various metal enolates **397** and **400**, furnishing the desired products in yields up to 96 % and with diastereomeric excess up to 99 % (Scheme 81) [172].



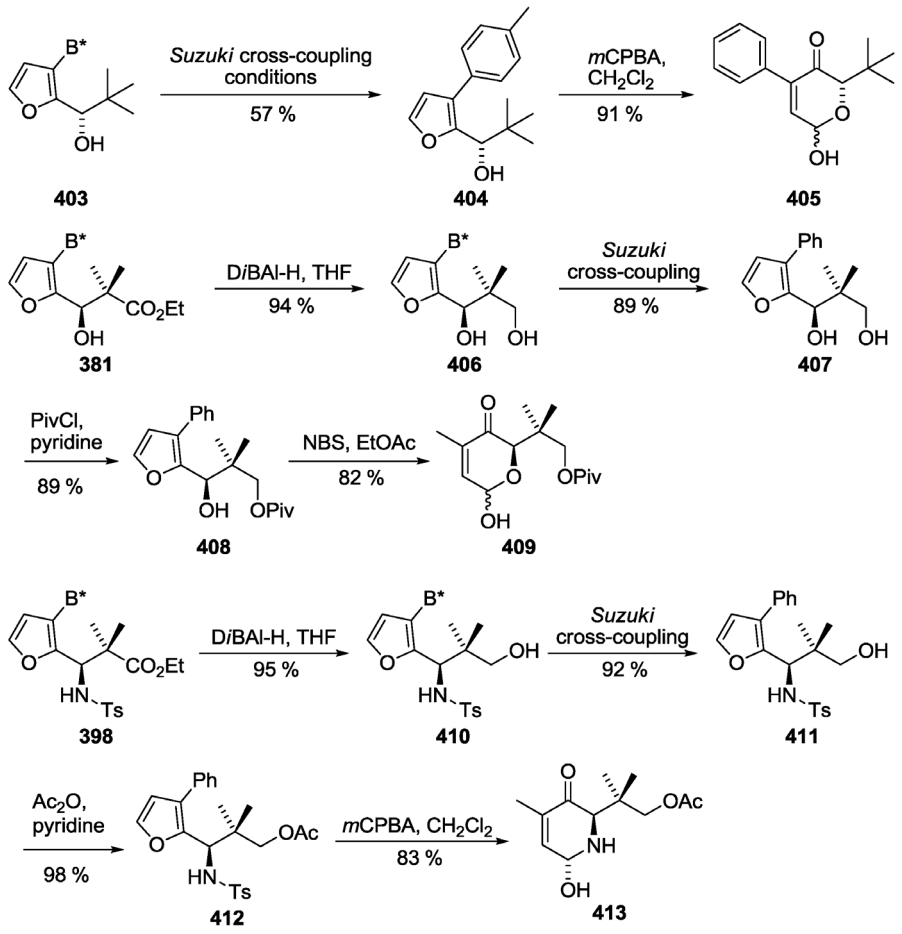
Scheme 81 Asymmetric Mannich reactions of furyl sulfonylimine **394**.

A variety of furylboronic esters was submitted to Suzuki–Miyaura cross-coupling yielding 2,3-disubstituted furyl alcohols, which were utilized as substrates for oxidative rearrangements to 6-hydroxy-2*H*-pyran-3(6*H*)-ones [110,170]. For example, the boronate group of compound **403** was exchanged for a tolyl group by Suzuki–Miyaura cross-coupling (Scheme 82). Thus obtained intermediate **404** was submitted to oxidative rearrangement yielding product **405** [110,170]. Notably, substrate **381** did not show any reactivity under Suzuki cross-coupling conditions unless the ester group was reduced to a hydroxyl group. In the presence of the activating hydroxyl group, various aryl-, alkenyl- and alkynyl halides were successfully coupled with the furanyl substrate [170]. In analogy, a selection of substrates was transformed to optically pure 2,3-disubstituted furyl sulfonylamides in good yields by Suzuki–Miyaura cross-coupling. Compound **412** was obtained from Suzuki–Miyaura cross-coupling of compound **410** and subsequent acetylation of intermediate **411**. When submitted to oxidative reaction conditions, substrate **412** yielded highly functionalized dihydropyridone **413** [172].

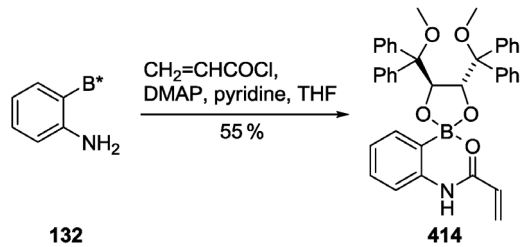
Hall and Kennedy reported the synthesis of chiral boronate-substituted acrylamide dienophile **414** and investigations concerning its reactivity and ability in 1,8-stereoinduction in Diels–Alder reaction with cyclopentadiene **34** (Scheme 83) [109].

The reactions of dienophile **414** proceeded with high yields and good diastereoselectivity in comparison to other boronates bearing chiral diols as protective and stereoinductive groups (Scheme 84). Despite the very remote position of the auxiliary, low diastereoselectivity in product formation was observed. Interestingly, when the solvent was changed from toluene/butylated hydroxytoluene (BHT) to dichloromethane the opposite isomer of the obtained *endo*-product was preferably formed compared to the reaction in toluene [109].

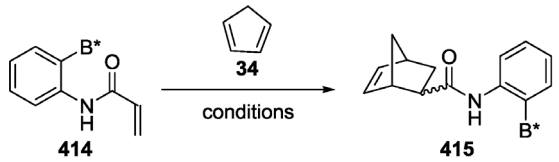
Molecular modeling analysis underlined the experimentally obtained results, showing that boronate **414** provides steric discrimination between the two faces of the dienophile. Although the chiral auxiliary of compound **414** is located closer to the acrylamide unit than the auxiliary units of analogous compounds tested, its position is still too far from the reaction center to induce high stereoselectivity [109].



Scheme 82 Derivatization of furanylboronates.



Scheme 83 Synthesis of boronate-substituted acrylamide dienophile.

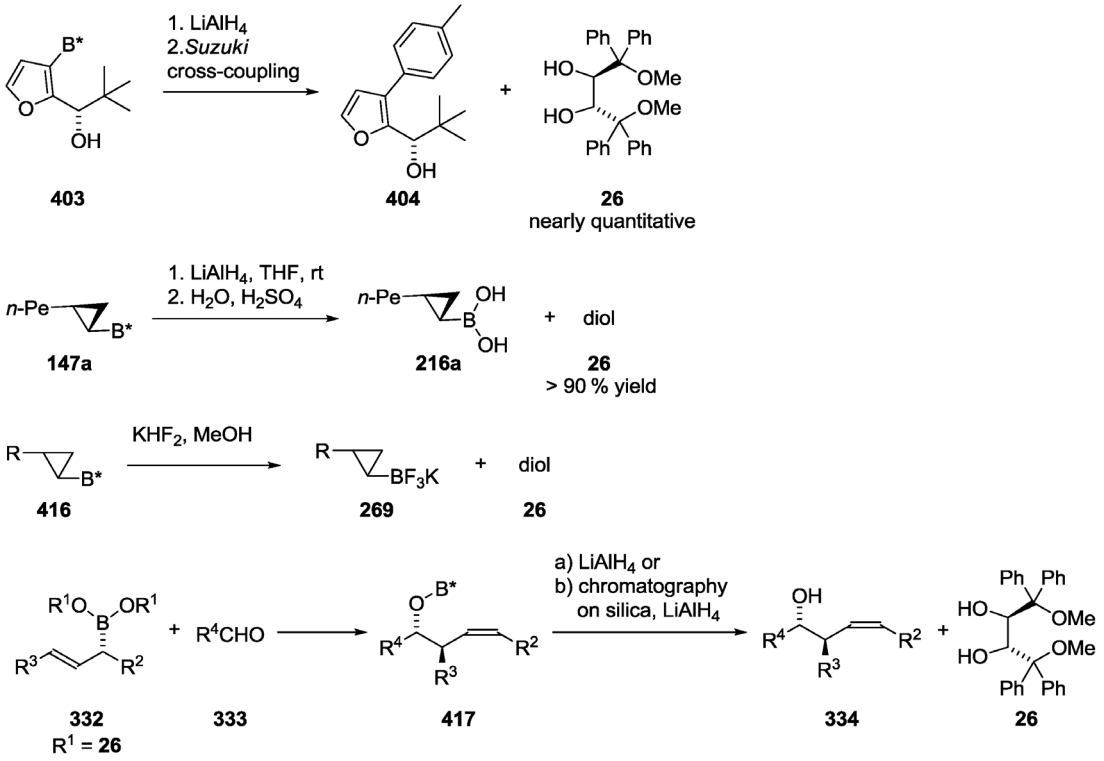


conditions	yield (NMR)	*endo*:*exo*	*de* (*endo*) (%)	*de* (*exo*) (%)
toluene, BHT, reflux, overnight	100	1.7:1	6	22
toluene, BHT, rt, overnight	73	1.9:1	9	18
CH_2Cl_2, rt, overnight	85	2.4:1	(-6)	22

Scheme 84 Influence of remote chiral boronate group on Diels–Alder reaction.

Recovery of diol 26

Although diol **26** is readily accessible in a few steps starting from inexpensive starting materials, it has to be pointed out that the protective group can be recovered at the end of a synthetic sequence in many cases (Scheme 85). Reduction of diol **26**-derived boronate **403** (see "Reactions of arylboronates") with



Scheme 85 Recovery of diol **26**.

$LiAlH_4$ prior to Suzuki–Miyaura coupling gave the corresponding furaneboronic acid along with diol **26** in nearly quantitative yield [110]. Similarly, activation of cyclopropylboronate **147a** with $LiAlH_4$ and subsequent hydrolysis gave cyclopropylboronic acid **216a** and over 90 % of recovered diol **26** (see "Reactivity and derivatization of 1,3,2-dioxaborolanes") [52]. When diol **26**-protected boronates were transformed to the corresponding trifluoroborates in order to activate them for further derivatization, the protective group could be recovered easily by extraction of the crude product with diethyl ether [137]. After performing allyl additions, there are two general ways of recovery of auxiliary **26**. If the allylation product **417** is compatible with $LiAlH_4$ reduction, this method can be chosen for cleavage of the borate intermediate obtained from allylation reaction, and diol **26** can be separated from the allylation product during column chromatography. In case hydrolysis of borate intermediate **417** on silica during column chromatography is preferred, the resulting dioxaborolanol **97** can be submitted to reduction by excess $LiAlH_4$, yielding diol **26** (see 3.**3.2.2 Which section?**). In general, the protective group **26** can be recovered from all diol **26**-containing boron residues by reduction with $LiAlH_4$ (see Supplementary Information) [53].

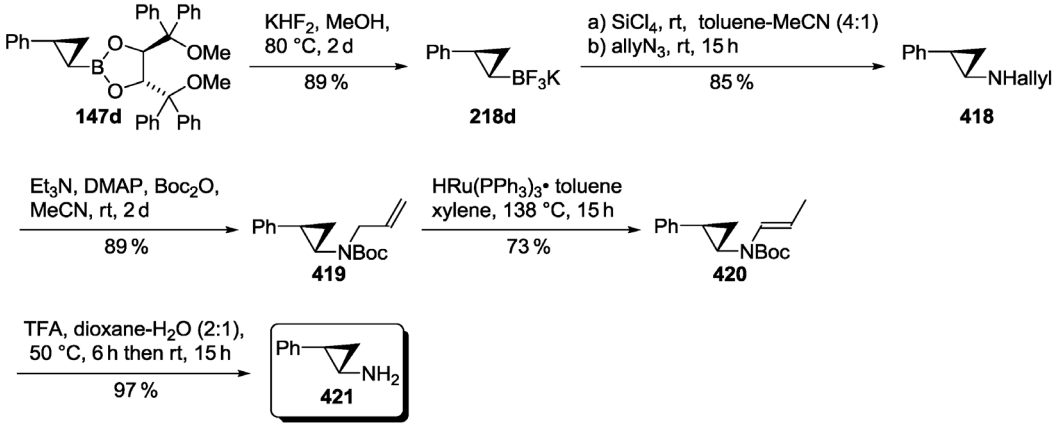
APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

Applications of cyclopropylboronates in natural product and drug synthesis

The capability of derivatization of stable cyclopropyl boronates **416** was demonstrated in the reactions discussed in previous chapter. Among the compounds obtained, some enable access to key intermediates for synthesis of natural products and enantiomerically pure drugs.

Tranylcypromine

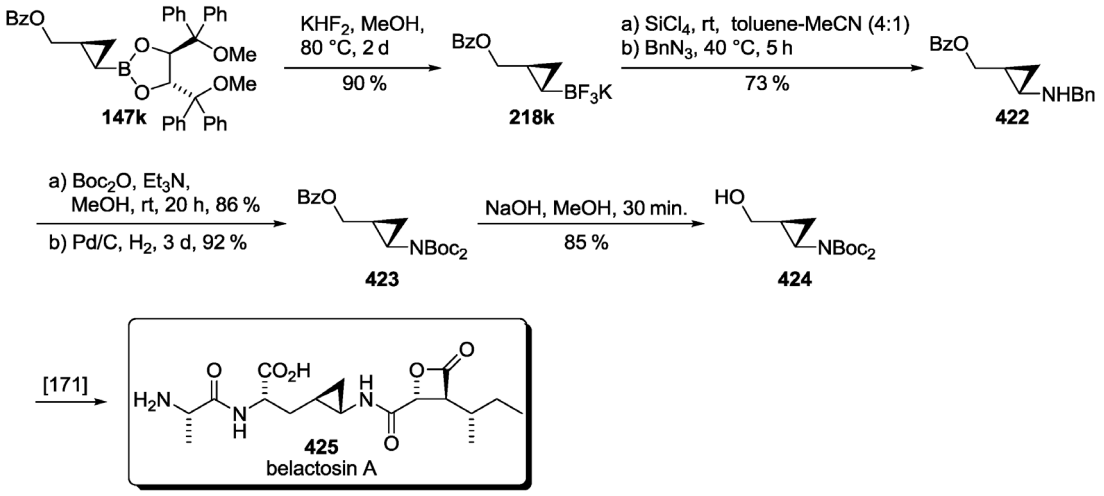
A first example for the application of the established methods was the synthesis of the monoamine oxidase (MAO) inhibitor tranylcypromine **421**, a drug for the therapy of depression and phobic anxieties (Scheme 86). The commercially available racemic mixture is commonly synthesized from the corresponding acid by a Curtius rearrangement, the four times more potent (1*S*,2*R*)-enantiomer **421** being obtained by kinetic resolution. Starting from boronate **147d**, the boron moiety was converted to the corresponding trifluoroborate **218d** first and subsequently transformed to amine **418** via C–B to C–N conversion in high yield. After *N*-Boc-protection, compound **419** was converted to enamine **420** by a Ru(I)-catalyzed isomerization of the allylic double bond in 73 % yield. Finally, enamine **420** was deprotected under acidic conditions yielding 97 % of the desired tranylcypromine **421** [122,158].



Scheme 86 Synthesis of tranylcypromine.

Belactosin A

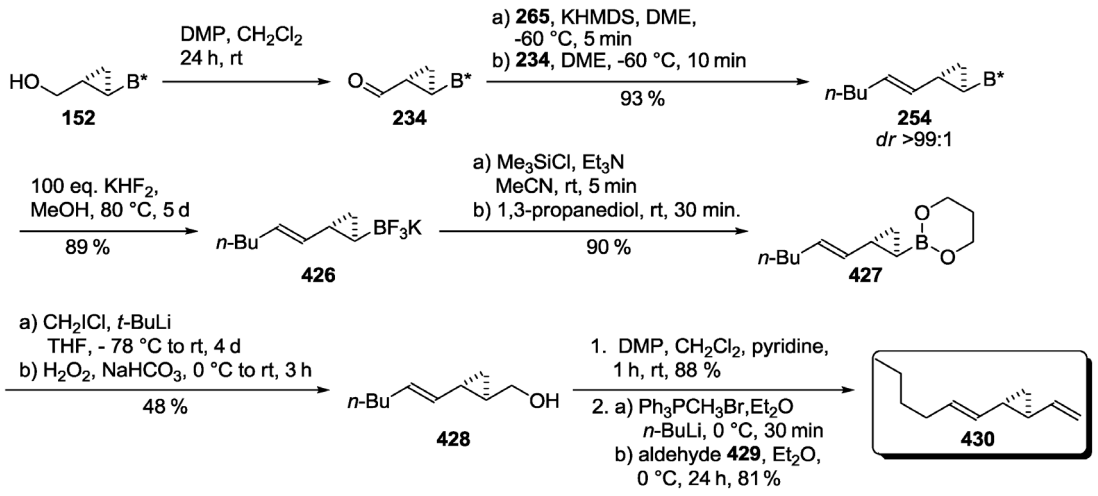
A similar sequence furnished a key intermediate for the synthesis of belactosin A **425**, which is a *Streptomyyces* metabolite possessing inhibitory activity to cyclin–cyclin-dependent kinase (CDK) complexes. Furthermore, **425** inhibits the cell-cycle progression of human tumor cells at the G2/M phase, and additionally it is known to be a ubiquitin-proteasome inhibitor [158]. Boronate **147k** was converted to the corresponding trifluoroborate **218k**, treatment with $SiCl_4$ and benzyl azide led to amine **422**. After protection of the amine moiety with the Boc-protective group, the benzylic ether of compound **423** was cleaved to the corresponding alcohol **424** [122,158]. This compound had already been successfully utilized in the total synthesis of belactosin A **425** (Scheme 87) [173].



Scheme 87 Formal synthesis of belactosin A.

Dictyopterene A

Cyclopropylboronates of type **152** allowed the synthesis of enantiomerically pure dictyopterene A, which belongs to the family of dictyopterenes (Scheme 88). These compounds comprise sexual pheromones of the marine brown algae and were first isolated by Moore and co-workers from the odoriferous oil of the Hawaiian seaweeds (genus *Dictyopteris*) [174]. Several syntheses of either optically pure dictyopterenes and racemic mixtures have been reported [175–180]. The synthetic approach relying on cyclopropylboronate **152** starts with oxidation of alcohol **152** to aldehyde **234** by DMP in high yield and the conversion to alkenylboronate **254**, which can be accomplished by different synthetic methods. Nearly all performed reactions, including the Wittig–Schlosser olefination as well as Wittig reaction and subsequent cross-metathesis led to good yields, but moderate diastereoselectivities were obtained and in addition separation of diastereomers was problematic. When performing Julia–Kocienski reaction under optimized conditions, boronate **254** was obtained in high yield and excellent diastereomeric ratio. The transformation to the corresponding trifluoroborate was straightforward, yielding 89 % of product **426**. Next, treatment of compound **426** with Me_3SiCl in the presence of triethylamine and esterification of the labile cyclopropylboronic dichloride with 1,3-propanediol yielded corresponding dioxaborinane **427**. After Matteson homologation and subsequent oxidation, the volatile alcohol **428** was obtained in 48 % yield, which was oxidized yielding 88 % of corresponding aldehyde **429**. The sequence was completed by final Wittig reaction affording enantiomerically pure dictyopterene A **430** in 81 % yield [142].



Scheme 88 Synthesis of dictyopterene A.

Ambruticin

The approach to vinylboronates **433** made the synthesis of the central part of ambruticin feasible (Fig. 6). This natural product **431**, which was first isolated in 1977 [181,182] and is an antifungal antibiotic, attracted interest due to both its pharmacological activity and its architectural framework representing a unique trisubstituted divinylcyclopropane subunit. The first total synthesis of ambruticin was reported by Kende and co-workers in 1990 [183,184] followed by several others [185–188]. In 2002, Markó and co-workers reported the synthesis of fragment B [189].

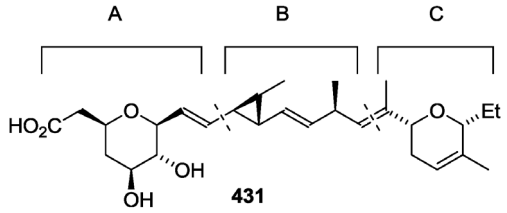
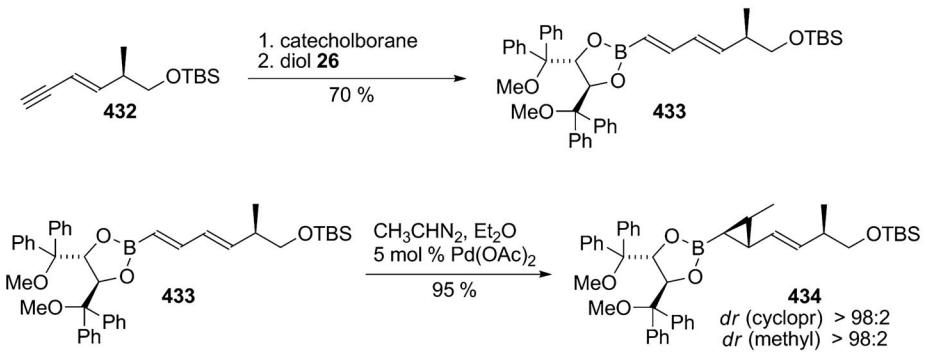


Fig. 6 Synthetic analysis of ambruticin A.

Starting with a hydroboration of the readily available optically pure enyne **432** with catecholborane and subsequent transesterification with diol **26**, vinylboronate **433** was obtained in 70 % overall yield (Scheme 89). Afterwards, cyclopropanation by palladium-catalyzed decomposition of diazoethane yielded 95 % of cyclopropylboronate **434** in high diastereoselectivity (*dr* cyclopropyl >98:2 and *dr* methyl >98:2). Markó and co-workers intended to connect fragment B with fragment A via Suzuki–Miyaura coupling. Fragment C should be finally attached by a modified Julia protocol [189]. Recently, the completion of ambruticin total synthesis was reported by Markó and co-workers [190]. Herein, diol **26**-derived boronates proved to be helpful intermediates, especially in regard to the introduction of the cyclopropyl moiety in a stereoselective way.



Scheme 89 Synthesis of middle fragment of ambruticin A.

Pietruszka and co-workers also made orienting investigations toward the synthesis of the central fragment of ambruticin, following a different retrosynthetic plan. Herein, trisubstituted cyclopropylboronate **171d** could be an alternative building block in ambruticin synthesis (Fig. 7) [89].

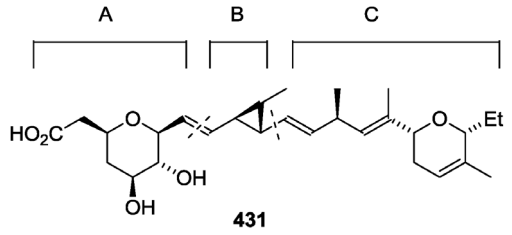


Fig. 7 Alternative synthetic analysis of ambruticin A.

Applications of chiral α-substituted allylboronates in natural product synthesis

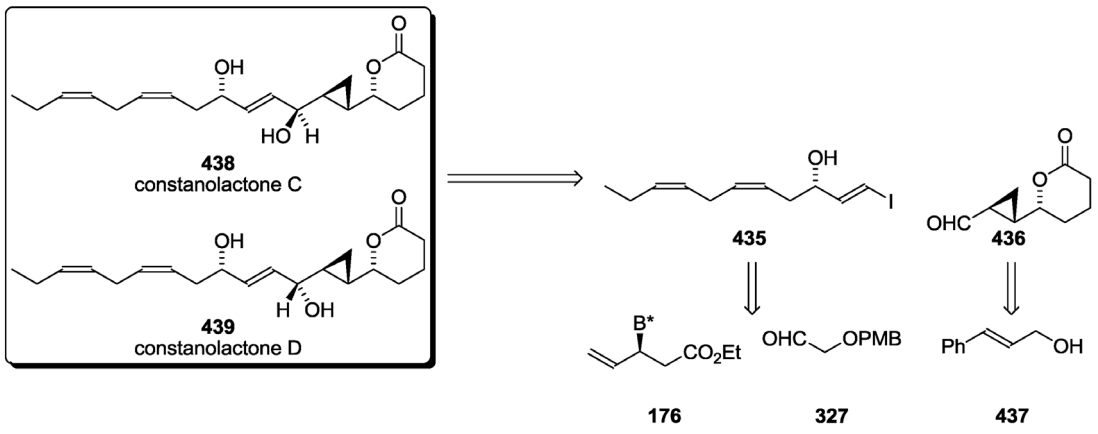
Chiral α-substituted allylboronates are valuable tools for the stereoselective construction of homoallylic alcohols [191]. As allylboronates of types **176** and **177** were shown to give predominantly (*Z*)-configured allylation products in high yield, their applicability in synthesis of natural products containing a (*Z*)-configured homoallylic alcohol moiety is obvious.

Total synthesis of constanolactones C/D and solandelactones C/D/G/H

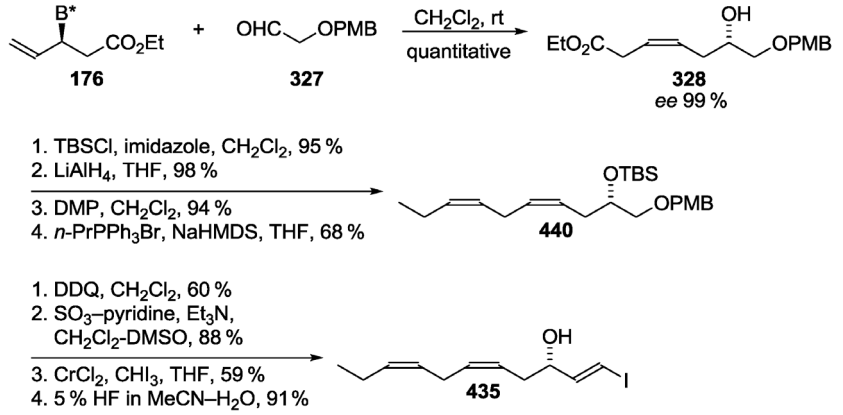
The first application of an enantiomerically pure α-chiral allylboronate of type **176** was reported in the synthesis of the marine oxylipins constanolactones C **438** and D **439** (Scheme 90) [192]. Retrosynthetic analysis led to enantiopure cyclopropylcarbaldehyde **436**, which had already been utilized in synthesis of constanolactones A and B [193] and iodoalkenyl side-chain **435**. The latter building block was considered to be available by addition of allylboronate **176** to PMB-protected glycolaldehyde **327** as a key step for enantioselective construction of the (*Z*)-homoallylic moiety [106].

The allylation reaction proceeded with excellent enantioselectivity and addition product **328** was isolated quantitatively with 99 % ee (Scheme 91). TBS protection and side-chain elongation gave intermediate **440**, which was converted to alkenyliodide **435** by a reaction sequence of PMB cleavage, oxidation, Takai–Utimoto reaction, and subsequent silylether cleavage [192].

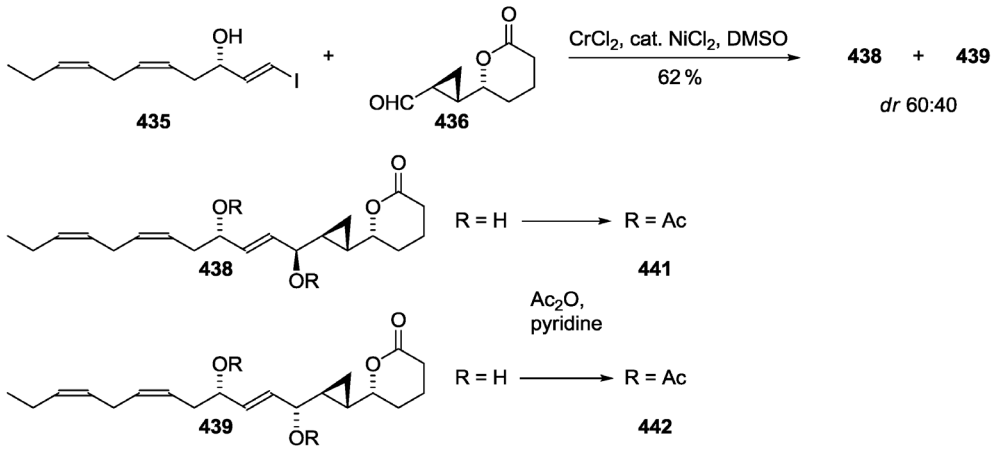
Finally, Nozaki–Hiyama–Kishi coupling with aldehyde **436** yielded the target compounds constanolactones C **438** and D **439** as a 60:40 mixture (Scheme 92). For final confirmation of identity, the separated compounds **438** and **439** were transformed to the corresponding acetates **441** and **442**. NMR data of thus obtained diacetates **441**, **442**, and of the originally isolated natural products' diacetylated



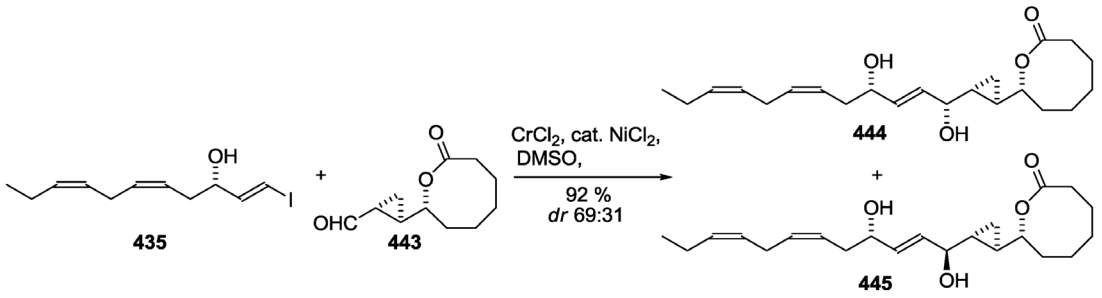
Scheme 90 Retrosynthetic analysis of constanolactones C and D.



Scheme 91 Synthesis of iodoalkenyl side-chain **456**.



Scheme 92 Completion of constanolactones C and D total synthesis.

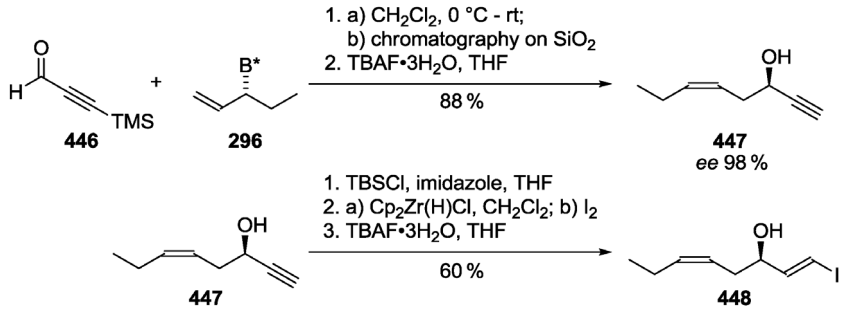


Scheme 93 Final step of solandelactones C and D total synthesis.

derivatives [194] were found to be completely identical [192]. The total synthesis of solandelactones C and D (as well as solandelactones G and H, not shown) was accomplished in analogy to the synthesis of constanolactones C **444** and D **445**, utilizing alkenyliodide **435** as key intermediate (Scheme 93) [195].

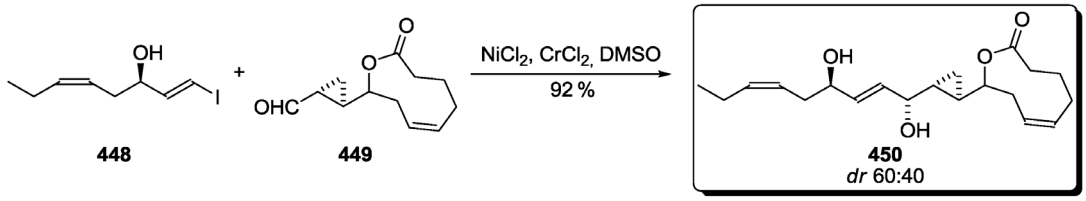
Total synthesis of neohalicholactone

In the total synthesis of neohalicholactone **450**, chiral α-substituted boronate **296** was utilized as key compound for construction of the (*Z*)-configured homoallylic moiety incorporated in the target molecule **450** (Scheme 94). By allylation of alkynal **446** with reagent **296** and subsequent removal of the TMS protective group, homoallylic alkynol **447** was obtained in high yield and excellent enantioselectivity (98 % ee). Protection of the hydroxyl group, hydrozirconation with Schwartz's reagent followed by quenching with an iodine solution and silylether cleavage resulted in isolation of alkenyliodide **448** in good overall yield [196].



Scheme 94 Synthesis of key intermediate in neohalicholactone total synthesis.

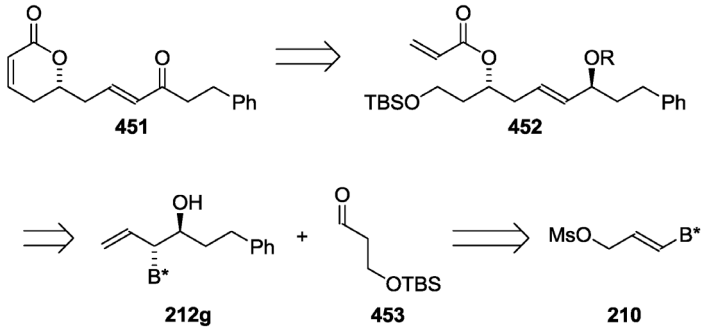
To obtain neohalicholactone **450** and its epimer *epi*-**450** with a yield of 92 % and diasteromeric ratio of 60:40, alkenyliodide **448** was reacted with aldehyde **449** in a Nozaki–Hiyama–Kishi coupling reaction (Scheme 95). The isolated mixture of epimers **450** and *epi*-**450** was separated by preparative high-performance liquid chromatography (HPLC), and the identity of both products was confirmed by correlation with the original natural product's NMR spectroscopic data [196–198].



Scheme 95 Final step of neohalicholactone total synthesis.

Total synthesis of rugulactone and its enantiomer

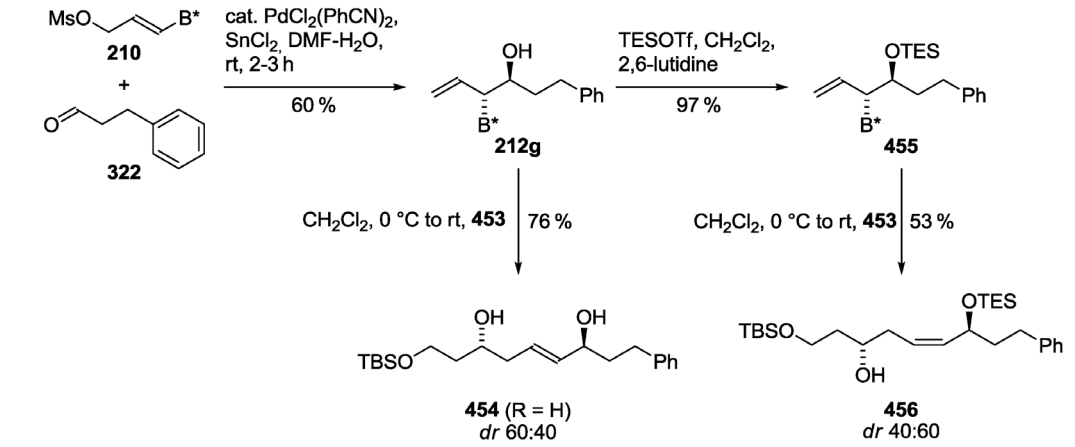
In contrast to the syntheses of constanolactones, solandelactones, and neohalicholactone, which have already been discussed and relied on allylboronates obtained from [3.3]-sigmatropic rearrangement [106], the total synthesis of rugulactone **451** and its enantiomer *ent*-**451** was based on allylboronates of types **212** and **213** provided by carbonyl allylation starting with mesylate **210** (Scheme 96) [128,129]. In a first retrosynthetic approach, allylboronate **212g** or the silylated derivative **455** was designated to play a central role in the synthesis, as addition to aldehyde **453** and subsequent acylation should give **452**, which obviously could have acted as a precursor of rugulactone **451** [199].



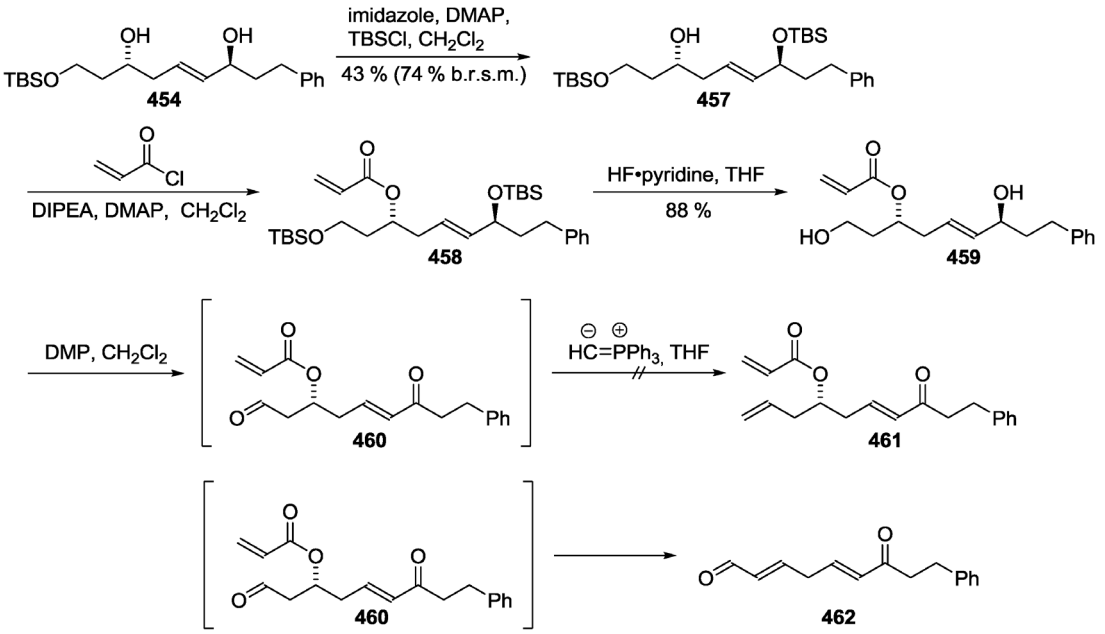
Scheme 96 Retrosynthetic analysis of rugulactone.

Following this plan, established conditions for carbonylallylation of aldehydes were applied to mesylate **210** and 3-phenylpropionaldehyde **322**, yielding 60 % of allylboronate **212g** (Scheme 97) [129]. Triethylsilyl (TES)-protected allylboronate **455** formed predominantly the (*Z*)-configured product **456** upon addition to aldehyde **454**, while utilization of allylboronate **212g** having an unprotected hydroxyl group did not only give the (*E*)-configured compound **454** as major diastereomer but significantly increased isolated yield [199].

Although synthesis of precursor **459** by a sequence of selective TBS etherification, acylation, and deprotection by silylether cleavage was successful, the approach turned out to be a dead end (Scheme 98). Instead of olefination, the double-oxidation product **460** underwent elimination reaction yielding **462** under Wittig conditions. For this reason, diolefin **461** required for product formation by ring-closing metathesis could not be obtained.



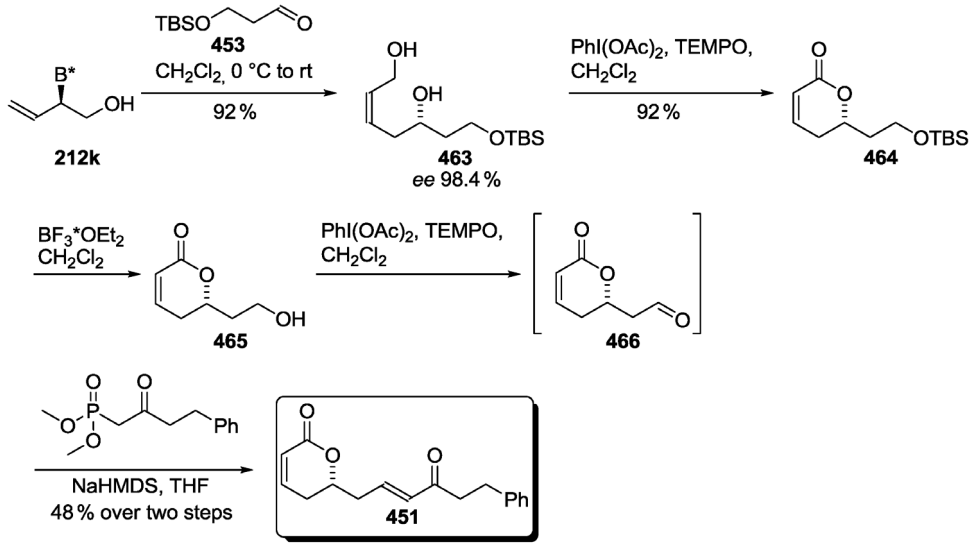
Scheme 97 Synthesis of a potential precursor for rugulactone.



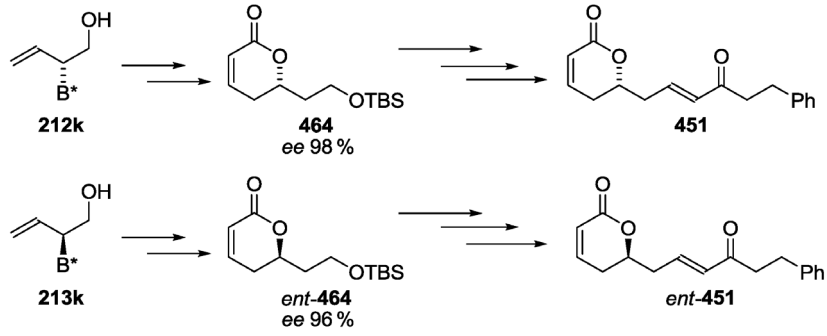
Scheme 98 Attempted synthesis of a direct precursor of rugulactone.

To overcome this problem, a new synthetic plan based on allylboronate **212k** was established (Scheme 99). Instead of forming the (*E*)-double-bond by allylation reaction, it was envisaged to make use of the nearly complete (*Z*)-selectivity of allylation reagent **212k** and to rely on the high (*E*)-selectivity of HWE olefination. Upon addition of allylboronate **212k** to aldehyde **453**, the primary hydroxyl group of resulting diol **463** was oxidized selectively to give lactone **464**. After silylether cleavage yielding **465** and oxidation to primary aldehyde intermediate **466**, rugulactone **451** was obtained in a straightforward fashion by (*E*)-selective HWE reaction in very good overall yield.

For the preparation of the natural product's enantiomer *ent*-rugulactone *ent*-**451**, the established synthetic route for synthesis of rugulactone starting from compound **213k** was applied (Scheme 100).



Scheme 99 Final route to rugulactone.



Scheme 100 Total synthesis of rugulactone and its enantiomer.

In both cases, TBS-protected lactones **464** and *ent*-**464** were obtained in excellent enantioselectivities, and both syntheses gave the desired products **451** and *ent*-**451** in overall yield of 38 % [199].

CONCLUSIONS

In summary, (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenylbutane-2,3-diol **26** has been demonstrated to be a useful reagent in asymmetric synthesis: Due to its extraordinary stability it can act as both protective group for the boronic acid moiety as well as chiral auxiliary and asymmetric inductor. The protective group itself can be easily prepared from readily available starting materials, likewise corresponding 1,3,2-dioxaborolanes can be synthesized via different routes. The boronates obtained are stable under various reaction conditions and enable a plethora of synthetic transformations of both carbon chain as well as boronate moiety. Often, diastereomeric mixtures can be separated by MPLC. After cleavage of the boronate moiety, diol **26** can be recovered nearly quantitatively in most cases. These properties make it a valuable and useful protective group for versatile reagents in asymmetric synthesis.

SUPPLEMENTARY INFORMATION

Supplementary information is available online (doi:10.1351/PAC-CON-12-03-04).

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