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Palladium-Catalyzed Synthesis of Enantiomerically Pure α-Substituted Allylboronic Esters and Their Addition to Aldehydes

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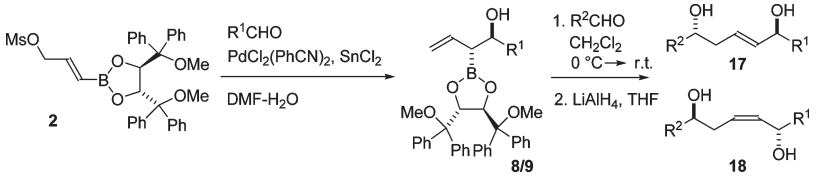

Tartrate-derived boronic esters **2** can be subjected to palladium-catalyzed carbonyl allylations with $SnCl_2$ to obtain enantiomerically pure α-substituted allylboronic esters **8** and **9**. The reaction proceeds regioselectively and with high, simple diastereoselectivity to form *anti*-products. Their addition to aldehydes yields enantiomerically enriched homoallylic alcohols **17** and **18**, respectively. Synthesis, characterization, and a mechanistic rational is presented here.

Introduction

The reaction of allylmetal reagents with carbonyl compounds to form homoallylic alcohols is one of the most powerful transformations in organic synthesis. In particular, allylboron reagents stand out because of their stability, nontoxicity, and predictable reactivity, allowing high yields and selectivity using mild reaction conditions.[1] Since the pioneering report by Hoffmann et al. in 1978,[2a] many research groups have designed chiral allylic boron reagents for asymmetric allylation[2] and crotylation[3] of carbonyl compounds. A closed chairlike transition state has been postulated to explain the stereoselectivity of these reactions, with an electron delocalization from the oxygen of the attacking aldehyde to the boron of the allylboron reagent controlling the course of the reaction.[4] Enantiomerically pure allylboronates should differentiate the two enantiotopic faces of aldehydes and allow an enantioselective formation of homoallylic alcohols. In addition, α-substituted allylboronic esters have been shown to be of special interest because of the possibility of controlling the selectivity by introducing a defined stereogenic center to the core of the transition state, which allows nearly complete transfer of chirality. However, their applicability is sometimes hampered since they are more difficult to prepare in an enantiomerically pure form. The first examples on this topic have been published by Hoffmann et al., who synthesized α-substituted allylboronic esters with a Matteson homologation starting from enantiomerically pure dichloromethylboronic esters.[5] Further methods have been

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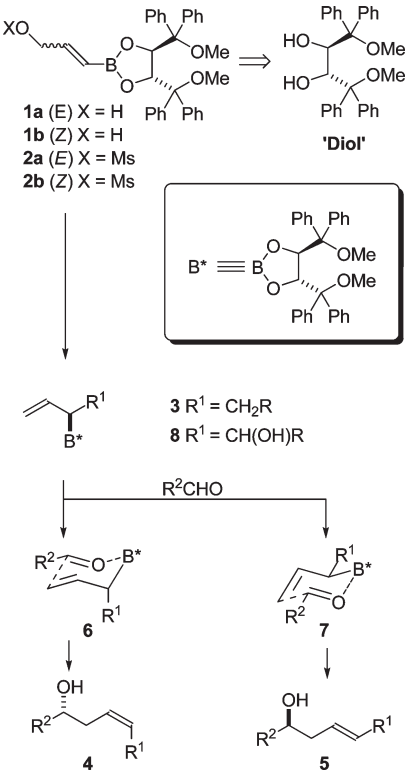
reported by other groups over the past few years, including hydroborations of allenylboronic esters with (−)-diisopinocampheylborane in a double allylboration reaction sequence,[6] palladium-catalyzed enantioselective diboration of allenes,[7] copper-catalyzed enantioselective substitution of allylic carbonates with diboron,[8] Diels−Alder reactions,[9] and others.[10] Recently, Aggarwal et al. developed a general protocol for the in situ conversion of enantioenriched allylic boron reagents into 1,2,4-substituted homoallylic alcohols with high levels of predictable control over the relative and absolute configuration: the boron reagent was obtained after selective α-lithiation of a carbamate reaction with alkenyl boron species.[10k] Lewis and Brønsted acid catalysts were shown to influence not only the rate but also the selectivity of allylborations.[10k,11]

SCHEME 1. Homoallylic Alcohols from Allylboronic Esters 1 and 2



In our group, we established highly stable alkenylboronic esters **1** as well as the corresponding mesylates **2** as versatile building blocks for the synthesis of allylboron reagents with a stereogenic center α to boron (Scheme 1):

(a) [3,3]-Sigmatropic rearrangements of esters **1** led to allylboronic esters **3**, and a variety of side chains "R" could be obtained.[12] The process utilizes the readily available and easily recoverable "diol" as a boron protecting group, which can be synthesized in both enantiomeric forms from tartrate.[13] The stability of esters **3** allowed subsequent transformations, opening the way to a family of boron reagents, which were stable against oxidation and hydrolysis and were hence storable and could be readily used subsequently. Their addition to aldehydes resulted in homoallylic alcohols with very high diastereo- and enantioselectivity forming almost exclusively *Z*-isomers **4**, with only minor amounts of *E*-isomers **5** detectable. The stereochemical course of the reaction depends on the substituent in the α-position and the steric bulk of the boronic ester; it can be explained in terms of steric and dipolar effects on the two competing transition structures **6** and **7**.[5c,14] (b) Furthermore, we have recently

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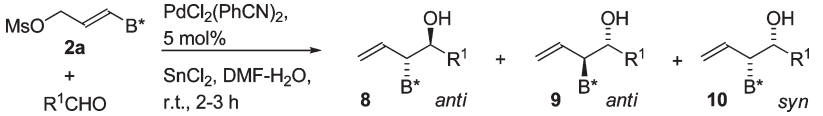
TABLE 1. Palladium-Catalyzed Carbonyl Allylation



	allylboronic esters			dr[b]
entry	compd	R^1	yield[a] (%)	**8**:**9**:**10**
1	**a**	Ph	79	100:0:0
2	**b**	3,4-$C_6H_3F_2$	86	96:4:0
3	**c**	C_6F_5	82	94:6:0
4	**d**	furfural	73	93:7:0
5	**e**	CO_2Et	79	91:9:0
6	**f**	PhCHCH	75	89:11:0
7	**g**	$PhCH_2CH_2$	80	75:18:7
8	**h**	$(CH_3)_2CH$	70	78:22:0
9	**i**	$(C/H_3)_2CHCH_2$	71	77:14:9
10	**j**	*c*-C_6H_{11}	79	78:18:4
11	**k**	H	85	50:50:0

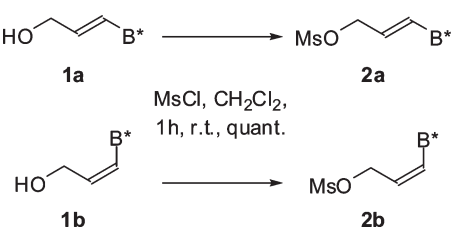
[a]Isolated mixture of diastereomers. [b]The ratio was determined by ^{1}H NMR spectroscopy.

shown that intermediates **2** are suitable precursors for palladium-catalyzed carbonyl allylations forming diastereoselectively α-substituted allylboronic esters **8**.[15] The allylation of carbonyl compounds based on the umpolung of π-allylpalladium complexes has been extensively investigated in the past few years.[16] In particular, the $Pd^0/SnCl_2$ system introduced by Masuyama et al. proved to be very powerful, where $PdCl_2(PhCN)_2$ is used as a catalyst to form electrophilic π-allylpalladium species from allylic substrates and $SnCl_2$ is used as a reducing agent for the nucleophilic allyl tin species (umpolung).[17] In this paper, we report on an asymmetric version of the palladium-catalyzed carbonyl allylation reaction with $SnCl_2$ in the synthesis of α-substituted allylboronic esters **8** and their addition to aldehydes in detail.

Results and Discussion

In our initial attempts to perform palladium-catalyzed carbonyl allylation reactions, boronic ester **1a** was treated with $PdCl_2(PhCN)_2$ (2 mol %) and $SnCl_2$ (3 mmol) in DMF with benzaldehyde (1 mmol) at room temperature, according to conditions reported by the Masuyama group.[17h] Unfortunately, no conversion was observed with our substrate, and the starting material was completely recovered after workup. This result suggested that the hydroxy group was too unreactive for the formation of the palladium π-complex. In order to activate the alcohol, we synthesized mesylated allylboronic esters **2a** and **2b** in a quantitative yield by adding mesyl chloride and triethylamine to a solution of allyl alcohols **1a** and **1b** in CH_2Cl_2, respectively (Scheme 2). The addition of mesylate **2a** to benzaldehyde under the aforementioned conditions produced allylboronic ester **8a** in 69% after 20 h. The transformation proceeded with complete selectivity with respect to both γ-addition (regiocontrol) and *anti*-addition (diastereocontrol). By increasing the amount of catalyst (from 2 to 5 mol %) and adding water (25 equiv), the reaction was completed in 2 h. Other solvents used in palladium-catalyzed carbonyl allylations with $SnCl_2$ such as DMI, THF, DME, or DMSO produced only traces of the addition product after long reaction times, recovering the starting material after workup. Under these conditions, mesylate **2a** was added to various aldehydes (Table 1):

SCHEME 2. Synthesis of Allylboronic Esters 2a and 2b



After complete conversion (as indicated by TLC after 2−3 h), the reaction mixtures were worked up and the crude products subjected to ^{1}H NMR spectroscopy in order to determine the diastereomeric ratio of the products. The obtained mixtures of α-substituted allylboronic esters were isolated by means of column chromatography and the diastereomers separated by MPLC. Only a single diastereomer **8a** was formed in the addition to benzaldehyde (entry 1,

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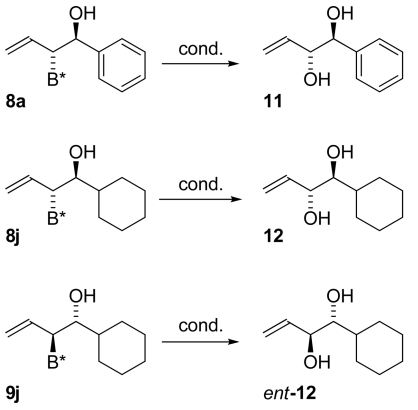
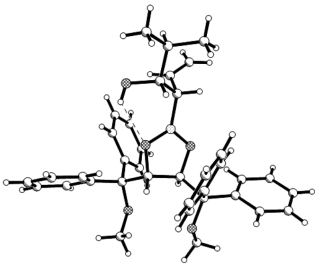
SCHEME 3. Assignment of Configuration of Boronic Esters



Cond. a) MeLi, THF; b) 30% H_2O_2 (analytical scale)

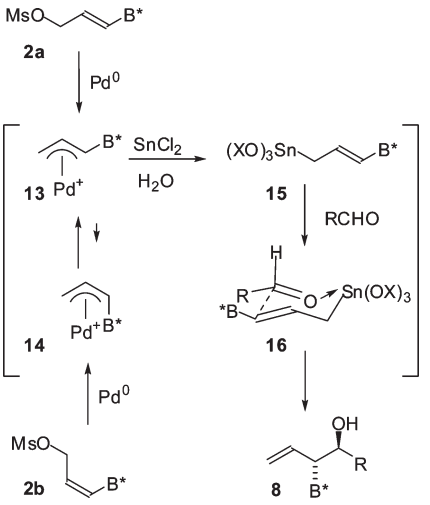


9h

79% yield). Furthermore, excellent selectivities **8/9** were achieved with substituted aromatic aldehydes (entry 2: 86% yield, dr 96:4; entry 3: 82% yield, dr 94:6), furfural (entry 4: 73% yield, dr 93:7), and ethyl glyoxalate (entry 5: 79% yield, dr 91:9). The addition to aliphatic aldehydes led to a slight increase in the ratio of the minor *anti*-diastereomer **9** (entries 6−10: 71−80% yield; dr from 4:1 to 10:1), while the *syn*-product **10** was also detected in some cases (entries 7, 9, and 10: 4−9%). As expected, no diastereoselective discrimination was observed using formaldehyde, giving the two possible isomers **8k** and **9k** in equal ratio (entry 11: 85% yield). In all cases, the major diastereomers **8** as well as minor *anti*-diastereomers **9h**+**j** (entries 8 and 10) and *syn*-diastereomer **10j** (entry 10) could be isolated by means of MPLC. The enantiomerically pure α-substituted allylboronic esters obtained were stable during purification procedures and were stored at room temperature without decomposition.

The configuration of the products was assigned by means of chemical correlations. Thus, oxidation of allylboronic esters **8a**, **8j**, and **9j** (in analytical scale) using MeLi followed by H_2O_2[18] gave the known[19] diols **11**, **12**, and *ent*-**12** (Scheme 3); the standard protocol for the oxidation with $NaOH/H_2O_2$ is reported to fail with this type of tartrate-derived boronic esters.[18] Since oxidations of the C−B bonds of allylic boronates to the corresponding alcohol are known to proceed with retention of configuration,[20] the performed transformation serves as proof of the absolute configuration of the boronic esters. The relative configuration of the allylboronic esters **8** and **9** was also confirmed to be *anti* by ^{1}H NMR spectroscopy:

SCHEME 4. Mechanistic Rational for the Preferred Formation of Ester 8



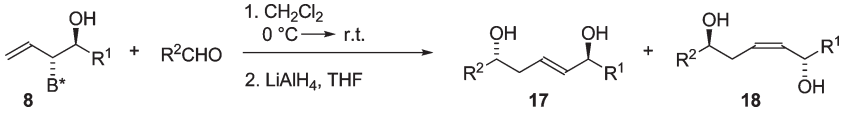
the coupling constants for the C*H*(OH)C*H*(B) protons (J = 3−6 Hz) were considerably smaller compared to the corresponding *syn*-isomers **10** (J = 9−11 Hz). Finally, X-ray crystallography of diol **12**[21] (and *ent*-**12**) and especially allylboronate **9h** (R = *i*-Pr) unequivocally verified the configuration. Interestingly, X-ray analysis showed an interaction between the hydroxy group and one of the oxygens of the oxaborolane, thus revealing the conformative disposition of the allylboronic esters **9** in the crystal (Scheme 3).

The use of (*Z*)-boronic ester **2b** in the palladium-catalyzed carbonyl allylation reaction provided comparable yields of allylboronic esters under the same conditions and with equivalent selectivity [R = Ph: 75% yield (**8a**), dr 100:0; R = c-C_6H_{11}: 78% yield (**8j** + **9j** + **10j**), dr 79:20:1; data not shown in Scheme 3]. A plausible mechanism for the reaction is shown in Scheme 4. The principle of the process relies on the transient formation of a η^3-allyl palladium complex (**13** and **14**), where the *anti*-complex **14** isomerizes in favor of the more stable *syn*-complex **13**[17c] (indeed, NMR studies in DMF-d_7 showed the formation of the same tin intermediate **15** in the following step). This complex is transformed by transmetalation into allyl tin intermediates **15** that cause nucleophilic attack to aldehydes. The addition of water may support the hydrolysis of the Sn(IV)−Cl bond, producing active aqueous organometallic cations Sn(IV)−$(OH_2)^+_{(aq)}$.[22] The carbonyl allylation is thought to proceed via the six-membered transition state **16**, with the oxygen of the aldehyde coordinating to the Sn(IV) species selectively giving *anti*-allylboronic esters **8**.[17d,h]

The observed high facial selectivity can be rationalized by considering steric interactions between the residue "R" of the aldehyde and the bulky substituent of the dioxaborolane moiety, which are in close proximity in a disfavored transition state or are far apart in a favored state (Scheme 5). The disfavored pseudoaxial position of the aldehyde's R^1 group makes the formation of the *syn*-addition products **10** difficult

(18) Luithle, J. E. A.; Pietruszka, J. *Liebigs Ann./Recueil* **1997**, 2297.
(19) Barrett, A. G. M.; Malecha, J. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1901.
(20) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686.
(21) For the crystal structure of compound **12**, see: Frey, W.; Fernández, E.; Pietruszka, J. *Z. Kristallogr. NCS* **2010**, *225*, 13.
(22) (a) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191. (b) Furlani, D.; Marton, D.; Tagliavini, G.; Zordan, M. *J. Organomet. Chem.* **1988**, *341*, 345.

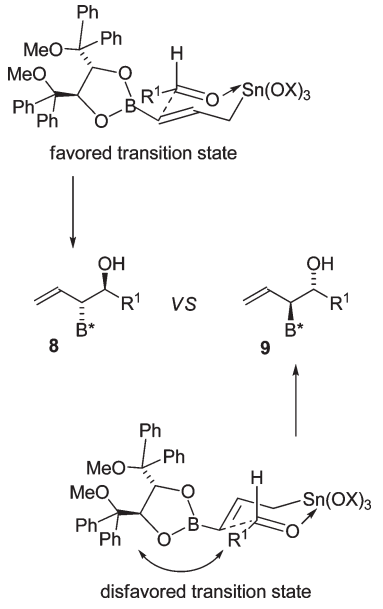
TABLE 2. Allyladditions of Boronic Esters 8



	2-ene-1,5-diols				dr[c]	ee[d] (%)	
entry	compd[a]	R^1	R^2	yield[b] (%)	**17**:**18**	**17**	**18**
1	**ka**	H	Ph	95	0:100		96/97[e]
2	**kg**	H	$PhCH_2CH_2$	89	0:100		95/93[e]
3	**cc**	C_6F_5	C_6F_5	90	33:67	>95	>95
4	**bb**	3,4-$C_6H_3F_2$	3,4-$C_6H_3F_2$	quant	40:60	>95	>95
5	**gk**	$PhCH_2CH_2$	H	71	46:54	>95	>95
6	**ja**	*c*-C_6H_{11}	Ph	91	50:50	>95	>95
7	**aa**	Ph	Ph	99	59:41	>95	>95
8	**gg**	$PhCH_2CH_2$	$PhCH_2CH_2$	98	59:41	>95	>95
9	**jg**	*c*-C_6H_{11}	$PhCH_2CH_2$	92	74:26	>95	>95
10	**hh**	$(CH_3)_2CH$	$(CH_3)_2CH$	66	82:18	>95	>95
11	**jj**	*c*-C_6H_{11}	*c*-C_6H_{11}	71	84:16	>95	>95

[a]The resulting homoallylic alcohols were numbered using letters after the corresponding number, with the first letter corresponding to the residue of aldehyde R^1 (see Table 1) and the second letter to aldehyde R^2. [b]Isolated mixture of diastereomers. [c]The ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d]Determined by the Mosher ester method. [e]Determined by chiral HPLC analysis.

SCHEME 5. Proposed Six-Membered Cyclic Transition States for Carbonyl Allylations

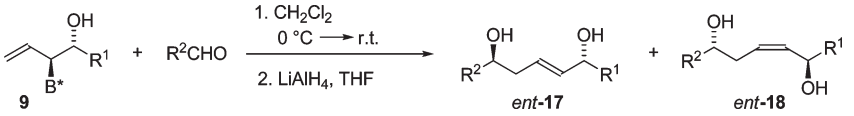


and no more than traces are produced (Table 1, entries 7, 9, and 10). However, an acyclic−antiperiplanar transition state for the formation of **10** cannot be ruled out.[17h]

To evaluate the efficiency of the new α-substituted allylboronic esters in asymmetric allylation, we added different aldehydes to produce homoallylic alcohols (Tables 2 + 3 and Scheme 7). In analogy to previously performed allylborations by Pietruszka et al.,[12] allyladditions using allylboronic esters **8**−**10** were carried out in CH_2Cl_2 and stirred at 0 °C for 12 h followed by stirring at room temperature until complete conversion (as judged by TLC). Subsequent treatment with $LiAlH_4$ in THF cleaved the boronic ester and released the homoallylic alcohols (2-ene-1,5-diols), which were subjected to ^{1}H NMR spectroscopy to determine the diastereomeric ratio. The obtained isomers were separated by means of column chromatography and occasionally by MPLC. The results of the addition of (1*R*,2*R*)-configured allylboronic esters **8** to aldehydes are summarized in Table 2. Allylboronic ester **8k** (R^1 = H) produced exclusively *Z*-isomers in excellent yields and enantioselectivities in the addition to benzaldehyde and phenylpropionaldehyde [entry 1: 95% yield (**18ka**), 97% ee; entry 2: 89% yield (**18 kg**), 93% ee]. The *Z*-selectivity decreased when allylboronic esters bearing substituents $R^1 \neq$ H were used, reaching *E*-selectivity in additions with ester **8h** (R^1 = *i*-Pr) and **8j** (R^1 = *c*-C_6H_{11}) to isobutyraldehyde [entry 10: 66% yield (**17** + **18hh**), *E*:*Z* = 82:18] and cyclohexylcarbaldehyde [entry 11: 71% yield (**17** + **18jj**), *E*:*Z* = 84:16], respectively. However, in all cases, good to excellent yields (entries 3−9: 71% to quant yield) and perfect enantioselectivities (>95%) were obtained.

While the unfavorable gauche interaction between the α-substituent and the bulky boronic ester generally favored the formation of *Z*-products, the observed decrease in *Z*-selectivity is obviously caused by the additional substituent in the side chain; it is reasonable to assume that the *syn*-pentane interaction is increased in the transition state with the α-substituent in the pseudoaxial position (**B**), thus favoring transition state **A** (Scheme 6). Hydrogen bond interaction between the OH group and one of the oxygens of the dioxaborolane, as demonstrated as a possibility by the X-ray structure analysis of **9h**, could also be feasible in solution and could thus also additionally influence the transition state. Hence, such an interaction may not only fix the conformation of the α-substituent in the allylboronic esters but also electrophilically activate the boron moiety, increasing the ratio of the allylboration and the *E*-selectivity.[11] While the configuration of the dioxaborolane would in this case be expected to only marginally influence the *E*/*Z* selectivity, for the second (minor) diastereoisomers **9** the interaction should be more pronounced. The higher *Z*-selectivity of the (*S*)-configured allylboronic esters [relative to the (*R*)-reagent] bearing the chiral auxiliary "diol" as a protecting group has been observed before by Pietruszka et al., and could be explained, in full analogy to the argument made in Scheme 5, by the considerable steric interaction between the α-substituent in the pseudoequatorial position

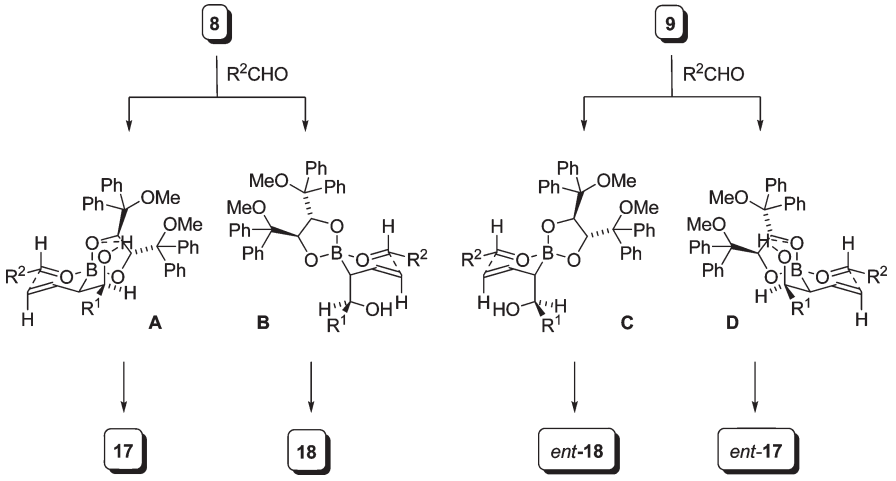
TABLE 3. Allyl Additions of Boronic Esters 9



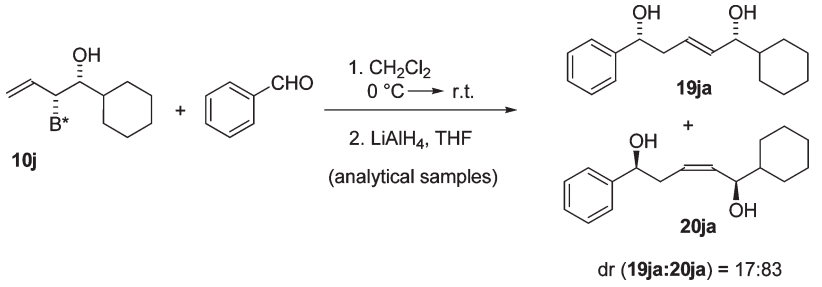
	2-ene-1,5-diols				dr[b]	ee[c] (%)	
entry	compd	R^1	R^2	yield[a] (%)	*ent*-**17**:*ent*-**18**	*ent*-**17**	*ent*-**18**
1	**ka**	H	Ph	94	0:100		95/98[d]
2	**kg**	H	$PhCH_2CH_2$	88	0:100		92/93[d]
3	**jj**	*c*-C_6H_{11}	*c*-C_6H_{11}	89	16:84	>95	>95
4	**jg**	*c*-C_6H_{11}	$PhCH_2CH_2$	85	24:76	>95	>95
5	**hh**	$(CH_3)_2CH$	$(CH_3)_2CH$	60	27:73	>95	>95
6	**ja**	*c*-C_6H_{11}	Ph	83	33:67	>95	>95

[a]Isolated mixture of diastereomers. [b]The ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Determined by the Mosher ester method. [d]Determined by chiral HPLC analysis.

SCHEME 6. Proposed Origin for the Selectivity of the Allyl Addition



SCHEME 7. Allyl Additions of Boronic Ester 10j to Benzaldehyde

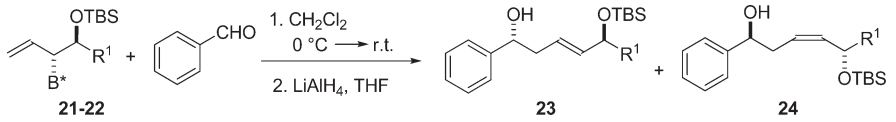


dr (**19ja**:**20ja**) = 17:83

(**D**) with one of the CPh_2OMe groups of the boronic ester (Scheme 6). The effect could even overrule the *syn*-pentane interaction in transition state **C**. It should be noted that only one possible conformation for the side chain ("R^1") is given, and consequently, H-bonds are feasible for all transition states. However, this would only be possible at the cost of considerable *syn*-pentane interactions, thus rendering the reaction path less likely. In order to confirm the assumption, allyl additions with (1*S*,2*S*)-configured allylboronates **9** were performed (Table 3). As expected, addition of allylboronic ester **9k** (R^1 = H) to benzaldehyde and phenylpropionaldehyde [entry 1: 94% yield (*ent*-**18ka**), 98% ee; entry 2: 88% yield (*ent*-**18 kg**), 93% ee] furnished in excellent yield and enantioselectivity exclusively the corresponding *Z*-isomer. The addition of allylboronic esters **9h** and **9j** to various aldehydes produced the expected diastereomeric mixtures of homoallylic alcohols *ent*-**17** and *ent*-**18** (entries 3−6: 60−89% yield, dr 16−33:84−67, >95% ee) with increased *Z*-selectivity.

To further elaborate the issue of the influencing factors for selectivity, the obtained minor (1*S*,2*R*)-configured allylboronic ester **10j** was also utilized. Upon addition to benzaldehyde on an analytical scale, diastereomers **19ja** and **20ja** were obtained as a diastereomeric mixture (Scheme 7, dr = 17:83). While the results appeared surprising at first, a more detailed

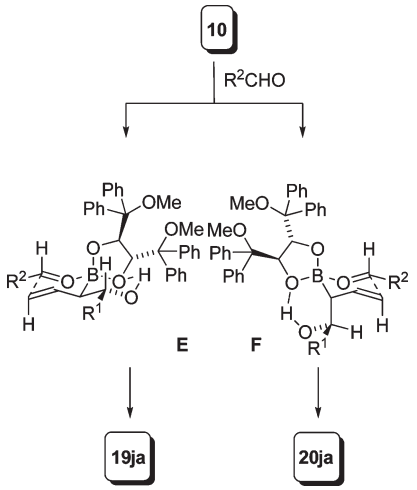
TABLE 4. Addition of Allylboronic Esters 21a, 21j, and 22j to Aldehydes



allylboronic ester		TBS-protected 2-ene-1,5-diols			dr[b]	ee[c] (%)	
entry	compd	compd	R^1	yield[a] (%)	**23**:**24**	**23**	**24**
1	**21a**	**aa**	Ph	58	50:50	>95	>95
2	**21j**	**ja**	*c*-C_6H_{11}	56	28:72	>95	>95
3	**22j**	*ent*-**ja**	*c*-C_6H_{11}	86	0:100[d]		>95

[a]Isolated mixture of diastereomers. [b]The ratio was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c]Determined by the Mosher ester method. [d]*ent*-**24ja** was obtained exclusively.

SCHEME 8. Proposed Transition State for the Addition of 10 to Aldehydes

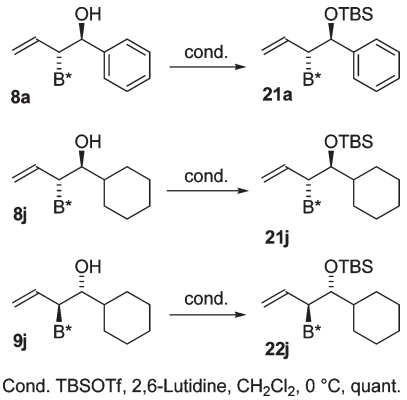


analysis of the potentially involved transition states could suggest hydrogen-bond interactions as an additional stabilizing factor. While the considerable *syn*-pentane interaction rendered the hydrogen bond in transition state **B** (Scheme 6) rather unlikely, the corresponding interaction is minimized in transition state **F** (Scheme 8). Hence, the pseudoaxial positioning of the α-substituent is favored over the pseudoequatorial position (transition state **E**). To obtain a complete picture, the missing *cis*-diastereomer should be investigated; unfortunately, it was not detected during the palladium-catalyzed carbonyl allylation.

Next, we investigated the silyl-protected allylboronic esters and the influence of this bulky group, which also disables hydrogen bonds based on the selectivity of the allyl addition. Allylboronic esters **8a**, **8j**, and **9j** were treated with TBSOTf and 2,6-lutidine in CH_2Cl_2, furnishing TBS-protected allylboronic esters **21a**, **21j**, and **22j** in a quantitative yield (Scheme 9).

The subsequent addition of the TBS-protected reagents to benzaldehyde resulted in monoprotected 1,5-diols **23** and **24** (Table 4). The addition of **21a** and **21j** gave rise to a higher *Z*-selectivity (*E*/*Z* = 50:50 and 28:72, respectively; entries 1 and 2) in comparison with the nonprotected allylboronic esters **8a** and **8j** (*E*/*Z* = 59:41 and 50:50, respectively; Table 2, entries 6 and 7). Despite the increased *syn*-pentane interactions (TBS versus H) of the pseudoaxial substituent, the steric interaction of the boronic ester with the α-substituent

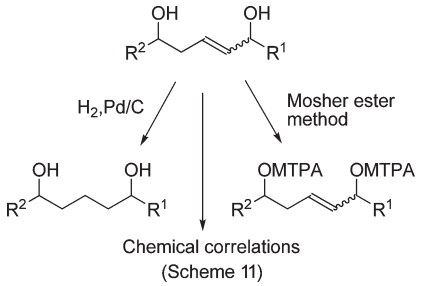
SCHEME 9. TBS Protection of Boronic Esters 8a, 8j, and 9j



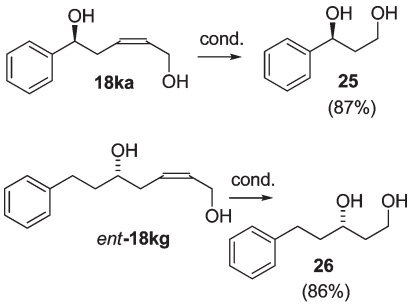
in the pseudoequatorial position seems to be more important, hence favoring the *Z*-product **24**. With the same argument and the lack of H-bond activation, the low rate of the transformation (15 d) can easily be explained. Allylboronic ester **22j** gave exclusively *Z*-homoallylic alcohol *ent*-**24ja** (Table 4, entry 3; 86% yield) in contrast to the *E*/*Z* = 33:67 ratio produced by the nonprotected allylboronic ester **9j** (Table 3, entry 6). Thus, the assumption that the larger substituent R^1 could improve the *Z*-selectivity was verified, and the preferred *Z*-selectivity of the (*S*)-configured allylboronic ester was also confirmed. In addition, the resulting transformation represents a valuable alternative for the synthesis of monoprotected 2-ene-1,5-diols.[23a]

Different methods were used to determine the configuration of the obtained 1,5-diols (Scheme 10; see the Supporting Information for more details). The relative configurations (*anti*/*syn*) of a number of 1,5-diols ($R^1 = R^2$) were assigned after hydrogenation of the double bond, thus obtaining the corresponding C_2-symmetric 1,5-diols (from *E*-configured diols **17**) and *meso*-1,5-diols (from *Z*-configured diols **18**). The *E*/*Z*-configuration was confirmed by measuring the coupling constants (*J*) of the olefinic protons in ^{1}H NMR spectroscopy (*E*-isomers: *J* = 15.4 Hz; *Z*-isomers: *J* = 11.0 Hz). In all cases, *E*-isomers showed longer retention times than the corresponding *Z*-isomers under the employed chromatographic conditions (60 g of silica gel per gram of 1,5-diol and elution with petroleum ether/ethyl acetate). The absolute configurations were established by comparing the ^{1}H NMR spectra of the corresponding (*S*)- and (*R*)-Mosher esters [(*S*)/(*R*)-MTPA].[24a] Furthermore, the assignments were also

SCHEME 10. Determination of Configuration of the 1,5-Diols



SCHEME 11. Assignment of the Configuration of Homoallyl Alcohols 18ka and *ent*-18kg



confirmed by comparing the spectroscopic data of diols **17ja**, **17aa**, **17gg**, *ent*-**17hh**, *ent*-**17jj**, **18ja**, **18gg**, and *ent*-**18jj** with those reported in the literature.[6a,23]

Diols **18ka** and *ent*-**18kg** were assigned by means of chemical correlations (Scheme 11). Ozonolysis followed by reduction with $LiAlH_4$ provided the known 1,3-diols **25** and **26**, whose spectroscopic data were in full agreement with those previously reported.[12d] Finally, X-ray crystallography of diol **17jg** additionally supported the assignment (see the Supporting Information).

The enantiomeric excess of diols **18ka**/*ent*-**18ka** and **18kg**/*ent*-**18kg** were found to be excellent (92−98% ee) by means of chiral HPLC analysis, which revealed a nearly complete chirality transfer of the new allylboronic esters. Attempts to determine the enantiomeric excess of the remaining diols by means of chromatographic methods failed. Derivatizations (quantitative esterification with benzoyl chloride, see the Supporting Information) in order to change the polarity of the products did not lead to better separation of enantiomers either. The Mosher ester method,[24] used in this work to determine the absolute configuration of the diols, also indirectly provided their enantiomeric excess (see the Supporting Information). Thus, except for diols **18ka**/*ent*-**18ka** and **18kg**/*ent*-**18kg** (92−98% ee), all products were found to be enantiomerically pure (> 95% ee), which can also be noticed in the increased optical rotation values for known products. Unsurprisingly, starting from diastereomerically pure allylboronic esters bearing a stereogenic center in the α-position chain and with no racemization expected during the addition, only one enantiomer of each isomer (*E*/*Z*) was formed.

(23) (a) Hicks, J. D.; Huh, C. W.; Legg, A. D.; Roush, W. R. *Org. Lett.* **2007**, *9*, 5621. (b) Flamme, E. M.; Roush, W. R. *Beilstein J. Org. Chem.* **2005**, 1:7. (c) Li, F.; Roush, W. R. *Org. Lett.* **2009**, *11*, 2932.

(24) (a) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2005**, *70*, 3778. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Conclusion

We have reported on the synthesis and the configurational assignment of new enantio- and diastereomerically pure α-substituted allylboronic esters by using a palladium-catalyzed carbonyl allylation in the presence of $SnCl_2$. The transformation proceeds smoothly and diastereoselectively, producing predominantly *anti*-products. The obtained allylboronic esters are moisture stable and could be stored for long periods of time without decomposition. Their potential as allylation reagents was investigated in detail, showing the effect of the stereogenic center in the α-position to boron on the selectivity of the addition to aldehydes, allowing the stereocontrolled formation of a wide variety of homoallylic alcohols (2-ene-1,5-diols).

Experimental Section

Only general procedures with a representative example are given. For full details, see the Supporting Information.

Synthesis of Boronic Esters 2 (Scheme 2). Et_3N (1.50 mmol) and $MeSO_2Cl$ (1.50 mmol) were added to a stirred solution of alcohol **1** (1.00 mmol) in dry CH_2Cl_2 (2 mL per mmol of **1**) at 0 °C under a dry nitrogen atmosphere. The solution was stirred at room temperature until the reaction was complete (as judged by TLC, 1 h). The reaction mixture was diluted with Et_2O, and satd aq $NaHCO_3$ (5 mL per mmol of **1**) was added. Stirring was continued for 15 min. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layer was washed successively with satd aq NH_4Cl, water, and brine. The extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvents were removed under reduced pressure to obtain methyl sulfonates **2** as colorless foams.

(4′*R*,5′*R*,2*E*)-3-[4′,5′-Bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]prop-2-en-1-yl Methanesulfonate (2a). According to the general procedure, allyl alcohol **1a** (9.90 g, 19.0 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (38 mL) and treated consecutively with Et_3N (3.96 mL, 28.6 mmol, 1.50 equiv) and $MeSO_2Cl$ (2.22 mL, 28.6 mmol, 1.50 equiv). Methyl sulfonate **2a** (11.4 g, 19.0 mmol, quant) was isolated as a colorless foam without further purification steps: R_f = 0.15 (petroleum ether/ethyl acetate, 85:15) and R_f = 0.52 (petroleum ether/ethyl acetate, 60:40); $[\alpha]^{20}_D$ = −65.4 (*c* 1.03, $CHCl_3$); mp 84−91 °C; IR (film) ν_{max} (cm^{-1}) = 2939, 2833, 1648, 1494, 1446, 1343, 1238, 1173, 1075, 1032, 1014, 967, 935, 758, 672; ^1H NMR (600 MHz, $CDCl_3$) δ 2.93 (s, 3H, SO_2CH_3), 3.00 (s, 6H, OCH_3), 4.59 (dd, J = 1.6, 5.1 Hz, 2H, 1-H), 5.37 (s, 2H, 4′-H and 5′-H), 5.40 (dt, J = 1.6 Hz, 18.0 Hz, 1H, 3-H), 6.14 (dt, J = 5.1, 18.0 Hz, 1H, 2-H), 7.25−7.37 (m, 20H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.2 (SO_2CH_3), 52.0 (OCH_3), 70.3 (C-1), 78.0 (C-4′ and C-5′), 83.5 (CPh_2OMe), 122.3 (br, C-3), 127.5, 127.6, 127.8, 128.0, 128.6, 129.8 (Ar−C), 141.1, 141.3 (Ar−C_{ipso}), 142.8 (C-2); ^{11}B NMR (192 MHz, $CDCl_3$) δ 29.55; MS (ESI, positive ion) *m*/*z* 621.0 (100) [(M + Na)$^+$], 394.9 (59), 197.1 (1) [(CPh_2OMe)$^+$]. Anal. Calcd for $C_{34}H_{35}BO_7S$ (598.5): C, 68.23; H, 5.89; S, 5.36. Found: C, 67.98; H, 6.00; S, 5.37.

Synthesis of Allylboronic Esters 8−10 (Table 1). $SnCl_2$ (3.00 mmol), $PdCl_2(PhCN)_2$ (5 mol %), H_2O (25 mmol), and the aldehyde (1.00 mmol) were added to a solution of mesylate **2** (1.00 mmol) in DMF (3 mL). The solution was stirred at room temperature until the reaction was complete (as judged by TLC, 2−3 h). The reaction mixture was diluted with Et_2O (120 mL) and washed successively with aq 10% HCl solution (10 mL), satd $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The extracts were dried over anhydrous $MgSO_4$ and filtered.

The solvent was removed under reduced pressure and the crude product subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 90:10) and MPLC (petroleum ether/ethyl acetate, 98:2) yielding α-substituted allylboronic esters **8**−**10** as colorless foams.

(1*R*,2*R*,4′*R*,5′*R*)-2-[4′,5′-Bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]-1-phenylbut-3-en-1-ol (8a). According to the general procedure, methyl sulfonate **2a** (3.00 g, 5.01 mmol, 1.00 equiv) was dissolved in DMF (16.7 mL). The solution was treated consecutively with $PdCl_2(PhCN)_2$ (96.1 mg, 0.25 mmol, 5 mol %), $SnCl_2$ (2.85 g, 15.0 mmol, 3.00 equiv), H_2O (2.25 mL, 125 mmol, 25.0 equiv), and benzaldehyde (500 μL, 5.00 mmol, 1.00 equiv). After column chromatography (180 g of silica gel, petroleum ether/ethyl acetate, 85:15), allylboronic ester **8a** (2.42 g, 3.96 mmol, 79%) was isolated as a colorless foam: $R_f = 0.72$ (petroleum ether/ethyl acetate, 60:40); $[\alpha]^{20}_D = -93.2$ (*c* 1.02, $CHCl_3$); mp 69−77 °C; IR (film) ν_{max} (cm^{-1}) = 3567, 3022, 2938, 2833, 1633, 1601, 1494, 1446, 1375, 1339, 1229, 1155, 1075, 756, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.85 (dd, *J* = 6.0, 9.7 Hz, 1H, 2-H), 2.02 (d, *J* = 2.3 Hz, 1H, O*H*), 2.97 (s, 6H, OCH_3), 4.57 (dd, *J* = 2.3, 6.0 Hz, 1H, 1-H), 4.73 (ddd, *J* = 0.7, 1.9, 17.1 Hz, 1H, 4-H_E), 4.89 (dd, *J* = 1.9, 10.2 Hz, 1H, 4-H_Z), 5.29 (s, 2H, 4′-H and 5′-H), 5.53 (ddd, *J* = 9.9, 9.9, 17.1 Hz, 1H, 3-H), 7.01−7.40 (m, 25H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 40.1 (C-2), 51.9 (O*C*H_3), 72.6 (C-1), 78.2 (C-4′ and C-5′), 83.6 (*C*Ph_2OMe), 117.7 (C-4), 126.5, 127.0, 127.6, 127.6, 127.7, 127.8, 128.0, 128.8, 129.8 (Ar-C), 134.2 (C-3), 141.2, 141.3, 143.1 (Ar-C_{ipso}); ^{11}B NMR (192 MHz, $CDCl_3$) δ 32.48; MS (ESI, positive ion) *m*/*z* 633.3 (100) [(M + Na)$^+$], 576.1 (60), 197.2 [($CPh_2OMe)^+$], 167.3 (8) [($C_{13}H_{11})^+$]. Anal. Calcd for $C_{40}H_{39}BO_5$ (610.3): C, 78.69; H, 6.44. Found: C, 78.26; H, 6.59.

Preparation of Diols 11, 12, and *ent*-12 (Analytical Samples; Scheme 3). MeLi (1.6 M in Et_2O) was added to a solution of allylboronic esters **8a**, **8j**, or **9j** in THF at 0 °C under a dry nitrogen atmosphere. The solution was stirred until the reaction was complete (as judged by TLC, 2 h). The oxidation was performed by careful addition of 30% H_2O_2; stirring was continued overnight. The resulting mixture was diluted with AcOEt, washed sequentially with saturated NH_4Cl solution, H_2O, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The product was subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 80:20) yielding 1,2-diols **11**, **12**, and *ent*-**12** as colorless oils.

(1*S*,2*R*)-1-Phenylbut-3-ene-1,2-diol (11). Prepared according to the general procedure. Spectroscopic data were in agreement with those previously reported:[19] $[\alpha]^{20}_D = +75.8$ (*c* 0.96, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (br, 1H, O*H*), 2.75 (br, 1H, O*H*), 4.29 (m_c, 1H, 2-H), 4.73 (d, *J* = 4.6 Hz, 1H, 1-H), 5.19 (ddd, *J* = 1.4, 1.4, 10.5 Hz, 1H, 4-H_Z), 5.25 (ddd, *J* = 1.4, 1.4, 17.2 Hz, 1H, 4-H_E), 5.78 (ddd, *J* = 6.1, 10.5, 17.2 Hz, 1H, 3-H), 7.27−7.36 (m, 5H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 77.6 (C-1), 77.8 (C-2), 118.3 (C-4), 127.2, 127.2, 128.4, 128.8, 128.8 (Ar-C), 136.3 (C-3), 140.3 (Ar-C_{ipso}).

Allyl Additions (Tables 2 and 3, Scheme 7). The aldehyde (1.20 mmol) was added to a stirred solution of allylboronic esters **8**−**10**, **21**, or **22** (1.00 mmol) in dry CH_2Cl_2 (0.5 mL) at 0 °C under a dry nitrogen atmosphere. The mixture was stirred and allowed to warm to room temperature overnight. After complete consumption of allylboronic ester (as judged by TLC, 3−15 d), the solvents were removed under reduced pressure. The residue was dissolved in THF (10 mL), and $LiAlH_4$ (4.00 mmol) was added. After 1 h, the mixture was diluted with Et_2O (10 mL), cooled to 0 °C, and treated successively with H_2O (184 μL), 15% aqueous NaOH (184 μL), and H_2O (544 μL). The solids were filtered off and washed thoroughly with Et_2O, and the filtrate was dried over anhydrous $MgSO_4$. Filtration and removal of the solvents under reduced pressure completed the process. The product was then subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 60:40) yielding 1,5-diols as colorless oils.

(5*S*,2*Z*)-5-Phenylpent-2-ene-1,5-diol (18ka) and (5*R*,2*Z*)-5-Phenylpent-2-ene-1,5-diol (*ent*-18ka). According to the general procedure, allylboronic ester **8k** (425 mg, 0.79 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (398 μL) and treated with benzaldehyde (122 μL, 1.20 mmol, 1.50 equiv). The reaction mixture was stirred at 0 °C for 12 h and at room temperature for 1 d. After column chromatography (40 g of silica gel, petroleum ether/ethyl acetate, 50:50), 1,5-diol **18ka** (132 mg, 0.74 mmol, 94%) was isolated as a colorless oil: $R_f = 0.13$ (petroleum ether/ethyl acetate, 60:40); $[\alpha]^{20}_D = -114$ (*c* 2.23, $CHCl_3$, ee 97%). Mosher ester: ee 96%. HPLC: ee 97%. According to the general procedure, allylboronic ester **9k** (300 mg, 0.56 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (280 μL) and treated with benzaldehyde (86.0 μL, 0.84 mmol, 1.50 equiv). The reaction mixture was stirred at 0 °C for 12 h and at room temperature for 2 d. After column chromatography (40 g of silica gel, petroleum ether/ethyl acetate, 50:50), 1,5-diol *ent*-**18ka** (95.0 mg, 0.53 mmol, 95%) was isolated as a colorless oil: $R_f = 0.13$ (petroleum ether/ethyl acetate, 60:40); $[\alpha]^{20}_D = +115.40$ (*c* 1.27, $CHCl_3$, ee 98%); Mosher ester ee 95%; HPLC ee 98%; HPLC (Chiralcel OB, heptane/*i*PrOH 97:3, flow = 0.7 mL/min, λ = 208 nm): t_R (**18ka**) = 39.4 min, t_R (*ent*-**18ka**) = 54.6 min; IR (film) ν_{max} (cm^{-1}) = 3315, 2876, 1493, 1452, 1308, 1201, 1010, 999, 875, 758, 700; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (br, 2H, O*H*), 2.50 (dddddd, *J* = 0.5, 0.5, 1.4, 4.6, 7.3, 14.2 Hz, 1H, 4-H_a), 2.62 (dddd, *J* = 1.1, 7.7, 8.7, 14.0 Hz, 1H, 4-H_b), 4.02 (ddddd, *J* = 0.5, 0.5, 0.9, 6.9, 12.3 Hz, 1-H_a), 4.13 (dddd, *J* = 0.5, 1.2, 7.2, 12.3 Hz, 1H, 1-H_b), 4.74 (dd, *J* = 4.6, 7.8 Hz, 1H, 5-H), 5.62 (ddddd, *J* = 1.2, 1.2, 7.3, 8.7, 10.9 Hz, 1H, 3-H), 5.86 (ddddd, *J* = 1.3, 1.3, 7.2, 7.2, 10.9 Hz, 1H, 2-H), 7.24−7.38 (m, 5H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.3 (C-4), 57.9 (C-1), 73.2 (C-5), 125.9 (Ar-C), 127.9 (C-3), 128.6, 129.0 (Ar-C), 131.9 (C-2), 144.1 (Ar-C_{ipso}); HRMS (ESI, positive ion) *m*/*z* calcd for $C_{11}H_{14}O_2$ [M + Na]$^+$ 201.2174, found 201.0885.

Synthesis of TBS-Protected Boronic Esters 21 and 22 (Scheme 9). 2,6-Lutidine (4.00 mmol) and TBSOTf (3.00 mmol) were added to a stirred solution of boronic esters **8** or **9** (1.00 mmol) in dry CH_2Cl_2 (10 mL per mmol of **8** or **9**) at 0 °C under a dry nitrogen atmosphere. The solution was stirred at room temperature until the reaction was complete (as judged by TLC, 2 h). The reaction mixture was diluted with CH_2Cl_2 and satd aq $NaHCO_3$ (5 mL per mmol of **8** or **9**) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was successively washed with water and brine. The extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. The crude product was finally subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 95:5) to yield α-substituted TBS-protected allylboronic esters **21** and **22** as colorless foams.

(1*R*,2*R*,4′*R*,5′*R*)-*tert*-Butyldimethylsilyl-2-[4′,5′-bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]-1-phenylbut-3-en-1-yl Ether (21a). According to the general procedure, allylboronic ester **8a** (319 mg, 0.52 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (5.23 mL) and treated consecutively with 2,6-lutidine (243 μL, 2.00 mmol, 4.00 equiv) and TBSOTf (360 μL, 1.57 mmol, 3.00 equiv). After column chromatography (30 g of silica gel, petroleum ether/ethyl acetate, 95:5), TBS-protected allylboronic ester **21a** (375 mg, 1.40 mmol, 99%) was isolated as a colorless foam: $R_f = 0.68$ (petroleum ether/ethyl acetate, 85:15); $[\alpha]^{20}_D = -97.0$ (*c* 1.05, $CHCl_3$); melting range 63−74 °C; IR (film) ν_{max} (cm^{-1}) = 2930, 2855, 1446, 1362, 1249, 1199, 1074, 835, 773, 757, 695; ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.43 (s, 3H, CH_3Si), −0.15 (s, 3H, CH_3Si), 0.72 (s, 9H, *t*-Bu), 1.80 (m, 1H, 2-H), 2.93 (s, 6H, OCH_3), 4.34 (d, *J* = 8.2 Hz, 1H, 1-H), 4.67 (ddd, *J* = 0.5, 2.0, 17.0 Hz, 1H, 4-H_E), 4.81 (ddd, *J* = 0.4, 2.1, 10.1 Hz, 1H, 4-H_Z), 5.17 (s, 2H, 4′-H and 5′-H), 5.58 (ddd, *J* = 9.9, 9.9, 17.0 Hz, 1H, 3-H), 6.90−7.32 (m, 25H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −4.7 (*C*H_3Si), −4.3 (*C*H_3Si), 18.3 (($CH_3)_3$*C*Si), 26.0 (($CH_3)_3$*C*Si), 41.6 (br, C-2), 51.9 (O*C*H_3), 74.5 (C-1), 77.8 (C-4′ and C-5′), 83.4 (*C*Ph_2OMe), 115.4 (C-4), 126.8, 127.3, 127.4, 127.5, 128.8, 129.9 (Ar-C), 136.5 (C-3),

141.5, 145.4 (Ar-C_{ipso}); ^{11}B NMR (192 MHz, $CDCl_3$) δ 32.63; MS (ESI, positive ion) m/z 747.2 (62) [$(M + Na)^+$], 617.0 (100)Anal. Calcd for for $C_{46}H_{53}BO_5Si$ (724.80): C, 76.23; H, 7.37. Found: C, 76.13; H, 7.33.

Ozonolysis and Reduction with $LiAlH_4$ (Scheme 11). The homoallyl alcohol (0.10 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C in a flask equipped with a Teflon stopcock and gas inlet frit (quickfit with Teflon gasket). A O_3/O_2 mixture was bubbled through the solution until it was a persistent blue color. Excess O_3 was expelled by a stream of O_2. Me_2S (1 mL) was added to the reaction mixture, which was allowed to warm to room temperature, before it was concentrated and dried under reduced pressure. The residue was dissolved in THF (10 mL), and $LiAlH_4$ (4.00 mmol) was added. After 1 h, the mixture was diluted with Et_2O (10 mL) and cooled to 0 °C. Successively, H_2O (121 μL), 15% aqueous NaOH (121 μL), and H_2O (358 μL) were carefully added and stirred (for about 30 min) until a filterable precipitate formed. The filter cake was washed thoroughly with Et_2O. The filtrate was concentrated under reduced pressure and subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate, 60:40), yielding 1,3-diols **25** and **26** as colorless oils.

(1*S*)-1-Phenylpropane-1,3-diol (25). According to the general procedure, 1,5-diol **18ka** (64.5 mg, 0.36 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (13 mL) and treated with an O_3/O_2 mixture. After column chromatography (8 g of silica gel, petroleum ether/ethyl acetate, 50:50), 1,3-diol **25** (47.2 mg, 0.31 mmol, 87%) was isolated as a colorless oil. The spectroscopic data were in full agreement with those reported in the literature.[12d] $[\alpha]^{20}_D = -65.8$ (*c* 0.96, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.90 (dddd, J = 3.6, 4.4, 5.8, 14.6 Hz, 1H, 2-H_a), 1.98 (dddd, J = 5.0, 7.0, 8.9, 14.6 Hz, 1H, 2-H_b), 2.83 (br, 1H, O*H*), 3.28 (br, 1H, O*H*), 3.80−3.83 (m, 2H, 3-H), 4.92 (dd, J = 3.7, 8.9 Hz, 1H, 1-H), 7.25−7.35 (m, 5H, Ar-H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 40.6 (C-2), 61.5 (C-3), 74.4 (C-1), 125.8, 127.7, 128.6 (Ar-C), 144.4 (Ar-C_{ipso}).

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Supporting Information Available: Full experimental details, compound characterization, copies of ^{1}H and ^{13}C spectra of all pure products, also including the complete experimental procedure for the synthesis of boronic ester **1a**, formation of benzoates for HPLC analysis, HPLC chromatograms for **18ka**/*ent*-**18ka** and **18kg**/*ent*-**18kg**, Mosher ester method exemplified for compound **17jg**, and X-ray structural analyses of compounds **17jg** and **28aa**. This material is available free of charge via the Internet at http://pubs.acs.org.