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Synthesis of Highly-Substituted Enantiomerically Pure Allylboronic Esters and Investigation of Their Stereoselective Addition to Aldehydes

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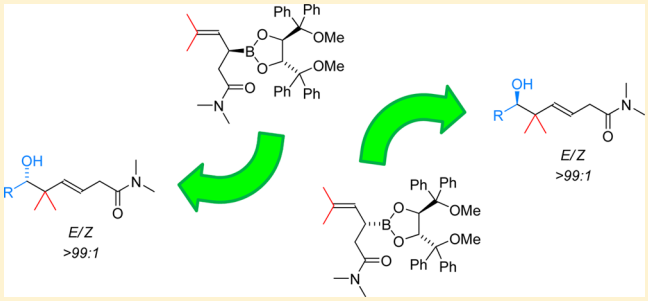
Supporting Information

ABSTRACT: Diastereomerically pure allylboronates bearing the readily available tartrate derivative were obtained via sigmatropic rearrangement. Allyl additions were performed, and the influence of γ-disubstituted allylboronates was studied. Highly γ-substituted boronic esters were found to lead to the corresponding enantiomerically enriched homoallyl alcohols with exclusively *E* configuration; their synthesis and the mechanism of the reaction is proposed here.



INTRODUCTION

Stereocontrolled carbon−carbon bond formation is one of the most attractive reactions in organic chemistry. During the last decades, aldehyde allylation has gained an important role in the context of the asymmetric synthesis of homoallyl alcohols, since they are important building blocks, e.g., for natural products. Among the range of possible allylmetal reagents, boron derivatives have shown outstanding properties in terms of yield, selectivity, and predictability.[1−7] After the pioneering discovery of Hoffmann and Zeiss on the regio- and diastereoselective outcome in the reaction between aldehydes and both regioisomers of crotylboronate,[8] many research groups have been interested in asymmetric allylation.[9−12] The predictable stereoselectivity was explained to go via the type I reaction mechanism of the allylboron reagents, proposed by Denmark in 1980,[13] in which a closed six-membered chairlike transition state is involved. Although an additional stereogenic center at the α-position with respect to the boronic ester has been shown to be important in providing increased chirality transfer, its applicability is often hampered by the challenging synthesis of enantiomerically pure starting materials.[14−24] Indeed, their instability at room temperature regularly led to product mixtures via 1,3-borotropic rearrangement.[8b,25,26] The first synthesis of α-substituted allylboronic esters was reported by Hoffman and Landmann.[27] In their reaction, the chiral α-substituted allylboronic reagent was obtained via Matteson homologation starting from diastereoisomerically pure dichloromethylboronate. In recent years, many methods have been developed for the control of the absolute configuration, including the diastereoselective one-pot double allylboration reaction, with the addition of two aldehydes sequentially,[28] or the stereoselective addition to a ketone followed by a 1,3-borotropic shift and subsequent aldehyde addition.[29] Additionally, Diels−Alder reactions were also applied using diastereoisomerically pure allylboronates[21,30−35] and many others.[36−44] More recently, the discovery of Lewis and Brønsted acid-catalyzed allylboration, in which the metal ion coordinates to an oxygen atom on the boronate group, has been shown to promote the allyl addition reaction while decreasing the reaction time.[6,45−51] Aggarwal and co-workers developed an enantioselective synthesis of α-substituted allylboron reagents that reacted in situ with aldehydes to give homoallylic alcohols with control over the relative and absolute stereochemistry.[52] Our group has established the synthesis of highly stable α-substituted allylboronates containing the readily available tartrate derivative ('**diol**') as a boron protecting group, which is easily synthesized in both enantiomeric forms.[53,54] A [3,3]-sigmatropic rearrangement of the alkenylboronic ester led to diastereoisomerically pure allylboronates (Scheme 1), which were then subjected to further transformations.[55−60]

Control of the absolute configuration in the allyl addition between carbonyl compounds and allylboronic reagents has always been a matter of interest. The selectivity for the two different diastereoisomeric homoallylic alcohol products was demonstrated to be dependent on two factors: the steric bulk of the boronic ester protecting group and the nature of the R^4 group (Scheme 2).[61] When small diols are used in the

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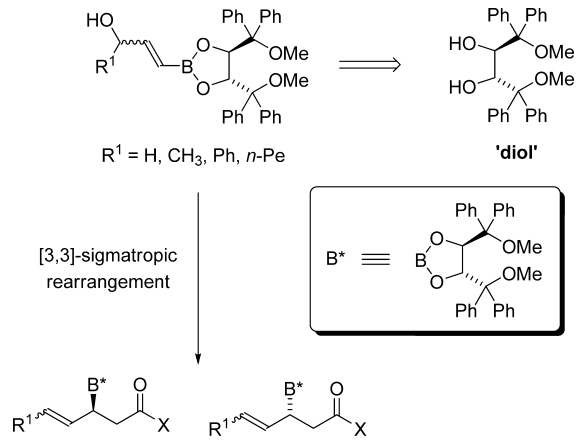
Scheme 1. Enantiomerically Pure Allylboronates via a [3,3]-Sigmatropic Rearrangement



allylboronates, *E* selectivity is predominantly observed.[62] With increasing steric bulk of the diol moiety at the boron, formation of the *Z*-configured product becomes more favorable.[55−60] Additionally, the use of an electron-withdrawing group at R^4 improves the *Z* selectivity, as it minimizes the stereoelectronic $\pi-\sigma^*$ delocalization in the transition states, thus rendering the transition state for the *Z* configuration more reactive.[19,21] Similarly, an electron-donating group favors the formation of the *E*-configured product. To the best of our knowledge, no study has focused on the effects of the R^2 and R^3 substituents on the configuration of the newly formed double bond. Here, we want to add a third factor in the allyl addition reaction with allylboronates: the *E*/*Z* selectivity of the reaction is highly dependent on the *γ*-substituents. Indeed, we found that allylboronates that are more highly substituted at the double bond ($R^2 = R^3 = CH_3$) selectively give *E* homoallyl alcohols, attractive moieties present in many natural products, e.g., bryostatins[63] and psymberine.[64] Despite the significance and usefulness of these highly functionalized homoallyl alcohols, only one report is known in the literature to utilize the corresponding allylboronates in allyl addition reactions.[65]

RESULTS AND DISCUSSION

Synthesis of *α*-Substituted Allylboronic Esters. Allylboronic ester **1** was obtained in high yield via a one-pot hydroboration−oxidation−transesterification[62c] sequence from silyl-protected 2-methyl 3-butyn-ol (**2**) (Scheme 3). Next, the deprotection of the silyl group was tested under different conditions (Table 1). Since tetrabutylammonium fluoride

Scheme 3. Synthesis of Allylboronic Ester 1

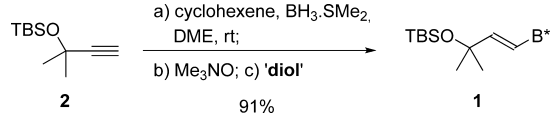
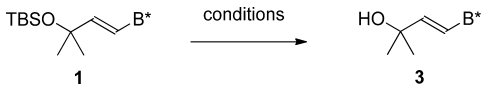


Table 1. Optimization of TBS Deprotection

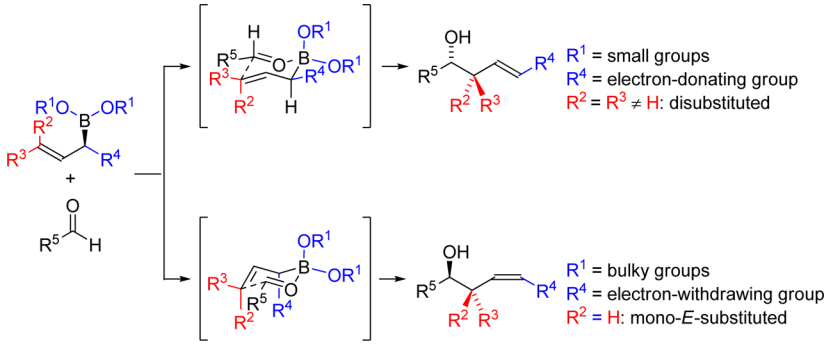


entry	solvent	conditions	*t* [h]	yield [%]
1	THF	TBAF (3.0 equiv)	72	no conversion
2	THF	HF−pyridine (1.5 equiv)	2	no conversion
3	THF	HF−pyridine (3.0 equiv)	2	45 (‘**diol**’)
4	CH_2Cl_2/MeOH	conc. HCl, 60 °C, *μ*w, 200 W	0.4	30 (**3**), 37 (**1**), 21 (‘**diol**’)
5	CH_2Cl_2/MeOH	conc. HCl	4	67 (**3**)

(TBAF) is a well-known reagent for silyl group deprotection, we started with this basic environment. Unfortunately, after 3 days no product was obtained (entry 1). The same result was observed when 1.5 equiv of a HF−pyridine complex was used (entry 2). Increasing the number of equivalents of HF−pyridine led to the decomposition of the starting material **1**, and a 45% yield of free ‘**diol**’ was released (entry 3). Nevertheless, strongly acidic conditions could be successfully applied (entries 4 and 5), and the best results were obtained with a concentrated HCl solution after 4 h (entry 5). The allylic alcohol derivative **3** was isolated as a crystalline solid, and the structure was confirmed by X-ray crystallography (see the Supporting Information for details). Although the yield of the TBS-group cleavage was not exceptional (67%) and the addition of more equivalents of concentrated HCl did not provide a better yield, no byproduct formation was detected and the starting material **1** could be recovered.

With tertiary allylic alcohol **3** in hand, we turned our attention toward [3,3]-sigmatropic rearrangements. We started our investigation with the Johnson rearrangement, for which two sets of conditions were tested and analyzed (Scheme 4). First, thermal conditions for the Johnson reaction were considered,[20] whereby allylic alcohol **3** was heated to 135 °C in an excess of triethyl orthoacetate in the presence of a catalytic amount of propionic acid. After 4 h, a 46:54 diastereoisomeric mixture of products **4** and **5** was obtained in 53% yield, and 25% of the starting material **3** was recovered.

Scheme 2. Factors Influencing the Diastereoselective Synthesis of Homoallylic Alcohols



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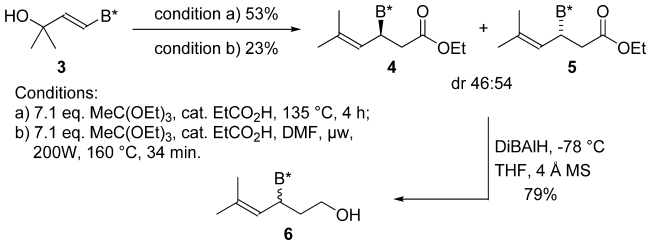
Scheme 4. Synthesis of Allylboronates 4−6

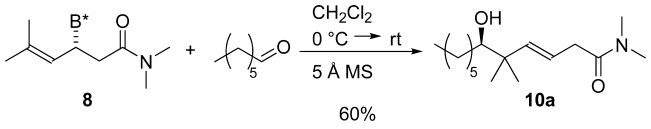


On the basis of recent investigations in our laboratories on microwave-assisted Johnson rearrangements,[57] we also tested these for substrate **3**. After 34 min in a closed vessel at 160 °C, only low yields of products **4** and **5** were obtained with the same diastereoselectivity as under the previous thermal conditions, and more than 50% of the starting material remained unreacted.

The diastereoisomeric mixture of allylboronic esters **4** and **5** obtained was separable after extensive chromatographic purification (MPLC). Despite the high stability of these chiral α-substituted allylic boronates, we decided that we would require more readily separable diastereomers of starting material for our subsequent investigation of the allyl addition reaction. Reduction of the carboxylic ester moiety in the mixture of reagents **4** and **5** was achieved by use of DiBAlH, but unfortunately, attempts to separate the diastereomers **6** were unsuccessful. At this stage, it was decided to form different allylboronates via another type of [3,3]-sigmatropic rearrangement. The Eschenmoser reaction was chosen, and under conventional reaction conditions (Scheme 5) a 69:31 diastereomeric mixture was isolated. To our delight, the obtained mixture of allylboronates was easily separable into amides **7** and **8** via flash column chromatography. Longer reaction times did not improve the yields, and again, 40% of the starting material **3** was recovered. These diastereomerically pure allylboronates were air-stable and were stored at room temperature. The absolute configuration of allylboronates **7** and **8** was assigned via X-ray crystallographic analysis (see the Supporting Information for details).

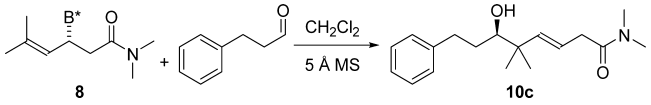
Synthesis of Enantiomerically Pure Allyl Alcohols. Having established a route toward diastereomerically pure chiral α-substituted allylboronates **7** and **8** for the first time, we turned our attention to the applicability of this method. First, we wanted to find the best conditions for the asymmetric allylation. Analogous to allylborations previously performed by our group,[54−60] we performed the reaction with allylboronate **8** in CH_2Cl_2 at room temperature. As a simple model aldehyde, heptanal was allowed to react with allylboronate **8** under different atmospheric conditions. Performing the reaction under an atmosphere of dry nitrogen improved the yield of alcohol **10a** from 45% to 57%. A slight further increase in the yield of product **10a** to 60% was achieved when 5 Å molecular sieves (MS) were added to the reaction mixture (Scheme 6). A possible explanation for these results was detected by monitoring the reaction via ^{1}H NMR spectroscopy. The

Scheme 6. Addition of Boronate 8 to Heptanal



aldehyde resonance of the starting material (9.77 ppm) and the allylic signal of the product (5.50 ppm) were monitored at various points throughout the reaction, and it was found that the aldehyde produced side products under normal atmospheric conditions. In fact, the integral of the aldehyde signal was shown to decrease during the reaction under normal atmospheric conditions with no further formation of product **10a**. In the reaction performed under a nitrogen atmosphere, the decrease in the aldehyde peak corresponded directly to an increase in the allylic peak, thereby indicating the importance of inert conditions. In addition to atmospheric effects, we were also interested in examining the influence of higher reaction temperatures on substrate **8** (Table 2), as the allyl addition is known to be a slow reaction.

Table 2. Thermal Dependence of the Allyl Addition Reaction



entry	T [°C]	t [days]	yield [%]	ee [%]
1	rt	10	55 (**10c**), 35 (**8**)	77
2	40	10	28	80
3	60	8	29	75

The reaction at room temperature (entry 1) went to completion in 10 days, and increasing the temperature did not show a notable influence on the reaction time. Indeed, at 40 °C the reaction took the same time as at room temperature (entry 2), and at 60 °C a slightly lower reaction time was observed (entry 3). Nevertheless, lower yields were obtained, suggesting the decomposition of starting material **8** after long periods at those temperatures; this was confirmed by NMR spectroscopy. Surprisingly, the ee also did not show any considerable thermal dependence. We reasoned that the temperature does not have a notable influence on the reaction time or, surprisingly, on the enantioselectivity of our allyl addition, but an unexpected negative influence on the yields was found. With the best reaction conditions in hand (inert conditions at room temperature), we screened a wide variety of aldehydes with the diastereomerically pure boronates **7** and **8** in the asymmetric allylation. All of the reactions were carried out under an inert atmosphere in absolute CH_2Cl_2, and the addition of the aldehyde was performed at 0 °C. The reaction mixture was allowed to warm to room temperature, and the reaction was monitored via ^{1}H NMR spectroscopy and TLC. The enantiomerically enriched homoallyl alcohols were

Scheme 5. Eschenmoser Rearrangement Starting from Allyl Alcohol 3

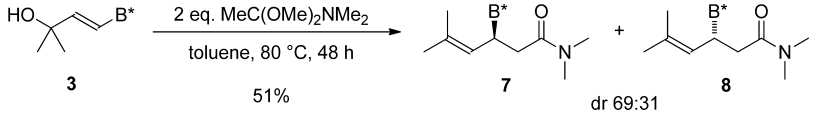


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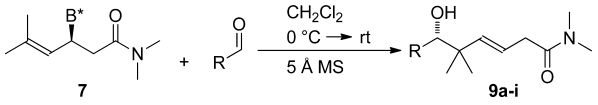
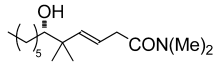
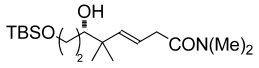
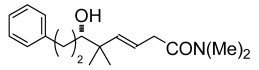
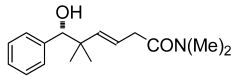
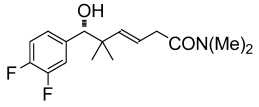
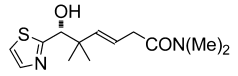
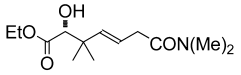
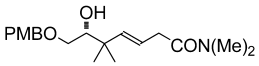
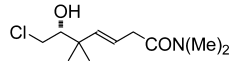
Table 3. Allyl Additions of Highly Substituted Allylboronic Ester 7



entry	9	R	product	yield[a] [%]	ee[b] [%]	E/Z[c]
1	**a**	n-C_6H_{13}		23	89	>99:1
2	**b**	TBSO$(CH_2)_2$		75	83	>99:1
3	**c**	Ph$(CH_2)_2$		80	90	>99:1
4	**d**	Ph		85	>99	>99:1
5	**e**	3,4-$C_6H_3F_2$		81	98	>99:1
6	**f**	thiazol-2-yl		73	>99	>99:1
7	**g**	COOEt		90	98	>99:1
8	**h**	$PMBOCH_2$		19	82	>99:1
9	**i**	CH_2Cl		0	0	0

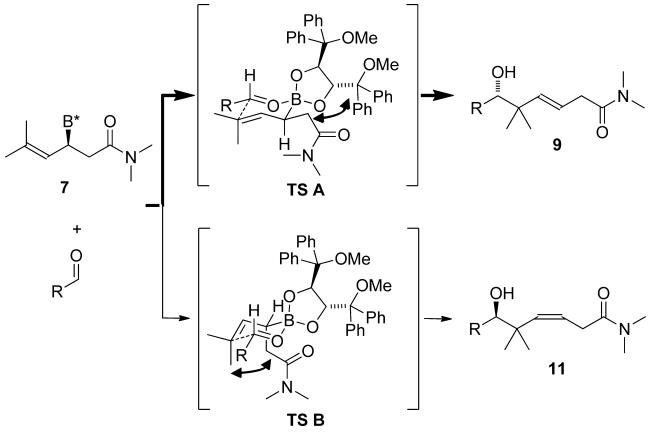
[a]Isolated enantiomers. [b]Determined by chiral HPLC analysis. [c]Determined by ^{1}H NMR spectroscopy after column chromatography.

obtained after hydrolysis of the chiral boron auxiliary via simple column chromatography. Subsequently, the diastereomeric ratio of the double bond was determined via ^{1}H NMR analysis.

When allylboronate **7** was used as the reagent (Table 3), the exclusively *E*-configured olefins **9a–i** were obtained. The addition of heptanal (23% yield, 89% ee; entry 1) led to unexpectedly low yields. Upon further analysis of the crude reaction mixture, a significant amount of a byproduct was formed (oxidation of the starting material) and 50% of the starting material was recovered. Good yields and selectivity were achieved with the addition of other alkyl derivatives (75% yield, 83% ee in entry 2; 80% yield, 90% ee in entry 3). A broad range of aryl derivatives, including phenyl (entries 4 and 5) and thiazole (entry 6) derivatives, were successfully employed to give good yields with excellent enantioselectivity. In addition, α-substituted derivatives were tested, and excellent yields and selectivities were obtained with the ethyl ester (90% yield, 98% ee; entry 7). The addition of $PMBOCH_2CHO$ (entry 8) led to the formation of a small amount of product. The addition of chloroacetaldehyde led only to decomposition of the aldehyde, and the starting material was recovered (no product formed; entry 9). All in all, a wide range of aldehydes, including aliphatic, aromatic, heteroaromatic, and ether-substituted, were found to be suitable substrates, and the products were obtained with excellent *E* selectivity, good yields, and excellent ee.

At first glance, this selectivity for the *E* configuration was unexpected, as the starting material **7** contains all of the principal factors to improve the *Z* selectivity, such as the sterically demanding '**diol**' covering the boron atom and an electron-withdrawing group at the α-position.[55−61] The inversion of selectivity can be understood by analyzing the reaction mechanism in detail (Scheme 7). With additional

Scheme 7. Proposed Mechanism for the Selective Allyl Addition with Boronate 7



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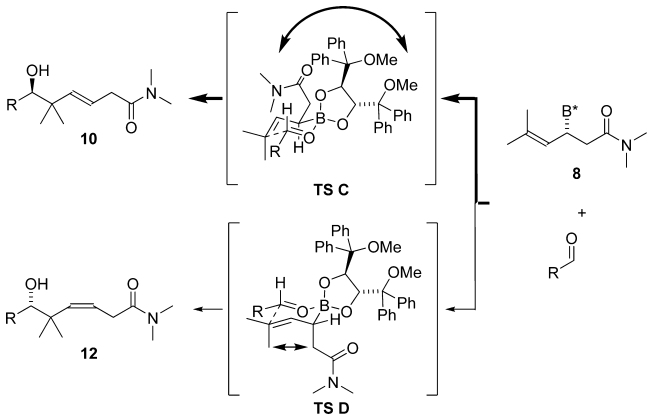
substituents on the double bond, transition state **B** (**TS B**) presents a highly unfavorable *syn*-pentane interaction between the amide and one of the methyl groups, both of which are in pseudoaxial positions. Moreover, the attack of the carbonyl group at the *si* face is prevented by the steric hindrance of the substituents in the pseudoaxial positions. On the other hand, **TS A** has the disadvantage of the interaction between the bulky '**diol**' and the amide, which should destabilize the chairlike transition state. Nevertheless, the assumption of pseudoequatorial positions by both the amide moiety and the side chain of aldehyde in **TS A** plays a dominant role and should favor this transition state. Furthermore, the attack of the carbonyl group at the *re* face is facilitated by less steric hindrance.

In order to confirm this assumption, the allyl addition reactions were also performed with the diastereomer **8**. Previous studies using unsubstituted or mono-*E*-substituted double bonds led to the observation of *Z* selectivity.[56−60] However, in our current study of disubstituted allylboronates, we observed an inversion of this diastereoselectivity. Again, nearly perfect control of the newly formed stereogenic centers was observed. Although the interaction between the amide group and the bulky '**diol**' is stronger in **TS C**, the preference for the equatorial positioning of all substituents supports this mechanism of reaction (Scheme 8). Moreover, the *syn*-pentane steric interaction is present when the amide derivative is in a pseudoaxial position (**TS D**), rendering this route difficult and thus unfavorable.

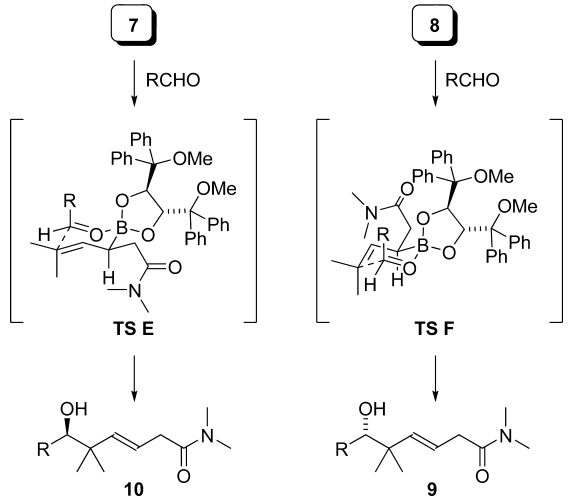
Scheme 8. Proposed Mechanism for the Selective Allyl Addition with Boronate 8



The yields and the ee's of compounds **10a−h** (Table 4) are comparable with those of the corresponding enantiomers **9a−i**. The addition of heptanal (entry 1) led to a good yield, and no byproduct formation was detected. The addition of TBSO-$(CH_2)_2$CHO showed a lower yield (27%; entry 2) as well as the formation of a side product, suggesting the elimination of the OTBS group, which results in the formation of the terminal alkene. Only in the case of the addition of 3-phenylpropanal (entry 4; yield given only for the *E* isomer) was a minor amount of the *Z*-configured product detected (*E*/*Z* 91:9). The isomers were easily separated via column chromatography. Excellent results were also obtained when aryl groups were used (entries 4−6). The addition of α-substituted aldehydes also led to high *E* selectivity.

Although the enantiomeric ratio of some of the obtained allyl alcohols was excellent for both enantiomers, others gave lower ee, and the reason for this is not yet completely understood. We have shown with **TS A** and **TS C** that the preference for all substituents to be at pseudoequatorial positions led to the formation of enantiomerically pure or enriched homoallyl alcohols **9a−i** and **10a−h**. The lower ee observed in some aldehyde additions could be explained with competitive transition states **TS E** and **TS F** from **7** and **8**, respectively (Scheme 9). The placement of the R substituent of the

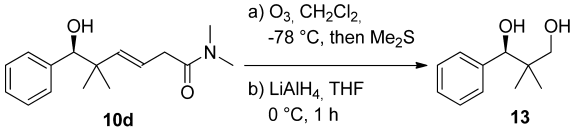
Scheme 9. Proposed Transition States for the Allyl Addition



aldehyde in a pseudoaxial position in those transition states leads to inversion of the configuration of the expected allylic alcohol, affording the enantiomers (**10** from **7** and **9** from **8**) and lowering the ee of the expected allylic alcohol. Another explanation for the lower ee could be that the reaction proceeds through a twist-boat transition state instead of the chairlike transition state.[66]

In order to unambiguously confirm the nearly complete transfer of the chirality of α-substituted allylboronates and establish the configuration of the newly formed allyl alcohols, we performed a chemical correlation. Ozonolysis of homoallyl alcohol **10d** followed by reduction with $LiAlH_4$, both known to proceed with retention of configuration, led to the corresponding known diol **13** (Scheme 10), proving the absolute

Scheme 10. Assignment of the Configuration of Homoallyl Alcohol 10d



$[\alpha]_D^{20}$ = -40 (c 0.5, $CHCl_3$)

$[\alpha]_D^{20}$ = -50 (c 1.0, $CHCl_3$) ref.[67]

configuration of the allyl alcohol. On the basis of the reported optical rotation,[67] the absolute configuration was readily assigned. The *E*/*Z* configuration was confirmed via analysis of ^{1}H NMR spectroscopy coupling constants.

CONCLUSION

For the first time, a study of the influence of γ-disubstitution in allylboronates on allylation reactions has been reported. Highly substituted enantio- and diastereomerically pure allylboronates were obtained via [3,3]-sigmatropic rearrangements, and their

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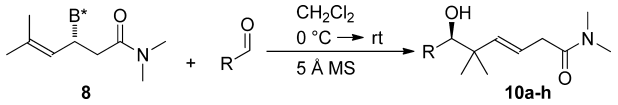
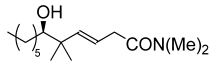
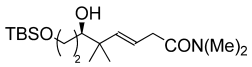
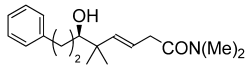
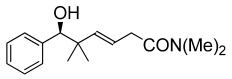
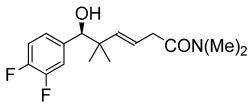
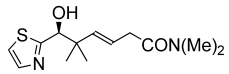
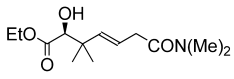
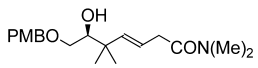
Table 4. Allyl Additions of Highly Substituted Allylboronic Ester 8



entry	10	R	product	yield[a] [%]	ee[b] [%]	E/Z[c]
1	a	n-C_6H_{13}		60	83	>99:1
2	b	TBSO$(CH_2)_2$		27	80	>99:1
3	c	Ph$(CH_2)_2$		55	77	>99:1
4	d	Ph		82	95	>99:1
5	e	3,4-$C_6H_3F_2$		85	98	>99:1
6	f	thiazol-2-yl		70	>99	>99:1
7	g	COOEt		90	98	>99:1
8	h	PMBOCH$_2$		50	57	>99:1

[a]Isolated enantiomers. [b]Determined by chiral HPLC analysis. [c]Determined by ^{1}H NMR spectroscopy after column chromatography.

addition to a broad variety of aldehydes has been shown to lead exclusively to *E*-configured products. The mechanism of the reaction has been described to proceed via a closed six-membered chairlike transition state in which the enantiofacial selectivity is controlled by the configuration of the α-stereogenic center of the reagent and the preference for a pseudoequatorial orientation of the substituents. The assignment of the configuration of the pure homoallyl alcohols has been confirmed via chemical correlation.

EXPERIMENTAL SECTION

General. Unless otherwise specified, the reactions were carried out using standard Schlenk techniques under dry N_2 with magnetic stirring. Glassware was oven-dried at 120 °C overnight. Solvents were dried and purified by conventional methods prior to use. Toluene, dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and diethyl ether (Et_2O) were dried in a solvent purification system. All of the reagents were used as purchased from commercial suppliers without further purification. Common solvents for chromatography (petroleum ether 40−60 °C, ethyl acetate) were distilled prior to use. Flash column chromatography was performed on silica gel 60, 0.040−0.063 mm (230−400 mesh). TLC to monitor the course of the reactions was performed on precoated plastic sheets with detection by UV (254 nm) and/or by coloration with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), conc. H_2SO_4 (60 mL), H_2O (940 mL)]. Preparative medium-pressure liquid chromatography (MPLC) was performed using a packed column (25 mm × 300 mm or 40 mm × 475 mm; Si 60, 15−25 μm) and a UV detector (254 nm). Enantiomeric excesses were determined by HPLC analysis using chiral columns (Chiralcel OD, Chiralcel OD-H, Chiralpak IA, and Chiralpak IC). Optical rotations were measured at 20 °C using a quartz cell with a capacity of 1 mL and a path length of 10 cm. Melting points are uncorrected. High-resolution mass spectra were recorded on FT-ICR mass spectrometers.

Synthesis of Allyl Alcohol 3. *tert-Butyldimethyl(1,1-dimethyl-prop-2-ynyloxy)silane (**2**).* Under an atmosphere of dry nitrogen, 2-methyl-3-butyn-2-ol (11.5 mL, 119 mmol, 1.00 equiv) in dry CH_2Cl_2 (175 mL) was treated with imidazole (16.2 g, 238 mmol, 2.00 equiv) and *tert*-butyldimethylsilyl chloride (26.9 g, 178 mmol, 1.50 equiv) at 0 °C. The solution was stirred at room temperature overnight. Hydrolysis with water (105 mL) was followed by extraction with Et_2O (3 × 70 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane/Et_2O 85:15) to obtain **2** (21.7 g, 109 mmol, 92%) as a yellowish oil. Spectroscopic data were in full agreement with those previously reported.[68] R_f = 0.80 (petroleum ether/ethyl acetate 95:5). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.00 [s, 6H, $(CH_3)_2Si$], 0.70 [s, 9H, $(CH)_3CSi$], 1.30 [s, 6H, $(CH_3)_2C$], 2.22 (s, 1H, 3-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ −3.0 [$(CH_3)_2Si$], 17.9 [$(CH_3)_3C$], 25.7 [$(CH)_3CSi$], 32.9 [$(CH_3)_2CO$], 66.1 (C-2), 70.6 [$(CH_3)_2CO$], 89.3 (C-3). IR (film) ν_{max} [cm^{-1}] = 3310, 2957, 2931, 2888, 2858, 1463, 1361, 1252, 1163, 1040, 930, 830, 775.

*(4′R,5′R,3E)-tert-Butyldimethylsilyl 4-[4′,5′-Bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]-2-methylbut-3-en-2-yl Ether (**1**).* Under an atmosphere of dry nitrogen, $H_3B{\cdot}Me_2S$ (1.64 mL of a 10 M solution in Me_2S, 17.4 mmol, 1.00 equiv) was dissolved in 1,2-dimethoxyethane (35 mL) in a 100 mL Schlenk flask. At 0 °C, cyclohexene (3.53 mL, 34.9 mmol, 2.00 equiv) was added via syringe, and the formation of a colorless precipitate due to the formation of dicyclohexylborane was noticed. After 15 min, the reaction mixture was warmed to room temperature and stirred for 1 h. Alkyne **2** (3.46 g,

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17.4 mmol, 1.00 equiv) was added at 0 °C, and the mixture was stirred at room temperature for 1 h until a clear solution was obtained. $Me_3NO{\cdot}2H_2O$ (3.87 g, 34.9 mmol, 2.00 equiv) was added slowly (*caution*: exothermic reaction!), followed after 1 h by the addition of '**diol**' (7.93 g, 17.4 mmol, 1.00 equiv). The reaction mixture was stirred overnight. The solvent was removed under reduced pressure, and the crude product was subjected to flash column chromatography (petroleum ether/ethyl acetate 90:10). A colorless foam of the title compound was obtained (10.5 g, 15.9 mmol, 91%). R_f = 0.44 (petroleum ether/ethyl acetate 95:5). $[\alpha]_D^{20}$ = −90.7 (*c* 1.8, $CHCl_3$). Melting range 74−83 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.00 [s, 6H, $Si(CH_3)_2$], 0.85 [s, 9H, $C(CH_3)_3$], 1.19 [d, 6H, $C(CH_3)_2$], 3.05 (s, 6H, OCH_3), 5.19 (d, *J* = 18.1 Hz, 1H, 4-H), 5.38 (s, 2H, 4′-H, 5′-H), 6.26 (d, *J* = 18.1 Hz, 1H, 3-H), 7.29−7.42 (m, 20H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 0.00 [$Si(CH_3)_2$], 28.0 [$C(CH_3)_3$], 31.8 (CH_3), 32.0 (C-1), 53.9, 54.0 (OCH_3), 76.0 (C-2), 79.8 (C-4′, C-5′), 85.5 (CPh_2OCH_3), 114.7 (C-4), 129.4, 129.6, 129.9, 130.6, 131.9 (arom. *C*H), 143.3, 143.6 (arom. C_{ipso}), 162.8 (C-3). IR (film) ν_{max} [cm^{-1}] = 3059, 2926, 2851, 1640, 1494, 1446, 1387, 1347, 1229, 1181, 1075, 1034, 1017, 967, 920, 886, 835, 773, 757, 733, 698. HRMS (ESI +, *m*/*z*): [M + Na]$^+$ calcd for $C_{41}H_{51}BO_5SiNa$, 685.3497; found, 685.3494.

*(4′R,5′R,3E)-4-[4′,5′-Bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]-2-methylbut-3-en-2-ol (**3**).* TBS-protected boronic ester **1** (6.10 g, 9.20 mmol, 1.00 equiv) was dissolved in CH_2Cl_2/MeOH (70 mL), and a solution of HCl (0.85 mL, 27.6 mmol, 3.00 equiv) in MeOH (13 mL) was added dropwise. The mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL), and the solvents were reduced under pressure. H_2O was added, and the separated aqueous phase was extracted three times with Et_2O. The combined organic layers was washed successively with brine and dried over $MgSO_4$. Filtration and subsequent removal of the solvent under reduced pressure gave a yellowish oil, which was subjected to flash chromatography to provide **3** (3.38 g, 6.16 mmol, 67%) as a colorless foam along with recovery of 30% of the starting material **1**. R_f = 0.28 (petroleum ether/ethyl acetate 85:15). $[\alpha]_D^{20}$ = −68.8 (*c* 0.5, $CHCl_3$). Melting range 97−100 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.10 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.93 (s, 6H, OCH_3), 5.12 (d, *J* = 18.2 Hz, 1H, 4-H), 5.28 (s, 2H, 4′-H, 5′-H), 6.22 (d, *J* = 18.2 Hz, 1H, 3-H), 7.17−7.29 (m, 20H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 29.0 (CH_3), 29.2 (C-4), 51.8 (OCH_3), 71.7 (C-3), 77.7 (C-4′, C-5′), 83.4 (CPh_2OCH_3), 112.7 (C-1), 127.3, 127.3, 127.5, 127.8, 128.5, 129.7 (arom. *C*H), 141.1, 141.4 (arom. C_{ipso}), 159.4 (C-2). ^{11}B NMR (192 MHz, $CDCl_3$): δ 29.4. IR (film) ν_{max} [cm^{-1}] = 3385, 3058, 2973, 2834, 1638, 1494, 1446, 1398, 1368, 1345, 1240, 1187, 1150, 1075, 1033, 1016, 966, 905, 849, 831, 795, 757, 735, 698. HRMS (ESI+, *m*/*z*): [M + Na]$^+$ calcd for $C_{35}H_{37}BO_5Na$, 571.2632; found, 571.2624. Anal. Calcd for $C_{35}H_{37}BO_5$ (548.2734): C 76.64, H 6.80. Found: C 76.31, H 6.83.

[3,3]-Sigmatropic Rearrangements. *(3S,4′R,5′R)- and (3R,4′R,5′R)-Ethyl 3-[4′,5′-Bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]-5-methylhex-4-enoate (**4** and **5**): Method A (Johnson Rearrangement).* In a two-neck round-bottom flask equipped with a Claisen condenser under a nitrogen atmosphere, allyl alcohol **3** (700 mg, 1.28 mmol, 1.00 equiv) was treated with triethyl orthoacetate (1.64 mL, 8.96 mmol, 7.00 equiv) and a catalytic amount of propionic acid (5.50 μL, 0.07 mmol). The reaction mixture was heated at 135 °C and stirred for 4 h while formed EtOH was removed. The dr, measured by ^{1}H NMR spectroscopy, was shown to be 46:54. After flash column chromatography (petroleum ether/ethyl acetate 85:15) a mixture of diastereomers was obtained (420 mg, 0.68 mmol, 53%). Several rounds of MPLC (petroleum ether/ethyl acetate 97:3, 98:2, 99:1) gave **4** as a pure white solid and a mixture containing 91% **5** and 9% **4**.

Method B (Microwave). In a microwave vessel equipped with a stir bar, allyl alcohol **3** (100 mg, 0.18 mmol, 1.00 equiv) was dissolved in DMF (300 μL). Triethyl orthoacetate (332.71 μL, 1.82 mmol, 10.00 equiv) and a catalytic amount of propionic acid (0.80 μL, 0.01 mmol) were added, and the mixture was heated in a microwave reactor for 34 min, reaching a temperature of 160 °C. After removal of volatile compounds under reduced pressure, flash column chromatography (petroleum ether/ethyl acetate 85:15) led to a mixture of diastereomers **4** and **5** (25 mg, 0.04 mmol, 23%) and starting material **3** (62 mg, 0.11 mmol, 56%).

Allylboronate **4**: R_f = 0.18 (petroleum ether/ethyl acetate 95:5). $[\alpha]_D^{20}$ = −103.2 (*c* 0.8, $CHCl_3$). Melting range 63−69 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.05 (t, *J* = 7.2 Hz, 3H, 2″-H), 1.25 (s, 3H, CH_3), 1.45 (s, 3H, 6-H), 1.76 (dd, *J* = 15.0, 10.7 Hz, 1H, 2-H_a), 1.94 (ddd, *J* = 10.7, 10.1, 4.3 Hz, 1H, 3-H), 2.03 (dd, *J* = 15.0, 4.3 Hz, 1H, 2-H_b), 2.92 (s, 6H, OCH_3), 3.85 (q, *J* = 7.2 Hz, 1H, 1″-H), 4.58 (d, *J* = 10.1 Hz, 1H, 4-H), 5.20 (s, 2H, 4′-H, 5′-H), 7.17−7.28 (m, 20H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.1 (C-2″), 17.9 (C-6), 20.5 (br, C-3), 25.7 (CH_3), 29.6 (CH_3), 35.4 (C-2), 51.7 (OCH_3), 59.9 (C-1″), 77.8 (C-4′, C-5′), 83.3 (CPh_2OCH_3), 123.3 (C-4), 127.3, 127.5, 127.7, 128.5, 129.7 (arom. *C*H), 131.2 (C-5), 141.3 (arom. C_{ipso}), 173.5 (C-1). IR (film) ν_{max} [cm^{-1}] = 3059, 2967, 2937, 2830, 1735, 1495, 1447, 1369, 1331, 1272, 1232, 1200, 1137, 1076, 1033, 967. 922, 901, 828, 795, 759, 733, 700. HRMS (ESI+, *m*/*z*): [M + Na]$^+$ calcd for $C_{39}H_{43}BO_6Na$, 641.3050; found, 641.3045.

Allylboronate **5**: R_f = 0.18 (petroleum ether/ethyl acetate 95:5). $[\alpha]_D^{20}$ = −107.5 (*c* 0.8, $CHCl_3$). Melting range 63−69 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.06 (t, *J* = 7.1 Hz, 3H, 2″-H), 1.26 (d, *J* = 1.4 Hz, 3H, CH_3), 1.46 (d, *J* = 1.4 Hz, 3H, 6-H), 1.82 (dd, *J* = 15.5, 11.4 Hz, 1H, 2-H_a), 1.94 (dd, *J* = 15.5, 3.8 Hz, 1H, 2-H_b), 1.94 (ddd, *J* = 11.4, 10.3, 3.8 Hz, 1H, 3-H), 2.91 (s, 6H, OCH_3), 3.86 (dq, *J* = 11.3, 7.1 Hz, 1H, 1″-H_a), 3.90 (dq, *J* = 11.3, 7.1 Hz, 1H, 1″-H_b), 4.48 (dq, *J* = 10.3, 1.3 Hz, 1H, 4-H), 5.21 (s, 2H, 4′-H, 5′-H), 7.16−7.27 (m, 20H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.2 (C-2″), 17.9 (C-6), 20.6 (br, C-3), 25.8 (CH_3), 35.7 (C-2), 51.8 (OCH_3), 59.9 (C-1″), 77.9 (C-4′, C-5′), 83.4 (CPh_2OCH_3), 123.0 (C-4), 127.2, 127.3, 127.5, 127.8, 128.5, 129.7 (arom. *C*H), 131.3 (C-5), 141.3, 141.4 (arom. C_{ipso}), 173.4 (C-1). IR (film) ν_{max} [cm^{-1}] = 3059, 2967, 2937, 2834, 1734, 1495, 1447, 1369, 1331, 1269, 1233, 1199, 1137, 1075, 1033, 967, 922, 901, 828, 796, 758, 734, 700. HRMS (ESI+, *m*/*z*): [M + Na]$^+$ calcd for $C_{39}H_{43}BO_6Na$, 641.3050; found, 641.3044.

*(4′R,5′R)-3-[4′,5′-Bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]-5-methylhex-4-enol (**6**).* Under an atmosphere of dry nitrogen, the mixture of allylboronates **4** and **5** (105 mg, 0.17 mmol, 1.00 equiv) was dissolved in anhydrous THF (1.7 mL) in a Schlenk flask. After addition of 4 Å MS, the reaction mixture was cooled to −78 °C, and DiBAlH (153 μL, 0.85 mmol, 5.00 equiv) was added dropwise. The mixture was stirred at room temperature, and the end of the reaction was judged by TLC (3 h). After dilution with Et_2O, the reaction was quenched with H_2O (0.3 mL), 2 M NaOH (0.5 mL), and H_2O (0.3 mL) and extracted several times. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was subjected to flash column chromatography (petroleum ether/ethyl acetate 85:15) to yield a mixture of diastereomers **6** (77 mg, 0.13 mmol, 79%) as a colorless foam. R_f = 0.31 (petroleum ether/ethyl acetate 85:15). $[\alpha]_D^{20}$ = −127.7 (*c* 0.8, $CHCl_3$). Melting range 73−78 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.13−1.18 (m, 2H, O*H*, 2-H_a), 1.28−1.33 (m, 1H, 2-H_b), 1.34 (d, *J* = 1.0 Hz, 3H, CH_3), 1.48 (d, *J* = 1.0 Hz, 3H, 6-H), 1.55 (td, *J* = 5.1, 10.1 Hz, 1H, 3-H), 2.92 (s, 6H, OCH_3), 3.20 (dt, *J* = 10.6, 6.8 Hz, 1H, 1-H_a), 3.28 (dt, *J* = 10.6, 6.8 Hz, 1H, 1-H_b), 4.54 (dp, *J* = 10.1, 1.3 Hz, 1H, 4-H), 4.64−4.66 (m, 1H, 4-H), 5.21 (s, 2H, 4′-H, 5′-H), 7.17−7.27 (m, 20H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 17.9 (C-6), 20.8 (br, C-3), 25.8 (CH_3), 33.7 (C-2), 51.8 (OCH_3), 62.6 (C-1), 77.6 (C-4′, C-5′), 83.4 (CPh_2OCH_3), 124.5 (C-4), 127.2, 127.3, 127.5, 127.8, 128.5, 129.7 (arom. *C*H), 130.6 (C-5), 141.3, 141.4 (arom. C_{ipso}). IR (film) ν_{max} [cm^{-1}] = 3402, 3059, 2935, 1495, 1447, 1375, 1340, 1232, 1200, 1137, 1076, 1033, 967, 922, 901, 828, 795, 759, 733, 700. HRMS (ESI+, *m*/*z*): [M + Na]$^+$ calcd for $C_{37}H_{41}BO_5Na$, 599.2945; found, 599.2941.

*(3S,4′R,5′R)- and (3R,4′R,5′R)-N,N-Dimethyl-3-[4′,5′-bis(methoxydiphenylmethyl)-1′,3′,2′-dioxaborolan-2′-yl]-5-methylhex-4-enamide (**7** and **8**).* Into a two-neck round-bottom flask equipped with a Claisen condenser, allyl alcohol **3** (9.0 g, 16.41 mmol, 1.00 equiv) was dissolved in toluene (33 mL), and *N*,*N*-dimethylacetamide dimethy-

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lacetal (4.80 mL, 32.82 mmol, 2.00 equiv) was added under an atmosphere of dry nitrogen. The reaction mixture was heated to 80 °C for 36 h, while the formed MeOH was removed. The mixture was concentrated under reduced pressure, and the dr was shown to be 31:69 (measured via ^{1}H NMR). After flash column chromatography (petroleum ether/ethyl acetate 70:30), the two diastereomerically pure solid foams **7** and **8** (5.2 g, 8.4 mmol, 51%) were obtained, and 15% of the starting material **3** was recovered.

Allylboronate **7**: R_f = 0.20 (petroleum ether/ethyl acetate 70:30). $[\alpha]_D^{20}$ = −98.0 (*c* 0.5, $CHCl_3$). Melting point 123 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.26 (d, *J* = 1.1 Hz, 3H, CH_3), 1.44 (s, 3H, 6-H), 1.77 (dd, *J* = 14.1, 9.1 Hz, 1H, 2-H_a), 1.97 (dd, *J* = 14.8, 5.5 Hz, 1H, 2-H_b), 2.10 (ddd, *J* = 9.2, 5.5, 3.6 Hz, 1H, 3-H), 2.63 [s, 6H, N(CH_3)$_2$], 2.93 (s, 6H, OCH_3), 4.58 (dp, *J* = 9.6, 1.4 Hz, 1H, 4-H), 5.20 (s, 2H, 4′-H, 5′-H), 7.16−7.26 (m, 20H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 18.1 (C-6), 26.0 (*C*H_3), 31.0 (C-3), 33.5 (C-2), 35.4 (N*C*H_3), 37.4 (N*C*H_3), 51.7 (O*C*H_3), 78.0 (C-4′, C-5′), 83.4 (*C*Ph$_2$OCH$_3$), 124.1 (C-4), 127.2, 127.3, 127.5, 127.7, 128.6, 130.0 (arom. *C*H), 141.2, 141.3 (arom. C_{ipso}), 172.8 (C-1). IR (film) ν_{max} [cm^{-1}] = 3058, 2972, 2931, 2830, 1632, 1493, 1446, 1393, 1376, 1361, 1345, 1265, 1226, 1197, 1154, 1101, 1077, 1059, 1032, 1010, 1000, 972, 935, 899, 855, 816, 785, 755, 734, 716, 697. HRMS (ESI+, *m*/*z*): [M + H]$^+$ calcd for $C_{39}H_{45}BNO_5$, 618.3391; found, 618.3383. Anal. Calcd for $C_{39}H_{44}BNO_5$ (616.33125): C 75.85, H 7.18, N 2.27. Found: C 75.74, H 7.27, N 2.01.

Allylboronate **8**: R_f = 0.17 (petroleum ether/ethyl acetate 70:30). $[\alpha]_D^{20}$ = −99.0 (*c* 1.0, $CHCl_3$). Melting point 141 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.35 (d, *J* = 1.1 Hz, 3H, CH_3), 1.47 (d, *J* = 1.1 Hz, 3H, 6-H), 1.89−1.96 (m, 2H, 2-H), 2.10 (ddd, *J* = 10.0, 5.5, 4.1 Hz, 1H, 3-H), 2.74 [s, 6H, N(CH_3)$_2$], 2.90 (s, 6H, OCH_3), 4.50 (dp, *J* = 10.0, 1.4 Hz, 1H, 4-H), 5.21 (s, 2H, 4′-H, 5′-H), 7.17−7.28 (m, 20H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 18.0 (C-6), 26.0 (*C*H_3), 30.1 (C-3), 33.9 (C-2), 35.4 (N*C*H_3), 37.4 (N*C*H_3), 51.8 (O*C*H_3), 77.8 (C-4′, C-5′), 83.4 (*C*Ph$_2$OCH$_3$), 123.4 (C-4), 127.2, 127.3, 127.5, 128.0, 128.5, 129.7 (arom. CH), 141.3, 141.4 (arom. C_{ipso}), 172.8 (C-1). IR (film) ν_{max} [cm^{-1}] = 3058, 2972, 2931, 2830, 1635, 1493, 1446, 1377, 1346, 1231, 1076, 1032, 1010, 1000, 968, 833, 757, 712, 701. HRMS (ESI+, *m*/*z*): [M + H]$^+$ calcd for $C_{39}H_{45}BNO_5$, 618.3391; found, 618.3384. Anal. Calcd for $C_{39}H_{44}BNO_5$ (616.33125): C 75.85, H 7.18, N 2.27. Found: C 75.74, H 7.25, N 2.04.

Allyl Additions. *General Procedure A.* To a Schlenk-flask equipped with a magnetic stir bar and a septum, 50 mg of 5 Å MS (previously dried at 100 °C under high vacuum and stored in an oven) was added under an atmosphere of dry nitrogen. The flask was filled with allylboronic ester (1.00 equiv) and dry CH_2Cl_2 (0.5 mL per mmol of allylboronic ester). At 0 °C the aldehyde (1.50 equiv) was added, and the mixture was allowed to warm to room temperature overnight. After complete transformation of the allylboronic ester (as judged by TLC and ^{1}H NMR), the reaction mixture was concentrated under reduced pressure. The crude product was subjected to flash column chromatography on silica gel; no pressure was applied during separation to yield the pure allyl alcohol.

*(6S,3E)-6-Hydroxy-5,5-dimethyldodec-3-enoic Acid Dimethylamide (**9a**) and (6R,3E)-6-Hydroxy-5,5-dimethyldodec-3-enoic Acid Dimethylamide (**10a**).* According to general procedure A, allylboronic ester **7** or **8** (150 mg, 0.24 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (120 μL) and treated with heptanal (103 μL, 0.73 mmol, 3.00 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 8 days. After flash column chromatography (20 g of silica gel, petroleum ether/ethyl acetate 10:90) **9a** was isolated from **7** (15 mg, 0.06 mmol, 23%; 89% ee by HPLC) as a clear oil along with a 10% yield of a byproduct. With the same procedure, allyl alcohol **10a** (38 mg, 0.14 mmol, 60%; 83% ee by HPLC) was obtained as a colorless oil starting from **8**. R_f = 0.36 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ (**9a**) = −17.8 (*c* 1.5, $CHCl_3$); $[\alpha]_D^{20}$ (**10a**) = +13.0 (*c* 1.6, $CHCl_3$). HPLC (Chiralpak IC, 90% heptane/*i*-PrOH, flow rate 0.5 mL/min): t_R (**9a**) = 58.2 min, t_R (**10a**) = 63.8 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.9 Hz, 3H, 12-H), 0.99 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.21−1.33 (m, 8H, 8-H, 9-H, 10-H, 11-H), 1.47 (dddd, *J* = 13.3, 10.6, 4.6, 1.8 Hz, 1H, 7-H), 1.54 (ddd, *J* = 12.2, 6.4, 4.6 Hz, 1H, 7-H), 2.46 (br, 1H, O*H*), 2.96−2.97 (m, 6H, NCH_3), 3.11 (dd, *J* = 5.9, 3.8 Hz, 2H, 2-H), 3.20 (dd, *J* = 10.6, 1.8 Hz, 1H, 6-H), 5.50 (d, *J* = 16.0 Hz, 1H, 3-H), 5.52 (dt, *J* = 16.0, 6.1 Hz, 1H, 4-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.1 (C-12), 22.1 (*C*H_3), 22.7 (C-8), 27.1 (C-7), 29.4 (C-9), 31.4 (C-10), 31.9 (C-11), 37.7 (N*C*H_3), 37.7 (C-2), 41.2 (C-5), 78.4 (C-6), 121.9 (C-3), 141.0 (C-4), 171.7 (C-1). IR (film) ν_{max} [cm^{-1}] = 3434, 2927, 2857, 1736, 1635, 1466, 1398, 1264, 1217, 1124, 1064, 976. HRMS (ESI+, *m*/*z*): [M + H]$^+$ calcd for $C_{16}H_{32}NO_2$: 270.2433; found, 270.2427.

*(6S,3E)-9-[tert-Butyldimethylsilyl)oxy]-6-hydroxy-5,5-dimethyloct-3-enoic Acid Dimethylamide (**9b**) and (6R,3E)-9-[tert-Butyldimethylsilyl)oxy]-6-hydroxy-5,5-dimethyloct-3-enoic Acid Dimethylamide (**10b**).* According to general procedure A, allylboronic ester **7** or **8** (200 mg, 0.32 mmol) was dissolved in dry CH_2Cl_2 (160 μL) and treated with [*tert*-butyldimethylsilyl)oxy]propanal (91.5 mg, 0.49 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 11 days. Flash column chromatography (15 g of silica gel, petroleum ether/ethyl acetate 10:90) yielded slightly impure colorless oil **9b** (82 mg, 0.24 mmol, 75%; 83% ee by HPLC) starting from allylboronic ester **7** and clear oil **10b** (30 mg, 0.09 mmol, 27%; 80% ee by HPLC) starting from **8**. R_f = 0.34 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ (**9b**) = −7.4 (*c* 2.3, $CHCl_3$); $[\alpha]_D^{20}$ (**10b**) = +1.7 (*c* 0.9, $CHCl_3$). HPLC (Chiralcel OD-H, 90% heptane/*i*-PrOH, flow rate 0.5 mL/min): t_R (**9b**) = 27.1 min, t_R (**10b**) = 29.2 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.00 [s, 6H, (CH_3)$_2$Si], 0.83 [s, 9H, (C*H*)$_3$CSi], 0.95 (s, 6H, CH_3), 0.96 (s, 6H, CH_3), 1.46 (tdd, *J* = 14.3, 10.2, 1.3 Hz, 2H, 7-H_a), 1.58 (tdd, *J* = 14.3, 10.2, 1.3 Hz, 2H, 7-H_b), 2.88 (s, 3H, NCH_3), 2.94 (s, 3H, NCH_3), 3.04−3.05 (m, 2H, 2-H), 3.42 (dd, *J* = 10.3, 1.3 Hz, 2H, 6-H), 3.72 (ddd, *J* = 13.4, 9.2, 4.7 Hz, 2H, 8-H_a), 3.80 (dd, *J* = 10.3, 4.7 Hz, 2H, 8-H_b), 5.45−5.52 (m, 2H, 3-H, 4-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 0.00 [Si(*C*H_3)$_2$], 26.5 (*C*H_3), 29.6 (*C*H_3), 31.4 [*C*(*C*H_3)$_3$], 37.8 (C-7), 41.1 (N*C*H_3), 42.7 (C-2), 42.8 (N*C*H_3), 46.5 (C-5), 68.0 (C-8), 84.0 (C-6), 128.0 (C-3), 146.7 (C-4), 177.3 (C-1). IR (film) ν_{max} [cm^{-1}] = 3337, 2926, 1722, 1621, 1497, 1457, 1403, 1376, 1259, 1128, 1078, 966, 832, 698. HRMS (ESI+, *m*/*z*): [M + H]$^+$ calcd for $C_{18}H_{38}NO_3Si$, 344.2621; found, 344.2617; [M + Na]$^+$ calcd for $C_{18}H_{37}NO_3SiNa$, 366.2440; found, 366.2436.

*(6S,3E)-6-Hydroxy-5,5-dimethyl-8-phenyloct-3-enoic Acid Dimethylamide (**9c**).* According to general procedure A, 3-phenylpropanal (37.5 μL, 0.29 mmol) was added to allylboronic ester **7** (120 mg, 0.19 mmol) in dry CH_2Cl_2 (100 μL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 8 days. After column chromatography (10 g of silica gel, petroleum ether/ethyl acetate 10:90) colorless oil **9c** (44 mg, 0.15 mmol, 80%; 90% ee by HPLC) was obtained. R_f = 0.36 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ = −21.3 (*c* 0.7, $CHCl_3$). HPLC (Chiralcel OD-H, 90% heptane/*i*-PrOH, flow rate 0.5 mL/min): t_R (**9c**) = 20.4 min, t_R (**10c**) = 27.5 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.09 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.64 (dddd, *J* = 13.9, 10.5, 4.9, 1.8 Hz, 1H, 7-H_a), 1.90 (dddd, *J* = 13.9, 10.5, 6.9, 1.8 Hz, 1H, 7-H_b), 2.36 (br, 1H, O*H*), 2.69 (ddd, *J* = 13.9, 6.8, 2.8, Hz, 1H, 8-H_a), 3.00−3.05 (m, 1H, 8-H_b), 3.03 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3), 3.18 (ddd, *J* = 15.8, 6.4, 1.2 Hz, 2H, 2-H), 3.34 (dd, *J* = 10.6, 1.8 Hz, 1H, 6-H), 5.56 (dt, *J* = 15.8, 1.2 Hz, 1H, 3-H), 5.64 (dt, *J* = 15.8, 6.4 Hz, 1H, 4-H), 7.25−7.38 (m, 5H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 22.0 (*C*H_3), 24.1 (*C*H_3), 33.4 (C-7, C-8), 35.7 (N*C*H_3), 37.4 (N*C*H_3), 37.6 (C-2), 41.3 (C-5), 77.6 (C-6), 122.4 (C-3), 125.8, 128.4, 128.6 (arom. *C*H), 141.0 (C-4), 142.7 (arom. C_{ipso}), 171.7 (C-1). IR (film) ν_{max} [cm^{-1}] = 3408, 2924, 2851, 1724, 1636, 1494, 1451, 1398, 1262, 1140, 1044, 976, 701. HRMS (ESI+, *m*/*z*): [M + H]$^+$ calcd for $C_{18}H_{28}NO_2$, 290.2120; found, 290.2114; [M + Na]$^+$ calcd for $C_{18}H_{27}NO_2Na$, 312.1940; found, 312.1935.

*(6R,3E)-6-Hydroxy-5,5-dimethyl-8-phenyloct-3-enoic Acid Dimethylamide (**10c**) and (6R,3Z)-6-Hydroxy-5,5-dimethyl-8-phenyloct-3-enoic Acid Dimethylamide (**12c**).* According to general procedure A, allylboronic ester **8** (150 mg, 0.24 mmol) was allowed to react with 3-phenylpropanal (48.4 μL, 0.36 mmol) in dry CH_2Cl_2 (120 μL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 10 days. After column chromatography (18 g of silica

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gel, petroleum ether/ethyl acetate 30:70), the mixture of diastereomers **10c** and **12c** (43 mg, 0.15 mmol, 61%, dr = 91:9) was isolated as a colorless oil, and starting material **8** (53 mg, 0.09 mmol, 35%) was recovered. Analytically pure **10c** (38 mg, 0.13 mmol, 55%; 77% ee by HPLC) and slightly impure **12c** (4 mg, 0.01 mmol, 6%) were obtained after column chromatography (15 g of silica gel, petroleum ether/ethyl acetate 10:90).

Thermal Conditions I. In a 10 mL Schlenk flask, allylboronate **8** (150 mg, 0.24 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (120 μL), and 3-phenylpropanal (48.4 μL, 0.36 mmol, 1.50 equiv) was added at 0 °C. The reaction mixture was stirred at 0 °C for 5 h and then at 40 °C for 10 days until ^{1}H NMR monitoring showed the consumption of all starting material. Column chromatography (15 g of silica gel, petroleum ether/ethyl acetate 10:90) afforded clear oil **10c** (19 mg, 0.07 mmol, 28%; 80% ee by HPLC).

Thermal Conditions II. In a 10 mL Schlenk flask, allylboronate **8** (150 mg, 0.24 mmol, 1.00 equiv) was dissolved in dry CH_2Cl_2 (120 μL) and 3-phenylpropanal (48.4 μL, 0.36 mmol, 1.50 equiv) was added at 0 °C. The reaction mixture was stirred at 0 °C for 5 h and then at 60 °C for 8 days until ^{1}H NMR monitoring showed the consumption of all starting material. Column chromatography (15 g of silica gel, petroleum ether/ethyl acetate, 10:90) yielded clear oil **10c** (20 mg, 0.07 mmol, 29%; 75% ee by HPLC).

$[\alpha]_D^{20}$ (**10c**) = +13.7 (*c* 2.7, $CHCl_3$). The spectroscopic data for **10c** were in full agreement with those described for **9c**.

The *Z* diastereomer **12c** (4 mg, 0.01 mmol, 6%) was isolated after column chromatography (18 g of silica gel, petroleum ether/ethyl acetate 10:90) as slightly impure colorless oil. R_f = 0.43 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ (**12c**) = −16.3 (*c* 0.3, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.09 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.63 (ddd, *J* = 13.5, 10.2, 4.8 Hz, 1H, 7-H_a), 1.77−1.84 (m, 1H, 7-H_b), 2.60−2.71 (m, 1H, 8-H_a), 2.93−2.97 (m, 1H, 8-H_b), 2.97 (s, 3H, NCH_3), 3.01 (s, 3H, NCH_3), 3.26 (d, *J* = 7.5 Hz, 2H, 2-H), 3.32 (d, *J* = 10.7, 1H, 6-H), 5.43 (d, *J* = 12.3 Hz, 1H, 3-H), 5.52 (dt, *J* = 12.3, 7.5 Hz, 1H, 4-H), 7.16−7.30 (m, 5H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 24.1 (CH_3), 25.9 (CH_3), 32.7 (C-7), 33.1 (C-8), 33.2 (C-2), 35.8 (NCH_3), 37.4 (NCH_3), 42.1 (C-5), 77.4 (C-6), 123.2 (C-3), 125.6, 128.3, 128.6 (arom. *C*H), 139.7 (C-4), 142.7 (arom. C_{ipso}), 171.9 (C-1). IR (film) ν_{max} [cm^{-1}] = 3418, 2926, 2851, 1722, 1634, 1497, 1453, 1393, 1276, 1261, 1143, 1034, 764, 751. HRMS (ESI+, *m*/*z*): $[M + H]^+$ calcd for $C_{18}H_{28}NO_2$, 290.2120; found, 290.2115; $[M + Na]^+$ calcd for $C_{18}H_{27}NO_2Na$, 312.1939; found, 312.1934.

*(6R,3E)-6-Hydroxy-5,5-dimethyl-6-phenylhex-3-enoic Acid Dimethylamide (**9d**) and (6S,3E)-6-Hydroxy-5,5-dimethyl-6-phenylhex-3-enoic Acid Dimethylamide (**10d**).* According to general procedure A, allylboronic ester **7** or **8** (160 mg, 0.26 mmol) was dissolved in dry CH_2Cl_2 (130 μL) and treated with benzaldehyde (39.5 μL, 0.39 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 7 days. Flash column chromatography (12 g of silica gel, petroleum ether/ethyl acetate 30:70 → 10:90) yielded analytically pure colorless oil **9d** (58 mg, 0.22 mmol, 85%; >99% ee by HPLC) starting from allylboronic ester **7** and clear oil **10d** (56 mg, 0.21 mmol, 82%; 95% ee by HPLC) starting from **8**. R_f = 0.18 (petroleum ether/ethyl acetate 30:70), 0.31 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ (**9d**) = +72.5 (*c* 1.36, $CHCl_3$); $[\alpha]_D^{20}$ (**10d**) = −72.5 (*c* 0.9, $CHCl_3$). HPLC (Chiralcel OD-H, 90% heptane/*i*-PrOH, flow rate 0.5 mL/min): t_R (**9d**) = 25.3 min, t_R (**10d**) = 29.8 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.93 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.33 (br, 1H, O*H*), 2.93 (s, 3H, NCH_3), 2.98 (s, 3H, NCH_3), 3.06−3.13 (m, 2H, 2-H), 4.37 (s, 1H, 6-H), 5.53−5.59 (m, 2H, 3-H, 4-H), 7.21−7.27 (m, 5H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.6 (CH_3), 25.0 (CH_3), 35.7 (NCH_3), 37.5 (NCH_3), 37.7 (C-2), 41.9 (C-5), 80.9 (C-6), 122.8 (C-3), 127.4, 127.5, 128 (arom. *C*H), 140.7 (C-4), 141.1 (arom. C_{ipso}), 171.6 (C-1). IR (film) ν_{max} [cm^{-1}] = 3377, 2922, 2856, 1735, 1635, 1492, 1451, 1401, 1373, 1264, 1044, 703. HRMS (ESI+, *m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{24}NO_2$, 262.1807; found, 262.1802; $[M + Na]^+$ calcd for $C_{16}H_{23}NO_2Na$, 284.1627; found, 284.1621.

*(6S,3E)-6-(3,4-Difluorophenyl)-6-hydroxy-5,5-dimethylhex-3-enoic Acid Dimethylamide (**9e**) and (6R,3E)-6-(3,4-Difluorophenyl)-6-hydroxy-5,5-dimethylhex-3-enoic Acid Dimethylamide (**10e**).* According to general procedure A, allylboronic ester **7** or **8** (150 mg, 0.24 mmol) was dissolved in dry CH_2Cl_2 (80 μL) and treated with 3,4-difluorobenzaldehyde (39.7 μL, 0.36 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 5 days. Flash column chromatography (10 g of silica gel, petroleum ether/ethyl acetate 10:90) yielded analytically pure clear oil **9e** (58 mg, 0.19 mmol, 81%; 98% ee by HPLC) starting from allylboronic ester **7** and clear oil **10e** (61 mg, 0.20 mmol, 85%; 98% ee by HPLC) starting from **8**. R_f = 0.34 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ (**9e**) = +49.9 (*c* 1.8, $CHCl_3$); $[\alpha]_D^{20}$ (**10e**) = −54.5 (*c* 1.8, $CHCl_3$). HPLC (Chiralcel OD-H, 96% heptane/*i*-PrOH, flow rate 0.5 mL/min): t_R (**9e**) = 64.9 min, t_R (**10e**) = 70.2 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 2.89 (s, 3H, NCH_3), 2.96 (s, 3H, NCH_3), 2.99−3.08 (m, 2H, 2-H), 4.27 (s, 1H, 6-H), 5.44 (d, *J* = 16.0 Hz, 1H, 3-H), 5.53 (dt, *J* = 16.0, 6.5 Hz, 1H, 4-H), 6.90−7.10 (m, 3H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.0 (CH_3), 24.9 (CH_3), 35.7 (NCH_3), 37.2 (NCH_3), 37.2 (C-2), 41.8 (C-5), 89.4 (C-6), 115.9, 116.5 (arom. *C*H), 123.4 (C-3), 123.8 (arom. *C*H), 140.2 (C-4), 171.5 (C-1). IR (film) ν_{max} [cm^{-1}] = 3383, 2964, 2871, 2856, 1725, 1626, 1514, 1471, 1431, 1400, 1276, 1206, 1112, 1052, 978, 878, 823, 770, 751. HRMS (ESI+, *m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{22}NO_2F_2$, 298.1619; found, 298.1612; $[M + Na]^+$ calcd for $C_{16}H_{21}NO_2F_2Na$, 320.1438; found, 320.1432.

*(6R,3E)-6-Hydroxy-5,5-dimethyl-6-(thiazol-2-yl)hex-3-enoic Acid Dimethylamide (**9f**) and (6S,3E)-6-Hydroxy-5,5-dimethyl-6-(thiazol-2-yl)hex-3-enoic Acid Dimethylamide (**10f**).* According to general procedure A, allylboronic ester **7** (150 mg, 0.24 mmol) was dissolved in dry CH_2Cl_2 (120 μL) and treated with 1,3-thiazole-2-carbaldehyde (31.7 μL, 0.36 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 11 days until ^{1}H NMR showed complete consumption of allylboronate. Flash column chromatography (20 g of silica gel, petroleum ether/ethyl acetate 30:70 → 10:90) yielded analytically pure colorless oil **9f** (47 mg, 0.18 mmol, 73%; >99% ee by HPLC). According to general procedure A, allylboronic ester **8** (150 mg, 0.24 mmol) was dissolved in dry CH_2Cl_2 (120 μL) and treated with 1,3-thiazole-2-carbaldehyde (31.7 μL, 0.36 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 5 days. Chromatography (20 g of silica gel, petroleum ether/ethyl acetate 30:70 → 10:90) furnished **10f** (45 mg, 0.17 mmol, 70%; >99% ee by HPLC) as a clear oil. R_f = 0.22 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ (**9f**) = +46.2 (*c* 0.9, $CHCl_3$); $[\alpha]_D^{20}$ (**10f**) = −45.7 (*c* 1.2, $CHCl_3$). HPLC (Chiralcel OD-H, 90% heptane/*i*-PrOH, flow rate 0.5 mL/min): t_R (**9f**) = 31.5 min, t_R (**10f**) = 25.8 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.97 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.93 (br, 1H, O*H*), 2.88 (s, 3H, NCH_3), 2.94 (s, 3H, NCH_3), 3.00−3.11 (m, 2H, 2-H), 4.65 (s, 1H, 6-H), 5.51−5.60 (m, 2H, 3-H, 4-H), 7.21 (dq, *J* = 3.3, 1.5 Hz, 1H, arom. C*H*), 7.65 (dd, *J* = 3.3, 1.5 Hz, 1H, arom. C*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.8 (CH_3), 24.0 (CH_3), 35.6 (NCH_3), 37.4 (C-2), 42.1 (C-5), 78.2 (C-6), 118.9 (arom. *C*H), 123.7 (C-3), 139.8 (C-4), 141.4 (arom. *C*H), 171.5 (C-1), 172.1 (arom. *C*). IR (film) ν_{max} [cm^{-1}] = 3317, 2963, 2929, 1731, 1623, 1498, 1465, 1399, 1263, 1131, 1048, 976, 896, 781, 728. HRMS (ESI+, *m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{21}N_2O_2S$, 269.1324; found, 269.1318.

*(6R,3E)-Ethyl 6-(Dimethylamino)-2-hydroxy-5,5-dimethyl-7-oxohept-4-enoate (**9g**) and (6S,3E)-Ethyl 6-(Dimethylamino)-2-hydroxy-5,5-dimethyl-7-oxohept-4-enoate (**10g**).* According to general procedure A, allylboronic ester **7** (150 mg, 0.24 mmol) was dissolved in dry CH_2Cl_2 (120 μL) and treated with ethyl glyoxylate (36.1 μL, 0.36 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and 11 days at room temperature until ^{1}H NMR showed complete consumption of allylboronate. Flash column chromatography (20 g of silica gel, petroleum ether/ethyl acetate 10:90) afforded pure colorless oil **9g** (55 mg, 0.21 mmol, 90%; 98% ee by HPLC). According to general procedure A, allylboronic ester **8** (150 mg, 0.24 mmol) was dissolved in dry CH_2Cl_2 (120 μL) and treated with ethyl glyoxylate (36.1 μL, 0.36 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 5 days, at which point ^{1}H NMR showed complete consumption of allylboronate. Chromatography (20 g of silica gel, petroleum ether/ethyl acetate 10:90) afforded

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enantiomerically pure **10g** (55 mg, 0.21 mmol, 90%; 98% ee by HPLC) as a clear oil. R_f = 0.14 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ (**9g**) = −9.8 (*c* 2.8, $CHCl_3$); $[\alpha]_D^{20}$ (**10g**) = +11.5 (*c* 3.6, $CHCl_3$). HPLC (Chiralcel OD-H, 80% heptane/*i*-PrOH, flow rate 0.5 mL/min): t_R (**9g**) = 15.7 min, t_R (**10g**) = 12.1 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.03 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.22 (t, *J* = 7.2 Hz, 3H, 2′-H), 2.88 (s, 3H, NCH_3), 2.94 (s, 3H, NCH_3), 3.02−3.07 (m, 2H, 2-H), 3.77 (s, 1H, 6-H), 4.15 (dddd, *J* = 17.9, 10.8, 7.1, 3.6 Hz, 2H, 1′-H), 5.48 (d, *J* = 15.9 Hz, 1H, 3-H), 5.53 (dt, *J* = 15.9, 6.4 Hz, 1H, 4-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.3 (C-2′), 23.5 (CH_3), 23.8 (CH_3), 35.5 (NCH_3), 37.4 (NCH_3), 37.8 (C-2), 40.8 (C-5), 61.3 (C-1′), 77.7 (C-6), 122.5 (C-3), 138.2 (C-4), 171.3 (C-1), 173.6 (C-7). IR (film) ν_{max} [cm^{-1}] = 3392, 2962, 2933, 1734, 1632, 1502, 1464, 1400, 1262, 1176, 1094, 1027, 976. HRMS (ESI+, *m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{24}NO_4$, 258.1705; found, 258.1700; $[M + Na]^+$ calcd for $C_{13}H_{23}NO_4Na$, 280.1520; found, 280.1525.

*(6S,3E)-6-Hydroxy-7-(4″-methoxybenzyloxy)-5,5-dimethylhept-3-enoic Acid Dimethylamide (**9h**) and (6R,3E)-6-Hydroxy-7-(4″-methoxybenzyloxy)-5,5-dimethylhept-3-enoic Acid Dimethylamide (**10h**).* According to general procedure A, allylboronic ester **7** or **8** (100 mg, 0.16 mmol) was dissolved in dry CH_2Cl_2 (80 μL) and treated with 2-(4-methoxybenzyloxy)acetaldehyde (43.8 mg, 0.24 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at room temperature for 14 days. Flash column chromatography (10 g of silica gel, petroleum ether/ethyl acetate 10:90) yielded analytically pure colorless oil **9h** (10 mg, 0.03 mmol, 19%; 82% ee by HPLC) starting from allylboronic ester **7** and clear oil **10h** (27 mg, 0.08 mmol, 50%; 57% ee by HPLC) starting from **8**. R_f = 0.19 (petroleum ether/ethyl acetate 10:90). $[\alpha]_D^{20}$ (**9h**) = −26.6 (*c* 1.1, $CHCl_3$); $[\alpha]_D^{20}$ (**10h**) = +4.6 (*c* 2.0, $CHCl_3$). HPLC (Chiralpak IC, 90% heptane/*i*-PrOH, flow rate 0.5 mL/min): t_R (**9h**) = 45.9 min, t_R (**10h**) = 42.1 min. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.96 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.87 (s, 3H, NCH_3), 2.90 (s, 3H, NCH_3), 3.01−3.03 (m, 2H, 2-H), 3.24 (dt, *J* = 9.8, 5.2 Hz, 2H, 6-H), 3.46−3.51 (m, 2H, 7-H), 3.74 (s, 3H, OCH_3), 4.39 (s, 2H, 1′-H), 5.44−5.54 (m, 2H, 3-H, 4-H), 6.79−6.84 (m, 2H, arom. CH), 7.16−7.20 (m, 2H, arom. CH). ^{13}C NMR (151 MHz, $CDCl_3$): δ 23.5 (CH_3), 23.6 (CH_3), 35.5 (NCH_3), 37.3 (NCH_3), 37.9 (C-2), 39.3 (C-5), 55.3 (OCH_3), 71.2 (C-6), 73.0 (C-1′), 76.7 (C-7), 113.8 (C-3″), 121.3 (C-3), 129.3 (C-2″), 130.1 (C-1″), 139.7 (C-4), 159.2 (C-4″), 171.4 (C-1). IR (film) ν_{max} [cm^{-1}] = 3428, 2957, 2931, 2861, 1634, 1514, 1465, 1400, 1300, 1248, 1173, 1103, 1027, 979, 820. HRMS (ESI+, *m*/*z*): $[M + H]^+$ calcd for $C_{19}H_{30}NO_4$, 336.2169; found, 336.2175; $[M + Na]^+$ calcd for $C_{19}H_{29}NO_4Na$, 358.1994; found, 358.1989.

Determination of Configuration. *(1R)-2,2-Dimethyl-1-phenylpropane-1,3-diol (**13**).* In a flask equipped with a Teflon stopcock and gas inlet frit (Quickfit with Teflon gasket), homoallylic alcohol **10e** (10 mg, 40 μmol, 1.00 equiv) was dissolved in CH_2Cl_2 (20 mL) and cooled to −78 °C. An O_3/O_2 mixture was bubbled through the solution until it was a persistent blue color (8 min). Excess O_3 was expelled by a stream of O_2. Me_2S (0.4 mL) was added to the reaction mixture, which was allowed to warm to room temperature. The solvent was removed under reduced pressure. The residue was dissolved in THF (5 mL), and $LiAlH_4$ (41.2 μL, 0.99 mmol, 26.00 equiv) was added at −78 °C. After 1 h, the mixture was diluted with Et_2O and cooled to 0 °C, and H_2O (50 μL), 15% aqueous NaOH (50 μL), H_2O (200 μL) were carefully added. The mixture was stirred for 30 min and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and subjected to flash column chromatography (2 g of silica gel, *n*-pentane/ethyl acetate 20:10) to yield **13** (5 mg, 30 μmol, 74%) as a clear oil. The spectroscopic data were in full agreement with those reported in the literature.[67] $[\alpha]_D^{20}$ = −40.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.79 (s, 3H, CH_3), 0.82 (s, 3H, CH_3) 2.45 (br, 1H, OH), 3.45 (d, *J* = 10.8 Hz, 1H, 3-H), 3.53 (d, *J* = 10.8 Hz, 1H, 3-H), 4.60 (s, 1H, 1-H), 7.19−7.27 (m, 5H, arom. CH). ^{13}C NMR (151 MHz, $CDCl_3$): δ 19.0 (CH_3), 22.7 (CH_3), 39.2 (C-2), 72.1 (C-3), 82.2 (C-1), 127.6 (arom. CH), 127.8 (arom. CH), 141.5 (arom. C). HRMS (ESI+, *m*/*z*): $[2M + H]^+$ calcd for $C_{22}H_{33}O_4$, 361.2379; found, 361.2372.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all isolated products and X-ray structural analyses of compounds **3**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Roush, W. R. In *Stereoselective Synthesis*, 3rd ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, Germany, 1996; Vol. *E21*, pp 1410−1486.
(2) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 299−402.
(3) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 403−490.
(4) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123.
(5) Matteson, D. S. *Stereodirected Synthesis with Organoborones*; Springer: Berlin, 1995.
(6) (a) *Boronic Acids*; Hall, D. G, Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 241−277. (b) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *73*, 3.
(7) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
(8) (a) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 306. (b) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309.
(9) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868. (c) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.
(10) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (c) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.
(11) (a) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (b) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878.
(12) (a) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044. (b) Canales, E.; Prasad, G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572.
(13) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.
(14) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065.
(15) Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc.* **1982**, *104*, 2330.
(16) Tsai, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236.
(17) (a) Hoffmann, R. W.; Weidmann, U. *J. Organomet. Chem.* **1980**, *195*, 137. (b) Hoffmann, R. W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903.
(18) (a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (b) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.
(19) Stürmer, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 59.
(20) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686.

(21) Deligny, M.; Carreaux, F.; Toupet, L.; Carboni, B. *Adv. Synth. Catal.* **2003**, *345*, 1215.
(22) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308.
(23) Touchet, S.; Macé, A.; Roisnel, T.; Carreaux, F.; Bouillon, A.; Carboni, B. *Org. Lett.* **2013**, *15*, 2712.
(24) Macé, A.; Tripoteau, F.; Zhao, Q.; Gayon, E.; Vrancken, E.; Campagne, J.-M.; Carboni, B. *Org. Lett.* **2013**, *15*, 906.
(25) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9.
(26) Bubnov, Y. N.; Gurskii, M. E.; Gridnev, I. D.; Ignatenko, A. V.; Ustynyuk, Y. A.; Mstislavsky, V. I. *J. Organomet. Chem.* **1992**, *424*, 127.
(27) (a) Hoffmann, R. W.; Landmann, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 437. (b) Review: Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123.
(28) (a) Flamme, E. F.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644. (b) Hicks, J. D.; Flamme, E. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509. (c) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 4315.
(29) González, A. Z.; Román, J. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1269.
(30) Vaultier, M.; Truchet, F.; Carboni, B. *Tetrahedron Lett.* **1987**, *28*, 4169.
(31) Renard, P.; Lallemand, J. *Tetrahedron: Asymmetry* **1996**, *7*, 2523.
(32) Tailor, J.; Hall, D. G. *Org. Lett.* **2000**, *2*, 3715.
(33) Zhang, A.; Kan, Y.; Jiang, B. *Tetrahedron* **2001**, *57*, 2305.
(34) (a) Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczk-Lesanko, A.; Hall, D. G. *Chem.—Eur. J.* **2003**, *9*, 466. (b) Gao, X.; Hall, D. G.; Deligny, M.; Favre, A.; Carreaux, F.; Carboni, B. *Chem.—Eur. J.* **2006**, *12*, 3132. (c) Carosi, L.; Hall, D. G. *Can. J. Chem.* **2009**, *87*, 650.
(35) Chen, J. L.-Y.; Scott, K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 5316.
(36) (a) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, 2275. (b) Beckmann, E.; Hoppe, D. *Synthesis* **2005**, 217.
(37) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328.
(38) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034.
(39) (a) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505. (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74.
(40) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856.
(41) (a) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913. (b) Peng, F.; Hall, D. G. *Tetrahedron Lett.* **2007**, *48*, 3305.
(42) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 359.
(43) Berrée, F.; Gernigon, N.; Hercouet, A.; Lin, C. H.; Carboni, B. *Eur. J. Org. Chem.* **2009**, 329.
(44) (a) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612. (b) Ding, J.; Lee, J. C. H.; Hall, D. G. *Org. Lett.* **2012**, *14*, 4462.
(45) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586.
(46) Ishiyama, T.; Ahiko, T.-a. *J. Am. Chem. Soc.* **2002**, *124*, 12414.
(47) (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (b) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (c) Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004**, *8*, 1290. (d) Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426.
(48) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.
(49) (a) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913. Review: (b) Hall, D. G. *Synlett* **2007**, 1644. (c) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236.
(50) Sakata, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12519.
(51) Unfortunately, all attempts to use Lewis acids to catalyze aldehyde additions with '**diol**'-derived allylboronates were unsuccessful and led to the decomposition of the starting material: Pietruszka, J.; Schöne, N. Unpublished results.
(52) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025.
(53) Nakayama, K.; Rainer, J. D. *Tetrahedron* **1990**, *46*, 4165.
(54) (a) Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287. (b) Bischop, M.; Cmrecki, V.; Ophoven, V.; Pietruszka, J. *Synthesis* **2008**, 2488.
(55) (a) Pietruszka, J.; Schöne, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5638. (b) Pietruszka, J.; Schöne, N. *Eur. J. Org. Chem.* **2004**, 5011. (c) Pietruszka, J.; Schöne, N. *Synthesis* **2006**, 24.
(56) (a) Pietruszka, J.; Rieche, A. C. M. *Adv. Synth. Catal.* **2008**, *350*, 1407. (b) Pietruszka, J.; Schöne, N.; Frey, W.; Grundl, L. *Chem.—Eur. J.* **2008**, *14*, 5178.
(57) Cmrecki, V.; Eichenauer, N. C.; Frey, W.; Pietruszka, J. *Tetrahedron* **2010**, *66*, 6550.
(58) Fernández, E.; Pietruszka, J.; Frey, W. *J. Org. Chem.* **2010**, *75*, 5580.
(59) (a) Böse, D.; Fernández, E.; Pietruszka, J. *J. Org. Chem.* **2011**, *76*, 3463. (b) Bartlett, S.; Böse, D.; Ghori, D.; Mechsner, B.; Pietruszka, J. *Synthesis* **2013**, *45*, 1106.
(60) Berg, A.; Eichenauer, N.; Pietruszka, J. *Pure Appl. Chem.* **2012**, *84*, 2339.
(61) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 1039.
(62) (a) Hoffmann, R. W.; Landmann, B. *Tetrahedron Lett.* **1983**, *24*, 3209. (b) Hoffmann, R. W.; Dresely, S. *Angew. Chem., Int. Ed.* **1986**, *25*, 189. (c) Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, 103. (d) Beckmann, E.; Hoppe, D. *Synthesis* **2005**, 217. (e) Andersen, M. W.; Hildebrandt, B.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 97. (f) Hoffmann, R. W.; Rohde, T.; Haeberlin, E.; Schafer, F. *Org. Lett.* **1999**, *1*, 1713.
(63) Wender, P. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 9228.
(64) Bielitza, M.; Pietruszka, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10960.
(65) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894.
(66) Li, Y.; Houk, N. *J. Am. Chem. Soc.* **1989**, *111*, 1236.
(67) Hulst, R.; Zijlstra, R. W. J.; Koen de Vries, N.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 1701.
(68) Shepard, M. S.; Carreira, E. M. *Tetrahedron* **1997**, *53*, 16253.