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Copper(I)-Catalyzed Enantioselective Synthesis of α-Chiral Linear or Carbocyclic (*E*)-(γ-Alkoxyallyl)boronates

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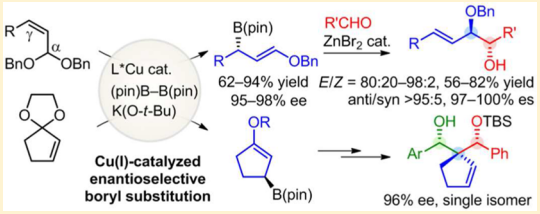
Supporting Information

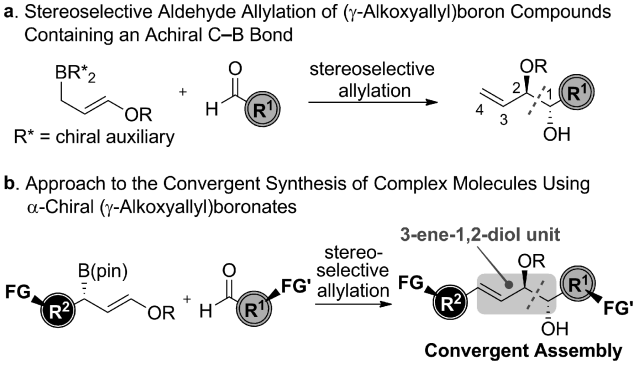
ABSTRACT: A new method has been developed for the catalytic asymmetric synthesis of α-chiral linear or carbocyclic (γ-alkoxyallyl)-boronates via the copper(I)-catalyzed γ-boryl substitution of allyl acetals. This reaction afforded the products in high yields with excellent *E*:*Z* selectivities and enantioselectivities [only (*E*)-product, 91−98% ee] and also exhibited high functional group compatibility. Subsequent allylation of aldehydes with the α-chiral (γ-alkoxyallyl)boronates provided the *anti*-1,2-diol derivatives in a highly stereospecific manner, and the utility of the α-chiral (γ-alkoxyallyl)boronates was further demonstrated by a convergent coupling of a complex polyol derivative using a (γ-alkoxyallyl)boronate and a chiral α-oxyaldehyde. The stereoselective modular construction of a complex 3,3-disubstituted cyclopentene containing three consecutive stereocenters including a quaternary chiral carbon was also reported. Useful transformations of the α-chiral linear (γ-alkoxyallyl)boronates were also demonstrated.



INTRODUCTION

The chiral 1,2-diol structure is important and is often found in natural products such as carbohydrates and polyketides.[1] Consequently, stereoselective coupling reactions constructing chiral 1,2-diol motifs with concurrent C−C bond formation between two functionalized synthetic fragments can be powerful tools for the efficient convergent synthesis of the complex polyols containing multiple stereocenters.[2] Addition reactions of enantioenriched γ-alkoxyallyl organometallic reagents to a carbonyl compound have been employed for the construction of the stereodefined 3-ene-1,2-diol structure with a concomitant C−C bond formation, and the double bond in the product can be further utilized through a number of selective functionalization reactions.[2n,o,3,4] Among the γ-alkoxyallyl organometallic reagents, (γ-alkoxyallyl)boron compounds are commonly used as versatile reagents for asymmetric synthesis because they react both reliably and predictably, exhibiting high levels of stability under atmospheric conditions and low toxicity.[5] Following from the initial studies of Hoffmann[6] and Wuts,[7] the stereoselective allylation of aldehydes with (γ-alkoxyallyl)boron compounds[8] has been used for the synthesis of polyoxygenated natural products and pharmaceuticals.[9] (γ-Borylallyl)- or (γ-silylallyl)boron compounds were also reported as flexible alternative reagents for the reaction.[10] In most cases, these reactions involve (γ-alkoxyallyl)boron compounds bearing an achiral primary C−B bond with a chiral boron auxiliary, which give 1,2-diol derivatives containing a terminal alkene moiety via aldehyde allylation (Scheme 1a). Although these known enantioenriched (γ-alkoxyallyl)boron compounds are highly useful, the boron compounds lack the substituent at the α-position and need a stoichiometric chiral auxiliary to construct the stereodefined 3-ene-1,2-diol unit after the aldehyde allylation step.

Scheme 1. Convergent Synthesis of Complex Molecules Bearing 3-Ene-1,2-diol Structures Using Aldehyde Allylation with α-Chiral (γ-Alkoxyallyl)boronates



In contrast, aldehyde allylation involving α-chiral (*E*)- or (*Z*)-(γ-alkoxyallyl)boronates affords stereodefined *anti*- or *syn*-1,2-diols containing an internal alkene moiety, the stereochemistry of which is controlled by the chiral C−B bond structure without the use of a chiral auxiliary.[11,12] This aldehyde allylation of the boronates is expected to be suitable for the convergent synthesis of complex molecules containing 3-ene-1,2-diol structures; it can make a new linkage between the functionalized fragments of the boronate and aldehyde moieties through the stereodefined 3-ene-1,2-diol unit in a highly stereospecific

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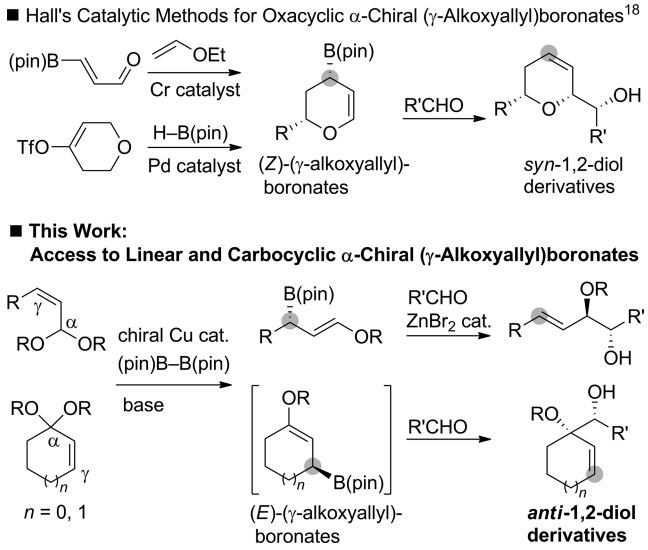
manner (Scheme 1b). However, only a few synthetic methods are available for the asymmetric construction of α-chiral (γ-alkoxyallyl)boronates. In addition, synthetic methods for other related optically active α-chiral γ-alkoxyallyl organometallic reagents such as organostannane[13] or organosilane[14] compounds are also limited. Hall et al. developed two catalytic methods for the construction of the boronates, including a Cr(III)-catalyzed enantioselective inverse electron demand hetero-[4 + 2] reaction[15a] and a Pd-catalyzed enantioselective boryl substitution[15b] (Scheme 2). Furthermore, the utility of

Scheme 2. Enantioselective Synthesis of α-Chiral (γ-Alkoxyallyl)boronates and Subsequent Aldehyde Allylation



these chiral boronates was demonstrated in the synthesis of highly oxygenated natural products[16] such as thiomarinol. These approaches, however, are limited to six-membered ring oxacyclic (Z)-(γ-alkoxyallyl)boronates. To the best of our knowledge, there have been no reports in the literature pertaining to the catalytic asymmetric synthesis of α-chiral linear or carbocyclic (γ-alkoxyallyl)boronates to date, and the development of an effective method for their synthesis is therefore highly desirable.

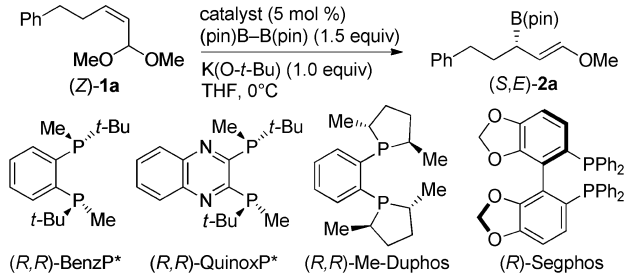
Herein, we report a novel approach to enantioenriched α-chiral linear or carbocyclic (E)-(γ-alkoxyallyl)boronates via the copper(I)/chiral bisphosphine-catalyzed γ-boryl substitution of allyl acetals and the subsequent conversion of these boronates to the corresponding *anti*-1,2-diol derivatives, which are generally more difficult to prepare than *syn*-1,2-diol derivatives, through a newly developed $ZnBr_2$-catalyzed aldehyde allylation (Scheme 2). This borylation/allylation process was found to be effective for the convergent synthesis of a complex polyol derivative with high stereoselectivity and functional group compatibility. The aldehyde allylation with carbocyclic (γ-alkoxyallyl)boronates afforded sterically congested *anti*-1,2-diol derivatives,[17] which were used for the unprecedented stereoselective modular synthesis of complex 3,3-disubstituted cyclopentenes containing three consecutive chiral centers, including a quaternary chiral carbon, via the iterative borylation/aldehyde allylation. We have also demonstrated useful transformations of the α-chiral linear boronates.

RESULTS AND DISCUSSION

Copper(I)-catalyzed borylation has emerged as a powerful method for the synthesis of organoboron compounds.[18] We previously reported a copper(I)-catalyzed asymmetric borylation using diboron that provided optically active allylboronates.[19] Guided by these successes, we proceeded to investigate the development of a copper(I)-catalyzed asymmetric synthesis of (γ-alkoxyallyl)boronates via the enantioselective γ-boryl substitution of allyl acetals (Scheme 2).[20] Pleasingly, while an extensive review of the literature revealed reports concerning the catalytic asymmetric α-substitution of allyl acetals, we could not find any reports describing the catalytic asymmetric γ-substitution of allyl acetals with nucleophiles of any type.[21]

We initially investigated suitable reaction conditions for the reaction of allyl acetal (Z)-**1a** with bis(pinacolato)diboron (Table 1). The results revealed that (*R*,*R*)-BenzP* was the best

Table 1. Optimization of the Reaction Conditions for the Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acetal (Z)-1a[a]



entry	catalyst	time (h)	yield[b] (%)	ee[c] (%)
1	CuCl/(*R*,*R*)-BenzP*	3	95 (83)	97
2[d]	CuCl/(*R*,*R*)-BenzP*	24	81	96
3[e]	Cu(O-*t*-Bu)/(*R*,*R*)-BenzP*	3	88	97
4	CuCl/(*R*,*R*)-QuinoxP*	8	63	93
5	CuCl/(*R*,*R*)-Me-Duphos	24	14	73
6	CuCl/(*R*)-Segphos	24	38	21
7	CuCl/(*R*,*S*)-Josiphos	45	43	11
8[f]	CuCl/(*R*,*R*)-BenzP*	3	86 (73)	34 (*R*)
9[f,g]	$Ni(cod)_2$/PPh_3	24	0	

[a]Reagents and conditions: CuCl (0.025 mmol), ligand (0.025 mmol), (Z)-**1a** (0.5 mmol), bis(pinacolato)diboron (0.75 mmol), and K(O-*t*-Bu)/THF (1.0 M, 0.5 mL, 0.5 mmol) in THF (0.5 mL) at 0 °C. [b]NMR yield. The isolated yield is shown in parentheses. [c]The ee value of (*S*,*E*)-**2a** was determined by HPLC analysis of the alcohol derived from the product boronate. [d]A 10 mol % concentration of K(O-*t*-Bu) was used. [e]Isolated Cu(O-*t*-Bu) was used, and K(O-*t*-Bu) was not added. [f](E)-**1a** (*E*:*Z* = 95:5) was used as the substrate. [g]Reagents and conditions: $Ni(cod)_2$ (10 mol %), PPh_3 (10 mol %), and bis(pinacolato)diboron (0.5 mmol) in EtOAc (0.4 mL) at 60 °C, 24 h.

ligand for the reaction.[22] The boryl substitution of (Z)-**1a** with CuCl/(*R*,*R*)-BenzP* (5 mol %), bis(pinacolato)diboron (1.5 equiv), and K(O-*t*-Bu) (1.0 equiv) in THF afforded the corresponding (*S*,*E*)-**2a** in excellent yield (95%) and ee (97%) (Table 1, entry 1). This reaction employed CuCl as a catalyst precursor, which can be used without a glovebox.[19e] It is noteworthy that none of the minor (Z)-product was observed. The boryl substitution reaction also proceeded smoothly in the presence of 10 mol % K(O-*t*-Bu), although the yield was slightly lower than that of the reaction conducted with a stoichiometric charge of the base and required a longer reaction time (Table 1, entry 2). The use of Cu(O-*t*-Bu) provided

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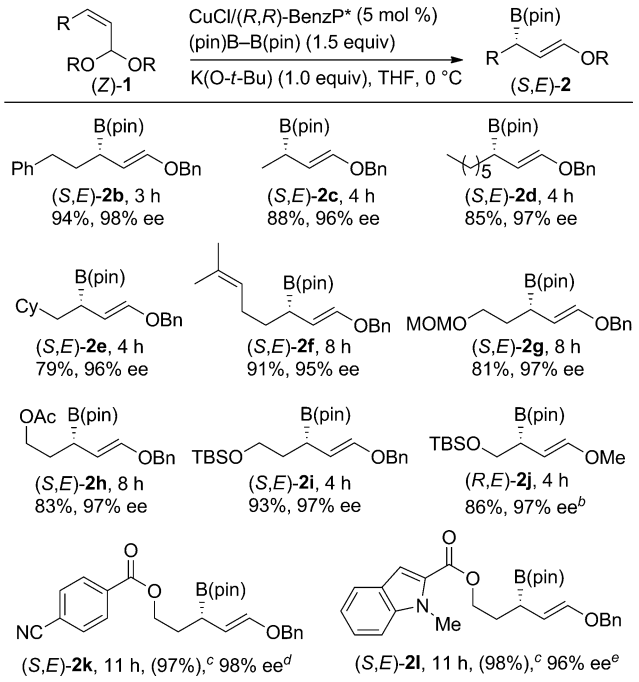
reactivity and stereoselectivity levels similar to those observed for CuCl/K(O-*t*-Bu) (Table 1, entry 3). The other ligands gave inferior results (Table 1, entries 4−7). Interestingly, the application of the optimum reaction conditions to (*E*)-**1a** instead of (*Z*)-**1a** resulted in a significantly lower ee (Table 1, entry 8). Recently, Morken et al. reported Ni-catalyzed γ-borylation of alkenyl acetal with a terminal carbon−carbon double bond.[20] We thus tested the Ni-catalyzed reaction of the substrate (*E*)-**1a**, which has an internal carbon−carbon double bond. However, no reaction occurred after 24 h at 60 °C (Table 1, entry 9).

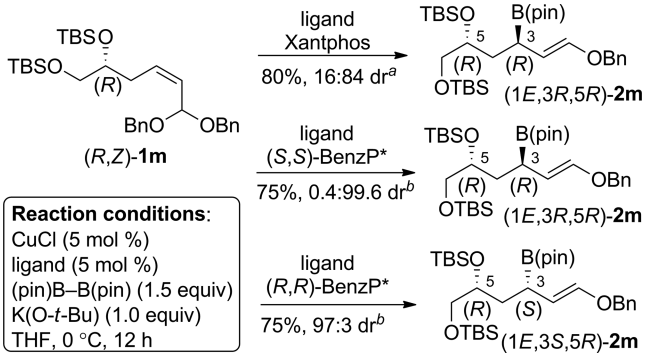
With the optimized conditions in hand, we examined the substrate scope of this reaction (Table 2). Pleasingly, the application of the optimized conditions to allyl dibenzyl acetal (*Z*)-**1b** gave the corresponding product (*S*,*E*)-**2b** in 94% yield with 98% ee. Substrates containing a methyl, hexyl, or methylcyclohexyl group [(*Z*)-**1c**−**e**] also afforded the products in high yields with excellent enantioselectivities [(*S*,*E*)-**2c**, 88% yield, 96% ee; (*S*,*E*)-**2d**, 85% yield, 97% ee; (*S*,*E*)-**2e**, 79% yield, 96% ee]. The (γ-alkoxyallyl)boronate (*S*,*E*)-**2f**, bearing a trisubstituted alkenyl group, was also formed in 91% yield with 95% ee. The allyl acetals (*Z*)-**1g**−**j**, bearing methoxymethyl ether, acetoxy, and silyl ether groups, respectively, also reacted smoothly to give the corresponding products in high yields and excellent enantioselectivities [(*S*,*E*)-**2g**, 81% yield, 97% ee; (*S*,*E*)-**2h**, 83% yield, 97% ee; (*S*,*E*)-**2i**, 93% yield, 97% ee; (*R*,*E*)-**2j**, 86% yield, 97% ee]. The use of nitrogen-containing substrates (*Z*)-**1k** and (*Z*)-**1l** provided the corresponding products (*S*,*E*)-**2k** and (*S*,*E*)-**2l** in high yields and excellent enantioselectivities without any degradation of the functional groups [(*S*,*E*)-**2k**, 97% yield, 98% ee; (*S*,*E*)-**2l**, 98% yield, 96% ee]. However, the products could not be fully isolated because of the presence of the byproducts; thus, the derivatizations of the crude products were conducted to check the product structure and yields (62% and 88% isolated yields, respectively). The reactions of substrate (*R*,*Z*)-**1m** containing an optically active silyl ether moiety are shown in Scheme 3.

Table 2. Substrate Scope of the Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acetal (*Z*)-1[a]



[a]Reagents and conditions: CuCl (0.025 mmol), (*R*,*R*)-BenzP* (0.025 mmol), (*Z*)-**1** (0.5 mmol), bis(pinacolato)diboron (0.75 mmol), and K(O-*t*-Bu)/THF (1.0 M, 0.5 mL, 0.5 mmol) in THF (0.5 mL) at 0 °C. The ee values of the products were determined by HPLC analysis of the saturated alcohols derived from the corresponding boronates. [b]The ee was determined after derivatization of (*R*,*E*)-**2j** to the related *p*-nitrobenzoyl ester. [c]NMR yield of the boronate in the crude reaction mixture. [d]The hydrogenated derivative was isolated in 62% yield after hydrogenation of crude (*S*,*E*)-**2k**. The ee value was determined by HPLC analysis of the hydrogenated derivative. [e]The alcohol derivative was isolated in 88% yield after hydrogenation of the alkene moiety and subsequent oxidation of the crude (*S*,*E*)-**2l**. The ee value was determined by HPLC analysis of the alcohol derivative.

Scheme 3. γ-Borylation of Substrate (*R*,*Z*)-1m with CuCl/Xantphos or Chiral BenzP* Ligands



[a]The dr values of the products were determined by ^{1}H NMR analysis of the crude products. [b]The dr values of the products were determined by HPLC analysis of the alcohols derived from the corresponding boronates.

The use of the Xantphos ligand afforded (1*E*,3*R*,5*R*)-**2m** in 80% yield and a diastereomeric ratio of 16:84, which was attributed to the steric effect of the chiral silyl ether group. The reactions of (*R*,*Z*)-**1m** with CuCl/(*S*,*S*)- and (*R*,*R*)-BenzP* proceeded to give the corresponding (1*E*,3*R*,5*R*)-**2m** and (1*E*,3*S*,5*R*)-**2m**, respectively, in good yields and excellent catalyst-controlled stereoselectivity (75% and 75% yields, 0.4:99.6 and 97:3 dr, respectively).

To date, there have been no reports in the literature describing the allylation of aldehydes with linear enantioenriched α-chiral (*E*)-(γ-alkoxyallyl)boronates to give the corresponding 1,2-diol derivatives with high *E*:*Z* and *anti*:*syn* selectivities and enantioselectivities. With this in mind, we investigated the optimum reaction conditions for the aldehyde allylation with the (γ-alkoxyallyl)boronates (Table 3). Without any catalyst, the allylboronate (*S*,*E*)-**2c** or (*S*,*E*)-**2i** reacted with benzaldehyde in CH_2Cl_2 or THF to give products with low *E*:*Z* selectivity but high enantiospecificity (es)[23] (Table 3, entries 1−4). It has been reported that the selectivity of aldehyde allylation can be improved by the presence of an acid catalyst. Carreaux reported the BF_3-catalyzed reaction of racemic (*E*)-(γ-alkoxyallyl)boronates to give products with high levels of *anti*:*syn* selectivity,[11] although the *E*:*Z* ratios were still in need of improvement. With this in mind, we screened a variety of Lewis acids, including $BF_3{\cdot}OEt_2$, $AlCl_3$, $FeCl_3$, $Sc(OTf)_3$, TMSOTf, and $ZnBr_2$. The results revealed that $ZnBr_2$, which had never been used as a Lewis acid catalyst for the allylation of aldehydes with allylboron reagents,[24,25] turned out to be the

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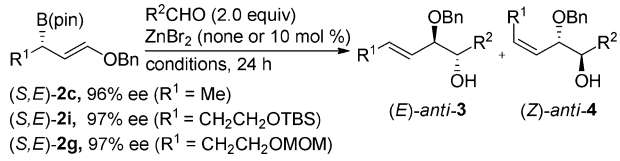
Table 3. Aldehyde Allylation with Optically Active (γ-Alkoxyallyl)boronates 2



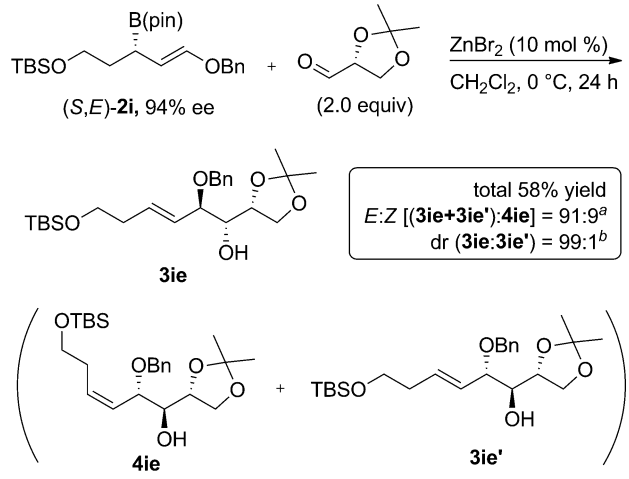
entry	substrate	R^2CHO	solvent	$E:Z^a$ (3:4)	yield[b] (%)	es[c] (%)
1[d,e]	(*S*,*E*)-**2i**	PhCHO	CH_2Cl_2	34:66	94	100
2[d]	(*S*,*E*)-**2c**	PhCHO	CH_2Cl_2	18:82	80	100
3[d]	(*S*,*E*)-**2i**	PhCHO	THF	29:71	80	98
4[d]	(*S*,*E*)-**2c**	PhCHO	THF	15:85	78	100
5[f]	(*S*,*E*)-**2i**	PhCHO	CH_2Cl_2	98:2	68	100
6[f]	(*S*,*E*)-**2c**	PhCHO	CH_2Cl_2	92:8	81	100
7[e,f]	(*S*,*E*)-**2i**	PhCHO	THF	33:67	91	100
8[f]	(*S*,*E*)-**2c**	PhCHO	THF	18:82	89	100
9[f]	(*S*,*E*)-**2i**	$C_7H_{15}CHO$	CH_2Cl_2	96:4	79	97
10[e,f]	(*S*,*E*)-**2i**	cinnamaldehyde	CH_2Cl_2	93:7	79	100
11[e,f]	(*S*,*E*)-**2i**	2-octynal	CH_2Cl_2	87:13	73	98
12[f]	(*S*,*E*)-**2c**	$C_7H_{15}CHO$	CH_2Cl_2	85:15	72	100
13[e,f]	(*S*,*E*)-**2g**	PhCHO	CH_2Cl_2	86:14	81	100

[a]The *E*:*Z* ratios (**3**:**4**) of the *anti*-products were determined by ^{1}H NMR and HPLC analysis. [b]Isolated yield of *anti*-products. The minor *syn*-isomers of **3** and **4** were present in less than trace amounts, which could be determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]See ref 23. The ee values of the major products were determined by HPLC analysis. [d]Reagents and conditions: (*S*,*E*)-**2** (0.2 mmol) and the aldehyde (0.4 mmol) in a solvent (0.4 mL) at 30 °C. [e](*S*,*E*)-**2i** with 94% ee was used. [f]Reagents and conditions: (*S*,*E*)-**2** (0.2 mmol), aldehyde (0.4 mmol), and dry $ZnBr_2$ (10 mol %) in a solvent (0.4 mL) at 0 °C. The use of dry $ZnBr_2$ is necessary for the high stereoselectivity.

most effective Lewis acid catalyst for the highly stereoselective aldehyde allylation with our boron compounds (Table 3, entries 5−13). The stereoselectivities of this aldehyde allylation were in good agreement with the mechanism that had been previously postulated in the literature (see the Supporting Information).[11,25] The use of CH_2Cl_2 solvent is necessary for the high stereoselectivity of this reaction; allylation in THF solvent in the presence of $ZnBr_2$ catalyst afforded inferior results, which would be due to the coordination of THF to $ZnBr_2$ catalyst (Table 3, entry 1 vs entry 7, entry 2 vs entry 8). The reaction of (*S*,*E*)-**2i** with octanal, cinnamaldehyde, or 2-octynal also afforded the corresponding alcohol products with high stereoselectivity (Table 3, entries 9−11). The reaction of (*S*,*E*)-**2c** with octanal provided the corresponding product in high selectivity and good *E*:*Z* ratio (Table 3, entry 12). The boronate (*S*,*E*)-**2g** bearing the methoxymethyl group also gave the product in high es and good *E*:*Z* ratio (Table 3, entry 13, *E*:*Z* = 86:14, 100% es). The reactions in entries 5, 11, and 12 resulted in slightly lower yields than those in other entries, but the *anti*:*syn* ratios were not changed. The reaction conditions were compatible with a chiral α-oxyaldehyde substrate leading to the desired product in 58% yield, high *E*:*Z* ratio, and high dr {Scheme 4, *E*:*Z* [(**3ie** + **3ie**′):**4ie**] = 91:9, dr (**3ie**:**3ie**′) = 99:1}. The dr value [(**3ie** + **3ie**′):**4ie** = 99:1] was higher than the expected value (97:3) based on the enantiomeric purity of (*S*,*E*)-**2i** (94% ee). This would be attributed to the kinetic resolution upon addition of the optically active allylboronate to the chiral α-oxyaldehyde.

Having established conditions for the aldehyde allylation, we probed the feasibility of the convergent synthesis of complex polyol deriatives using the borylation/aldehyde allylation procedure (Scheme 5). The reaction of the boronate (1*E*,3*S*,5*R*)-**2m** with (*R*)-glyceraldehyde acetonide successfully proceeded to afford the desired complex allylation product **3m** in good yield and selectivity {total 56% yield, *E*:*Z* [(**3m** + **3m**′):**4m**] = 80:20, dr (**3m**:**3m**′) = 97:3}.

Scheme 4. Aldehyde Allylation of (*R*)-Glyceraldehyde Acetonide and Optically Active (γ-Alkoxyallyl)boronate 2i



[a]The *E*:*Z* ratio [(**3ie** + **3ie**′):**4ie**] was determined by ^{1}H NMR analysis after derivatization to the corresponding *p*-nitrobenzoic acid esters. [b]The dr (**3ie**:**3ie**′) was determined by HPLC analysis of the corresponding *p*-nitrobenzoic acid esters.

We then proceeded to examine the borylation of cyclic allyl ketals, which could provide access to 1,2-diol derivatives containing sterically congested vicinal stereogenic centers through a subsequent aldehyde allylation (Scheme 6). The boryl substitution of allyl ketal **1n** proceeded smoothly under the standard conditions, although the isolation of the product boronate was not successful. Thus, we carried out borylation of **1n** and sequential allylation of aldehyde without isolation of the allylboronate, which afforded the corresponding product (1*R*,1′*S*)-**4n** in good yield with high levels of diastereo- and enantioselectivity without the need for a Lewis acid catalyst. No proton signals of the minor diastereomer were detected in the

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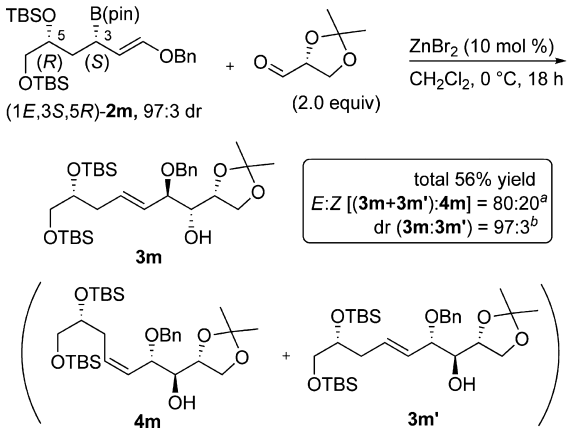
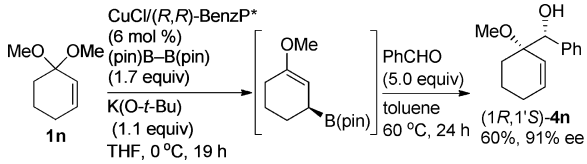
Scheme 5. Convergent Coupling for Polyol Derivative Synthesis via Aldehyde Allylation of Complex Boronates and Aldehydes



[a]The *E*:*Z* ratio [(**3m** + **3m**′):**4m**] was determined by ^{1}H NMR analysis after derivatization to the corresponding *p*-nitrobenzoic acid esters. [b]The dr (**3m**:**3m**′) was determined by HPLC analysis of the corresponding *p*-nitrobenzoic acid esters.

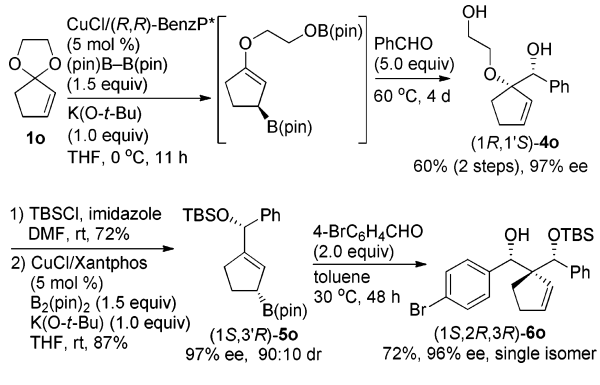
Scheme 6. Enantioselective Boryl Substitution/Aldehyde Allylation of Allyl Ketal 1n



^{1}H NMR spectra of the crude reaction mixture. The single isomeric product was isolated in 60% yield with 91% ee after chromatographic purification.

The above borylation/aldehyde allylation procedure generated an allyl ether moiety in the products, and it was envisaged that this structural feature could be used as a reactive site for the subsequent copper(I)-catalyzed borylation. With this in mind, we proceeded to investigate the stereoselective modular construction of an optically active 3,3-disubstituted cyclopentene scaffold, which contained three consecutive chiral centers, including a quaternary carbon, using an iterative borylation/aldehyde allylation procedure[19c] (Scheme 7). Substrate **1o** underwent the first borylation/aldehyde allylation

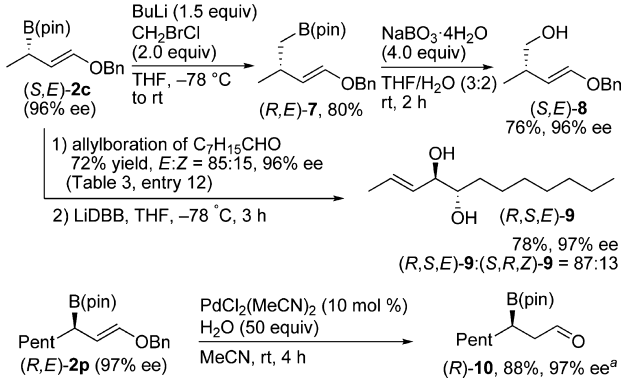
Scheme 7. Stereoselective Modular Construction of a Complex 3,3-Disubstituted Cyclopentene



to give the diol (1*R*,1′*S*)-**4o** in good yield, with excellent diastereo- and enantioselectivity (dr of the crude reaction mixture, 98:2; 60% isolated yield after recrystallization as a single isomer with 97% ee). In this reaction, the allylation of benzaldehyde proceeded with high diastereoselectivity. Following TBS protection of the hydroxy groups in (1*R*,1′*S*)-**4o**, a second diastereoselective borylation with the achiral copper(I)/Xantphos catalyst[19e] was conducted to give the corresponding allylboronate (1*S*,3′*R*)-**5o** via a *syn*-S_N2' mechanism (90:10 dr), which occurred as a consequence of the steric effect imposed by the bulky silyl group.[26] The configurations of (1*R*,1′*S*)-**4o** and (1*S*,3′*R*)-**5o** were determined by X-ray crystallographic analysis (see the Supporting Information). Finally, a second allylation of *p*-bromobenzaldehyde with (1*S*,3′*R*)-**5o** provided monoprotected 1,3-diol (1*S*,2*R*,3*R*)-**6o** in good yield with high diastereo- and enantioselectivity (72% yield, single diastereomer, 96% ee). During the allylation of *p*-bromobenzaldehyde with (1*S*,3′*R*)-**5o**, the reaction of the major isomer of (1*S*,3′*R*)-**5o** proceeded selectively prior to that of the minor isomer, which led to the observed higher diastereomeric ratio of the product. The absolute configuration of the product (1*S*,2*R*,3*R*)-**6o** was determined by X-ray crystallographic analysis of the corresponding deprotected 1,3-diol (see the Supporting Information). This synthetic method could be used as a general strategy to provide novel chirally functionalized cycloalkene scaffolds for drug discovery.[27]

We further demonstrated the transformations of these α-chiral linear (*E*)-(γ-alkoxyallyl)boronates (Scheme 8). The

Scheme 8. Transformations of α-Chiral Linear (*E*)-(γ-Alkoxyallyl)boronates



[a]The ee value was determined by HPLC analysis after derivatization to a known compound.

boronate (*S*,*E*)-**2c** underwent homologation to give the corresponding homoallylboronate (*R*,*E*)-**7** in 80% yield followed by oxidation to afford alcohol (*S*,*E*)-**8** in 76% yield with 96% ee, where the alkenyl ether moiety remained intact. In addition, the feasibility of 3-ene-*anti*-1,2-diols was also confirmed by using lithium di-*tert*-butylbiphenyl (LiDBB) reagent. Deprotection of the benzyl group in the allylation product from (*S*,*E*)-**2c** and octyl aldehyde provided the corresponding diol in 78% yield without lowering its enantiomeric purity and *anti*:*syn* and *E*:*Z* ratios [97% ee, (*R*,*S*,*E*)-**9**:(*S*,*R*,*Z*)-**9** = 87:13; the *syn*-isomer could not be observed by ^{1}H NMR] . The boronate (*R*,*E*)-**2p** prepared by the present enantioselective borylation was subjected to a Pd-catalyzed hydrolysis[28] to give the β-boryl aldehyde (*R*)-**10** in 88% yield.[29] We further carried out a total synthesis of

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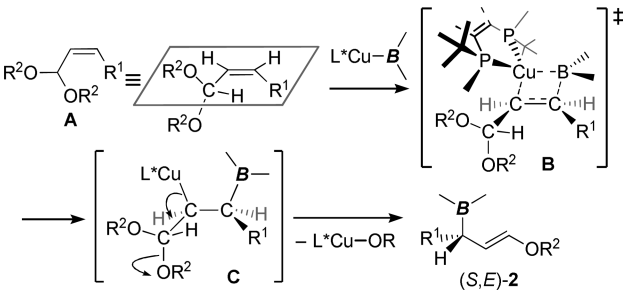
(−)-massoialactone from (*R*)-**10** (Supporting Information, p S50).

A reaction mechanism has been proposed to account for the stereochemical outcome of this boryl substitution (Scheme 9).

Scheme 9. Proposed Mechanism [L* = (*R*,*R*)-BenzP*]



The selective enantiofacial addition of the Cu−B bond of the in situ generated borylcopper(I) species to the C−C double bond of the allyl acetal **A** would occur through the transition structure **B** to give the alkylcopper intermediate **C**. The conformation of the allyl acetal would be fixed due to 1,3-allylic strain, which would also account for the observed preferential formation of (*E*)-products. Subsequent *β*-alkoxy elimination would afford the optically active (*γ*-alkoxyallyl)boronate (*S*,*E*)-**2**.

CONCLUSION

In conclusion, we have developed a copper(I)-catalyzed enantioselective boryl substitution of allyl acetals, providing a novel approach to optically active *α*-chiral linear or carbocyclic (*E*)-(*γ*-alkoxyallyl)boronates. Furthermore, we have developed a highly stereoselective, zinc Lewis acid-catalyzed aldehyde allylation with these boronates. This borylation represents the first example of an enantioselective *γ*-substitution of allylic acetals. The utility of the borylation/aldehyde allylation procedure has been demonstrated by the convergent synthesis of the complex polyol derivatives and the stereoselective modular construction of a complex cyclopentene scaffold. Furthermore, we have demonstrated the useful transformations of the enantioenriched linear (*E*)-(*γ*-alkoxyallyl)boronate.

ASSOCIATED CONTENT

Supporting Information

General experimental procedures, preparation of allyl acetal substrates, characterization of boryl substitution products, procedures for aldehyde allylations and characterization of the products, single-crystal X-ray structural analyses, application of linear (*γ*-alkoxyallyl)boronates, chiral stationary-phase HPLC charts, ^{1}H and ^{13}C NMR spectra, and CIF data. 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) For selected reviews, see: (a) Casiraghi, G.; Zanardi, F. *Chem. Rev.* **1995**, *95*, 1677. (b) Marco, J. A.; Carda, M.; Murga, J.; Falomir, E. *Tetrahedron* **2007**, *63*, 2929. (c) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109*, 3012.

(2) For examples of reactions constructing stereodefined 1,2-diols with concomitant C−C bond formation, see: (a) Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760 (for Ir-catalyzed alkoxyallylation). (b) Park, J. K.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2717 (for cross-metathesis/asymmetric allylic substitution). (c) Kim, D.; Lee, J. S.; Kong, S. B.; Han, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 4203. For examples of chiral auxiliary-mediated or diastereoselective aldol reactions affording *anti*-1,2-diols, see: (d) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753. (e) Andrus, M. B.; Sekhar, B. B. V. S.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035. (f) Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937 (for Ni-catalyzed reductive couplings of alkyne and *α*-oxyaldehyde). (g) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441. (h) Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445 (for diastereoselective organozinc addition to *α*-oxyaldehydes). (i) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 320 (for allylboration of *α*-oxyaldehyde). (j) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (k) Savall, B. M.; Powell, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 3057 (for (*α*-alkoxypropargyl)stannane addition to aldehydes). For examples of catalytic asymmetric aldol reactions, see: (l) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (m) Denmark, S. E.; Chung, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1890. For a review about *α*-hydroxyallylation reactions, see: (n) Lombardo, M.; Trombini, C. *Chem. Rev.* **2007**, *107*, 3843. For a review about allylation of *α*-oxyaldehydes, see: (o) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595.

(3) For references on the allylation of carbonyl compounds, see: (b) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723.

(4) For a review about the synthetic utility of allylic alcohols, see: Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 1890.

(5) (a) Chemler, S. R.; Roush, W. R. Recent applications of the allylation reaction to the synthesis of natural products. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; pp 403−490. (b) Kennedy, J. W. J.; Hall, D. G. Recent advances in the preparation of allylboronates and their use in tandem reactions with carbonyl compounds. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005.

(6) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1981**, *22*, 5263.

(7) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1982**, *47*, 2498.

(8) For references on stereoselective aldehyde allylation with (*γ*-alkoxyallyl)boronates, see: (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (b) Moriya, T.; Suzuki, A.; Miyaura, N. *Tetrahedron Lett.* **1995**, *36*, 1887. (c) Ganesh, P.; Nicholas, K. M. *J. Org. Chem.* **1997**, *62*, 1737. (d) Yamamoto, Y.; Miyairi, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem.* **1999**, *64*, 296. (e) Hoffmann, R. W.; Krüger, J.; Brückner, D. *New J. Chem.* **2001**, *25*, 102. (f) Muñoz-Hernández, L.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 2571.

(9) For several examples of applications for natural product synthesis, see: (a) Burgess, K.; Chaplin, D. A.; Henderson, I. *J. Org. Chem.* **1992**, *57*, 1103. (b) Jadhav, P. K.; Woerner, F. J. *Tetrahedron Lett.* **1994**, *35*, 8973. (c) Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2002**, *67*, 7547. (d) Yin, N.; Wang, G.; Qian, M.; Negishi, E.

Angew. Chem., Int. Ed. **2006**, *45*, 2916. (e) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1988**, *53*, 5023.
(10) (a) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 957. (b) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243. (c) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686. (d) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413. (e) Vincent, G.; Mansfield, D. J.; Vors, J.-P.; Ciufolini, M. A. *Org. Lett.* **2006**, *8*, 2791. (f) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602. (g) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174. (h) Mukherjee, P.; Roy, S. J. S.; Sarkar, T. K. *Org. Lett.* **2010**, *12*, 2472. (i) Han, J.-L.; Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 3028.
(11) Possémé, F.; Deligny, M.; Carreaux, F.; Carboni, B. *J. Org. Chem.* **2007**, *72*, 984.
(12) (a) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (b) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612.
(13) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.
(14) (a) Rehders, F.; Hoppe, D. *Synthesis* **1992**, 859. (b) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425. (c) Nakazaki, A.; Nakai, T.; Tomooka, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2235.
(15) (a) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (b) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612.
(16) (a) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 1628. (b) Gao, X.; Hall, D. G.; Deligny, M.; Favre, A.; Carreaux, F.; Carboni, B. *Chem.—Eur. J.* **2006**, *12*, 3132. (c) Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.
(17) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2005.
(18) For selected examples, see: (a) Ito, H.; Yamanaka, H.; Tateiwa, J.-i.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821. (b) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 126. (c) Laitar, D. S.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196. (d) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887. (e) Lillo, V.; Fructos, M. R.; Ramírez, J.; Braga, A. A. C.; Maseras, F.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E. *Chem.—Eur. J.* **2007**, *13*, 2614. (f) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350. (g) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160. (h) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; Mcquade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410. (i) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem.—Eur. J.* **2012**, *18*, 4179.
(19) (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (c) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 560. (d) Ito, H.; Kunii, S.; Sawamura, M. *Nat. Chem.* **2010**, *2*, 972. (e) Ito, H.; Miya, T.; Sawamura, M. *Tetrahedron* **2012**, *68*, 3423.
(20) Morken et al. reported on γ-selective boryl substitution of an allyl acetal containing a terminal alkene moiety using an achiral nickel(0) catalyst; see: Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1416.
(21) Several asymmetric α-selective allylic substitution reactions of allyl acetals have been reported; see: (a) Trost, B. M.; Lee, C. B.; Weiss, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 7247. (b) Umebayashi, N.; Hamashima, Y.; Hashizume, D.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4196. (c) Kobayashi, S.; Arai, K.; Yamakawa, T.; Chen, Y.-J.; Salter, M. M.; Yamashita, Y. *Adv. Synth. Catal.* **2011**, *353*, 1927. (d) Rueping, M.; Volla, C. M. R.; Atodiresei, I. *Org. Lett.* **2012**, *14*, 4642. (e) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7096. See also ref 2a.
(22) (*R*,*R*)-BenzP* is available commercially; see: Tamura, K.; Sugiya, M.; Yoshida, K.; Yanagisawa, A.; Imamoto, T. *Org. Lett.* **2010**, *12*, 4400.
(23) The term enantiospecificity [es (%) = (product ee/starting material ee) × 100] has been used to describe the conservation of optical purity over the course of stereospecific reactions: (a) Denmark, S. E.; Vogler, T. *Chem.—Eur. J.* **2009**, *15*, 11737. (b) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.
(24) For basic zinc(II)-catalyzed α-selective aldehyde allylation through transmetalation, see: Kobayashi, S.; Endo, T.; Schneider, U.; Ueno, M. *Chem. Commun.* **2010**, *46*, 1260.
(25) (a) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981. (b) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. (c) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (d) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586.
(26) Examples of *syn*-S_N2' selectivity were reported in our previous study; see refs 19c and 19d.
(27) (a) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104. (b) Wu, J.; Becerril, J.; Lian, Y.; Davies, H. M. L.; Porco, J. A., Jr.; Panek, J. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5938. (c) MacLellan, P.; Nelson, A. *Chem. Commun.* **2013**, *49*, 2383.
(28) Aoyama, H.; Tokunaga, M.; Hiraiwa, S.; Shirogane, Y.; Obora, Y.; Tsuji, Y. *Org. Lett.* **2004**, *6*, 509.
(29) For synthesis of β-borylaldehydes via asymmetric β-borylations of the α,β-enals, see: (a) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659. (b) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277. (c) Ibrahem, I.; Breistein, P.; Córdova, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 12036.