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

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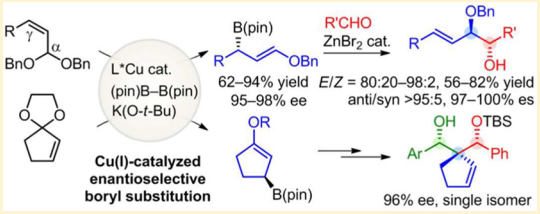
Supporting Information

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.

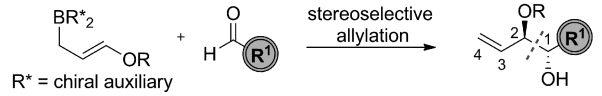


INTRODUCTION

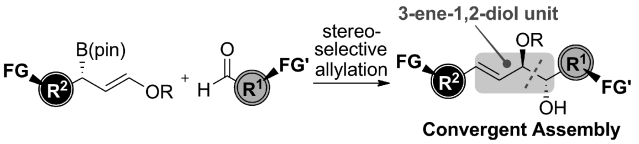
The chiral 1,2-diol structure is important and is often found in natural products such as carbohydrates and polyketides.[1] Consequently, stereoselective coupling reactions constructing chiral 1,2-diol motifs with concurrent C−C bond formation between two functionalized synthetic fragments can be powerful 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

a. Stereoselective Aldehyde Allylation of (γ-Alkoxyallyl)boron Compounds Containing an Achiral C–B Bond



b. Approach to the Convergent Synthesis of Complex Molecules Using α-Chiral (γ-Alkoxyallyl)boronates



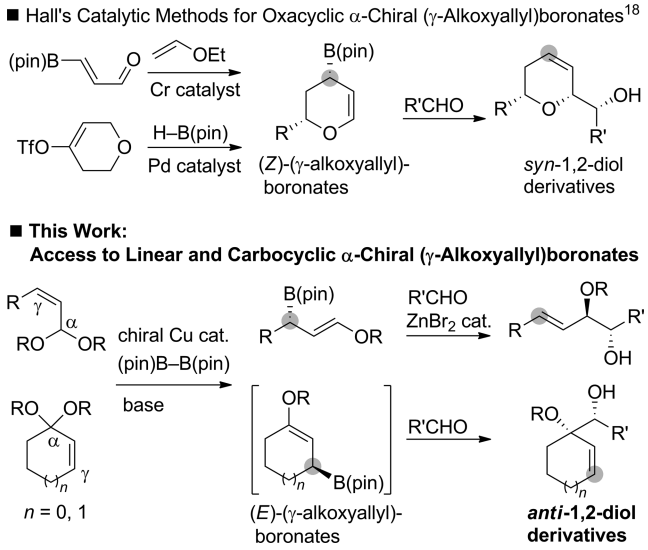
In contrast, aldehyde allylation involving α-chiral (*E*)- or (*Z*)-(γ-alkoxyallyl)boronates affords stereodefined *anti*- or *syn*-1,2-diols containing an internal alkene moiety, the stereochemistry of which is controlled by the chiral C−B bond structure without the use of a chiral auxiliary.[11,12] 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

Received: June 27, 2014

   dx.doi.org/10.1021/ja506284w | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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.

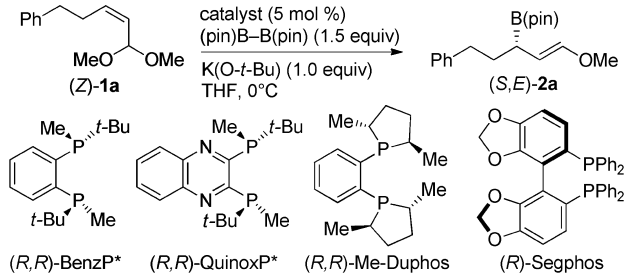
Herein, we report a novel approach to enantioenriched α-chiral linear or carbocyclic (E)-(γ-alkoxyallyl)boronates via the copper(I)/chiral bisphosphine-catalyzed γ-boryl substitution of allyl acetals and the subsequent conversion of these boronates to the corresponding *anti*-1,2-diol derivatives, which 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.

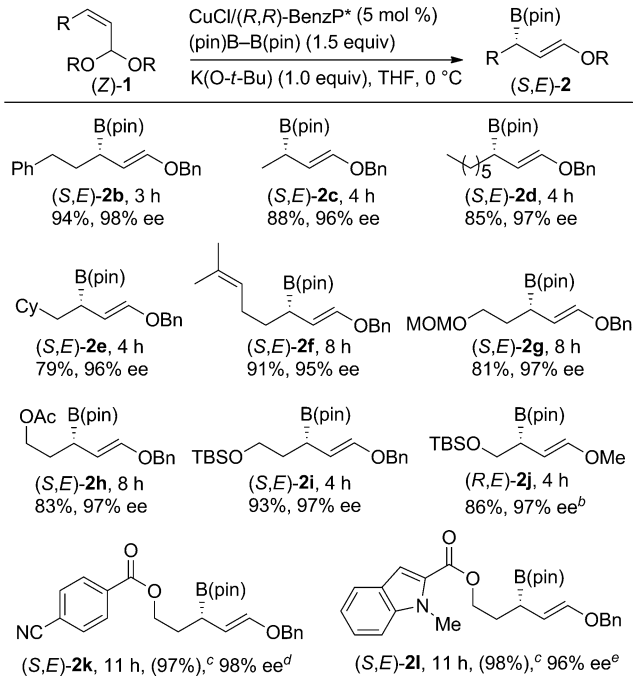
ligand for the reaction.[22] The boryl substitution of (Z)-**1a** with CuCl/(*R*,*R*)-BenzP* (5 mol %), bis(pinacolato)diboron (1.5 equiv), and K(O-*t*-Bu) (1.0 equiv) in THF afforded the corresponding (*S*,*E*)-**2a** in excellent yield (95%) and ee (97%) (Table 1, entry 1). This reaction employed CuCl 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

dx.doi.org/10.1021/ja506284w | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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

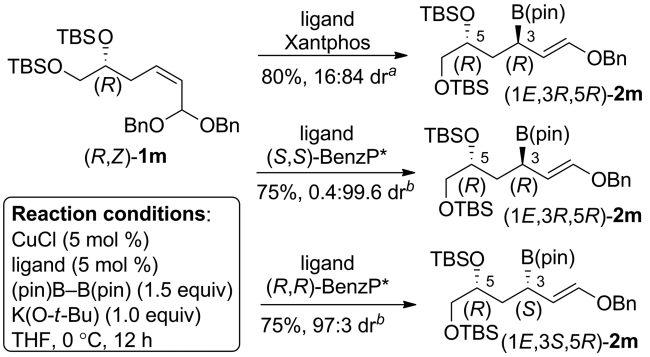
Table 2. Substrate Scope of the Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acetal (*Z*)-1[a]



[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.

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.

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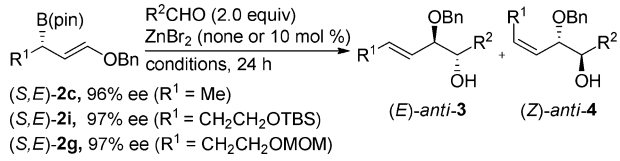
Table 3. Aldehyde Allylation with Optically Active (γ-Alkoxyallyl)boronates 2



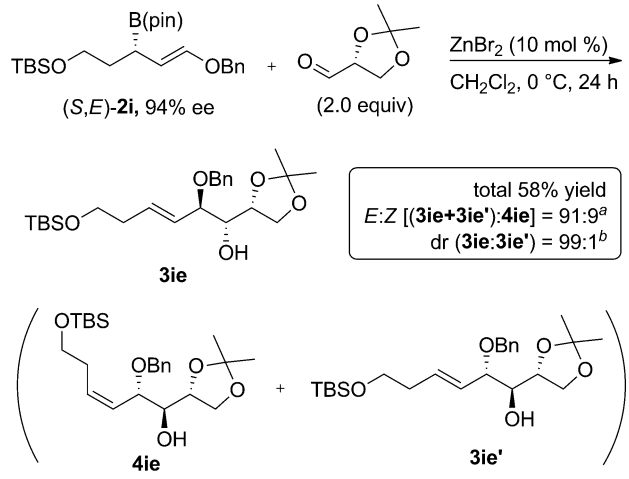
entry	substrate	R^2CHO	solvent	$E:Z^a$ (3:4)	yield[b] (%)	es[c] (%)
1[d,e]	(*S*,*E*)-**2i**	PhCHO	CH_2Cl_2	34:66	94	100
2[d]	(*S*,*E*)-**2c**	PhCHO	CH_2Cl_2	18:82	80	100
3[d]	(*S*,*E*)-**2i**	PhCHO	THF	29:71	80	98
4[d]	(*S*,*E*)-**2c**	PhCHO	THF	15:85	78	100
5[f]	(*S*,*E*)-**2i**	PhCHO	CH_2Cl_2	98:2	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

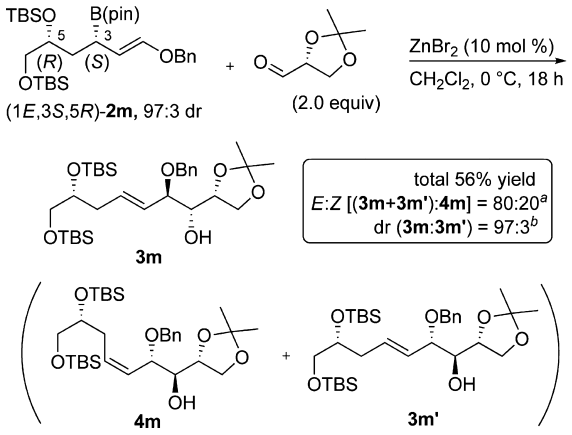


[a]The *E*:*Z* ratio [(**3ie** + **3ie**′):**4ie**] was determined by ^{1}H NMR analysis after derivatization to the corresponding *p*-nitrobenzoic acid esters. [b]The dr (**3ie**:**3ie**′) was determined by HPLC analysis of the corresponding *p*-nitrobenzoic acid esters.

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

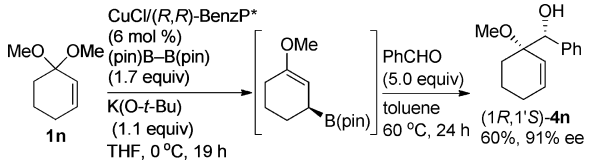
dx.doi.org/10.1021/ja506284w | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

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.

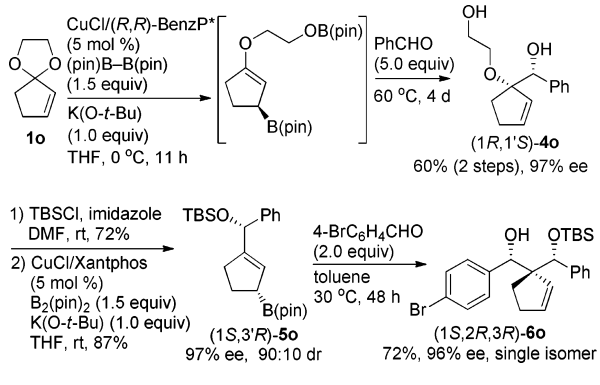
Scheme 6. Enantioselective Boryl Substitution/Aldehyde Allylation of Allyl Ketal 1n



^{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

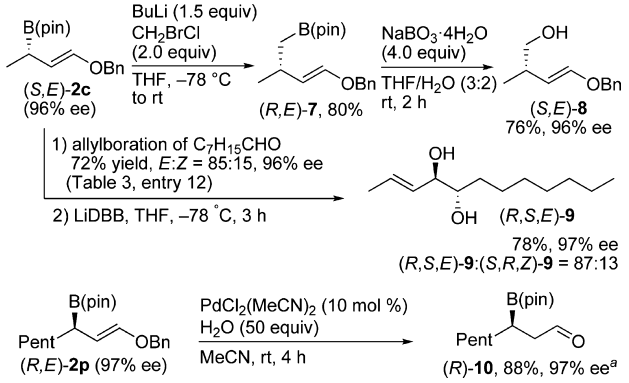
Scheme 7. Stereoselective Modular Construction of a Complex 3,3-Disubstituted Cyclopentene



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.

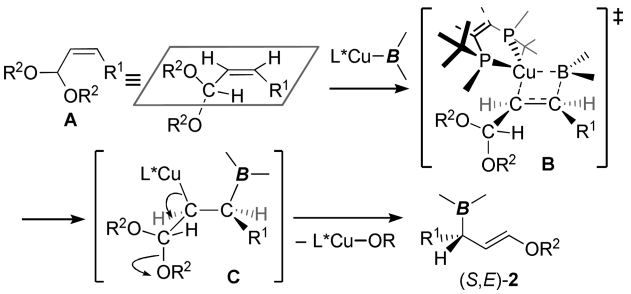
boronate (*S*,*E*)-**2c** underwent homologation to give the corresponding homoallylboronate (*R*,*E*)-**7** in 80% yield followed by oxidation to afford alcohol (*S*,*E*)-**8** in 76% yield with 96% ee, where the alkenyl ether moiety remained intact. In addition, the feasibility of 3-ene-*anti*-1,2-diols 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

dx.doi.org/10.1021/ja506284w | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(−)-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.

ACKNOWLEDGMENTS

We thank Prof. T. Seki and K. Sakurada (Hokkaido University) for their great technical assistance with the X-ray crystallographic analysis. We thank Prof. K. Tanino (Hokkaido University) for a fruitful discussion. We appreciate Prof. M. Sawamura and S. Ito for their assistance. The Funding Program for Next Generation World-Leading Researchers (NEXT Program, GR002) is gratefully acknowledged. This work was supported by JSPS KAKENHI Grant 26·2447. E.Y. was supported by a Grant-in-Aid for Japan Society for the Promotion of Science (JSPS) Fellows.

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