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Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acylals: An Efficient Approach for Enantioenriched α-Chiral γ-Acetoxyallylboronates
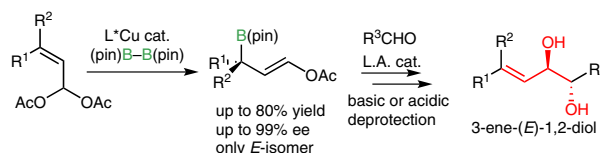
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Abstract A novel approach has been developed for the enantioselective synthesis of α-chiral γ-acetoxyallylboronates via the copper(I)-catalyzed γ-boryl substitution of allyl acylals. This reaction proceeded with high E/Z selectivity and enantioselectivity (E/Z = >99:1, up to 80% yield, up to 99% ee). The subsequent allylation of aldehyde with the allylboronate afforded the monoprotected *anti*-1,2-diol derivative with high stereoselectivity.

The asymmetric allylation of aldehydes with allylboronates is a useful transformation in organic synthesis because of the high synthetic utility of the 1,2-diol products.[1] Allylboronates bearing a substituent at their γ-position relative of the boron atom are especially important organometallic reagents for the construction of consecutive chiral centers via C–C bond-forming reactions because they can react with aldehydes in a highly stereospecific manner through a six-membered transition state.[2] In particular, optically active γ-alkoxyallylboronates have been widely used for the preparation of chiral 1,2-diol moieties, which can be found in a wide range of natural products and synthetic drugs.[3] However, the synthetic methods used for the construction of these boronates typically require a boron source bearing stoichiometric chiral auxiliary.[4]

We previously reported the first catalytic synthesis of α-chiral linear or carbocyclic γ-alkoxyallylboronates via the copper(I)-catalyzed γ-boryl substitution of allyl acetals (Scheme 1).[5] Although our previous reaction showed high enantioselectivity and broad substrate scope in terms of its functional-group compatibility, it was not amenable to sterically hindered substrates because they exhibited poor re-

activity toward the boryl copper nucleophile. In addition, this reaction required harsh reaction conditions to allow for the removal of the benzyl groups from the monoprotected 1,2-diols, which were obtained by the allylation of aldehydes with the corresponding γ-alkoxyallylboronates. Furthermore, the route required for the synthesis of the dibenzyl acetal substrates showed limited substrate scope, as well as being a laborious and time-consuming procedure.[6]
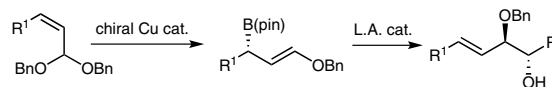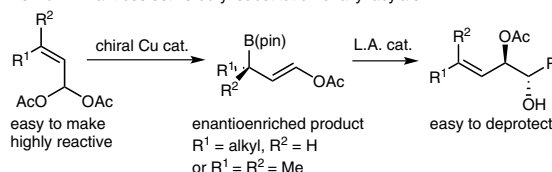
Scheme 1 Copper(I)-catalyzed enantioselective boryl substitution of allyl acylals

To address these issues, we focused on allyl acylals as alternative substrates for the copper-catalyzed boryl substitution reaction. Allyl acylals have been shown to be well suited to nucleophilic substitution reactions, such as palladium-catalyzed asymmetric alkylations[7] or Lewis acid catalyzed cyanation.[8] We therefore expected that allyl acylals would be more reactive than allyl acetals toward nucleophilic boryl substitution reactions because the acetoxy group in the former is more electron withdrawing than the ether group in the latter, making the LUMO of the allyl acylal substrate lower in energy and more reactive toward a nucleophilic boryl copper intermediate.

Furthermore, acetyl groups can be removed under milder conditions than those required to remove ether groups, making this process more efficient than our previous method.[9] Notably, a facile synthetic method has been reported for the direct construction of allyl acylals from aldehydes and acetic anhydride using an acid catalyst.[10]

Herein, we report the enantioselective synthesis of α-chiral γ-acetoxyallylboronates using a chiral copper catalyst and bis(pinacolato)diboron [$B_2(pin)_2$] as a boron source. Notably, this reaction was successfully applied to a wide range of allyl acylal substrates, including sterically hindered compounds, to give the desired products in good yields.

Initial optimization studies focused on the E/Z selectivity and enantioselectivity of the copper(I)-catalyzed boryl substitution of an allyl acylal to give the corresponding allylboronate. The reaction of acylal (Z)-**1a** with $B_2(pin)_2$ in the presence of CuCl/(R,R)-BenzP* as a ligand (5 mol%) and KOt-Bu as a base (1 equiv) in THF or toluene afforded mixtures of the corresponding E and Z products (Table 1, entries 1 and 2).[11] In our previous study involving the borylation of allyl acetals, we only ever observed the formation of the E iso-mer as a single product, which we attributed to the substrate undergoing an anti S_N2' reaction mechanism with a fixed conformation because of the 1,3-allylic strain of the substrate (see the Supporting Information).[5,12]

The use of 1,3-dimethyl-2-imidazolidinone (DMI) as a solvent provided the E product with high E/Z selectivity and excellent enantioselectivity (73% yield, E/Z = 98:2, 89% ee; Table 1, entry 3). Several other chiral ligands, including (R,R)-QuinoxP*, (R)-Segphos, and (R,R)-Me-Duphos, were also tested, but resulted in poor yields and E/Z selectivities (Table 1, entries 4–6). The amounts of base and $B_2(pin)_2$ added to the reaction also had a considerable impact in the reactivity. For example, the use of a catalytic amount of KOt-Bu (10 mol%) yielded a trace amount of the desired product, whereas the use of small excesses of KOt-Bu (1.5 equiv) and $B_2(pin)_2$ (2.0 equiv) resulted in high yield with excellent E/Z selectivity and enantioselectivity (79% yield, E/Z = >99:1, 95% ee; Table 1, entry 8).[13]

As shown in Scheme 2, various α-chiral γ-acetoxyallyl-boronates were obtained in high yields and enantioselectivities under the optimized reaction conditions. Furthermore,

Table 1 Optimization of the Reaction Conditions for the Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acylal (Z)-**1a**[a]
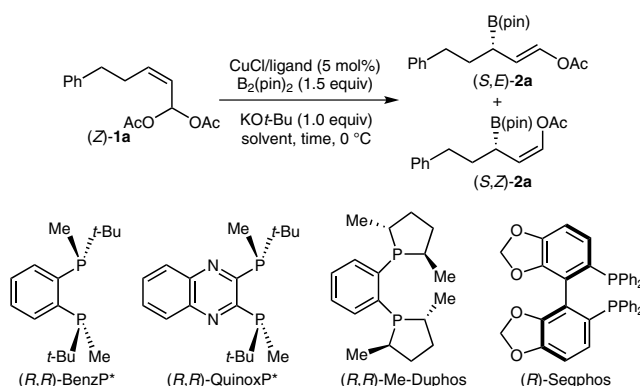
Entry	Solvent	Ligand	Time (h)	E/Z[b]	Yield (%)[c]	ee (%)[d]
1	THF	(R,R)-BenzP*	30	82:18	78	93
2	toluene	(R,R)-BenzP*	48	76:24	74	92
3	DMI	(R,R)-BenzP*	45	98:2	73	89
4[e]	DMI	(R,R)-QuinoxP*	24	90:10	30	–
5[e]	DMI	(R)-Segphos	24	87:13	23	–
6[e]	DMI	(R,R)-Me-Duphos*	24	79:21	30	–
7[f]	DMI	(R,R)-BenzP*	24	–	trace	–
8[g]	DMI	(R,R)-BenzP*	28	>99:1	79	95

[a] Reagents and conditions: CuCl (0.01 mmol), ligand (0.01 mmol), (Z)-**1a** (0.2 mmol), $B_2(pin)_2$ (0.3 mmol), and KOt-Bu (0.2 mmol) in solvent (0.4 mL) at 0 °C.
[b] The E/Z selectivity was determined by GC.
[c] NMR yield.
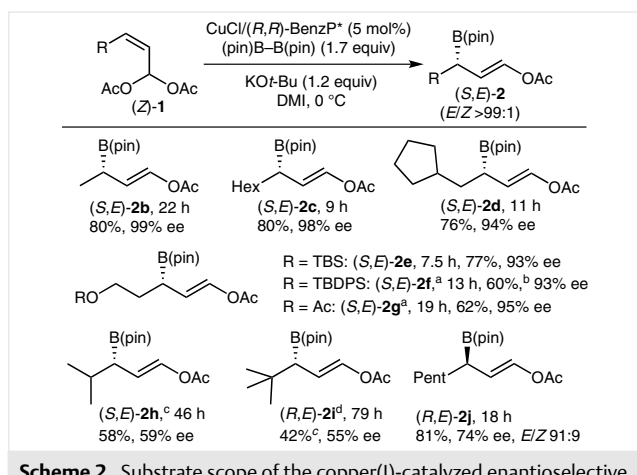[d] The ee values of the products were determined by HPLC analysis.
[e] The ee value of the major product was difficult to determine using HPLC analysis because both SiO2 and chiral column chromatography resulted in an insufficient separation of the major product and the unconsumed substrate.
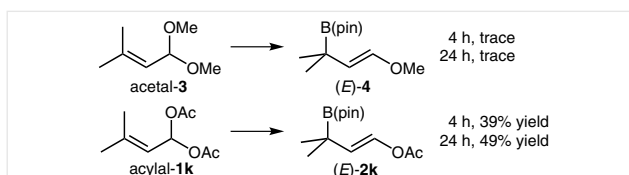[f] 10 mol% of KOt-Bu was used.
[g] 2.0 equiv of $B_2(pin)_2$ and 1.5 equiv of KOt-Bu were used; 0.5 mmol scale.

several optically active products bearing an alkyl substituent (e.g., R = Me, hexyl, methylcyclopentyl) were obtained in high yields and enantioselectivities [(*S,E*)-**2b**, 80% yield, 99% ee; (*S,E*)-**2c**, 80% yield, 98% ee; (*S,E*)-**2d**, 76% yield, 94% ee]. This reaction also showed good functional-group tolerance, as exemplified by the boryl substitution of substrates bearing a silyl ether or acetoxy group, which proceeded in high yield and excellent enantioselectivity without any degradation of the functional groups [(*S,E*)-**2e**, 77% yield, 93% ee; (*S,E*)-**2f**, 60% yield, 93% ee; (*S,E*)-**2g**, 62% yield, 95% ee]. σ-Branched allyl acylals [(*Z*)-**1h** and (*Z*)-**1i**], which have steric congestion around their C=C bond, also reacted smoothly to afford the corresponding borylated products (58% and 42% yield, respectively), but the enantiopurities of these products were unfortunately low (59% and 55% ee, respectively), compared with **2b** and **2c**. The borylation of the *E* substrate (*E*)-**1j** (*E/Z* = 95:5) proceeded with poor enantioselectivity to give the corresponding product with the opposite absolute configuration for the boron atom [(*R,E*)-**2j**, 81% yield, 74% ee, *E/Z* = 91:9].
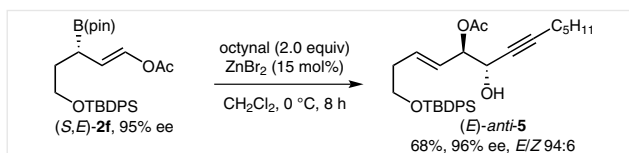

Scheme 2 Substrate scope of the copper(I)-catalyzed enantioselective boryl substitution of allyl acyal (*Z*)-**1**. *Reagents and conditions*: CuCl (0.025 mmol), (*R,R*)-BenzP* (0.025 mmol), (*Z*)-**1** (0.5 mmol), B₂(pin)₂ (0.85 mmol) and KO*t*-Bu (0.6 mmol) in DMI (1.0 mL) at 0 °C. The ee values of the products were determined by HPLC analysis. [a] 1.5 equiv of KO*t*-Bu and 2.0 equiv of B₂(pin)₂ were used. [b] NMR yield. [c] THF (0.3 mL) and DMI (0.3 mL) were used as a solvent; 10 mol% of CuCl and (*R,R*)-BenzP* were used. [d] THF (1.0 mL) was used as a solvent; 15 mol% of CuCl and (*R,R*)-BenzP* were used; 0.2 mmol scale.

We then proceeded to compare the reactivities of the allyl acetal and acyal substrates. Ally acetal **3** and acyal **1k**, which both have a trisubstituted alkene moiety, were selected as model substrates. The boryl substitution of acetal **3** provided only a trace amount of the corresponding borylated product (*E*)-**4** in 4 hours. Even after an extended reaction time (>24 h), the allyl acetal **3** remained largely intact. The low conversion of the acetal substrate was attributed to steric hindrance around the C=C double bond of the sub-
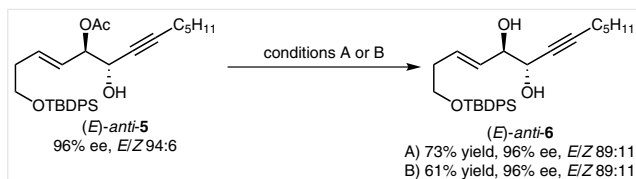
strate and the poor leaving group ability of the methyl ether group compared with the acetyl group. In contrast, the acylal substrate **1k** reacted much more effectively than the acetal to give the borylated product in 49% yield after 24 hours (Scheme 3). These results therefore demonstrate that acylal substrates can undergo allyl substitution much more effectively than the corresponding acetals.

Scheme 3 γ-Borylation of trisubstituted allyl acetal and acylal with Cu-Cl/Xantphos catalyst system. *Reagents and conditions*: CuCl/Xantphos (5 mol%), B₂(pin)₂ (1.5 equiv), KO*t*-Bu (1.0 equiv), THF, 30 °C.

The allylboronates (*S,E*)-**2f** prepared using our new method were subsequently applied to the stereoselective allylation of aldehyde (Scheme 4). Octynal was successfully allylated with boronate (*S,E*)-**2f** in the presence of ZnBr₂, which was added as a Lewis acid catalyst.[14,15] We previously found that ZnBr₂ is an efficient catalyst for enhancing the stereoselectivity and accelerating the reaction rate for the allylation of aldehydes with γ-alkoxyallylboronates.[5] With this in mind, we investigated the reaction of octynal with (*S,E*)-**2f** in the presence of ZnBr₂. Pleasingly, this reaction provided the desired product in high stereoselectivity and good *E/Z* selectivity [(*E*)-*anti*-**5**, 68% yield, 96% ee, *E/Z* = 94:6].

Scheme 4 Aldehyde allylation with optically active γ-acetoxyallylboronate (*S,E*)-**2f**. *Reagents and conditions*: (*S,E*)-**2f** (0.2 mmol), aldehyde (0.4 mmol), and dry ZnBr₂ (15 mol %) in CH₂Cl₂ (0.4 mL) at 0 °C. Dry ZnBr₂ was required to obtain high levels of stereoselectivity. (*S,E*)-**2f** with 95% ee was used. The minor *syn* isomers of **5** were present in trace amounts, which were detected by ¹H NMR analysis of the crude reaction mixtures. The ee value of the major product was determined by HPLC analysis. The *E/Z* ratios of the *anti* product were determined by ¹H NMR and HPLC analyses.

The acetyl group in the allylation product (*E*)-*anti*-**5** was readily removed under acidic conditions (Scheme 5, conditions **A**) to give the corresponding diol in 73% yield without lowering its enantiomeric purity. The acetyl group was also removed under basic conditions to afford the desired product (*E*)-*anti*-**6** in good yield without any degradation of the functional group or loss of optical purity (conditions **B**).

Scheme 5 Deprotection of the acetyl group in the allylation products under acidic and basic conditions. Conditions A: Sc(OTf)$_3$ (2.0 equiv), MeOH–H$_2$O, r.t., 24 h; conditions B: K$_2$CO$_3$ (2.0 equiv), MeOH–H$_2$O, r.t., 30 min.

In summary, we have developed a new method for the asymmetric synthesis of chiral γ-acetoxyallylboronates via the copper(I)-catalyzed boryl substitution of allyl acylals. The resulting allylboronates were used to achieve the highly stereoselective allylation of aldehydes. Furthermore, the acetyl groups of the allylated products were readily removed under basic and acidic conditions to give the corresponding 1,2-diols. This reaction therefore represents a useful method for the synthesis of 3-(E)-alkenyl-anti-1,2-diols.

Acknowledgment

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588354.

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(6) Representative examples of the routes used to synthesize the acetal and acylal substrates

  (a) **A Synthesis of Z-Allyl Dibenzyl Acetal (Scheme 6)**
The allyl acetal substrates were synthesized over several steps (a). The synthesis started from commercially available propargyl diethyl acetal, which was subjected to an acid-catalyzed acetal-exchange reaction with benzyl alcohol to give the corresponding dibenzyl acetal. The subsequent deprotonation of the alkyne moiety, followed by the alkylation of the alkynyl lithium and partial reduction of the carbon–carbon triple bond gave the allyl acetal substrate. Although the exchange reaction generally proceeded in high yield, the subsequent alkylation of the terminal alkyne with an alkyl halide was typically low-yielding.

  (b) **A Synthesis of Z-Allyl Acylal (Scheme 7)**
In contrast to the acetal substrates, the acylal substrates were much easier to prepare (b). The formylation of a terminal alkyne, followed by the *gem*-diacetylation of the resulting carbonyl moiety provided the corresponding propargyl acylals in moderate to high yields. The subsequent Z-selective reduction of the alkyne moiety in these propargyl acylals yielded the desired allylic substrates.

Scheme 6

Scheme 7
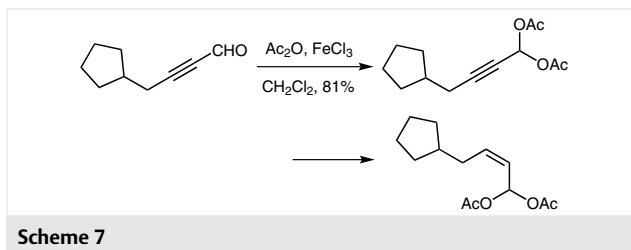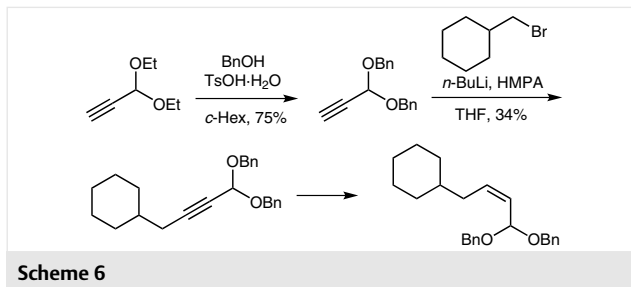
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(13) **Typical Procedure for the Enantioselective Boryl Substitution of Allyl Acylals**
CuCl (2.6 mg, 0.026 mmol), (*R,R*)-BenzP* (7.2 mg, 0.026 mol), B$_2$(pin)$_2$ (254.8 mg, 1.00 mmol), and KO*t*-Bu (84.3 mg, 0.75 mmol) were placed in a screw-capped test tube in a glove box under an argon atmosphere. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the test tube was removed from the glove box and connected to a vacuum/nitrogen manifold through a needle. Then, dry DMI (1.0 mL) was added to the mixture via a syringe with stirring at r.t. After 15–30 min, acylal (*Z*)-**1a** (129.5 mg, 0.5 mmol) was added to the reaction mixture with vigorous stirring at 0 °C. After the completion of the reaction, the mixture was directly filtered through a short silica gel column with hexane–EtOAc (90:10) as the eluent. After removal of the solvents under reduced pressure, NMR yield was determined by ^{1}H NMR analysis of the crude reaction mixture [(*S,E*)-**2a**; 79%] by using mesitylene (26.7 mg, 0.22 mmol) as the internal standard. The crude product was purified with flash chromatography (SiO$_2$, hexane–Et$_2$O = 100:0 to 90:10) to give the corresponding γ-acetoxyallylboronate (*S,E*)-**2a** (84.8 mg, 0.257 mmol, 52% isolated yield).
^{1}H NMR (392 MHz, CDCl$_3$): δ = 1.25 (s, 12 H), 1.63–1.93 (m, 3 H), 2.11 (s, 3 H), 2.52–2.71 (m, 2 H), 5.45 (dd, *J* = 9.4, 12.5 Hz, 1 H), 7.09 (d, *J* = 12.2 Hz, 1 H), 7.13–7.31 (m, 5 H). ^{13}C NMR (99 MHz, CDCl$_3$): δ = 20.7 (CH$_3$), 22.9 (br, BCH), 24.6 (CH$_3$), 24.7 (CH$_3$), 32.8 (CH$_2$), 35.0 (CH$_2$), 83.4 (C), 115.4 (CH), 125.6 (CH), 128.2 (CH), 128.4 (CH), 135.2 (CH), 142.3 (C), 168.1 (C). HRMS (EI): *m/z* [M]$^+$ calcd for C$_{19}$H$_{27}$BO$_4$: 329.20387; found: 329.20481. [α]$_D^{22,2}$ +5.4 (*c* 1.0, CHCl$_3$, 95% ee). The ee value was determined by HPLC analysis [Daicel CHIRALPAK OD-3, 2-PrOH–hexane = 0.25:99.75, 0.5 mL/min, 40 °C]: *t*$_R$ (major) = 25.44 min; *t*$_R$ (minor) = 24.83 min.

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