Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acylals: An Efficient Approach for Enantioenriched -Chiral- Acetoxyallylboronates

Author(s)
Takenouchi, Yuta; Kojima, Ryoto; Momma, Riko; Ito, Hajime

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Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acylals: An Efficient Approach for Enantioenriched α-Chiral γ-Acetoxyallylboronates

Y. Takenouchi
R. Kojima
R. Momma
H. Ito*

Division of Applied Chemistry and Frontier Chemistry Center, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido, 060-8628, Japan.
E-mail: hajito@eng.hokudai.ac.jp

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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 mono-protected anti-1,2-diol derivative with high stereoselectivity.

Key words boron, enantioselectivity, copper, catalysis, allylation

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. Allylboronates bearing a substituent at their γ-position relative to 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. 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. However, the synthetic methods used for the construction of these boronates typically require a boron source bearing stoichiometric chiral auxiliary.

We previously reported the first catalytic synthesis of α-chiral linear or carboyclic γ-alkoxyallylboronates via the copper(I)-catalyzed γ-boryl substitution of allyl acetalts. 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 reactivity toward the boryl copper nucleophile. In addition, this reaction required harsh reaction conditions to allow for the removal of the benzyl groups from the mono-protected 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.

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 or Lewis acid-catalyzed cyanation. 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.

### Scheme 1 Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acylals

- **Previous work:** Enantioselective boryl substitution of allyl acetalts
- **This work:** Enantioselective boryl substitution of allyl acylals

Easy to make
High-reactive
Enantioenriched product R₁ = allyl, R₂ = allyl, H
Easy to deprotect
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. Notably, a facile synthetic method has been reported for the direct construction of allyl acylals from aldehydes and acetanhydride using an acid catalyst.

Herein, we report the enantioselective synthesis of α-chiral γ-acetoxyallylboronates using a chiral copper catalyst and bis(pinacolato)diboron \( \text{B}_2\text{(pin)}_2 \) 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 \( (Z) - \text{1a} \) with \( \text{B}_2\text{(pin)}_2 \) in the presence of CuCl/(R,R)-BenzP* as a ligand (5 mol \%) and K(O-t-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).

In our previous study involving the borylation of allyl acetals, we only ever observed the formation of the \( (E) \)-isomer as a single product, which we attributed to the substrate undergoing an \( \text{anti-SN}_2' \) reaction mechanism with a fixed conformation because of the 1,3-allylic strain of the substrate (see Electronic Supplementary Information).

<table>
<thead>
<tr>
<th>Table 1 Optimization of the Reaction Conditions for the Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acylal (( Z )-1a)</th>
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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*, \( (R,R)\)-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 \( \text{B}_2\text{(pin)}_2 \) added to the reaction also had a considerable impact in the reactivity. For example, the use of a catalytic amount of K(O-t-Bu) (10 mol \%) yielded a trace amount of the desired product, whereas the use of small excesses of K(O-t-Bu) (1.5 equiv.) and \( \text{B}_2\text{(pin)}_2 \) (2.0 equiv.) resulted in high yield with excellent \( E/Z \) and enantioselectivity (79% yield, \( E/Z = 99:1 \), 95% ee; Table 1, entry 8). As shown in Table 2, various α-chiral γ-acetoxyallylboronates were obtained in high yields and enantioselectivities under the optimized reaction conditions. Furthermore, several optically active products bearing an allyl substituent (e.g., \( R = \text{Me} \), 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 borylation of substrates bearing a silyl ether or acetox 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). α-Branched allyl acylals ([Z]-1h and ([Z]-1i), which have steric congestion around their \( \text{C}_2\text{C} = \text{C} \) 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 \( (Z) \)-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 ([E,E]-2j, 81% yield, 74% ee, \( E/Z = 91:9 \).
We then proceeded to compare the reactivities of the allyl acetate and acylal substrates. Allyl acetate 3 and acylal 1k, which both have a tri-substituted alkene moiety, were selected as model substrates. The borylation of acetal 3 provided only a trace amount of the corresponding borylated product (E)-4 in 4 h. Even after an extended reaction time (>24 h), the allyl acetate remained largely intact. The low conversion of the acetal substrate was attributed to steric hindrance around the C=C double bond of the substrate and the poor leaving group ability of the methyl ether group compared with the acetyl group. In contrast, the acylal substrate react much more effectively than the acetal to give the borylated product in 49% yield after 24 h. These results therefore demonstrate that acylal substrates can undergo allyl substitution much more effectively than the corresponding acetals.

The allylboronates (S,E)-2f prepared using our new method were subsequently applied to the stereoselective alkylation of aldehyde (Scheme 3). Octynal was successfully allylated with boronate (Scheme 3). CuCl/Xantphos Catalyst System

\[
\text{CuCl} / \text{Xantphos} \quad (\text{S,E})-2f \quad (0.2 \text{ mmol}) + \text{aldehyde} (0.4 \text{ mmol}) \quad \text{CH}_2\text{Cl}_2 \quad \text{0 °C} \quad \text{8 h} \quad \text{88% yield, E/Z = 94:6.}
\]

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 alkylation of aldehydes. Furthermore, the acetyl groups of the alkylation 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

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Supporting Information

YES

Primary Data

NO

References and Notes

(1) (a) D. G. Hall, Boronic Acid: Preparation, Applications in Organic Synthesis and Medicine, Wiley-VCH, Weinheim, Germany, 2005
(8) A synthesis of \((Z)\)-allyl dibenzyl acetal

\[
\text{CHO} \xrightarrow{\text{AcO}, \text{FeCl}_3} \text{CH}_2\text{Cl}_2, 81\%
\]

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 yielded the desired allyl acetal. Although the exchange reaction generally proceeded in high yield, the subsequent alkylation of the terminal alkyne with an alkyl halide was typically low yielding. In contrast to the acetal substrates, the acylal substrates were much easier to prepare (b). The formylation of a terminal alkyne with benzyl alcohol to give the corresponding propargyl acylal proceeded in high yield, the subsequent alkylation of the terminal acylal moiety provided the corresponding propargyl acylals in moderate yield. The formylation of a terminal alkyne with benzyl alcohol to give the corresponding propargyl acylal proceeded in high yield, the subsequent alkylation of the terminal acylal moiety yielded the desired allylic acylal.

(a) A synthesis of \((Z)\)-allyl dibenzyl acetal

\[
\text{CHO} \xrightarrow{\text{AcO}, \text{FeCl}_3} \text{CH}_2\text{Cl}_2, 81\%
\]

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

\[
\text{CHO} \xrightarrow{\text{AcO}, \text{FeCl}_3} \text{CH}_2\text{Cl}_2, 81\%
\]

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 acylals.