Asymmetric Catalysis

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Enantioselective Synthesis of Allylboronates and Allylic Alcohols by Copper-Catalyzed 1,6-Boration**

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Abstract: *Chiral secondary allylboronates are obtained in high enantioselectivities and 1,6:1,4 ratios by the copper-catalyzed 1,6-boration of electron-deficient dienes with bis(pinacolato)-diboron ($B_2(pin)_2$). The reactions proceed efficiently using catalyst loadings as low as 0.0049 mol%. The allylboronates may be oxidized to the allylic alcohols, and can be used in stereoselective aldehyde allylborations. This process was applied to a concise synthesis of atorvastatin, in which the key 1,6-boration was performed using only a 0.02 mol% catalyst loading.*

Enantioselective transition-metal-catalyzed reactions have transformed the way in which enantiomerically enriched chiral compounds can be prepared. However, the majority of industrial-scale catalytic asymmetric processes developed to date employ precious second- or third-row transition metals that are costly and limited in availability.[1] Moreover, the chiral ligands employed in these reactions are often expensive. Therefore, new enantioselective reactions that are catalyzed by earth-abundant metals, and that proceed efficiently at very low catalyst loadings to minimize the quantity of chiral ligand employed, are in high demand.

Given the ability of electron-deficient dienes to serve as effective substrates for various catalytic asymmetric 1,6-addition reactions,[2,3] we became interested in the enantioselective 1,6-boration of α,β,γ,δ-unsaturated carbonyl compounds as a potential method to prepare functionalized chiral allylboronates[4] and allylic secondary alcohols,[5] which are versatile building blocks for synthesis. Although enantioselective 1,4-borations of electron-deficient alkenes are well-established using chiral catalysts based upon copper,[6–8] other metals,[9] or by using organocatalysts,[10] the enantioselective 1,6-boration of electron-deficient dienes is not well-developed. Progress has been made in related processes, such as enantioselective copper-catalyzed monoboration[4h] and platinum-catalyzed 1,4-diboration of 1,3-dienes.[11] Kobayashi and co-workers also recently reported four examples of enantioselective Cu^{II}-catalyzed 1,6-borations of α,β,γ,δ-unsaturated cyclic ketones with 33–89% *ee*, using a 5 mol% catalyst loading.[2j] However, these substrates were disubstituted at the β-position, and acyclic α,β,γ,δ-unsaturated carbonyls lacking an additional group at the β-carbon underwent exclusive 1,4-boration.

Herein, we describe highly enantioselective copper-catalyzed 1,6-borations of acyclic α,β,γ,δ-unsaturated esters and ketones. High selectivities for 1,6-boration over 1,4-boration are achieved without a "blocking" substituent at the β-carbon. Furthermore, the chiral copper complex employed exhibits high stability, allowing the reactions to proceed effectively at catalyst loadings as low as 0.0049 mol%. Application of this method to the synthesis of the cholesterol-lowering drug atorvastatin is also described.

This study began with a search for an effective method for the enantioselective copper-catalyzed 1,6-addition of bis(pinacoloto)diboron (**1**, 1.2 equiv) to benzyl sorbate (**2a**) (Scheme 1; see the Supporting Information for full details). The best results were obtained using [$CuF(PPh_3)_3{\cdot}2MeOH$] and the Josiphos ligand **L1**[6c,d,8c,f] in THF at room temperature, in the presence of *i*PrOH (2.0 equiv) as a protic additive.[6c,8f] The 1,6-boration of **2a** proceeded smoothly on a 0.50 mmol scale using only 0.20 mol% of the copper complex [$CuF(PPh_3)_3{\cdot}2MeOH$/**L1**] (Scheme 1). After the reaction was complete, filtration of the mixture through a short plug of silica using EtOAc as the eluent and removal of the solvent provided the *E*-allylboronate **3a**, accompanied by HOB(pin). Oxidation of this mixture with $NaBO_3{\cdot}4H_2O$[12] then gave the allylic alcohol **4a** in 91% yield of isolated product over the two steps and in 95% *ee*.[13] Alternatively, pure allylboronate **3a** was isolated in 80% yield and 96% *ee* by using 5% Et_2O/hexane in the filtration of the 1,6-boration reaction mixture.[14] A range of other α,β,γ,δ-unsaturated benzyl esters also underwent enantioselective 1,6-boration–oxidation to provide allylic alcohols **4a**–**4f** in 70–92% yield, high regioselectivities (>19:1 ratio of 1,6:1,4-addition) and high enantioselectivities (95–96% *ee*). Along with benzyl sorbate (**2a**), substrates containing other linear alkyl groups at the δ-position were effective (**4b** and **4c**). The process is compatible with nitrogen-containing substituents (**4d** and **4h**), an alkyl chloride (**4e**), and silyl ethers (**4f** and **4g**). Substrates containing ethyl esters (**4g** and **4h**) or *tert*-butyl

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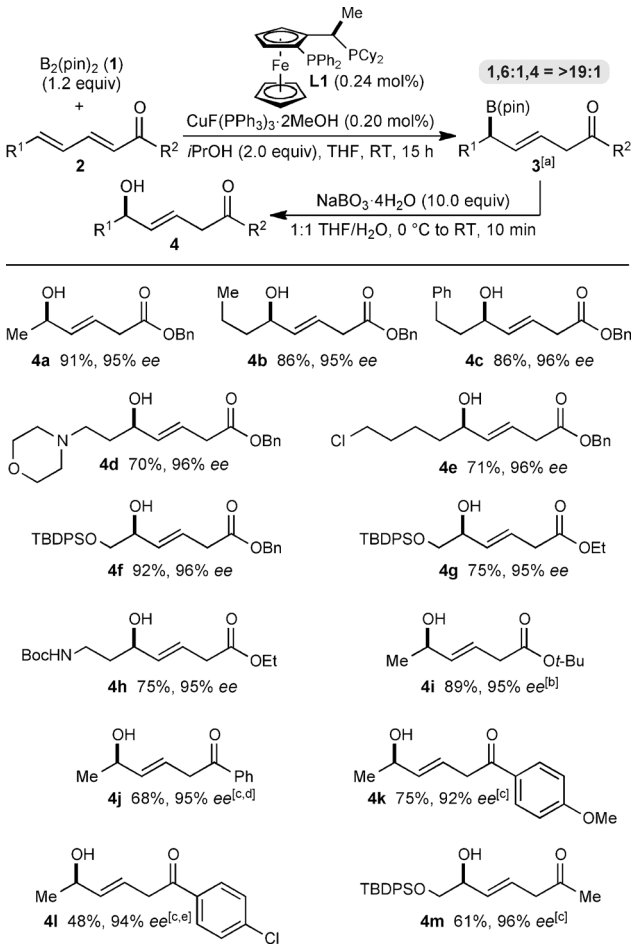
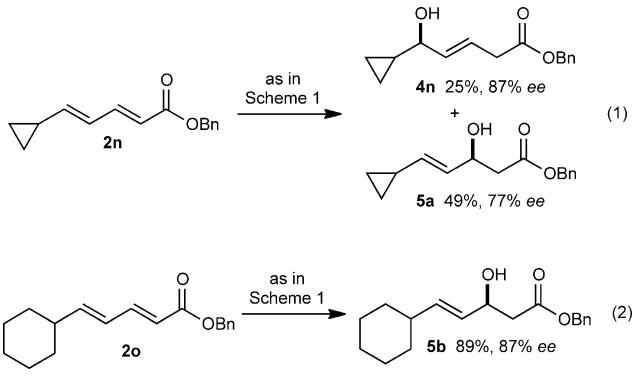


Scheme 1. Scope of enantioselective 1,6-boration–oxidation. Reactions were conducted with 0.50 mmol of **2**. Cited yields are of isolated material. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a] Pure allylboronate **3a** (R^1 = Me, R^2 = OBn) was isolated in 80% yield and 96% *ee* without performing the oxidation. [b] Enantiomeric excess determined on the corresponding benzoate ester. [c] Oxidation was performed using 5.0 equiv of $NaBO_3·4H_2O$. [d] Isolated as a 12:1 inseparable mixture of **4j** and the *E*-conjugated enone. [e] Isolated as a 15:1 inseparable mixture of **4l** and the *E*-conjugated enone.

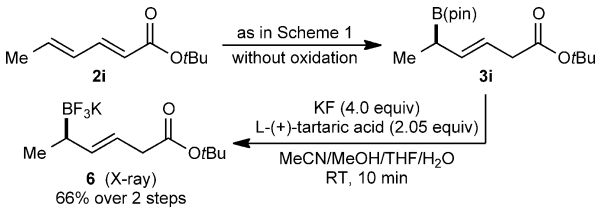
esters (**4i**) were also tolerated. However, a substrate containing a phenyl group at the δ-position provided a complex mixture of unidentified products. The process is not limited to esters as the activating group; α,β,γ,δ-unsaturated aryl and alkyl ketones were also effective (**4j**–**4m**).

The selectivity for 1,6-boration over 1,4-boration is sensitive to steric effects, as shown by the boration–oxidation of **2n**, which contains a δ-cyclopropyl group. This reaction gave the 1,4-adduct **5a** as the major product in 49% yield and 77% *ee*, while the 1,6-adduct **4n** was isolated in 25% yield and 87% *ee* [Eq. (1)]. Increasing the size of the δ-substituent further led to exclusive 1,4-boration, as shown by the cyclohexyl-substituted substrate **2o**, which gave the β-hydroxyester **5b** only, in 89% yield and 87% *ee* [Eq. (2)].

The sense of enantioinduction in these reactions was determined by X-ray crystallography of potassium allyltrifluoroborate **6**, which was obtained by 1,6-boration of **2i**

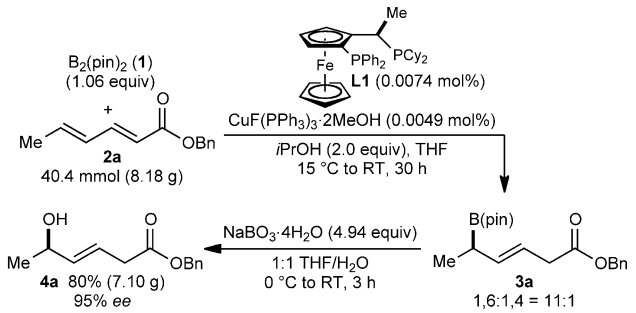


followed by immediate treatment of the resulting allylboronate **3i** with KF and L-(+)-tartaric acid according to procedure of Lennox and Lloyd-Jones[15] (Scheme 2).[16]



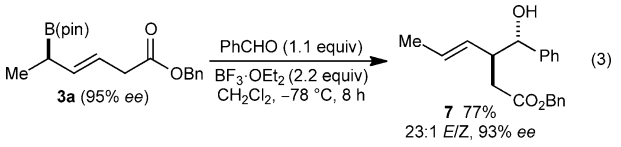
Scheme 2. Conversion of **2i** into the allyltrifluoroborate **6**.

Next, larger scale 1,6-borations were conducted to assess whether the catalyst loading could be decreased.[17] A 40.4 mmol scale 1,6-boration of **2a** with 1.06 equiv of $B_2(pin)_2$ (**1**), 0.0049 mol% of $CuF(PPh_3)_3·2MeOH$ and 0.0074 mol% of **L1** was complete in 30 h, providing **3a** as an 11:1 mixture of 1,6:1,4-boration isomers (Scheme 3). Oxidation of **3a** then gave **4a** in 80% yield and 95% *ee* over the two steps. Notably, in this experiment, only 1.9 mg of the chiral ligand **L1** was required to prepare 7.10 g of **4a**.[17]



Scheme 3. Larger scale 1,6-boration-oxidation of **2a**.

Along with oxidation to allylic alcohols, the allylboronates resulting from 1,6-boration can be employed in stereoselective carbonyl allylborations. For example, treatment of **3a** with benzaldehyde in the presence of $BF_3·OEt_2$ provided homoallylic alcohol **7** in 77% yield as a 23:1 inseparable mixture of *E*/*Z* isomers, and in 93% *ee* for the *E*-isomer [Eq. (3)].[18]



As a further demonstration of its utility, the enantioselective 1,6-boration was applied in a concise synthesis of atorvastatin (**13**), a well-known inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase and the active ingredient in Lipitor, currently the best-selling pharmaceutical in history.[19–21] The synthesis began with the preparation of diene **8**.[22] Enantioselective 1,6-boration–oxidation of geometrically pure **8** (obtained in 39% overall yield from commercial starting materials) on a 0.40 mol scale gave the allylic alcohol **9** in 87% yield and 95% *ee* (Scheme 4, top). However, multiple recrystallizations were required to obtain **8** in geometrically pure form, and for reasons of practicality as well as overall yield, it was preferable to use a 16:1 *E*:*Z* mixture of **8** (obtained in 60% overall yield from commercial starting materials) in the synthesis of atorvastatin (Scheme 4, bottom).[22]

Enantioselective 1,6-boration of this 16:1 *E*:*Z* mixture of **8** on a 7.40 mmol scale proceeded smoothly using only 0.02 mol% of the Cu^{I}-Josiphos complex, and oxidation of the resulting allylboronate with $NaBO_3 \cdot 4H_2O$ provided the allylic alcohol **9** in 84% *ee* (Scheme 4, bottom). The lower enantioselectivity of this reaction is due to the presence (ca. 6%) of the minor 2*E*,4*Z*-isomer of diene **8**.[23] Without purification, **9** was isomerized to the conjugated ester **10** with catalytic DBU in MeCN at room temperature. The crude α,β-unsaturated ester **10** was then reacted with benzaldehyde and KO*t*Bu according to the method of Evans and Gauchet-Prunet,[24] which gave the benzylidene acetal-protected *syn*-1,3-diol **11** with high diastereoselectivity (>19:1 d.r.).[21c] Recrystallization of **11** from *i*PrOH/hexane led to selective crystallization of the racemate, which enabled isolation of an enantioenriched sample of **11** (>99% *ee*) in 34% yield over the four steps from **8** after concentration of the mother liquor. Deprotection of the acetal of **11** with HCl was followed by basic hydrolysis of the ester with NaOH to give the sodium salt **12** of atorvastatin (**13**) in 89% yield, which was converted into atorvastatin (**13**) itself in 94% yield by acidification.

In conclusion, we have reported highly enantioselective copper-catalyzed 1,6-borations of α,β,γ,δ-unsaturated carbonyl compounds with bis(pinacoloto)diboron (**1**). For the first time, high selectivities for 1,6-boration over 1,4-boration are achieved without a "blocking" substituent at the β-carbon. The reactions proceed at ambient temperature and are promoted by a Cu^{I}-Josiphos complex at catalyst loadings as low as 0.0049 mol% to provide chiral allylboronates on the way to chiral secondary allylic alcohols. Application of this process on a 40.4 mmol scale has been demonstrated. The allylboronates may also be employed in highly stereoselective allylborations of aldehydes. Finally, the utility of this method was demonstrated by a concise synthesis of atorvastatin (**13**), the well-known cholesterol-lowering drug. Efforts to understand the origin of the selectivity for 1,6-boration over 1,4-boration, which is currently unclear, along with the development of other catalytic enantioselective 1,6-additions, are topics for future study in our laboratory.

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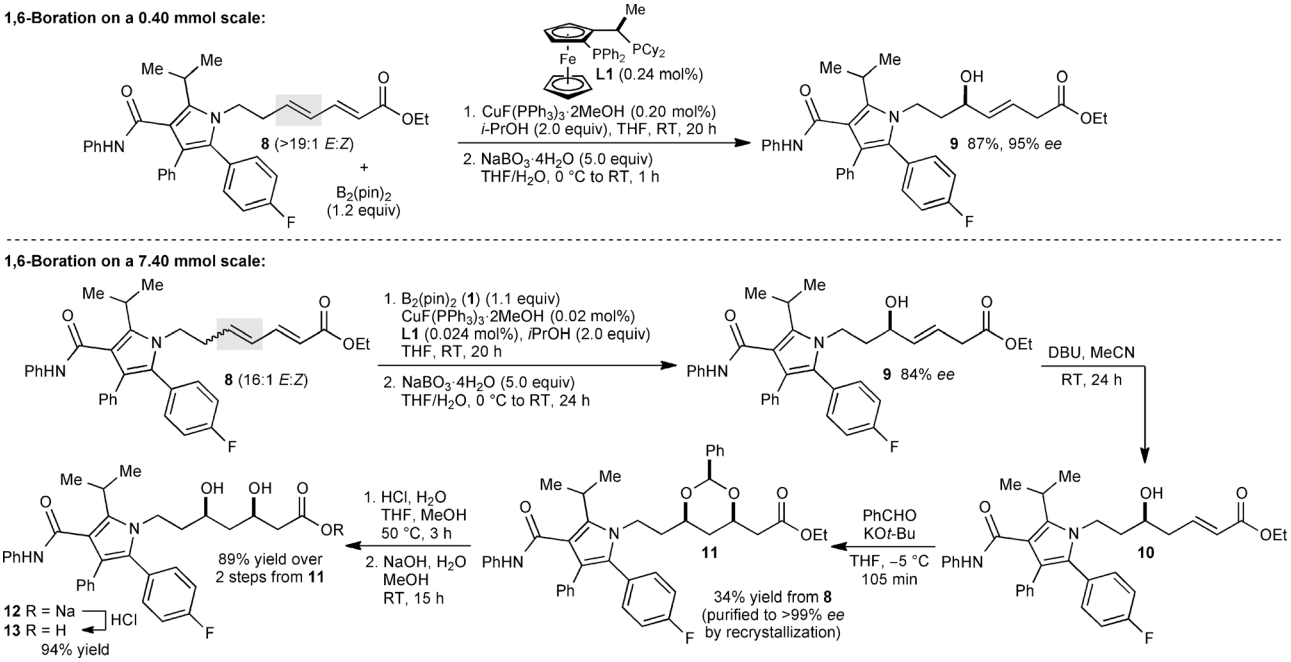

Scheme 4. Enantioselective synthesis of atorvastatin (**13**).

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[13] The absolute configurations of the products of this study were assigned by analogy with the allyltrifluoroborate **6**, which was determined by X-ray crystallography (see the Supporting Information).

[14] The lower yield of **3a** compared with that of **4a** obtained in the two-step procedure is due to decomposition of **3a** on silica during the longer duration of the filtration.

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[17] A 25.0 mmol scale 1,6-boration of **2a** with a 0.02 mol% catalyst loading was complete in 15 h, and provided **4a** in 92% yield and 94% *ee* after oxidation of **3a** (see the Supporting Information for full details).

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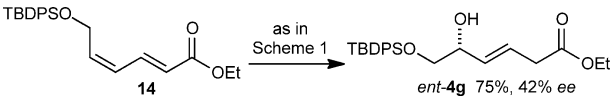
[22] See the Supporting Information for details of the synthesis of **8**.

[23] The 2*E*,4*Z*-α,β,γ,δ-unsaturated ester **14** underwent 1,6-boration–oxidation to give *ent*-**4g** in only 42% *ee*, with the opposite absolute configuration to that depicted in Scheme 1.



[24] D. A. Evans, J. A. Gauchet-Prunet, *J. Org. Chem.* **1993**, *58*, 2446 – 2453.

