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Letter

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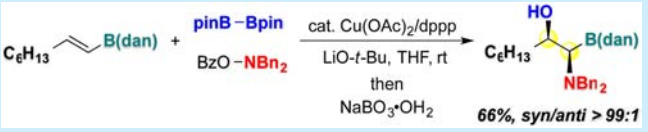
Copper-Catalyzed Regio- and Stereoselective Aminoboration of Alkenylboronates

Daiki Nishikawa, Koji Hirano,* and Masahiro Miura*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

Supporting Information

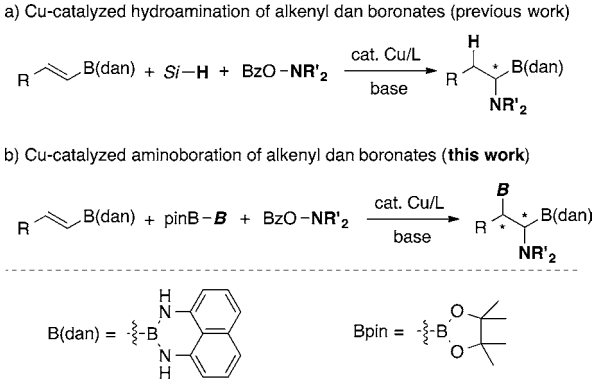
ABSTRACT: A copper-catalyzed aminoboration of alkenyl dan boronates (dan = 1,8-diaminonaphthyl) with diboron reagents and hydroxylamines has been developed. The reaction proceeds regio- and stereoselectively to form the corresponding β-boryl-α-aminoboronic acid derivatives of potent interest in medicinal chemistry. Additionally, the ligand-controlled *syn*/*anti* diastereoselectivity switching and preliminary asymmetric catalysis are also described.



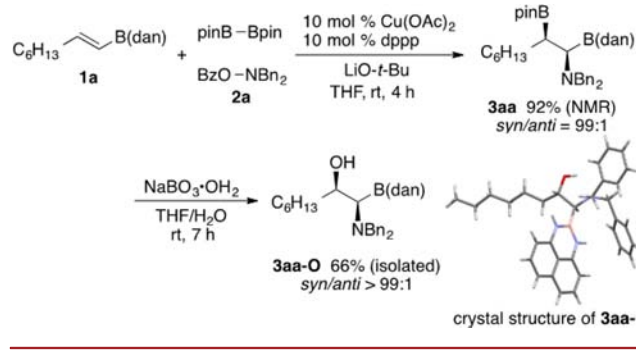
In recent decades, α-aminoboronic acid derivatives have received great attention because of their important applications in medicinal chemistry,[1] as exemplified by proteasome inhibitors[2] such as Bortezomib, Ixazomib, and Delanzomib.[3] Additionally, they are useful synthetic building blocks in metal-catalyzed cross-coupling chemistry[4] as well as key motifs in sensing systems.[5] The enormous potential of α-aminoboronic acids prompts many synthetic chemists to develop protocols for their efficient preparation.[6] Representative reported strategies include the nucleophilic boryl addition to imines,[7] Matteson's homologation,[8] hydroboration of enamides,[9] C−H borylation α to amines,[10] and Curtius-type rearrangement of α-borylcarboxylic acids.[11] Despite certain progress, further developments for more efficient and versatile syntheses of α-aminoboronic acids are still strongly desired. In this context, we recently developed the copper-catalyzed net hydroamination approach using hydrosilanes and *O*-benzoylhydroxylamines as the hydride and electrophilic amination reagent,[12,13] respectively. The electrophilic amination by copper catalysis can uniquely convert the alkenyl dan boronates (dan = 1,8-diaminonaphthyl)[14] to the desired α-aminoboronic acids with high regio- and stereoselectivity (Scheme 1a).[15] During our continuous interest in this chemistry, we envisioned that the replacement of hydrosilanes with diborons could allow aminoboration[16] of the alkenylboronates, providing α-aminoboronic acid derivatives with the post-functionalized boryl group at the β position, which are difficult to prepare by other means (Scheme 1b). In this letter, we report preliminary results of this study, including ligand-controlled *syn*/*anti* diastereoselectivity switching and application to asymmetric catalysis.

We began optimization studies with (*E*)-2-octenyl dan boronate **1a**, bis(pinacolato)diboron (pinB−Bpin), and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**) as model substrates. After an extensive screening of various reaction parameters, we found that the aminoboration proceeded smoothly in THF at room temperature in the presence of a $Cu(OAc)_2$/dppp catalyst and LiO-*t*-Bu base to deliver the desired β-boryl-α-aminoboronate **3aa** in 92% NMR yield with 99:1 *syn*/*anti* diastereoselectivtiy (Scheme 2). The product **3aa** was unstable

Scheme 1. Copper-Catalyzed Electrophilic Amination Approaches to α-Aminoboronic Acids



Scheme 2. Optimal Conditions for Copper-Catalyzed Aminoboration of Alkenyl dan Boronate 1a with *O*-Benzoyl-*N*,*N*-dibenzylhydroxylamine (2a)



to chromatographic purification and thus was oxidized by $NaBO_3 \cdot OH_2$ into the β-hydroxyl-α-aminoboronate **3aa-O** (66% overall yield, *syn*/*anti* > 99:1). The structure and relative

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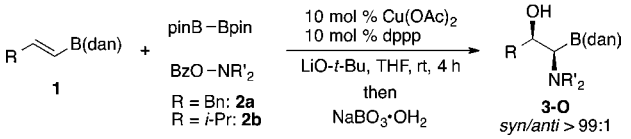
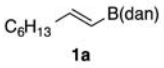
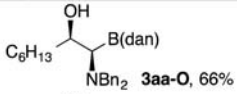
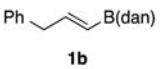
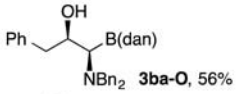
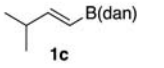
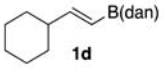
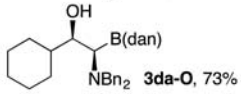
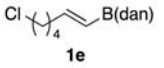
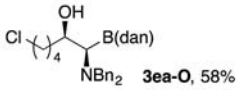
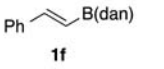
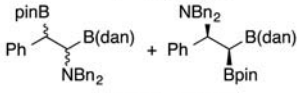
stereochemistry of **3aa-O** were unambiguously determined by X-ray analysis.[17] Additionally, in contrast to our previous hydroamination,[12a] the corresponding pinacol boronate (*E*)-**1a-Bpin** and *N*-methyliminodiacetic acid boronate (*E*)-**1a-B(MIDA)** could also be employed, albeit with lower NMR yields (data not shown).[18] In the latter case, however, we detected the aminoboration product not in the B(MIDA) form but in the Bpin form, thus suggesting in situ ligand exchange between pinacol and *N*-methyliminodiacetic acid followed by the aminoboration.[19]

With conditions in Scheme 2, we investigated the scope and limitation of the alkenyl dan boronates **1** (Table 1). In addition

Table 1. Copper-Catalyzed Aminoboration of Various Alkenyl dan Boronates 1[a]



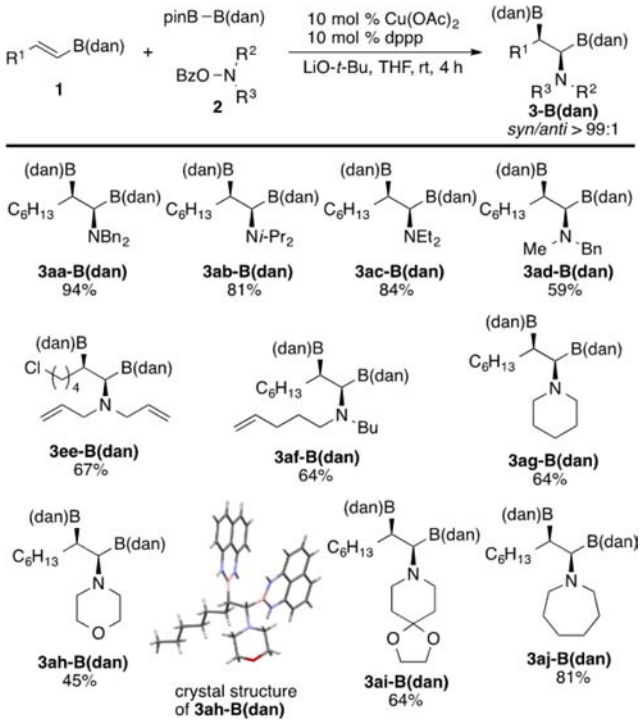
entry	1	2	3, yield (%)[b]
1	 **1a**	**2a**	 **3aa-O**, 66%
2	 **1b**	**2a**	 **3ba-O**, 56%
3	 **1c**	**2b**	 **3cb-O**, 61%
4	 **1d**	**2a**	 **3da-O**, 73%
5	 **1e**	**2a**	 **3ea-O**, 58%
6	 **1f**	**2a**	 **3fa**, 57%, 1/2/1.8[c]

[a]Reaction conditions: **1** (0.25 mmol), pinB−Bpin (0.38 mmol), **2** (0.38 mmol), $Cu(OAc)_2$ (0.025 mmol), dppp (0.025 mmol), LiO-*t*-Bu (0.38 mmol), THF (1.5 mL), N_2, 4 h. Oxidation conditions: $NaBO_3 \cdot OH_2$ (2.5 mmol), THF/H_2O (1/1), open flask, 7 h. [b]Isolated yield. [c]^1H NMR yield in the Bpin form. The ratio of three isomers is shown.

to **1a**, more sterically demanding benzyl-, isopropyl-, and cyclohexyl-substituted substrates also underwent the aminoboration smoothly and stereoselectively at room temperature. Also in these cases, products were isolated as the corresponding *β*-hydroxyl-*α*-aminoboronates **3ba-O**, **3cb-O**, and **3da-O** after the oxidation with $NaBO_3 \cdot OH_2$ (entries 2−4). The alkyl-Cl group in **1e** was tolerated under the copper catalysis, and **3ea-O** was formed in an acceptable overall yield (entry 5). However, the styrylboronate **1f** gave a complicated mixture of regio- and stereoisomers (entry 6), which arises from the effective phenyl−vinyl conjugation over the hyperconjugation of the vinyl boronate moiety (vide infra).

We next attempted the aminoboration with various hydroxylamines **2** other than **2a** and **2b**; however, we immediately found that the product was highly unstable even for the oxidative conditions with $NaBO_3 \cdot OH_2$ as well as aq. H_2O_2.[20] Thus, we turned our attention to pinB−B(dan)[14b] instead of pinB−Bpin to introduce the more stable and easy-to-handle B(dan) moiety to the product. Pleasingly, the standard $Cu(OAc)_2$/dppp catalyst system was directly applied to the aminoboration with pinB−B(dan), and the desired B(dan)-incorporated products were selectively formed.[21] Representative results were demonstrated in Scheme 3. The reaction was

Scheme 3. Copper-Catalyzed Aminoboration of Alkenyl dan Boronates 1 with Various Hydroxylamines 2



compatible with acyclic amines such as *N*,*N*-diethyl- and *N*-benzyl-*N*-methylamines (**3ac-B(dan)** and **3ad-B(dan)**). The unactivated terminal olefins remained intact, and the aminoboration proceeded exclusively at the alkenyl boronate moiety (**3ee-B(dan)** and **3af-B(dan)**). Owing to the better stability of the B(dan), *N*,*N*-dibenzyl- and *N*,*N*-diisopropylamine derivatives were also obtained in higher isolated yields, compared to the case with pinB−Bpin (**3aa-B(dan)** vs **3aa-O** and **3ab-B(dan)** vs **3cb-O**). Additionally, cyclic piperizine, morpholine, acetal-protected piperidone, and azepane also participated in the reaction to deliver the *β*-boryl-*α*-aminoboronates **3ag-B(dan)**−**3aj-B(dan)** in good yields with >99:1 syn/anit selectivity. The relative stereochemistry of **3ah-B(dan)** was also confirmed by crystallographic analysis.[17]

While still preliminary, application to asymmetric catalysis is also possible. A brief survey of chiral bisphosphine ligands identified (*R*,*R*)-Ph-BPE to be a promising candidate, and the enantioenriched *β*-hydroxyl-*α*-aminoboronates **3aa-O** and **3ea-O** were obtained with 88:12 and 85:15 er, respectively (Scheme 4). Efforts for improvement of the enantiomeric ratio and determination of the absolute configuration are ongoing.

In the course of the ligand optimization studies, we found that the diastereoselectivity of **3aa** was largely dependent on the external ligand: 1,2-bis{di(4-methoxyphenyl)phosphino}-benzene (MeO-dppbz) in 1,4-dioxane switched the stereochemistry of the reaction to form **3aa** with 14:86 *syn*/*anti*

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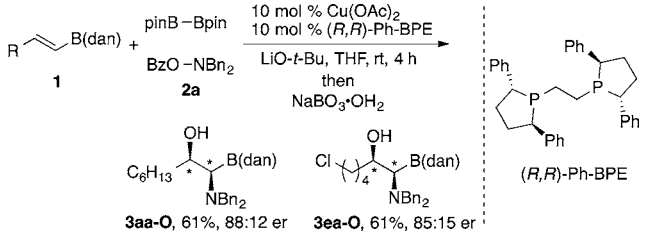
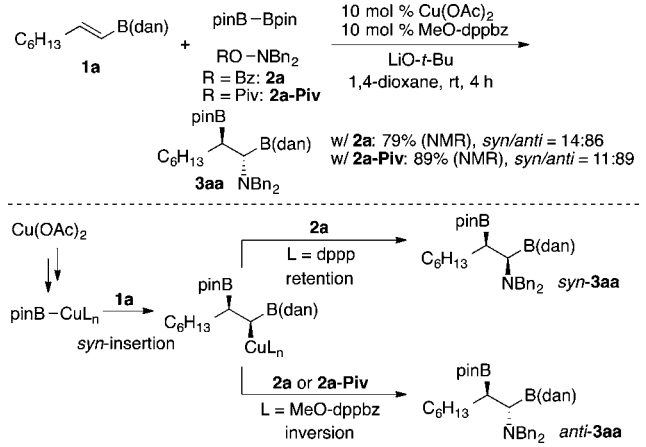
Scheme 4. Preliminary Results of Enantioselective Aminoboration



selectivity (Scheme 5).[18] The use of *O*-pivaloylhydroxylamine **2a-Piv** instead of **2a** further increased the *anti* selectivity to

Scheme 5. Copper-Catalyzed *anti*-Selective Aminoboration of 1a with 2a and Proposed Pathway



11:89. From a mechanistic point of view, the stereochemical switching can occur at the C–N bond-forming step following regioselective *syn*-borylcupration[22] controlled by the hyperconjugation between the Cu–C σ bond and the empty p orbital on boron.[23] In the case of the dppp ligand, the stereoretentive amination[15f,16a,24] proceeds while the MeO-dppp-ligated alkylcopper intermediate couples with **2a** with inversion of configuration. Similar condition-dependent stereoretentive and/or -invertive bond formations using benzylcopper species were recently reported by several groups.[25] However, a detailed mechanism still remains to be elucidated.[26]

In conclusion, we have developed a copper-catalyzed regio- and stereoselective aminoboration of alkenyl dan boronates with diboron reagents and hydroxylamines to deliver the corresponding β-boryl-α-aminoboronates in good yields. The boryl group at the β position can be a useful synthetic handle for further manipulations, and as such an example, it could be readily oxidized into the hydroxyl group upon treatment with $NaBO_3{\cdot}OH_2$, thus providing the β-hydroxyl-α-aminoboronate being otherwise difficult to prepare. Additionally, preliminary asymmetric catalysis and unique ligand-controlled *syn*/*anti* diastereoselectivity switching are also disclosed. Further manipulations of the products for more valuable and highly functionalized α-aminoboronic acids[27,28] are now under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02338.

^{1}H, ^{13}C{^{1}H}, and ^{11}B NMR spectra for products and ORTEP drawings (PDF)

Crystallographic data for **3aa-O** (CIF)

Crystallographic data for **3ah-B(dan)** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: k_hirano@chem.eng.osaka-u.ac.jp.

*E-mail: miura@chem.eng.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

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(17) Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Center (CCDC 1496616 and 1496617). See the Supporting Information for details. The relative stereochemistry of other products is tentatively assigned by analogy.
(18) See the Supporting Information for more detailed optimization studies.
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(20) We tested H_2O_2-mediated oxidation of the products under various pH conditions. However, the aminoboration products completely decomposed. Thus, at present, the use of Bdan is indispensable.
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(26) Unfortunately, the MeO-dppbz-promoted *anti*-selective aminoboration was not general, being specific to the reaction of **1a** with pinB−Bpin and **2a**: With the alkenylboronate **1c** and diisopropylamine **2b** under otherwise identical conditions, the syn/anti diastereoselectivity was nearly 50:50.
(27) We tried the deprotection of the dan moiety under various conditions. The corresponding free boronic acid can be formed under HCl-promoted acidic conditions; however, the isolation was difficult at present. Particularly, the separation from the diaminonaphthalene·2HCl salt was quite problematic.
(28) We tested the several transformations, such as the Suzuki−Miyaura coupling, of the C−B bond at the germinal amino boronate carbon. At present, however, the reactions remain unsuccessful.

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