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Asymmetric Synthesis of α-Aminoboronic Acid Derivatives by Copper-Catalyzed Enantioselective Hydroamination

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Supporting Information

ABSTRACT: A copper-catalyzed regio- and enantioselective hydroamination of alkenyl dan boronates (dan =1,8-diaminonaphthyl) with hydrosilanes and hydroxylamines proceeds to deliver the chiral α-aminoboronic acids in good yields with high enantiomeric ratios. The key to success is the introduction of an umpolung, electrophilic amination strategy. The copper catalysis can provide an unprecedented catalytic asymmetric approach to alkyl-substituted chiral α-aminoboronic acid derivatives of great potential in the fields of organic synthesis and medicinal chemistry.

Organoboron compounds are ubiquitous synthetic intermediates in modern organic synthesis because C−B bonds can be readily transformed into versatile C−C and C−heteroatom bonds.[1] Additionally, some unique biological activities of organoborons themselves have recently been uncovered.[2] Among them, optically active α-aminoboronic acids have now received significant attention since they are pharmacophores in proteasome inhibitors such as Bortezomib and Ixazomib (Figure 1),[3] and are synthetically useful chiral

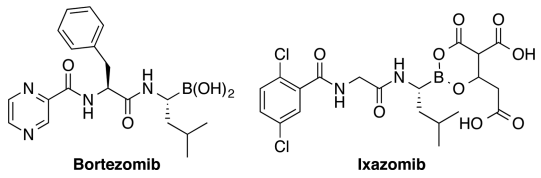
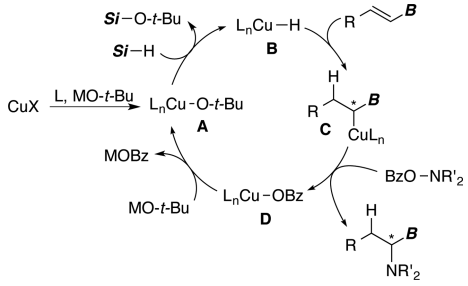


Figure 1. α-Aminoboronic acids as pharmacophores in proteasome inhibitors.

building blocks in the Pd-catalyzed cross-coupling chemistry.[4] However, their synthesis largely relies on diastereoselective methods with a stoichiometric amount of chiral auxiliaries: Matteson's homologation[5] with pinanediol;[4] Curtius rearrangement of α-borylacetic acids protected with a pinene-derived iminodiacetic acid;[6] Cu-catalyzed borylation of optically active *N*-*tert*-butanesulfinyl aldimines.[7] Fernández,[8a] Morken,[8b] and Liao[8c] independently succeeded in the catalytic enantioselective boryl addition to aromatic aldimines, but there still remains a great challenge for application to aliphatic aldimines, namely preparation of optically active α-aminoboronic acids bearing alkyl substituents, which are key motifs in the above proteasome inhibitors. Thus, further development of asymmetric catalysis for the preparation of optically active α-aminoboronic acids is greatly appealing. Herein, we report a Cu-catalyzed regio- and enantioselective hydroamination[9,10] of alkenyl dan boronates (dan =1,8-diaminonaphthyl) with hydrosilanes and hydroxylamines. The Cu catalysis can provide the first catalytic enantioselective approach to chiral α-aminoboronic acids that have unactivated alkyl side chains, to the best of our knowledge.[11]

Our scenario illustrated in Scheme 1 is based on recent advances in the electrophilic amination with chloro- and

Scheme 1. Working Hypothesis (L = Ligand)



hydroxylamines,[12,13] particularly, Cu-catalyzed hydroamination independently developed by us[13e,f,i] and Buchwald[14] research group. Initial off-cycle salt metathesis of Cu salts with the alkoxide base and ligand coordination form the starting L_nCuO-*t*-Bu **A**. A L_nCu-H species **B** is then generated by the action of the hydrosilane,[15,16] and subsequent regioselective insertion of the boron-substituted alkene affords the alkylcopper intermediate **C**.[16] The electrophilic amination with the hydroxylamine delivers the desired chiral α-aminoboronic derivative along with the $L_nCu-OBz$ complex **D**. The catalytic cycle is completed by the regeneration of **A** through ligand exchange with the alkoxide base. The enantioselectivity can be determined in the insertion step (**B** to **C**), and the following C−N formation occurs with retention of configuration.[12f,13d] The regioselectivity issue is also expected, but hyperconjugation between the Cu−C σ bond and the empty p orbital on boron[17] in **C** can control the regioselectivity in the insertion step.

To check the feasibility of the working hypothesis, we first attempted to develop the nonenantioselective variant. Pleasingly, our previous optimal conditions (a $Cu(OAc)_2/CF_3$-dppbz catalyst, polymethylhydrosiloxane (PMHS), LiO-*t*-Bu, DCE, rt)[13e] could be directly applied to the reaction of 1,8-diaminonaphthalene-protected alkenyl dan boronate **1a**[18] with morpholino benzoate (**2a**), and the α-aminoboronic acid

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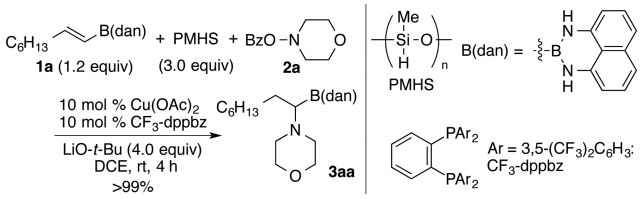
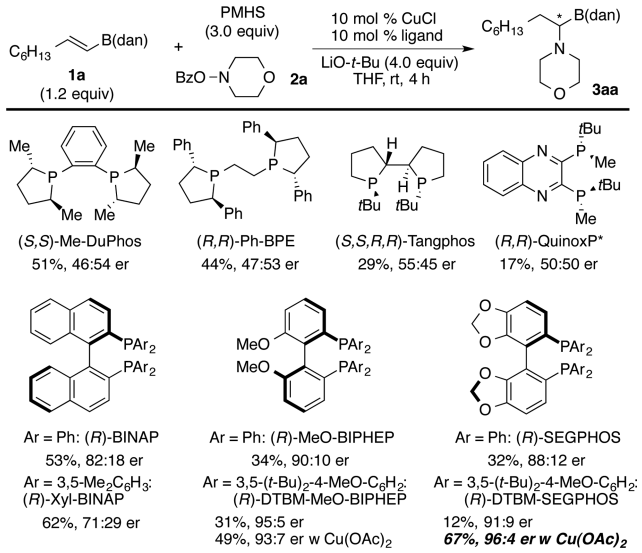
derivative **3aa** was obtained quantitatively with the shown perfect regioselectivity (Scheme 2). Some additional observations are to be noted: pinacol- or iminodiacetic-acid-protected alkenylboronates **1a-Bpin** and **1a-B(MIDA)** gave no hydroaminated product; sterically and electronically related other monodentate and bidentate phosphine ligands are less effective.[19]

Scheme 2. Development of Non-enantioselective Conditions



Prompted by the success in Scheme 2, we began our optimization studies on the enantioselective Cu catalyst by evaluation of chiral ligands combined with CuCl (Scheme 3).

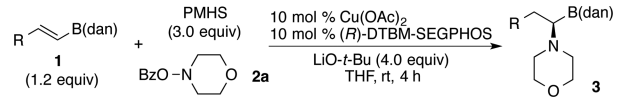
Scheme 3. Optimization Studies for Copper-Catalyzed Enantioselective Hydroamination of 1a with 2a

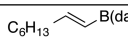
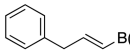
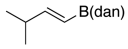
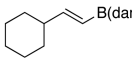
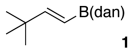
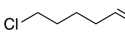
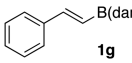
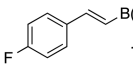
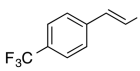


Unfortunately, the previous systems including (*S,S*)-Me-DuPhos and (*R,R*)-Ph-BPE were insufficient. Structurally similar (*S,S,R,R*)-Tangphos and (*R,R*)-QuinoxP* also remained unsuccessful. On the other hand, some chiral biarylbisphosphine ligands induced good enantioselectivity. Particularly, bulky (*R*)-DTBM-MeO-BIPHEP and (*R*)-DTBM-SEGPHOS gave promising results (95:5 and 91:9 er). Subsequent screening of Cu salts identified a combination of $Cu(OAc)_2$ and (*R*)-DTBM-SEGPHOS to be optimal in view of the yield and enantiomeric ratio, and the desired **3aa** was isolated in 67% yield with 96:4 er. Without LiO-*t*-Bu, no reaction occurred under otherwise identical conditions (data not shown).[19]

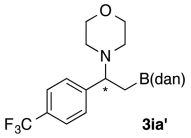
With the optimized conditions in hand, we performed the catalytic enantioselective hydroamination of an array of alkenyl dan boronates **1** with **2a** (Table 1). In addition to the simple **1a** (entry 1), the Cu catalysis accommodated bulky substituents at the allylic position, including benzyl (**1b**), isopropyl (**1c**), and cyclohexyl (**1d**) groups, and the corresponding hydroaminated products **3ba**–**3da** were formed in synthetically useful yields (53–79%) with good enantiomeric ratios (92:8–98:2 er; entries 2–4). Exceptionally, *tert*-butyl-substituted **1e** gave somewhat lower enantioselectivity (89:11 er; entry 5). The alkyl-Cl moiety in **1f** was compatible under the standard reaction conditions, and **3fa** was obtained with 97:3 er (entry 6). The styryl dan boronate derivatives could also be employed: **1g** and **1h** underwent the hydroamination regioselectively[20] and enantioselectively to furnish the optically active **3ga** and **3ha** with 94:6 and 99:1 er, respectively (entries 7 and 8). On the other hand, the highly electron-withdrawing CF_3 group perturbed the hyperconjugation proposed in Scheme 1, and regioisomeric **3ia** and **3ia′** were isolated in 17 and 67% yields (entry 9). However, the enantiomeric ratios of both products were still so high (99:1 er for **3ia** and 96:4 er for **3ia′**, respectively).

Table 1. Copper-Catalyzed Enantioselective Hydroamination of Various Alkenyl dan Boronates 1 with 2a[a]



entry	1	3, yield (%),[b] er[c]
1	 1a	**3aa**, 67%, 96:4
2	 1b	**3ba**, 68%, 98:2
3	 1c	**3ca**, 53%, 92:8
4	 1d	**3da**, 79%, 95:5
5	 1e	**3ea**, 64%, 89:11
6	 1f	**3fa**, 53%, 97:3
7	 1g	**3ga**, 49%, 94:6
8	 1h	**3ha**, 58%, 99:1
9[d]	 1i	**3ia**, 17%, 99:1

[a]Conditions: $Cu(OAc)_2$ (0.025 mmol), (*R*)-DTBM-SEGPHOS (0.025 mmol), **1** (0.30 mmol), **2a** (0.25 mmol), PMHS (0.75 mmol, based on SiH), LiO-*t*-Bu (1.0 mmol), THF (1.5 mL), rt, 4 h, N_2. [b]Isolated yields are given. [c]Determined by HPLC analysis on a chiral stationary phase. [d]The regioisomer **3ia′** was also obtained in 67% yield with 96:4 er.



We subsequently investigated the scope of hydroxylamines **2** (Scheme 4). The asymmetric Cu catalysis was tolerated with a wide range of cyclic amines involving piperidine (**3ab**), tetramethylpiperidine (**3ac**), azepane (**3jd**), piperazine (**3ae**), acetal-protected piperidone (**3cf**), tetrahydroisoquinoline (**3ag**), and tetrahydrothienopyridine (**3ah** and **3jh**). Additionally, the enantiomeric ratios are generally good to high (90:10–99:1 er), except for **3ag** (88:12 er). The enantioselective hydroamination involving acyclic amines also proceeded

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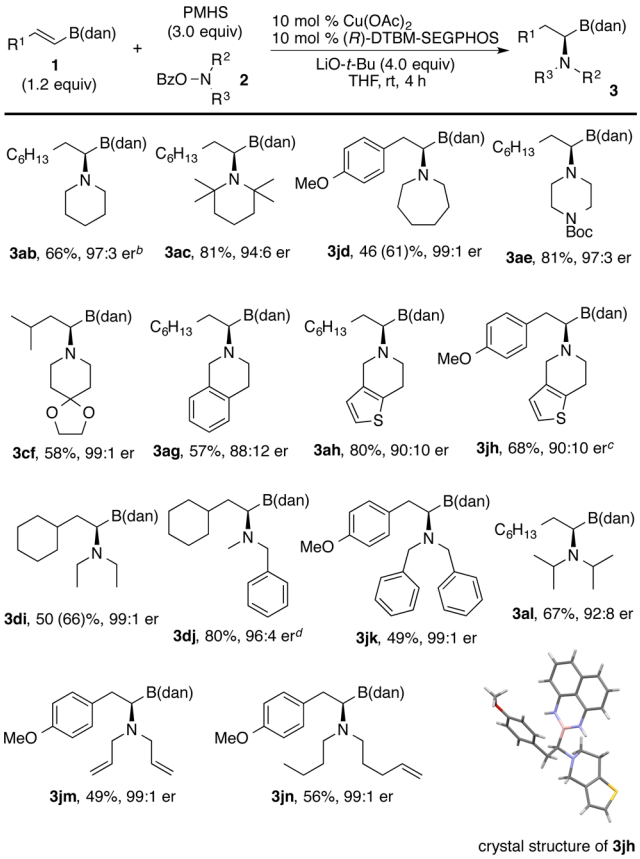
Scheme 4. Copper-Catalyzed Enantioselective Hydroamination of Alkenyl dan Boronates 1 with Various Hydroxylamines 2[a]

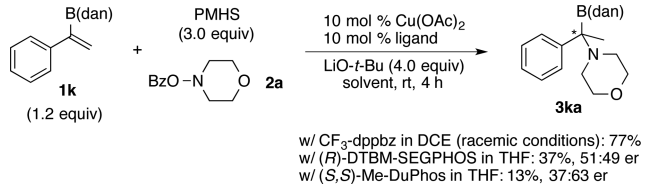


[a]Conditions: see footnote *a* in Table 1. Isolated yields are given. ^{1}H NMR yields are in parentheses. The enantiomeric ratios are determined by chiral HPLC analysis. [b]In CPME. [c]**1j** (0.25 mmol), **2h** (0.38 mmol). [d]**1d** (0.25 mmol), **2j** (0.30 mmol).

smoothly: *N*,*N*-diethyl-, *N*-benzyl-*N*-methyl-, *N*,*N*-dibenzyl-, and *N*,*N*-diisopropylamines coupled with the alkenyl dan boronates **1** to deliver α-aminoboronic acids **3di**, **3dj**, **3jk**, and **3al** with 92:8−99:1 er. Notably, isolated terminal olefins[21] remained untouched, and the boryl-substituted alkene moiety was preferably hydroaminated with high enantioselectivity (**3jm**, 99:1 er; **3jn**, 99:1 er). The formation of the usual hydroaminated product **3jn** also indicates that an aminyl radical pathway is unlikely.[22] The absolute configuration of the sulfur-containing **3jh** was determined to be *R* by X-ray analysis,[23] and the configurations of others are tentatively assigned by analogy. As seen in Scheme 4, the enantioselectivity was somewhat dependent on the electronic and steric nature of the hydroxylamine. The observed trend suggests that the insertion of the alkenyl dan boronate to the Cu−H species (**B** to **C** in Scheme 1) is reversible and that the product-determining step is the C−N forming step (**C** to **D** in Scheme 1). Thus, if the reactivity of the hydroxylamine toward the desired alkyl Cu intermediate **C** was relatively poor, the diastereomeric alkyl Cu species would be formed in equilibrium between **B** and **C** to give the undesired enantiomer.

While preliminary, we also tested the reaction of the internal substrate **1k** (Scheme 5). Whereas the reaction proceeded smoothly and regioselectively under racemic conditions, the enantioselective catalysis still remained underdeveloped.

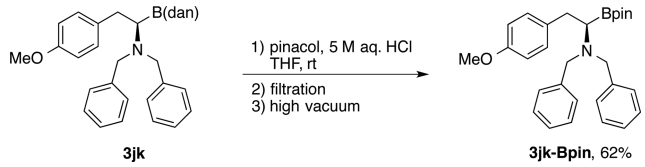
Scheme 5. Attempts To Apply Internal Substrate 1k



Further efforts for the asymmetric synthesis of α-amino tertiary boronic acids are ongoing.[11b]

The B(dan) group of the product can be readily deprotected. The ligand exchange of **3jk** with pinacol under acidic conditions was followed by simple filtration and removal of the residual pinacol under high vacuum to afford the corresponding **3jk-Bpin** in an analytically pure form (Scheme 5).[24]

Scheme 6. Conversion of B(dan) to Bpin



In conclusion, we have developed a Cu-catalyzed enantioselective hydroamination approach to optically active α-aminoboronic esters of high potential in medicinal chemistry. The present Cu catalysis enables the otherwise difficult construction of chiral centers that contain unactivated alkyl side chains at the α position. Further manipulations of the products, expansion of the substrate scope, and development of related enantioselective amination catalysis 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/jacs.5b09773.

Procedures and characterization data (PDF)
X-ray crystallographic data for **3jh** (CIF)

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Notes

The authors declare no competing financial interest.

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(20) In the case of simple styrenes, the opposite regioselectivity was observed: the amino group was selectively introduced at the benzylic position. See refs 13e and 14a.

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(24) The **3jk-Bpin** was relatively unstable under chiral HPLC analytical conditions, and thus the correct er value could not be determined. See the SI for preliminary data.

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