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Copper-Catalyzed Asymmetric Reduction of β,β-Disubstituted Alkenylboramides

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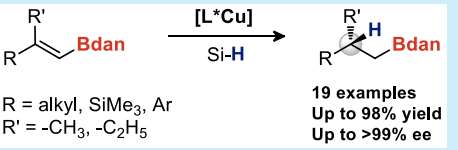
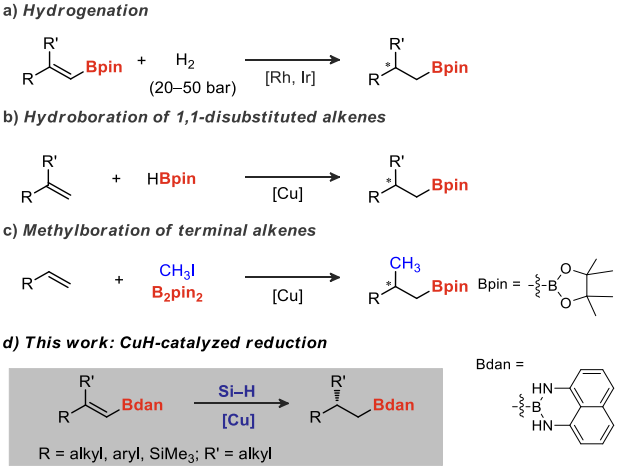
Supporting Information

ABSTRACT: A highly enantioselective copper-catalyzed reduction of β,β-disubstituted alkenylboron compounds was developed using hydrosilane. The copper hydride catalyst coordinated with chiral Josiphos ligand efficiently discriminated β-geminal substituents to generate corresponding β-chiral alkylboramides with excellent enantioselectivities up to 99% ee. The enantioselective reduction protocol provides a facile approach to β-chiral alkylboron compounds with less sterically discriminating substituents and spans a wide substrate range including aryl-substituted borylalkenes with effective functional group tolerance.



Chiral organoboron compounds represent an important class of synthetic precursors due to their versatility in organic synthesis.[1] Therefore, the development of enantioselective catalytic strategies for these compounds is desirable with advances in stereospecific transformation of C−B bonds into other functionalities.[2] While asymmetric hydroboration of alkenes is the most widely used approach to chiral organoboron compounds,[3] asymmetric hydrogenation of prochiral alkenylboron precursors is an attractive alternative to overcome possible regioselectivity issues and the limited substrate scope involved in hydroboration. Enantioselective hydrogenations of alkenylboron compounds (Scheme 1, a) have been developed using Rh,[4] Ir,[5] and Ni[6] catalysts since the first reported Rh-catalyzed hydrogenation of vinyl-bis(boronates) by the Morken group.[4a] However, the use of high hydrogen pressure often limits their efficient application in organic synthesis.

Scheme 1. Synthesis of β-Chiral Organoboron Compounds



Recently, our group reported a copper-catalyzed enantioselective hydroboration of nonfunctionalized 1,1-alkenes without coordinating and directing groups, yielding β-chiral organoboron compounds with high enantioselectivity.[7] The methodology successfully enabled enantiodiscrimination between geminal alkyl substituents for the synthesis of β-chiral organoboronates (Scheme 1, b). However, the discrimination between methyl and primary alkyl groups at the geminal carbon was a challenge due to moderate enantioselectivity (64% ee). Furthermore, transition-metal-catalyzed carboborations of alkenes[8] can provide facile access to β-branched organoboron compounds; however, only a single report of enantioselective methylboration[8d] of alkene is available to date (Scheme 1, c) with moderate enantioselectivity (76−78% ee) for aliphatic olefins. Moreover, the hydrogenation protocols did not resolve such challenges. Therefore, a new synthetic approach for the development of enantioenriched β-chiral organoboron compounds containing sterically less discriminating alkyl groups at the geminal carbon is desirable and remains unexplored.

Alkenylboron compounds containing a 1,8-naphthalenediaminatoboryl (Bdan) group previously served as regioselective substrates in our investigation of copper-catalyzed asymmetric hydroboration for the synthesis of 1,1-diborylalkanes[9] despite the low Lewis acidity of the Bdan group.[10] We envisioned that successful enantioselective CuH reduction[11] of such substrates provides β-chiral organoboron compounds, which are otherwise difficult to obtain. Herein, we report copper-catalyzed enantioselective synthesis of β-chiral organoboron compounds via asymmetric reduction of β,β-disubstituted alkenylboramides using hydrosilane as the stoichiometric reductant under mild reaction conditions.

We initiated our investigation using (*E*)-alkenylboramide containing β-methyl and phenethyl substituents (**1a**) as a

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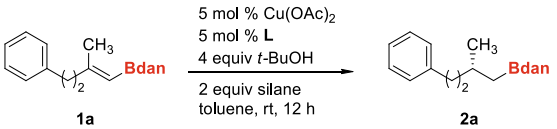
model substrate in the presence of copper(II) acetate, hydrosilane, *tert*-butyl alcohol, and a chiral bisphosphine ligand under various reaction conditions (Table 1). Instead

Table 1. Optimization of Reaction Conditions



entry	ligand (L)	silane	% conv[a]	ee[b] (%)
1	**L1**	DEMS[c]	23	54
2	**L2**	DEMS	38	92
3	**L3**	DEMS	31	94
4	**L4**	DEMS	32	92
5	**L5**	DEMS	>99 (95)[d]	95
6	**L5**	TMDSO[e]	80	91
7	**L5**	PMHS[f]	>99 (89)[d]	92
8[g]	**L5**	DEMS	81	92
9[h]	**L5**	DEMS	39	94
10[i]	**L5**	DEMS	>99 (90)[d]	93

[a]Conversion of **1a** was determined by ^{1}H NMR analysis using DMF as an internal standard. [b]ee was determined by chiral HPLC analysis. [c]Methyldiethoxysilane ($(EtO)_2MeSiH$). [d]Isolated yields of **2a** are indicated in parentheses. [e]1,1,3,3-Tetramethyldisiloxane. [f]Poly(methylhydrosiloxane). [g]Et_2O was used as solvent. [h]THF was used as solvent. [i]60 °C.

of alkenyl boramides, reduction of alkenyl pinacol boronates resulted in low conversion or formation of deborylated alkene products and could not be used efficiently under current conditions.[12] Among the chiral bisphosphine ligands screened (Figure 1), the use of chiral Josiphos ligand (**L5**) resulted in

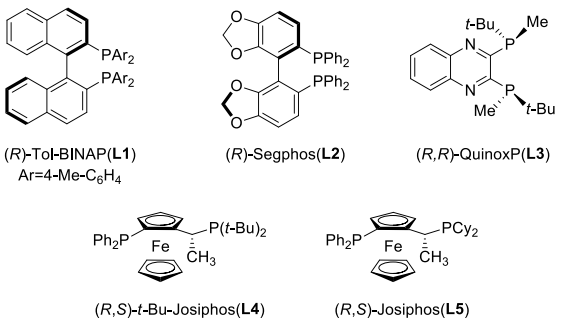
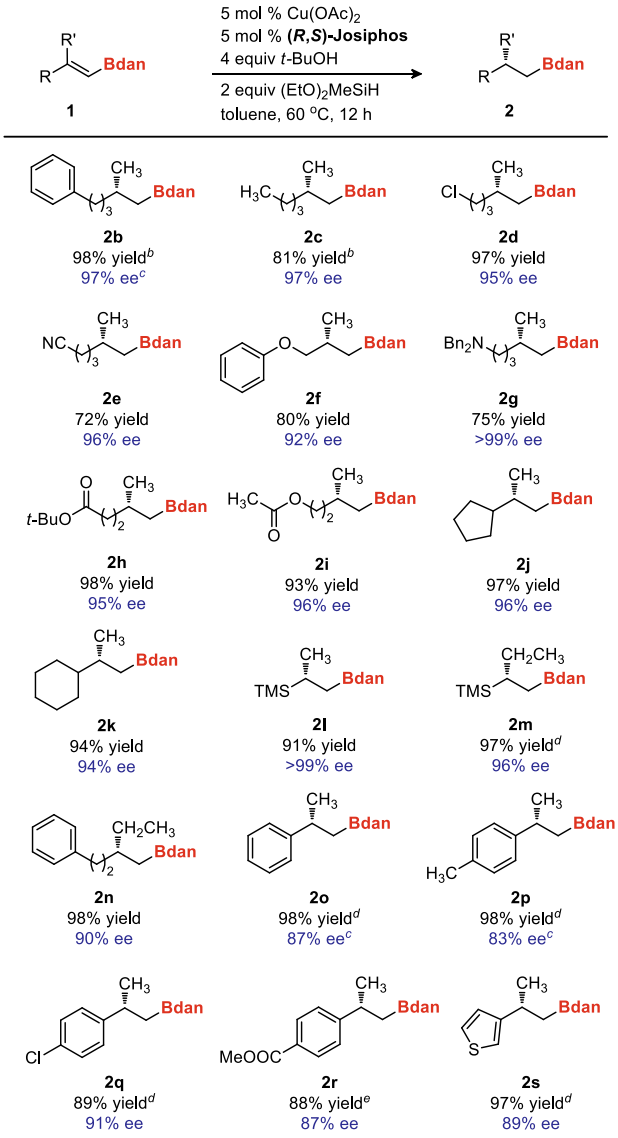


Figure 1. Structures of the chiral ligands screened.

high reactivity and enantioselectivity yielding **2a**[13] using methydiethoxysilane (DEMS) as the reducing reagent. Other ligands did not facilitate the effective conversion of the starting material, although good enantioselectivities were observed (entries 1−5). Dimeric hydrosilane (TMDSO) and polymeric hydrosilane (PMHS) were less effective in asymmetric reduction, resulting in slightly lower product yields and ee values (entries 6 and 7). Changing the solvent from toluene to ethereal solvents such as diethyl ether or tetrahydrofuran did not improve the yield or enantioselectivity (entries 8 and 9), and when the reaction temperature was increased, the enantioselectivity was slightly decreased as expected (entry 10).

After establishing the optimized conditions for the enantioselective reduction of alkenyl boramides, we explored the substrate scope of the reaction (Scheme 2). A variety of β,β-disubstituted alkenylboramides were examined to obtain

Scheme 2. Scope of CuH-Catalyzed Asymmetric Reduction[a]



[a]Reactions were conducted using 0.30 mmol of alkene (**1**) in toluene (0.2 M) at 60 °C for 12 h unless otherwise stated. [b]Room temperature was used for **1b** and **1c**. [c]Determined by HPLC analysis of the corresponding hydroxyl compound after oxidation. [d]Using 4 equiv of $(EtO)_2MeSiH$ and 24 h. [e]Using 4 equiv of $(EtO)_2MeSiH$ and 36 h.

the corresponding β-chiral alkylboramides with high degrees of enantioselectivity.[13] Alkenylboramides (**1b**−**1i**) carrying methyl and primary alkyl groups at the β-carbon were efficiently reduced to yield products with excellent enantioselectivities (92−99% ee), and various functional groups including chloro, nitrile, ether, amine, and ester groups were tolerated. Reactions using substrates (**1j** and **1k**) with secondary alkyl groups yielded products with good yield and high enantioselectivity. Substrates (**1l** and **1m**) carrying a TMS substituent showed excellent enantioselectivity in the reduction; however, in general, substrates with a bulky group such as *tert*-butyl led to partial conversion.[14] Surprisingly, the substrate (**1n**) with primary alkyl groups at the β-carbon was appropriate for

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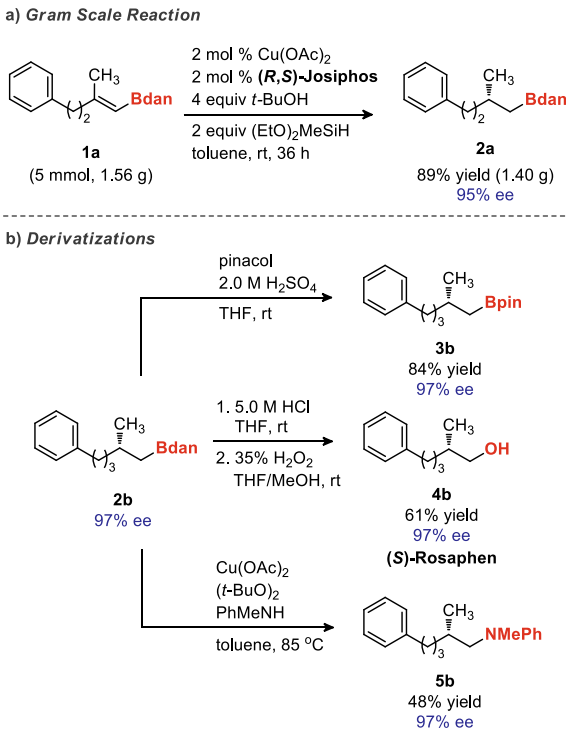
enantiodiscrimination, but a slightly decreased ee value (90% ee) was observed. The Josiphos–copper catalyst was also efficient for aryl- and methyl-substituted alkenylboramides (**1o**–**1s**), resulting in the corresponding products in good yield with moderate to good enantioselectivities (83–91% ee). Overall, the current catalytic system is sensitive to steric hindrance of the β-carbon reaction center and most efficient in discriminating methyl and primary alkyl groups, encompassing substrates with alkyl and aryl substituents.

The gram-scale reaction was successfully conducted with a reduced amount of catalyst and ligand to afford **2a** in 89% yield without decrease in enantioselectivity, although a longer reaction time was required for complete conversion (Scheme 3, a). The Bdan group of enantioenriched **2b** was directly

Scheme 3. Gram-Scale Synthesis and Organic Transformations of Chiral Dialkyl Boron 2b

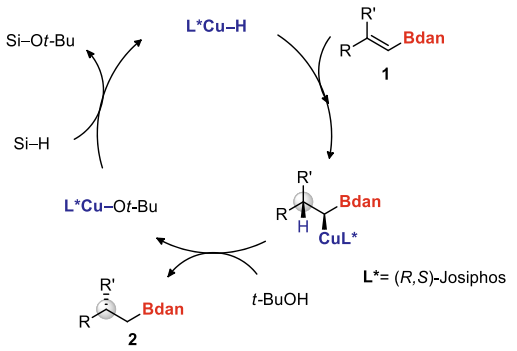


converted to the corresponding Bpin (**3b**)[15] and hydroxyl group (**4b**; (*S*)-Rosaphen[16]) by oxidation[17] and amine group (**5b**) via amination[18] with retention of the original enantioselectivity (Scheme 3, b).

The catalytic cycle is proposed in Scheme 4. The L*Cu–H species, generated from reaction of $Cu(OAc)_2$, ligand (L*), and DEMS, reacts with borylalkene (**1**) to generate a chiral alkylcopper intermediate with stereoinduction. Protonation of the C–Cu bond with *t*-BuOH and regeneration of Cu–H by a silane complete the catalytic cycle resulting in the synthesis of the desired compound **2**.

In summary, we have developed a copper-catalyzed asymmetric reduction of β,β-disubstituted alkenylboramides for the synthesis of β-chiral alkylboramide compounds with excellent enantioselectivity. The Josiphos–copper catalyst is an efficient catalyst for stereodiscrimination of β-alkyl substituents, yielding β-chiral dialkyl-substituted boron compounds with high efficiency, which are otherwise difficult to obtain. This method tolerates a wide range of functional groups and

Scheme 4. Proposed Catalytic Cycle



can even be used for aryl-substituted alkenylboramides. The resulting chiral products were further transformed to other organic functionalities, demonstrating their utility in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03400.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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