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Copper-Catalyzed Enantioselective Hydroboration of Unactivated 1,1-Disubstituted Alkenes

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Supporting Information

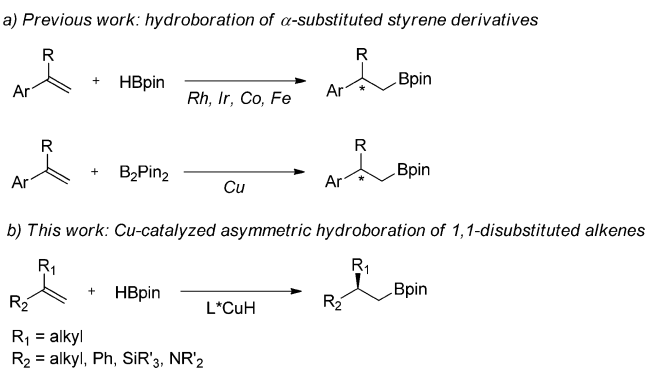
ABSTRACT: We report an efficient and highly enantioselective hydroboration of aliphatic 1,1-disubstituted alkenes with pinacolborane using a phosphine-Cu catalyst. The method allows facile preparation of enantiomerically enriched β-chiral alkyl pinacolboronates from a range of 1,1-disubstituted alkenes with high enantioselectivity up to 99% ee. Unprecedented enantiodiscrimination between the geminal alkyl substituents was observed with functional group compatibility in the hydroboration. Furthermore, a catalyst loading as low as 1 mol % furnished the desired product without a decrease in yield or selectivity, demonstrating its efficiency in gram scale synthesis.

Asymmetric hydroboration of alkenes has been developed as one of the most powerful methods for the synthesis of chiral alkylboron compounds.[1] Due to a growing number of versatile transformations of the C−B bonds of the resulting alkylboronic acid derivatives, their regio- and enantioselective preparation has become important.[2] While stoichiometric methods using chiral hydroborating reagents[3] and transition-metal-catalyzed hydroboration[4] of prochiral alkenes have been continuously developed, asymmetric hydroboration of 1,1-disubstituted alkenes imposes a great challenge in this research area due to the difficulty of discriminating two similar substituents at the geminal position.[5,6]

For the asymmetric hydroboration of 1,1-disubstituted alkenes, strategic approaches have been designed by using an equivalent chiral boron reagent or a chiral transition metal catalyst. Since the pioneering work by Brown and co-workers, a number of chiral organoboranes have been developed, but have shown low enantioselectivities.[5] The Soderquist group reported that a chiral hydroborating agent, 9-borabicyclo[3.3.2]decane, was highly enantioselective for the hydroboration of 1,1-disubstituted alkenes including 1,1-dialkyl substituted alkenes.[7] However, high enantioselectivity over 90% ee was observed only when there was a significant difference between the geminal substituents, such as *tert*-butyl and methyl.

On the other hand, various transition-metal-catalyzed systems such as Rh,[8] Ir,[9] Co,[10] and Fe[11] catalysts have been developed to avoid the use of stoichiometric chiral organoborane reagents (Scheme 1a). Rh-catalyzed hydroboration of 1,1-disubstituted alkenes with catecholborane provided low regio- and enantioselectivity.[8] The Mazet group reported an Ir-catalyzed asymmetric hydroboration of α-methylstyrene in 92% ee.[9a] Co-catalyzed asymmetric hydroboration of 1,1-disubstituted aryl alkenes by the Huang and Lu groups, respectively, resulted in high enantioselectivity.[10] Formal hydroboration approaches using a diboron reagent and methanol under copper catalysis were recently reported for α-substituted styrene derivatives[12a] and 1,1-diaryl alkenes[12b] despite low boron atom economy. However, all of these hydroboration methods were effective and enantioselective only for the 1,1-disubstitued alkenes with a requisite aryl substituent. Recently, Takacs and co-workers described a carbonyl-directed, Rh-catalyzed asymmetric hydroboration of 1,1-dialkyl substituted alkenes with high enantioselectivity.[13] However, in this case, the hydroboration requires a coordinating carbonyl group as a directing group. Therefore, development of the asymmetric hydroboration of simple 1,1-dialkyl-substituted alkenes remains a challenge and is very necessary.

Scheme 1. Metal-Catalyzed Asymmetric Hydroboration of 1,1-Disubstituted Alkenes



Recently, we disclosed that bisphosphine−copper complexes are efficient catalysts for the highly regio- and enantioselective hydroboration of mono- and 1,2-disubstituted alkenes with pinacolborane.[14,15] Herein, we report a copper-catalyzed high regio- and enantioselective asymmetric hydroboration of unactivated 1,1-disubstituted olefins as a practical and general method for the synthesis of chiral primary alkylboronate esters. This hydroboration method is efficient for nonaryl-containing, 1,1-dialkyl-substituted alkenes affording products in high enantioselectivities.

We started our investigation by examining hydroboration of 2,3-dimethyl-1-butene (**1a**) with moderately discriminating substituents (2° alkyl vs methyl) under various reaction conditions (Table 1). A copper catalyst combined with racemic bisphosphine ligands such as 1,2-bis(diphenylphosphino)-

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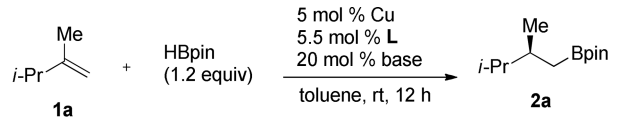
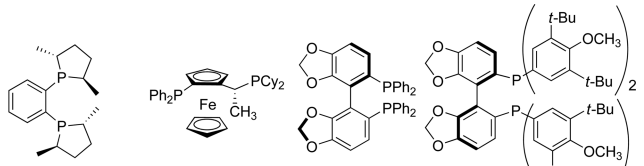
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions



entry	[Cu]/ligand	base	yield (%)[a]	ee (%)[b]
1	CuCl/dppbz	NaO*t*-Bu	0	–
2	CuCl/xantphos	NaO*t*-Bu	0	–
3	IMesCuCl	NaO*t*-Bu	0	–
4	CuCl/**L1**	NaO*t*-Bu	0	–
5	CuCl/**L2**	NaO*t*-Bu	0	–
6	CuCl/**L3**	NaO*t*-Bu	0	–
7	CuCl/**L4**	NaO*t*-Bu	36	86
8	CuTC[c]/**L4**	–	0	–
9	CuTC/**L4**	KO*t*-Bu	18	87
10	CuCl/**L4**	KO*t*-Bu	94	87



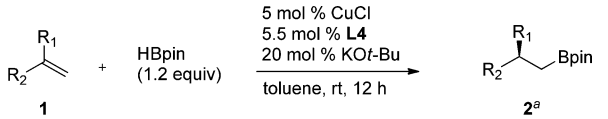
(*R*,*R*)-Me-Duphos (**L1**) (*R*,*S*)-Josiphos (**L2**) (*R*)-Segphos (**L3**) (*R*)-DTBM-Segphos (**L4**)

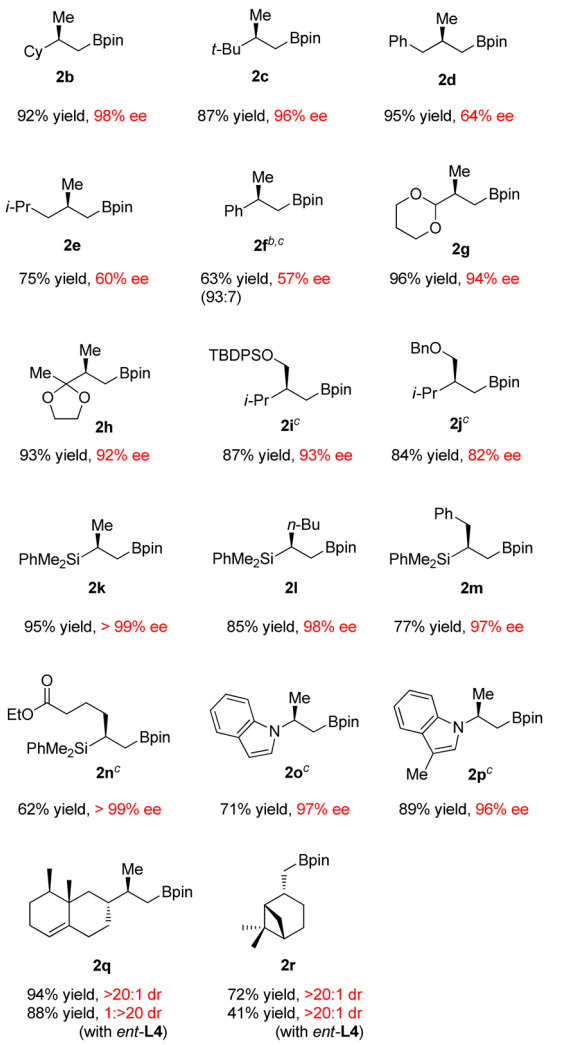
[a]Isolated yield. [b]Ee was determined by HPLC analysis. [c]CuTC = copper(I)-thiophene-2-carboxylate.

benzene (dppbz) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos), and an NHC-copper catalyst did not show any reactivity (entries 1–3). Chiral bisphosphine ligands, **L1**, **L2**, or **L3** also displayed no reactivity (entries 4–6). With the bulky (*R*)-DTBM-Segphos ligand (**L4**),[14−16] the reaction eventually proceeded to the target product in a partial conversion but with good enantioselectivity (entry 7). The use of copper(I)-thiophene-2-carboxylate, which is known to generate active Cu–H species without base,[17] was ineffective in the hydroboration (entry 8). Addition of KO*t*-Bu slightly increased the yield, but led to an incomplete reaction (entry 9). The results suggest that a base plays an important role in the reactivity of the hydroboration. Finally, the use of KO*t*-Bu as the base with CuCl increased the isolated yield from 36% to 94% yield, and the desired product (*S*)-**2a**[18] was obtained with good enantioselectivity (entry 10). Therefore, we chose the conditions used in entry 10 as optimal among the screened conditions.

The optimized reaction conditions were applied to a variety of 1,1-disubstituted alkenes (Table 2). It was found that the enantioselectivities obtained in the hydroboration was correlated with the steric difference between the two substituents at the geminal carbon. The hydroboration of **1b** and **1c** furnished the desired anti-Markovnikov addition products with 98% and 96% ee, respectively, much higher than that of **1d** (64% ee) and **1e** (60% ee) possessing a 1°-alkyl and methyl substituent. Most of the entries in Table 2 proceeded with high regioselectivity except for product **2f** with an aryl substituent, of which a regioisomeric mixture (93:7) was formed with moderate enantioselectivity for the major isomer. Successful hydroborations of alkenes with a wide range of functional groups were carried out. Acetal (**1g**), ketal (**1h**), silyl ether (**1i**), benzyl ether (**1j**), ester (**1n**), and silyl groups (**1k**–**1n**) were

Table 2. Copper-Catalyzed Enantioselective Hydroboration of 1,1-Disubstituted Alkenes





[a]Absolute configuration was assigned by analogy with **2a** and **2m**, of which the absolute configurations were determined by comparison with the literature optical data after oxidation. [b]Reaction temperature was 40 °C. [c]Reaction time was 24 h.

compatible with the standard reaction conditions. Especially, the hydroboration products (**2g** and **2h**) containing an acetal and ketal could be used as surrogates for asymmetric aldol products with formaldehyde as the electrophile,[19] after oxidation. Alkenes containing a silyl group afforded highly enantioenriched alkylboron products (**2k**–**2n**) containing a silicon-stereogenic center. Moreover, the asymmetric hydroboration reaction of enamine substrates containing an indole group furnished the chiral *β*-amino boronic esters (**2o** and **2p**) in 97% ee and 96% ee.[20] Finally, we investigated the efficiency of the current catalytic system in controlling the diastereoselectivity of enantiopure natural 1,1-disubstututed alkenes as reaction substrates (**1q** and **1r**). (+)-Valencene (**1q**) and (−)-*β*-pinene (**1r**) were hydroborated to the products with excellent diastereoselectivities (>20:<1 dr). Interestingly, the

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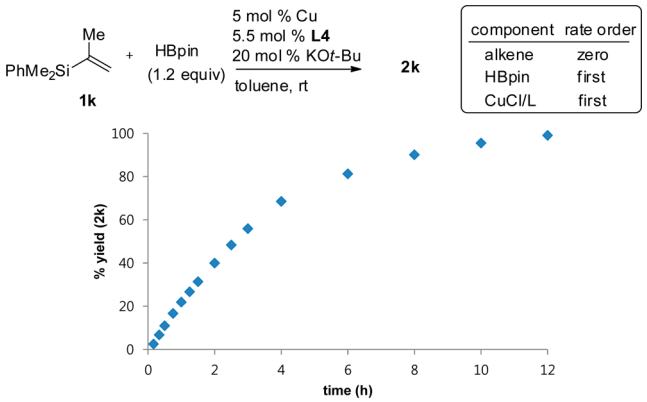
formation of diastereomers in the hydroboration of **1r** was completely controlled by the catalyst applied, while that of pinene was substrate-controlled to give the same diastereomer with two catalysts of the opposite chirality, indicating that *ent*-**L4** was mismatched.

The hydroboration of **1k** was chosen for our investigation on the kinetics, and the reaction progress was followed by ^{1}H NMR. The hydroboration process consists of olefin insertion to Cu−H and transmetalation of the resulting alkyl copper with HBpin to form product and the CuH catalyst.[14b,16] Initial rate experiments showed that the reaction was zero-order in substrate and first-order in catalyst and HBpin, suggesting that the transmetalation is the turnover-limiting step (Scheme 2, see the Supporting Information for details).

Scheme 2. Reaction Profile of Hydroboration of 1k and Observed Rate Orders



To gain insight into the origin of the enantioselectivity, we carried out DFT calculations of transition states for the insertion step of the alkene **1a** into **L4**Cu−H, based on the hydroboration mechanism. The calculated, enantiodiscriminating transition state models of the hydroboration of **1a** are shown in Figure 1. The favored transition state (**TS1**) leading to the major enantiomer is lower than that of the minor enantiomer by ∼5 kcal/mol.[21] This difference in energy of the transition states apparently results from steric repulsion between the isopropyl group of the alkene and an aromatic substituent of the chiral phosphine ligand. In addition, the distance between the copper and the alkene carbon of **TS1** (2.01 Å) is noticeably shorter than that of **TS2** (2.20 Å), which indicates a more favorable interaction with the alkene.

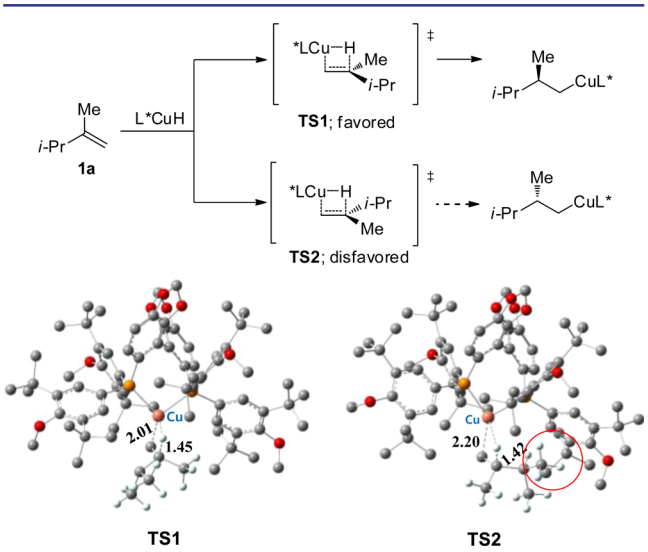
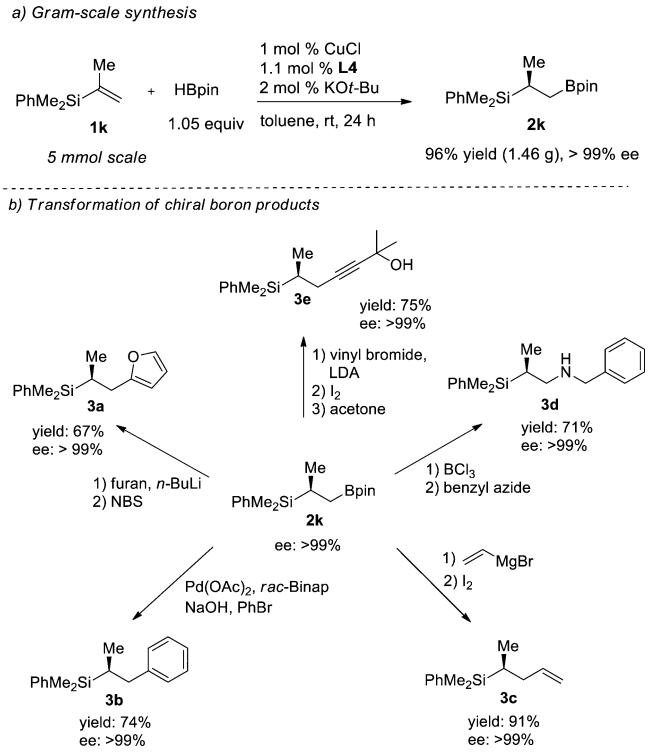


Figure 1. Stereochemical models of the copper-catalyzed hydroboration based on DFT calculations.

The hydroboration protocol was suitable for large scale synthesis. A 1.0 mol % loading of the copper catalyst was sufficient to perform the reaction on a 5 mmol scale (Scheme 3a). Despite the reduced amounts of catalyst and ligand, **2k** was produced in 96% yield and 99% ee. To demonstrate the utility of the resulting chiral organoboron product, we also carried out transformation of the C−B bond into various functional groups. Heteroarylation[22a] and the Suzuki coupling of **2k** afforded products **3a** and **3b**, respectively. Alkenylation[22b] of **2k** using Grignard reagent produced **3c** in 91% yield, and C−N bond formation[22c] furnished the corresponding benzyl-protected amine **3d**. Finally, **3e** was generated by alkynylation.[22d] In all of these reactions, the original ee was preserved without deterioration.

Scheme 3. Gram-Scale Synthesis and Transformation of *β*-Chiral Alkylboron Products



In summary, we developed a copper-catalyzed regio- and enantioselective hydroboration of unactivated 1,1-dialkyl-substituted alkenes with pinacolborane. The DTBM-Segphos-copper catalyst was most effective with a wide range of 1,1-alkene substrates with alkyl, silyl, and amine substituents, furnishing useful *β*-chiral alkylboronates in high enantioselectivities. This hydroboration method is unique and complementary to other metal-catalyzed hydroborations efficient for 1,1-disubstituted aryl alkenes. Moreover, the protocol could be easily scaled up to gram-scale synthesis, and useful transformations of the resulting alkylboronate to various compounds proved its utility.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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