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Copper(I)-Catalyzed Asymmetric Monoborylation of 1,3-Dienes: Synthesis of Enantioenriched Cyclic Homoallyl- and Allylboronates

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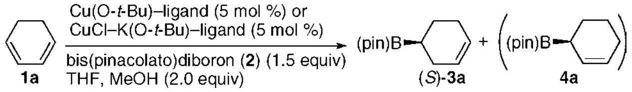
The synthesis of enantioenriched α-chiral organoboron compounds has attracted considerable attention in organic synthesis because C−B bonds can be converted to C−O, C−N, or C−C bonds in a stereospecific manner.[1] Asymmetric hydroboration of alkenes is one of the most important methods used for the preparation of such compounds; however, the reaction with an asymmetric catalysis is limited to aromatic alkenes, alkenes with an amide directing group, and cyclopropenes.[2,3] Asymmetric hydroboration of 1,3-dienes provides homoallylic (1,2-addition) or allylic (1,4-addition) boron compounds. These synthesized compounds are highly useful, if they can be prepared in a regio- and enantioselective manner, because further derivatization using the remaining alkene moiety as well as the boron group easily leads to multifunctional chiral compounds. Although the stoichiometric asymmetric reaction of 1,3-diene using diisopinocamphenylborane (Ipc_2BH) was pioneered by H. C. Brown a quarter of a century ago,[3b] the asymmetric catalytic hydroboration of 1,3-dienes with high enantio- and diastereoselectivities has not been reported.[4,5]

Here, we report the first asymmetric catalytic monoborylation of 1,3-dienes with a copper(I) catalyst. This reaction produced unprecedented cyclic optically active homoallylboronates with high regio- and enantioselectivity.[6] In addition, a drastic change of product preference between homoallyl- and allylboronates was found for the reaction of 1,3-cyclopentadiene and 1,3-cycloheptadiene. Enantioenriched cyclic allylboronates, which are useful synthetic reagents but difficult to prepare, were also synthesized.[6]

A number of asymmetric copper(I)-catalyzed reactions with diboron have been reported.[2d,7−9] Yun reported the acceleration effect of proton sources,[8] and the importance of the low LUMO levels of the substrate has also been reported.[2d,9,10] Guided by these findings, we anticipated that 1,3-dienes can also be used in the copper(I)-catalyzed borylation in combination with an appropriate proton source. The reaction was first carried out by the addition of 2.0 equiv of methanol to a mixture of 1,3-cyclohexadiene (**1a**), 1.5 equiv of bis(pinacolato)diboron (**2**), 5 mol % of Cu(O-*t*-Bu), and (*R*,*R*)-Me-Duphos in THF at room temperature. The reaction reached completion within 3 h to afford homoallylboronate (*S*)-**3a** in 96% yield with 87% ee (Table 1, entry 1). No allylboronate (**4a**) and multiborylated products were detected. Using other chiral ligands resulted in moderate to high yields with lower enantio- and regioselectivities (69−97% yield, 61−86% ee, **3a**/**4a** 96:4−>99:1, entries 2−5). The enantioselectivity was improved to 94% ee with (*R*,*R*)-Me-Duphos at −20 °C (92% yield, entry 6). The reaction with a mixture of CuCl and K(O-*t*-Bu), which is more readily available than Cu(O-*t*-Bu), gave almost comparable results, but the regioselectivity was slightly decreased (entry 7).

Table 1. Copper(I)-Catalyzed Monoborylation of 1,3-Cyclohexadiene[a]

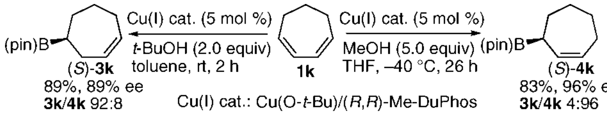


entry	ligand	time (h)	temp	**3a**/**4a** ratio[b]	yield[c] (%)	ee[b] (%)
1	(*R*,*R*)-Me-Duphos	3	rt	>99:1	96	87
2	(*R*,*R*)-QuinoxP*	3	rt	98:2	97	86
3	(*R*)-BINAP	3	rt	>99:1	69	61
4	(*R*)-Segphos	3	rt	96:4	70	67
5	(*R*,*R*)-*i*-Pr-DuPhos	3	rt	97:3	92	83
6	(*R*,*R*)-Me-DuPhos	24.5	−20 °C	>99:1	92	94
7[d]	(*R*,*R*)-Me-DuPhos	26	−20 °C	98:2	97	94

[a] Conditions: **1a** (0.25 mmol), **2** (0.375 mmol), Cu(O-*t*-Bu) (5 mol %, 0.0125 mmol), ligand (5 mol %, 0.0125 mmol), THF (0.25 mL), and methanol (2.0 equiv). [b] The ee and **3**/**4** ratio values were determined by HPLC analysis of the benzoate ester of the homoallylic alcohol obtained after H_2O_2/NaOH oxidation of **3a**. [c] Isolated yield. [d] The reaction was carried out at 0.5 mmol scale with 5 mol % CuCl and 20 mol % of K(O-*t*-Bu) in THF (0.7 mL).

The scope of the reaction was subsequently examined (Table 2). 1,3-Cyclohexadiene derivatives **1b**−**e** were converted into the corresponding optically active homoallylboronates **3b**−**e** in high yields with high ee values (90−97%, 93−95% ee, entries 1−4). The reaction of **1f** also gave **3f** (99%, 88% ee, entry 5), which has silyl enol ether functionality. The attempted reaction of **1g** failed probably due to the large steric hindrance (entry 6). The reaction with acyclic 1,3-dienes gave homoallylboronates with high regioselectivity (entries 7 and 8), but a poor ee value was observed in **3i** (42% ee).

The reactions of **1a** predominantly afforded the homoallylboronate **3a** at room temperature and at −20 °C (Table 1). Conversely, the regioisomeric preferences in the reaction of 1,3-cyclopentadiene (**1j**) and 1,3-cycloheptadiene (**1k**) were switched by changing the reaction temperature (Table 3).[10] The copper(I)-catalyzed reaction of **1j** at a low temperature of −40 °C using methanol in THF predominantly gave allylboronate (*S*)-**4j** with a high ee (entry 1, 87%, 96% ee, **3j**/**4j** 7:93). At room temperature, the major product was homoallylboronate **3j** (entry 2, 73%, **3j**/**4j** 71:29). The regioselectivity of **3j** at room temperature was improved by using *tert*-butanol in toluene (entry 3, 77%, **3j**/**4j** 92:8). The reaction with *tert*-butanol in toluene at −40 °C gave predominantly (*S*)-**4j**, indicating the reaction temperature is the most important factor in controlling the **3j**/**4j** selectivity (entry 4, 86%, 97% ee, **3j**/**4j** 6:94). A similar condition-dependent selectivity profile was also observed in the reaction of **1k** with high regio- and enantioselectivities (eq 1).



(1)

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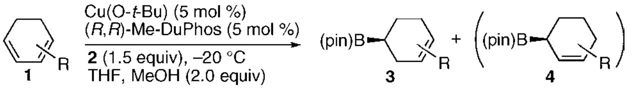
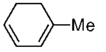
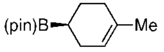
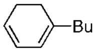
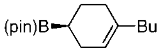
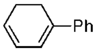
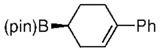
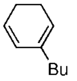
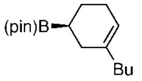
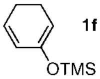
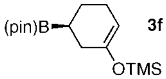
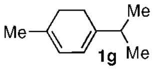
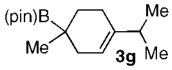
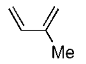
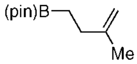
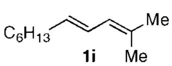
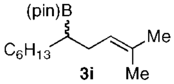
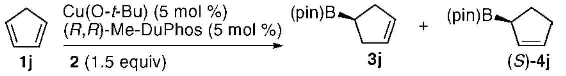
Table 2. Substrate Scope[a]



entry	diene	time (h)	product	3/4 ratio[b]	yield[c] (%)	ee[d] (%)
1	 **1b**	17	 **3b**	>20:1	90	95
2	 **1c**	17	 **3c**	>20:1	97	95
3[e]	 **1d**	25	 **3d**	94:6	95	95
4	 **1e**	22.5	 **3e**	>20:1	91	93
5	 **1f**	16	 **3f**	>20:1	99	88
6	 **1g**	24	 **3g**	–	0	–
7[f]	 **1h**	1.5	 **3h**	>20:1	97	–
8[g]	 **1i**	20	 **3i**	91:9	78	42

[a] Conditions: **1** (0.5 mmol), **2** (0.75 mmol), Cu(O-*t*-Bu) (5 mol %, 0.025 mol), ligand (5 mol %, 0.025 mmol) in THF (0.5 mL). [b] Determined by ^{1}H NMR or HPLC. [c] Isolated yield. [d] Determined by HPLC analysis. [e] 0.25 mmol scale. [f] 1.1 equiv of **2** was used. [g] The reaction was carried out on 0.25 mmol scale at 0 °C with 10 mol % of Cu(O-*t*-Bu) and ligand.

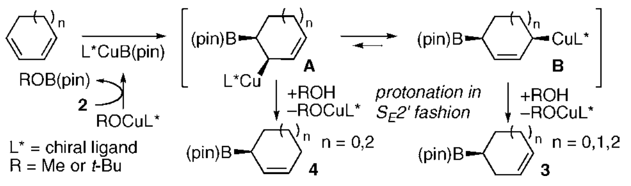
Table 3. Product Switch in Copper(I)-Catalyzed Monoborylation of 1,3-Dienes[a]



entry	solvent	alcohol	temp	time (h)	3/4 ratio[b]	yield[c] (%)	ee[d] (%)
1[e]	THF	MeOH	−40 °C	27	7:93	87	96 (**4j**)
2[f]	THF	MeOH	rt	5	71:29	73	–
3[f]	toluene	*t*-BuOH	rt	5	92:8	77	–
4[e]	toluene	*t*-BuOH	−40 °C	26	6:94	86	97 (**4j**)

[a] Conditions: **1** (0.5 mmol), **2** (0.75 mmol), Cu(O-*t*-Bu) (5 mol %, 0.025 mol), ligand (5 mol %, 0.025 mmol), solvent (0.5 mL), and alcohol. [b] Determined by GC or HPLC. [c] Isolated yield. [d] Determined by HPLC analysis. [e] 5.0 equiv of alcohol were used. [f] 2.0 equiv of alcohol were used.

Scheme 1. Possible Reaction Mechanism



A possible reaction mechanism is depicted in Scheme 1.[11,12] The borylcopper(I) formed from copper(I) alkoxide, and diboron **2** undergoes a *syn*-addition across one of the carbon−carbon double bonds to form a σ-allylcopper species **A**. Protonation of the kinetic product **A** at the lower temperature proceeded in an S_E2' fashion to provide allylboronate **4**. At higher temperatures, **A** rapidly isomerizes to thermodynamically stable **B** and slow protonation of **B** gives homoallylboronate **3**. The slower protonation rate under the *tert*-butanol/toluene conditions is assumed to be responsible for the higher regioselectivity (Table 3). **3a** was only obtained in the reaction of **1a** (Table 1). This observation can be explained by the very rapid isomerization from **A** to **B** even at a low temperature.

In summary, we have shown the regio- and enantioselective monoborylation of 1,3-dienes through a copper(I)-catalyzed reaction. This should be a versatile method to obtain optically active cyclic homoallyl- and allylboronates, which were inaccessible by other catalytic methods. Further studies concerning the reaction mechanism and the expansion of the reaction scope are underway.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) It was reported that the regioselectivity in hydroboration of 1,3-dienes with Ipc$_2$BH is substrate dependent. 1,3-Cyclopentadiene gave the homoallylborane; 1,3-cyclohexa-, hepta-, and nonadiene gave the allylboranes. See: (a) Brown, H. C.; Bhat, K. S.; Jadhav, P. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2633–2638. (b) Hess, H. M.; Brown, H. C. *J. Org. Chem.* **1967**, *32*, 4138–4139.

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