Asymmetric Hydroboration

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Highly Regio- and Enantioselective Copper-Catalyzed Hydroboration of Styrenes**

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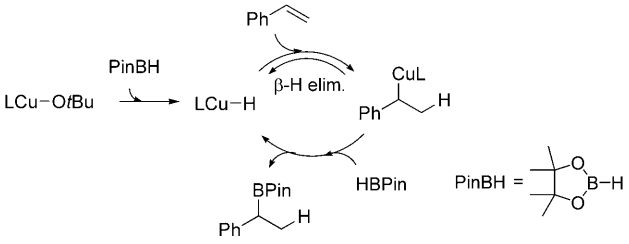
Transition-metal-catalyzed hydroboration reactions of alkenes[1] have attracted much interest, as they provide opportunities for unique regio- and enantioselectivity. In particular, the asymmetric hydroboration of styrene derivatives to afford nonracemic α-borylated products is a useful reaction, since the resulting C–B bond can be transformed with retention of configuration into a C–N, C–O, or C–C bond.[1b,2] Although many catalytic systems, including ruthenium,[3a] nickel,[3b] samarium,[3c] and lanthanum[3d] catalysts, have been employed for the transformation, the development of a highly regio- and enantioselective hydroboration still remains as a challenge; so far, only combinations of rhodium complexes and catecholborane (CatBH) at low temperatures have shown the desirable high regio- and enantioselectivity.[4,5] Given the instability of catecholborane and the resulting borylated product, it is necessary to develop efficient regioselective catalytic systems that are compatible with more stable (but less reactive) hydroboration reagents, react with disubstituted olefins, and can readily be rendered enantioselective by the use of nonracemic ligands.

Herein, we report that copper(I) complexes coordinated with chelating phosphine ligands can catalyze the regio- and enantioselective hydroboration of styrenes with pinacolborane (PinBH) to afford the corresponding α-borated products. Reactions proceed with better than 99:1 site selectivity and with high enantioselectivity in the presence of chiral ligands for copper between room temperature and 40 °C. This process also involves the first stereoselective copper-to-boron transmetalation at a benzylic carbon atom.

During our studies on the development of new enantioselective catalytic processes based on the addition of copper hydride[6] and copper boryl reagents,[7] we became interested in how we could make use of the Cu–C bond that formed upon the addition of the copper species to electron-deficient alkenes, instead of destroying the bond by simple protonation with an alcohol.[6,7] Since the in situ generation of copper hydride in the presence of pinacolborane has been suggested,[8] we were intrigued by the possibility of forming a new hydroboration cycle with copper. Although no precedent example of metathesis between Cu–C(sp^3) and PinBH exists, and it is known that a similar metathesis reaction between Cu–C and B–B is difficult,[9] we envisioned that a copper(I) hydride coordinated with an appropriate ligand would undergo regioselective addition to styrene and facilitate an efficient transmetalation[10] of the resulting Cu–C bond[11] with pinacolborane, rather than β-hydride elimination,[12] to afford the desired branched boronate ester (Scheme 1).



Scheme 1. Expected catalytic cycle.

After exploring a variety of catalytic reaction conditions,[13] we found that styrene reacted slowly with pinacolborane (1.2 equiv) in the presence of the catalyst CuCl/KO*t*Bu/dppbz (5 mol %) in toluene at room temperature to 96 % conversion in 48 h. The same reaction at 60 °C reached completion within 7 h to give the desired isomer **2** with high regioselectivity [Eq. (1)]. This reaction is the first highly regioselective copper-catalyzed hydroboration of styrene.[14] The observed high regioselectivity could be explained by the regioselective insertion of styrene into the Cu–H bond; the interaction of Cu–H σ molecular orbital and the π* orbital (LUMO) of the alkene is possibly important in the insertion step. The phenyl substituent makes the methylene carbon atom more electrophilic by shifttng π-electron density from the carbon atom (greater orbital contribution of the methylene carbon in the LUMO)[15] and directs the addition of H^- toward the methylene carbon atom. The copper catalyst is presumed to allow this insertion mode to form the organocopper intermediate without exerting too much steric strain around the benzylic carbon at which the copper is located.

The development of an enantioselective copper-catalyzed hydroboration provided a new challenge, as both the addition and transmetalation steps affect the formation of the stereogenic center.[16] We investigated the asymmetric hydroboration of styrene with a variety of chiral ligands; representative results are shown in Table 1. In our first attempt with (*R*)-*p*-Tol-binap, we were pleased to observe moderate enantioselectivity (64 % *ee*), although conversion was low (Table 1, entry 1). The use of (*R*,*S*)-josiphos and the duphos ligand **4**

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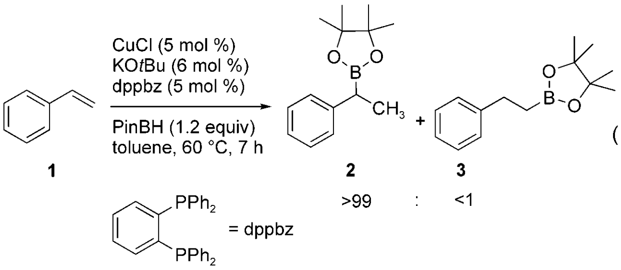
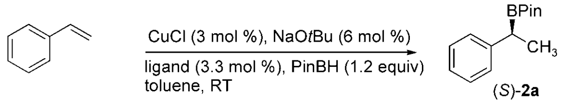


(1)

Table 1: Copper-catalyzed enantioselective hydroboration of styrene with various ligands.[a]



Entry	Ligand	*t* [h]	Conv. [%]	Yield [%][b]	*ee* [%][c]
1	(*R*)-*p*-Tol-binap	24	32	–	64
2	(*R*)-MeO-biphep	24	34	–	70
3	(*R*,*S*)-josiphos·EtOH	5	100	89	70
4	(*S*,*S*)-Me-duphos (**4**)	5	100	83	83 (*R*)
5	(*S*,*S*)-Et-duphos	24	26	–	8 (*R*)
6	(*S*,*S*,*R*,*R*)-tangphos (**5**)	3	100	86	92

[a] Reactions were performed under N_2. Compound **2a** was formed exclusively in all cases. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC analysis on a chiral phase of the corresponding alcohol obtained by oxidation of **2a**. Cy = cyclohexyl.

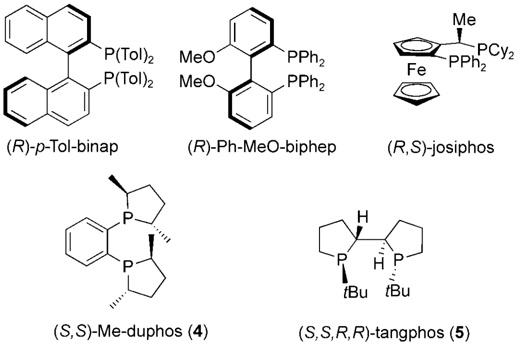
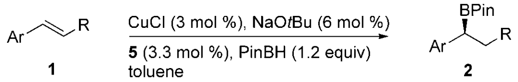
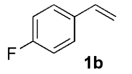
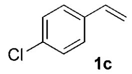
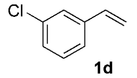
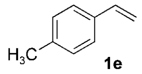
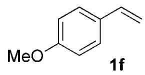
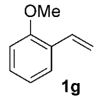
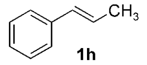
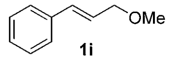
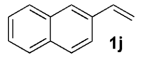
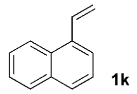


Table 2: Copper-catalyzed enantioselective hydroboration of styrene derivatives with ligand **5**.



Entry	Substrate	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	 **1b**	RT	24	91 (100)	92
2	 **1c**	RT	24	90 (100)	87
3	 **1d**	RT	24	95 (100)	82
4	 **1e**	40	24	88 (100)	90
5	 **1f**	RT	48	82 (92)	93
6	**1f**	40	24	90 (99)	90
7	 **1g**	40	24	90 (100)	91
8	 **1h**	40	40	71 (79)	95
9[c]	**1h**	RT	48	88 (98)	88
10	 **1i**	40	24	61 (70)	88
11[c]	**1i**	RT	48	78 (89)	87
12	 **1j**	RT	5	90 (100)	51
13	 **1k**	RT	12	90 (100)	60

[a] Yield of the isolated product. Conversion is shown in parentheses. [b] The *ee* value was determined by HPLC analysis on a chiral phase. [c] Ligand **4** was used.

enhanced the reactivity and enantioselectivity of the hydroboration to provide **2a** in good yield with improved enantioselectivity (Table 1, entries 3 and 4). Finally, the best results were obtained with the P-chiral tangphos ligand **5**, which afforded **2a** with 92 % *ee* and greater than 99:1 regioselectivity (Table 1, entry 6).

Various styrene derivatives, including β-alkyl-substituted styrenes, were subjected to the hydroboration catalyzed by the copper(I)–tangphos complex with pinacolborane as the hydroborating reagent (Table 2). In all cases, the regioselectivity was excellent, and good to high enantioselectivities were observed. The electronic nature of the substituent affected conversion; vinyl arenes **1e–g** with an electron-donating substituent on the phenyl group reacted slowly at room temperature (22 °C) and required a higher temperature for reasonable conversion with a slight drop in enantioselectivity (compare entries 5 and 6, Table 2). Whereas styrene derivatives with a *para* substituent afforded products **2** with similar levels of enantioselectivity to that observed with styrene (92 % *ee*; Table 1, entry 6), *meta*-chlorostyrene (**1d**) was hydroborated with decreased enantioselectivity (82 % *ee*; Table 2, entry 3). Remarkably, *ortho*-methoxystyrene (**1g**) reacted with the same high enantioselectivity observed for *para*-methoxystyrene (Table 2, entry 7). The β-substituted styrenes[17] **1h** and **1i** reacted slowly at 40 °C;[18] however, good to high enantioselectivities were observed (Table 2, entries 8 and 10). With these hindered substrates, the duphos ligand **4** was more efficient in terms of conversion and afforded the products with 88 and 87 % *ee*, respectively (Table 2, entries 9 and 11). Vinyl naphthalene derivatives reacted with moderate enantioselectivity with the copper–tangphos system (Table 2, entries 12 and 13); better enantioselectivity was observed with the (*R*,*S*)-josiphos ligand.[19]

In conclusion, we have developed an enantioselective hydroboration reaction of styrene derivatives under the catalysis of chiral copper(I)–bisphosphine complexes with pinacolborane as the hydroborating reagent. This method shows that a stereoselective transmetalation of a benzylic carbon–copper bond is possible with pinacolborane; further studies are needed to elucidate details of the mechanism. The desired stable α-borated product can be obtained with high regio- and enantioselectivity under mild conditions. Further studies on the mechanism of catalysis and the application of the catalytic system to other classes of olefins are in progress.

Experimental Section

General procedure: A mixture of CuCl (0.015 mmol, 1.5 mg), NaO*t*Bu (0.03 mmol, 3.0 mg), and (*S*,*S*,*R*,*R*)-tangphos (**5**; 0.0165 mmol, 4.7 mg) in anhydrous toluene (0.2 mL) was stirred for 10 min in a Schlenk tube under an atmosphere of nitrogen. Pinacolborane (0.6 mmol, 89.8 μL) was added to the reaction mixture, and stirring was continued for 10 min at room temperature. Styrene or a styrene derivative (0.5 mmol) and tetradecane (0.25 mmol) as an internal standard were added in toluene (0.1 mL), and the reaction tube was washed with further toluene (0.2 mL) and sealed. The reaction was monitored by TLC and GC. Upon completion of the reaction, the reaction mixture was filtered through a pad of Celite and concentrated. The product was purified by chromatography on silica gel.

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[17] We found that *Z* alkenes, such as (*Z*)-β-methylstyrene and indene, were not reactive.

[18] We observed 63% conversion of **1h** in 24 h at 40 °C.

[19] Compounds **2j** and **2k** were obtained with 66 and 78% *ee*, respectively.