Asymmetric Catalysis

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# Regio- and Enantioselective Copper(I)-Catalyzed Hydroboration of Borylalkenes: Asymmetric Synthesis of 1,1-Diborylalkanes**

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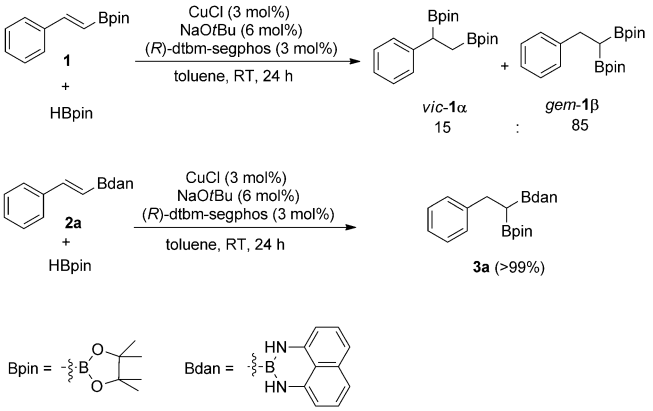
Efficient stereoselective transition-metal-catalyzed hydroboration reactions of alkenes have received much attention, and are valuable synthetic methods for the preparation organoborane intermediates.[1] These reactions give products with different selectivities to those obtained by traditional stoichiometric hydroboration reactions, thus broadening the scope of hydroboration reactions. Although rhodium catalysts have predominantly been used in the hydroboration of alkenes,[2] we recently reported that phosphine-coordinated copper(I) complexes are effective catalysts for the hydroboration of vinyl arenes, with pinacolborane as the hydroborating reagent.[3]

Multiborylated compounds, including 1,1-diboryl derivatives, are interesting synthetic intermediates as polyfunctional organometallic reagents.[4] The recent reports by the Shibata group and Hall group[5] on 1,1-diborylalkanes made this type of compounds containing two borons attached to the same $sp^3$ carbon atom attractive for further functionalization.[6] However, previous reports have described the formation of multiborylated compounds as a regioisomeric mixture by hydroboration or diboration.[7]

We envisioned that regio- and stereoselective copper-catalyzed hydroboration of borylalkenes with would provide easy access to either 1,2- or 1,1-diboryl compounds. Moreover, enantiomerically enriched 1,1-diboryl derivatives possessing two different boryl groups at the stereogenic carbon center might be obtained through the copper-catalyzed reaction of appropriate borylalkenes in an atom-economical fashion. Similar non-asymmetric hydroboration approaches involving rhodium catalysis have been developed.[6c,8] However, these approaches have some limitations, such as low regioselectivity and low to moderate yields as a result of side reactions involving reduction and β-hydride elimination. Furthermore, only one asymmetric synthesis of 1,1-diboryl compounds through conjugate boration[9] has been reported so far.[5b] Herein, we report a highly regio- and enantioselective copper-catalyzed hydroboration of borylalkenes to produce enantiomerically enriched 1,1,-diboryl compounds with high atom efficiency. This method uses a catalytic combination of CuCl, NaO*t*Bu, and either (*R*)-dtbm-segphos or (*R*,*S*)-josiphos as the chiral ligand.

In preliminary experiments, we evaluated the regioselectivity of the hydroboration of pinacolboronate-substituted styrene **1**. By using a copper/dtbm-segphos catalyst[3b] and pinacolborane (HBpin) as the hydroborane source, 1,2-diboronyl (*vic*-**1α**) and 1,1-diboronyl (*gem*-**1β**) were generated in a 15:85 ratio with complete conversion (Scheme 1).




***Scheme 1.*** Regioselectivity of the copper-catalyzed hydroboration of borylalkenes.

The copper/phosphine-catalyzed hydroboration of simple styrene derivatives was exclusively α regioselective, whereas the use of this catalyst resulted in inverse regioselectivity for the reaction of borylalkene **1** to mainly give the *gem*-**1β** product. We believe the electron-withdrawing nature of the Bpin group possibly altered the regioselectivity of the hydroboration.[10]

In search of substrates giving better selectivity, we tested a substrate containing a 1,8-naphthalenediaminatoboryl (Bdan) group instead of the Bpin group. Despite the lower Lewis acidity of the Bdan group, owing to electron-donating nitrogen atoms,[11] the reaction of **2a** proceeded to 100% conversion at room temperature in 24 h and produced 1,1-diborylated product (**3a**) as the major regioisomer. The enantiomeric excess of **3a** was measured by HPLC analysis on a chiral stationary phase and determined as 96% *ee*.

To investigate the effect of other chiral bisphosphine ligands on regioselectivity and enantioselectivity, a range of chiral ligands were screened. With **2a** as the model substrate, all reactions showed complete regioselectivity to give **3a**. When the (*R*)-tol-binap ligand was used, the reaction did not proceed to complete conversion (Table 1, entry 2; 72%),

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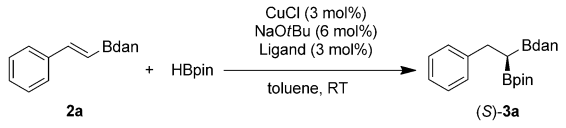
whereas the use of the short-tethered quinoxP and Me-duphos ligands, resulted in complete conversion and good *ee* values (82–85% *ee*; Table 1, entries 3 and 4). Utilization of (*R*,*S*)-josiphos as the ligand resulted in an efficient reaction

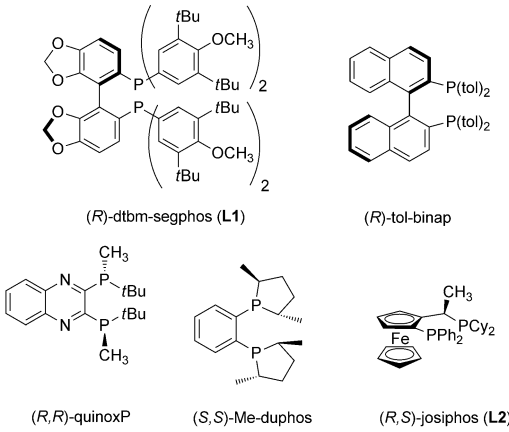
***Table 1:*** Optimization of reaction conditions.




**2a** (*S*)-**3a**

| Entry | Ligand | *t* [h] | Conv. [%] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | (*R*)-dtbm-segphos | 24 | 100 | 89 | 96(*S*) |
| 2 | (*R*)-tol-binap | 24 | 72 | 45 | 62(*S*) |
| 3 | (*R*,*R*)-quinoxP | 24 | 100 | 80 | 82(*S*) |
| 4 | (*S*,*S*)-Me-duphos | 12 | 100 | 83 | 85(*R*) |
| 5 | (*R*,*S*)-josiphos | 6 | 100 | 82 | 94(*S*) |

[a] Yield of the isolated product. [b] Determined by HPLC analysis on a chiral stationary phase.

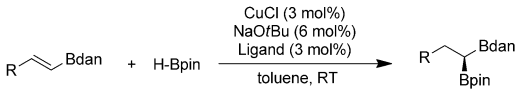



with full conversion achieved in 6 h, to afford (*S*)-**3a** in 82% yield and 94% *ee* (Table 1, entry 5).

With optimized reaction conditions including dtbm-segphos or josiphos as the chiral ligand established, the hydroboration reactions of a variety of β-Bdan-substituted styrene derivatives were examined (Table 2, entries 1–6). The hydroboration reactions provided the corresponding 1,1-diborylalkane compounds with excellent levels of regio- and enantioselectivity.[12] The steric and electronic properties of aryl groups did not significantly affect enantioselectivity. Both ligands could be used successfully, but the use of the josiphos ligand generally resulted in shorter reaction times, although with slightly reduced *ee* values, than use of the segphos ligand.

Electrophilic alkene substrates are better for copper-catalyzed hydroboration,[13] therefore simple alkyl-substituted alkenes are often considered as less efficient substrates because they contain electron-donating alkyl groups. However, the current catalytic system could be successfully applied to alkyl-substituted borylalkenes (**2g–i**) to afford products in good yield and excellent *ee* values (Table 2, entries 7–10). For the hydroboration of **2i**, bearing a secondary alkyl group, the more-reactive **L2** ligand was required to obtain high conversion in a reasonable reaction time.

***Table 2:*** Copper-catalyzed enantioselective hydroboration of boryl-alkenes (**2**).



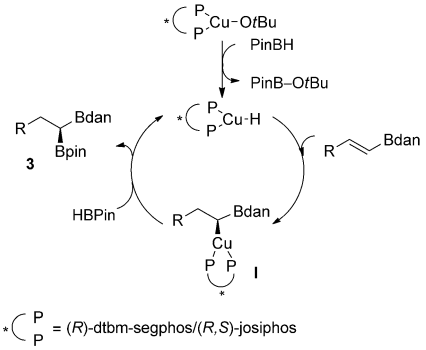

**2** **3**

| Entry | R | Ligand | *t* [h] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | *o*-$FC_6H_4$ (**2b**) | **L1** | 63 | 81 | 93 |
| 2 | *o*-$FC_6H_4$ (**2b**) | **L2** | 19 | 80 | 91 |
| 3 | *m*-$FC_6H_4$ (**2c**) | **L1** | 36 | 81 | 93 |
| 4 | *p*-$FC_6H_4$ (**2d**) | **L1** | 24 | 87 | 98 |
| 5 | *p*-$MeC_6H_4$ (**2e**) | **L1** | 24 | 85 | 97 |
| 6 | 2-naphthyl (**2f**) | **L2** | 24 | 80 | 93 |
| 7 | *n*Bu (**2g**) | **L1** | 12 | 90 | 95 |
| 8 | *n*Bu (**2g**) | **L2** | 12 | 85 | 93 |
| 9 | $(CH_3)_2CHCH_2CH_2$ (**2h**) | **L1** | 24 | 80 | 97 |
| 10[c] | cyclohexyl (**2i**) | **L2** | 24 | 89 | 97 |

[a] Yield of the isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] 5 mol% of CuCl, 5 mol% of **L2**, and 10 mol% of NaO*t*Bu were used.

A variety of Bdan-substituted alkene compounds could be hydroborated with high levels of enantioselectivity when the copper/bisphosphine catalysts were used. The *ee* values were similar for all the substituted alkenes (R = aryl or primary or secondary alkyl), thus indicating the minimal influence of the R substituent (remote from the Bdan group) on enantioselectivity with the current catalyst system.

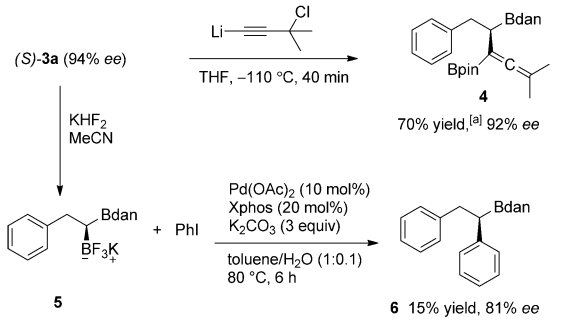
Regarding the mechanism of the catalytic borylalkene hydroboration, we postulated that the hydroboration is initiated by a LCu–H (L = chiral phosphine ligand) catalyst, generated from the reaction of copper *tert*-butoxide with pinacolborane;[14] this pathway is distinct from that of similar copper-catalyzed formal hydroboration reactions involving Cu–B species generated from bis(pinacolato)diboron ($B_2pin_2$; Scheme 2).[15] Subsequent Cu–H addition to the borylalkene would afford a chiral organocopper intermediate **I**, the stereogenic center of which contains both C–B and C–Cu bonds. Stereoretentive transmetalation of the Cu–C bond with pinacolborane would produce the desired product and regenerate the active Cu–H catalyst.[3b,13] The Cu–H addition step determines the regioselectivity and the hydride




***Scheme 2.*** A proposed catalytic cycle for hydroboration involving two stereodetermining steps, hydrocupration, and subsequent transmetalation.

addition to the β-carbon atom from the Bdan (or Bpin) group is considered to be mainly determined by the electronic nature of the boronyl group.[10,16] In the case of activated borylalkenes in which R = phenyl group (**1** vs. **2a**, Scheme 1), the possible hydride addition to the β-carbon atom from the phenyl (or α-carbon atom from B) and L–Cu addition to the benzylic carbon atom can lower the regioselectivity, as was the case with **1**. The flat Bdan group, containing a naphthyl moiety, presumably accommodates the L–Cu moiety better than the Bpin group, thus delivering higher regioselectivity.

Next, we briefly examined applications of these novel chiral 1,1-diborylalkane compounds (Scheme 3). First, a homologation reaction of **3a** with 3-chloro-3-methylbut-1-




***Scheme 3.*** Reactions of chiral alkylborane **3a**. [a] The yield was determined by GC analysis.

ynyllithium provided allenylboronate **4**, and the *ee* value was retained. Next, we tried Suzuki–Miyaura cross-coupling reactions of compounds **3** (see the Supporting Information for details). Compared to Suzuki–Miyaura cross-coupling reactions of alkylboron ($C(sp^3)$–B) compounds containing a coordinating carbonyl group,[5b,17] the coupling reactions of the current compounds led to a low yield of the product with a decrease in *ee* value. Interestingly, the absolute configuration of the major enantiomer of **6** was determined to be *R*, thus indicating the reaction proceeded with retention of configuration. This result clearly shows the importance of the activating carbonyl group for the transmetalation in the previous couplings.[5b,17] While further improvement is needed, this example constitutes the first stereoretentive coupling of an enantioenriched 1,1-diborylalkane that does not contain an additional coordinating group. Further investigation of this coupling is underway in our laboratory.

In summary, we have described a copper-catalyzed hydroboration of borylalkene compounds for the atom-economical preparation of enantiomerically enriched 1,1-diborylalkane compounds. The reaction was highly regio- and enantioselective to form the desired compounds with high efficiency. Investigations into further applications of the products are underway.

## Experimental Section

General procedure for the enantioselective hydroboration with (*R*,*S*)-josiphos ligand: A mixture of CuCl (0.015 mmol, 1.5 mg), NaO*t*Bu (0.03 mmol, 3.0 mg), and (*R*,*S*)-josiphos (0.015 mmol, 9.6 mg) in anhydrous toluene (0.4 mL) was stirred for 10 min in a Schlenk tube under an atmosphere of nitrogen. Pinacolborane (0.6 mmol, 90 μL) was added to the reaction mixture, which was stirred for another 10 min at room temperature. Substrate **2** (0.5 mmol) in toluene (0.4 mL) and tetradecane (0.25 mmol), as an internal standard, were added to the reaction mixture. The reaction tube was washed with toluene (0.2 mL) and sealed. The reaction was monitored by TLC and GC. When the reaction was complete, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The product was purified by chromatography on silica gel (hexanes/ethyl acetate = 10:1).

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