VIP Asymmetric Catalysis

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Catalytic Asymmetric Boration of Acyclic α,β-Unsaturated Esters and Nitriles**

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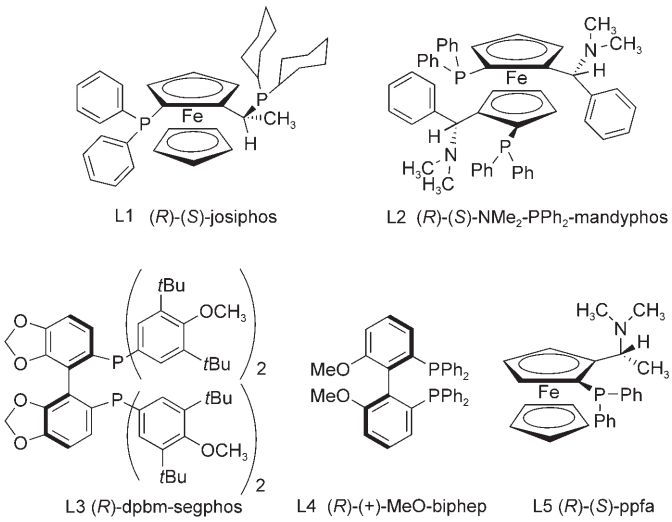
Organoboranes are versatile synthetic intermediates for the preparation of a wide range of organic molecules. An increasing effort has been devoted to the efficient synthesis of organoboron compounds. One of the important tools for the synthesis of organoboranes is transition-metal-catalyzed addition of diboron reagents such as bis(pinacolato)diboron to carbon–carbon multiple bonds, which has been the subject of extensive research.[1] In comparison with electron-rich alkene or alkyne substrates, the reaction with α,β-unsaturated carbonyl compounds has not been studied as extensively. Since introducing a boronate group at the β-position to a carbonyl using conventional hydroboration methods is not possible, the metal-catalyzed β-boration of α,β-unsaturated carbonyl compounds provides an interesting approach. Such reactions have been reported using systems based on platinum,[2] rhodium,[3] and copper[4] but with limitations such as high catalyst loading, high temperature, low to moderate yield, and narrow substrate scope.

Recently, we reported an efficient copper-catalyzed addition of bis(pinacolato)diboron (B_2pin_2) to a range of α,β-unsaturated carbonyl compounds, the substrate scope of which was extended from enones to more challenging α,β-unsaturated esters, nitriles, and phosphonates.[5] In view of the variety of stereospecific transformations available to stereogenic carbon–boron bonds,[6] we envisioned that catalytic enantioselective boration of α,β-unsaturated carbonyl compounds would easily provide functionalized enantioenriched organoboron compounds. However, an asymmetric boration of such compounds has not been reported yet. Herein, we describe the enantioselective β-boration of α,β-unsaturated esters and nitriles catalyzed by a nonracemic copper phosphine complex.

In our previous study on the copper-catalyzed β-boration, we found that both a suitable ligand and methanol additive were required for complete conversion. Especially the alcohol was critical to the enhanced rate of reaction; even a reaction with no ligand proceeded with great conversion in the presence of methanol. Because this methanol effect could be deleterious to enantioselectivity, minimizing the background reaction would be the key for the successful development of an asymmetric variant of the β-boration.

In preliminary experiments, we chose cinnamonitrile as a model substrate and (*R*)-(*S*)-josiphos (L1, Scheme 1) as a nonracemic ligand on the basis of its successful use in the asymmetric reduction of acrylonitriles,[7] and we examined a range of reaction conditions. Variable enantiomeric excesses (50–85% *ee*) were obtained without reproducibility when a 1:1 combination of CuCl and NaO*t*Bu was employed. We surmised that insufficient reaction of the two inorganic salts in THF, an inadvertent shortage of the nonracemic ligand relative to copper, or a combination of these two factors might increase the concentration of catalytic species that cause nonselective reactions. Increasing the amount of base to 1.5 equivalents relative to copper and measuring the exact amount or a slight excess of ligand were effective and reproducibly afforded the β-borylated product with a higher enantioselectivity. Using a given set of conditions (3 mol% CuCl, 4.5 mol% NaO*t*Bu, 3 mol% ligand, 1.1 equiv B_2pin_2, 2 equiv MeOH, THF, room temperature), a series of other ligands[8] were screened, including bidentate phosphines and P,N ligands (Scheme 1); representative results are shown in Table 1. Josiphos (L1) and mandyphos (L2) were equally effective in giving the best results. Moreover, L2 was less sensitive to the ratio of copper to base and consistently gave a reproducible enantiomeric excess with both 1:1 and 1:1.5 copper/base. The C_2-symmetric ligands L3 and L4 displayed



Scheme 1. Structures of ligands.

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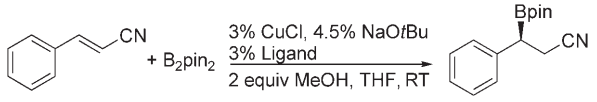
Table 1: Enantioselective β-boration of cinnamonitrile.[a]



Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	L1	97	94
2	L2	93	94
3[d]	L2	96	94
4	L3	92	80
5	L4	92	−3
6	L5	93	55

[a] Complete conversion was achieved within 7 h. [b] Yield of isolated borylated product. [c] Enantiomeric excess of the corresponding β-hydroxy nitrile compound obtained by oxidation with $NaBO_3$ in THF/H_2O (1:1). [d] 3 mol% NaO*t*Bu.

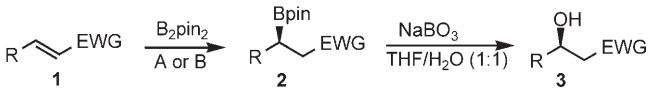
inferior enantioselectivities. The P,N ligand L5 also gave satisfactory conversion within the reaction time but yielded the product with poor enantioselectivity.

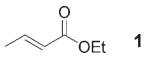
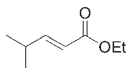
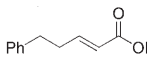
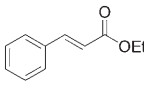
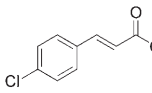
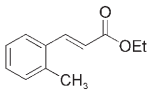
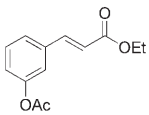
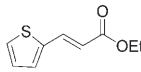
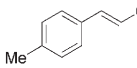
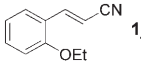
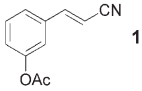
On the basis of these results, we chose condition A (2 mol% CuCl, 3 mol% NaO*t*Bu, 4 mol% L1)[9] and condition B (3 mol% CuCl, 3 mol% NaO*t*Bu, 3 mol% L2) as the optimal reaction conditions along with two equivalents of MeOH in THF at room temperature and applied them to the enantioselective conjugate addition of diboronate to various α,β-unsaturated esters and nitriles (Table 2). All reactions proceeded smoothly in reasonable reaction times (7–24 h) to provide the addition products in excellent yields and with high levels of enantioselectivity. All of the products could be isolated by silica gel chromatography and further transformed by oxidation to the corresponding hydroxy compounds[10] for the determination of the enantiomeric excess. Assignments of stereochemistry were made by comparison of the optical rotations of the hydroxy compounds **3** with those in the literature.[11]

Both β-alkyl substituted (entries 1–3, Table 2) and β-aryl substituted unsaturated esters (entries 4–6, Table 2) provided the products with almost the same levels of enantioselectivity (89–91% *ee*). However, *meta* substitution and *ortho* substitution at the aryl ring slightly lowered the enantioselectivity of the reaction (entries 7–9, Table 2). The heteroaromatic thiophene-substituted substrate **1h** afforded **2h** with a lower enantioselectivity (82% *ee*) as well. The nitrile substrates were generally more efficient than the ester substrates with regard to both reactivity[12] and enantioselectivity and afforded the addition products with high enantioselectivities regardless of the substitution pattern at the aromatic ring (entries 11–13, Table 2).

It is of note that the nature of the electron withdrawing group (CO_2Et vs. CN) affected the enantioselectivity. For example, when the mandyphos ligand was used, substrate **1d**, an ester analogue of cinnamonitrile, afforded **2d** in 87% *ee* (entry 5, Table 2), while cinnamonitrile gave 94% *ee* (entry 3, Table 1). The unsaturated ester **1g** provided **2g** in 84% *ee* (entry 9, Table 2), and the corresponding nitrile **1k** led to 91% *ee* (entry 13, Table 2). We also observed that the methyl ester (89% *ee*) and the more bulky *tert*-butyl ester (89% *ee*) derivatives of cinnamic acid provided asymmetric inductions

Table 2: Asymmetric β-boration of acyclic α,β-unsaturated esters and nitriles.[a]



Entry	Substrate	Condition[b]	Yield of **2** [%][c]	*ee* of **3** [%][d]
1	 **1a**	A	94	90 (*R*)
2	 **1b**	A	92	91 (*S*)
3	 **1c**	A	97	89
4	 **1d**	A	93	90 (*S*)
5		B	94	87 (*S*)
6	 **1e**	A	90	91 (*S*)
7	 **1f**	A	87	88
8	 **1g**	A	95	87
9		B	89	84
10	 **1h**	A	93	82
11	 **1i**	A	94	90 (*S*)
12	 **1j**	A	90	92
13	 **1k**	B	94	91

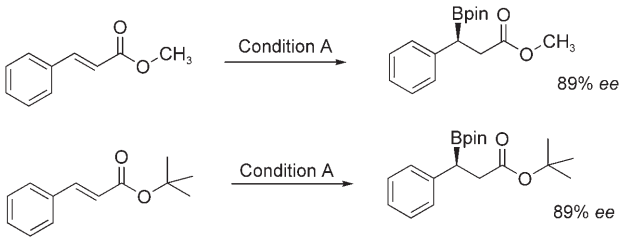
[a] EWG = electron-withdrawing group (CN or C(O)OR'). [b] Condition A: 2% CuCl, 3% NaO*t*Bu, 4% L1; condition B: 3% CuCl, 3% NaO*t*Bu, 3% L2 with 1.1 equiv B_2pin_2 in THF at room temperature. [c] Yield of borylated product (**2**) isolated by chromatography. [d] Determined by either GC or HPLC.

that were very similar to that found for **1d** under the condition A (90% *ee*, Table 2; Scheme 2). The results suggest that the structures of different ester moieties do not significantly influence the enantioselectivity of this reaction.

In summary, we have described the first asymmetric β-boration of acyclic α,β-unsaturated carbonyl compounds that provides ready access to functionalized chiral organoboron compounds under mild reaction conditions. Excellent yields and high enantiomeric excesses were obtained using planar chiral ligands L1 and L2 at room temperature.

Experimental Section

General procedure (condition A): THF (0.45 mL) was added under nitrogen to CuCl (0.010 mmol, 1.0 mg), NaO*t*Bu (0.015 mmol, 1.4 mg), and (*R*)-(*S*)-josiphos ligand (0.020 mmol, 12.8 mg) in an



Scheme 2. Effect of ester structure on the enantioselectivity of the conjugate addition.

oven-dried Schlenk tube. The reaction mixture was stirred for 30 min at room temperature, at which time bis(pinacolato)diboron (0.55 mmol, 139.7 mg) and THF (0.30 mL) were added. The reaction mixture was stirred for 10 min. Then, the α,β-unsaturated carbonyl compound (0.5 mmol) and subseqently MeOH (1.0 mmol, 0.04 mL) were added. The reaction tube was washed with THF (0.2 mL), sealed, and stirred until no starting material was detected by TLC. The reaction mixture was filtered through a pad of celite and concentrated. The product was purified by silica gel chromatography.

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[8] Other diphosphine ligands, such as various josiphos analogues and binap, were also surveyed in the boron addition reaction with **1e** but gave poorer enantioselectivities (less than 50% *ee*). In this case, the best result was again obtained with josiphos. Other ligands, such as 2-(diphenylphosphino-2′-methoxy-1,1′-binaphthyl) (mop) and binapthol-derived phosphoramidite, gave incomplete conversion and very low asymmetric inductions (less than 7% *ee*).

[9] The condition A gave slightly better enantioselectivities (0–2% *ee*) than the reaction conditions using the 1:1.5:1 combination of copper/base/L1.

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[11] The major enantiomer of the other unknown products **3** was assumed to have the same configuration as the known cases (**3a**, **3b**, **3d**, **3e**, and **3i**).

[12] With the ester substrates, longer reaction times (16–24 h) were required than with the nitriles substrates (less than 12 h) for complete conversion.

