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Copper-Catalyzed Enantioselective β-Boration of Acyclic Enones

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Abstract: The enantioselective β-boration of various acyclic enones has been studied by using chiral diphosphine–copper complexes. Good to excellent yields and enantioselectivities (up to 97% *ee* (enantiomeric excess)) were observed for a range of substrates under optimized conditions. In this transformation, the addition of a controlled amount of alcohol, especially methyl alcohol, is critical to obtain products in high *ee* and yield. This methodology accommodates structural variation of acyclic enones and provides access to a range of functionalized chiral organoboronates in high enantiomeric purity.

Keywords: asymmetric catalysis · boron · conjugate addition · copper · enones

Introduction

The conjugate addition of organometallic nucleophiles to electron-deficient olefins constitutes one of the most important strategies for bond construction in organic synthesis.[1] Transition-metal-catalyzed enantioselective conjugate additions have been extensively studied and remarkable progress is continually being made. Acyclic enones have proven to be particularly challenging substrates in many asymmetric conjugate additions, although a few notable examples have recently been disclosed.[2]

In recent years, the transition-metal-catalyzed addition of diboron reagents to α,β-unsaturated carbonyl compounds, which affords organoboronate products with carbonyl functionalities at the β position, has been a subject of interest. This transformation has been studied with platinum,[3] rhodium,[4] copper,[5] and nickel[6] catalyst systems by several groups, including ours. Despite recent developments in metal-catalyzed conjugate boration methodology, there are few catalytic enantioselective methods that provide access to enantiomerically enriched organoboronates by this approach;[7] only recently have we described the first enantioselective β-boration reaction of α,β-unsaturated esters and nitriles.[8,9] Boronate esters are versatile intermediates in organic synthesis but the current routes to chiral boronates are relatively limited. In this regard, the asymmetric conjugate addition of diboron reagents to acyclic enones would provide an expedient preparation method of chiral β-borylated ketones.

The development of a highly enantioselective β-boration of enones with copper catalysts appeared particularly challenging, apart from the structural variations of acyclic enones. Neither Hosomi's[5a] nor Miyaura's[5b] copper catalytic systems developed for the β-boration of enones can be directly applied to enantioselective reactions because of their low reactivity and the type of ligands employed.[10] In our recent study of the β-boration of α,β-unsaturated esters and nitriles by using CuCl, NaO*t*Bu, a diphosphine ligand, and methanol, we observed a dramatic rate acceleration effect due to the alcohol additive.[5c] Although our catalyst system can possibly solve the low reactivity problem of the previous copper systems, it does not guarantee high enantioselectivity even with chiral ligands of adequate architecture in the light of possible nonselective background reactions with the inclusion of the alcohol additive. Herein we report the copper-catalyzed enantioselective addition of bis(pinacolato)diboron (B_2pin_2, **1**) to the challenging class of acyclic enones. A variety of acyclic enones undergo highly enantioselective and efficient conjugate addition of the boron reagent catalyzed by a chiral copper–phosphine complex under mild reaction conditions.

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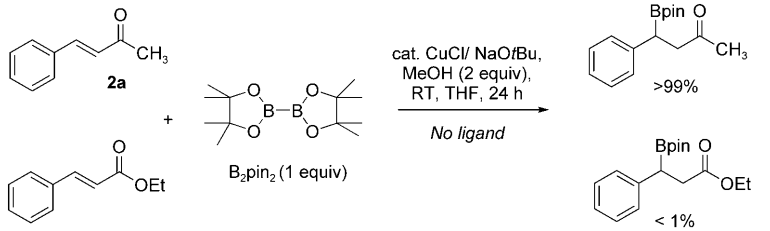
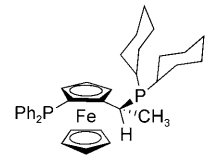
Results and Discussion

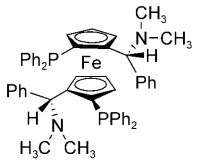
First, to estimate the extent of the "methanol effect" on the β-boration of acyclic enones, we set up an experiment in which one equivalent of 4-phenyl-3-buten-2-one (**2a**) and one equivalent of *trans*-ethyl cinnamate competitively reacted with one equivalent of diboron (**1**) in the absence of coordinating ligands (Scheme 1). As expected, the enone reacted faster than the ester, but surprisingly, complete consumption of the enone to the product was detected whereas less than 1% of the ester reacted; the addition of MeOH was sufficient for complete conversion of the enone! Bearing the easy progress of this ligandless reaction in mind, we sought to explore the asymmetric β-boration of acyclic enones.



Scheme 1. Competitive β-boration reaction of **2a** and cinnamate in the absence of ligand.



L1 (*R*)-(*S*)-josiphos

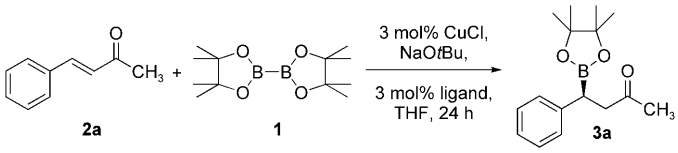


L2 (*R*)-(*S*)-NMe$_2$-PPh$_2$-mandyphos

Initially, we chose (*R*)-(*S*)-josiphos (**L1**) and (*R*)-(*S*)-mandyphos (**L2**) as starting nonracemic ligands for the investigation of the β-boration of **2a**.[11] Copper catalysts complexed by these ligands alone and without an alcohol additive were not effective for the complete β-boration even at elevated temperatures (Table 1, entries 1, 2, and 6). While some of the *ee*s (enantiomeric excesses) obtained under these conditions appeared to reasonably reflect the enantioselectivity of each ligand (68% *ee* with **L1** at RT and 77% *ee* with **L2** at 60°C), the reaction performed at 60°C with ligand **L1** resulted in poor conversion and *ee* (Table 1, entry 2). Therefore, using alcohol additives for rate acceleration in this transformation was unavoidable and a number of conditions with different alcohols were screened to identify the optimal conditions. When **2a** was subjected to reaction conditions with two equivalents of methanol, lower levels of enantioselectivity were obtained (Table 1, entries 3 and 7).[12] Sterically bulky *t*BuOH (Table 1, entry 4) and *i*PrOH (Table 1, entry 10) were not as effective as MeOH in terms of turnover numbers,[13] but afforded product **3a** with the desirable levels of enantioselectivity. We were pleased to find that either reducing the amount of methanol to one equivalent (Table 1, entries 5 and 8) or employing a slight excess of *i*PrOH (Table 1, entry 11) was effective in giving **3a** in good yields with the expected levels of enantioselectivity.

Next the effect of solvent on enantioselectivity was determined with **2a** and chalcone (**2b**) by employing one equivalent of MeOH (Table 2). When mandyphos (**L2**) was used as the ligand, reactions in toluene resulted in a significant decrease in stereoinduction (Table 2, entries 2 and 4). On the other hand, with josiphos ligand **L1** no significant drop in *ee* was detected in either THF or toluene (Table 2, entries 6 and 7). However, reactions in diethyl ether appeared to be slightly less selective (Table 2, entries 5 and 8). Of note is the

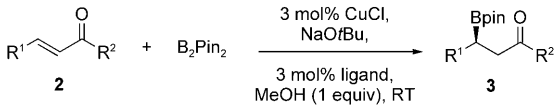
Table 1. Optimization of the asymmetric boration of enone **2a**.

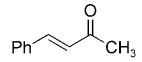
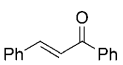


Entry	Ligand	Additive (equiv)	*T* [°C]	Conv. [%]	Yield[a] [%]	*ee*[b] [%]
1	**L1**	–	RT	21	18	68 (*S*)
2	**L1**	–	60	53	48	56 (*S*)
3	**L1**	MeOH (2)	RT	100	80	37 (*S*)
4	**L1**	*t*BuOH (2)	RT	92	80	68 (*S*)
5	**L1**	MeOH (1)	RT	100	93	68 (*S*)
6	**L2**	–	60	56	54	77 (*S*)
7	**L2**	MeOH (2)	RT	100	68	74 (*S*)
8	**L2**	MeOH (1)	RT	100	95	80 (*S*)
9	**L2**	*t*BuOH (2)	RT	100	95	79 (*S*)
10	**L2**	*i*PrOH (1)	RT	95	90	80 (*S*)
11	**L2**	*i*PrOH (1.2)	RT	100	92	80 (*S*)

[a] Isolated yield. [b] Determined by chiral HPLC analysis of the corresponding β-hydroxy ketone obtained by oxidation.

Table 2. Effect of solvent on the enantioselectivity of the boration.

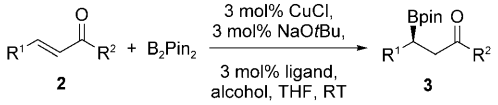


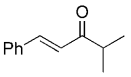
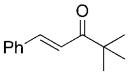
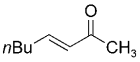
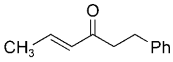
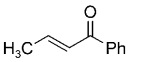
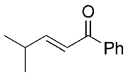
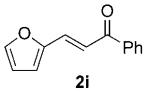
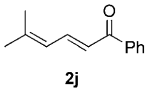
Entry	Substrate	Ligand	Solvent	*ee* [%]
1		**L2**	THF	80
2		**L2**	toluene	67
	2a			
3		**L2**	THF	70
4		**L2**	toluene	62
5	**2b**	**L2**	Et_2O	68
6		**L1**	THF	96
7		**L1**	toluene	95
8		**L1**	Et_2O	90

fact that substrate **2b**, which has a phenyl group instead of a methyl group (**2a**, 68% *ee*), reacted with an excellent level of enantioselectivity (96% *ee*; Table 2, entry 6) with a copper–josiphos complex.[14]

Encouraged by the enantioselectivities achieved with the model substrates, we continued to survey additional acyclic enone substrates with the following sets of reaction conditions; **L1** or **L2** was used as the ligand and MeOH (1 equiv) or *i*PrOH (1.2 equiv) as the additive with 3 mol% CuCl and 3 mol% NaO*t*Bu, in THF at room temperature (Table 3).[15]

Table 3. Enantioselective β-boration of acyclic enones.



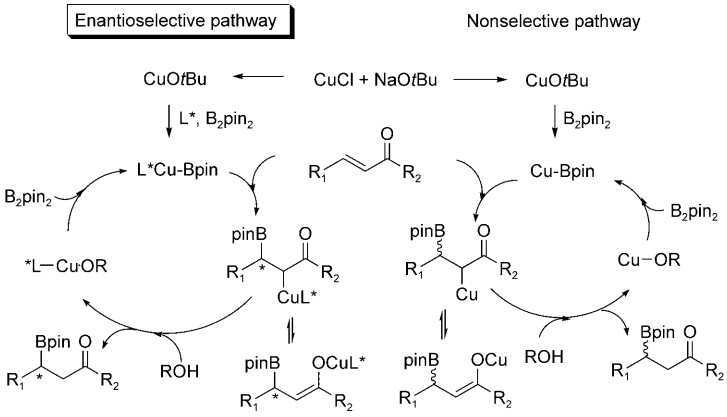
Entry	Substrate	Ligand	Additive	Yield[a] [%]	*ee*[b] [%]
1	**2b**	**L1**	*i*PrOH	94	95
2		**L1**	MeOH	79	89[c]
3	 **2c**	**L2**	MeOH	93	93[c]
4		**L1**	MeOH	89	81[c]
5	 **2d**	**L2**	MeOH	91	8[c]
6		**L1**	MeOH	93	90
7	 **2e**	**L2**	MeOH	86	30
8		**L1**	MeOH	95	90
9		**L1**	*i*PrOH	90	88
10	 **2f**	**L2**	MeOH	96	30
11	 **2g**	**L1**	MeOH	97	97
12	 **2h**	**L1**	MeOH	94	97
13		**L1**	MeOH	72[d]	92
14	 **2i**	**L1**	*i*PrOH	72[d]	91
15		**L1**	MeOH	93	96
16	 **2j**	**L1**	*i*PrOH	–[e]	95

[a] Isolated yield. [b] Determined by chiral HPLC or GC analysis of the corresponding β-hydroxy ketone obtained by the oxidation of **3**. [c] Determined by chiral HPLC analysis of the borylated product. [d] Compound **3i** was unstable upon silica gel chromatography and was thus transformed to the corresponding β-hydroxy ketone. Yield over two steps. [e] ≈70% conversion after 50 h.

In general, with MeOH as the additive all the reactions reached completion in between 9 and 24 h and good yields of the desired products were obtained. For β-phenyl-substituted enones with methyl (**2a**; Table 1), *iso*-propyl (**2c**; Table 3), and phenyl (**2b**; Table 2) side groups, the enantioselectivities increased from 68 to 96% *ee*, and then decreased to 81% *ee* for *tert*-butyl enone **2d** (Table 3) when **L1** was employed as the ligand. On the other hand, when **L2** was used, the highest enantioselectivity (93% *ee*; Table 3, entry 3) was obtained with the *iso*-propyl-substituted enone and lower enantioselectivities were observed with the *tert*-butyl- (8% *ee*; Table 3, entry 5) and phenyl-substituted enones (70% *ee*; Table 2).

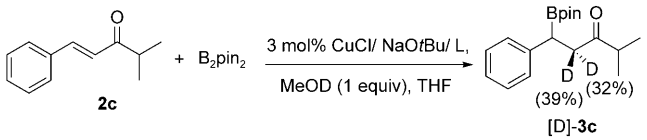
In the reactions of alkyl enones **2e** and **2f**, ligand **L1** was more selective than **L2** and afforded both the desired products in 90% *ee* (entries 6 and 8). The josiphos ligand was again more efficient for the reaction of other phenyl enones (**2g–j**), affording products with excellent enantioselectivity up to 97% *ee*.[17] It appears that steric factors at the β-position, which the boron addition takes place at, do not play a major role in determining the enantioselectivity with **L1** as the ligand, as the different phenyl enones were β-borylated with similar levels of enantioselectivity. It is worth noting that the extended conjugate substrates **2i**[16] and **2j** reacted stereoselectively to give the corresponding 1,4-addition products in high yield and excellent *ee* (Table 3, entries 13 and 15). *i*PrOH was generally as effective as MeOH, but in some cases it led to poorer results in terms of reactivity. For example, using *i*PrOH in the reaction of **2j** resulted in a very slow reaction (30% conversion in 22 h, 70% in 50 h; Table 3, entry 16). Overall, the combination of Cu–josiphos (**L1**) and one equivalent of MeOH in THF allows for complete conversion and good to high *ee* for a range of acyclic enones.

A possible catalytic cycle for the conjugate boration of enones is proposed in Scheme 2. The conjugate additions



Scheme 2. Proposed reaction mechanism.

proceed via an intermediate copper enolate that undergoes protolytic cleavage by an alcohol to form the protonated product and a copper alkoxide. The copper alkoxide reacts with diboron to regenerate the active copper boryl complex. To obtain evidence on the proposed reaction pathway, an experiment with enone **2c** and MeOD as the alcohol additive was conducted (Scheme 3).[18] The reaction afforded [D]-**3c** with deuterium incorporated at the α position in accordance with the proposed mechanism. This result also suggests that the rate enhancement of the alcohol additive may



Scheme 3. Deuterium labeling study.

be due to more rapid quenching of the copper enolate by alcohol than by the diboron.

Recently, Marder, Lin, and coworkers have shown by using DFT studies on the diboration of aldehydes that σ-bond metathesis between a Cu–O bond and a B–B bond is almost barrierless, while the metathesis process between a Cu–C bond and a B–B bond has a higher barrier.[19] We reasoned that the slow reaction rates observed by Hosomi et al. and Miyaura et al. and in some of our results without alcohol should result from slow σ-bond metathesis between the copper enolate and diboron reagent. Therefore, the sluggishness of the enolate boration in comparison to the boration of copper alkoxides might be the result of a preference for a C-bound copper enolate over an O-bound copper enolate. Overall, the rate acceleration effect of alcohol additives can be explained by the facile formation of Cu–OR bonds from the copper enolate, followed by the barrierless boration of the copper alkoxide with B_2pin_2 to regenerate the active Cu–B catalyst.

The experiment conducted in Scheme 1 shows that the rate of the nonselective pathway can also be significantly enhanced by the addition of alcohol additives, a mechanistic representation of which is also shown in Scheme 2. The fact that a highly enantioselective β-boration of enones has been realized in the presence of alcohol additives indicates that the nonselective pathway is effectively suppressed under our optimal conditions. Because keeping the concentration of the free Cu–B species, Cu–Bpin, as low as possible is essential for high enantioselectivity, the coordination ability of the chiral ligand (L*) to the metal as well as its inherent facial selectivity should be an important factor to consider in this asymmetric transformation.[11] We also observed that the level of enantioselectivity is dependent on the amount and size of the alcohol additive and the nonselective reaction takes place to a great extent with excess methanol. With bulkier alcohols (*i*PrOH and *t*BuOH), slower reaction rates were observed but the enantioselectivity was preserved in most cases. This might be attributed either to the rate of the background reaction being slowed down to a greater extent than the rate of the enantioselective route or to less perturbation of the ligand–metal association by an increase in the size of the alcohol. The effect of solvent on *ee* can be explained by the degree of the nonselective pathway allowed in different solvents.

Conclusion

In summary, we have developed a catalytic enantioselective conjugate boration method of acyclic enones that provides ready access to chiral organoboronates that have a boronate group at the stereocenter β to the carbonyl. It was found that the addition of alcohol additives was crucial for higher yields of the desired products and that controlling the amount of alcohol depending on its size was essential to obtain high and reproducible *ee*. Notably, a copper–josiphos complex generally gave excellent levels of enantioselectivity, up to 97% *ee*, with various acyclic enones.

Experimental Section

General procedure for the asymmetric β-boration of acyclic enones: CuCl (0.015 mmol, 1.5 mg), NaO*t*Bu (0.015 mmol, 1.4 mg), and (*R*)-(*S*)-josiphos ligand (0.015 mmol, 9.7 mg) were placed in a resealable Schlenk tube and THF (0.40 mL) was added under nitrogen. The reaction mixture was stirred for 30 min at RT, after which time bis(pinacolato)diboron (0.55 mmol, 140 mg) in THF (0.30 mL) was added. The reaction mixture was stirred for 10 min, then the enone substrate (0.5 mmol) and MeOH (0.5 mmol, 0.02 mL) were successively added. The reaction tube was washed with THF (0.30 mL), sealed, and stirred until no starting material was detected (monitored by TLC). The reaction mixture was filtered through a Celite pad and concentrated, then the product was purified by silica gel chromatography. See the Supporting Information for details of the synthesis and characterization of individual compounds.

Acknowledgements

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[9] For a recent preparation of β-borylated amides by the catalytic asymmetric hydroboration of β,γ-unsaturated amides, see: S. M. Smith, N. C. Thacker, J. M. Takacs, *J. Am. Chem. Soc.* **2008**, *130*, 3734–3735.
[10] Miyaura's conditions also indicate the possible interference of non-selective reactions by nonligated copper species at elevated temperatures.
[11] We have screened other types of ligands, such as salen-type ligands, oxazolines, and Pfaltz's-type ligands, but all led to an almost racemic product. See the Supporting Information for details.
[12] When a 1:2 ratio of copper–**L1** was employed with two equivalents of MeOH as the additive, we observed that the enantioselectivity increased to 70% *ee*. However, with **L2**, both 1:1 and 1:2 combination of copper–ligand in the presence of two equivalents of MeOH gave variably lower levels of enantioselectivity than the expected *ee*. In this study, we pursued the development of a simple, general protocol in which excess ligand is not employed, for future screening of various ligands for their effectiveness.
[13] See also entry 16 in Table 3.
[14] The (di-*tert*-butyl)phosphine analogue of josiphos gave a lower enantioselectivity (90% *ee*).
[15] All of the products (**3**) could be isolated by silica gel chromatography except for **3i**,[16] which partially decomposed into the corresponding protodeboronated product upon chromatography. Assignments of the absolute configuration of **3a**,**b**,**g**,**h**, and **i** were made by comparison of the optical rotations of their hydroxy derivatives with those in the literature. The other unknown products were assumed to have the same configuration as the known cases.
[16] Filtration of the crude reaction mixture through a Celite pad afforded a fairly clean ^{1}H NMR of **3i** that was slightly contaminated with boron impurities. See the Supporting Information for the spectra.
[17] Mandyphos ligand gave poor to moderate *ee*s for these substrates (25–64% *ee*).
[18] DPEphos (bis(2-diphenylphosphinophenyl)ether) was used as the ligand, see: P. C. J. Kamer, P. W. N. M. Van Leeuwen, J. N. H. Reek, *Acc. Chem. Res.* **2001**, *34*, 895–904.
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