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Catalytic Asymmetric Synthesis of Chiral Tertiary Organoboronic Esters through Conjugate Boration of β-Substituted Cyclic Enones

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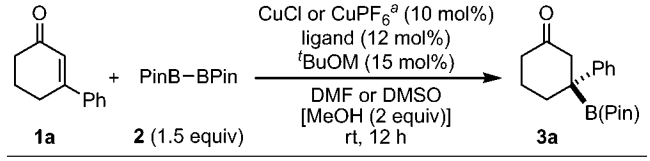
Catalytic asymmetric conjugate addition reactions are a fundamental synthetic methodology to introduce functionalities at the β-position of carbonyl groups.[1] Despite the plethora of catalytic asymmetric conjugate addition reactions using β-monosubstituted α,β-unsaturated carbonyl substrates, methods applicable to the synthesis of β-tetrasubstituted carbonyl compounds using β,β-disubstituted substrates are still limited.[2] This is partly due to the markedly lower reactivity of β,β-disubstituted substrates compared to β-monosubstituted substrates. In addition, chirality is difficult to control due to the smaller steric difference between the β-substituents. Enhanced catalyst activity and enantioselectivity are required to achieve catalytic asymmetric β-tetrasubstituted carbon construction.

To overcome these hurdles, we focused on Cu(I)-catalyzed conjugate boration using bis(pinacolato)diboron (**2**). The basic methodology was originally developed independently by Hosomi[3] and Miyaura[4] in racemic systems. The reaction proceeds through a borylcopper species generated via transmetalation.[5] Yun recently identified the remarkable acceleration effects of protic additives in developing the first enantioselective version using linear β-monosubstituted α,β-unsaturated carboxylic acid derivatives as substrates and phosphines as ligands,[6a−d] and subsequently Fernández and Guiry employed chiral NHC and P−N ligands, respectively.[6e,f] Chiral organoboron compounds are versatile synthetic intermediates due to the convertibility of C−B bonds to a variety of functional groups.[7,8] Furthermore, chiral organoboronic acids exhibiting unique biological activities were identified.[9] Based on the reaction mechanism for an analogous Cu-catalyzed allylic boration proposed by Ito and Sawamura,[10] chirality on the copper atom of the borylcopper species exists proximal to the prochiral carbon in the four-membered cyclic (Cu−B−β-C−α-C) transition state. This is advantageous for the strict enantio-differentiation required to overcome the above-mentioned difficulty in enantio-selection. Here we report a catalytic enantioselective conjugate boration of β-substituted cyclic enones that produces enantiomerically enriched tertiary organoboronates.

We first optimized racemic reaction conditions using 3-phenyl-2-cyclohexen-1-one (**1a**) as a substrate and racemic BINAP as a ligand (Table 1, entries 1−3). Using a CuO^{t}Bu complex generated in situ from CuCl and NaO^{t}Bu in the presence of 2 equiv of MeOH in THF (Yun's conditions), the reaction did not proceed at all. On the other hand, product **3a** was obtained in 10% yield in DMF *in the absence of MeOH* (entry 1). After a systematic survey of copper sources and metal alkoxides, the optimized conditions were determined to be a combination of $CuPF_6(CH_3CN)_4$ and LiO^{t}Bu; **3a** was obtained in 55% yield (entry 2). The detrimental effects of additive MeOH in this reaction were confirmed again at this point; yield decreased to 11% in the presence of 2 equiv of MeOH (entry 3).

The optimized conditions were next extended to an asymmetric version in the presence of chiral phosphines (entries 4−8). (*R*,*R*)-QuinoxP* containing a P-chirality[11] was the optimum chiral ligand; excellent enantioselectivity (91% ee) was obtained with a yield of 78% (entry 8). DMSO was a better solvent than DMF, affording **3a** in 90% yield with 98% ee (entry 9). Catalyst loading was reduced to 5 mol % without affecting the enantioselectivity (entry 10). Interestingly, the enantioselectivity was not very sensitive to the hard metals of *t*-butoxides. The chemical yield, however, was significantly lower when using NaO^{t}Bu and KO^{t}Bu instead of LiO^{t}Bu (entries 10−12).

Table 1. Optimization of Reaction Conditions



1a **2** (1.5 equiv) **3a**

entry	M	ligand	solv.	MeOH	yield (%)[b]	ee (%)[c]
1	Na	*rac*-BINAP	DMF	−	10	−
2	Li	*rac*-BINAP	DMF	−	55	−
3	Li	*rac*-BINAP	DMSO	+	11	−
4	Li	tol-BINAP	DMF	−	82	48
5	Li	DTBM-SEGPHOS	DMF	−	23	11
6	Li	Ph-BPE	DMF	−	90	27
7	Li	JOSIPHOS	DMF	−	55	20
8	Li	QuinoxP*	DMF	−	78	91
9	Li	QuinoxP*	DMSO	−	90	98
10[d]	Li	QuinoxP*	DMSO	−	88	98
11[d]	Na	QuinoxP*	DMSO	−	61	96
12[d]	K	QuinoxP*	DMSO	−	57	93

[a] In entry 1, CuCl was used. In other entries, $CuPF_6(CH_3CN)_4$ was used. [b] Isolated yield. [c] Determined by chiral GC. [d] 5 mol % of catalyst.

The substrate scope was then investigated under the optimized conditions (Table 2). Generally high enantioselectivity (93−98% ee) was obtained from β-aromatic-substituted enones. Neither electron-donating nor withdrawing *para*- and *meta*-substitution on the β-aromatic ring affected the yield or enantioselectivity (entries 1−6). Methyl- and branched-alkyl substituted enones were competent substrates as well (entries 7−9). In addition to the 6-membered cyclic enones, 5- and 7-membered cyclic enones produced excellent to synthetically useful enantioselectivity (entries 10−12).

This reaction is a useful platform for the synthesis of various chiral building blocks that are otherwise difficult to access (Scheme 1). Oxidation of **3a** with $NaBO_3$[8b] afforded tertiary alcohol **4** in high yield with minimum loss of enantioselectivity (eq 1). Unique chiral tertiary organoboronic acid **5**, which might be an interesting pharmaceutical lead, was produced through acid hydrolysis (eq 2). Unlike Yun's conditions,[6] the present reaction did not require protic additives. Therefore, the products in the reaction mixtures are corresponding boron enolates that can react further with electrophiles. This advantage was illustrated by extension to a catalytic asymmetric three-component reaction using **1a**, **2**, and benzaldehyde (eq 3). Product **6**, derived through enantioselective conjugate

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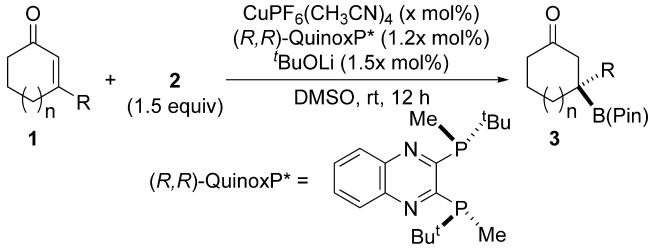
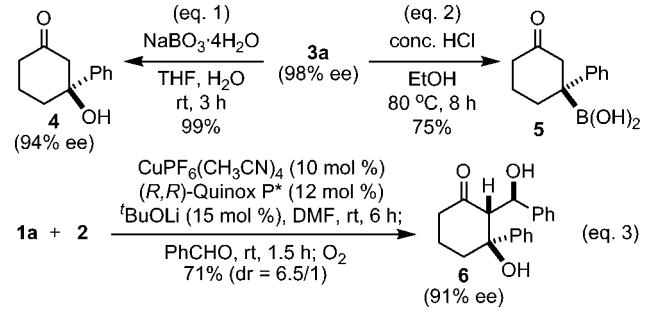
Table 2. Catalytic Enantioselective Conjugate Boration of β-Substituted Cyclic Enones



entry	substrate	*x* (mol %)	yield (%)[a]	ee (%)[b]
1	R = Ph, *n* = 1 (**1a**)	5	88	98[d]
2	R = *p*-MeO-C_6H_4, *n* = 1 (**1b**)	10	84	93
3	R = *p*-Me-C_6H_4, *n* = 1 (**1c**)	10	86	95
4	R = *p*-F-C_6H_4, *n* = 1 (**1d**)	5	80	93
5	R = *m*-MeO-C_6H_4, *n* = 1 (**1e**)	10	83	95
6	R = *m*-Me-C_6H_4, *n* = 1 (**1f**)	10	89	98
7[c]	R = Me, *n* = 1 (**1g**)	5	91	81
8	R = ^{i}Pr, *n* = 1 (**1h**)	10	91	94
9	R = ^{t}Bu, *n* = 1 (**1i**)	10	92	85
10	R = Ph, *n* = 0 (**1j**)	10	85	98
11	R = ^{t}Bu, *n* = 0 (**1k**)	10	94	70
12	R = Ph, *n* = 2 (**1l**)	10	99	98

[a] Isolated yield. [b] Determined by chiral GC or HPLC. [c] NaO^{t}Bu was used instead of LiO^{t}Bu. [d] Absolute configuration was assigned to be (*R*).[13]

Scheme 1. Synthetically Useful Conversions of the Products and Extension to a Catalytic Asymmetric Three-Component Reaction



boration, diastereoselective aldol reaction, and oxidation in one pot, was obtained in 71% yield with 91% ee (only two diastereomers were detected; dr = 6.5/1). Thus, the stereochemistries of three contiguous stereogenic centers involving a tetrasubstituted carbon were controlled in a high level, including their absolute configuration.[12]

Although it is not yet clear why protic additives are not necessary for this reaction, we currently believe that a catalytic amount of $LiPF_6$ generated in the active catalyst (CuO^{t}Bu) formation step from $CuPF_6$ and LiO^{t}Bu accelerates the probable turnover-limiting catalyst regeneration step.[14,15] The acceleration effect of $LiPF_6$ was confirmed by comparison with a reaction using Li-free CuO^{t}Bu[16] catalyst (5 mol %); **3a** was obtained only in 31% yield with 75% ee (cf. Table 2, entry 1). The yield of **3a** improved to 80% (87% ee) when $LiPF_6$ (5 mol %) was added to this reaction mixture.

In conclusion, we developed an enantioselective conjugate boration of β-substituted cyclic enones to produce enantiomerically enriched tertiary boronates, catalyzed by a Cu-QuinoxP* complex. Catalytic $LiPF_6$ had positive effects on reactivity. Detailed mechanistic studies especially upon the role of $LiPF_6$ are currently ongoing.

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

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