Catalytic enantioselective boron conjugate addition to cyclic carbonyl compounds: a new approach to cyclic β-hydroxy carbonyls[†]

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The highly enantioselective conjugate boration of six-membered and seven-membered cyclic enones and unsaturated esters was achieved by the use of a copper–(R,S)-Taniaphos complex with up to 99% ee under optimal conditions.

Catalytic boration reactions of unsaturated C–C bonds with diboron reagents have emerged as a novel synthetic tool to afford a variety of organoboron compounds.¹ In particular, the conjugate addition of a diboron reagent to α , β -unsaturated carbonyl compounds provides ready access to functionalized organoboron compounds by incorporating a boron group at the β -position to the carbonyl. This transformation has been studied with transition metals such as Pt,² Rh,³ Cu,⁴ Ni⁵ and very recently, with *N*-heterocyclic carbenes.⁶ However, there are only a few reports on asymmetric conjugate boration reactions^{4f,7} and the enantioselective boration of cyclic substrates has not been reported yet.⁸

Herein, we report a highly enantioselective copper–boryl (Cu–B) catalyst system effective for the boration of cyclic carbonyl compounds. Cyclic substrates including enones and unsaturated lactones served as good substrates for the copper-catalyzed boration, and β -boryl cyclic compounds were obtained with a high level of enantioselectivity up to 99% ee.

In initial experiments, a series of copper(1)-chiral phosphine catalysts were generated in situ by combining a chiral bisphosphine, CuCl and NaOt-Bu in THF. Their catalytic efficiency and enantioselectivity were screened using cyclohexenone as substrate using bis(pinacolato)diboron as reagent. As shown in Table 1, full conversion of the starting cyclic enone was obtained with all the ligands screened. However, only low to moderate enantioselectivities were obtained with the axially chiral bisphosphine ligands (BINAP, *p*-tol-BINAP, SEGPHOS), the Duphos and Tangphos ligands (entries 1-5). The Josiphos ligand (L5), which was quite effective for acyclic substrates in our previous studies, 7a,7b gave the lowest ee of all for the reaction of cyclohexenone (entry 6). We were pleased to obtain high levels of enantioselectivity with the copper-Walphos (L6) and copper-Taniaphos (L7) complexes. When L7 was employed as the ligand, the resulting boronate product was produced with particularly high enantiomeric purity (98% ee) and determined to have the (R) configuration⁹ (entry 8). The addition of 2 equiv. of MeOH was necessary for complete

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conversion when L6 or L7 were used. When the amount of alcohol was limited to 1 equiv. relative to the cyclic enone, the conversion was not complete ($\sim 80\%$) in 24 h although the enantioselectivity did not change significantly.¹⁰

Chiral β -hydroxy carbonyl compounds are useful building blocks and a successful enantioselective β -boration–oxidation sequence for cyclic carbonyl compounds can provide an easy route to the synthesis of such compounds. In contrast to acyclic β -hydroxy carbonyls, enantiomerically enriched cyclic β -hydroxy carbonyl compounds are not easily accessible by either aldol reaction or direct oxy-Michael reactions.¹¹ Enantioselective epoxidation–regioselective ring opening is another interesting option.¹² In this context, the conjugate boration of several cyclic enones was examined with the established, optimal reaction conditions using ligand L7 and methanol (Table 2).

Table 1Ligand screening.



^{*a*} Condition A: CuCl (3 mol%), NaO*t*-Bu (3 mol%), ligand (3 mol%) and MeOH (1 equiv.); condition B: CuCl (2 mol%), NaO*t*-Bu (3 mol%), ligand (4 mol%) and MeOH (2 equiv.) with 1.1 equiv. B_2pin_2 in THF. ^{*b*} Determined by chiral HPLC analysis of the corresponding β-hydroxy naphthoate derivative.



L1 = (*R*)-*p*-TolBinap L2 = (*R*)-SEGPHOS L3 = (*S*,*S*)-Me-Duphos L4 = (*S*,*S*,*R*,*R*)-Tangphos



L5 = (R,S)-Josiphos L6 = (R,R)-Walphos L7 = (R,S)-Taniaphos

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	+ $B_2 pin_2$ n = 0,1,2	2 mol% CuCl, 3 mol% Na 4 mol% L7 2 equiv. MeOH, THF, rt, 2	Ot-Bu →→ R ^{-[} 24 h	o n ^m Bpin 2
Entry	Substrate	Conversion $(\%)^a$	Yield $(\%)^b$	ee (%) ^c
1	0 1a	100	93 (70) ^d	98
2	<u>о</u> 1b	83	78	95
3 ^e	1b	100	94 (75)	88
4		96	92 (72)	> 99
5	1d	0		_
6] 1e 100	93 (79)	dr = 43:57 96, >99
7	1f	100	95	90
8	0 ↓ 1g	100	76	74

Table 2 Asymmetric conjugate boration of cyclic enones with (R,S)-Taniaphos (L7)

^{*a*} Conversion was determined on the basis of consumed starting material by GC analysis with an internal standard. ^{*b*} Isolated yield of **2**. ^{*c*} Determined by chiral GC or HPLC analysis. See ESI for details.† ^{*d*} Yield in parentheses corresponds to that of β -hydroxy ketone obtained *via* a sequential boration–oxidation reaction (NaBO₃ in THF–H₂O). ^{*e*} L1 was used instead of L7.

Cyclohexenones having different substitution patterns were generally good substrates, giving the corresponding borylated products 2 with excellent enantioselectivities over 95% ee.¹³ However, the reaction of 1b, bearing two methyl groups at the α' -position, had a slower rate of reaction, giving 83% conversion with the Taniaphos ligand (entry 2). The copper-L1 complex was more catalytically active for the reaction of **1b** but the enantioselectivity obtained was slightly lower (88% ee; entry 3). Cyclic enone 1d with two substituents at the γ position showed no reactivity. This is probably due to too much steric congestion near the reaction site and defines the scope of the current catalytic system. Reaction of the benzylsubstituted enone le afforded a diastereomeric mixture of boronate products in a 1:1.3 ratio, with excellent ee values of 96% and >99%, respectively (entry 6). The conjugate boration of cycloheptenone also produced the desired product in high yield and ee (entry 7). However, cyclopentenone, when



Scheme 1 Catalytic β -boration of other cyclic carbonyl compounds.

reacted with the copper-L7 catalyst, produced the desired product 2g with a modest level of enantioselectivity (entry 8).

The optimized reaction protocol was employed with unsaturated lactone substrates (Scheme 1). Pentenolide **3** produced the boronate ester product in high yield and ee. Also, initial studies on the formation of chiral tertiary C–B centers were conducted with β -methylcyclohexenone. Complete conversion of the starting enone was obtained only with L3 or L4 among the ligands tested in Table 1.¹⁴ However, the enantioselectivities achieved with these ligands were only modest and are yet to be improved.

In summary, copper–boryl complexes coordinated with the Taniaphos ligand is an efficient catalyst system for the asymmetric conjugate boration of six- and seven-membered unsaturated cyclic carbonyl compounds. Efficient enantioselective formation of secondary C–B bonds was achieved in good yields and with excellent enantioselectivity. This method also provides a new catalytic synthetic route to chiral cyclic β -hydroxy ketones, which are difficult to access otherwise.

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