Asymmetric Catalysis

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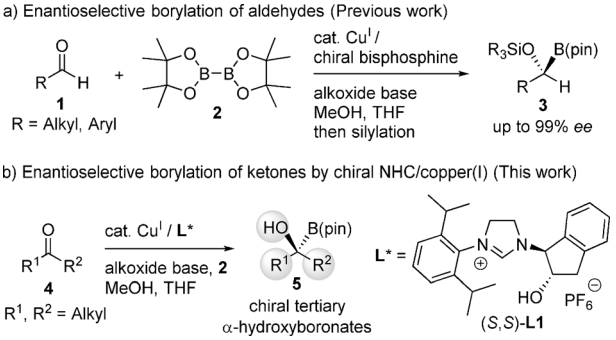
Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aliphatic Ketones: Synthesis of Enantioenriched Chiral Tertiary α-Hydroxyboronates

*Koji Kubota, Shun Osaki, Mingoo Jin, and Hajime Ito**

Abstract: *A new method was developed for the first catalytic enantioselective borylation of aliphatic ketones. A variety of substrates reacted efficiently with bis(pinacolato)diboron in the presence of a copper(I)/chiral N-heterocyclic carbene complex catalyst to furnish optically active tertiary α-hydroxyboronates with moderate to high enantioselectivities (up to 94% ee). Notably, the product could be converted into the chiral tertiary alcohol derivative using a stereospecific boron functionalization process. The theoretical study of the mechanism for the enantioselectivity is also described.*

Chiral α-heteroatom-substituted organoboron compounds have attracted considerable interest because of their wide range of potential applications in asymmetric synthesis and medicinal chemistry.[1] The development of efficient routes for the preparation of compounds belonging to this structural class has therefore captured the imagination of several research groups. The asymmetric addition of a boron nucleophile to a polarized carbon–heteroatom double bond is one of the most straightforward methods for the synthesis of chiral α-heteroatom-substituted organoborons.[2–4] For example, Ellman and co-workers[2a] reported that the copper(I)-catalyzed asymmetric diboration of aldimines in the presence of a chiral auxiliary gave the corresponding chiral α-aminoboronates, which are inhibitors of serine protease. The groups of Fernández,[3a] Lin,[3b] Liao,[3c] and Morken[3d] independently reported the catalytic enantioselective borylation of aldimines to afford the corresponding α-aminoboronates with high enantioselectivity. Most recently, we reported the first enantioselective borylation of a C=O double bond (Scheme 1a).[4] A series of aldehydes (**1**) reacted with bis(pinacolato)diboron (**2**) in the presence of a chiral copper(I) catalyst to produce the corresponding enantiomerically enriched α-alkoxyboronates **3**. Despite recent advances toward the development of enantioselective methods for the borylation of prochiral carbon–heteroatom double bonds, there are currently no methods available for the synthesis of chiral tertiary α-hydroxyboronates from ketones. The development of an efficient method for the enantioselective nucleophilic borylation of ketones is therefore highly desired to facilitate the synthesis of new pharmacophores and chiral intermediates for synthesis.[5] The main challenge to the development of such a method is the fact that ketones exhibit a much smaller degree of steric contrast between the substituents attached to their carbonyl group compared with aldehydes.[6] Catalytic enantioselective addition of aliphatic ketones is extremely difficult, although this approach can construct a chiral quaternary carbon center with high enantioselectivity.[6] For example, to the best of our knowledge, there is only one example of catalytic enantioselective arylation of aliphatic ketones to give chiral tertiary alcohols with high enantioselectivity (> 80% *ee*).[7]



Scheme 1. Umpolung nucleophilic enantioselective borylation of carbonyl compounds. THF = tetrahydrofuran.

Clark and co-workers conducted a pioneering study of the catalytic borylation of ketones in 2010, and found that an achiral N-heterocyclic carbene (NHC)/copper(I) complex could be used to catalyze the diboration of various ketones to give the corresponding racemic tertiary α-hydroxyboronates in high yields.[8,9] However, this work has not yet been extended to the development of an enantioselective process.[10,11] Herein, we report for the first time the enantioselective borylation of the aliphatic ketones **4** with **2** in the presence of a chiral NHC/copper(I) complex catalyst to give the corresponding chiral tertiary α-hydroxyboronates **5** with moderate to high enantioselectivities (Scheme 1b).

The results of an extensive optimization study revealed that 1-cyclohexylethan-1-one (**4a**) reacted with **2** (1.1 equiv) in THF at ambient temperature in the presence of CuCl (5 mol%) and an NHC salt, derived from *trans*-1-amino-2-indanol (*S*,*S*)-**L1** (5 mol%),[12] KO*t*Bu (1.0 equiv), and MeOH (2.0 equiv) as a proton source, to afford the corresponding chiral tertiary α-hydroxyboronate (*S*)-**5a** in good yield with high enantioselectivity (Table 1, entry 1). Several other *trans*-1-amino-2-indanol-based chiral NHC salts [(*S*,*S*)-**L2**–(*S*,*S*)-**L5**] were also evaluated, but afforded lower enantioselectiv-

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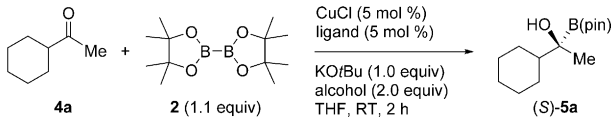
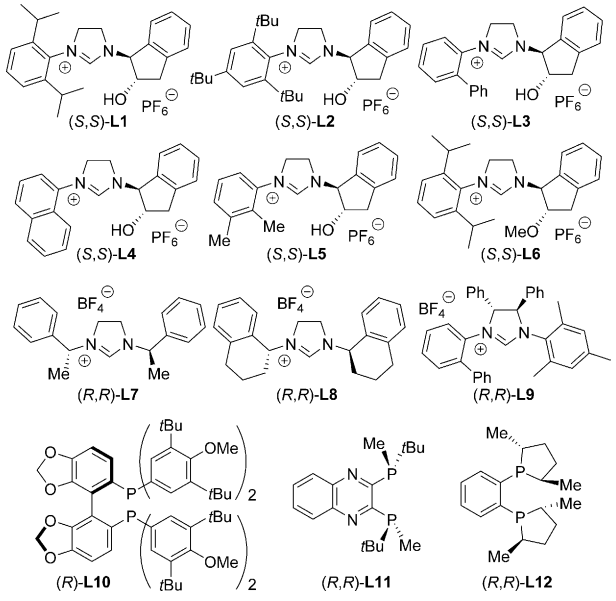
Table 1: Optimization of the reaction conditions.[a]



Entry	Ligand	Alcohol	Yield [%][b]	*ee* [%][c]
1	(*S*,*S*)-**L1**	MeOH	96	92
2[d]	(*S*,*S*)-**L2**	MeOH	50	35
3	(*S*,*S*)-**L3**	MeOH	91	56
4	(*S*,*S*)-**L4**	MeOH	85	63
5	(*S*,*S*)-**L5**	MeOH	84	67
6	(*S*,*S*)-**L6**	MeOH	60	21
7	(*R*,*R*)-**L7**	MeOH	87	10
8	(*R*,*R*)-**L8**	MeOH	65	3
9	(*R*,*R*)-**L9**	MeOH	14	0
10	(*R*)-**L10**	MeOH	< 5	–
11	(*R*,*R*)-**L11**	MeOH	58	1
12	(*R*,*R*)-**L12**	MeOH	99	5
13	(*S*,*S*)-**L1**	*i*PrOH	84	91
14	(*S*,*S*)-**L1**	*t*BuOH	33	83
15	(*S*,*S*)-**L1**	none	86	81
16[e]	(*S*,*S*)-**L1**	MeOH	86	89
17[f]	(*S*,*S*)-**L1**	MeOH	86	84
18[g]	(*S*,*S*)-**L1**	MeOH	72	73
19[h]	(*S*,*S*)-**L1**	MeOH	28	79

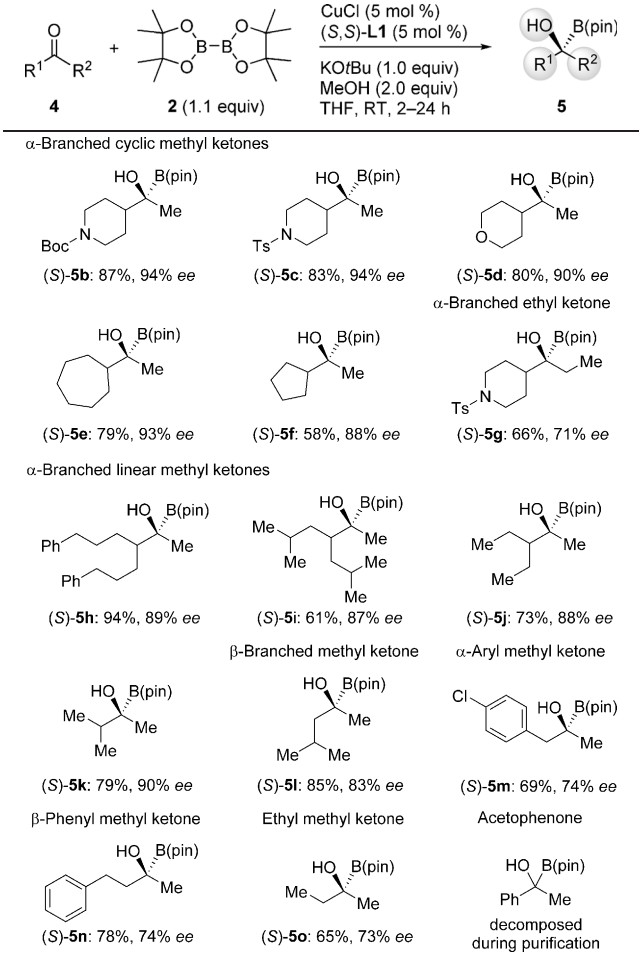


[a] Reaction conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **4a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.55 mmol), alcohol (1.0 mmol), and KO*t*Bu (0.5 mmol) in THF (1.0 mL) at room temperature. [b] Determined by NMR spectroscopy. [c] The *ee* values of (*S*)-**5a** were determined by HPLC analysis after the acylation of the resulting alcohol. [d] The reaction time was 18 h. [e] KO*t*Bu (0.5 equiv, 0.25 mmol) was used. [f] NaO*t*Bu (1.0 equiv, 0.5 mmol) was used instead of KO*t*Bu. [g] LiO*t*Bu (1.0 equiv, 0.5 mmol) was used instead of KO*t*Bu. [h] The reaction was conducted without CuCl over 48 h.

ities (entries 2–5). The use of the NHC salt (*S*,*S*)-**L6**, bearing a methoxy group instead of a hydroxy group, also provided the desired product (60% yield), but with a much lower enantioselectivity than (*S*,*S*)-**L1** (entry 6). The C_2- and C_1-symmetric NHC salts (*R*,*R*)-**L7**–(*R*,*R*)-**L9**[10a,13] also showed low enantioselectivities (entries 7–9). The reaction was also evaluated using chiral bis(phosphine) ligands (entries 10–12). The use of the bulky (*R*)-DTBM-SEGPHOS ligand (*R*)-**L10**, which was found to be effective for the enantioselective borylation of aldehydes,[4] resulted in no reaction (entry 10). In contrast, chiral ligands bearing electron-donating alkyl substituents on the phosphine atoms, for example, (*R*,*R*)-QuinoxP* [(*R*,*R*)-**L11**] and (*R*,*R*)-Me-Duphos [(*R*,*R*)-**L12**], provided access to the desired product, but showed poor enantioselectivities (entries 11 and 12). The nature of the proton source was also found to be important to the reactivity and enantioselectivity of this transformation (entries 13–15). The use of increasingly bulky proton sources such as *i*PrOH and *t*BuOH, instead of MeOH, resulted in lower yields and enantioselectivities (entries 13 and 14). Furthermore, the reaction gave a lower yield and enantioselectivity when it was conducted in the absence of MeOH (entry 15). Although the borylation proceeded smoothly with only 0.5 equivalents of KO*t*Bu, we observed a slight decrease in the enantioselectivity (entry 16). Several other alkoxide bases were also evaluated in this reaction, including NaO*t*Bu and LiO*t*Bu, but all afforded lower levels of enantioselectivity (entries 17 and 18). To exclude the possibility that this reaction could proceed by a metal-free mechanism[14] involving the activation of the diboron reagent by either the Lewis basic KO*t*Bu or the carbene generated in situ, we conducted the borylation in the absence of a copper(I) salt (entry 19). The reaction of **4a** with **2** in the presence of (*S*,*S*)-**L1** and no copper afforded a much lower yield of the desired product (28%) even after an extended reaction time (48 h). This reaction also resulted in a lower enantioselectivity (79% *ee*), thus discounting the possibility of a metal-free mechanism.

With the optimized reaction conditions in hand, we proceeded to evaluate of the substrate scope of this reaction (Table 2). Methyl ketones bearing α-branched aliphatic rings (**4b–f**) reacted smoothly to give the corresponding chiral tertiary α-hydroxyboronates [(*S*)-**5b–f**] with excellent enantioselectivities (88–94% *ee*). The ethyl ketone **4g** also reacted well under the optimized reaction conditions, but gave a lower enantioselectivity, thus indicating that the ability of the catalyst to differentiate between a methyl group and an α-branched structure was responsible for the high enantioselectivity of this reaction. Various ketones bearing α-branched linear aliphatic chains (**4h–k**) were also borylated with high enantioselectivities (87–90% *ee*). The current catalytic system was also effective for the borylation of the β-branched methyl ketone **4l**, thus providing facile access to the corresponding product (*S*)-**5l** with good enantioselectivity (83% *ee*). The α-aryl- and β-phenyl-substituted methyl ketones **4m** and **4n**, respectively, also reacted to provide the corresponding borylated products (*S*)-**5m** and (*S*)-**5n** with good yields and enantioselectivities. The reaction of butan-2-one (**4o**), which represents one of the most challenging substrates for this method, provided the product (*S*)-**5o** with good enantioselectivity (73% *ee*). Although acetophenone was also borylated under the optimization reaction conditions, the product decomposed during purification by column chromatography over silica gel.

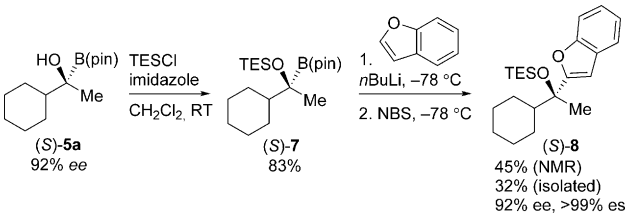
Table 2: Substrate scope.[a,b]



[a] Reaction conditions: CuCl (0.025 mmol), (*S*,*S*)-**L1** (0.025 mmol), **4** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.55 mmol), MeOH (1.0 mmol), and KO*t*Bu (0.5 mmol) in THF (1.0 mL) at room temperature. [b] Yield of isolated product.

The absolute stereochemistry of the borylation product **5a** was determined by X-ray crystallographic analysis of its acylated derivative **6** (Figure 1). The results of this analysis confirmed the structure of **6** and revealed that the absolute configuration of its chiral center was *S*.

Enantioenriched tertiary α-hydroxyboronates prepared in the current study could be used as synthetic building blocks for the preparation of various functionalized chiral compounds.[5] With this in mind, we conducted a preliminary investigation of the stereospecific C–C bond-forming reaction of the chiral boronates (Scheme 2). The Aggarwal cross-coupling reaction[15] of the silyl-protected product (*S*)-**7** with



Scheme 2. Stereospecific cross-coupling reaction with benzofuran. NBS = *N*-bromosuccinimide, TES = triethylsilyl.

benzofuran proceeded to afford the arylated, chiral tertiary alcohol (*S*)-**8** with excellent stereospecificity (> 99 % es). This result therefore suggested that the borylation product will provide attractive synthetic pathways for useful chiral tertiary alcohols, which could not be synthesized by previous methods.

This copper(I)-catalyzed ketone borylation reaction presumably goes through the formation of a borylcopper(I) complex, followed by its 1,2-addition of substrates **4** (see the Supporting Information for the proposed reaction pathway).[8,16] Density functional theory (DFT) calculations (wB97XD/SDD$_{THF(PCM)}$: Cu and K// wB97XD/6-311G(d)$_{THF(PCM)}$: other atoms) were used to investigate the mechanism for the unprecedented high enantioselectivity of the reaction (Figure 2; see also the Supporting Information for details). The results revealed that the addition of the (*S*,*S*)-**L1**/borylcopper(I) complex to **4k** would give the transition states **TS1** and **TS2**, in which the alkoxide anion resulting from deprotonation of the hydroxy group in (*S*,*S*)-**L1** coordinates to the copper center to form the bidentate carbene complex.[12] The calculation also suggested that the

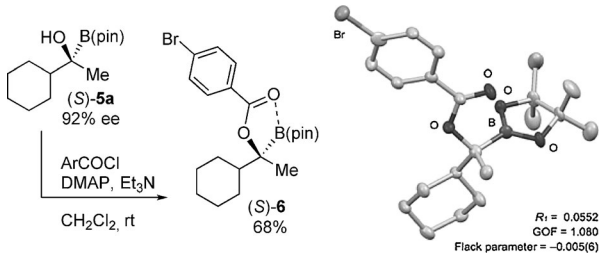


Figure 1. Molecular structure of **6** (thermal ellipsoids set at 50% probability; hydrogen atoms omitted for clarity). DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

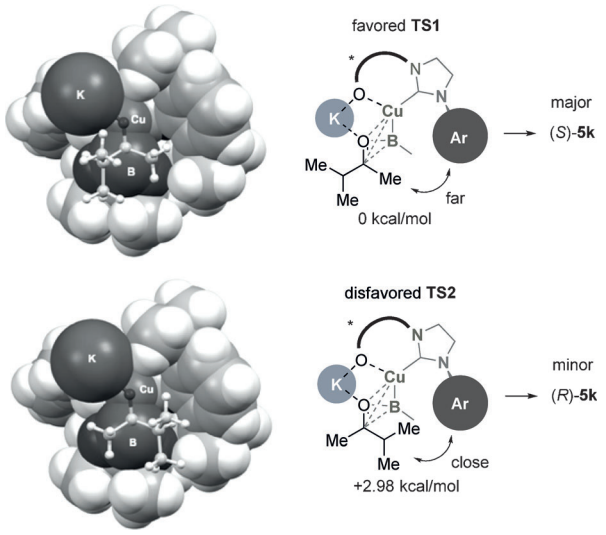


Figure 2. DFT calculations (wB97XD/SDD$_{THF(PCM)}$: Cu and K//wB97XD/6-311G(d)$_{THF(PCM)}$: other atoms) of the transition states for the (*S*,*S*)-**L1**/copper(I)-catalyzed enantioselective borylation of the ketone **4k**. Relative *G* value (kcal mol^{-1}) were obtained at 273 K.

carbonyl oxygen atom in the substrate coordinates to the potassium cation to give a conformationally rigid transition state. The addition of the complex to the *Re*-face to give transition state **TS1** would be free from steric congestion between the copper complex and the substituents of the substrates, and would therefore afford the *S* isomer as the major product. This arrangement is consistent with the observed absolute configuration of the borylated product (Figure 1). In contrast, the activation barrier for the addition of the complex to the *Si*-face to give **TS2** was $+2.98\ \text{kcal mol}^{-1}$ higher in energy than that of **TS1**. This difference in the activation barrier was attributed to steric congestion between the isopropyl moiety in the substrate and the aryl group in the ligand, thereby explaining the observed enantioselectivity of this reaction. As noted above, (*S*,*S*)-**L6**, bearing a methoxy group instead of a hydroxy group on its indane ring, resulted in a lower enantioselectivity (Table 1, entry 6, 20% *ee*). Thus, these theoretical and experimental results suggest that the formation of the bidentate carbene complex as well as the interaction between the potassium cation and the substrate are key factors in providing a higher selectivity in this reaction.

In summary, we have developed the first enantioselective nucleophilic borylation of aliphatic ketones, which are generally difficult substrates for catalytic enantioselective reactions, by using a copper(I)/chiral carbene complex catalyst. The method provides facile access to chiral tertiary α-hydroxyboronates with moderate to high enantioselectivities. It is noteworthy that the borylated product of this reaction could be stereospecifically converted into the chiral tertiary alcohol derivative using a C–C bond-forming reaction. We therefore believe that this work will provide a platform for the preparation of useful chiral functionalized tertiary alcohols which are difficult to access using any other method.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · borylation · copper · ketones · synthetic methods

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Communications

Asymmetric Catalysis

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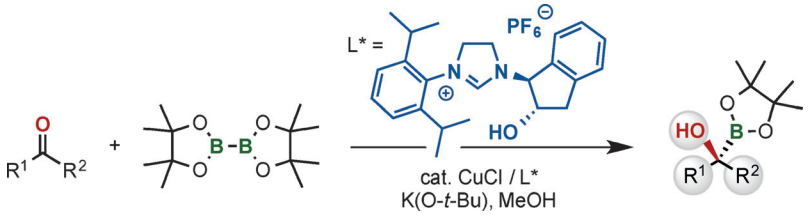
Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aliphatic Ketones: Synthesis of Enantioenriched Chiral Tertiary α-Hydroxyboronates



Ketone functionalization: The first catalytic enantioselective borylation of ketones is presented. A variety of aliphatic ketones reacted efficiently with bis(pinacolato)diboron in the presence of a copper(I)/chiral N-heterocyclic carbene complex to furnish the corresponding tertiary α-hydroxyboronate esters with moderate to high enantioselectivities.

