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Copper(I)−Secondary Diamine Complex-Catalyzed Enantioselective Conjugate Boration of Linear β,β-Disubstituted Enones

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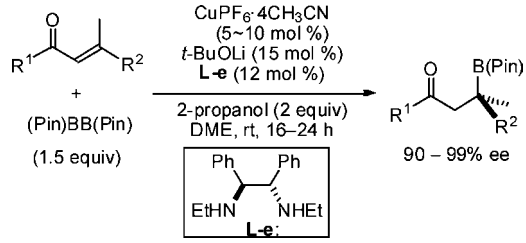
ABSTRACT



A copper(I)−chiral *secondary* diamine (L-e) complex catalyzes an enantioselective conjugate boration of β,β-disubstituted enones in high yields and up to 99% ee. Product chiral tertiary organoboronates can be converted to enantiomerically enriched cross-aldol products between ketones without any racemization.

Catalytic asymmetric conjugate addition is a fundamentally important method in organic synthesis.[1] Various reactions in this category have been developed using β-monosubstituted α,β-unsaturated carbonyl substrates. A variant using β,β-disubstituted substrates to construct chiral β-tetrasubstituted carbons, however, is still difficult to accomplish.[2] This is due both to the lower reactivity and smaller steric and electronic differences between two substituents on prochiral carbons of substrates for tetrasubstituted carbon construction, compared to those for tertiary carbon construction.

Among several candidate reactions for the catalytic enantioselective construction of β-tetrasubstituted carbons, we are especially interested in the conjugate boration[3] of β,β-disubstituted α,β-unsaturated carbonyl substrates. Chiral organoboron compounds[4] are versatile synthetic intermediates because C−B bonds can be converted to various functional groups.[5] Furthermore, α-chiral organoboron molecules exhibiting unique biological activities were identified,

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(1) (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *36*, 5969. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796. (d) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824.

(2) For examples, see: (a) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988. (b) d'Augustin, M.; Palais, L.; Alexakis, A. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376. (c) Lee, K.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182. (d) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774. (e) Brown, M. B.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097. (f) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588. (g) Matsumoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578. (h) May, T.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358. (i) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211. (j) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801. (k) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795. (l) Mazet, C.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762. (m) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862.

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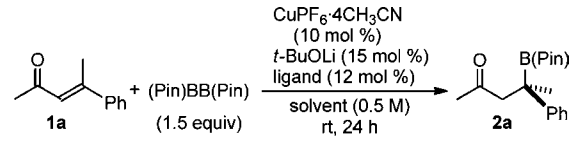
such as potent inhibitors of the proteasome, thrombin, and histone deacetylases.[6]

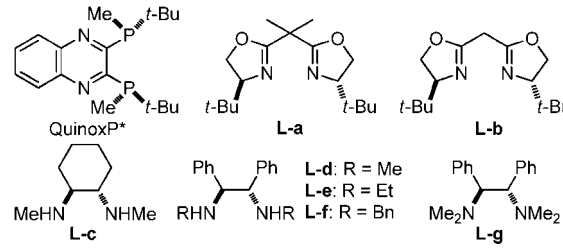
We previously developed the catalytic enantioselective conjugate boration of cyclic β-substituted enones using a catalyst prepared from $CuPF_6(CH_3CN)_4$ modified by QuinoxP*[7] and LiO^tBu, bis(pinacolato)diboron (PinBBPin) as a borylating reagent, and DMSO as a solvent.[8] Due to the importance of α-chiral organoboron compounds, we wanted to expand the substrate scope further to linear β,β-disubstituted enones. Identifying remarkable ligand effects, we report herein a catalytic enantioselective boration of linear β,β-disubstituted enones.

We first applied the previously optimized reaction conditions for cyclic enones to the model substrate (*E*)-4-phenylpent-3-en-2-one (**1a**) (Table 1, entry 1). The desired product **2a** was obtained in excellent yield; however, enantioselectivity was only moderate (38% ee). After comprehensive screening of various chiral phosphine ligands, the enantioselectivity was still unsatisfactory.[9] Therefore, we turned our attention to the use of chiral amine ligands. Despite several advantages of chiral amine ligands to phosphine ligands (such as high stability toward oxidation, low cost, and easy tunability), there were few efficient asymmetric reactions to date using a nucleophilic Cu(I)−chiral amine complex as a catalyst.[10] This is likely due to the weaker affinity of amine ligands for Cu(I) compared to phosphine ligands. Because the target reaction was a ligand-accelerated process and no reaction proceeded in the absence of ligand, we speculated that even dative chiral amine ligands could induce high enantioselectivity.

Table 1. Optimization of Reaction Conditions



entry	ligand	solvent	yield (%)[a]	ee (%)[b]
1	QuinoxP*	DMSO	>99	38
2	**L-a**	DMSO	75	1
3	**L-b**	DMSO	30	10
4	**L-c**	DMSO	78	31
5	**L-d**	DMSO	90	53
6	**L-d**	DME	88	85
7	**L-e**	DME	54	93
8	**L-f**	DME	<5	–
9[c]	**L-e**	DME	86	92
10[c,d]	**L-e**	DME	71	92
11[c]	**L-g**	DME	66	10



[a] Isolated yield. [b] Determined by chiral HPLC. [c] The reaction was run in the presence of *i*-PrOH (2 equiv). [d] Slow addition of *i*-PrOH for 12 h.

As expected, the reaction still proceeded using bisoxazoline-type ligands; however, the enantioselectivity was low (Table 1, entries 2 and 3). The use of ligand **L-c** with a 1,2-cyclohexanediamine scaffold afforded **2a** in good yield with moderate enantioselectivity (31% ee; entry 4). The use of ligand **L-d** containing a 1,2-diphenylethylenediamine skeleton afforded better results, and **2a** was obtained in 90% yield with 53% ee (entry 5).[11] At this stage, solvent effects were examined and 1,2-dimethoxyethane (DME) was the optimum solvent with enantioselectivity improved to 85% ee without affecting the reactivity (entry 6).[9] Further structural tuning of the chiral ligand was examined using DME as a solvent. The use of ligand **L-e** containing *N*-ethyl substituents produced **2a** with 93% ee; however, the yield decreased to 54% (entry 7). Increasing the steric nature of the ligand nitrogen substituents dramatically decreased the reactivity (**L-f**; entry 8).

To improve the reactivity, several additives were next examined using **L-e** as the ligand. Although phosphine oxide

(3) (a) Mun, S.; Lee, J.; Yun, J. *Org. Lett.* **2006**, *8*, 4887. (b) Lee, J.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145. (c) Sim, H.; Feng, X.; Yun, J. *Chem.*−*Eur. J.* **2009**, *15*, 1939. (d) Chea, H.; Sim, H.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855. (e) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659. (f) Fleming, W. J.; Müller-Bunz, H.; Lillo, V.; Fernández, E.; Guiry, P. J. *Org. Biomol. Chem.* **2009**, *7*, 2520. (g) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194. (h) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5130. (i) During the preparation of this manuscript, Hoveyda's group reported the catalytic enantioselective conjugate boration of linear β,β-disubstituted α,β-unsaturated carbonyl compounds. See: O'Brien, J. M.; Lee, K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630.

(4) For other examples of the catalytic asymmetric synthesis of chiral organoboron compounds (hydroboration and diboration), see: (a) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160. (b) Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734. (c) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702. (d) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717. (e) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (f) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134. (g) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210. (h) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634.

(5) For example, see: (a) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861. (b) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *Tetrahedron Lett.* **1989**, *30*, 1483. (c) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555. (d) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778. (e) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (f) Ros, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6289. (g) Bagutsu, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142.

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(9) See the Supporting Information.

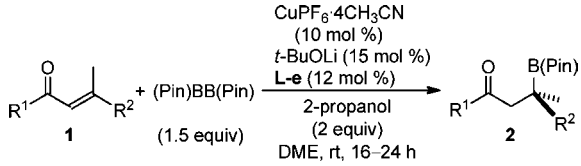
(10) Cu(I)-chiral arylamine complexes are used as catalytst, see: ref 2a and: (a) Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2008**, *49*, 379. (b) Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005**, 1689. Lewis acidic Cu(II)−chiral amine complexes are excellent asymmetric catalysts for various reactions; see: (c) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936. (d) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507. (e) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757.

(11) Only a trace amount of **2a** was produced in the absence of copper (in the presence of *t*-BuOLi and **L-d**).

additives, previously identified as an accelerator in a related Cu(I) catalysis,[12] proved to give less satisfactory results, addition of 2 equiv of ^{i}PrOH markedly improved the yield without affecting the excellent enantioselectivity (entry 9).[13] No further improvement was observed with the slow addition of 2-propanol (entry 10). Interestingly, chiral *tertiary*-diamine ligand **L-g** without NH groups afforded dramatically decreased enantioselectivity (entry 11), suggesting that the NH group had a profound role in enantio-induction (see below).

The substrate generality of this asymmetric conjugate boration of linear β,β-disubstituted enones is summarized in Table 2. Products derived from β-aromatic-substituted

Table 2. Catalytic Enantioselective Conjugate Boration of β,β-Disubstituted Enones

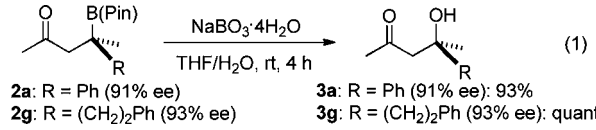


entry	substrate: R^1, R^2	yield[a] (%)	ee[b] (%)
1	**1a:** Me, (*E*)-Ph	86	92[d]
2[c]	**1a:** Me, (*E*)-Ph	80	90[d]
3	**1b:** Me, (*E*)-*p*-tolyl	87	92
4	**1c:** Me, (*E*)-*m*-tolyl	87	95
5	**1d:** Me, (*E*)-3-Cl-C_6H_4	71	96
6	**1e:** Me, (*E*)-3-F-C_6H_4	91	93
7	**1f:** Et, (*E*)-Ph	80	96
8	**1 g:** Me, (*E*)-$(CH_2)_2$Ph	87	94
9	**1 h:** Ph$(CH_2)_2$, (*E*)-Bu	95	94
10[e]	**1i:** Ph$(CH_2)_2$, (*Z*)-Bu	93	96
11	**1j:** *c*-Hex, (*E*)-Bu	80	94
12[f]	**1k:** *c*-Hex, (*Z*)-Bu	83	99

[a] Isolated yield. [b] Determined by chiral HPLC. [c] 5 mol % of catalyst. [d] Absolute configuration of the product was determined as shown in eq 1. [e] The enantiomer of the product obtained in entry 9 was produced. [f] The enantiomer of the product obtained in entry 11 was produced.

enones were obtained in high yield and excellent enantioselectivity (entries 1−7). Catalyst loading was reduced to 5 mol % in an ideal case (entry 2). In addition to methyl-substituted enones, linear and branched alkyl-substituted enones also produced excellent results (entries 7−12).[14] β,β-Dialkyl-substituted enones, generally quite challenging acyclic substrates for asymmetric conjugate addition reactions using chiral copper(I) catalysts,[15] were competent as well (entries 8−12). The products were obtained both from (*E*)- and (*Z*)-substrates in comparably high, but opposing, enantioselectivities (entries 9−12). This result is also noteworthy because (*E*)- and (*Z*)-substrates are completely different substrates for asymmetric catalysts in a general sense.[4e]

Due to the synthetic versatility of organoboron compounds, a variety of synthetically useful conversions of the products are conceivably possible. Here we demonstrate a typical example (eq 1). Boronate **2a** was converted to chiral β-hydroxy ketone **3a** in high yield without any racemization through oxidation of **2a** with sodium perborate, and the same conditions could be applied in the oxidation of aliphatic chiral boronate to afford the corresponding product, **3g**.[5b] Enantiomerically enriched β-hydroxy ketones **3a** and **3g** are cross aldol-type products between ketones. There is no report of catalytic asymmetric aldol reaction to ketones using ketone-derived nucleophiles to date.[16]



To gain preliminary insight into the reaction mechanism, including the critical role of the NH group of the chiral ligand,[17] we performed the following experiments. The first fundamental mechanistic question is whether the chiral diamine ligand coordinates to the lithium atom of $LiPF_6$ or the copper atom of CuB(Pin) when the enantioselective conjugate boration proceeds.[18] To answer this question, we examined a reaction under Li-free CuO-*t*-Bu[19]-**L-e** system. As a result, product **2a** was obtained in 89% yield with 92% ee. This result clearly indicates that the diamine coordinates to the copper atom at the enantio-differentiating step even in the presence of the cationic lithium atom.

(12) (a) Chen, I.-H.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 5151. (b) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 5522.

(13) The dramatic acceleration of the reaction rate by the addition of MeOH in the catalytic enantioselective conjugate boration was originally reported by Yun (ref 3a−d). In our present reaction, however, addition of MeOH did not improve the yield (43% yield with 90% ee vs 86% yield with 92% ee using *i*-PrOH; Table 1, entry 9).

(14) α,β-Unsaturated esters were not reactive under the current conditions. Phenyl ketones produced mixtures of many unidentified products.

(15) Only a limited number of examples giving high enantioselectivity in catalytic conjugate addition to linear β,β-dialkyl-substituted enones as the substrates were published. See refs 2f (Rh catalyst), 2l (Al catalyst), 2m (Sr catalyst), and 3i (Cu catalyst).

(16) For examples of catalytic asymmetric aldol reactions of ketones using ester enolates, see: (a) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233. (b) Moreau, X.; Bazan-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288. (c) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164. (d) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292. (e) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440. (f) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439.

(17) For examples of asymmetric catalysis using secondary amine-derived ligands, see: (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyrori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285. (b) Yamakawa, M.; Ito, H.; Noyrori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466. (c) Tobe, M. L. *Adv. Inorg. Bioinorg. Mech.* **1983**, *2*, 1. (d) Egami, H.; Oguma, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 5886. (e) Matsumoto, K.; Sawada, Y.; Saito, B.; Sakai, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4935. (f) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036. (g) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302. (h) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694.

(18) For a DFT calculation study of Cu−phosphine complex-catalyzed conjugate boration, see: Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443.

(19) (a) Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658. (b) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147.

ESI-MS experiments were then conducted to gain information about the intermediates in the catalytic cycle. A Cu^{+}/**L-e** = 1:1 complex (**4**) was observed as a sole species in a mixture of **L-e** ligand and $CuPF_6$•$4CH_3CN$. A new peak corresponding to **5** (Figure 1) then emerged [MW = 892 (m/z)] again as a sole peak under cation-mode observation when *t*-BuOLi and (Pin)BB(Pin) were added to **4**.[9,20]

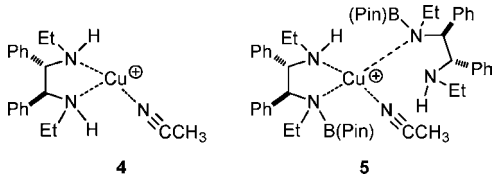
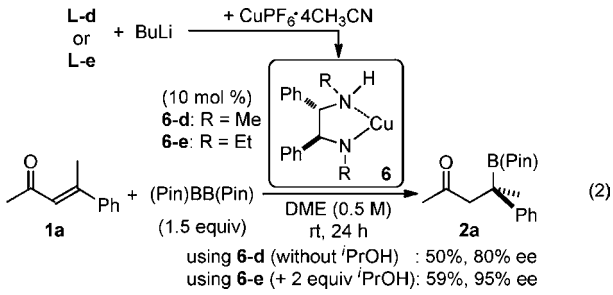


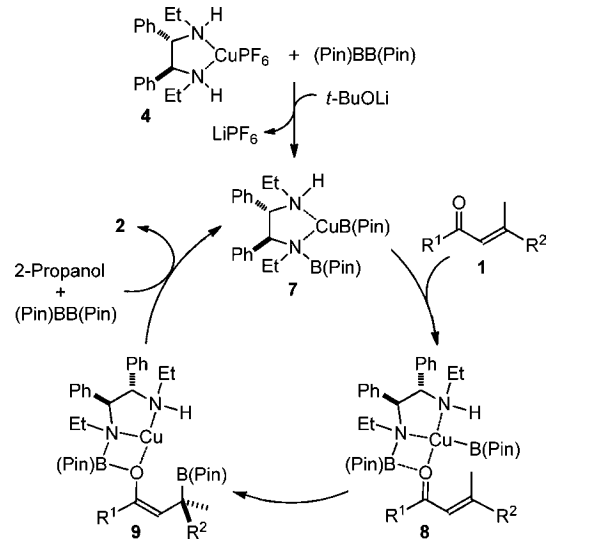
Figure 1. Chiral secondary diamine−copper(I) complex **4** and borylated diamine ligand−copper(I) complex **5**.

This observation suggested that a copper amide species **6-e** might be generated from **4** and LiO-*t*-Bu, and the copper−nitrogen bond cleaves (Pin)BB(Pin) through metathesis, generating copper boronate complex **7** containing an *N*-borylated ligand. To provide support for this hypothesis, we prepared copper amide complexes **6** from $CuPF_6$•$4CH_3CN$ and lithium amides derived from **L-d** and **L-e**, respectively, and used **6** as enantioselective catalysts (eq 2). Product **2a** was produced with comparable enantioselectivities to that obtained under $CuPF_6$•$4CH_3CN$−LiO-*t*-Bu−**L-d** and −**L-e** systems (cf. Table 1, entry 6 and 9).[21]



Based on these results, we proposed a working hypothesis for the catalytic cycle as shown in Scheme 1. After generation of borylcopper species **7** either through metathesis between copper amide and (Pin)BB(Pin) or CuO-*t*-Bu and (Pin)BB(Pin) followed by *N*-boration, the carbonyl oxygen atom of the substrate might coordinate to the Lewis acidic boron atom of the aminopinacolyl boronate part of the catalyst, generating a pretransition state complex **8**.[22] Enantioselective conjugate boration from **8** would produce boron enolate complex **9** (or a copper enolate complex, alternatively), which would be protonated by 2-propanol,[23] and reactive species **7** would be regenerated by reaction with (Pin)BB(Pin). This proposed mechanism is in accordance with the low enantioselectivity observed when using diamine ligands without an ability to form copper amides (**L-a,b,g**).

Scheme 1. Proposed Catalytic Cycle



In conclusion, we have developed a catalytic enantioselective conjugate boration of linear β,β-disubstituted enones by identifying the copper(I)−*secondary*-diamine **L-e** catalytic system. Products were converted to ketone−ketone cross aldol-type compounds in excellent yields without any racemization. Considering the facile structural tunability of amine ligands, this study might provide a foundation for developing further chiral amine−transition-metal-catalyzed enantioselective reactions. More detailed mechanistic studies are currently ongoing.

Acknowledgment. Financial support was provided by Grant-in-Aid for Scientific Research (S) from JSPS. We thank Mr. S. Ito at The University of Tokyo for partial contribution to this work.

Supporting Information Available: Experimental procedure, characterization data, MS analysis of catalytic intermediates, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Complex **5** would be formed via dissociation of the *N*-borylated **L-e** from a copper atom of complex **7**, *re*-association to another **7**, and ionization in the ESI-MS apparatus by eliminating $(Pin)B^{-}$ from the copper atom.

(21) The result of the reaction using **6-d** in the absence of ^{i}PrOH indicates that a copper amide can, at least, activate (Pin)BB(Pin) through *N*-boration. However, we cannot exclude the involvment of a pathway starting from CuO^{t}Bu and without *N*-boration under the optimized conditions (Table 2), because the product yield was not comparable when using **6** instead of $CuPF_6$ + ^{t}BuOK. More direct observation of proposed **8** awaits further studies.

(22) Molecular modeling study indicated that the Cu−B σ bond can overlap with the enone π^* orbital in **8**.

(23) In the absence of 2-propanol, the boron enolate liberated from **9** should be the product in the reaction mixture (Table 1, entry 6).