DOI: 10.1002/adsc.200900040

Copper-Catalyzed Conjugate Addition of Diboron Reagents to α,β-Unsaturated Amides: Highly Reactive Copper-1,2-Bis(diphenylphosphino)benzene Catalyst System

Heesung Chea,[a] Hak-Suk Sim,[a] and Jaesook Yun[a,*]

[a] Department of Chemistry and Institute of Basic Science, Sungkyunkwan University, Suwon 440-746, Korea
Fax: (+82)-31-290-7075; e-mail: jaesook@skku.edu

Received: January 19, 2009; Revised: March 24, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900040.

Abstract: An efficient copper catalyst system for the β-boration of α,β-unsaturated amides has been developed. Copper-bisphosphine complexes with small bite angles generate efficient catalyst systems for the successful conjugate addition of bis(pinacolato)diboron to a variety α,β-unsaturated amides under mild conditions. This method was utilized in the formal synthesis of (*S*)-fluoxetine.

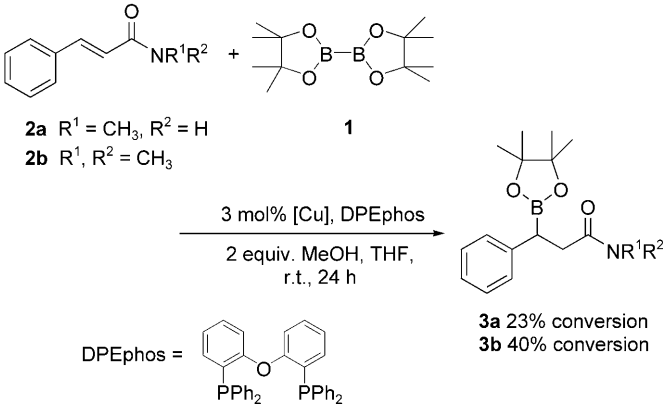
Keywords: amides; boron; conjugate addition; copper; ligand effects; phosphine ligands

Construction of chemical bonds *via* conjugate addition of organometallic nucleophiles to electron-deficient olefins is one of the most fundamental methods in organic synthesis. In recent years, transition metal-catalyzed addition of diboron reagents to α,β-unsaturated carbonyl compounds[1] has become a subject of interest for the synthesis of organoboron derivatives and we recently reported an efficient copper catalyst system where a copper-boryl complex could conjugatively add to α,β-unsaturated esters and efficiently generate β-borylated products.[2]

Although a number of copper-catalyzed conjugate additions of organometallic reagents to α,β-unsaturated carbonyl compounds have been reported,[3] catalytic systems effective for simple α,β-unsaturated amides with no suitable protecting/activating groups on the nitrogen are rare due to their inherent low reactivity.[4] Herein, we report an efficient conjugate addition reaction of diboron reagents to α,β-unsaturated amides catalyzed by copper(I) complexes coordinated to chelating bisphosphines with narrow bite angles. To the best of our knowledge, this transformation constitutes the first example of the copper-catalyzed conjugate addition of organometallic reagent to simple α,β-unsaturated amides.

In our previous study on the copper-catalyzed β-boration of α,β-unsaturated esters, the active catalyst was generated *in situ* from CuCl, NaO-*t*-Bu and DPEphos ligand in the presence of bis(pinacolato)diboron (**1**) and a dramatic rate acceleration was observed by the use of methanol.[2a] This method expanded the substrate scope from enones to challenging α,β-unsaturated esters and nitriles. However, the β-boration of α,β-unsaturated amides, which are less reactive Michael acceptors, turned out to be more challenging;[5] the same catalytic system drove the reaction with α,β-unsaturated amides **2a** and **2b** only to partial conversion (Scheme 1).

In the course of studying the copper-catalyzed boration of α,β-alkynoates,[6] we noticed slight ligand effects on the reactivity from the ratio of mono- and diborylated products while the overall reactivity was greatly affected by the methanol additive. The Xantphos ligand[7] with a large bite angle and rigid backbone was more selective for the formation of mono-



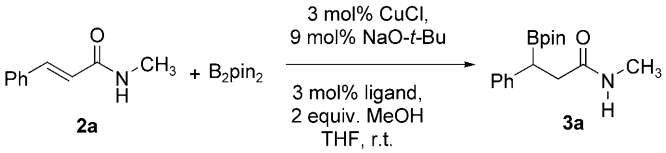
Scheme 1. Boration of α,β-unsaturated amides using DPEphos as a ligand.

addition product than DPEphos. The dppf ligand yielded more of the diborylated product than DPEphos and Xantphos. Although copper complexes coordinated with phosphines with large bite angles were known as effective catalysts for similar addition reactions,[8] we presumed that they might not be the best ligands for the β-boration and decided to investigate the ligand effects on the β-boration of α,β-unsaturated amides.

For ligand screening, we focused on the bidentate phosphine ligands[9] that had been reported to chelate a single copper center, affording mononuclear Cu(I) complexes[10] or halogen-bridged binuclear complexes, $[LCu(\mu\text{-}X)_2CuL]$.[11] Ligands, such as bis(diphenylphosphino)methane (dppm) and bis(diphenylphosphino)ethane (dppe) possessing short and flexible chains were excluded[12] since these ligands were reported to bridge two copper atoms to form multinuclear complexes.[13] 1,2-Bis(diphenylphosphino)benzene (dppbz) having a narrow P–Cu–P angle[14] was chosen as a substitute for the flexible dppe.

The β-boration of the methyl amide **2a** with bis(pinacolato)diboron was conducted with the selected ligands, and the influence of the ligands on catalyst reactivity was investigated (Table 1). With dppf as a ligand, the reaction proceeded with greater conversion than with DPEphos (entry 1). It was found that dppp and dppbz drove the reaction to completion in 2 h and formed the desired compound in high yield (entries 2 and 3). The (di-*tert*-butyl)phosphine analogue of dppf, which is more-electron rich than dppf, brought the reaction to completion as well (entry 4). These new ligands formed more reactive catalytic systems with copper than the phosphines used in our original procedures.

Table 1. Ligand screening for the copper-catalyzed β-boration of **2a**.



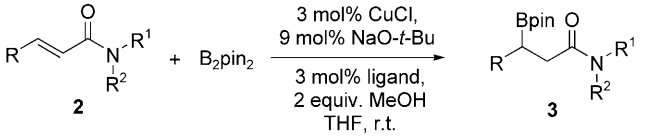
2a **3a**

Entry	Ligand (L)[a]	*T* [h]	Conversion [%][b]	Yield [%][c]
1	dppf	2	78	–[d]
2	dppp	2	100	88
3	dppbz	2	100	91
4	dtpf	2	100	91

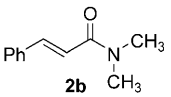
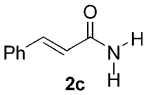
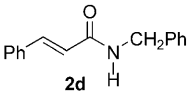
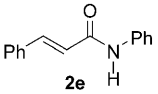
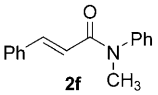
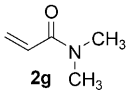
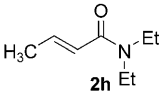
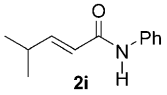
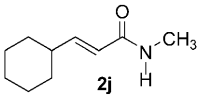
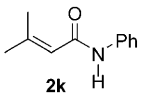
[a] Abbreviaitions: dppf = 1,1′-bis(diphenylphosphino)ferrocene, dppp = 1,3-bis(diphenylphosphino)propane, dtpf = 1,1′-bis(di-*tert*-butylphosphino)ferrocene.
[b] Determined by GC analysis.
[c] Isolated yield.
[d] Not cleanly isolable from **2a**.

The catalytic β-boration of various α,β-unsaturated amides was examined by using dppbz or dtpf as the ligand and MeOH as an additive (Table 2). First, a variety of amide derivatives (**2b**–**2e**) of cinnamic acid were investigated. All the structurally different primary (**2c**), secondary (**2d**, **2e**) and tertiary amides (**2b**,

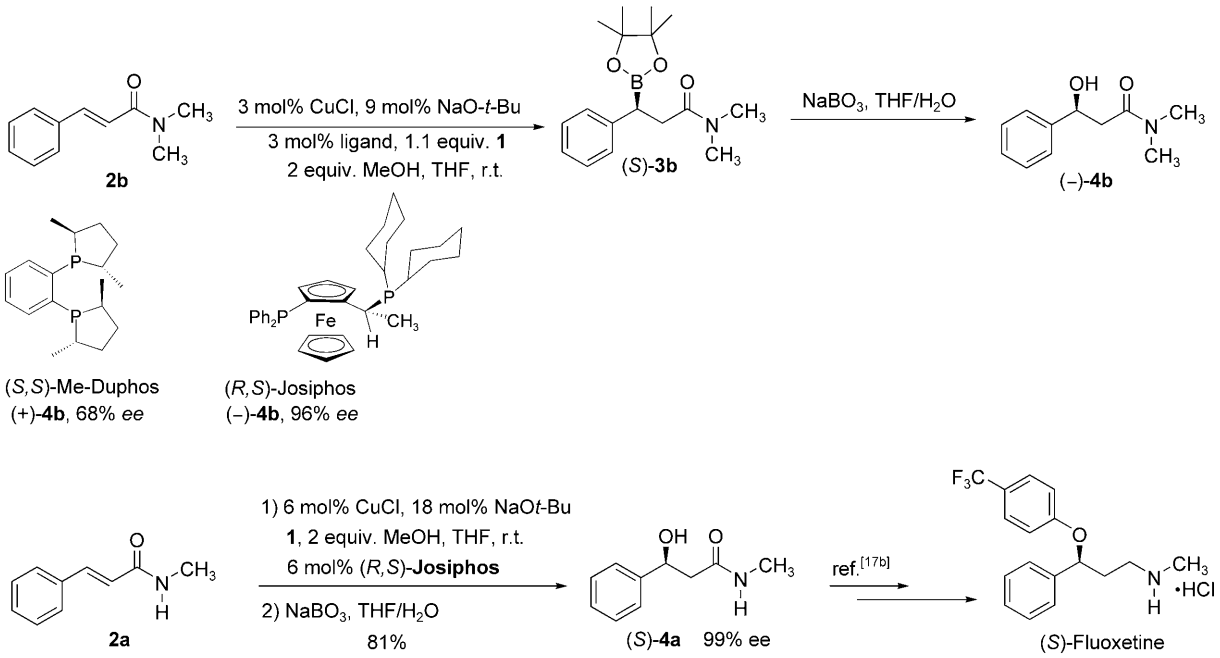
Table 2. Copper-catalyzed conjugate addition of diboron to various α,β-unsaturated amides.



2 **3**

Entry	Substrate (**2**)	Ligand (L)	*T* [h]	Yield [%][a]
1	 **2b**	dppbz	2	96
2	**2b**	dtpf	3	92
3	 **2c**	dppbz	12	89
4	 **2d**	dppbz	2	96
5[b]	**2d**	dtpf	3	92
6	 **2e**	dppbz	1	95
7	 **2f**	dppbz	5	96
8	**2f**	dtpf	8	92
9	 **2g**	dppbz	1	87
10	 **2h**	dppbz	2	90
11	**2h**	dtpf	6	88
12	 **2i**	dppbz	3	95
13	 **2j**	dppbz	1	95
14	 **2k**	dppbz	15	74[c]

[a] Isolated yield.
[b] 6 mol% of NaO-*t*-Bu was used.
[c] Conversion determined by GC analysis with an internal standard.



Scheme 2. Asymmetric synthesis of β-hydroxy amides.

2f) tested gave the addition products in high yields within reasonable reaction times. In general, the dppbz ligand displayed a better reactivity than dtpf. *N*-Alkyl- and *N*-phenyl-substituted amides were all reactive and β-alkyl-substituted α,β-unsaturated amides also provided the corresponding products within hours. However, neither ligand was effective for complete reaction of sterically demanding β,β-disubstituted α,β-unsaturated amides; only incomplete conversion of *N*-phenyl-3-methylbutenamide (**2k**) was obtained with dppbz.[15]

Oshima and et al. recently reported a nickel-catalyzed system that showed excellent reactivity for the β-boration of α,β-unsaturated esters and amides, even for sterically demanding substrates.[1g] However, the types of substituent allowed at the β-position and the nitrogen[16] seemed to be limited to alkyl, as aromatic groups such as phenyl and furanyl gave very low yields. Therefore, this new copper-catalyst system complements the nickel system.

Next, the enantioselective β-boration of amide **2b** was briefly conducted by using chiral bisphosphine ligands Duphos and Josiphos, whose backbones or chain lengths are similar to those of dppbz or dppp, respectively. Both ligands led the reaction to completion in hours and yielded the enantioenriched boron-addition product **4b** (Scheme 2). In particular, the β-hydroxy product (*S*)-**4a** was obtained from **2a** in 99% *ee* by the asymmetric boration reaction with the (*R*,*S*)-Josiphos ligand and consecutive oxidation of **3a**. (*S*)-**4a** is an appropriate intermediate for the construction of optically active fluoxetine,[17] which is an antidepressant drug and currently marketed as a racemate. This application demonstrates the usefulness of this current method.

In conclusion, we have developed a highly efficient copper catalyst system that works for the β-boration of a variety of α,β-unsaturated amides. Copper-bisphosphine complexes with small bite angles generated more efficient catalyst systems and led to successful conjugate addition of bis(pinacolato)diboron to α,β-unsaturated amides. The usefulness of this method was demonstrated in the formal synthesis of (*S*)-fluoxetine. Further studies are in progress.

Experimental Section

General Procedure for the β-Boration of α,β-Unsaturated Amides using the Dppbz Ligand[18]

In a resealable Schlenk tube were placed CuCl (0.015 mmol, 1.5 mg), NaO-*t*-Bu (0.045 mmol, 4.5 mg) and dppbz ligand (0.015 mmol, 6.7 mg). THF (0.40 mL) was added under nitrogen. The reaction mixture was stirred for 30 min at room temperature, after which time bis(pinacolato)diboron (0.55 mmol, 141 mg) in THF (0.30 mL) was added. The reaction mixture was stirred for 10 min and then the α,β-unsaturated amide (0.50 mmol) in THF (0.30 mL) was added, followed by MeOH (1.0 mmol, 40 μL). The reaction tube was washed with THF (0.30 mL), sealed, and stirred until no starting material was detected by TLC. The reaction mixture was filtered through a pad of Celite and concentrated. The product was purified by silica gel chromatography.

Acknowledgements

This work was supported by a Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MEST) (No. R01-2008-000-20332-0).

References

[1] Platinum: a) Y. G. Lawson, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice, *Chem. Commun.* **1997**, 2051–2052; b) H. A. Ali, I. Goldberg, M. Srebnik, *Organometallics* **2001**, *20*, 3962–3965; c) N. J. Bell, A. J. Cox, N. R. Cameron, J. S. O. Evans, T. B. Marder, M. A. Duin, C. J. Elsevier, X. Baucherel, A. A. D. Tulloch, R. P. Tooze, *Chem. Commun.* **2004**, 1854–1855; rhodium: d) G. W. Kabalka, B. C. Das, S. Das, *Tetrahedron Lett.* **2002**, *43*, 2323–2325; copper: e) H. Ito, H. Yamanaka, J. Tateiwa, A. Hosomi, *Tetrahedron Lett.* **2000**, *41*, 6821–6825; f) K. Takahashi, T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2001**, *625*, 47–53; nickel: g) K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 5031–5033.

[2] a) S. Mun, J.-E. Lee, J. Yun, *Org. Lett.* **2006**, *8*, 4887–4889; b) J.-E. Lee, J. Yun, *Angew. Chem.* **2008**, *120*, 151–153; *Angew. Chem. Int. Ed.* **2008**, *47*, 145–147.

[3] For reviews, see: a) N. Krause, A. Hofmann-Röder, *Synthesis* **2001**, 171–196; b) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061; c) B. L. Feringa, R. Naasz, R. Imbos, L. A. Arnold, in: *Modern Organocopper Chemistry*, (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp 224–258; d) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279–1300.

[4] For examples of copper-catalyzed conjugate additions to protected amides, such as imides, carbamates, oxazolidinones, see: a) M. Pineschi, F. Del Moro, F. Gini, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2004**, 1244–1245; b) M. Pineschi, F. Del Moro, V. Di Bussolo, F. Macchia, *Adv. Synth. Catal.* **2006**, *348*, 301–304.

[5] One preparation example of organotrifluoroborate salt from dimethyl acrylamide *via* two steps by using our copper-catalyzed method as the first step was reported, but the efficiency of the step was not reported; G. A. Molander, D. E. Petrillo, *Org. Lett.* **2008**, *10*, 1795–1798.

[6] J.-E. Lee, J. Kwon, J. Yun, *Chem. Commun.* **2008**, 733–734.

[7] Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene.

[8] a) D. Kim, B.-M. Park, J. Yun, *Chem. Commun.* **2005**, 1755–1757; b) H. Zheng, Q. Zhang, J. Chen, M. Liu, S. Cheng, J. Ding, H. Wu, W. Su, *J. Org. Chem.* **2009**, *74*, 943–945; c) H. Ito, C. Kawakami, M. Sawamura, *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035.

[9] In our study on the asymmetric β-boration of acyclic enones, we found that a rigid and strong coordination between ligand and catalyst would be needed for high enantioselectivity. Therefore, we excluded P,N- and N,N-type ligands and monophosphine ligands for future application of this current study on the asymmetric synthesis of β-borylamides: H.-S. Sim, X. Feng, J. Yun, *Chem. Eur. J.* **2009**, *15*, 1939–1943.

[10] For a series of copper(I) halide complexes [(P–P)CuX–S] with a chelating phosphine (P–P) and heterocyclic thiones, see: a) P. Aslanidis, P. J. Cox, A. Kaltzoglou, A. C. Tsipis, *Eur. J. Inorg. Chem.* **2006**, 334–344; b) P. Aslanidis, P. J. Cox, S. Divanidis, A. C. Tsipis, *Inorg. Chem.* **2002**, *41*, 6875–6886; c) P. J. Cox, A. Kaltzoglou, P. Aslanidis, *Inorg. Chim. Acta* **2006**, *359*, 3183–3190. For these series, the P–Cu–P angles for dppbz (86.7°), dppp (99.6°) and Xantphos (113.2°) were taken from the X-ray structures.

[11] a) J. Díez, M. P . Gamasa, J. Gimeno, M. Lanfranchi, A. Tiripicchio, *J. Organomet. Chem.* **2001**, *637–639*, 677–682; b) Effendy, C. Di Nicola, M. Fianchini, C. Pettinari, B. W. Skelton, N. Somers, A. H. White, *Inorg. Chim. Acta* **2005**, *358*, 763–795; c) A. Tsuboyama, K. Kuge, M. Furugori, S. Okada, M. Hoshino, K. Ueno, *Inorg. Chem.* **2007**, *46*, 1992–2001.

[12] Dppe gave complete conversion in the reaction of **2a** as well.

[13] a) P. J. Cox, P. Aslanidis, P. Karagiannidis, *Polyhedron* **2000**, *19*, 1615–1620; b) S. Daly, M. F. Haddow, A. G. Orpen, G. T. A. Rolls, D. F. Wass, R. L. Wingad, *Organometallics* **2008**, *27*, 3196–3202.

[14] The P–Cu–P angle (89.0°) was taken from the X-ray structure of $[Cu(\mu\text{-}Cl)dppbz]_2$ reported in ref.[11c] This value can be compared with the angle of dppp (103.6°) and that of dppf (111.3°).

[15] The reaction did not proceed further even after a longer reaction time. Incomplete consumption of the starting material makes it difficult to cleanly separate the borylated product from the starting material. A ~72% yield was obtained by NMR analysis of a coeluted mixture of **2k** and **3k**.

[16] Only reactions with tertiary alkyl amides were reported. The boration reactions of β-phenyl-substituted amides were not reported either.

[17] a) Y. Li, Z. Li, F. Li, Q. Wang, F. Tao, *Org. Biomol. Chem.* **2005**, *3*, 2513–2518; b) H. Kakei, T. Nemoto, T. Ohshima, M. Shibasaki, *Angew. Chem.* **2004**, *116*, 321–324; *Angew. Chem. Int. Ed.* **2004**, *43*, 317–320; c) E. J. Corey, G. A. Reichard, *Tetrahedron Lett.* **1989**, *30*, 5207–5210; d) A. Kumar, D. H. Ner, S. Y. Dike, *Tetrahedron Lett.* **1991**, *32*, 1901–1904.

[18] An alternative activation procedure in which CuCl, NaO-*t*-Bu, ligand and diboron are mixed and stirred altogether for 15 min in THF is equally effective.

