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Nickel-Catalyzed β-Boration of α,β-Unsaturated Esters and Amides with Bis(pinacolato)diboron

Koji Hirano, Hideki Yorimitsu,* and Koichiro Oshima*

*Department of Material Chemistry, Graduate School of Engineering, Kyoto University,
Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan*

oshima@orgrxn.mbox.media.kyoto-u.ac.jp; yori@orgrxn.mbox.media.kyoto-u.ac.jp

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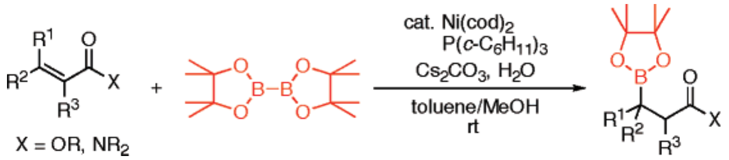
ABSTRACT



A nickel catalyst system for β-boration of α,β-unsaturated esters and amides with bis(pinacolato)diboron has been developed. The catalyst system enables the boration of di-, tri-, and tetrasubstituted substrates in good yields.

Organoboron compounds are ubiquitous in organic synthesis[1] and can also display biological activity.[2] Transition-metal-catalyzed boration of unsaturated C−C bonds with diboron reagents is one of the most attractive methods for synthesis of organoboron derivatives. Since the pioneering work reported by Miyaura and Suzuki,[3] a variety of catalysts for boration of various unsaturated molecules involving asymmetric variants have been explored.[4] In the course of the development of this chemistry, β-boration of α,β-unsaturated carbonyl compounds with diborons ranks as the most important procedure for the preparation of organoborons having carbonyl functionalities at the β position. So far, platinum,[5] rhodium,[6] and copper[7] complexes are known to catalyze the β-boration of α,β-unsaturated aldehydes and ketones effectively. Although some catalyst systems mentioned above achieved the boration of disubstituted α,β-unsaturated esters,[5a,b,6,7b,c] the type of transformation with α,β-unsaturated esters and amides has still been challenging. Moreover, the reaction of sterically demanding multisubstituted esters and amides is not trivial. During our studies on the catalytic activity of nickel complexes, we have found nickel-catalyzed additions of trialkylboranes to carbonyl compounds.[8] Herein, we wish to report β-boration of α,β-

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[1] (a) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagent*; Academic Press; London, 1988. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (c) Davison, M.; Hughes, A. K.; Marder, T. B.; Wade, K. *Contemporary Boron Chemistry*; RSC: Cambridge, U.K., 2000.

[2] Irving, A. M.; Vogels, C. M.; Nikolcheva, L. G.; Edwards, J. P.; He, X.-F.; Hamilton, M. G.; Baerlocher, M. O.; Decken, A.; Westcott, S. A. *New J. Chem.* **2003**, *27*, 1419−1424.

[3] Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018−11019.

[4] Palladium: (a) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328−16329. Platinum: (b) Iverson, C. N.; Smith, M. R., III. *Organometallics* **1997**, *16*, 2757−2759. (c) Marder, T. B.; Norman, N. C.; Rice, C. R. *Tetrahedron Lett.* **1998**, *39*, 155−158. Rhodium: (d) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B. *Chem. Commun.* **1998**, 1983−1984. (e) Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77−85. (f) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702−8703. Gold: (g) Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1336−1338. Silver: (h) Ramírez, J.; Corberán, R; Sanaú, M.; Peris, E.; Fernandez, E. *Chem. Commun.* **2005**, 3056−3058.

[5] (a) Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun.* **1997**, 2051−2052. (b) Ali, H. A.; Goldberg, I.; Srebnik, M. *Organometallics* **2001**, *20*, 3962−3965. (c) Bell, N. J.; Cox, A. J.; Cameron, N. R.; Evans, J. S. O.; Marder, T. B.; Duin, M. A.; Elsevier, C. J.; Baucherel, X.; Tulloch, A. A. D.; Tooze, R. P. *Chem. Commun.* **2004**, 1854−1855.

[6] Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2323−2325.

[7] (a) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821−2325. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47−53. (c) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887−4889.

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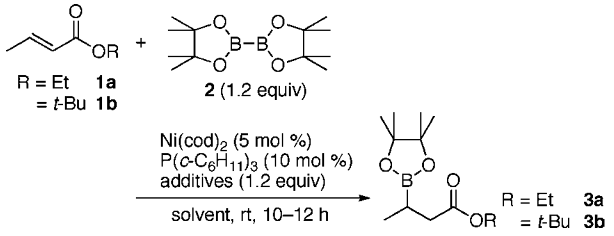
unsaturated esters and amides with bis(pinacolato)diboron under nickel catalysis.[9] The catalyst system enables the β-boration of di-, tri-, and tetrasubstituted substrates.

Our initial attempt on β-boration of crotonate ester **1a** with 1.2 equiv of bis(pinacolato)diboron (**2**) using 5 mol % of $Ni(cod)_2/2P(c\text{-}C_6H_{11})_3$ as a catalyst in toluene at room temperature resulted in no conversion, and the starting materials were recovered intact (Table 1, entry 1). On the basis of our previous observation,[8] the effect of base as an activator of diboron **2** was examined. To our delight, an addition of cesium hydroxide monohydrate led to the formation of the desired product **3a** although the results were not reproducible, and the yields varied from 2−40% (entry 2). After some optimizations, a toluene/MeOH cosolvent system was found to be essential for good reproducibility (entry 3). This is probably because MeOH could be a good proton source to boryl enolate formed in the catalytic cycle (vide infra). The combination of cesium carbonate and water instead of cesium hydroxide monohydrate improved the yield to 64% (entry 4). The boration of bulkier *tert*-butyl (*E*)-crotonate (**1b**) provided a better result (entry 5). Finally, with 1.5 equiv of diboron **2**, the borylated product **3b** was obtained in 77% yield (entry 6).[10]

Table 1. Optimization Studies[a]

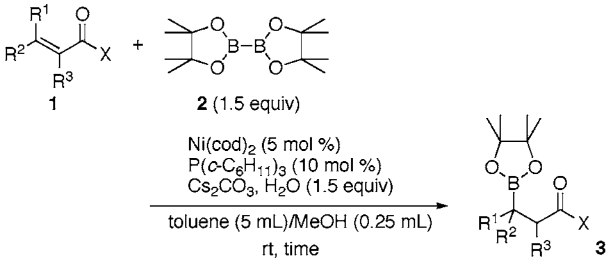


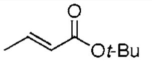
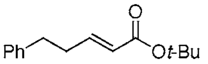
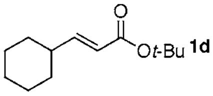
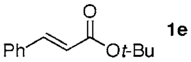
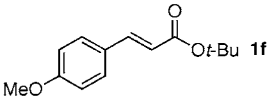
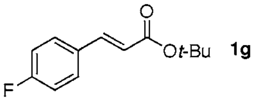
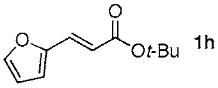
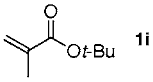
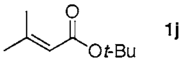
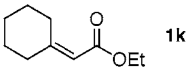
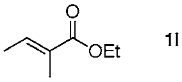
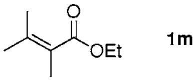
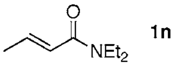
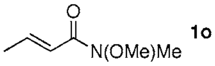
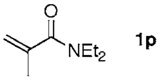
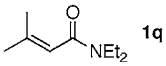
entry	1	additives	solvent	3, yield (%)[b]
1	**1a**	none	toluene	**3a**, 0
2	**1a**	$CsOH \bullet OH_2$	toluene	**3a**, 2−40[c]
3	**1a**	$CsOH \bullet OH_2$	toluene /MeOH	**3a**, 52
4	**1a**	$Cs_2CO_3+H_2O$	toluene /MeOH	**3a**, 64
5	**1b**	$Cs_2CO_3+H_2O$	toluene /MeOH	**3b**, 70
6[d]	**1b**	$Cs_2CO_3+H_2O$	toluene /MeOH	**3b**, 77

[a] A mixture of **1** (0.5 mmol), **2** (1.2 equiv), $Ni(cod)_2$ (5 mol %), $P(c\text{-}C_6H_{11})_3$ (10 mol %), and additives (1.2 equiv) was stirred in toluene (5 mL) or toluene (5 mL)/MeOH (0.25 mL) at 10−12 h at room temperature. [b] Isolated yield. [c] About half of unreacted **1a** was detected in the crude mixtures. [d] With 1.5 equiv of **2**, Cs_2CO_3, and H_2O.

Subsequently, the β-boration was conducted with a range of substrates under the optimized conditions (Table 2). The reactions of phenylethyl- and cyclohexyl-substituted acrylates

Table 2. Nickel-Catalyzed β-Boration of α,β-Unsaturated Esters and Amides with Bis(pinacolato)diboron[a]



entry	1	time (h)	3, yield (%)[b]
1	 **1b**	11	**3b**, 77
2	 **1c**	12	**3c**, 56
3	 **1d**	11	**3d**, 63
4	 **1e**	14	**3e**, 14
5	 **1f**	10	**3f**, 72
6	 **1g**	10	**3g**, (50)[c]
7	 **1h**	12	**3h**, (47)[c]
8	 **1i**	12	**3i**, 71
9[d]	 **1j**	10	**3j**, 60
10[d]	 **1k**	12	**3k**, 76
11	 **1l**	7.5	**3l**, 82[e]
12[d]	 **1m**	12	**3m**, 83
13	 **1n**	3	**3n**, 75
14	 **1o**	3	**3o**, 61
15	 **1p**	4	**3p**, 70
16	 **1q**	7	**3q**, 80

[a] A mixture of **1** (0.5 mmol), **2** (1.5 equiv), Cs_2CO_3 (1.5 equiv), H_2O (1.5 equiv), $Ni(cod)_2$ (5 mol %), and $P(c\text{-}C_6H_{11})_3$ (10 mol %) was stirred in toluene (5 mL)/MeOH (0.25 mL) at room temperature. [b] Isolated yield. [c] The borylated product was unstable so that the corresponding β-hydroxy ester was isolated after oxidation (see Supporting Information for the procedure). [d] With 2.0 equiv of **2**, Cs_2CO_3, and H_2O. [e] A 1:1 mixture of diastereomers. The stereochemistry of each isomer was not determined.

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[8] (a) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2005**, *7*, 4689−4691. (b) Hirano, K.; Yorimitsu, H.; Oshima, K. *Adv. Synth. Catal.* **2006**, *348*, 1543−1546. (c) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1541−1544.

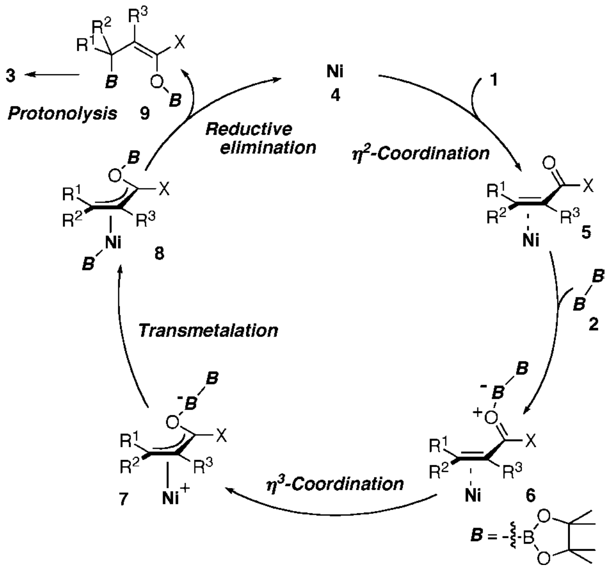
[9] Nickel-catalyzed reactions with diboron reagents are quite rare. See: (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435−3462. (b) Yu, C.-M.; Youn, J.; Yoon, S.-K.; Hong, Y.-T. *Org. Lett.* **2005**, *7*, 4507−4510.

[10] The use of $P(t\text{-}Bu)_3$, $P(n\text{-}Bu)_3$, and PPh_3 instead of $P(c\text{-}C_6H_{11})_3$ gave the product in lower yields (ca. <20%).

1c and **1d** gave **3c** and **3d** in 56% and 63% yields, respectively (entries 2 and 3). However, cinnamate ester **1e** was converted to the desired product in low yield and a large amount of **1e** remained untouched (entry 4). Interestingly, the substitutions of methoxy and fluoro groups on the benzene ring improved the yield (entries 5 and 6).[11] Heterocyclic compound **1h** took part in the reaction albeit the yield was moderate (entry 7). Fortunately, α-substituted substrate, methacrylate ester **1i**, also underwent the boration smoothly (entry 8). It should be noted that the borations of β,β-disubstituted esters **1j** and **1k** proceeded to furnish **3j** and **3k** without any difficulties (entries 9 and 10). Moreover, tri- and tetrasubstituted substrates **1l** and **1m** participated in the reaction despite their steric hindrance (entries 11 and 12). The β-boration of α,β-unsaturated amides as well as esters was possible, which is unprecedented to the best of our knowledge. Various substitution patterns were tolerant toward the conjugate boration as observed in the case of the boration of esters (entries 13−16). Notably, amides reacted with diboron **2** much faster than the corresponding esters. For instance, the boration of crotonamide **1n** was completed within 3 h to afford **3n** in 75% yield.

We are tempted to assume the mechanism of the reaction as follows (Scheme 1). A nickel(0) species **4** initially reacts with **1** to generate η^2-coordinated complex **5**. The coordination of the carbonyl moiety of **5** to diboron **2** gives the intermediate **6**.[12] The Lewis acidity of the boron promotes the formation of η^3-coordinated nickel complex **7** followed by transmetalation of the boryl group to furnish the boryl-nickel species **8**.[13,14] Finally, reductive elimination from **8** affords **9** along with the starting nickel complex to complete the catalytic cycle. Protonolysis of boryl enolate **9** with MeOH would provide **3**. The exact roles of cesium base are not clear at this stage. It can enhance the transmetalation step through its coordination to the boron center of **7**.[15] Moreover, MeOH also can accelerate the transmetalation.

Scheme 1



In summary, we have developed an effective nickel catalyst system for the β-boration of α,β-unsaturated esters and amides with bis(pinacolato)diboron. The catalytic reaction provides a facile route to primary, secondary, and tertiary alkylboronates bearing esters and amides functionalities at the β position.

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

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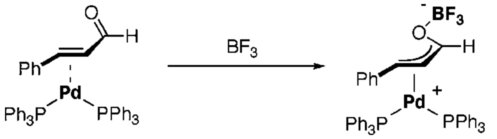
[11] A similar trend was observed in our previous work (see ref 8c and ref 12).

[12] The fact that the substrates **1f** and **1g** bearing π-donor substituents on the benzene ring were more reactive than **1e** is consistent with the existence and importance of the coordination (Table 2, entry 4 vs. entries 5 and 6). Namely, the more electron-rich carbonyl oxygen of nickel-coordinated **1f** and **1g** would have stronger interaction with bis(pinacolato)-diboron. The differences of reaction rates between amides and esters also support the assumption since the carbonyl oxygen of amides would be more electron-rich than that of esters (Table 2, entries 13−16).

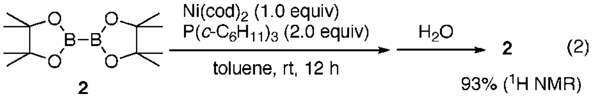
[13] Ogoshi and Kurosawa reported that the η^2-coordinated palladium complexes with cinnamaldehyde were converted to η^3-coordinated ones in the presence of BF_3 with the aid of the Lewis acidity of boron (see eq 1). Furthermore, they also described that palladium-catalyzed 1,4-addition of disilanes to α,β-unsaturated aldehydes and ketones initiated by Me_3SiOTf would proceed through a similar η^3-coordinated intermediate but not oxidative addition of the Si−Si bond of disilanes to the palladium complex. (a) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944−1950. (b) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598−11599.



(1)

[14] Chlorotrialkylsilane is known to promote transformation of η^2-coordinated nickel complexes with α,β-unsaturated aldehydes and ketones to the corresponding η^3-complexes. (a) Grisso, B. A.; Johson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160−5165. (b) Ikeda, S.-i.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975−5976. In nickel-catalyzed 1,4-addition of allylboronic acid pinacol ester to styryl ketones, the η^3-coordinated nickel complexes with the ketones formed by the action of the boronate was proposed as the key intermediate. (c) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214−2215.

[15] Although the mechanism involving the oxidative addition of B−B bond of bis(pinacolato)diboron (**2**) to the nickel complex could not be completely excluded, treatment of diboron **2** with a stoichiometric amount of $Ni(cod)_2/2P(c\text{-}C_6H_{11})_3$ followed by quench with H_2O resulted in 93% recovery of **2** (see eq 2). Nevertheless, in the catalytic reaction, we added cesium carbonate and methanol to the reaction mixture. These additives could change the reactivity of **2** or nickel complexes.



(2)