

Ligandless Copper-Catalyzed β -Boration of α,β -Unsaturated Compounds in Aqueous Solution[†]

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Catalytic boration reactions of unsaturated C-C bonds promoted by transition metal catalysts can provide a variety of organoboron compounds of defined regio- and stereochemistry.¹ In recent years, the transition-metal catalyzed addition of diboron reagents to α,β -unsaturated carbonyl compounds² has received much attention and has emerged as an important method for the preparation of functionalized organoboron compounds.

Previously, we reported a copper catalyzed protocol for the β -boration of α,β -unsaturated carbonyl compounds in which methanol was employed as an additive.^{3a} The use of methanol with copper-bisphosphine catalysts dramatically enhanced the reaction rates and expanded the substrate scope from enones to the more challenging α,β -unsaturated esters, nitriles, and amides.³ Recently, in the absence of base and phosphine ligand, Santos and coworkers reported a copper-catalyzed β -boration of α,β -unsaturated carbonyl compounds using a mixed diboron as the borylating reagent.⁴ This protocol, however, showed limited substrate scope as reactions went to completion only with simple substrates having no substituents at the α and β positions. Efficient catalysis without specific coordinating ligands on the metal catalysts would be desirable. Herein, we report a ligandless protocol for the copper-catalyzed β -boration of α,β -unsaturated carbonyl compounds in aqueous THF solution. The use of water as a co-solvent and a reaction promoter exerted a positive effect on catalytic efficiency and resulted in the efficient β -boration of α,β -unsaturated carbonyl compounds including substituted enones and esters. This new, operationally simple method is useful for the preparation of racemic organoboron compounds.

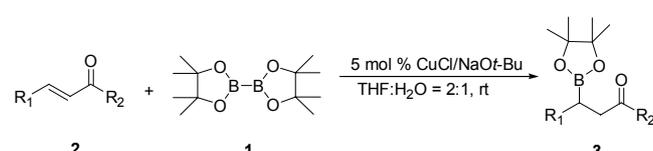
Our investigation of the boration reaction under ligand-free conditions began with β -monosubstituted enones using 5 mol % CuCl, 5 mol % NaOt-Bu and 1.1 equivalent of bis(pinacolato)-diboron (**1**). We previously proposed that proton sources such as methanol act as reaction promoters by decomposing C-bound copper enolate intermediates formed by addition of a boryl group to α,β -unsaturated carbonyl compounds.^{2d,3a,5} Therefore, we screened various substrates with protic additives, especially water, as the proton source in this study. The results are summarized in Table 1.

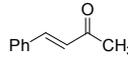
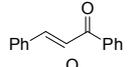
Methyl vinyl ketone (entry 1) and β -monosubstituted enones (entries 2-4) were good substrates, leading to the desired pro-

ducts in good yields at room temperature under the ligandless conditions. Next, sterically demanding β -substituted cyclic enones were tested (entries 5-8). While the reaction of 3-methylcyclohexenone reached completion under the given conditions, 3-methylcyclopentenone (entry 7) and the sterically more demanding 3-phenylcyclohexenone⁶ (entry 8) were converted to products in moderate yields. Using methanol instead of water as the additive for the reaction of 3-methylcyclohexenone resulted in a lower conversion (entries 5 and 6).

Using the same conditions as in Table 1, other classes of α,β -

Table 1. Ligandless copper-catalyzed β -boration of enones^a

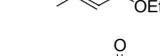
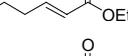


entry	substrate	time (h)	conversion (%) ^b	yield (%) ^c
1		1	100	84
2		3	100	91
3		3	100	90
4		1	100	90
5		3	100	85
6 ^d		3	90	77
7 ^e		3	87	76
8		6	42	39 ^f

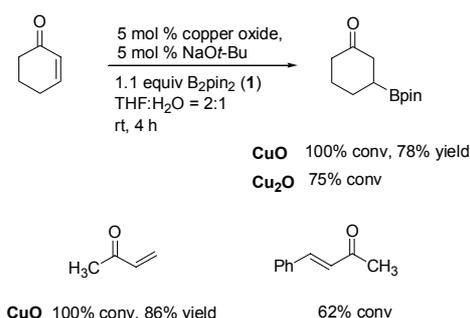
^aReaction conditions: enone (0.5 mmol), CuCl (5 mol %), NaOt-Bu (5 mol %), **1** (1.1 equiv), THF (1.0 mL) and H₂O (0.5 mL) were used unless otherwise noted. ^bConversion was determined by GC analysis. ^cIsolated yield. ^dMeOH (0.5 mL) was used instead of H₂O. ^e10 mol % of catalyst was used. ^fNMR yield.

[†]This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.

Table 2. β -Boration of α,β -unsaturated esters and amides^a

entry	substrate (4)	time (h)	conversion (%) ^b	yield (%) ^c
1	 4a	1	100	81
2	 4b	1	100	75
3	 4c	1	100	76
4	 4d	3	100	79
5	 4e	3	70	60
6	 4f	6	56	42

^aReaction conditions: enone (0.5 mmol), CuCl (5 mol %), NaOt-Bu (5 mol %), **1** (1.1 equiv), THF (1.0 mL) and H₂O (0.5 mL) were used unless otherwise noted. ^bConversion was determined by GC analysis. ^cIsolated yield.

**Scheme 1.** Use of copper oxides as catalysts

unsaturated carbonyl compounds such as esters and amides were examined (Table 2). Simple acrylate (**4a**) and acrylamide (**4b**) afforded the corresponding products in good yields. Methyl-substituted esters, for example, methacrylate (**4c**) and ethyl crotonate (**4d**) were completely converted to the desired products in a few hours. However, β -substituted unsaturated esters having a substituent larger than methyl slowed down the reaction, affording the desired products in moderate yields (entries 5 and 6).

According to our proposed mechanism,^{3a} the use of water instead of methanol as the proton source would generate copper(I) hydroxide as an intermediate after one catalytic turnover, which would react with diboron to generate an active copper-boryl catalyst. Since copper hydroxides are known to be unstable and eventually decompose to the corresponding oxides,⁷ we carried out boration reactions using copper oxides (CuO, Cu₂O) as the copper precursors, as shown in Scheme 1. While CuO showed better reactivity than did Cu₂O, their overall reactivities were lower than that of our current system starting with CuCl. Based on these results, decomposition of the copper precursor to the oxide during the reaction and the low solubility of the

resulting oxide could be contributing factors that limit the lifetime of the catalytic system.

In summary, we have shown that an efficient β -boration of α,β -unsaturated carbonyl compounds can be conducted under ligandless conditions in aqueous solution. Although our catalytic system in aqueous solution does not constitute a completely stable system, it does offer sufficient reactivity for the β -boration of unhindered unsaturated esters, amides and β -substituted enones, yielding the desired products in short reaction times. This system also obviates the need for anhydrous solvents and reagents and provides a cost-effective pathway for the preparation of boron compounds.

General procedure. In a one-neck round bottom flask were placed CuCl (0.025 mmol, 2.5 mg) and NaOt-Bu (0.025 mmol, 2.5 mg) in THF (0.4 mL). The reaction mixture was stirred for 10 min at room temperature under a nitrogen balloon, and then bis(pinacolato)diboron (0.55 mmol, 141 mg) in THF (0.3 mL) was added. The reaction mixture was stirred for 10 min, and the α,β -unsaturated carbonyl compound (0.50 mmol) in THF (0.3 mL) was added, followed by H₂O (27 mmol, 0.5 mL). The reaction was monitored by TLC and GC. Brine (5 mL) was added to the reaction mixture, and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The product was purified by silica gel chromatography (Table 1, entry 1). ¹H NMR (300 MHz, CDCl₃) δ 2.55 (t, J = 7.0 Hz, 2H), 2.09 (s, 3H), 1.19 (s, 12H), 0.85 (t, J = 7.0 Hz, 2H); ¹³C NMR (75.4 MHz, CDCl₃) δ 209.5, 83.2, 38.5, 29.4, 24.9, 24.8, 5.2 (C-B).

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- For this specific enone, Shibasaki *et al.* reported no conversion under our original conditions (CuCl, NaOt-Bu, 2 equiv MeOH in THF) using BINAP as the ligand. See: Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664. However, the data (entry 8 in Table 1) and our data (100% conversion) obtained under the same conditions using bis(diphenylphosphino)benzene (= dpbz) as the ligand^{3c} prove that the BINAP ligand is not good for reactivity.
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