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Copper-Catalyzed β-Boration of α,β-Unsaturated Carbonyl Compounds: Rate Acceleration by Alcohol Additives[†]

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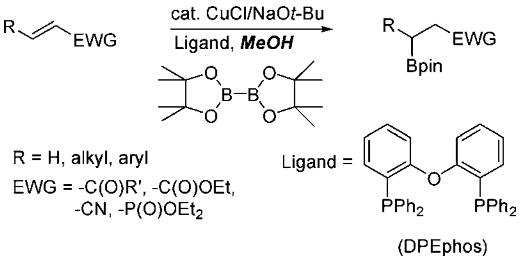
ABSTRACT



The efficient addition of bis(pinacolato)diboron to α,β-unsaturated carbonyl compounds with a copper–diphosphine catalyst has been carried out. A dramatic rate acceleration of the reaction was realized by adding alcohol additives. With use of this procedure, a variety of α,β-unsaturated carbonyl compounds including conjugated substrates at the acid oxidation level such as esters and nitriles were reacted to give to the corresponding β-boryl carbonyl compounds in high yields.

Transition metal-catalyzed boration of unsaturated C−C bonds is an attractive method to produce the organoboron derivatives with defined regio- and stereochemistry and has greatly expanded the potential application of boron derivatives in synthetic organic chemistry.[1] While the addition of diboronates such as bis(pinacolato)diboron (**1**) and bis(catecholato)diboron to alkenes and alkynes has been extensively studied with Pd,[2] Pt,[3] and Rh[4] catalysts, few examples employing other metals have been reported.[5] Recently, copper-catalyzed conjugate addition reactions of bis(pinacolato)diboron to α,β-enones have been independently reported by Hosomi et al.[6] and Miyaura et al.[7] and applied to the synthesis of boronated amino acids as a key synthetic step. These acids are potential therapeutic agents.[8] Although the reported copper-catalyzed reaction systems afford β-boryl enones in reasonable yields, these reactions have some limitations; only enones among other α,β-unsaturated carbonyl compounds are reactive and high catalyst loadings (10−110 mol %) are often required. Herein, we report an efficient β-boration method of various α,β-

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[†] Dedicated to Professor Eun Lee on the occasion of his 60th birthday.

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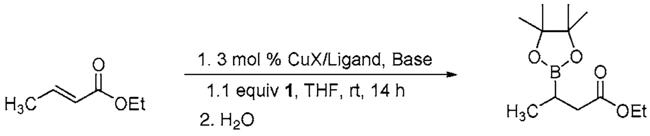
unsaturated carbonyl compounds with a copper−diphosphine catalyst in the presence of alcohol additives.

For the past few years, our laboratory has engaged in the development of the reduction reactions of ketones and α,*β*-unsaturated carbonyl compounds catalyzed by copper−phosphine complexes in the presence of stoichiometric hydrosilanes.[9] Recently, we have reported that complexes of a copper salt and xanthene-based ligands such as Xantphos (9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene) and DPEphos (bis(2-diphenylphosphinophenyl)ether) are particularly efficient for the conjugate reduction of α,*β*-unsaturated nitriles.[10] On the basis of the observations that the Xantphos-type ligands increased the nucleophilic reactivity of copper hydride species, we envisioned that similar copper boryl complexes coordinated with those ligands would be efficient for the catalytic *β*-boration of α,*β*-unsaturated carbonyl compounds.

Initially, we examined the *β*-boration of (*E*)-ethyl crotonate by using a catalytic amount of copper salt and ligand in the presence of 1.1 equiv of bis(pinacolato)diboron (**1**) in THF at room temperature. Catalytic *β*-boration of conjugated carbonyl systems at the acid oxidation level is especially challenging.[7,11] For example, a stoichiometric amount of copper salt and an elevated temperature were necessary for the conjugate addition of the diboron to α,*β*-unsaturated esters, giving the desired products only in moderate yields.[7] As shown in Table 1, copper(I) chloride, a more easily accessible Cu(I) salt than Cu(OAc), gave a slightly higher conversion in the presence of NaO*t*-Bu (entry 1 vs 2) and DPEphos performed better than Xantphos as ligands (entry 2 vs 3). However, all the reactions investigated proceeded to a partial conversion and longer reaction times gave only a small increase in conversion before decomposition. We decided to use alcohol additives as in the conjugate reduction of α,*β*-unsaturated nitriles,[10] hoping that the additives would promote reaction rates by effectively protonating organocopper species[12] generated by the addition of copper boryl species to the ester. Indeed, addition of alcohols to the reaction mixture led to an enhanced rate of reaction (entries 4 and 5). Methanol was a better additive than sterically bulky *t*-BuOH. Both DPEphos ligand and MeOH additive were necessary for an efficient reaction, as other monophosphine ligands (entries 6 and 7) and the ligandless reaction (entry 8) resulted in incomplete conversion after 14 h.

Table 1. Catalytic Addition of Diboron (**1**) to (*E*)-Ethyl Crotonate under Various Conditions

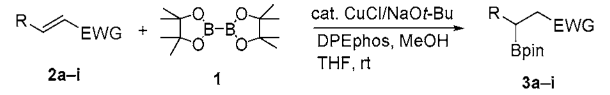


entry	CuX	ligand	base (mol %)	additive (equiv)	convn (%)[a]
1	Cu(OAc)	DPEphos			26
2	CuCl	Xantphos	NaO*t*-Bu (9)		30
3	CuCl	DPEphos	NaO*t*-Bu (9)		48
4	CuCl	DPEphos	NaO*t*-Bu (9)	*t*-BuOH (2)	82
5	**CuCl**	**DPEphos**	**NaO*t*-Bu (9)**	**MeOH (2)**	**>98**
6	CuCl	PBu_3	NaO*t*-Bu (9)	MeOH (2)	85
7	CuCl	PCy_3	NaO*t*-Bu (9)	MeOH (2)	82
8	CuCl		NaO*t*-Bu (9)	MeOH (2)	84

[a] Conversion was determined by GC analysis.

With an optimal reaction protocol using DPEphos ligand and MeOH as additives, the catalytic *β*-boration of various α,*β*-unsaturated carbonyl compounds was examined. As shown in Table 2, a range of α,*β*-unsaturated substrates were regioselectively borylated at room temperature in excellent yields. Simple ethyl acrylate (**2a**), ethyl crotonate (**2b**), and cinnamate (**2c**) afforded the corresponding products in high yields (entries 1−3). The reaction of cinnamate derivatives bearing an electron-donating group and an electron-withdrawing group yielded products in excellent yields as well (entries 4 and 5). Especially, substrate **2d** with an electron-donating methoxy group reacted faster than the cinnamate itself. α,*β*-Unsaturated ketones (entries 6 and 7) were borylated more efficiently under our optimal reaction conditions than Hosomi's conditions employing CuOTf and PBu_3. It is noteworthy that the present catalytic system is tolerant of steric hindrance at the *β*-carbon and reacted with

Table 2. Copper-Catalyzed *β*-Boration of Various Unsaturated Carbonyl Compounds[a]



entry	substrate	R	EWG	time (h)	**3**, yield (%)[b]
1	**2a**	H	C(O)OEt	1.5	98
2	**2b**	CH_3	C(O)OEt	14.5	95
3	**2c**	Ph	C(O)OEt	11	91
4	**2d**	4-MeOC_6H_4	C(O)OEt	3	98
5	**2e**	4-ClC_6H_4	C(O)OEt	16	93
6	**2f**	Ph	$C(O)CH_3$	14	95
7[c]	**2g**	3-methyl-2-cyclohexen-1-one		14	90
8	**2h**	Ph	CN	6.5	95
9	**2i**	Ph	$P(O)OEt_2$	15	91[d]

[a] Conditions: 3 mol % of CuCl, 3 mol % of DPEphos, 9 mol % of NaO*t*-Bu, 1.1 equiv of **1**, 2 equiv of MeOH, THF, room temperature. [b] Isolated yield. [c] 5 mol % of catalyst was used. [d] GC yield.

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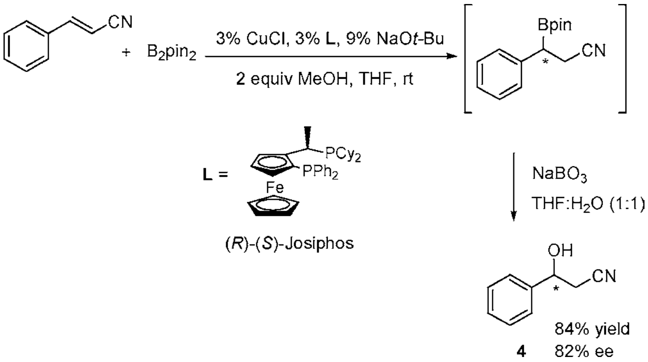
sterically hindered β,β-disubstituted enone **2g** that was inert under Hosomi's conditions (entry 7). Other α,β-unsaturated nitriles and phosphonates[13] were suitable substrates as well (entries 8 and 9).

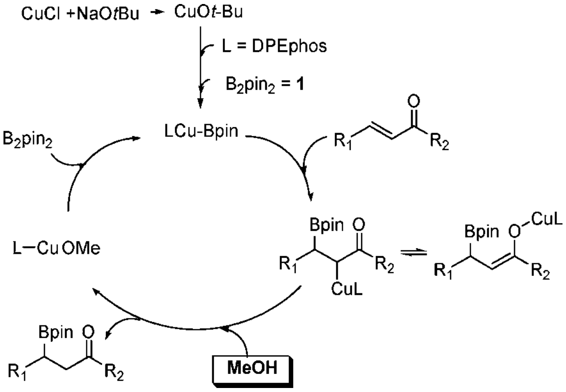
In preliminary experiments to show the utility of this reaction protocol, the asymmetric β-boration of cinnamonitrile and subsequent oxidation[14] were attempted by using Josiphos as the chiral ligand (Scheme 1). These transformations yielded β-hydroxy nitrile compound **4**[15] of 82% ee in 84% overall yield, which could be further transformed to other useful functionalities.

Scheme 1. Application of β-Borylated Product



A possible catalytic cycle for the alcohol accelerated β-boration process is shown in Scheme 2. Our current view is that a diphosphine ligated copper boryl complex[16] is the key intermediate and its conjugate addition to α,β-unsaturated carbonyl compounds takes place. The resulting organocopper species reacts with MeOH to yield the protonated product and a copper alkoxide. The latter then regenerates the active catalyst with diboron **1**.

Scheme 2. A Proposed Mechanism



In summary, we disclose a highly efficient protocol for the conjugate addition of bis(pinacolato)diboron to various α,β-unsaturated carbonyl compounds by using the combination of catalytic amounts of CuCl, NaO*t*-Bu, and DPEphos in the presence of methanol as additives. The addition of MeOH was essential for the successful β-boration and enhancement of the reaction scope. Future studies are aimed at establishing the full scope of this method, investigation of mechanistic issues, and the application of boron derivatives to organic synthesis. Establishment of asymmetric tertiary and quaternary stereocenter by this method is in progress as well.

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Supporting Information Available: Experimental procedures and chracterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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