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sp^2-sp^3 Hybridized Mixed Diboron: Synthesis, Characterization, and Copper-Catalyzed *β*-Boration of α,*β*-Unsaturated Conjugated Compounds

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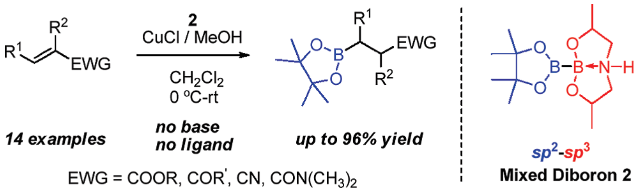
ABSTRACT



A novel sp^2-sp^3 hybridized mixed diboron and its reactivity on the copper-catalyzed *β*-boration of α,*β*-unsaturated conjugated compounds to afford the corresponding *β*-borated compounds is reported. The presence of sp^3-hybridized boron provides a mild *β*-boration condition in the absence of phosphine and base additives. Finally, our investigations demonstrate that the sp^2-hybridized boron of the mixed diboron is selectively transferred to the *β*-carbon of conjugated substrates.

Organoboron compounds are important in medicine because of their diverse biological activities and in organic synthesis due to their versatility as synthetic intermediates.[1,2] One of the important methods for the synthesis of organoboron derivatives is the transition-metal-catalyzed addition of diboron reagents to α,*β*-unsaturated carbonyl compounds. These boration reactions have been extensively studied using platinum,[3] rhodium,[4] nickel,[5] and copper[6] catalyst systems. While these reactions provide a convenient method for the installation of boron, some suffer from limitations such as high catalyst loading, narrow substrate scope, and high reaction temperature. In the copper-catalyzed *β*-boration of α,*β*-unsaturated carbonyl compounds, Yun and co-workers reported an improved procedure and a dramatic rate acceleration in the presence of methanol.[6d] However, additives such as phosphine ligand and base were still

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required.[3−6] The boron source in these transformations is derived from diboron reagents such as B$_2$cat$_2$,[3a] B$_2$neop$_2$,[4] and B$_2$pin$_2$ **1**[3−6] (cat = catecholato = 1,2-O$_2$C$_6$H$_4$; neop = OCH$_2$CMe$_2$CH$_2$O, pin = pinacolato = OCMe$_2$CMe$_2$O); all contain sp^2-hybridized boron. Herein, we report the synthesis and characterization of a novel sp^2−sp^3 hybridized mixed diboron **2** and its reactivity on the copper-catalyzed boration of α,*β*-unsaturated esters, ketones, nitriles, and amides at room temperature. **2** allows the *β*-boration of α,*β*-unsaturated conjugated compounds under mild reaction conditions without the need for additives such as phosphine ligand and base.

Treatment of **1** with bis(2-hydroxypropyl)amine (cis/trans mixture) in a combination of ether/CH$_2$Cl$_2$ readily provided mixed diboron **2** (Figure 1a). This method can easily provide gram-scale amounts of **2** with 31% recovered starting material (**1**) that can be recycled. Analysis of the ^{11}B NMR of **2** shows the appearance of two distinct peaks at *δ* 35.51 and 8.95 and the loss of starting material signal (*δ* 31.14), consistent with the presence of tri- and tetracoordinate boron centers, respectively (Figure 1b).[7] To our knowledge, this is the first report of an sp^2−sp^3 hybridized diboron. Both 1D (^{1}H, ^{13}C) and 2D (COSY, HMQC) NMR studies indicate the structure of **2** to be a diastereomeric mixture of trans/cis form (1:1.2), as expected from the starting diol.[8]

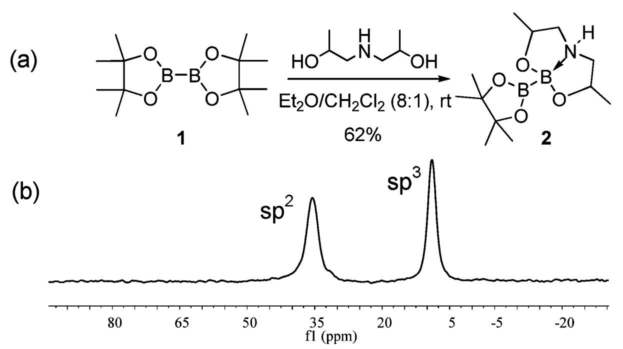
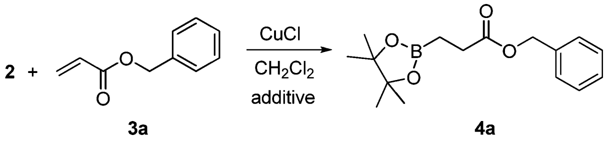


Figure 1. (a) Synthesis of mixed diboron **2** and (b) ^{11}B NMR (160 MHz) of **2** in CD$_3$CN at room temperature.

We were intrigued by a report that addition of base improved the copper-catalyzed boration of unsaturated carbonyl compounds with **1**.[6c] It has been suggested that the base acts to activate the B−B bond by complexation prior to transfer at the copper center, in effect generating an sp^2−sp^3 hybridized diboron. We hypothesized that a "preactivated" diboron can undergo the same transformation without the need for an alkoxide, providing a milder reaction condition.

Table 1. Cu-Catalyzed Addition of Mixed Diboron **2** to Benzyl Acrylate under Various Conditions[a]



entry	additive	equiv of **2**	time (h)	% yield[b] (%)[c]
1	none	1.1	24	60(81)
2	none	1.5	36	67(82)
3	DPEphos[d]	1.5	48	42(65)
4	DPEphos, MeOH[d,e]	1.5	48	76
5	(^{n}Bu)$_3$P, MeOH[d,e]	1.5	48	30(36)
6	*ICy*, MeOH[d,e]	1.5	48	70
7	none	2.0	48	82(86)
8	none	2.0	96	82
9	NaO^{t}Bu[f]	2.0	48	80
10	**MeOH**[e]	**2.0**	**24**	**95**
11	MeOH[e]	1.1	24	65
12	NaO^{t}Bu, MeOH[e,f]	2.0	13	94
13	NaO^{t}Bu, DPEphos, MeOH[d,e,f]	2.0	24	94
14	MeOH[e,g]	2.0	24	0
15	MeOH[e,h]	2.0	24	0

[a] Each reaction was performed at least three times. General procedure: **2** in CH$_2$Cl$_2$ was added to a solution of CuCl (0.05 equiv) in CH$_2$Cl$_2$ at rt followed by **3a** (1 equiv) at 0 °C, then the mixture was allowed to warm to rt. [b] Isolated yield. [c] Corrected yield with recovered **3a**. [d] Ligand (0.03 equiv). [e] MeOH (4 equiv). [f] NaO^{t}Bu (0.05 equiv). [g] In the absence of CuCl. [h] **1** was used instead of **2**.

With mixed diboron **2** in hand, we examined its reactivity in the *β*-boration of benzyl acrylate **3a** (Table 1). Using a catalytic amount of CuCl in the presence of 1.1 equiv of mixed diboron reagent **2** dissolved in CH$_2$Cl$_2$, **3a** was found to undergo the *β*-boration to afford product **4a** in moderate yield (entry 1). Analysis of **4a** demonstrated that the sp^2-hybridized boron was selectively transferred to the *β*-carbon of **3a**. This finding is consistent with the *β*-boration mechanism proposed by Miyaura, where a base functions to activate a diboron reagent generating, in situ, a mixed sp^2−sp^3 hybridized diboron.[6c] Increasing the equiv of **2** to 1.5 provided a slight increase in yield (67%, entry 2). Addition of DPEphos[9] led to a decrease in yield (entry 3), but the concomitant addition of MeOH provided a higher yield (entry 4). Encouraged by these results, we changed the ligand to (^{n}Bu)$_3$P and a better *σ* donor N-heterocyclic carbene *ICy*.[9] However, both ligands provided unsatisfactory yields (entries 5 and 6). Increasing the equivalency of **2** as well as the reaction time to 96 h afforded **4a** in good yield (entries 7 and 8). Attempts with added base did not improve the yield (entry 9). Surprisingly, optimum conditions were found when using MeOH (4 equiv) and **2** (2 equiv) to provide the *β*-boration product in 95% yield within 24 h (entry 10). A lower equiv of **2** provided the product in moderate yield (entry 11). No further improvement in yield was observed when adding either base only or base with ligand (entries 12 and 13). As expected, the reaction did not work when

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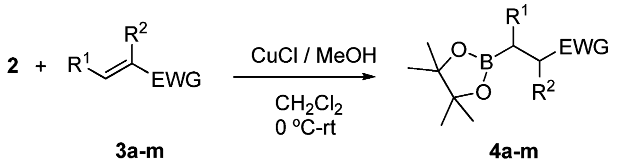
(8) See the Supporting Information for details.

(9) DPEphos = bis(2-diphenylphosphinophenyl)ether, *ICy* = 1,3-dicyclohexylimidazoline-2-ylidene.

no copper catalyst was present (entry 14). Under the same reaction conditions as entry 10, no reaction products were detected when **1** instead of **2** was used (entry 15).

With the optimal reaction conditions determined (entry 10, Table 1), the generality of this copper-catalyzed boration was demonstrated by reaction with various α,*β*-unsaturated conjugated compounds (Table 2). Simple esters such as benzyl acrylate **3a**, methyl acrylate **3b**, ethyl acrylate **3c**, *tert*-butyl acrylate **3d**, and *n*-butyl acrylate **3e** afforded the corresponding products **4a**−**e** in excellent yields (91−96%) within 24 h (entries 1−5). However, methacrylate esters **3f**−**h** were converted to the desired products **4f**−**h** only in moderate yields, although some starting material was recovered (entries 6−8). Fortunately, α,*β*-unsaturated ketones were borated in good yields. Treatment of methyl vinyl ketone with mixed diboron **2** under optimal conditions afforded **4i** in 76% yield (entry 9). Sterically encumbered substrate **3j** and 2-cyclopentenone **3k** were also borated in high yields, although an increase in reaction time was necessary (entries 10 and 11). The difference in reactivity between esters and ketones can arise from the decreased electrophilicity of the ester. Interestingly, acrylonitrile **3l** and *N*,*N*-dimethylacrylamide **3m** also underwent the *β*-boration reaction smoothly in good yield (entries 12 and 13).

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

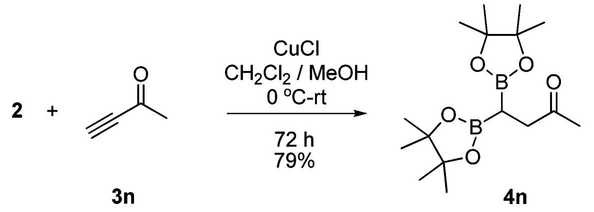


entry	substrate	R^1	R^2	EWG	time (h)	% yield[b] (%)[c]
1	**3a**	H	H	CO_2Bn	24	95
2	**3b**	H	H	CO_2Me	15	92
3	**3c**	H	H	CO_2Et	18	96
4	**3d**	H	H	$CO_2{}^tBu$	24	96
5	**3e**	H	H	$CO_2{}^nBu$	24	91
6	**3f**	H	Me	CO_2Me	36	41
7	**3g**	H	Me	CO_2Et	72	47(53)
8	**3h**	H	Me	CO_2Bn	72	40(87)
9	**3i**	H	H	COMe	48	76(84)
10	**3j**	Ph	H	COMe	72	81(94)
11	**3k**	2-cyclopentenone			72	85(93)
12	**3l**	H	H	CN	48	52
13	**3m**	H	H	$CONMe_2$	48	80(90)

[a] Each reaction was performed at least three times. Conditions: **2** (2.0 equiv), CuCl (0.05 equiv), **3** (1 equiv), and MeOH (4 equiv), 0 °C→rt. [b] Isolated yield. [c] Corrected yield with recovered **3**.

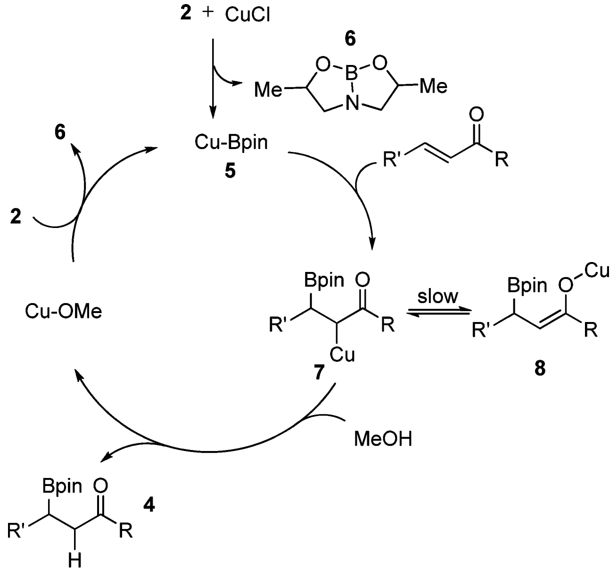
Finally, we attempted the *β*-boration reaction with mixed-diboron **2** to 3-butyn-2-one **3n**. Surprisingly, **3n** undergoes the boration twice to furnish *β*,*β*-diborated product **4n** in 79% yield (Scheme 1). To the best of our knowledge, this is the first example of catalytic addition of a diboron reagent to an α,*β*-acetylenic ketone affording *β*,*β*-diborated product.[10] We can envision the transformation of these types of products into other useful functional groups.

Scheme 1. Copper-Catalyzed Diboration of 3-Butyn-2-one



On the basis of the above experimental results, a possible catalytic cycle for the copper-catalyzed boration is shown in Scheme 2. The activated sp^2−sp^3 hybridized mixed diboron **2** initially reacts with CuCl to generate oxazaborole **6** and boryl-cuprate intermediate **5** that undergoes conjugate addition to α,*β*-unsaturated conjugated compounds. The resulting organocuprate **7/8** undergoes protolytic cleavage by MeOH to form product **4**, and a copper alkoxide, which regenerates **5** in the presence of mixed diboron **2**.[6d]

Scheme 2. Proposed Catalytic Cycle



In summary, we disclose the first synthesis and characterization of a novel mixed sp^2−sp^3 hybridized diboron reagent **2**. We also demonstrated its reactivity, in the absence of phosphine or alkoxide additives, toward copper-catalyzed *β*-boration of α,*β*-unsaturated conjugated compounds (up to 96% yield achieved). Finally, our results established that the sp^2-hybridized boron of the mixed diboron reagent is selectively transferred

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[10] Recently, Yun et al. reported the addition of bis(pinacolato)diboron to α,*β*-acetylenic esters providing the corresponding monoborated products. See reference 6e.

to the β-carbon of conjugated substrates. The mechanism, synthetic utility, and synthesis of chiral mixed diboron compounds are currently under investigation.

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

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