

# Regio- and stereoselective copper-catalyzed $\beta$ -borylation of allenates by a preactivated diboron<sup>†‡</sup>

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**A mild and efficient copper-catalyzed borylation of electron deficient allenates using an  $sp^2$ - $sp^3$  mixed hybridized diboron regioselectively installs a boron moiety on the  $\beta$ -position with exclusive (*Z*)-double bond geometry.**

In recent years, allenes have emerged as an important structural unit in the construction of complex molecules.<sup>1</sup> For example, cycloaddition, radical, nucleophilic addition and metalation reactions demonstrate the versatility and unique reactivity of allenes.<sup>2</sup> Because of their potential in organic synthesis and other applications, their preparation is subject to intense investigation. In particular, the reactivity of electron-deficient allenes can be tuned to produce either  $\beta,\gamma$ -unsaturated carbonyl compounds or  $\gamma$ -addition products depending on the reaction conditions. For example, Shibasaki and co-workers elegantly developed the construction of highly functionalized  $\delta$ -lactones with tetrasubstituted chiral centers using a three component assembly of dialkylzincs, allenic esters and ketones.<sup>3</sup> Jorgensen *et al.* demonstrated the organo-catalytic asymmetric conjugate addition to electron-deficient allenes to form tertiary and quaternary stereogenic centers.<sup>4</sup> These reactions produce  $\beta,\gamma$ -unsaturated carbonyl compounds, and examples in the literature are limited. However, the regioselectivity of the reaction can be reversed. Indeed, Lewis bases such as phosphines catalyze  $\gamma$ -additions of carbon, nitrogen, oxygen and sulfur nucleophiles to allenates.<sup>5</sup>

Transition metal-catalyzed reactions of electrophilic allenates generate molecular scaffolds with functional and structural diversity.<sup>1a,6</sup> For example, 2,3-allenyl carboxylic acids cyclo-isomerize in the presence of Cu(I) source<sup>7</sup> or undergo halolactonization with  $CuX_2$  ( $X = Br, Cl$ ).<sup>8</sup> These intermediates are useful building blocks in the synthesis of more elaborate chemical structures, especially with cross-coupling reactions. As complementary reacting partners, organoboron compounds increasingly provide access to the formation of difficult carbon-carbon bonds. Indeed, the Suzuki-Miyaura coupling reaction, which employs a boronic acid and organohalide, is a powerful method for the construction of complex molecules partly because of its functional group tolerance.<sup>9</sup> Thus far, silaboration,<sup>10</sup> cyanoboration,<sup>11</sup> and diboration<sup>12</sup> have been achieved with allenes using transition metals.

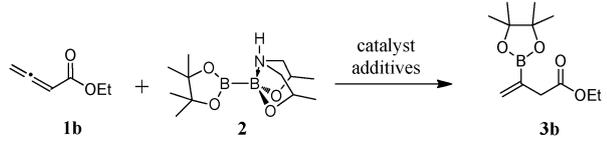
To date, however, direct borylation of electron-deficient allenes has not been reported. We recently disclosed the synthesis of an internally activated,  $sp^2$ - $sp^3$  hybridized diboron compound, PDIPA diboron (pinacolato diisopropanol-aminato diboron, **2**), and demonstrated its utility in the copper-catalyzed,  $\beta$ -borylation of  $\alpha,\beta$ -unsaturated conjugated compounds.<sup>13</sup> In pursuit of expanding the scope of this reaction to more intricate substrates, we investigated the utility of **2** to the borylation of electrophilic allenates. These substrates are attractive because they give rise to  $\beta,\gamma$ -unsaturated carbonyl compounds, as opposed to acetylenic esters which produce  $\alpha,\beta$ -unsaturated carbonyl compounds,<sup>14</sup> allowing for further functionalization of the resulting nonconjugated olefin. In addition, we were excited by the possibility that a racemic mixture of the starting allenate forms a product containing a defined double bond geometry and a vinyl boronic ester, which is potentially a Suzuki-Miyaura cross-coupling partner.<sup>9</sup>

To explore the feasibility of the borylation reaction, we investigated reaction conditions to generate  $\beta$ -borylated  $\beta,\gamma$ -unsaturated ethyl ester **3b** using ethyl 2,3-butadienoate (**1b**) as the substrate. As shown in Table 1, agents with strong sigma bond donor capacity to activate bis(pinacolato)diboron such as N-heterocyclic carbenes (NHC),<sup>15</sup> (Ime)CO<sub>2</sub><sup>16</sup> and (ICy)BF<sub>4</sub>,<sup>17</sup> promoted the borylation reaction with good yields (entries 1 and 2). However, the use of a strong base to generate the carbene can be a disadvantage for sensitive substrates. In addition, NHC ligands are expensive and difficult to handle. With the effort to use milder reaction conditions, we investigated whether a preactivated diboron<sup>13</sup> also effects the desired transformation. To our delight, treating allenate **1b** with a catalytic amount of CuCl, trifluoroethanol (TFE) and **2** in dichloromethane produced **3b** in excellent yield (entry 3).<sup>18</sup> Running the reaction in the absence of TFE successfully provided the product (entries 4 and 12). Other additives such as base and phosphine ligand were effective although a copper stabilizing DPEphos dramatically decreased the product yield (entries 5–7). As expected, when the reaction was attempted without a copper catalyst, the reaction was sluggish (entry 8). Evaluation of the effect of solvent revealed that the reaction was tolerant of aprotic solvents used, although the reaction performed in THF was most effective (entries 4, 9 and 10). We also screened the effect of temperature on the reaction and discovered that the borylation reaction is efficient at room temperature in the presence of TFE (compare entries 1–10 vs. 11). CuCl as the copper source appears to be important since CuBr or other Cu(II) sources afforded the product in moderate yields (entries 12–14). Finally, an examination of other transition metals such as Rh, Pt, Ni and Ag resulted in minor or undetectable product formation

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<sup>‡</sup> Electronic supplementary information (ESI) available: Detailed experimental procedures, synthesis and characterization of unknown allenates, analytical data for  $\beta$ -borylated  $\beta,\gamma$ -unsaturated esters. See DOI: 10.1039/c0cc02270e

**Table 1** Optimization of reaction conditions<sup>a</sup>


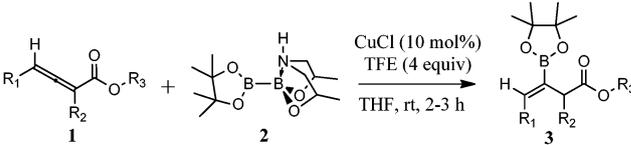
Entry	Catalyst	Solvent	Additives (equiv.)	Conv% <sup>b</sup>
1	CuCl <sup>c</sup>	ACN	(IMe)CO <sub>2</sub> (0.1)	81.3
2	CuCl <sup>c</sup>	THF	(ICy)BF <sub>4</sub> (.05) NaO <sup>t</sup> Bu (0.1)	95.1
3	CuCl <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	TFE (4)	96.9
4	CuCl <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	—	96.4
5	CuCl <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	NaO <sup>t</sup> Bu (0.1)	98.3
6	CuCl <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	DPEphos (0.1)	45.7
7	CuCl <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	NaO <sup>t</sup> Bu (0.1) TFE (4)	97.5
8	— <sup>d</sup>	CH <sub>2</sub> Cl <sub>2</sub>	—	4.9
9	CuCl <sup>d</sup>	DMF	—	78.0
10	CuCl <sup>e</sup>	THF	—	98.3
11	CuCl <sup>f</sup>	THF	TFE (4)	96.7
12	CuBr <sup>e</sup>	THF	—	87.8
13	CuBr <sub>2</sub> <sup>e</sup>	THF	—	76.6
14	CuCl <sub>2</sub> <sup>e</sup>	THF	—	86.7
15	[Rh(cod)Cl] <sub>2</sub> <sup>e</sup>	THF	—	ND
16	Pt(cod)Cl <sub>2</sub> <sup>e</sup>	THF	—	ND
17	Ni(cod) <sup>e</sup>	THF	—	ND
18	Ag(NO <sub>3</sub> ) <sup>e</sup>	THF	—	1.5

<sup>a</sup> PDIPA diboron (**2**, 1.2 equiv.), catalyst (0.1 equiv.), and additives were suspended in solvent and stirred for 5 minutes. Ethyl 2,3-butadienoate (1.1 equiv.) was then added and the reaction was stirred for 2 hours at the indicated temperature. <sup>b</sup> Conversion was determined by GC analysis of the crude material. <sup>c</sup> The reaction was performed at rt and bis(pinacolato)diboron was used instead of **2**. <sup>d</sup> The reaction was heated to 40 °C. <sup>e</sup> The reaction was heated to 70 °C. <sup>f</sup> The reaction was performed at rt. Abbreviations: DPEphos = bis(2-diphenylphosphinophenyl)ether; (IMe)CO<sub>2</sub> = 1,3-dimethylimidazolium carboxylate; (ICy)BF<sub>4</sub> = 1,3-dicyclohexylimidazolium tetrafluoroborate; TFE = 2,2,2-trifluoroethanol; ND = none detected.

(entries 15–18). Thus, subsequent investigations used 10 mol% CuCl, 4 equiv. TFE, allenolate substrate and **2** in THF at room temperature.

With the optimized conditions in hand, we next investigated the scope of the reaction using various allenolates. The results of our study are summarized in Table 2. Increasing the size of the ester moiety from methyl to ethyl on unsubstituted allenolates provided the β-borylated β,γ-unsaturated ethyl esters **3a** and **b** in good yields (entries 1 and 2). A change to the bulkier 3-phenylpropyl ester **1c** resulted in slight decrease in yield with some unreacted starting material isolated (entry 3). Gratifyingly, the presence of a bulky phenyl substituent on the γ-position allowed the borylation to proceed in moderate yields (entries 4–6). When the phenyl substituent was replaced with a less sterically demanding methyl group, the product was isolated in good yield (58–78%, entries 7–10). The presence of a bulky *o*-nitrobenzyl moiety resulted in a much lower yield in part because this group is sensitive to light (entry 11). Finally, α,γ-disubstituted ethyl allenolate **11** was converted to the product in moderate yield presumably because of the bulkiness of the substrate (entry 12).

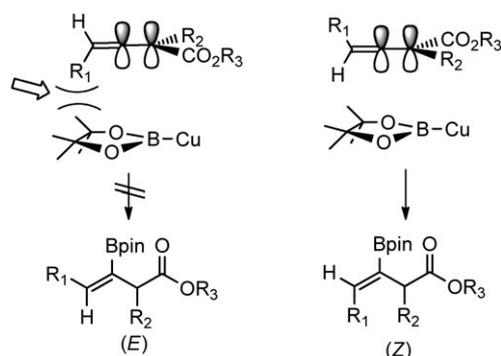
It is important to highlight that the copper catalyzed β-borylation reaction proceeded not only regioselectively but

**Table 2** β-Borylation of allenolates<sup>a</sup>


Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Product	Z/E <sup>b</sup>	% <sup>c</sup> Yield (%) <sup>d</sup>
1	H	H	Me	<b>3a</b>	—	59
2	H	H	Et	<b>3b</b>	—	60
3	H	H	(CH <sub>2</sub> ) <sub>3</sub> Ph	<b>3c</b>	—	41 (71)
4	Ph	H	Me	<b>3d</b>	100 : 0	41
5	Ph	H	Et	<b>3e</b>	100 : 0	46
6	Ph	H	(CH <sub>2</sub> ) <sub>3</sub> Ph	<b>3f</b>	100 : 0	14 (45)
7	Me	H	Me	<b>3g</b>	100 : 0	72
8	Me	H	Et	<b>3h</b>	100 : 0	58
9	Me	H	<sup>t</sup> Pr	<b>3i</b>	100 : 0	78
10	Me	H	<sup>t</sup> Bu	<b>3j</b>	100 : 0	71
11	Me	H	<i>o</i> -Nitrobenzyl	<b>3k</b>	100 : 0	33 (75)
12	Me	Me	Et	<b>3l</b>	100 : 0	38 <sup>e</sup> (81)

<sup>a</sup> For detailed synthetic procedure, see ESI.† <sup>b</sup> The ratio of *E*/*Z* isomers were determined by GC and the geometry of the product was assigned based on NOESY experiments. <sup>c</sup> Isolated yield. <sup>d</sup> Corrected yield with recovered starting material. <sup>e</sup> Reaction was stirred 24 hours before workup. Product contaminated with 22% α,β-unsaturated isomer.

also diastereoselectively. In contrast with phosphine-catalyzed reactions to electrophilic allenolates that afford γ-substituted products,<sup>5</sup> the copper-catalyzed reaction regioselectively installed the boryl moiety on the β-position. In addition, under the reaction conditions of our investigation, we did not observe any cycloisomerization products seen in other copper-catalyzed reactions with allenolates (*vide infra*).<sup>7</sup> Interestingly, the geometry of the double bond on the resulting product was determined to be *Z* based on NOESY experiments, and <sup>1</sup>H NMR and GC-MS analysis of the crude reaction mixture showed exclusive formation of this product.<sup>19</sup> The stereoselectivity of the reaction can be rationalized by analysis of the approach of the boryl-copper intermediate (Fig. 1). Since the two double bonds are orthogonal to each other, boryl addition to the β-carbon is expected to occur on the opposite side of the γ-substituent of the allenolate because of a strong steric interaction. Furthermore, 1,3-allylic strain in the (*E*)-isomer should favor the formation of the more stable (*Z*)-isomer. Indeed, only the (*Z*)-product was observed.

**Fig. 1** Steric interactions lead to exclusive formation of the (*Z*)-isomer.

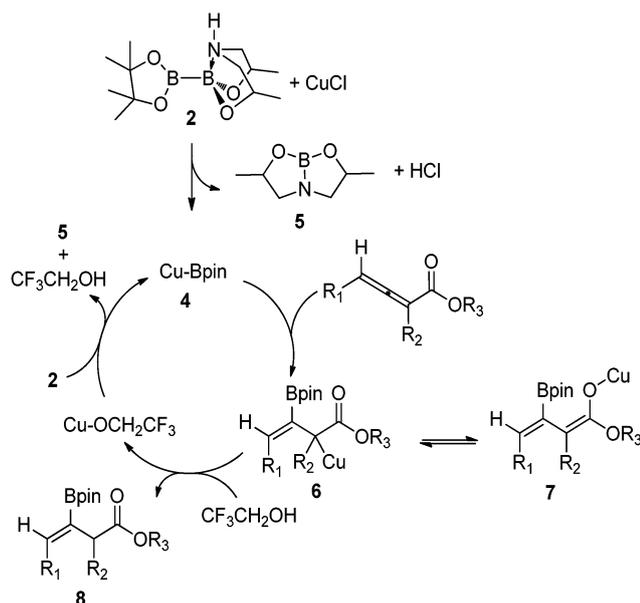


Fig. 2 Proposed reaction mechanism.

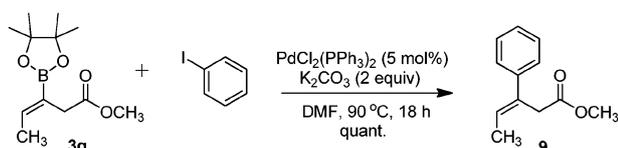


Fig. 3 Coupling of  $\beta$ -boronic ester with iodobenzene.

Finally, we were pleased to find that although the allenolate substrates were used as racemic mixtures, the reaction provides a single product.

A possible catalytic cycle for the  $\beta$ -borylation reaction is shown in Fig. 2. Preactivated  $sp^2$ – $sp^3$  hybridized diboron **2** is sufficiently activated to transmetalate with CuCl to generate nucleophilic boryl species **4**. DFT calculations on the copper-catalyzed borylation of related  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>20</sup> suggest the formation of metalated intermediates **6/7** that can be protonated to yield the desired  $\beta$ -borylated  $\beta,\gamma$ -unsaturated ester **8** with the simultaneous regeneration of copper–alkoxide that continues the catalytic cycle. The essential role of TFE is to accelerate the reaction by protonation of **6/7** and formation of copper–alkoxide.<sup>18</sup>

To demonstrate the utility of the regio- and stereoselective borylation reaction, Suzuki–Miyaura cross coupling reaction between **3g** and iodobenzene was attempted. In this case, the coupled product **9** was isolated in quantitative yield (Fig. 3). In contrast, **9** was previously synthesized as a mixture of *E/Z* isomers at 52% yield from a cyclopropanone acetal derivative.<sup>21</sup>

In conclusion, an efficient and catalytic copper-catalyzed regioselective borylation of allenolates was developed. To the best of our knowledge, this reaction is the first example of a boryl addition to electrophilic allenolates. The reaction provided  $\beta$ -borylated  $\beta,\gamma$ -unsaturated esters with exclusive

(*Z*)-double bond geometry. These borylated products are useful intermediates for subsequent elaboration to more complex structures.

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