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protoboration of allenates: access to Z- $\beta,\gamma$ -unsaturated  $\beta$ -  
boryl esters**

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## COMMUNICATION

# Regio- and stereoselective copper-catalyzed $\alpha,\beta$ -protoboration of allenates: access to Z- $\beta,\gamma$ -unsaturated $\beta$ -boryl esters

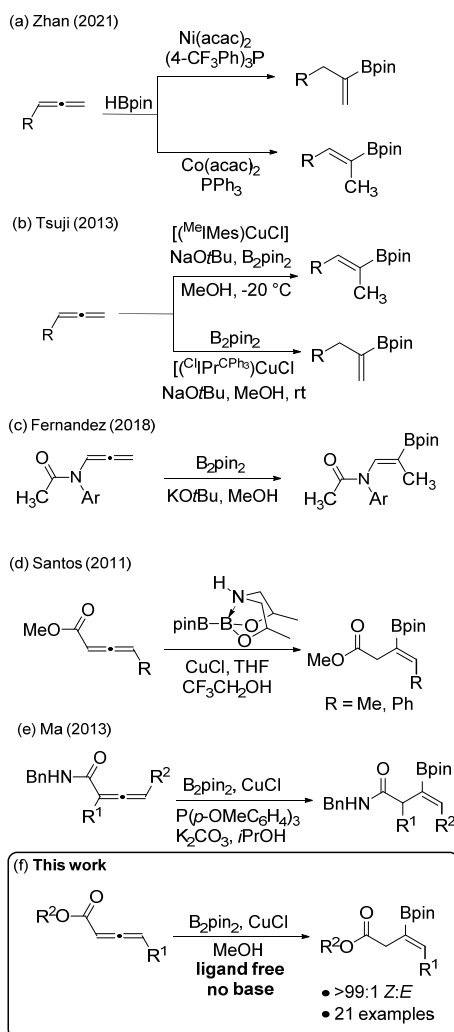
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A highly efficient regio- and stereoselective method for allenolate borylation has been developed. Using CuCl and bis(pinacolato)diboron in methanol, a variety of allenates underwent  $\beta$ -boration,  $\alpha$ -protonation to afford the corresponding Z- $\beta,\gamma$ -unsaturated  $\beta$ -boryl esters under mild conditions with up to 81% yields.

Organoboron compounds continue to be pivotal in organic synthesis, materials science, and pharmaceutical chemistry.<sup>1</sup> In particular, vinylboronic acids have garnered much attention for being a special class of compounds capable of undergoing a multitude of transformations, most notably the Suzuki-Miyaura cross-coupling.<sup>2</sup> Vinyl boronic acids can be synthesized from alkyne hydroboration, Miyaura borylation, or the dehydrogenative borylation of alkenes.<sup>3</sup> Despite these advances, novel methods to access vinylboronic acid derivatives remains to be investigated. Allenes have emerged as important commodity chemicals to generate diverse products in organic synthesis.<sup>4</sup> Borylation of allenenes has received increased attention because of the large number of subsequent functional group interconversions possible.<sup>5</sup> Borylation of electron deficient allenenes can produce a multitude of products ranging from  $\beta,\gamma$ -unsaturated carbonyl compounds to  $\gamma$ -addition notwithstanding stereochemical issues. Regio- and stereoselective addition of boron to allenenes permits subsequent chemical transformations, *e.g.*, carbon-carbon couplings, that are otherwise difficult.<sup>6</sup> Recently, Zhan and co-workers reported an elegant regiodivergent hydroboration of the internal or terminal olefin in allenenes with Ni(acac)<sub>2</sub> or Co(acac)<sub>2</sub>, respectively (Scheme 1a).<sup>7</sup> Similarly, Tsuji and co-workers reported a regiodivergent hydroboration of the internal or terminal olefin in allenenes with CuCl and either pinacolborane (HBpin) or *bis*(pinacolato)diboron (B<sub>2</sub>pin<sub>2</sub>), respectively (Scheme 1b).<sup>8</sup> While allene borylations are well established in the literature<sup>9</sup>, such as the silaboration<sup>10</sup> and diboration,<sup>11</sup> achieving the desired



Scheme 1 Strategies toward allene borylation and current approach.

regio- and stereoselectivity while minimizing undesired side products continues to be a challenge.<sup>7</sup>

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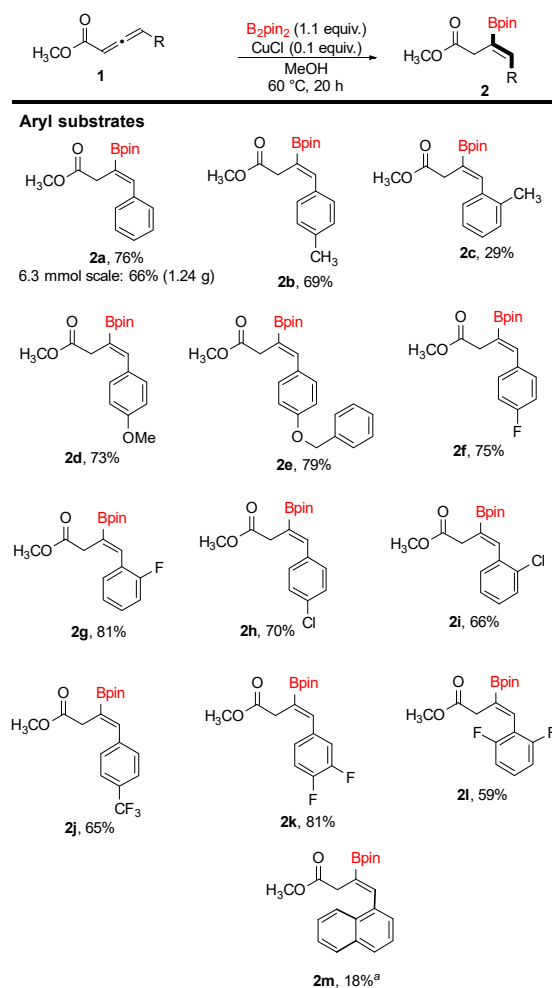
Table 1 Optimization of reaction conditions<sup>a</sup>

Entry	Catalyst <sup>b</sup>	Solvent	Temp. (°C)	E:Z	Yield <sup>c</sup>
1	CuCl	THF	50	1:>99	35
2	CuI	THF	50	-	trace
3	CuCl <sub>2</sub>	THF	50	-	0
4	PBu <sub>3</sub>	THF	50	-	0
5	CuCl	toluene	50	1:>99	34
6	CuCl	CH <sub>2</sub> Cl <sub>2</sub>	50	1:>99	55
7	CuCl	MeCN	50	1:>99	23
8	CuCl	toluene	60	1:>99	40
9	CuCl	toluene	70	1:>99	38
10	CuCl	toluene	80	1:>99	30
11 <sup>d</sup>	CuCl	toluene	60	1:>99	45
12	<b>CuCl</b>	<b>MeOH</b>	<b>60</b>	<b>1:&gt;99</b>	<b>76</b>
13 <sup>e</sup>	CuCl	MeOH	60	19:81	74
14	CuCl	EtOH	60	1:>99	39
15	CuCl	<i>n</i> -BuOH	80	1:>99	42
16	-	MeOH	60	-	0

<sup>a</sup>Premix B<sub>2</sub>pin<sub>2</sub> (0.85 mmol) and CuCl (0.085 mmol) in solvent for 20 min followed by allenamide **1a** (0.80 mmol) at indicated temp. <sup>b</sup>0.1 equiv. used. <sup>c</sup>Isolated yields. <sup>d</sup>MeOH (2 equiv.). <sup>e</sup>KO<sup>t</sup>Bu (0.1 equiv.).

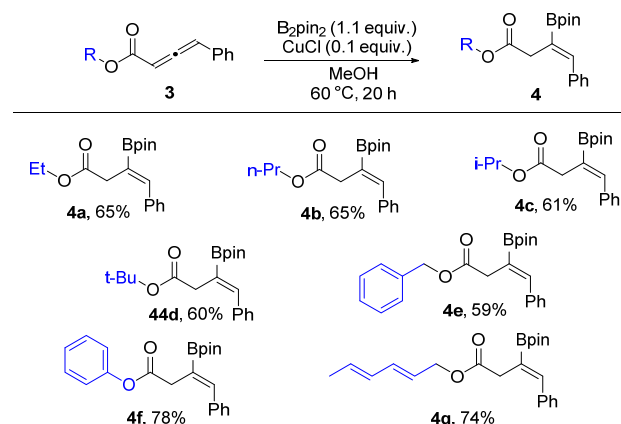
Methodology towards direct borylation of acylated or electron deficient allenenes are scarce. Fernandez and co-workers developed a base-catalyzed, transition metal-free borylation of allenamides to produce the corresponding (Z)-enamide exclusively, although this reaction has a limited scope and required *para* electron donating groups on the aryl ring (Scheme 1c).<sup>12</sup> Interestingly, hydroboration occurred on the terminal alkene affording the β-boryl, β-methyl acetamides. Our group previously reported the copper-catalyzed β-borylation of allenates with pinacolato diisopropanolaminato diboron (PDIPA), furnishing β,γ-unsaturated β-boryl esters (Scheme 1d).<sup>13</sup> Unfortunately, this reaction had limited substrate scope, low yields, and was susceptible to isomerization to the α,β-unsaturated β-boryl esters. However, this previous report indicated the preactivation using a sp<sup>3</sup>-sp<sup>2</sup> diboron species was necessary for the reaction to occur. With electron deficient allenamides, Ma and co-workers reported a regio- and stereoselective borylation using a copper (I) catalyst to produce Z-β-borylated β,γ-unsaturated enoamides (Scheme 1e).<sup>14</sup> In this particular case, a net hydroboration resulted from 1,4-conjugate addition. In this report, we developed a copper-catalyzed method for the sequential borylation-protonation of allenates to generate Z-β,γ-unsaturated β-boryl esters exclusively (Scheme 1f). The β-borylation proceeds on the under mild reaction conditions without the necessity for additional copper ligand and use of base additive.

We began our optimization using B<sub>2</sub>pin<sub>2</sub> and CuCl in THF at 50 °C (Table 1, entry 1). Interestingly, we exclusively observed reactivity on the α,β-double bond to produce **2a** in modest yield and unreacted starting material. Switching the catalyst to CuI or Cu<sup>2+</sup> source resulted



**Scheme 2** Scope of phenyl substituted allenenes. Isolated yields reported and >99:1 E/Z unless otherwise noted. Selectivity determined by GC of the crude reaction mixture. <sup>a</sup>With 0.3 equiv. CuCl for 72 hrs. <sup>b</sup>E:Z = 2:98, <sup>c</sup>E:Z = 3:97, <sup>d</sup>E:Z = 6:94, <sup>e</sup>E:Z = 5:95.

in no reaction (entries 2-3). Use of PBu<sub>3</sub> an organocatalyst was equally inefficient<sup>15</sup> (entry 4). A survey of solvents revealed that toluene gave similar selectivity and yield as THF (entries 5-7) while increasing the reaction temperature up to 80 °C indicated 60 °C as optimal (entries 8-10). Interestingly, methanol as an additive improved yield to 45% and switching the solvent to methanol gave product **2a** in 75% yield with exclusive Z selectivity (entries 11-12). Additives such as *tert*-butoxide, which was used in the hydroboration of allenamides,<sup>12</sup> resulted in a mixture of E/Z isomers while ethanol or *n*-butanol decreased product yield (entries 13-15). Removal of

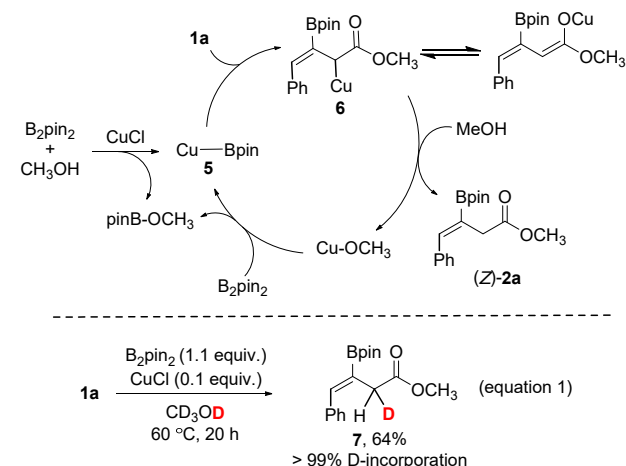


**Scheme 3** Scope of ester substituted allenes. Isolated yields reported and >99:1 *E/Z* as determined by GC of the crude reaction mixture.

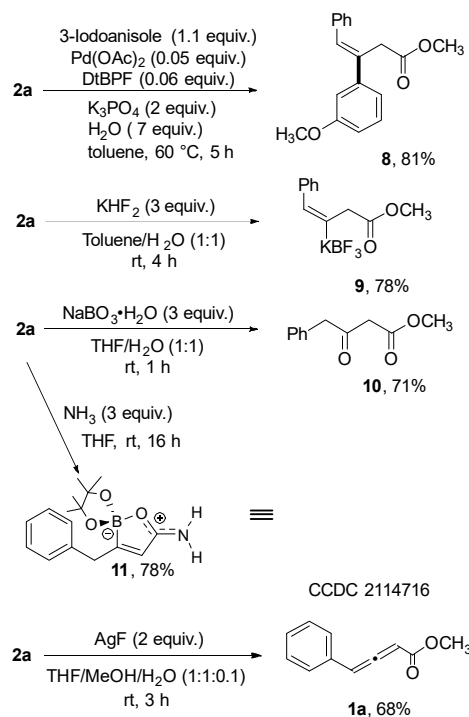
CuCl resulted in no reaction, suggesting the critical role of copper in catalyzing the reaction. Finally, the stereochemistry of **2a** was established using nuclear Overhauser effect NMR studies (see SI for details).

With the optimized conditions in hand using  $B_2pin_2$  (1.1 equiv) and CuCl (0.1 equiv.) in methanol at 60 °C (Table 1, entry 12), we evaluated the scope and limitations of the method (Scheme 2). We focused our initial studies to explore the functional group tolerance on the phenyl ring. Thus, treatment of **1a** under standard conditions afforded **2a** in 76% yield. To demonstrate scalability, we performed a large scale of the reaction **1a** (6.3 mmol) and isolated 1.24 g of product **2a** in 66% yield. *para*-Methyl substituted aryl ring (**2b**) was likewise well tolerated (69% yield) whereas the corresponding *ortho* substitution (**2c**) gave 29% yield, suggesting the sensitivity of the reaction to steric effects. Electron donating groups such as methoxy (**2d**) or benzyloxy (**2e**) were afforded in 73% and 79% yields, respectively. Electron withdrawing groups such as fluorine or chlorine were well tolerated at the *ortho* or *para* position (**2f–2i**). Moreover, a trifluoromethyl group in **2j** was generated in 65% yield. Disubstitution with fluorine at the *meta* and *para* positions in **1k** gave product **2k** in excellent yield. However, 2,6-difluoro derivative **1l** resulted in a lower yield of 59% and in combination with a low yield in **2m**, which required 30 mol% copper catalyst and longer reaction time, further indicates sensitivity to steric effects. We next investigated whether alkyl groups were efficient substrates. Cyclopentyl bearing allenoate **1n** afforded product **2n** in 66% with exclusive *Z* selectivity. Linear chain alkyl groups ranging from pentyl to heptyl groups were also efficiently converted to the corresponding *Z*- $\beta,\gamma$ -unsaturated  $\beta$ -boryl esters (**2o–2q**) albeit in slightly reduced stereoselectivity. Limitations to the substrate scope were primarily due to access of allenoate starting materials. For example, treatment of 4-nitrophenyl-, thiophen-2-yl-, and 3-pyridyl-acetyl chloride with methyl 2-(triphenyl- $\lambda$ 5-phosphaneylidene)acetate and triethylamine did not afford the corresponding allenoates.

Next, we investigated the effect of the ester substituent of the allenoate (Scheme 3). Increasing the alkyl group from ethyl (**3a**), *n*-propyl (**3b**), isopropyl (**3c**) to *tert*-butyl (**3d**) afforded the corresponding products (**4a–4d**) in good yields. Benzyl (**5e**) or phenyl (**5f**) esters were also efficient substrates. Lastly, introduction of



**Scheme 4** Plausible catalytic cycle.



**Scheme 5** Synthetic transformations of **2a**.

(*2E,4E*)-hexa-2,4-dienyl ester **3g** gave the corresponding borylated product **4g** in 74% yield. This is notable because copper-catalyzed borylation of 1,3-dienes have been reported<sup>16</sup> and highlights the chemoselectivity of the current reaction conditions.

A plausible catalytic cycle is shown in Scheme 4.<sup>13</sup> In the presence of methanol, B<sub>2</sub>pin<sub>2</sub> and CuCl at elevated temperature, boryl-copper species **5** is generated, which undergoes boryl-cupration to intermediate **6** with the steric interaction between the phenyl ring

and incoming boron complex **5** driving the stereoselectivity of the reaction. In the presence of methanol, the C- or O-bound copper complex becomes protonated to yield Z-β,γ-unsaturated β-boryl ester **2a**. The resulting copper-alkoxide undergoes transmetalation with B<sub>2</sub>pin<sub>2</sub> to regenerate the active catalyst **5**. Deuteration studies confirm that methanol is the proton source on the alpha carbon of **7** (equation 1).

With the protoboration protocol established, we set out to demonstrate the application of the products (Scheme 5). Treatment of **2a** with 3-iodoanisole under Suzuki-Miyaura cross-coupling conditions generated compound **8** in 81% yield whereas boron protecting group interconversion from pinacol to a trifluoroborate **9** proceeded in 78% yield.<sup>17</sup> Oxidation of **2a** using sodium perborate produced β-ketoester **10** in 71% yield. β-Ketoesters are essential synthetic intermediates in drug discovery, allowing for a simple and high yielding method towards medicinal drugs.<sup>18</sup> Conversion of **2a** to a primary amide with ammonia occurred in 78% yield with concomitant isomerization to the iminooxaborole **11**. Single crystal X-ray diffraction studies unambiguously establish the structure of **11** with *E* geometry and a five membered ring sp<sup>3</sup> hybridized boron atom coordinating to the carbonyl oxygen.<sup>19</sup> Finally, we attempted a protodeboration procedure in the presence of AgF.<sup>20</sup> To our surprise, we isolated allenolate **1a** in 68% yield. To the best of our knowledge, this is the first example of a vinylboronic acid derivative transformation to an allene.

In conclusion, an efficient, ligandless, and base-free copper-catalysed regio- and stereoselective borylation of allenolates was developed. The utility of the resulting β-borylated β,γ-unsaturated esters is demonstrated in a multitude of functional group transformations.

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