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Maria Eduarda Contreira, Diogo S. Lüdtkke, Angélica V. Moro

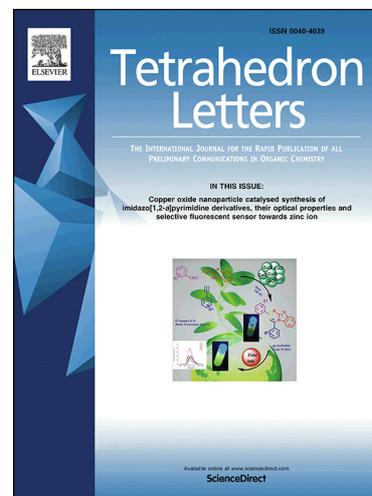
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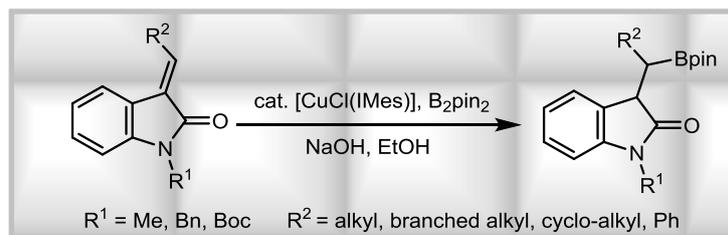
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Maria Eduarda Contreira, Diogo S. Lüdtké\*, Angélica V. Moro





## Copper-catalyzed hydroboration of alkenyl oxindoles

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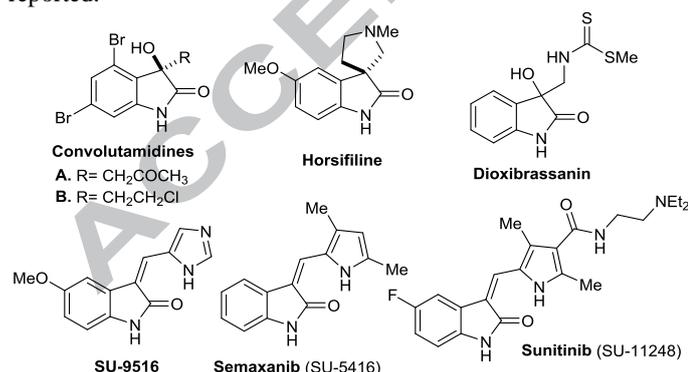
boron compounds  
borylation  
copper catalysis  
isatin  
green solvents

### ABSTRACT

Herein we describe the NHC-Cu(I)-catalyzed hydroboration of alkenyl oxindoles. The corresponding boronates were obtained in good yields, under operationally simple and environmentally friendly conditions, using ethanol as the solvent. Our studies revealed that water-based systems were not very effective. Furthermore, the obtained products are amenable to further elaboration and can be useful to the synthesis of a broader range of oxindole-containing molecules with biological relevance.

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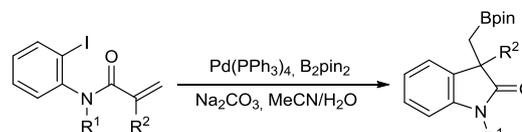
The oxindole heterocyclic system has attracted the attention from the synthetic<sup>1</sup> and medicinal chemistry<sup>2</sup> communities with a number of biologically relevant molecules bearing this substructural unit reported in the literature. Examples of natural products include the convolutamidines,<sup>3</sup> horsifiline,<sup>4</sup> and dioxibrassinin.<sup>5</sup> In addition, the synthetic tyrosine-kinase inhibitors SU-9516, semaxanib (SU-5416) and sunitinib (SU-11248), displaying antiangiogenic properties, have also been reported.<sup>6</sup>



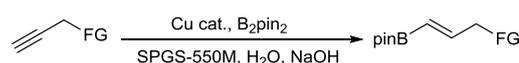
**Figure 1.** Representative examples of oxindoles

Reports regarding strategies for the synthesis of oxindole systems bearing a boronate moiety are scarce in the literature. To the best of our knowledge, the only reported approach was independently described by Van der Eycken<sup>7</sup> and Ma/Xu,<sup>8</sup> both using the Pd-catalyzed intramolecular Heck reaction, followed Miyaura borylation with B<sub>2</sub>pin<sub>2</sub> to assemble the desired compounds (Scheme 1A).

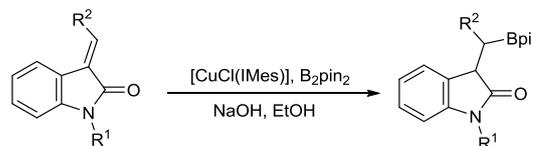
#### A) Palladium-catalyzed Heck Reaction/Miyaura Borylation



#### B) Previous work: Cu-catalyzed hydroboration of alkynes



#### C) This work: NHC-Cu(I)-catalyzed Borylation



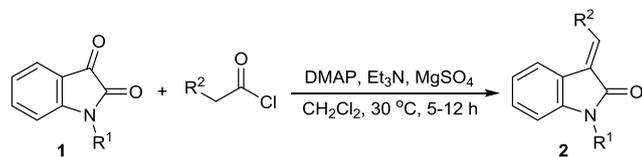
**Scheme 1.** Literature precedents for the borylation of isatins and this work

Recently, we have been interested in developing efficient and environmentally friendly synthetic methods using organoboron chemistry and we have developed a copper-catalyzed borylation of propargyl-functionalized alkynes that enabled the synthesis of vinylboronates in water, in the presence of a surfactant (Scheme 1B).<sup>9</sup> Furthermore we have further expanded the concept and developed the one-pot, dual metal catalytic synthesis of arylallylamines in water, through a Cu-catalyzed borylation, followed by a Pd-catalyzed Suzuki coupling.<sup>10</sup>

Considering the growing interest on the synthesis of organoboron compounds with potential biological activities<sup>11</sup> and the pressing need for the replacement of hazardous solvents by

greener alternatives,<sup>12</sup> herein we report our studies for the copper-catalyzed borylation of alkenyl oxindoles in ethanol and water, that are solvents with excellent EHS (Environmental, Health and Safety) properties (Scheme 1C).

We started our investigation by the synthesis of the required unsaturated starting materials, by the cyclization/decarboxylation method reported by Xu and Wang (Scheme 2).<sup>13</sup> The method consists is reaction of the *N*-alkylated isatin **1** with acyl chlorides, in the presence of DMAP, Et<sub>3</sub>N and MgSO<sub>4</sub>. Under these conditions the desired alkenyl oxindoles have been obtained in 45-88% yield.



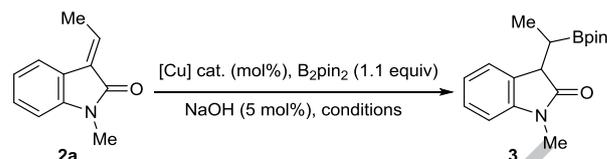
- 2a** R<sup>1</sup> = Me, R<sup>2</sup> = Me: 70% yield  
**2b** R<sup>1</sup> = Bn, R<sup>2</sup> = Me: 60% yield  
**2c** R<sup>1</sup> = Boc, R<sup>2</sup> = Me: 45% yield  
**2d** R<sup>1</sup> = Bn, R<sup>2</sup> = Ph: 40% yield  
**2e** R<sup>1</sup> = Bn, R<sup>2</sup> = Cy: 53% yield  
**2f** R<sup>1</sup> = Bn, R<sup>2</sup> = *i*-Pr: 88% yield  
**2g** R<sup>1</sup> = Bn, R<sup>2</sup> = *t*-Bu: 50% yield  
**2h** R<sup>1</sup> = Me, R<sup>2</sup> = C<sub>5</sub>H<sub>11</sub>: 75% yield  
**2i** R<sup>1</sup> = Bn, R<sup>2</sup> = C<sub>8</sub>H<sub>17</sub>: 45% yield

**Scheme 2.** Preparation of the starting materials

With the required starting material in hand, we started to investigate the conditions for the hydroboration of the conjugated double bond present at the alkenyl oxindole system.<sup>14</sup> Compound **2a** with R<sup>1</sup> and R<sup>2</sup> as methyl groups was chosen as the model substrate for the optimization studies, and the results are depicted in Table 1.

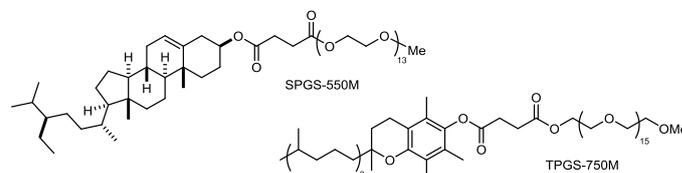
First, we have submitted **2a** to the catalytic conditions that have been previously used with success in our work for the hydroboration of propargyl-functionalized alkynes, using micellar conditions.<sup>9</sup> Reaction using Cu(OAc)<sub>2</sub> as the copper source and diphenylphosphinoethane (dppe) as the ligand in SPGS-550M/water<sup>15</sup> as the solvent resulted in the desired product in only low yield (Table 1, entry 1). Slight increase in the yield was achieved with the use of the *N*-heterocyclic carbene-based catalyst [CuCl(IMes)] and the product was obtained in 54% yield (entry 2). An attempt to further increase the yield by increasing the amount of B<sub>2</sub>pin<sub>2</sub> from 1.1 equiv to 1.5 equiv didn't result in any significant improvement (entry 3). Gratifyingly, we observed that the reaction time could be shortened to only 4 h without compromising the yield of the isolated product. Importantly, the work-up method has a significant impact on the isolated yield and when the product was extracted from the reaction mixture using a conventional extraction procedure, the isolated yield increased from 55 to 83% (compare entries 4 and 5). Despite this significant improve in the product recovery, we still sought to find a greener alternative. Pleasingly, we found out that simply filtering the reaction mixture directly through sodium polyacrylate (readily found in baby's diapers<sup>15c</sup>) placed at the top of a silica gel column easily retained the water present in the reaction mixture, allowing the easy recovery of the pure product from the chromatographic procedure in the same yield as obtained in conventional extraction with EtOAc (entry 6). Additional decrease in the reaction time to 2 h resulted in a decrease yield (entry 4-6). Using a different NHC-Cu complex also led to lower reaction yield of the desired product (entry 8).

**Table 1.** Optimization of the reaction conditions for the Cu-catalyzed hydroboration



Entry	[Cu] cat. (mol%)	solvent	time (h)	Yield (%) <sup>a</sup>
1 <sup>b</sup>	Cu(OAc) <sub>2</sub> (8) dppe (10)	SPGS-550M/H <sub>2</sub> O	18	37
2 <sup>b</sup>	[CuCl(IMes)] (5)	SPGS-550M/H <sub>2</sub> O	18	54
3 <sup>b,c</sup>	[CuCl(IMes)] (5)	SPGS-550M/H <sub>2</sub> O	18	65
4 <sup>b</sup>	[CuCl(IMes)] (5)	SPGS-550M/H <sub>2</sub> O	4	55
5 <sup>d</sup>	[CuCl(IMes)] (5)	SPGS-550M/H <sub>2</sub> O	4	83
6 <sup>e</sup>	[CuCl(IMes)] (5)	SPGS-550M/H <sub>2</sub> O	4	83
7 <sup>e</sup>	[CuCl(IMes)] (5)	SPGS-550M/H <sub>2</sub> O	2	81
8 <sup>e</sup>	[CuCl(IPr)] (5)	SPGS-550M/H <sub>2</sub> O	4	41
9 <sup>e</sup>	[CuCl(IMes)] (5)	TPGS-550M/H <sub>2</sub> O	4	80
10 <sup>d</sup>	[CuCl(IMes)] (5)	H <sub>2</sub> O	4	87
11 <sup>e</sup>	[CuCl(IMes)] (5)	H <sub>2</sub> O	4	85
<b>12</b>	<b>[CuCl(IMes)] (5)</b>	<b>EtOH</b>	<b>4</b>	<b>97</b>

<sup>a</sup>Isolated yield; experiments performed on a 0.3 mmol scale. <sup>b</sup>work-up by the addition of anhydrous MgSO<sub>4</sub> and washing with EtOAc (3 x 1 mL). <sup>c</sup>1.5 equiv B<sub>2</sub>pin<sub>2</sub>. <sup>d</sup>conventional work-up using brine and EtOAc (3 x 5 mL). <sup>e</sup>direct filtration of the reaction mixture through sodium polyacrylate (from a baby's diaper) at the top of a silica gel column. Note: SPGS-550M and TPGS-750M are commercially available as 2 wt% in water.

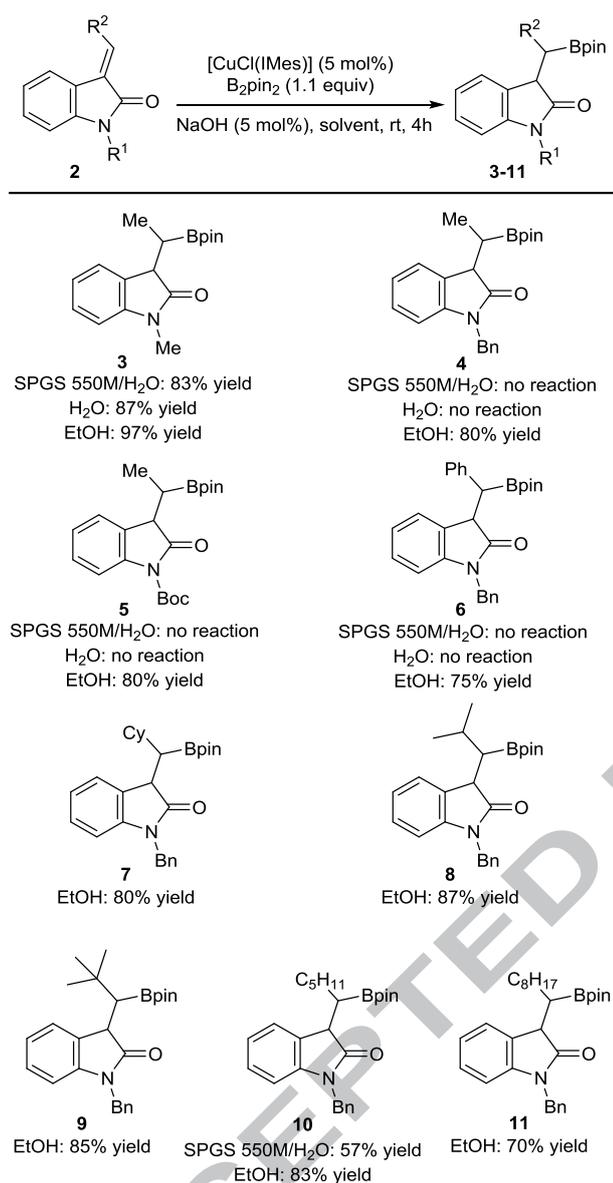


Our next study involved evaluation of the role of the reaction solvent. Changing the surfactant from SPGS-550M to TPGS-550M didn't result in any change in the reaction (entry 9). On the other hand, using pure water resulted in a slight increase in the yield to 87% (entries 10-11). Gratifyingly, when the water-based systems were replaced by ethanol, full conversion was achieved and the desired product **3** was isolated in 97% yield (entry 12). Importantly, the reaction is performed in an open vessel, without any precautions to exclude air and moisture, and using undried 95% ethanol as the solvent.

With the optimized conditions, we have studied the reaction using different substituent both at R<sup>1</sup> and R<sup>2</sup> in order to examine the scope of this Cu-catalyzed hydroboration reaction (Scheme 3).

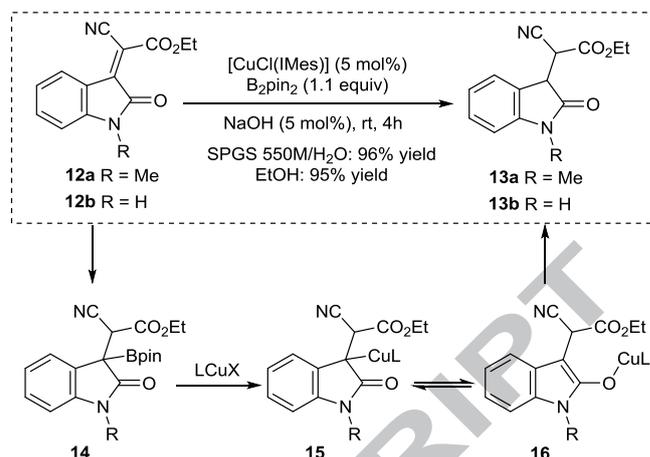
Examining the scope of the reaction reveals that our protocol is tolerant to the presence of common protecting groups at the nitrogen such as the *N*-Bn and *N*-Boc derivatives **4** and **5**. The reaction also works efficiently for different alkyl chains at the R<sup>2</sup> position and it tolerates branched (**8-9**), longer linear (**11**), and cyclic chains (**7**). Additionally, the presence of a phenyl group was also possible and the corresponding product **6** was obtained in 75% yield. It's worth pointing out that ethanol is a more robust solvent for the reactions, while in water (with or without

surfactant) did not result in efficient formation of the desired products.



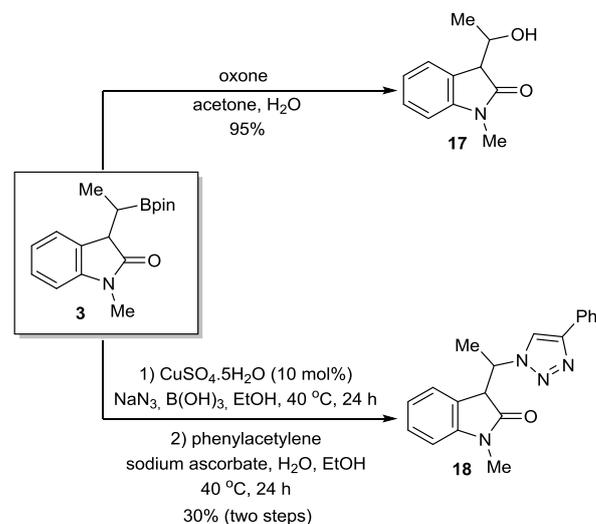
**Scheme 3.** Scope of the Cu-catalyzed borylation

Interestingly, when an alkenyl oxindoles **12a-b** bearing two electron-withdrawing group at the double bond was tested as substrates for the hydroboration reaction,<sup>16</sup> the borylated products were not isolated. Instead, the products of the reduction of the double bond **13**, were isolated in excellent yields, presumably through a hydroboration/protodeboration sequence either using aqueous micellar conditions or ethanol as the solvent (Scheme 4). In this system, the borylation reaction would have occurred with reverse regioselectivity, yielding boronate **14**. This compound underwent fast transmetalation with the catalyst to form a Cu(I)-enolate **16**, that can be protonated delivering the observed product **13**.<sup>17</sup>



**Scheme 4.** Borylation/protodeboration of alkenyl oxindole **12**

To highlight the utility of the obtained boronates, we have reacted boronate **3** with oxone in an acetone/water solution resulted in the oxidation of the Bpin moiety to deliver the corresponding alcohol **17** in 95% yield (Scheme 5). Additionally, the boronate was also converted to corresponding 1,2,3-triazole **18**, through a two-step, one-pot, copper-catalyzed azidation-[3+2]-cycloaddition reaction. The azide was generated *in situ* by a azidation of the boronate with NaN<sub>3</sub>. After the consumption of the boronate, phenylacetylene and sodium ascorbate were added to the reaction mixture and the 1,2,3-triazole was obtained as the final product in 30% yield (two steps).



**Scheme 5.** Utility of the product

In summary, we have described the copper-catalyzed hydroboration of alkenyl oxindoles. The corresponding boronates were obtained in good yields, under operationally simple and environmentally friendly conditions, using ethanol as the solvent. Water-based systems were not very effective. Furthermore, the obtained products are amenable to further elaboration and can be useful to the synthesis of a broader range of oxindole-containing molecules with biological relevance.

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## Supplementary Material

Supplementary material available: Detailed experimental procedures and analytical data. Copies of NMR spectra.

**Highlights:**

Synthesis of organoboron compounds  
with potential biological activities

Pressing need for the replacement of  
hazardous solvents by greener  
alternative

Cu-catalyzed borylation of alkenyl  
oxindoles in ethanol and water

Boronates obtained in good yields,  
under environmentally friendly  
conditions