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Synthesis of β-Boryl-α,β-unsaturated Carbonyl Compounds via Palladium-Catalyzed Cross-Coupling Reaction of Bis(pinacolato)diboron with Vinyl Triflates

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Received XXXX
Use for Graphical Abstract Only

\[
\text{pin}_2\text{B}_2 + \text{TiO} \quad \overset{\text{PdCl}_2(\text{PPh}_3)_2-Z\text{PPh}_3}{\text{base}} \quad \rightarrow \quad \text{pinB} \quad \overset{\text{R}_1}{\text{R}_2} \quad \overset{\text{Y}}{\text{COY}}
\]

\[\text{pin} = \text{Me}_3\text{C}_2\text{O}_2 \quad \text{Y} = \text{OR}, \text{NR}_2, \text{R}\]
Abstract: Cross-coupling reaction of bis(pinacolato)diboron with β-(trifluoromethanesulfonyloxy)-α,β-unsaturated carbonyl compounds was carried out in the presence of PdCl$_2$(PPh$_3$)$_2$-2PPh$_3$ (3 mol%) and KOPh in toluene or K$_2$CO$_3$ in dioxane for the synthesis of cyclic and acyclic β-boryl-α,β-unsaturated esters, amides, and ketones in high yields.

Key words: diboron, vinyl triflate, palladium, cross-coupling, catalysis

β-Boryl-α,β-unsaturated carbonyl compounds are attractive synthetic intermediates which allow inter- or intramolecular Diels-Alder reaction, asymmetric dipolar cycloaddition or 1,4-addition, cyclopropanation, and radical addition. Although β-borylacrylates are available via hydroboration of propiolic acid esters, preparation of the corresponding ketone and aldehyde derivatives requires a multi-step procedure and there are few reports for cyclic or polysubstituted derivatives. In connection with our interest in the synthesis of organoboron compounds via the cross-coupling reaction of diborons with organic electrophiles including aryl, vinyl, allyl, and benzyl halides or triflates, we wish to disclose here a palladium-catalyzed cross-coupling reaction of bis(pinacolato)diboron (pin$_2$B$_2$, pin = Me$_4$C$_2$O$_2$) (1) with vinyl triflates (2) to yield the corresponding β-boryl-α,β-unsaturated carbonyl compounds (3) (Eq. 1).

The effects of bases and solvents on the reaction are shown in Table 1. The conditions previously reported for the coupling of pin$_2$ B$_2$ with vinyl halides or triflates (PdCl$_2$(PPh$_3$)$_2$-2PPh$_3$/KOPh/toluene/50 °C) gave borylated products in high yields for most of the vinyl triflates, but the reaction often resulted in very low yields due to a competitive base-induced side-reaction. For example, the reaction of 1 (1.1 mmol) with ethyl 2-(trifluoromethanesulfonyloxy)-1-cyclopentenecarboxylate (1.0 mmol) in the presence of PdCl$_2$(PPh$_3$)$_2$-2PPh$_3$ (0.03 mmol) and KOPh (1.5 mmol) in toluene (6 ml) at 50 °C resulted in 9% yield (Entry 1). Analysis of the reaction mixture revealed the formation of phenyl triflate (90%) resulted by ester-exchange between the triflate and KOPh. A sterically more hindered 2-MeC$_6$H$_4$OK base, which is expected to inhibit the ester-exchange, also produced the corresponding triflate in 69% yield (Entry 2). Alternatively, use of a K$_2$CO$_3$ base in dioxane was found to be effective for such substrates sensitive to the phenoxy anion to promote the desired
coupling in 67% yield (Entry 3). Although $\text{K}_2\text{CO}_3$ was prone to induce further coupling of 3 with 2 giving a dimer of 2 (ca. 30%), stronger bases such as $\text{K}_3\text{PO}_4$ further enhanced the dimerization (Entry 4) and weaker bases such as $\text{KOAc}$ did not promote the coupling (Entry 5). Use of less-polar solvents such as toluene resulted in low conversion (Entry 6). Although the reactions using $\text{K}_2\text{CO}_3$ took longer times at 50 °C, the same reactions were completed at 80 °C within 5 h in dioxane and 24 h in toluene, respectively (Entries 7 and 8).

\[
\text{Table 1}
\]

The palladium-catalyzed cross-coupling of pin$_2\text{B}_2$ 1 with the representative vinyl triflates 2 in the presence of KOPh in toluene at 50 °C (Method A) or $\text{K}_2\text{CO}_3$ in dioxane at 80 °C (Method B) is summarized in Table 2. All 2 including cyclic or acyclic ester, amide, and ketone derivatives were converted into the corresponding β-boryl-α,β-unsaturated carbonyl compounds 3 in high yields by either Method A or B. The reactions were faster under the conditions of Method A than those of Method B; however, the yields highly depended upon the substrates. Method A resulted in low yields due to the formation of phenyl triflate (30-90%) for substrates sensitive to the phenoxy anion, including five-membered ester (Entry 1), six-membered amide (Entry 5), five-membered ketone (Entry 6), and less-hindered six-membered ketone having no substituent at the α carbon (Entry 8). On the other hand, Method A was a better choice for seven- and eight-membered esters (Entries 3 and 4), and acyclic ester (Entry 10), because Method B resulted in the formation of symmetrical 1,3-dienes (15-30%) arising from dimerization of 2. The borylation of acyclic ester and amide derivatives of 2 having $E$ stereochemistry retained completely the configuration of the double bond to give isomerically pure ($Z$)-3 in high yields (Entries 10 and 11).

\[
\text{Table 2}
\]

In general, $E$ or $Z$ configuration of 1-alkenyl halides or triflates can be retained completely in the cross-coupling of organoboron compounds; however, the amide derivative of triflate ($Z$)-4 unexpectedly provided the borylated product ($Z$)-5 by Method A and a mixture of ($Z$)-5 and ($E$)-5 (64:36) by Method B (Eq. 2). Monitoring of a benzene-$d_6$ solution of the ($Z$)-4 or ($E$)-5 in the presence of Pd($\text{PPh}_3$)$_4$ and KOPh by $^1\text{H}$ NMR and GC at 50 °C resulted in no conversion into ($E$)-4 or ($Z$)-5, suggesting the isomerization during the catalytic process. It remains unclear which step is responsible for such isomerization; however, a vinylpalladium(II) species generated by oxidative addition of a vinyl halide or triflate to a palladium(0) complex often undergoes $E$-$Z$ isomerization.
The direct preparation of $\beta$-boryl-$\alpha,\beta$-unsaturated carbonyl compounds 3 from pin$_2$B$_2$ 1 and the corresponding vinyl triflates 2 now allows a one-pot, two-step procedure for the synthesis of ketone or ester derivatives of unsymmetrical 1,3-dienes 7 (Table 3). The stereoselective syntheses of three dienes 7 were easily achieved in 76%, 76%, and 77% yields when the borylation of 2 (1.1 mmol) with 1 (1.1 mmol) was directly followed by the coupling with another vinyl triflate 6 (1.0 mmol). A combination of PdCl$_2$(dppe) (0.03 mmol) and K$_3$PO$_4$ (3.0 mmol) in dioxane at 80 °C was recognized to be the best conditions for the second coupling. 17

References and Notes
(10) (a) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. Chem. Lett. 2000, 126. (b) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. J. Am. Chem. Soc. 2002, 124, 8001 and difficulties to apply the reaction conditions used for the borylation of aryl electrophiles to that of vinyl electrophiles have been described therein.
A representative procedure for 3: A flask placed with PdCl$_2$(PPh$_3$)$_2$ (0.03 mmol), PPh$_3$ (0.06 mmol), pin$_2$B$_2$ (1.1 mmol), and KO$\text{P}$h or K$_2$CO$_3$ (1.5 mmol) was flushed with nitrogen. Toluene or dioxane (6 ml) and ethyl 2-(trifluoromethanesulfonyloxy)-1-cyclohexenecarboxylate (1.0 mmol) were then added. The resulting mixture was stirred at 50 °C or 80 °C for the period shown in Table 2. The product was isolated by chromatography over silica gel followed by Kugelrohr distillation to give an analytically pure sample: $^1$H NMR (400 MHz, CDCl$_3$, TMS) $\delta$ 1.27 (t, 3 H, $J$ = 7.2 Hz), 1.33 (s, 12 H), 1.55-1.65 (m, 4 H), 2.20-2.25 (m, 4 H), 4.21 (q, 2 H, $J$ = 7.2 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$, TMS) $\delta$ 14.25, 21.42, 21.85, 24.12, 24.77, 27.93, 60.70, 83.34, 134.24, 169.19; HRMS, Found: m/z, 280.1846. Caled for C$_{15}$H$_{25}$BO$_4$: M$^+$, 280.1846. (17) Recent reviews: (a) Miyaura, N.; Suzuki, A. Chem. Rev. 1995, 95, 2457. (b) Suzuki, A. In Metal-Catalyzed Cross-Coupling Reactions; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, 49. (c) Miyaura, N. Top. Curr. Chem. 2002, 219, 11. (18) (a) Zargarian, D.; Alper, H. Organometallics 1991, 10, 2914. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. Eur. J. Org. Chem. 1999, 1137. (19) The 1,3-dienes 7 shown in Table 3 could be purified by column chromatography over silica gel to give analytically pure samples.
### Table 1 Effects of Bases and Solvents$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base/Solvent</th>
<th>Temp/$^\circ$C</th>
<th>Time/h</th>
<th>Yield/%$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOPh/toluene</td>
<td>50</td>
<td>2</td>
<td>9$^c$</td>
</tr>
<tr>
<td>2</td>
<td>2-MeC$_6$H$_4$OK/toluene</td>
<td>50</td>
<td>2</td>
<td>4$^d$</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$/dioxane</td>
<td>50</td>
<td>16</td>
<td>67$^e$</td>
</tr>
<tr>
<td>4</td>
<td>K$_3$PO$_4$/dioxane</td>
<td>50</td>
<td>16</td>
<td>58$^e$</td>
</tr>
<tr>
<td>5</td>
<td>KOAc/dioxane</td>
<td>50</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$CO$_3$/toluene</td>
<td>50</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>K$_2$CO$_3$/dioxane</td>
<td>80</td>
<td>5</td>
<td>67$^e$</td>
</tr>
<tr>
<td>8</td>
<td>K$_2$CO$_3$/toluene</td>
<td>80</td>
<td>24</td>
<td>65$^e$</td>
</tr>
</tbody>
</table>

$^a$The coupling reaction of diboron 1 (1.1 mmol) with ethyl 2-(trifluoromethanesulfonyloxy)-1-cyclopentene-carboxylate (1.0 mmol) was carried out in the presence of PdCl$_2$(PPh$_3$)$_2$ (0.03 mmol), PPh$_3$ (0.06 mmol), and base (1.5 mmol) in 6 ml of solvent.

$^b$GC yields based on the triflate.

$^c$The reaction accompanied PhOTf (90%).

$^d$The reaction produced 2-MeC$_6$H$_4$OTf (69%).

$^e$The reactions gave a dimer of the triflate (30-40%).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Triflate 2</th>
<th>Yield/%&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Method A&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Triflate 2" /></td>
<td>9 (2 h)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Triflate 2" /></td>
<td>78 (1 h)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Triflate 2" /></td>
<td>76 (1 h)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Triflate 2" /></td>
<td>72 (1 h)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Triflate 2" /></td>
<td>60 (6 h)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Triflate 2" /></td>
<td>21 (1 h)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Triflate 2" /></td>
<td>81 (2 h)</td>
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<tr>
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<td><img src="image8" alt="Triflate 2" /></td>
<td>25 (2 h)</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Triflate 2" /></td>
<td>72 (1 h)</td>
</tr>
<tr>
<td>10</td>
<td><img src="image10" alt="Triflate 2" /></td>
<td>75 (1 h)</td>
</tr>
<tr>
<td>11</td>
<td><img src="image11" alt="Triflate 2" /></td>
<td>93 (1 h)</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were conducted by using diboron 4 (1.1 mmol), triflate 2 (1.0 mmol), PdCl₂(PPh₃)₂ (0.03 mmol), PPh₃ (0.06 mmol), base (1.5 mmol), and solvent (6 ml).

<sup>b</sup>GC yields based on triflates 2.

<sup>c</sup>Method A: KOH/toluene/50 °C.

<sup>d</sup>Method B: K₂CO₃/dioxane/80 °C.
Table 3 One-Pot Synthesis of 1,3-Dienes 7<sup>a</sup>

\[
1 \rightarrow 2 \xrightleftharpoons{\text{Pd cat}} \xrightarrow{\text{base}} [3] \rightarrow 7 \quad \text{Y} = \text{OR, R}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,3-Diene 7&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield/%&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1" alt="Diagram" /></td>
<td>76&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="2" alt="Diagram" /></td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td><img src="3" alt="Diagram" /></td>
<td>77</td>
</tr>
</tbody>
</table>

<sup>a</sup>To a solution of 1-alkenylboronate 3 resulted by the reaction of diboron 1 (1.1 mmol) with triflate 2 (1.1 mmol) in toluene or dioxane (4 ml) were added second triflate 6 (1.0 mmol), PdCl<sub>2</sub>(dpff) (0.03 mmol), K<sub>3</sub>PO<sub>4</sub> (3.0 mmol), and dioxane (4 ml), and the mixture was stirred at 80 °C for 16 h.

<sup>b</sup>Left part of dotted line comes from 2 and right part from 6.

<sup>c</sup>Isolated yields based on triflates 6.

<sup>d</sup>GC yield after 5 h.
\[
\text{pin}_2\text{B}_2 + \text{SHO} + \text{COY} \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2-2\text{PPH}_3, \text{base}} \text{R}^1 \text{COY} \rightarrow \text{pinB} \text{COY} \quad (1)
\]

\[
\text{1} \quad \text{2} \quad \text{3}
\]

Y = OR, NR_2, R

\[
\text{1} + \text{TFO} + \text{CONET}_2 \xrightarrow{\text{PdCl}_2(\text{PPH}_3)_2-2\text{PPH}_3, \text{base}} \text{pinB} \quad \text{CONET}_2 \rightarrow \quad (2)
\]

\[
\text{4} \quad \text{5}
\]

\[
Z > 99% \\
K_2\text{CO}_3/\text{dioxane}/80 \degree\text{C}/5 \text{ h}: \quad 91% \ (Z = 64%)
\]

\[
\text{KOPh/toluene}/50 \degree\text{C}/1 \text{ h}: \quad 88% \ (Z > 99%)
\]