Title

Instructions for use

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Synthesis of Pinacol Allylic Boronic Esters via Olefin Cross-Metathesis between Pinacol Allylboronate and Terminal or Internal Alkenes

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Abstract: The ruthenium-catalyzed olefin cross-metathesis between pinacol allylboronate, \( \text{CH}_2=\text{CHCH}_2\text{B(O}_2\text{C}_2\text{Me}_4) \), and \( \text{RCH}=\text{CH}_2 \) giving \( \text{RCH}=\text{CHCH}_2\text{B(O}_2\text{C}_2\text{Me}_4) \) was carried out in refluxing \( \text{CH}_2\text{Cl}_2 \) in the presence of an alkylidene-ruthenium complex (3 mol%).

Key words: allylboron, olefin cross-metathesis, ruthenium catalyst

Reactions of allylboronates with aldehydes or ketones have proved to be very efficient for diastereoselective building of several adjacent chiral centers.\(^1\) Allylboronic esters can be best synthesized by transmetalation between an allylmagnesium or -lithium reagent and \((\text{RO})_3\text{B}.\(^2\) A more general approach including synthesis of chiral allylboronates is to add an isomerically pure alkenylmetal to a \((\alpha\text{-haloalkyl})\text{boronic ester}.\(^3\) These methods utilizing lithium or magnesium reagents are convenient for unfunctionalized derivatives, but they are limited by the lack of compatibility with functional groups. Herein, we report an alternative method for the synthesis of allylic boronic esters via olefin cross-metathesis\(^4\) between a pinacol allylboronate (2) and a terminal or internal alkene (Scheme 1). Grubbs's alkylidene-ruthenium complexes (3, 4) in refluxing \( \text{CH}_2\text{Cl}_2 \) provided variously functionalized allylboronic esters (5) in high yields. Although the metathesis reaction has been used much less frequently for the preparation of organoboron compounds, synthesis of cyclic alkenylboronates via ring-closing metathesis has recently been demonstrated by Renaud and Ouellet.\(^7\)

Pinacol allylboronate 2 in \( \text{CH}_2\text{Cl}_2 \) was treated with an alkene (1, 2 equivs) in the presence of an alkylidene-ruthenium complex (3 or 4, 3 mol%). After being refluxed for 24 h, the reaction mixture was directly treated with benzaldehyde (2 equivs) to quantitatively convert pinacol allylboronate 5 to homoallyl alcohol 89. The reaction was run in a flask equipped with an oil bubbler at the top of a condenser and at the reflux temperature of \( \text{CH}_2\text{Cl}_2 \). The slow bubbling of argon into the \( \text{CH}_2\text{Cl}_2 \) solution to release ethylene generated by the metathesis or the reaction in benzene or 1,2-dichloroethane resulted in significantly low yields. Pinacol can be the best protecting group of allylboronic acid since the reaction failed for the corresponding 2,2-dimethyl-1,3-propanediol ester or 1,2-ethanediol ester.

The reaction of 2 with a stoichiometric amount of styrene giving the desired cross-metathesis product 5 (R=Ph, 40%) was accompanied by the formation of two homodimerization products 6 (20%) and 7 (R=Ph, trace). The product ratio was highly depended on the stoichiometry of added styrene. For example, homodimerization of 2 afforded a high yield of 6 (85%), whereas it was very slow for styrene (7: R=Ph, 37%). Thus, all reactions were carried out in the presence of a large excess of alkene, typically 2 equivalents of a terminal or internal alkene, to minimize the formation of 6. Under these conditions, pinacol cinnamylboronate 5 (R=Ph) was selectively produced and was easily isolated by Kugelrohr distillation \textit{in vacuo} (74%, \( E/Z = 91/9 \)).
however, selective synthesis of 5 can be more difficult for aliphatic derivatives because the reactivity of aliphatic alkenes is comparable to that of 2.

Due to the difficulty in isolating pure 5 in small-scale runs, the reaction mixture was directly trapped with benzaldehyde; however, the formation of 5 and their cis/trans ratios can be estimated from the yields and the diastereomeric ratios of 8/9. In situ treatment of the reaction mixture of 2 and styrene, or the isolated 5 (R=Ph, E/Z=90/10), with benzaldehyde at room temperature overnight afforded 1,2-diphenyl-3-butenol 8/9 (R=Ph, 91/9). Thus, the correlation between the E/Z ratio of 5 and anti/syn selectivity (8/9) was consistent with the previous findings that E-5 affords 8 and Z-5 yields 9 in allylboration of aromatic and aliphatic aldehydes.3c

The results of the olefin cross-metathesis between 2 and representative alkenes are summarized in Table 1. Aliphatic and terminal alkenes afforded the corresponding homoallyl alcohols in 55-94% yields with 52-96% anti-selectivities (entries 1-7). Among them, methyl 3-butenoate exhibited an exceptionally high anti-selectivity (anti/syn=96/4), thus suggesting a predominant formation of the E-allylboronate ester (entry 6), which in striking contrast to the corresponding molybdenum-catalyzed reaction of allyltrimethylsilane5 or allyltributylstanane6 that resulted in a mixture of cis- and trans-isomers. Such an effect of a neighboring group can be best explained by chelation of a carbonyl oxygen to the ruthenium metal center (10), as was suggested to occur in analogous metathesis reactions of unsaturated amides (11 and 12)8,9 (Scheme 2). Internal alkenes such as (E)- and (Z)-4-octene afforded comparable yields and selectivities to those of terminal alkenes (entries 8 and 9). The ruthenium catalyst 4 was used for the methallyl ester due to inefficiency of 3 for such 1,1-disubstituted alkenes (entry 10). High yields and high diastereoselectivities exceeding 90% were commonly achieved for styrene and its para-substituted derivatives (entries 11-13). The bulkiness of the aryl ring may serve to increase (E)-selectivity and to reduce homodimerization to 1,2-diarylethene. On the other hand, all attempts at metathesis of 2 with acrylonitrile, ethyl acrylate, or phenyl vinyl ether failed.

Finally, the utility of the protocol was demonstrated in the synthesis and reaction of a chiral allylboration reagent 14 (Scheme 3). Under conditions analogous to those used for the pinacol ester, cross-metathesis between tartrate ester 13 and methyl 3-butenoate was completed within 24 h. Allylboration of aldehydes at -78 °C for 5 h was followed by acid-catalyzed lactonization to provide 16a-c (syn/anti=96/4). Although the enantioselectivities depended greatly upon the aldehydes employed, the reaction with 3-methyl-2-butenal achieved 82%ee.10
Representative procedure: A 25-ml flask, connected through the condenser to a nitrogen source and an oil bubbler, was charged with a ruthenium catalyst (3, 0.03 mmol) and flushed with argon. Dry dichloromethane (5 ml), styrene (2 mmol), and pinacol allylboronate (2, 1 mmol) were added successively. After being refluxed for 24 h, benzaldehyde (2 mmol) was added and the mixture was then stirred at room temperature overnight. The product was extracted with ether, washed with brine, dried over MgSO₄, and finally chromatographed over silica gel with hexane/ether (2/1). 8 (R=Ph): ¹H NMR (400 MHz, CDCl₃) δ 7.04-7.38 (m, 10 H), 6.25 (ddd, 1 H, J=17.1, 10.2 and 8.9 Hz), 5.27 (d, 1 H, J=10.2 Hz), 5.23 (d, 1 H, J=17.1 Hz), 4.85 (dd, 1 H, J=7.8 and 2.4 Hz), 3.55 (dd, 1 H, J=8.3 and 8.3 Hz), 2.30 (d, 1 H, J=2.7 Hz); minor signals of 9 appeared at δ 5.90 (ddd, 1 H, J=17.2, 10.3 and 7.8 Hz), 4.91 (d, 1 H, J=8.3 Hz), 3.64 (dd, 1 H, J=8.1 and 8.1 Hz).

References and Notes
2000, 39, 3101.
10. 16c: HPLC on Chiralcel OB-H (Dcel Co., Ltd) with hexane/2-propanol (99.5/0.5) showed 82% ee; $[\alpha]_D^{25} = +37.5$ (c 1.02, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.73 (ddd, 1 H, $J$=17.1, 10.2 and 8.3 Hz), 5.11-5.29 (m, 4H), 3.24 (dddd, 1 H, $J$=7.6 Hz), 2.69 (dd, 1 H, $J$=17.3 and 8.0 Hz), 2.50 (dd, 1 H, $J$=17.3 and 7.6 Hz), 1.78 (s, 1 H), 1.71 (s, 1 H). Two percent of NOE was observed between two hydrogens at the carbon atoms attached to ethenyl and 2-methyl-1-propenyl group; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 18.4, 25.8, 34.3, 43.7, 79.7, 117.7, 118.7, 134.3, 140.3, 176.2; exact mass calcd for C$_{10}$H$_{14}$O$_2$ 166.0994, found 166.0992
Table 1. Synthesis of Pinacol Allylic Boronates via Cross-Metathesis between 2 and Terminal or Internal Alkenes<sup>a</sup>

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>yield/%&lt;sup&gt;b&lt;/sup&gt;</th>
<th>anti/syn (8/9)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1-octene</td>
<td>62</td>
<td>75/25</td>
</tr>
<tr>
<td>2</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>55</td>
<td>52/48</td>
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<tr>
<td>3</td>
<td>BrCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>69</td>
<td>78/22</td>
</tr>
<tr>
<td>4</td>
<td>BrCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>71</td>
<td>69/31</td>
</tr>
<tr>
<td>5</td>
<td>PhOCH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>79</td>
<td>67/33</td>
</tr>
<tr>
<td>6</td>
<td>MeO&lt;sub&gt;2&lt;/sub&gt;CCH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>94</td>
<td>96/4</td>
</tr>
<tr>
<td>7</td>
<td>MeCO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>67</td>
<td>63/36</td>
</tr>
<tr>
<td>8</td>
<td>(E)-4-octene</td>
<td>55</td>
<td>78/22</td>
</tr>
<tr>
<td>9</td>
<td>(Z)-4-octene</td>
<td>57</td>
<td>73/27</td>
</tr>
<tr>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>PhCO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;C(CH&lt;sub&gt;3&lt;/sub&gt;)=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>49</td>
<td>81/19</td>
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<tr>
<td>11</td>
<td>PhCH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>88</td>
<td>91/9</td>
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<tr>
<td>12</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>87</td>
<td>91/9</td>
</tr>
<tr>
<td>13</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CH=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>76</td>
<td>90/10</td>
</tr>
</tbody>
</table>

<sup>a</sup>A mixture of pinacol allylboronate (2, 1 mmol), alkene (2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was refluxed for 24 h in the presence of a ruthenium catalyst (3, 3 mol%). The reaction mixture was then treated with PhCHO (2 mmol) at room temperature for 24 h, unless otherwise noted.

<sup>b</sup>Isolated yields.

<sup>c</sup>Ruthenium catalyst (4, 3 mol%) was used.
Scheme 1. Olefin Cross-Metathesis for Synthesis of Allylboronates (5)
Scheme 2. Chelation Effect
Scheme 3. Synthesis of Chiral Allylboronates