The First Preparation of 4-Substituted 1,2-Oxaborol-2(5H)-ols and their Palladium-Catalyzed Cross-Coupling with Aryl Halides to Prepare Stereodefined 2,3-Disubstituted Allyl Alcohols

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Abstract: 4-Substituted 1,2-oxaborol-2(5H)-ols were prepared through copper-catalyzed carbomagnesation of propargyl alcohol, followed by the transmetallation of magnesium to boron in a one-pot procedure. The Suzuki–Miyaura cross-coupling of these new 2,2-disubstituted alkenylboronic acids with aryl halides afforded stereodefined 2,3-disubstituted allyl alcohols in good to excellent yields.

Key words: alkenylboronic acids, copper-catalyzed carbomagnesation, Suzuki–Miyaura cross-coupling, stereodefined trisubstituted alkenes, disubstituted allyl alcohols

Organoboron reagents, more specifically, alkenylboron compounds (acids, esters, salts, etc.), play an important role in organic transformations and synthesis. In most cases, monosubstituted trans- and cis-alkenylboron compounds were applied to the Suzuki–Miyaura cross-coupling reaction because they were relatively easily available through the hydroboration of alkynes or by other means. There are only a few examples of the synthesis of stereodefined disubstituted alkenylboron compounds (Scheme 1), thus, new methods for the preparation of stereodefined substituted alkenylboronic acids are still required.

Stereodefined trisubstituted alkenes exist widely in both natural and non-natural products, but their synthesis is still a challenging problem in synthetic organic chemistry. Both trisubstituted alkenes and disubstituted allyl alcohols are also important intermediates in organic synthesis which can, for example, be hydrogenated or isomerized to aldehydes enantioselectively. Substituted allyl alcohols are usually prepared by the Reformatsky reaction of the corresponding ketone or by a Horner–Wadsworth–Emmons reaction, but a mixture of isomers is often obtained. It was reported that stereodefined 3,3-disubstituted allyl alcohols were obtained through the palladium-catalyzed cross-coupling of 3-hydroxypropylstannane (Scheme 2) or -aluminum (Scheme 3) with electrophiles; while 2,3-disubstituted allyl alcohols were available through the copper-catalyzed carbomagnesation of 3-substituted propargyl alcohols, followed by hydrolysis of the alkenylmagnesium intermediates (Scheme 4).
Herein, we wish to report the synthesis of a new series of stereodefined 2,2-disubstituted alkenylboronic acids via copper-catalyzed carboxynamnesation of propargyl alcohol, followed by transmetalation from magnesium to boron, and their palladium-catalyzed coupling with aryl halides to give stereodefined 2,3-disubstituted allyl alcohols (Scheme 5) which have a different configuration than that obtained via the route showed in Scheme 4.

Our starting point was a report on the catalytic addition (CuI, 10%; below –10 °C) of organomagnesium reagents to the triple bond of propargyl alcohol, which afforded intermediate 2 (Scheme 5). After some modifications, such as using 2.2 equivalents of Grignard reagents and THF in place of diethyl ether as solvent, the intermediate 2 was obtained, and in situ reaction with trisopropyl borate below –60 °C gave the desired products 3 after hydrolysis in moderate yields (Table 1).

We attempted the reaction with one equivalent of BuLi instead of one equivalent of Grignard reagent to form the lithium salt of propargyl alcohol; subsequent addition of 1.2 equivalents of Grignard reagent gave the same desired compounds 3 after usual workup (Scheme 6). The structures of alkenylboronic acids 3 were confirmed by 1H–1H NOESY, HRMS (EI), and other spectral analyses.

The Suzuki–Miyaura cross-coupling reaction has become a powerful method for the formation of carbon–carbon bonds, and furthermore milder reaction conditions can be used with bulky phosphorus ligands or other types of ligands. After obtaining the new series of 2,2-disubstituted alkenylboronic acids, we investigated their palladium-catalyzed cross-coupling reactions with aryl halides especially with aryl chlorides using Buchwald’s phosphorus ligands. The optimum conditions for the coupling of 2,2-disubstituted alkenylboronic acids with aryl halides were studied using 3b as an example (Table 2). Under standard Suzuki–Miyaura conditions (Table 2, entries 1 and 2), the cross-coupling reactions of 2,2-disubstituted alkenylboronic acid with aryl bromide proceeded smoothly in moderate yields. Using 2-(di-tert-butylphosphino)bi-phenyl as ligand the cross-coupling reaction of 2,2-disubstituted alkenylboronic acids with aryl bromides proceeded at room temperature in high yield (Table 2, entry 3). None of the desired cross-coupling product was obtained under the standard conditions with aryl chloride as the electrophile, in fact, aryl chloride was recovered from the reaction mixture (Table 2, entry 4). With 2-(dicyclohexylphosphino)biphenyl as ligand, toluene as solvent, and raising the reaction temperature to 100 °C, the cross-coupling product formed in satisfying yield (Table 2, entry 5).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>A New Series of 2,2-Disubstituted Alkenylboronic Acids 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>R</td>
</tr>
<tr>
<td>1</td>
<td>Ph</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
</tr>
<tr>
<td>3</td>
<td>n-Pr</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
</tr>
<tr>
<td>6</td>
<td>(CH2)2Ph</td>
</tr>
<tr>
<td>7</td>
<td>i-Bu</td>
</tr>
</tbody>
</table>

* Reagents: Grignard reagent (220 mmol), propargyl alcohol (100 mmol).

b Isolated yields based on propargyl alcohol.

c Propargyl alcohol (1.0 equiv).

d BuLi (1.0 equiv) used instead of Grignard reagent (1.0 equiv).
The optimized conditions (Table 2, entry 3 for aryl bromides and entry 5 for aryl chlorides) were subsequently applied to the coupling reactions of other substrates (Table 3). The cross-coupling reaction of various 2,2-disubstituted alkenylboronic acids with aryl bromides or aryl chlorides proceeded in good to excellent yields.

\[ \text{HO-BO} \xrightarrow{\text{Pd}[\text{R}]\text{X}} \text{C}_6\text{H}_5\text{OH} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Reaction conditions</th>
<th>Yield (^b) (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>PhBr</td>
<td>PdCl(_2)(PPh_3)_2 (3 mol%), K_3PO_4·3H_2O, toluene, 100 °C</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>PhBr</td>
<td>PdCl(_2)(PPh_3)_2 (3 mol%), K_2CO_3, THF, reflux</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>PhBr</td>
<td>Pd(OAc)_2 (2 mol%), Ligand I (4 mol%), KF·2H_2O, THF, ambient temperature</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>PhCl</td>
<td>PdCl(_2)(PPh_3)_2 (3 mol%), K_3PO_4·3H_2O, toluene, 100 °C</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>PhCl</td>
<td>Pd(OAc)_2 (2 mol%), Ligand II (4 mol%), K_3PO_4·3H_2O, toluene, 100 °C</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>PhCl</td>
<td>Pd(OAc)_2 (2 mol%), Ligand I (4 mol%), KF·2H_2O, THF, ambient temperature</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\) Reagents: 3b (1.0 equiv), PhX (1.2 equiv), base (3.0 equiv), solvent (4.0 mL).
\(^b\) Isolated yields based on the boronic acids used.
\(^c\) Ligand I is 2-(di-tert-butylphosphino)biphenyl; Ligand II is 2-(dicyclohexylphosphino)biphenyl.

The optimized conditions (Table 2, entry 3 for aryl bromides and entry 5 for aryl chlorides) were subsequently applied to the coupling reactions of other substrates (Table 3). The cross-coupling reaction of various 2,2-disubstituted alkenylboronic acids with aryl bromides or aryl chlorides proceeded in good to excellent yields.

\[ \text{HO-BO} \xrightarrow{\text{Pd}[\text{R}]\text{X}} \text{C}_6\text{H}_5\text{OH} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acids 3</th>
<th>ArX</th>
<th>Products 4</th>
<th>Yield (^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3b</td>
<td></td>
<td>4a</td>
<td>86 (A)</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td></td>
<td>4a</td>
<td>89 (A)</td>
</tr>
<tr>
<td>3</td>
<td>3d</td>
<td></td>
<td>4b</td>
<td>83 (A)</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td></td>
<td>4c</td>
<td>80 (B)</td>
</tr>
</tbody>
</table>

\[ \text{HO-BO} \xrightarrow{\text{Pd}[\text{R}]\text{X}} \text{C}_6\text{H}_5\text{OH} \]

Table 3 Cross-Coupling of 2,2-Disubstituted Alkenylboronic Acids 3 with Aryl Halides

In the 1H–1H NOESY spectrum of 4a, proton Hα (δ = 6.42 ppm) showed a strong NOE interaction with Hβ (δ = 2.42–2.35 ppm) with no interaction between Hα and Hγ (δ = 4.29 ppm). The 2D-NOESY spectrum of 4a showed that the product had the same configuration as 3b (Figure 1). In the cross-coupling reaction, the configuration of the double bond was retained.

In conclusion, we have described the first stereodefined preparation of 4-substituted 1,2-oxaborol-2(5H)-ols, a new series of disubstituted alkenylboronic acids. The Suzuki–Miyaura type reaction of the stereodefined organoborons with various haloarenes including unactivated aryl chlorides proceeded well under modified conditions to obtain the corresponding stereodefined 2,3-disubstituted alkenes in good to excellent yields. Haloarenes substituted with various functional groups are tolerated, thus, we have described an efficient method for the preparation of stereodefined 2,3-disubstituted allyl alcohols.

All reactions were carried out under argon unless otherwise noted. B(Oi-Pr)3, Et2O, EtOAc, toluene, aryl chlorides and aryl bromides, CuI, propargyl alcohol, Pd(OAc)2, phosphorous ligand 2-(di-tert-butylphosphino) biphenyl and 2-(dicyclohexylphosphino)biphenyl were obtained from commercial sources and used in reactions without further purification. THF was distilled from sodium benzophenone ketyl. 1H NMR spectra were recorded in CDCl3 on a Varian 300 MHz spectrometer. IR spectra were obtained using a Perkin-Elmer 983 instrument. Mass spectra were obtained using a HP 5989A mass spectrometer.

### Table 3 Cross-Coupling of 2,2-Disubstituted Alkenylboronic Acids 3 with Aryl Halidesa (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acids 3</th>
<th>ArX</th>
<th>Products 4</th>
<th>Yield (%)b</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>3b</td>
<td>Cl</td>
<td></td>
<td>83 (B)</td>
</tr>
<tr>
<td>6</td>
<td>3d</td>
<td>CF3</td>
<td></td>
<td>87 (B)</td>
</tr>
<tr>
<td>7</td>
<td>3b</td>
<td>Cl</td>
<td></td>
<td>85 (B)</td>
</tr>
<tr>
<td>8</td>
<td>3b</td>
<td>Br</td>
<td></td>
<td>84 (A)</td>
</tr>
<tr>
<td>9</td>
<td>3b</td>
<td>COMe</td>
<td></td>
<td>79 (A)</td>
</tr>
</tbody>
</table>

a Reagents: boronic acid (1.0 equiv), aryl halide (1.2 equiv), of Pd(OAc)2 (2 mol%), ligand (4 mol%), base (3.0 equiv), solvent (4.0 mL/mmol), 20 h.
b Isolated yields based on the boronic acids used. A: 2-(di-tert-butylphosphino)biphenyl as ligand, KF·2H2O, THF, ambient temperature; B: 2-(dicyclohexylphosphino)biphenyl as ligand, K3PO4·3H2O, toluene, 100 °C, 20 h.
4-Phenyl-1,2-oxaborol-2(5H)-ol (3a)
White solid.
IR (KBr): 3359, 3030, 2932, 1570, 1497, 1464, 1424, 1228 cm⁻¹.

1H NMR (300 MHz, CDCl₃–D₂O): δ = 7.51–7.37 (m, 5 H), 6.22 (s, 1 H), 4.99 (s, 2 H).

13C NMR (75.5 Hz, CDCl₃–D₂O): δ = 166.6, 133.5, 129.4, 128.7, 125.5, 116.2, 72.5.

MS (EI): m/z (%) = 160 (88), 159 (66), 131 (19), 129 (20), 116 (77), 115 (100), 77 (16), 69 (36).

HRMS (EI): m/z calcd for C₁₁H₁₃BO₂, 180.0695; found, 160.0715.

4-Ethyl-1,2-oxaborol-2(5H)-ol (3b)
Colorless liquid.
IR (liquid film): 3392, 2971, 1602, 1459, 1412, 1197 cm⁻¹.

1H NMR (300 MHz, CDCl₃–D₂O): δ = 5.52 (s, 1 H), 4.46 (s, 2 H), 2.26 (q, J = 7.5 Hz, 2 H), 1.13 (t, J = 7.5 Hz, 3 H).

13C NMR (75.5 Hz, CDCl₃–D₂O): δ = 174.4, 115.6, 74.4, 23.8, 12.0.

MS (EI): m/z (%) = 112 (35), 97 (93), 96 (26), 83 (74), 68 (100), 67 (64), 53 (55).

HRMS (EI): m/z calcd for C₇H₁₃BO₂ [M⁺ – CH₃], 97.0461; found, 97.0459.

4-Propyl-1,2-oxaborol-2(5H)-ol (3c)
Colorless liquid.
IR (liquid film): 3333, 2930, 1601, 1427, 1379, 1203 cm⁻¹.

1H NMR (300 MHz, CDCl₃–D₂O): δ = 5.52 (s, 1 H), 4.45 (s, 2 H), 2.25 (t, J = 7.6 Hz, 2 H), 1.57 (m, 2 H), 0.95 (t, J = 7.5 Hz, 3 H).

13C NMR (75.5 Hz, CDCl₃–D₂O): δ = 72.3, 116.3, 73.9, 32.4, 20.6, 13.5.

MS (EI): m/z (%) = 126 (16), 98 (17), 97 (100), 96 (28), 83 (24), 67 (28), 53 (27), 41 (14).

HRMS (EI): m/z calcd for C₉H₁₉BO₂, 126.0852; found, 126.0858.

4-Butyl-1,2-oxaborol-2(5H)-ol (3d)
Colorless liquid.
IR (liquid film): 3383, 2932, 1602, 1458, 1415, 1240 cm⁻¹.

1H NMR (300 MHz, CDCl₃–D₂O): δ = 5.52 (s, 1 H), 4.45 (s, 2 H), 2.26 (t, J = 7.6 Hz, 2 H), 1.51 (m, 2 H), 1.34 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H).

13C NMR (75.5 Hz, CDCl₃–D₂O): δ = 172.6, 116.0, 74.0, 30.1, 29.5, 22.2, 13.6.

MS (EI): m/z (%) = 98 (27), 97 (100), 96 (61), 81 (29), 67 (27), 54 (52), 53 (43), 41 (44).

HRMS (EI): m/z calcd for C₁₁H₂₁BO₂, 140.1009; found, 140.0988.

4-Isopropyl-1,2-oxaborol-2(5H)-ol (3e)
Colorless liquid.
IR (liquid film): 3437, 2967, 1596, 1457, 1415, 1267 cm⁻¹.

1H NMR (300 MHz, CDCl₃–D₂O): δ = 5.51 (s, 1 H), 4.53 (s, 2 H), 2.53 (m, 1 H), 1.14 (d, J = 6.2 Hz, 6 H).

13C NMR (75.5 Hz, CDCl₃–D₂O): δ = 178.6, 114.4, 72.9, 30.0, 21.4.

MS (EI): m/z (%) = 111 (54), 84 (32), 83 (34), 82 (95), 67 (100), 53 (37), 43 (62), 41 (45).

HRMS (EI): m/z calcd for C₁₁H₁₉BO₂, 126.0852; found, 126.0840.
IR (KBr): 3333, 1617, 1328, 1018 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.92 (d, J = 7.6 Hz, 2 H), 7.33 (d, J = 7.6 Hz, 2 H), 6.47 (s, 1 H), 4.28 (s, 2 H), 2.60 (s, 3 H), 2.34 (t, J = 7.6 Hz, 2 H), 1.59 (m, 2 H), 1.41 (m, 2 H), 0.93 (t, J = 7.2 Hz, 3 H).

13C NMR (75.5 Hz, CDCl₃): δ = 198.0, 144.2, 142.3, 134.3, 134.7, 128.7, 128.2, 126.7, 60.3, 35.1, 30.1, 24.6, 13.9.

MS (EI): m/z (%) = 211 (50), 105 (20), 91 (17), 85 (20), 43 (100).

HRMS (EI): m/z calcd for C₁₁H₁₇F₃O, 230.0986; found, 230.1004.

(Z)-2-[2-Ethyl-3-(4-chlorophenyl)]-2-propen-1-ol (4b)

Colorless liquid.

IR (KBr): 3337, 1617, 1328, 1052 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.29 (d, J = 8.4 Hz, 2 H), 7.18 (d, J = 8.4 Hz, 2 H), 6.39 (s, 1 H), 4.25 (s, 2 H), 2.34 (q, J = 7.4 Hz, 2 H), 1.16 (t, J = 7.4 Hz, 3 H).

13C NMR (75.5 Hz, CDCl₃): δ = 143.5, 135.7, 132.4, 130.0, 128.3, 126.1, 60.9, 28.3, 12.7.

MS (EI): m/z (%) = 196 (46), 179 (37), 167 (100), 128 (35), 127 (39), 115 (40), 55 (35).

HRMS (EI): m/z calcd for C₁₁H₁₁ClO, 196.0462; found, 196.0470.

Z)-1-[2-[2-(Hydroxymethyl)-1-butenyl]benzoate (4i)

Colorless liquid.

IR (KBr): 3337, 1617, 1328, 1016 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.36–7.21 (m, 5 H), 6.45 (s, 1 H), 4.30 (s, 2 H), 2.35 (q, J = 7.5 Hz, 2 H), 1.17 (t, J = 7.5 Hz, 3 H).

13C NMR (75.5 Hz, CDCl₃): δ = 142.8, 137.2, 128.6, 128.0, 126.9, 126.5, 60.7, 30.0, 12.6.

MS (EI): m/z (%) = 162 (36), 145 (100), 133 (50), 129 (16), 115 (25), 105 (22), 91 (37), 55 (15).

HRMS (EI): m/z calcd for C₁₁H₁₃O₃, 162.1045; found, 162.1074.

(Z)-2-[2-Butyl-3-[3,5-di(trifluoromethyl)phenyl]-2-propen-1-ol (4f)

Colorless liquid.

IR (KBr): 3333, 1649, 1467, 1019 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.74 (s, 1 H), 7.72 (s, 2 H), 6.48 (s, 1 H), 4.24 (d, J = 4.7 Hz, 2 H), 2.38 (t, J = 7.6 Hz, 2 H), 1.58 (m, 4 H), 1.38 (m, 2 H), 0.97 (t, J = 7.2 Hz, 3 H).

13C NMR (75.5 Hz, CDCl₃): δ = 145.4, 139.2, 132.1, 131.7, 131.2, 130.8, 128.7, 128.6, 125.3, 125.17, 121.56, 120.30, 120.24, 120.19, 120.14, 120.09, 119.97, 60.17, 35.17, 30.15, 22.48, 13.78.

19F NMR (282.3 MHz, CDCl₃): δ = –63.29.

MS (EI): m/z (%) = 220 (9), 189 (68), 160 (100), 159 (60), 145 (80), 143 (75), 131 (80), 128 (41).

HRMS (EI): m/z calcd for C₁₂H₁₆F₂O, 220.1100; found, 220.1101.

Acknowledgment

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References