Enantio- and diastereoselective synthesis of β-substituted-δ-aminoboronic esters from nitriles

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**A B S T R A C T**

The first stereocontrolled synthesis of the title δ-aminoboronic esters—proceeding from commercially available nitriles—via a reduction, Brown's 'allyl' boration reaction, a Boc-protection, a hydroboration, an oxidative elimination of α-pinene, and an esterification reaction, has been reported in excellent enantio- and diastereoselectivities.

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[Figure 1. Bortezomib (Velcade™).]
Asymmetric synthesis of Boc-protected \( \delta \)-aminoboronic esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile</th>
<th>Homoallylic amine</th>
<th>( \delta )-Aminoboronic ester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>R</td>
<td>No.</td>
</tr>
<tr>
<td>1</td>
<td>1a</td>
<td>C(_6)H(_5)–</td>
<td>2a</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>4- Me-C(_6)H(_4)–</td>
<td>2b</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>4- MeO-C(_6)H(_4)–</td>
<td>2c</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2-Thiophenyl–</td>
<td>2d</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>2-F-C(_6)H(_4)–</td>
<td>2e</td>
</tr>
</tbody>
</table>

\(^a\) Yields refer to analytically pure material (flash chromatography) after three steps.
\(^b\) Yields refer to analytically pure material (flash chromatography) after five steps.
\(^c\) Enantiomeric ratios were determined by Mosher amide analysis using \(^{19}\)F NMR.
\(^d\) Yields are from previous report.\(^{11}\)
\(^e\) Reduction was performed using DIBAL-H.
bulky Ipc₂BH, followed by oxidation with excess acetaldehyde, hydrolysis with dilute hydrochloric acid, and esterification with pinacol provided the product 1-aryl-1-amino-δ-boronic esters 3 in very good overall yields and excellent enantiomeric ratios. The product boronate esters, which were stable under conditions of column chromatography, were obtained as the major enantiomer shown in Table 1. A comparison with literature values of similar compounds was used as confirmation that the stereochemical outcome was the one expected for imine allylation. This stereochemistry, when considered in the context of the stereochemical consistency of other reports of analogous imine allylations, is very reasonable.

The application of these conditions to Brown’s crotyl, and methoxallylboronation reactions was also studied. These synthetic analogs provide an excellent means to introduce further substituents or functionalities vicinal to the amine. We initially explored these reactions, again using lithium triethylborohydride as the nitrile reductant. We found, however, that the use of the less expensive disobutylaluminum hydride (DIBAL-H) offered comparably high enantio- and diastereoselectivities at the expense of only a slight decrease in isolated yield (Table 2).

By following a methodology similar to that above, the formation of crotyl-derived amines was realized. For example, the use of 4-methyl and 4-methoxybenzonitriles, when subjected to the formation of the expected products, again protection, followed reactions was also studied. These synthetic analogs provide an excellent means to introduce further substituents or functionalities vicinal to the amine. We initially explored these reactions, again using lithium triethylborohydride as the nitrile reductant. We found, however, that the use of the less expensive disobutylaluminum hydride (DIBAL-H) offered comparably high enantio- and diastereoselectivities at the expense of only a slight decrease in isolated yield (Table 2).

By following a methodology similar to that above, the formation of crotyl-derived amines was realized. For example, the use of 4-methyl and 4-methoxybenzonitriles, when subjected to the sequential reduction and crotylation conditions, resulted in the formation of the expected products. Again, protection, followed by hydroboration, controlled ligand oxidation, hydrolysis, and esterification, furnished the desired δ-aminoboronic esters. In these cases, the use of the chiral isopinocamphey ligand provided very high levels of stereinduction, with enantiomeric ratios as high as 99:1 or better. As expected, the crotylation of the imines proceeded with excellent diastereomatic ratios.

In conclusion, we have presented herein the first synthesis of δ-aminoboronic esters in a fully stereocontrolled manner. The very high levels of enantio- and diastereoselectivity, when considered in the context of the high synthetic yields obtained, make this a very attractive methodology, and opens a new route for the exploration of these potentially useful δ-aminoboronic esters.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.076.

References and notes

15. Racemic Ipc₂BH was used for hydroboration. Although hydroboration with Br₂BH followed by hydrolysis can be used (Ref. 8a,b), we opted instead for the use of Ipc₂BH, followed by oxidative elimination with acetaldehyde, since this protocol is more economical on a molar basis (Sigma–Aldrich chemical catalog). Furthermore, α-pinene is completely eliminated and is recoverable during this process.

Table 2
Asymmetric synthesis of methylated and methoxylated δ-aminoboronic esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile</th>
<th>Homoallicy amine</th>
<th>δ-Aminoboronic ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>4-Me-CSH₂</td>
<td>4b (69)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>4-Me-CSH₂</td>
<td>5b (56)</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>4-Me-CSH₂</td>
<td>6b (63)</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>4-MeO-CSH₂</td>
<td>4c (59)</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>4-MeO-CSH₂</td>
<td>5c (63)</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>4-MeO-CSH₂</td>
<td>6c (56)</td>
</tr>
</tbody>
</table>

Yields refer to analytically pure material (flash chromatography) after three steps. The yields refer to analytically pure material (flash chromatography) after five steps. The diastereomeric ratios were determined by ¹H NMR analysis of the crude reaction mixture. The enantiomeric ratios were determined by Mosher amide analysis of the major diastereomer using both ¹H and ¹³C NMR.
20. Representative experimental:

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\overset{\text{NH$_2$}}{\text{NHBoc}} & \quad \overset{\text{B(OH)$_2$}}{\text{R}}
\end{align*}
\]

A RB flask was charged with 176 mg KO-t-Bu dissolved in 3 mL THF and cooled to −78 °C. 0.34 mL of E-2-butene (2.5 equiv) was added to the solution, and the mixture was stirred for 5 mins. 0.63 mL of n-butyllithium (1.3 equiv) was then added, and the mixture was stirred for 45 mins at −55 °C. After re-cooling to −78 °C, 1.5 equiv (−)-B-methoxydisopinocamphenylborane (1.44 M in THF) was added, and the mixture was stirred for 1 h. Subsequently, 1.0 equiv N-aluminoimine (1 M in THF) was added, followed by the slow addition of 0.05 mL methanol. After stirring for 4 h at −78 °C, 0.8 mL 3 M NaOH (aq) and 0.5 mL H$_2$O$_2$ (30%) were added sequentially to the mixture. The mixture was warmed to 25 °C over 12 h while maintaining a N$_2$ atmosphere. The product was extracted with Et$_2$O, and the solvent was removed in vacuo. The crude product 4b was then isolated via column chromatography in 69% yield. The material (1.0 equiv) was then transferred into a RB flask, and dissolved in Et$_2$O (0.19 M). To this was added 1.1 equiv Boc$_2$O, followed by 1.2 equiv Et$_3$N. After stirring for 6 h, the solvent was removed in vacuo. The crude material was dissolved in THF (1 M), then was transferred into a suspension of 1.5 equiv disopinocampheyborane in THF (0.84 M). The reaction was stirred for 4 h, then excess acetaldehyde was added. After stirring for 36 h, 1 M HCl (aq) was added, then the product was then extracted with Et$_2$O. The organic layer was concentrated in vacuo, then 1.5 equiv pinacol were added. After stirring for an additional 12 h, the product was extracted with Et$_2$O, and the combined organic layers were washed with brine, dried with Na$_2$SO$_4$, filtered, and concentrated. Purification via column chromatography then furnished the desired (1S,2S)-N-(t-butoxycarbonyl)-2-methyl-1-(4-methylphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-amine product 7b in 64% yield.