Stereodivergent Addition of 4-Silyloxy-1,2-Allenes to Aldehydes by Hydroboration

Carolina Sánchez, Xavier Ariza,* Josep Cornellà, Jaume Farràs, Jordi Garcia,* and Jordi Ortiz[a]

Dedicated to Prof. Pelayo Camps on the occasion of his 65th birthday

Chiral allyl- and crotylboron reagents have demonstrated their value for the stereoselective conversion of aldehydes into homoallicylic alcohols.1 Asymmetric induction is usually controlled by terpenes2,3 and tartrate1 ligands linked to boron or by using chiral aldehydes, or by both methods. However, the use of chiral allyl or crotyl moieties has been less explored.1,4 A careful analysis of the chair-like transition state involved in such additions (Scheme 1) shows that the δ position of the crotyl group can have a direct effect on the stereoselection since it is near to the new C–C bond. In fact, this position (R* in Scheme 1) is as close to the new C–C bond as the α carbon of the aldehyde (R’). Since R’ can exert a pivotal role in the stereoselectivity of the reaction in chiral aldehydes,1 we anticipated that the unexplored use of crotylboron reagents (I) with a stereocenter at the δ position would also provide satisfactory stereoselection.

\[
\text{H} \\
\text{R}^* \begin{array}{c}
\text{O} \\
\text{B} \\
\text{R}\end{array} \begin{array}{c}
\text{O} \\
\text{B} \\
\text{R}\end{array} \begin{array}{c}
\text{H} \\
\text{R}^* \end{array}
\]

Scheme 1. Crotylboron addition to aldehydes

A serious challenge in the allylboration of aldehydes arises from the stereoselective preparation of the required crotylboron reagents, particularly when they are highly functionalized. In many cases, preparation involves the use of 2-alkenyl metal reagents that are incompatible with some functionalities.1d The hydroboration of allenes5 might be a versatile alternative to the preparation of crotylborane I since it obviates the use of transient reactive organometallics.1d In our search for new methods for the preparation of polyols,7 we anticipated that the hydroboration of allene II, which has a stereocentre next to the allenyl moiety, followed by the addition to an aldehyde would afford 1,3 diols with high stereoselectivity (Scheme 2).

Our initial proposal for allene II was (S)-nonan-1,2-dien-3-ol protected as tert-butyldimethylsilil ether ((S)-1), which is easily obtained from commercially available (S)-3-octin-1-ol in two steps.8 Thus, allene (S)-1, was hydroborated with dicyclohexylborane (1.1 eq) in CH₂Cl₂ at rt for two hours (Scheme 3) and then isobutyraldehyde (1.4 eq) was added at -78 °C. Pleasingly, the reaction afforded the expected 1,3-diol as a major isolable syn,syn-3a stereoisomer (>99:1 er),9 in good yield. In addition to the major syn,syn isomer, a small amount of a 7:3 mixture of anti,syn and anti,anti was also isolated.

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The observed syn,syn and anti,anti relative configurations for the major isomer of 3a agree with those expected for the addition of thermodynamically favoured 2-alkenylborane (E)-2 to both faces of the aldehyde through a chair-like transition state (Scheme 1), whereas the anti,anti isomer could have arisen in a similar way from (Z)-2. Thus, we concluded that although the Z isomer is probably formed faster in the hydroboration step for sterics, it undergoes extensive isomerization to its $E$ isomer at rt by a known boratropic allylic rearrangement. According to the data, the facial selectivity of the crotal reagent (E)-2 generated in situ in the addition was 93:7 (ratio syn,syn:anti,anti).

We explored the scope of this reaction with a set of representative aldehydes (Table 1). Satisfactory yields of isolable syn,syn-3 were consistently obtained for both aliphatic and aromatic aldehydes, again showing the high facial selectivity (ratio syn,syn:anti,syn) of the transient E crotal reagent generated by hydroboration ($E$/Z ratio ~95:5).

The effect of the protecting group in the allene was also examined. When TBS was replaced by TBDPS in allene 1 similar yields and selectivities were observed in the addition to benzaldehyde. The corresponding homoallylic alcohol was obtained in 77% yield with a 95:5 syn,syn/anti,anti diastereomeric ratio. Other $O$-protecting groups on nonan-1,2-dien-3-ol such as acetyl or benzyl or even the unprotected allenol did not afford the expected products.

Major syn,syn isomer could be also isolated in good yield when we extended our protocol to the addition of other racemic allenes (R = Me, i-Pr and Ph) to a variety of aliphatic, $\alpha$,$\beta$-unsaturated and aromatic aldehydes. As shown in Table 2, in all the cases the facial selectivity of the major $E$ crotal reagent ($E$/Z ratio ~95:5) was at least 92:8.

Table 1. Hydroboration of 1 followed by addition of aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R’ (aldehyde)</th>
<th>Major product</th>
<th>Facial selectivity$^{[a]}$</th>
<th>$E$/Z$^{[b]}$</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ethyl</td>
<td>syn,syn-3b</td>
<td>91:9</td>
<td>93:7</td>
<td>59%</td>
</tr>
<tr>
<td>2</td>
<td>n-pentyl</td>
<td>syn,syn-3c</td>
<td>89:11</td>
<td>96:4</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>phenyl</td>
<td>syn,syn-3d</td>
<td>95:5</td>
<td>95:5</td>
<td>71%</td>
</tr>
<tr>
<td>4</td>
<td>2-furyl</td>
<td>syn,syn-3e</td>
<td>93:7</td>
<td>97:3</td>
<td>95%</td>
</tr>
</tbody>
</table>

[a] syn,syn:anti,syn ratio. [b] Ratio of (syn,syn + anti,anti)/(anti,anti + syn,anti) isomers.

Table 2. Hydroboration of allenes 4-6 followed by addition of aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R (allene)</th>
<th>R’ (aldehyde)</th>
<th>Major product</th>
<th>Facial selectivity$^{[a]}$</th>
<th>$E$/Z$^{[b]}$</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methyl</td>
<td>ethyl</td>
<td>syn,syn-7a</td>
<td>93:7</td>
<td>95:5</td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td>methyl</td>
<td>isopropyl</td>
<td>syn,syn-7b</td>
<td>93:7</td>
<td>96:4</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>methyl</td>
<td>2-furyl</td>
<td>syn,syn-7c</td>
<td>93:7</td>
<td>96:4</td>
<td>81%</td>
</tr>
<tr>
<td>4</td>
<td>isopropyl</td>
<td>n-pentyl</td>
<td>syn,syn-8a</td>
<td>95:5</td>
<td>96:4</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>isopropyl</td>
<td>phenyl</td>
<td>syn,syn-8b</td>
<td>96:4</td>
<td>96:4</td>
<td>65%</td>
</tr>
<tr>
<td>6</td>
<td>isopropyl</td>
<td>1-nonenyl</td>
<td>syn,syn-8c</td>
<td>98:2</td>
<td>96:4</td>
<td>83%</td>
</tr>
<tr>
<td>7</td>
<td>phenyl</td>
<td>n-pentyl</td>
<td>syn,syn-9a</td>
<td>92:8</td>
<td>96:4</td>
<td>88%</td>
</tr>
<tr>
<td>8</td>
<td>phenyl</td>
<td>isopropyl</td>
<td>syn,syn-9b</td>
<td>95:5</td>
<td>95:5</td>
<td>79%</td>
</tr>
</tbody>
</table>

[a] syn,syn:anti,anti ratio. [b] Ratio of (syn,syn + anti,anti)/(anti,anti + syn,anti) isomers.
Nevertheless, none of these attempts to control the Z/E configuration of the boron intermediate during the hydroboration step was completely satisfactory. Neither the change of the temperature\textsuperscript{17} nor the use of other hydroborating agent\textsuperscript{18} was successful.

Although borane or alkylborane species can reduce aldehydes and ketones, this process is slow at low temperatures.\textsuperscript{19} Thus, we envisaged that the hydroboration of the allene might be possible in the presence of the aldehyde. We hypothesized that when the allene was hydroborated to form the kinetic Z boron reagent it would be immediately trapped by the aldehyde. Therefore, the unprecedented idea of hydroboring the allene in the presence of the aldehyde should allow us to isolate anti,anti-3 or syn,anti-3 as major isomers rather than the syn,syn-3.\textsuperscript{20} As expected, when dicyclohexylborane (1.1 eq) was added to a mixture of allene 1 and ethanol in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C anti,anti-3b (entry 1, Table 3) was isolated as major isomer at rt. The analysis of the minor stereoisomers revealed a notable 6:94 facial diastereoselectivity (syn,anti,anti,anti ratio) in the addition of the Z alkenyl borane intermediate to the aldehyde. The main minor isomer detected was syn,syn-3b possibly resulting from the partial isomerization of (Z)-2 to (E)-2 (Z/E ratio 86:14). The same behaviour was observed for the addition of racemic allenes to aliphatic, aromatic and heteroaromatic aldehydes (Table 3).\textsuperscript{13}

In an effort to improve our control of the Z/E ratio of the 2-alkenyl borane intermediate, alternative hydroborating agents were considered. Thus, 9-BBN under the conditions of Scheme 3 gave the same major stereoisomer (syn,syn-3a) but in lower yield and diastereomeric ratio (83:17). Interestingly, when (S)-1 was hydroborated at rt with (+)-Ipc\textsubscript{2}BH the anti,anti-3a isomer, presumably arising from the (Z)-2 borane intermediate, was obtained (d.r.: 85:15)\textsuperscript{13} in 54% yield. The diastereomeric ratio was improved to 91:9 when the same reaction was performed at -25 °C (55% yield). The mismatch reaction with (+)-Ipc\textsubscript{2}BH at rt yielded a disappointing mixture (40 (anti,anti); 40 (syn,anti); 20 (anti,syn)). On the other hand, we also explored the effect of the temperature on the selectivity of the hydroboration. Surprisingly, when the hydroboration of 1 with dicyclohexylborane was performed at lower temperature (40 °C) the stereoselectivity switched to the anti,anti-3a isomer (d.r.: 88:12)\textsuperscript{13} but in low yield (17%) probably due to the fact that the hydroboration was incomplete under these conditions.

These experiments suggest that when dicyclohexylborane or 9-BBN was used, (Z)-2 was first formed in the hydroboration step (probably between -40 and -20 °C) but it easily isomerized at rt to the more stable isomer (E)-2. However, at lower temperatures or when a more hindered hydroborating agent is involved (Ipc\textsubscript{2}BH), the Z/E isomerization could be slow enough to achieve the addition of (Z)-2 to the aldehyde\textsuperscript{14,16}.

![Image](image-url)
Keywords: ab initio calc. • allenes • asymmetric synthesis • 1,3-diols • hydroboration

Acknowledgements

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[9] The enantiomer of syn,syn-3a was also prepared from allene (R)-1. The enantiomeric purity was >99:1 as determined by HPLC analysis of the corresponding benzoates using a Chirpak IA column (see Supporting Information).

[10] An analogous cyclic transition state for (Z)-2 was assumed to account the formation of anti,anti- and syn,anti-3a.

[11] For the relative configurational assignments, see Supporting Information.


[13] Detailed data of the isomeric product composition of crude mixtures are given in the Supporting Information.


[15] The main minor isomer was syn,syn-3a.

[16] The sterically hindered disiamylborane gave also anti,anti-3a (d.r.: 80/9/11 anti,anti,syn,anti,syn) as the major isomer.

[17] For a successful control of the E/Z configuration by changing the temperature, see: Ref. 6g.

[18] For the stereoselective formation of (Z)-boron intermediates by hydroboration, see: Refs. 6d and 6f.


[20] Major anti,anti and syn,anti products of Table 3 were easily separated from the mixture of the rest of minor isomers by flash chromatography. The same applies for the syn,syn major compounds in Tables 1 and 2.


[22] In contrast with the performed ab initio calculations for the addition of (E)-2-alkenylboranes to aldehydes in which the chair-like transition states are predicted to dominate over boat-like arrangements, the situation is less clear for the (Z)-2-alkenyl boranes where different transition states of similar energy could be found.

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**Stereodivergent Addition of 4-Silyloxy-1,2-Allenes to Aldehydes by Hydroboration**

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**All-ene one!** Three out of four stereoisomers of 2-vinyl-1,3-diols can be obtained from a single allene. A simple variation of the reaction conditions modifies the stereochemical outcome of the addition of an allene to an aldehyde via hydroboration. Stereocontrol is dependent upon the order in which the reagents are mixed (leading to E or Z boron species) and the type of aldehyde (aliphatic or aromatic) used.