A double diastereoselective approach to chiral syn- and anti-1,3-diol analogues through consecutive catalytic asymmetric borylations

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Abstract

Homoallylic boronate carboxylate esters derived from unsaturated aldehydes via an imination, β-borylation, imine hydrolysis and Wittig trapping sequence, were subjected to a second boryl addition to give 1,3-diborylated carboxylate esters. Control of the absolute and relative stereochemistry of the two new 1,3-stereogenic centres was achieved through: 1) direct chiral catalyst controlled asymmetric borylation of the first stereocentre on the unsaturated imine with high e.e.; and 2) a double diastereoselectively controlled borylation of an unsaturated ester employing a chiral catalyst to largely overcome directing effects from the first chiral boryl centre to give poor (mismatched) to good (matched) diastereocontrol. Subsequently, the two C-B functions were transformed into C-O systems to allow unambiguous stereochemical assignment of the two borylation reactions involving oxidation and acetal formation.
Introduction

Organoborane compounds provide exceptional chemical features for transforming into a wide range of functional groups, often with high degrees of stereochemical control. Amongst the range of applications, their use as intermediates in asymmetric synthesis is perhaps the most valuable and especially for preparing key chiral building blocks, often in an enantioselective manner by the addition of boron reagents to C-C multiple bonds. In this respect, the β-borylation reaction has emerged as an increasingly important and flexible approach for the preparation of chiral organoboron compounds, leading to a wide range of borylated compounds. Allylic and homoallylic boronates are particularly useful reagents in synthesis due to the potential for further derivatisation to access key building blocks for constructing multi-functional chiral compounds. Indeed, in previous work, our group has developed effective enantioselective, one-pot methodologies for the synthesis of homoallylic boronate carboxylate esters starting from α,β-unsaturated aldehydes (Scheme 1). This non-trivial approach requires a four-reaction synthetic sequence that necessarily requires hindered imine formation to control the borylation process in order to circumvent stability issues of the various intermediates involved and the chemoselectivity of the boryl addition.
Having achieved the synthesis of homoallylic boronate esters 5 in previous work (see Scheme 1), this system offered an opportunity for the introduction of a second boryl moiety, and hence, creating a second C-B chiral centre with a 1,3-stereochemical relationship. In turn, and in this work (see Scheme 1), we report how we exploited the opportunity for developing further applications in wider asymmetric synthesis through the synthesis of chiral 1,3-diborylated ester derivatives 6. Indeed, the development of effective synthetic strategies towards 1,3-diols 7 with high stereochemical control is a key area for the synthesis of natural and bioactive products, for example, as found in important pharmaceuticals such as diospongion A\(^7\) or erythromycin,\(^8\) and the 3,5-dihydroxy acid fragment widely present in statins\(^9\) (see Figure 1).
Figure 1 Selected examples of compounds with biological interest containing a syn- or anti-1,3-diol moiety.

The control of both the relative and absolute stereochemistry in 1,3-diol analogues still represents a substantial challenge, since only a few building blocks are available for the synthesis of a wide range of structurally quite diverse compounds. In fact, it is generally found that small substrate changes in well-known synthetic procedures for accessing such compounds can result in a decrease in the yield and loss of stereoselectivity.\textsuperscript{10} Therefore, there is still a need for alternative, flexible and highly stereoselective syntheses of key building blocks to add to the current list of aldol reactions,\textsuperscript{11} reductions,\textsuperscript{12} alkoxide additions\textsuperscript{13} and enzymatic reduction of 1,3-diketones.\textsuperscript{14} Hence, in this paper, we report the use of chiral homoallylic boronate esters 5 as substrates for further asymmetric copper(I)-catalysed \( \beta \)-borylation and examine the stereochemical control effects involved in accessing the 1,3-diborylated compounds 6. Moreover, methods were developed to provide both relative and absolute stereocontrol at each new asymmetric stereocentre using the copper(I) phosphine ligands to effect stereocontrol. The two boryl units were then examined for transformation into functionalities which would allow unambiguous stereochemical assignment of the two borylation reactions.
Results and discussion

Homoallylic boronate ester 5 synthesis and optimization

In previous studies (Scheme 2),\(^6\) the asymmetric formation of homoallyl boronates 5 was reported, carried out in \(\text{\textsuperscript{1}PrOH}\) as favoured solvent. Although this reaction worked well on smaller scales, larger scale synthesis proved challenging, presumably due to mass transfer issues, \textit{i.e.} it was not possible to work scales larger than 2.0 mmol without significant loss of yield. In addition, when examining this reaction (Scheme 2) on model substrate cinnamaldehyde, the use of \(\text{\textsuperscript{1}PrOH}\) as reaction medium was also found to cause undesired transesterification during the subsequent Wittig reaction, resulting in a mixture of homoallylic boronate esters 5a and 5ai (Scheme 2).

\[
\begin{align*}
\text{Ph} & \quad \text{1a} \\
\text{H}_2\text{NCH(Ph)}_2 (1.0 \text{ equiv.}) & \quad \text{3 A-MS, \text{\textsuperscript{1}PrOH, RT}} \\
\text{CuCl (3 mol%), \{(R)-DM-BINAP L2 (3 mol%), NaO}^\text{Bu (9 mol%), B_2\text{pin}_2 (1.0 equiv.), \text{\textsuperscript{1}PrOH, 16 h, RT}} \\
\text{Ph}_3\text{PCHCO}_2\text{Me (1.5 equiv., CuSO}_4 (2.0 \text{ equiv., H}_2\text{O (10.0 equiv.)}, \text{\textsuperscript{1}PrOH, 5 h, RT}} \\
\end{align*}
\]

\textbf{Scheme 2} Model process for the synthesis of unsaturated esters 5 and associated transesterification due to the use of \(\text{\textsuperscript{1}PrOH}\) as reaction medium.

Scheme 2 therefore graphically showed the need for optimization, both in terms of the \(\beta\)-boryl aldimine addition and subsequent hydrolysis, as well as the \textit{in situ} Wittig reaction. We therefore examined the rate of addition of a preformed solution of the boryl imine 3a to a solution of copper(II) sulfate and ylide; Tables 1 and 2 summarize the results.
Table 1 Effect of the rate of addition of boryl imine 3a to the hydrolysis/Wittig reaction.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Addition rate</th>
<th>IY\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 mL/ 30 min\textsuperscript{c}</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>1 mL/ 15 min\textsuperscript{c}</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>1 mL/ 10 min\textsuperscript{d}</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>N/A\textsuperscript{e}</td>
<td>22</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: see Experimental. \textsuperscript{b}Isolated yield calculated on homoallylic boronate ester 5a. \textsuperscript{c}Addition in batches of 1 mL. \textsuperscript{d}Dropwise addition via syringe pump. \textsuperscript{e}Comparative batch reaction (direct addition of Wittig reagent and copper salt directly to 3a).

Table 1 shows that compared to the standard batch reaction (Entry 4, Table 1), the slow addition of the aldimine 3a to a stirred hydrolysis/Wittig reaction mixture (Entries 1-3, Table 1) resulted in higher yields of the target homoallylboronate 5a, \textit{i.e.} improved yields were obtained, from 22\% up to 61\% mainly due to cleaner products being directly obtained.

To solve the issue of transesterification, the same reaction sequence outlined in Scheme 2 was carried out in different solvents for the imine hydrolysis-Wittig step, as summarised in Table 2.

Table 2 Solvent optimisation for the imine hydrolysis-Wittig step converting imine 3a to homoallyl boronate 5a (see Scheme 2).\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction solvent</th>
<th>β-Boryl aldimine solvent\textsuperscript{b}</th>
<th>Presence of 5ai\textsuperscript{c}</th>
<th>Yield of 5a\textsuperscript{d} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iPrOH</td>
<td>iPrOH</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>iPrOH</td>
<td>Yes</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>MeOH</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>THF</td>
<td>No</td>
<td>89</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: see experimental. \textsuperscript{b}Solid residue of the crude β-boryl aldimine 3a was redisolved in the stated solvent. \textsuperscript{c}Transesterification product 5ai observed by \textsuperscript{1}H NMR (crude product). \textsuperscript{d}Isolated yield of pure homoallylboronate 5a.

From Table 2 it became apparent that the use of an alcohol solvent for the imine hydrolysis-Wittig step (either to solvate the copper salt-Wittig reagent, or the aldimine) was not ideal either due to the transesterification or diminished yields (Entries 1-3, Table 2). However, after boryl addition to the unsaturated imine in THF (Entry 4, Table 2) the subsequent hydrolysis/Wittig sequence gave good yields on the desired product 5a with complete suppression of the transesterification. Also, this set of reaction conditions were readily scaled up for further use.
Stereocontrolled $\beta$-borylation of homoallylic boronate carboxylate esters

Having examined solvent and scale up effects on the formation of homoallyl boronate 5, we then turned to examine the second borylation step, i.e. the conversion of 5 to give diboryl system 6 (Eqn. 1).

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Me} \\
\text{O} & \quad \text{B} \\
\text{O} & \quad \text{B} \\
\text{5a} & \quad \text{5a} \\
\text{Ph} & \quad \text{Ph} \\
\downarrow & \quad \downarrow \\
\text{B}_2\text{pin}_2 (1.0 \text{ equiv}) & \quad \text{CuCl (3 mol%), PPh}_3 \text{ L1 (6 mol%), NaO}^\text{tBu} (9 \text{ mol%), } \text{iPrOH, RT, 16 h} \\
\text{O} & \quad \text{B} \\
\text{O} & \quad \text{B} \\
\text{Ph} & \quad \text{Ph} \\
\text{6a} & \quad \text{6ai} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Pr}
\end{align*}
\]

Initial attempts to perform a $\beta$-borylation on racemic homoallylic boronate ester 5a and under racemic borylation conditions gave the corresponding diborylated ester 6a, as indicated by complete consumption of substrate 5a (conversion >99% according to crude $^1$H NMR). However, the presence of an additional product, compound 6ai (Fig. 2), was also detected due to the undesired transesterification when using $^\text{i}$PrOH as solvent and in the presence of NaO$^\text{tBu}$. Separation of these two esters 6a and 6ai for further use also proved impossible

**Figure 2** Structures corresponding to the different diborylated esters 6a and 6ai.

In order to avoid the transesterification during the $\beta$-borylation reaction of homoallylic boronate 5a, the solvent/additive system was changed to THF/MeOH (Eqn. 2) which successfully provided the target diborylated ester 6a as a 1:1 mixture of diastereoisomers in a 42% isolated yield.
For the purpose of following the second boryl addition outlined in Eqn. 2 to the α,β-unsaturated ester of homoallylic boronate ester 5 to give the diborylated ester 6 on larger scales, we examined the use of in situ IR spectroscopy (ReactIR), providing an opportunity to examine different reaction parameters, i.e. time, temperature and ligand effects. Therefore, using the model racemic reaction (Eqn. 2), the reaction was followed over time at room temperature, to give the results shown in Fig. 3.

![ReactIR study of the β-borylation reaction on homoallylic boronate ester 5a at RT.](image)

Figure 3 ReactIR study of the β-borylation reaction on homoallylic boronate ester 5a at RT.

From Fig. 3 it was observed that the signal corresponding to the B-O stretch (1126 cm⁻¹) decreased smoothly along with the consumption of the α,β-unsaturated ester 5a (1720 cm⁻¹) and formation of the product 6a (1734 cm⁻¹) over 3 h. From this reaction, pure product 6a was obtained in a 47%
yield; a result which was comparable to that previously reported for the first attempt in the case of the 16 h reaction (42% IY), and showing that longer reaction times were not required for this transformation.

When the reaction was examined at both higher (50 °C) and lower temperatures (0 °C), respectively, an initial decrease in the B$_2$pin$_2$ concentration took place, however, there was no other obvious influence of temperature on the reaction time (see Figs. 4 and 5).

**Figure 4** ReactIR study of the β-borylation reaction on homoallylic boronate ester 5a at 50 °C.

**Figure 5** ReactIR study of the β-borylation reaction on homoallylic boronate ester 5a at 0 °C.
Finally, the effect of the phosphine ligand was examined, and hence, a diphosphine [(R),(S)-Josiphos L4] was compared with triphenylphosphine L1 in order to probe the chiral catalysed reaction. The results are shown in Fig. 6.

![Figure 6](image)

**Figure 6** ReactIR study of the β-borylation reaction on homoallylic boronate ester 5a using (R),(S)-Josiphos L4 ligand, replacing PPh₃ L1.

Comparing Figs. 3 and 6, it was clear that the presence of a more bulky, bidentate and chiral (R),(S)-Josiphos L4 ligand did not have a significant influence on the reaction time. However, the initial consumption of B₂pin₂ was considerably faster than in the racemic reaction using triphenylphosphine L1, suggesting that a rather more reactive phosphinyl-copper-boryl system was generated. Nonetheless, the subsequent reaction proceeded similarly with high conversion over approximately 3 h, confirming that the homoallylic boronate carboxylate esters 5 were suitable substrates for the β-boryl addition reaction, providing access to diborylated esters 6.

*Control of the relative and absolute 1,3-diboryl stereochemistry: double diastereoselectivity effects*

Once the conjugate addition of boron to homoallylic boronate carboxylate ester 5a was exemplified, giving a mixture of diastereoisomeric diboryl product 6a (using PPh₃ L1 as ligand), we then
examined the copper-catalyzed borylation using chiral ligands to provide enantioselective generation of the C-B bond.\textsuperscript{15} A set of reactions (Scheme 3) were, therefore, carried out using both enantiomers of DM-Binap L\textsubscript{2-3} as ligands, since previously this ligand had provided high e.e.s on related borylation systems.\textsuperscript{16} Table 3 shows the results obtained.

\textbf{Scheme 3} Borylations of α,β-unsaturated aldimines 2\textsubscript{a} (1\textsuperscript{st} borylation) and homoallylboronate esters 5\textsubscript{a} (2\textsuperscript{nd} borylation).

\textbf{Table 3} Evaluation of the diastereoisomeric ratio of 6\textsubscript{a} depending on the enantiomer of the chiral ligand used.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>d.r.\textsuperscript{b}</th>
<th>IY\textsuperscript{c} (%)</th>
<th>Conv.\textsuperscript{d} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-DM-Binap L\textsubscript{2}</td>
<td>4:1</td>
<td>35</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>(R)-DM-Binap L\textsubscript{2}</td>
<td>1:1.7</td>
<td>35</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>(S)-DM-Binap L\textsubscript{3}</td>
<td>4:1</td>
<td>50</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>(S)-DM-Binap L\textsubscript{3}</td>
<td>1:1.7</td>
<td>30</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: see experimental. \textsuperscript{b}Diastereoisomeric ratio of 6\textsubscript{a} determined by \textsuperscript{1}H NMR. \textsuperscript{c}Isolated yield on 1,3-diborylated ester 6\textsubscript{a}. \textsuperscript{d}Determined by \textsuperscript{1}H NMR on pure 1,3-diborylated ester 6\textsubscript{a}.

Table 3 confirmed that the conversion of imine 2\textsubscript{a}, generated in situ, followed by the first asymmetric borylation, hydrolysis, Wittig olefination, and finally a second asymmetric borylation, provided high conversions and stereocontrol in diboryl compound 6\textsubscript{a} that was clearly subject to double diastereocontrol effects.\textsuperscript{17} Hence, use of the same enantiomer of DM-Binap for both borylation step led to a 4:1 ratio of diastereoisomers 6\textsubscript{a}, with the first chiral centre matching the chiral catalyst used for second borylation, whereas a mismatched stereoselection occurred when
using different enantiomers for the borylations. Hence, having ascertained that good matched
diastereocntrol was possible by this approach using DM-Binap on the cinnamaldehyde-derived
model, we were then able to examine the use of a wider range of chiral ligands, since (R),(S)-
Josiphos L4 and (R),(S)-NMe2-PPh2-Mandyphos L6, for example, have found efficient utility for
the asymmetric borylation of copper-mediated β-borylation on α,β-unsaturated esters and nitriles.\textsuperscript{15b}

Hence, ligands outlined in Figure 7 were tested in the sequence shown in Scheme 4, by starting with
a sample 5a derived from a copper(I)-(R)-DM-Binap catalysed first borylation of 2a, \textit{i.e.} examining
the diastereocntrol for the second borylation step to access 6a, as summarised in Table 4.

\begin{center}
\textbf{Scheme 4} Asymmetric induction in the synthesis of the diborlated ester 6a.
\end{center}
Figure 7 Phosphine ligands for the Cu(I)-mediated β-borylation on homoallylic boronate esters 5.

Table 4 Diastereoisomeric ratio resulting from the borylation of 5a to give the diborylated ester 6a.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>d.r.</th>
<th>Y (%)</th>
<th>Conv. (%)</th>
<th>d.r.</th>
<th>Y (%)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R),(S)-Josiphos L4</td>
<td>6:1</td>
<td>50</td>
<td>&gt;99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(S),(R)-Josiphos L5</td>
<td>1:6</td>
<td>30</td>
<td>&gt;99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(R),(S)-NMe₂-PPh₂-Mandyphos L6</td>
<td>3:1</td>
<td>44</td>
<td>&gt;99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(S),(R)-NMe₂-PPh₂-Mandyphos L7</td>
<td>3:1</td>
<td>24</td>
<td>&gt;99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(R,R)-Me-DuPhos L8</td>
<td>1.85:1</td>
<td>42</td>
<td>&gt;99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(S,S)-Me-DuPhos L9</td>
<td>1.4:1</td>
<td>35</td>
<td>&gt;99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(S,S)-Dipamp L10</td>
<td>2.45:1</td>
<td>32</td>
<td>&gt;99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(R,R)-Dipamp L11</td>
<td>2:1</td>
<td>41</td>
<td>&gt;99</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aReaction conditions: see experimental. b Determined by ¹H NMR on the diborylated ester 6a pure sample. c Determined on the pure diborylated ester 6a.

d Determined by ¹H NMR.

Table 4 shows that the ferrocene-based ligands (Entries 1-4, Table 4) did indeed provide higher levels of double diastereoccontrol for the introduction of a second boryl unit into an α,β-unsaturated ester 5a, with Josiphos (Entries 1 and 2, Table 4) standing out giving a 6:1 diastereoisomeric ratio,
and notably irrespective of the enantiomer used. Less bulky ligands (Entries 5-8, Table 4) showed lower diastereocntrol in general, and some differences between the matched and mismatched system.

In order to evaluate the effect of the Cβ-substituent (R1) of the homoallylic boronate ester 5 on the both the rate of the second borylation reaction (Scheme 4) and subsequent diastereocntrol, different substrates 5 were subjected to the chiral copper catalysed borylation and initially monitored by ReactIR to examine reaction progress (see ESI). Table 5 summarises the results obtained examining different substrates 5, using diphosphine ligands L4 and L5.

Table 5 Substrate scope for the 2nd β-borylation reaction of unsaturated esters 5 (Scheme 5)a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1 substituent on 5</th>
<th>Reaction time (h)b</th>
<th>d.r.c (Ligand)</th>
<th>Conv. (%)d</th>
<th>IY, %</th>
<th>d.e.s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pClPh 5b</td>
<td>6</td>
<td>1:1 (L1)</td>
<td>88 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>pClPh 5b</td>
<td>6</td>
<td>8:1 (L4)</td>
<td>89 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>pClPh 5b</td>
<td>6</td>
<td>1:5 (L5)</td>
<td>89 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>pMeOPh 5e</td>
<td>6</td>
<td>1:1 (L1)</td>
<td>&gt;90% (e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Me 5d</td>
<td>4</td>
<td>1:1' (L1)</td>
<td>96 (51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Me 5d</td>
<td>4</td>
<td>1:1.38' (L4)</td>
<td>&gt;99 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Me 5d</td>
<td>4</td>
<td>1:1.38' (L5)</td>
<td>&gt;99 (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>nPr 5e</td>
<td>4</td>
<td>1:1' (L1)</td>
<td>&gt;99 (78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>nPr 5e</td>
<td>4</td>
<td>1:2.5' (L4)</td>
<td>&gt;99 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>nPr 5e</td>
<td>4</td>
<td>1:5:1' (L5)</td>
<td>&gt;99 (70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>iPr 5f</td>
<td>2</td>
<td>1:1' (L1)</td>
<td>&gt;99 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>iPr 5f</td>
<td>2</td>
<td>1:11' (L4)</td>
<td>&gt;99 (72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>iPr 5f</td>
<td>2</td>
<td>7:1' (L5)</td>
<td>&gt;99 (69)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aReaction conditions: see experimental. bReaction followed by in situ ReactIR. cDetermined by pure diborylated ester 1H NMR. dDetermined by crude diborylated ester 1H NMR. eNot possible to obtain clean product due to decomposition (see ESI for crude 1H NMR). fDetermined by 700 MHz 1H NMR using D8-toluene as solvent.

As shown in Table 5, the linear alkyl substrates 5d and 5e (entries 5-10, Table 5) performed well in the second borylation reaction, providing excellent conversions and moderate-good yields, with the p-chlorophenyl system being slower to react and resulting in lower yields (entries 1-3, Table 5).

Interestingly, use of p-methoxyphenyl (entry 4, Table 5) had an even less beneficial effect on the reaction, and in fact, it was not possible to obtain a clean sample of the corresponding diborylated ester 6c. In contrast, asymmetric induction on the new C-B bond followed an inverse trend, i.e. generally higher d.e.s were observed for the aryl substituted substrates (entries 2 and 3, Table 5).
Since the alkyl substituent systems 5d and 5e gave faster and cleaner reactions, a more hindered system was examined, *i.e.* 4-methyl-2-pentenal-derived homoallylic boronate ester 5f, initially under racemic conditions and monitored by ReactIR. Surprisingly, the reaction was complete in only 2 h with the 1,3-diborylated ester 6f being obtained as a 1:1 mixture of diastereoisomers in 60% (entry 11, Table 5). When the second β-borylation reaction was carried out using both enantiomers of Josiphos, *i.e.* (R),(S)-Josiphos L4 and (S),(R)-Josiphos L5 (entries 12 and 13, Table 5), the diborylated ester 6f was obtained in good yields (72% and 69%, respectively) and with excellent diastereoisomeric ratios, *i.e.* 1:11 and 7:1, respectively. Hence, despite the sterically larger iPr substituent, Josiphos was still able to largely overcome the impact of the existing chiral centre to give high levels of ligand-controlled diastereoccontrol for the introduction of the second boryl moiety.

*Stereochemical identification*

Once it was confirmed that the conjugate addition of second boryl group to the homoallylic boronate carboxylate esters 5 was possible and that moderate to excellent diastereoccontrol was possible, it was necessary to confirm the identity of the diastereoisomers, and therefore separation through transformation to suitable derivatives was required. Diastereoisomers of 6a were examined as the test substrate using two strategies: 1) transformation of 6a into the six-membered ring acetals 8a or 9a; and 2) formation of the diethanolamine-boron complex 10a (see Scheme 5).
Scheme 5 Synthetic pathways studied to obtain cyclic structures that allow the determination of the relative stereochemistry.

Firstly, the strategy involving a six-membered ring acetal 8a formation was examined through a double B-C bond oxidation, leading to the 1,3-diol intermediate 7a, followed by acetal incorporation. Initially, we decided to examine non-aqueous conditions to avoid water soluble products being lost upon work up by using trialkylamine N-oxides, which have been widely demonstrated to oxidise the B-C bond in a range of systems (Eqn. 3). Application of 4-methylmorpholine-N-oxide (4-MMNO) to access the 1,3-diol intermediate 7a from 6a resulted in the formation of the diol, however, after purification by silica gel chromatography, of the resulting 1,3-diol 7a was complicated by the high loadings of the oxidising agent (8.0 equiv.) used. Use of
trimethylamine $N$-oxide (TMANO)$^{19}$ proved to be superior being readily used in lower loadings and the products more readily purified, as summarised in Table 6.

![Chemical structure of 6a and 7a](image)

**Table 6** Oxidation conditions to obtain 1,3-diol 7a from the diborylated ester 6a.$^{a}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>$N$-Oxide (equiv.)</th>
<th>Reaction time (h)</th>
<th>Temp. (°C)</th>
<th>Isolated yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MMNO (2)</td>
<td>6</td>
<td>RT</td>
<td>52$^c$</td>
</tr>
<tr>
<td>2</td>
<td>4-MMNO (4)</td>
<td>16</td>
<td>RT</td>
<td>23$^d$</td>
</tr>
<tr>
<td>3</td>
<td>TMANO (2)</td>
<td>6</td>
<td>RT</td>
<td>26$^e$</td>
</tr>
<tr>
<td>4</td>
<td>TMANO (2)</td>
<td>3</td>
<td>50</td>
<td>60$^f$</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: see experimental. $^b$ Isolated yield of pure diol 7a. $^c$ For full conversion (>90%) longer reaction times (up to 32 h) as well as addition of extra oxidising agent (2 or 4 equiv.) were required. $^d$ Reaction stirred during additional 3 h to ensure full completion.

Table 6 shows the suitability of TMANO as oxidant, especially by running the reaction at 50 °C (entry 4, Table 6), under which conditions, the racemic diboronate 6a could be successfully transformed into the target diol 7a in a 60% yield. However, when this methodology was tested on isopropyl substituted analogue diboryl ester 6f (Eqn. 4), the reaction was not as effective as it was for the model substrate 6a and longer reaction times, as well as larger amounts of TMANO (up to 48 h and 8.0 equivalents, respectively) were required. Hence, a more general oxidative transformation needed to be identified, and further oxidants were examined, as outlined in Table 7 using the more hindered substrate 6f.
Table 7 Conditions for the oxidation of diborylated ester 6f.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant reagent (equiv.)</th>
<th>Solvent</th>
<th>Conv.-6f (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBO₃.4H₂O (6.0)</td>
<td>THF/H₂O</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>Oxone (6.0)</td>
<td>MeOH</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>MCPBA (6.0)</td>
<td>DCM</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

*aReaction conditions: For a 0.2 mmol reaction scale, stirred at RT during 2h, monitoring by TLC. bDetermined by crude ¹H NMR.

For diboryl system 6f, NaBO₃.4H₂O (entry 1, Table 7) was found to be an ideal reagent for the oxidation of the two C-B bonds. In contrast, Oxone surprisingly did not yield into the desired 1,3-diol 7f, whereas MCPBA gave complete conversion to the desired diol 7f, however, the reaction was not as clean as with sodium perborate.

With the oxidation step optimised using sodium perborate, the acetal formation was then studied to determine the optimal conditions for this transformation (Eqn. 5). Benzaldehyde was initially examined, as outlined in Table 8 for the synthesis of acetal 8a from diol 7a.

Table 8 Conditions for the synthesis of acetal 8a from the diol 7a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PhCHO (equiv.)</th>
<th>3 Å-MS</th>
<th>Temp. (°C)</th>
<th>Reaction Time (h)</th>
<th>Conv. 8a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>No</td>
<td>0</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>No</td>
<td>RT</td>
<td>1.5</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>Yes</td>
<td>RT</td>
<td>1.5</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>No</td>
<td>50</td>
<td>1.5</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>No</td>
<td>RT</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>Yes</td>
<td>50</td>
<td>1.5</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>Yes</td>
<td>50</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>Yes</td>
<td>50</td>
<td>6</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

*aReaction conditions: see experimental. bDetermined by crude ¹H NMR on the acetal 8a. cToluene was used as solvent. dPhCH(OMe)₂ used instead of PhCHO, using 4 Å M.S.
Using benzaldehyde under a wide variety of reactions conditions (entries 1-7, Table 8), formation of
the acetal proved problematic, due to lack of clean reaction. However, use of benzaldehyde
dimethyl acetal readily provided the target acetal 8a (entry 8, Table 8) starting from a mixture of
diastereoisomers. Hence, we then examined the diborylated ester 6a, obtained from (R),(S)-Josiphos
L4 and (S),(R)-Josiphos L5 catalyzed borylation reactions.

Using (R),(S)-Josiphos L4 as ligand, the acetal 8a was obtained in good conversion \(i.e. >99\%\) as a
4:1 mixture of diastereoisomers (Scheme 6) which was purified by silica gel chromatography, to
give the major diastereoisomers with less than 5\% of the minor (a mixed fraction was also obtained,
with these fractions representing 15 and 55\% yields, respectively). NMR analysis (see ESI) allowed
the determination of the relative stereochemistry of the major diastereoisomer which corresponded
to the \textit{anti}-diastereoisomer (Scheme 6).

\begin{align*}
\text{Ph} & \text{O} \quad \text{Ph} \\
\text{CO}_2\text{Me} & \text{CO}_2\text{Me} \\
\text{Ph} & \text{O} \quad \text{Ph} \\
\text{O} & \text{O} \quad \text{O} \\
5a & \rightarrow \\
\text{B}_2\text{pin}_2 \text{ (1.0 equiv.), } & \text{CuCl} \text{ (3 mol\%), } (R),(S)-\text{Josiphos L4} \\
& \text{ (3 mol\%), } \text{NaO}^\text{Bu} \text{ (9 mol\%), } \\
& \text{PrOH, RT, 16 h} \\
& \text{51\%, 4:1 d.r.} \\
\text{6a} & \rightarrow \\
\text{TMANO} \text{ (2.0 equiv.), } & \text{CHCl}_3, 50 ^\circ \text{C, 3 h} \\
& \text{62\%} \\
\text{PhCH(OMe)}_2 \text{ (1.5 equiv.), } & \text{TsOH} \text{ (10 mol\%), } 4 \AA-\text{MS, Ph} \\
& \text{50 ^\circ \text{C, 5 h}} \\
& \text{70\% (mixture of diastereoisomers)} \\
\end{align*}

\textbf{Scheme 6} Coupling constants for the \textit{anti}-configuration of the 6-membered ring acetal 8a.
Surprisingly, when NMR analysis was carried out on what was thought to be the minor diastereoisomer, instead of the expected syn-diastereoisomer, a different acetal configuration of the anti-diastereoisomer was discovered (see ESI). These different diastereoisomeric acetals likely interconvert under the reaction formation conditions, with the equilibrium ratio of diastereoisomers I and II being biased by minimisation of 1,3-diaxial interactions of the phenyl groups (Scheme 7). The interconversion between these diastereoisomers can take place due to ring opening/ring closing of the acetal in the presence of catalytic amounts of acid during their formation. In this case the benzylidene acetal position changes as results of the opening of this group and generation of the oxonium ion which subsequently closes, as outlined in Scheme 8. Hence, a thermodynamic ratio of acetal configurations is expected. Indeed, subsequent re-examination of the crude $^1$H NMR showed a 1:1 ratio of acetals I and II of 8a (see Scheme 7).

**Scheme 7** Acetal configuration interconversion for the 6-membered ring phenyl-substituted acetal 8a.

Similar derivatization studies on the isopropyl substituted system 6f was also examined due to its excellent diastereoselectivity (up to 1:11 and 7:1, for (R),(S)-Josiphos L4 and (S),(R)-Josiphos L5, respectively) as outlined in Scheme 8.
It was interesting to note that the oxidation of 6f was found to be slower in comparison to the Ph-substituted system, for both the TMANO and NaBO\textsubscript{3}.4H\textsubscript{2}O conditions. However, the target chiral acetal 8f was successfully obtained in good yields from two samples, derived from different reactions, \textit{i.e.} 64\% and 70\% having used ligands \textbf{L4} and \textbf{L5}, respectively (see Scheme 8). For these acetal samples, preparative HPLC purification was required in order to obtain a diastereomerically pure sample suitable for NMR analysis. Hence, using chiral ligand \textbf{L4} during the borylation, giving a 1:11 d.r. (see ESI for structural analysis) acetal 8f, HPLC separation resulted in a pure sample of acetal 8f\textit{I} (Scheme 7) and a mixed sample of both 8f\textit{I} and \textit{II}. By comparing the \textsuperscript{1}H NMR spectra of both samples (see ESI), the relative stereochemistry and assignment of each, could be made, as indicated by the key coupling constant shown in Scheme 7.

\textbf{Scheme 8} Coupling constants for one of the \textit{anti}-configuration 6-membered ring acetal analogues, 8f\textit{I}.
Due to the complications of acetal stereochemistry at the benzylidene centre, the use of an acetonide acetal was considered to potentially simplify the stereochemical analysis protocol. Acetonides have been widely reported for the protection of 1,2- and 1,3-diols\textsuperscript{24} and in fact, \textsuperscript{13}C NMR analysis has proved an excellent tool for the determination of the relative stereochemistry in such systems.\textsuperscript{25} Rychnovsky \textit{et al.} reported\textsuperscript{26} a method based on the different chemical shifts for the methyl groups of the acetonide functionality, depending on their relative orientation and acetal ring conformation; a method which has proved effective for the assignment of relative configurations, not only for diols, but also for polyols and polyene macrolides. Based on this approach, the synthesis of the acetonide acetal 9a was approached (Scheme 9).

![Scheme 10 Synthesis of the chiral acetonide-substituted 6-membered ring acetal 9a.](image)

Hence, 1,3-diol 7a was prepared as outlined above, using either (\(R\))\textsubscript{\(R\)},(\(S\))-Josiphos L\textsubscript{4} or (\(S\))\textsubscript{\(R\)},(\(R\))-Josiphos L\textsubscript{5} as chiral borylation ligand, to give the 6-membered ring acetals 9a in moderate isolated yields (32\% and 20\%, respectively). In both cases, the acetal was obtained as a mixture of diastereoisomers (4:1 and 2:1, respectively); a lower level of diastereoselectivity than expected...
suggesting loss of one of the diastereoisomers during the oxidation/acetal/purification sequence and returning the low yields. Hence, in order to improve yields and minimise losses, a one-pot method avoiding the chromatography between each step was carried out. While yields did not improve, the target acetals in isolated in a consistent ratio to those obtained previously for the precursor diborylated esters 6a, i.e. 6:1 (23% IY) and 1:4 (12% IY), respectively. Moreover, separation by preparative chiral HPLC provided clean samples of the major diastereoisomer in both cases to allow $^1$H NMR and $^{13}$C NMR analysis of the acetonides to be carried out (see ESI).

For the assignment of the relative stereochemistry for the case of using (R),(S)-Josiphos L4 for the synthesis of the diborylated ester 6a, the signals corresponding to H-2 and H-2’ (δ 2.10-1.95 ppm) appeared as ddds in both cases, with two different $^3$J couplings in each case; i.e. 9.8 and 5.8 Hz for H-2, and 9.3 and 6.3 Hz for H-2’, as well as the expected germinal coupling between these protons (13.1 Hz). Figure 8 presents an analysis of the couplings for H-2 of acetal 9a, showing a large coupling (9.8 Hz) to H-1 indicating that these protons are trans-diaxial, whilst the other $^3$J coupling of H-2 corresponds to a cis-coupling to H-3 (9.8 Hz). The analysis of these signals indicates that the 6-membered ring acetal 9a is in a twisted boat conformation which corresponds to the anti-diastereoisomer. Furthermore, in order to confirm this observation, the NOESY spectrum showed a trans-ring coupling between H-1 and one of the methyl groups from the acetonide functionality (signal at δ 1.42 ppm) as well as between H-3 and the other methyl group on the acetonide (signal at δ 1.45 ppm) (see ESI).
In order to complete this study, the same analysis was carried out on another sample of chiral acetal 9a, however, in this case, the chiral diphosphine ligand employed for the 2nd β-borylation reaction was (S),(R)-Josiphos L5 (see ESI). The most relevant feature of the resulting NMR spectrum was the multiplicity observed for H-2, which unlike for the case of using L4, this proton appeared as a dt (instead of a ddd) indicating that in this case, the syn-diastereoisomer was obtained. In this case, the 6-membered ring acetal adopts a more chair-like conformation meaning that H-2 couples with H-1 giving a doublet with a small coupling constant of 2.6 Hz, as well as coupling with H-4 and H-4’ giving a triplet with a large coupling constant of 15.4 Hz and overall resulting in the observed dt as shown in Figure 9. In addition, a second double triplet was expected (which would correspond to H-2’) which could not be observed in the ¹H NMR spectrum (see ESI) because it appeared in the same region where larger signals were observed (δ 1.6-1.4 ppm). However, these samples were also analysed by the [¹³C]-acetonide method confirming the relative stereochemistry; when using (R),(S)-Josiphos L4 as the ligand, the ¹³C NMR spectrum showed the two methyl signals at 24.9 and 24.6 ppm of the acetonide, meaning that in this case, these two groups were in a similar chemical environment, indicating conformational flexibility due to interconversion between chair-like and twist-boat-like conformations and due to the anti-diastereoisomeric configuration. To confirm this, the opposite enantiomeric ligand L5 product gave a ¹³C NMR spectrum showing two
distinct methyl signals at $\delta$ 30.53 (equatorial) and $\delta$ 20.10 (axial) ppm (see ESI) clearly indicating the presence of the syn-diastereoisomer (Figure 9).

![Figure 9](image_url) Conformational analysis of the syn-diastereoisomer of acetal 9a.

Once the relative stereochemistry was elucidated for the phenyl systems outlined above, these results needed to be corroborated by studying an additional substrate, i.e. the isopropyl substituted analogue (Eqn. 6).

![Chemical reaction](image_url) 1. NaBO$_3$·4H$_2$O (6.0 equiv.), THF:H$_2$O, RT, 2 h
2. (CH$_3$)$_2$C(OCH$_3$)$_2$:acetone (1:1), TsOH (10 mol%), 4 Å-MS, RT, 24 h

In this case, although the efficiency of the reaction differed depending upon the enantiomer of the chiral ligand used for the $\beta$-borylation reaction on the homoallylic boronate ester 6f, i.e. from a low yield in the final acetal for the case of L4 (10%) to a moderate yield for its opposite enantiomer (37%), a matching/mismatching effect was observed (Scheme 10).
Scheme 10 Synthesis of the chiral acetonide-substituted 6-membered ring acetal 9f.

The low yield could be associated to the poor effectivity presented by the C-B oxidation reaction for these systems as previously reported. Nevertheless, the pure acetals (obtained as mixture of diastereoisomers after column chromatography) were further purified by preparative HPLC, being possible to develop the study of the $J$ coupling constants and the $^{13}$C acetonide method on samples containing exclusively the major diastereoisomer for each case.

According to the $^{13}$C acetonide method the use of (R),(S)-Josiphos ligand L4 led to the anti-diastereoisomer; methyl groups at $\delta$ 24.95 ppm and 24.55 ppm, i.e. similar chemical environment, whilst the use of (S),(R)-Josiphos L5 lead into the syn-diastereoisomer; one methyl in equatorial position ($\delta$ 30.02 ppm) and the other methyl in the axial position ($\delta$ 19.66 ppm) (see ESI).

Hence, it was concluded that the nucleophilic boryl unit adds into the homoallylic boronate ester substrate either from the same face were the first boryl unit is already allocated or from its opposite face upon the enantiomer of the diphosphine ligand used for the generation of this reactive boryl
unit, as displayed in Figure 10. Hence, the stereochemical control being predominantly ligand controlled, but with some double diastereocontrol tining the final diastereoisomeric ratios.

![Figure 10](image)

**Figure 10** Stereoselectivity observed upon the addition of the 2\textsuperscript{nd} boryl unit into chiral homoallylic boronate esters based on the enantiomer of the chiral diphosphine ligand used.

Complimentarily, another strategy for determining the relative stereochemistry was approached; the synthesis of the diethanolamino-boron complex 10\textsubscript{a}, with the hope that X-ray crystallography would be useful to confirm the stereochemistry. After years of research and with several studies,\textsuperscript{27} the facility for forming coordinating bonds with its neighbouring elements, \textit{e.g.} N or O, exhibited by acidic tricoordinated sp\textsuperscript{2} boron atoms has been demonstrated. Taking into account this interesting property, it was envisioned that the reaction of the diborylated ester 6\textsubscript{a} with diethanolamine\textsuperscript{28} could afford the formation of the bicyclic structure stabilised by the B-N interaction (Eqn. 7).
The diborylated ester 6a was treated with diethanolamine (6.0 equiv), which after azeotropic removal of the pinacol with toluene and extraction of the remaining excess of diethanolamine to give a semi-crystalline material. Further attempts to crystallise from diethyl ether-DCM resulted in an amorphous solid not suitable for X-ray diffraction. Alternative methodologies, such as distillation in a Kugelrohr for the removal of pinacol as well as the diethanolamine in excess were examined. It was not possible to obtain the desired complex due to possible decomposition processes associated to the distillation. Moreover, N-substituted diethanolamine (e.g. N-methyldiethanolamine)\textsuperscript{39} was also evaluated for the B-N complex formation (Eqn. 8), being not possible to obtain compound 11a.

**Conclusions**

In summary, unsaturated benzhydryl imines 2 are readily borylated efficiently and with high e.e. to derive boryl imines 3 on >99% e.e. using DM-Binap L2. The intermediate β-boryl imines are inherently unstable, however, an *in situ* hydrolysis-Wittig trapping protocol was developed that provided the corresponding homoallylic boronate carboxylate esters 5, which were confirmed as ideal substrates for the β-borylation reactions (see summary Table 9). The resulting diboryl esters 6 could be readily isolated and hence, we were able to examine the relative stereocontrol of the
second boryl chiral stereocentre through a double diastereocontrolled approach. For the introduction of the second boryl group, Josiphos ligands proved superior to other systems, showing interesting double diastereoselective effects, which in broad terms showed that the original chiral centre chirality could be overridden so that any particular diastereoisomeric combination is accessible with reasonable to high diastereocontrol. There were clearly observable effects from the different substituents on Cβ with alkyl substituted substrates (5d and e) providing lower diastereocontrol. The more hindered isopropyl-substituted system 5f, however, gave an 11:1 (matched) versus 1:7 (mismatched) diastereocontrol with Josiphos, to give the corresponding bis-boryl esters efficiently. Interesting, the aryl-substituted systems showed moderate to good diastereocntrol, though the final bis-boryl compounds varied in terms of their chemical stability, with the more electron rich p-methoxy system 6b being particularly unstable; the origin of which is not clear. The relative stereochemistry of the bis-boryl esters 6 was not easily examined by conversion to potentially crystalline diethanolamine analogues 11, however, oxidative C-B cleavage and conversion to 1,3-diol-derived acetals did provide relative stereochemical confirmation. Further application of this stereochemical control is underway for the synthesis of bioactive, 1,3-dihydroxylated derivatives and will be reported in due course.
Table 9 Summary of imines 2, borylated products 3 and 5, and final diastereoisomers prepared.

<table>
<thead>
<tr>
<th>Entry</th>
<th>α,β-Unsaturated aldime</th>
<th>1st Borylated product</th>
<th>Homoallylboronate ester</th>
<th>2nd Borylated product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph ( \rightarrow ) Ph</td>
<td>BPin ( \rightarrow ) Ph ( \rightarrow ) BPin ( (R) )-DM-Binap L2 99% e.e. (R), &gt;99% conv. *</td>
<td>6a ( (R),(S) )-Josiphos L4 6:1 d.r. (Anti), 50% IY</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph ( \rightarrow ) Ph ( \rightarrow ) pCl ( \rightarrow ) Ph</td>
<td>BPin ( \rightarrow ) pCl ( \rightarrow ) BPin ( (R) )-DM-Binap L2 98% e.e. (R), &gt;99% conv. *</td>
<td>6b ( (R),(S) )-Josiphos L4 8:1 d.r. (Anti), 19% IY</td>
<td>6b ( (S),(R) )-Josiphos L5 1:6 d.r. (Syn), 30% IY</td>
</tr>
<tr>
<td>3</td>
<td>Ph ( \rightarrow ) Ph ( \rightarrow ) pMeO ( \rightarrow ) Ph</td>
<td>BPin ( \rightarrow ) pMeO ( \rightarrow ) BPin ( (R) )-DM-Binap L2 87% e.e. (R), &gt;99% conv. *</td>
<td>6c ( (R),(S) )-Josiphos L4 1:1.38 d.r. (Anti), 52% IY</td>
<td>6c ( (S),(R) )-Josiphos L5 1:1.38 d.r. (Syn), 42% IY</td>
</tr>
<tr>
<td>4</td>
<td>Ph ( \rightarrow ) Ph ( \rightarrow ) Me ( \rightarrow ) Ph</td>
<td>BPin ( \rightarrow ) Me ( \rightarrow ) BPin ( (R) )-DM-Binap L2 82% e.e. (R), &gt;99% conv. *</td>
<td>6d ( (R),(S) )-Josiphos L4 1:2.5 d.r. (Anti), 73% IY</td>
<td>6d ( (S),(R) )-Josiphos L5 1:5:1 d.r. (Syn), 70% IY</td>
</tr>
<tr>
<td>5</td>
<td>Ph ( \rightarrow ) Ph ( \rightarrow ) nPr ( \rightarrow ) Ph</td>
<td>BPin ( \rightarrow ) nPr ( \rightarrow ) BPin ( (R) )-DM-Binap L2 96% e.e. (R), 50% IY</td>
<td>6e ( (R),(S) )-Josiphos L4 1:1.11 d.r. (Anti), 72% IY</td>
<td>6e ( (S),(R) )-Josiphos L5 1:1.11 d.r. (Syn), 70% IY</td>
</tr>
<tr>
<td>6</td>
<td>Ph ( \rightarrow ) Ph ( \rightarrow ) iPr ( \rightarrow ) Ph</td>
<td>BPin ( \rightarrow ) iPr ( \rightarrow ) BPin ( (R) )-DM-Binap L2 60% e.e. (R), &gt;99% conv. *</td>
<td>6f ( (R),(S) )-Josiphos L4 1:11 d.r. (Anti), 72% IY</td>
<td>6f ( (S),(R) )-Josiphos L5 1:11 d.r. (Syn), 70% IY</td>
</tr>
</tbody>
</table>
Experimental

General experimental

All the reactions herein reported were performed under air unless specified otherwise. The reagents were purchased directly from standard chemical suppliers and used as received from the supplier without further purification. All solvents were also used as received from the supplier, except THF, MeOH and \textsuperscript{i}PrOH which were stored over a dehydrating agent and deoxygenated before use. Molecular Sieves, 3 Å 1-2 mm beads and 4 Å 1-2 mm beads, were supplied from Alfa Aesar and stored at 220 °C (>48 h). The purification of the crude reaction mixtures was performed using medium-pressure column chromatography, which was carried out on Silica gel (230-400 mesh, 40-63 μm, 60 Å) supplied from Sigma Aldrich and were monitored by TLC analysis using POLYGRAM® SIL G/UV254 (40 x 80 mm) plates with a 254 nm fluorescent indicator. In all cases, the TLC plates were visualised under a UV lamp operating at short (254 nm) and long (365 nm) wavelength ranges. Visualisation was aided by dipping the plates into an alkaline potassium permanganate solution or a \textit{p}-anisaldehyde solution.

Deuterated chloroform (CDCl\textsubscript{3}) was used as solvent for routine NMR measurements, unless stated otherwise. \textsuperscript{1}H NMR spectra were recorded on a Bruker Advance-400 at 400 MHz or a Varian VNMRS-700 at 700 MHz, operating at ambient probe temperature unless specified elsewhere. Coupling constants (\textit{J}) are given in Hz, and the multiplicity of the NMR signals is described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). \textsuperscript{13}C NMR spectra were recorded on a Bruker Advance-400 at 100.6 MHz or a Varian VNMRS-700 at 176 MHz, operating at ambient
probe temperature unless specified elsewhere. $^1$H NMR and $^{13}$C NMR chemical shifts are reported in ppm ($\delta$) relative to tetramethylsilane, references to the chemical shifts of residual solvent resonances. $^{11}$B NMR spectra were recorded on a Varian Bruker Advance-400 operating at a frequency of 128 MHz and the chemical shifts are reported in ppm ($\delta$) relative to BF$_3$(CH$_3$)$_2$O.

Mass spectra for liquid chromatography mass spectrometry (LCMS) were obtained using a Waters (UK) TQD mass spectrometer (low resolution ESI+, electrospray in positive ion mode, ES+) unless stated elsewhere. Accurate mass spectrometry was obtained on a TOF MS, electrospray in positive mode, ES+ TIC mass analyzer.

IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer with an ATR attachment.

HPLC analysis were carried out on an Agilent 1100 series instrument, fitted with a Perkin Elmer series 200 degasser on chiral columns: OJ-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.60 mm); and OD-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.60 mm); were used to achieve chiral resolution. Mixtures of hexane and $^3$PrOH were used as eluent, unless otherwise stated. To prepare the samples, the solid residue (1.0 mg) was dissolved in a mixture of hexane and $^3$PrOH in proportions 20:1. Preparative scale HPLC separations were carried out on a PerkinElmer Series 200 HPLC system equipped with a UV-Vis detector operating at 254 nm. Reversed-phase purifications used a Waters Sunfire C18 column (100 x 19mm, 5µm) with a gradient elution using a CH$_3$CN/H$_2$O mobile phase. Chiral purification was achieved using a YMC-Actus CHIRAL ART Amylose-SA column (250 x 10mm, 5µm) fitted with a guard cartridge (20 x 10mm, 5µm), using mixtures of hexane: EtOH: DCM as the mobile phase.

In some cases the reaction was monitored by in situ IR spectroscopy using a Metler-Toledo ReactIR 4000 equipped with an MCT detector (ConcIRT, window 1900–900 cm$^{-1}$; Advanced setting, Laser WN 7901–415 cm$^{-1}$; Apodization Happ General; Probe, Prob A DiComp (Diamond) connected via
K6 Conduit (16 mm probe); Sampling 4000–6500 at 8 cm\(^{-1}\) resolution; Scan option auto select, gain 2\(\times\).

**General procedure for the optimised synthesis of homoallylic boronate carboxylate esters from \(\alpha,\beta\)-unsaturated aldehydes**

To a round bottom flask containing \(^1\)PrOH (8.0 mL) and oven-dried 3 Å-molecular sieves (2.0 g) was added an \(\alpha,\beta\)-unsaturated aldehyde (2.0 mmol) and benzhydrylamine (345.0 µL, 2.0 mmol, 1.0 equiv.) and the reaction mixture was stirred at RT. After 5-8 h, an aliquot of the *in situ* formed \(\alpha,\beta\)-unsaturated imine (2.0 mL, 0.5 mmol) was transferred to a Schlenk-tube (under Ar) containing CuCl (1.50 mg, 0.015 mmol, 3 mol%), PPh\(_3\) L1 (7.9 mg, 0.03 mmol, 6 mol%) or (R)-DM-Binap L2 (11.0 mg, 0.015 mmol, 3 mol%), NaOtBu (4.3 mg, 0.045 mmol, 9 mol%) and B\(_2\)pin\(_2\) (127.0 mg, 0.5 mmol, 1.0 equiv.). The reaction mixture was stirred during 16 h at RT, then the solid residue of the resulting \(\beta\)-boryl aldimine was re-dissolved in THF (2.0 mL) and drop-wise added into a stirring solution of then methyl(triphenylphosphoranylidene)acetate (0.25 g, 0.75 mmol, 1.5 equiv), CuSO\(_4\) (0.16 g, 1.0 mmol, 2.0 equiv) and H\(_2\)O (90 µL, 5 mmol, 10.0 equiv). The mixture was stirred for 1 h at RT. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The combined organic phase was separated and washed with CuSO\(_4\) (sat.) (3 x CuSO\(_4\)), and dried over MgSO\(_4\). After filtration, the organic layer was removed *in vacuo* to yield the crude homoallylic boronate ester, was purified by SiO\(_2\) chromatography using as hexane: EtOAc (20:1 and 10:1) as eluent.

**Compound 5f.** Yield 395 mg (60%, yellow oil): R\(_f\) 0.1; IR (neat) \(\nu_{\text{max}}\) (cm\(^{-1}\)) 2955 (m), 1724 (l), 1655 (s), 1436 (s), 1379 (m), 1318 (m), 1268 (m), 1196 (m), 1142 (l), 1043 (s), 971 (m), 849 (m), 700 (m), 578 (s); \(^1\)H NMR (400 MHz, D\(_8\)-toluene) \(\delta\) 7.02-6.94 (dt, \(J\) 14.48, 7.2 Hz, 1H), 5.85-5.80 (dt, \(J\) 15.61, 1.48 Hz, 1H), 3.71 (s, 3H), 2.37-2.23 (m, 2H), 1.78-1.70 (m, 1H), 1.23 (s, 12H), 1.07-1.00 (m, 1H), 0.96-0.94 (d, \(J\) 6.78 Hz, 3H), 0.93-0.91 (d, \(J\) 6.76 Hz, 3H); \(^13\)C NMR (101 MHz, D\(_8\)-toluene) \(\delta\) 175.3 (COOR), 158.9, 146.5, 138.1, 137.9, 137.6, 137.2, 137.2, 137.0, 136.9, 136.7,
136.7, 134.4, 134.1, 133.9, 130.6, 92.1, 59.7, 41.4, 39.0, 34.0, 33.8, 31.5, 30.4, 30.0, 29.8, 29.6, 29.4, 29.2, 29.0, 28.9; $^{11}$B NMR (128 MHz, CDCl$_3$) $\delta$ 33.5; LRMS (ESI+) m/z: [M + Na]$^+$ 305.2 (100%); HRMS (ESI+-TOF) m/z:[M+H]$^+$ Calcd for C$_{15}$H$_{28}$BO$_4$ 282.2117; Found 282.2117; Enantiomeric excess was determined by HPLC using an OJ-H-CHIRALCEL column (250 x 4.60 mm) fitted with guard cartridge (50 x 4.6 mm), 25 °C, 0.2 mL/min, 254 nm, hexane:$^t$PrOH (99 : 1), t$_R$ (S) = 21.4 min; t$_R$ (R) = 22.1 min.

**General procedure for the synthesis of 1,3-diborylated esters via the $?$-borylation reaction on homoallylic boronate carboxylate esters**

The solid residue of homoallylic boronate carboxylate ester 5 (2.5 mmol) was dissolved in THF (10.0 mL) and this solution transferred to a Schlenk tube (under Ar) containing CuCl (7.4 mg, 0.075 mmol, 3 mol%), PPh$_3$ L1 (40 mg, 0.15 mmol, 6 mol%) or L4-L5 (0.075 mmol, 3 mol%) and B$_2$pin$_2$ (0.63 g, 2.5 mmol, 1.0 equiv.) after 5 minutes MeOH (0.25 mL, 6.25 mmol, 2.5 equiv.) was added and the mixture was stirred for 10 minutes followed by NaO$_t$Bu (21.6 mg, 0.23 mmol, 9 mol%). The reaction mixture was stirred at RT for 2-6 h and the resulting solution partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc) and the combined organic phases were dried (MgSO$_4$), filtered and evaporated in vacuo. The reaction crude mixture was purified by SiO$_2$ chromatography using petroleum ether:EtOAc (5:1 and 3:1) as eluent.

**Compound 6a.** Yield 103 mg (47%, yellow oil) with an R$_f$ 0.61: IR (neat) $\nu_{\text{max}}$ 3025 (s), 2978 (m), 2929 (s), 1734 (l), 1601 (s), 1493 (s), 1481 (s), 1452 (m), 1436 (m), 1379 (l), 1371 (l), 1315 (m), 1271 (m), 1214 (m), 1198 (m), 1166 (m), 1140 (l), 1109 (s), 1032 (s), 1005 (s), 967 (m), 863 (m), 850 (m), 767 (s), 737 (s), 701 (m), 671 (s), 520 (s); $^1$H NMR (400 MHz, CDCl$_3$) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer) $\delta$ 7.24–7.08 (m, 5H), 3.61 (s, 3H), 2.50–2.41 (m, 1H), 2.41–2.36 (m, 1H), 2.07–1.98 (m, 1H), 1.88–1.80 (m, 2H), 1.71–1.63 (m, 1H), 1.24 (s, 12H), 1.18 (s, 12H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.1 (COOR), 142.6, 128.6, 128.3, 124.9, 82.6, 51.3, 36.1, 35.7, 32.5, 32.2, 25.0; $^{11}$B NMR (128 MHz,
CDCl$_3$ $\delta$ 33.2; LRMS (ESI+) m/z: [M+H]$^+$ 445.0 (99%), 466.0 (40%), 465.6 (18%); HRMS (ESI+-TOF) m/z: [M+H]$^+$ Calcd for C$_{24}$H$_{39}$B$_2$O$_6$ 443.3005; Found 443.2998.

**Compound 6b.** Yield 93 mg (20%, yellow oil) with an R$_f$ 0.68: IR (neat) $\nu_{max}$ 2978 (s), 1735 (l), 1662 (s), 1598 (s), 1490 (m), 1472 (s), 1447 (m), 1436 (m), 1411 (m), 1379 (m), 1371 (m), 1358 (m), 1318 (m), 1271 (s), 1213 (m), 1166 (m), 1139 (l), 1109 (s), 1014 (m), 967 (m), 861 (m), 851 (m), 731 (s), 703 (m), 637 (m), 639 (m); $^1$H NMR (400 MHz, CDCl$_3$) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer) $\delta$ 7.21–7.10 (m, 4H), 3.61 (s, 3H), 2.49–2.40 (m, 1H), 2.40–2.34 (m, 1H), 2.02–1.94 (m, 1H), 1.84–1.77 (m, 2H), 1.69–1.60 (m, 1H), 1.24 (s, 6H), 1.22 (s, 6H), 1.21 (s, 6H), 1.18 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.0 (COOR), 141.4, 130.0, 129.7, 128.4, 83.5, 83.1, 51.3, 35.9, 35.0, 32.8, 32.5, 24.8, 24.6; $^{11}$B NMR (128 MHz, CDCl$_3$): $\delta$ 33.1. LRMS (ESI+) m/z: [M+Na]$^+$ 501.6 (100%), 480.8 (60%); HRMS (ESI+-TOF) m/z: [M+H]$^+$ Calcd for C$_{24}$H$_{38}$B$_2$O$_6$ 477.2616; Found 477.2603.

**Compound 6d.** Yield 97 mg (51%, yellow oil) with an R$_f$ 0.6: IR (neat) $\nu_{max}$ 2977 (m), 1737 (l), 1461 (s), 1379 (l), 1371 (l), 1312 (l), 1267 (m), 1214 (m), 1165 (m), 1140 (l), 1111 (s), 1007 (m), 967 (m), 861 (l), 670 (m), 578 (s); $^1$H NMR (700 MHz, D$_8$-toluene) $\delta$ 3.46 (s, 3H), 2.18–2.12 (m, 1H), 2.10–2.06 (m, 1H), 2.02–1.95 (m, 1H), 1.67–1.61 (m, 1H), 1.40–1.34 (m, 2H), 1.30 (d, $J$ 8.4, 3H), 1.16 (s, 12H), 1.14 (s, 12H); $^{13}$C NMR (101 MHz, D$_8$-toluene) $\delta$ 184.5 (COOR), 183.6 (COOR), 147.5, 93.0, 92.6, 60.8, 46.5, 46.3, 45.7, 44.8, 44.5, 44.1, 41.1, 40.0, 35.0, 34.8, 28.1, 26.4, 26, 24.9; $^{11}$B NMR (128 MHz, D$_8$-toluene): $\delta$ 34.1 ppm; LRMS (ESI+) m/z: [M+Na]$^+$ 405.3 (100%); HRMS (ESI+-TOF) m/z: [M+H]$^+$ Calcd for C$_{19}$H$_{37}$B$_2$O$_6$ 381.2849; Found 381.2842.

**Compound 6e.** Yield 318 mg (78%, yellow oil) with an R$_f$ 0.71: IR (neat) $\nu_{max}$ 2977 (m), 1737 (l), 1379 (l), 1371 (l), 1313 (l), 1249 (s), 1197 (m), 1165 (m), 1140 (l), 967 (m), 861 (l), 670 (m), 578 (s); $^1$H NMR (700 MHz, D$_8$-toluene) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer) $\delta$ 3.74 (s, 3H), 2.74–2.71 (m, 1H), 2.68–2.61 (m, 1H), 2.12–2.06 (m, 1H), 1.83–1.89 (m, 1H), 1.82–1.77 (m, 1H), 1.76–1.68 (m, 2H), 1.66–1.62 (m, 2H), 1.48–1.43 (m, 1H), 1.24 (s, 6H), 1.23 (s, 6H), 1.17 (s, 6H), 1.15 (s, 6H), 1.09–1.06 (dd, $J$ 14, 7
Hz, 3H); $^{13}$C NMR (101 MHz, D$_8$-toluene) δ 184.2 (COOR), 183.0 (COOR), 147.5, 93.0, 92.8, 92.7, 60.8, 46.7, 45.5, 44.7, 44.3, 43.2, 42.2, 33.0, 32.7, 24.8, 24.7; $^{11}$B NMR (128 MHz, D$_8$-toluene) δ 33.9 ppm. LRMS (ESI+) m/z: [M + Na]$^+$ 433.9 (96%), [M]$^+$ 410.0 (88%); HRMS (ESI+-TOF) m/z: [M+H]$^+$ Calcd for C$_{21}$H$_{41}$B$_2$O$_6$ 409.3162; Found 409.3170.

Compound 6f. Yield 245 mg (60%, yellow oil) with an R$_f$ 0.75; IR (neat) $\nu_{\text{max}}$ 2977 (m), 1737 (l), 1436 (s), 1379 (s), 1371 (s), 1311 (s), 1269 (m), 1212 (m), 1197 (m), 1165 (m), 1140 (s), 1111 (m), 1005 (l), 971 (m), 863 (s), 849 (m), 670 (m); $^1$H NMR (700 MHz, D$_8$-toluene) (mixture of diastereoisomers further analysis was required for the determination of the major diastereoisomer) δ 3.48 (s, 3H), 2.78–2.74 (m, 1H), 2.65 – 2.61 (m, 1H), 2.09–2.12 (m, 1H), 1.86–1.81 (m, 1H), 1.40–1.36 (m, 1H), 1.34–1.31 (m, 2H), 1.24 (s, 12H), 1.19 (s, 12H), 1.16 (s, 6H); $^{13}$C NMR (176 MHz, D$_8$-toluene) δ 178.7, 178.5 (COOR), 87.6, 87.5, 87.4, 87.3, 55.3, 41.8, 39.7, 35.7, 35.3, 34.64, 34.4, 29.6, 29.5, 29.5, 29.4, 27.6, 27.4, 26.2, 26.1; $^{11}$B NMR (128 MHz, D$_8$-toluene): δ 33.4 ppm; LRMS (ESI+) m/z: [M + Na]$^+$ 433.8 (100%); HRMS (ESI+-TOF) m/z: [M+H]$^+$ Calcd for C$_{21}$H$_{41}$B$_2$O$_6$ 409.3162; Found 411.3071.

**General procedure for the oxidation of 1,3-diborylated esters using TMANO**

To a solution of the diborylated ester 6 (1.0 mmol) in DCM (10.0 mL) under Ar was added trimethylamine-N-oxide (TMANO) dihydrate (222.3 mg, 2.0 mmol, 2.0 equiv.). The mixture was stirred at 50 °C for 3 h, allowed to cooled to RT and excess TMANO removed by filtration. The solvent was removed in vacuo, giving the crude 1,3-diol.

**General procedure for the oxidation of 1,3-diborylated esters**

The diborylated ester 6 (2.0 mmol) was dissolved in a mixture of THF:H$_2$O (1:1 by volume, 20.0 mL), followed by the addition of NaBO$_3$·4H$_2$O (1.85 g, 12.0 mmol, 6.0 equiv.). The reaction mixture was stirred at RT for 2 h, the solvent was removed in vacuo, and the remaining white solid re-dissolved in EtOAc and filtered leading into the crude 1,3-diol.
Synthesis of 6-membered ring acetals

Procedure a) Synthesis of phenyl substituted 6-membered ring acetals

The solid residue of 1,3-diol 7 synthesised following the general procedure for the oxidation of diborylated esters (0.9 mmol) was dissolved in toluene (15.0 mL), benzaldehyde dimethyl acetal (202 µL, 1.35 mmol, 1.5 equiv.) was added along with TsOH (17.11 mg, 0.09 mmol, 10 mol%). After stirring for 10 minutes, 4 Å molecular sieves (1.5 g) were added and mixture heated for 6 h at 50 °C. The molecular sieves were removed by filtration and the solvent removed in vacuo, to give a crude product that was purified by SiO₂ chromatography using a mixture of petroleum ether:EtOAc (5:1, 3:1 and 0:1) as eluent which gave the pure phenyl-substituted six-membered ring acetal.

Compound 8a. Yield 68 mg (70%, yellow oil) with an Rₕ 0.5: IR (neat) νₘₐₓ 2951 (m), 1733 (l), 1495 (s), 1451 (m), 1436 (m), 1339 (s), 1312 (s), 1205 (m), 1161 (l), 1104 (l), 1009 (l), 905 (l), 855 (s), 752 (l), 696 (l), 609 (m), 538 (m); ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.31 (m, 10 H), 5.67 (s, 1H), 5.44 (d, J 5.8 Hz, 1H), 4.45 (dtd, J 11.6, 6.7, 2 Hz, 1H), 3.71 (s, 3H), 2.78 (dd, J 16, 7.3 Hz, 1H), 2.60 (dd, J 16, 6.7 Hz, 1H), 2.52 (dt, J 13.6, 2 Hz, 1H), 2.30 (ddd, J 13.5, 11.3, 5.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 171.0, 141.4, 138.4, 128.9, 128.6, 128.4, 127.9, 126.4, 125.9, 100.9, 78.7, 73.5, 51.8, 40.7, 38.7; LRMS (ESI+) m/z: [M + Na]+ 335.2 (100%); HRMS (ESI+~TOF) m/z: [M+Na]+ Calcd for C₁₉H₂₀O₄Na 335.1259; Found 335.1267.

Compound 8f. Yield 45 mg (64%, yellow oil), enantiomers separated by HPLC (Sunfire C18 column, 250 x 10 mm, 5 µm; H₂O: CH₃CN gradient 90:10, 4.4 mL.min⁻¹, 254 nm) tᵣ = 5.14 min., tᵣ = 5.43 min.: IR (Et₂O film) νₘₐₓ 2958 (m), 1737 (l), 1452 (s), 1436 (m), 1384 (m), 1398 (s), 1362 (s), 1302 (m), 1255 (s), 1192 (m), 1170 (m), 1105 (l), 1070 (s), 1027 (m), 986 (m), 900 (s), 862 (s), 698 (l), 653 (s); ¹H NMR (400 MHz, CDCl₃) 7.48 – 7.31 (m, 5H), 5.80 (s, 1H), 4.75 (m, J 6.9 Hz, 1H), 3.66 (ddd, J 9.1, 6.7, 2.4 Hz, 1H), 3.12 (dd, J 14.5, 8.6 Hz, 1H), 2.73 (dd, J 14.5, 6.9 Hz, 1H), 2.07 (dd, J 11.9, 6.3 Hz, 1H), 2.03 (dd, J 11.9, 6.3 Hz, 1H), 1.80 (h, J 6.7 Hz, 1H), 1.02 (d, J 6.7
38 Hz, 3H), 0.94 (d, J 6.7 Hz, 3H); LRMS (ESI+) m/z: [M + Na]+ 301.8 (100%); HRMS (ESI+-TOF) m/z: [M+Na]+ Caled for C_{16}H_{22}O_{4}Na 301.1416; Found 301.1423.

Procedure b) Synthesis of acetonide substituted six-membered ring acetals

The solid residue of 1,3-diol 7 synthesised following the general procedure for the oxidation of diborylated esters (2.0 mmol) was then re-dissolved in a mixture of acetone:2,2′-dimethoxypropane (1:1 by volume, 100.0 mL), followed by the addition of TsOH (38 mg, 0.2 mmol, 10 mol%). This mixture was stirred at RT during 10 minutes, then 4 Å molecular sieves (2.0 g) were added and the reaction mixture was stirred for a further 24 h. After filtration, the solvent was removed in vacuo to give the crude acetal which was purified by SiO₂ chromatography using a mixture of petroleum ether:EtOAc (5:1, 3:1 and 2:1) as eluent to give the pure acetonide-substituted six-membered ring acetal.

Compound 9a. Yield 109 mg (23%, yellow oil), enantiomers separated by HPLC (chiral ART amylose-SA column, 250 x 10 mm, 5 μm; Hexane: EtOH: DCM, 97: 2: 1; 4.4 mL.min⁻¹, 254 nm) tₚ (anti-diastereoisomer) = 7.02 min; tₚ (syn-diastereoisomer) = 6.94 min; with an Rₚ 0.72: IR (neat) ν max (cm⁻¹) 2988 (s), 1739 (l), 1661 (s), 1494 (s), 1437 (m), 1379 (m), 1317 (s), 1275 (s), 1223 (m), 1165 (l), 1073 (m), 1000 (s), 956 (s), 905 (s), 843 (s), 752 (s), 697 (l), 604 (s), 543 (m), 362 (m); ¹H NMR (400 MHz, CDCl₃) (mixture of diastereoisomers), Anti-diastereoisomer δ 7.38 – 7.33 (m, 5H), 4.89 (dd, J 9.8, 6.3 Hz, 1H), 4.44 (m, 1H), 3.70 (s, 3H), 2.64 (dd, J 15.7, 7.9 Hz, 1H), 2.52 (dd, J 15.7, 5.6 Hz, 1H), 2.08 (ddd, J 13.1, 9.8, 5.8 Hz, 1H), 1.95 (ddd, J 13.1, 9.3, 6.3 Hz, 1H), 1.45 (s, 3H), 1.44 (s, 3H); Syn-diastereoisomer: δ 7.39 – 7.33 (m, 5H), 4.94 (dd, J 11.6, 2.6 Hz, 1H), 4.48 (m, 1H), 3.69 (s, 3H), 2.61 (dd, J 15.6, 6.8 Hz, 1H), 2.43 (dd, J 15.6, 6.2 Hz, 1H), 1.83 (dt, J 15.3, 2.6 Hz, 1H), 1.58 (s, 3H), 1.49 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) (mixture of diastereoisomers), Anti-diastereoisomer: δ 171.6 (COOR), 128.8, 128.8, 128.6, 127.8, 126.4, 126.3, 101.5, 77.5, 77.3, 77.2, 68.8, 64.0, 52.0, 41.0, 39.7, 30.0, 25.3, 25.0, 23.0, 1.4; Syn-diastereoisomer: δ 171.7 (COOR), 128.8, 128.0, 126.3, 99.7, 77.5, 77.3, 77.2, 71.7, 66.5, 52.0, 41.5, 39.2, 30.5, 30.0, 20.1, 14.5; LRMS (ESI+) m/z: [M+Na]+ 287.2 (100%); HRMS (ESI+-TOF) m/z: [M+Na]+
Calcd for C_{15}H_{20}O_{4}Na 287.1259; Found 287.1263. All spectroscopic and analytical data were identical to those reported in the literature.\(^7\)

Compound 9f. Yield 169 mg (32%, yellow oil); enantiomers separated by HPLC (chiral ART amylose-SA column, 250 x 10 mm, 5 \(\mu\)m; Hexane: EtOH: DCM, 95: 4: 1; 4.4 mL.min\(^{-1}\), 254 nm) \(R_T\) (\(anti\)-diastereoisomer) = 6.82 min; \(R_T\) (\(syn\)-diastereoisomer) = 6.94 min; with an \(R_f\) 0.6: IR (neat) \(\nu_{\text{max}}\) (cm\(^{-1}\)); 2956 (m), 1741 (l), 1663 (s), 1437 (m), 1378 (l), 1316 (s), 1257 (m), 1202 (l), 1168 (l), 1145 (l), 1072 (l), 1096 (m), 998 (m), 975 (m), 932 (s), 839 (l), 703 (l), 639 (s), 544 (m), 472 (s), 400 (m), 370 (s), 354 (l); \(^1\)H NMR (400 MHz, CDCl\(_3\)) (mixture of diastereoisomers), \(Anti\)-diastereoisomer 4.21 (m, 1H), 3.67 (s, 3H), 3.42 (m, 1H), 2.54 (dd, \(J\) 15.5, 8.26 Hz, 1H), 2.44 (dd, \(J\) 15.5, 5.2 Hz, 1H), 1.74 (dd, \(J\) 9.6, 5.9 Hz, 1H), 1.71 (dd, \(J\) 9.6, 5.9 Hz, 1H), 1.64 (h, \(J\) 6.8 Hz, 1H), 1.34 (s, 3H), 1.31 (s, 3H), 0.92 (d, \(J\) 6.7 Hz, 3H), 0.85 (d, \(J\) 6.7 Hz, 3H); \(Syn\)-diastereoisomer 4.26 (m, 1H), 3.69 (s, 3H), 3.51 (ddd, \(J\) 9.1, 6.6, 2.3 Hz, 1H), 2.56 (dd, \(J\) 15.5, 6.5 Hz, 1H), 2.39 (dd, \(J\) 15.5, 6.5 Hz, 1H), 1.61 (h, \(J\) 6.5 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 0.91 (d, \(J\) 6.7 Hz, 3H), 0.86 (d, \(J\) 6.7 Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) (mixture of diastereoisomers), \(Anti\)-diastereoisomer \(\delta\) 171.9 (COOR), 129.1, 128.8, 128.7, 128.4, 128.1, 127.9, 127.0, 100.9, 99.0, 77.6, 77.4, 77.2, 74.1, 71.9, 70.2, 66.4, 64.0, 52.0, 41.8, 41.0, 36.2, 33.7, 33.3, 32.0, 30.5, 25.0, 24.6, 20.09, 19.05, 18.72, 18.0, 17.9; \(Syn\)-diastereoisomer \(\delta\) 171.9 (COOR), 99.0, 77.6, 77.4, 77.2, 74.1, 66.4, 52.0, 41.8, 33.7, 33.3, 32.0, 30.5, 30.1, 23.3, 23.0, 20.1, 18.7, 18.0, 14.5, 1.4; LRMS (ESI+) m/z: [M + Na]\(^+\) 253.1 (100%); HRMS (ESI+-TOF) m/z: [M+Na]+Calcd for C_{12}H_{22}O_{4}Na 253.1416; Found 253.1425.

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Supplementary Information
Asymmetry borylation conditions/ligand screening; ReactIR studies/substrate scope; chiral and preparative HPLC data; relative stereochemistry assignment data; $^1$H, $^{13}$C and $^{11}$B NMR and HRMS data.

References


Graphical abstract

anti-diastereoisomer

syn-diastereoisomer

Double diastereoccontrolled β-borylation

C-B oxidation

{(S),(R)}-Josiphos

{(R),(S)}-Josiphos

R → CO₂Me

R → CO₂Me