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

Alba Pujol and Andrew Whiting*

Centre for Sustainable Chemical Processes, Department of Chemistry, Durham University

University, Science Laboratories, South Road, Durham DH1 3LE, UK.

E-mail: andy.whiting@durham.ac.uk

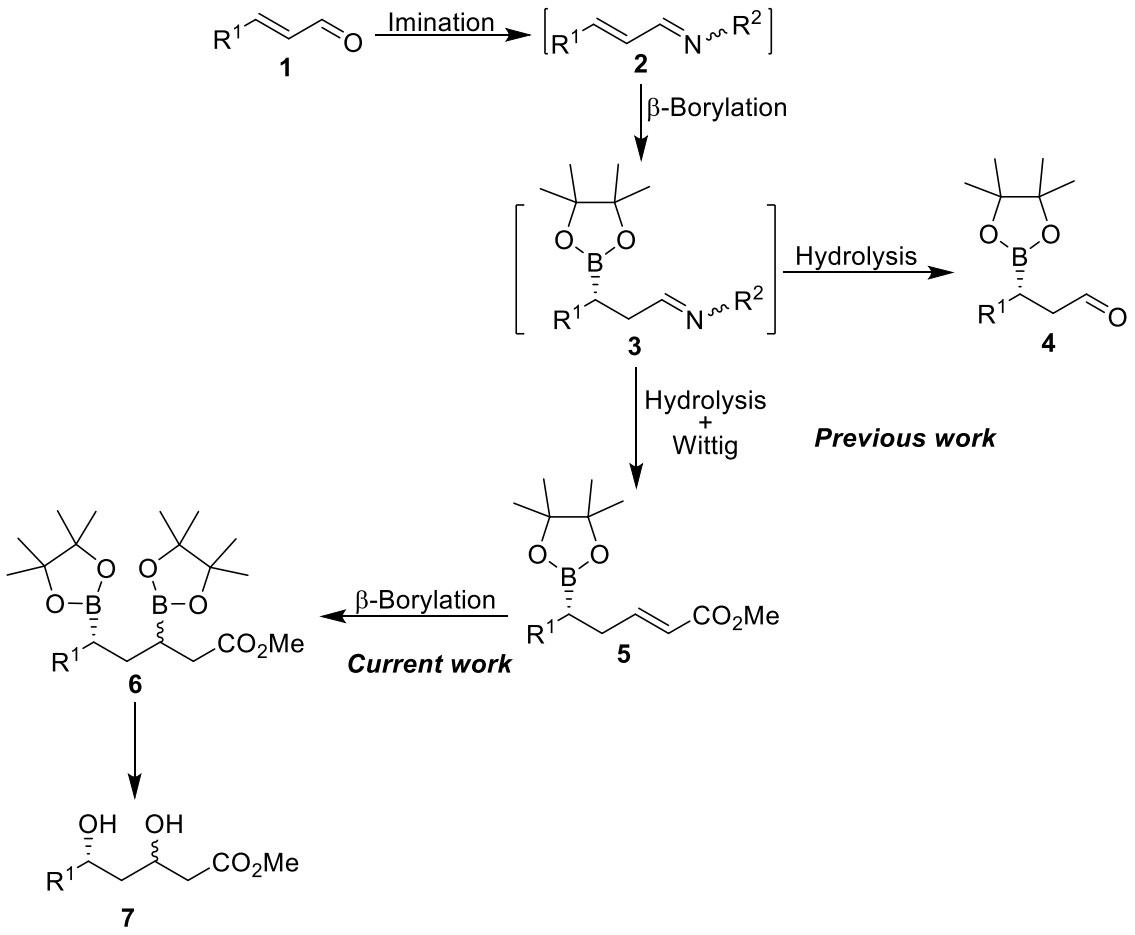
https://www.dur.ac.uk/chemistry/staff/profile/?id=204

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.[1] Amongst the range of applications, their use as intermediates in asymmetric synthesis is perhaps the most valuable[2] and especially for preparing key chiral building blocks, often in an enantioselective manner by the addition of boron reagents to C-C multiple bonds.[3] 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.[4] Allylic and homo-allylic 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.[5] Indeed, in previous work, our group has developed effective enantioselective, one-pot methodologies for the synthesis of homoallylic boronate carboxylate esters **5** starting from α,β-unsaturated aldehydes **1** (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.[6]



Scheme 1 Proposed route to access chiral 1,3-diols **7** *via* homoallylic boronates **5** and diboronates **6** from α,β-unsaturated aldehydes **1**.

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 diospongin A[7] or erythromycin,[8] and the 3,5-dihydroxy acid fragment widely present in statins[9] (see Figure 1).

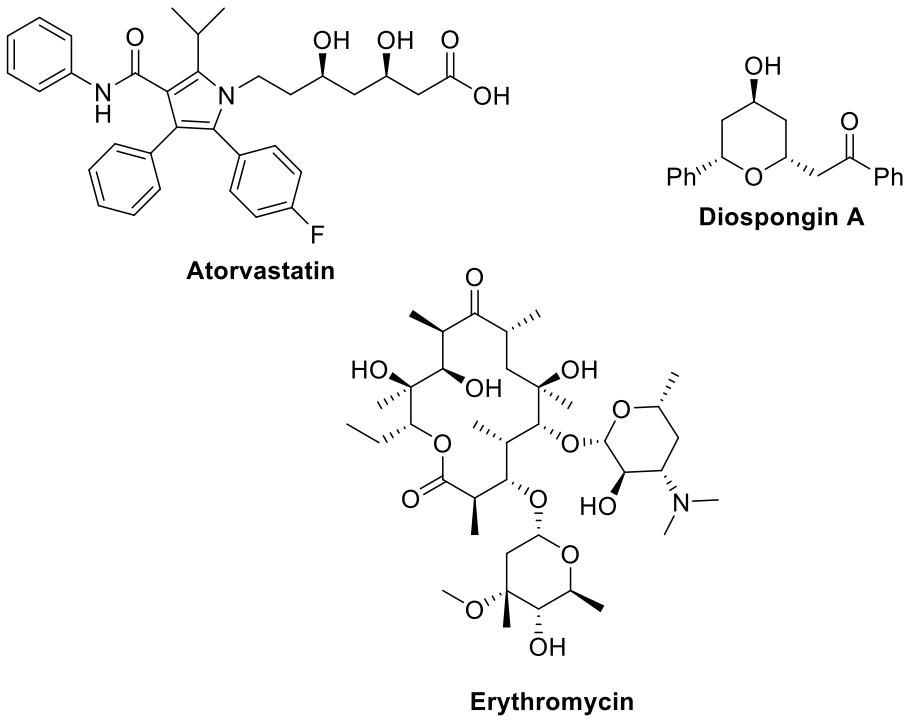


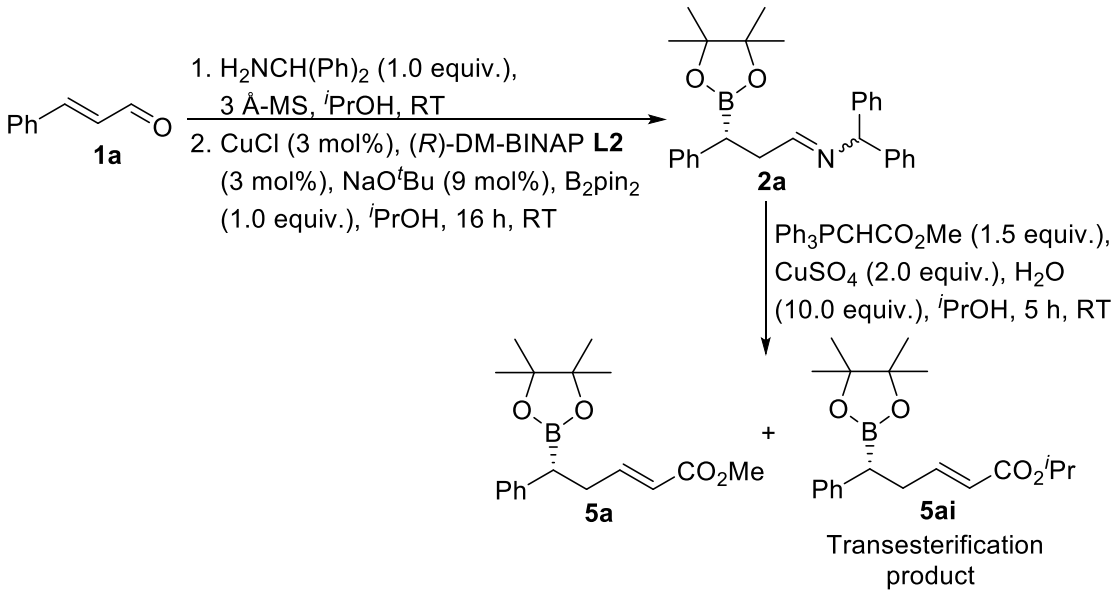
Figure 1 Selected examples of compounds with biological interest containing a *syn*- or *anti*-1,3-diol moiety.

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.[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,[11] reductions,[12] alkoxide additions[13] and enzymatic reduction of 1,3-diketones.[14] Hence, in this paper, we report the use of chiral homoallylic boronate esters **5** as substrates for further asymmetric copper(I)-catalysed β-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 ^{i}PrOH as favoured solvent. Although this reaction worked well on smaller scales, larger scale synthesis proved challenging, presumably due to mass transfer issues, *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 ^{i}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)**.**



Scheme 2 Model process for the synthesis of unsaturated esters **5** and associated transesterification due to the use of ^{i}PrOH as reaction medium.

Scheme 2 therefore graphically showed the need for optimization, both in terms of the β-boryl aldimine addition and subsequent hydrolysis, as well as the *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.[a]

Entry	Addition rate	IY[b] (%)
1	1 mL/ 30 min[c]	32
2	1 mL/ 15 min[c]	54
3	1 mL/ 10 min[d]	61
4	N/A[e]	22

[a]Reaction conditions: see Experimental. [b]Isolated yield calculated on homoallylic boronate ester **5a**. [c]Addition in batches of 1 mL. [d]Dropwise addition *via* syringe pump. [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**, *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).[a]

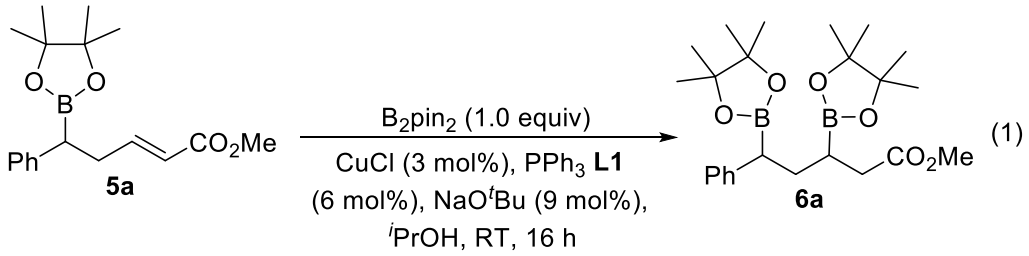
Entry	Reaction solvent	β-Boryl aldimine solvent[b]	Presence of **5ai**[c]	Yield of **5a**[d] (%)
1	^{i}PrOH	^{i}PrOH	Yes	20
2	MeOH	^{i}PrOH	Yes	17
3	MeOH	MeOH	No	12
4	THF	THF	No	89

[a]Reaction conditions: see experimental. [b]Solid residue of the crude β-boryl aldimine **3a** was redisolved in the stated solvent. [c]Transesterification product **5ai** observed by ^{1}H NMR (crude product). [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 β-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).



(1)

Initial attempts to perform a β-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 ^{i}PrOH as solvent and in the presence of NaO^{t}Bu. Separation of these two esters **6a** and **6ai** for further use also proved impossible

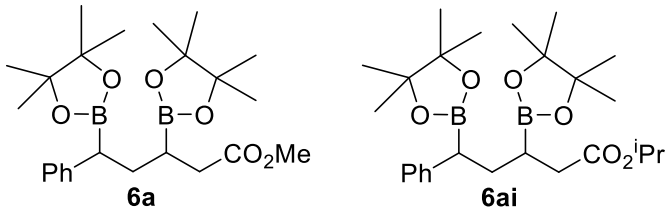
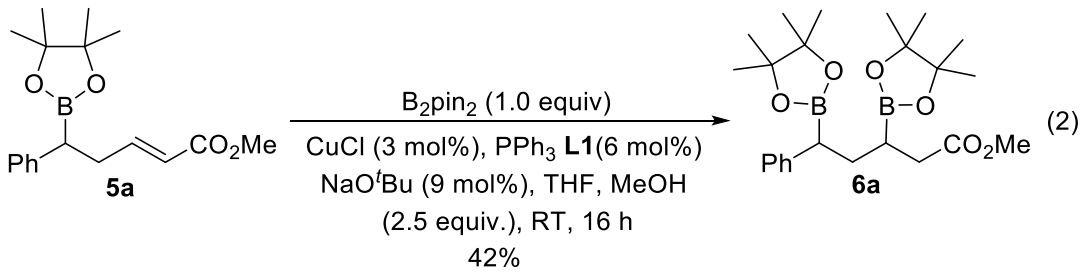


Figure 2 Structures corresponding to the different diborylated esters **6a** and **6ai**.

In order to avoid the transesterification during the β-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.

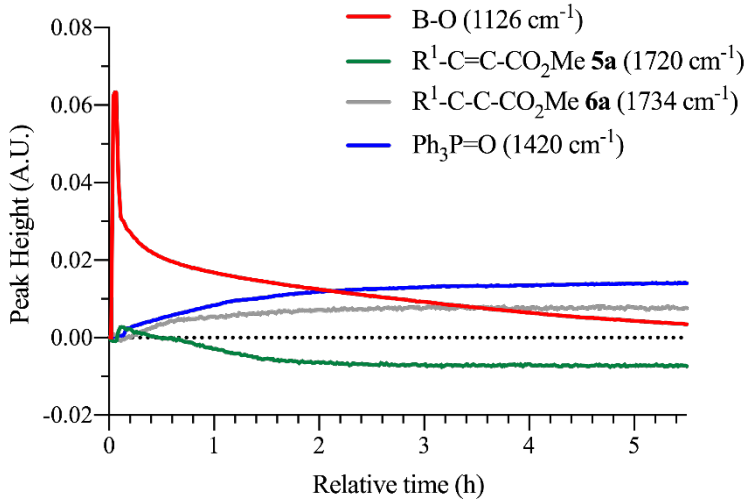


Figure 3 ReactIR study of the β-borylation reaction on homoallylic boronate ester **5a** at RT.

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_2pin_2 concentration took place, however, there was no other obvious influence of temperature on the reaction time (see Figs. 4 and 5).

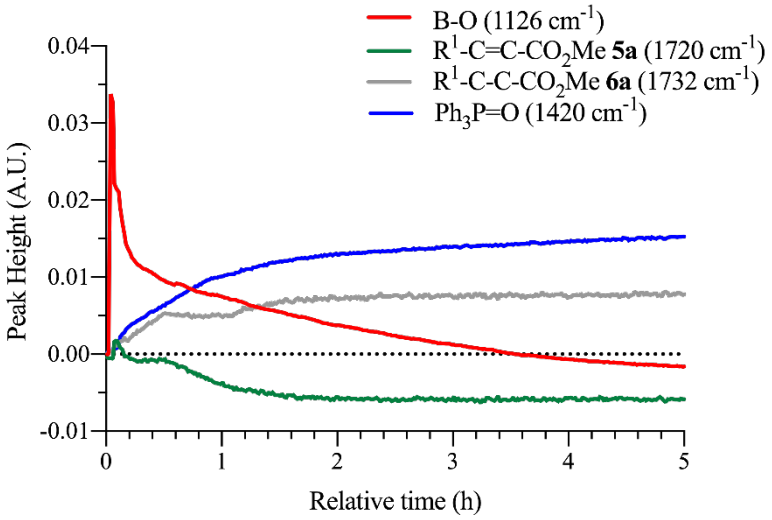


Figure 4 ReactIR study of the β-borylation reaction on homoallylic boronate ester **5a** at 50 °C.

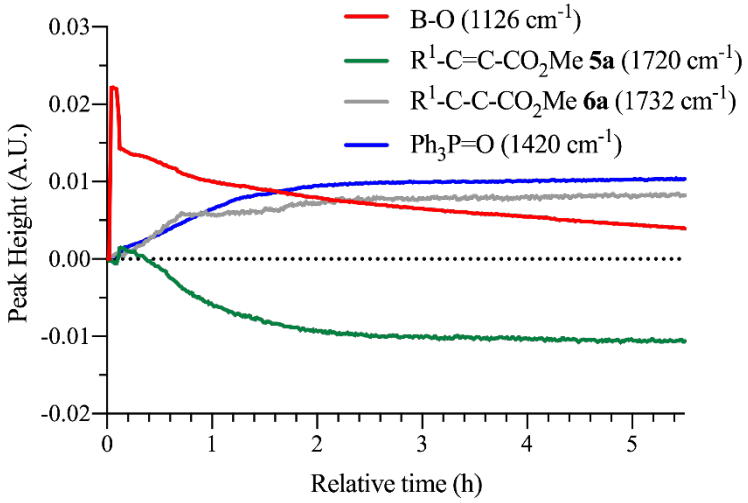


Figure 5 ReactIR study of the β-borylation reaction on homoallylic boronate ester **5a** at 0 °C.

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.

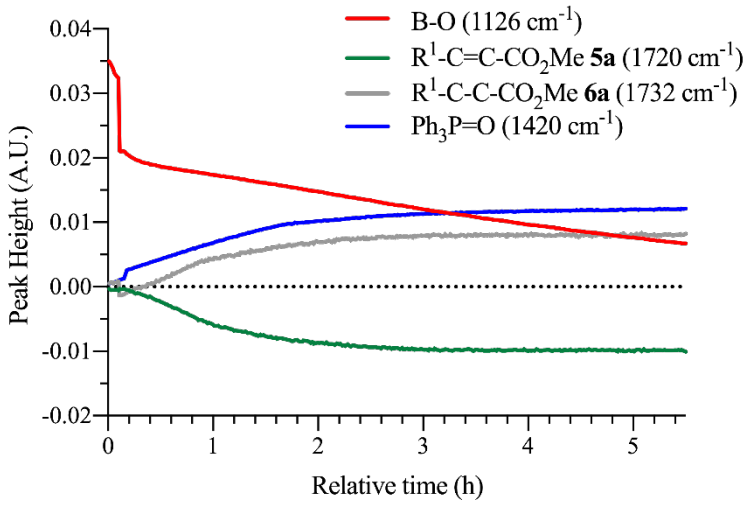


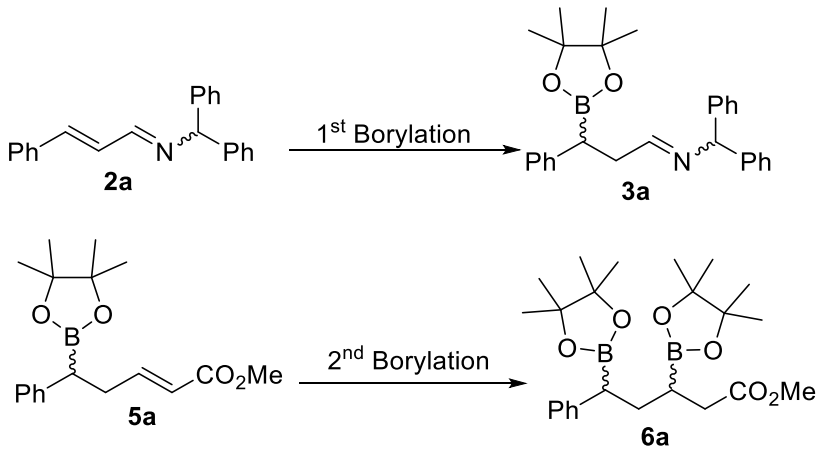
Figure 6 ReactIR study of the β-borylation reaction on homoallylic boronate ester **5a** using (*R*),(*S*)-Josiphos **L4** ligand, replacing PPh_3 **L1**.

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 B_2pin_2 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 PPh_3 **L1** as ligand), we then

examined the copper-catalyzed borylation using chiral ligands to provide enantioselective generation of the C-B bond.[15] A set of reactions (Scheme 3) were, therefore, carried out using both enantiomers of DM-Binap **L2**-**3** as ligands, since previously this ligand had provided high e.e.s on related borylation systems.[16] Table 3 shows the results obtained.



Scheme 3 Borylations of α,β-unsaturated aldimines **2a** (1st borylation) and homoallylboronate esters **5a** (2nd borylation).

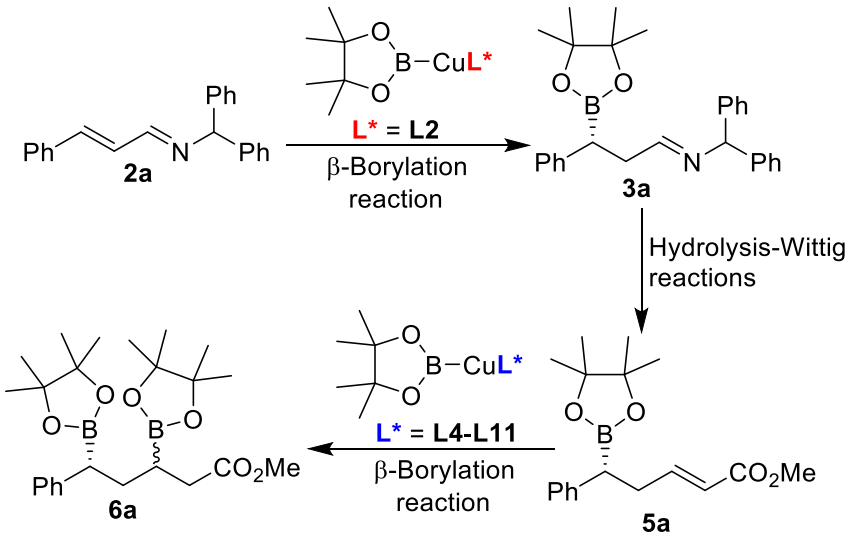
Table 3 Evaluation of the diastereoisomeric ratio of **6a** depending on the enantiomer of the chiral ligand used.[a]

Entry	Ligand		d.r.[b]	IY[c] (%)	Conv. (%)[d]
	1st Borylation	2nd Borylation			
1	(*R*)-DM-Binap **L2**	(*R*)-DM-Binap **L2**	4:1	35	>99
2	(*R*)-DM-Binap **L2**	(*S*)-DM-Binap **L3**	1:1.7	35	>99
3	(*S*)-DM-Binap **L3**	(*S*)-DM-Binap **L3**	4:1	50	>99
4	(*S*)-DM-Binap **L3**	(*R*)-DM-Binap **L2**	1:1.7	30	>99

[a]Reaction conditions: see experimental. [b]Diastereoisomeric ratio of **6a** determined by ^{1}H NMR. [b]Isolated yield on 1,3-diborylated ester **6a**. [c]Determined by ^{1}H NMR on pure 1,3-diborylated ester **6a**.

Table 3 confirmed that the conversion of imine **2a**, 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 **6a** that was clearly subject to double diastereocontrol effects.[17] Hence, use of the same enantiomer of DM-Binap for both borylation step led to a 4:1 ratio of diastereoisomers **6a**, 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 diastereocontrol 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*)-NMe_2-PPh_2-Mandyphos **L6**, for example, have found efficient utility for the asymmetric borylation of copper-mediated β-borylation on α,β-unsaturated esters and nitriles.[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**, *i.e.* examining the diastereocontrol for the second borylation step to access **6a**, as summarised in Table 4.



Scheme 4 Asymmetric induction in the synthesis of the diborylated ester **6a**.

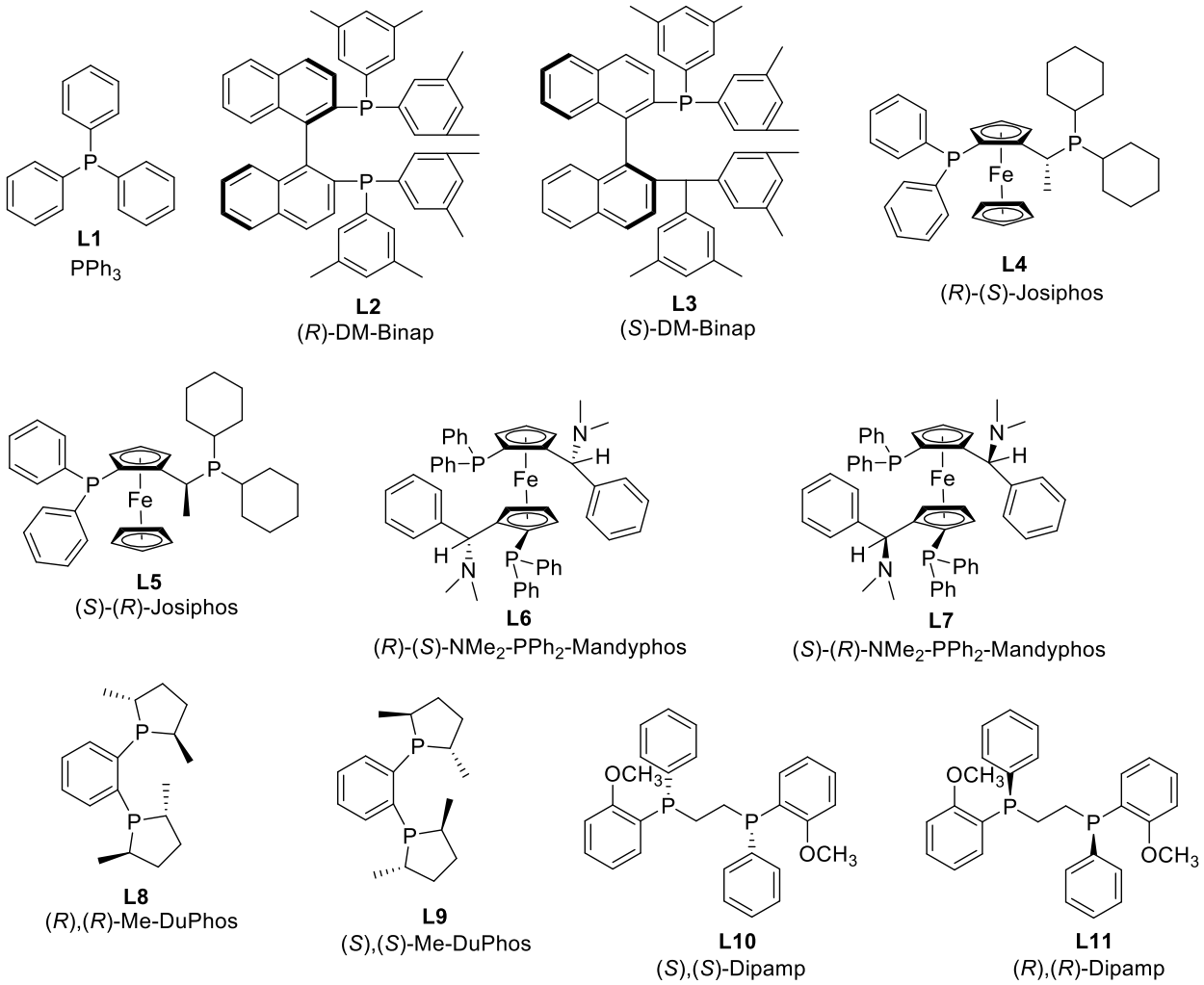


Figure 7 Phosphine ligands for the Cu(I)-mediated β-borylation on homoallylic boronate esters **5**.

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

Entry	Ligand	d.r.[b]	IY[c] (%)	Conv. (%)[d]
1	*(R),(S)*-Josiphos **L4**	6:1	50	>99
2	*(S),(R)*-Josiphos **L5**	1:6	30	>99
3	*(R),(S)*-NMe_2-PPh_2-Mandyphos **L6**	3:1	44	>99
4	*(S),(R)*-NMe_2-PPh_2-Mandyphos **L7**	3:1	24	>99
5	*(R,R)*-Me-DuPhos **L8**	1.85:1	42	>99
6	*(S,S)*-Me-DuPhos **L9**	1.4:1	35	>99
7	*(S,S)*-Dipamp **L10**	2.45:1	32	>99
8	*(R,R)*-Dipamp **L11**	2:1	41	>99

[a]Reaction conditions: see experimental. [b]Determined by ^{1}H NMR on the diborylated ester **6a** pure sample. [c]Determined on the pure diborylated ester **6a**. [d]Determined by ^{1}H NMR.

Table 4 shows that the ferrocene-based ligands (Entries 1-4, Table 4) did indeed provide higher levels of double diastereocontrol 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 diastereocontrol in general, and some differences between the matched and mismatched system.

In order to evaluate the effect of the C_β-substituent (R^1) of the homoallylic boronate ester **5** on the both the rate of the second borylation reaction (Scheme 4) and subsequent diastereocontrol, 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]

Entry	R^1 substituent on **5**	Reaction time (h)[b]	d.r.[c] (Ligand)	Conv. (%)[d] (IY, %)
1	*p*ClPh **5b**	6	1:1 (**L1**)	88 (20)
2	*p*ClPh **5b**	6	8:1 (**L4**)	89 (19)
3	*p*ClPh **5b**	6	1:5 (**L5**)	89 (18)
4	*p*MeOPh **5c**	6	1:1 (**L1**)	>90% (-)[e]
5	Me **5d**	4	1:1[f] (**L1**)	96 (51)
6	Me **5d**	4	1:1.38[f] (**L4**)	>99 (52)
7	Me **5d**	4	1:1.38[f] (**L5**)	>99 (42)
8	*n*Pr **5e**	4	1:1[f] (**L1**)	>99 (78)
9	*n*Pr **5e**	4	1:2.5[f] (**L4**)	>99 (73)
10	*n*Pr **5e**	4	1.5:1[f] (**L5**)	>99 (70)
11	*i*Pr **5f**	2	1:1[f] (**L1**)	>99 (60)
12	*i*Pr **5f**	2	1:11[f] (**L4**)	>99 (72)
13	*i*Pr **5f**	2	7:1[f] (**L5**)	>99 (69)

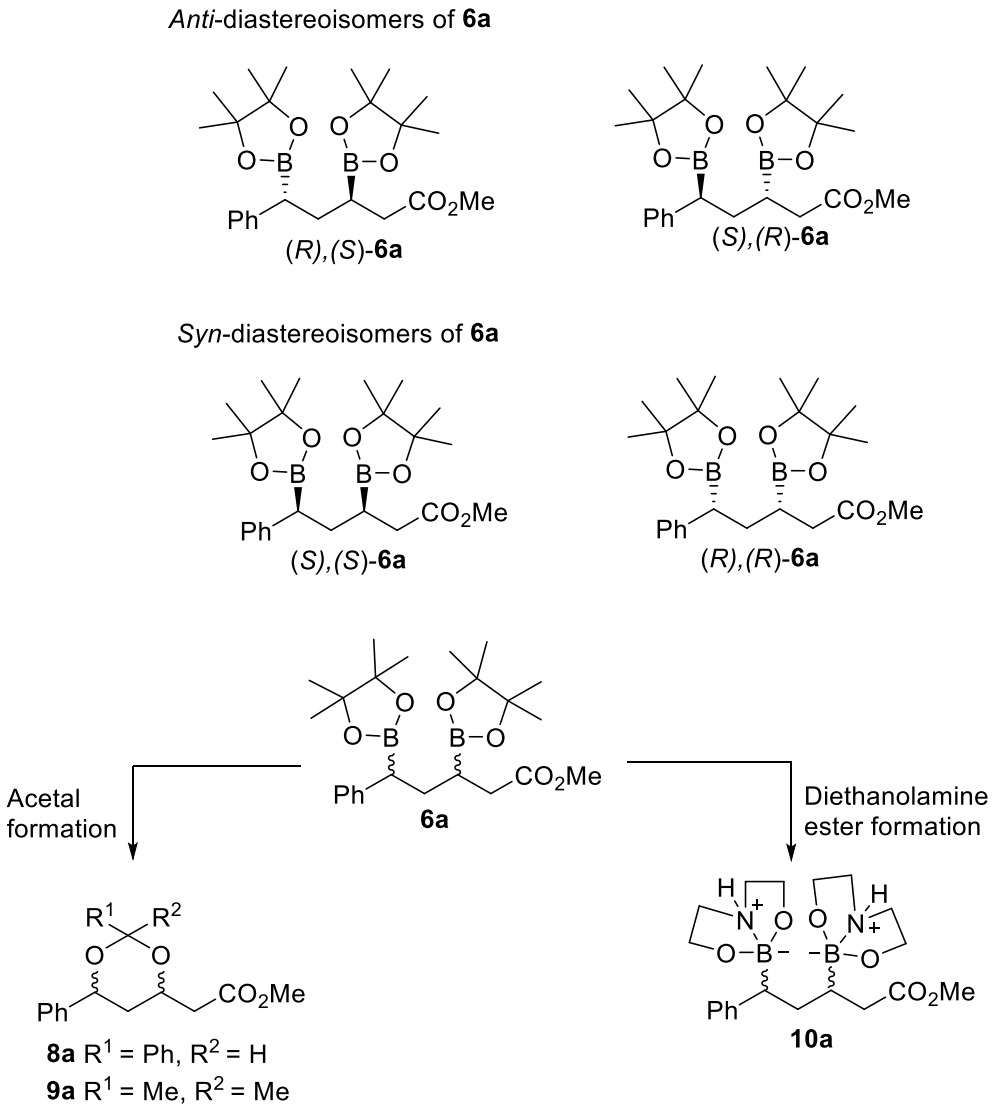
[a]Reaction conditions: see experimental. [b]Reaction followed by *in situ* ReactIR. [c]Determined by pure diborylated ester ^{1}H NMR. [d]Determined by crude diborylated ester ^{1}H NMR. [e]Not possible to obtain clean product due to decomposition (see ESI for crude ^{1}H NMR). [f]Determined by 700 MHz ^{1}H NMR using D_8-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 *i*Pr substituent, Josiphos was still able to largely overcome the impact of the existing chiral centre to give high levels of ligand-controlled diastereocontrol for the introduction of the second boryl moiety.

Stereochemical identification

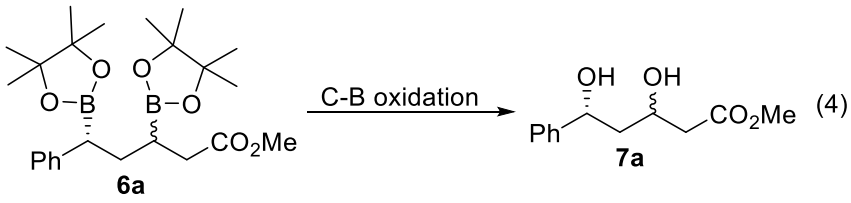
Once it was confirmed that the conjugate addition of second boryl group to the homoallylic boronate carboxylate esters **5** was possible and that moderate to excellent diastereocontrol was possible, it was necessary to confirm the identity of the diastereoisomers, and therefore separation through transformation 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[18] 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.



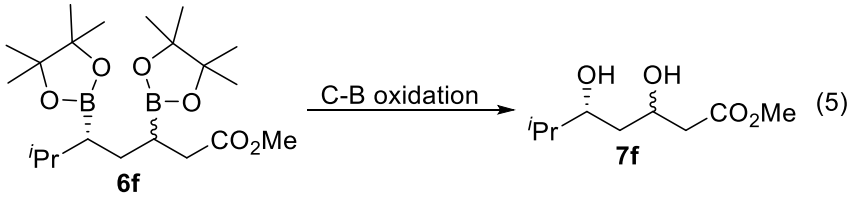
(4)

Table 6 Oxidation conditions to obtain 1,3-diol **7a** from the diborylated ester **6a**.[a]

Entry	*N*-Oxide (equiv.)	Reaction time (h)	Temp. (°C)	Isolated yield[b] (%)
1	4-MMNO (2)	6	RT	52[c]
2	4-MMNO (4)	16	RT	23[c]
3	TMANO (2)	6	RT	26[c]
4	TMANO (2)	3	50	60[d]

[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**.



(5)

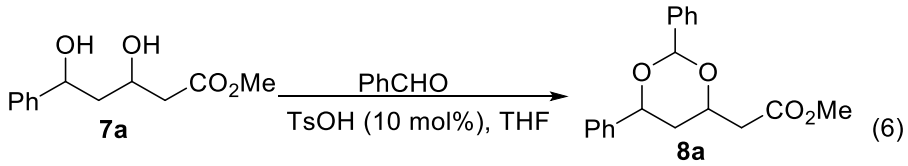
Table 7 Conditions for the oxidation of diborylated ester **6f.**[a]

Entry	Oxidant reagent (equiv.)	Solvent	Conv.-**6f**[b] (%)
1	$NaBO_3.4H_2O$ (6.0)	THF/H_2O	>99
2	Oxone (6.0)	MeOH	0
3	MCPBA (6.0)	DCM	>99

[a]Reaction conditions: For a 0.2 mmol reaction scale, stirred at RT during 2h, monitoring by TLC. [b]Determined by crude ^{1}H NMR.

For diboryl system **6f**, $NaBO_3.4H_2O$ (entry 1, Table 7) was found to be an ideal reagent for the oxidation of the two C-B bonds.[20] In contrast, Oxone surprisingly[21] did not yield into the desired 1,3-diol **7f**, whereas MCPBA[22] 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[23] was initially examined, as outlined in Table 8 for the synthesis of acetal **8a** from diol **7a**.



(6)

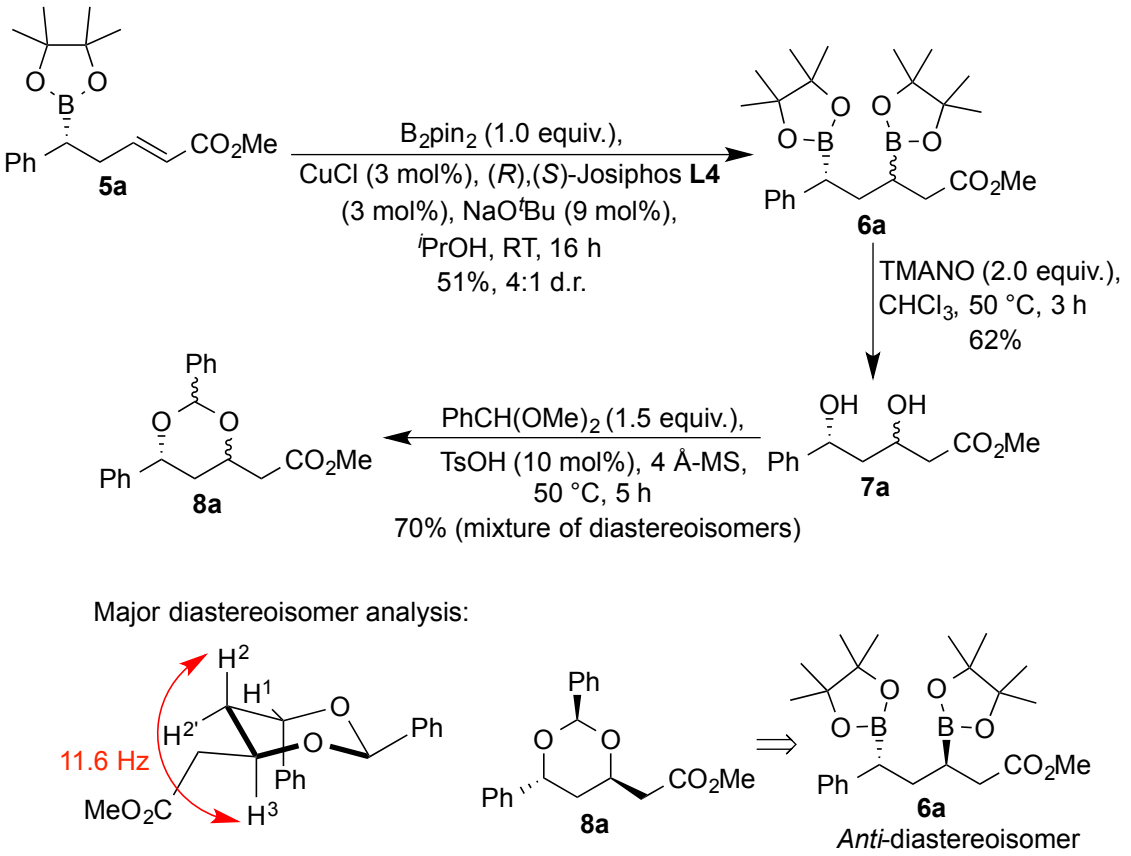
Table 8 Conditions for the synthesis of acetal **8a** from the diol **7a**.[a]

Entry	PhCHO (equiv.)	3 Å-MS	Temp. (°C)	Reaction Time (h)	Conv. **8a**[b] (%)
1	1.1	No	0	1.5	-
2	2.5	No	RT	1.5	24
3	1.1	Yes	RT	1.5	20
4	1.1	No	50	1.5	25
5	1.1	No	RT	1.5	-[c]
6	2.5	Yes	50	1.5	50
7	2.5	Yes	50	1.5	-[c]
8	1.5[d]	Yes[d]	50	6	>99

[a]Reaction conditions: see experimental. [b]Determined by crude ^{1}H NMR on the acetal **8a**. [c]Toluene was used as solvent. [d]$PhCH(OMe)_2$ used instead of PhCHO, using 4 Å M.S.

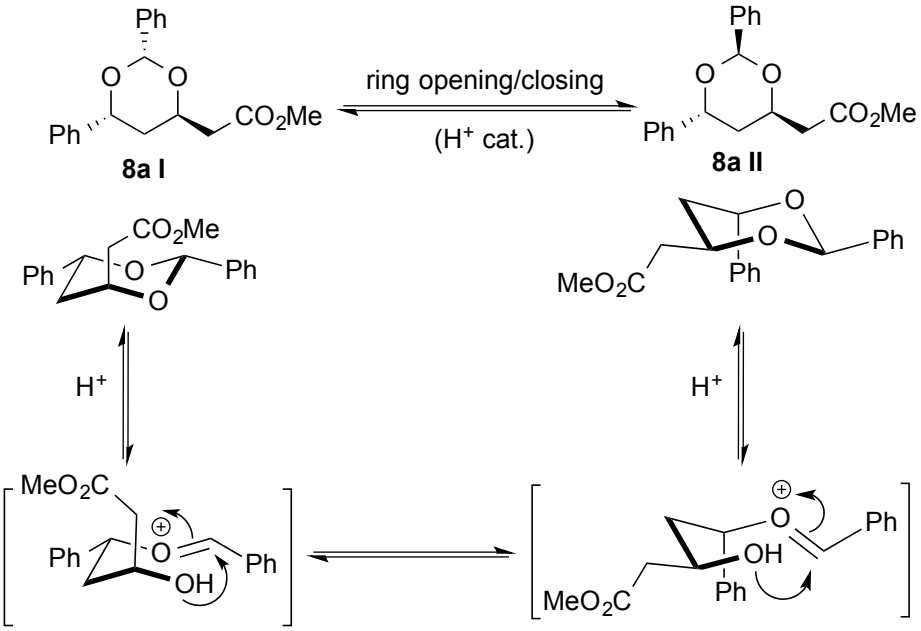
Using benzaldehyde under a wide variety of reactions conditions (entries 1-7, Table 8), formation of the acetal proved problematic, due to lack of clean reaction. However, use of benzaldehyde dimethyl acetal readily provided the target acetal **8a** (entry 8, Table 8) starting from a mixture of diastereoisomers. 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 alos obtained, with these fractions representing 15 and 55% yields, respectively). NMR analysis (see ESI) allowed the determination of the relative stereochemistry of the major diastereosiomer which corresponded to the *anti*-diastereoisomer (Scheme 6).



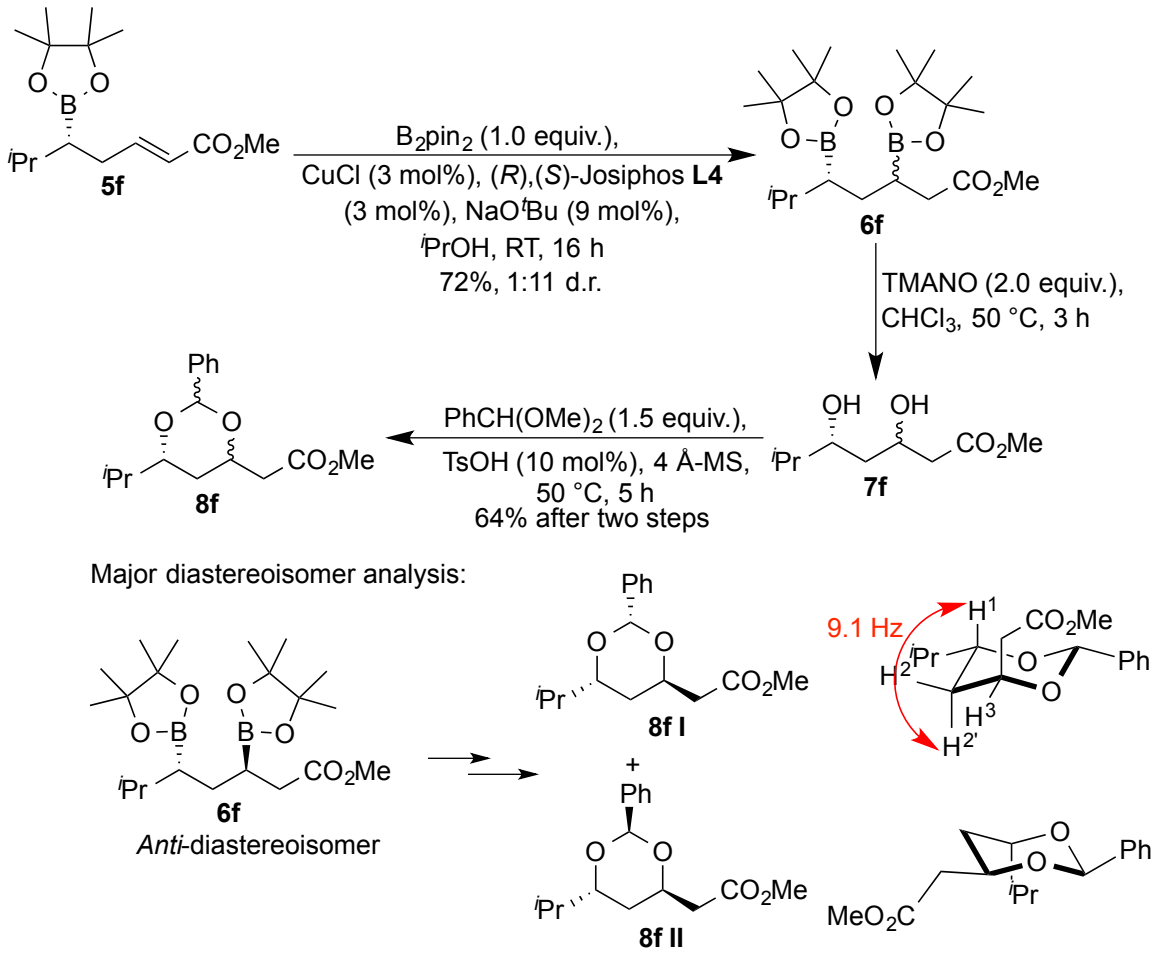
Scheme 6 Coupling constants for the *anti*-configuration of the 6-membered ring acetal **8a**.

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 diastereosiomers **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**.

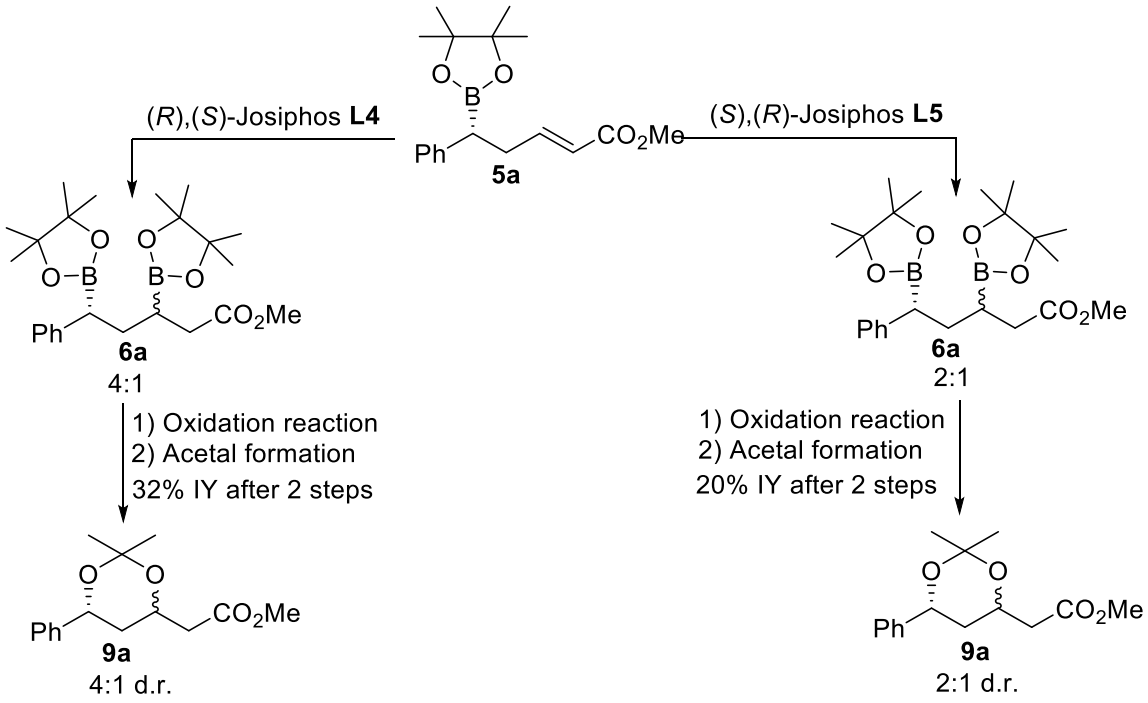
Similar derivatization studies on the isopropyl substituted system **6f** was also examined due to its excellent diastereoselectivity (up to 1:11 and 7:1, for (*R*),(*S*)-Josiphos **L4** and (*S*),(*R*)-Josiphos **L5**, respectively) as outlined in Scheme 8.



Scheme 8 Coupling constants for one of the *anti*-configuration 6-membered ring acetal analogues, **8f I**.

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 $NaBO_3.4H_2O$ conditions. However, the target chiral acetal **8f** was successfully obtained in good yields from two samples, derived from different reactions, *i.e.* 64% and 70% having used ligands **L4** and **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 **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 I** (Scheme 7) and a mixed sample of both **8f I** and **II**. By comparing the ^{1}H NMR spectra of both samples (see ESI), the relative stereochemistry and assigment of each, could be made, as indicated by the key coupling constant shown in Scheme 7.

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[24] and in fact, ^{13}C NMR analysis has proved an excellent tool for the determination of the relative stereochemistry in such systems.[25] Rychnovsky *et al.* reported[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**.

Hence, 1,3-diol **7a** was prepared as outlined above, using either (*R*),(*S*)-Josiphos **L4** or (*S*),(*R*)-Josiphos **L5** 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).

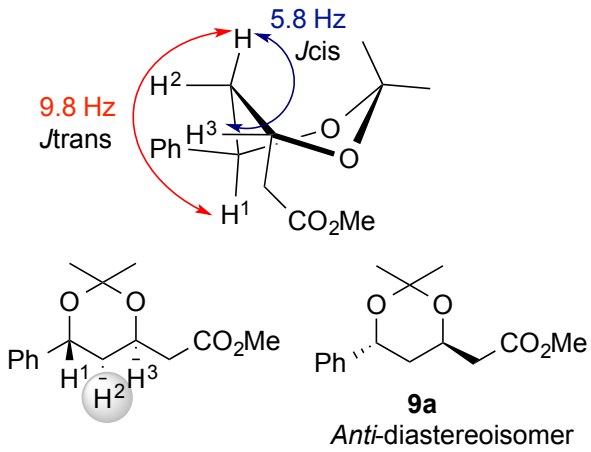


Figure 8 Coupling constants analysis for the *anti*-diastereoisomer of 6-membered ring acetal **9a**.

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 ^{1}H 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 [^{13}C]-acetonide method confirming the relative stereochemistry; when using (*R*),(*S*)-Josiphos **L4** as the ligand, the ^{13}C 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 ^{13}C NMR spectrum showing two

distinct methyl signals at δ 30.53 (equatorial) and δ 20.10 (axial) ppm (see ESI) clearly indicating the presence of the *syn*-diastereoisomer (Figure 9).

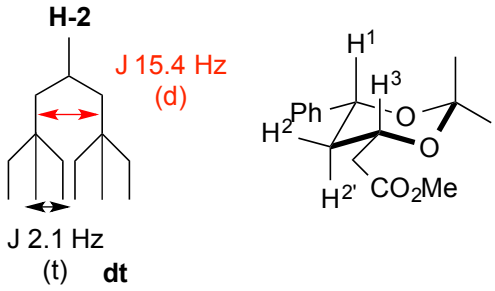
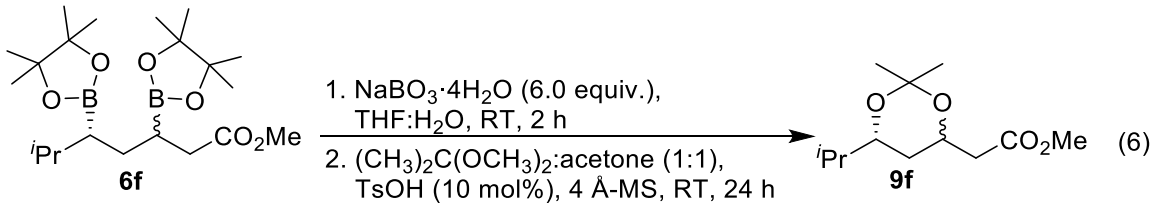
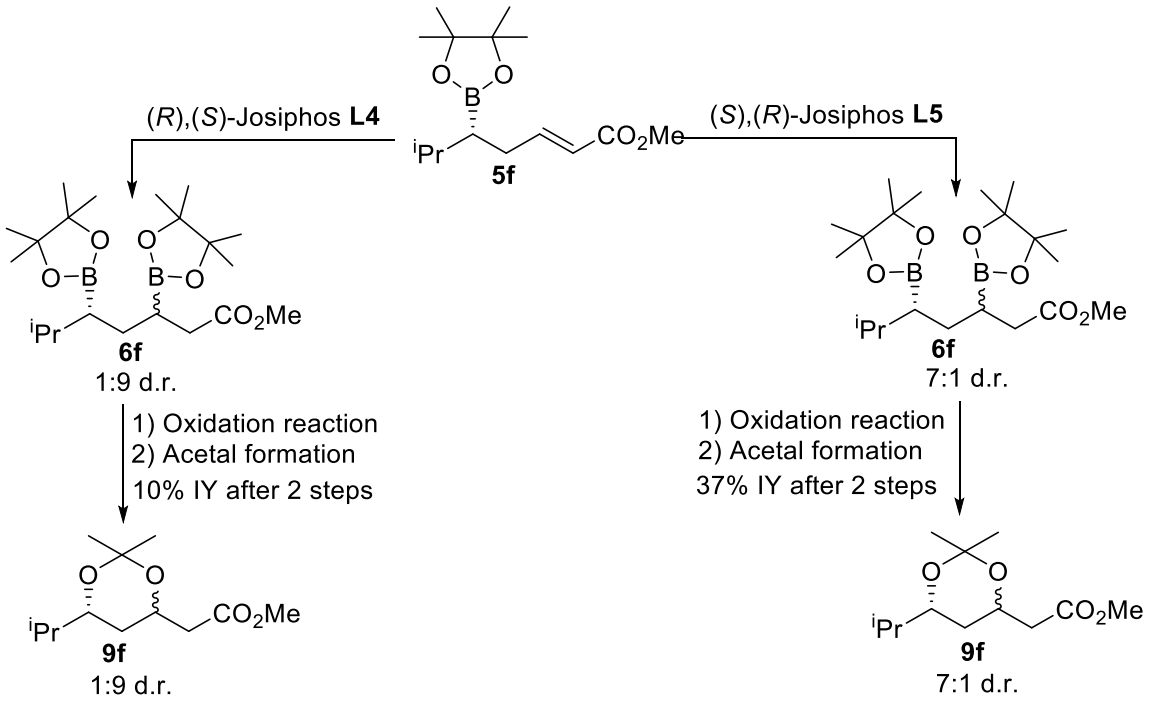


Figure 9 Conformational analysis of the *syn*-diastereoisomer of acetal **9a**.

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).



In this case, although the efficiency of the reaction differed depending upon the enantiomer of the chiral ligand used for the β-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 δ 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 (δ 30.02 ppm) and the other methyl in the axial position (δ 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 predomoninatly ligand controlled, but with some double diastereocontrol tining the final diastereoisomeric ratios.

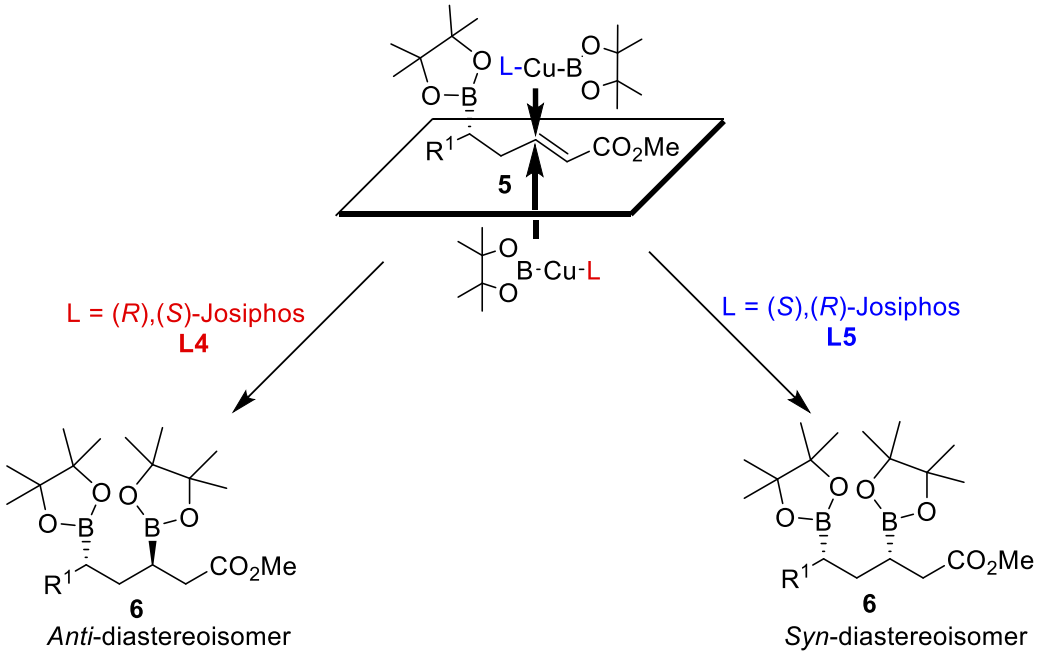
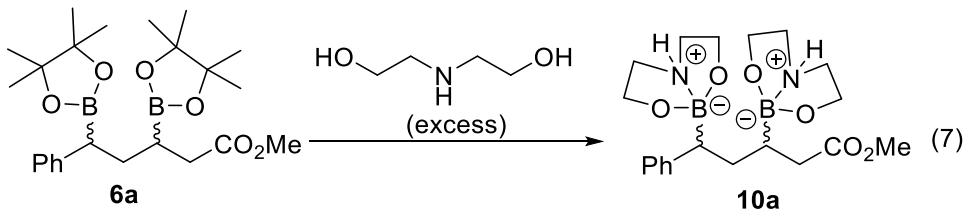
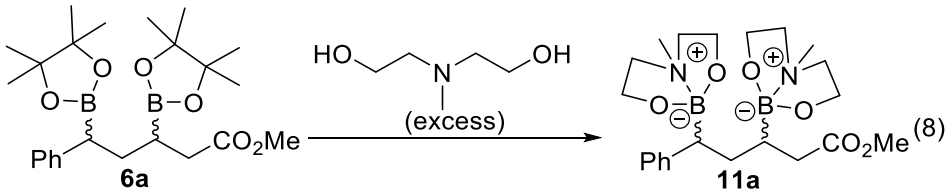


Figure 10 Stereoselectivity observed upon the addition of the 2nd boryl unit into chiral homoallylic boronate esters based on the enantiomer of the chiral diphosphine ligand used.

Complimentarily, another strategy for determining the relative stereochemistry was approached; the synthesis of the diethanolamino-boron complex **10a**, with the hope that X-ray crystallography would be useful to confirm the stereochemistry. After years of research and with several studies,[27] the facility for forming coordinating bonds with its neighbouring elements, *e.g.* N or O, exhibited by acidic tricoordinated sp^2 boron atoms has been demonstrated. Taking into account this interesting property, it was envisioned that the reaction of the diborylated ester **6a** with diethanolamine[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)[29] was also evaluated for the B-N complex formation (Eqn. 8), being not possible to obtain compound **11a**.

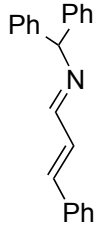
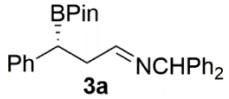
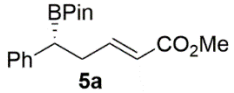
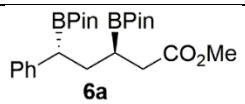
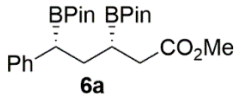
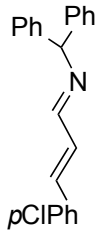
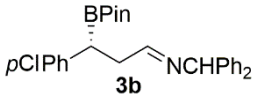
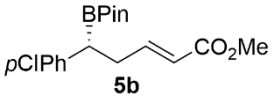
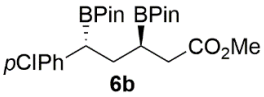
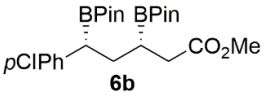
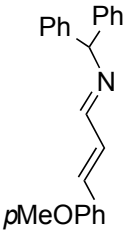
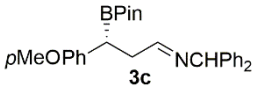
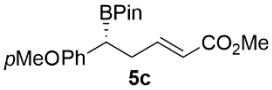
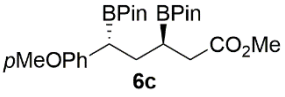
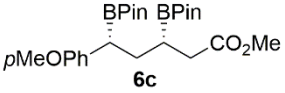
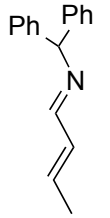
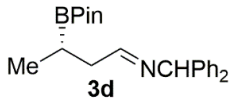
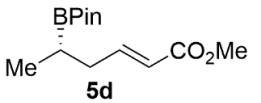
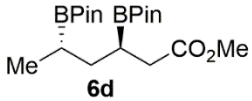
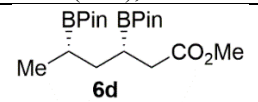
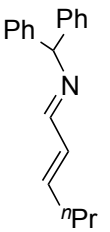
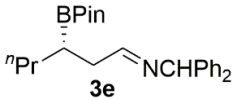
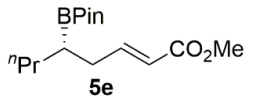
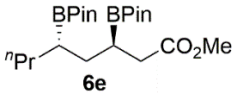
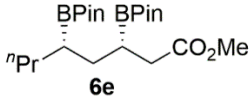
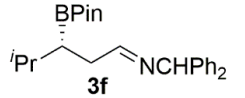
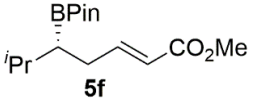
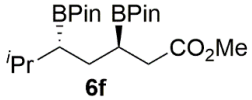


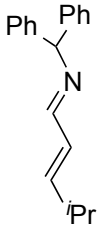
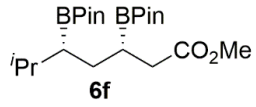
Conclusions

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 diasteroselective 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 C_β with alkyl substitued substrates (**5d** and **e**) providing lower diastereocontrol. The more hindered *iso*propyl-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.

Entry	α,β-Unsaturated aldimine	1st Borylated product	Homoallylboronate ester	2nd Borylated product
1	 **2a**	 **3a** (*R*)-DM-Binap **L2** 99% e.e. (*R*), >99% conv.[a]	 **5a** (*R*)-DM-Binap **L2** 99% e.e. (*R*), 66% IY	 **6a** (*R*),(*S*)-Josiphos **L4** 6:1 d.r. (*Anti*), 50% IY  **6a** (*S*),(*R*)-Josiphos **L5** 1:6 d.r. (*Syn*), 30% IY
2	 **2b**	 **3b** (*R*)-DM-Binap **L2** 98% e.e. (*R*), >99% conv.[a]	 **5b** (*R*)-DM-Binap **L2** 98% e.e. (*R*), 38% IY (>99% conv.)[a]	 **6b** (*R*),(*S*)-Josiphos **L4** 8:1 d.r. (*Anti*), 19% IY  **6b** (*S*),(*R*)-Josiphos **L5** 1:5 d.r. (*Syn*), 18% IY
3	 **2c**	 **3c** (*R*)-DM-Binap **L2** 87% e.e. (*R*), >99% conv.[a]	 **5c** (*R*)-DM-Binap **L2** 87% e.e. (*R*), 40% IY (>99% conv.)	 **6c**  **6c**
4	 **2d**	 **3d** (*R*)-DM-Binap **L2** 82% e.e. (*R*), >99% conv.[a]	 **5d** (*R*)-DM-Binap **L2** 82% e.e. (*R*), 37% IY (>99% conv.)	 **6d** (*R*),(*S*)-Josiphos **L4** 1:1.38 d.r. (*Anti*), 52% IY  **6d** (*S*),(*R*)-Josiphos **L5** 1:1.38 d.r. (*Syn*), 42% IY
5	 **2e**	 **3e** (*R*)-DM-Binap **L2** 96% e.e. (*R*), >99% conv.[a]	 **5e** (*R*)-DM-Binap **L2** 96% e.e. (*R*), 50% IY	 **6e** (*R*), (*S*)-Josiphos **L4** 1:2.5 d.r. (*Anti*), 73% IY  **6e** (*S*),(*R*)-Josiphos **L5** 1.5:1 d.r. (*Syn*), 70% IY
6		 **3f** (*R*)-DM-Binap **L2** 60% e.e. (*R*), >99% conv.[a]	 **5f** (*R*)-DM-Binap **L2** 60%	 **6f** (*R*),(*S*)-Josiphos **L4** 1:11 d.r. (*Anti*), 72% IY

 **2f**	e.e. (*R*), 59% IY	 **6f** (*S*),(*R*)-Josiphos **L5** 7:1 d.r. (*Syn*), 69% IY

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 ^{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 **º**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 *p*-anisaldehyde solution.

Deuterated chloroform ($CDCl_3$) was used as solvent for routine NMR measurements, unless stated otherwise. ^{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 (*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). ^{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 (δ) relative to tetramethylsilane, references to the chemical shifts of residual solvent resonances. ^{11}B NMR spectra were recorded on a Varian Brüker Advance-400 operating at a frequency of 128 MHz and the chemical shifts are reported in ppm (δ) relative to $BF_3(CH_3)_2O$.

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 ^{i}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 ^{i}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_3CN/H_2O 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×.

General procedure for the optimised synthesis of homoallylic boronate carboxylate esters from α,β-unsaturated aldehydes

To a round bottom flask containing ^{i}PrOH (8.0 mL) and oven-dried 3 Å-molecular sieves (2.0 g) was added an α,β-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 α,β-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%), NaO^{t}Bu (4.3 mg, 0.045 mmol, 9 mol%) and B_2pin_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 β-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_2O (90 μL, 5 mmol, 10.0 equiv). The mixture was stirred for 1 h at RT. The resulting solution was partioned 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) ν_{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) δ 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) δ 175.3 (*C*OOR), 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, $CDCl_3$) δ 33.5; LRMS (ESI+) m/z: [M + Na]+ 305.2 (100%); HRMS (ESI+-TOF) m/z:[M+H]+ Calcd for $C_{15}H_{28}{}^{10}BO_4$ 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 ºC, 0.2 mL/min, 254 nm, hexane:^{i}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 β-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_2pin_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) ν_{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) δ 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, $CDCl_3$) δ 174.1 (*C*OOR), 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,

$CDCl_3$) δ 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 $C_{24}H_{39}{}^{10}B_2O_6$ 443.3005; Found 443.2998.

Compound **6b**. Yield 93 mg (20%, yellow oil) with an R_f 0.68: IR (neat) ν_{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) δ 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, $CDCl_3$) δ 174.0 (<u>C</u>OOR), 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, $CDCl_3$): δ 33.1. LRMS (ESI+)m/z: [M+Na]+ 501.6 (100%), 480.8 (60%); HRMS (ESI+-TOF) m/z: [M+H]+ Calcd for $C_{24}H_{38}{}^{10}B_2{}^{35}ClO_6$ 477.2616; Found 477.2603.

Compound **6d**. Yield 97 mg (51%, yellow oil) with an R_f 0.6: IR (neat) ν_{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) δ 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) δ 184.5 (<u>C</u>OOR), 183.6 (<u>C</u>OOR), 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): δ 34.1 ppm; LRMS (ESI+) m/z: [M + Na]+ 405.3 (100%); HRMS (ESI+-TOF) m/z: [M+H]+ Calcd for $C_{19}H_{37}{}^{10}B_2O_6$ 381.2849; Found 381.2842.

Compound **6e**. Yield 318 mg (78%, yellow oil) with an R_f 0.71: IR (neat) ν_{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) δ 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 (*C*OOR), 183.0 (*C*OOR), 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]+ Calcdfor $C_{21}H_{41}{}^{10}B_2O_6$ 409.3162; Found 409.3170.

Compound **6f**. Yield 245 mg (60%, yellow oil) with an R_f 0.75; IR (neat) ν_{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 (*C*OOR), 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, 29.5, 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 $C_{21}H_{41}{}^{10}B_2O_6$ 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 filteration. 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_2O (1:1 by volume, 20.0 mL), followed by the addition of $NaBO_3.4H_2O$ (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 SiO_2 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 R_f 0.5: IR (neat) ν_{max} 2951 (m), 1733 (l), 1495 (s), 1451 (m), 1436 (m), 1339 (s), 1312 (s), 1205 (m), 1161 (l), 1104 (l), 1009 (l), 905 (s), 855 (s), 752 (l), 696 (l), 609 (m), 538 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{19}H_{20}O_4Na$ 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; H_2O: CH_3CN gradient 90:10, 4.4 mL.min^{-1}, 254 nm) t_R = 5.14 min., t_R = 5.43 min.: IR (Et_2O film) ν_{max} 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); ^{1}H NMR (400 MHz, $CDCl_3$) 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

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]+ Calcd for $C_{16}H_{22}O_4Na$ 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 SiO_2 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) t_R (*anti*-diastereoisomer) = 7.02 min; t_R (*syn*-diastereoisomer) = 6.94 min; with an R_f 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), 401 (s), 362 (m); ^{1}H NMR (400 MHz, $CDCl_3$) (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); ^{13}C NMR (101 MHz, $CDCl_3$) (mixture of diastereoisomers), *Anti*-diastereoisomer: δ 171.6 (<u>C</u>OOR), 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 (<u>C</u>OOR), 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 $C_{15}H_{20}O_4Na$ 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 μm; 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) ν_{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 δ 171.9 (*C*OOR), 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, 33.2, 30.5, 25.0, 24.6, 20.09, 19.05, 18.72, 18.0, 17.9; *Syn*-diastereoisomer δ 171.9 (*C*OOR), 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 $C_{12}H_{22}O_4Na$ 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.

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Graphical abstract