

# TETRAHEDRON: ASYMMETRY REPORT NUMBER 19

## The Rational Design and Systematic Analysis of Asymmetric Aldol Reactions Using Enol Borinates: Applications of Transition State Computer Modelling.

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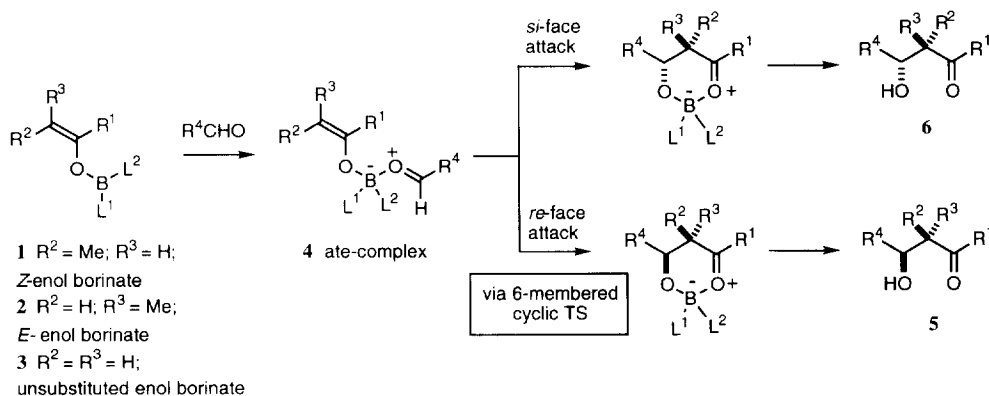
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### Contents

1.	Introduction	2613
2.	The development of the aldol transition state model	2614
3.	Analysing the origins of stereoselectivity in known aldol reactions of enol borinates	2617
4.	$\pi$ -Face selectivity in enol borinate additions to $\alpha$ -chiral aldehydes	2620
5.	The design and synthesis of new chiral boron reagents for asymmetric aldol reactions	2626
6.	Validity of the model and its limitations	2631
7.	Details of the development of the aldol force field model	2632
8.	Concluding remarks	2633

### 1. Introduction



Scheme 1: Stereocontrolled aldol addition using enol borinates

There is a continuing need for the development of new asymmetric methods together with innovative strategies to achieve absolute stereocontrol in organic synthesis. There are many different methods for asymmetric synthesis available, which have largely been developed from empirical findings, *i.e.* based on

intuition and trial and error processes. A valuable alternative to such time-consuming and expensive efforts would be to adopt a rational approach based on computer modelling of the transition states (TS) for individual reaction classes over a wide range of substitution. These quantitative TS models would then aid the design of new chiral reagents, which might then have general utility in asymmetric synthesis.

The boron-mediated aldol reaction<sup>1</sup> is an important carbon-carbon bond-forming process which has found widespread use in asymmetric synthesis. In this reaction (**Scheme 1**), a regio- and stereodefined enol borinate, as in **1–3**, is added to an aldehyde to initially generate a reactive ate-complex **4**, which then undergoes bond reorganization through a highly ordered cyclic TS to give an aldol adduct. On hydrolysis, a single stereoisomer **5** or **6** should ideally be generated by control of the *re-* vs *si-*face selectivity on nucleophilic attack on the aldehyde component. The quantitative prediction of stereoselectivity, over a wide range of substrate structures, and the design of new chiral enol borinates requires an understanding of the detailed reaction process outlined in **Scheme 1**. An early attempt to do this,<sup>2</sup> which only considered the preferred structure of the enol borinate component, *e.g.* see **Figure 1**,<sup>3</sup> was unsuccessful in accounting for the observed stereoselectivity. A model of the carbon-carbon bond-forming cyclic TS was clearly essential for a fuller understanding of the factors which control aldol stereoselectivity.

This Report provides an overview of the results of a collaborative project between the Milano and Cambridge groups over an 8-year period (1987-1995). The project was targeted at: (i) the systematic analysis of stereocontrol in asymmetric aldol reactions using enol borinates derived from ketones; and (ii) the rational design and synthesis of new chiral enol borinates. We first describe the development of a quantitative TS model for the prediction of stereoselectivity in the boron-mediated aldol reaction of ketones with aldehydes. This model provides qualitative insights into the factors contributing to the stereochemical outcome. We then go on to describe the application of this Milano-Cambridge force field model to a variety of systems of synthetic importance, and the design and preparation of new chiral enol borinates. Finally, we outline the limitations of the model and the scope for future work.

## 2. The development of the aldol transition state model

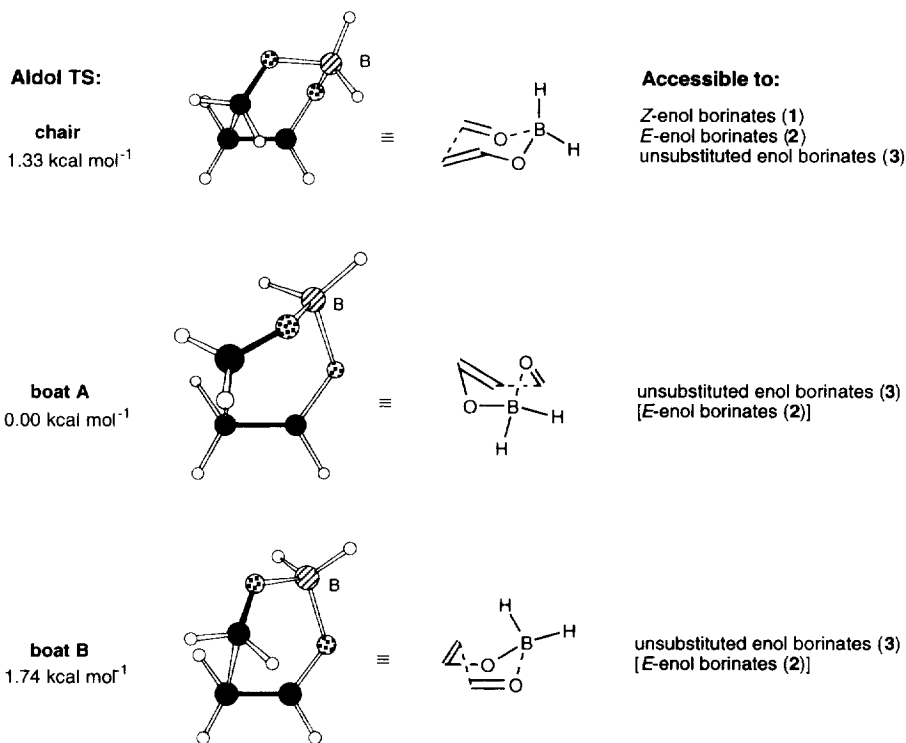
The boron-mediated aldol reaction is kinetically controlled, so all accessible transition structures must be calculated. This can be achieved using *ab initio* MO theory, but not molecular mechanics. However, to analyse the sense of asymmetric induction in systems of synthetic significance *ab initio* MO theory requires too much computer time, and molecular mechanics must be used instead. An alternative procedure would be to use semi-empirical methods (such as MNDO or AM1), which had been valuable in an earlier study at Milano of a similar reaction.<sup>4</sup> It was decided not to extend this approach, because of concerns about the accuracy of these ground-state parameterised methods when applied to transition states. At Cambridge, a theoretical study<sup>2</sup> of enol borinates using *ab initio* MO theory combined with molecular mechanics had indicated that this would be a more promising approach. This has the advantage of combining the accuracy of *ab initio* MO methods, with the speed of molecular mechanics, allowing the analysis of large, conformationally flexible systems.

However, both of these earlier studies had only looked at ground states. Could the method be extended to transition states? The pioneering work of Houk's group<sup>5</sup> had shown that this may be possible. Following Houk's lead, *ab initio* MO theory was used to calculate the properties of the TS "core" of the boron-mediated aldol reaction, where bonds were being broken and formed, and molecular mechanics was used to analyse the properties of the rest of the system, *i.e.* the parts of the structure that were not directly involved in the reaction, but which provided the steric and electronic effects necessary for stereoselectivity. This approach is based on the observation that bond lengths and other geometrical parameters of transition structures calculated for several reaction classes have a relatively narrow range of values.<sup>5,6</sup> This supports the idea that transition structures of complex organic reactions could be calculated by molecular mechanics

using the values calculated *ab initio* for less complex cases (transition structure “cores”) as “natural” bond lengths and angles for the forming and breaking bonds. Thus this approach appeared to be well suited to a study of the boron-mediated aldol reaction in **Scheme 1**.

### 2.1 *Ab Initio* MO calculations

A long series of *ab initio* MO calculations were undertaken. At first (1988), the transition structures were rather limited in size, typically featuring the addition of the  $\text{BH}_2$  enol borinate derived from acetaldehyde to formaldehyde. The computer power available increased dramatically through the project, so this calculation became progressively easier. This simplest reaction presented a challenge, because several competing cyclic transition structures were likely to be involved. Houk had previously shown that the chair and boat A transition structures shown in **Scheme 2** and **Figure 2**<sup>3</sup> were important.<sup>7</sup> However, there may be other accessible transition structures, even for this system (see Sections 2.3 and 6.3).



**Scheme 2: The three aldol transition structures from *ab initio* MO theory**

Having performed many calculations on this simplest system, we systematically replaced each hydrogen by a methyl group, one at a time. The 7 new structures were all investigated, for each of the transition state geometries (chair and boat A, leading to a total of 14 structures). Until recently (1991), it was not possible for us to study larger structures, nor to use larger basis sets than 3-21G. Now we are able to study slightly larger structures at a higher level of theory, and the results do not change qualitatively.

## 2.2 Force Field Models

The simplest way to extend the *ab initio* data to larger systems is the “rigid transition state model”: the atoms involved in bonding changes are fixed at the transition state geometry (either by fixing their cartesian coordinates or some internal coordinates, *i.e.* bond lengths and angles), and the geometries of all attached groups are optimized using molecular mechanics. This procedure was not accurate enough for this study, so we moved on to the “flexible transition state model”, in which the positions of all atoms, including those involved in bonding changes, are optimized. This can only work in a normal molecular mechanics framework if all the bonds have positive force constants. This means that the transition state, a saddle point on the potential energy surface, is treated as a minimum. In a one-dimensional potential surface, this would look extraordinary, because a peak is turned into a trough. However, the systems of interest have many dimensions, and a saddle point has negative curvature in only one direction (the negative force constant corresponds to motion along the reaction coordinate). All other vibrational motions have positive force constants, exactly like energy minima on potential surfaces. Thus, only one normal mode needs to be inverted, in a system that has tens or hundreds of normal modes.<sup>5</sup>

The “flexible transition state model” approach requires the development of new parameters, and often a large number of them. While many parameters in force fields are thoroughly tested and well documented, the new parameters developed for the transition state core (the atoms involved in bonding changes) are usually developed by trial and error based on a limited set of *ab initio* data, and they may or may not be good. In this study, we concentrated on comparisons of several, very similar, transition states (*e.g.* the same reagent under the same conditions attacking one face of a carbonyl or the other, leading to diastereomeric products). It is reasonable to expect, therefore, that many of the inherent deficiencies of the force field parameters will tend to cancel, and the preferred pathway may be determined qualitatively or even semi-quantitatively.

## 2.3 Development of the Milano-Cambridge force field

The Milano-Cambridge model is based on Allinger’s widely used MM2 force field.<sup>8</sup> The additional parameters were developed by trial and error. This labour intensive process took many months, because if any one of the many parameters was altered, the whole force field had to be retuned. Bond lengths and bond angles were included by averaging the values from the *ab initio* calculations. Initial values for bond strengths and angle bending were taken from the MM2 force field, and reduced when they involved forming and breaking bonds. Atom-centred point charges were taken from Löwdin population analyses of the *ab initio* data. Torsion parameters were developed empirically. All these parameters had to be tuned so that together they made a coherent force field. Section 7 provides details on the development of the force field model.

Early on in this process, the new transition structure boat B, shown in **Scheme 2** and **Figure 2**, was produced by the force field. At the time, this did not correspond to any of the *ab initio* results. This structure was used as the input to the MO program, and it proved to be a genuine transition structure (see also Section 6.3). The same structure was later located by F. Bernardi’s group (Bologna) at the MC-SCF/3-21G level.<sup>9</sup>

Eventually, a useful force field was developed which was able to reproduce the geometries and the relative energies of the *ab initio* structures. At last (1990), we were in a position to use the model to analyse experimental results and to predict the likely outcome of future experiments. The parameters for the force field have all been published, and are also available in the current distributed version of Clark Still’s MacroModel (4.5).<sup>10</sup> The force field reproduced the experimental *syn:anti* stereoselectivities for the aldol reactions of *Z* and *E* substituted enol borinates from ethyl ketones with aldehydes.<sup>11</sup> In order to analyse a stereochemical result for a chiral enol borinate aldol reaction, or to predict the likely outcome of a future experiment, the system has to be entered into MacroModel and then conformation searches performed.<sup>12</sup>

The searches give two sets of diastereomeric low energy structures (*si* face transition structures; *re* face transition structures). A Boltzmann distribution at the reaction temperature (usually 195 K), within 2.5 kcal mol<sup>-1</sup>, gives the calculated  $\pi$ -face selectivity for attack on the aldehyde component, *i.e.* corresponding to the *si:re* ratio.

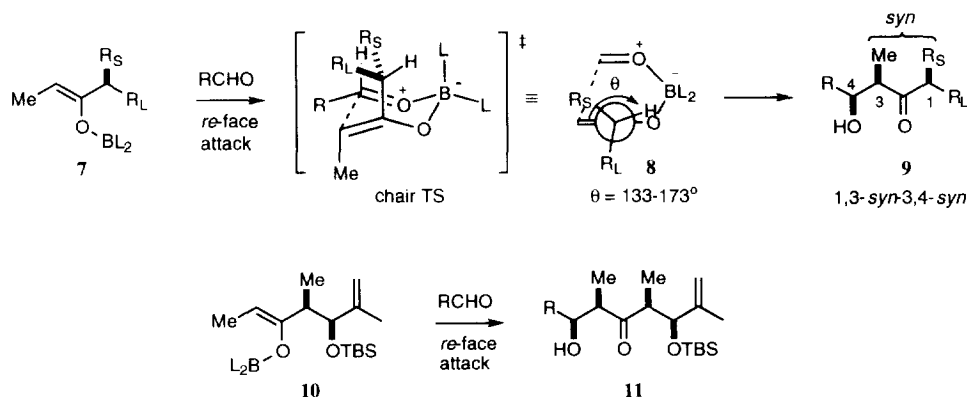
### 3. Analysing the origins of stereoselectivity in known aldol reactions of enol borinates

The force field model described in Section 2 was used to assess the energetic effects of chiral substitution and hence reaction stereoselectivity in synthetically interesting aldol reactions.<sup>13,14</sup> The model reproduced the sense and degree of stereoselectivity for known aldol reactions of enol borinates, particularly regarding the effects of substitution in the carbonyl components and the ligands on boron. This helped clarify the relative importance of the various structural factors involved in determining the stereochemical outcome of various known asymmetric aldol reactions.

#### 3.1 *Z*-Enol borinates from ethyl ketones

Our force field was tested first on the aldol reactions of *Z*-enol borinates with simple achiral aldehydes.<sup>13</sup> This is the most straightforward case, because most experiments show high *syn* selectivity for this series. The calculations suggested that of the three possible transition state geometries, only the chair structure in **Scheme 2** and **Figure 2**<sup>3</sup> was accessible to the reaction. The steric effect of a *Z* methyl group raised the energies of the two boat transition structures so much that they were no longer feasible reaction pathways. The force field gave a meaningful value for the *syn:anti* selectivity of a wide range of aldol reaction types, and also for the *si:re* face selectivity of the addition of chiral *Z*-enol borinates to aldehydes.

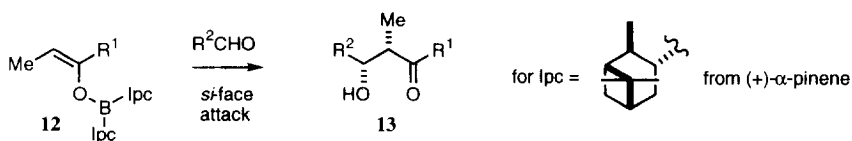
*Substrate control.* As shown in **Scheme 3**, for the reactions of *Z*-enol borinates **7** derived from  $\alpha$ -chiral ethyl ketones with achiral aldehydes, a general model was devised by inspection of the preferred transition structures in a number of cases.<sup>13</sup> In the preferred chair TS corresponding to **8**, the hydrogen on the  $\alpha$ -stereogenic centre is directed towards the boron ligand (*i.e.* the dihedral angle C=C\*-H is in the range  $\theta = 153 \pm 20^\circ$ ), the large group R<sub>L</sub> is opposite to the incoming aldehyde, and the small group R<sub>S</sub> points towards the forming C-C bond of the chair transition structure. This model adequately accounts for the sense of  $\pi$ -face selectivity in the reactions of *Z*-enol borinates of general type **7** leading preferentially to *syn* aldol products **9**. For example, the aldol addition<sup>15</sup> of chiral enol borinate **10** which gives **11** with high selectivity was calculated to proceed predominantly through the chair TS corresponding to *re*-face attack. The disfavoured chair TS for *si*-face attack on methacrolein is shown in **Figure 3**.<sup>3</sup>



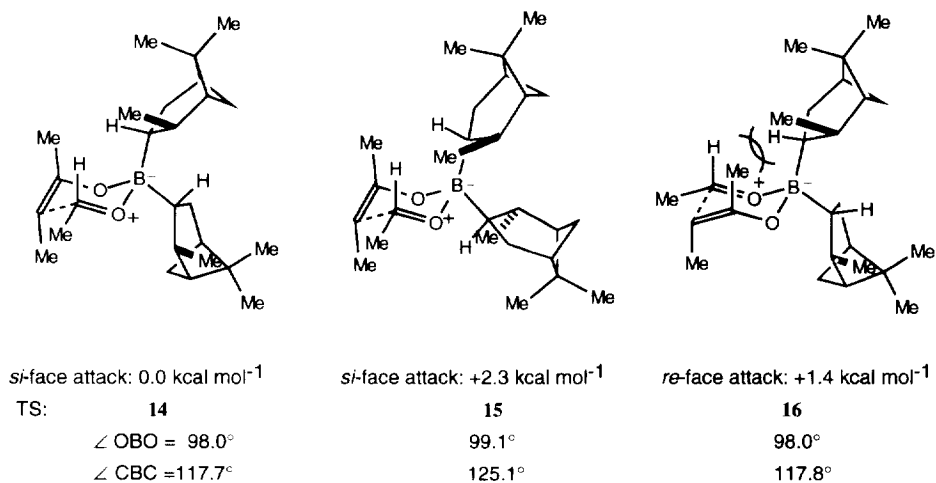
**Scheme 3:** A general transition state model for *Z*-enol borinates derived from  $\alpha$ -chiral ketones

**Reagent control.** As shown in **Scheme 4**, for *syn* aldol reactions of ethyl ketones operating under reagent control, we analysed initially the origins of stereoselectivity for enol diisopinocampheyl borinates **12** adding to aldehydes to give **13** preferentially.<sup>16a,17</sup> Note that the minimum energy structure of this general class of chiral enol borinate is already shown in **Figure 1**.<sup>3</sup> For the aldol reaction of the *Z*-enol borinate of butanone (Ipc ligands derived from (+)- $\alpha$ -pinene) with acetaldehyde, the calculated chair transition structures **14**, **15** and **16** are shown in **Scheme 4**.<sup>13</sup> The lowest energy chair TS, *i.e.* **14**, corresponding to *si*-face attack on the aldehyde is also depicted in **Figure 4**. The calculated *si:re* selectivity in this reaction is 19:1, while the experimental value is 10:1 for the related case of diethylketone.<sup>16a,17</sup> Transition structures **14** and **15** were found within 2.5 kcal mol<sup>-1</sup> of the minimum energy conformation for reaction on the aldehyde *si*-face, whilst only structure **16** was found for *re*-face attack (+1.4 kcal mol<sup>-1</sup>).

From examination of these chair transition structures, it appears that in the favoured *si*-face attack mode, the methyl group adjacent to boron on the axial Ipc ligand is oriented towards the aldehyde hydrogen in **14**, *i.e.* away from the methyl group on the enol borinate. In the *re*-face attack mode, this same methyl on the axial ligand is directed towards the enolate methyl in **16**, which may explain its higher energy relative to **14** for *si*-face attack. As expected, for a force field calculation, the strain energy cannot be localised to a single interaction but is distributed throughout the structure.



**Scheme 4:** Asymmetric *syn* aldol reaction using Ipc ligands on boron



**Scheme 5:** Chair transition structures for the *Z*-enol borinate of butanone (Ipc ligands) adding to acetaldehyde

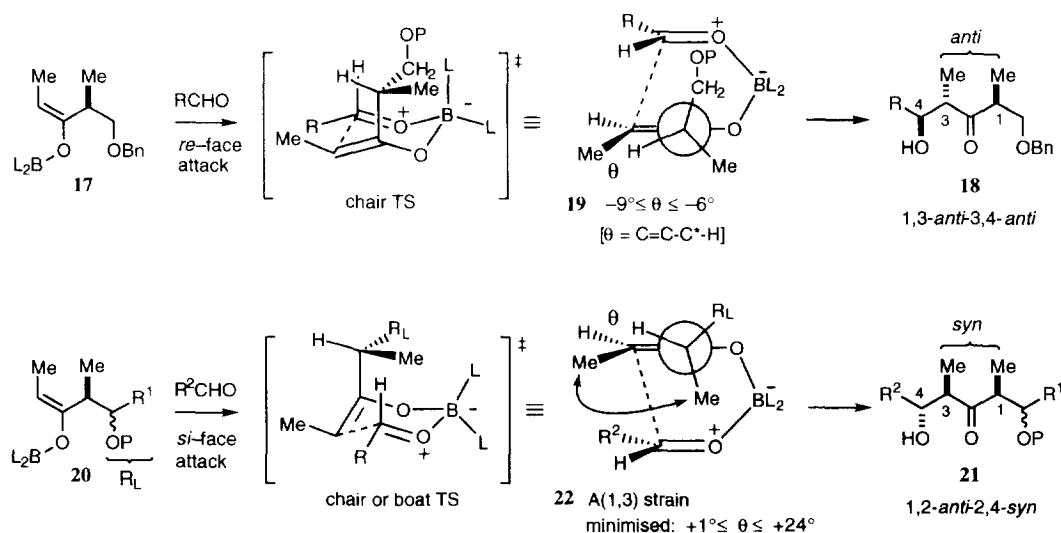
We obtained similar results for related reactions with other aldehydes performed at Cambridge, *e.g.* methacrolein and isobutyraldehyde.<sup>16a,17</sup> The calculated ratios in these cases were in good agreement with the experimental results (methacrolein, *si:re* calc. = 24:1, *cf.* exp. = 27:1; isobutyraldehyde, *si:re* calc. = 5:1, *cf.* exp. = 5:1). While the relative energies of the transition structures changed, there was no evident

change in the conformations relative to the acetaldehyde case in **Scheme 5**, which would allow us to rationalize these differences.

From inspection of the diastereomeric transition structures **14** and **16**, it is evident that the Ipc ligands hold the same relative orientation. Note that the methyl groups adjacent to boron on the two ligands are on the same side. This suggests that the ligands are locked relative to each other in the low energy forms for both *re*- and *si*-face attack. From this analysis, and from a number of other cases, it appears that both pseudo-axial and pseudo-equatorial chiral ligands are important in determining face selectivity, *i.e.* all of the ligand structure is important in determining the observed stereoselectivity. The equatorial ligand is not merely acting as a bulky group, but it contributes to generate the conformational lock that ultimately provides the energy difference in the diastereomeric transition structures. A different relative orientation of the two Ipc ligands in **15** results in a conformation of substantially higher energy (+2.3 kcal mol<sup>-1</sup>), where the CBC bond angle has opened out to 125°, compared to 118° for the other two cases. In fact, this is a C<sub>2</sub>-symmetric form for the B(Ipc)<sub>2</sub> group, *i.e.* with the methyl groups adjacent to boron on the two Ipc ligands on opposite sides. This is underlined by similar calculations performed on an analogous enol borinate, where the *gem*-dimethyl bridge of the Ipc ligands was deleted. These indicated that there are now three transition structures within 2.5 kcal mol<sup>-1</sup> of the lowest energy conformation for both *si*- and *re*-face attack, leading to the prediction of much poorer enantioselectivity relative to the parent Ipc reaction.<sup>13</sup>

### 3.2 *E*-enol borinates from ethyl ketones

As summarised in **Scheme 2**, *Z*-enol borinates have access predominantly to only one transition structure arrangement, *i.e.* the chair. In comparison, *E*-enol borinates are more of a problem, both experimentally and computationally, because the boat-type transition structures (boats A and B in **Scheme 2** and **Figure 2**) are close in energy to the chair form. Nevertheless, application of the force field to the aldol reactions of *E*-enol borinates also led to good agreement with the available experimental data.<sup>14</sup>



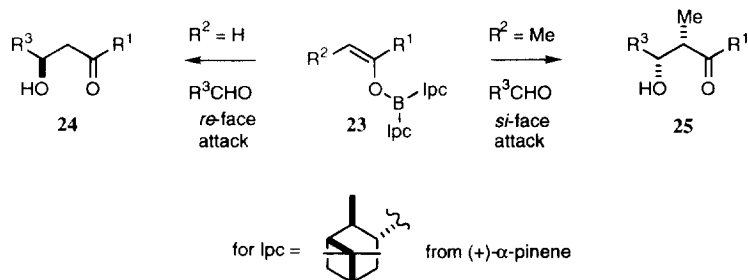
**Scheme 6:** General transition state models for *E*-enol borinates derived from  $\alpha$ -chiral ethyl ketones

As shown in **Scheme 6**, the high levels of stereoselectivity obtained<sup>18</sup> for the *E*-enol borinate **17** giving **18** was explained by the reaction proceeding predominantly through chair TS **19**, corresponding to

*re*-face attack on the aldehyde. For the addition of **17** to methacrolein, the favoured transition structure (*cf.* **19**) is shown in **Figure 5**.<sup>3</sup> This contra-steric outcome was ascribed to an electronic repulsion (lone-pair  $\leftrightarrow$  lone-pair) involving the benzyl ether and enolate oxygens, which is more serious for attack on the aldehyde *si*-face. Replacing the CH<sub>2</sub>OBn group by a larger substituent like CH(OP)C(Me)=CH<sub>2</sub> or CH(OP)*i*-Pr, as in *E*-enol borinate **20**, leads to the aldol reaction favouring formation of adduct **21**.<sup>19,20</sup> In this case, the modelling indicates that the aldol addition proceeds *via* **22**, which now can be either a chair or a boat TS.<sup>14</sup> In this steric model, the hydrogen on the  $\alpha$ -stereogenic centre approximately eclipses the enol borinate double bond to minimise allylic strain. The large group R<sub>L</sub> is directed away from the incoming aldehyde and the smaller methyl group is pointing towards it. The steric effect from a large R<sub>L</sub> group now overcomes any electronic preference from the ether oxygen orientation, leading to the observed reversal in  $\pi$ -face selectivity. Note that the above *E*-enol borinate transition state models differ substantially from that developed earlier for the corresponding *Z*-enol borinates in **Scheme 3**.<sup>13</sup>

### 3.3 Unsubstituted enol borinates from methyl ketones

While the force field model worked well for *Z*- and *E*-enol borinates derived from ethyl ketones, it appeared inadequate for analysing the selectivity in aldol reactions involving unsubstituted enol borinates derived from methyl ketones. This is due to the relative weighting of chair and boat transition structures in these systems (see Section 6.3). Reasonable agreement with experimental results available for methyl ketone aldol reactions is possible, however, if it is assumed that the boat A transition structures shown in **Scheme 2** and **Figure 2**<sup>3</sup> dominate (*i.e.* all the chair and boat B transition structures are "filtered" and discarded from the calculations).<sup>21</sup> The new protocol accounts for the reversal in aldehyde  $\pi$ -face selectivity observed for aldol reactions of enol diisopinocampheyl borinates **23** in **Scheme 7**, where adduct **24** is obtained for methyl ketones while **25** is obtained for ethyl ketones (*cf.* **Scheme 4**).<sup>17</sup>



**Scheme 7:** Reversal in aldehyde  $\pi$ -face selectivity for the Ipc-mediated aldol reactions of methyl and ethyl ketones

## 4. $\pi$ -Face selectivity in enol borinate additions to $\alpha$ -chiral aldehydes

### 4.1 Additions of *Z*-enol borinates to $\alpha$ -chiral aldehydes

Nucleophilic additions to  $\alpha$ -chiral aldehydes is commonly analysed by the Felkin-Anh model,<sup>22</sup> but this simple approach does not account for all experimental results. When a *Z*-enol borinate is reacting through a chair transition structure, the favoured conformation proposed by the Felkin-Anh model contains a (+/-) double gauche pentane interaction.<sup>23</sup> This unfavourable steric interaction raises the energy of the Felkin pathway in **Scheme 8** and other transition structures become important. A modified orientation proposed by Roush<sup>24</sup> may enhance attack by the Felkin pathway, but attack on the opposite face of the aldehyde by an "anti-Felkin" pathway may be preferred. However, the relative contributions of three competing transition structures are hard to assess intuitively.



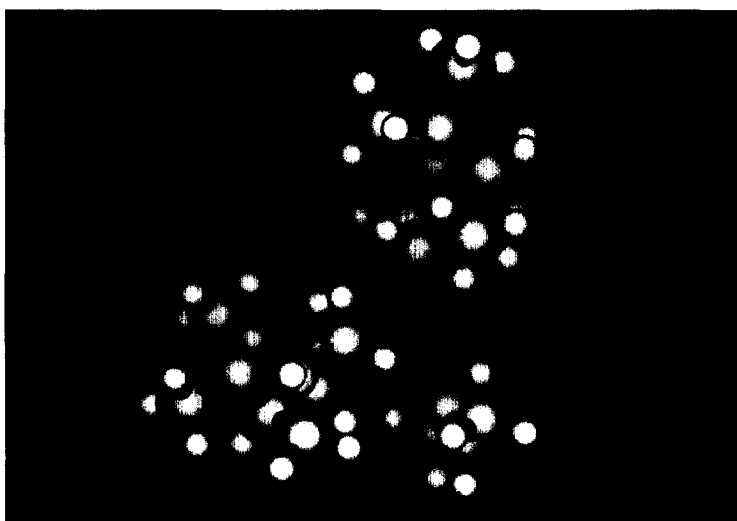


Figure 1: Z-enol borinate of butanone, with isopinocampheyl ligands on boron

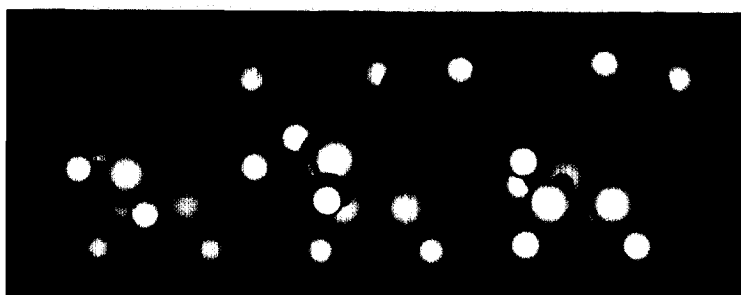


Figure 2: The three transition structures from *ab initio* MO theory: chair; boat A; boat B  
(multiple bonds are pink; forming and breaking bond are yellow/green)

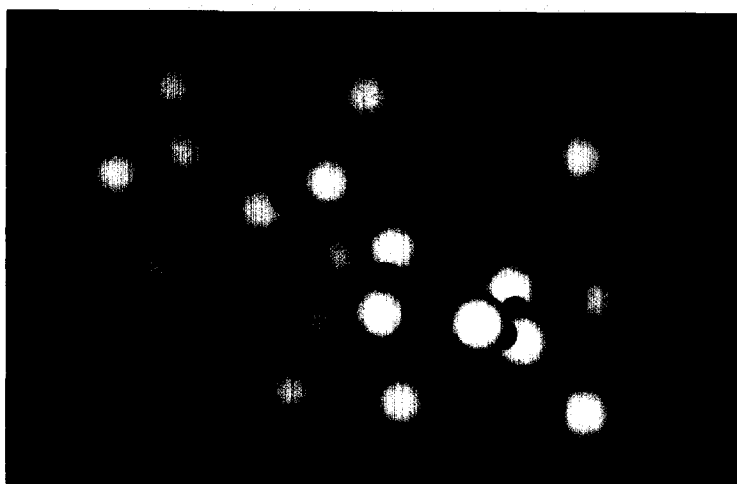
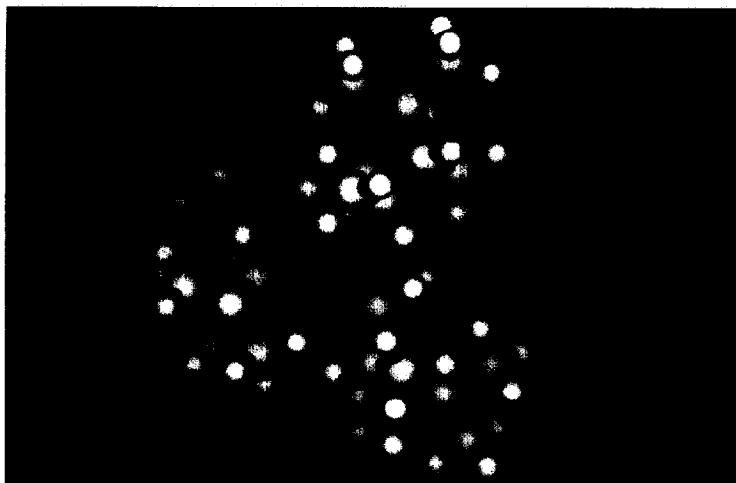
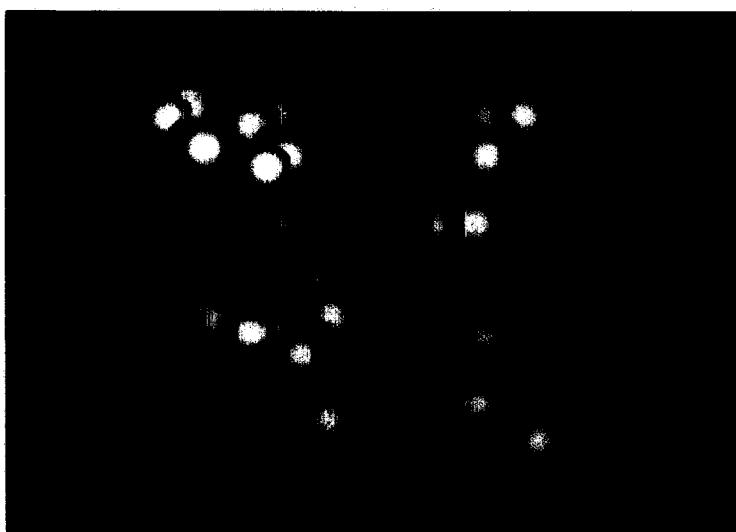


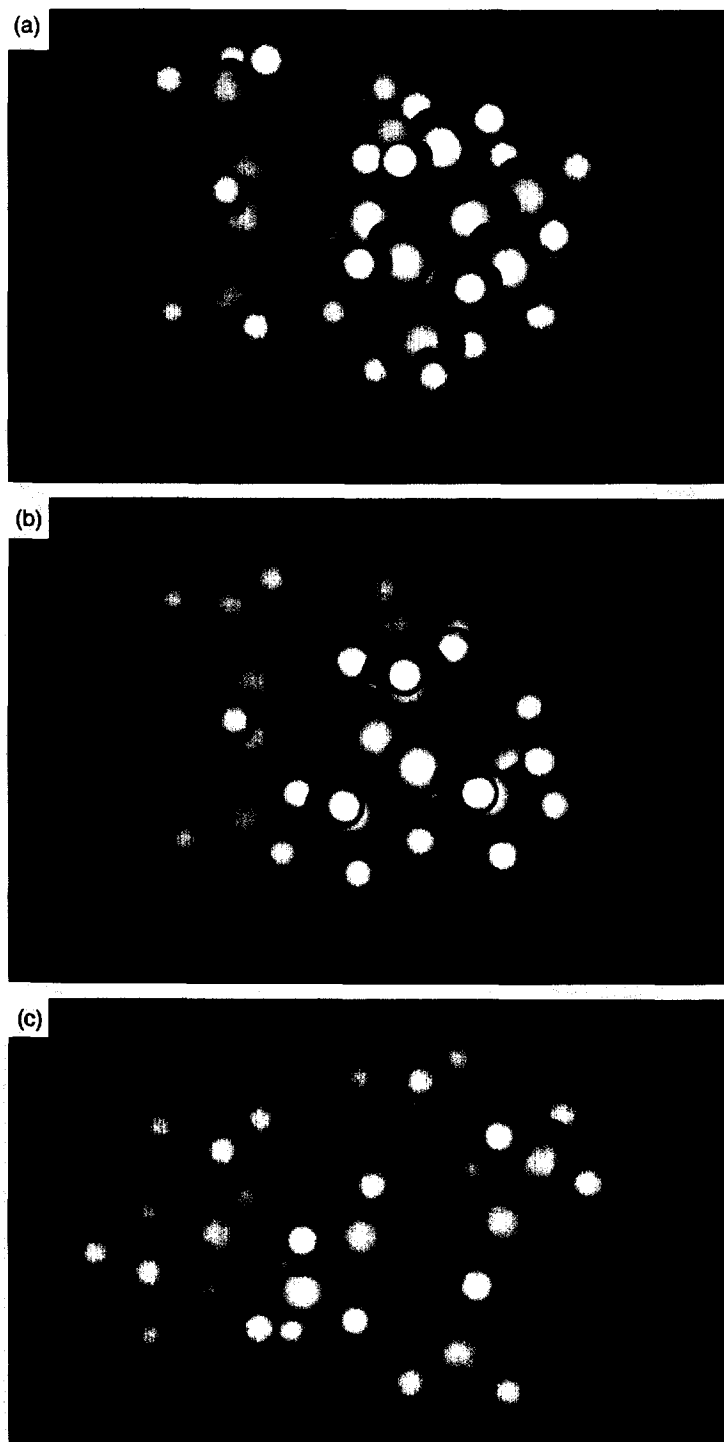
Figure 3: The disfavoured transition structure (*si*-face attack) for a substrate-controlled reaction



**Figure 4:** Transition structure for the *Z*-enol borinate of butanone reacting with methacrolein (*si*-face attack, isopinocampheyl ligands on boron)



**Figure 5:** *E*-enol borinate of an  $\alpha$ -chiral ketone reacting with methacrolein (*re*-face attack, cyclohexyl ligands on boron)



**Figure 6: Felkin, Roush and anti-Felkin transition structures**  
(multiple bonds are pink; forming and breaking bond are yellow/green)

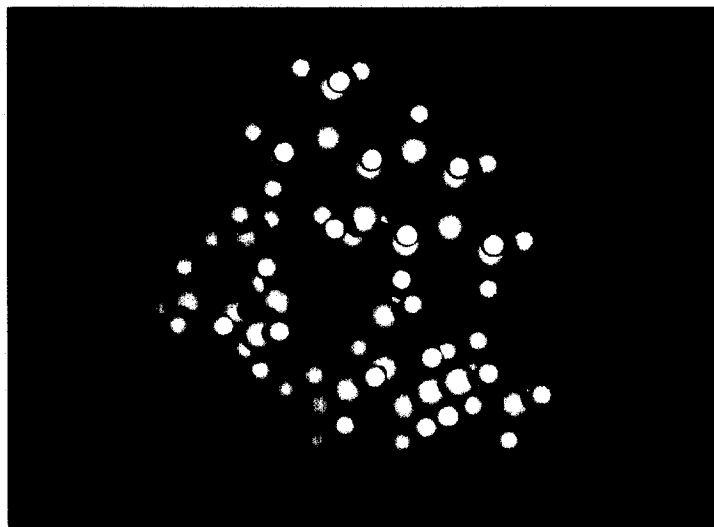


Figure 7: Transition structure leading to *si*-face attack with menthone-derived ligand system

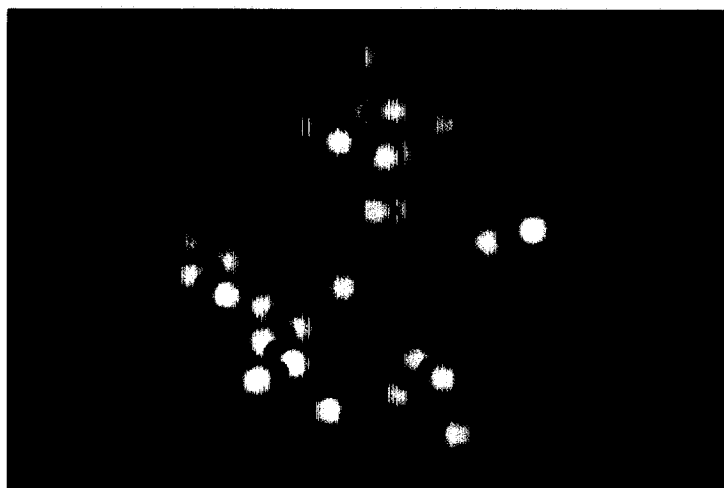
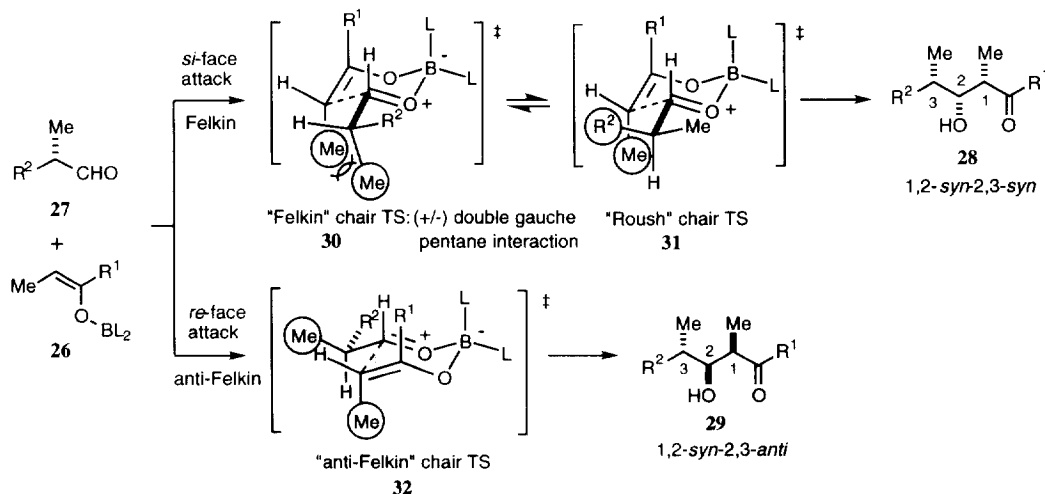


Figure 8: The less selective ate-complex of the isopinocampheyl-menthone mixed ligand enol borinate

The Milano-Cambridge force field was used to analyse the origins of stereocontrol in the *syn* aldol reaction of various *Z*-enol borinates **26** with  $\alpha$ -chiral aldehydes **27** to give diastereomeric adducts **28** and **29**.<sup>25</sup> The force field's quantitative analysis was compared with the experimental results and with Roush's qualitative conclusions.<sup>24</sup> The force field approach suggested that the three transition structures **30**, **31** and **32** (these are also shown in **Figure 6**) play a dominant role in controlling  $\pi$ -facial selectivity in *Z*-enol borinate additions to chiral  $\alpha$ -methyl aldehydes. The "Felkin" chair TS **30** partially relieves the strain energy of the ( $-60^\circ/+60^\circ$ ) double gauche pentane interaction (due to the presence of the *Z*-enol borinate methyl group) by opening the CH---C(O)-C\*-Me dihedral angle from  $+60^\circ$  to *ca.*  $+100^\circ$ . The analysis suggested that non-bonded interactions play the most important role in determining aldehyde diastereofacial selectivity in the aldol reactions with *Z*-enol borinates, and that stereoelectronic effects are possibly overridden by steric effects. Reactions with aldehydes bearing relatively small and "flat" substituents (Ph, H<sub>2</sub>C=CH, Me<sub>2</sub>C=CH) are 2,3-*syn* selective (Felkin pathway), while reactions with aldehydes bearing bulkier groups (various alkyls) are 2,3-*anti* selective (anti-Felkin pathway). This last result is essentially due to destabilisation of both structures **30** and **31** relative to **32**. Note that this computational approach alleviates the need to decide which of several groups is the most sterically demanding in a particular reaction.

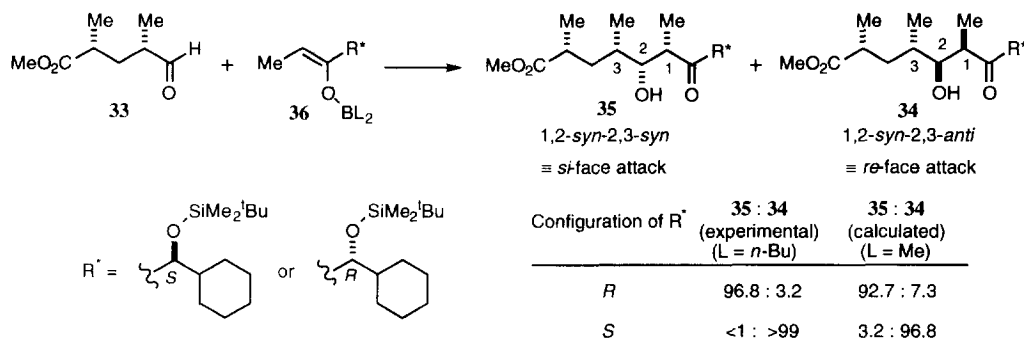


Scheme 8: Competing aldol chair transition structures for *Z*-enol borinates adding to  $\alpha$ -chiral aldehydes

#### 4.2 Double and triple asymmetric induction in enol borinate aldol reactions

The force field approach is able to predict both the sense and degree of stereochemical control in boron-mediated aldol reactions between chiral ketones and chiral aldehydes (double asymmetric induction), and to indicate which of the two components dominates.<sup>25</sup> An interesting example is shown in **Scheme 9**, an application of Masamune's "reagent control" through the use of a chiral enol borinate.<sup>26</sup> Aldehyde **33** reacts with achiral *Z*-enol borinates with a small intrinsic preference for the 2,3-*anti* isomer **34** over the 2,3-*syn* isomer **35**, while reactions of the chiral *Z*-enol borinate **36** with achiral aldehydes proceed with high stereoselectivity.<sup>13</sup> Using (*S*)-**36** with aldehyde **33**, the selectivity is matched and the isomer ratio is  $>99 : 1$  in favour of **34**. Whereas using (*R*)-**36**, the selectivity is mismatched and the product ratio is reduced to  $96.8 : 3.2$ , now in favour of **35**. This complex example was modelled using the Milano-Cambridge force field, and the results were in good agreement with the experiment.<sup>25</sup>

In principle, triple asymmetric induction (aldol coupling of a chiral aldehyde with a chiral ketone using a chiral boron reagent) could be approached in the same way. In this case, however, huge conformational searches are required, which are presently beyond the power of our computers. In many situations, the balance between the effects of all three components would be delicate, and so the correct prediction of triple asymmetric induction requires a force field of high accuracy. It is not clear if the present force field is accurate enough for this demanding application.



Scheme 9: Double asymmetric induction using Masamune's chiral enol borinates

## 5. The design and synthesis of new chiral boron reagents for asymmetric aldol reactions

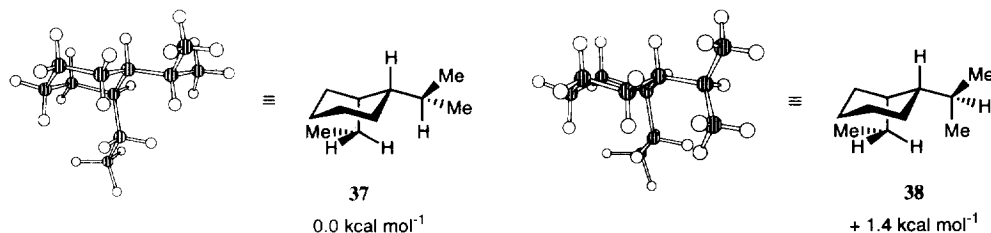
All of the findings in Sections 3-4 suggested that the Milano-Cambridge aldol force field should provide a useful tool for predicting the sense and degree of stereoselection in new situations. We reasoned that the force field could also be applied to the *de novo* design of chiral enol borinates for asymmetric synthesis. *Syn* aldols are easily obtained with good levels of enantiocontrol from chiral *Z*-enol borinates because they have access to a single chair transition structure. High stereoselectivity for *anti* or  $\alpha$ -unsubstituted aldol reactions is more difficult to achieve because unsubstituted and (partly) *E*-enol borinates also have access to boat transition structures (*cf.* Scheme 2). This competition among transition structures of similar energy (usually many conformers for each TS core) makes good levels of stereocontrol more difficult to attain.

In calculating the stereoselectivity of *E*-enol borinate aldol reactions, good agreement with the experimental findings was generally obtained (*cf.* Section 3.2). This gave us some confidence that the force field could now be used to design new chiral ligands for *E*-enol borinates to achieve enantioselective *anti* aldol reactions for ethyl ketones. This would then complement the *Ipc*-mediated *syn* aldol reactions of ethyl ketones already developed at Cambridge (*cf.* Scheme 4). We decided to start with a long list of chiral boron ligands essentially derived from *Ipc* (isopinocampheyl). We reasoned that: (i) nature produces  $\alpha$ -pinene, but we might do better; and (ii) we could have a quick preliminary evaluation of the reagents using computer modelling, instead of the more arduous laboratory work. Following these lines of reasoning, we screened more than a dozen new reagents with discouraging results — none of them were any better than *Ipc* and they were all more difficult to synthesise!

We learned from these failures and the analysis of the conformational preferences of the diisopinocampheylboron group (*cf.* Scheme 5) that the relative orientation of the boron ligands with respect to the chair transition structure core, as well as the relative orientation and restrained rotation of one ligand relative to the other were fundamental for determining the reaction stereoselectivity. So, the crucial point was to design a new ligand with limited conformational flexibility.

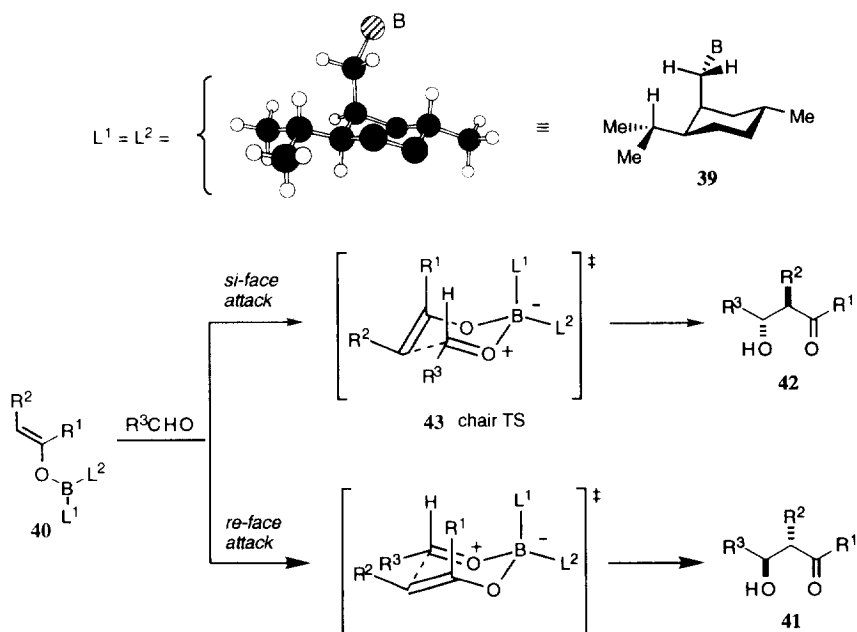
## 5.1 The menthone-derived ligand system

We decided to look for conformationally locked systems which were different from Ipc. The case of *cis*-1,2-ethyl isopropyl cyclohexane appeared as an interesting example of a conformational lock based on the avoidance of (+/-) double gauche pentane interactions (**Scheme 10**).<sup>27</sup> There is only one conformation, *i.e.* **37**, of the chair and side chains that does not possess any (+/-) double gauche pentane interactions, while other rotamers like **38** are higher in energy.



**Scheme 10** : The case of *cis*-1,2-ethyl isopropyl cyclohexane

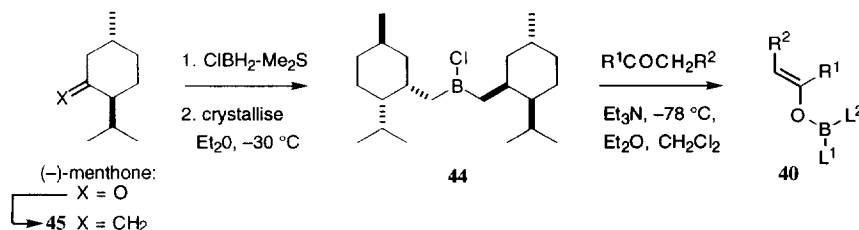
The terminal methyl group of the ethyl side chain in **37** was substituted with a boron atom. An equatorial methyl group was also added to the cyclohexane ring for reasons of synthetic accessibility (this modification had little influence on the computed stereoselectivity), giving the new ligand **39** in **Scheme 11**. After running a test conformational search of *si:re* face selectivity for *E*-enol borinate **40** with this new ligand substructure, we were delighted to discover substantial enantioselectivity was predicted in favour of *anti* aldol isomer **41** over **42**, far surpassing Ipc or any other designed reagent. The disfavoured chair TS **43** corresponding to *si*-face attack in this virtual reaction is shown in **Figure 7**.



**Scheme 11** : The menthone-derived ligand system

The synthesis of the computer-designed reagent **44**, which is shown in **Scheme 12**, took considerable effort to develop due to the need for separation from diastereomeric dialkylboranes formed in the hydroboration of menthone-derived alkene **45**. The minor diastereomeric chloroboranes were shown both computationally and experimentally to be low-stereoselectivity reagents for the aldol reaction. Eventually, the required C<sub>2</sub>-symmetric chloroborane **44** was purified by low temperature crystallization from ether. This reagent is nicely stable and is currently prepared uneventfully and stored as a stock solution in dichloromethane.

The *E*-enol borinates **40** derived from reagent **44** gave rise to ketone-derived *anti*-aldols, which had eluded earlier attempts at effective asymmetric synthesis *via* direct aldol-type addition. Although the *re:si* selectivity was lower than predicted by the computer in **Scheme 11** (the aldol force field is less well calibrated for *E*-enol borinates than *Z*-enol borinates), the enantioselectivities (55–88% ee) were the highest reported for such a transformation.<sup>28</sup> The menthone-derived reagent **44** also proved effective for methyl ketones giving aldol adducts with somewhat reduced enantioselectivity (55–76% ee).<sup>28</sup>



**Scheme 12:** Synthesis of the menthone-derived reagent

The Milano group later developed independently the bromoborane analogue of **44**, which proved very effective in the enantioselective synthesis of thioester-derived *anti* ( $\geq 98\%$  ee; R<sup>1</sup> = SBut, R<sup>2</sup> = Me) and unsubstituted aldols (87–97% ee; R<sup>1</sup> = SBut, R<sup>2</sup> = H).<sup>29</sup> The same reagent, readily synthesised in either enantiomeric form from (+)- or (-)-menthone, also proved valuable in the aldol reactions of  $\alpha$ -heterosubstituted (Cl, Br, OR) thioacetates,<sup>30</sup> and in the reagent-controlled aldol addition of chiral enol borinates to chiral aldehydes.<sup>31</sup>

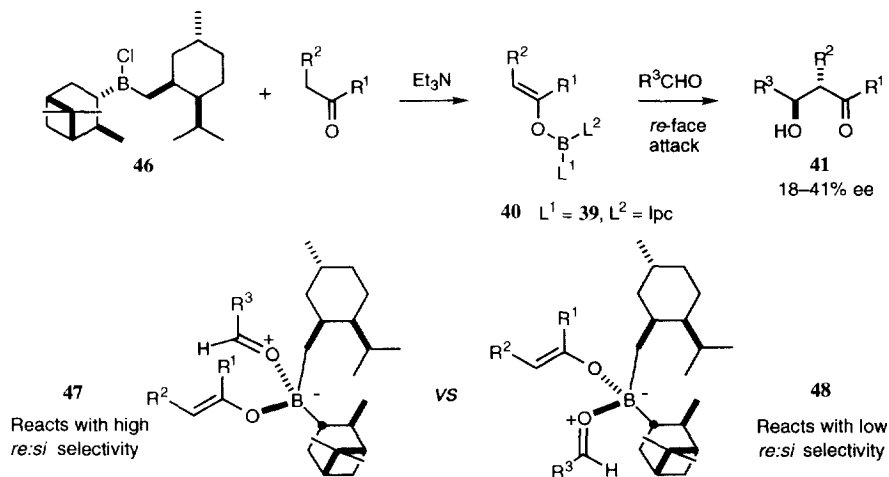
### 5.2 A mixed chiral ligand system; the role of ate-complexes in the boron-mediated aldol reaction

Encouraged by the success with the menthone-derived reagents, we considered the use of "mixed ligand" boron reagents, *i.e.* where the two chiral ligands attached to boron are different (L<sub>1</sub> ≠ L<sub>2</sub> in **Scheme 13**). Computer modelling of the aldol transition state was used to design appropriate matched ligands, which were predicted to infer a high level of stereocontrol, even higher than with L<sup>1</sup> = L<sup>2</sup> = **39**.<sup>32</sup> Here again the computational work was easy, the difficult part was the synthesis of the reagent. Eventually, the desired reagent **46** was prepared by a reasonably direct route. However, the observed selectivities for aldol reactions mediated by **46** giving *anti* adducts **41** were found ( $\leq 41\%$  ee) to be much less than predicted ( $> 95\%$  ee).<sup>32</sup>

This unexpected discrepancy between theory and experiment prompted a consideration of the role of the ate complex in determining the stereoselectivity of the aldol reaction. In particular, the presence of two different ligands on boron makes it a pro-stereogenic centre in the enol borinate **40**, and two diastereomeric ate-complexes can be formed on coordination of the aldehyde giving **47** and **48** in **Scheme 13**. If these complexes interconvert more slowly than they react, their relative energies rather than the C–C bond forming transition states determine the final stereochemical result. The experimental results are similar to those predicted for reaction *via* the less selective ate-complex **48**, which is also reproduced in **Figure 8**. Hence, the utility of a transition state model of the carbon-carbon bond forming step in the boron-mediated



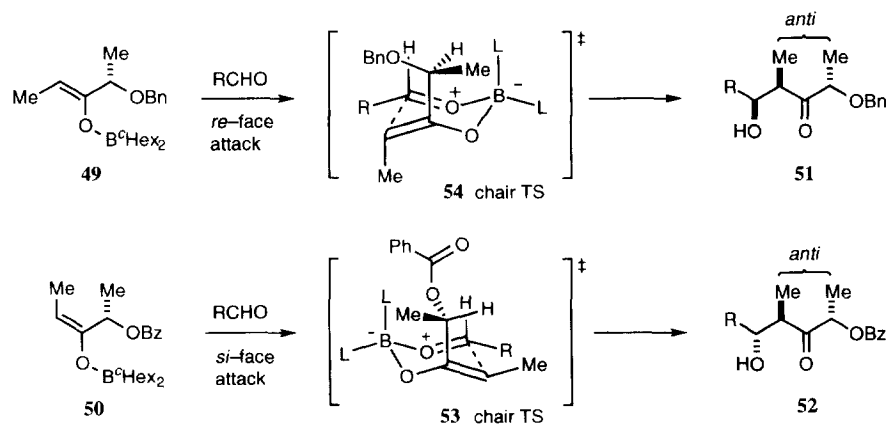
aldol reaction appears to be limited to those cases where the boron reagent is  $C_2$ -symmetric (*i.e.*  $L^1 = L^2$ ). The future development of quantitative models for mixed ligand reactions (*i.e.*  $L^1 \neq L^2$ ) will require consideration of the whole reaction coordinate.



Scheme 13: The "mixed ligand" system and the diastereomeric ate-complexes

### 5.3 Lactate-derived enol borinates

Following the excellent results obtained for the *anti* aldol reactions of the *E*-enol borinate **17** (*cf.* **Scheme 6**),<sup>18</sup> the corresponding lactate-derived *Z*- and *E*-enol borinates **49** and **50** in **Scheme 14** were examined at Cambridge.<sup>33,34</sup> High  $\pi$ -face selectivity was expected because of the relative steric and electronic contributions of the substituents (H, Me, OBn or OBz) at the enolate stereocentre in the respective chair transition structures.

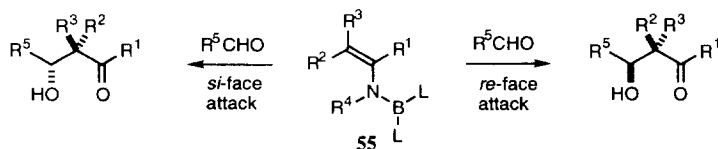


Scheme 14: Aldol reactions of lactate-derived enol borinates

We were pleased to find that the (*S*)-lactate-derived *Z*- and *E*-enol borinates **49** and **50** add to aldehydes to give *syn* and *anti* aldol adducts, **51** and **52** respectively, with synthetically useful levels of  $\pi$ -face selectivity. The latter addition is especially noteworthy, where up to 200:1 diastereoselectivity was achieved. The aldol adducts **51** and **52** (together with their enantiomeric forms obtained from (*R*)-lactate) can be manipulated to provide a wide range of enantiomerically-pure  $\beta$ -hydroxy carbonyl compounds and derivatives. For *E*-enol borinate **50**, computer modelling suggested that aldol chair TS **53** was preferred. It minimises A(1,3) allylic strain with the *E*-enol methyl group, with the benzoate directed inwards and the other methyl outwards. This analysis is analogous to that employed for *E*-enol borinate **17** (Scheme 6, Section 3.2),<sup>18</sup> where the observed  $\pi$ -facial preference for attack on the aldehyde is believed to have an electronic origin. The selectivity obtained for *Z*-enol borinate **49** giving **51** originates from the chair TS **54**, which is in line with other cases (*cf.* Scheme 3, Section 3.1) including analogous *syn* aldol reactions developed by Masamune<sup>35a</sup> and Heathcock.<sup>35b</sup>

#### 5.4 Related reactions: aza-aldol addition

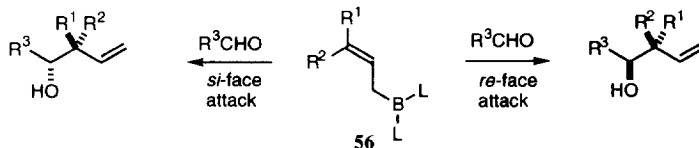
Replacement of the oxygen atom of an enol borinate with nitrogen leads to a aza-modified aldol reaction. In this system (Scheme 15), there is the potential for asymmetric induction from an appended chiral group, R<sup>4</sup>, on the nitrogen in enaminy borinate **55** as well as that from chiral ligands on boron. In practice,<sup>36,37</sup> poor yields were encountered due to low reactivity, presumably because the nitrogen lone pair reduces the boron's Lewis acidity. Nevertheless, good enantioselectivities were observed in some cases. These stereochemical findings were rationalised by assuming that the reaction proceeds exclusively through boat transition structures.<sup>36</sup>



Scheme 15: The aza-aldol reaction

#### 5.5 Related reactions: allylboration

The allylboration of aldehydes shown in Scheme 16 is a close analogue of the boron-mediated aldol reaction, which similarly proceeds through a 6-membered cyclic transition state. *Ab initio* MO calculations show that only chair transition structures are of importance in the allylboration process. A molecular mechanics model of the transition state for the addition of allyl and crotylboranes **56** to aldehydes was developed, based on *ab initio* calculations. Using trial and error optimization, a force field was created which reproduced the relative energies and geometries of the chair-like *ab initio* transition structures.<sup>38</sup> An automated procedure for the optimization of the torsional parameters was developed and used to improve the way the force field reproduces the *ab initio* data (geometries and relative energies).



Scheme 16: The allylboration reaction

The optimized force field reproduced the experimental *syn-anti* selectivity of *E* and *Z* crotyl borane addition to aldehydes. The force field was then used to analyse the stereoselectivity of various synthetically interesting reactions. This study provided an insight into the factors controlling stereoselectivity in allyl and crotylboration (**Scheme 16**), predicting the observed sense of asymmetric induction and the effect of double asymmetric induction in a number of cases.<sup>38</sup> An extension of this force field model to allylboration with two alkoxy substituents on the boron was subsequently developed independently at Milano.<sup>39</sup> The combined force field is available in the current distributed version of MacroModel.<sup>10</sup>

## 6. Validity of the model and its limitations

It has been remarked that our aldol force field calculations reproduce the experimental data with an accuracy "too good to be true", *i.e.* the model can pick up energy differences that are often smaller than 0.5–0.6 kcal mol<sup>-1</sup>. For example, the results with diisopinocampheyl *Z*-enol borinates (methacrolein, *si* : *re* calculated = 24:1, *cf.* experimental = 27:1; isobutyraldehyde, *si* : *re* calculated = 5:1, *cf.* experimental = 5:1). An empirical model such as this can only be evaluated on the basis of its predictive power. For the Milano-Cambridge aldol transition state model, this has been tested in a large number of cases, and almost always found to work. However, it should be noted that the best agreement with the experiments is obtained for reactions of *Z*-enol borinates. Only the chair transition structure is available for these reactions, which reduces the importance of transition state-core parameterisation (chair *vs* boat) in the calculations. The aldol force field described here is well designed for treating *Z*-enol borinates (where the boat is not an accessible transition structure), but is likely to be less accurate for *E*-enol borinates and inadequate for unsubstituted boron enolates. Indeed, the lack of quantitative agreement in the force field calculations in the acetone-derived enol borinate cases may reflect the importance of the boat transition state in the unsubstituted cases (see Section 3.3). In the case of *Z*-substituted enol borinates, a full conformational search of the transition structure "core" was able to generate only chairs, while several transition structures within 1.5 kcal mol<sup>-1</sup> were found in the unsubstituted case, including a few chairs and a majority of boats A and B.

Another important point is that enol borinates appear to be well behaved monomers, and similar stereochemical results are obtained in various different solvents, from polar THF or dichloromethane to non-polar hexane. Taken together, this suggests that the force field has a reasonable prospect of accuracy. However, there are a number of potential problems which we would like to raise.

### 6.1 Entropic Effects

The calculations take no direct account of entropic effects. These may be relevant for flexible molecules. The accuracy of the computed ratios could be increased in such cases by using molecular dynamics protocols, rather than energy minimizations. This would be time consuming, because boron aldol additions are run at low temperatures. At -78 °C (constant temperature), molecular dynamics (MD) calculations cross energy barriers rather slowly, and the time required to uniformly explore the potential surface may be prohibitively long, even for simple double well potentials. A second problem arises because the parametrization of the transition structure core was based on the relative energy of the transition structures (minima in the force field), and so the potential in between them is unknown. This may not invalidate the molecular dynamics approach, provided the effect of the inversion of a single normal mode is taken into account. However, the inaccuracy introduced by arbitrary barriers is likely to override the advantage of obtaining time-mediated enthalpy values.

### 6.2 Electrostatic Effects

In the development of the force field, atom-centred point charges must be assigned to the atoms of the transition structure. These charges were based on Löwdin analyses of the *ab initio* results, but, as the

force field became more sophisticated, this simple method became the weak link in the development and the main source of uncertainty.<sup>40</sup> A study into the various ways of deriving the atom-centred point charges, which were used to model electrostatics in the MacroModel implementation of MM2 force field, suggested that this simple framework did not have sufficient flexibility to analyse both electrostatic interactions within the core of the transition structure and also with the surrounding substituent groups. The latter interactions could be improved using partial charges derived from a least-squares fit to the electrostatic potential around the transition structures, calculated using CHELPG.<sup>40</sup> However, this improvement was at the expense of the geometry of the core transition structure. It seemed best to maintain the core geometry, and accept that the electrostatic interactions around it remain the weak point of the model.

### 6.3 Boat B and second generation force fields

To assess the importance of boat B in **Scheme 2** (Section 2.3), the geometries of 6 structures were calculated (RHF/3-21G), each bearing a methyl substituent on a different position. Boat B was found to be an important transition structure in all cases examined, except for the addition of the *Z*-enol borinate of propionaldehyde to formaldehyde, where only the chair (and partially boat A) are accessible. We set about parameterizing a force field which would describe these new structures, as well as the original 14 structures (6+14 = 20 structures). Larger barriers had to be introduced to ensure the existence of minima, which made it more difficult to tune the force field to the presence of individual substituents. As a result, a field was obtained whose fit to the *ab initio* data was an order of magnitude worse than that of the previous field.<sup>40</sup> The reproduction of experimental data was also unsatisfactory. We can conclude that the trial and error approach to the development of parameters may not be the most effective way of attempting a description of systems which are too complex and flexible.

### 6.4 The effect of intermediates

The studies of the reagents with two different ligands on the boron revealed another area for caution (*cf.* **Scheme 13**, Section 5.2). In these studies, the experimental results and the computational results were very different.<sup>32</sup> This was the first case where the enol borinate was not C<sub>2</sub>-symmetric, and so the formation of the ate-complex played a part in determining the stereoselectivity of the process. Without a computational model of this stage of the reaction, it was necessary to abandon the analysis of this class of reactions.

### 6.5 The physical meaning of the model

Menger and Sherrod<sup>41a-c</sup> have suggested that transition state models do not necessarily model transition states, and illustrated their arguments with a study of intramolecular hydride transfers. They demonstrated that models which were not related to the transition state could reproduce the data for this reaction rather well. We have no irrefutable evidence that the computational model described here actually models the transition state of the boron-mediated aldol reaction. However, it is hard to find alternative explanations for why the model works well in a much more complicated system than that of hydride transfers.<sup>41d</sup> Even if the model is shown to have no relationship to the actual chemistry of the transition states, we believe we have developed a useful tool for synthetic organic chemists.

## 7. Details on the development of the aldol force field model

The aldol transition state force field was developed with the following features: (a) the values of bond lengths and angles were obtained by averaging the bond lengths and angles calculated *ab initio* for the 14 transition structures; (b) stretching force constants resulted from interpolation from standard MM2 values and actual bond orders; (c) bending force constants were reduced by 15–50% compared to MM2 values,

where the major reductions (50%) involved bond angles containing a forming bond; (d) torsional parameters were developed by trial and error.

Initially, a set of parameters for the ring atoms was defined in such a way that the MM2 calculations would reproduce the 1.3-1.4 kcal mol<sup>-1</sup> difference between the unsubstituted boat A and chair in **Scheme 2**. We then verified by a conformational search of the 6-membered unsubstituted ring that no additional minima other than boat A and chair were present. Then we divided the monosubstituted structures (12) in 4 classes, depending on which core atom had been substituted. Class 1: carbonyl carbon (4 structures, 2 chairs and 2 boats); class 2: enol borinate  $\alpha$ -carbon (2 structures, 1 chair and 1 boat); class 3: boron atom (2 structures, 1 chair and 1 boat); class 4: enol borinate  $\beta$ -carbon (4 structures, *Z*-enol borinate: 1 chair and 1 boat; *E*-enol borinate: 1 chair and 1 boat). For each class, the bond lengths and angles, and the corresponding constants involving the methyl substituent were defined as described above. The torsional parameters involving the methyl substituent were determined by trial and error fitting of the energy differences in each class. A geometric criterion was included by evaluating the RMS value of superimposition between the force field minimized structure and the *ab initio* structure. In each case, a conformational search of the 6-membered monosubstituted ring was performed to ensure that no spurious minima had been introduced.

Standard MM2 Van der Waals parameters were used for C, H and O. The Van der Waals parameters for boron had already been developed for enol borinates,<sup>2</sup> and were used as such. The electrostatic terms were introduced in the MacroModel implementation of the MM2 force field as point charges for each atom. The determination of the values of the point charges from *ab initio* calculations was not straightforward. We used methods of summing electron density from *ab initio* calculations and localising it on particular atoms. The Mulliken population analysis is the simplest of these methods, but it gives very large values for the partial charges, and these are probably non-optimal for force fields, although they reproduce the molecular dipoles fairly well. Löwdin analysis gives numbers that seem of a more realistic magnitude, and also generates good values for the total dipole moment of the system. Therefore, the force field was based on the Löwdin values.<sup>11</sup> Bond dipoles for the core substituents were not set, and zero charge was assigned to the hydrogen atoms in the force field. Therefore, the *ab initio* calculated partial charge of the hydrogen atoms was added to that of the attached carbon and boron atoms.<sup>11</sup>

## 8. Concluding remarks

The Milano-Cambridge force field model allows a stereochemical analysis of the aldol addition reactions of enol borinates with aldehydes in many synthetically important situations. While its physical significance may be questionable, this transition state model has proved to be a useful computational tool in the prediction of stereoselectivity in new situations and in the *de novo* design of new chiral boron reagents for asymmetric aldol reactions.

## Background to the Milano-Cambridge collaboration

The collaborative project described in this Report is concerned with the design and synthesis of novel and effective reagents for asymmetric synthesis, and the prediction and rationalisation of experimental results. The project started in Cambridge during the 10th International Symposium on Synthesis in Organic Chemistry in July 1987. In the course of the last 8 years, 14 people from around Europe (Mark Gardner and Cheryl Hewkin from UK, Anna-Maria Capelli, Angiolina Comotti, Andrea Cassinari, Francesco Molinari, and Anna Vulpetti from Italy, Achim Schlappbach, Siegfried Vieth, and Volker Leue from Germany) have contributed to the work. The collaboration was initially supported by NATO (1988-1992) and the EC (Twinning Grant between Milano and Cambridge 1990-1993). More recently (1993-), this project has become part of a wider collaboration between eight groups within Europe as a HCM network on the rational

design of new organic molecules and synthetic methods. Some contributions from other groups in this network programme appear elsewhere in this issue of *Tetrahedron: Asymmetry*.

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