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ORIGINS OF STEREOSELECTIVITY IN CHIRAL BORON ENOLATE ALDOL REACTIONS: A COMPUTATIONAL STUDY USING TRANSITION STATE MODELLING.[1]

Anna Bernardi,[a] Anna M. Capelli,[a] Angiolina Comotti,[a] Cesare Gennari,*[a] Mark Gardner,[b] Jonathan M. Goodman,[b] and Ian Paterson*[b]

[a] *Dipartimento di Chimica Organica e Industriale, Universita' di Milano, via Venezian 21, 20133 Milano, Italy*

[b] *University Chemical Laboratory, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, England.*

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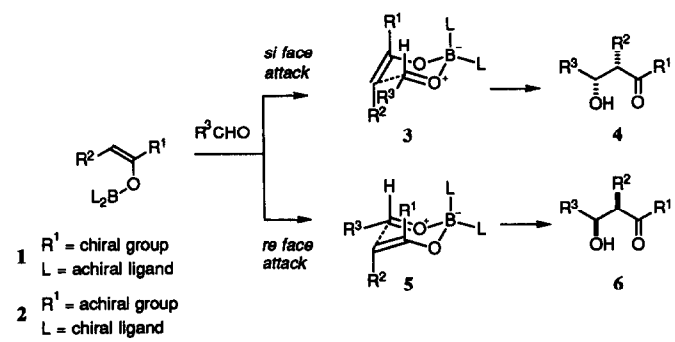
Summary: A molecular mechanics model of the boron enolate aldol transition state is used to analyse the stereoselectivity of various synthetically interesting reactions. The model reproduces the sense and degree of stereoselectivity for several examples in **Scheme 1**, including reactions involving chiral ketones, as in **1** (substrate control) and chiral ligands on boron, as in **2** (reagent control). The origins of the stereoselectivity in the aldol reactions of Z enol diisopinocampheyl borinates are analysed in detail. It is concluded that the relative orientation of the 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, are important for determining the reaction selectivity. For chiral ketone cases, a general model **59** can be devised by inspection of the preferred transition structures viewed as the Newman projections (**31**, **38** and **44**). This model has the hydrogen on the stereogenic centre of the enol borinate directed towards the boron ligand (*i.e.* the dihedral angle C=C-C*-H is in the range 133-173°), the large group opposite to the incoming aldehyde, and the small group pointing towards the forming C-C bond of the chair transition structure. As shown by the work described here, our force field model of the boron aldol transition state is useful in understanding the origins of the stereoselectivity over a wide range of substrates. The aldol force field model, therefore, may also have predictive value in new situations.

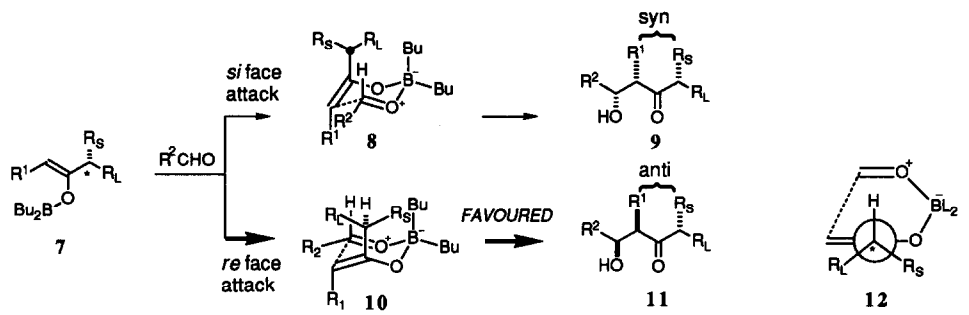


Scheme 1

We recently described the development of a force field model for the aldol reactions of ketone derived enol borinates with aldehydes.[2] This force field is based on MM2, and on new parameters developed from *ab initio* calculations on the cyclic transition structures (chair and boat) and from trial and error optimization. The model reproduces the geometries and relative energies of simple unsubstituted and monosubstituted *ab initio* transition structures. It also reproduces the experimental *syn* : *anti* stereoselectivities for the aldol reactions of

simple *Z* and *E* substituted enol borinates from ethyl ketones with aldehydes. Furthermore, the model also reproduces the aldehyde *si* : *re* selectivity for the *syn* selective aldol reactions of a range of chiral *Z* enol borinates **1** and **2** in **Scheme 1**.[2] This includes asymmetric aldol reactions under either substrate control using chiral ketones, as in **1**, or reagent control using chiral ligands attached to boron, as in **2**. In these cases, the force field predicts that only chair-like transition structures are important, *i.e.* **3** → **4** and **5** → **6** for R^2 = alkyl. In this paper, we discuss in detail the use of this force field approach for rationalizing the observed stereoselectivity of various chiral *Z* enol borinates in synthetically useful aldol reactions.

We are aware of recent controversy in the literature regarding the merits of transition state modelling.[3,4] The success of our transition state modelling treatment of the boron enolate aldol reaction indicates that this method is clearly useful in such a complicated situation, where ground state models are not generally successful.[5] This model has successfully reproduced experimental results and may, therefore, have predictive value in new situations. We consider our model solely as a working approximation to the key physical event involved in transforming the reactants into the products along the reaction coordinate.



Scheme 2

Several empirical models have been introduced to explain the sense of π-face selectivity in chiral boron enolate aldol reactions.[5-15] Evans was the first to suggest a general model (**Scheme 2**) for rationalising the stereoselectivity of boron aldol reactions involving chiral ketones bearing an α-stereogenic centre with simple aldehydes.[7] In this substrate controlled situation, the substituents at the enolate stereogenic centre in **7** are considered in terms of steric size (*i.e.* comparable to Cram type arguments for asymmetric induction in nucleophilic addition to chiral aldehydes having an α-stereogenic centre). Evans argues that the smallest substituent, H, points towards the inside of the chair transition structure to minimise steric interactions. The next most important interaction is between the other substituents (R_S, R_L) on the stereocentre and the ligands on boron. In TS **8**, corresponding to si face attack → **9**, the larger substituent, R_L, is directed towards the butyl ligands on boron. This is argued to be disfavoured relative to TS **10**, corresponding to *re*-face attack → **11**, where R_L is replaced by the smaller substituent R_S. The Newman projection **12** roughly corresponds to the preferred transition structure **10**. This model appears to work for a few special cases, but does not explain the observed sense of stereoselectivity in many other boron mediated aldol reactions subsequently investigated. Consequently, other workers have introduced specific transition structure models to account for the stereoselectivity in these other reactions. These include contributions from the groups of Masamune,[8] Thornton,[9] Paterson,[10] and Enders.[11] In the case of chiral reagent controlled boron aldol reactions (chiral ligands at boron), the empirical models available include those of Paterson,[12] Corey,[13] Masamune,[14] and Reetz.[15] In this paper,

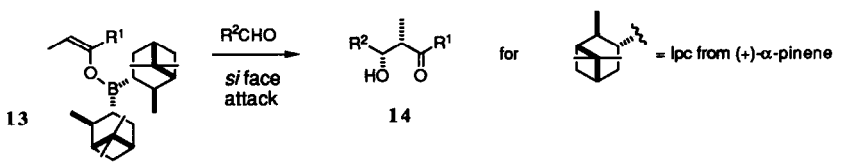
we consider many of these cases using our computational approach and comment on the validity of these simple empirical models.

Results and discussion

Computational Methods

Using the parameters developed in our earlier work, MacroModel[16] was used to generate accessible transition structures for the boron enolate aldol reaction of interest. The conformational space was searched with Multiconformer[17] using a 30° or 60° resolution for each dihedral angle. In selected cases, we tested for the presence of boat transition structures by including all rotatable bonds of the transition structure "core." Boats were found to be unimportant, because of their high energies relative to the chairs. Two separate Multiconformer runs were necessary: one with attack at the aldehyde *si*-face and the other with attack at the *re*-face. An alternative procedure made use of the Still-Chang-Guida usage-directed torsional Monte Carlo search[18] as implemented in the BATCHMIN program.[19] The two methods usually gave comparable results and were used in concert to make sure that our conformational analysis was not dependent on the search method used.[20] The transition structures found by these searches were analyzed by a Boltzmann distribution at -78 °C of the various conformers (within 2.5 kcal mol^{-1}) leading to each of the possible aldol stereoisomers. The force field calculations predicted essentially complete *syn* selectivity for achiral *Z* enolates (*cf.* experimental *syn* : *anti* > 95:5), *i.e.* the chair pathway dominates over the boat, and the correct sense of aldehyde π-facial selectivity.

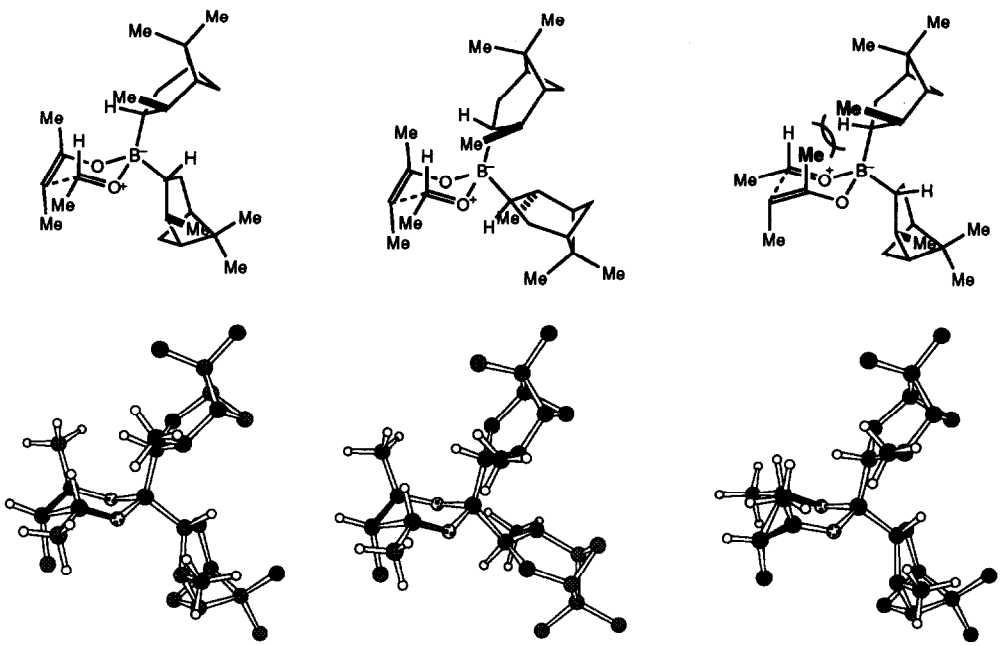
Chiral reagent control in boron enolate aldol reactions



Scheme 3

We first consider the application of our model to understanding the origins of stereoselectivity in ethyl ketone aldol reactions using enol diisopinocampheyl borinates, as in **13** → **14** in **Scheme 2**.[12] The calculated transition structures for the aldol reaction of the *Z* enol diisopinocampheylborinate of butanone (Ipc ligands derived from (+)-α-pinene) with acetaldehyde are shown in **Figure 1**. The calculated *si* : *re* selectivity in this reaction is 19:1, while the experimental value is 10:1 for the related case of diethylketone.[12,21] Two structures, **15** and **16**, were found within 2.5 kcal mol^{-1} of the minimum energy conformation for reaction on the aldehyde *si* face, whilst only structure **17** was found for *re*-face attack (+1.4 kcal mol^{-1}). From examination of these 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 **15**, *i.e.* away from the methyl group on the enolate (shown with hydrogens attached). In the *re*-face attack mode, this same methyl on the axial ligand is directed towards the enolate methyl in **17**, which may explain its higher energy relative to **15** 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. The transition state model is in general agreement with the qualitative model previously proposed by one of us.[12] We obtained similar results for the related reactions with other aldehydes, *e.g.* methacrolein and

isobutyraldehyde. The calculated ratios in these cases were in good agreement with the experimental results (methacrolein, *si* : *re* calculated = 24:1, *cf.* experimental = 27:1; isobutyraldehyde, *si* : *re* calculated = 5:1, *cf.* experimental = 5:1).[12,21] While the relative energies of the transition structures changed, there was no evident change in the conformations relative to the acetaldehyde case (**Figure 1**) which would allow us to rationalize these differences.



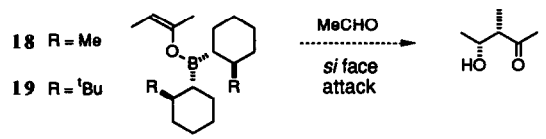
	15	**16**	**17**
	si-face attack: 0.0 kcal mol^{-1}	*si*-face attack: +2.3 kcal mol^{-1}	*re*-face attack: +1.4 kcal mol^{-1}
∠ OBO =	98.0°	99.1°	98.0°
∠ CBC =	117.7°	125.1°	117.8°

Figure 1

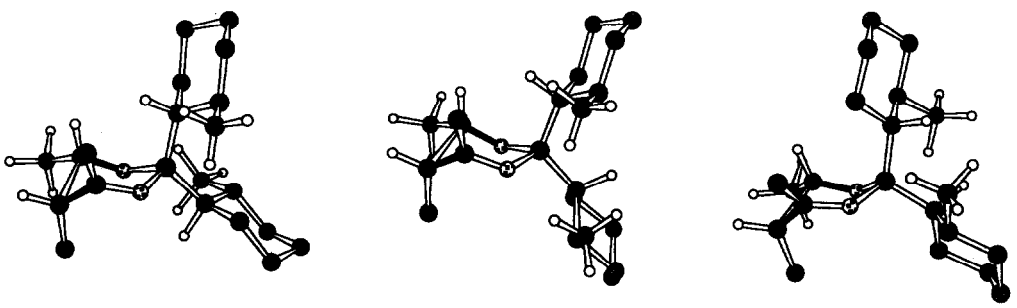
From inspection of the diastereomeric transition structures **15** and **17**, it is evident that the Ipc ligands hold the same relative orientation. Note that the methyl groups adjacent to boron (shown with hydrogens) on the two ligands are on the same side. This suggests that the ligands are locked relative to each other in the low energy forms for both *re*- and *si*-face attack. It appears that both pseudo-axial and pseudo-equatorial chiral ligands are important in determining face selectivity. The equatorial ligand is not merely acting as a bulky group.[22] A different relative orientation of the two Ipc ligands in **16** results in a conformation of substantially higher energy (+2.3 kcal mol^{-1}), where the CBC bond angle has opened out to 125°, compared to 118° for the other two cases. In fact, this is a C_2 -symmetric form for the B(Ipc)$_2$ group, *i.e.* with the methyl groups adjacent to boron on the two Ipc ligands on opposite sides. From this analysis, it appears that all of the ligand structure is important in determining the observed stereoselectivity.

This is underlined by similar calculations performed on the analogous enol borinate **18**, where the *gem*-dimethyl bridge of the Ipc ligands has been removed. These indicate that there are now three transition structures

within 2.5 kcal mol^{-1} of the lowest energy conformation for both *si*- and *re*-face attack. These are shown in **Figure 2** as structures **20-25**. In this case, we have no experimental results for direct comparison. The predicted *si* : *re* selectivity at -78 °C is 3:1 compared to 19:1 for the parent Ipc case. There are now several relative orientations of the ligands with comparatively small energy differences between them. As a result, the selectivity shown in **Scheme 4** is predicted to be poor with this ligand system.



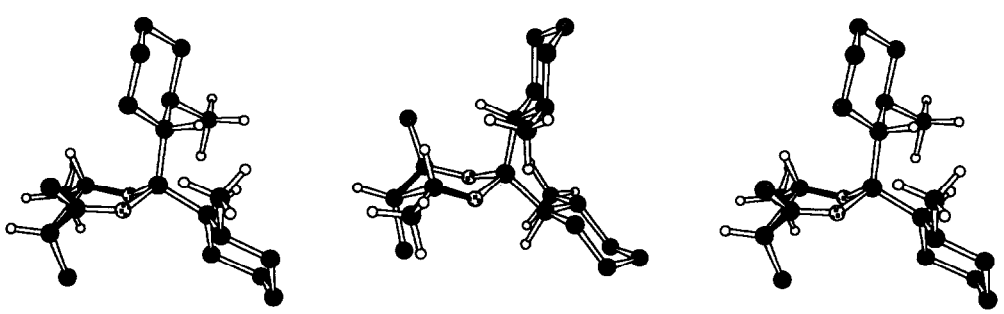
Scheme 4



20
si-face attack: 0.0 kcal mol^{-1}

21
+0.3 kcal mol^{-1}

22
+1.2 kcal mol^{-1}



23
re-face attack: +0.6 kcal mol^{-1}

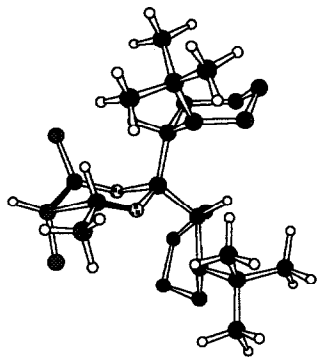
24
+0.7 kcal mol^{-1}

25
+0.9 kcal mol^{-1}

Figure 2

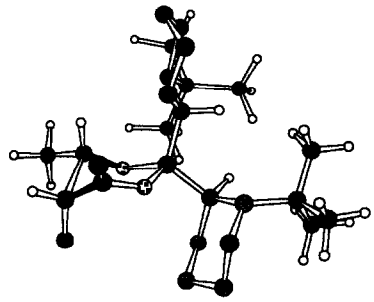
Replacing the methyl group on the cyclohexyl ring of the ligand with a *t*-butyl group to give enol borinate **19** again locks the ligands relative to each other, and restores high selectivity (**Figure 3**). Although there are eleven available conformations for *si*-face attack within 2.5 kcal mol^{-1} of the lowest energy structure, all of them have the *t*-butyl groups in the same relative orientation as shown in the minimum energy structure **26**. Attack on the *re*-face has only one available conformer **27** (+2.4 kcal mol^{-1}). Hence, the selectivity shown in **Scheme 4** is predicted to be high (>300:1). However, one of the ligands in the lowest energy structure **26** takes up a boat

conformation and the other has both substituents axial on the chair. This is probably the result of the steric crowding caused by the *t*-butyl substituent and suggests that this transition structure may be inaccessible in practice.



26

si-face attack: 0.0 kcal mol^{-1}



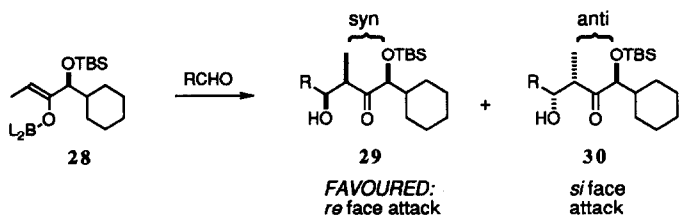
27

re-face attack: +2.4 kcal mol^{-1}

Figure 3

These examples illustrate that the orientation of the ligands with respect to the transition structure core, as well as the ligand-ligand relative orientation and restrained rotation, are important in determining the reaction selectivity. Such considerations will clearly be important in the future design of novel chiral boron reagents for enantioselective aldol reactions.

Substrate control in boron enolate aldol reactions using chiral ketones



Scheme 5

We initially considered the substrate controlled aldol reactions of the chiral *Z* enol borinate **28** as reported by Masamune *et al.* (**Scheme 5**).[8] Using the enolate **28** with (*S*)-configuration, the aldol reaction selectively provides adduct **29** *via* *re*-face attack on the aldehyde (*e.g.* for R = Et, **29**:**30** ≥ 17:1). The chair transition structures calculated for this aldol reaction with acetaldehyde (9-BBN ligand) are shown in **Figure 4**. These are viewed along the C*-C bond connecting the stereogenic centre with the enolate carbon (*i.e.* corresponding to a Newman projection along this bond). The calculated *si* : *re* face selectivity in this reaction is 1:16, which compares favourably with the experimental ratio of 1:17 reported by Masamune for aldol addition to propionaldehyde.[8] For both *si*- and *re*-face attack, only a single accessible transition structure was found. Both these structures **31** and **32** show essentially the same enolate geometry with attack at either the *si*- or *re*-face of

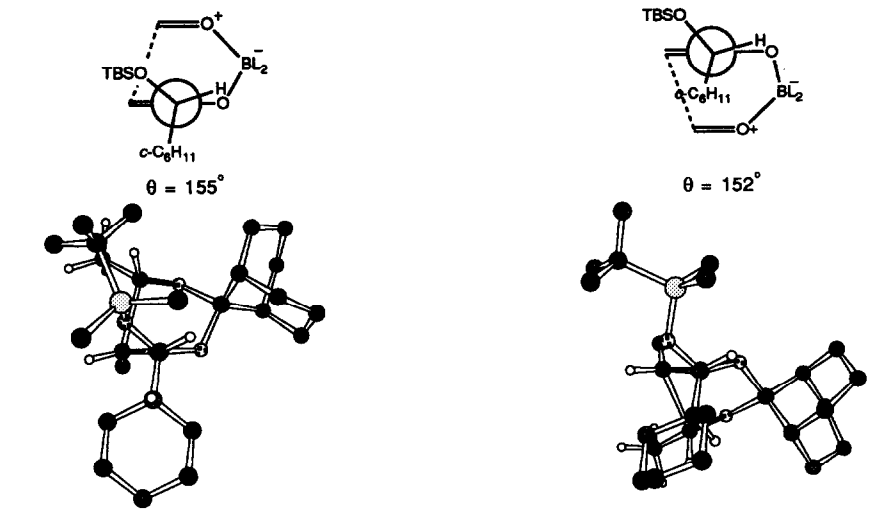
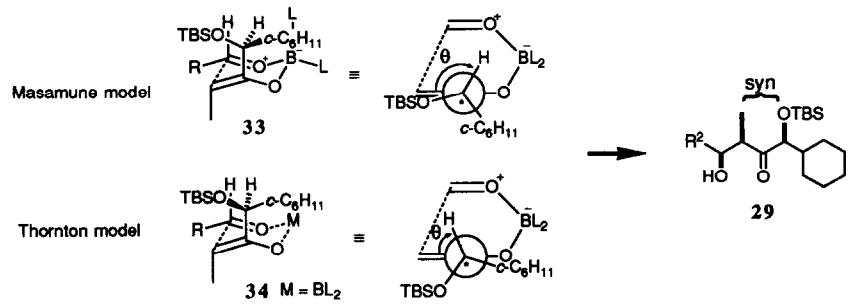


Figure 4

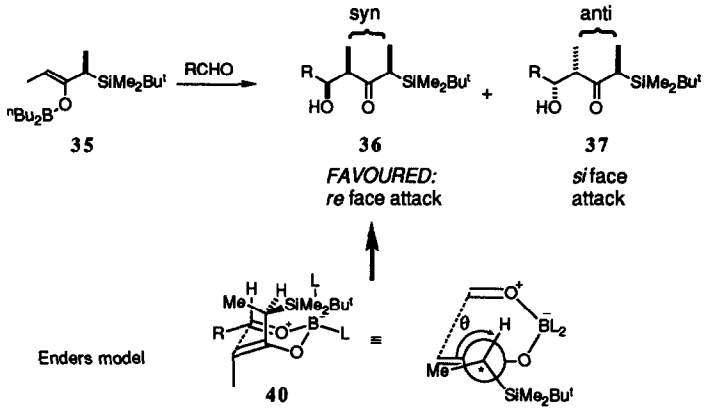
the aldehyde: the dihedral angle C=C-C*-H in **31** and **32** is 155° and 152°, respectively. Attack of the enolate on the *re*-face is preferred because the aldehyde approaches the enolate face opposite the large cyclohexyl group with the hydrogen of the stereocentre oriented towards the boron ligand in **31**. For *si*-face attack on the aldehyde in **32**, the enolate is reacting on the same side as the cyclohexyl group and hence is clearly disfavoured on steric grounds. Experimentally it is found that increasing the ligand size on boron increases the stereoselectivity of the reaction.[8] This can be rationalised by a reduced contribution from the *si*-face attack mode by increased interaction between the cyclohexyl group and a more sterically demanding ligand on boron.



Scheme 6

Our calculated model for the favoured *re*-face attack pathway **31** is comparable to the qualitative one proposed by Masamune *et al.* (**Scheme 6**),[8,23] but differs from the Evans model (see **12** in **Scheme 2**). In the Masamune favoured transition structure **33**, the C-OTBS bond is considered to eclipse the C=C bond of the enolate. This corresponds to a dihedral angle C=C-C*-H of $\theta \equiv 120°$, compared to our calculated model **31** where $\theta = 155°$. A further empirical model based on the preferred pathway **34** has been proposed by Thornton,[9]

which is substantially different from **31** and **33** with the dihedral angle C=C-C*-H of $\theta \cong 60°$. We do not find a low energy transition structure that corresponds to the Thornton model, presumably because **34** incorporates a close approach between the cyclohexyl group of the enolate and the ligand on boron, which we would expect to be disfavoured. Our *si*-face attack model also differs from that of Thornton.



Scheme 7

The Enders aldol reaction involves the use of the chiral *Z* enol di-*n*-butylborinate **35** with (*R*)-configuration (**Scheme 7**), where the substituents at the attached stereogenic centre are hydrogen, methyl, and *t*-butyldimethylsilyl.[11] Our calculations were performed using 9-BBN in place of di-*n*-butylboron, which removes the complication of additional degrees of freedom due to the butyl ligands. The lowest energy transition structures calculated for attack on each face of acetaldehyde are shown in **Figure 5**; again viewed along the C*-C bond connecting the stereogenic centre with the enolate carbon.

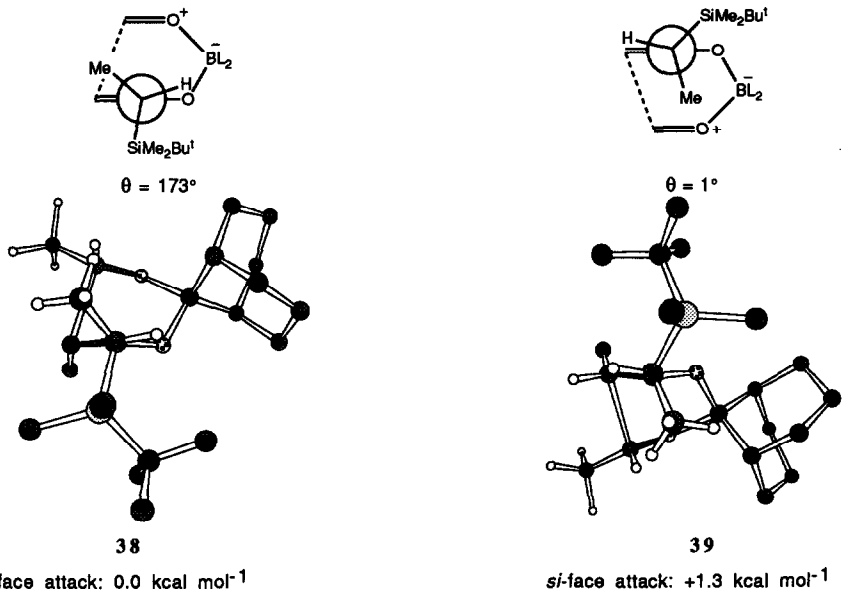
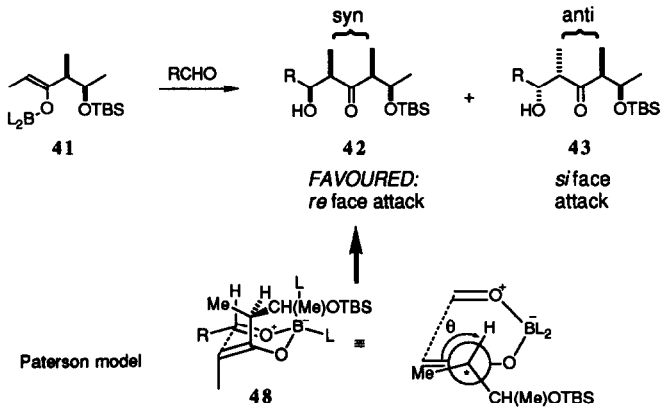


Figure 5

The calculated *si* : *re* selectivity in this reaction is 1:24, while the experimental ratio reported by Enders is 1:99 for the same aldehyde and using *n*-butyl ligands attached to boron.[11] For the preferred *re*-face attack → **36**, two families of four and two transition structures each were found within 2.5 kcal mol^{-1} of the minimum (group 1: relative energies 0.0, +1.0, +1.0, +1.3 kcal mol^{-1}; group 2: +1.7, +1.9 kcal mol^{-1}). The first group is characterised by a value for the C=C-C*-H dihedral angle of $\theta = 167 \pm 6°$, whereas the second group has $\theta = 143 \pm 2°$. Within these groups there is a larger variation of the dihedral angle C-C*-Si-C, which is not considered in our discussion. Since the second group are higher in energy, only the lowest energy structure **38** of the first group is shown here. For *si*-face attack → **37**, there are three structures in one group (relative energies +1.3, +2.1, +2.2 kcal mol^{-1}). These all have a C=C-C*-H dihedral angle of $\theta = -3 \pm 4°$ and the lowest energy structure **39** is shown.

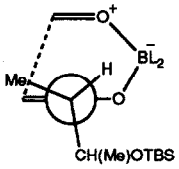
Our rationalization for preferential *re*-face attack is similar to that discussed in the Masamune case. Attack on the *re*-face is preferred, because the aldehyde approaches the enolate face opposite the large $SiMe_2Bu^t$ group with the H attached to the stereogenic centre oriented towards the boron ligand in **38**. However, attack on the *si*-face of the aldehyde for this enolate conformation appears to be impossible due to the steric shielding from the large $SiMe_2Bu^t$ group. Consequently, attack on the *si*-face of the aldehyde takes place through a different conformation **39**, where the methyl group on the stereogenic centre is pointing towards the ligand on boron and the aldehyde attacks on the face opposite the $SiMe_2Bu^t$ group. Our calculated preferred transition structure **38**, $\theta = 173°$, resembles that proposed by Enders, *cf.* **40** in **Scheme 7**, where $\theta \cong 120°$.[11] The main difference is that our model has the methyl group on the stereogenic centre staggered relative to the enol double bond and with the $SiMe_2Bu^t$ group essentially antiperiplanar to the forming bond to the aldehyde. Enders observes the opposite face selectivity if the aldehyde is changed to benzaldehyde (*i.e. si* : *re* of 100:1 in favour of **37**),[11] which cannot be explained by any of these models. We calculate the selectivity for attack of enol borinate **35** on benzaldehyde to be in the same sense as acetaldehyde with *si* : *re* = 1:28.



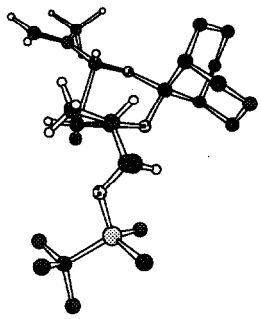
Scheme 8

The *syn*-selective aldol reaction of the chiral *Z* enol borinate **41** has been studied by the Paterson group (**Scheme 8**).[10] In this case, there is now a β- as well as an α-stereogenic centre in the enol borinate. This is the most complicated situation so far considered, since there are now more rotatable bonds and hence degrees of

freedom. The lowest energy structure **44** calculated for the aldol reaction of **41** with acetaldehyde is shown in **Figure 6**. This corresponds to preferred *re*-face attack → **42** and is representative of a family of some 25 structures within 2.5 kcal mol^{-1}. All of these have a closely related value for the dihedral angle C=C-C*-H (θ = 133° for **44**), but many variations in the geometry of the CH(Me)OTBS group are found, which have low barriers to interconversion and small energy differences. For attack on the *si*-face of the aldehyde → **43**, three structures **45-47** are shown and each of these represents the lowest energy member of three families of conformations (altogether there are some 20 structures within 2.5 kcal mol^{-1}). The values of the dihedral angle C=C-C*-H for **45**, **46** and **47** are θ = 190°, 313° and 16°, respectively, which are representative for the individual families. Again, within these families the major variations are in the CH(Me)OTBS group.

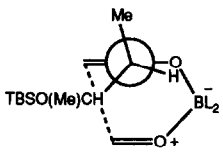


θ = 133°

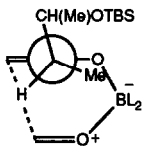


44

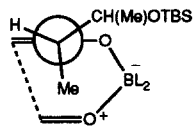
re-face attack: 0.0 kcal mol^{-1}



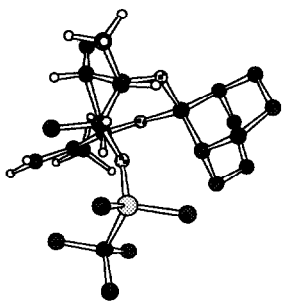
θ = 190°



θ = 313°

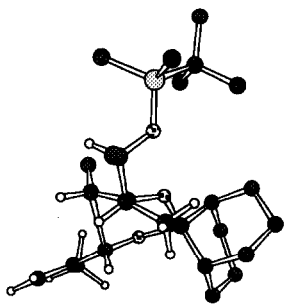


θ = 16°



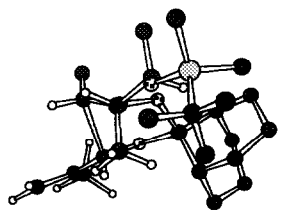
45

si-face attack: +0.5 kcal mol^{-1}



46

+0.5 kcal mol^{-1}

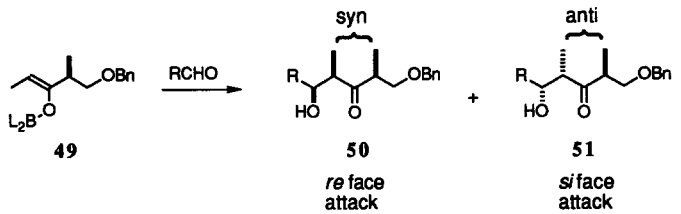


47

+0.8 kcal mol^{-1}

Figure 6

The preferred transition structure **44** ($\theta = 133°$) involves attack on the enol borinate opposite to the large CH(Me)OTBS substituent, where the H on the α-stereogenic centre is directed towards the boron ligand. The calculated model for this *re*-face attack mode is closely related to the empirical model **48** ($\theta \equiv 120°$) proposed earlier by one of us (see **Scheme 8**).[10] The *si*-face attack transition structures are all apparently destabilized by some nonbonded interactions, *e.g.* in **45** the aldehyde comes in close to the large CH(Me)OTBS group, in **46** the methyl group on the proximate stereogenic centre is directed towards the boron ligand, and in **47** the aldehyde approaches from the same side as the methyl group.[24] The calculated *si* : *re* selectivity is 1:3.1 (Boltzmann distribution at -78 °C), while the experimental value is 1:17. A possible reason for this discrepancy is the very large number of conformations, which probably have low barriers to interconversion.[25] The Boltzmann distribution analysis assumes that each of the conformations is confined to its own potential well, and that the shape of the well has no effect. If the barriers between adjacent wells are much less than kT, these assumptions are not reasonable. A Boltzmann distribution suggests that two potential wells with a very low barrier will have a completely different contribution to the overall distribution to one broad potential well, but this is not the case.



Scheme 9

The aldol reactions of the chiral *Z* enol borinate **49** with (*S*)-configuration have also been studied experimentally (**Scheme 9**), where the substituents at the α-stereogenic centre are hydrogen, methyl and

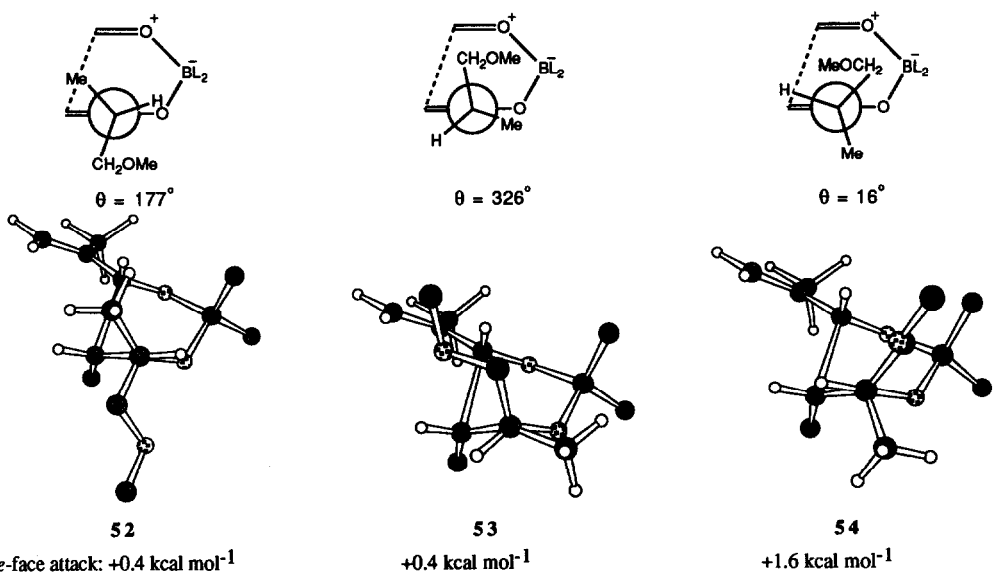
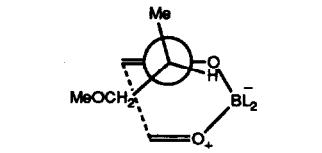
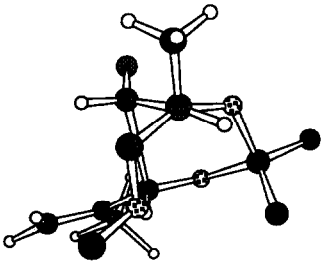


Figure 7

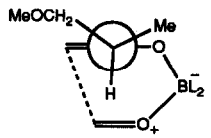


θ = 191°

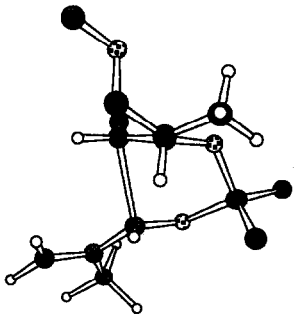


55

si-face attack: 0.0 kcal mol^{-1}

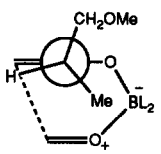


θ = 272°

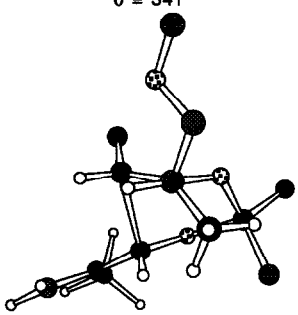


56

+0.8 kcal mol^{-1}

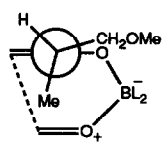


θ = 341°

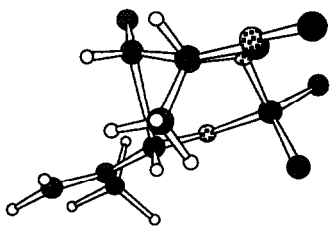


57

si-face attack: +1.0 kcal mol^{-1}



θ = 45°



58

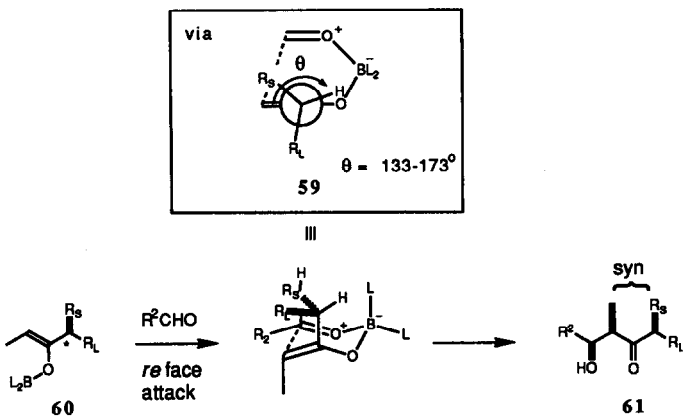
+1.6 kcal mol^{-1}

Figure 7 (contd.)

benzyloxymethyl.[26] In the calculation, the benzyl ether was replaced by a methyl ether and methyl ligands were attached to boron. Again there are several families of transition structures with different values for the C=C-C*-H dihedral angle (representative structures are shown in **Figure 7**: **52**, **53** and **54**, which are all *re*-selective; **55**, **56**, **57** and **58**, which are all *si*-selective). These families include several members with different conformations of the CH_2OMe group. This calculation reproduced the experimental *si* : *re* ratio of 1:1 for addition to methacrolein.[26] This result is not surprising considering the similar size of Me and CH_2OR at the stereogenic centre.[27]

Conclusions

The stereoselectivity of the aldol reaction of chiral *Z* enol borinates appears to be decided by a large number of competing effects rather than one or two factors, which is then best modelled by a force field analysis. For chiral ligand situations, the orientation of the ligands with respect to the transition structure core, as well as the ligand-ligand relative orientation and restrained rotation, are all important in determining the reaction selectivity. For chiral ketone cases, a new general transition state model **59** (**Scheme 10**) can be devised by inspection of the preferred transition structures **31**, **38** and **44**. This model features the hydrogen on the α-stereogenic centre directed towards the boron ligand (*i.e.* the dihedral angle C=C-C*-H is in the range $\theta = 153 \pm 20°$), the large group R_L opposite to the incoming aldehyde, and the small group R_S pointing towards the forming C-C bond of the chair transition structure. This model adequately accounts for the sense of π-face selectivity in the aldol reactions of enol borinates **28**, **35**, **41** and **49**. In general terms, these are represented as a preference for **60** → **61**. As shown by the work described here, our force field model of the boron aldol transition state is useful in understanding the origins of reaction stereoselectivity over a wide range of substrates and may also have predictive value in new situations.



Scheme 10

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