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Origins of π-Face Selectivity in the Aldol Reactions of Chiral *E*–Enol Borinates: a Computational Study Using Transition State Modelling.

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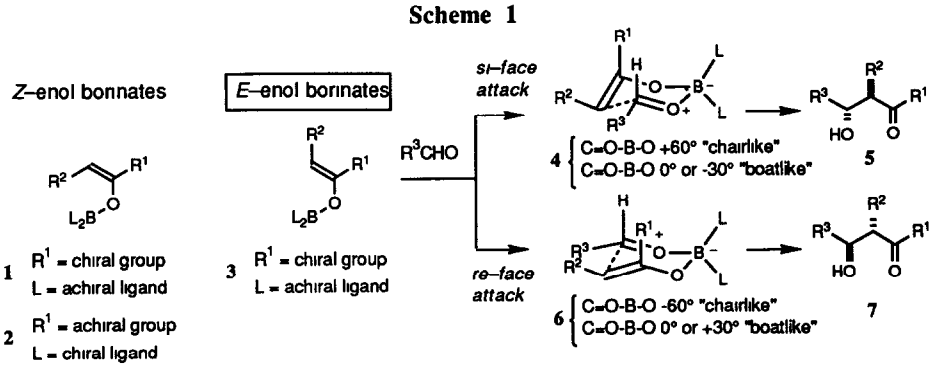
Abstract: A molecular mechanics transition state model is used to analyse the stereoselectivity of a series of aldol reactions of *E*-enol borinates of type 3 with aldehydes The model reproduces the sense and degree of π-face selectivity for the chiral *E*-enol borinates **8**, **11**, **13** and **14** in the **Table** Enolates **8** and **10** preferentially attack the *re*-face of aldehydes, which is explained (**Scheme 5**) by the aldol addition proceeding through the preferred transition structure *TS-A* for both electronic and steric reasons In contrast, enolates **11**, **13** and **14** preferentially attack the *si*-face of aldehydes solely for steric reasons, which is explained by invoking the favoured transition structure *TS-B* derived from the modelling results These two transition state models, *TS-A* and *TS-B*, which apply to *E*-enol borinates, differ substantially from the transition state model, *TS-C*, used for chiral *Z*-enol borinates with similar substituents Our force field model of the boron aldol transition state is shown to be useful in understanding the origins of the π-face selectivity over a wide range of substrates

Scheme 1

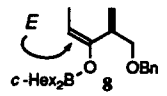
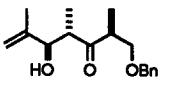
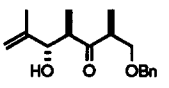
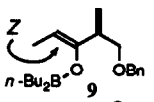
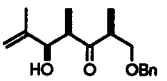
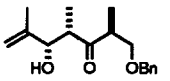
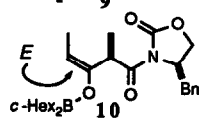
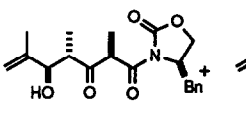
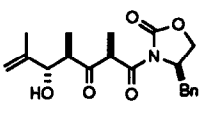
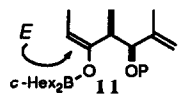
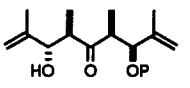
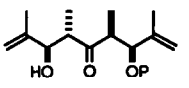
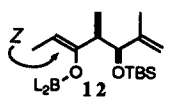
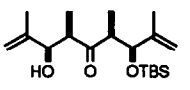
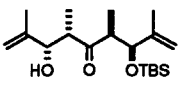
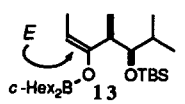
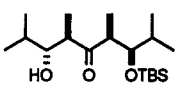
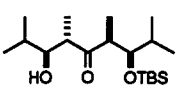
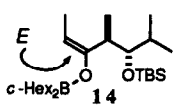
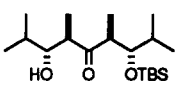
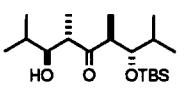


The boron aldol reaction of ketones with aldehydes has become a powerful method for the control of both relative and absolute stereochemistry in organic synthesis [1] This includes aldol reactions under (*i*) substrate control using chiral ketones and (*ii*) reagent control using chiral ligands attached to boron As part of a programme to analyse and understand the origins of this stereocontrol,[2-5] we have developed a general 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 chair and boat cyclic transition structures. The model reproduces the geometries and relative energies of simple unsubstituted and monosubstituted *ab initio* transition structures,[3] and the experimental *syn anti* stereoselectivities for the aldol reactions of *Z*– and *E*–enol borinates from ethyl ketones with aldehydes For *Z*–enol borinates, it also reproduces the aldehyde *si* . *re* selectivity for *syn* selective aldol reactions under substrate or reagent control[4a] and can be extended to reactions

of chiral aldehydes.[4b] For *E*-enol borinates, it was recently used to design and develop new chiral boron ligands for highly enantioselective *anti*-aldol reactions of ethyl ketones.[5]

In a previous paper,[4a] this force field model allowed us to rationalize the observed stereoselectivity in various synthetically useful aldol reactions using chiral *Z*-enol borinates of type **1** and **2**, see **Scheme 1.**

Table π-Face selectivities in the aldol reactions of chiral *E*– and *Z*–enol borinates with methacrolein or isobutyraldehyde (TBS = $SiMe_2{}^tBu$, TIPS = Si^iPr_3).

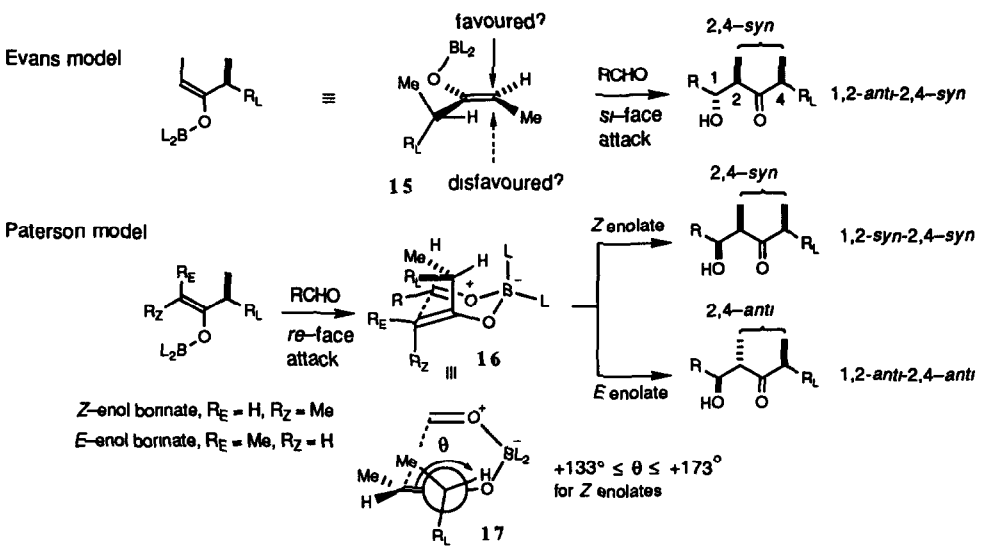
entry	enol borinate	π-face selectivity on aldehyde	aldol adducts *MAJOR*	minor	exp ratio	ref
1		*re*			98 2	7a
2		*re* + *si*			54 46	7b
3		*re*			84 16	8
4		*si*			82 18, P = TBS 87 13, P = TIPS	7c
5		*re*			≥ 92 8	9
6		*si*			94 6	8
7		*si*			96 4	8

In contrast to *Z*–enol borinates, the aldol reactions of chiral *E*–enol borinates have not been well studied experimentally Initial difficulties in achieving *E* selective enolisation of ethyl ketones were only recently solved by Brown's group.[6] There are now several examples[7a,c-f,8] of *anti* selective aldol reactions of chiral *E*–enol borinates of type **3** with aldehydes, which proceed with synthetically useful levels of substrate control, *i e* **4** → **5** *vs* **6** → **7** in **Scheme 1** These are listed in the **Table (8, 10, 11, 13, 14)**, together with some related examples[7b,9] for *Z*–enol borinates (**9, 12**) The sense of aldehyde *si re* selectivity appears to be highly sensitive to the nature of the R^1 group in the enolate with *re*-face selectivity for entries 1 and 3 *vs si*-face selectivity for entries 4, 6 and 7 Also, there are striking differences between these π-face selectivities and those of the corresponding *Z*–enol borinates, *e g* entry 1 *vs* 2 and entry 4 *vs* 5

Previously, empirical models have been used to qualitatively explain the sense of π-face selectivity in several, *but not all*, of the chiral *E*–enol borinate aldol reactions shown in the **Table**. These models are based on the relative steric demands of the substituents attached to the adjacent stereocentre R^1 in **3**.[7a,8] Evans[8] has suggested a reactant-like model (**Scheme 2**) in which A(1,3) allylic strain[10] forces the smallest substituent, hydrogen, to eclipse the enolate double bond in **15**. The aldehyde is then expected to attack the more accessible top face of the enolate away from the large group R_L. This simple model accounts for the observed sense of stereoselectivity in entries 4, 6 and 7 [7c,8] However, it does not satisfactorily account for the reversal in aldehyde π-face selectivity in entries 1 and 3, since both the *N*-acyloxazolidinone and benzyloxymethyl should be sterically more demanding than a methyl group In attempting to rationalise the common sense of π-face selectivity for the *E*– and *Z*–enol borinates in entries 1 and 5, the Paterson group[7a] had earlier considered the preferred chair transition structure **16** This model works well for *Z*–enol borinates (R_Z = Me, R_E = H)[9] and is supported by our calculations,[4a] where the Newman projection **17** corresponds to transition structure **16**. However, it fails to explain the results obtained later[7c,8] for the more highly substituted *E*–enol borinates in entries 4, 6 and 7

Using our computational approach to analyse the accessible aldol transition structures, we now consider all the available results and discuss the finely balanced steric and electronic factors contributing to the stereocontrol in these systems

Scheme 2



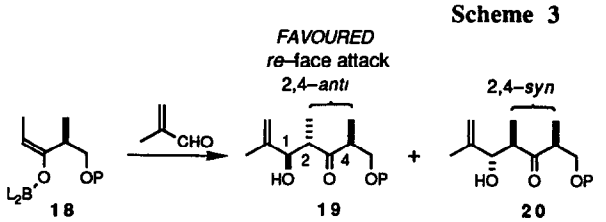
Results and Discussion

For the aldol reactions of *Z*-enol borinates, only chair transition structures are important, and these give *syn* products exclusively For *E*-enol borinates, both chair and boat transition structures are accessible.[2,3] Test calculations demonstrated that the formation of *syn* products from *E*-enolates is insignificant This is supported by experimental results, where the percentage of *syn* product is small and may be due to contaminating Z-enol

bornates.[7a,7c,8] Therefore, this study only considers transition structures leading to *anti* products. All the transition structures found (both "chairs" and "boats") have similar C=C---C=O dihedral angles (+55°±5°). They differ principally in their C=O-B-O dihedral angles ("chairs" *ca* -60°, "boats" *ca* 0° or +30°, see **Scheme 1**). All the "boats" resemble "boat B", which has been located using molecular orbital calculations and previously described.[2]

Paterson *et al* [7a] have reported the first example of a highly stereoselective aldol reaction of a chiral *E*-enol bornate (**Table**, entry 1) The enolate **8** reacts with aldehydes *via re*-face attack to give the 1,2-*anti*-2,4-*anti* adduct with ≥ 95% diastereoselectivity For cyclohexyl ligands on boron, the aldehyde π-face selectivity is uniformly excellent (*re si* ≥ 30 1) and this reaction is being extensively used in the stereocontrolled synthesis of polypropionate natural products [7d-f] Smaller ligands like *n*-butyl lead to reduced selectivity (*re* · *si* = 5 : 1).[7b] In contrast, the corresponding *Z*-enol bornate **9** shows no real facial preference in its reaction with aldehydes (entry 2) [7b] Thus the steric and electronic differences associated with the substituents (H, Me and CH_2OBn) on the enolate stereocentre only induce high π-face selectivity with the *E* enolate Evans *et al* have shown that the *E*-enol bornate **10** (entry 3) undergoes similar aldol reactions to give predominantly the 1,2-*anti*-2,4-*anti* isomer (*re si* = 5 · 1).[8] The stereochemical outcome is controlled by the C-2 stereocentre, while the oxazolidinone stereocentre does not appear to have any influence [8]

Scheme 3



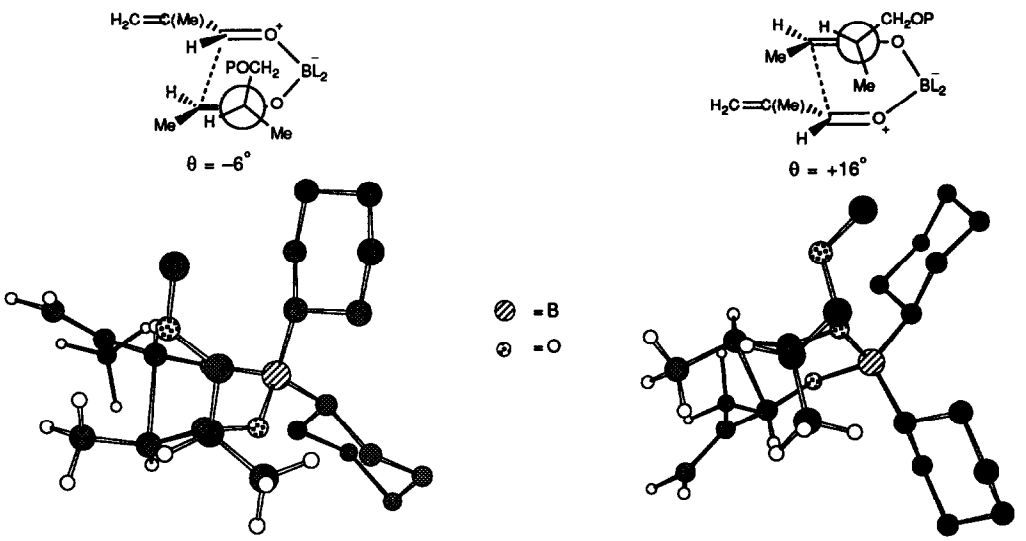
	2,4-*anti* : *syn*	
P = Bn, L = *c*-Hex →	Exp 98	2 (−78 °C)
P = Me, L = *c*-Hex →	Calc. 85	: 15
P = Bn, L = *n*-Bu →	Exp. 83	17 (0 °C)
P = Me, L = *n*-Bu →	Calc. 62	38

We investigated this system by running computer simulations of the aldol reaction of the enol bornate **18** (**Scheme 3**) for cyclohexyl and *n*-butyl ligands attached to boron A methyl rather than a benzyl ether was employed to simplify the analysis The lowest energy aldol transition structure **21**, calculated for the addition of **18** (L = *c*-Hex) to methacrolein, is shown in **Figure 1** viewed along the C*-C bond connecting the stereogenic centre with the enol bornate carbon (*i e* corresponding to a Newman projection along this bond) This corresponds to *re*-face attack → **19** and is representative of a group of some seven chair transition structures within 2 0 kcal mol^{-1} of the lowest energy structure All of these have a closely related value for the dihedral angle C=C-C*-H (θ = –6° for **21**), but there are variations in the conformation of the CH_2OMe group and of the equatorial boron ligand For *si*-face attack → **20**, a group of nine chair transition structures was found within 2 0 kcal mol^{-1} of the lowest energy structure, characterised by a C=C-C*-H dihedral angle of θ = +13 ± 5° The lowest energy structure **22** has θ = +16° For *si*-face attack two boat transition structures were also found at relative energy ≥ 1 71 kcal mol^{-1} above the global minimum, with a C=C-C*-H dihedral angle of θ = +26 ± 2° A very similar analysis also applies for *n*-butyl ligands on boron, although the selectivity in this case is reduced

The calculations reproduce the experimental sense and degree of *re si* face selectivity relatively well The force field suggests that avoidance of allylic strain in the aldol transition structures is important, as suggested by

the Evans model in **Scheme 2**. It appears that the CH_2OP moiety prefers to be directed inside the chair with the methyl taking the outside position This cannot be due to their relative steric hindrance (A = 1 75 for CH_2OMe, A = 1 70 for Me),[11] but may be related to an unfavourable electrostatic interaction between the oxygen atoms of the enol borinate and the CH_2OP group (or lone-pair repulsion)[12], which is expected to be greater in **22** than in **21** The calculation was repeated using a CH_2CH_2Me substituent (A = 1 75)[11] instead of CH_2OMe, and a 53 . 47 (2,4-*syn* 2,4-*anti*) ratio of products was predicted The lowest energy transition structures for *re*- and *si*-face attack are analogous to **21** and **22** (θ = +2° and +13°), but now have approximately the same energy Repeating the calculation with a CH_2CH_2OMe substituent instead of CH_2OMe suggested a similar 53 . 47 ratio of 2,4-*syn* 2,4-*anti* isomers

Figure 1



21 (chair)
re-face attack 0 00 kcal mol^{-1}

22 (chair)
si-face attack 0 71 kcal mol^{-1}

The role of the ether oxygen in this system is also underlined by the following two experiments Replacement of the ether oxygen in enol borinate **8** by a methylene led to a substantial lowering in π-face selectivity· 72 28 *vs* 98·2 for **8** itself [13] The sense of induction has not been determined, but is probably now turned over in favour of the 2,4-*syn* isomer Replacement of the benzyl with a bulkier triisopropylsilyl (TIPS) ether in enol borinate **8** gave a noticeable reduction in selectivity for the 2,4-*anti* isomer· **19** . **20** = 10 1 for P = TIPS [14] Hence, the combination of A(1,3) allylic strain[10] and the electronic effect of the proximate ether oxygen seem to account for the high level of selectivity shown by enol borinate **8** A similar electronic effect is presumably operating from the *N*-acyloxazolidinone group in the Evans enolate **10** (entry 3), but now steric factors will act in opposition leading to reduced selectivity (as is also observed for the TIPS analogue of **8**)

The aldol reaction of the more highly substituted *E* enol borinates **11** reported by Paterson *et al* [7c] (**Table**, entry 4) was next investigated In this case, the Evans model predicts *si*-face attack on the aldehyde in

agreement with the observed selectivity for formation of the 2,4-*syn* adduct **23** (**Scheme 4**) The transition structures calculated for this aldol reaction, where P = TMS was used in place of TBS, are shown in **Figure 2.**

Scheme 4

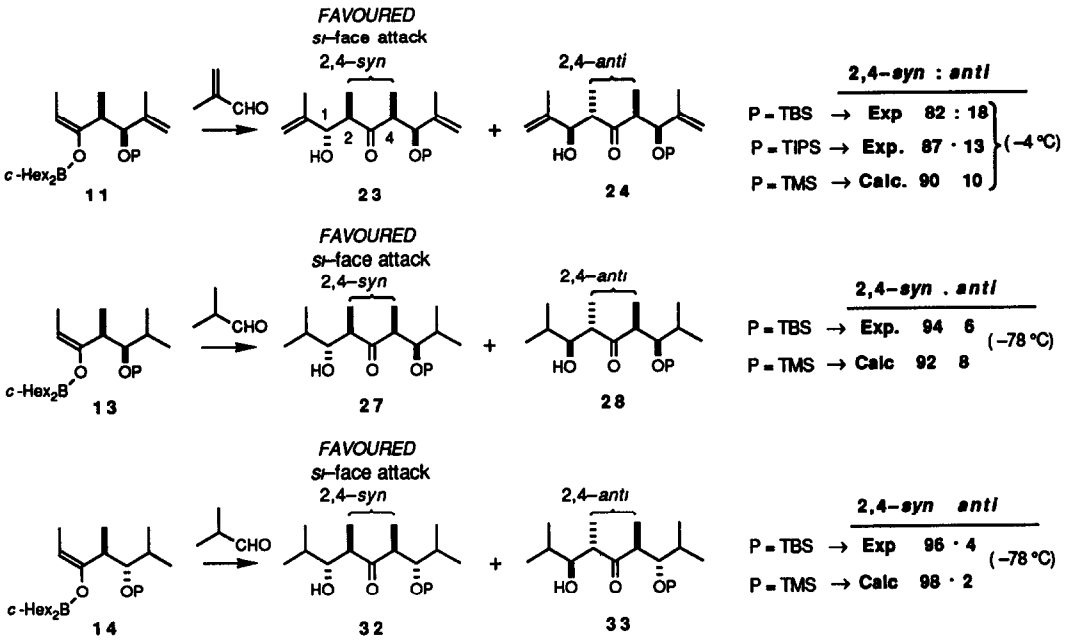
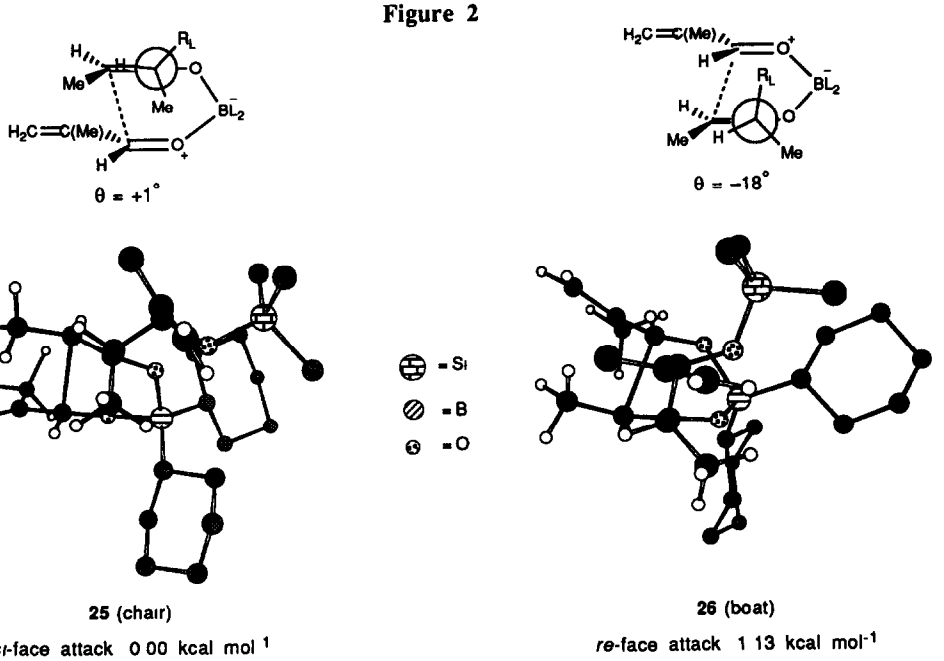


Figure 2

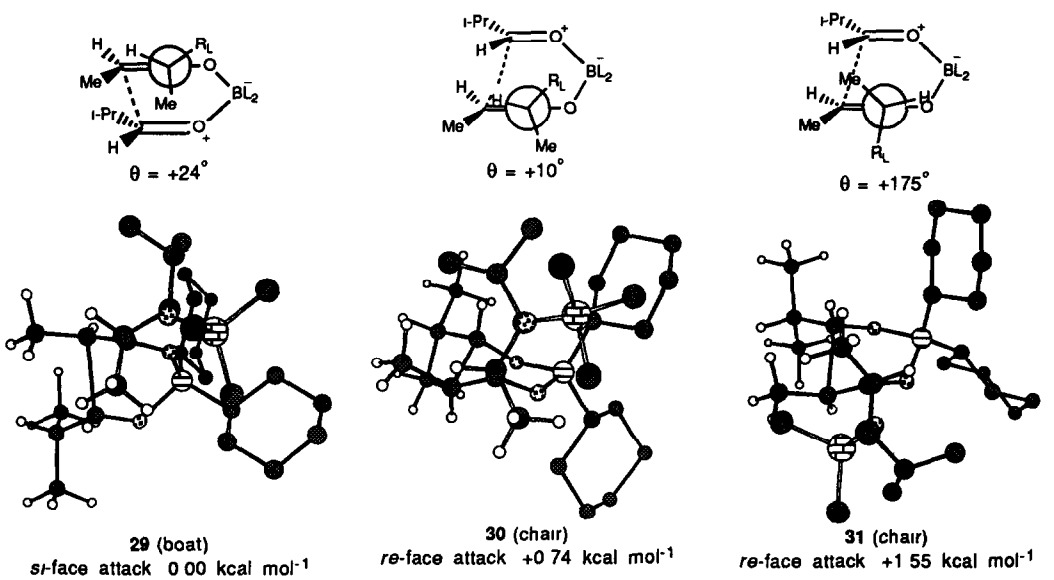


The calculated *si* : *re* face selectivity in this reaction is 90 · 10 (P = TMS), which compares favourably with the experimental ratios of 82 18 (P = TBS) and 87 13 (P = TIPS) [7c] For the preferred *si*-face attack → **23**, three groups (of twenty three, eleven, and six chair transition structures each) were found within 2 0 kcal mol^{-1} of the minimum. The first group, including the lowest energy transition structure **25** (θ = +1°), is characterised by a C=C-C*-H dihedral angle of θ = +13 ± 12° The second and third groups have θ = –43 ± 2° (lowest relative energy = +0.11 kcal mol^{-1}) and +145 ± 2° (lowest relative energy = +1 34 kcal mol^{-1}), respectively Within these groups there are many variations in the conformation of the CH(OTMS)C(Me)=CH_2 group and of the equatorial boron ligand. Boat transition structures for *si*-face attack were found at relative energy ≥ 1 35 kcal mol^{-1} above the global minimum, and were characterized by C=C-C*-H dihedral angles similar to the ones described for the chairs

For *re*-face attack → **24**, two groups of transition structures were found within 2.0 kcal mol^{-1} of the lowest energy transition structure. The first is a group of fourteen boat transition structures characterised by a C=C-C*-H dihedral angle of θ = –22 ± 4° and its lowest energy structure **26** (θ = –18°) is 1 13 kcal mol^{-1} above **25** The second group (two chairs) has θ = –35° and the lowest relative energy = +1 73 kcal mol^{-1} The enol borinate is now reacting on the same side as the large group and so the *re*-face pathway is disfavoured on steric grounds

The aldol reactions of a similar series of chiral *E*–enol borinates (**Table**, entries 6, 7) have been studied by the Evans group.[8] The enol borinate **13** gives predominantly the 2,4-*syn* adduct **27** *via si*-face attack on isobutyraldehyde (**27** **28** = 94 6, **Scheme 4**) The transition structures calculated for this aldol reaction (P = TMS) are shown in **Figure 3**

Figure 3



29 (boat)
si-face attack 0 00 kcal mol^{-1}

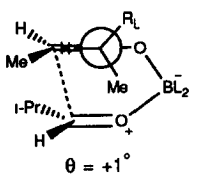
30 (chair)
re-face attack +0 74 kcal mol^{-1}

31 (chair)
re-face attack +1 55 kcal mol^{-1}

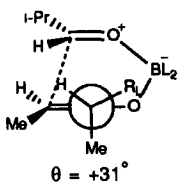
The calculated *si* · *re* face selectivity in this reaction is 92 8, which compares favourably with the experimental ratio of 94 6 (P = TBS) [8] For the preferred *si*-face attack → **27**, two groups (of thirty six boat and thirty one chair transition structures each) were found within 2 0 kcal mol^{-1} of the minimum All of these have similar dihedral angles C=C-C*-H (θ = +17 ± 9°), but there are many variations in the conformation of the CH(*i*-Pr)OTMS group and of the equatorial boron ligand The first group (boats) includes the lowest energy transition structure **29** (θ = +24°), while the second group (chairs) has its lowest energy structure (θ = +9°) which is 0 04 kcal mol^{-1} above **29** For attack on the *re*-face of the aldehyde → **28**, two structures **30** and **31** are shown and these are the lowest energy members of two groups of chair conformations (there are fifteen chair transition structures within 2.0 kcal mol^{-1} for *re*-face attack). The dihedral angles C=C-C*-H for **30** and **31** are θ = +10° and +175°, respectively, which are representative of the two groups A third group (of ten boat transition structures, θ = +24 ± 4°) has its lowest energy structure (θ = +24°) which is 0.82 kcal mol^{-1} above the global minimum. Within these groups, the major structural variations are in the equatorial boron ligand and in the CH(*i*-Pr)OTMS group

Similarly, the aldol reaction of the epimeric enol borinate **14** selectively gives the 2,4-syn adduct **32** *via* *si*-face attack on the aldehyde (**32** **33** = 96 . 4, Scheme 4) [8] The transition structures calculated for this aldol reaction with isobutyraldehyde (P = TMS → calculated *si* *re* = 98 2) are shown in **Figure 4**

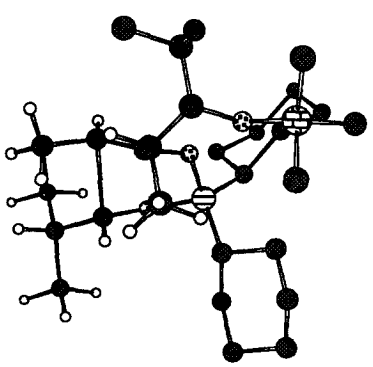
Figure 4



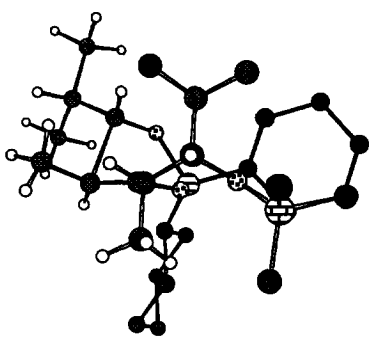
θ = +1°



θ = +31°



34 (chair)
si-face attack 0 00 kcal mol^{-1}



35 (boat)
re-face attack +1 36 kcal mol^{-1}

The lowest energy structure **34** (chair, θ = +1°) corresponds to preferred *si*-face attack → **32** and is representative of twenty eight structures (fourteen chairs and fourteen boats, θ = +3 ± 12°) within 2 0 kcal mol^{-1} of the lowest energy structure The first boat transition structure (θ = +15°) was found at +1 45

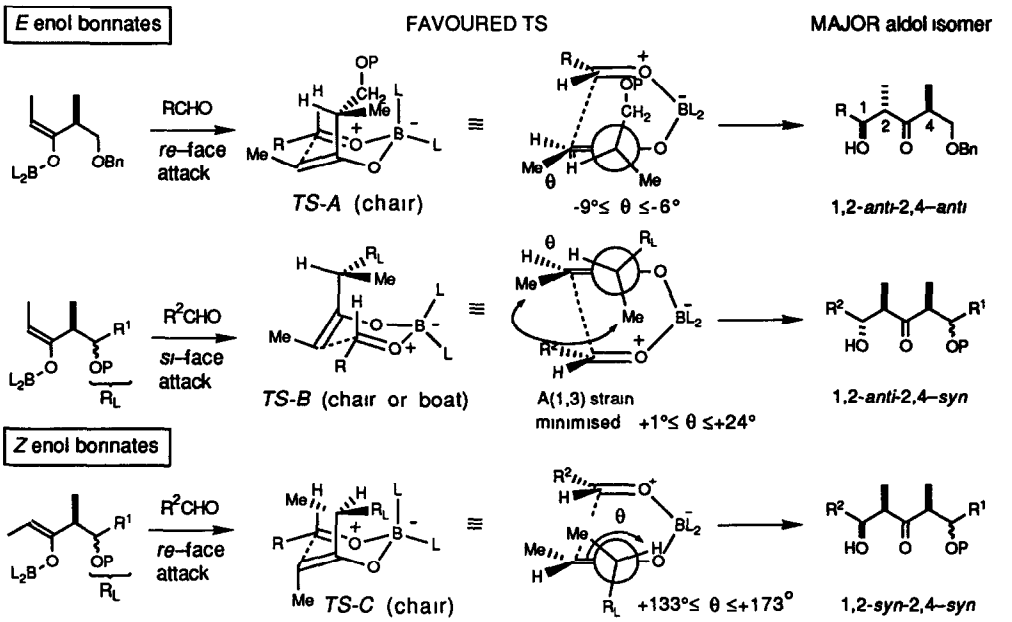
kcal mol^{-1} above **34**. For attack on the *re*-face of the aldehyde → **33**, **35** (θ = +31°) is the lowest energy structure of three boats found within 2.0 kcal mol^{-1} of the global minimum.

In these last three cases, attack on the aldehyde *si*-face by the enol borinate is clearly preferred on steric grounds where the aldehyde approaches away from the large group R_L = CH(OP)*i*-Pr or CH(OP)C(Me)=CH_2. The hydrogen of the stereocentre eclipses the *E*–enol borinate double bond, locking the position of the large group. For *re*-face attack on the aldehyde, the enol borinate is reacting on the same side as the large group and this is disfavoured on steric grounds.

Conclusions

The stereoselectivity of the aldol reaction of chiral *E* enol borinates appears to be decided by a large number of competing effects rather than one or two factors, and so is best described by a force field analysis. Our molecular modelling studies suggest that the favoured *TS-A* in **Scheme 5**, corresponding to *re*-face attack on the aldehyde, explains the preference for the 1,2-*anti*-2,4-*anti* isomer obtained for the *E*–enol borinate **8**.

Scheme 5



There must be an electronic repulsion involving the benzyl ether and enolate oxygens, which is more serious for attack on the aldehyde *si*-face. Replacing the CH_2OBn group by a larger substituent like CH(OP)C(Me)=CH_2 or CH(OP)*i*-Pr leads to the aldol reaction proceeding preferentially *via TS-B* (which can be

either a chair or a boat), devised by inspection of the preferred transition structures **25**, **29**, and **34** This is directly comparable to Evans model in **Scheme 2**.[8] The hydrogen on the α-stereogenic centre of the enol borinate is approximately eclipsed with the enol borinate double bond (*i e* the dihedral angle C=C-C*-H, θ, is $+1° \leq \theta \leq +24°$). The large group, R_L, is directed away from the incoming aldehyde and the smaller methyl group is pointing towards it. The steric effect from a large R_L group now overcomes any electronic preference from the ether oxygen orientation, leading to a reversal in π-face selectivity and formation of the 1,2-*anti*-2,4-*syn* isomer. The Evans oxazolidinone-substituted system **10** presumably also reacts largely through *TS-A* for similar electronic reasons to that for enolate **8**, but the greater steric demands of the auxiliary group relative to benzyloxy lead to competing reaction through *TS-B* and lower overall stereoselectivity (as is also found for the TIPS ether analogue of **8**)

The above *E*–enol borinate models differ substantially from that developed for the corresponding *Z* enolates, which have previously been studied using the aldol force field.[4a] For the *Z*–enol borinate **12** (*cf* entry 5 in the **Table**), the preferred aldol transition structure *TS-C* corresponds to *re*-face attack on the aldehyde leading to the 1,2-*syn*-2,4-*syn* isomer [9] Here steric factors are again dominant, but since there is no *E* methyl group on the enolate, the dihedral angle θ can be much larger (≥ 133°) and the aldehyde attacks from the face away from the bulky R_L group For the *Z*–enol borinate **9** (*cf.* entry 2),[7b] there is negligible selectivity due to the similar steric demands of the $BnOCH_2$ and Me groups

This study further demonstrates that the force field model[2-5] is useful in understanding the origins of reaction stereoselectivity in the boron aldol transition state over a wide range of substrates and may have predictive value in new situations

Computational Methods

The parameters developed in our earlier work[2] were augmented and modified as follows. *Additional torsional parameters* (see ref 4b, 10b) (a) $C(sp^2)=C(sp^2)-C(sp^3)-H$ $V_1 = 0\ 00$, $V_2 = 0\ 00$, $V_3 = -0\ 30$ (b) $C(sp^2)=C(sp^2)-C(sp^3)-C(sp^3)$ $V_1 = -0\ 54$, $V_2 = 0\ 44$, $V_3 = -0\ 60$ (c) C(enolate)---C(carbonyl)-$C(sp^3)$-$C(sp^3)$ $V_1 = 0\ 50$, $V_2 = 0\ 00$, $V_3 = 0\ 00$ *Additional bending parameter* C(enolate)---C(carbonyl)-$C(sp^2)$ = 100° (0 1 mdyn rad^{-2})

MacroModel[15a] was used to generate accessible transition structures for the enol borinate aldol reactions of interest The conformational space was searched with the Still-Chang-Guida usage-directed torsional Monte Carlo routine[16] as implemented by the BATCHMIN program [15b] Four different Monte Carlo runs were necessary to fully establish the product distribution of *E*–enol borinates, *i e* the relative energies had to be evaluated for structures featuring (1) *si*-face attack, 1,2–*anti* relative stereochemistry, (2) *re*-face attack, 1,2–*anti* relative stereochemistry, (3) *si*-face attack, 1,2–*syn* relative stereochemistry, (4) *re*-face attack, 1,2–*syn* relative stereochemistry This full search was done in selected cases to confirm that *E*–enol borinates were completely 1,2–*anti* selective Routinely only two runs (*si* face attack *vs re* face attack) were used The presence of boat transition structures was tested by including all rotatable bonds of the transition structure "core" Torsional constraints were applied to preserve the enol borinate geometry and prevent *Z*/*E* mixing Chirality checks were used for all stereocentres, and were also applied to the carbonyl carbon and the enol borinate β-carbon, to ensure stereochemical integrity of the products The energy window for the search was 12 kcal mol^{-1}, and structures were stored within 2 5 kcal mol^{-1} Occasionally an alternative procedure making use of Multiconformer[17] with a

30° or 60° resolution for each dihedral angle was also used. The results were comparable with those obtained using the Monte Carlo procedure and showed that our conformational analysis was not dependent on the search method used [18] The diastereomeric ratios (*anti vs syn* and *re vs. si*) were calculated by a Boltzmann distribution at the reported temperature (195 K or 273 K) of all conformers within 2.5 kcal mol^{-1} above the global minimum

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