Enantioselectivity in the boron aldol reactions of methyl ketones†

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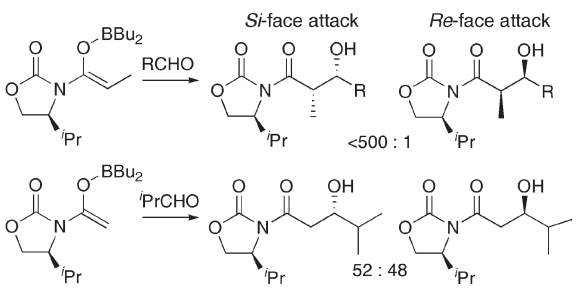
DFT computed transition states quantitatively explain the surprising stereochemical outcome of unsubstituted enolborinates in diastereoselective and enantioselective boron aldol reactions.

The kinetically controlled, boron-mediated aldol reaction allows the construction of new carbon–carbon bonds in a regio-, diastereo-, and enantioselective manner.[1] Compared to other metal enolates, the boron–oxygen bond in boron enolates is relatively short which, on addition to aldehydes, leads to tight cyclic transition states and high levels of stereoselectivity. Asymmetric reactions using chiral auxiliaries attached to the boron enolate or using chiral ligands on boron are frequently employed to control the relative and absolute stereochemistry of the aldol products. The ability to achieve such highly controlled C–C bond formation using boron enolates enables their application to the synthesis of the carbon and oxygen skeleton of stereochemically rich, polyol-containing, natural products.[2]

Boron aldol reactions mediated by a covalently attached chiral auxiliary are powerful tools for acyclic stereocontrol. The most widely used are the Evans auxiliaries,[3] based on oxazolidinone heterocycles (see Scheme 1). *Z*-Enolborinates prepared by enolisation of the parent imide with a boron triflate reagent and hindered tertiary amine base ($^{i}Pr_2NEt$ or Et_3N) lead to *syn* aldol products with diastereoselectivities of up to 500 : 1. In contrast, the development of auxiliary-controlled acetate-type aldol reactions has met with limited success, as unsubstituted enolborinates show significantly reduced levels of diastereoselectivity.

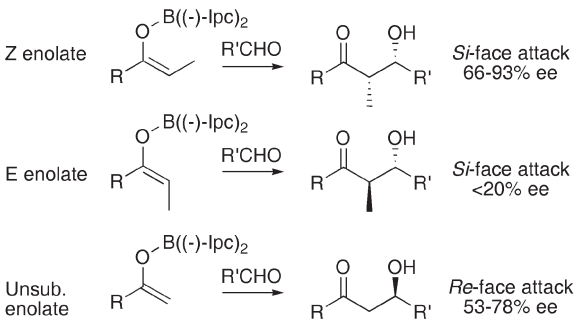
Enol diisopinocampheylborinates, derived from ethyl and methyl ketones by enolisation in the presence of a tertiary amine base, undergo enantio- and diastereoselective aldol reactions with aldehydes (see Scheme 2).[4] This chiral reagent method provides a valuable alternative to the use of a chiral auxiliary attached to the boron enolate, eliminating the need for auxiliary introduction and removal. In situations where the underlying substrate control is moderate, the isopinocampheyl (Ipc) ligand can be employed in a matched sense to enhance the stereoselectivity to synthetically useful levels, or in a mismatched sense to overturn the π-facial selectivity.[5] Rather surprising, however, is the finding that the aldehyde enantioface selectivity upon the addition of a methyl-ketone derived (unsubstituted) enolborinate is reversed relative to a substituted enolborinate.[6] *E*-Enolborinates also display much less enantioselectivity than the corresponding *Z*-enolborinate.



Scheme 1 Reactions with chiral oxazolidinone auxiliaries.

We report here the results of density functional calculations[7] which both qualitatively and quantitatively explain the surprising stereochemical behaviour of methyl ketones. Computation of competing transition structures show that boron aldol reactions are characterised by a chair and two distinct boat structures. Reactions of *Z*-enolborinates proceed exclusively *via* chair transition structures, whilst those of *E*- and unsubstituted enolborinates proceed instead *via* boats.

Fig. 1 shows the transition structures for the addition of the *E*- and *Z*-enolborinates of butan-2-one and the enolborinate of acetone to ethanal. Methyl ligands on boron were used as a computationally reasonable model system. As previously shown by Houk[8] and Bernardi[9] for smaller model systems, there exist two distinct boats and a chair shaped aldol transition structures. The aldehyde can be oriented in two possible ways in each structure and in the preferred transition structures the alkyl substituent occupies the less crowded position (boat A, boat B and chair). The relative populations at −78 °C of the competing transition structures calculated from the Boltzmann factors are shown in Scheme 3. For *Z*-enolborinates, the chair is predominant, but for *E*- and unsubstituted enolborinates there is competition between the chair and the two boats. These boat structures are favoured because they relieve the 1,3-diaxial repulsion between one of the ligands and the enolate side chain. For *Z*-enolborinates only, boat



Scheme 2 Aldol reactions utilising chiral ^{d}Ipc ligands on boron.

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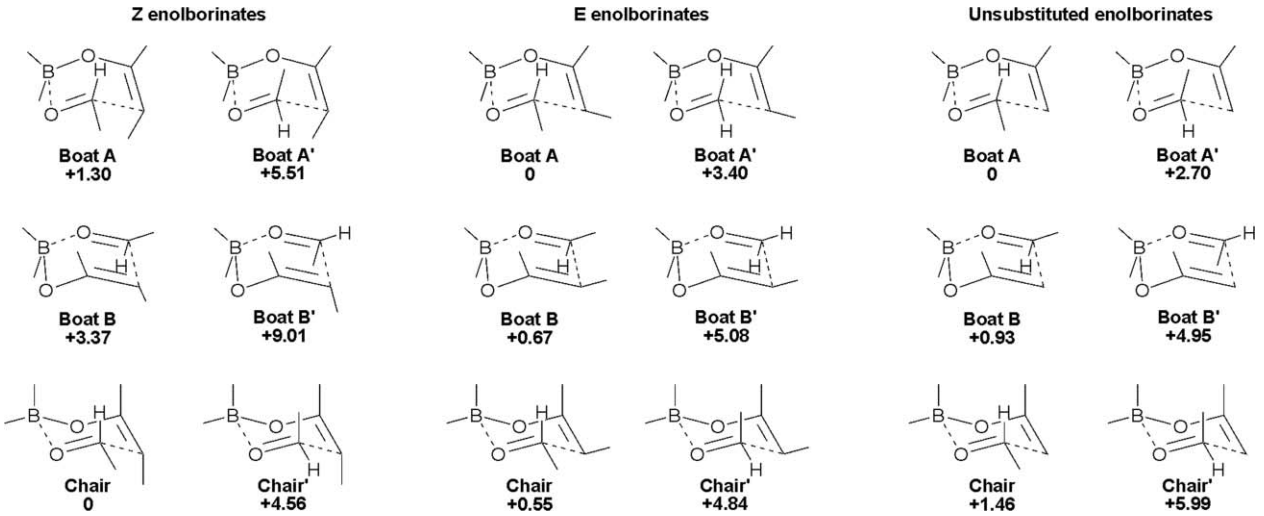
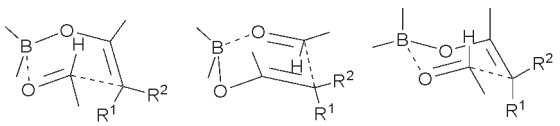


Fig. 1 Competing transition structures in the aldol reactions of *Z*-, *E*- and unsubstituted enolborinates with ethanal (relative energies in kcal mol^{-1}).‡



	Z-enolborinate (R^1 = Me,R^2 = H)	E-enolborinate (R^1 = H,R^2 = Me)	Unsub. enolborinate (R^1 = H,R^2 = H)
Boat A	3.4%	70.4%	89.7%
Boat B	0.0%	12.6%	8.1%
Chair	96.6%	17.0%	2.1%

Scheme 3 Boltzmann populations for competing transition structures calculated at the standard reaction temperature of −78 °C.

transition structures are destabilised by a 1,4-steric interaction between one of the ligands on boron and the enolate R_1 substituent. In accordance with experimental results, the calculated populations predict that *Z*-enolborinates favour the *syn*-adduct (100 : 0) and *E*-enolborinates the anti-adduct (87 : 13).

Competing diastereomeric transition structures were then calculated for the asymmetric boron aldol reaction of *E*- and *Z*-enolborinates of butan-2-one and the enolborinate of acetone using chiral (−)-Ipc ligands. All those transition structures based on boat A, boat B and the chair were considered.

In each case, the orientation of the Ipc ligands with respect to each other is identical—these large sterically demanding groups are conformationally locked. Rotation about the boron–carbon bond is extremely difficult, and we were not able to optimise any structures arising from manual rotation of these bonds. In the one favourable conformation the Ipc ligand in the most crowded position (pseudo-axial) is oriented as to minimise unfavourable steric interactions with the six-membered transition structure core. The other Ipc ligand is oriented to minimise unfavourable steric interactions between itself and the neighbouring Ipc ligand. Stereofacial discrimination in attacking the aldehyde arises due to destabilising steric interactions between the enolate side chain and the methyl groups of the ligands in one of the diastereomeric transition structures. As before, the reactions of *Z*-enolborinates proceed *via* chair transition structures whilst *E*- and unsubstituted enolborinates proceed *via* boats.

For *Z*-enolborinates, the competing transition structures are both chair-shaped (Fig. 2). In attacking the aldehyde *Re*-face there is an unfavourable steric interaction between the enolate side chain and the methyl group on the pseudoaxial Ipc ligand. These calculations predict a *syn* : *anti* ratio of 100 : 0, with the *Si*-product being formed in 88% ee, consistent with experimental results for a *Z*- substituted diisopinocampheylenolborinate reacting with methacrolein, benzaldehyde, butanal, crotonaldehyde and isobutyraldehyde leading to this enantiomer in 66–93% ee.

For unsubstituted enolborinates the most important transition structures are those based on boat A (Fig. 2).[10] This causes a reversal in enantioselectivity (relative to the reactions of *Z*-enolborinates) since in the boat *Si*-facial attack leads to an

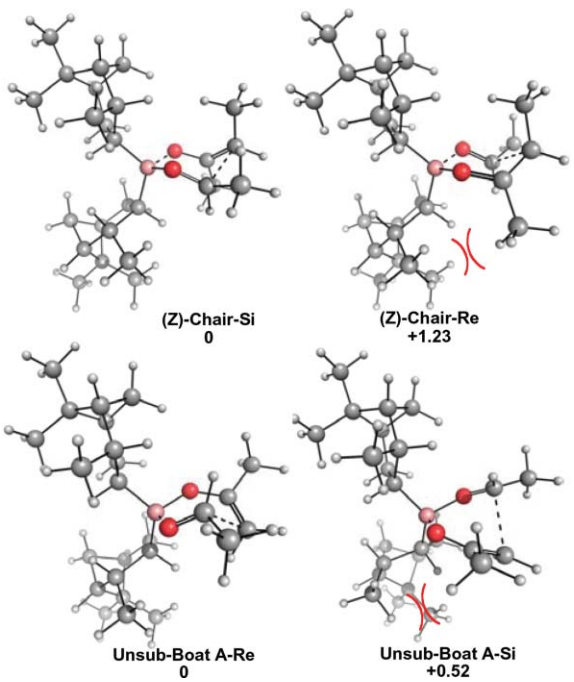


Fig. 2 Transition structures for *Z* enolborinates (top) and unsubstituted enolborinates (below) with [d]Ipc ligands (energies in kcal mol^{-1}).

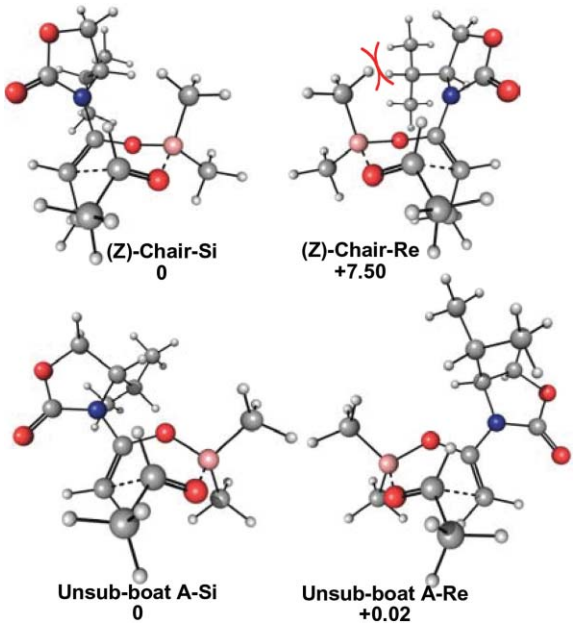


Fig. 3 TS for *Z*-enolborinates (top) and unsubstituted enolborinates (below) with oxazolidinone auxiliaries (energies in kcal mol^{-1}).

unfavourable steric interaction between the enolate and the lower Ipc ligand such that *Re*-facial attack is preferred. There is a smaller energy difference between stereodiscriminating transition structures than for the *Z*-enolborinates, consistent with the lower levels of experimental enantioselectivity. These calculations predict the re-product will be formed in 52% ee, in agreement with experimental results where the reaction of diisopinocampheylborinates derived from acetone with a variety of aldehydes (methacrolein, benzaldehyde, butanal) led to this enantiomer in 53–78% ee.

For *E*-enolborinates, boat A transition structures are preferred favouring *Re*-facial attack, but boat B and chair structures are also significant favouring *Si*-facial attack. This competition between all three geometries results in low levels of enantioselectivity. Our calculations predict an *anti* : *syn* diastereoselectivity of 84 : 16, with the *anti* adduct being formed in 28% ee, favouring *Re*-facial attack. In agreement with experiment, *E*-substituted diisopinocampheylborinates are predicted to be of limited synthetic use due to their poor enantioselectivity.

To investigate the auxiliary-controlled boron aldol reaction competing transition structures were calculated for the propionimide derived *Z*-enolborinate and *N*-acetyl imide derived unsubstituted enolborinate both reacting with ethanal. The oxazolidinone derived from (*S*)-valine was used and all transition structures based on boat A, boat B and the chair were considered. The effects of rotation about the C–N bond and of the isopropyl group were considered and the results are summarised in Fig. 3.

As before, the predominant transition structure for the *Z*-enolborinate reacting is chair shaped. In the lowest energy structure the N–C=O π-system of the auxiliary is coplanar with the enolate, the C–O dipoles are opposed and the isopropyl group points away from the ligands on boron. In the diastereomeric chair shaped transition structure the isopropyl group is oriented towards the pseudoaxial ligand leading to an unfavourable steric interaction which disfavours this structure by 7.5 kcal mol^{-1}. The large energy difference between the pathways to the two diastereomeric *syn*-aldol products predicts a dr of 99.95 : 0.05, consistent with the high levels of selectivity observed.

The unsubstituted enolborinate prefers to react *via* a boat A transition structure and in the most favourable structure the oxazolidinone is coplanar with the enolate with the C–O dipoles counteraligned. In the boat conformation, however, 1,3-diaxial interactions are significantly reduced and now there is no energetic preference for the isopropyl group to point either away from or towards the ligands on boron. Thus there is a negligible energetic difference in diastereomeric pathways predicting a dr of 50 : 50, in excellent agreement with the reported value on 52 : 48 (see Fig. 1).

In summary, our calculations show that the boron aldol reaction of *Z*-enolborinates proceed *via* chair transition structures, whilst those of *E*- and unsubstituted enolborinates proceed instead *via* boats. This qualitative conclusion has been suggested by Paterson[4] and Evans,[11] who considered the chair and boat B. It is this subtle difference that leads to major differences in enantio- and diastereoselectivity. The origins of stereoinduction in reactions using chiral isopinocampheyl (Ipc) ligands can be explained with these transition structures. Ipc ligands adopt a single conformation which favours aldehyde *Si*-facial attack in the case of chair-shaped transition structures and *Re*-facial attack in the case of boats. The stereofacial discrimination results from unfavourable steric interactions between one Ipc methyl group and the enolate side-chain. Chiral oxazolidinones impart high levels of diastereomeric discrimination in chair shaped transition structures but not in boat structures, for which 1,3-diaxial interactions are much reduced. Hence the reactions of *Z* enolborinates are highly diastereoselective and those of unsubstituted enolborinates much less so. The prediction of diastereoselectivity and enantioselectivity in each example is in excellent agreement with experiment.

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