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Mechanistic Insights from *Ab Initio* Calculations on a Nitrogen Analogue of the Boron-Mediated Aldol Reaction

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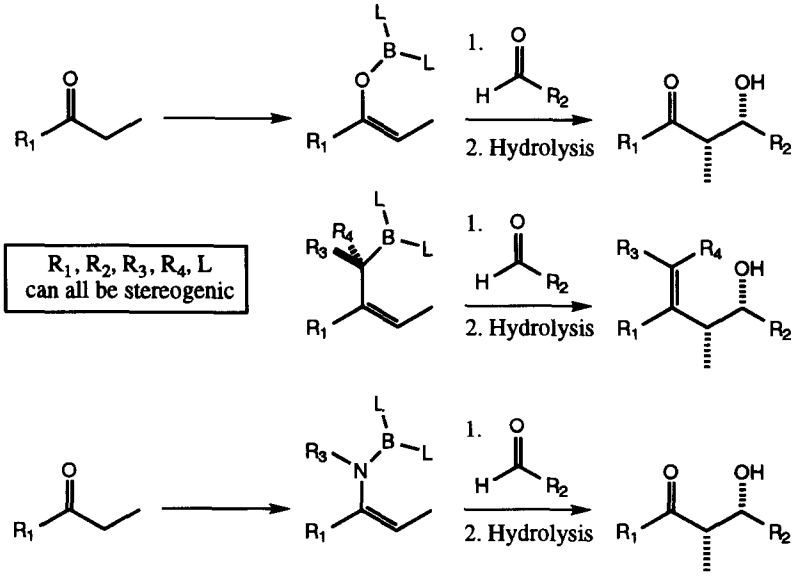
Abstract: Molecular orbital calculations were used to study a nitrogen analogue of the boron mediated aldol reaction. Experimental results show that high selectivity can be obtained in some cases, at the cost of low yields. The molecular orbital calculations are used to analyse the experimental results and to suggest modifications to the experimental procedure. The results suggest an explanation for a puzzling reversal of selectivity in the aldol reactions of methyl ketones.

INTRODUCTION

Both the aldol reaction and the allylboration reaction have important places in asymmetric organic synthesis.[1] The allylboration reaction tends to give better stereoselectivity using chiral ligands on boron than the corresponding aldol reaction, but the products of the reaction often need to be converted to carbonyls requiring an additional synthetic manipulation.



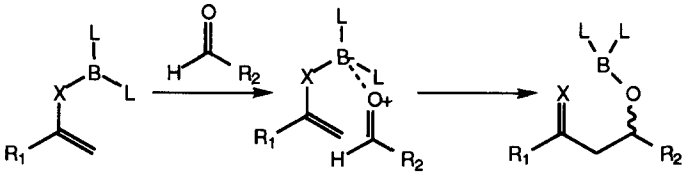
Scheme 1: General scheme for aldol, allylboration, and aza-aldol reactions

Neither reaction provides a complete solution to the problem of stereoselective carbon-carbon bond formation. The starting materials for the allylboration reaction can be harder to prepare than the corresponding enolborinates for the aldol reaction. Despite recent advances,[2] the aldol reaction does not provide a general method for making α-unsubstituted-β-hydroxy-ketones enantioselectively. In fact, the reaction of methyl ketones is particularly troublesome, as it does not seem amenable to analysis by transition state modelling, a technique that has been useful in the other cases.[2e,3] A reaction that could solve these problems would be very widely used in asymmetric synthesis.

The use of nitrogen instead of carbon or oxygen might combine the advantages of both reactions, giving the excellent stereoselectivity of the allylboration, and a product that could be hydrolysed in workup to give the aldol reaction product (**Scheme 1**).[4] The introduction of a nitrogen atom gives a new site for the incorporation of a stereogenic group into the molecule, like the allylboration reaction, thus increasing the possibilities for reagent controlled reactions. Further, the enaminyl borinate can be made from a ketone without the need for allyl or crotyl metal reagents as in the allylboration reaction.

MOLECULAR ORBITAL RESULTS

The aldol reaction, allylboration and the aza-aldol reaction all proceed in two steps. First, the enol borinate or the allylborane species forms an 'ate complex' with the aldehyde (**Scheme 2**). This ate complex then rearranges to form a new carbon-carbon bond, *via* a cyclic transition state. *Ab initio* calculations have previously been reported for allylboration (X = CH_2)[5a,d] and for the aldol reaction (X = O).[3a,6] We have now performed similar calculations for the nitrogen analogue (X = NR_3) of these reactions.



X = CH_2, NR_3, or O; L = alkyl

Scheme 2: Reaction mechanism *via* ate complex

Calculations were carried out at the Hartree-Fock level, using the 3-21G[7] and 6-31G* basis sets and the CADPAC[8] and GAUSSIAN82 programs.[9] Initial calculations were performed on enaminyl borinates, and then on the ate complexes of these enaminyl borinates with formaldehyde. Finally, transition states were investigated, beginning with the known geometries of the transition structures for the aldol reaction. The transition structure optimisations were performed using Baker's algorithm.[10] It is not possible to be certain that all relevant transition structures were found, because the conformational space available is so large. However, the regions around the geometries of the known aldol transition structures were searched thoroughly, and so no similar transition structures are likely to exist. The results are summarised in **Table 1**.

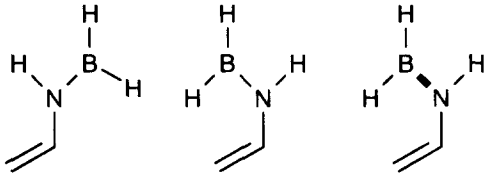
Enaminyl Borinate:

The enaminyl borinate calculations produced results much as expected from earlier studies of enol borinates (**Figure 1**).[11] There is a strong tendency for the boron-nitrogen bond to be coplanar with the carbon-carbon double bond, and this may be because the vacant orbital on the boron and the nitrogen lone pair are particularly well matched in geometry and energy. The nitrogen appears to be sp^2 rather than sp^3 hybridized, and the nitrogen-boron bond is effectively a double bond (see B-N values in **Table 1**).

Table 1: 3-21G *Ab Initio* Energies for Structures on the Reaction Coordinate of the Aza-Aldol

Structure	Energy (Hartrees)	(kJ mol^{-1})	B-N (Å)	B-O (Å)	C=C-N-B
Enaminyl borinate (**1**, *s*-trans)	-157.493023	18.84	1.411	—	180°
Enaminyl borinate (**2**, *s*-cis)	-157.487980	32.08	1.441	—	0°
Enaminyl borinate (**3**, non-planar)	-157.488024	31.96	1.411	—	19°
Ate complex (**4**)	-270.722100	0.00	1.425	2.543	179°
Ate complex (**5**)	-270.720925	11.94	1.428	2.606	18°
Ate complex (**6**)	-270.722018	2.87	1.415	2.702	179°
Chair (**9**)	-270.695947	68.45	1.579	1.618	97°
Boat A (**10**)	-270.705873	42.38	1.518	1.691	18°
Boat B (**11**)	-270.702066	52.38	1.527	1.676	3°

This is reflected in the geometry of the non-planar form, **3**, which is very close to planar. The dihedral angle between the B-N bond and the double bond is only 19°, compared with 50° for the corresponding enol borinate. The structure in which the B-N bond is constrained to be perpendicular to the double bond was also investigated. This structure had a slightly longer C-N bond and a much higher energy than the planar structures, suggesting that the C-N bond has some double bond character. The barrier for rotation around the C-N bond, which occurs when C=C-N-B is 96°, is 26 kJ mol^{-1}, compared with a barrier of 8.5 kJ mol^{-1} for the C-O bond of the corresponding enol borinate.



1 **2** **3**

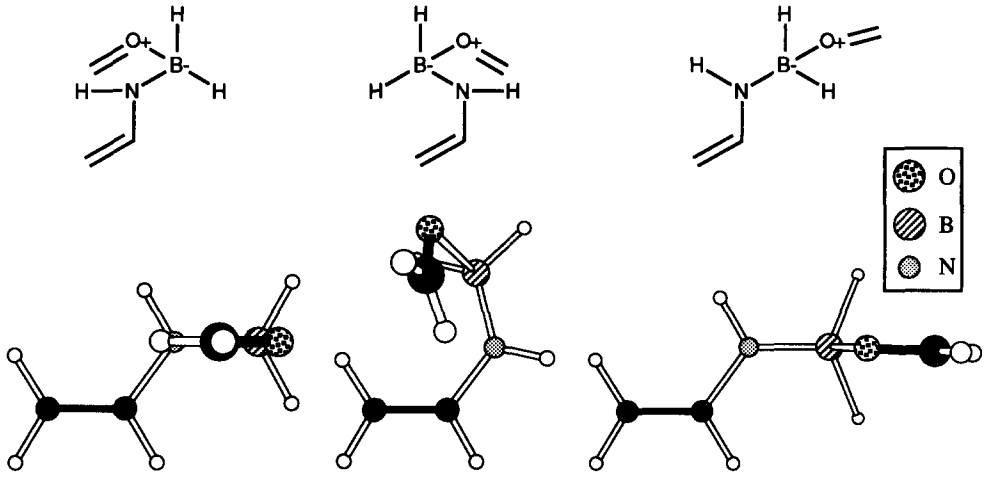
Figure 1: Enaminyl Borinates

Aza-Ate Complexes:

The boron and the nitrogen are both sp^2 in the ate complex (as judged by their geometries, **Figure 2**), and so the nitrogen-boron bond is effectively a double bond as in the starting enaminyl borinates. The nitrogen lone pair orbitals match the boron in geometry and energy better than oxygen lone pairs. As a result,

the strength of the association between the carbonyl and the boron Lewis acid is much weaker than for the aldol and the allylboration reactions (**Table 2**).

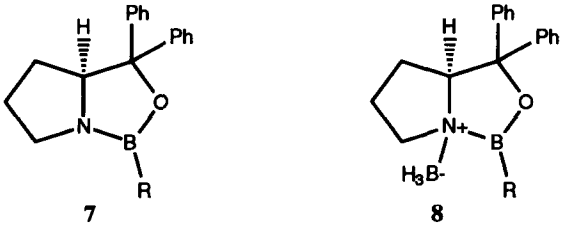
The structures in **Figure 2** look similar to the analogous aldol structures, but this disguises a striking geometrical difference between the aza-ate complexes and those of the aldol reaction and the allylboration reaction: the length of the B-O bond. In the aldol, this is about 1.6 Å, in allylboration it is 1.7 Å, but in the aza-aldol it is 2.6 Å (see **Table 1**).



4 **5** **6**

Figure 2: Ate Complexes

Studies of the complexes of carbonyl compounds with boron Lewis acids bearing one electronegative group have shown that the electronegative group has a strong preference to eclipse the carbonyl double bond.[12] The ate complexes of the aldol reaction display this effect. We expected, therefore, that this preference would also be present in the aza-ate complexes. We were surprised to discover that this is not the case: **4** and **6** have similar energies (**Figure 2**). This may be because the B-O bond is extremely long. The increased length of the bond reduces the anomeric effect which enforces the eclipsed conformation in related systems.[12]



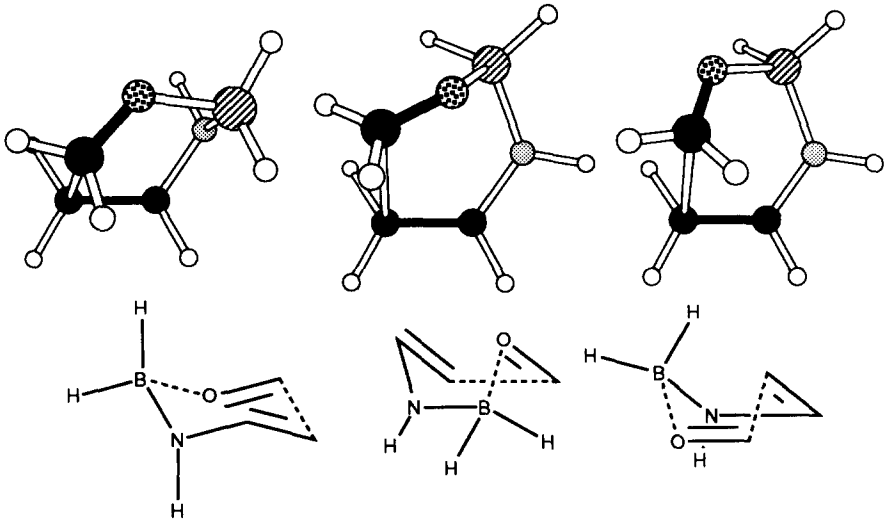
7 (inactive, weak Lewis acid) **8** (active, strong Lewis acid)

Figure 3: The CBS Reducing Agent

In the analogous system of the CBS reducing agent,[13] Nevalainen has calculated that a similar effect is present.[14] The reducing agent (**7**, **Figure 3**) does not form a strong complex with carbonyls until the nitrogen lone pair is complexed by a second boron (**8**).

Aza-Aldol Transition Structures:

Three distinct transition structures were found for the aza-aldol reaction, one chair and two boat forms (**Figure 4**). These are similar in geometry to the transition structures of the aldol reaction. In particular, the B-O bond is about 1.7 Å in all cases, which is similar to the aldol results, but represents a large change from the geometry of the ate complexes. All the transition structures have a single reaction-coordinate vibrational mode associated with an imaginary frequency, and in each case this corresponds to a movement which shortens the new carbon-carbon bond, and so moves towards the product of the reaction.



9 (Chair)	**10** (Boat A)	**11** (Boat B)
H-N-C=C 30°	H-N-C=C 177°	H-N-C=C 173°
B-N-C=C 97°	B-N-C=C 18°	B-N-C=C 3°
C···C 2.238 Å	C···C 2.489 Å	C···C 2.375 Å

Figure 4: Transition Structures

In the chair transition structure, the nitrogen atom is sp^3 hybridised rather than sp^2, and so the hydrogen it bears could be either axial or equatorial with respect to the ring. The hydrogen prefers to be axial, not in the less sterically hindered equatorial position.[15] We attempted to find a transition structure for which the hydrogen was in the equatorial position, but the search was unsuccessful. The stability of the axial hydrogen may be due to a reverse anomeric effect, in which the nitrogen lone pair donates into the boron-oxygen anti-bonding orbital. Such an effect has been reported by Cramer in a similar situation.[16] Houk has investigated the Diels-Alder and ene reactions of formaldimine,[17] and found that lone pairs appear to be more sterically demanding than the hydrogen. Houk attributes this to repulsion between π-electrons and the lone pair, but that cannot be the explanation in the aza-aldol reaction.

In the other transition structures, the nitrogen is quite flat (close to sp^2 hybridisation), although there is a slight distortion suggesting that the nitrogen lone pair would prefer to be *anti* to the boron oxygen bond. Both the boats are much lower in energy than the chair (**Table 2**).

There is a big difference in geometry between the ate complexes and the transition structures, for the aza-aldol. This is reflected in the energy barrier found by the molecular orbital calculations. However, molecular orbital calculations give the potential energy of the system, not the free energy (G). The difference between these quantities is based on the entropy of the system. A much larger reorganisation of the structure is required to go from an enaminyl borinate to the transition structure than for the corresponding aldol reaction. This is likely to reinforce the calculated energy barrier, making the aza-aldol reaction even harder than the molecular orbital energies suggest. The entropy of association for the formation of the ate complexes is likely to affect the energies in the opposite way, because the reorganisation required to form the aldol ate complex is greater than to form the aza-aldol ate complex.

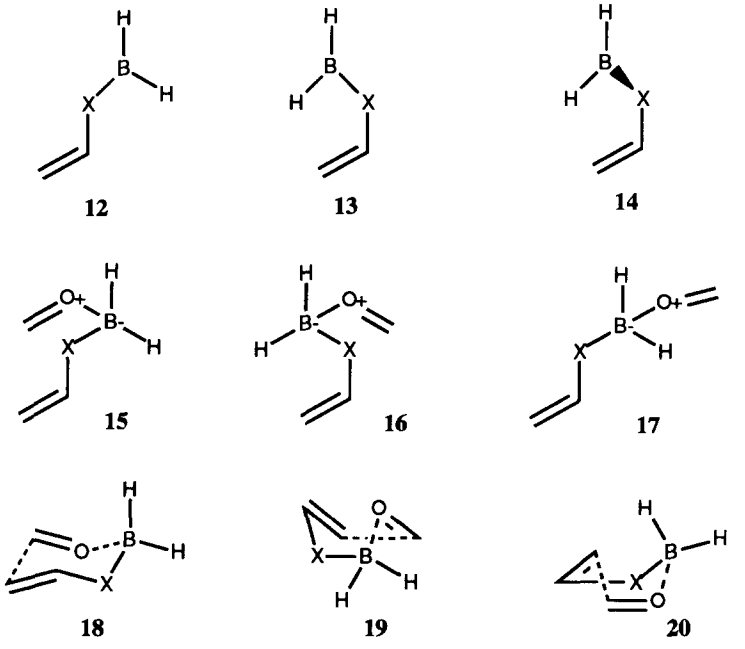


Figure 5: Intermediates and transition states for allylboration (X = CH_2), aza-aldol (X = NH), and aldol (X = O) reactions.

COMPARISON OF THE THREE REACTIONS

A simple rationale based on periodicity for the nitrogen analogue of these reactions suggests that it should have intermediate behaviour between the carbon case and the oxygen case. The *ab initio* calculations show that this is not true.

The reaction profiles for the three reactions are illustrated in **Figure 6**. The energies in the figure are based on the highest level of theory available for each reaction. The starting materials react to form an ate

complex, (the first dip in the graph), then overcome an energy barrier (the carbon-carbon bond forming transition state) to form the final products. In the allylboration case much less energy is required to form a new carbon-carbon bond than to break up the ate complex. In the aldol case, less energy is gained by forming the ate complex, and the carbon-carbon bond forming transition state is higher in energy. For the aza-aldol, the trend continues. The benefit of forming an ate complex decreases further, and the final step becomes harder. Entropy effects (discussed above) will probably reinforce this trend in the enthalpy.

Table 2: *Ab initio* energies (kJ mol^{-1}), relative to the ate complex 15, for 3-21G geometries

Structure	X = CH_2[a]	Aldol (X = O)			Aza-aldol (X = N-H)		
	3-21G	3-21G	6-31G*	MP2[e]	3-21G	6-31G*	MP2[e]
Borinate (**12**, *s*-trans)		43.52[b]	4.15[b]	42.58[b]	18.84[b]	2.10[b]	29.37[b]
Borinate (**13**, *s*-cis)		46.57[b]	6.43[b]	53.85[b]	32.08[b]	16.85[b]	44.46[b]
Borinate (**14**, non-planar)	72.31[b]	45.47[b]	3.32[b]	49.40[b]	31.96[b]	16.70[b]	43.79[b]
Ate complex (**15**)	0.00	0.00	0.00	0.00	0.00	0.50	—
Ate complex (**16**)		0.91	3.54	2.24	11.94	14.09	10.8
Ate complex (**17**)		16.82[c]	—[d]	—[d]	2.87	0.0	0.00
Chair (**18**)	7.52	50.93	56.03	18.25	68.45	87.40	25.97
Boat A (**19**)	42.22	45.35	53.70	16.13	42.38	74.40	17.90
Boat B (**20**)		52.64	61.18	24.74	52.38	87.37	32.46

(a) From reference 5a. (b) Relative to ate complex **15**, allowing for the contribution of isolated formaldehyde (-113.221820 Hartrees (3-21G//3-21G); -113.865286 Hartrees (6-31G*//3-21G); -114.166810 Hartrees (MP2/6-31G*//3-21G) (c) Taken from reference 6. (d) The potential surface is very flat in this area, but we could not find a minimum at the 3-21G//3-21G level. (e) Calculations at the MP2/6-31G*//3-21G level.

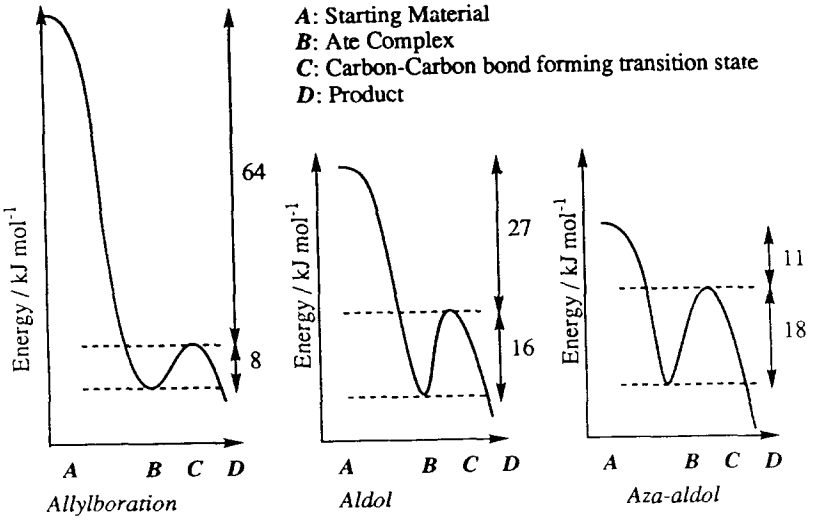


Figure 6: Comparison of the reaction coordinates

These results suggest that the ate complex becomes increasingly important to the course of the reaction changing from N to O to C. This means that a model of the carbon-carbon bond forming transition structure is most likely to have predictive properties in the nitrogen case. We have shown that the aldol reaction can be analysed in terms of the carbon-carbon bond forming transition state,[2e,3] but also that there is some correlation between the enol borinate geometry and the reaction products.[11b] If the ate complex is more important in the allylboration case, then a model for this reaction should take account of the entire reaction coordinate in order to predict selectivity.

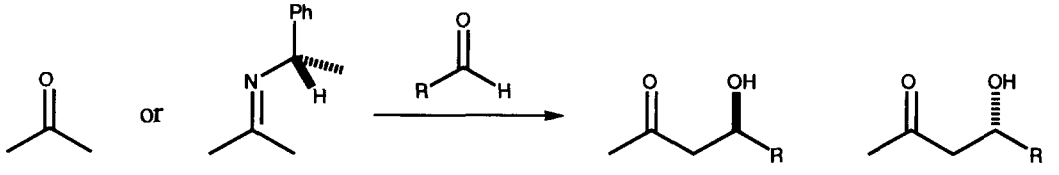
Force field models for the transition state between the ate complex and the product (carbon-carbon bond forming transition state) have been developed for the allylboration reaction that give good correlation with experiment,[5b-d] although this transition state may not be the stage of the reaction coordinate which controls selectivity. This does not invalidate our conclusions for reasons outlined by Menger and Sherrod.[18] A model that reproduces experimental results is not guaranteed to have a close relationship to the actual reaction coordinate. The value of the transition state force fields remains, because they can predict selectivity.

EXPERIMENTAL RESULTS

An experimental study of the nitrogen analogue of the aldol reaction has been undertaken, but the yields were generally low. Is this because of a problem in the experimental procedure, or is it because there is a fundamental problem with the reaction that must be overcome for it to be useful synthetically? The molecular orbital study suggests an answer to this question.

The results of an experimental study with Ipc-derived boron chlorides and boron triflates and the chiral acetone imine **21** (**Scheme 3**) are given in **Table 3**. **Table 4** shows results from the corresponding aldol reaction.[19] The yields of the aza-aldol reactions are rather low, but the selectivities are sometimes high. Experiments were also performed using diethylketone instead of acetone, but in these cases no aldol product could be isolated. It is clear from entries 1-4 (**Table 3**) that the α-pinene chirality is controlling the sense of the asymmetric induction, in the same direction as for the aldol reaction (**Table 4**). It is possible, therefore, that these reactions proceed through a similar transition state, and it is likely that this is a boat (*i.e.* boat A, **19**),[3a,18] because the boat transition structures have much the lowest energies.

The combination of (+)-Ipc$_2$BX and the *(S)*-amine results in a matched pair (compare entries 1, 2 with entries 3,4 in **Table 3**). The large differences in the product enantiomeric excess between the chloride and triflate reagents (entries 1-4) are surprising, and are not reflected in the aldol reaction results.



21 **22** **23**

Scheme 3: Enantioselectivity of the aza-aldol reaction

Table 3: Experimental results for the aza-aldol reactions of 21 (see Scheme 3).[a]

entry	R	Reagent	Major Product[b]	ee[c]	yield
1	H_2C=(Me)C-	(-)-Ipc_2BCl	**22**	38%	22%
2	H_2C=(Me)C-	(-)-Ipc_2BOTf	**22**	46%	16%
3	H_2C=(Me)C-	(+)-Ipc_2BCl	**23**	66%	27%
4	H_2C=(Me)C-	(+)-Ipc_2BOTf	**23**	86%	26%
5	^{n}Pr-	(+)-Ipc_2BOTf	**22**	12%	20%
6	Ph-	(+)-Ipc_2BOTf	**23**	96%	27%
7	Furyl-	(+)-Ipc_2BOTf	**22**	8%	25%

(a) The procedure was similar to that for the boron-mediated aldol reaction.[2d] Details are given in the experimental section. (b) Determined by correlation with literature results.[2d] (c) Measured by Mosher ester analysis.

Table 4: Experimental results for the aldol reactions of acetone[a] (Scheme 3).

entry	R	Reagent	Major Product	ee	yield
1	H_2C=(Me)C-	(-) Ipc_2BCl	**22**	62%	67%
2	H_2C=(Me)C-	(-) Ipc_2BOTf	**22**	68%	61%
3	^{n}Pr-	(-) Ipc_2BOTf	**22**	78%	68%
4	Ph-	(-) Ipc_2BOTf	**22**	57%	78%

(a) reference 18.

In contrast to the aldol reaction, the aza-aldol shows a great variation in selectivity as the aldehyde is varied (entries 4-7, **Table 3**; entries 1-4, **Table 4**). In addition, the aza-aldol gave no detectable product when the imine from diethyl ketone was used as the substrate, again in contrast to the aldol reaction which gives high yields and stereoselectivities with diethyl ketone.

These observations can be rationalised by suggesting that both the aza-aldol and the aldol reaction of methyl ketones go through boat transition states, with a geometry similar to **19** (boat A).[20] This suggestion explains why the sense of asymmetric induction with methyl ketone Ipc-enolborinates is inverted in the aldol reaction with respect to ethyl ketone Ipc-(*Z*)-enolborinates, which are believed to prefer chair transition states (e.g. **18**).[3a] It also explains why the aza-aldol and the aldol reaction of methyl ketones show the same sense of stereoinduction from α-pinene chirality. Finally it suggests a reason for the variation in selectivity with aldehydes which occurs for the aza-aldol and not for the aldol (**Table 3**, entries 4-7; **Table 4**, entries 2-4). In boat A (**19**) there may be an interaction between the aldehyde R residue and the nitrogen substituent in the transition state leading to the minor diastereomer (**Fig. 7**). This structure was obtained by building from the *ab initio* structure using standard bond lengths and angles. The hydrogen of the stereocentre adjacent to nitrogen is oriented towards the centre of the transition structure, the most sterically demanding direction). If the aldehyde is benzaldehyde (**Fig. 7**) or methacrolein, then this steric interaction is present. If the aldehyde is butanal or furfural, such nonbonded interaction should not occur because these aldehydes are less sterically

demanding in the region of the carbonyl. Thus the stereoselectivity is reinforced for aldehydes of a suitable shape, such as benzaldehyde and methacrolein, in a direction which is in accord with experiment. This effect is not available for the aldol reaction, so the aldehyde effect is barely present.

Figure 7 is an attempt to illustrate this three-dimensional concept. A clearer representation is available *via* the World-Wide-Web,[21] on URL: `http://www.ch.cam.ac.uk/MMRG/azaaldol.html`

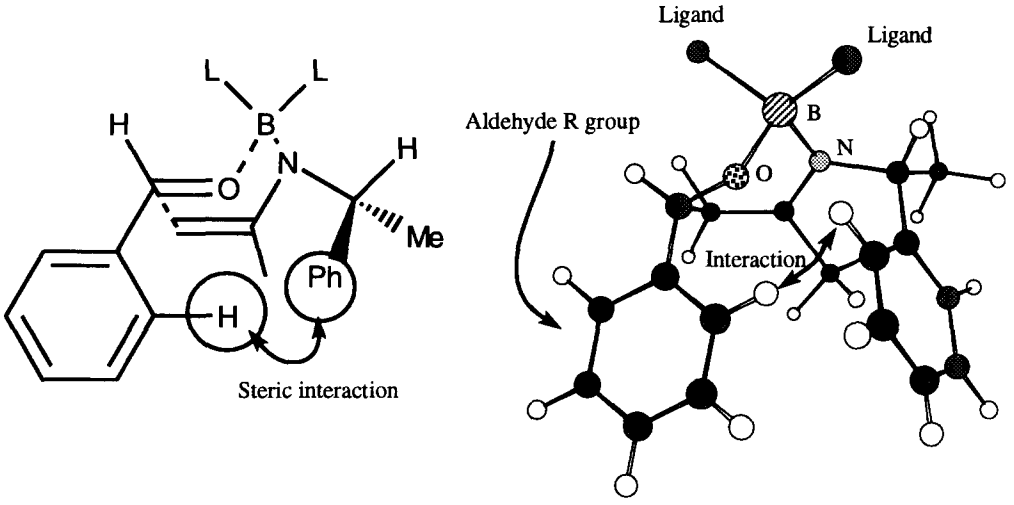


Figure 7: Transition state (boat A, **19**) for enaminyl borinate reaction with benzaldehyde leading to minor enantiomer **22**

Why does the aza-aldol reaction of enaminyl borinates derived from ethyl ketones give no product? We have shown that the aldol reaction of enolborinates derived from ethyl ketones probably goes through a chair transition state,[3] which is of an accessible energy. The nitrogen analogue has a chair transition state available, but it is of a very high energy (**Table 2**). The observation lends further support to the suggestion that the aza-aldol and the aldol reactions of methyl ketones go through boat transition states (boat A, **19**).

IMPLICATIONS FOR THE EXPERIMENTAL PROCEDURE

The large energy barrier for passing even the lowest energy transition state and the small barrier for breaking the ate complex have implications for the preferred experimental procedure. Experience with the aldol reaction[2d] has shown the importance of adding the aldehyde after formation of the enol borinate, because free Lewis acid will cause the aldehyde to undergo undesirable side reactions. In the aldol case, the ate complex rearranges quickly to form the new carbon-carbon bond, and so the aldehyde does not have time to undergo side reactions after activation by the enol borinate. In the nitrogen analogue, the enaminyl borinate and the ate complex are likely to be much longer lived species, because of the higher barrier for the formation of a new carbon-carbon bond. The ate complex will have time to behave as an aldehyde activated by a Lewis acid, and undergo the side reactions that could be avoided in the aldol case.

By analogy with the CBS reducing agent,[13] the reaction might work better if the nitrogen lone pair could be prevented from deactivating the boron. One way to do this might be to convert the nitrogen into a sulphonamide group. If a sulphoxide could be used for the same purpose, then a new stereocentre could be introduced next to the nitrogen and close to the transition state.

CONCLUSIONS

Ab initio calculations have been performed on the nitrogen analogue of the aldol reaction. The calculations suggest that the aza-aldol will follow a similar course to the aldol and to allylboration. However, the benefit of forming an ate complex is decreased and the barrier to carbon-carbon bond formation is increased, so aza-aldol behaviour cannot be explained by interpolation between the oxygen and the carbon analogues.

The calculations suggest that a transition state model for the carbon-carbon bond formation is more likely to be applicable to the aza-aldol than to the allylboration reaction, and the aldol will be intermediate in its behaviour. Experimental results for the nitrogen analogue of the boron-aldol reaction can be rationalised by a boat transition state. The poor reactivity of the enaminyl borinates is because the nitrogen lone pair reduces the Lewis acidity of the boron, and improvements for the reaction could be based on this conclusion.

EXPERIMENTAL DETAILS

All solvents used in the reactions were dried (THF: Na/benzophenone; DCM: CaH_2; Et_2O, hexane: Na-wire; all amines: CaH_2). Ketones were distilled from magnesium sulfate; aldehydes were freshly distilled from $CaCl_2$. Flash column chromatography was carried out using Merck kieselgel 60 (230-400 mesh) silica. All aldol reactions were carried out under argon. Enantiomeric excess of the aldol products was determined by ^{19}F- or ^{1}H-NMR of the corresponding Mosher ester. Mosher's acid, and (*S*)-(-)-1-phenylethylamine were commercially available and used without further purification. ^{1}H- and ^{19}F-NMR spectra were recorded on a Bruker WH 250 or a WH 400 instrument. Triflates were prepared following the procedure in reference 2d.

*2-propyliden-(S)-1-phenylethylimine (**21**)*

A mixture of one equivalent of (S)-(-)-1-phenylethylamine, 3 equivalents of acetone and a catalytic amount of p-toluenesulfonic acid in 50 ml hexanes was refluxed for two days under argon with 10 g $MgSO_4$. The solvent was evaporated, the mixture filtrated under argon and distilled *in vacuo*. 2.6 g (21 mmol) of product were obtained (55 %). bp 45 °C/0.1 mm; ^{1}H-NMR($CDCl_3$): 7.25 (5H, m) Ph; 4.57 (1H, q, 6.6 Hz) C-H; 2.04 (3H, s) Z-CH_3; 1.85 (3H, s) E-CH_3; 1.46 (3H, d, 6.6 Hz) CH_3

Aza-Aldol reactions

A solution of the boron lewis acid (Ipc_2BCl or Ipc_2BOTf, 1-2 mmol) in 10 ml DCM was prepared at -78 °C. If this solution was yellow, the Hünig base was added dropwise until it became colourless, then a further 1.5 eq of the amine was added. The imine (**21**, 0.8 eq) was added dropwise, the mixture warmed to 0 °C and stirred for 5 hrs. At the end of this time the aldehyde was added (4 eq) and the mixture left overnight at 0 °C. It was then poured into pH 7 buffer and extracted with ether. The ether was evaporated and the product dissolved in 1 ml pH 7 buffer/ 5 ml MeOH. After addition of 3 ml H_2O_2 (30 %) the mixture was

stirred for 2 hrs. Then it was quenched with $NaHCO_3$, extracted with DCM and the organic layer extracted again with brine. The DCM was removed and the product purified by chromatography.

4-hydroxy-5-methyl-5-hexen-2-one (**Table 3,** entries 1-4)
υ_{max}(liquid film) 3350-3500, 1700, 1640 cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 4.99 (2H, m), 4.48 (1H, t, J = 6.0 Hz), 2.65 (2H, d, J = 6.1 Hz), 2.18 (3H, s), 1.72 (3H, s); ^{13}C NMR δ(100 MHz, $CDCl_3$) 209.2, 145.6, 111.1, 71.0, 48.4, 30.8, 16.3; HRMS (CI) M^+ 129.0918, $C_7H_{12}O_2$ requires 129.0915.

(S)-4-hydroxy-2-heptanone (**Table 3**, entry 5).
υ_{max} (liquid film) 3500-3600, 1710 cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 4.02 (1H, m), 2.96 (1H, br s), 2.58 (1H, d, J = 3.2 Hz), 2.54 (1H, d, J = 8.7 Hz), 2.16 (3H, s), 1.23-1.52 (4H, m), 0.91 (3H, t, J = 7.0 Hz); HRMS (EI) M^+ 129.0922, $C_7H_{13}O_2$ requires 129.0915.

(S)-4-hydroxy-4-phenyl-2-butanone (**Table 3**, entry 6).
υ_{max}(liquid film) 3500-3600, 1700 cm^{-1}; ^1H NMR δ(250 MHz, $CDCl_3$) 7.35 (5H, m), 5.16 (1H, dd, J = 3.9, 8.5 Hz), 2.86 (1H, d, J = 8.7 Hz), 2.83 (1H, d, J = 4.2 Hz), 2.18 (3H, s); ^{13}C NMR δ(100 MHz, $CDCl_3$) 209.0, 142.6, 128.5, 127.6, 125.6, 69.8, 52.0, 30.7; HRMS (EI) M^+ 164.0834, $C_{10}H_{12}O_2$ requires 164.0837.

(R)-4-hydroxy-4-furyl-2-butanone (**Table 3**, entry 7).
^1H NMR δ(250 MHz, $CDCl_3$) 7.30 (1H, m), 6.31 (1H, m), 6.24 (1H, d, J = 3.2), 5.13 (1H, dd, j = 3.6, 8.7), 3.44 (1H, br s), 3.04 (1H, dd, J = 8.7, 18), 2.89 (1H, dd, J = 3.6, 18), 2.19 (3H, s).

Mosher ester

A solution of dicyclohexyl carbodiimide (5 eq) and 4-dimethylaminopyridine (catalytic) in 1 ml DCM was added to a solution of the hydroxyketone (5 mg) in 1 ml DCM. Then a solution of Mosher acid (3 eq) in 0.5 ml DCM was added to this mixture. The reaction turned cloudy and was sonicated for one hour at room temperature. After completion of the reaction (TLC) the ester was purified by flash chromatography over a short column. The ratios of diastereoisomers were measured using ^{19}F NMR.

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REFERENCES AND NOTES

1. "Comprehensive Organic Synthesis", ed. Trost, B. M. and Fleming, I., Pergamon Press, Oxford, **1991**, Vol.2 (Heathcock, C.H. editor): (a) Roush, W. R., chapter 1.1, page 1; (b) Heathcock, C. H., chapter 1.5, page 133; chapter 1.6, page 181; (c) Kim, M.; Williams, S. F.; Masamune, S., chapter 1.7, page 239; (d) Paterson, I., chapter 1.9, page 301-319; (e) Martin, S. F., chapter 1.16, page 475; (f) Bergbreiter, D. E.; Momongan, M., chapter 1.17, page 503; (g) Gennari, C., chapter 2.4, page 629; (h) Franklin, A. S.; Paterson, I. *Contemporary Organic Synthesis* **1994**, *1*, 317.

2. (a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77. (c) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (d) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross. R. D. *Tetrahedron* **1990**, *46*, 4663. (e) Gennari, C.; Hewkin, C. T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1992**, *57*, 5173. (f) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233. (g) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (h) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (i) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (j) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483. (k) Kaneko, Y.; Matsuo, T.; Kiyooka, S.-I. *Tetrahedron Lett.* **1994**, *35*, 4107. (l) Bach, T. *Angew Chem., Int. Ed. Engl.* **1994**, *33*, 417. (m) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507. (n) Paterson, I.; Smith, J. D. *Tetrahedron Lett.* **1993**, *34*, 5351.

3. (a) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576. (b) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471. (c) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439. (d) Bernardi, A.; Cassinari, A.; Comotti, A.; Gardner, M.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4183. (e) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685. (f) Bernardi, A.; Comotti, A.; Gennari, C.; Hewkin, C. T.; Goodman, J. M.; Schlapbach, A.; Paterson, I. *Tetrahedron* **1994**, *50*, 1227.

4. For an earlier study of the boron-mediated aza-aldol, see: Sugusawa, T.; Toyada, T. *Tetrahedron Lett.* **1979**, *16*, 1423.

5. (a) Li, Y.; Houk. K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236. (b) Hoffmann, R. W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387. (c) Brinkmann, H.; Hoffmann. R. W. *Chem. Ber.* **1990**, *123*, 2395. (d) Vulpetti, A.; Gardner, M.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1993**, *58*, 1711.

6. Li, Y.; Paddon-Row, M. N.; Houk. K. N. *J. Org. Chem.* **1990**, *55*, 481.

7. Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

8. Cambridge Analytical Derivatives Package, issue 5.0. Handy, N. C.; Amos, R. D. Department of Chemistry, Cambridge Univesity, U.K.

9. Binkley, J. S. ; Frisch, M. J. ; DeFrees, D. J. ; Raghavachari, K. ; Whiteside, R. A. ; Schlegel, R. A. ; Fluder, E. M. ; Pople, J. A. Carnegie-Mellon University, PA 15213 U.S.A.

10. Baker, J. *J. Comp. Chem.* **1986**, *7*, 385.

11. (a) Goodman, J. M.; Paterson, I.; Kahn, S. D. *Tetrahedron Lett.* **1987**, *28*, 5209-5212. (b) Goodman, J. M.; Kahn, S. D.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3295.

12. Goodman, J. M. *Tetrahedron Lett.* **1992**, *33*, 7219.

13. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

14. (a) Nevalainen, V. *Tetrahedron Asymmetry* **1992**, *3*, 921-932. (b) Nevalainen, V. *Tetrahedron Asymmetry* **1992**, *3*, 1441. (c) Nevalainen, V. *Tetrahedron Asymmetry* **1992**, *3*, 1563.

15. For piperidine, axial and equatorial conformers have similar energies, but the equatorial is preferred. See, for example, Brouwer, A. M.; Krijnen, B. *J. Org. Chem.* **1995**, *60*, 32.
16. Cramer, C. J. *J. Org. Chem.* **1992**, *57*, 7034.
17. (a) McCarrick, M. A.; Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1499. (b) Thomas, B. E.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 790.
18. (a) Sherrod, M. J.; Menger, F. M. *J. Am. Chem. Soc.* **1989**, *111*, 2611. (b) Sherrod, M. J. *Tetrahedron Lett.* **1990**, *31*, 5085. (c) Menger, F. M.; Sherrod, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8071; (d) Eurenius, K. P.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 9943.
19. Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997.
20. This has recently been suggested for a related lithium mediated aldol reaction: (a) Lagu, B. R.; Crane, H. M.; Liotta, D. C. *J. Org. Chem.* **1993**, *58*, 4191. (b) Lagu, B. R.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 4485.
21. Rzepa, H. S.; Whitaker, B. J.; Winter, M. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1907

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