Pergamon

Tetrahedron Vol. 50, No. 4, pp. 1227-1242, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0072-N

Computer-Assisted Design of Chiral Boron Enolates: The Role of Ate Complexes in Determining Aldol Stereoselectivity.

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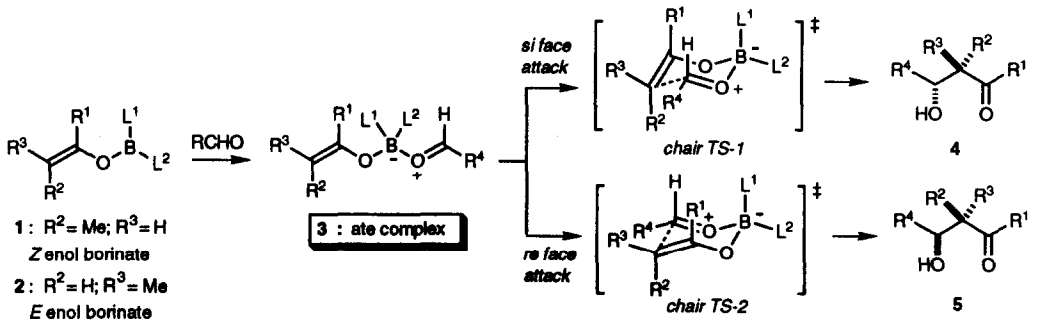
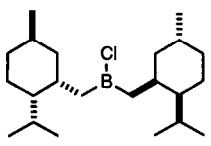
Abstract: Transition-state modelling for the aldol reaction of chiral *Z* and *E* enol borinates (**1** and **2**, **Scheme 1**) bearing mixed ligands (L^1 = Ipc, L^2 = **9**) predicted higher enantioselectivities than those calculated and experimentally tested with C_2 symmetric systems ($L^1 = L^2$ = Ipc, $L^1 = L^2$ = **9**). Reagent **8** was prepared and used to generate *E* enol borinates **24**, which reacted with aldehydes to give the anti aldol products **25–28** with substantially lower enantiomeric excesses than predicted. This unexpected result suggested that ate complex formation may be an important factor in controlling the selectivity of the boron-mediated aldol reaction. In particular, the presence of two different ligands on boron makes it a prostereogenic centre, and two diastereomeric ate complexes (**29** and **30**) can be formed on aldehyde complexation. These ate complexes are calculated to display different *re* : *si* face selectivities. The experimental results are similar to the ones predicted if the aldol reaction proceeds *via* the less selective ate complex **29**.

Tremendous advances have been made in recent years in the development of new methodology for asymmetric synthesis. At present, new enantioselective reactions are largely developed from empirical findings combined with intuition and trial-and-error processes. A valuable adjunct to such efforts would be to use computer modelling to analyse the mechanistic details and stereochemical preferences for individual reaction classes.[1] These quantitative models would aid the design of new chiral reagents, which might then have general utility in asymmetric synthesis. We have adopted such a rational approach for the investigation of asymmetric aldol reactions[2] of chiral boron enolates with aldehydes (**Scheme 1**), which lead to the stereodefined formation of a new carbon-carbon bond through a highly ordered cyclic transition state.



Scheme 1

In the initial phase of this programme, an MM2 force field model was developed for the aldol reactions of ketone derived enol borinates with aldehydes, which was parameterised from *ab initio* calculations on the chair and boat cyclic transition structures.[3a-c] This model reproduces the aldehyde *si* : *re* selectivity for the syn aldol reactions of chiral *Z* enol borinates **1**,[3a,d,e] as well as for the anti aldol reactions of *E* enol borinates **2**.[3f-h] There was excellent agreement between the experimental and calculated ratios of **4** *vs* **5** over a wide range of substituents, R^1–R^4, and ligands on boron, L^1 and L^2. More recently, we have used transition-state modelling to design new chiral boron reagents for asymmetric aldol reactions. Using this rational approach, a novel chiral boron reagent was developed for achieving enantioselective anti aldol reactions of ketones with aldehydes.[3g] This new reagent **6**, which is derived from (-)-menthone, compliments diisopinocampheylboron triflate (**7**, Ipc_2BOTf) which was already used for enantioselective syn aldol reactions.[4] Both these cases make use of C_2-symmetric dialkyl boron reagents, *i.e.* where $L^1 = L^2$ in **Scheme 1**.



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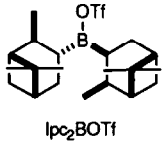

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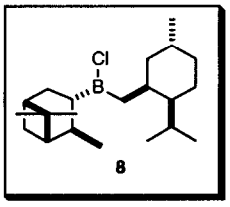

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In this paper, we now consider the use of "mixed ligand" chiral boron reagents, *i.e.* where $L^1 \neq L^2$ in **Scheme 1**. Here computer modelling of the aldol transition state is used to design appropriate matched ligands, which are predicted to infer a high level of stereocontrol. However, the observed selectivities for *anti* aldol reactions mediated by the corresponding reagent **8** are found to be much lower than predicted. This suggests that the ate complex **3**, formed between the electron-deficient boron atom in the enol borinate and the aldehyde lone-pair, may actually play an important role in determining stereoselectivity. Notably, these observations suggest the need to consider the entire reaction coordinate, not just the carbon-carbon bond forming step, in rationalising the origins of stereocontrol in certain boron aldol reactions.

Results and Discussion

Reagent Design

In our previous work,[3d] dealing with the asymmetric syn aldol reactions of *Z* enol diisopinocampheyl borinates (**1**, $L^1 = L^2$ = Ipc, in **Scheme 1**) with aldehydes, the force field model[3a] suggested that the following factors were important in determining the relative contributions of the diastereomeric chair transition structures (***TS-1*** *vs* ***TS-2***) to the stereoselectivity: (*i*) the conformational rigidity of the boron ligand; (*ii*) the relative orientation of the ligands with respect to the chair transition structure core; (*iii*) the relative orientation and restrained rotation around the B–C bonds of one ligand relative to the other.

These observations prompted us to consider as ligand candidates, structures known tc possess a limited conformational freedom. Ligand **9** (**Figure 1**) was designed[3g] from the known[5] conformational preferences of the parent hydrocarbon, which are based on avoidance of (+/-)-double gauche pentane interactions.[6] This particular ligand is prepared from (-)-menthone. For the corresponding *Z* enol borinates (**1**, $L^1 = L^2 = 9$, in **Scheme 1**), the *si* : *re* selectivity was predicted to be equal to or slightly lower than that for the Ipc ligand.[3g] Hence, the new ligand **9** would not be expected to offer any improvement over the *syn* aldol reactions of Z enol

diisopinocampheyl borinates (**1** for $L^1 = L^2$ = Ipc; 66-93% ee).[4] The calculations for the corresponding *E* enol borinates **2**, which give rise to ketone derived anti aldol adducts,[4c] proved to be synthetically more interesting. Ligand **9** was now predicted to be much more selective (66-96% ee) than Ipc. These predictions were substantiated by experiment: *E* enol borinates (**2** for $L^1 = L^2 = \mathbf{9}$), derived from chloroborane **6**, underwent anti aldol reactions with good enantiomeric excess (56-88% ee).[3g]

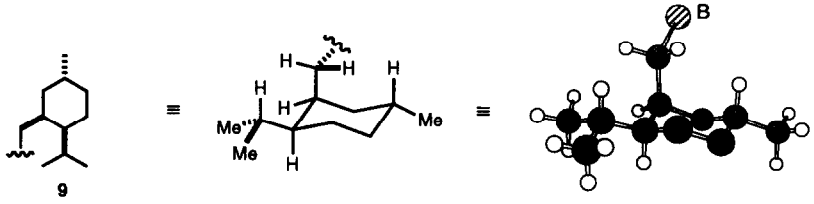
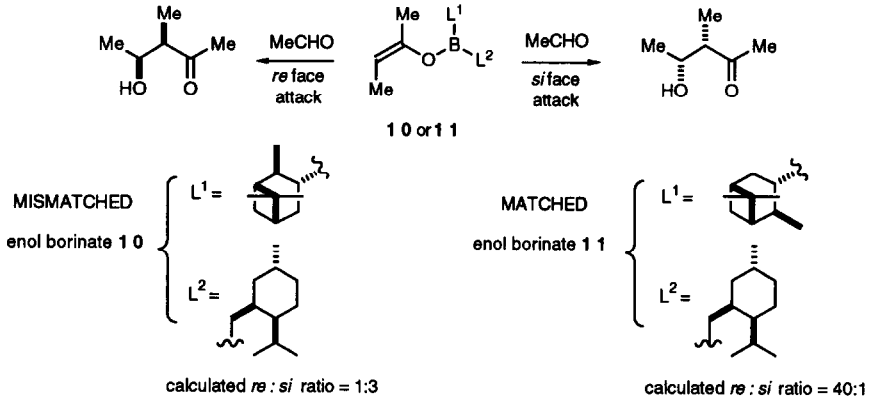


Figure 1: Lowest energy conformation of (-)-menthone-derived ligand **9**.

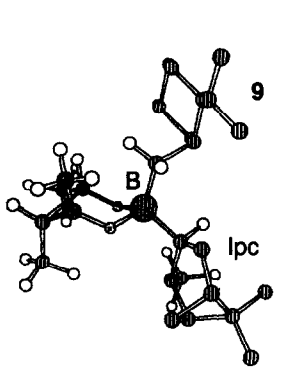
Previous investigations of aldol reactions using "mixed ligand" boron reagents[4a,c] have proved to be less successful than C_2-symmetric reagents, perhaps due to a mismatch in the ligand chirality. Using our aldol force field, we now have the opportunity to investigate both matched and mismatched cases. The C_2-symmetric reagent **7**, derived from (+)-α-pinene, is known to be *si*-selective for *Z* enol borinates.[4a,c] Whereas reagent **6**, derived from (-)-menthone (incorporating ligand **9**), is *re*-face selective.[3g] Therefore, the optimum case should be a reagent derived from (-)-α-pinene and (-)-menthone. As shown in **Scheme 2**, calculations on the *Z* enol borinates **10** and **11** indicated a mismatched and a matched pair of ligands, respectively. In enolate **10**, the presence of a *si*-face selective ligand (L^1 = Ipc, derived from (+)-α-pinene) and a *re*-face selective one ($L^2 = \mathbf{9}$, derived from (-)-menthone) was calculated to give rise to a modest *si* : *re* ratio of 3 : 1 for aldol addition to acetaldehyde. The use of the matched pair in **11**, however, resulted in a calculated *re* : *si* selectivity of 40 : 1.



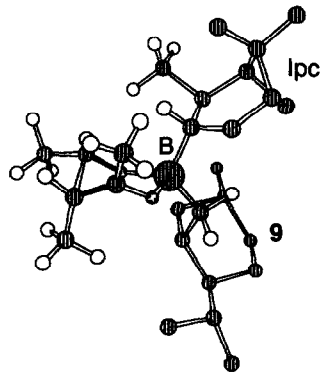
Scheme 2: Calculated *re* : *si* selectivities for the aldol addition of "mixed ligand" *Z* enol borinates **10** and **11** to acetaldehyde.

Note that the calculations are less straightforward than for C_2-symmetric reagents, since the boron atom is now a stereogenic centre in the diastereomeric transition structures, ***TS-1*** and ***TS-2*** in **Scheme 1**. Therefore, twice as many transition structures must be considered, corresponding to attack on each enantioface of the aldehyde for each epimer at boron. Four different modes of attack are possible for *Z* enol borinates leading to syn

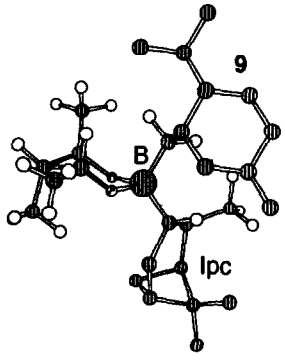
aldols: *ax-re* (aldehyde *re*-face attack, where ligand **9** takes up the *axial* position), and correspondingly *eq-re*, *ax-si*, and *eq-si*.



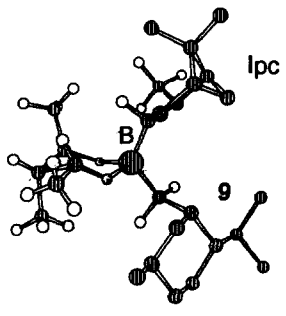
12 *(ax-re, 0.0 kcal mol^{-1})*



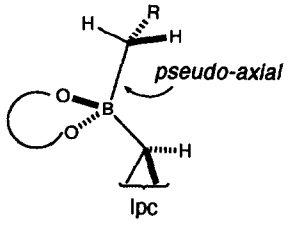
13 *(eq-re, +1.17 kcal mol^{-1})*



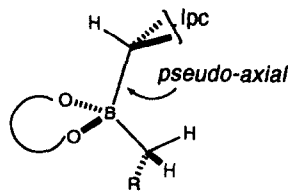
14 *(ax-si, +1.91 kcal mol^{-1})*



15 *(eq-si, +1.91 kcal mol^{-1})*



conformation A

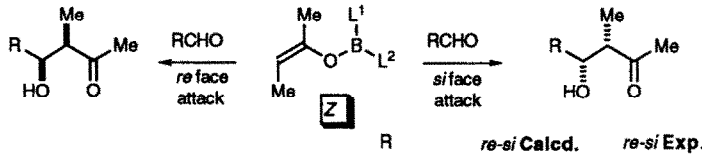


conformation B

Figure 2: Lowest energy transition structures for the four diastereomeric modes of addition of *Z* enol borinate **11** to acetaldehyde.

The lowest energy transition structures **12–15** (only relevant hydrogens are shown) for each of these modes of attack of *Z* enol borinate **11** on acetaldehyde are depicted in **Figure 2**, together with their calculated relative energies. In all cases, the conformation adopted by ligand **9** is the one expected on the basis of the *cis*-1-ethyl-2-isopropylcyclohexane model[3g,5] (cf. **Figure 1**). The rotational freedom around the B–C bonds is severely restricted, such that in the chair transition structures **12–15** there are only two relative orientations of the ligands. Conformation A shows the relative orientation of the ligands in the transition structures **12** and **14**, while conformation B illustrates that present in **13** and **15**. Conformation A is more stable than B having fewer adverse non-bonded interactions between the ligands. **Table 1** summarises the calculated results for *Z* enol borinates with various chiral ligands attached to boron: $L^1 = L^2$ = Ipc; $L^1 = L^2$ = **9**; L^1 = Ipc, L^2 = **9**. The overall *re* : *si* selectivity was derived from a Boltzmann distribution of all the accessible transition structures. Where available, the experimental results are also indicated. Note that the mixed ligand situation is predicted to confer higher levels of *re* : *si* selectivity over a range of aldehydes compared to the symmetrical case when $L^1 = L^2$ = Ipc or ligand **9**.

Table 1: Comparison between predicted *re* : *si* ratios for *Z* enol borinates with various chiral ligands attached to boron.



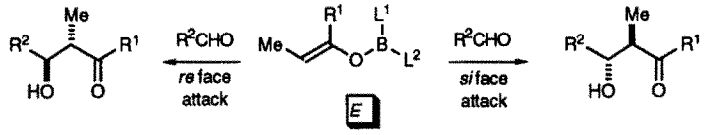
	R	*re-si* Calcd.	*re-si* Exp.[a]
$L^1 = L^2$ = (Ipc from (-)-α-pinene)	Me	19:1	10:1
	C(Me)=CH$_2$	24:1	27:1
	^{i}Pr	5:1	5:1
$L^1 = L^2$ = (**9**)	Me	15:1	?
	C(Me)=CH$_2$	21:1	
	^{i}Pr	3:1	
L^1 = , L^2 =	Me	40:1	?
	C(Me)=CH$_2$	112:1	
	^{i}Pr	17:1	

[a] See ref. 4a,c.

We then repeated these calculations for the corresponding *E* enol borinates with these same chiral ligands attached to boron: $L^1 = L^2$ = Ipc; $L^1 = L^2$ = **9**; L^1 = Ipc, L^2 = **9**. **Table 2** summarises the results, where the overall *re* : *si* selectivity was derived from a Boltzmann distribution of all the accessible transition structures. Where available, the experimental results are also indicated. Note that the mixed ligand situation is again predicted to confer higher levels of *re* : *si* selectivity over a range of aldehydes compared to the symmetrical case when $L^1 = L^2$ = Ipc or ligand **9**. Hence, this new ligand arrangement (L^1 = Ipc, L^2 = **9**) might offer significant improvements in enantioselectivity relative to that already found for *E* enol borinates based only on ligand **9**. As

described in the following section, we set out to prepare the appropriate dialkylchloroborane reagent **8** to experimentally test this prediction.

Table 2: Comparison between predicted *re* : *si* ratios for *E* enol borinates with various chiral ligands attached to boron.

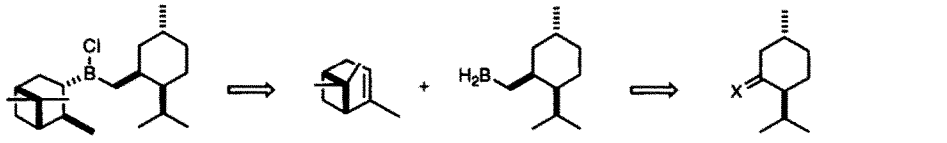


		R^1	R^2	*re-si* Calcd.	*re-si* Exp.[a]
$L^1=L^2=$	(Ipc from (-)-α-pinene)	Me	Me	4.9:1[a]	
		Me	$C(Me)=CH_2$	2.8:1[a]	1.0-1.5:1[a,b]
$L^1=L^2=$	(9)	Me	Me	24:1[a]	9.2:1[a,c]
		Me	$C(Me)=CH_2$	22:1[a]	7.0:1[a,c]
$L^1=$	$L^2=$	Me	Me	33:1[d]	
		Me	$C(Me)=CH_2$	29:1[d]	?
		Et	$C(Me)=CH_2$	40:1[d]	
		^iPr	$C(Me)=CH_2$	58:1[d]	

[a]Boltzmann distribution and experiment at 195 K. [b]See ref. 4c. [c]See ref. 3g.
[d]Boltzmann distribution at 273 K.

Synthesis of Reagent 8

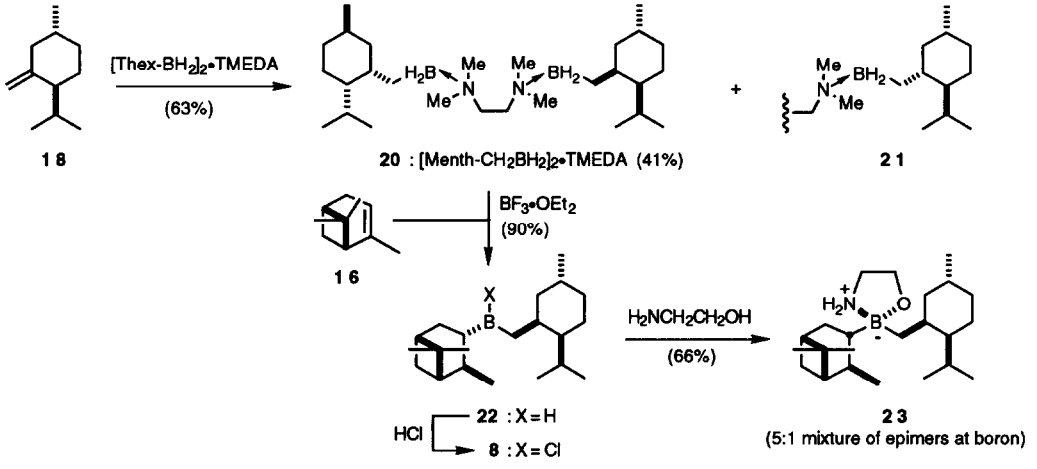
As outlined in **Scheme 3**, the chloroborane reagent **8** should be available by hydroborating (-)-α-pinene (**16**) with the monoalkylborane **17**. We have previously examined the hydroboration of alkene **18**, readily available[3g] by Wittig methylenation of (-)-menthone (**19**), for the synthesis of the C_2-symmetric reagent **6**. However, selective access to stereochemically pure borane **17** cannot be achieved by simple hydroboration of **18** with various boranes, since attack occurs on both faces of the alkene.



Scheme 3: Starting materials for the preparation of "mixed ligand" reagent **8**.

This problem was solved, as shown in **Scheme 4**, by first preparing the N,N,N',N'-tetramethylethylenediamine (TMEDA) complex of **17** and recrystallising to stereochemical homogeneity. [Menth-CH_2BH_2]$_2$•TMEDA complex (**20**) was synthesised by ligand exchange on boron *via* the reaction of alkene **18**

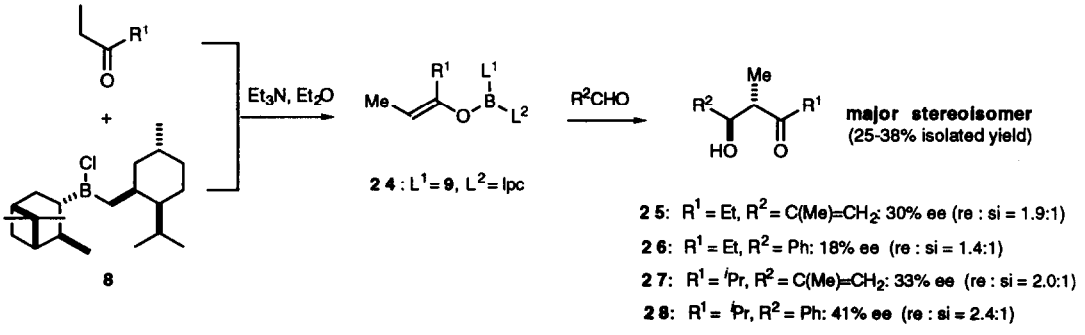
with the reagent [Thex-BH_2]$_2$•TMEDA, prepared by the method of Brown *et al.*[7] The axial borane complex **20** was obtained in 41% yield after separation from the unwanted equatorial isomer **21** by crystallization from hexane-dichloromethane. The free Menth-CH_2BH_2 (**17**) was then liberated from its TMEDA complex **20** using BF_3•OEt_2.[7] Addition of (-)-α-pinene (98% ee) in THF then led to controlled hydroboration to generate the required secondary borane **22**. This was characterised as its ethanolamine complex **23**, which was isolated in 66% yield as a 5 : 1 mixture of diastereomers by ^{13}C NMR due to the presence of the new stereogenic centre at boron. Finally, treatment of borane **22** with HCl in dry ether gave the desired chloroborane **8**, which was used for aldol reactions without further purification.



Scheme 4: Synthesis of "mixed ligand" reagent **8**.

Anti Aldol Reactions of Ethyl Ketones Promoted by Reagent 8

We adapted the conditions previously used for the anti aldol reactions of ethyl ketones with dicyclohexylchloroborane[8] and the menthene-derived C_2 reagent **6**[3g] to the new mixed ligand chloroborane **8**. The results are shown in **Scheme 5**.

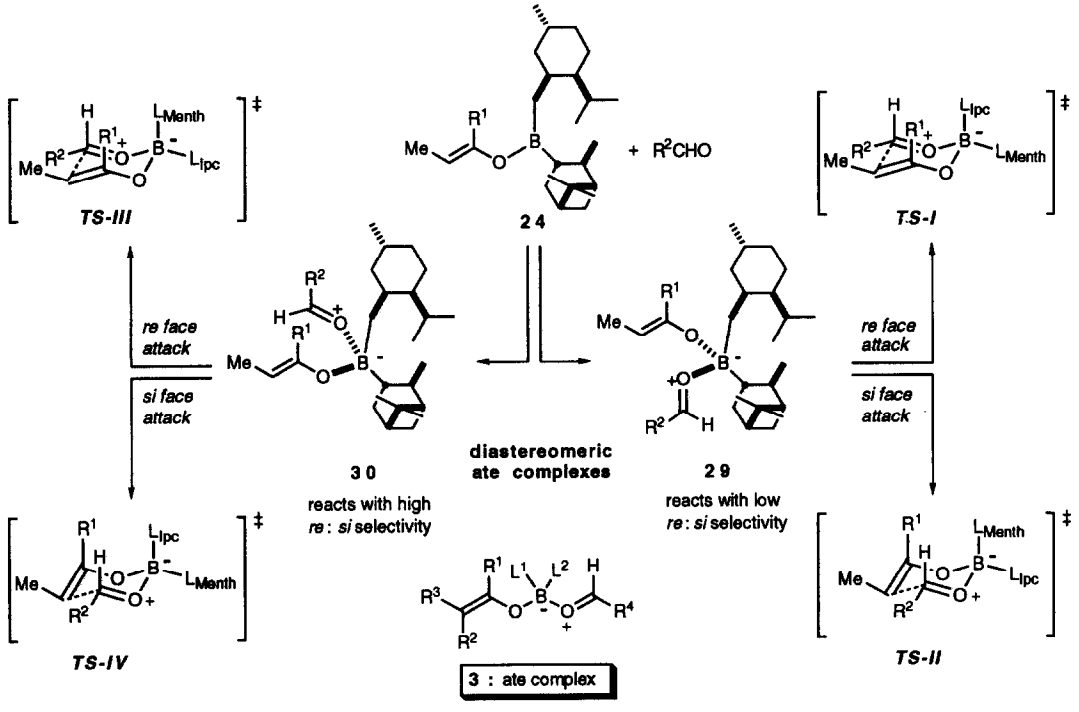


Scheme 5: Asymmetric anti aldol reactions of ethyl ketones using reagent **8**.

Enolisation of ethyl ketones with reagent **8** and triethylamine in ether gave the corresponding *E* enol borinate **24** selectively (together with varying amounts of the *Z* isomer), which was reacted with methacrolein or benzaldehyde. The resulting aldol products were analysed by ^{1}H NMR and GC to determine the anti : syn ratios in each case (70 : 30 for diethylketone; >98 : 2 for 2-methylpentan-3-one). The major anti isomers **25–28** were isolated by chromatography and their enantiomeric excesses were determined by either ^{1}H NMR analysis of the derived MPTA esters or by chiral GC. In all four cases examined, the anti aldol adduct was obtained in low enantiomeric enrichment (18-41% ee) with only a small bias towards the isomer corresponding to *re*-face attack on the aldehyde. These results were particularly disappointing as the modelling studies had predicted a pronounced preference by the *E* enol borinates **24** for *re*-face attack on aldehydes (cf. **Table 2**). In view of the significant quantitative discrepancy between theory and experiment, we sought a rationalisation for these results.

The Role of Ate Complexes in Aldol Stereoselection

Why are the experimental results for the mixed ligand *E* enol borinates **24** so inconsistent with the computational predictions? This may be due to a stereochemical feature not present in any of our earlier transition state modelling work – *the boron atom of the enol borinate is now a prostereogenic centre.* Thus, the role of the ate complexes **3** in determining the aldol stereoselectivity now needs to be assessed.



Scheme 6

As shown in **Scheme 6**, the two faces of the sp^2 hybridized boron in the enol borinate **24** are non-equivalent. The initial attack of the aldehyde can occur in two different ways to form the diastereomeric tetrahedral ate complexes **29** and **30**, where the boron is attached to the more accessible aldehyde lone pair. A further mode

of attack, where the Lewis acidic boron complexes the other aldehyde lone pair, *i.e. cis* to the R group, is presumably strongly disfavoured due to steric interactions. Note that initial formation of the ate complex serves to activate the aldehyde carbonyl carbon to nucleophilic attack by withdrawing electron density and, simultaneously, promoting the enolate nucleophilicity. The ate complex can then undergo intramolecular carbon-carbon bond formation through a cyclic transition state or dissociate back to the enol borinate and aldehyde. Each of the two ate complexes can access two different chair transition structures, *i.e.* there are four in all: ***TS-I*** – ***TS-IV***. These diastereomeric transition structures are shown for **29** (***TS-I vs TS-II***) and **30** (***TS-III vs TS-IV***).

The use of transition state modelling to predict kinetic selectivity assumes that any intermediates on the reaction coordinate preceding the transition state of interest are equilibrating more rapidly than they are reacting, and so their relative concentrations have no effect on the overall selectivity of the reaction (Curtin-Hammett principle). This assumption is not necessarily true for the boron-mediated aldol reaction. The energy required to break up the ate complex into the enol borinate and aldehyde is calculated to be similar to the energy barrier for the C–C bond forming process.[3c,9a] This is unimportant in cases for which the boron atom of the ate complex **3** is non-stereogenic (*i.e.* $L^1 = L^2$), because all the possible conformations can interconvert by low energy rotational processes. However, if the boron atom is stereogenic (*i.e.* **3** for $L^1 \neq L^2$), interconversion of the ate complexes can only occur by epimerising at boron, *i.e.* by breaking and reforming the ate complex. This process may have a higher activation energy than the C–C bond forming step, and so the relative energies of the diastereomeric cyclic aldol transition structures no longer control the selectivity of the reaction. If the ate complexes rearrange to form the aldol products more quickly than the boron stereogenic centre can epimerise by dissociation and reassociation, then the rate of formation of the diastereomeric ate complexes will now directly affect the stereochemical outcome of the aldol reaction.

Table 3: Calculated *re* : *si* ratios for ate complexes **29** and **30**.

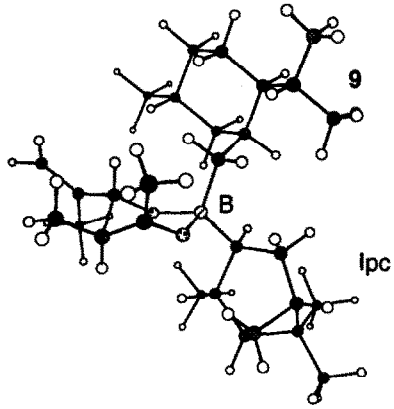
entry	**24** : R^2	R^1	combined[a]	*via* **30** only[a]	*via* **29** only[a]	experimental[b]
1	C(Me)=CH_2	Me	29 : 1	99 : 1	1.6 : 1	—
2	C(Me)=CH_2	Et	40 : 1	360 : 1	1.3 : 1	1.9 : 1
3	C(Me)=CH_2	^{i}Pr	58 : 1	166 : 1	4.0 : 1	2.0 : 1
4	Ph	Et	45 : 1	106 : 1	1.9 : 1	1.4 : 1
5	Ph	^{i}Pr	73 : 1	126 : 1	7.6 : 1	2.4 : 1

(a) Ratio of enantiomeric *anti* products, calculated from Boltzmann factors at 273 K; (b) Experiment performed at 273 K.

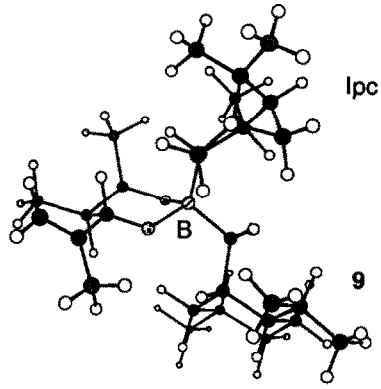
This last hypothesis was tested by assuming that each diastereomeric ate complex, **29** and **30**, separately undergoes aldol C–C bond formation. The individual *re* : *si* selectivities calculated for the two ate complexes can now be compared with the combined values obtained previously (cf. **Table 2**) using a Boltzmann distribution of *all* the accessible transition structures. As can be seen from **Table 3**, it is clear that ate complex **30** is predicted to undergo aldol bond formation with substantially higher selectivity than that for **29**. Furthermore, the less selective route *via* the latter ate complex **29** reproduces the experimental result reasonably well. The four lowest energy aldol transition structures (**31**–**34**) calculated for the addition of *E* enol borinate **24** (R^1 = Me) to methacrolein are illustrated in **Figure 3**, together with their calculated relative energies. Thus, the ate complex **30** in **Scheme 6** is predicted to react through the chair transition structures **31** and **32** with high *re* : *si* selectivity, while the diastereomeric ate complex **29** reacts through transition structures **33** and **34** with low *re* :

si selectivity. Hence, the low *re* : *si* selectivity observed experimentally suggests that the aldol reaction is proceeding through ate complex **29** and, unfortunately, not through **30**.

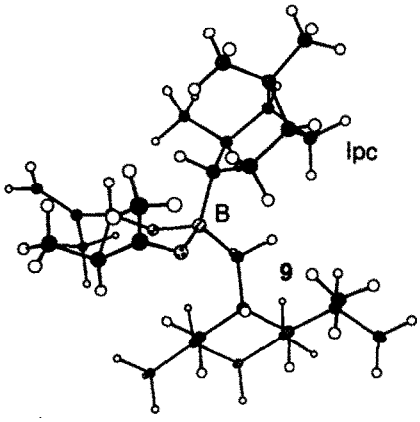
The foregoing analysis suggests either that both diastereomeric ate complexes are formed and **29** is much more reactive than **30**, or ate complex **29** is formed exclusively for kinetic reasons. Distinguishing between these possibilities would require models for the formation and for the reactivity of the ate complexes which are not available at present. Molecular orbital calculations[3b,9a] do not detect an energy barrier for the formation of the ate complex from an enol borinate and an aldehyde. This suggests that the barrier is small, and so the transition state for this reaction is expected to be similar to the starting enol borinate. A force field is available for enol borinates,[9b] and this could be used to gain an idea of the preferred face of attack. However, further work is required to quantify the contribution of ate complex formation to aldol stereoselection.



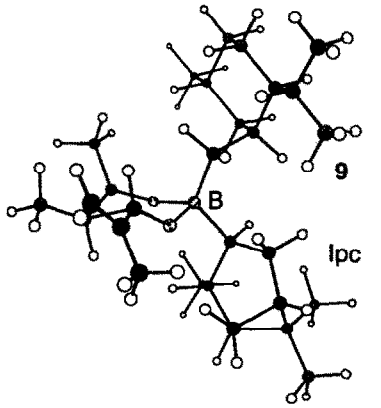
31 *(re-face attack, 0.0 kcal mol^{-1})*
from ate complex **30** ≡ ***TS-III***



32 *(si-face attack, +2.56 kcal mol^{-1})*
from ate complex **30** ≡ ***TS-IV***



33 *(re-face attack, +1.72 kcal mol^{-1})*
from ate complex **29** ≡ ***TS-I***



34 *(si-face attack, +1.98 kcal mol^{-1})*
from ate complex **29** ≡ ***TS-II***

Figure 3: Lowest energy transition structures for the four diastereomeric modes of addition of *E* enol borinate **24** (R^1 = Me) to methacrolein.

Conclusions

Modelling the transition structures for the aldol reaction of *Z* and *E* enol borinates (**1** and **2, Scheme 1**) bearing two different boron ligands (L^1 = **9**, L^2 = Ipc) predicted stereoselectivities which are higher than those calculated and experimentally tested with $L^1 = L^2$ = Ipc and $L^1 = L^2$ = **9**. The mixed-ligand reagent **8** (L^1L^2BCl for L^1 = **9**, L^2 = Ipc), which was predicted to give optimum asymmetric induction, was synthesised from (-)-menthone and (-)-α-pinene. However, the derived *E* enol borinates **24** reacted with aldehydes to give anti aldol products with much lower enantiomeric excesses than predicted. This discrepancy between theory and experiment prompted a consideration of the role of the ate complex in determining the stereoselectivity of the aldol reaction. In particular, the presence of two different ligands on boron makes it a prosterogenic centre in the enol borinate, and two diastereomeric ate complexes can be formed. These ate complexes, **29** and **30**, are calculated to display substantially different stereoselectivities. The experimental results are similar to those predicted for reaction *via* the less selective ate complex **29**. Hence, the utility of a transition state model of the carbon-carbon bond forming step in the boron mediated aldol reaction appears to be limited to those cases where the boron reagent is C_2 symmetric (*i.e.* $L^1 = L^2$). The future development of quantitative models for mixed ligand reactions (*i.e.* $L^1 \neq L^2$) will require consideration of the whole reaction coordinate.

Computational Section

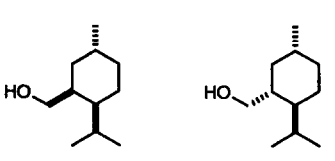
MacroModel 3.5[10] was used to generate all accessible transition structures for the boron enolate aldol reactions of interest. This version of MacroModel includes the parameters developed in our earlier work.[3] The conformational space was searched with the Still-Chang-Guida usage-directed torsional Monte Carlo search[11] as implemented in the BATCHMIN program.[12] Eight different Monte Carlo runs were necessary to fully establish the product distribution of *E* and *Z* enol borinates when two different ligands were used. For both diastereomeric ate complexes, the relative energies had to be evaluated for: (*i*) *si*-face attack, *anti* relative stereochemistry, (*ii*) *re*-face attack, *anti* relative stereochemistry, (*iii*) *si*-face attack, *syn* relative stereochemistry, and (*iv*) *re*-face attack, *syn* relative stereochemistry. In most cases, this full search was done to confirm that *Z* enol borinates were *syn* selective and *E* enol borinates were *anti* selective. Sometimes only four runs (*si* face attack vs. *re* face attack for both diastereomeric ate complexes) were carried out because the relationship, Z → *syn* and *E* → *anti*, was assumed to hold. Torsional constraints were applied to preserve the enolate geometry and prevent *Z/E* mixing. A chirality check was used for all stereocentres, and was also applied to the carbonyl carbon and the enolate 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[13] with a 30° or 60° resolution for each dihedral angle was also used. The results were comparable with those obtained using Monte Carlo and showed that our conformational analysis was not dependent on the search method used.[14]

The diastereomeric ratios (*anti* vs. *syn* and *re* vs. *si*) were calculated by a Boltzmann distribution at 195 K or 273 K of the various conformers within 2.5 kcal mol^{-1} from the global minimum. The force field calculations predicted essentially complete *syn* selectivity for *Z* enol borinates and complete *anti* selectivity for *E* enol borinates.

Experimental Section

Preparation of (-)-18 from (-)-menthone. To a suspension of methyltriphenylphosphonium bromide (30.1 g, 84.3 mmol) in dry THF (270 ml) at 0 °C under an atmosphere of argon, n-Butyl lithium (52.67 ml, 84.3 mmol; 1.6 M solution in hexanes) was added dropwise. The resulting yellow mixture was warmed to room temperature and stirred for 1 h, then (-)-menthone (10 g, 64.8 mmol; 95% pure) was added dropwise. The reaction mixture was maintained for 2 h at 65 °C followed by 16 h at room temperature. Ether (600 ml), ammonium chloride (45 ml; saturated aqueous solution) and water (45 ml) were added and the organic layer was separated. The aqueous phase was extracted with pentane (3 x 100 ml), the organic layers were combined, dried (Na_2SO_4) and evaporated *in vacuo*. Pentane (100 ml) was added to the resulting residue and the solid triphenylphosphine oxide was filtered off under vacuum and carefully washed with more pentane (250 ml). The filtrate was concentrated to give a yellow oil which was chromatographed using pentane as the eluant. The product (-)-**18** was obtained as a colourless oil (8.6 g, 87%) in the first fractions, detectable by GC. It had spectroscopic data in agreement with that reported in the literature.[15]

Preparation of [Menth-CH_2BH_2]$_2$•TMEDA (20). To borane-dimethylsulphide complex (6.0 ml, 60.0 mmol; 10 M), under an atmosphere of argon at 0 °C, was added 2,3-dimethyl-2-butene (10.7 ml, 90.0 mmol) dropwise with stirring. The reaction mixture was warmed to room temperature for 105 min then dry N,N,N',N'-tetramethylethylenediamine (4.50 ml, 30 mmol) was added dropwise. After 20 min, the alkene (-)-**18** (9.60 g, 63.0 mmol) was added, followed by dry ether (12.0 ml). After 20 h, the resulting fine white solid was filtered off under argon, washed with pentane (4 x 30 ml), then blown dry using a stream of argon to give the [Menth-CH_2BH_2]$_2$•TMEDA complex (8.50 g, 63%). A small sample of this solid was analyzed as follows: a few crystals were dissolved in dichloromethane (0.5 ml) and the solution treated with BF_3•OEt_2 (five drops). After 15 min, methanol (0.5 ml) was added and the mixture evaporated *in vacuo*. The residue was treated with methanol (1.5 ml), NaOH solution (0.4 ml, 3 M), and 30% H_2O_2 (0.4 ml) at 0 °C, followed by stirring at room temperature for 3 h. Methanol was distilled off, ethyl ether (1.5 ml) was added, and the ethereal solution was washed with a saturated $NaHCO_3$ solution and brine. The ether phase (containing the corresponding primary alcohols) was dried (Na_2SO_4) and evaporated. The ratio of axial -CH_2OH (1*S*, 2*S*, 5*R*) *vs* equatorial -CH_2OH (1*R*, 2*S*, 5*R*) was determined by capillary GC as *ca.* 30:1. Authentic samples of axial [**35**: (1*S*,2*S*,5*R*)] and equatorial [**36**: (1*R*,2*S*,5*R*)] primary alcohols were obtained *via* hydroboration/peroxide treatment of (-)-**18** using BH_3•Me_2S in n-hexane [**35**:**36** ratio = 3.3:1] (see below).



35 **36**

Further purification of [Menth-CH_2BH_2]$_2$•TMEDA (**20**) was achieved as follows: the crystals (8.50 g) were dissolved in dry dichloromethane (45 ml) under argon while heating to a gentle reflux. n-Hexane (100 ml) was added to the solution while still warm, and the mixture was left to crystallize at room temperature (crystals formed

after a few minutes). The mixture was kept overnight at -4 °C (refrigerator), and then filtered under argon. The crystals were washed with dry n-hexane (3 times), and then blown dry using a stream of argon to give **20** (5.46 g, 64%) [1*S*,2*S*,5*R* : 1*R*,2*S*,5*R* ratio ≥ 200:1 by GC of the corresponding alcohols **35** and **36**]. ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 55.83, 50.89, 50.73, 49.60, 40.40, 36.22, 34.20, 29.54, 26.13, 25.05, 22.97, 21.61, 20.81, 10 (broad, C-B). ^{11}B NMR [THF/$CDCl_3$, δ ppm relative to BF_3•Et_2O (0.0)]: -3.35. MS (FAB$^+$): 447 (M-1). Anal. Calcd for $C_{28}H_{62}B_2N_2$: C, 74.99; H, 13.94; N, 6.25. Found: C, 74.97; H, 13.78; N, 6.17.

*Preparation of authentic alcohols **35** and **36**.* The alkene (-)-**18** was hydroborated with various reagents in a range of solvents. The resulting primary alcohols **35** (1*S*,2*S*,5*R*) and **36** (1*R*,2*S*,5*R*) were obtained in the following ratios: 3.3:1 (BH_3•Me_2S, *n*-hexane), 1.3:1 ([Ipc]BH_2, THF, Ipc from (1*S*)-(-)-α-pinene), 2.8:1 ($ClBH_2$, THF), 3.1:1 ($ClBH_2$, CH_2Cl_2), 2.1:1 ($ClBH_2$, Et_2O), 1.9:1 ($ClBH_2$, *n*-hexane). The ratios of **35**:**36** were determined by capillary GC (OV-1 column, 70-150 °C) and ^{13}C NMR spectroscopy, while structural assignments were made *via* ^{13}C NMR spectroscopy: the CH_2OH resonance chemical shift in the axial alcohol **35** is at higher field (59.89 ppm) compared to the equatorial alcohol **36** (65.16 ppm) due to steric compression. Alcohol **35** (1*S*,2*S*,5*R*) had ^{13}C NMR δ(100.6 MHz, $CDCl_3$): 20.75, 21.64, 22.63, 25.79, 26.10, 29.43, 35.61, 36.37, 37.93, 46.72, 59.89. Alcohol **36** (1*R*,2*S*,5*R*) ^{13}C NMR ($CDCl_3$) selected value: δ65.16.

*Preparation of [MenthCH$_2$]BH(Ipc) (**22**) and [MenthCH$_2$]BCl(Ipc) (**8**).*[16] To a stirred solution of [MenthCH$_2$-BH_2]$_2$•TMEDA (0.90 g, 2.0 mmol) in dry THF (15 ml), under an atmosphere of argon at room temperature, boron trifluoride etherate (0.49 ml, 4.0 mmol) was added. The reaction mixture was stirred for 110 min, during which time a precipitate of TMEDA•$(BF_3)_2$ was deposited. (*a*) Characterization of [MenthCH$_2$]•BH_2. Filtration under argon to remove the precipitated TMEDA•$(BF_3)_2$ and solvent evaporation gave MenthCH$_2$$BH_2$. ^{13}C NMR δ($CDCl_3$): 48.16, 41.95, 35.83, 30.73, 29.55, 25.78, 24.44, 22.75, 21.37, 20.58, 12.5 (broad, C-B). ^{11}B NMR [CH_2Cl_2 + CD_2Cl_2, δ ppm relative to BF_3•Et_2O (0.0)]: 23.28. (*b*) Alternatively, the process was continued by addition of (1*S*)-(-)-α-pinene (0.64 ml, 4.0 mmol; 98% ee) to the reaction mixture in THF. The mixture was stirred for 6 h then filtered under argon to remove the precipitated TMEDA•$(BF_3)_2$. (*c*) Characterization of [MenthCH$_2$]BH(Ipc). Solvent evaporation gave [MenthCH$_2$]BH(Ipc) which was characterised as follows: ^{13}C NMR δ($CDCl_3$) 48.25, 47.98, 42.09, 41.27, 37.06, 35.81, 34.06, 31.19, 29.54, 28.51, 28.28, 26.01, 24.57, 24.45, 23.32, 22.75, 22.65, 21.34, 20.63, 17 (broad, C-B), 13 (broad, C-B); ^{11}B NMR [CH_2Cl_2 + CD_2Cl_2, δ ppm relative to BF_3•Et_2O (0.0)]: 53.23 (monomer), 31.62 (dimer). (*d*) Synthesis of [MenthCH$_2$]BCl(Ipc) (**8**). Solvent evaporation after stage (*b*) gave a residue to which dry Et_2O (8.0 ml) was added. To the solution was added HCl (4.0 ml, 4.0 mmol, 1 M Et_2O solution) leading to strong hydrogen evolution. After a further 15 min, the resulting solution of [MenthCH$_2$]BCl(Ipc) (**8**) was used in the aldol reactions described later.

*Preparation of ethanolamine complex (**23**).* To a stirred solution of [MenthCH$_2$]BH(Ipc) (**22**) (0.605 g, 2.00 mmol) in Et_2O (5.0 ml) was added dry methanol (0.10 ml, 2.50 mmol) at room temperature. After 1 h, the solvent and excess methanol were removed *in vacuo*. The residue was again dissolved in Et_2O (2.0 ml) and ethanolamine (0.122 ml, 2.00 mmol) was added. After stirring for 2 h, the solvent was removed *in vacuo*. After recrystallisation from n-hexane, the ethanolamine complex **23** (0.470 g, 66%) was obtained as a 5 : 1 mixture of diastereomers. ^{13}C NMR (major isomer) δ(100.6 MHz, $CDCl_3$): 63.79, 49.65, 48.72, 42.22, 41.90, 41.64,

39.01, 38.31, 36.26, 33.85, 32.45, 30.71, 29.31, 28.30, 26.42, 24.60, 24.25, 22.84, 22.73, 21.63, 21.08, 13.2 (broad); HRMS (FAB$^+$) $[M+H]^+$ 362.3614, $C_{23}H_{45}BNO$ requires 362.3594.

General procedure for aldol reactions using reagent 8. To a stirred solution of [MenthCH$_2$]BCl(Ipc) (**8**) (0.820 g, 2.00 mmol) in dry Et_2O (8.0 ml), cooled at 0 °C under an argon atmosphere, dry Et_3N (2.00 mmol, 0.280 ml) and subsequently the ketone (1.20 mmol) were added dropwise. The enolborinate was generated with concurrent formation and precipitation of Et_3N•HCl. After 3 h at 0 °C, the aldehyde (4.00 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 5 h, then it was allowed to warm to room temperature over a period of 5 h. Aqueous phosphate buffer (pH7, 10 ml) was added and the aqueous phase was extracted with Et_2O (2 x 10 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in MeOH (8 ml) and phosphate buffer (3 ml) at 0 °C, and treated with 30% H_2O_2 (3 ml). After 1 h stirring at room temperature, the mixture was diluted with water and extracted with CH_2Cl_2 (3 x 15 ml). The organic phase was washed with saturated $NaHCO_3$ solution, saturated brine, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was flash chromatographed to give the desired aldol compound. The enantiomeric excess was determined by ^{1}H NMR spectroscopy ($CDCl_3$) of the derived (*R*)- and (*S*)-MTPA Mosher esters or by chiral GC analysis using a Hewlett Packard 5790A Gas Chromatograph fitted with a 25 m SGE β-cyclodextrin column (He carrier gas, 20 psi).

(4S,5R)-4,6-dimethyl-5-hydroxy-6-hepten-3-one (25). This compound was prepared following the general procedure using diethylketone (0.121 ml, 1.20 mmol) and methacrolein (0.331 ml, 4.00 mmol). After flash chromatography (dichloromethane) of the crude product, 0.070 g (0.45 mmol, 37%) of aldol product was obtained. The anti : syn ratio was determined by ^{1}H NMR to be 70 : 30. The enantiomeric excess of the anti isomer was 30% (MTPA ester and chiral GC analysis: programmed at 100 °C, 5 min, 2 °C min^{-1} up to 150 °C; R_t for major anti isomer = 19.0 min; R_t for minor anti isomer = 18.8 min). ^{1}H NMR δ(250 MHz, $CDCl_3$) 4.92 (1H, bs), 4.91 - 4.88 (1H, m), 4.15 (1H, dd, *J* = 8.3, 4.3 Hz), 2.76 (1H, dq, *J* = 8.3, 7.2 Hz), 2.58 - 2.47 (3H, m), 1.71 (3H, bs), 1.03 (3H, t, *J* = 7.2 Hz), 0.97 (3H, d, *J* = 7.2 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 215.91, 144.60, 113.91, 78.35, 48.26, 36.35, 16.80, 14.18, 7.37; this spectral data is in agreement with that reported in the literature for the racemate.[4c] The absolute configuration was determined as (4*S*,5*R*) by ^{1}H NMR analysis of the derived (*R*)- and (*S*)-MTPA esters.[17]

(1R,2S)-1-hydroxy-2-methyl-1-phenyl-3-pentanone (26). This compound was prepared following the general procedure using diethylketone (0.121 ml, 1.2 mmol) and benzaldehyde (0.407 ml, 4.0 mmol). Flash chromatography (petrol ether 40/60 : ethyl acetate, 4 : 1) of the crude product gave 0.065 g (0.34 mmol, 28 %) of aldol product. ^{1}H NMR analysis indicated an anti : syn ratio of 70 : 30. The enantiomeric excess of the anti isomer was determined to be 18% (chiral GC: programmed at 150 °C, 5 min, 2 °C min^{-1} up to 200 °C; R_t for major anti isomer = 19.2 min; R_t for minor anti isomer = 18.9 min). ^{1}H NMR δ(250 MHz, $CDCl_3$) 7.38-7.21 (5H, m), 4.75 (1H, d, *J* = 8.2 Hz), 2.93 (1H, dq, *J* = 8.2, 7.2 Hz), 2.88 (1H, bs), 2.61-2.28 (2H, m), 1.02 (3H, t, *J* = 8.2 Hz), 0.93 (3H, d, *J* = 7.2 Hz); ^{13}C NMR δ(100.6 MHz, $CDCl_3$) 216.04, 142.16, 128.41 (2C), 127.89, 126.49 (2C), 76.61, 52.58, 36.41, 14.39, 7.37; this spectral data is in agreement with that reported in the literature for the racemate.[18]

(4S,5R)-2,4,6-trimethyl-5-hydroxy-6-hepten-3-one (27). This compound was prepared following the general procedure using 2-methylpentan-3-one (0.148 ml, 1.2 mmol) and methacrolein (0.331 ml, 4.0 mmol). After flash chromatography (petrol ether 40/60 : ethyl acetate, 3 : 1) of the crude product, 0.078 g (0.46 mmol, 38%) of aldol product was obtained as a single anti isomer (^{1}H NMR). Mosher ester analysis indicated an enantiomeric excess of 33%. ^{1}H NMR δ(250 MHz, $CDCl_3$) 4.93-4.88 (2H, m), 4.16 (1H, d, J = 8.0 Hz), 2.92 (1H, dq, J = 8.0, 7.2 Hz), 2.72 (1H, sept, J = 6.9 Hz), 2.50 (1H, bs), 1.72 (3H, s), 1.09 (3H, d, J = 6.9 Hz), 1.07 (3H, d, J = 6.9 Hz), 0.98 (3H, d, J = 7.2 Hz); ^{13}C NMR δ(63 MHz, $CDCl_3$) 219.05, 144.75, 113.70, 78.46, 46.69, 41.26, 17.80, 17.70, 16.89, 14.53; Anal. Calcd. for $C_{10}H_{18}O_2$: C 70.55; H 10.66. Found: C 70.52; H 10.73. The absolute configuration was determined as (4*S*,5*R*) by ^{1}H NMR analysis of the derived (*R*)- and (*S*)-MTPA esters.[17]

(1R,2S)-1-hydroxy-2,4-dimethyl-1-phenyl-3-pentanone (28). This compound was prepared following the general procedure using 2-methylpentan-3-one (0.148 ml, 1.2 mmol) and benzaldehyde (0.205 ml, 2.0 mmol). After flash chromatography (petrol ether 40/60 : ethyl acetate, 4 : 1) of the crude product, 0.106 g (0.51 mmol, 43%) of aldol product was obtained as a single anti isomer (^{1}H NMR). An enantiomeric excess of 41% was determined (chiral GC: programmed at 150 °C, 5 min, 2 °C min^{-1} up to 200 °C; R_t for major anti isomer = 19.9 min; R_t for minor anti isomer = 19.6 min).. ^{1}H NMR δ(400 MHz, $CDCl_3$) 7.35-7.24 (5H, m), 4.73 (1H, d, J = 7.6 Hz), 3.06 (1H, dq, J = 7.6, 7.1 Hz), 2.89 (1H, bs), 2.64 (1H, sept, J = 6.9 Hz), 1.07 (3H, d, J = 7.1 Hz), 0.98 (3H, d, J = 6.9 Hz), 0.96 (3H, d, J = 7.1 Hz); ^{13}C NMR δ(63 MHz, $CDCl_3$) 219.42, 142.44, 128.37 (2C), 127.77, 126.38 (2C), 76.76, 51.02, 41.31, 17.65 (2C), 14.92; this spectral data is in agreement with that reported in the literature for the racemate.[18]

Acknowledgements: This work was supported by the Commission of the European Communities [Grants SC1*.0324.C(JR), ERBCHRXCT930141], NATO (Grant 0368/88), SERC (UK), MURST (Rome), and CNR (Rome). We thank The Royal Society for a research fellowship (CTH) and Clare College (Cambridge) for a research fellowship (JMG).

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(*Received in UK* 7 *October* 1993; *accepted* 20 *October* 1993)