The Rational Design of Highly Stereoselective Boron Enolates Using Transition-State Computer Modeling: A Novel, Asymmetric Anti Aldol Reaction for Ketones[1]

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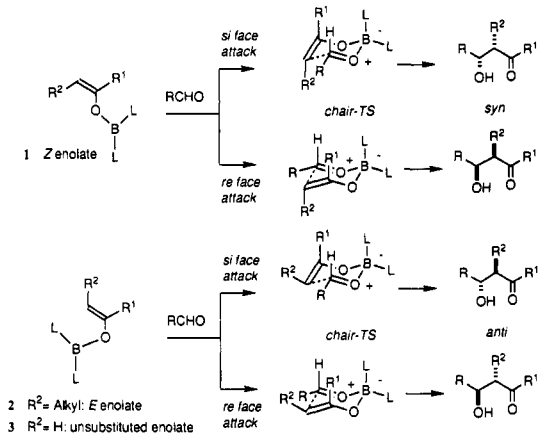
The design and development of highly enantioselective anti aldol reactions based on computer-aided transition-state modeling is reported. The new chiral boron ligand L = 6 was conceived based on its conformational preferences and on minimization of (±) double gauche pentane interactions. Modeling the transition structures for the aldol reaction of *Z* enolates 1 (L = 6) predicted a selectivity which is equal to or slightly lower than that calculated and experimentally tested with L = Ipc (isopinocampheyl) (see Table I). The predictions for *E* enol borinates (2) were synthetically more interesting: the new ligand (6) was calculated to be much more selective than Ipc (see Table II). Preparation of the boron reagent {[(Menth)CH_2]$_2$BCl–OEt_2} (11) necessary for the synthesis of ligand 6-derived *E* enolates is reported, starting from commercially available enantiomerically pure (–)-menthone. Enolization of a range of cyclic and acyclic ketones {[(Menth)CH_2]$_2$BCl–OEt_2, Et_3N, 1:1 CH_2Cl_2–Et_2O, –78 °C} and addition of an aldehyde (–78 °C) gave anti aldols with high diastereoselectivity (86:14 to 100:0 anti:syn) and in good enantiomeric excess (56–88% ee). These conditions ensured high stereoselectivity toward formation of the *E* enolate (2), which then reacted preferentially by attack on the *re* face of the aldehyde (*re:si* 3.5:1 to 15.6:1). Also in the aldol reactions with methyl ketone enolates (3) the new reagent compared favorably with the existing methods.

Forming carbon–carbon bonds in a diastereo- and enantiocontrolled manner is an increasingly important prerequisite for the efficient chemical synthesis of chiral compounds. The many different methods presently available for enantioselective synthesis have been largely developed from empirical findings, and are based on intuition and/or trial and error processes. We have adopted an alternative approach, aimed at the rational design of new methods for asymmetric synthesis, making use of computer-aided transition-state modeling. Our initial efforts have been targeted at rationalizing the stereoselective aldol reactions of chiral *Z* boron enolates 1 with aldehydes (Scheme I).[2a,b] We now report on the design and development of highly enantioselective anti aldol reactions using the new chiral boron ligand 6 (*E* boron enolates 2, Scheme I).

Scheme I



Results and Discussion

Design of Boron Ligands and Transition-State Modeling. We recently described a force field model for the aldol reactions of ketone-derived enol borinates with aldehydes.[2a] This force field is based on MM2 and on new parameters developed from ab initio calculations on the cyclic aldol transition structures (chair and boat).[2c] The model reproduces the aldehyde *si:re* selectivity for the syn-selective aldol reactions of a range of chiral *Z* enol borinates 1 (Scheme I),[2a,b] as well as for the anti-selective reactions of *E* enolates 2.[2d] For the asymmetric syn aldol reactions of *Z* enol diisopinocampheylborinates (1, L = Ipc), the force field model suggested that the following factors were important in determining the stereoselectivity: (a) the conformational rigidity of the Ipc boron ligand, (b) the relative orientation of the ligands with respect to the chair transition structure core, and (c) the relative orientation and restrained rotation around the B–C bonds of one Ipc ligand relative to the other.[2b] These observations prompted us to consider as ligand candidates structures known to possess a limited conformational freedom. One way to restrict the conformational space available to molecules is to make use of (±) double gauche pentane interactions.[3] Recently Still and co-workers pointed out that an interesting example of this conformational lock is found in *cis*-1-ethyl-2-isopropylcyclohexane (4, Figure 1).[4]

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(2) (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) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684; *J. Org. Chem.* **1990**, *55*, 481. (d) Bernardi, A.; Cassinari, A.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4183.

(3) (a) Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521. (b) Allinger, N. L.; Miller, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 2145. (c) Abe, A.; Jernigan, R. L.; Flory, P. *J. Am. Chem. Soc.* **1966**, *88*, 631. (d) Scott, R. A.; Scheraga, H. A. *J. Chem. Phys.* **1966**, *44*, 3054. (e) Sykora, S. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3514. (f) For a list of interesting applications of the (±) double gauche pentane interactions to stereochemical control, see: Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151 and footnotes 27 and 28 in that paper.

(4) Still, W. C.; Cai, D.; Lee, D.; Hauck, P.; Bernardi, A.; Romero, A. *Lect. Heterocycl. Chem.* **1987**, *9*, 33.

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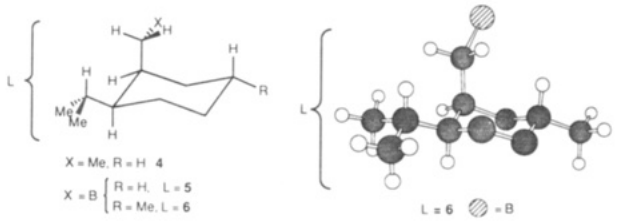


Figure 1. Lowest energy conformation of compound **4** and boron ligands **5** and **6**.

Table I. Predicted and Experimental Ratios for the Syn Aldol Reactions of *Z* Enol Borinates (1)

				re:*si* ratio	
entry	R	R^2	L	calcd	expt
1	Me	Me	Ipc[a]	1:19[b,c]	1:10[d]
2	$C(CH_3)=CH_2$	Me	Ipc[a]	1:24[b]	1:27[e]
3	^{i}Pr	Me	Ipc[a]	1:5[b]	1:5[d]
4	Me	Me	**5**	18:1[b,f]	
5	Me	Me	**6**	15:1[b,g]	
6	$C(CH_3)=CH_2$	Me	**6**	21:1[b]	
7	^{i}Pr	Me	**6**	3:1[b]	

[a] Ipc from (+)-α-pinene. [b] R^1 = Me. [c] Pictures of the relevant transition structures shown in ref 2b. [d] R^1 = Et, ref 6a. [e] R^1 = Me, ref 6b. [f] Pictures of the relevant transition structures shown in Figure 2. [g] Pictures of the relevant transition structures shown in Figure 3.

For this molecule there is only one conformation of the chair and of the side chains that does not possess any (±) double gauche pentane interaction: this conformation (shown in **4**) is the global minimum and 1.4 kcal mol^{-1} lower in energy than the second best one.[4] Substitution of the terminal methyl group of the ethyl chain in *cis*-1-ethyl-2-isopropylcyclohexane with a boron atom gives a new ligand (**5**) which, for the foregoing reasons, represents an interesting candidate for the modeling process. Even more interesting is the analogous 5-methyl derivative (**6**), which can be synthesized starting from commercially available enantiomerically pure (−)-menthone or (−)-menthol (vide infra, Scheme II).[5]

Modeling the transition structures for the aldol reaction of both *Z* and *E* enol borinates **1** and **2** (L = **5**, **6**), showed that the conformation of the isopropylcyclohexyl ligands is the one expected on the basis of the *cis*-1-ethyl-2-isopropylcyclohexane model (**4**).[4] Moreover, the conformational freedom around the B–C bonds is severely restricted, and the relative orientation of the two ligands (the pseudoaxial and the pseudoequatorial on the chair transition structure) is the same in the lowest energy structures for the addition to both the *re* and *si* face of the aldehyde. Addition to the *re* face of the aldehyde is relatively free of steric hindrance, since the "axial" boron ligand orients the hydrogens of the BCH_2 group toward the inside of the chair transition structure core and the isopropylcyclohexyl group toward the outside. On the contrary, a bad interaction between the R^1 group of the enolate and the isopropylcyclohexyl group of the "axial" ligand is experienced in the addition to the *si* face. An example is shown in Figure 2.

For *Z* enolates **1** the selectivity predicted with the new ligands **5** and **6** (50–91% ee; Table I, entries 4–7) is equal to or slightly lower than that calculated with Ipc (66–92% ee; Table I, entries 1–3). This suggests that the new ligands would not offer significant improvements in enantioselectivity relative to that already found experimentally for *Z* enol diisopinocampheylborinates (**1**, L = Ipc; 66–93% ee).[6]

(5) The other enantiomer is also easily obtainable, as (+)-menthone can be prepared in high yield via Jones oxidation of commercially available (1*S*,2*R*,5*S*)-(+)-menthol.

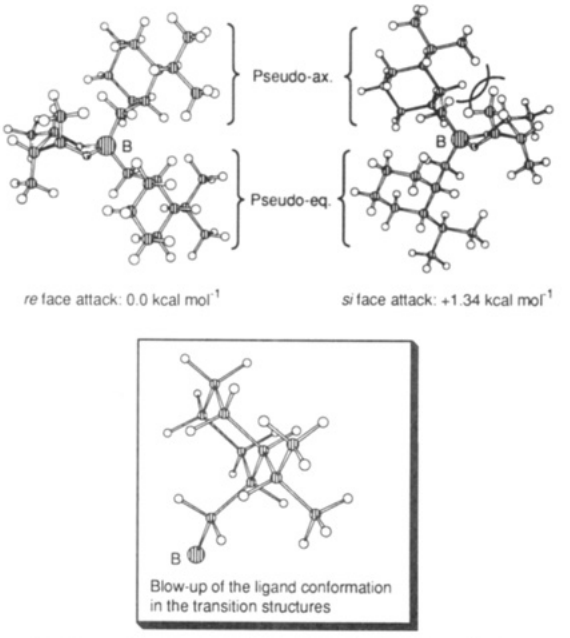
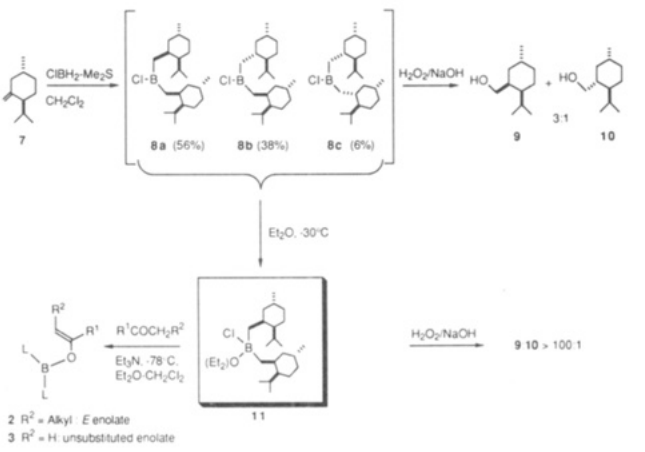


Figure 2. Lowest energy conformations for the two diastereomeric modes of addition of butanone L_2B–*Z*-enolate (L = **5**) to CH_3CHO (Table I, entry 4).

Scheme II



The predictions for *E* enol borinates (**2**) are synthetically more interesting. To our delight the new ligand (**6**) is predicted to be much more selective than Ipc in the case of *E* enolates (Table II, cf. entries 1, 2). *E* enol borinates give rise to ketone derived anti aldol adducts, which have eluded earlier attempts at effective asymmetric synthesis via direct aldol-type condensation.[6c,7]

Preparation of Boron Reagent 11 and Aldol Addition Reactions. Preparation of the boron reagent (**11**) necessary for the synthesis of ligand **6**-derived *E* enolates started with a Wittig reaction ($Ph_3P=CH_2$) on (−)-menthone to give (−)-(**7**).[5] Hydroboration ($ClBH_2$–Me_2S) of (−)-(**7**) gave a mixture of **8a** with **8b** and **8c** (Scheme

(6) (a) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787. (b) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997. (c) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

(7) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2 (Heathcock, C. H., Ed.): (a) Heathcock, C. H., Chapter 1.5, pp 133–179; Chapter 1.6, pp 181–238. (b) Kim, M.; Williams, S. F.; Masamune, S., Chapter 1.7, pp 239–275. (c) Paterson, I., Chapter 1.9, pp 301–319. (d) Martin, S. F., Chapter 1.16, pp 475–502. (e) Bergbreiter, D. E.; Momongan, M., Chapter 1.17, pp 503–526. (f) Gennari, C., Chapter 2.4, pp 629–660.

Table II. Predicted and Experimental Ratios for the Aldol Reactions of *E* and Unsubstituted Enol Borinates (2, 3)

entry	R	R^1	R^2	L	*re:si* ratio calcd	*re:si* ratio expt	% yield
1	$C(CH_3)=CH_2$	Et	Me	Ipc[n]	1:2.8[a,b]	1:1.0–1.5[c]	80[c,d]
2	$C(CH_3)=CH_2$	Et	Me	6	22:1[a,b,e]	7.0:1	62[f]
3	$C(CH_3)=CH_2$	^{i}Pr	Me	6	59:1[b,e]	15.6:1	51[g]
4	Et	Et	Me	6	24:1[a,b,h]	9.2:1	50[i]
5	Et	^{i}Pr	Me	6		12.1:1	50[j]
6	c-C_6H_{11}	^{i}Pr	Me	6		6.6:1	54[g]
7	$C(CH_3)=CH_2$	$-(CH_2)_3-$		6	5:1[b]	6.7:1	60[g]
8	$C(CH_3)=CH_2$	$-(CH_2)_4-$		6		3.5:1	59[g]
9	$C(CH_3)=CH_2$	Ph	Me	6	15:1[b]	13.0:1	60[k]
10	$C(CH_3)=CH_2$	^{i}Pr	H	6		7.3:1	66
11	$C(CH_3)=CH_2$	^{i}Bu	H	6		3.4:1	80[j]
12	$C(CH_3)=CH_2$	^{t}Bu	H	6		7.1:1	62
13	$C(CH_3)=CH_2$	Me	H	6		3.9:1	65[l]
14	$C(CH_3)=CH_2$	Ph	H	6		5.5:1	81[l]
15	$CH_2CH_2CH_3$	Me	H	6		6.5:1	65[l]
16	$C(CH_3)=CH_2$	Et	H	6		4.4:1	51[l,m]

[a] R^1 = Me. [b] Calculated anti:syn 100:0. [c] Reference 6c. [d] Anti:syn, 80:20, ref 6c. [e] Pictures of the relevant transition structures shown in Figures 4 and 5. [f] Anti:syn, 93:7. [g] Anti:syn, 100:0. [h] R = Me. [i] Anti:syn, 92:8. [j] Anti:syn, 97:3. [k] Anti:syn, 86:14. [l] Enolization and aldol addition in 100% dichloromethane. [m] Only enolization at the methyl group was detected. [n] Ipc from (+)-α-pinene.

II).[8a] Recrystallization (Et_2O, −30 °C) gave [(Menth)CH_2]$_2$BCl–OEt_2 (11) (**8a:8b** ≥ 50:1, **9:10** ≥ 100:1) which was used for the experiments shown in Table II.[8b,c]

Highly selective formation of *E* enolates (**2**, L = **6**) was obtained by treating a range of cyclic and acyclic ketones with [(Menth)CH_2]$_2$BCl–OEt_2 (11) and Et_3N in 1:1 CH_2Cl_2–Et_2O at −78 °C.[9] Addition of an aldehyde (−78 °C) gave anti aldols with high diastereoselectivity (86:14 to 100:0 anti:syn) and in good enantiomeric excess (56–88% ee, see Table II, entries 2–9). The absolute configuration was established by $[\alpha]_D$ comparison (see table in the supplementary material) and found to be in accord with the predicted preferential attack on the *re* face of the aldehyde (*re:si* 3.5:1 to 15.6:1). Although the quantitative agreement between the calculated and the experimental values is not as tight as for the *Z* enolates (see Table I),[2a,b] the new reagent is presently the best ever reported for the enantioselective anti aldol reactions of ketones.[7]

Also in the aldol reactions with methyl ketone enolates (**3**, R^2 = H; see Table II, entries 10–16) our new reagent compares favorably with the existing methods.[6b,c,7,10] It is worth noting that with ligand **6** the aldehyde enantioface preference is the same (*re* face) for both ethyl and methyl ketone additions. On the contrary, when Ipc is used as ligand, a change in the aldehyde enantioface selectivity for ethyl vs methyl ketone additions is observed [Ipc from (+)-α-pinene: *Z* enolates add selectively to the aldehyde *si* face, unsubstituted enolates to the aldehyde *re* face].[6b,c]

Conclusions

A project toward the rational design and synthesis of new enantioselective reagents was started in 1988. Initially, the modeling part was set up by parameterizing a force field for the enol borinate aldol transition structures.[2a] Then this model was used to rationalize the observed selectivity of various chiral enolates.[2b] Finally we designed new reagents and tested them using our computational approach. Many of these reagents were not selective, others appeared to be very promising but would be extremely difficult to synthesize. Eventually we designed the new menthone-derived ligands for the boron-mediated aldol condensation which are the subject of the present paper. They performed exceptionally in the computer, which justified attempting their synthesis. The synthesis was not trivial, and particularly the chloroborane purification required many efforts. Now that the procedure is worked out, one can synthesize grams of the pure crystalline reagent (11) in 1 day and keep it in a stock solution for months. The new reagents also performed extremely well in the laboratory, allowing the enantioselective synthesis of ketone-derived anti aldols, which had so far eluded every attempt of efficient enantioselective synthesis.

Apart from the synthetic value, these results have shown that one can *use transition-state computer modeling to design new effective reagents*. More work in this area is in progress.

Computational Section

Using the parameters developed in our earlier work,[2a] MacroModel[11] was used to generate accessible transition structures for the boron enolate aldol reactions of interest. The conformational space was searched with the Still–Chang–Guida usage-directed torsional Monte Carlo search[12] as implemented by the BATCHMIN program.[13]

Four different Monte Carlo runs were necessary to fully establish the product distribution of *E* and *Z* enolates, i.e. the relative energies had to be evaluated for structures featuring: (1) *si*-face attack, anti relative stereochemistry, (2) *re*-face attack, anti relative stereochemistry, (3) *si*-face attack, syn relative stereochemistry, (4) *re*-face attack, syn relative stereochemistry. This full search was done in

(8) (a) A similar preference for equatorial attack resulting in axial $-CH_2B-$ was reported for the hydroboration of 1-methylene-2-isopropylcyclohexane, see: Senda, Y.; Kamiyama, S.; Imaizumi, S. *Tetrahedron* **1977**, *33*, 2933. (b) Calculations have also shown that the enolates derived from **8b** and **8c** are nonstereoselective. Preliminary results using the crude mixture (**8a:8b:8c**, 56:38:6) gave a *re:si* ratio of 2.5:1 for the case reported in Table II, entry 3. (c) [(Menth)CH_2]$_2$BCl–OEt_2 11 (**8a:8b** ≥ 50:1; **9:10** ≥ 100:1) was obtained in 20% yield after two recrystallizations: a stock solution in dichloromethane (0.75 M) was prepared and kept for weeks in the refrigerator at 0 °C without any appreciable decomposition.

(9) (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441. (b) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (c) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499.

(10) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041.

(11) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. We thank Professor Clark Still (Columbia University, NY) for providing copies of his programs and advice on their use.

(12) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(13) BATCHMIN is the noninteractive modeling program connected to MacroModel. Version 3.1 was used on a Silicon Graphics Iris 4D-20 workstation.

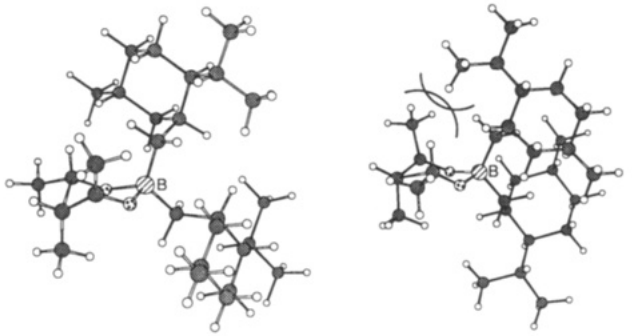


Figure 3. Lowest energy conformations for the two diastereomeric modes of addition of butanone L_2B–*Z*-enolate (L = **6**) to CH_3CHO (Table I, entry 5).

selected cases to confirm that *Z* enolates were syn selective and *E* enolates were anti selective. Routinely only two runs (*si*-face attack vs *re*-face attack) were necessary.

For *Z* enolates, only chair transition structures are important;[2] therefore, only extraannular bonds were allowed to rotate. In the case of *E* enolates, we tested for the presence of boat transition structures by including all rotatable bonds of the transition structure "core". Boats were found to be relatively unimportant, because of their high energies relative to the chairs.

Torsional constraints were applied to preserve the enolate geometry and prevent *Z*/*E* mixing. Chirality check was used for all stereocenters 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[14] 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.[15]

The diastereomeric ratios (anti vs syn and *re* vs *si*) were calculated by a Boltzmann distribution at 195 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* enolates and complete anti selectivity for *E* enolates, i.e. the chair pathway dominates over the boat.

Figure 3 shows the lowest energy transition structures for the *re*-face and *si*-face addition to acetaldehyde of butanone $[(Menth)CH_2]_2B$–*Z*-enolate leading to the syn aldol (Table I, entry 5).

Figure 4 shows the lowest energy transition structures for the *re*-face and *si*-face addition to methacrolein of isopropyl ethyl ketone $[(Menth)CH_2]_2B$–*E*-enolate leading to the anti aldol (Table II, entry 3). All the relevant structures found were chairs, and the predicted *re*:*si* ratio was 59:1. Figure 5 shows the lowest energy transition structures for the *re*-face and *si*-face addition to methacrolein of butanone $[(Menth)CH_2]_2B$-*E*-enolate leading to the anti aldol (Table II, entry 2). All the relevant structures found were chairs, and the predicted ratios were anti:syn ≥ 99:1 (the first syn selective structure is 2.5 kcal mol^{-1} higher in energy), and *re*:*si* = 22:1. This last example shows that the pseudoequatorial ligand is relatively free to move: a more detailed analysis of these computational aspects will be published elsewhere.

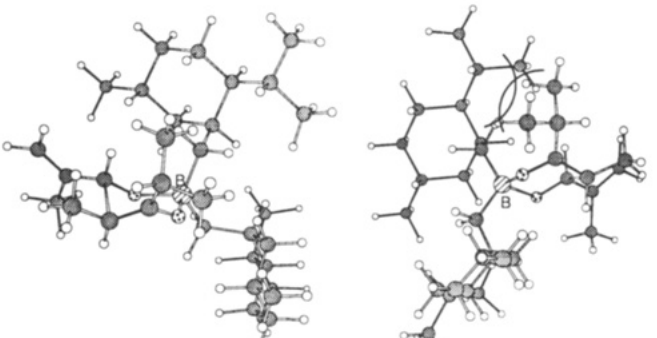


Figure 4. Lowest energy conformations for the two diastereomeric modes of addition of isopropyl ethyl ketone L_2B–*E*-enolate (L = **6**) to CH_2=C(Me)CHO (Table II, entry 3).

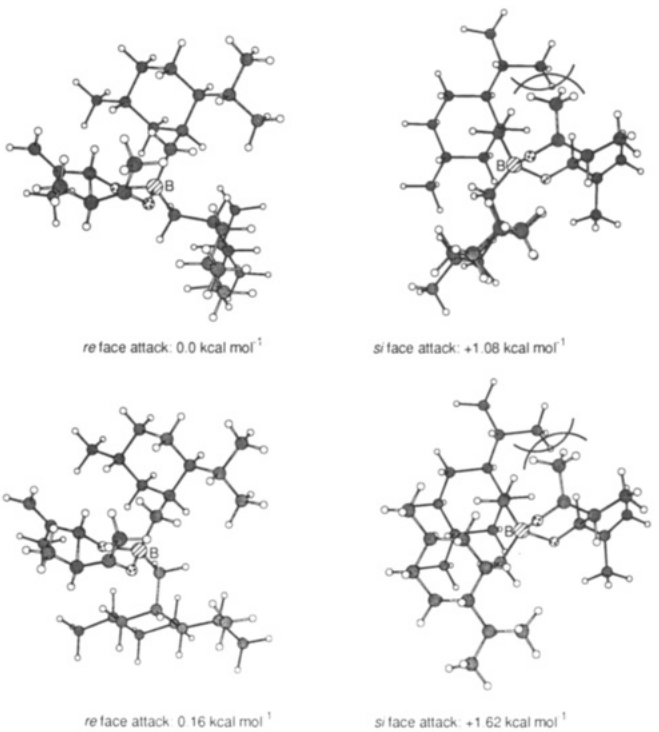


Figure 5. Lowest energy conformations for the two diastereomeric modes of addition of butanone L_2B–*E*-enolate (L = **6**) to CH_2=C(Me)CHO (Table II, entry 2).

Experimental Section

Preparation of (−)-7 from (−)-Menthone. *n*-Butyllithium (52.67 mL, 84.3 mmol; 1.6 M solution in hexanes; supplier: Aldrich) was added dropwise to a suspension of methyltriphenylphosphonium bromide (30.1 g, 84.3 mmol; supplier: Aldrich) in dry tetrahydrofuran (270 mL) at 0 °C under an atmosphere of nitrogen. The resulting yellow mixture was warmed to room temperature and stirred for 1 h, and then (−)-menthone (10 g, 64.8 mmol; 95% pure, supplier: Aldrich) was added dropwise. The flask was warmed to 65 °C for 2 h and then stirred overnight at room temperature. Ethyl 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 × 100 mL), and the organic layers were combined, dried (Na_2SO_4), and evaporated under reduced pressure. Pentane (100 mL) was added to the resulting residue, and the solid was filtered under vacuum and carefully washed with more pentane (250 mL). The filtrate was concentrated on the rotary evaporator to give a yellow oil which was chromatographed using pentane as the eluant. The product (−)-7 is obtained as a colorless oil (8.6 g, 87%) in the first fractions,

(14) Lipton, M.; Still, W. C. *J. Comput. Chem.* **1988**, *9*, 343.
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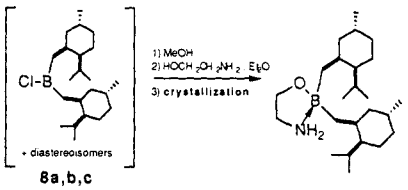
detectable by GC. Spectroscopic data was in agreement with that in the literature.[16]

Preparation of Chloroboranes 8a–c.[17] A solution of (–)-7 (0.722 g, 5.079 mmol) in freshly distilled dichloromethane (2.5 mL) was treated with $ClBH_2$–SMe_2 (Aldrich) (0.265 mL, 2.539 mmol) at 0 °C, under nitrogen, with stirring. The reaction mixture was stirred at room temperature for 2 h. The solvent dichloromethane and dimethyl sulfide liberated during hydroboration were removed under vacuum, and the residue was taken up in dry *n*-hexane with formation of a white precipitate; the supernatant solution was cannulated into another flask (white powder removed), and *n*-hexane was evaporated to give chloroborane (8) which was blown dry using a stream of nitrogen. ^{13}C NMR ($CDCl_3$) selected values: δ 20.59 [CH_3, major (56%), (**8a**), (diaxial-CH_2)$_2$BCl], 20.71 [CH_3, minor (19%), (**8b**), (axial-CH_2)-BCl(equatorial-CH_2)], 20.82 [CH_3, minor (6%), (**8c**), (diequatorial-CH_2)$_2$BCl], 20.94 [CH_3, minor (19%), (**8b**), (axial-CH_2)BCl-(equatorial-CH_2)]. The ratio between equatorial and axial hydroboration (3:1) was determined by decomposition with hydrogen peroxide and VPC analysis (OV-1 column, 70–150 °C) of alcohols **9** and **10**.[18]

Characterization as Aminoethanol Complex.[19] A solution of chloroborane **8** (0.408 g, 0.98 mmol) in freshly distilled methanol (0.4 mL) was stirred for 30 min at room temperature. The solvent was evaporated at reduced pressure, and the residue [(Menth)-CH_2]$_2$BOMe was dissolved in freshly distilled ethyl ether (1.0 mL). The resulting solution was treated with 2-aminoethanol (0.057 mL, 0.95 mmol). After the solution was stirred for 20 min at room temperature a white precipitate formed. Recrystallization from ethyl ether (twice) gave the pure aminoethanol complex as white needles. ^{13}C NMR ($CDCl_3$): δ 65.52, 48.86, 42.62, 41.93, 35.98, 31.82, 29.41, 26.24, 24.51, 22.76, 21.45, 20.71, 16 (broad, C-B). Anal. Calcd for $C_{24}H_{48}BNO$: C, 76.37; H, 12.82; N, 3.71. Found: C, 76.30; H, 12.90; N, 3.65.



8a,b,c

The ratio between axial and equatorial –CH_2B (≥100:1) was determined by decomposition with hydrogen peroxide and VPC analysis (OV-1 column, 70–150 °C) of alcohols **9** and **10**.[18]

Preparation of Chloroborane 11. A solution of (–)-7 (95%, 5.330 g, 35.0 mmol) in freshly distilled dichloromethane (17.5 mL) was treated with $ClBH_2$–SMe_2 (95%, Aldrich) (1.825 mL, 17.5 mmol) at 0 °C, under nitrogen, with stirring. The reaction mixture was stirred at room temperature overnight. The solvent dichloromethane and dimethyl sulfide liberated during hydroboration were removed under vacuum (0.1 mmHg), and the residue (a thick liquid) was dissolved in dry diethyl ether (13.0 mL). The solution was cooled to –55 °C and left to crystallize for 1.5 h. The solvent was removed via cannula under nitrogen at –55 °C, the remaining white crystals were washed with cold ether (3.5 mL) with vigorous stirring at –55 °C, and the solvent was again removed via cannula. The crystals were then dissolved in dry diethyl ether (9.0 mL) at room temperature and cannulated off of a small amount of insoluble residue (white powder) into another flask. The solution was cooled (SLOWLY) to –30 °C, and after 1.5 h the mother liquor was removed via cannula from the crystals formed. The solid was washed with cold diethyl ether (3 × 2 mL) under vigorous stirring at –45 °C, the solvent was again removed via cannula, and the crystals were blown dry using a stream of nitrogen (1.43 g, 20%). The ratio between **8a** and **8b** (≥50:1) was determined by decomposition with hydrogen peroxide and VPC analysis (OV-1 column, 70–150 °C) of alcohols **9** and **10** (≥100:1).[18] [(Menth)CH_2]$_2$BCl–OEt_2 (**11**), ^{11}B NMR [$CDCl_3$, δ ppm relative to BF_3–Et_2O (0.0)]: 53.60. ^1H NMR ($CDCl_3$): δ 0.7–1.0 (28 H, m), 1.19 (6 H, OCH_2CH_3, t, J = 7.3 Hz), 1.4–1.8 (m, 12 H), 2.1–2.3 (m, 2 H), 3.50 (4 H, OCH_2CH_3, q, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 65.63 (CH_2O, Et_2O), 48.23, 42.07, 35.76, 31.23, 29.45, 25.82, 24.48, 22.59, 21.24, 20.53, 17 (broad, C-B), 15.02 (CH_3, Et_2O).

A stock solution of [(Menth)CH_2]$_2$BCl–OEt_2 (**11**) in dichloromethane (0.75 M) was prepared and kept for weeks in the refrigerator at 0 °C without any appreciable decomposition.

General Procedure for the Aldol Reaction. To a stirred solution of [(Menth)CH_2]$_2$BCl-OEt_2 (**11**) (0.614 g, 1.44 mmol) in 1:1 dichloromethane–ethyl ether (3.84 mL), cooled at –78 °C under nitrogen atmosphere, Et_3N (1.728 mmol, 0.240 mL) and subsequently the ketone (1.152 mmol) were added dropwise. Enol borinate was generated with concurrent formation and precipitation of Et_3N–HCl. After 2.5 h at –78 °C the aldehyde (3.456 mmol) was added dropwise. The resulting mixture was stirred at –78 °C for 5–18 h and then quenched with Et_2O (5 mL) and pH 7 phosphate buffer (5 mL). The aqueous phase was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH (3.5 mL) and phosphate buffer (1 mL) at 0 °C and treated with 30% H_2O_2 (1 mL). After 1 h of stirring at room temperature, the mixture was diluted with water and extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was washed with a saturated $NaHCO_3$ solution and saturated brine, dried (Na_2SO_4), and evaporated. The crude product was flash chromatographed to give the desired aldol compound. The enantiomeric excess was determined by ^1H-NMR spectroscopy ($CDCl_3$) in the presence of Eu(hfc)$_3$ and by comparison with the known optical rotation values.[6b-c,7,20]

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Supplementary Material Available: $[\alpha]_D$ values of the aldol products (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(18) (–)-(7) was hydroborated with various reagents and in various solvents. Hydrogen peroxide/NaOH treatment gave primary alcohols **9** (1*S*,2*S*,5*R*) and **10** (1*R*,2*S*,5*R*), which were obtained according to 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 ($ClBH_2$–Me_2S, THF), 3.0:1 ($ClBH_2$–Me_2S, CH_2Cl_2), 2.1:1 ($ClBH_2$–Me_2S, Et_2O), 1.9:1 ($ClBH_2$–Me_2S, *n*-hexane). The ratios were determined by capillary VPC (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 **9** is at higher field (59.89 ppm) compared to the equatorial alcohol **10** (65.16 ppm) due to steric compression. Alcohol **9** (1*S*,2*S*,5*R*) ^{13}C NMR ($CDCl_3$): δ 20.75, 21.64, 22.63, 25.79, 26.10, 29.43, 35.61, 36.37, 37.93, 46.72, 59.89. Alcohol **10** (1*R*,2*S*,5*R*) ^{13}C NMR ($CDCl_3$) selected value: δ 65.16.

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