chemistry of substituted derivatives of 1 of fixed conformation.[10,11] Although there are cases reported in the literature in which different carbene conformers give rise to different products,[32] there has been little evidence that the initial carbene conformation can be product determining. However, the situation in which the initial carbene conformation determines the product formed may be more general in carbene chemistry than is generally supposed. Carbenes often have low barriers to intramolecular reaction, and stabilization of these reactive intermediates by electron delocalization involving adjacent substituents may lead to preferred conformations which undergo intramolecular reaction faster than they interconvert.

Experimental Section

Cyclopropyldiazomethane (2). The diazo compound was prepared in a sequence of reactions starting from cyclopropylmethylamine[33] via 3-(*N*-nitroso-*N*-(cyclopropylmethyl)amino)-3-methyl-2-butanone[34] by the method of Adamson and Kenner.[30] Compound 2 was purified by trap to trap vacuum distillation and stored at 77 K: IR 2073 cm^{-1} (C$=$N$_2$); ^{1}H NMR (pentane-d_{12}, 213 K) δ 3.76 (d, 1 H, J = 2.0 Hz), 1.55 (m, 1 H), 0.78 (m, 2 H), 0.44 (m, 2 H).

Flash Vacuum Pyrolysis of 2. Compound 2 (0.42 mmol) was distilled at 0.2 Torr through a 25 mm × 50 cm quartz tube packed with quartz chips and heated by an external furnace to the desired temperature. The pyrolysis products were trapped in two consecutive traps at 77 K. Products were vacuum transferred to an NMR tube, and the ethylene–1,3-butadiene ratio was determined by NMR integration in CDCl$_3$ solvent. Observed integrations were corrected for a small difference in solubilities of gaseous butadiene and ethylene through the use of a standard of known concentration. Absolute yields were determined by NMR integration using *p*-dioxane as an internal standard. Total product yields were typically 70%. No cyclobutenes could be detected by the NMR analysis.

Low-Temperature Photolysis of 2. Compound 2 was condensed into a pyrex NMR tube and sealed off. The solvent was isopentane except for the 77 K photolysis in which propane was used. The tube containing 2 was then placed in a pentane bath in a quartz Dewar flask, which could be cooled in a stream of N$_2$ and photolyzed at various low temperatures with an Oreil 1000-W Hg/Xe medium-pressure lamp until the yellow color of 2 disappeared (about 15 min). After photolysis, NMR analysis of the contents of the tube revealed the presence of cyclobutene (δ 2.52, 5.97), ethylene (δ 5.30), and acetylene (δ 1.87). The ratio of cyclobutene to ethylene was measured by integration of their NMR signals. Photolysis from 300 to 320 nm was accomplished using the same apparatus with light passed through a Photon Technology International Model 001 monochrometer.

Acknowledgment. M.L.M. thanks the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support. P.B.S. and J.-H.C. are grateful to the National Science Foundation for financial support.

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Theoretical Studies of Aldol Stereoselectivity: The Development of a Force Field Model for Enol Borinates and the Investigation of Chiral Enolate π-Face Selectivity

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Ab initio calculations on enol borinate structures have been used to generate empirical force field parameters for the title systems. The optimized structures of enol borinates are nonplanar with the BR$_2$ group twisted out of the enolate plane, rendering the enolate π-faces nonequivalent. The resulting force field model has been used for a preliminary investigation of the aldol stereoselectivity of enol borinates with chiral groups attached either to boron or to the carbonyl carbon. This suggests that the π-facial selectivity of *Z*-enol diisopinocampheyl borinates derived from ethyl ketones may be explained by the conformational bias of the enolate and a Zimmerman–Traxler chair transition state with the aldehyde. The reversed aldehyde enantioface selectivity observed for enol diisopinocampheyl borinates derived from methyl ketones does not fit this pathway, and alternative boat transition states are required.

The aldol addition reaction of enol borinates is an important method for attaining absolute stereocontrol in the synthesis of β-hydroxy carbonyl compounds (Scheme I). This process often relies on a specially designed chiral auxiliary R^1 built into the starting carbonyl compound 1, which then controls the enolate π-face selectivity in addition to an aldehyde.[1] For the *Z* enolates of certain chiral ethyl ketones or propionimides, i.e., 2 for R^2 = Me, a high level of π-face selectivity is accompanied by high syn diastereoselectivity leading to selective formation of aldol adducts 4 or 5. The use of enol borinate derivatives of α-alkoxy ketones, 6,[2] α-silyl ketones, 7,[3] and oxazolidinone imides, 8,[4] are noteworthy examples (Table I, entries 1–3).

[†] University of Cambridge.

[§] University of Illinois.

[1] Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2.

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0022-3263/90/1955-3295$02.50/0

Scheme I

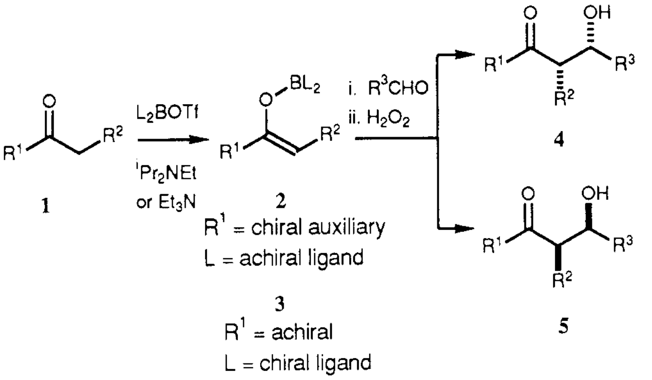
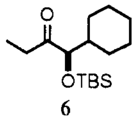
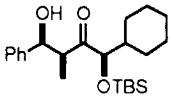
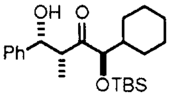
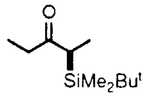
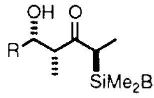
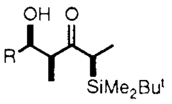
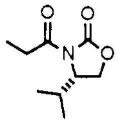
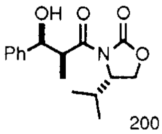
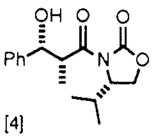
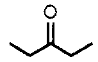
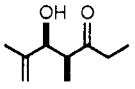
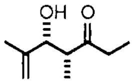
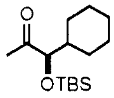
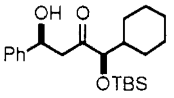
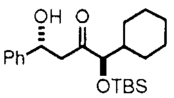
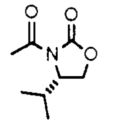
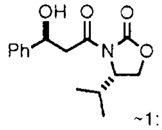
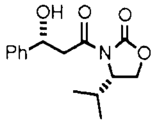
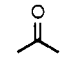
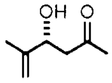
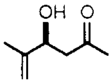


Table I. Aldol Stereoselectivities Using Chiral Enol Borinates

entry	boron reagent (aldehyde)	aldol products: major	ratio [ref]	minor
1  6	$(c\text{-}C_5H_9)_2BOTf$ (PhCHO)		75:1 [2]	
2  7	Bu_2BOTf (RCHO)		R = Me 100:1; R = Ph 1:100 [3]	
3  8	Bu_2BOTf (PhCHO)		200:1 [4]	
4 	(-)-Ipc_2BOTf (CH_2=CHMeCHO)		20:1 [8]	
5  9	9-BBN-OTf (PhCHO)		~1:1 [6]	
6  10	Bu_2BOTf (PhCHO)		~1:1 [4]	
7 	(-)-Ipc_2BOTf (CH_2=CHMeCHO)		5:1 [9]	

Absolute stereocontrol is also possible by employing chiral ligands, L, attached to boron in the enol borinate **3** in Scheme I.[5-8] For example, the reaction of the *Z*-enol diisopinocampheyl borinate derived from diethyl ketone with aldehydes proceeds with high levels of π-face selectivity and gives the syn aldol adducts in good enantiomeric excess (entry 4).[8]

In contrast to the high stereoselectivity observed for the aldol reactions of the *Z*-enol borinates **2** for R^2 = Me, the corresponding unsubstituted enols (i.e., R^2 = H) often exhibit much lower stereoselectivity, e.g., the reactions of **9** and **10** (entries 5 and 6). This effect is also noticeable in the aldol reactions of **3** for R^2 = H, i.e., using chiral ligands on boron. In the case of enol diisopinocampheyl borinates, not only is the reaction enantioselectivity lower with methyl ketones, relative to ethyl ketones, but the sense of aldehyde enantioface selectivity is also reversed (entry 7 vs entry 4).[9]

While some qualitative rationalizations of the aldol reactions in Table I have been attempted, there is no satisfactory unified model for enol borinates which accounts for all of these diverse stereochemical results.[1] With the goal of providing a workable quantitative model for investigating the conformational preferences and aldol stereoselectivities of such chiral enol borinates, we have used ab initio molecular orbital calculations[10] to augment Allinger's MM2 force field[11] for enol borinates. This approach to obtaining molecular mechanics parameters has precedent (see, for example, Bowen and Allinger's treatment of ketones and aldehydes[12]), but previously there has not been a standard procedure available for extracting all of the necessary data from ab initio calculations. The use of calculations which correspond to molecules in the gas phase to represent species in solution is considered reasonable for enol borinates, since their corresponding aldol reactions do not exhibit a strong solvent dependence.

The analysis of the full potential surface for enol borinate aldol reactions with aldehydes remains a longer term goal. Ultimately, reliable predictions of aldol stereoselectivity may then become feasible, together with the rational design of powerful new chiral boron reagents for enantioselective aldol reactions. We have already reported preliminary MM2 parameters for enol dihydro borinates[13] and now present a full set of parameters for enol dialkyl borinates. Use of this parameter set in MacroModel[14] allows the modelling of the structurally more complex chiral enol borinates of synthetic significance. The influence of both substrate and reagent centered chirality, i.e., the effect of the ligands on boron, can then each be explored.

Computational Details

Ab initio calculations were performed at the Hartree–Fock level with the 3-21G split valence basis set,[15] using the GAUSSIAN82 series of programs.[16] The nature of each stationary point was characterized via the calculation of the associated force constant matrix using analytical sec-

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[5] Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229.

[6] Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.

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[9] Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997.

[10] For other efforts along these lines, see, inter alia: (a) Spellmayer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (b) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698.

[11] (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington D.C., 1982.

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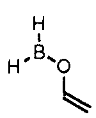
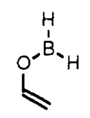
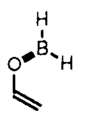
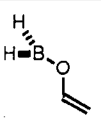
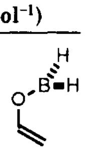
[13] Goodman, J. M.; Paterson, I.; Kahn, S. D. *Tetrahedron Lett.* **1987**, *28*, 5209.

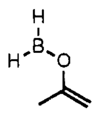
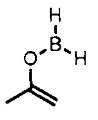
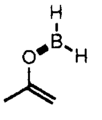
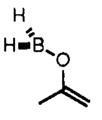
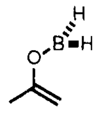
[14] Still, W. C., et al., Columbia University, New York. We thank Professor Still for a copy of the MacroModel program (version 1.1).

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

[16] GAUSSIAN82: 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: Pittsburgh, PA, 1982.

Table II. Relative Energies of Different Conformations of the Simplest Enol Borinates (energies in kcal•mol^{-1})

	 **11**	 **12**	 **13**	 **14**	 **15**
3-21G//3-21G	0.00	0.73	0.47	relaxes to *s-cis*	9.11
6-31G*//3-21G	0.00	2.53	1.78		—
6-31G*//6-31G*	0.00	2.72	1.78		—

	 **16**	 **17**	 **18**	 **19**	 **20**
3-21G//3-21G	0.00	-0.53	-0.82	relaxes to *s-cis*	7.58
6-31G*//3-21G	0.00	-0.10	-0.99		—

ond derivatives. Atomic charges were assessed through the procedure of Löwdin[17] and were used to account for the dipole moments of discrete bonds.

The 3-21G basis set is a relatively small one, but the 3-21G//3-21G level is thought to be good for closed-shell organic molecules,[18] and the use of a small basis set makes possible the study of quite large molecules (cf. substituted enol borinates). It is possible to use a larger basis set for the simplest unsubstituted enol borinate and a comparison is made in Table II. Here 6-31G*//6-31G* gives results almost identical with 6-31G*//3-21G, and this shows that the geometry of the enol borinates is not greatly altered by the use of a larger basis set. Moreover, the energies calculated by 6-31G*//3-21G and 3-21G//3-21G show the same trends. While the use of 6-31G* throughout might be more accurate, for our purposes only the relative energies, in a qualitative sense, are important in deriving the parameter set. Hence the 3-21G//3-21G level was viewed as appropriate. Furthermore, a correction for electron correlation at the 3-21G level would not improve the accuracy of the result.[19]

The five different conformations illustrated in Table II represent a thorough search of the conformational space of the system. The possibility of the oxygen atom being sp hybridized is ruled out because the structures **14** and **19** relax without barrier to **15** and **20**, respectively, passing through a linear form. This shows that a sp-hybridized structure cannot correspond to a minimum on the potential surface.

Average bond lengths and angles for monomeric enol borinate structures[20] were obtained from the calculated structures collected in the supplementary material. A mean value of 1.3865 ± 0.003 Å results for the O–B equilibrium bond length and has been used without further modification. The distribution of the B–C bond length was bimodal (1.5897 ± 0.002 Å and 1.5792 ± 0.001 Å) and the smaller value was chosen, which corresponded to the B–C bond positioned s-trans to the O–C bond, on the grounds that the longer bonds were all perturbed to some extent, by nonbonded interactions with the H or Me groups on the double bond. The difference of 0.01 Å was felt to be insignificant and would not alter the results of the modelling studies. The same bimodal distribution arose for several of the bond angles, where the largest mean to mean separation was observed for the O–B–C angle (~8°). Once again the smaller value was chosen for the force field.

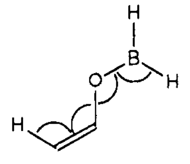


Figure 1. Selectively constrained rotation (only the marked angles are allowed to relax).

The stretching and bending parameters were extracted from the calculated force constant matrices using a harmonic approximation of the potential:

$$E_s = 71.94k_s(l - l_0)^2 \qquad E_\theta = 71.94k_\theta(\theta - \theta_0)^2$$

(for l in Å, k_s in mdyn·Å^{-1}, E in kcal·mol^{-1}, θ in radians, k_θ in mdyn·Å·rad^{-2}).

While the individual normal modes did not generally correspond uniquely to a single angle bend or bond stretch, careful analysis permitted the assignment of each normal mode to simple valence distortions of the molecule. These assignments were facilitated by comparisons with very simple systems for which the normal modes could be unambiguously assigned (e.g., $H_3C–BH_2$, and $HO–BH_2$) and with the few known literature values.[21] The assignments were confirmed by comparing all the normal modes analyses. The frequency of a particular normal mode differed by less than 2% for most structures. The frequencies which fell outside this range could be related to strain in the system concerned, shown by anomalous bond lengths or angles. Particular frequencies were absent only when the systems of atoms to which they were assigned were also absent. The improper torsional term, which has been included for out-of-plane bending of the L_2BO moiety, was also related to a particular normal mode frequency. The associated stretch–bend cross term was set to zero as this is only significant for three- and four-membered rings. Ab initio frequencies were reduced by 12% in the usual manner to correct for the systematic errors in Hartree–Fock derived harmonic force constants.[22] It has been shown that the use of a higher level of theory to obtain these values would allow the use of a smaller scaling factor, but would not improve the accuracy of the final result.[23] The van der Waals interaction terms for

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(17) Löwdin, P. O. *Phys. Rev.* **1955**, *97*, 1474.

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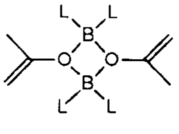
(20) Dimeric structures such as:



are unlikely to be important in the boron-mediated aldol reaction, because of the adverse steric interactions between the ligands, which would be held close to the four-membered ring by the short B–C bonds. This contrasts with the lithium-mediated reaction, for which the enolates are known to form aggregates (see, for example: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624).

(21) (a) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (b) de Moor, J. E.; van der Kelen, G. P.; Eeckhaut, Z. *J. Organmet. Chem.* **1967**, *9*, 31. (c) Axelrad, G.; Halpern, D. *J. Chem. Soc., Chem. Commun.* **1971**, 291.

(22) (a) Pople, J. A.; Schlegel, H. B.; Krishnan, R.; DeFrees, D. J.; Binkley, J. S.; Frisch, M. J.; Whiteside, R. A.; Hout, R. F., Jr.; Hehre, W. J. *Int. J. Quantum Chem.: Quantum Chem. Symp.* **1981**, *15*, 269. For an alternative scheme, see: (b) Pulay, P.; Meyer, W. *Mol. Phys.* **1974**, *27*, 473.

(23) Hout, R. F., Jr.; Levi, B. A.; Hehre, W. J. *J. Comput. Chem.* **1982**, *3*, 234.

Table III. MM2 Parameters for Enol Borinates Derived from ab Initio Molecular Orbital Theory

quantity	atoms	frequency[a]	parameter		
Bond Length			K_r[b]	r_o[c]	
	B-C	1240 (1091)	4.0268	1.5771	
	O-B	1445 (1271)	6.2081	1.3865	
Bond Angle			K_θ[d]	θ_o[e]	
	O-B-C	424 (373)	1.2427	116.688°	
	H-C-B	933 (821)	0.4540	111.588°	
	C-B-C	312 (275)	0.6095	122.070°	
	B-O-C	512 (451)	1.3247	127.808°	
	C-C-B	277 (244)	0.4900	115.524°	
Atomic Charge			Q_i[f]		
	B		0.2770		
	O		-0.2700		
	C (-B)		-0.3100		
Improper Torsion			K_ω[d]		
	O-B-C | C	1104 (972)	0.4250		
Torsional Terms[g]			V_1	V_2	V_3
	B-O-C=C		-0.9390	1.6410	-0.2529
	B-O-C-C		1.2630	1.9561	0.1957
	C-B-O-C		0.0000	4.5000	0.0000
	H-C-B-O		0.0000	0.0000	-0.0800
	H-C-B-C		0.0000	0.0000	0.0800
	H-C-C-B		0.0000	0.0000	0.7500
	C-C-B-O		0.0631	0.9738	0.4647
	C-C-B-C		0.0000	0.0000	0.0000[h]
	C-C-C-B		2.3980	-1.4400	3.5250

[a] cm^{-1} (corrected).[22] [b] mdyn·Å^{-1}. [c] Å. [d] mdyn·rad^{-2}. [e] Degrees. [f] Electrons. [g] kcal·mol^{-1}. [h] The single-point calculations did not allow us to distinguish between the C–C–B–O and the C–C–B–C contributions to the potential surface. Since in all cases, these interactions must occur together, the combined potential is given by the C–C–B–O term. The C–C–B–C term must be included for the MacroModel program to recognize the substructure.

boron were found by extrapolating from the existing force field values.

The torsional parameters V_1, V_2, and V_3, are obtained from a linear least-squares fit to the truncated Fourier expansion,[24]

$$E_{\text{torsion}} = \frac{V_1}{2}(1 + \cos(\omega)) + \frac{V_2}{2}(1 - \cos(2\omega)) + \frac{V_3}{2}(1 + \cos(3\omega))$$

where the energies were calculated using selectively constrained rotation. The rotational profile of a bond was modelled by increasing the torsional angle ω in 30° increments, minimizing at each step all the bond angles which would alleviate repulsive intramolecular interactions caused by the rotation. All other bond angles, bond lengths, and dihedral angles were held constant during the calculation. For example, the enol borinate of acetaldehyde was modelled by incrementing the C=C—O—B torsional angle in 30° steps, minimizing the four bond angles indicated in Figure 1. This gave a potential surface that fitted well to a truncated Fourier series. If the selected angles were not minimized, the fit was poor. In the simplest case, the calculation was repeated increasing ω in 10° steps, and this showed that the surface could be well represented by 30° increments. The goodness of fit to the Fourier series was evaluated by the standard deviation, σ_ω. When σ_ω was greater than 0.10 kcal·mol^{-1} the rotational profile was repeated, relaxing more bond angles. This procedure resulted in σ_ω values less than 0.07 kcal·mol^{-1} in all but one case. In this case, the C(sp^3)–C(sp^2)–O–B potential, the various attempts to improve the fit were not wholly successful. The standard deviation was reduced to 0.15 kcal·mol^{-1} (vide infra).

Table IV. MacroModel Substructure Definition for Enol Borinates

(a) Main field: van der Waals interactions for boron (specified as Z0[a])

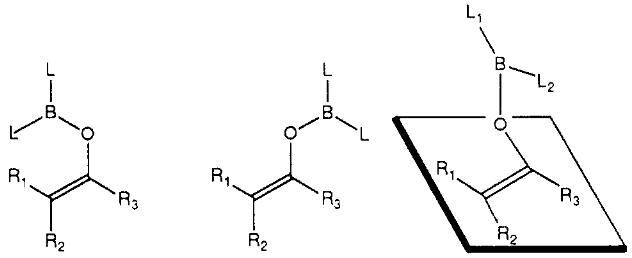
```
6   Z0          1.9800  0.0340  0.00
```

(b) Substructure: enol borinate parameters (boron specified as Z0[a])

```
-3
C  Alkyl Enol Borinate Substructure
9  C3-C3(-H1)-C3(-H1)-Z0(-C3)-O3-C2(-C3)=C2
-2
1   4  6            1.5771   4.0268
1   6  8            1.3865   6.2081
2   6  8  9       127.8080   1.3247
2   5  4  6       111.5880   0.4540
2   4  6  7       122.0700   0.6095
2   2  4  6       115.5240   0.4900
2   4  6  8       116.6880   1.2427
4   5  4  6  8      0.0000   0.0000  -0.0800
4   5  4  6  7      0.0000   0.0000   0.0800
4   3  2  4  6      0.0000   0.0000   0.7500
4   6  8  9  11    -0.9390   1.6410  -0.2529
4   6  8  9  10     1.2630   1.9561   0.1957
4   4  6  8  9      0.0000   4.5000   0.0000
4   2  4  6  8      0.0631   0.9738   0.4647
4   2  4  6  7      0.0000   0.0000   0.0000
4   1  2  4  6      2.3980  -1.4480   3.5250
5   6  8  4  7      0.0000   0.4250
-4
8  -0.1400 -0.1400  0.0800 -0.3100  0.1100  0.2770 -0.3100
```

[a] MacroModel is designed to have one user defined atom, Z0. We assign it as boron.

Scheme II



21 *s-cis*

22 *s-trans*

23 *non-planar*

The definition of bond stretching and angle bending parameters gives the force field an implicit potential surface for torsional angles. This was investigated by setting V_1, V_2, V_3 = 0 kcal·mol^{-1}, and carrying out single point calculations with the constrained molecules in the MM2 force field, analogous to the calculations using GAUSSIAN82. This potential surface was also fitted to the Fourier series, to give terms V_1^{MM2}, V_2^{MM2}, and V_3^{MM2}. These values were subtracted from the ab initio terms, V_1^{G82}, V_2^{G82}, and V_3^{G82}. The differences were incorporated into the MM2 force field in the MacroModel program as a substructure, as summarized in Tables III and IV. We call this process SCRIPTION (Selectively Constrained Rotation, Implicit Potential correcTION), and we believe that SCRIPTION could be used to advantage in deriving parameters for other systems.

Enol Borinate Structure. The earlier work of Hoffmann[25] and Gennari,[26] supported the assignment of the conformational minima corresponding to the planar forms

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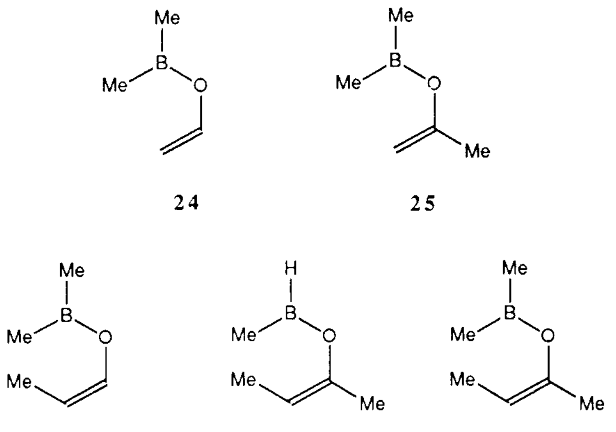
(24) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371.

(25) Hoffmann, R. W.; Ditrich, K.; Fröch, S.; Cremer, D. *Tetrahedron* **1985**, *41*, 5517.

(26) Gennari, C.; Todeschini, R.; Beretta, M. G.; Favini, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 612.

Scheme III

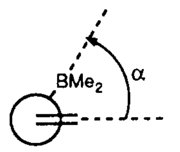


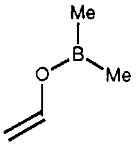
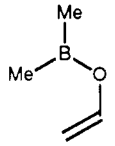
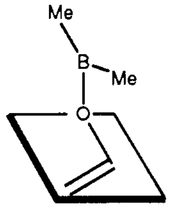
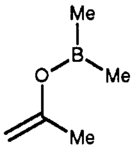
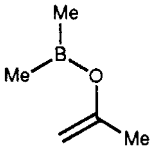
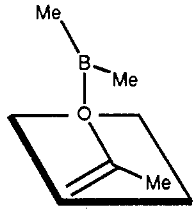
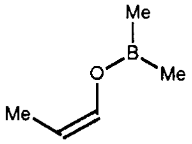
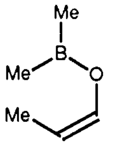
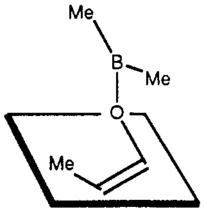
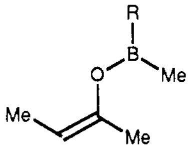
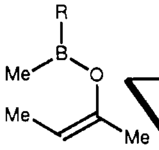
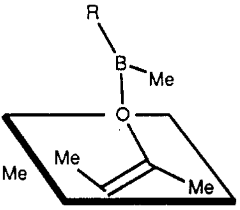
21 and 22 (Scheme II). Our original study for enol dihydroborinates[13] concentrated on such conformations. We have found that the *nonplanar* structures 23, for which the O-B bond is not parallel to the C=C bond, are preferred in most cases, despite the loss of conjugation between the double bond, the oxygen lone pair, and the vacant orbital on the boron. This is more than compensated by the decreased steric interaction between the alkyl ligands on the boron and the double bond substituents. In this present work, we have investigated not only the s-cis 21 and s-trans conformations 22, but also the nonplanar conformations 23, which, in many cases, proved to be of lowest energy.

The results of the calculations on the simple enol borinates, 21, 22, and 23, using GAUSSIAN82 are given in the supplementary material. Owing to computational size limitations, no more than three of the substituents may be methyl groups. The rest must be hydrogens. As the size of the alkyl ligand L_2 on boron increases, the s-cis and s-trans structures are found to rise almost equally in energy, and the nonplanar forms are increasingly favored. If R_1 = H is replaced by a R_1 = Me group in these calculations, then the C=C—O—B dihedral angle increases from about 40° to about 65° for L_2 = H and from 55° to 90° for L_2 = Me. The L_1L_2B-O-C moiety tends to remain approximately planar, with a barrier of about 10 kcal·mol^{-1} to rotation about the O-B bond. In the nonplanar structures, the L_1L_2BO moiety pyramidalizes slightly, with L_2 being pushed out of the plane, away from the double bond. This slight pyramidalization may make the face of the boron on the side of the double bond (i.e., the apex of the pyramid) more susceptible to nucleophilic attack by the aldehyde carbonyl oxygen, since the vacant orbital has become more accessible on this side.

Since the conformational preferences of enol borinates are not well-characterized, the reliability of the force field is hard to assess. There is little direct experimental evidence, with which to compare the results. Using NOE studies on a related system, Hoffmann[25] concluded that the s-cis structure 21 is the preferred conformation. However, the possibility of *nonplanar* structures, such as 23, which are also consistent with the data, was not considered. In the absence of other experimental data, the force field has been checked by comparing the structures it predicts with the structures found by GAUSSIAN82. The data for the force field were derived mainly from the various different conformations of 24 and 25 (Scheme III). Ab initio calculations were also performed on 26 and 27. We checked, therefore, that these structures could be modelled accurately by the proposed parameter set.

Table V. Comparison of Empirical and ab Initio Energies (kcal•mol^{-1})



				α (°)
ab initio	0.00	-1.60	-0.74	50
empirical	0.00	-1.80	-1.17	46
				
ab initio	0.00	-2.10	-3.24	53
empirical	0.00	-2.11	-3.24	44
				
ab initio	0.00	9.56	relaxes without barrier to *s-trans*, for both models	
empirical	0.00	12.13		
				
ab initio (R = H)	0.00	6.71	-2.35	90
empirical (R =Me)	0.00	10.02	-2.97	69

First it was verified that 24 and 25 were well-represented. As can be seen from the results in Table V, the energies are well reproduced in both cases. As was mentioned above the C(sp^3)-C(sp^2)-O-B potential fitted the truncated Fourier series less well than the other torsional potentials. This is probably due to the complicated nonbonding interactions in this case, between the ligands on the boron and the enolate substituents. The potential surface for the rotation is fairly flat in the region of the minimum. The difference of 9° between the ab initio value for the dihedral angle α and the empirical one is unlikely to be significant, when bulkier groups are attached to the boron. The difficulty in fitting this potential is compounded by the systematic difference between the ab initio values for bond lengths and the values already found in the force field, the latter being longer by about 2%, as shown in Figure 2. This small difference is due to the use of electron diffraction data and not ab initio data for defining the bond lengths in the main body of the force field, and it will lead to an increase in the interaction between

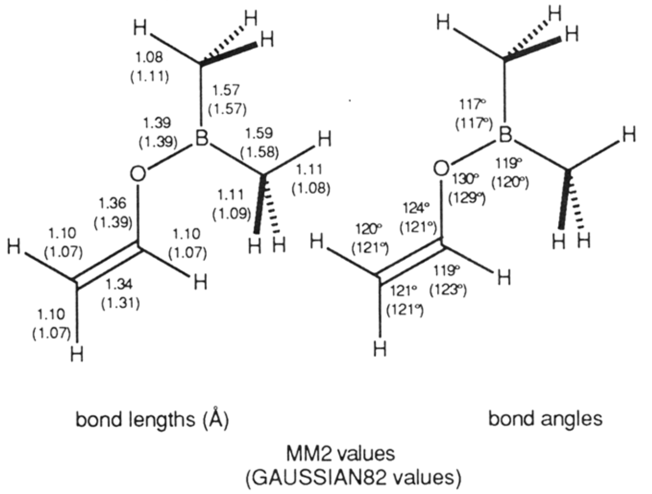


Figure 2. Comparisons between empirical and ab initio structural minima.

the methyl groups on the boron, and the methyl group on the double bond. This will tend to decrease the value of α for the empirical calculation. It was decided that it was best to leave this inconsistency uncorrected, rather than trying to adjust all new parameters to be in line with the standard MM2 parameters, since this process of "correction" would introduce new errors which would be much harder to quantify.

It would have been disturbing had the MM2 predictions been very different from the ab initio calculations for **24** and **25**; the fact that they are very similar is not particularly significant, since this merely confirms that the force field can well reproduce the data used to produce it, and does not indicate whether it could have any predictive use. The comparison of **26** and **27** is more interesting. Since **28** is too large for ab initio calculations, using the computers that were available, the calculations were performed instead on **27**. The discrepancy between the ab initio and the molecular mechanics values for **26** is acceptably small. The s-cis form of an *E*-enol borinate is highly strained and so the inconsistency between the standard MM2 parameters and our new parameters is accentuated. This is because the force field uses a harmonic approximation to the potential energy function, which becomes unreliable in highly distorted structures. The difference between the actual potential surface and the harmonic approximation suggests that the force field will predict too high a value for the energy of a greatly distorted structure. This fits with the observed behavior of our force field. This same problem is also present for **27**, exacerbated by the need to do the modelling on two different molecules. The lack of a methyl group in the ab initio case might be expected to allow the Me–B–O angle to widen more easily, further lowering the energy of the ab initio calculated s-cis form with respect to the force field energy.

Application of the Force Field to Chiral Enol Borinates. The force field has been used for calculations on enol borinates with chiral ligands on boron for which experimental results are already known.[8,9] These enol borinates react rapidly with aldehydes, under conditions of kinetic control, to give boron aldolates, which have a syn stereochemical relationship if the enolate has the *Z* configuration.[1,27] This diastereoselectivity is usually explained by a Zimmerman–Traxler cyclic transition state,[28] in which the aldehyde first coordinates the boron,[29] followed by carbon–carbon bond formation via a chair-like system. Various empirical and qualitative attempts have been made to account for enolate π-face selectivity in such situations,[1-6] but none have found general favor.

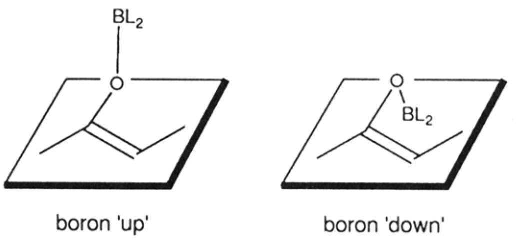
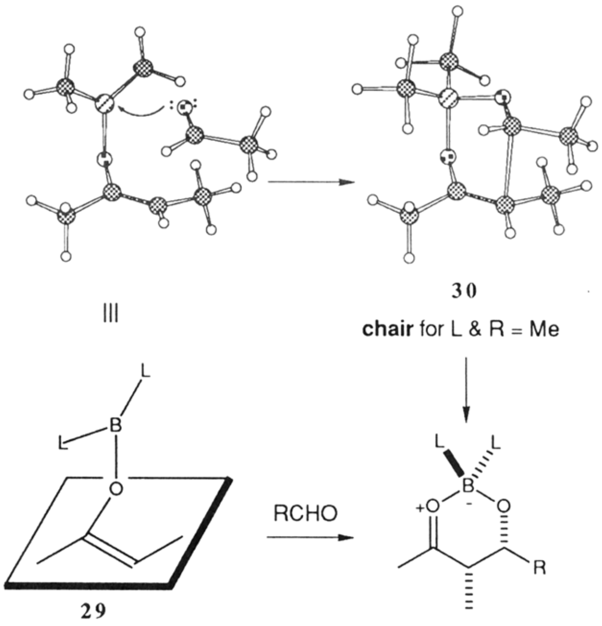


Figure 3. The two possible enol borinate conformations.

Scheme IV



For all enol borinates derived from ketones, the B—O—C=C moiety is calculated to be nonplanar. This is a prediction that has not been confirmed by experiment, although it is consistent with the little experimental data available.[25] We confidently hope that future experiments will confirm this prediction.

For enol borinates derived from achiral ketones and ligands, two enantiomeric forms will exist: boron "up" and boron "down" as shown in Figure 3. If the ketone or the ligands are chiral, then these two forms will effectively be diastereomeric, and so have different energies. If the energy difference is sufficiently large, then only one of the two groups of conformers will have significant population, and so the π-faces will become nonequivalent.

The nonplanar enol borinates, as depicted by **29**, require only a small change in their geometry to access a Zim-

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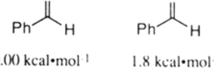
[27] Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* *13*, 1.

[28] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[29] It seems likely that the aldehyde will prefer to coordinate the boron with its alkyl chain away from the Lewis acid. Experimental results[8] show that the stereoselectivity seems to increase if a bulky aldehyde is used, which would probably help fix the configuration of the complex. This is confirmed, in a similar case, by Reetz's calculations, although the two configurations are surprisingly close in energy:



0.00 kcal•mol^{-1} 1.8 kcal•mol^{-1}

(a) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. See also: (b) LePage, T. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 6642. (c) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

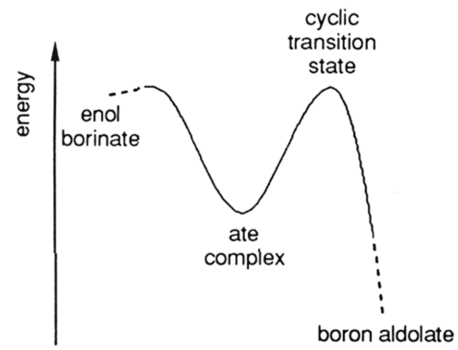
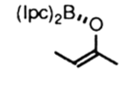
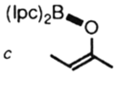
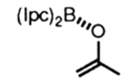
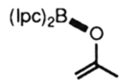


Figure 4. The reaction coordinate for the enol borinate of acetaldehyde reacting with formaldehyde.

merman–Traxler transition state as shown in Scheme IV. The aldehyde may prefer to attack the appropriate face of the boron, because of the pyramidalization of this atom. The boron is not quite planar sp^2 but is slightly twisted, because the double bond of the enol pushes the lower ligand out of the plane. This gives the boron some sp^3 character, with the vacant orbital pointing toward the enol double bond. Paquette[30a] and Houk[30b] suggest that such pyramidalization may have an important effect in controlling the stereochemistry of additions to alkenes. In the same way, the small pyramidalization of the boron may encourage the aldehyde oxygen to attack the inner face in **29**. This leads directly to the Zimmerman–Traxler transition state **30**. It may be, therefore, that the predominant enol borinate geometry influences the preferred geometry of the transition state and so the stereochemistry of the final product. The reaction coordinate may be sketched using our calculations and those of Houk[31] for the case of acetaldehyde reacting with formaldehyde with hydrogen ligands on the boron; this is illustrated in Figure 4. It shows, in this case, that the starting materials and the aldol transition state have about the same energy. It is not obvious how the relative energies of the transition states and the starting materials will change for synthetically significant reactions. If the energy of the aldol cyclic transition state rises, then this transition state will control the reaction. If the energy of the aldol transition state drops, relative to the reactants, then the transition state for the formation of the "*ate*" *complex* will have an important role to play and this will be very similar to the isolated enol borinate, by application of the Hammond postulate.[32] If the latter situation applies, then the force field may perhaps be used to predict the stereochemistry of the aldolate, by calculating the conformational preferences of the enol borinate. In the latter case, the conformational preferences of the enol borinate may be related to the stereochemistry of the aldolate, and this can be investigated using the force field. We have investigated this approach to calculating aldol stereoselectivity by analyzing the preferred enol borinate conformations of reactions for which there are experimental data.

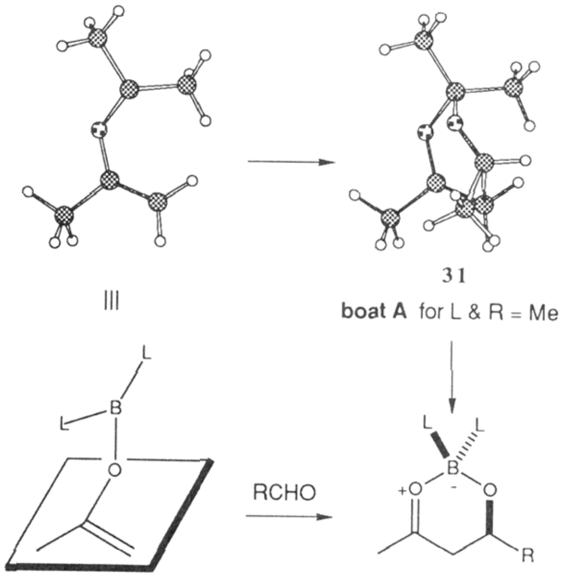
The lowest energy conformation found for the *Z*-enol diisopinocampheyl borinate derived from 2-butanone is illustrated in Figure 5 as a stereoview.[33] Assuming that the aldehyde attacks the inner face of the boron and that C–C bond formation proceeds through a Zimmerman–Traxler chair transition state with the R group of the aldehyde equatorial, as in **29** → **30** in Scheme IV, this conformer would give the observed product stereochemistry. The ratios of the two enol borinate forms (i.e., boron "up" and boron "down") were calculated assuming a Boltzmann distribution at the temperature of the experiment. The ratios of the two groups of conformers, as summarized in entry 1 of Table VI, is only 5:2 at −78 °C, compared with the observed reaction enantioselectivity of 27:1 (i.e., 93% ee).[13] However, if all the conformers for which α is greater than 100° are excluded from the calculations, on the grounds that in such conformers the enolate and the aldehyde carbonyl carbons are too distant to interact, the selectivity is now calculated to be 35:1. Similar studies were performed on some enol borinates derived from chiral ketones (i.e., substrate centered chirality), but the correlation between the enol borinate geometry and the product stereochemistry was poor.

Table VI. Calculated Ratios of Enol Borinate Conformers vs Observed Aldol Stereoselectivities

	enol borinate conformers modeled[a,b] calculated ratio			experimental aldol isomer ratio (see Table I)
entry	major		minor	
1		5:2 or 35:1[c]		27:1[8]
2		3:1		1:5[9]

[a] $(Ipc)_2B$ from (+)-α-pinene. [b] The ratios of isomers were obtained by thoroughly sampling the conformational space of each enol borinate, using the Multiconformer option of MacroModel. The starting conformations were generated using 60° increments for all dihedral angles, except for the methyl groups. [c] Ratio calculated ignoring conformations with α > 100°.

Scheme V



The force field shows that the reversal in selectivity which is observed for methyl ketones using enol diisopinocampheyl borinates does not correspond to a reversal in the preferred conformation of the enol borinate, as shown by the calculated ratio in entry 2 of Table VI. This is most likely due to the accessibility of competing transition states. Evans[27] has suggested that the chair and boat transition states have similar energies in some systems.

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(33) Jones, R. *Nature (London)*, **1989**, *339*, 433.

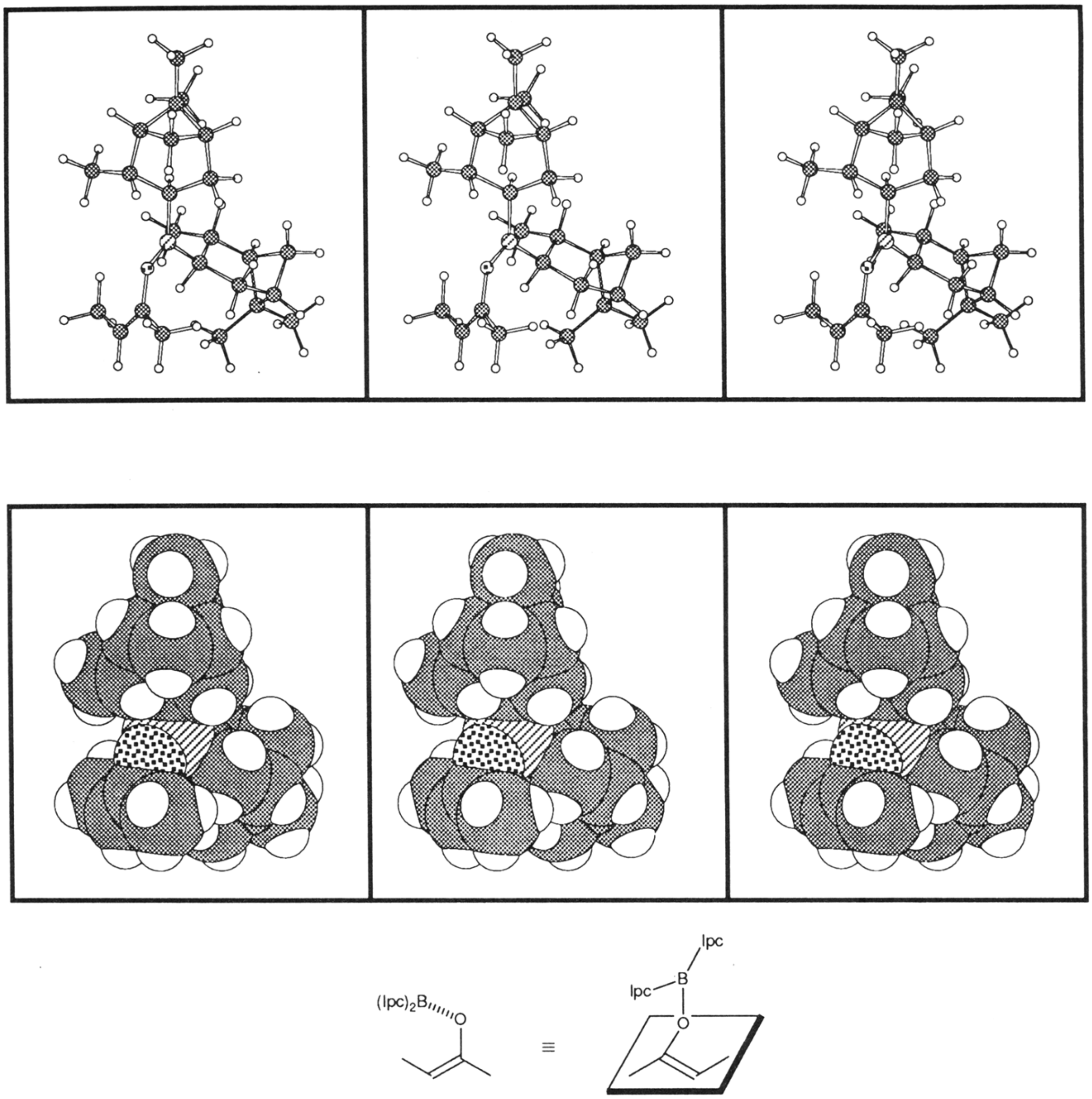


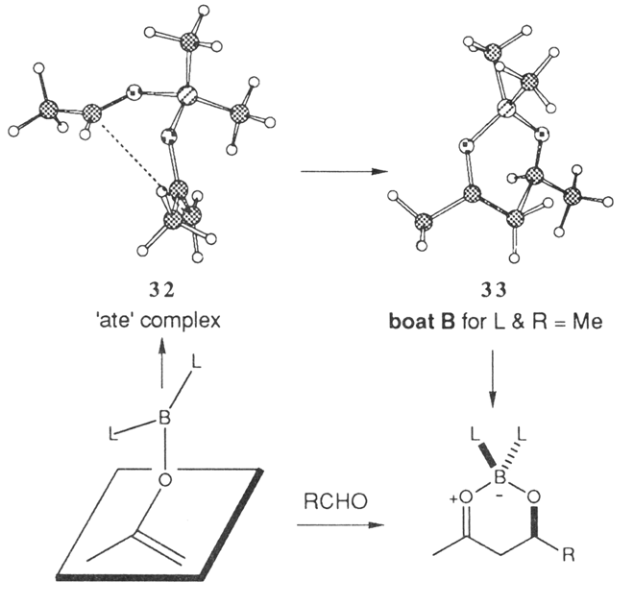
Figure 5. Stereoviews[33] and schematic representations of the lowest energy conformation for the *Z*-enol diisopinocampheyl borinate of 2-butanone using (−)-Ipc_2BOTf.

Houk[31] has supported this idea with calculations carried out at the HF/3-21G level on the reaction of the enol dihydro borinate of acetaldehyde with formaldehyde. Houk reported a chair transition structure, corresponding to the Zimmerman–Traxler transition state **30** shown in Scheme IV, and a twist–boat transition state, corresponding to boat A **31** in Scheme V. Boat A is 1.4 kcal·mol^{-1} lower in energy than the chair. This energy gap is small and so both transition states may be accessible in synthetically significant systems. Boat A is raised in energy by the addition of a *Z*-methyl group on the double bond, suggesting that this may be a better transition structure for methyl ketones than for ethyl ketones.

Preliminary calculations on the formation of the aldehyde "ate" complex have shown that a low-energy conformation has the long O–B bond crossing the plane of the enol borinate, as shown in Scheme VI. Such a conformation is almost certain to be accessible for enol borinates from methyl ketones, though it will not necessarily have the lowest energy. It is probably not accessible for *Z*-enolates from ethyl ketones, because the *Z*-methyl group would destabilize it by interfering with the ligands on the boron. If this is an accessible conformation, then a boat-like transition state **33** naturally follows, which is different from boat A. We have located a saddle point on the HF/3-21G potential surface reaction of the enol dihydro borinate of acetaldehyde with formaldehyde, which corresponds to **33**. This further transition state, referred to as boat B, like boat A leads to the reversed stereochemistry relative to the chair transition state and is only 0.4 kcal·mol^{-1} higher in energy than the chair transition state found by Houk. Methyl ketones may then have three competing reaction pathways, one going through a chair transition state as in Scheme IV, the other two going through boats as in Schemes V and VI. The boat transition states would both give rise to the reversed sense of aldehyde enantioface selectivity that is observed for methyl ketones, and the lower selectivity may be attributed to the competing reaction pathway through the chair transition state.

J. Org. Chem. **1990**, *55*, 3303–3310

Scheme VI



Conclusions

The force field developed enables the prediction of preferred enol borinate geometries in synthetically useful chiral systems. The preferred geometry is calculated to be nonplanar in all cases, and we look forward to an experimental test of this prediction. The preferred geometry appears to be decided by a large number of competing effects, rather than one or two factors, and so cannot be easily considered by model building, nor by a simple division of the substituents at the chiral centers into large, medium, and small groups. Studies of these systems using the force field suggest that the sense of π-face stereoselectivity may be predicted from the preferred enol borinate conformation using a Zimmerman–Traxler argument for *Z*-methyl enol borinates, with isopinocampheyl ligands as the chiral directing groups. If the chiral directing group is in the ketone, the enol borinate geometry does not appear to be directly related to the observed aldol product stereochemistry. Here the structure of the "ate" complex and the aldol transition state must be important and we are now considering these in more detail.

The calculations have suggested a possible explanation for the surprising reverse in the sense of aldehyde enantioface selectivity between methyl and ethyl ketones using enol diisopinocampheyl borinates. The reversed sense of the stereoselectivity may be due to competing transition states and not to different enolate π-face selectivity.

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Supplementary Material Available: A listing of all enol borinate structures discussed (31 pages). Ordering information is given on any current masthead page.

On the Regioselectivity of 4-Nitroanisole Photosubstitution with Primary Amines. A Mechanistic and Theoretical Study

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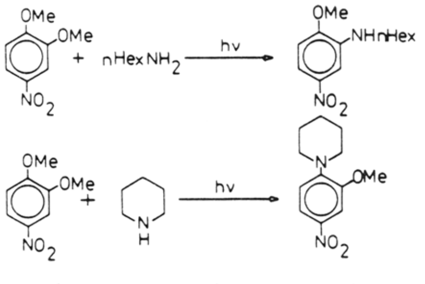
4-Nitroanisole photoreacts with *n*-hexylamine and ethyl glycinate, giving rise to regioselective methoxy and nitro group photosubstitution, respectively. Mechanistic evidence indicates that the latter is produced through a $S_N2^3Ar^*$ reaction, whereas the former arises from a radical ion pair via electron transfer from the amine to a 4-nitroanisole triplet excited state. AM1 semiempirical calculations on the actually involved excited states and intermediates indicate that the change of regioselectivity between the ground-state and the triplet-state substitution can be justified on the basis of frontier orbital considerations. On the other hand, neither the frontier orbital nor the net charge can explain the regioselectivity when the reaction involves electron transfer. A discussion of the influence of other previously neglected factors such as the intermediate stabilities is advanced.

Introduction

Nucleophilic aromatic photosubstitutions have been the object of intense research since their discovery in 1956.[1] In spite of the effort, mechanistic studies have been for years restricted almost to photohydrolysis reactions.[2-4] Many reported experimental facts remain unexplained, especially in cases when nucleophiles others than OH^- are used.

Scheme I



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