Origins of Stereoselectivity in the Addition of Chiral Allyl- and Crotylboranes to Aldehydes: The Development and Application of a Force Field Model of the Transition State

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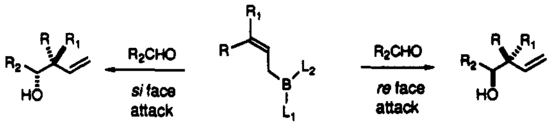
A molecular mechanics model of the transition state for the addition of allyl- and crotylboranes to aldehydes was developed based on ab initio calculations. A force field was created (FF1), based on a process of trial and error optimization, which reproduces the relative energies and geometries of the chairlike ab initio transition structures. An automated procedure for the optimization of the torsional parameters was developed and used to improve the way the force field reproduces the ab initio data (geometries and relative energies). The optimized force field (FF2) reproduces the syn-anti selectivity of *E* and *Z* crotylborane addition to aldehydes. The force field is used to analyze the stereoselectivity of various synthetically interesting reactions. The model reproduces the sense and degree of stereoselectivity in a number of cases.

The stereocontrolled formation of carbon–carbon bonds is of great importance in organic synthesis.[1] Among the available methods, the aldol reaction of metal enolates with aldehydes is one of the most useful and widely used for acyclic stereocontrol[1b–g] and constitutes one of the fundamental carbon–carbon bond constructions in biosynthesis. The addition reaction of allylmetal reagents to aldehydes is an alternative approach.[1a,2]

Like the aldol reaction of metal enolates, the addition of a crotyl metal reagent to an aldehyde generates two new stereocenters and can potentially give rise to four stereoisomers. In particular, the use of allyl- and crotylborane reagents has been shown to be a valuable method for the construction of carbon–carbon bonds with excellent stereocontrol (Scheme I).[1a] The stereochemical results have been rationalized in terms of a chairlike six-center cyclic transition state. Recently, Houk et al. located chair and twist-boat transition structures for the reaction of formaldehyde with allylborane using ab initio molecular orbital calculations at the RHF/6-31G*//3-21G level (**1**, **2**; Figure 1).[3a] The twist-boat transition structure was calculated to be ≥8 kcal mol^{-1} higher in energy than the chair.[3a]

By transferring these ab initio calculated structural parameters to a force field environment, Hoffmann et al. have developed a force field model for the allylboration reaction,[4] following an approach pioneered by Houk.[3b,c] In the Hoffmann study, the geometry of the ab initio core transition structure was kept rigid and used as a model of the transition state ("fixed core" procedure). This model was used to rationalize the asymmetric induction in the reaction of allyl and crotyl boronates with chiral aldehydes.[4]

Scheme I



We report here the development of a force field model using a "flexible core" procedure, which allows all the atoms of the core transition structure to move. This implied using ab initio molecular orbital calculations to locate a certain number of substituted transition structures (**3**–**11**; Figure 1). This model is able to reproduce the stereoselectivity of known reactions of allyl and crotyl boranes with aldehydes. We also discuss the use of this force field approach for rationalizing the observed stereoselectivity of various chiral allyl- and crotylborane additions to aldehydes in synthetically useful reactions. This model has successfully reproduced experimental results and therefore may have predictive value in new situations.

Results and Discussion

We recently described a force field model for the aldol reactions of ketone-derived enol borinates with aldehydes.[5a] This force field was based on MM2[6a,b] as implemented in Still's MacroModel,[6c] new parameters developed from ab initio calculations on the cyclic aldol transition structures (chair and boat), and trial and error optimization.[5a] The model reproduces the aldehyde *si*/*re* selectivity for the

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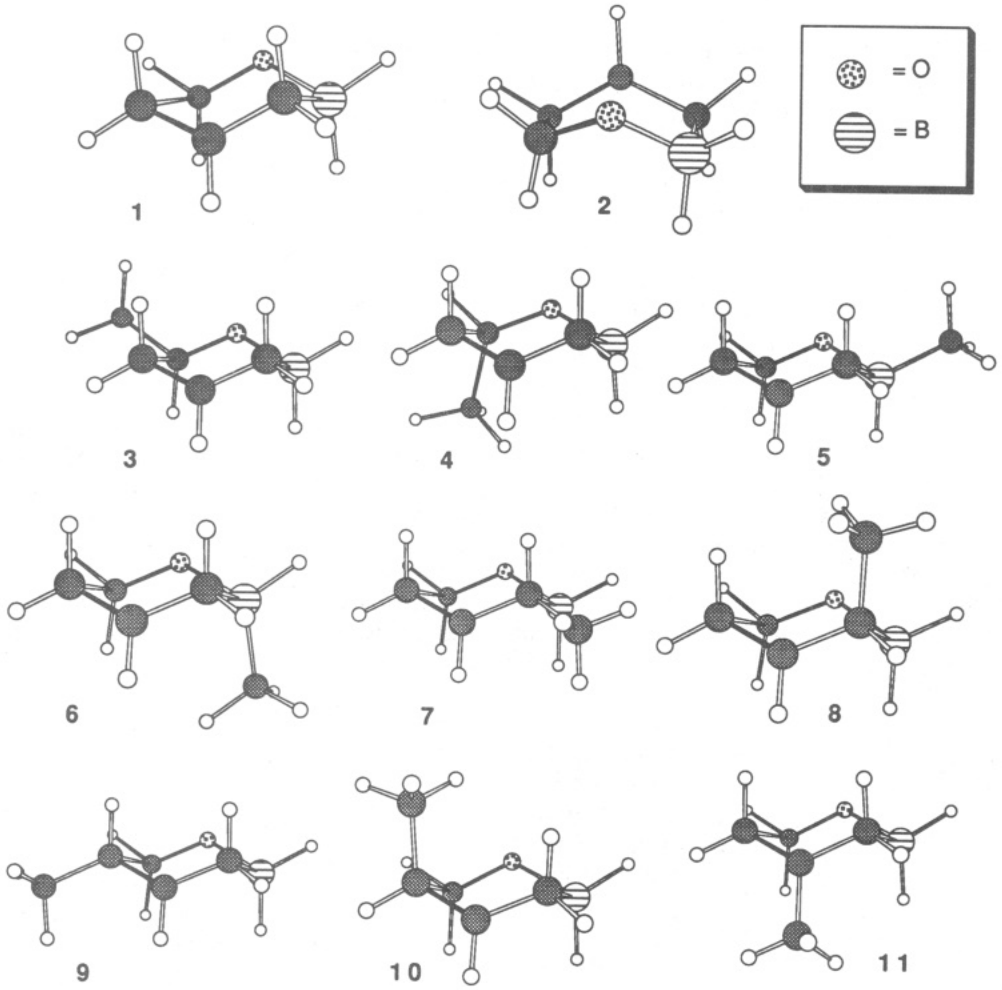

Figure 1. Ab initio calculated transition structures: "all-hydrogen" cases (**1**, **2**) and monomethyl-substituted cases (**3**–**11**).

syn-selective aldol reactions of a range of chiral *Z* enol borinates,[5a–c] as well as for the anti-selective reactions of *E* enolates.[5d]

The success of this model led us to develop a force field for the reaction of allyl- and crotylboranes with aldehydes. The model assumes that the experimental stereoselectivity, obtained under kinetically controlled conditions, is determined by the relative energies of all the competing transition structures; i.e., the reaction is within the boundaries of the Curtin–Hammett principle.[7] The work was organized in the following two phases: first, the relevant transition structures for the addition reactions were determined using ab initio molecular orbital calculations. Second, based on the ab initio data a set of empirical force field parameters for those bonds that are forming or breaking was created and optimized to augment the MM2 force field.

Ab Initio Calculations. Ab initio molecular orbital calculations were carried out with the Gaussian-90 program[8] at the RHF level with the 3-21G basis set.[9] We started from the chair (**1**) and twist-boat (**2**) transition structures (Figure 1) for the allylborane addition to formaldehyde (the "all-hydrogen" case), for which the ab initio geometries and energies were available from the work of Houk.[3a] We then located nine additional transition structures (**3**–**11**) by replacing one hydrogen at a time with a methyl group in the nine possible positions of the "all-hydrogen" chair. The geometry of this new methyl group was locally optimized using the Berny optimization algorithm with gradient calculation,[10a] and then the transition structures were located using an eigenvector-following optimization method.[10b] Each stationary point was characterized according to the eigenvalues of the final force constant Hessian matrix, and all had only one negative eigenvalue. The optimized geometries are shown in Figure 1 (structures **3**–**11**; energies and Cartesian coordinates available in the supplementary material). The corresponding boatlike transition structures were not considered because they are likely to be much higher in energy (≥ 8 kcal mol^{-1}).[3a]

Force Field Development: Trial and Error (FF1). For the second phase of the procedure, i.e., the creation

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of appropriate parameters for the force field, we made use of the existing parameters for boron (van der Waals radius, ϵ).[11] Bond angles and lengths were assigned from the average of the ab initio values. The corresponding force constants were either taken from Allinger's MM2 force field[6a,b] or from those developed for the aldol reaction of enol borinates,[5a] adjusting them as it seemed appropriate. The forming carbon–carbon bond was assigned a "zero-order" bond and given a small force-constant (3.0 mdyn Å^{-1}).

The nonbonded electrostatic interactions were modeled by assigning a partial charge to each atom.[12a] Earlier studies have shown that molecular electrostatic potential (MEP)-derived analyses of charge distributions did not give improved force fields for the boron aldol reaction.[12b] Therefore, charges derived from Mulliken population analyses were used,[13] scaled by a correction factor (divided by 2.5–4.5) so that they became comparable in size to the CHELPG charges (MEP-derived) used for the boron enolate aldol force field.[12b]

Torsional parameters were added as necessary to hold the geometries and the relative energies to the ab initio values. The sizes of the torsional terms V_1, V_2, and V_3 were found following Allinger's recommendations[14] and by trial and error. Out-of-plane bending terms were set to zero for all the sp^2 carbons.

In this way, a force field was created (FF1), which can reproduce the relative energies and geometries of the chairlike ab initio structures (1, 3–11). This force field was unable to duplicate the geometry of the twist-boat transition structure (2) and to reproduce the relative energies of the unsubstituted chair and twist-boat transition structures (1 and 2, ≥8 kcal mol^{-1} energy difference by ab initio calculations). The twist-boat collapses, during the minimization process using FF1, to a different boat structure, ca. 4 kcal mol^{-1} above the chair. Nevertheless, the FF1 force field is a reasonable model and is able to give a good agreement between the calculated and the experimentally observed stereoselectivities for allyl- and crotylborane aldol additions (vide infra) because the twist-boat transition structure is high enough in energy to be insignificant.

Force Field Development: Automatic Optimization of the Parameters (FF2). In general, torsional parameters (V_1, V_2, V_3) are hard to assign because they have no direct physical significance and so cannot be fitted to anything that can be directly measured or calculated. The quality of a force field can be judged quantitatively by the rms (root mean square) difference between the ab initio and force field values for the relative energies of the transition structures (P_{energy}) and from the rms difference between the ab initio and force field torsional angles (P_{angle}). We used an automated procedure to optimize the torsional parameters of the FF1 force field so that P_{energy} and P_{angle} were reduced. The procedure generates a "trial" force field by changing the value of each of the torsion angle parameters in the best force field available (as judged by P_{energy}) by a small amount. The small increments applied to each of the parameters at each iteration of the program are not random but are chosen by analysis of how the current force field performs such that a new one should be an improvement. This process (described in the Methods section) produced a new force field (FF2, Table I), which gives a better fit to the ab initio data, as judged by P_{energy} [P_{energy}(FF1) = 4.09; P_{energy}(FF2) = 0.82].[15]

At first, each successive force field the program suggested was an improvement on the previous one. After a while, however, the program would suggest force fields that were not as good as their predecessors. This was usually because one of the transition structures had changed conformation on minimization. Torsional parameter optimization by this method may gradually reduce the barrier between two transition structures. The change between a very small barrier and no barrier may be small, in terms of the change in the parameters, but dramatic, in its effect on P_{energy}, because two different transition structures will suddenly begin to be minimized to the same geometry, and so the new force field is likely to be not as good as its predecessor. In this situation, the program goes back to the best force field it has found so far and introduces a random multiplication factor into the calculated increments to the torsional parameters of the next force field, in order to avoid duplication of effort.

FF2 was developed from FF1, which was already quite a good force field. The program was also tested by starting from a force field in which all the torsional parameters were set to zero. This led to the development of a third force field, FF3, which was able to reproduce the ab initio energies and geometries surprisingly well [P_{energy}(FF3) = 1.89]. However, the double bonds in the transition structures were not given high barriers to rotation. This result may be linked to the observation that repeated iterations of the program eventually lead to worse force fields that do not maintain the integrity of all the transition structures.

No information about the higher energy regions of the potential energy hyperspace is available from the ab initio calculations. This kind of information is crucial to the development of torsional parameters for ground-state force fields. For example, the H–C–C–H torsional parameter is calculated using a knowledge of the barrier to rotation about the C–C bond in ethane. This leads to the conclusion that FF2 is likely to be more useful in the interpretation of experimental results than FF3 because the torsional parameters are based on those in FF1 which were taken,

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(12) (a) MacroModel uses the partial charge (optional in MM2) treatment of electrostatics instead of the MM2 standard dipole–dipole electrostatics. The MacroModel default is to use a distance-dependent dielectric ($\epsilon_r = r$ in atomic units). (b) Bernardi, A.; Cassinari, A.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4183.

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(15) FF2 represents an improvement over FF1, mainly because of the better description of the high-energy ab initio twist-boat structure, which the FF2 force field locates 7.49 kcal mol^{-1} higher in energy than the chair, and with a geometry very similar to the ab initio structure 2. FF2 locates this structure as a saddle point using both the PRCG (Polak–Ribiere conjugate gradient)[16a] and the TNCG (truncated Newton conjugate gradient)[16b] minimization methods during the optimization process. Further minimization of this structure (with a different minimization method than that used in the optimization process, e.g., TNCG after PRCG or PRCG after TNCG) leads to a twist-boat which is a minimum 5.80 kcal mol^{-1} higher in energy than the chair and also very similar to the ab initio twist-boat structure. The optimization program was misled into using the saddle-point as a true minimum, and so optimized the field toward it. However, FF2 behaves quite well despite this because the +7.49 kcal mol^{-1} twist-boat (f.f. saddle point) is similar in geometry to the +5.80 kcal mol^{-1} twist-boat (f.f. minimum) and to the +8.30 kcal mol^{-1} twist-boat (ab initio transition structure).

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Table I. Force Field Parameters for Allyl- and Crotylborane Transition Structures (FF2)

	main force field			radius (Å)	E (kcal mol^{-1})	offset (Å)	
6	Z0			1.9800	0.0340	0.0000	
						Substructure	
−3							
C	allyl borane transition state: charges						
9	Z0–C3–C2═C2·C2═O2 (.1)						
−4							
8	−0.0500		−0.0600	0.0400	−0.0250	0.2750	−0.1800
−3							
C	allyl borane transition state						
9	Z0–C3–C2═C2·C2═O2 (.1)						
−2							
1	1	H1			1.0999	4.6000	
1	2	H1			1.0000	4.6000	
1	3	H1			1.0000	4.6000	
1	4	H1			0.9900	4.6000	
1	5	H1			0.9800	4.6000	
1	1	C3			1.6120	4.0000	
1	1	2			1.6810	4.5000	
1	2	3			1.4560	4.5000	
1	3	4			1.3540	9.6000	
1	4	5			2.2700	3.0000	
1	5	6			1.2690	8.0000	
1	6	1			1.5570	5.5000	
2	C3	1	C3		118.0000	0.3000	
2	C3	5	4		101.0000	0.1000	
2	C3	4	5		96.3000	0.3000	
2	C3	1	2		113.2000	0.3000	
2	C3	1	6		110.8000	0.1000	
2	H1	C3	1		111.7000	0.3000	
2	C3	1	H1		115.8000	0.3000	
2	C3	2	3		115.1000	0.4000	
2	C3	2	1		108.5000	0.4000	
2	C3	4	3		123.5000	0.4000	
2	2	1	6		100.5100	0.3000	
2	1	6	5		121.6100	0.7700	
2	6	5	4		102.4400	0.4600	
2	5	4	3		88.7200	0.3800	
2	4	3	2		124.1600	0.5000	
2	3	2	1		107.0000	0.3000	
2	H1	4	5		97.7500	0.1000	
2	4	5	H1		91.7900	0.1000	
2	6	1	H1		110.0100	0.1000	
2	H1	1	H1		116.1100	0.3000	
2	H1	1	2		110.3500	0.3000	
2	H1	4	3		120.3300	0.3000	
2	H1	4	H1		116.5800	0.3000	
2	H1	3	4		117.9200	0.3000	
2	2	3	H1		112.8200	0.3000	
2	H1	2	3		112.8200	0.3000	
2	1	2	H1		106.4300	0.1000	
2	H1	2	H1		110.6200	0.3000	
2	C3	4	5		96.3000	0.3000	
4	00	1	2	00	0.0000	0.0000	0.0000
4	00	2	3	00	0.0000	0.0000	0.0000
4	00	3	4	00	0.0000	0.0000	0.0000
4	00	4	5	00	0.0000	0.0000	0.0000
4	00	5	6	00	0.0000	0.0000	0.0000
4	00	6	1	00	0.0000	0.0000	0.0000
4	H1	C3	1	C3	0.0000	0.0000	0.0000
4	C3	C3	1	2	0.0000	0.0000	0.0000
4	C3	C3	1	6	0.0000	0.0000	0.0000
4	C3	C3	1	C3	0.0000	0.0000	0.0000
4	H1	C3	C3	1	0.0000	0.0000	0.0000
4	C3	C3	C3	1	0.0000	0.0000	0.0000
4	C3	C3	3	4	0.0000	0.0000	0.0000
4	C3	C3	3	2	0.0000	0.0000	0.0000
4	H1	C3	4	5	0.0000	0.0000	0.0000
4	H1	C3	4	3	0.0000	0.0000	0.0000
4	H1	3	4	C3	0.0020	7.9693	0.1263
4	H1	4	3	C3	0.0020	7.9699	0.1778
4	C3	4	3	C3	0.0000	8.0000	0.0000
4	C3	4	3	2	0.0000	8.0000	0.0000
4	C3	3	2	1	0.0000	−2.0000	0.0000
4	H1	C3	5	4	0.0045	−0.0252	0.2130
4	H1	C3	5	6	0.0000	0.0000	0.0000
4	C3	5	6	1	1.9635	1.2421	0.0592
4	C3	1	2	3	0.9302	0.1815	0.1780
4	C3	1	6	5	0.9417	0.0950	0.0973
4	H1	C3	1	2	0.0000	0.0000	0.0000
4	H1	C3	1	6	0.0000	0.0000	0.0000
4	H1	C3	1	H1	−0.0003	0.0091	0.2001
4	C3	2	1	6	0.4233	0.1190	0.1819
4	3	4	5	6	0.2364	−0.5065	1.5680
4	1	2	3	4	0.5368	−2.8386	−0.4791
4	2	3	4	H1	0.0000	5.0000	0.0000
4	H1	3	4	H1	−0.0008	7.9950	−0.0163
4	6	1	2	3	0.2293	−0.5415	0.5957
4	4	5	6	1	0.3737	−1.2703	2.4437
4	H1	4	3	2	0.0029	7.9553	0.0444
4	H1	4	5	H1	0.0686	−0.1094	0.1464
4	H1	4	5	6	−0.0966	0.1238	0.4131
4	H1	1	2	3	−0.0771	0.2543	0.3831
4	H1	1	2	H1	0.0775	−0.1948	0.0827
4	H1	2	1	6	−0.0856	0.0803	0.0908
4	H1	3	2	1	−0.6000	−2.4855	1.4233
4	C3	C3	5	4	0.5000	0.0000	0.0000
4	4	5	C3	O3	0.5000	0.0000	2.0000
4	6	5	C3	O3	0.0000	−1.0000	0.5000
4	O3	C3	5	H1	0.0000	−2.0000	1.0000
5	3	00	00	00	0.0000	0.0000	
5	4	00	00	00	0.0000	0.0000	
5	5	00	00	00	0.0000	0.0000	

Table II. Comparison between ab Initio and Force Field Calculations (Energies in kcal mol^{-1})

structure		ab initio	FF1	FF2
CH_2O + allylborane	chair (**1**)	0.00	0.00	0.00
	boat (**2**)	8.30	4.21	7.49[a]
CH_3CHO + allylborane	chair, Me equatorial (**3**)	0.00	0.00	0.00
	chair, Me axial (**4**)	2.36	2.29	2.41
CH_2O + *B*-methylallylborane	chair, Me equatorial (**5**)	0.00	0.00	0.00
	chair, Me axial (**6**)	1.52	1.46	1.40
CH_2O + 1-methylallylborane	chair, Me equatorial (**7**)	0.00	0.00	0.00
	chair, Me axial (**8**)	0.71	0.78	0.73

[a] This structure is a saddle point on the FF2 surface, but close to a minimum at 5.80 kcal mol^{-1}.

in part, from the standard MM2 force field, which incorporates information about the higher energy regions of the potential energy hypersurface.

The relative energies for the structures 1–8 (Figure 1) calculated by FF2 are compared to the corresponding ab initio values in Table II.

A conformational analysis was performed for the chair structure, in order to make sure that no "unwanted" minima were present on the potential surface. No such minima were found within 2.5 kcal mol^{-1} of the global minimum energy for allylboranes, nor for *Z* and *E* crotylboranes.

Reproduction of Experimental Stereoselectivity. The force field was applied to cases with more than one methyl group, and it was found that the extra methyl groups did not result in serious distortion of the transition structures. From the results for the *Z* and *E* crotylborane addition to acetaldehyde, the model seems well behaved (Figure 2). A Boltzmann distribution, calculated at −78 °C for the competing transition structures, predicts essentially complete syn selectivity (syn:anti = 99.9:0.1) for the reaction of the *Z* crotyldimethylboranes and anti selectivity (anti:syn = 99.7:0.3) from the corresponding transition structures for the *E* crotylboranes. The last

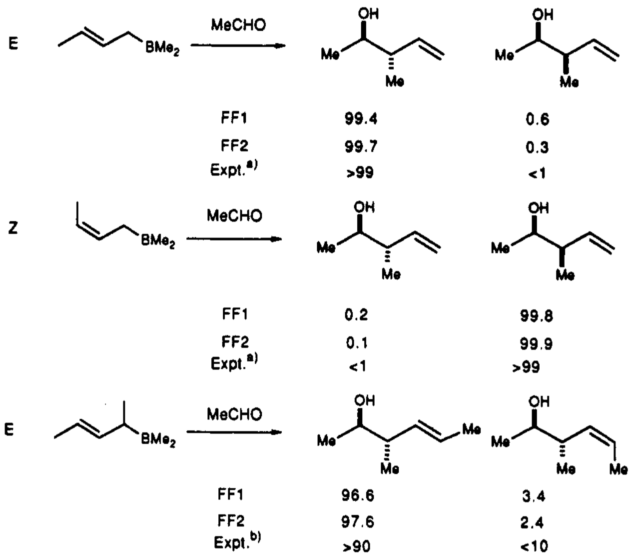


Figure 2. Syn/anti ratios of *E* and *Z* crotylboranes. Key: (a) experimental value is for the reaction of $(Ipc)_2$crotylborane (Brown);[18] (b) experimental value is for the reaction with ethyl ligands on the boron (Mukaiyama).[17]

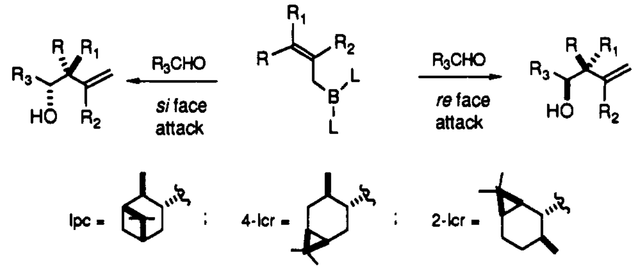
entry of Figure 2 shows the preference for an α-methyl group to occupy the equatorial rather than the axial position on the chair transition structure (compare 7 and 8 in Figure 1 and Table II). The structure with the equatorial methyl group (cf. 7) leads to the *E* double bond (expt[17] >90%), while the structure with the axial methyl group (cf. 8) leads to the *Z* double bond (expt[17] <10%).

We used our force field to model the transition structures of a number of chiral allyl- and crotylborane additions for which the experimental results are available.[1a,18,19a–g,20] A qualitative agreement between the calculated and experimental aldehyde *si*/*re* face ratios was found in all cases examined.

Brown Chemistry. For the asymmetric addition of allyl- and crotylboranes to acetaldehyde with isopinocampheyl ligands attached to boron, the force field predicts the correct sense of stereoselectivity and is close to being quantitatively correct (Table III, entries 1–5).[18,19g,20] The transition structures for the addition of *B*-allyldiisopinocampheylborane [Ipc ligands derived from (+)-α-pinene] to acetaldehyde are shown in Figure 3. The calculated *si*/*re* selectivity in this reaction is 98.8:1.2 (Table III, entry 1), while the experimental value is 96:4.[20]

Two structures were found within 2.5 kcal mol^{-1} of the minimum energy conformation for the reaction on the aldehyde *si*-face and two structures for the aldehyde *re*-face attack. Inspection of the diastereomeric transition structures **12** (*si* face) and **14** (*re* face) shows that the Ipc ligands have the same relative orientation. The ligand methyl groups adjacent to boron (shown with hydrogens in Figure 3) are on the same side. A different relative orientation of the two Ipc ligands in **13** (*si* face) results in a conformation of substantially higher energy compared to **12** (+1.52 kcal mol^{-1}), where the C–B–C bond angle is reduced to about 110°, compared to 118° for the other cases. The different orientation of the two Ipc groups in **13** is due to a rotation of the axial boron–ligand bond, which is presumably more flexible. Conformation **13** is pseudo-C_2-symmetric for the $B(Ipc)_2$ group; i.e., the methyl groups adjacent to boron on the two Ipc ligands are on opposite sides. The increase in energy due to the different ligand–ligand orientation is high for the *si*-face attack (+1.52 kcal mol^{-1}) but not for the *re*-face attack (+0.12 kcal mol^{-1}, compare **14** with **15**). This suggests that the ligands are locked relative to each other in a low-energy arrangement, for *si*-face attack, and that both the axial and the equatorial ligands are important in determining face selectivity.

Table III. Brown Chemistry: Calculated and Experimental Selectivities (All Reactions and Calculations at −78 °C)



entry	L	R	R_1	R_2	R_3	*re*:*si* (calcd)	*re*:*si* (exptl)
1[a]	Ipc	H	H	H	Me	1.2:98.8	4.0:96.0
2[a]	Ipc	H	H	H	*i*-Pr	0.4:99.6	6.0:94.0
3[b]	Ipc	H	H	Me	Me	0.0:100.0	5.0:95.0
4[c]	Ipc	Me (*Z*)	H	H	Me	0.4:99.6	5.0:95.0
5[c]	Ipc	H	Me (*E*)	H	Me	1.2:98.8	5.0:95.0
6[d]	4-Icr	H	H	H	Me	16.7:83.3	3.0:97.0
7[d]	4-Icr	H	H	H	*i*-Pr	28.2:71.8	2.5:97.5
8[d]	2-Icr	H	H	H	Me	98.2:1.8	99.0:1.0

[a] See ref 20. [b] See ref 19g. [c] See ref 18. [d] See ref 19b.

The orientation of the ligands with respect to the transition structure core is very important for determining the face selectivity. Examination of the lowest energy diastereomeric transition structures (**12** and **14**) shows that in the favored *si*-face attack mode (**12**) the methyl groups adjacent to boron on both the Ipc ligands are directed toward the aldehyde oxygen atom, while for *re*-face attack (**14**) these methyl groups are directed toward the allyl-CH_2 fragment. The energy gap between transition structures **12** and **14** (+2.12 kcal mol^{-1}) suggests that these methyl groups, located on the ligands, sense the steric difference between the allyl-CH_2 fragment and the aldehyde oxygen atom.[21]

The same factors appear to be important for the addition reactions of *Z* and *E* crotylboranes (Table III; entries 4, 5), *B*-allyldi(2-isocaranyl)borane and *B*-allyldi(4-isocaranyl)borane (Table III; entries 6–8) to aldehydes.[19b]

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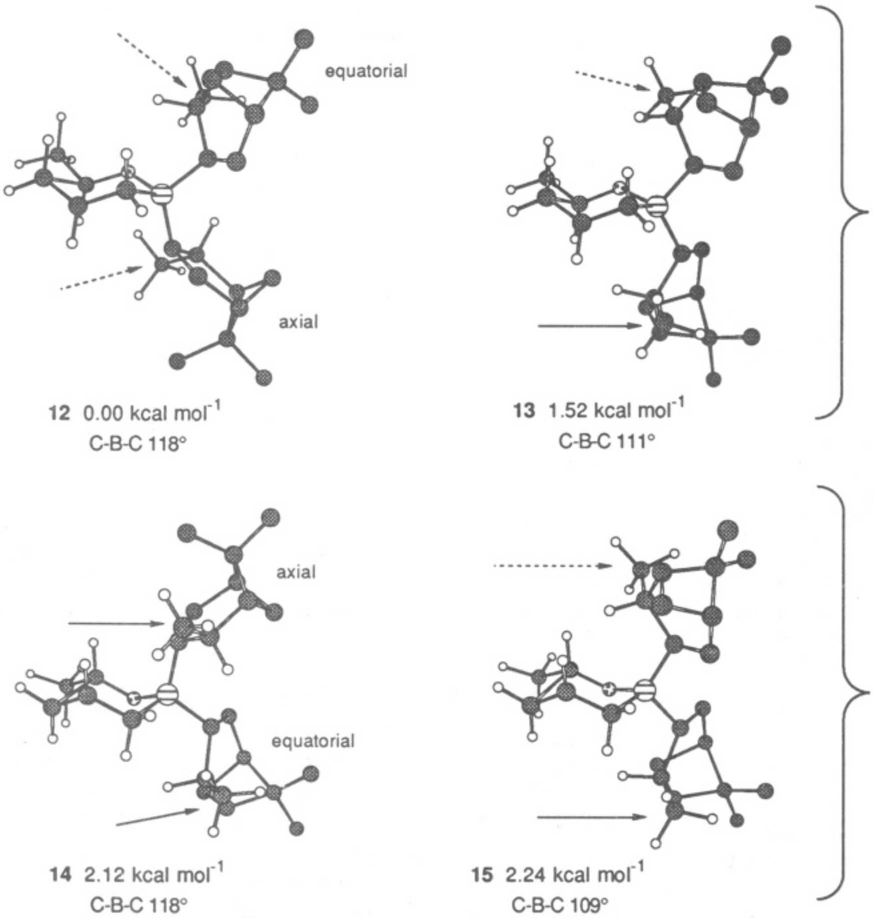
(17) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 993.

(18) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

(19) (a) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (b) Brown, H. C.; Randad, S. R.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389. (c) Brown, H. C.; Randan, S. R. *Tetrahedron* **1990**, *46*, 4457. (d) Masamune, S.; Short, R. P. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (e) Brown, H. C.; Bhat, K. S.; Randad, S. R. *J. Org. Chem.* **1987**, *52*, 319. (f) Brown, H. C.; Bhat, K. S.; Randad, S. R. *J. Org. Chem.* **1989**, *54*, 1570. (g) Brown, H. C.; Jadhav, K. P.; Perumal, T. *Tetrahedron Lett.* **1984**, *25*, 5111.

(20) Brown has recently published a paper describing the effect of using salt-free conditions for allylboration. The absence of Mg^{2+} ions speeds up the reaction, but it does not affect the enantioselectivity, and so we felt justified in ignoring this effect. See: Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(21) This is confirmed by comparing the distances from the carbon atoms of the (axial and equatorial) ligand-methyl groups to the aldehyde-oxygen atom and the allyl-CH_2 group. Structure **12** (*si* face attack): (a) 3.08 Å Me(eq. ligand)···O separation and 3.42 Å Me(ax ligand)···O separation, (b) 4.67 Å Me(eq. ligand)···CH_2 separation and 4.95 Å Me(ax. ligand)···CH_2 separation. Structure **14** (*re* face attack): (a) 3.43 Å Me(eq. ligand)···CH_2 separation and 3.61 Å Me(ax. ligand)···CH_2 separation, (b) 4.46 Å Me(eq. ligand)···O separation and 4.94 Å Me(ax. ligand)···O separation.



12 0.00 kcal mol^{-1} C-B-C 118°

13 1.52 kcal mol^{-1} C-B-C 111°

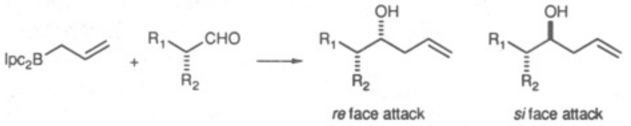
14 2.12 kcal mol^{-1} C-B-C 118°

15 2.24 kcal mol^{-1} C-B-C 109°

Figure 3. Transition structures for the addition of *B*-allyldiisopinocampheylborane [Ipc ligands derived from (+)-α-pinene] to acetaldehyde.

Poor agreement is obtained between the predicted and experimental stereoselectivity for the allyldi(4-isocaranyl)-borane (4-$Icr_2BAllyl$) addition to acetaldehyde (Table III; entries 6, 7). Note, however, that the inversion of stereoselectivity that occurs when 2-isocaranyl (2-Icr) ligands are used is predicted correctly (Table III; entry 8). The isocaranyl ligands can assume two different conformations (half-chair and boat) in contrast to the Ipc ligand which is rigid. The optimum ligand–ligand orientation, which occurs in the lowest energy structures for the *si* and *re* face attack of 2-$Icr_2BAllyl$ and 4-$Icr_2BAllyl$ to acetaldehyde, has the axial ligand in a half-chair conformation and the equatorial ligand in a boat conformation. A large number of minima (8–9) are found within 2.5 kcal mol^{-1} of the global minimum, and these differ mainly in the conformation of the isocaranyl ring. The poor quantitative agreement between calculated and experimental results in entries 6 and 7 could be due to the poor description of fused ring systems in MM2[6a,b] (small-ring and fused-ring systems are better parametrized in the MM3 force field).[22]

Table IV. Brown Chemistry–Double Asymmetric Induction: Calculated and Experimental Selectivities (All Reactions and Calculations at –78 °C)



entry		R_1	R_2	*re*:*si* (calcd)	*re*:*si* (exptl)[a]
1	matched	Et	Ph	1.0:99.0	3.0:97.0
2	mismatched	Ph	Et	48.0:52.0	33.0:67.0
3	matched	Me	OBn[b]	1.0:99.0	4.0:96.0
4	mismatched	OBn[b]	Me	16.5:83.5	6.0:94.0
5	matched	CH_2OBn[b]	Me	1.2:98.8	2.0:98.0
6	mismatched	Me	CH_2OBn[b]	0.2:99.8	4.0:96.0

[a] All experimental data taken from Brown.[19e,f] [b] The calculations were simplified by substituting a methoxy group for the benzyloxy.

The addition reactions of Ipc_2-BAllyl [Ipc from (+)-α-pinene] to various chiral aldehydes[19e,f] (Table IV, entries 1–6) were modeled in order to investigate diastereofacial selectivity and double asymmetric induction. The calculations account for high Felkin selectivity (anti-products) for the addition of Ipc_2-BAllyl to (*S*)-2-phenylbutyraldehyde (Table IV, entry 1, matched case) and a low diastereofacial selectivity for the corresponding mismatched reaction with (*R*)-2-phenylbutyraldehyde (Table IV, entry 2) in accord with the experimental results.

For the remaining cases (entries 3–6), the calculations were simplified by substituting the benzyloxy group with a methoxy group. The addition to an α-oxyaldehyde (entries 3, 4) required new force field parameters to be developed (see Methods section), and this may account for the lesser accuracy of these results. However, the sense of the selectivity was reproduced well. The force field suggests that the selectivity of the two final cases (entries

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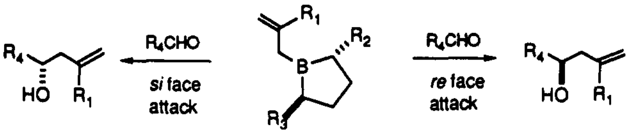
[22] (a) Allinger, N. L.; Lii, J. H.; Yuh, Y. H. *J. Am. Chem. Soc.* **1989**, *111*, 8552. (b) Allinger, N. L.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8566. (c) Allinger, N. L.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8576. (d) Allinger, N. L.; Rahman, M. *J. Am. Chem. Soc.* **1990**, *112*, 8293. (e) Allinger, N. L.; Schmitz, L. R. *J. Am. Chem. Soc.* **1990**, *112*, 8307. (f) Allinger, N. L.; Lii, J. H.; Yan, L. *J. Comput. Chem.* **1990**, *11*, 848. (g) Allinger, N. L.; Lii, J. H.; Yan, L. *J. Comput. Chem.* **1990**, *11*, 868.

Table V. Masamune's Chiral Reagents:[19d] Calculated and Experimental Selectivities (All Reactions and Calculations at –78 °C)



entry	R_1	R_2	R_3	R_4	*re:si* (calcd)	*re:si* (exptl)
1	H	Me	Me	Et	7.5:92.5	3.5:96.5
2	H	Me	Me	*i*-Pr	8.9:91.1	7.5:92.5
3	Me	Me	Me	*i*-Pr	16.5:83.5	36.5:63.5
4	H	*t*-Bu	H	*i*-Pr	1.5:98.5	14.0:86.0
5	H	*i*-Pr	H	*i*-Pr	10.6:89.4	38.0:62.0
6	H	$SiMe_3$	H	*i*-Pr	0.4:99.6	2.0:98.0
7	Me	$SiMe_3$	H	*i*-Pr	0.2:99.8	9.5:90.5
8	H	$SiMe_3$	$SiMe_3$	*i*-Pr	4.4:95.6	14.5:85.5

5, 6) should be entirely controlled by the Ipc group, and this is as observed experimentally.

Masamune Chemistry. Some of the chiral reagents developed by Masamune[19d] were analyzed, and the results are reported in Table V. The new force field parameters, which were required for the borolanes, were estimated from semiempirical calculations (see Methods section) and will be less reliable than those developed for the transition structure "core" itself. In all cases, the force field predicts high selectivity in the experimentally observed direction (aldehyde *si* face). The force field correctly reproduces the trends in the experimental selectivities for entries 1–3, for which the source of chirality is a C_2-symmetric dimethylborolane, and for entries 4, 5 and entries 7, 8. In addition, the model reproduces the improved stereoselectivity of the mono(trimethylsilyl)borolane (entry 6) over the dimethylborolane reagent. Masamune suggested that the source of the stereoselectivity in this reaction is purely steric,[19d] and the force field should reproduce this fairly well. Failure to reproduce the experimental stereoselectivity in a more quantitative way (entries 3–5, 7, 8) may be due to a nonsteric effect or poor parameterization of the borolane ring.

Comparison with the Aldol Reactions of Enol Borinates. For the asymmetric aldol reactions of enol diisopinocampheyl borinates, our 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 transition structure core, and (c) the relative orientation and restrained rotation around the B–C bonds of one Ipc ligand relative to the other.[5] These factors also appear to be important for the control of selectivity in the allylboration reaction. The aldol force field was not able to explain the behavior of methyl ketones, which gave reduced selectivity in the aldol reaction,[1b–d,5d,23] and this behavior was attributed to the presence of boat transition structures.[5a] This erosion of selectivity does not occur for allylboration, and the new force field can cope with allylboranes as well as crotylboranes (Table III).

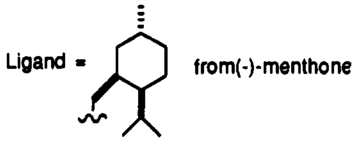


Figure 4. Menthone derived boron ligand.

Using the aldol force field, a new ligand was designed to give higher stereoselectivity (*re:si* ratios = calcd 3–59:1, exptl 3.4–15.6:1).[5d] This ligand, which is derived from menthone (Figure 4), was analyzed by the force field (FF2) for its use in allylboration, but the predicted selectivity is very low (*si:re* = 60:40), and so it was decided not to perform experiments on this system. In the transition structures the CH_2 group of the allyl boron fragment (which substitutes the enolate oxygen of the aldol reaction) interacts with the equatorial ligand, which therefore changes its conformation (with respect to the aldol reaction). This interaction is particularly relevant in the *re*-face selective lowest energy transition structure, with the result of making the reaction slightly *si*-selective or unselective.

Conclusions

In summary, a force field model for the addition of allyl- and crotylboranes to aldehydes has been developed, which can reproduce the ab initio geometries and energies of the relevant transition structures of this reaction. It also reproduces the experimental syn/anti stereoselectivity for the addition of *Z* and *E* crotylboranes to acetaldehyde.

The force field gives an insight into the factors controlling stereoselectivity in allyl- and crotylboration and correctly predicts the sense of asymmetric induction and the effect of double asymmetric induction in a number of cases.

Methods

Program for the Automatic Optimization of the Parameters. The program assigns a small value to be added to (or subtracted from) each of the original torsional parameters (V_{orig}) in turn. The small changes in each parameter are calculated as shown

$$V_{new} = V_{orig} + K\langle\Delta\rangle$$

where K is chosen to ensure that the changes in the parameters are small (we use $K = 0.02$ kcal mol^{-1}); $\langle\Delta\rangle$ is the average value of the sum $(K_1\Delta^k_{energy} + K_2\Delta^k_{angle})$ defined for each of the angles affected by the torsion parameter; Δ^k_{energy} and Δ^k_{angle} are designed to improve the torsion parameter with respect to relative energy and geometry respectively; K_1 (= 0.45 mol^2 kcal^{-2}) and K_2 (= 5.0) are constants that balance the effect of the correction for energy with that for geometry. The program calculates Δ^k_{energy} and Δ^k_{angle} for each torsional parameter, V_i as follows:

$$\Delta^k_{energy} = \Delta E(V_i,\theta_k) = (E(\theta^{\ddagger}_k) - E(\theta^{ff}_k))\cdot|E(\theta^{\ddagger}_k) - E(\theta^{ff}_k)|\cdot T(V_i,\theta^{ff}_k)$$

$$\Delta^k_{angle} = (T(V_i,\theta^{\ddagger}_k) - T(V_i,\theta^{ff}_k))\cdot|T(V_i,\theta^{\ddagger}_k) - T(V_i,\theta^{ff}_k)|$$

$\theta^{\ddagger}_k$ is the *k*th torsion angle in the ab initio structures and θ^{ff}_k the *k*th torsion angle in the force field minimized structure. $E(\theta^{\ddagger}_k)$ is the relative ab initio energy of the transition structure containing angle $\theta^{\ddagger}_k$, and $E(\theta^{ff}_k)$ is the total MM2 relative energy of the transition structure containing the same angle (θ^{ff}_k) after minimization. $T(V_i,\theta^{ff}_k)$ is the contribution of a particular angle to the total torsional energy:

$$T(V_1,\theta^{ff}_k) = 1 + \cos\theta^{ff}_k; \quad T(V_2,\theta^{ff}_k) = 1 - \cos 2\theta^{ff}_k; \quad T(V_3,\theta^{ff}_k) = 1 + \cos 3\theta^{ff}_k$$

If these changes result in a force field that improves the RMS difference between the ab initio and force field derived relative

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(23) (a) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997. (b) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (c) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357. (d) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587.

energies of the transition structures then the new force field is adopted as the force field upon which further changes will be based. If this is not the case then the trial force field is discarded and a new one proposed. To avoid production of the same new force field in such cases, a random multiplication factor is introduced in *K*.

Calculations. Molecular mechanics calculations were performed with MacroModel version 3.1X[6c] and Batchmin (version 3.1)[24] on a Silicon Graphics 4D-20 Iris workstation. The conformational space was searched with the Still–Chang–Guida usage-directed torsional Monte Carlo search,[25] using the MM2 force field,[6a,b] and the PRCG or the TNCG energy minimization algorithms.[16a,b]

The data in Figure 2 required two different Monte Carlo runs to fully establish the product distribution of *E* and *Z* crotylboranes; i.e., the relative energies had to be evaluated for structures featuring (a) anti relative stereochemistry [aldehyde methyl axial for the *Z* crotylborane, equatorial for the *E* crotylborane] and (b) syn relative stereochemistry [aldehyde methyl equatorial for the *Z* crotylborane, axial for the *E* crotylborane].

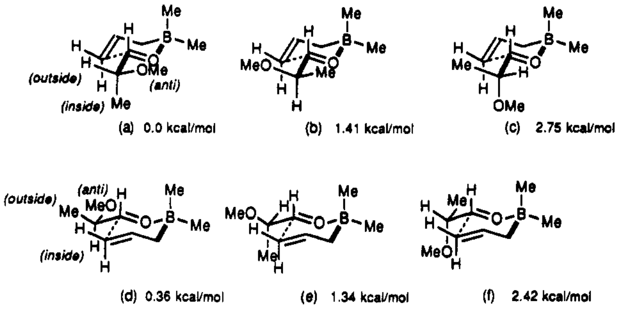
For both *Z* and *E* crotylboranes, we tested for the presence of boat transition structures by including all rotatable bonds of the transition structure "core". Boats were found to be unimportant because of their high energies relative to the chairs. In all the other cases studied (Tables III–V) two separate Monte Carlo runs were necessary: one with attack at the aldehyde *si* face and the other with attack at the *re* face. Torsional constraints were applied to preserve the double-bond geometry and prevent *Z*:*E* mixing, and chirality checks (including the sp^2 reacting centers) were made when necessary. The energy window for the search was 12 kcal mol^{-1}, and structures were stored within 2.5 kcal mol^{-1}. 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.

Additional Force Field Parameters. *α*-Methyl Aldehydes. The calculations make use of the additional parameters developed to reproduce the ab initio calculated selectivities for nucleophilic additions to *α*-methyl aldehydes [$\mathrm{C(sp^3)–C(sp^3)–C({=}O)\cdots C(nucl)}$; $V_1 = 0.5$, $V_2 = 0.0$, $V_3 = 0.0$].[6c]

***α*-Oxy Aldehydes.** Additional parameters were developed to better describe reactions involving *α*-oxy aldehydes (Table IV, entries 3, 4). The new parameters were set to reproduce the trend of the ab initio relative energies of the six diastereomeric transition structures for cyanide anion attack on 2-fluoropropanal and/or for hydride attack on 2-chloropropanal, for which ab initio results are available.[26] We considered only those calculations making use of naked anions[26a,c] in order to avoid the chelating effects which greatly stabilize those transition structures that have the polar atom X (chloride or fluoride) in the *inside* position (X-inside). It is reasonable to believe that these kinds of effects are not present in the allylboration reactions. In the absence of chelating effects the most stable conformers are the X-anti rotamers, in which the C–X bond adopts the antiperiplanar conformation. According to the ab initio calculations, in the lowest energy transition structure the halogen atom occupies the anti position and the methyl group the inside one (Felkin attack). This structure lies about 1.36–1.80 kcal mol^{-1} below the corresponding X-anti/methyl-outside conformer (anti–Felkin attack).

The preference for the *inside*-methyl (alkyl) rotamer is determined in our force field by the original MM2 torsional parameters of the aldehyde [i.e., $\mathrm{C(sp^3)–C(sp^3)–C{=}O}$], together with the $\mathrm{C(sp^3)–C(sp^3)–C({=}O)\cdots C(nucl)}$ torsional parameter (vide supra, the paragraph on *α*-methyl aldehydes).

Chart I. Felkin (a–c) and Anti-Felkin (d–f) Transition Structures for the Dimethylallylborane Attack on (*R*)-2-Methoxypropanal Calculated Using FF2 Force Field, which Includes the Additional Torsional Parameters Described in the Text



(a) 0.0 kcal/mol (b) 1.41 kcal/mol (c) 2.75 kcal/mol

(d) 0.36 kcal/mol (e) 1.34 kcal/mol (f) 2.42 kcal/mol

The preference for the anti-X rotamer, with respect to the inside and outside rotamers, is determined by the torsional parameter: $\mathrm{C(nucl)\cdots C({=}O)–C(sp^3)–O(sp^3)}$: $V_1 = 0.5$, $V_2 = 0.0$, $V_3 = 2.0$. The correct trend among the other rotamers [the Felkin and anti-Felkin transition structures which have C–X in the outside position (b and e, Chart I) are energetically preferred to those in which the C–X group is inside (c and f, Chart I)] is determined by adding two other torsional parameters: $\mathrm{O(sp^2){=}C(sp^2)–C(sp^3)–O(sp^3)}$: $V_1 = 0.0$, $V_2 = -1.0$, $V_3 = 0.5$ and $\mathrm{O(sp^3)–C(sp^3)–C({=}O)–H}$: $V_1 = 0.0$, $V_2 = -2.0$, $V_3 = 1.0$.

The three added torsional parameters were determined using the model structures reported in Chart I, i.e., the six transition structures for the dimethylallylborane attack on (*R*)-2-methoxypropanal. Three of these structures (a–c) lead to the formation of the Felkin product, whereas the remaining three (d–f) lead to the formation of the anti-Felkin product. The additional torsional parameters gave rise to the energy distribution reported in Chart I, which nicely reproduces the ab initio trend.[26]

Borolane. Additional force field parameters for the borolane ring were based on semiempirical (AM1) calculations on the borolane shown in Figure 5. The boron–carbon bond was set to 1.58 Å, with a force constant of 4.0 mdyn Å^{-1}. The exocyclic C–C–B angles were set to 117.5° and the corresponding H–C–B angles to 103.6°. The C–B–C angle was set to 110.7°, and all the other angles around the boron atom were set to 110.0°. The endocyclic C–C–B angle was set to 103.4°. All angle bending force constants were set to 0.3 mdyn rad^{-2}. The new torsional terms were all set to zero. A table containing the relevant parameters is available in the supplementary material (Table VI).

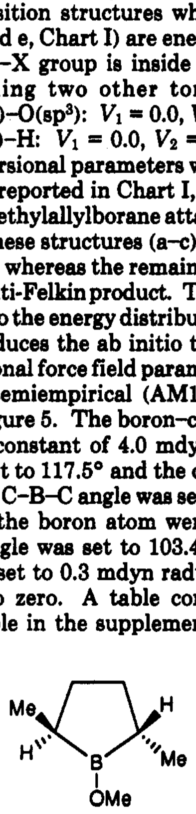


Figure 5. Borolane used for the semiempirical (AM1) calculations.

Acknowledgment. We thank the Commission of the European Community (Grant SCI*.0324.C-[JR]), NATO (Grant 0368/88), SERC, and CNR for financial support. We thank Clare College, Cambridge, for a Research Fellowship (to J.M.G.).

Supplementary Material Available: Additional force field parameters for the borolane ring (Table VI) and energies and Cartesian coordinates of structures 1–11 (5 pages). This material is contained in 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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[24] BATCHMIN is the non interactive modeling program connected to MacroModel. Version 3.1 was used on a Silicon Graphics Iris workstation.

[25] Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

[26] (a) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456. (b) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327. (c) Frenking, G.; Koehler, K. F.; Reetz, M. T. *Tetrahedron* **1991**, *47*, 9005.