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THEORETICAL STUDIES OF STEREOSELECTIVE HYDROBORATIONS

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Abstract—Asymmetric hydroborations of alkenes are outstanding examples of reactions which proceed with high acyclic stereoselection to give synthetically useful functionality. We have undertaken computational studies of these reactions as a part of our more general studies of stereoselective organic reactions. We wish to develop understanding of those factors which control stereoselectivity in known cases, and to develop both qualitative and quantitative methods to predict stereoselectivities of cases not yet investigated. Here, we detail our progress in understanding hydroborations, and in subsequent publications, we will report similar studies for other types of organic reactions, such as intermolecular and intramolecular cycloadditions, epoxidations, radical reactions, nucleophilic additions, and aldol condensations.

Stereoselective hydroborations of alkenes have been employed in the synthesis of many natural products.[2] Hydroboration with optically active boranes followed by oxidation gives optically active alcohols, often with high enantiomeric excess.[3] An example is given in Fig. 1(a). Chiral alkenes undergo attack by achiral boranes preferentially from one side of the double bond. This occurs when the chiral center is attached to the C which is attacked by boron (Fig. 1b),[4] or when the chiral center is attached to the C to which hydride is transferred (Fig. 1c).[5,6] High asymmetric induction is found even when the chiral center is one atom removed from the C to which hydride is being transferred (Fig. 1d).[7] Thus, chiral centers attached to boron or to either alkene C can promote highly stereoselective reactions.

What factors cause these reactions to be stereoselective? Can the modest stereoselectivity observed in some of these cases be enhanced by alternative substituents on reagents or substrates? Can these stereochemical control features be incorporated into other organic reactions to produce useful stereoselectivities?. Is it possible to predict the stereoisomer ratios in such reactions? Our computational studies have addressed these questions, and in this manuscript, we report the results of our initial investigations.

Ab initio calculations can be used to locate the transition structures of various organic reactions. We use the word "structure" in the sense advocated by Pople, to emphasize that the calculations give a structure which corresponds to a saddle point on the electronic energy surface, not a real state as is implied by the word, "state". These calculations can also give detailed information about the geometries, energies, and vibrational motion of transition structures. However, computations with sufficiently large basis sets and adequate correlation energy corrections can still only be carried out practically with relatively small systems. Many insights can be achieved by appropriate calculations on small model systems, but most organic reactions involve quantum mechanically monstrous systems, which cannot (yet) be studied by direct *ab initio* calculations. Nevertheless, it is desirable to compute quantitative information about all of the electronic and steric effects which may influence the rates of reactions of such large systems. We have explored small model systems at the *ab initio* level, and have devised a modified force field model based upon Allinger's MM2 method,[8] which has proven useful for the computational study of highly substituted systems.

Ab initio *transition structures*

The hydroboration of ethylene with BH_3 has been studied theoretically with a variety of techniques.[9-14] Both *ab initio* and semiempirical techniques predict that BH_3 and ethylene will form a weakly bound π-complex in the gas phase, and that the conversion of this complex to the addition product is the higher barrier to be surmounted in the addition reaction. The transition structure corresponding to the highest barrier is a four-center one, which avoids orbital symmetry forbiddenness since it is a "pseudopericyclic reaction" having little or no cyclic four-electron conjugation.[9]

However, in non-coordinating solvents, borane dimerizes to diborane, while Lewis basic solvents form complexes with borane. Thus, in solution, monomeric borane is not the actual hydroborating reagent,[15] although some sterically hindered dialkylboranes do react as monomeric species. How then can gas phase calculations on monomeric BH_3 reactions have any relevance to solution experiments?

Clark, Wilhelm and Schleyer have carried out a theoretical study which suggests that gas phase and solution hydroboration transition structures are very similar to each other. They studied the reaction of a BH_3–water complex with ethylene, as a model for solution hydroboration reactions.[13] The π-complex of

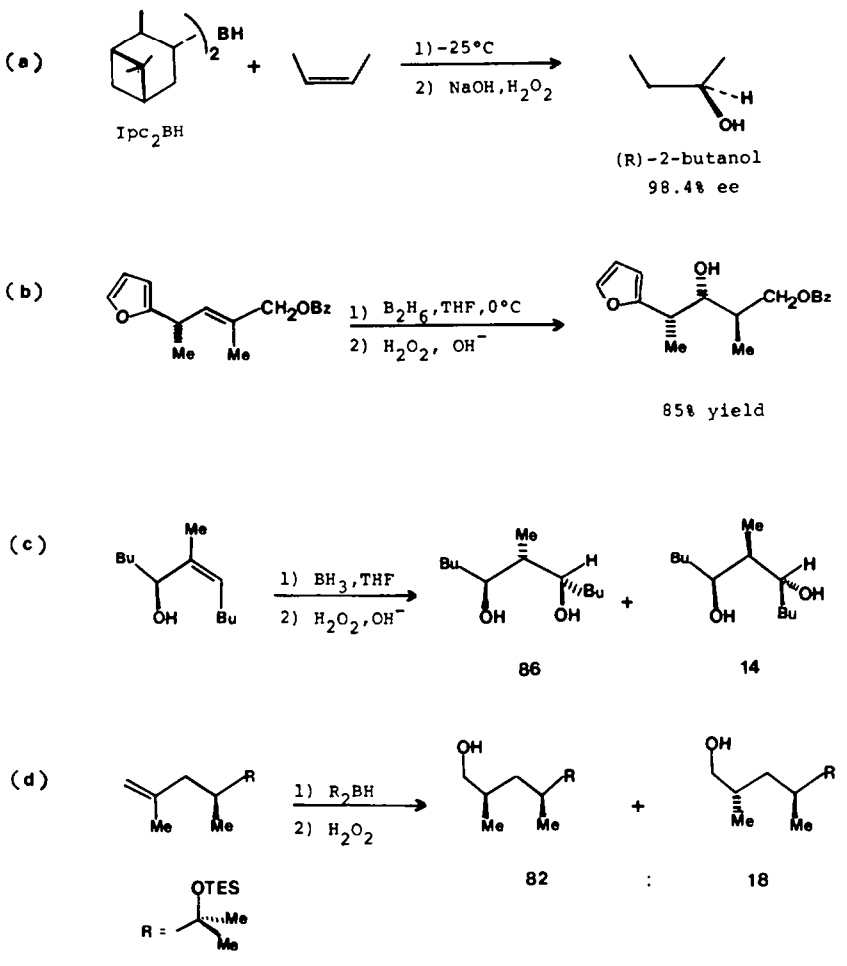


Fig. 1. Examples of several stereoselective hydroboration reactions.

BH_3 and ethylene is no longer an energy minimum due to stronger coordination of BH_3 with water than with ethylene. The single transition state which now separates reactants from products is similar in its main geometrical features to that calculated for the BH_3-ethylene reaction, with the solvent molecule, water, nearly completely displaced from BH_3 in the transition state. The activation energy is greatly increased by coordination of the BH_3, and the transition state is somewhat "later" in terms of CB bond formation. Nevertheless, the details of the four-centered transition state are quite similar in gas phase and these model solution phase reactions. For that reason, as well as for reasons of practicality, we have not attempted to include solvent explicitly in our calculations.

Location of the transition states for substituted cases also indicates a relative insensitivity of the transition structure to substituents and reveals a new conformational feature. The transition structure that we have obtained for the parent reaction using the 3-21G basis set[16] and gradient optimization techniques[17] is shown in Fig. 2. Transition structures for the hydroboration of propene in both the preferred ("anti-Markovnikov") and disfavored ("Markovnikov") directions were published recently,[14] and are shown for comparison. We have also obtained the transition structure for the hydroboration of ethylene by methylborane. This is also shown in Fig. 2. Various conformers and configurations of transition structures for the hydroboration on allyl alcohol by borane will be described later.

The activation energies, without zero-point energy corrections, are shown below each drawing in Fig. 2. These numbers are the total energies, in kcal/mol, relative to the isolated monomeric reactants. The activation energies calculated at the 3-21G level are all too high, since the reaction of BH_3 with ethylene in the gas phase has an activation energy of only 2–3 kcal/mol.[18] Morokuma *et al.* have shown that use of polarization functions and CI lowers the calculated barrier to a more reasonable 5.6 kcal/mol.[12] It is probable that relocation of the transition state with CI would give an earlier transition state, while inclusion of solvent would give a later transition state. Because of neglect of these two counteracting influences, our 3-21G results may be fortuitously close to actual solution transition structures.

As shown in Fig. 2, a Me substituent at the alkene terminus away from boron lowers the activation energy slightly, and gives a slightly more advanced, or "later", transition structure. These results are

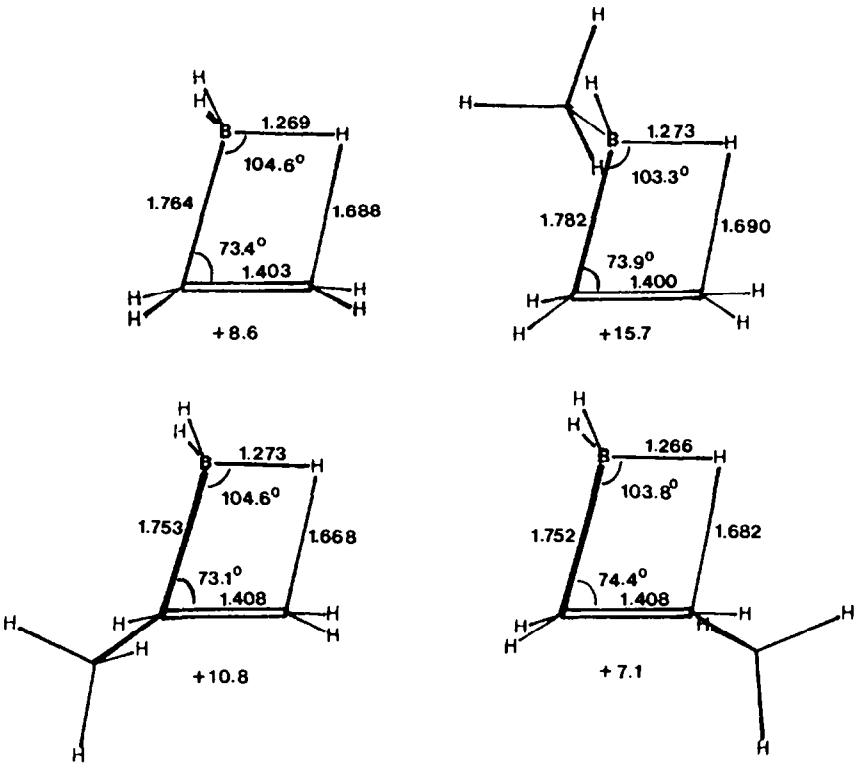


Fig. 2. Transition structures (3-21G) for hydroborations of ethylene by BH_3, ethylene by $MeBH_2$, and propene by BH_3 in two orientations.

compatible with expectation for an electrophilic process. A Me at the alkene terminus near boron raises the activation energy, primarily, we assume, for steric reasons.[10,15] The Me on boron raises the activation energy, primarily by stabilizing the isolated borane relative to the transition state. None of the geometries of the Me-substituted transition structures are very different from that found for the parent reaction. The bond angles in the four-center transition structures are within a few degrees of each other, and the forming and breaking bond lengths change at most by several hundredths of an Ångstrom.

Each transition structure has the Me CH bonds staggered with respect to the partially formed or broken bonds, and with respect to the bonds of the partially pyramidalized alkene carbons or nearly tetrahedral boron. This staggering is shown more clearly by the Newman structures given in Fig. 3. This staggering effect follows our earlier generalization,[14,19,20] and the deduction made for nucleophilic additions by Felkin[21] and subsequently supported theoretically by Anh.[22] A 180° rigid rotation of the Me group in any of these structures causes an increase in energy of 2.6–3.0 kcal/mol. We have also evaluated these "transition state rotational barriers" in several more sophisticated ways for the Markovnikov addition of BH_3 to propene and found only slight changes from the values evaluated by rigid rotation.[14] Thus, the barriers to rotation of groups attached to atoms undergoing bonding changes are similar to those of the products, even though these are relatively early transition structures. We conclude that alkyl substituent conformations in transition structures are of similar rigidity to those of alkyl groups in alkanes. This simple conclusion allows powerful predictions about transition structures. These predictions are always quantitatively different from those based upon an assumption that substituents in transition structures adopt reactant-like conformations, and these predictions may even lead to qualitatively different predictions in some cases.

In hydroborations such as the first three shown in Fig. 1, one atom attached to boron or to either alkene C is a chiral center. Figure 3 shows that bonds to the chiral center will be staggered with respect to partially formed bonds. In order to predict the stereoselectivity of an asymmetric hydroboration, it is also necessary to know which of the three non-equivalent staggered positions for each type of chiral center will be preferentially occupied by a given type of substituent.

Model calculations which assess the steric requirements of an alkyl substituent in each location are summarized in Fig. 4. The relative energies of different Et group conformations were obtained with the 3-21G basis set by substituting a standard Me group ($r_{CH} = 1.09$ Å, $r_{CC} = 1.54$ Å, $<CCH = 109.47°$) in place of the corresponding Me hydrogen. These numbers should overemphasize the differences in energies for different conformations, since no geometrical relaxation of the structures is permitted. Nevertheless, the qualitative conclusions are clear: alkyl groups prefer to be *anti-periplanar* (hereafter called *anti*) to the partially formed bonds. The *anti*

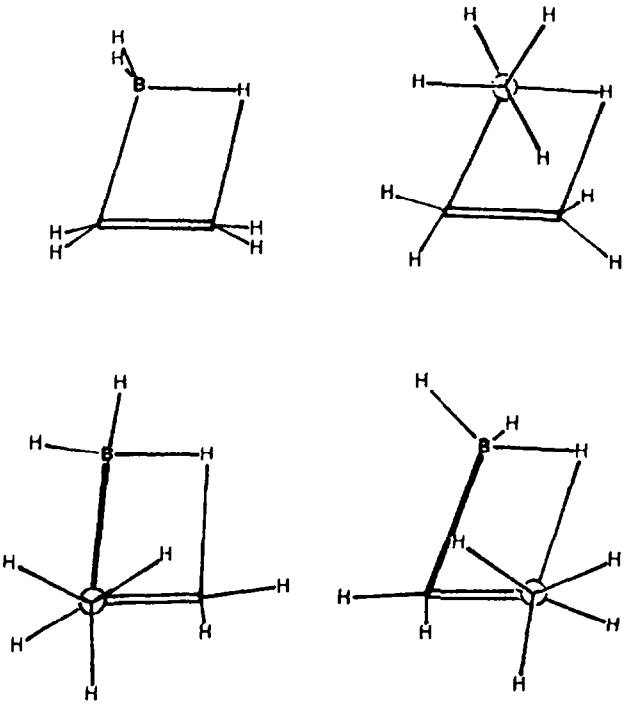


Fig. 3. Newman projections of the four transition structures shown in Fig. 2.

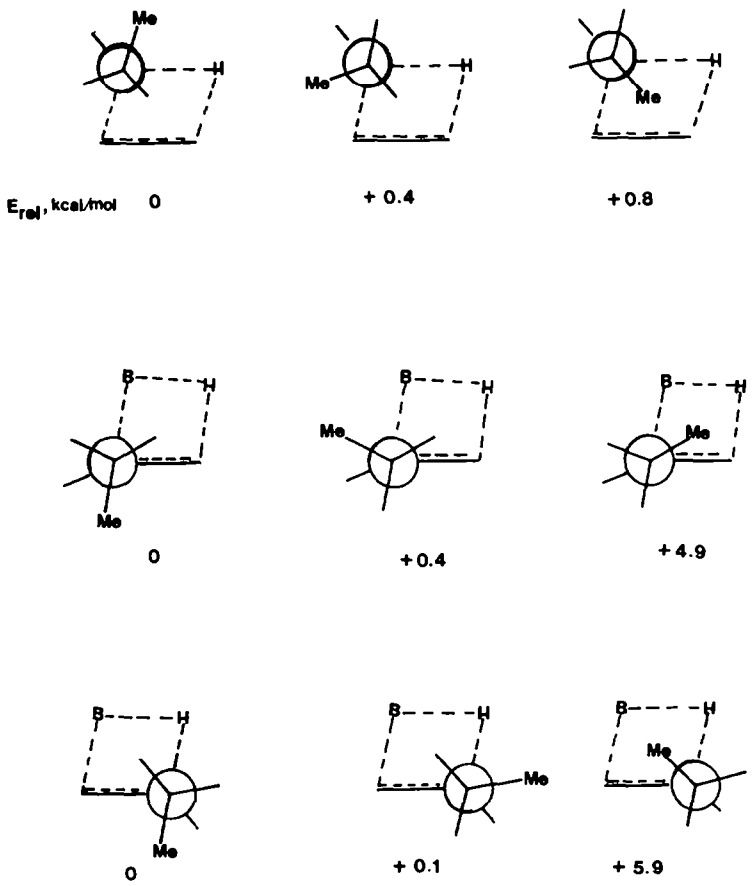


Fig. 4. Relative energies (3-21G) of model transition structures for hydroboration of ethylene by ethylborane and of 1-butene by BH_3 in both orientations. Energies were calculated for geometries obtained by substitution of a standard methyl group for a hydrogen.

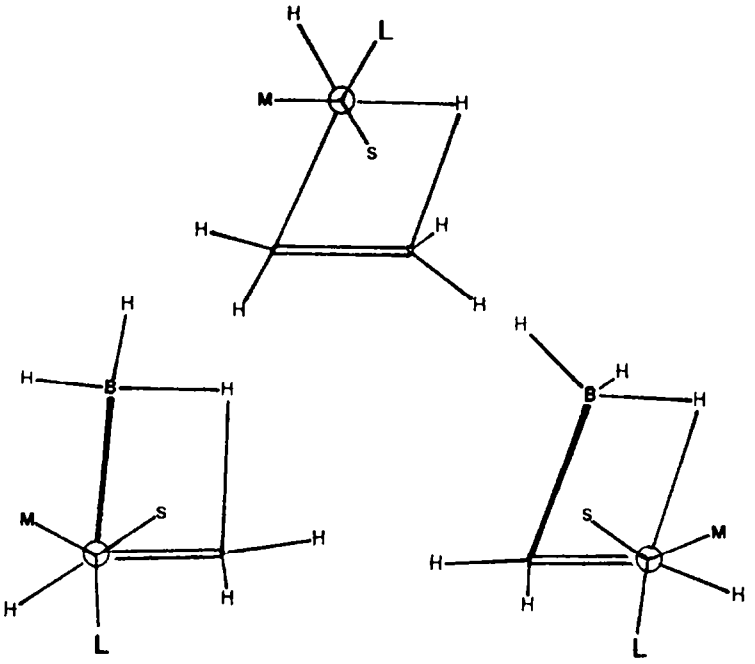
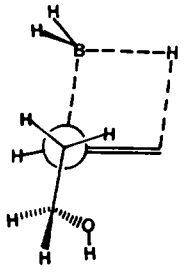


Fig. 5. Qualitative models for asymmetric hydroborations with groups of different size, but no specific electronic effects.

positions are clearly the sterically least crowded positions in each case. The "outside" positions (away from the alkene double bond) are somewhat more crowded, while the Me groups "inside" the four-centered transition structure are clearly in the most crowded locations.

Based on these results, we can make qualitative predictions about stereochemically preferred transition structures when the chiral centers consist of groups which interact with other atoms or groups sterically, but do not interact in any other specific electronic way. Alkyl groups are presumably closest to this steric ideal. Figure 5 shows these steric models. It is tempting to ascribe the stereoselectivity shown in Fig. 1b to the steric model, with furyl = L (large), Me = M (medium), and hydrogen = S (small). In fact, we have succumbed to this temptation![14] However, as described later, the furyl and Me groups differ very little in effective size, so that we also investigated the possible electronic role of the homoallylic oxygen present in the furyl group and alkoxymethyl groups present in analogous examples from Kishi's laboratories.[4] For computational economy, we attached a standard hydroxymethyl group with the CCOH dihedral angle fixed at 180° in place of one the CH bonds of Me in the Markovnikov propene–BH_3 transition state. This model mimics the conformation about the CO bond expected for ethers. We then calculated the energies of the nine possible conformations obtained by 120° rotations about C_1C_2 or C_2C_3 bonds. The results of single point 3-21G calculations are shown in Fig. 6.



CH_2OH-anti
<CCCO=60°

CH_2OH	<CCCO		
	60°	180°	-60°
anti	0.0	1.6	1.1
outside	0.9	1.4	7.1
inside	23.2	7.4	4.3

Fig. 6. Relative energies (kcal/mol) of model transition structures for hydroborations of homoallyl ethers. The preferred conformation is shown, and the energies of nine additional transition structures are summarized in the table.

The preferred conformation has the CH_2OH group *anti* to the partially-formed BC bond, and has the CO bond in that *gauche* conformation which places the O atom nearest the alkene. Although the distances from the homoallylic O to the alkene carbons are 2.9 and 3.1 Å, there is apparently a considerable interaction which stabilizes the transition state. Full optimization might lead to closer approach of the oxygen to the double bond, and a further preference for this conformation.

Since BH_3 is an electrophilic species, the double bond should become somewhat electron-deficient in the transition state of the reaction. A neighboring oxygen can stabilize the transition state either electrostatically, or by through-space interaction of an oxygen lone-pair orbital with the π orbitals of the alkene. Accelerations of electrophilic additions to alkenes by through-space interactions of an ether with alkene π-bonds have been noted previously in more rigid systems.[23]

These calculations show why a homoallylic ether group prefers the *anti* conformation in hydroborations. Although a CH_3 and a CH_2CH_2OR group are essentially identical in steric requirements (see later), the latter can stabilize the transition state when *anti*. Thus, Kishi's many examples[4] of the general type shown in Fig. 1(b) result from an electronic preference for the homoallylic ether to be *anti*, along with a steric preference for Me to be *outside* rather than *inside*.

Figure 1(c) shows another type of asymmetric synthesis in which a hydroxyl group is located on the allylic C adjacent to the alkene C to which hydride is delivered upon hydroboration. To investigate the possible electronic effect of an allylic alcohol on these reactions, we carried out *ab initio* calculations on the hydroboration of allyl alcohol by BH_3. Six different transition states were calculated, and these are shown in Fig. 7. The two transition structures shown at the top of Fig. 7 with OH *outside* or *inside* are preferred, and have activation energies slightly lower than that for hydroboration of propene. These preferred allyl alcohol transition states have the OH directed so that it can hydrogen bond with the alkene, as is preferred for allyl alcohol itself. In fact, when calculations were carried out on the allyl alcohol fragments of these transition states (i.e. with BH_3 removed), the relative energies are in the same order, although the energy differences between conformers are smaller.

The three highest energy transition structures, shown at the bottom of Fig. 7, should be good models for the hydroboration of allylic ethers. The relative ener-

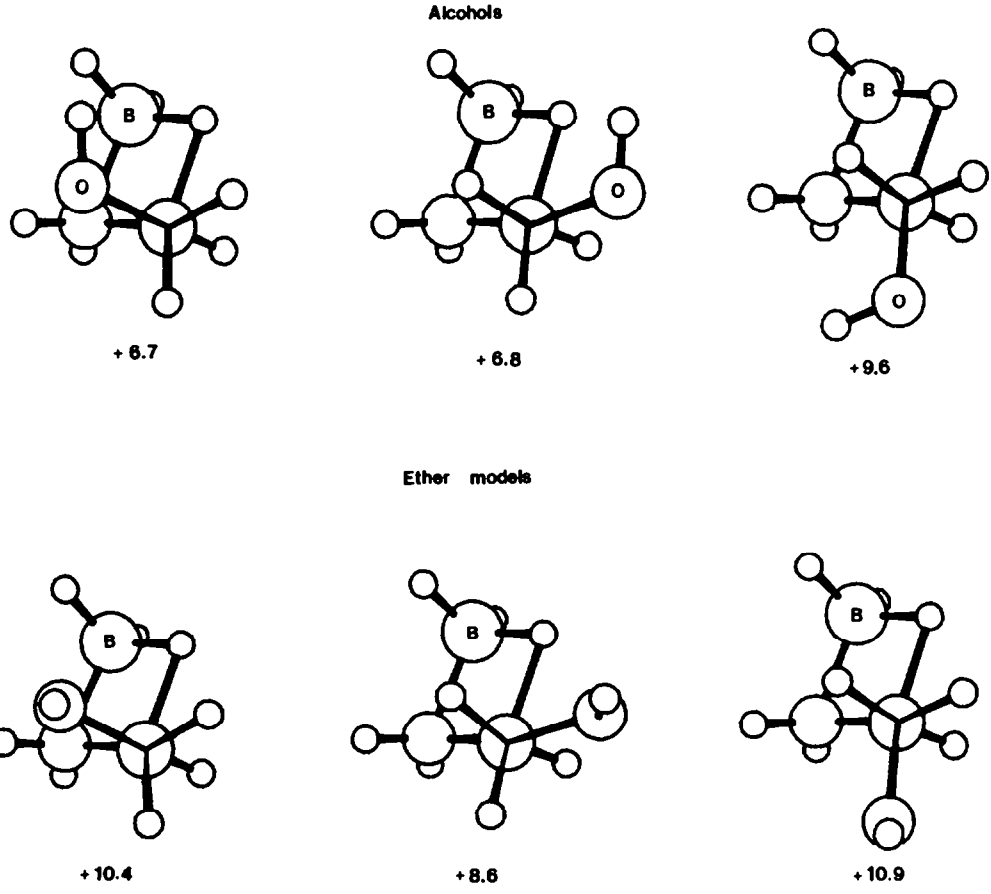


Fig. 7. 3-21G Transition structures for hydroboration of allyl alcohol. Activation energies (kcal/mol) are shown below each structure. The three "ether models", which started at geometries with $<HOCC = 180°$, are less stable than the alcohol models. The lowest ether model is 1.9 kcal/mol higher in energy than the lowest energy alcohol model.

gies increase in the order: *outside* < *inside* < *anti*. This order is different from that found earlier for butene, where the Me group is preferentially *anti*. Thus, the allylic O is exerting an electronic effect, which favors having the allylic CO bond nearly in the alkene plane (as in the *inside* or *outside* conformations) rather than perpendicular to this plane (as in the *anti* conformations). We believe that this electronic effect arises from the electrophilic nature of the reaction. When the allylic CO bond is nearly coplanar with the double bond, it withdraws electron density less than when it is perpendicular, where there is overlap of the σ^*_{CO} orbital with the alkene π orbitals. Thus, an allylic CO bond destabilizes the electrophilic transition state less when it is coplanar with the doubly bonded carbons than when it is perpendicular. We have noted a similar effect for the electrophilic nitrile oxide cycloadditions to allylic ethers.[24] The preferred conformation of an allylic CO bond in these electrophilic reactions is different from that found for nucleophilic additions, where an *anti* CO maximizes electron-withdrawal.[22] We shall describe the stereoselectivities of the type shown in Fig. 1(c) in more detail in a later section of this paper.

MM2[3-21G] *transition structure models*

The 3-21G calculations described in the previous section give good semi-quantitative ideas about how steric and electronic effects influence the preferred conformations of allylic alkyl or oxygen substituents on the alkene, or alkyl substituents on boron, in the transition states of hydroboration reactions. However, we desired to evaluate simultaneously and quantitatively, these various effects for large, multiply substituted systems, such as those given in Fig. 1. It is currently not possible to do such calculations at the *ab initio* level in a finite period of time, so we have devised a practical alternative model which is described here.

We have developed a standard model for the transition structures of hydroborations, and have used Allinger's MM2 force-field,[8] modified as described below, to optimize the geometries of substituents in various conformations and configurations. The lowest energy conformation of each stereoisomeric transition structure is then compared, in order to predict the relative energies of transition structures leading to stereochemically different products. If several conformations of a given transition structure configuration are within a few kcal/mol in energy, then a Boltzmann distribution over all minimum energy conformations is used to obtain a predicted ratio of stereoisomeric products.

Schleyer,[25] DeTar,[26] Müller,[27,28] and Still[29] have used force-field techniques to estimate activation energies for various reactions. Schleyer developed a force-field for carbocations, and applied it to solvolysis and radical-forming reactions, assuming the transition states for the reactions to resemble the cationic or radical intermediates.[25] DeTar used a hydrocarbon force-field to study steric effects on ester hydrolysis, using a hydrocarbon model to simulate the tetrahedral intermediate.[26] Müller used a hydrocarbon model to simulate the transition state of nucleophilic additions to carbonyls,[27] and calculated alcohol and ketone energies for simulation of the activation energies of alcohol oxidations and solvolysis reactions.[28] Still has studied the stereochemistries of nucleophilic additions and macro-ring formation by MM2 calculations on reactants and products.[29] However, our model has several advantages over these prior force-field models, particularly in the use of a relatively precise *ab initio* model for the transition state, as well as through certain useful tricks to account for forces which are present in the transition state, but not in reactants and products. Garbisch *et al.* devised a technique closest in spirit to ours. He developed a force-field model to study the rates of diimide reductions of substituted alkenes.[30] The method was very successful, but required the Herculean development of a force-field specific to the transition structure studied. The Garbisch model incorporated both modifications of bond-changing processes as well as substituent influences, but required numerous judicious guesses about transition state force constants.

Our model attributes differences in the energies of diastereomeric transition structures to differences in energies of interaction of substituents with each other, or with the atoms undergoing bonding changes. We assume that the positions of atoms involved in bond-changing processes are unaltered by substituents. This assumption appears somewhat drastic, but seems to work rather well. The model currently does not take into account possible entropy differences between diastereomeric transition structures. This assumption may prove to be problematical for some cases, but seems like a reasonable initial assumption. In any case, all the assumptions of the model can only be vindicated by the comparisons of predictions to results, given here.

The specifics of our model are described as follows. As demonstrated in Figs. 2 and 7, the bond lengths and angles of the partially formed and partially broken bonds in the various hydroboration transition structures are relatively constant. Although larger changes are expected for more highly substituted cases, our model makes the assumption that the four bond lengths and angles for the four atoms intimately involved in bonding changes in the four-centered transition state (CCBH) are constant.

The angles of atoms attached to B or to the alkene carbons change somewhat more, in accord with the fact that angle bending is considerably easier than bond stretching or compression. In our model, positions of hydrogens on C–C---B which are present both in the ethylene–borane transition structure and in the substituted case are kept fixed. Substituents attached to C–C---B which replace a hydrogen in the calculated ethylene–borane transition state are given equilibrium bond angles with respect to the three geminal bonds which are identical to those calculated for the parent reaction. The coordinates of the substituent atoms are allowed to vary, with force constants equal to those for the corresponding product atoms. That is, the alkene carbons are treated as sp^3 carbons. Torsional interactions around bonds from the transition state atoms C–C---B to the first substituent atom are assumed to be sp^3–sp^3 (for two carbons), in order to reproduce the tendency for staggering which our *ab initio* calculations suggest is very much like that in the product. The remaining parameters are normal. That is, all parameters involving only substituent atoms are Allinger's recom-

mended MM2 values.[8] Van der Waals' interactions between all atoms on substituents and those involved in bonding changes are also included.

The treatment of bonds to boron is somewhat problematical, since parameters for tetracoordinated boron are not available. We have assumed that substituent atoms which are attached directly to boron have distances and angles fixed at the values for the CH_3BH_2–ethylene transition state. This makes the model too inflexible about boron, and future models will utilize *ab initio* force constants calculated for the transition state to provide more quantitative predictions.

SPECIFIC CASES

1. *Asymmetric hydroborations with isopinocampheyl and diisopinocampheyl boranes*

Brown *et al.* have explored the use of optically active boranes for the enantioselective synthesis of alcohols from alkenes.[3] Diisopinocampheylborane, known also as di-3-pinanylborane, prepared from α-pinene, and mono-3-pinanylborane show high stereoselectivities with some types of alkenes. Figure 8 summarizes the stereoselectivities observed with these reagents and various types of alkenes. With *trans*-disubstituted and trisubstituted alkenes, loss of α-pinene from the di-pinanyl reagent accompanies hydroboration,[3] so that the ratios of enantiomers with di-3-pinanylborane are probably a result of hydroboration by the mono-pinanyl compound, di-pinanyl compound, and the 3-pinanyl-alkylborane, where the alkyl group is derived from the alkene being reduced. Examples of stereoselective hydroboration-oxidation of additional alkenes, as well as allenes, will be described later.

Many models have been proposed to rationalize these and related results.[31-35] Our conclusions differ in significant ways from all of these, since we have been able to numerically evaluate the preferred conformation of the pinanyl groups in these reactions. A brief comparison with previous models will be made later.

We have applied the model described in the previous section to the study of these asymmetric hydroborations. The calculated preferred conformations of mono- and di-pinanyl borane are shown in Fig. 9,[36]

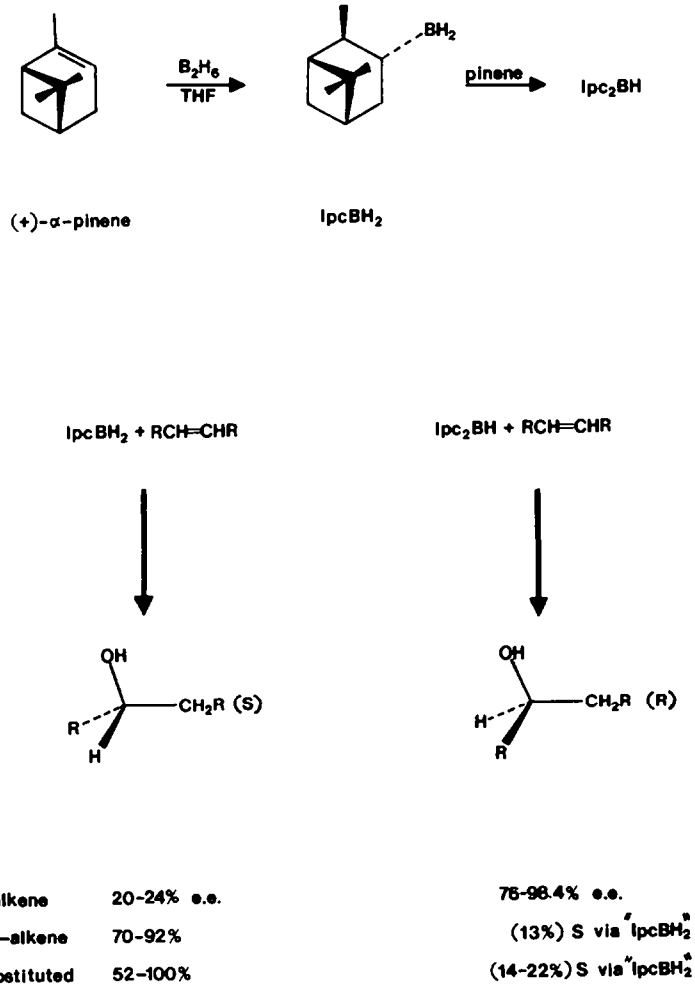


Fig. 8. Preparations of mono- and di-3-pinanylboranes ($IpcBH_2$ and Ipc_2BH) from (+)-α-pinene, and summary of stereoselectivities of alkene hydroboration-oxidations with these reagents.

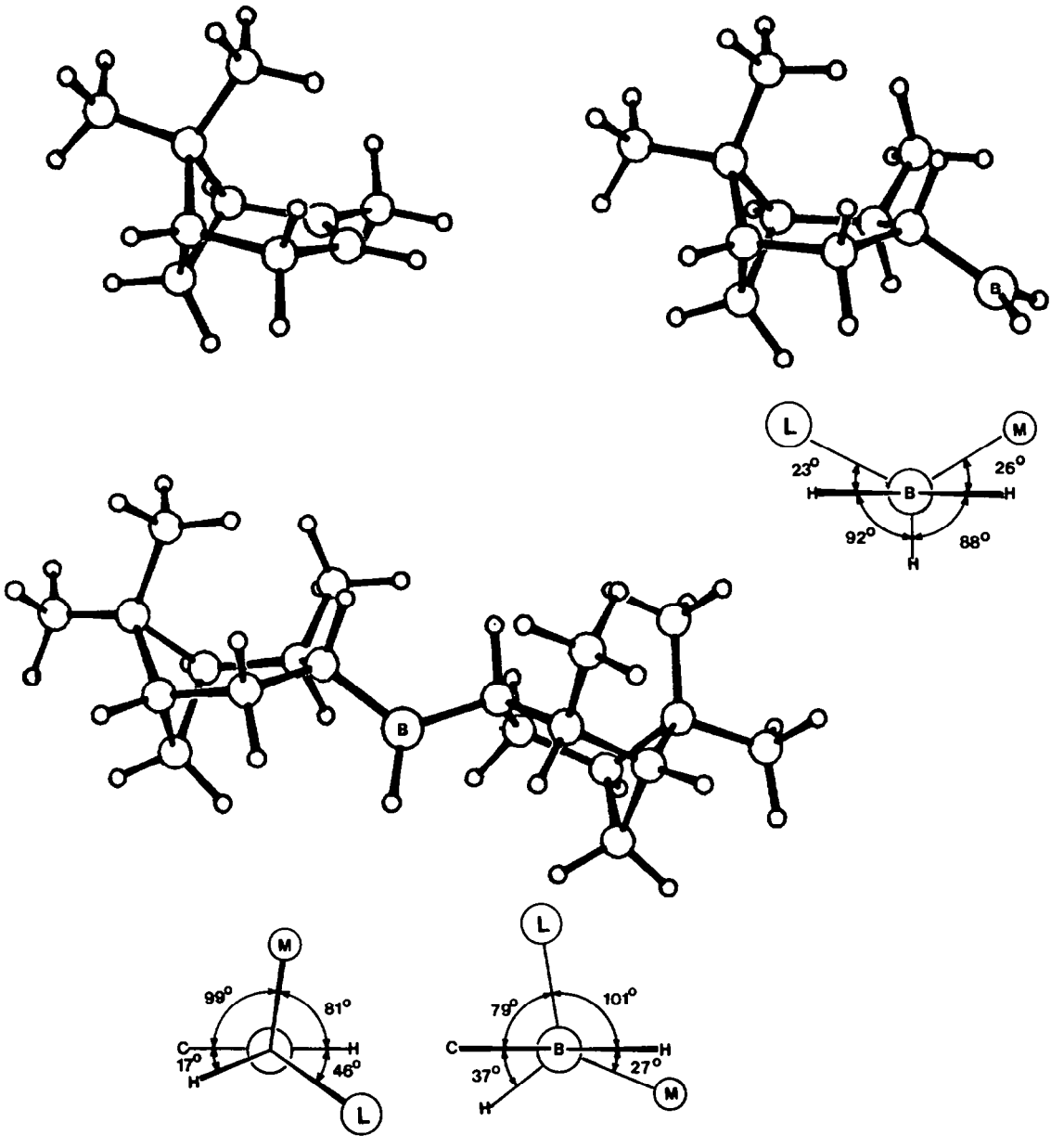


Fig. 9. The MM2 structures of (+)-α-pinene and mono- and di-3-pinanylboranes. The shorthand notation used in later figures is given at the bottom.

along with sketches of the starting (+)-α-pinene from which these reagents are derived, and a shorthand for the chiral center as proposed by Brown *et al.*, and used in a variety of models for this reaction which have been proposed in the literature. Although the conventional drawing of the 3-pinanyl group suggests a chair conformation with Me and boron equatorial on the 3-C bridge, the MM2 calculations suggest a much more flattened ring, which must arise from both the presence of the cyclobutane ring, which opens up the C7-C1-C2 and C7-C5-C4 angles, and because flattening of the ring relieves eclipsing around the C1-C2 and C4-C5 bonds.

Several of the previous models have concentrated on the preferred conformation of the starting borane or borane dimer. Our model focusses directly on the preferred transition state conformation, since not only is the reactant conformation irrelevant in principle, but it is found here not to correspond to the preferred conformation in the transition state.

Mono-3-pinanylborane reactions. For the reaction of a simple alkene such as *cis*-2-butene with monopinanylborane, there are a large number of minimum energy conformations possible in the transition state. As we have described earlier in this paper, there is always a preference for staggering about the bond from boron to the substituent. Thus, the pinanyl group can have three distinct staggered conformations about this B–C bond. The alkene can then approach the borane from above or below the boron plane. Finally, there are two possible orientations of the butene Me groups with respect to the pinanyl

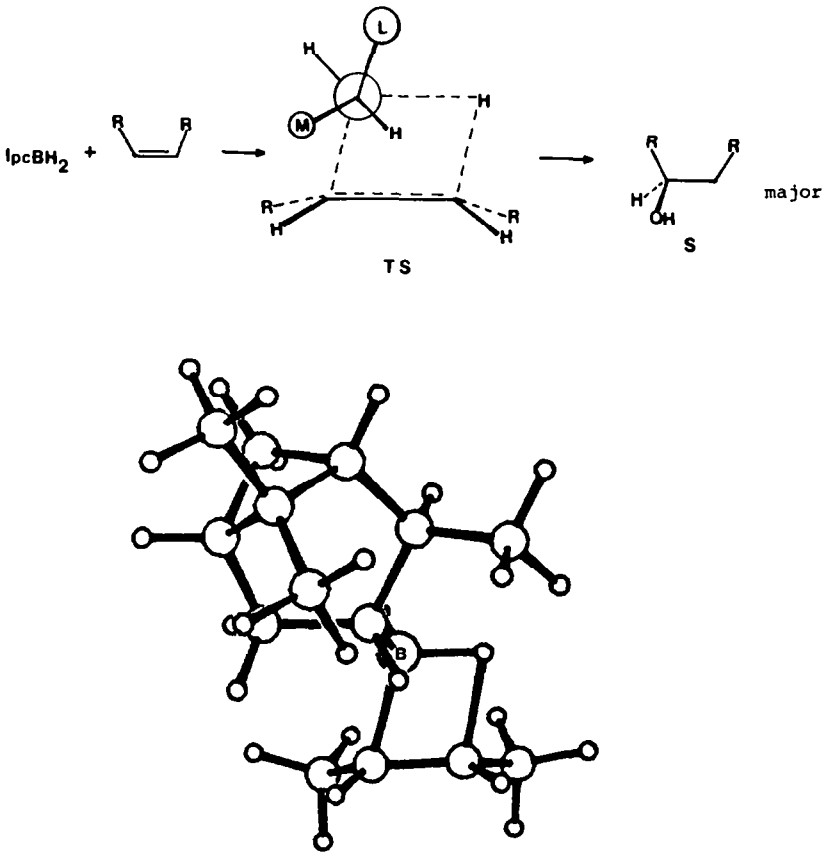


Fig. 10. The preferred conformation of the MM2[3-21G] transition structure of the reaction of 3-pinanylborane (from (+)-α-pinene) with *cis*-2-butene. This leads to the S (major) alcohol.

group. Thus, for *cis*-2-butene there are twelve reasonable staggered conformations, which served as the starting points for our transition state computations. Six of these would give the *S*-alcohol after oxidation of the borane product, while the other six would give the *R* alcohol. The lowest energy transition structure leading ultimately to the *S* alcohol is shown in Fig. 10. This, and the preferred transition structure for formation of the *R* (minor) alcohol (Fig. 11), both have the pinanyl group *anti* to both alkene Me groups. The lower energy transition state, which gives the *S* alcohol, has the best arrangement possible for the pinanyl group: the smallest group on the chiral center, H, is *inside*, the medium-sized group, $-CH_2-$, is *outside*, and the largest group, –CHMe–, is *anti*. The preferred transition structure for formation of the minor (*R*) alcohol is quite similar, but when the butene attacks from the other face of the borane, the best possible pinanyl arrangement has the largest group, –CHMe–, *outside*, and the medium-sized group, $-CH_2-$, *anti*. This is higher in energy than that shown in Fig. 10 because the methyl group of CHMe now experiences non-bonded repulsions with the neighboring atoms of *cis*-2-butene.

The calculated difference in energy between the two transition structure models shown in Figs. 10 and 11 is 1.1 kcal/mol, favoring formation of the *S* alcohol. This agrees with experiment qualitatively, but the difference in energy is higher than expected from the ratio found experimentally, undoubtedly due to the rigidity built into our model around the B atom, and the inflexibility of the alkene H's and the four atoms involved in bonding changes. We have also calculated the energies of the other ten minimum energy conformations, and the energies of all twelve transition structures were used to calculate a predicted ratio of diastereomers of 74% *S* and 26% *R*, or 48% enantiomeric excess. The only transition structures sufficiently low in energy to contribute significantly to these ratios are those in which the pinanyl group and the butene Me groups are *anti*. For the preferred transition state, which leads to the *S*-alcohol, the transition structures involving ~120° and 240° rotation of the pinanyl group are 2.6 and 1.9 kcal/mol higher in energy than that shown in Fig. 10. For the transition state leading to the *R*-product, 120° and ~240° rotations give transition states only 0.4 and 0.7 kcal/mol less stable than the best *R*-transition state. Thus, the *R*-transition states are always higher in energy than the best *S*-transition state, but there are several conformations of the *R*-transition state which are similar in energy, so that stereoselectivity is only modest.

Experimentally, the stereoselectivity observed with

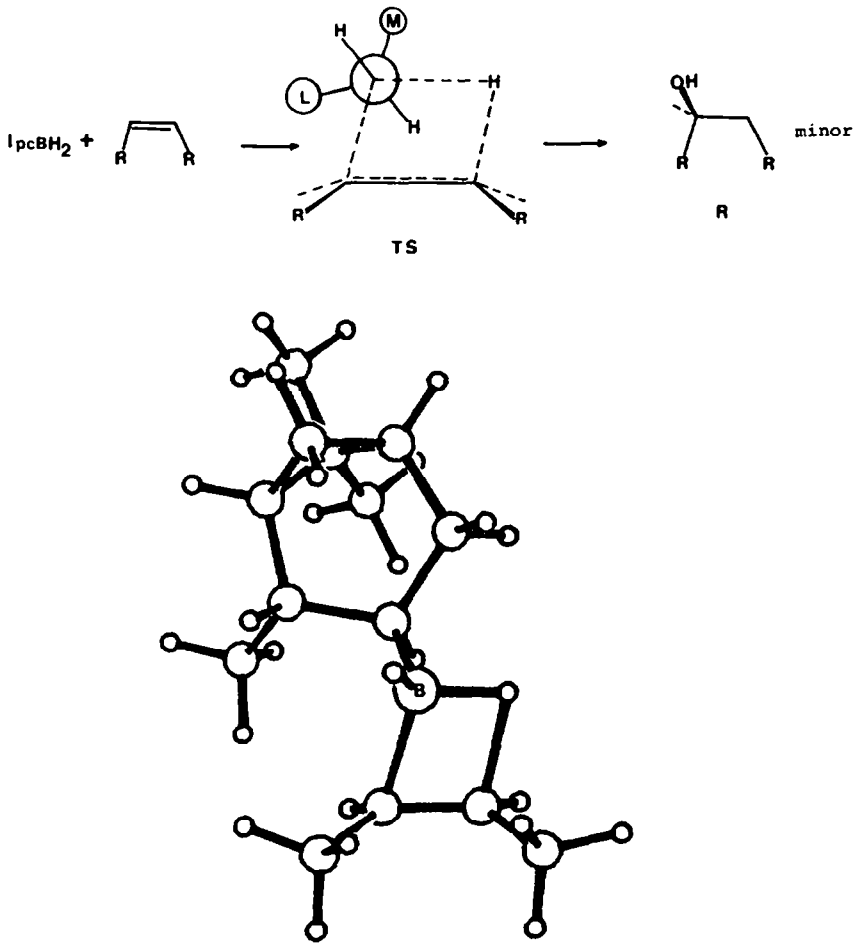


Fig. 11. The preferred MM2[3-21] transition structure for formation of the R (minor) alcohol.

trans-alkenes and mono-3-pinanylborane is much higher than that with *cis*-alkenes. The drawings of transition states for the *trans*-butene reaction, shown in Figs. 12 and 13, are very similar to those shown in Figs. 10 and 11. The preferred transition state has the Me at the butene C becoming bonded to boron disposed *anti* to the pinanyl group. This, of necessity, forces the other butene Me to be *syn* to the pinanyl group. This Me causes the conformations with H (inside) to be much more stable than those with M or L (inside). The two transition states shown in Figs. 12 and 13 are 1.0 kcal/mol different in energy, and there are no other conformations of either *R* or *S* transition states which are within 1.3 kcal/mol of the best transition state. The predicted ratio for *trans*-2-butene is 78% *S* + 22% *R*, a 56% enantiomeric excess, somewhat higher than that predicted for *cis*-2-butene. Our model predicts only a small increase in selectivity, whereas experimentally the selectivity is more than doubled.

The high stereoselectivity observed experimentally with *trans*-alkenes is paralleled by that found for trisubstituted alkenes. We have not calculated models for these cases, but they are expected to be very similar to those for the *trans*-2-butene case, with the Me group *syn* to the pinanyl producing strong preference for the transition state with the H *inside*, and "M" and "L" preferring the *outside* and *anti* arrangements.

Di-pinanylborane. The most obvious difference between the mono- and di-pinanylborane reactions is that the former (from (+)-α-pinene) preferentially forms *S*-alcohols, while the latter gives *R* predominantly. The reason for this is shown quite clearly in the transition structure for the reaction of di-pinanylborane with *cis*-2-butene, shown in Fig. 14. Only one of the pinanyl groups can achieve the ideal conformation with the H *inside*, the $-CH_2-$ *outside*, and the –CHMe– *anti*.

The second pinanyl group, which is in back of boron in Fig. 14, assumes a conformation which places the largest group, –CHMe–, *inside*! The reason for this unexpected behavior is clearly the direct interaction between the two pinanyl groups. This conformation is also predicted to be favored for the dipinanylborane-ethylene transition state. It relieves steric repulsion between M and L, or L and L, on the two pinanyl groups. The preferred transition structure now clearly makes the two pinanyl groups effectively very different in size. The Me group at the

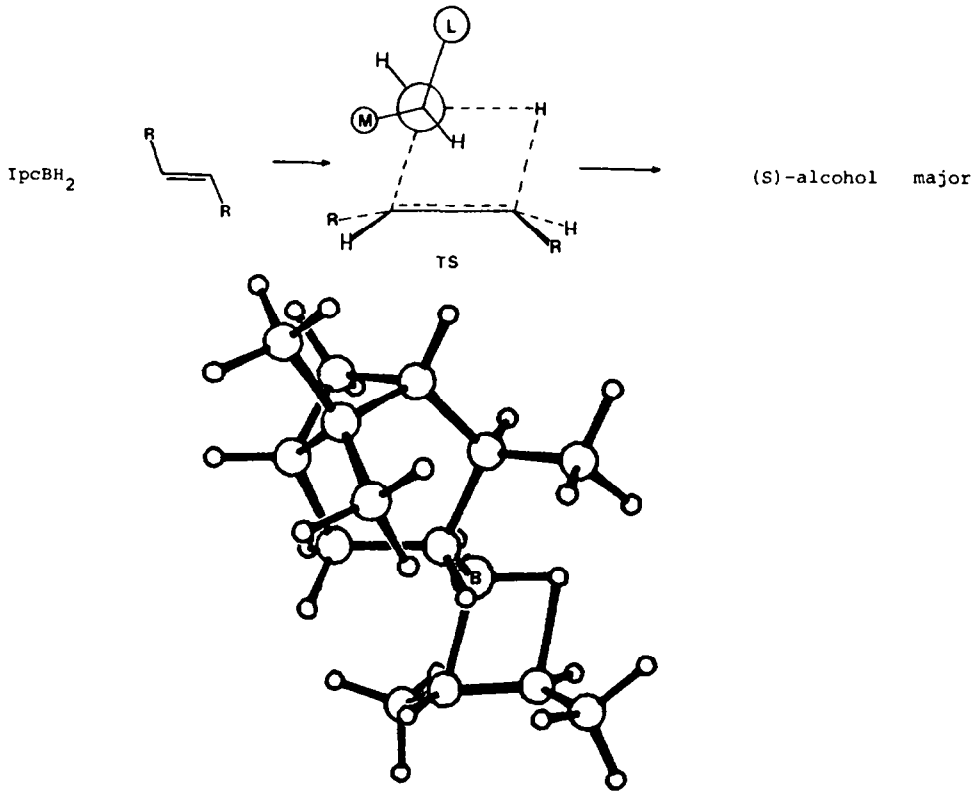


Fig. 12. Preferred conformations of MM2(3-21G] transition structure for mono-3-pinanylborane hydroboration of *trans*-2-butene to form the S (major) alcohol.

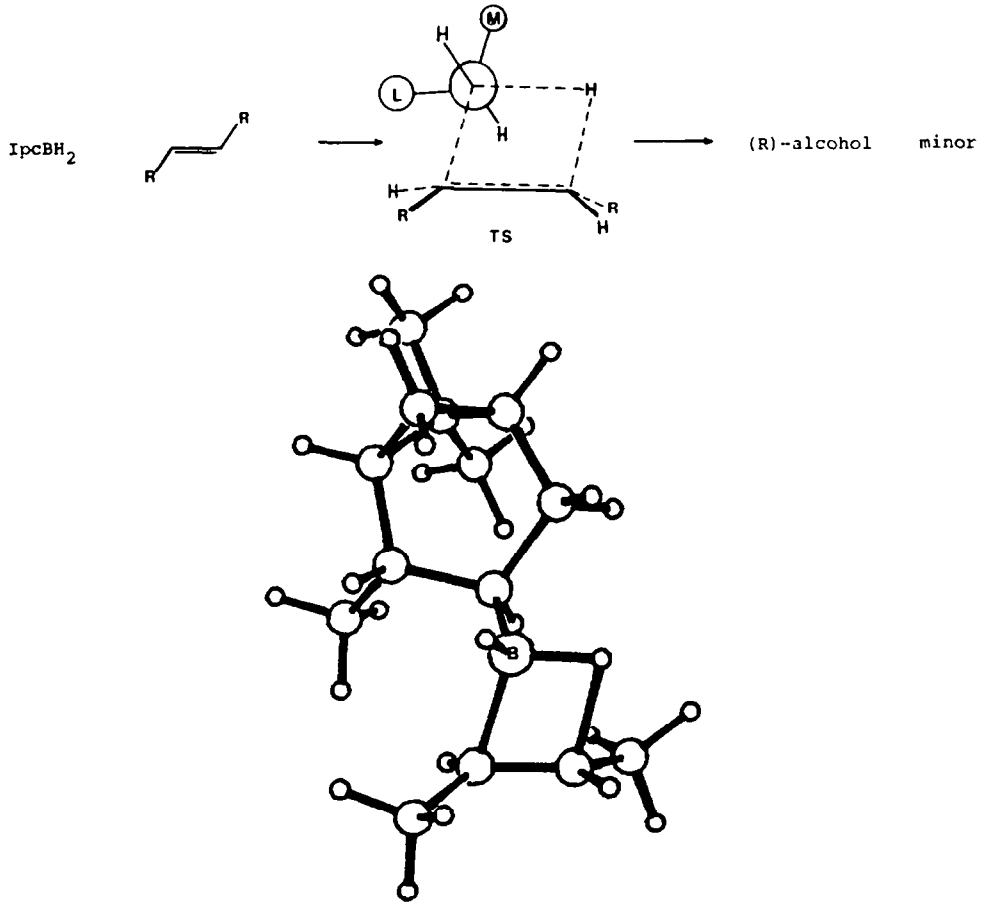
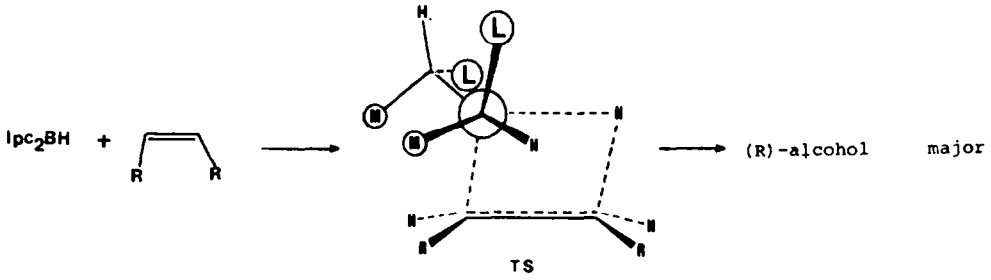


Fig. 13. Preferred transition structure for formation of the R (minor) alcohol from *trans*-2-butene.



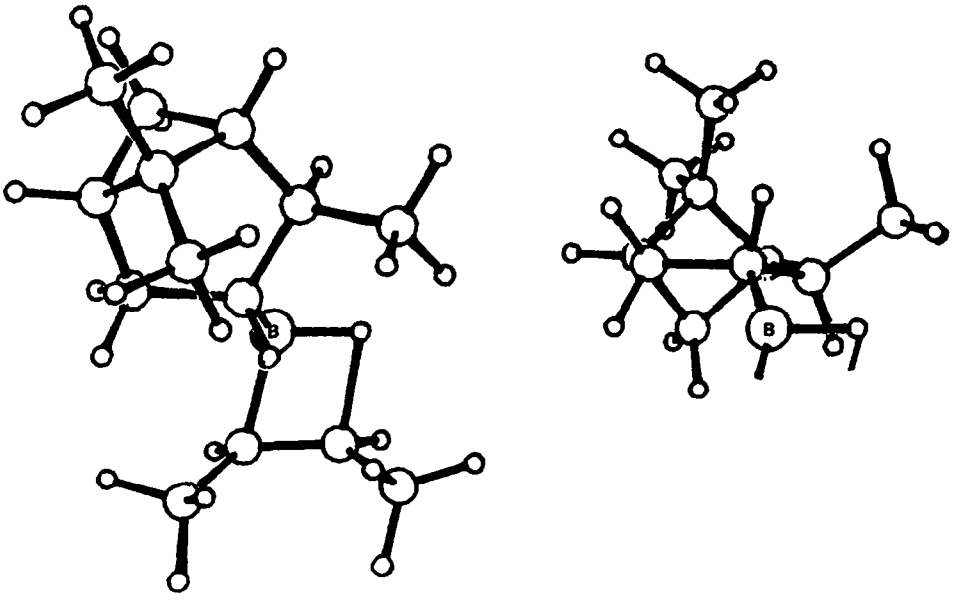


Fig. 14. Preferred MM2[3-21G] transition structure for hydroboration of *cis*-2-butene with di-3-pinanylborane. The computer drawing on the left shows the front pinanyl group connected to the transition state atoms, while the drawing at the right shows only the back pinanyl attached to BH.

alkene C becoming bonded to boron prefers to be near the (front) pinanyl group which is in the preferred conformation. In this way, it is near the CH_2 (M) and H of the front pinanyl group, rather than near the CH_2 (M) and the CHMe(L) of the back pinanyl. The stereoselectivity with *cis*-alkenes is now very high because the transition structure shown is 3.7 kcal/mol lower in energy than the best one leading to the S product. The S transition structure (not shown) has the H's of both pinanyls *inside*, to relieve the repulsions between the butene methyl and the L group of the back pinanyl.

trans-Alkenes and trisubstituted alkenes react very sluggishly with dipinanylborane, and α-pinene is frequently displaced when hydroboration occurs. Thus, hydroborations of *trans* or hindered alkenes occur not by a simple reaction of dipinanylborane with the alkene, but by the reaction of monopinanylborane, pinanyl-alkylborane (where the alkyl group is formed from the alkene), and perhaps by some reaction of dipinanylborane, as well. We predict that the *S*-product should be slightly favored with dipinanylborane and *trans*-butene, but by a small amount, since all conformations are similar, and quite high in energy. The reason for the low reactivity of the dipinanyl reagent with *trans* or trisubstituted alkenes is the severe crowding between the alkene alkyl group which is *syn* to the effectively larger pinanyl group. Some of this repulsion can be relieved by rotation of the back pinanyl group to the conformation with H *inside*, but only at the expense of increased pinanyl–pinanyl repulsions.

1-Alkenes also form alcohols stereoselectively when a D label is present on the alkene to establish the direction of attack of the borane. Figure 15 shows the preferred transition structures for formation of the major product. As with *cis*-2-butene, the major factors controlling preference for this product are the preferred conformation of the pinanyl groups, which makes the back group effectively larger, and the placement of the alkene alkyl group near the effectively smaller pinanyl group.

Although we have not yet carried out computations on other systems, the model developed above can be applied to understand the stereochemistry of reactions of dipinanylborane with 1,1-disubstituted alkenes and with allenes, as well. Figure 15 shows the transition states which we propose for these reactions. For 1,1-disubstituted alkenes, the larger of the two alkyl groups prefers to be away from the effectively larger pinanyl group. This leads to the prediction of formation of the *R*-alcohol,

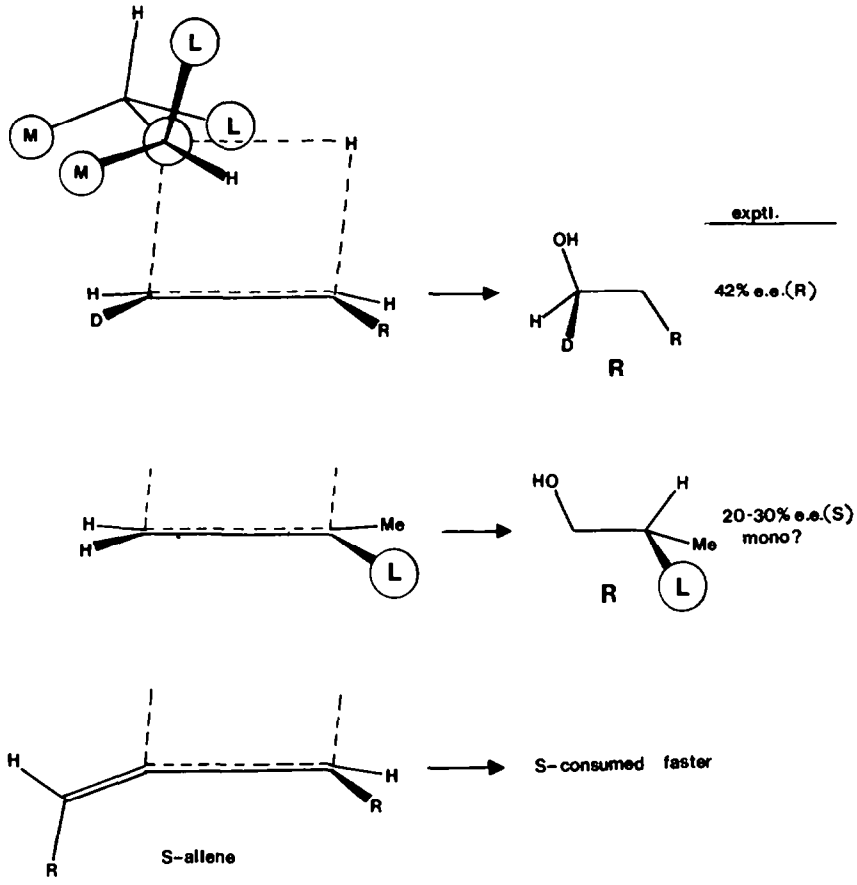


Fig. 15. Expected transition structures for hydroboration of 1-alkenes, 1,1-disubstituted alkenes, and 1,3-disubstituted allenes with dipinanylborane.

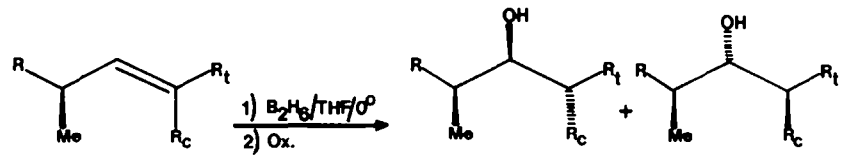
whereas a modest preference for *S* is actually observed. We believe that this must arise from displacement of α-pinene, and reaction with monopinanylborane or monopinanyl-alkylborane, as for *trans*- and trisubstituted alkenes.

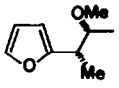
Caserio and Moore have found that *S*-allenes are hydroborated faster than *R*-allenes.[35] Our model, shown in Fig. 15, shows the origin of this preference. The least hindrered approach leads to fastest reaction. The *R*-allene could only be hydroborated through a transition state with one of the alkyls in a more hindered location than in the transition state for reaction of the *S*-allene.

How does our model differ from those suggested earlier? The major advance afforded by our model is the relative certainty about transition structure conformations achieved by the model *ab initio* calculations, and the heretofore unrecognized preference for staggering about the forming CB and breaking BH bonds in the transition states of these reactions. There is a relatively simple and obvious way that substituents attach to this transition state in a sterically least-hindered fashion. Other models generally considered the conformation of the starting borane and attempted to deduce how an olefin approaches the borane.

For dipinanylborane, our model implies that stereochemical preferences arise from repulsions between alkyl substituents and the small (H) group on the "front" pinanyl group versus the large (CHMe) on the back. Brown's model and Streitwieser's attributed stereoselectivity to competition between Me interactions with S or M.[31,32] Varma and Caspi also attributed differences to S and L, as in our model, although the preferred conformation of the borane in the transition state was not the staggered one we propose.[33] The McKenna model uses the dimer,[34] but is otherwise like the Brown model, while Moore's model for allenes uses a non-planar transition state.[35] Neither of these subtleties are necessary to explain stereoselectivity.

Chiral centers on C . . . . . B. Kishi has discovered a variety of examples of hydroborations of this type, and has proposed a model to rationalize these results.[4] Figure 16 summarizes the stereoselectivities observed for several reactions of this type, along with Kishi's model to rationalize these results. Kishi proposed that the alkene would align itself in the conformation shown, which is expected to be that favored for the ground state of alkenes, with the smallest of the groups (H) on the chiral center eclipsed with the alkene double bond. The borane



R	R_c	R_t		
$BzOCH_2$-	-Me	$-CH_2OCH_2OMe$	71	: 29
$BzOCH_2$-	$-CH_2OCH_2OMe$	-Me	75	: 25
	-Me	$-CH_2OBz$	92	: 8
	$-CH_2OH$	-Me	89	: 11

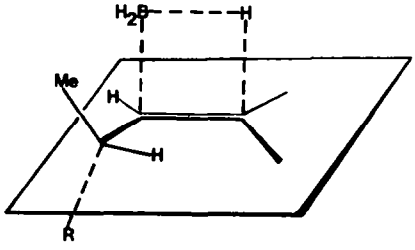


Fig. 16. Stereoselectivities of hydroborations of chiral homoallylic ethers. Kishi's "reactant-conformer", steric-approach model is shown at the bottom.

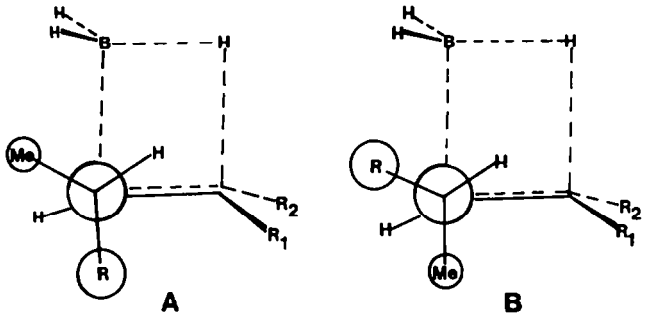
then approaches from the side of the medium-sized substituent (Me) rather than the side of the larger O-containing substituent.

Our version of this steric model, which is staggered, but otherwise similar to Kishi's, has been described earlier in this paper (Fig. 5) and in an earlier article.[14] However, we were concerned about why groups such as 2-furyl or alkoxymethyl should be substantially larger than methyl, since most of the bulk of these groups could easily be directed away from the remaining atoms involved in the transition state.

Indeed, when various model systems were calculated with our MM2 technique, we could find essentially no difference in steric effects for the preferred conformation of transition states for *re* or *si* attack for such molecules. Figure 17 shows the relative energies of several diastereomeric transition states calculated by MM2. The generalizations made earlier do hold for groups which are clearly different in size, such as H, Me and t-Bu. We predict moderate stereoselectivities in such cases, as shown by the relative energies of diastereomeric transition states given in Fig. 17. However, the two types of substituents attached to the chiral center in Kishi's reactions are too similar to exert any significant steric effect on stereoselectivity, as shown in the last three cases.

However, the *ab initio* calculations described earlier for homoallyl ether interactions in the hydroboration transition state show that there can be a significant stabilizing interaction between a homoallyl ether and the alkene when this substituent is *anti*. Since this interaction is a unique electronic interaction (anchimeric assistance) in the transition state which is not accounted for by MM2, our model will not reproduce these results. However, we can correct our MM2 model in the following way to give reasonable qualitative rationalizations of Kishi's results. As noted previously, 3-21G calculations indicate that an *anti* alkoxymethyl group prefers the *anti* conformation over the *outside* by 0.9 kcal/mol. The corresponding difference is only 0.4 kcal/mol for the Me group. Thus, the alkoxymethyl *anti* preference is 0.5 kcal/mol greater than the Me *anti* preference, and the ratio of products from A and B should be approx. 70:30, somewhat lower than is observed (Fig. 16).

These results also suggest that homoallylic amines and sulfides, and to a lesser extent, halides, will



R	R_1	R_2	$E_B - E_A$
t-Bu	H	H	0.50
t-Bu	Me	H	0.21
$-CH_2OMe$	H	H	0.03
$-CH_2OMe$	H	Me	0.04
$-CH_2OMe$	Me	H	0.08

Fig. 17. Preferred transition structures and relative energies according to the MM2[3-21G] model for hydroborations of 3,4,4-trimethyl-1-pentene, 4-methoxy-3-methyl-1-butene, and methyl derivatives.

exhibit the same stereochemical preferences shown by the homoallylic ethers, since these atoms are also capable of this type of anchimeric assistance.

Chiral center at the H----C *terminus*

1. *Alkyl substituents.* We already described a qualitative model for pure alkyl cases. Although simple examples have not been tested experimentally, Midland has reported several cases involving a steroid nucleus as the chiral moiety.[5] The results fit our qualitative model satisfactorily. Examples of chiral ketone reductions are also known,[5] and can be rationalized by a similar model.

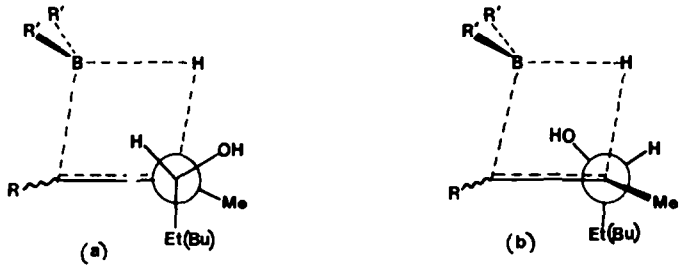
2. *Allylic alcohols and ethers.* For the parent system, we have described calculations which indicate a preference for an allylic OH substituent to be *inside* or *outside*, while an allylic ether prefers the *outside* conformation. An MM2 model constructed in the usual way provides the same prediction, but also allows us to compute how alkyl substituents on boron, or additional substituents on the alkene, will influence stereoselectivity. Figure 18 compares some calculated results obtained from the MM2 model to experimental results obtained by Still.[6] For computational simplicity, we substituted Et groups in place of the Bu groups present in Still's examples, and we placed Me's on boron to model the dialkylboranes used in some experiments.

For the 3-hydroxyalkenes with an unsubstituted terminus, or those with a *trans*-Bu-substituted terminus at C-1, little stereochemical preference is obtained upon hydroboration with diborane. This is also found computationally. When a dialkylborane is used, or when there is a *cis* substituent at C-1 of the alkene, a strong preference for formation of the diastereomer arising from the "H-*inside*, OH-*outside*, R-*anti*" transition state is found. In these cases, the *inside* conformation is sterically hindered, so the OH strongly prefers the *outside* position. With ethers, the OR *outside* conformation is always preferred, although here the calculations underestimate the degree of preference.

3. 1,3-*Asymmetric induction.* Finally, Evans *et al.* have reported several hydroborations involving molecules with chiral centers which are homoallylic to the disubstituted terminus of an alkene (Fig. 1d). We have applied our MM2 model to an example of this type, and the best transition states for formation of the major and minor diastereomers are shown in Fig. 19. These differ in energy by 0.8 kcal/mol, predicting a ratio of ~80:20 at room temperature, in good agreement with the ratios found experimentally.[7]

Our calculations indicate that the origin of this 1,3-asymmetric induction is precisely that proposed by Evans.[7] The forming C---H bond causes the large allylic substituent to move into the sterically least crowded *anti* position, while the two allylic hydrogens are located in the *inside* and *outside* positions. There is staggering around the C(allylic)-C(homoallylic) bond, and the largest substituent on the homoallylic C is aligned *anti* to the bond to the alkene C. In the preferred (*R*,*S*)-transition state, the homoallylic Me substituent is away from the alkene Me, while in the (*S*,*S*)-transition state, the homoallylic Me and alkene Me experience significant repulsion. The double-headed arrows show these different interactions in the two transition structures.

Since similar effects are operative for chiral centers at either alkene terminus or even on boron, other examples of 1,3-asymmetric induction are likely to be



		E_{rel} (kcal/mol)		Experimental	
R	R'	(a)	(b)	Ratio	$\Delta\Delta G^{\ddagger}$
H	H	0	-0.1	1:1.4	-0.2
	Me(R)	0	0.9	2.5-41:1	0.5-1.4
trans-Et(Bu)	H	0	-0.1	1:1	0
	Me(R)	0	0.8	8-9:1	1.2-1.3
cis-Et(Bu)	H	0	0.5	6:1	1.1
	Me(R)	0	0.4	>15:1	>1.6

Fig. 18. Comparisons of MM2[3-21G] predicted diastereomer ratios, and Still's experimental results for related cases.

found. Indeed, the chiral center in longifolylborane, a useful optically active hydroborating reagent,[4] is located β to the boron.

CONCLUSIONS

We have identified a number of conformational, steric, and electronic factors which lead to stereoselectivities in a variety of known hydroborations. Having identified these, and developed a numerical method which provides good estimates of stereoselectivity, we are in a position to undertake real challenge, the prediction of the unknown! The ideas developed here allow us to develop reliable design criteria to be used in arriving at promising new avenues of experimental study. In subsequent papers, we will use the principles and methods reported here to predict useful new stereoselective reagents.

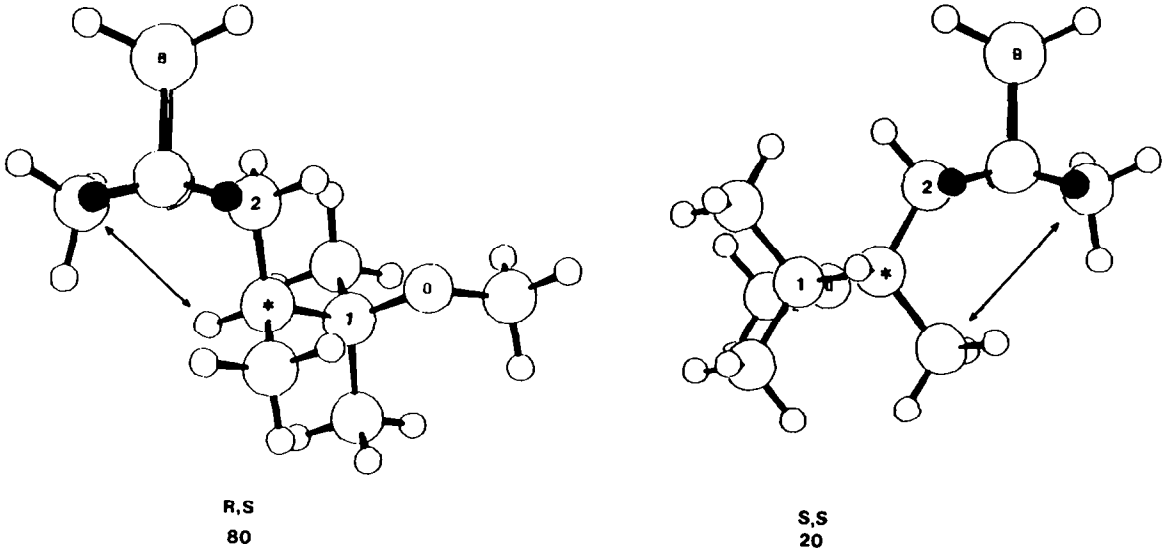


Fig. 19. Computed transition structures for formation of *R,S* (major) and *S,S* (minor) products in Evan's hydroborations.

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[36]The figures are drawn from calculations in which the boron and three attached atoms were constrained to lie in a plane. Calculations in which this constraint was removed resulted in conformations very similar to those shown, but with a pyramidal borane group. The parameters used in these calculations were normal, except for boron, for which force constants for stretching, bending, and torsion were set equal to those of sp^2 carbon. The equilibrium CB and CH bond lengths and CBC, CBH and HBH angles were taken from *ab initio* calculations on methylborane and dimethylborane. The van der Waals radius of boron was used in the calculation of van der Waals repulsions involving the B atom.