the small preferences which are seen at C_2 suggest electrophilic attack *anti* to methyl in **2b** and *syn* to methyl in **2c** and **2d**. The noted preferences in **2d** (the conformer with the highest HOMO energy and presumaby the most reactive) are also very small; were this species to play a major role in the overall process, the FMO model would be at a loss to indicate stereochemistry.

Stereochemical preferences in the three conformers serving as models for cyclic allylic alcohols and ethers are also small and, except for that in structure **2i**, also change with regiochemistry. Attack onto C_1 (the preferred regiochemistry) of the most stable conformer **2g** is indicated to occur from the side of hydrogen, while addition onto C_1 in structure **2h** is suggested to be from the side of the OH group. The highest energy form, **2i**, shows no preference at C_1. Insignificant orbital polarizations are also noted of all stable conformers for all three allylic fluorides.

Supplementary Material Available: Appendices B (The Construction and Application of Chemical Reactivity Models), C (Improved Treatments of Electrophilic Reactivity. The Role of the Polarization Potential), and D (Calculated Equilibrium Structures) (10 pages). Ordering information is given on any current masthead page.

Modeling Chemical Reactivity. 5. Facial Selectivity in Diels-Alder Cycloadditions

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Abstract: Diastereofacial selectivity in Diels-Alder cycloadditions involving chiral dienes and dienophiles is influenced by electrostatic interactions, independent of topological distortions involving the participating molecular orbitals. Modeling studies indicate that for reactions involving electron-rich dienes and electron-deficient dienophiles, addition occurs preferentially onto the diene face which is the more reactive toward electrophiles and onto the face of the dienophile which is the more reactive toward nucleophiles. Comparisons with available experimental stereochemical data are favorable except for reactions involving bridgehead dienophiles, where steric factors may come into play. Rules for the assignment of the reactive diene and dienophile diastereotopic faces are presented.

The simultaneous creation of four contiguous chiral centers continues to spur development in Diels-Alder cycloaddition chemistry.[1] Recent reports[2-12] have shown that allylic substitution on a diene or dienophile with heteroatom functionality effects marked diastereofacial selectivity in the ensuing carbon-carbon bond-forming reaction, and moreover, in at least one case, that "equivalent" diene and dienophile substitutions result in opposite stereochemical biases.[2a] Previous discussions of diastereofacial selective Diels-Alder cycloadditions have relied on simple steric arguments[13] or alternatively on topological distinctions involving the relevant frontier oribitals,[14,15] i.e., the HOMO on the diene and LUMO on the dienophile. In light of recent experience, which suggests that FMO theory is an ineffective tool for the elucidation of reaction regiochemistry[15a] and stereochemistry,[15b-d] we approach the latter class of arguments with considerable skepticism. The purpose of this paper is to suggest an alternative rationale for the observed diastereofacial selectivity in Diels-Alder cycloadditions and to provide a set of simple rules allowing predictive assignments to be made for new systems. Our developments are founded on the matching of complementary energy surfaces for the two cycloaddends and have resulted from our continuing efforts to develop simple and broadly applicable models for chemical reactivity.[16,17] They provide a consistent rationale for the complementary selectivities observed upon diene and dienophile substitution.

Discussion

It has been established that the observed regiochemistry of Diels-Alder cycloadditions of electron-rich dienes and electron-

(1) (a) Desimoni, G.; Tacconi, G.; Barlo, A.; Pollini, G. P. *Natural Products Synthesis through Pericyclic Reactions*, ACS Monograph no. 180, American Chemical Society, Washington, DC, 1983. (b) Petrizilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.

(2) (a) Franck, R. W.; Argade, S.; Subramanian, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187. (b) Franck, R. W.; John, T. V. *J. Org. Chem.* **1983**, *48*, 3269. (c) Franck, R. W.; John, T. V.; Olejniczak, K. *J. Am. Chem. Soc.* **1982**, *104*, 1106. (d) Franck, R. W.; John, T. V. *J. Org. Chem.* **1980**, *45*, 1170.

(3) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911.

(4) (a) Yoshida, K.; Grieco, P. A. *Chem. Lett.* **1985**, 155. (b) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *J. Am. Chem. Soc.* **1983**, *105*, 1403.

(5) Grēe, R.; Kessabi, J.; Mosset, P.; Martelli, J.; Carriē, R. *Tetrahedron Lett.* **1984**, *25*, 3697.

(6) (a) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1983**, *105*, 5874. (b) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1980**, 6.

(7) Horton, D.; Machinami, T.; Takagi, Y. *Carbohydr. Res.* **1983**, *121*, 135.

(8) Schmidlin, T.; Burckhardt, P. E.; Waspe-Šarčevič, N.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 450.

(9) Jones, D. W., *J. Chem. Soc., Chem. Commun.* **1980**, 739.

(10) (a) Jurczak, J.; Tkacz, M. *Synthesis* **1979**, 42. (b) Jurczak, J. *Polish J. Chem.* **1979**, *53*, 209.

(11) CF. Winstein, S.; Shavatsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183.

(12) Mant, L.; Peters, J. A.; Prazeres, M. A. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 205.

(13) There are examples of steric effects exerting control over diastereofacial selectivity in Diels-Alder cycloadditions. See: Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, and references therein.

(14) Diastereofacial selectivity has been discussed in terms of "orbital tilting", see: Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 32 and references therein.

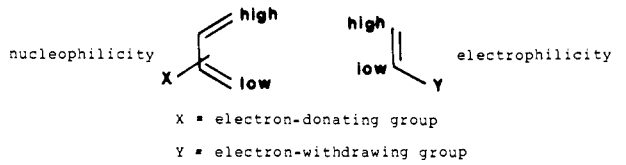
(15) For a discussion of "orbital factors" controlling diastereofacial selectivity, see: Anh, N. T. *Tetrahedron* **1973**, *29*, 3227.

(16) (a) Kahn, S. D.; Pau, C. F.; Overman L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381. (b) Kahn, S. D.; Pau, C. F.; Hehre, W. J. *Ibid.* **1986**, *108*, 7396. (c) Kahn, S. D.; Hehre, W. J. *Ibid.* **1986**, *108*, 7399. (d) Part 4: Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *Ibid.* in this issue.

(17) (a) Pau, C. F.; Hout, R. F., Jr.; Francl, M. M.; Hehre, W. J. *J. Comput. Chem.*, submitted for publication. (b) Hehre, W. J. Pau, C. F.; Hout, R. F., Jr.; Francl, M. M. *Molecular Modeling. Computer-Aided Descriptions of Molecular Structure and Reactivity*; Wiley: New York, 1987.

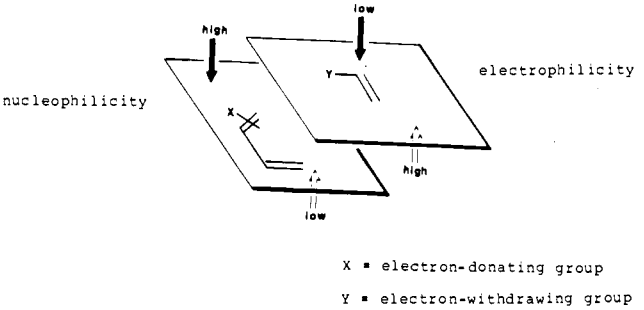
0002-7863/87/1509-0663$01.50/0

deficient dienophiles follows from matching the nucleophilicity of the diene (as a function of position) and the electrophilicity of the dienophile,[16a,18] i.e.,



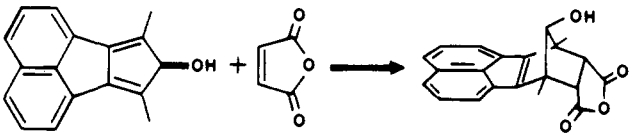
This suggests that electrostatic interactions play a major role in dictating regioselectivity. The application of reactivity models to the description of regiochemistry in Diels–Alder reaction, while outwardly similar to the frontier molecular orbital (FMO) approach,[15] whereby regiochemistry is specified by the pairing of the larger (terminal) HOMO coefficient in the diene, with the larger LUMO coefficient in the dienophile, differs fundamentally from the FMO approach in that it is based on the comparison of interaction energies rather than orbital coefficients. It has also been pointed out that, although the FMO model generally provides an adequate account of the regiochemistry of Diels–Alder reactions involving simple (monosubstituted) dienes, it fails to properly describe the relative regiodirecting abilities of different substituents or of the same substituent on different diene positions.[16a] In view of the considerable synthetic utility of Diels–Alder chemistry of highly functionalized dienes,[20] this shortcoming of the simple (FMO) theory is indeed unfortunate. On the other hand, the reactivity models have been shown to be successful in accounting for the observed regiochemistry of cycloadditions involving both simple dienes as well as polyfunctionalized systems.[16a]

Extension of electrostatic considerations to the description of diastereofacial selectivity in Diels–Alder reactions involving chiral dienes and dienophiles is straightforward. Simply stated, *cycloadditions involving electron-rich dienes and electron-poor dienophiles should occur preferentially onto the diene face which is the more nucleophilic and onto the face of the dienophile which exhibits the greater electrophilicity*, i.e.,



These generalizations (as well as those above describing preferred regiochemistry) will reverse for reactions of electron-deficient dienes and electron-rich dienophiles.[16a,21] It is to be reminded that the observed diastereofacial biases of the nucleophilic and electrophilic reactivity surfaces are not a consequence of nonequivalent orbital extension[16d,22] although in some cases they may reflect topological asymmetry.

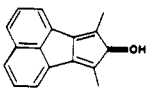
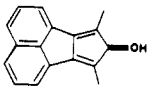
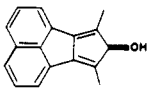
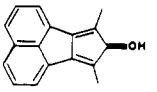
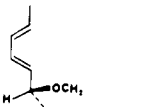
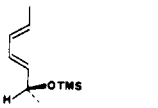
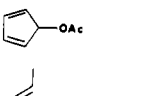
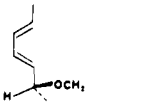
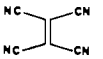
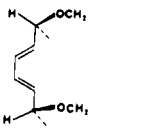
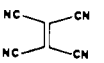
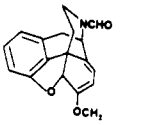
Investigation by modeling techniques of asymmetric induction about chiral allylic double bonds has established an inherent preference for the addition of electrophiles *syn* to a lone-pair-containing allylic substituent, e.g., or, and *anti* to an electropositive allylic substituent, e.g., SiR_3.[16b,d,23] This result suggests that the approach of a dienophile (an "electrophile") to a chiral diene will occur *syn* to the directing allylic functionality for groups having lone pairs, e.g., alcohols, amines, and their derivatives, and *anti* to electropositive allylic substituents, e.g., silanes (Table I). There is experimental support. For example, Jones[9] has demonstrated the stereoselective *syn* addition of maleic anhydride to a 1-hydroxycyclopenta-2,4-diene, i.e.,



The remaining experimental data on related cycloadditions[2a,5,11,12] summarized in Table I are also in accord.

Conversely, modeling studies of nucleophilic addition to chiral vinyl sulfoxides[16c] as well as a variety of other electron-deficient olefins and allenes[24] have demonstrated the pronounced preference for addition of nucleophiles *anti* to electron-rich centers, e.g., the lone pair on sulfur or the sulfoxide oxygen. Again, in the present context, this finding indicates that substituted dienophiles will be

Table I. π-Facial Selectivity of Dienes with α-Chiral Centers Containing Heteroatom Functionalities

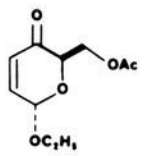
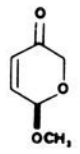
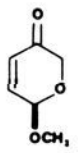
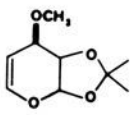
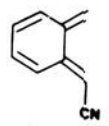
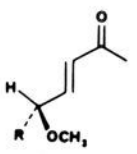
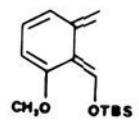
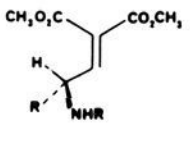
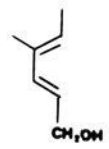
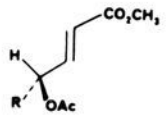
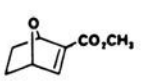
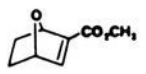
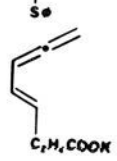
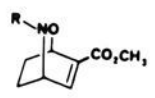
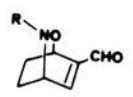
entry	diene	dienophile	selectivity[a]	ref
1			*syn*	9
2			*syn*	9
3			*syn*	9
4			*syn*	9
5			*syn*	2a
6			*syn*	2a
7			*syn*	11
8			*syn*	5
9			*syn*	5
10			*syn*	12

[a] With respect to the heteroatom functionality on the diene.

(18) For examples of these complementary reactivity surfaces, see ref 16a.
(19) For a discussion, see ref 16a and ref 1 and 2 contained therein.
(20) For a recent discussion, see ref 1b.
(21) Kahn, S. D.; Overman, L. E.; Hehre, W. J., research in progress.
(22) (a) Anh, N. T., *J. Chem. Soc., Chem. Commun.* **1968**, *1089*. (b) Inagaki, S.; Fukui, K. *Chem. Lett.* **1974**, 509. (c) Fukui, K. *Theory of Orientation and Stereoselection*; Springer-Verlag: New York, 1975. (d) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703 and references therein to earlier work.

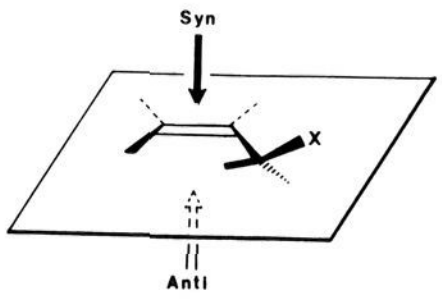
(23) This is to be contrasted with a previously stated empirical rule[2a] which does not take account of the electronic nature of the directing group. It remains to be established experimentally whether the stereochemical course of diastereoselective Diels–Alder cycloadditions vary upon replacement of an allylic alcohol with an allylic silane.
(24) Kahn, S. D.; Hehre, W. J. research in progress.

Table II. π-Facial Selectivity of Dienophiles with α-Chiral Centers Containing Heteroatom Functionalities

entry	dienophile	diene	selectivity[a]	ref
1			*anti*	6a
2			*anti*	10a
3			*anti*	10a
4			*anti*	2b
5			*anti*	2c
6			*anti*	8
7			*anti*[b] *syn*	7
8			*syn*	4b
9			none	4a
10			*syn*	3
11			*syn*	3

[a] With respect to the heteroatom functionality on the dienophile. [b] $AlCl_3$ used as a catalyst.

attacked by a diene (the "nucleophile") *anti* to a lone-pair-containing allylic substituent. Taken together with the aforementioned results on electrophilic additions, this allows elaboration of a set of rules, enabling predictive assignments of the diastereoselectivity in cycloaddition reactions. There rules, based on electrostatic considerations, prove to be broadly successful in accounting for the variety of experimental stereochemical data[2-12] discussed herein.



	ELECTROPHILE	NUCLEOPHILE
X=ELECTRON RICH	SYN	ANTI
X=ELECTRON POOR	ANTI	SYN

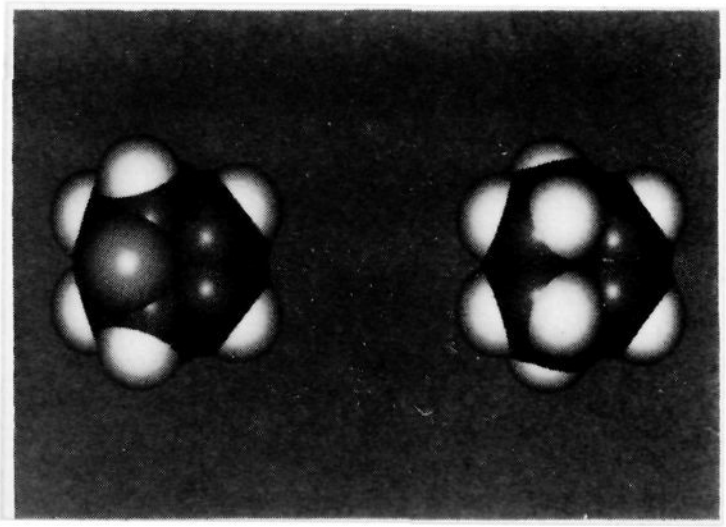
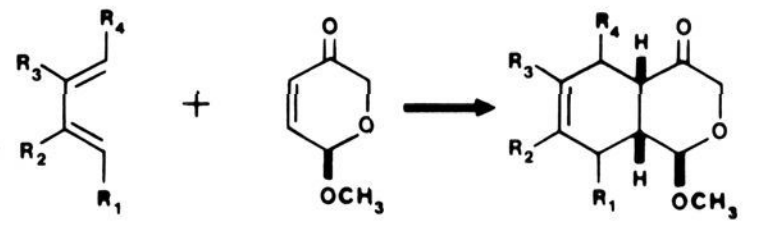


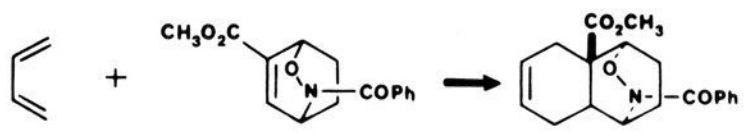
Figure 1. Space-filling models for 7-oxabicyclo[2.2.1]hept-2-ene showing faces of the π bond *syn* (left) and *anti* (right) to the oxygen bridge.

The available experimental data for stereoselective Diels–Alder reactions involving dienophiles with heteroatom containing chiral functionality (Table II) provide further support for the proposed rules. Indeed, Jurczak and Tkacz[10a] have shown that the cycloaddition of 2-methoxy-5,6-dihydro-2*H*-pyran to various methylated butadienes occurs stereoselectively, with the diene adding *anti* to the directing methoxy group on the dienophile, i.e.,



R_1, R_2, R_3, R_4 = H, Me

The preferred direction of attack on the "nucleophilic" diene onto the dienophile, i.e., away from the lone-pair-containing ether functionality, is in accord with known preferences for nucleophilic additions to chiral olefins.[16c] While several other experimental studies provide further support for the selectivity rule,[2,6,8] data for reactions involving bridgehead dienophiles are in disagreement with the conclusions of the simple model.[3,4] For example, Boger and co-workers[3] have established that the cycloaddition of butadiene with methyl *N*-benzoyl-3-aza-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate proceeds stereoselectivity *syn* to the NO bridge, i.e.,



Note, however, that permanganate oxidation of this compound occurs preferentially *anti* to the NO bridge.[13] While the nature of MnO_4^- as a reagent remains to be firmly established, previous[16d] and ongoing[24] theoretical work suggests that it is best modeled as a nucleophile. Therefore, it is reasonable to hypothesize that the inherent electronic bias in this system, i.e., directing approach of a nucleophile (or "nucleophilic" diene) *anti* to the NO bridge, is overridden by some factor which is unaccounted for the modeling treatment. We suspect that steric interactions may be involved. Indeed, examination of space-filling models for 7-oxabicyclo-[2.2.1]hept-2-ene (Figure 1) clearly reveals that the face of the

double bond *syn* to heteroatom bridge is less crowded than the anti face. Whether steric factors alone are sufficient to subjugate what would appear to be a strong electronic preference resulting from heteroatom functionality remains a matter for further investigation.

We conclude that electrostatic interactions play an important role in determining diastereofacial selectivity in Diels–Alder cy-

cloadditions (just as we believe they exert considerable influence on product regiochemistry[16a]) and have proposed a set of simple rules to assign facial stereochemistry based on these interactions. Steric effects also appear to be important in some instances, although the proper relative weighting of the two remains to be established. Further efforts to explore this issue as well as the eventual consequences of electrostatic control of reaction regio- and stereochemistry are presently underway in our laboratory.[21]

Note Added in Proof. Fleming and Williams[25] have found that addition of 2,5-di(trimethylsilyl)cyclopentadiene with tetracyanoethylene gives rise to a single product, corresponding to the addition of the dienophile *anti* to the electropositive trimethylsilyl group on the diene. This result, which is in full accord with electrostatic dictates, would also have been reached on the basis of steric arguments.

(25) Fleming, I.; Williams, R. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 684.

Modeling Chemical Reactivity. 6. Comparison of Conformational Energy Profiles and Electrophilic Reactivities and Stereoselectivities of Chiral Allylic Alcohols and Ethers. Evidence against Intramolecular Hydrogen Bonding in Allylic Alcohols

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Abstract: Conformational energy profiles for 3-buten-2-ol and 2-methoxy-3-butene, obtained from a uniform level of nonempirical molecular orbital theory, are qualitatively similar; the differences between the two appear to arise primarily because of steric interactions. The lowest energy conformers for both position the OH (OR) group directly over the double bond, casting doubt on the previously advanced interpretation that the equilibrium conformation of the allylic alcohol is directed in part by hydrogen bonding between the hydroxylic hydrogen and the π bond. It suggests instead that the conformational biases in both the alcohol and ether are influenced primarily by minimization of oxygen lone pair–π bond repulsion. Electrostatic potentials indicate a preference for electrophilic attack *anti* to the OR group in the high-abundance but low-reactivity conformers of 2-methoxy-3-butene and *syn* to OR in the less abundant but much more reactive conformers, the same preferences as have previously been noted in 3-buten-2-ol. Given that electrophilic addition to allylic alcohols and ethers generally occurs *syn* to the OH (OR) functionality, the results of the theory support a notion that the overall reaction stereochemistry in these systems is influenced more by relative conformer reactivity than by relative abundance.

The use of alcohols and their derivatives for asymmetric induction is widespread and well-documented.[1,2] The entire spectrum of organic reaction types, i.e., oxidation, reduction, electrophilic and nucleophilic additions, and pericyclic processes, may be rendered stereoselective upon judicious incorporation of OR functionality in the substrate. Differences in reactivities of alcohols and their analogous ethers have generally been assumed to be steric in nature,[3] substitution at oxygen either effecting a change in the distribution of conformers (in flexible acyclic systems) or acting to "shield" the double bond from an incoming reagent. In fact, very little quantitative data actually exist with which to test such a "steric hypothesis". Only recently have the conformational preferences of a simple chiral alcohol been established experimentally,[4a] and there is virtually no experimental information regarding changes in the conformational profile of such a system as a result of substitution at oxygen. Because of the lack of experimental data, and in view of their obvious synthetic importance, we have undertaken a theoretical study to compare and contrast the conformational preferences and inherent reactivity differences of free alcohols with their methyl ether analogues.

Here we examine the conformational energy profiles for a simple chiral allylic alcohol, 3-buten-2-ol, and for its corresponding methyl ether, 2-methoxy-3-butene, as obtained from a uniform level of nonempirical (ab initio) molecular orbital theory. These particular systems have been chosen because they function as prototypes for a class of compounds of considerable importance to asymmetric synthesis[2] and because of the availability of a microwave spectrum for 3-buten-2-ol,[4a] in which structures and relative energies for the two (presumed) lowest energy conformers have been assigned. These data allow assessment of the performance of the theory.

Both allylic alcohol structures uncovered in the microwave study show the hydroxylic hydrogen proximate to the allylic π system; this has been interpreted as evidence for intramolecular hydrogen bonding.[4] Were this the primary factor responsible for the conformational preferences in 3-buten-2-ol, it would be expected that the conformational profile for the corresponding methyl ether, where "hydrogen bonding" can no longer occur, would be markedly different. The possibility that allylic alcohols and ethers might exhibit significant differences in equilibrium conformer populations would then provide the basis for explaining differences in their reactivity. Here we compare and contrast the conformational profiles of 2-methoxy-3-butene and its analogous alcohol, 3-buten-2-ol, and in so doing subject the hydrogen-bonding hypothesis to test.

Our second objective is to examine the similarities and differences in the electrophilic reactivities of analogous allylic alcohol

(1) For general reviews of asymmetric synthesis see: (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice Hall: New York, 1971. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (c) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, Vol. 2, 1983; Vol. 3, 1984; Vol. 4, 1985; Vol. 5, 1985.

(2) For several recent applications, see: Tetraheron. Symposia-in-Print: *Control of Acyclic Stereochemistry*: Mukaiyama, T., Ed. *Tetrahedron* **1984**, *40*, 2197–2343.

(3) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247 and references therein.

(4) (a) Smith, Z.; Carballo, N.; Wilson, E. B.; Marstokk, K.-M.; Møllendal, J. *J. Am. Chem. Soc.* **1985**, *107*, 1951. The microwave spectra of other allylic alcohols have been reported: (b) Murty, A. N.; Curl, R. F., Jr. *J. Chem. Phys.* **1967**, *46*, 4176. (c) Lum, D. K.; Bauman, L. E.; Malloy, T. B., Jr.; Cook, R. L. *J. Mol. Struct.* **1978**, *50*, 1. (d) Horn, A.; Marstokk, K.-M.; Møllendal, H.; Priebe, H. *Acta Chem.. Scand.* **1983**, *A37*, 679.

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