Ab Initio-Based Force Field Modeling of the Transition States and Stereoselectivities of Lewis Acid Catalyzed Asymmetric Diels−Alder Reactions

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Abstract: Transition states for the Diels−Alder reactions of butadiene and cyclopentadiene with methyl acrylate coordinated to BH_3 have been located with ab initio molecular orbital calculations and the 3-21G basis set; the activation energies were also evaluated by single point calculations with the 6-31G* basis set. In addition a solvent cavity (SCRF) calculation at the RHF/3-21G level was performed for the reaction of cyclopentadiene and methyl acrylate coordinated to BH_3 in a medium with a dielectric constant of 9.08. These data have been used to develop a modified MM2 force field applicable to the prediction of stereochemistries of Lewis acid catalyzed reactions of chiral acrylates to dienes. This force field has been shown to reproduce the selectivities of a number of literature examples. It has also been applied to the predictions of stereoselectivities of new reactions. Insights into the controlling elements in the stereoselectivity are obtained.

Introduction

Asymmetric synthesis is one solution to the important practical problem of producton of pure stereoisomers.[1,2] Successful stereoselectivity requires control of weak molecular interactions in the transition states of the reactions. There have been remarkable achievements in asymmetric synthesis, such as the Sharpless oxidation[3] and bis-hydroxylation,[4] the Knowles hydrogenation,[5] Evans' aldol reaction,[6] and various catalyzed Diels−Alder cycloadditions,[7] including Corey's "chemzymes".[8] It is a theoretical challenge to understand how these work and to apply that knowledge to the design of new reactions, reagents, and catalysts.

In this paper, we describe the development of a quantitative method for the calculation of stereoselectivity in one type of asymmetric reaction, the Lewis acid-catalyzed Diels−Alder cycloadditions of chiral acrylates to dienes. A force field has been developed and applied to a number of literature examples of asymmetric reactions, involving acrylates derived from chiral alcohols (**1**−**4** and **6**) and acrylamide **5** derived from valine (Scheme 1). We have also predicted the stereoselectivities of new reactions using the chiral auxiliaries, cyclopentanol **7** and oxazolidine **8**, and the naturally occurring chiral alcohols, picropodophyllotoxin **9** and podophyllotoxin **10**. We have analyzed the factors which control stereoselectivity in these cycloadditions, including dienophile conformations and steric interactions between diene and dienophile. Research in progress involves the application of this force field to reactions involving chiral Lewis acids and to the predictions of new reactions and catalysts.

Background

Diels−Alder cycloadditions are widely-used valuable synthetic tools.[9,10] The reactions are regioselective and stereoselective,[10a] and many are subject to Lewis acid catalysis[10b] which influences the rate of reaction as well as regioselectivity and stereoselectivity.[11] There are a number of examples of asymmetic Diels−Alder reactions in which the asymmetry is introduced by placing the chiral auxiliary in the dienophile (Scheme 2).[12] The first example of the use of a chiral auxiliary, the menthyl group (**1**), in a Diels−Alder reactions was reported by Walborsky and co-workers,[13] who found that the addition

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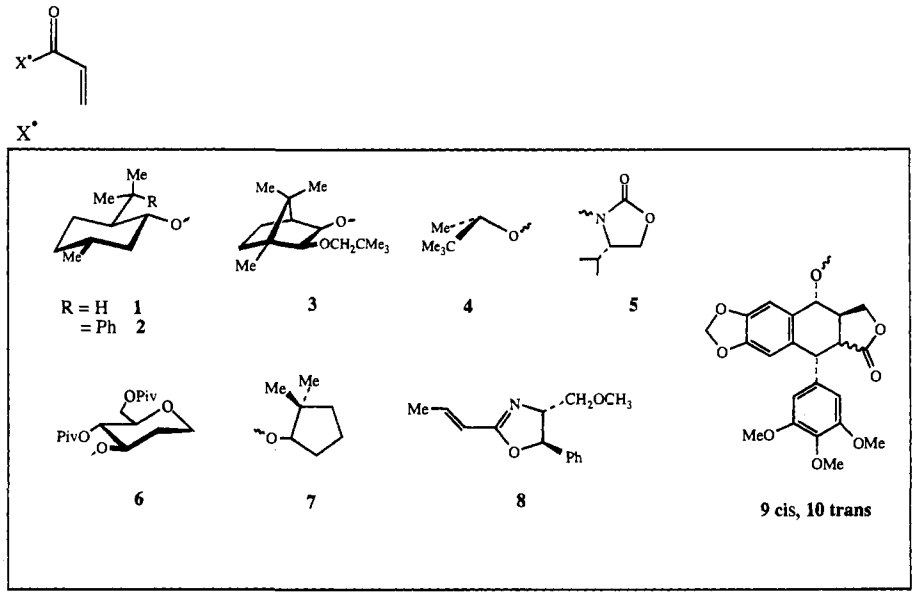
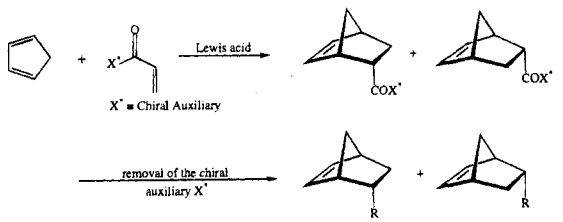
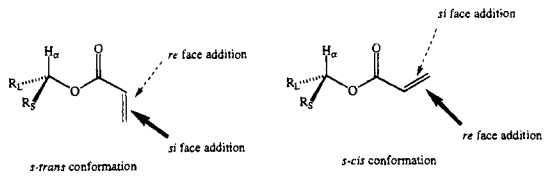
Scheme 1



Scheme 2



Scheme 3



of dimenthyl fumarate to 1,3-butadiene in the presence of $TiCl_4$ as Lewis acid catalyst afforded the Diels–Alder cycloadduct with a diastereomeric excess of 78%. Corey and co-workers[14] later introduced the 8-phenylmenthyl group (**2**), a very efficient chiral auxiliary used in the asymmetric synthesis of a prostaglandin intermediate. Most examples of asymmetric Diels–Alder reactions involve the use of α,β-unsaturated esters or amides bearing the chiral auxiliary.[12] These types of dienophiles are studied here.

We have recently reported the use of a force field model for the study of intramolecular Diels–Alder reactions.[15] This model is based on the MM2 force field developed by Allinger[16] with the inclusion of a set of parameters for the Diels–Alder transition structure derived from ab initio calculations. This combination of molecular mechanics and ab initio methods has been called *transition state modeling* and has been employed previously in the study of other organic reactions.[17]

Methods

The molecular mechanics calculations were performed with the MM2 force field.[16] Transition state parameters were derived from ab initio calculations on model systems as described in the text.[15,17] The complete list of MM2 parameters is available as supplementary material. The ab initio calculations on the Diels–Alder reaction of butadiene and cyclopentadiene with methyl acrylate complexed with BH_3 were carried out with the GAUSSIAN series of programs.[18a] The self-consistent reaction field (SCRF) calculations involve the optimization of structures in a spherical dielectric cavity.[18b]

Results and Discussion

We earlier reported[15] a force field based on ab initio calculations on the reaction of butadiene with BH_3-complexed acrolein.[19] This proved useful for the prediction of Lewis acid catalyzed intramolecular Diels–Alder reactions of terminally activated dienophiles. These calculations were performed with RHF/3-21G and 6-31G* calculations and led to a very asynchronous lowest energy transition structure for this reaction in which the acrolein reacts in an *s-cis* conformation. Ab initio calculations on the structure of the Lewis acid complexed acrylates have suggested an *s-trans* conformation for catalyzed reactions of esters.[20] The conformation of the dienophile in the transition state is an important element controlling the stereochemical outcome of the Diels–Alder reactions of chiral dienophiles.[12] If the diene adds only to the less hindered face

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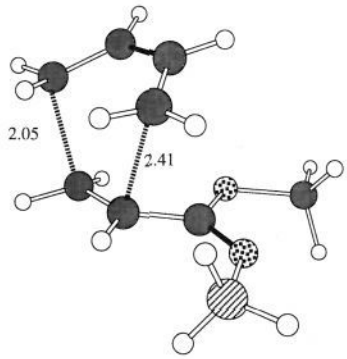
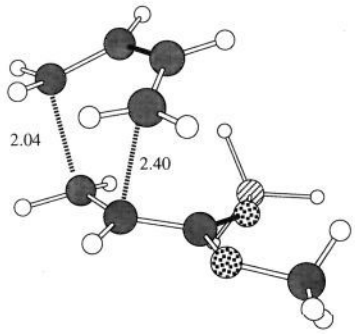
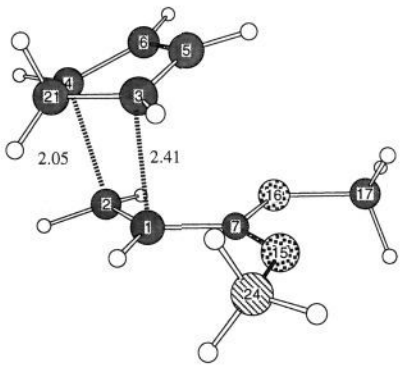


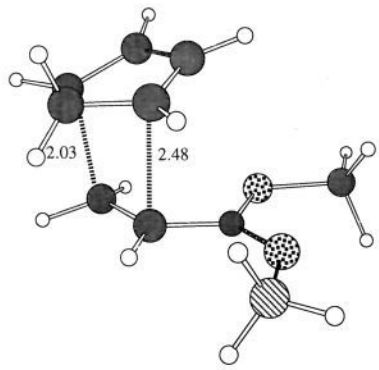
RHF/3-21G *s-trans* Transition Structure (TS 1)



RHF/3-21G *s-cis* Transition Structure (TS 2)



RHF/3-21G *s-trans* Transition Structure (TS 3)



RHF/3-21G SCRF *s-trans* Transition Structure (TS 4)

Figure 1. Ab initio transition structures for Diels–Alder reaction of butadiene and cyclopentadiene with methyl acrylate coupled to BH_3.

of the dienophile, then the *s-cis* and *s-trans* conformers will give opposite topicities (see Scheme 3). We performed ab initio calculations on the reactions of butadiene and cyclopentadiene with the methyl acrylate–BH_3 complex in order to determine the main geometrical requirements of the transition states for the Diels–Alder reactions of different dienes to esters.

Ab Initio Transition Structures for Lewis Acid Catalyzed Diels–Alder Reactions of Butadiene and Cyclopentadiene with Methyl Acrylate. Two transition structures for the Diels–Alder reaction of butadiene with the complex formed between the BH_3 and methyl acrylate were optimized with RHF/3-21G calculations (Figure 1). Energies were evaluated with 6-31G* single points on 3-21G geometries. Previous work demonstrates that the geometries, unlike energies, are not particularly sensitive to the basis set.[21] The *s-cis* and *s-trans* conformations of the acrylate moiety were studied. We only considered the endo approach, because the Diels–Alder reactions of chiral acrylates under study are very endo selective. The BH_3 group was located in the sterically unencumbered *anti* position to the OMe group in both structures; according to previous calculations,[20] this is the most stable complex between methyl acrylate and BH_3. These transition structures are somewhat less asynchronous than the endo *s-cis* transition structure of Diels–Alder reaction of butadiene with the BH_3–acrolein complex.[19] The forming bond lengths are 2.04 and 2.40 Å in the *s-cis* transition structure and 2.05 and 2.41 Å in the *s-trans*. The 3-21G activation energies are 29.9 kcal/mol for the *s-cis* transition structure and 26.6 kcal/mol for the *s-trans*. The *s-cis* transition structure is less stable than the *s-trans* by 3.3 kcal/mol at the 3-21G level, and by 3.8 kcal/mol at the 6-31G*//3-21G level. According to these calculations, the Lewis acid catalyzed Diels–Alder reaction of acrylic esters proceeds via the *s-trans* conformation of the dienophile. Another difference with the acrolein reaction is that the charge transfer from the butadiene to the acrylate moiety is smaller (~0.19 electron) as compared to that in the acrolein reaction (0.31 electron).

Table 1. Bond Lengths (Å) for the RHF/3-21G-Optimized Transition Structures for the Reaction of the BH_3–Methyl Acrylate Complex with Butadiene and Cyclopentadiene (See Scheme 4)

	butadiene		cyclopentadiene	
bond	TS 1	TS 2	TS 3	TS 4
C1–C3	2.41	2.40	2.41	2.48
C2–C4	2.05	2.04	2.05	2.03
C1–C2	1.39	1.39	1.38	1.38
C1–C7	1.43	1.43	1.42	1.41
C7–O16	1.34	1.34	1.33	1.33
O16–C17	1.46	1.46	1.46	1.46
C7–O15	1.25	1.22	1.25	1.26
O15–B24	1.64	1.66	1.64	1.62
C3–C5	1.36	1.36	1.37	1.37
C5–C6	1.40	1.39	1.40	1.40
C4–C8	1.38	1.38	1.39	1.40
C4–C21			1.52	1.52
C3–C21			1.51	1.50

The catalyzed reaction of cyclopentadiene with methyl acrylate was also studied and again only the endo approach and the *s-trans* conformation were considered. The BH_3 was located in the same position as before. The transition structure does not show any major change in geometry (Figure 1 and Table 1) compared to the corresponding butadiene transition structure. The forming bond lengths are now 2.05 and 2.41 Å, and the energy is 18.7 kcal/mol with RHF/3-21G calculations, nearly 8 kcal/mol below that for the butadiene reaction.[22]

To account for solvents effects, a SCRF calculation was performed for the cyclopentadiene reaction using the dielectric constant for CH_2Cl_2. The transition structure for the endo approach is slightly more asynchronous than in the absence of

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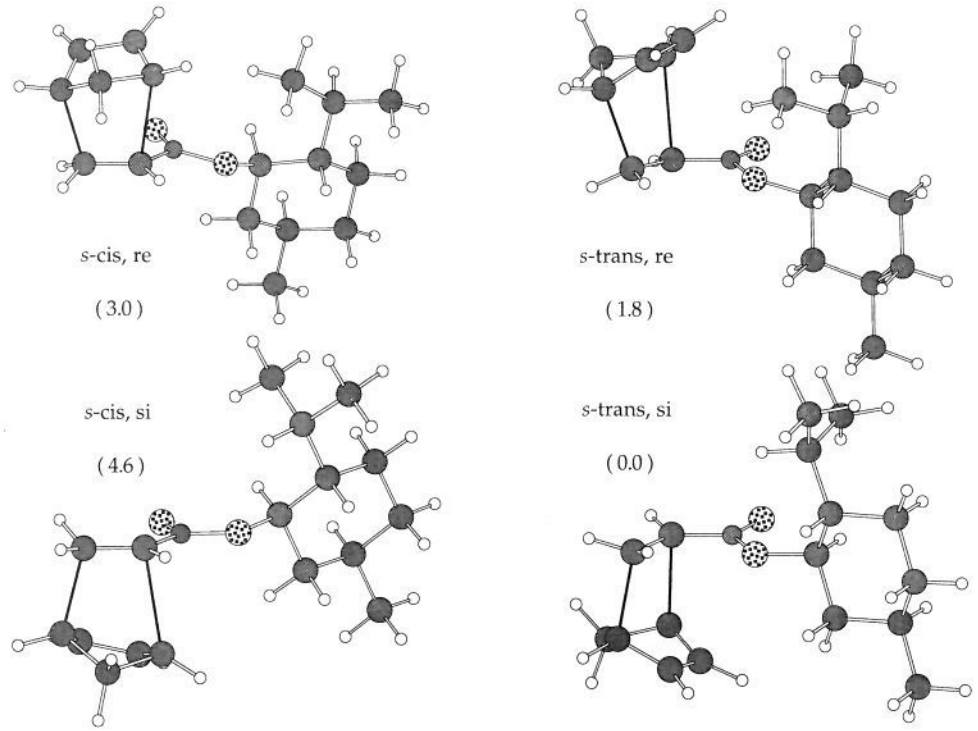

Figure 2. Endo transition structures for the reaction of cyclopentadiene with dienophile **1** (relative energies, kcal/mol).

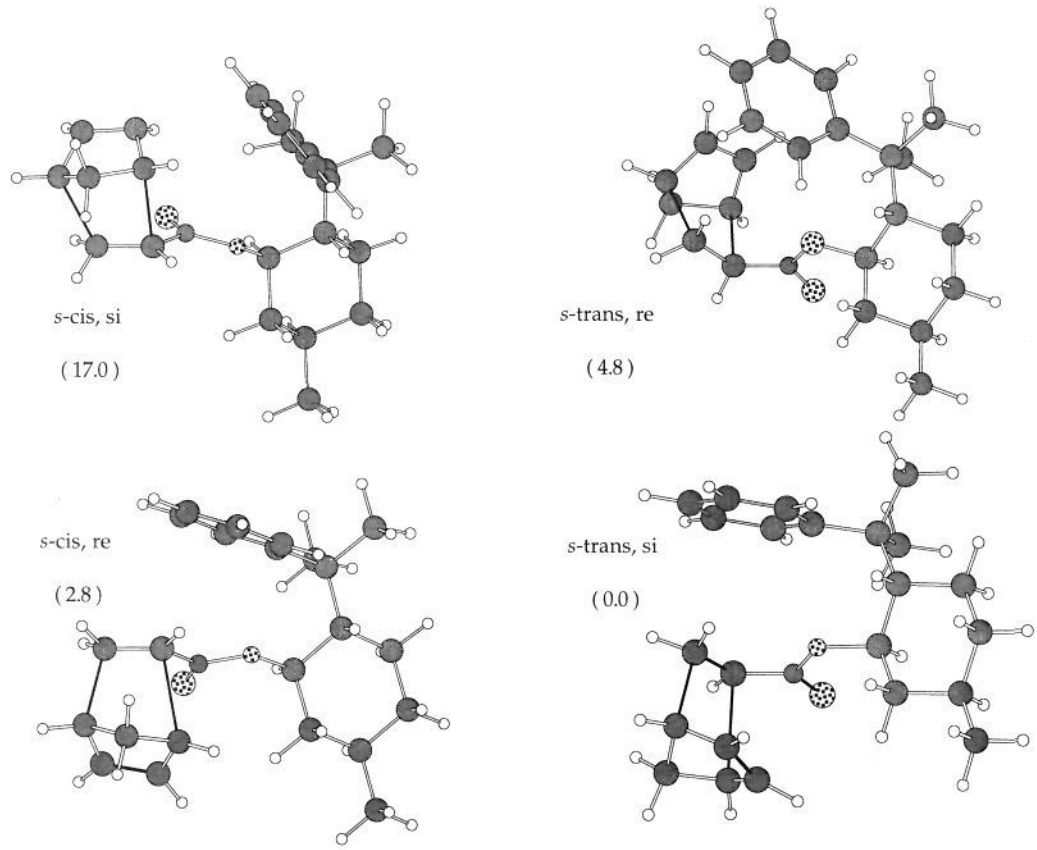

Figure 3. Endo transition structures for the reaction of cyclopentadiene with dienophile **2** (relative energies, kcal/mol).

the solvent cavity, with the forming bond lengths of 2.03 and 2.48 Å. Ruiz-López et al. reported a calculation of the transition structure for the reaction of cyclopentadiene and methyl acrylate in a medium with a dielectric constant of 78.[23] They found a minor change in the geometry of the transition structure. We developed the force field based on transition structures for the gas phase reaction between butadiene and the methyl acrylate–BH_3 complex.

Force Field Calculations on the Diels–Alder Reactions of Chiral Dienophiles 1–7. The catalyzed acrylate force field was developed as a modification of the butadiene, acrolein–BH_3 force field.[15] Changes were introduced in the parameters

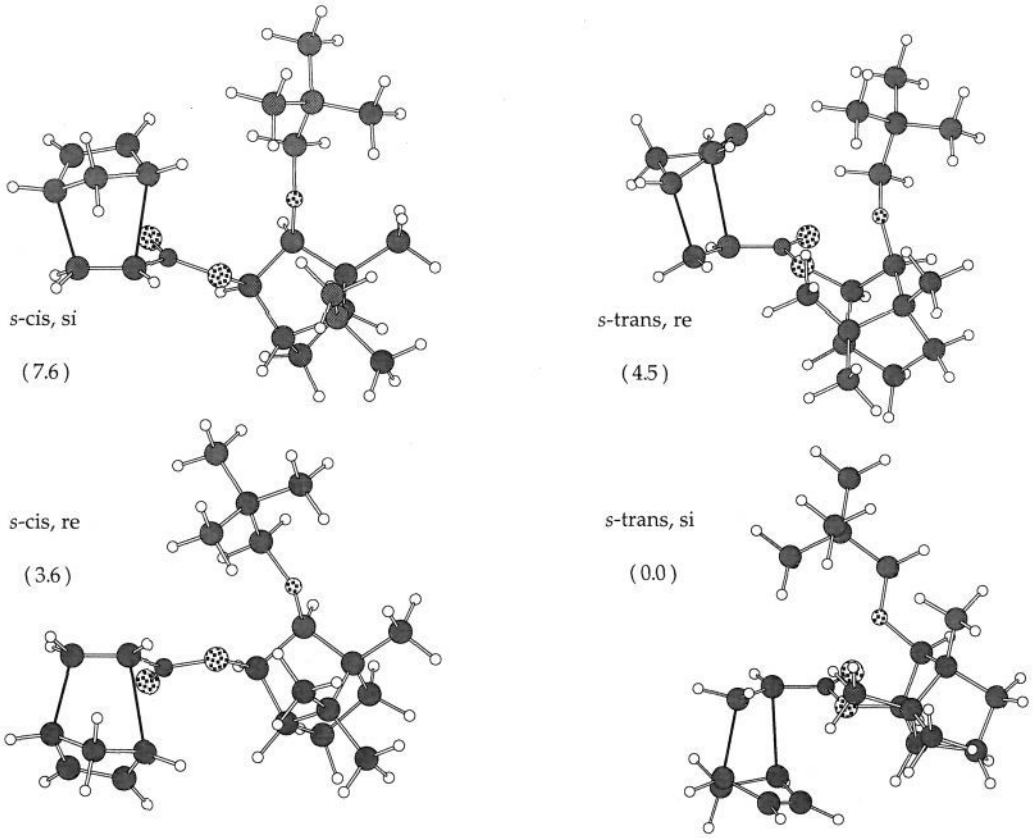

Figure 4. Endo transition structures for the reaction of cyclopentadiene with dienophile **3** (relative energies, kcal/mol).

of the force field in order to take into account the differences encountered in our ab initio calculations with methyl acrylate. The most important changes were the equilibrium bond-forming lengths which were set equal to 2.052 and 2.400 Å; the corresponding force constants for these forming bonds were set to 1.5 and 0.5 mdyn/Å^2. There are slight modifications of values discussed extensively in our previous work.[15] The torsional parameters of the CC single bond of the dienophile were chosen to make the *s-trans* transition structure more stable than the *s-cis* by 3.8 kcal/mol. These alterations proved to give results in satisfactory agreement with the experimental data on the stereoselectivity of the reactions with the chiral dienophiles **1** and **2**.

Calculations using the modified force field were performed on the Diels−Alder reactions of cyclopentadiene with the chiral dienophiles shown in Scheme 1. The results of these calculations are shown in Table 2. Each will be discussed in detail below. The four relevant transition states, corresponding to the *s-cis* and *s-trans* conformation of the dienophile and to addition of the diene to the *si* and *re* faces of the chiral dienophile, were studied in all cases (Figures 2−7). Stereoselectivity ratios were calculated from the relative energies of the lowest energy conformations of the ester alkyl group in each diastereomeric transition state. For the reactions of **4** and **7**, a complete conformational study of the four possible endo transition states was performed. In other cases, at least three conformers corresponding to H−C−O−C or H−C−N−C torsional angles of 0, +30, and −30° were optimized, and the lowest energy local minimum was taken into account to calculate the diastereomeric excess listed in Table 2.

The force field calculations on the transition states of these Diels−Alder reactions predict the topicity of the cycloadditions shown in Table 2. There is a good agreement between the experimental and calculated selectivities in the case of dienophiles bearing menthyl **1** (Figure 2), 8-phenylmenthyl **2** (Figure 3), and camphor derivative **3** (Figure 4), although the calculated selectivities are overestimated. For the D-glucose derivative **6**[24] (Figure 7), the observed diastereoselectivity is also predicted. Calculations in the case of **4** and **5** (Figure 6) underestimate the selectivities, but the correct stereoisomers are predicted as the major products.

It is important to determine the origin of the stereoselectivity of the reactions of chiral dienophiles, so that these principles can be used to design new chiral auxiliaries. It has been suggested that the enhanced diastereoselection observed when the 8-phenylmenthyl is used as chiral auxiliary as compared with menthyl originates by a combination of steric and π-stacking effects.[12] Recent experimental work from Corey[7] and Hawkins[25] on the study of asymmetric catalysis in Diels−Alder reaction supports this proposal. However, the comparison of the experimental and theoretical results obtained in the cases of the dienophiles **2** and **3** suggests that it is not necessary to have an aromatic group to produce high asymmetric induction. Aliphatic bulky groups, such as the neopentyl ether of the

(22) The calculated energies (au) for the reactants and transition structures are *s-trans*-acrolein−BH_3 −329.249990 (RHF/3-21G), −331.080095 (RHF/6-31G*), −329.225109 (RHF/3-21G, SCRF), −331.084603 (6-31G*//3-21G, SCRF); cyclopentadiene −191.717113 (RHF/3-21G, SCRF), −192.791742 (RHF/6-31G*, SCRF); TS1 −483.267119 (RHF/3-21G), −485.938935 (6-31G*//3-21G), TS2 −483.261730 (RHF/3-21G), −485.932851 (6-31G*//3-21G); TS3 −520.937333 (RHF/3-21G), −523.8214802 (6-31G*//3-21G); TS4 −520.943776 (RHF/3-21G, SCRF) and −523.837462 (6-31G*//3-21G, SCRF).

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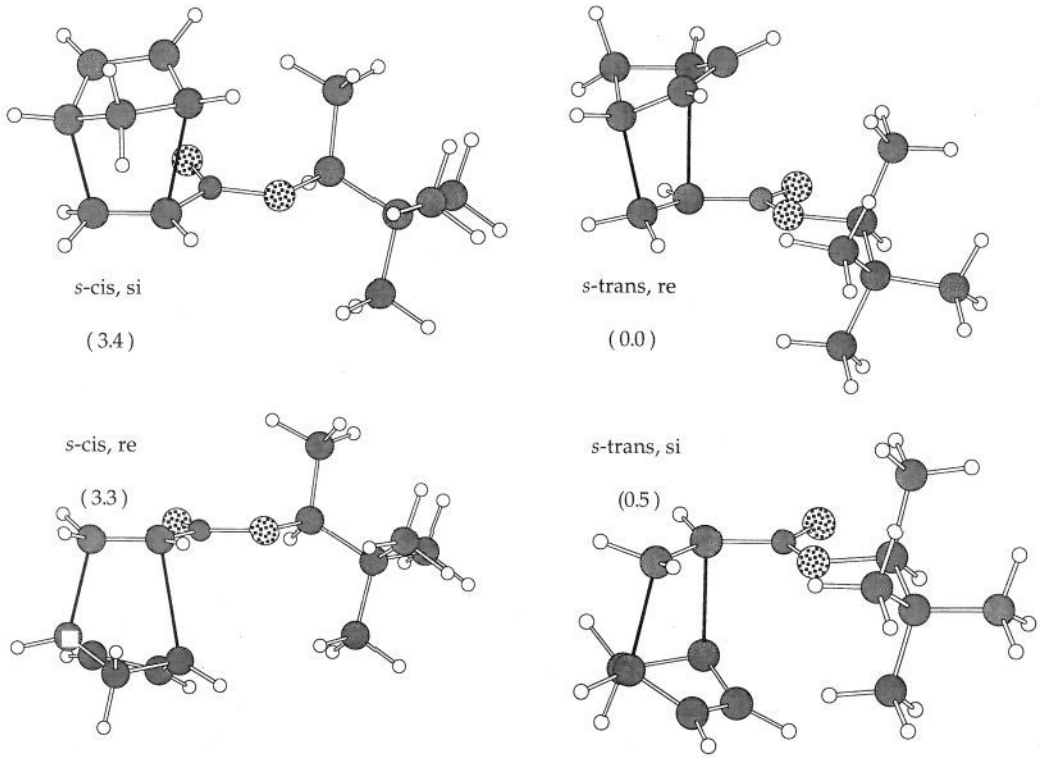


Figure 5. Endo transition structures for the reaction of cyclopentadiene with dienophile **4** (relative energies, kcal/mol).

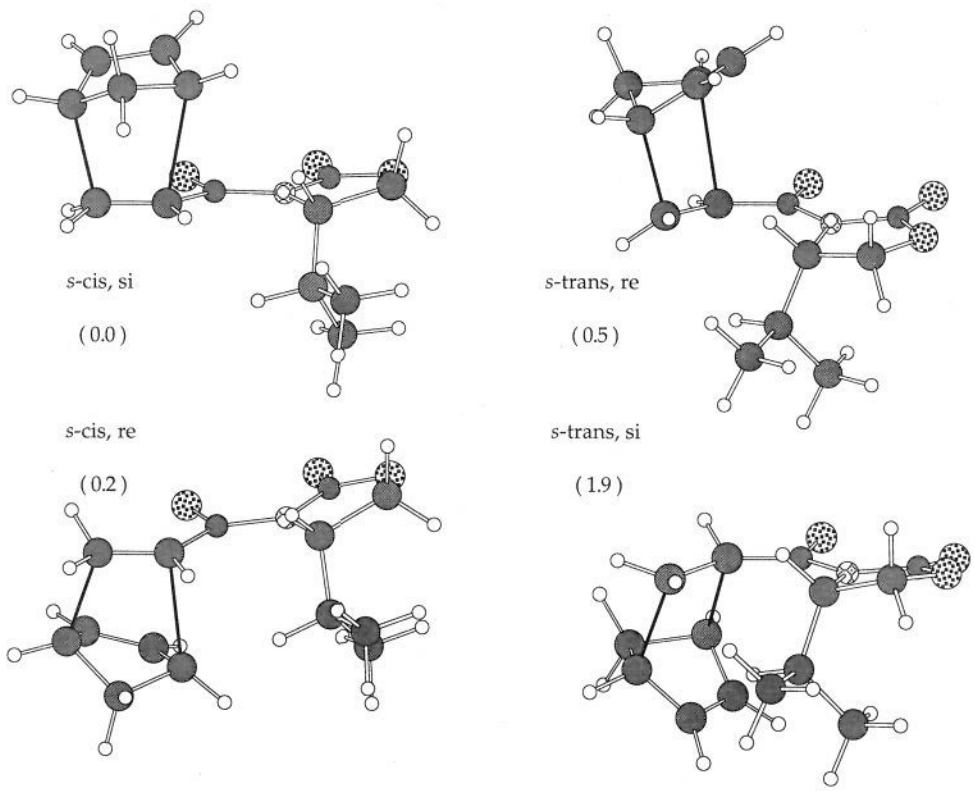


Figure 6. Endo transition structures for the reaction of cyclopentadiene with dienophile **5** (relative energies, kcal/mol).

auxiliary (**3**) or the bulky protected sugar (**6**),[26] also achieved this effect.

As shown in Figure 2, the two lowest energy transition states have the ester carbonyl nearly eclipsed with the nearby axial CH bond of the cyclohexane ring. This is the conformation generally found in cyclohexyl acetates. Approach of cyclopentadiene from the *si* face is less hindered; the isopropyl group hinders approach from the *re* face. The *s-cis* conformers give the opposite preference but are of higher energy due to the *s-cis* conformation of the acrylate.

A much larger preference is found, as expected, with the phenylmenthyl derivative **2** (Figure 3). The phenyl nicely shields one face of the acrylate. Attack on the phenyl side requires substantial distortions away from the ideal confor-

(26) Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 288.

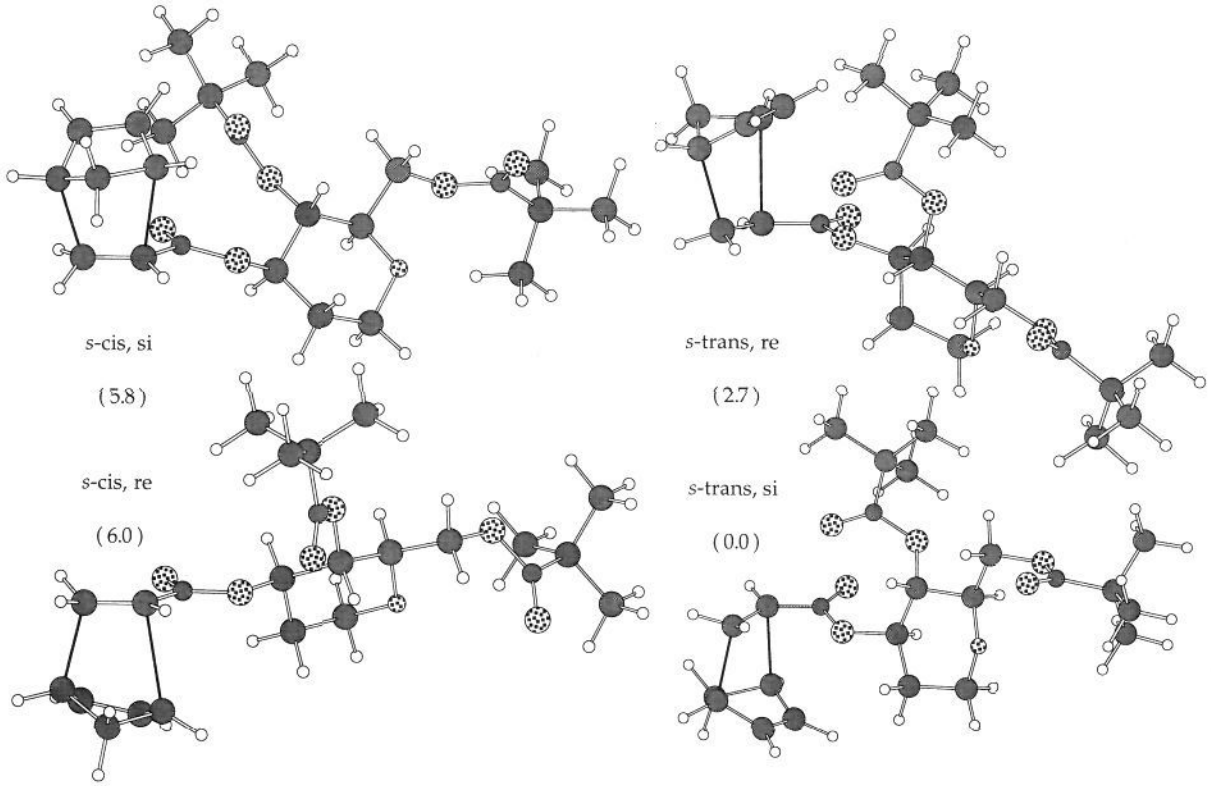
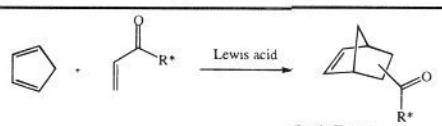
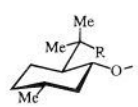
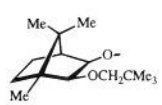
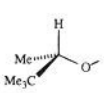
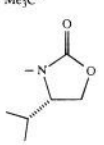
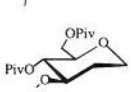


Figure 7. Endo transition structures for the reaction of cyclopentadiene with dienophile **6** (relative energies, kcal/mol).

Table 2. Calculated Steric Energies for the Lewis Acid Catalyzed Diels–Alder Reaction of **1**–**6** with Cyclopentadiene. Experimental and Calculated de are also given.[a]

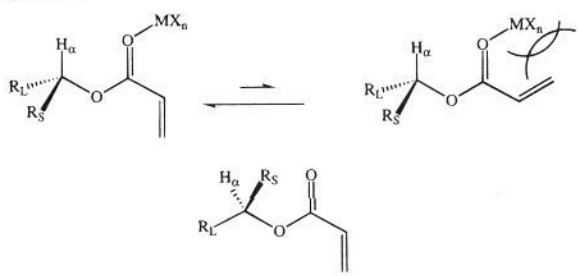


No.	Dienophile	R	Transition State	Steric Energy (kcal/mol) E(calc)	E (rel)	Calc. d.e. (%)	Exp. d.e. (%)
1		H	*s-cis*, re	-14.9	(3.0)	94 *R*	41-62 *R*[13]
			s-cis, si	-13.3	(4.6)		
			s-trans, re	-16.1	(1.8)		
			s-trans, si	-17.9	(0.0)		
2		Ph	*s-cis*, re	-15.0	(2.8)	100 *R*	90-99 *R*[14]
			s-cis, si	-0.8	(17.0)		
			s-trans, re	-13.0	(4.8)		
			s-trans, si	-17.8	(0.0)		
3			*s-cis*, re	10.3	(3.6)	100 *R*	99 *R*[12]
			s-cis, si	14.3	(7.6)		
			s-trans, re	11.2	(4.5)		
			s-trans, si	6.7	(0.0)		
4			*s-cis*, re	-20.5	(3.3)	50 *S*	74-88 *S*[29]
			s-cis, si	-20.4	(3.4)		
			s-trans, re	-23.8	(0.0)		
			s-trans, si	-23.3	(0.5)		
5			*s-cis*, re	-2.5	(0.2)	38 *R*	86-90 *R*[12]
			s-cis, si	-2.7	(0.0)		
			s-trans, re	-2.2	(0.5)		
			s-trans, si	-0.8	(1.9)		
6			*s-cis*, re	-15.5	(6.0)	99 *R*	96 *R*[24]
			s-cis, si	-15.7	(5.8)		
			s-trans, re	-18.8	(2.7)		
			s-trans, si	-21.5	(0.0)		

[a] The configuration of the major isomer is indicated.

mation. Here the minor product is predicted to arise from attack on the *s-cis* acrylate. A similar pattern is found for the bulky auxiliary **4** (Figure 5), and for the protected sugar derivative **6** (Figure 7).

Scheme 4



These calculations support the generally accepted model of asymmetric induction in the Diels–Alder reactions of chiral acrylates: the dienophile has the *s-trans* conformation in the transition state, and this is favored by the carbonyl coordination to the Lewis acid. In addition, a nearly *syn* periplanar relationship between the hydrogen H_α of the alkoxy group (see Scheme 4) and the carbonyl group of the ester is generally favored; this places the large group R_L of the dienophile out of the plane, shielding one of the faces of the CC double bond, so the addition of the diene takes place to the opposite, less hindered face.

In cases where there is some rotation toward the conformation postulated by Prelog to explain the stereoselectivities of nucleophilic additions to glyoxylates[27] (Scheme 4), with the large group oriented *anti* to the carbonyl group, stereoselectivity is reduced. For the 1,2,2-trimethylpropyl group **4** (Figure 5), the sterically demanding *tert*-butyl group is located almost in the plane of the ester, and the hydrogen and the methyl group are out of the plane. We performed a detailed conformational study for this reaction, obtaining the energy of the different transition states when the dihedral angle H–C–O–C was set

(27) Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308. Prelog, V.; Tsatsas, G. *Ibid.* **1953**, *36*, 1178.

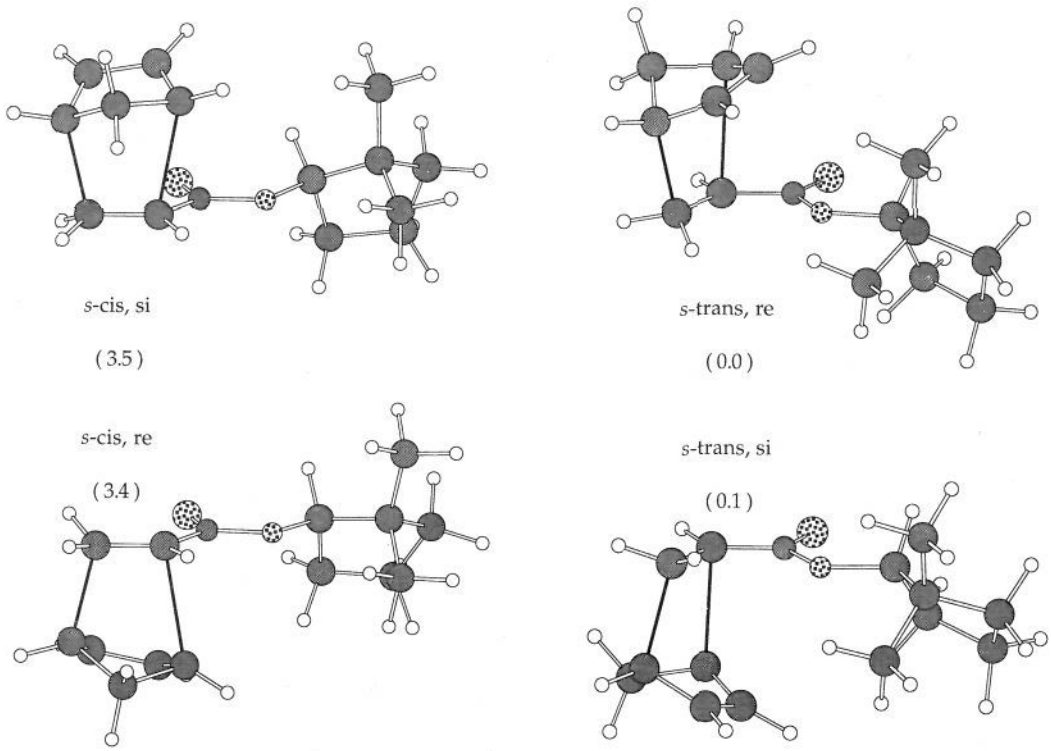
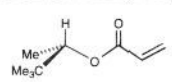
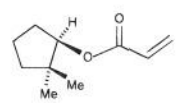


Figure 8. Endo transition structures for the reaction of cyclopentadiene with dienophile **7** (relative energies, kcal/mol).

Table 3. Calculated Steric Energies for the Lewis Acid Catalyzed Diels–Alder Reactions of **4** and **7** with Cyclopentadiene. Values for the Calculated H–C–O–C Dihedral Angles Are Also Given

No.	Dienophile	Transition State	Steric Energy (kcal/mol) E(calc)	E (rel)	Dihedral angle H-C-O-C (°)
4		*s-cis*, re	-20.4	(3.4)	-38.0
		s-cis, si	-20.5	(3.3)	-42.4
		s-trans, re	-23.8	(0.0)	-30.1
		s-trans, si	-23.3	(0.5)	-33.9
7		*s-cis*, re	-12.6	(3.5)	+40.6
		s-cis, si	-12.9	(3.4)	+55.8
		s-trans, re	-16.3	(0.0)	+53.7
		s-trans, si	-16.2	(0.1)	+64.2

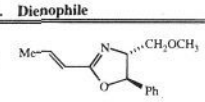
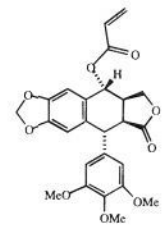
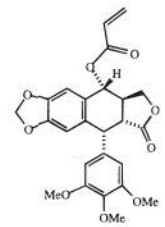
to different values of 30° intervals. We found that the lowest energy transition states (Table 3) correspond to values between −30° and −43°, rather than 0°. In such cases, the predicted stereoselectivity is highly dependent upon the conformations, and a complete geometry search, and Boltzmann average over all low-energy conformations, is required for accurate stereoselectivity predictions.

In fact, in initial computational studies of the reactions of **4**, results in contradiction to the two experimental reports were obtained because of inadequate conformational searches. Consequently, the experimental study of the reaction of **4** was repeated.[28] We followed the procedure described in the literature[21] (BF_3·$O(C_2H_5)_2$, −78 °C), but the determination of the diastereomeric excess was performed by GC/MS, rather than by optical rotation of the reaction product, as was done previously. The results obtained were in complete agreement with previous work: a 87:11:3 mixture of endo-*S*, endo-*R*, and exo cycloadducts, respectively (88.5:8.5:3.0 in the literature[29]). This same reaction was also carried out under thermal conditions (CH_2Cl_2, −40 °C), leading to a mixture of 40:33:14:13 of endo-*S*, endo-*R*, exo-*R* and exo-*S* cycloadducts, respectively, attesting to the importance of the catalyst in enforcing stereoselectivity.

(28) Pascual-Teresa, B. D.; Houk, K. N. *Tetrahedron Lett.* **1994**, *35*, 231.

(29) Le Drian, C.; Greene, A. *J. Am. Chem. Soc.* **1982**, *104*, 5473.

Table 4. Calculated Steric Energies for the Lewis Acid Catalyzed Diels–Alder Reactions of **8**–**10** with Cyclopentadiene

No.	Dienophile	Transition State	Steric Energy (kcal/mol) E(calc)	E(rel)
8		*s-cis*, re	-27.8	(0.1)
		s-cis, si	-27.9	(0.0)
		s-trans, re	-24.5	(3.4)
		s-trans, si	-27.2	(0.7)
9		*s-cis*, re	-9.1	(2.1)
		s-cis, si	-8.6	(2.6)
		s-trans, re	-11.2	(0.0)
		s-trans, si	-10.9	(0.3)
10		*s-cis*, re	-9.2	(2.4)
		s-cis, si	-7.5	(4.1)
		s-trans, re	-9.6	(2.0)
		s-trans, si	-11.6	(0.0)

Some calculations were carried out on the model system **7** in order to get more insight into this conformational problem. Four endo transition states were considered (Figure 8). The results are summarized in Table 3. The dihedral angle H–C–O–C is found to have a value around 40°. A conformational study on these transition states, similar to that carried out with **4**, demonstrated that the lowest energy conformation corresponds to a disposition of the bulkier group almost *anti* to the carbonyl group, predicting very low stereoselectivity for this auxiliary.

Evans' oxazolidinone **5** (Figure 6) was studied in conformations with two amide carbonyls eclipsed, which is presumably the favored arrangement upon Lewis acid complexation. There

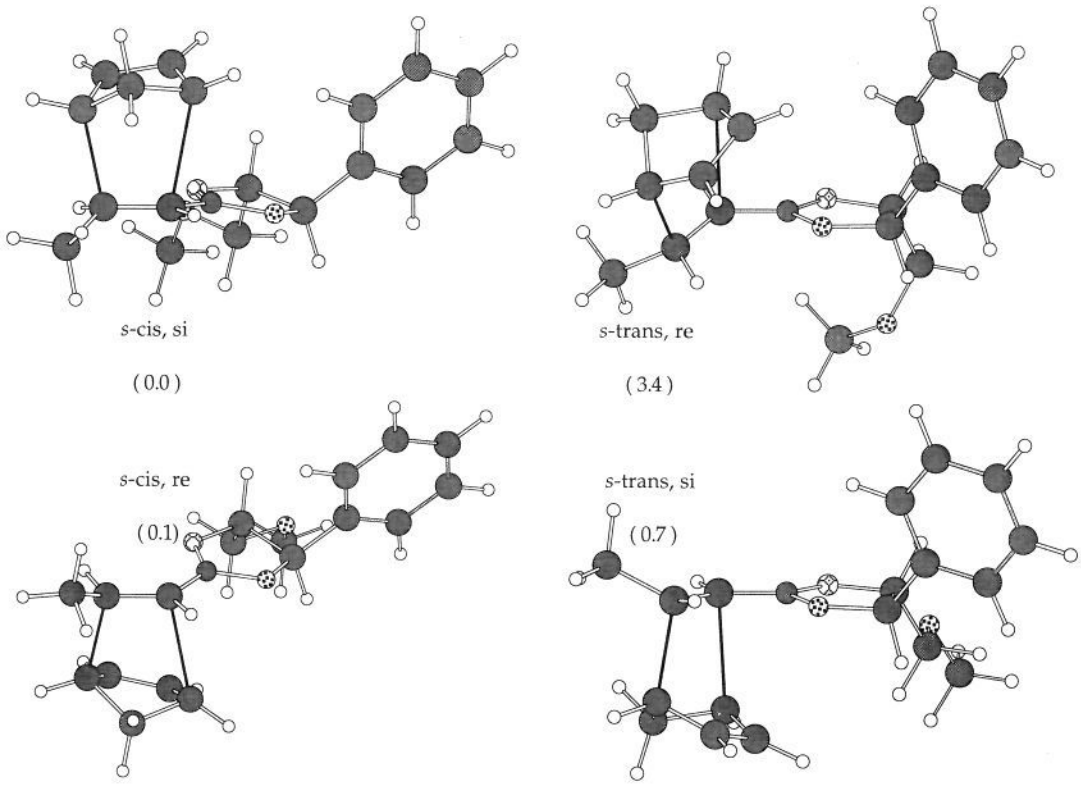


Figure 9. Endo transition structures for the reaction of cyclopentadiene with dienophile **8** (relative energies, kcal/mol).

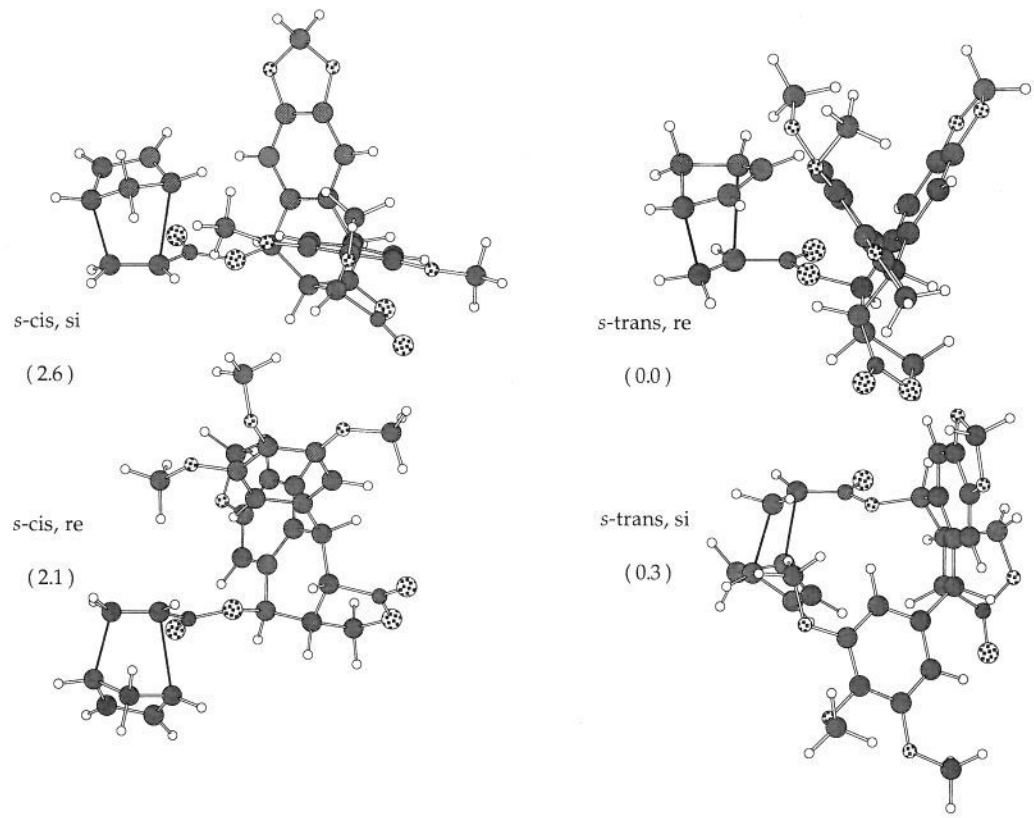


Figure 10. Endo transition structures for the reaction of cyclopentadiene with dienophile **9** (relative energies, kcal/mol).

is a surprisingly small preference for attack on the H, rather than iPr face, and furthermore, not much preference for the *s-cis* or *s-trans* conformation of the α,β-unsaturated amide in the transition state. These factors conspire to produce low stereoselectivity, although the experimental selectivity is higher than that calculated.

Predictions of Stereoselectivity for Chiral Dienophiles 8−10. The vinyloxazolidine **8** has been used as a chiral electrophile capable of undergoing conjugate additions to furnish optically active β,β-disubstituted carboxylic acids and valerolactones.[30] We investigated the potential applicability of this chiral crotonate for the asymmetric Diels−Alder cycloaddition.

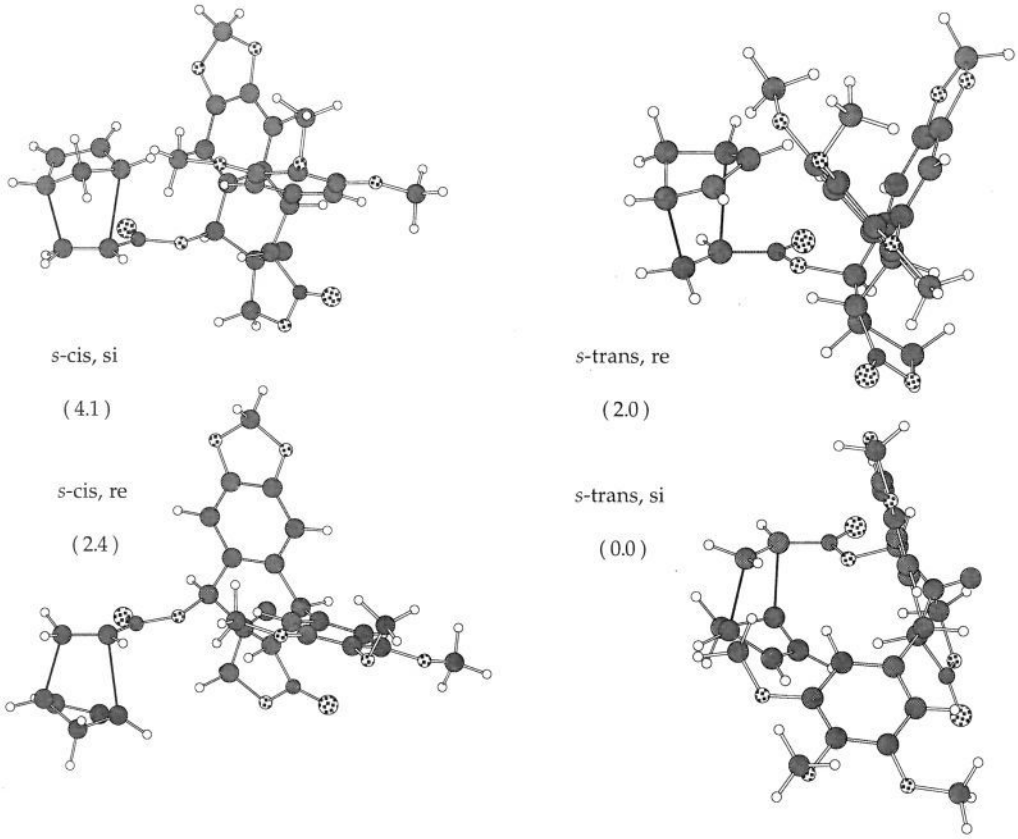


Figure 11. Endo transition structures for the reaction of cyclopentadiene with dienophile **10** (relative energies, kcal/mol).

The results are summarized in Table 4, and the corresponding transition states are shown in Figure 9. We did not go to any special lengths to parameterize the oxazolidine conformational preference with respect to the propenyl group of the dienophile, so in the following we discuss the *s-cis* and *s-trans* stereoselectivity separately. Force field calculations predict that the *s-cis* (C=C−C=N) conformation will react with low selectivity. Here the pseudo-equatorial methoxy group has little effect. However, if the reaction takes place through a *s-trans* conformation of the dienophile, we predict high stereoselectivity, since attack away from the phenyl is favored.

Calculations were also carried out on two chiral acrylates derived from natural commercially available chiral alcohols, in order to make further predictions with our force field model. For this study we used picropodophyllotoxin, a lignan type isolated as a major product from *Juniperus thurifera* L.[31] and podophyllotoxin. The prediction for the Lewis acid catalyzed reaction between cyclopentadiene and picropodophyllotoxin acrylate (**9**) gives a low selectivity for the *S* stereoisomer (see Table 4 and Figure 10). The reaction with the acrylate derivative of podophyllotoxin (**10**) led to a reversal in stereoselectivity and is predicted to react with high selectivity for the *R* stereoisomer as shown in Table 4 and Figure 11. These predictions will be the subject of future experimental tests.

(30) Meyers, A. I.; Witten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266. Meyers, A. I.; Witten, C. E.; Smith, R. K. *J. Org. Chem.* **1979**, *44*, 2250. Meyers, A. I.; Witten, C. E. *Heterocycles* **1976**, *4*, 1687.

(31) San Feliciano, A.; Medarde, M.; López, J. L.; Puebla, P.; Miguel del Corral, J. M.; Barrero, A. F. *Phytochemistry* **1992**, *31*, 267. San Feliciano, A.; Miguel del Corral, J. M.; López, J. L.; Pascual-Teresa, B. D. *Phytochemistry* **1992**, *31*, 267.

Conclusions

A modified version of a previous force field model for the study of Lewis acid-catalyzed Diels−Alder reactions has been developed, in which new parameters for the reactions of acrylic esters are derived from ab initio calculations in model systems. This model has been used in the study of the Diels−Alder reactions of several of the most synthetically useful chiral auxiliaries in order to obtain an approximate description of the stereoselectivity of these reactions. It has also been employed to predict stereoselectivities of new reactions. The applications of the force field to the design of new chiral auxiliaries will be the subject of future studies.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this reasearch, the Ministerio de Educación y Ciencia (Spain) and the Fulbright Commission for a MEC/Fulbright Fellowship to J.G., the Fundación Ramón-Areces (Spain) for a Fellowship to BPT, and the Ministerio de Educación y Ciencia (Spain) for a Fellowship to A.A.

Supplementary Material Available: The complete list of MM2 parameters, the full geometries and energies of all the ab initio transition structures (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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