Strained Allenes as Dienophiles in the Diels−Alder Reaction: An Experimental and Computational Study

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Strained allenes, such as 1,2-cyclohexadiene, undergo facile Diels−Alder reactions with otherwise unreactive dienes. Substituted cyclohexa-1,2-dienes add to furan via a Diels−Alder reaction, forming only two of four possible regioisomers and stereoisomers. Alkyl cyclohexa-1,2-diene carboxylates yield the nonconjugated endo adduct as the major product. However, chiral cyclohexa-1,2-dienecarboxylates, such as *l*-menthyl and *l*-bornyl cyclohexa-1,2-dienecarboxylate, show no diastereoselectivity in [4 + 2] cycloadditions. DFT (B3LYP/6-31G*) calculations were performed in order to explain these results. A comparison to the calculated B3LYP/6-31G* transition structures and intermediates along the reaction paths of 1,2-cyclohexadiene with 1,3-butadiene and with furan (as well as propadiene with butadiene) show that the diradical stepwise pathways are preferred over the concerted paths. At the same time, the concerted transition structures are extremely asynchronous. A QM/MM study indicates a minimal influence of the chiral auxiliary even in the concerted scenario.

Introduction

Strained allenes have provided fruitful ground for a number of theoretical and experimental investigations into the effect of strain on reactivity.[1] They are nonplanar, chiral allenes rather than planar zwitterionic or carbene-like species, even in the case of the highly strained 1,2-cyclohexadiene.[2,3] 1,2-Cyclohexadiene is stable in a frozen matrix below 170 K. It has been studied spectroscopically[3a] and by trapping experiments.[3b,c] Above 190 K, 1,2-cyclohexadiene dimerizes via a [2 + 2] cycloaddition involving diradical intermediates in the absence of trapping agents.[3c]

In earlier studies, we developed a method for the generation of strained allenes through thermal and photochemical chloride expulsion from 2-chloroallyl anions.[4] We have also been interested in the determination of the symmetry of Diels−Alder transition states through the use of "cooperativity" by chiral auxiliaries[5] and of high-level calculations.[6] Because of their inherent asymmetry, allenes are expected to lead to extremely asymmetric concerted transition structures or even to stepwise pathways. In contrast, fumarates represent the symmetric extreme. We explored the possibility of chiral induction by using *l*-bornyl and *l*-menthyl 1,2-cyclohexadiene carboxylates. If the reaction of 1,2-cyclohexadiene is concerted, its chirality is transferred to the reaction products, and the incorporation of a chiral auxiliary might influence the formation of the chiral center. The additional driving force provided by the relief of strain can prompt otherwise unreactive dienophiles to react.

In contrast to extensive studies on simple dienophiles, allenic systems are only now being explored by computational methods.[7] We have examined the reaction of 1,2-cyclohexadiene and of the parent allene, 1,2-propadiene, with dienes, such as 1,3-butadiene and furan using density functional theory (DFT) in order to explain the experimentally observed results. DFT methods provided excellent results for the Diels−Alder reaction between ethylene and 1,3-butadiene,[8] as well as for other pericyclic reactions.[9]

The Diels−Alder reaction can proceed by two mechanisms. The first is a concerted, allowed [4 + 2] cycloaddition, while the second is a two-step mechanism involv-

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(1) (a) Christl, M.; Braun, M. *Chem. Ber.* **1989**, *122*, 1939. (b) Christl, M.; Schreck, M. *Chem. Ber.* **1987**, *120*, 915. (c) Christl, M.; Schreck, M. *Angew. Chem.* **1987**, *99*, 474.

(2) Schmidt, M. W.; Angus, R. O., Jr.; Johnson, R. P. *J. Am. Chem. Soc.* **1982**, *104*, 6838.

(3) (a) Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem.* **1983**, *95*, 551; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 542. (b) Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7607. (c) Moore, W. R.; Moser, W. R. *J. Am. Chem. Soc.* **1970**, *92*, 5469.

(4) (a) Tolbert, L. M.; Islam, Md. N.; Johnson, R. P.; Loiselle, P. M.; Shakespeare, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 6416. (b) Tolbert, L. M.; Siddiqui, S. *J. Am. Chem. Soc.* **1984**, *106*, 5538. In this case, the distinction between a planar isoindenylidene and a nonplanar 4,5-benzo-1,2,4-cyclopentatriene was not resolved. However, recent computational evidence by Johnson supports the nonplanar structure: Johnson, R. P. Private communication.

(5) (a) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1981**, *103*, 2104. (b) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1984**, *106*, 3806.

(6) (a) Borden, W. T.; Loncharich, R. J.; Houk, K. N. *Annu. Rev. Phys. Chem.* **1988**, *39*, 213. (b) Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554. (c) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 7478.

(7) (a) The use of allene and fluoroallenes as dienophiles in Diels−Alder reactions has been studied by semiempirical methods: Manohan, M.; Venuvanalingam, P. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1423. (b) The [2 + 2] and [2 + 4] reactivity of heterocumulenes and ketenes was studied: Fabian, W. M. F.; Janoschek, R. *J. Am. Chem. Soc.* **1997**, *119*, 4253. (c) Salzner, U.; Bachrach, S. M. *J. Org. Chem.* **1996**, *61*, 237. (e) The reactivity of strained allenes in [2 + 2] cycloadditions was also studied: Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218.

(8) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *117*, 6036.

(9) (a) E.g., the vinylcyclopropane rearrangement: Houk, K. N.; Nendel, M.; Wiest, O.; Storer, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 10545. (b) As well as the Cope and Claisen rearrangements: Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336.

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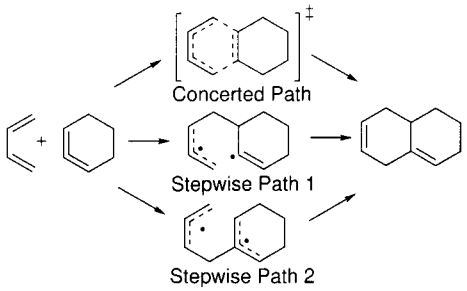
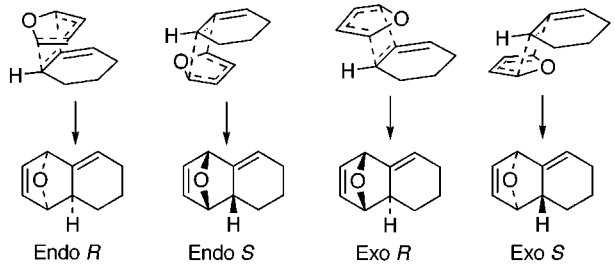
Scheme 1. Possible Mechanisms of the Reaction between 1,2-Cyclohexadiene and 1,3-Butadiene



Scheme 2. Different Concerted Transition States and Corresponding Products for the Reaction between 1,2-Cyclohexadiene and Furan

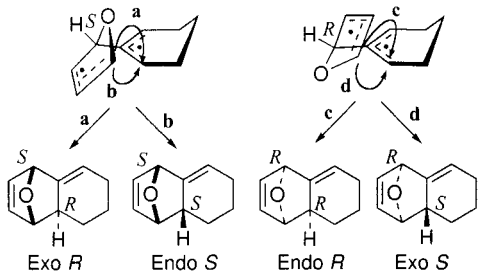


ing a diradical intermediate. In the case of the parent Diels–Alder reaction between 1,3-butadiene and ethylene, the concerted path is computed to be favored by 2–7 kcal/mol, and B3LYP/6-31G* predicts this preference to be 3.4 kcal/mol.[8]

The introduction of a cumulated double bond is expected to exert a significant perturbation on the synchronicity of the concerted transition structures. The release of strain associated with the formation of diradical intermediates should exert an additional driving force for the stepwise path: one of the diradical intermediates of the stepwise path contains two allyl radicals (Scheme 1). An estimate of the heats of formation by Benson's group additivity rules[10] predicts that the diallylic diradical intermediate of the stepwise path 2 is 1 kcal/mol above the reactants. The heat of formation of the reactants (in particular that of 1,2-cyclohexadiene) is underestimated compared to the heat of formation of the diradical intermediate by this method. There are no experimental data about the strain exerted by the introduction of a normally linear allene into a six-membered ring. While it can be assumed that this strain is significant, an allyl radical will not experience much strain in such a system. Therefore, the heat of formation of the reactants is underestimated compared to the diradical intermediate, leading to an overestimation of the heat of reaction by Benson's group additivity rules.

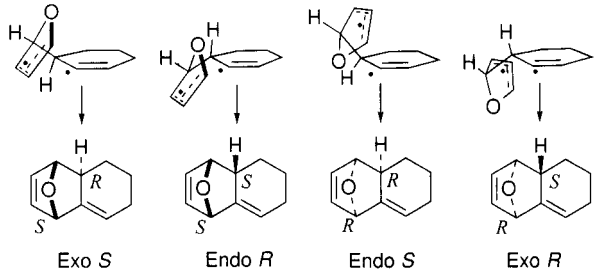
There are three distinct stereochemical scenarios in the case of the reaction between 1,2-cyclohexadiene and a dienophile, one for each possible mechanism. Four stereochemically different transition structures can be formed in the concerted case (Scheme 2). Two result in endo products, while the other two provide exo products.[11] The stereochemistry of the initial attack is transferred to the products. The influence of the chiral substituents on the orientation of the reactants in the initial attack will be reflected in the product ratio.

Scheme 3. Two Stereochemically Distinct Intermediates and the Corresponding Products of the Stepwise Path 2 of the Reaction between 1,2-Cyclohexadiene and Furan[a]



[a] The stereochemistry of the chiral center opposite to the bridgehead carbon is indicated as well.

Scheme 4. Four Stereochemically Distinct Intermediates and the Corresponding Products of the Stepwise Path 1 of the Reaction between 1,2-Cyclohexadiene and Furan



In the stepwise path 2, the stereochemistry of the bridgehead carbon is fully determined only in both steps. Two stereochemically distinct intermediates can be formed, again leading to the four different products (Scheme 3), but either intermediate leads only to two products. The stereochemistry is thus predetermined in the first step. A chiral auxiliary would have to influence the *R*/*S* stereochemistry of the chiral center on the diene moiety in the first step and influence the exo/endo selectivity in the second step to lead only to one product.

If the other stepwise path (path 1) is taken, the chiral center is formed in the first step, and the geometry of the initial approach is transferred to the products. There are four stereochemically distinct intermediates (Scheme 4).

A substituted 1,2-cyclohexadiene can also lead to regioisomeric products, which differ in the position of the substituent relative to the double bond. The *R*/*S* stereochemistry described by Schemes 2–4 can be applied. Only the position of the substituent shifts, increasing the possible products from four to eight.

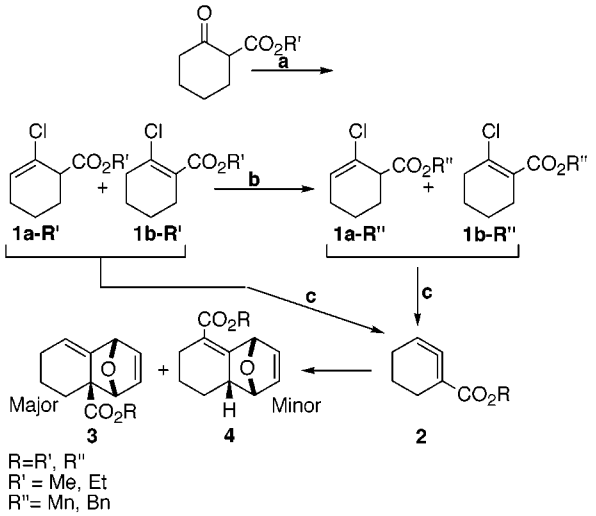
Experimental Results

Preparation and Trapping Experiments with Alkyl 1,2-Cyclohexadienecarboxylates. Methyl 2-chlorocyclohex-2-enecarboxylate (**1a-Me**) and its conjugated isomer methyl 2-chlorocyclohex-1-enecarboxylate (**1b-Me**), as well as the ethyl esters **1a-Et** and **1b-Et**, were prepared as a 72:28 (77:23 for **1-Et**) mixture of isomers by chlorodeoxygenation of the corresponding alkyl cyclohexanone-2-carboxylate with triphenylphosphine in car-

(10) Benson, S. W. *Thermochemical Kinetics. Methods for Estimation of Thermochemical Data and Rate Parameters*, 2nd ed.; Wiley: New York, 1976.

(11) Endo and exo refer to the position of the diene relative to the former cyclohexadiene, rather than to the position of the substituent on the ring.

Scheme 5. Preparation and Trapping of 2-Alkylcyclohexa-1,2-diene Carboxylate[a]



[a] Key: (a) PPh_3, CCl_4, reflux; (b) 1-hydroxy-3-isothiocyanatotetrabutyldistannoxane (0.1 equiv), R″OH, toluene, reflux; (c) KO-*t*-But, furan, THF.

bon tetrachloride (Scheme 5).[12] The corresponding *l*-menthyl and *l*-bornyl cyclohexenecarboxylates **1a-Mn**, **1b-Mn**, **1a-Bn**, and **1b-Bn** were prepared by catalytic transesterification of **1-Et** with *l*-menthol or *l*-borneol and 1-hydroxy-3-isothiocyanatotetrabutyldistannoxane.[13] The chlorocyclohexene carboxylates **1** were subjected to a potassium *tert*-butoxide elimination in a 50:50 solution of furan/THF. Of the four possible regio- and stereoisomeric trapping products from methyl 1,2-cyclohexadienecarboxylate **2-Me**, two were formed in 66% yield and in a ratio of 3.4:1. The major regioisomer (**3-Me**) is substituted at the bridgehead position. The substituent of the minor product (**4-Me**) was in conjugation with the remaining double bond. The ethyl, *l*-menthyl, and *l*-bornyl esters produced the analogous products **3-Et**, **4-Et**, **3-Mn**, **4-Mn**, **3-Bn**, and **4-Bn** in a ratio of 2:1, 2.1:1, and 2.9:1, respectively. In each case, the isomers were separated by preparative thick-layer silica gel chromatography.

^{1}H NMR experiments and comparison to the Diels–Alder reaction product of 1-phenylcyclohexa-1,2-diene indicated that both regioisomers, **3** and **4**, were the endo adducts with the cyclohexyl endo relative to furan and the bridgehead substituent exo relative to the cyclohexyl (Scheme 2).[5a] The fact that only the endo adducts were observed was also predicted by computations, which indicate that the endo pathway is favored. Thus, the reaction is stereoselective.

Use of the chiral shift reagent tris[3-heptafluoropropylhydroxymethylene-*d*-camphorato]europium(III) allowed separation of the δ 6.4 olefinic absorption into two absorptions. In the case of the ethyl esters, **3-Et**, as well as the *l*-bornyl and *l*-menthyl esters **3-Bn** and **3-Mn**, the integrated areas for the two absorptions were 1.0:1.0 within experimental error.

(12) (a) Gruber, L.; Tömösközi, I.; Radics, L. *Synthesis* **1975**, 708. (b) Isaacs, N. S.; Kirkpatrick, D. *J. Chem. Soc., Chem. Commun.* **1972**, 443.

(13) Otera, J.; Ioka, S.; Nozaki, H. *J. Org. Chem.* **1989**, *54*, 4013.

Discussion

The reaction is regioselective (the formation of the bridgehead-substituted product is preferred) and endo stereoselective[11] with alkyl 1,2-cyclohexadienecarboxylates, **2**. By contrast, there is a complete lack of *R*/*S* diastereoselectivity with the chiral dienophiles **2-Bn** and **2-Mn**. The selectivity for the endo product **3** as well as for the conjugated product **4** is within expectations for a concerted reaction, but the absence of diastereoselectivity is surprising, given at least minimal diastereoselectivity observed with simple chiral acrylates.[14] An explanation can be found by studying the transition structures obtained by computations.

Computational Methodology

GAUSSIAN94 was used for the density functional theory calculations.[15] The reported energies are corrected by unscaled zero point energies. The B3LYP functional was used for calculating the ground states and concerted transition structures, while the open-shell UB3LYP was used for structures on the stepwise pathways. This functional provided structures and energies in good agreement with experimental results in the case of the parent reaction and other pericyclic reactions.[8,9] The 6-31G* basis set was used in all calculations. We also computed the spin projected energies of the open-shell structures using the procedure developed by Yamaguchi et al.[16] However, the results did not change the relative order of the pathways, and we choose to include these energies only in the Supporting Information. MACROMODEL and the MM2* force field were used for the QM/MM molecular modeling.[17]

Results and Discussion of the Computations

The Diels–Alder Reaction between Propadiene and 1,3-Butadiene. Structures along the concerted and both stepwise pathways were located for the reaction of propadiene and 1,3-butadiene using (U)B3LYP/6-31G* computations.

The concerted transition structure is asynchronous (Figure 1) and has a computed activation energy of 29.1 kcal/mol, about 5 kcal/mol higher than in the case of 1,3-butadiene and ethylene.[8] This result is surprising insofar as the reaction of 1,3-butadiene and the parent allene is exothermic by 44.3 kcal/mol, 8 kcal/mol more so than the

(14) E.g., the reaction of cyclopentadiene with (−)-menthyl acrylate: (a) Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 6359. (b) Sauer, J.; Kredel, J. *Angew. Chem.* **1965**, *77*, 1037; *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 989. (c) Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, *31*, 2418. (d) Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 731. Or the reaction of butadiene with di-(−)-menthyl fumerate: (e) Korolev, A.; Mur, V. *Dokl. Akad. Nauk USSR* **1948**, *59*, 251. (f) Korolev, A.; Mur, V. *Chem. Abstr.* **1948**, *42*, 6776. (g) Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333. (h) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 4778.

(15) Gaussian 94 (Revision B.1): Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Peterson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.

(16) (a) Yamaguchi, K.; Jensen, F.; Dorigo, A.; Houk, K. N. *Chem. Phys. Lett.* **1988**, *149*, 537. (b) Yamakami, S.; Kawakami, T.; Nagao, H.; Yamaguchi, K. *Chem. Phys. Lett.* **1994**, *231*, 25.

(17) (a) MM2* is a modified version of Allinger's MM2 force field: Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) MACROMODEL V5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

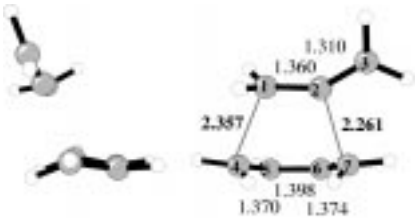


Figure 1. Two views of the transition structure of the concerted pathway of the reaction between butadiene and propadiene (selected bond lengths in Å).

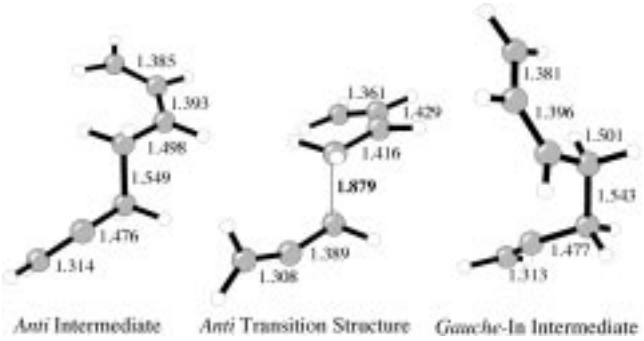


Figure 2. Structures along the stepwise path 1 of the reaction between butadiene and propadiene (selected bond lengths in Å).

butadiene–ethylene reaction.[18] The forming bond between butadiene and C-2 of allene is almost 0.1 Å shorter than that between butadiene and C-1 (2.261 Å compared to 2.357 Å). In comparison, the corresponding forming bond lengths are 2.273 Å in the transition structure for the reaction between ethylene and butadiene.[8] Despite the considerable asynchronicity of the transition structure, the intrinsic reaction coordinate (IRC) of the transition structure leads directly to reactants and products.

Two intermediates and one transition structure were found on the stepwise path 1 of Scheme 1, in which the first bond is formed to C-1 of allene (Figure 2). The 1,3-butadiene moiety is anti to the allene moiety in one intermediate, while it is gauche-in in the other.[19] Both have essentially the same relative energy: the anti intermediate is 30.2 kcal/mol above the reactants, compared to 30.1 kcal/mol in the case of the gauche-in intermediate.[20] The transition structure leads to the anti intermediate. It is 33.5 kcal/mol above the reactants. This barrier is 4.4 kcal/mol higher in energy than that of the concerted path (Scheme 6). The forming bond length is similar to that in the corresponding transition structure of the ethylene–butadiene reaction (1.879 Å compared to 1.884 Å).[8] The transition structure for the ring closure could not be located, as it is the case of the reaction between butadiene and ethylene. This second step is therefore expected to have no significant barrier.[18b]

Only one structure was found on the stepwise path 2. It is the gauche-in diradical intermediate (Figure 3). This

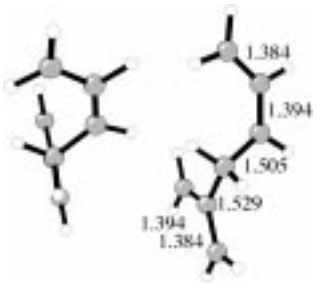
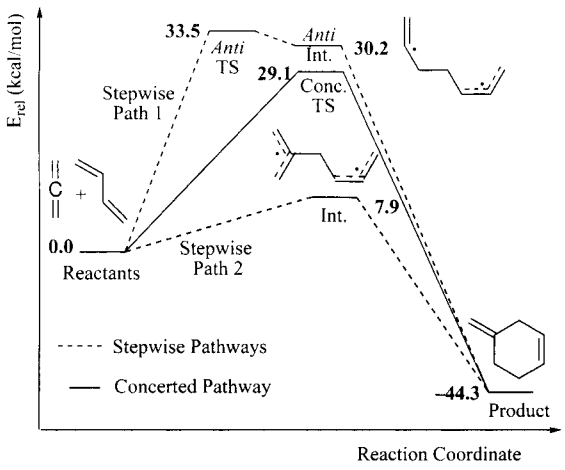


Figure 3. Two views of the diradical intermediate of the stepwise path 2 of the reaction between butadiene and propadiene (selected bond lengths in Å).

Scheme 6. Schematic Energy Diagram of the Reaction between *s-trans*-1,3-Butadiene and Propadiene



intermediate is 7.9 kcal/mol above the reactants, 26.0 kcal/mol below the concerted transition structure, and 21.2 kcal/mol below the transition structure leading to the other diradical intermediate.[21] An extensive search did not produce any transition structure on this path. The region of the hypersurface immediately surrounding the intermediate is flat, and the spin contamination increases quickly with an increase in the forming bond length. It will be necessary to use CASSCF calculations in a future study to map accurately this region of the potential energy surface.

Concerted versus Stepwise Mechanism. The relative energies are summarized in Scheme 6. The less favored stepwise path is only 4.4 kcal/mol higher in energy than the concerted pathway. Unfortunately, no transition structures were located on the more favored stepwise path, but the hypersurface surrounding the intermediate was flat. If the energy difference between transition structure and intermediate is similar to the first stepwise mechanism, the barrier of this second stepwise mechanism will still be about 11 kcal/mol lower in energy than the concerted transition state. This reaction therefore proceeds via a stepwise mechanism.

The Diels–Alder Reaction between 1,2-Cyclohexadiene and 1,3-Butadiene. In this case, not only one concerted and two stepwise pathways but also endo and exo concerted transition structures have to be considered. While the endo and exo concerted transition

(18) (a) The reaction of ethylene and butadiene is exothermic by 36.6 kcal/mol (ref 8). (b) The experimental barrier of the reaction of 1,3-butadiene and ethylene is 25.1 ± 2 kcal/mol: Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem.* **1991**, *104*, 711; *Angew. Chem., Int. Ed. Engl.* **1991**, *31*, 682. (c) The experimental heat of formation is 38.5 kcal/mol: Uchiyama, M.; Tomioka, T.; Amano, A. *J. Phys. Chem.* **1964**, *68*, 1878.

(19) Since the propadiene moiety is at the "inside" of the former butadiene, it is referred to as "gauche-in".

(20) The structures on the stepwise pathways are diradicals with $\langle S^2 \rangle \approx 1$.

(21) Geometry optimizations starting with either an anti or a gauche-out conformation about the newly formed bond provide the structure of Figure 3.

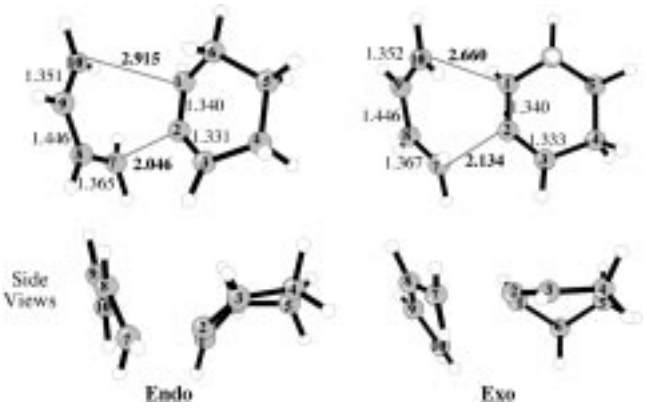


Figure 4. Concerted transition structures for the reaction of 1,2-cyclohexadiene and 1,3-butadiene (selected bond lengths in Å).

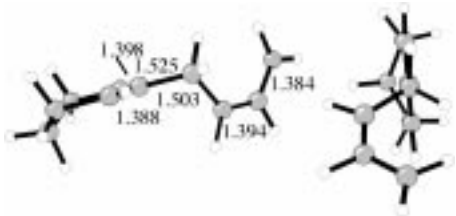


Figure 5. Diradical intermediate of stepwise path 2 of the reaction between butadiene and 1,2-cyclohexadiene (selected bond lengths in Å).

structures are geometrically distinct, the corresponding products cannot be distinguished.

Both concerted transition structures are extremely asynchronous (Figure 4). In the endo case, the forming bond between C-2 and C-7 is 2.046 Å, about 0.5 Å shorter than that between C-1 and C-10. In the exo case, the difference is even larger. C-2 and C-7 are 2.134 Å apart, almost 0.9 Å closer than C-1 and C-10. In comparison, the corresponding value is 0.1 Å in the reaction of propadiene and 1,3-butadiene. However, the transition vectors (motion along the directions of negative curvature) of the transition states indicate that both structures belong to the concerted pathways. Exo and endo transition structures are close in energy. The exo path is favored by 0.2 kcal/mol over the endo. It is 7.2 kcal/mol above the separate reactants, and the reaction is exothermic by 75.5 kcal/mol.

The extremely low activation energy and the high heat of reaction are due to the strain of 1,2-cyclohexadiene. The geometry of 1,2-cyclohexadiene undergoes only small changes to reach the transition structure and the product, so that bond formation to C-2 is easy. At the same time, the bond formation releases the inherent strain of the allene.

The relative ease of formation of the bond to C-2 is even more pronounced in the formation of the diradical intermediate of the stepwise path 2. This intermediate has two allyl radical moieties, the bond has been formed to C-2. The gauche-in conformer is 27.6 kcal/mol more stable than the reactants (Figure 5). The cyclohexadiene ring is in an envelope conformation, the atoms of the allyl radical site and those connected to it are located in the same plane. The *R*/*S* stereochemistry of the bridgehead carbon in the product is determined in the second step of path 2. This is also the case for the endo/exo stereochemistry, since the former butadiene part is perpendicular to the six-membered ring. The influence of the ring conformation on the relative energy is negligible. A structure in which the ring was flipped "out" relative to the butadiene moiety, rather than being flipped "in" as in Figure 6, is 0.1 kcal/mol higher in energy. The ring itself is expected to flip easily between the two conformations.[22]

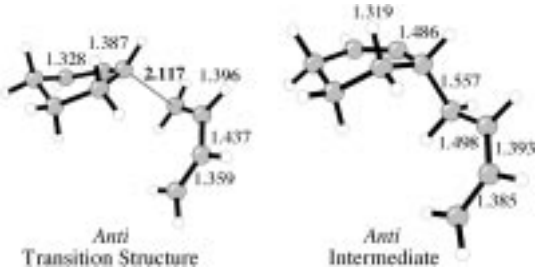
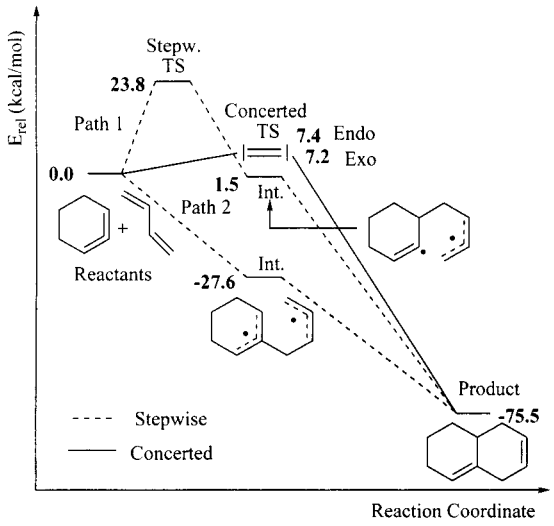


Figure 6. Diradical intermediate and transition structure of stepwise path 1 of the reaction between *s-trans*-1,3-butadiene and 1,2-cyclohexadiene (selected bond lengths in Å).

Scheme 7. Schematic Energy Diagram of the Reaction between 1,2-Cyclohexadiene and *s-trans*-1,3-Butadiene



In the reaction between allene and butadiene, the transition structure of the stepwise path 1 was close in energy to the intermediate; however, this is not the case here. The anti intermediate of stepwise path 1, in which a vinyl radical is formed, is only 1.5 kcal/mol above the reactants (Figure 6),[23] but the transition structure leading to this intermediate is located 23.8 kcal/mol above the separate reactants (Scheme 7). The transition structure is early. The forming bond length is 2.117 Å, 0.242 Å longer than in the reaction between ethylene and 1,3-butadiene.[8] Therefore, not much strain of the allene is released at this point. The approach also forces the proton on C-1 out of planarity and crowds the transition structure relative to the concerted transition state where the forming bond to C-1 is significantly longer (2.66 and 2.92 Å).

(22) In the case of cyclopentene, a typical example for a molecule with an envelope conformation, the ring flip requires only 0.8 kcal/mol: Cavagnat, D.; Roberts, M. P.; Cavagnat, R. M.; Vahedi-Banisaeid, S. *J. Phys. Chem.* **1991**, *95*, 134.

(23) This is the lowest energy conformer. The other conformers are located within 1.7 kcal/mol above it.

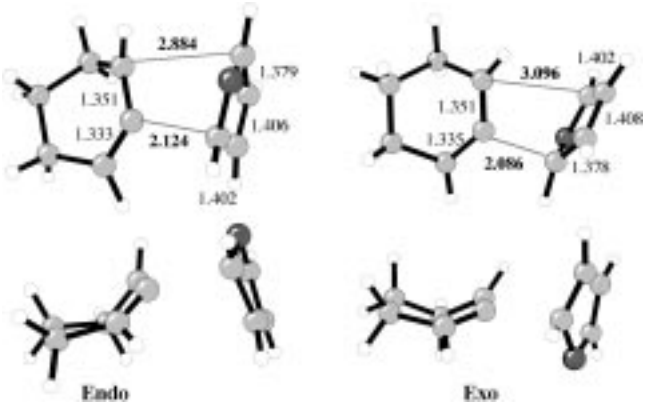


Figure 7. Concerted endo and exo transition structures of the reaction of 1,2-cyclohexadiene and furan (selected bond lengths in Å).

The energies are summarized in Scheme 7. Although no transition structure was located on the second, lower energy, stepwise path, it can be assumed that the transition structures of this path will be lower in energy than the concerted transition states. The energy difference between the intermediate and the transition structure in the nonfavored stepwise case is 22.3 kcal/mol. Even if the difference is in the same order of magnitude in the most favored case, the energy of the transition structure would be 5.3 kcal/mol below the reactants. The transition structure is thus expected to be very early and to have a similar energy to the reactants.

The Diels–Alder Reaction between 1,2-Cyclohexadiene and Furan. In contrast to the reaction of 1,2-cyclohexadiene and 1,3-butadiene, the endo and exo products can be distinguished in the reaction of 1,2-cyclohexadiene and furan. The formation of the endo adduct is exothermic by 38.9 kcal/mol, and its formation is favored by 0.8 kcal/mol over that of the exo product. The concerted transition structures are extremely asynchronous (Figure 7). In the endo structure, the two forming bonds differ by almost 0.8 Å. In the exo case, the difference is slightly more than 1.0 Å, the largest difference of the systems we studied in this account. The barrier of the concerted endo pathway is 7.0 kcal/mol, 0.9 kcal/mol lower than the concerted exo path. The endo product is thus kinetically favored, if the reaction proceeds via a concerted mechanism.

In analogy to the reaction between 1,2-cyclohexadiene and 1,3-butadiene, an anti transition structure and intermediate were located on the stepwise path 1. The intermediate is 12.8 kcal/mol above the reactants, 5.8 kcal/mol above the concerted endo transition state (Figure 8, Scheme 8). The activation barrier for its formation is 28.2 kcal/mol. The energy difference between the transition structure and the intermediate is again large compared to the reaction between allene and butadiene. The transition structure in Figure 8 leads to the diastereomer of the intermediate, but because this path requires 21.2 kcal/mol more energy than the concerted endo path, no attempt was undertaken to explore the conformational space of the intermediate or transition structure.

The intermediate of the more favored stepwise path is located 16.2 kcal/molbelow the reactants, 23.2 kcal/mol below the concerted path (Figure 9). Again, no transition structure could be located on this pathway, and the formation of this intermediate is considered barrierless for practical purposes.

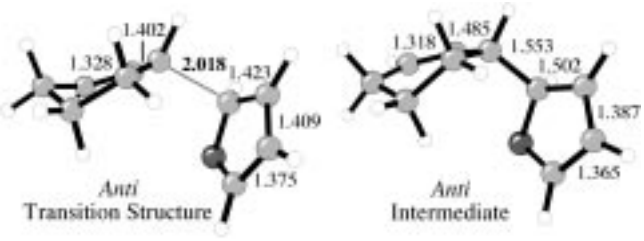


Figure 8. Intermediate and transition structure on the stepwise path 1 of the reaction between furan and 1,2-cyclohexadiene (selected bond lengths in Å).

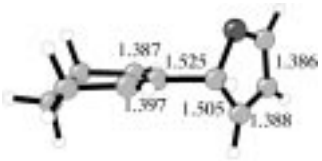
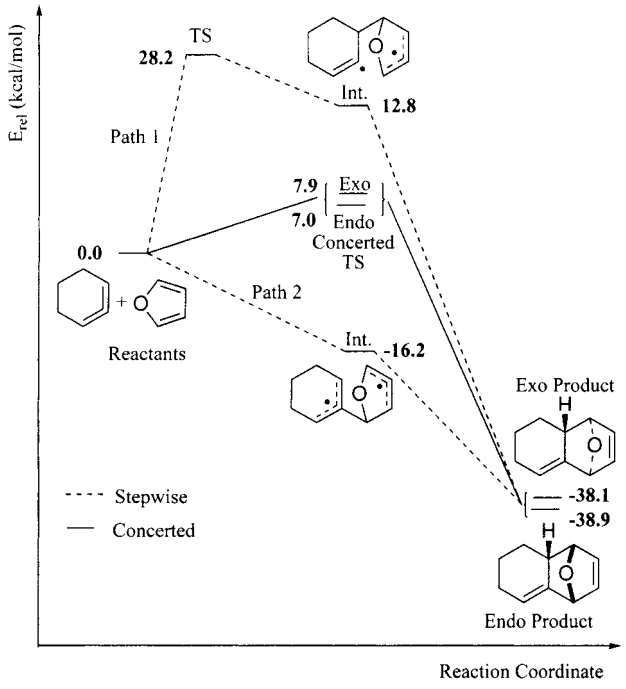


Figure 9. Intermediate of the more favored stepwise path (path 2) of the reaction between furan and 1,2-cyclohexadiene (selected bond lengths in Å).

Scheme 8. Schematic Energy Diagram of the Reaction of 1,2-Cyclohexadiene and Furan



The energy gap between the stepwise path 2 and the concerted reaction is not as large as in the case of the reaction between 1,2-cyclohexadiene and 1,3-butadiene, but it is still large enough to make the concerted paths improbable (Scheme 8). Two regioisomers are observed experimentally, while there is no chiral induction. The experimental results are consistent with two scenarios. (1) The reaction is concerted, but the influence of the chiral auxiliary is very small due to the long forming bond to C-1. (2) Path 2 is taken, but the chiral auxiliary has no influence on the formation of the chiral center opposite to C-1. The formation of the endo product is controlled by the second step. The energetics depicted in Scheme 8 clearly show that the second scenario is more likely.

Another experimental observation is in favor of this scenario: two regioisomers are formed with a maximal selectivity of 3.9:1. If the reaction followed a concerted pathway, electronic factors should govern the regiochemistry significantly and the product ratios should be more weighted toward the product resulting from reaction at the more electron-deficient bond.

No transition structure could be located for the ring closure, and the endo/exo stereochemistry is determined in the second step of the reaction. The exclusive formation of the endo product can be explained by secondary orbital interactions. In the formation of the exo product, the two-carbon unit of furan will have approximately the same distance to the cyclohexadiene ester substituent as the oxygen atom in the transition state leading to the endo product. The distance between the oxygen atom and the bridgehead hydrogen atom of the endo product is 2.54 Å, and the distance to the two-carbon unit in the exo product is 2.54 Å as well. The steric requirements are expected to be similar in the formation of both products, but stabilizing interactions between the empty orbitals of the oxygen and the ester substituent on C-1 are possible, when the endo product is formed. Therefore secondary orbital interaction should lower the barrier to the formation of the endo product in the second half of the stepwise path 2.

Because no transition structures were located on the stepwise path 2, we modeled the concerted pathway for the *l*-bornyl reaction using a QM/MM approach. The B3LYP/6-31G* concerted transition structures of 1,2-cyclohexadiene and furan which lead to the major regioisomer were substituted with the bornyl ester, and the ester substituent was optimized with MM2*. The interactions of furan and the chiral substituent would be similar to, if weaker than, those observed in the reactions of 1,3-diphenylisobenzofuran and *l*-bornyl fumarates described earlier.[5a] Figure 10 shows the endo transition structures. The exo transition structures were considered as well, and the relative energies are listed in Table 1. Because the ester can be in either a *E* or a *Z* conformation (relative to 1,2-cyclohexadiene), there are eight conformations to be considered for each regiochemical scenario.

As can be seen in Table 1, the *R*/*S* stereochemical induction by the chiral substituent is minimal. The four transition structures are located within 0.4 kcal/mol of each other in the endo case and within 0.7 kcal/mol in the exo transition structures. The energy difference between the lowest *R* and *S* structures is only 0.2 kcal/mol, well within the expected error of this method. In similar QM/MM studies, the induction by a chiral substituent is generally overestimated; i.e., the differences in relative energies in Table 1 are even smaller, so that they are no longer chemically significant.[24] Therefore, the QM/MM method predicts no stereoselectivity for the *l*-bornyl cyclohexadiene carboxylate cycloadditions.

Our DFT results show that the reaction proceeds via stepwise path 2. The stereochemistry is determined in the first and the second step. Two diastereomeric diradical intermediates can be formed, and either one can only lead to two of four products (Scheme 4). The endo products are favored and formed exclusively in the experiments (within the limits of detection); the stereochemistry of the bridgehead carbon is determined in the step forming the diradical intermediate. If a chiral auxiliary influences the formation of either diastereomeric intermediate, this influence will be reflected in the product ratio. However, the influence on the formation of the intermediate will be even less than on the concerted transition structure. The bond to C-2 is formed first and it is reasonable to assume that the distance of the dienophile to C-1 will be even larger than in the concerted case, thus allowing for less steric and electronic interactions. Therefore, modeling the concerted path provides an upper limit to the diastereomeric ratio. Since no transition structure was found on this path, this hypothesis could not be verified by molecular modeling.

(24) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439.

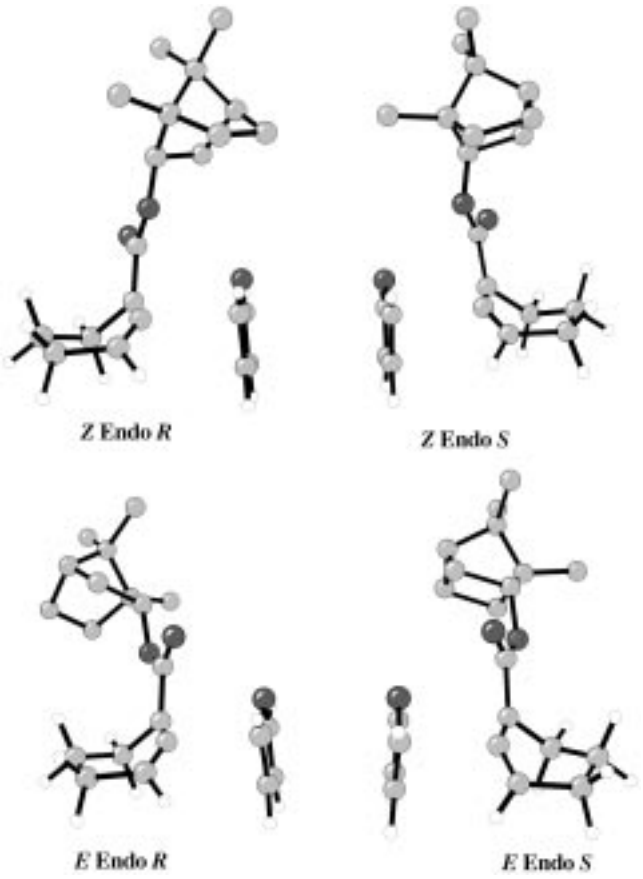


Figure 10. Endo transition structures of the reaction of *l*-bornylcyclohexa-1,2-diene carboxylate and furan leading to the nonconjugated product (the hydrogen atoms of the bornyl ester are removed for clarity).

Table 1. Relative MM2* Energies of the Different Concerted Transition Structures of the Reaction between Furan and 1-(−)-Bornylcyclohexa-1,2-dienecarboxylate

	C=C−C=O dihedral (deg)	E_{rel} (kcal/mol)
Z endo *R*	2	0.0
Z endo *S*	−4	0.5
E endo *R*	171	0.5
E endo *S*	179	0.2
Z exo *R*	−22	6.4
Z exo *S*	24	6.1
E exo *R*	167	6.3
E exo *S*	−171	6.8

Conclusions

The incorporation of a cumulated double bond into an otherwise unreactive cyclohexene carboxylate provides

a useful method for generating a reactive dienophile as well as other similarly activated dienophiles. These are open to trapping by Diels−Alder reactions with kinetically controlled regiochemistry.

The reaction of propadiene with 1,3-butadiene is stepwise. Further perturbation of the dienophile, such as its integration into a six-membered ring as in the case for 1,2-cyclohexadiene, increases the energetic gap between the stepwise and concerted pathways even further. No detectable diastereoselectivity was observed in the *l*-bornyl and *l*-menthyl cyclohexa-1,2-diene carboxylate cycloadditions, consistent with the computational preference of the stepwise mechanism

Experimental Section

Analyses. ^{1}H NMR spectra were recorded at 250, 300, and 400 MHz using tetramethylsilane as internal reference; couplings are expressed in hertz. Thin-layer chromatography (TLC) was performed with Analtech precoated silica gel GF (250-micron) plates and with basic alumina IB-F sheets (J. T. Baker), both 2.5 cm × 7.5 cm. Preparative TLC was performed with Analtech precoated silica gel GF (1000 μm, 20 cm × 20 cm) plates.

Methyl 2-Chlorocyclohexenecarboxylate (1-Me). Triphenylphosphine (22.30 g, 84.9 mmol, dried under vacuum over P_2O_5 for 8 h) was dissolved in CCl_4 (40 mL, Aldrich, freshly distilled from P_2O_5 onto molecular sieves), and methyl cyclohexanone-2-carboxylate (4.50 mL, 5.00 g, 32.0 mmol, Fluka) was added. The reaction was heated to reflux and kept under argon. After 4 days, the mixture was added to hexane (250 mL). Stirring was maintained for an additional 12 h, and the mixture was cooled in an ice bath and filtered, yielding 16.40 g of brown crystals that were washed by an additional hexane (250 mL). The solvent was evaporated under reduced pressure, yielding yellow-white crystalline triphenylphosphine oxide and a brown oil (2.14 g). Distillation at 50 °C (0.75 Torr) gave a pale yellow oil (1.35 g), containing the starting material (34%) and methyl 2-chloro-2-cyclohexenecarboxylate (**1a-Me**) and methyl 2-chloro-1-cyclohexenecarboxylate (**1b-Me**, 66% of **1a-Me** and **1b-Me**, 8% purified yield) in a ratio of 72:28. HRMS: calcd for $C_8H_{11}O_2Cl$ 174.0448, found 174.0450. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.05 (t, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.30 (t, 1 H), 2.45 (m, 2 H), 2.38 (m, 2 H), 2.20 (m, 2 H, 2.00 (m, 2 H), 1.70 (m, 6 H).

Ethyl 2-chlorocyclohexenecarboxylate (1-Et) was prepared similarly (see the Supporting Information).

l-Menthyl 2-Chlorocyclohexenecarboxylate (1-Mn). A flask equipped with a coldfinger condenser and trap was charged with 2.00 g (10.6 mmol) of ethyl 2-chlorocyclohexene carboxylate **1-Et**, 1.66 g (10.6 mmol) of (1*R*,2*S*,5*R*)-(−)-menthol (Aldrich), 0.59 g (1.06 mmol) of 1-hydroxy-3-isothiocyanatotetrabutyldistannoxane, and 8 mL of toluene (Fisher). The solution was heated at reflux for 2.5 days. The condensate (5.5 mL) was found by infrared spectroscopy to contain 11%, or 0.61 mL (98% yield), of ethanol. The dark brown solution was evaporated to give 3.90 g of residue. Silica gel column chromatography (29 cm × 2.2 cm, 32 g, 85:15 hexane/ethyl acetate yielded 2.45 g of a high R_f fraction that was distilled to give 1.93 g (66%) of colorless liquid, bp 111−115 °C (0.18 Torr). Further basic alumina column chromatography of a 1.63 g sample (hexane, then 95:5 hexane/ethyl acetate) allowed isolation of menthyl 2-chlorocyclohexenecarboxylate from ethyl 2-chlorocyclohexenecarboxylate. The yield of **1-Mn** was 1.12 g (66%) of colorless liquid, bp 105−110 °C (0.085 Torr).

Integration of the ^{1}H NMR signal at 5.98−6.06 ppm relative to the bornyl methine proton at 4.63−4.90 ppm indicated that a mixture of 84% menthyl 2-chlorocyclohexenecarboxylate **1b-Mn** and 16% menthyl 2-chlorocyclohex-2-enecarboxylate **1a-Mn** was obtained. Anal. Calcd for $C_{17}H_{27}O_2Cl$: C, 68.32; H, 9.11; Cl, 11.86. Found: C, 68.32; H, 9.27; Cl, 11.90. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.98−6.06 (16 H, m), 4.63−4.90 (l H, dt, J = 4.3, 10.9), 3.21−3.32 (0.16 H, m), 2.30−2.70 (3 H, m), 1.85−2.25 (H, m), 1.60−1.85 (5.68 H, m), 1.30−1.60 (2 H, m), 0.80−1.20 (9 H, m), 0.70−0.80 (3 H, d, J = 7). FTIR (thin film): 1725, 1665, 1627, 1456, 1341, 1277, 1252, 846, 757, 667 cm^{-1}. MS: (EI); 283 °C, *m*/*z* (relative intensity): 302.1 (M + 2, 8.9), 301.1 (M + 1, 30.6), 300.2 (M, 19.8), 143.0 (64.3), 109.1 (8.4), 81.1 (25.1).

Bornyl 2-chlorocyclohexenecarboxylate (1-Bn) was prepared similarly to **1-Mn** (see the Supporting Information).

Cycloaddition of Allenes to Furan. A. Methyl Cyclohexa-1,2-diene-1-carboxylate (2-Me). A flask was charged with 0.69 g of a mixture of 66% methyl chlorocyclohexenecarboxylate **1** and 34% of methyl cyclohexanone-2-carboxylate in an argon atmosphere. Furan (150 mL, Lancaster, dried over $MgSO_4$) and THF (75 mL, freshly distilled over sodium benzophenone, Baker) were added. Potassium *tert*-butoxide (0.60 g, 1.4 mol equiv) dissolved in THF (75 mL) was added to the stirred mixture over 30 min. Stirring was continued for 24 h, and the reaction was quenched with water (3 × 50 mL). The combined aqueous phases were saturated with sodium chloride and extracted three times with diethyl ether (50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 0.94 g of a yellow oil. The product mixture was separated by flash silica gel column chromatography (9:1 hexane/ethyl acetate). The Diels−Alder adducts were the last two fractions. The nonconjugated **3-Me** was the major product (0.25 g, 1.2 mmol, 44%), while the conjugated **4-Me** was the minor one (0.07 g, 0.4 mmol, 13%). Major product **3-Me**. HRMS: calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0943. MS (EI$^+$, 51 °C): 207.1 (M + 1), 206.1 (M), 174.1, 147.1, 77.1, 65.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.489 (dd, 1 H, J = 5.6, 1.7), 6.122 (dd, 1 H, J = 1.6), 5.722 (t, 1 H, J = 3.5), 5.248 (broad s, 1 H), 5.159 (broad s, 1 H), 3.721 (s, 3 H), 2.225 (m, 1 H), 1.950 (m, 2 H, J = 8.0), 1.710 (m, 1 H), 1.425 (m, 1 H, J = 20.0, 16.0, 12.0, 4.0), 0.569 (m, 1 H, J = 14.1, 12.1, 4.0). Minor product **4-Me**. HRMS: calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0940. MS (EI$^+$, 46 °C): 207.1 (M + 1), 206.1 (M), 174.1, 146.1, 77.1, 65.0. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): 6.415 (dd, 1 H, J = 5.7, 2.0), 6.186 (dd, 1 H, J = 1.7),5.949 (broad s, 1 H), 5.037 (broad d, 1 H, J = 4.5), 3.760 (s, 3 H), 2.420 (m, 1 H), 2.160 (m, 1H), 2.020 (m, 1 H), 1.900 (m, 1 H), 1.560 (m, 2 H), 0.380 (m, 1 H).

B. Ethyl 1,2-Cyclohexadienecarboxylate (2-Et). C. Menthyl 1,2-Cyclohexadienecarboxylate (2-Mn). D. Bornyl 1,2-Cyclohexadienecarboxylate (2-Bn). 2-Et, **2-Mn**, and **2-Bn** were treated similarly to **2-Me** (see the Supporting Information).

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research and to the San Diego Supercomputer Center and UCLA's Office of Academic Computing for computational support.

Supporting Information Available: Experimental details and Cartesian coordinates of the computed structures including energies and zero point energies as well as $\langle S^2 \rangle$ values and triplet single point energies of the UB3LYP structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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