Stereochemical Features of the (2 + 2) Cycloaddition Reactions of Chiral Allenes. 1. The Cycloaddition of Enantioenriched 1,3-Dimethylallene with the Monosubstituted Alkenes Acrylonitrile and Methyl Acrylate

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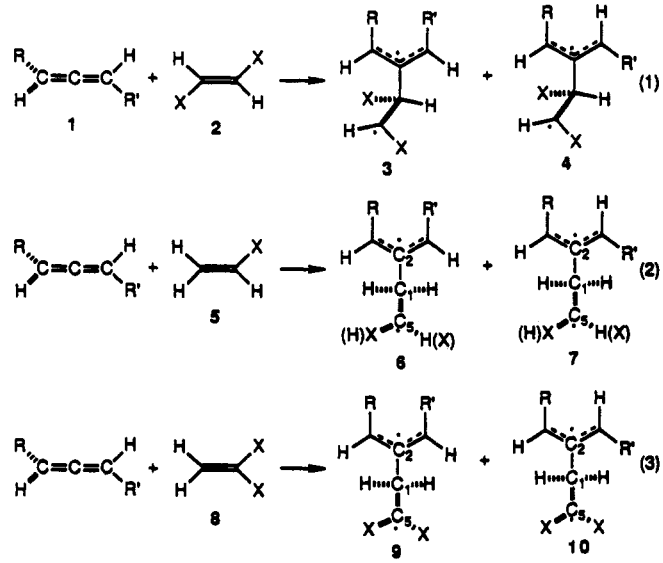
The various stereochemical features of the (2 + 2) cycloaddition reactions of symmetrically and unsymmetrically 1,3-disubstituted allenes with 1,1- and 1,2-disubstituted and monosubstituted alkenes are discussed. Experimental studies have been carried out for the case of the cycloaddition reaction of a symmetrically substituted chiral allene (1,3-dimethylallene, 13DMA) with the monosubstituted alkenes acrylonitrile (ACN) and methyl acrylate (MAC). The cycloaddition reaction of an excess of enantioenriched 13DMA with ACN produces four optically active cycloadducts, two retaining only a small amount of the enantiomeric excess (ee) of the starting 13DMA, and two cycloadducts retaining a significantly higher level of the ee of the starting 13DMA. The recovered unreacted 13DMA possesses within experimental error the same ee as that of the starting 13DMA, implying irreversible formation of the diradical intermediates. The results are discussed in terms of the preferred conformation of approach of the ACN and 13DMA to the activated complexes for the formation of the diradical intermediates, the preferred conformations of the intermediate diradicals and their intrinsic total asymmetry, possible racemization modes of the intermediates, and the effect of the regioselectivity of ring closure to form the cycloadducts. The ee's of the cycloadducts derived with MAC are significantly higher than those of the cycloadducts derived with ACN, which is attributed to a greater diastereoselectivity in progressing to the activated complexes with MAC.

Introduction

Over the past decade, one of the major research interests in our laboratories has focused on studies of the mechanistic details of the (2 + 2) cycloaddition reactions of substituted allenes. Employing the cycloaddition reaction of alkyl-substituted allenes with 1,1-dichloro-2,2-dichloroethene (1122), the stereochemical, relative reactivity, and kinetic isotope effects characteristic of a two-step, diradical intermediate cycloaddition process with alkyl-substituted allenes were established.[1] A comparison of the characteristics of this cycloaddition process with those of the cycloaddition reactions of alkyl-substituted allenes with other radicophiles indicated that the (2 + 2) cycloaddition reactions of alkyl-substituted allenes all proceed via two-step, diradical intermediate processes.[2] The results of these studies have provided information as to what factors determine the relative stereoselectivities in the formation of the allyl radical portion of the diradical intermediates, the preferred conformations about the alkyl radical portion of the intermediates, and some of the factors that determine the stereo- and regioselectivities of ring closure to the product substituted alkylidenecyclobutanes.[1,2]

One feature of the cycloaddition processes that has been difficult to assess is the question of reversibility of formation of the diradical intermediates. In our previous investigations, reversibility of formation of the diradical intermediates was indicated by the cis to trans isomerization of the substituted alkene, which does not occur in the absence of the substituted allene, or from the stereochemistry about the exocyclic double bonds in the cycloadducts.[2] The number of cis- and trans-related disubstituted alkenes in which cis to trans isomerization of the alkene can be monitored are extremely limited. The use of chiral allenes appeared to be an ideal approach to this problem, the reversibility of formation of the diradical intermediates being indicated by the loss of enantiomeric excess (ee) of the starting allene and a decrease in the ee of the cycloadducts with extent of reaction.

The results derived from investigations of the cycloaddition reactions of chiral allenes will also provide stereochemical information on the formation of the diradical intermediates and on their ring closure. A detailed analysis of the various possible combinations of reactants in the cycloaddition reactions of chiral allenes 1 with variously substituted radicophiles presents some very intriguing stereochemical features of these cycloaddition reactions. These are illustrated in eqs 1-3. Let us first consider the



cycloaddition of a symmetrically-substituted chiral allene 1 (R = R'), for example, 1,3-dimethylallene (13DMA), with a 1,2-disubstituted alkene 2 via the diradical intermediates 3 and 4 (eq 1). In the formation of 3 and 4, the axial dissymmetry of 1 is transferred to the newly formed asymmetric centers in 3 and 4. If the formation of 3 and 4 is reversible, and if the degree of the transfer of the ee from 1 to 3 and 4 is less than 100%, then the unreacted 1 will suffer a loss of ee during the course of the reaction, as will also the cycloadducts. Once formed, however, the asymmetry of 3 and 4 is "locked in"; there is no intramolecular process that will allow for racemization, and the

(1) Pasto, D. J.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3670.
(2) Pasto, D. J.; Heid, P. F.; Warren, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3676. Pasto, D. J.; Yang, S.-H. *J. Am. Chem. Soc.* **1984**, *106*, 152. Pasto, D. J.; Yang, S.-H. *J. Org. Chem.* **1986**, *51*, 1676. Pasto, D. J.; Warren, S. E.; Weyenberg, T. *J. Org. Chem.* **1986**, *51*, 2106. Pasto, D. J.; Yang, S.-H. *J. Org. Chem.* **1986**, *51*, 3611.

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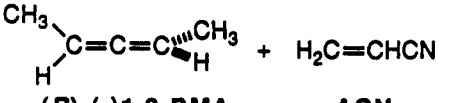
ee will be completely transferred to the cycloadducts. An interesting question arises, however, as to whether the extent of the transfer of ee from 1 to 3 and 4, if less than 100%, will be the same. The diradical intermediates 3 and 4 differ stereochemically in a very subtle manner. In 4 there is no local, vertical plane of symmetry in the allyl radical portion of the intermediate, whereas in 3 there is a local, vertical plane of symmetry in the allyl radical portion of the intermediate when R = R′. Thus, 3 and 4 differ in their "intrinsic" total asymmetry and might not be expected to be formed with the same extent of the transfer of the ee from 1 nor result in the formation of *R*- or *S*-configuration cycloadducts to the same extent. In the cycloaddition reaction of an unsymmetrically 1,3-disubstituted allene 1 (R ≠ R′), neither 3 nor 4 possesses a local plane of symmetry in the allyl radical portion of the diradical intermediates. Again, the question is what effect this will have on the extent of the transfer of the ee of 1 to 3 and 4 during their formation?

Equation 2 illustrates the cycloaddition of a chiral allene with a monosubstituted alkene 5. In this case, an asymmetric atom is not formed, but planar asymmetry is developed in the diradical intermediates. In the diradical intermediate 7 formed from a symmetrically disubstituted 1 (R = R′), there is an asymmetric plane that encompasses the entire intermediate. In 6, however, there is a local, vertical plane of symmetry in the allyl radical portion of the intermediate giving 6 a lower intrinsic asymmetry. In contrast to 3 and 4, in which there is no intramolecular mechanism for racemization, racemization of 6 and 7 can occur by a 180° rotation about the C_1–C_2 and/or C_1–C_5 bonds in the alkyl radical portion of the intermediates. When R = R′, racemization of 6 occurs by a 180° rotation about the C_1–C_5 or the C_1–C_2 bond, but when R ≠ R′ racemization requires rotation about both the C_1–C_2 and C_1–C_5 bonds. The racemization of 7, whether R = R′ or R ≠ R′, requires 180° rotations about both the C_1–C_2 and C_1–C_5 bonds. In this case, what will be the extent of the transfer of the ee of 1 to 6 and 7, and to what extent will that ee be transferred to the cycloadducts?

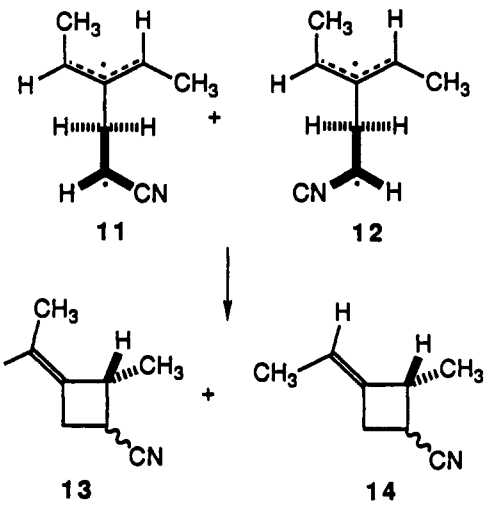
Equation 3 illustrates the final possibility, that being the cycloaddition of a chiral allene with a 1,1-disubstituted radicophile 8 that produces the diradical intermediates 9 and 10. When R = R′, there is a full plane of symmetry in intermediate 9, and thus any products derived from 9 must be racemic. When R ≠ R′, there is a local plane of symmetry in the alkyl radical portion of 9 and a local asymmetric plane in the allyl radical portion of 9. In this case, the intermediate will be chiral and racemization will occur by a 180° rotation about only the C_1–C_2 bond. With 10, whether R = R′ or R ≠ R′, there is no local plane of symmetry in the allyl radical portion of 10, and racemization can occur by a 180° rotation about the C_1–C_2 bond. Again, the interesting question arises as to what extent the ee of 1 will be transferred to intermediate 10 (R = R′), and 10 and 11 (R ≠ R′), and to what extent that ee will be transferred to the cycloadducts.

This paper presents the results of the first of a series of stereochemical studies on the various types of cycloaddition reactions illustrated in eqs 1–3. In the present article are described the results of the stereochemical studies on two examples of the cycloaddition of a symmetrically 1,3-disubstituted allene, 1,3-dimethylallene (1 (R = R′ = CH_3), 13DMA), with the monosubstituted alkenes acrylonitrile (ACN) and methyl acrylate (MAC).

The results of a preliminary study of Baldwin and Roy in 1969 on the cycloaddition of (*R*)-(−)-13DMA with ACN showed that all four of the stereoisomeric cycloadducts 13 and 14 were optically active.[3] The absolute configurations at the methyl-substituted ring carbon atom of the cycloadducts were shown to be *R* by ozonolysis of the cycloadducts to the corresponding cyclobutanones and analysis by ORD.[3] The authors proposed that the cycloaddition of (*R*)-(−)-13DMA with ACN occurred via the formation



(*R*)-(-)1,3-DMA ACN

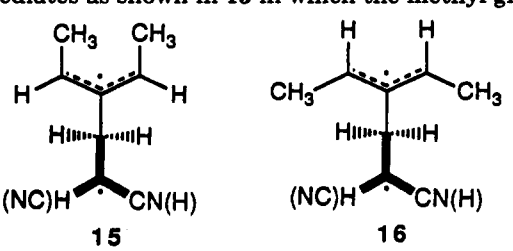


11 12

13 14

of the asymmetric diradical intermediates 11 and 12, having the absolute stereochemistry as shown in the structures, by the approach of the ACN from the least sterically hindered direction with the rotation of the methyl at the terminus of the 13DMA toward the approaching ACN and with ring closure occurring more rapidly than any internal carbon–carbon bond rotation process that would result in racemization. The stereochemistry of the four cycloadducts was not determined, nor were the ee's of the cycloadducts relative to that of the starting 13DMA.

In the accompanying paper, we presented the results of a structural study on the cycloadducts formed in the cycloaddition reactions of 13DMA with a variety of radicophiles, including ACN and MAC. The assignment of the stereochemistry of the cycloadducts was in no way a simple, straightforward process as it involved extensive NMR decoupling and NOE studies and ab initio and molecular mechanics calculations.[4] The results of the studies on the cycloaddition reaction of 13DMA with ACN indicated that, in addition to the formation of diradical intermediates 11 and 12, diradical intermediates must also be formed having the stereochemistry about the allyl radical portion of the intermediates as shown in 15 in which the methyl group



15 16

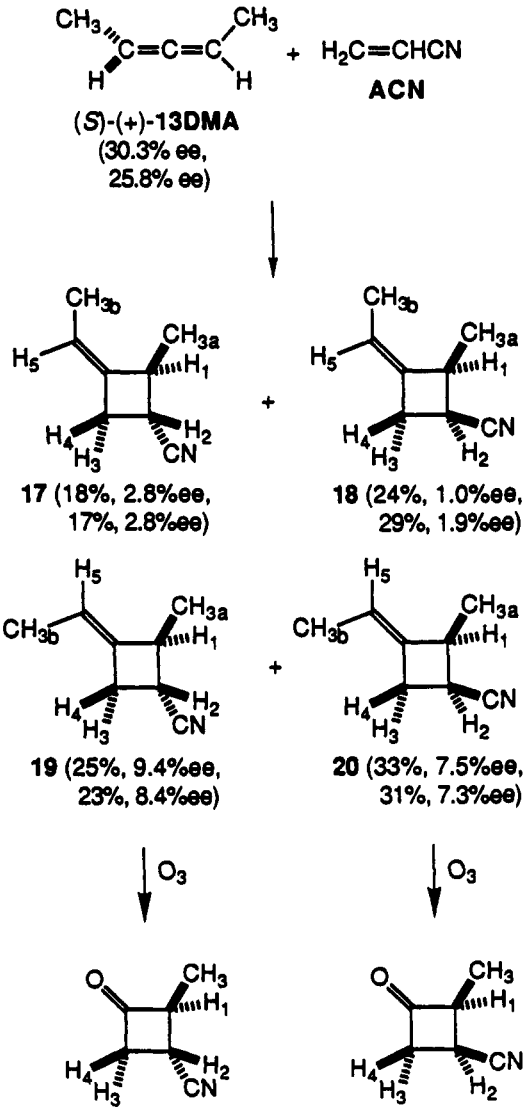
at the terminus of the 13DMA has rotated away from the

(3) Baldwin, J. E.; Roy, U. V. *J. Chem. Soc. D* **1969**, 1225.
(4) Pasto, D. J.; Sugi, K. D. *J. Org. Chem.*, previous paper in this issue.

approaching ACN. Diradical intermediates having the stereochemistry about the allyl radical portion of the intermediates as shown in 16 are considered not to be formed in the cycloaddition process for steric reasons, the approach of the ACN to the 13DMA involving the more sterically hindered approach and the more sterically hindered direction of rotation of the methyl group.[4] The stereochemistry of formation of the diradical intermediates has been analyzed by molecular mechanics calculations using the CHEM-X program,[5] the results of the calculations correlating nicely with the original proposal of Baldwin and Roy[3] concerning the proposed absolute configurations of the diradical intermediates 11 and 12 that would be formed from (*R*)-(−)-13DMA. The results of the present studies also support our suggestion that diradical intermediates having the stereochemistry about the allyl radical as shown in structure 15 are also formed, which possess lower intrinsic asymmetries ultimately producing cycloadducts of much lower ee.

Results and Discussion

Cycloaddition of (*S*)-(+)-1,3-Dimethylallene with Acrylonitrile. The cycloaddition of (*S*)-(+)-13DMA with ACN has been carried out in toluene-d_8 solution at 160 °C with a 2:1 excess of 13DMA. The reaction was periodically monitored until the complete disappearance of the ACN had occurred. The NMR spectrum of the reaction solution showed the presence of only the four cycloadducts and unreacted 13DMA. No resonances were evident indicative of oligomerization or polymerization. The excess unreacted 13DMA was recovered, and its ee was determined. Two separate experiments were carried out; in the first experiment the ee of the starting 13DMA was 30.3% and that of the recovered 13DMA was 28.3%, while in the second experiment the ee's were 25.8 and 25.0%, respectively. The ee's of the starting and recovered 13DMA are within the experimental error of the optical rotation measurements and suggest that either the formation of the diradical intermediates is irreversible or, if the intermediates are formed reversibly, there is essentially the complete transfer of the chirality of the 13DMA to the intermediates (as must also be the extent of the transfer of the chirality of the diradical intermediates back to the 13DMA on cleavage of the diradical intermediates on the basis of the principle of microscopic reversibility).



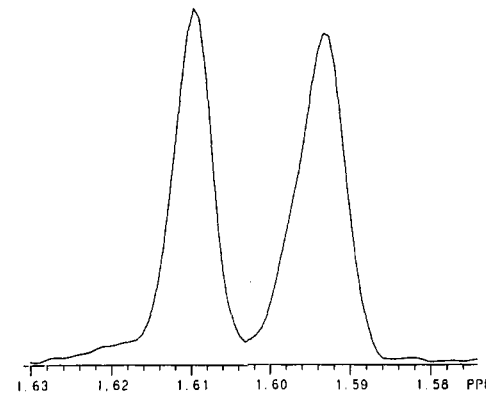


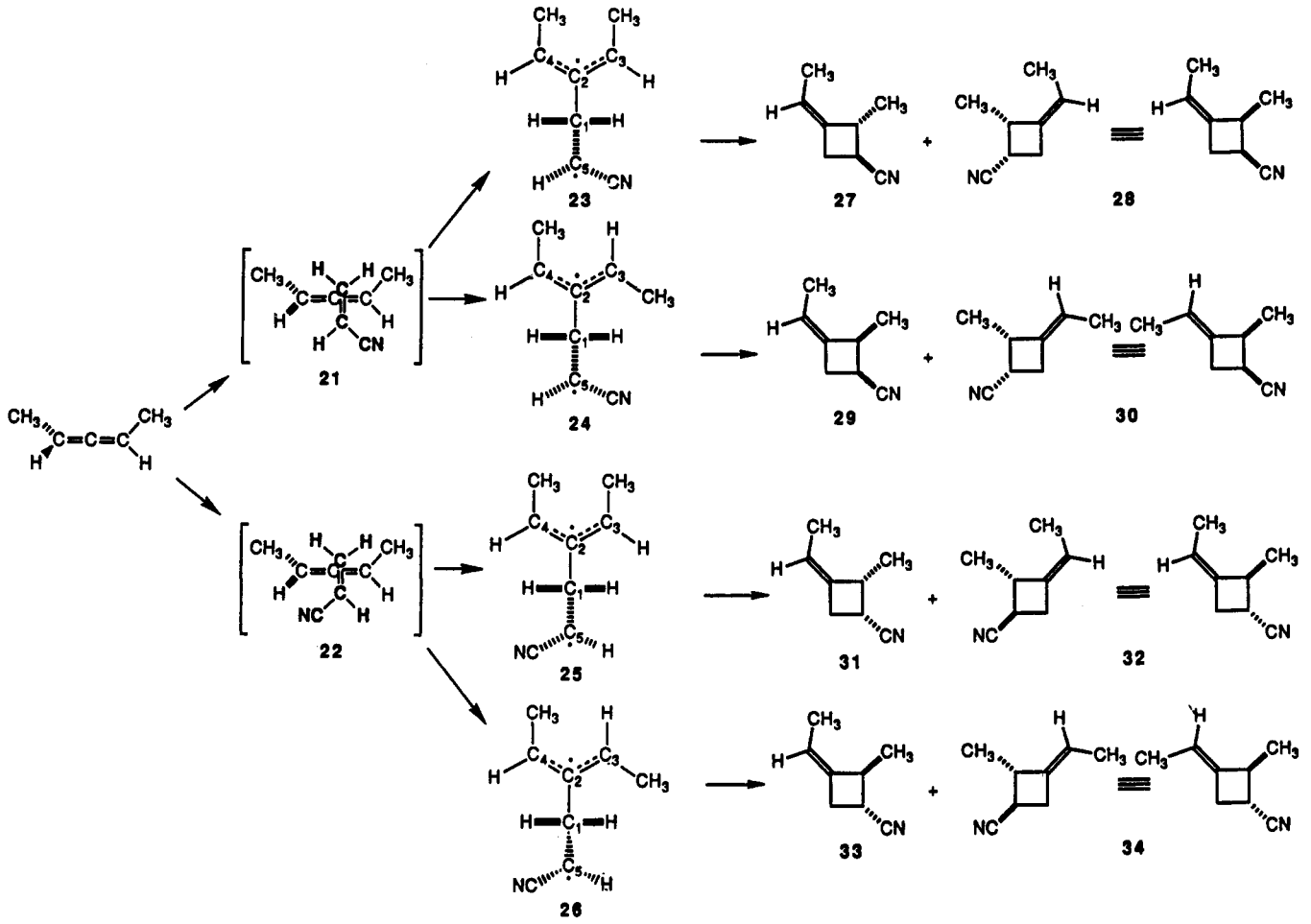
Figure 1. NMR spectrum of the methyl region of the cyclobutanone derived from cycloadduct **20** in the presence of tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) with double resonance of the C_2 hydrogen.

The cycloadducts were separated by preparative GLC. Attempted direct ee analysis of the cycloadducts by the use of several chiral NMR chemical shift reagents failed. Ozonolysis of the individual cycloadducts to the corresponding substituted cyclobutanones[3] was successfully carried out in methylene chloride/pyridine solution at −70 °C. NMR analysis of the resulting cyclobutanones derived from the individual fractions indicated that no cis,trans isomerization of the substituted cyclobutanones occurred during the ozonide decomposition or workup procedure. Analysis of the ee's of the substituted cyclobutanones using a europium chemical chiral shift reagent, along with the use of double resonance techniques, allowed for the baseline resolution of the ring-methyl resonances of the diastereomerically related complexes (see Figure 1). The derived percent ee's and the percent yields of the cycloadducts for the two experiments are given below the structures. Two of the cycloadducts, **17** and **18**, possess greatly diminished ee's relative to that of the starting 13DMA, while the other two cycloadducts, **19** and **20**, have retained a significant amount of the ee of the starting 13DMA.

A detailed analysis of the mechanism of formation of the individual cycloadducts is shown in Scheme I. The results of molecular mechanics calculations on the possible orientations of approach of the ACN to (*S*)-(+)-13DMA indicate that the approaches illustrated in **21** and **22** are lower in energy than those in which the ACN is oriented in the upward direction (diastereoisomers of **21** and **22**), with approach **21** being lower in energy than **22**.[4] On

(5) CHEM-X, developed and distributed by Chemical Design, Ltd., Oxford.

Scheme I



proceeding from the activated-complex model 21 to the diradical intermediates, rotation of the methyl group at the right end of the 13DMA away from the approaching ACN produces 23, while rotation of the methyl group toward the approaching ACN produces 24. On proceeding from the activated-complex model 22 to the diradical intermediates, rotation of the methyl group away from the approaching ACN leads to 25, while rotation toward the approaching ACN leads to 26.

Intermediates 23 and 25 are of lower intrinsic total asymmetry, are related as enantiomers, and are interconverted by rotation about the newly formed C_1–C_2 bond or by rotation about the C_1–C_5 bond. The results of ab initio calculations on the parent homotrimethylenemethane (HTMM) diradical indicates an energy barrier of 1.61 kcal mol^{-1} for rotation about the C_1–C_2 bond and 1.67 kcal mol^{-1} for rotation about the C_1–C_5 bond.[6] Although the energy barriers for ring closure are not known, these rotational energy barriers would appear to be of a magnitude similar to those for ring closure; otherwise, all ee would have been lost in the cycloadducts derived from 23 and 25.

Intermediates 24 and 26 are related as diastereoisomers, each with its own associated enantiomer. Racemization of 24 and 26 requires 180° rotations about both the C_1–C_2 and C_1–C_5 bonds. The minimum calculated energy barrier for the rotation about the C_1–C_2 bond involving passage of the C_1–H bond past the *syn*-methyl group in the appropriate methyl-substituted HTMM is 2.89 kcal mol^{-1}.[6] The energy barrier for rotation of the C_1–CH_2 bond past the *syn*-methyl group is calculated to be 5.68 kcal mol^{-1} in the methyl-substituted HTMM.[6] These energy barriers appear to be significantly higher than those for ring closure, and thus, little, or no, racemization of 24 and 26 is expected to occur prior to ring closure. In the preceeding paper, this was concluded from an analysis of the product distribution that the anti,syn diradical intermediates 24 and 26 are formed preferentially over the anti,anti diradical intermediates 23 and 25 by an approximate ratio of 60:40. The following discussion analyzes the various modes of ring closure of the diradical intermediates 23–26 and the potential impact of these ring-closure modes on the ee's retained in the cycloadducts.

Let us first consider the ring closure of diradical intermediate 23. Ring closure to the right end of the allyl radical in a least motion[7] manner produces 27, which possesses the *R* configuration at C_2. Ring closure to the left end of the allyl radical produces 28, which possesses the *S* configuration at C_2. Thus, the lower intrinsic asymmetry of diradical intermediate 23 is manifest in the formation of cycloadducts with opposite configurations at C_2 in the cycloadducts. Even though 27 and 28 are diastereomeric, the net effect on the ee's of the cycloadducts formed from the diradical intermediates of lower intrinsic asymmetry will not be appreciated until one considers the ring-closure modes of the other low intrinsic asymmetry diradical intermediate 25.

The ring closure of the diradical intermediate 24 at the right end of the allyl radical produces 29 possessing the *S* configuration at C_2, which is identical with 28. Ring closure to the left end of the allyl radical produces 30, possessing the *S* configuration at C_2. This is the only

(6) Pasto, D. J.; Benn, D. C. Unpublished observations.

(7) Least-motion ring closure implies a ring closure mode involving the least amount of rotation of the two radical centers.

diradical intermediate that can give rise to **30**, and being of relative higher intrinsic asymmetry produces product of a higher retained ee. Diradical intermediate **24** is of higher intrinsic asymmetry than **23** and produces only cycloadducts possessing the *S* configuration at C_2. Herein lies the result of the subtle differences in the total intrinsic asymmetries possessed by the diradical intermediates **23** and **24** alluded to earlier that are formed in this type of (2 + 2) cycloaddition reaction with a symmetrically substituted 1,3-dialkylallene.

The ring closure of diradical intermediate **25** to the right end of the allyl radical produces **31**, which possesses the *R* configuration at C_2 of the cycloadduct. Ring closure to the left end of the allyl radical produces **32**, possessing the *S* configuration at C_2 of the cycloadduct. Again, the diradical intermediate of lower intrinsic asymmetry produces cycloadducts possessing both *R* and *S* configurations at C_2 of the cycloadducts. Furthermore, **32** is enantiomeric with **27** and **31** is enantiomeric with **28**. The net result is that the cycloadducts formed from **23** and **25** effectively cancel each other's contributions to product ee's.

Ring closure of the diradical intermediate **26** at the right end of the allyl radical produces **33**, possessing the *S* configuration at C_2. Ring closure at the left end of the allyl radical produces **34**, also possessing the *S* configuration at C_2. Diradical intermediate **26** is the sole precursor of **34**, and being of relative higher intrinsic asymmetry produces product retaining a higher level of ee.

To summarize, cycloadducts **17** and **18** can each be formed via three different reaction channels; for **17**, those leading the formation of **27**, **32**, and **33**, and for **18**, those leading to the formation of **28**, **29**, and **31**. In both of these two sets of reactions channels, two produce ring-closed products possessing the *S* configuration at C_2 and one having the *R* configuration at C_2. The latter channels result in a reduction of the ee transferred to the cycloadducts **17** and **18**. In addition, the energy barriers for racemization of **23** and **25** appear to be low enough to allow for some competitive racemization, further reducing the ee's retained in **17** and **18**. The observed ee's of **17** and **18** are in all probability derived from ring closure of the diradical intermediates **24** and **26** to form **29** and **33**, respectively, in Scheme I, which are of higher intrinsic asymmetry and are not capable of undergoing racemization competitive with ring closure. Unfortunately, it is not possible to estimate quantitatively the relative contributions of the three reaction channels to the formation of **17** and **18**. What is required is a system in which diradical intermediates having only the anti,anti or only anti,syn stereochemistry can be formed. This is currently being explored.

In contrast, cycloadducts **19** and **20** are both formed only via single reaction channels, both leading to the *S* configuration at C_2 in the cycloadducts. This, along with the expectation that racemization of **24** and **26** will not be competitive with ring closure will result in higher transfers of the ee of the 13DMA to these cycloadducts. The fact that only 37 and 29% of the ee of the starting 13DMA has been transferred to the cycloadducts, along with the fact that the recovered unreacted 13DMA has not loss any ee during the course of the reaction, implies that the diradical intermediates **23–26** are formed irreversibly.

Cycloaddition of (*S*)-(+)-13DMA with Methyl Acrylate. The cycloaddition of (*S*)-(+)-13DMA (30.3% ee) with MAC (2:1 molar ratio) quantitatively produces the four cycloadducts **37–40** (the relative yields are given in parentheses), which were separated by preparative GLC. The unreacted 13DMA was recovered and was shown to possess 30.2% ee. There is no loss in the ee of the 13DMA during the course of this cycloaddition reaction, which, in view of the fact that the derived cycloadducts possess ee's less than the starting 13DMA, indicates that the formation of the diradical intermediates is irreversible.

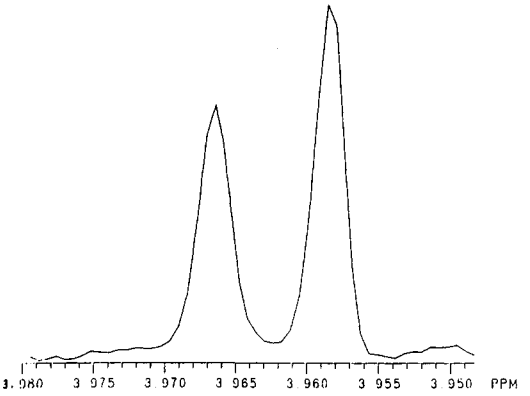
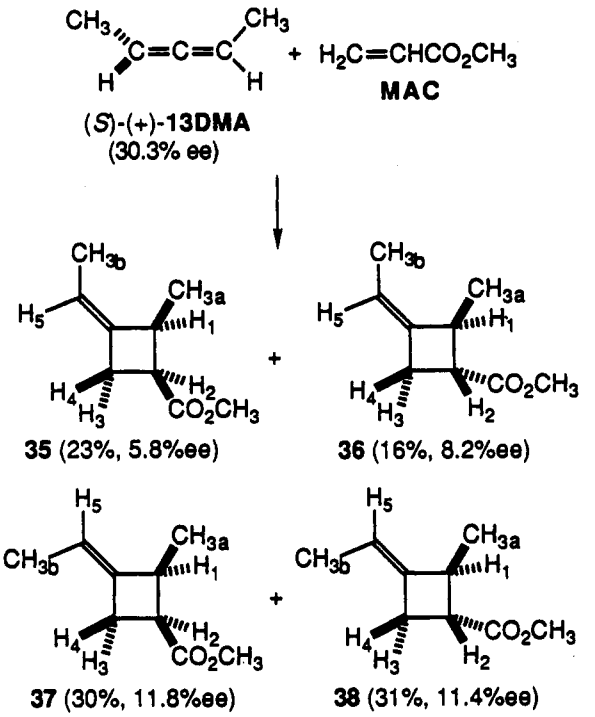
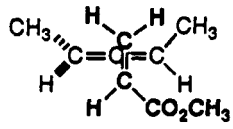


Figure 2. NMR spectrum of the ester methyl region of **38** in the presence of tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III).



The percent ee's of the cycloadducts were determined by the use of a chiral europium NMR chemical shift reagent. Baseline resolution was obtained for the ester methyl resonances of the diastereomeric complexes, allowing for an accurate integration of the NMR resonances and the determination of the ee's of the cycloadducts (see Figure 2). The ee's are given in parentheses under the structures.

It is interesting to note that the relative yields of the stereochemically related cycloadducts derived with ACN and MAC are very similar. The ee's of the cycloadducts derived with MAC, however, are significantly higher than those possessed by the cycloadducts derived with ACN. Cycloadducts **37** and **38**, for example, are formed with 46 and 44% transfer of the ee of the starting 13DMA! Molecular mechanics calculations using the CHEM-X program[5] on models for the approach to the activated complexes for the reaction of MAC with the 13DMA indicate greater preferences for the approaches shown in **39** and **40** compared to the approaches in which the ester groups are



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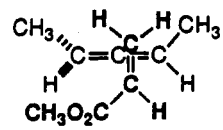

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oriented in an upward manner (diastereoisomers of **39** and **40**) than calculated for the ACN–13DMA case. This is then expected to result in greater diastereoselectivity in the formation of the activated complexes. In a similar manner, the larger size of the methyl ester function compared to the cyano group will result in an increase in the energy barriers for the rotation about the C_1–C_5 bond and potentially about the C_1–C_2 bond, thus resulting in less racemization of the intermediates.

The formation of the cycloadducts **35–38** exactly parallels that illustrated in Scheme I for the formation of the diradical intermediates and cycloadducts with ACN and does not require further discussion.

Summary

The results of the present study have indicated that the diradical intermediates formed in the cycloaddition reactions of 13DMA with ACN and MAC are in all probability formed irreversibly. The results also show that a surprisingly large amount of the ee of the 13DMA is transferred to the diradical intermediates, the extent of which is dependent on the size of the substituent attached to the radicophile. The extent of racemization of the diradical intermediates also appears to be quite sensitive to the size of the substituent on the radicophile.

Future investigations will focus on cycloaddition reactions in which only diradical intermediates having the anti,anti stereochemistry about the allyl radical portion of the intermediates can be formed as well as cycloaddition reactions with unsymmetrically substituted allenes and with 1,2- and 1,1-disubstituted alkenes.

Experimental Section

Preparation of Enantioenriched 13DMA. The preparation of (*S*)-(+)-13DMA was carried out by the asymmetric hydroboration procedures of Waters, Linn, and Caserio,[8] and Rossi and Diversi.[9] Boron trifluoride dimethyl etherate (11.67 g, 102 mmol) was added slowly to 15.7 g (115 mmol) of (+)-α-pinene (+47.1° from Aldrich, distilled from lithium aluminum hydride) and 2.9 g (76.8 mmol) of sodium borohydride in 70 mL of diglyme (freshly distilled from lithium aluminum hydride) at 0 °C under a nitrogen atmosphere. After the solution was stirred for 8 h at 0 °C, another 15.7 g of (+)-α-pinene was added[10] and the reaction mixture was allowed to stand another 8 h. Racemic 13DMA (14 g, 205 mmol) was rapidly added, and the reaction mixture was stirred for 4 h at 0 °C, after which time the volatiles were removed at 50 °C under slight reduced pressure. The resulting mixture of 13DMA and ether was separated by preparative GLC using a 12 ft × $^1/_4$ in. 20% SE-30 on Chromosorb P column at 60 °C, giving 4.2 g (30%) of (*S*)-(+)-13DMA (α = 0.261 ± 0.001°, *c* = 1.25, 25.9% ee[11] ether). The ee of the 13DMA derived from different runs varied from 25.9 to 30.3%.

Cycloaddition of (*S*)-(+)-1,3-Dimethylallene with Acrylonitrile. In a 9 in. × 5 mm NMR tube were placed 140 mg (2.06 mmol) of (*S*)-(+)-13DMA (experiment 1 α 0.152 ± 0.001°, *c* = 0.62, ether, 30.3% ee; experiment 2 α = 0.261 ± 0.001°, *c* = 1.25, 25.8% ee, ether), 56.7 mg (1.03 mmol) of ACN, 500 μL of toluene-d_8, and 5 mg of hydroquinone. The contents of the tube were triply freeze–degassed, and the tube was sealed under reduced pressure. The tube was heated in the vapor of refluxing nonane (148 °C) until all of the ACN was reacted (by NMR analysis, 5 d). Only resonances for the four cycloadducts **17–20** and unreacted 13DMA were present in the 300-MHz ^{1}H NMR spectrum. The tube was opened, and the volatiles were removed from the sample on a vacuum line. The unreacted 13DMA was isolated by preparative GLC on a 12 ft × $^1/_4$ in. 20% SE-30 on Chromosorb P column at 90 °C. The optical rotation of the recovered 13DMA was recorded (experiment 1 α 0.062 ± 0.001°, *c* 0.27, 28.3% ee, ether; experiment 2 α = 0.354 ± 0.001°, *c* = 1.75, 24.9% ee, ether).

The mixture of the four cycloadducts was separated by preparative GLC on a 39 ft × $^1/_4$ in. 20% Carbowax 20M on Chromosorb P column at 180 °C, giving milligram quantities of the pure cycloadducts. (Insufficient quantities of the cycloadducts were recovered to allow for the accurate determination of optical rotations.) The relative yields of the cycloadducts were determined by a combination of integration of the 300-MHz ^{1}H NMR spectrum of the crude reaction mixture and the integration of the gas chromatogram.

Ozonolysis of the 13DMA–ACN Cycloadducts.[3] In a precooled (dry ice/acetone bath) 5-mL vial were placed the sample of the cycloadduct, 2 mL of methylene chloride, and 0.1 mL of pyridine. A stream of ozone was bubbled through the solution until a pale blue solution persisted. Nitrogen was then bubbled through the solution for 5 min. The reaction mixture was allowed to warm to 0 °C and was washed with cold 10% hydrochloric acid and water. The organic layer was dried ($MgSO_4$), and the methylene chloride was carefully evaporated by a stream of dry nitrogen. The NMR spectra of the cyclobutanones derived from the individual cycloadducts indicated the presence of a single stereoisomer, identical cyclobutanones being derived from **17** and **19** and from **18** and **20**. No parent ions could be observed for the substituted cyclobutanones by EIMS.

***cis*-3-Cyano-2-methylcyclobutanone**: NMR ($CDCl_3$) δ 1.33 (d, *J* = 7.43 Hz, 3 H), 2.73 (dt, *J* = 9.00, 7.51 Hz, 1 H), 3.34 (ddd, *J* = 17.69, 9.00, 2.15 Hz, 1 H), 3.46 (ddd, *J* = 17.69, 7.51, 2.69 Hz, 1 H), and 3.78 (dqdd, *J* = 7.51, 7.43, 2.69, 2.15 Hz, 1 H).

***trans*-3-Cyano-2-methylcyclobutanone**: NMR ($CDCl_3$) δ 1.42 (d, *J* = 7.43 Hz, 3 H) and 3.4–3.7 (complex multiplets not interpretable on a first-order basis).

Determination of the ee's of the 3-Cyano-2-methylcyclobutanones. To the $CDCl_3$ NMR solutions of the substituted cyclobutanones was added incremental amounts of tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) dissolved in $CDCl_3$ until suitable resolution of the methyl resonances was achieved on double resonance of the C_2 hydrogen. The ee's were calculated from the integrals of the two methyl resonances. The derived ee's of the four cycloadducts are given under the structures.

Cycloaddition of (*S*)-(+)-13DMA with Methyl Acrylate. In a 9 in. × 5 mm NMR tube were placed 140 mg (2.06 mmol) of (*S*)-(+)-13DMA (α = 0.152 ■ 0.001°, *c* = 0.62, 30.3% ee, ether), 88.6 mg (1.03 mmol) of MAC, 500 μL of toluene-d_8, and 5 mg of hydroquinone. The contents of the tube were triply freeze–degassed, and the tube was sealed under vacuum. The tube was heated in a sand bath at 160 °C for 3 d, after which time analysis by 300-MHz ^{1}H NMR spectroscopy showed the presence of only the four cycloadducts and unreacted 13DMA. The tube was opened, and the volatiles were removed on a vacuum line. The unreacted 13DMA was isolated by preparative GLC on a 12 ft × $^1/_4$ in. 20% SE-30 on Chromosorb P column at 90 °C. The optical rotation of the recovered 13DMA was determined (α =

(8) Waters, W. L.; Linn, W. S.; Caserio, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6741.

(9) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25.

(10) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.

(11) A review of the literature provides values ranging from ~78° to 227° for the maximum rotation of 13DMA. Owing to some very unusual results obtained in our laboratories after submission of this manuscript, it became necessary to unambiguously determine the ee of the partially resolved samples of 13DMA and the maximum rotation of optically pure 13DMA. This has been accomplished directly by NMR with the use of a 1:1 mixture of Ag(fod) and tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]ytterbium(III) (Aldrich Chemical Co.)[12] by integration of the methyl region of the 13DMA while irradiating the vinyl protons. The average calculated maximum rotation of optically pure 13DMA has been determined to be 81.0 ± 0.2° (ether). These results and a discussion of the prior literature on chiral 13DMA will be described elsewhere.

(12) Mannschreck, A.; Munninger, W.; Burgmeister, T.; Gore, J.; Cazes, B. *Tetrahedron* **1986**, *42*, 399.

0.099 ± 0.001°, c = 0.405, 30.2% ee, ether).

The cycloadducts were separated by preparative GLC on a 39 ft × 1/4 in. 20% Carbowax 20M on Chromosorb P column at 190 °C, providing milligram quantities of the pure cycloadducts. (Insufficient quantities were available to allow for the accurate measurement of the optical rotations.) The ee's of the cycloadducts were determined by the use of tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) and integration the methyl resonances of the ester methyl groups (see Figure 2). The corresponding ee's are given under the structures.

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Use of Radical Ring-Opening for Introduction of Alkyl and Substituted Alkyl Groups with Stereochemical Control: A Synthetic Application of Cyclopropylcarbinyl Radicals

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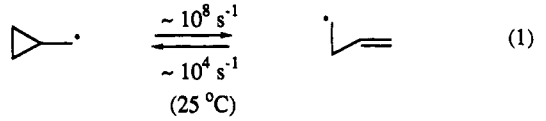
Cyclopropylcarbinols **2a** and **2b** (see Scheme I), which are accessible by a number of routes, can be converted into the corresponding radicals **3a** and **3b**, respectively. These radicals undergo peripheral ring-opening of the cyclopropyl substructure to afford substituted cycloalkenes **4a** and **4b**. The whole sequence represents a general method for attaching alkyl, and substituted alkyl, groups to an existing cyclic structure, and it can often be carried out with predictable stereo- and regiochemical control. Reaction conditions for the ring-opening depend on the substitution pattern of the cyclopropane: where the non-bridgehead carbon of the cyclopropane carries a strongly electron-withdrawing group, the ring-opening can be done at the reflux temperature of benzene. However, in the absence of such electron-withdrawing groups, a low temperature is best used in order to suppress ring expansion. Various methods that accommodate these requirements are available for generating the radicals.

We describe here details of a free radical method for attaching substituents to cyclic substructures.[1] The basic procedure, which is summarized in Scheme I, involves regioselective opening of cyclopropylcarbinyl radicals and allows placement of the substituent on either face of the starting material.[2,3]

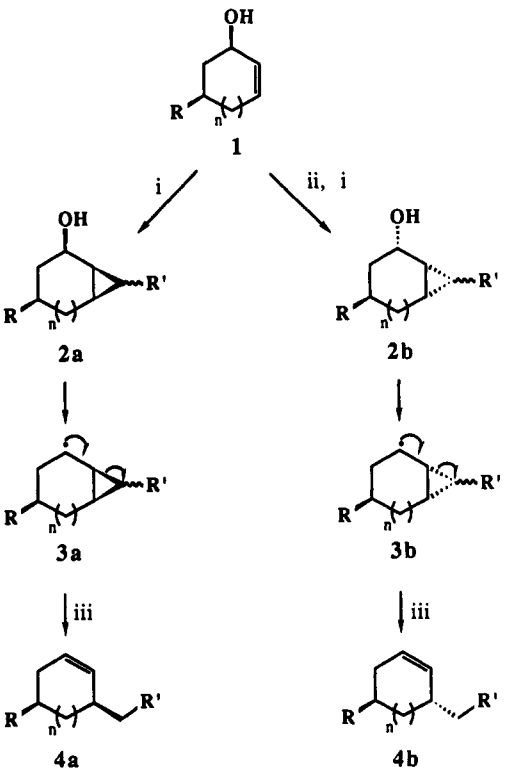
Although radical ring-closure is being investigated intensively[4] as a method for the construction of organic compounds, the synthetic applications of the reverse process—radical ring-opening—have received much less attention. In contrast, the physical organic chemistry of radical ring-opening is a well-studied area, particularly for carbocyclic systems. Most of the reported measurements[5] involve small rings, especially the cyclopropylcarbinyl system (eq 1), because opening of larger rings—at least in



(1)

the absence of substituents that stabilize the product radical—does not usually occur at an adequate rate.[5,6] The rate constants for the parent system of eq 1 are known over a range of temperatures[7,8a] and kinetic data are also availble for those cases in which substituents such as

Scheme I[a]



[a] (i) Cyclopropanation; (ii) Mitsunobu inversion; (iii) stannane. R' = H, alkyl group, or electron-withdrawing group.

(1) Preliminary communication: Clive, D. L. J.; Daigneault, S. *J. Chem. Soc., Chem. Commun.* **1989**, 332.
(2) Cf. Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 2361.
(3) Cf. Degueil-Castaing, M.; Rahm, A.; Dahan, N. *J. Org. Chem.* **1986**, *51*, 1672. Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745.
(4) Reviews: Curran, D. P. *Synthesis* **1988**, 417 and 489. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. Hart, D. J. *Science* **1984**, *223*, 883.
(5) E.g. *Landolt-Börnstein, Numerical Data and Functional Relationships in Science and Technology. New Series*; Fischer, H., Ed.; Springer-Verlag: Berlin, 1984; Vol. 13, subvol. a. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangement in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Chapter 4.
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