

δ 5.42 (1 H, s), 5.09 (1 H, s), 4.31 (1 H, s), 4.10 (1 H, s).

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Sulfur as a Regiochemical Control Element. Cycloadditions of 2-Alkoxy(acyloxy)-3-alkyl(aryl)thiobuta-1,3-dienes

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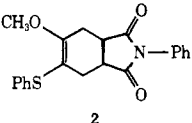
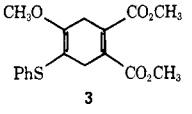
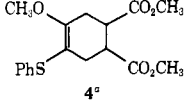
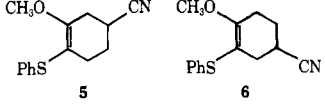
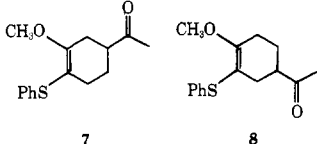
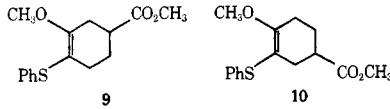
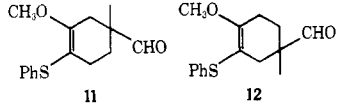
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Abstract: The cycloadditions of 2-methoxy-3-phenylthiobuta-1,3-diene, the 4'-chlorophenylthio and 2'-pyrimidylthio derivatives, and 2-acetoxy-3-phenylthiobuta-1,3-diene and its 4'-methoxyphenylthio derivative with unsymmetrical dienophiles are examined. The effect of silica gel, boron trifluoride etherate, and magnesium bromide on the regiochemistry is probed. In situ generation of the diene from the precursor cyclobutene and cycloaddition is a promising technique for sluggish dienophiles such as cyclohex-2-en-1-one. The use of a cisoid diene, 2,3-dimethylene-1,4-oxathiin, has also been examined. By variation of the substituents and use of thermal vs. Lewis acid catalysis, either sulfur or oxygen dominance of regiochemistry is possible. The former, combined with desulfurization, offers an approach to 1,3-substituted cyclohexanes via cycloaddition chemistry—a type of substitution not available in the normal Diels-Alder reaction. Thus, sulfur serves as a regiochemical control element. Rationalization of these results in terms of current concepts is presented. The frontier-orbital approach modified by consideration of charge-transfer (polar) interactions best accounts for the results. The site of complexation of the Lewis acids in these reactions also appears open to question.

The introduction of heteroatom-substituted dienes as cycloaddition partners has allowed the creation of cyclohexanes with functional groups in masked forms. For example, 2-methoxybuta-1,3-diene¹ is the equivalent of $-\text{CH}_2\text{C}(\text{O})-\text{CH}_2\text{CH}_2-$ and 1,1-dithiobuta-1,3-dienes² are the equivalent of $-\text{COCH}=\text{CHCH}_2-$. The synthesis of 1-methoxy-3-

trimethylsiloxybuta-1,3-diene³ has led to several creative applications in complex synthesis. In our program to expand the horizons of β -keto sulfides in synthesis, we sought cycloaddition routes to them.^{4,5} As outlined in the previous paper, this has led to synthesis of 2-alkoxy(acyloxy)-3-alkyl(aryl)thiobuta-1,3-dienes and the theoretical question regarding re-

Table I. Reactions of 2-Methoxy-3-phenylthiobuta-1,3-diene (**1**)

entry	dienophile	conditions	adducts	ratio	% yield
1	<i>N</i> -phenylmaleimide	PhCH ₃ , reflux			61
2	dimethyl acetylenedicarboxylate	PhCH ₃ , reflux			61
3	maleic anhydride	PhCH ₃ , reflux			48 ^a
4	acrylonitrile	neat, reflux		5:6, ~4:1	63
5	methyl vinyl ketone	(a) neat, reflux (b) neat, MgBr ₂ , 20 °C (c) on silica gel, 20 °C		7:8, ~4:1 7:8, ~1.5:1 7:8, ~3:2	75 91 42
6	methyl acrylate			9:10, ~4:1	65
7	methacrolein	neat, reflux		11:12, ~8:1	72

^a The initial adduct was subjected to methanolysis and then diazomethane before isolation.

giochemistry.^{6,7} In this paper, we want to report the use of such dienes in cycloaddition, the regioselectivity of such reactions, and the effect of Lewis acids on these reactions.

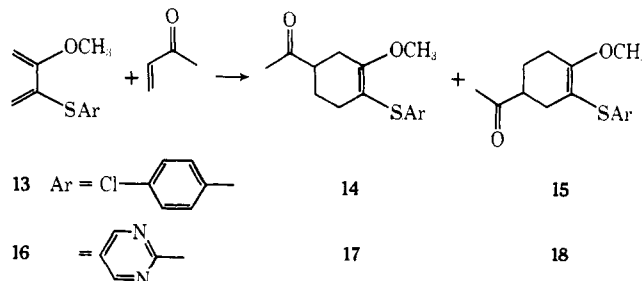
Cycloadditions

Reactions of 2-methoxy-3-phenylthio-1,3-butadiene (**1**) with dienophiles, either neat or in toluene solution at reflux, gave the desired adducts (see Table I). Generally, the regioselectivity of the cycloaddition could be determined by the expansion and integration of the methoxy region of the 270-MHz NMR spectrum. For example, for the cycloaddition with methyl vinyl ketone (MVK) (entry 5, Table I) the 270-MHz NMR spectrum of the cycloadducts revealed resonances at δ 3.64 and 3.62 in the ratio of ~4:1 for the methoxy protons of **7** and **8**, respectively. That the phenylthio substituent was the controlling element in the cycloaddition was confirmed by structural modification (vide infra).

The cycloaddition of **1** and MVK was subject to a marked acceleration by magnesium bromide. The adducts **7** and **8** were obtained in a 91% isolated yield at room temperature; however, their ratio decreased to 3:2. An intriguing way to catalyze the Diels-Alder reaction is to deposit the reactants onto a silica gel surface.⁸ Indeed, absorbing a mixture of diene **1** and MVK onto silica gel so that the silica gel remains as a free-flowing powder led to the cycloadducts **7** and **8** in a 3:2 ratio after standing at room temperature for 24 h. The realization of the increased importance of the oxygen substituent's role in determining regiochemistry in the Lewis acid catalyzed reaction

prompted us to investigate the effects of modifying the substituents.

The replacement of the phenylthio substituent with a 4-chlorophenylthio substituent should increase the inductive effect of the benzene ring and, therefore, decrease the electron density at sulfur and its ability to control the regiochemistry in both the thermal and catalytic reactions. Thus, thermal cycloaddition of 2-(4'-chlorophenylthio)-3-methoxybuta-1,3-diene (**13**) with MVK (neat, reflux, 2.5 h) gave adducts **14** and **15** in a ratio of 1.5:1 as determined by the integration



of the singlets at δ 3.65 and 3.60, which were assigned as the methoxyl protons of the major and minor isomers, respectively. The reaction was repeated with magnesium bromide catalysis at room temperature to give adducts **14** and **15** in a ratio of 1:1.5. The reaction of **13** with methacrolein gave two adducts in a 3:1 ratio with sulfur controlling, a decrease from the 8:1 ratio with diene **1**. Although the degree of the change was

Table II. Reactions of 2-Acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene

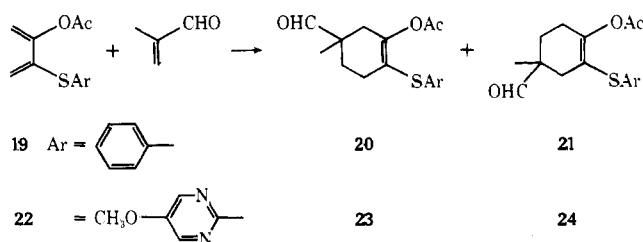
entry	R	EWG	conditions	yield, %	ratio A:B
1	CH ₃	CHO	(a) neat, reflux (b) BF ₃ , ^b ether, RT ^c (c) MgBr ₂ , ^b ether, RT ^c	84 94 55	13:1 >50:<1 >50:<1
2	CH ₃	CO ₂ CH ₃	(a) neat, reflux (b) BF ₃ , ^b ether, RT ^c	93 95	9:1 >50:<1
3	H	COCH ₃	neat, reflux	86	10:1
4	H	CN	neat, reflux	72	^a
5	H	CO ₂ CH ₃	neat, reflux	91	10:1

^a Not determined. ^b 5 mol % of catalyst was employed. ^c Room temperature.

small, the direction of the change indicated the increased importance of oxygen for control of the regioselectivity with diene **13** relative to diene **1**.

An attempt was made to significantly decrease the electron density at sulfur by replacing the phenylthio substituent of diene **1** with the 2-pyrimidylthio substituent. Thus, thermal reaction of 2-methoxy-3-(2'-pyrimidylthio)-1,3-butadiene (**16**) with MVK (neat, reflux, 4 h) gave adducts **17** and **18** in a ratio of 1:1.3 as determined by the integration of resonances at δ 3.66 and 3.63 (which together integrate for 3 H) in the 270-MHz NMR spectrum. When catalyzed with magnesium bromide at room temperature, the same cycloaddition gave **17** and **18** in a ratio of 1:8. In order to establish unambiguously that in the Lewis acid catalyzed reaction oxygen controls the regioselectivity, further chemical elaborations of the adducts were necessary (vide infra).

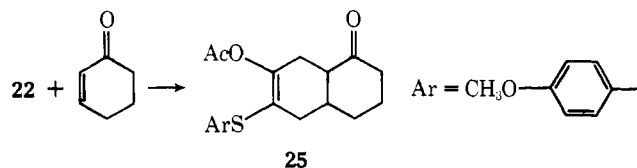
Having developed a diene in which oxygen controlled the regioselectivity to a synthetically useful degree, attention was directed toward modifying the diene to enhance the role of the sulfur substituent. Analogously it was reasoned that, if the substituent on oxygen was more electronegative than methyl, then oxygen's controlling influence would be reduced. Thus, thermal reaction of 2-acetoxy-3-phenylthio-1,3-butadiene (**19**) and methacrolein (neat, reflux, 18 h), gave adducts **20** and **21**



in a ratio of 9:1 as determined by integration of resonances at δ 9.46 and 9.38 in the 100-MHz NMR spectrum, which were assigned as the aldehyde protons of adducts **20** and **21**, respectively. The increase in regioselectivity satisfied prediction, i.e., an increase in the control of regioselectivity by sulfur. A further step was taken to increase the electron density at sulfur and thus its ability to control regioselectivity. The phenyl group was replaced by the 4-methoxyphenyl group realizing that the para electron-releasing substituent would serve such a role. Thermal reaction of 2-acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene (**22**) and methacrolein (neat, reflux, 17 h) gave adducts **23** and **24** in a ratio of 13:1 as determined by the integration of the resonances at δ 9.42 and 9.32 in the 100-MHz NMR spectrum, which were assigned as the aldehyde protons of **23** and **24**, respectively. The reactions of this diene with various dienophiles are summarized in Table II. The boron

trifluoride etherate catalyzed reaction of **22** with methacrolein gave **23** and **24** in a ratio of >50:1 in 94% isolated yield. In this case, the Lewis acid catalysis reinforced the controlling effect of sulfur.

A similar observation was made for the normally very poor dienophile cyclohex-2-enone. While thermal cycloaddition with preformed diene led only to decomposition of the diene (vide infra for an alternative approach), addition of 5 mol % of boron trifluoride etherate gave an 80–85% yield of a single re-



gioisomer, subsequently shown to be **25**, as a mixture of ring juncture isomers.

The *p*-methoxy group's effect on the rate of thermal reaction was approximated by reacting equimolar amounts of dienes **19** and **22** with methacrolein and examining the cycloadduct ratio at half reaction (neat, reflux, 6 h). The products of cycloaddition with diene **19**, adducts **20** and **21**, were successfully separated from the products of cycloaddition with diene **22**, adducts **23** and **24**, by preparative TLC. The ratio of (**20** + **21**)/(**23** + **24**), thus k_{19}/k_{22} , was determined to be 1.04 by isolation.

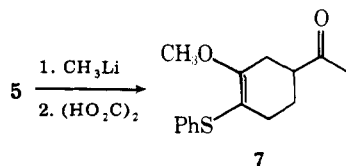
Structural Identification and Transformations of the Adducts

As already indicated, 270-MHz NMR spectroscopy played a major role in determining that the mixture of products was indeed only one isomer. To illustrate in one case, the mixture from diene **22** and methyl methacrylate revealed only resonances associated with the Diels–Alder products. Singlets at δ 1.25 and 1.18 together integrated for 3 H and were assigned as the methyl group α to the ester. Symmetrical doublet of triplet ($J = 15, 7$ Hz) patterns at δ 1.93 and 1.60 were assigned as the allylic methylene β to the acetate. The AB quartet ($J = 15.3$ Hz) at δ 2.74 and 2.22 was assigned as the allylic methylene β to the sulfide. Two singlets at δ 2.19 and 2.17 which together integrated for 3 H were assigned as the acetoxy protons for each regioisomer. The multiplet at δ 2.01–2.13 which integrated for 2 H was assigned as the nonallylic methylene group. Singlets at δ 3.65 and 3.61 and at δ 3.78 and 3.77, each set of which integrated for 3 H, were assigned as the methoxy and carbomethoxy protons, respectively. The doublets at δ 6.80 ($J = 8$ Hz) and at 7.26 ($J = 8$ Hz), each of which integrated for 2 H, were assigned as the aromatic protons. The spectrum was devoid of any extraneous resonances, indicating

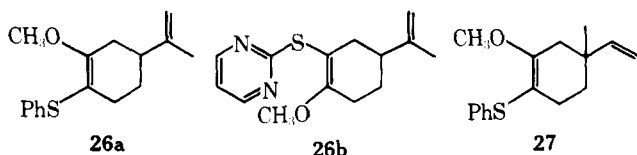
that the mixture was isomerically pure. The accuracy of the elemental analyses confirmed that the mixtures were purely isomeric. In addition, many of the adducts were subsequently chemically modified.

The adducts contain a masked β -keto sulfide and it was the utility of this functionality that we sought to exploit. Performing such transformations had a second goal—the identification of the positional isomers obtained in the initial cycloaddition. Our first work centered upon the adducts from 2-methoxy-3-phenylthiobuta-1,3-diene.

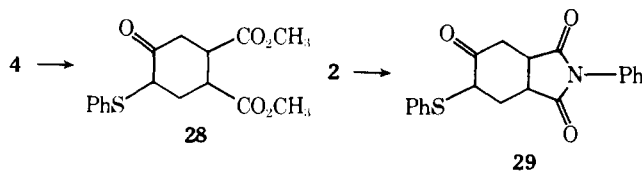
With the β -keto sulfide moiety in a protected form in these initial adducts, we selectively reacted the functional group which arose from the original dienophile. For example, adduct **5** (**5:6** ~4:1) was condensed with methyl lithium and then chemoselectively hydrolyzed to give **7** (**7:8** ~4:1), the same



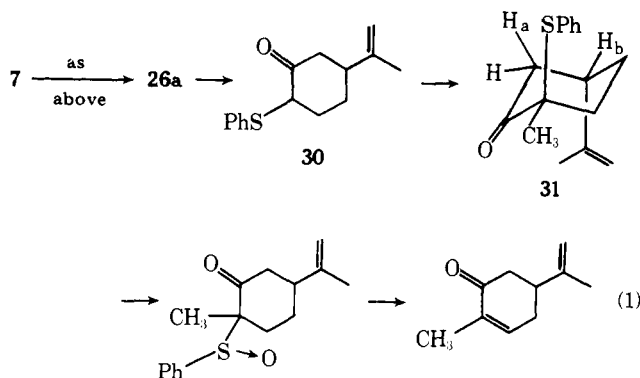
compound obtained from the cycloaddition of MVK. This reaction also indicated that the major regioisomer in the acrylonitrile case corresponded to the major regioisomer in the MVK case. Adducts **7**, **18**, and **11** were selectively methylated to **25a**, **26b**, and **27**, respectively, with triphenylphosphonium methyliide.



Unmasking the β -keto sulfide utilized 10% aqueous hydrochloric acid in THF at 20 °C (e.g., **4** \rightarrow **28**) or 50:1 acetonitrile–60% aqueous perchloric acid (**2** \rightarrow **29**), with the latter conditions generally preferred. With the availability of such

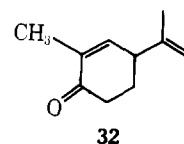


β -keto sulfides from the adducts, additional structural confirmation was sought in many cases. For example, **26a** was correlated with carvone as outlined in eq 1. Hydrolysis of **26**



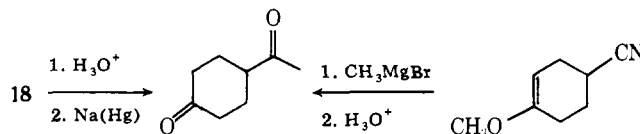
was best accomplished with aqueous perchloric acid to give the β -keto sulfide **30** in 42% overall yield from **7**. Methylation is directed by sulfur to give **31** (77% yield). Examination of the NMR spectrum of **31** revealed the regiochemistry. The axial H(6) was deshielded by an axial 2-phenylthio substituent and appeared at δ 3.30, dd, $J = 16, 5$ Hz.⁹ The presence of only geminal and a single vicinal coupling indicated the isopropenyl

substituent to be at C(5). The fact that $J_{a,b}$ is only 5 Hz suggested the stereochemistry depicted. We previously noted the preference for a phenylthio group at the 2 position of a cyclohexanone to be axial.⁹ After oxidation and sulfoxide thermal elimination, **31** gave carvone in 66% yield. VPC analysis revealed two peaks in the ratio of 1:10 in which the major component proved identical with authentic carvone. The minor component was assumed to be **32**, which would have arisen



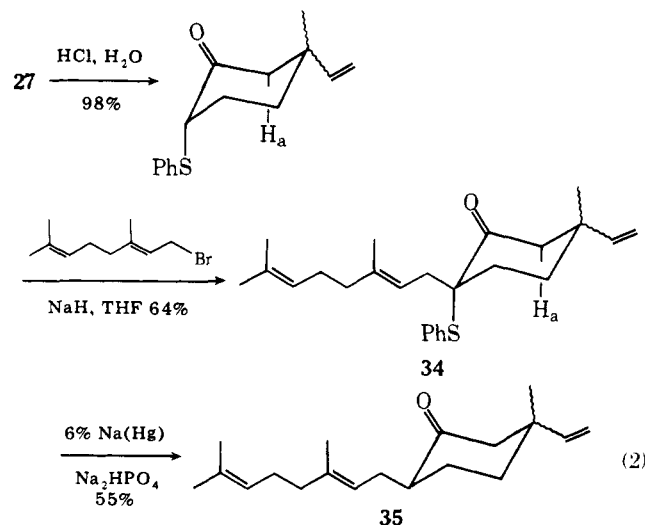
from the minor adduct of the original Diels–Alder reaction. The obtention of carvone from **7** not only illustrated the utility of the adducts, but also proved the regiochemistry of **7** as depicted. Since **5** was correlated to **7**, this sequence also proved the regiochemistry of **5**.

Once the sulfur substituent has served its role as a regiochemical control element, it can be reductively removed.¹¹ For example, the cycloadduct from **16** and MVK, formed under conditions of catalysis by magnesium bromide, was hydrolyzed with aqueous perchloric acid. The β -keto sulfide was subjected to 6% sodium amalgam in methanol at 0 °C to give 4-acetylcyclohexanone which was identical with an au-



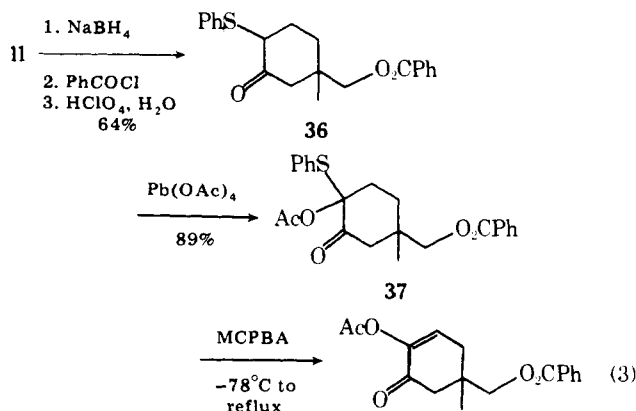
thentic sample prepared from the Diels–Alder adduct of 2-methoxybuta-1,3-diene and acrylonitrile. Thus, in the case of the catalyzed additions of **16**, oxygen, not sulfur, dominated the regiochemistry.

The ability to reductively remove the sulfur substituent led to combining the regioselective alkylation with reductive desulfurization as in eq 2. Both **33** and **34** were mixtures of two

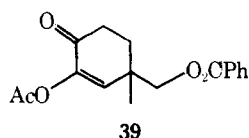


isomers in both of which the phenylthio group preferred to be axial. Thus, **33** and **34** each showed two axial protons at C(6) (**33**, δ 2.76 and 2.89; **34**, δ 3.28 and 3.40) with only geminal coupling—a fact which indicated that C(5) was a quaternary carbon. In the product from the alternative Diels–Alder regioisomer, this proton would have showed further coupling to a methylene group. This proved that the regiochemistry of cycloaddition of α -methacrolein with diene **1** was controlled by sulfur.

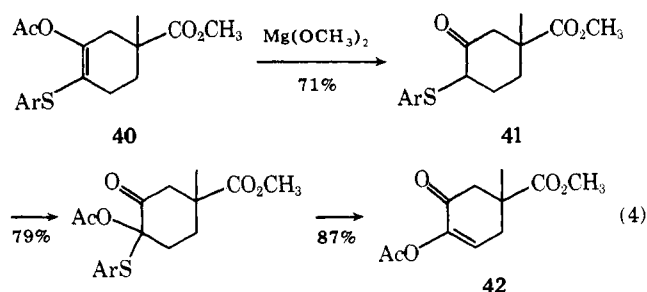
An alternative sequence confirmed this conclusion and illustrated a synthesis of diosphenols. Thus, **11** was reduced,



benzoylated, and then hydrolyzed to give **36** (eq 3). Acetoxylation with lead tetraacetate¹² gave **37**, which is a protected form of an α -diketone in which the α -diketone can be liberated under mild base conditions.¹³ On the other hand, a regiocontrolled diosphenol synthesis was also in hand by taking advantage of the sulfoxide pyrolysis.⁹ Thus, subjection of **37** to MCPBA in methylene chloride, initially at low temperature and eventually raising the temperature to reflux, gave **38**—a specifically enolized α -diketone in the form of its monoacetate. The low temperature ($\sim 40^\circ\text{C}$) required for this sulfoxide pyrolysis was presumably a reflection of the combined activating effect of the keto and acetoxy groups. In **38**, the vinyl proton appeared at δ 6.18 as a triplet, $J = 5$ Hz, indicative of an adjacent methylene group. From **12**, **39** would have been obtained which would have shown a singlet for this proton.

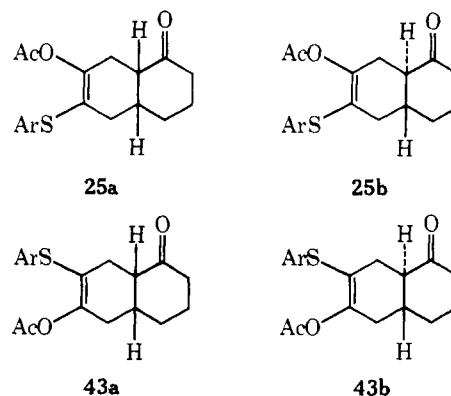


A similar sequence was used to verify the regiochemistry of the major adduct **40** from methyl methacrylate and diene **22**. In contrast to the adducts with diene **1**, adducts using diene **22** can be hydrolyzed under basic conditions as well as acidic conditions. Thus, keto sulfide **41** was smoothly produced when **40** was subjected to magnesium methoxide in methanol at room temperature (see eq 4). The remaining steps were identical

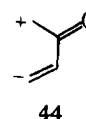


with those used in eq 3 to give diosphenol acetate **42**, which showed a vinyl proton at δ 6.49 as a triplet, $J = 4$ Hz. Thus, for diene **22** sulfur again dominated the regioselectivity but to a greater extent than with diene **1**.

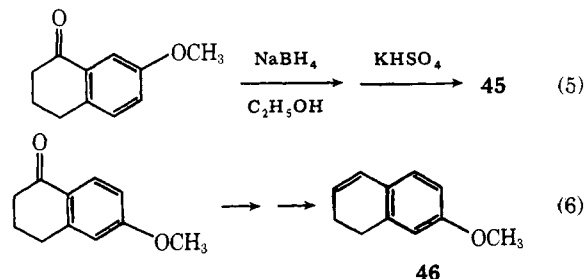
The obtention of a mixture of adducts from cyclohexenone and diene **22** in the presence of a Lewis acid catalyst led us to consider four isomeric structures (**25a**, **25b**, **43a**, and **43b**). The two adducts were separable by TLC. Subjection of each one to 5 mol % boron trifluoride etherate in methylene chloride led to an identical 60:40 mixture—indicating that the adducts were *E/Z* mixtures at the ring juncture and not regioisomeric substances, i.e., **25a** + **25b** or **43a** + **43b**. The fact that the epimerization conditions were the same as those for the cycloaddition suggested that the kinetic *Z* product isomerized under the conditions of cycloaddition.¹⁴



To differentiate **25** from **43**, the sequence outlined in Scheme I was performed. The sequence illustrates the ability to selectively manipulate the functionality and the use of the diene as an equivalent of **44**. The obtention of a single dihy-



dronaphthalene **45** from the mixture of isomeric adducts further confirms their stereoisomeric rather than regioisomeric nature. However, we could not a priori distinguish **45** from dihydronaphthalene **46**. To determine the regiochemistry, authentic samples of **45** and **46** were prepared as shown in eq 5 and 6.¹⁵ NMR spectroscopy allowed differentiation between

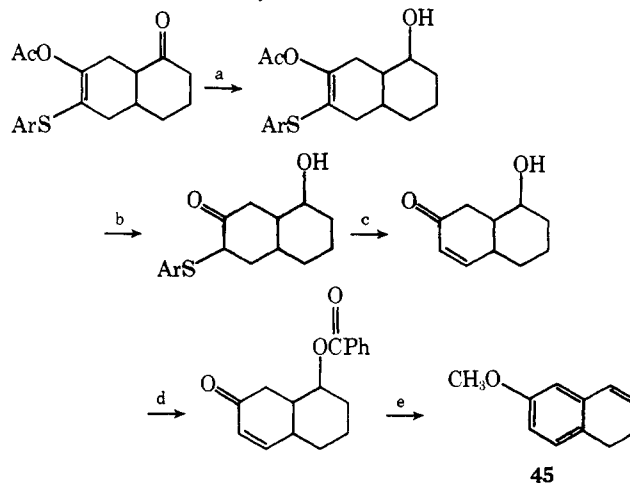


45 and **46** and thus confirmed the assignment of regiochemistry as represented in **25**.

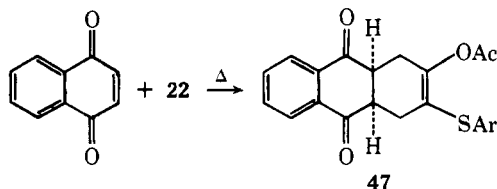
Adducts with Naphthoquinones

To probe the usefulness of diene **22** in the synthesis of anthracycline antitumor agents and tetracycline antibiotics,

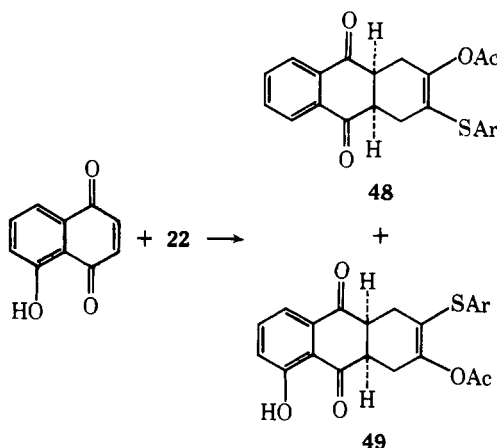
Scheme I. Correlation of Cyclohexenone Adducts



cycloadditions with 1,4-naphthaquinone and juglone were investigated.¹⁶ Thermal reaction (neat, 80 °C) with 1,4-naphthaquinone gave a 65% yield of crystalline adduct **47**.

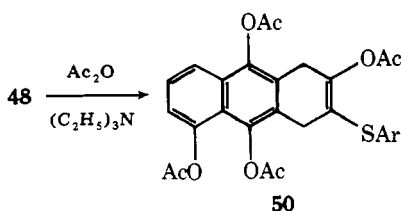


Thermal reaction with juglone (benzene, reflux) gave adducts **48** and **49** in 72% yield. Crystallization of **48** and **49** from methanol gave a 1:1 mixture of adducts as determined by the integration of resonances at δ 3.94 and 3.96 in the 270-MHz NMR spectrum, which were assigned as the methoxy protons for **48** and **49**. However, comparison of the NMR spectrum

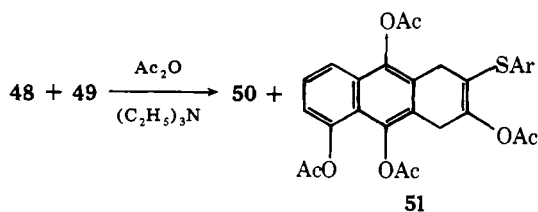


of the crystallized product with the NMR spectrum obtained from the crude reaction mixture indicated that originally one of the regioisomers was favored by approximately a 2:1 ratio with crystallization occurring selectively as a 1:1 mixture of each regioisomer.

The boron trifluoride etherate catalyzed reaction of **22** and juglone in methylene chloride at -20 °C gave a 61% yield of a single regioisomer. Initially the reaction mixture was clear and orange, although after several minutes the color turned greenish-brown. Treatment of this regioisomer with acetic anhydride and triethylamine at room temperature gave an 84% yield of crystalline tetraacetate **50**. Similar treatment of the



1:1 crystalline mixture (from the thermal reaction) gave a crystalline mixture of two tetraacetates **50** and **51**.

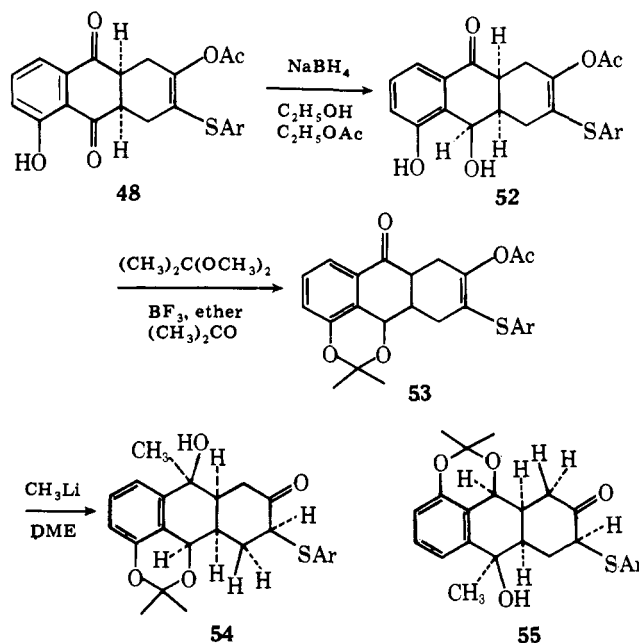


The 270-MHz NMR spectrum of the mixture of tetraacetates **50** and **51** contained eight distinct singlets (δ 2.14, 2.23, 2.27, 2.28, 2.31, 2.37, 2.42, and 2.48) which were all of equal intensity and which were assigned as the eight possible acetates. By comparison with the spectrum of pure tetraacetate **50**,

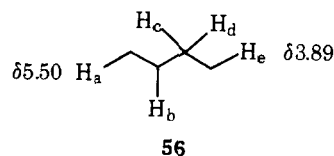
which had four distinct singlets (δ 2.14, 2.28, 2.31, and 2.48), it was possible to determine which resonances of the mixture belonged to the regioisomer lost in the Lewis acid catalyzed reaction, i.e., **51**.

The crude reaction mixture from the thermal reaction, containing unequal amounts of **48** and **49**, was also treated with acetic anhydride and triethylamine to determine the ratio of the adducts and to establish if the major or minor regioisomer was enhanced by Lewis acid catalysis. Comparison of spectra revealed an unexpected result: *the minor regioisomer of the thermal reaction was the exclusive regioisomer formed in the catalytic reaction*. This result demands one of two possibilities: either sulfur dominated the regioselectivity in the thermal reaction and oxygen completely dominated in the catalytic reaction or vice versa. In all the previous reactions, we established that, with diene **22**, sulfur dominated in the thermal reaction and completely dominated in the catalytic reaction. Either of the possibilities presented an unusual departure from the normal reactivity of **22**.

The single regioisomer from the catalytic reaction was chemically modified to establish its regiochemistry. Selective reduction with sodium borohydride in ethanol and ethyl acetate at 0 °C gave **52**, which was directly treated with 2,2-dimethoxypropane, boron trifluoride etherate, and acetone to give acetonide **53**. Treatment of this acetonide with methyl lithium in dimethoxyethane at -78 °C gave β -keto sulfide **54**.



Decoupling experiments on the 270-MHz NMR instrument were conducted to differentiate between the two possible structures of the β -keto sulfide, **54** and **55**. Two resonances could be assigned unambiguously. The doublet ($J = 3.9$ Hz) at δ 5.50 was assigned as the benzylic proton on carbon bearing oxygen and the doublet of doublets ($J = 12.75, 6.0$ Hz) at δ 3.89 was assigned as the proton on carbon bearing sulfur. The structure would be determined if these resonances could be related. The spin decoupling experiments in Chart I established this relationship. Thus, as in partial structure **56**, H_a is coupled



to H_b , H_b is coupled to H_a , H_c , and H_d , and H_e is also coupled to H_c and H_d ; therefore, the spin system illustrated below is

Chart I. Spin Decoupling Experiments for **54**^a

signal	δ 5.50	δ 3.89	irradiation at δ 3.17	δ 2.57	δ 1.53
δ 5.50 (H_a) ^b					
d		c	s	c	c
$J = 3.9$ Hz					
δ 3.89 (H_e) ^b					
d,d	c		c	d	d
$J = 12.75, 6.0$ Hz				12.75	6.0
δ 3.35					
d,d,d	c	c	d,d	c	c
$J = 6.85, 3.9, 1.65$ Hz			6.85, 1.65		
δ 3.17 (H_b) ^b					
d,q	d,t	c		d,t	q
$J = 12.75, 3.9$ Hz	12.75, 3.9			12.75, 3.9	3.9
δ 2.57 (H_c) ^b					
d,d,d	c	d,d	d,d		d,d
$J = 12.75, 6.0, 3.9$ Hz		12.75, 3.9	12.75, 6.0		6.0, 3.9
δ 1.53 (H_d) ^b					
q	c	t	t	t	
$J = 12.75$ Hz		12.75	12.75	12.75	

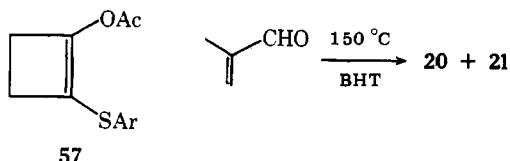
^a Performed at 270 MHz. ^b See partial structure **56**. ^c No effect.

a necessary feature of the β -keto sulfide. Only in β -keto sulfide **54** does such a system occur.

The remaining coupling constants were determined by irradiation of the signal at δ 3.35 (now assigned as the bridgehead adjacent to carbon bearing hydroxy and methyl), which simplified the doublet of doublets ($J = 14.25, 6.85$ Hz) at δ 2.68 into a doublet ($J = 14.25$ Hz) and the doublet of doublets ($J = 14.25, 1.65$ Hz) at δ 3.70 into a doublet ($J = 14.25$ Hz). Thus, the couplings to the resonance at δ 3.35 were identified and the methylene α to the carbonyl group was located. Confirmation of these assignments was obtained by irradiating at δ 2.68 and 3.70 (now assigned as the methylene group α to the carbonyl group), which in turn showed collapse of their 14.25-Hz geminal coupling and the absence of the appropriate coupling to the bridgehead proton at δ 3.35. Fortunately, the resonances were sufficiently separated and well enough defined to allow complete and unambiguous assignment of structure **54**. Therefore, in the thermal reaction of diene **22** and juglone, sulfur dominates the regioselectivity by an approximately 2:1 ratio. However, in the boron trifluoride etherate catalyzed reaction, oxygen completely dominates the regioselectivity.

Cycloadditions via in Situ Generation of Diene

In all of the reactions described above, the appropriate diene was obtained by the thermolysis of the corresponding cyclobutene prior to cycloaddition. Preformation of the diene allowed the temperature of the Diels-Alder reaction to be kept at a minimum and permitted Lewis acid catalysis of the cycloaddition. However, thermolysis of the cyclobutene in the presence of the dienophile would allow the diene to undergo cycloaddition as it was formed. Loss of diene due to decomposition could be avoided as well as reducing the required manipulation of reactants and products. Thus, a solution of 1-acetoxy-2-(4'-methoxyphenylthio)cyclobutene (**57**), 2,6-



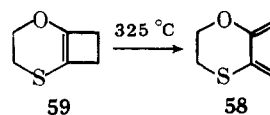
di-*tert*-butyl-4-methylphenol, and methacrolein was sealed under reduced pressure in a glass tube. Thermolysis at 150 °C gave adducts **20** and **21** in a 99% yield and in a ratio of 8:1, respectively. Although the regioselectivity of the cycloaddition decreased slightly as a result of the increased temperature of reaction (ratio of 20:21 was 13:1 when the temperature of

cycloaddition was 80–85 °C), this experimental method offered versatility to the diene.

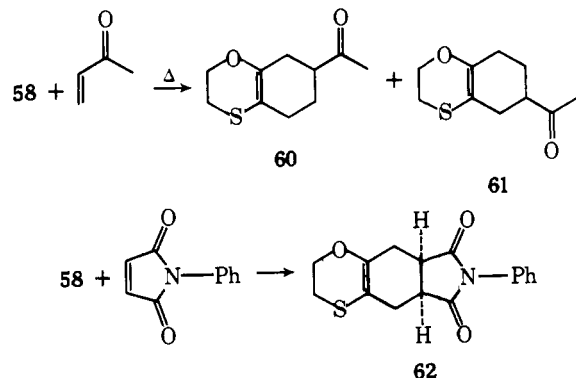
Difficult cycloadditions that required elevated temperatures and which normally led to diene decomposition were reasoned possible because the slow production of the diene in a large excess of dienophile increased the probability of cycloaddition at the expense of the decomposition of the diene. The thermal reaction of diene **22** and 2-cyclohexen-1-one, a notoriously poor dienophile,¹⁷ did not occur at 85 °C and led only to diene decomposition if heated above 100 °C. However, reaction of **57** and 2-cyclohexen-1-one in a sealed glass tube that had been deactivated with *O,N*-bis(trimethylsilyl)acetamide gave two sets of cycloadducts in 65% yield. The 270-MHz NMR spectrum of the less polar set of adducts (72% of the mixture) contained resonances identical with those of *cis*-7-acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -octalone (**25a**) and similar resonances which were assigned to the alternative regioisomer, *cis*-6-acetoxy-7-(4'-methoxyphenylthio)- Δ^6 -1-octalone (**43a**), in a ratio estimated to be 3:1 based on comparison of resonances at δ 1.81 and 1.87 assigned as the acetate protons of each adduct, respectively. The 270-MHz NMR spectrum of the more polar set of adducts (28% of the mixture) contained resonances identical with those of *trans*-7-acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone (**25b**) and similar resonances which were assigned to the alternative regioisomer, *trans*-6-acetoxy-7-(4'-methoxyphenylthio)- Δ^6 -1-octalone (**43b**), in a ratio estimated to be 1.5:1 as determined by comparison of peak heights or resonances at δ 1.82 and 1.83 which were assigned as the acetate protons of each adduct. Assuming that the ratios estimated from the peak heights are correct, the regioselectivity for the cycloaddition would be $\sim 2.5:1$ with sulfur controlling. Although under the reaction conditions epimerization occurred and the regioselectivity observed was not overwhelming, the fact that 2-cyclohexen-1-one underwent thermal cycloaddition at all is important in itself and illustrates the usefulness of the experimental method.

Cycloadditions with 2,3-Bis(methylene)-1,4-oxathiane

The observation that dienes held rigidly in the cisoid conformation have increased reactivities¹⁸ led us to investigate the possibility of developing a diene in which the oxygen and sulfur substituents at C-2 and C-3 were fused in a ring as in **58**. In the

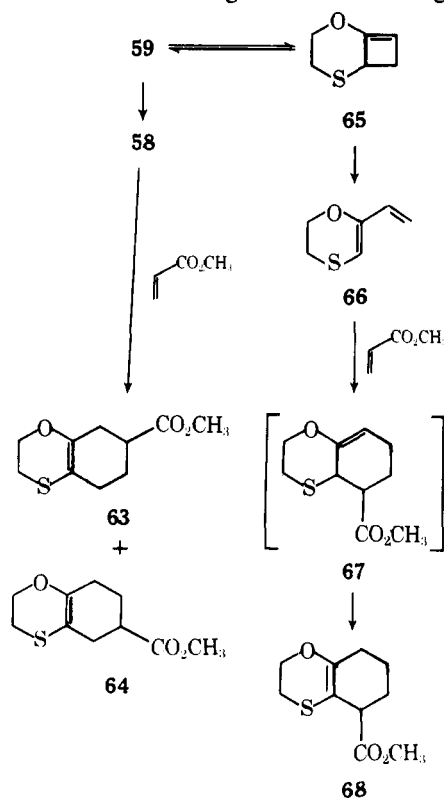


initial experiments with diene **58**, it was prepared from the appropriate cyclobutene **59** prior to the Diels–Alder reaction. The thermolysis of **59** was attempted using a vertical hot column and by distillation through a horizontal hot tube. In either experimental procedure, the diene could not be obtained without substantial decomposition or without recovering a large portion of cyclobutene **59** when performed at lower reaction temperatures. Nonetheless, Diels–Alder reactions were carried out with diene of the quality obtained when the thermolysis was run to complete consumption of starting material. Thermal reaction of **58** and methyl vinyl ketone gave a 40% yield of adducts **60** and **61** in approximately a 1:1 ratio as de-



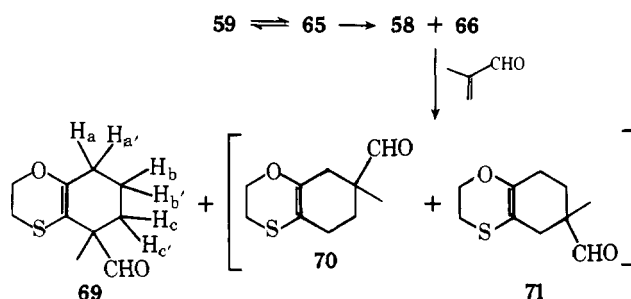
termined by the peak heights of the resonances at δ 2.09 and 2.11 of the 100-MHz NMR spectrum assigned as the methyl ketone protons of each regioisomer. Cycloaddition with *N*-phenylmaleimide was complete in 1 h at room temperature and gave adduct **62** in a 55% yield.

The problems of diene decomposition and/or polymerization are a manifestation of the enhanced reactivity of diene **58**. Experiments were conducted in which the diene was produced slowly in the presence of excess dienophile as described earlier. Thus, cyclobutene **59**, methyl acrylate, and 2,6-di-*tert*-butyl-4-methylphenol were sealed under reduced pressure in a glass tube and then heated to 160 °C. The reaction gave two separable bands by preparative TLC: an inseparable mixture of adducts **63** and **64** and a single adduct **68** arising from cy-



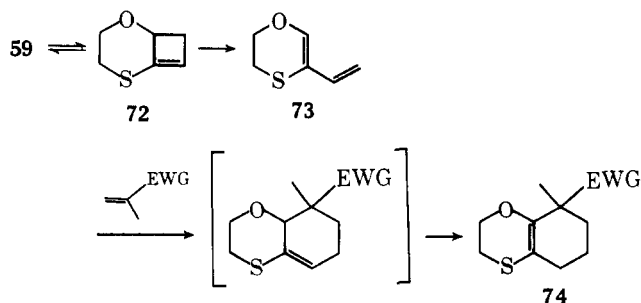
cloaddition of methyl acrylate with diene **66**. The structure of this adduct rests on analogy to the subsequent cycloadditions. Formation of this diene involved an initial isomerization of cyclobutene **59** to cyclobutene **65** probably involving a protonation–deprotonation sequence. Thermolysis of cyclobutene **65** gave diene **66**, which underwent cycloaddition with methyl acrylate to originally give cycloadduct **67** which isomerized under the reaction conditions to the thermodynamically more stable adduct **68**. Attempted reactions with 1-methoxy-2-phenylthio-1,3-butadiene (**19**) generated in situ gave products attributable to the same type of isomerization prior to the cyclobutene opening.

Methacrolein was reacted with cyclobutene **59** using the same technique and gave one adduct, **69**. Adducts **70** and **71**,

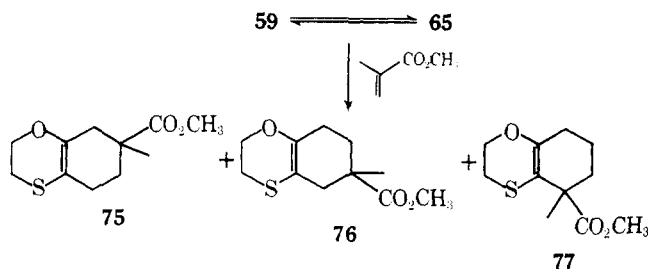


also expected under these conditions, could not be separated from polymerized methacrolein and, therefore, were not characterized. Detailed 270-MHz decoupling experiments established that adduct **69** had three contiguous methylene groups. Irradiation of the triplet ($J = 6.5$ Hz) at δ 1.97 simplified only the multiplet at δ 1.21–1.41. Irradiation of the doublet of doublets of doublets ($J = 13.0, 7.9, 3.7$ Hz) at δ 1.575 resulted in simplification of the multiplet at δ 1.21–1.41 as well as removal of the largest coupling constant in the doublet of doublets of doublets ($J = 13.0, 9.3, 3.3$ Hz) at δ 1.045. Irradiation at δ 1.045 revealed coupling to the multiplet at δ 1.21–1.41 and confirmed the 13.0-Hz coupling constant with the resonance at δ 1.575. Finally, irradiation of the multiplet at δ 1.21–1.41 collapsed the triplet at δ 1.97 to a singlet, as well as collapsing the doublets of doublets of doublets at δ 1.575 and 1.045 to an AB quartet ($J = 13.0$ Hz). The only plausible explanation of these decoupling experiments was to have three contiguous methylene groups with each terminal methylene bonded to a quaternary center. Such a structural feature was only common with compounds **69** or **74** (EWG = CHO).

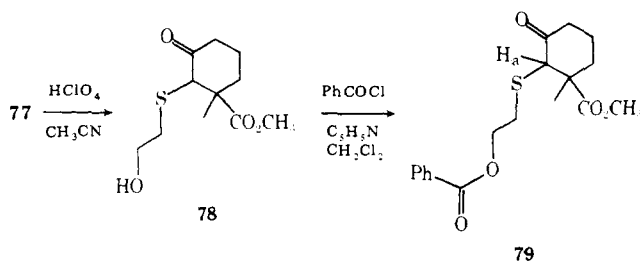
Although the relative position of the methyl and formyl substituents on the cyclohexene ring was established, the orientation of oxygen and sulfur remained uncertain. It was possible that the initial isomerization had occurred in the alternative sense to cyclobutene **72**, followed by thermolysis to diene **73**, cycloaddition, and rearrangement to adduct **74**, a structure which would also be consistent with the decoupling experiments.



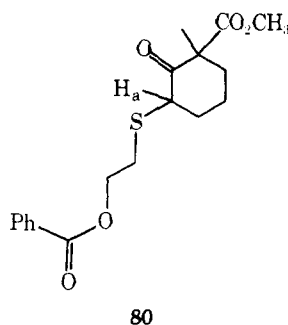
To explore this question further, methyl methacrylate and cyclobutene **59** were reacted in a sealed tube. The adducts **75** and **76**, which were realized in a 57% yield, were separable from adduct **77**, which was obtained in a 35% yield. Adduct



77 was hydrolyzed with perchloric acid in acetonitrile at 0 °C to give β -keto sulfide **78** which, in turn, was benzoyleated to give **79**. The 270-MHz NMR spectrum of **79** contained resonances

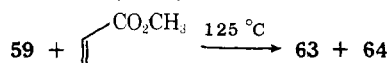


at δ 3.41 and 3.81 which together integrated for one hydrogen and which were assigned as the α hydrogens (H_a) on carbon bearing sulfur for each diastereomer. That these resonances were singlets broadened only by long-range couplings established that the cycloaddition occurred with diene **65** and not diene **72**. Treatment of cycloadduct **74** (EWG = CO_2CH_3) as described would have produced compound **80**. The reso-



nance attributable to the α hydrogen on carbon bearing sulfur would have appeared as a triplet or doublet of doublets and clearly not as a broadened singlet. Having established that the structure of the abnormal adduct from methyl methacrylate was **77**, we assigned the same type of substitution to the abnormal adducts **68** and **69** from methyl acrylate and methacrolein, respectively. The regiochemistry of cycloaddition with **66** agrees with that determined by Cohen for 1-phenylthio-2-alkoxy-1,3-butadienes.

The possibility that the isomerization of cyclobutene **59** to cyclobutene **65** was catalyzed by active sites on the surface of the glass tube prompted us to pretreat the tube with *O,N*-bis-(trimethylsilyl)acetamide and triethylamine (1:1 v:v) prior to introducing the reactants. Deactivation in this manner coupled with lowering the temperature of reaction to 125 °C gave only adducts **63** and **64** (~1:1) in a 79% yield when cyclobutene **59** was reacted with methyl acrylate.



Alternatively, addition of the appropriate acid catalyst might enhance isomerization to cyclobutene **65** and ultimately give only products that arise from cycloaddition with diene **66**. Unfortunately, the conditions that would completely change the substitution of sulfur and oxygen in the diene from 2,3 to 1,2 were not determined. Nonetheless, the simultaneous sealed tube thermolysis and Diels-Alder cycloaddition experimental

method solved the problem of diene decomposition and thereby improved the yields of cycloaddition. The method also introduced the possibility that a single cyclobutene (e.g., **59**) could produce two different dienes (e.g., **58** and **66**) dependent on reaction conditions.

MINDO/3 Calculations

In an attempt to illustrate the effect of substitution on the frontier orbital coefficients of butadiene, the orbital energies and wave functions of several C-2 monosubstituted and C-2, C-3 disubstituted dienes were calculated within the framework of MINDO/3.²⁰ Calculations were made employing the MINDO/3 computer program available from the Quantum Chemistry Program Exchange (No. 279) which was adapted²¹ for use with the Harris/7 computing system of the University of Wisconsin—Madison Chemistry Department.

The geometry of the dienes was defined in the cisoid conformation and planar. The bond lengths, bond angles, and dihedral angles were optimized for butadiene; then these values were used in subsequent calculations without further optimization. In the substituted diene calculated published values²⁰ for bond lengths and bond angles were used without optimization. Only the dihedral angle of the substituent relative to the plane of the diene was optimized. The HOMO and LUMO orbital coefficients obtained by this treatment are listed in Table III. The energies of the HOMO and LUMO orbitals as well as the ionization potential, heat of formation, and dipole moment calculated for each diene are listed in Table IV.

Discussion

A discussion of the effect of substitution on the regioselectivity of the Diels-Alder cycloadditions reported here must rationalize the following: (1) cycloadditions with methoxy-substituted dienes are in general controlled thermally by sulfur, but upon Lewis acid catalysis show increased control by oxygen (see entries 1, 2, and 3 in Table V); (2) cycloadditions with acetoxy-substituted dienes are in general controlled thermally by sulfur with enhancement of sulfur control upon Lewis acid catalysis (see entries 4 and 5 in Table V); (3) cycloadditions of 2-acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene and juglone stand alone in that the thermal reaction is controlled by sulfur while the catalytic reaction is exclusively controlled by oxygen (see entry 6 in Table V).

The most successful rationalization of Diels-Alder reactions employs a frontier molecular orbital approach (FMO).²² Extension of these concepts also covered the Lewis acid catalyzed reaction.²³ At first glance, the thermal reactions appear to be in accord with this general concept. Calculations indicate that the coefficient for C(1) is higher than for C(4) in the HOMO of most of the dienes under consideration here. Thus, FMO theory predicts that sulfur is a more effective regiochemical control element than oxygen in concerted cycloadditions.²⁴ However, several observations lead to concern as to whether such a simple explanation really pertains. For example, qualitatively FMO theory predicts that going from OCH_3 to OAc should lead to increased control by oxygen. Experimentally, control by sulfur increases from ~4:1 to ~10:1. The FMO approach predicts that diene **16** exhibit about as high a regioselectivity, with control by sulfur, as diene **1** or **19**. Experimentally, oxygen controls the regioselectivity (O:S ~1.3:1.0).

The effect of Lewis acids is even more confusing in the context of the FMO approach. For all dienes, enhanced regioselectivity with control by sulfur should be expected upon the addition of a Lewis acid. Experimentally, quite varied results are obtained. With diene **1** and **16** addition of a Lewis acid enhances control by oxygen, whereas with diene **22** addition of a Lewis acid enhances control by sulfur. The case of juglone

Table III. Coefficients of the Dienes Calculated by MINDO/3



		HOMO				LUMO			
R	R'	C-1	C-2	C-3	C-4	C-1	C-2	C-3	C-4
H	H	0.563	0.427	-0.427	-0.563	-0.561	0.429	0.429	-0.561
OCH ₃	H	0.649	0.415	-0.276	-0.408	-0.438	0.326	0.304	-0.410
SCH ₃	H	0.530	0.381	-0.263	-0.373	-0.451	0.350	0.334	-0.446
OAc	H	0.641	0.395	-0.235	-0.355	-0.451	0.360	0.343	-0.466
OAc·H ⁺	H	0.610	0.407	-0.415	-0.484	-0.287	0.217	0.137	-0.237
SPh	H	0.532	0.330	-0.112	-0.197	-0.522	0.418	0.451	-0.580
SH	OH	0.522	0.320	-0.254	-0.472	-0.590	0.479	0.396	-0.466
SPh	OCH ₃	0.512	0.306	-0.149	-0.292	-0.453	0.359	0.385	-0.487
SPh	OAc	0.490	0.294	-0.152	-0.311	-0.436	0.335	0.387	-0.478
SPh	OAc·H ⁺	0.464	0.313	-0.075	-0.194	-0.172	0.101	0.201	-0.269
	OCH ₃	0.520	0.321	-0.181	-0.338	-0.472	0.374	0.385	-0.491

Table IV. Orbital Energies, Ionization Potentials, and Dipole Moments of the Dienes Calculated by MINDO/3

R	R'	HOMO, eV	LUMO, eV	IP, eV	heat of form.	dipole moment
H	H	-9.13	1.13	9.13	32.5137	0.02
OCH ₃	H	-8.76	1.02	8.76	42.4711	1.64
SCH ₃	H	-8.92	1.03	8.76	74.3370	3.17
OAc	H	-9.02	0.64	9.02	-1.5976	4.77
OAc·H ⁺	H	-13.16	-3.26	13.16	153.0797	9.04
SPh	H	-8.43	1.03	8.41	58.8467	2.10
SH	OH	-8.62	1.00	8.62	-30.0648	2.86
SPh	OCH ₃	-8.40	0.91	8.28	17.2661	2.78
SPh	OAc	-8.62	0.61	8.48	-23.0121	6.20
SPh	OAc·H ⁺	-11.83	-3.04	11.37	130.0027	7.77
	OCH ₃	-8.63	0.77	7.91	15.9555	3.06

and diene **22** is an exception since here addition of a Lewis acid totally reverses the selectivity (see Table V).

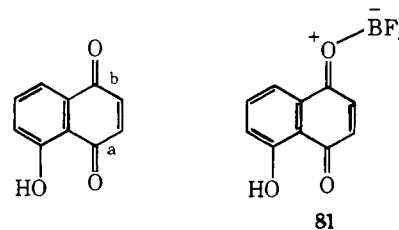
The results with Lewis acids may deviate from the FMO predictions because our general notion that complexation of the Lewis acid occurs with the dienophile is incorrect. Normally, in Lewis acid catalyzed reactions, the catalyst complexes only with the dienophile because the dienes employed are usually not functionalized. In the case of highly functionalized dienes, it is reasonable to anticipate that a competition for the Lewis acid between the diene and dienophile could exist. Consider the cycloaddition reactions of the acetoxy-substituted diene **22**. The Lewis acid can coordinate with the diene in addition to or in lieu of the dienophile. If under such circumstances it should coordinate to the acetoxy group, the result would be to diminish the contributing effect of oxygen. Reduction of the interaction of oxygen with the diene should enhance the observed regiochemical control exercised by sulfur. With dienophiles that are not as effective at coordinating with Lewis acids as juglone, e.g., α -methacrolein, the above effect can lead to an enhancement of the sulfur directing ability.

Application of the above arguments also rationalizes the experimental fact that in the catalyzed reaction of 2-methoxy-3-(2'-pyrimidylthio)-1,3-butadiene (**16**) the role of oxygen in determining regioselectivity increases relative to the uncatalyzed reaction. The nitrogens of the pyrimidine ring are Lewis bases which could effectively compete for the Lewis acid. If complexation does occur at the pyrimidine ring, the effect would be to decrease the electron density at sulfur available to interact with the diene. Thus, the effectiveness of oxygen in controlling regioselectivity should increase (see Table V).

Table V. Effect of Electronegativity on Regioselectivity

entry	diene	dienophile	S:O control (Δ)	S:O control (cat.)
1	1	methyl vinyl ketone	~4:1.0	1.5:1.0
2	13	methyl vinyl ketone	1.5:1.0	1.0:1.5
3	16	methyl vinyl ketone	1.0:1.3	1.0:8.0
4	19	methacrolein	10.0:1.0	
5	22	methacrolein	13.0:1.0	>50:1.0
6	22	juglone	3.0:1.0	1.0:>50

While such a modification can account for the Lewis acid catalyzed reactions not following the FMO predictions, it still cannot account for the case of juglone. Furthermore, the difference of juglone from all other dienophiles cannot be rationalized by using the usual idea for complexation of the Lewis acid as modified by Valenta²⁶ where it would be argued that, owing to steric hindrance, complexation occurs at the less hindered carbonyl group as in **81** leading to control of reg-

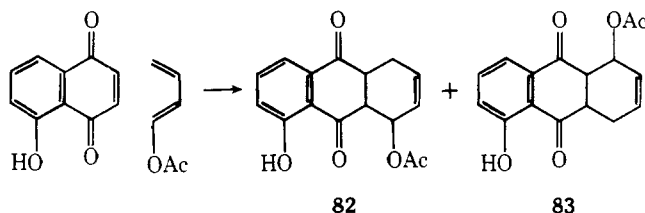


ioselectivity by carbonyl group "b" in the presence of Lewis acids but by carbonyl group "a" in the absence of such cata-

Table VI. Effect of Electronegativity on the Ionization Potential and the Dipole Moment of the Dienes

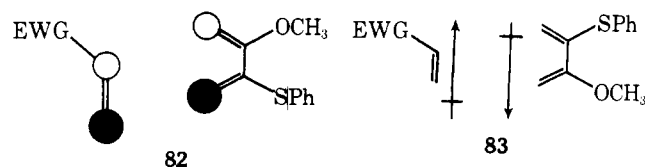
entry	diene	IP, eV	dipole moment, D
1	1	8.28	2.78
2	16	7.91	3.06
3	22	8.48	6.20

lysts. If such an explanation were correct, then the reaction of juglone and 1-acetoxybuta-1,3-diene should lead to a ratio of **82:83** > 1 in the thermal reaction but < 1 in the catalyzed re-



action. Experimentally, the ratio of **82:83** increases from ~3:1²⁷ to >50:1²⁸ upon the addition of a Lewis acid. Thus, such catalysts enhance the regiochemical control exerted by carbonyl group "a" of juglone. While the case of juglone must still be rationalized, the experimental results suggest that our general acceptance of complexation only with the dienophile may be in error.

A qualitative rationalization of the observed regioselectivity, as outlined in more detail in the preceding paper, considers a diradical and a dipolar transition state as two extreme representations of the cycloaddition.²⁹⁻³² For diene **1** the former follows the FMO approach as shown in **82**, whereas the latter may involve alignment of dipoles as shown in **83**; i.e., opposite



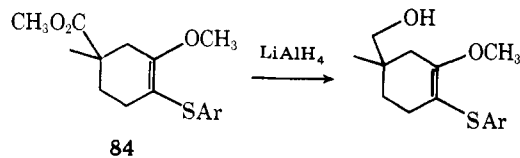
regiochemistry is predicted. Space limitations of the journal preclude a more detailed discussion of this suggestion, but competition between these two potentially opposing effects nicely accommodates all of the results reported herein, including that of juglone.³³⁻³⁷ Support for this suggestion derives from consideration of the relationship of the charge distribution in the dienes as measured by ¹³C NMR chemical shifts (see Table VI) and the regiochemistry of the cycloaddition.³⁸ The effect of increasing the electronegativity of the benzene ring attached to sulfur in the series of dienes **1**, **13**, and **16** was to decrease the electron density at C-1 while the electron density at C-4 remained relatively unchanged. On the other hand, substitution of the 4-methoxyphenyl for the phenyl group increased the electron density at C-1 more than at C-4. Replacement of the methoxy substituent of diene **1** with an acetoxy substituent (**22**) resulted in a significant decrease in the electron density at C-4. The difference in the chemical shifts of the terminal carbons ($\delta_4 - \delta_1$) is qualitatively in agreement with the trends of regiochemical control by oxygen and sulfur observed experimentally (see Table V). This correlation between the difference in the ¹³C NMR chemical shifts of the terminal carbons ($\delta_1 - \delta_4$) of related dienes and the regioselectivity of their cycloadditions may be general. The ¹³C NMR data support the regiochemical arguments outlined earlier in that, as the interaction of oxygen with the diene increases (decreases), the regiochemical control of oxygen, especially in the catalyzed reaction, also increases (decreases). A similar analysis of the ¹H NMR data shows a correlation between the

regioselectivity of the cycloaddition and the averaged chemical shifts for each terminal pair of protons.

The limited regioselectivity observed in the cycloadditions of 2,3-bis(methylene)-1-oxa-4-thiacyclohexane (**58**) is a consequence of the increased reactivity of the diene and the elevated (>130 °C) temperatures at which the cycloadditions occur. It is interesting to note that, when isomerization occurs prior to cyclobutene opening, the resulting diene, 2-vinylloxathiin (**66**), undergoes cycloaddition yielding the regioisomer of sulfur control exclusively. This regiochemical result confirms the experimentally observed fact that 1 substitution more effectively controls regioselectivity than 2 substitution.³⁹

The structure modification sequences used to define the regioselectivity of the cycloadditions also illustrate the versatility of the dienes in synthesis. A useful difference was observed between the hydrolysis of the enol acetates formed from cycloaddition of the acetoxy dienes and the hydrolysis of the methyl enol ether formed from the cycloaddition of the methoxy dienes. The enol acetates were hydrolyzed at room temperature with sodium or magnesium methoxide in methanol and were relatively unaffected by acid over short periods of time (e.g., 4 h at room temperature). On the other hand, the methyl enol ethers were rapidly hydrolyzed at 0 °C with catalytic perchloric acid in acetonitrile and were unaffected by sodium methoxide in methanol at room temperature. Therefore, the β -keto sulfide functionality can remain protected after the cycloaddition whether acidic or basic reaction conditions are required by the synthetic sequence.

Aldehydes and ketones, e.g., **11** and **25**, were selectively reduced with sodium borohydride without unmasking the β -keto sulfide when it was protected as the enol acetate. In addition, an ester, i.e., **84**, could be reduced without depro-



tection of the methyl enol ether. The enol ether **5** underwent addition of an organolithium and imine hydrolysis and the enol ethers **7** and **11** underwent Wittig reactions while maintaining the β -keto sulfide in its protected form.

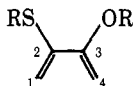
Conversion of the cycloadduct **25** of 2-cyclohexen-1-one and 2-acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene into 1,2-dihydro-6-methoxynaphthalene exemplified the use of the cycloaddition of the diene as an aromatic ring annulation.

Finally, the catalytic cycloaddition of 2-acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene and juglone coupled with the structural elaboration to **55** which was necessary to establish the regioselectivity illustrates the potential use of the diene in anthracycline and tetracycline natural product syntheses. The asymmetry of the D ring (tetracycline nomenclature) in juglone has been translated to the B ring, which could enable the regiocontrolled introduction of the A rings.

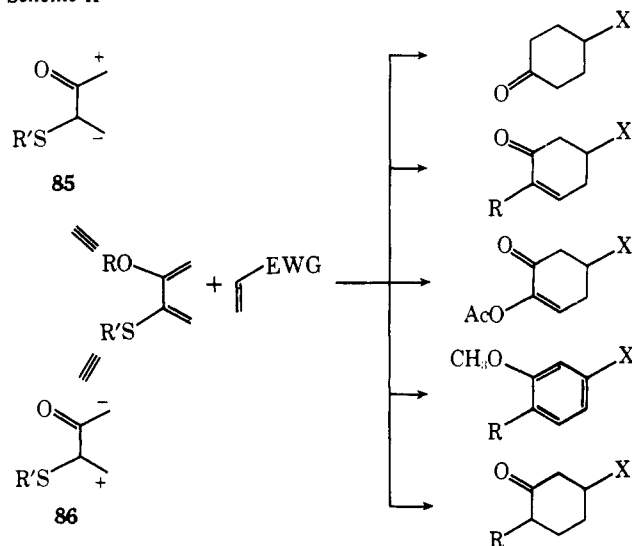
Conclusions

Within this text are described the preparations and cycloaddition reactions of a series of 2,3-diheterosubstituted 1,3-butadienes. The cycloadditions offer several advantages: (1) the versatile β -keto sulfide moiety is introduced in a protected form which allows modification elsewhere; (2) dependent on diene substitution and reaction conditions, regiochemical control ranging from >50:1 with sulfur controlling to 1:8 with oxygen controlling has been attained and creates the equivalent of either dipole **85** or **86**; (3) the regiochemistry obtained by sulfur control complements the normal regiochemistry obtained with 2-oxygenated dienes (combined with the ease with which sulfur can be removed from organic molecules may make this a general approach to reversing the

Table VII. ^{13}C NMR Chemical Shifts of the Dienes (ppm)

entry	R	R'	diene					
				δ_1	δ_2	δ_3	δ_4	$\delta_1 - \delta_4$
1	C_6H_5	CH_3	1	117.5	138.5	157.6	86.5	31.0
2	4- ClC_6H_4	CH_3	13	120.0	137.8	157.9	86.4	33.6
3	$\text{C}_4\text{N}_2\text{H}_3$	CH_3	16	126.1	133.4	158.6	86.1	40.0
4	C_6H_5	Ac	19	119.7	136.6	150.4	106.6	12.4
5	4- $\text{CH}_3\text{OC}_6\text{H}_4$	Ac	22	115.1	139.0	150.4	105.6	9.5

Scheme II



normal orientation of Diels-Alder reactions);⁴¹ (4) the transformations in Scheme II have been demonstrated.

Rationalization of the experimentally observed regioselectivities of the dienes suggests that several competing factors may be important in transition-state stabilization. Dependent on the substitution of the diene and of the dienophile, the transition state may be described as a hybrid of atom-atom (maximum orbital coefficients in FMO) and dipole-dipole (DD) interactions with varying degrees of importance. Furthermore, the rationalization recognized that these two interactions may favor *alternative* orientations in the transition state. The experimental results indicate that polar factors (dipole-dipole interactions) which are not explicitly included in the FMO explanation can have an important role in determining the regioselectivity of the Diels-Alder cycloaddition.

Experimental Section

General. All reactions were run under a positive pressure of dry nitrogen. Infrared spectra were obtained as solutions in the indicated solvent on a Beckman IR-8 or a Perkin-Elmer 267 spectrophotometer. NMR spectra were determined in the indicated solvent on a Jeolco MH-100 (100 MHz) or a Bruker WH270 (270 MHz) instrument; chemical shifts are reported in parts per million downfield from tetramethylsilane (Me_4Si). ^{13}C NMR spectra were determined in the indicated solvent on a Jeolco FX-60 (15.1 MHz) instrument; chemical shifts are reported in parts per million downfield from Me_4Si . Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; addition of b indicates a broadened pattern. Coupling constants are given in hertz. Mass spectra were recorded on an AEI-MS-902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 mA unless otherwise specified. Melting points were obtained on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. Boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. VPC analyses were performed on a Varian Aerograph Model 90P. Thin layer or preparative thick layer (1.5 mm) plates were made of E. Merck AG Darmstadt silica gel PF-254 or

Brinkmann silica gel P/UV-254 no. 66 and activated by drying at 140 °C for 2 h. Eluting solvents are indicated in the text. Removal of material from the silica gel was accomplished by successive washings with ether or ethyl acetate. The term LC is used for high- (or medium-) pressure solid-liquid chromatography and refers to the use of a standard 2.5 (i.d.) \times 100 cm column with a precolumn filter of 1.5 (i.d.) \times 25 cm dimensions, both of which were packed with 32-63 μm Woelm silica gel and preequilibrated with the indicated solvent mixture. The system utilized a single stage constant flow pump at approximately 22 mL/min.

In experiments requiring dry solvents, ether, tetrahydrofuran, dioxane, and dimethoxyethane were distilled from sodium benzophenone ketyl. Benzene, toluene, methylene chloride, dimethylformamide, triethylamine, xylene, hexane, and pyridine were distilled from calcium hydride. Acetic anhydride was distilled from 5 mol % quinoline. Acetone was distilled from potassium carbonate. Methyl vinyl ketone, acrylonitrile, methyl acrylate, methyl methacrylate, methacrolein, and 2-cyclohexen-1-one were distilled from hydroquinone immediately before use. Juglone (100 °C (0.2 mm)) and 1,4-naphthoquinone (80 °C (0.5 mm)) were purified by sublimation. Apparatus for experiments requiring anhydrous conditions was dried by flaming in a stream of nitrogen.

Cycloadditions with 2-Methoxy-3-phenylthiobuta-1,3-diene (1). **With Solvent. Preparation of 7,9-Dioxo-3-methoxy-8-phenyl-4-phenylthio-8-aza-cis-bicyclo[4.3.0]non-3-ene (2).** A solution of 144 mg (0.75 mmol) of diene **1**, 173 mg (1.0 mmol) of *N*-phenylmaleimide, and 5 mg of BHT in 1 mL of toluene was refluxed for 2 h. The solvent was removed in vacuo and the residue purified directly by preparative TLC (CHCl_3 and then 1% ether in CHCl_3) to give 195 mg (71%) of **2** as a white, crystalline solid, mp 133.5-134.5 °C. IR (CHCl_3): 1720, 1385 cm^{-1} . NMR δ (CDCl_3): 2.4-2.7 (3 H, m), 2.95-3.6 (3 H, m), 3.68 (3 H, s), 7.1-7.65 (10 H, m). Calcd for $\text{C}_{21}\text{H}_{11}\text{NO}_3\text{S}$: 365.1086. Found: 365.1108.

The full experimental details for the preparation of dimethyl 4-methoxy-5-phenylthiocyclohex-4-ene-*cis*-1,2-dicarboxylate (**4**) and dimethyl 3,6-dihydro-4-methoxy-5-phenylthiophthalate (**3**) appear in the microfilm edition.

Neat. Preparation of 4-Acetyl-2-methoxy-1-phenylthiocyclohex-1-ene (7). 2-Methoxy-3-phenylthiobuta-1,3-diene (380 mg, 2 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (BHT stabilizer, 100 mg) were refluxed in 1 mL of freshly distilled MVK for 2 h. The solvent was removed in vacuo and the residue was subjected to preparative layer chromatography on a 40-cm silica gel plate eluting once with 5% ether in chloroform. The major band (R_f 0.27) was extracted with ether and the solvent was removed under reduced pressure to give the **Diels-Alder adduct** (395 mg, 75%) as a light yellow, mobile oil. IR (CHCl_3): 1715, 1638, 1360 cm^{-1} . NMR (CDCl_3): δ 1.4-3.0 (10 H, m including singlets at 2.18 and 2.08 in 4:1 ratio), 3.63 and 3.66 (3 H, two s, 4:1), 7.0-7.4 (5 H, m). Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2\text{S}$: 262.1028. Found: 262.1018.

The full experimental details for the preparation of 4-cyano-2-methoxy-1-phenylthiocyclohex-1-ene (**5**), 4-carbomethoxy-2-methoxy-1-phenylthiocyclohex-1-ene (**9**), and 3-methoxy-1-methyl-4-phenylthiocyclohex-3-ene-1-carboxaldehyde (**11**) appear in the microfilm edition.

Reaction of 1 and MVK in the Presence of Lewis Acid. A. With Magnesium Bromide. To a solution of 15 mg (0.075 mmol) of anhydrous magnesium bromide in 0.4 mL of MVK were added 96 mg (0.50 mmol) of diene **1** and 20 mg of BHT. After 16 h at room temperature workup as above gave, after purification by preparative TLC (CHCl_3), 120 mg (91%) of adducts **7** and **8** determined to be $\sim 1.5\!:\!1$ by the ratio peaks at δ 3.66-3.63 and 2.18-2.08.

B. On Silica Gel. A solution of 96 mg (0.5 mmol) of diene **1** and 40 mg of BHT in 1 mL of MVK was shaken with 5 g of W. R. Grace silica

gel until it became a homogeneous, free-flowing powder. After storing for 24 h at room temperature, the silica gel was washed with ether, the ether layer evaporated under reduced pressure, and the residue subjected to preparative TLC to give 55 mg (42%) of adducts **7** and **8** in a ratio of 3:2 as determined above.

Cycloadditions with 2-Methoxy-3-(4'-chlorophenylthio)buta-1,3-diene. With Methacrolein. As for the neat reactions above, 32 mg (0.14 mmol) of diene **13** and 50 mg of BHT in 6 mL of methacrolein gave, after 19 h and after preparative TLC (20% ether in hexane, two elutions), 23 mg (55%) of cycloadduct. Analysis of the products by NMR revealed two singlets at δ 9.38 and 9.32 which were assigned as the aldehyde protons of 1-(4'-chlorophenylthio)-4-formyl-2-methoxy-4-methyl-1-cyclohexene and 2-(4'-chlorophenylthio)-4-formyl-1-methoxy-4-methyl-1-cyclohexene and which integrated for a ratio of 3:1, respectively. IR (CHCl₃): 2810, 1730, 1640, 1580, 1480, 1460, 1440 cm⁻¹. NMR (100 MHz, CDCl₃): δ 1.04 and 1.14 (3 H, 2 singlets), 1.4–2.9 (6 H, m), 3.68 (3 H, s), 7.0–7.3 (4 H, m), 9.32 and 9.38 (1 H, 2 singlets). Calcd for C₁₅H₁₇ClO₂S: 296.0638. Found: 296.0635.

With MVK. As for the neat reactions above, 167 mg (0.74 mmol) of diene **13** and 10 mg of BHT in 3 mL of freshly distilled MVK gave, after 12 h and purification by preparative TLC (40% ether in hexane), 182 mg (83%) of adducts **14** and **15**. Analysis of the adducts by 270-MHz NMR revealed two singlets at δ 3.65 and 3.60 which were assigned as the methoxy protons for 4-acetyl-1-(4'-chlorophenylthio)-2-methoxy-1-cyclohexene and 4-acetyl-2-(4'-chlorophenylthio)-1-methoxy-1-cyclohexene and which integrated in a ratio of 1.5:1, respectively. IR (CHCl₃): 1705, 1355 cm⁻¹. NMR (270 MHz, CDCl₃): δ 2.11 and 2.21 (3 H, 2 singlets), 1.51 and 3.86 (7 H, m), 3.60 and 3.65 (3 H, 2 singlets), 7.05–7.37 (4 H, m). Calcd for C₁₅H₁₇ClO₂S: 296.0638. Found: 296.0632.

With MVK and Magnesium Bromide. Anhydrous magnesium bromide (28 mg, 0.152 mmol) was added to a stirred solution of 2-(4'-chlorophenylthio)-3-methoxy-1,3-butadiene (150 mg, 0.665 mmol) and freshly distilled methyl vinyl ketone (2 mL) containing 2,6-di-*tert*-butyl-4-methylphenol (10 mg) at room temperature. The resulting solution was stirred at room temperature for 12 h. After the reaction mixture was quenched with saturated aqueous sodium bicarbonate and diluted with ether, the phases were separated. The organic portion was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (40% ether in hexane) to give 134 mg (68%) of Diels-Alder adducts, *R_f* 0.3. Analysis of the adducts by 270-MHz NMR revealed the two singlets at δ 3.65 and 3.60 for **14** and **15**, respectively, in a ratio of 1:1.5.

Cycloadditions with 2-Methoxy-3-(2'-pyrimidylthio)-1,3-butadiene. With MVK. As above for the neat reaction, 70 mg (0.36 mmol) of diene **16** and 10 mg of BHT in 5 mL of freshly distilled MVK in 4 h gave, after purification by preparative TLC (50% ether in hexane, four elutions), 64 mg (67%) of adducts **17** and **18**. Analysis of the adducts by 270-MHz NMR revealed two singlets at δ 3.63 and 3.66 which were assigned as the methoxy protons of 4-acetyl-1-methoxy-2-(2'-pyrimidylthio)-1-cyclohexene (**18**) and 4-acetyl-2-methoxy-1-(2'-pyrimidylthio)-1-cyclohexene (**17**) and which integrated in a ratio of 1.3:1, respectively. IR (CHCl₃): 2930, 1700, 1635, 1545, 1372, 1350 cm⁻¹. NMR (270 MHz, CDCl₃): δ 1.63–1.93 (1 H, m), 2.05–2.16 (1 H, m), 2.21 and 2.26 (3 H, 2 singlets), 2.39–2.92 (5 H, m), 3.63 and 3.66 (3 H, 2 singlets), 6.88–6.94 (1 H, m), 8.40–8.50 (2 H, m). Calcd for C₁₃H₁₆N₂O₂S: 264.0933. Found: 264.0928.

With MVK and MgBr₂. Anhydrous magnesium bromide (110 mg, 0.60 mmol) was added at once to a stirred solution of 152 mg (0.79 mmol) of diene **16** and 25 mg of BHT in 3 mL of freshly distilled MVK. After 16 h at room temperature, the reaction mixture was diluted with ethyl acetate and worked up as in the case of **13** to give, after preparative TLC (10% acetone, 2% triethylamine, 88% chloroform), 132 mg (63%) of **17** and **18**. Analysis of the mixture by 270-MHz NMR revealed the two singlets at δ 3.63 and 3.66 for **18** and **17**, respectively, in an 8:1 ratio. IR (CHCl₃): 2930, 1700, 1635, 1545, 1372, 1350 cm⁻¹. NMR (270 MHz, CDCl₃): δ 1.77–1.94 (1 H, m), 2.04–2.83 (6 H, m), 2.21 (3 H, s), 3.63 and 3.66 (3 H, 2 singlets), 6.91 (1 H, t, *J* = 5.0 Hz), 8.44 (2 H, d, *J* = 5.0 Hz).

Cycloaddition with 2-Acetoxy-3-phenylthiobuta-1,3-diene. As for the neat reactions above, 61 mg (0.28 mmol) of diene **19** and 60 mg of BHT in 3 mL of freshly distilled methacrolein in 18 h gave, after purification by preparative TLC (40% ether in hexane and 5% ether in chloroform), 68 mg (84%) of **20** and **21**. Analysis of the product by

NMR, especially the expansion and integration of the aldehyde region, revealed two singlets at δ 9.46 and 9.38 which were assigned as the aldehyde protons of **20** and **21** in a ratio of 9:1. IR (CHCl₃): 3060, 2960, 2930, 1765, 1735, 1375, 1215 cm⁻¹. NMR (100 MHz, CDCl₃): δ 1.12 (3 H, s), 1.4–2.0 (5 H, m), 2.15 (3 H, s), 2.65 (1 H, bd, *J* = 20 Hz), 7.2–7.4 (5 H, bs), 9.46 and 9.38 (1 H, 2 singlets). Calcd for C₁₆H₁₈O₃S: 290.0976. Found: 290.0976.

Cycloadditions with 2-Acetoxy-3-(4'-methoxyphenylthio)buta-1,3-diene. With Methacrolein. As above for the neat reactions, 127 mg (0.508 mmol) of diene **22** and 20 mg of BHT in 8 mL of methacrolein in 17 h gave, after purification by preparative TLC (45% ether in hexane), 132 mg (82%) of **23**. Analysis of the adduct by NMR revealed two singlets at δ 9.42 and 9.32 in a ratio of 13:1 for **23** and **24**, respectively. IR (CCl₄): 2750, 1760, 1733, 1590, 1500, 1465, 1445, 1373, 1290, 1250 cm⁻¹. NMR (100 MHz, CCl₄): δ 1.00 and 1.08 (3 H, 2 singlets), 1.40–2.20 (4 H, m), 2.12 (3 H, s), 2.54 (2 H, bd, *J* = 18 Hz), 3.76 (3 H, s), 6.75 (2 H, d, *J* = 10 Hz), 7.21 (2 H, d, *J* = 10 Hz), 9.32 and 9.42 (1 H, 2 singlets). Anal. (C₁₇H₂₀O₄S): C, H.

With Methacrolein and BF₃. As for the catalyzed reaction of diene **16**, 170 mg (0.68 mmol) of diene **22**, 25 mg of BHT, and 6.5 mg (0.035 mmol) of boron trifluoride etherate in 2 mL of freshly distilled methacrolein for 1.6 h gave, after purification by preparative TLC (45% ether in hexane), 204 mg (94%) of **23**.

With Acrylonitrile. As above, 128 mg (0.51 mmol) of diene **22** and 25 mg of BHT in 8 mL of acrylonitrile for 12 h gave, after purification by preparative TLC, 111 mg (72%) of adduct (**3**). The major product was assigned as the regioisomer of sulfur control in analogy to the other thermal cycloadditions of 2-acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene with various dienophiles. Evidence for a minor product (of oxygen control), however, was not observed. Therefore, although a meaningful ratio of sulfur to oxygen control could not be determined, the major, if not exclusive, product was assigned as 2-acetoxy-4-cyano-1-(4'-methoxyphenylthio)-1-cyclohexene. IR (CHCl₃): 3000, 2940, 2840, 1755, 1668, 1590, 1497, 1465, 1445, 1375, 1290 cm⁻¹. NMR (100 MHz, CDCl₃): δ 2.17 (3 H, s), 1.80–3.10 (7 H, m), 3.79 (3 H, s), 6.84 (2 H, d, *J* = 8.0 Hz), 7.33 (2 H, d, *J* = 8.0 Hz). Calcd for C₁₆H₁₇NO₃S: 303.0929. Found: 303.09236.

With MVK. As above, 130 mg (0.52 mmol) of diene **22** and 20 mg of BHT in 1.2 mL of freshly distilled MVK for 2 h gave, after purification by preparative TLC (60% ether in hexane), 141 mg (86%) of adduct. Analysis of the product by 270-MHz NMR revealed two singlets at δ 2.08 and 2.01 in a 10:1 ratio which were assigned as the methyl ketone protons of 2-acetoxy-4-acetyl-1-(4'-methoxyphenylthio)-1-cyclohexene and 1-acetoxy-4-acetyl-2-(4'-methoxyphenylthio)-1-cyclohexene. IR (CCl₄): 1765, 1720, 1500, 1375, 1290 cm⁻¹. NMR (100 MHz, CCl₄): δ 1.30–2.80 (7 H, m), 2.08 and 2.01 (3 H, 2 singlets), 2.71 (3 H, s), 6.68 (2 H, d, *J* = 9.0 Hz), 7.16 (2 H, d, *J* = 9.0 Hz). Calcd for C₁₇H₂₀O₄S: 320.1082. Found: 320.1081.

With Methyl Acrylate. As above, 101 mg (0.405 mmol) of diene **22** and 25 mg of BHT in 2 mL of freshly distilled methyl acrylate for 18 h gave, after filtering through 5 g of silica gel and Celite with ether and purification by preparative TLC (40% ether in hexane), 106 mg (70%) of adduct. Analysis by NMR revealed two singlets at δ 3.61 and 3.59 which were assigned as the carbomethoxy protons of 2-acetoxy-4-carbomethoxy-1-(4'-methoxyphenylthio)-1-cyclohexene and 1-acetoxy-4-carbomethoxy-2-(4'-methoxyphenylthio)-1-cyclohexene and which integrated in a ratio of 10:1, respectively. IR (CCl₄): 1760, 1740, 1670, 1590, 1570, 1495, 1460, 1440 cm⁻¹. NMR (100 MHz, CCl₄): δ 1.50–2.80 (7 H, m), 2.12 (3 H, s), 3.61 and 3.59 (3 H, 2 singlets), 3.74 (3 H, s), 6.70 (2 H, d, *J* = 9.0 Hz), 7.18 (2 H, d, *J* = 9.0 Hz). Calcd for C₁₇H₂₀O₅S: 336.1031. Found: 336.1031.

With Methyl Methacrylate. As above, 108 mg (0.43 mmol) of **22** and 60 mg of BHT in 1.2 mL of methyl methacrylate for 22 h gave, after purification by preparative TLC (60% ether in hexane), 123 mg (82%) of adduct. Analysis by NMR revealed two sets of singlets at δ 1.19 and 1.12 and at δ 3.61 and 3.59, each in a ratio of 9:1, which were assigned as the methyl protons and the carbomethoxy protons of 2-acetoxy-4-carbomethoxy-1-(4'-methoxyphenylthio)-4-methyl-1-cyclohexene and 1-acetoxy-4-carbomethoxy-2-(4'-methoxyphenylthio)-4-methyl-1-cyclohexene. IR (CCl₄): 1768, 1740, 1670, 1592, 1500, 1468, 1440, 1372 cm⁻¹. NMR (100 MHz, CCl₄): δ 1.12 and 1.19 (3 H, 2 singlets), 1.20–2.40 (5 H, m), 2.08 (3 H, s), 2.68 (1 H, bd, *J* = 20.0 Hz), 3.61 and 3.59 (3 H, 2 singlets), 3.72 (3 H, s), 6.70 (2 H, d, *J* = 9.0 Hz), 7.18 (2 H, d, *J* = 9.0 Hz). ¹³C NMR (15.1 MHz, CDCl₃): 20.7, 23.7, 26.3, 31.7, 37.6, 42.4, 52.0, 55.3, 114.5, 119.1,

123.2, 134.2, 144.6, 159.4, 168.5, 176.6. Calcd for $C_{18}H_{22}O_5S$: 350.1188. Found: 350.1190.

With Cyclohex-2-en-1-one. Boron trifluoride etherate (2 μ L, 2.3 mg, 0.016 mmol) was added via syringe to a stirred solution of diene **22** (79.0 mg, 0.314 mmol) and 2-cyclohexen-1-one (1.0 mL) containing 2,6-di-*tert*-butyl-4-methylphenol (25 mg) at room temperature. After 12 h at room temperature, the reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate and diluted with ethyl acetate. The phases were separated and the aqueous portion was back-extracted with ethyl acetate. The combined organic portions were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (40% ether in hexane) to give 36.2 mg (33%) of *cis*-7-acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone, R_f 0.5 (five elutions), and 53.4 mg (49%) of *trans*-7-acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone, R_f 0.55 (five elutions). The scale of the reaction was increased to 4.0 mmol of 2-acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene and the adducts were routinely isolated as mixtures in yields ranging from 75 to 85%. For example, reaction of 0.960 g (3.84 mmol) of 2-acetoxy-3-(4'-methoxyphenylthio)-1,4-butadiene with excess 2-cyclohexen-1-one gave 1.04 g (80%) of *cis*- and *trans*-7-acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone. *cis*-7-Acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone: IR (CHCl₃) 2930, 1745, 1710, 1590, 1490, 1365 cm^{-1} ; NMR (270 MHz, benzene-*d*₆) δ 0.56–0.70 (1 H, m), 0.99–1.40 (4 H, m), 1.58–1.91 (3 H, m), 1.81 (3 H, s), 2.04–2.19 (2 H, m), 2.47 (1 H, bd of d, J = 18, 5 Hz), 2.75–2.92 (1 H, m), 3.13 (3 H, s), 6.65 (2 H, d, J = 8 Hz), 7.43 (2 H, d, J = 8 Hz). Calcd for $C_{19}H_{22}O_4S$: 346.1239. Found: 346.1251.

trans-7-Acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone: IR (CHCl₃) 2930, 1710, 1590, 1490, 1365 cm^{-1} ; NMR (270 MHz, benzene-*d*₆) δ 1.06–1.44 (4 H, m), 1.68–2.32 (7 H, m), 1.82 (3 H, s), 2.80 (1 H, bd, J = 14 Hz), 3.14 (3 H, s), 6.58 (2 H, d, J = 8.0 Hz), 7.38 (2 H, d, J = 8.0 Hz). Calcd for $C_{19}H_{22}O_4S$: 346.1238. Found: 346.12416. Anal. ($C_{19}H_{22}O_4S$, mixture of *cis* and *trans*): C, H, S.

Reaction of Adduct 5 with Methylolithium. To a solution of 117 mg (0.47 mmol) of adduct **5** in 1 mL of ether at room temperature was added 0.60 mL (0.98 mmol) of a 1.65 M solution of methylolithium in hexane. After 5 h, 125 mg of oxalic acid dihydrate, 1 mL of water, and 5 mL of THF were added with maintenance of stirring for an additional 2 h. The reaction mixture was dried over anhydrous K_2CO_3 and applied directly to a preparative TLC plate, eluting with 1:1 ether-hexane, to give 53 mg (35%) of **7**, identical with the sample obtained previously.

Reaction of Adducts with Triphenylphosphonium Methylide. Reaction of Adduct 7. To a 0 °C solution of 2.0 mmol of the ylide, prepared from 890 mg (2.5 mmol) of methyltriphenylphosphonium bromide and 1.3 mL (2.0 mmol) of a 1.54 M solution of *n*-butyllithium in hexane, in 2.5 mL of dry THF was added dropwise 331 mg (1.27 mmol) of adduct **7** in 4 mL of dry THF. The reaction mixture was allowed to warm to room temperature, stirred for 3.5 h, diluted with ether, and then filtered. After concentration in vacuo, the residue was triturated with 4 \times 10 mL of hexane. The hexane extracts were concentrated in vacuo to 211 mg (64%) of **26a**. This was used directly in the next reaction. A sample from a 1:1 mixture of adducts **7** and **8** was subjected to preparative TLC (CHCl₃) to give purified product. IR (CHCl₃): 1640, 1476, 890 cm^{-1} . NMR (CDCl₃): δ 1.2–2.0 (5 H, m with two singlets at δ 1.67 and 1.76 in ~1:1 ratio), 2.0–2.5 (5 H, m), 3.63 and 3.66 (3 H, two s, ~1:1), 4.65 and 4.85 (2 H, two broad s), 7.05–7.5 (5 H, m).

Reaction of Adduct 18. As above, 194 mg (1.0 mmol) of adduct **18** (obtained from a catalyzed reaction) in 3 mL of dry THF was reacted with 1.25 mmol of triphenylphosphonium methylide in 3 mL of dry THF to give, after purification by preparative TLC (5% ether in chloroform), 72 mg (67% based upon 40 mg of recovered starting material) of **26b**. IR (CHCl₃): 1720, 1640, 1580, 1475, 1440 cm^{-1} . NMR (100 MHz, CDCl₃): δ 1.76 (3 H, s), 1.8–2.0 (1 H, m), 2.2–2.6 (6 H, m), 3.66 (3 H, s), 4.80 (2 H, bs), 6.94 (1 H, t, J = 5.0 Hz), 8.50 (2 H, d, J = 5.0 Hz). Calcd for $C_{14}H_{18}N_2OS$: 262.1140. Found: 262.1145.

Reaction of Adduct 11. As above, 378 mg (1.44 mmol) of aldehyde **11** in 3 mL of dry THF was reacted with 1.86 mmol of triphenylphosphonium methylide in 3 mL of dry THF to give, after purification by preparative TLC (20% ether in hexane), 249 mg (67%) of **27**. IR (CCl₄): 1640, 1475, 1438 cm^{-1} . NMR (CCl₄): δ 1.04 (3 H, s), 1.3–1.6 (2 H, m), 1.9–2.4 (4 H, m), 3.57 (3 H, s), 4.75–5.08 (2 H, m), 5.94

(1 H, dd, J = 16, 11 Hz), 6.9–7.3 (5 H, m). Calcd for $C_{16}H_{20}OS$: 260.1235. Found: 260.1246.

Hydrolysis of Adduct 2. A solution of 530 mg (1.45 mmol) of adduct **2** in 5 mL of acetonitrile containing 0.15 mL of 40% aqueous perchloric acid was stirred at 0 °C for 4 h. Chloroform (50 mL), 0.5 mL of water, and solid potassium carbonate were added. After filtering, the solution was concentrated in vacuo and the resulting foam directly subjected to preparative TLC (12% ether in chloroform) to give 479 mg (97%) of **29** as a sticky solid. IR (CHCl₃): 1710 cm^{-1} . NMR (CDCl₃): δ 2.3–3.85 (7 H, m), 7.0–7.6 (10 H, m). Calcd for $C_{20}H_{17}NO_3S$: 351.0929. Found: 351.0928.

Hydrolysis of Adduct 4. A solution of 63 mg (0.48 mmol) of adduct **4** in 4 mL of THF and 1 mL of 10% aqueous hydrochloric acid was stirred for 4 h at 20 °C. A 1:1 mixture of hexane and ether (40 mL) followed by solid potassium carbonate was added. The mixture was filtered, evaporated in vacuo, and directly subjected to preparative TLC (60% ether in hexane) to give 102 mg (66%) of **28**. IR (CHCl₃): 1735, 1437 cm^{-1} . NMR (CDCl₃): δ 2.0–4.0 (13 H, m with singlets at 3.71 and 3.68), 7.1–7.5 (5 H, m).

Preparation of (\pm)-Carvone from 26a. Enol ether **26a** (211 mg, 0.80 mmol) was hydrolyzed as for **2** to give, after purification by preparative TLC (20% ether in hexane), 130 mg (42% overall from **7**) of **30**. IR (CHCl₃): 1710, 1440, 895 cm^{-1} . NMR (CDCl₃): δ 1.4–3.3 (10 H, m with bs at δ 1.76), 3.64–4.08 (1 H, m), 4.76 (2 H, bs), 7.1–7.5 (5 H, m). Calcd for $C_{15}H_{18}OS$: 246.1078. Found: 246.1073.

To a suspension of 35 mg (57% dispersion, 0.8 mmol) of sodium hydride in 1 mL of dry THF was added dropwise a solution of 192 mg (0.78 mmol) of **30** in 2 mL of dry THF. After hydrogen evolution ceased (~15 min), 142 mg (1.0 mmol) of methyl iodide was added and the reaction mixture stirred at 20 °C for 4 h. The reaction mixture was poured into 10 mL of water and then extracted into ether. After the mixture was washed with brine, dried (K_2CO_3), evaporated in vacuo, and purified by preparative TLC (20% ether in hexane), there was obtained 158 mg (7) of **31**. IR (CHCl₃): 1700, 1436, 895 cm^{-1} . NMR (CDCl₃): δ 1.0–2.9 (13 H, m with singlets at δ 1.22 (sharp), 1.68 (broad), and 1.73 (broad)), 3.30 (1 H, dd, J = 15, 6 Hz), 4.68–4.96 (2 H, m), 7.15–7.60 (5 H, m). Calcd for $C_{16}H_{20}OS$: 260.1235. Found: 260.1227.

A solution of 74 mg (85% pure, 0.37 mmol) of MCPBA in 2 mL of methylene chloride was added dropwise over 20 min to 96 mg (0.37 mmol) of **31** at –78 °C. After 30 min, the solution was allowed to warm to room temperature and stirred for an additional 1 h. Trimethyl phosphite (50 mg) was added and the solution was refluxed for 8 h. The reaction mixture was applied directly onto a preparative TLC plate (two elutions, 10% ether in hexane) to give 37 mg (66%) of (\pm)-carvone. VPC (10% XE-60 on Chromosorb W column at 100 °C) revealed two peaks at 6 and 7.25 min in a 1:10 ratio. The latter, by coinjection and comparison of IR spectra with that of authentic sample, was identified as (\pm)-carvone. The minor component is presumed to arrive from the alternative regioisomer in the original adduct and therefore is assigned structure **32**.

Preparation of 2-(*E*)-Geranyl-5-methyl-5-vinylcyclohexanone (35). The enol ether **27** (142 mg, 0.55 mmol) was hydrolyzed as for adduct **4** to give 133 mg (98%) of **33**. IR (CHCl₃): 1705, 1440 cm^{-1} . NMR (CDCl₃): δ 1.04 and 1.08 (3 H, two s), 1.4–2.4 (5 H, m), 2.76 and 2.89 (1 H, two d, J = 14 Hz), 3.56–3.80 (1 H, m), 4.76–5.1 (3 H, m), 5.4–5.84 (1 H, m), 7.1–7.4 (5 H, m). An analytical sample was prepared by preparative TLC (20% ether in hexane). Calcd for $C_{15}H_{18}OS$: 246.1078. Found: 246.1088.

As in the preparation of **31**, 197 mg (0.80 mmol) of **33**, 35 mg (57% dispersion, 0.80 mmol) of sodium hydride, and 220 mg (1.5 mmol) of geranyl bromide gave, after purification by preparative TLC (2 ether in hexane), 194 mg (64%) of **34**. IR (CHCl₃): 1693 cm^{-1} . NMR (CDCl₃): δ 0.96 and 1.14 (3 H, two s), 1.4–1.75 (11 H, m), 1.85–2.4 (9 H, m), 3.2–3.58 (1 H, m), 4.8–5.3 (4 H, m), 5.4–6.1 (1 H, m), 7.2–7.4 (5 H, m). Calcd for $C_{25}H_{34}OS$: 382.2330. Found: 382.2325.

To 194 mg (0.51 mmol) of the above alkylated product in 5 mL of methanol at 0 °C containing 350 mg (2.5 mmol) of disodium hydrogen phosphate was added 3 g of powdered 6% sodium amalgam. After 1 h, the solution was filtered and the solid washed with ether. The combined organic layers were washed with brine and dried ($MgSO_4$). After evaporation in vacuo, the residue was distilled in a Kugelrohr apparatus (110 °C, 0.2 Torr) to give 76 mg (55%) of **35**. IR (CHCl₃): 1703, 1445, 1375, 908 cm^{-1} . NMR (CDCl₃): δ 0.97 and 1.08 (3 H, two s), 1.1–2.5 (21 H, m with two bs at δ 1.59 and 1.67), 4.8–5.2 (4

H, m), 5.45–6.0 (1 H, m). Calcd for $C_{19}H_{30}O$: 274.2297. Found: 274.2311.

Preparation of 2-Acetoxy-5-benzoyloxymethyl-5-methylcyclohex-2-enone (38). Solid sodium borohydride (38 mg, 1.0 mmol) was added to a solution of 291 mg (1.1 mmol) of aldehyde **11** in 2.5 mL of methanol at 0 °C. After 10 min, 0.1 mL of water was added and the solvent removed in vacuo. The residue was taken up in 10 mL of water and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give 271 mg (93%) of 4-hydroxymethyl-2-methoxy-4-methyl-1-phenylthiocyclohexene. IR ($CHCl_3$): 1640, 1580, 1460, 1440 cm^{-1} . NMR ($CDCl_3$): δ 0.94 and 0.99 (3 H, two s), 1.2–2.5 (7 H, m), 3.41 (4 H, s), 3.63 (3 H, s), 7.0–7.5 (5 H, m). Calcd for $C_{15}H_{20}O_2S$: 264.1184. Found: 264.1194.

Benzoyl chloride (210 mg, 1.5 mmol) was added dropwise to a solution of the above alcohol (271 mg, 1.02 mmol) in 2 mL of pyridine at 0 °C. After 1 h, the mixture was warmed to 20 °C and then poured into dilute aqueous hydrochloric acid. After extraction with ether, the ether phase was washed with dilute aqueous hydrochloric acid and saturated aqueous sodium bicarbonate, dried (K_2CO_3), and evaporated in vacuo to give 372 mg (quantitative) of the crude benzoate. IR ($CHCl_3$): 1712 cm^{-1} . NMR ($CDCl_3$): δ 1.04 and 1.12 (3 H, two s), 1.4–2.6 (7 H, m), 3.59 (3 H, s), 4.08 (2 H, s), 7.0–7.6 (8 H, m), 7.8–8.2 (2 H, m).

A solution of 372 mg (1.0 mmol) of the above benzoate was hydrolyzed as for **2** to give, after purification by preparative TLC (40% ether in hexane), 228 mg (64% overall) of keto sulfide **36**. IR ($CHCl_3$): 1710 cm^{-1} . NMR ($CDCl_3$): δ 1.04 and 1.07 (3 H, two s), 1.3–2.5 (5 H, m), 2.64 and 3.14 (1 H, two d, $J = 14$ Hz), 3.6–3.9 (1 H, m), 4.04 and 4.07 (2 H, two s), 7.0–7.6 (8 H, m), 7.8–8.1 (2 H, m). Calcd for $C_{21}H_{22}O_3S$: 354.1290. Found: 354.1291.

Lead tetraacetate (200 mg, 0.40 mmol) was added to a refluxing solution of 112 mg (0.32 mmol) of β -keto sulfide **36** in 4 mL of benzene. After 10 min, the reaction mixture was allowed to cool and then quenched with 0.1 mL of glycol. After 30 min, it was poured onto 10 mL of water and extracted with ether. The combined organic extracts were washed with saturated aqueous sodium carbonate and then dried. Removal of the solvent in vacuo gave 116 mg (89%) of acetoxylated β -keto sulfide **37**. IR ($CHCl_3$): 1748, 1720 cm^{-1} . NMR ($CDCl_3$): δ 1.12 and 1.20 (3 H, two s), 2.06 and 2.08 (3 H, two s) superimposed upon 1.4–3.2 (6 H, m), 4.08 (s) and 4.32 and 4.12 (AB quartet, 2 H, $J = 12$ Hz), 7.0–7.5 (8 H, m), 7.8–8.05 (2 H, m). A sample was purified by preparative TLC (20% ether in hexane) with some decomposition occurring on the plate for analysis. Calcd for $C_{23}H_{24}O_5S$: 412.1341. Found: 412.1345.

To a solution of 82 mg (0.20 mmol) of **37** in 1 mL of methylene chloride at –78 °C was added a solution of 40 mg (85% pure, 0.20 mmol) of MCPBA in 2 mL of methylene chloride. After 30 min, the reaction mixture was warmed to room temperature (16 h) and then refluxed for 8 h. Purification by preparative TLC (three elutions, 50% ether in hexane) gave 52 mg (86%) of the diosphenol acetate **38**. IR ($CHCl_3$): 1763, 1710, 1695 cm^{-1} . NMR ($CDCl_3$): δ 1.20 (3 H, s), 2.16 (3 H, s), 2.1–2.8 (4 H, m), 4.02 (2 H, s), 6.18 (1 H, t, $J = 5$ Hz), 7.0–7.4 (3 H, m), 7.6–7.8 (2 H, m). Calcd for $C_{17}H_{18}O_5$: 302.1154. Found: 302.1151.

Preparation of 4-Acetylcyclohexanone. From Adduct 18. Adduct **18** (60 mg, 0.23 mmol), available from the catalyzed reaction, was hydrolyzed as for adduct **2**. Purification by preparative TLC (10% methanol in chloroform) gave 55 mg (97%) of 4-acetyl-2-(2'-pyrimidylthio)-1-cyclohexanone containing a small amount of the positional isomer. IR ($CHCl_3$): 1710, 1450, 1385, 915 cm^{-1} . NMR (270 MHz, C_6D_6): δ 1.30–2.59 (7 H, m), 1.65 and 1.81 (3 H, two s), 4.44 (d of d, $J = 12$, 6 Hz) and 4.69 (d of d, $J = 8$, 5 Hz), together represent 1 H, 6.03–6.13 (1 H, m), 7.83–7.95 (2 H, m). Calcd for $C_{12}H_{14}N_2O_2S$: 250.0776. Found: 250.07710.

Disodium phosphate (162 mg, 1.13 mmol) was added to 71 mg (0.283 mmol) of above compound in 2.8 mL of anhydrous methanol at 0 °C (ice bath). Pulverized 6% sodium amalgam (425 mg) was added at once to the slurry and then the stirring was continued at 0 °C for 1 h. The reaction mixture was then diluted with ether and filtered through Celite to remove the insoluble salts. The filtrate was washed with saturated aqueous ammonium chloride and with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. The solution was carefully concentrated by distillation through a 10-cm column packed with glass helices. The residual oil was purified by preparative TLC (3% acetone in chloroform) to give 12 mg (31%)

of a clear, colorless oil, R_f 0.4. Analysis of product(s) by 270-MHz NMR revealed signals identical with those obtained from an authentic sample of 4-acetylcyclohexanone. Extraneous signals were not observed; therefore, the expected minor product, 3-acetyl-1-cyclohexanone, must have been fractionated during the reaction and/or purification sequence. IR ($CHCl_3$): 1715, 1420, 1355 cm^{-1} . NMR (270 MHz, $CDCl_3$): δ 2.13–2.34 (2 H, m), 2.45–2.59 (2 H, m), 2.55 (3 H, s), 2.62–2.86 (4 H, m), 3.12 (1 H, t of t, $J = 10$, 3.8 Hz). Calcd for $C_8H_{12}O_2$: 140.0837. Found: 140.0839.

From 4-Cyano-1-methoxy-1-cyclohexene. To a stirred solution of 310 mg (1.86 mmol) of 1,1-ethylenedioxy-4-cyanocyclohexene in 2 mL of anhydrous benzene at room temperature was added via syringe 1.0 mL (2 mmol) of a 2 M freshly prepared methylmagnesium iodide solution in ether. After heating at 60 °C for 4 h, the reaction mixture was cooled to room temperature and quenched by the dropwise addition of saturated aqueous ammonium chloride. The solution was then poured into a separatory funnel containing ether. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was dissolved in benzene (3.0 mL) and added to 3.0 mL of 3 N aqueous hydrochloric acid. The resulting reaction mixture was refluxed for 10 h, cooled to room temperature, and poured into a separatory funnel containing ether and saturated aqueous sodium bicarbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated by distillation through a 10-cm Vigreux column. The residual oil was distilled at reduced pressure to give 175 mg (63% overall yield) of 4-acetylcyclohexanone as a clear, colorless oil, bp 96–100 °C (8 mm) (lit.⁴⁰ bp 115–120 °C (10 mm)). The spectral properties were identical with those of the sample from the above experiment.

Preparation of 2-Acetoxy-5-carbomethoxy-5-methylcyclohex-2-en-1-one (42). A freshly prepared solution of magnesium methoxide (24 mg of magnesium metal, 1.0 mg-atom) in methanol (1.0 mL) was added via syringe to a stirred solution of 182 mg (0.52 mmol) of **40** in 1.0 mL of anhydrous methanol at room temperature. After stirring at room temperature for 30 min, the reaction mixture was poured into a separatory funnel containing chloroform and saturated aqueous ammonium chloride. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (two elutions, 50% ether in hexane) to give 114 mg (71%) of 5-carbomethoxy-2-(4'-methoxyphenylthio)-5-methyl-1-cyclohexanone. IR ($CHCl_3$): 1720, 1590, 1490, 1460, 1445, 1285 cm^{-1} . NMR (100 MHz, $CDCl_3$): δ 1.20 and 1.36 (3 H, 2 singlets), 1.5–3.3 (6 H, m), 3.62 and 3.72 (3 H, 2 singlets), 3.5–3.8 (1 H, m), 6.75 (2 H, d, $J = 9.0$ Hz), 7.28 (3 H, d, $J = 9.0$ Hz). Calcd for $C_{16}H_{20}O_4S$: 308.1082. Found: 308.1089.

As in the case of **36**, 217 mg (0.500 mmol) of lead tetraacetate was reacted with 110 mg (0.358 mmol) of **41** in 2 mL of dry benzene to give, after purification by preparative TLC (60% ether in hexane, two elutions), 102 mg (79%) of **37**. IR ($CHCl_3$): 1740, 1725, 1590, 1490, 1455, 1435, 1365 cm^{-1} . NMR ($CDCl_3$): δ 1.27 and 1.35 (3 H, two s), 1.98 and 2.04 (3 H, two s), 1.6–3.0 (5 H, m), 3.24 (1 H, bd, $J = 16$ Hz), 3.63 and 3.67 (3 H, two s), 3.74 (3 H, s), 6.74 (2 H, d, $J = 9.0$ Hz), 7.29 (2 H, d, $J = 9.0$ Hz). Calcd for $C_{18}H_{22}O_6S$: 366.1137. Found: 366.1124.

As in the case of **37**, 100 mg (0.273 mmol) of 2-acetoxy-5-carbomethoxy-2-(4'-methoxyphenylthio)-5-methyl-1-cyclohexanone was oxidized with 58 mg (85% pure, 0.28 mmol) of MCPBA in 1.2 mL of methylene chloride and then eliminated by refluxing for 16 h to give 53 mg (87%) of diosphenol acetate **42** after purification by preparative TLC (three elutions, 60% ether in hexane). IR (CCl_4): 1760, 1725, 1695, 1450, 1435, 1370, 1310 cm^{-1} . NMR ($CDCl_3$): δ 1.36 (3 H, s), 2.20 (3 H, s), 2.52 (1 H, d, $J = 16$ Hz), 2.54 (1 H, d of d, $J = 16$, 4 Hz), 3.00 (1 H, d, $J = 16$ Hz), 3.02 (1 H, d of d, $J = 16$, 4 Hz), 3.70 (3 H, s), 6.49 (1 H, t, $J = 4$ Hz). Calcd for $C_{11}H_{14}O_5$: 226.0841. Found: 226.0840.

Preparation of (Z)- and (E)-3-(4'-Methoxyphenylthio)decalin-2,8-dione. To a stirred solution of 60 mg (0.17 mmol) of (Z)- and (E)-7-acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone in 1.0 mL of THF at room temperature was added via syringe 1.0 mL of a 15% aqueous sodium hydroxide solution. The reaction mixture was stirred at room temperature for 36 h and then poured into a separatory funnel containing ether and saturated aqueous ammonium chloride. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in

vacuo. The residual oil was purified by preparative TLC (two elutions, 60% ether in hexane) to give 33.5 mg (65%) of an undefined mixture of (Z)- and (E)-3-(4'-methoxyphenylthio)decalin-2,8-dione. IR (CHCl₃): 1720, 1590, 1497, 1290, 1250 cm⁻¹. NMR (CDCl₃): δ 1.0–2.9 (12 H, m), 3.81 (3 H, s), 3.05–3.85 (1 H, m), 6.85 (2 H, d, J = 8.0 Hz), 7.34 (2 H, d, J = 8.0 Hz). Calcd for C₁₇H₂₀O₃S: 304.113 30. Found: 304.112 47.

Preparation of (Z)- and (E)-2-Acetoxy-8-hydroxy-3-(4'-methoxyphenylthio)- Δ^2 -octalin. Sodium borohydride (28.5 mg, 0.75 mmol) was added at once to a stirred solution of 210 mg (0.61 mmol) of **25** in 6 mL of absolute ethanol and 5 mL of tetrahydrofuran at 0 °C (ice bath). After stirring for 4 h, the reaction mixture was quenched at 0 °C by dropwise addition of water until the hydrogen evolution subsided. The solution was then poured into a separatory funnel containing ether and saturated aqueous sodium bicarbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (80% ether in hexane) to give 192 mg (91%) of a mixture of (Z)- and (E)-2-acetoxy-8-hydroxy-3-(4'-methoxyphenylthio)- Δ^2 -octalin. IR (CHCl₃): 3600, 3550–3300 (broad), 2920, 1740, 1588, 1489, 1360 cm⁻¹. NMR (CDCl₃): δ 1.0–2.4 (12 H, m), 2.16 (3 H, s), 2.70 (1 H, bs), 3.76 (3 H, s), 3.6–3.8 (1 H, m), 6.80 (2 H, d, J = 8.0 Hz), 7.28 (2 H, d, J = 8.0 Hz). Calcd for C₁₉H₂₄O₄S: 348.139 52. Found: 348.138 67.

Preparation of (Z)- and (E)-8-Hydroxy-3-(4'-methoxyphenylthio)-decalin-2-one. As in the case of **40**, 95.0 mg (0.275 mmol) of a mixture of (Z)- and (E)-2-acetoxy-8-hydroxy-3-(4'-methoxyphenylthio)- Δ^2 -octalin was hydrolyzed by 1.0 mmol of magnesium methoxide in 1 mL of methanol for 9 h. Preparative TLC (5% methanol in chloroform) gave 71 mg (85%) of a mixture of (Z)- and (E)-8-hydroxy-3-(4'-methoxyphenylthio)decalin-2-one. IR (CHCl₃): 3600–3300 (broad), 2930, 1700, 1590, 1590 cm⁻¹. NMR (CDCl₃): δ 3.0 (13 H, m), 3.2–4.0 (2 H, m), 3.76 (3 H, s), 6.76 (2 H, d, J = 8 Hz), 7.30 (2 H, d, J = 8 Hz). Calcd for C₁₇H₂₂O₃S: 306.1290. Found: 306.1293.

Preparation of (Z)- and (E)-8-Hydroxy- Δ^3 -octalin-2-one. A solution of 363 mg (1.19 mmol) of (Z)- and (E)-8-hydroxy-3-(4'-methoxyphenylthio)decalin-2-one in 5 mL of methanol was added to 2 mL (1.4 mmol) of a 0.7 M aqueous solution of sodium metaperiodate at room temperature. After stirring for 3.5 h, the resulting slurry was filtered through Celite and the filtrate concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was dissolved in 5 mL of toluene and refluxed for 4 h. The reaction mixture was then cooled and poured into a separatory funnel containing ether and saturated aqueous sodium bicarbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (two elutions, 1 acetone in chloroform) to give 127 mg (84%) of (Z)- and (E)-8-hydroxy- Δ^3 -octalin-2-one. IR (CHCl₃): 3600, 3550–3400 (broad), 1675, 1640, 1595, 1495 cm⁻¹. NMR (CDCl₃): δ 1.0–4.0 (12 H, m), 5.96 (1 H, bd, J = 10 Hz), 6.76 (bd, J = 10 Hz), and 6.94 (d of d, J = 10, 5 Hz) together 1 H. Calcd for C₁₀H₁₄O₂: 166.0994. Found: 166.0994.

Preparation of (Z)- and (E)-8-Benzoxo- Δ^3 -octalin-2-one. Benzoyl chloride (244 μ L, 281 mg, 2.0 mmol) was added via syringe to a stirred solution of (Z)- and (E)-8-hydroxy- Δ^3 -octalin-2-one in 1.0 mL of anhydrous pyridine at approximately 0 °C (ice bath). The reaction mixture was kept in the refrigerator (\sim 2 °C) overnight and then poured into a separatory funnel containing ether and saturated aqueous sodium carbonate. The organic phase was separated, washed twice with saturated aqueous sodium carbonate and with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (3% acetone in chloroform) to give 107 mg (95%) based on **35** mg of recovered starting material of (Z)- and (E)-8-benzoxo- Δ^3 -octalin-2-one. IR (CHCl₃): 1710, 1680, 1450, 1275 cm⁻¹. NMR (CDCl₃): δ 1.0–3.0 (10 H, m), 4.7–5.2 (1 H, m), 6.04 (1 H, d, J = 10 Hz), 6.78 (1 H, d, J = 10 Hz), 7.4–7.7 (3 H, m), 7.9–8.2 (2 H, m). Calcd for C₁₇H₁₈O₃: 270.1256. Found: 270.1256.

Preparation of 1,2-Dihydro-6-methoxynaphthalene (45). To a stirred solution of (Z)- and (E)-8-benzoxo- Δ^3 -octalin-2-one (30 mg, 0.11 mmol) in 0.6 mL of chloroform and 50 μ L of anhydrous methanol at room temperature was added 23 mg (0.13 mmol) of recrystallized *N*-bromosuccinimide. After refluxing for 2 h, the solution was cooled

and poured into a separatory funnel containing ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated by distillation through a 10-cm Vigreux column. The residual oil was purified by preparative TLC (25% hexane in chloroform) to give 11 mg (54%) of 1,2-dihydro-6-methoxynaphthalene. The spectral properties were identical with those of an authentic sample of 1,2-dihydro-6-methoxynaphthalene prepared by a literature procedure.¹⁵ IR (CHCl₃): 1600, 1570, 1480, 1465, 1300, 1260 cm⁻¹. NMR (270 MHz, CDCl₃): δ 2.21–2.30 (2 H, m), 2.69 (2 H, t, J = 8.0 Hz), 3.73 (3 H, s), 6.01 (1 H, d of t, J = 9.5, 4.3 Hz), 6.39 (1 H, bd, J = 9.5 Hz), 6.575 (1 H, d, J = 2.5 Hz), 6.638 (1 H, d of d, J = 8.1, 2.5 Hz), 6.97 (1 H, d, J = 8.1 Hz). Calcd for C₁₁H₁₂O: 160.0888. Found: 160.0888.

Preparation of 2-Acetoxy-3-(4'-methoxyphenylthio)-1,4,9a(S*),-4a(R*)-tetrahydroanthraquinone (47). A 5-mL round-bottomed flask was rinsed with *O,N*-bis(trimethylsilyl)acetamide (1 mL) and then charged with 70 mg (0.28 mmol) of 2-acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene and 45 mg (0.28 mmol) of naphthoquinone. The neat solution was heated to 80 °C and maintained there for 4 h. Anhydrous methanol (2.0 mL) was added to the solution and then the heating bath was removed. Crystallization on standing at room temperature overnight gave 74 mg (65%) of **47** as white needles, mp 130–133 °C. IR (CHCl₃): 1750, 1695, 1665, 1595, 1492, 1370, 1285, 1240 cm⁻¹. NMR (270 MHz, CDCl₃): δ 2.18 (3 H, s), 2.10–2.33 (1 H, m), 2.40–2.61 (2 H, m), 2.85 (1 H, d of d, J = 17, 5 Hz), 3.35–3.42 (1 H, m), 3.48–3.57 (1 H, m), 3.78 (3 H, s), 6.81 (3 H, d, J = 8 Hz), 7.31 (2 H, d, J = 8 Hz), 7.68–7.76 (2 H, m), 7.94–8.07 (2 H, m). Anal. (C₂₃H₂₀O₅S): C, H, S, mol wt.

Reaction of 2-Acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene and Juglone (Thermal Reaction). A solution of 120 mg (0.48 mmol) of diene **22**, 35 mg of 2,6-di-*tert*-butyl-4-methylphenol, and 84 mg (0.48 mmol) of juglone in 0.5 mL of anhydrous benzene was heated to approximately 75 °C for 12 h. The reaction mixture was cooled and concentrated in vacuo. The residue was recrystallized from methanol and a minimal amount of chloroform (\sim 2%) to give 165 mg (72%) of a mixture of 2-acetoxy-5-hydroxy-3-(4'-methoxyphenylthio)-1,4,4a(R*),9a(S*)-tetrahydroanthraquinone (**48**) and 2-acetoxy-8-hydroxy-3-(4'-methoxyphenylthio)-1,4,4a(R*),9a(S*)-tetrahydroanthraquinone (**49**) as a crystalline (white needles) mixture, mp 177–179 °C. Analysis of the adducts with 270-MHz NMR revealed two singlets at δ 3.94 and 3.96 which were assigned as the methoxyl protons of each adduct and which integrated in ratio of approximately 1:1, respectively. IR (CHCl₃): 3550–3450 (broad), 2950, 2840, 1780, 1755, 1705, 1650, 1590, 1495, 1460 cm⁻¹. NMR (270 MHz, CDCl₃): δ 2.18 and 2.20 (3 H, two s), 2.28–2.67 (3 H, m), 2.85 and 2.93 (1 H, two bd, J = 18 Hz), 3.33–3.44 (1 H, m), 3.48–3.55 (1 H, m), 3.94 and 3.96 (3 H, two s), 6.81 (2 H, d of d, J = 8, 2 Hz), 7.18–7.33 (3 H, m), 7.46 (1 H, bd, J = 7 Hz), 7.57 (1 H, t, J = 7 Hz). Anal. (C₂₃H₂₀O₆S): C, H, S, mol wt.

Preparation of 3-(4'-Methoxyphenylthio)-2,5,9,10-tetraacetoxy-1,4-dihydroanthracene (50) and 2-(4'-Methoxyphenylthio)-3,5,9,10-tetraacetoxy-1,4-dihydroanthracene (51). A 1:1 mixture of **48** and **49** (28 mg, 0.066 mmol) in 0.5 mL of anhydrous benzene was treated successively with 0.2 mL of triethylamine and 0.5 mL of acetic anhydride at room temperature. After stirring for 1 h, the reaction mixture was poured into a separatory funnel that contained chloroform and saturated aqueous sodium carbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was recrystallized from methanol to give 26 mg (73%) of a crystalline mixture of **50** and **51** as off-white feathers, mp 150–200 °C. IR (CHCl₃): 1740, 1720, 1595, 1490, 1280 cm⁻¹. NMR (270 MHz, CDCl₃): δ 2.14, 2.23, 2.27, 2.28, 2.31, 2.37, 2.42, 2.48 (12 H, eight s), 3.30–3.39 (2 H, m), 3.55–3.65 (2 H, m), 3.83 (3 H, s), 6.89 (2 H, d, J = 8 Hz), 7.08 (1 H, d of t, J = 7, 1.5 Hz), 7.35–7.44 (3 H, m), 7.59 (1 H, t, J = 7 Hz). Anal. (C₂₉H₂₆O₉S): C, H, S, mol wt.

Reaction of 2-Acetoxy-3-(4'-methoxyphenylthio)-1,3-butadiene and Juglone (Catalyzed Reaction). Boron trifluoride etherate (50 μ L, 58 mg, 0.40 mmol) was added via syringe to a stirred solution of 420 mg (1.68 mmol) of diene **22**, 293 mg (1.68 mmol) of juglone, and 20 mg of 2,6-di-*tert*-butyl-4-methylphenol in 5 mL of anhydrous methylene chloride at -78 °C (2-propanol/dry ice bath). After stirring for 30 min, the 2-propanol/dry ice bath was replaced with an aqueous calcium chloride/dry ice bath and the temperature allowed to increase to -25 °C over 1.5 h. The reaction mixture was quenched at -25 °C

by the addition of saturated aqueous sodium bicarbonate and then poured into ethyl acetate (200 mL). The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was recrystallized from ethyl acetate to give 435 mg (61%) of adduct **48** as light tan platelets, mp 183–185 °C. IR (CHCl₃): 3550–3400 (broad), 2950, 2840, 1780, 1755, 1700, 1655, 1595, 1498, 1460, 1365, 1250 cm⁻¹. NMR (270 MHz, CDCl₃): δ 2.18 (3 H, s), 2.28–2.67 (3 H, m), 2.85 (1 H, bd, J = 18 Hz), 3.33–3.43 (1 H, m), 3.48–3.55 (1 H, m), 3.96 (3 H, s), 6.80 (2 H, d, J = 8 Hz), 7.10–7.33 (3 H, m), 7.44 (1 H, d, J = 7 Hz), 7.56 (1 H, t, J = 7 Hz). Anal. (C₂₃H₂₀O₆S): C, H, S, mol wt.

Preparation of 1,4-Dihydro-3-(4'-methoxyphenylthio)-2,5,9,10-tetraacetoxyanthracene (50). Triethylamine (0.5 mL) and acetic anhydride (0.5 mL) were successively added via syringe to a stirred solution of 28 mg (0.066 mmol) of adduct **48** in 1.0 mL of anhydrous benzene at room temperature. Stirring was continued at room temperature for 1 h and then the reaction mixture was poured into a separatory funnel that contained chloroform and saturated aqueous sodium carbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was recrystallized from methanol to give 30 mg (84%) of tetraacetate **50** as white feathers, mp 221–224 °C. IR (CHCl₃): 1740, 1720, 1650, 1595, 1490, 1280 cm⁻¹. NMR (270 MHz, CDCl₃): δ 2.14 (3 H, s), 2.28 (3 H, s), 2.31 (3 H, s), 2.48 (3 H, s), 3.07–3.33 (2 H, m), 3.53–3.65 (2 H, m), 3.83 (3 H, s), 6.94 (2 H, d, J = 8 Hz), 7.07 (1 H, d, J = 7 Hz), 7.39 (2 H, d, J = 8 Hz), 7.43 (1 H, d, J = 7 Hz), 7.59 (1 H, d, J = 7 Hz). Anal. (C₂₉H₂₆O₉S): C, H, S, mol wt.

Preparation of 2-Acetoxy-5,10-isopropylidenedioxy-3-(4'-methoxyphenylthio)-9-oxo-1,4,4a(R*),9,9a(S*),10(R*)-hexahydroanthracene (53). Sodium borohydride (65 mg, 1.7 mmol) was added at once to a stirred suspension of 700 mg (1.65 mmol) of adduct **48** in 5 mL of ethyl acetate and 4 mL of absolute ethanol at approximately 0 °C (ice bath). After stirring for 4 h, the reaction was quenched at 0 °C by the dropwise addition of 5% aqueous acetic acid until hydrogen evolution subsided. The solution was poured into a separatory funnel that contained ethyl acetate. The organic phase was separated, washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was suspended in 5 mL of anhydrous acetone and 5 mL of 2,2-dimethoxypropane. Boron trifluoride etherate (100 μ L, 114 mg, 0.74 mmol) was added via syringe to the stirred suspension at 0 °C (ice bath). After stirring for 4 h, the reaction was quenched at 0 °C by the addition of saturated aqueous sodium bicarbonate and then the reaction mixture was poured into a separatory funnel that contained ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was recrystallized from ether to give 486 mg (64%) of **53** as tan needles, mp 142–144 °C. IR (CHCl₃): 3650, 1740, 1680, 1590, 1490, 1460, 1370, 1350, 1280 cm⁻¹. NMR (270 MHz, CDCl₃): δ 1.52 (3 H, s), 1.57 (3 H, s), 1.72–1.88 (1 H, m), 2.07 (3 H, s), 2.13–2.26 (1 H, m), 2.41–2.55 (1 H, m), 2.87–2.98 (2 H, m), 3.20 (1 H, bd, J = 18 Hz), 3.76 (3 H, s), 5.44 (1 H, d, J = 5 Hz), 6.70 (2 H, d, J = 8 Hz), 6.94 (1 H, d of d, J = 8, 1 Hz), 7.37 (2 H, d, J = 8 Hz), 7.54 (1 H, d, J = 8 Hz), 7.83 (1 H, d of d, J = 8, 1 Hz). Anal. (C₂₆H₂₆O₆S): C, H, S, mol wt.

Reaction of 2-Acetoxy-5,10-isopropylidenedioxy-3-(4'-methoxyphenylthio)-9-oxo-1,4,4a(R*),9,9a(S*),10(R*)-hexahydroanthracene with Methylolithium. A solution of 95 mg (0.20 mmol) of **53** in 1.0 mL of anhydrous DME was added via syringe to 0.62 mL (1.00 mmol) of 1.6 M solution of methylolithium in ether at –78 °C (2-propanol/dry ice bath). The reaction mixture was allowed to warm to –20 °C over 1.5 h, quenched directly by the addition of saturated aqueous ammonium chloride, and poured into a separatory funnel containing ethyl acetate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was recrystallized from ether to give 35 mg (39%) of 9-hydroxy-5,10-isopropylidenedioxy-3-(4'-methoxyphenylthio)-9-methyl-2-oxo-1,2,3(S*),4,4a(R*),9(S*),9a(S*),10(R*)-octahydroanthracene as pale green platelets, mp 169–172 °C dec. IR (CHCl₃): 1705, 1640, 1585, 1490, 1440 cm⁻¹. NMR (270 MHz, CDCl₃): δ 1.53 (1 H, q, J = 12.8 Hz), 1.68 (9 H, s), 2.57 (1 H, d of d of d, J = 12.8, 6.0, 3.9 Hz), 2.68 (1 H, d of d, J = 14.3, 6.8 Hz), 3.17 (1 H, d of q, J = 12.8, 3.9 Hz), 3.35 (1 H, d of

d of d, J = 6.9, 3.9, 1.7 Hz), 3.70 (1 H, d of d, J = 14.3, 1.7 Hz), 3.89 (1 H, d of d, J = 12.8, 6.0 Hz), 3.93 (3 H, s), 5.50 (1 H, d, J = 3.9 Hz), 6.93 (2 H, d, J = 8 Hz), 7.19 (1 H, d, J = 7 Hz), 7.40 (1 H, q, J = 7 Hz), 7.48 (2 H, d, J = 8 Hz), 7.66 (1 H, d, J = 7 Hz). Calcd for C₂₅H₂₈O₅S: 440.1657. Found: 440.1647.

Cycloadditions via In Situ Generation of Diene. With Methacrolein. A solution of 68 mg (0.27 mmol) of 1-acetoxy-2-(4'-methoxyphenylthio)cyclobutene (**57**) and 20 mg of 2,6-di-*tert*-butyl-4-methylphenol in freshly distilled methacrolein (0.5 mL) was transferred into a thick-walled glass tube (length 14 cm, inner diameter 5 mm, wall thickness 2 mm). The open end of the tube was connected to a vacuum pump and the solution subjected to three freeze-thaw cycles under reduced pressure (0.1 mm). The evacuated tube was sealed and fitted with a fiberglass jacket. The entire tube was submerged into a silicon oil bath preheated to 155 °C. After 5 h the tube was removed, cooled, and thoroughly rinsed with methylene chloride. The combined rinsings were concentrated in vacuo and purified by preparative TLC (40% ether in hexane) to give 86 mg (99%) of a clear, light yellow oil, R_f 0.4. Analysis of product by NMR revealed two singlets in the ratio of 8:1 at δ 9.42 and 9.32 which were assigned as the aldehyde protons of **20** and **21**, respectively.

With Cyclohex-2-en-1-one. As above, 60 mg (0.24 mmol) of cyclobutene **57**, 69 mg of 2,6-di-*tert*-butyl-4-methylphenol, and 0.5 mL of cyclohex-2-en-1-one gave, after purification by preparative TLC (eight elutions, 40% ether in hexane), 39.5 mg (47%) of a 3:1 mixture of **25a** and **43a** and 15.4 mg (18%) of a 1.5:1 mixture of **24b** and **43b**.

(*Z*)-7-Acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone and (*Z*)-6-acetoxy-7-(4'-methoxyphenylthio)- Δ^6 -1-octalone: IR (CHCl₃) 1750, 1710, 1595, 1485, 1360, 1280 cm⁻¹; NMR (270 MHz, C₆D₆) δ 0.53–0.79 (1 H, m), 0.98–1.45 (4 H, m), 1.57–1.83 (3 H, m), 1.81 and 1.87 (3 H, two s), 2.02–2.20 (2 H, m), 2.48 (1 H, bd of d, J = 18, 5 Hz), 2.78–2.93 (1 H, m), 3.16 and 3.19 (3 H, two s), 6.59 and 6.65 (2 H, two d, J = 8.0 Hz), 7.43 and 7.48 (2 H, two d, J = 8.0 Hz). Calcd for C₁₉H₂₂O₄S: 346.123 87. Found: 346.124 99.

(*E*)-7-Acetoxy-6-(4'-methoxyphenylthio)- Δ^6 -1-octalone and (*E*)-6-acetoxy-7-(4'-methoxyphenylthio)- Δ^6 -1-octalone: IR (CHCl₃) 1745, 1595, 1490 cm⁻¹; NMR (270 MHz, C₆D₆) δ 1.06–1.5 (4 H, m), 1.82 and 1.83 (3 H, two s), 1.63–2.31 (7 H, m), 2.72–2.87 (1 H, m), 3.15 and 3.17 (3 H, s), 6.61 and 6.69 (2 H, two d, J = 8 Hz), 7.39 and 7.55 (2 H, two d, J = 8 Hz). Calcd for C₁₉H₂₂O₄S: 246.123 87. Found: 346.124 16.

Preparation of N-Phenyl-1-oxa-4-thia-1,2,3,4,5,6(R*),7(S*),8-octahydro-6,7-naphthalimide (62). A solution of 61 mg (0.475 mmol) of crude diene **58**, 82.0 mg (0.475 mmol) of maleimide, and 20 mg of 2,6-di-*tert*-butyl-4-methylphenol in carbon tetrachloride was stirred at room temperature for 30 min. The reaction mixture was concentrated in vacuo and the residual oil purified by preparative TLC (50% ether in hexane, two elutions) to give 79 mg (55%) of adduct **62**. IR (CHCl₃): 1840, 1780, 1720, 1655, 1500, 1390 cm⁻¹. NMR (CCl₄): δ 2.50–2.80 (4 H, m), 2.90–3.10 (2 H, m), 3.2–3.4 (2 H, m), 4.20–4.40 (2 H, m), 7.20–7.70 (5 H, m). Calcd for C₁₆H₁₅NO₃S: 301.0773. Found: 301.0776.

Preparation of 6-Acetyl-1-oxa-4-thia- $\Delta^{4a(8a)}$ -octalin (60) and 7-Acetyl-1-oxa-4-thia- $\Delta^{4a(8a)}$ -octalin (61). A solution of 128 mg (1.0 mmol) of crude diene **58** in 1.5 mL of freshly distilled methyl vinyl ketone containing 20 mg of 2,6-di-*tert*-butyl-4-methylphenol was stirred at room temperature for 1 h. Then the reaction mixture was poured into a separatory funnel containing benzene and saturated aqueous sodium bicarbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (25% ether in hexane, three elutions) to give 81 mg (40% for two steps) of a mixture of **60** and **61**. Analysis of the mixture by 270-MHz NMR revealed two singlets at δ 2.09 and 2.11 in the ratio of 1:1 which were assigned as the methyl ketone protons of each adduct. IR (CCl₄): 1715, 1660, 1350 cm⁻¹. NMR (CCl₄): δ 1.3–3.0 (7 H, m), 2.09 and 2.11 (3 H, two s), 2.8–3.1 (3 H, m), 3.9–4.3 (2 H, m). Calcd for C₁₀H₁₄O₂S: 198.071 45. Found: 198.071 63.

Preparation of 5-Formyl-5-methyl-1-oxa-4-thia- $\Delta^{4a(8a)}$ -octalin (69). A solution of 65 mg (0.52 mmol) of cyclobutene **59** and 30 mg of 2,6-di-*tert*-butyl-4-methylphenol in 0.8 mL of freshly distilled methacrolein was reacted according to the procedure for in situ generation of diene to give, after purification by preparative TLC (5% acetone in benzene, two elutions), 63 mg (63%) of **69**. IR (CHCl₃): 1720, 1450, 1375, 1300 cm⁻¹. NMR (270 MHz, C₆D₆): δ 1.28 (3 H,

s), 1.045 (1 H, d of d of d, $J = 13.0, 9.3, 3.3$ Hz), 1.21–1.41 (2 H, m), 1.575 (1 H, d of d of d, $J = 13.0, 7.9, 3.7$ Hz), 1.97 (2 H, t, $J = 6.5$ Hz), 2.21 (1 H, d of d of d, $J = 13.0, 5.3, 2.9$ Hz), 2.39 (1 H, d of d of d, $J = 13.0, 6.6, 3.3$ Hz), 3.31–3.51 (2 H, m), 9.56 (1 H, s). Calcd for $C_{10}H_{14}O_2S$: 198.0715. Found: 198.0714.

Reaction of Cyclobutene 59 and Methyl Acrylate (Deactivated Sealed Tube Experiment). A solution of 112 mg (0.87 mmol) of cyclobutene **59** and 30 mg of 2,6-di-*tert*-butyl-4-methylphenol in 0.5 mL of freshly distilled methyl acrylate was reacted according to the procedure for in situ generation of the diene in a sealed tube which had been rinsed twice with 0.5-mL portions of *O,N*-bis(trimethylsilyl)-acetamide to give, after purification by preparative TLC (two elutions, 50% ether in hexane), 101 mg (79% based upon recovered starting material) of Diels–Alder adducts. Analysis of the adducts by ^{13}C NMR revealed two sets of resonances at δ 143.1 and 141.8 and at δ 98.1 and 96.8 both in the ratio of $\sim 1:1$, which were assigned as the quaternary sp^2 carbons of **64** and **63**, respectively. IR ($CHCl_3$): 1720, 1655, 1430, 1370, 1295 cm^{-1} . NMR ($CDCl_3$): δ 1.60–2.95 (7 H, m), 3.0–3.20 (2 H, m), 3.76 (3 H, s), 4.05–4.55 (2 H, m). ^{13}C NMR (15.1 MHz, $CDCl_3$) 174.17, 143.1 and 141.8, 98.1 and 96.8, 65.2, 51.7, 39.8, 31.0, and 30.8, 28.0, 26.2, 25.7, and 25.4 ppm. Calcd for $C_{10}H_{14}O_3S$: 214.06636. Found: 214.06605.

Reaction of Cyclobutene 59 with Methyl Acrylate (Sealed Tube). As in the procedure for in situ generation of diene, 212 mg (1.66 mmol) of cyclobutene **59** and 30 mg of BHT in 0.5 mL of freshly distilled methyl acrylate gave, after purification by TLC (five elutions, 20% ether in hexane), 165 mg (47%) of a mixture of **63** and **64** and 138 mg (39%) of **68**. The spectral properties of the latter are as follows. IR ($CHCl_3$): 1720, 1640, 1430, 1290 cm^{-1} . NMR ($CDCl_3$): δ 1.60–2.30 (6 H, m), 2.95–3.30 (3 H, m), 3.76 (3 H, s), 4.24–4.44 (2 H, m). ^{13}C NMR (15.1 MHz, $CDCl_3$): 174.3, 146.6, 96.4, 65.5, 51.8, 45.3, 28.6, 27.0, 26.0, 20.0 ppm. Calcd for $C_{10}H_{14}O_3S$: 214.0664. Found: 214.0662.

Reaction of Cyclobutene 59 with Methyl Methacrylate (Sealed Tube). As in the procedure for in situ generation of diene, 160 mg (1.25 mmol) of cyclobutene **59** and 20 mg of BHT in 0.6 mL of freshly distilled methyl methacrylate gave, after purification by preparative TLC (six elutions, 20% ether in hexane), 133 mg (57%) of a 1:1 mixture of **76** and **75** and 82 mg (35%) of **77**. Analysis of the mixture of **75** and **76** by ^{13}C NMR revealed two sets of resonances at δ 37.8 and 27.7 and at δ 31.7 and 31.4 which were assigned as the allylic carbons of each adduct.

75 and 76: IR ($CHCl_3$) 1720, 1665, 1440, 1300 cm^{-1} ; NMR (270 MHz, $CDCl_3$) δ 1.29 (3 H, s), 1.50–2.80 (4 H, m), 3.00 (2 H, d of d, $J = 6.0, 4.0$ Hz), 3.69 (3 H, s), 4.22 (2 H, d of d, $J = 6.0, 4.0$ Hz); ^{13}C NMR (15.1 MHz, $CDCl_3$) 176.9, 141.6, 97.1, 65.2, 51.8, 42.2, 37.8 and 37.7, 31.7 and 31.4, 26.2 (two coincident resonances), 24.0 ppm. Calcd for $C_{11}H_{16}O_3S$: 228.0820. Found: 228.0817.

77: IR ($CHCl_3$) 1840, 1775, 1740, 1670, 1460 cm^{-1} ; NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.5–2.30 (6 H, m), 2.80–3.03 (2 H, m), 3.64 (3 H, s), 4.15–4.40 (2 H, m); ^{13}C NMR (60 MHz, $CDCl_3$) 176.5, 145.7, 102.6, 65.7, 52.0, 47.4, 35.9, 29.1, 25.8, 24.2, 19.0 ppm. Calcd for $C_{11}H_{16}O_3S$: 228.0820. Found: 228.0814.

Preparation of 2-(2-Benzoxethylthio)-3-carbomethoxy-3-methyl-1-cyclohexanone (79). To a stirred solution of 80 mg (0.35 mmol) of **77** in 3 mL of anhydrous acetonitrile at approximately 0 °C (ice bath) was added 0.1 mL of 60% aqueous perchloric acid. The cooling bath was removed and the reaction mixture allowed to warm to room temperature. After stirring at room temperature for 18 h, the reaction mixture was poured into a separatory funnel containing ethyl acetate and saturated aqueous sodium bicarbonate. The organic portion was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was dissolved in anhydrous benzene (0.5 mL) and stirred at room temperature while pyridine (16 μ L) and benzoyl chloride (20 μ L) were successively added via syringe. Stirring was continued at room temperature for 8 h and then the reaction mixture was poured into a separatory funnel containing ether and saturated aqueous sodium carbonate. The organic phase was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residual oil was purified by preparative TLC (3% acetone in chloroform) to give 18 mg (70% based on 10.3 mg of recovered starting material) of 2-(2-benzoxethylthio)-3-carbomethoxy-3-methyl-1-cyclohexanone. IR ($CHCl_3$): 1720, 1710, 1450, 1265 cm^{-1} . NMR (270 MHz, C_6D_6): δ 0.99 and 1.24 (3 H, two s), 1.18–1.80 (4 H, m), 1.88–2.16 (2 H, m), 2.46–2.92 (2 H,

m), 3.22 and 3.32 (3 H, two s), 3.34 and 3.81 (1 H, two s), 4.13–4.44 (2 H, m), 6.88–7.0 (3 H, m), 8.01–8.13 (2 H, m). Calcd for $C_{18}H_{22}O_5S$: 350.1198. Found: 350.1190.

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Supplementary Material Available. Full experimental details for the preparation of compounds **3**, **4**, **5**, **9**, and **11** (2 pages). Ordering information is given on any current masthead page.

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Reaction of Olefins with Palladium Trifluoroacetate

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Abstract: The reaction of palladium trifluoroacetate with acyclic olefins (including monosubstituted olefins) and some alkylidenecycloalkanes led in high yield to π -allylpalladium complexes. The chemo- and regioselectivity of the reaction were examined. Reactions of cyclohexenes led to disproportionation. A catalytic dehydrogenation to substituted benzenes evolved by use of maleic acid as a hydride acceptor. The mechanistic implications with respect to olefin vs. allylic oxidation and oxidation vs. π -allylpalladium formation are discussed.

Introduction

The reaction of olefins with palladium salts has been intensively studied as a result of its relevance to the important Wacker process.¹ For monosubstituted olefins, the major reaction is oxidation, normally to the methyl ketone.^{1,2} For internal olefins, both oxidation of the olefin and at an allylic position are observed.^{1,2} In these olefins, formation of π -allyl complexes sometimes can be accomplished by suitable modification of reaction conditions.³⁻¹⁴ At this point, the factors which control the product (i.e., oxidation vs. π -allyl formation) remain obscure. Our recent interest¹⁵ in the utilization of π -allylpalladium complexes in synthesis led us to explore this competition—especially in conjunction with our interest in generating a catalytic procedure for allylic alkylation.¹⁶

Palladium trifluoroacetate, first prepared by Wilkinson,¹⁷ was unexplored in its reactions with organic substrates. Such a salt has particular interest since, while it is strongly electrophilic, it possesses a nonbasic and relatively nonnucleophilic counterion. The oxidation of olefins appears to involve the attack of an oxygen nucleophile on an olefin-palladium complex,^{2,18} whereas the formation of the π -allyl species has been thought to require a base.^{5,7} The absence of both features in palladium trifluoroacetate makes its reactions with olefins especially instructive.

From a preparative point of view, we required an improved procedure for the synthesis of π -allylpalladium complexes. In our hands, the most general procedure involves the use of palladium chloride, cupric chloride, sodium chloride, and sodium acetate in a mixture of acetic anhydride and acetic acid at 60–90 °C.¹¹ The use of milder conditions and nonacidic

solvents might improve the selectivity of the reaction and facilitate isolation. Most importantly, all methods for formation of such complexes involve an excess of olefin. While it is frequently recoverable, a procedure which allowed a 1:1 olefin:palladium salt ratio clearly is desirable. In this paper, we wish to report a method that fulfills these desires and to describe its limitations. We also report a particularly facile disproportionation of cyclohexenes.

Results

Palladium trifluoroacetate (**1**) is prepared by the reaction of commercially available palladium acetate with excess trifluoroacetic acid¹⁷ or by conversion of palladium chloride to its oxide followed by treatment with trifluoroacetic acid at 80 °C.¹⁹ The former procedure was generally preferred for convenience and better reproducibility. Dissolving β -pinene (**2**) in acetone-*d*₆ and adding palladium trifluoroacetate led, in the NMR spectrum, to rapid replacement of the olefin signals at δ 4.54 by a multiplet at δ 4.40 and broad singlets at δ 3.83 and 3.25 which correspond nicely to the signals of the π -allylpalladium complex **3**. Apparently at room temperature and in a

