Intramolecular Cycloaddition Reactions of Ketenes and Keteniminium Salts with Alkenes

BARRY B. SNIDER

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254

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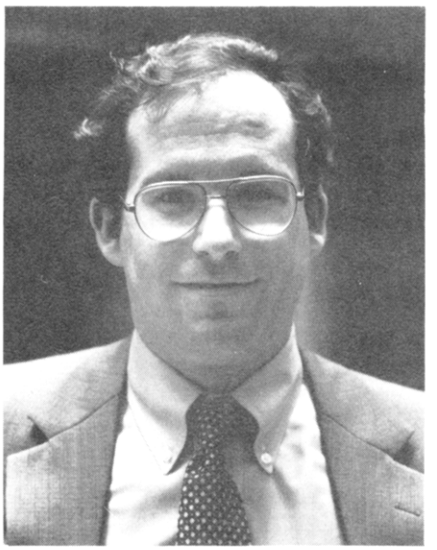
Contents



Barry B. Snider was born in Chicago and is a graduate of the University of Michigan (B.S.) and Harvard University (Ph.D.). After postdoctoral training at Columbia University he joined the faculty of Princeton University. Since 1981 he has been at Brandeis University, where he is now Professor of Chemistry. He has been an Alfred P. Sloan fellow and a Dreyfus teacher scholar. His research interests are in the area of development of new synthetic methods and natural product synthesis. Current interests include Lewis acid induced and catalyzed reactions, ene reactions, oxidative free radical cyclization, and ketene cycloadditions.

I. Introduction

Pericyclic reactions, such as Diels–Alder and ene reactions, and 1,3-dipolar and [2 + 2] cycloadditions, are valuable methods in modern organic synthesis. The intramolecular versions of Diels–Alder, ene, and 1,3-dipolar cycloadditions have been extensively developed over the past decade and have been shown to be very valuable for the synthesis of polycyclic compounds. The first examples of intramolecular [2 + 2] cycloaddition of ketenes to alkenes were reported in the 1960s. Although, numerous isolated examples were reported in the following 20 years, no attempt was made to develop the reaction into a general synthetic method. In the early 1980s several groups began a systematic exploration of this reaction and exploitation of it in the synthesis of complex natural products. These intramolecular cycloadditions and those of the related keteniminium salts are reviewed here.

The intermolecular stereospecific [2 + 2] cycloaddition of ketenes to alkenes is a valuable method for the synthesis of cyclobutanones and compounds that can be derived from them.[1] It is one of the few general methods for the carbofunctionalization of alkenes. The cycloaddition proceeds in poor yield with ketene itself. Cycloadditions of ketenes containing electron-withdrawing substituents such as chlorine, oxygen, or sulfur are more general.[1] Dichloroketene has been most widely used and reacts with a wide variety of alkenes. More recently, excellent results have been obtained with α,β-unsaturated ketenes.

A. Ketene Generation

The general form for an intramolecular ketene cycloaddition is shown in eq 1. A ketene precursor is converted to the ketene. Numerous methods have been used to carry out this transformation. Base-induced elimination of hydrogen chloride from an acid chloride,[3–27] Wolff rearrangement of an α-diazo ketone,[28–34]

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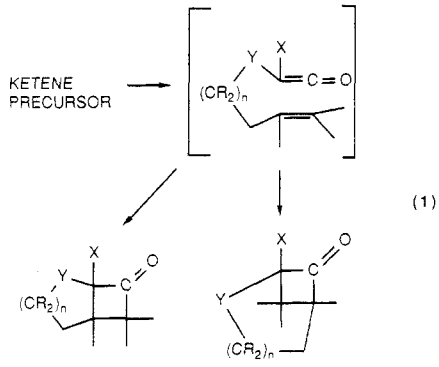
and zinc reduction of an α-chloro acid chloride[35] are some of the more commonly used methods. Pyrolysis of esters,[36-39] 1,5-sigmatropic rearrangements of conjugated dienals,[40,41] ring opening of cyclobutenones,[25] elimination from mixed anhydrides,[42-45] and a variety of photolytic fragmentation processes[45] have been used with good success in special cases.



(1)

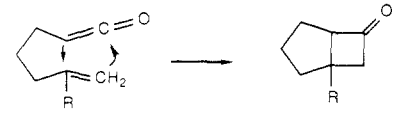
Unlike the addends in Diels–Alder or 1,3-dipolar cycloaddition reactions, ketenes are reactive intermediates that are rarely observed spectroscopically, let alone isolated. Ketenes readily dimerize and oligomerize and react with nucleophiles. The success of an intramolecular cycloaddition is therefore critically dependent on the relative rates of the cycloaddition and unproductive decomposition reactions. These rates are influenced by the choice of substituents, X and Y, on the ketene, the length and nature of the tether, the substituents on the double bond, the concentration of the ketene, and the temperature of the reaction. The most pronounced effects are due to the substituents X and Y on the ketene. The field will therefore be surveyed from this context in approximate chronological order. A brief discussion of the other factors is inserted here since they apply to all classes of ketenes to be discussed.

B. Tether Length

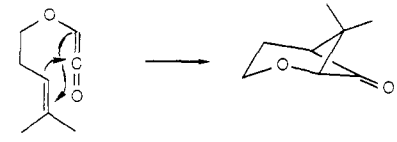
The length and nature of the tether influences $\Delta S^{\ddagger}$ for the cycloaddition without affecting the rate of the decomposition processes. If the ketene and alkene are held in close proximity by a rigid tether, good yields of cycloadducts can be obtained even with aldoketenes, which are generally not suitable addends.[4-10,22,28,29,50] If the ketene and alkene are connected by a floppy tether, other factors must be optimized to obtain an acceptable yield of adduct. Two atom tethers will lead to unstable bicyclo[2.2.0]hexanones or bicyclo[2.1.1]hexanones,[13] products that are rarely observed in these reactions. Intramolecular cycloadditions with three-atom tethers are quite general. Three atom tethers offer the best compromise between strain of product and entropy of activation. The bicyclo[3.2.0]heptanones or bicyclo[3.1.1]heptanones that are produced are relatively unstrained. The entropy of activation with a flexible three-atom tether is significantly less negative than with longer tethers. Cycloaddition reactions with a longer tether are quite rare and have been achieved only with keteniminium salts[10,52] and alkoxyketenes,[11,16] and in cases with conformationally restricted tethers.[18]

C. Effect of Substituents on the Alkene

The mechanism of ketene cycloadditions is still in question.[1] Most of the results are consistent with a Woodward–Hoffmann allowed $[_{\pi}2_s + _{\pi}2_a]$ cycloaddition. Stepwise reactions undoubtedly occur in some cases and may be the rule rather than the exception. Experimentally, it is clear that the ketene is the electrophilic component and the alkene is the nucleophilic component. This has two important consequences. Firstly, the regiochemistry of the cycloaddition is determined by the substitution pattern on the double bond.[11,20] Substrates in which the internal alkene carbon is more substituted will give bicyclo[n.2.0]alkanones (see eq 2). Substrates in which the terminal alkene carbon is more substituted will give bicyclo[*n*.1.1]alkanones (see eq 3). Secondly, the yield of the reaction will be higher with more nucleophilic alkenes.[11] In most cases, compounds containing a disubstituted alkene carbon give higher yields of products than mono- or 1,2-disubstituted alkenes.



(2)



(3)

Cycloadditions of ketenes or keteniminium salts with alkenes are particularly sensitive to steric hindrance. Much higher yields are obtained with trans- than cis-1,2-disubstituted alkenes in intramolecular cycloadditions with certain classes of ketenes.[35] Keteniminium salts, on the other hand, give better yields of cycloadducts with cis-1,2-disubstituted alkenes. Reactions of ketoketenes appear to be particularly sensitive to steric hindrance induced by substituents on the alkene.[24]

D. Reaction Conditions

Success can also be achieved in difficult cases by paying careful attention to reaction conditions. The yield of cycloadduct will depend on the relative rates of cycloaddition and side reactions. The rate of intramolecular cycloaddition is concentration independent. Most of the unproductive side reactions are bimolecular and therefore concentration dependent. Optimal results will therefore be obtained at high dilution.[18] In favorable cases, reactions can be carried out at 0.05–0.2 M.[21] Increased yields may sometimes be obtained by carrying out the cycloadditions at higher temperatures. The bimolecular side reactions with a larger negative $\Delta S^{\ddagger}$ will be relatively favored at low temperatures. Even in cases where ketenes can be generated at or below room temperature, better yields of cycloadducts may be obtained at 80–120 °C.

II. Substituents on the Ketene

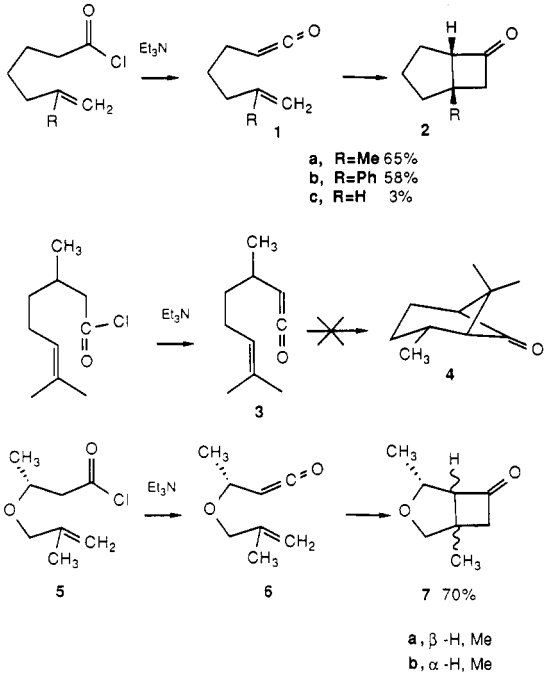
As indicated above, the substituents on the ketene play a profound effect on the nature of the cycloaddition. Only limited success has been obtained with aldoketenes. Substituents such as chlorine or oxygen which lower the energy of the LUMO of the ketene increase the rate of the cycloaddition so that good yields of cycloadducts are generally obtained.[1] Excellent re-

sults have also been obtained with arylketenes and α,β-unsaturated ketenes. It is not clear whether success in these cases is due to acceleration of the cycloaddition or retardation of the side reactions. The cycloadditions of keteniminium salts, pioneered by Ghosez and coworkers, provide an attractive alternative to ketenes in some cases.[10] These reactions, most studied with aldoketeniminium salts and monosubstituted double bonds, proceed in acceptable yield regardless of the length of the tether.

A. Aldoketenes

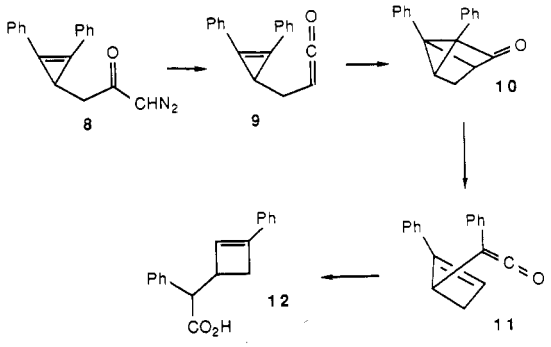
1. Thermal Cycloadditions

Aldoketenes undergo rapid dimerization and oligomerization reactions. These side reactions have prevented their use in intermolecular cycloadditions and have limited their use in intramolecular cycloadditions. Baldwin,[5] Cheer,[6] and Agosta[53] investigated the role of intramolecular cycloadditions of ketenes in the homo-Favorskii rearrangement. They demonstrated that ketenes **1a** and **1b**, generated by treatment of the acid chloride with Et_3N, gave cycloadducts **2a** and **2b** in 65% and 58% yield, respectively, but that ketenes are not involved in the homo-Favorskii rearrangement. On the other hand, Greuter and Ghosez[10] demonstrated that ketene **1c**, prepared from the acid chloride, gave cyclobutanone **2c** in only 3% yield and we have shown that ketene **3** does not give **4**.[11] Mori has made use of the intramolecular cycloaddition of ketene **6** in the synthesis of (+)- and (−)-grandisol.[22] Treatment of **5** with Et_3N in CH_2Cl_2 gave a 3:1 mixture **7a** and **7b** in 70% yield.



These results demonstrate the limitations of aldoketenes in intramolecular cycloadditions. Even with an optimal three-carbon tether, satisfactory results are only obtained with the most nucleophilic 1,1-disubstituted alkenes. Much greater success has been obtained in systems in which the ketene is held in close proximity to the alkene by a rigid tether.

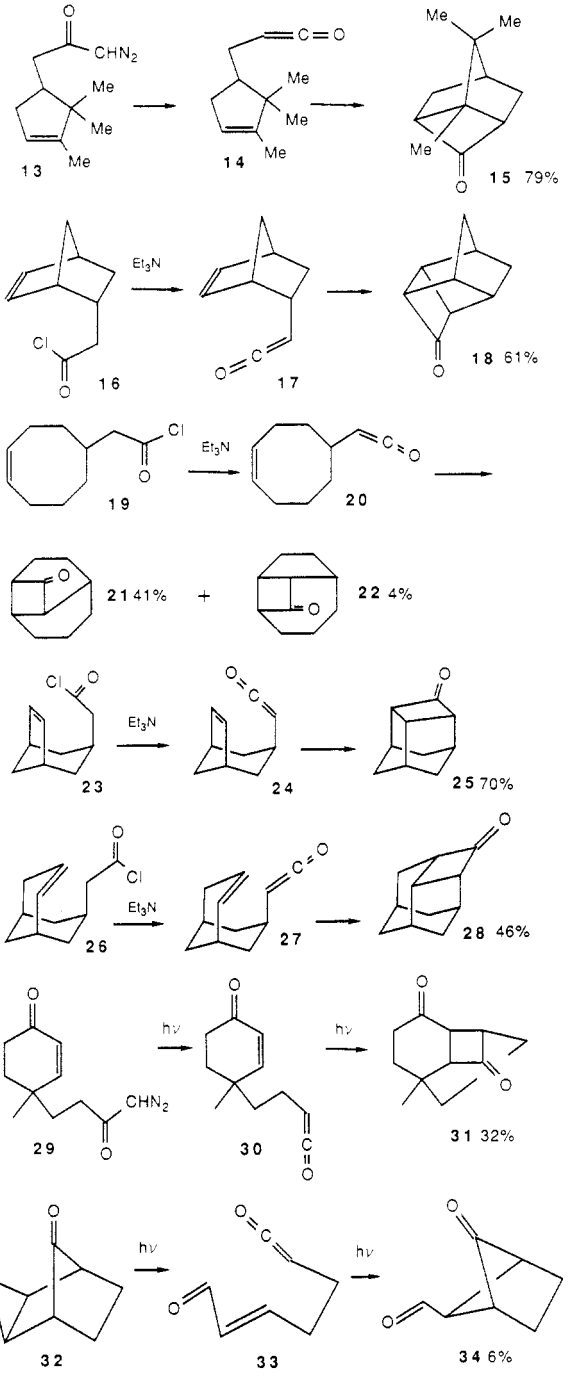
Masamune found that either photochemical or silver-catalyzed Wolff rearrangement of diazo ketone **8** gave ketene **9**, which reacted further to give the strained, unstable cycloadduct **10**.[28] Cycloadduct **10** could be isolated, but not purified. It underwent ring opening to give the isomeric ketene **11**, which could be trapped as acid **12**.



Yates found that photochemical Wolff rearrangement of diazo ketone **13** gave ketene **14**, which underwent cycloaddition to give **15** in 79% yield.[29] Ketene **14** could also be generated by treatment of the acid chloride with Et_3N. Sauers demonstrated that treatment of acid chloride **16** with Et_3N gave ketene **17**, which underwent cycloaddition to give **18** in 61% yield.[4] Moon established that treatment of acid chloride **19** with Et_3N gave ketene **20**, which reacted further to give a 10:1 mixture of **21** and **22** in 45% yield.[7] Murray found that treatment of acid chloride **23** with Et_3N gave ketene **24**, which reacted further to give cycloadduct **25** in 54–76% yield,[8] while Sasaki found that treatment of the homologous acid chloride **26** with Et_3N gave ketene **27**, which reacted further to give cycloadduct **28** in 46% yield.[9] The regioisomeric adduct was not observed. These results clearly indicate that aldoketenes are suitable addends for intramolecular cycloadditions in systems with tethers that restrict rotational freedom.

2. Photochemical Addition of Aldoketenes to the Double Bonds of α,β-Unsaturated Carbonyl Compounds

Becker and co-workers have reported a series of cycloadditions of ketenes to the double bond of 2-cyclohexenones.[30,31,33] Photolysis of diazo ketone **29** through a Pyrex filter in cyclohexane containing 0.01 M benzene as a triplet sensitizer gave ketene 30. Futher absorption of light converted the unsaturated ketone of **30** to its excited state, which added to the double bond of the ketene to give **31**. Ketene **30** generated by nonphotolytic methods did not add to the electron-deficient double bond of the enone. This reaction is not a thermal cycloaddition of a ketene to an alkene but rather a photochemical addition of an enone to a double bond which happens to be part of a ketene. This reaction is successful only in those cases with a three-atom tether connecting the unsaturated ketone to the ketene. The carbonyl carbon of the ketene adds exclusively to the β-carbon of the unsaturated ketone to give products with a 1,4-dicarbonyl group. This reaction is not successful with either ketoketenes or 2-cyclopentenones. The additional examples reported by Becker are shown in Table I. Agosta described a related example.[53] Photolysis of epoxy ketone **32** gave ketene **33**, which underwent cycloaddition to give adduct **34** in ≈6% yield.

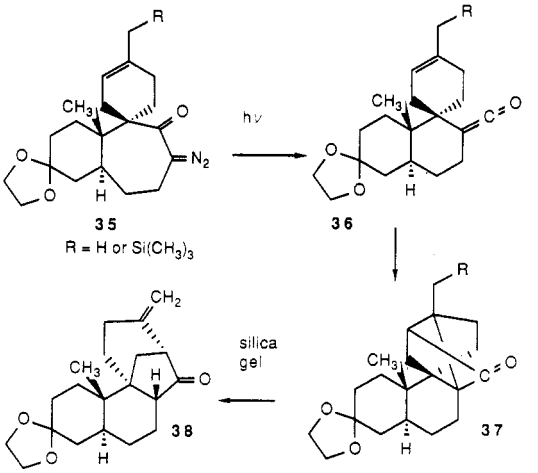


B. Ketoketenes

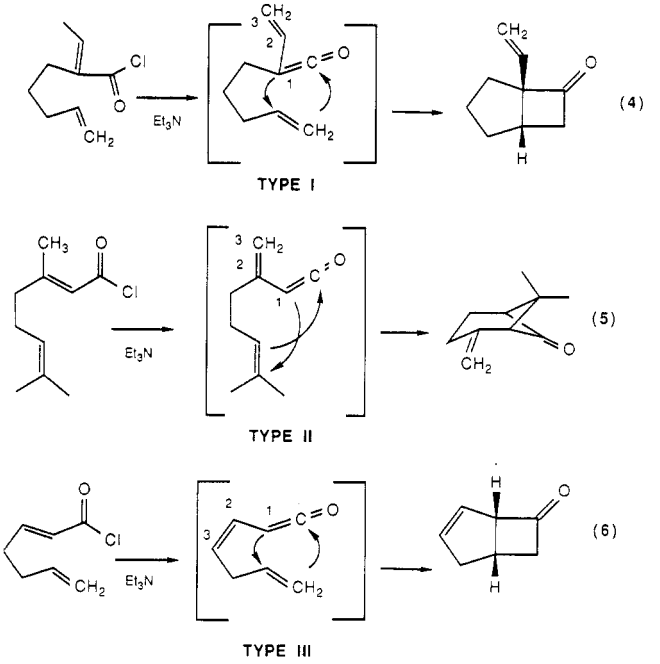
Reports of successful intramolecular cycloadditions of ketoketenes are rarer than those with aldoketenes. Introduction of the second alkyl substituent of a ketoketene increases steric hindrance and raises the LUMO energy of the ketene, making the cycloaddition more problematic. Success has been achieved in systems where the ketene is held in close proximity to the double bond. Ireland reported that photolysis of diazoketone **35** in ether at −75 °C gave **37** via the intermediacy of ketene **36**. Treatment of **37** (R = $Si(CH_3)_3$) with silica gel gave the aphidocolin intermediate **38**.[34]

C. α,β-Unsaturated Ketenes

Intramolecular cycloadditions of α,β-unsaturated ketenes have proven to be much more general than those of saturated aldo- or ketoketenes. The role of the



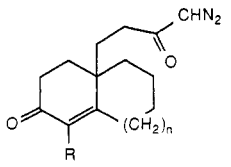
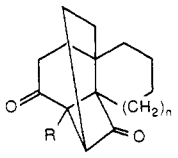
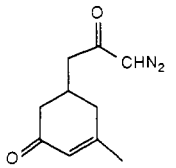
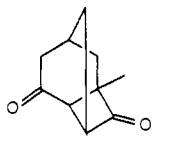
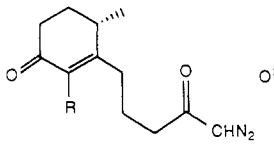
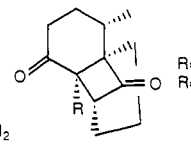
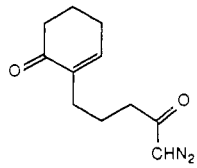
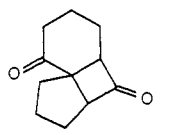
conjugated double bond may be to accelerate the cycloaddition by lowering the HOMO energy or simply to retard dimerization, oligomerization, and other side reactions. Conjugated ketenes are particularly attractive addends since the alkene-containing side chain can be attached to the vinylketene at three different positions (see eq 4–6) and the resulting vinylcyclobutanones are versatile synthetic intermediates.



We have classified these three types of reactions as type I, II, or III depending on whether the alkene-containing side chain is attached to carbons 1, 2, or 3 of the unsaturated ketene. Type III cycloadditions (eq 6) should be quite facile since the double bond restricts conformational freedom in the tether. However, only the thermodynamically less stable cis isomer can undergo a cycloaddition. In type I and II cycloadditions, the double bond has little effect on conformational freedom in the tether. Type I cycloaddition of necessity involve ketoketenes. Type II or III cycloadditions can use either aldo- or ketoketenes.

The 2-vinylcyclobutanones produced in these cyclobutanones are versatile synthetic intermediates. Ring expansion of 2-vinylcyclobutanones to give five-, six-, and eight-member rings have been developed by Cohen,[54] Danheiser,[55] Dreiding,[56] and Gadwood.[57] The

TABLE I. Photochemical Addition of Ketenes to Unsaturated Ketones

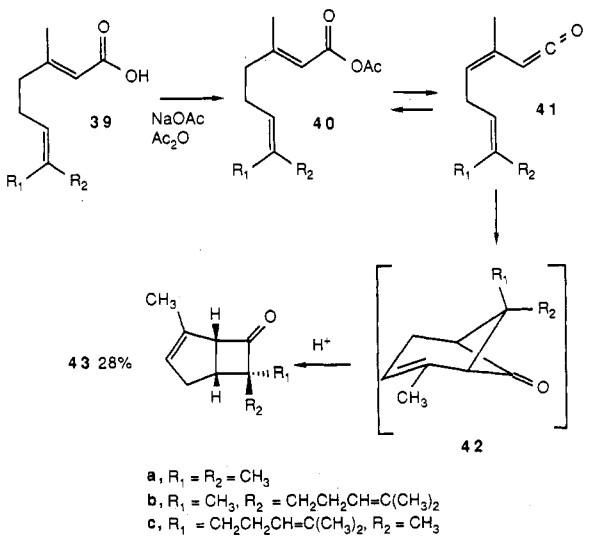
diazo ketone	product (% yield)
	 R=H, n=1 31% R=H, n=2 40% R=Me, n=1 30%
	 28%
	 R=H 34% R=Me 30%
	 39%

application of these reactions in total synthesis has been limited by the inaccessibility of 2-vinylcyclobutanones, a situation ameliorated by the development of intramolecular ketene cycloadditions.

1. Type III Cycloadditions of α,β-Unsaturated Ketenes

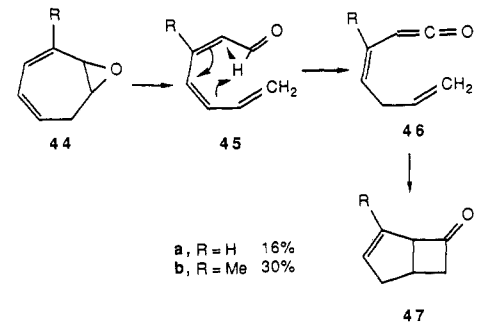
The general form of a type III intramolecular cycloaddition is shown in eq 6. Attachment of the tether to the β-carbon of the unsaturated ketene requires that the conjugated double bond be cis, complicating the synthesis of the ketene. However, once the ketene is formed, cycloaddition should be very facile since the presence of a cis double bond in the tether will decrease rotational freedom resulting in a less negative entropy of activation.

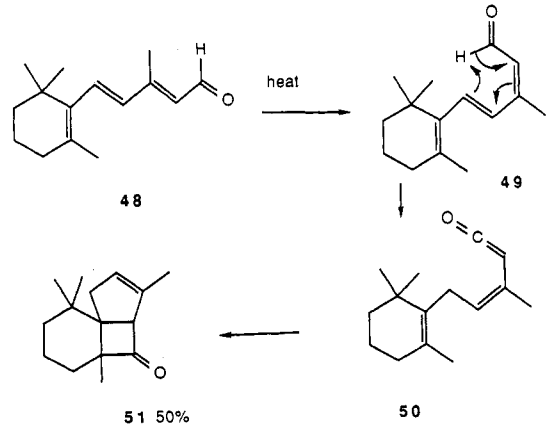
The earliest known intramolecular ketene cycloadditions fall into this class. Beereboom reported that treatment of geranic acid (**39a**) with acetic acid and sodium acetate at reflux gave filifolone (**43a**) in 28% yield.[42] More recently, this reaction was extended to both (6*E*)- and (6*Z*)-farnesic acid (**39b** and **39c**), which stereospecifically gave **43b** and **43c**, respectively.[43] Erman et al. have studied the mechanism of this reaction.[58] They proposed that **39a** is converted to the mixed anhydride **40a**, which loses acetic acid to give **41a**, which cyclizes to give chrysanthenone (**42a**). Under the reaction conditions chrysanthenone is not stable but rearranges to filifolone (**43a**) by a series of Wagner–Meerwein shifts initiated by protonation of the carbonyl group. In support of this mechanism they showed that treatment of **42a** with acetic acid or boron trifluoride etherate led to a mixture containing a significant amount of **43a**. This mechanistic proposal has been born out by more recent studies.[21,23] Ketene **41** should add to the double bond to give the bicyclo[3.1.1]heptanone **42** rather than the bicyclo[3.2.0]heptanone **43**.



a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$, $R_2 = CH_2CH_2CH{=}C(CH_3)_2$
c, $R_1 = CH_2CH_2CH{=}C(CH_3)_2$, $R_2 = CH_3$

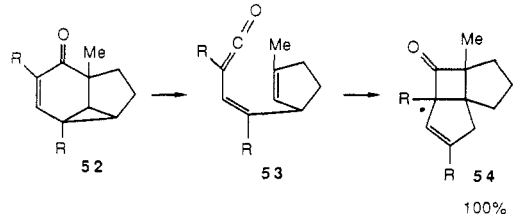
Schiess and Wisson reported that pyrolysis of **44a** at 0.1 Torr at 315 °C gave a 16% yield of **47a** and many other products.[40] Ring opening occurred to give trienal **45a**, which underwent a 1,5-sigmatropic rearrangement to give **46a**, which reacted to give the expected cycloadduct. Similar pyrolysis of the methyl derivative **44b** gave a 30% yield of **47b** and traces of isomers containing the methyl group at other positions. Geluk and co-workers have established that distillation of β-ionylideneacetaldehyde (**48**) in vacuo gave a 50% yield of the cycloadduct **51**.[41] Reversible isomerization leads to the (*Z*)-aldehyde **49**, which undergoes a 1,5-sigmatropic hydrogen shift to give unsaturated ketene **50**, which undergoes an intramolecular cycloaddition to give **51**. 1,5-Sigmatropic rearrangement of dienals must lead exclusively to the *Z*-conjugated ketene and is therefore an attractive method for the preparation of precursors for type III cycloadditions.



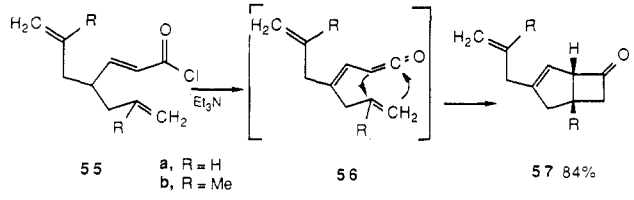


Schultz and co-workers reported that photolysis of ketone **52** (R = Me) at 360 nm gave cyclobutanone **54**

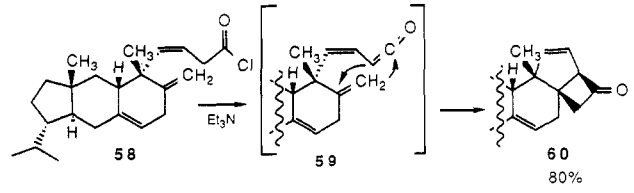
(R = Me) in quantitative yield via the intermediacy of unsaturated ketene **53**.[51] In this example a *Z*-conjugated ketene and an alkene are stereospecifically produced by a photochemical retro [4 + 2] cycloaddition of a 2-cyclohexenone. Different products are obtained if R = *tert*-butyl or trimethylsilyl.



Preparative examples of this class of cycloaddition are due to Ernst and Greuter who prepared cyclobutanone **57a** in 83% yield via the intermediacy of ketene **56a** by treatment of α,β-unsaturated acid chloride **55a** with Et_3N.[10] Similar treatment of **55b** gave **57b** in 84% yield. The problem of stereochemical control of the conjugated ketene was circumvented by placement of two identical substituents on the γ-position of **55** so that a symmetrical unsaturated ketene is formed.

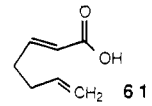
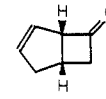
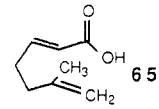
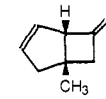
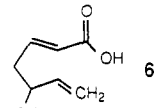
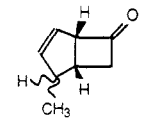
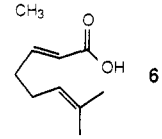
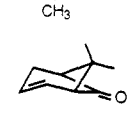
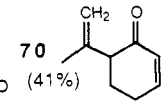
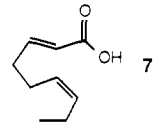
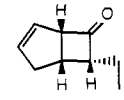
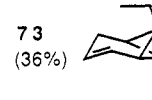
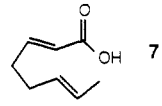
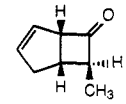
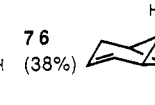
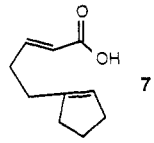
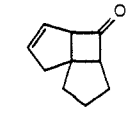
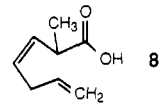
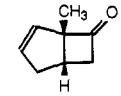


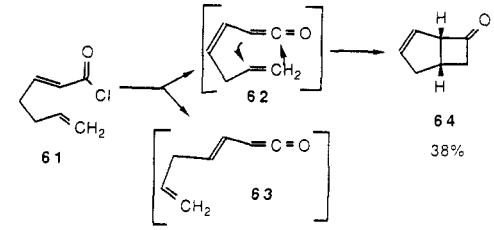
Corey, Desai, and Engler used a type III cycloaddition as a key step in their synthesis of retigeranic acid.[12] β,γ-Unsaturated acid chloride **58** was prepared by a Wittig reaction with the acid protected as a cyclic ortho ester, followed by introduction of the *exo*-methylene double bond. Treatment of **58** with Et_3N gave **60** in 80% yield via the intermediacy of ketene **59**. This Wittig procedure provides a general route to cis-β,γ-unsaturated acid chlorides from aldehydes. Preparation of precursors for type III cycloadditions will require the use of β,γ-unsaturated aldehydes in the Wittig reaction. Unfortunately, only α,α-disubstituted β,γ-unsaturated aldehydes, which cannot isomerize, can be used. Therefore this Wittig reaction could not be used, for instance, to prepare the unsubstituted ketene in eq 6.



We have explored alternative methods to generate *Z*-unsaturated ketenes.[15,26] Treatment of trans-α,β-unsaturated acid chlorides such as **61** with Et_3N in benzene at reflux gave a 1:1 mixture of ketenes **62** and **63**. The *Z*-ketene of **62** reacted with the double bond to give **64**, which is obtained in 38% overall yield from the acid precursor to **61**. These results establish that, unlike the deprotonation of related esters with LDA,[59] deprotonation of α,β-unsaturated acid chlorides does not lead selectively to the *Z* isomer. However, the accessibility of the trans-α,β-unsaturated acid chloride, the operational simplicity of this method, and the ease of separation of the desired cyclobutanone from the more polar byproducts makes this an attractive method well-suited for exploration of the scope and limitations of type III cycloadditions.

TABLE II. Type III Intramolecular Cycloadditions of Unsaturated Ketenes and Alkenes

acid	cyclobutanone (% yield)
 61	 64 (38%)
 65	 66 (43%)
 67	 68a (29%) β-Me 68b (8%) α-Me
 69	 70 (41%)  71 (16%)
 72	 73 (36%)  74 (7%)
 75	 76 (38%)  77 (9%)
 78	 79 (50%)
 80	 81 (48%)

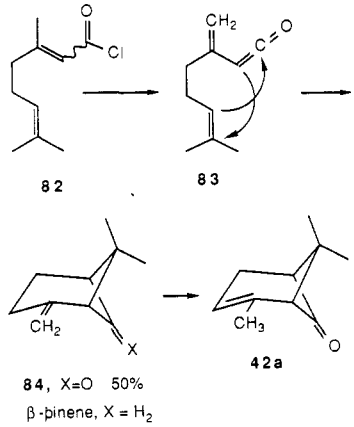


Several examples of intramolecular type III cycloadditions of α,β-unsaturated ketenes prepared by this procedure are shown in Table II. The regiochemistry of the cycloaddition is controlled by the electronic effects of the substituents on the double bond. The least substituted end of the double bond adds to the carbonyl group of the ketene. Introduction of two methyl groups on the terminal end of the double bond leads, as expected,[1] exclusively to the bicyclo[3.1.1]heptane apochrysanthenone (**70**). If the double bond is present in a ring, as in acid **78**, then a tricyclic cyclobutanone **79**, a model for the synthesis of triquinane sesquiterpenes, is formed in 50% yield. Cycloaddition of the ketenes derived from acids **72** and **75** are stereospecific, but lead to a mixture of regioisomers in which the bicyclo-

[3.2.0]heptanone predominates. Type III cycloadditions can also be carried out with the ketoketene prepared from acid **80**. Like many other intramolecular cycloadditions of ketenes,[10] the reaction fails with four-carbon tethers.

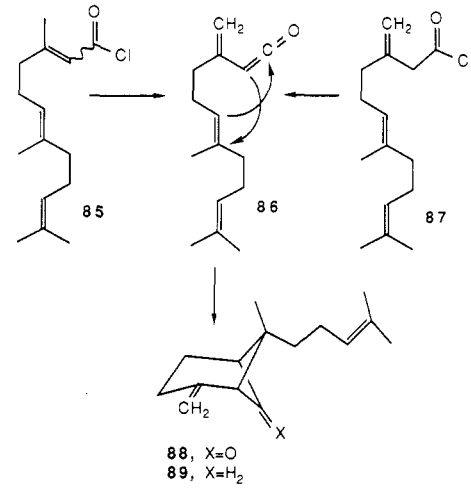
2. *Type II Cycloadditions of α,β-Unsaturated Ketenes*

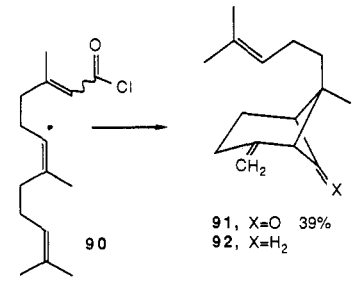
The general form of a type II intramolecular cycloaddition is shown in eq 5. We found that α,β-unsaturated ketene **83** can be prepared regioselectively by treatment of either stereoisomer of acid chloride **82** with Et_3N in toluene or benzene at reflux. Deprotonation occurs largely on the less substituted γ-carbon (methyl > methylene > methine) due to the greater kinetic acidity of protons on a less substituted alkyl group. This regioselectivity had previously been demonstrated by Bedoukian and Wolinsky for the *E* isomer only.[60] For instance, treatment of geranoyl chloride (**82**) with Et_3N in toluene at reflux gave a 40–50% yield of **84** and only ≈5% of the isomer **42a** containing an endocyclic double bond. Cycloadduct **84** can be converted to chrysanthenone (**42a**) by isomerization over palladium and to β-pinene by Wolff–Kishner reduction. The formation of **84** from **82** is particularly remarkable in view of the exclusive formation of **43a** via bicyclo[3.1.1]heptenone **42a** from the mixed anhydride of acetic and geranic acids. This is consistent with kinetically controlled formation of **83** from **82** and reversible thermodynamically controlled formation of **41a** from **40a**.



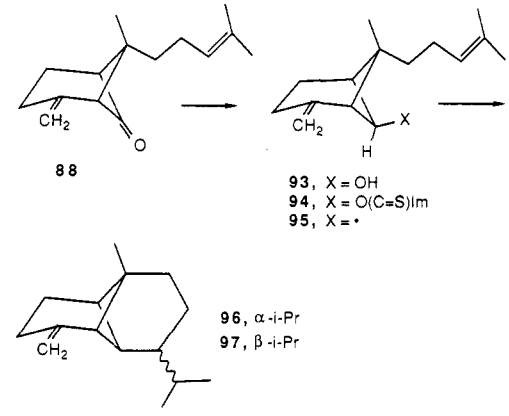
Both we and Corey have used this reaction for a short synthesis of β-*trans*-bergamotene (**89**).[13,14,21] Treatment of (6*E*)-farnesoyl chloride **85** with Et_3N in toluene at reflux gave a 49% yield of **88** via the intermediacy of ketene **86**.[13,21] Corey and Desai prepared **88** in 43% yield by treatment of acid chloride **87** with diisopropylamine in toluene at reflux.[14] This procedure generates ketene **86** unambiguously, but requires the preparation of β,γ-unsaturated acid chloride **87**. Wolff–Kishner reduction of **88** gave β-*trans*-bergamotene (**89**). In a similar manner (6*Z*)-farnesoyl chloride (**90**) was converted to **91** and thence to *cis*-β-bergamotene **92**.[13,21]

The bicyclo[3.1.1]heptanone **88** appeared to be a very attractive intermediate for the synthesis of β-copaene (**96**) and β-ylangene (**97**) since completion of the synthesis would only require formation of a bond between the carbonyl carbon and proximal end of the double bond with a concomitant four electron reduction.[21,61]



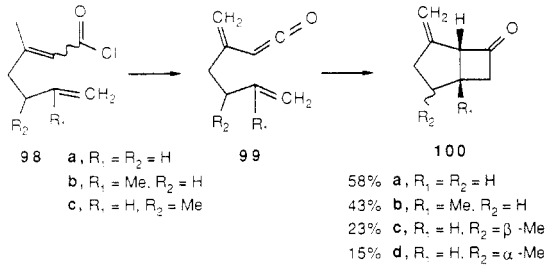


The Barton–McCombie method[62] for the deoxygenation of secondary alcohols appeared to offer an attractive method to accomplish this transformation. Reduction of **88** with LAH gave **93** in 84% yield, which was converted to the thiocarbonyl imidazolide **94** in 76% yield. Addition of a mixture of **94**, 2 equiv of *n*-Bu_3SnH, and 0.1 equiv of AIBN in toluene to a solution of toluene at reflux over 12 h resulted in fragmentation to give the radical **95**, which added to the double bond prior to abstraction of a hydrogen to give a 46% yield of a 1:1 mixture of β-copaene (**96**) and β-ylangene (**97**).

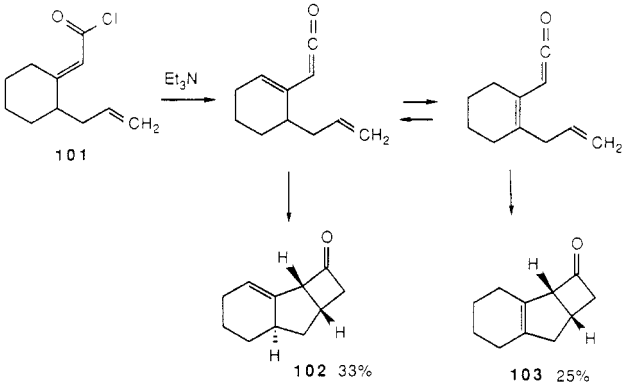


Bicyclo[3.2.0]heptan-6-ones can also be prepared by type II cycloadditions. Treatment of acid chlorides **98a** and **98b** with Et_3N in toluene at reflux gave adducts **100a** and **100b** in 58% and 43% yield, respectively.[23] Small, variable amounts of the isomer with an endocyclic double bond were also isolated. Acid chloride **98c** gave a 39% yield of a 1.5:1 mixture of **100c** and **100d**.

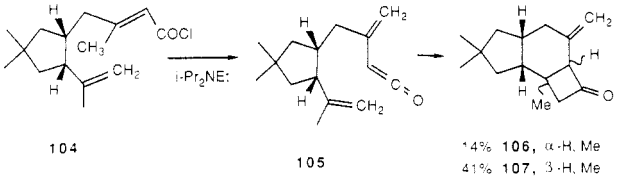
To our surprise, similar treatment of acid chloride **101** gave a 33% yield of **102** and a 25% yield of **103**.[23] The formation of **103** was not anticipated since proton abstraction should have occurred selectively from the more acidic methylene group. We established that an identical mixture of products was obtained from the *Z*



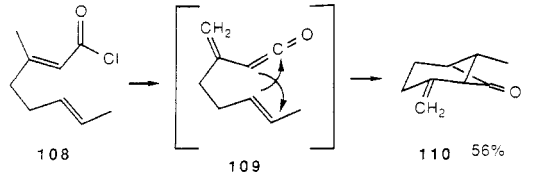
isomer of **101** and that abstraction of a proton from the methylene group is the kinetically preferred process. Apparently, in this case equilibration of α,β-unsaturated ketenes is faster than cycloaddition.



Oppolzer and Nakao converted acid chloride **104** to a 1:3 mixture of adducts **106** and **107** in 57% yield as a key step in the synthesis of 6-protoilludene.[18] This is a rare example of the successful use of an intramolecular ketene cycloaddition to prepare a bicyclo[4.2.0]octanone. The reaction is probably successful because the four-atom tether is conformationally restricted and the ketene is prepared in dilute solution (0.003 M).

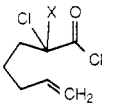
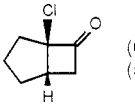
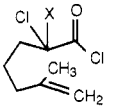
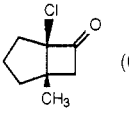
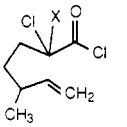
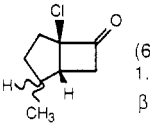
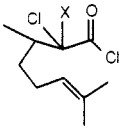
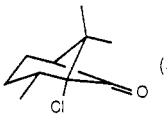
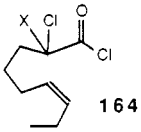
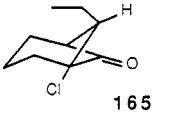
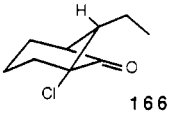
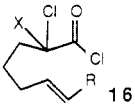
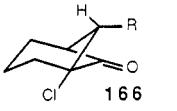


The cycloaddition of ketene **109** was examined to determine the regioselectivity of the cycloaddition with 1,2-disubstituted double bonds. Treatment of acid chloride **108** with Et_3N in benzene at reflux for 2 h gave only bicyclo[3.1.1]heptanone **110** in 56% yield.[35] No cycloadduct was obtained from the isomeric ketene with a cis double bond. This result contrasts markedly with that obtained in the type III reactions described above in which both stereoisomers give comparable yields of cycloadducts and the bicyclo[3.2.0]heptanone predominates.



Why does the *trans*-ketene **109** undergo cycloaddition in good yield while the cis isomer does not? *cis*-Alkenes

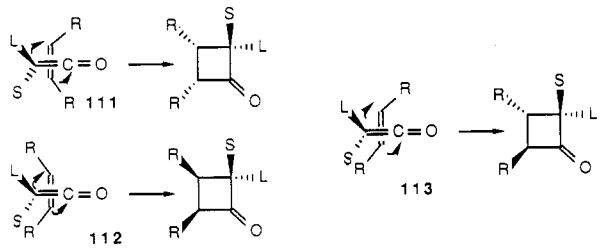
TABLE III. Intramolecular Cycloadditions of Chloroketenes and Alkenes

acid chloride	X = H (Et_3N) X = Cl (Zn)	cyclobutanone (% yield)
	X = H X = Cl	 (68%) (58%)
	X = Cl	 (64%)
	X = Cl	 (65%) 1.6:1 β,α-Me
	X = H	 (55%)
 164	X = H X = Cl	 (26%) (20%) 165
		 (14%) (10%) 166
 167	X = Cl	 166

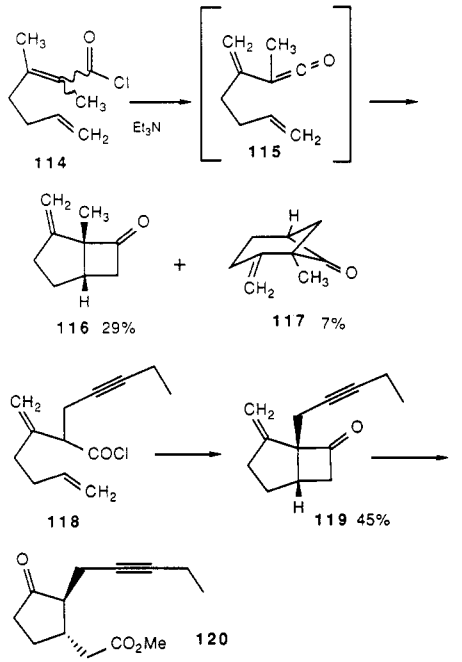
R = Et (57%), R = Me (66%)

are much more reactive than *trans*-alkenes in intermolecular cycloadditions with ketenes.[1] Cycloadditions with *cis*-alkenes are always stereospecific, while loss of stereochemistry has occasionally been observed with *trans*-alkenes.[1] These results have been used as evidence for a concerted reaction proceeding through a [$_\pi2_s$ + $_\pi2_a$] transition state. Intermolecular cycloaddition of a ketene with a *cis*-alkene can occur through unhindered transition state **111** or very hindered transition state **112**, where S and L are the small and large substituents on the ketene. The stereochemistry of the cycloadducts confirms that cycloaddition proceeds through **111**. Intermolecular cycloaddition of a ketene with a *trans*-alkene must occur through the moderately hindered transition state **113**. This cycloaddition is slower due to steric hindrance. Loss of stereocontrol will occur when steric hindrance is sufficient to allow stepwise reaction to occur at a competitive rate.[1] In contrast, similar analysis suggests that *trans*-alkenes should be more reactive than *cis*-alkenes in intramolecular cycloadditions. Intramolecular cycloaddition of a ketene with a *trans*-alkene will still occur through the moderately hindered transition state **113**. However, intramolecular cycloaddition of a ketene with a *cis*-alkene must occur through the very hindered transition state **112** since the unhindered transition state **111** is not accessible with a three-atom tether.

Type II intramolecular cycloadditions of ketoketenes offer new insights into this reaction. Treatment of acid



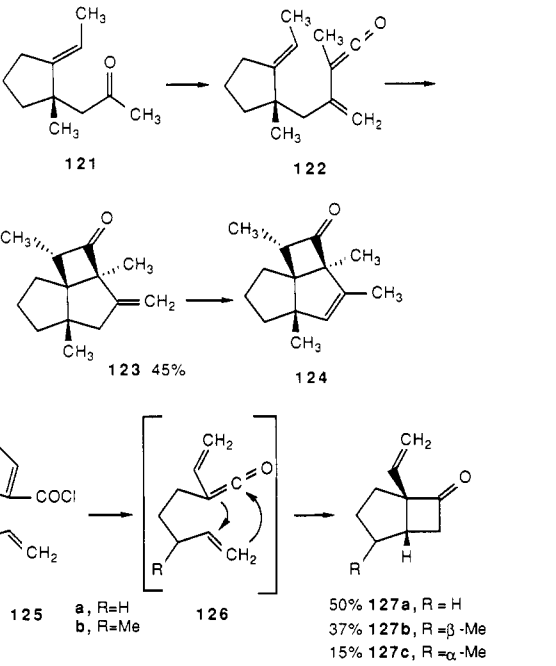
chloride **114** with Et_3N gave ketene **115**, which reacted further to give a 4:1 mixture of the expected adduct **116** and **117**.[24] This is an unusual case where the substituents on the double bond do not fully control the regiochemistry of the cycloaddition. Treatment of **118** with Et_3N gave a 4:1 mixture of **119** and the isomer corresponding to **117** in 45% yield. Ozonolysis of **119** and cleavage of the resulting diketone with methanolic potassium carbonate gave methyl dehydrojasmonate (**120**) in 47% yield.



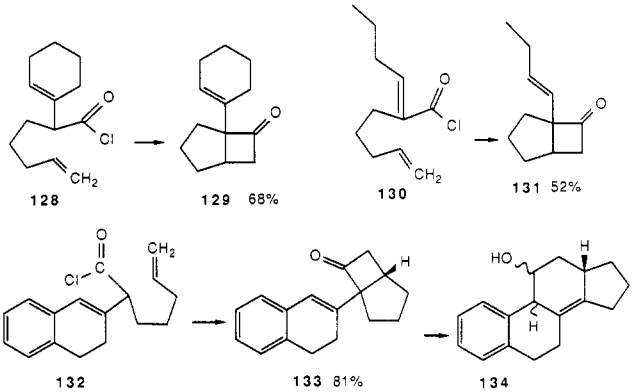
We have used this cycloaddition to prepare a late intermediate in Wenkert's isocomene synthesis.[63] Reaction of ketone **121** with the lithium salt of ethyl 2-(trimethylsilyl)propionate, hydrolysis of the ester, conversion of the acid to the acid chloride, and reaction of the acid chloride with Et_3N gave cyclobutanone **123** in 45% overall yield via the intermediacy of ketene **122**.[64] Isomerization of the double bond of **123** could be accomplished by treatment with hydriodic acid in benzene to give Wenkert's intermediate **124**.[64]

3. Type I Cycloadditions of α,β-Unsaturated Ketenes

Substrates for type I intramolecular cycloadditions are easily prepared by alkylation of α,β-unsaturated esters.[15,25] Alkylation of methyl crotonate with 5-bromo-1-pentene, conjugative hydrolysis of the ester, and conversion to the acid chloride gave **125a**. Treatment of **125a** with Et_3N in toluene at reflux gave **127a** in 50% yield via ketene **126a**. Similar treatment of **125b** gave a 2.5:1 mixture of **127b** and **127c** in 52% yield. Bicycloheptanone **127b** has been prepared by a longer route by Gadwood and used as a key intermediate in the synthesis of poitediol.[57b]

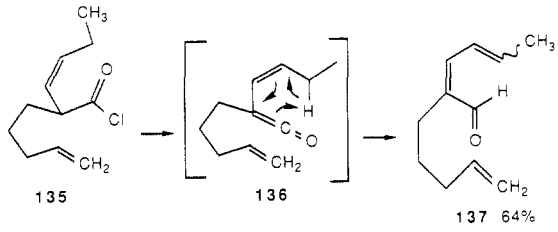


Treatment of acid chlorides **128**, **130**, and **132** with Et_3N give cyclobutanones **129**, **131**, and **133**, in yields of 68%, 52%, and 81% via the intermediacy of the ketene.[25] Reduction of **133** and treatment of the resulting alcohol with potassium hydride as described by Cohen[54] and Danheiser[55] gave **134** resulting from 1,3-sigmatropic rearrangement.[25] This approach should be readily applicable to the synthesis of A-ring aromatic steroids.

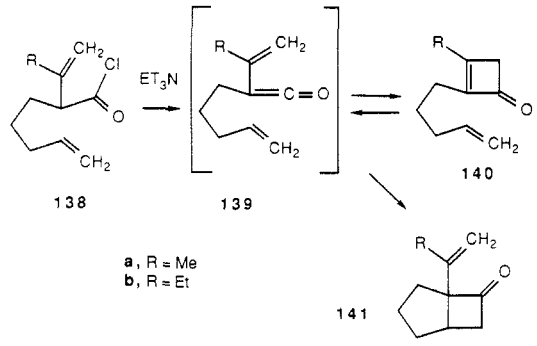


The reactions of α,β-unsaturated ketene **136** demonstrated a potential side reaction when there is a *cis*-alkyl substituent on the conjugated ketene.[25] Conversion of acid chloride **135** to ketene **136** proceeds normally. However, **136** does not undergo a cycloaddition but instead undergoes a 1,5-sigmatropic hydrogen shift to give dienal **137** in 64% yield as a 5:1 mixture of 4*E* and 4*Z* isomers. We have not observed 1,5-sigmatropic hydrogen shifts in the reactions of corresponding *Z*-α,β-unsaturated aldoketenes generated by the same method. The additional substituent on the ketene carbon in ketoketenes facilitates the sigmatropic hydrogen shift by retarding oligomerization and, probably more importantly, by stabilizing the s-cis conformer relative to the s-trans conformer. Only the s-cis conformer can undergo a 1,5-sigmatropic hydrogen shift.

Unsaturated ketenes **139a** and **139b** demonstrate another alternative mode of reaction for α,β-unsaturated ketenes.[25] Treatment of **138a** with Et_3N in tolu-



ene at reflux for 3 h gave a 56% yield of cyclobutenone **140a**. The interconversion of unsaturated ketenes and cyclobutenones is a well-known thermally allowed concerted reaction.[55b,65] It has often been used for the preparation of unsaturated ketenes. It is not generally suitable for the preparation of cyclobutenones. At higher temperatures the conversion of **139a** to **140a** is reversible and the reaction can be driven to the more stable bicycloheptanone **141a**. Heating **140a** for 4 days at 125–130 °C gave a 76% yield of **141a**. Similar results were obtained with **138b**.

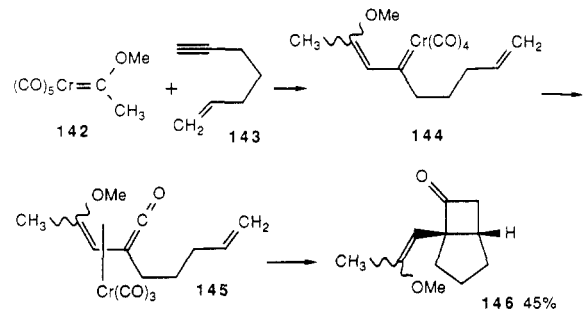


Electrocyclic ring closure of **139** to give **140** is faster than cycloaddition to give **141**. On the other hand, the cycloaddition is faster than ring closure for the closely related unsaturated ketenes described above. This difference in behavior appears to be due to faster electrocyclic ring closure for **139** than for the other ketenes. Electrocyclic ring closure occurs in good yield only with α,β-unsaturated ketenes containing a substituent on both the ketene and α-carbons and an unsubstituted β-carbon. Substituents on the ketene and α-carbon will perturb the equilibrium between the s-cis and s-trans conformers. Alkyl substituents at all three positions will perturb both the cycloaddition and electrocyclic ring closure due to electronic effects. Although the reasons for the perturbation of relative rates of cycloaddition and electrocyclic ring closure by alkyl substituents are obscure, the empirical rule fits all of the available data.

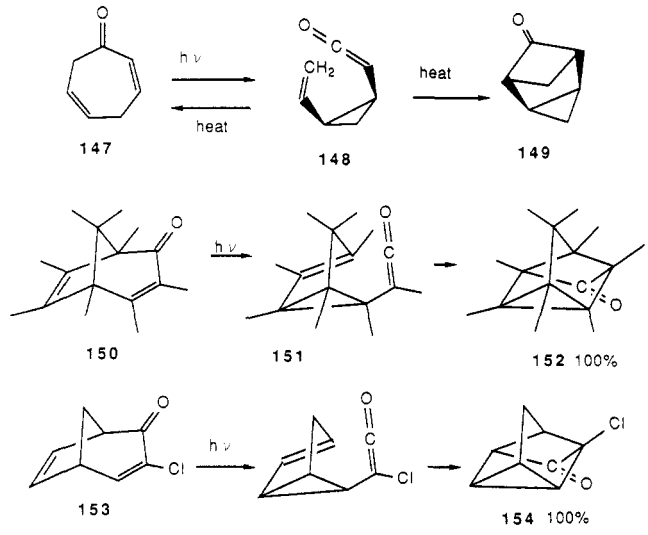
Wulff and Kaesler have described a novel method for construction of α,β-unsaturated ketenes.[66] Reaction of chromium carbene complex **142** with enyne **143** in acetonitrile gave a 45% yield of **146** as a mixture of stereoisomers. Chromium complex **142** reacted with the acetylene moiety of **143** to give **144**. Carbonyl insertion gave **145**, which reacted to give **146**. It is not certain whether the cycloaddition is mediated by the metal or occurred after the free vinylketene is decomplexed from the metal. Further extensions of this reaction have been outlined.[66b,c]

D. Cyclopropylketenes

2-Alkenylcyclopropylketenes (**148**) have been prepared by photolysis of 2,5-cycloheptadienones

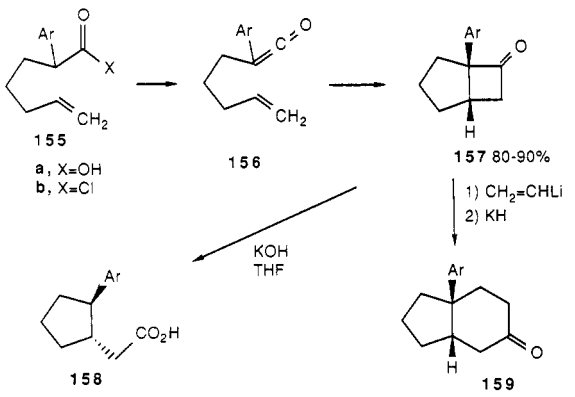


(**147**).[3,45–49] In all cases examined the cycloheptane is part of a bicyclic ring system. The ketenes **148** are stable at low temperature but revert to starting enone by a Cope rearrangement in which the ketene double bond participates.[3,45–47] If certain substituents are present, intramolecular cycloaddition to give **149** is observed in excellent yield. Hart reported that photolysis through pyrex of **150** as 1% solution in methanol gave a quantitative yield of **152**, via the intermediacy of ketene **151**.[48] No cyclobutanone was obtained in the parent system lacking the methyl substituents. Goldschmidt and co-workers found that similar photolysis of **153** gave **154** as the sole product.[49] As expected,[1] the chloro group on the ketene facilitates cycloaddition so that cyclobutanone **154** is obtained even in the absence of methyl substituents.



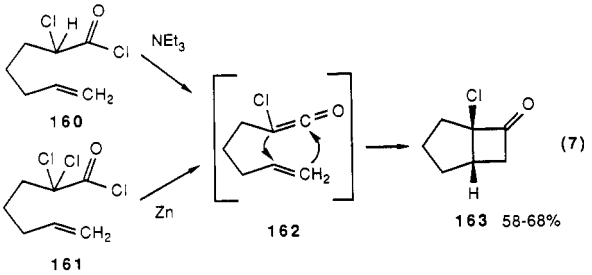
E. Arylketenes

Snider and Niwa have found that arylketenes of type **156** undergo cycloaddition in very high yield.[67] Alkylation of the dianion of an arylacetic acid with 5-bromo-1-pentene gave **155a** in excellent yield. Conversion of **155a** to the acid chloride **155b** and treatment of the acid chloride with Et_3N in toluene at reflux gave **157** in 80–90% yield. Since arylketenes are not particularly reactive in intermolecular cycloadditions, it is likely that the aryl group increases the yield of cyclobutanone by slowing down side reactions rather than by accelerating the cycloaddition. These 2-phenylcyclobutanones are versatile intermediates. Reaction of **157** with KOH in THF gave **158**. Reaction of **157** with vinyllithium and treatment of the resulting alcohol with KH in THF at −40 °C gave the 1,3-sigmatropic rearrangement product **159**.



F. Chloroketenes

Introduction of a chlorine in the α-position is a particularly attractive approach to activate ketenes for intramolecular cycloadditions since dichloroketene and chloroalkylketenes have been used with good success in intermolecular cycloadditions.[1] Intramolecular [2 + 2] cycloadditions of α-chloroketenes proceed in excellent yield even in those cases where the cycloaddition fails in the absence of the chlorine (e.g. **2c**, **3**). We have found that unsaturated α-chloroketenes can be prepared by treatment of α-chloro acid chlorides with Et_3N[1] in benzene at reflux or by reduction of α,α-dichloro acid chlorides with zinc dust in THF[1] at reflux (see eq 7).[11,20,35]

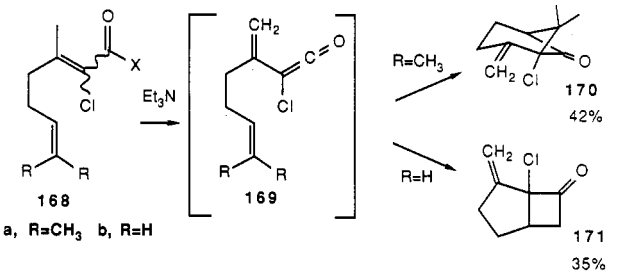


Unsaturated α-chloro acids were prepared in high yield in a single step by treatment of the acid dianion in THF–HMPA with excess carbon tetrachloride, as a source of electrophilic chlorine, at −78 °C. Treatment of the unsaturated α-chloroacyl chlorides (e.g. **160**) prepared from these acids with Et_3N in benzene at reflux gave the corresponding unsaturated α-chloroketenes (e.g. **162**), which underwent intramolecular [2 + 2] cycloaddition to provide bicyclo[3.2.0]heptan-6-ones (e.g. **163**) and bicyclo[3.1.1]heptan-6-ones in good yield. Additional examples are shown Table III.

Unsaturated α,α-dichloro acids were prepared by treatment of the lithium enolate of isopropyl dichloroacetate with a primary halide at −20 to −30 °C in THF to give the alkylated ester in 80–90% yield. Hydrolysis of the ester with excess potassium hydroxide gave the acid, which was converted to acid chloride **161**. Crude **161** was heated at reflux in THF containing a suspension of 2–3 equiv of zinc dust for 5 h to give cycloadduct **163** in 58% yield. Additional examples are shown in Table III.

The results obtained from the intramolecular cycloadditions of α-chloroketenes with 1,2-disubstituted double bonds are of particular interest. Ketenes derived from acid chlorides **167a** and **167b**, with a trans double bond, reacted stereospecifically to give bicyclo[3.1.1]-heptanones **166a** and **166b** in 57–66% yield. Unsaturated ketene derived from acid chloride **164**, with a cis double bond, reacted with loss of stereochemistry to give a 2:1 mixture of **165** and **166b** in 30–40% yield. The effect of double bond stereochemistry on these cycloadditions is similar to that observed in the type II cycloadditions of α,β-unsaturated ketenes discussed above (see **109–113**).

Since both the α-chloro group and the α,β-unsaturated double bond facilitate the cycloaddition, we chose to combine them in a single ketene in order to produce a more highly functionalized adduct. α-Chloro-α,β-unsaturated ketenes have been prepared by Dreiding and co-workers by treatment of β-substituted α-chloroacryloyl chlorides with base and used with good success in intermolecular cycloadditions.[68] Reaction of **168a** with Et_3N in toluene at reflux gave a 42% yield of cycloadduct **170**. Reaction of **168b** with Et_3N in benzene at reflux gave a 35% yield of cycloadduct **171**. The presence of both the chlorine and the double bond on the ketene leads to a more highly functionalized adduct. The yield of the cycloadduct, however, is comparable to that obtained from monoactivated ketenes.

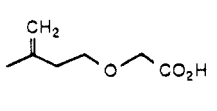
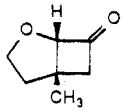
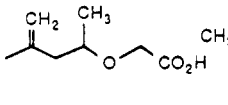
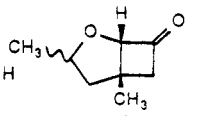
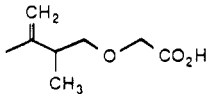
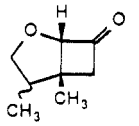
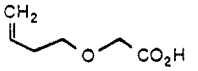
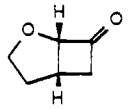
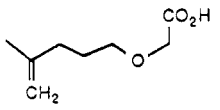
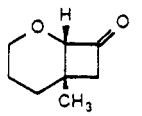
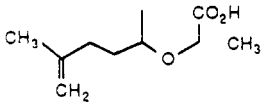
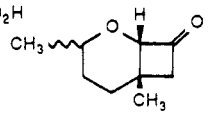
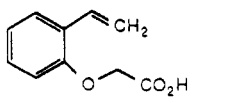
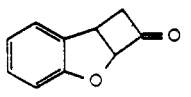
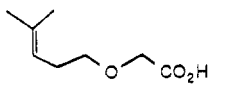
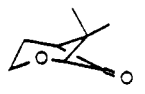
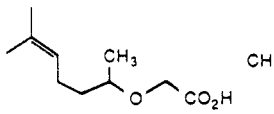
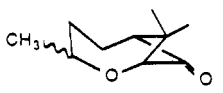
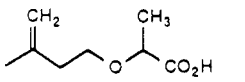
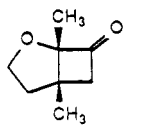
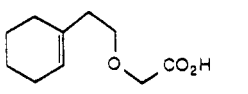
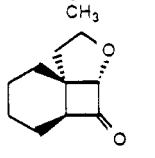
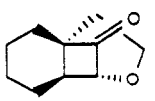
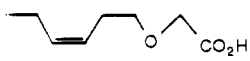


G. Alkoxyketenes

Snider and Hui[11,16] and Brady and co-workers[17,19,44,52] have extensively explored the intramolecular cycloadditions of alkoxyketenes. Alkoxyketenes were particularly well-suited for initial exploration of the scope and limitations of intramolecular cycloadditions of ketenes.[11,16] Alkoxyketenes are much more reactive in cycloadditions than simple aldoketenes.[69] The (alkenyloxy)acetic acids necessary for these studies are readily available through the Williamson ether synthesis using bromoacetic acid and unsaturated alcohols. The presence of the oxygen simplifies the NMR spectra of the cycloadducts, facilitating structure determination. Finally, Baeyer–Villiger oxidation of the cycloadducts give furofuranones of a type closely related to the furofurans present in insect antifeedants and aflatoxins.

(Alkenyloxy)acetic acids were converted to the acid chloride with oxalyl chloride in benzene at reflux. A 0.04 M solution of the acid chloride and 1.1–1.5 equiv of Et_3N in benzene was heated at reflux for 1.5–24 h to give the ketene, which reacted to give the cyclobutanone. The results are shown in Table IV. Alkenes in which the internal carbon is more substituted react to give bicyclo[3.2.0]heptanones or bicyclo[4.2.0]heptanones (entries 1–7, 10, 11). Alkenes in which the terminal carbon is more substituted react to give bicyclo[3.1.1]heptanones or bicyclo[4.1.1]octanones (entries 8, 9). Unlike most other classes of ketenes, cycloadditions of alkoxyketenes proceed in good yield even

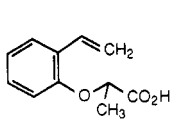
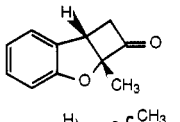
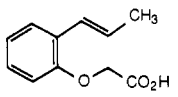
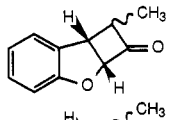
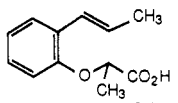
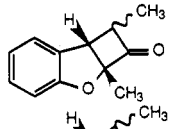
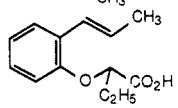
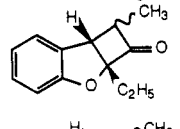
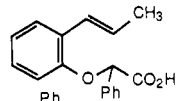
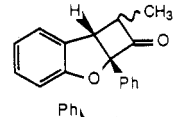
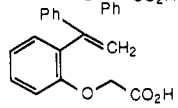
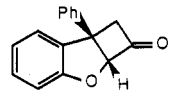
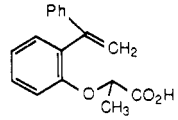
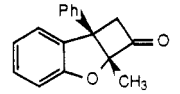
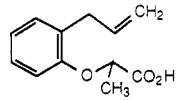
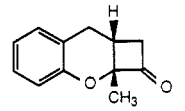
TABLE IV. Intramolecular [2 + 2] Cycloaddition Reactions of Ketenes Derived from (Alkenyloxy)acetic Acids

entry	alkenyloxy acid	cyclobutanone	% yield
1			72
2			7 β-Me 66 α-Me
3			28 β-Me 35 α-Me
4			16
5			62
6			58 (3:2)
7			70
8			52
9			13 β-Me 17 α-Me
10			50
11			58
			5
12		—	

with a four-atom tether (entires 5, 6). Low yields are obtained with monosubstituted alkenes (entry 4) and cis-1,2-disubstituted alkenes do not react at all (entry 12).

Brady and Giang reported a related study of the intramolecular cycloaddition of phenoxyketenes to alkenyl groups to provide polycyclic cyclobutanones (see Table V).[17] (*o*-Alkenylphenoxy)acetic acids were prepared from the phenol and α-halo carboxylic acid. The acid chloride was added to Et_3N in benzene at reflux

TABLE V. Intramolecular [2 + 2] Cycloaddition Reactions of Phenoxyketenes Derived from (*o*-Alkenylphenoxy)acetic Acids

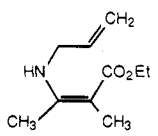
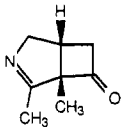
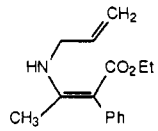
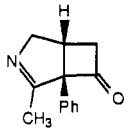
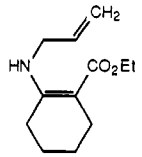
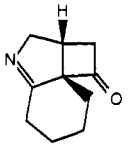
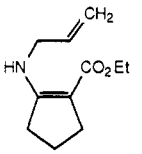
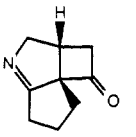
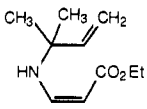
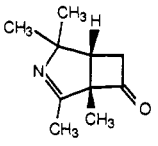
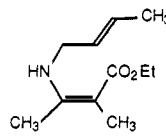
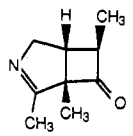
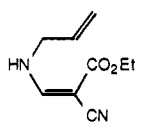
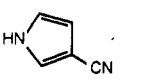
entry	acid	cyclobutanone	% yield
1			60
2			72
3			76
4			71
5			85
6			88
7			84
8			43
9			49

to give the cyclobutanone via the intermediacy of the ketene. Bicyclo[3.2.0]heptanones were prepared in 60–88% yield from (*o*-vinylphenoxy)ketenes (entries 1–7) and bicyclo[4.2.0]octanones were prepared in 43–49% yield from (*o*-allylphenoxy)ketenes (entries 8, 9). Brady and co-workers have developed a one-pot procedure for conversion of the carboxylic acid to the cyclobutanone via the ketene without the intermediacy of the acid chloride.[44] The acid, *p*-toluenesulfonic chloride, and Et_3N are heated together in benzene at reflux. A mixed anhydride is formed, which eliminates *p*-toluenesulfonic acid to give the ketene.

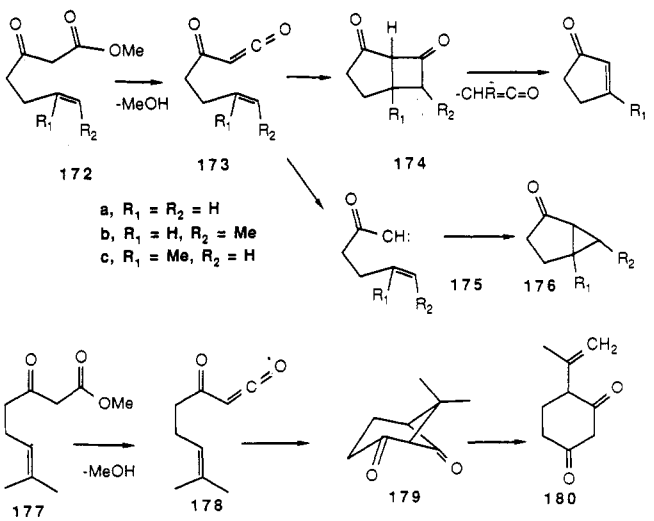
H. α-Ketoketenes

Pyrolysis of β-keto esters results in loss of alcohol, yielding an α-ketoketene. Leyendecker and Conia have used this procedure to generate an unsaturated α-ketoketene.[36,37] Pyrolysis of **172a** at 550 °C at 10^{-2} Torr (contact time of 2 s) gave ketene **173a**. Cycloaddition gave **174a**, which underwent a cycloreversion to give 2-cyclopentenone in 80% yield and ketene, which is trapped as methyl acetate. Ketene **173a** also loses carbon monoxide to give carbene **175a**, which adds to the double bond to give **176a** in 20% yield. Pyrolysis of **172b** also gave 2-cyclopentenone while **172c** gave 3-methyl-2-cyclopentenone. Pyrolysis of **177** gave

TABLE VI. Intramolecular [2 + 2] Cycloaddition Reactions of Iminoketenes

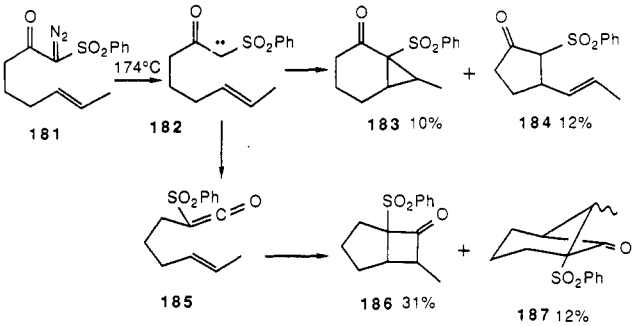
enamino ester	cyclobutanone	% yield
		62
		60
		33
		32
		67
		46
		30

ketene **178**, which reacted to give the expected product bicyclo[3.1.1]heptanedione **179**. Ring opening occurred under the reaction conditions to give the isolated product **180**.



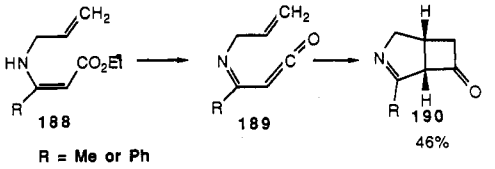
I. Sulfonylketenes

Kuwajima et al. reported the pyrolysis of a series of α-diazo-β-keto sulfones.[32] Pyrolysis of **181** in decane at 174 °C gave carbene **182**. Addition of the carbene to the double bond gave **183** in 10% yield. Insertion of the carbene into the C–H bond gave **184** in 12% yield. Wolff rearrangement of carbene **182** gave ketene **185**, which underwent an intramolecular cycloaddition to give **186** in 31% yield and **187** in 12% yield. No cyclobutanones were isolated in the two related examples studied.



J. Iminoketenes

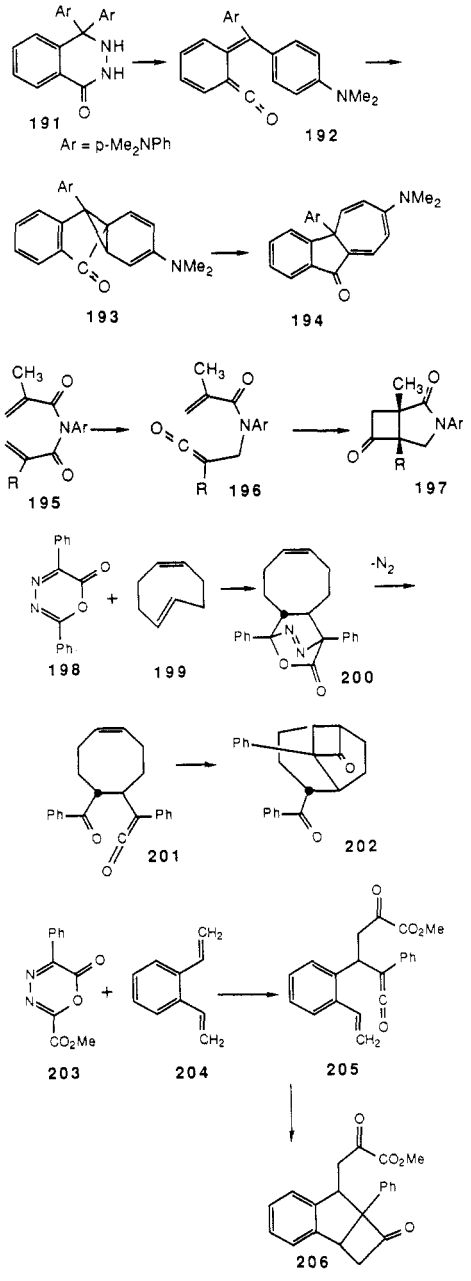
Chuche and co-workers found that pyrolysis of *N*-allyl enamino ester **188** gave 3-azabicyclo[3.2.0]heptenones **190** in 46% yield.[38,39] Loss of ethanol from **188** gave ketene **189**, which underwent an intramolecular cycloaddition to give **190**. Pyrolysis was accomplished by addition of a THF solution of **188** through a vertical Pyrex tube heated to 400 °C at 10^{-2} Torr. The examples studied are shown in Table VI. 3-Cyanopyrrole, the last entry in Table VI, is formed by cycloreversion, with loss of ketene, of the initially formed cyclobutanone.



K. Miscellaneous Ketenes

Several isolated methods of ketene generation for intramolecular cycloaddition have been described. Kuzuwa and co-workers reported that oxidation of **191** with lead tetraacetate at low temperature gave **192**, which added to the aromatic ring to give **193**, which rearranged to give **194** as the sole isolable product.[70] Alder and Bellus reported that thermolysis of **195** in 1,3-dichlorobenzene at 210 °C for 3–16 h gave a mixture of products including cyclobutanone **197**.[71] The cyclobutanone was obtained in yields of 6, 7.5, 9, and 57% for R = H, CH_3, C_6H_5, and $Si(CH_3)_3$, respectively. A plausible mechanism for the formation of **197** involves the intermediacy of ketene **196**.

Christl and co-workers have found that 1,3,4-oxadiazin-6-ones (**198**, **203**) undergo inverse electron demand Diels–Alder reactions with alkenes to give adducts that fragment with loss of nitrogen to give a ketone and ketene.[72] Addition of **198** to **199** gave adduct **200**, which lost nitrogen to give ketene **201**, which underwent an intramolecular cycloaddition to give **202** in 69% overall yield. Similarly, **203** reacted with **204** to give **205** and thence **206**.



L. Cycloaddition of Ketenes to Carbonyl Compounds

Brady and Giang have described the intramolecular cycloaddition of phenoxyketenes to carbonyl compounds to give β-lactones which lose carbon dioxide.[19] For instance, addition of acid chloride **207** to Et_3N in benzene at reflux gave ketene **208**, which added to the carbonyl group to give **209**, which lost carbon dioxide to give **210** in 75% yield. Several other examples were reported.[19]

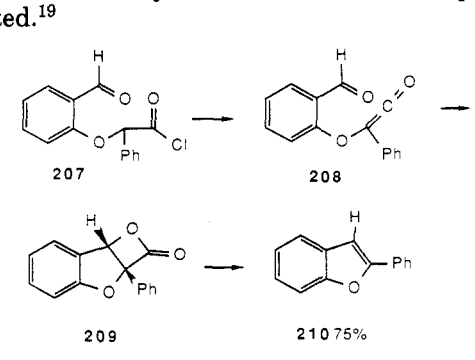
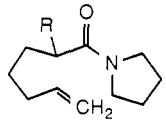
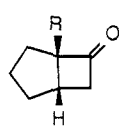
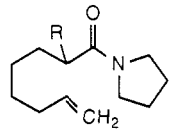
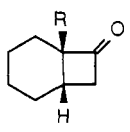
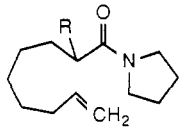
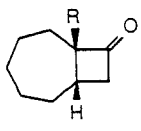
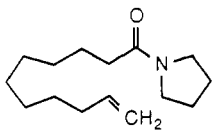
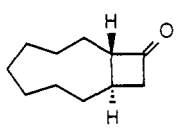
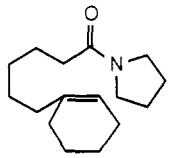
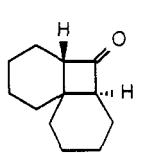
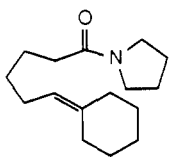
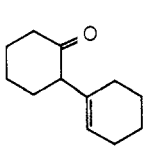


TABLE VII. Intramolecular Cycloaddition of Keteniminium Salts Derived from Unsaturated Acids

unsaturated amide	cyclobutanone	% yield
		R = H, 75% R = Me, 87%
		R= H, 65% R = Me, 89%
		R= H, 71% R = Me, 78%
		72%
		30%
		55%

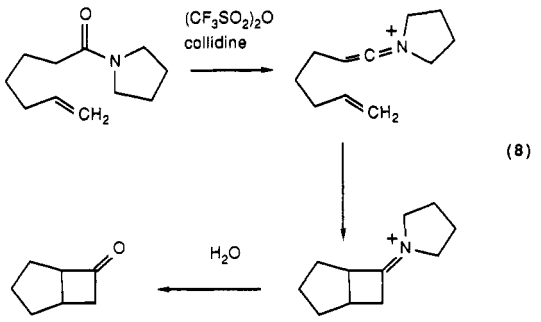
III. Keteniminium Salts

A. Aldo- and Ketoketiniminium Salts

Ghosez has pioneered the use of keteniminium salts as an attractive alternative to ketenes for cycloaddition with alkenes to give cyclobutanones.[73] Keteniminium salts are more electrophilic than ketenes and they do not dimerize. They can be prepared easily by treatment of an amide with collidine and triflic anhydride in an inert solvent or from α-halo enamines.[73] The cycloadditions of keteniminium salts are stepwise, not concerted, and are occasionally accompanied by loss of stereochemistry.[73c] Of greater concern is the fact that the intermolecular cycloaddition of 1,1-disubstituted alkenes with keteniminium salts proceeds in low yield. The major product is the Friedel–Crafts product.

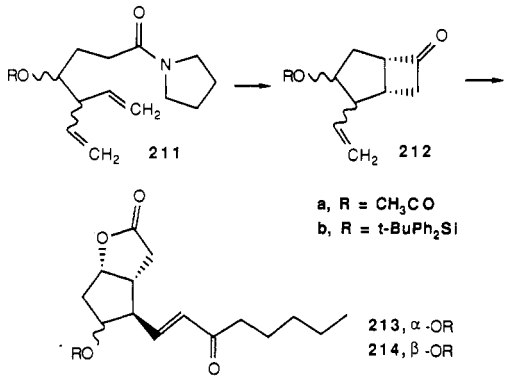
Ghosez and co-workers have explored the intramolecular cycloadditions of aldo- and ketoketeniminium salts (see eq 8).[10,74] Their results are shown in Table VII. Bicyclo[3.2.0]heptan-6-one is formed in 75% yield as opposed to 3% from the corresponding ketene. The reaction can be used with three-, four-, five-, and seven-atom tethers, unlike the ketene cycloaddition, which is restricted to three-atom and occasionally four-atom tethers. The final example in Table VII indicates a limitation of the reaction. If there is an allylic hydrogen trans to the tether, an intramolecular ene reaction will occur to give, after hydrolysis, the Friedel–Crafts product.

Ghosez has used this reaction as the key step in a short route to a prostaglandin intermediate.[74,75] Gen-



(8)

eration of the keteniminium salt from **211a** gave **212a** in 94% yield as a 4:2:2:1 mixture of stereoisomers. Baeyer–Villiger oxidation, ozonolysis, equilibration and Wittig–Horner reaction gave a 1:2 mixture of the prostaglandin intermediate **213a** and its epimer **214a**. Use of **211b** with a bulkier protecting group gave a 1:55 mixture of **213b** and **214b**.



B. Alkoxyketeniminium Salts

Snider and Hui explored the reactivity of (alkenyloxy)keteniminium salts.[11,16] Treatment of an unsaturated alcohol with sodium hydride and bromo-*N*,*N*-dimethylacetamide gave the amides shown in Table VIII. Treatment of the amide with triflic anhydride and collidine in benzene, dichloromethane, or 1,2-dichloroethane at reflux gave a keteniminium salt that added to the double bond to give, after hydrolysis, the cyclobutanone (see eq 8). The results are shown in Table VIII.

Comparison of these results with the results obtained with comparable ketenes shown in Table IV indicates that there are both advantages and disadvantages to the use of keteniminium salts. Alkoxyketeniminium salts underwent intramolecular cycloaddition reactions with monosubstituted and cis-1,2-disubstituted alkenes in moderate to good yield (entries 4, 7–11) as compared to the ketene series in which the monosubstituted alkene reacted in low yield and the cis-disubstituted alkene did not react. On the other hand, the stepwise keteniminium reaction causes problems with alkenes containing an allylic hydrogen trans to the tether as in entry 11. Much lower yields are obtained in entry 6 than in the corresponding ketene cycloaddition since the intermediate undergoes competing reactions to give the 3-furanone. The stereoselectivity of the cycloadditions of ketenes and keteniminium salts are markedly different as indicated by entries 2 and 3 in Tables IV and VIII.

Brady and co-workers have further explored the cycloadditions of phenoxy-, alkoxy-, and (alkenyloxy)-keteniminium salts. The results shown in Table IX confirm the suitability of keteniminium cycloadditions for the formation of cycloadducts with four- to seven-atom tethers.[52]

TABLE VIII. Intramolecular [2 + 2] Cycloaddition Reactions of Keteniminium Salts Derived from (Alkenyloxy)acetamides

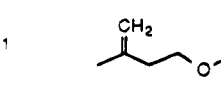
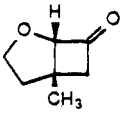
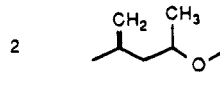
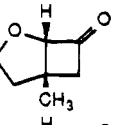
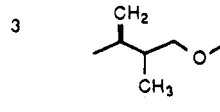
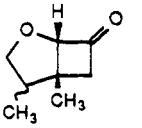
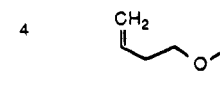
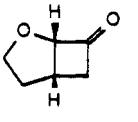
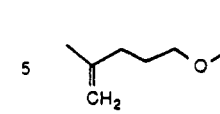
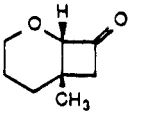
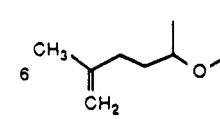
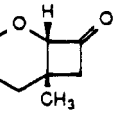
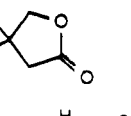
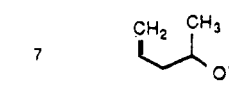
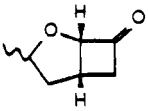
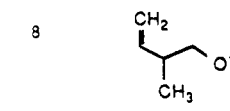
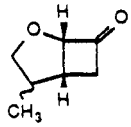
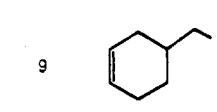
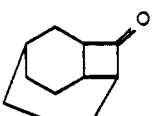
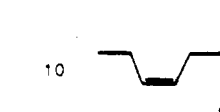
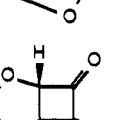
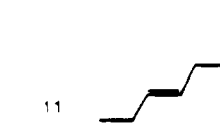
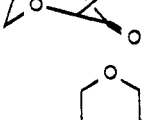
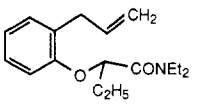
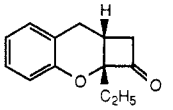
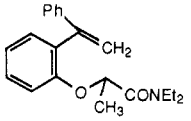
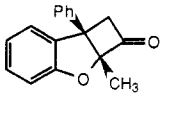
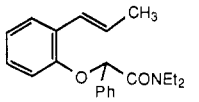
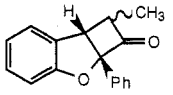
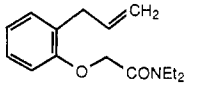
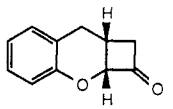
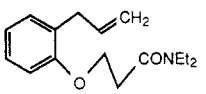
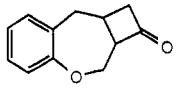
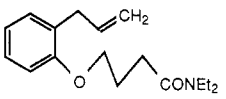
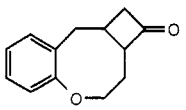
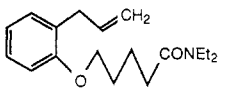
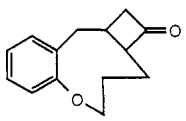
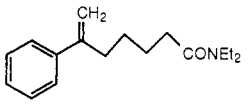
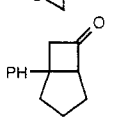
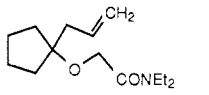
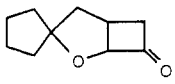
entry	(alkenyloxy)acetamide	cyclobutanone	% yield
1			85
2			65 β-Me 9 α-Me
3			15 β-Me 62 α-Me
4			79
5			33
6			16
			19
7			53 β-Me 5 α-Me
8			27 β-Me 33 α-Me
9			24
10			33 β-Et 7 α-Et
			9
11			64

TABLE IX. Intramolecular [2 + 2] Cycloaddition Reactions of Keteniminium Salts

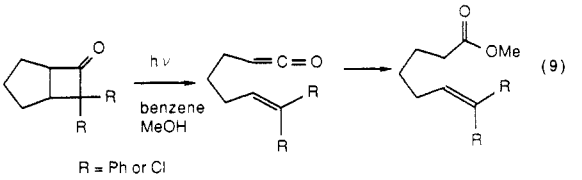
entry	amide	cyclobutanone	% yield
1			32
2			70
3			66
4			44
5			18
6			10
7			4
8			73
9			50

IV. Cycloreversion of Polycyclic Cyclobutanones

The intramolecular cycloaddition of alkenes and ketenes is a Woodward–Hoffmann allowed [$_{\pi}2_s + _{\pi}2_a$] cycloaddition and is of course reversible. The reverse reaction, cycloreversion of a polycyclic cyclobutanone to give an alkene and a ketene connected by a tether, has occasionally been the subject of study. Erman established that chrysanthenone (**42a**) isomerizes on heating at 81 °C with a half-life of 1–2 days.[58] This isomerization almost definitely occurs by cycloreversion to the achiral ketene **41a** and cycloaddition to give racemic **42a**. Schiess and co-workers have studied the flash vacuum pyrolysis of bicyclo[3.2.0]hept-3-en-6-ones which gave a complex mixture of products derived from the acyclic ketene.[76] This is the reverse of the type III cycloadditions of unsaturated ketenes discussed above. Lee-Ruff's group has photolyzed a series of bicyclo[3.2.0]heptan-6-ones in benzene containing methanol.[77] The unsaturated ketene was formed which reacted with methanol to give the methyl ester (see eq 9).

V. Conclusion

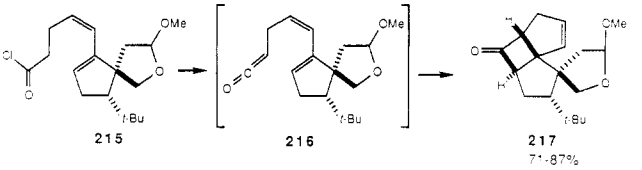
The results described above indicate that intramolecular cycloadditions of alkenes and ketenes or keteniminium salts can be carried out with a wide variety of ketenes and keteniminium salts. A wide variety of highly functionalized polycyclic cyclobutanone containing adducts can be obtained in good overall yield. Since cyclobutanones are versatile synthons that can be used for the construction of a variety of targets that no longer contain a four-member ring, this intramolecular cycloaddition will be of value for the synthesis of a wide variety of natural products and other targets.



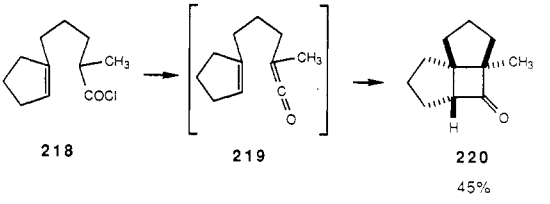
(9)

VI. Addendum

Several additional papers on this subject have appeared since this review was prepared. Corey and coworkers have reported the intramolecular cycloaddition of an aldoketene to a diene to give **217**, a key tetracyclic intermediate in the synthesis of ginkgolide B.[78] Addition of acid chloride **215** to 10 equiv of Bu_3N in toluene at reflux gave adduct **217** in 71–87% yield via the intermediacy of ketene **216**.

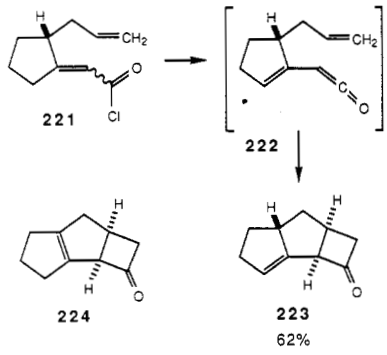


Yadav and co-workers have reported the application of intramolecular cycloaddition to the synthesis of angularly fused triquinanes.[79] Intramolecular cycloaddition of ketene **219**, prepared from acid chloride **218** by treatment with Et_3N in toluene at reflux, gave **220** in 45% yield.



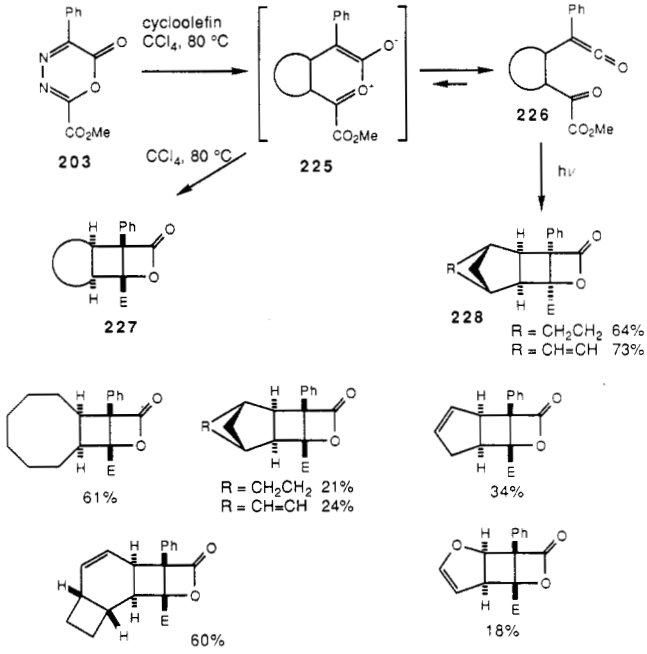
Ernst and co-workers have reported the application of intramolecular cycloaddition to the synthesis of linearly fused triquinanes.[80] Treatment of acid chloride **221** with Et_3N in chloroform at 25 °C gave cycloadduct **223** in 62% yield via the intermediacy of ketene **222**. Unless great care was used in the preparation of the acid, double bond migration into the ring occurred and cyclobutanone **224** was isolated as the major product.

Brady, Marchand, and co-workers have reported several additional examples of intramolecular [2 + 2] cycloadditions of phenoxyketenes to carbonyl compounds to give β-lactones which lose carbon dioxide to give benzofurans (see **208–210**).[19,81] The ketenes were prepared by treatment of the acid chloride with Et_3N in benzene at reflux, by reaction of the acid with tosyl chloride and Et_3N in benzene at reflux,[44] and by reac-



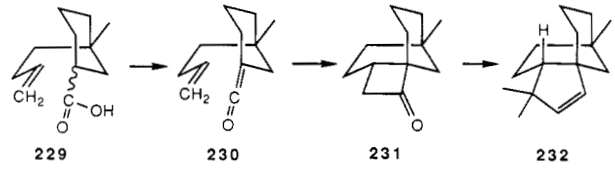
tion of the acid with 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) and Et_3N in THF at reflux.

Christl and co-workers have reported that oxadiazinone **203** reacts with alkenes in CCl_4 at 80 °C to give **225**.[82] Zwitterion **225** opens reversibly to give γ-oxoketene **226** and closes to give β-lactone **227**. Photolysis of **226** in benzene through pyrex gives 228, the stereoisomer of the thermal product **227**.

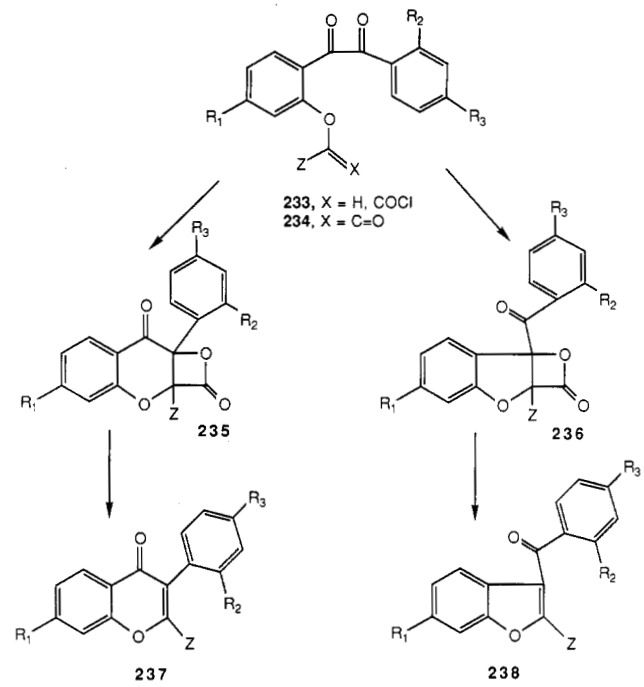


Geisel et al. have extended Yates' study[29] on the conversion of diazo ketone **13** to **15** via ketene **14** by carrying out the same series of reactions in the analogue lacking all three methyl groups.[83]

Funk and co-workers have used an intramolecular cycloaddition of a ketene as the key step in a short synthesis of clovene.[84] Reaction of acid **229** with *N*-methyl-2-chloropyridinium iodide and Et_3N in acetonitrile at reflux gave cyclobutanone **231** in 35–47% yield via the intermediacy of ketene **230**. Cyclobutanone **231** was converted to clovene (**232**) in five steps. This example indicates the importance of steric constraints in the tether connecting the ketene and alkene since bicyclo[4.2.0]octanones cannot usually be prepared by intramolecular ketene cycloadditions.

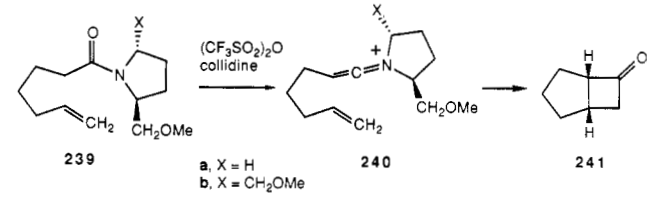


Brady and co-workers have extended their study of the intramolecular cycloaddition of ketenes to carbonyl compounds to benzil derivatives.[85] Reaction of acid chloride **233** with Et_3N in benzene at 50 °C gave ketene **234** which underwent cycloaddition to one of the two carbonyl groups to give **235** and **236**. Decarboxylation of **235**, Z = H, and **236** occurred under the reaction conditions to give **237** and **238**. Decarboxylation of **235**, Z = Me was accomplished by heating at 150 °C to give **237**.



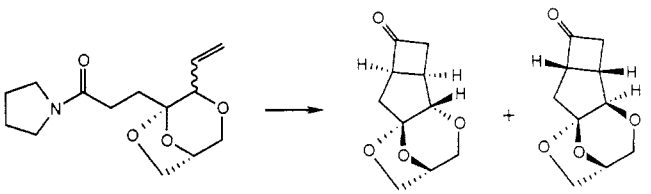
	23%	$R_1 = R_2 = R_3 = Z = H$	50%
	55%	$R_1 = R_3 = Z = H$, $R_2 = OMe$	15%
	59%	$R_1 = R_2 = R_3 = OMe$, $Z = H$	--
(**235**)	trace	$R_1 = R_2 = R_3 = H$, $Z = Me$	63%
(**235**)	49%	$R_1 = R_3 = H$, $R_2 = OMe$, $Z = Me$	24%
(**235**)	57%	$R_1 = R_2 = R_3 = OMe$, $Z = Me$	--

Ghosez and co-workers have reported that intramolecular cycloaddition of the chiral keteniminium salt **240a** prepared from **239a** gives **241** with only 27% enantiomeric excess.[86] On the other hand excellent results are obtained from **240b**, derived from a C_2 symmetric chiral pyrrolidine which yields **241** with >95% enantiomeric excess.



Finch and co-workers have used intramolecular cycloadditions of keteniminium salts in a route to chiral 13-oxa prostanoids.[87] Reaction of a mixture of amides **242a** and **242b** with triflic anhydride and collidine in 1,2-dichloroethane at reflux gave a 40% yield of a mixture of **243** and **244**. Amide **242a** gives only **243**, and amide **242b** gives only **244**. Small amounts (ca. 3%) of an "endo" isomer were also isolated.

Acknowledgments. The work from my laboratory described above was generously supported by the Na-



tional Institutes of Health. I gratefully acknowledge the contributions of my co-workers whose names are cited in the references below.

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