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Ylide Formation from the Reaction of Carbenes and Carbenoids with Heteroatom Lone Pairs

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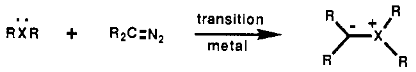
Contents

I. Introduction

Ylides can be viewed as species in which a positively charged heteroatom is connected to a carbon atom possessing an unshared pair of electrons. These reactive intermediates are known to undergo synthetically useful transformations. One method of preparing ylides involves the deprotonation or desilylation of onium salts.[1,2] An alternate approach consists of the interaction of carbenes with the unshared electron pairs of heteroatoms.[3] Singlet carbenes, in particular, can function as Lewis acids by interacting with a pair of nonbonding electrons contributed by a Lewis base.[4] If the Lewis base is an uncharged species, the end result of such an acid–base reaction is an ylide. Nucleophilic species that are known to trap carbenes include ethers, thioethers, amines, and halides. Compounds containing heteroatoms in the sp^2 or in the sp state of hybridization interact similarly with carbenes. Examples of such functional groups include aldehydes, esters, ketones, imines, thiocarbonyl compounds, and nitriles. More recently, ylide generation has been achieved by the transition-metal-catalyzed decomposition of diazo compounds in the presence of a heteroatom. The reactive intermediate preceding ylide formation is a carbenoid species.



Carbene complexes of transition metals are well known, thoroughly studies species.[5] Among the carbene complexes which generate ylides, those formed with use of copper and rhodium salts are especially prominent.[6] Until the late 1970's, catalytic decomposition reactions of diazo compounds were usually carried out in the presence of copper in different oxidation states. As a result of a systematic screening of transition-metal compounds, rhodium(II) carboxylates[7] have emerged as highly efficient catalysts for ylide generation from diazo compounds. Doyle has suggested that reactions catalyzed by rhodium(II) carboxylates can be viewed as taking place at the carbenic carbon which protrudes from the metal embedded in a wall constructed from its ligands.[8] The rhodium(II)-catalyzed decomposition of diazocarbonyl compounds is believed to involve a metallocarbenoid intermediate which retains the highly electrophilic properties associated with free carbenes. Such an intermediate can readily react with an available heteroatom to effect ylide formation.

In recent years there has occurred a widespread upsurge of activity in the application of ylides to new synthetic transformations.[9] This research has also stimulated interest in the use of carbenes and carbenoids as reactive intermediates for ylide generation. A rather diverse range of chemistry has already surfaced. It is the intent of this review to define the boundaries of our present knowledge in this area. Such an overview will put into perspective what has been accomplished and hopefully will provide impetus for further investigation of this general approach for ylide formation.

II. Formation of Sulfonium Ylides

The chemistry of sulfur ylides has been the subject of extensive investigation, largely because of the syn-

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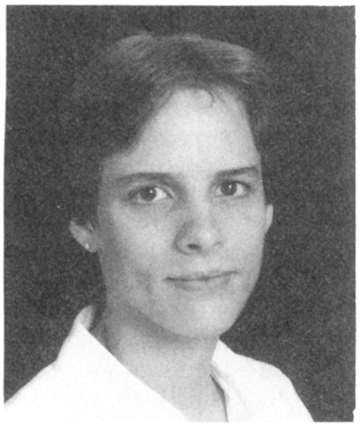
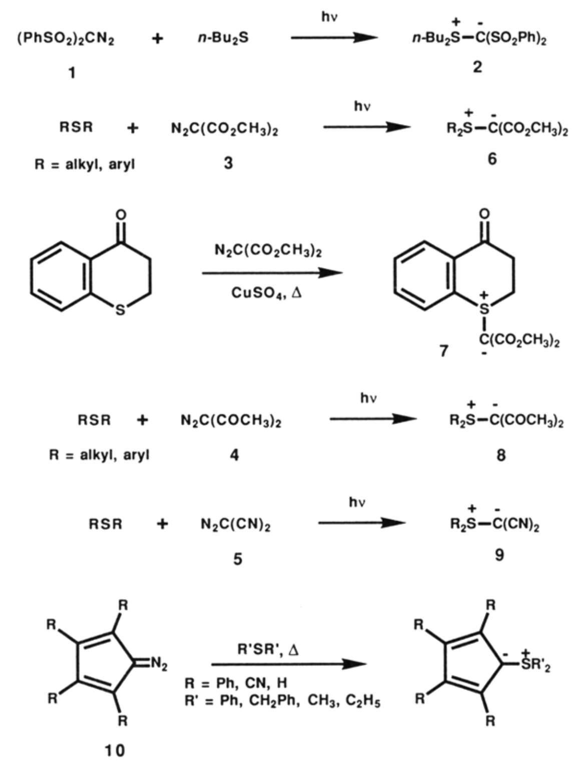


Susan Hornbuckle was born in 1963 and received a B.S. degree, Magna Cum Laude, (1985) at Columbus College where she majored in chemistry. In 1985 she began her graduate studies at Auburn University where she carried out research under the direction of Peter D. Livant and received her M.S. degree in organic chemistry in 1987. She is currently completing requirements for her Ph.D. at Emory University under the direction of Albert Padwa. Her present research interests are in the area of the development of synthetic methodology involving tandem cyclization–cycloaddition chemistry via carbonyl ylide intermediates.

thetic ease of making stable molecules of this kind and because of the interesting rearrangements which they often undergo. These ylides are becoming increasingly useful in synthetic chemistry and some evidence is also available suggesting their involvement in biochemical processes.[10] Sulfur ylides have been utilized for the synthesis of a number of β-lactam antibiotics,[11–31] pyrrolizidine alkaloids,[32,33] and other natural products.[34] The most common method for sulfur ylide generation involves the removal of a proton from a sulfonium salt.[9] However, a more direct method makes use of the reaction between a carbene (or carbenoid) and a sulfide.

SCHEME 1

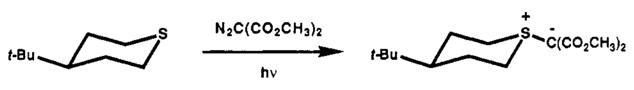


A great variety of sulfur compounds, including cyclic and acyclic alkyl and aryl sulfides, are known to trap carbenes. Even compounds in which the sulfur lone pair is highly delocalized, such as vinyl sulfides, thiophene, and dibenzothiophene, have been shown to react with appropriate carbenes to give stable sulfonium ylides. Thus, the reaction of carbenes with sulfur compounds represents a useful approach to the generation of sulfonium ylides and to the study of their chemistry.

A. Stable Sulfonium Ylides

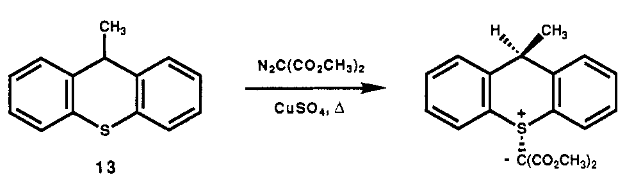
The carbene approach to sulfur ylide formation has been extensively explored by Ando and his co-workers, who have generally used carbenes with strongly electron-withdrawing substituents.[35] This type of substitution has the effect of stabilizing the resulting ylides so that they can often be isolated and thoroughly characterized. These sulfonium ylides are prepared and isolated much more readily than analogous ylides involving other heteroatoms due to the stabilizing effect of the d orbitals of the sulfur atom. The earliest report of a stable sulfonium ylide formed by this method was by Diekmann in 1965.[36] During an investigation of the photolysis of bis(phenylsulfonyl)diazomethane (**1**), it was found that reaction with dibutyl sulfide resulted in the formation of a stable sulfonium ylide **2** (Scheme 1). Similar results were obtained in the thermal, photolytic, or catalytic decomposition of dimethyl diazomalonate (**3**), 3-diazopentane-2,4-dione (**4**), or diazomethanedicarbonitrile (**5**) with a series of alkyl or aryl sulfides giving rise to ylides **6**–**9**.[37–43] The reactions are all assumed to occur by conversion of the diazo compound into an electrophilic singlet carbene or carbenoid, which is attacked by the nonbonding electron pair of a sulfur atom to produce a sulfur ylide. Charge delocalization onto the electron-withdrawing substituents (i.e. ester, nitrile, sulfone, etc.) helps to stabilize these ylides. Ylide stabilization can also be accomplished by delocalization of charge through an aromatic ring. Indeed, the thermal or photolytic decomposition of various substituted diazocyclopentadienes (e.g. **10**) in the presence of aryl or alkyl sulfides led to the formation of stable sulfonium ylides.[44-47] In competitive experiments, the interaction of the carbene with a lone pair of electrons on a sulfur atom was found to be several times faster than attack on the π-bond of an olefin.[48]

Carbenes and carbenoids have been shown to add to sulfides in a stereoselective fashion.[49,50] For example, irradiation of dimethyldiazomalonate in the presence of 4-*tert*-butylthiacyclohexane (**11**) resulted in the exclusive formation of ylide **12**.[49] Formation of this species is consistent with equatorial addition of the carbene onto the sulfur atom. Kinetic rather than thermodynamic control of the addition was demonstrated by the nonequivalence of the geminal protons of the methylene group adjacent to sulfur in the analogous ylide derived from thiacyclohexane. In marked contrast to the selectivity exhibited in the carbene reactions, treatment of thiacyclohexane **11** with nitrenes afforded a mixture of diastereomeric iminosulfuranes. The greater selectivity with the carbenes is presumably due to the greater degree of steric compression associated with axial entry of the effectively bulkier reagents.



11 12

The addition of bis(methoxycarbonyl)carbene to thioxanthene was also found to be stereoselective.[50] Treatment of thioxanthene **13** with dimethyl diazomalonate at 90 °C gave exclusively the trans-substituted thioxantheniobis(methoxycarbonyl)methylide **14**. Single-crystal X-ray analysis established that the bis(methoxycarbonyl)methyl group was in the equatorial position and the methyl group was located in the axial position. The exclusive formation of the more stable trans isomer may be the result of a steric effect, caused by the bulky substituents of the reagent and/or the high temperature required.



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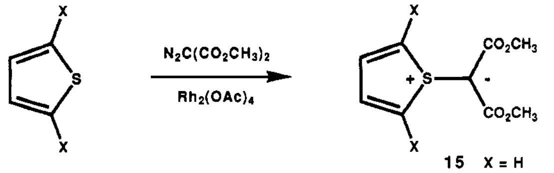
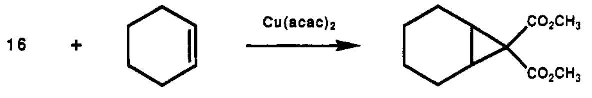
Porter and co-workers have reported the synthesis of sulfonium ylide **15** via the rhodium(II) acetate catalyzed reaction of dimethyl diazomalonate with thiophene.[51-53] The analogous reaction with 2,5-dichlorothiophene gave 2,5-dichlorothiophenium bis(methoxycarbonyl)methylide (**16**) as a stable crystalline solid.[54,55] Ylides prepared by this method are obtained in high yields, require no purification, and are ideal intermediates for further structural transformation. Sulfur ylide **16** is an excellent source of bis(methoxycarbonyl)carbene. For example, treatment of **16** with copper(II) acetylacetonate in the presence of cyclohexene afforded the cyclopropanated product **17** in high yield. A variety of olefins were found to react similarly to produce a number of bis(methoxycarbonyl)cyclopropane derivatives.[54,55] This dissociation is probably a consequence of the steric bulk of the two chlorine atoms coupled with a weakening of the carbon–sulfur bond due to the inductive electron-withdrawing effect of the two chlorine atoms.



15 X = H
16 X = Cl



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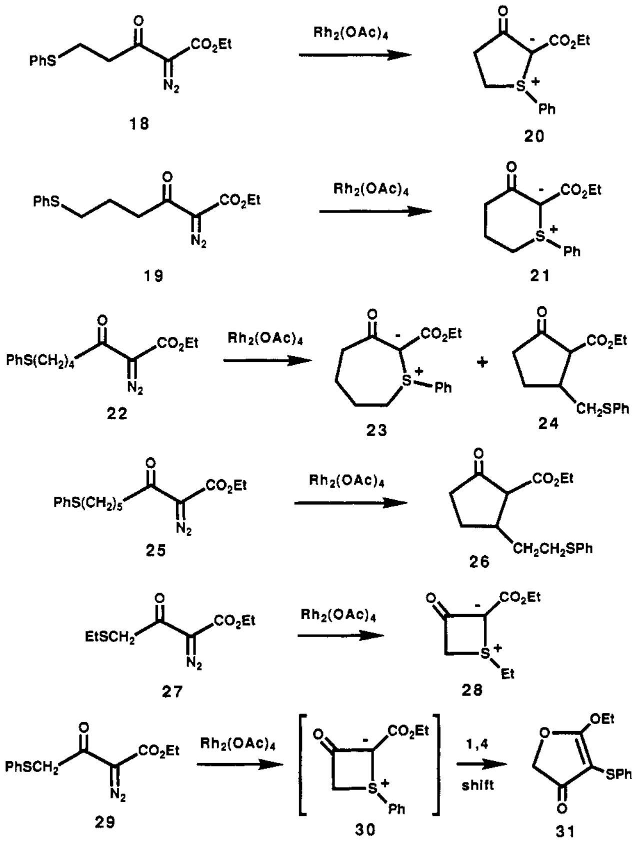
Cyclic sulfonium ylides, resulting from intramolecular sulfide attack on a tethered carbenoid species, have been reported.[56] Through variation of the tether length that connects the carbenoid precursor and the sulfur atom, four-, five-, six-, and seven-membered cyclic sulfonium ylides have been prepared. Treatment of diazo sulfides **18** and **19** with a catalytic amount of rhodium(II) acetate gives the five- and six-membered cyclic ylides **20** and **21**, respectively (Scheme 2). Extension of the tether to four methylene units allows for

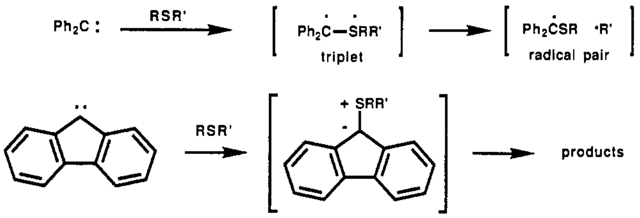
SCHEME 2



the formation of the seven-membered cyclic ylide **23** in 45% yield. In this case, however, C–H insertion was a competing process producing cyclopentanone **24** in 16% yield. Efforts to form larger rings only resulted in the C–H insertion product. The four-membered cyclic ylide **28** was isolated in 53% yield from the reaction of diazo sulfide **27** with rhodium(II) acetate. The closely related phenyl sulfide **29** failed to give a four-membered cyclic ylide. The only isolable material obtained was compound **31**. This product is most likely the result of a 1,4-rearrangement through the ester carbonyl group. Even though many of these sulfonium ylides are quite stable at room temperature, they tend to undergo rearrangement on extended heating.

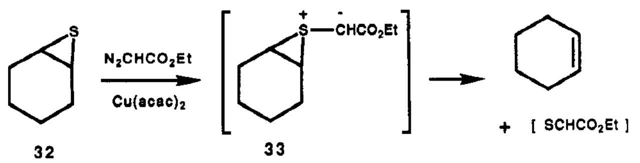
B. Intermolecular Formation of Sulfur Ylides

Many aliphatic carbenes have singlet ground states, so that reaction with sulfides leads directly to ground-state ylides, without any requirement for spin inversion. The reactions between carbenes with triplet ground states and sulfur-containing compounds have, by contrast, received little attention. Griller and co-workers have investigated the reaction between diphenylcarbene and fluorenylidene with a variety of sulfides and disulfides by using electron paramagnetic resonance (EPR) spectroscopy, laser flash photolysis, and product studies.[57] These workers found that triplet diphenylcarbene reacts with sulfides and disulfides by a mechanism which is like the homolytic substitution process. This would lead initially to a triplet pair of radicals whose immediate recombination would be spin forbidden. The radical pairs would therefore diffuse apart and would ultimately react with other radicals in the system to give the final products. The free radicals obtained were detected by both EPR and optical spectroscopy. For fluorenylidene, the chemistry was quite different. No EPR signals due to free radicals were detected, and the optical absorption spectra were consistent with ylide rather than radical pathways. These results conform to the general observation that triplet fluorenylidene is readily able to access the singlet manifold, whereas diphenylcarbene generally displays chemistry characteristic of the triplet state.



Desulfurization of episulfides via a process involving sulfonium ylide intermediates has been investigated by Hata and co-workers.[58] Reaction of cyclohexene sulfide **32** with ethyl diazoacetate in the presence of copper(II) acetylacetonate at 110 °C gave the corresponding olefin. This reaction is thought to proceed via sulfonium ylide **33** which undergoes simultaneous cleavage of the two C–S bonds in the episulfide ring. The procedure was found to be general for other episulfides.

In contrast to dicarbomethoxycarbene which reacted with a number of alkyl sulfides to give stable ylides, carboethoxycarbene did not. Instead, this reactive species produced products which are considered to be formed by subsequent reactions of the corresponding ylide. For example, ethyl (*tert*-butylthio)acetate (**35**) was the major product isolated from the irradiation of ethyl diazoacetate in di-*tert*-butyl sulfide.[59] Formation of both of these materials can be rationalized by electrophilic addition of the carbene onto the sulfur atom to generate a sulfonium ylide which then undergoes a β-elimination reaction.



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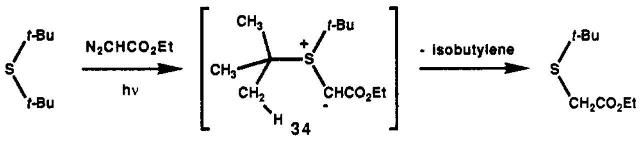

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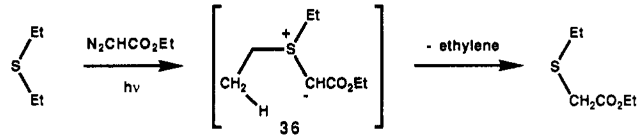

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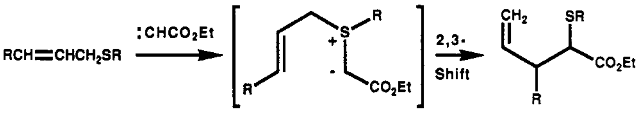
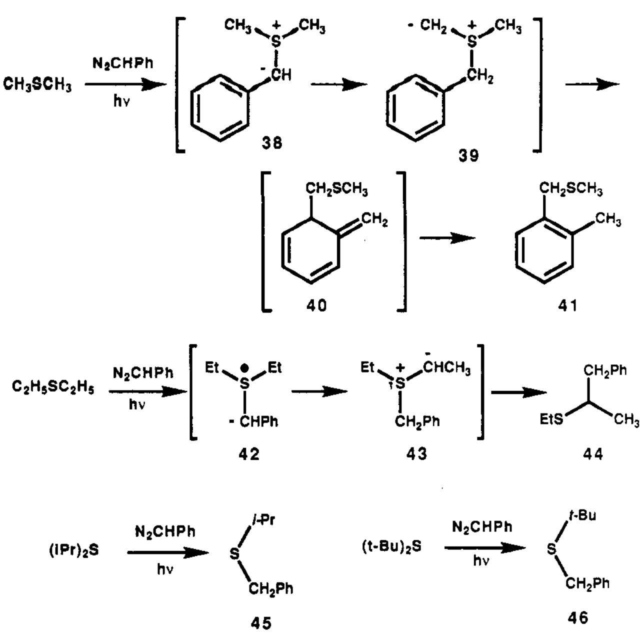
The formation of rearranged insertion products that result from the reaction of carbenes with compounds containing heteroatoms in the allylic position can be explained in terms of the ylide mechanism. The relative rate of ylide formation to addition onto the π-bond depends on the nucleophilic characteristics of the heteroatom present in the allylic compound (S > O > Cl). This trend is consistent with the idea that ylides are produced by electrophilic attack of the carbene on the heteroatom. The copper-catalyzed process favors ylide formation in contrast with the photochemical reaction. This may be due to the fact that the attacking species in copper-catalyzed reactions are Cu-complexed carbenoids which are more selective than the free carbenes generated by photochemical methods.



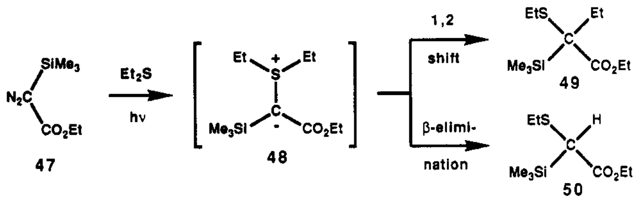
Photolysis of phenyl- and diphenyldiazomethanes in dimethyl sulfide gives ortho-substituted sulfur compounds through a sulfonium ylide intermediate.[60] For example, irradiation of phenyl diazomethane in dimethyl sulfide at room temperature produced *o*-methylbenzyl methyl sulfide (**41**) (Scheme 3). The formation of sulfide **41** involves initial generation of an unstable sulfonium ylide **39** which subsequently undergoes a Sommelet–Hauser rearrangement to give the observed product. In contrast, the photochemical decomposition of phenyldiazomethane in diethyl sulfide afforded sulfide **44**. This product results from a proton shift of the initially formed sulfonium ylide **42** to produce the rearranged ylide **43**, which then undergoes a subsequent Stevens rearrangement. Photolysis of a mixture of phenyldiazomethane and diisopropyl or di-*tert*-butyl sulfide gave **45** and **46** as the major products.

In recent years there has been an increased interest in the chemistry of reactive intermediates bearing an organosilyl group. One typical example involves the

SCHEME 3

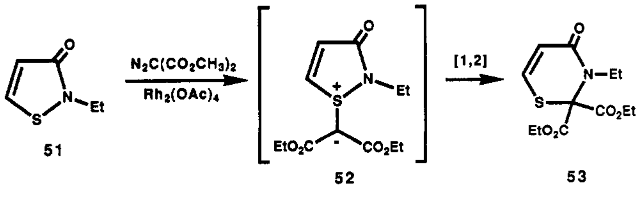


irradiation of ethyl(trimethylsilyl)diazoacetate (**47**) in excess diethyl sulfide which produced ethyl α-(methylthio)-α-(trimethylsilyl)butyrate (**49**) as the major product.[61] Formation of this material is consistent with

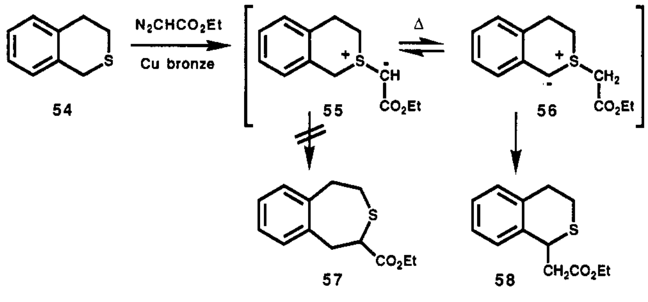


a mechanism involving addition of the carbene onto the sulfide to give sulfonium ylide **48** which then undergoes a 1,2-shift to give the observed product. The isolation of ylide **48** when the reaction was carried out at low temperature provides good support for this mechanism. Ethyl (ethylthio)(trimethylsilyl)acetate (**50**) was also formed as a minor product and corresponds to a β-elimination of the intermediate sulfonium ylide **48**. Photolysis of ethyl (trimethylsilyl)diazoacetate (**47**) with other dialkyl sulfides gave similar results.

The transition-metal-catalyzed reaction of 2-substituted isothiazol-3(2*H*)-ones with diazo compounds results in the formation of 3,4-dihydro-1,3-thiazin-4-(2*H*)-ones.[62] Treatment of *N*-ethylisothiazol-3(2*H*)-one (**51**) with dimethyl diazomalonate using rhodium(II) acetate as the catalyst afforded 3,4-dihydro-1,3-thiazin-4(2*H*)-one **53** in 70% yield. This reaction is thought to proceed via a mechanism which involves trapping of the carbenoid species by the nucleophilic sulfur atom to give sulfonium ylide **52** which then undergoes ring expansion by a 1,2-shift. This reaction sequence is notable in that it constitutes a new type of S–N cleavage of the isothiazole ring system induced by carbenoids. No products of carbenoid addition to the double bond were detected in the crude reaction mixture.

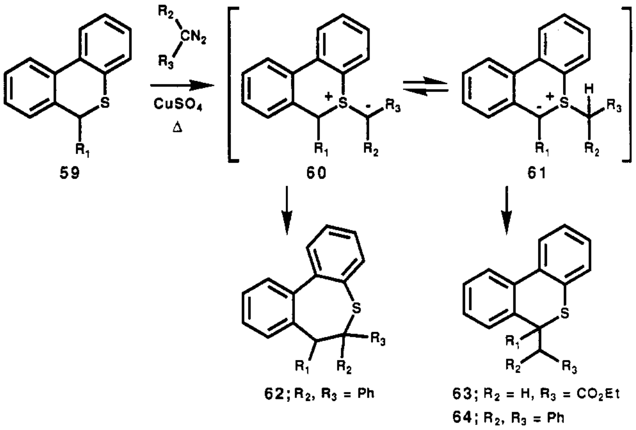


Pellicciari and co-workers have investigated the rearrangement of isothiochroman sulfonium ylides which proceed via a *thermal ylide exchange* reaction.[63] The copper–bronze-catalyzed decomposition of ethyl diazoacetate in isothiochroman (**54**) did not produce the expected Stevens-type rearrangement product **57**.



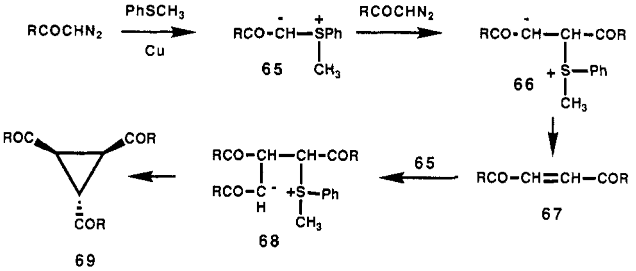
Instead, the major material isolated corresponded to ethyl isothiochroman-1-ylacetate (**58**). Formation of **58** was rationalized in terms of a mechanism involving addition of the carbenoid species onto the sulfur atom to generate an unstable sulfonium ylide **55**. This species is transformed into the endocyclic ylide **56** by the thermal ylide exchange reaction. A nonconcerted Stevens-type rearrangement of **56** would account for the formation of ethyl isothiochroman-1-ylacetate (**58**).

An analogous transformation was encountered upon treatment of 6-phenyl-6*H*-dibenzo[*b*,*d*]thiopyran (**59**) with ethyl diazoacetate in the presence of copper(II) sulfate.[64] This result is most consistent with a mechanism involving the thermal ylide exchange process. Treatment of 6-phenyl-6*H*-dibenzo[*b*,*d*]thiopyran (**59**) with diphenyldiazomethane gave rise to a mixture of 6,6-diphenyl-6,7-dihydrodibenzo[*b*,*d*]thiepin (**62**) and 6-(diphenylmethyl)-6*H*-dibenzo[*b*,*d*]thiopyran (**64**).

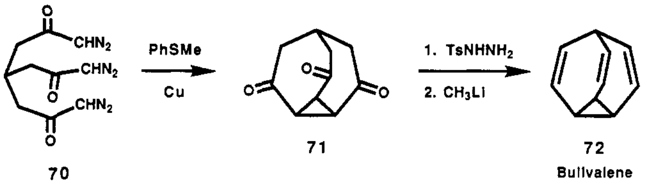


This result suggests that the ylides **60** and **61** undergo rapid exchange in competition with a possible Stevens rearrangement. The relative yields of the products were found to be markedly influenced both by the presence of a 6-phenyl substituent and by the nature of the R groups linked to the ylide methanide carbon. This observation is explicable in terms of relative stabilities of the first formed ylide **60**, which depend on the electron-withdrawing ability of the R_2 and R_3 groups and the enhanced migratory aptitude of C_6, that arises from the 6-phenyl substituent.

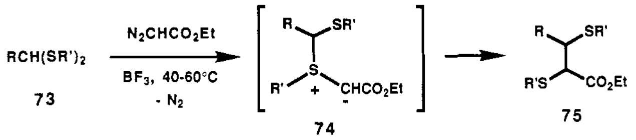
The catalytic decomposition of α-diazo ketones in the presence of thioanisole resulted in the formation of cyclopropane derivatives in good yield.[65-67] Mechanistic investigations suggest initial involvement of ylide **65** which reacts with an additional molecule of diazo ketone followed by elimination of thioanisole to produce alkene **67**. Further reaction of **67** with ylide **65** ultimately affords the observed cyclopropane derivative **69**.



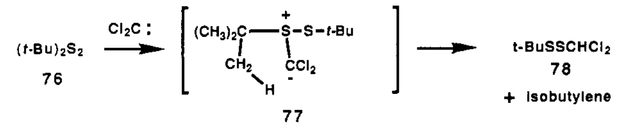
The analogous intramolecular reaction was also carried out by heating methylidynetris(α-diazoacetone) (**70**) with copper(II) sulfate and thioanisole.[67] This resulted in the formation of trione **71** which was subsequently reduced to bullvalene (**72**) in modest yield.



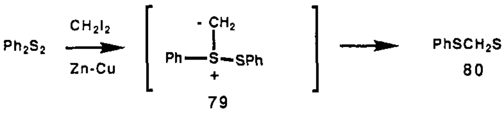
Treatment of thioacetal **73** with ethyl diazoacetate in the presence of boron trifluoride afforded the vicinal bissulfide **75**.[68] Formation of this material can be accommodated by the initial generation of sulfonium ylide **74** which then undergoes a selective 1,2-shift to give the observed product. An alternate explanation, equally possible, is that the Lewis acid acts upon the thioacetal forming RCH$^+$SR′ which adds to ethyl diazoacetate. The reaction appears to be general for thioacetals derived from alkyl and aryl aldehydes.



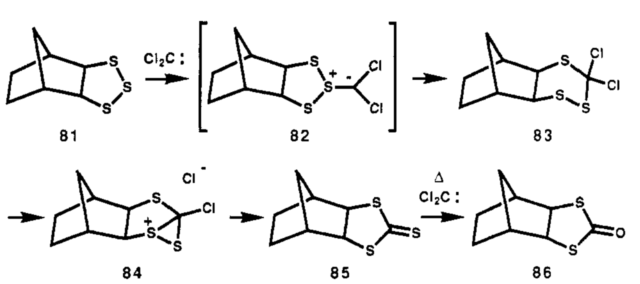
Although the disulfide linkage can be readily cleaved by a variety of reagents,[69] selective scission of the C–S bond of a disulfide is much more difficult to achieve. Searles and Wann reported several years ago that the reaction of a carbene with a disulfide resulted in selective C–S bond cleavage, with the disulfide linkage remaining intact.[70] For example, treatment of *tert*-butyl disulfide (**76**) with dichlorocarbene resulted in the formation of *tert*-butyl dichloromethyl disulfide (**78**) in 80% yield. This transformation was rationalized in terms of an electrophilic addition of the carbene onto one of the sulfur atoms to form intermediate sulfonium ylide **77**. This reactive species then undergoes β-elimination, producing 1,1-dimethylethene and disulfide **78**. Similar results were also observed by Ando and coworkers in their studies dealing with the irradiation of phenyl- or diphenyldiazomethane in the presence of dialkyl disulfides.[60]



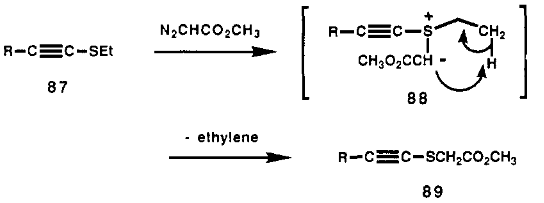
Although dichlorocarbene does not react with diaryl disulfides, zinc and copper carbenoid species do react to produce S–S bond insertion products.[71] With the Simmons–Smith reagent (ICH$_2$ZnI), several diaryl disulfides underwent insertion of CH$_2$ between the sulfur atoms to give bis(phenylthio)methanes (**80**). The reaction is consistent with a mechanism involving addition of the zinc carbenoid onto the disulfide to give sulfonium ylide **79** which then undergoes a 1,2-shift of a thiophenyl group to afford the observed product.



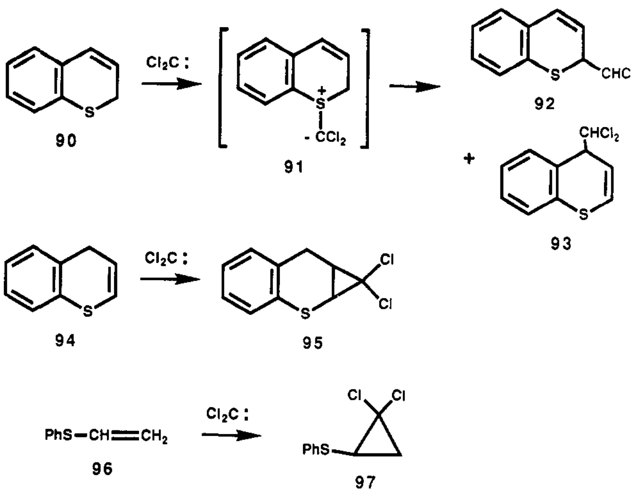
The reaction of cyclic trisulfides (i.e. **81**) with dichloro- and dibromocarbene under phase-transfer catalysis results in the formation of thiocarbonate (**86**).[72] When the reaction was carried out for short periods of time, trithiocarbonate **85** was produced. Reaction of trithiocarbonate **85** with dichlorocarbene under the experimental conditions used gave thiocarbonate **86** and is consequently thought to be a reaction intermediate. The formation of trithiocarbonate **85** was rationalized in terms of electrophilic attack of the dichlorocarbene onto the central sulfur atom to generate ylide **82** which could then undergo bond rearrangement to give the neutral species **83**. Once **83** is formed, the nucleophilicity of sulfur and the propensity of chloride to act as a leaving group allows for the formation of **85** via sulfonium intermediate **84**.



Alkynes are generally less reactive than sulfides toward carbenes and carbenoids. Increasing the electron density of the π-system with an alkyl sulfide, however, enhances the reactivity and affords (alkynylthio)-acetates. This reaction proceeds via an acetylenic sulfonium ylide which undergoes a β-elimination.[73] Heating an equimolar mixture of methyl diazoacetate and acetylenic sulfide **87** in the presence of a catalytic amount of anhydrous copper(II) sulfate at 60 °C gave sulfide **89** in 85% yield. No cyclopropene derivatives or rearrangement products were observed. In competitive experiments, acetylenic sulfide **87** was found to be more reactive toward carboethoxycarbene than di-



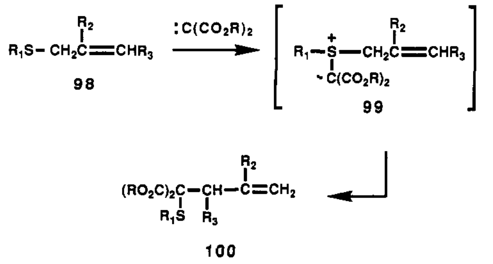
SCHEME 4



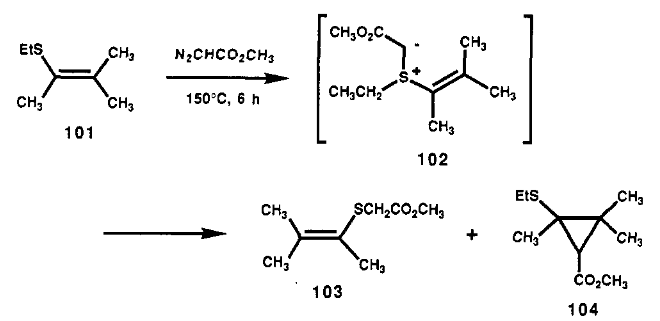
ethyl sulfide. This selectivity is probably due to the contribution from the resonance structure RC$^-$=C=S$^+$Et, which is possible because sulfur can expand its valence shell.

Halocarbenes react with dihydropyran to give cyclopropyl adducts. Similarly, vinyl sulfides react with halocarbenes to give cyclopropanes as well (i.e. 94 → 95; 96 → 97). In contrast, the reaction of 2*H*-1-benzothiopyran (**90**) with dichlorocarbene affords the insertion products 2-(dichloromethyl)-2*H*-1-benzothiopyran (**92**) and 4-(dichloromethyl)-4*H*-1-benzothiopyran (**93**)[74] (Scheme 4). These products are derived from sulfonium ylide **91** which undergoes a proton transfer followed by a 1,2- or 1,4-shift of the dichloromethyl group. Notably, dichlorocarbene did not add across the C–C double bond to form a cyclopropane derivative. Interestingly, the reaction of the isomeric 4*H*-1-benzothiopyran (**94**) with dichlorocarbene gives only the cyclopropanated product **95**. The remarkable reactivity difference of these two olefins was attributed to the difference in conjugation of sulfur with the olefinic π-bond. As would be expected, treatment of the acyclic vinyl sulfide **96** with dichlorocarbene gave dichlorocyclopropane **97** in excellent yield.[75] Sulfur 3p orbital interaction with the olefinic π-bond in **94** effectively activates the double bond toward reaction with the electrophilic carbene.

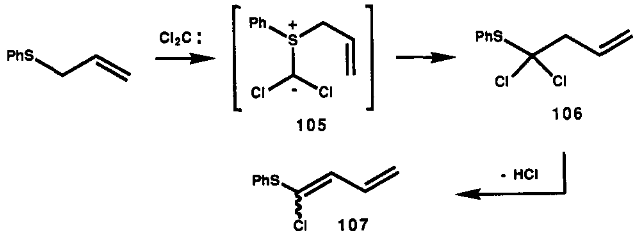
The reaction of allylic sulfides with carboalkoxycarbenes under thermal and photolytic conditions produces C–S insertion products and, to a lesser degree, some addition products to the olefin.[59,76] The reaction with allyl sulfide involves a sulfur ylide intermediate (**99**) followed by a 2,3-sigmatropic rearrangement, since the carbene attacks a sulfur atom more readily than a carbon–carbon double bond.



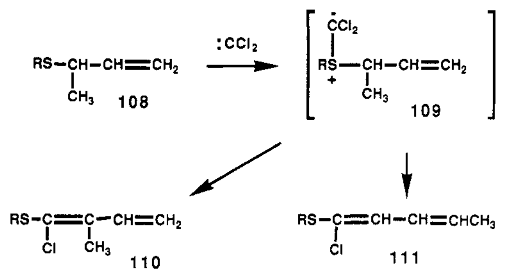
The reaction of vinyl sulfides with carboethoxycarbene leads to the formation of methyl (vinylthio)acetate as the major product and to a cyclopropane adduct as the minor product.[77] This is illustrated by the thermal decomposition of methyl diazoacetate in the presence of trimethyl(ethylthio)ethylene (**101**) to give a 6:1 mixture of methyl (vinylthio)acetate **103** (39%) and cyclopropane **104** (6%). Methyl (vinylthio)acetate **103** is thought to be produced via a mechanism involving formation of sulfonium ylide **102** which then gives **103** by a β-elimination process. Cyclopropane **104**, on the other hand, is derived by cyclopropanation of **101** with methyl diazoacetate. Other vinyl sulfides react to form the analogous methyl (vinylthio)acetates. In cases where no β-hydrogens were present, cyclopropanes were formed as the major product. The data reveal that attack of carbomethoxycarbene on sulfur appears to be 4–5 times faster than addition onto the double bond. On the other hand, the electrophilic carbenoid, derived from the copper sulfate catalyzed reaction, attacks the vinyl sulfide less efficiently in comparison with the attack on an alkyl sulfide sulfur. It has been argued that the electron density on the vinyl sulfide sulfur is decreased somewhat because the lone of electrons on sulfur is delocalized to some extent by overlap of the 3p-orbital of sulfur with the carbon 2p orbital.



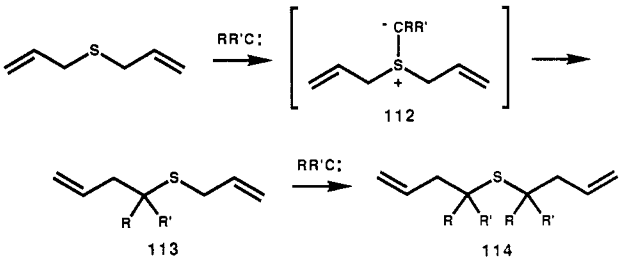
The 2,3-sigmatropic rearrangement of allylsulfonium ylides generated by the addition of a carbene onto an allyl sulfide has been extensively studied.[34,78-93] One of the earliest examples was reported by Parham and Groen in 1964.[78-80] Treatment of noncyclic allyl sulfides with dichlorocarbene led to the formation of 1-chloro-1-substituted-thiobutadienes in high yield. In the case of allyl phenyl sulfide, reaction with dichlorocarbene resulted in the formation of 1-chloro-1-(phenylthio)butadiene (**107**) in 60% yield. This result was interpreted to proceed through the formation of sulfonium ylide **105** which then undergoes a 2,3-sigmatropic rearrangement to produce dichloride **106**. Subsequent elimination of hydrogen chloride afforded the observed product.



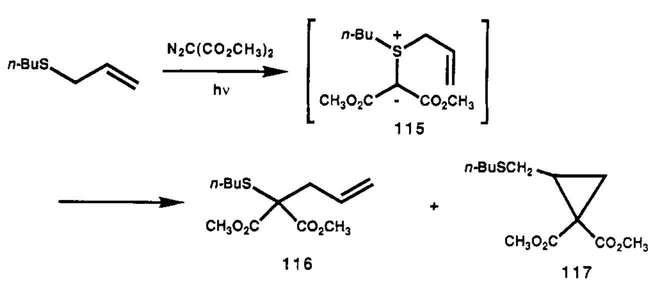
With appropriately substituted allylic sulfides, Parham and co-workers were able to establish a duality of mechanisms. The isolated butadiene **111** (37%) was formed by a process involving a 2,3-sigmatropic rearrangement of sulfonium ylide **109**. For the minor product **110** (20%), the α-insertion reaction (**108** → **110**) was suggested to proceed by a mechanism analogous to the Stevens rearrangement.



Treatment of diallyl sulfide with diazomethane in the presence of a copper catalyst generated sulfonium ylide **112** which was found to undergo a 2,3-sigmatropic rearrangement to produce allyl sulfide **113**.[81,82] Formation of sulfide **113** could also be explained by assuming that sulfonium ylide **112** undergoes a 1,2-shift of the allyl group. However, deuterium labeling studies unequivocably established that this reaction only occurs via the 2,3-sigmatropic rearrangement pathway. In the presence of excess diazomethane, homoallylic sulfide **114** was isolated as the major product.

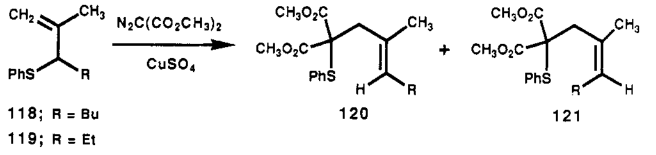


Diazo compounds have been known to produce singlet carbenes in thermal or photolytic reactions,[94] triplets in photosensitized decompositions,[95] and carbenoids in transition-metal-catalyzed reactions.[96] The photochemical decomposition of dimethyl diazomalonate in the presence of allyl *n*-butyl sulfide afforded the homoallyl sulfide **116** as the major product (57%) together with some cyclopropane **117** (11%).[76]

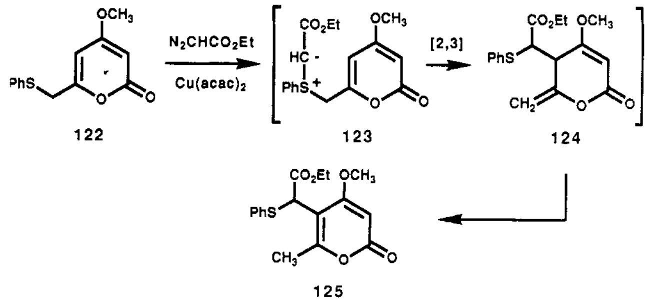


The formation of sulfide **116** is consistent with a mechanism involving initial generation of sulfonium ylide **115** followed by a 2,3-sigmatropic rearrangement. In contrast to these results, the photosensitized reaction led to the formation of cyclopropane **117** as the major product in 55% yield with lesser quantities of **116** (28%). This result indicates the preference of a triplet carbene to add to the olefinic π-bond instead of to the sulfur atom which is the preferred route of singlet carbenes. The copper sulfate catalyzed reaction of dimethyl diazomalonate in allyl *n*-butyl sulfide, on the other hand, produced only sulfide **116** in 93%. The reaction of allyl sulfides with ethyl diazoacetate produced similar results.[59] This high selectivity was explained in terms of a copper complex of the carbene which corresponds to a more selective species.

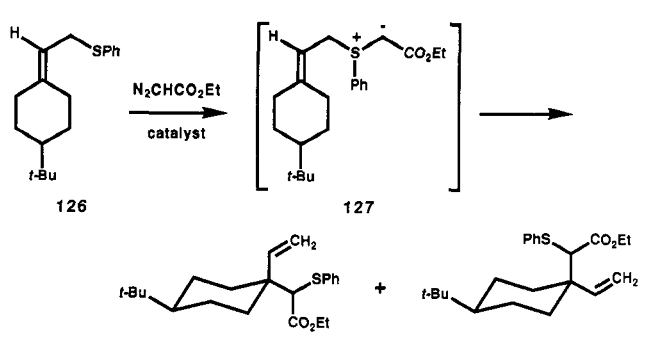
Although allylic sulfonium ylides are readily generated by the addition of a carbene precursor to a sulfide, few studies have been done to demonstrate the stereospecificity of this reaction. This reaction is of potential interest for the synthesis of trisubstituted olefins. Grieco and co-workers were the first to develop an elegant stereoselective trisubstituted olefin synthesis employing allylic sulfonium ylides.[83] When dimethyl diazomalonate and an α-substituted methallyl sulfide (e.g. **118**; R = butyl) in the presence of a catalytic amount of anhydrous copper sulfate were heated, a 9:1 mixture of the *E* and *Z* olefins **120** and **121** were produced, respectively. The analogous reaction using α-substituted methallyl sulfide **119** (R = ethyl) also afforded a 9:1 mixture of the *E* and *Z* olefins in high overall yield. These transformations demonstrate the potential of the 2,3-sigmatropic rearrangement in olefin synthesis.



The paucity of good methods to prepare 2-pyrones with substituent groups in the C_3 and C_5 positions has retarded efforts to synthesize natural products containing this functionality. One method that has been utilized involves the treatment of 4-methoxy-6-[(phenylthio)methyl]-2-pyrone (**122**) with an excess of ethyl diazoacetate in the presence of copper(II) acetylacetonate to give the 5-substituted-2-pyrone **115** in good yield.[84] Formation of this rearranged material is consistent with the generation of sulfonium ylide **123** which undergoes a subsequent 2,3-sigmatropic rearrangement to produce intermediate **124**. A 1,3-sigmatropic hydrogen shift affords the observed 2-pyrone **125**.



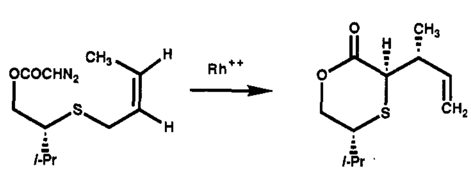
The stereochemistry of the 2,3-sigmatropic rearrangement of sulfonium ylides with a conformationally biased cyclohexylidene ring system has been investigated.[85] Treatment of allyl sulfide **126** with ethyl diazoacetate in the presence of a catalytic amount of (triethyl phosphite)copper(I) chloride resulted in a 9:1 mixture of the unsaturated sulfide esters **128** and **129**. Treatment of allyl sulfide **126** with dichlorocarbene afforded a similar distribution of products. The overall process offers a potentially versatile method for the stereoselective synthesis of quaternary centers flanked by useful functional groups. The results obtained suggest that the extreme sensitivity of these 2,3-sigmatropic processes to the steric environment may be



126 127 128 129

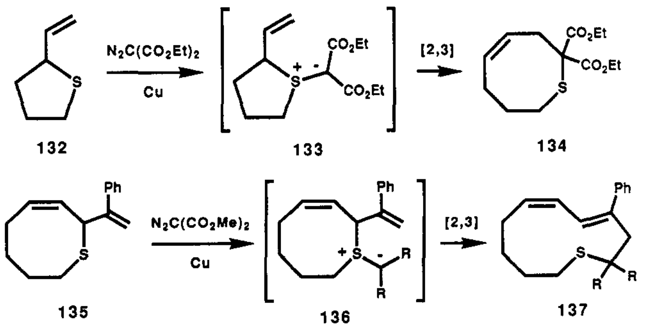
a general attribute to this class of reactions.

A thioxanone-based 2,3-sigmatropic rearrangement strategy has been used by Kurth and co-workers for the synthesis of Cβ-chiral pent-4-enoic acid.[86] The reaction was found to proceed with good Cβ-induction and without the requirements of an allylic alcohol resolution. Rhodium(II) acetate decomposition of *Z*-α-diazo ester **130** produced the four possible thioxones. The major isomer (**131**) was formed with 78% diastereoselectivity. A slightly improved diastereoselectivity was obtained by using hexarhodium hexadecacarbonyl as the catalyst.



130 131

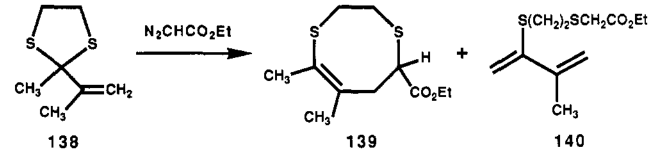
During the past 15 years, there have been a number of reports describing the synthesis of macrocyclic products[87-92] by a series of 2,3-sigmatropic shifts. This process has been described as a "*ring growing sequence*" to denote an easily repeatable reaction scheme which allows for systematic ring enlargement.[89] The first ring expansion on a sulfur substrate was performed by using a carbenoid route to sulfur ylides from a copper-catalyzed diazomalonate decomposition.[88] Thus, treatment of allyl sulfide **132** with diethyl diazomalonate in the presence of copper bronze at 100 °C afforded the ring-expanded product **134** in 50% yield. Likewise, the reaction of allyl sulfide **135** with diethyl diazomalonate gave **137** as the major product. The formation of both of these macrocycles is consistent with the initial generation of a sulfonium ylide intermediate (i.e. **133** or **136**) which subsequently undergoes a 2,3-sigmatropic rearrangement.



132 133 134 135 136 137

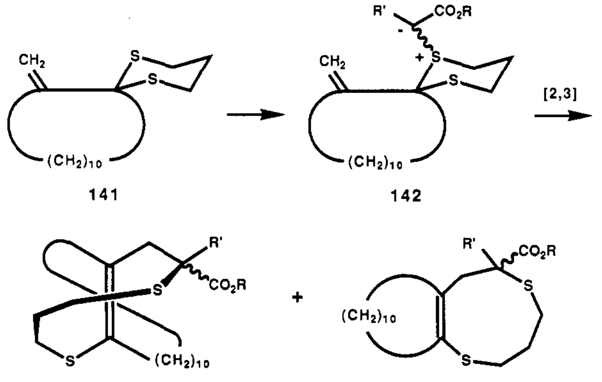
R = CO$_2$Me

Although the catalytic method for ylide generation is applicable to the general classification of allylic substrates, its most advantageous use is in the preparation of allylic ylides that are not amenable to generation by the base-promoted methodology. The base-promoted reaction, developed primarily by Vedejs and co-workers, has been used with notable success for macrolide synthesis,[97] whereas the catalytic method for ylide generation was reported to be inadequate.[98] However, recent results by Doyle with 1,3-dithione **138** suggests that the use of rhodium(II) acetate with diazo esters is an attractive alternative to the base promoted method.[90] Thus, Doyle has found that the reaction of **138** with ethyl diazoacetate in the presence of a Rh^{2+} catalyst gives a 2:3 mixture of **139** and **140**. It should be noted that the rhodium catalyst is employed at temperatures that are significantly lower than those previously used with copper catalysts. The higher temperatures required for ylide generation with sulfur- or nitrogen-containing substrates compared with oxygen or halide containing substrates, can be attributed to coordination of rhodium(II) acetate with the sulfur or nitrogen atoms thereby inhibiting the catalytic decomposition of these diazo compounds. Copper catalysts are also inhibited by coordination with sulfur, and the even higher temperatures required for their action on diazo compounds is due to this association. Also, in Vedejs' use of copper catalysts, yields of **134** greater than 50% could not be obtained despite all possible variations in reaction conditions.



138 139 140

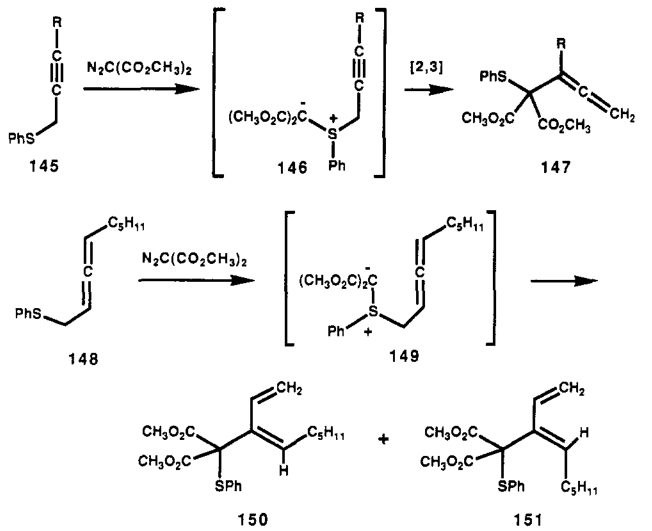
Synthesis of the betweenanene ring system has been reported independently by Nickon[91] and Fava[92] and is based on Vedejs' earlier "ring growing sequence". When dithioketal **141** was heated with ethyl diazoacetate and copper sulfate, the derived sulfonium salt **142** produced the desired betweenanene **143** and its *Z* isomer **144** in a 4:1 ratio. This finding indicates that the second sulfur atom in dithioketals does not obstruct the 2,3-sigmatropic rearrangement when ylides are generated by reaction with diazo esters. It should be noted that with this system, eliminations and Steven's-type 1,2-shifts prevailed when strong bases act on a preformed methylsulfonium salt.



141 142 143 144

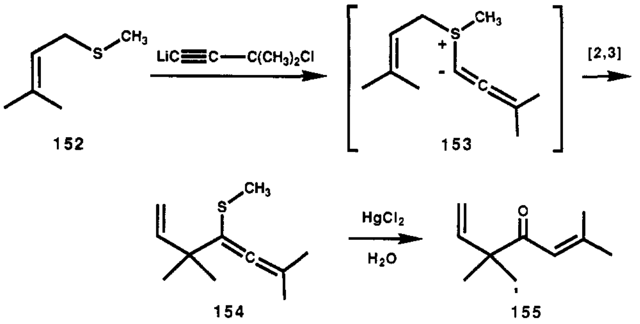
The 2,3-sigmatropic rearrangement of acetylenic and allenic sulfonium ylides results in the formation of allenes and conjugated dienes in good yield.[93] Heating a mixture of dimethyl diazomalonate and acetylenic sulfide **145** in the presence of a catalytic amount of

SCHEME 5



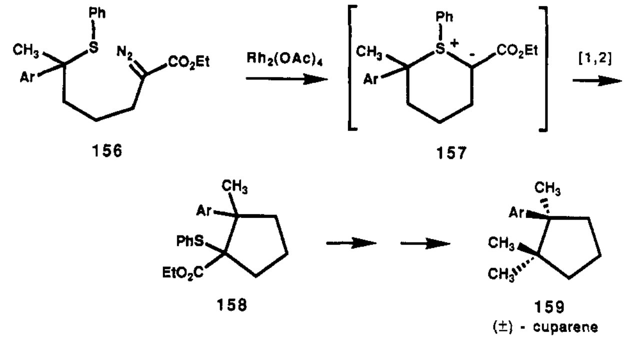
anhydrous copper sulfate at 100 °C resulted in a 71% isolated yield of allene **147** (Scheme 5). 2,3-Sigmatropic rearrangements are also applicable to allenic sulfonium ylides as was demonstrated by the smooth conversion of allenic sulfide **148** into a 4:1 mixture of dienes **150** and **151** by reaction with dimethyl diazomalonate in the presence of copper sulfate.

The synthetic potential of the 2,3-sigmatropic rearrangement of allylic sulfonium ylides is nicely illustrated by the synthesis of Artemisia ketone.[34] Treatment of allylic sulfide **152** with a vinylidene precursor[99] generated the allenic ylide **153** in situ which rapidly underwent a 2,3-sigmatropic rearrangement to produce thioether **154** as the major product. Hydrolysis of this material in the presence of mercury(II) chloride gave the Artemisia ketone **155** in excellent yield.



C. Intramolecular Formation of Sulfur Ylides

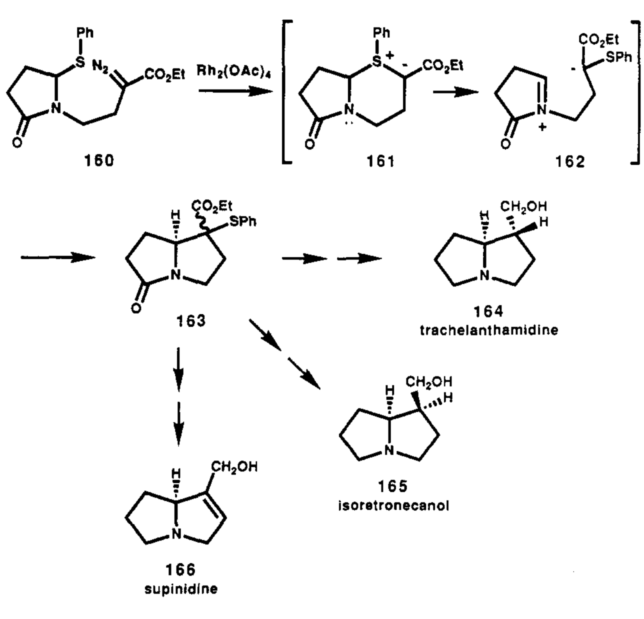
Interest in the development of new methods for the construction of quaternary carbon centers continues unabated, not only for synthetic reasons, but also because of the observation of such centers in a variety of natural products.[100] A number of aromatic sesquiterpenes contain the 1-aryl-1,2,2-trimethylcyclopentane ring system. The key step in the Kametani approach to the aromatic sesquiterpene (±)-cuparene (**159**), consisted of an intramolecular carbenoid displacement reaction of a benzyl sulfide derivative.[32] Treatment of diazo ketone **156** with a catalytic amount of rhodium(II) acetate in refluxing benzene gave arylcyclopentane **158**. This result was rationalized by the formation of sulfonium ylide **157** followed by a 1,2-ring contraction. Cyclopentane **158** was subsequently converted to (±)-cuparene. This example nicely illustrates that the intramolecular carbenoid displacement reaction represents a novel method for the construction of quaternary carbon centers.

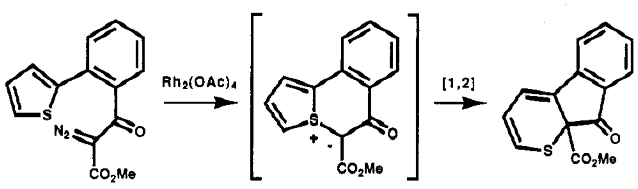


This same strategy was also used for the synthesis of several pyrrolizidine alkaloids.[33] Treatment of diazo ketone **160** with a catalytic amount of rhodium(II) acetate in refluxing benzene produced amide **163** in 55% yield.[33] The formation of this material is consistent with a mechanism involving addition of the carbenoid onto the sulfur atom to form sulfonium ylide **161** which then fragments to give iminium ion **162**. Cyclization of this species affords the observed product. Subsequent modification of structure **163** allows for the synthesis of three pyrrolizidine alkaloids: (±)-trachelanthamidine (**164**), (±)-isoretronecanol (**165**), and (±)-supinidine (**166**) (Scheme 6). This intramolecular carbenoid displacement approach should be applicable to the synthesis of other naturally occurring necine bases.

Only a few carbenes are known to react with thiophenes to give sulfur ylides.[51-53] In an attempt to isolate the aromatic thiophenium ylide **168**, α-diazo ketone **167** was treated with rhodium(II) acetate catalyst in benzene.[101] None of the expected ylide **168** could be isolated. Instead, the major product isolated was **169** resulting from a Stevens rearrangement of ylide **168**. The fact that sulfur ylide **168** was not stable enough to isolate is somewhat surprising considering that Porter and co-workers were able to isolate the related sulfonium ylide **15** from the reaction of thiophene with a distabilized rhodium carbenoid.[51-53]

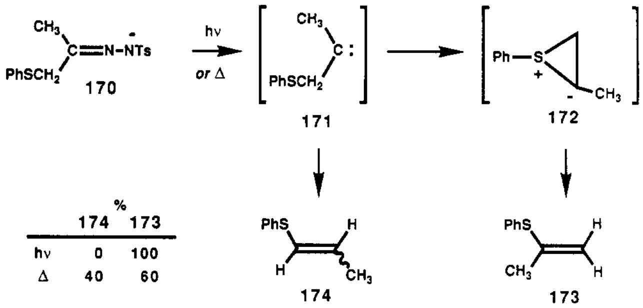
SCHEME 6





167 168 169

α-(Arylthio)alkylcarbenes were found to form labile episulfonium ylides which subsequently rearranged to vinyl sulfides.[102] An example of this process was uncovered in the thermal or photolytic decomposition of the tosylhydrazone sodium salt **170** which gave thioenol ether **173** as the major product.[102] A 1,2-hydrogen shift of carbene **171** would be expected to afford olefin **174**.

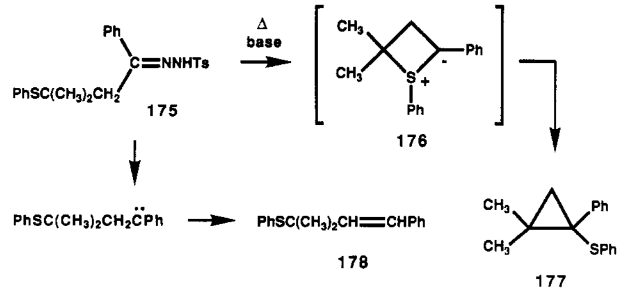


170 171 172 174 173

	% 174	173
hν	0	100
Δ	40	60

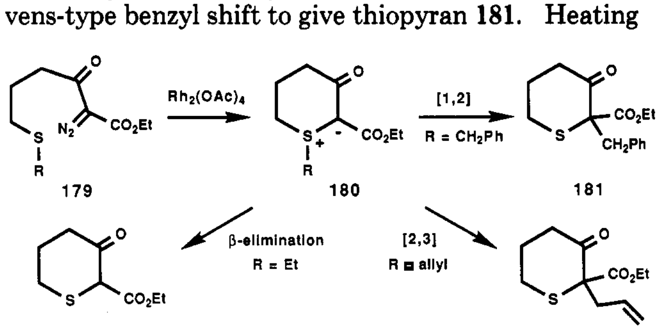
However, this material is only observed as a minor product. Formation of the thioenol ether **173** is consistent with a mechanism involving addition of the carbenoid onto the sulfur atom to give cyclic sulfonium ylide **172** which then rearranges to the observed product.

When a sulfide linkage is introduced into the same molecule as a carbene, it can be expected that the carbene carbon will be transformed into the ylide carbon by intramolecular ylide cyclization. Introduction of an additional methylene group allows for the preparation of cyclopropanes. This sequence was demonstrated by heating tosylhydrazone **175** with sodium methoxide in diglyme and isolating cyclopropane **177** in 44% yield.[102] This result can be rationalized by cyclic sulfonium ylide generation (i.e. **176**) which is then followed by ring contraction to give the observed product. A 1,2-hydrogen shift of the carbene to form alkene **178** (50%) was also encountered as a competing process. The relative dominence of these two processes seems to be markedly affected by the nature of the substituents. Ylide formation was enhanced by phenyl substitution on the carbene carbon since the aromatic ring helps to stabilize the charges in the ylide intermediate. The results also indicate that the ylide process gains an advantage over the hydrogen migration path when the resulting thietanonium ylide can undergo a facile rearrangement.



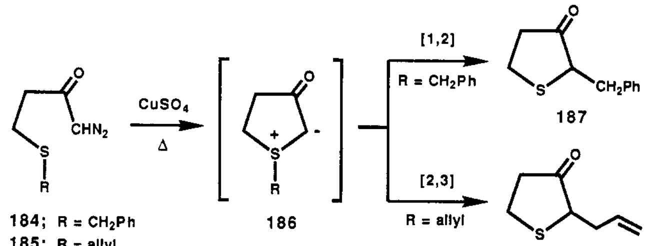
175 176 178 177

Attempts to effect the intramolecular version of the sulfide–carbene reaction have usually resulted in products arising from rearrangement of nonisolable cyclic sulfonium ylides. One example where a stable cyclic ylide is formed has been reported by Moody and Taylor.[103] Reaction of diazo sulfide **179** (R = benzyl or ethyl) with rhodium(II) acetate in refluxing benzene produced the stable cyclic ylide **180**. Thermolysis of the benzyl sulfonium ylide **180** resulted in a 1,2-Stevens-type benzyl shift to give thiopyran **181**. Heating the ethyl sulfonium ylide **180** in xylene produced thiopyran **182**. Formation of this material is consistent with loss of ethylene via a β-elimination reaction. The *S*-allyl sulfonium ylide **180** can not be isolated due to its propensity to undergo a 2,3-sigmatropic rearrangement to produce thiopyran **183**.



179 180 181 182 183

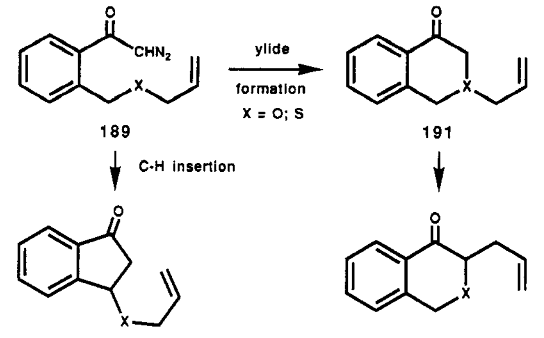
An analogous set of results were encountered from carbenes generated from 4-(benzylthio)- and 4-(allylthio)-1-diazobutan-2-ones (**184** and **185**).[104] The copper(II) sulfate catalyzed decomposition of **184** resulted in the formation of cyclic ylide **186** (R = benzyl) which subsequently undergoes a Stevens 1,2-shift of the benzyl group to ultimately yield thiolanone **187** in 51% yield.



184; R = CH_2Ph
185; R = allyl
186 187 188

Reaction of 4-(allylthio)-1-diazobutan-2-one (**185**) under identical conditions afforded thiolanone **188** in 77% yield. Formation of this material is consistent with a mechanism involving intramolecular electrophilic addition of the carbenoid onto the sulfur atom to generate the cyclic sulfonium ylide **186** (R = allyl) which then undergoes a 2,3-sigmatropic rearrangement to produce the observed product.

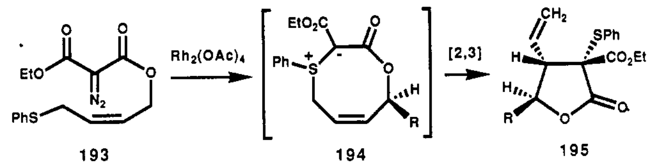
Metal-catalyzed reactions of diazo compounds with a broad selection of allylic substrates result in products derived from 2,3-sigmatropic rearrangement of intermediate allylic ylides. A related process also occurs upon treatment of diazo compounds of type **189** (X = O) with rhodium(II) acetate. In this case, a 1:1 mixture of two compounds corresponding to C–H insertion (**190**) and ylide rearrangement (**192**) were isolated. In order to assess the significance of the heteroatom to the product distribution, the Rh^{2+}-catalyzed reaction of the thio-substituted diazo ketone (X = S) was examined.[105] In this case, the ratio of ylide formation to C–H insertion was 9:1, in marked contrast to the 1:1 ratio ob-



189 191 190 192

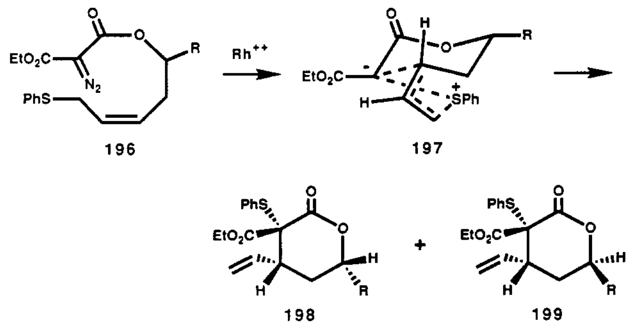
tained from the oxygen system. This would suggest that the larger and more polarizable sulfur atom is much more effective in coordination with the metal carbene center. The product distribution is also consistent with the relative nucleophilicities of the two heteroatoms.

The stereoselective synthesis of contiguously substituted butyrolactones based on the cyclic allylsulfonium ylide rearrangement has been reported by Yoshikoshi and co-workers.[106] α-Diazomalonates of Z-4-(phenylthio)-2-buten-1-ol homologues stereoselectively provide γ-alkyl-α-(ethoxycarbonyl)-α-(phenylthio)-β-vinylbutyrolactones by 2,3-sigmatropic rearrangement of a cyclic sulfonium ylide which was generated intramolecularly. For example, treatment of diazomalonate **193** with a catalytic amount of rhodium(II) acetate in refluxing benzene gave butyrolactone **195** in 70% yield. The stereochemistry of the final product demonstrates that an alkyl group (R) prefers to orient itself in the equatorial position in the transition state of the rearrangement.



193 194 195

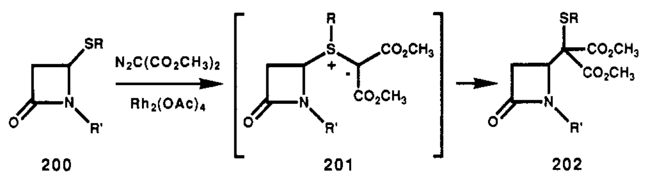
A new entry into the perhydrofuro[2,3-*b*]furan ring system using a similar sequence of reactions has also been explored by Yoshikoshi and co-workers.[107] Treatment of the α-diazomalonate **196** with rhodium(II) acetate stereoselectively provided a 4:1 mixture of substituted valerolactones **198** and **199** via a 2,3-sigmatropic rearrangement of a nine-membered cyclic allylsulfonium ylide. The rearrangement product was subsequently converted to the 5-alkylperhydrofuro-[2,3-*b*]furan ring system by ozonolysis followed by acid treatment. The stereochemistry of substituents on the lactone ring of **198** is understandable if one considers the most favorable conformation (i.e. **197**) for the transition state of the rearrangement.



196 197 198 199

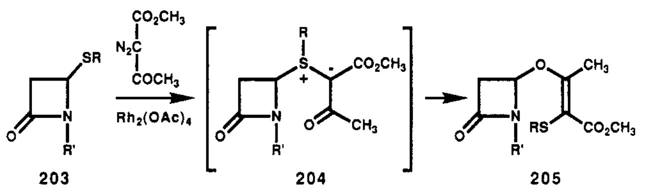
D. Involvement of Sulfur Ylides in β-Lactam Antibiotic Syntheses

Interest in the chemistry of β-lactam antibiotics continues to thrive.[108] The interaction of carbenes or carbenoids with sulfur atoms has also been applied to the conversion of the penicillin nucleus into cephalosporin derivatives by a number of research groups.[11-31] One example involves the reaction of 4-thioazetidinones **200** with dimethyl diazomalonate in the presence of rhodium(II) acetate to give sulfides **202** in good yield.[11,12] Formation of this product can be explained by carbenoid addition to the sulfur atom producing sulfonium ylide **201** which then undergoes a 1,2-shift. When the starting 4-thioazetidinone was substituted in the 3-position, addition of the carbenoid was found to occur stereoselectively from the least-hindered side to generate a trans-substituted product.



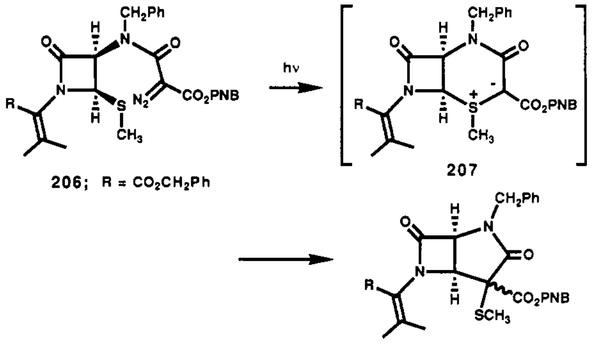
200 201 202

In contrast, treatment of 4-(phenylthio)-2-azetidinone **203** with α-diazoacetoacetate in refluxing benzene in the presence of a catalytic amount of rhodium(II) acetate afforded the 4-oxa-2-azetidinone **205**.[12] Mechanistically, this result can be explained by initial formation of sulfonium ylide **204** followed by nucleophilic displacement by the carbonyl oxygen atom to give the observed product. No product resulting from a 1,2-shift of the intermediate sulfonium ylide was observed.



203 204 205

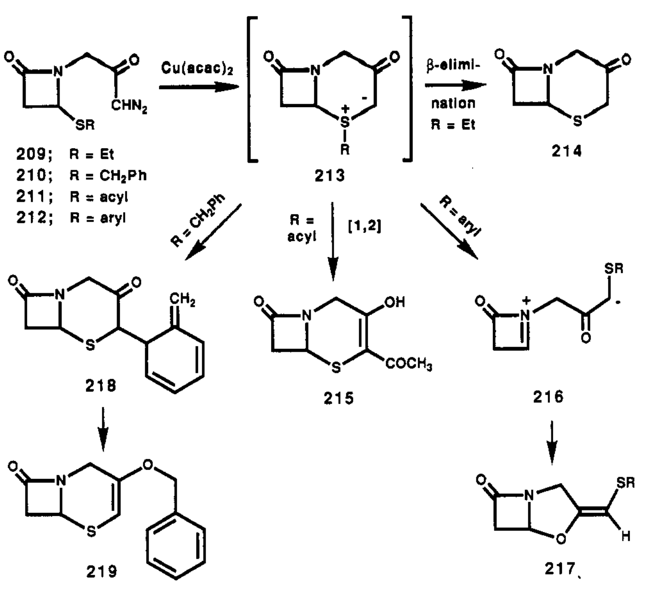
A carbon chain could be stereospecifically introduced at the C_4 position of an azetidinone by using an intramolecular carbene cyclization reaction as the key step.[13] Irradiation of diazo ester **206** in carbon tetrachloride gave bicyclic β-lactam **208** in 72% yield. The overall reaction involves introduction of a carbon unit at the C_4 position of azetidinone with the desired chirality. Further work on the synthesis of 6-amidocarbapenem antibiotics using this strategy should be forthcoming.



206; R = CO₂CH₂Ph 207 208

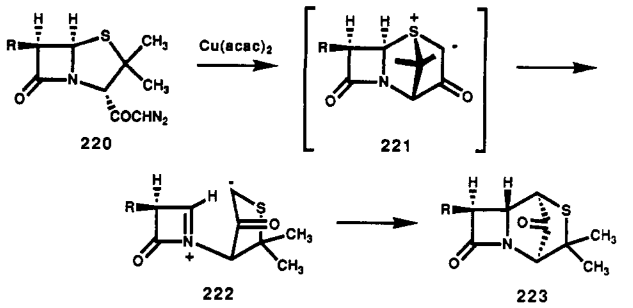
The transition-metal-catalyzed decomposition of α-diazo ketones derived from 4-thio-substituted azetidi-

SCHEME 7

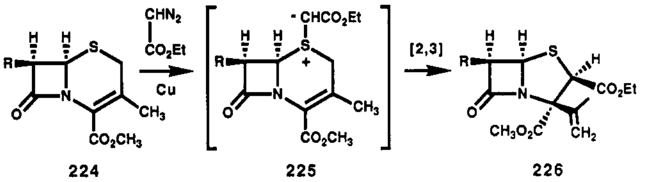


non-1-yl acetic acids provides access to a large variety of functionalized bicyclic β-lactams.[14-17] The reaction path was found to be largely dependent on the nature of the 4-thio substituent. Treatment of 4-ethylthio diazo ketone **209** with copper powder gave 3-oxocephem (**214**).[14] Mechanistically, this result can be explained by sulfonium ylide formation followed by a subsequent β-elimination to give ethylene and the observed product. Reaction of the closely related 4-benzylthio diazo ketone **210** with copper(II) acetylacetonate gave bicyclic β-lactam **219**[14] (Scheme 7). The isolation of **219** is consistent with a mechanism which involves attack of the carbene onto the sulfur atom to provide an intermediate sulfonium ylide which then undergoes a 2,3-sigmatropic rearrangement to produce intermediate **218**. A subsequent 3,3-sigmatropic rearrangement of this transient species generates the bicyclic β-lactam **219**. Reaction of acylthio diazo ketone **211** under similar experimental conditions afforded enol **215**.[14] The formation of compound **215** can best be rationalized by direct acyl-migration of ylide **213**, followed by enolization. When the sulfur atom is substituted with a phenyl group, the reaction proceeds via a totally different pathway. Thus, treatment of 4-(phenylthio)-2-acetidinone (**212**) with copper powder in refluxing benzene afforded oxapenam **217** as the major product.[15-17] The formation of this product also involves initial generation of sulfonium ylide **213** which is followed by successive cleavage of the C–S bond to produce **216** as a transient species. Subsequent ring closure by attack of the ketone oxygen on the iminium cation results in the formation of oxapenam **217**. Thus, the metal-catalyzed decomposition of α-diazo ketones derived from 4-thio-substituted azetidinon-1-yl acetic acids provides access to a large variety of functionalized bicyclic β-lactams.

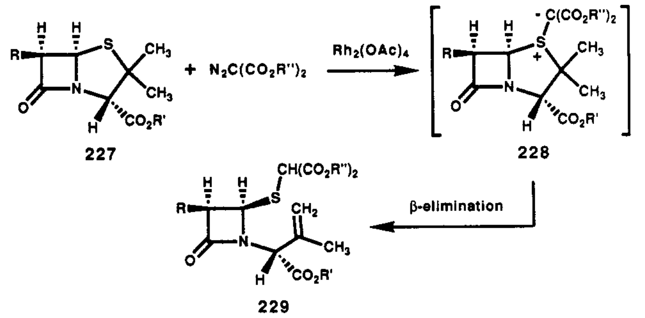
Treatment of the penicillin-derived diazo ketone **220** with a catalytic amount of copper(II) acetylacetonate in refluxing benzene gave tricyclic ketone **223** as a single stereoisomer.[18-20] It was suggested that compound **223** was formed from the strained sulfonium ylide **221**. This species undergoes cleavage of the C–S bond by participation of the nonbonding electrons of the azetidinone nitrogen atom to give zwitterion **222**. Finally, reclosure by backside attack of the carbanion onto C_5 gives the observed product. Nucleophilic attack by the carbanion occurs from the α-face of the proposed azetidinone iminium intermediate **222** presumably due to conformational factors.[20]



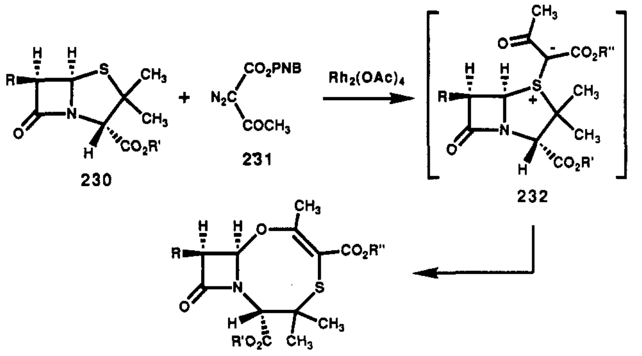
The skeletal conversion of the cephalosporin to the penicillin ring system has also been achieved by a metallocarbenoid reaction.[21] Ethyl diazoacetate was added dropwise to a mixture containing methyl 3-methyl-7-(phenylacetamido)-3-cephem-4-carboxylate (**224**) and copper powder. After the reaction was heated at reflux for 3 h, penicillin **226** was isolated in 50% yield. The formation of **226** is consistent with a mechanism involving α-side addition of the copper carbenoid onto the sulfur atom of cephalosporin to give the β-oriented ylide intermediate **225**. 2,3-Sigmatropic rearrangement of this species occurs in a suprafacial manner to give the observed product as a single stereoisomer.



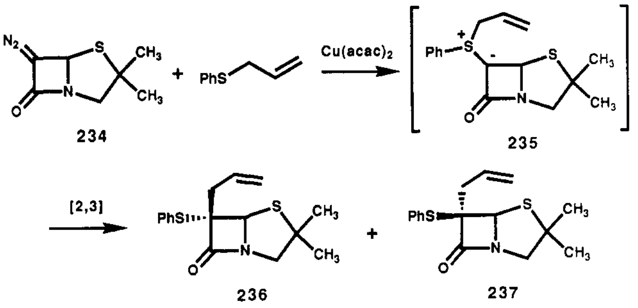
Cleavage reactions of the C_2–S_1 bond of penicillin derivatives have been carried out and produce 1,2-secopenicillinates in modest to good yields.[22-25] For example, treatment of penicillinate **227** with diazomalonate in the presence of rhodium(II) acetate gave the corresponding 1,2-secopenicillin derivative **229** in 83% yield. The isolation of this material is consistent with the formation of sulfonium ylide **228** which then undergoes a subsequent β-elimination to give the observed product. This is an important result since 1,2-secopenicillin derivatives can be easily cyclized to produce cepham antibiotics.[22-24] The overall process represents a method by which penicillins can be transposed into the cepham nucleus.



The ring expansion of penicillin derivatives has been used to stereoselectively synthesize eight-membered oxa-β-lactams.[26] Reaction of penicillin derivatives with metallocarbenoids derived from *p*-nitrobenzyl α-diazoacetoacetate gives the corresponding ring-expanded oxa derivatives in modest yield.[26] A typical example involves the reaction of penicillin **230** with *p*-nitrobenzyl α-diazoacetoacetate (**231**) in the presence of a catalytic amount of rhodium(II) acetate to give bicyclic β-lactam **233**. This result was rationalized by assuming the initial formation of sulfonium ylide **232**. The second step involves nucleophilic addition by the carbonyl oxygen and a concomitant displacement of the sulfonium moiety.

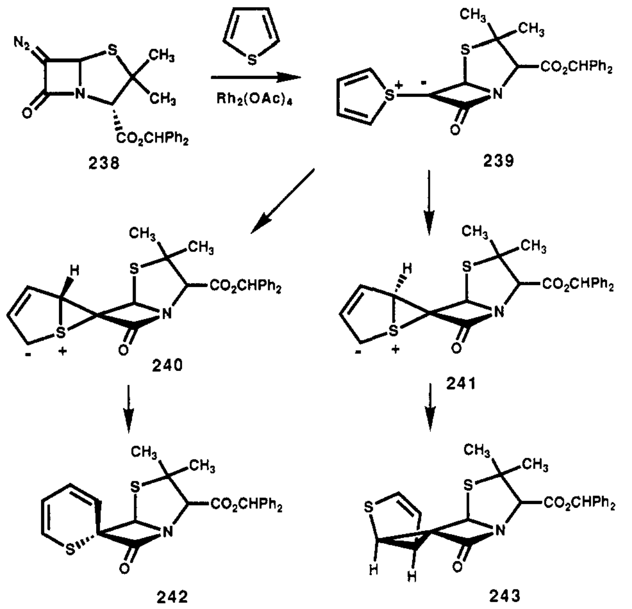


Since the discovery of derivatives of olivanic acid[27] and thienamycin,[28] the synthesis of penicillin analogues with a carbon side chain at C_6 has attracted considerable attention. The transition-metal-catalyzed reaction of 6-diazopenicillinates with allyl sulfides represents a convenient method for synthesizing these 6-substituted penicillin analogues.[29,30] Addition of copper(II) acetylacetonate to a mixture of phenyl allyl sulfide and 6-diazopenicillinate (**234**) in dichloromethane resulted in the formation of 6,6-disubstituted penicillinates **236** and **237**. This result can best be interpreted as proceeding by the initial formation of sulfonium ylide **235** which undergoes a subsequent 2,3-sigmatropic rearrangement. This reaction is related to the 2,3-rearrangements of 6-(alkylamino)penicillinates previously reported by Baldwin and co-workers.[109]



In a related study, Chan and Matlin have reported on the rhodium(II)-catalyzed reaction of 6-diazopenicillinate with thiophene to give spiroadducts **242** and **243** in 11% and 22% yield, respectively[31] (Scheme 8). Structure **242** is unique in being the first recorded example of the formation of a 2*H*-thiopyran by carbenoid ring expansion. Both products are considered to be formed via the thiophenium ylide **239** which then suffers internal attack at C_α. This is followed by either ring expansion or bond migration. This mechanistic picture requires movement of the thiophenium ring toward the α-face of sulfur ylide **239**. The overall ring expansion of thiophene to 2*H*-thiophene **242** corresponds to a heterocyclic analogue of the Buchner reaction,[110] in which a carbenoid derived from a diazo compound inserts into a benzene ring to give a cycloheptatriene.

SCHEME 8



E. Sulfoxonium Ylides

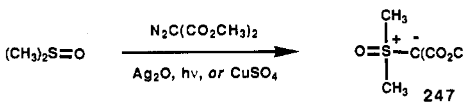
Although many studies have been carried out dealing with the formation of stable sulfonium ylides by the reaction of carbenes with sulfides, only few reports describe the reaction of carbenes with sulfoxides.[35,36,111-116] This reaction is not widely used as a route to sulfoxonium ylides, since it is complicated by a competing attack of the carbene on oxygen resulting in deoxygenation of the sulfoxide.[117] Also, simple sulfoxonium ylides can usually be prepared from the versatile Corey dimethylsulfoxonium ylide.[118] Alkylcarbenes generally react on the oxygen atom of sulfoxides whereas acylcarbenes and arylcarbenes show a preference for reaction on the sulfur atom.[111-120]

Dichlorocarbene efficiently deoxygenates most sulfoxides to produce the corresponding sulfides and phosgene under the basic phase transfer conditions used.[117,119,120] A mechanism which accounts for the formation of the sulfide involves initial coordination of the electrophilic dichlorocarbene with the nucleophilic oxygen atom of the sulfoxide to give the 1,3-zwitterionic intermediate **244** which is subsequently converted to the products. Decomposition of benzophenone tosylhydrazone (**245**) in the presence of dimethyl sulfoxide has been found to proceed similarly to give benzophenone and dimethyl sulfide.[117]

$$R_2S{=}O \xrightarrow{:CCl_2} \underset{244}{\left[R_2\overset{+}{S}{-}O{-}\overset{-}{C}Cl_2 \right]} \longrightarrow R_2S + COCl_2$$

$$\underset{245}{Ph_2C{=}NNH\text{-}p\text{-}Ts} \xrightarrow[(CH_3)_2S=O]{} \underset{246}{\left[(CH_3)_2\overset{+}{S}{-}O{-}\overset{-}{C}Ph_2 \right]} \longrightarrow (CH_3)_2S + Ph_2CO$$

Acylcarbenes, on the other hand, react with sulfoxides to give stable sulfoxonium ylides.[111-114] For example, the silver oxide decomposition of dimethyldiazomalonate in dimethyl sulfoxide produced sulfoxonium ylide **247** in 85% yield.[111,112] This work was extended to a study of the photochemical or copper sulfate catalyzed thermal reactions of diazo compounds with various alkyl and aryl sulfoxides. The reactions proceeded smoothly leading to sulfoxonium ylides in high yield.[113] The copper(I) cyanide decomposition of diazo ester **248** in dimethyl sulfoxide was also found to give sulfoxonium ylide **249** in 93% yield.



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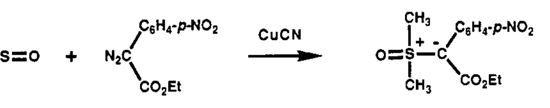
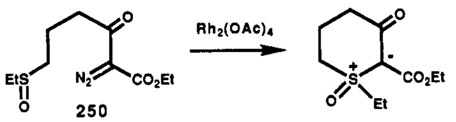
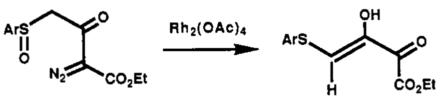


248 249

The rhodium(II) acetate decomposition of diazo sulfoxide **250** gave the cyclic sulfoxonium ylide **251** in 78% yield. A single-crystal X-ray study unequivocably established the structure of ylide **251**. The geometry of the sulfur atom was found to be pyramidal with the sulfoxide oxygen located in the axial position. In an attempt to prepare a 4-membered cyclic sulfoxonium ylide, diazo sulfoxide **252** was decomposed in benzene in the presence of rhodium(II) acetate. In this case, deoxygenation of the sulfoxide by the carbenoid was the predominant reaction, and the tricarbonyl compound **253** was the only product obtained.

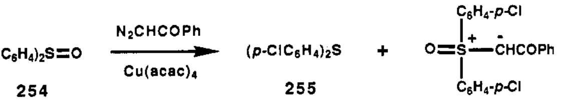


250 251



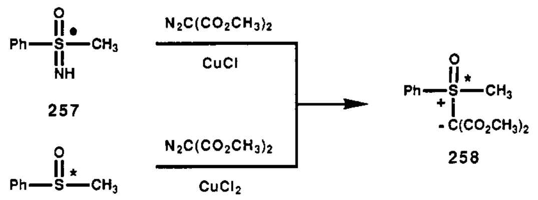
252 253

The copper chelate catalyzed reaction of α-diazoacetophenones with substituted diphenyl sulfoxides gave two types of products, namely diaryl sulfides and sulfoxonium ylides. The product ratio was dependent on the substituent groups present.[115] For example, treatment of α-diazoacetophenone with copper(II) acetylacetonate at 50 °C in the presence of bis(*p*-chlorophenyl) sulfoxide (**254**) gave bis(*p*-chlorophenyl) sulfide (**255**) and sulfoxonium ylide **256** in 30% and 33% yields, respectively. Sulfide **255** is formed via carbenoid addition to the oxygen atom followed by a subsequent deoxygenation.



254 255 256

The reaction of carbenoid species with sulfoximines has been investigated by Furukawa and co-workers.[116] The copper(I) chloride catalyzed reaction of dimethyl diazomalonate with optically active methyl phenyl sulfoximine (**257**) led to the formation of optically active sulfoxonium ylide **258** with 60% retention of configuration. Reaction of methyl phenyl sulfoxide under identical experimental conditions resulted in the formation of ylide **258** with 93% retention of configuration. This approach to oxosulfonium ylides proceeds with overall retention of configuration around the sulfur atom and may be of some synthetic utility.

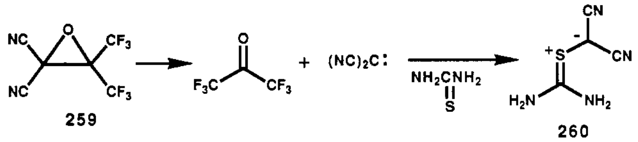


257 258

III. Formation of Thiocarbonyl Ylides

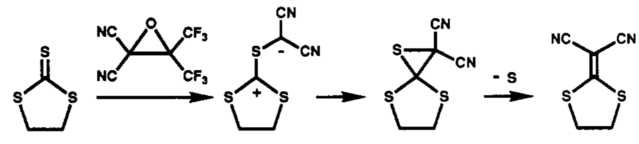
Thiocarbonyl ylides have been the subject of much interest in recent years due to their potential role as intermediates in a variety of reactions, including the formation of episulfides and five-membered ring sulfur heterocycles. Ylide production has been achieved by a variety of pathways. 1,3-Dipolar cycloaddition of diazo compounds with thioketones to produce Δ^3-1,3,4-thiodiazolines followed by elimination of nitrogen represents one common method for thiocarbonyl ylide generation.[121] Other methods involve the addition of thioketones to oxiranes[122] and photorearrangement of aryl vinyl sulfides.[123] The formation of thiocarbonyl ylides via the interaction of carbenes or carbenoids with thiocarbonyl compounds has not been investigated to the same extent as the corresponding carbonyl ylide system (vide infra). Some recent studies by Danishefsky and co-workers serve to adumbrate the utility of thiocarbonyl ylides for the synthesis of a variety of alkaloids.[124-127]

The first reported isolation of a stable thiocarbonyl ylide was made by Middleton in 1966.[122] 2,2-Dicyano-3,3-bis(trifluoromethyl)oxirane (**259**) was found to react with thioureas by transferring a dicyanomethylene group to the sulfur atom to produce a stable thiocarbonyl ylide (**260**).[122] It seems likely that the compound owes its unusual stability to the fact that both the positive and negative charges can be distributed over a number of atoms. Other thioureas react with oxirane **259** to give related dipoles.



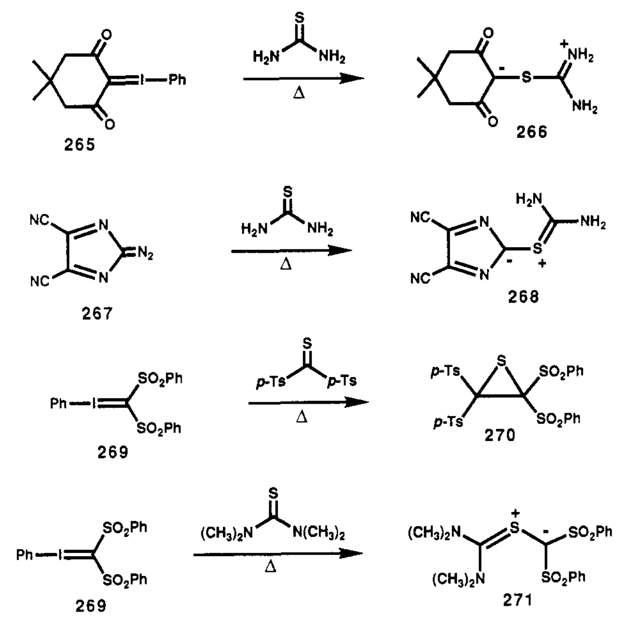
259 260

Certain thiocarbonyl compounds that contain methyl or thio groups attached directly to the C=S group undergo reaction with oxirane **259** and ultimately result in the replacement of the sulfur atom with a dicyanomethylene group. For example, ethylene trithiocarbonate (**261**) reacts to give **264** with elimination of elemental sulfur. Similarly, thioacetamide and thioacetanilide react with oxirane **259** to produce 2-



261 262 263 264

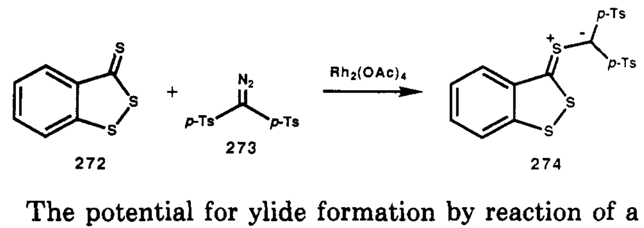
SCHEME 9



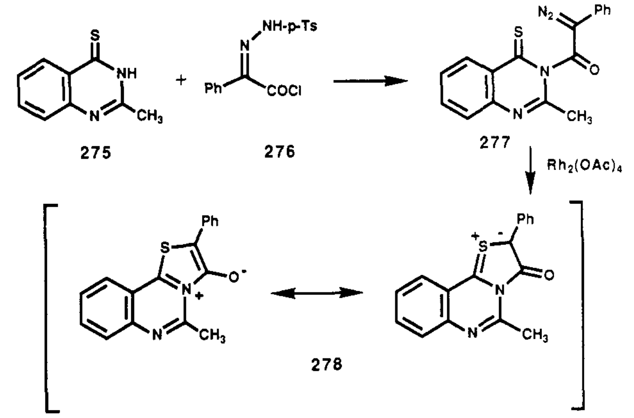
amino-1,1-dicyanopropene and 2-(phenylamino)-1,1-dicyanopropene, respectively. Formation of these products can be explained by postulating that the first step of the reaction involves attachment of the dicyanomethylene group to the sulfur atom to give a thiocarbonyl ylide (i.e. **262**). Charge neutralization occurs by collapse to an episulfide ring (**263**). Episulfides containing electron-withdrawing groups are known to readily lose sulfur and give olefins.[128]

Three other examples of isolable thiocarbonyl ylides which involve the reaction of various carbene precursors with thiourea have been reported (Scheme 9). When phenyldimedonyliodone (**265**) was allowed to react with thiourea, the delocalized thiocarbonyl ylide **266** was obtained in 67% yield.[129] Reaction of 2-diazo-4,5-dicyano-2*H*-imidazole (**267**) with thiourea afforded the extensively delocalized zwitterion **268**.[130] Finally, Varvoglis[131] described the reaction of phenyliodonium methylide **269** with several thiocarbonyl compounds to give episulfides (i.e. **270**) as well as a stable thiocarbonyl ylide (**271**) when the more nucleophilic thiourea was used. An extremely interesting property of phenyliodonium ylides is their ability to serve as carbene (or carbenoid) precursors.[132,133] The majority of iodonium ylides are prepared from active methylene compounds, especially β-diketones, in which both hydrogen atoms have been replaced by the phenyliodonio group.

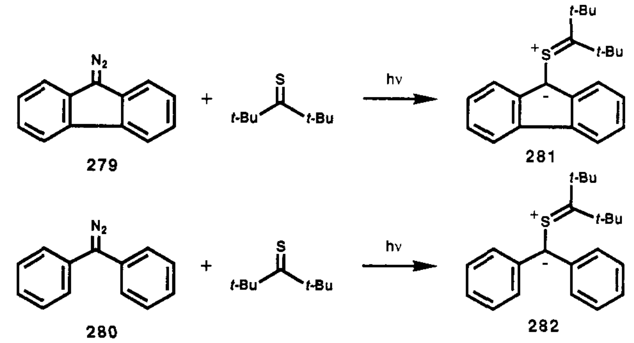
Stable thiocarbonyl ylides have also been isolated using 1,2-benzodithiole-3-thione (**272**).[134] This material was chosen as a consequence of its thermal stability. Heating **272** in benzene with bis(tolylsulfonyl)diazomethane (**273**) in the presence of a catalytic amount of copper acetylacetonate gave the stable ylide **274** as a red crystalline solid.



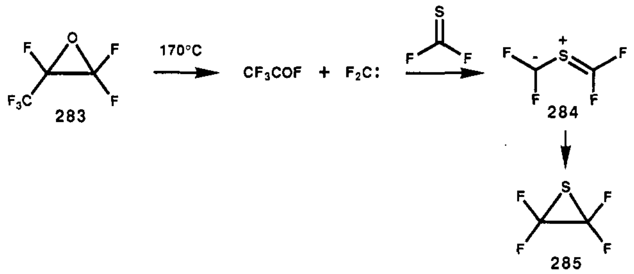
The potential for ylide formation by reaction of a nucleophilic heteroatom with an electron-deficient carbene has been exploited by Potts to prepare the mesoionic anhydro-4-hydroxythiazolium hydroxide system.[135] A mixture of 3*H*-quinazoline-4-thione (**275**) and α-(tosylhydrazono)phenylacetyl chloride (**276**) in the presence of triethylamine gave diazothioamide **277**. This compound afforded the aromatic mesoionic system **278** in 86% yield upon treatment with rhodium(II) acetate. Only one of the two possible mesoionic systems was formed. This intramolecular carbenoid-type cyclization provides an efficient synthesis of the mesoionic thiazolium hydroxide dipole. As α-keto acids are readily available, considerable potential exists for varying the substituents on the acetyl chloride.



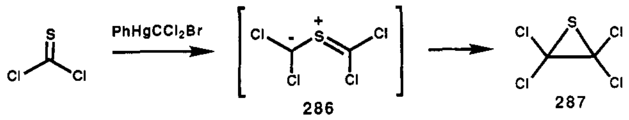
The formation and characterization of thiocarbonyl ylides from the reaction of fluorenylidene and diphenylcarbene with di-*tert*-butyl thioketone and adamantanethione has been studied by Scaiano and McGimpsey.[136] Laser flash photolysis of diazo compounds **279** and **280** led to the corresponding carbenes which were readily trapped by the thioketones to give thiocarbonyl ylides **281** and **282**. The results obtained show conclusively that the formation of the ylides proceeds directly from the triplet carbene and not from the singlet in equilibrium with the triplet. The singlet carbene is not present in sufficient quantities to account for the near diffusion controlled rate of ylide formation observed for some of the reactions. It was suggested that the reactions involve radical-like triplet carbene attack on the thioketone followed by rapid intersystem crossing to the singlet ground state ylide. The difference in reactivity for the two systems is probably related to the difference in steric hindrance as well as the higher reactivity of fluorenylidene relative to diphenylcarbene.



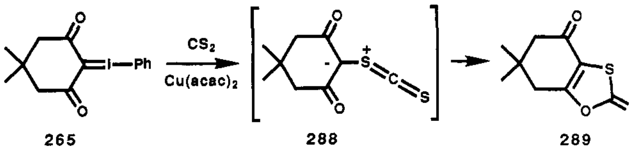
The stability of the thiocarbonyl ylide dipole is related to the ability of the functional groups to stabilize the charged dipole. Ylides which are not substituted with stabilizing groups frequently cyclize to form episulfides. One of the earliest examples of episulfide formation involve the use of hexafluoropropene oxide (**283**) as a source of difluorocarbene.[137] Treatment of this material with thiocarbonyl fluoride gave rise to the transient thiocarbonyl ylide **284** which spontaneously cyclized to produce tetrafluorothiirane (**285**). The episulfide of hexafluoropropene was prepared in an analogous fashion by using trifluorothioacetyl fluoride as the thiocarbonyl reactant.



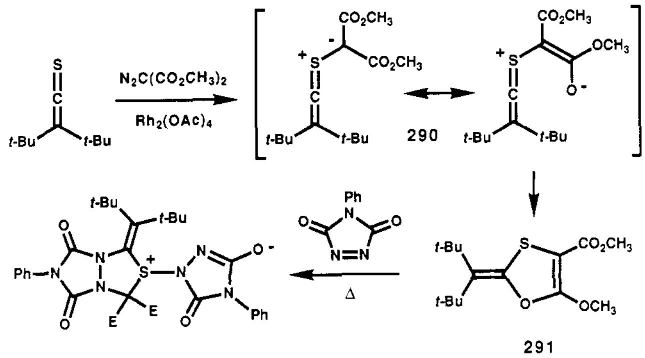
Other diazoalkanes are also known to react with thiocarbonyl compounds to give episulfides.[138] However, work by Middleton has shown that these products are formed via an intermediate thiadiazoline instead of carbene attack on the thiocarbonyl group.[139] Seyferth and co-workers found that the reaction of phenyl(trihalomethyl)mercury reagents with thiophosgene represents an effective method for preparing tetrachlorothiirane (**287**).[140] A related reaction also occurred when thiobenzophenone was used. Overall, the process involves addition of CX_2 to the C=S bond. The exact mechanism of the reaction remains open. One possibility involves a two-step process in which decomposition of the organomercury reagent gives a dihalocarbene which then subsequently adds to the C=S bond. Such an addition could either occur as a concerted cycloaddition or as a process in which thiocarbonyl ylide **286** is formed prior to ring closure. Another possibility would be a direct interaction between the organomercurial and the thiocarbonyl compound to effect CX_2 transfer.



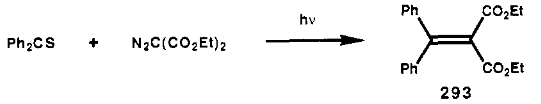
α,β-Unsaturated thiocarbonyl ylides often undergo intramolecular cyclization to give five-membered heterocycles instead of episulfides. For example, when a suspension of iodonium ylide **265** in carbon disulfide was heated at reflux in the presence of a catalytic amount of copper acetylacetonate, 1,3-benzoxathiole-2-thione (**289**) was formed in 85% yield.[141] More than likely, the formation of this compound involves thiocarbonyl ylide **288** as a key intermediate.



Thioketene S-ylides, the methylene homologue of thiocarbonyl ylides, have also been postulated as intermediates in carbene additions with thioketenes. Ando and co-workers[142] have found that the reaction of di-*tert*-butylthioketene with bis(alkoxycarbonyl)carbenes results in the facile formation of 2-alkylidene-1,3-oxathiole **291**. Structure **291** was fairly labile and was readily converted to an allene episulfide upon heating in carbon tetrachloride. When this same oxathiole was treated with 4-phenyl-1,2,4-thiazoline-3,5-dione, a 1:2-adduct (i.e. **292**) was obtained in 64% yield. The formation of this material involves the intermediacy of thioketene *S*-methylide **290** which undergoes 1,3-dipolar cycloaddition followed by further reaction with the triazolidinedione.

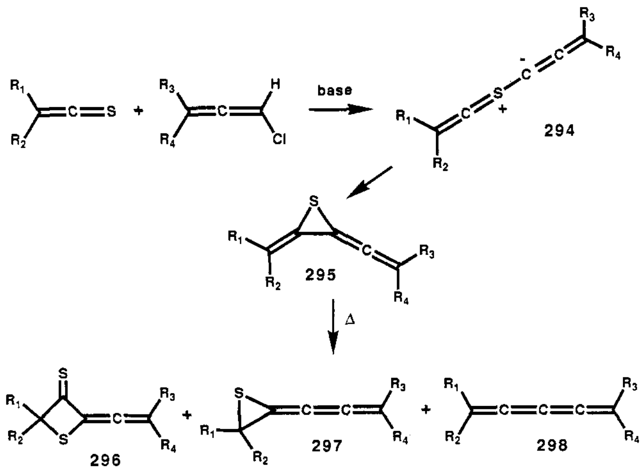


In certain cases, thiocarbonyl ylides produce olefins presumably by a sequence of reactions involving cyclization to a transient episulfide followed by loss of sulfur to give the alkene. An example of this process was first encountered by Weininger in 1969.[143] Photolysis of diethyl diazomalonate in the presence of thiobenzophenone produced diethyl 2,2-diphenylethylene-1,1-dicarboxylate (**293**) as a major product. This compound was suggested to be formed by attack of the initially generated carbene onto thiobenzophenone with formation of a thiocarbonyl ylide. The reactive dipole cyclizes to generate an episulfide which then loses sulfur to form the alkene. Thermolysis of diethyl diazomalonate and thiobenzophenone in refluxing diglyme also afforded good yields of olefin **293**.

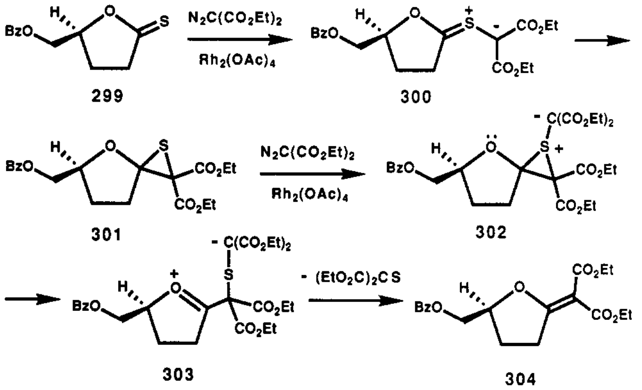


Various types of cumulenes and cumulene episulfides can be synthesized by alkenylidene carbene addition to thioketene.[144] The tetraene episulfides **295** were isolated as stable crystalline solids. However, they readily underwent C–S bond cleavage upon heating to give the corresponding 2-alkenylidenethietane-3-thione **296** in addition to the isomerized 1-episulfide **297** and desulfurized tetraene **298** (Scheme 10).

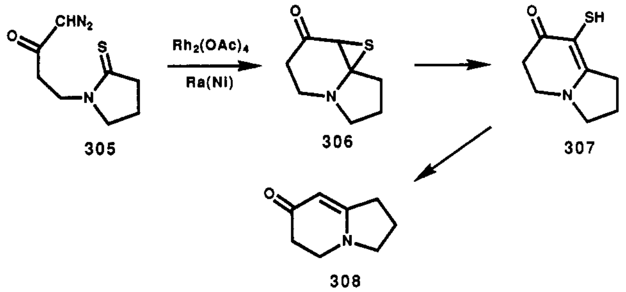
SCHEME 10



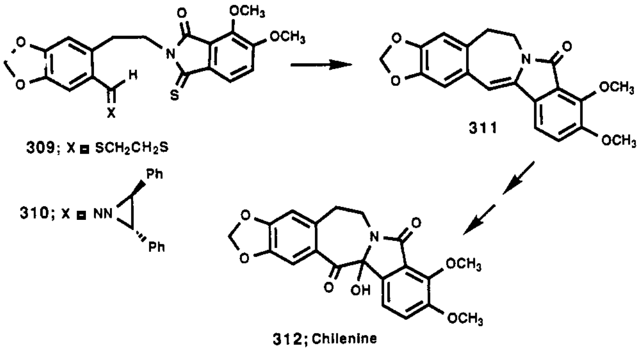
Reaction of tetrahydro-2-furanthione **299** with diethyl diazomalonate in the presence of rhodium(II) acetate affords 2-(acylmethylene)tetrahydrofuran **304** in good yield.[145] 2-(Acylmethylene)tetrahydrofuran derivatives, such as **304**, are usually obtained in much poorer yield by the condensation of lactone acetals with active methylene compounds.[146] The formation of **304** was interpreted to involve the sequential formation of the corresponding sulfur ylide **300** by reaction of **299** with the carbenoid generated from the diazo compound. Cyclization of the thiocarbonyl ylide to form episulfide **301** followed by further reaction of the three-membered heterocycle with excess carbenoid accounts for the formation of the product. The reaction pathway is reminiscent of the Eschenmoser sulfide-contraction reaction using thiolactam substrates.[147]



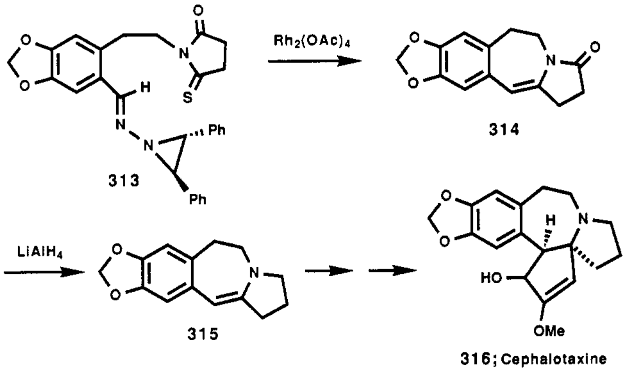
Danishefsky and co-workers have extended this reaction to the synthesis of a variety of novel heterocyclic natural products.[124-127] One example involves the annulation of diazomethyl vinyl ketone with a variety of secondary thiolactams to give heterocycles such as **305**. This diazo ketone afforded **308** upon treatment with rhodium(II) acetate in refluxing benzene followed by Raney nickel desulfurization.[124] The intermediate involved in the conversion of **305** to **308** prior to treatment with Raney nickel was identified as ene thiol **307**. In this case the initially formed thiocarbonyl ylide intermediate cyclizes to episulfide **306** which undergoes subsequent isomerization to produce **307**.



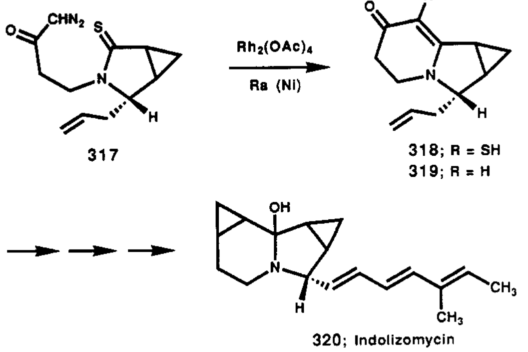
A key step in the total synthesis of the isoindolobenzazepine alkaloid chilenine **312** was the transition-metal-catalyzed reductive coupling of a dithiolane (or 2,3-diphenyl-*N*-aziridinohydrazone) with an unsymmetrical dimethoxyphthalimide.[125] Heating **309** in the presence of 2 equiv of tungsten hexacarbonyl effected the reductive cyclization of the dithiolane–monothiophthalimide to provide enamide **311** in modest yield. A more efficient method to prepare **311** involved the addition of hydrazone **310** to a refluxing suspension of rhodium(II) acetate in toluene. Under these conditions, hydrazone **310** lost *trans*-stilbene to generate a transient diazo compound which reacted with rhodium(II) acetate in the usual fashion to produce a carbenoid complex which subsequently cyclized to a thiocarbonyl ylide. Ring closure followed by rearrangement and desulfurization afforded enamide **311**.



In an effort to expand the scope of this method to include pyrrolobenzazepine structures related to cephalotaxine **316**, Danishefsky investigated the hydrolytic succinoylation and subsequent reductive ring closure of several substituted dihydroisoquinolines.[126] In the formal synthesis of cephalotaxine **316**, Weinreb's[148] key intermediate **315** was formed by the addition of hydrazone **313** to a refluxing suspension of rhodium(II) acetate in toluene. This resulted in the formation of enamide **314** which was further reduced with lithium aluminum hydride to give **315**.



Application of this newly developed lactam annulation methodology has also been applied to the synthesis of indolizomycin (**320**).[127] Treatment of thioamide **317** with rhodium(II) acetate in benzene under reflux afforded a crude product which was directly treated with Raney nickel to give dihydropyridone **319**. This material was eventually taken on to the natural product. The key step in the conversion of **317** to **319** involved the intermediacy of a thiocarbonyl ylide dipole.

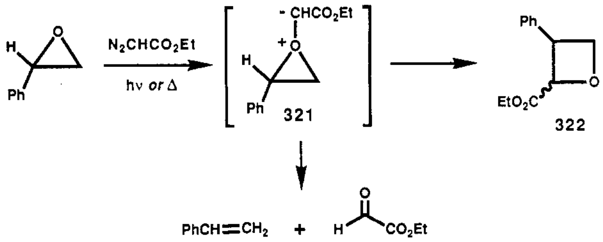


IV. Formation of Oxonium Ylides

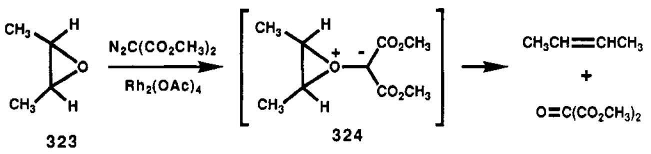
Two fundamentally different approaches to the generation of oxonium ylides exist. One route involves either the deprotonation or desilylation of appropriate oxonium ions.[1] The deprotonation route to these oxygen ylides is believed to play an important role in the zeolite-catalyzed conversion of methanol to ethylene.[149] The alternate approach involves the interaction of carbenes with the unshared electron pairs of an oxygen atom. For the majority of reactions encountered, direct C–O insertion is not readily distinguished from the formation and subsequent rearrangement of oxonium ylides. Conclusive evidence for the two-step mechanism comes from the 2,3-sigmatropic rearrangements observed with allylic substrates (vide infra). Unlike the situation with the related sulfonium ylide system, stable and isolable oxonium ylides have not yet been reported in the literature. This difference in stability is probably due to the absence of p_π–d_π orbital interaction which helps stabilize the charge on the sulfur atom. Oxonium ylides are reactive species which readily undergo the Stevens rearrangement, β-hydride elimination, and [2,3]-sigmatropic reorganization.

A. Oxygen-Transfer Reactions

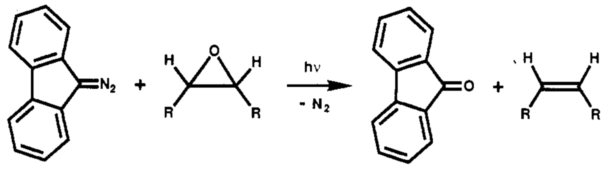
Although the reaction of carbenes with open chain ethers has been extensively studied, only a few examples have been recorded of their reaction with cyclic ethers. Wittig and Schlosser[150] have described the copper-catalyzed decomposition of diazomethane with 2-phenyloxirane to give styrene. This transformation has been ascribed to the oxygen abstracting ability of the intermediary carbene. More recently, Nozaki and coworkers[151] have reported that the reaction of carboethoxycarbene with 2-phenyloxirane not only involves a deoxygenation but also undergoes an insertion reaction leading to ring expansion. Oxygen ylide **321** is formed by electrophilic attack of the singlet carbene onto the oxygen atom of 2-phenyloxirane. This is followed by decomposition to styrene and ethyl glyoxylate or isomerization to a cis–trans mixture of oxetane **322**. Secondary attack of each product with either carboethoxycarbene or ethyl glyoxylate leads to further products which complicate the reaction mixture.



The reaction of dimethyl diazomalonate with catalytic quantities of binuclear rhodium(II) carboxylate salts has been reported to generate a reagent which rapidly and cleanly deoxygenates most epoxides under neutral conditions without alkene isomerization or cyclopropanation.[152] Elevated temperatures were required when rhodium(II) acetate was used as the catalyst because of its low solubility at room temperature in most solvents. The more soluble rhodium(II) pivalate dimer readily catalyzed the reduction at room temperature. However, it was generally found to be more expedient to work at 60–80 °C. The deoxygenation reaction converts the diazo compound into dimethyl oxamalonate, an easily hydrated byproduct that can be readily removed along with the catalyst by filtration through a short silica gel column.

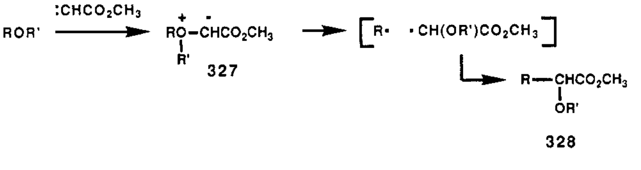


The photolysis of 9-diazofluorene (**325**) in the presence of epoxides using a nitrogen laser yields 9-fluorene (**326**) and an equal amount of the alkene derived from the stereospecific deoxygenation of the epoxide.[153] The ground state of fluorenylidene is known to possess triplet multiplicity. Despite this fact, a significant fraction of the bimolecular reactions of this carbene originate from its electrophilic singlet state. The evidence found in these studies supports the involvement of an oxonium ylide intermediate in the epoxide deoxygenation reaction. The ylide, however, could not be detected directly by transient absorption spectroscopy. This is probably due to its low steady-state concentration owing to the relatively slow rate of its formation and a suspected rapid subsequent reaction. The highly stereoselective nature of the deoxygenation reaction is consistent with concerted fragmentation of the oxonium ylide. Facile epoxide deoxygenation is a much sought-after synthetic process and these results should guide the search toward carbenes which could be useful in this regard.



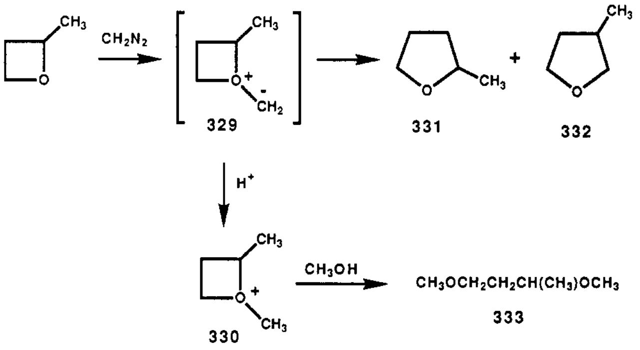
B. Stevens Rearrangement and β-Hydride Eliminations

In contrast with the nearly random insertion of methylene into various C–H bonds, the reaction of electrophilic (methoxycarbonyl)carbene with ethers is characterized by two types of reactions, namely, insertion into the C–O bond and displacement of one of the alkyl groups. Electrophilic attack of the carbene on the lone pair of electrons forms oxonium ylide **327** which then undergoes a 1,2-shift. This sequence nicely accounts for the products formed. Concerted 1,2-shifts are forbidden processes according to the Woodward–Hoffmann rules.[154] The oxonium ylide apparently rearranges by a homolysis–recombination mechanism.

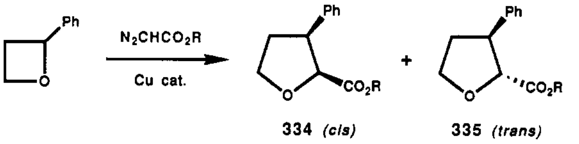


This mechanism was established on the basis of CIDNP data.[155] The proton NMR spectra are consistent with an oxonium ylide intermediate which undergoes homolytic cleavage to produce a singlet radical pair which is then followed by cage recombination.

There are a number of reports in the literature where oxonium ylides have been found to undergo a formal 1,2-alkyl shift.[156] A notable example was described by Kirmse[157] in a study of the formation and rearrangement of ylides formed by the interaction of oxetanes and carbenes. Ylides generated from carbenes ($:CH_2$, $:CHCO_2Et$, $:CHPh$) and oxetanes in the presence of methanol undergo a Stevens rearrangement and protonation competitively, yielding tetrahydrofurans and 1,3-dialkoxypropanes as major products. Although metal carbenoids undergo C–H insertion with hydrocarbons,[158] this process is completely suppressed in favor of attack at the oxetane oxygen. The selectivity displayed by rhodium carbenoids in competitive cyclopropanations of olefins has been attributed to the development of positive charge in the transition state.[8] Likewise, accommodation of the negative charge by rhodium and development of positive charge on the migrating carbon nicely rationalizes the regioselectivity and complete racemization encountered in the catalyzed Stevens rearrangement of these oxonium ylides.

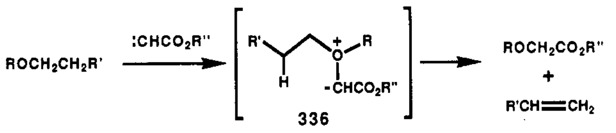


Nozaki[159] has carried out a similar study which involves the reaction of ethyl diazoacetate with 2-phenyloxetane in the presence of a copper catalyst. This results in a cis–trans mixture of ethyl 3-phenyltetrahydrofuran-2-carboxylate (**334** and **335**). When



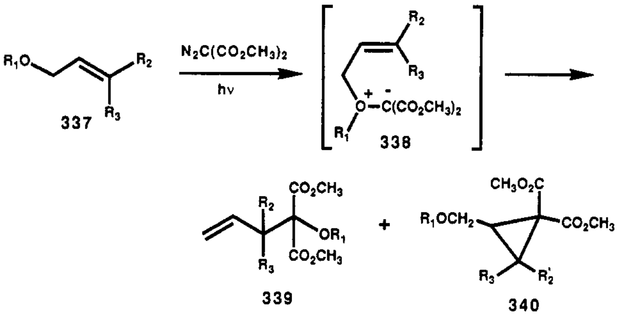
a chiral copper catalyst was used, optically active ethyl 3-phenyltetrahydrofuran-2-carboxylate was obtained. This result is consistent with the intermediacy of a copper carbenoid presumably having a square-pyramidal structure. Its reasonable to assume that a chiral carbenoid is responsible for the asymmetric induction encountered.

Oxonium ylides which possess a β-hydrogen (i.e. **336**) will frequently undergo β-hydride elimination to form an ether and an olefin. An early example of this reaction was reported by Franzen.[160] CIDNP studies have shown that this reaction does not involve radical intermediates and therefore probably proceeds via intramolecular abstraction of the β-hydrogen by the negatively charged carbon atom of the ylide followed by a subsequent loss of alkene and ether formation.[161] Bimolecular studies designed to investigate the β-hydride elimination are complicated by competing processes such as C–H insertion, and thus product mixtures are usually very complex.[162–164]



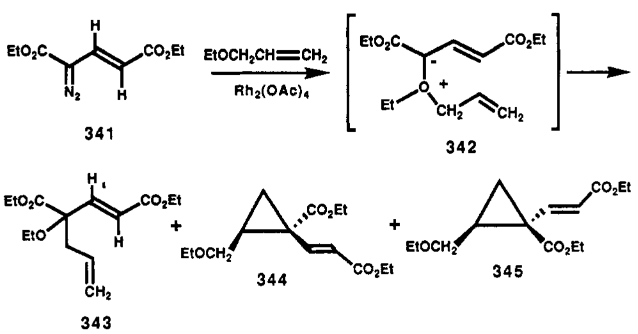
C. 2,3-Sigmatropic Shifts

As was the case with allyl sulfonium ylides, a major reaction of allyl substituted oxonium ylides is the 2,3-sigmatropic rearrangement. In a study designed to compare oxonium ylide formation versus cyclopropanation, a mixture containing dimethyl diazomalonate in various allyl ethers was irradiated with a high-pressure mercury lamp.[48] The reaction was found to give a product derived from a 2,3-sigmatropic shift of an oxonium ylide (**339**) as well as a cyclopropanated product (**340**). In the parent system, ylide formation was favored by a factor of 3:2. Steric factors, however, were found to cause a variation in the ratio of products. Steric bulk near the allyl group favors oxonium ylide formation, whereas steric bulk near the oxygen atom promotes the cyclopropanation reaction. Interestingly, with the closely related allyl sulfide system, ylide formation always predominates. This variation in behavior is probably related to the difference in nucleophilicities of the oxygen and sulfur atoms as well as the inherent stability of their ylides. The intermediate sulfur ylides can be stabilized by d_π–p_π interactions, while such a contribution to stabilization can not occur with the oxygen ylides. As a consequence, reactions proceeding through an oxonium ylide are less favorable than reactions proceeding through a sulfonium ylide.

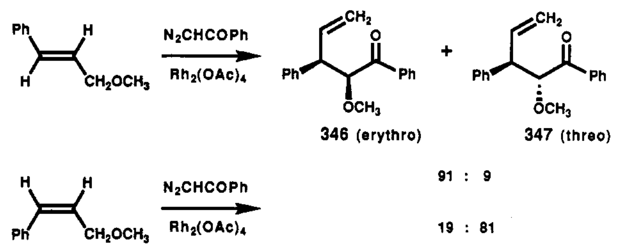


In a related study designed to investigate stereoselective cyclopropanations using vinylcarbenoids, Davies and co-workers[165] found that the reaction of vinyl diazomethane **341** with ethyl allyl ether afforded a mixture of the expected cyclopropanes **344** and **345** as well as structure **343**. This compound arose by capture of the carbenoid by the oxygen atom producing oxonium ylide **342** which then undergoes a 2,3-sigmatropic rearrangement to give **343**.

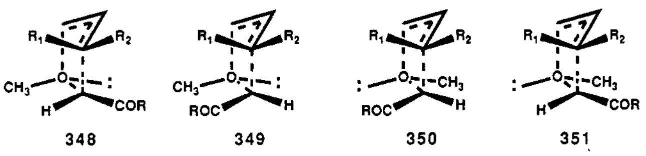
Doyle and co-workers[166] have found that allylic oxonium ylides, generated by the rhodium(II) acetate catalyzed decomposition of diazo carbonyl compounds in the presence of allyl methyl ethers, undergo the 2,3-sigmatropic rearrangement with a high degree of stereospecificity. Treatment of *trans*-cinnamyl methyl ether at room temperature with α-diazoacetophenone in the presence of $Rh_2(OAc)_4$ afforded mostly the er-



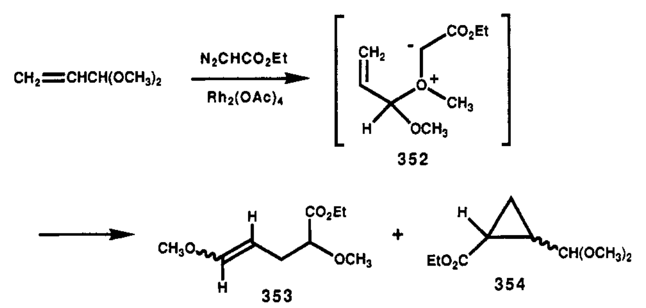
ythro homoallyl ether **346**. Similarly, treatment of *cis*-cinnamyl methyl ether at room temperature with α-diazoacetophenone in the presence of a rhodium catalyst gave rise to mostly threo homoallyl ether **347**.



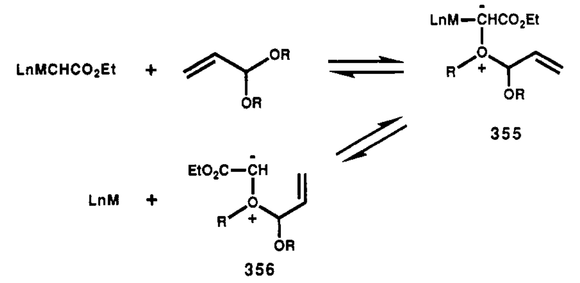
These results can be explained by steric influences in the transition state. Transition-state structures **349** and **351** are of higher energy than **348** and **350** because of eclipsing interactions between the *O*-methyl and the COR groups. Accordingly, the observed diastereoselectivity is a function of the relative transition-state energies for **348** and **350** with **350** dominant in product selection. Other rhodium(II) carboxylate catalysts did not change the diastereoselectivity of the 2,3-sigmatropic rearrangement from that found with rhodium(II) acetate. This result would suggest that the 2,3-sigmatropic rearrangement occurs from the free ylide rather than from a metal-associated ylide.



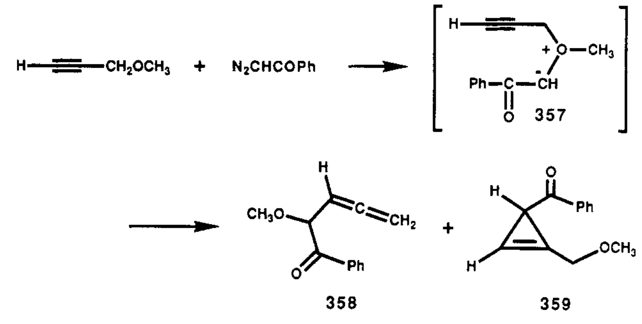
Allyl acetals also undergo ylide formation when the reaction is carried out with use of diazo esters with rhodium(II) carboxylates as the catalyst. The oxonium ylide subsequently rearranges to produce 2,5-dialkoxy-4-alkenoates.[90] Cyclopropanation and Stevens rearrangement compete with the 2,3-sigmatropic rearrangement in certain cases. Thus, treatment of the dimethyl acetal of acrolein with ethyl diazoacetate at 25 °C in the presence of rhodium(II) acetate resulted in the formation of enol ether **353** and cyclopropane **354** in a ratio of 3.3.[90] Enol ether **353** is formally derived from a 2,3-sigmatropic rearrangement of the oxonium ylide **352**. Comparative results with allyl ethers demonstrate that heteroatom substitution on the allylic carbon accelerates ylide rearrangement. Because of steric congestion and the electron-withdrawing influence of the α-alkoxy substituent, the facility which allyl acetals undergo 2,3-sigmatropic rearrangements cannot result from the stability of intermediate ylides derived from acetals relative to ethers. Rather, this acceleration of ylide rearrangement is thought to be associated with the electronic influence of the α-alkoxy substituent.



Comparison of relative reactivities of ylide rearrangement and cyclopropanation between acetals and ethers suggests that the electrophilic metal carbene responsible for these competitive transformations exists in dynamic equilibrium with the metal-associated ylide.



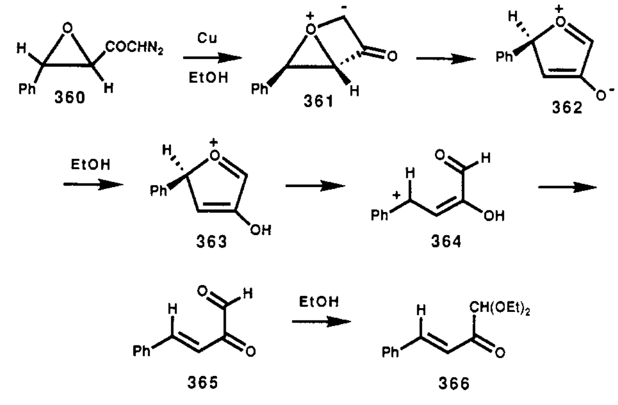
Prop-2-yn-1-yl oxonium ylides[167] (i.e. **357**) provide a potentially useful pathway to highly substituted and synthetically versatile allenes through the 2,3-sigmatropic rearrangement. The high oxophilicity of metal carbenes formed in the rhodium(II) perfluorobutyrate catalyzed decomposition of diazocarbonyl compounds allows for selective ylide generation from methyl prop-2-ynyl ethers and subsequent formation of substituted allenes. Methyl prop-2-ynyl ether and α-diazoacetophenone reacted in the presence of rhodium(II) perfluorobutyrate to give allene **358** and cyclopropene **359** in an 82:18 product ratio, respectively.



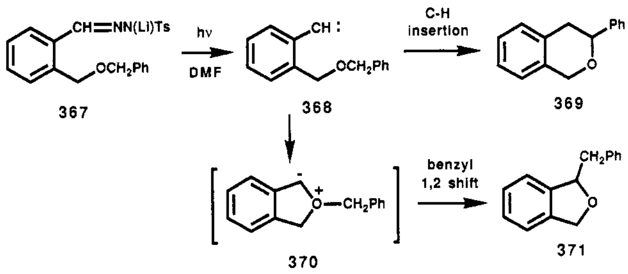
In contrast, cyclopropene **359** was produced to the virtual exclusion of allene **358** when rhodium(II) acetate was used as the catalyst. The variation in reactivity of these two rhodium carbenoid intermediates has been attributed to the relative electrophilicity differences of the catalysts. In terms of hard and soft acids and bases, the metal carbene derived from rhodium perfluorobutyrate is a harder acid than that from rhodium(II) acetate.

D. Intramolecular Formation of Oxonium Ylides

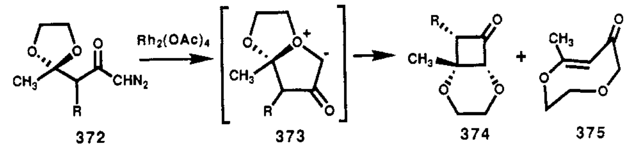
Reactions of α,β-epoxy diazomethyl ketones with activated copper powder or copper sulfate in hydroxylic solvents result in an intramolecular oxygen transfer to produce alkene oxoacetals in good yields.[168] Thus, treatment of diazoketone **360** with activated copper in refluxing ethanol gave dialkoxybutenone **366** in 80% yield. This process of oxygen transfer is thought to proceed via an initially generated keto-carbenoid which reacts intramolecularly with the epoxide moiety to give the bicyclic ylide intermediate **361**. Release of strain and subsequent ring opening produces acetal **366**. Both the cis and trans epoxides lead to the same product (i.e. **366**) when treated with copper sulfate in methanol. This stereochemical result was explained by invoking a stepwise nonsynchronous solvolysis of the initial ring-opened zwitterion **362**. Protonation of **362** by methanol produces **363** which then opens to cation **364** which ultimately gives **366**.

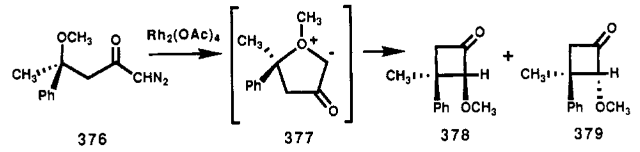


Cyclic oxonium ylides are readily generated from arylcarbenes possessing alkoxyalkyl groups in the ortho position by flash pyrolysis or photolysis of the appropriate tosylhydrazone sodium salts. Interaction of the carbene with the lone pair of electrons on oxygen competes efficiently with insertion into C–H bonds. Photolysis of the lithium salt **367** in dimethyl formamide produced 3,4-dihydro-3-phenyl-1*H*-2-benzopyran (**369**) and 1-benzyl-1,3-dihydroisobenzofuran (**371**) in a 1:4.5 ratio.[169] Dihydroisobenzofuran **371** is formed via oxonium ylide generation (i.e. **370**) followed by a formal 1,2-shift of the exocyclic benzyl group. In contrast to the analogous ammonium ylides, these ylides strongly prefer to undergo the nonconcerted 1,2-alkyl shift rather than the 2,3-sigmatropic Sommelet rearrangement. In terms of the radical pair mechanism of the Stevens rearrangements, these observations suggest a more facile homolysis of oxonium ylides as compared with ammonium ylides.

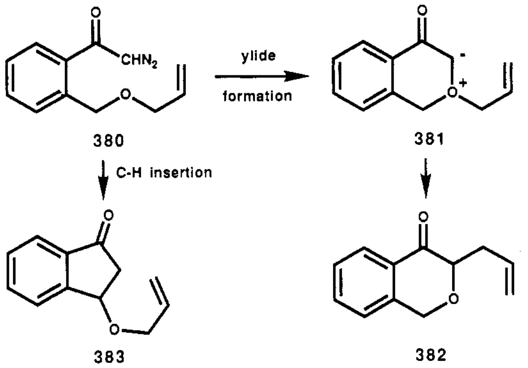


Roskamp and Johnson[170] have investigated the synthetic utility of oxonium ylides. When diazo ketone **372** was treated with rhodium(II) acetate in benzene at room temperature, two compounds were isolated and identified as structures **374** and **375**. These products are consistent with a mechanism involving formation of a carbenoid species which is captured by an oxygen atom of the ethylene ketal to produce the transient oxonium ylide **373**. Subsequent rearrangement gives the observed products. Similarly, treatment of diazo ketone **376** with rhodium(II) acetate gave oxygen ylide **377** which rearranged to cyclobutanones **378** and **379**. The key to cyclobutanone formation appears to be stabilization of electron deficiency at the α′-carbon by oxygen or an aryl substituent. Simple tertiary center stabilization does not appear to be effective.

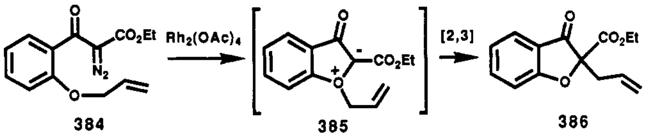


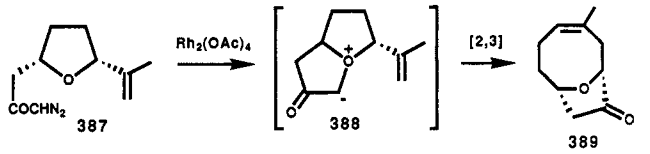


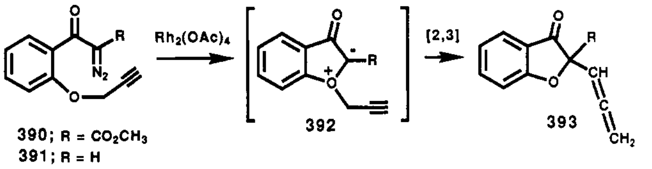
The intramolecular generation of allylic oxonium ylides and their subsequent 2,3-sigmatropic rearrangement represents an excellent method for producing a variety of interesting and useful oxygen heterocycles. For example, when diazo ketone **380** was treated with rhodium(II) acetate in benzene at room temperature, 3-allyl-2-isochroman-4-one (**382**) and 2,3-dihydro-3-(2-propenyloxy)-1*H*-inden-1-one (**383**) were formed in 43% and 35% yield, respectively.[106] Structure **382** is consistent with carbenoid generation followed by addition onto the neighboring oxygen atom to produce oxonium ylide **381** which then undergoes a 2,3-sigmatropic rearrangement. Indenone **383** was formed by a competitive C–H insertion reaction which occurs between the metal-stabilized carbene and the benzylic hydrogens. In the analogous system where the oxygen atom has been replaced by a sulfur, sulfonium ylide formation predominates.



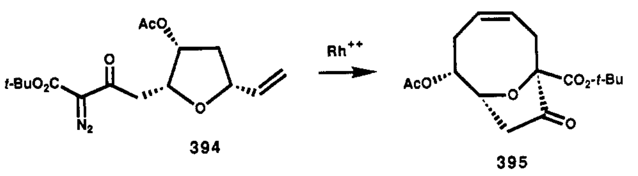
A further extension of this methodology has been developed by Pirrung and Werner to synthesize novel five-, six-, and eight-membered oxygen heterocycles.[171] Treatment of diazo ketone **384** with rhodium(II) acetate in benzene at room temperature produced benzofuranone **386** in excellent yield. When diazo ketone **387** was treated in a similar fashion, the eight-membered ring oxygen heterocycle **389** was obtained. This ring expansion clearly illustrates the preference of ylide **388** to undergo the symmetry-allowed 2,3-sigmatropic rearrangement over the symmetry-forbidden 1,2-process. Another interesting example involves the reaction of diazo ketone **390** in the presence of rhodium(II) acetate catalyst to give allene **393** in 92% yield. It should be noted that when diazo ketone **391** was treated under the same conditions, no allenic product could be isolated. This difference is probably due to the instability of the product and is not related to oxonium ylide formation.







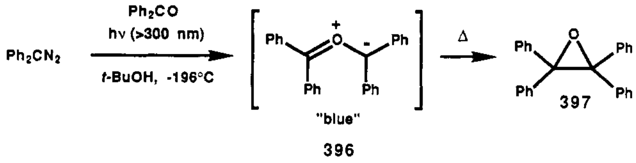
More recently, Pirrung has convincingly demonstrated that the intramolecular generation and 2,3-sigmatropic rearrangement of oxonium ylides (i.e. **394** → **395**) represents a synthetically useful approach for the preparation of eight-membered oxygen heterocycles.[172] This method is currently being used for the synthesis of several marine natural products.



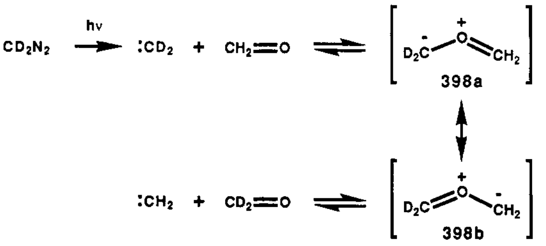
V. Formation of Carbonyl Ylides

The stereoselective preparation of highly substituted oxygen heterocycles has attracted considerable attention and provides a challenging synthetic problem.[173] Over the past decade there has been a growing interest in the use of carbonyl ylides as 1,3-dipoles for the synthesis of oxygenated heterocycles.[174] The development of methodology using these reactive intermediates, however, has lagged behind those based on other 1,3-dipoles.[175] Common methods for carbonyl ylide generation involve the thermolysis or photolysis of epoxides possessing electron-withdrawing substituents,[176-178] the thermal extrusion of nitrogen from 1,3,4-oxadiazolines,[179-181] and the loss of carbon dioxide from 1,3-dioxolan-4-ones.[182] One of the simplest routes for the generation of carbonyl ylides involves the addition of a carbene or carbenoid onto the oxygen atom of a carbonyl group.

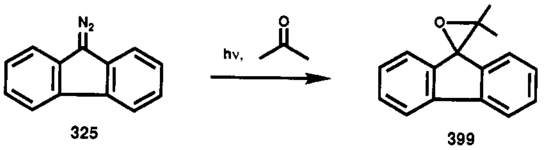
Quite a number of recent studies support the intermediacy of carbonyl ylides in reactions involving the interaction of a carbene with a carbonyl oxygen.[183-187] The irradiation of diphenyldiazomethane in a 5% benzophenone/*tert*-butyl alcohol mixture at −196 °C resulted in a rapid change in the original wine-red color of the reaction mixture to a deep blue, which rapidly faded to a light yellow solution when the matrix was thawed in the dark.[183] The major product formed was oxirane **397**. The transient formation of the blue species is very reminiscent of a carbonyl ylide which had been previously detected in the low-temperature irradiation of oxirane **397**.[188] Attempts to spectroscopically identify ylide **396** were not successful as a consequence of the extremely low transmission of the matrix.



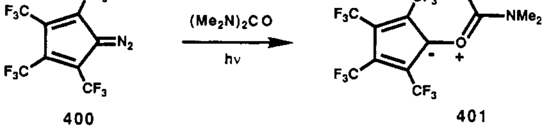
Olah and co-workers[184] have irradiated dideuteriodiazomethane with monomeric formaldehyde in an ether solution and found evidence supporting the formation of carbonyl ylide **398**. Fragmentation of this dipole produced dideuterioformaldehyde which could be detected by mass spectrometric analysis. The symmetrical nature of formaldehyde *O*-methylide was also probed theoretically, and ab initio calculations indicate that formaldehyde *O*-methylide shows a strong preference for equal C–O bond lengths indicating an allyl type resonance interaction (**398a** ↔ **398b**).[189]



A carbonyl ylide intermediate has also been detected in the photolysis of 9-diazofluorene (**325**) with acetone used as the solvent.[185,186] This dipole has an absorption spectrum with $\lambda_{max} = 640$ nm and, in the absence of quenchers, underwent ring closure to the corresponding oxirane. The absorption spectra of related carbonyl ylides could be quenched with rate constants of ca. 10^7 M^{-1} s^{-1} by electron-deficient olefins or oxygen. The decay kinetics were unaffected by the concentration of the ketone; hence the reverse reaction with the ketone did not compete with ring closure.



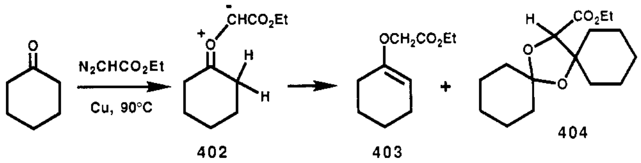
Very few examples of stable carbonyl ylides have been reported in the literature. One particularly interesting case, however, involves an ylide stabilized by a "push–pull" electronic substitution pattern.[187] Irradiation of diazotetrakis(trifluoromethyl)cyclopentadiene (**400**) in the presence of tetramethylurea produced carbonyl ylide **401** as a crystalline solid. The structure of this species has been elucidated by X-ray crystallographic analysis. Most interesting was the fact that the two carbon–oxygen bonds are quite different in length with



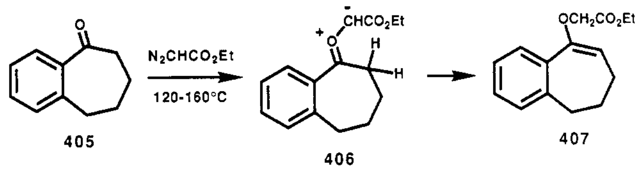
a distance of 134.8 ppm at the onium terminus and 142.2 pm at the ylide terminus. These distances suggest a partial C–O π-bond between the carbonium center and oxygen while the oxygen cyclopentadienylide bond appears to be a single σ-bond. This situation differs from the analogous sulfur ylide in which both C–S bonds were found to be of the same length.

A. Proton Transfer

One characteristic reaction of carbonyl ylides derived from the reaction of diazoalkanes with ketones consists of an intramolecular proton transfer reaction to give enol ethers. The earliest example of this process was reported by Kharasch and co-workers in 1953.[190] Treatment of ethyl diazoacetate in cyclohexanone with a catalytic amount of copper powder at 90 °C afforded a 43% yield of ethyl (cyclohexen-1-oxy)ethanoate (**403**) and a 4% yield of the 2:1 adduct **404**. The mechanism proposed for the formation of enol ether **403** starts with the generation of a copper carbenoid which then adds to the carbonyl oxygen of cyclohexanone to produce carbonyl ylide **402**. This reactive species then undergoes an intramolecular proton transfer. Deuterium labeling studies were carried out to establish that the proton-transfer step does occur in an intramolecular fashion.[191] Adduct **404** was formed via 1,3-dipolar cycloaddition of ylide **402** across the carbonyl group of cyclohexanone. In a related reaction, benzosuberone (**405**) was found to react smoothly with ethyl diazoacetate at 120–160 °C to give ethyl 6,7-dihydro-9-oxy-5*H*-cycloheptabenzeneacetate (**407**) in 51% yield presumably via carbonyl ylide **406**.[192]

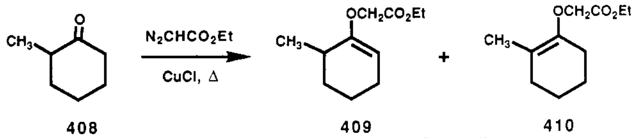


402 403 404



405 406 407

These proton-transfer reactions were found to proceed with high regiospecificity.[193] When unsymmetrical ketones were used, formation of the least-substituted enol ether is the dominant pathway. For example, the reaction of 2-methylcyclohexanone (**408**) with ethyl diazoacetate in the presence of a copper catalyst results primarily in the formation of enol ethers **409** and **410**.

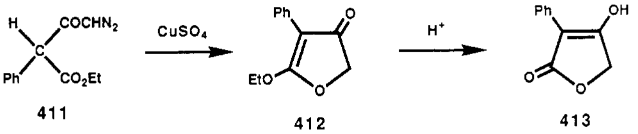


408 409 410

12 : 1 ratio

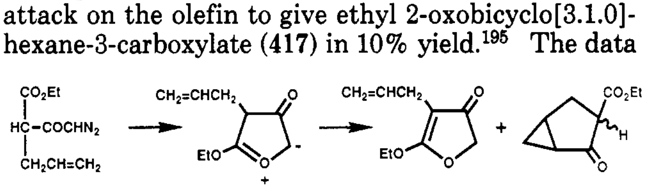
The regiochemistry observed can be accommodated by considering various reasonable starting configurations and conformations for the essential carbonyl ylide in which the C–H bond of the migrating hydrogen is approximately perpendicular to the plane of the ylide. Minimization of steric interactions of the various groups rationalizes the regiospecificity encountered.

Bien and Gillon have utilized the proton-transfer reaction for the preparation of 3(2*H*)-furanones.[194] Intramolecular attack of a metallocarbenoid onto an adjacent carbonyl oxygen produces a carbonyl ylide in a five-membered ring which undergoes a subsequent proton transfer to afford the 3-furanone system. For example, the copper sulfate catalyzed decomposition of ethyl 2-phenyl-4-diazoacetoacetate (**411**) gave 5-ethoxy-4-phenyl-3(2*H*)-furanone (**412**) as well as 4-hydroxy-3-phenyl-2(5*H*)furanone (**413**). The formation of furanone **413** can be attributed to hydrolysis of furanone **412** during workup. In fact, furanone **412** was converted into **413** in 75% yield when stirred overnight in the presence of ether and aqueous hydrochloric acid.



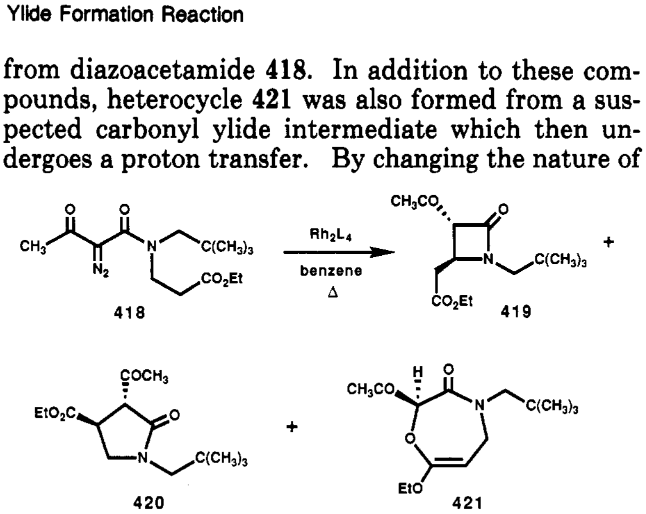
411 412 413

The transition-metal-catalyzed decomposition of 2-allyl-4-diazoacetoacetate (**414**) produces a metal carbenoid which cyclizes onto the neighboring carbonyl oxygen to form carbonyl ylide **415**. This reactive species then undergoes proton loss to produce **416** in 58% yield. A competitive path also encountered involves carbenoid attack on the olefin to give ethyl 2-oxobicyclo[3.1.0]-hexane-3-carboxylate (**417**) in 10% yield.[195] The data obtained by varying the catalyst clearly demonstrates the dependence of the product ratio on the nature of the catalyst used. Cyclopropanation could be induced with high selectivity by using palladium catalysts of various types. However, rhodium(II) acetate or copper(I) phosphite complexes strongly favor ylide formation which ultimately produces dihydrofuranone **416**. Thermal decomposition of **414** also gives the same dihydrofuranone **416**. The product distribution data suggest that the reaction is coordination-controlled and is thus influenced by the nature of the metal and/or the steric demands of the catalyst. The results obtained with bis(benzoylacetonato)palladium and copper, which are identical in ligand and stereochemistry but differ in the metal component, suggest that the steric requirements of these catalysts significantly influence the product distribution. Rhodium(II) acetate exists as a binuclear reagent whereas palladium(II) acetate exists as a trimer, thus being more sterically congested. Initial catalyst–olefin coordination prior to carbenoid formation was considered to be the preferred path for the palladium catalysts. Whereas Pd(II)–olefin complexation[196] is well-established, Rh(II)–olefin complexes are rare and unstable. Consequently, cyclopropanation would be expected to be favored with the palladium catalysts.



414 415 416 417

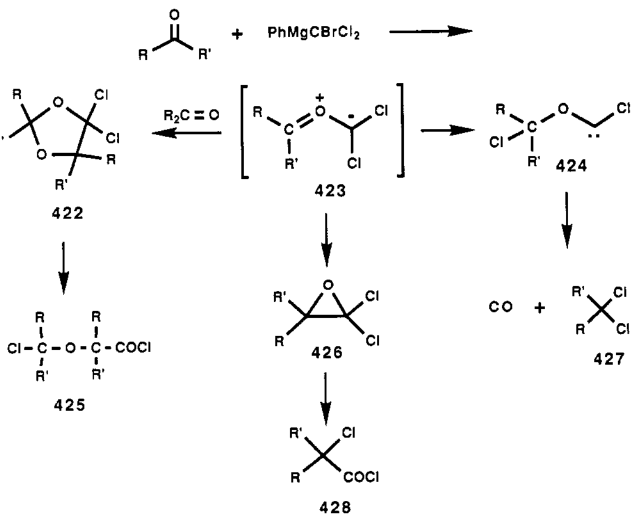
Doyle and co-workers have reported a new methodology for the synthesis of β-lactam compounds through intramolecular C–H insertion caused by the rhodium(II) acetate catalyzed decomposition of *N*-alkyldiazoacetoacetamides.[197,198] Products **419** and **420** were produced by C–H insertions of the rhodium carbenoid derived from diazoacetamide **418**. In addition to these compounds, heterocycle **421** was also formed from a suspected carbonyl ylide intermediate which then undergoes a proton transfer. By changing the nature of the rhodium catalyst employed, significant manipulation of the product distribution could be achieved. The yield of heterocycle **421** increases with the electron-withdrawing capabilities of the bridging ligands of the dirhodium(II) catalyst. This implies that the more electron-deficient carbenoids prefer to interact with the electron-rich carbonyl oxygen. Conformational preferences were found to dominate over electronic influences in governing the regioselectivity for catalytic C–H insertions.



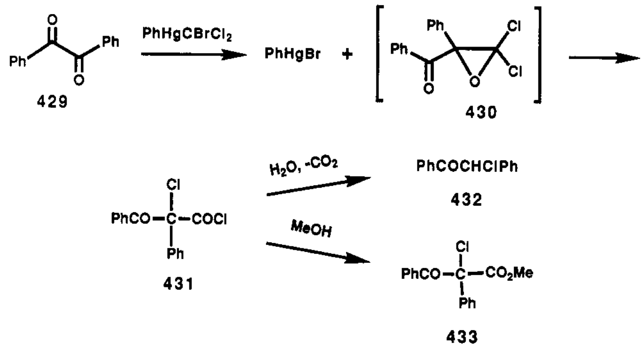
B. α-Halocarbonyl Ylides

Treatment of phenyl(bromodichloromethyl)mercury with an excess of an aromatic aldehyde or benzophenone results in the formation of a mixture of products (i.e. **425**–**428**)[199,200] (Scheme 11). Although definitive conclusions about some of the pathways leading to the observed products remains tentative, the evidence obtained suggests that attack of dichlorocarbene onto the aldehyde or ketone occurs to generate a dichlorocarbonyl ylide **423**. Once formed, ylide **423** can follow three distinct paths. The ylide derived from benzophenone undergoes ring closure and this is followed by rearrangement to produce chloroacetyl chloride **428** as the major product. In contrast, the carbonyl ylide generated from an aromatic aldehyde produces dichloride **427** and acid chloride **425**. This difference in product formation can be rationalized as follows: conversion of **423** into **427** requires a 90° twist of the CCl_2 group followed by 1,3-migration of chloride ion. Production of the acid chloride **425** proceeds via an initial 1,3-dipolar cycloaddition of carbonyl ylide **423** across the C–O double bond of the aromatic aldehyde followed by rearrangement of the dichlorodioxolane **422**. Attempts to independently synthesize **422** resulted in the isolation of **425**. The difference in reactivity of aromatic aldehydes versus benzophenone may be partly due to steric interactions between the *o*-hydrogen of benzophenone and the chlorine atom in carbonyl ylide **423** which promotes rapid conrotatory closure to the oxirane. Once formed, the epoxide would be expected to open readily to the acid chloride **425**.

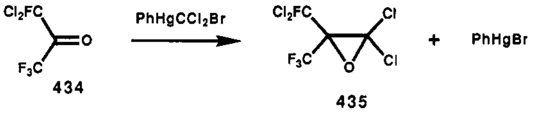
SCHEME 11



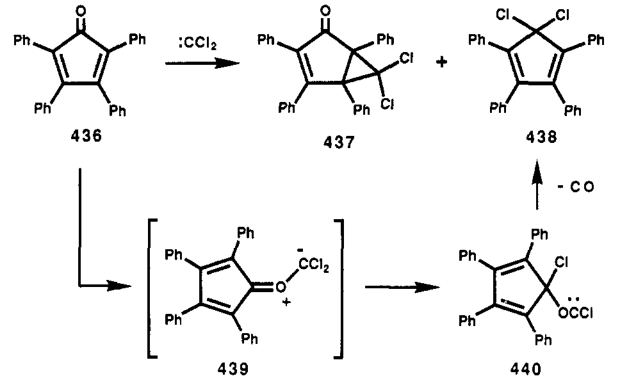
In a related study, benzil and phenyl(bromodichloromethyl)mercury were heated in benzene at reflux for 6 h.[201] After filtration and extraction, the reaction mixture was treated with methanol and pyridine to give α-chloro-α-carbomethoxy-α-phenylacetophenone (**433**) in 89% yield. When the reaction mixture was treated with a sodium acetate buffer in aqueous tetrahydrofuran, α-chloro-α-phenylacetophenone (**432**) was produced in 68% yield. The formation of these products is consistent with the generation of a carbonyl ylide that undergoes ring closure to epoxide **430** which then rearranges to acid chloride **431**. Hydrolysis or methanolysis of **431** affords products **432** and **433**, respectively.



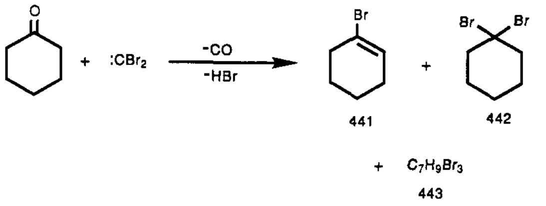
Perfluorooxiranes are known to be very thermally stable. In an attempt to isolate the epoxide intermediate postulated in the above reaction, phenyl(bromodichloromethyl)mercury was treated with fluorinated ketones.[202] In the case where phenyl(bromodichloromethyl)mercury was allowed to react with pentafluorochloroacetone (**434**), epoxide **435** was isolated. This observation provides strong support for the mechanism proposed for the formation of compounds **428** and **431**.



Dihalocarbenes are also known to deoxygenate carbonyl compounds to give dihaloalkanes and carbon monoxide.[203-205] Addition of dichlorocarbene to tetraphenylcyclone (**436**) afforded products **437** and **438**.[204] Cyclopentenone **437** was derived by 1,2-cycloaddition of the carbene across the double bond of tetracyclone **436**. The formation of cyclopentadiene **438**, on the other hand, involves attack of the carbene on the carbonyl oxygen to produce the intermediate carbonyl ylide **439**, which undergoes a subsequent rearrangement and loss of carbon monoxide. A 1,4-cycloaddition followed by elimination of carbon monoxide can not be ruled out as an alternative mechanism for the formation of cyclopentadiene **438**.

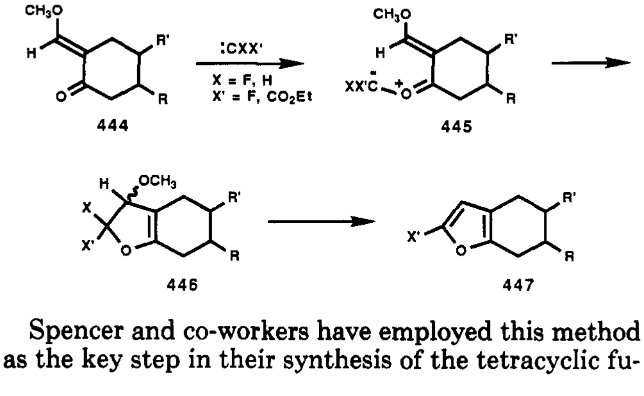


Landgrebe and co-workers[205] have encountered a similar transformation from the reaction of phenyl(tribromomethyl)mercury with various aldehydes and ketones. Thus, cyclohexanone reacts with dibromocarbene to produce compounds **441–443** in an 8:1:1 ratio. The deoxygenation reaction lends support for the carbonyl ylide intermediate postulated in the formation of cyclopentadiene **438**, since a 1,4-cycloaddition would be impossible in this system. Treatment of the product mixture with phenylmercuric bromide in benzene at 80 °C for 5 h resulted in minimal interconversion of dibromide **442** to bromoalkene **441**. This observation establishes **441** as a primary product.

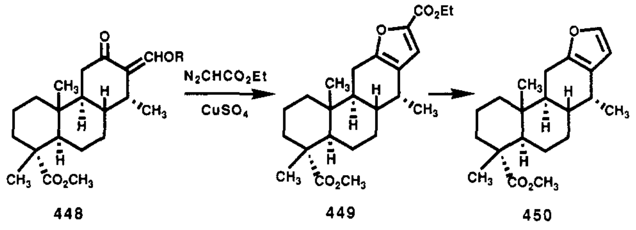


C. Cyclization of α,β-Unsaturated Carbonyl Ylides

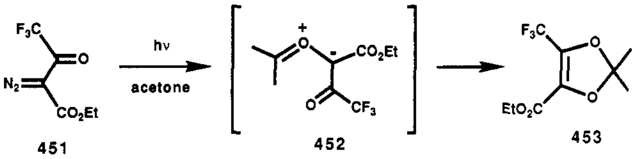
Furan rings are found in many natural products and other important compounds.[206-208] Synthetic methods allowing for the facile construction of furans are actively sought after. The reaction of carboethoxycarbene with α-methoxymethylene-substituted ketones such as **444** gave rise to furan **447**. The overall process corresponds to a net 1,4-addition of the carbene across the conjugated ketone.[209] The isolation of furan **447** is consistent with attack of the carbene onto the carbonyl oxygen to produce carbonyl ylide **445** which then undergoes a 6π-electrocyclization to give **446** followed by elimination of methanol.



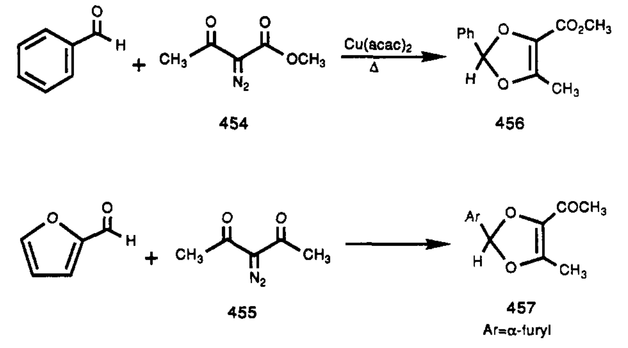
Spencer and co-workers have employed this method as the key step in their synthesis of the tetracyclic furanoid diterpene methyl vinhaticoate (**450**).[210] Treatment of the α-methoxymethylene ketone **448** with ethyl diazoacetate in the presence of copper sulfate at 160 °C afforded furoic ester **449** as the major product. This material was selectively hydrolyzed and decarboxylated to give the natural product.



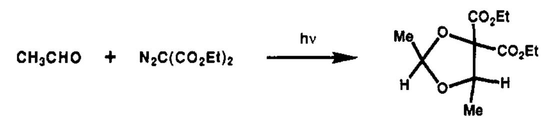
The chemistry of α-diazocarbonyl compounds continues to attract the attention of organic chemists over 90 years after their first exploration of their chemistry.[211] Dioxoles can be formed by the reaction of these compounds with ketones and aldehydes. Irradiation of ethyl diazotrifluoroacetoacetate (**451**) in acetone gave 2,2-dimethyl-5-(trifluoromethyl)-4-(ethoxycarbonyl)-1,3-dioxole (**453**) in a preparatively useful yield. This result is consistent with the formation of carbonyl ylide **452** which then cyclizes to produce heterocycle **453**. No product corresponding to 1,3-dipolar cycloaddition of dipole **452** across the carbonyl group of acetone was detected in the crude reaction mixture.



The copper-catalyzed interaction of methyl 2-diazo-3-oxobutyrate (**454**) and 3-diazo-2,4-pentanedione (**455**) with various aldehydes gave substituted 1,3-dioxoles in good yield.[212,213] The formation of the dioxole ring system is remarkably free of several competing transformations which could be expected (i.e. epoxidation, C–H insertion, homologation, aldol condensation, carbene dimerization, and Wolff rearrangement).



The reaction of dicarbomethoxycarbene with both acetaldehyde and simple ketones was studied by Jones and co-workers.[214] Singlet dicarbomethoxycarbene reacts with acetaldehyde to give dioxolane **458**, the ultimate product derived from formation of a carbonyl ylide and subsequent addition to a second molecule of aldehyde. Some minor products were also formed resulting from both C–H insertion and hydrogen transfer. When the photolysis was carried out in the presence of a triplet sensitizer, the yield of these minor byproducts was greatly increased and the yield of dioxolone **458** was



458

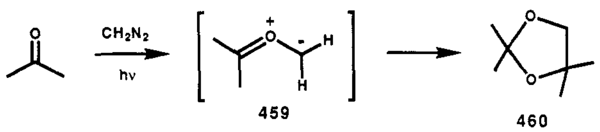
diminished. This observation supports "singlet" carbene attack on the carbonyl oxygen atom to form the 1,3-dipole.

D. 1,3-Dipolar Cycloaddition Reactions

Conceptually, the 1,3-dipolar cycloaddition of carbonyl ylides with π-bonds represents an attractive strategy for tetrahydrofuran formation. In recent years there has been increasing interest in the use of these 1,3-dipoles in heterocyclic synthesis. In many instances, the 1,3-dipolar cycloadditions are both regio- and stereospecific, lending it well to natural product synthesis. Of the three categories described by Sustmann,[215] type II is particularly common for carbonyl ylides since they possess one of the smallest HOMO–LUMO energy gaps of all the common 1,3 dipoles.[216] The HOMO of the dipole is dominant in reactions with electron-deficient dipolarophiles whereas the LUMO of the dipole is the controlling molecular orbital in reactions with electron-rich dipolarophiles. In general, all the regiochemistry results encountered with carbonyl ylides can be readily accommodated in terms of perturbation theory.

1. Intermolecular Carbonyl Ylide Formation

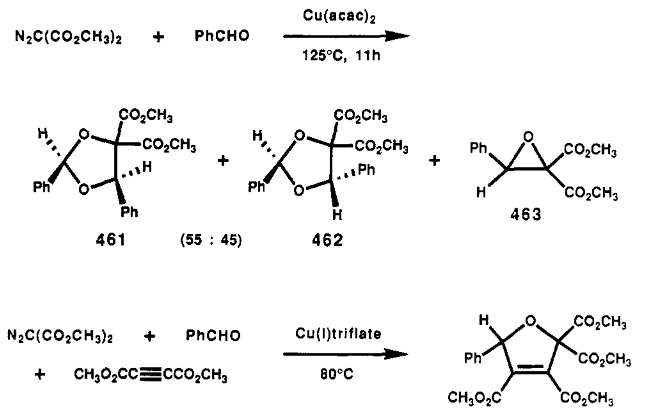
Carbonyl ylides can be formed by the bimolecular reaction of carbenes and carboyl compounds as well. In 1963, Bradley and Ledwith[217] investigated the irradiation of diazomethane in acetone and found that 2,2,4,4-tetramethyl-1,3-dioxolane (**460**) was produced as the major product. This result is consistent with the formation of a singlet carbene which attacks the carbonyl oxygen atom of acetone to give carbonyl ylide intermediate **459**. Ylide **459** then undergoes a 1,3-dipolar cycloaddition across the carbonyl group of another molecule of acetone to give heterocycle **460**.



459 460

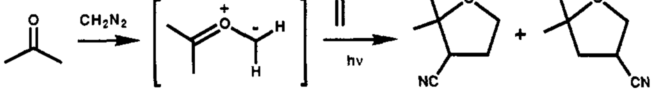
Reactions of carboalkoxycarbenes with carbonyl compounds have been described as early as 1885,[218] and the structures of the dioxolane products were proposed in 1910.[219] Huisgen and de March were the first to examine the reaction in detail and to trap a carbonyl ylide with a number of reagents, including the carbonyl compound itself to produce a dioxolane.[220,221] These workers examined the reaction of dimethyl diazomalonate with benzaldehyde at 125 °C. The reaction mixture contained dioxolanes **461** and **462** and epoxide **463** (Scheme 12). The yield of these products was significantly improved by the use of a transition-metal catalyst. Benzaldehyde plays a double role, first as a constituent of the carbonyl ylide and, subsequently, as a dipolarophile in the trapping of the dipole. These carbonyl ylides were also found to react especially well with dimethyl acetylenedicarboxylate to produce dihydrofurans such as **464**.

SCHEME 12



461 462 463 464

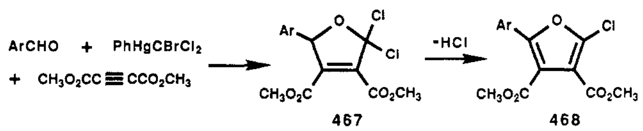
In a related study, Turro[222] reported that the irradiation of diazomethane in acetone in the presence of acrylonitrile gave a 2:1 mixture of cycloadducts **465** and **466**. Frontier molecular orbital theory correctly rationalizes the regiochemistry of the major isomer in this 1,3-dipolar cycloaddition. The fact that the reaction of the carbonyl ylide with an unsymmetrical dipolarophile gives a 2:1 mixture of two regioisomers indicates that, in the HOMO of the carbonyl ylide, the electron density at the unsubstituted carbon is greater than that at the disubstituted carbon atom. The ylide is produced by electrophilic attack of the singlet CH_2 onto the lone pair of electrons of the oxygen atom in acetone.



459 465 466

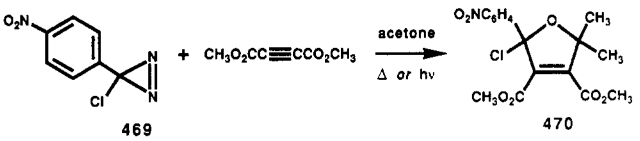
By using photoacoustic calorimetry, the heat of formation of the carbonyl ylide derived from methylene and acetone was determined as 4.5 kcal/mol.[223] The lifetime of this species in acetone was measured and found to be 53 ± 5 ns. The bimolecular rate for the reaction of acetone (17.2 M) with the ylide was found to be $1.1 \times 10^6\ M^{-1}\ s^{-1}$. Several reports indicate that thermal fragmentation of substituted carbonyl ylides to carbenes and ketones can also occur.[224] The activation energy associated with fragmentation of the ylide to singlet methylene and acetone was determined to be 45 kcal/mol.

Dichlorocarbene reacts intermolecularly with an aldehyde and a dipolarophile to produce furans. Accordingly, dichlorocarbene, generated by the thermal decomposition of phenyl(bromodichloromethyl)mercury, in the presence of aryl aldehydes and dimethyl acetylenedicarboxylate resulted in the formation of dimethyl 2-chloro-5-arylfuran-3,4-dicarboxylate (**468**).[225]



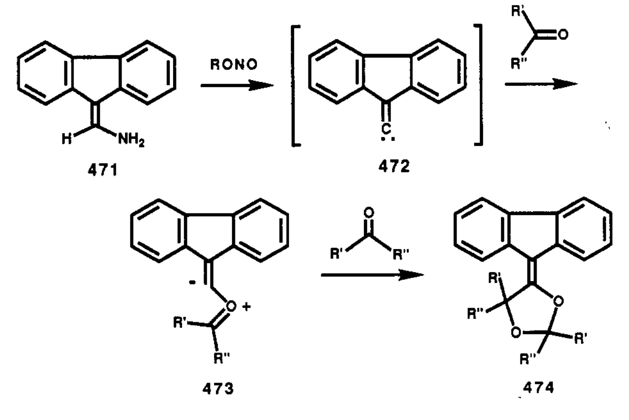
467 468

This product is the result of selective electrophilic attack of the carbene onto the aldehyde oxygen to produce a carbonyl ylide which is then captured by the electrophilic dipolarophile (i.e. DMAD). In the absence of DMAD, however, the carbonyl ylide intermediate is trapped by benzaldehyde. Cycloadduct **467** undergoes a spontaneous loss of hydrogen chloride to afford furan **468**. Ibata and Liu[226] have employed chlorodiazirines as precursors for electrophilic carbenes which react with aldehydes and ketones to form carbonyl ylides. One example involves the photolytic or thermal decomposition of 3-chloro-3-(*p*-nitrophenyl)diazirine (**469**) in the presence of a mixture of acetone and dimethyl acetylenedicarboxylate to give dimethyl 2-hydroxy-5,5-dimethyl-2-(*p*-nitrophenyl)-2,5-dihydrofuran-3,4-dicarboxylate (**470**). Kinetic analysis was carried out with



use of laser flash photolysis conditions, and the results obtained show that an equilibrium exists between phenylchlorocarbene, acetone, and the corresponding ylide. In the absence of a dipolarophile, the carbonyl ylide cyclizes to produce an epoxide. Electron-withdrawing substituents on the carbene were found to increase the rate of ylide formation and to decrease the rate of cyclization to the epoxide, thus enhancing the dipolar cycloaddition reaction.

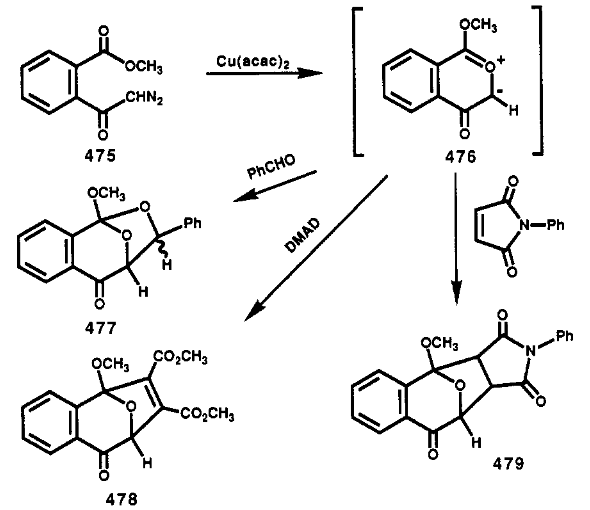
An interesting example of dioxolane formation which involves the addition of vinylidene **472** onto a carbonyl oxygen to form carbonyl ylide **473** was carried out by Kuo and Nye.[227] Reaction of 9-(aminomethylene)fluorene (**471**) with butyl nitrite in the presence of acetone produced 2,2,4,4-tetramethyl-5-fluorenylidene-1,3-dioxolane (**474**). This product is consistent with a mechanism which involves formation of a diazonium salt followed by loss of nitrogen and a proton to give carbene **472**. This reactive species adds to the carbonyl oxygen of acetone affording ylide **473** which subsequently undergoes dipolar cycloaddition with another molecule of solvent to give the observed product.



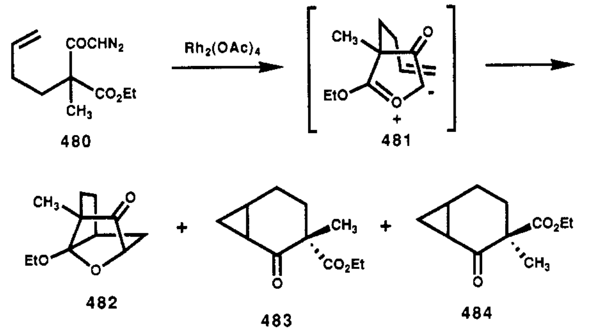
2. Intramolecular Carbonyl Ylide Formation

Intramolecular carbene–carbonyl cyclization represents one of the most effective methods for generating carbonyl ylides. Ibata and co-workers[228] were the first to demonstrate the utility of the method by studying the transition-metal-catalyzed decomposition of *o*-(alkoxycarbonyl)-α-diazoacetophenone in the presence of various dipolarophiles. A typical example involves treating *o*-(alkoxycarbonyl)-α-diazoacetophenone (**475**) with a catalytic amount of copper acetylacetonate. Evolution of nitrogen followed by carbonyl ylide formation generates a reactive dipole, which can be trapped by dipolarophiles such as benzaldehyde, dimethyl acetylenedicarboxylate, or *N*-phenylmaleimide to give cycloadducts **477**, **478**, and **479**, respectively (Scheme 13). Cycloadditions using the benzopyrylium oxide ylide **476** have been extensively studied by Ibata and his co-workers.

SCHEME 13

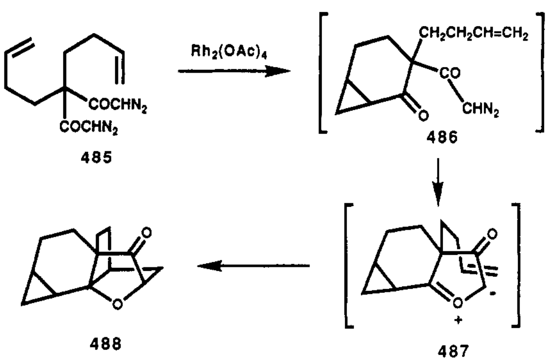


The tandem cyclization–cycloaddition methodology was further extended by the intramolecular trapping of the carbonyl ylide dipole with a C–C double bond suitably placed within the molecule. Bien and co-workers[229] reported on the transition-metal-catalyzed decomposition of diazo ketone **480** to give 8-ethoxy-1-methyl-9-oxatricyclo[3.2.1.1]nonan-2-one (**482**) as the major product together with lesser quantities of **483** and **484**. This result is consistent with the formation of a five membered cyclic carbonyl ylide which is followed by intramolecular trapping by the tethered olefin.

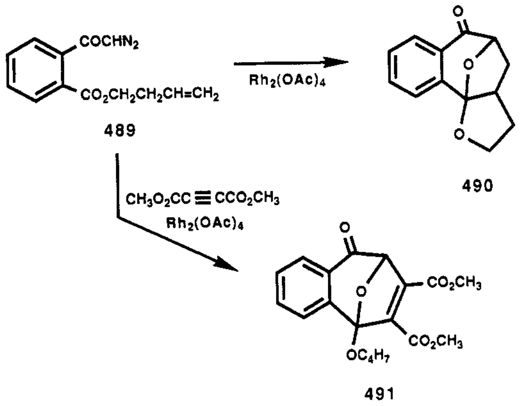


These same workers have also studied the catalytic decomposition of bis(diazo ketone) **485**.[229] The formation of cycloadduct **488** represents a unique case in which two diazo ketone moieties in the same molecule, under the influence of the same catalyst, react in different ways. One of the diazo groups undergoes addition to the double bond to give bicyclo[4.1.0]hexane **486** which subsequently cyclizes to generate the carbonyl ylide intermediate **487**. Intramolecular trapping of this ylide ultimately affords the isolated product **488**. The structure of **488** was unequivocally established by single-crystal X-ray crystallographic analysis.

An attractive feature of the above tandem cyclization–cycloaddition process is the opportunity to control the stereochemistry of the product at several different centers. The resulting product represents a highly

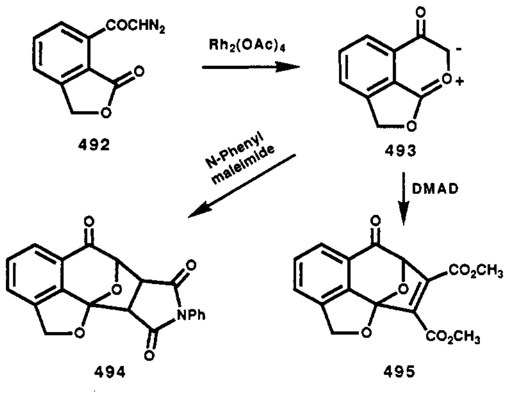


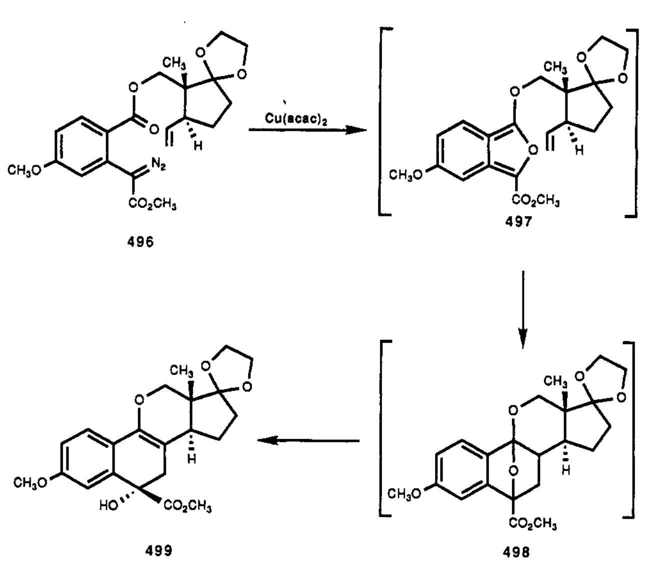
functionalized rigid bicyclic system that is amenable to subsequent synthetic elaboration. Padwa and co-workers have examined this tandem cyclization–cycloaddition sequence in some detail. Treatment of *o*-alkyl-2-(enoxycarbonyl)-α-diazoacetophenone **489** with rhodium(II) acetate resulted in initial cyclization to produce a six-membered ring carbonyl ylide which underwent a subsequent intramolecular dipolar cycloaddition with the neighboring double bond to give cyclohepta[1,2-*b*]furanone **490** in 87% yield.[230,231] When the reaction was carried out in the presence of dimethyl acetylenedicarboxylate, the only product obtained corresponded to the bimolecular dipolar cycloadduct **491**. In this case, the stabilized carbonyl ylide preferred to cycloadd with the activated external dipolarophile instead of undergoing reaction with the unactivated internal π-bond.



A related system was also studied where freedom of rotation about the C–C bond connecting the ester and the aromatic ring was severely restricted by the incorporation of the carbonyl group into a lactone ring.[231,232] Treatment of diazo ketone **492** with rhodium(II) acetate in the presence of *N*-phenylmaleimide or dimethyl acetylenedicarboxylate afforded cycloadduct **494** or **495**, respectively (Scheme 14).

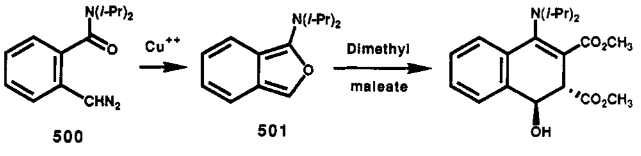
SCHEME 14





Friedrichsen and co-workers[233] have used the transition-metal-catalyzed cyclization reaction to synthesize 6-functionalized-11-oxasteroids. The copper-catalyzed decomposition of diazo ketone **496** produced isobenzofuran **497** which underwent an intramolecular Diels–Alder reaction followed by a subsequent ring opening to give **499**. This process augers well for the synthesis of many oxasteroid derivatives.

In a related study, Beak and Chen have used *o*-diazobenzamides (i.e. **500**) to form 2-azaisobenzofurans (**501**) in situ which can be trapped by dienophiles to give 3,4-dihydronaphthalene derivatives **502** after cleavage of one of the central C–O bonds.[234] This sequence of reactions corresponds to an overall annulation of an aryl amide and should be useful for the preparation of substituted naphthalenes.



Most of the examples of intramolecular carbonyl ylide formation reported involve systems in which the keto–metallocarbenoid, and the remote ester carbonyl group are substituted ortho to one another on a benzene ring. This arrangement provides interatomic distances and bond angles that are ideal for dipole formation. The 1-diazo-2,5-pentanedione system **503** was studied in order to test the geometric and electronic requirements of dipole formation[235,236] (Scheme 15). Note that in this system the dipole is generated by attack of a less nucleophilic ketonic carbonyl and that the tether is a simple dimethylene chain, which introduces conformational flexibility not available to the more rigid benzo systems of the previous studies. Diazo ketone **503** was treated with rhodium(II) acetate in the presence of various dipolarophiles.

When dimethyl acetylenedicarboxylate was used as the trapping agent, cycloadduct **504** was produced in excellent yield. In the presence of benzaldehyde, only one regioisomer was formed (i.e. **505**). The reaction of **503a** with methyl propiolate afforded cycloadduct **506a**

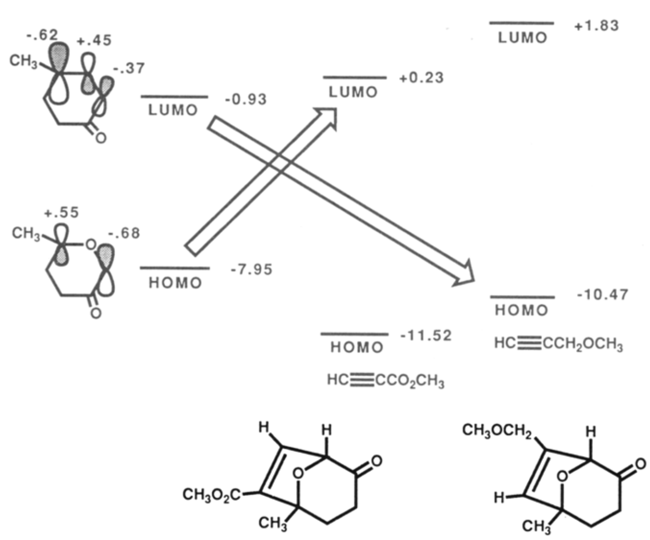
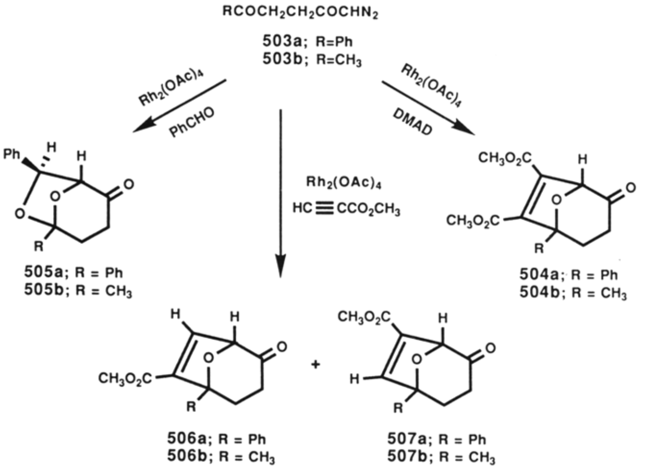


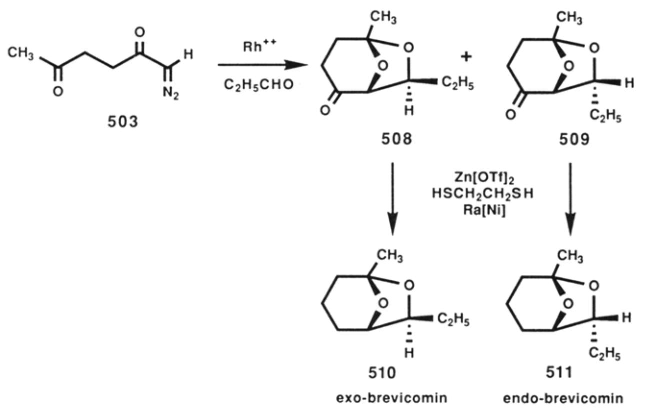
Figure 1. Regiochemistry results.

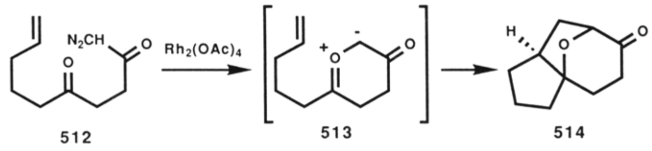
SCHEME 15

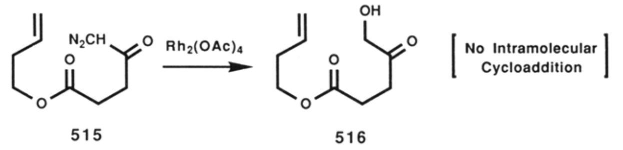


whereas the cycloaddition of **503b** with the same alkyne gave rise to a 4:1 mixture of two regioisomers (**506b** and **507b**) in 78% overall yield. The major regioisomer formed is consistent with the expected product predicted by FMO theory. The most favorable FMO interaction is between the HOMO of the dipole and the LUMO of the dipolarophile (Figure 1).

This methodology has been applied to the synthesis of *exo*- and *endo*-brevicomin.[236,237] The exo and endo isomers of brevicomin (**510** and **511**) are exuded by the female Western Pine Beetle and the exo isomer is known to be a key component of the aggregation pheromone of this destructive pest.[238,239] Thus, treatment of 1-diazo-2,5-hexanedione with rhodium(II) acetate in the presence of propionaldehyde afforded the 6,8-dioxabicyclo[3.2.1]octane ring system in 60% isolated yield as a 2:1 mixture of exo and endo isomers, **508** and **509**, respectively. The isomers were separated by silica gel chromatography and were subsequently carried on to *exo*- and *endo*-brevicomin (**510** and **511**, respectively) in good yield.

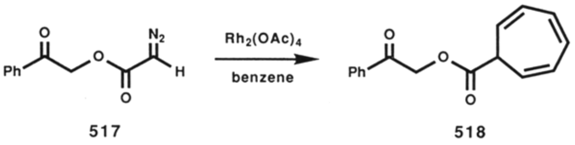




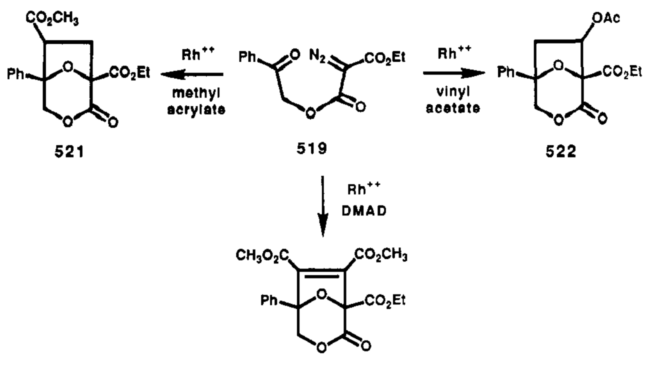


The use of aliphatic esters to form carbonyl ylides has also been examined.[105] Treatment of diazo keto ester **515** with a catalytic amount of rhodium(II) acetate in benzene led to the formation of **516** (53%) together with a complex mixture of products, none of which appeared to arise from cycloaddition of a carbonyl ylide intermediate. This result was found to be quite general for a series of aliphatic esters. It should be noted that when the closely analogous keto system **512** was treated under identical conditions, the intramolecular cycloadduct **514** was produced in excellent yield. The results encountered with these two systems suggest that the electronic difference between an ester and a ketone creates alternate competing pathways in these aliphatic systems. A complete understanding of how the exchange of an ester moiety for the ketone on the side chain can completely change the reaction path remains elusive.

Replacement of a methylene group in the two carbon tether with an oxygen atom would generate precursors for various dioxanones following the cyclization–cycloaddition sequence.[240] However, when diazo ester **517** was treated with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate, cycloheptatriene **518** was the only product formed. No cycloadduct resulting from carbonyl ylide formation was observed. One possible explanation for the differing reactivity of the α-diazoacetate system is the inherent decrease in electrophilic character conferred upon the intermediate rhodium carbenoid when the diazo ketone is replaced by a diazoacetate functionality. This decrease in electrophilicity may attenuate the rate of carbenoid attack on the remote carbonyl group to the point where an alternative pathway can occur. In order to compensate for this diminished electrophilicity, the hydrogen of the diazo carbon atom was substituted with an electron-withdrawing group. Thus, treatment of ethyl diazomalonate **519** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate, methyl acrylate, or vinyl acetate produced cycloadducts **520–522**, respectively.

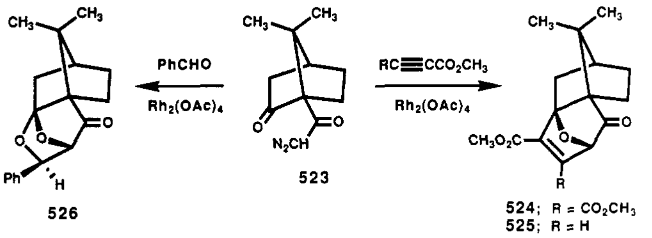


The primary spatial requirement for carbonyl ylide formation is that the distance between the two reacting



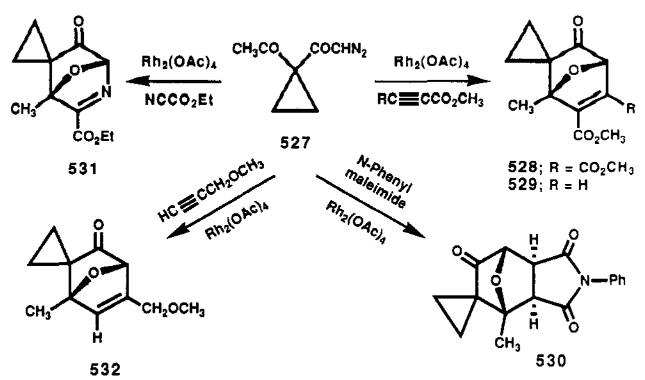
centers should be sufficiently close so that effective overlap of the lone pair of electrons on the carbonyl group with the metallocarbenoid center can occur. The effect that variation in the spatial proximity between the carbonyl group and the diazo ketone would have on the course of the reaction was studied by varying the length of the methylene tether separating the two functionalities. The majority of systems examined in the literature involved the formation of a six-membered ring carbonyl ylide intermediate. Diazoalkanediones which lead to five- and seven-membered ylides have recently been examined.[241]

Treatment of diazo ketone **523** with a catalytic amount of rhodium(II) acetate at 25 °C in benzene with dimethyl acetylenedicarboxylate afforded cycloadduct **524** in 85% yield.[241] The cycloaddition reaction proceeded with complete diastereofacial selectivity with approach of the dipolarophile from the α-face. Similar treatment of **523** with methyl propiolate produced cycloadduct **525** in 72% isolated yield. The tandem cyclization–cycloaddition reaction was also carried out in the presence of benzaldehyde to give the bicyclic ketal **526** in 66% yield. Approach from the α-face of the dipole is the preferred process as a consequence of the severe steric interaction with the bridgehead gem dimethyl group associated with β-attack.

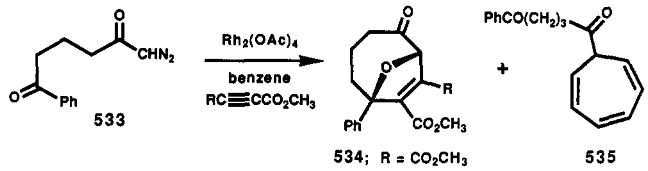


Cyclopropyl-substituted diazo ketone **527** was also treated with rhodium(II) acetate in the presence of various dipolarophiles (i.e. dimethyl acetylenedicarboxylate, methyl propiolate, *N*-phenylmaleimide, ethyl cyanoformate, and methyl propargyl ether) producing the analogous cycloadducts **528–532** in high yield[241] (Scheme 16). It would appear that decreasing the methylene side chain by one carbon atom does not significantly effect the facility by which diazo ketones undergo the cyclization reaction.

SCHEME 16



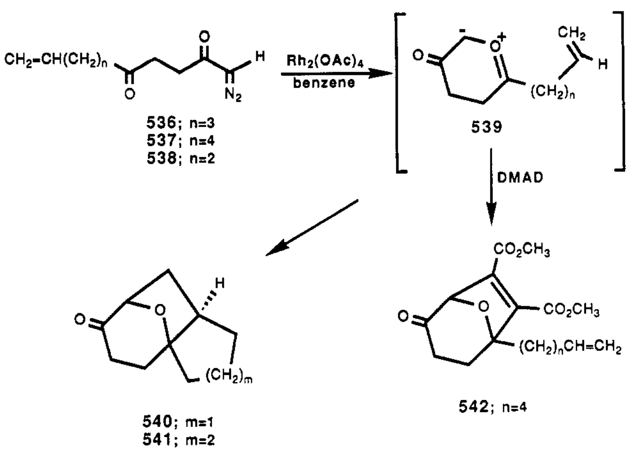
When the connecting chain contains three methylene units, a seven-membered ring carbonyl ylide intermediate was expected to form.[241] Indeed, the rhodium(II)-catalyzed reaction of 1-diazo-6-phenyl-2,6-hexanedione (**533**) in benzene using dimethyl acetylenedicarboxylate (or methyl propiolate) afforded a 2:1 mixture of products. The major product corresponds to the expected cycloadduct **534** (45%) whereas the minor component was identified as cycloheptatriene **535** (22%). This material is derived from a bimolecular addition of the rhodium carbenoid onto benzene followed by ring tautomerization. The formation of a mixture of products in this case indicates that extending the tether to three methylene groups sufficiently retards the rate of intramolecular cyclization so as to allow the bimolecular reaction with benzene to occur.



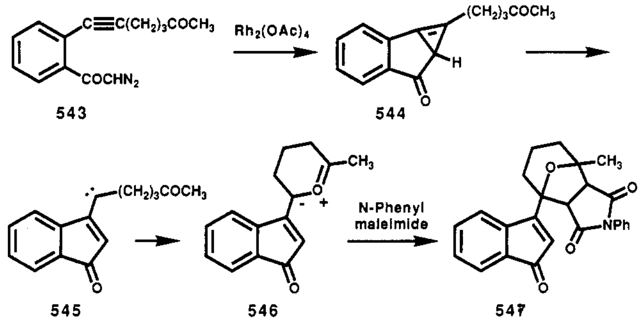
The intramolecular trapping of carbonyl ylide dipoles has proven to be an effective method for synthesizing complex polycyclic heterocycles. Varying the length of the tether that separates the olefin from the carbonyl ylide dipole allows for the synthesis of a variety of interesting oxopolycyclic ring systems. Diazo ketones tethered to the carbonyl group by three methylene units were shown to cyclize most efficiently. Thus, when diazo ketone **536** was treated with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate, cycloadduct **540** was the only product formed[242] (Scheme 17). The intramolecular trapping reaction occurs at such a fast rate that the bimolecular cycloaddition reaction cannot compete with it. The homologous diazo ketone **537** was also treated with catalytic rhodium(II) acetate in benzene at 25 °C producing cycloadduct **541** in 50% yield. In this case, the carbonyl ylide could be readily trapped with dimethyl acetylenedicarboxylate giving the bimolecular cycloadduct **542** as the exclusive cycloadduct. Increasing the length of the tether to five methylene units gave no internal cycloadduct. Apparently, the π-bond is not in close enough proximity to the dipole centers to allow the cycloaddition to occur. Diazo ketone **538**, which contains only two methylene units in the tether, produced none of the internal cycloadduct. Clearly the intramolecular trapping of carbonyl ylides by tethered olefins occurs best when the tether contains three or four methylene units. The internal cycloaddition fails to occur when the tether contains less than three or more than four methylene carbons.

A similar cyclization–cycloaddition reaction was also found to occur with the vinylogous keto carbene **545**. Treatment of diazo ketone **543** with rhodium(II) acetate in the presence of *N*-phenylmaleimide gave adduct **547**

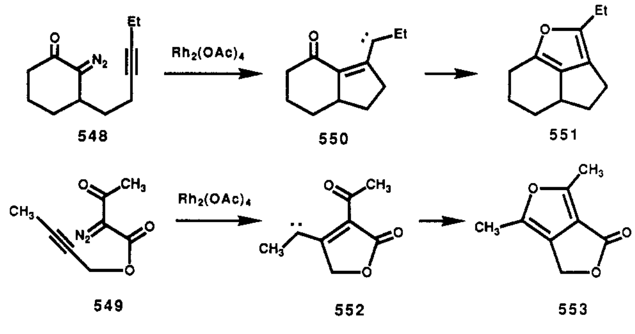
SCHEME 17



in 60% yield. While the intermediates have not been isolated or detected, this result is consistent with intramolecular cyclopropenation of the alkyne by the rhodium carbenoid to give the highly strained cyclopropene **544** which undergoes further ring opening to produce vinyl carbene **545**. Carbene interaction with the adjacent carbonyl oxygen generates the resonance stabilized dipole **546**, which then cycloadds across the activated π-bond of *N*-phenylmaleimide to produce product **547**. This structure was established by an X-ray single-crystal structure analysis.[243]

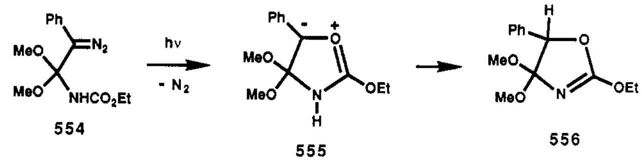


One of the more frequently encountered reactions of dienylcarbenes involves rearrangement to indenes, cyclopentadienes, or furans.[244] Diazo ketones **548** and **549** were found to undergo this type of cyclization in the presence of a rhodium catalyst. The reaction proceeds via formation of a transient vinyl carbene which attacks the carbonyl oxygen to give a carbonyl ylide which subsequently tautomerizes to furans **551** and **553**, respectively.[245]

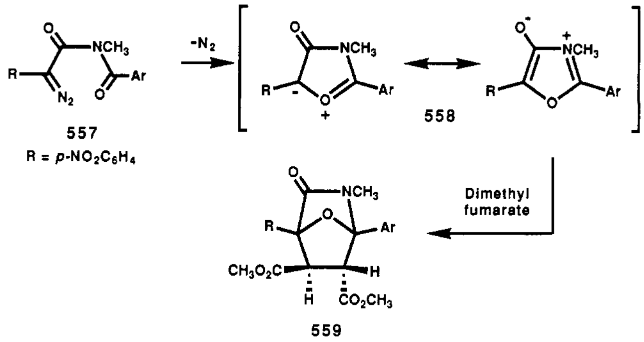


3. Carbonyl Ylide Formation from Imides, Carbamates, Amides, and Anhydrides

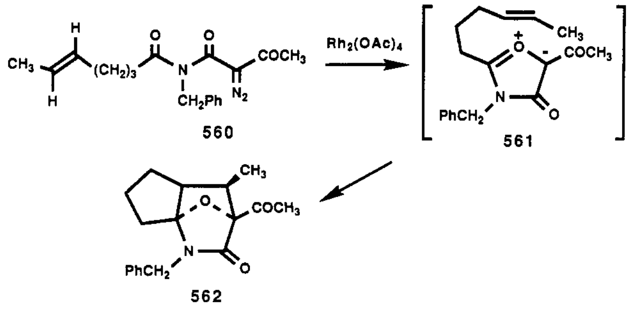
Carbonyl ylide formation involving the C–O double bond of a carbamate has been reported by Graziano and co-workers.[246] Photolysis of 1-phenyl-2,2-dimethoxy-2-[(ethoxycarbonyl)amino]diazoethane (**554**) in cyclohexane using a high-pressure mercury lamp gave Δ^2-oxazoline **556** as the major product. The formation of this material is consistent with carbonyl ylide formation (i.e. **555**) followed by proton transfer.



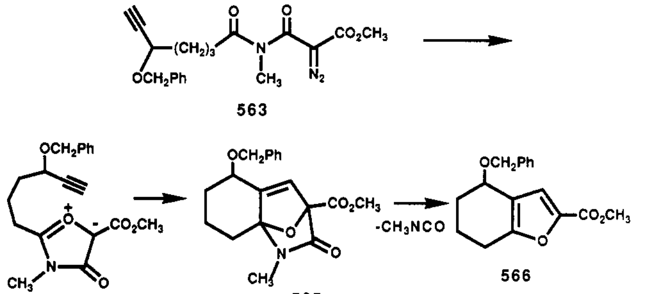
Although carbonyl ylides have been postulated as intermediates in many reactions, very few of these dipoles have actually been isolated and characterized.[187] One of the earliest examples involving the isolation of a stable carbonyl ylide was reported by Ibata and Hamaguchi in 1974.[247] Diazo amide **557** was heated in benzene at 80 °C under a nitrogen atmosphere in the presence of Cu(acac)$_2$, producing 2-phenyl-5-(*o*-nitrophenyl)anhydro-4-hydroxy-1,3-oxazolium hydroxide (**558**) in 85% yield as a red crystalline solid, which was stable in air for several weeks. Mesoionic oxazolium ylides such as **558** have been termed isomünchnones and correspond to the cyclic equivalent of a carbonyl ylide. This dipole was found to react with dimethyl fumarate in benzene at 80 °C, giving rise to cycloadduct **559** in only a few minutes in quantitative yield.



Intramolecular cycloadditions of isomünchnones, formed by the rhodium(II) acetate decomposition of *N*-diazoacetato(acetyl)alkenylamides, have been realized by Maier and co-workers.[248] A solution of diazo amide **560** in toluene was added dropwise to a refluxing mixture of rhodium(II) acetate in toluene producing cycloadduct **562** in 91% yield. The intermediate isomünchnone **561** was not isolated in this case. The relative stereochemistry of cycloadduct **562** was established by X-ray analysis, which showed that the addition of the olefin took place endo with regard to the 1,3-dipole and anti to the methyl group on the π-bond chain.

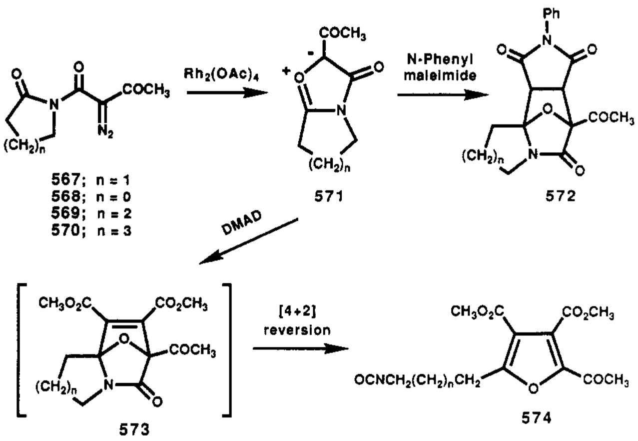


The cycloadducts derived from the intramolecular cycloaddition reactions of acetylenic isomünchnones fragment spontaneously under the reaction conditions to afford annulated furans.[249] Thus, treatment of acetylenic diazoamide **563** under the same conditions as used above, produced 4,5,6,7-tetrahydrobenzofuran **566** in 60% yield. This result was interpreted in terms of carbonyl ylide formation (**564**) followed by 1,3-dipolar cycloaddition across the tethered acetylene to give cycloadduct **565** which then undergoes a subsequent cycloreversion reaction to give furan **566**.

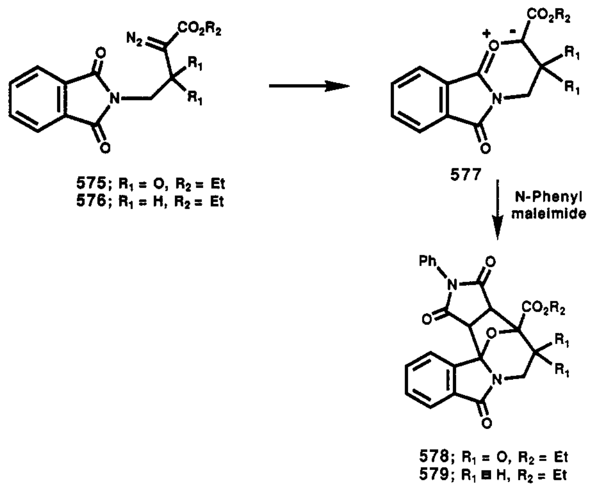


An analogous isomünchnone–alkyne internal cycloaddition–fragmentation process was also reported by Padwa and co-workers.[198,250] Treatment of diazo imide **567** ($n = 1$) with rhodium(II) acetate at 80 °C in benzene produced an isomünchnone dipole **571** (Scheme 18). 1,3-Dipolar cycloaddition of this species with dimethyl acetylenedicarboxylate gave cycloadduct **573** which subsequently fragments via a retro-Diels–Alder reaction into furan **574** in 85% yield. Trapping of dipole **571** with *N*-phenylmaleimide gave cycloadduct **572** in 78% yield. The generality of this method was demonstrated by varying the cyclic imide so as to probe any geometric effects of ring size on the outcome of the cyclization–cycloaddition reaction. The ring size was reduced to a four-membered ring (**568**; $n = 0$) (61%) and enlarged to a six-membered (**569**; $n = 2$) (85%) and a seven-membered ring (**570**; $n = 3$) (75%). In all cases, high yields of the expected cycloadduct derived from *N*-phenylmaleimide were obtained. Interestingly, the cyclic cases where $n = 1$ and $n = 3$ showed little exo/endo selectivity, but the cases of $n = 0$ and $n = 2$ resulted in formation of single stereoisomers. The conformational rigidity imposed by the cyclic imide ring was demonstrated to be inconsequential by carrying out the tandem cyclization–cycloaddition sequence with acyclic amides.

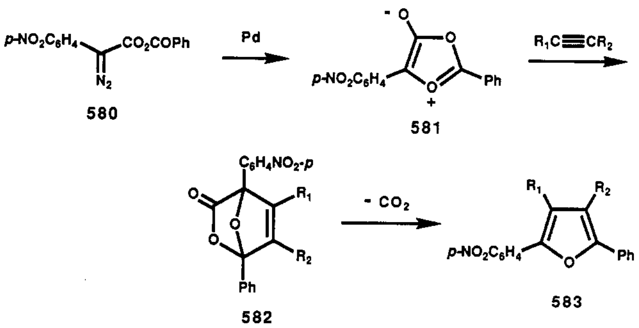
SCHEME 18



Extending the length of the tether by one methylene unit gave rise to a six-membered ring carbonyl ylide which was not stabilized by any isomünchnone-type delocalization.[198,250] Thus, treatment of diazo phthalimido ester **575** with rhodium(II) acetate in refluxing benzene in the presence of *N*-phenylmaleimide afforded cycloadduct **578** in 87% yield. Similar treatment of the less-activated diazo phthalimido ester **576** with rhodium(II) octanoate at 25 °C in the presence of *N*-phenylmaleimide gave the related cycloadduct **579** which is derived from dipole **577**.

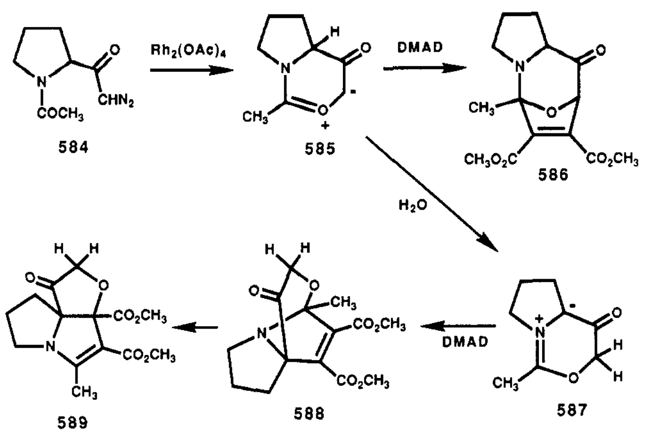


The novel anhydro-4-hydroxy-1,3-dioxolium hydroxide **581** was generated by an intramolecular carbene–carbonyl cyclization reaction. Catalytic decomposition of α-diazoacetic anhydride **580** gave the mesoionic dipolar species **581** which could be trapped with acetylenes to produce furan derivatives as the final product.[251] For example, when a π-allyl palladium complex was added to a benzene solution containing diazo acid anhydride **580** and dimethyl acetylenedicarboxylate at 80 °C, furandicarboxylate **583** was isolated in 86% yield. The formation of this material is consistent with a mechanism that involves intramolecular carbonyl ylide formation followed by 1,3-dipolar cycloaddition to give bicyclic intermediate **582** which spontaneously loses carbon dioxide.



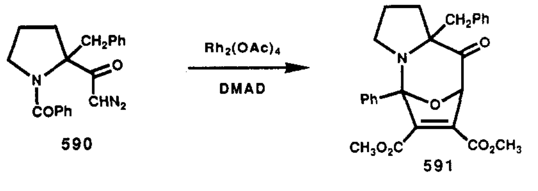
1,3-Dipoles are extremely valuable intermediates in synthetic organic chemistry. Their best known reaction corresponds to a 1,3-dipolar cycloaddition reaction. Less attention, however, has been placed on the interconversion of one dipole into another. A new method for azomethine ylide formation was recently developed which involves a cascade of dipoles. This novel process

SCHEME 19

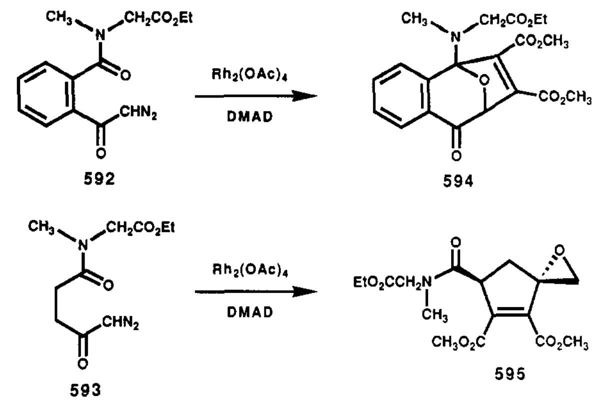


was uncovered during an examination of the reaction of (*S*)-1-acetyl-2-(1-diazoacetyl)pyrrolidine (**584**) with 1.5 equiv of dimethyl acetylenedicarboxylate in the presence of a catalytic quantity of rhodium(II) acetate (Scheme 19). Very little (<10%) of the expected carbonyl ylide derived cycloadduct (i.e. **586**) was obtained.[252] Instead, the major product (90%) corresponded to structure **589**. A mechanism that rationalizes the formation of this product involves generation of the expected carbonyl ylide dipole **585** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. Isomerization of **585** to the thermodynamically more stable azomethine ylide **587** occurred via proton exchange with a small amount of water that was present in the reaction mixture. 1,3-Dipolar cycloaddition with dimethyl acetylenedicarboxylate provides cycloadduct **588**, which undergoes a subsequent 1,3-alkoxy shift to generate the tricyclic dihydropyrrolizine **589**. The overall process has been refered to as a "dipole cascade". MNDO calculations show that cyclic carbonyl ylides of type **585** have higher heats of formation (ca. 15 kcal/mol) than the corresponding azomethine ylide **587**. Some of this energy difference is presumably responsible for the facility with which the dipole reorganization occurs.

In the dipole cascade reaction, a proton must be removed from the α-carbon atom in order to generate the azomethine ylide. When the α-position of the pyrrolidine ring was blocked by a benzyl group, formation of the azomethine ylide dipole could not occur. In fact, treatment of diazo ketone **590** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate afforded only the carbonyl ylide derived cycloadduct **591** in 95% yield.[252]



In the case of α-diazo keto amide **592**, the carbonyl ylide dipole is sufficiently stabilized via resonance to be trapped by dimethyl acetylenedicarboxylate to give cycloadduct **594** in 90% yield.[253] No signs of any material derived from azomethine ylide cycloaddition were observed. The closely related α-diazo keto amide **593** was also examined. Most interestingly, treatment of **593** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate afforded cycloadduct **595** in 60% yield. The initial reaction involved generation of the expected carbonyl ylide dipole **597** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group (Scheme 20). This highly stabilized dipole does not readily undergo 1,3-dipolar cycloaddition but rather lost a proton to produce the cyclic ketene *N*,*O*-acetal **598**. This material reacts further with the activated π-bond of the dipolarophile to produce zwitterion **599**. The anionic portion of **599** adds to the adjacent carbonyl group, affording a new zwitterionic intermediate **600**. Under anhydrous conditions, epoxide formation occurred with charge dissipation to give the observed cycloadduct **601**.



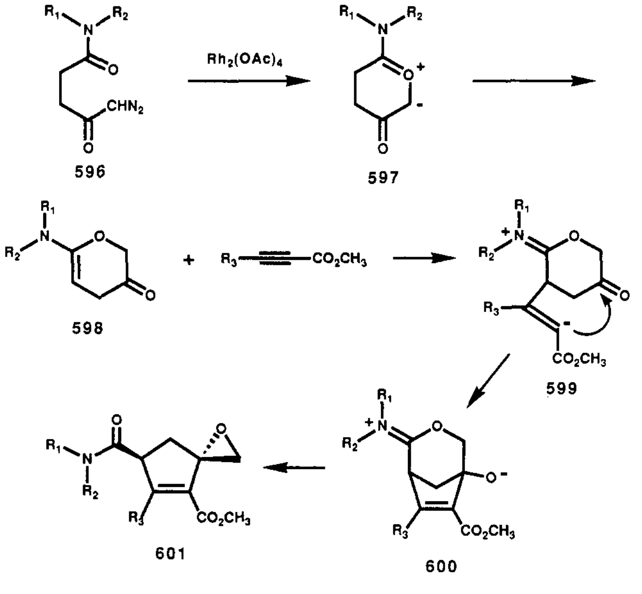
The high efficiency of the dipole cascade, in conjunction with the intriguing chemistry of the resulting cycloadducts, presents numerous synthetic possibilities for the preparation of complex heterocycles. Obviously, further work in this area will be carried out by a number of research groups.

VI. Formation of Nitrogen Ylides

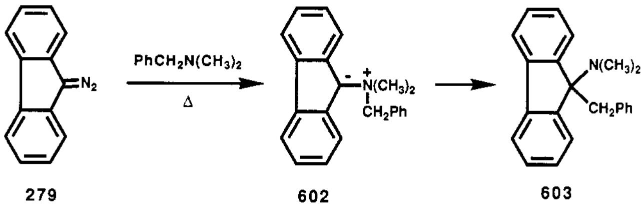
A. Ammonium Ylides

Carbenoid generation of nitrogen ylides represents a useful alternative to the widely employed base-promoted methodology.[254] The reaction of aliphatic diazo compounds with tertiary amines was first investigated

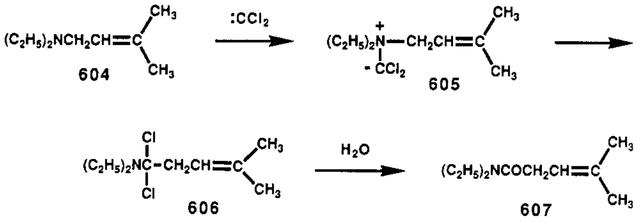
SCHEME 20



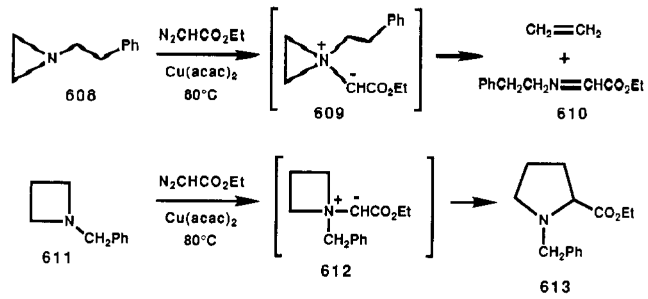
by Bamford and Stevens in 1952.[255] The formation of α-benzyl-α-(dimethylamino)fluorene (**603**) from the reaction of diazofluorene with benzyldimethylamine is consistent with a mechanism that involves generation of ammonium ylide **602** which then undergoes a 1,2-benzyl shift. The Stevens rearrangement is one of the most common reactions for the degradation of quaternary ammonium ylides.[256] Although detailed mechanistic studies for the 1,2-shift of ammonium ylides have not been carried out, one can assume that it occurs via a diradical process as has been established for the analogous sulfonium and oxonium ylides.[40,155]



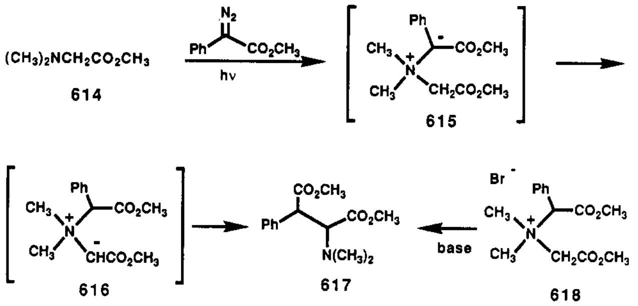
The reaction of dichlorocarbene with allylamines was found to be quite different from that observed with the corresponding allyl sulfide system.[257] With the amines, reaction of dichlorocarbene with the olefinic π-bond occurs predominantly to give cyclopropane derivatives. The difference in behavior may be in part a consequence of the relative stabilities of the nitrogen and sulfur ylides. The sulfur ylide is stabilized through resonance involving participation of the sulfur d orbitals. Consequently, reactions proceeding through a nitrogen ylide are less likely to occur than those proceeding through a sulfur ylide. Steric bulk adjacent to the allylic center, however, enhances ammonium ylide formation. Thus, treatment of *N*,*N*-diethyl-3-methyl-2-butenamine (**604**) with dichlorocarbene produced *N*,*N*-diethyl-4-methyl-2-pentenamide (**607**) as the major product. The formation of this material was attributed to the generation of ammonium ylide **605** followed by a 1,2-allylic shift to give intermediate **606** which then hydrolyzed during workup and gave amide **607**. No product resulting from a 2,3-sigmatropic rearrangement of ylide **605** was detected in the crude reaction mixture.



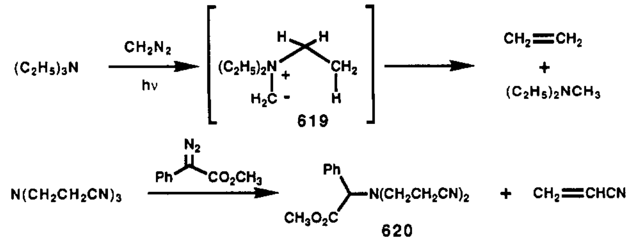
The chemistry of ammonium ylides formed from the reaction of cyclic amines with carbenes was found to be dependent on the ring size of the amine.[258] For example, treatment of 1-benzylazetidine (**611**) with ethyl diazoacetate in the presence of a copper(II) catalyst afforded pyrrolidine **613** in 96% yield. This result requires formation of an ammonium ylide (**612**) followed by ring expansion. In contrast, the reaction of 1-phenethylaziridine (**608**) with the copper catalyst gave the fragmentation product **610** in quantitative yield. Similar results were observed from the reaction of aziridine **608** with dichlorocarbene.[259] On the other hand, treatment of 1-phenethylpyrrolidine with ethyl diazoacetate in the presence of a copper(II) catalyst afforded only recovered starting material. Important factors which probably influence the course of these reactions are (1) the amount of ring-strain energy released and (2) the heat of formation of the resulting ethylene π-bond.



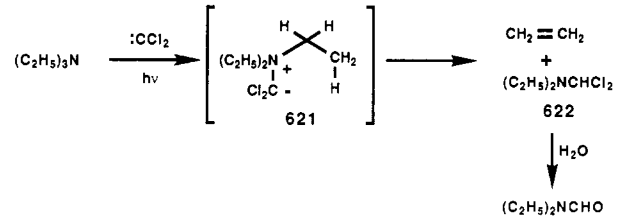
It has generally been recognized that the insertion of carbenes into C–H bonds adjacent to a heteroatom is preferred.[4] For example, (methoxycarbonyl)phenylcarbene is known to undergo a C–H insertion reaction with triethylamine.[260] Other amines bearing electron withdrawing β-substituents (i.e. **614**), when treated with (methoxycarbonyl)phenylcarbene, afford compounds corresponding to the least-favored C–H insertion products.[260] An electrophilic carbene should prefer to insert into the most electron rich C–H bond. This selectivity can be explained by a mechanism that involves carbene addition onto the nitrogen atom to generate ammonium ylide **615**. A 1,3-proton transfer produces zwitterion **616** which then underwent a 1,2-shift to give the observed amine **617**. Support for the above mechanism was obtained by treating ammonium bromide **618** with sodium methoxide and finding that amine **617** is formed in almost quantitative yield.



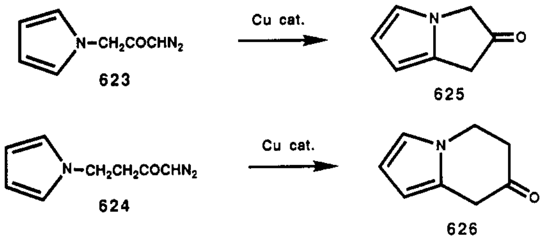
Ammonium ylides that possess a β-hydrogen often undergo an elimination reaction to provide the corresponding amine and alkene.[260–264] For example, the irradiation of diazomethane in the presence of triethylamine gave dimethylamine and ethylene.[261,262] In a similar manner, treatment of (methoxycarbonyl)phenylcarbene with tris(cyanoethyl)amine produced acrylonitrile and amine **620**.[260] These two transformations occur via β-hydride elimination from a transient ammonium ylide such as **619**.

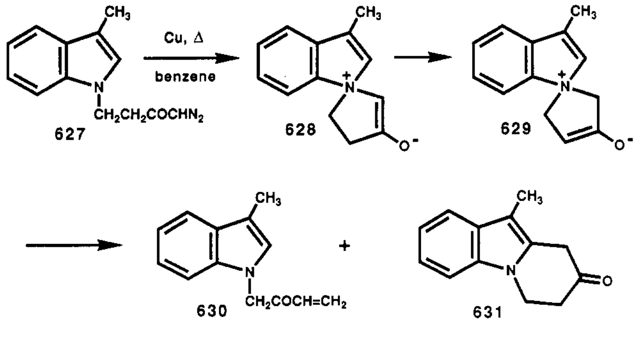


The reaction of triethylamine with dichlorocarbene produced diethylformamide as the major product.[263] This result is also consistent with β-elimination from an initially formed nitrogen ylide **621** to give diethyl(dichloromethyl)amine (**622**) and ethylene. Hydrolysis of dichloride **622** ultimately afforded diethylformamide.

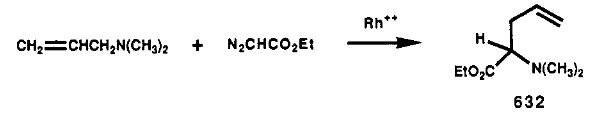


Although suitable for ylide production, carbenes generated photochemically and thermally in the presence of organic compounds containing heteroatoms are relatively indiscriminate. The potentially more general catalytic approach to carbenoid generation began to evolve with the use of copper catalysts.[18,19,48,59,85,261,264,265] The carbenoid species formed from the copper-catalyzed reaction of 1-diazo-3-pyrrol-1-yl-2-propanone (**623**) and 1-diazo-4-pyrrol-1-yl-2-butanone (**624**) afforded annulated pyrroles in excellent yields.[266] The use of the copper catalyst ensures that a Wolff rearrangement is suppressed. The same catalyzed reaction that involved indolo diazo ketone **627** afforded the annulated indole **631** in low yield. The major product produced in this case corresponded to enone **630**. A plausible mechanism for the formation of enone **630** involves addition of the electrophilic carbenoid onto the indole nitrogen to produce the azaspirocyclic zwitterion **628** which then isomerized to give zwitterion **629**. β-Elimination of intermediate **629** afforded enone **630**. The difference in reactivity of the pyrrole and indole systems was attributed to the decreased nucleophilicity at the α-carbon of the indole nucleus.





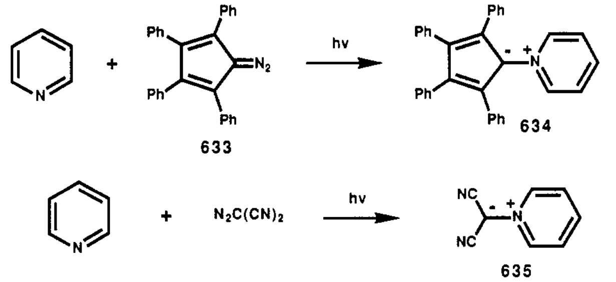
Rhodium(II) carboxylates have also been used as effective catalysts for nitrogen ylide generation. Stable metal carbenes characteristically undergo nucleophilic addition at the carbene carbon and in certain cases, stable addition products have been obtained from the reaction of amines with carbene complexes.[267] Doyle and co-workers were the first to study the reaction of tertiary allyl amines with various rhodium carboxylates.[268] The rhodium catalysts were found to be superior to copper catalysts for the generation of ammonium ylides. Thus, treatment of dimethylallylamine with ethyl diazoacetate in the presence of rhodium(II) acetate or hexadecacarbonylhexarhodium produced a nitrogen ylide which underwent a 2,3-sigmatropic rearrangement to give amine **632** in good yield. No products resulting from cyclopropanation or C–H insertion were observed in the crude reaction mixture.



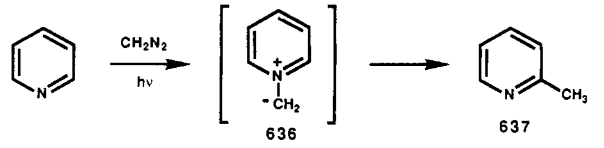
B. Nitrogen Ylides Derived from Pyridines, Imines, and Oximes

The interaction of a carbene or carbenoid with an imine nitrogen atom to give a transient azomethine ylide has attracted some attention over the past decade. Some of the standard methods for generating azomethine ylides involve the thermal or photolytic ring opening of aziridines,[269] desilylation[2] or dehydrohalogenation[270] of iminium salts, and proton abstraction from imine derivatives of α-amino acids.[271] Azomethine ylides are of interest because these dipoles undergo facile 1,3-dipolar cycloaddition with π-bonds to give pyrrolidines which, in turn, have been used to prepare a variety of alkaloids.

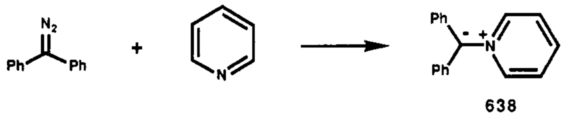
A number of examples dealing with the preparation of stable pyridinium ylides have been reported in the literature.[272-275] As early as 1960, pyridinium tetraphenylcyclopentadienylide (**634**) was synthesized by heating 2,3,4,5-tetraphenyldiazocyclopentadiene (**633**) at reflux in pyridine. Addition of water precipitated the purple ylide **634** in almost quantitative yield.[272-274] This process appears to be general for a number of substituted pyridines (i.e. 2-picoline, 3-picoline, and 2,6-lutidine). In an analogous fashion, *N*-dicyanomethylide **635** was prepared by heating diazomethanedicarbonitrile in pyridine.[275]



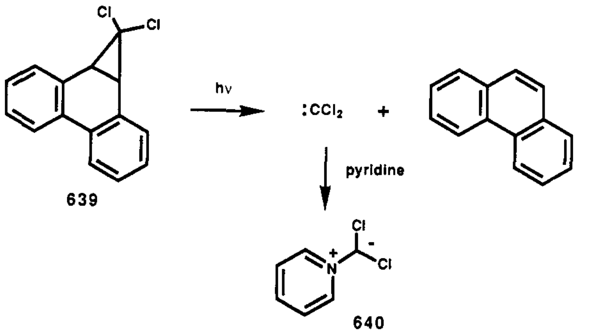
These same pyridinium ylides have been generated photochemically. Irradiation of diazomethane in pyridine gave 2-picoline (**637**) in 83% yield.[276] The high yield and specificity of attack at the 2-position of the ring seems to be in variance with electrophilic carbene insertion into a C–H bond as this reaction would prefer to occur at the 3-position. This result is consistent, however, with initial electrophilic attack of the carbene at the nitrogen atom of pyridine to form dipole **636** which then underwent intramolecular reorganization.



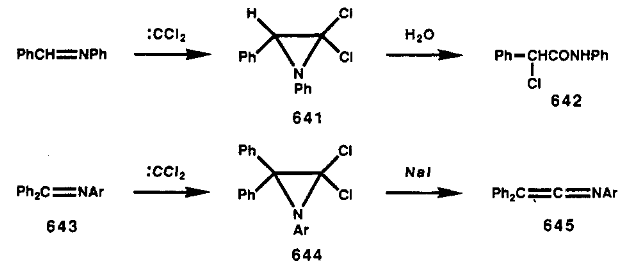
The kinetics of the reaction of triplet diphenylcarbene with pyridine has been studied.[277] Laser flash photolysis of diphenyldiazomethane in the presence of pyridine resulted in the formation of pyridinium ylide **638**. This reactive species shows an absorption band of 500 nm. Due to the low activation energy of the reaction, it was concluded that the data was inconsistent with a simple preequilibrium model. Instead, it was suggested that the intersystem crossing step occurred at a point other than at the minimum of singlet diphenylcarbene.[277]



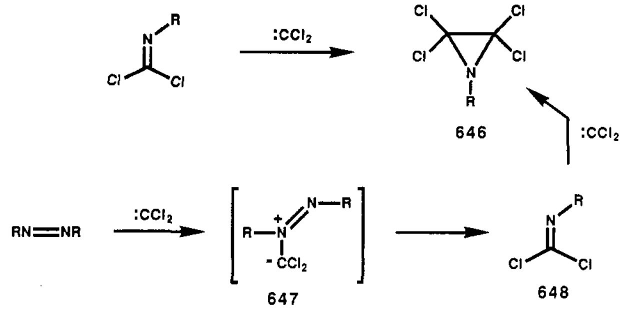
The absolute kinetics of the formation of ylide **640** from dichlorocarbene and pyridine has been measured.[278] Platz and co-workers have demonstrated that ground-state singlet carbenes react with pyridine to form pyridinium ylides which possess intense absorptions that have successfully been used to competitively measure both the inter- and intramolecular kinetics of several "invisible" alkylcarbenes.[279] Laser flash photolysis of **639** in the presence of pyridine resulted in the absorption spectrum of the pyridinium ylide of dichlorocarbene **640** which showed a maximum at 390 nm. The bimolecular rate constant was obtained by monitoring the pseudo first-order growth rate of **640** at various pyridine concentrations.



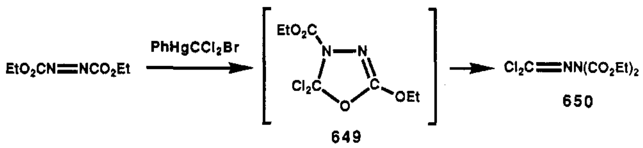
The addition of dihalocarbenes to C–N double bonds to produce dihaloaziridines was first uncovered by Fields and Sandri in 1959.[280] Dichlorocarbene was found to undergo addition to *N*-benzylideneaniline to give 1,3-diphenyl-2,2-dichloroethyleneimine (**641**) in 55% yield. This reaction is thought to proceed via an azomethine ylide intermediate which cyclized to produce the observed product. Treatment of aziridine **641** with water converted it to α-chloro-α-phenylacetanilide (**642**). A similar process was observed upon treating (diphenylmethylene)arylamine **643** with dichlorocarbene.[281] Reaction of the resulting dichloroaziridine **644** with sodium iodide gave ketenimine **645** in excellent yield.



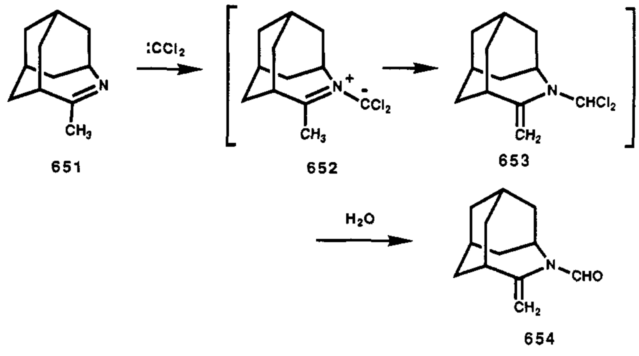
Phenyl(bromodichloromethyl)mercury has been found to transfer CCl_2 to alkyl- and arylcarbonimidoyl dichlorides, producing 1-alkyl-(or 1-aryl)-2,2,3,3-tetrachloroaziridine **646** in good yield.[282] Interestingly, treatment of azobenzene under the same reaction conditions also gave tetrachloroaziridine **646**. This result has been rationalized in terms of the initial generation of ylide **647** which then fragments to afford phenylcarbonimidoyl dichloride **648** and phenyl nitrene. The latter species reacts with dichlorocarbene or phenyl(bromodichloromethyl)mercury to give more phenylcarbonimidoyl dichloride **648**. Dichlorocarbene then added to the dichloride to generate tetrachloroaziridine **646**.



The decomposition of phenyl(bromodichloromethyl)mercury in the presence of azodicarboxylate ester gave a compound which was identified as structure **650**.[283] The formation of this material seemingly involves azomethine ylide generation followed by cyclization producing intermediate **649** which subsequently rearranges to dichloride **650**. The appearance and disappearance of intermediate **649** could be observed by monitoring the reaction by NMR and IR spectroscopy. The disappearance of the spectroscopic signals corresponding to **649** was concurrent with the appearance of signals due to product **650**.

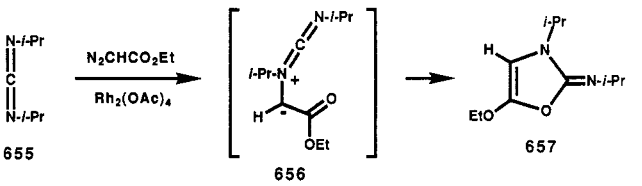


4-Azahomoadamantane derivatives are known as potential biologically active compounds and several synthetic routes to this skeleton have been reported.[284] The reaction of 5-methyl-4-azahomoadamant-4-ene (**651**) with dichlorocarbene resulted in the formation of 4-formyl-5-methylene-4-azahomoadamantane (**654**) in 66% yield.[285] The isolation of this material is consistent with a mechanism involving carbene addition onto the imine nitrogen to generate an azomethine ylide



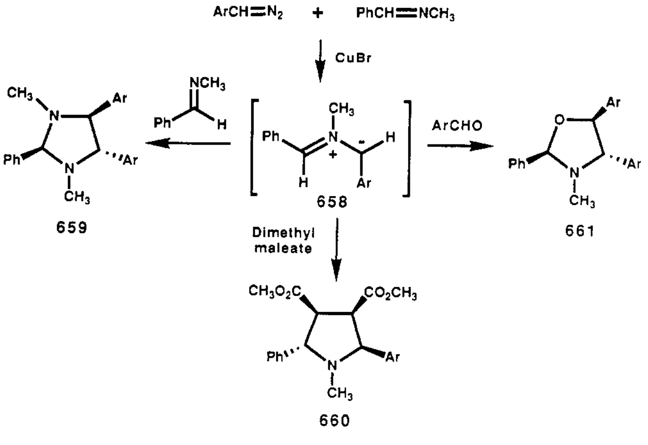
(**652**). Loss of a proton or hydrogen migration gave **653** which underwent a subsequent hydrolysis of the dichloromethyl group to produce the observed product.

Hubert and co-workers have reported that alkyl diazoacetates react with *N*,*N*′-diisopropylcarbodiimide in the presence of transition-metal salts gave 2-(isopropylimino)-3-isopropyl-5-alkoxy-4-oxazolines.[286] For example, treatment of ethyl diazoacetate with rhodium(II) acetate in the presence of *N*,*N*′-diisopropylcarbodiimide (**655**) produced 2-(isopropylimino)-3-isopropyl-5-ethoxy-4-oxazoline (**657**) in good yield. The formation of oxazoline **657** was interpreted in terms of an addition of (ethoxycarbonyl)carbene onto one of the nitrogen atoms of the carbodiimide to give the transient ylide **656** which then cyclized to produce the resulting heterocycle.

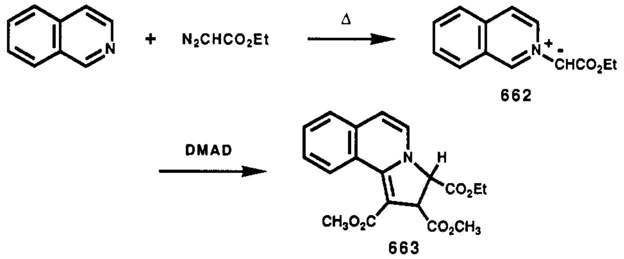


The reaction of carbenes with simple imines to form azomethine ylides which then undergo 1,3-dipolar cycloaddition with various dipolarophiles was first reported in 1972.[287] Treatment of ethyl diazoacetate with copper bronze in the presence of excess benzalimine resulted in the isolation of imidazoline **659** (Scheme 21). Formation of this product was rationalized by carbenoid addition onto the imine nitrogen to give azomethine ylide **658** which then underwent a 1,3-dipolar cycloaddition with another molecule of imine to produce the observed product. Bartnik and Mloston subsequently extended this observation by using other dipolarophiles.[288] For example, catalytic decomposition of phenyldiazomethane and *N*-benzylidenemethylamine in the presence of dimethyl maleate or benzaldehyde gave pyrrolidine **660** and oxazolidine **661**, respectively. In both cases, no product resulting from the trapping of the ylide with a molecule of imine could be observed. Catalytic decomposition of phenyldiazomethane with other Schiff bases was found to proceed via formation of a trans-1,3-dipole. Depending on the size and quantity of the substituent groups, the ylide either undergoes cyclization in a conrotatory sense to a *cis*-aziridine or [3 + 2]-cycloaddition to an available π-bond. The reactivity of double bonds toward the ylide was found to decrease in the order of C=C > C=O > C=N.

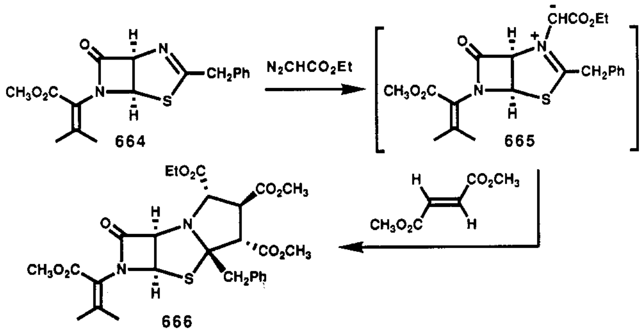
SCHEME 21



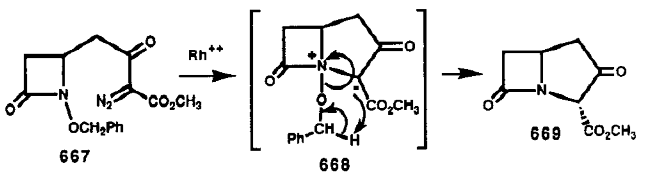
Isoquinoline–carboethoxymethylide **662** was prepared by the thermal decomposition of ethyl diazoacetate in the presence of isoquinoline.[289] The same ylide could also be obtained from *N*-carboethoxymethylene isoquinolinium bromide by the elimination of hydrogen bromide. Ylide **662** is a red crystalline solid which is stable in the absence of moisture. The dipolar character of **662** was established by its reaction with dimethyl acetylenedicarboxylate which led to the formation of cycloadduct **663**.



Since they were first isolated from penicillins, thiazoloazetidinones such as **664** have become versatile intermediates in the synthesis of various β-lactam antibiotics. Soft electrophiles prefer to attack at the sulfur atom whereas hard electrophiles react with the thiazoline nitrogen. Thomas and co-workers have investigated the reaction of thiazoloazetidinone **664** with copper carbenoids.[290] Treatment of **664** with a large excess of ethyl diazoacetate in the presence of copper(II) acetoacetonate and dimethyl fumarate gave the bis(methoxycarbonyl) adduct **666**. The formation of this material involves an initial addition of the (ethoxycarbonyl)carbenoid onto the thiazoline nitrogen to produce azomethine ylide **665**. This reactive dipole undergoes a subsequent 1,3-dipolar cycloaddition with the added dipolarophile to give the observed product. The reaction was found to be both regio- and stereoselective. No products derived from the reaction of the carbenoid at the sulfur atom or at the C–C double bond were observed. The stereochemistry at C-3 of the cycloadduct is consistent with approach of the fumarate ester from the less-hindered side of the ylide.

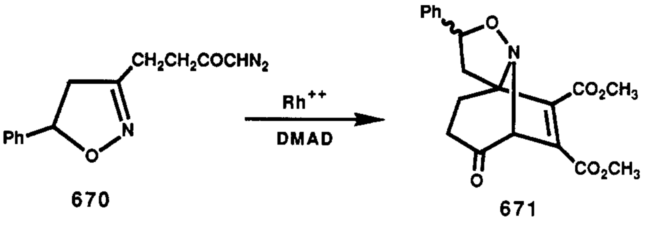


α-Diazo ester **667** in the presence of catalytic rhodium(II) acetate was found to undergo an unprecedented ring closure to provide carbapenam **669**.[291] The mechanism suggested involves interaction of the initially generated carbenoid with the *N*-alkoxylactam electron lone pair to give intermediate **668**. Abstraction of a proton from the benzylic position by the ylide intermediate, followed by carbonyl formation and N–O bond cleavage afforded the cyclized product and benz-



aldehyde. This unique rearrangement conveniently circumvents the well-documented procedure for the debenzylation and N-O bond reduction of *N*-(benzyloxy)-β-lactams.[292]

The first example of the formation and intramolecular dipolar cycloaddition of an azomethine ylide formed by carbenoid addition to a C-N double bond was reported by Padwa and co-workers.[293] Rhodium(II) octanoate catalyzed reaction of diazo ketone **670** with dimethyl acetylenedicarboxylate (DMAD) afforded the azomethine ylide derived cycloadduct **671** as a 4:1 mixture of diastereomers in 65% yield.



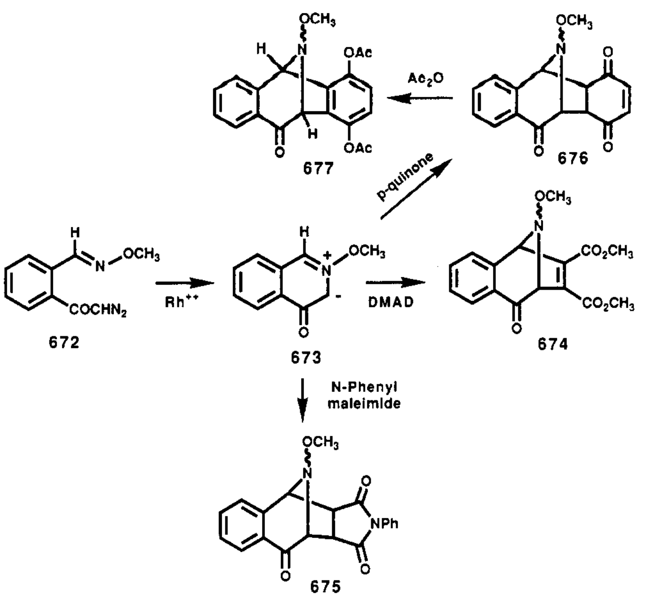
The facility of the tandem cyclization–cycloaddition process with this isoxazolidine derivative suggested that acyclic oxime ethers would also function as suitable azomethine ylide precursors.[293] In fact, treatment of 2-(diazoacetyl)benzaldehyde *O*-methyl oxime (**672**) with rhodium(II) octanoate in the presence of dimethyl acetylenedicarboxylate or *N*-phenylmaleimide produced cycloadducts **674** and **675**, respectively (Scheme 22). The cycloaddition was also carried out with *p*-quinone as the dipolarophile. The major product isolated corresponded to cycloadduct **676**. Treatment of this material with excess acetic anhydride in pyridine afforded diacetate **677** in 67% overall yield from **672**. These results demonstrate the ability of imine derivatives to undergo the rhodium(II)-induced cyclization with α-diazo ketones to form cyclic azomethine ylides.

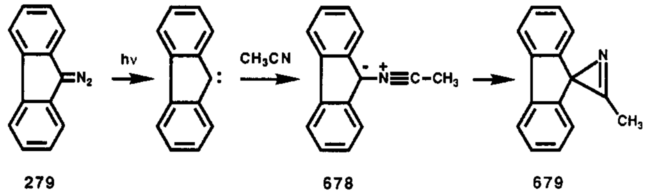
C. Nitrogen Ylides Derived from Nitriles

The reaction of a carbene or carbenoid with a nitrile to produce an intermediate nitrile ylide has emerged as a useful method for generating these dipoles. Some of the more traditional methods used to prepare nitrile ylides include the thermal elimination of hydrogen chloride from imidoyl chlorides,[294] cycloelimination of carbon dioxide from oxazolin-5-ones,[295] extrusion of alkyl esters of phosphoric acid from 2,3-dihydro-1,4,2λ^5-oxazaphospholes,[296] and the photolytic ring opening of 2*H*-azirines.[297] Nitrile ylides are versatile intermediates which readily undergo 1,3-dipolar cycloaddition to give complex heterocycles.[175] These same species are also known to undergo [1 + 2]-, [1 + 3]-, and [3 + 6]-cycloadditions.[175]

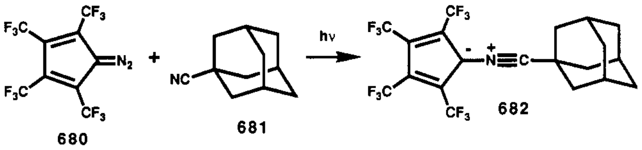
The potential of laser flash photolysis in the study of carbene reactions with heteroatoms has come to be recognized in recent years. A number of kinetic studies using this technique have been carried out with carbene precursors in nitrile solvents.[298-303] An absorption band at 470 nm was observed in the laser flash photolysis of diazofluorene (**279**) in inert solvents. This band was assigned to triplet fluorenylidene. In acetonitrile, however, a second band was also detected at 400 nm and whose buildup is concurrent with the decay at 470 nm.[298] Laser flash experiments in other nitrile solvents (i.e. benzonitrile and pivalonitrile) also produced a transient absorption band which was very similar to that observed in acetonitrile. The band at 400 nm was assigned to an intermediate nitrile ylide (**678**). This absorption could be quenched upon addition of an electron-deficient olefin providing good support for its assignment. In the absence of a dipolarophile, nitrile ylide **678** cyclized to form azirine **679**. Other diazo aromatic compounds were also used to study the interaction of carbenes with nitriles and gave similar results.[301-303]

SCHEME 22



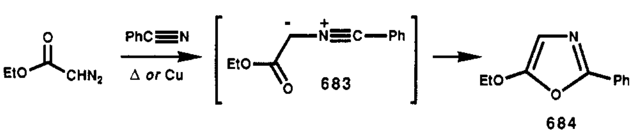


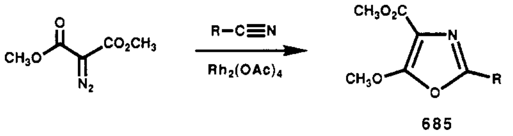
The first example of a stable nitrile ylide formed via carbene addition to a nitrile was reported by Arduengo and co-workers in 1984.[304] Irradiation of diazotetrakis(trifluoromethyl)cyclopentadiene (**680**) in the presence of 1-adamantyl nitrile (**681**) afforded the stable nitrile yield **682** as a crystalline solid. This structure was unequivocally established by using single-crystal X-ray analysis. The central ylidic system is very close to linear with only 4° bends at the nitrilium carbon and nitrogen centers. The nitrogen to cyclopentadienyl bond is fairly short at 138.9 pm while the central nitrilium CN bond is only 113.1 ppm. These bond lengths and angles more closely resemble a nitrile oxide than previously studied theoretical models. The stability of



this ylide is partially due to the steric bulk of the adamantane moiety which renders cycloaddition with a second 1-adamantyl nitrile molecule very difficult. Charge delocalization into the cyclopentadienyl ring system also helps to stabilize the dipole.

1,3-Oxazoles of various substitution patterns are well-known heterocycles for which a number of methods of synthesis have been reported.[305] Acyl carbenes or functionally equivalent species have been found to undergo cyclization with nitriles to give oxazoles in high yield. This reaction can be induced to occur under thermolytic, photolytic, or catalytic conditions.[305-307] Huisgen and co-workers were the first to study this process in some detail.[306] Thermolysis (or copper catalysis) of a mixture of ethyl diazoacetate and benzonitrile resulted in the formation of oxazole **684**. The isolation of this product is most consistent with a mechanism involving carbene addition onto the nitrile nitrogen atom to generate dipole **683** which then cyclizes to produce oxazole **684**.

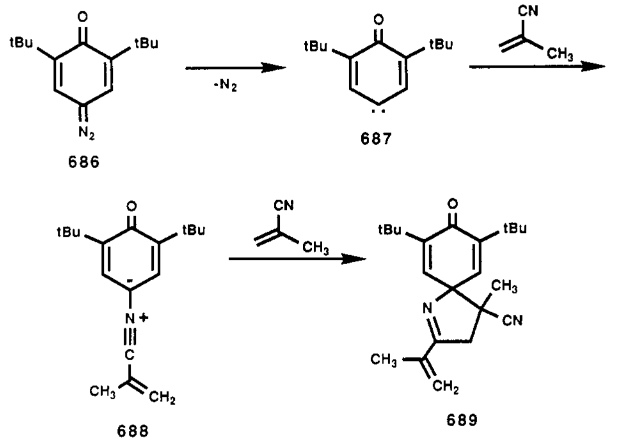




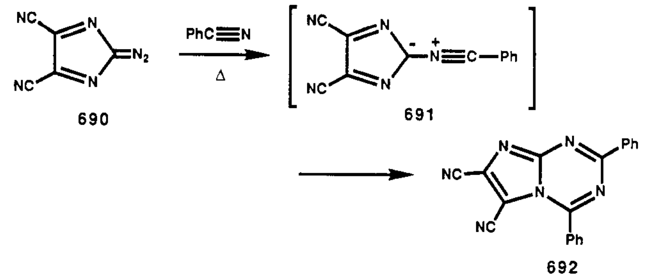
Dimethyl diazomalonate undergoes reaction with nitriles in the presence of rhodium(II) acetate to give 2-substituted-4-carbomethoxy-1,3-oxazoles (**685**). The reaction proceeds with a wide range of nitriles; however cyclopropanation is a competing process in the case of unsaturated nitriles.[305]

Kende and co-workers have reported on the formation of a nitrile ylide intermediate from carbenes and methacrylonitrile. Thermolysis of *p*-diazo oxide **686** in methylacrylonitrile as solvent gave spirocyclic product **689** in 48% yield[308] (Scheme 23). The formation of **689** was interpreted in terms of the generation of nitrile ylide **688** followed by 1,3-dipolar cycloaddition across the C–C double bond of a second molecule of methacrylonitrile. The regiochemistry of the cycloaddition is consistent with FMO theory. In a somewhat similar manner, diazodicyanoimidazole (**690**) was found to give the fused heterocycle **692** when heated in benzonitrile.[309]

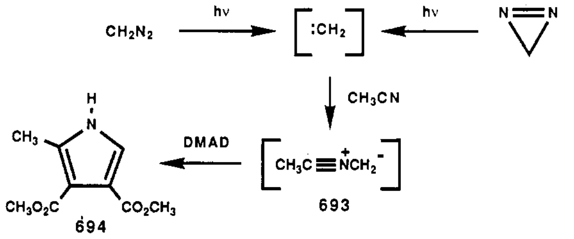
SCHEME 23



This reaction presumably involves the intermediacy of nitrile ylide **691**.

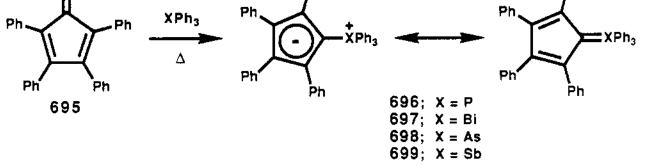


Pulsed excimer laser photolysis of diazomethane or diazirine in acetonitrile at room temperature produced a transient absorption with λ_{max} at 280 nm.[310] This transient absorption band is not observed in the absence of acetonitrile or the methylene precursor. On the basis of the products formed and by comparison with the absorption spectra of other nitrile ylides, the intense absorption at 280 nm was assigned as methylnitrile ylide (**693**). When carried out in the presence of a variety of dipolarophiles, 1,3-dipolar cycloaddition occurred to produce typical cycloadducts (i.e. **694**). The dipole is formed by the addition of singlet methylene onto the nitrogen atom of acetonitrile. The relative rates of formation of the 1,3-dipolar cycloadduct and the quenching of the transient absorption were found to be in excellent agreement. The decay of the absorption spectrum of the nitrile ylide derived from pulsed laser photolysis of diazirine in acetonitrile solution followed clean first-order kinetics at high olefin concentration.

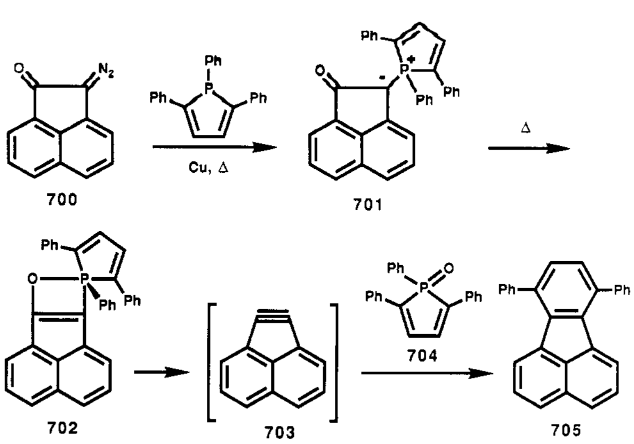


VII. Miscellaneous Ylides

The formation of ylides via the interaction of a carbene or carbenoid with sulfur, oxygen, and nitrogen atoms has been extensively studied. In contrast to this situation, very few investigations have been reported dealing with the generation of ylides using other group V and VI elements. Cyclopentadienylides of group V elements have proven to be readily obtainable by the carbenic decomposition of diazotetraphenylcyclopentadiene in the presence of these elements.[311-315] For example, treatment of diazotetraphenylcyclopentadiene (**695**) with triphenylphosphine at 150 °C produced a yellow solid which was identified as phosphonium ylide **696**.[311,312] Likewise, treatment of **695** with triphenylbismuth, triphenylarsine, or triphenylantimony resulted in the formation of ylides **697**–**699**, respectively.[313-315]



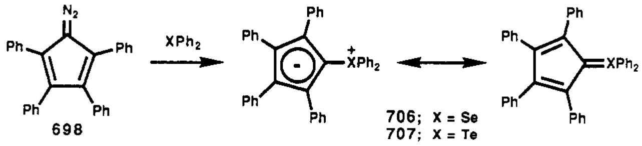
SCHEME 24



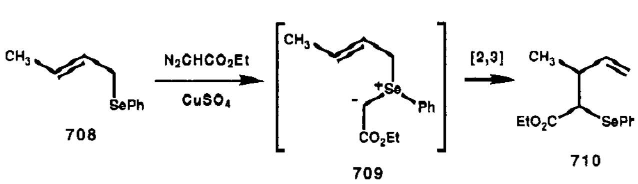
It is interesting to note that whereas the corresponding phosphonium, arsonium, and stibonium ylides are yellow, the bismuthonium analogue is deep blue in color. Apparently the vacant 6d orbitals of bismuth, unlike the 4d or 5d orbitals of arsenic or antimony, cannot effectively overlap with the 2p orbitals of the anionic group. The bismuth ylide, therefore, possesses a shorter wave length absorption maximum.

1,2,5-Triphenylphosphole reacts with 1-diazoacenaphthen-2-one (**700**) at 150 °C in the presence of copper powder to give the corresponding phosphole ylide **701**[316] (Scheme 24). Thermal decomposition of this ylide at 175 °C gave 7,10-diphenylfluoranthene (**705**) in 64% overall yield. Although the mechanism of this rearrangement has not been completely elucidated, an attractive explanation for the formation of **705** involves cyclization of ylide **701** to generate intermediate **702**. Subsequent fragmentation of this reactive species gives 1,2-acenaphthyne (**703**) and 1,2,5-triphenylphosphole oxide (**704**), which together react via cycloaddition to produce the observed product. Although attempts to trap aryne **703** with tetraphenylcyclopentadienone were unsuccessful, alternative mechanisms involving intramolecular rearrangement or bimolecular reaction of the ylide **701** seem unlikely because they would require pathways which possess very formidable steric barriers.

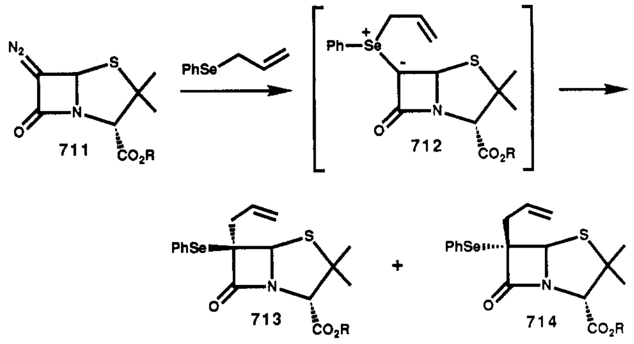
Stable ylides derived from group VI elements and carbenes have been reported by Lloyd and co-workers.[317,318] For example, the thermal decomposition of diazotetraphenylcyclopentadiene (**698**) in the presence of diphenyl selenide or diphenyl telluride resulted in the formation of ylide **706** and **707**, respectively. Ylide **706** is stable in air in the absence of light. Like its diphenylsulfonium and diphenylselenonium analogues, the telluronium ylide is an extremely weak base.



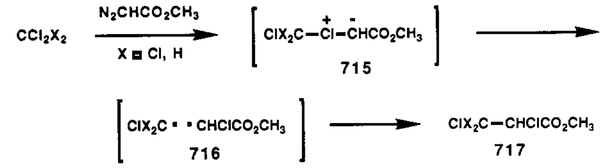
Reactions between diazo compounds and organo selenides have not been extensively studied. However, recent studies show that allylic selenium ylides undergo a 2,3-sigmatropic rearrangement analogous to that observed with allylic sulfonium ylides.[29,30,319] For example, treatment of 2-butene phenyl selenide (**708**) with ethyl diazoacetate in the presence of copper(II) sulfate gave the homoallylic phenyl selenide **710**.[319] Formation of this material is consistent with electrophilic addition of the transient copper carbenoid species onto the selenium atom to generate the intermediate ylide **709** which then undergoes a 2,3-sigmatropic rearrangement to give the observed homoallylic phenyl selenide **710**.

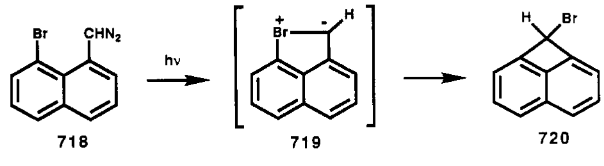


Thomas and co-workers have utilized the above process in a synthesis of substituted penicillinates.[29,30] The transition-metal-catalyzed reaction of 6-diazopenicillinates with allyl selenides was found to be a convenient process for the preparation of 6-substituted penicillin analogues. Addition of copper(II) acetylacetonate to a mixture of phenyl allyl selenide and 6-diazopenicillinate (**711**) in dichloromethane resulted in the rapid evolution of nitrogen and formation of the 6,6-disubstituted penicillinates **713** and **714**. This result can best be interpreted as proceeding by initial formation of selenium ylide **712** which then undergoes a subsequent 2,3-sigmatropic rearrangement.

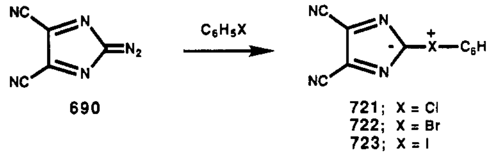


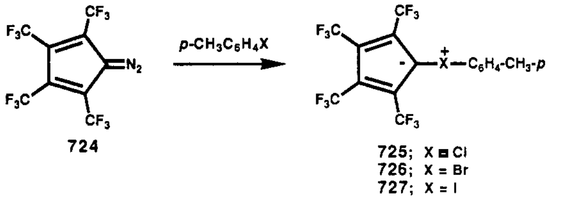
Halonium ylides have been proposed as intermediates in the photochemical reaction of α-diazo ketones with alkyl and aryl halides.[48,59,268,320,328] The photolysis of methyl diazoacetate in carbon tetrachloride, chloroform, or methylene chloride has been investigated by C^{13}-CIDNP studies and was found to produce the insertion product **717**.[320] Prior to this investigation, the reaction was thought to proceed via a radical chain mechanism.[329] However, the CIDNP pattern obtained suggested that the insertion product **717** is formed by recombination from the geminate radical pair **716** which, in turn, is generated by cleavage of the corresponding chloronium ylide **715**. A similar reaction path was proposed to account for the product (i.e. **720**) formed from the photolysis of (8-bromo-1-naphthyl)diazomethane (**718**).[321]



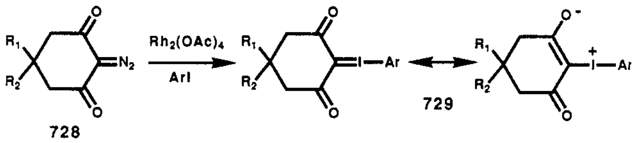


The involvement of halonium ylide intermediates in the above reactions gained strong support by the actual isolation of a halonium ylide by Sheppard and Webster.[330] Thermal decomposition of diazodicyanoimidazole (**690**) in the presence of chlorobenzene, bromobenzene, or iodobenzene resulted in the generation of ylides **721–723**, respectively. Formation of stable halonium ylides can also be achieved via a photochemical pathway. Irradiation of diazotetrakis(trifluoromethyl)cyclopentadiene (**724**) in the presence of *p*-chlorotoluene results in the isolation of the stable chloronium ylide **725**.[47] The analogous bromonium ylide **726** was also prepared by this route. The iodonium ylide **727** is photolabile under the reaction conditions and cannot be isolated. The aryl bromonium and chloronium ylides, however, are quite stable and can be stored indefinitely at room temperature.



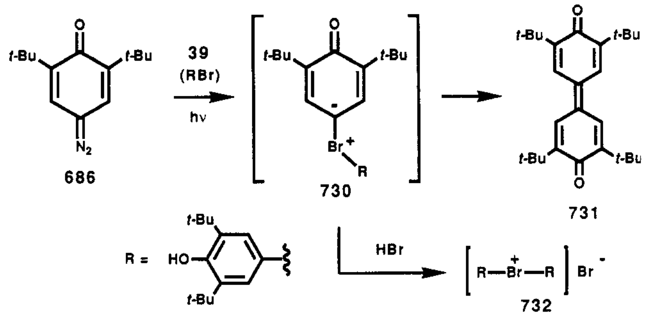


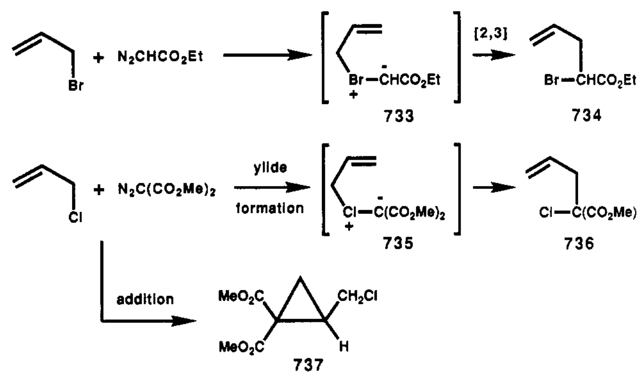
Moriarty and co-workers have demonstrated the aryl iodide capture of a β-diketo carbene generated from the rhodium(II)-catalyzed reaction of diazo ketone **728**. The initially produced rhodium carbenoid species attacks the aryl iodide to give the stable iodonium ylide **729** as a crystalline solid.[331] Rhodium(II) acetate was found to be the catalyst of choice for carbene capture by aryl iodides. Copper catalysts (i.e. copper bronze, copper(II) chloride, copper(II) acetylacetonate) required higher temperatures and longer reaction times, causing a subsequent rearrangement of the initially formed iodonium ylide. This reaction is of some synthetic interest since it extends the scope of the methods available for iodonium ylide formation.



Bromonium ylide **730** was proposed as an intermediate in the photochemical reaction of 1-diazo-3,5-di-*tert*-butylbenzeneoxide (**686**) with bromobenzene to give diphenoquinone **731**.[322,323] Photolysis at low temperature resulted in the isolation of the bromonium bromide **732**. This material is considered to arise via hydrobromination of the initially formed bromonium ylide **730**. Regeneration of the ylide **730** could be accomplished by treating **732** with an amine base. Clearly, the bromide salt **732** is a convenient source of bromonium ylides and offers an unambiguous approach to the study of these intermediates.

The reaction of allyl halides with carbenes has been studied by several groups of workers using a variety of experimental conditions.[48,59,268,324-328] The first reported example was made in 1951 by D'yakonov and Vinogradova.[324,325] These workers found that the thermolysis of a mixture of allyl bromide and ethyl diazoacetate gave rise to ethyl 2-bromo-4-pentenoate (**734**) as the major product. The formation of **734** was interpreted in terms of a mechanism involving carbene addition onto the bromine atom to generate bromonium ylide **733** which then undergoes a 2,3-sigmatropic rearrangement.

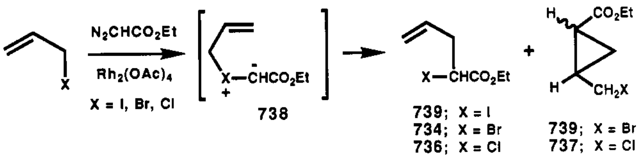




The photolytic decomposition of dimethyl diazomalonate in the presence of allyl chloride resulted in the formation of both the insertion product **736** and the addition product **737**.[48,59,326,327] When the reaction was carried out with triplet sensitized conditions, only the addition product **737** was produced. This result suggests that only the singlet carbene is capable of reacting with the chlorine atom to give the chloronium ylide **735**. Singlet carbenes are known to be converted to triplet carbenes by collision with inert solvents,[332] particularly those possessing heavy atoms.[322] Ando and co-workers found that the product ratios (i.e. **736**:**737**) were markedly affected by the type of solvent used and the concentration at which the reaction was carried out. Concentrated solutions favored ylide formation which ultimately produced the insertion product **736**, presumably because more singlet carbene is present to react with the allyl chloride. The ratio of insertion (**736**) and addition (**737**) was found to be the highest in methylene chloride and the lowest in methylene iodide. This distribution is in agreement with the findings that the singlet–triplet interconversion is more effective with heavy halogen solvents. In the direct photolysis, the insertion reaction with allyl chloride was about 1.25 times faster than addition, whereas with allyl bromide it was about 8 times faster than addition. Since the reactivities of the double bonds toward the attacking carbene species are not considered to be very different in these two allylic substrates, the change in ratio of insertion to addition may be due to the difference in nucleophilicity between a chlorine and bromine atom.

In a related study, Kirmse and co-workers investigated the copper-catalyzed decomposition of diazomethane in the presence of allyl chloride.[328] Addition of the carbenoid to the allylic double bond occurred in competition with ylide formation. The reaction was performed with use of a variety of copper catalysts, solvents, and reaction temperatures. The optimal condition for chloronium ylide formation involved using pentane at 40–45 °C with copper powder as the catalyst. Under these conditions a 2:1 mixture of the insertion product **736** to the addition product **737** was obtained.

Doyle and co-workers also found that the distribution of insertion to addition products derived from a series of allylic halides was intimately related to the nucleophilicity of the halogen present. Nucleophilic addition of the halogen lone pair to catalytically generated metal carbenes forms the halonium ylide **738** in competition with cyclopropanation. The rhodium(II) acetate catalyzed reaction of ethyl diazoacetate with allyl iodide gave mostly the insertion product **739** whereas reaction with allyl bromide afforded a 3:1 mixture of both insertion and addition (i.e. **734** and **739**).[268] In contrast, the rhodium(II) acetate catalyzed reaction of ethyl diazoacetate with allyl chloride afforded mostly cyclopropane **737** with only a small amount of the insertion product **736** being formed. Copper catalysis was found to result in significantly higher yields of ylide derived products, relative to cyclopropane products, than did rhodium catalysis in reactions with allyl bromides and chlorides. It would appear that copper carbenoids are more electrophilic than rhodium carbenoids.



738

739; X = I
734; X = Br
736; X = Cl

739; X = Br
737; X = Cl

VIII. Conclusion

It is apparent from the many contributions in the area that ylide generation from the reaction of carbenes and carbenoids with heteroatoms continues to be of great interest both mechanistically and synthetically. Effective ylide formation in transition-metal-catalyzed reactions of diazo compounds depends on the catalyst, the diazo species, the nature of the heteroatom, and competition with other processes. For many of these transformations, rhodium(II) carboxylates offer considerable advantages in reaction conditions and yields over alternative catalysts. Certainly many important applications of this method remain undiscovered. In particular, the extension of these methods to more highly substituted ylide precursors remains to be studied. At the moment, relatively little use has been made of this procedure for the synthesis of complex natural products. In view of the mild conditions, the carbenoid route seems most promising for intramolecular ylide trapping and for reactions involving complex structures. Given the recent explosion of research in this area, one can only assume that additional work will be forthcoming.

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