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Application of Intramolecular Carbenoid Reactions in Organic Synthesis

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I. Introduction

The prominent role that metal complexed carbenes play in the elaboration of a variety of organic molecules has become increasingly apparent in recent years.[1] In the realm of synthesis, in which a premium is put on the rapid construction of polyfunctionalised, highly bridged carbon and heteroatom frameworks, the intramolecular reaction of transition metal complexes has now emerged as a prominent synthetic method.[2] One of the most attractive features of this process is the ability to control the stereochemical outcome of the reaction at several centers. The combination of intramolecular addition/cyclization with other pericyclic reactions offers a number of interesting synthetic possibilities. The additional advantages gained from entropy, reactivity, and diastereoselectivity also account for some of the explosive growth in this area. Several excellent reviews of this topic that cover the early

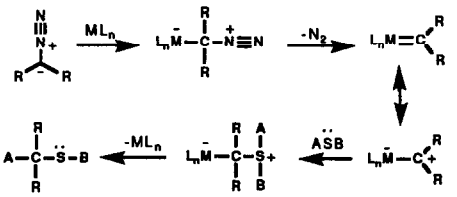
literature are available.[1-10] In the present article, an exhaustive discussion of the primary literature dealing with intramolecular carbenoid chemistry has not been provided. Rather, we have attempted to present an overview of the synthetically more useful intramolecular reactions that carbenoids undergo. Wherever possible, references to the most relevant review articles are provided, and at appropriate points throughout the text, recent examples are used to illustrate important principles. It is hoped that general and specific points in need of study will be revealed, stimulating further work in this fertile field.

Since its conception, the term *carbene* has been used rather loosely to describe any divalent carbon species.[11] A closer inspection of the chemistry of *carbenes* indicates the existence of three distinct classes of divalent carbon: *free carbenes, stable metal carbenes* and *reactive transition metal carbene complexes.* Free carbenes, or simply carbenes, are considered to be the parent class of divalent carbon. These reactive transients were the first to be investigated in some detail and most accurately adhere to the definition of divalent carbon.[12-18] Transition metal carbenoids do not literally exist as divalent carbon intermediates. Instead, these species acquire stabilization by interaction with a transition metal. Stable metal carbenes, like the Fischer carbenes, and reactive transition metal complexes, like those generated in catalytic reactions, cover a spectrum of stabilities and differentiation between them is not easily made. Interaction of the divalent carbon with the transition metal enables the *metal-carbene complex* to be more selective in its behavior relative to the free carbene.

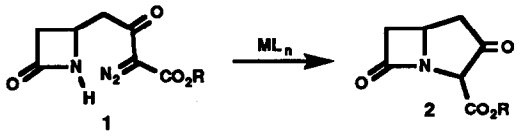
In spite of our longstanding knowledge of their chemistry, free carbenes have not been extensively used in organic synthesis. This is probably a consequence of the high reactivity and low selectivity exhibited by carbenes. The most popular method for generating carbenes involves the decomposition of diazo compounds[19,20]. In particular, the role of α-diazo carbonyl compounds in organic synthesis is now well established. The Arndt-Eistert sequence employs the Wolff rearrangement of an α-diazoketone to a ketene in the one-carbon homologation of carboxylic acids.[19,20] Ring contraction of cyclic α-diazoketones represents a general method for the preparation of highly strained small ring compounds.[21] α-Diazo carbonyl compounds are also precursors to metallo-carbenoid intermediates when exposed to many metal complexes or salts[1]. Intramolecular cyclization of α-carbonyl carbenes and carbenoids derived from α-diazoketones has found widespread application for the preparation of a variety of theoretically and biologically interesting compounds.[3]

During the early investigations of diazo chemistry, it was discovered that the problems of selectivity and reactivity could be significantly reduced by employing transition metals for the decomposition[22,23]. Although this catalytic decomposition had been known since the early part of the century,[24] the mechanism involved (see Scheme I) was not proposed until 1952.[25] It is now thought that nitrogen extrusion from the diazo compound is the consequence of nucleophilic attack by the diazo group onto the electrophilic metal complex. The metal stabilized carbene then reacts with some electron-rich substrate and regenerates the catalytic species. The ability of a transition metal complex to function as a catalyst is dependent upon unsaturation in the coordination sphere of the metal.[1]

Scheme I



The term carbenoid[26] has been used to describe the metal-complexed intermediates formed from the decomposition of diazo compounds in the presence of a transition metal. Coordination of the carbene with the metal tempers the reactivity of the divalent carbon species and imparts greater selectivity to the reaction. Carbenoids are usually generated from late transition metal catalysts and differ considerably in their stability and reactivity from the transition metal carbene complexes obtained from early transition metals. One of the most significant intramolecular carbenoid reactions of recent years is outlined below and represents the key step in the Merck synthesis of carbapenams[27]. Since the transition metal catalyzed decomposition of α-diazoketones involves a metal carbenoid intermediate rather than a free carbene, the above type of cyclization is probably better regarded as a nucleophilic attack by the lactam NH on the metal carbenoid, rather than an insertion into the NH bond.



1 2

A survey of the literature dealing with the topic of catalytic diazo decomposition can be both enlightening and frustrating. There are a wide variety of transformations that occur upon treatment of diazo compounds with transition metal catalysts. The availability of different catalysts allows for a significant latitude in chosing the experimental conditions for a specific transformation. The effect of a particular catalyst can be dependent on the system involved, and selection of the best catalyst can be problematic.[1,3]

II. Catalysts

Early work in this area made use of the insoluble copper catalysts; copper powder, copper bronze, Cu_2O, CuO, $CuSO_4$, CuCl, and CuBr.[3] Although these catalysts are still employed today, their use has decreased significantly with the advent of homogeneous copper catalysts[28,29] and catalysts based on other metals.[30-48] The discovery by Teyssie and coworkers[31] that rhodium (II) carboxylates facilitate nitrogen loss from diazo compounds rekindled significant interest in the field of diazo/carbenoid chemistry. Other rhodium complexes, as well as palladium and cobalt complexes have also been utilized, but none to the same degree as rhodium (II) carboxylates.

Much of what is known about individual catalysts has resulted from studies dealing with the addition of carbenoids to olefins. In an effort to classify the great wealth of information pertaining to catalysts and their ability to effect cyclopropanations, many of the species involved have been categorized on the basis of the number of available coordination sites.[1]

A. Multiple Coordination Site Catalysts

The ability to coordinate with an olefin is what distinguishes the multi-coordination site catalysts from the others. The catalyst that has been most extensively utilized is copper (I) triflate because of its very reactive nature.[29] The other copper catalysts do not fall into this multicoordination site category. It is the weakly coordinating nature of the triflate ligand that allows for further coordination with an olefin.[49] Since copper (I) triflate is difficult to handle,[50] copper (II) triflate[51] is generally used and is reduced to copper (I) by the diazo compound.[29] The reduction of copper (II) by diazo compounds is known to occur readily with copper (II) chloride.[52] The rate of diazo compound decomposition is inversely proportional to the concentration of the olefin.[29] Dissociation of the alkene from the catalyst is necessary for activation of the catalyst towards the diazo compound.[1] The ability of palladium (II) complexes to coordinate to olefins is well known.[53] Palladium (II) acetate[54,55] is an effective catalyst[42] for the generation of carbenoids and exhibits selectivity comparable to copper (I) triflate.[56]

B. Single Coordination Site Catalysts

Rhodium (II) carboxylates have been the most extensively used catalysts for cyclopropanation reactions in recent years. These species can be classified as catalysts that have only one available coordination site. Since they exist as dimers, two vacant coordination sites are available per unit of catalyst; one axial site per metal atom.[57-59] Although olefin complexes exist in both the gas and solid phase for rhodium (II) acetate,[60] these complexes do not exist in solution.[56-59] The particular carboxylate ligand attached to the rhodium center is known to influence the ability of the metal to accept electrons and therefore effect its reactivity and selectivity.[38-40] Olefin complexes have been observed for rhodium (II) trifluoroacetate in solution,[61] but little mention of its effect on reactivity and chemical selectivity has been reported in the literature.[1]

C. Reactivity

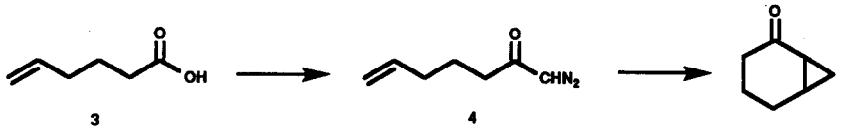
Information in the following Section outlines the reactivity differences for a number of catalysts traditionally used in cyclopropanation reactions. Although the specific data pertains to bimolecular reactions, the general trends encountered nicely extrapolate to intramolecular cyclopropanations as well. Although other metal complexes have been used, $Rh_2(OAc)_4$, $Pd(OAc)_2$, and $Cu(OTf)_2$ are the most popular and extensively utilized catalysts at the current time.[56] Rhodium (II) acetate is certainly the most effective and versatile of the three catalysts. It also reacts with molecules that can function as donor ligands, such as nitriles and amines, which further modify its catalytic activity.[38-40] Other rhodium (II) carboxylate catalysts have been developed to achieve better solubility and more efficient cyclopropanation than that observed with rhodium (II) acetate.[62] The more soluble rhodium (II) butanoate and rhodium (II) pivalate catalysts result in higher yields of cyclopropanes from monoolefins than does rhodium (II) acetate.[32,56] Rhodium (II) trifluoroacetate ($Rh_2(OOCCF_3)_4$) leads to lower yields of cyclopropanes, presumably as a consequence of its ability to form complexes with olefins.[42]

Palladium (II) acetate shows a tendency to react with terminal or less hindered olefins and works well with both strained and conjugated olefins. Dienes present a problem in that the cyclopropanation reaction is extremely slow, if it occurs at all. These observations are consistent with the hypothesis that an initial olefin-metal complex is first formed in the cyclopropanation reaction.[3] Copper (II) triflate generally affords lower yields of cyclopropanes than does rhodium (II) acetate, but works better than palladium (II) acetate.[3] It has been suggested that Cu (I) is the actual catalytic species and is generated *in situ via* reduction of Cu (II) by the diazo compound.[29,52]

III. Intramolecular Additions to C-C π-Bonds

A. Reactions wih Alkenes

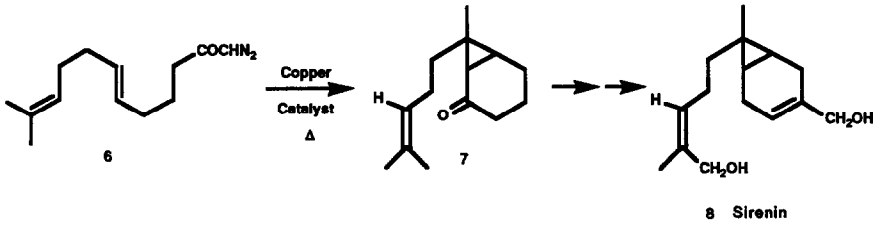
The first example of an intramolecular cyclopropanation reaction utilizing an α-diazoketone in the presence of a transition metal catalyst was reported by Stork and Ficini in 1961.[63] 5-Hexenoic acid was converted to α-diazoketone **4** and subsequent treatment of **4** with copper bronze afforded the bicyclic cyclopropane **5**.



3 **4** **5**

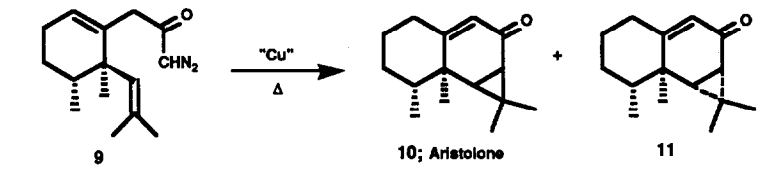
A general review of intramolecular diazo carbonyl addition reactions appeared in 1979,[2] and since then, many further publications on transition metal catalyzed reactions have extended the scope of this methodology.[64] The synthetic work in this area can be divided into two broad categories: (a) *targets containing cyclopropyl rings*, and (b) *initial cyclopropanation followed by a subsequent manipulation of the three-membered ring*. One of the first

molecules to be prepared using an intramolecular carbenoid cyclopropanation was the sperm attractant *sirenin* (8), with three different research groups reporting syntheses between 1969 and 1970.[65] The major effort focused on the transformation of α-diazoketone **6** to bicyclic cyclopropane **7**. The catalyst used was either copper bronze, cupric sulfate, or a combination of both in refluxing cyclohexane. Bicyclic cyclopropane **7** was subsequently transformed into *sirenin* (**8**).[66]

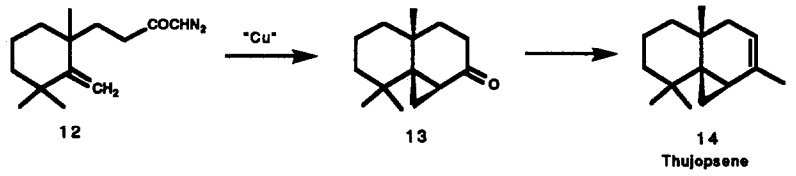


6 7 8 Sirenin

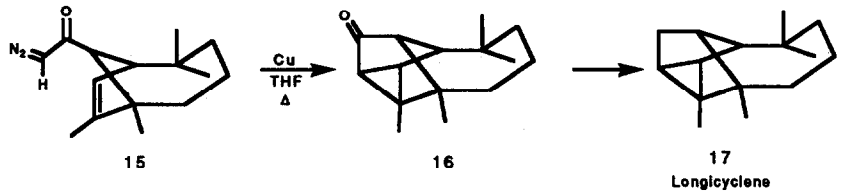
Piers and coworkers reported the synthesis of the sesquiterpene (-)-*aristolone* (**10**) from α-diazoketone **9** in 42% yield using catalytic cupric sulfate in refluxing cyclohexane.[67] The 6,7-*epi*-*aristolone* **11** was also formed in 20% yield. A related cyclopropanation reaction was used for the formation of *thujopsene* (**14**).[68] In a similar vein, *longicyclene* (**17**) was prepared from cyclopropyl ketone **16**, which in turn was synthesized by an intramolecular cyclopropanation reaction of α-diazoketone **15**.[69]



9 10; Aristolone 11

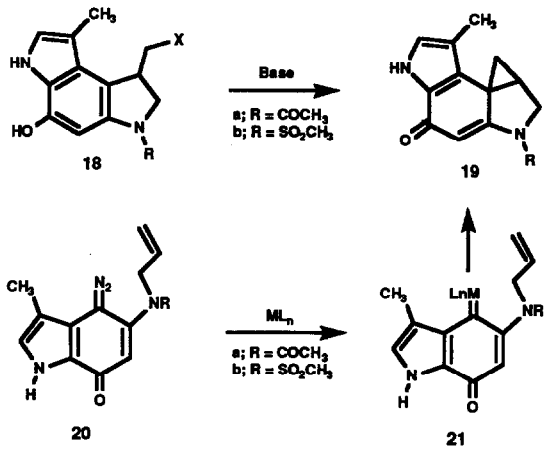


12 13 14 Thujopsene

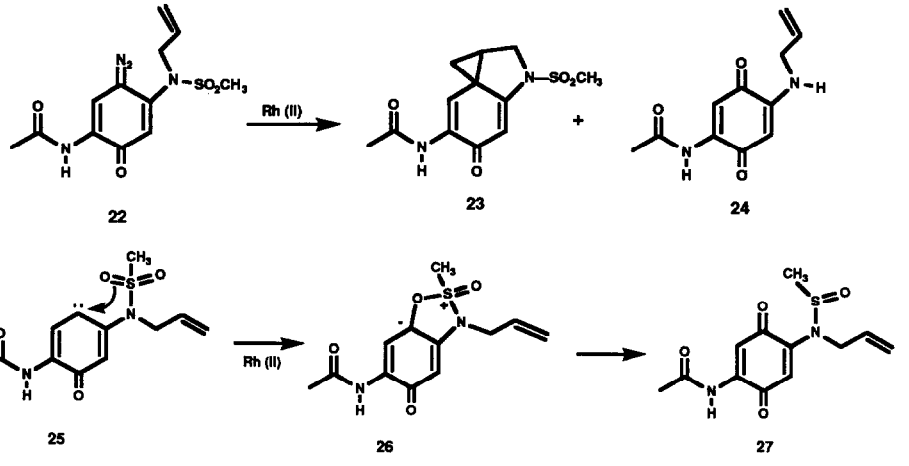


15 16 17 Longicyclene

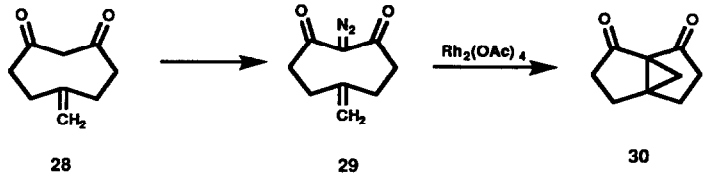
More recently, Sundberg and coworkers were able to synthesize the left-hand portion (i.e. **19**) of the antitumor antibiotic CC-1065 via an intramolecular carbenoid addition to a neighboring olefinic bond.[70] This approach differs from the previous syntheses of this portion of the molecule in that it does not involve an intramolecular phenolate alkylation (i.e. **18**→**19**).[71]



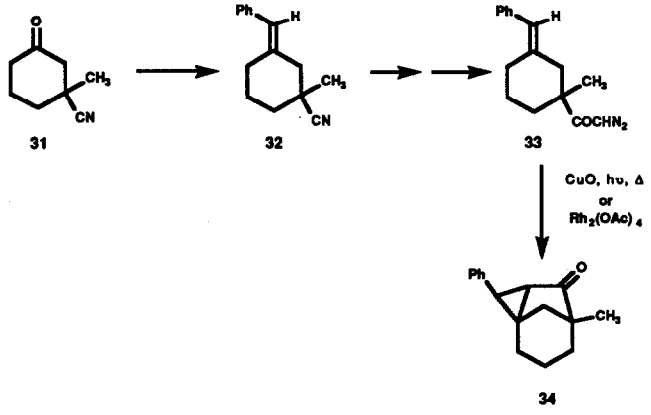
Catalytic decomposition of diazoketone **22** with rhodium (II) pivalate at 40°C for 2 h proved to be the most effective conditions for cyclopropanation. The desulfonylated quinone **24** was also formed in varying yield depending upon the particular catalyst and conditions used. Its origin was traced to an intramolecular oxygen transfer to the carbenoid carbon atom producing **27** which was hydrolyzed to **24** under the reaction conditions.



The structurally interesting [3.3.1]propellane-2,8-dione system **30** was synthesized by a transannular addition of a carbenoid to an exocyclic double bond.[72] Thus, the rhodium (II) acetate catalyzed decomposition of 2-diazo-6-methylene-1,3-cyclooctanedione (**29**) gave **30** in quantitative yield. 6-Methylenecyclooctane-1,3-dione (**28**) was available from an acyloin condensation followed by a ring expansion reaction.[73]

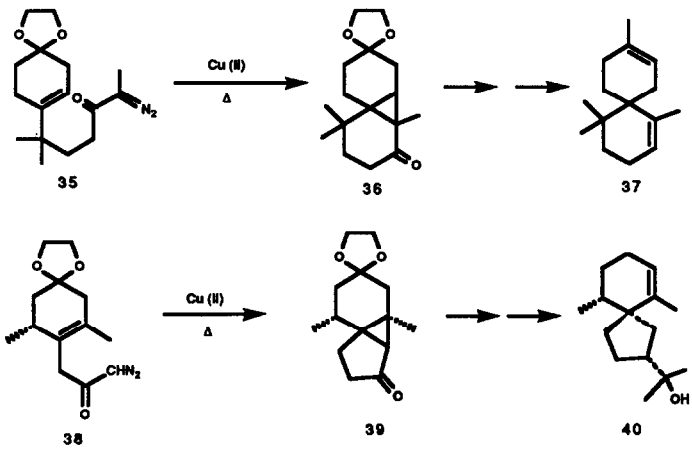


Another interesting strained ring system which has been prepared by intramolecular cyclopropanation is cyclopropanobicyclo[3.2.1]octanone **34**.[74] This molecule was initially reported in 1976[75] but its structure was subsequently questioned at a later point in time.[76] Wenkert and co-workers repeated the original synthesis by carrying out a Wittig reaction on keto-nitrile **31** forming the olefinic nitrile **32**. Alkaline hydrolysis followed by reaction of the resulting acid chloride with diazomethane gave the requisite α-diazo ketone **33**. Treatment of **33** under the original conditions (light, heat, and cupric oxide) or by using rhodium (II) acetate as a catalyst gave tricyclic cyclopropane **34** by an intramolecular carbenoid addition to the olefinic π-bond.



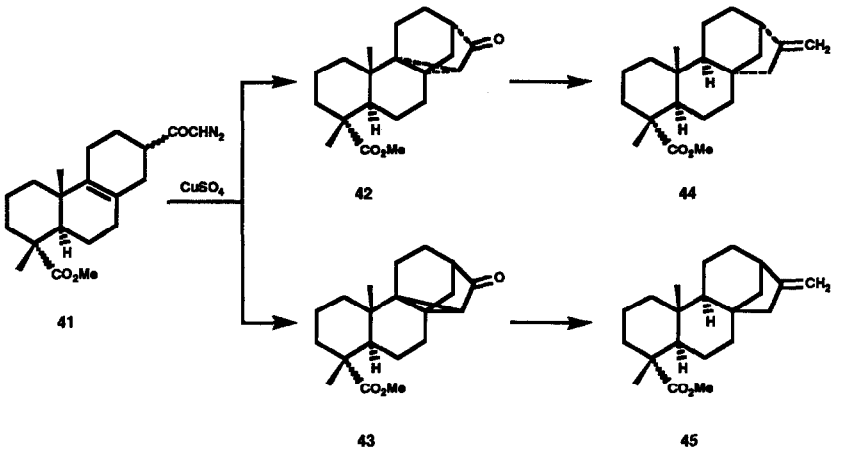
31 32 33 34

Over the past two decades, the intramolecular cyclopropanation reaction followed by subsequent manipulation of the cyclopropyl ring has become a general strategy for the synthesis of complex molecules. Several methods which have been used to cleave the strained polycyclic intermediate include hydrogenolysis,[77] protonolysis,[78] lithium/ammonia reduction,[79] and Lewis acid induced cleavage.[80] A recent review by Hudlicky and coworkers nicely documents the various techniques that have been used for further cyclopropane manipulation.[81]

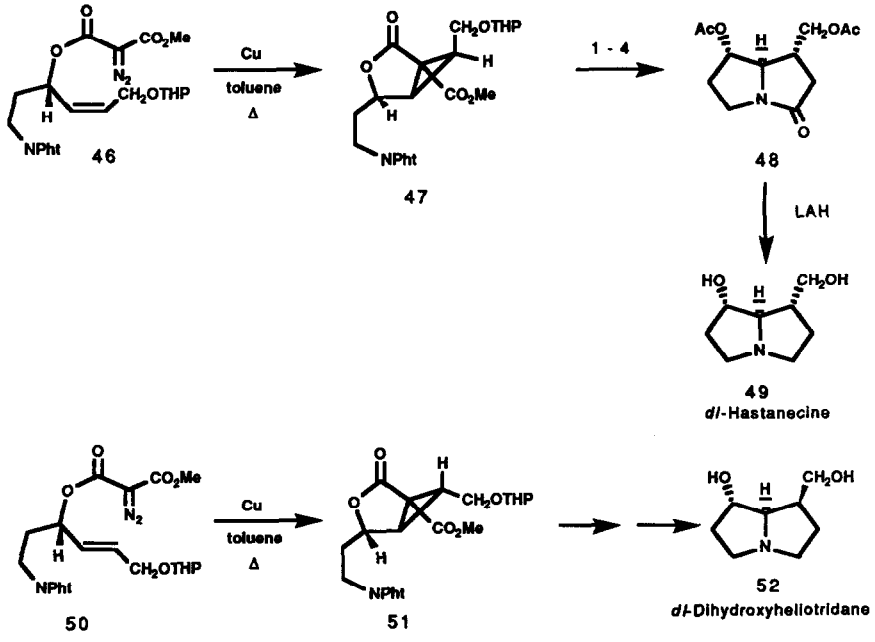


35 36 37 38 39 40

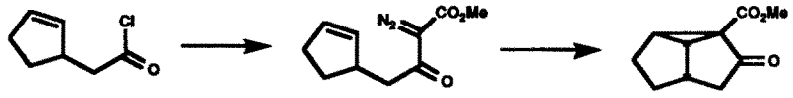
Some of the early syntheses of natural products which utilize this strategy include the conversion of α-diazoketones **35** and **38** to the spiro sesquiterpenoids α-*chamigrene* (**37**)[82] and *epihinesol* (**40**).[78,83] The tetracyclic diterpenes *kaurene* (**44**) and *phyllocladene* (**45**) were also prepared using this approach.[84]



Danishefsky and co-workers[85] were able to stereospecifically synthesize *dl-hastanecine* (**49**) and *dl-dihydroxyheliotridane* (**52**) using an intramolecular cyclopropanation reaction followed by a subsequent ring cleavage. Thus, treatment of α-diazomalonate **46** with copper bronze at 110°C afforded cyclopropane **47** as a single diastereomer. This compound was converted to diacetoxylactam **48** by successive treatment with (1) hydrazine, (2) aqueous HCl, (3) sodium methoxide and (4) pyridine-acetic anhydride. Subsequent reaction of **48** with lithium aluminum hydride afforded *dl-hastanecine* (**49**) in 81% yield. The exclusive formation of this stereoisomer was rationalized on the basis that the transition state would arrange itself such that the bulky β-phthalimidoethyl group would emerge on the convex face of the cup-shaped bicyclo[3.1.0]oxahexanone system. *dl-Dihydroxyheliotridane* (**52**) was prepared in an analogous fashion.

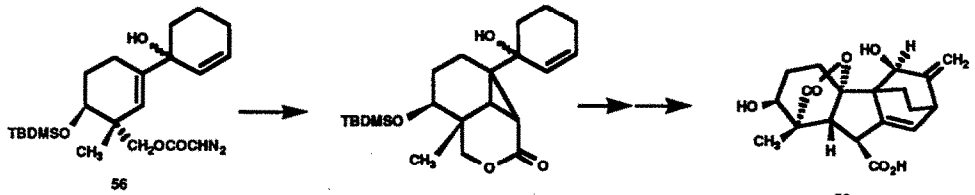


Vandewalle and co-workers developed an interesting reaction sequence which utilizes a *cis*-bicyclo[3.1.0]octane as a template in order to set the stereochemistry of a number of 5,5-cis-fused ring systems.[86] Thus, heating cyclopentenyl α-diazomalonate **54** in toluene with $Cu(acac)_2$ resulted in the formation of tricyclic ketoester **55** in 65% yield.



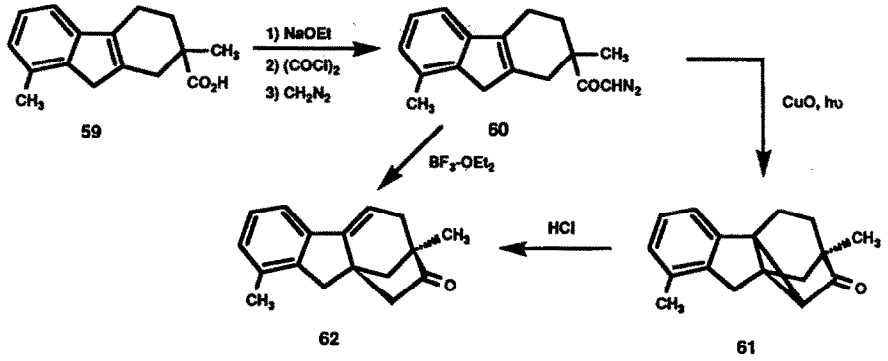
53 54 55

Cyclopropyllactone **57** was prepared as a key intermediate in an approach toward the synthesis of the antheridiogen *Andemia phyllitidis* A (**58**).[87,88] α-Diazoester **56** was reacted with *bis*-(*t*-butyl-salicylaldiminato)copper (II) in refluxing toluene. The resulting carbenoid added to the proximal double bond to produce cyclopropyllactone (**57**) in 92% yield.



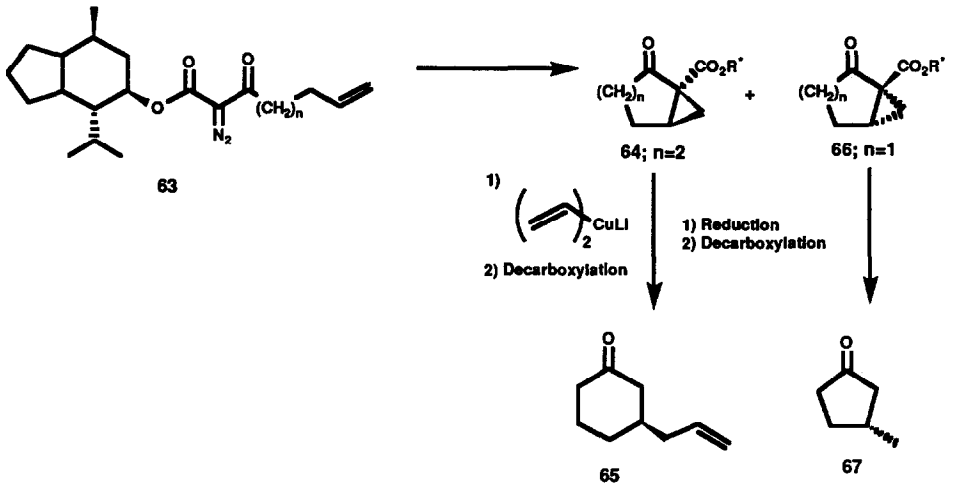
56 57 58

Gibberone (**62**) is a degradation product derived from gibberellic acid. A key feature of the molecule is the bridged cyclopentanone ring. Treatment of α-diazoketone **60** with activated CuO under a tungsten lamp gave the cyclopropanated ketone **61** in 63% yield.[89] Gibberone **62** was then obtained from **61** by an acid catalyzed ring fragmentation. Interestingly, treatment of α-diazoketone **60** with boron trifluoride etherate led directly to **62**.

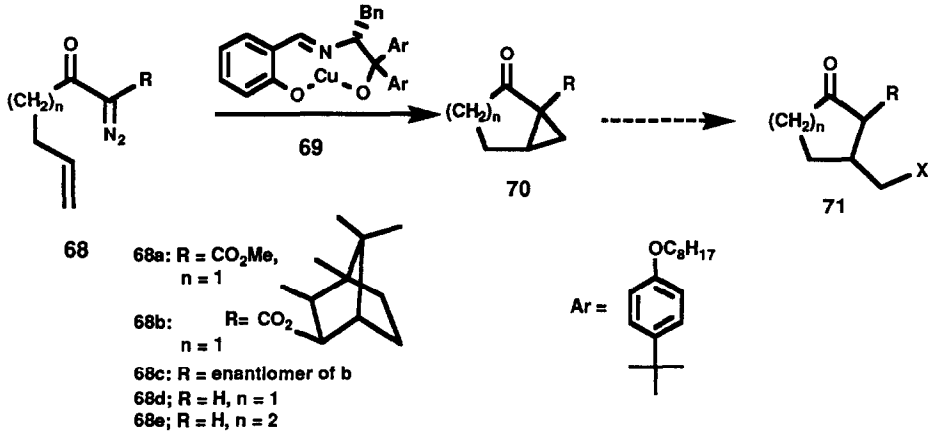


59 60 62 61

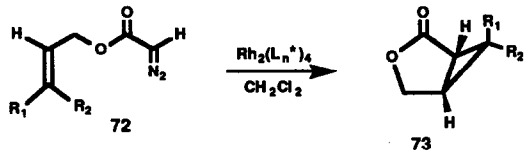
An important and continuing need in organic synthesis is the preparation of cyclopentanones and cyclohexanones of high optical purity. Cyclopropyl substituted cycloalkanones offer a facile entry toward optically pure substrates because of the presence of a key β-chiral center.[90] The internal cyclopropanation reaction of α-diazoketoester **63** gave rise to a 1:1 mixture of the diastereotopic bicyclic cyclopropanes **64** and **66** which were easily separated by silica gel chromatography. Homoconjugate addition of a nucleophile or dissolving metal reduction produced cycloalkanones **65** and **67** with known absolute configurations.



In recent years, great strides have been made in metal catalyzed asymmetric cyclopropanations of α-ketocarbenoids with the development of several highly effective chiral copper[91] and rhodium catalysts.[92] Dauben and coworkers have recently explored a method for generating enatiomerically pure cyclopentanones directly.[93] Treatment of α-diazo-β-ketoesters **68a-c** with the Aratani chiral copper catalyst (**69**) produced little chiral induction (0-13% *ee*) in the resulting bicyclic cyclopropanes **70a-c**. Switching the catalyst to a chiral semicorrinato cobalt species gave much higher enantioselectivity for the bicyclo[4.1.0] product (**70e**, n=2) (*ee* = 80%) as compared to the bicyclo[3.1.0] skeleton (**70d, n=1**) (*ee*=60%). Based upon this finding, the substrate-catalyst relationship of **69** appears to be highly specific.[91,94]

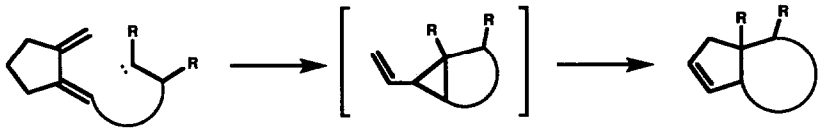


More recently, chiral rhodium (II) carboxamides having two nitrogen-rhodium bonds in the *cis* geometry at each rhodium face have been found to be particularly effective catalysts for enantioselective cyclopropanation reactions[92]. Thus, slow addition of **72** to a solution of the chiral catalyst delivered the corresponding 3-oxabicyclo[3.1.0]hexan-2-one **73** with very good enantioselectivity (65% to greater than 94%)[92]. These rhodium catalysts offer unique advantages for enantioselective intramolecular cyclopropanations, since both enantiomers of a cyclopropyl lactone may be efficiently prepared with high enantioselectivity from a single allylic diazoester.



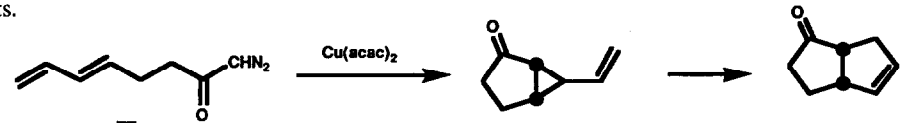
72 73

Compared to the intramolecular cyclopropanation reaction of olefins, the addition of carbenoids to conjugated dienes has not been as extensively studied. Some early experiments dealing with the addition of carbenoids to 1,3-dienes pointed to the potential use of this reaction for total synthesis.[95] More recently, Hudlicky and coworkers have developed this reaction into a viable synthetic protocol for the synthesis of a variety of fused cyclopentenyl polycycles. As one can imagine, the length of the tether was very critical with respect to the success of the transformation. The optimal separation between the two reacting moieties corresponded to either two or three methylene units.



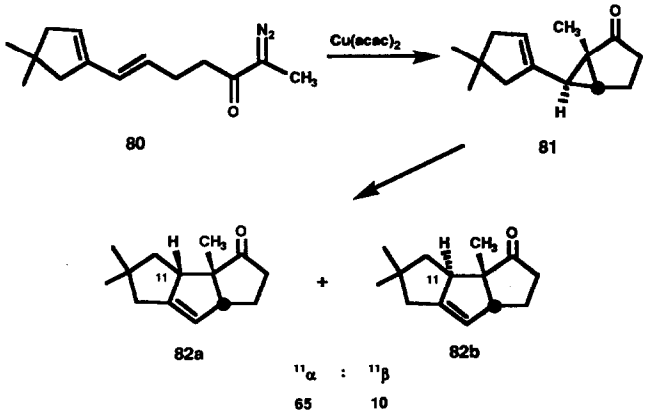
74 75 76

Treatment of α-diazoketone **77** with $Cu(acac)_2$ produced vinylcyclopropane **78** in 94% yield. Shortening the tether to one methylene unit effectively shut down the reaction (<5%). This is presumably related to the significant amount of strain involved in the formation of the fused 3,4-bicyclic system. Increasing the tether length to four methylene units afforded a much lower yield of product. In all cases, formation of the vinylcyclopropane ring proved to be both regio- and stereospecific. Pyrolysis of these compounds consistently produced good yields of *cis* fused products.



77 78; 94% 79; 65%

Studies[95] dealing with the stereochemistry of the vinylcyclopropane-cyclopentene rearrangement indicated a distinct preference for *cis* closure even when substituents were introduced onto the diazo carbon. Placement of



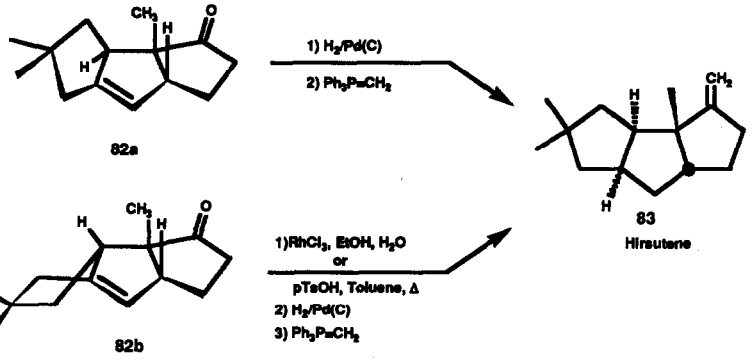
80 81 82a 82b

$^{11}\alpha$: $^{11}\beta$

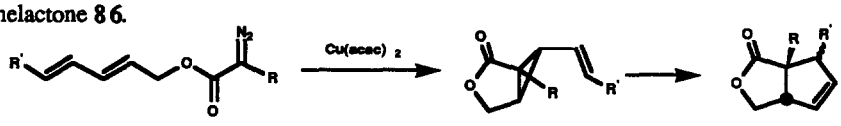
65 10

an alkyl group on the terminal carbon of the diene resulted in a preference for the *endocyclic* fused cyclopentene. Interestingly, when the rearrangement was carried out at lower temperatures using $(C_2H_4)_2Rh(acac)_2$ as the catalyst, a reversal in product stereochemistry was observed. Under these conditions, the *exocyclic* diastereomer was the favored isomer, sometimes to the exclusion of the *endocyclic* isomer.

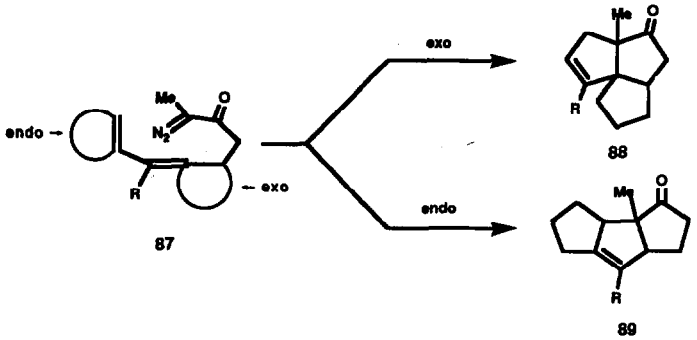
The two diastereomers of **82**, which are formed upon pyrolysis of **81**, were separated and both were converted to *hirsutene* (**83**).

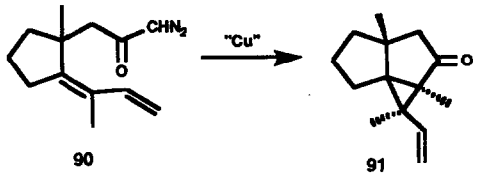


Formation of cyclopentenelactones has also been realized by replacing the α-methylene unit in the tether with an oxygen atom.[96] α-Diazoesters of type **84** reacted with copper sulfate or $Cu(acac)_2$ in refluxing benzene to give the bicyclic cyclopropane skeleton **85**. Pyrolysis of **85** afforded a modest yield of the *cis*-fused cyclopentenelactone **86**.

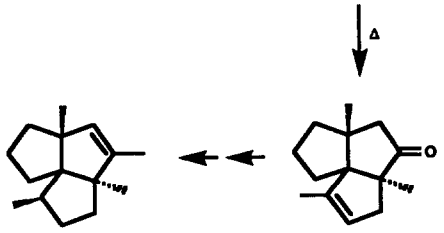


Incorporation of a ring into either the *exo* or *endo* position of the diene (i.e. **87**) allows the targeting of angular and linear triquinanes. For example, (±)-*epiisocomene* (**93**) was synthesized by incorporating an *exo*-ring into the tether. Thus, treatment of α-diazoketone **90** under the normal catalytic conditions resulted in the formation of tricyclic cyclopropane **91** in 93% yield. Thermolysis of **91** at 580°C brought about rearrangement to the angular triquinane ring system **92** in 82% yield. Three subsequent steps eventually afforded *epiisocomene* **93**.





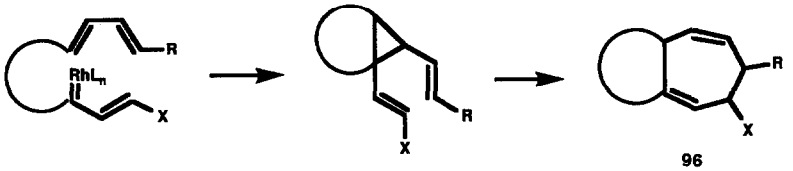
90 91



93 92

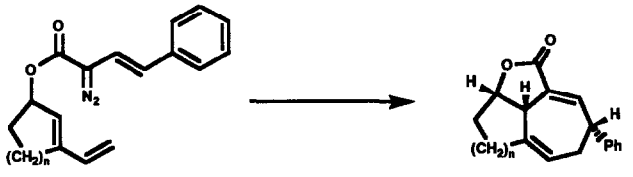
Epilsocomene

In recent years, Davies and co-workers have developed a [4+1]-annulation method similar to that described by Hudlicky, except that it involves the addition of a vinyl carbenoid to a conjugated diene.[97] Thus, rhodium (II) acetate stabilized vinyl-carbenoids were found to undergo formal [3+4]-cycloaddition with both cyclopentadiene[98] and furan[99] to produce seven-membered rings. The overall strategy is based upon a 3,3-sigmatropic rearrangement of an initially formed divinylcyclopropane intermediate (i.e. **95**). The intramolecular version of the reaction allows for the direct formation of substrates containing fused seven membered rings, such as the pseudoguaianolides and other sesquiterpenes.



94 95 96

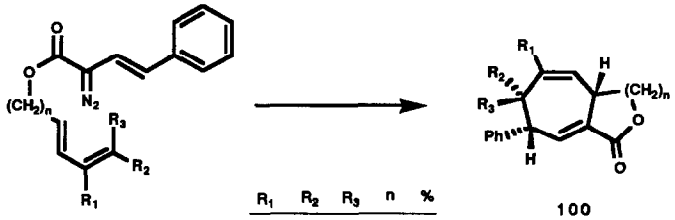
The rhodium (II) acetate catalyzed decomposition of **97** in dichloromethane resulted in the clean formation of the [3+4]-cycloadduct **98** in 61% yield as the only diastereomer.



97; n=1,2 98; n=1,2

The stereochemistry of the final product was found to be controlled by the initial diene geometry.[100] An example of this involves the transformation of α-diazoketone **99** to cycloheptadiene **100**. Increasing the length of the tether connecting the diazo carbonyl group to the diene to two methylene units resulted in low yields of product. Only a trace of the 6,7-fused product (i.e. **100**, n=2) was isolated. Presumably, the additional methylene unit

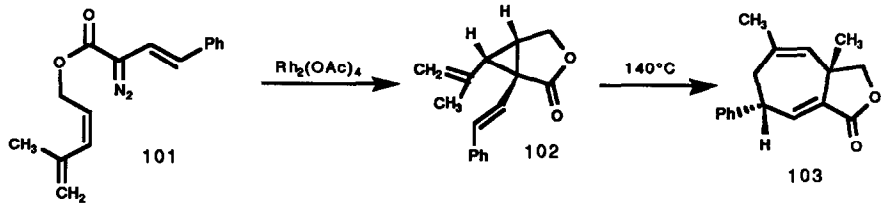
incorporates too much flexibility into the system and prevents the carbenoid from achieving the correct geometry for the cyclopropanation reaction.



99 100

	R_1	R_2	R_3	n	%
a	H	CH_3	H	1	76
b	H	H	CH_3	1	53
c	H	H	H	1	68
d	H	H	H	2	<5
e	CH_3	H	H	1	60

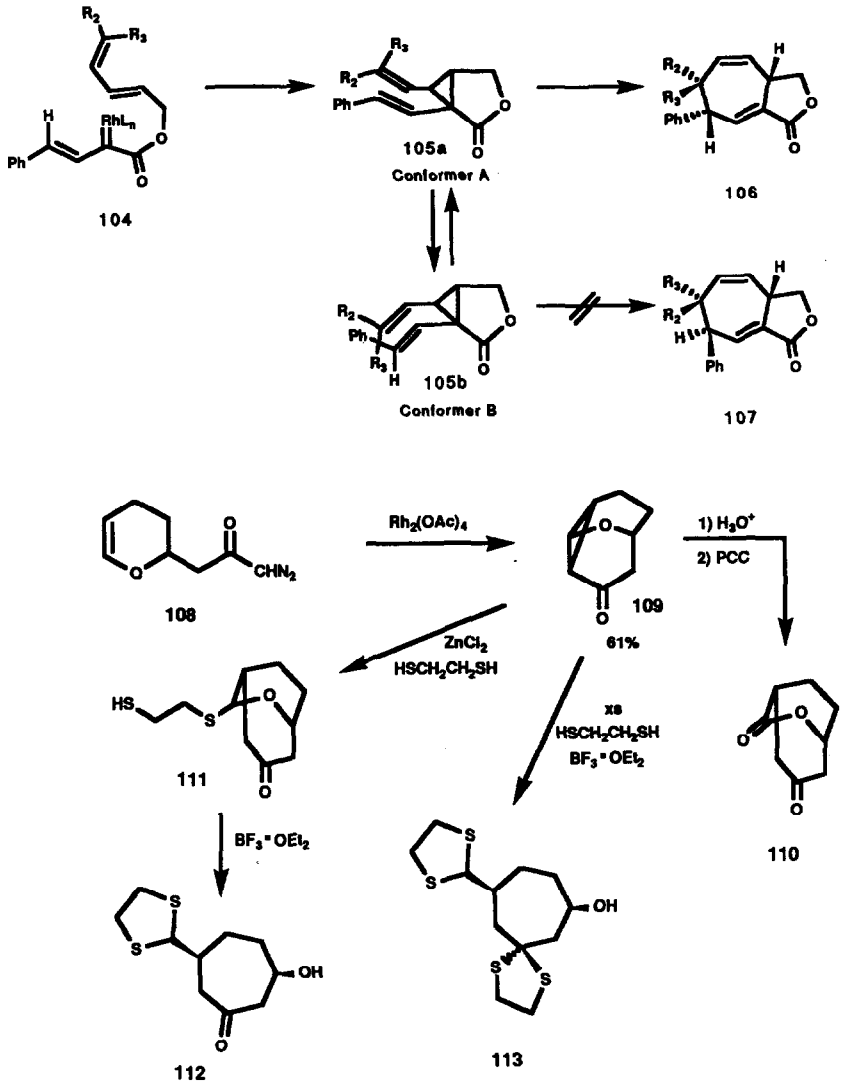
The examples illustrated so far involve internal addition to a *trans* π-bond. When the olefinic π-bond was *cis*-substituted (i.e. **101**), the reaction proceeded smoothly to give cyclopropane **102** (94%) and then stopped. The fact that a 3,3-sigmatropic rearrangement did not occur at room temperature is in accord with literature precedent, since it is known that *trans* divinyl substituted cyclopropanes do not readily rearrange.[101] Heating the divinyl compound **102** to higher temperatures, however, produced the same product (i.e. **103**) as that observed when the olefin was *trans*-substituted. Presumably, this involves an initial rearrangement of the *trans* isomer to the *cis* divinyl cyclopropane which rapidly undergoes the Cope rearrangement.



101 102 103

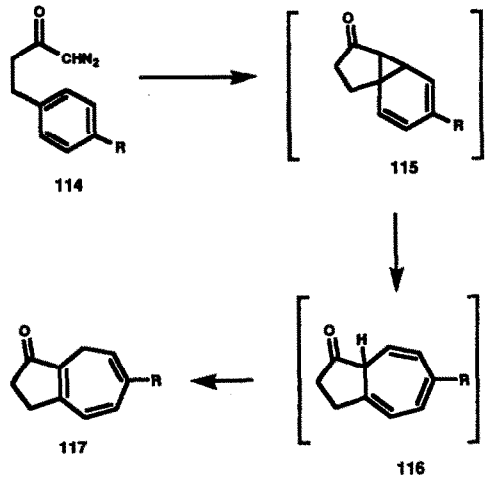
The stereospecific formation of the fused cycloheptadiene ring system is consistent with a divinylcyclopropane intermediate. When the double bond nearest the tether is *trans* substituted, intramolecular cyclopropanation results in the exclusive formation of a *cis*-divinyl substituted cyclopropane which undergoes further rearrangement. Of the two possible boat conformers available for rearrangement (A and B), conformer A is favored probably as a consequence of greater orbital overlap.[102]

An interesting approach to medium-sized carbocycles using α-diazoketones has been recently reported by Adams and coworkers.[103] The process involves intramolecular cyclopropanation of an enol ether followed by subsequent addition of a nucleophile so as to open the cyclopropane ring. The strategy is illustrated below using dihydropyranyl α-diazoketone **108**. Treatment of **108** with rhodium (II) acetate in dichloromethane at room temperature produced tricyclic lactone **109** in 61% yield. Ring opening of the cyclopropane with aqueous acid produced a hemiacetal which was subsequently oxidized with PCC to lactone **110**. Tricyclic ketone **109** was also treated with excess ethanedithiol in the presence of $BF_3{\cdot}OEt_2$ to give the 7-membered ring *bis*(dithioketal) **113**. A third sequence that was used involved differentiating the two carbonyl groups by a zinc catalyzed reaction using one equivalent of ethanedithiol followed by thioacetalization with boron trifluoride etherate (**112**).

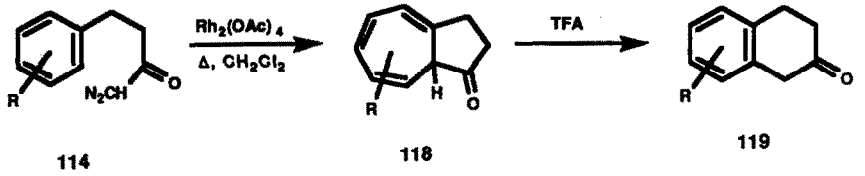


B. Aromatic Cycloadditions

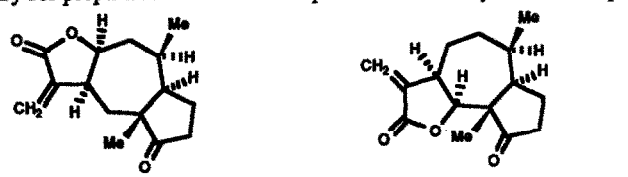
Cyclopropanations using transition metal carbenoids are not limited to isolated alkenes or conjugated dienes. Aromatic double bonds are quite susceptible to attack by these stabilized divalent carbon species. For example, the major product derived from the decomposition of α-diazoketone **114** is the fused cycloheptatriene **117**. The initially formed carbenoid adds to the tethered phenyl ring to produce norcaradiene **115**. This intermediate was not isolated but underwent spontaneous ring opening to the fused 5,7-bicyclic system **116**. Further rearrangement by means of a 1,7-sigmatropic hydrogen shift ultimately led to **117**. Isolation of the initially formed bicyclo[5.3.0]-decane framework is difficult when copper catalysts are used because of the high temperatures necessary for the reaction to occur.[3]

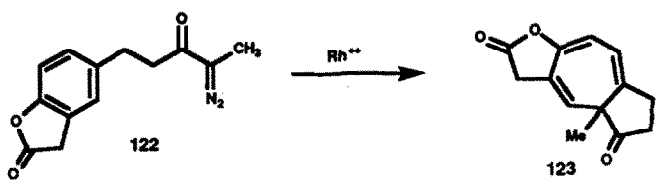


McKervey and coworkers[104] reported that rhodium (II) acetate efficiently induces the conversion of 1-diazo-4-arylbutan-2-ones **114** into bicyclo[5.3.0]decanones **118** in high yields. Equally important was the finding that the reaction occurs at temperatures low enough to allow for isolation of the unconjugated isomer **118**. The direction of cyclization was very dependent on the nature of the substituent group. The fused cycloheptatriene ring system **118** was easily converted in high yield to 2-tetralone **119** by treatment with trifluoroacetic acid.

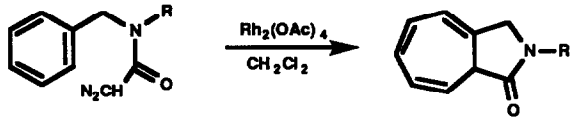


The intramolecular Büchner reaction has been utilized for the synthesis of several members of the pseudoguaianolide family (i.e. **120** and **121**). Model studies using α-diazoketone **122** resulted in the formation of cycloheptatriene **123** which contains the gross ring system of *confertin*. Unfortunately, attempts to incorporate the functionality necessary for preparation of the natural product into the cyclization step were unsuccessful.[105]



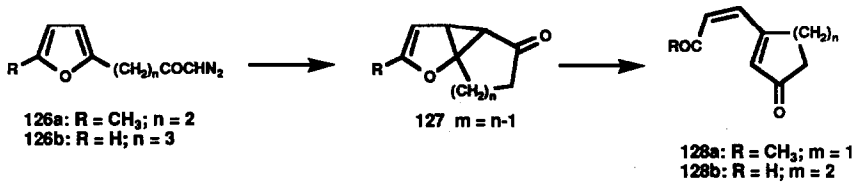


The incorporation of a heteroatom into the tether connecting the α-diazoketone to the aromatic ring has also been examined.[106] Doyle and coworkers found that the rhodium (II) acetate catalyzed reaction of N-benzyldiazoacetamide **124** resulted in a high yield of the desired azabicyclo[5.3.0]decatrienone **125**.[107] Unlike their carbocyclic counterparts, the 5,7-nitrogen analogues were impervious to prolonged treatment with trifluoroacetic acid and did not rearrange to the 6,6-system.



124 **125**

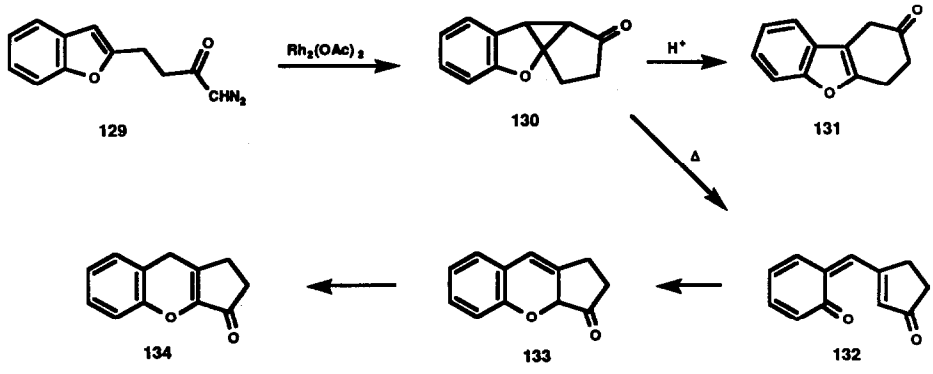
Heteroaromatic compounds have also been found to undergo the intramolecular cyclopropanation reaction. Padwa and coworkers demonstrated that α-diazoketone **126** gave cycloalkenone **128** in excellent yield when exposed to rhodium (II) acetate in benzene at 25°C.[108] The reaction involved initial addition of the keto carbenoid across the furanyl π-bond to produce an oxabicyclo[3.1.0]hex-2-ene intermediate (i.e. **127**) which underwent a subsequent cycloreversion reaction.[109] Support for the postulated mechanism was obtained by the isolation of cyclopropyl ketone **130** from the reaction of α-diazoketone **129** with rhodium (II) acetate at 25°C. Thermolysis of **130** afforded benzopyranone **134**. This reaction proceeded by initial ring cleavage of **130** to form *o*-quinoidal **132** and subsequent electrocyclic ring closure followed by a 1,3-hydrogen migration. The acid catalyzed reaction of **130** produced benzofuranone **131**.



126a: R = CH_3; n = 2
126b: R = H; n = 3

127 m = n-1

128a: R = CH_3; m = 1
128b: R = H; m = 2

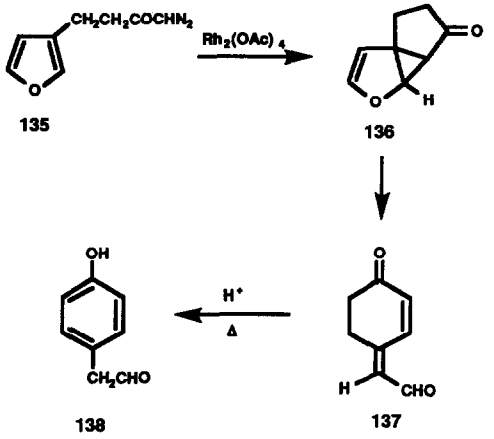


129 **130** **131**

132 **133** **134**

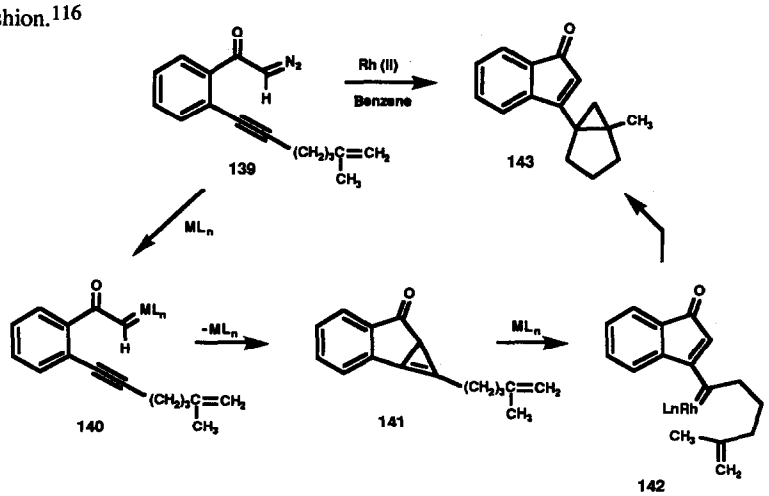
Switching the tethered diazoketone moiety from the 2- to the 3-position of the furan ring resulted in the formation of a cyclohexenone ring rather than a cyclopentenone. Thus, the addition of rhodium (II) acetate to a

solution of furan **135** in benzene produced *cis*-(4-oxo-2-cyclohexen-1-ylidene)acetaldehyde **137** in 88% yield. A rapid [4+2]-cycloreversion of the initially formed cyclopropane **136** nicely accounts for the formation of **137**.[110] On further treatment with acid, **137** rearranged to the thermodynamically more stable phenol **138**.

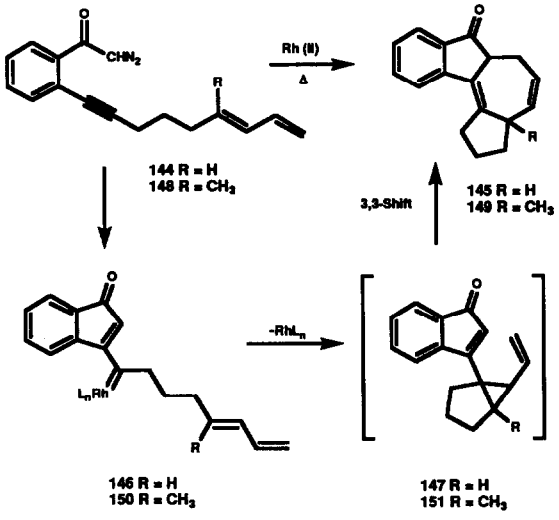


C. Reactions with Alkynes

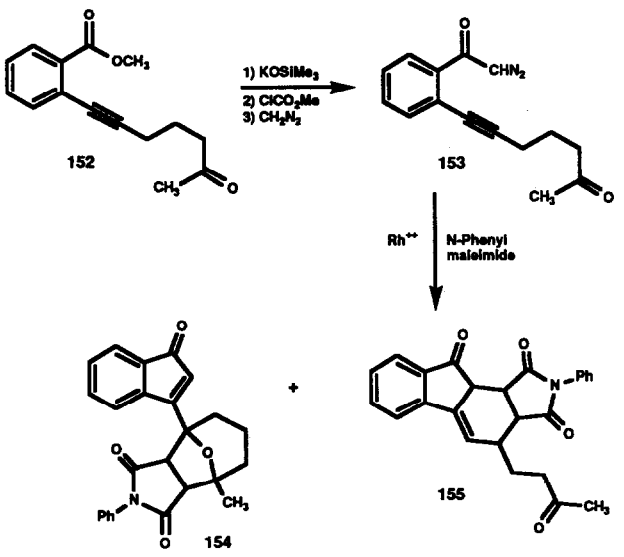
In contrast to the enormous body of data dealing with the intramolecular addition of carbenoids to olefins, much less is known about the same type of reaction using alkynes. This is surprising considering the numerous examples of bimolecular addition of carbenoids to acetylenes as a method for synthesizing cyclopropenes.[111] The first example in the literature describing the intramolecular addition of a diazo compound to an acetylene was reported by Jones and coworkers.[112] More recently, the transition metal catalyzed reaction of *o*-(6-methyl-6-hepten-1-ynyl)-α-diazoacetophenone (**139**) using rhodium (II) acetate was examined.[113] The isolation of cyclopropyl indenone **143** in 60% yield has been rationalized by formation of a vinyl carbenoid intermediate (**142**) which subsequently adds across the tethered olefin. It is also conceivable that a highly strained cyclopropene derivative (**141**) is first formed and then rearranges to **142**. It is well known that cyclopropenes ring-open to vinyl carbenes at ambient temperatures[114] and that these reactive intermediates may be trapped by alkenes in an inter[115] and intramolecular fashion.[116]



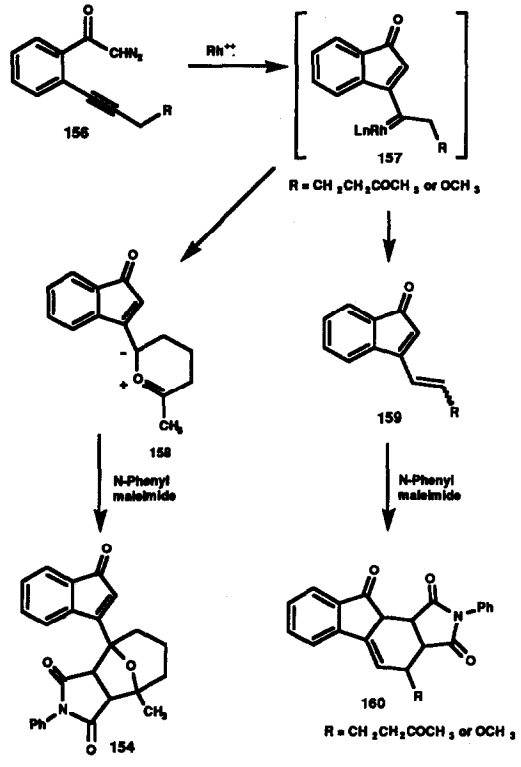
The above cyclization process was also carried out on the closely related diene **144**. In this case, treatment of α-diazoketone **144** with rhodium (II) mandelate at 0°C in methylene chloride produced **145** in 58% yield. A similar transformation occurred with **148**. The reaction undoubtedly proceeds by addition of the vinyl carbenoid onto the dienyl π-bond. The resulting *cis*-divinyl cyclopropane rapidly undergoes a Cope rearrangement to produce the observed product.[117] It should be noted that intramolecular cyclopropanation of dienes by simple carbenoids followed by rearrangement of the vinylcyclopropanes has been effectively utilized in synthesis.[118] The overall process is closely related to the earlier work of Davies, who developed a synthesis of fused seven-membered carbocycles based on a formal intramolecular [3+4]-cycloaddition of vinyl carbenoids with dienes[100].



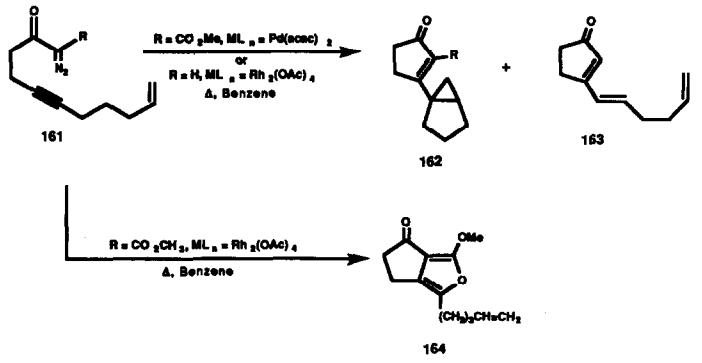
The reaction of α-diazoketone **153** with rhodium (II) mandelate in the presence of N-phenylmaleimide afforded a 1:1 mixture of epoxycycloheptapyrrole **154** as well as cycloadduct **155**. Both products are derived from



a common vinyl carbenoid intermediate (i.e. **157**). Cyclization of **157** onto the adjacent carbonyl group produces carbonyl ylide **158** which undergoes a subsequent 1,3-dipolar cycloaddition reaction with the added dipolarophile. The formation of compound **160** has been attributed to an initial 1,2-hydrogen shift to give diene **159** followed by a bimolecular Diels-Alder cycloaddition. The latter reaction sequence becomes the predominant path when the acetylenic tethered ketone is replaced with a propargyl ether. Thus, compound **160** (R=OCH_3) was formed in 60% yield from diene **159** (R=OCH_3) and can be rationalized by a 1,2-hydrogen shift followed by a 4+2-cycloaddition.[113]

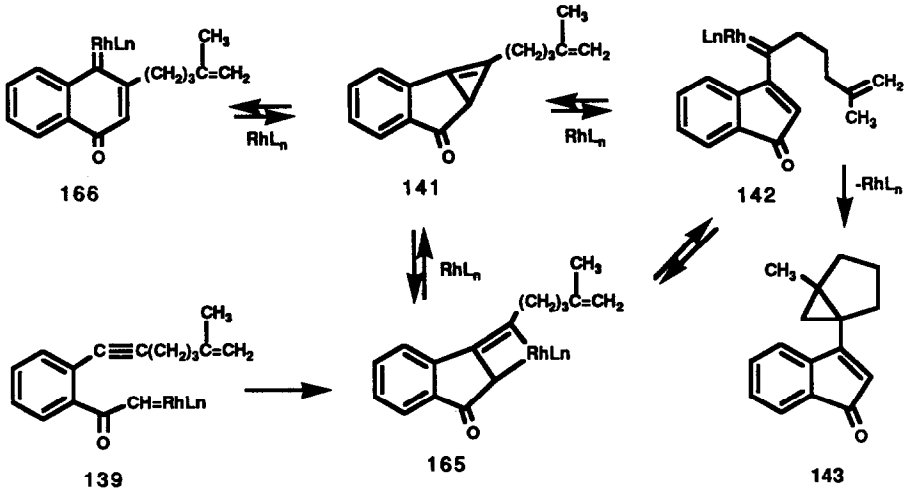


Hoye and Dinsmore have also been involved in a study of the intramolecular carbenoid additions to acetylenes.[119] Their results indicate that the product distribution is markedly dependent upon the nature of the catalyst. For example, treatment of α-diazoketone **161** with catalytic palladium (II) acetoacetonate produced

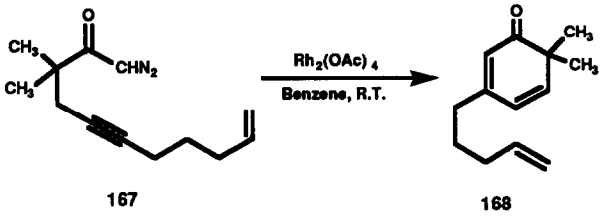


cyclopropane **162** (R=CO_2Me) in 78% yield. However, when rhodium (II) acetate was used as the catalyst, cyclopropane **162** was not formed. Instead, furan **164** was isolated in 65% yield. This compound arises by a 1,5-electrocyclization reaction of the initially produced vinylcarbenoid. Removal of the stabilizing ester carbonyl gave both cyclopropane **162** (R=H) as well as the 1,2-hydrogen shift product **163**. These results clearly indicate that the nature of the catalyst is important in determining the reaction pathway.

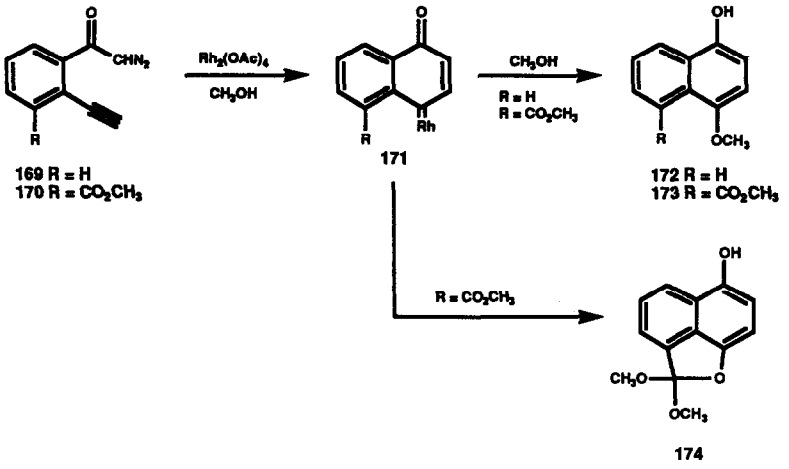
The fact that these α-diazoketo alkyne insertion reactions are catalyst dependent suggests that a metalated species is involved in the product-determining step. One possibility is that the rhodium metal migrates from the original diazo carbon to the alkyne carbon *via* a metallocyclobutene such as **165**. Other possible variations are also conceivable. The highly strained cyclopropene **141** could be rapidly converted into an organometallic species such as **165**, **142**, or **166** under the reaction conditions.[120]



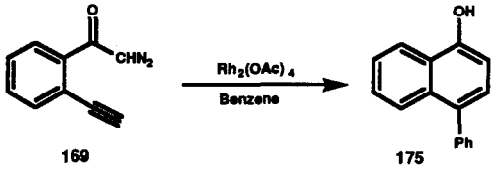
The exclusive formation of bicyclo[3.1.0]hexene **143** suggests that this product arises by either a regiocontrolled ring opening of **141** or is the result of a reversible process that involves selective trapping of intermediate **142**. It is still not clear as to whether an intramolecular metathesis reaction is taking place or whether a cyclopropene is first formed which then reacts further with the rhodium metal.[121] To further complicate the matter, in certain cases products derived from a 6-*endo* carbene intermediate are also formed. For example, cyclohexadienone **168** was observed as one of the products from the treatment of α-diazoketone **167** with rhodium (II) acetate.[119]



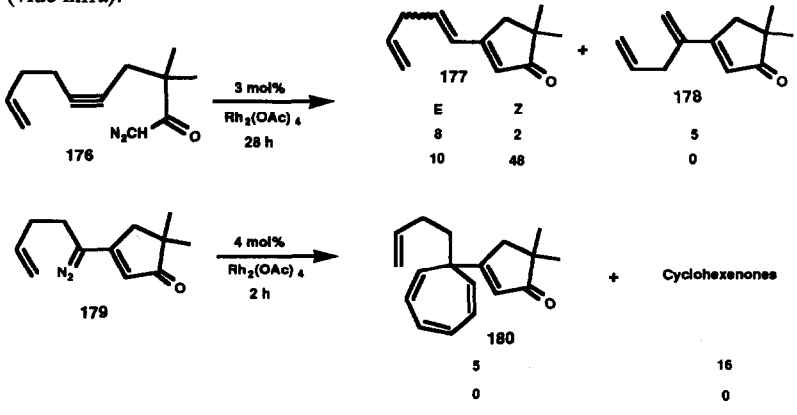
When α-diazoketone **169** (or **170**) was treated with $Rh_2(OAc)_4$, the major product corresponded to naphthol **172** (or **173**). This structure was also derived from a 6-*endo* carbenoid intermediate (i.e. **171**).[113]



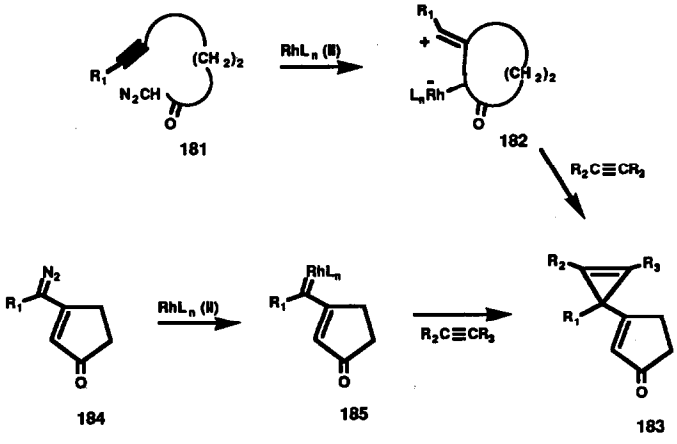
Further indication for the formation of a 6-*endo* vinylcarbenoid comes from a study of the rhodium (II) catalyzed decomposition of α-diazoketone **169**. The major product isolated from this reaction was naphthol **175**. The formation of **175** is most compatible with insertion of the 6-*endo* carbenoid into the solvent followed by an aromatization reaction.[122]



Hoye and Dinsmore have suggested that migration of the metal from the diazo to the alkyne carbon does not occur via a metallocyclobutene intermediate. This conclusion was based upon a comparison of product distribution obtained from the decomposition of α-diazoketone **176** with that obtained from the isomeric diazocyclopentenone **179**.[123] The rhodium carbenoid intermediate formed from **176** should correspond to the same species as that derived from **179** if a metallocyclobutene intermediate is involved. Consequently, one would expect identical product ratios. The distinct difference in product distribution obtained from the two isomeric diazo alkynes **176** and **179** is not compatible with a common intermediate. Instead, the reaction has been proposed to proceed in a stepwise fashion (*vide infra*).

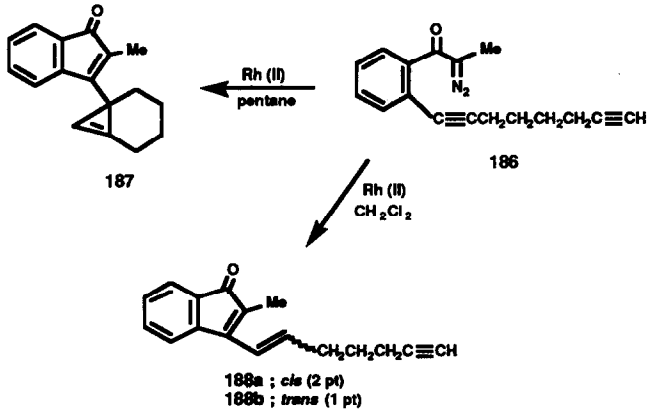


More recently, this same group reported on the Rh (II) catalyzed double internal-external alkyne insertion reaction of an acetylenic α-diazo ketone.[124] The initially formed rhodium carbenoid intermediate was suggested to undergo internal insertion into the tethered alkyne unit followed by a bimolecular addition to produce a cyclopropenyl substituted cyclopentenone derivative (*i.e.* **183**). Migration of the rhodium metal to the remote alkyne carbon via a [2+2]-cycloaddition/cycloreversion path (*i.e.* **181**→**185**) was discounted on the basis that the distribution of products derived from **181** differed significantly from those obtained from the rhodium carbenoid species **185**, generated from the vinylogous diazo ketone precursor **184**. These results were rationalized *via* the intermediacy of zwitterion **182**.



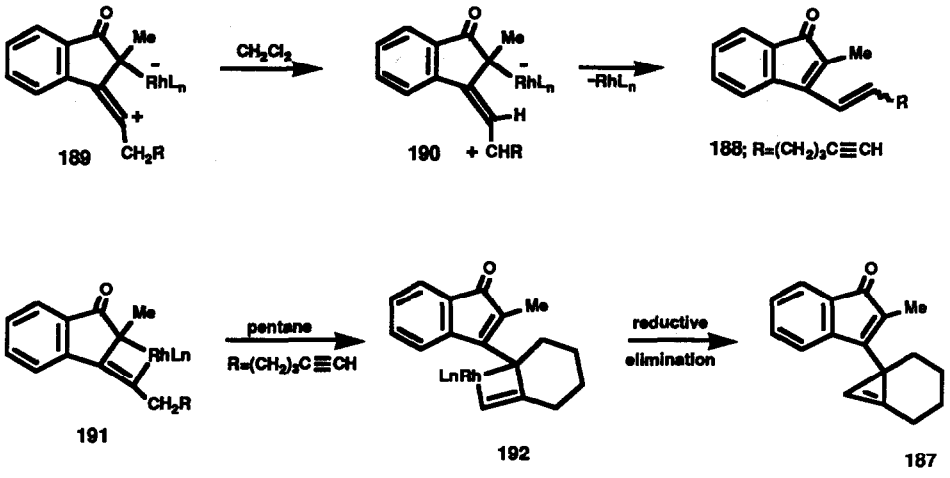
181 182 184 185 183

Results in the Padwa laboratory showed, however, that the reaction mechanism is markedly dependent on the solvent employed in these Rh(II) catalyzed insertion reactions.[122] Reaction of α-diazoketone **186** with rhodium (II) octanoate in pentane resulted in a double internal/internal alkyne insertion reaction producing the labile bicyclo[4.1.0]hept-1(7)ene derivative **187**. Changing the solvent from pentane to methylene chloride resulted in the formation of a 2:1-mixture of *cis* and *trans*-alkenyl substituted indenones **188**. Stepwise cyclization involving a set of dipolar intermediates took place in methylene chloride whereas metallocyclobutenes **191** and **192** were involved in pentane.

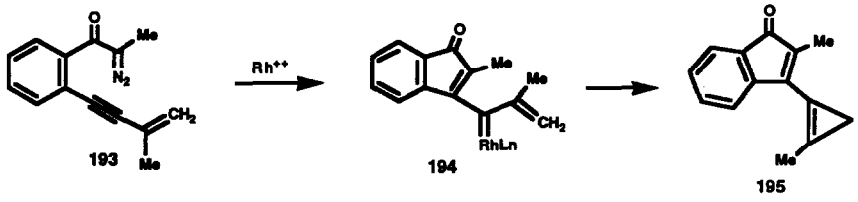


187 186

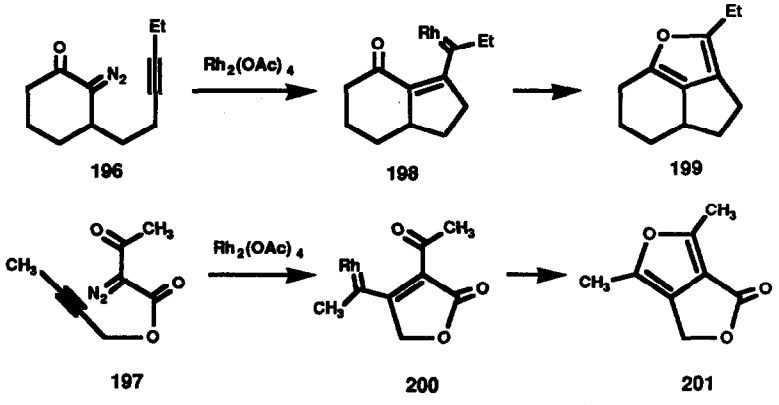
188a ; *cis* (2 pt)
188b ; *trans* (1 pt)



Treatment of o-alkynenyl substituted α-diazoacetophenone **193** with rhodium (II) acetate produced the cyclopropenyl substituted indenone **195** in high yield.[125] In this case, the initially formed vinyl carbenoid **194** undergoes rapid cyclization to give the cyclopropene ring.



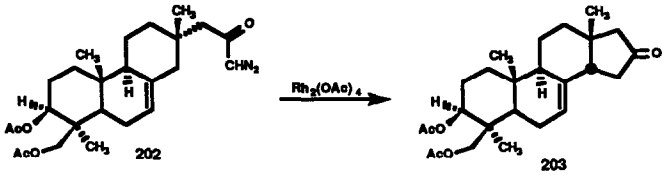
One of the more frequently encountered reactions of dienylcarbenes involves rearrangement to indenes, cyclopentadienes, or furans.[126] Diazo ketones **196** and **197** were found to undergo this type of cyclization in the presence of a rhodium catalyst. The reaction proceeds *via* formation of a transient vinyl carbene which then attacks the adjacent carbonyl oxygen to give a carbonyl ylide, which subsequently tautomerizes to furans **199** and **201** respectively.[127]



IV. Insertion Reactions

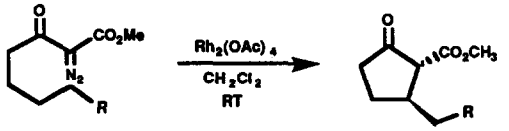
A. Aliphatic C-H Insertions

Although carbene insertion into aliphatic C-H bonds has been known for quite sometime,[8] this reaction was not utilized for organic synthesis until 1982, when Wenkert and coworkers transformed a diterpene into a steroid skeleton.[128] The 13-α-vinyl group present in *virescenol B diacetate* was converted into the corresponding α-diazoketone **202**. Reaction of **202** with rhodium (II) acetate at room temperature produced the cyclopentanone-containing steroid skeleton **203** in 59% yield. This same transformation was also carried out using catalytic cupric sulfate, but rhodium (II) acetate proved to be a more effective catalyst.



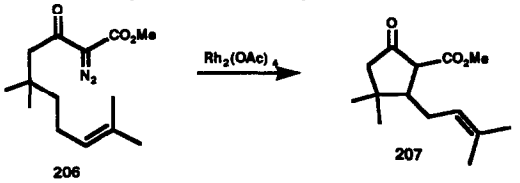
202 203

Much of what is known today about intramolecular carbenoid C-H insertions has come from studies carried out by Taber and coworkers.[129] Initial reports involved the reaction of α-diazo-β-ketoester **204** with rhodium (II) acetate as the catalyst. The major product isolated from this reaction corresponded to the 2-carboalkoxy substituted cyclopentanone system **205**. This seminal report clearly demonstrated that C-H insertion can be an efficient process with freely rotating acyclic systems.[129]

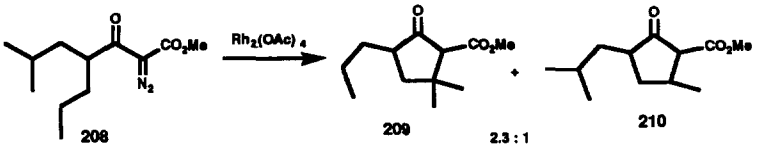


204 205

A systematic investigation of both steric and electronic effects associated with the intramolecular carbenoid insertion was carried out and the reaction was found to be very general and predictable.[129] By using substrates which contain two competing sites for reaction (*i.e.* **206**), insertion into a methylene C-H bond was found to be significantly favored over insertion into a methyl C-H bond. When α-diazo ketoester **208** was treated with Rh (II) acetate, a 2.3:1 mixture of cyclopentanones **209** and **210** was observed. This result indicates a preference for insertion into a methine C-H bond over a methylene C-H bond by a factor of 4.6 to 1.



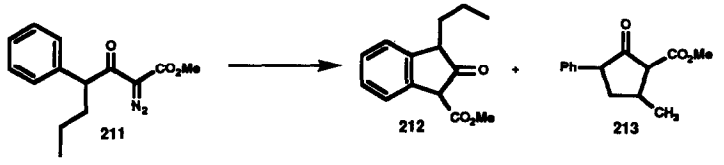
206 207



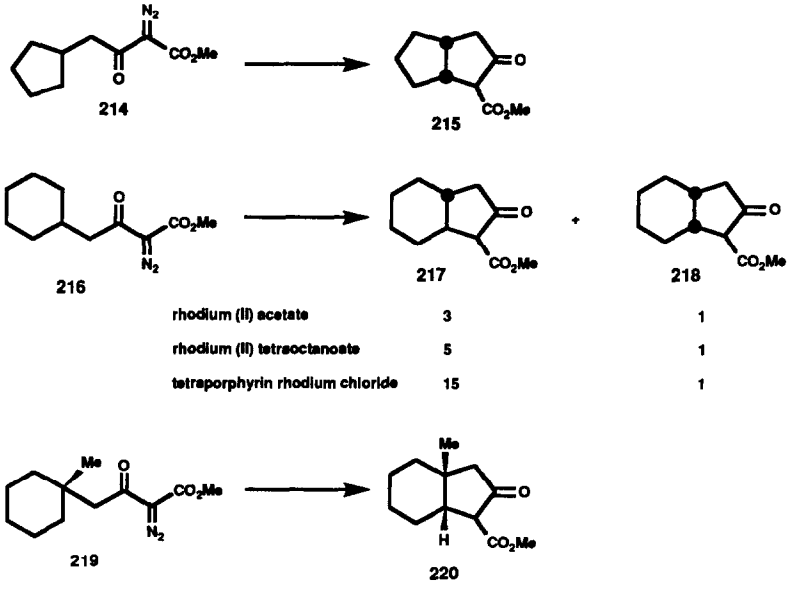
208 209 2.3 : 1 210

The observed order of reactivity (methine>methylene>methyl) is consistent with that observed for free carbenes,[130] but differs from earlier results reported by Bergman.[131] The fact that alkyl substitution enhances the insertion reaction while vinyl and phenyl substitution diminish the process, was rationalized by the relative ability of each substituent to donate electron density toward the reacting carbenoid center. Alkyl substitution about a carbon atom enhances electron density around that center, and therefore, it is not at all surprising that C-H insertion at a methine carbon proceeds most efficiently. Phenyl and vinyl substitution, on the other hand, withdraw electron density from the carbon center, making insertion into the benzylic and allylic C-H bonds more difficult. Insertion into a methine C-H bond is very competitive with cyclopropanation. A rapid reversible precomplexation of the rhodium carbenoid with the C-H bond was suggested to be an important factor for the insertion reaction. This rationale is similar to that proposed by Jones to explain intermolecular C-H activation.[132]

Aromatic carbon-hydrogen bonds were found to undergo insertion more readily than aliphatic C-H bonds in bimolecular processes.[132] Interestingly, intramolecular aliphatic C-H insertion was found to be very competitive with aromatic C-H insertion.



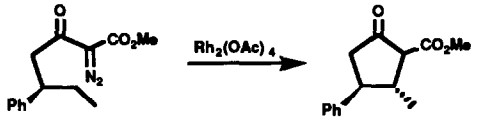
Steric factors also play a role in determining insertion ratios. Thus, when C-H insertion into a cyclopentyl ring occurs,[133] only *cis* substituted products are formed (i.e. **214→215**). However, when insertion occurs into a cyclohexyl ring, the observed *cis* to *trans* ratio depends on the nature of the catalyst. For example, treatment of methyl 4-(1-cyclohexyl)-2-diazo-3-oxo-butanoate (**216**) with rhodium (II) acetate led to a 3:1 mixture of the *trans*



rhodium (II) acetate	3	1
rhodium (II) tetraoctanoate	5	1
tetraporphyrin rhodium chloride	15	1

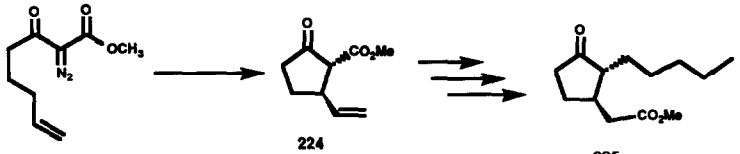
and *cis* insertion products **217** and **218**, respectively. Changing the catalyst to rhodium (II) tetraoctanoate increased the ratio to 5:1. With the even larger tetraphenylporphyrin rhodium chloride, the ratio increased to 15:1 in favor of the *trans* product. In contrast, when methyl 2-diazo-4-(1-methyl-1-cyclohexyl)-3-oxobutanoate (**219**) was used as the substrate, only *cis*-octahydro-1H-indene-carboxylate (**220**) was observed. In this case the angular methyl group blocks the approach of the rhodium-carbenoid to the equatorial hydrogen, which is responsible for the formation of the *trans* product.

The stereoselectivity observed with α-diazoketone **219** was further extended toward a diastereoselective synthesis of *trans*-3,4-dialkyl substituted cyclopentanes. Thus, treatment of α-diazo-β-ketoester **221** with rhodium (II) acetate in CH_2Cl_2 at room temperature resulted in the exclusive formation of cyclopentanone **222**.



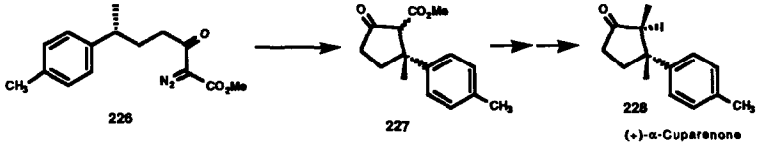
221 **222**

As with all new methodology, its real synthetic value can best be gauged by the synthesis of complex target molecules. Taber and coworkers elegantly demonstrated the synthetic applicability of the method toward complex natural product targets. The formation of cyclopentanone **224** from α-diazo ketoester **223** represents a formal synthesis[129] of methyl dihydrojasmonate (**225**).[134]



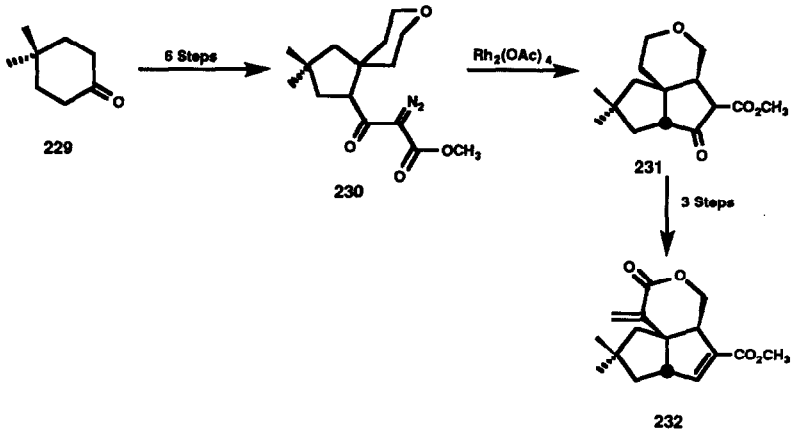
223 **224** **225**

Taber's group made use of the fact that C-H insertion occurs with retention of stereochemistry in their synthesis of (+)-α-*cuparenone* (**228**).[135] Treatment of α-diazo ketoester **226** with rhodium (II) acetate in methylene chloride afforded cyclopentanone **227** in 67% yield. Four subsequent steps produced (+)-*cupranone* (**228**) in 96% optical purity, confirming the fact that the rhodium catalyzed C-H insertion proceeds with almost complete retention of configuration.



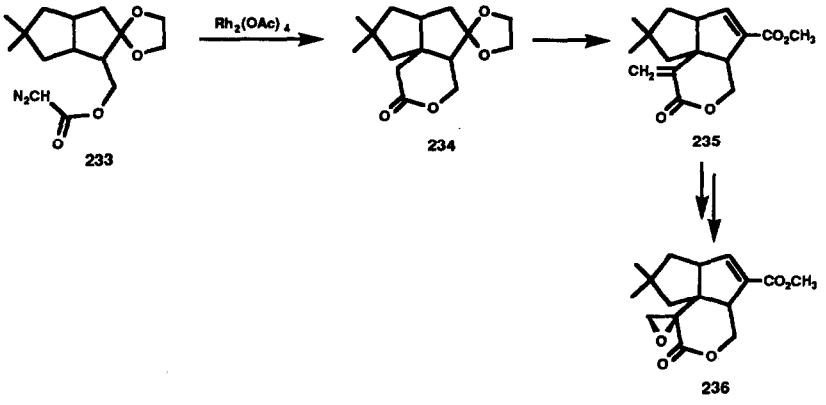
226 **227** **228** (+)-α-Cuparenone

The sesquiterpene antibiotic *pentalenolactone E methyl ester* (**232**) was also synthesized by a procedure that involves intramolecular C-H insertion of a rhodium carbenoid into a methylene bond.[136] Starting with readily available 4,4-dimethylcyclohexanone (**229**), α-diazo-β-ketoester **230** was prepared in six steps. Treatment of **230** with a catalytic amount of rhodium (II) acetate afforded tricyclic ether **231** in 91% yield. This compound was easily converted into the sesquiterpene antibiotic **232** in three subsequent steps.



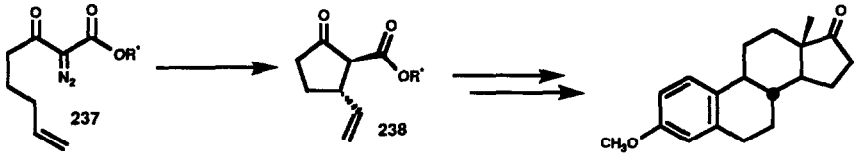
229 230 231 232

An approach to (±)-*pentalenolactone F methyl ester* (**236**) which utilized an intramolecular carbenoid C-H insertion was developed by Cane and Thomas.[137] Diazobicyclo[3.3.0]octan-3-one **233** was found to undergo clean C-H insertion upon treatment with $Rh_2(OAc)_4$ to give lactone **234**. This material was eventually converted to **236** in several additional steps.



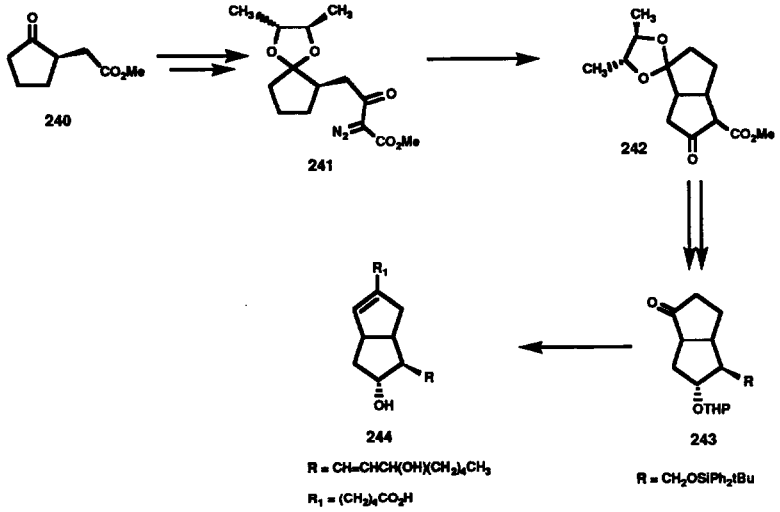
233 234 235 236

A high yielding asymmetric synthesis of (+)-*estrone methyl ether* (**239**) was carried out by Taber and coworkers.[138] This was accomplished by the use of a chiral α-diazoketoester, the chiral nature of the ester group inducing stereoselection in the insertion reaction. The *trans* substituted cyclopentanone **238** necessary for the synthesis of **239** was produced in 92% yield from α-diazoketone **237**. The most effective chiral auxiliary for the induction of diastereoselectivity was the naphthyl norborneol ester.

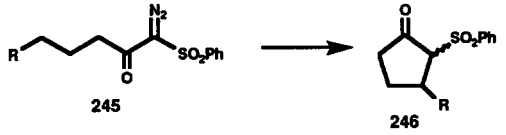


237 238 239

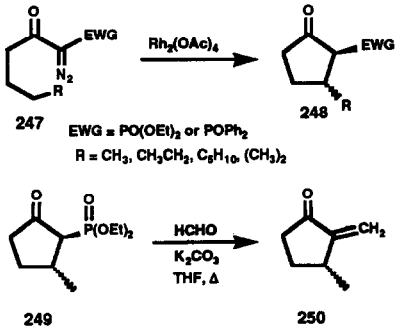
Ikegami and coworkers[139] capitalized upon the exclusive formation of *cis*-bicyclic products in their synthesis of compound **243**. The synthetic sequence starts from the readily available (R)-(+)-methyl 2-oxo-1-cyclopentane acetate (**240**) which was used to generate α-diazo-β-ketoester **241**. Treatment of **241** with 5% rhodium (II) acetate in methylene chloride at 20°C afforded the bicyclo[3.3.0] ring system **242**. This compound was then transformed into the desired intermediate **243** which was eventually converted to *isocarbacyclin* **244**.



In all of the examples illustrated thus far, the diazo group was generated from a β-ketoester. The following two examples demonstrate that electron withdrawing groups other than esters can be used for the synthesis of cyclopentanones. Acyclic α-diazo-β-ketophenylsulfone **245** was observed to undergo smooth intramolecular carbenoid cyclization under rhodium (II) catalysis to give the α-phenylsulfonyl substituted cyclopentanone **246**.[140] The requisite starting diazo compound was efficiently prepared from a β-keto-sulfone.[141]

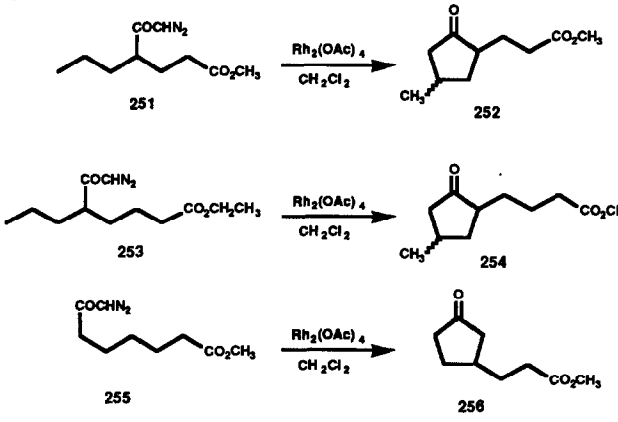


The synthesis of the α-phosphorylated cyclopentanone **248** was achieved by an intramolecular carbenoid insertion reaction using α-diazo-β-ketoalkylphosphonate **247**.[142] Like the α-diazo-β-ketoester system studied by

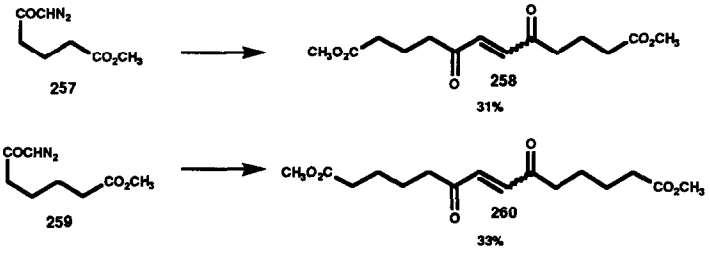


Taber and coworkers,[138] the phosphorus substituted α-diazo ketone was prepared by diazo transfer and was found to exhibit similar behavior when exposed to catalytic quantities of rhodium (II) acetate. The resulting cyclopentanone derivative could easily be converted to an α-methylene cyclopentanone (i.e.**250**).

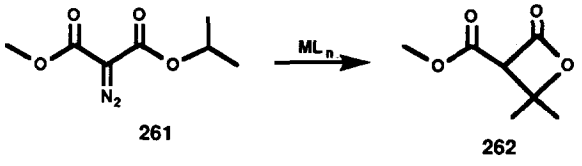
Stork and Nakatani discovered that an electron withdrawing group such as an ester, when attached to the α-diazoketo side chain, significantly influenced the regiochemistry of the C-H insertion.[143] The ester functionality directed carbenoid insertion away from the α-methylene hydrogens. Thus, treatment of α-diazoketones **251** and **253** with rhodium (II) acetate produced cyclopentanones **252** and **254** in 83% and 81% yield, respectively. α-Diazoketone **255** was found to undergo C-H insertion to give **256**, thereby indicating that the ester group doesn't deactivate the γ-hydrogens.



Interestingly, diazoketones **257** and **259** did not undergo C-H insertion to produce a cyclopentanone. The only products isolated corresponded to enediones **258** and **260** which resulted from dimerization of the α-diazo functionality. Clearly, the ester funtionality markedly influenced the carbenoid insertion behavior.

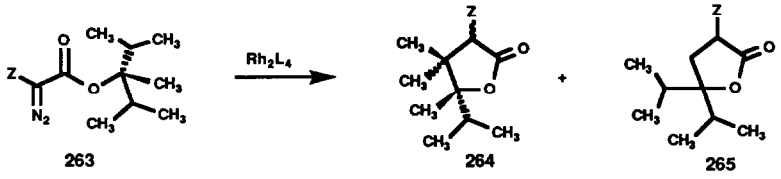


Carbocycles are not the only ring systems that can be formed from intramolecular C-H insertion reactions of transition metal carbenoids. Heterocycles have also been obtained from these catalytic reactions. Lee and coworkers[144] demonstrated that lactones can be formed and found and that the selectivity is dependent upon the substituent groups.



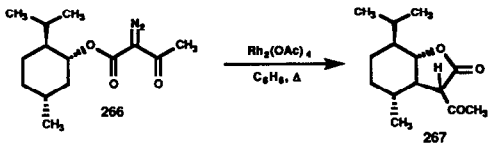
β-Lactone formation is the preferred process when β-methine C-H bonds are available for insertion. If a γ-methine C-H bond is present, high yields of γ-lactones are obtained. However, β-lactone formation is preferred when both β- and γ-methine protons are available. The preference for β-lactone formation has been attributed to a conformational bias of the metallocarbenoid species formed from the α-diazomalonate rather than the consequence of an electronic factor.

Doyle and co-workers demonstrated the viability of carbenoid C-H insertion reactions for the synthesis of more complex lactones.[145] Thus, treatment of α-diazoester **263** (Z=H) with rhodium (II) acetate afforded a 1:1 mixture of γ-lactones **264** (Z=H) and **265** (Z=H). The large quantity of **265** (Z=H) produced from this reaction is a bit surprising in light of the previously determined preference for insertion (3°>2°>1°). When a less discriminate catalyst such as rhodium (II) perfluorobutyrate was used, the yields of **264** and **265** (Z=H) correspond to a statistical distribution based on hydrogens available for C-H insertion. The methine C-H insertion product **264** was the exclusive product when rhodium (II) acetamide was used. Similar results were obtained with related β-ketoesters.

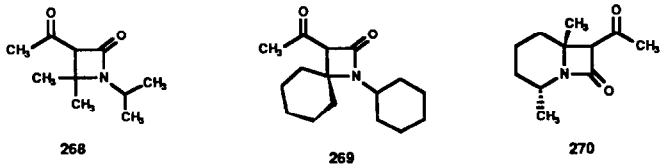


Rh_2L_4	Z = H yield, %	relative yield 264	265	Z = CH_3CO yield,%	relative yield 264	265
$Rh_2(pfb)_4$	56	32	68	45	45	55
$Rh_2(OAc)_4$	81	53	47	97	90	10
$Rh_2(acam)_4$	96	>99	<1	89	>99	<1

The exclusive formation of bicyclic γ-lactone **267** from the reaction of α-diazo ketoester **266** with rhodium (II) acetate was surprising considering the fact that tertiary C-H bonds are more reactive toward insertion than secondary ones. More than likely, the distribution of products with this system is related to steric factors and insertion into the tertiary C-H bond is precluded on geometric grounds.

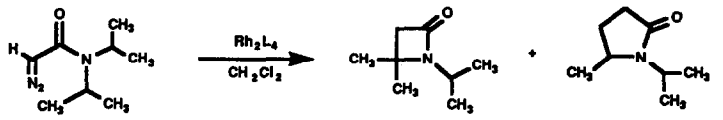


β-Lactam formation can also be achieved *via* the intramolecular C-H insertion reaction of metal carbenoids.[146] For example, the rhodium (II) acetate catalyzed decomposition of α-diazoacetoacetamides derived from diisopropylamine, dicyclohexylamine, and *trans*-2,6-dimethylpiperidine produced the corresponding β-lactams in high yield.



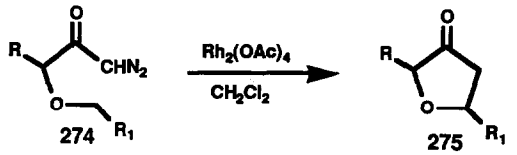
Removal of the acetyl group from the starting diazo compound also afforded insertion products upon treatment with rhodium (II) acetate. With this system, however, competition between β-C-H and γ-C-H insertion

was significant. Thus, treatment of N,N-diisopropyl diazoacetamide **271** with $Rh_2(OAc)_4$ in methylene chloride afforded β-lactams **272** and **273** in 95% yield. In this case, β-lactam formation was favored by a factor of 4:1. Switching the catalyst to rhodium (II) perfluorobutyrate or rhodium (II) 2-phenoxy benzoate did not significantly alter the ratio of products.



271 272 273

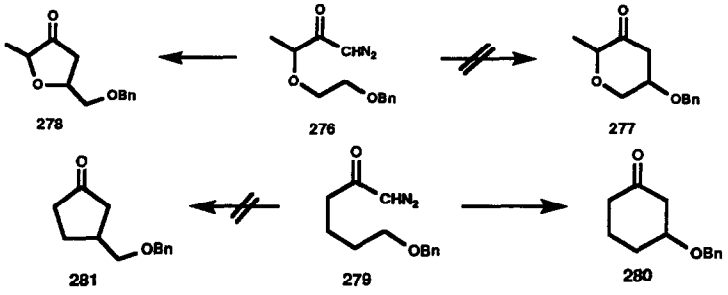
The reaction of α-diazoketone **274** which possesses an α-alkoxy group with rhodium (II) acetate was exploited as a method for synthesizing the (2H)-furanone system **275**.[147]



274 275

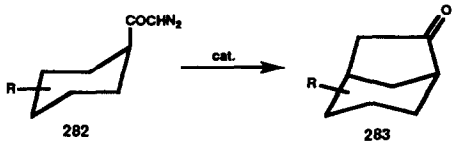
R = alkyl, aromatic, CF_3, alkoxy
R_1 = aromatic, alkyl, alkoxy
yields = 34 - 84%

It is well known that C-H insertion to form a five-membered ring is generally the dominant reaction pathway.[129] This is also the case when two ether functionalities are present, the potential therefore existing for both five- and six-membered ring formation. Thus, catalytic decomposition of α-diazoketone **276** afforded furanone **278** as the exclusive product. Interestingly, α-diazoketone **279** gave the six membered ring **280**. Activation by the alkoxy group is apparently the dominant factor here since no cyclopentanone (i.e. **281**) was observed.



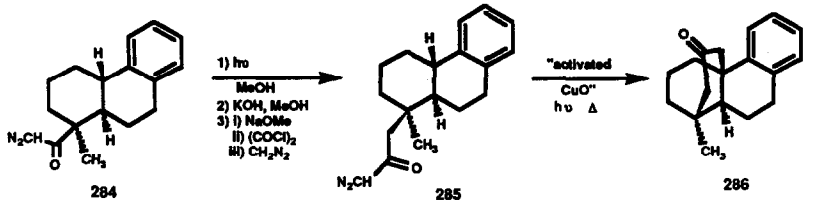
278 276 277 281 279 280

Rhodium (II) carboxylates are not the only catalysts that have been used for the C-H insertion reaction of diazo compounds. Agosta and Wolff used both silver and copper catalysts for the synthesis of bicyclo[3.2.1]octan-6-ones **283**.[148] Copper sulfate in refluxing benzene was found to be a superior catalyst to silver benzoate. As expected, methine C-H insertion was the major pathway followed here.



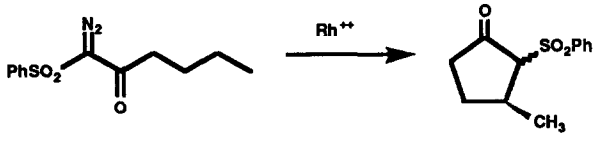
282 283

A benzylic methine C-H insertion route has been used for the synthesis of the bridged bicyclo[3.3.1]nonanone system **286** which is closely related to a newly discovered insect attractant, (±)-*9a-carbomorphinan.*[149]



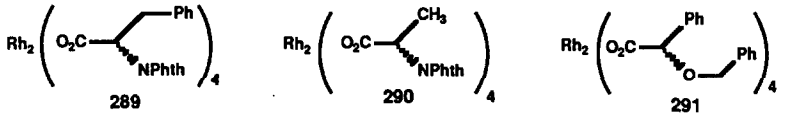
284 **285** **286**

An example of asymmetric synthesis in a C-H insertion reaction of an α-diazoketone was recently reported by McKervey and coworkers.[150] Treatment of α-diazoketosulfone **287** with rhodium (II) N-benzenesulfonyl-*L*-prolinate in dichloromethane afforded a *cis/trans* mixture of **288** in 90% yield. This reaction proceeded with an enantiomeric excess of 30%.

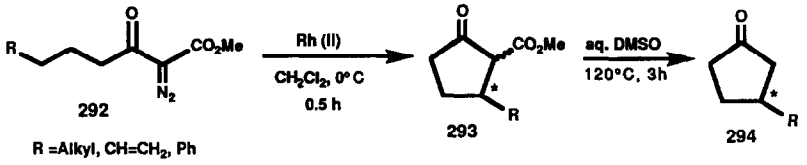


287 **288**

Ikegami and coworkers achieved somewhat higher enantioselectivity by using homochiral rhodium (II) carboxylates.[151] The homochiral rhodium (II) carboxylates **289-291** were prepared from rhodium (II) acetate by an exchange reaction with N-phthaloyl-(S)-phenylalanine, N-phthaloyl-(S)-alanine, and (S)-2-benzyloxphenylacetic acid, respectively. The cyclic β-ketoesters **293** were produced as an equilibrium mixture of keto and enol forms. The absolute configuration of **293** was determined by demethoxycarbonylation to the known 3-substituted cyclopentanone system **294**. Enantiomeric excesses were estimated to occur in the range of 10-46%. Asymmetric synthesis of lactones with high enantioselectivity by intramolecular C-H insertions of alkyl diazoacetates catalyzed by chiral rhodium (II) carboxamides has recently been reported by Doyle and coworkers.[152]



289 **290** **291**



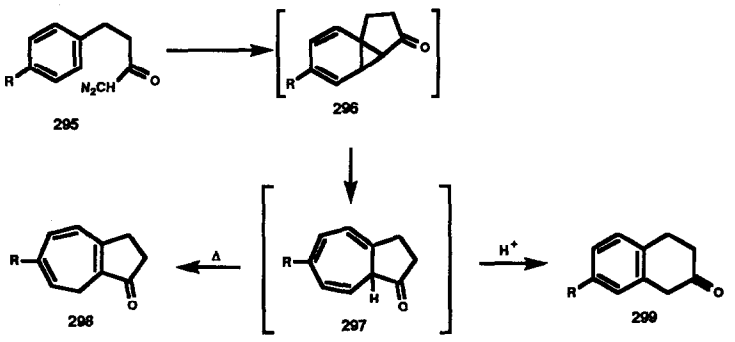
292 **293** **294**

R =Alkyl, CH=CH_2, Ph

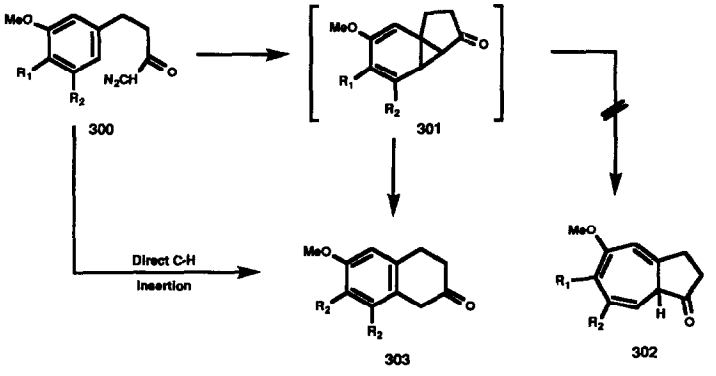
B. Aromatic C-H Insertions

The transition metal catalyzed reactions of α-diazoketones possessing an aromatic ring generally produce cycloheptatrienes *via* cyclopropanation of an aromatic π-bond.[3] The initially formed bicyclic intermediate **297** is thermally isomerized to the conjugated bicyclic cycloheptatriene (**298**).[153] Compound **297** can also rearrange to

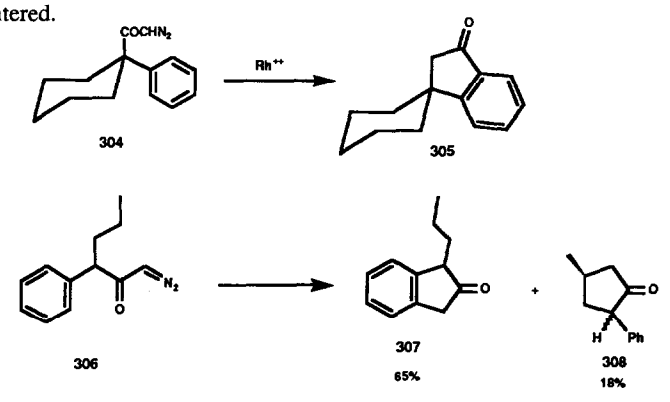
the 6,6-bicyclic system **299** via acid catalysis.[150] In certain cases it was possible to isolate the 5,7-bicyclic cycloheptatriene **297** in high yield.



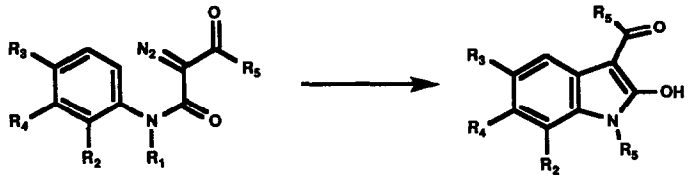
The reaction of α-diazoketone **300** with rhodium (II) acetate produced 6-methoxy tetralone **303** rather than the expected bicyclo[5.3.0]decatrienone **302**. This observation suggested that **303** is formed by direct insertion into an aromatic C-H bond.[150]



Synthesis of the 2-indanone system **305** is also thought to proceed *via* a direct insertion reaction.[154] Thus, treatment of cyclohexyl α-diazoketone **304** with rhodium (II) acetate in methylene chloride afforded 2-indanone **305** in 98% yield. No bicyclo[3.2.1]octanone, resulting from aliphatic C-H insertion, was observed. In systems where the α-position of the α-diazo ketone was monosubstituted (i.e. **306**), competitive aliphatic C-H insertion (**308**) was also encountered.



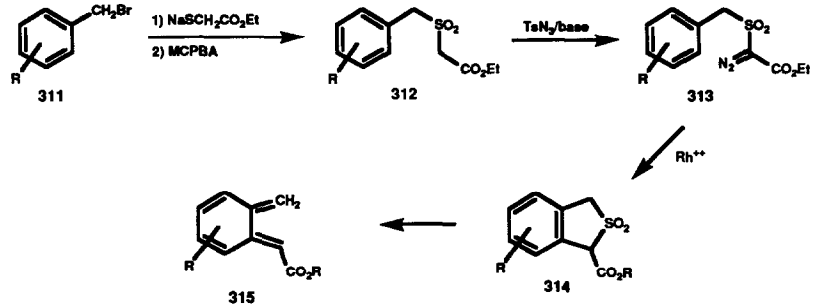
Aromatic insertion reactions were also used to prepare the 3-acetyl-2-hydroxyindole system **310**. Thus, treatment of α-diazoanilide **309** with rhodium (II) acetate in refluxing benzene gave the indole derivative **310** in high yield.[155]



309 **310**

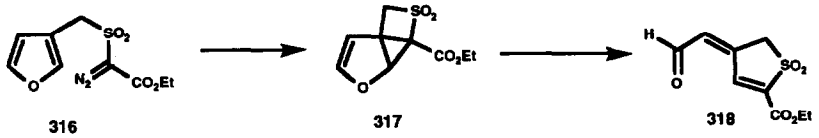
R_1	R_2	R_3	R_4	R_5	% Indole
CH_3	H	H	H	CH_3	77
CH_3	CH_3	OCH_3	H	CH_3	77
Ph	H	H	H	CH_3	87
$PhCH_2$	H	H	Cl	CH_3	>95
$PhCH_2$	H	H	NO_2	CH_3	0
H	H	H	H	CH_3	0

The use of reactive dienes such as **315** as intermediates for the synthesis of natural products has been effectively utilized by both Oppolzer[156] and Kametani.[157] More recently, Durst and coworkers developed a novel method for the generation of these reactive dienes by an intramolecular C-H aromatic insertion reaction of α-diazoketone **313** followed by extrusion of SO_2 upon thermolysis.[158] Thus, treatment of α-diazosulfonate ester **313**



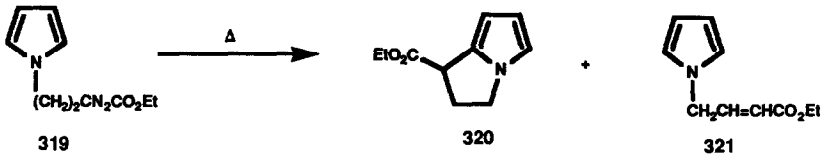
311 **312** **313** **314** **315**

with rhodium (II) acetate in methylene chloride afforded the 1,3-dihydrothiophene-2,2-dioxide **314** in good yield. Upon thermolysis, compound **314** extruded SO_2 to generate the transient diene **315**.[158] Attempts to extend the methodology to furan derivatives such as **316** failed. The major products isolated were derived by an initial cyclopropanation of the furan ring followed by a subsequent rearrangement to produce compound **318**.



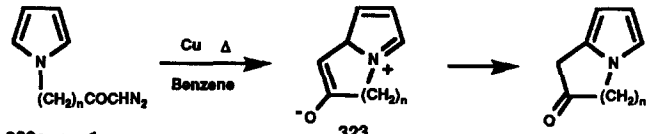
316 **317** **318**

The first example involving intramolecular attack of a α-keto carbenoid onto a pyrrole nucleus was reported in 1983 by Galeazzi and coworkers.[159] This reaction was not synthetically useful since the insertion product **320** was only formed in 35% yield, a significant quantity of the 1,2-hydrogen shift product **321** also being obtained.



319 320 321

More recently, Jefford and Johncock were able to circumvent the competing hydrogen shift pathway by modifying the structure of the diazo compound.[160] Heating a sample of pyrrole **322a** (or **322b**) in benzene in the presence of a copper catalyst afforded pyrrolizinone **324a** (or dihydroindolizinone **324b**) in near quantitative yield. The initially formed carbenoid adds to the α-position of the pyrrole since this corresponds to the most nucleophilic position. The resulting zwitterion **323** then rearranges *via* a proton shift.

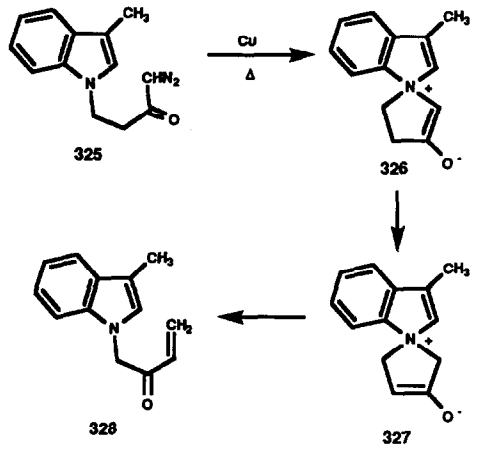


322a; n = 1
322b; n = 2

323

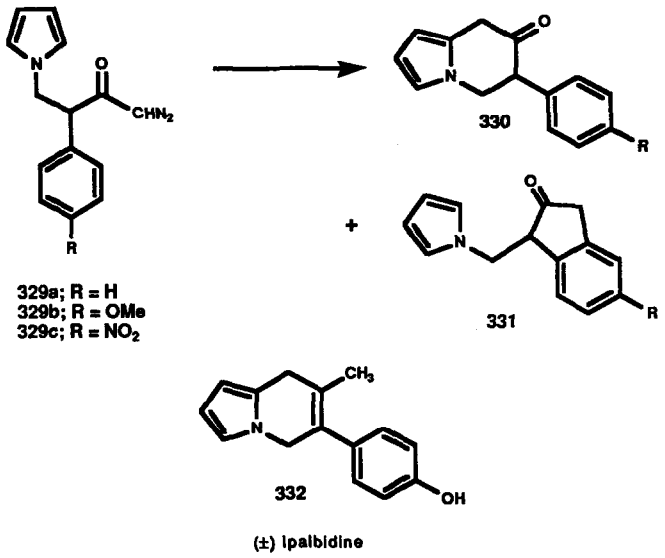
324a; n = 1
324b; n = 2

The same reaction was carried out with indole **325** but only a low yield of the C-H insertion product was obtained. The failure of **325** to cyclize was attributed to the diminished nucleophilic character at the α-position of the indole nucleus.[161] Instead of cyclizing, the indole nitrogen attacked the carbenoid to give zwitterion **326**. Isomerization and cleavage finally generated the unsaturated ketone **328**.

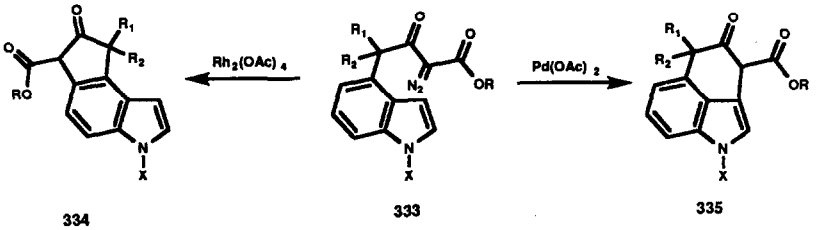


325 **326** **327** **328**

Efforts to exploit this methodology for the synthesis of alkaloids such as *ipalbidine* (**332**) led to the observation that insertion into a pyrrole ring is favored over insertion into a phenyl ring.[162] Thus, treatment of α-diazoketone **329a** (R=H) with rhodium (II) acetate produced a 6:1 mixture of indolizinone **330a** and indanone **331a**. The p-methoxy derivative **329b** produced a 3.5:1 mixture of **330b** and **331b**, whereas the p-nitro compound **329c** afforded indolizinone **330c** as the exclusive product. The change in product distribution is more or less what one would expect on the basis of electronic factors.

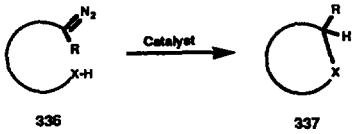


The hapalindole family of alkaloids was prepared in high yield using an intramolecular indole C-H insertion reaction.[163] When copper(acac)$_2$ was used as the catalyst, tricyclic compound **334** was formed in 20% yield. This material results from insertion of the carbenoid into the 5-position of the indole ring. Switching the catalyst to rhodium (II) acetate still afforded the undesired adduct **334**, but in much higher yield (89%). Interestingly, palladium (II) acetate in methanol gave the desired compound **335** in 71% yield. The mechanism involved in the palladium catalyzed reaction was suggested to proceed via a zwitterionic intermediate which is favored by polar solvents and results in cyclization at the 3-position of the indole. The rhodium catalyzed reaction prefers to take place via a five-membered transition state.



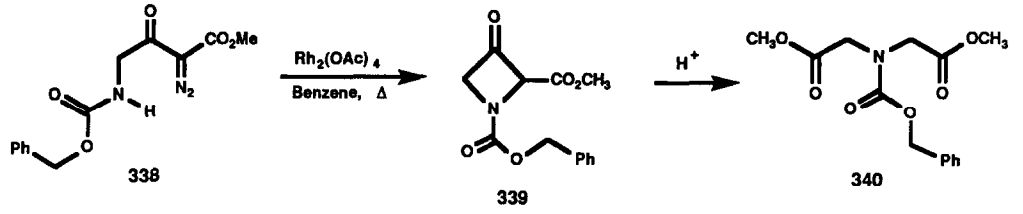
C. Hetero-Hydrogen Atom Insertions

Insertion into heteroatom-hydrogen bonds is also known to occur with various carbenoids. Thus, intramolecular insertion into OH, NH and SH bonds occurs readily and results in the formation of novel heterocycles from various diazo precursors.



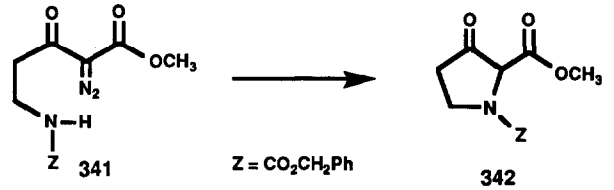
A variety of catalysts are capable of promoting the X-H insertion reaction, but the most efficient ones are rhodium (II) carboxylates. Rapaport and coworkers elegantly demonstrated that the rhodium (II) acetate catalyzed carbenoid insertion reaction represents a mild, efficient, and regiospecific method for the construction of numerous heterocycles.[164]

The rhodium acetate catalyzed cyclization of diazo amide **338** produced 3-oxoazetidine **339** in quantitative yield. Attempts to chromatograph **339** resulted in the isolation of **340** via an acid catalyzed ring opening promoted by silica gel.



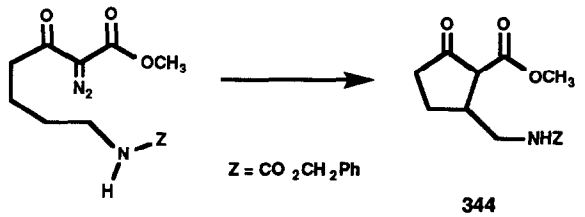
338 339 340

Reaction of **341** under identical conditions afforded 2-carboxy-3-oxo-pyrrolidine (**342**) in quantitative yield. Increasing the tether length by an additional methylene unit gave both five- and six-membered rings whose yields were dependent upon the nature of the catalyst used.



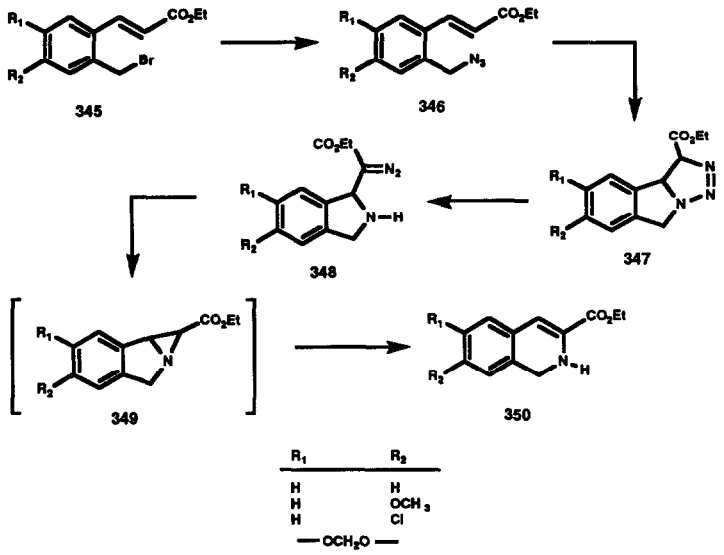
341 342

Heating a sample of diazo ketoester **343** in benzene with 2 mol % of rhodium (II) acetate gave cyclopentanone **344** as the only isolable product in 39% yield. In this case, neither azacycloheptanone nor any six-membered ring C-H insertion product were observed.

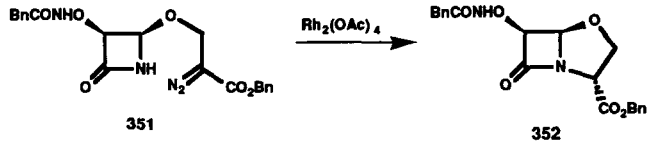


343 344

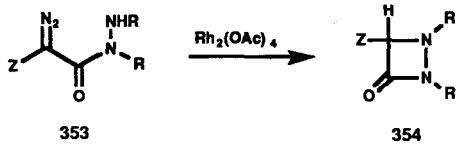
The N-H carbenoid insertion reaction was used by Sha for the synthesis of 1,2-dihydroisoquinoline **350**.[165] Treatment of bromide **345** with sodium azide gave **346** which readily underwent intramolecular 1,3-dipolar cycloaddition. Rearrangement of the resulting cycloadduct **347** on silica gel afforded diazo compound **348**. Decomposition of **348** in benzene at room temperature gave 1,2-dihydroisoquinoline **350** in 66% yield. This compound was claimed to be derived from the initially formed aziridine **349**.



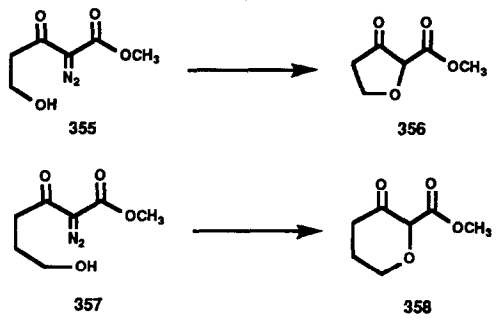
One of the more important applications of the intramolecular N-H insertion reaction involves the construction of β-lactam antibiotics. The first example was described in 1978 and involved the catalytic cyclization of α-diazoester **351** to oxapenam **352** using rhodium (II) acetate.[166] This reaction has become the method of choice for synthesizing many types of bicyclic β-lactams (carbapenam, oxapenam, carbacephem, and oxacephem systems) from diazocarbonyl substituted 2-azetidinones.[167]



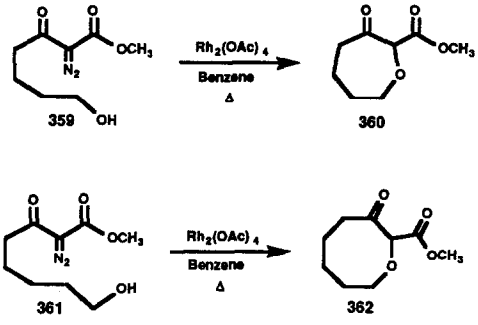
In an analogous fashion, the synthesis of 1,2-diazetidinones of the type **354** made use of a N-H carbenoid insertion reaction. Diazo hydrazide **353** afforded aza-β-lactam **354** in good yield upon treatment with catalytic rhodium (II) acetate.



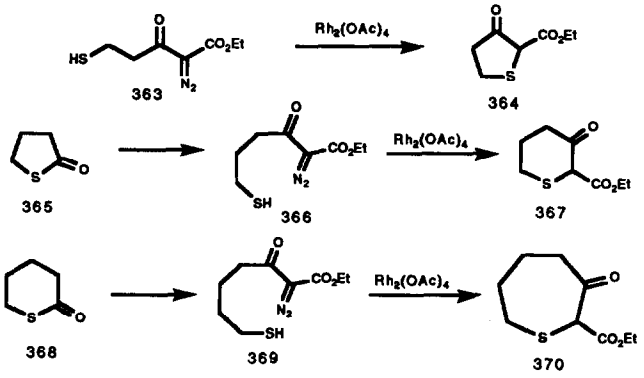
The preparation of α-alkoxyketones from the bimolecular reaction of α-diazo carbonyl compounds and alcohols is well established.[3] Several research groups have demonstrated that the intramolecular counterpart represents a viable approach toward the synthesis of cyclic ethers.[164,168]



Moody and coworkers showed that seven membered ring ethers were formed in excellent yields and eight membered rings could also be obtained, but in lower yield.[169] Although O-H bonds are thermodynamically stronger than C-H bonds, competing C-H insertion processes were not encountered.



Examples of intramolecular S-H insertion reactions are also known. α-Diazoketo mercaptan **363** produced thioether **364** in 73% yield,[164] while the six- and seven-membered ring analogues **367** and **370** were formed in 35% yield.[168] Most rhodium (II) acetate catalyzed reactions possess an emerald green color, but in the case of the sulfur systems, the solution was deep red, suggesting coordination of sulfur with some site on the rhodium catalyst. This may, in part, be responsible for the diminished yields with these systems.[164]



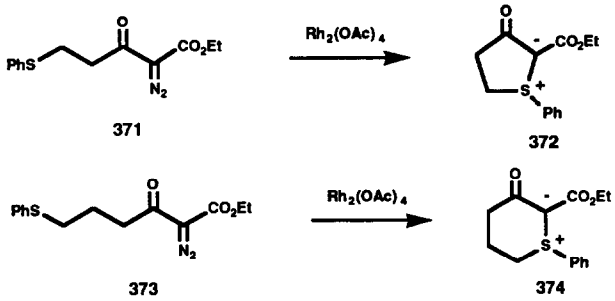
V. Intramolecular Ylide Formation

Singlet carbenes or carbenoids can function as Lewis acids by interacting with a pair of nonbonding electrons contributed by a Lewis base.[8] 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. In recent years a widespread upsurge of activity in the application of ylides to new synthetic transformations has occurred .[170] This research has also stimulated interest in the use of carbenes and carbenoids as reactive intermediates for ylide generation, with a diverse range of chemistry already surfacing.

A. Sulfonium Ylides

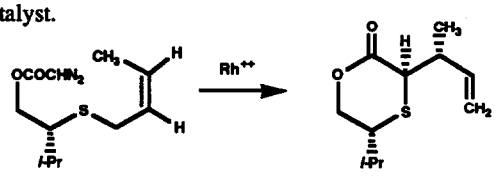
The chemistry of sulfur ylides has been the subject of extensive investigation, largely because of the synthetic ease in making stable molecules of this kind and because of the interesting rearrangements which they often undergo.[171] These ylides are becoming increasingly useful in synthetic chemistry and evidence also exists for their involvement in biochemical processes.[172] A large 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. 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.

Cyclic sulfonium ylides, resulting from intramolecular sulfide attack on a tethered carbenoid species, have been reported.[173] 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 diazosulfides **371** and **373** with a catalytic amount of rhodium (II) acetate gives the five- and six-membered cyclic ylides **372** and **374**, respectively. Extension of the tether to four methylene units allows for the formation of the seven membered cyclic ylide in 45% yield. In this case, however, C-H insertion was a competing process producing cyclopentanone in 16% yield. Efforts to form larger rings only resulted in C-H insertion products.



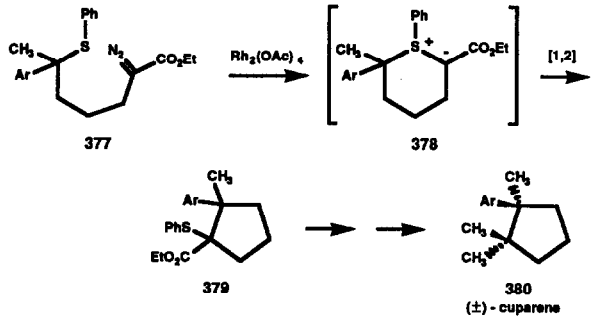
The 2,3-sigmatropic rearrangement of allylsulfonium ylides generated by the addition of a carbene onto an allyl sulfide has been extensively studied.[174] A thioxanone based 2,3-sigmatropic rearrangement strategy has been used by Kurth and coworkers for the synthesis of Cβ-chiral pent-4-enoic acid.[175] 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-diazoester **375** produced the four possible thioxones. The major isomer (**376**) was formed

with 78% diastereoselectivity. Slightly improved diastereoselectivity was observed using hexarhodium hexadecacarbonyl as the catalyst.



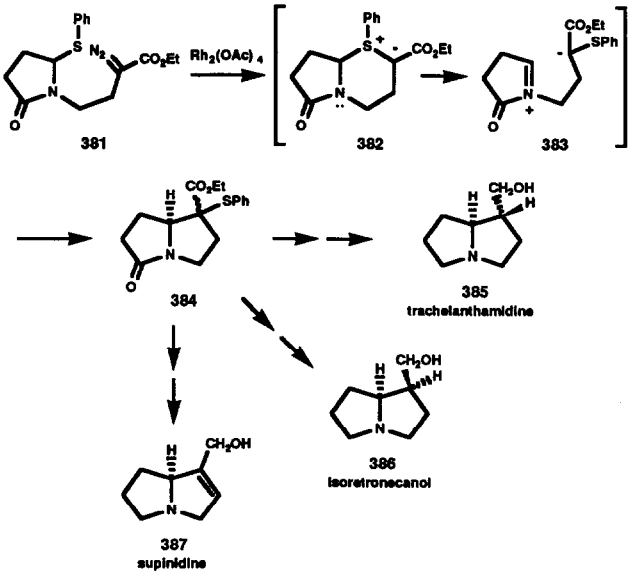
375 376

The key step in the Kametani approach to the aromatic sesquiterpene (±)-cuparene (**380**), consisted of an intramolecular carbenoid displacement reaction of a benzyl sulfide derivative.[176] Treatment of diazoketone **377** with a catalytic amount of rhodium (II) acetate in refluxing benzene gave arylcyclopentane **379**. This result was rationalized by the formation of sulfonium ylide **378** followed by a 1,2-ring contraction. Cyclopentane **379** 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.



377 378 379 380 (±)-cuparene

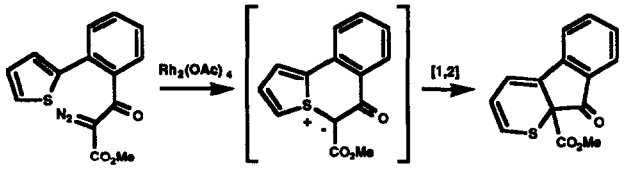
This same stratagy was also used for the synthesis of several pyrrolizidine alkaloids.[177] Treatment of diazoketone **381** with a catalytic amount of rhodium (II) acetate in refluxing benzene produced amide **384** in 55%



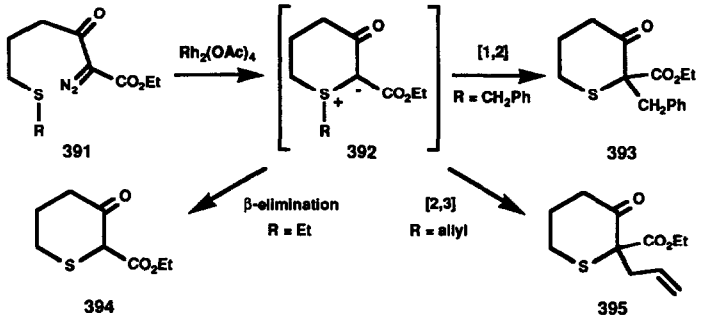
381 382 383 384 385 trachelanthamidine 386 isoretronecanol 387 supinidine

yield.[177] The formation of this material is consistent with a mechanism involving addition of the carbenoid onto the sulfur atom to form sulfonium ylide **382** which then fragments to give iminium ion **383**. Cyclization of this species then afforded the observed product. Subsequent modification of structure **384** allowed for the synthesis of three pyrrolizidine alkaloids; (±)-trachelanthamidine (**385**), (±)-isoretronecanol (**386**), and (±)-supinidine (**387**) to be realized. This intramolecular carbenoid displacement approach should be applicable to the synthesis of other naturally occuring necine bases.

Only a few carbenes have been known to react with thiophenes to give sulfur ylides.[178,179] In an attempt to isolate the aromatic thiophenium ylide **389**, α-diazoketone **388** was treated with catalytic rhodium (II) acetate in benzene.[180] None of the expected ylide **389** could be isolated. Instead, the major product isolated was **390** resulting from a Steven's rearrangement of ylide **389**. The inability to isolate sulfur ylide **389** was somewhat surprising, considering that Porter and co-workers were able to isolate a related sulfonium ylide from the reaction of thiophene with a rhodium carbenoid.[178,179]

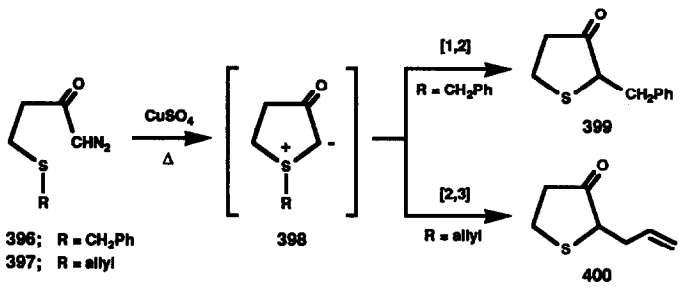


The intramolecular variant of the sulfide-carbene reaction frequently results in products arising from rearrangement of non-isolable cyclic sulfonium ylides. One example where a stable cyclic ylide is formed has been reported by Moody and Taylor.[181] Reaction of diazosulfide **391** (R = benzyl or ethyl) with rhodium (II) acetate in refluxing benzene produced the stable cyclic ylide **392**. Thermolysis of the benzyl sulfonium ylide **392** resulted in a 1,2-Stevens type benzyl shift to give thiopyran **393**. Heating the ethyl sulfonium ylide **392** in xylene produced thiopyran **394**. Formation of this material is consistent with loss of ethylene *via* a β-elimination reaction. The S-allyl sulfonium ylide **392** could not be isolated due to its propensity to undergo a 2,3-sigmatropic rearrangement producing thiopyran **395**.

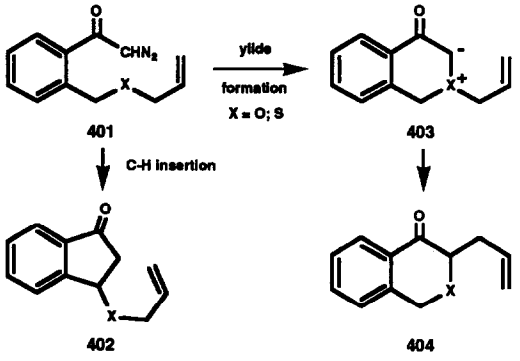


Analogous results were encountered from carbenes generated from 4-benzyl and 4-allylthio-1-diazobutan-2-ones (**396** and **397**).[182] The copper (II) sulfate catalyzed decomposition of **396** resulted in the formation of cyclic ylide **398** (R = benzyl) which subsequently underwent a Steven's 1,2-shift of the benzyl group to ultimately yield thiolanone **399** in 51% yield. Reaction of 4-allylthio-1-diazobutan-2-one (**397**) under identical conditions afforded

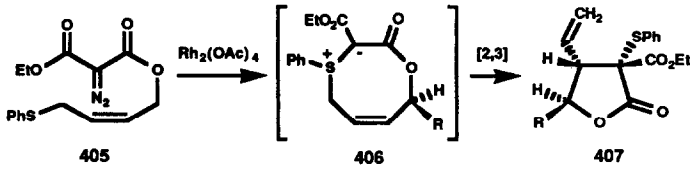
thiolanone **400** in 77% yield. Formation of this material is consistent with a mechanism involving intramolecular electrophilic addition of the carbenoid onto the sulfur atom to generate the cyclic sulfonium ylide **398** (R = allyl), which then undergoes a 2,3-sigmatropic rearrangement giving the observed product.



Metal catalyzed reactions of diazo compounds with a broad selection of allylic substrates results in products derived from 2,3-sigmatropic rearrangement of intermediate allylic ylides. A related process also occurs upon treatment of diazo compounds of type **401** (X=O) with rhodium (II) acetate. In this case, a 1:1 mixture of two compounds corresponding to C-H insertion (**402**) and ylide rearrangement (**404**) were isolated. In order to assess the significance of the heteroatom to the product distribution, the Rh(II) catalyzed reaction of the thio substituted diazo ketone (X=S) was examined.[183] In this case, the ratio of ylide formation to C-H insertion was 9:1, in marked contrast to the 1:1 ratio obtained from the oxygen system. This suggests 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.

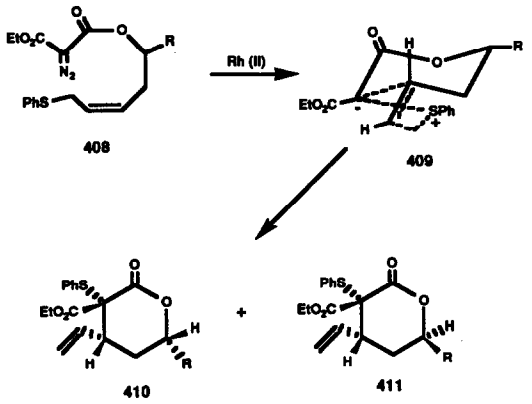


The stereoselective synthesis of contiguously substituted butyrolactones based on the cyclic allylsulfonium ylide rearrangement has been reported by Yoshikoshi and coworkers.[184] α-Diazomalonates of Z-4-phenylthio-2-buten-1-ol homologues stereoselectively provide γ-alkyl-α-ethoxycarbonyl-α-phenylthio-β-vinylbutyrolactones

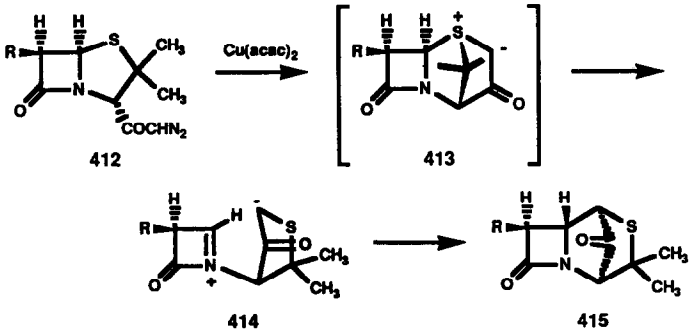


by 2,3-sigmatropic rearrangement of a cyclic sulfonium ylide which was generated intramolecularly. For example, treatment of diazomalonate **405** with a catalytic amount of rhodium (II) acetate in refluxing benzene gave butyrolactone **407** in 70% yield. The stereochemistry of the final product demonstrates that an alkyl group (R) prefers to orient itself in the equatorial position in the transition state of the rearrangement reaction.

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.[185] Treatment of the α-diazomalonate **408** with rhodium (II) acetate stereoselectively provided a 4:1 mixture of substituted valerolactones **410** and **411** 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 **410** is understandable if one considers the most favorable conformation (i.e. **409**) for the transition state of the rearrangement.



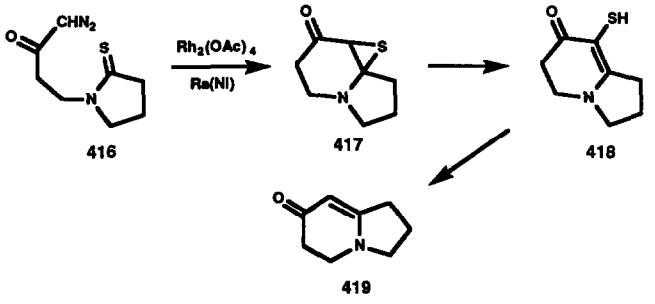
Treatment of the penicillin-derived diazoketone **412** with a catalytic amount of copper (II) acetylacetonate in refluxing benzene gave tricyclic ketone **415** as a single stereoisomer.[186-188] It was suggested that compound **415** was formed from the strained sulfonium ylide **413**. This species undergoes cleavage of the C-S bond which is promoted by participation of the lone pair of electrons on the azetidinone nitrogen atom giving zwitterion **414**. Final 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 **414** presumably due to conformational factors.[188]



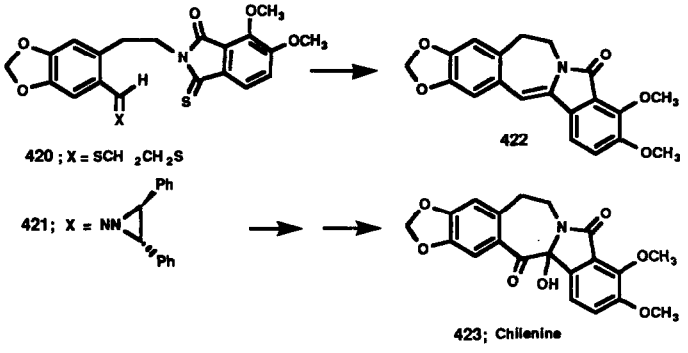
B. Thiocarbonyl Ylides

Thiocarbonyl ylides have been the subject of much interest in recent years due to their potential 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. 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 coworkers serve to adumbrate the utility of thiocarbonyl ylides for the synthesis of a variety of alkaloids.[189-192]

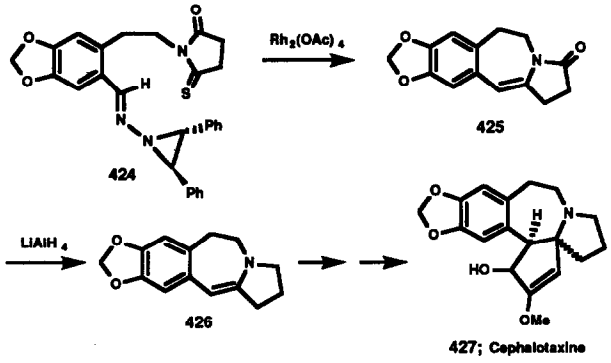
One example involves the annulation of diazomethyl vinyl ketone with a variety of secondary thiolactams to give heterocycles such as **416**. This diazoketone afforded **419** upon treatment with rhodium (II) acetate in refluxing benzene followed by Raney nickel desulfurization.[189] The intermediate involved in the conversion of **416** to **419** prior to treatment with Raney nickel was identified as ene thiol **418**. In this case the initially formed thiocarbonyl ylide intermediate cyclizes to episulfide **417** which undergoes subsequent isomerization to produce 418.



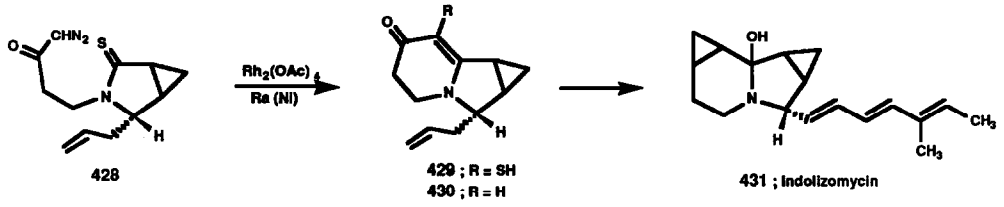
A key step in the total synthesis of the isoindolobenzazepine alkaloid *chilenine* **423** was the transition metal catalyzed reductive coupling of a dithiolane (or 2,3-diphenyl-N-aziridinohydrazone) with an unsymmetrical dimethoxyphthalimide.[190] Heating **420** in the presence of two equivalents of tungsten hexacarbonyl effected the reductive cyclization of the dithiolane-monothiophthalimide to provide enamide **422** in modest yield. A more efficient method to prepare **422** involved the addition of hydrazone **421** to a refluxing suspension of rhodium (II) acetate in toluene. Under these conditions, hydrazone **421** 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 422.



In an effort to expand the scope of this method to include pyrrolobenzazepine structures related to *cephalotaxine* **427**, Danishefsky investigated the hydrolytic succinoylation and subsequent reductive ring closure of several substituted dihydroisoquinolines.[191] In the formal synthesis of *cephalotaxine* **427**, Weinreb's[193] key intermediate **426** was formed by the addition of hydrazone **424** to a refluxing suspension of rhodium (II) acetate in toluene. This resulted in the formation of enamide **425** which was further reduced with lithium aluminum hydride to give **426**.



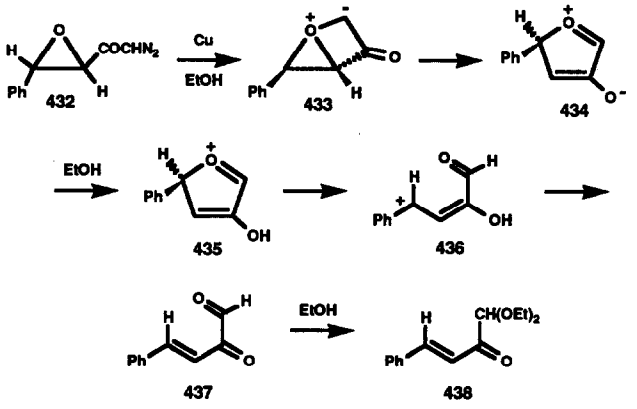
Application of this newly developed lactam annulation methodology has also been applied to the synthesis of *indolizomycin* (**431**).[192] Treatment of thioamide **428** with rhodium (II) acetate in benzene under reflux afforded a crude product which was directly treated with Raney nickel to give dihydropyridone **430**. This material was eventually taken on to the natural product. The key step in the conversion of **428** to **430** involved the intermediacy of a thiocarbonyl ylide dipole.



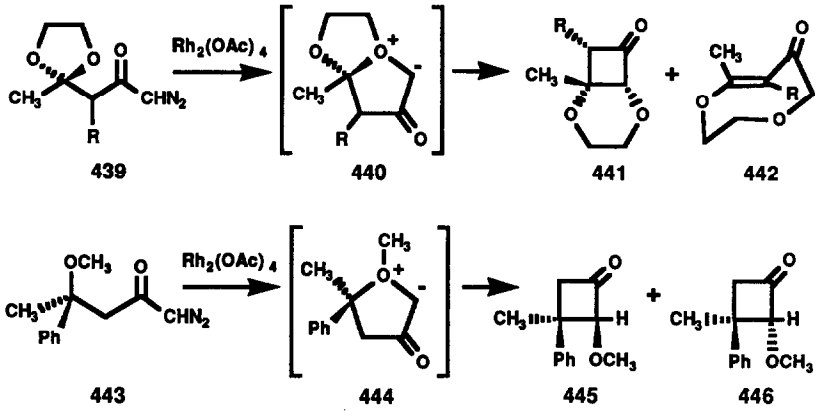
C. Oxonium Ylides

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 Steven's rearrangement, β-hydride elimination, and [2,3]-sigmatropic reorganization. One of the earliest examples of intramolecular oxonium ylide formation involves the reaction of α,β-epoxy diazomethyl ketones with activated copper powder or copper sulfate in hydroxylic solvents to produce alkene oxoacetals in good yields.[194] Thus, treatment of diazoketone **432** with activated copper in refluxing ethanol gave dialkoxybutenone **438** 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 **433**. Release of strain and subsequent ring opening produces acetal **438**. Both the *cis* and *trans* epoxides lead to the same product (i.e. **438**) when treated with copper sulfate in methanol. This stereochemical result was explained by invoking a stepwise non-

synchronous solvolysis of the initial ring opened zwitterion **434**. Protonation of **434** by methanol produces **435** which then opens to cation **436** which ultimately gives **438**.

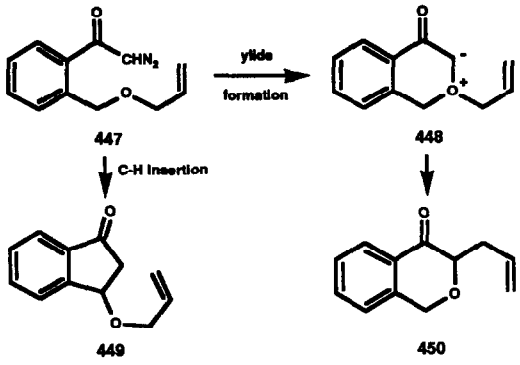


Roskamp and Johnson[195] have investigated the synthetic utility of oxonium ylides. When diazoketone **439** was treated with rhodium (II) acetate in benzene at room temperature, two compounds were isolated and identified as structures **441** and **442**. These products are consistent with a mechanism involving formation of a carbenoid species which is captured by an oxygen atom of the ethylene ketal to produce the transient oxonium ylide **440**. Subsequent rearrangement gives the observed products. Similarly, treatment of diazoketone **443** with rhodium (II) acetate gave oxygen ylide **444** which rearranged to cyclobutanones **445** and **446**. 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.

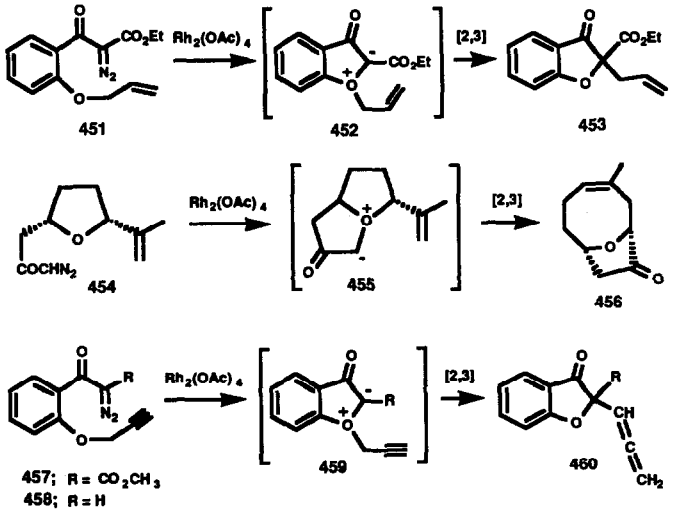


The intramolecular generation of allylic oxonium ylides and their subsequent [2,3]-sigmatropic rearrangement represents an excellent method for producing a variety of interesting and useful oxygen heterocycles. For example, when diazoketone **447** was treated with rhodium (II) acetate in benzene at room temperature, 3-allyl-2-isochroman-4-one (**450**) and 2,3-dihydro-3-(2-propenyloxy)-1H-inden-1-one (**449**) were formed in 43% and 35% yield, respectively.[184] Structure **450** is consistent with carbenoid generation followed by addition onto the neighboring oxygen atom to produce oxonium ylide **448** which then undergoes a [2,3]-sigmatropic rearrangement.

Indenone **449** 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.

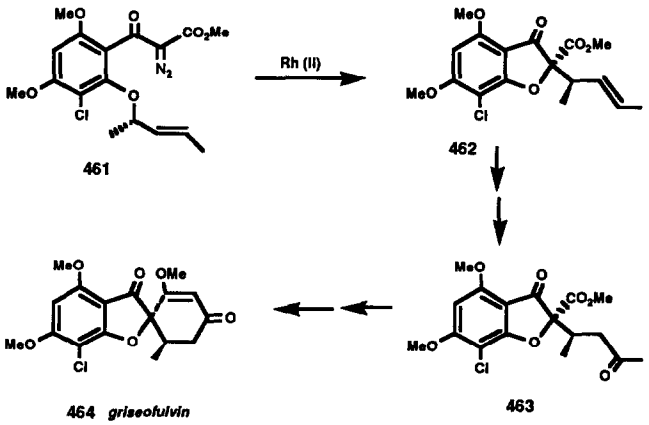


A further extension of this methodology has been developed by Pirrung and Werner to synthesize novel five, six-, and eight-membered oxygen heterocycles.[196] Treatment of diazoketone **451** with rhodium (II) acetate in benzene at room temperature produced benzofuranone **453** in excellent yield. When diazoketone **454** was treated in a similar fashion, the eight-membered ring oxygen heterocycle **456** was obtained. This ring expanion clearly illustrates the preference of ylide **455** to undergo the symmetry-allowed [2,3]-sigmatropic rearrangement over the symmetry-forbidden [1,2]-process. Another interesting example involves the reaction of diazoketone **457** in the presence of rhodium (II) acetate catalyst to give allene **460** in 92% yield. It should be noted that when diazoketone **458** 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.



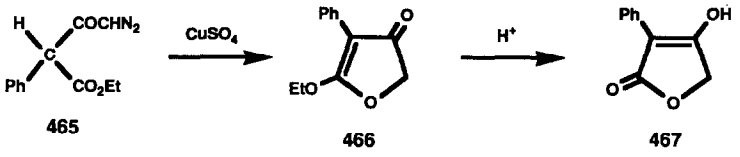
More recently, Pirrung has convincingly demonstrated that the intramolecular generation and 2,3-sigmatropic rearrangement of oxonium ylides represents a synthetically useful approach for the preparation of (+)-*griseofulvin*

(464).[197] Decomposition of **461** using rhodium pivalate as the catalyst in refluxing benzene provided the sigmatropically rearranged product **462** in 62% yield. The synthesis was completed by conversion of **462** to methyl ketone **463**, which in racemic form had already been converted to *griseofulvin*.[198] The stereochemistry of the 2,3-sigmatropic shift involved in the conversion of **461** to **462** can be understood in terms of a transition state model that resembles an oxabicyclo[3.3.0]octane ring system with the methyl group located on the convex face.



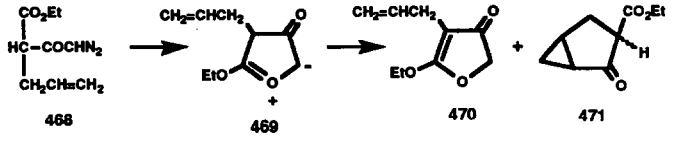
D. Carbonyl Ylides

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.[199-203] One of the first examples of intramolecular addition of a carbenoid onto a neighboring carbonyl group was described by Bien and Gillon[204]. Intramolecular attack of the metallo-carbenoid derived from **465** onto the nearby ester oxygen produced a carbonyl ylide intermediate which underwent a subsequent proton transfer to afford 3-furanone **466** as well as 4-hydroxy-3-phenyl-2(5H)furan-one (**467**). The formation of furanone **467** can be attributed to hydrolysis of furanone **466** during workup. In fact, furanone **466** was converted into **467** in 75% yield when stirred overnight in the presence of ether and aqueous hydrochloric acid.



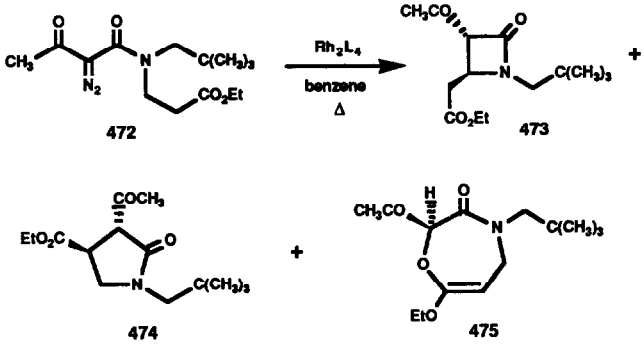
The transition metal-catalyzed decomposition of 2-allyl-4-diazoacetoacetate (**468**) produces a metal carbenoid which cyclizes onto the neighboring carbonyl oxygen to form carbonyl ylide **469**. This reactive species then undergoes proton loss to produce **470** in 58% yield. A competitive path also encountered involves carbenoid attack on the olefin to give ethyl 2-oxobicyclo[3.1.0]hexane-3-carboxylate (**471**) in 10% yield.[205] 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 using palladium catalysts of various types. However, rhodium (II) acetate or copper (I)-phosphite complexes strongly favor ylide formation which ultimately produces

dihydrofuranone **470**. Thermal decomposition of **468** also gives the same dihydrofuranone **470**. The product distribution data suggests 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. Initial catalyst-olefin coordination prior to carbenoid formation was considered to be the preferred path for the palladium catalysts. Whereas Pd(II)-olefin complexation[206] is well established, Rh(II)-olefin complexes are rare and unstable. Consequently, cyclopropanation would be expected to be favored with the palladium catalysts.



468 **469** **470** **471**

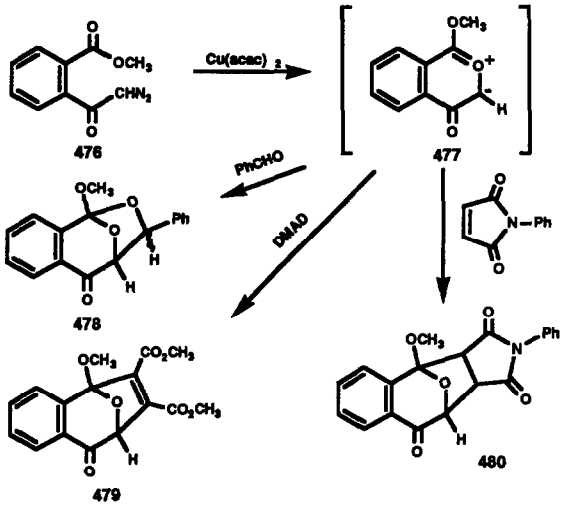
Doyle and coworkers have reported a new methodology for the synthesis of β-lactam compounds through intramolecular C-H insertion initiated by the rhodium (II) acetate catalyzed decomposition of N-alkyl diazoacetoacetamides.[207,208] Products **473** and **474** were produced by C-H insertions of the rhodium carbenoid derived from diazoacetamide **472**. In addition to these compounds, heterocycle **475** 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 **475** 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.



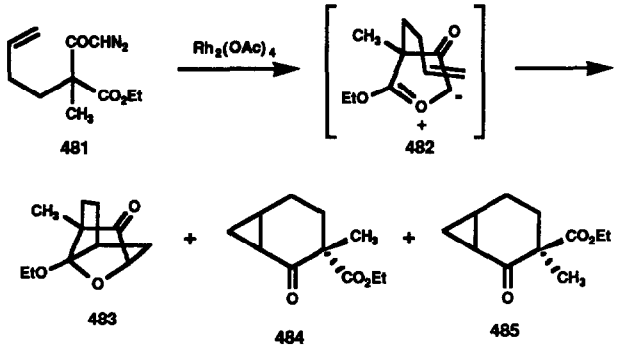
472 **473** **474** **475**

In recent years it has been amply demonstrated that the intramolecular carbenoid-carbonyl cyclization reaction represents one of the most effective methods for generating carbonyl ylides. Ibata and coworkers[209] 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 (**476**) with a catalytic amount of copper acetylacetonate. Evolution of nitrogen followed by carbonyl ylide formation generates a reactive dipole which can be trapped by

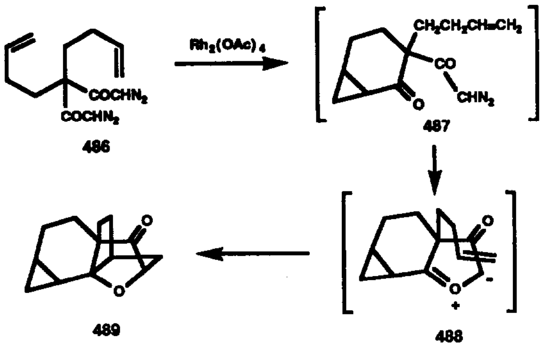
dipolarophiles such as benzaldehyde, dimethyl acetylenedicarboxylate, or N-phenylmaleimide to give cycloadducts **478**, **479**, and **480**, respectively. Cycloadditions using the benzopyrylium oxide ylide **477** have been extensively studied by Ibata and his coworkers.[209]



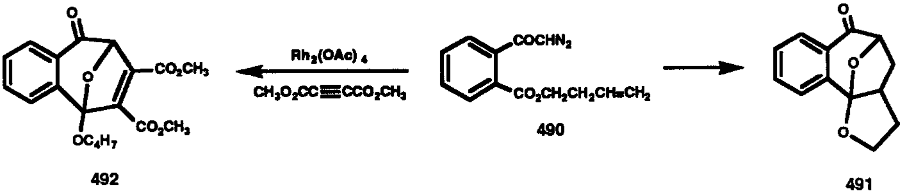
The tandem cyclization-cycloaddition methodology was further extended by the intramolecular trapping of the carbonyl ylide dipole with a C-C double bond suitably placed within the molecule. Bien and coworkers[210] reported on the transition metal catalyzed decomposition of diazoketone **481** to give 8-ethoxy-1-methyl-9-oxatricyclo[3.2.1.1]nonan-2-one (**483**) as the major product together with lesser quantities of **484** and **485**. This result is consistent with the formation of a five membered cyclic carbonyl ylide which is followed by intramolecular trapping by the tethered olefin.



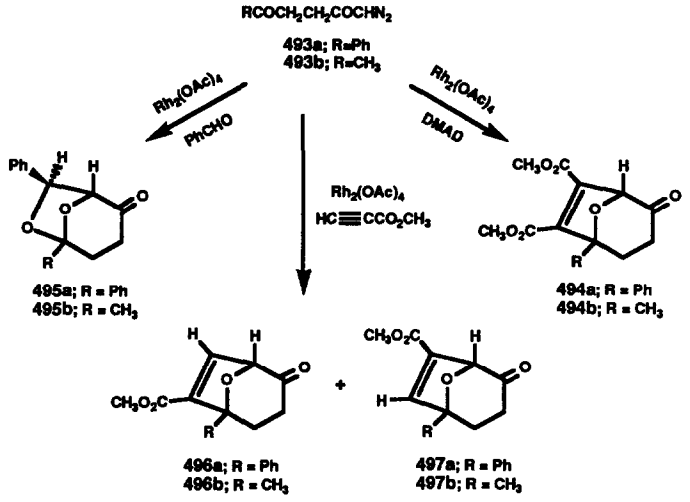
These same workers have also studied the catalytic decomposition of *bis*-diazoketone **486**.[210] The formation of cycloadduct **489** represents a unique case in which two diazoketone moieties in the same molecule, under the influence of the same catalyst, react in different ways. One of the diazo groups undergoes addition to the double bond to give bicyclo[4.1.0]hexane **487** which subsequently cyclizes to generate the carbonyl ylide intermediate **488**. Intramolecular trapping of this ylide ultimately affords the isolated product **489**. The structure of **489** was unequivocally established by single crystal X-ray crystallographic analysis.



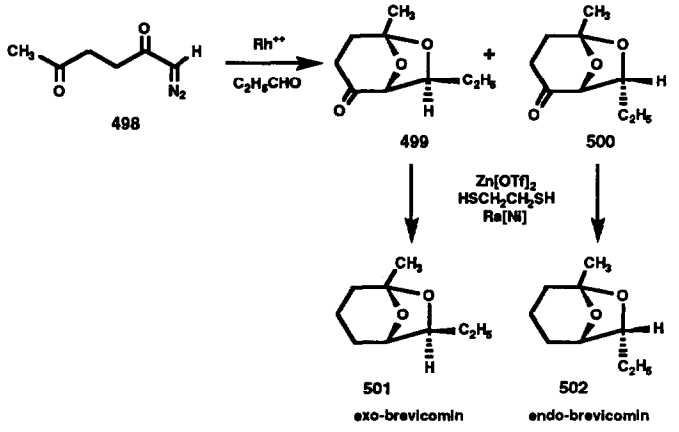
An attractive feature of the above tandem cyclization-cycloaddition process is the opportunity to control the stereochemistry of the product at several different centers. The resulting product represents a highly functionalized rigid bicyclic system that is amenable to subsequent synthetic elaboration. Padwa and coworkers have examined this tandem cyclization-cycloaddition sequence in some detail. Treatment of *o*-alkyl-2-enoxycarbonyl-α-diazoacetophenone **490** 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 **491** in 87% yield.[211,212] When the reaction was carried out in the presence of dimethyl acetylenedicarboxylate, the only product obtained corresponded to the bimolecular dipolar cycloadduct **492**. In this case, the stabilized carbonyl ylide prefers to cycloadd with the activated external dipolarophile instead of reacting with the unactivated internal π-bond.



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 **493** was studied in order to test the geometric and electronic requirements of dipole formation.[213,214] 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. Diazoketone **493** was treated with rhodium (II) acetate in the presence of various dipolarophiles. When dimethyl acetylenedicarboxylate was used as the trapping agent, cycloadduct **494** was produced in excellent yield. In the presence of benzaldehyde, only one regioisomer was formed (i.e. **495**). The reaction of **493a** with methyl propiolate afforded cycloadduct **496a** whereas the cycloaddition of **497b** with the same alkyne gave rise to a 4:1 mixture of two regioisomers (**496b** and **497b**) 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.[215]

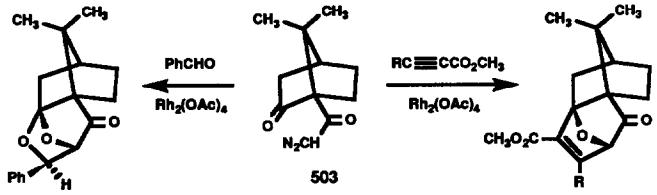


This methodology has been applied to the synthesis of *exo* - and *endo-brevicomin*.[216] The *exo* and *endo* isomers of *brevicomin* (**501** and **502**) are exuded by the female Western Pine Beetle and the *exo* isomer is known to be a key component of the aggregation pheromone of this destructive pest.[217,218] Thus, treatment of 1-diazo-2,5-hexanedione (**498**) 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* (**499**) and *endo* (**500**) isomers. The isomers were separated by silica gel chromatography and were subsequently carried on to *exo*- and *endo*- (**501** and **502**) in good yield.



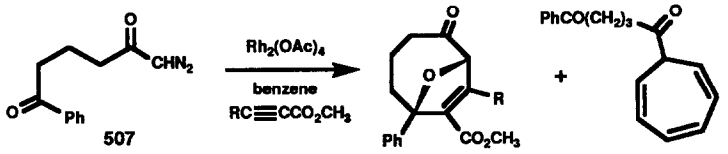
The primary spatial requirement for carbonyl ylide formation is that the distance between the two reacting centers should be sufficiently close so that effective overlap of the lone pair of electrons on the carbonyl group with the metallocarbenoid center can occur. The effect that variation in the spatial proximity between the carbonyl group and the diazoketone 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 have involved the formation of a six membered ring carbonyl ylide intermediate. Diazoalkanediones which lead to five and seven-membered ylides have also been examined.[219]

Treatment of diazoketone **503** with a catalytic amount of rhodium (II) acetate at 25°C in benzene with dimethyl acetylenedicarboxylate afforded cycloadduct **504** in 85% yield.[219] The cycloaddition reaction proceeded with complete diastereofacial selectivity with approach of the dipolarophile from the α-face. Similar treatment of **503** with methyl propiolate produced cycloadduct **505** in 72% isolated yield. The tandem cyclization-cycloaddition reaction was also carried out in the presence of benzaldehyde to give the bicyclic ketal **506** 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.



506 **503** **504; R = CO_2CH_3** **505; R = H**

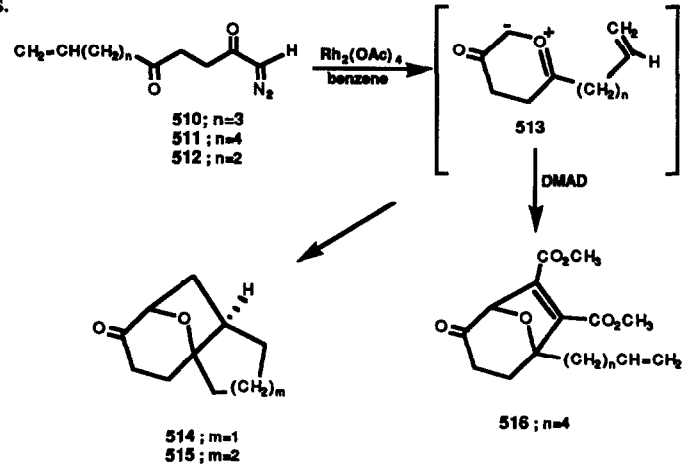
When the connecting chain contains three methylene units, the formation of a seven membered ring carbonyl ylide intermediate was expected.[219] Indeed, the rhodium (II) catalyzed reaction of 1-diazo-6-phenyl-2,6-hexanedione (**507**) in benzene using dimethyl acetylenedicarboxylate (or methyl propiolate) afforded a 2:1 mixture of products. The major product corresponded to the expected cycloadduct **508** (45%) whereas the minor component was identified as cycloheptatriene **509** (22%). This material was 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 indicated that extending the tether to three methylene groups sufficiently retarded the rate of intramolecular cyclization so as to allow the bimolecular reaction with benzene to occur.



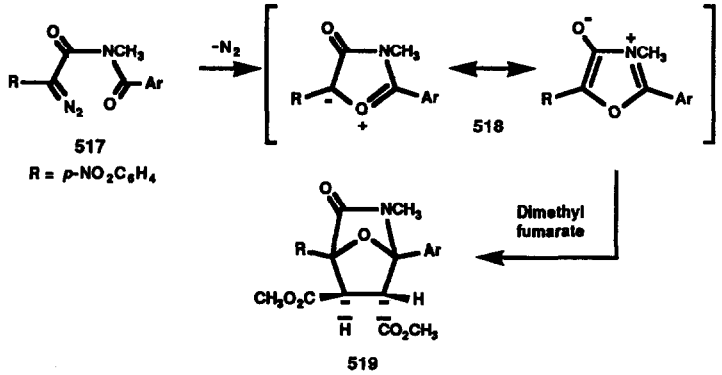
507 **508; R = CO_2CH_3** **509**

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. Diazoketones tethered to the carbonyl group by three methylene units were shown to cyclize most efficiently. Thus, when diazoketone **510** was treated with rhodium (II) acetate in the presence of dimethyl acetylenedicarboxylate, cycloadduct **514** was the only product formed.[214] The intramolecular trapping reaction occurs at such a fast rate that the bimolecular cycloaddition reaction cannot compete with it. The homologous diazoketone **511** was also treated with catalytic rhodium (II) acetate in benzene at 25°C producing cycloadduct **515** in 50% yield. In this case, the carbonyl ylide could be readily trapped with dimethyl acetylenedicarboxylate giving the bimolecular cycloadduct **516** 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. Diazoketone **512**, which contained only two methylene units in the tether, produced none of the internal cycloadduct. Clearly the

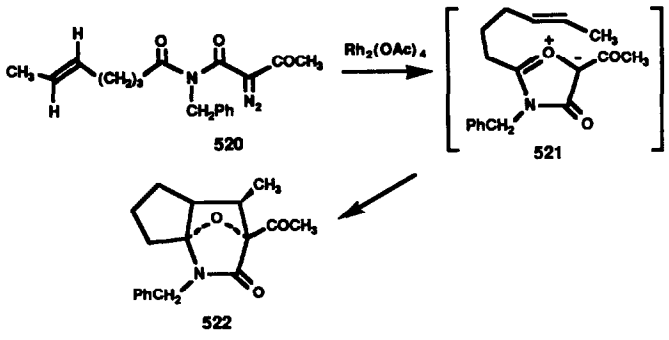
intramolecular trapping of carbonyl ylides by tethered olefins occurs best when the tether contains three or four methylene units. Internal cycloaddition does not occur when the tether contains less than three or more than four methylene carbons.



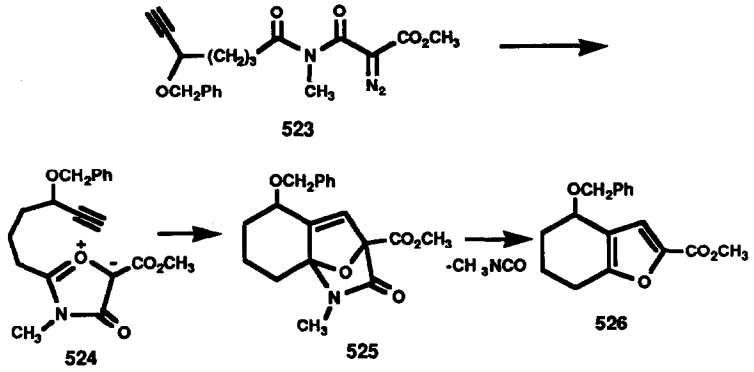
Although carbonyl ylides have been postulated as intermediates in many reactions, very few of these dipoles have actually been isolated and characterized.[203] One of the earliest examples involving the isolation of a stable carbonyl ylide was reported by Ibata and Hamaguchi in 1974.[220] Diazoamide **517** 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 (**518**) in 85% yield as a red crystalline solid, which was stable in air for several weeks. Mesoionic oxazolium ylides such as **518** 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 **519** in only a few minutes in quantitative yield.



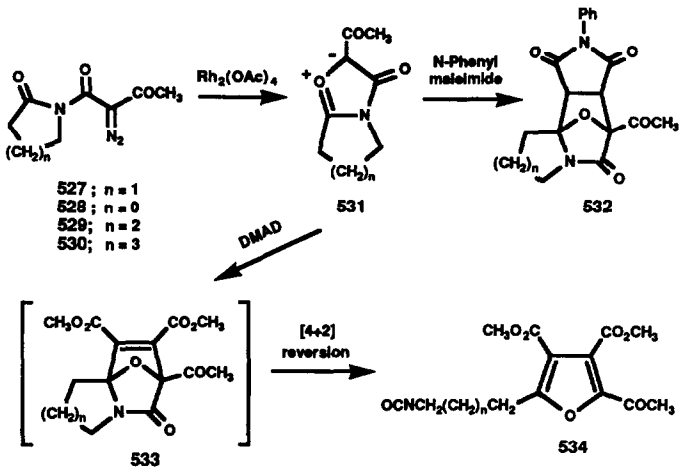
Intramolecular cycloadditions of isomünchnones, formed by the rhodium (II) acetate decomposition of N-diazoacetato(acetyl)alkenylamides, have been realized by Maier and coworkers.[221] A solution of diazoamide **520** in toluene was added dropwise to a refluxing mixture of rhodium (II) acetate in toluene producing cycloadduct **522** in 91% yield. The intermediate isomünchnone **521** was not isolated in this case. The relative stereochemistry of cycloadduct **522** 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 double bond.



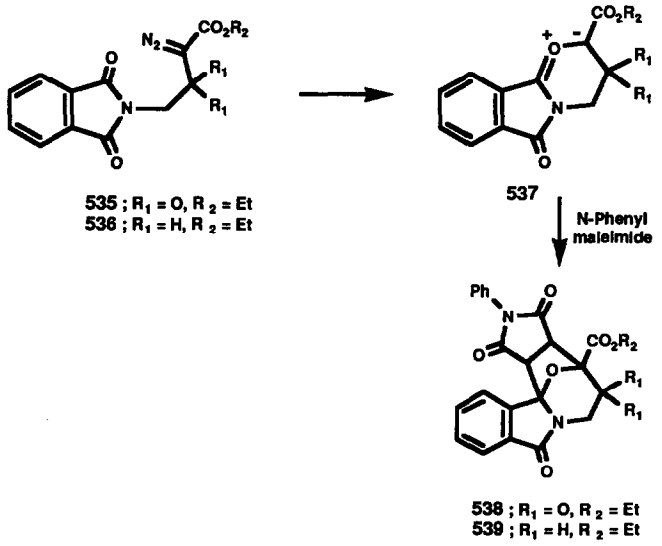
The cycloadducts derived from the intramolecular cycloaddition reactions of acetylenic isomünchnones fragment spontaneously under the reaction conditions to afford annulated furans.[222] Thus, treatment of acetylenic diazoamide **523** under the same conditions as used above, produced 4,5,6,7-tetrahydrobenzofuran **526** in 60% yield. This result was interpreted in terms of carbonyl ylide formation (**524**) followed by 1,3-dipolar cycloaddition across the tethered acetylene to give cycloadduct **525** which then undergoes a subsequent cycloreversion reaction to give furan **526**.



An analogous isomünchnone/alkyne internal cycloaddition-fragmentation process was also reported by Doyle and Padwa.[208,223] Treatment of diazoimide **527** (n=1) with rhodium (II) acetate at 80°C in benzene produced an isomünchnone dipole **531**. 1,3-Dipolar cycloaddition of this species with dimethyl acetylenedicarboxylate gave cycloadduct **533** which subsequently fragments *via* a retro Diels-Alder reaction into furan **534** in 85% yield. Trapping of dipole **531** with N-phenylmaleimide gave cycloadduct **532** 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 (**528**; n=0) (61%) and enlarged to a six (**529**; n=2) (85%) and a seven (**530**; n=3) (75%) membered ring. 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 using acyclic amides.

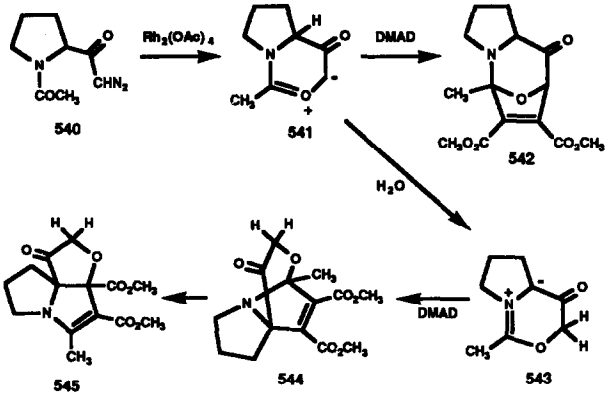


Extending the length of the tether by one methylene unit gave rise to a six membered ring carbonyl ylide which was not stabilized by any isomünchnone type delocalization.[208,223] Thus, treatment of diazophthalimidoester **535** with rhodium (II) acetate in refluxing benzene in the presence of N-phenylmaleimide afforded cycloadduct **538** in 87% yield. Similar treatment of the less activated diazo phthalimidoester **536** with rhodium (II) octanoate at 25°C in the presence of N-phenylmaleimide gave the related cycloadduct **539** which is derived from dipole **537**.

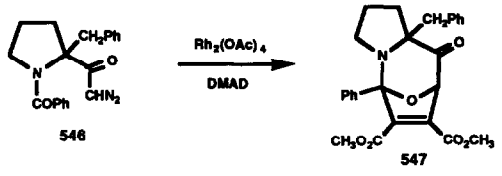


A novel cyclization process was uncovered during an examination of the reaction of (S)-1-acetyl-2-(1-diazoacetyl)pyrrolidine (**540**) with 1.5 equiv. of dimethyl acetylenedicarboxylate in the presence of a catalytic quantity of rhodium (II) acetate. Very little (<10%) of the expected carbonyl ylide derived cycloadduct (i.e. **542**) was obtained.[224] Instead, the major product (90%) corresponded to structure **545**. A mechanism that rationalizes the formation of this product involves generation of the expected carbonyl ylide dipole **541** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. Isomerization of **541** to the thermo-

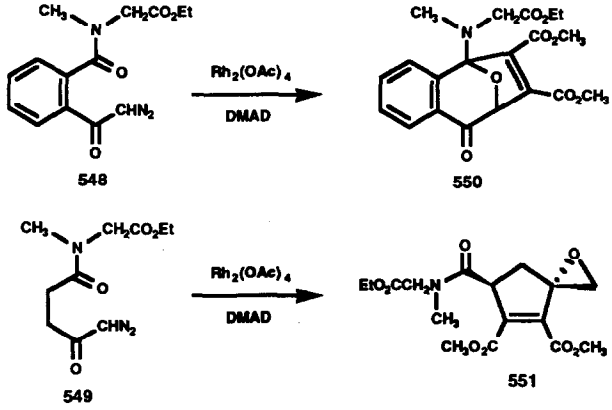
dynamically more stable azomethine ylide **543** occurred *via* proton exchange with a small amount of water that was present in the reaction mixture. 1,3-Dipolar cycloaddition with dimethyl acetylenedicarboxylate provided cycloadduct **544**, which underwent a subsequent 1,3-alkoxy shift to generate the tricyclic dihydropyrrolizine **545**. The overall process has been refered to as a "*dipole cascade*". MNDO calculations show that cyclic carbonyl ylides of type **541** have higher heats of formation (*ca.* 15 kcal/mol) than the corresponding azomethine ylide **543**. This energy difference is presumably responsible for the facility with which the dipole reorganization occurs.



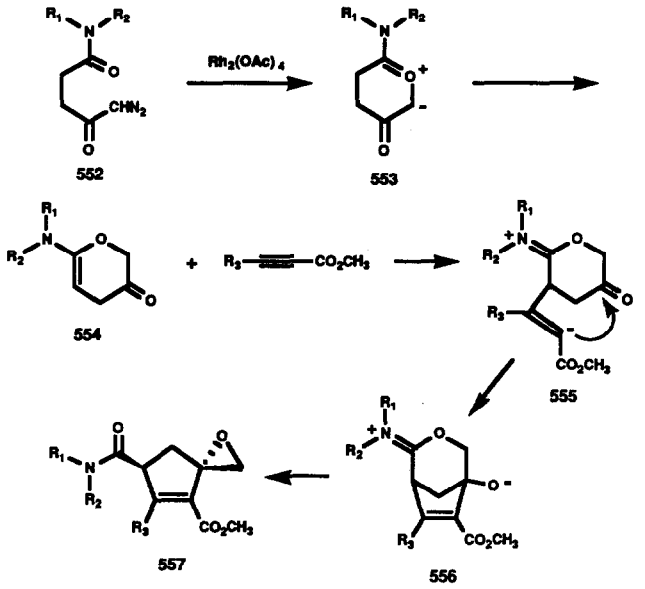
In the dipole cascade reaction, a proton must be removed from the α-carbon atom in order to generate the azomethine ylide. When the α-position of the pyrrolidine ring was blocked by a benzyl group, formation of the azomethine ylide dipole could not occur. In fact, treatment of diazoketone **546** with rhodium (II) acetate in the presence of dimethyl acetylenedicarboxylate afforded only the carbonyl ylide derived cycloadduct **547** in 95% yield.[224]



In the case of α-diazo ketoamide **548**, the carbonyl ylide dipole is sufficiently stabilized *via* resonance to be trapped by dimethyl acetylenedicarboxylate to give cycloadduct **550** in 90% yield.[225] No signs of any material



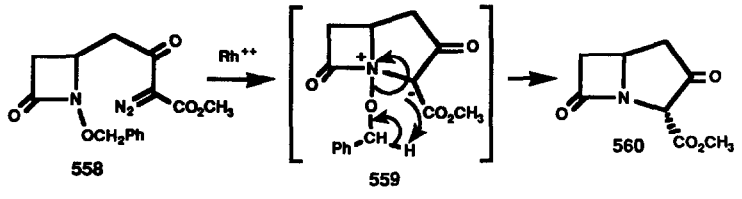
derived from azomethine ylide cycloaddition were observed. The closely related α-diazo ketoamide **549** was also examined. Most interestingly, treatment of **549** with rhodium (II) acetate in the presence of dimethyl acetylenedicarboxylate afforded cycloadduct **551** in 60% yield. The initial reaction involved generation of the expected carbonyl ylide dipole **553** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. This highly stabilized dipole did not readily undergo 1,3-dipolar cycloaddition but rather lost a proton to produce the cyclic ketene N,O-acetal **554**. This material reacted further with the activated π-bond of the dipolarophile to produce zwitterion **555**. The anionic portion of **555** then adds to the adjacent carbonyl group, affording a new zwitterionic intermediate **556**. Under anhydrous conditions, epoxide formation occurred with charge dissipation to give the observed cycloadduct **557**.



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.

E. Ammonium Ylides

Carbenoid generation of nitrogen ylides represent a useful alternative to the widely employed base-promoted methodology.[226] α-Diazoester **558** in the presence of catalytic rhodium (II) acetate was found to undergo an unprecedented ring closure to provide carbapenam **560**.[227] The mechanism suggested involves interaction of the initially generated carbenoid with the N-alkoxylactam electron lone pair to give intermediate **559**. 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 benzaldehyde. This unique rearrangement conveniently circumvents the well documented procedure for the debenzylation and N-O bond reduction of N-benzyloxy-β-lactams.[228]

The many structurally diverse and highly successful examples cited in this review clearly indicate that intramolecular carbenoid chemistry continues to be of value for the synthesis of carbocycles as well as heterocycles. It is a reasonable expectation that future years will see a continued evolution of the useful cyclization chemistry of transition metal carbenoids in organic synthesis.

Acknowledgement: AP would especially like to thank his student and postdoctoral collaborators whose names are listed with the references and without whom much of this report would not have been possible. Financial support for our program was provided by the National Cancer Institute (Grant No. CA-26751).

VI. REFERENCES

1. Doyle, M.P. *Acc. Chem. Res.* **1986**, *19*, 348; *Chem. Rev.* **1986**, *86*, 919.
2. Burke, S.D.; Grieco, P.A. *Org. React. (N.Y.)* **1979**, *26*, 361.
3. Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75.
4. Wulfman, D.S.; Linstrumelle, G.; Cooper, C.F. in "*The Chemistry of the Diazonium and Diazo Groups*", ed. Patai, S., Wiky, New York; **1978**, part 2, p 821.
5. Wulfman, D.S.; Poling, B. in "*Reactive Intermediates*"; Abramovitch, R.A. Ed.; Plenum: New York, **1980**; Vol 1, p 321.
6. Dave, V.; Warnhoff, E.W. *Org. React. (N.Y.)*, **1970**, *18*, 217.
7. Moody, C.J. *Organic Reaction Mechanisms*; Wiley Interscience; **1983**, Chapter 6.
8. Kirmse, W. Ed. *"Carbene Chemistry"*; Academic Press: New York, **1971**.
9. Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.
10. Demonceau, A.; Noels, A. F.; Hubert, A. J. *"Aspects of Homogeneous Catalysis"*Ugo, R., Ed.; Reidel, Dordrecht, **1988**, Vol. 6, 199.
11. Weygand, F.; Bestmann, H.J. *"Newer Methods of Preparative Organic Chemistry"*; Foerst, W., Ed.; Academic: New York, 1964; Vol. 3, p 451. Smith, A.B. *Tetrahedron* **1981**, *37*, 2407.
12. Stang, P. J. *Chem. Rev.* **1978**, *78*, 383.
13. Dumas, J.B. *Ann. Chim. Phys.* **1835**, *58*, 28.
14. Regnault, H.V. *Ann. Chim. Phys.* **1839**, *71*, 427.
15. Nef, J.U. *Ann.* **1897**, *298*, 202.
16. Staudinger, H.; Kupfer J., *Ber. Deut. Chem. Ges.* **1911**, *44*, 2197. Staudinger, H.; Endle, R. *Ber. Deut Chem. Ges.* **1913**, *46*, 1437. Staudinger, H.; Goldstein, J. *Ber. Deut Chem. Ges.* **1923**, *49*, 1916. Staudinger, H; Anthes, E.; Pfenninger, F. *Ber. Deut. Chem. Ges.*, **1916**, *49*, 1928.
17. Meerwein, H; Rathjen, H.; Werner, H. *Ber. Deut. Chem. Ges.* **1942**, *75*, 1610.
18. Doering, W.v.E; Knox, L.H. *J. Am. Chem. Soc.* **1956**, *78*, 4947. Doering, W.v.E.; Buttery, R.G.; Laughlin, R.G.; Chaudhun, N. *J. Am. Chem. Soc.* **1956**, *78*, 3224.
19. Regitz, M.; Mass, G. in"*Diazo Compounds: Properties and Synthesis*"; Academic Press, Orlando, Fl. 1986, p 185.
20. Ando, W. in "*The Chemistry of the Diazonium and Diazo Groups*"; Patai, S., Ed.; Wiley: New York, 1978, part 1, p 458.

21. Meier, H.; Zeller, K.P. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32.
22. Thorton, D.E.; Gosavi, P.K.; Strausz, O.P. *J. Am. Chem. Soc.* **1970**, *92*, 1768. Csizmadia, I.G.; Gunning, H.E.; Gosavi, R.K.; Strausz, O.P. *J. Am. Chem. Soc.* **1973**, *95*, 133. Strausz, O.P. *J. Chem. Phys.* **1977**, *67*, 3057. Novoa, J.; McDouall, J.J.W.; Robb, M.A. *J. Chem. Soc., Faraday Trans. 2* **1987**, *83*, 1629. Dewar, M.J.S.; Ramsden, C.A. *J. Chem. Soc., Chem. Commun.* **1973**, 688. Hopkinson, A.C. *J. Chem. Soc. Perkin Trans. 2* **1973**, 794. Csizmadia, I.G.; Font, J.; Strauz, O.P. *J. Am. Chem. Soc.* **1968**, *90*, 7360.
23. Kirmse, W.; Dietrich, H.; Backing, H.W. *Tetrahedron Lett.* **1967**, 1933.
24. Silberrad, O; Roy, C.S. *J. Chem. Soc.* **1906**, *89*, 179.
25. Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 5376.
26. Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5239.
27. Ratcliffe, R.W.; Salzmann, T.N.; Christensen, B.G. *Tetrahedron Lett.* **1980**, 31. Saltzmann, T.N.; Ratcliffe, R.W.; Christensen, B.G.; Bouffard, F.A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
28. Moser, W.R. *J. Am. Chem. Soc.* **1969**, *91*, 1135, 1141.
29. Salomon, R.G.; Kochi, J.K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.
30. Paulissen, R.; Hubert, A.J.; Teyssie, P. *Tetrahedron Lett.* **1972**, 1465.
31. Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A.J.; Teyssie, P. *Tetrahedron Lett.* **1973**, 2233.
32. Hubert, A.J.; Noles, A.F.; Anciaux, A.J.; Teyssie, P. *Synthesis*, **1976**, 600.
33. Doyle, M.P.; Griffin, J.H.; Bagheri, V.; Dorow, R.L. *Organometallics*, **1984**, *3*, 53.
34. Nakamura, A.; Koyama, T.; Otsuka, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 593.
35. Nakamura, A; Konishi, A.;Tsujitani, R.; Kudo, M.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3449.
36. Nakamura, A.; Konishi, A.; Tatsuno, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3443, 6544.
37. Tatsuno, Y.; Konishi, A.; Nakamura, A.; Otsuka, S. *J. Chem. Soc., Chem. Commun.* **1974**, 588.
38. Drago, R.S.; Long, J.R.; Cosmano, R. *Inorg. Chem.* **1982**, *21*, 2196.
39. Drago, R.S.; Long, J.R.; Cosmano, R. *Inorg. Chem.* **1981**, *20*, 2920
40. Drago, R.S.; Tanner, S.P.; Richman, R.M.; Long, J.R. *J. Am. Chem. Soc.* **1979**, *101*, 2897.
41. Charan, M.Y.; Zhu, T.P.; Lin, X.Q. Ahsan, M.Q.; Bear, J.L. Kadish, K.M. *Inorg. Chem.* **1984**, *23*, 4538. Bear, J.L.; Zhu, T.P.; Malinski, T.; Dennis, A.M.; Kadish, K.M *Inorg. Chem.* **1984**, *23*, 674. Deddins, A.M.; Korp, J.D.; Bernal, I.; Howard, R.A.; Bear, J.L. *Inorg. Chem.* **1983**, *22*, 1522. Duncan, J.; Malinski, T.; Zhu, T.P.; Hu, Z.S.; Kadish, K.M.; Bear, J.L. *J. Am. Chem. Soc.* **1982**, *104*, 5507. Kadish, K.M.; Lancon, D.; Dennis, A.M.; Bear, J.L. *Inorg. Chem.* **1982**, *21*, 2987. Dennis, A.M.; Howard, R. A.; Lancon, D.; Kadish, K.M.; Bear, J.L. *J. Chem. Soc., Chem. Commun.* **1982**, 339.
42. Doyle, M.P.; Dorow, R.L.; Buhro, W.E; Griffin, J.H.; Tamblyn, W.H.; Trudell, M.L. *Organometallics*, **1984**, 3, 44.
43. Doyle, M.P.; Tamblyn, W.H.; Buhro, W.E.; Dorow, R.L. *Tetrahedron Lett.* **1981**, *22*, 1783.
44. Doyle, M.P.; Tamblyn, W.H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094.
45. Callot, H.J.; Piechocki, C. *Tetrahedron Lett.* **1980**, *21*, 3489.
46. Callot, H.J.; Metz, F.; Piechocki, C. *Tetrahedron* **1982**, *38*, 2365.
47. Hoye, T.R.; Dinsmore, C.J.; Johnson, D.S.; Korkowski, P.F. *J. Org. Chem.* **1990**, *55*, 4518.
48. Anciaux, A.J.; Hubert, A.J.; Noels, A.F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695.
49. Salomon, R.G.; Kochi, J.K. *J. Chem. Soc., Chem. Commun.* **1972**, 559.
50. Salomon, R.G.; Koch, J.K. *J. Am. Chem. Soc.* **1973**, *95*, 1889.

51. Salomon, R.G.; Salomon, M.F.; Heyne, T.R. *J. Org. Chem.* **1975**, *40*, 756.
52. Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* **1961**, *650*, 1.
53. Hartley, F.R. *Chem. Rev.* **1973**, *73*, 163.
54. Block, T.F.; Fenske, R.F.; Casey, C.P. *J. Am. Chem. Soc.* **1976**, *98*, 441.
55. Doyle, M.P.; Wang, L.C.; Loh, K-L. *Tetrahedron Lett.* **1984**, *25*, 4087.
56. Anciaux, A.J.; Hubert, A.J.; Noels, A.F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695.
57. Felthouse, T.R. *Prog. Inorg. Chem.* **1982**, *29*, 73.
58. Cotton, F.A.; Walton, R.A. *"Multiple Bonds Between Metal Atoms"*; Wiley: New York, 1982; p 311.
59. Boyar, E.B.; Robinson, S.D. *Coord. Chem. Rev.* **1983**, *50*, 109.
60. Schurig, V.; Bear, J.L.; Zlatkis, A. *Chromatographia* **1972**, *5*, 301.
61. Doyle, M.P.; Colsman, M.R.; Chinn, M.S. *Inorg. Chem.* **1984**, *23*, 3684.
62. Doyle, M.P.; Mahapatro, S.N.; Caughey, A.C.; Chinn, M.S.; Colsman, M.R.; Harn, N.K.; Redwine, A.E. *Inorg.Chem.* **1987**, *26*, 3070.
63. Stork, G.; Ficini, J. *J. Am. Chem. Soc*, **1961**, *83*, 4678.
64. Reissig, H.U. in "*The Chemistry of the Cyclopropyl Group*", ed. Rappoport, Z. Wiley, New York, 1987, part 1 p 375.
65. Plattner, J.J.; Bhalerao, U.T.; Rapoport, H. *J. Am. Chem. Soc* **1969**, *91*, 4933. Mori, K.; Matsui, K. *Tetrahedron Lett.* **1969**, 4435. Bhalerao, U.T.; Plattner, J.J.; Rapoport, H. *J. Am. Chem. Soc* **1970**, *92*, 3429. Mori, K.; Matsui, K. *Tetrahedron Lett.* **1970**, 2801. Mandai, T.; Hara, K.; Kawada, M.; Nokami, J. *Tetrahedron, Lett.* **1983**, *24*, 1517.
66. Corey, E.J.; Achiwa, K. *Tetrahedron Lett.* **1969**, 1837. Mori, K.; Matsui, M. *Tetrahedron Lett.* **1969**, 2729. Coates, R.M.; Freidinger, R.M. *J. Chem. Soc., Chem. Commun.* **1969**, 1837. Vig, O.P. *J. Indian Chem. Soc.* **1970**, *47*, 506.
67. Piers, E.; Britton, R.W.; Waal, W. de. *Can. J. Chem.* **1969**, *47*, 831.
68. Mori, K.; Ohki, O.; Kobayashi, A.; Matsui, M. *Tetrahedron*, **1970**, *26*, 2815.
69. Welch, S.C.; Wallers, R.L. *Synth. Commun* **1973**, *3*, 15.
70. Sundberg, R.J.; Baxter, E.W.; Pitts, W.J.; Ahmed-Schofield, R.; Nishiguchi, T. *J. Org. Chem.* **1988**, *53*, 5097.
71. Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5261. Warpehoski, M.A.; Gebhard, I.; Kelly, R.C.; Krueger, W.C.; Li, L.H; McGovern, J.P.; Prairie, M.D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590. Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y.-S.; Anathanarayan, T.P. *J. Am Chem. Soc.* **1987**, *109*, 2706. Kraus, G.A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 283. Moody, C.J.; Pass, M.; Rees, C.W.; Tojo, G. *J. Chem. Soc., Chem. Commun.* **1986**, 1062. Boger, D.L.; Coleman, R.S. *J. Am Chem. Soc.* **1988**, *110*, 1321.
72. Reingold, I.D.; Drake, J. *Tetrahedron Lett.* **1989**, *30*, 1921.
73. Pirrung, M. C.; Webster, N.J.G. *J. Org. Chem.* **1987**, *52*, 3603.
74. Wenkert, E.; Ceccherelli, P.; Curini, M.; Marcotullio, M.C. *J. Org. Chem.* **1986**, *51*, 738.
75. Sarkar, A.; Chatterjee, S.; Dutta, P.C. *Tetrahedron Lett.* **1976**, 4633.
76. Chatterjee, S. *Tetrahedron Lett.* **1979**, 3249. Chatterjee, S. *J. Chem. Soc., Chem. Commun.* **1979**, 620.
77. Dasgupta, S.K.; Sarama, A.S. *Tetrahedron Lett.* **1968**, 2983. Dasgupta, S.K.; Dasgupta, R.; Ghosh, S.R.; Ghatak, U.R. *J. Chem. Soc., Chem. Commun.* **1969**, 1253. Chakrabortly, P.N.; Dasgupta, R.; Dasgupta, S.K.; Ghosh, S.R.; Ghatak, U.R. *Tetrahedron*, **1972**, *28*, 4653. Becker, D.; Lowenthal, H.J.E. *Isr. J. Chem.* **1972**, *10*, 375. Dasgupta, S.K.; Sarma, A.S. *Tetrahedron*, **1973**, *29*, 309. Ghatak, U.R. Chakraborti, P.C.;

Ranu, B.C.; Sanyal, B. *J. Chem. Soc., Chem. Commun.* **1973**, 548.

78. Beames, D.J.; Mander, L.N. *J. Chem. Soc., Chem. Commun.* **1969**, 498. Mongrain, M.; Bélanger, A.; Deslongchamps, P. *Can. J. Chem.* **1970**, *48*, 3273. Beames, D.J.; Halleday, J.A.; Mander, L.N. *Aust. J. Chem.* **1972**, *25*, 137.
79. Mander, L.N.; Prager, R.H.; Turner, J.V. *Aust. J. Chem.* **1974**, *27*, 2645.
80. Stork, G.; Grieco, P.A. *J. Am. Chem. Soc.* **1969**, *91*, 2407. Stork, G.; Marx, M. *ibid.*, 2371. Stork, G.; Grieco, P.A. *Tetrahedron Lett.* **1971**, 1807.
81. Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
82. White, J.D.; Torii, S.; Nogami, J. *Tetrahedron Lett.* **1974**, 2879. White, H.D.; Ruppert, J.F.; Avery, M. A.; Torii, S.; Nokami, J. *J. Am. Chem. Soc.* **1981**, *103*, 1813.
83. McCurry Jr., P.M. *Tetrahedron Lett.* **1971**, 1845.
84. Tahara, A.; Shimagaki, M. ; Ohara, S.; Nakata, T. *Tetrahedron Lett.* **1973** 1701.
85. Danishefsky, S.; Mckee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 7711.
86. Vandewalle, M.; Callant, P.; DeWilde, H. *Tetrahedron*, **1981**, *37*, 2079.
87. Corey, E.J.; Myers, A.G. *Tetrahedron Lett.* **1984**, *25*, 3559.
88. NäF, U.; Hakanishi, K.; Endo, M. *Bot. Rev.***1975**, *41*, 315.
89. Ghatak, U.R.; Chakraborti, P.C. *J. Org. Chem.* **1979**, *44*, 4562.
90. Taber, D.F.; Saleh. S.A.; Korsmeyer, R.W. *J. Org. Chem.* **1980**, *45*, 4699.
91. Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, 685. Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta.*, **1988**, *71*, 1553. Lowenthal, R.E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, 6005. Evans, D.A.; Woerpel, K.A.; Hinman, M.M.; Nozaki, H.; Faul, M.M. *J. Am. Chem. Soc.* **1991**, *113*, 736. Nozaki, H.; Moriuti, S.; Takaya, H,; Noyori, R. *Tetrahedron Lett.* **1966**, 5239.
92. Doyle, M.P.; Brandes, B.D.; Kazala, A.P.; Pieters, R.J.; Jarstfer, M.B.; Watkins, L.M.; Eagle, C.T. *Tetrahedron Lett.* **1990**, 6613. Doyle, M.P.; Pieters, R.J.; Martin, S.F.; Austin, R.E.; Oalmann, C.J.; Muller,P. *J. Am. Chem. Soc.* **1991**, *113*, 1423.
93. Dauben, W.G.; Hendricks, R.T.; Luzzio, M.J.; Ng, H.P. *Tetrahedron Lett.* **1990**, *31*, 6969.
94. Pfaltz, A. "*Modern Synthetic Methods*" **1989**, *5*, 199.
95. Hudlicky, T.; Sheth, J.P.; Gee, V.; Barnvos, D. *Tetrahedron Lett.* **1979**, 4889. Hudlicky, T.; Koszyk, F.P.; Kutchan, T.M.; Sheth, J.P. *J. Org. Chem.* **1980**, *45*, 5020.
96. Hudlicky, T.; Bhaskar-Reddy, D.; Govindan, S.V.; Kulp, T.; Still, B.; Sheth. J.P. *J. Org. Chem.* **1983**, *48*, 3422.
97. Davies, H.M.L.; Oldenburg, C.E.M.; McAfee, M.J.; NOrdahl, J.G.; Henretta, J.P.; Romines, K.R. *Tetrahedron Lett.* **1988**, *29*, 975.
98. Davies, H.M.L.; Smith, H.D.; Korkor, O. *Tetrahedron Lett.* **1987**, *28*, 1853.
99. Davies, H.M.L.; Clark, D.M.; Smith, T.K. *Tetrahedron Lett.* **1985**, *26*, 5659. Davies, H.M.L.; Clark, D.M.; Alligood, O.B.; Eiband, G.R. *Tetrahedron*, **1987**, *43*, 4265.
100. Davies, H.M.L.; McAfee, M.J.; Oldenburg, C.F.M. *J. Org. Chem.* **1989**, *54*, 930.
101. This is in accord with literature precedent: Marino, J.P.; Kaneko, T. *Tetrahedron Lett.* **1973**, 3975. Marino, J.P.; Browne, L.J. *Tetrahedron Lett.* **1976**, 3245. Piers, E.; Bagakura, I.; Morton, H.E. *J. Org. Chem.* **1978**, *43*, 3630. Piers, E. Ruediger, E.H. *J. Chem. Soc., Chem. Commun.* **1979**, 166. Piers, E.; Jung, G.L; Mossk H. *Tetrahedron Lett.* **1984**, *25*, 3959. Piers, E.H.; Moss, N. *Tetrahedron Lett.* **1985**, *26*, 2735. Wender,

P.A.; Filosa, M.P. *J. Org. Chem.* **1976**, *41*, 3490.

102. Rhoads, S.J.; Raulinus, N.R. *Org. React.*, **1975**, *21*, 1. Piers, E.; Nagkura, I. *Tetrahedron Lett.* **1976**, 3237.
103. Adams, J.; Belley, M. *Tetrahedron Lett.* **1986**, *27*, 2075. Adams, J.; Frenette, R.; Belley, M.; Chibante, F.; Springer, J.P. *J. Am Chem. Soc.* **1987**, *109*, 5432.
104. Kennedy, M.; McKervey, M.A.; Maguire, A.R.; Tuladhar, S.M.; Twohig, M.F. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1047.
105. Duddeck, H.; Ferguson, G.; Kaitner, B.; Kennedy, M.; McKervery, M.A.; Maguire, A.R. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1055.
106. Pusino, A.; Saba, A.; Rosnati, V. *Tetrahedron*, **1986**, *42*, 4319. Chan, L.; Matlin, S.A. *Tetrahedron Lett.* **1981**, *22*, 4025. Ledon, H.; Linstrunelle, G.; Julia, S. *Bull. Soc. Chim. Fr.* **1973**, 2065.
107. Doyle, M. P.; Shanklin, M. S.; Pho, H.Q. *Tetrahedron Lett.* **1988**, *29*, 2639.
108. Padwa, A.; Wisnieff, T.J. *J. Org. Chem.* **1986**, *51*, 5036.
109. Adams, J.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 35. Wenkert, E.; Guo, M. Pizzo, R.; Ramachandran, K. *Helv. Chim. Acta.* **1987**, *70*, 1429. Wenkert, E.; Decorzant, R.; Näf, F. *Helv. Chim. Acta.* **1989**, *72*, 756.
110. Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299. Padwa, A.; Au, A. Owens, W. *J. Chem. Soc., Chem. Commun.* **1974**, 675.
111. Moss, R.A. *"Selective Organic Transformations"*; Thyagarajan, B.S., Ed.; Wiley: New York, 1970; Vol. 1, pp 35-88
112. Mykytka, J.P.; Jones, W.M. *J. Am. Chem. Soc.* **1975**, *97*, 5933.
113. Padwa, A.; Krumpe, K.E.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 2633. Padwa, A.; Chiacchio, U.; Garreau, Y.; Kassir, J.M.; Krumpe, K.E.; Schoffstall, A.M. *J. Org. Chem.* **1990**, *55*, 414. Padwa, A.; Krumpe, K.E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523.
114. Baird, M.S. *"Synthetic Application of Cyclopropenes, Topics in Current Chemistry"*; de Meijere, A., Ed.; Springer-Verlag; New York, 1988; Vol. 144, p 138. Halton, B.; Bansell, M.G. *"Cyclopropenes in the Chemistry of Cyclopropanes"*; Rappoport, Z., Edl; Wiley: New York, 1988; Vol. 2.
115. Padwa, A. *Acc. Chem. Res.* **1979**, *12*, 310. Al-Dulayymi, J.; Gaird, V.S.; Clegg, W. *Tetrahedron Lett.* **1988**, *29*, 6149. Petiniot, N.; Anciaux, A.J.; Noels, A.F.; Hubert, A.J.; Teyssie, P. *Tetrahedron Lett.* **1978**, 1239.
116. Padwa, A. *Org. Photochem.* **1979**, *4*, 261.
117. Doering, W.v.E.; Roth, W.R. *Tetrahedron*, **1963**, *19*, 715.
118. Hudlicky, T.; Natchuz, M. G.; Zingde, G. S. *J. Org. Chem.* **1987**, *52*, 4644.
119. Hoye, T.R.; Dinsmore, C.J.; Johnson, D.S.; Korkowski, P.F. *J. Org. Chem.* **1990**, *55*, 4518.
120. Binger, P.; Buch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. Binger, P.; Muller, P.; Benn, R.; Mynott, R. *Angew. Chem. Int. Ed. Engl* **1989**, *28*, 610.
121. Muller, P.; Pautex, N.; Doyle, M. P.; Bagheri, V. *Helv. Chim. Acta* **1991**, *73*, 1233.
122. Padwa, A. unpublished results.
123. Hoye, T.R.; Dinsmore, C.J. *J. Am Chem. Soc.* **1991**, *113*, 4343.
124. Hoye, T.R.; Dinsmore, C.J. *Tetrahedron Lett.* **1991**, 3755.
125. Padwa, A.; Austin, D. J.; Xu, S.L. *Tetrahedron Lett.* **1991**, 4103.
126. Padwa, A. *"Rearrangement in Ground and Excited States"*; Demayo, P., Ed.; Academic Press: New York, 1980; Vol. 3, p 501. Taylor, E.C.; Turchi, I. *J. Chem Rev.*, **1979**, *79*, 181. Huisgen, R. *Angew. Chem. Int.*

Ed. Engl., **1980**, *19*, 947.

127. Padwa, A.; Kinder, F.R. *Tetrahedron Lett.* **1990**, *31*, 6835. Padwa, A. Chiacchio, U., Gareau, Y.; Kassir, J. M.; Krumpe, K.E.; Schoffstall, A. M. *J. Org. Chem.* **1990**, *55*, 414.
128. Wenkert, E.; Davis, L.L.; Mylari, B.L.; Solomon, M.F.; da Silva, R.R.; Shulman, S.; Warnet, R.J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242.
129. Taber, D.F.; Petty, E.H. *J. Org. Chem.* **1982**, *47*, 4808. Taber, D.F.; Amedio Jr., J.C.; Sherrill, R.G. *J. Org. Chem.* **1986**, *51*, 3382. Taber, D.F.; Ruckle Jr., R.E. *Tetrahedron Lett.* **1985**, *26*, 3059. Taber, D.F.; Amedio Jr.; J.C.; Raman, K. *J. Org. Chem.* **1988**, *53*, 2984. Taber, D.F.; Hennessy, M.J.; Hoerner, R.S.; Raman, K.; Ruckle Jr, R.E.; Schuchardt, J.S. *"Catalysis of Organic Reactions"*, Blackburn, D.W., ed. Marcel Dekker: New York 1988, Ch. 4, p 43. Taber, D.F.; Ruckle Jr., R.E. *J. Am Chem. Soc.* **1986**, *108*, 7686.
130. Gilbert, J.C.; Giamalva, D.H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251.
131. Periana, R.A.; Bergman, R.G. *Organometallics*, **1984**, *3*, 508. Yang, G.K.; Bergman, R.G. *Organometallics*, **1985**, *4*, 129.
132. Jones, W.D.; Feher, F.J. *J. Am Chem. Soc.* **1985**, *107*, 620.
133. Cane, D.E. ; Thomas, P.J. *J. Am Chem. Soc.* **1984**, *106*, 1650.
134. Tsuji, J. Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475.
135. Taber, D.F.; Petty, E.H.; Raman, K. *J. Am Chem. Soc.* **1985**, *107*, 196.
136. Taber, D.F.; Schuchardt, J. L. *J. Am Chem. Soc.* **1985**, *107*, 5289.
137. Cane, D.E.; Thomas, P.J. *J. Am Chem. Soc.* **1984**, *106*, 5295.
138. Taber, D.F.; Raman, K.; Gaul, M.D. *J. Org. Chem.* **1987**, *52*, 28.
139. Ikegami, S.; Hasimoto, S.; Shinoda, T.; Shimada, Y.; Honda, T. *Tetrahedron Lett.* **1987**, *28*, 637.
140. Monteiro, H.J. *Tetrahedron Lett.* **1987**, *28*, 3459.
141. Monteiro, H.J. *Syn. Comm.*, **1987**, *17*, 983.
142. Corbel, B.; Hernot, D.; Haelters, H.; Sturtz, G. *Tetrahedron Lett.* **1987**, *28*, 6605.
143. Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.
144. Lee, E.; Jung, K.W.; Kim, Y.S. *Tetrahedron Lett.* **1990**, *31*, 1023.
145. Doyle, M.P.; Bagheri, V.; Pearson, M.M.; Edwards, J.D. *Tetrahedron Lett.* **1989**, *30*, 7001.
146. Doyle, M.P.; Shanklin, M.S. Oon, S.; Pho, H.Q.; van der Heide, F.R.; Veal, W.R. *J. Org. Chem.* **1988**, *53*, 3386.
147. Adams, J.; Poupart, M. Grenier, L.; Schallen, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749.
148. Agosta, W.C.; Wolff, S. *J. Org. Chem.* **1975**, *40*, 1027.
149. Chhanda, R.; Saha, B.; Ghatak, U.R. *Tetrahedron*, **1990**, *46*, 2857.
150. Kennedy, M.; McKervey, M.A.; Maguire, A.R.; Rous, G.H.P. *J. Chem. Soc., Chem. Commun.* **1990**, 361. McKervey, M.A.; Tuladhar, S.M.; Twohig, M.F. *J. Chem. Soc., Chem. Commun.* **1984**, 129.
151. Ikegami, S.; Shun-ichi, H.; Watanabe, N. *Tetrahedron Lett.* **1990**, 5173.
152. Doyle, M.P.; Ooveren, A.; Westrum, L.J.; Protopopova, M.N.; Clayton, T.W. *J. Am. Chem. Soc.* **1991**, *113*, 8982.
153. Constantino, A.; Linstrumelle, G.; Julia, S. *Bull. Soc. Chim. Fr.*, **1990**, 907, 912. Scott, L.T.; Minton, M.A.; Kirms, M.A. *J. Am. Chem. Soc.* **1980**, *102*, 6311.
154. Nakatani, K. *Tetrahedron Lett.* **1987**, *28*, 165.
155. Etkin, N.; Babu, S.D.; Fooks, C.J.; Durst, T. *J. Org. Chem.* **1990**, *55*, 1093. *see also* Doyle, M.P.; Shanklin,

M.S.; Pho, H.Q.; Mahapatro, S.N. *J. Org. Chem.* **1988**, *53*, 1017.
156. Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833.
157. Kametani, T.; Nemoto, H.; *Tetrahedron*, **1981**, *37*, 3.
158. Babu, S.D.; Hrytsak, M.D.; Durst, T. *Can. J. Chem.* **1989**, *67*, 1071.
159. Galeazzi, E.; Guzman, A.; Pinedo, A.; Saldaña, A.; Torre, D.; Muchowski, J.M. *Can. J. Chem.* **1983**, *61*, 454.
160. Jefford, C.W.; Johncock, W. *Helv. Chim. Acta.* **1983**, *66*, 2666.
161. Nanetkin, S.S.; Melnikov, N.N.; Bokarev, K.S. *Zh. Prikl. Khim (Leningrad)*, **1956**, *29*, 459.
162. Jefford, C.W.; Kubota, T.; Zaslona, A. *Helv. Chim. Acta.* **1986**, *69*, 2048. Jefford, C.W.; Zaslona, A. *Tetrahedron Lett.* **1985**, *26*, 6035.
163. Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479.
164. Moyer, M.P.; Feldman, P.L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.
165. Liu, J.M.; Young, J.J.; Li, Y.J.; Sha, C.K. *J. Org. Chem.* **1986**, *51*, 1120.
166. Cama, L.D.; Christensen, B.G. *Tetrahedron Lett.* **1978**, 4233.
167. Ratcliffe, R.W.; Salzman, T.N.; Christensen, B.G. *Tetrahedron Lett.* **1980**, *21*, 31. Kametani, T.; Honda, T.; Sasaki, J.; Terasawa, H.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1884.
168. Moody, J.C.; Taylor, R.J. *Tetrahedron Lett.* **1987**, *28*, 5351.
169. Moody, J.C.; Heslin, J.C.; Slawin, A.M.Z.; Williams, D.J. *Tetrahedron Lett.* **1986**, *27*, 1403.
170. Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.
171. Trost, B. M.; Melvin, L. S. "*Sulfur Ylides: Emerging Synthetic Intermediates*"; Academic Press, N. Y., 1975.
172. Huxtable, R. J. "*Biochemistry of Sulfur*", Plenum Press, New York, N.Y., 1986.
173. Davies, H. M. L.; Crisco, L. V. T. *Tetrahedron Lett.* **1987**, 371.
174. Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.
175. Kurth, M. J.; Tahir, S. H.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 2286.
176. Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc. Chem. Commun.* **1985**, 1324.
177. Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc. Chem. Commun.* **1986**, 651.
178. Gillespie, R. J.; Porter, A. E. A.; Willmott, W. E. *J. Chem. Soc. Chem. Commun.* **1978**, 85. Gillespie, R. J.; Porter, A. E. A. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2624.
179. Murray-Rust, P.; McManus, J.; Lennon, S. P.; Porter, A. E.A.; Rechka, J. A. *J. Chem. Soc. Perkin Trans. I* **1984**, 713.
180. Storflor, H.; Skramstad, J.; Nordenson, S. *J. Chem. Soc. Chem. Commun.* **1984**, 208.
181. Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1988**, *29*, 6005; *Tetrahedron* **1990**, *46*, 6501.
182. Kondo, K.; Ojima, I. *J. Chem. Soc. Chem. Commun.* **1972**, 860.
183. Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817.
184. Kido, F.; Sinha, S. C.; Abiko, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1989**, *30*, 1575.
185. Kido, F.; Sinha, S. C.; Abiko, T.; Watanabe, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 418.
186. Ernest, I. *Tetrahedron* **1977**, *33*, 547.
187. Ponsford, R. J. *Tetrahedron Lett.* **1980**, 2451.
188. Mak, C. P.; Baumann, K.; Mayerl, F.; Mayerl, C.; Fliri, H. *Heterocycles* **1982**, *19*, 1647.
189. Fang, F. G.; Prato, M.; Kim, G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, 3625.

190. Fang, F. G.; Danishefsky, S. J.. *Tetrahedron Lett.*. **1989**, 2747.
191. Fang, F. G.; Maier, M. E.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 831.
192. Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 2003.
193. Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, *94*, 7172.
194. Thijs, L.; Zwanenburg, B. *Tetrahedron*, **1980**, *36*, 2145.
195. Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.
196. Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060.
197. Pirrung, M. C.; Brown, W., L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561.
198. Day, A. L.; Nabney, J.; Scott, A. I.; *J. Chem. Soc.* **1961**, 4067.
199. Tomioka, H.; Miwa, T.; Suzuki, S.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 753.
200. Prakash, G. K. S.; Ellis, R. W.; Felberg, J. D.; Olah, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 1341.
201. Wong, P. C.; Griller, D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 6631.
202. Scaiano, J. C.; McGimpsey, W. G.; Casal, H. L. *J. Am. Chem. Soc.* **1985**, *107*, 7204.
203. Janulis, Jr., E. P.; Arduengo, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 5929.
204. Bien, S.; Gillon, A. *Tetrahedron Lett.* **1974**, 3073.
205. Bien, S.; Gillon, A.; Kohen, S. *J. Chem. Soc. Perkin Trans. I* **1976**, 489.
206. Livingstone, S. E. in "*Comprehensive Inorganic Chemistry*", Trotman-Dickenson, E. F. ed., Pergamon, Oxford and New York,, 1973, vol. 3, p. 1245.
207. Doyle, M. P.; Taunton, J. Pho; H. Q. *Tetrahedron Lett.* **1989**, 5397.
208. Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.
209. Ibata, T.; Toyoda, J.; Sawada, M.; Tanaka, T *J. Chem. Soc., Chem. Commun.* **1986**, 1266; Ibata, T.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2489; Toyoda, J.; Ibata, T.; Tamura, H.; Ogawa, K.; Nishino, T.; Takebayashi, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2212; Ibata, T.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1787; Tamura, H.; Ibata, T.; Ogawa, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 926; Ibata, T.; Toyoda, J. *Chem. Lett.* **1983**, 1453; Ibata, T.; Jitsuhiro, K.; Tsubokura, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 240; Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1976**, 287; Ibata, T.; Toyoda, J.; Sawada, M.; Takai, Y.; Tanaka, T. *Tetrahedron Lett.* **1988**, 317; Ibata, T.; Motoyama, T.; Hamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2298; Ibata, T. *Chem. Lett.* **1976**, 233; Veda, K.; Ibata, T.; Takebayashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2779.
210. Gillon, A.; Ovadia, D.; Kapon, M.; Bien, S. *Tetrahedron* **1982**, *38*, 1477.
211. Padwa, A.; Carter, S. P.; Nimmesgern, H. *J. Org. Chem.* **1986**, *51*, 1157.
212. Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894.
213. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem.* **1988**, *53*, 2877.
214. Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhang, Z. J. *J. Org. Chem.* **1991**, *56*, 3271.
215. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.
216. Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, 1491.
217. Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889; Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. *Science* **1976**, *192*, 896.
218. Vite, J. P.; Renwich, J. A. A. *Naturwissenschaften* **1971**, *58*, 418; Payne, T. L.; Coster, J. E.; Richerson, J. V.; Edson, L. J.; Hart, E. R. *Environ. Entomol.* **1978**, *7*, 578.

219. Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhi, L. *Tetrahedron Lett.* **1989**, 301.
220. Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1975**, 499; Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, 4475.
221. Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, 1677.
222. Maier, M. E.; Schoffling, B. *Chem. Ber.* **1989**, *122*, 1081.
223. Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett.* **1989**, 4077.
224. Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1989**, *111*, 6451.
225. Padwa, A.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 2037.
226. Pine, S. H. *Org. React.*, **1970**, *18*, 403.
227. Williams, M. A.; Miller, M. J. *Tetrahedron Lett.* **1990**, 1807.
228. Miller, M. J.; Mattingly, P. G. *J. Org. Chem.* **1980**, *45*, 410.