Cascade Processes of Metallo Carbenoids

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I. Introduction

A major challenge in organic synthesis today is to devise reactions that can form several carbon−carbon bonds in one operation leading to the construction of polycyclic structures with proper regio- and stereochemical control.[1−3] Tandem or cascade processes occupy a central role in molecular construction,[4] and new methods which lead to synthetically versatile arrays are particularly valuable. Over the past several years, tandem-induced chemistry by transition metals has gained significant importance in organic synthesis.[5−11] The transition metal-catalyzed reactions of diazo compounds, discovered over 80 years ago, continues to find wide application in organic synthesis.[12] Although the historically important copper-based catalysts are still widely used, rhodium(II) carboxylates, introduced by Teyssié and co-workers in the early 1970s,[13] are often the catalysts of choice for the decomposition of diazocarbonyl compounds. These catalysts mediate a wide range of synthetic transformations such as cyclopropanation, C−H and X−H insertion, and ylide formation. The intermediate rhodium carbenoids often show high levels of stereoselectivity despite their high reactivity.[14−23]

In recent years the research efforts of the Padwa group have been concerned with the rhodium(II)-catalyzed reaction of α-diazocarbonyl compounds and application of the resulting metallo carbenoid to the selective formation of polycyclic systems. Several distinct synthetic methodologies have been formulated on the basis of this strategy. The three major classes correspond to (1) tandem cyclization−cycloaddition, (2) alkyne−carbenoid metathesis, and (3) sigmatropic rearrangement of onium ylides. Our primary purpose in writing this review is to highlight the importance of tandem processes of metallo carbenoids in organic synthesis. It is the intent of this article to broadly define the boundaries of our present knowledge in this field. Such an overview will put into perspective what has been accomplished and will hopefully provide impetus for further investigation of this general approach.

II. Tandem Cyclization–Cycloaddition Sequence of Rhodium Carbenoids

The stereoselective preparation of highly substituted oxygen heterocycles, especially structurally complex tetrahydrofurans and tetrahydropyrans, has attracted considerable attention in recent years.[24,25] These medium-sized cyclic ethers are becoming increasingly recognized as common structural units in naturally occurring compounds such as the ionophores,[26] the brevetoxins,[27] and other marine natural products.[28] Due to the increasing interest in these bioactive molecules and the well-recognized problems in building midsize rings, the synthesis of such systems becomes a challenging objective. Although a variety of methods exist for dihydro- and tetrahydrofuran synthesis,[24,29] few of these are based on an annulation strategy,[30] and, of those that are, single-step procedures are uncommon.[31,32] Conceptually, the 1,3-dipolar cycloaddition of carbonyl ylides with π-bonds represents an attractive strategy for tetrahydrofuran formation.[33] Common methods for

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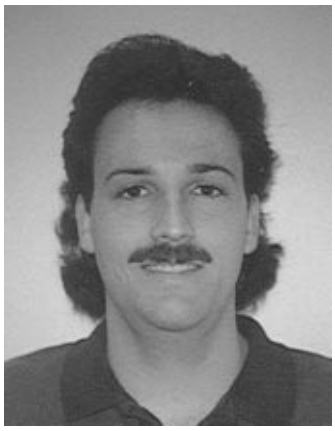
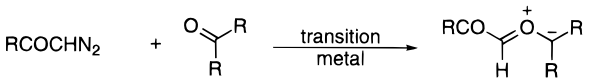


M. David Weingarten was born in New York City in 1969 and received his B.S. degree (1991) from the University of West Florida (Pensacola) where he majored in chemistry. In 1991 he began his Ph.D. studies at Emory University carrying out research under the direction of Albert Padwa. He was a recipient of a graduate fellowship from the Organic Chemistry Division of the American Chemical Society in 1994–1995 sponsored by Proctor & Gamble Co. His present research interests are in the area of organometallic chemistry, synthetic methodology and computational methods. He has recently joined Clark Still's group at Columbia University as a postdoctoral fellow pursuing studies in the general area of combinatorial chemistry.

carbonyl ylide generation involve the thermolysis or photolysis of epoxides possessing electron-withdrawing substituents,[34−36] the thermal extrusion of nitrogen from 1,3,4-oxadiazolines,[37−39] and the loss of carbon dioxide from 1,3-dioxolan-4-ones.[40] One of the simplest methods for generating carbonyl ylides involves the addition of a metallo carbenoid onto the oxygen atom of a carbonyl group. This can be readily achieved by the rhodium(II) metal-catalyzed decomposition of an α-diazo ketone in the presence of a carbonyl functionality[41−45] (Scheme 1). These rhodium-mediated carbenoid reactions generally proceed under much milder conditions than is common for classical synthetic methodology with copper or its complexes.[46,47]

Scheme 1



In recent years, an upsurge of activity in the application of carbonyl ylides to new synthetic transformations has occurred.[33] This research has also stimulated interest in the use of metallo carbenoids as reactive intermediates for the generation of other types of ylides.[48] A diverse range of chemistry has already surfaced.[42] In many instances, the 1,3-dipolar cycloadditions are both regio- and stereospecific, lending them well to natural product synthesis. Frontier molecular orbital theory generally rationalizes the regioselectivity of most 1,3-dipolar cycloadditions. Of the three categories described by Sustmann,[49] type II is particularly common for carbonyl ylides since they possess one of the smallest HOMO−LUMO energy gaps of all the common 1,3-dipoles.[50] The HOMO of the dipole is dominant in reactions with electron-deficient dipolarophiles, whereas the LUMO of the dipole is the controlling molecular orbital in reactions with electron-rich dipolarophiles. In general, all the regiochemistry results encountered with carbonyl ylides can be readily accommodated in terms of perturbation theory.

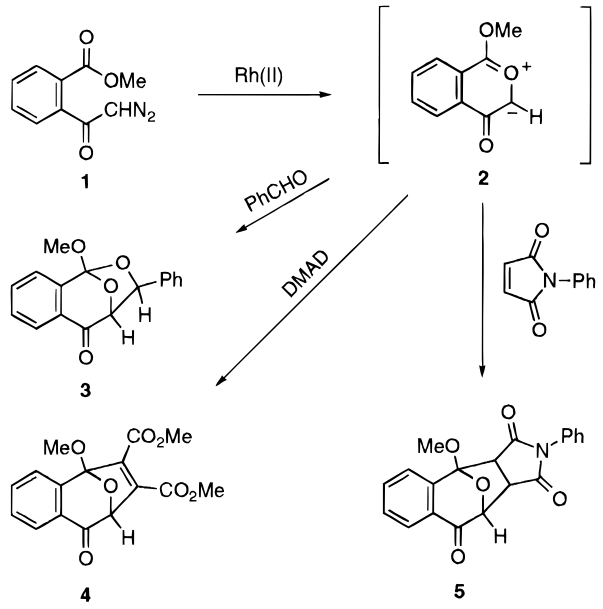
A. Six-Membered Ring Carbonyl Ylide Cyclizations

The tandem intramolecular carbenoid−carbonyl cyclization represents one of the most effective methods for generating carbonyl ylides.[51] Ibata and coworkers[52] demonstrated the utility of the method by studying the transition metal-catalyzed decomposition of *o*-(alkoxycarbonyl)-α-diazoacetophenone in the presence of various dipolarophiles. Treatment of *o*-(alkoxycarbonyl)-α-diazoacetophenone (**1**) with a catalytic amount of a rhodium(II) carboxylate generates carbonyl ylide **2** which is readily trapped by dipolarophiles such as benzaldehyde, dimethyl acetylenedicarboxylate, or *N*-phenylmaleimide to give cycloadducts **3**, **4**, or **5**, respectively (Scheme 2).

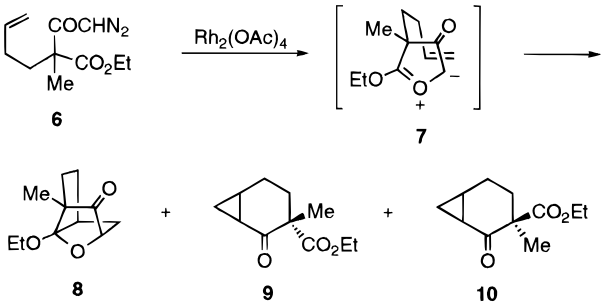
The tandem cyclization−cycloaddition methodology was further extended by the intramolecular trapping of the carbonyl ylide dipole with a C−C double bond suitably placed within the molecule. The rhodium(II) carboxylate-catalyzed decomposition of diazo ketone **6** afforded 8-ethoxy-1-methyl-9-oxatricyclo-[3.2.1.1]nonan-2-one (**8**) as the major product together with lesser quantities of **9** and **10**[53] (Scheme 3). The products can be attributed to the formation of the five-membered cyclic carbonyl ylide **7** which is subsequently trapped by the tethered olefin.

The formation of cycloadduct **14** from the catalytic decomposition of bis-diazo ketone **11** represents an example in which two diazo ketone moieties in the same molecule, under the influence of the same catalyst, react in different ways. Addition of the

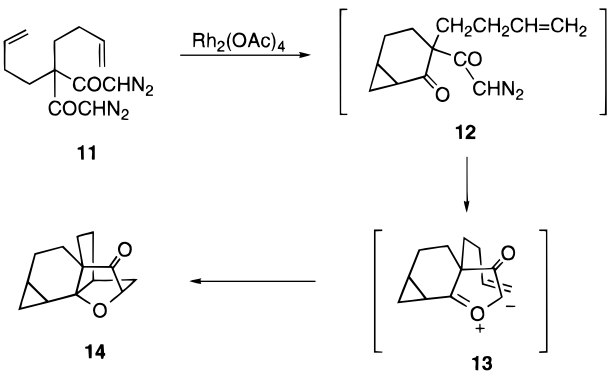
Scheme 2



Scheme 3



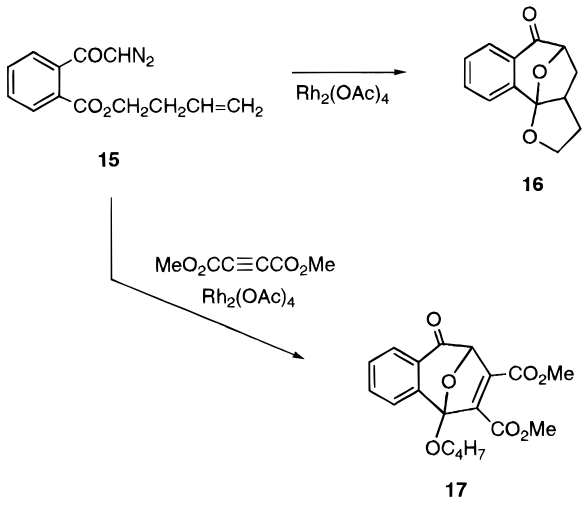
Scheme 4



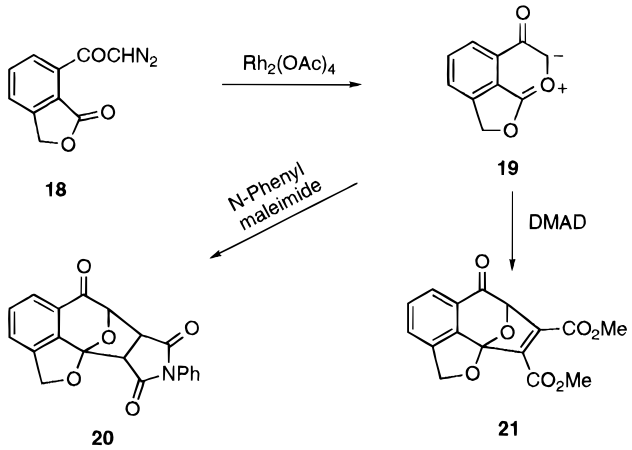
initially formed carbenoid to the double bond gave bicyclo[4.1.0]hexane **12** which subsequently cyclizes to produce carbonyl ylide **13**. Intramolecular trapping of this ylide ultimately affords cycloadduct **14** whose structure was unequivocally established by an X-ray crystallographic study (Scheme 4).

An attractive feature of the above tandem cyclization−cycloaddition process is the opportunity to control the stereochemistry of the product at several centers. The final product represents a highly functionalized rigid bicyclic system that is amenable to subsequent synthetic elaboration. The author's research group has examined this tandem cyclization−cycloaddition sequence in some detail.[51] One of the early systems studied involved treatment of *o*-[(alk-

Scheme 5



Scheme 6

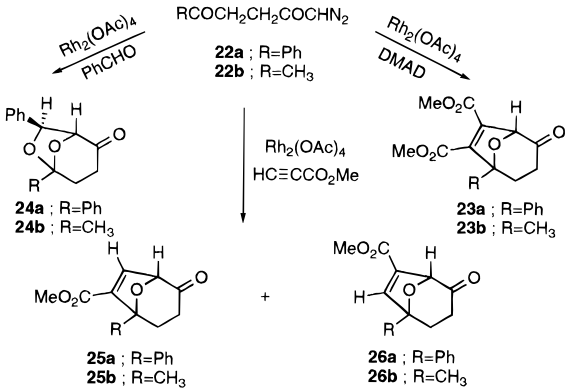


2-enyloxy)carbonyl]-α-diazoacetophenone **15** with rhodium(II) acetate. Cyclization produced a six-membered ring carbonyl ylide which underwent a subsequent intramolecular dipolar cycloaddition with the neighboring double bond to give cyclohepta[1,2-*b*]furanone **16** in 87% yield[54,55] (Scheme 5). Carrying out the reaction in the presence of dimethyl acetylenedicarboxylate afforded the bimolecular dipolar cycloadduct **17**. With this system, the dipole prefers to cycloadd with the activated external dipolarophile instead of reacting with the unactivated internal π-bond.

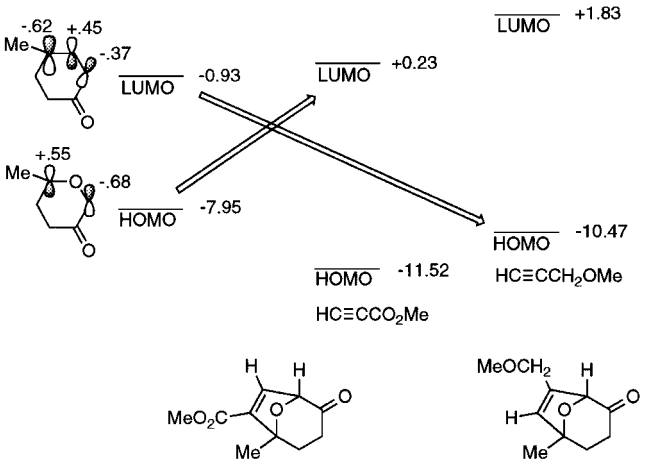
A related system was also studied where freedom of rotation about the C−C bond connecting the ester and the aromatic ring was severely restricted by the incorporation of the carbonyl group into a lactone ring.[56,57] Treatment of diazo ketone **18** with rhodium(II) acetate in the presence of *N*-phenylmaleimide or dimethyl acetylenedicarboxylate afforded cycloadduct **20** or **21**, respectively (Scheme 6).

The early work involved systems in which the keto metallo carbenoid and the remote ester carbonyl group were substituted *ortho* to one another on a benzene ring. This arrangement provides interatomic distances and bond angles that are ideal for dipole formation. In order to test the geometric and electronic requirements of dipole formation, the 1-diazo-2,5-pentanedione system **22** was examined.[58,59] With this system the ylide was formed by reaction

Scheme 7



Scheme 8

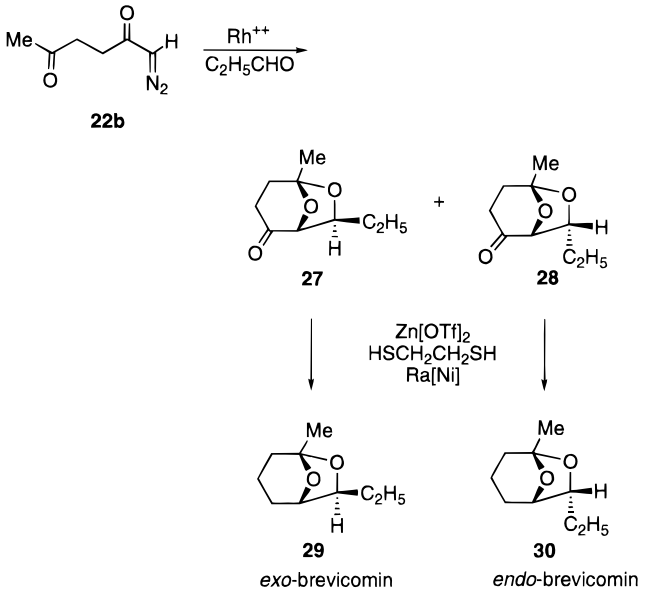


of the less nucleophilic ketonic carbonyl on the rhodium carbenoid center. The tether utilized corresponds to a simple dimethylene chain, which introduces a certain conformational flexibility not available to the more rigid benzo systems.

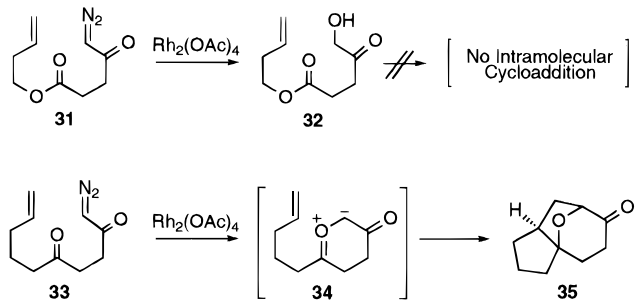
Reaction of diazo ketone **22** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate gave cycloadduct **23** in excellent yield. Trapping the dipole with benzaldehyde afforded a single regioisomer (*i.e.*, **24**). Cycloaddition of **22a** with methyl propiolate afforded **25a**, whereas the reaction of **22b** with the same alkyne afforded a 4:1 mixture of two regioisomers (**25b** and **26b**) in 78% overall yield (Scheme 7). The most favorable FMO interaction is between the HOMO of the dipole and the LUMO of the dipolarophile, and this nicely rationalizes the formation of the major regioisomer (Scheme 8).

Application of this methodology to the synthesis of *exo*- and *endo*-brevicomin has been carried out.[59,60] The *exo* and *endo* isomers of brevicomin (**29** and **30**) 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.[61,62] Cycloaddition of 1-diazo-2,5-hexanedione (**22b**) with rhodium(II) acetate using propionaldehyde as the dipolarophile afforded the 6,8-dioxabicyclo[3.2.1]-octane ring system in 60% isolated yield as a 2:1 mixture of *exo* (**27**) and *endo* (**28**) isomers. Separation of the diastereomers followed by reduction of the carbonyl group afforded *exo*- and *endo*-brevicomin (**29** and **30**) in good yield (Scheme 9).

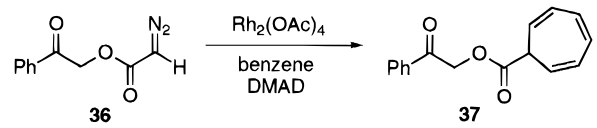
Scheme 9



Scheme 10



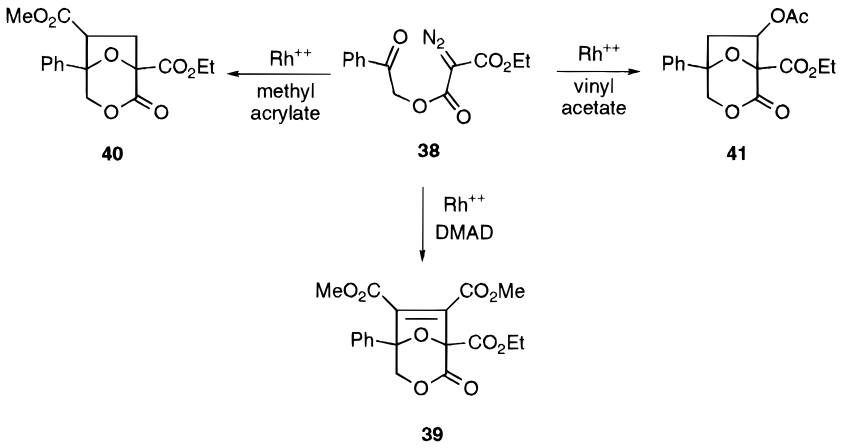
Scheme 11



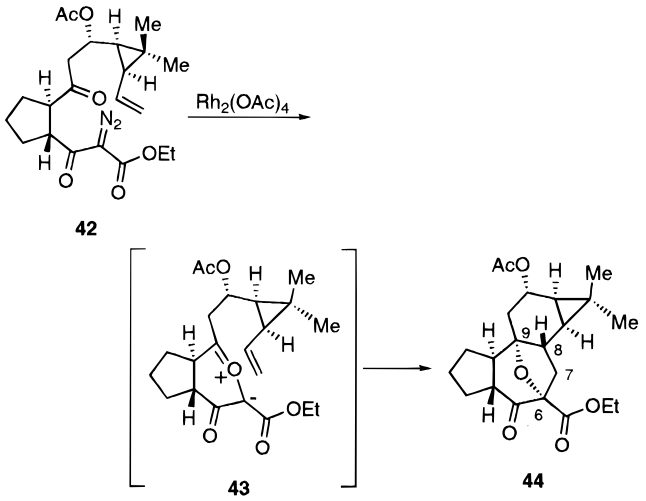
Attempts to use aliphatic esters to form carbonyl ylides was also carried out.[63] Reaction of diazo keto ester **31** with rhodium(II) acetate in benzene afforded **32** (53%) together with a complex mixture of products, none of which appeared to arise from cycloaddition of a carbonyl ylide intermediate. This result was found to be quite general for a series of aliphatic esters. Treatment of the closely analogous keto system **33** gave the intramolecular cycloadduct **35** in excellent yield (Scheme 10). This difference in chemical behavior clearly indicates that the electronic characteristics of an ester and a keto carbonyl group play a major role in the cyclization efficiency.

Replacement of one of the methylene groups in the two-carbon tether with an oxygen atom could generate the dioxanone ring system following the cyclization−cycloaddition sequence.[63] However, treatment of diazo ester **36** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate gave only cycloheptatriene **37** (Scheme 11). This product is derived by bimolecular addition of the rhodium carbenoid onto benzene followed by cyclopropyl ring opening. No cycloadduct resulting from carbonyl ylide formation was observed.

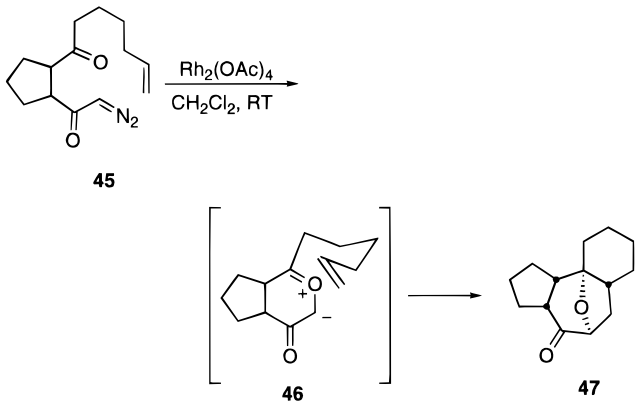
Scheme 12



Scheme 13



Scheme 14



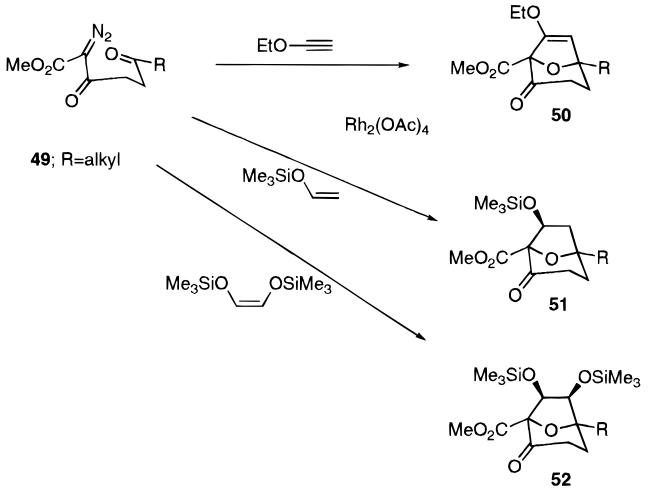
A possible explanation to account for the differing reactivity of the α-diazoacetate system is the decrease in electrophilic character conferred upon the intermediate rhodium carbenoid when the diazo ketone is replaced by a diazoacetate functionality. The diminished electrophilicity may attenuate the rate of carbenoid attack on the remote carbonyl group to the point where an alternative pathway can occur. To compensate for this diminished electrophilicity, the hydrogen of the diazo carbon atom was substituted with an electron-withdrawing group. Indeed, the reaction of ethyl diazomalonate **38** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate, methyl acrylate, or vinyl acetate produced cycloadducts **39**−**41**, respectively (Scheme 12).

The intramolecular trapping of carbonyl ylide dipoles with an alkene represents an effective method for the synthesis of a variety of novel oxypolycyclic ring systems.[51] An interesting application of this method is found as the central step of Dauben's synthesis of the tigliane ring system.[64] Carbonyl ylide **43**, generated from the diazocarbonyl **42** in the presence of a catalytic amount of rhodium(II) acetate, underwent an intramolecular addition with the olefin to form the C_6,C_9-oxido-bridged tigliane ring system **44** (Scheme 13). The two new stereocenters at C-8 and C-9 were formed with the correct configurations relative to C_{14} and C_{15} presented by the natural tigliane compounds. The high stereospecificity in the ring closure reaction could be related to steric interactions or the introduction of conformational strain in the tether which disfavors the transition state where the cyclopropane ring and the oxido bridge are on the same side of the molecule.

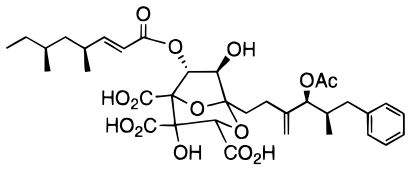
Another successful cyclization of this type was recently carried out by McMills[65] to produce a simple phorbol analogue devoid of most of the oxygenation. Reaction of diazo ketone **45** with $Rh_2(OAc)_4$ produced the transient oxonium ylide **46** which was trapped by the tethered olefin in a 1,3-dipolar cycloaddition reaction to form tetracyclic ether **47** as a single isomer in 55% yield (Scheme 14). An X-ray crystal structure analysis showed the C-8 hydrogen to be located in a *syn* relationship with the protons which are *cis* at the A/B ring fusion. The stereoselectivity of addition of the tethered olefin to the 1,3-dipole was attributed to nonbonded interactions in the transition state where the olefinic side chain adopts a chairlike conformation in the *endo* mode. This tandem cyclization−cycloaddition strategy represents a particularly efficient approach for the construction of the basic phorbol skeleton.[66]

The rhodium(II)-induced tandem cyclization−cycloaddition process has also been applied with notable success to the core structure of zaragozic acid by the Merck Research group.[67] Zaragozic acid A (**48**) was discovered as a metabolite from an unidentified sterile fungus and was identified as a potent inhibitor of squalene synthase in recent years.[68] This compound has been actively pursued as a synthetic target

Scheme 15



because of its potential as a cholesterol lowering agent as well as its unique structure.[69] The rhodium



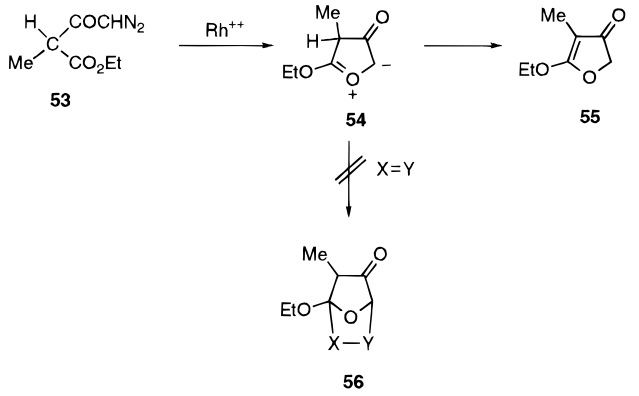
48 - Zaragozic Acid

carbenoid cycloaddition approach allows for the rapid assemblage of the bicyclic core structure of zaragozic acid in a single step. The stereochemistry of the resulting cycloadducts (*i.e.*, **50**−**52**) was confirmed by NOESY spectra as well as single-crystal X-ray analysis. The cycloadditions represent the first examples of using vinyl oxytrialkylsilanes and an alkoxyacetylene as dipolarophiles in the cyclization−cycloaddition reaction (Scheme 15). Interestingly, relatively electron-deficient dipolarophiles such as methyl acrylate or methyl propiolate failed to trap the 1,3-dipole, even though they added smoothly to simpler diazo ketones. Thus, the order of dipolarophile reactivity switches depending on the presence or absence of an extra carboxyl group on the dipole and can be nicely accommodated by FMO theory.

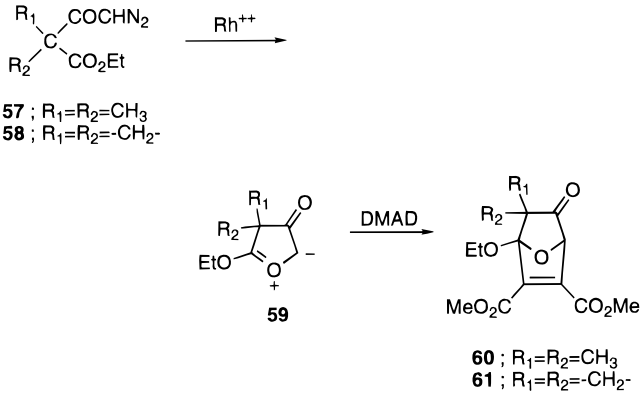
B. Five-Membered Ring Carbonyl Ylide Cyclizations

The primary spatial requirement for carbonyl ylide formation is that the distance between the two reacting centers should be sufficiently close so that effective overlap of the lone pair of electrons on the carbonyl group with the metallocarbenoid center can occur. The effect that variation in the spatial proximity between the carbonyl group and the diazo ketone would have on the course of the reaction was studied by varying the length of the methylene tether separating the two functionalities.[70] The majority of systems examined in the literature involved the formation of a six-membered ring carbonyl ylide intermediate. The ease of ring closure as a function of ring size generally increases on going from three- to five-membered rings and then decreases rapidly.[71]

Scheme 16



Scheme 17

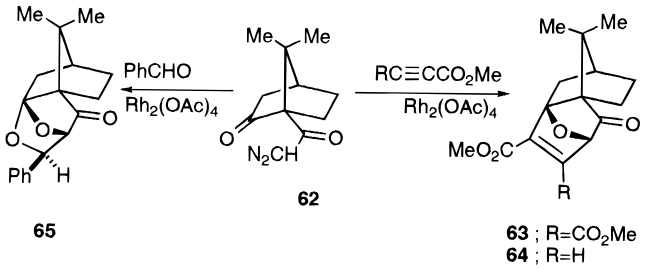


This observation is perfectly compatible with the fact that five-membered ring carbonyl ylide formation occurs smoothly upon treatment of 1-diazobutanediones with rhodium(II) carboxylates.[70] For example, the reaction of ethyl 4-diazo-2-methyl-3-oxobutyrate (**53**) with the Rh(II) catalyst afforded 5-ethoxy-4-methyl-3-(2*H*)-furanone (**55**) in 90% isolated yield (Scheme 16). The mechanism by which **53** is converted into **55** involves rapid cyclization of the rhodium carbenoid onto the neighboring carbonyl group to give the five-membered ring carbonyl ylide **54**, which undergoes a subsequent proton transfer.[72] All attempts to trap the suspected 1,3-dipole **54** with a variety of dipolarophiles failed to produce a dipolar cycloadduct. Apparently the highly stabilized dipole **54** transfers a proton at a faster rate than bimolecular cycloaddition. The formation of furanone **55** comes as no real surprise since one of the characteristic reactions of carbonyl ylides derived from the reaction of α-diazoalkanes with ketones consists of an intramolecular proton transfer.[72]

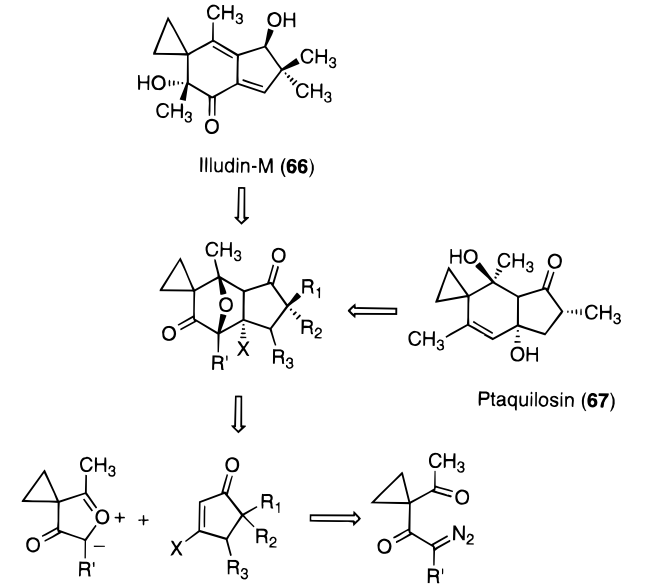
When the α-position of the 1-diazobutanedione skeleton was blocked with two substituent groups (*i.e.*, **57** or **58**), the rhodium-catalyzed cycloaddition with DMAD led to the carbonyl ylide cycloadducts **60** (85%) or **61** (55%), respectively[70] (Scheme 17).

In a similar manner, treatment of diazo ketone **62** with a catalytic amount of rhodium(II) acetate at 25 °C in benzene with dimethyl acetylenedicarboxylate afforded cycloadduct **63** in 85% yield[70] (Scheme 18). The cycloaddition reaction proceeded with complete diastereofacial selectivity with approach of the dipo-

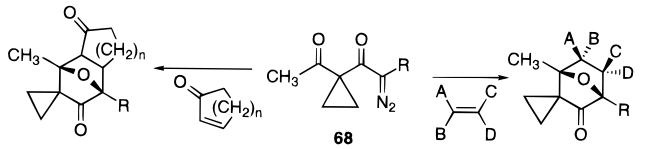
Scheme 18



Scheme 19



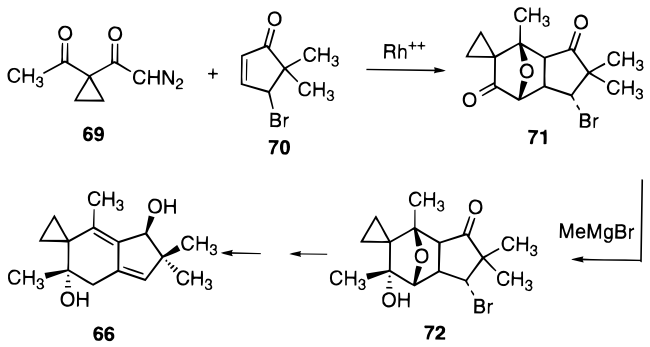
Scheme 20



larophile from the less hindered α-face. Reaction of **62** with methyl propiolate produced cycloadduct **64** in 72% isolated yield. The tandem cyclization−cycloaddition reaction was also carried out in the presence of benzaldehyde to give the bicyclic ketal **65** 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.

Products of five-ring carbonyl ylide cycloaddition derived from α-diazo ketone **68** can undergo cleavage of the oxabicyclic ring system to produce the core structure of the illudin (**66**) and ptaquilosin (**67**) family of sesquiterpenes[73] (Scheme 19). This strategy provides for a rapid assembly of the basic core unit of the target molecules having most of the functionality in place. Thus, the Rh(II)-catalyzed reaction of cyclopropyl-substituted α-diazo ketones of type **68** cycloadd to a variety of acyclic and cyclic alkenes. The resulting oxabicyclo[2.2.1]octanes could be readily cleaved with base or samarium iodide producing the desired skeleton (Scheme 20).

Scheme 21



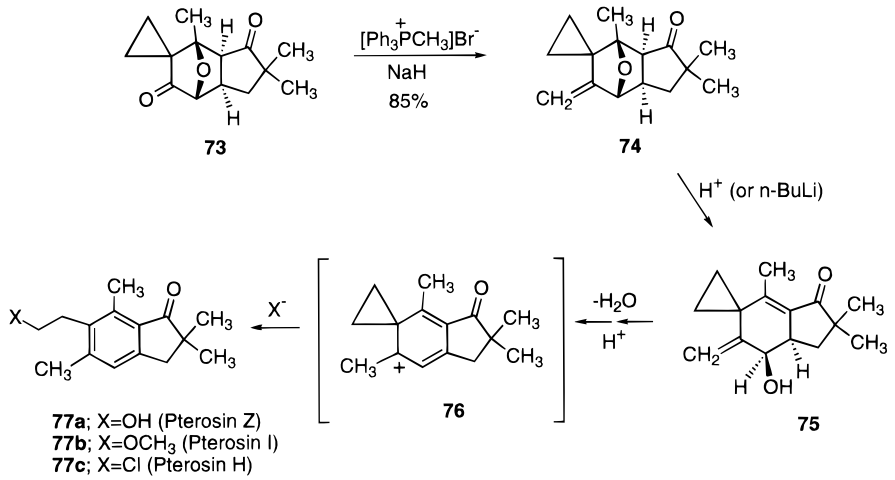
(±)-Illudin M (**66**), a toxic sesquiterpene isolated from the jack-o'-lantern mushroom, has been synthesized via the same tandem cyclization−cycloaddition strategy involving diazo ketone **69**. The first and key step of the synthesis consisted of a carbonyl ylide 1,3-dipolar cycloaddition reaction with cyclopentenone **70** to form cycloadduct **71** with high diasteroselectivity. Several functional group manipulations were carried out to eventually give illudin M (**66**) in modest yield[74] (Scheme 21).

Several members of the pterosin family of sesquiterpenes were also synthesized by a related tandem cyclization approach.[75] A major obstacle to the synthesis of the pterosins is the problem of regioselective construction of the pentasubstituted aromatic ring. The earlier approaches have relied heavily on classical electrophilic substitution reactions with their inherent problems of regiocontrol.[76] Recently, the facile preparation of pterosins H, I, and Z was reported by the author's group[75] which relies on a dipolar cycloaddition of a cyclic carbonyl ylide dipole as the key step of the synthesis. The synthesis involved treating cycloadduct **73** with triphenylmethylphosphonium bromide in the presence of sodium hydride and isolating the expected Wittig product **74**. By using the appropriate acid−solvent combination, it was possible to obtain each of the pterosins in one step from the key reactive intermediate **76** (Scheme 22).

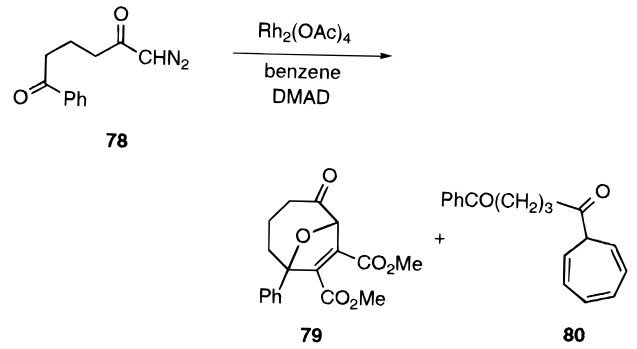
Separating the carbonyl group from the carbenoid center with three methylene units resulted in the formation of a seven-membered ring carbonyl ylide intermediate.[70] Thus, the rhodium(II)-catalyzed reaction of 1-diazo-6-phenyl-2,6-hexanedione (**78**) in benzene using dimethyl acetylenedicarboxylate afforded a 2:1 mixture of cycloadduct **79** (45%) as well as cycloheptatriene **80** (22%) (Scheme 23). It would appear that by extending the tether to three methylene groups, the rate of intramolecular cyclization is sufficiently retarded to allow the bimolecular reaction with benzene to occur.

Varying the length of the tether that separates the olefin from the carbonyl ylide dipole also allows for the synthesis of a variety of interesting oxopolycyclic ring systems. Diazo ketones tethered to the carbonyl group by three methylene units were shown to cyclize most efficiently. For example, treatment of diazo

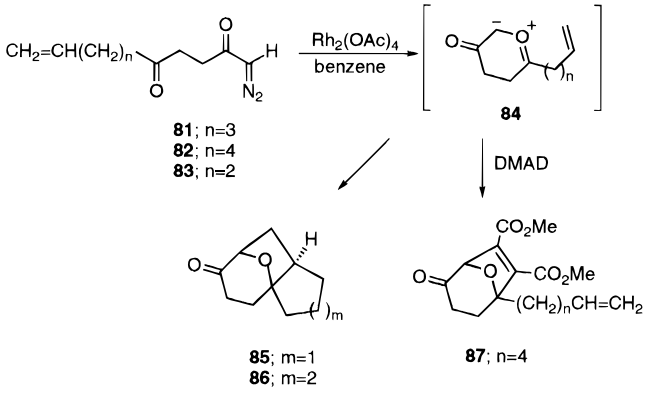
Scheme 22



Scheme 23

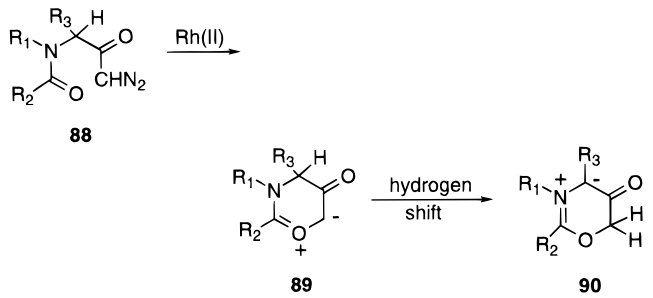


Scheme 24



ketone **81** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate gave cycloadduct **85** in high yield[70] (Scheme 24). In this case, the intramolecular trapping reaction occurs at such a fast rate that the bimolecular cycloaddition reaction cannot compete with it. The homologous diazo ketone **82** was also treated with catalytic rhodium(II) acetate in benzene at 25 °C producing cycloadduct **86** in 50% yield. With this system, the carbonyl ylide was readily trapped with the added dipolarophile affording the bimolecular cycloadduct **87** as the exclusive cycloadduct. Increasing the length of the tether to five methylene units gave no internal cycloadduct. Apparently, the π-bond is not in close enough proximity to the dipole centers to allow the cycloaddition to occur. Diazo ketone **83**, which contains only two

Scheme 25



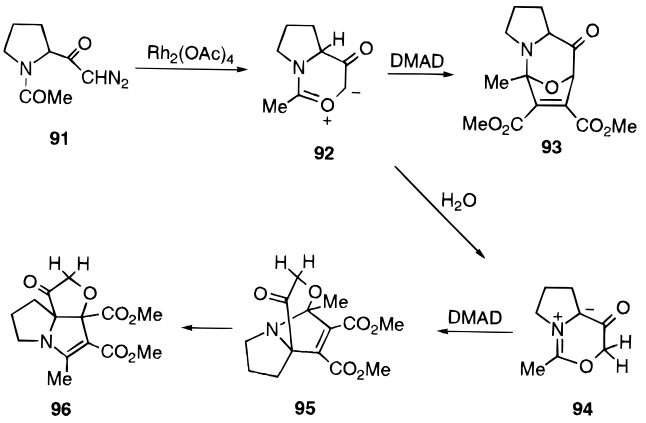
methylene units in the tether, produced none of the internal cycloadduct. Clearly the intramolecular trapping of carbonyl ylides by tethered olefins occurs best when the tether contains three or four methylene units.

C. Dipole Cascade Processes

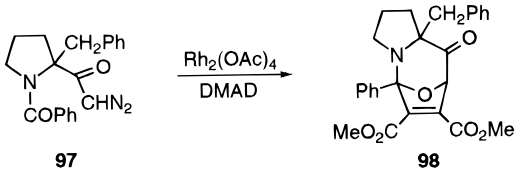
1,3-Dipoles are extremely valuable intermediates in synthetic organic chemistry. Their best known reaction corresponds to a 1,3-dipolar cycloaddition reaction. Less attention, however, has been placed on the interconversion of one dipole into another.[77−81] Rearrangement of 1,3-dipoles is far less frequently encountered than analogous carbocation,[82−84] carbene,[85,86] or radical reorganizations.[87−89] Those rearrangements which do occur can be classified into a small number of types, defined either by the overall structural change or by the nature of the individual steps involved. Several years ago our research group introduced a new method for azomethine ylide formation in which the key step involved a dipole rearrangement. This reaction, which we have termed a "*dipole cascade*" involves three distinct classes of 1,3-dipoles.[90] It is initiated by a rhodium(II)-catalyzed α-diazo ketone (**88**) cyclization onto a neighboring carbonyl group to generate a carbonyl ylide dipole (**89**) which then undergoes a subsequent proton shift to give an azomethine ylide (**90**) (Scheme 25).

The wealth of strategically located functionality that results from this novel cascade process was uncovered during an examination of the reaction of (*S*)-1-acetyl-2-(1-diazoacetyl)pyrrolidine (**91**) 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

Scheme 26



Scheme 27

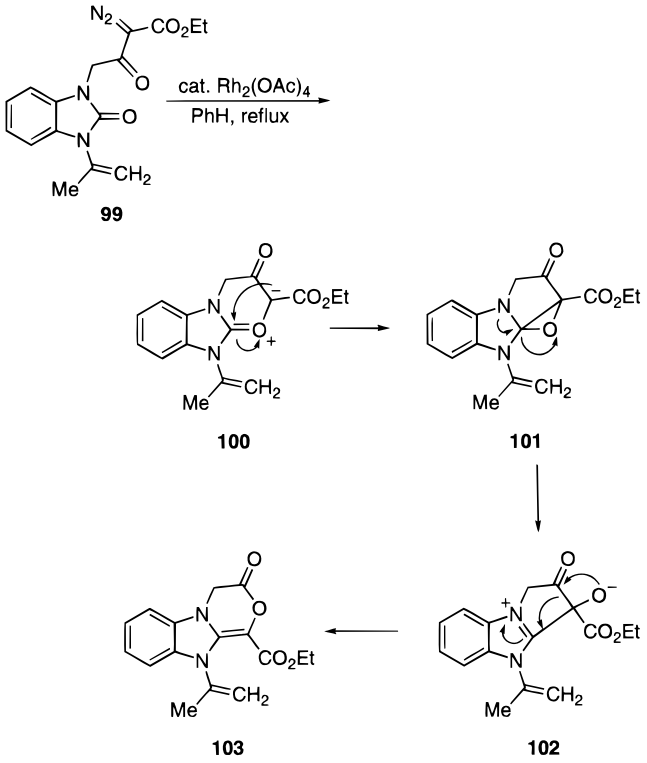


derived cycloadduct (*i.e.*, **93**) was obtained.[90] Instead, the major product (90%) corresponded to structure **96** (Scheme 26). A mechanism that rationalizes the formation of this product involves generation of the expected carbonyl ylide dipole **92** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. Isomerization of **92** to the thermodynamically more stable azomethine ylide **94** occurs via proton exchange with a small amount of water that was present in the reaction mixture. 1,3-Dipolar cycloaddition with dimethyl acetylenedicarboxylate provides cycloadduct **95**, which undergoes a subsequent 1,3-alkoxy shift to generate the tricyclic dihydropyrrolizine **96**. MNDO calculations show that cyclic carbonyl ylides of type **92** have higher heats of formation (*ca.* 15 kcal/mol) than the corresponding azomethine ylide **94**. Some of this energy difference is presumably responsible for the facility with which the dipole reorganization occurs.

In the dipole cascade reaction, a proton must be removed from the α-carbon atom in order to generate the azomethine ylide. When the α-position of the pyrrolidine ring was blocked by a benzyl group, formation of the azomethine ylide dipole could not occur. In fact, treatment of diazo ketone **97** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate afforded only the carbonyl ylide-derived cycloadduct **98** in 95% yield[90] (Scheme 27).

A further example of the dipole cascade process was encountered in a study of the Rh(II)-catalyzed decomposition of α-diazo ketone **99** which gave the novel carbonyl rearrangement product **103**[91] (Scheme 28). Intramolecular trapping of the rhodium carbenoid by the benzimidazolone carbonyl group generates the stabilized carbonyl ylide **100**. Collapse of **100** to the epoxide **101** followed by ring opening gave the zwitterion **102**. Attack of the alkoxide ion on the more electrophilic carbonyl (ketone *vs* ester) and carbon migration then gave product **103**.

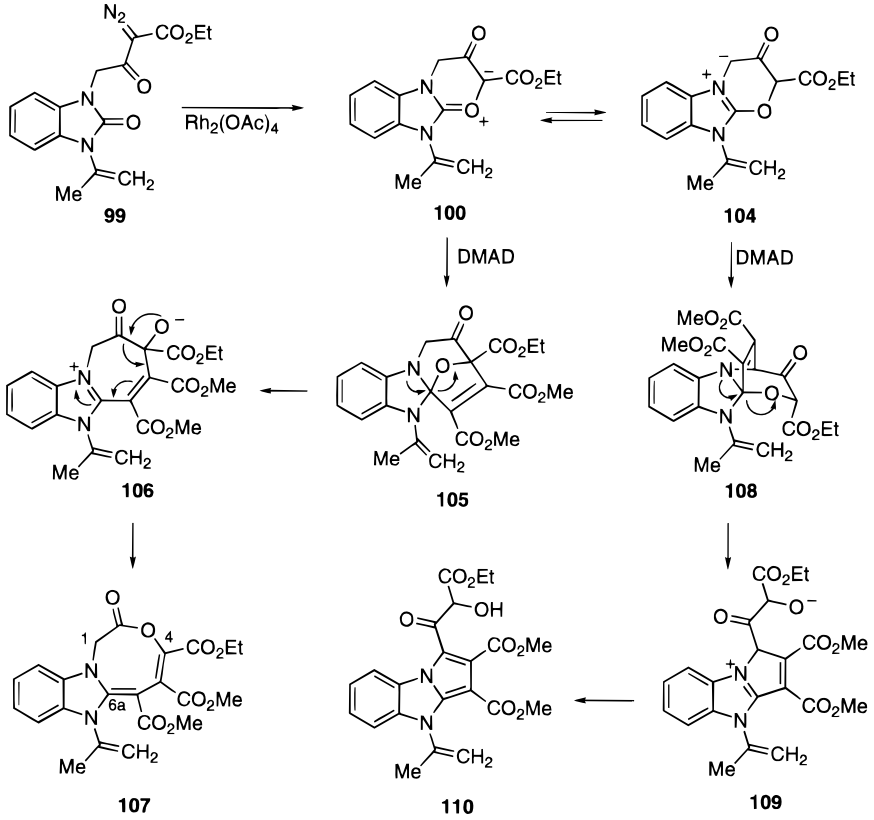
Scheme 28



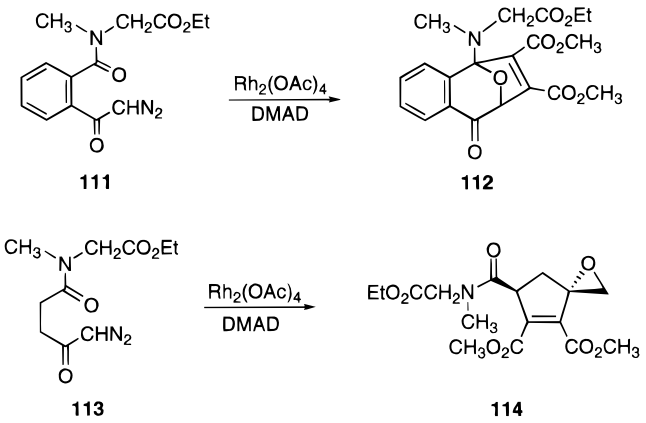
When the reaction of **99** was carried out in the presence of DMAD, two unusual addition/rearrangement products were obtained and were identified as compounds **107** and **110** in 33% and 24% yield, respectively (Scheme 29). Under these conditions none of the rearrangement product **103** was observed. Formation of the unexpected products **107** and **110** resulted from the trapping of two isomeric ylides. Bimolecular cycloaddition of the expected carbonyl ylide **100** with DMAD gave the [3 + 2]-cycloadduct **105**, which under the reaction conditions fragmented to zwitterion **106**. Carbon to oxygen acyl migration then generated the eight-membered dienol lactone **107**. Rearrangement of **106** to **107** can be seen as a vinylogous rearrangement of **102** to **103** and underscores the thermodynamic driving force for this type of transformation. Formation of **110** requires the tandem cascade of carbonyl ylide **100** to azomethine ylide **104**. Condensation of **104** with DMAD resulted in the [3 + 2]-cycloaddition product **108**. Fragmentation to zwitterion **109** followed by proton transfer eventually afforded pyrrolobenzimidazole **110**.

In the case of α-diazo keto amide **111**, the carbonyl ylide dipole is sufficiently stabilized via resonance to be trapped by dimethyl acetylenedicarboxylate to give cycloadduct **112** in 90% yield[92] (Scheme 30). No signs of any material derived from azomethine ylide cycloaddition were observed. The closely related α-diazo keto amide **113** was also examined. Most interestingly, treatment of **113** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate afforded cycloadduct **114** in 60% yield. The initial reaction involved generation of the expected carbonyl ylide dipole **116** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. This highly stabilized dipole does not readily undergo 1,3-dipolar cycloaddition but rather loses a proton to produce the cyclic ketene N,O-acetal **117**

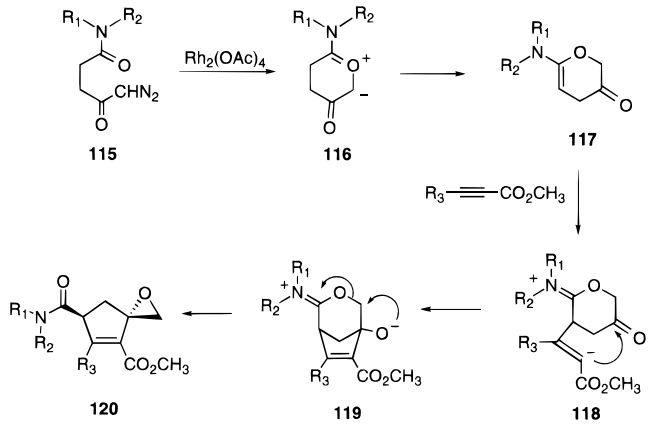
Scheme 29



Scheme 30



Scheme 31



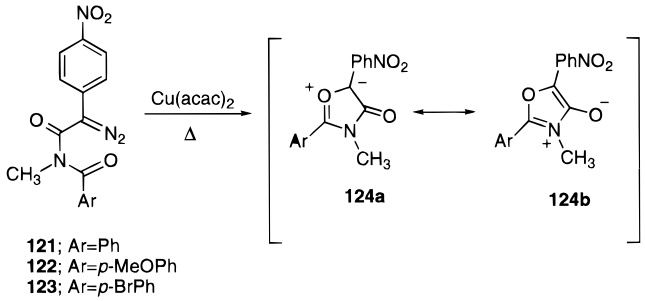
(Scheme 31). This material reacted further with the activated π-bond of the dipolarophile to produce zwitterion **118**. The anionic portion of **118** added to the adjacent carbonyl group, affording a new zwitterionic intermediate **119**. Under anhydrous conditions, epoxide formation occurred with charge dissipation to give the observed cycloadduct **120**. 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.

III. Isomünchnone Cycloadditions

The 1,3-oxazolium 4-oxides (isomünchnones) are readily obtained through the catalytic cyclization of a suitable diazo imide.[93] This type of mesoionic oxazolium ylide corresponds to the cyclic equivalent of a carbonyl ylide and readily undergoes 1,3-dipolar cycloaddition. The first successful preparation and isolation of an isomünchnone was described by Ibata and Hamaguchi in 1974.[94] These workers observed that when diazo imide **121** was heated in the presence of a catalytic amount of $Cu_2(acac)_2$, a red crystalline material precipitated from the reaction mixture (Scheme 32). The red solid was assigned as isomünchnone **124** on the basis of its spectral data and elemental analysis. Mesoionic ylide **124** was found to be air stable for several weeks and its overall stability was attributed to its dipolar aromatic resonance structure. Formation of the isomünchnone ring can be rationalized by initial generation of a metallo carbenoid species which is then followed by intramolecular cyclization onto the neighboring carbonyl oxygen to form the dipole.[53]

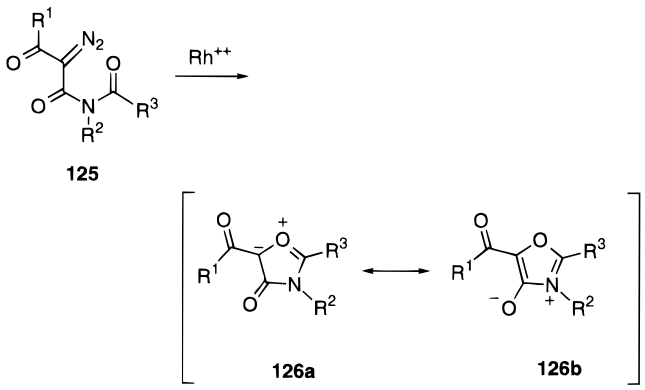
Maier[95] and Padwa[96] have independently utilized the Rh(II)-catalyzed reaction of diazo imides as a

Scheme 32



121; Ar=Ph
122; Ar=*p*-MeOPh
123; Ar=*p*-BrPh

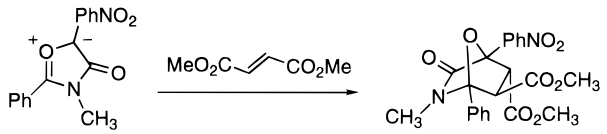
Scheme 33



125

126a **126b**

Scheme 34

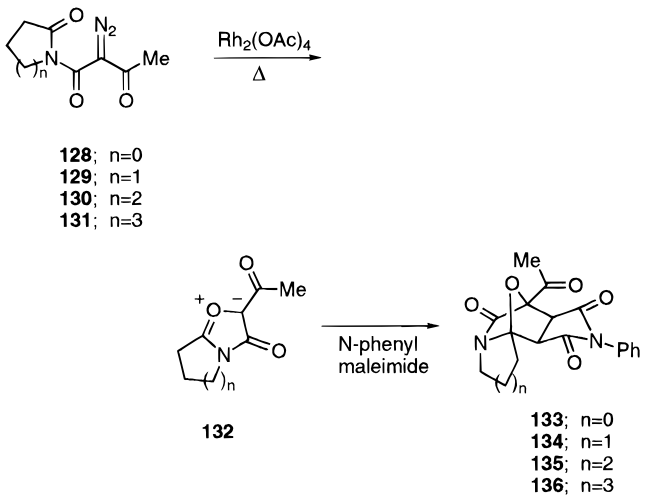


124 **127**

method for generating isomünchnones. The starting diazo imides are readily constructed by acetoacylation[97] or malonylacylation[98] of the corresponding amides followed by standard diazo transfer techniques.[99] Intramolecular trapping of the rhodium carbenoid by the lone pair of electrons of the neighboring carbonyl group leads to the desired mesoionic system **126** (Scheme 33). Both research groups have shown that these reactive species can be trapped with dipolarophiles to give cycloadducts in high yield.

Ibata was the first to show that the "*masked*" carbonyl ylide embedded within the isomünchnone framework would readily undergo 1,3-dipolar cycloaddition with various dipolarophiles.[100] The isolable isomünchnone **124** was observed to react with dimethyl fumarate to produce cycloadduct **127** which possesses the 7-oxa-2-azabicyclo[2.2.1]heptane skeleton (Scheme 34). When the reaction of **124** was carried out using catalytic amounts of $Cu(acac)_2$ in the presence of various dipolarophiles, smooth dipolar cycloaddition was observed to occur giving mixtures of *endo* and *exo* isomers. In most cases, the *exo* isomers were favored. All of Ibata's isomünchnone cycloadditions contain aromatic substituent groups, presumably selected to facilitate dipole formation. The synthetic utility of the cycloaddition reaction is diminished, however, because of the low reactivity of the aromatic substituents toward further manipulation.

Scheme 35



128; n=0
129; n=1
130; n=2
131; n=3

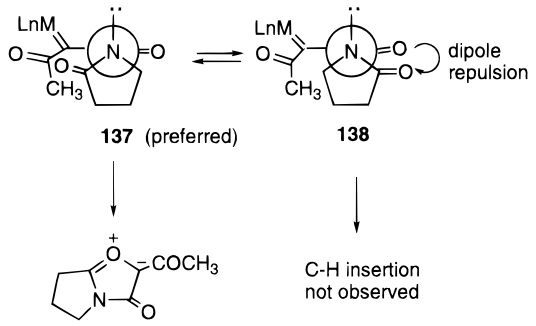
132

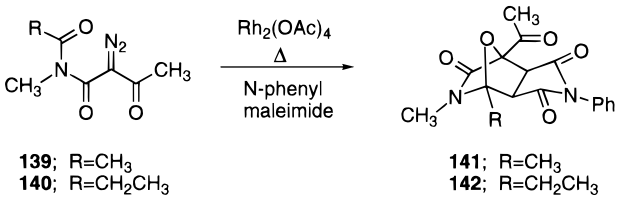
133; n=0
134; n=1
135; n=2
136; n=3

Several years ago the author's research group became interested in using the dipolar cycloaddition of isomünchnones for the construction of a variety of alkaloid systems.[18c] Since little was known about the interaction of rhodium carbenoids with amido carbonyl groups, we sought to answer several questions: (1) would a nucleophilic amide or imide functionality cyclize more or less efficiently than a keto group to form a carbonyl ylide; (2) would the reactive diazo ketone in the presence of an activated π-bond be subject to cycloaddition across the diazo group producing a pyrazoline cycloadduct; and (3) would the given propensity for metal carbenoids to undergo addition and C−H insertion reactions be competitive with isomünchnone formation.[18c] To help answer these questions, the Rh(II)-catalyzed reactions of cyclic diazo imides **128**−**131** were investigated.[18c] When diazo imide **129** ($n = 1$) was treated with $Rh_2(OAc)_4$ in benzene (80 °C), the initially formed rhodium carbenoid cyclized onto the adjacent imide carbonyl group to generate isomünchnone **132** (Scheme 35). This reactive species readily underwent 1,3-dipolar cycloaddition with *N*-phenylmaleimide to give cycloadduct **134** ($n = 1$) as a 1.2:1 mixture of *exo*/*endo* isomers in 78% yield. No evidence of β-lactam formation, derived from competitive C−H insertion, was observed in the crude reaction mixture.[18c] The ring size was reduced to a four-membered ring (**128**; $n = 0$) and enlarged to a six (**130**; $n = 2$) and seven (**131**; $n = 3$) membered ring. In all cases, high yields (*i.e.*, 70−90%) of the expected cycloadducts (**133**, **135**, and **136**) were obtained. Interestingly, the cyclic cases where $n = 1$ and $n = 3$ (*i.e.*, **129** and **131**) showed little *exo*/*endo* selectivity, but the cases of $n = 0$ and $n = 2$ (**128** and **130**) resulted in a single diastereomer.

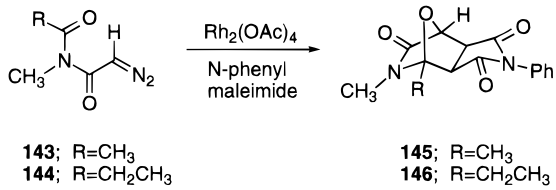
The results obtained clearly demonstrated that the initially formed rhodium carbenoid prefers to cyclize onto the adjacent imide carbonyl group to form an isomünchnone rather than undergo C−H insertion. The explanation proposed to rationalize this result is that the preferred rhodium carbenoid conformer **137** is the one which avoids unfavorable dipole repulsion between the two carbonyl groups of the imide (*i.e.*, **138**, Scheme 36). The conformational rigidity imposed by the cyclic imide ring was dem-

Scheme 36





Scheme 37

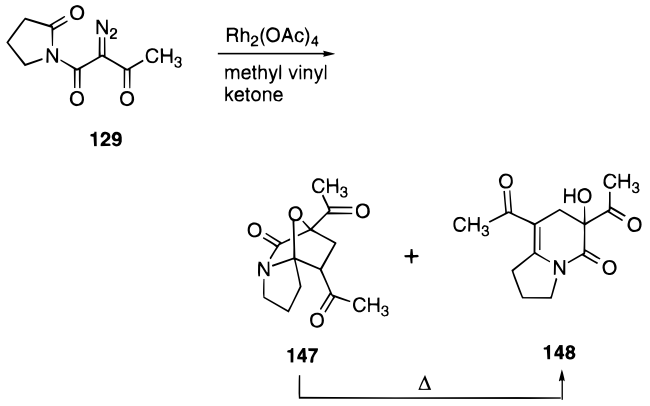


onstrated to be inconsequential for carbonyl ylide formation. This was shown by carrying out the tandem cyclization−cycloaddition sequence with acyclic imides **139** and **140**. Both substrates readily reacted with *N*-phenylmaleimide to give diastereomeric mixtures of cycloadducts **141** and **142** in good yield. Again, no products derived from C−H insertion into the *N*-methyl or *N*-ethyl substituents were observed.

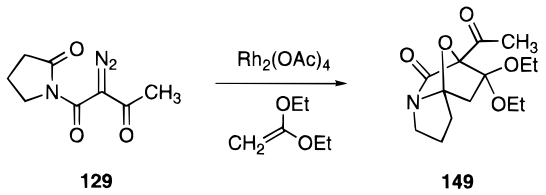
When diazo imide **139** (or **140**) was deacetylated[101] and the resulting diazoamide **143** (or **144**) was subjected to rhodium(II) acetate, the yield of the corresponding cycloadduct (*i.e.*, **145** or **146**) was significantly diminished (Scheme 37). One explanation for this different reactivity is the inherent decrease in electrophilic character conferred upon the intermediate rhodium carbenoid when the diazo carbon bears a hydrogen atom rather than an acetyl group. This decrease in electrophilicity may alter the rate of carbenoid attack on the remote carbonyl group to the point where alternative reactions can occur. Another possible explanation to account for the diminished reactivity is that the preferred conformation of the intermediate rhodium carbenoid may not be the one that results in carbonyl ylide formation.[18c]

Unsymmetrical dipolarophiles were found to undergo intermolecular cycloaddition with isomünchnones with high regioselectivity.[96c] For example, the decomposition of diazo imide **129** with $Rh_2(OAc)_4$ in the presence of methyl vinyl ketone resulted in the formation of two products identified as **147** and **148** in 27% and 44% yield, respectively (Scheme 38). The regiochemical outcome is consistent with FMO considerations.[96c] Prolonged heating of cycloadduct **147** afforded the bicyclic lactam **148**. This rearrangement presumably occurs through nitrogen lone pair-assisted opening of the oxygen bridge of **147** to give an acyl iminium ion which then undergoes proton loss.

Scheme 38



Scheme 39



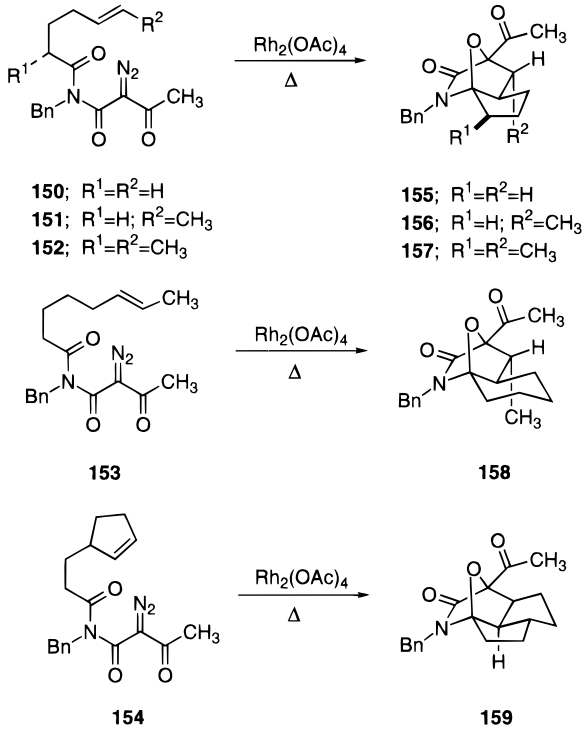
The first example of a bimolecular 1,3-dipolar cycloaddition between an isomünchnone and an electron-rich dipolarophile was reported recently.[96c] The reaction of diethyl ketene acetal and isomünchnone **129** gave cycloadduct **149** in high yield (Scheme 39). Again, only one regioisomer was obtained and the regiochemistry encountered is consistent with cycloaddition involving the HOMO of diethyl ketene acetal and the LUMO of isomünchnone **132** ($n = 1$).

A. Intramolecular Isomünchnone Cycloadditions

An interesting example of an intramolecular 1,3-dipolar cycloaddition of an isomünchnone with an unactivated alkene to produce a complex polycyclic compound in one step has been reported.[95,96] The isomünchnones derived from the $Rh_2(OAc)_4$-catalyzed reaction of acyclic diazo imides **150**−**154** were found to undergo facile cycloaddition onto the tethered π-bond to provide polycyclic adducts **155**−**159** (Scheme 40). A notable feature of this cycloaddition is that only one diastereomer is formed. The relative stereochemistry of cycloadduct **159** was determined by X-ray crystallography.[95a] This confirmed the fact that addition of the olefin took place *endo* with regard to the isomünchnone dipole. Only low yields of cycloadducts were observed when the deacylated diazo imides were subjected to the cyclization−cycloaddition reaction.[95a] This result indicates that the reactivity of the 1,3-dipole is significantly diminished in the absence of the electron-withdrawing acyl group and that alternative pathways then become competitive.

This methodology was further extended, leading to an increase in complexity of the resulting polyheterocyclic systems, by employing a series of cyclic diazo imides.[96b] Treatment of cyclic diazo imides **160**-**162**

Scheme 40



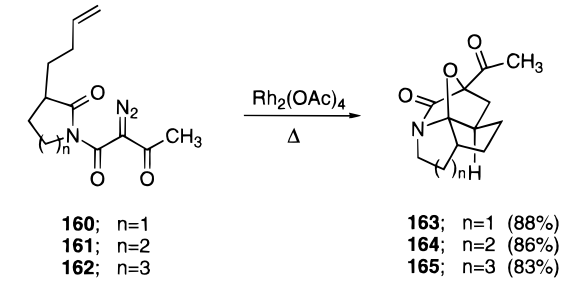
150; R^1=R^2=H
151; R^1=H; R^2=CH_3
152; R^1=R^2=CH_3

155; R^1=R^2=H
156; R^1=H; R^2=CH_3
157; R^1=R^2=CH_3

153 **158**

154 **159**

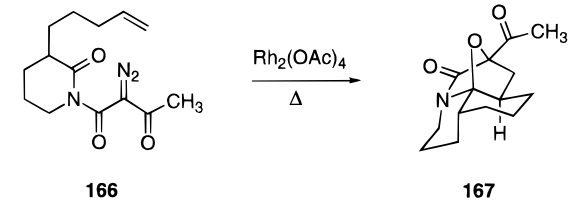
Scheme 41



160; n=1
161; n=2
162; n=3

163; n=1 (88%)
164; n=2 (86%)
165; n=3 (83%)

Scheme 42



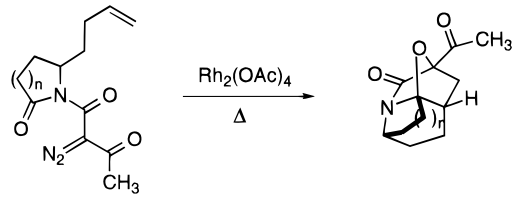
166 **167**

with $Rh_2(OAc)_4$ led to good yields of cycloadducts **163**-**165**. Only one diastereomer was produced in each cycloaddition. Once again, the stereochemical outcome is the result of an *endo* cyclization of the π-bond onto the isomünchnone dipole and this was confirmed by an X-ray crystallographic analysis of cycloadduct **163**[96b] (Scheme 41).

Lengthening the alkenyl tether by one carbon atom was observed to have no effect on the ability of the isomünchnone to cycloadd across the olefinic π-bond. This was shown in a study of the cycloaddition behavior of diazo imide **166** which afforded cycloadduct **167** in 86% yield as a single diastereomer[96b] (Scheme 42).

The generality of the method was further demonstrated by synthesizing cyclic diazo imides **168** and **169** in which the alkenyl tether was placed α to the nitrogen atom[96b] (Scheme 43). When these diazo imides were treated with a catalytic amount of $Rh_2(OAc)_4$, the tandem cyclization−cycloaddition process gave polycycles **170** and **171** in 69% and 76% yield, respectively. With both of these systems, the length of the alkenyl tether proved to be crucial for the intramolecular cycloaddition reaction across the isomünchnone dipole. Only when the tether was a butenyl group was cycloaddition observed. If the length of the tether was increased or decreased by one methylene unit, no products derived from intramolecular cycloaddition were encountered.[96b]

Scheme 43



168; n=1
169; n=2

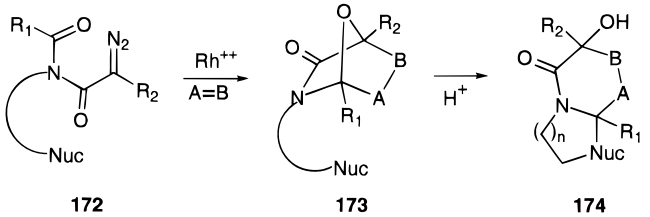
170; n=1
171; n=2

B. Cyclization–Cycloaddition–Cationic π-Cyclization Reactions

The 1,3-dipolar cycloaddition of isomünchnones derived from α-diazo imides of type **172** provides a uniquely functionalized cycloadduct (*i.e.*, **173**) containing a "*masked*" *N*-acyliminium ion. By incorporating an internal nucleophile on the tether, annulation of the original dipolar cycloadduct **173** would allow the construction of a more complex nitrogen heterocyclic system, particularly B-ring homologues of the erythrinane family of alkaloids.[102] By starting from simple acyclic diazo imides **172**, our research group has established a tandem cyclization−cycloaddition−cationic π-cyclization protocol as a method for the construction of complex nitrogen polyheterocycles of type **174** (Scheme 44).

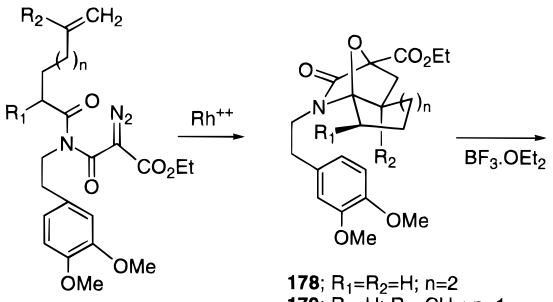
The first example of such a process involved the treatment of diazo imides **175**, **176**, and **177** with a catalytic quantity of rhodium(II) perfluorobutyrate in CH_2Cl_2 at 25 °C which provided cycloadducts **178** (98%), **179** (95%), and **180** (90%) (Scheme 45). Formation of the *endo* cycloadduct with respect to the carbonyl ylide dipole in these cycloadditions is in full accord with molecular mechanics calculations which show a large energy difference between the two diastereomers. When the individual cycloadducts were exposed to $BF_3{\cdot}OEt_2$ (2 equiv) in CH_2Cl_2 at 0 °C, the cyclized products **181** (97%), **182** (95%), and **183** (85%) were isolated as single diastereomers. The *cis* stereochemistry of the A/B ring junction for **181**−**183** was assigned by analogy to similar erythrinane products obtained via a Mondon-enamide-type

Scheme 44



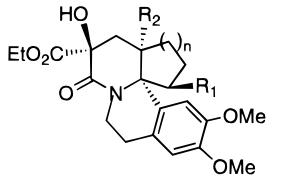
172 **173** **174**

Scheme 45



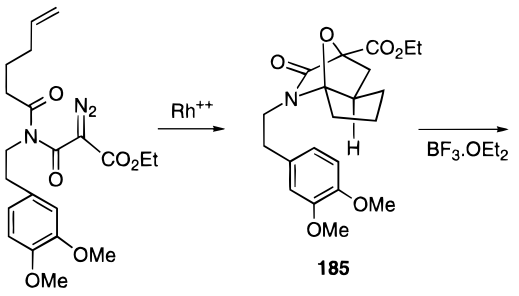
175; $R_1=R_2=H$; n=2
176; $R_1=H$; $R_2=CH_3$; n=1
177; $R_1=CH_3$; $R_2=H$; n=1

178; $R_1=R_2=H$; n=2
179; $R_1=H$; $R_2=CH_3$; n=1
180; $R_1=CH_3$; $R_2=H$; n=1



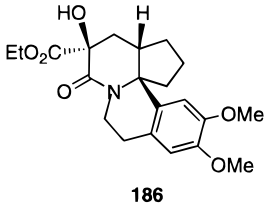
181; $R_1=R_2=H$; n=2
182; $R_1=H$; $R_2=CH_3$; n=1
183; $R_1=CH_3$; $R_2=H$; n=1

Scheme 46



184

185



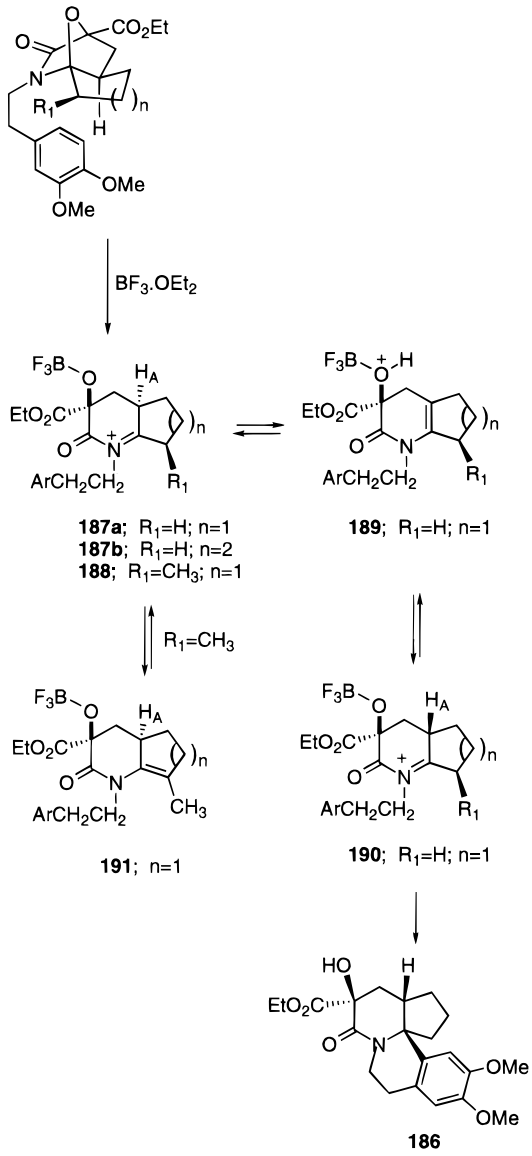
186

cyclization[103−105] and was unequivocally verified by an X-ray crystal analysis of all three cycloadducts. In all three cases the *anti* stereochemical relationship is still maintained between the hydroxyl stereocenter (from the oxygen bridge) and the bridgehead proton (R_2 = H) or methyl (R_2 = CH_3) group.

When the dipolar cycloadduct **185** derived from the unsubstituted alkenyl diazo imide **184** was exposed to BF_3·OEt_2, the resulting cyclized product **186** (90%) was identified as the all *syn* tetracyclic lactam **186** by an X-ray crystal analysis (Scheme 46). Thus, in contrast to the other three systems, the bridgehead proton of **186** lies *syn* to the hydroxyl stereocenter of the original cycloadduct.

It is assumed that the intermediate *N*-acyliminium ions formed from the Lewis acid-assisted ring opening of the isomünchnone cycloadducts undergo rapid proton loss to produce tetrasubstituted enamides. In the case of **185**, this process is clearly evident as

Scheme 47



187a; $R_1=H$; n=1
187b; $R_1=H$; n=2
188; $R_1=CH_3$; n=1

189; $R_1=H$; n=1

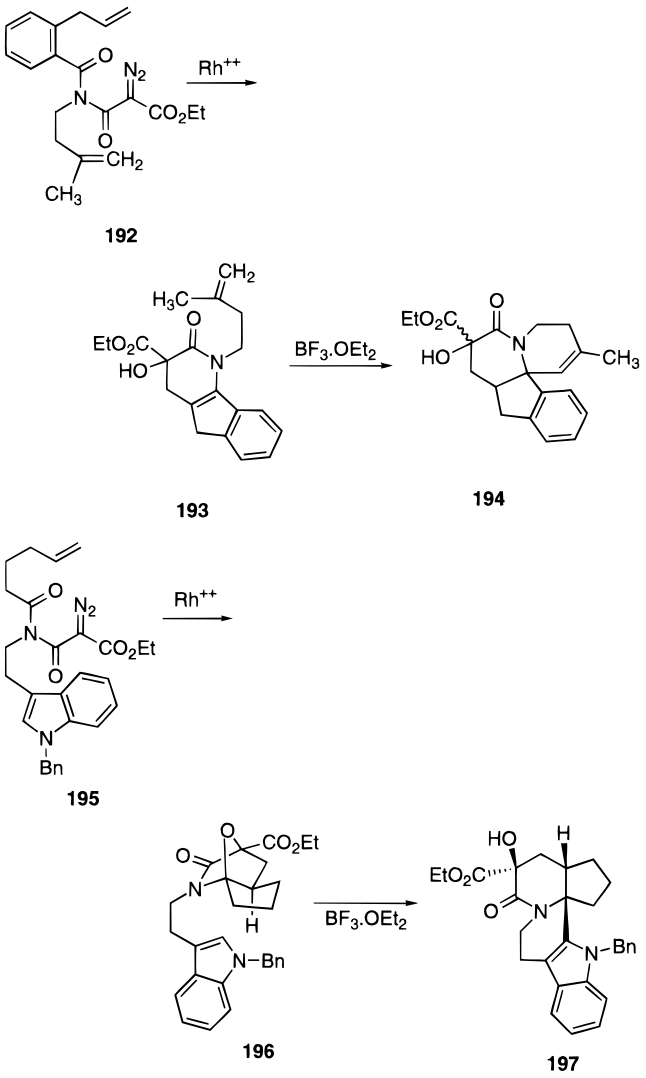
191; n=1

190; $R_1=H$; n=1

186

witnessed by the stereochemical outcome observed in product **186**. Loss of the bridgehead proton H_A in **187** (dihedral angle 90° with respect to the *N*-acyliminium ion π-bond) is fast relative to π-cyclization. Intramolecular axial reprotonation of enamide **189** from the β-face generates the diastereomeric iminium ion **190** which then undergoes intramolecular cationic π-cyclization from the least sterically congested face to give the observed all-*syn* isomer **186** (Scheme 47). Molecular mechanics calculations show that the *cis* A/B ring fusion in **186** is 4.6 kcal favored over the *trans* diastereomer and presumably some of this thermodynamic energy difference is reflected in the transition state for cyclization. The additional methyl group present in the related 6/5 cycloadduct (*i.e.*, **188**) promotes loss of the proton adjacent to it and this results in the formation of enamide **191**. Stereoselective reprotonation from the least congested α-face regenerates **188** which is trapped intramolecularly by the aromatic nucleus. Cyclization always occurs from the least hindered side as has already been established by Mondon and coworkers.[103] Cationic cyclizations of this type are known to be governed by steric control.[106] In the case

Scheme 48



192 193 194 195 196 197

of cycloadduct **179**, the bridgehead proton does not exist and thus deprotonation can only occur in one direction. Apparently the initially formed iminium ion derived from **178** (*i.e.*, **187b**; $n = 2$) undergoes fast π-cyclization prior to proton loss. In this case, the deprotonation step is significantly slower than in the 6/5 system due to the larger dihedral angle (113°) between proton H_A and the π-system of the *N*-acyliminium ion. The stereochemical outcome in **181** is the result of a stereoelectronic preference for axial attack by the aromatic ring of the *N*-acyliminium ion from the least hindered side.

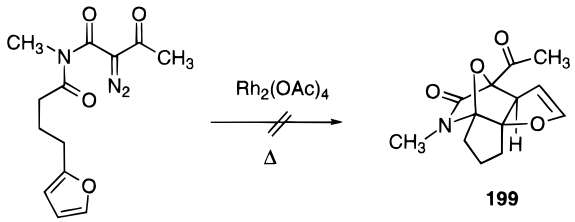
Two additional systems which illustrate the scope and variety of π-systems which can be employed in this tandem process are outlined below. The Rh(II)-catalyzed reaction of diazo imide **192** gave rise to a transient bicyclic adduct that was not isolable, as it underwent rapid ring opening to give the conjugated indenyl enamide **193** (85%). Exposure of **193** to $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 40 °C resulted in a 3:1 mixture of diastereomeric tetracyclic lactams **194** in 88% yield thereby demonstrating that tethered alkenes can also be utilized in the third step of these cascade reactions (Scheme 48). Another substitution variation that was investigated corresponded to the placement of an indolyl tether on the amide nitrogen. Thus, treatment of diazo imide **195** with $Rh_2(pfb)_4$ gave cycloadduct **196** (98%) which was readily converted into **197** in 60% isolated yield as a single diastereomer. The stereochemical assignment is based on analogy to the tetracyclic system **186**.

C. Cycloadditions across Heteroaromatic π-Systems

Given the propensity for isomünchnones to undergo dipolar cycloaddition with electron-rich dipolarophiles, systems in which the alkenyl group was incorporated into a heteroaromatic ring were also studied.[96b] Nitrile oxides and nitrile imines are known to undergo intramolecular 1,3-dipolar cycloaddition with furan and thiophenes.[107−110] This observation led our group to synthesize furanyl diazo imides **198** and **203** with the hope that intramolecular cycloaddition across the heteroaromatic system would occur. The Rh(II)-catalyzed reaction of **198**, however, failed to give the desired furanyl cycloadduct **199** (Scheme 49). However, in the presence of DMAD a novel sequence of cycloadditions occurred. The initial transient isomünchnone **200** first underwent bimolecular cycloaddition with DMAD to provide cycloadduct **201** which, in turn, underwent a subsequent intramolecular Diels−Alder reaction to give polycycle **202**[96b] (Scheme 50).

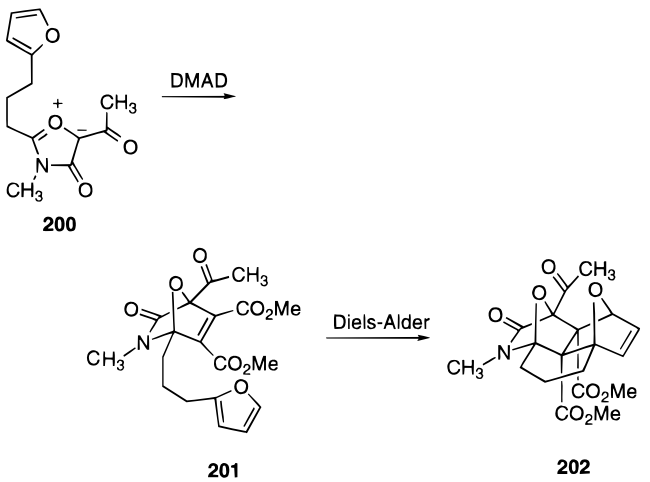
As was mentioned earlier, the chain length of the tethered alkenyl group can influence the outcome of the cycloaddition reaction. When the chain length between the furanyl and isomünchnone ring was increased by one methylene unit, as in **203** (Scheme 51), intramolecular dipolar cycloaddition occurred producing cycloadduct **204** in high yield.[111] The ability of diazo imide **203** to undergo the intramolecular cycloaddition is presumably due to proper

Scheme 49



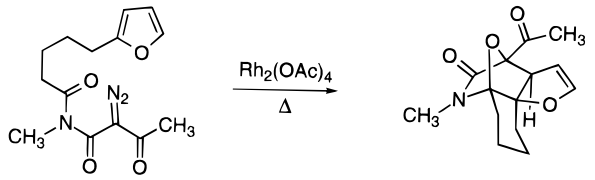
198 199

Scheme 50



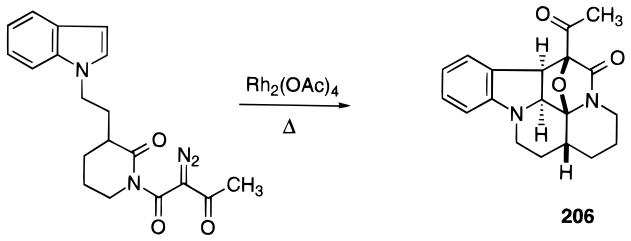
200 201 202

Scheme 51



203 204

Scheme 52



205 206

orbital overlap between the dipole and dipolarophile which is undoubtedly assisted by formation of the six-membered ring.

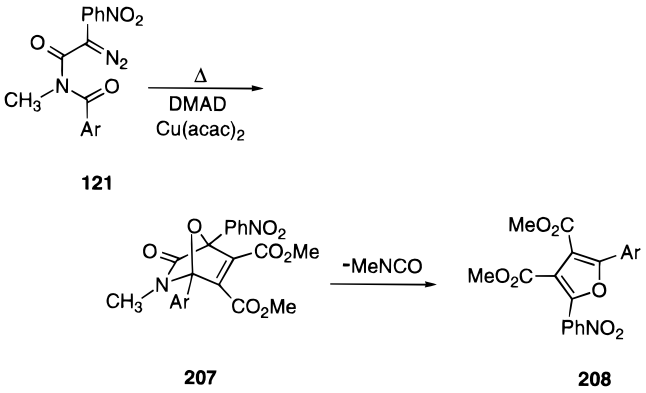
Our group has also encountered success in cycloadding an isomünchnone dipole across an indole double bond.[96b] Cycloadduct **206** was generated in high yield as a single diastereomer from the $Rh_2(OAc)_4$-catalyzed reaction of diazo imide **205** (Scheme 52). The assignment was unequivocally established by an X-ray crystal structure. The ready construction of these polyheterocycles in one step, and in high overall yield, clearly demonstrates the potential of intramolecular dipolar cycloadditions of isomünchnones as a strategy for natural product synthesis.

D. Cycloadditions across Triple Bonds

Sydnones and münchnones are known to undergo cycloaddition with acetylenic dipolarophiles to give pyrazoles and pyrroles by spontaneous extrusion of carbon dioxide from the initially formed cycloadducts.[112−122] Analogously, the cycloaddition of isomünchnones with acetylenic dipolarophiles followed by the extrusion of an alkyl or aryl isocyanate (RNCO) has proven to be an effective method for the synthesis of substituted furans. The Ibata group investigated the bimolecular 1,3-dipolar cycloaddition of aryl-substituted isomünchnones with a number of acetylenic dipolarophiles.[123] Aryl diazo imides of type **121** were heated in the presence of a catalytic amount of $Cu(acac)_2$ and the appropriate acetylenic dipolarophile (Scheme 53). Formation of the substituted furan was found to be temperature dependent; higher temperatures (*ca.* 120 °C) were needed for complete conversion to the furan. It was reasoned that the extrusion of methyl isocyanate was not as facile as the loss of carbon dioxide from sydnones and münchnones.[123]

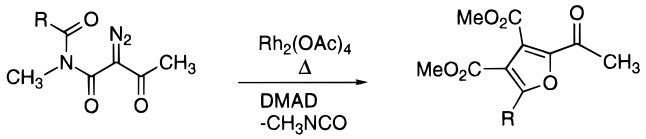
Non-aryl-substituted isomünchnones also undergo the same transformation but under less rigorous conditions. Thus, when acyclic diazo imides **139** and **140** were subjected to $Rh_2(OAc)_4$ catalyzed decomposition in the presence of DMAD, cycloaddition followed by extrusion of methyl isocyanate occurred to give the substituted furans **209** and **210**[18c] (Scheme 54).

Scheme 53



121 207 208

Scheme 54



139; R=CH_3
140; R=CH_2CH_3

209; R=CH_3
210; R=CH_2CH_3

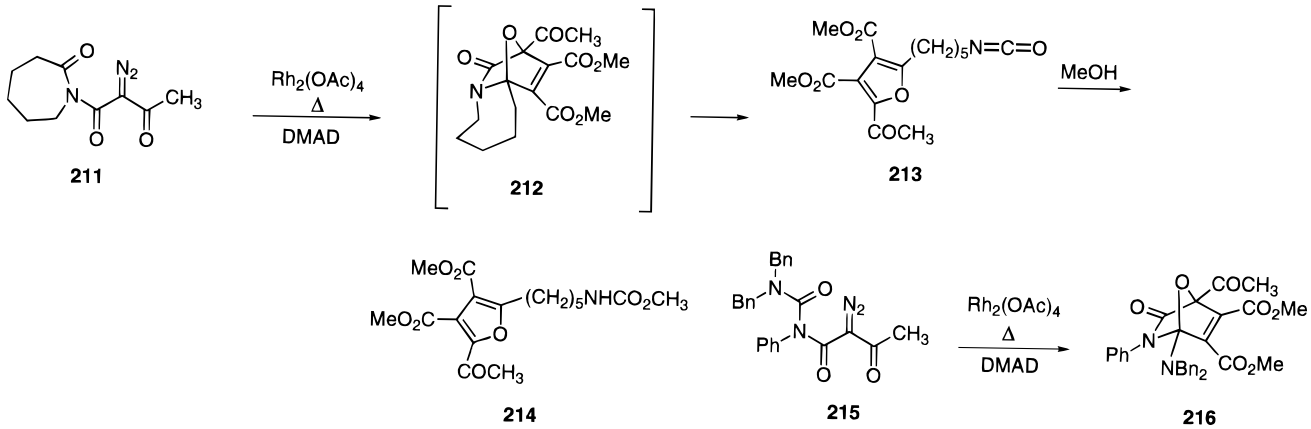
Instead of losing methyl isocyanate, the extrusion of a tethered alkyl isocyanate occurred when the bicyclic diazo imide **211** was used. The rhodium(II) acetate-catalyzed reaction of **211** in the presence of DMAD produced furanoisocyanate **213** in 85% yield (Scheme 55). The anticipated cycloadduct **212** was not isolated, but instead underwent a subsequent [4 + 2] cycloreversion under the reaction conditions to give the observed product. The initially formed furanoisocyanate **213** was characterized as its urethane derivative **214** by reaction with methanol.[96] Interestingly, treatment of the structurally related dibenzyl(diazoacetyl)urea **215** with $Rh_2(OAc)_4$ and DMAD afforded cycloadduct **216** which was stable enough to be isolated.[96]

Several additional examples of the intramolecular cycloaddition of unactivated acetylenes with isomünchnones were reported by Maier.[95b] This cycloaddition approach represents an efficient method to provide rapid access to annulated furans present in several sesqui- and diterpenes, such as the paniculides,[124] furanonaphthoquinones,[125] furodysin, and furodysinin.[126,127] The decomposition of acyclic acetylenic diazo imides **217** and **218** with $Rh_2(OAc)_4$ resulted in cycloaddition and retro-Diels−Alder extrusion of methyl isocyanate to give annulated furans **219** and **220** in good yield (Scheme 56). The overall transformation is closely related to the intramolecular Diels−Alder reactions of acetylenic oxazoles extensively studied by Jacobi and co-workers.[128]

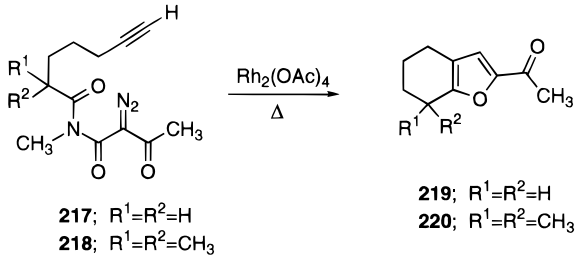
An interesting feature of isomünchnones is their ability to undergo 1,3-dipolar cycloaddition with carbonyl compounds, a reaction which is unprecedented with münchnones.[129] This is illustrated by the reaction of diazo imide **221** with $Cu(acac)_2$ in the presence of several different aldehydes and ketones which resulted in the formation of cycloadducts of type **222**−**224** (Scheme 57). When benzil was used as the dipolarophile, the regioselectivity was reversed giving rise to cycloadduct **225** as the only regioisomer.

The use of diazo thioamides to generate thioisomünchnones has also been used in the author's

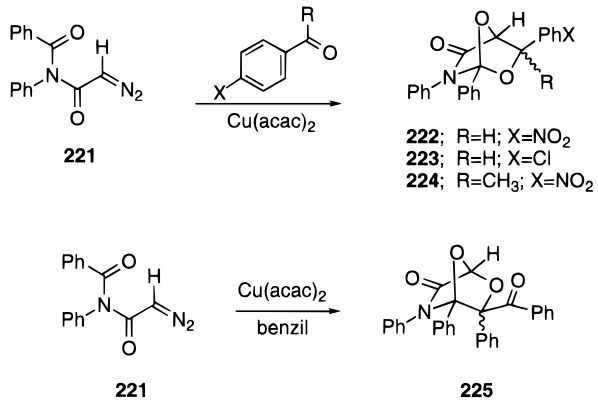
Scheme 55



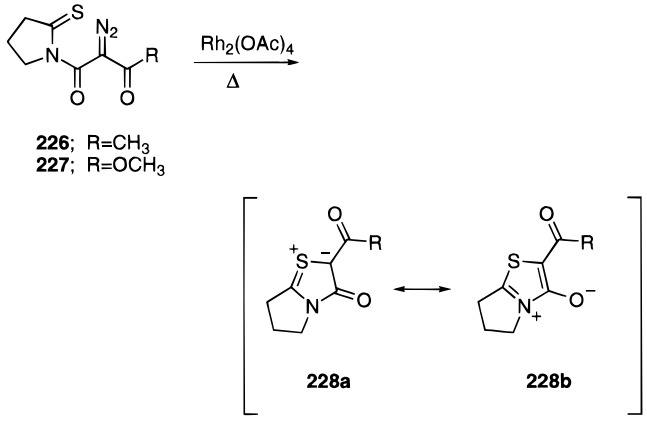
Scheme 56



Scheme 57



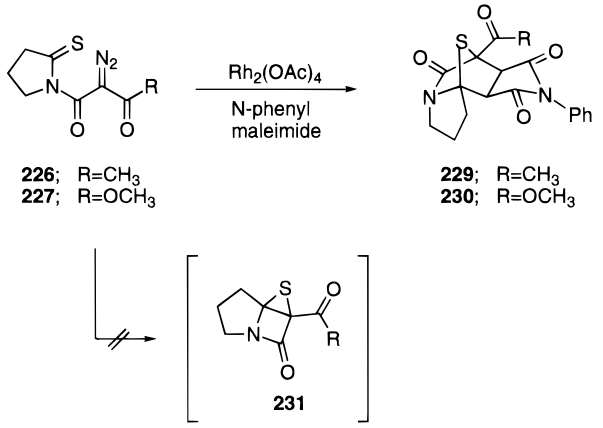
Scheme 58



laboratory.[130] Thus, the $Rh_2(OAc)_4$-catalyzed reaction of diazothioamide **226** or **227** results in the formation of thioisomünchnone **228** (Scheme 58).

This transient dipole readily cycloadds with *N*-phenylmaleimide to give diastereomeric mixtures of

Scheme 59

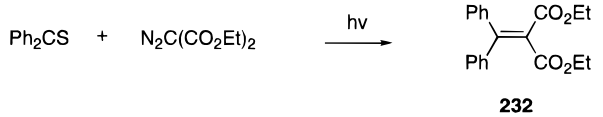


cycloadduct **229** or **230**. The facility with which the cycloaddition occurs is undoubtedly related to the stability of the aromatic mesoionic dipole. Ring closure to the episulfide **231** would not only destroy the aromatic character of the dipole, but would also lead to a highly strained ring[130] (Scheme 59).

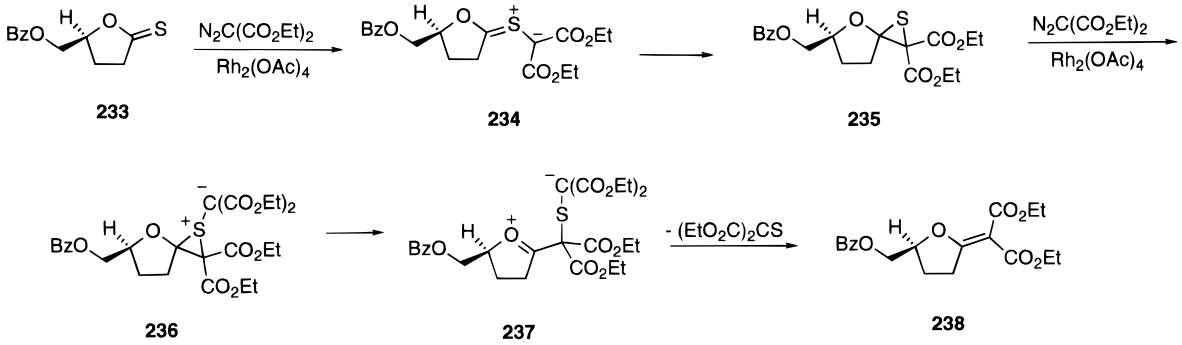
IV. Formation of Thiocarbonyl Ylides

Thiocarbonyl ylides have been the subject of much interest in recent years due to their potential role as intermediates in a variety of reactions. Generation of thiocarbonyl ylides via the interaction of metallo carbenoids with thiocarbonyl compounds has not been extensively investigated.[131−133] In certain cases, thiocarbonyl ylides produce olefins presumably by a sequence of reactions involving cyclization to a transient episulfide followed by loss of sulfur to give the alkene. An example of this process was first encountered by Weininger in 1969.[134] Photolysis of diethyl diazomalonate in the presence thiobenzophenone produced diethyl 2,2-diphenylethylene-1,1-dicarboxylate (**232**) as the major product (Scheme 60). This compound was suggested to be formed by attack of the initially generated carbene onto thiobenzophenone with formation of a thiocarbonyl ylide. The

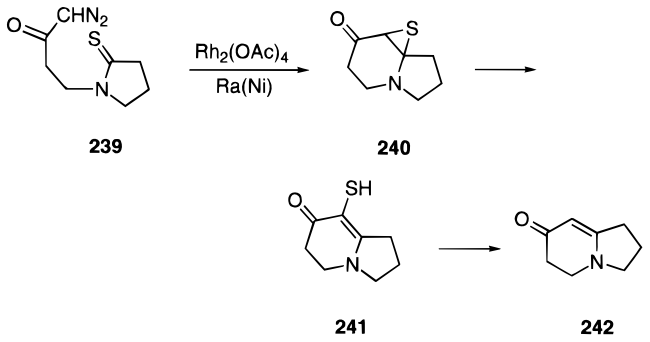
Scheme 60



Scheme 61



Scheme 62



reactive dipole cyclizes to generate an episulfide which then loses sulfur to form the alkene. Thermolysis of diethyl diazomalonate and thiobenzophenone in refluxing diglyme also afforded good yields of olefin **232**.

Reaction of tetrahydro-2-furanthione **233** with diethyl diazomalonate in the presence of rhodium(II) acetate affords 2-(acylmethylene)tetrahydrofuran **238** in good yield[135] (Scheme 61). 2-(Acylmethylene)-tetrahydrofuran derivatives, such as **238**, are usually obtained in a much poorer yield by the condensation of lactone acetals with active methylene compounds.[136] The formation of **238** was interpreted to involve the sequential formation of the corresponding sulfur ylide **234** by reaction of **233** with the carbenoid generated from the diazo compound. Cyclization of the thiocarbonyl ylide to form episulfide **235** followed by further reaction of the three-membered heterocycle with excess carbenoid accounts for the formation of the product. The reaction pathway is reminiscent of the Eschenmoser sulfide-contraction reaction using thiolactam substrates.[137]

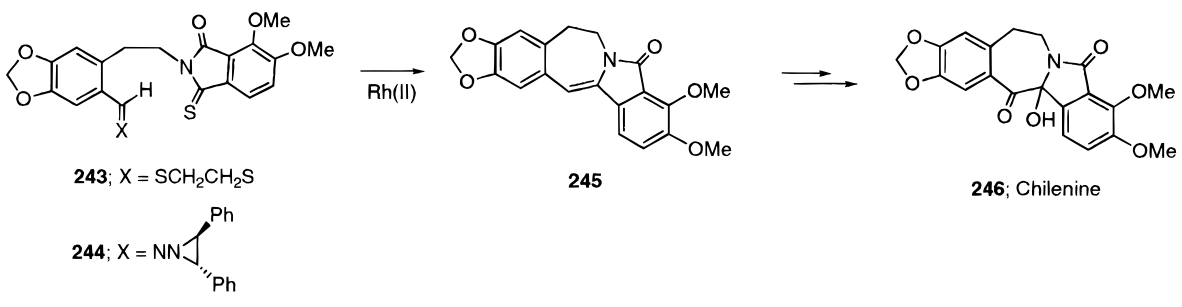
Danishefsky and co-workers have extended this tandem reaction sequence to the synthesis of a variety of novel heterocyclic natural products.[138−141] A typical example involves the annulation of diazomethyl vinyl ketone with a variety of secondary thiolactams to give diazothioamido ketones such as **239**. Treatment of **239** with rhodium(II) acetate in refluxing benzene followed by Raney nickel desulfurization afforded the novel heterocycle **242**[138] (Scheme 62). The initially formed intermediate from the Rh(II)-catalyzed reaction was identified as ene thiol **241**. This compound was formed by cyclization of the ylide to episulfide **240** followed by a subsequent isomerization to produce **241**.

Synthesis of the isoindolobenzazepine alkaloid chilenine (**246**) was achieved by a transition metal-catalyzed reductive coupling of a dithiolane (or 2,3-diphenyl-*N*-aziridinohydrazone) with an unsymmetrical dimethoxyphthalimide[139] (Scheme 63). Thermolysis of **243** in the presence of tungsten hexacarbonyl resulted in reductive cyclization of the dithiolane−monothiophthalimide to give enamide **245** in modest yield. Another method used to synthesize **245** involved the addition of hydrazone **244** to a refluxing suspension of rhodium(II) acetate in toluene. In the first step, hydrazone **244** lost *trans*-stilbene to give 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 **245**.

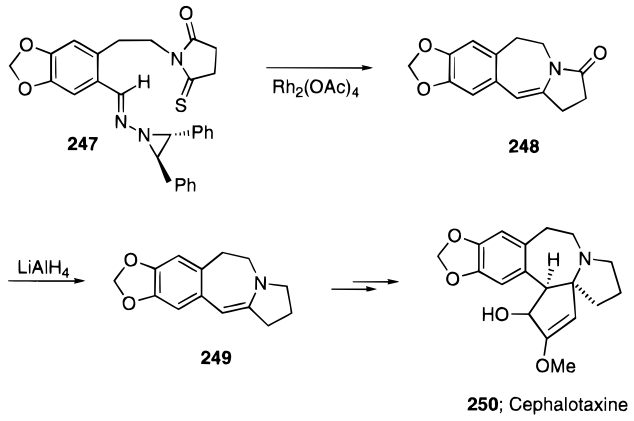
Danishefsky also investigated the hydrolytic succinoylation and subsequent reductive ring closure of several substituted dihydroisoquinolines.[140] Weinreb's[142] key intermediate **249** used in an earlier cephalotaxin synthesis was prepared by the addition of hydrazone **247** to a refluxing suspension of rhodium(II) acetate in toluene (Scheme 64). This resulted in the formation of enamide **248** which was further reduced with lithium aluminum hydride to give **249**.

The lactam annulation methodology was also applied to the synthesis of indolizomycin (**254**).[141]

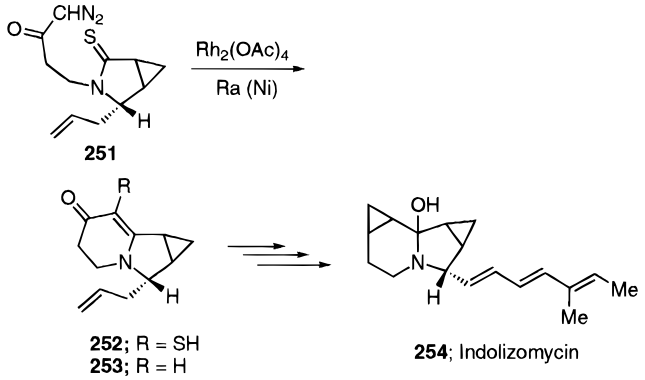
Scheme 63



Scheme 64



Scheme 65



Reaction of thioamide **251** with rhodium(II) acetate followed by treatment of the initially formed product with Raney nickel gave dihydropyridone **253**, which was eventually taken on to the natural product (Scheme 65). The key step in the conversion of **251** to **253** involved the intermediacy of a thiocarbonyl ylide dipole.

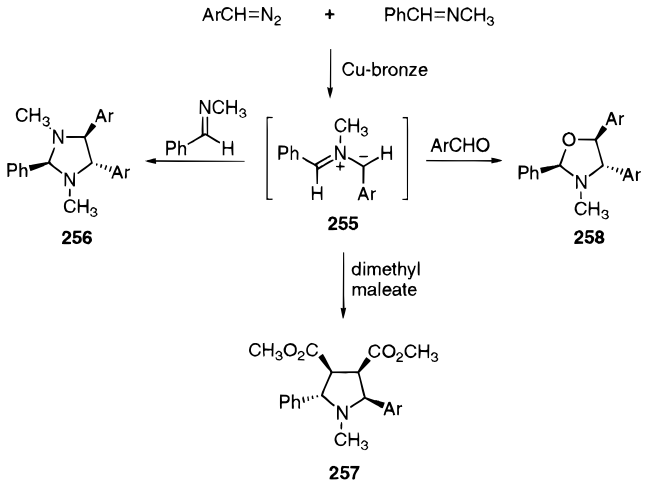
V. Formation of Nitrogen Ylides

A. Azomethine Ylides Derived from Imines and Oximes

The interaction of a metallo carbene with an imine nitrogen atom to give a transient azomethine ylide has attracted attention over the past decade.[48] Some of the standard methods for generating azomethine ylides involve the thermal or photolytic ring opening of aziridines,[143] desilylation,[144] or dehydrohalogenation[145] of iminium salts, and proton abstraction from imine derivatives of α-amino acids.[146] Azomethine ylides are of interest because these dipoles undergo facile 1,3-dipolar cycloaddition with π-bonds to give pyrrolidines which, in turn, have been used to prepare a variety of alkaloids.[33]

The tandem reaction of carbenoids with simple imines to form azomethine ylides which then undergo 1,3-dipolar cycloaddition with various dipolarophiles was first reported in 1972.[147] Thus, treatment of phenyldiazomethane with copper bronze in the presence of excess *N*-benzylidenemethylamine resulted in the isolation of imidazoline **256** (Scheme 66).

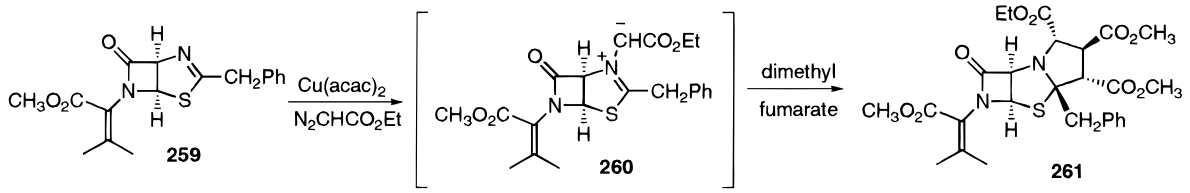
Scheme 66



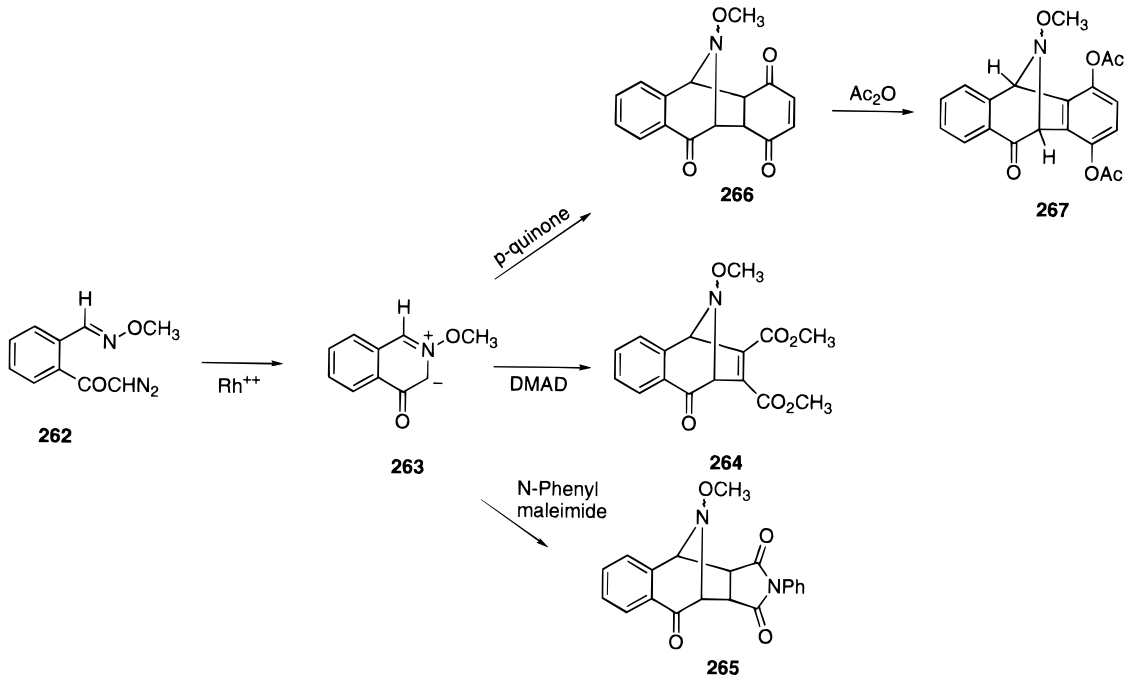
Formation of this product was rationalized by carbenoid addition onto the imine nitrogen to give azomethine ylide **255** which then underwent a 1,3-dipolar cycloaddition with another molecule of imine to produce the observed product. Bartnik and Mloston subsequently extended this observation by using other dipolarophiles.[148] For example, catalytic decomposition of phenyldiazomethane and *N*-benzylidenemethylamine in the presence of dimethyl maleate or benzaldehyde gave pyrrolidine **257** and oxazolidine **258**, respectively. In both cases, no product resulting from the trapping of the ylide with a molecule of imine could be observed. Catalytic decomposition of phenyldiazomethane with other Schiff bases was found to proceed via formation of a *trans*-1,3-dipole. Depending on the size and quantity of the substituent groups, the ylide either undergoes cyclization in a conrotatory sense to a *cis*-aziridine or [3 + 2]-cycloaddition to an available π-bond. The reactivity of double bonds toward the ylide was found to decrease in the order of C=C > C=O > C=N.

Since they were first isolated from penicillins, thiazoloazetidinones such as **259** have become versatile intermediates in the synthesis of various β-lactam antibiotics. Soft electrophiles prefer to attack at the sulfur atom, whereas hard electrophiles react with the thiazoline nitrogen. Thomas and coworkers have investigated the reaction of thiazoloazetidinone **259** with metal carbenoids[149] (Scheme 67). Treatment of **259** with a large excess of ethyl diazoacetate in the presence of copper(II) acetoacetonate and dimethyl fumarate gave the bis-methoxycarbonyl adduct **261**. The formation of this material involves an initial addition of the ethoxycarbonyl carbenoid onto the thiazoline nitrogen to produce azomethine ylide **260**. This reactive dipole undergoes a subsequent 1,3-dipolar cycloaddition with the added dipolarophile to give the observed product. The reaction was found to be both regio- and stereoselective. No products derived from the reaction of the carbenoid at the sulfur atom or at the C−C double bond were observed. The stereochemistry at C-3 of the cycloadduct is consistent with approach of the

Scheme 67



Scheme 68

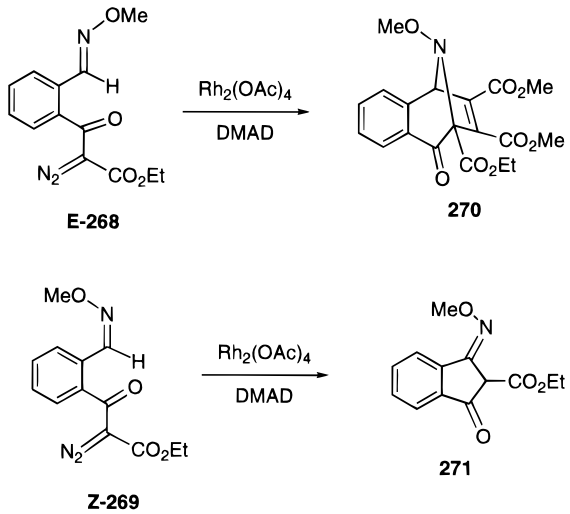


fumarate ester from the less hindered side of the ylide.

The formation and intramolecular dipolar cycloaddition of azomethine ylides formed by carbenoid reaction with C−N double bonds has recently been studied by the author's group.[150] Treatment of 2-(diazoacetyl)benzaldehyde *O*-methyl oxime (**262**) with rhodium(II) octanoate in the presence of dimethyl acetylenedicarboxylate or *N*-phenylmaleimide produced cycloadducts **264** and **265**, respectively (Scheme 68). The cycloaddition was also carried out using *p*-quinone as the dipolarophile. The major product isolated corresponded to cycloadduct **266**. The subsequent reaction of this material with excess acetic anhydride in pyridine afforded diacetate **267** in 67% overall yield from **262**. This latter compound incorporates the basic dibenzo[*a*,*d*]cyclohepten-5,10-imine skeleton found in MK-801,[151] which is a selective ligand for brain cyclidine (PCP) receptors that has attracted considerable attention as a potent anticonvulsive and neuroprotective agent.[152,153]

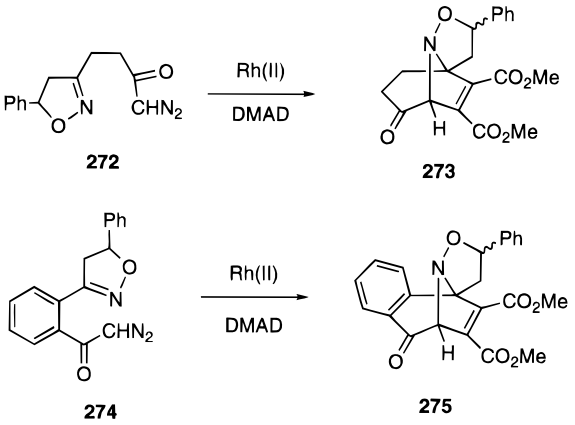
The oxime nitrogen lone pair of electrons must be properly oriented so as to interact with the rhodium carbenoid.[150] Thus, subjection of the *E*-oximino isomer **268** to a catalytic quantity of $Rh_2(OAc)_4$ in CH_2Cl_2 (40 °C) with a slight excess of DMAD afforded the bimolecular cycloadduct **270** in 93% yield (Scheme 69). In sharp contrast, when the isomeric *Z*-oximino diazo derivative **269** was exposed to the same reaction conditions, only indanone oxime **271** (80%) was obtained. The formation of this product is most likely derived by an intramolecular C−H insertion reaction.

Scheme 69



The success achieved with the Rh(II)-catalyzed transformations of *E*-oximino diazo carbonyl compounds prompted our group to study some additional systems where the C−N π-bond was configurationally locked so that azomethine ylide formation would readily occur. Toward this end, we investigated the Rh(II)-catalyzed behavior of isoxazoline **272** in the presence of DMAD. This reaction afforded the azome-

Scheme 70



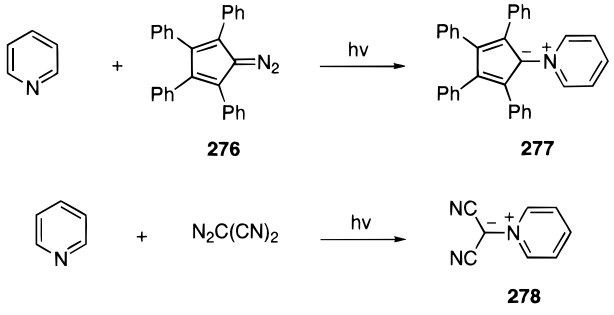
thine-derived cycloadduct **273** as a 4:1 mixture of diastereomers in 65% yield. A similar transformation occurred using the α-diazoacetophenone derivative **274** which produced isoxazolo[3,2-*a*]isoquinoline **275** as a 2:1 mixture of diastereomers in 82% yield (Scheme 70).

B. Pyridinium Ylides

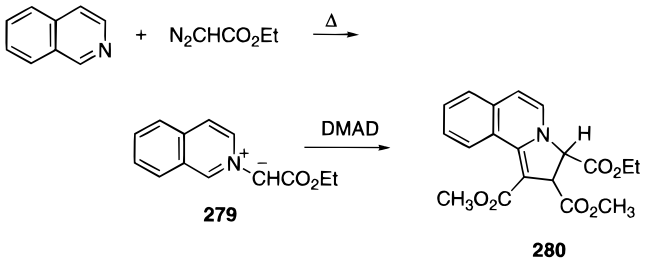
Since their introduction in 1960,[154] pyridine ylides have become increasingly popular probes of the dynamics of carbenes which lack chromophores.[155−160] The combination of high reactivity, favorable spectroscopic properties, and long ylide lifetime has allowed the study of the dynamics of a variety of "*invisible*" carbenes.[161] The technique has found use in the study of aryl, arylhalo, alkyl, alkylalkoxy, alkylhalo, arylsiloxy, and dialkyl carbenes.[162−165] A number of examples dealing with the preparation of stable pyridinium ylides have also been reported in the literature.[166−169] Pyridinium tetraphenylcyclopentadienylide (**277**) was synthesized by irradiating 2,3,4,5-tetraphenyldiazocyclopentadiene (**276**) in pyridine. Addition of water precipitated the purple ylide **277** in almost quantitative yield[166−168] (Scheme 71). This process appears to be general for a number of substituted pyridines (*i.e.*, 2-picoline, 3-picoline, and 2,6-lutidine). In an analogous fashion, *N*-dicyanomethylide **278** was prepared from the photolysis of diazomethanedicarbonitrile in pyridine.[169]

Although the transition metal-catalyzed reaction of α-diazocarbonyl compounds with aromatic molecules has received much attention in recent years,[12] the metal-catalyzed behavior of these compounds with *N*-containing heteroaromatics has not been extensively studied. An early example involved the

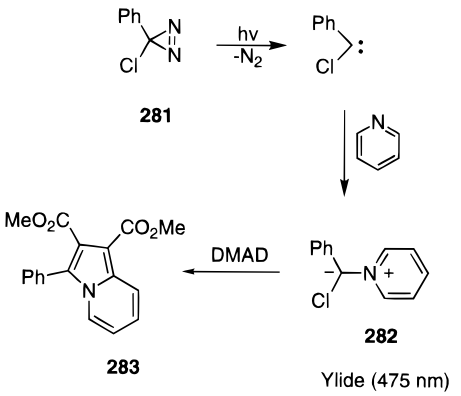
Scheme 71



Scheme 72



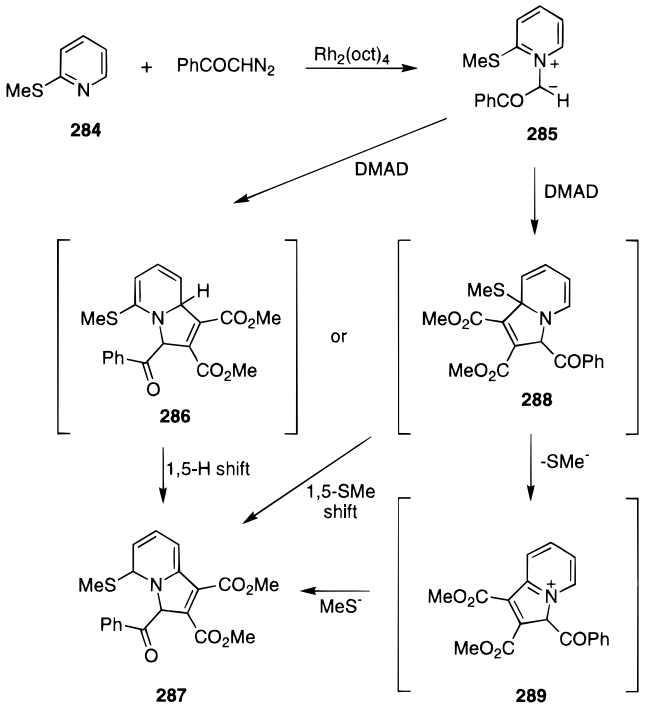
Scheme 73



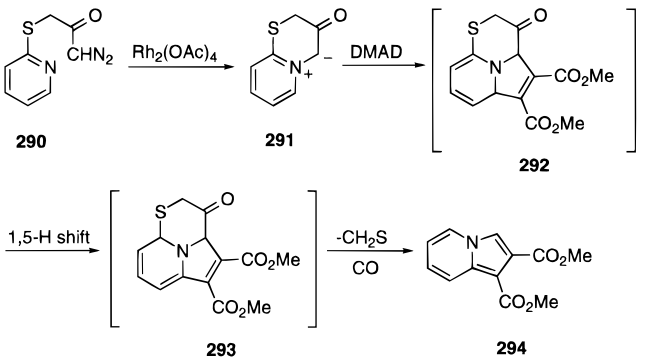
preparation of isoquinoline−carbethoxymethylide **279** by the thermal decomposition of ethyl diazoacetate in the presence of isoquinoline[170] (Scheme 72). The same ylide could also be obtained from *N*-carbethoxymethylene isoquinolinium bromide by the elimination of hydrogen bromide. Ylide **279** is a red crystalline solid which is stable in the absence of moisture. The dipolar character of **279** was established by its reaction with dimethyl acetylenedicarboxylate which led to the formation of cycloadduct **280**. Platz and co-workers reported that the photolysis of phenylchlorodiazirine **281** in the presence of both pyridine and DMAD produced cycloadduct **283** in 30% yield by dipolar cycloaddition of DMAD to the ylide followed by loss of HCl[171] (Scheme 73).

As part of our group's continuing involvement with the chemistry of azomethine ylides, we became interested in examining the cyclization of α-diazo substituted N-containing heteroaromatic systems as a method for ylide generation. Aside from the above examples using pyridines[162] and isoquinolines,[170] little was known about the diazo cyclization process with *N*-heteroaromatic systems when we initiated our work in this area.[172] The Rh(II)-catalyzed reaction of α-diazoacetophenone in the presence of 2-(methylthio)pyridine and dimethyl acetylenedicarboxylate gave 3-benzoyl-1,2-(dicarbomethoxy)-3,5-dihydro-5-(methylthio)indolizine (**287**) (Scheme 74). The formation of **287** proceeds via a pyridinium ylide formed by attack of the nitrogen lone pair on the electrophilic keto carbenoid. Subsequent dipolar cycloaddition of ylide **285** with DMAD occurs at the less substituted carbon atom to give cycloadduct **286**. This transient species is converted to **287** by means of a 1,5-sigmatropic hydrogen shift. The results are also consistent with the formation of the regioisomeric cycloadduct **288** which undergoes a 1,5-thiomethyl shift perhaps via the tight ion pair **289**.

Scheme 74



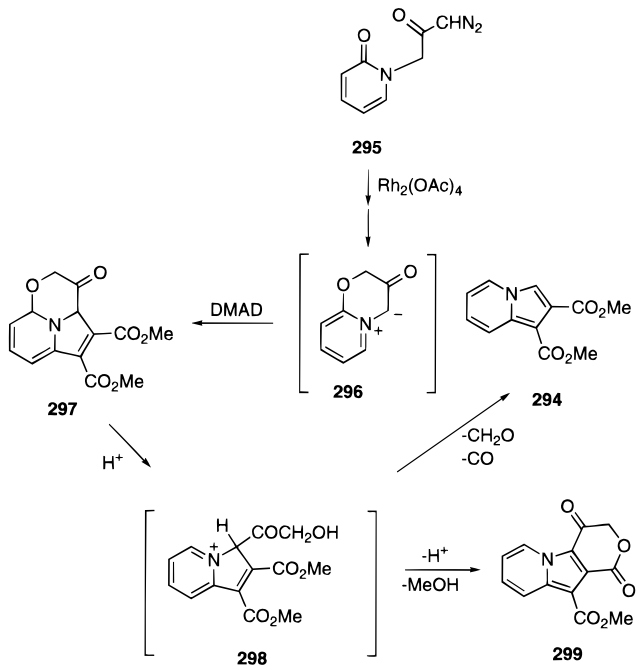
Scheme 75



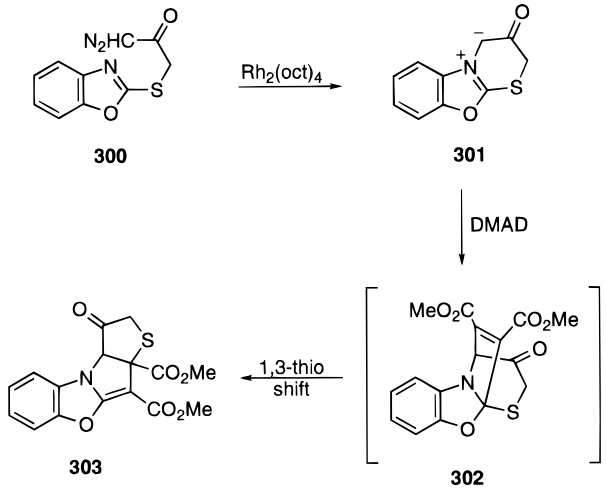
A related cyclization occurred using 1-diazo-3-(2-pyridylthio)-2-propanone (**290**). The initial reaction involves generation of the expected pyridinium ion **291** by intramolecular cyclization of the keto carbenoid onto the nitrogen atom of the pyridine ring (Scheme 75). Dipolar cycloaddition of **291** with DMAD affords cycloadduct **292** which undergoes a subsequent 1,5-hydrogen shift to give **293** followed by fragmentation of CO and CH_2S to produce indolizine **294**.

Interestingly, the Rh(II)-catalyzed reaction of 1-(3-diazoacetonyl)-2-pyridone (**295**) with DMAD was found to give cycloadducts derived from an azomethine ylide. The initial reaction involves generation of the expected carbonyl ylide dipole by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. A subsequent proton exchange generates the thermodynamically more stable azomethine ylide **296** which is trapped by DMAD eventually producing cycloadduct **297** (Scheme 76). The formation of products **294** and **299** from cycloadduct **297** proceeds by an acid-catalyzed C−O bond cleavage giving pyridinium ion **298**. This transient species can lose a proton and lactonize to

Scheme 76



Scheme 77

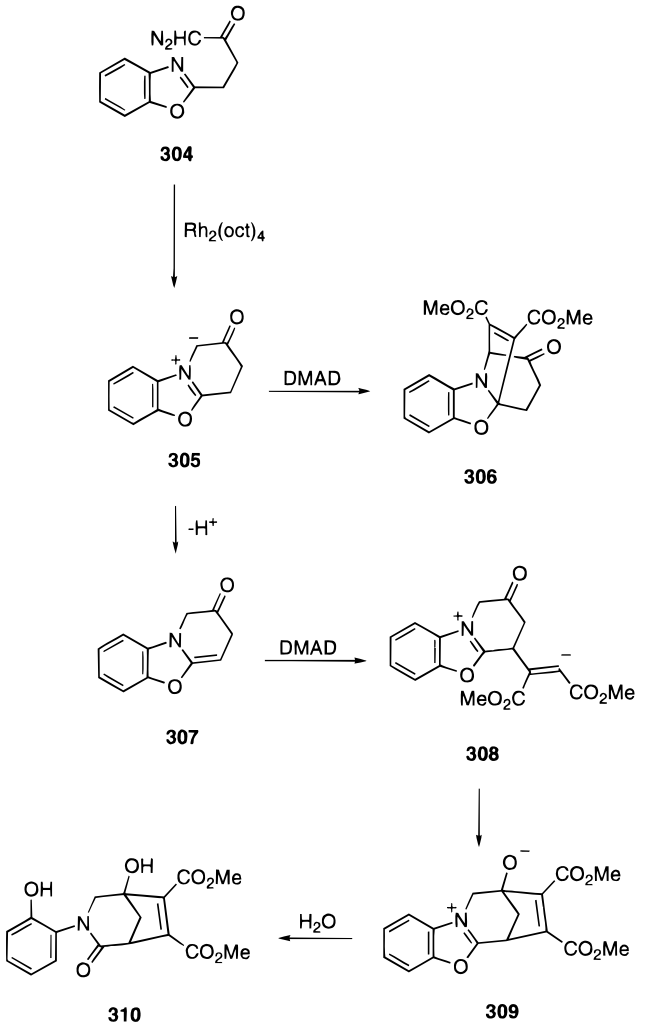


299 or else undergo fragmentation to afford formaldehyde, carbon monoxide, and indolizine **294**.

Azomethine ylide cycloadducts derived from keto carbenoid cyclization onto a thiobenzoxazole have also been encountered in our studies. When 1-diazo-3-(2-benzoxazolylthio)-2-propanone (**300**) was used, the initially formed cycloadduct **302** undergoes a subsequent 1,3-sigmatropic thio shift to give the thermodynamically more stable product **303**. Good analogy exits in the literature for the suggested 1,3-sigmatropic shift[173] (Scheme 77).

An entirely different reaction occurred when 2-(4-diazo-3-oxobutyl)benzoxazole (**304**) was treated with Rh(II) octanoate. In addition to undergoing dipolar cycloaddition to produce cycloadduct **306** (20%), the highly stabilized dipole (*i.e.*, **305**) formed from the benzoxazole loses a proton to produce the cyclic ketene *N*,*O*-acetal **307** (Scheme 78). This compound reacts further with the activated π-bond of DMAD to give zwitterion **308**. The anionic portion of **308** then adds to the adjacent carbonyl group, producing a new zwitterionic intermediate **309**. In the presence

Scheme 78



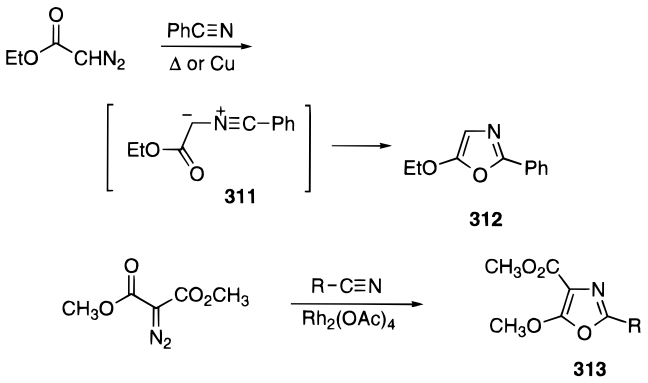
of water, this species is converted to the observed phenolic lactam **310**.

C. Nitrogen Ylides Derived from Diazocarbonyls and Nitriles

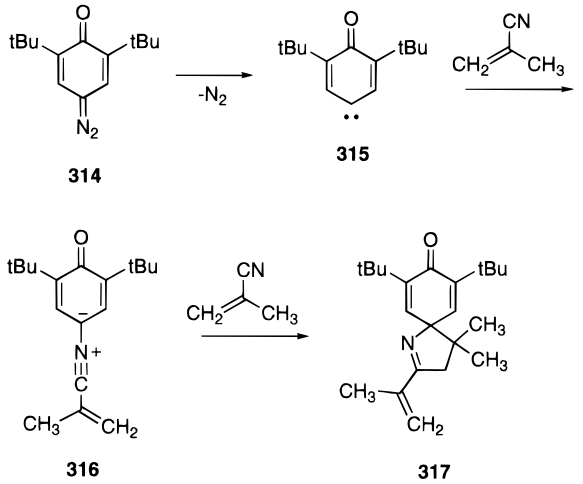
1,3-Oxazoles of various substitution patterns are well-known heterocycles for which a number of methods of synthesis have been reported.[174] Acyl carbenes or functionally equivalent species have been found to undergo cyclization with nitriles to give oxazoles in high yield via nitrile ylide intermediates.[175,176] This reaction can be induced to occur under thermal, photolytic, or catalytic conditions.[174,177,178] Huisgen and co-workers were the first to study this process in some detail.[177] Thermolysis (or copper catalysis) of a mixture of ethyl diazoacetate and benzonitrile resulted in the formation of oxazole **312**. The isolation of this product is most consistent with a mechanism involving metallo carbene addition onto the nitrile nitrogen atom to generate dipole **311** which then cyclizes to produce oxazole **312** (Scheme 79).

Dimethyl diazomalonate undergoes reaction with nitriles in the presence of rhodium(II) acetate to give 2-substituted 4-carbomethoxy-1,3-oxazoles (**313**). The

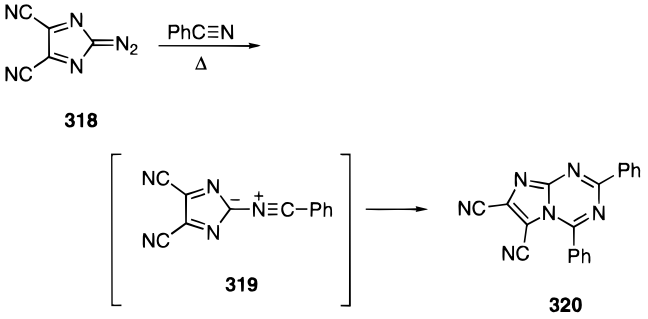
Scheme 79



Scheme 80



Scheme 81



reaction proceeds with a wide range of nitriles;[178−184] however, cyclopropanation is a competing process in the case of unsaturated nitriles.[174]

Kende and co-workers have reported on the formation of a nitrile ylide intermediate from carbenes and methyl acrylonitrile. Thermolysis of *p*-diazo oxide **314** in methyl acrylonitrile as solvent gave spirocyclic product **317** in 48% yield[185] (Scheme 80). The formation of **317** was interpreted in terms of the generation of nitrile ylide **316** followed by 1,3-dipolar cycloaddition across the C−C double bond of a second molecule of methylacrylonitrile. The regiochemistry of the cycloaddition is consistent with FMO theory.

In a somewhat similar manner, diazodicyanoimidazole (**318**) was found to give the fused heterocycle **320** when heated in benzonitrile.[186] This reaction presumably involves the intermediacy of nitrile ylide **319** (Scheme 81).

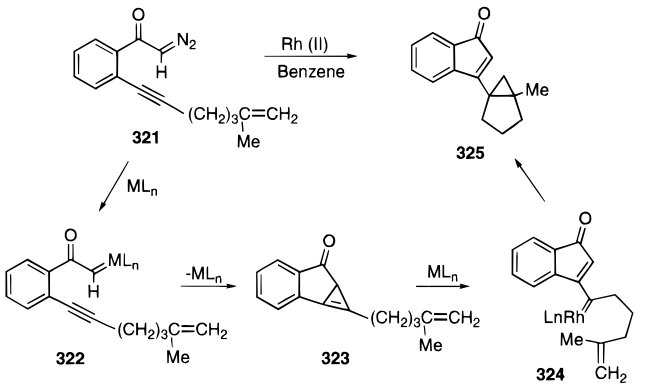
VI. Alkyne Metathesis Reaction

The first example in the literature describing the intramolecular addition of a diazo compound to an acetylene was reported by Jones and co-workers.[187] More recent work by our group,[188] as well as Hoye's,[189] has shown that the rhodium(II)-catalyzed reaction of α-diazo ketones bearing tethered alkyne units represents a powerful method for the construction of a variety of complex polycyclic skeletons. The tandem metal-catalyzed reaction of *o*-(6-methyl-6-hepten-1-ynyl)-α-diazoacetophenone (**321**) using rhodium(II) acetate was initially examined.[190] Isolation of cyclopropyl indenone **325** in 60% yield can be rationalized in terms of the formation of a vinyl carbenoid intermediate (*i.e.*, **324**) which subsequently adds across the tethered olefin (Scheme 82). It is also conceivable that a highly strained cyclopropene derivative (*i.e.*, **323**) is first formed and then rearranges to **324**. It is well known that cyclopropenes ring open to vinyl carbenes at ambient temperatures[191,192] and that these reactive intermediates may be trapped by alkenes in an inter-[193] and intramolecular fashion.[194] A related reaction occurred with α-diazo ketones **326a** and **326b** which afforded the bicycloalkanes **328** and **329** derived from intramolecular cyclopropanation[195] (Scheme 83).

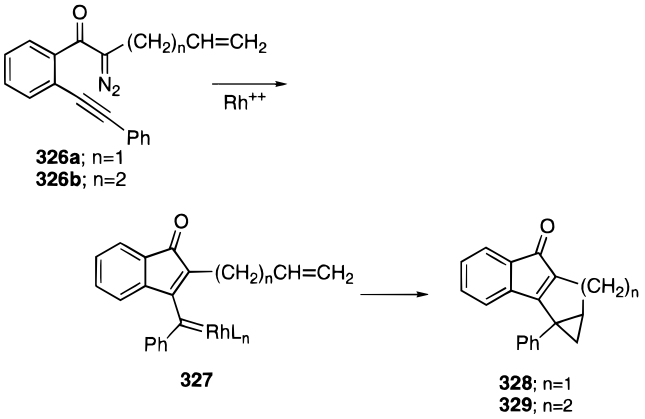
A related cyclization process was also carried out using the dienyl-substituted diazo keto alkyne **330** which afforded **331** in 58% yield. A related transformation also occurred with **334**. Addition of the vinyl carbenoid onto the dienyl π-bond gives rise to a *cis*-divinylcyclopropane which rapidly undergoes a Cope rearrangement to produce the observed product[196] (Scheme 84). Intramolecular cyclopropanation of dienes with carbenoids followed by rearrangement of the initially formed vinylcyclopropanes has been effectively utilized in synthesis.[197] The above process is analogous to some 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.[198]

Hoye and Dinsmore have also been involved in a study of the intramolecular carbenoid additions to acetylenes.[190] Their results indicate that the product distribution is markedly dependent upon the nature of the catalyst. For example, treatment of α-diazo ketone **338** with catalytic palladium(II) acetoacetonate produced cyclopropane **339** (R = CO_2Me) in 78% yield (Scheme 85). However, when rhodium(II) acetate was used as the catalyst, cyclopropane **339** was not formed. Instead, furan **341** 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 **339** (R = H) as well as the 1,2-hydrogen shift product **340**.

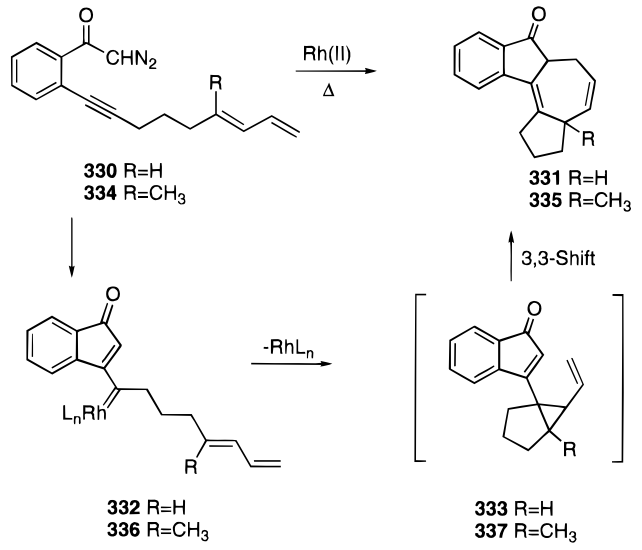
Scheme 82



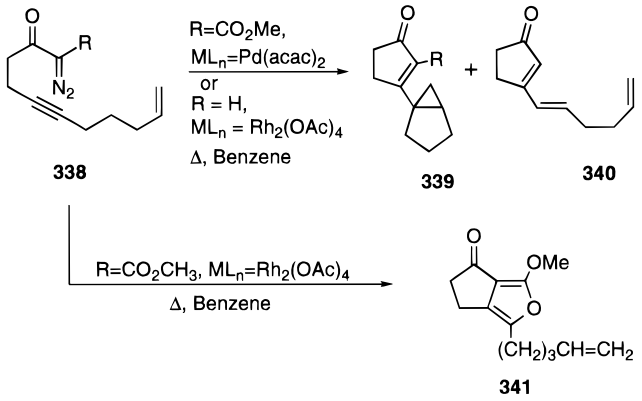
Scheme 83



Scheme 84



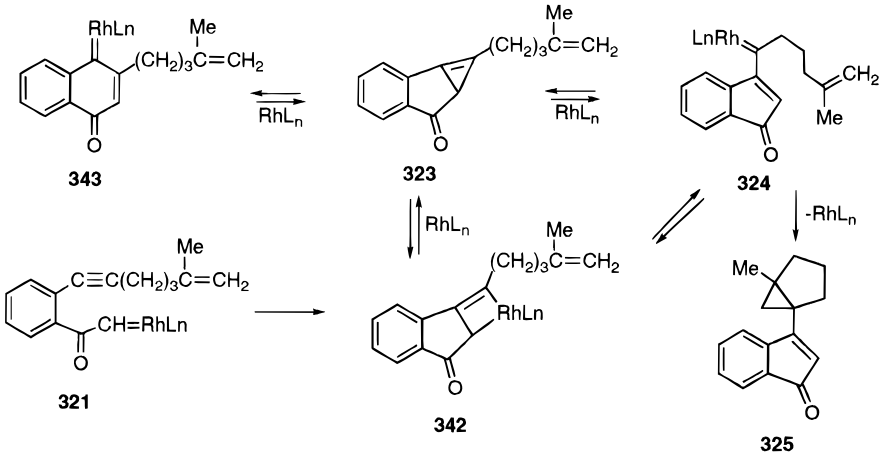
Scheme 85



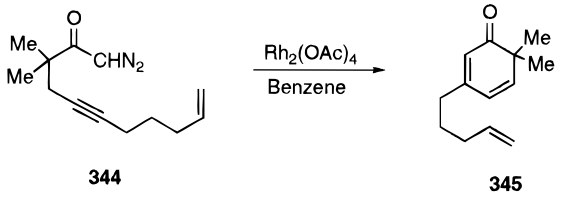
A. Mechanistic Details

The α-diazo keto alkyne insertion reactions is dependent on the catalyst used thereby suggesting that a metalated species is involved in the product-

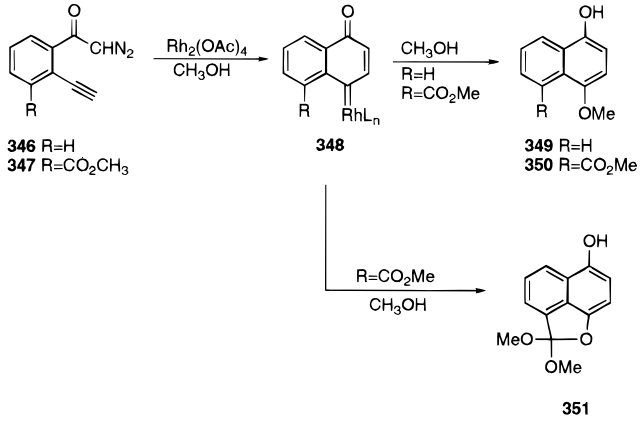
Scheme 86



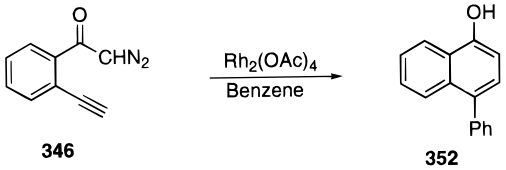
Scheme 87



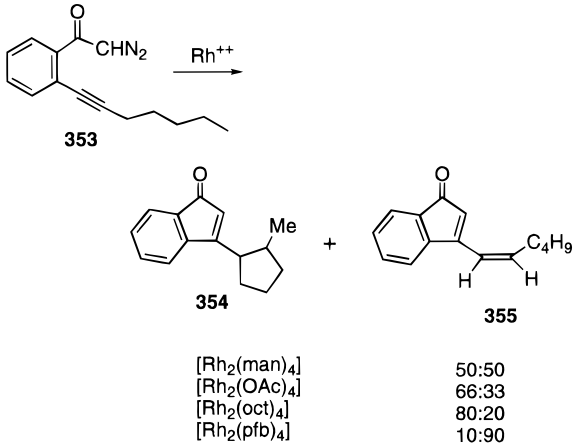
Scheme 88



Scheme 89



Scheme 90



determining step. A reasonable mechanism involves migration of the rhodium metal from the original diazo carbon to the alkyne carbon via a metallocyclobutene such as **342**. Another possibility involves the highly strained cyclopropene **323** which could be converted into an organometallic species such as **342**, **324**, or **343** under the reaction conditions[199] (Scheme 86). 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.[200]

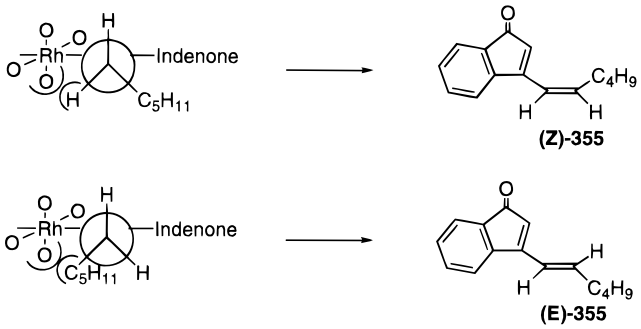
It was suggested that the exclusive formation of bicyclo[3.1.0]hexene **325** occurs by either a regiocontrolled ring opening of **323** or is the result of a reversible process that involves selective trapping of intermediate **324**.[199] To further complicate the matter, in certain cases products derived from a 6-*endo* carbene intermediate are also formed. For example, cyclohexadienone **345** was observed as one of the products from the treatment of α-diazo ketone **344** with rhodium(II) acetate[190] (Scheme 87).

When α-diazo ketone **346** (or **347**) was treated with $Rh_2(OAc)_4$, the major product corresponded to naphthol **349** (or **350**) (Scheme 88). This structure was also derived from a 6-*endo* carbenoid intermediate (*i.e.*, **348**).[191]

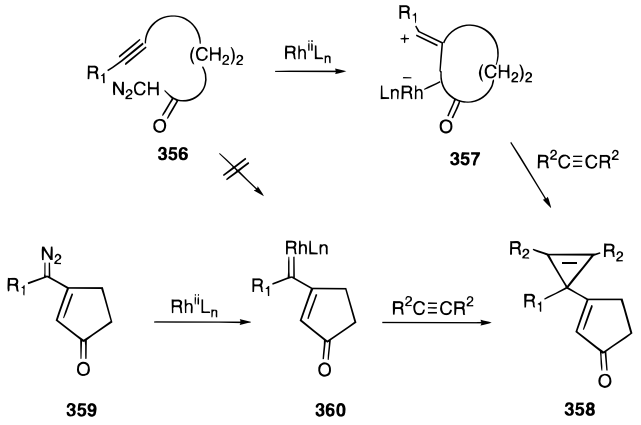
Evidence for the involvement of a 6-*endo* vinylcarbenoid was obtained by a study of the rhodium(II)-catalyzed decomposition of α-diazo ketone **346** (Scheme 89). The major product isolated from this reaction was naphthol **352** and its formation is most easily rationalized by insertion of the 6-*endo* carbenoid into benzene followed by aromatization.[191]

An interesting ligand effect was encountered in a study of the Rh(II)-catalyzed reaction of *o*-alkynyl-substituted α-diazoacetophenone derivatives.[201] A variety of structural influences were observed by varying the nature of the substituent group attached to the alkyne carbon atom. The cyclization reaction involves addition of a rhodium-stabilized carbenoid onto the acetylenic π-bond to generate a vinyl carbenoid. The vinyl carbenoid was found to undergo both C−H and C−C migration as well as δ-CH insertion into the alkyl backbone. The α-diazo alkyne insertion reactions in this system were found to be

Scheme 91



Scheme 92

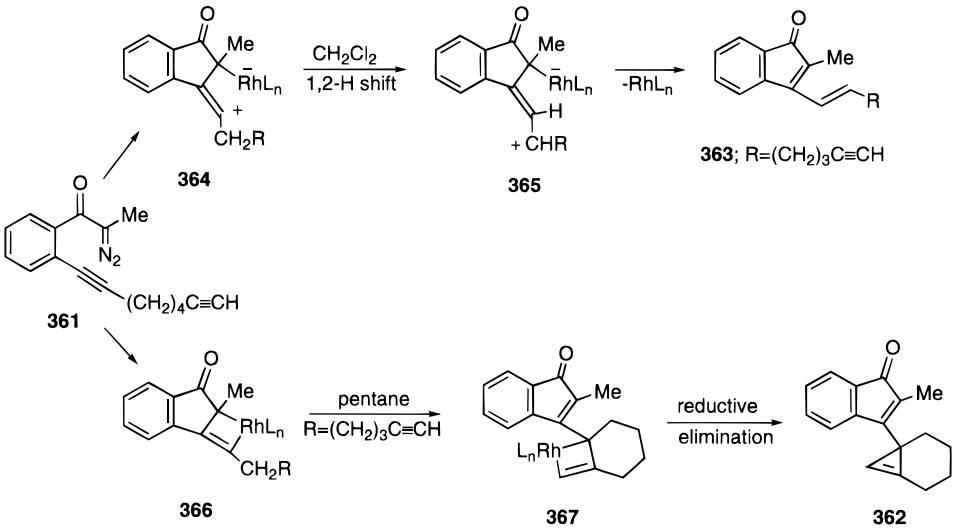


ligand dependent, thereby demanding that a metalated species is involved in the product-determining step. By changing the catalyst from Rh(II) mandelate to Rh(II) acetate to Rh(II) perfluorobutyrate, significant manipulation of the product distribution was achieved (Scheme 90). The data indicate that the more electron-withdrawing perfluorobutyrate ligand favors β-hydride elimination, while 1,5-insertion is favored by the more electron-donating ligands. The intermediate rhodium carbenoid is highly electron deficient at the carbon center and is further destabilized by an electron-withdrawing ligand. With this more reactive intermediate, the entropically less demanding β-hydride elimination pathway is favored as noted earlier. Another point worth noting is the preferential formation of the thermodynamically less stable *Z* isomer **355** which is derived from the 1,2-hydrogen shift. This stereochemical result can be attributed to constraints by the face of the rhodium carboxylate on orientation of the alkyl chain for hydrogen migration in the metal carbene intermediate.[202−204] Complicating the problem is the fact that the mechanism of reaction as well as chemoselectivity is markedly influenced by the solvent used (*vide infra*). Many intermediates may be envisioned along the pathway from **353** to **355**, and it is not an easy task to identify the mechanistic differences (Scheme 91).

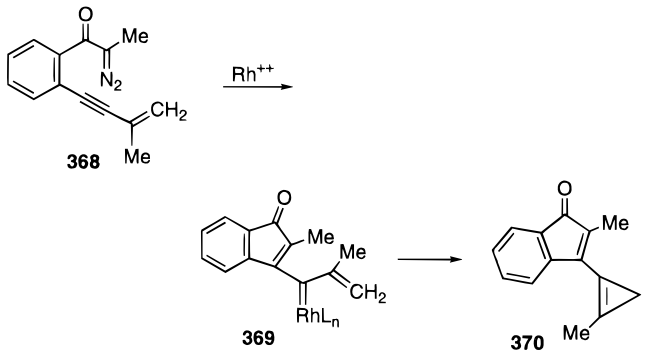
In a further study of the alkyne insertion reaction, Hoye and Dinsmore reported on the Rh(II)-catalyzed double internal−external alkyne insertion reaction of an acetylenic α-diazo ketone.[205] The initially formed rhodium carbenoid intermediate was suggested to undergo internal insertion into the tethered alkyne unit followed by a second external addition to produce a cyclopropenyl-substituted cyclopentenone derivative (*i.e.*, **358**). Migration of the rhodium metal to the remote alkyne carbon via a 2 + 2-cycloaddition/cycloreversion path (*i.e.*, **356** → **360**) was discounted on the basis that the distribution of products derived from **356** differed significantly from that obtained from the rhodium carbenoid species **360** generated from the vinylogous diazo ketone precursor **359**. Instead, the results were rationalized via the intermediacy of zwitterion **357** (Scheme 92).

Subsequent studies showed that the reaction mechanism is markedly dependent on the solvent employed in these Rh(II)-catalyzed insertion reactions.[206] Treating α-diazo ketone **361** 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 **362** (Scheme 93). When the solvent was changed from pentane to methylene chloride, a 2:1 mixture of *cis*- and *trans*-alkenyl-substituted indenones **363** was formed. What is so remarkable is the degree to which chemoselectivity can be achieved by simply changing the solvent from CH_2Cl_2 to pentane. The mechanism proposed to account for the formation of indenone **363** involves stepwise cyclization of the initially formed carbenoid in accord with the Hoye−Dinsmore pro-

Scheme 93



Scheme 94



posal.[205] A 1,2-hydrogen shift from **364** would result in the formation of **365**, and this is followed by collapse to **363** and regeneration of the rhodium catalyst. The intermediates involved in the formation of **363** are dipolar, which would explain why the generation of **363** is strongly inhibited in pentane. When pentane is used as the solvent, metal migration occurs via the metallocyclobutene intermediates **366** and **367** so as to avoid charge buildup. Treatment of *o*-alkynenyl-substituted α-diazoacetophenone **368** with rhodium(II) acetate produced the cyclopropenyl-substituted indenone **370** in high yield.[207] In this case, the initially formed vinyl carbenoid **369** undergoes rapid cyclization to give the cyclopropene ring (Scheme 94).

B. Rearrangement of Alkynyl Carbenoids

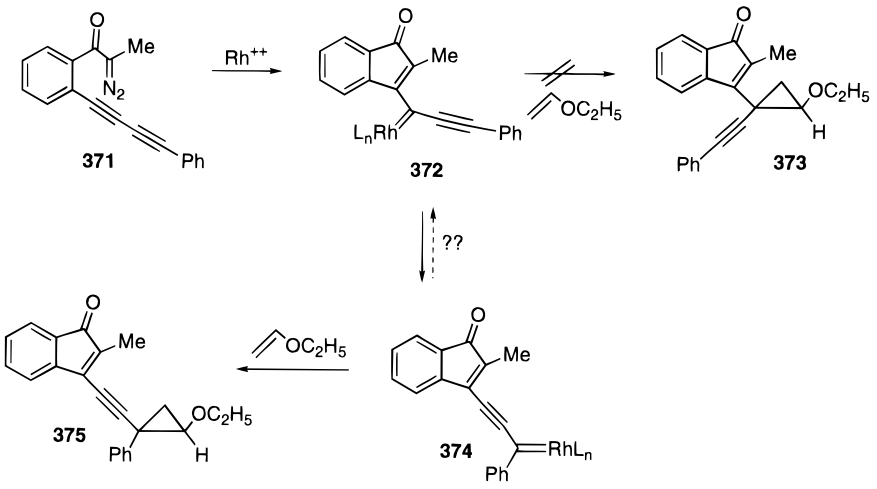
The ease with which α-diazo ketone **368** underwent the Rh(II)-catalyzed cyclization to give cyclopropenyl substituted indenones suggested that a related transformation might occur with a diacetylenic system. We therefore prepared α-diazo ketone **371** and investigated its Rh(II)-catalyzed behavior. Treatment of **371** with a catalytic quantity of rhodium(II) acetate at 25 °C in the presence of ethyl vinyl ether afforded cyclopropane **375** with notable efficiency (90% chemical yield) and selectivity (>95% isomeric purity)[208] (Scheme 95). No signs of the isomeric cyclopropane **373** could be detected in the crude reaction mixture. The exclusive formation of cyclopropane **375** can be attributed to a slower rate of trapping of carbenoid **372** by ethyl vinyl ether, perhaps as a consequence of a more congested transition state. An alternate explanation is that the equilibrium between the two carbenoids lies completely in favor of the more stable phenyl substituted isomer (*i.e.*, **374**).

The success achieved by the Rh(II)-catalyzed transformation of **371** was also extended to α-diazo ketone **376**. The intention here was to generate vinyl carbenoid **378** from the Rh(II)-catalyzed reaction and evaluate the intramolecular cyclopropanation reaction.[86] Treatment of **376** with a catalytic quantity of $Rh_2(OAc)_4$ at 25 °C in methylene chloride proceeded smoothly to give benzobicyclohexene **379** (Scheme 96). Of particular note in this latter example is the high efficiency of the tandem cyclization−rearrangement−cyclopropanation sequence leading to the final product in 95% yield.

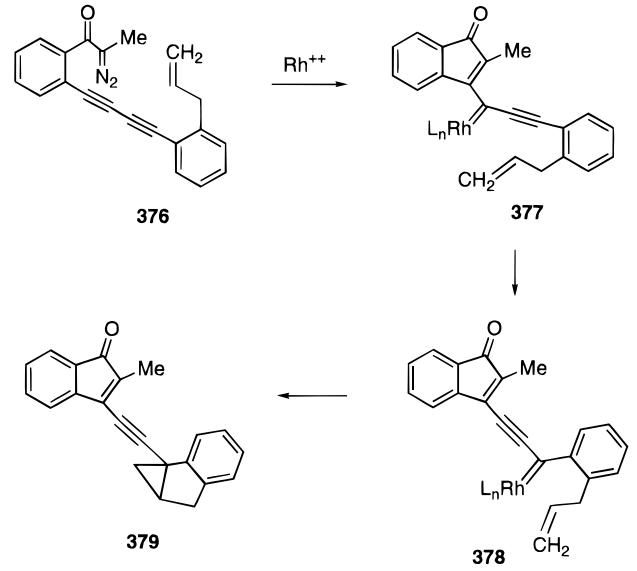
Clearly, the initially formed α-keto carbenoid **380** is readily converted to vinyl carbenoid **381** in which carbene-like reactivity has appeared on one of the original alkyne carbon atoms (Scheme 97). A further electrocyclization of **381** with the adjacent alkyne produces metallocycle **382**. This transient intermediate rapidly undergoes ring opening to either regenerate **381** or form the rearranged carbenoid **383**.

There are several alternate ways to represent metallocycle **382**. The alkynyl carbene unit consists of two orthogonal π-systems. The alkynyl carbene complex can be represented in the ionic form **384** which is comparable to a η^1-allyl complex. Binding the metal in an η^3-fashion gives **385** from which the metal can then further migrate to form the η^1-allyl intermediate **386**. With π-orbitals drawn, this can also be represented as shown in Scheme 98. In intermediate **385**, there is considerable bonding between the metal and the middle carbon of the conjugated π-system. The proposed metallocycle **382** is also similar in many respects to a tungstenacyclobutadiene complex isolated previously by Schrock and co-workers.[209] Thus, the Rh(II)-catalyzed tandem reaction of α-diazo ketones bearing dialkynyl-substituted side chains provides a promising new cyclization strategy for generating complex polycyclic ring systems. The tandem cyclization−rearrangement−cyclopropanation sequence proceeds with high chemoselectivity, and the cyclized products contain

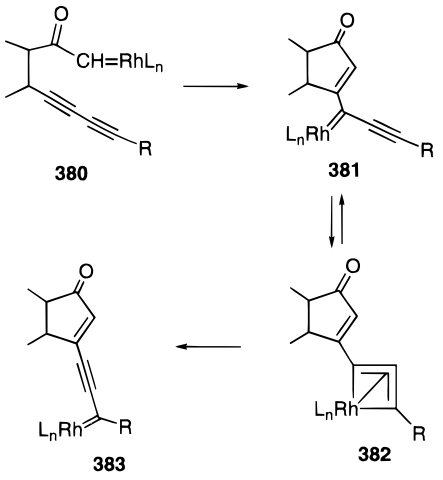
Scheme 95



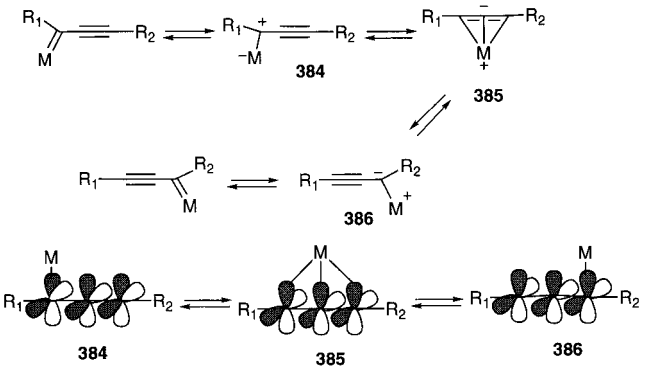
Scheme 96



Scheme 97



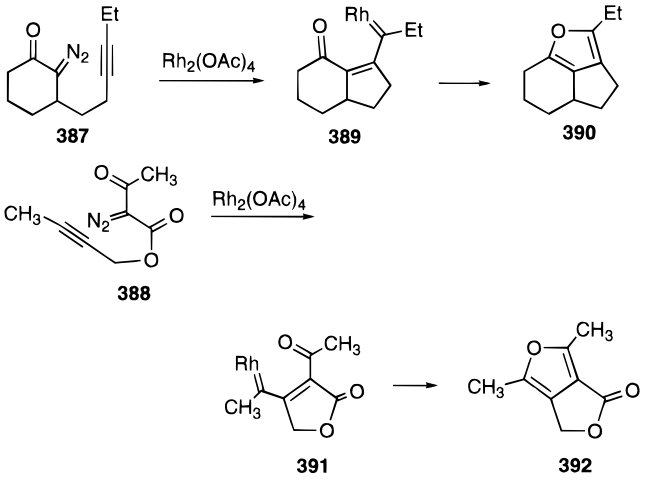
Scheme 98



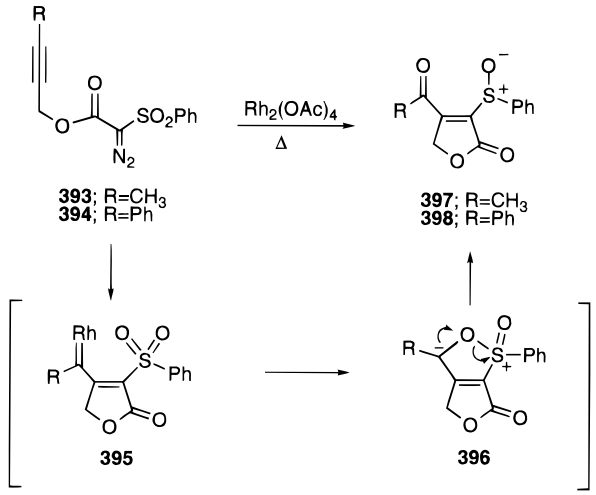
functionality that should prove useful for further synthetic transformations.

A frequently encountered reaction of dienylcarbenes involves rearrangement to indenes, cyclopentadienes, or furans.[210,211] Diazo ketones **387** and **388** were found to undergo this type of cyclization in the presence of a rhodium(II) catalyst. The initially formed vinyl carbenoid undergoes cyclization on the adjacent carbonyl oxygen to give a carbonyl ylide intermediate, which tautomerizes to produce furans **390** and **392**, respectively[212] (Scheme 99).

Scheme 99



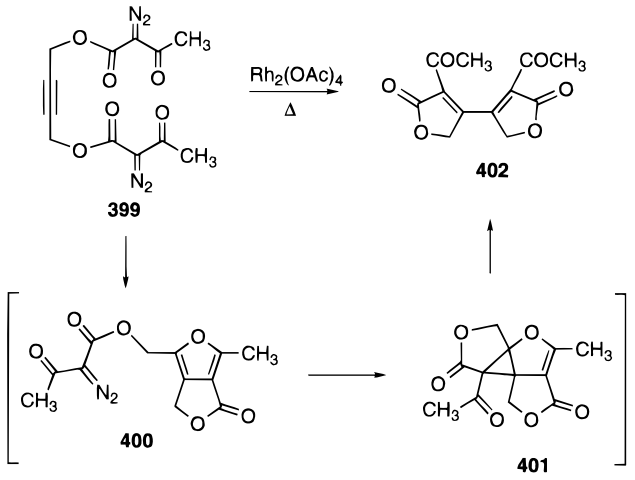
Scheme 100



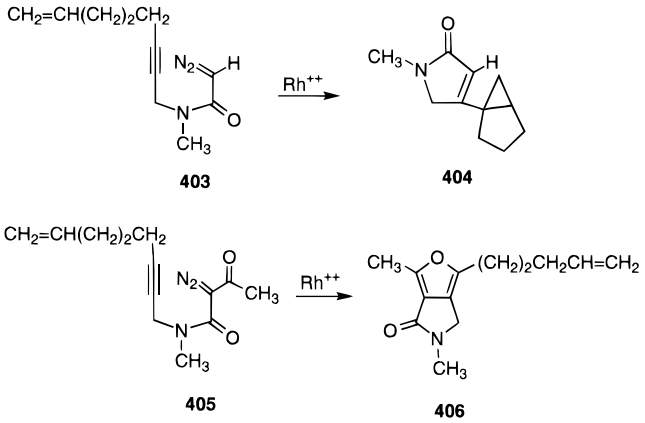
α-Diazo sulfones have previously been used for carbene-mediated C−H insertion and cyclopropanation reactions.[213−215] In order to appraise the role of this substituent group on the cyclization process, our group prepared diazo alkynyl sulfones **393** and **394.** Treatment of these compounds with Rh(II) acetate at 80 °C gave sulfoxides **397** and **398** in 60 and 90% yield, respectively[212] (Scheme 100). This novel oxygen transfer reaction can be rationalized by sulfone oxygen attack onto the vinyl carbenoid **395** producing the dipolar species **396**. Subsequent collapse of this transient affords the ring-opened butenolides **397** and **398**.[216]

Very few examples of the chemistry of bis(diazo ketones) have been reported.[52] This is not surprising when one considers the number of possible complications that may arise from the combination of two reactive carbenoid centers in the same molecule. Since the rhodium(II)-catalyzed carbenoid cascade reaction occurs in a stepwise fashion, we felt that it would be possible to control the tandem process. Indeed, heating a benzene solution of bis(diazo ketone) **399** with $Rh_2(OAc)_4$ at reflux gave rise to a 90% yield of bis(butenolide) **402** (Scheme 101). The mechanism of this unusual reaction requires that one diazo ester group react with the alkyne to generate a vinyl carbenoid which subsequently cyclizes to produce furan **400**. Further reaction of **400** with

Scheme 101



Scheme 102



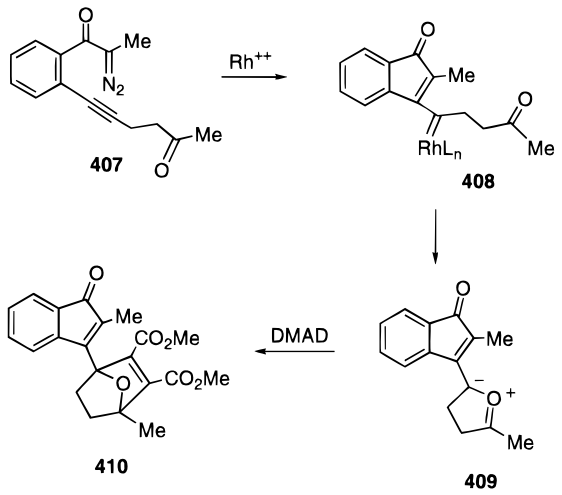
rhodium acetate generates a second carbenoid which undergoes an intramolecular cyclopropanation onto the furan ring.[217] The resulting cycloadduct **401** then undergoes a typical cyclopropanated furan fragmentation reaction to give the symmetrical product **402**.[218]

N-Alkynyl-substituted 2-diazoacetamides were also found to cyclize onto the tethered alkyne π-bond.[219] For example, treatment of diazoamide **403** with rhodium(II) acetate afforded bicyclohexane **404** in 58% yield. The related distabilized diazoamide **405**, however, afforded bicyclic furan **406** (78%) thereby indicating that the cyclized carbenoid prefers to undergo a 1,5-electrocyclization reaction rather than intramolecular cyclopropanation (Scheme 102).

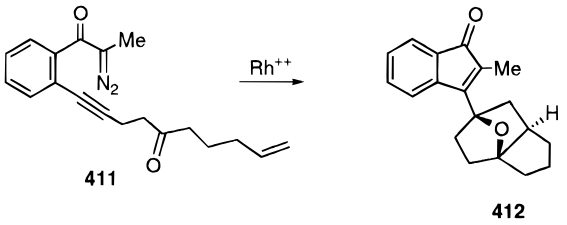
C. Merged Alkyne Metathesis Tandem Cyclization Reaction

As was mentioned earlier, our group has developed the tandem cyclization−cycloaddition reaction of α-diazo ketones as an effective method for the formation of oxapolycyclic ring systems.[53] The ease with which α-diazo ketones containing tethered carbonyl groups undergo this tandem process suggests that a similar sequence could also occur with vinylogous keto carbenoids. In order to test this possibility, we studied the Rh(II)-catalyzed behavior of diazo ketone **407** in the presence of 1 equiv of dimethyl acetylenedicarboxylate and noted that cycloadduct **410** was formed in 97% yield (Scheme 103). This result can

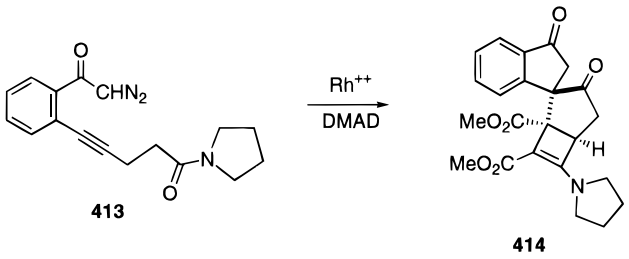
Scheme 103



Scheme 104



Scheme 105

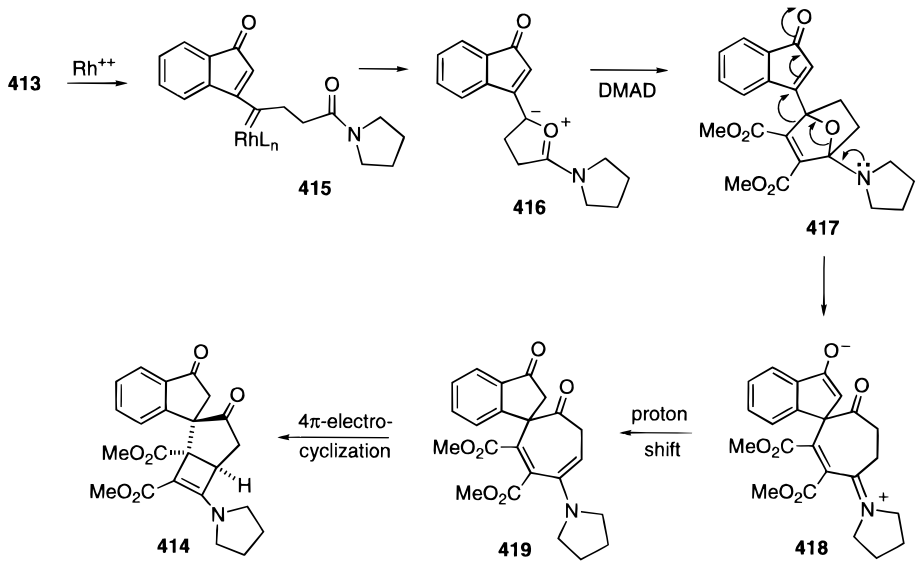


easily be accounted for in terms of the intermediacy of vinyl carbenoid **408** which cyclizes onto the oxygen atom of the neighboring carbonyl group to give the resonance-stabilized dipole **409**. Dipolar cycloaddition of **409** across the activated π-bond of DMAD afforded cycloadduct **410**.

The above domino transformation can also be performed intramolecularly by attaching the trapping agent directly to the carbonyl group. Thus, diazo ketone **411** underwent the cyclization sequence in excellent yield producing cycloadduct **412** (Scheme 104). The formation of this tricyclic ether illustrates the high synthetic potential of the annulation sequence.[220] The overall process leads to a large increase in molecular complexity in a single experimental operation. The simplicity and availability of the starting materials makes this tandem annulation sequence a powerful method for cyclopentenone construction.

Most of the previously examined cases of intramolecular carbonyl ylide formation involved systems in which the remote carbonyl was a keto group.[53] A few cases using amides and esters[56] to trap the rhodium carbenoid were also studied, but these investigations involved systems where the keto metallo carbenoid and the remote amido or ester functionalities were

Scheme 106



substituted *ortho* to each other on a benzene ring.[221,222] To simultaneously test the electronic and geometric requirements of dipole formation using the tandem annulation approach, we also examined the Rh(II)-catalyzed behavior of diazo ketoamide **413** (Scheme 105). Note that with this system, formation of the carbonyl ylide involves participation of the amido group. Moreover, the tether is a simple dimethylene chain, introducing a conformational "floppiness" not available in the previously studied benzo systems.

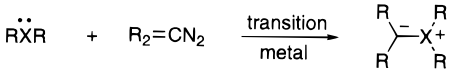
Incorporation of the amido carbonyl group on the side chain was found to dramatically alter the course of the tandem annulation reaction.[220] Thus, treatment of diazo keto amide **413** with rhodium(II) octanoate in CH_2Cl_2 at 25 °C in the presence of DMAD gave the rearranged cycloadduct **414** as a 1:1 mixture of diastereomers in 70% overall yield. The cyclization−cycloaddition reaction to produce **414** is quite remarkable in its facility and mildness of reaction conditions. The mechanism of this unusual reaction has not been unequivocally established, but one reasonable possibility is outlined in Scheme 106. Here it is proposed that the cyclization−cycloaddition sequence produces dipole **416** in the normal manner which cycloadds with DMAD to give **417**. Cycloadduct **417** can then proceed to **414** via a series of reactions. The first step involves oxabicyclic ring opening which is driven by the lone pair of electrons on nitrogen resulting in a Wagner−Meerwein rearrangement to give **418**. This zwitterionic species then undergoes a proton shift to produce **419** which subsequently reacts via a stepwise 4π-electrocyclization to generate the final product.[223]

VII. Cascade Reactions Derived from Onium Ylides

Onium ylides can be viewed as species in which a positively charged heteroatom is connected to a carbon atom possessing an unshared pair of electrons. These reactive intermediates are known to undergo synthetically useful transformations. One method of preparing ylides involves the deprotonation or desilylation of onium salts.[224,225] An alternate approach consists of the interaction of carbenes with the unshared electron pairs of heteroatoms.[226] Singlet carbenes, in particular, can function as Lewis acids by interacting with a pair of nonbonding electrons contributed by a Lewis base.[227] 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 (Scheme 107). The reactive intermediate preceding ylide formation is a carbenoid species.

Carbene complexes of transition metals are well-known, thoroughly studied species.[228] Among the carbene complexes which generate ylides, those formed using copper and rhodium salts are especially prominent.[229,230] Doyle has suggested that reactions catalyzed by rhodium(II) carboxylates can be viewed as taking place at the carbenic carbon which protrudes from the metal embedded in a wall constructed from its ligands.[231] The rhodium(II)-catalyzed decomposition of diazocarbonyl compounds is believed to involve a metallo carbenoid intermediate which retains the highly electrophilic properties associated with free carbenes. Such an intermediate can readily react with an available heteroatom to effect ylide formation which can subsequently be used for a host of synthetic transformations. Indeed, the tandem generation and rearrangement of cyclic onium ylides from diazo carbonyl precursors has evolved over the past decade as an important strategy in organic synthesis.

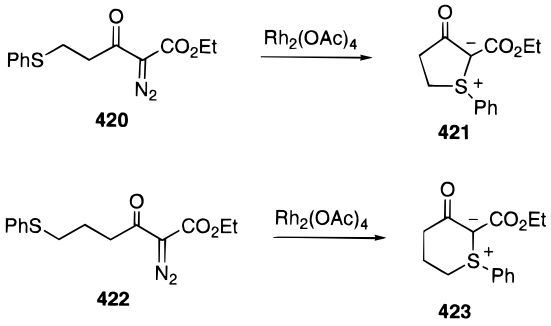
Scheme 107



A. Formation of Sulfonium Ylides

Sulfur ylides are useful intermediates in synthetic chemistry[232] and have been utilized for the synthesis of a number of β-lactam antibiotics,[233−253] pyrrolizidine alkaloids,[254,255] and other natural products.[256] The most common method for sulfur ylide generation involves the removal of a proton from a sulfonium salt.[257] However, a more direct method makes use of the reaction between a metallo carbenoid and a sulfide. A great variety of sulfur compounds, including cyclic and acyclic alkyl and aryl sulfides, are known to trap metallo carbenoids. Even compounds in which the sulfur lone pair is highly delocalized, such as vinyl sulfides, thiophenes, and dibenzothiophenes, have been shown to react with appropriate metal carbenoids to give stable sulfonium ylides. Intramolecular sulfide attack on a tethered carbenoid species generates cyclic sulfonium ylides.[258] 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. Thus, treatment of diazo sulfides **420** and **422** with a catalytic amount of rhodium(II) acetate gives the five- and six-membered cyclic ylides **421** and **423**, respectively (Scheme 108). Efforts to form larger rings only resulted in C−H insertion products.

Scheme 108



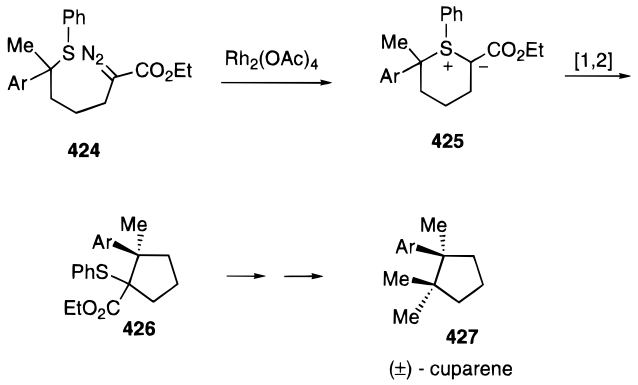
B. 1,2-Rearrangement of Sulfonium Ylides

Intramolecular carbenoid cyclization of a benzyl sulfide derivative has been used to synthesize the aromatic sesquiterpene (±)-cuparene (**427**). Treatment of diazo ketone **424** with a catalytic amount of rhodium(II) acetate in refluxing benzene gave arylcyclopentane **426** (Scheme 109). The initially formed sulfonium ylide **425** underwent a 1,2-ring contraction and the resulting cyclopentane **426** was subsequently converted to (±)-cuparene. This example nicely illustrates the tandem cyclization−rearrangement reaction as a method for the construction of quaternary carbon centers.

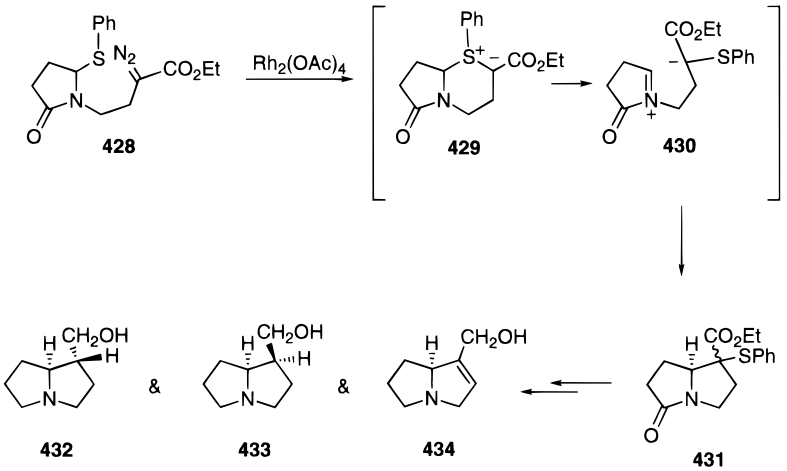
Several pyrrolizidine alkaloids were also synthesized via the same strategy.[255] Reaction of diazo ketone **428** with a catalytic amount of rhodium(II) acetate in refluxing benzene afforded amide **431** in 55% yield.[255] Addition of the carbenoid onto the sulfur atom generates sulfonium ylide **429** which fragments to produce iminium ion **430**. Cyclization of this species gave rise to the observed product. Structural modification of **431** resulted in the synthesis of three pyrrolizidine alkaloids; (±)-trachelanthamidine (**432**), (±)-isoretronecanol (**433**), and (±)-supinidine (**434**) (Scheme 110). This intramolecular tandem cyclization method should also be applicable to the synthesis of other naturally occurring necine bases.

Use of the tandem intramolecular carbenoid reaction toward the preparation of C-glycosides has recently been reported.[259] Treatment of 1-β-(phenylthio)furanoside **435** with rhodium(II) acetate gave lactone **438** in 56% yield (Scheme 111). The initially formed sulfonium ylide **436** fragments to produce oxonium ion **437** which cyclizes to the observed lactone **438**. Desulfurization of **438** with Raney/Ni gave structure **439** which corresponds to the key

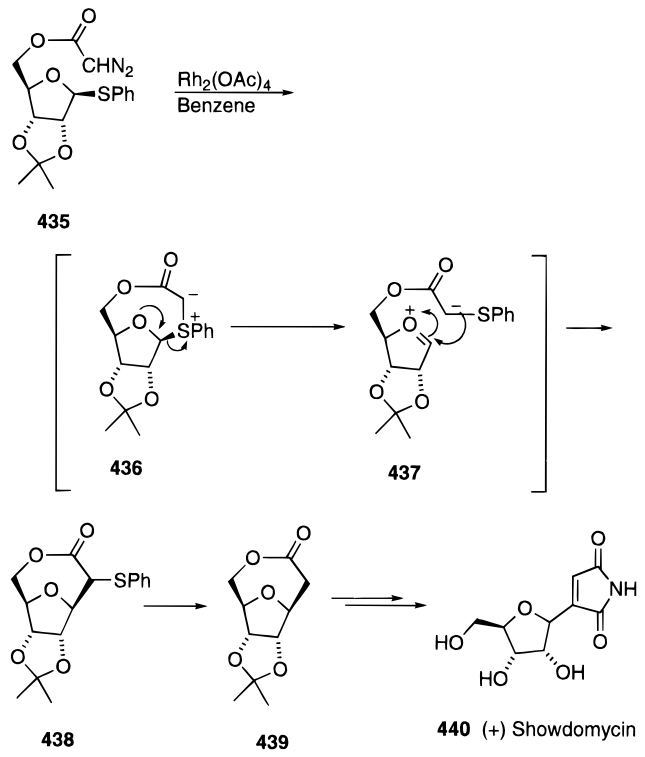
Scheme 109



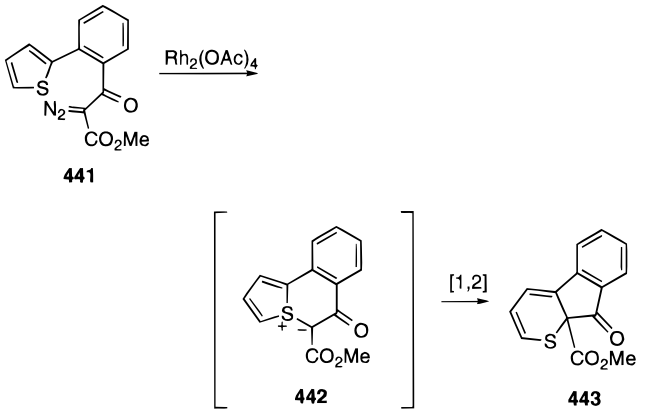
Scheme 110



Scheme 111



Scheme 112

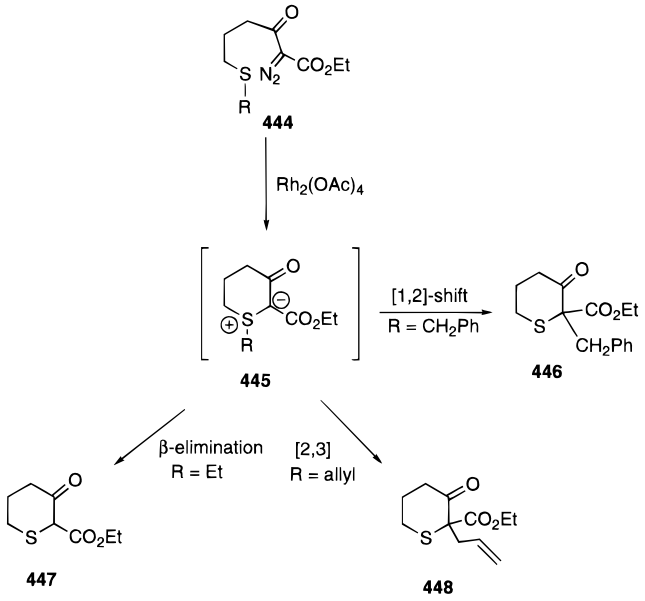


intermediate used for the synthesis of several C-nucleosides[260,261] including (+)-showdomycin (**440**).[259]

Only a few metallo carbenes have been known to react with thiophenes to give sulfur ylides.[262,263] In one example, α-diazo ketone **441** was treated with catalytic rhodium(II) acetate in benzene. The major product formed was **443** resulting from a Stevens rearrangement of ylide **442** (Scheme 112). The inability to isolate sulfur ylide **442** was somewhat surprising, considering that Porter and co-workers were able to isolate a related sulfonium ylide from the reaction of thiophene with a distabilized rhodium carbenoid.[262,263]

Moody and Taylor reported that the reaction of diazosulfide **444** (R = benzyl or ethyl) with rhodium-(II) acetate in refluxing benzene produced the stable sulfonium ylide **445**[265] (Scheme 113). The *S*-benzyl ylide **445** undergoes a Stevens-type 1,2-rearrangement to give thiopyran **446** on heating. Thermolysis of the *S*-ethyl ylide **445** in xylene, on the other hand, produced thiopyran **447**. Formation of this material

Scheme 113



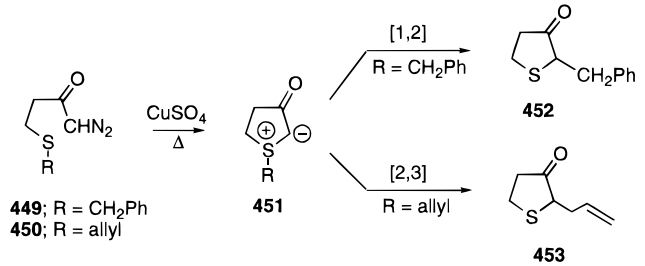
is consistent with loss of ethylene via a *β*-elimination reaction. The *S*-allyl sulfonium ylide **445** was never isolated due to its propensity to undergo a 2,3-sigmatropic rearrangement producing thiopyran **448**.

C. 2,3-Sigmatropic Rearrangements

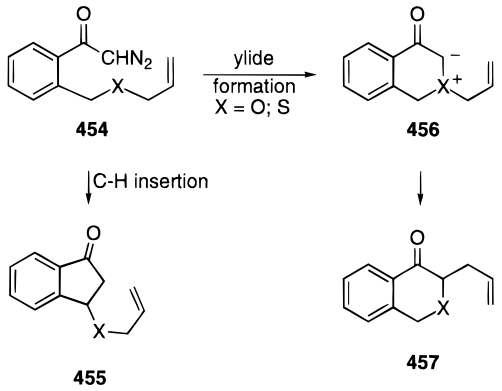
Carbenoids generated from 4-(benzylthio)- and 4-(allylthio)-1-diazobutan-2-ones (**449** and **450**) interact with the neighboring thio group to generate sulfonium ylides which readily rearrange[266] (Scheme 114). For example, the copper(II) sulfate-catalyzed decomposition of **449** resulted in the formation of cyclic ylide **451** (R = benzyl) which subsequently underwent a Stevens 1,2-shift of the benzyl group to ultimately yield thiolanone **452** in 51% yield. Reaction of 4-(allylthio)-1-diazobutan-2-one (**450**) under identical conditions afforded thiolanone **453** in 77% yield. The overall process involves an intramolecular electrophilic addition of the carbenoid onto the sulfur atom to generate the cyclic sulfonium ylide **451** (R = allyl), which then undergoes a 2,3-sigmatropic rearrangement giving the observed product.

The metal-catalyzed reactions of diazo compounds with allylic sulfides afford products derived from 2,3-sigmatropic rearrangement of intermediate allylic sulfonium ylides. A related transformation also occurs upon treatment of diazo compounds of type **454** (X = O) with rhodium(II) acetate. In this case, a 1:1 mixture of two compounds corresponding to C−H insertion (**455**) and ylide rearrangement (**457**) were isolated (Scheme 115). In order to assess the

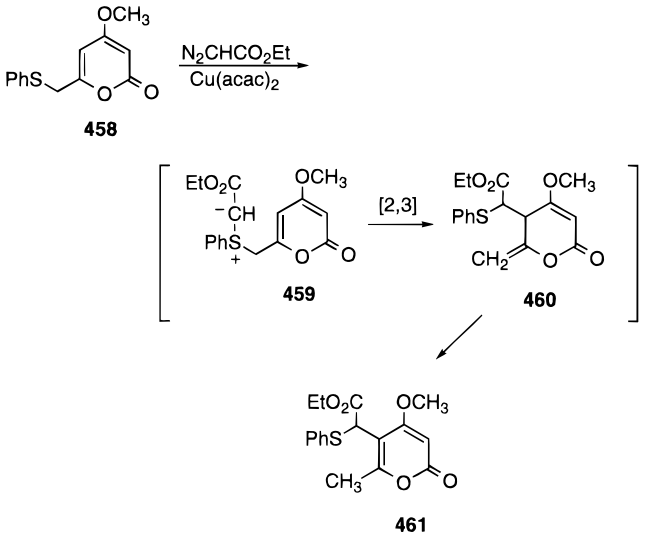
Scheme 114



Scheme 115



Scheme 116

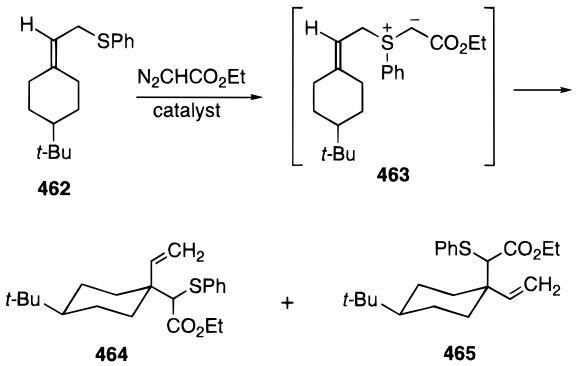


significance of the heteroatom to the product distribution, the Rh(II)-catalyzed reaction of the thio-substituted diazo ketone (X = S) was examined.[62] In this case, the ratio of ylide formation to C−H insertion was 9:1, in marked contrast to the 1:1 ratio obtained from the oxygen system. This suggests 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.

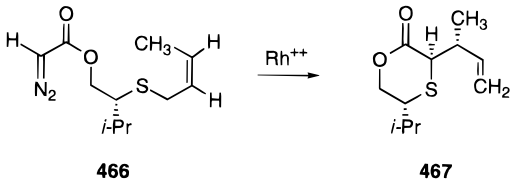
The paucity of good methods to prepare 2-pyrones with substituent groups in the C_3 and C_5 positions has retarded efforts to synthesize natural products containing this substructure. One method that has been utilized involves the treatment of 4-methoxy-6-(phenylthio)methyl-2-pyrone (**458**) with an excess of ethyl diazoacetate in the presence of copper(II) acetylacetonate to give the 5-substituted 2-pyrone **461** in good yield[267] (Scheme 116). Formation of the rearranged pyrone is consistent with the initial generation of sulfonium ylide **459** which undergoes a subsequent 2,3-sigmatropic rearrangement to produce intermediate **460**. A 1,3-sigmatropic hydrogen shift leads to the observed 2-pyrone **461**.

The stereochemistry of the 2,3-sigmatropic rearrangement of sulfonium ylides with a conformationally biased cyclohexylidene ring system has been investigated.[268] Treatment of allyl sulfide **462** with ethyl diazoacetate in the presence of a catalytic

Scheme 117



Scheme 118



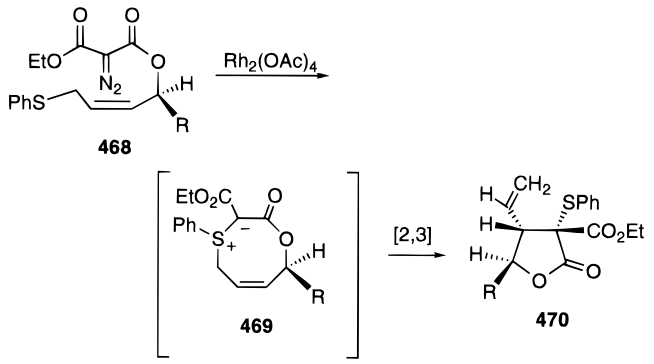
amount of (triethyl phosphite)copper(I) chloride resulted in the formation of a 9:1 mixture of the unsaturated sulfide esters **464** and **465** (Scheme 117). Treatment of allyl sulfide **462** with dichlorocarbene afforded a similar distribution of products. The overall process offers a potentially versatile method for the stereoselective synthesis of quaternary centers flanked by useful functional groups. The results obtained suggest that the extreme sensitivity of these 2,3-sigmatropic processes to the steric environment may be a general attribute of this class of reactions.

A thioxanone-based 2,3-sigmatropic rearrangement strategy was used by Kurth and co-workers for the synthesis of Cβ-chiral pent-4-enoic acid.[269] The reaction was found to proceed with good Cβ-induction and without the requirements of allylic alcohol resolution. The rhodium(II) acetate decomposition of Z-α-diazoester **466** produced the four possible thioxones (Scheme 118). The major isomer (**467**), however, was formed with 78% diastereoselectivity. A slight improvement in diastereoselectivity was encountered using hexarhodium hexadecacarbonyl as the catalyst.

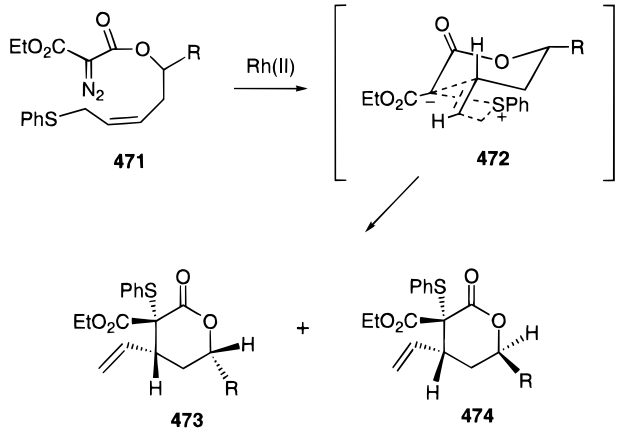
Yoshikoshi and co-workers have reported the stereoselective synthesis of contiguously substituted butyrolactones on the basis of the cyclic allylsulfonium ylide rearrangement.[270] α-Diazomalonates of (*Z*)-4-(phenylthio)-2-buten-1-ol homologues stereoselectively provide γ-alkyl-α-(ethoxycarbonyl)-α-(phenylthio)-β-vinylbutyrolactones by 2,3-sigmatropic rearrangement of a cyclic sulfonium ylide which was generated intramolecularly. Thus, treatment of diazomalonate **468** with rhodium(II) acetate afforded butyrolactone **470** in 70% yield (Scheme 119). 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 facile entry into the perhydrofuro[2,3-*b*]furan ring system using a related sequence of reactions was also described by Yoshikoshi and co-workers.[271] Treatment of the α-diazomalonate **471** with rhodium(II) acetate stereoselectively provided a 4:1 mixture of

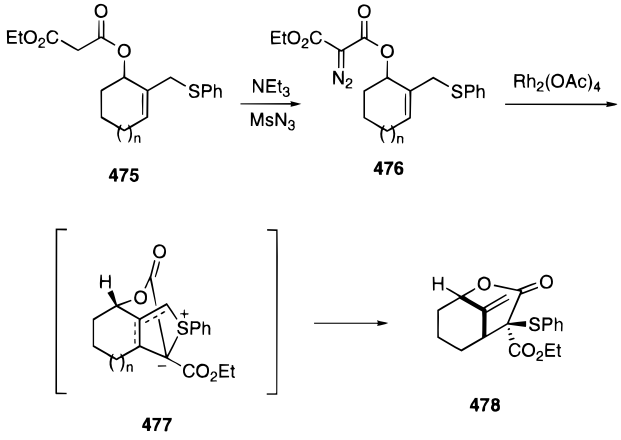
Scheme 119



Scheme 120



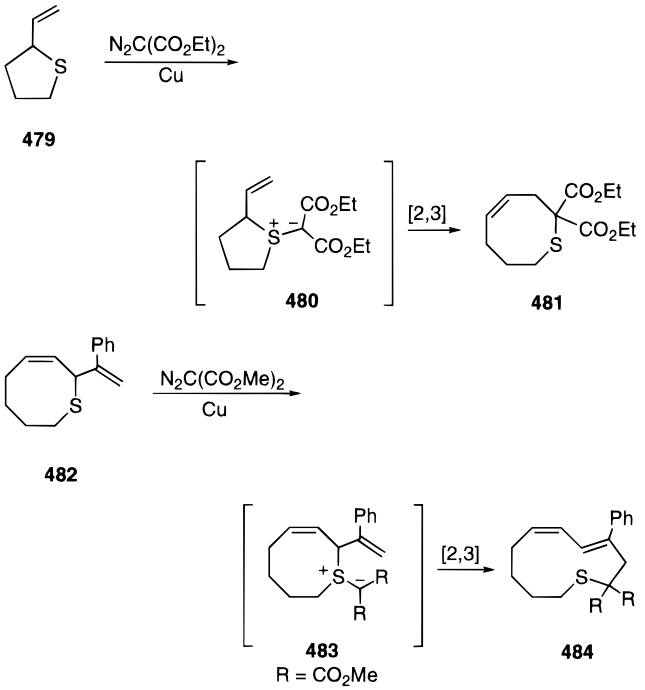
Scheme 121



substituted valerolactones **473** and **474** via a 2,3-sigmatropic rearrangement of a nine-membered cyclic allylsulfonium ylide (Scheme 120). The rearrangement product was converted to the 5-alkylperhydrofuro[2,3-*b*]furan ring system by ozonolysis followed by acid treatment. The stereochemistry about the lactone ring of **473** is understandable in terms of the most favorable conformation (*i.e.*, **472**) for the transition state of the rearrangement.

The 2,3-sigmatropic rearrangement of a cyclic sulfonium ylide intermediate has been used for the synthesis of bridged δ-lactones.[272] Diazotization of alkene **475** with mesyl azide followed by reaction with rhodium(II) acetate afforded the bridged δ-lactone **478** in high yield (Scheme 121). The stereochemistry about the carbon bearing the sulfur atom was rationalized by assuming that the reaction

Scheme 122

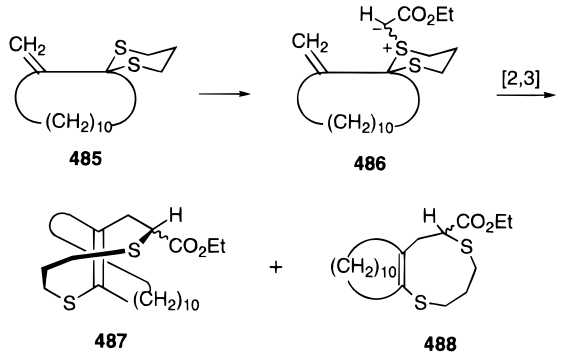


proceeds by the favored transition state conformation **477**.[272]

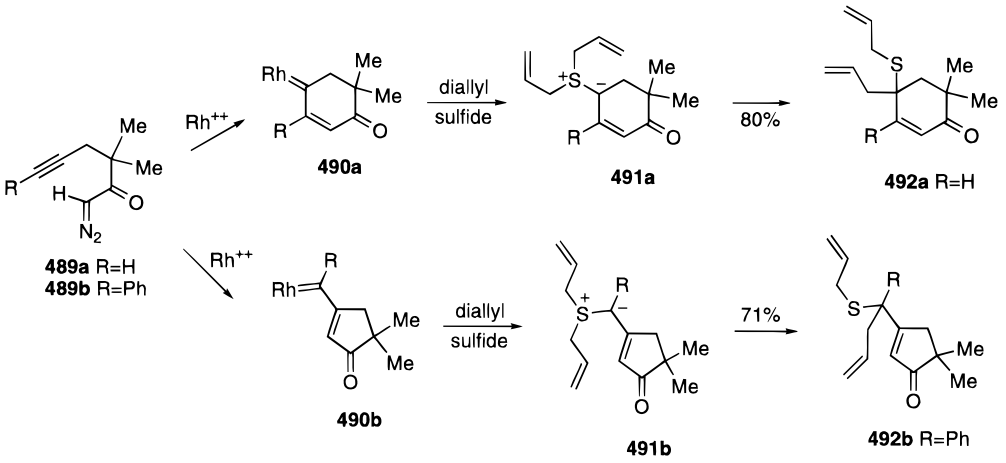
During the past 20 years, there have been a number of reports describing the synthesis of macrocyclic products[273−278] by a series of 2,3-sigmatropic shifts. This process has been described as a "ring-growing sequence" to denote an easily repeatable reaction scheme which allows for systematic ring enlargement.[275] The first ring expansion on a sulfur substrate was performed using a carbenoid route to sulfur ylides from a copper-catalyzed diazomalonate decomposition.[274] Thus, treatment of allyl sulfide **479** with diethyl diazomalonate in the presence of copper bronze at 100 °C afforded the ring-expanded product **481** in 50% yield (Scheme 122). Likewise, the reaction of allyl sulfide **482** with dimethyl diazomalonate gave **484** as the major product. The formation of both of these macrocycles is consistent with the initial generation of a sulfonium ylide intermediate (*i.e.*, **480** or **483**) which subsequently undergoes a 2,3-sigmatropic rearrangement.

Synthesis of the betweenanene ring system has been reported independently by Nickon[277] and Fava[278] and is based on Vedejs' earlier "ring-growing sequence". When dithioketal **485** was heated with

Scheme 123



Scheme 124



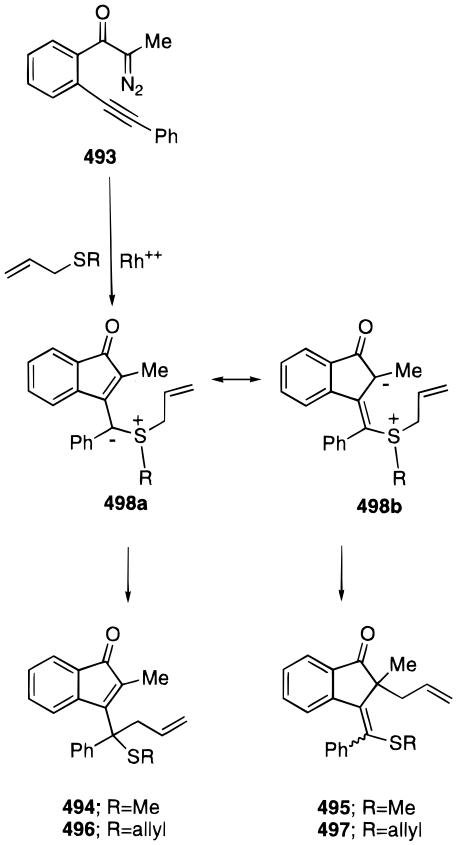
ethyl diazoacetate and copper sulfate, the derived sulfonium salt **486** produced the desired betweenanene **487** and its *Z* isomer **488** in a 4:1 ratio (Scheme 123). This finding indicates that the second sulfur atom in dithioketals does not obstruct the 2,3-sigmatropic rearrangement when ylides are generated by reaction with diazo esters. It should be noted that with this system, elimination and Stevens-type [1,2] shifts prevailed when strong bases act on a preformed methylsulfonium salt.

Acetylenic α-diazo ketones of type **489**, when treated with a Rh(II) catalyst and diallyl sulfide, undergo sequential alkyne metathesis−ylide formation−sigmatropic rearrangement to produce α-allylthio cyclic enones[279] (Scheme 124). This series of reactions was used as an indirect method by Hoye and Dinsmore to identify regioisomeric carbenoid intermediates in the alkyne metathesis reaction.[279] For example, when α-diazo ketone **489a** containing a terminal triple bond was treated with $Rh_2(OAc)_4$ in benzene with diallyl sulfide, cyclohexenone **492a** was formed in 80% yield with no trace of cyclopentenone **492b**. In contrast, subjection of α-diazo ketone **489b** (R = Ph) to the same reaction conditions gave cyclopentenone **492b** as the exclusive product.

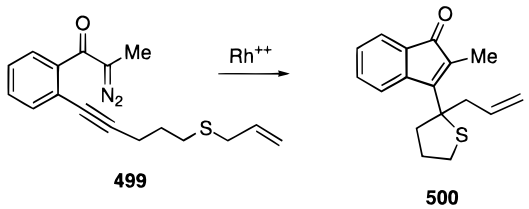
Our own group noted that the reaction of α-diazo ketone **493** with $Rh_2(OAc)_4$ in CH_2Cl_2 at 25 °C behaved in a similar manner, producing indenone **494** (86%) along with a 1:1 *E*/*Z* mixture of the isomeric vinyl sulfide **495** in 10% yield[220] (Scheme 125). A related reaction also occurred using diallyl sulfide which resulted in the formation of a 9:1 mixture of **496** and **497**. The possibility that **495** (or **497**) was the result of a Cope rearrangement of **494** (or **496**) was excluded by the finding that the thermolysis of **494** (or **496**) did not produce any detectable quantities of **495** (or **497**). The formation of **494** and **496** was rationalized by a tandem sulfur lone pair insertion−ylide rearrangement. Presumably, structures **495** and **497** arise via a novel antarafacial [3,4]-sigmatropic rearrangement of sulfonium ylide **498b**.

The ease with which the intermolecular sulfonium ylide generation−[2,3]-rearrangement sequence occurred suggested that a similar process might take place intramolecularly by incorporating the allyl sulfide functionality onto the alkyne unit.[280] Indeed, a rhodium-catalyzed carbenoid generation−sulfonium ylide formation−[2,3]-sigmatropic shift occurred upon stirring diazo ketone **499** with $Rh_2(OAc)_4$ in CH_2Cl_2. The sole product isolated in 81% yield corresponded to tetrahydrothiophene **500**[257] (Scheme 126).

Scheme 125

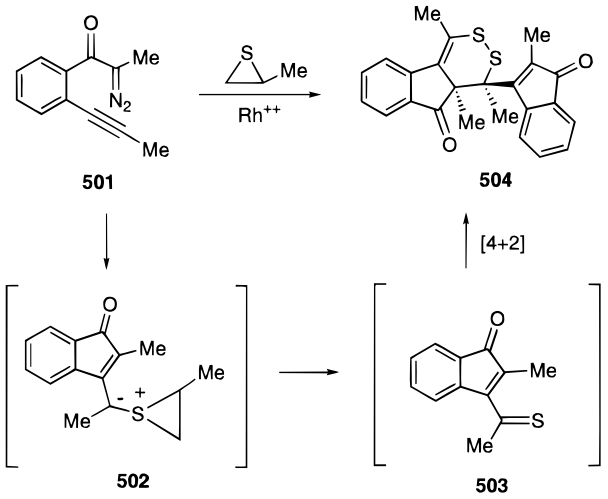


Scheme 126



Another example of the tandem carbenoid cyclization−sulfonium ylide rearrangement sequence in-

Scheme 127



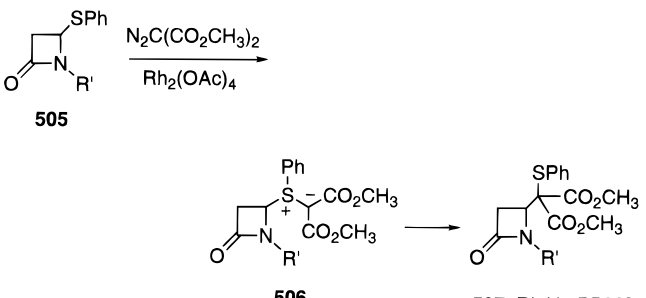
501 504 502 503

volves the Rh(II)-catalyzed reaction of α-diazo ketone **501** in the presence of propylene sulfide (Scheme 127). The only product formed corresponded to the novel cyclic sulfide dimer **504** which was isolated in 97% yield as a crystalline solid. Initial cyclization gives rise to the expected vinyl carbenoid which reacts with propylene sulfide followed by fragmentation of the ylide. The resulting thioketone **503** undergoes spontaneous Diels−Alder cycloaddition across the C−S double bond of another molecule to eventually give dimer **504**. This transformation is closely related to Hata's finding[281] that cyclopropyl sulfonium ylides readily undergo cleavage of both C−S bonds to produce alkenes in high yield. It should be noted that simple α,β-unsaturated thioketones, formed from the corresponding ketones by thionation, readily dimerize at ambient temperature to give structures related to **504**.[282−284]

D. Sulfur Ylides in β-Lactam Antibiotic Syntheses

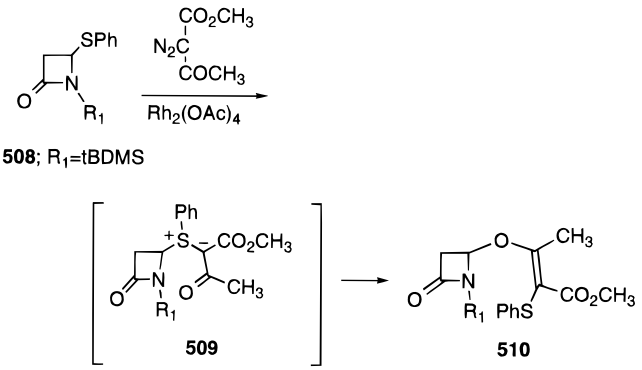
Interest in the chemistry of β-lactam antibiotics continues to thrive.[285] The tandem cyclization−rearrangement reaction of carbenoids with sulfur atoms has also been applied to the conversion of the penicillin nucleus into cephalosporin derivatives by a number of research groups.[233−253] One example involves the reaction of 4-thioazetidinone **505** with dimethyl diazomalonate in the presence of rhodium(II) acetate to give sulfide **507** in good yield[233,234] (Scheme 128). Formation of this product can be explained by carbenoid addition to the sulfur atom producing sulfonium ylide **506** which then undergoes

Scheme 128



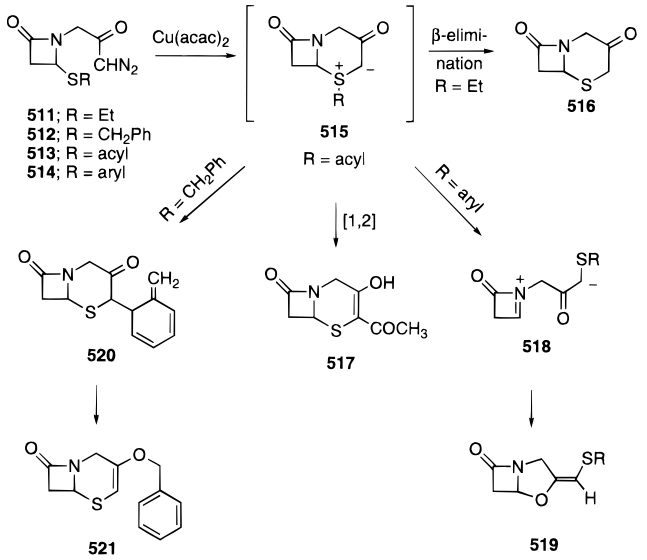
505 506 507; R'=H; tBDMS

Scheme 129



508; R1=tBDMS 509 510

Scheme 130

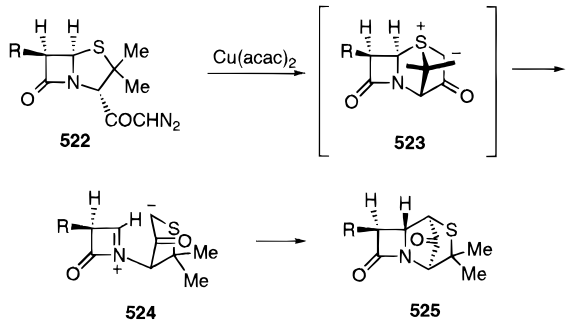


a [1,2]-shift. When the starting 4-thioazetidinone was substituted in the 3-position, addition of the carbenoid was found to occur stereoselectively from the least hindered side to generate a *trans*-substituted product.

In contrast to this result, treatment of 4-(phenylthio)-2-azetidinone **508** with α-diazoacetoacetate in refluxing benzene in the presence of a catalytic amount of rhodium(II) acetate afforded the 4-oxa-2-azetidinone **510**[234] (Scheme 129). Mechanistically, this result can be explained by initial formation of sulfonium ylide **509** followed by nucleophilic displacement by the carbonyl oxygen atom to give the observed product. No product resulting from a [1,2]-shift of the intermediate sulfonium ylide was observed.

The transition metal-catalyzed decomposition of α-diazo ketones derived from 4-thio-substituted azetidinon-1-yl acetic acids provides access to a large variety of functionalized bicyclic β-lactams.[236−239] The reaction path was found to be largely dependent on the nature of the 4-thio substituent. Treatment of 4-ethylthio diazo ketone **511** with copper powder gave 3-oxocephem **516**[236] (Scheme 130). A reasonable mechanistic explanation involves sulfonium ylide formation followed by a subsequent β-elimination to give ethylene and the observed product. Reaction of the closely related 4-benzylthio diazo ketone **512** with copper(II) acetylacetonate gave bicyclic β-lactam **521**.[236] The isolation of **521** is consistent with a

Scheme 131

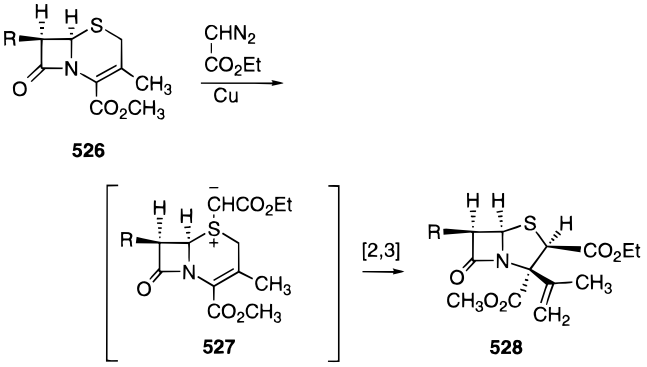


mechanism which involves attack of the carbenoid onto the sulfur atom to provide an intermediate sulfonium ylide which then undergoes a [2,3]-sigmatropic rearrangement to produce intermediate **520**. A subsequent [3,3]-sigmatropic rearrangement of this transient species generates the bicyclic β-lactam **521**. Reaction of thioacyl diazo ketone **513** under similar experimental conditions afforded enol **517**.[236] The formation of compound **517** can best be rationalized by direct acyl migration of ylide **515**, followed by enolization. When the sulfur atom is substituted with a phenyl group, the reaction proceeds via a different pathway. Thus, treatment of 4-(phenylthio)-2-azetidinone **514** with copper powder in refluxing benzene afforded oxapenam **519** as the major product.[237−239] The formation of this product also involves initial generation of sulfonium ylide **515** which is followed by successive cleavage of the C−S bond to produce **518** as a transient species. Subsequent ring closure by attack of the ketone oxygen on the iminium cation results in the formation of oxapenam **519**. Thus, the metal-catalyzed decomposition of α-diazo ketones derived from 4-thio-substituted azetidinon-1-yl acetic acids provides access to a large variety of functionalized bicyclic β-lactams.

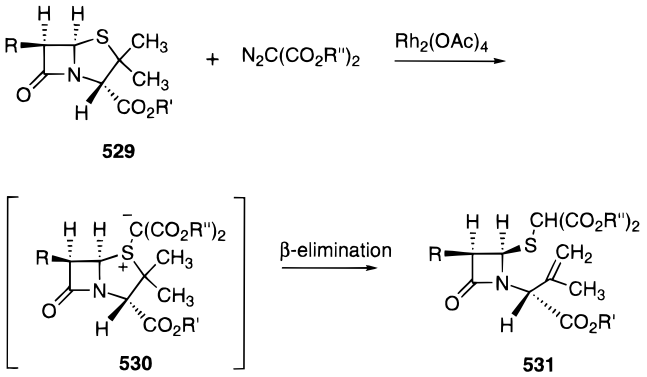
When the penicillin-derived diazo ketone **522** was treated with a catalytic amount of copper(II) acetylacetonate, the tricyclic ketone **525** was produced as a single stereoisomer[240−242] (Scheme 131). The suggestion was offered that compound **525** was formed from the strained sulfonium ylide **523** which undergoes cleavage of the C−S bond by participation of the nonbonding electrons of the azetidinone nitrogen atom to give zwitterion **524**. Finally, reclosure by backside attack of the carbanion onto C_4 gives the observed product. Nucleophilic attack by the carbanion occurs from the α-face of the proposed azetidinone iminium intermediate **524** presumably due to conformational factors.[242]

The skeletal conversion of the cephalosporin to the penicillin ring system has also been achieved by a metallo carbenoid reaction.[243] Ethyl diazoacetate was added dropwise to a mixture containing methyl 3-methyl-7-phenylacetamido-3-cephem-4-carboxylate (**526**) and copper powder. After heating at reflux for 3 h, penicillin **528** was isolated in 50% yield (Scheme 132). The formation of **528** is consistent with a mechanism involving α-side addition of the copper carbenoid onto the sulfur atom of cephalosporin to give the β-oriented ylide intermediate **527**. [2,3]-Sigmatropic rearrangement of this species occurs in a suprafacial manner to give the observed product as a single stereoisomer.

Scheme 132



Scheme 133

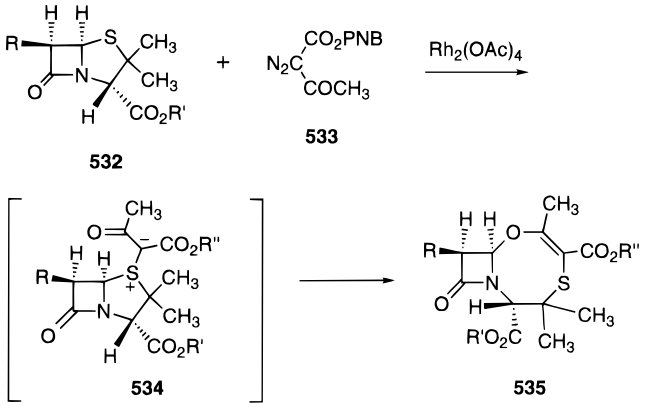


Cleavage reactions of the C_2-S_1 bond of penicillin derivatives have been carried out and produce 1,2-secopenicillinates in modest to good yields.[244−247] For example, treatment of penicillinate **529** with diazomalonate in the presence of rhodium(II) acetate gave the corresponding 1,2-secopenicillin derivative **531** in 83% yield (Scheme 133). The isolation of this material is consistent with the formation of sulfonium ylide **530** which then undergoes a subsequent β-elimination to give the observed product. This is an important result since 1,2-secopenicillin derivatives can be easily cyclized to produce cepham antibiotics.[244−246] The overall process represents a method by which penicillins can be transposed into the cepham nucleus.

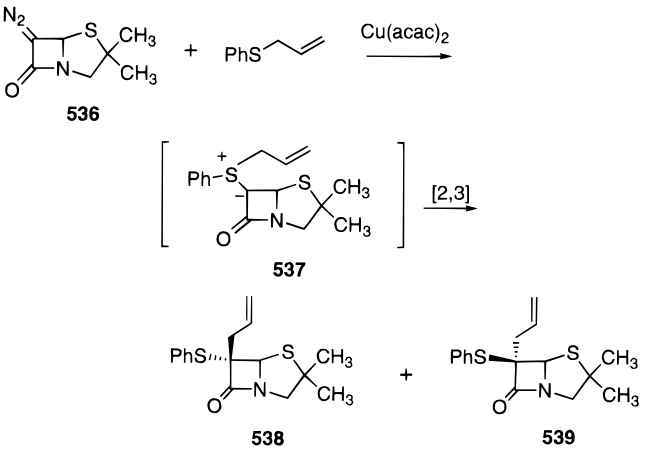
The ring expansion of penicillin derivatives has been used to stereoselectively synthesize eight-membered oxa-β-lactams.[248] Reaction of penicillin derivatives with metallo carbenoids derived from *p*-nitrobenzyl α-diazoacetoacetate gives the corresponding ring-expanded oxa derivatives in modest yield.[248] A typical example involves the reaction of penicillin **532** with *p*-nitrobenzyl α-diazoacetoacetate (**533**) in the presence of a catalytic amount of rhodium(II) acetate to give bicyclic β-lactam **535** (Scheme 134). This result was rationalized by assuming the initial formation of sulfonium ylide **534**. The second step involves nucleophilic addition by the carbonyl oxygen and a concomitant displacement of the sulfonium moiety.

Since the discovery of derivatives of olivanic acid[249] and thienamycin,[250] the synthesis of penicillin analogues with a carbon side chain at C_6 has attracted considerable attention. The transition metal-catalyzed reaction of 6-diazopenicillinates with allyl sulfides represents a convenient method for synthe-

Scheme 134



Scheme 135

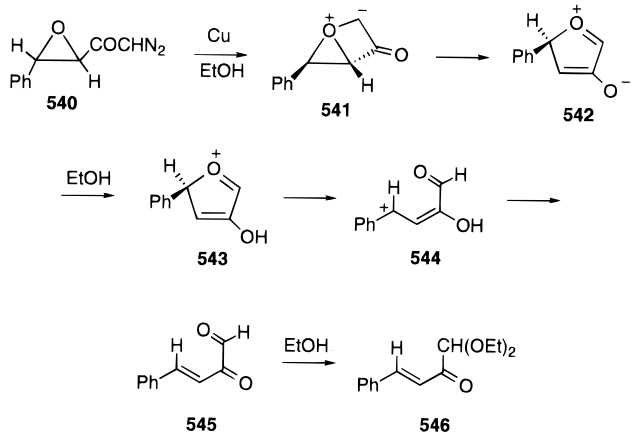


sizing these 6-substituted penicillin analogues.[251,252] Addition of copper(II) acetylacetonate to a mixture of phenyl allyl sulfide and 6-diazopenicillinate (**536**) in dichloromethane resulted in the formation of 6,6-disubstituted penicillinates **538** and **539** (Scheme 135). This result can best be interpreted as proceeding by the initial formation of sulfonium ylide **537** which undergoes a subsequent [2,3]-sigmatropic rearrangement. This reaction is related to the [2,3]-rearrangements of 6-(alkylamino)penicillanates previously reported by Baldwin and co-workers.[286]

E. Oxonium Ylides

Two fundamentally different approaches to the generation of oxonium ylides exist. One route involves either the deprotonation or desilylation of appropriate oxonium ions.[224] The deprotonation route to these oxygen ylides is believed to play an important role in the zeolite-catalyzed conversion of methanol to ethylene.[287] The alternate approach involves the interaction of carbenoids with the unshared electron pairs of an oxygen atom. For the majority of reactions encountered, direct C−O insertion is not readily distinguished from the formation and subsequent rearrangement of oxonium ylides. Conclusive evidence for the two-step mechanism comes from the [2,3]-sigmatropic rearrangements observed with allylic substrates (*vide infra*). Unlike the situation with the related sulfonium ylide system, stable and isolable oxonium ylides have not yet been reported in the literature. This difference in stability

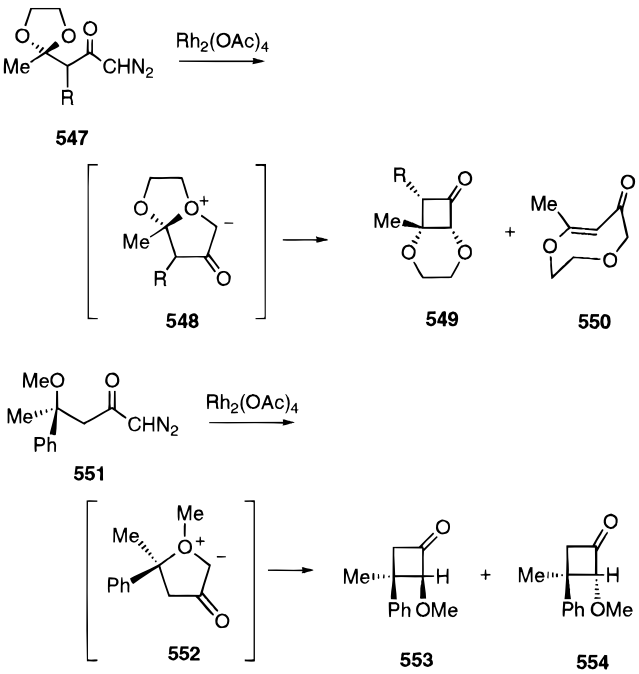
Scheme 136



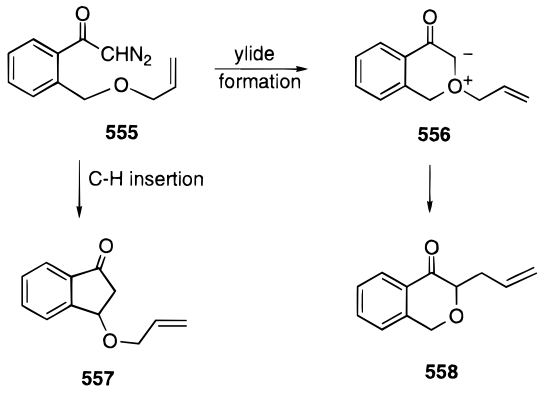
is probably due to the absence of $p_\pi-d_\pi$ orbital interaction which helps stabilize the charge on the sulfur atom. Oxonium ylides are reactive species which readily undergo the Stevens rearrangement, β-hydride elimination, and [2,3]-sigmatropic reorganization.

One of the earliest examples of intramolecular oxonium ylide formation involves the reaction of α,β-epoxy diazomethyl ketones with activated copper powder producing alkene oxoacetals in good yield.[288] Thus, treatment of diazo ketone **540** with activated copper in refluxing ethanol gave dialkoxybutenone **546** in 80% yield (Scheme 136). 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 **541**. Release of strain and subsequent ring opening affords acetal **546**. Both the *cis*- and *trans*-epoxides lead to the same product (*i.e.*, **546**) when treated with copper sulfate in methanol. This stereochemical result was explained by invoking a stepwise nonsynchronous solvolysis of the initial ring opened zwitterion **542**. Protonation of **542** by metha-

Scheme 137



Scheme 138



nol generates **543** which then opens to cation **544** which ultimately gives **546**.

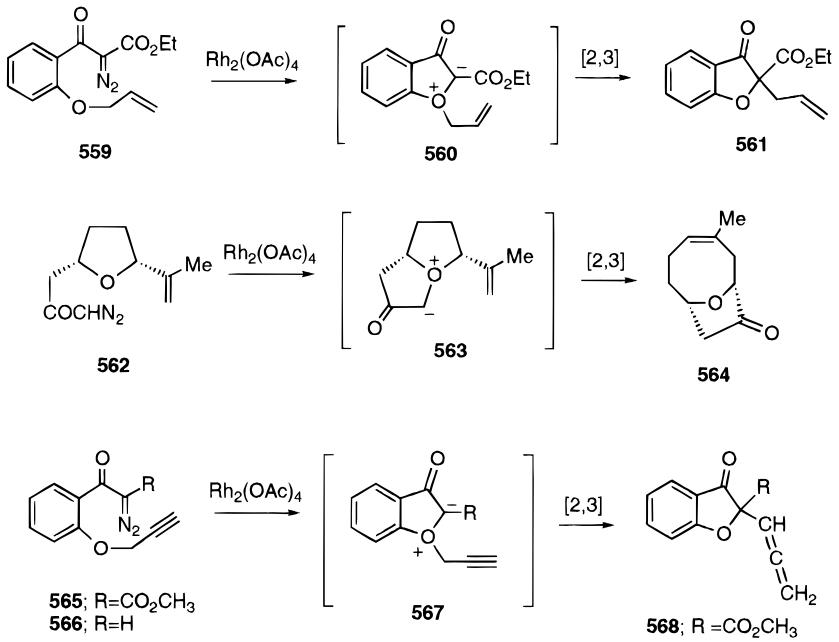
The reaction of diazo ketone **547** with rhodium(II) acetate in benzene at room temperature resulted in the rearranged products **549** and **550**[289] (Scheme 137). The formation of these compounds involves capture of the rhodium carbenoid by the oxygen atom of the ethylene ketal to produce the transient oxonium ylide **548**. Subsequent rearrangement gives the observed products **549** and **550**. Similarly, treatment of diazo ketone **551** with rhodium(II) acetate afforded oxonium ylide **552** which rearranged to cyclobutanones **553** and **554**. A major factor for cyclobutanone formation involves stabilization of electron deficiency at the α′-carbon by oxygen or a phenyl substituent. Simple tertiary center stabilization does not appear to be effective.

The tandem formation of allylic oxonium ylides and their subsequent [2,3]-sigmatropic rearrangement represents an efficient method for producing a variety of interesting and useful oxygen heterocycles. Thus, treatment of diazo ketone **555** with rhodium(II) acetate gave 3-allyl-2-isochroman-4-one (**558**) and 2,3-dihydro-3-(2-propenyloxy)-1*H*-inden-1-one (**557**) in 43% and 35% yield, respectively[270] (Scheme 138). The formation of structure **558** involves carbenoid generation followed by addition onto the neighboring oxygen atom to produce oxonium ylide **556** which then undergoes a [2,3]-sigmatropic rearrangement. Indenone **557** 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.

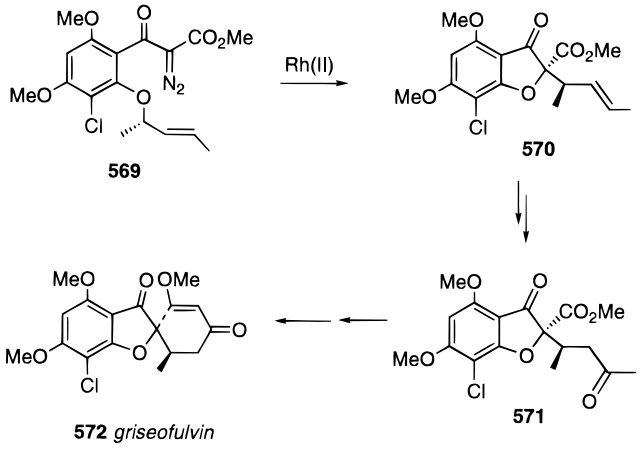
Pirrung and Werner further developed this methodology for the synthesis of novel five-, six-, and eight-membered oxygen heterocycles.[290] Treatment of diazo ketone **559** with rhodium(II) acetate produced benzofuranone **561**, whereas diazo ketone **562** afforded the eight-membered ring oxygen heterocycle **564** (Scheme 139). This ring expansion clearly illustrates the preference of ylide **563** to undergo the symmetry-allowed [2,3]-sigmatropic rearrangement over the symmetry-forbidden [1,2]-process. Another variation of this process involves the reaction of diazo ketone **565** in the presence of rhodium(II) acetate catalyst to give allene **568** in 92% yield. It should be noted that when diazo ketone **566** 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.

The tandem chemistry of oxonium ylides has been utilized as an approach for the synthesis of (+)-griseofulvin (**572**).[291] Treatment of **569** with rhodium(II) pivalate as the catalyst provided the rearranged product **570** in 62% yield (Scheme 140). The synthesis was completed by conversion of **570** to methyl ketone **571**, which had already been converted to griseofulvin.[292] The stereochemistry of the [2,3]-sigmatropic shift involved in the conversion of **569** to **570** 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.

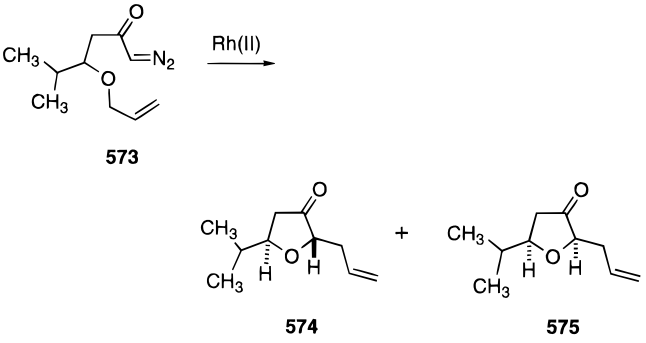
Scheme 139



Scheme 140



Scheme 141



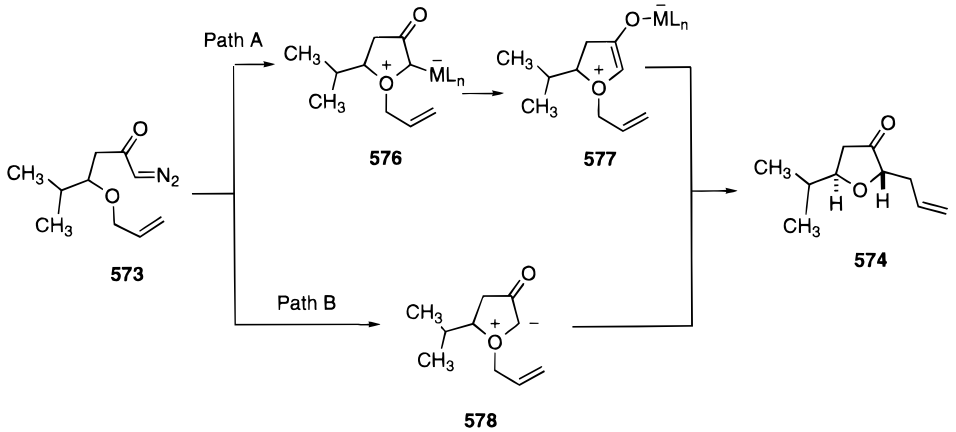
The factors influencing diastereocontrol in the synthesis of 2,5-dialkyl tetrahydrofuran-3-ones by the intramolecular tandem carbenoid insertion−ylide rearrangement reaction has recently been examined by Clark.[293] Diazo ketone **573** was treated with $Rh_2(OAc)_4$ in CH_2Cl_2 at 25 °C and gave a mixture of **574** and **575**, with a modest preference for the thermodynamically disfavored *trans*-tetrahydrofuran-3-one **574** (Scheme 141). The formation of **574** and **575** is understandable in terms of intramolecular insertion of the allyl ether into the rhodium carbenoid followed by rearrangement of the resulting oxonium ylide. By using $Cu(acac)_2$, a dramatic improvement in both the yield (85%) and the diastereoselection (>97:3) was observed.

The ability to significantly control the level of diastereoselection by changing the catalyst suggests that the rearrangement occurs via a metal-bound ylide-enolate species such as **576** or **577** (path A), rather than by selective insertion of one of the diastereotopic oxygen lone pairs (path B) into the carbenoid center to form **578**[293] (Scheme 142).

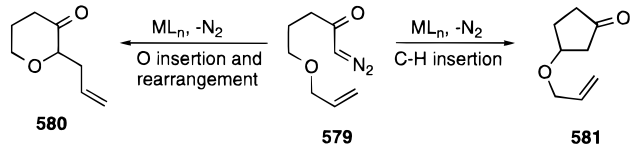
Clark and co-workers also used this tandem oxonium ylide formation−[2,3]-sigmatropic rearrangement sequence as a general method for the synthesis of six-, seven-, and eight-membered cyclic ethers.[294] Thus, the $Rh_2(OAc)_4$-catalyzed decomposition of diazo ketone **579** in CH_2Cl_2 at reflux led to a mixture of cyclic ether **580** (41%) and the C−H insertion product **581** (18%) (Scheme 143). By employing $Cu(acac)_2$ as the catalyst, only a marginal improvement in the yield of pyran-3-one **580** was observed. Copper(II) trifluoroacetylacetonate [$Cu(tfacac)_2$] and copper(II) hexafluoroacetylacetonate [$Cu(hfacac)_2$][295] proved to be very effective at eliminating the C−H insertion product **581** and increasing the formation of the oxonium ylide derived product **580**. These same authors also examined the formation of larger oxacycles by this tandem sequence.[296] Treating allyl ether **582** (or **585**) with $Rh_2(OAc)_4$ did not afford any of the desired cyclic ether **583** (or **586**). However, when $Cu(hfacac)_2$ was used as the catalyst, diazo ketone **582** cyclized to oxepan-3-one **583** in 76% yield (Scheme 144). Cyclization of **585** under similar reaction conditions afforded the cyclic ether **586** in 40% yield. The specific role played by the catalyst in these reactions is unclear at the moment.

Fused bicyclic oxonium ylides, generated by the reaction of $Rh_2(OAc)_4$ with cyclic ethers bearing a tethered diazo ketone, have been shown by West and co-workers[297] to undergo [1,2]- or [2,3]-shifts to give O-bridged seven- or eight-membered carbocycles. For example, addition of $Rh_2(OAc)_4$ in CH_2Cl_2 at 25 °C to *cis*-tetrahydrofuran **587a** led to a 60% yield of the diastereoisomeric cycloheptanones **588a** and **588b** in a 19:1 ratio (Scheme 145). *trans*-Tetrahydrofuran **587b** underwent an analogous reaction producing **588a** and **588b** but with a much lower degree of stereocontrol. In each case the major diastereomer arose from migration with retention of configuration of the oxonium ylide, but the *cis* substrate **587a** showed a much higher degree of retention of stereochemistry. Loss of stereoselectivity was attributed to a biradical intermediate formed by bond homolysis.

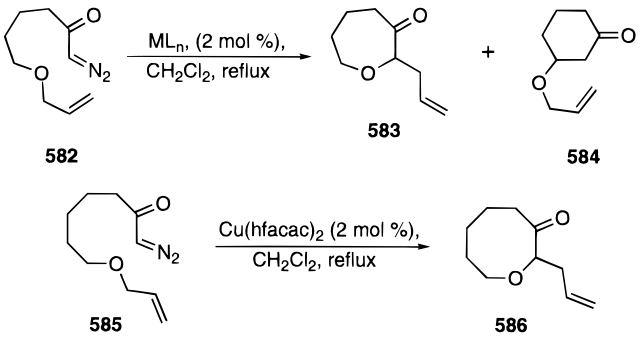
Scheme 142



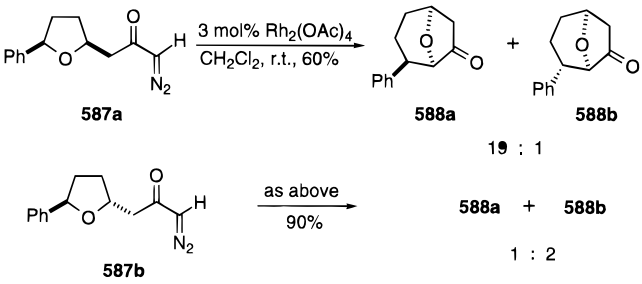
Scheme 143



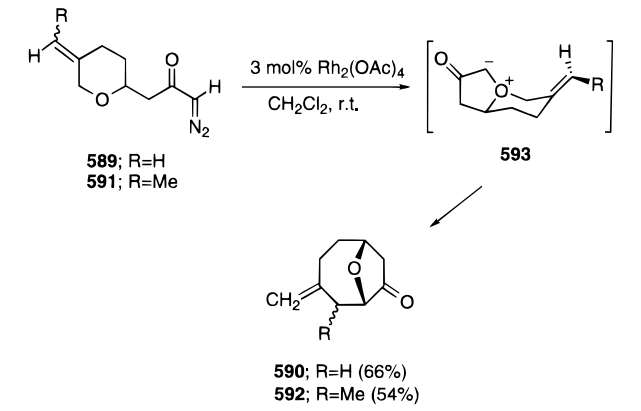
Scheme 144



Scheme 145



Scheme 146



The carbon bearing the best radical stabilizing substituent migrates preferentially.[298,299]

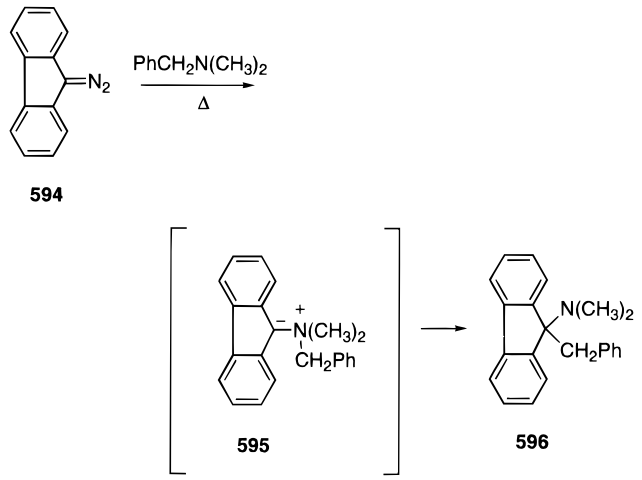
In a related fashion, diazo ketone **589** was cleanly converted into methylene cyclooctene **590** (Scheme 146). This transformation could, in theory, occur by a [2,3]-sigmatropic rearrangement of ylide **593** rather than a [1,2]-shift. The substituted analogue **591** was prepared in order to distinguish between these two mechanisms. Treatment of **591** with $Rh_2(OAc)_4$ afforded a mixture of the diastereomers of cyclooctanone **592** as the exclusive product. Although homolytic cleavage followed by regioselective recombination at the more substituted allylic carbon can not be disproven, the above result suggests that the concerted [2,3]-shift is the preferred pathway.[297]

F. Ammonium Ylides

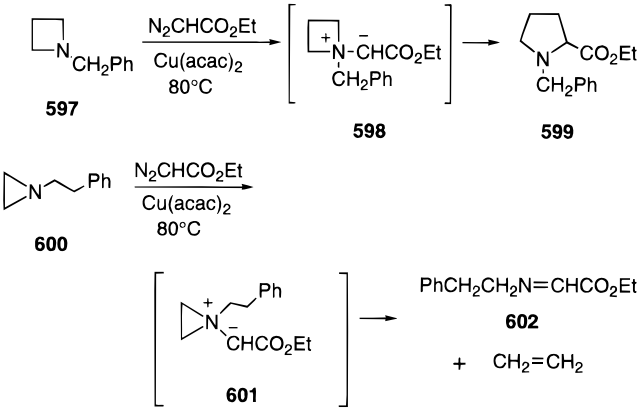
Carbenoid generation of nitrogen ylides represents a useful alternative to the widely employed base-promoted methodology.[300] The reaction of aliphatic diazo compounds with tertiary amines was first investigated by Bamford and Stevens in 1952.[301] The formation of α-benzyl-α-(dimethylamino)fluorene (**596**) from the reaction of diazofluorene with benzyldimethylamine is consistent with a mechanism that involves generation of ammonium ylide **595** which then undergoes a [1,2]-benzyl shift (Scheme 147). The Stevens rearrangement is one of the most common reactions for the degradation of quarternary ammonium ylides.[302] Although detailed mechanistic studies for the [1,2]-shift of ammonium ylides have not been carried out, one can assume that it occurs via a biradical process as has been established for the analogous sulfonium and oxonium ylides.[303,304]

The chemistry of ammonium ylides formed from the reaction of cyclic amines with carbenoids was found to be dependent on the ring size of the amine.[305] For example, treatment of 1-benzylazetidine (**597**) with ethyl diazoacetate in the presence of a copper(II) catalyst afforded pyrrolidine **599** in 96% yield (Scheme 148). This result requires formation of an ammonium ylide (**598**) followed by ring expansion. In contrast, the reaction of 1-phenethylaziridine (**600**) with the copper catalyst gave the fragmentation product **602** in quantitative yield. Important factors which probably influence the course

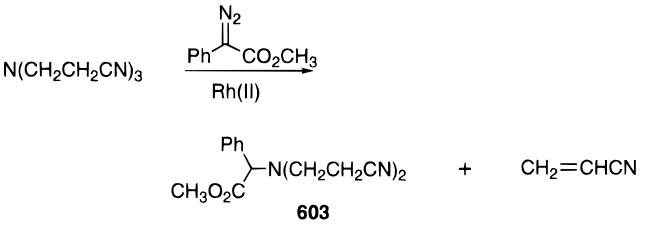
Scheme 147



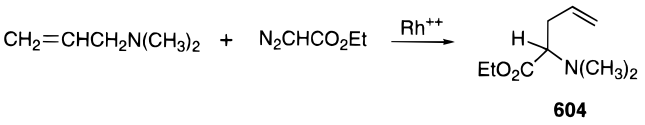
Scheme 148



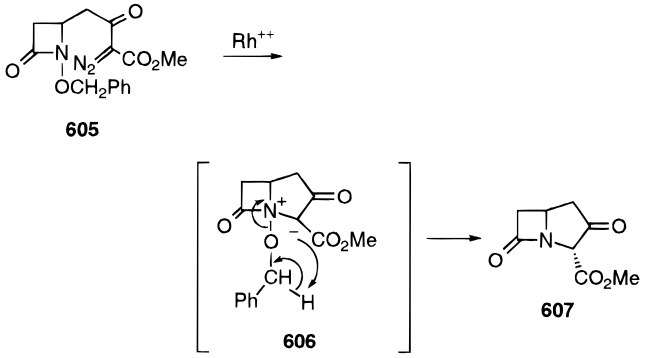
Scheme 149



Scheme 150



Scheme 151



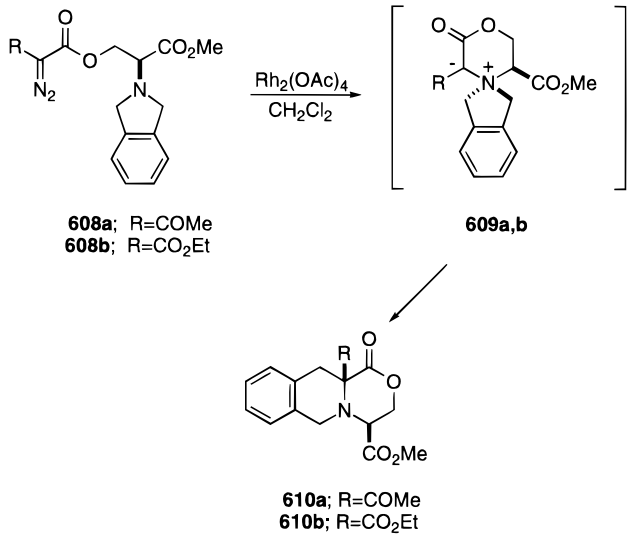
of these reactions are (1) the amount of ring strain energy released and (2) the heat of formation of the resulting ethylene π-bond.

Ammonium ylides that possess a β-hydrogen often undergo an elimination reaction to provide the corresponding amine and alkene.[306−310] A typical example involves the reaction of (methoxycarbonyl)-phenylcarbene with tris(cyanoethylamine) which afforded acrylonitrile and amine **603**[306] (Scheme 149). These two transformations occur via β-hydride elimination from a transient ammonium ylide.

Although suitable for ylide production, carbenes generated photochemically and thermally in the presence of amines are relatively indiscriminate. The more general catalytic approach to ammonium ylides involve both copper and rhodium(II) catalysts. Stable metal carbenes characteristically undergo nucleophilic addition at the carbene carbon and in certain cases, stable addition products have been obtained from the reaction of amines with carbene complexes.[311] Doyle and co-workers were the first to study the reaction of tertiary allyl amines with various rhodium(II) carboxylates.[312] They found that the treatment of dimethylallylamine with ethyl diazoacetate in the presence of rhodium(II) acetate produced a nitrogen ylide which underwent a [2,3]-sigmatropic rearrangement to give amine **604** in good yield (Scheme 150). No products resulting from cyclopropanation or C−H insertion were observed in the crude reaction mixture.

The reaction of α-diazo ester **605** with rhodium(II) acetate resulted in an unprecedented ring closure to provide carbapenam **607**[313] (Scheme 151). The suggested mechanism involves interaction of the initially generated carbenoid with the *N*-alkoxylactam electron lone pair to give ammonium ylide **606**. Abstraction of a proton from the benzylic position by the ylide intermediate, followed by carbonyl formation and N−O bond cleavage resulted in the formation of the cyclized product and benzaldehyde. This unique rearrangement represents an alternative to the well-documented procedure for the debenzylation and N−O bond reduction of *N*-benzyloxy β-lactams.[314]

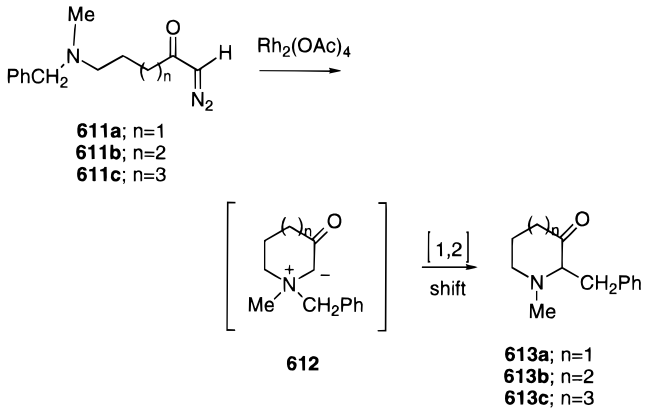
Scheme 152



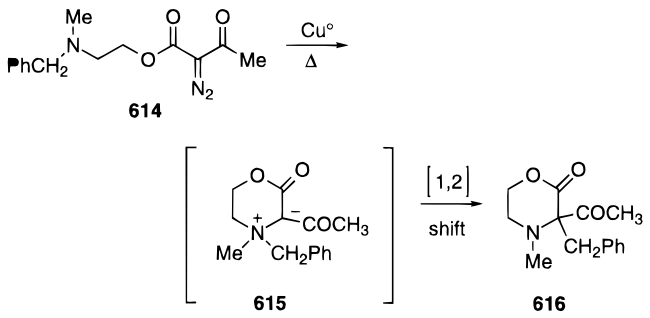
Ammonium ylides obtained from the cyclization of L-serine-derived diazo esters have been used to synthesize enantiomerically pure derivatives of tetrahydroisoquinoline which display interesting pharmacological properties.[315] The $Rh_2(OAc)_4$-catalyzed decomposition of diazo esters **608a** and **608b** furnished tetrahydroisoquinoline derivatives **610a** (52%) and **610b** (19%) as single diastereomers (Scheme 152). The relative configuration of ester **610b** was determined by X-ray structural analysis. The stereochemical outcome of this reaction implies that in the ammonium ylides **609a**,**b**, the benzylic methylene group *anti* to the methoxycarbonyl group migrates during the rearrangement This result suggests that the stereoselectivity of the rearrangement is not controlled by steric repulsion between the methoxycarbonyl and the migrating methylene group but by electronic effects.[315]

A new route to substituted piperidines involving a [1,2]-shift of an ammonium ylide has recently been described.[316] Generation of the required cyclic ammonium ylide involved the transition metal-catalyzed decomposition of amino-substituted diazo ketones of type **611**. The reactivity of these substrates was found to be highly sensitive to the catalyst used. Rhodium(II) acetate was unsuitable as a general catalyst due to saturation of empty sites on the Rh−Rh dimer by the neighboring amino group. Interestingly, $Cu(acac)_2$ furnished **613** in high yield (Scheme 153), suggesting a remarkably efficient and selective capture of the copper carbenoid by the amine to give a medium-sized cyclic ylide in preference to other carbenoid pathways. The reputedly greater electrophilicity of copper carbenoids[312] may work in concert with a diminished propensity for C−H insertion[317] and in favor of ylide formation. Equilibration between ylides and Rh carbenoids has previously been

Scheme 153



Scheme 154



suggested,[291,297] and it is possible that ylide to carbenoid reversal may be less favorable in the case of Cu carbenoids. In all cases, only benzyl group migration occurred which is consistent with the assumption that the carbon bearing the best radical stabilizing substituent will migrate.[318] It is clear that the overall tandem sequence of carbenoid generation/ammonium ylide formation/Stevens [1,2]-shift utilizing acyclic δ-dialkylamino diazocarbonyl substrates represents an efficient method for the synthesis of six-membered nitrogen heterocycles.

Linkage of the carbenoid precursor and the nucleophilic amine via an ester has also been studied by the West group.[319] Heating 2-(dialkylamino)ethyl diazoacetoacetate **614** in the presence of catalytic copper afforded morpholinone **616**, presumably via the intermediacy of a copper carbenoid and the cyclic ammonium ylide **615** (Scheme 154). The key step in this sequence is exceedingly simple and does not require high-dilution or slow-addition conditions. Moreover, use of homogeneous Cu(II) catalysts greatly enhances the production of products derived from cyclic ammonium ylides.

VIII. Conclusion

Tandem ylide generation from the reaction of metallo carbenoids with heteroatoms continues to be of great interest both mechanistically and synthetically. Effective ylide formation in transition metal-catalyzed reactions of diazo compounds depends on the catalyst, the diazo species, the nature of the heteroatom, and competition with other processes. The many structurally diverse and highly successful examples cited in this review clearly indicate that the tandem reaction of metallo carbenoids has evolved as an important strategy in heterocyclic and carbocycle synthesis. It is a reasonable expectation that future years will see a continued evolution of the cascade chemistry of transition metal carbenoids derived from diazocarbonyls in organic synthesis. As is the case in all new areas of research using catalysts, investigation of the chemistry of these transition metal complexes in the future will be dominated by the search for asymmetric synthesis.

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X. References

(1) 1. Ho, T. L. *Tandem Organic Reactions*; John Wiley and Sons: New York, 1992.
(2) (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Posner, G. H.; Asirvatham, E.; Hamill, T. G.; Webb, K. S. *J. Org. Chem.* **1990**, *55*, 2132 and references cited therein.
(3) (a) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. (b) Danishefsky, S.; Harrison, P.; Silvestri, M.; Seqmuller, B. *J. Org. Chem.* **1984**, *49*, 1319. (c) Bunce, R. A.; Wamsley, E. J.; Pierce, J. D.; Shellhammer, A. J.; Drumright, R. E. *J. Org. Chem.* **1987**, *52*, 464.
(4) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.
(5) (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 24. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491.
(6) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
(7) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813.
(8) Owczarczyk, Z.; Lamaty, F.; Vanter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091.
(9) Grigg, R.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *32*, 3855.
(10) Meyer, F. E.; Henniges, H.; De Meijere, A. *Tetrahedron Lett.* **1992**, *33*, 8039.
(11) van der Baan, J. L.; van der Heide, T. A. J.; van der Louw, J.; Klumpp, G. W. *Synlett* **1995**, 1.
(12) (a) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (b) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (c) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (d) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091.
(13) Paulissen, R.; Reimlinger, H.; Hayez, A.; Hubert, A. J.; Teyssié, P. H. *Tetrahedron Lett.* **1973**, 2233.
(14) (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. (b) Taber, D. F.; Amedio, J. C., Jr.; Sherill, R. G. *J. Org. Chem.* **1986**, *51*, 3382. (c) Taber, D. F.; Ruckle, R. E., Jr. *Tetrahedron Lett.* **1985**, *26*, 3059. (d) Taber, D. F.; Amedio, J. C., Jr.; Raman, K. *J. Org. Chem.* **1988**, *53*, 2984. (e) Taber, D. F.; Hennessy, M. J.; Hoerrner, R. S.; Raman, K.; Ruckle, R. E., Jr.; Schuchardt, J. S. In *Catalysis of Organic Reactions*; Blackburn, D. W., Ed.; Marcel Dekker: New York, 1988; Chapter 4, p 43. (f) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686.
(15) Doyle, M. P.; Westrum, L. J.; Wolthuis, N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.
(16) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 1650.
(17) (a) Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709. (b) Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1508.
(18) (a) Doyle, M. P.; Shanklin, M. S.; Oon, S. M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384. (b) Doyle, M. P.; Tauton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397. (c) Doyle, M. P.; Pieters, R. J.; Tauton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.
(19) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.
(20) Taber, D. F.; M. Hennessy, J.; Louey, J.-P. *J. Org. Chem.* **1992**, *57*, 436.
(21) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479.

(22) Sundberg, R. J.; Baxter, E. W.; Pitts, W. J.; Schofield, R. A.; Nishiguchi, T. *J. Org. Chem.* **1988**, *53*, 5097.
(23) (a) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (c) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Price, A. T. *Tetrahedron Lett.* **1992**, *33*, 6427.
(24) For general reviews, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 6. (c) Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825.
(25) For recent examples of stereoselective tetrahydrofuran syntheses, see: (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950. Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. (b) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641. (c) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1986**, *108*, 2105. Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. (d) Noda, I.; Horita, K.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, 1917. (e) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748.
(26) (a) Westley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols. I and II. (b) Kishi, Y.; Schmid, G.; Fukuyama, T.; Akasaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 259.
(27) (a) Lin, Y. Y.; Risk, M.; Ray, S. M.; Engen, D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) Shimizu, Y.; Chou, H. N.; Bando, H.; Duyne, G. V.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 514.
(28) Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. I.
(29) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.
(30) (a) Piers, E.; Karunaratne, V. J. *J. Org. Chem.* **1983**, *48*, 1774. (b) Magnus, P.; Gange, D.; Bass, L.; Arnold, E. V.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 2134. (c) Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746. (d) Bruckner, C.; Reissig, H. U. *J. Org. Chem.* **1988**, *53*, 2440.
(31) For some examples, see: (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, 809. (b) Eberbach, W.; Burchardt, B. *Chem. Ber.* **1978**, *111*, 3665. (c) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 627. (d) Ochiai, H.; Nishihara, T.; Tamaru, Y.; Yoshida, Z. *J. Org. Chem.* **1988**, *523*, 1343. (e) Drewes, S. E.; Hoole, R. P. A. *Synth. Commun.* **1985**, *15*, 1067.
(32) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902.
(33) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.
(34) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 572.
(35) Griffin, G. W.; Padwa, A. In *Photochemistry of Heterocyclic Compounds*; Buchart, O., Ed.; Wiley: New York, 1976; Chapter 2.
(36) Das, P. K.; Griffin, G. W. *J. Photochem.* **1985**, *27*, 317.
(37) Bekhazi, M.; Smith, P. J.; Warkentin, J. *Can. J. Chem.* **1984**, *62*, 1646.
(38) Shimizu, N.; Bartlett, P. D. *J. Am. Chem. Soc.* **1978**, *100*, 4260.
(39) Hoffmann, R. W.; Luthardt, H. *J. Chem. Ber.* **1968**, *101*, 3861.
(40) (a) Keus, D.; Kaminski, M.; Warkentin, J. *J. Org. Chem.* **1984**, *49*, 343. (b) Bèkhazi, M.; Warkentin, J. *J. Am. Chem. Soc.* **1983**, *105*, 1289. (c) Bèkhazi, M.; Warkentin, J. *Can. J. Chem.* **1983**, *61*, 619.
(41) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348.
(42) Maas, G. *Top. Curr. Res.* **1987**, *137*, 75.
(43) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644.
(44) Wulff, W. D. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1990; Vol. 5.
(45) For a review, see: Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley Interscience: New York, 1978; Part 2, Chapter 18.
(46) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797.
(47) (a) Paulissen,R.; Reimlinger, E.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1974**, *16*, 607. (b) Petinoit, N.; Noels, A. F.; Anciaux, A. J.; Hubert, A. J.; Teyssie, P. *Fundamental Research in Homogeneous Catalsis*; Tsutsui, M., Ed.; Plenum: New York, 1979; Vol. 3, p 421. (c) Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssie', P. *Synthesis* **1976**, 600.
(48) Padwa, A.; Hornbuckle, S. H. *Chem. Rev.* **1991**, *91*, 263.
(49) (a) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717. (b) Sustmann, R.; Trill, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 838.
(50) (a) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.
(51) Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22.
(52) (a) Ibata, T.; Toyoda, J.; Sawada, M.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1266. (b) Ibata, T.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2489. (c) Toyoda, J.; Ibata, T.; Tamura, H.; Ogawa, K.; Nishino, T.; Takebayashi, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2212. (d) Ibata, T.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1787. (e) Tamura, H.; Ibata, T.; Ogawa, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 926. (f) Ibata, T.; Toyoda, J. *Chem. Lett.* **1983**, 1453. (g) Ibata, T.; Jitsuhiro, K.; Tsubokura, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 240. (h) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1976**, 287. (i) Ibata, T.; Motoyama, T.; Hamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2298. (j) Ibata, T. *Chem. Lett.* **1976**, 233. (k) Veda, K.; Ibata, T.; Takebayashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2779.
(53) Gillon, A.; Ovadia, D.; Kapon, M.; Bien, S. *Tetrahedron* **1982**, *38*, 1477.
(54) Padwa, A.; Carter, S. P.; Nimmesgern, H. *J. Org. Chem.* **1986**, *51*, 1157.
(55) Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894.
(56) Padwa, A.; Stull, P. D. *Tetrahedron Lett.* **1987**, 5407.
(57) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem.* **1988**, *53*, 2877.
(58) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.
(59) Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, 1491.
(60) (a) Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889. (b) 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.
(61) (a) Vite, J. P.; Renwich, J. A. A. *Naturwissenschaften* **1971**, *58*, 418. (b) Payne, T. L.; Coster, J. E.; Richerson, J. V.; Edson, L. J.; Hart, E. R. *Environ. Entomol.* **1978**, *7*, 578.
(62) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817.
(63) Dean, D. C.; Krumpe, K. E.; Padwa, A. *J. Chem. Soc., Chem. Commun.* **1989**, 921.
(64) Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993**, *58*, 7635.
(65) McMills, M. C.; Zhuang, L.; Wright, D. L.; Watt, W. *Tetrahedron Lett.* **1994**, 8311.
(66) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D. J.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957.
(67) Koyama, H.; Ball, R. G.; Berger, G. D. *Tetrahedron Lett.* **1994**, *35*, 9185.
(68) Wilson, K. E.; Burk, R. B.; Biftn, T.; Ball, R. G.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 7151.
(69) (a) Burke, R. M.; Berger, G. D.; Bugianesi, R. L.; Girotra, N. N.; Parsons, W. H.; Ponpipom, M. M. *Tetrahedron Lett.* **1993**, *34*, 75. (b) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 773.
(70) (a) Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhi, L. *Tetrahedron Lett.* **1989**, 301. (b) Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhang, Z. J. *J. Org. Chem.* **1991**, *56*, 3271.
(71) Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311.
(72) (a) Kharasch, M. S.; Rudy, T.; Nudenberg, W.; Buchi, G. *J. Org. Chem.* **1953**, *18*, 1030. (b) Lottes, A.; Landgreb, J. A.; Larsen, K. *Tetrahedron Lett.* **1989**, *30*, 4089.
(73) Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667.
(74) Kinder, F. R.; Bair, K. W. *J. Org. Chem.* **1994**, *59*, 6965.
(75) Curtis, E. A.; Sandanayaka, V. P.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 1989.
(76) Neeson, S. J.; Stevenson, P. J. *Tetrahedron* **1989**, *45*, 6239.
(77) (a) Grigg, R.; Ardill H.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S. *J. Chem. Soc., Chem. Commun.* **1986**, 602. (b) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.
(78) (a) Burger, K.; Schickaneder, H.; Zettle, C. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 54. (b) Burger, K.; Schinkander, H.; Zeittl, C. *Justus Liebigs Ann. Chem.* **1982**, 1730.
(79) Wentrup, C. *Helv. Chim. Acta* **1978**, *61*, 1755.
(80) (a) Sha, C. K.; Young, J. *Heterocycles* **1984**, *22*, 2571. (b) Liu, J. M.; Young, J. J.; Li, Y. J.; Sha, C. K. *J. Org. Chem.* **1986**, *51*, 1120. (c) Sha, C. K.; Ougang, S. L.; Hsieh, D. Y.; Chang, R. C.; Chang, S. C. *J. Org. Chem.* **1986**, *51*, 1490.
(81) (a) Padwa, A.; Caruso, T.; Nahm, S.; Rodriguez, R. *J. Am. Chem. Soc.* **1982**, *104*, 2864. (b) Padwa, A.; Dent, W. H.; Schoffstall, A. M.; Yeske, P. E. *J. Org. Chem.* **1989**, *54*, 4430.
(82) Nenitzecu, C. D. In *Carbonium Ions*; Olah, G., Schleyer, P. v. R., Eds.; Wiley Interscience: New York, 1968; Vol. I, Chapter 1, p 1.
(83) Saunders, M.; Chandrasekhar L.; Schleyer, P. v. R. In *Rearrangement in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. I.
(84) Brouwer, D. M.; Hogeveen, H. *Prog. Phys. Org. Chem.* **1972**, *9*, 179.
(85) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971.
(86) Jones, W. M. In *Rearrangement in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. I.
(87) Walling, C. In *Molecular Rearrangements*; de Mayo, P., Ed.; Wiley Interscience: New York, 1963; Part I.
(88) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.
(89) Beckwith, A. L.; Ingold, K. U. In *Rearrangement in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. I.

(90) (a) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1992**, *114*, 593. (b) Padwa, A.; Dean, D. C.; Lin, Z. *J. Am. Chem. Soc.* **1989**, *111*, 6451.
(91) Rodgers, J. D.; Caldwell, G. W.; Gauthier, A. D. *Tetrahedron Lett.* **1992**, *33*, 3273.
(92) Padwa, A.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 2037.
(93) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123.
(94) Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, 4475.
(95) (a) Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, 1677. (b) Maier, M. E.; Schöffling, B. *Chem. Ber.* **1989**, *122*, 1081.
(96) (a) Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett.* **1989**, *30*, 4077. (b) Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, *33*, 4731. (c) Padwa, A.; Hertzog, D. L. *Tetrahedron* **1993**, *49*, 2589.
(97) Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 1315.
(98) Marino, J. P., Jr.; Osterhout, M. H.; Padwa, A. Unpublished results.
(99) Regitz, M.; Hocker, J.; Leidhergener, A. In *Organic Synthesis*; John Wiley: New York, 1973; Collect. Vol. 5, pp 179−183.
(100) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1975**, 499.
(101) Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1985**, *50*, 245.
(102) (a) Hill, R. K. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 483. (b) Dyke, S. F.; Quessy, S. N. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 18, p 1.
(103) (a) Mondon, A.; Hansen, K. F.; Boehme, K.; Faro, H. P.; Nestler, H. J.; Vilhuber, H. G.; Böttcher, K. *Chem. Ber.* **1970**, *103*, 615. (b) Mondon, A.; Seidel, P. R. *Chem. Ber.* **1971**, *104*, 2937. (c) Mondon, A.; Nestler, H. J. *Chem. Ber.* **1979**, *112*, 1329.
(104) Haruna, M.; Ito, K. *J. Chem. Soc., Chem. Commun.* **1976**, 345.
(105) Ishibashi, H.; Sato, K.; Ikeda, M.; Maeda, H.; Akai, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1985**, 605.
(106) Dean, R. T.; Rapoport, H. A. *J. Org. Chem.* **1978**, *43*, 4183.
(107) Dehaen, W.; Hassner, A. *J. Org. Chem.* **1991**, *56*, 896.
(108) Prajapat, D.; Bhuyan, P.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 607.
(109) Prajapart, D.; Sandhu, J. S. *Synthesis* **1988**, 342.
(110) Tsuge, O.; Veno, K.; Kanemasa, S. *Chem. Lett.* **1984**, 285.
(111) Padwa, A.; Hertzog, D. L.; Nadler, W. R. *J. Org. Chem.* **1994**, *59*, 7072.
(112) Potts, K. T. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.
(113) Ohta, M.; Kato, H. In *Nonbenzenoid Aromatics*; Snyder, J. P., Ed.; Academic Press: New York, 1969; pp 117−248.
(114) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.
(115) Ollis, W. D.; Ramsden, C. A. In *Advances In Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1976; Vol. 19, p 1.
(116) Newton, C. G.; Ramsden, C. A. *Tetrahedron* **1982**, *38*, 2965.
(117) Baker, W.; Ollis, W. D.; Poole, V. D. *J. Chem. Soc.* **1949**, 307.
(118) Baker, W.; Ollis, W. D.; Poole, V. D. *J. Chem. Soc.* **1950**, 1542.
(119) Huisgen, R.; Gotthardt, H.; Grashey, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 49.
(120) Gotthardt, H.; Huisgen, R. *Chem. Ber.* **1968**, *101*, 552.
(121) Huisgen, R.; Grashey, R.; Gotthardt, H. *Chem. Ber.* **1968**, *101*, 829.
(122) Baker, W.; Ollis, W. D. *Chem. Ind.* **1955**, *33*, 910.
(123) Ibata, T.; Hamaguchi, M.; Kiyohara, H. *Chem. Lett.* **1975**, 21.
(124) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodung, U. E. *Tetrahedron* **1987**, *43*, 5475.
(125) Zani, C. L.; de Oliveria, A. B.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 6561.
(126) Carte, B.; Kernan, M. R.; Barrabee, E. B.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 3528.
(127) Hirota, H.; Kitano, K.; Komatsubara, T.; Takahishi, T. *Chem. Lett.* **1987**, 2079.
(128) Jacobi, A.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585.
(129) Hamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1978**, 247.
(130) Padwa, A.; Kinder, F. R.; Nadler, W. R.; Zhi, L. *Heterocycles* **1993**, *35*, 367.
(131) Cameron, T. B.; Pinnick, H. W. *J. Am. Chem. Soc.* **1979**, *101*, 4755.
(132) Middleton, W. J. *J. Org. Chem.* **1966**, *31*, 3731.
(133) Herstroeter, W. G.; Schultz, A. G. *J. Am. Chem. Soc.* **1984**, *106*, 5553.
(134) Kaufman, J. A.; Weininger, S. J. *J. Chem. Soc., Chem. Commun.* **1969**, 593.
(135) Takano, S.; Tomita, S.; Takahashi, M.; Ogasawara, K. *Synthesis* **1987**, 1116.
(136) (a) Ohno, M.; Okamoto, M.; Kawabe, N.; Umezawa, H.; Takeuchi, T.; Linuma, H.; Takahashi, S. *J. Am. Chem. Soc.* **1971**, *93*, 1285. (b) Tsujikawa, T.; Nakagawa, Y.; Tsukamura, K.; Masuda, K. *Heterocycles* **1977**, *6*, 261. (c) Tsujikawa, T.; Nakagawa, Y.; Tsukamura, K.; Masuda, K. *Chem. Pharm. Bull.* **1977**, *25*, 2775. (d) Bates, H. A.; Farina, J. *J. Org. Chem.* **1985**, *50*, 3843.
(137) Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
(138) Fang, F. G.; Prato, M.; Kim, G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, 3625.
(139) Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, 2747.
(140) Fang, F. G.; Maier, M. E.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 831.
(141) Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 2003.
(142) Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, *94*, 7172.
(143) (a) Huisgen, R.; Scheer, W.; Mader, H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 602. (b) Heine, H. W.; Peavy, R. *Tetrahedron Lett.* **1965**, 3123. (c) Padwa, A.; Hamilton, L. *Tetrahedron Lett.* **1965**, 4363.
(144) Vedjs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.
(145) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Huisgen, R.; Grashey, R.; Steingruber, E. *Tetrahedron Lett.* **1963**, 1441.
(146) (a) Grigg, R.; Kemp, J.; Sheldrick, G.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109. (b) Grigg, R.; Kemp, J. *Tetrahedron Lett.* **1980**, 2461.
(147) Baret, P.; Buffet, H.; Pierre, J. L. *Bull. Soc. Chim. Fr.* **1972**, *6*, 2493.
(148) Bartnik, R.; Mloston, G. *Tetrahedron* **1984**, *40*, 2569.
(149) Mara, A. M.; Singh, O.; Thomas, E. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2169.
(150) (a) Padwa, A.; Dean, D. C. *J. Org. Chem.* **1990**, *55*, 405. (b) Padwa, A.; Dean, D. C.; Osterhout, M. H.; Precedo, L.; Semones; M. A. *J. Org. Chem.* **1994**, *59*, 5347.
(151) Clineschmidt, B. V.; Martin, G. E.; Bunting, P. R. *Drug. Dev. Res.* **1982**, *2*, 123.
(152) Loo, P. A.; Braunwalder, A. F.; Williams, M.; Sills, M. A. *Eur. J. Pharmacol.* **1987**, *135*, 261.
(153) McDonald, J. W.; Silverstein, F. S.; Johnston, M. V. *Eur. J. Pharmacol.* **1987**, *140*, 359.
(154) Daniels, R.; Salerni, O. L. *Proc. Chem. Soc.* **1960**, 286.
(155) Band, I. B. M.; Loyd, D.; Singer, M. I. C.; Wasson, F. I. *J. Chem. Soc., Chem. Commun.* **1966**, 544.
(156) Lloyd, D.; Singer, M. I. C. *J. Chem. Soc. (C)* **1971**, 2939.
(157) Durr, H.; Hev, G.; Ruge, B.; Scheppers, G. *J. Chem. Soc., Chem. Commun.* **1972**, 1257.
(158) Jones, M. B.; Maloney, V. M.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 2163.
(159) Zugravescu, I.; Petrovanu, M. *N-Ylid Chemistry*; McGraw Hill: New York, 1976.
(160) Platz, M. S.; Maloney, V. M. *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum: New York, 1990; pp 239−252.
(161) (a) Chen, N.; Jones, M.; White, W. R.; Platz, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 4981. (b) Barcus, R. L.; Hadel, L. M.; Johnston, L. J.; Platz, M. S.; Savino, T. G.; Scaiano, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3928. (c) Hadel, L. M.; Platz, M. S.; Scaiano, J. C. *Chem. Phys. Lett.* **1983**, *97*, 446. (d) Barcus, R. L.; Wright, B. B.; Platz, M. S.; Scaiano, J. C. *Tetrahedron Lett.* **1983**, *24*, 3955.
(162) (a) Jackson, J. E.; Soundararajan, N.; Platz, M. S.; Doyle, M. P.; Liu, M. T. H. *Tetrahedron Lett.* **1989**, *30*, 1335. (b) Jackson, J. E.; Soundararajan, N.; White, W.; Liu, M. T. H.; Bonneau, R.; Platz, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 6874. (c) White, W. R.; Platz, M. S.; Chen, N.; Jones, M., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 7794. (d) Perrin, H. M.; White, W. R.; Platz, M. S. *Tetrahedron Lett.* **1991**, *32*, 4443. (e) Morgan, S.; Jackson, J. E.; Platz, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 2782. (f) Jones, M. B.; Platz, M. S. *J. Org. Chem.* **1991**, *56*, 1694. (g) Sugiyama, M. H.; Celebi, S.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 966.
(163) (a) Bonneau, R.; Liu, M. T. H.; Rayez, M. T. *J. Am. Chem. Soc.* **1989**, *111*, 5973. (b) Liu, M. T. H.; Bonneau, R. *J. Phys. Chem.* **1989**, *93*, 7298.
(164) Chateaunef, J. E.; Johnson, R. P.; Kirchoff, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 3217.
(165) (a) Moss, R. A.; Ho, G. J.; Shen, S.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1990**, *112*, 1638. (b) Moss, R. A.; Ho, G. J. *Tetrahedron Lett.* **1990**, 1225.
(166) Moss, R. A.; Turro, N. J. *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum: New York, 1990; pp 213−238.
(167) Ho, G. J.; Krogh-Jespersen, K.; Moss, R. A.; Shen, S.; Sheridan, R. S.; Subramanian, R. *J. Am. Chem. Soc.* **1989**, *111*, 6875.
(168) White, W. R., III; Platz, M. S. *J. Org. Chem.* **1992**, *57*, 2841.
(169) Rieser, J.; Friedrich, K. *Liebigs Ann. Chem.* **1976**, 666.
(170) Zugrãvescu, I.; Rucinschi, E.; Surpãteanu, G. *Tetrahedron Lett.* **1970**, 941.
(171) Jackson, J. E.; Soundararajan, N.; Platz, M. S. *J. Am. Chem. Soc.* **1988**, *110*, 5595.
(172) Padwa, A.; Austin, D. J.; Precedo, L.; Zhi, L. *J. Org. Chem.* **1993**, *58*, 1144.
(173) Kulyk, M. S.; Neckers, D. C. *J. Org. Chem.* **1983**, *48*, 1275.
(174) Connell, R.; Scavo, F.; Helquist, P.; Akermark, B. *Tetrahedron Lett.* **1986**, *27*, 5559.
(175) Doyle, M. P.; Buhro W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3667.
(176) Turchi, I. J., Ed. *Oxazoles*; Wiley Interscience: New York, 1986.
(177) Huisgen, R.; Sturm, H. J.; Binsch, G. *Chem. Ber.* **1964**, *97*, 2865.

(178) (a) Buu, N. T.; Edward, J. T. *Can. J. Chem.* **1972**, *50*, 3730. (b) Shi, G.; Xu, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 607.
(179) Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761; *Synthesis* **1994**, 1021.
(180) Connell, R.; Tebbe, M.; Helquist, P.; Akermark, B. *Tetrahedron Lett.* **1991**, *32*, 17.
(181) Yoo, S. K *Tetrahedron Lett.* **1992**, *33*, 2169.
(182) Doyle, K. J.; Moody, C. J. *Tetrahedron Lett.* **1992**, *33*, 7769.
(183) Gangloff, A. R.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797.
(184) Connell, R.; Tebbe, M.; Gangloff, A. R.; Helquist, P.; Akermark, B. *Tetrahedron* **1993**, *49*, 6446.
(185) Kende, A. S.; Hebeisen, P.; Sanfilippo, P. J.; Toder, B. H. *J. Am. Chem. Soc.* **1982**, *104*, 4244.
(186) Sheppard, W. A.; Gokel, G. W.; Webster, O. W.; Betterton, K.; Timberlake, J. W. *J. Org. Chem.* **1979**, *44*, 1717.
(187) Mykytka, J. P.; Jones, W. M. *J. Am. Chem. Soc.* **1975**, *97*, 5933.
(188) Padwa, A.; Krumpe, K. E.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 2633.
(189) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990**, *55*, 4518.
(190) (a) Padwa, A.; Chiacchio, U.; Garreau, Y.; Kassir, J. M.; Krumpe, K. E.; Schoffstall, A. M. *J. Org. Chem.* **1990**, *55*, 414. (b) Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523.
(191) Moss, R. A. *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley: New York, 1970; Vol. 1, pp 35−88
(192) (a) Baird, M. S. *Synthetic Application of Cyclopropenes, Topics in Current Chemistry*; de Meijere, A., Ed.; Springer-Verlag; New York, 1988; Vol. 144, p 138. (b) Halton, B.; Bansell, M. G. *Cyclopropenes in the Chemistry of Cyclopropanes*; Rappoport, Z., Ed.; Wiley: New York, 1988; Vol. *2*.
(193) (a) Al-Dulayymi, J.; Gaird, V. S.; Clegg, W. *Tetrahedron Lett.* **1988**, *29*, 6149. (b) Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1978**, *19*, 1239.
(194) Padwa, A. *Org. Photochem.* **1979**, *4*, 261.
(195) Mueller, P. H.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D.; Padwa, A. *Tetrahedron Lett.* **1993**, *34*, 4285.
(196) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1963**, *19*, 715.
(197) Hudlicky, T.; Natchuz, M. G.; Zingde, G. S. *J. Org. Chem.* **1987**, *52*, 4644.
(198) Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. F. M. *J. Org. Chem.* **1989**, *54*, 930.
(199) (a) Binger, P.; Buch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (b) Binger, P.; Muller, P.; Benn, R.; Mynott, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 610.
(200) Muller, P.; Pautex, N.; Doyle, M. P.; Bagheri, V. *Helv. Chim. Acta* **1991**, *73*, 1233.
(201) Padwa, A.; Krumpe, K. E.; Kassir, J. M. *J. Org. Chem.* **1992**, *57*, 4940.
(202) Shankar, B. K. R.; Shechter, H. *Tetrahedron Lett.* **1982**, *23*, 2277.
(203) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4163.
(204) Doyle, M. P.; High, K. G.; Oon, S. M.; Osborn, A. K. *Tetrahedron Lett.* **1989**, *30*, 3049.
(205) (a) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1991**, *32*, 3755. (b) Hoye, T. R.; Dinsmore, C. J. *J. Am Chem. Soc.* **1991**, *113*, 4343.
(206) Padwa, A.; Austin, D. J.; Xu, S. L. *J. Org. Chem.* **1992**, *57*, 1330.
(207) Padwa, A.; Austin, D. J.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 4103.
(208) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am Chem. Soc.* **1993**, *115*, 2637.
(209) McCullough, L. G.; Listemann, M. L.; Schrock, R. R.; Churchill, M. R.; Ziller, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 6729.
(210) Padwa, A. *Rearrangement in Ground and Excited States*; DeMayo, P., Ed.; Academic Press: New York, 1980; Vol. 3, p 501.
(211) (a) Taylor, E. C.; Turchi, I. J. *Chem Rev.* **1979**, *79*, 181. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947.
(212) Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21.
(213) Babu, S. D.; Hrytsak, M. D.; Durst, T. *Can. J. Chem.* **1989**, *67*, 1071.
(214) Hrytsak, M. D.; Etkin, M.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 5679.
(215) Monteiro, H. J. *Tetrahedron Lett.* **1987**, *28*, 3459.
(216) Sundberg, R. J.; Baxter, E. W. *Tetrahedron Lett.* **1986**, *27*, 2687.
(217) (a) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299. (b) Wenkert, E.; Guo, M.; Pizzo, F.; Ramachandran, K. *Helv. Chim. Acta* **1987**, *70*, 1429. (c) Nwaji, M. N.; Onyiriuka, O. O. *Tetrahedron Lett.* **1974**, *15*, 2255.
(218) (a) Adams, J.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 35. (b) Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185.
(219) Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L. *J. Org. Chem.* **1993**, *58*, 4646.
(220) (a) Kassir, J. M.; Semones, M. A.; Weingarten, M. D.; Padwa, A. *Tetrahedron Lett.* **1993**, *34*, 7853. (b) Padwa, A.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D. *J. Org. Chem.* **1995**, *60*, 53.
(221) Taylor, K. G. *Tetrahedron* **1982**, *38*, 159.
(222) Ibata, T.; Toyoda, J.; Sawada, M.; Takai, Y.; Tanaka, T. *Tetrahedron Lett.* **1988**, *29*, 317.
(223) Marrell, E. N. In *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980.
(224) Olah, G. A.; Doggweiler, H.; Felberg, J. D. *J. Org. Chem.* **1984**, *49*, 2112.
(225) Vedjs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.
(226) Nicolaev, V. A.; Korobitsyna, I. K. *Zh. Vses Khim. Ova.* **1979**, *24*, 496.
(227) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971.
(228) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Weinheim, 1983.
(229) Maas, G. *Topics in Current Chemistry*; Springer-Verlag: Berlin, West Germany, 1987; Vol. 137, p 75.
(230) Anciaux, A. J.; Hubert, A. F.; Noels, N.; Petinot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695.
(231) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348; *Chem. Rev.* **1986**, *86*, 919.
(232) Huxtable, R. J. *Biochemistry of Sulfur*; Plenum Press: New York, 1986.
(233) Prasad, K.; Kneussel, P.; Schulz, G.; Stütz, P. *Tetrahedron Lett.* **1982**, 1247.
(234) Kametani, T.; Kanaya, N.; Mochizuki, T.; Honda, T. *Heterocycles* **1982**, *19*, 1023.
(235) Kametani, T.; Nakayama, A.; Itoh, A.; Honda, T. *Heterocycles* **1983**, *20*, 2355.
(236) Fliri, H.; Mak, C. P.; Prasad, K.; Schulz, G.; Stütz, P. *Heterocycles* **1983**, *20*, 205.
(237) Prasad, K.; Schulz, G.; Mak, C. P.; Hamberger, H.; Stütz, P. *Heterocycles* **1981**, *16*, 1305.
(238) Oida, S.; Yoshida, A.; Ohki, E. *Heterocycles* **1980**, *14*, 1999.
(239) Prasad, K.; Stütz, P. *Heterocycles* **1982**, *19*, 1597.
(240) Ernest, I. *Tetrahedron* **1977**, *33*, 547.
(241) Ponsford, R. J. *Tetrahedron Lett.* **1980**, 2451.
(242) Mak, C. P.; Baumann, K.; Mayerl, F.; Mayerl, C.; Fliri, H. *Heterocycles* **1982**, *19*, 1647.
(243) Yoshimoto, M.; Ishihara, S.; Nakayama, E.; Soma, N. *Tetrahedron Lett.* **1972**, 2923.
(244) Yoshimoto, M.; Ishihara, S.; Nakayama, E.; Shoji, E.; Kuwano, H.; Soma, N. *Tetrahedron Lett.* **1972**, 4387.
(245) Numata, M.; Imashiro, Y.; Minamida, I.; Yamaoka, M. *Tetrahedron Lett.* **1972**, 5097.
(246) Kametani, T.; Kanaya, N.; Mochizuki, T.; Honda, T. *Heterocycles* **1983**, *20*, 435.
(247) Kametani, T.; Kanaya, N.; Mochizuki, T.; Honda, T. *Heterocycles* **1983**, *20*, 455.
(248) Kametani, T.; Kanaya, N.; Mochizuki, T.; Honda, T. *Tetrahedron Lett.* **1983**, 221.
(249) Corbett, D. F.; Eglington, A. J.; Howarth, T. T. *J. Chem. Soc., Chem. Commun.* **1977**, 953.
(250) Albers-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratchliffe, R. W.; Walton, E.; Ruswinkel, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.
(251) Giddings, P. J.; John, D. I.; Thomas, E. J. *Tetrahedron Lett.* **1980**, 395.
(252) Giddings, P. J.; John, D. I.; Thomas, E. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2757.
(253) Chan, L.; Matlin, S. A. *Tetrahedron Lett.* **1981**, 4025.
(254) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1324.
(255) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1986**, 651.
(256) Michelot, D.; Linstrumelle, G.; Julia, S. *J. Chem. Soc., Chem. Commun.* **1974**, 10.
(257) Trost, B. M.; Melvin, L. S. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic Press: New York, 1975.
(258) Davies, H. M. L.; Crisco, L. V. T. *Tetrahedron Lett.* **1987**, 371.
(259) Kim, G.; Kang, S.; Kim, S. N. *Tetrahedron Lett.* **1993**, 7627.
(260) Noyori, R.; Sato, T.; Hayakawa, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2561.
(261) Sato, T.; Hayakawa, Y.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2515.
(262) (a) Gillespie, R. J.; Porter, A. E. A.; Willmott, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 85. (b) Gillespie, R. J.; Porter, A. E. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2624.
(263) Murray-Rust, P.; McManus, J.; Lennon, S. P.; Porter, A. E. A.; Rechka, J. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 713.
(264) Storflor, H.; Skramstad, J.; Nordenson, S. *J. Chem. Soc., Chem. Commun.* **1984**, 208.
(265) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1988**, *29*, 6005.
(266) Kondo, K.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1972**, 860.
(267) de March, P.; Moreno-Mañas, M.; Ripoll, I. *Synth. Commun.* **1984**, *14*, 521.
(268) Andrews, G.; Evans, D. A. *Tetrahedron Lett.* **1972**, 5121.
(269) Kurth, M. J.; Tahir, S. H.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 2286.

(270) Kido, F.; Sinha, S. C.; Abiko, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1989**, *30*, 1575.
(271) Kido, F.; Sinha, S. C.; Abiko, T.; Watanabe, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 418.
(272) Kido, F.; Kawada, Y.; Kato, M.; Yoshikoshi, A. *Tetrahedron Lett.* **1991**, *32*, 6159.
(273) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem.* **1977**, *89*, 602. Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683.
(274) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878.
(275) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.
(276) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; Van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917.
(277) Nickon, A.; Rodriguez, A. D.; Ganguly, R.; Shirhatti, V. *J. Org. Chem.* **1985**, *50*, 2767.
(278) Ceré, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1981**, *46*, 486.
(279) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1992**, 169.
(280) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146.
(281) Hata, Y.; Watanabe, M.; Inoue, S.; Oae, S. *J. Am. Chem. Soc.* **1975**, *97*, 2553.
(282) (a) Karakasa, T.; Satsumabayashi, S.; Motoki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 335. (b) Motoki, S.; Saito, T.; Karakasa, T.; Matsushita, T.; Furono, E. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2943. (c) Karakasa, T.; Moriyama, S.; Motoki, S. *Chem. Lett.* **1988**, 1029.
(283) Guemas, J. P.; Quiniou, H. *Sulfur Lett.* **1984**, *2*, 121.
(284) Ohno, M.; Sasaki, T. *Yuki Gosei Kagaku Kyokai Shi* **1984**, *42*, 125.
(285) Gregory, G. I., Ed. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Royal Society of Chemistry: London, 1981.
(286) Kaiser, G. V.; Ashbrook, C. W.; Baldwin, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 2342.
(287) Olah, G. A.; Doggweiler, H.; Felberg, J. D.; Frohlich, S.; Grdina, M. J.; Karpeles, R.; Keumi, T.; Inaba, S.; Lammertsma, K.; Salem, G.; Tabor, D. C. *J. Am. Chem. Soc.* **1984**, *106*, 2143.
(288) Thijs, L.; Zwanenburg, B. *Tetrahedron* **1980**, *36*, 2145.
(289) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.
(290) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060.
(291) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561.
(292) Day, A. L.; Nabney, J.; Scott, A. I. *J. Chem. Soc.* **1961**, 4067.
(293) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193.
(294) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385.
(295) Glidewell, C.; Lloyd, D.; Metcalfe, S. *Synthesis* **1988**, 319.
(296) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83.
(297) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2857.
(298) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177.
(299) West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis* **1993**, 977.
(300) Pine, S. H. *Org. React.* **1970**, *18*, 403.
(301) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4675.
(302) Johnson, A. W. *Ylide Chemistry*; Academic Press: New York, 1966.
(303) Ando, W.; Yagihara, T.; Tozune, S.; Imai, I.; Suzuki, J.; Toyama, T.; Nakaido, S.; Migita, T. *J. Org. Chem.* **1972**, *37*, 1721.
(304) Iwamura, H.; Imahashi, Y. *Tetrahedron Lett.* **1975**, 1401.
(305) Hata, Y.; Watanabe, M. *Tetrahedron Lett.* **1972**, 4659.
(306) Tomioka, H.; Suzuki, K. *Tetrahedron Lett.* **1989**, 6353.
(307) Kirmse, W.; Arold, H. *Chem. Ber.* **1968**, *101*, 1008.
(308) Franzen, V.; Kuntze, H. *Liebigs Ann. Chem.* **1959**, *627*, 15.
(309) Saunders, M.; Murray, R. W. *Tetrahedron* **1960**, *11*, 1.
(310) Phillips, D. D.; Champion, W. C. *J. Am. Chem. Soc.* **1956**, *78*, 5452.
(311) (a) Kreissl, F. R.; Held, W. *J. Organomet. Chem.* **1975**, *86*, C10. (b) Schmidbaur, H. *Acc. Chem. Res.* **1975**, *8*, 62.
(312) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094.
(313) Williams, M. A.; Miller, M. J. *Tetrahedron Lett.* **1990**, 1807.
(314) Miller, M. J.; Mattingly, P. G. *J. Org. Chem.* **1980**, *45*, 410.
(315) Zaragoza, F. *Synlett* **1995**, 237.
(316) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892.
(317) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol 3, Chapter 4.2.
(318) Ollis, W. D.; Rey, M.; Suterland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009.
(319) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051.

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