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Rhodium (II) Catalyzed Reactions of Diazo-carbonyl Compounds*

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Contents

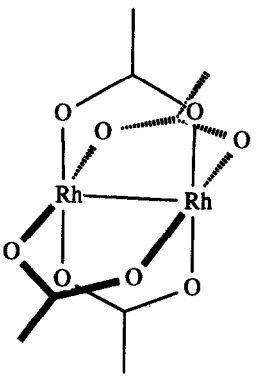
I. Introduction

The focus of this report deals with the use of Rh(II) complexes and their ability to catalyze a variety of important reactions Diazo-carbonyl compounds are ideal substrates for Rh(II) based catalysts and react under mild conditions to form what is probably a Fischer-type carbenoid These carbenoids have never been observed, due to the high reactivity of the putative intermediate metal-carbene. Rhodium (II) acetate dimer is the prototypical catalyst for the diazo-transfer process, although ligand modifications have resulted in various improvements for specific circumstances (vide infra)

This review will cover four important reactions of Rh(II) carbenes cyclopropanation, carbon-hydrogen bond insertion, heteroatom-hydrogen bond insertion, and ylide formation and subsequent reactions. The diversity of reactions as well as the unique bond forming capabilities is an impressive feature of the rhodium generated carbenes Free carbenes have long been regarded as highly energetic species which have interesting properties, though of limited value in organic synthesis. Metal-carbenes in general, have generated a wealth of novel and useful reactions. This review will attempt to demonstrate the scope of the rhodium catalyzed carbene reactions with a view to practical synthetic construction, and briefly address some of the mechanistic issues which make the rhodium based catalysts useful reagents for synthetic chemistry.

* This Report is dedicated to Professor W D Ollis on the occasion of his 65th birthday

Rhodium acetate dimer is prepared by heating $RhCl_3 \cdot 3H_2O$ in acetic acid Other rhodium carboxylates may be obtained by the analogous procedure or by ligand exchange with $Rh_2(OAc)_4$ Rhodium (II) carboxylates possess an octahedral D4 symmetry with four bridging carboxylates complexed to the binuclear rhodium atoms This has been refered to as the "lantern" structure The inorganic chemistry of rhodium (II) carboxylates has been extensively reviewed by Boyer and Robinson,[1b] and will not be addressed in this paper



Rhodium Acetate Dimer

II. Cyclopropanation

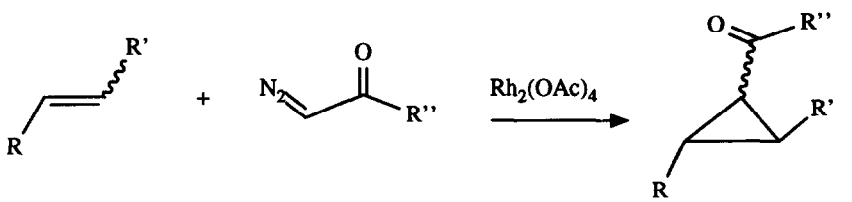
The synthesis of cyclopropanes and their use in ring cleavage reactions remains an important area of research in organic chemistry, and several recent reviews have explored these themes [1-4] As mentioned in the introduction, rhodium II mediated reactions of α-diazo carbonyl compounds may result in addition to unsaturated systems to produce 3-membered ring products The most commonly used reaction leads to the formation of cyclopropyl derivatives Historically the use of various copper catalysts[5-7] were prevalent and only the emergence of the group VIII metals in the late 1960's and early 1970's challenged the efficacy of the copper based catalysts [8-12] The pioneering work of Belgian chemists Paulissen, Hubert, Teyssié, Anciaux and other collaborators was paramount in identifying the rhodium (II) carboxylates as efficient catalysts for carbenoid mediated cyclopropanations [13-16]

A systematic screening of common transition metal complexes revealed that Rh(II) species were the mildest and most efficient catalysts for cyclopropanation [17,18] Air stable Rh(II) carboxylates, most notably $Rh_2(OAc)_4$, having one coordination site per metal, form highly reactive complexes with carbenes derived from diazo precursors These carbenoids add rapidly to available carbon -carbon double and triple bonds (and, as will be reviewed, are capable of single bond

insertion reactions) By contrast, the traditional copper metal catalysts which mediate the same reactions to varying degrees, probably do so via different mechanisms Copper-olefin complexation has been proposed to direct the cyclopropanation reaction Rhodium catalysts with the single available coordination site do not form complexes with olefins and this is inferred from the near random chemo-selectivity observed with different olefins [17,18] The catalyst selection is critical since competing processes such as the Wolff rearrangement (seen with silver based catalysts or C-H insertion reactions (observed with Pd catalysts) are also options for α-ketocarbenes.[19] Rh(II) catalysis is documented to be very specific for cyclopropanation

A note on the general reaction conditions is in order Catalytic efficiency is generally high, requiring 1-3% catalyst (by weight) and best results are obtained at ambient temperature (solubility permitting) in non-reactive solvents such as methylene chloride or other halogenated hydrocarbons Reaction rates are extremely rapid and no intermediate carbenoid complexes have ever been isolated, unlike the well known tungsten or chromium carbenoids A general correlation of olefin reactivity indicates that the more electron-rich double bonds will react preferentially [17] Even ketene acetals react with diazoacetate to give the desired cyclopropyl acetal, but only when Rh(II) was chosen for catalysis [20] Electron deficient olefins (i e α,β unsaturated olefins) often fail to generate cyclopropanes, but rather form pyrazolines Barring steric factors, cis olefins react slightly faster than trans olefins

Scheme 1: General Cyclopropanation Reaction

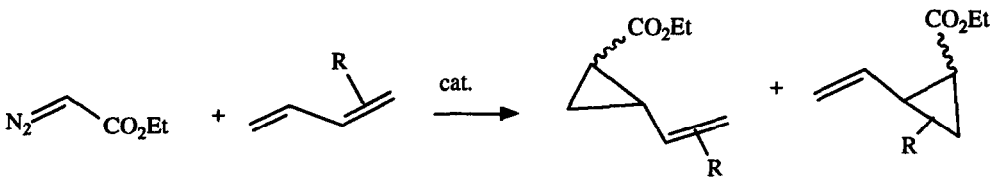


Conjugated dienes and trienes are also reactive, and cyclopropanation at the more nucleophilic double bond is predominant.[21-23] By the same token, acetylenes represent good substrates for Rh(II) mediated carbene additions and lead to highly strained (and reactive) cyclopropenes [24] In general the copper catalysts fail to produce any product at all As already mentioned, the more nucleophilic the reacting substrate the more rapid the reaction This was demonstrated by Petiniot et al [24] who performed a competition experiment between 1-hexyne and 1-octene, where the cyclopropene product predominated over the cyclopropane by a ratio of 2 1

Such selectivities amongst olefins, dienes and trienes have been extensively documented in the literature [17,18,25,26] Much of the earlier literature addressed the intermolecular reactions with respect to regiochemical and stereochemical aspects of cyclopropanation Doyle and co-workers have conducted the most systematic investigations with regards to mechanism and rhodium catalyst comparisons [18,27] Doyle's initial efforts confirmed the superiority of $Rh_2(OAc)_4$ as the catalyst of choice for cyclopropanation, observing superior yields under the mild reaction conditions

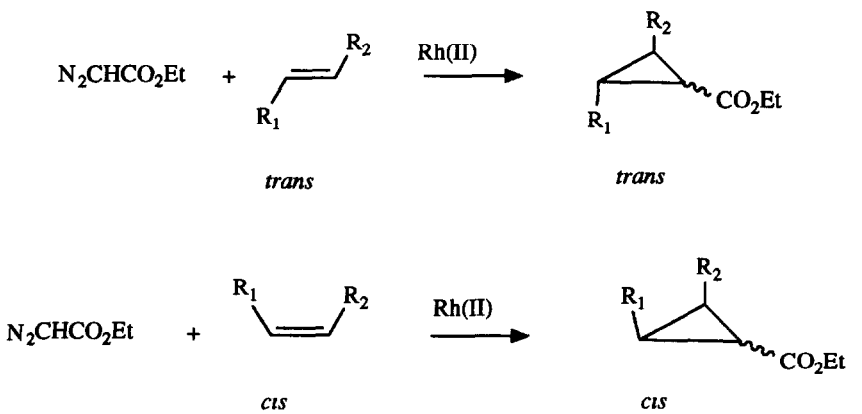
Nevertheless $Rh_2(OAc)_4$ tends to exhibit slightly less regioselectivity compared to copper catalysts The reaction of ethyl diazoacetate and monosubstituted dienes was used to establish a "metal-carbene regioselectivity index "[25] Product analysis of the competing double bonds of the diene gave results that were mechanistically diagnostic This exercise confirmed the tendency of Rh(II) to form reactive metal-carbene complexes with no coordination to the reacting olefin As initially proposed by the Belgian investigators electron-rich olefins were more reactive towards cyclopropanation with the electrophilic ethyl acetate carbenoid(Scheme 2)

Scheme 2: Diazoacetate Addition to Mono-susbstituted Dienes



Doyle and colleagues also undertook a systematic investigation of the stereoselectivity in the ethyl diazoacetate cyclopropanation reaction [28] In general the reaction tends towards little if any selectivity The trans isomer predominates to a small degree (1-2·1 trans/cis) except if a sterically demanding group or groups influence the reaction outcome Trans olefins react to produce cyclopropanes where the two substituents derived from the olefin maintain the trans relationship in the cyclopropane product The same applies to cis substituted olefins

Scheme 3: Stereospecificity of Olefin Substituents in Cyclopropanation

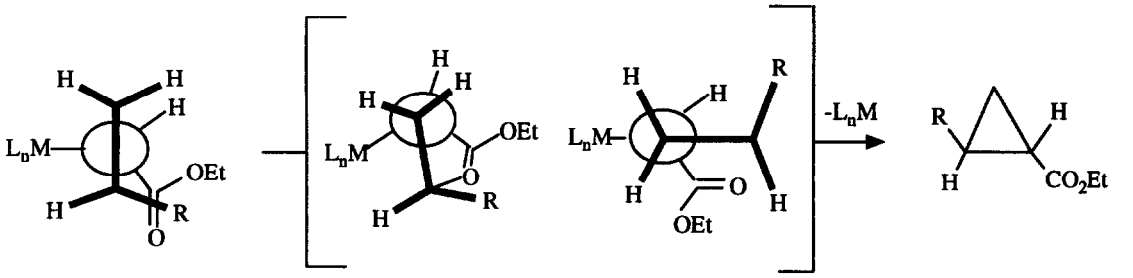


Doyle correctly points out that four variables contribute to the resulting regio- and stereochemical course of cyclopropanation. the transition metal, its associated ligands, the diazo compound and the olefin The olefin is generally the weakest contributor to the stereochemical outcome

Further mechanistic evaluation by Doyle, using kinetic competition experiments and product analysis, led to the comparison of the stable tungsten metal-carbene, $(CO)_5WCHPh$, for cyclopropanation, and the rhodium acetate catalyzed reaction of phenyl diazomethane.[29] Though the relative reactivities were much faster in the tungsten catalyzed system (10^3-10^4 times) the order of olefin reactivity remained the same as for the $Rh_2(OAc)_4$ case This is good evidence for the assumption of a rhodium-carbene complex which has been extended to hold true for diazo-carbonyl carbenes as well

A pictorial assessment which accounts for the slight preference for the trans-cyclopropane isomer in mono- substituted olefins was put forth by Doyle, as shown in Scheme 4 While such an account is reasonable, caution must be employed in considering this mechanism since none of the intermediate transition states have ever been observed Nevertheless, as a point of departure, this analysis is consistent with mechanistic principles and accounts for the experimental observations

Scheme 4: Doyle's Mechanism of Cyclopropanation [29]



Following the initial investigations with $Rh_2(OAc)_4$, Doyle et al proceeded to demonstrate both the ligand effects on Rh(II) and the steric effects of the reacting diazo carbonyl Both rhodium acetamide, $Rh_2(NHCOCH_3)_4$ and rhodium perfluorobutyrate, $Rh_2(OCOC_3F_7)_4$ were found to affect the trans-selectivity in the reaction of diazo-carbonyls with styrene [30] The results are summarized in the table below

Table 1: Stereoselectivity Enhancement in Catalytic Cyclopropanation of Styrene

	trans/cis (yield, %)			
Catalyst	$N_2CHCOOEt$	$N_2CHCOOMe(iPr)_2$	$N_2CHCONMe_2$	$N_2CHCON(iPr)_2$
$Rh_2(OCOC_3F_7)_4$	1.1 (81)	1 1 (83)	1 5 (67)	12 (51)
$Rh_2(OAc)_4$	1.6 (95)	2 4 (95)	2 2 (74)	64 (53)
$Rh_2(NHCOCH_3)_4$	2 1 (89)	4.4 (87)	2 4 (70)	114 (47)

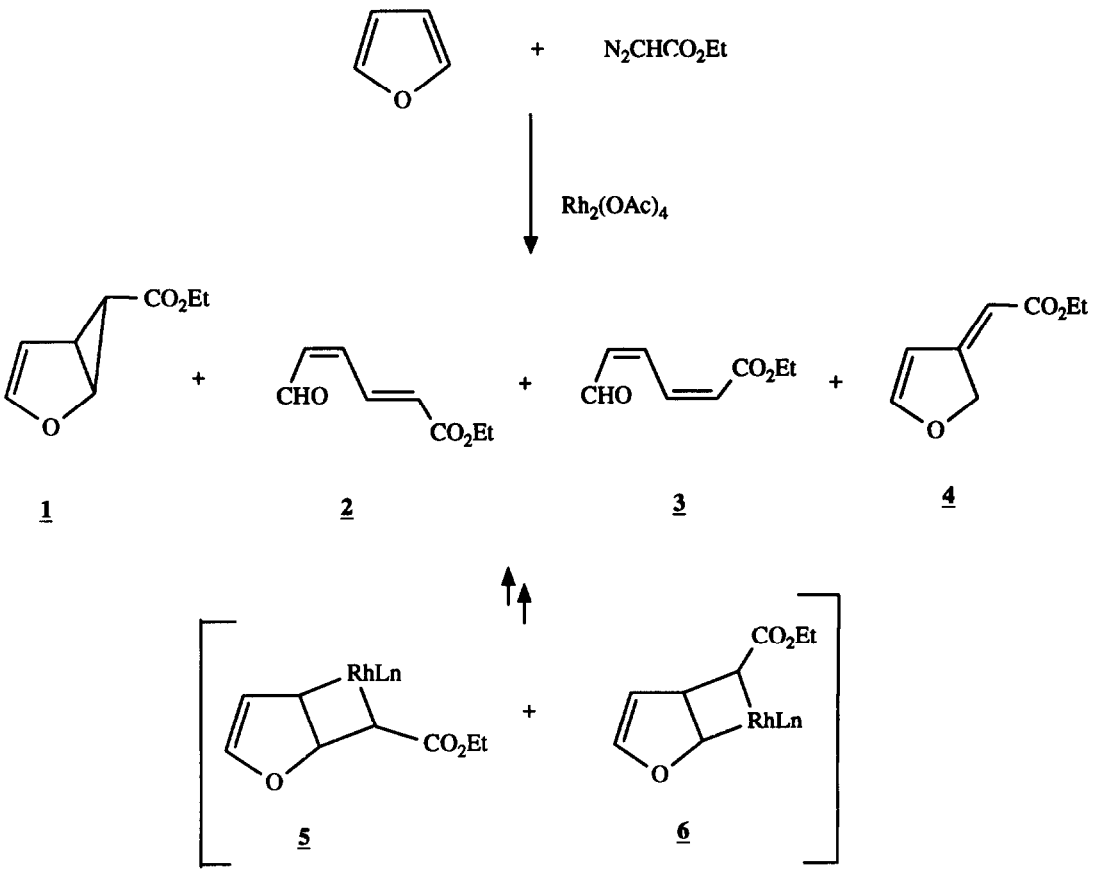
The electron withdrawing effects of the perfluorobutyrate ligand adversely influences the trans selectivity while the acetamide catalyst enhances trans selectivity As well, the steric bulkiness of the reacting diazo carbonyl contributes to the trans stereochemistry although the yields tend to diminish Alternatively, Callot and Metz were able to effect cis stereoselectivity in cyclopropanation with the use of bulky 2,4,6-triarylbenzoate ligands on Rh(II) [31] A detailed account of the stereoselectivity in catalytic cyclopropanation reactions was recently published and includes further studies involving ligand modification of the catalyst and diazo carbonyl compounds [32]

An interesting application of the intermolecular reaction demonstrating the power of the Rh(II) catalyzed cyclopropanation is the reaction of ethyl diazoacetate and furan (Scheme 5) With furan as the solvent, rapid evolution of nitrogen ensued and a mixture of products was obtained Wenkert et al analyzed the products **1-4** and put forth an interesting mechanistic rationale to account for their observations In contrast to Doyle's hypothesis, two rhodium based metallocycles **5** and **6** (differing in their regiochemistry) were postulated to explain the experimental findings [33]

The Merck Frosst Canada group has made use of the furan-diazo carbonyl addition chemistry to prepare cis-trans dienes in the synthesis of the arachadonic acid metabolites, hydroxy eicosatetraenoic acids (HETEs) [34-36]

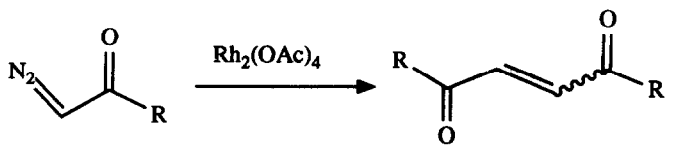
It can, however, be concluded that the intermolecular cyclopropanation reaction is relatively non-selective (by today's standards) unless particular attention is paid to "matching" the olefin, the catalyst and the diazo carbonyl substrates accordingly Another potential problem arises with the intermolecular reaction Due to the nature of highly reactive carbenoid intermediates, dimerization is often an accompanying side reaction Typically the intermolecular reaction has been run using an excess of the olefin substrate, often as the solvent itself Dimerization can be minimized as well by controlling the rate of addition of the diazo carbonyl to the reaction mixture, effectively maintaining a low concentration of the carbene in solution

Scheme 5: Reaction of Ethyl Diazoacetate with Furan



1 2 3 4 5 6

Scheme 6: Dimerization of Carbenoids (a side reaction)

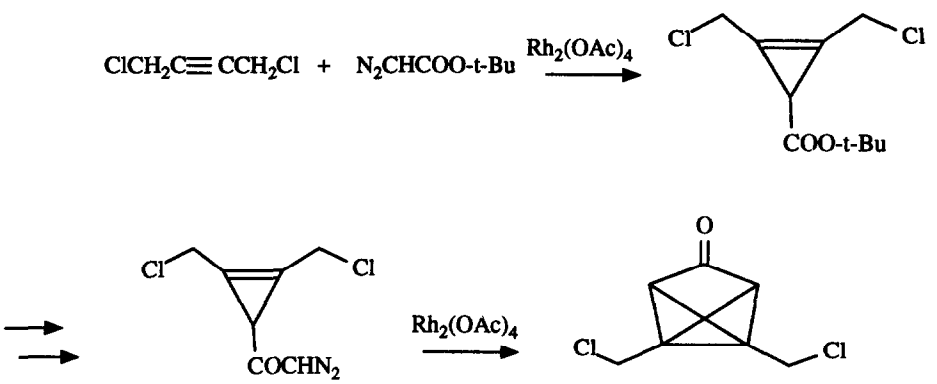


By contrast the intramolecular reaction provides greater synthetic utility due to the geometric constraints of forming the cycle and the entropic advantages minimizing the dimerization of the carbene Several particularly interesting demonstrations of the carbene-olefin additions which underscore the mildness and high specificity of the intramolecular process are exemplified below Dowd performed a cyclopropenation followed by cyclopropanation to prepare highly strained tricyclo [2 1 0 $0^{2,5}$] pentan-3-one **7**[37](Scheme 7)

The first to use cyclopropanation in an intramolecular sense were Stork and Ficini[38] although at the time the more efficient Rh(II) catalysts had not yet been described [38] In many cases the traditional copper catalysts suffice (albeit in lower yield) but reactions sensitive to elevated temperatures or Lewis acidic media require the use of Rh(II)

Given the limited preparative utility of the intermolecular reaction, many more useful synthetic constructions have been devised with the intramolecular process We have attempted in this report to highlight some of the more useful and outstanding reactions, particularly the cases that required the mild Rh(II) catalysis and failed with other transition metal catalysts

Scheme 7: Formation of Highly Strained Cyclopropanes

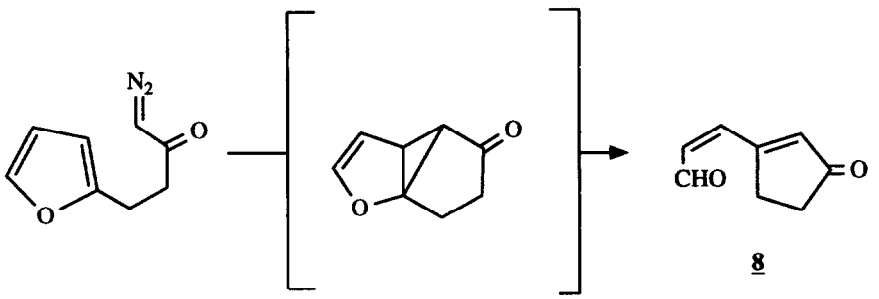


7

Following the work on the cyclopropanation of furan, Padwa[39] and Wenkert[33] independently investigated the intramolecular process in some detail The intermediate cyclopropane was so labile in the unimolecular reaction that it was not observed, but its intermediacy was inferred from the geometry of the exocyclic double bond in the product (see Scheme 8) Thus a general synthesis of cyclic 1,4-diacyl-2,4-cis,trans butadienes (i e **8**) was developed

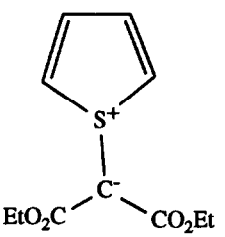
Padwa expanded on this theme using benzofuran cyclizations as well as reaction with thiophenes.[39,40] In some of these cases the intermediate cyclopropane was observed spectroscopically or even isolated. The intramolecular reaction with thiophenes is interesting mechanistically and contrasts somewhat with the bimolecular reaction with diazo carbonyls. Gillespie and Porter have reported a stable ylide intermediate with diazomalonate, **9**, for which an X-ray crystal structure was determined [41] This complex does not react further to produce the cyclopropanated thiophene The authors rationalized this result by stating that the two electron withdrawing esters render the ylide too stable for rearrangement. They proposed that the diazoacetate addition to thiophene may also proceed via a less stable (and not observed) ylide prior to cyclopropanation Further discussion regarding the correlation between ylide formation and cyclopropanation may be found by reading the work of Doyle [42]

Scheme 8: Intramolecular Diazoketone Reaction with Furan



8

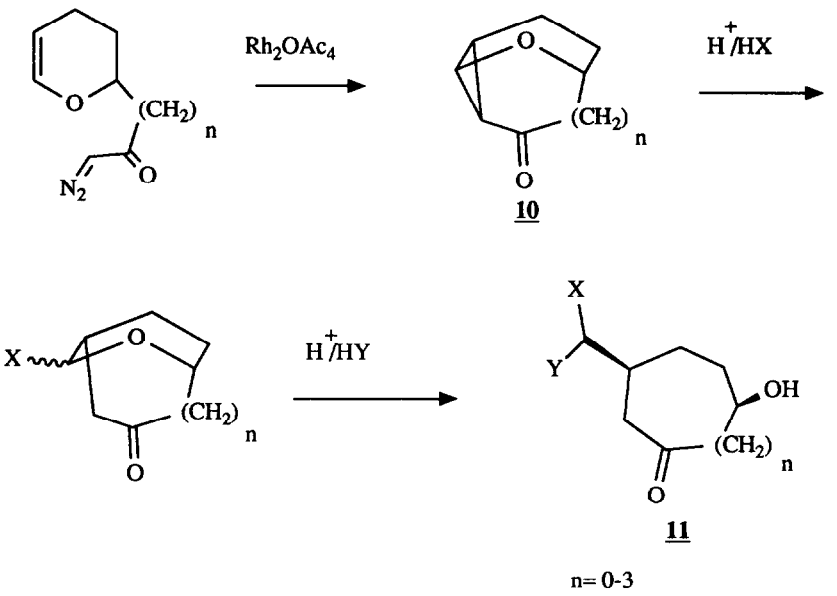
Scheme 9: Thiophene-Malonate Ylide



9

In a similar vein we have examined the intramolecular reaction on the relatively nucleophilic enol ether olefin in dihydropyrans.[43] The oxa-tricyclic ketone products, **10**, were found to be useful intermediates for the synthesis of small and medium ring carbocycles. The sequential carbon-carbon and oxygen-carbon bond cleavages afforded carbocyclic ketones, **11**, with syn-disubstitution The limit of ring size formation was addressed vis a vis competing C-H insertion (Scheme 10) This synthetic approach was employed in the total syntheses of natural products eucalyptol[44] and β-chamigrene[45]

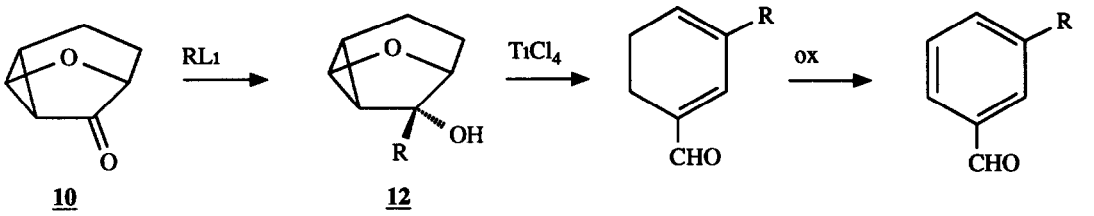
Scheme 10: Intramolecular Addition of Diazoketones on Dihydropyrans



The addition of alkyl or aryllithium or Grignard reagents to the carbonyl of the simplest oxa-tricyclic ketone (n=0), **10**, led to carbinols, **12**, which upon Lewis acid treatment ($TiCl_4$) provided a novel entry to cyclohexadienes or eventually meta-substituted aromatic compounds [46]

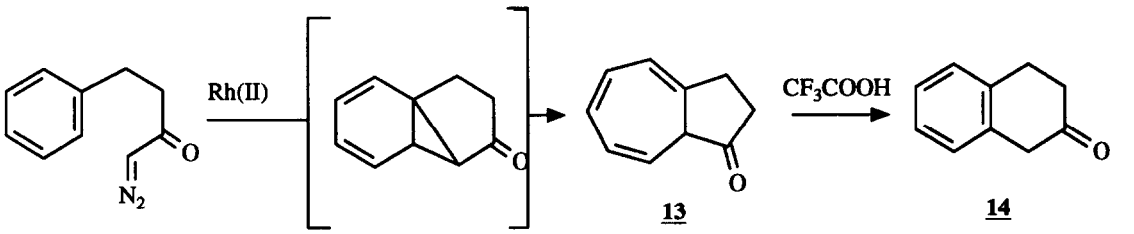
Another novel ring construction owing to $Rh_2(OAc)_4$ catalyzed cyclopropanation was described by McKervey and used to prepare fused cycloheptatriene compounds [47] Once again, the use of Rh(II) is critical since copper catalysis or photochemical methods fail The general scheme involves the conversion of aryl propionic acids to cycloheptatrienes, **13**, via intermediate fused cyclopropanes Tetralones, **14**, could be obtained by treating the cycloheptatrienes with trifluoroacetic acid [47] Doyle applied the same reaction pathway to prepare azabicyclo [5 3 0] decatrienones[48](Scheme 12)

Scheme 11: Synthesis of Cyclohexadienes and m-Substituted Aromatic Compounds



10 12

Scheme 12: Synthesis of Fused Cycloheptatrienes and Tetralones



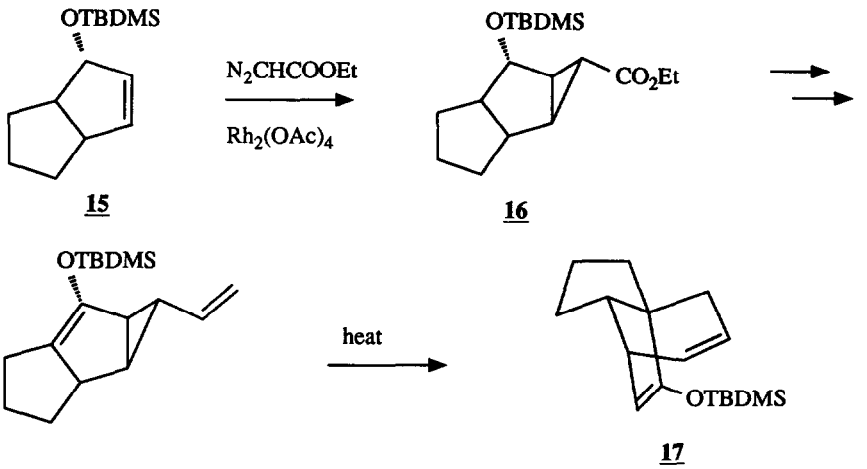
13 14

Piers et al made use of an elegant intermolecular addition of diazoacetate to a cyclopentane derivative, **15**, to set up a divinyl cyclopropane rearranagement, which afforded a unique bridged tricyclic construction, **17**, en route to the natural product quadrone [49] Here the cyclopropanation occured with high exo selectivity and the stereochemical preference was dictated by the 5,5 fused cyclopentane substrate, **15** (Scheme 13)

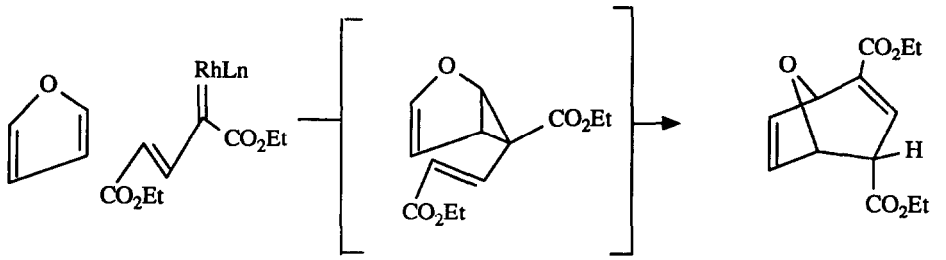
One particularly novel and elegant application of a carbenoid-olefin addition is the reaction of the rhodium-vinyl carbenoid with dienes resulting in a formal 3 + 4 cycloaddition This work, pioneered by Davies, adds a new dimension to the cyclopropanation repertoire An example of this process is the addition of diethyl 4-diazo-2-pentendioate to furan (Scheme 14) [50] Evidence was presented favoring a cyclopropanation-divinylcyclopropane (or Cope) rearrangement based on the endo selectivity for the carbenoid addition [51]

On the same theme, Davies also applied the same methodology in an intramolecular sense to prepare fused 5,7 membered carbocycles and heterocycles (Scheme 15) [52,53] Once again the remarkable endo selectivity of the cyclopropanation accounts for the facile tandem process to afford the observed products (i e **18**)

Scheme 13: Divinyl Cyclopropane Rearrangement

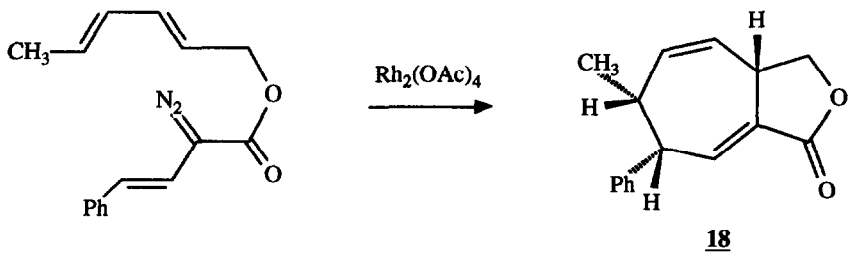


Scheme 14: Formal 3 + 4 Cycloaddition of a Vinyl Carbene to Furan



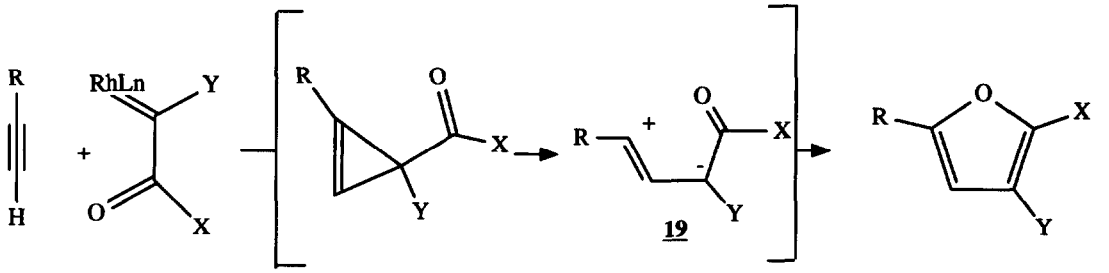
Endo Product

Scheme 15: Intramolecular Tandem Cyclopropanation/Cope Reactions



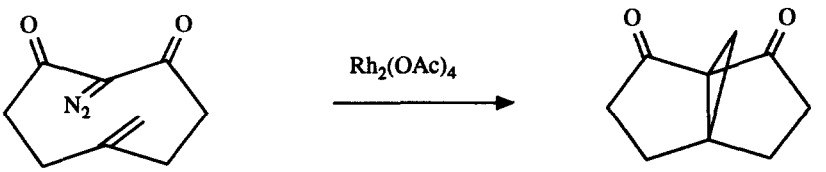
Another clever application by Davies allows for the synthesis of substituted furans.[54] Recognition that α-keto cyclopropenes could be formed under the mild Rh(II) conditions, using diazomalonates and keto-esters, led to the observed furan products. This reaction is formally related to a vinyl cyclopropane rearrangement. The polarization of the zwitterionic keto-olefin intermediate, **19**, serves to accelerate this process leading to furans (Scheme 16) [54]

Scheme 16: Cyclopropenation and Synthesis of Furans

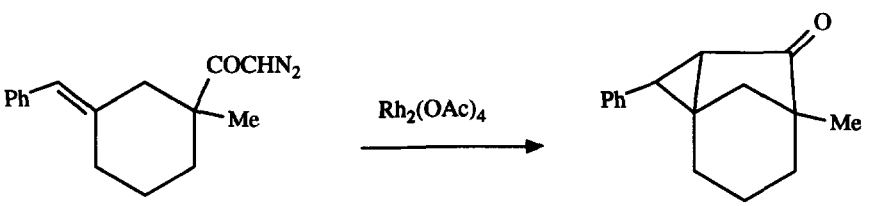


Recent examples of intramolecular processes leading to unusually strained ring systems are noted below (Scheme 17) [55,56] These examples further demonstrate the power of this chemistry This account is by no means an exhaustive catalogue of all known cyclopropanations, but rather an instructive literature survey and critical assessment of the potential for useful synthetic construction. Chemists in the future will surely witness further developments and application of this chemistry

Scheme 17: Highly Strained Cyclopropane Rings[55,56]



[3 3 1]-Propellane-2,8-dione

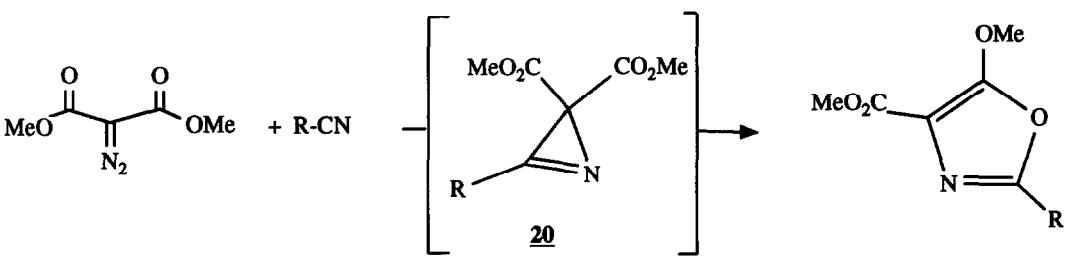


Cyclopropanobicyclo [3 2 1] octanone

The chemistry described so far has been restricted to diazo carbonyl additions to olefins. The extension of the Rh(II) based carbenoid additions has been extended to other electron deficient carbenes. Dailey and O'Bannon have recently made use of ethyl nitrodiazoacetate and nitrodiazomethane to form cyclopropanate alkenes [57,58] Once again $Rh_2(OAc)_4$ was successfully employed where thermal or photochemical methods failed

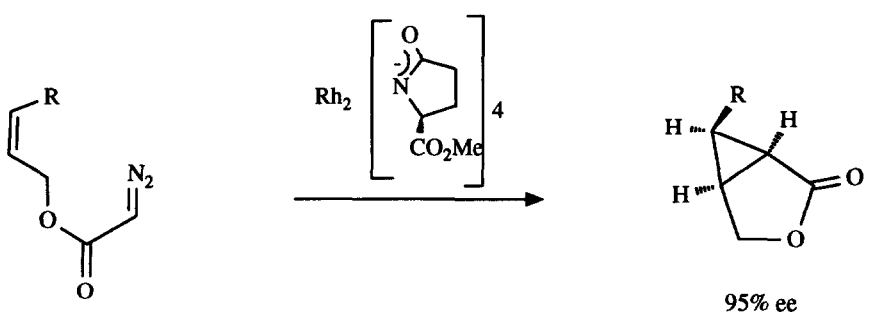
Another interesting development was the report of the rhodium catalyzed reaction of diazomalonate with nitriles to form oxazoles Formally one could consider a dipolar addition as proposed by Helquist et.al.[59] Nevertheless, it is tempting to speculate that a 3-membered imine species, **20**, may also be possible, similar to the Davies synthesis of furans (Scheme 18). Precedent for an imino aziridine intermediate exists from the previous work of Hubert et al.[60]

Scheme 18: Preparation of Oxazoles from Diazomalonate Addition to Nitriles



One remaining area to explore in cyclopropanation chemistry is the prospect for asymmetric catalysis Some examples are already described using a copper based catalyst, but the enantiomeric excesses (ee) observed have been relatively modest[61-64] We have attempted to prepare chiral Rh(II) catalysts using amino acids and other chiral acids but so far have been unsuccessful in obtaining asymmetric induction [65] At the time of this writing we became aware of the work of Stephen Martin (U of Texas) and Micahel Doyle (Trinity University) who described the general reaction shown below (Scheme 19) [66] This encouraging result bodes well for future advances in this field and may provide additional useful avenues for the Rh(II) based catalytic cyclopropanation chemistry

Scheme 19: Asymmetric Induction Using a Chiral Rh(II) Catalyst

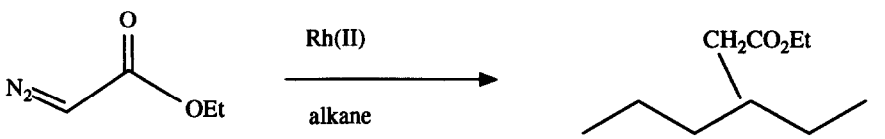


95% ee

III. C-H Insertion:

Free carbenes have long been known to be capable of inserting into C-H bonds, although both low yields and lack of chemical control have mitigated against reliable and useful synthetic applications [67] With the advent of Rh(II) carboxylates, the carbenoids generated from α-diazo carbonyl compounds were found to be effective in C-H insertion under extremely mild conditions. Belgian chemists Noels et al reported the Rh(II) catalyzed C-H insertion of ethyl diazoacetate using a variety of alkane hydrocarbon solvents, at ambient tempertature[68] (Scheme 20) While the overall yields were generally good, no useful regioselectivity was seen Some preference for secondary C-H bonds was observed with $Rh_2(OAc)_4$, and increasing the size of the carboxylate ligand on rhodium (i e 9-triptycene carboxylate) enhanced the ratio of primary C-H bond insertion Nevertheless, the intermolecular reaction has no real preparative value since mixtures of isomers are formed [69,70]

Scheme 20: Intermolecular C-H Insertion of Hydrocarbon Solvents



mixture of products

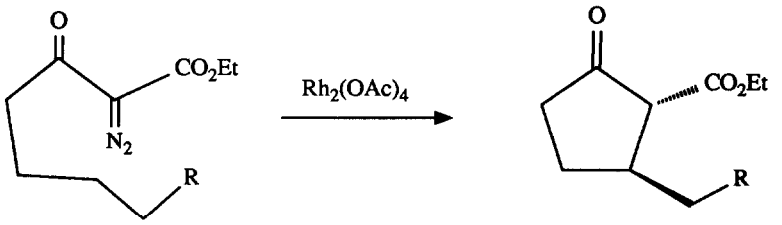
(2°y > 1°y)

The realization by Taber[71] and Wenkert[72] independently that the utility of the carbene-metal catalyzed C-H insertion process could be exploited in an intramolecular sense was demonstrated in the preparation of cyclopentanone derivatives Both groups found that the cyclization of carbenoids derived from diazo ketones and keto esters preferentially formed 5-membered carbocycles This process had been previously described with copper catalysts, but once again Rh(II) species proved to be more selective, higher yielding and proceeded at ambient temperature[73](Scheme 21)

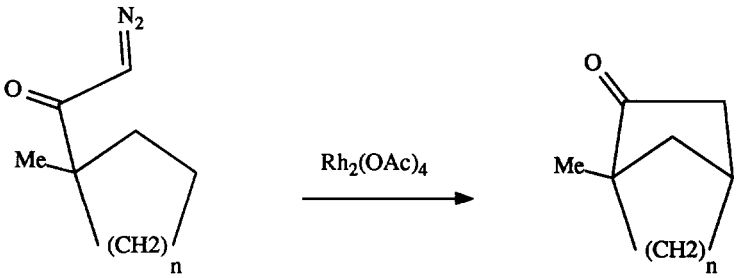
The preference for 5-membered ring formation is not absolute, and is strongly influenced by the local steric and electronic environment of the reacting carbenoid Interestingly, Taber et al

Scheme 21: Intramolecular C-H Insertion to Cyclopentanones

Taber



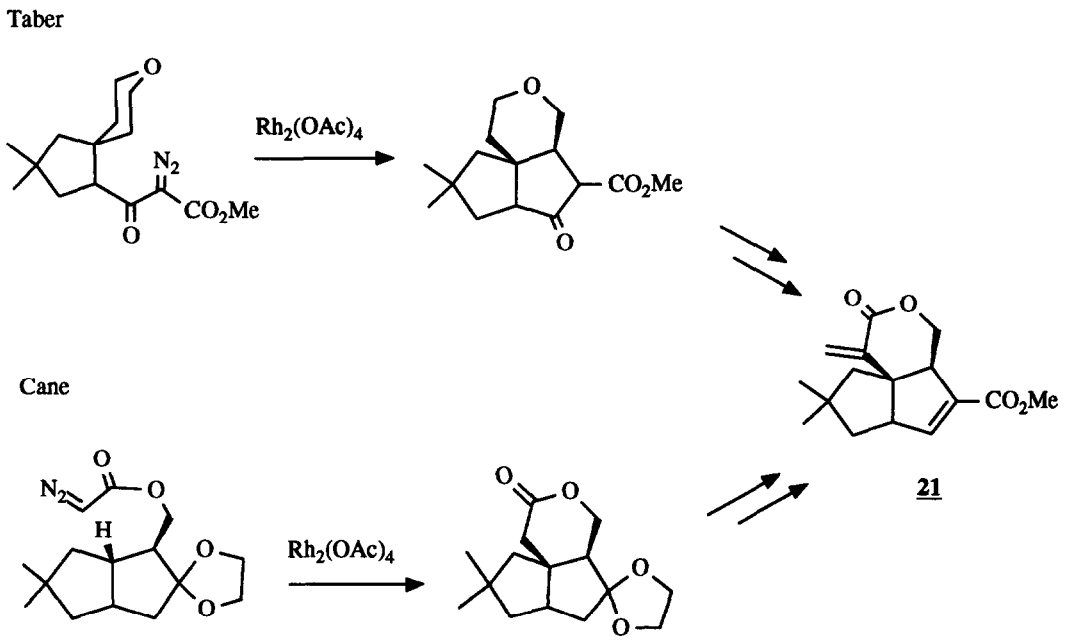
Wenkert



published a synthesis of pentalenolactone, **21**, whereby the tricyclic skeleton was assembled through a rhodium-carbene mediated cyclization to form a 5-membered ring [74] By contrast, the Cane group also constructed pentalenolactone, **21**, but the key cyclization step involved a C-H insertion to form a 6-membered lactone In the Cane approach, the possibility for 5-membered formation exists, but the 6-membered ring is formed since it is the more sterically accessible option The two successful yet differing synthetic constructions underscore the versatility of the intramolecular C-H insertion reaction (Scheme 22)

Taber and Ruckle conducted a systematic study of this reaction and concluded that the order of reactivity for C-H insertion in an aliphatic hydrocarbon was methine > methylene > methyl, which is consistent with the observations of the intermolecular reaction [76] Furthermore, it was determined that allylic and benzylic C-H bond insertions were disfavored Taber rationalized that alkyl groups are inductively electron donating and increase the electron density of the C-H bond, thus making it

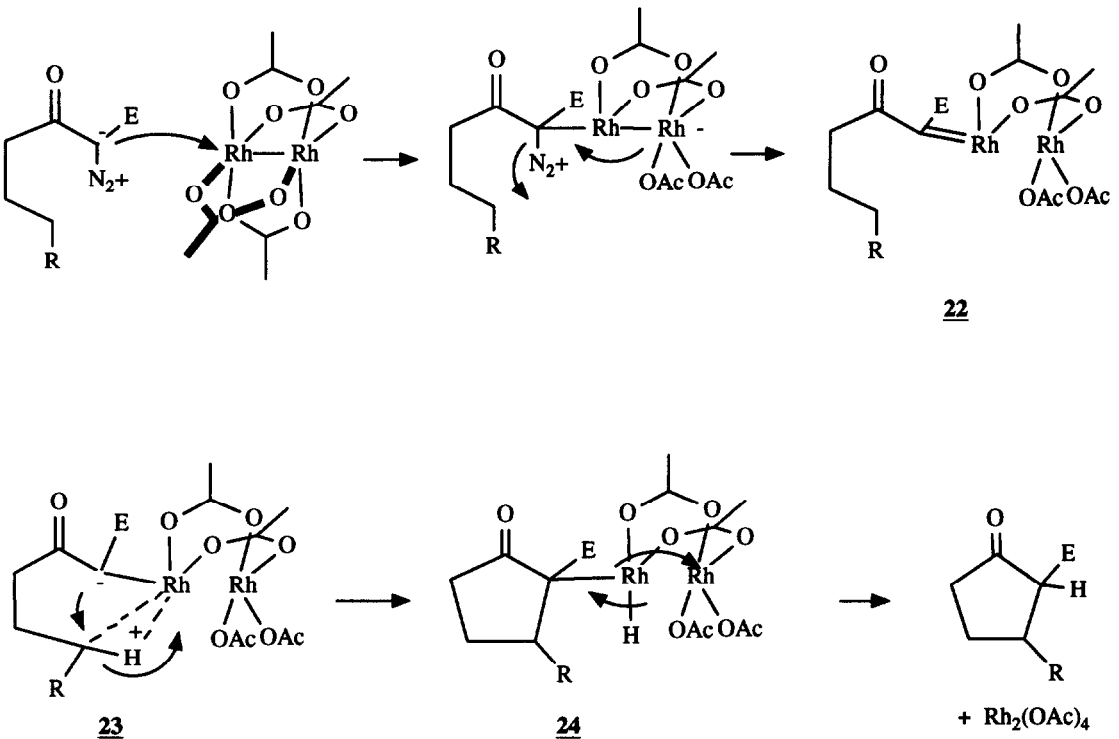
Scheme 22: Syntheses of Pentalenolactone



more susceptible to the electrophilic Rh(II) carbenoid The mechanistic implications of this have been exploited by others and will be described later in this chapter (vide infra)

Though little is known about the mechanism for the rhodium-carbenoid C-H insertion reaction, Taber offered a plausible hypothesis which accounts for preferential 5-membered ring formation[76] (Scheme 23) The first step requires the formation of a Fischer-type metal-carbene complex, **22**, at a vacant coordination site on rhodium (a well accepted assumption based on the cyclopropanation mechanism) In the next step, it is unknown whether or not the C-H insertion is a concerted 3-bond process (intermediate **23**) Also unknown, is the role of the carboxylate ligands on the metal In any case, a hydrogen atom ends up on the rhodium,(**24**) and the final step requires β-hydride transfer from the metal to regenerate the catalyst and afford the observed cyclopentanone

Scheme 23: Mechanism of Aliphatic C-H Insertion

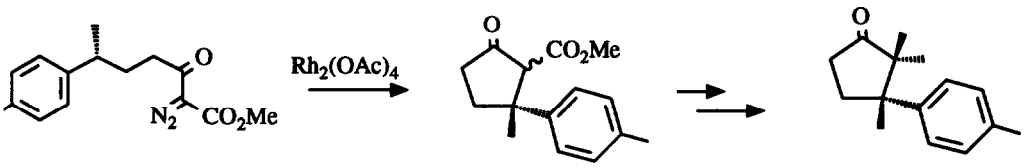


Taber et al. also determined that C-H insertion proceeded with retention of stereochemistry at the reacting carbon center and made use of this knowledege to synthesize (+)-α-cuparenone[77] (Scheme 24) This enantioselective process represents a general strategy for constructing cycles containing quaternary centers

A further development by the Taber group demonstrated the trans selectivity of 3,4 dialkyl cyclopentanone substituents [78] This is significant since it indicates a highly ordered transition state geometry whereby unfavorable steric interactions are minimized(Scheme 25)

Taber's cyclopentanone synthesis employed a diazoketo-ester precursor, whereby the ester functionality could be removed by hydrolysis and decarboxylation following cyclization This

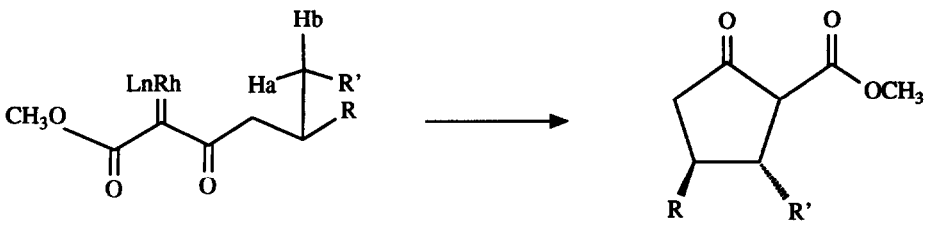
Scheme 24: Synthesis of (+)-α-Cuparenone



Insertion at C-H with Retention

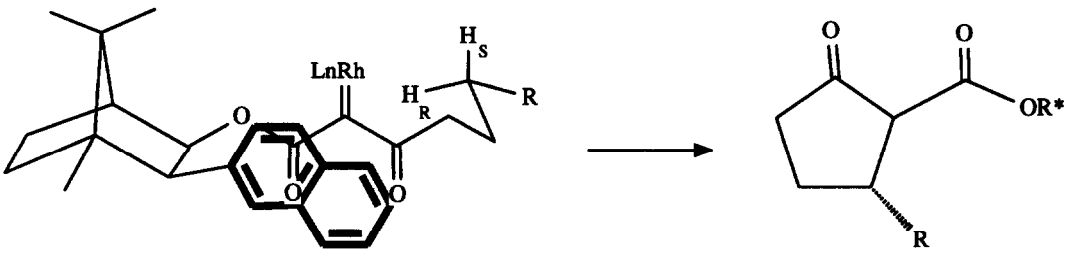
α-cuparenone

Scheme 25: Synthesis of Trans-3,4 Dialkyl Cyclopentanones



provided an opportunity to explore disposable chiral auxillaries in place of simple esters to achieve enantioselective carbocyclization[79] (Scheme 26) This was indeed realized by the Taber group as they prepared a naphthalene substituted (+)-camphor derivative, **25** Excellent diastereoselectivity (> 80%) was observed in the C-H insertion reaction These results suggested an ordered chair-like transition state whereby the bulky naphthalene moiety of the the chiral ester effectively shielded one face of the pendant chain of the substrate The assumption that the carbenoid ester exists in an extended conformation directs the mode of cyclization towards H_R This application provides a convenient synthesis of chiral cyclopentanones

Scheme 26: Asymmetric Induction Using a Chiral Auxillary

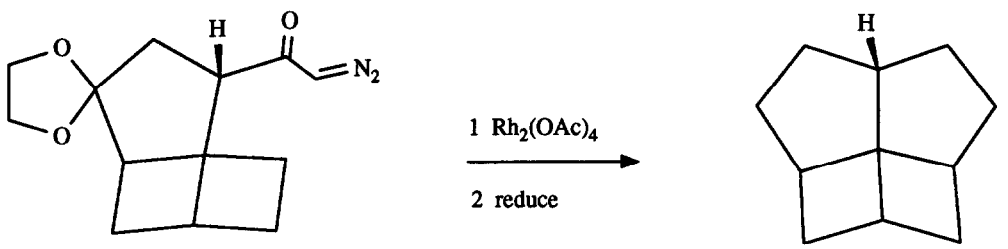


25

diastereoselectivity > 80%

Other examples of 5-membered ring products are described in the literature [80,81] In general polycyclic systems tend to be well suited for the C-H insertion process and the stereochemical outcome is usually predictable The synthesis of [4 4.5 5] fenestrane, **26**, by Agosta et al illustrates this point[82-84] (Scheme 27) The constraints imposed by strain in the ring system led to the predicted result.

Scheme 27: Synthesis of [4.4.5.5] Fenestrane



26

Formal aromatic C-H insertion is well documented As discussed in the cyclopropanation section, it may not be possible to distinguish between direct C-H insertion and apparent C-H

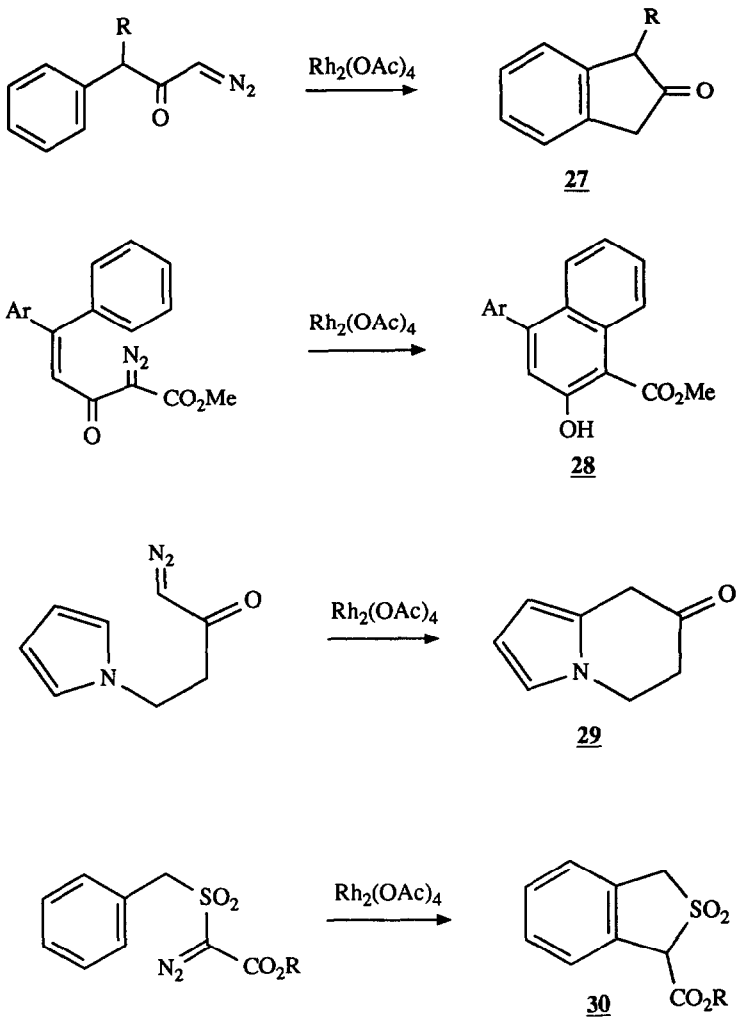
insertion arising from an unobserved cyclopropyl intermediate which then rearranges to the final product. Shown below are several examples of aromatic insertion to form indanones, **27**,[85] naphthalenes, **28**,[86] fused pyrroles, **29**,[87,88] and 1,3 dihydrothiophene 2,2 dioxides, **30**[89,90] (Scheme 28) The versatility of this process allows for convenient preparation of a variety of 5-membered fused heterocycles Perhaps the most unexpected example was reported by Matsumo and co-workers in the cyclization of 2-diazo-4-(4-indolyl)-3-oxobutanoic esters, **31** [91] Catalysis by $Rh_2(OAc)_4$ gave exclusively the 5-membered fused indole, **32**, while reaction with $Pd(OAc)_2$ afforded the 6-membered product, **33**, presumably via a cationic mechanism (Scheme 29)

The early work of Taber suggested that some stereoelectronic control exists in the C-H insertion process The more electron rich C-H bond tends to be kinetically more reactive This phenomenon was also observed in our laboratory, when we first noticed the susceptibility towards insertion of C-H bonds α to ether oxygens Our first experience with this reaction involved the trans-annular cyclization of a diazoketone appended to a tetrahydropyran ring, **34**, which produced a single product of insertion at the 6-position ether C-H, **35**, and no insertion at the aliphatic methylene This construction led to the total synthesis of the natural insect attractant endo-1,3-dimethyl-2,9 dioxabicyclo[3 3 1]nonane, **36** [92]

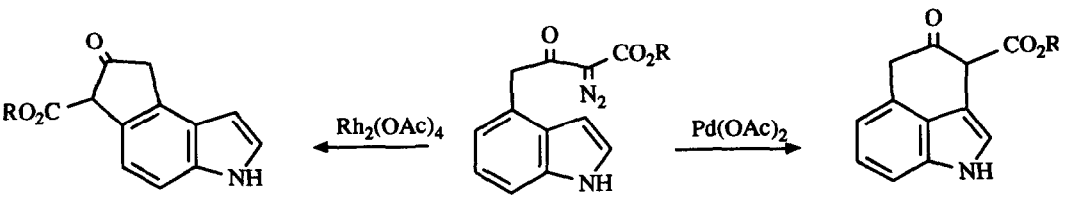
Further studies in our group indicated that this selectivity for ether C-H bonds could be applied to the intermolecular reaction of ethyl diazoacetate with ether solvents.[93] The intermolecular reaction is mechanistically instructive, but suffers from the same disadvantages discussed previously, and holds little synthetic interest Alternatively the intramolecular cyclization of diazoketones derived from 2-hydroxy carboxylic acids provided a general route to furanones, **37** (Scheme 31) The 5-membered rings were favored in the cyclization as witnessed by the reaction of diazoketone, **38**,in which both the 5-membered and 6-membered rings (**39** and **40**) are possible as both methylenes are flanked by ether oxygens Furthermore, when we studied the cyclization of the diazoketone, derived from 6-benzyloxy pentanoic acid, **41**, the carbon analogue, the 6-membered ring, **42**, was formed (albeit in low yield) owing to the ether oxygen activation, and no cyclopentanone, **43**, was observed (Scheme 32)

While we were pursuing the phenomenon of ether C-H insertion, the findings of Stork and Nakatani described a complementary C-H insertion reaction under stereoelectronic control[94] (Scheme 33) They observed that the inductive effects of electron withdrawing esters disfavored C-H insertion at methylenes α or even β to the ester As a result they were able to direct C-H insertion at an unactivated methylene of a proximal aliphatic chain to generate cyclopentanones, **44**, in a selective manner

Scheme 28: Fused Aromatic Rings

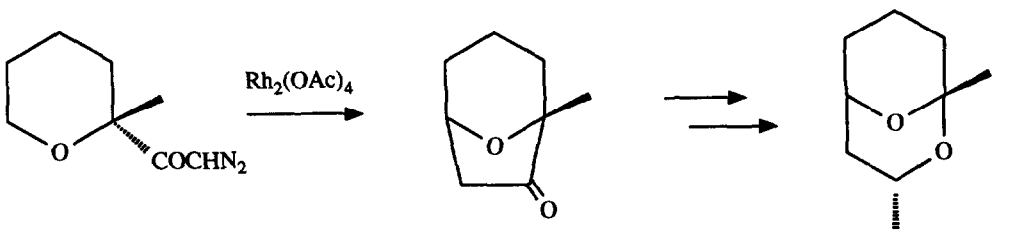


Scheme 29: Cyclization of Indoles



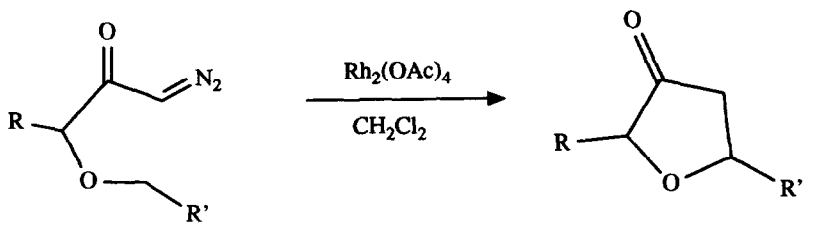
32 31 33

Scheme 30: Trans-Annular Cyclization



34 35 36

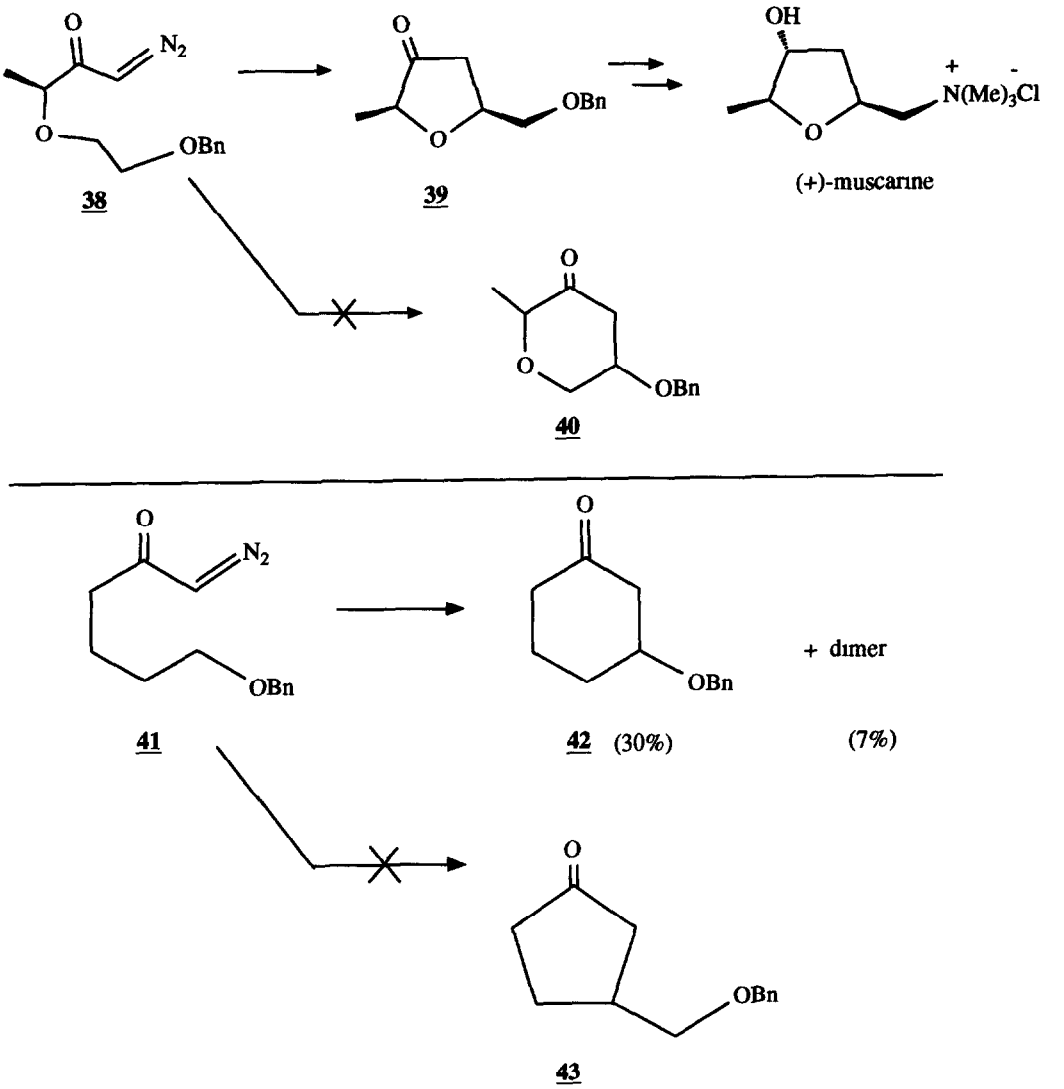
Scheme 31: Synthesis of 2(H)-3-Furanones



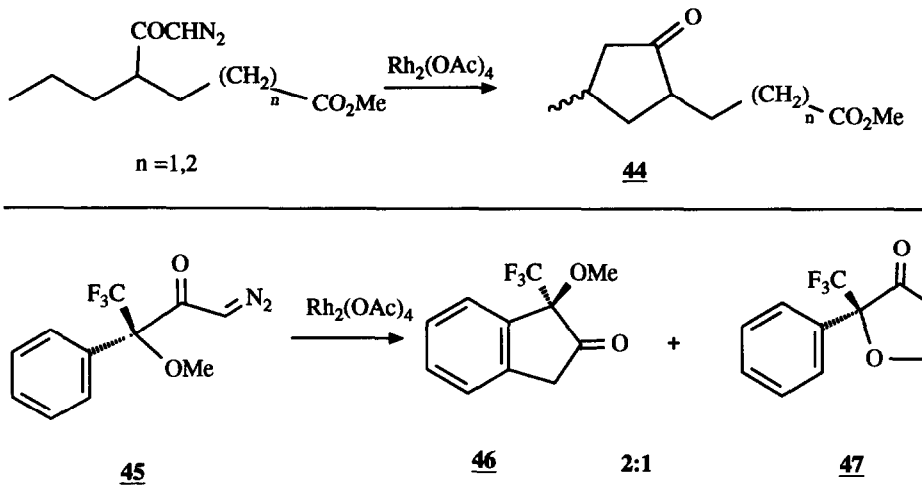
37

(3-8 1 cis/trans)

Scheme 32: Intramolecular Cyclization Ether Competition



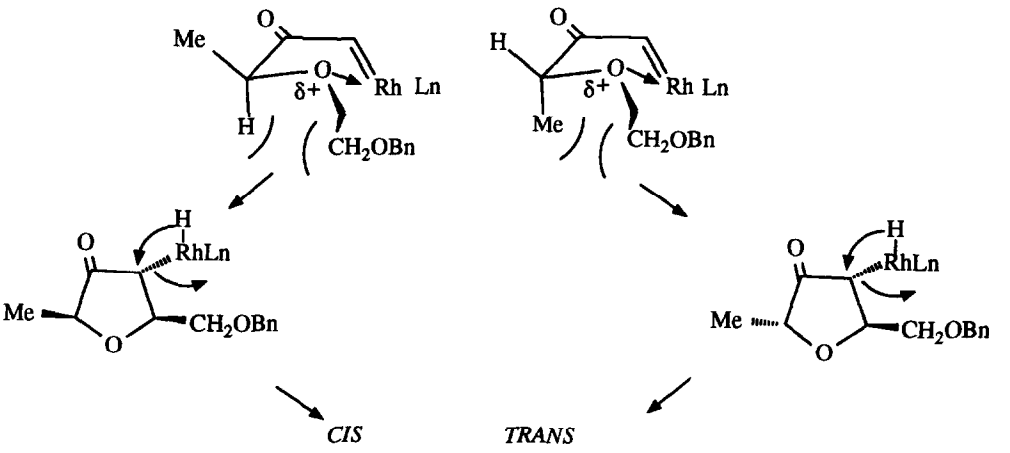
Scheme 33: Stereoelectronic Effect of Electron Withdrawing Groups



The report of Stork and Nakatani was significant to us since we had observed that the cyclization of a the diazoketone derived from Mosher's acid (2-methoxy-2-trifluoromethyl phenylacetic acid) **45**, led predominantly to aromatic C-H product, **46**, insertion with the minor product, **47**, arising from C-H insertion at the methyl ether This could be explained by the inductive electron withdrawing effect of the trifluoromethyl group which serves to partially cancel the ether activation (Scheme 33)

Further studies in the preparation of unsymmetrical 2,5- disubstituted furanones led to the observation that the reaction favored the cis disubstituted isomer [95] This appears to be the result of kinetic control and an ordered transition state involving the metal-carbene complex Base catalyzed equilibration of the product furanones provided a thermodynamic mixture wherein the cis/trans ratio is essentially 1 1 An attempt to rationalize the results was put forth in a mechanistic hypothesis (Scheme 34) The proposal relies on Taber's original mechanism which calls for hydrogen transfer to rhodium The electron donating ether oxygen facilitates this process, and participates in the transition state by chelating the rhodium in such a way as to minimize substituent interactions

Scheme 34: Proposed Mechanism for Furanone synthesis

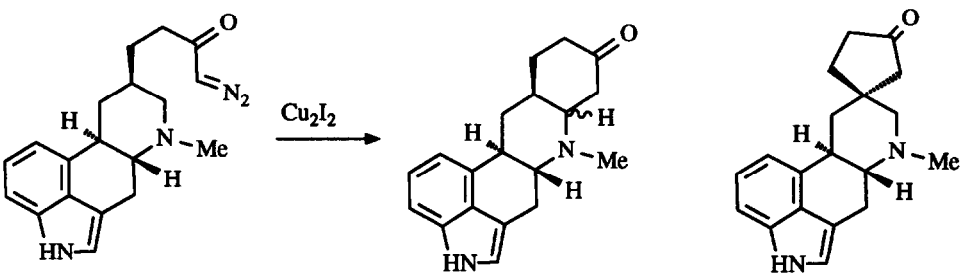


In order to highlight the useful application of our findings, both the furanone construction and the cis-selectivity of the C-H insertion mediated by $Rh_2(OAc)_4$ were exploited in a total synthesis of the natural product (+)-muscarine[95] (Scheme 32)

A related C-H insertion process in which the carbene was directed α to nitrogen was observed by Ruggieri and co-workers in the preparation of ergoline derivatives[96] (Scheme 35) In their case Cu_2I_2 was used as the catalyst to generate the carbene Here $Rh_2(OAc)_4$ failed to catalyze the reaction because the metal forms strong complexes with basic nitrogens and renders the catalyst inactive This represents a limitation for Rh(II) catalyzed processes Nevertheless, the mechanism proposed is similar to our hypothesis for ether activated C-H insertion, and the electron donating capacity of the nitrogen lone pair directs the mode of cyclization Although mixtures of isomers were obtained, **48** and **49**, including some cyclization at an unactivated C-H bond (9%), this reaction further emphasizes the stereoelectronic effect of heteroatom activation of the C-H bond

Doyle recently described a very effective C-H insertion to prepare β-lactams, **51**, from diazo-β-ketoamides, **50**, in which the nitrogen of the amide bore a bulky t-butyl or branched alkyl substituent [97] The usual 5-membered ring products were seen using the catalyst in dichloromethane at ambient temperature However, in benzene at reflux a different reaction prevailed and β-lactam, **51**, was obtained Doyle argued that the selectivity in the reaction is not of an electronic nature, but

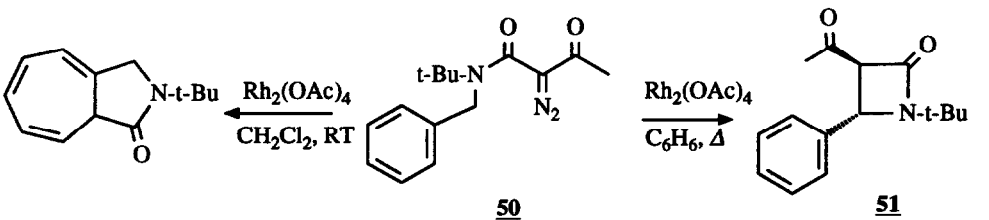
Scheme 35: C-H Insertion α to Nitrogen



48 91·9 49

rather that the C-H bonds in closest proximity to the reactive rhodium-carbene center led to the preferred β- and not γ-lactam products This suggests a very stable amide conformation which is governed by the bulky substituent on nitrogen (Scheme 36)

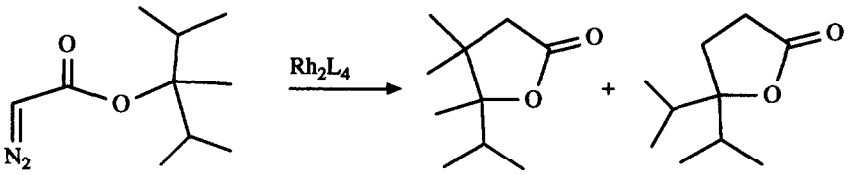
Scheme 36: Synthesis of β-Lactams



50 51

In contrast when Doyle studied the analogous reaction using diazoesters and diazoketo-esters no β-lactone formation was observed, but rather the normal 5-membered ring leading to γ-lactone construction prevailed [98] Interestingly, ligand effects on rhodium led to dramatic regiochemical preferences A competition for C-H insertion of diazoester, **52**, yielded product mixtures (**53** and **54**) using $Rh_2(OAc)_4$ or $Rh_2(OCOC_3F_7)_4$ (Scheme 37) However when rhodium acetamide, $Rh_2(NHCOCH_3)_4$, was employed as the catalyst the reaction was totally regioselective. These results suggest, as in the cyclopropanation chemistry, that the ligands on rhodium play an important role in the C-H insertion process

Scheme 37: Synthesis of γ-Lactones



52 53 54

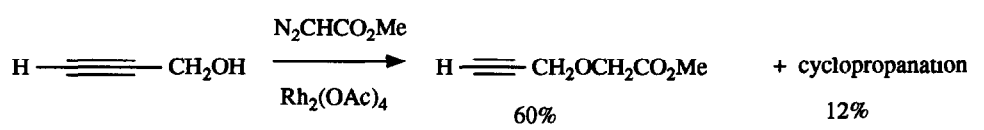
Rh_2L_4		
$Rh_2(OAc)_4$	53	47
$Rh_2(NHCOCH_3)_4$	>99	<1

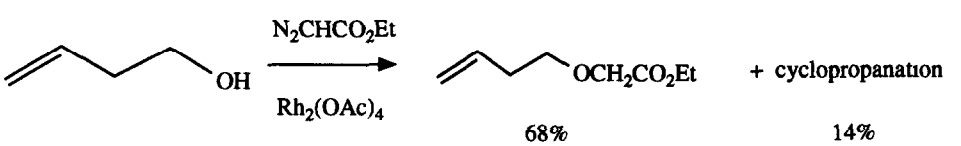
The C-H insertion chemistry of rhodium mediated carbenes is still relatively new and has only received limited attention over the past decade It remains to be seen what future combinations of catalyst selection and stereoelectronic control in the reacting substrate will reveal in establishing regio-, stereo-, and eventually enantio-specific control in the carbene C-H insertion reaction

IV. Heteroatom-H Insertion

Since the pioneering work of Yates on the copper-catalyzed decomposition of diazoketones in alcohols and phenol,[99] the insertion of carbenes and carbenoids into hydroxylic bonds has been extensively investigated Teyssié reported rhodium-catalyzed insertion of ethyl diazoacetate into the hydroxylic bond of simple alcohols,[100,101] as well as unsaturated alcohols.[102] In the case of ethylenic and acetylenic alcohols there is a preference for O-H insertion over cyclopropanation,[102] and examples are shown in Scheme 38

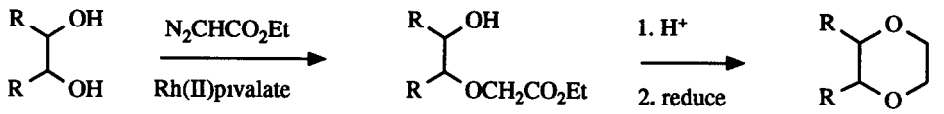
Scheme 38: O-H Insertion of Unsaturated Alcohols





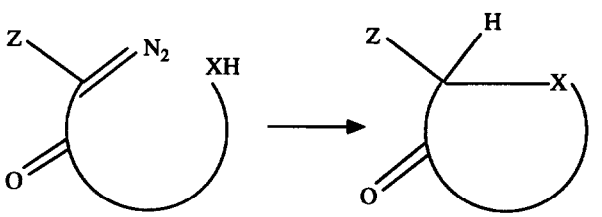
The intermolecular O-H insertion of rhodium carbenoids has been used to convert diols to dioxanes.[103] Diols treated with ethyldiazoacetate and catalytic rhodium (II) pivalate afforded a mono O-H insertion product. Subsequent acid catalyzed lactonization followed by reduction yielded a dioxane (Scheme 39)

Scheme 39: Synthesis of Dioxanes



The intramolecular O-H insertion of rhodium carbenoids has been exploited to make five[104] through eight membered oxygen containing rings [105] Moody explored the rhodium carbenoid cyclizations as a general route to oxygen, sulfur, and nitrogen containing rings as shown in Scheme 40 [105]

Scheme 40: Synthesis of Lactones, Thiolactones, and Lactams

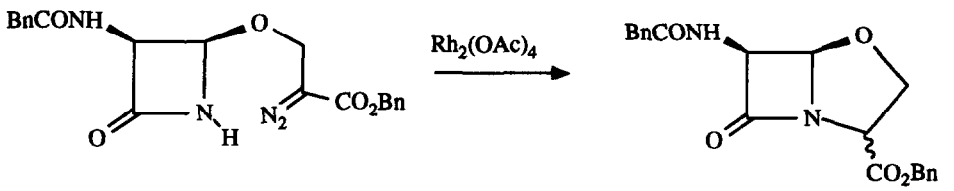


X= O, S, N

Moderately good yields were obtained for the formation of six and seven membered rings The yield of cyclization to eight membered rings was lower due to competing C-H insertion. When X = sulfur, cyclic six and seven membered thioethers were obtained albeit in low yield (30-35%) [105b] When X = tert-butyloxycarbonyl (Boc) or pivaloyl protected nitrogen only C-H insertion was observed to afford cyclopentanones,[105b,105c] instead of seven or eight membered rings The authors propose that the failure of N-H insertion was probably due to the fact that the Boc or pivaloyl-protected nitrogen is too hindered and non-nucleophilic to intercept the electrophilic rhodium carbenoid However, the formation of four, five and six membered rings by rhodium carbenoid insertion into N-H bonds has been reported and is a reliable process [104,106]

An important synthetic application of the N-H insertion reaction was the construction of β-lactam antibiotics. The earliest version of this reaction was reported by workers at Merck Sharp & Dohme, where diazoketone, **55**, was cyclized to the oxepenam, **56**, with catalytic rhodium (II) acetate[107] (Scheme 41)

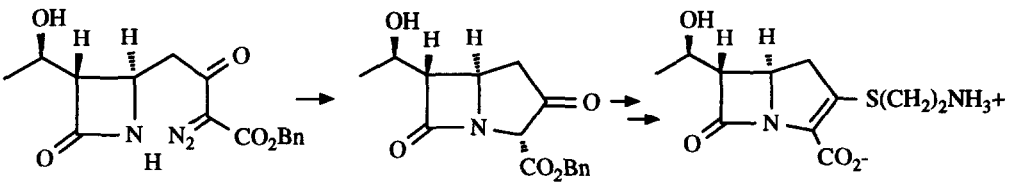
Scheme 41 Synthesis of Oxepenams



55 **56**

Merck has also applied the rhodium (II) catalyzed N-H insertion towards the synthesis of carbapenem ring systems, and found this method preferable to photochemical methods [108] Photolytic decompostion of the diazoketones gave Wolff rearranged products in addition to the desired N-H insertion A rhodium (II) catalyzed intramolecular N-H insertion was used as a key step in the total synthesis of the carbapenem thienamycin and is even used in the commercial manufacturing of the drug[109,110](Scheme 42)

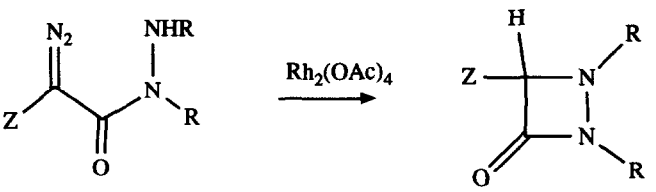
Scheme 42: Synthesis of Thienamycin



Thienamycin

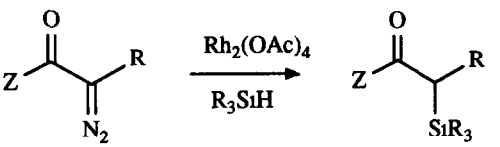
Synthetic approaches to 1,2-diazetidinones have been investigated by Moody and Pearson [111] Aza-β-lactams can be prepared in high yield from the Rh(II) catalyzed decomposition of diazo hydrazides (Scheme 43)

Scheme 43: Synthesis of Aza-β-Lactams



The insertion reaction of carbenoids into Si-H bonds to form carbon-silicon bonds is a synthetically useful procedure Doyle has recently published a general procedure for the formation of α-silyl carbonyl compounds by the rhodium (II) catalyzed decomposition of diazoketones in the presence of organosilanes[112] (Scheme 44) In general the yields are high and this methodology offers an alternative to enolate anion displacement of chloride from chlorosilanes

Scheme 44: Preparation of α-Silyl Carbonyl Compounds



V. Ylide Formation and Reactivity

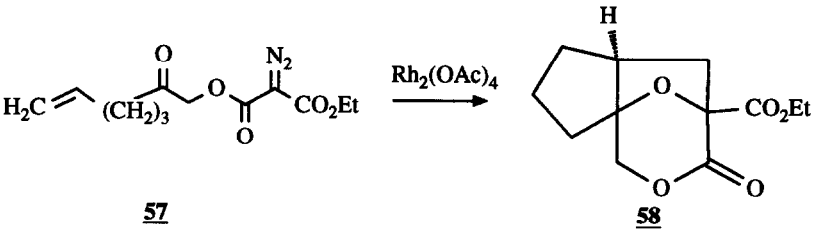
The reaction of carbenes with heteroatoms to form ylides has been known for many years [113] Recently there has been renewed interest in these reactions due to the synthetic utility of the reactive ylide In the following section the reactions of rhodium (II) acetate derived carbenoids with oxygen, sulfur, and nitrogen is reviewed

a) Carbonyl Ylide Formation

The reaction of an α-ketocarbenoid with a lone pair of electrons on a carbonyl group generates a carbonyl ylide Recently synthetic chemists have made use of the carbonyl ylide as a 1,3-dipole, trapping the reactive species with olefins, [115a] acetylenes, carbonyls and hetero-multiple bonded dipolarophiles The Padwa group has been a major contributor to this area of research and some of this work is reviewed below

Padwa et al have constructed a number of interesting ring systems using a carbonyl ylide [2,3] cycloaddition strategy [117] For example, oxapolycyclic lactones can be synthesized by the rhodium (II) acetate catalyzed reaction of 1-acyl-1-diazoacetates [114] The intramolecular cycloaddition of a mixed diazomalonate ester, **57**, with a suitably positioned olefin affords the tricyclic lactone, **58** (Scheme 45) In order for cyclization to occur, the diazoacetate must have an electron withdrawing group on the carbon bearing the diazo moiety In similar systems when the electron withdrawing group is replaced by hydrogen, no cycloaddition occurs, presumably because the intermediate rhodium carbenoid has diminished electrophilicity and therefore does not react with the carbonyl to form the ylide [114]

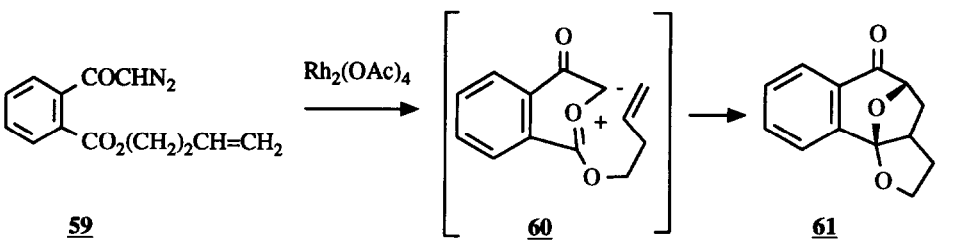
Scheme 45: Intramolecular Carbonyl Ylide Formation and 2,3 Cycloaddition



57 58

The same group also prepared unsaturated ω-alkoxyacyl-α-diazoacetophenones, **59**, and investigated rhodium (II) acetate catalyzed cyclizations Compound, **59**, was treated with catalytic rhodium (II) acetate and cycloadduct, **61**, was isolated (Scheme 46) Experimental support for the formation of the intermediate carbonyl ylide, **60**, was provided by trapping with dimethylacetylene dicarboxylate (DMAD) As seen in Scheme 46, the ylide intermediate is suitably disposed for the 2 + 3 cycloaddition process

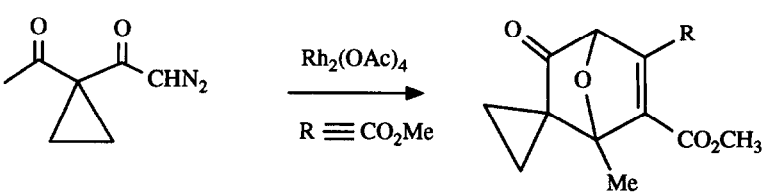
Scheme 46: Cyclization of Diazoacetophenone Derived Ylides



59 60 61

In the first two examples (Schemes 45 and 46) the tandem cyclization-cycloaddition sequence occurred with six membered ring carbonyl ylides Also reported are similar sequences with five and seven membered ring carbonyl ylides [116] When cyclopropyl substituted diazoketone, **62**, was treated with rhodium (II) acetate, the intermediate five membered ring ylide was trapped with DMAD to afford, **63**[116] (Scheme 47) Methyl propiolate, N-phenylmaleimide, ethyl cyanoformate and methyl propargyl ether were also used as 1,3-dipolarophiles

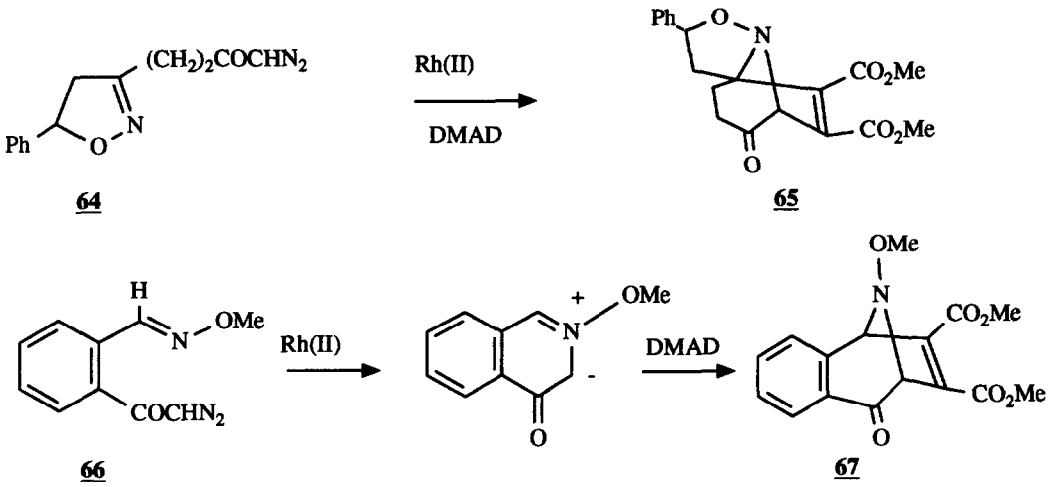
Scheme 47: Cyclization of Diazo-β-Diketones with Acetylenes



62 63

The rhodium (II) catalyzed reaction of α-diazoketones with neighboring oxime ethers also has been investigated [118] Cyclization to the azomethine ylide occurs only if the oxime ether exists in such a conformation that the lone pair of electrons on nitrogen are accessible to the carbenoid The rhodium (II) octanoate catalyzed reaction of **64** and DMAD afforded the azomethine ylide derived cycloadduct, **65** [118] Similarly **66** could be converted to **67** (Scheme 48)

Scheme 48: Oxime Ylides and 1,3 Cycloaddition

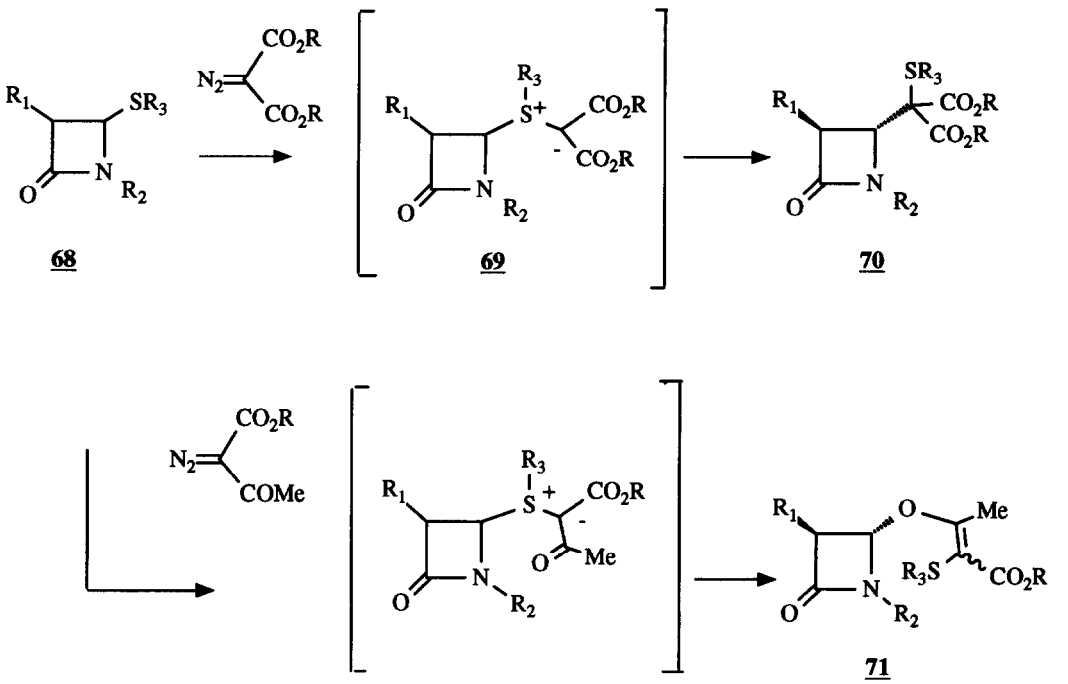


b) Sulfonium Ylides

The reaction of carbenes with the lone pair of electrons on sulfur to form sulfonium ylides is finding increasing utility in organic synthesis.[119, 120, 121] Kametani has demonstrated the synthesis of penicillin derivatives utilizing sulfonium ylides as intermediates Carbon can be introduced at the C-4 position of azetidinones by employing a rhodium-catalyzed decomposition reaction of α-diazomalonate[120] with 4-phenylthioazetidinones, **68**[122] (Scheme 49) The formation of the C-4 carbon substituted azetidinone, **70**, occurs through the ylide intermediate, **69** Oxygen functionality can be introduced at C-4 of the azetidinone by treatment of **68** with α-diazoacetoacetate. In both cases, the substituents at C-3 and C-4 end up trans

As an extension of this work, the reaction of penicillin, **73**, with the rhodium carbenoid of p-nitrobenzyl α-diazoacetoacetate afforded eight-membered oxa-derivatives, **74**[123] (Scheme 50)

Scheme 49: C-4 Substitution of Azetidinones

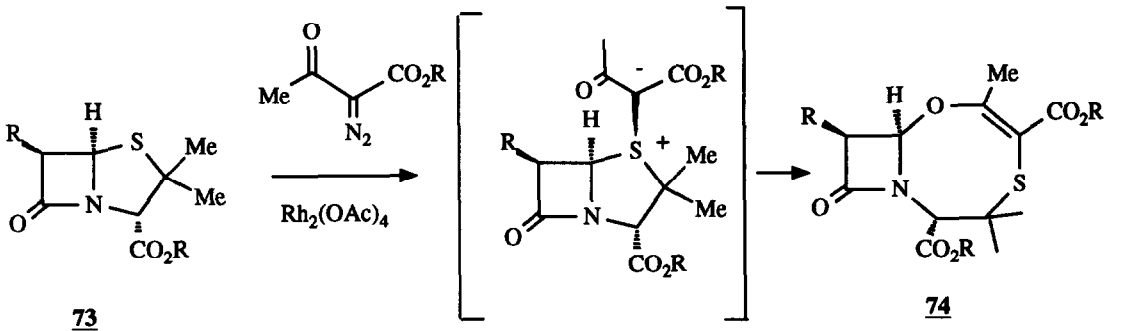


The approach of the carbene is from the less hindered β-face of the penicillin bicyclic system The conversion of 4-thioxo-2-azetidinones into 4-alkylidine-2-azetidinones has also been reported [134]

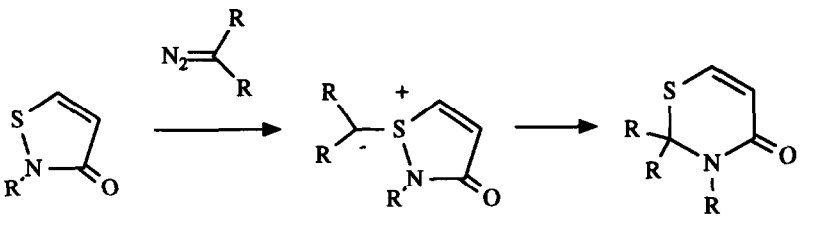
A novel synthesis of 3,4-dihydro-1,3-thiazin-4(2H)-ones, **77**, also made use of a carbene addition-ring expansion sequence [124] The rhodium-catalyzed reaction of diazo compounds with 2-substituted isothiazol-3(2H)-ones, **75**, afforded an intermediate sulfonium ylide, **76**, which rearranged to the six membered ring, **77** (Scheme 51)

Ando and co-workers have investigated the reaction of cyclic disulfides with carbenes to afford 1,3-dithianes, or desulfurization products if the disulfide and the carbene are sterically hindered [125] In most cases the authors used CuCl to catalyze carbene formation, however, some examples employed rhodium (II) acetate and the results did not depend on the method of carbene generation In general, the yields for the desulfurization reactions are approximately 30% The yields for the S-S insertion products are typically greater than 65%

Scheme 50: Ring Expansion of Penicillins



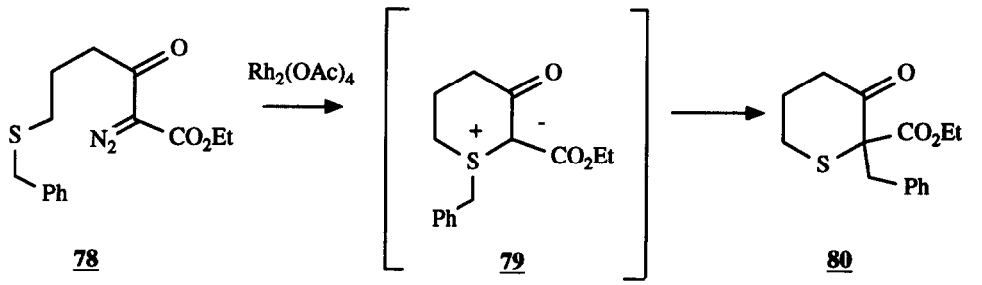
Scheme 51: Synthesis of Dihydro-thiazinones



It is well known that sulfonium ylides are isolable when stabilized by two electrons withdrawing groups [121,126] Stable cyclic sulfonium ylides are less well known although some have been prepared by the treatment of cyclic sulfonium salts with base [127] Stable cyclic sulfonium ylides formed via a carbene route have been reported by Davies[128] and Moody[129] Moody demonstrated that in the presence of catalytic rhodium (II) acetate the diazosulfide, **78**, gave the stable ylide, **79**, in 24% yield (Scheme 52). Further heating in toluene effected a Stevens type [1,2]-rearrangement to the thiapyrone, **80**

Thiophenes react with diazomalonates under rhodium (II) acetate catalysis to give thiophenium methylides [130] Initially, copper catalysis was investigated as the means for generating the carbene but these reactions were impractically slow, typically taking eight days at reflux with incomplete reaction [130] In contrast the rhodium (II) acetate reactions are complete in 18h at room

Scheme 52: Sulfonium Ylides and Stevens Rearrangement



78 79 80

temperature Otto Meth-Cohn found that 2,5-dichlorothiophenes reacted with diazoketones to yield ylides which readily underwent thermal rearrangement to give oxathiocines [131]

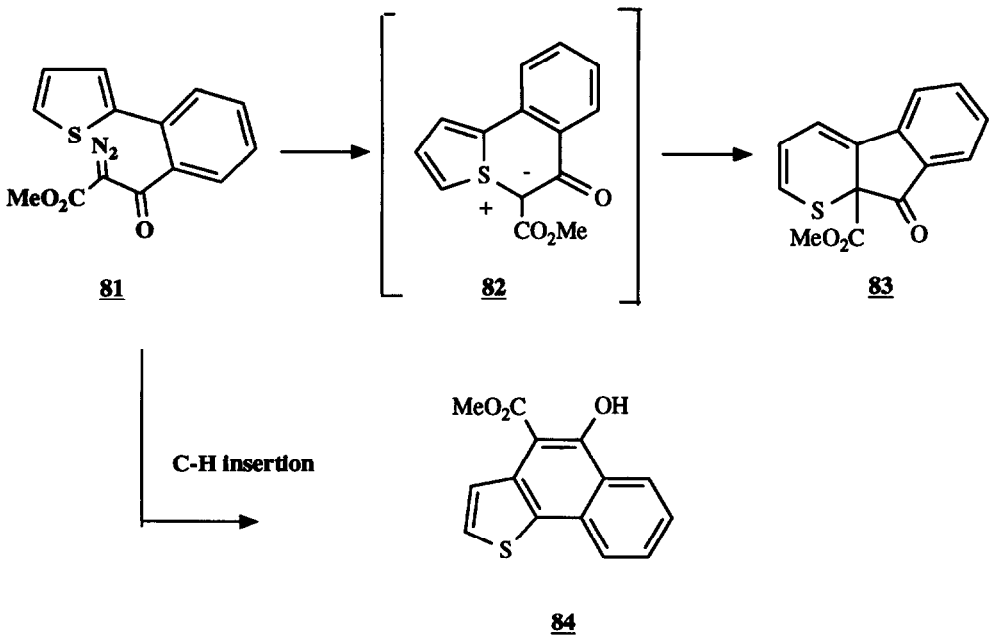
Intramolecular versions of thiophenium ylide formation have also been reported in the literature [132] Rhodium (II) acetate catalyzed decomposition of the diazo compound, **81**, gave cyclized **83** as the major product, presumably arising from a Stevens rearrangement of ylide, **82**[133](Scheme 53) In addition, the C-H insertion product, **84**, was isolated in 25% yield

c) Oxonium Ylides

Oxonium ylides have been postulated as intermediates when diazo compounds decompose in the presence of 2-phenyl-1,3-dioxolane,[135] styrene oxides,[136] allylic ethers,[137] aliphatic ethers,[138,139] allylic acetals,[140] oxetanes[141] and furans [142] Carbenoids react with the oxygen of epoxides[143] and sulfoxides[144] effecting transfer of oxygen to the carbene center Oxonium ylides have also been generated by deprotonation[145] and desilylation[145] of oxonium ions and they are involved in the zeolite catalyzed conversion of methanol to ethylene[146]

Johnson has designed aliphatic, alkoxysubstituted diazoketones and utilized their rhodium (II) acetate decompositions to yield cycloalkanones [147] The presence of an intermediate oxonium ylide was proposed An example of this work is shown in Scheme 54 Diazoketone, **85**, was decomposed in the presence of rhodium (II) acetate to form cyclobutanone, **87**, and cyclooctenone, **89** When the methyl substituted diazoketone, **86**, was subjected to the reaction conditions the resulting cyclobutane, **88**, was formed in high diasteroselectivity (97 3) with the cis vicinal methyl groups of the cyclobutanone ring as the major diastereoisomer

Scheme 53: Thiophenium Ylides

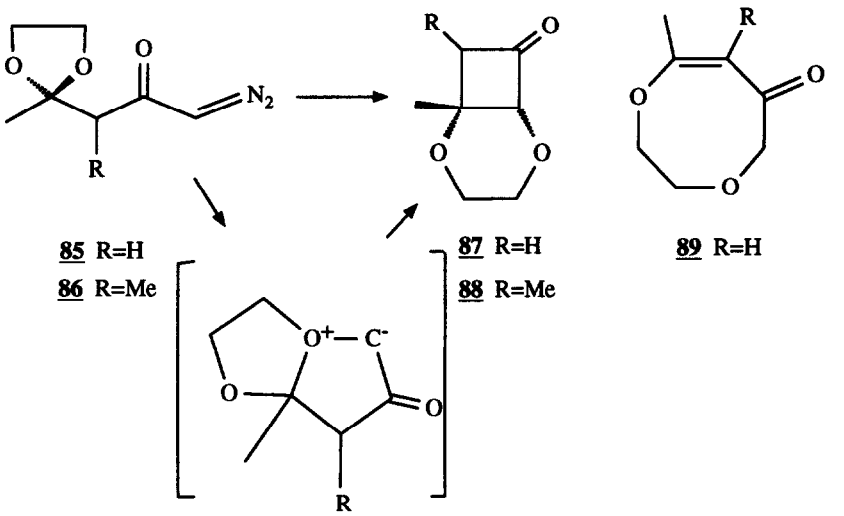


Pirrung[148] has reported results on the intramolecular generation of allylic oxonium ylides and their subsequent [2,3]-sigmatropic rearrangement to give five-, six-, and eight- membered oxygen heterocycles In a generalized scheme diazoketone, **90**, was treated with rhodium (II) acetate to form an allylic oxonium ylide, **91**, which underwent a [2,3]-sigmatropic rearrangement to form an oxygen containing ring, **92** (Scheme 55)

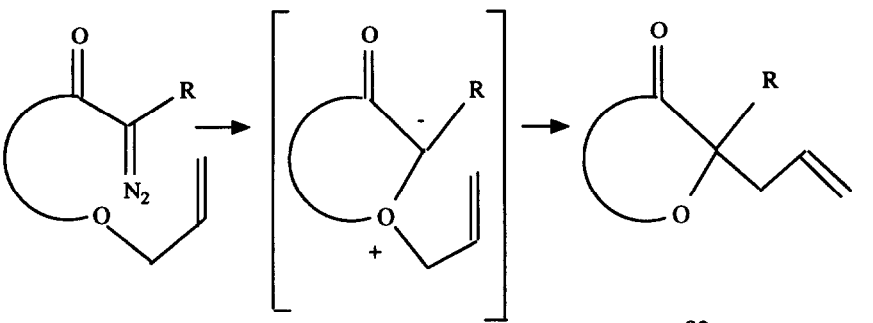
In the majority of examples the highest yields were obtained when R=CO_2R^1 Alternative pathways available to the carbenoid (e g , C-H insertion, cyclopropanation and dimerization) were minimized by the kinetic preference for five-membered ring formation Furanones are formed in very good yields (**93**→**94**), whereas pyranone formation occurs in modest yield (**95**→**96**) due to competing C-H insertion (Scheme 56)

Padwa has also observed that for the formation of six-membered rings, C-H insertion can be competitive with ylide formation and subsequent [2,3] sigmatropic rearrangement [149] In addition he

Scheme 54: Intramolecular Cyclization of Oxonium Ylides

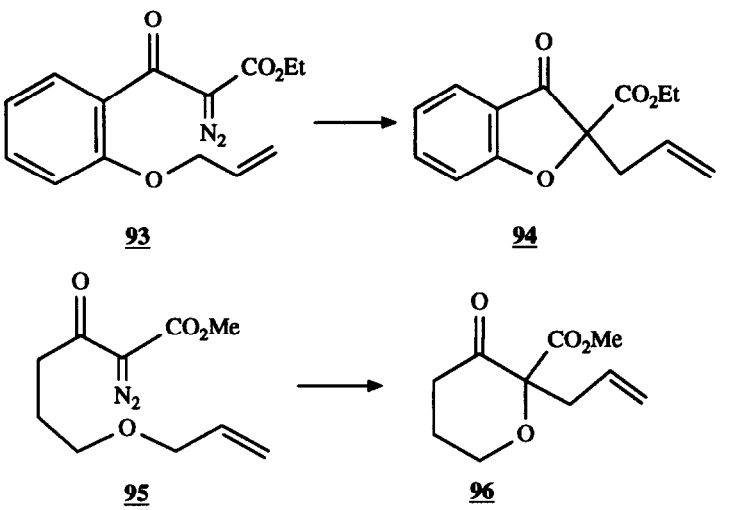


Scheme 55: Allylic Oxonium Ylide



noted that the replacement of allyl substituted oxygen with sulfur resulted in primarily ylide derived products Moody has also studied the [2,3]-rearrangements of S-allyl sulfonium ylides to form six-membered rings [129]

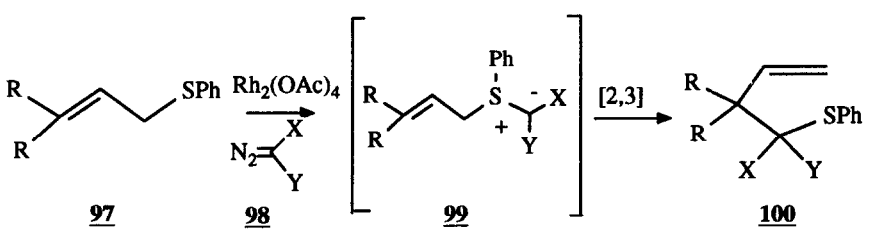
Scheme 56: Synthesis of Furanones and Pyranones



d) Intermolecular Reactions of Carbenes with Allylic Hetero Compounds

Intermolecular reactions of rhodium carbenoids with allylic hetero compounds are widely recognized The [2,3]-sigmatropic rearrangement of S-allyl sulfonium ylides, generated by the reaction of a diazoketone and an allyl alkyl sulfide, has been studied by Takano [150] In a typical procedure allylphenylsulfide, **97**, and diazo compound, **98**, were heated to reflux in toluene in the presence of rhodium (II) acetate to form the intermediate sulfonium ylide, **99**, which underwent 2,3 sigmatropic rearrangement to form **100** (Scheme 57)

Scheme 57: Intermolecular Ylide Formation with Allylic Sulfides



With simple alkyl allyl sulphides, [2,3]-sigmatropic rearrangement was the major pathway However with more complex systems, such as 2-vinyl derivatives of 1,3-dithiane and 1,3-dithiolane, elimination reactions of the intermediate ylides was competitive with [2,3]-sigmatropic rearrangement [140]

Allyl acetals underwent ylide generation in rhodium (II) acetate catalyzed reactions with diazoesters to form 2,5-dialkoxy-4-alkenoates by [2,3]-sigmatropic rearrangement.[140] Competing cyclopropanation, and in some cases Stevens rearrangements, occurred The product distributions were dependent on the catalyst, diazo compound, acetal and temperature

Metal catalyzed decomposition of diazoesters in the presence of allyl halides can afford halonium ylides, but cyclopropanation is competitive with ylide generation and rearrangement Competition between cyclopropanation and ylide generation can be manipulated by varying the nucleophilicity of halogen in the reactant allyl halide. Reactions with allyl iodide resulted solely in the product from [2,3]-sigmatropic rearrangement, whereas cyclopropanation occured predominantly with allyl chloride [150b,151] Catalyst selection was also important: Cu catalysis afforded more complex reaction mixtures due to C-Br bond cleavage Another method of increasing the relative yield of ylide derived product was through the use of rhodium (II) perfluorobutyrate [151]

In summary, the chemistry of ylide formation resulting from Rh(II) catalyzed diazo-carbonyl decomposition is very rich and diverse, allowing for many novel synthetic applications Nevertheless, optimum utility of these processes requires analysis of the reacting substrates, the catalyst employed and the reaction conditions, since the reaction pathways of ylide intermediates are numerous

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