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Rhodium(II) mediated cyclizations of diazo alkynyl ketones

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Abstract

The rhodium(II)-catalyzed reaction of α-diazo ketones bearing tethered alkyne units represents a new and useful method for the construction of a variety of substituted cyclopentenones. The process proceeds by addition of the rhodium-stabilized carbenoid onto the acetylenic π-bond to give a vinyl carbenoid intermediate. The resulting rhodium complex undergoes a wide assortment of reactions including cyclopropanation, 1,2-hydrogen migration, CH-insertion, addition to tethered alkynes and ylide formation. The exact pathway followed is dependent on the specific metal/ligand employed and is also influenced by the nature of the solvent. Sulfonium ylide formation occurred both intra and intermolecularly when the reaction was carried out in the presence of a sulfide. In the case where an ether oxygen was present on the backbone of the vinyl carbenoid, cyclization afforded an oxonium ylide which underwent a [1,2] or [2,3]-sigmatropic shift to give a rearranged product. These cyclic metallocarbenoids were also found to interact with a neighboring carbonyl π-bond to produce carbonyl ylide dipoles that could be trapped with added dipolarophiles. The domino transformation was also performed intramolecularly by attaching an alkene directly to the carbonyl group. When 2-alkynyl-2-diazo-3-oxobutanoates were treated with a Rh(II)-catalyst, furo[3,4-c]furans were formed in excellent yield. The 1,5-electrocyclization process involved in furan formation has also been utilized to produce indeno[1,2-c]furans. Rotamer population was found to play a significant role in the cyclization of α-diazo amide systems containing tethered alkynes. In this account, an overview of our work in this area is presented.

Keywords: Diazocarbonyl; Rhodium(II); Catalyst; Alkyne; Vinyl carbenoid

1. Introduction

The chemistry of transition metal carbene complexes has been a subject of intense activity over the past two decades.[1] Current interest in this area stems from the role of metal carbenes in alkene metathesis [2], in alkene and alkyne polymerization [3], in cyclopropanation chemistry [4] and as intermediates in an impressive array of synthetic methodology [5,6]. The intramolecular reactions of metal carbene complexes derived from α-diazo carbonyl compounds have been extensively studied from both a mechanistic and synthetic viewpoint [7]. Rhodium(II) carboxylates are particularly effective catalysts for the decomposition of diazo compounds and many chemical syntheses are based on this methodology [8]. Doyle's group has been particularly active in the use of rhodium(II) catalysts containing chiral ligands for asymmetric synthesis [9]. Among the more synthetically useful processes of the resulting rhodium carbenoid intermediates are cyclopropanation [9], intramolecular C–H insertion [10] and ylide generation [11]. In contrast to these processes, the corresponding reaction of alkynes with metal carbenes has been far less studied. Only in recent years has some attention been focused on the intramolecular cyclization reactions of α-diazo ketones containing tethered alkynes (i.e. **1**) in the presence of transition metal catalysts. The overall reaction observed is believed to proceed via an initial decomposition of the α-diazo ketone to generate a rhodium carbenoid intermediate (**2**). Attack on the carbenoid carbon by the tethered alkyne generates a new intermediate (**3**) in which carbene-like character has been transferred to the β-carbon of the alkyne. The intermediate vinyl carbenoid may then react further in either an intramolecular or intermolecular fashion to give novel products. In this account, studies involving this cascade that were carried out in the author's laboratory will be described (Scheme 1).

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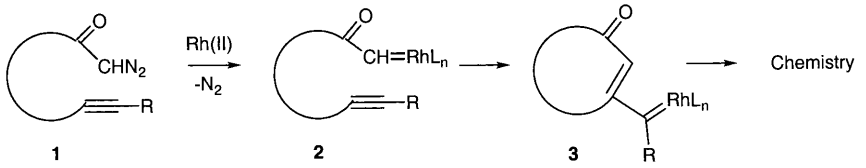


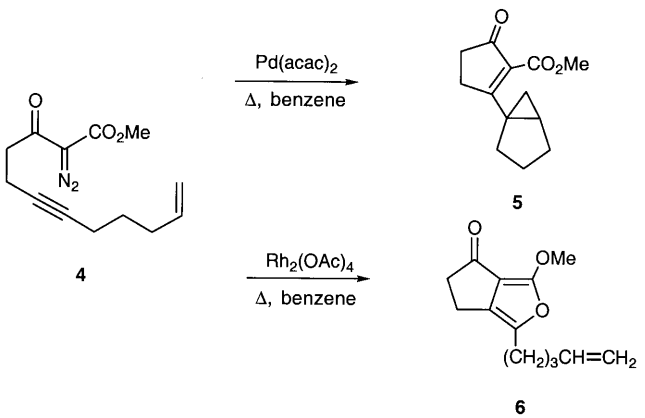
Scheme 1.

2. General mechanistic considerations

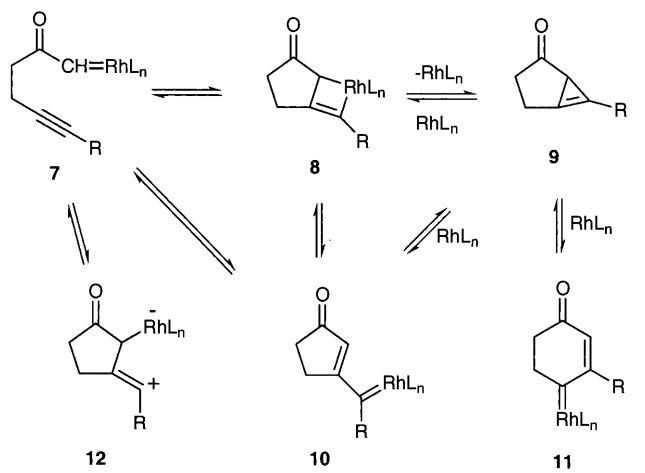
The mechanism of the metallocarbenoid–alkyne cyclization reaction has been the subject of some study over the past several years [6,12]. In an early report, Hoye and Dinsmore demonstrated that the distribution of products was markedly dependent on the nature of the metal catalyst used [13]. For example, treatment of α-diazo ketoester (**4**) with catalytic palladium(II) acetoacetonate produced cyclopropane **5** in 78% yield, while the reaction with rhodium(II) acetate provided furan **6** in 56% yield. Furan **6** arises from a 1,5-electrocyclization of the initially produced vinyl carbenoid intermediate onto the adjacent carbonyl group (vide infra) [13]. The fact that the chemistry of **4** is catalyst dependent suggests that a metalated species is involved in the product-determining step. One possible mechanism to explain the products involves the initial decomposition of the α-diazo moiety to give the metal carbenoid **7**. In the next step, the rhodium metal migrates from the original diazo carbon to the alkynyl carbon via a metathesis reaction and ultimately produces metallocyclobutene **8** (Scheme 2). This intermediate could then ring open to furnish the vinyl carbenoid **10** which goes on to afford the observed products. Another possible variation would be formation of the highly strained cyclopropene **9**. This intermediate could then be rapidly converted into the 5-*exo* vinyl carbenoid **10** or the 6-*endo* carbenoid **11**, both of which can undergo further chemistry. This pathway has precedent from the known metal catalyzed ring opening of cyclopropenes to vinyl carbenes [14–18]. It should be noted, however, that Hoye and Dinsmore have dismissed this sequence and have suggested instead, the formation of a zwitterionic intermediate **12** which proceeds on to the observed products (vide infra) [13,15] (Scheme 3).

In contrast to the Hoye mechanism, the intermediacy of metallocyclobutene **8** and the transfer of rhodium to the alkyne carbon to form vinyl carbenoid **10** was initially postulated in the author's laboratory [16] and is related to work described by Jones in 1975 [17]. Hoye's mechanistic conclusion was based upon a comparison of the product distribution obtained from the decomposition of α-diazo ketone **13** with that obtained from the isomeric diazo cyclopentenone **14**. Hoye argued that the rhodium carbenoid intermediate formed from **13** should correspond to the same species as that derived from **14** if a metallocyclobutene intermediate is involved. Consequently, one would expect identical product ratios. The distinct difference in product distribution obtained from the two isomeric diazo alkynes **13** and **14** does not seem to be compatible with a common intermediate such as **10**. This observation led these authors to propose that the cyclization reaction proceeds in a stepwise fashion (vide infra) [15] (Scheme 4).

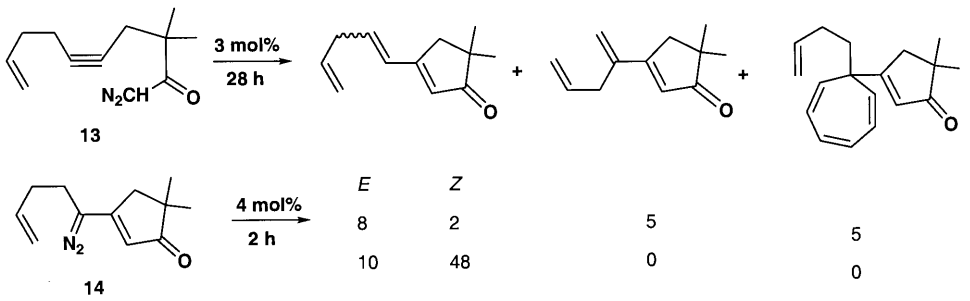
These same authors reported on the Rh(II)-catalyzed *double internal–external alkyne insertion reaction* of an acetylenic α-diazo ketone such as **15** [20]. The initially formed rhodium carbenoid intermediate was suggested to undergo internal insertion into the tethered alkyne bond and this was followed by bimolecular addition to



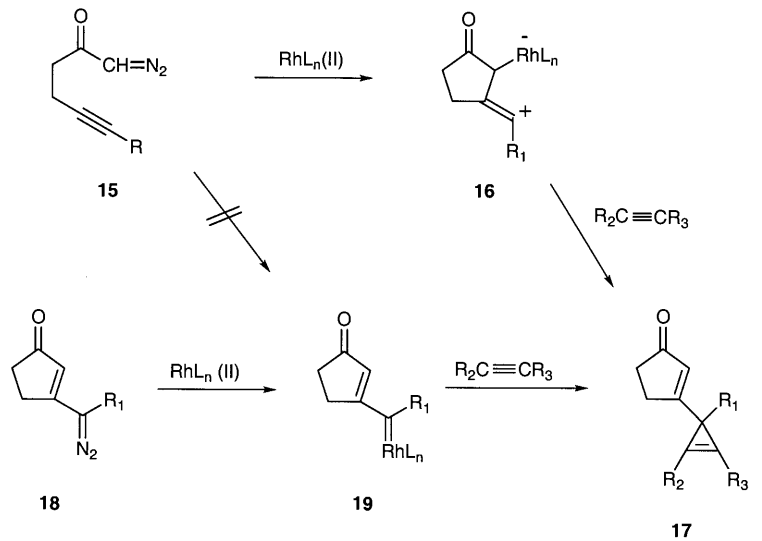
Scheme 2.



Scheme 3.



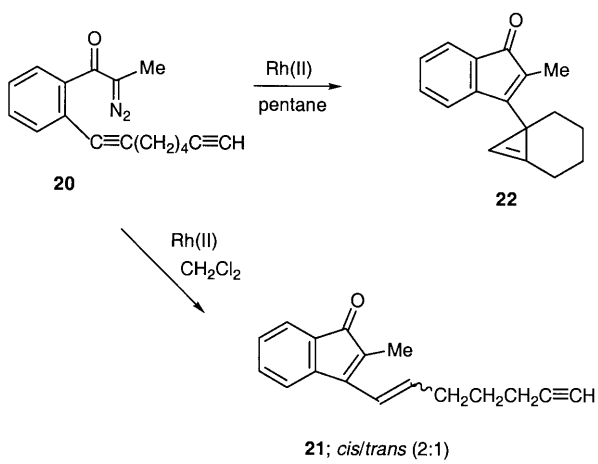
Scheme 4.



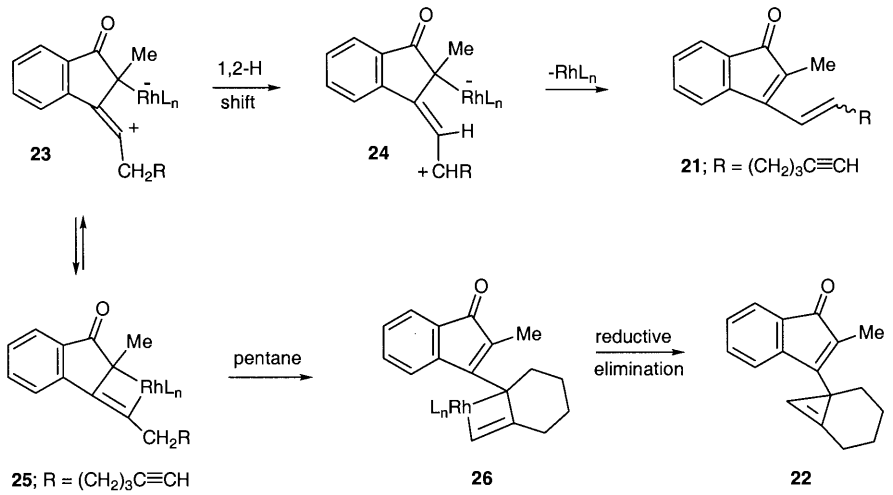
Scheme 5.

the external alkyne to produce a cyclopropenyl substituted cyclopentenone derivative **17**. Once again, migration of the rhodium metal to the remote alkyne carbon *via* a [2 + 2]-cycloaddition/cycloreversion path (i.e. **15** → **19**) was discounted on the basis that the distribution of products derived from **15** differed significantly from those obtained from the rhodium carbenoid species **19**, which was generated from the vinylogous α-diazo ketone precursor **18**. Zwitterion **16** was postulated as the key intermediate in the transformation of **15** to **17** [20] (Scheme 5).

More recent results in our laboratory showed, however, that the reaction mechanism is markedly dependent on the solvent employed in these Rh(II)-catalyzed insertion processes [27, 28]. Thus, treatment of **20** with a catalytic amount of rhodium(II) acetate resulted in a 2:1-mixture of the cis and *trans*-alkenyl substituted indenones **21** (85% combined yield) (Scheme 6). No signs of cyclopropene **22** (< 2%) could be detected in the crude reaction mixture by NMR spectroscopy. Interestingly, when pentane was used as the solvent, cyclopropene **22** (80%) was the exclusive product. The degree of chemoselectivity that was achieved in this reaction by simply changing the solvent from dichloromethane to pentane is most remarkable [21]. A reasonable explanation that nicely accounts for the formation of indenone **21** involves stepwise cyclization of the initially formed keto carbenoid in accord with the Hoye–Dinsmore proposal to give **23** (Scheme 7). A 1,2-hydrogen shift results in the formation of allylic cation **24** and this is followed by collapse to **21** and



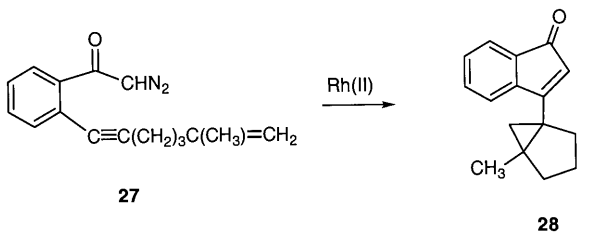
Scheme 6.



Scheme 7.

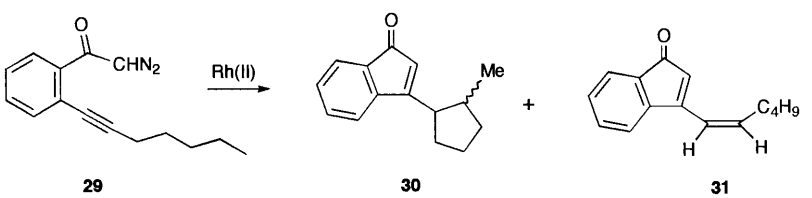
regeneration of the rhodium catalyst. The intermediates involved in the formation of **21** are dipolar, which would explain why the formation of **21** is strongly inhibited in nonpolar solvents. When pentane is used as the solvent, metal migration occurs via the metallocyclobutene intermediates **25** and **26** so as to avoid charge buildup [21]. Thus, it would appear as though the reaction mechanism of these alkyne cyclizations is markedly dependent on the nature of the solvent used.

Further complicating the mechanistic picture is the occasional dependence of the process on the ligand groups attached to the rhodium metal. In certain cases, no ligand dependence was noted as was found in the case of diazo ketone **27**. Varying the ligands from the electron withdrawing trifluoroacetate group to the more electron donating mandelate or acetate ligand always afforded a 60% yield of indenone **28** as the only observed product [14]. In other systems, however, the cyclization reaction was found to be ligand dependent. For example, treatment of α-diazoacetophenone **29** with a Rh(II) catalyst in benzene at 25°C afforded mixtures of the δ-CH insertion product **30** (1:2-*cis*/*trans*) as well as the *Z*-substituted alkene **31** derived from 1,2-hydride migration to the carbenoid center (Schemes 8 and 9). Varying the catalyst from rhodium(II) octanoate to rhodium(II) perfluorobutyrate caused a significant change in product distribution [22]. The data indicates that the more electron-withdrawing

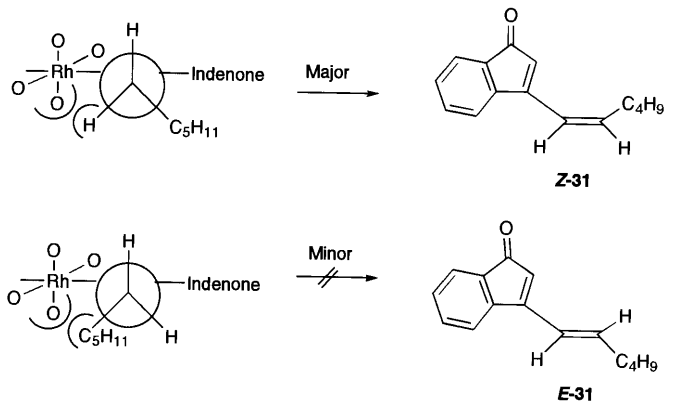


Scheme 8.

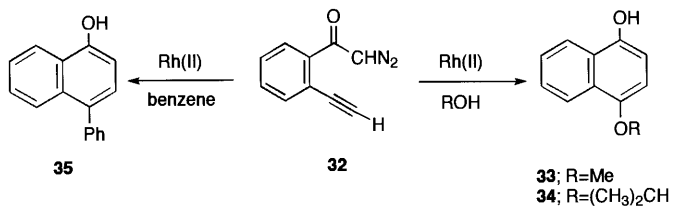
perfluoro-butyrate ligand favors 1,2-hydride migration, whereas the 1,5-insertion reaction is favored by the more electron-donating ligands. It has been well recognized that rhodium carbenoid intermediates are highly electron deficient at the carbon center and are destabilized by the presence of an electron-withdrawing ligand on the metal. Thus, when the ligand corresponds to an electron withdrawing group, the entropically less demanding 1,2-hydride migration pathway is favored. Related ligand dependencies have been found with other systems [21,23]. Another point worth noting is the preferential formation of the thermodynamically less stable *Z*-isomer **31** which is formed from the 1,2-hydride shift. This stereochemical result has been attributed to steric constraints associated with the orientation of the alkyl chain for hydride migration in the metal carbene intermediate (Scheme 10) [22,24].



Scheme 9.



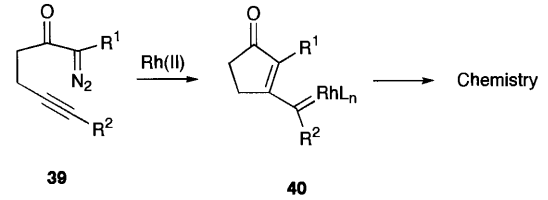
Scheme 10.



Scheme 11.

Still an additional point worth noting is the preference for formation of the 5-*exo* vinyl carbenoid **10** over the 6-*endo* vinyl carbenoid **11**. Although most work published on these systems show a propensity for 5-*exo* vinyl carbenoid formation, there are some exceptions [15,20,22,25]. In an effort to shed light on the source of this preference, we carried out some studies dealing with the nature of the substituent group on the alkyne and how it effects the mode of cyclization. Our initial efforts focused on the rhodium(II) catalyzed reaction of 2-ethynyl-α-diazoacetophenone **32**. The reaction of **32** with rhodium(II) mandelate in methanol or isopropanol afforded naphthols **33** or **34** as the only products formed in good yield (Scheme 11). When the reaction was carried out using benzene as the solvent, 4-phenyl-1-naphthol (**35**) was obtained in 70% yield [22].

Experimental results [26] as well as theoretical MO calculations indicate that thermodynamic factors are not important in influencing the 5-*exo* versus 6-*endo* cyclization selectivity with the *o*-alkynyl substituted α-diazoacetophenone system [22]. Rather, the regioselectivity of cyclization seems to be highly dependent on



Scheme 13.

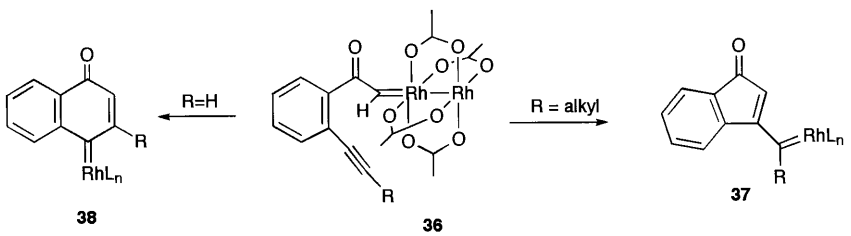
the nature of the substituent group attached to the alkyne tether. The 5-*exo* versus 6-*endo* selectivity appears to be primarily due to steric interactions between the substituent group on the alkyne and the ligand groups present on the catalyst. When the keto carbenoid intermediate **36** possesses a terminal hydrogen (R = H), products derived primarily from 6-*endo* closure are observed (Scheme 12). On the other hand, alkynyl substituted α-diazo ketones which contain a terminal alkyl group (R = alkyl), produce products derived from 5-*exo* cyclization. Steric factors combined with the ability of the substituent group (R) to stabilize the vinylogous carbenoid intermediate **37** seemingly determines the chemoselectivity [22,25].

3. Reactions of conformationally constrained systems

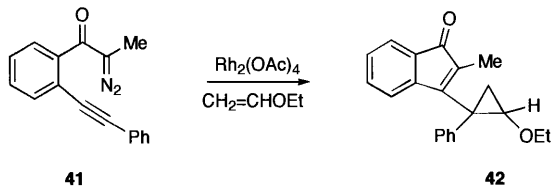
Regardless of the precise mechanistic pathway followed by these cyclizations, vinyl carbenoid intermediates such as **40** are seemingly formed from the Rh(II)-catalyzed reaction. This cyclization represents a novel approach for creating substituted cyclopentenones from acyclic precursors. Added to the arsenal of other synthetic methods such as the Nazarov cyclization and the Pauson–Khand $Co_2(CO)_8$-mediated cyclization, this reaction expands the availability of these biologically important ring systems [29]. Our group has exploited intermediates such as **40** to obtain a broad spectrum of products ranging from simple cyclopropanation and insertion adducts, to polycyclic heterocycles resulting from ylide formation and subsequent 1,3-dipolar cycloadditions (Scheme 13).

4. Cyclopropanation

Many of the earlier systems studied involved trapping the vinyl carbenoid intermediate as a cyclopropane

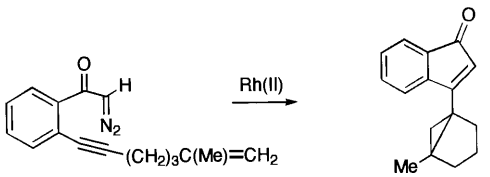


Scheme 12.



41 42

Scheme 14.



43 44

Scheme 15.

via reaction with external or tethered alkenes [13,15,16,30,31]. What is most interesting about this reaction is the formation of three new rings in one step from an acyclic precursor. A typical example is outlined in Scheme 14. Treatment of **41** with a catalytic quantity of rhodium(II) acetate in the presence of 2 equiv. of vinyl ether afforded cyclopropane **42** in 91% yield [30].

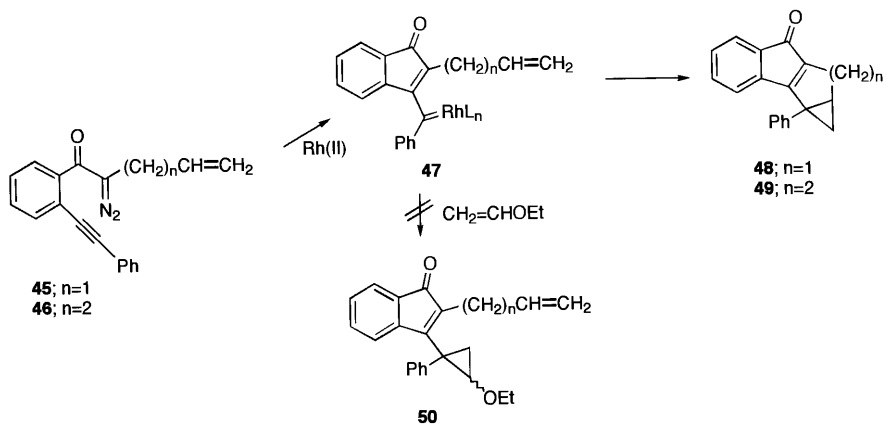
In the case of intramolecular trapping with tethered alkenes, two basic structural variations are possible. These will depend on the point of attachment of the alkenyl group and each variation will lead to very different cyclization products. In type I systems, the alkenyl group is tethered onto the alkynyl carbon atom and this is illustrated with α-diazo ketone **43**. Treatment of **43** with a catalytic quantity of rhodium(II) acetate gave indenone **44** in 60% yield [16] (Scheme 15).

On the other hand, for type II systems, the alkenyl group is tethered onto the diazo carbon as in diazo ketone **45** (or **46**). In these cases, bicycloalkanes **48** or **49** were formed in 67% and 81% yields, respectively [31] (Scheme 16).

Attempts to trap the cyclized carbenoid intermediate **47** by carrying out the reaction in the presence of a large excess of ethyl vinyl ether failed to give bimolecular adducts such as **50**. This observation indicates that bimolecular trapping of the cyclized rhodium carbenoid is significantly slower than intramolecular cyclopropanation [31].

A number of experiments designed to probe the scope and generality of the intramolecular alkyne cyclopropanation reaction were carried out in an effort to exploit this tandem sequence as a synthetic method. Initial efforts focused on the rhodium(II) catalyzed reaction of *o*-(6,8-nonadien-1-ynyl)-α-diazoacetophenone **51**. Treatment of **51** with a catalytic quantity of rhodium(II) mandelate gave cycloheptadiene **53** in 58% yield. In a similar manner, treating the closely related diazo ketone **52** ($R = CH_3$) with rhodium(II) mandelate also gave cyclopent[*g*]azulenone **54** [14]. The formation of the fused cycloheptadienes **53** and **54** can be rationalized by assuming that the reaction proceeds through the divinylcyclopropane intermediate **56** (Scheme 17). When the internal double bond of the diene possesses *E*-geometry, intramolecular cyclopropanation gives rise to a *cis*-divinyl cyclopropane, which rapidly undergoes a Cope rearrangement [32] under the conditions used [14]. It should be noted that intramolecular cyclopropanation of dienes by simple carbenoids followed by rearrangement of the resulting vinylcyclopropane has been used effectively in several elegant syntheses [33]. The overall process is also closely related to work by Davies who developed a synthesis of fused seven membered carbocycles based on a formal intramolecular [3 + 4]-cycloaddition of vinyl carbenoids with dienes [34].

Carbenes are known to insert into C–H bonds and rearrange by hydrogen or alkyl group migration.[35] Often these processes are in competition with each other and therefore mixtures of products result. A typical example of this competitition was encountered on treatment of **29** with a catalytic quantity of rhodium(II)



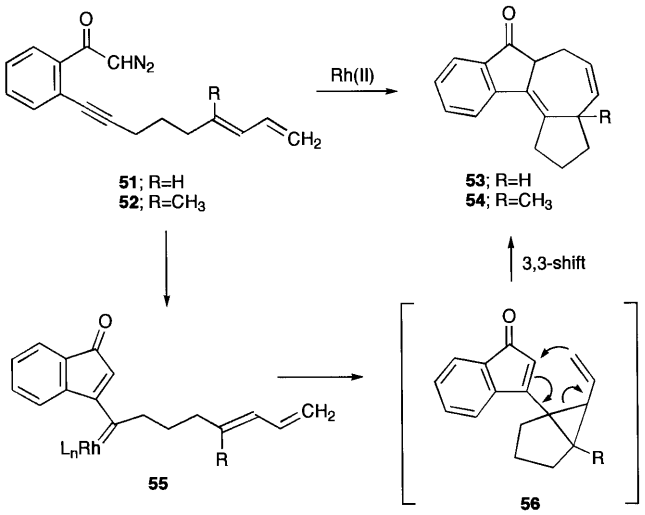
45; n=1
46; n=2

47

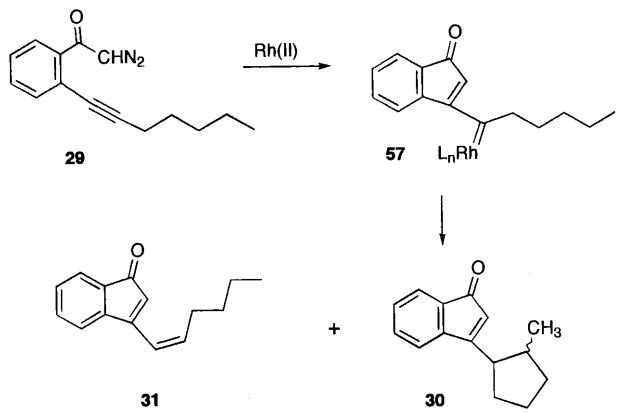
48; n=1
49; n=2

50

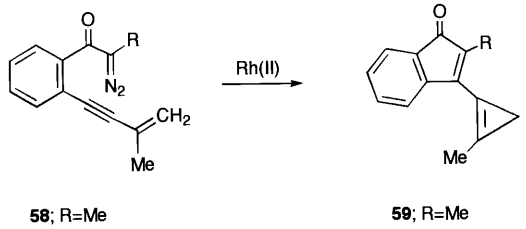
Scheme 16.



Scheme 17.



Scheme 18.



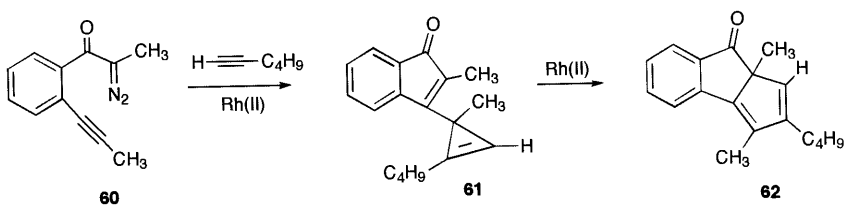
Scheme 19.

octanoate at 25°C in benzene (Scheme 18). Under these conditions, a 1:1-mixture of indenones **30** and **31** was formed in 94% yield. The observed products are derived from vinyl carbenoid **57** which reacts by way of either a 1,2-hydrogen shift to give **31** or insertion into the δ-hydrogen bond to produce **30** [19].

Cyclization of vinyl carbenoids to produce cyclopropenes is another common reaction that is often encountered with these systems [36–38]. For example, treatment of α-diazo ketone **58** with a catalytic quantity of rhodium(II) acetate afforded cyclopropene **59** in 95% yield (Scheme 19).

A *double internal/external alkyne* cyclization of acetylenic α-diazo ketone **60** with 1-hexyne was also studied in our laboratory. Stirring this mixture in the presence of rhodium(II) acetate at 25°C for 1 h afforded the novel cyclopentadiene derivative **62** in 81% yield. Control experiments established that the initial product that was first formed was indenone **61**. This product is the result of the vinyl carbenoid adding across the acetylenic π-bond of 1-hexyne. When the reaction was carried out for only 10 min at 25°C, indenone **61** could be isolated in 85% yield. Further stirring of **61** with rhodium(II) acetate induced a subsequent rearrangement and ultimately produced **62** in 92% yield [39] (Scheme 20).

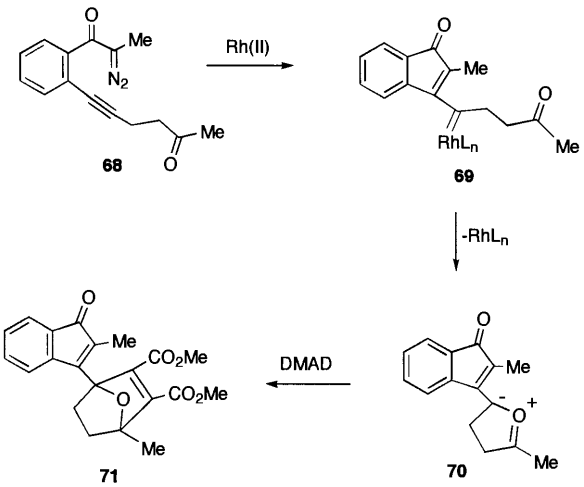
The ease with which these systems undergo the rhodium(II) catalyzed cyclization to give cyclopropenyl substituted indenones suggested that a similar transformation might occur with diacetylenic systems [40]. Such a study was carried out using diazo ketone **63**. A critical issue is whether the cyclization will occur to give products derived from the fully rearranged carbenoid **65** or from the initially formed carbenoid **64**. In fact, treatment of **63** with a catalytic quantity of rhodium(II) acetate at 25°C in the presence of ethyl vinyl ether afforded cyclopropane **66** with notable efficiency (90% chemical yield) and diasteroselectivity (> 95% isomeric purity). No signs of the isomeric cyclopropane **67** could be detected in the crude reaction mixture [41]. The exclusive formation of cyclopropane **66** was attributed to a slower rate of trapping of vinyl carbenoid **64** by ethyl vinyl ether, perhaps as a consequence of a more congested transition state. Another possibility is that the equilibrium between the two carbenoids lies completely in favor of the more stable phenyl substituted isomer **65** [40] (Scheme 21).



Scheme 20.

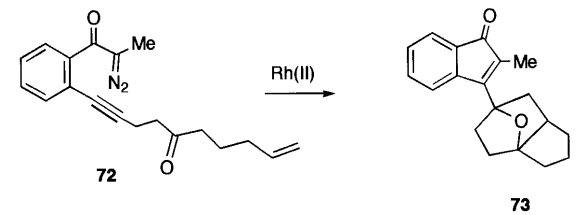
5. Ylide formation and subsequent rearrangements

Over the past several years, our group has studied the Rh(II)-induced α-diazo ketone cyclization onto a neighboring carbonyl group followed by dipolar-cycloaddition of the resulting carbonyl ylide dipole as a method for generating oxapolycyclic ring systems [42]. The ease with which α-diazo ketones containing tethered carbonyl groups undergo this tandem process suggested that a similar sequence could also occur with a vinylogous keto carbenoid. In order to test this possibility, the Rh(II) catalyzed behavior of diazo ketone **68** was studied. Treatment of **68** with a catalytic amount of rhodium(II) octanoate in the presence of 1 equiv. of dimethyl acetylenedicarboxylate afforded cycloadduct **71** in 97% yield. This result can be accounted for in terms of the intermediacy of vinyl carbenoid **69** which cyclizes onto the oxygen atom of the neighboring carbonyl group to give the resonance-stabilized dipole **70**. Dipolar cycloaddition of **70** across the activated π-bond of DMAD affords cycloadduct **71** [43] (Scheme 22).



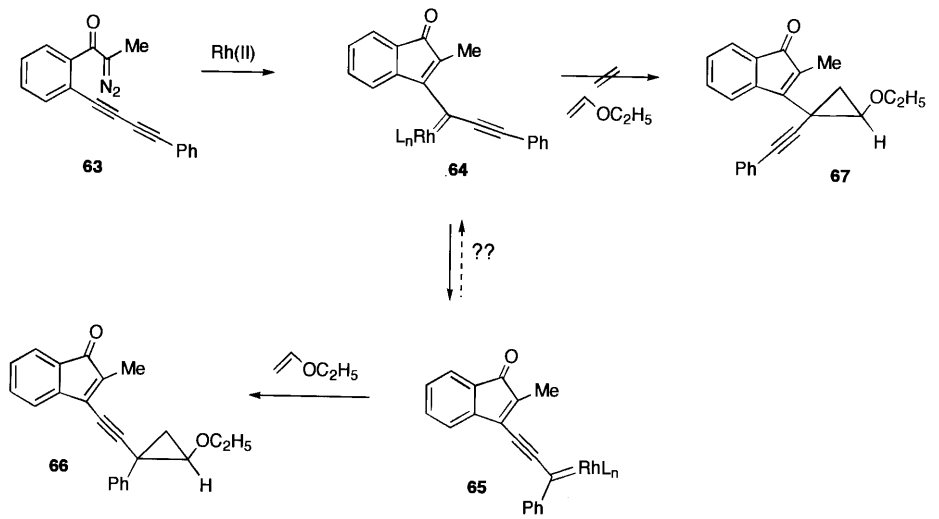
Scheme 22.

The above domino transformation can also be performed intramolecularly by attaching the trapping agent directly to the carbonyl group. Thus, treatment of diazo ketone **72** with rhodium(II) acetate produced cycloadduct **73** in excellent yield [43] (Scheme 23).

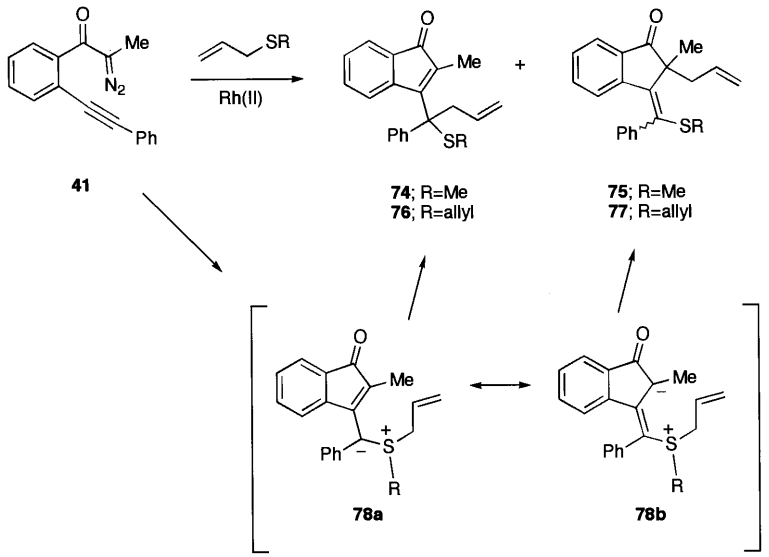


Scheme 23.

Formation of sulfonium ylides derived from the interaction of a vinyl carbenoid with a sulfur lone pair of electrons has also been examined. The reaction of electrophilic carbenes and carbenoids with unsaturated divalent sulfur compounds to give sulfonium ylides which then undergo a [2,3]-sigmatropic rearrangement is a well described process in the literature [44]. It is believed that the lone pair of electrons on the sulfur atom adds to the electrophilic carbenoid intermediate and this is followed by a subsequent dissociation of the catalyst to produce the sulfonium ylide [44]. The symmetry-allowed [2,3]-sigmatropic rearrangement is widely recognized as a facile bond reorganization process, especially for allylic sulfides [45]. The reaction of diazo ketone **41** with rhodium(II) acetate in the presence of methyl allyl sulfide behaved similarly, producing indenone **74** (86%) along with a 1:1 *E*/*Z* mixture of



Scheme 21.

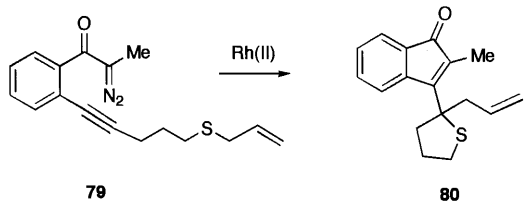


Scheme 24.

the isomeric vinyl sulfide **75** in 10% yield. A related reaction occurred using diallyl sulfide which resulted in the formation of a 9:1 mixture of **76** and **77**. The possibility that the formation of **75** (or **77**) was the result of a Cope rearrangement of **74** (or **76**) was excluded by the finding that the thermolysis of **74** (or **76**) did not produce any detectable quantities of **75** (or **77**). The formation of **74** and **76** occurs by reaction of the sulfur lone pair of electrons with the carbenoid center followed by a subsequent ylide rearrangement via **78a**. Presumably, compounds **75** and **77** arise via a novel antarafacial [3,4]-sigmatropic rearrangement of sulfonium ylide **78b** [29] (Scheme 24).

The ease with which the intermolecular *sulfonium ylide [2,3]-rearrangement* sequence occurred suggests that a similar process might take place intramolecularly by incorporating the allyl sulfide functionality onto the alkyne unit. Indeed, we found that stirring a sample of diazo ketone **79** with rhodium(II) acetate furnished tetrahydrothiophene **80** as the sole product. A number of related intramolecular sulfonium ylide rearrangement reactions were also studied [29](Scheme 25).

There have been several reports in the literature where cyclic oxonium ylides are formed by the intramolecular rhodium carbenoid addition to an ether oxygen followed by either a [1,2] or [2,3]-sigmatropic

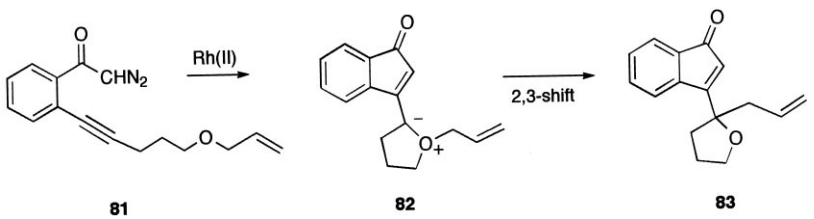


Scheme 25.

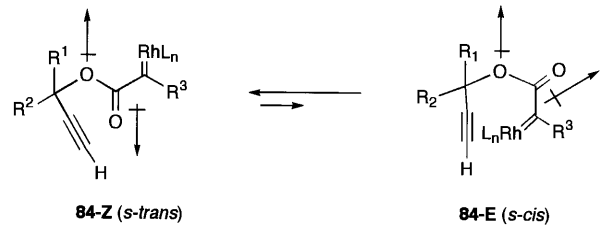
shift [46]. Work in our laboratory demonstrated that the *intramolecular tandem generation/[2,3]-sigmatropic rearrangement* of an oxonium ylide derived from a diazo ketone also took place. The overall process corresponds to a formal insertion of a vinyl carbenoid into a C–O bond with concomitant generation of a cyclic ether. This is nicely illustrated by the catalytic decomposition of diazo ketone **81** which furnished the rearranged ether **83** in 81% yield [29] (Scheme 26).

6. Diazoester cyclizations

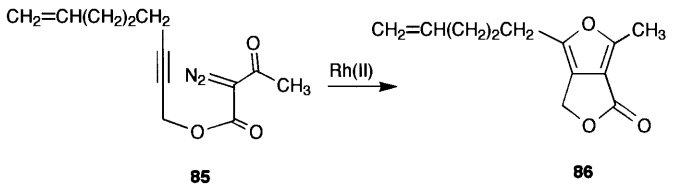
Introduction of a heteroatom α to the diazo carbonyl group may further complicate the cyclization chemistry. It is well known that esters exist primarily in the *Z* or *s-trans* (i.e. **84**-*Z*) conformation about the carbonyl



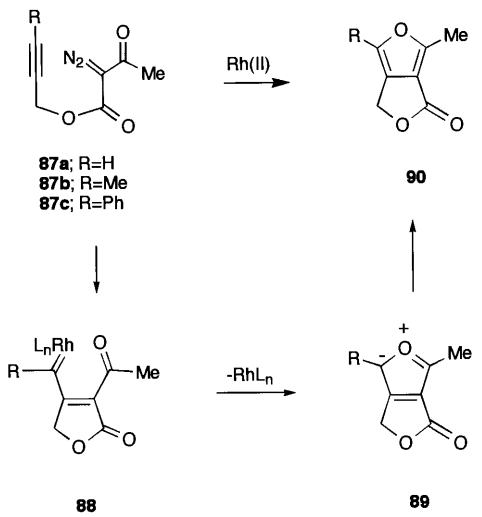
Scheme 26.



Scheme 27.



Scheme 28.

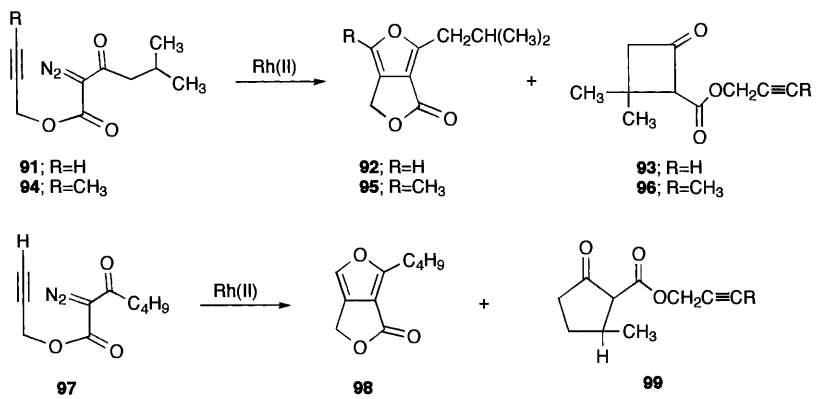


Scheme 29.

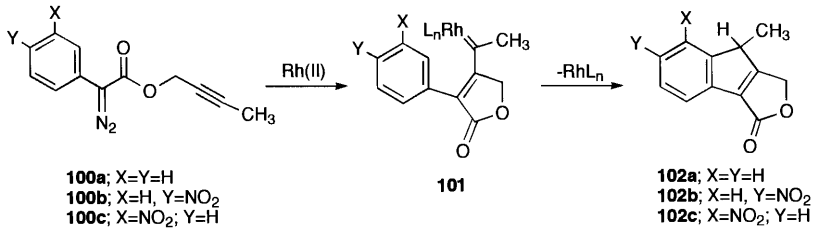
π-bond (Scheme 27). Esters are more stable in this conformation for several reasons, one of which is to minimize the overall dipole effect [47]. In this orientation, intramolecular cyclization of the rhodium carbenoid onto the alkyne π-bond cannot occur. In order for cyclization to take place, there must be rotation about the ester bond to generate the *E* or *s-cis* conformer **84**-*E*, which can then achieve the necessary geometry to allow the cyclization to proceed [48].

We have found that cyclization of the distabilized diazo ketoester **85** with rhodium(II) octanoate furnished furan **86** in 77% yield [49]. This transformation proceeds by addition of the rhodium-stabilized carbenoid onto the acetylenic π-bond to produce an electrophilic vinyl carbenoid intermediate (i.e. **88**) which is subsequently attacked by the adjacent carbonyl oxygen bond (Scheme 28). The resulting dipole **89** undergoes subsequent collapses to give furan **90** [50,51]. 6π-Electrocyclization reactions to produce five membered rings are well precedented transformations in heterocyclic chemistry [51,52]. Related furan cyclizations have also been observed in *ortho* constrained systems [53] Scheme 29.

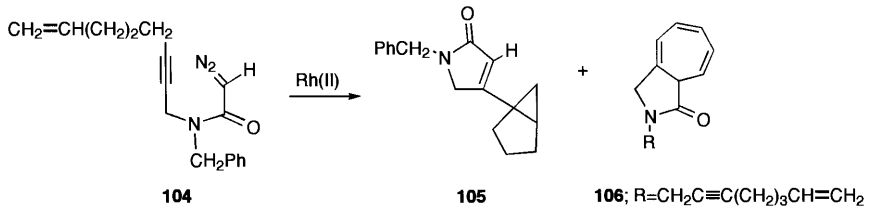
The author's group also examined the competition between C–H insertion and furan formation in systems where both pathways are possible. Insertion of electrophilic rhodium carbene complexes into a C–H bond results in the preferential formation of five-membered rings in acyclic, conformationally mobile systems [54]. The order of insertion reactivity into the C–H bond is generally: methine > methylene ≫ methyl [55]. There are also several examples in the literature where C–H insertion can lead to four and six-membered rings [56,57]. The results indicate that site selectivity depends on the nature of the α-diazo carbonyl compound, and also suggests that it is governed by steric, conformational, and electronic factors. We discovered that the C–H insertion reaction can compete with furan formation when an alkyl group is attached to the keto functionality. Thus, a 1:1-mixture of cyclization (**92**) and insertion (**93**) products was observed when diazo ester **91** was treated with rhodium(II) acetate at 80°C (Scheme 30). This ratio could be slightly altered to favor cyclobu-



Scheme 30.



Scheme 31.



Scheme 32.

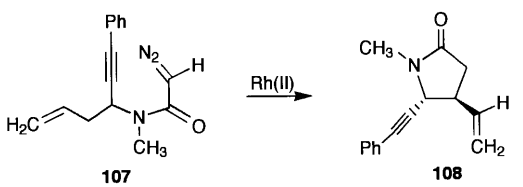
tanone formation (i.e. **95**:**96** = 1:1.5) when a methyl group was placed onto the terminal position of the alkynyl group. In both cases, insertion into the tertiary C–H bond to give a cyclobutanone is favored over insertion into one of the methyl groups. In a related fashion, the unbranched diazo ester **97** preferentially underwent a five ring insertion reaction over cyclization (**98**:**99** = 1:3) [48].

The 1,5-electrocyclization process involved in furan formation has also been utilized to produce indeno[1,2-c]furans such as **102a**–**c** in 45–60% yield. Treatment of the starting α-diazo esters **100a**–**c** with rhodium(II) catalysts gave indenes **102a**–**c** via an electrocyclization of the transient vinyl carbenoid **101** [48]. There seemed to be little effect displayed by the nature of the substituent groups on the aromatic ring as indeno[1,2-c]furans **102b** and **c** were isolated as the exclusive products. The fact that the insertion reactions occurs *ortho* to the nitro group (i.e. **100c** → **102c**) rather than producing a mixture of *ortho* and *para* isomers, suggests that subtle factors play a role in this process as well [48] (Scheme 31).

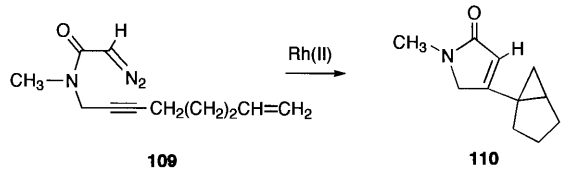
Rotamer population can play a significant role in determining the chemoselectivity of rhodium(II) catalyzed reactions of α-diazo amide systems containing tethered alkynes. The reaction of diazo amide **104** with rhodium(II) octanoate was found to undergo attack on the π-system of the acetylenic tether to give a transient vinyl carbenoid. The next step involved an internal cyclopropanation reaction to produce **105** in 41% yield. Cycloheptatriene **106**, which is derived by insertion of the carbenoid into the *N*-benzyl substituent, was also isolated from this reaction in 33% yield [49]. Rotamer populations nicely account for the behavior of this system (Scheme 32).

Amide rotamers generally interconvert in solution with lifetimes of 10^{-1}–10^{-2} s [58]. The geometry of a typical amide C–N bond will be fixed during the entire lifetime of the acyl rhodium carbenoid intermediate. Assuming that both amide rotamers are equally reactive toward π-addition, the relative amounts of compounds **105** and **106** that are formed are determined by the equilibrium concentration of the starting rotamers [49].

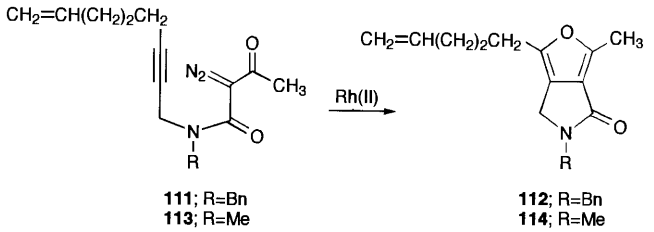
The complex nature of these reactions becomes even more apparent in further studies with related amide systems. In order to avoid the aromatic insertion reaction (i.e. **104** → **106**), the methyl substituted diazo amides **107** and **109** were studied. The rhodium(II) catalyzed decomposition of **107** did not afford products derived by internal attack on the acetylenic π-bond. Instead, only pyrrolidinone **108** was obtained in 65% yield [49] (Scheme 33). The exclusive formation of **108** is consistent with the rotamer population of the starting amide controlling the course of the reaction. Overlap of the nitrogen nonbonded electrons with the carbonyl π-bond fixes the amide conformation so that the larger allylic substituent is oriented toward the rhodium carbenoid center so as to minimize A-strain [1,3] with the methyl group on the nitrogen atom [59]. This places the allylic hydrogens close to the carbenoid center for an easy C–H insertion. The exclusive production of **108** at 25°C suggests that at this temperature, the rate of C–H



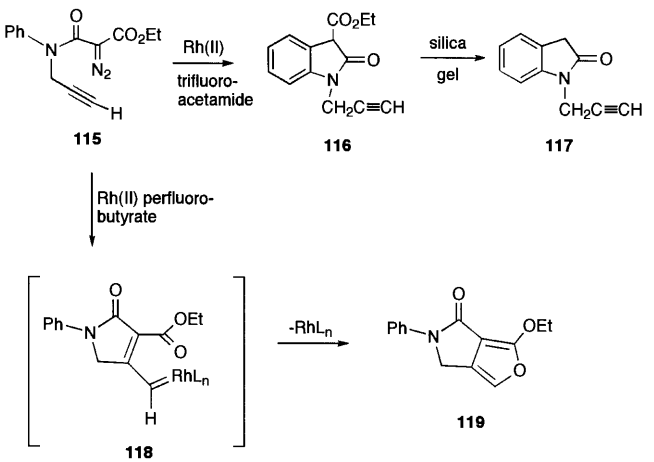
Scheme 33.



Scheme 34.



Scheme 35.



Scheme 36.

insertion is greater than the rate of conformer interconversion. When C–H insertion is not a viable option, as in **109**, internal cyclopropanation becomes the exclusive process leading to bicyclohexane **110**. The success of this reaction clearly indicates that internal attack at the alkyne is electronically viable and that conformational factors may dictate the course of the reaction with these acyclic diazo amide systems [49] (Scheme 34).

Cyclization reactions of distabilized α-diazo amides have also been studied. Thus, the reaction of **111** and **113** with rhodium(II) octanoate gave rise to bicyclic furans **112** and **114** in 82 and 72% yields, respectively. Here, electrocyclization of the vinylogous rhodium carbenoid onto the neighboring acetyl group is faster than cyclopropanation with the tethered alkenyl π-system. This result is analogous to that encountered with the distabilized α-diazo ester system (i.e. **85**→**86**) [49] (Scheme 35).

In one study, the mode of cyclization of a distabilized α-diazo amide was varied by changing the ligands on the rhodium catalyst. Reaction of **115** with rhodium(II) trifluoroacetamide in benzene at 25°C provided oxoindole **116** in 87% yield. On the other hand, when rhodium(II) perfluorobutyrate was used as a catalyst, furanopyrrolone **119** was formed in 98% yield [60], in line with previous observations [61].

7. Conclusion

It is clear from the above discussion that the reaction of α-diazo carbonyl compounds with tethered alkynes is both a mechanistically complex and synthetically useful process. Four major factors dictate the mode of reaction of the initially formed rhodium carbenoid species. The electronics about the carbenoid center are perhaps the most important factor (Scheme 36). Conformation of the molecule is also quite impactful. The geometrical orientation can be influenced by both the nature of the carbenoid stabilizing group (amide vs. ester vs. ketone), and by substitution on the carbonyl group. Steric factors appear to influence the process in subtle ways. Finally, the polarity of the solvent used in these reactions has also been shown to influence both the mechanism and chemoselectivity of the reaction. These factors can be exploited and manipulated in many ways to generate a wide variety of interesting products. Application of the methodology to the synthesis of natural products is still relatively unexplored.

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