DIOXYCARBENES AND 3,3-DIOXYVINYLCARBENES IN THE SYNTHESIS OF NOVEL HETEROCYCLES

By

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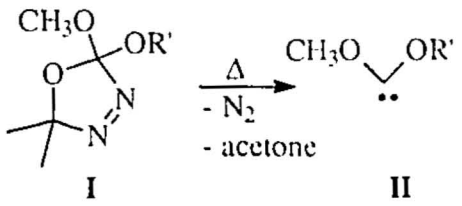
ABSTRACT

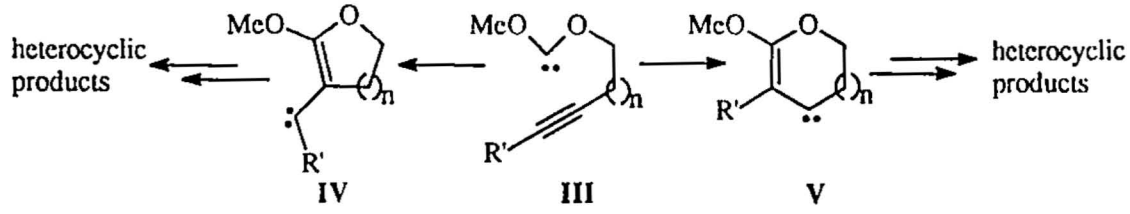
Carbocyclic and heterocyclic compounds are ubiquitous in nature. Therefore, the discovery and development of new ring forming reactions are of paramount interest to synthetic organic chemists. Recently, the intramolecular cyclization of reactive intermediates, such as anions, cations, and radicals have provided a number of new methods by which known and novel ring systems can be constructed. Cyclizations involving tandem, or multiple sequences have gained considerable popularity due to their high overall efficiency and remarkable speed by which these processes can yield complex polycyclic ring systems.

Carbenes are another interesting class of reactive intermediates which undergo characteristic reactions. The cyclization reactions of carbenes have not been studied to a significant extent. In particular, the work described in this thesis outlines the only study of the intramolecular cyclization of dioxycarbenes onto a tethered alkyne moiety.

The first section of this dissertation details the development of a convenient new class of thermal dioxycarbene precursors, dioxyoxadiazolines **I**, which display many significant advantages over previously used sources of dioxycarbenes **II**.



The second section of this dissertation details the use of dioxyoxadiazolines possessing a tethered triple bond for the thermal generation of dioxycarbenes **III** which are capable of intramolecular cyclization. It was found that the cyclization of a dioxycarbene onto a tethered triple bond results in the regioselective generation, of another reactive intermediate, a 3,3-dioxyvinylcarbene (**IV** or **V**, depending on the nature of R'), which can undergo a number of interesting intermolecular reactions. This approach leads to the rapid construction of some interesting and rather complex polycyclic heterocyles which are, in many cases, obtained with high regioselectivity and sometimes even high stereoselectivity.



The results described in this thesis mark the discovery and development of a new synthetic methodology which may, by appropriate choice of the starting material, provide a valuable tool for the rapid and selective synthesis of a number of heterocyclic ring systems.

Acknowledgments

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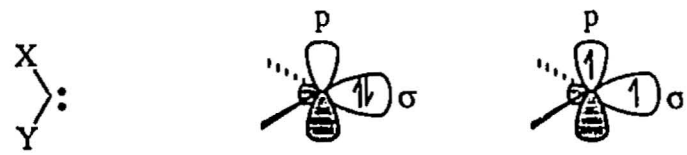
Table of Contents

List of Tables

List of Figures

Chapter 1: INTRODUCTION

"Carbenes", a term coined in the back of a Chicago taxi cab by Doering, Winstein, and Woodward,[1] refers to a broad class of reactive intermediates that possess a divalent carbon atom with two non-bonding electrons. These compounds (**1**) clearly violate the "natural tetravalence of carbon" and, as a result, have intrigued both physical chemists and theoreticians for many decades.[2-8] Because of their divalence, carbenes are generally highly reactive species that undergo rapid characteristic reactions with a number of different substrates. In some cases these reactions display considerable synthetic potential.



1 **2** (S_0) **3** (T_1)

Figure 1

1.1 Electronic Configuration of Carbenes.

Carbenes have two low-lying states, a singlet (**2**) and a triplet (**3**). The electronic configuration of a singlet carbene (**2**) consists of two paired electrons that occupy an *in-plane*, "sp^2 like", σ molecular orbital. A higher energy p orbital, which is perpendicular to the carbene molecular plane, is vacant in this state. Triplet carbenes (**3**), on the other

hand, have two unpaired electrons with the same spin; each of the electrons occupy one of the two mutually perpendicular σ and p orbitals.

The reactivities of singlet and triplet carbenes are generally very different and easy to distinguish; the former behave as electrophiles and/or nucleophiles, whereas the latter are more like radicals. The ground state configuration of a carbene (singlet or triplet) is dependent upon the relative energies of the σ and p orbitals which, in turn, are determined by the nature of the substituents X and Y. Although carbenes can undergo reactions in the excited state, most carbene reactions proceed via the ground state.

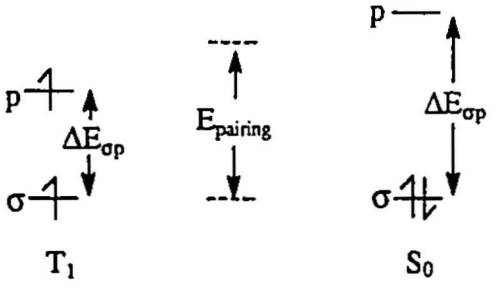


Figure 2

As illustrated in Figure 2, a carbene will have a triplet (T_1) ground state when the energy difference between the σ and p orbitals, denoted as $\Delta E_{\sigma p}$, is smaller than the energy ($E_{pairing}$) required to overcome electron-electron repulsion between two paired electrons in the same orbital. Conversely, if the $\Delta E_{\sigma p}$ is larger than $E_{pairing}$, then the singlet (S_0) ground state is favored. The energy difference between the triplet and singlet state for any given

carbene is defined as ΔE_{ST}. By this definition, ΔE_{ST} is negative for triplet carbenes and positive for singlet carbenes.

A number of experimental[9,10] approaches have been used to determine the ground state as well as the magnitude of ΔE_{ST} for a variety of carbenes. Computational methods have also been extensively applied toward this purpose.[11-15] Recent advances in computing power allow the use of ab-initio methods with very large basis sets and large configuration-interaction (CI) to provide reasonable estimates of ΔE_{ST} for a variety of carbenes.[3,16] Moreover, the dissociation-consistent CI method (DCCI), when combined with experimental data, provides ΔE_{ST} with unprecedented reliability for a handful of carbenes.[17,18]

The parent carbene (X = Y = H), methylene, has a triplet ground state. The most recent experimentally determined value of ΔE_{ST} for this carbene[19] has been found to be - 9.02 kcal/mol. The use of computational methods to compute the geometry and the ΔE_{ST} of methylene accurately has been an issue of much controversy[11] ever since the first ab-initio investigation of methylene conducted by Foster and Boys in 1960.[20] Recently, high level ab-initio calculations using a very large basis set (through g functions on carbon and d functions on hydrogen) and a large CI (over 70,000 configurations) have allowed estimation of ΔE_{ST} for methylene to within 0.1 kcal / mol of the experimental value.[16]

Substituents on the carbene have been shown to either increase or decrease ΔE_{ST} with respect to that of methylene. In general, π-electron withdrawing substituents, and substituents that are more electropositive than carbon, favor a triplet ground state, whereas, substituents that are π–donating or highly electronegative, favor a singlet ground state. Because of the unique character of singlet carbenes, the latter case is of particular interest. For singlet carbenes a general trend, of increasing ΔE_{ST} with increasing π-donor ability or increasing electronegativity of the substituent(s), is evident. Two apparently opposing arguments which account for these trends in ΔE_{ST} have emerged in the literature.

The most popular explanation attributes singlet stabilization to the ability of the carbene substituent(s) to take part in π-donation.[14,21-23] As illustrated below (Figure 3a), the mixing of a relatively high lying π orbital of a substituent with the carbene vacant p orbital stabilizes two π electrons of the substituent and, therefore, lowers the energy of the singlet. Although this type of mixing can also stabilize the triplet (Figure 3b), the effect is, to a significantly lesser extent, attributable to partial destabilization of one electron. It was generally believed by a number of groups that π-donation by the substituent(s) was the only factor responsible for the observed trend in ΔE_{ST}, and that other related and inseparable factors, such as substituent electronegativity, were either minor or even irrelevant. In fact, Houk and co-workers demonstrated, using ab-initio methods, that ΔE_{ST} shows a linear correlation with subtituent π-donor ability for a series of substituted carbenes.[21]

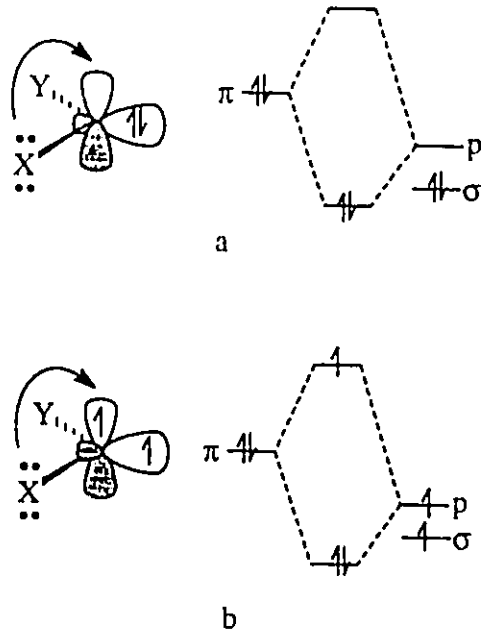


Figure 3

The other explanation of this observed trend is based on inductive effects of the carbene substituent(s).[15,24,25] It was found that, ΔE_{ST} generally increases with increasing electronegativity of the substituent(s). This was attributed to the fact that, as the substituent electronegativity increases, inductive electron withdrawal from the *in-plane* σ orbital leads to an increase in s-character of that orbital. Such a change in hybridization lowers the energy of the orbital, and the singlet - which has two electrons in the σ orbital, is stabilized with respect to the triplet. In fact, as one would expect from such a change of hybridization, the X-C-Y bond angle of carbenes show a considerable dependence upon spin state; singlets generally have X-C-Y bond angles of about 100 to 110 degrees, whereas, triplets have larger bond angles of 120 to 140 degrees. Moreover, ΔE_{ST} usually shows an inverse correlation with the magnitude of the carbene X-C-Y bond angle.[26]

Recently, Goddard and co-workers[12] have claimed that inductive withdrawal and π-donation by the carbene substituent(s), discussed above, are both important factors in determining ΔE_{ST}, and that they act in a synergistic manner to stabilize the singlet with respect to the triplet. Note that these effects are readily united by the following argument: electronegative substituents inductively withdraw charge from the filled non-bonding σ orbital. This inductive withdrawal consequently makes the carbene carbon more positive, and hence a better π-acceptor. As a result, π-donation from the substituent is enhanced. The extent to which each of these two effects contribute to the overall stabilization of the singlet varies according to the nature of the substituent(s). Evidence of Goddard's synergistic model[12] is derived from a linear correlation of calculated ΔE_{ST} with both charge on the carbene carbon, and also with π-donation from the carbene substituents.

Experimental support for this synergistic bonding model comes from the nuclear quadrupole coupling constants for $:CCl_2$, which indicate a transfer of 0.26 electron from C to Cl through the σ framework, and transfer of 0.32 electron from Cl back to C via π–donation.[27]

1.2 Singlet Carbene Philicity

Singlet carbenes can be thought of as 1,1-dipoles (4), and are inherently both electrophilic and nucleophilic species. As indicated in Figure 4, the electron deficient p orbital of a carbene can undergo reaction in an electrophilic manner with an electron rich nucleophilic substrate ($Nuc^{\delta-}$) by transfer of electrons from the substrate to the carbene (a). On the other hand, the filled σ orbital of the carbene can react in a nucleophilic

manner with an electron deficient electrophilic substrate ($E^{\delta+}$) by transfer of electrons from the carbene to the substrate (b). Either pathway (a) or (b) can dominate, depending upon the relative electrophilicity and nucleophilicity of both the substrate and the carbene.[28,29]

The former mode of carbene reactivity (a) is dominant in most cases and has been evident since the discovery of singlet carbene reactions. The nucleophilic reactivity of carbenes (b) is, *a priori*, counterintuitive since carbenes are after all, "electron deficient" species. This mode of carbene reactivity was not well recognized until the 1960's.[30] Like ΔE_{ST}, the philicity of a carbene is also determined by the nature of the substituents X and Y (*vide infra*).

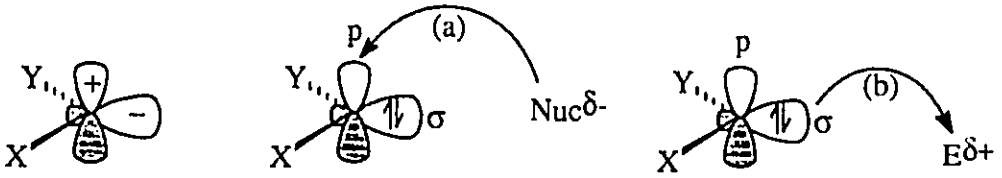


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Figure 4

Although carbene "philicity" is a relative term which depends upon the nature of both the carbene and the substrate, certain substituted carbenes only react with electron rich substrates in an electrophilic manner - these are termed "electrophilic carbenes" and include the majority of known singlet carbenes. Substituents that are mild π–electron donors, such as Cl or F, give rise to electrophilic carbenes, and examples of these carbenes include, $:C(CH_3)Cl$, $:CCl_2$, and $:CF_2$. Electrophilic carbenes are generally very reactive and show little selectivity. Conversely, carbenes that possess strong π-electron donor substituents such as N or O, react exclusively in a nucleophilic manner - these are

referred to as "nucleophilic carbenes". Examples of nucleophilic carbenes include $:C(OMe)_2$, and $:C(NH_2)_2$. In contrast to their electrophilic counterparts, because of resonance delocalization (Scheme 5),[28] these carbenes are highly stabilized and react with considerable selectivity. Carbenes in which either the electrophilic (a) or nucleophilic (b) reactivity can dominate, depending upon the nature of the substrate, are classified as "ambiphilic carbenes". Examples include, :C(MeO)Cl and $:C(OCH_2CF_3)Cl$.

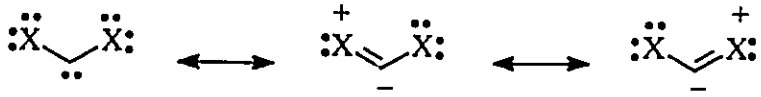


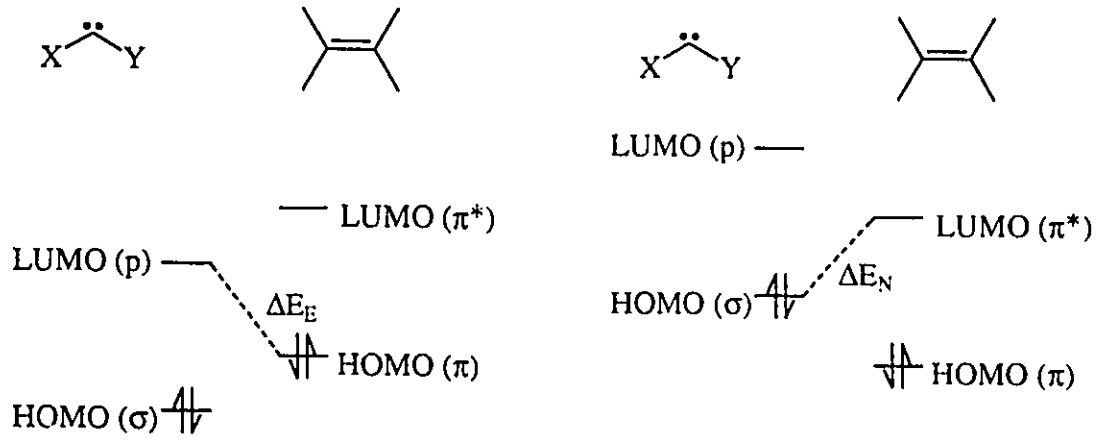
Figure 5

1.2.1 The [1+2] Cycloaddition of Singlet Carbenes with Alkenes

The [1+2] cycloaddition of a singlet carbene with an olefin is probably the most extensively studied reaction of carbenes. Moss and co-workers have used this "simplest of cycloadditions" to investigate the philicity and reactivity of a wide variety of substituted carbenes.[28,29] This endeavor has consequently provided considerable insight into how various substituents control carbene reactivity.

Consider the Frontier Molecular Orbitals (FMO) [28,29,31,32] involved in the [1+2] cycloaddition of a singlet carbene with an alkene. The σ orbital is the highest occupied molecular orbital (HOMO) of the carbene, and the carbene vacant p orbital is the lowest unoccupied molecular orbital (LUMO). For the alkene, the π and π^* orbitals are the HOMO and LUMO, respectively. In the transition state for the [1+2] cycloaddition, both

the [$HOMO_{carbene}(\sigma)$ - $LUMO_{alkene}$ (π^*)] and the |$LUMO_{carbene}$ (p) - $HOMO_{alkene}$ (π)| interactions are operative. The net charge transfer, which determines the philicity of the carbene, depends upon both the differential energies, and on the extent of orbital overlap of these HOMO/LUMO interactions at the transition state.



(a) Electrophilic Carbenes (b) Nucleophilic Carbenes

Figure 6

Considering differential energies alone, the carbene acts as an electrophile when the [$LUMO_{carbene}$ (p) - $HOMO_{alkene}$ (π)] energy gap (ΔE_E) is smaller than [$HOMO_{carbene}$ (σ) - $LUMO_{alkene}$ (π^*)] energy gap (ΔE_N) as indicated in Figure 6a. Conversely, when ΔE_N is smaller than the ΔE_E, the carbene acts as a nucleophile and net transfer of electron density is from the carbene to the alkene (Figure 6b).

According to FMO theory, again neglecting orbital overlap, a smaller HOMO/LUMO differential energy results in a more rapid reaction rate. Therefore electrophilic carbenes, which characteristically have a low-lying LUMO, only react with

electron-rich alkenes, which generally have a high-lying HOMO, via electrophilic attack (Figure 6a). As the electron donating ability of the alkene substituent increases, so does the HOMO energy of the alkene and, as a result, the reaction rate is enhanced because of a smaller ΔE_E. Conversely, nucleophilic carbenes, which characteristically have a high-lying HOMO and a high-lying inaccessible LUMO, only react with electron deficient olefins which have a low-lying LUMO. As the olefin becomes more electron deficient, its LUMO becomes lower in energy, and the reaction rate increases as a result of a smaller ΔE_N (Figure 6b).

Ambiphilic carbenes undergo reaction with both electron-rich and electron-deficient alkenes. These carbenes react in an electrophilic manner with the former and, conversely, in a nucleophilic manner with the latter. In going from electron-rich to electron-deficient alkenes, this mechanism change leads to a parabolic dependence in the rate of the [1+2] cycloaddition for ambiphilic carbenes. [33]

The differential HOMO/LUMO energies, described above, are the overriding factors in determining the dominant FMO interaction in the transition state, and usually suffice to rationalize or to predict carbene philicity qualitatively.[29] For a more rigorous treatment however, the differential orbital overlaps of the two competing HOMO/LUMO interactions must also be considered. The orbital overlaps for the [1+2] cycloaddition can be estimated from the calculated overlap integrals, which are derived from the geometries and orbital coefficients for the carbene/alkene pair in the transition state.[34]

Houk and co-workers have developed an index, PI_{CXY} (referred to as the PROPHETIC index), which allows prediction, using ab-initio calculations, as to whether a

specific singlet carbene can be categorized as electrophilic, nucleophilic, or ambiphilic (Equation 1).[34] The term E_{stab} in Equation 1 is the calculated (4-31G) stabilization energy of the carbene in the isodesmic reaction shown below. An empirically derived second order polynomial in this term fits very well with the calculated electrophilic and nucleophilic FMO overlaps for a variety of [1+2] cycloadditions, and therefore provides a convenient and reasonable estimate of the differential orbital overlaps. The terms $E_{HOMO(CXY)}$ and $E_{LUMO(CXY)}$ are simply the calculated (4-31G) HOMO and LUMO energies of the carbene. The value of PI_{CXY} is less than 1 for electrophilic carbenes, greater than 1 for nucleophilic carbenes and approximately equal to 1 for ambiphilic carbenes. This index has a purely theoretical origin and has been demonstrated to categorize a number of carbenes accurately according to their philicities.[34] For example, PI = 0.27 for $:CCl_2$ (an electrophilic carbene), PI = 1.15 for :CFOH (an ambiphilic carbene), and PI is 1.37 for $:C(OH)_2$ (a nucleophilic carbene).

Equation 1

$$PI_{CXY} = (0.072\, E_{stab} - 0.00048\, E_{stab}^{2} - 1.03)\left[\frac{5.3 + E_{LUMO(CXY)}}{-E_{HOMO(CXY)} + 0.12}\right]$$

$$:CH_2 + CH_3X + CH_3Y \xrightarrow{-E_{stab}} :CXY + 2\,CH_4$$

The [1+2] cycloaddition of a singlet carbene with an alkene involves a two phase mechanism; an electrophilic phase, and a nucleophilic phase.[35] At large distances the carbene approaches the alkene in an electrophilic manner as illustrated in Figure 7a. In this approach, the carbene and the alkene molecular planes are coplanar to result in

maximum overlap between the carbene vacant p orbital and the filled alkene π orbital. At shorter distances the carbene begins to go off-centre and pivots about the divalent carbon so that the carbene lone pair of electrons moves toward one of the alkene carbons (Figure 7b - d). At this point, referred to as the nucleophilic phase, the carbene lone pair of electrons becomes involved in bonding.

Using ab-initio SCF theory, Rondan, Houk, and Moss investigated the [1+2] cycloadditions of a series of substituted carbenes with ethylene. The carbenes modeled in this study were $:CCl_2$ (a relatively unselective electrophilic carbene), $:CF_2$, (a somewhat more selective electrophilic carbene), :CFOH (an ambiphilic carbene), and $:C(OH)_2$ (a nucleophilic carbene).

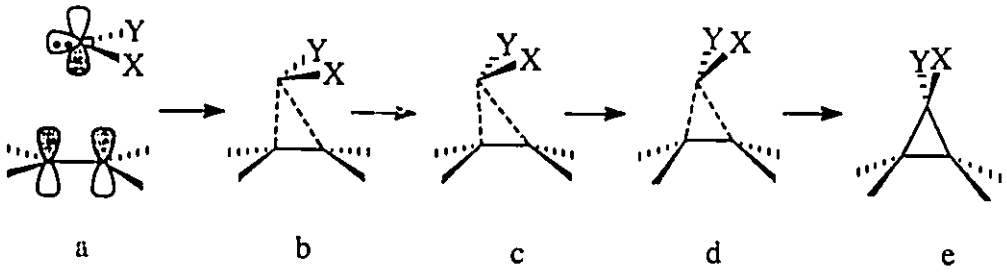


Figure 7

It was found that all four of the carbenes studied followed the two phase approach in the [1+2] cycloaddition to ethylene. The results from this investigation, in brief, can be summarized as follows. π-Electron donating groups increase the nucleophilicity and also the thermodynamic stability of the carbene by resonance delocalization. Therefore, as the thermodynamic stability of the carbene is increased, the reaction becomes less exothermic

and has a larger activation energy barrier. In accord with the Hammond postulate,[36] the transition state is located later along the reaction coordinate. For example, the transition state for the [1+2] cycloaddition of $:CCl_2$ with ethylene is early and closely resembles Figure 7b, whereas the transition state for $:C(OH)_2$ is late and is more like Figure 7e. A transition state that is later along the reaction coordinate implies a stronger interaction between the carbene and the olefin, and hence, a greater selectivity. This is in keeping with the experimental observation that, as nucleophilicity of a carbene increases so does its selectivity.[28]

1.3 Diaminocarbenes

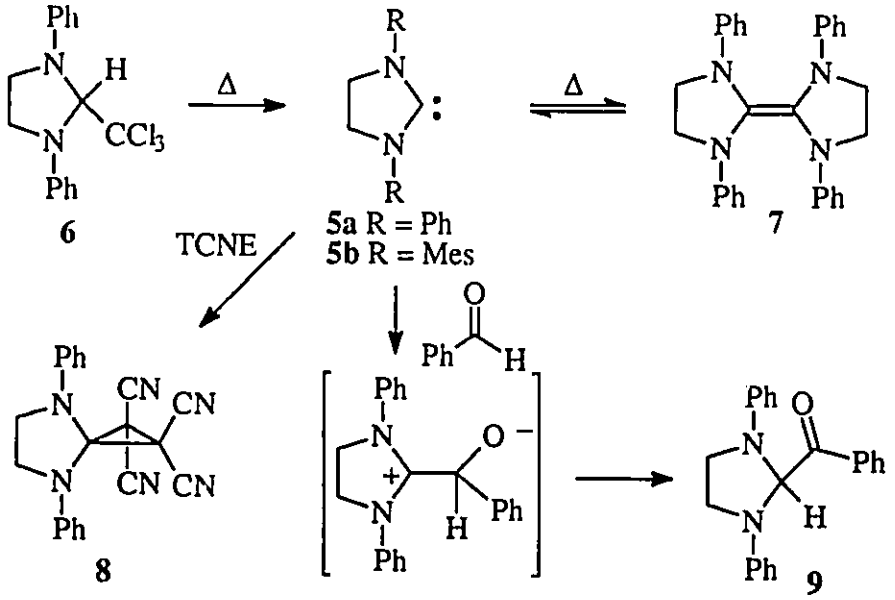
At the extreme nucleophilic end of the "philicity scale" are diaminocarbenes. The highly π–donating nitrogen substituents make these carbenes strongly nucleophilic and highly selective. These carbenes are very interesting and provide considerable insight into the structure and reactivity of nucleophilic carbenes in general.

In the 1960's, Wanzlick and co-workers demonstrated that diaminocarbenes **5a** can be readily generated by the thermolysis of **6** (Scheme 1).[30] In the absence of a suitable carbene trap, tetraaminoethylene **7** is formed via carbene dimerization. Moreover, **7** was also shown to dissociate at reasonable temperatures to re-generate **5a**, thus indicating that dimerization of **5a** is readily reversible. The fact that **5a** was easily generated from **6** or **7**, allowed either compound to be used as a thermal source of **5a**.

In contrast to the electrophilic nature of the other carbenes known at that time, **5a** clearly displayed strong nucleophilic reactivity. For example, this carbene did not react with electron rich alkenes such as α-pinene (a typical electrophilic carbene trap), however,

generation of **5a** in the presence of tetracyanoethylene (TCNE), a highly electron deficient alkene, resulted in an efficient [1+2] cycloaddition to give cyclopropane **8**. Also in keeping with its nucleophilic character, carbene **5a** was found to react with benzaldehyde by a mechanism that likely involves initial nucleophilic attack onto the carbonyl carbon of the aldehyde, to give a tetrahedral intermediate, followed by a 1,2-H shift to provide **9**. The reactions of **5a** with other carbonyl compounds, in which the carbene reactivity clearly mimics that of standard nucleophiles, have also been reported.[30,37]

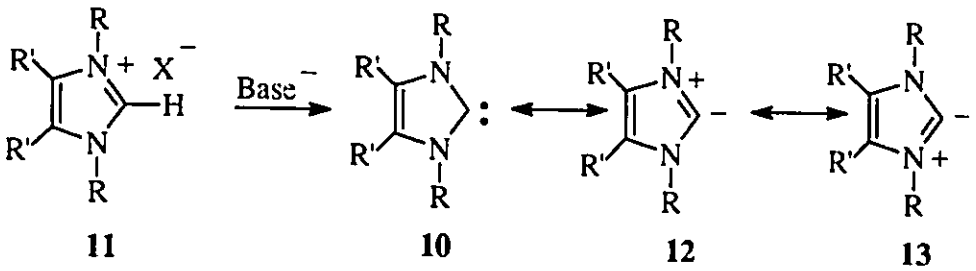
Scheme 1



Aduengo and co-workers demonstrated in 1991, that diaminocarbene **10a**, which is an unsaturated analog of **5a**, is actually stable enough to be isolated as a crystalline

compound, and is readily characterized by X-ray crystallography.[38] This was the first example of a 'bottle-able" carbene. Generation of **10a** involved deprotonation of **11a** with a strong base. Since this discovery, Arduengo and co-workers have reported the generation, isolation, and characterization of a number of analogs of **10a**, as well as their reactivity toward various substrates. The stability of carbenes **10** is in dramatic contrast to the high reactivity of other singlet carbenes which, in the absence of an appropriate carbene trap, undergo reactions such as insertion into the solvent, or dimerization.

Scheme 2



11 **10** **12** **13**

a R = 1-Ad, R' = H
b R = Mes, R' = H
c R = Me, R' = Me

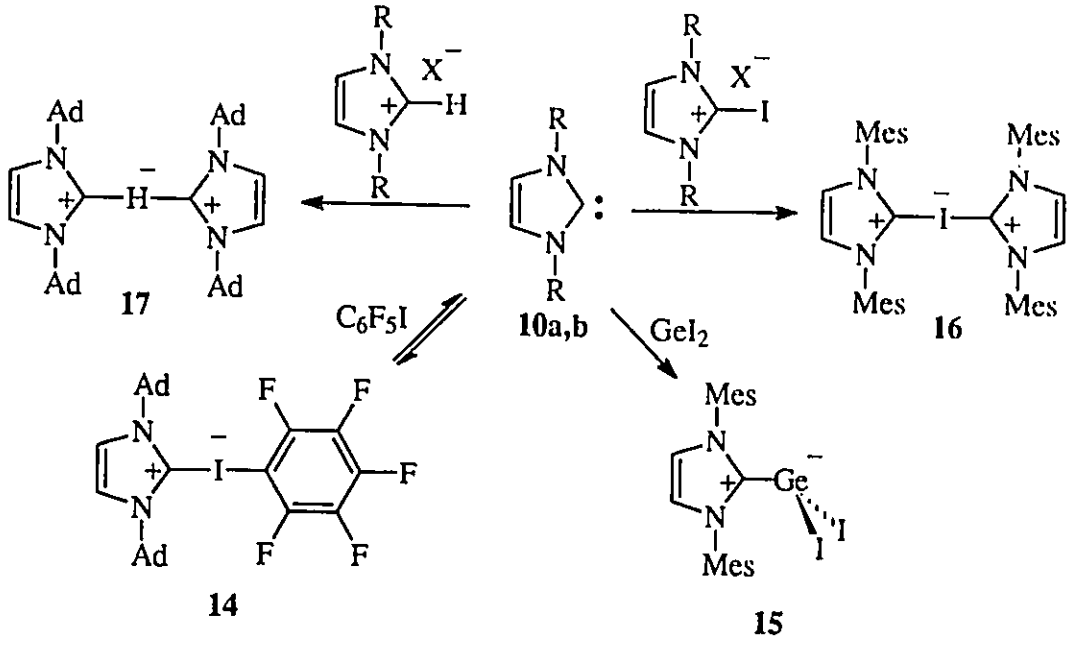
It was initially argued that significant π–donation from the nitrogen substituents into the carbene vacant p orbital leads to a major contribution from the ylidic structures **12** and **13** and therefore **10** cannot be referred to as "true" carbenes.[39] Although π-donation is certainly responsible for the stability and nucleophilicity of these carbenes, Arduengo

and co-workers refuted the belief that **10** are not "true" carbenes by showing, with the use of neutron and X-ray diffraction, that the electron density of **10c**, in agreement with density functional calculations, does in fact resemble that of a "true" carbene with only minor ylidic character. Moreover, the experimentally determined and the calculated electron distribution of **10c**, which are nearly identical, closely resemble the calculated electron distribution of $:CF_2$, a simple singlet carbene. In addition, the N-C-N bond angle for these carbenes was found to be between 101 and 102 degrees, which is in keeping with the expected range for singlet carbenes.

According to Arduengo, the stability of these highly nucleophilic carbenes is attributable to a complete lack of electrophilic reactivity (reactions derived from the vacant p orbital),[40] which in turn results from high electron density above and below the molecular plane of the carbene because of the nitrogen lone pair of electrons. Therefore, a nucleophile approaching from above or below the molecular plane of the carbene will not react with the formally vacant p orbital owing to considerable electron-electron repulsion.

The electrophilic reactivity of a carbene is important for insertion reactions into σ and π bonds and, moreover, it has been demonstrated that the more electrophilic a carbene, the more rapidly and less selectively it undergoes these reactions.[28] Therefore, because of the complete lack of electrophilic reactivity, carbenes **10** do not react with the solvent. Similarly, singlet carbene dimerization, which is believed to involve attack by the σ orbital of one carbene onto the p orbital of another carbene,[41-43] is also suppressed for the same reason. The absence of electrophilic reactivity in carbenes **10** therefore allows isolation of these species.

Scheme 3

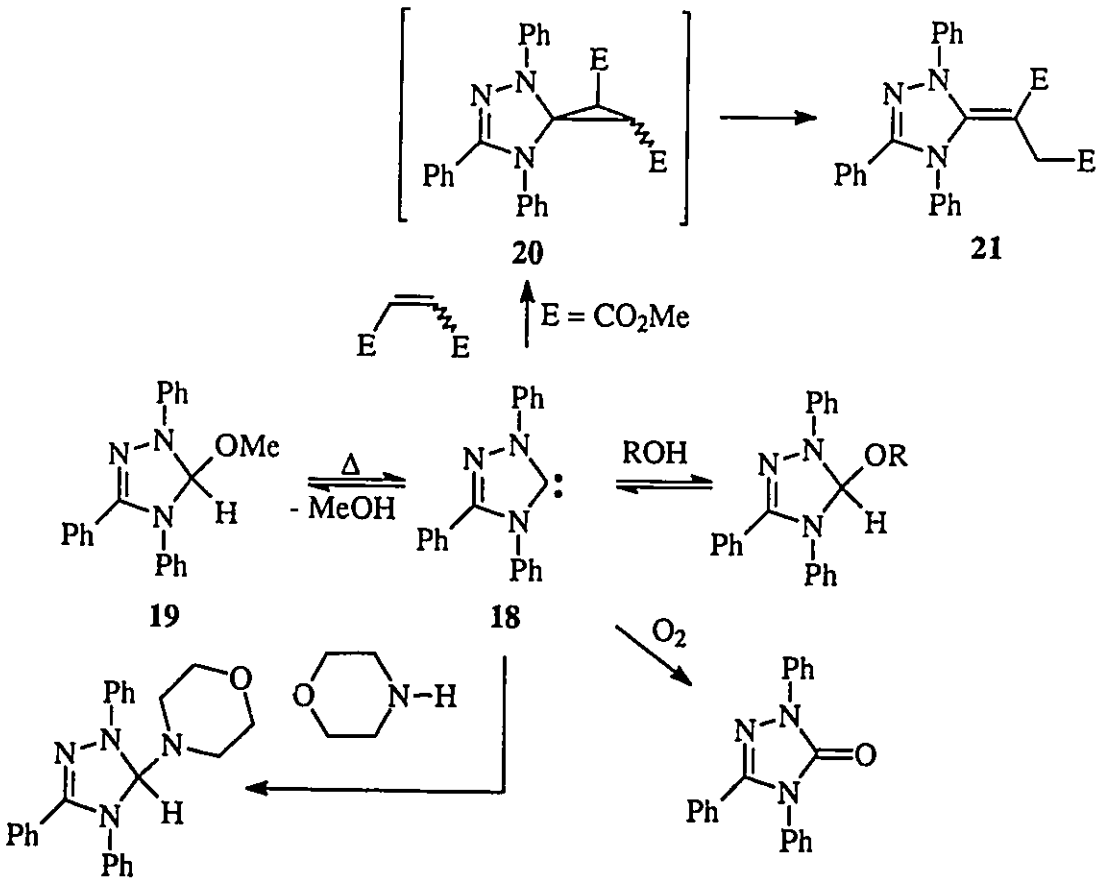


Carbenes **10** do, however, undergo reactions in a nucleophilic manner with a number of non-standard carbene traps as illustrated in Scheme 3. The reaction of **10a** with iodopentafluorobenzene results in the reversible formation of a "reverse ylide" (**14**).[44] The reaction of **10b** with GeI_2 gives adduct **15**.[45] This reaction closely mimics the "non-least motion pathway" for singlet carbene dimerization.[41-43] The reaction of **10b** with 2-iodo-1,3-dimesitylimidazolium salt gives a bis(carbene) adduct of iodine(+1) (**16**).[46] And similarly, the reaction of **10a** with 1,3-dimesitylimidazolium salt gives a bis(carbene) - proton complex (**17**).[47] Furthermore, the reaction of these stable carbenes (**10**) with a number of metal complexes has been reported to give some interesting products.[48,49] All of

the above carbene derived products were isolated as stable crystalline compounds and were characterized by X-ray crystallography.

It was initially believed that the ring double bond is required for isolation of the carbenes **10** because of the fact that **5a** readily undergoes dimerization (Scheme 1). However, Arduengo and co-workers[50] have recently isolated a stable diaminocarbene, **5b**, which is a close analog of **5a**. The kinetic stability of **5b** in comparison to **5a** is likely attributable to the extra steric hindrance of the carbene centre, provided by the bulky mesityl groups, which prevents dimerization.

Scheme 4



Recently, in 1995, Enders *et al.* reported the generation of **18**, another stable nucleophilic carbene.[51] This carbene is generated from the thermolysis of **19** at 80 °C and can be characterized by single crystal X-ray diffraction. The N-C-N bond angle for **18** was found to be 100.1°, which is similar to the corresponding angle for **10 a,b**, and **c** and also within the limits expected for a singlet carbene.

Carbene **18** undergoes reactions that are more typical of nucleophilic carbenes (Scheme 4), these include [1+2] cycloaddition with electron-deficient olefins to give a cyclopropane (**20**) (which in this case is followed by rearrangement to give **21**), insertion into O-H and N-H bonds, and also autoxidation in the presence of oxygen.

1.4 Dioxycarbenes

Like diaminocarbenes, dioxycarbenes (Figure 8) have a singlet ground state[52] and display considerable nucleophilic character. However, since oxygen is a poorer π-electron donor than nitrogen, dioxycarbenes are slightly less nucleophilic than their diamino counterparts and are therefore somewhat more reactive. Nevertheless, dioxycarbenes are still nucleophilic enough to undergo reactions with considerable selectivity.

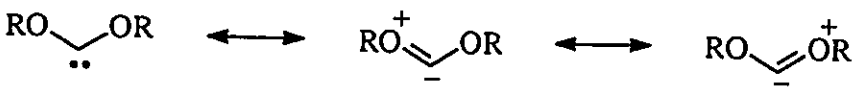


Figure 8

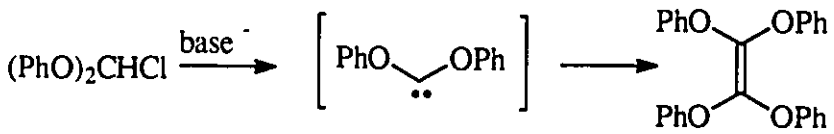
1.4.1 Dioxycarbene Precursors

(a) Early dioxycarbene precursors

Although dioxycarbenes had been reported in the literature as early as 1936,[53] it was not until the discovery of a convenient dioxycarbene source, first reported in 1964 by the groups of Hoffmann[54] and Lemal,[55] that the chemistry of these interesting carbenes began to be unveiled.

The literature prior to 1964 is scattered with reports of reactions in which dioxycarbenes may have been possible intermediates. For example, Scheibler and co-workers first reported in 1936 that diphenoxycarbene (**22**), or a carbenoid equivalent, is a likely intermediate in the reaction of diphenoxychloromethane (**23**) with a strong base.[53,56] Evidence for the intermediacy of diphenoxycarbene comes from the fact that tetraphenoxyethylene (**24**), presumably derived from carbene dimerization, was isolated from this reaction (Scheme 5). Base treatment of dialkoxychloromethanes also gives the corresponding dioxycarbenes, or carbenoid equivalents.[57] Note that, in contrast to diaminocarbenes **5a**, the dimerization of dioxycarbenes is not reversible.

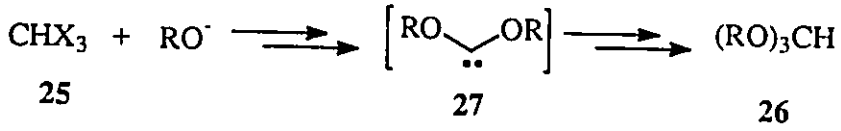
Scheme 5



23 **22** **24**

In 1960, Hine and co-workers claimed that the reaction of haloforms (**25**) with alkoxides gave orthoesters (**26**) and that the mechanism of this reaction likely involves dioxycarbenes (**27**) as possible intermediates[58] (Scheme 6). The proposed mechanism of this reaction is complex and also includes the intermediacy of other substituted carbenes.

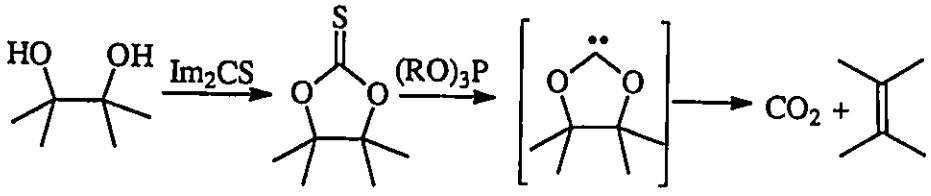
Scheme 6



25 **27** **26**

In 1963, Corey's group showed that desulfurization of 1,2-thionocarbonates **28**, derived from 1,2-diols, likely gave cyclic dioxycarbenes (**29**) which fragment to produce carbon dioxide and the corresponding olefin.[59,60] (Scheme 7). This finding was developed more as a synthetic route for converting 1,2-diols to the corresponding olefin, than as a route to dioxycarbenes. It is now well known that cyclic five membered dioxycarbenes do, in fact, undergo such decomposition[55,56] which is surely driven by the thermodynamic stability of the products.

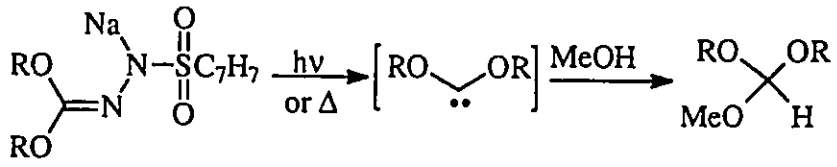
Scheme 7



28 **29**

Crawford and Rapp in 1964 demonstrated that the thermal or photochemical decomposition of sulfonylhydrazone salts, such as **30**, gave dioxycarbenes **27**, or carbenoid equivalents.[61] Carbene formation from this source was substantiated by an experiment in which the intermediate carbene was trapped with methanol by an overall O-H insertion reaction (*vide infra)* (Equation 4) to give the corresponding orthoformate (**31**).

Scheme 8



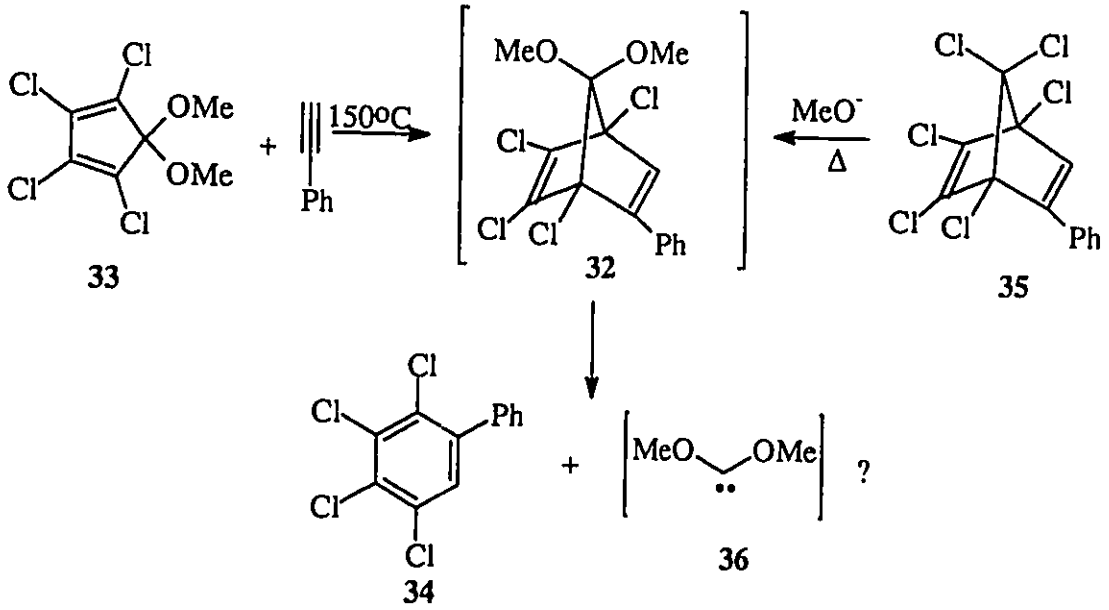
Although the above reports indicate the possible intermediacy of dioxycarbenes, these systems, because of their complex reaction conditions, were difficult ones from which to extract information about the properties of these interesting carbenes. In addition, there was considerable ambiguity in most of the cases, as to whether the reactive intermediate was actually a free carbene or a carbene-metal complex (carbenoid). An investigation of 7,7-norbornadienone ketals as potential dioxycarbene sources led to the development of the first well-established, unambiguous source of these carbenes.

(b) Norbornadienone Ketals

In 1955, McBee and co-workers reported[62,63] that the attempted preparation of 7,7-norbornadienone ketal **32** by the Diels-Alder reaction (150 °C) of tetrachloro-cyclopentadienone ketal **33** with phenylacetylene did not give the expected [4+2] cycloadduct, but instead, led to the isolation of 2,3,4,5-tetrachlorobiphenyl (**34**). Similarly, the attempted preparation of **32** by treatment of **35** with sodium methoxide under thermal conditions also gave **34** as the only identified product[63] (Scheme 9).

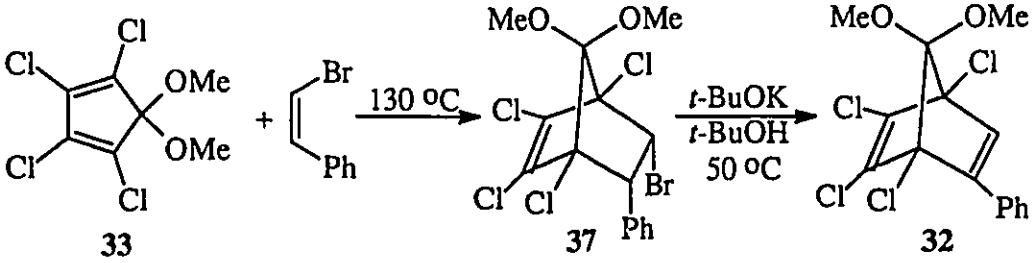
These results were attributed to the initial formation of the desired ketal (**32**), which undergoes a cycloelimination under the reaction conditions to give **34** and dimethoxycarbene (**36**). Although dimethoxycarbene was postulated as a likely intermediate in this reaction, no direct experimental evidence for its formation was observed at that time.

Scheme 9



In the next decade, a re-investigation of McBee's results was conducted by the groups of Hoffmann[54] and Lemal[55] in hope of establishing **32** as a dioxycarbene precursor. In 1964 both of these groups independently reported that 7,7-norbornadienone ketal **32** can indeed be formed as a relatively stable compound. Hoffmann and co-workers demonstrated a two-step synthesis of **32** which involves the Diels-Alder reaction of tetrachlorocyclopentadienone ketal (**33**) with β-bromostyrene (130 °C) to give the thermally stable norbornenone ketal **37**, followed by an elimination reaction using a strong base (t-BuOK, 50°C) to give **32** (Scheme 10). Lemal and co-workers, on the other hand, simply found that the Diels-Alder reaction between **33** and phenylacetylene can proceed at a lower temperature (70 °C) than used by McBee, and that under these conditions, **32** can be isolated in good yield.

Scheme 10

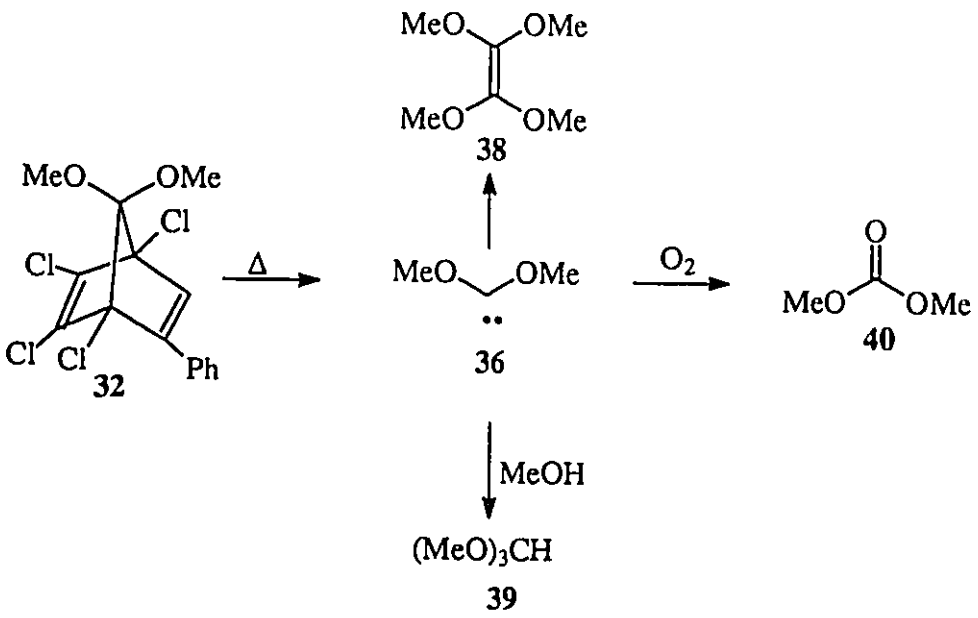


33 **37** **32**

Of primary interest, was the fact that both of these groups demonstrated that **32** undergoes thermal decomposition at temperatures ranging from 100 to 150 °C to give tetramethoxyethylene (**38**) in addition to the previously observed tetrachlorobiphenyl **34** (Scheme 11). Tetramethoxyethylene (**38**), a product not reported by McBee, was

believed to be derived from carbene dimerization and therefore provided direct experimental evidence that the thermolysis of **32** does in fact lead to the generation of dimethoxycarbene (**36**). Additional evidence for the intermediacy of dimethoxycarbene from this source was based on the facts that thermolysis of **32** in the presence of methanol gave trimethylorthoformate (**39**) by an overall O-H insertion reaction of the carbene (*vide infra*), and that thermolysis of **32** in the presence of oxygen led to dimethylcarbonate (**40**) as a carbene autoxidation product[54,64] (Scheme 11).

Scheme 11

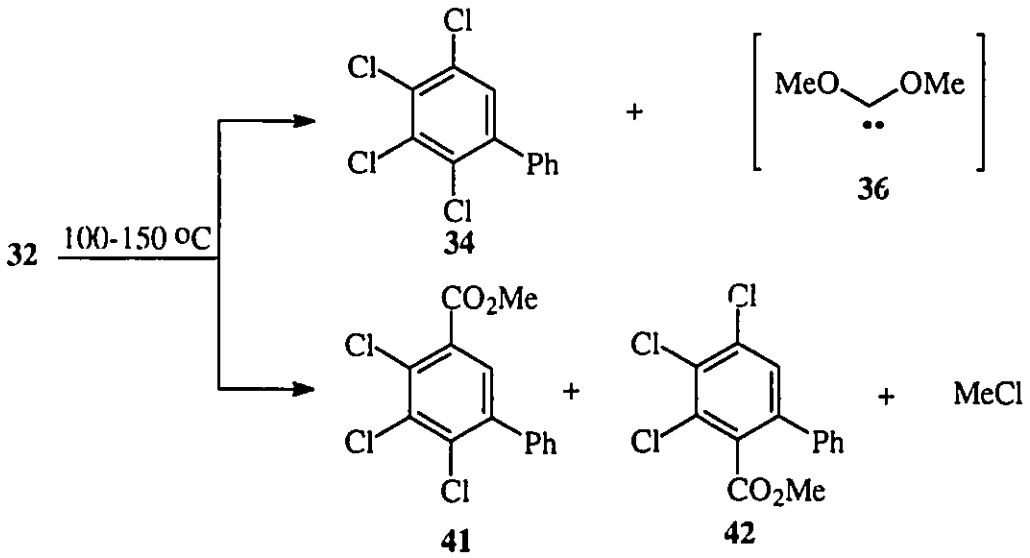


Based on these findings, 7,7-norbornadienone ketals became the first well-established thermal precursors of dioxycarbenes[64-67] and many of the early studies on the reactions of these carbenes[68-73] were conducted using this source. Norbornadienone ketals are very convenient dioxycarbene sources since they are easily prepared, they decompose at reasonable temperatures, they can be used in a variety of solvents, and most importantly, in contrast to previously known dioxycarbene sources, they do not require a

co-reactant which may interfere with the desired carbene reaction. Moreover, there is no ambiguity whether this source leads to the generation of a carbene or a carbenoid.

There are, however, some fundamental problems associated with the use of 7,7-norbornadienone ketals as dioxycarbene precursors. As mentioned above, carbene formation involves the co-production of the non-volatile by-product **34**. In addition, a side reaction which competes with carbene formation also gives non-volatile products, **41** and **42** (Scheme 12). Therefore, the use of **32** as a dioxycarbene source requires isolation of the desired carbene-derived products from the non-volatile by-product (**34**) and side reaction products (**41** and **42**). Another inherent shortcoming of this dioxycarbene source is that, because of the difficulty in preparing unsymmetric cyclopentadienone ketals, only symmetric dioxycarbenes (i.e. dimethoxycarbene) can be generated. Nonetheless, 7,7-norbornadienone ketals served as the only well-established dioxycarbene source for the next fifteen years.

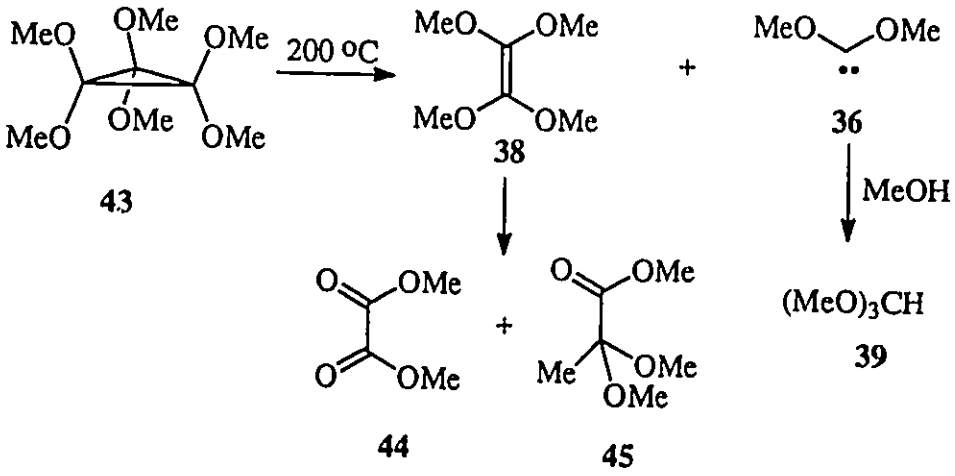
Scheme 12



(c) Hexamethoxycyclopropane

The generation of dioxycarbenes from a single source, as in the case of **32**, is very convenient in that the carbene can be generated without interference from a co-reactant. In 1985, Moss and co-workers investigated the possibility of using the thermal decomposition of hexamethoxycyclopropane (**43**) to generate dimethoxycarbene.[74] It was postulated that **43** may undergo a thermal [1+2] cycloreversion, as reported for perfluorocyclopropane,[75] to give dimethoxycarbene (**36**) and tetramethoxyethylene (**38**). It was found that **43** does in fact undergo a thermal reaction, but only at temperatures as high as 200 °C, to yield **44**, **45**, and **39**. The products **44** and **45** are known thermolysis products of tetramethoxyethylene (**38**) at this temperature[76] and therefore provide evidence of its formation. Tetramethoxyethylene can be formed directly from the cycloreversion of **43**, and via dimerization of dimethoxycarbene. The orthoformate **39** is likely derived from the capture of dimethoxycarbene with methanol (the origin of methanol was unclear).

Scheme 13

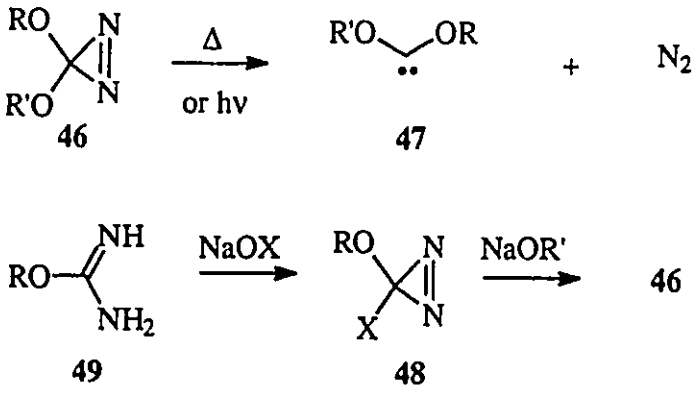


Unfortunately, the inconveniently high temperatures required for the thermolysis of **43** rule out its use as a dimethoxycarbene precursor, primarily because of the thermal instability of most carbene traps at 200 °C.

(d) Diazirines

Diazirines have been used as precursors for a variety of carbenes.[77] In 1989, Moss and co-workers reported that 3,3-dioxydiazirines (**46**) undergo thermal or photochemical cycloelimination of nitrogen to give the corresponding dioxycarbenes (**47**) (Scheme **14**). Both symmetric (R = R') and unsymmetric (R ≠ R') dioxycarbenes can be generated by this method and carbene formation is a remarkably clean process since the only by-product is nitrogen (Scheme **14**).

Scheme 14



Dioxydiazirines (**46**) are prepared by the "diazirine exchange reaction" of readily-obtained 3-oxy-3-halodiazirines (**48**) with alkoxide.[29] Halodiazirines **48**, in turn, are prepared by Graham oxidation[78] of the corresponding amidine (**49**) with hypohalite. The

diazirine exchange route is convenient in the sense that a variety of symmetric and unsymmetric dioxycarbene precursors can be prepared from a common precursor (**48**). Currently a handful of dioxycarbenes are available by this route, these include: dimethoxycarbene,[52] methoxyphenoxycarbene,[79] methoxy(2,2,2-trifluoroethoxy)carbene,[80] and bis(2,2,2-trifluoroethoxy)carbene.[80]

Unfortunately dioxydiazirines are unstable and have been reported to undergo explosion under certain conditions. Therefore, extreme caution must be used when working with these compounds. Because of their instability dioxydiazirines cannot be isolated, they can only be obtained at high dilution in hydrocarbon solvent and must be used immediately upon preparation ($\tau_{1/2}$= 20 - 60 min. in pentane at 25 °C).[29] As a result, diazirines are inconvenient dioxycarbene sources, especially for synthetic applications.

Nevertheless, diazirines are currently the only known photochemical source of dioxycarbenes. Consequently, these precursors permitted the first direct IR and UV spectroscopic observation of dioxycarbenes. In addition, diazirines are well suited for matrix isolation and kinetic studies which has allowed the determination of absolute rate constants, and activation parameters of a variety of dioxycarbene reactions.[52,81,82]

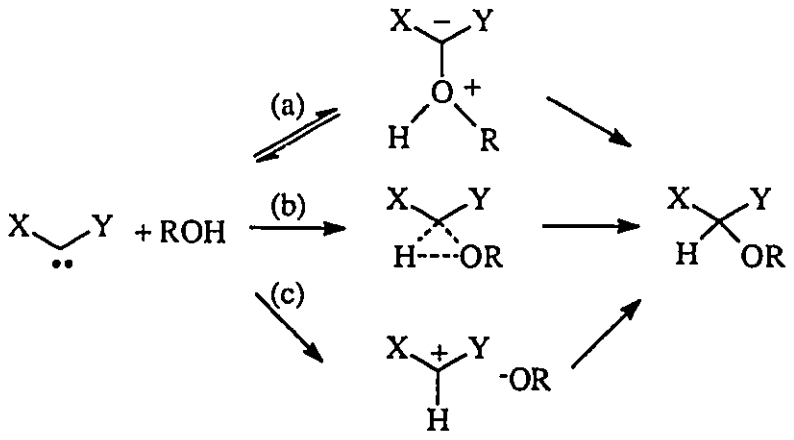
Because of their unique electronic character, dioxycarbenes undergo a number of reactions with a high degree of selectivity. These reactions are both mechanistically interesting and synthetically valuable. Some typical reactions of dioxycarbenes are illustrated in the following section.

1.4.2 Reactions of Dioxycarbenes

(a) Reaction of dioxycarbenes with alcohols

The reaction of a singlet carbene with an alcohol (or phenol) results in an overall O-H insertion of the carbene. As seen previously, this reaction can be used to confirm or to establish the intermediacy of a carbene. The O-H insertion may proceed by one of three possible mechanistic pathways (Scheme 15): (a) by electrophilic attack of the carbene onto the oxygen atom of the alcohol to form an ylide (possibly reversibly), which then undergoes an oxygen to carbon proton transfer; (b) by a concerted O-H insertion involving three atoms; or (c) by proton transfer from the alcohol to the carbene, followed by ion pair collapse.

Scheme 15



Although all three mechanisms lead to the same product, electrophilic carbenes would be expected to react via pathway (a) or (b), whereas nucleophilic carbenes, such as dioxycarbenes, would be expected to follow mechanism (c), or possibly (b).

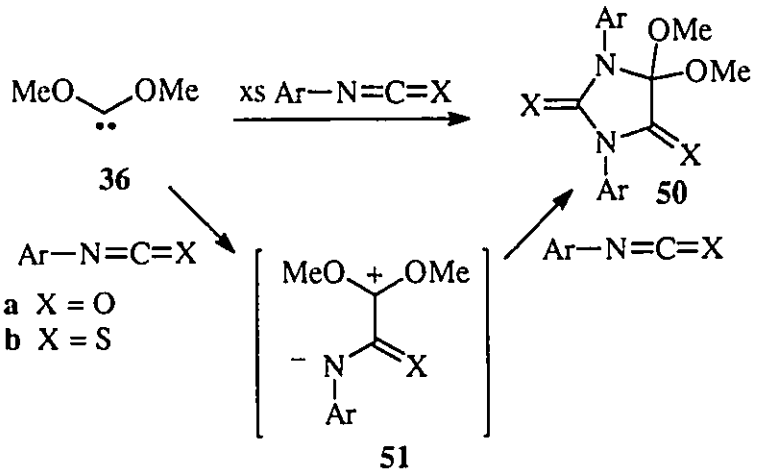
The ability to generate dioxycarbenes photochemically using the diazirine precursor has allowed Moss and co-workers to investigate the kinetics of this very basic reaction of dioxycarbenes using laser flash photolysis.[81] For the reaction of dimethoxycarbene with oligomeric MeOH in pentane at 20 °C, the second order rate constant is $6.36 \pm 0.39 \times 10^6$ $M^{-1}s^{-1}$, whereas, that for the corresponding reaction with oligomeric MeOD under the same conditions is $1.95 \pm 0.27 \times 10^6$ $M^{-1}s^{-1}$. Thus, the kinetic isotope effect (KIE) is $k_H/k_D = 3.3 \pm 0.5$. This relatively large KIE indicates substantial cleavage of the O-H bond in the transition state for O-H insertion, which is suggestive of mechanism (c) or possibly (b), as expected for the nucleophilic carbene.

(b) Reaction of dioxycarbenes with isocyanates or isothiocyanates

The thermal generation of **36**, from 7,7-norbornadienone ketal **32**, in the presence of either aryl isocyanates (ArNCO) or aryl isothiocyanates (ArNCS) was found to provide 5,5-dimethoxyhydantoins **50a** or 5,5-dimethoxythiohydantoins **50b**, respectively.[69] The proposed mechanism which accounts for the products **50a** or **50b** proceeds with the initial formation of a dipolar intermediate **51** by the reaction of **36** with the arylisocyanate (or arylisothiocyanate). The product, **50**, is then derived by a regioselective [3+2] cycloaddition reaction between the 1,3-dipole (**51**) and the C=N bond of another molecule of arylisocyanate (or arylisothiocyanate). A linear free energy plot, constructed for

competition experiments between a series of aryl isocyanates and phenyl isothiocyanate for a limited amount of dimethoxycarbene,[72] gave a ρ–value of +2.0. The positive sign of the ρ–value[83] clearly indicates that the carbene is reacting as a nucleophile with respect to aryl isocyanates.

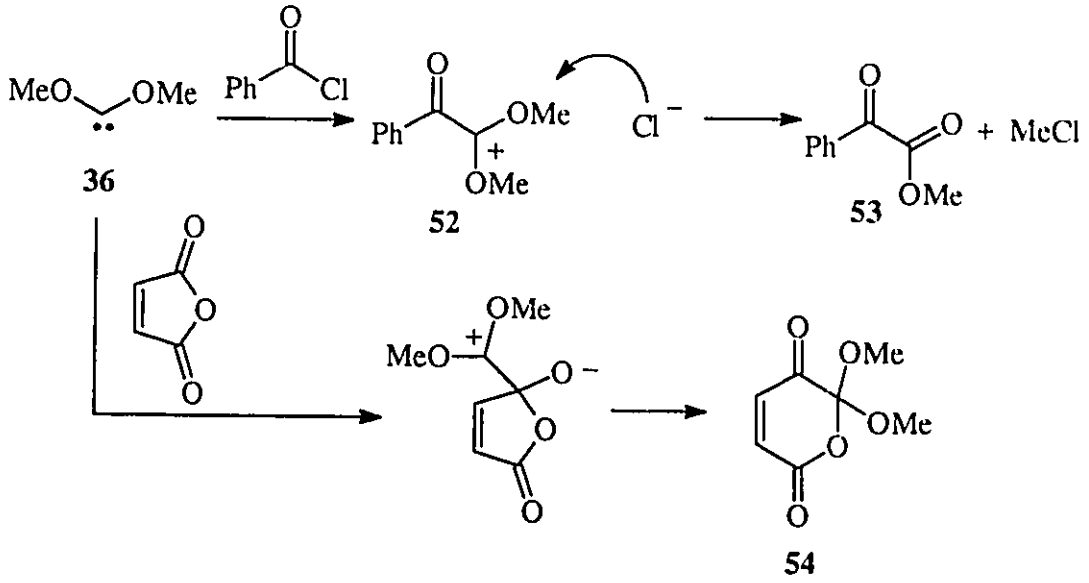
Scheme 16



(c) Reaction of dioxycarbenes with carbonyl compounds

The reaction of dioxycarbenes with certain reactive carbonyl compounds is clearly indicative of the nucleophilic nature of these carbenes. Hoffmann and co-workers,[70] demonstrated that the reaction of dimethoxycarbene (**36**) with benzoylchloride gives **52**. The mechanism for this reaction involves nucleophilic attack of the carbene onto the carbonyl carbon, to give **53** via a tetrahedral intermediate which loses Cl^-, then followed by demethylation of **52** with Cl^- to provide the observed product (**53**).

Scheme 17

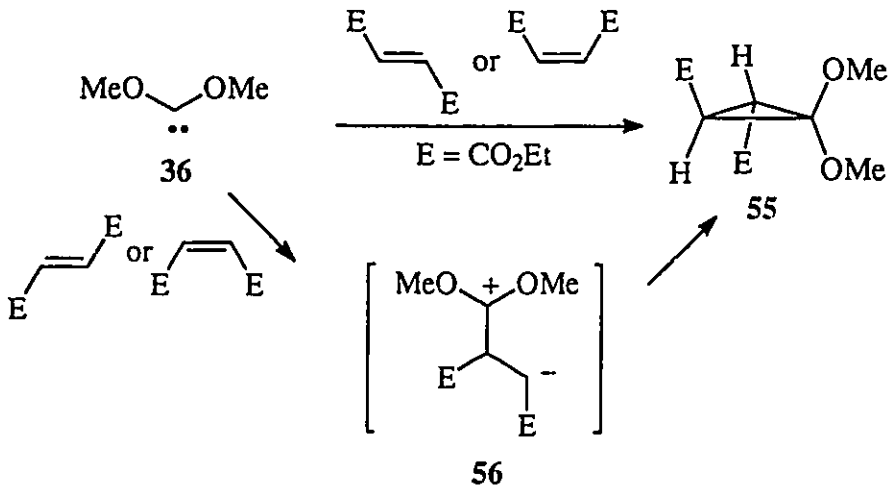


Recently Pole and Warkentin[84] have demonstrated that dioxycarbenes, generated from the corresponding dioxyoxadiazoline (*vide infra*, Results and Discussion), undergo reaction with anhydrides as illustrated in Scheme 17 to give a ring expansion product **54** by an overall C-O insertion of the carbene. This reaction is believed to proceed via an initial nucleophilic attack of the carbene onto the carbonyl carbon of the anhydride, followed by reformation of the carbonyl moiety concurrent with ring expansion.

(d) Reaction of dioxycarbenes with alkenes

Because of their nucleophilic nature, dioxycarbenes do not undergo reaction with electron rich olefins such as ketene acetals,[65] cyclohexene,[65] or other alkyl substituted alkenes.[52] These carbenes, however, react effectively with electron deficient alkenes such as ethyl cinnamate, styrene, diethyl fumarate, or diethyl maleate.

Scheme 18

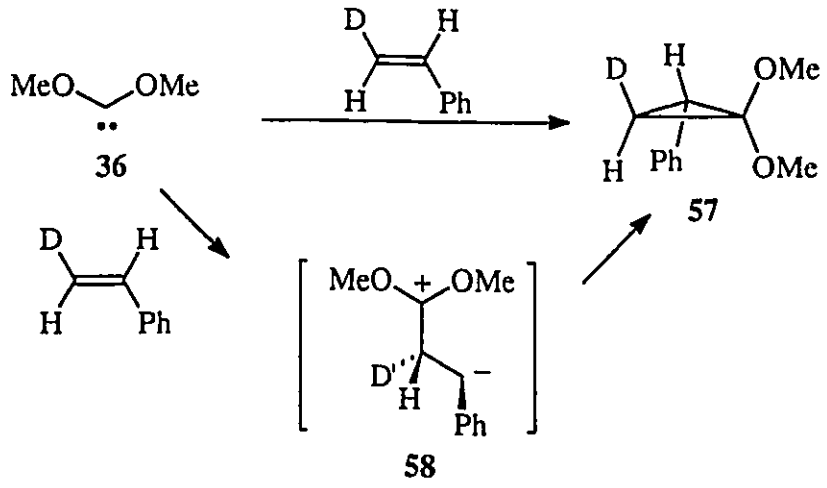


Dimethoxycarbene (**36**), thermally generated from the 7,7-norbornadienone ketal precursor (**32**), reacts with diethyl fumarate or diethyl maleate to give only the *trans* substituted cyclopropane **55**.[70] The *trans*-selective formation of **55** can be attributed to stepwise nucleophilic addition of the carbene onto one of the carbon atoms of either fumarate or maleate, in a Michael type reaction, to generate a common dipolar intermediate, **56**. The 1,3-dipole (**56**) can then collapse to the thermodynamically favored *trans*-cyclopropane (**55**). An alternative mechanism may involve a concerted [1+2] cycloaddition between the carbene and the olefin followed by, in the case of diethyl maleate, thermal isomerization of an initially formed *cis*-cyclopropane to the thermodynamically favored *trans*-adduct via the dipolar intermediate **56**.

In contrast to the above result, Moss and co-workers demonstrated that the thermolysis of 7,7-norbornadienone ketal **32** in the presence of either cis or trans-β-

deuteriostyrene (illustrated only for trans) led to stereospecific addition of **36** with complete retention of alkene geometry (Scheme 19) to give **57**.[73] The retention of stereochemistry indicates that this cycloaddition likely proceeds by a concerted mechanism. It should be noted, however, that stereospecific formation of **57** does not preclude a stepwise mechanism, via **58**, in which the rate of closure is faster than the rate of isomerization of **58**. Indeed, the dipolar intermediate **58** would be expected to be considerably less stabilized than **56**.

Scheme 19

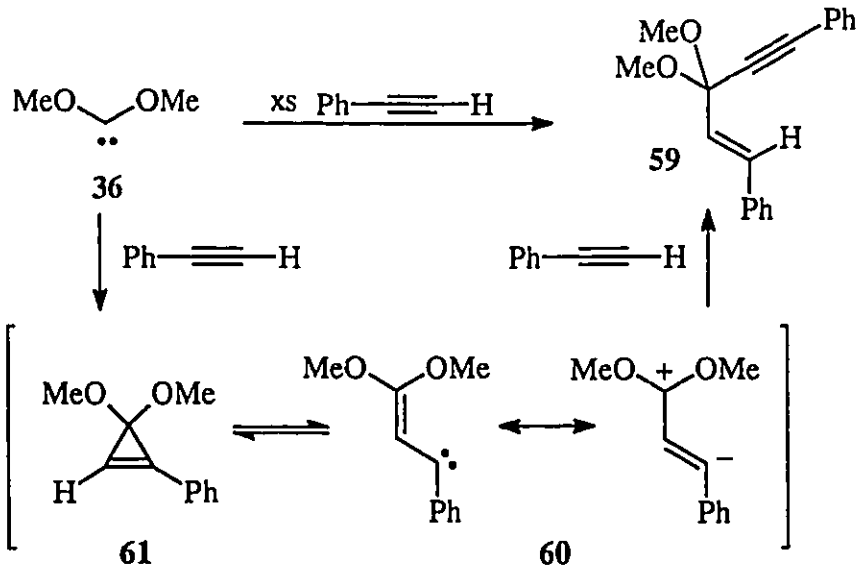


(e) Reaction of dioxycarbenes with alkynes

In comparison to the reactions of dioxycarbenes with alkenes, reactions with alkynes have also led to the formation of products that are derived from dipolar intermediates. For example, the reaction of **36** with phenylacetylene gives a 2 to 1 adduct, **59**, in good yield.[70] The formation of this product can be attributed to a mechanism

involving an intermediate 3,3-dioxyvinylcarbene **60** which is isoelectronic with the corresponding 1,3-dipole. This intermediate (**60**) can be attributed to either, (a) a concerted [1+2] cycloaddition, to give cyclopropenone ketal **61**, followed by regioselective ring opening as illustrated in Scheme 20, or to (b) direct regioselective addition of the carbene onto the unsubstituted alkyne carbon atom. In either scenario, upon formation, **60** reacts with another unit of phenylacetylene by protonation of the carbene/vinyl-anion moiety, followed by ion pair collapse to give **59**.

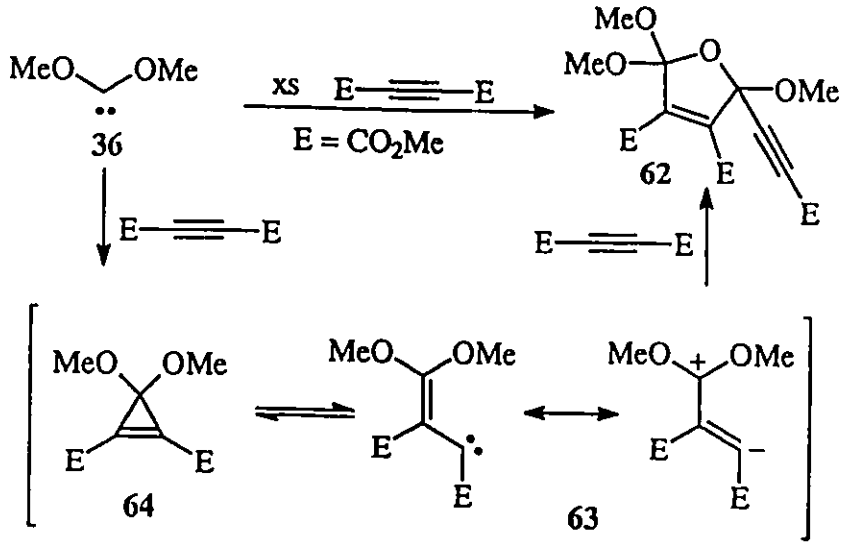
Scheme 20



The reaction of **36** with dimethylacetylenedicarboxylate (DMAD) also gives a 2 to 1 adduct. Hoffmann and co-workers reported that this reaction leads to the formation of an interesting product, **62**, in 30 - 40 % yield[70] (Scheme 21). The mechanism which accounts for the formation of **62** also involves a 3,3-dioxyvinylcarbene/1,3-dipole

intermediate (63). As shown in the previous example the vinylcarbene intermediate may be formed either via a cyclopropenone ketal (64), or by direct stepwise addition of 36 onto one of the carbon atoms of the alkyne. The product (62) can then be derived by a formal [3+2] cycloaddition between 63 and the C=O bond of another molecule of DMAD.

Scheme 21



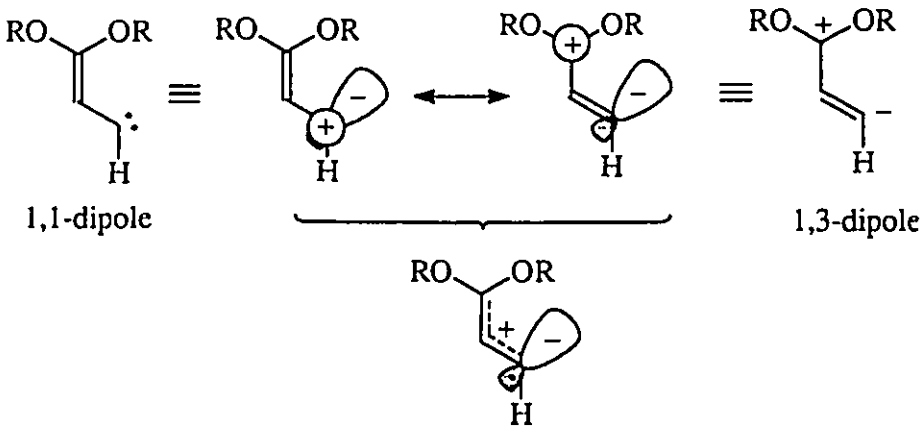
The above mechanisms are of particular interest since they indicate that the reaction of a dioxycarbene with an alkyne leads to the *in situ* formation of another transient intermediate, a 3,3-dioxyvinylcarbene/1,3-dipole.

1.5 3,3-Dioxyvinylcarbenes

3,3-Dioxyvinylcarbenes (Scheme 21) are a very interesting and synthetically useful class of reactive intermediates. Like dioxycarbenes, 3,3-dioxyvinylcarbenes have a singlet ground state (the ΔE_{ST} has been estimated to be 8.7 kcal/mol)[85] and also display considerable nucleophilic character. These properties can be attributed to conjugative π-

electron donation into the formally vacant carbenic p-orbital by the two oxygen substituents.

Scheme 22



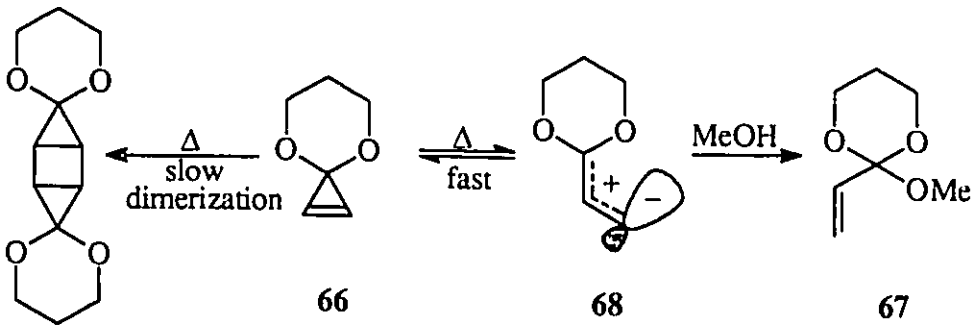
65

It has been demonstrated that the 3,3-dioxyvinylcarbenes can react either as 1,1- or 1,3-dipoles (*vide infra).* In agreement with this observed dual reactivity, ab-initio calculations with electron correlation (at the MP2/6-31^{++}G(d)//6G-31^{++}G(d) level) on 3,3-dihydroxyvinylmethylene reveal that the *anti* π-delocalized closed shell singlet (**65**, R=H) is the most stable state of this vinylcarbene.[85] 3,3-Dioxyvinylcarbenes, which can be represented as either 1,1- or 1,3 dipoles, will hereafter be illustrated as π-delocalized vinylcarbenes **65** (Scheme 22).

The only well-established direct route to generating 3,3-dioxyvinylcarbenes is by the thermal ring opening of the corresponding cyclopropenone ketals. The initial recognition of the intermediacy of a 3,3-dioxyvinylcarbene from the thermal ring opening of a cyclopropenone ketal, was inferred from the fact that heating **66** in the presence of

methanol at 80 °C in benzene gave orthoacrylate **67**. The half-life of this reaction is less than 15 minutes. Moreover, the thermal reaction of **66** at 80 °C in the absence of an effective reaction partner leads to the recovery of the cyclopropene along with the slow formation of a dimer, ($t_{1/2}$ = 10 h, benzene, 80 °C) which is derived from a thermal [2+2] cycloaddition of **66**. This result indicates that the thermal ring opening of **66** is reversible, and that ring closure of the vinylcarbene is competitive with intermolecular reaction with an appropriate substrate, or thermal [2+2] cycloaddition of **66**.[86] The intermediacy of 3,3-dioxyvinylcarbenes from the thermal reaction of cyclopropenone ketals was later unambiguously established based on the large number of thermal reactions with various substrates, which would require the intermediacy of such a species.

Scheme 23



Thermally generated, π-delocalized 3,3-dioxyvinylcarbenes have been shown to participate productively in [1+2], [3+2], and [3+4] cycloaddition reactions with a variety of electron deficient substrates to provide a number of interesting and synthetically useful cycloadducts.[85] The cycloadditions are rate determining and generally very efficient.

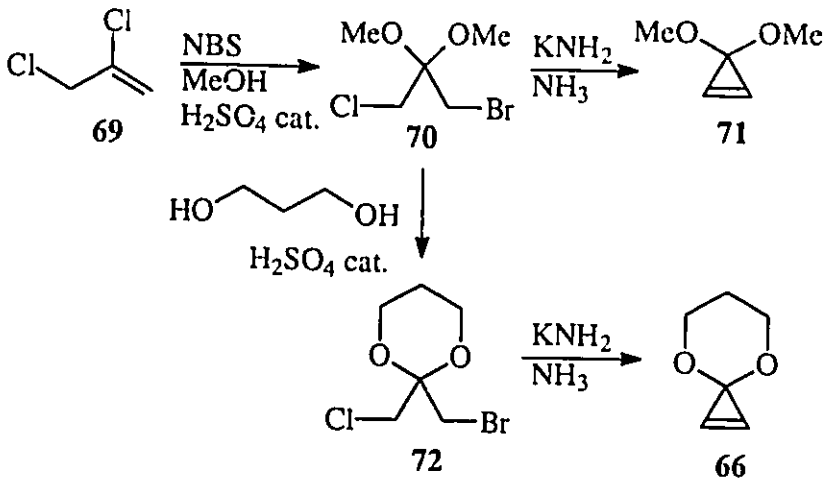
Moreover, these reactions proceed with periselectivity that is, in most cases, completely substrate dependent.

1.5.1 Generation of 3,3-Dioxyvinylcarbenes

The preparation of cyclopropenone ketals was developed by Baucom and Butler[87] in 1972. As outlined below (Scheme 24), the preparation involves treatment of 2,3-dichloropropene (**69**) in methanol with NBS (N-bromosuccinimide) to provide 1-bromo-3-chloro-2,2-dimethoxypropane (**70**). Subsequent reaction of **70** with potassium amide in liquid ammonia results in cyclization to 3,3-dimethoxycyclopropenone ketal **71**. The spirobicyclic analog, **66**, is derived by treating **70** with 1,3-propanediol in the presence of a catalytic amount of H_2SO_4, leading to the formation of **72**, followed by cyclization. Cyclopropenone ketal **66** undergoes the same reactions as **71** but has the advantage of being considerably more stable. Cyclopropenone ketal **66** can be handled easily at room temperature and can be stored at - 20 °C for over six months without significant decomposition. Consequently, **66** was widely used in the study of 3,3-dioxyvinylcarbene reactions.

Early studies on the thermal reactions of cyclopropenone ketals with a variety of substrates proved to be rather interesting.[87-89] However, it was not until the extensive study, conducted by Boger and Brotherton, on the thermal reactions of **71** and **66**, that the intermediacy of 3,3-dioxyvinylcarbenes was established.

Scheme 24

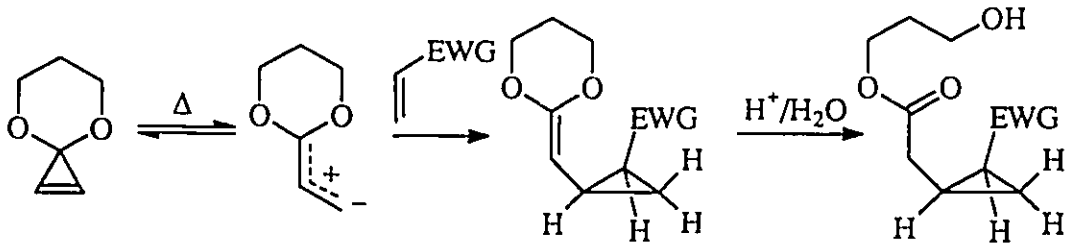


1.5.2 Reactions of 3,3-Dioxyvinylcarbenes

(a) [1+2] Cycloaddition of 3,3-dioxyvinylcarbenes with alkenes

In keeping with their nucleophilic nature, 3,3-dioxyvinylcarbenes do not undergo reaction with cyclohexene or ketene acetals.[85] However, the generation of a 3,3-dioxyvinylcarbene in presence of a moderately electron deficient olefin[85,86,90] (one without geminal electron withdrawing groups) such as methyl acrylate, methyl methacrylate, acrylonitrile, methacrylonitrile, or dimethyl fumarate leads to the capture of the intermediate 3,3-dioxyvinylcarbene with the olefin in a [1+2] cycloaddition. As illustrated for **68** in Scheme 25, the [1+2] cycloaddition gives a cyclopropane ketene acetal (**73**). Because of the fact that ketene acetals are labile compounds which are prone to hydrolysis or polymerization, they are intentionally hydrolyzed in aqueous acid to give the corresponding cyclopropane esters (**74**) which can be isolated in modest yields by chromatography.

Scheme 25



66 68 73 74

As seen above for dioxycarbenes, the formation of a cyclopropane by the reaction of a carbene with an alkene may involve a concerted [1+2] cycloaddition, or stepwise addition via a zwitterionic intermediate. The reaction of 3,3-dioxyvinylcarbenes with moderately electron deficient alkenes has been shown to proceed with absolute rate constants that are relatively insensitive to solvent polarity which suggests that a zwitterionic intermediate is not formed, and that a concerted pathway is likely operative for this reaction.

Contrary to expectations, the [1+2] cycloadditions lead to the thermodynamically less favorable *cis* isomers **73** as the major cycloadducts. In addition, the *cis*-stereoselectivity was found to decrease with increasing solvent polarity. This result is consistent with a [1+2] cycloaddition in which the observed stereoselectivity is derived from a proximal endo stabilizing interaction between the olefin electron withdrawing substituent and the allylic cation component of the π-delocalized singlet vinylcarbene (Figure 9).

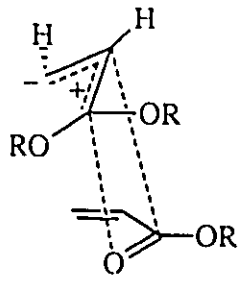
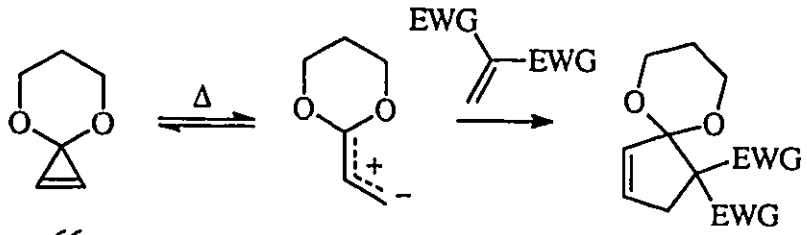


Figure 9

(b) [3+2] Cycloaddition of 3,3-dioxyvinylcarbenes with alkenes

In contrast to the [1+2] cycloadditions illustrated above, the reaction of 3,3-dioxyvinylcarbenes (**68**) with highly electron deficient alkenes, such as benzylidenemalononitrile or diethyl benzylidenemalonate, led to a [3+2] cycloaddition reaction. This reaction gives substituted cyclopentenone ketals **75** in good to excellent yield[85,86,90,91] (Scheme 26).

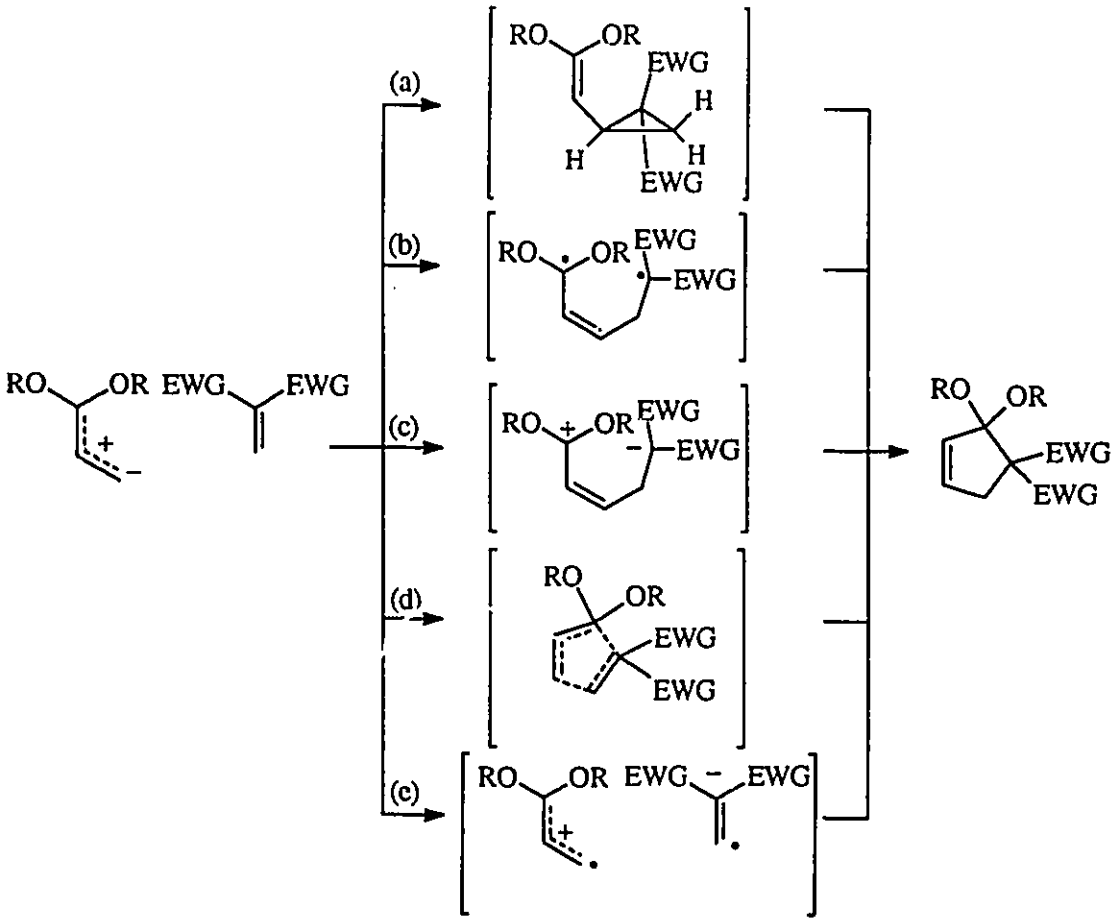
Scheme 26



A number of possible mechanistic pathways may be envisioned for the [3+2] cycloaddition (Scheme 27). These include: (a) initial formation of a cyclopropane ketene acetal (as shown above in Scheme 25) by a [1+2] cycloaddition, followed by facile biradical or zwitterionic vinylcyclopropane rearrangement; (b) a stepwise addition-

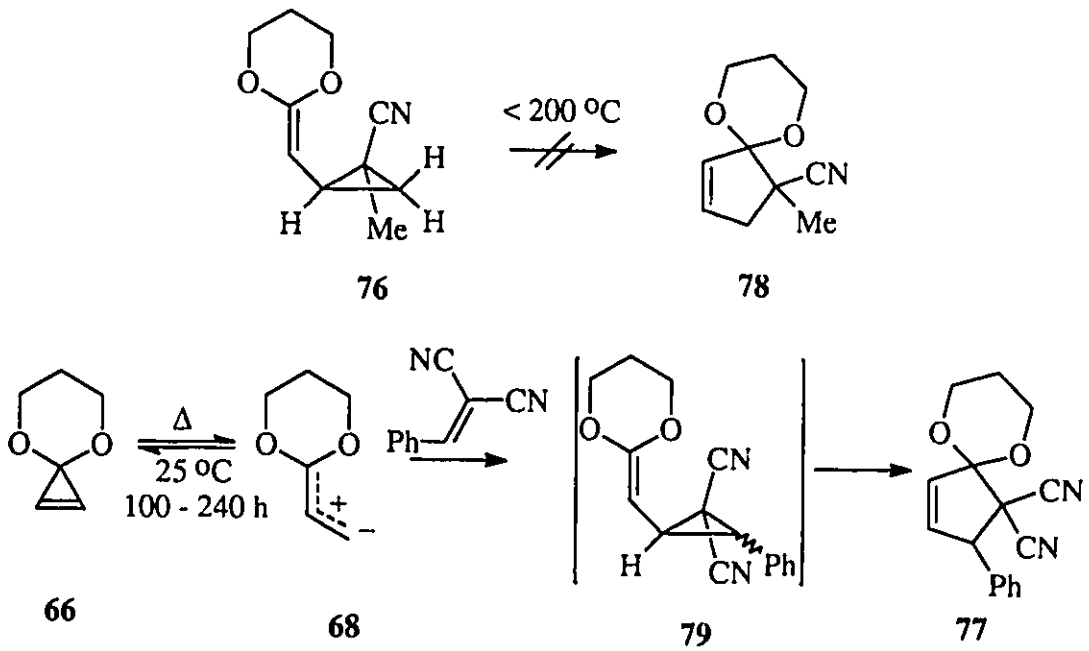
cyclization of a partially delocalized triplet carbene via a biradical intermediate; (c) a stepwise addition-cyclization of a partially delocalized singlet carbene via a zwitterionic intermediate; (d) a concerted [π2s+π2a], [3+2] cycloaddition of the π-delocalized vinyl carbene with the alkene, and; (e) a pathway involving a single electron transfer from the nucleophilic, electron rich vinylcarbene to an electron deficient alkene to generate a π-delocalized radical cation and a radical anion, followed by subsequent radical anion / radical cation combination.

Scheme 27



Pathway (a) was eliminated based on the results that cyclopropane ketene acetal **76**, with one electron withdrawing substituent, failed to undergo a vinylcyclopropane rearrangement even at temperatures as high as 200 °C. In addition, **77** can be formed at temperatures as low as 25 °C (100 - 240 h) in trace amounts by the reaction between **68** and benzylidenemalononitrile with no evidence of the formation of an intermediate cyclopropane ketene acetal (**79**). Therefore, because **76** does not undergo this proposed vinylcyclopropane rearrangement at elevated temperatures, it seems unlikely that the closely related, albeit more reactive, hypothetical intermediate **79**, undergoes the same rearrangement at a temperature 175 °C lower. Other carefully detailed experiments also failed to detect the intermediacy of cyclopropane ketene acetals such as **79** .[85,92]

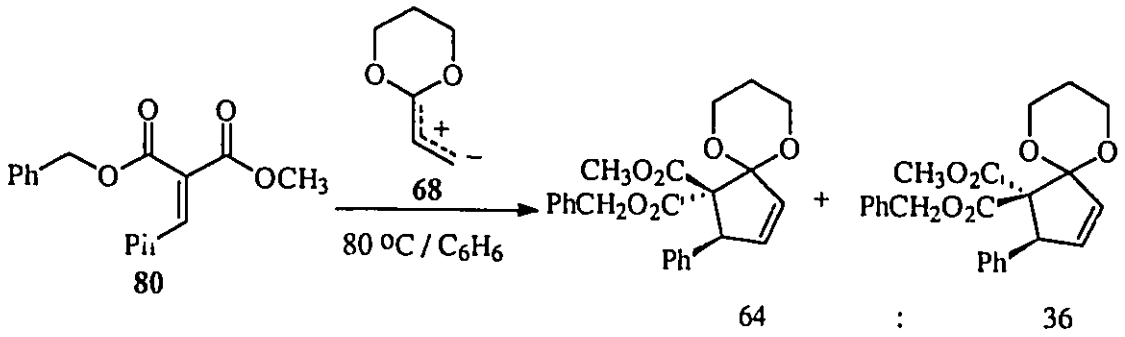
Scheme 28



The [3+2] cycloadditions proceed equally well in the presence of free radical initiators, as well as in the presence of free radical and triplet carbene traps. As a result, pathway (b) can be ruled out. Also, contrary to expectation for a zwitterionic intermediate, as postulated in pathway (c), this reaction showed little rate dependence on the polarity of the solvent.

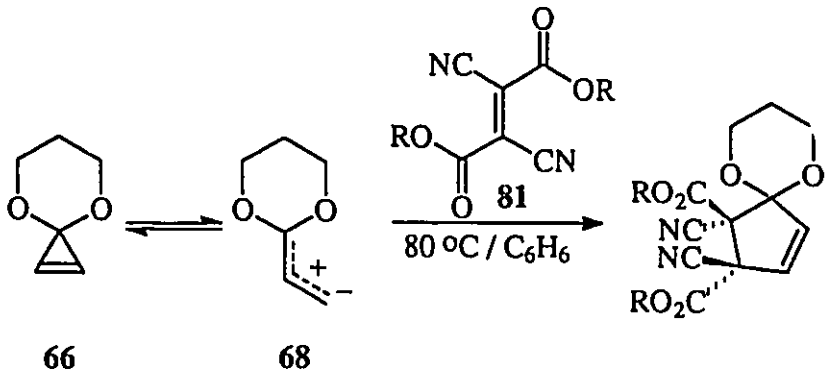
If a [π2s + π2a] concerted pathway is operative, the [3+2] cycloaddition should proceed with complete retention of olefin geometry. This was tested by conducting [3+2] cycloaddition of **68** with E and Z isomeric alkenes (**80**) containing two comparable, but distinguishable, geminal electron withdrawing groups (illustrated for only one isomer). Contrary to the expected result for a concerted cycloaddition, partial loss of olefin geometry (10 - 34 %) was observed. Furthermore, the conformational stability of the substrate alkenes and the products were thoroughly tested under the reaction conditions to confirm that loss of alkene geometry was occurring concurrent with, and not independent of, the cycloaddition. The loss of alkene geometry was also shown to be solvent dependent. In dramatic contrast to the result expected for a zwitterionic intermediate in the [3+2] cycloaddition, in which the loss of alkene geometry would be expected to increase with increasing solvent polarity, the loss of alkene geometry was actually found to decrease with increasing solvent polarity. Therefore, these results clearly rule out a completely concerted mechanism (d), and provide further evidence against the intermediacy of a zwitterionic intermediate as postulated in pathway (c).

Scheme 29



Contrary to the [3+2] cycloaddition of **68** with **80** (or the corresponding Z isomer, not shown) which displayed partial loss of alkene geometry, the tetra-substituted alkene **81**, undergoes the [3+2] cycloaddition with complete retention of stereochemistry.

Scheme 30



Clearly, the thorough and detailed mechanistic study of the [3+2] cycloadditions of 3,3-dioxyvinylcarbenes, reviewed by Boger and Brotherton,[85] indicates that this reaction involves considerable mechanistic complexity.

Boger and Brotherton claim that the mechanism which best fits all of the experimental data obtained so far is (e), a pathway involving a single electron transfer from the nucleophilic, electron rich carbene to the electron deficient olefin to generate a π-delocalized radical cation and a radical anion, followed by subsequent radical anion / radical cation combination. A single electron transfer would be expected to occur only with alkenes that are very good single electron acceptors. Therefore, this accounts rather nicely for the fact that the [3+2] cycloaddition is observed exclusively for alkenes with geminal electron withdrawing groups. To be consistent with the experimental data, the radical-anion / radical-cation combination has to proceed with no solvent dependence in a stepwise, or synchronous manner, at a rate which is competitive with stereochemical scrambling of the radical-anion.

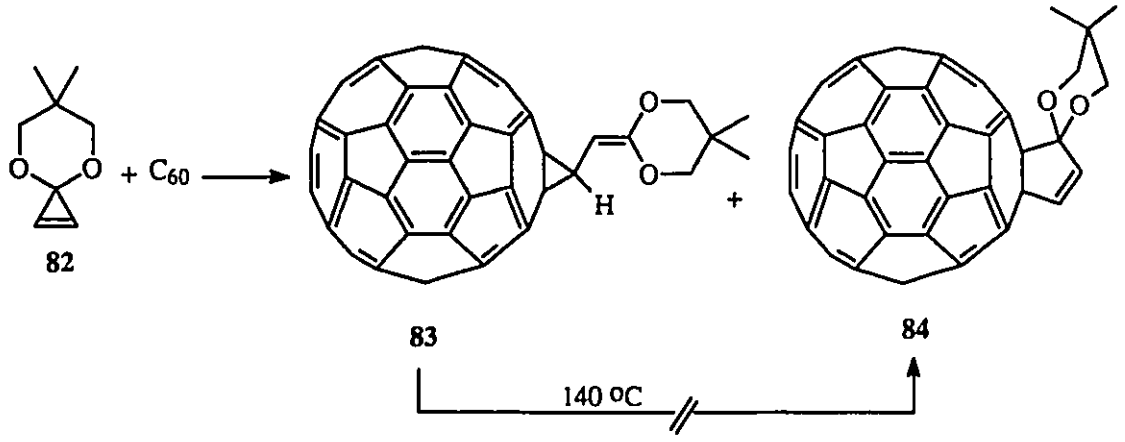
If this pathway is operative, the radical-anion / radical-cation combination cannot proceed via a biradical combination followed by subsequent zwitterionic collapse since, contrary to the observed solvent dependence, this path would be expected to display loss of alkene geometry with increasing solvent polarity. Although the mechanistic details of this pathway are not entirely clear, nor are they thoroughly confirmed, a stepwise zwitterionic combination followed by subsequent biradical combination accounts for the inverted solvent dependence for the stereoselectivity of the [3+2] cycloaddition.

Despite the mechanistic complexity of this reaction, it displays considerable synthetic potential. This cycloaddition is unique to this particular class of vinylcarbenes,[93] and is one of a few all-carbon [3+2] cycloadditions[94] which may provide a valuable compliment to the Diels-Alder reaction

(c) [1+2] and [3+2] Cycloaddition of 3,3-dioxyvinylcarbenes with C_{60}

Buckminsterfullerene (C_{60}) is an ideal trap for nucleophilic carbenes because of its well documented electrophilic character.[95] Nakamura and co-workers have demonstrated[96] that 3,3-dioxyvinylcarbenes behave with unique reactivity towards this substrate. The thermal reaction of cyclopropenone ketal **82** in the presence of C_{60} gave a mixture of two products, **83** and **84**, derived from the [1+2] and the [3+2] cycloadditions of the 3,3-dioxyvinylcarbene with C_{60} (Scheme 31). As seen above, the reaction of 3,3-dioxyvinylcarbenes with other alkenes always proceed with periselectivity that is strictly dependent upon the nature of the alkene. This is the first example in which both the [1+2] and [3+2] cycloadducts were obtained for a particular alkene.

Scheme 31



82 **83** **84**

Moreover, the ratio of **83** : **84**, formed in this reaction, was shown to have a very interesting temperature dependence; thermolysis of **82** at 80 °C in the presence of C_{60} led to the formation of **83** and **84** in a ratio of 91 : 9 in 31 % isolated yield, whereas, the reaction conducted at 140 °C gives the same products in a ratio of 7 : 93 in 44 % isolated yield. The complete reversal in product distribution at 140 °C was initially believed to be attributed to the conversion of **83** to **84** by a vinylcyclopropane rearrangement at the elevated temperature. Heating adduct **83** at 140 °C, however, did not give **84**, therefore confirming that these products are formed independently. The authors claim that the mechanistic details of this dual participation of the vinyl carbene are still unknown. Nevertheless, this dichotomy is useful from a synthetic point of view since the two fullerene adducts, **83** and **84**, can be prepared selectively, simply by varying the thermolysis temperature.

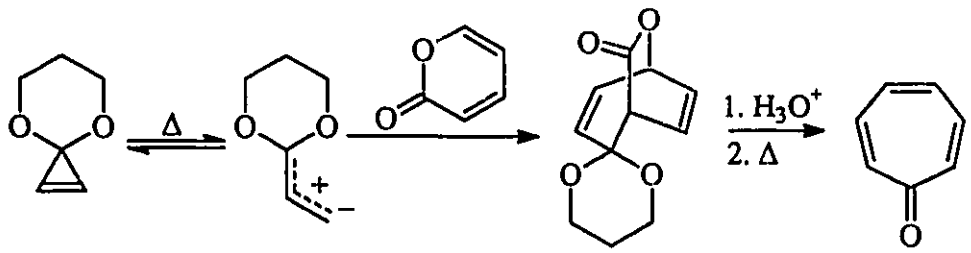
We believe that the dual participation of the vinylcarbene in the above reaction may be derived from subtle entropic differences between the [1+2] and the [3+2] cycloaddition pathways. If the [3+2] cycloaddition is occurring via a single electron transfer, as postulated by Boger,[85] then the entropy term at the transition state ($\Delta S^{\neq}$) for this reaction may be rather small and negative attributable to the fact that, although the reaction is bimolecular, it likely proceeds without large geometric constraints. The [1+2] cycloaddition, on the other hand, is concerted and must have severe geometric constraints, as evidenced by the high observed cis-selectivity,[85,86,90] therefore, $\Delta S^{\neq}$ for the [1+2] would be expected to be negative and large.

Since $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$, the more negative the $\Delta S^{\neq}$ term, the larger is $\Delta G^{\neq}$ and, since $\Delta G^{\neq} = -RT \ln k$, the smaller is k. As a result, in keeping with the periselectivity observed for the thermal reaction of **82** with C_{60}, the [1+2] cycloaddition would be expected to be disfavored relative to the [3+2] cycloaddition at high temperature because of a large negative $T\Delta S^{\neq}$ term. This rationalization is in support of Boger's single electron transfer mechanism[85] for the [3+2] cycloaddition.

(d) [3+4] Cycloaddition of 3,3-dioxyvinylcarbenes with α-pyrones

The reaction of 3,3-dioxyvinylcarbenes **68** with unsubstituted and substituted α-pyrones results in a [3+4] cycloaddition.[85,86,97] As illustrated in Scheme 32, the thermal reaction (70 - 80 °C) of **66** with α-pyrone, gives the [3+4] cycloadduct **85**. This reaction likely proceeds via a [π2s+π4s] concerted cycloaddition between **68** and α-pyrone. Hydrolysis of the ketal moiety of **85** using aqueous acid, followed by subsequent thermal decarboxylation gives tropone (**86**). This approach was used by Boger and Brotherton to prepare a variety of unique substituted tropones.[86,97,98]

Scheme 32

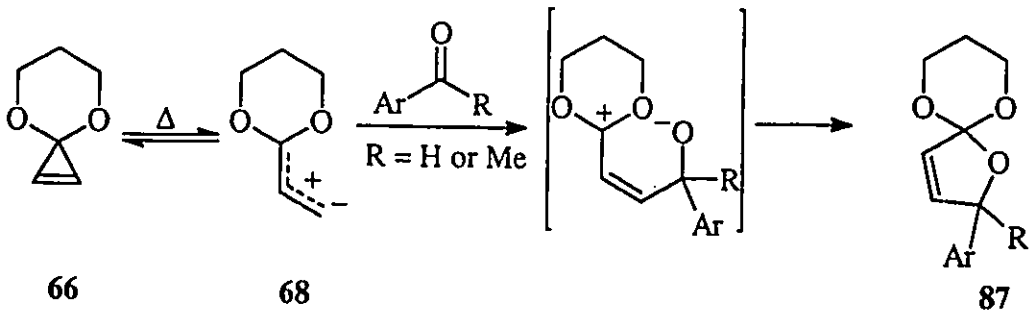


66 **68** **85** **86**

(e) [3+2] Cycloaddition of 3,3-dioxyvinylcarbenes with carbonyl compounds

A number of carbonyl compounds also participate in a [3+2] cycloaddition reaction with 3,3-dioxyvinylcarbenes, generated from the corresponding cyclopropenone ketals, to provide butenolide orthoester cycloadducts.[85,86,99] As shown in Scheme 33, the formal [3+2] cycloaddition of **68** with p-nitrobenzaldehyde or p-nitrobenzophenone gives **87**.[85,99] A number of mechanistic pathways can be envisioned for this reaction, among these possible pathways is - nucleophilic attack by the vinylcarbene onto the electron deficient carbonyl carbon, followed by collapse of the zwitterionic intermediate.

Scheme 33



66 **68** **87**

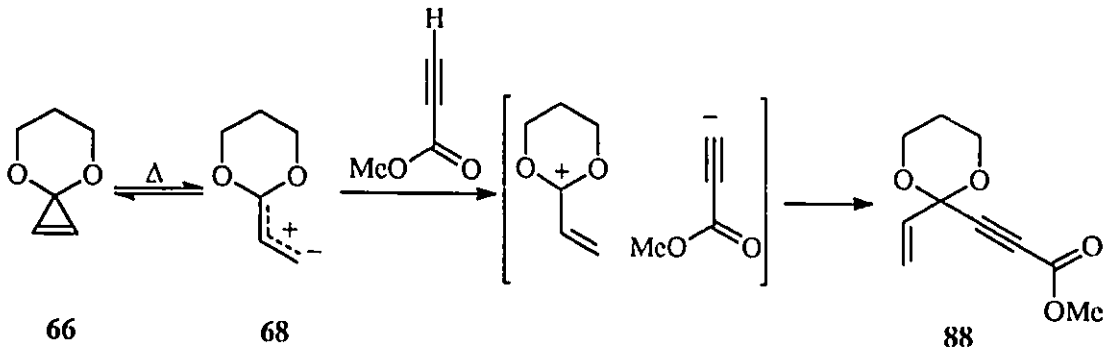
Ar = p-NO_2Ph

(f) Reactions 3,3-dioxyvinylcarbenes with alkynes

A few reactions of 3,3-dioxyvinylcarbenes with alkynes have been attempted. It was found that the thermal generation of a 3,3-dioxyvinylcarbene **68**, from **66**, in the presence of DMAD gives a complex mixture of products.[86] The reaction of **68** in the presence of methylpropiolate,[86] however, leads to a product derived from protonation of

the vinyl-anion moiety of the π-delocalized vinylcarbene with the acidic alkyne proton, followed by ion pair collapse to give **88**.

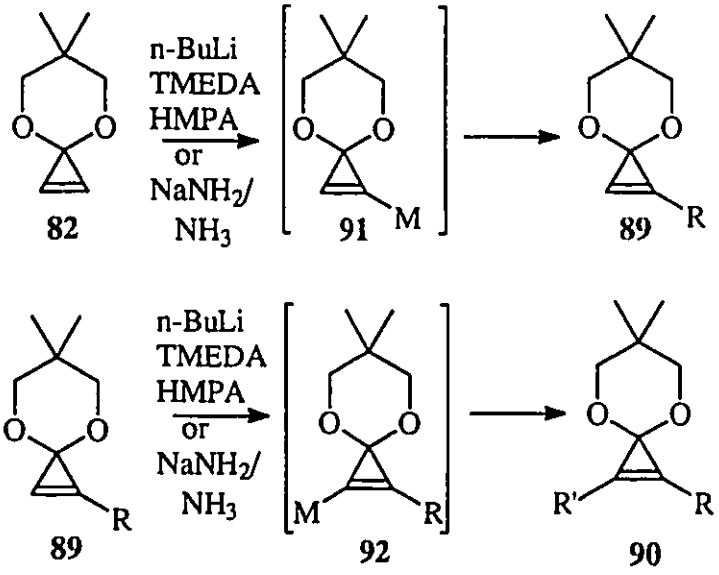
Scheme 34



1.6 1- and/or 2- Substituted 3,3-Dioxyvinylcarbenes

1.6.1 Generation of 1- and/or 2- substituted 3,3-Dioxyvinylcarbenes

Scheme 35

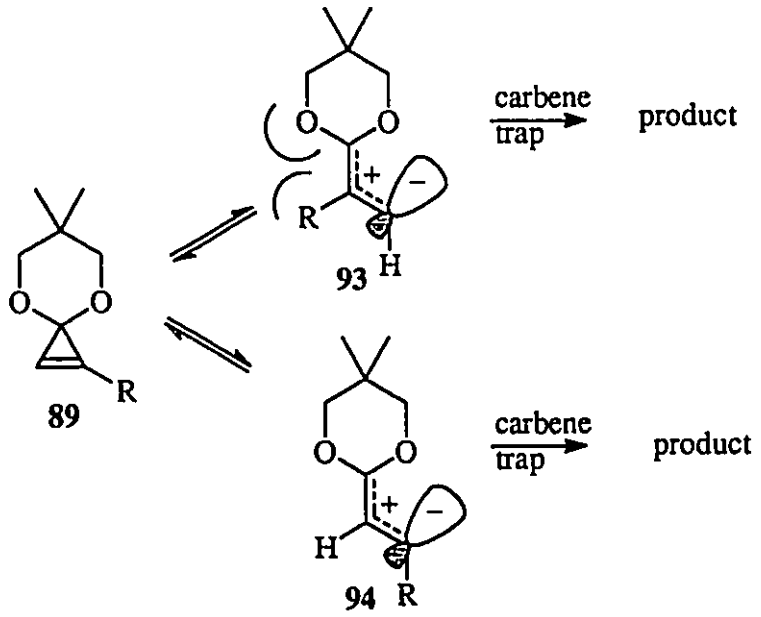


In 1991 Nakamura and co-workers reported[100,101] that a variety of 1- and 1,2-substituted cyclopropenone ketals (**89** and **90**) can be prepared by the reaction of stable metal salts **91** and **92** with the appropriate electrophiles (R^+). The metal salts **91** or **92** are, in turn, prepared by treatment of cyclopropenone ketals **82** and **89** with a strong base.

1.6.2 Regioselectivity of 3,3-Dioxyvinylcarbene Formation

The presence of C-1 substituents on the cyclopropenone ketal gives rise to the issue of regioselectivity for the cyclopropene ring opening (i.e. **93** versus **94**). Electronic and steric factors are expected to influence the stability of each of the isomeric vinylcarbenes. For example, considering the electronic structure of 3,3-dioxyvinylcarbenes, it is expected that an anion stabilizing group (R) would favor the formation of **94**. Steric factors may also destabilize **93** and favor of the formation of **94**.

Scheme 36



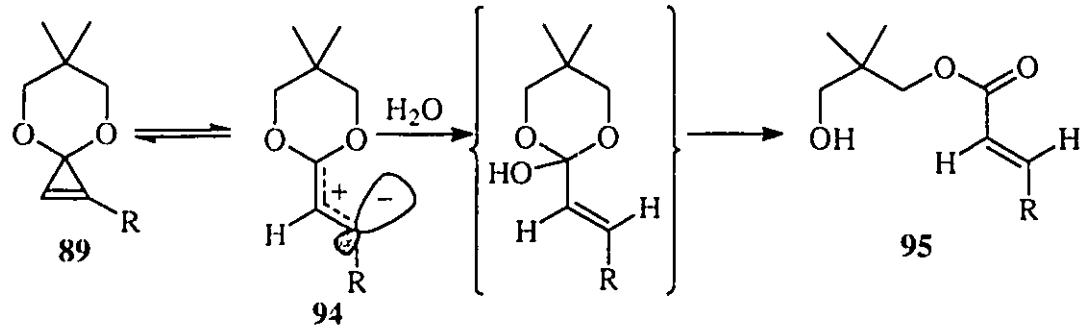
In order to determine the effect of a number of different substituents on the regioselectivity of cyclopropenone ketal ring opening, Nakamura and co-workers investigated the thermal ring opening of 1- or 1,2- substituted cyclopropenone ketals in the presence of a number of effective carbene traps.[102,103] Since both the 3,3-dioxyvinylcarbenes, **93** and **94**, may be in equilibrium with the cyclopropenone ketal **89**, product ratios reflect either the kinetic or thermodynamic stability of the carbenes, or the relative reactivity of each of the isomeric carbenes toward the particular carbene trap.

1.6.3 Reactions of Substituted Dioxyvinylcarbenes

(a) Reaction of 1- and/or 2- substituted 3,3-dioxyvinylcarbenes with water

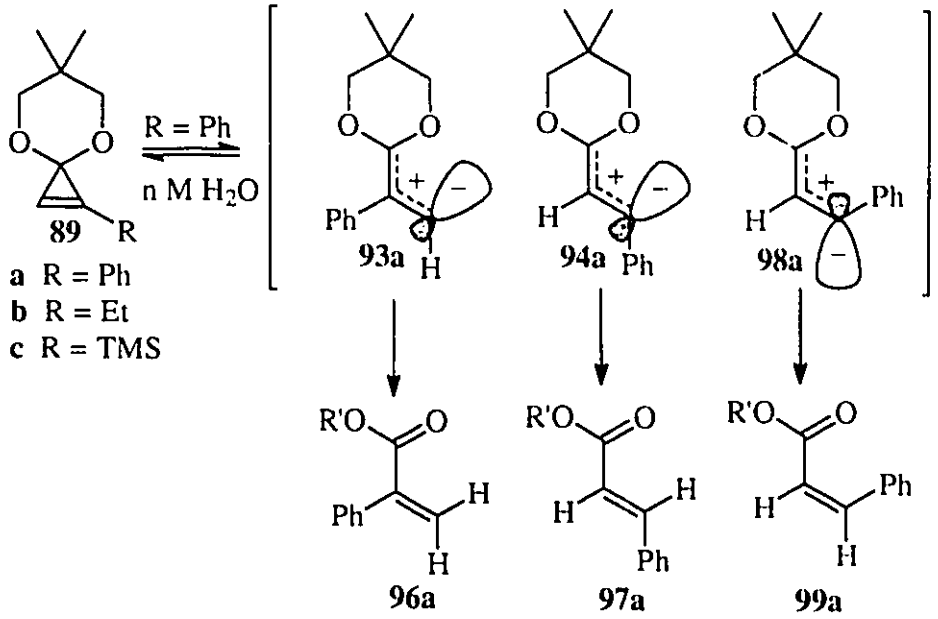
Initially, water was used to trap the vinylcarbenes.[102] It was demonstrated that 0.5 M solution of the cyclopropenone ketal in acetonitrile in the presence of a high concentration (25 M) of water kinetically traps the initially formed vinylcarbenes, whereas, 1 M water allows equilibration of the carbene isomers. Therefore, kinetic and thermodynamic regioselectivity of cyclopropene ring opening could be obtained by this method. The products of trapping by water are α,β-unsaturated esters (i.e. **95**) which are derived according to the mechanism shown in Scheme 37.

Scheme 37



The thermal ring opening of the 1-phenyl substituted 3,3-cyclopropenone ketal **89a** under kinetic quenching conditions (25 M H_2O) gave **96a** and **97a** in a ratio of 58 : 42 (Scheme 38). The esters **96a** and **97a** are derived from trapping of the isomeric vinylcarbenes **93a** and **94a**, respectively. Lowering the water concentration to 5 M and 1 M resulted in a change of the **96a** to **97a** ratios to 46 : 54 and 35 : 63, because of equilibration of the isomeric carbenes. Based on these results, under both kinetic and thermodynamic conditions, formation of **93a** and **94a** from **89a** was shown to be non-regioselective. The Z-cinnamate ester **99a**, expected from trapping the E-vinylcarbene **98a**, was not identified in significant amounts in any of the reactions, therefore indicating that the vinylcarbene **94a** does not undergo stereoisomerization to **98a**.

Scheme 38

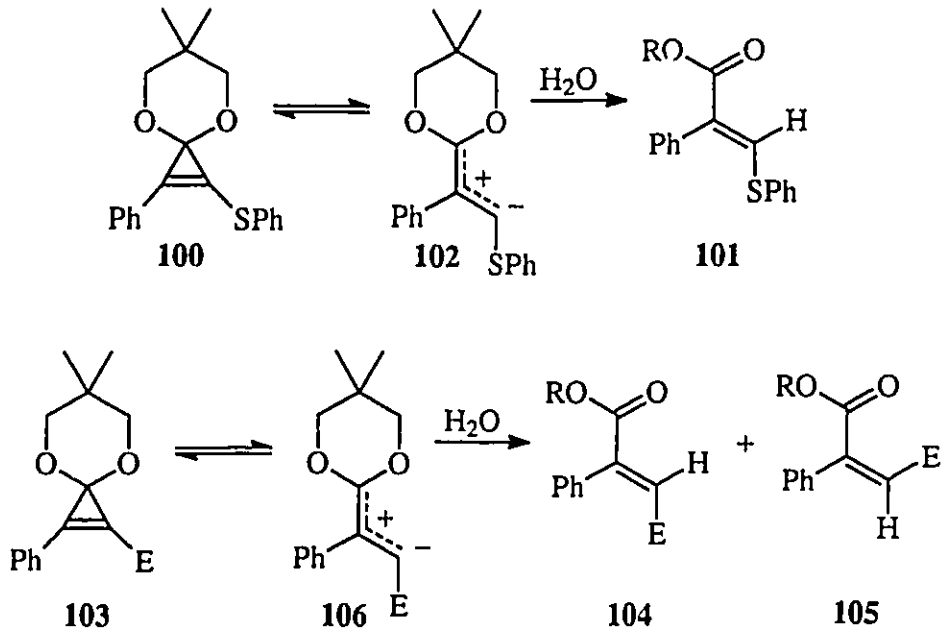


R' = $CH_2C(CH_3)_2CH_2OH$

	96a	97a	99a	yield
n = 25	58	42	<1	83 %
n = 5	46	54	<1	84 %
n = 1	35	63	<2	48 %

Similar experiments were conducted on the ethyl substituted cyclopropenone ketal **89b**. It was found that the alkyl substituent greatly retards the rate of ring opening of the cyclopropenone ketal; at 70 °C **89b** barely reacted, and at 100 °C a complex mixture of products was obtained. The thermal ring opening of the trimethylsilyl substituted cyclopropenone ketal **89c** in the presence of water was complicated as a result of desilylation. However, from the available data, the thermal ring opening of **89c**, as inferred by trapping with water, also seems to proceed with little regioselectivity.

Scheme 39



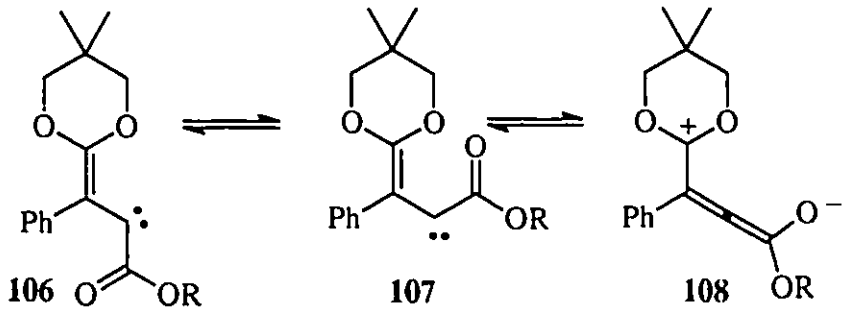
R = $CH_2C(CH_3)_2CH_2OH$
E = CO_2-*i*-Pr

In contrast to the above results, anion stabilizing substituents, such as ester or phenylthio, display a pronounced effect on the regioselectivity of the cyclopropene ring opening. In addition, these substituents were shown to decrease the temperature required for ring opening significantly. In fact, the phenylthio substituted cyclopropenone ketal **100** undergoes totally regioselective ring opening below room temperature. Consequently, it cannot be isolated, and upon aqueous work-up, gives **101**, which is derived from trapping of the intermediate vinylcarbene **102** with water.

The ester substituted cyclopropenone ketal **103** also undergoes ring opening at low temperatures. In this case, however, the cyclopropenone ketal is stable enough to be

isolated at room temperature by non-aqueous work-up. Upon addition of water to **103**, at ambient temperature, the esters **104** and **105** are formed. The fact that products derived from only the terminally substituted vinylcarbene were formed, indicates that **103** also undergoes totally regioselective ring opening. The reaction, however, displays poor stereoselectivity (i.e. **104** vs. **105**). This could be attributed to the fact that either the E (**106**) and Z (**107**) isomeric vinylcarbenes are of comparable energy, the E/Z isomerization barrier for the vinylcarbenes is extremely low, or that the vinylcarbene actually has the structure **108**, which has no relevant stereochemical issue (Scheme 40).

Scheme 40

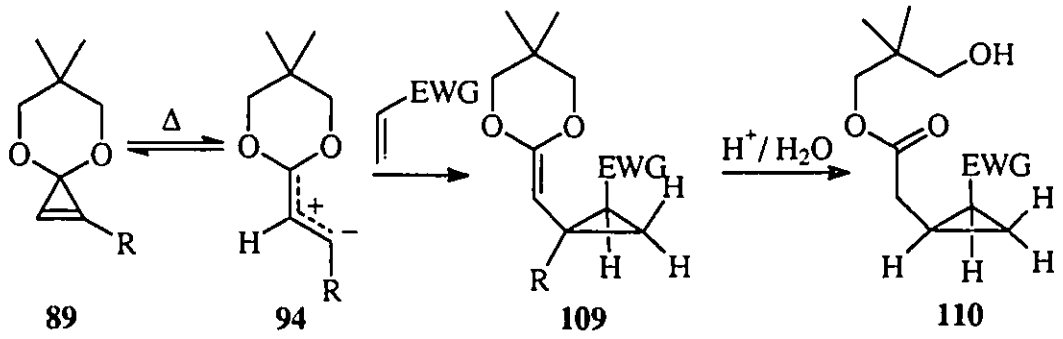


(b) [1+2] Cycloaddition of 1-substituted 3,3-dioxyvinylcarbenes with alkenes

In contrast to the regioselectivity (kinetic and thermodynamic) observed upon trapping of the isomeric mono-substituted vinylcarbenes **89a**, **b**, and **c** with water, which was generally poor, trapping of these vinylcarbenes with moderately electron deficient alkenes, such as methylacrylate or acrylonitrile, proceeds with excellent regioselectivity (>

91 %). In every case, following hydrolysis of the initially formed [1+2] cycloadducts (**109**), the cis substituted cyclopropanes, **110**, were the only product isolated, thus indicating that only the terminally substituted 3,3-dioxyvinylcarbenes (**94**) were trapped by the olefin.[103] This dramatic difference in regioselectivity, between trapping of the isomeric carbenes, **93** and **94,** with water or an alkene must reflect the different reactivities of the carbenes towards the particular carbene trap. As observed with the unsubstituted 3,3-dioxyvinylcarbenes (**68**), the [1+2] cycloadditions of the substituted 3,3-dioxyvinylcarbenes (**94**) proceed with significant (> 75 %) cis-selectivity.

Scheme 41



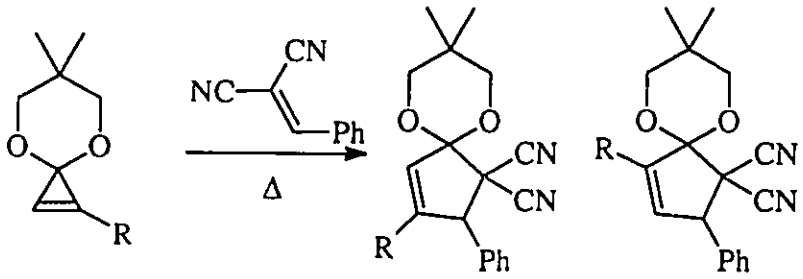
The [1+2] cycloaddition of substituted 3,3-dioxyvinylcarbenes with moderately electron-deficient alkenes therefore represents a highly regioselective and cis-stereoselective reaction, which leads to the diastereoselective formation of interesting cyclopropane ketene acetals.

(c) [3+2] Cycloaddition of 1- and/or 2-substituted 3,3-dioxyvinylcarbenes with alkenes

Substituted cyclopropenone ketals were also found to undergo regioselective [3+2] cycloadditions effectively with highly electron deficient alkenes.[102] The thermal ring opening of the ethyl substituted cyclopropenone ketal **89b** in the presence of benzylidenemalononitrile led to a 71 : 29 mixture of regioisomers **111b** and **112b**. The major cycloadduct **111b** is derived from trapping of the internally substituted 3,3-dioxyvinylcarbene (**93b**). This result is in direct contrast to the [1+2] cycloaddition reaction of **89b** with acrylonitrile, which led to the exclusive capture of only the terminally substituted 3,3-dioxyvinylcarbene (**94b**), therefore indicating a significant mechanistic difference between the [1+2] and the [3+2] cycloaddition reactions.

Although only moderate regioselectivity was observed for the above [3+2] cycloaddition, the phenyl and trimethylsilyl substituted cyclopropenone ketals **89a** and **89c** displayed excellent regioselectivity and gave a single regioisomer. In the latter two cases, the cycloadducts **111a** and **111c** are derived from exclusive trapping of the terminally substituted vinylcarbene (**94**), as observed for the [1+2] cycloadditions.

Scheme 42

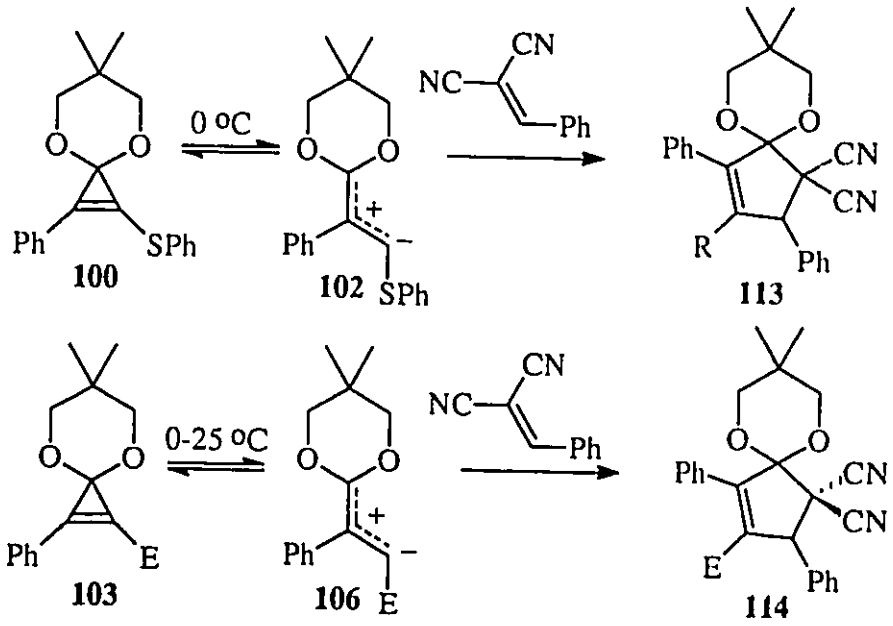


89 **111** **112**

R	111	112	yield (%)
a Ph	100 :	0	76
b Et	29 :	71	82
c TMS	100 :	0	62

As indicated by the trapping experiments with water, cyclopropenone ketals **100** and **103**, possessing strongly electron-withdrawing substituents, undergo totally regioselective thermal ring opening at very low temperatures (0 - 25 °C). The intermediate vinylcarbenes **102** and **106** can also effectively be trapped by a [3+2] cycloaddition with highly electron deficient alkenes to give the cycloadducts **113** and **114** respectively. Because of the thermal instability of these cyclopropenone ketals, however, the alkene must be added to the cyclopropenone ketal immediately upon preparation, without work-up.

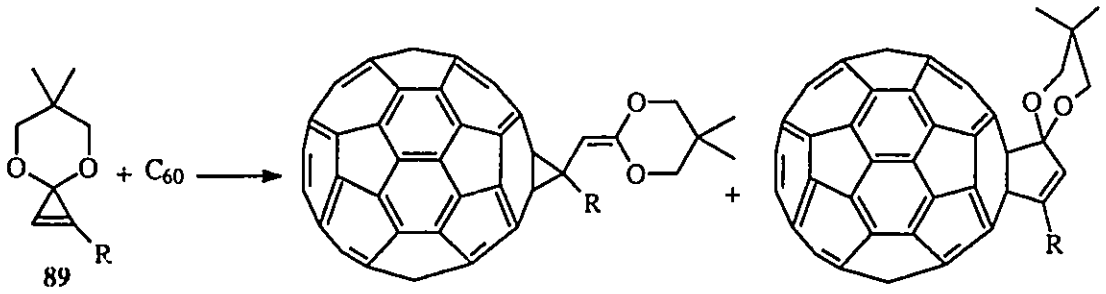
Scheme 43



(d) [1+2] and [3+2] Cycloaddition of 1-substituted 3,3-dioxyvinylcarbenes with C_{60}

The thermal reaction of C-1 substituted 3,3-dioxyvinylcarbenes with C_{60} displays the same temperature-dependent dichotomy as observed for the unsubstituted 3,3-dioxyvinylcarbenes (Scheme 31).[101] As illustrated below (Scheme 44), the reaction of **89a** in the presence of C_{60} at 80 °C gives a mixture of **115a** and **116a** (ratio not reported), whereas, the reaction conducted at 140 °C provides predominantly **116a**. Moreover, the reaction of **89b** and **89c** at elevated temperatures gave the [3+2] cycloadducts **116b** and **116c** exclusively.

Scheme 44



115 116

R	temp. (°C)	115:116	%yield
a Ph	80	mixture	--
a Ph	140	7 : 93	30
b Et	150	0 : 100	40
c TMS	170	0 : 100	52

As illustrated, 3,3-dioxyvinylcarbenes, from the corresponding cyclopropenone ketals, undergo mechanistically interesting and synthetically useful reactions with a number of substrates to give a variety of interesting cycloadducts.

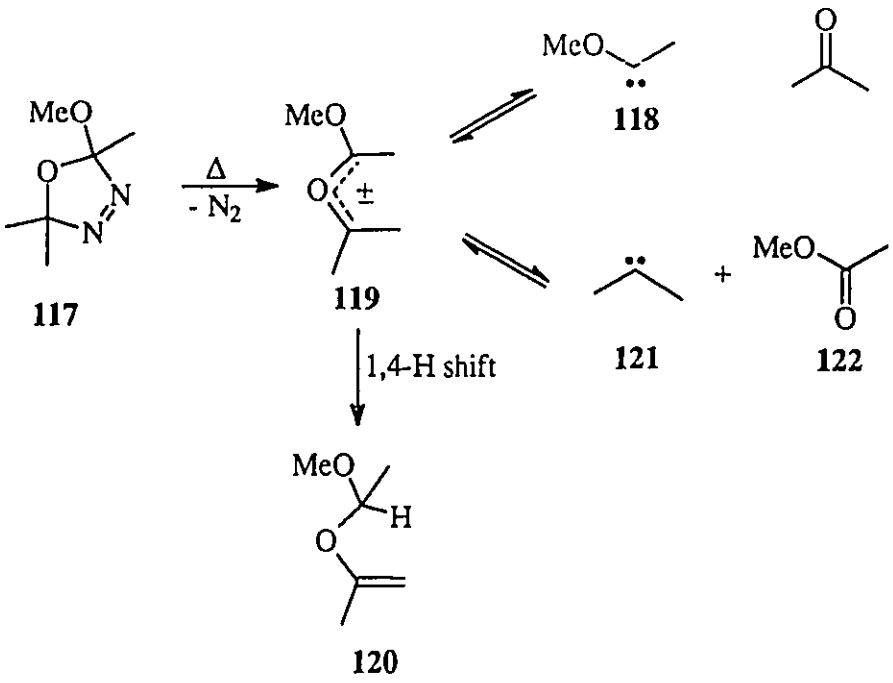
Chapter 2: RESULTS AND DISCUSSION

2.1 Oxadiazolines: Convenient New Dioxycarbene Precursors

Although 7,7-norbornadienone ketals and dioxydiazirines are well established as dioxycarbene precursors, they suffer from a number of inherent limitations (*vide supra*, Introduction). The work described in this section details the development of a new class of dioxycarbene precursors, 2,2-dioxy-Δ^3-1,3,4-oxadiazolines, which display a number of obvious advantages over 7,7-norbornadienone ketals and dioxydiazirines. This work has been published in the Journal of the American Chemical Society in 1992, and was a result of a combined effort by several members of our group.[104]

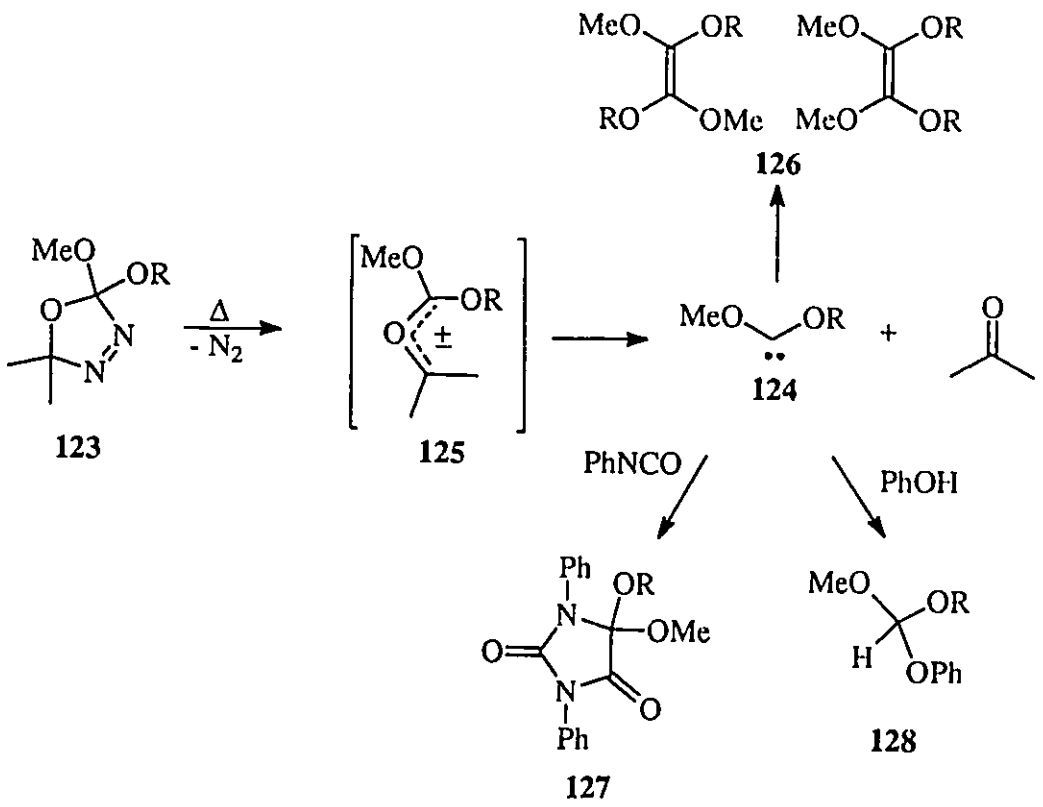
Prior to this work, Warkentin and Békhazi[105,106] demonstrated that the thermolysis of oxadiazolines bearing one oxygen substituent, i.e. **117**, resulted in the generation of oxycarbene **118**, albeit in low yield. Carbene formation was shown to proceed *via* fragmentation of a short-lived carbonyl ylide intermediate (**119**) which is generated by a thermal [3+2] cycloelimination of N_2 from **117**. The reactions that compete with the desired fragmentation of **119** to oxycarbene **118** are a 1,4-H shift to give **120**, and also fragmentation of **119** in the opposite sense to give the dialkylcarbene **121** along with the corresponding ester **122** (Scheme 45). The poor selectivity in the fragmentation of ylide **119** detracted from the use of **117** as an oxycarbene precursor.

Scheme 45



In contrast to the above result, the thermolysis of 2,2-dioxy-Δ^3-1,3,4-oxadiazolines (**123**) cleanly provides oxygen substituted carbenes **124** with very high efficiency (Scheme 46). In accord with the mechanism proposed by Békhazi and Warkentin for the thermolysis of **117**, dioxycarbene formation from **123** may proceed via fragmentation of an intermediate carbonyl ylide **125**. The fragmentation of the ylide in this case would have to proceed exclusively in one sense. Alternatively, considering the thermodynamic stability of dioxycarbenes, the thermal decomposition of **123** may proceed via a concerted cycloreversion in which both N_2 and acetone are simultaneously lost. In fact, there is currently no firm experimental evidence for the intermediacy of **125**.

Scheme 46



Thermolysis of **123** (R = Me) in benzene at 100 °C (sealed NMR tube) followed the first order kinetics with k = 1.2 x 10^{-5} s^{-1}. Similarly, thermolysis of **123** (R = $CH_2CH_2C{\equiv}CH$) at 110 °C also follows first order kinetics with k = 3.4 x 10^{-5} s^{-1}. Evidence for the intermediacy of dioxycarbenes from the thermolysis of dioxyoxadiazolines (**123**) was inferred by the formation of acetone (>80 %) and, most notably, by the formation of tetraalkoxyethanes **126** which, as shown in the Introduction, are derived from carbene dimerization. Upon thermolysis of unsymmetrically substituted oxadiazolines (i.e. **123**, R = Et) that are not capable of intramolecular reaction (*vide infra*), both the E and Z isomers were obtained.

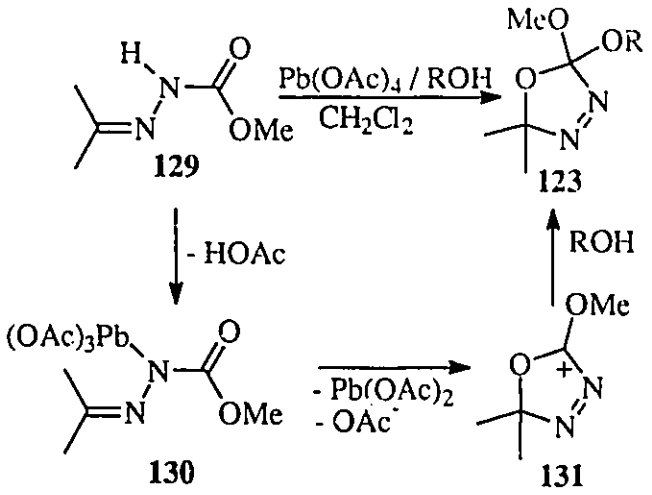
Further evidence that dioxycarbenes are generated from the thermolysis of dioxyoxadiazolines was provided by the fact that the thermolysis of **123** (R = Me) in the presence of phenylisocyanate (PhNCO) gives **127** in 65-80 % yield. This product is derived from the reaction of dioxycarbene with two equivalents of phenylisocyanate as previously reported by Hoffmann and co-workers[69] (Scheme 46). In addition, the thermolysis of **123** in the presence of a phenol or an alcohol provides the corresponding orthoformate **128** in high yield by an overall O-H insertion of the carbene.

2.2 Preparation of Dioxyoxadiazolines

2.2.1 The Lead Tetraacetate Oxidation Method

Dioxyoxadiazolines can be prepared by oxidative cyclization of the carbomethoxy hydrazone of acetone (**129**) in the presence of the appropriate alcohol. Either phenyliodo-diacetate[107] (PIDA) or lead tetraacetate[104] (LTA) can be used as oxidants for the cyclization. The most commonly used oxidant for this reaction is LTA. The proposed mechanism for LTA oxidation of **129** involves initial complexation of lead to the carbamate nitrogen atom of **129** (Scheme 47) to give **130**. Oxidative cyclization then leads to the elimination of $Pd(OAc)_2$ and forms the stabilized cation **131**. The oxadiazoline **123** is then derived by trapping of the cation **131** with the alcohol.

Scheme 47



As dioxycarbene precursors, oxadiazolines display a number of advantages over 7,7-norbornadienone ketals and dioxydiazirines. In contrast to the thermolysis of 7,7-norbornadienone ketals, which produce the non-volatile by-product **34** and the side-products **41** and **42** upon generation of dioxycarbenes, thermal decomposition of oxadiazolines give dioxycarbenes cleanly, and the by-products of carbene formation, namely acetone and nitrogen, are easily removed from the crude reaction mixture following thermolysis. In addition, a variety of symmetric and unsymmetric oxadiazolines can easily be prepared by this method. In contrast to dioxydiazirines, which are difficult to obtain and decompose just minutes after they are prepared, oxadiazolines are prepared with relative ease and can be stored at room temperature for several years without any sign of decomposition. For these reasons, oxadiazolines are very attractive thermal dioxycarbene precursors, especially for use in synthetic applications.

2.2.2 The Acetoxy Exchange Method

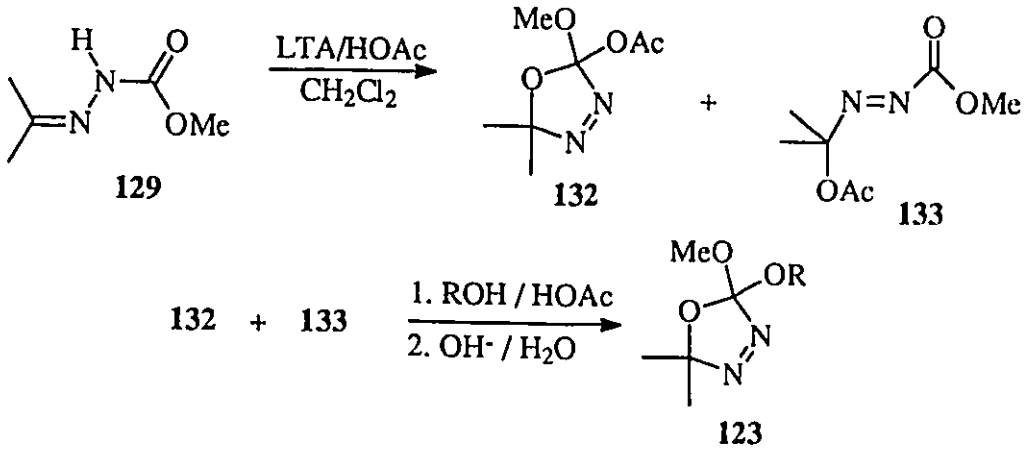
Many dioxyoxadiazolines (**123**) can be prepared by LTA oxidation of the methoxycarbonyl hydrazone of acetone (**129**) in the presence of an appropriate alcohol, as described in the previous section. In certain cases, however, the yields of oxadiazoline are rather low (for example, the reaction involving 3-butyn-1-ol gives the corresponding oxadiazoline in only 37 % yield), and in many cases the oxidation does not proceed cleanly, as a result, tedious purification by chromatography or distillation is often required to obtain the pure oxadiazoline. Moreover, oxadiazolines cannot be formed using alcohols that are unstable under the oxidation conditions. Consequently, trifluoroethanol and phenols gave none of the anticipated oxadiazoline product using the conventional LTA oxidation method.

This section describes the development of a common precursor, 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**132**), which allows the preparation of a large number of dioxyoxadiazolines (**123**) with great ease. This work, which was initiated by the author of this thesis has, in part, been published in the Journal of the American Chemical Society in 1994.[108]

The use of the 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**132**) as a convenient new source of dioxyoxadiazolines alleviates the aforementioned problems. It was found that this compound undergoes facile substitution with a number of alcohols or phenols to provide the corresponding dioxyoxadiazolines. The acetoxy oxadiazoline (**132**) (Scheme 48) is easily prepared in 75 % yield by LTA oxidation of **129** in the presence of acetic acid in dichloromethane solvent. The only by-product of this reaction, which

accounts for the remainder of the mass balance, is azocarboxylate **133**. Attempts to minimize the formation of this by-product by changing a variety of reaction conditions (i.e. by changing the oxidant, reaction temperature, solvent, and the order of addition of the reagents) were unsuccessful.

Scheme 48



Purification of the acetoxymethoxyoxadiazoline (**132**) from the mixture of **132** and **133** is possible by slow bulb to bulb distillation. This process, however, is tedious and is not required for the preparation of pure dioxyoxadiazolines (**123**). Instead, the crude mixture containing both **132** and **133** (which may be conveniently stored in the refrigerator for an indefinite period of time after work-up) can be treated with an alcohol or a phenol in the presence of acetic acid in dichloromethane solvent to give the corresponding dioxyoxadiazoline (**123**). The exchange can be monitored by either NMR, GC, or TLC, and is usually complete within 24 to 48 hours at room temperature for most alcohols. The exchange involving phenols is slower and requires somewhat longer reaction times and/or

must be carried out at a higher temperature (i.e. refluxing CH_2Cl_2). Once the exchange is complete, purification of the sample is simple. Since dioxyoxadiazolines are stable to base, addition of aqueous potassium hydroxide results in the sclective hydrolysis of **133** to provide pure **132** upon work-up. Alternatively, since there is only one by-product (**133**), **123** can easily be purified by chromatography or distillation. As illustrated in Table 1, the acetoxy exchange route provides a number of oxadiazolines from **132** in good to excellent yields.

Significantly, 2-trifluoroethoxy (**123g**) and 2-aryloxy (entries **123j-l**) substituted oxadiazolines, which could not be prepared by the previous method, are available for the first time. The carbenes derived from the 2-aryloxy[109] and the 2-trifluoroethoxy substituted[84,110] oxadiazolines have unique electronic character and undergo some interesting chemistry.

Table 1: Yields of Dioxyoxadiazolines (**123**) by the Acetoxy Exchange Route from **132**

123	R	yield (%)[a]	**123**	R	yield (%)[a]
a	Me	94	**g**	CH_2CF_3	84
b	Et	90	**h**	$CH_2CH_2C{\equiv}CH$	86
c	Pr	92	**i**	$CH_2CH_2\ CH_2C{\equiv}CH$	78
d	i-Pr	74	**j**	C_6H_5	61
e	Bu	82	**k**	C_6H_4-p-CN	67
f	t-Bu	67	**l**	C_6H_4-p-OCH_3	68

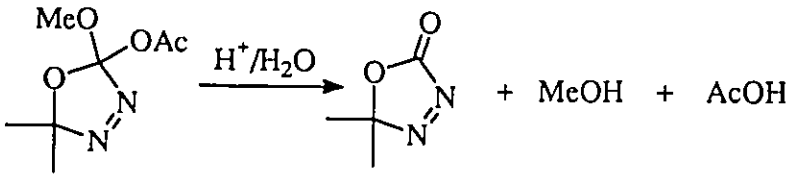
[a] yield of isolated product from exchange.
Note: the preparation of other oxadiazolines by this method are reported in the appropriate sections.

The exchange reactions that provide the dioxyoxadiazolines likely proceed via the cationic intermediate **131**, in an S_N1 type mechanism. The fact that acid is required to facilitate the exchange is in keeping with this proposed mechanism. It was found that a stronger acid, such as p-toluenesulfonic or benzoic acid, can be used to further enhance the rates of exchange. And in addition, exchanges conducted at elevated temperatures also proceed faster. However the use of stronger acids and/or elevated temperatures generally result in lower yields of oxadiazoline.

Initially, we were surprised to find varying (0 to 10 %) amounts of dimethoxyoxadiazoline (**123a**) from some of the exchange reactions. It was later discovered that the presence of adventitious water leads to hydrolysis of the acetoxymethoxyoxadiazoline (**132**) to give lactone **134**, acetic acid, and methanol (Scheme 49). The methanol generated from the hydrolysis then undergoes exchange with additional **132** to give dimethoxyoxadiazoline **123a**, which must then be removed from the desired oxadiazoline product.

The source of **123a** was confirmed by an experiment in which ≈ 0.5 equivalent of water and acetic acid were intentionally added to a solution of **132** in $CDCl_3$. After about 24 hours at room temperature, dimethoxyoxadiazoline (**123a**) was formed in approx. 50 % yield from **132** as indicated by ^1H NMR. The formation of **123a** in 50% was expected from the proposed source since half of the available **132** would be consumed in generating methanol whereas the other half undergoes exchange with the methanol generated.

Scheme 49

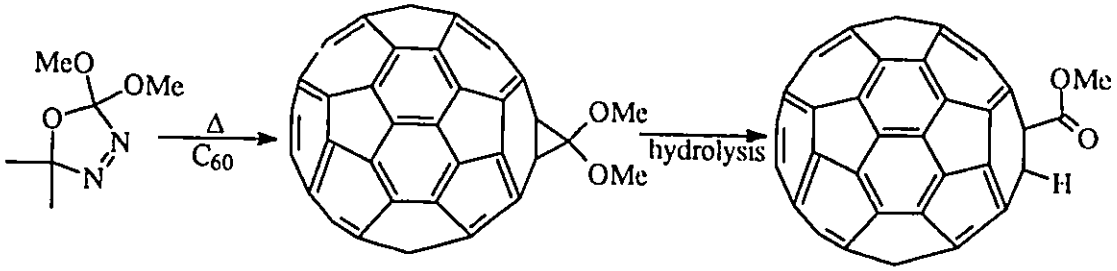


132 134

Recently, Warkentin and Er have demonstrated that thiols also undergo exchange with **132** to give oxythio substituted oxadiazolines.[111,112] These oxadiazolines thermally decompose at significantly lower temperatures (ca 40 °C) than their dioxy analogs to provide the corresponding oxythiocarbenes, which show interesting reactivity. A particularly intriguing aspect of the acetoxy exchange reaction is whether nucleophiles other than alcohols, phenols, or thiols may also take part in the exchange. For example, CN^-, F^-, or amines, may give the corresponding oxadiazolines. This would then provide oxadiazolines which may be potential convenient thermal sources for a variety of interesting carbenes.

A number of groups now use oxadiazolines as dioxycarbene precursors.[113,114] For example Wudl and co-workers, in collaboration with our group,[114] have demonstrated that dimethoxycarbene undergoes a [1+2] cycloaddition with buckminsterfullerene (C_{60}) to give **135**. Hydrolysis of the ketal moiety of **135**, using a number of different methods, leads to the formation of ester **136** (Scheme 50).

Scheme 50



123a 135 136

2.3 Intramolecular Cyclization of a Dioxycarbene with an Unsubstituted Tethered Alkyne

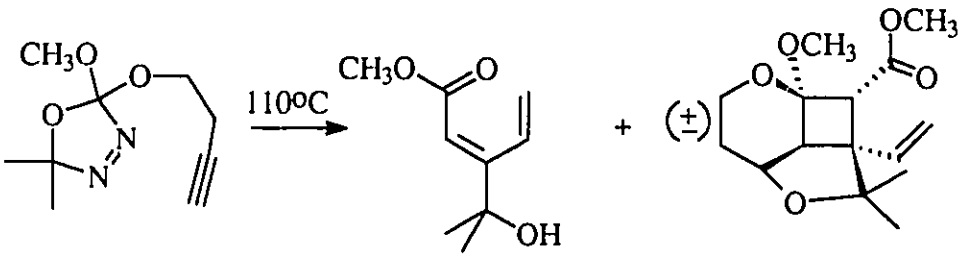
Because of the ubiquitous nature of carbocyclic and heterocyclic compounds, the development of new methodologies for ring formation is of primary interest in organic synthesis. Recently, ring forming reactions via cyclization of reactive intermediates such as anions, cations and radicals have commanded much attention.[115]

The intramolecular cyclizations of carbenes, however, have been studied to a significantly lesser extent. In particular, there is only one investigation on the intramolecular cyclization of a nucleophilic carbene onto a tethered alkene,[116] and the work described in the following sections of this thesis is, to date, the only study on the intramolecular cyclization of dioxycarbenes onto a tethered alkyne. For reasons described in the previous sections, oxadiazolines were well-suited as thermal dioxycarbenes precursors for this study.

2.3.1 Thermolysis of Oxadiazoline 123h: A Remarkable Cascade of Carbene and Other Reactions in One Pot

Oxadiazoline **123h** was prepared in order to investigate the possible intramolecular reactions of the corresponding dioxycarbene with a tethered alkyne. Thermolysis of **123h** in benzene (sealed tube / 110 °C) or in toluene (reflux / 1 atm.) for 25 hours gave two very unusual products (Scheme 51).

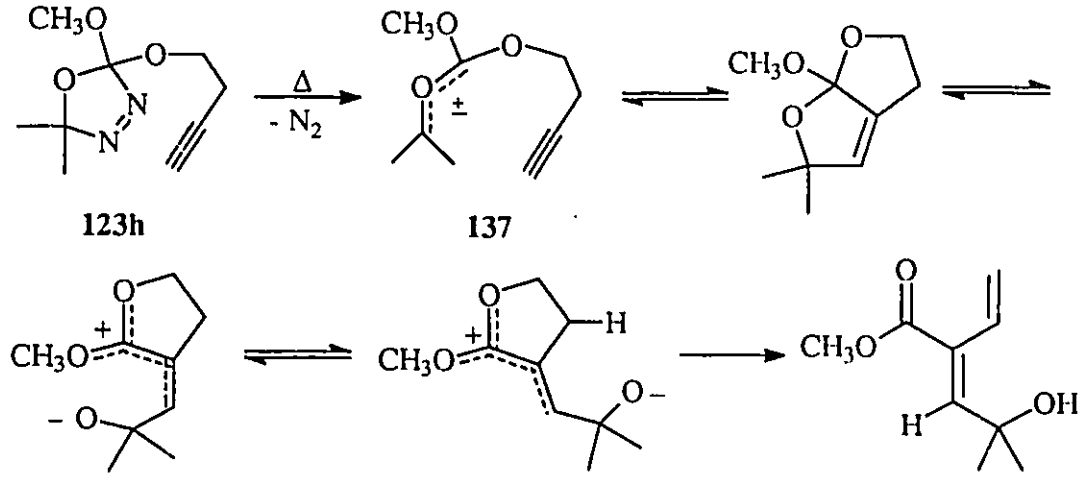
Scheme 51



123h **139** (5 %) **140** (74 %)

A minor product from this reaction, which was isolated in approximately 5 % yield, was found to have the same mass as that of the proposed ylide intermediate (**137**) (Scheme 52), by CI mass spectrometry. Initially, based on spectroscopic data, the structure of this product was believed to be that of **138**, and its formation was attributed to a intramolecular [3+2] cycloaddition of the ylide with the tethered alkyne, followed by bond reorganization according to Scheme 52 or a variant.[104] The structure of this product was later determined to be incorrectly assigned.[117] As will be subsequently detailed, the minor product of this reaction was later firmly established to be (E)-methyl-3-ethenyl-4-hydroxy-4-methylpentenoate (**139**) (Scheme 51).

Scheme 52



The major product, (1α, 1aα, 3aα, 6aα, 6bα) methyl-1a-ethenyl-octahydro-6a-methoxy-2,2-dimethyl-3,6-dioxacyclobut[*cd*]indene-1-carboxylate (**140**) (Scheme 51), was isolated by chromatography in 74 % yield. The structure and stereochemistry of **140** were initially determined by an extensive application of 1-D and 2-D NMR techniques. This assignment was later confirmed by means of single crystal X-ray diffraction[118] (Figure 10). Compound **140** has a unique and interesting structure. Although there are a few reported all carbon tricyclic systems of this sort,[119] **140** is, to the best of our knowledge, the first and only heterocycle possessing this skeleton. This product was formed as a single (±) diastereomer and possesses five contiguous stereocentres.

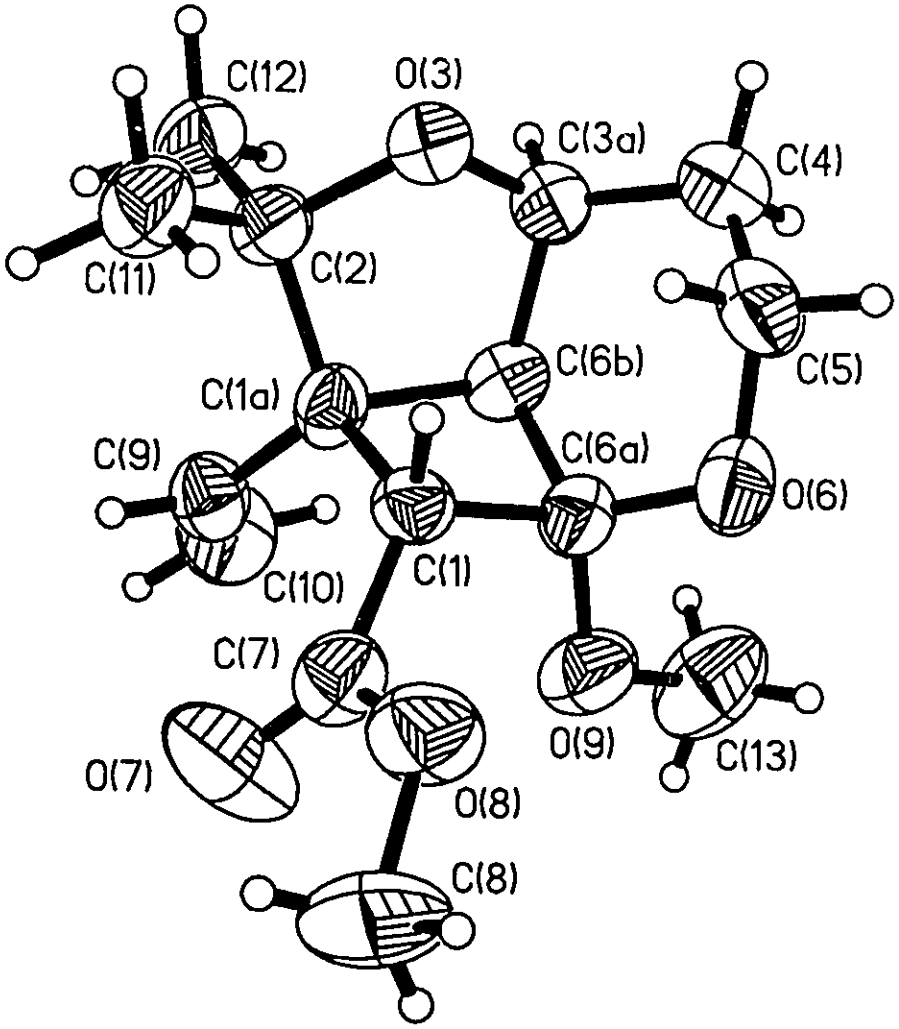
Close inspection of the structure of **140** revealed that it may actually be derived from the minor product **139**. In addition, **140** has a molecular composition which is

formally that of **139** plus one carbene unit. The following proposed mechanistic pathway (Scheme 53) accounts for **139**, as well as its role in the formation of **140**. This mechanism involves a series of about ten sequential steps and provides some interesting chemistry.

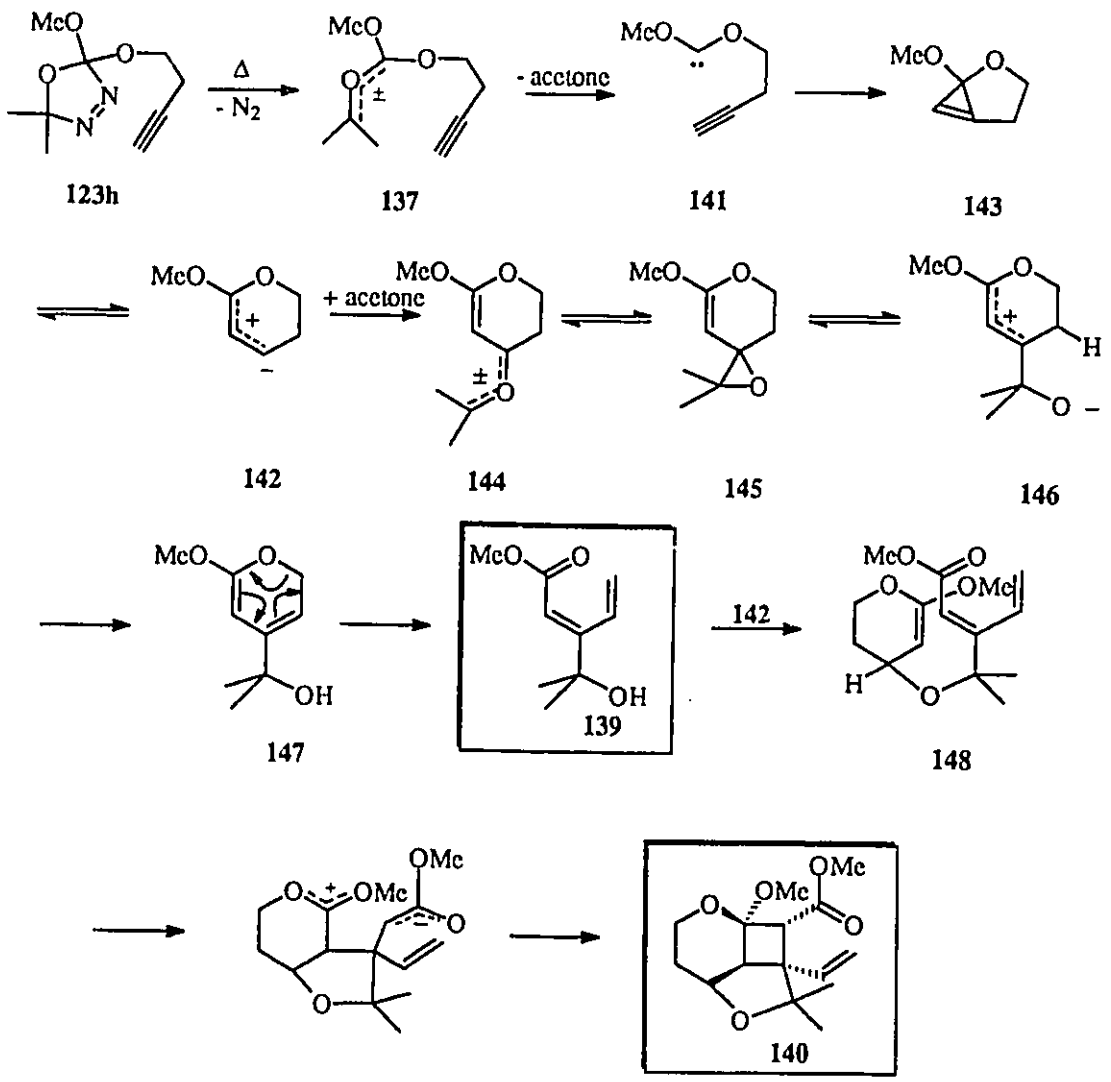
As discussed above, carbene formation from the oxadiazoline may proceed either directly by a concerted loss of both nitrogen and acetone or via an intermediate carbonyl ylide as shown in Scheme 53. The ylide **137**, if it is actually an intermediate along the reaction pathway, does not undergo any observable reactions other than fragmentation to give acetone and (3-butyn-1-oxy)methoxycarbene (**141**).

Because of the nucleophilic nature of dioxycarbenes (Introduction), reactions with unsubstituted multiple bonds are unprecedented.[28] The relatively high temperature (110 ^{o}C) required to generate the carbene from the oxadiazoline, coupled with the intramolecular nature of this system appears to make intramolecular cyclization of the carbene onto the alkyne feasible. A direct analogy can been drawn from the fact that intermolecular radical addition to ethylene proceeds only under extreme conditions,[120] whereas, the cyclization of the 1-hexenyl radical proceeds rapidly at room temperature under very mild conditions[121] as a result of the intramolecularity of the system.

Figure 10: X-Ray Structure of **140.**



Scheme 53



Cyclization of **141** leads to the generation of an endocyclic π-delocalized 3,3-dioxyvinylcarbene **142** via either direct regioselective addition of the carbene onto the terminal alkyne carbon atom, or via a [1+2] cycloaddition of the carbene onto the alkyne,

to give a cyclopropenone ketal **143**, followed by regioselective ring opening as illustrated in Scheme 53.

Carbene **142** does not give products from a possible 1,2-H migration, which is a commonly observed reaction for carbenes with α–hydrogens.[2,6,8] Instead the carbene (**142**) goes on to react with acetone, formed earlier in the decomposition of **123h**, to give **144**, **145**, or **146**. Considering the expected nucleophilicity of this carbene, direct formation of **146** via nucleophilic attack of the carbene is most likely. Dipole **146**, whether formed directly by the reaction of **142** and acetone or via precursors **144** and/or **145**, affords **147** by a proton abstraction. This is the intramolecular equivalent of the second step of an E1 reaction.

Note that the π–delocalized vinylcarbene **142** and acetone do not undergo a formal [3+2] cycloaddition, a reaction which has been observed for other 3,3-dioxyvinylcarbenes with carbonyl compounds (*vide supra*, Introduction).[99,122] This is not surprising since a [3+2] cycloaddition, in this case, would lead to a highly strained compound containing a bridgehead double bond.

An electrocyclic ring opening, closely related to a Claisen rearrangement,[123-125] converts **147** to **139**. There are a number of closely related examples in the literature for the conversion of **147** to **139**.[126] Therefore, the mechanistic pathway described so far accounts for the formation of **139**, which was isolated as the minor product of this reaction.

Compound **139** does not accumulate under the reaction conditions. Instead, as an alcohol, **139** is a highly efficient trap for carbene **142** and affords **148** by an overall O-H

insertion. The fact that the acyclic carbene **141** is not trapped by **139** in a similar manner indicates that intramolecular cyclization of **142** is faster than intermolecular trapping by the alcohol. This is because of the fact that a sufficiently low enough concentration of **139** is maintained throughout the reaction in order to allow **141** to rearrange to **142**.

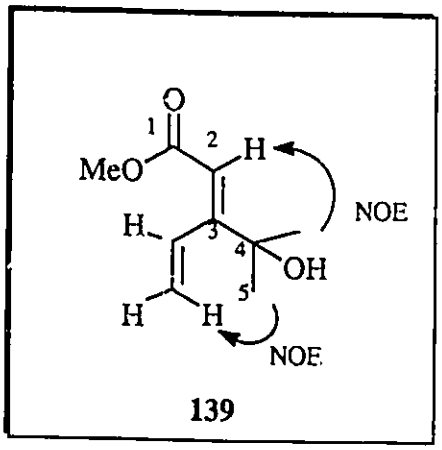
Compound **148** is ideally set up for an intramolecular, thermal, [2+2] cycloaddition between an electron-rich ketene acetal and an electron-poor α,β-unsaturated ester to give the major product (**140**). Analogous intermolecular thermal [2+2] cycloadditions are well known.[127,128] Since a thermal [2+2] cycloaddition is a symmetry forbidden process,[31] this reaction likely proceeds through a short-lived 1,4-zwitterionic intermediate, as shown in Scheme 53. Notice that the initially formed stereocentre, from the O-H insertion of **142** onto **139**, controls the π-facial selectivity of the [2+2] cycloaddition and, therefore, determines the relative stereochemistry of the remaining four stereocentres.

Although the steps in the above mechanism were based either on precedence or valid reasoning, the proposed mechanism was scrutinized carefully because of the incredible efficiency of this multi-step cascade of reactions. The mechanism was tested thoroughly by means of a number of experiments which included deuterium labeling at various positions, as well as trapping of key reactive intermediates.

First, the overall pathway was tested by thermolysis of labeled oxadiazoline **123h**-d_1 (alkyne labeled). This reaction afforded **140**-d_2. The ^{1}H NMR spectrum clearly showed the absence of signals for H-1 and H-6β (Figure 10) as well as the loss of coupling caused by the latter nuclei. Deuterium labeling at these positions (H-1 and H-6β) is in accord with the proposed mechanism (Scheme 53).

The structure of the minor product, **139**, as well as its role in the formation of **140** was firmly established by the following experiment: In this experiment, a small sample of **139** (0.003 mol), isolated from the thermolysis of **123h**, was added to a dilute toluene solution of **123h**-d_1 (0.005 mol) (aikyne labeled). Incorporation of **139** into the major product, as indicated in Scheme 53, should yield **140**-d_1 (H-6β labeled), whereas, the reaction involving only **123h**-d_1 gives **140**-d_2 (H-1 and H-6β labeled), as seen previously. Analysis of the crude thermolysis product by GCMS showed that both **140**-d_1 and **140**-d_2 were indeed formed in a ratio of 46 : 54, respectively, as judged by the relative intensities of the molecular ion peaks. This result confirms the intermediacy of **139** in the formation of **140** as indicated by the postulated mechanism.

Figure 11



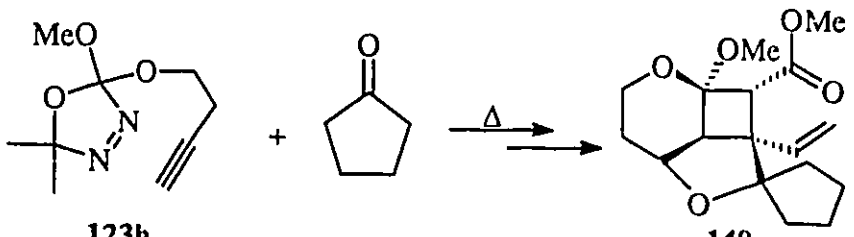
139

The stereochemistry (E or Z) about the central double bond of **139** is most likely maintained, for the most part, in the [2+2] cycloaddition[127,128] that gives the major product **140**. However, to confirm the E stereochemistry of **139**, as is indicated from the structure of **140**, a NOE difference ^{1}H NMR experiment was performed on **139**. Upon saturation of the gem-dimethyl signal at 1.11 ppm the transitions at 5.44 ppm and 6.18 ppm (H-2) were

enhanced (Figure 11). The latter enhancement confirms the E configuration at the central double bond. Therefore, the above results firmly establish the structure and stereochemistry of **139**, and also confirm that the stereochemistry of **139** is maintained in the [2+2] cycloaddition which gives **140**.

The incorporation of acetone from solution as implied by Scheme 53 was tested by thermolyzing **123h** in the presence of acetone-d_6 (4 equivalents). The ^{1}H NMR spectrum of the major product from this reaction was identical to that of **140**, except that the methyl signals were dramatically reduced in intensity because of the formation of **140**-d_6. From the ^{1}H NMR spectrum, the ratio of **140**-d_6 : **140** was estimated to be about 80 : 20, while the mass spectrum gave a comparable ratio of 87 : 13. Therefore, as postulated, acetone from solution is definitely incorporated into the final product (**140**). To further test this aspect of the mechanism, the thermolysis of **123h** was conducted in the presence of cyclopentanone (12.6 equivalents). The major product from this reaction was the cyclobutanone ketal **149** (Scheme 54), which was isolated in 60 % yield. Therefore, trapping of **142** with carbonyl compounds other than acetone is also possible, and provides a means of introducing additional functionality into the major product.

Scheme 54

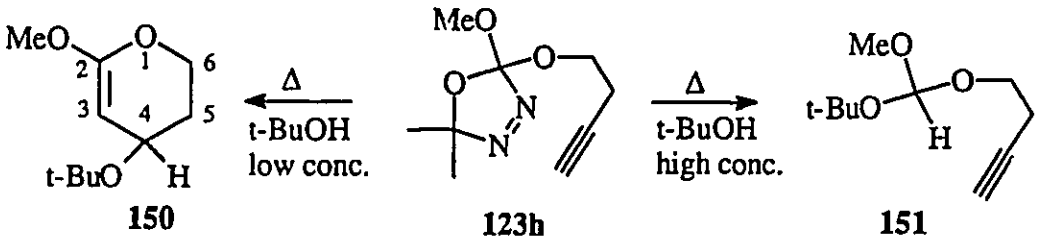


123h **149**

The intermediacy of carbene **142** was demonstrated by trapping the carbene with an alcohol other than **139**. Thermolysis of a dilute toluene solution of **123h** (0.005 M) in the presence of *t*-butyl alcohol (0.015 M) gave the cyclic ketene acetal **150** as the major product (> 95 % by ^{1}H NMR) (Scheme 55) . Attempts to purify **150** by chromatography or by distillation resulted in decomposition. The structure of **150**, however, could be successfully established using spectroscopic data of the crude thermolysis product: in particular, the ^{1}H NMR spectrum contained a one proton, vinyl multiplet at relatively high field (δ = 3.83 ppm, H-3), which is typical for a ketene acetal system.[129] The connectivity around the ring was successfully established by a series of spin decoupling ^{1}H NMR experiments. In addition, long range, four bond couplings between H-5β and H-3, as well as between H-6α and H-4, were indicative of the proposed structure.

In contrast to the above reaction, thermolysis of **123h** (0.05 M) in the presence of *tert*-butyl alcohol at a higher concentration (0.5 M), allowed trapping of the acyclic carbene **141** to a large extent before it could cyclize to **142**. The resulting orthoformate **151** (Scheme 55) was obtained in approximately 90 % yield, and its structure could be successfully assigned from the spectroscopic data of the crude thermolysis product.

Scheme 55

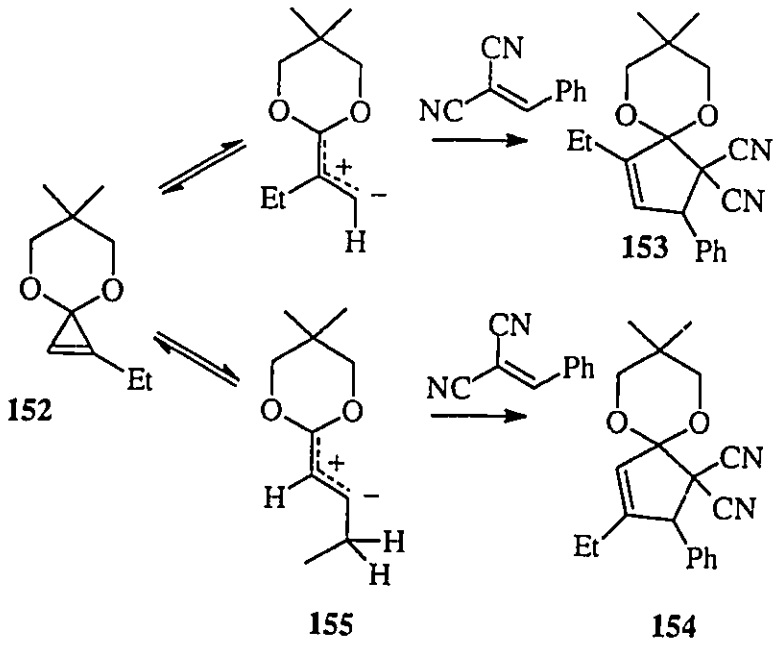


150 **123h** **151**

Of particular interest is the fact that no products derived from a possible 1,2-H migration of carbene **142** (Scheme 53) were observed. There is now excellent precedence for slow 1,2-H migrations in oxygen stabilized carbenes. Moss and co-workers have found that the activation energy for a 1,2-H shift increases with increasing π-electron donor ability of the carbene substituent.[130] Carbenes with substituents that can interact conjugatively with the formally vacant p-orbital have significant π-bonding between the substituents and the divalent carbon (*vide supra*, Introduction). Consequently, such carbenes do not resemble carbocations as much as their more electrophilic counterparts do, and the 1,2-H migration, characteristic of carbocations, is impeded. This observation is in accord with theoretical calculations by Houk.[131] More significantly, as demonstrated by Nakamura and co-workers, the thermal reaction of cyclopropenone ketal **152** with benzylidenemalononitrile affords cycloadducts **153** and **154** in a ratio of 29 : 71 in 82 % overall yield[102] (Scheme 56). Cycloadduct **154** is derived from vinylcarbene **155**, which is a close analog of **142**. In particular, **155** has the same option of 1,2-H migration versus intermolecular reaction. The carbene clearly eschews the former pathway.

One of the most interesting aspects of this amazing cascade of reactions from the thermolysis of **123h** (Scheme 53), is the formation of an intermediate 3,3-dioxyvinylcarbene **142**. Further evidence of this intermediate is provided in the following sections.

Scheme 56



2.3.2 Thermolysis of Oxadiazoline 123h in the Presence of DMAD

The thermolysis of oxadiazoline **123h** in the presence of DMAD was investigated, and some very interesting results were found. An initial thermolysis was conducted with **123h** and DMAD present in 0.051 and 0.106 mol/L concentrations, respectively. This led to the formation of four products, **156**, **157**, **158**, and **159** which were isolated by chromatography in 27, 10, 2, and 1 % yield respectively (Scheme 57). Moreover, variation of the relative concentrations of **123h** and DMAD resulted in significant changes in the product ratios as indicated in Table 2.

Scheme 57

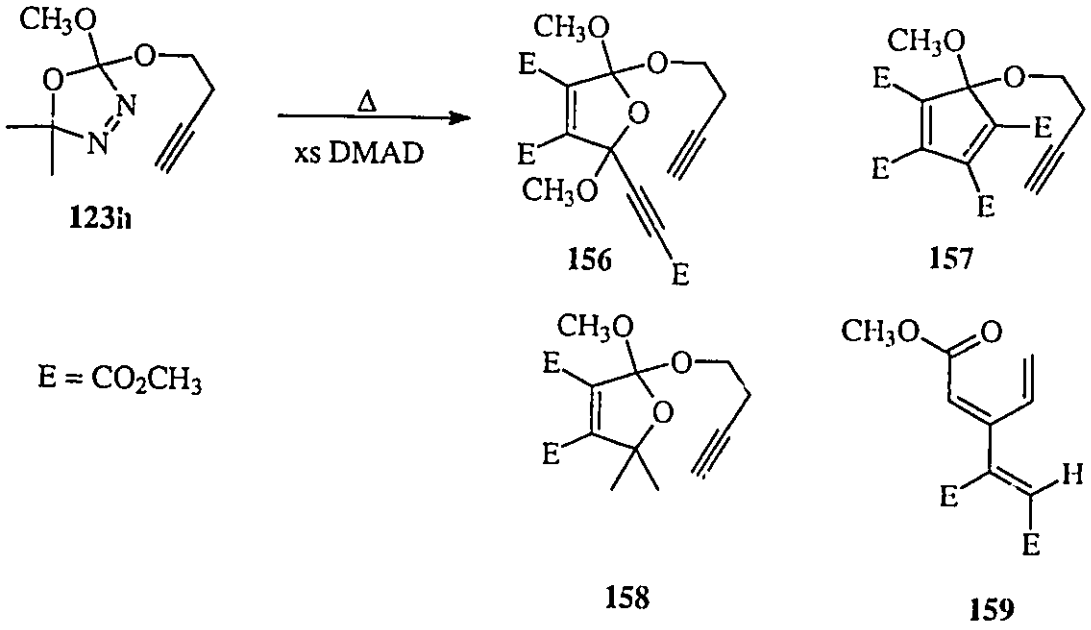


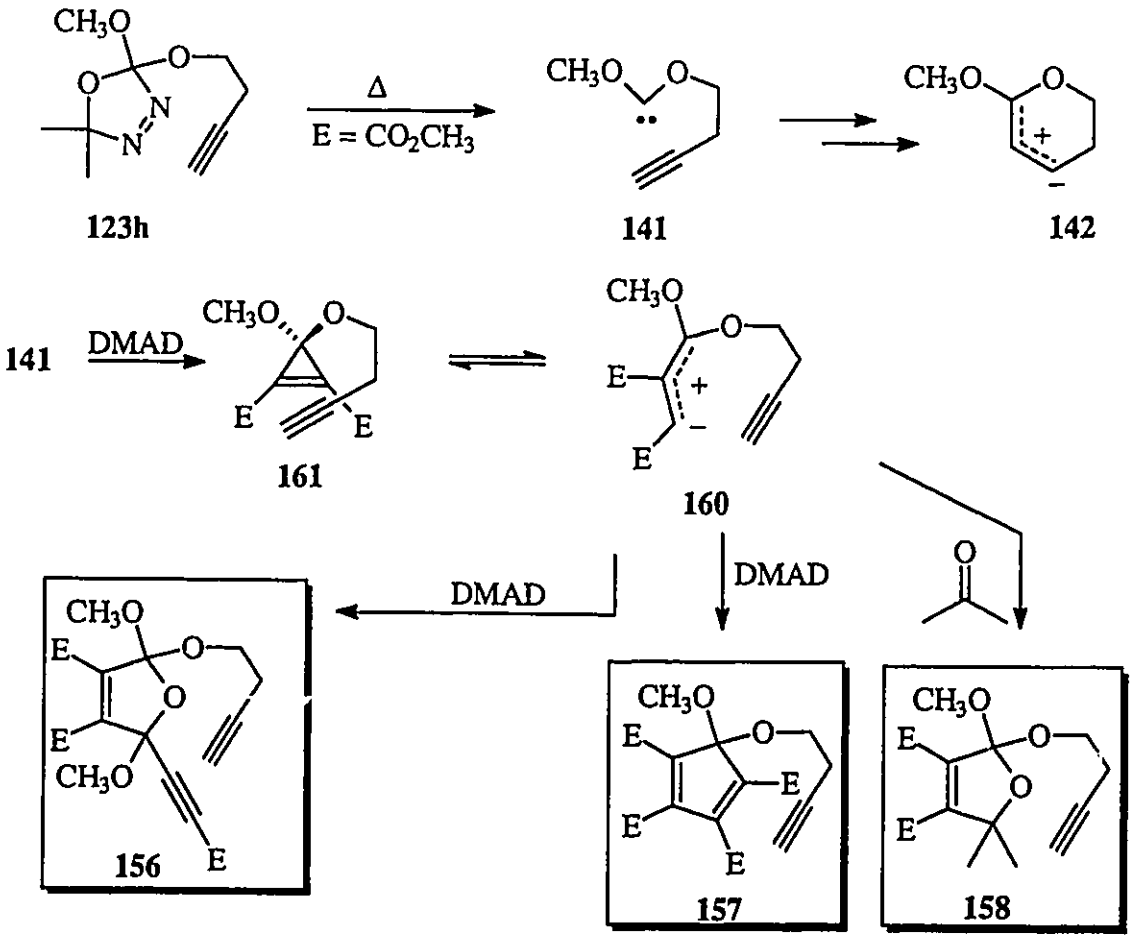
Table 2: Product Ratios from Thermolysis of **123h** in the Presence of DMAD.

Concentration in Toluene (mol / L)		Product ratios (% isolated yield)			
123h	DMAD	**156**	**157**	**158**	**159**
0.051	0.106	27	10	2	1
0.0040	0.012	21	6	-	9
0.0020	0.0020	-	-	-	20

The 2 to 1 adduct **156**, which is the major product at high concentration, is analogous to the only product (**62**, Introduction) reported by Hoffmann and co-workers for the reaction of dimethoxycarbene with DMAD.[70] One possible route to **156** is by a

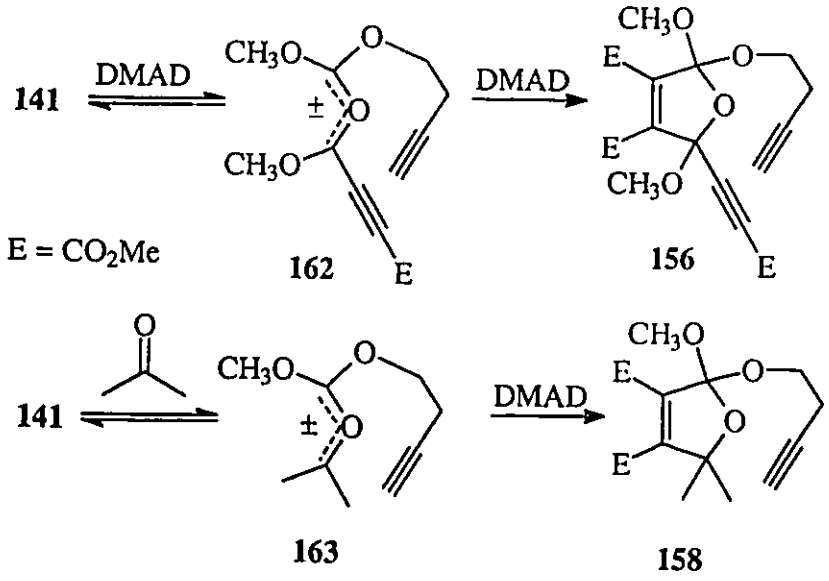
two step mechanism which involves the initial formation of a π-delocalized 3,3-dioxyvinylcarbene **160**, followed by a [3+2] cycloaddition of **160** with the C=O bond of another molecule of DMAD. The vinylcarbene (**160**) may be formed either directly via nucleophilic attack of the carbene onto one of the carbon atoms of DMAD, or via a concerted [1+2] cycloaddition between the carbene and DMAD followed by thermal ring opening of the resulting cyclopropeneone ketal **161** as indicated in Scheme 58.

Scheme 58



An alternative route to adduct **156** may involve the initial formation of a carbonyl ylide **162** by the reaction of carbene **141** with the carbonyl oxygen of DMAD. The ylide **162** can then undergo a [3+2] cycloaddition with the alkyne moiety of another DMAD molecule to give **156** (Scheme 59). In fact, Warkentin and Békhazi have reported a product similar to **156** which is derived from trapping of a carbonyl ylide, generated by the thermolysis of a mono-oxy substituted oxadiazoline, in a [3+2] cycloaddition with DMAD.[106]

Scheme 59

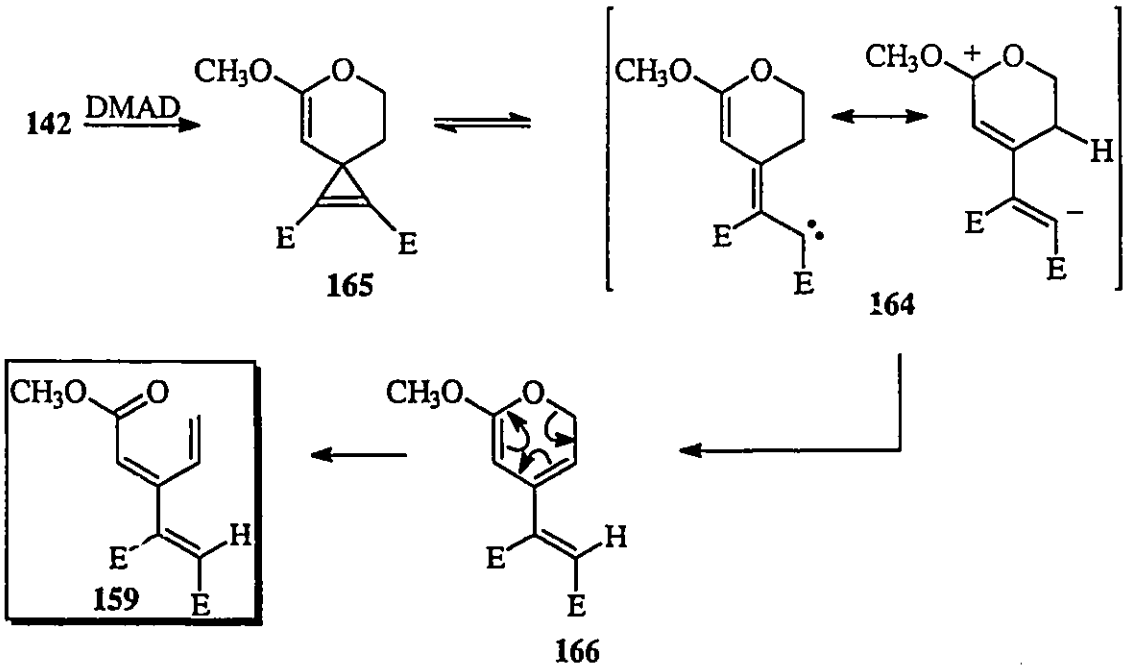


Adduct **158** is composed of a carbene (**141**), a DMAD, and an acetone unit. The same mechanistic arguments presented for the formation of **156** may be applied to the formation of **158**, except for the fact that the carbonyl compound in the case of **158** is acetone instead of DMAD. Again, the adduct may be derived via the initial formation of the π-delocalized 3,3-dioxyvinylcarbene (**160**) as indicated in Scheme 58 or via a carbonyl

ylide (**163**) (Scheme 59). Recall that acetone is generated as a by-product from the thermolysis of the oxadiazoline.

Adduct **157** is derived from a [3+2] cycloaddition of the intermediate π–delocalized 3,3-dioxyvinylcarbene **160** with the alkyne moiety of DMAD. The formation of **157** clearly demonstrates the intermediacy of **160** and suggests that **156** and **158** are likely derived, at least in part via the same intermediate. In fact, given the known proclivity for dioxycarbene attack at the carbonyl carbon, the ylide mechanism (Scheme 59) seems unlikely. A product analogous to **157** was surprisingly not reported by Hoffmann and co-workers[70] in their investigation of the reaction of dimethoxycarbene with DMAD. This may have been because of isolation problems which are normally encountered with the use of 7,7-norbornadienone ketals as dioxycarbene precursors, owing to the formation of a non-volatile by-product and side products.

Scheme 60



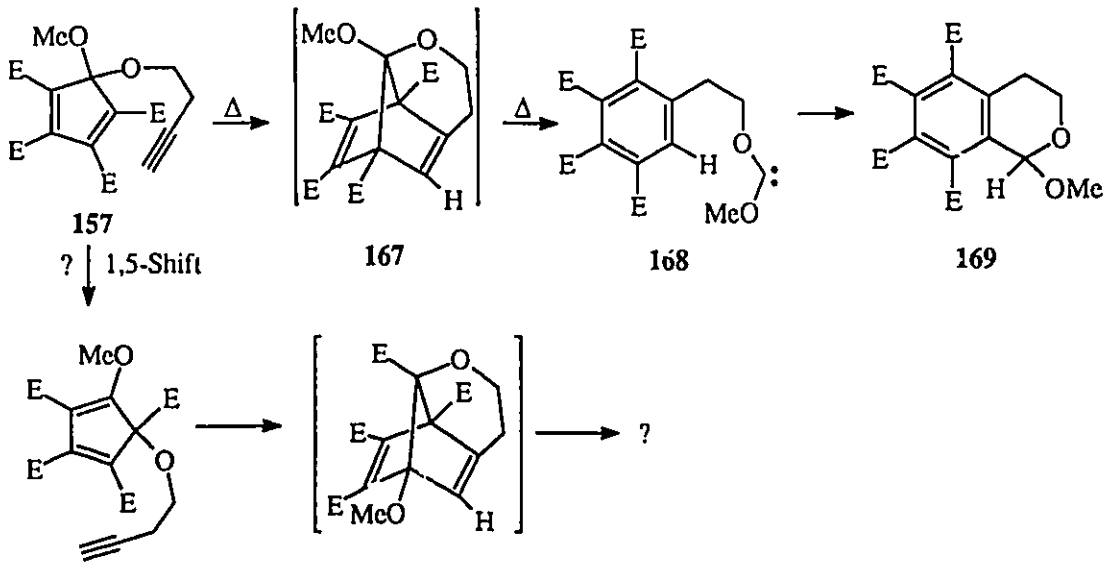
As the concentration of DMAD is lowered with respect to the oxadiazoline concentration, the yield of the products **156**, **157**, and **158** decreases. On the other hand, the yield of **159** increases and moreover at very low overall concentration, **159** is the sole product, which indicates that it is derived from the π–delocalized vinylcarbene **142**. This product (**159**) consists of one carbene unit plus one unit of DMAD.

As illustrated in Scheme 60, **159** is derived from the initial reaction of the cyclic π–delocalized 3,3-dioxyvinylcarbene **142** with DMAD to result in the generation of another reactive intermediate which can be referred to as either a 5,5-dioxyvinylcarbene/1,5-dipole or a π–delocalized 5,5-dioxyvinylcarbene (**164**). The generation of **164** may be via either direct nucleophilic attack of **142** onto one of the alkyne carbons of DMAD, or via ring opening of cyclopropene **165**, which is derived from a [1+2] cycloaddition as illustrated in Scheme 60. Upon formation of **164**, an intramolecular proton abstraction yields **166**. Adduct **159** is then formed from **166** by an electrocyclic thermal ring opening, similar to the one postulated for **147** (Scheme 53).

Although **157** is formed only in a maximum yield of 10 %, this adduct is potentially capable of undergoing an interesting intramolecular Diels-Alder reaction. Such a reaction would produce a 7,7-norbornadienone ketal **167**. Of particular interest is the fact that this adduct, in comparison to 7,7-norbornadienone ketal **32**, would be expected to generate the corresponding dioxycarbene (**168**) under thermal conditions. One possible fate of **168** may be intramolecular insertion into the C-H bond of the aromatic ring as shown in Scheme 61.

Upon heating **157** in toluene (sealed tube) at 150 °C for 48 hours, a mixture of three products were obtained in 12, 26, and 10 % isolated yield. These products, which were isolated by chromatography, all had the same mass as **157**. The ^{1}H NMR and ^{13}C NMR spectra of these products were very similar, and the complex ^{1}H NMR coupling patterns of the two methylene groups in all of these products indicated that the tethered alkyne moiety in **157** must be a part of a ring system as in **169**. Because of the number of quaternary carbons in these products, however, very little structural information could be derived from the NMR data. Although all three of the products seem to be solids, attempts to grow X-ray quality crystals failed in every case.

Scheme 61



One of the three products derived from this reaction may actually be **169**, however this could not be confirmed on the basis of spectroscopic data. The other products, of the same mass as **169**, may be derived from a possible 1,5-shift through the cyclopentadiene system[83] prior to an intramolecular Diels-Alder cycloaddition, as illustrated for an alkoxy shift in Scheme 61. Although the products derived from this reaction may prove to be very interesting, because of the low yield of **157** this reaction was not further investigated.

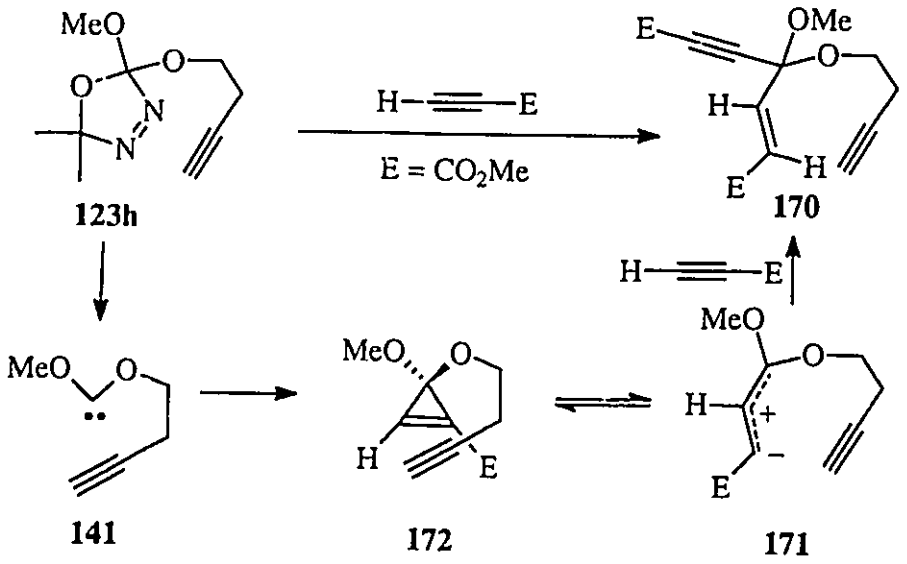
2.3.3 Thermolysis of Oxadiazoline 123h in the Presence of Methylpropiolate

Similar to the thermolysis of **123h** in the presence of DMAD, the thermolysis of this oxadiazoline in the presence of methylpropiolate gave products that were dependent upon the concentration of the trap. Thermolysis of **123h** in the presence of methylpropiolate in high concentration was found to lead to a 2 to 1 adduct which is derived from dioxycarbene **141**, whereas thermolysis at low concentration was found to give two 1:1 adducts which are derived from the cyclic π–delocalized 3,3-dioxyvinylcarbene **142**.

At a high concentration of **123h** and methylpropiolate, adduct **170** is isolated in 28 % yield. This adduct can be attributed to the initial formation of a π–delocalized 3,3-dioxyvinylcarbene **171**, as observed in the reaction of **141** with DMAD. The 3,3-dioxyvinylcarbene, **171**, can either be formed directly or *via* cyclopropenone ketal **172**, as illustrated in Scheme 62. Intermediate **171** is basic enough to deprotonate methylpropiolate to result in an ion pair, which collapses to **170**. This adduct is analogous to **59**, reported earlier by Hoffmann and co-workers,[70] which is derived from the reaction of dimethoxycarbene with phenylacetylene (Introduction). In addition, the last step of this

mechanism bears a striking similarity to the reaction of 3,3-dioxyvinylcarbene **68** with methylpropiolate which was reported by Boger and co-workers[86] (Introduction).

Scheme 62

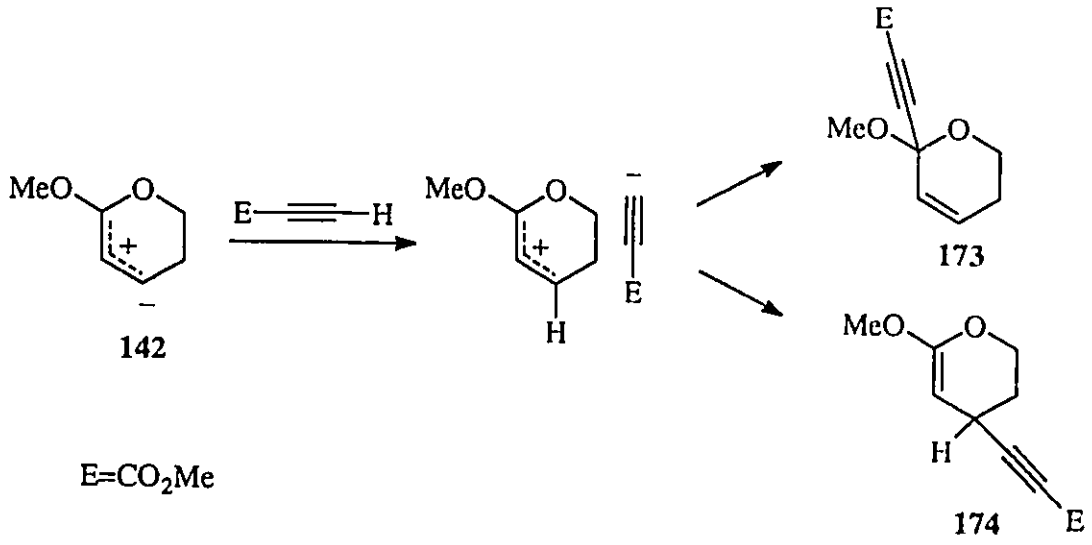


The thermolysis of **123h** in the presence of methylpropiolate in low concentration gives a mixture of products. By GCMS, **170** could not be detected and two major products were observed that have a mass which corresponds to the carbene **141** (or **142**) plus one unit of methylpropiolate. Moreover, analysis of the ^{1}H NMR spectrum of the crude thermolysis product indicates that these products are likely derived from the cyclic carbene **142**, because of the complex coupling pattern of the methylene protons. Upon chromatography isolation of only one of the two products was possible. This product was identified as **173** based on its spectral data. The formation of **173** can be attributed to

initial protonation of the π–delocalized vinylcarbene **142** with methylpropiolate, followed by ion-pair collapse.

The other major product from this reaction, which decomposed during chromatography, may be **174** which is derived from overall insertion of **142** into the C-H bond of methylpropiolate. In fact, the observed sensitivity of this product is in keeping with a ketene acetal structure of **174**. There is, however, no definitive proof for the presence of **174** from the ^{1}H NMR spectra of the crude thermolysis product.

Scheme 63



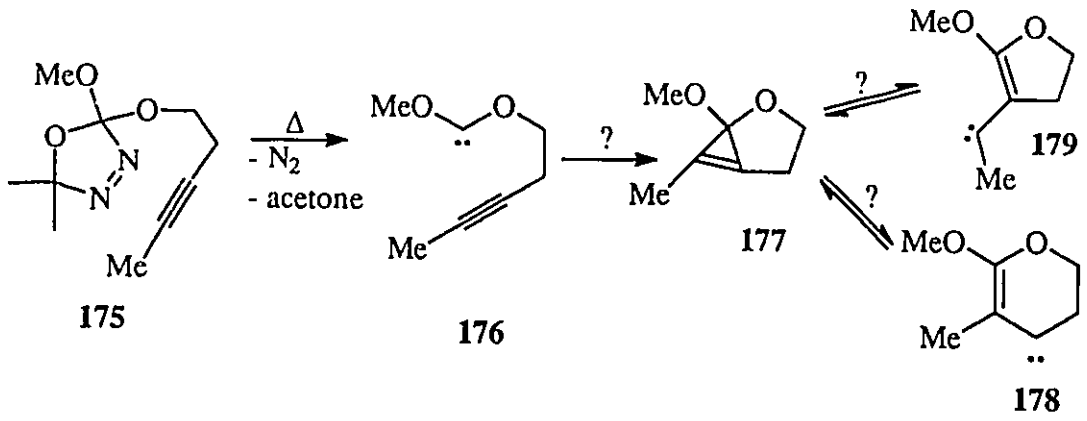
In all of the reactions described above, of particular interest was the fact that the intramolecular reaction of carbene **141** with the tethered alkyne results in the totally regioselective formation of only the endocyclic π–delocalized 3,3-dioxyvinylcarbene **142**. To determine the factors responsible for the highly regioselective formation of **142**, we

investigated the thermolysis of a variety of oxadiazolines which possess substituted tethered alkynes.

2.4 Oxadiazolines with a Substituted Tethered Alkyne

2.4.1 Methyl Substituent

Scheme 64



Oxadiazoline **175** was obtained in 67 % by the acetoxy exchange route, described previously, using commercially available 3-pentyn-1-ol. This oxadiazoline (**175**) was prepared in order to investigate whether the corresponding carbene (**176**) obtained from thermolysis would undergo intramolecular cyclization onto the alkyne moiety and, if so, whether the resulting π–delocalized vinylcarbene would be formed regioselectively (Scheme 64). The π–delocalized vinylcarbene, as mentioned previously, can be derived by either regioselective nucleophilic attack of the carbene onto one of the alkyne carbons or

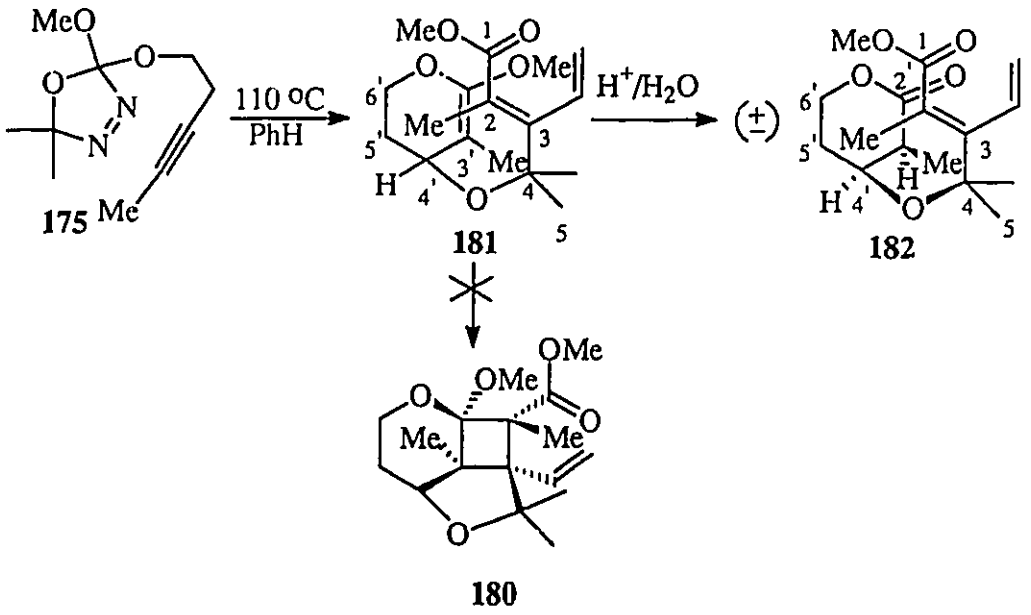
via regioselective ring opening of a cyclopropenone ketal intermediate as illustrated in Scheme 64. Initially, it was believed that the choice between generation of a secondary and a primary vinylcarbene might be the determining factor for the highly regioselective cyclization of **141** to the endocyclic carbene **142** (Scheme 53). Carbene **176** does not have the same choice (Scheme 64) since both the endocyclic (**178**) and the exocyclic (**179**) vinylcarbenes are secondary.

The thermolysis of **175** in benzene (110 °C / sealed tube) afforded a single identifiable product (> 80 % by NMR) which had the mass of two carbene units and one unit of acetone. Although this product was of the correct composition to be a dimethyl analog of **140** (i.e. **180**) (Scheme 65), its ^{13}C NMR spectrum differed dramatically from that of **140**. Furthermore, **140** was easily purified by chromatography, whereas the product from **175** was hydrolyzed during attempted purification by the same method.

The structure of the product obtained from the thermolysis of **175** was firmly established to be **181**, on the basis of spectroscopic data. As further evidence of this structure, the ketene acetal moiety of **181** was hydrolyzed with dilute aqueous acid to give lactone **182**, which was isolated by chromatography. Interestingly, **182** was obtained as a single (±) diastereomer from the hydrolysis of **181**. The magnitude of the coupling constant (^3J = 4.3 Hz) between the two methine protons on the ring indicates that the hydrolysis of **181** proceeded with π-facial selectivity by protonation of the ketene acetal only on the face *anti* to the unsaturated ester moiety. This cis stereochemical assignment was confirmed by estimation of ^3J using a molecular mechanics calculation (PC Model).

The calculated values were found to be ^3J(cis) = 4.4 Hz and ^3J(trans) = 10.7 Hz. The former value matches with the observed coupling constant of ^3J = 4.3 Hz.

Scheme 65



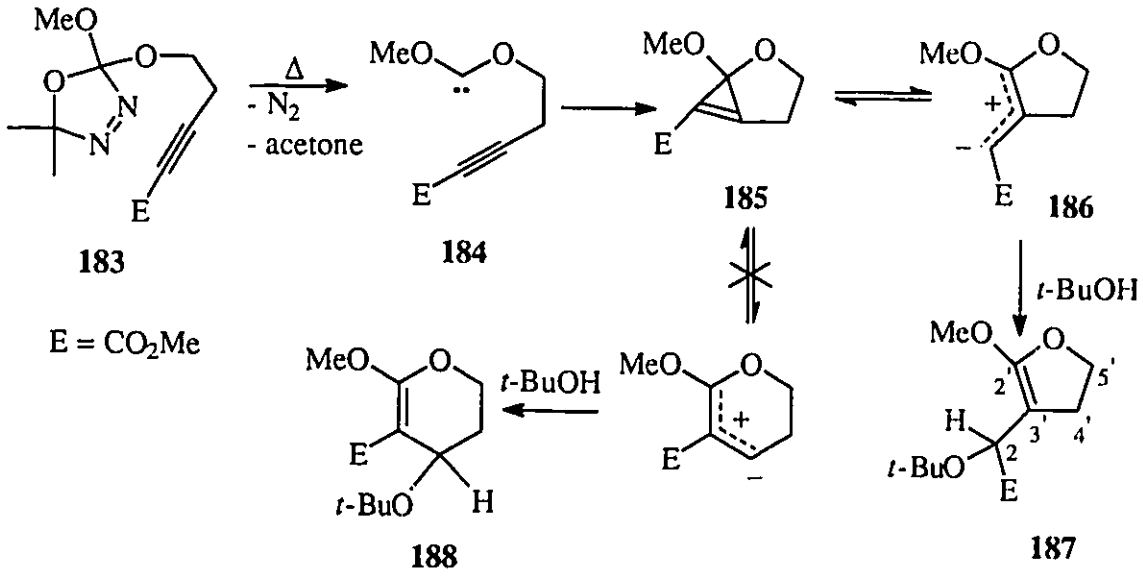
The formation of **181** can be attributed to a cascade of reactions as illustrated in Scheme 53 with the exception that **181** cannot undergo the intramolecular [2+2] cycloaddition to give **180** because of the bulk of the two additional methyl groups. This result is in agreement with Scheeren's finding that disubstituted ketene acetals do not undergo thermal [2+2] cycloadditions with electron-deficient olefins that have only one electron-withdrawing substituent.[127] Formation of **181** verifies that **148** is indeed an intermediate in the thermolysis of **123h** as postulated in Scheme 53.[117] The fact that **181** is formed in high yield indicates that carbene cyclization onto an internal alkyne is facile

(Scheme 64) and gives the endocyclic vinylcarbene **178** with high endo-regioselectivity as observed for **41** (Scheme 53).

2.4.2 Ester Substituent

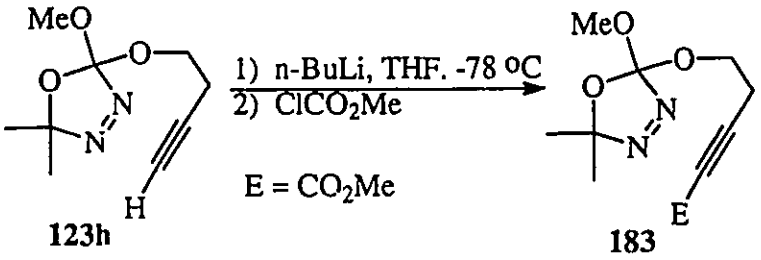
As mentioned in the Introduction, Nakamura and co-workers[102] have shown that anion stabilizing groups, such as ester or phenylthio, demonstrate overwhelming control over regioselectivity in the ring opening of cyclopropeneone ketals.

Scheme 66



Oxadiazoline **183** was prepared in order to investigate whether the ester substituent could be used to direct the cyclization of carbene **184**, which may involve an intermediate cyclopropene (**185**), toward the exocyclic vinylcarbene **186** (Scheme 66).

Scheme 67



123h **183**

Oxadiazoline **183** was prepared by the reaction of **123h** with n-butyllithium to generate the acetylide, followed by treatment of the acetylide with methylchloroformate (Scheme 67). This reaction proceeds without any detectable decomposition of the oxadiazoline ring, thus indicating that oxadiazolines are relatively robust to such synthetic manipulations.

a) Thermolysis of **183** *in the presence of tert-butyl alcohol*

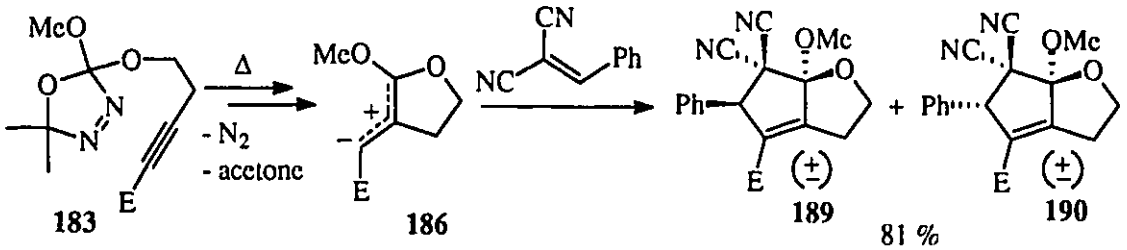
Upon thermolysis (toluene / reflux) of oxadiazoline **183** in the presence of *tert*-butyl alcohol at a low concentration, ketene acetal **187** was obtained in high yield (>85 % by ^{1}H NMR spectroscopy). The absence of other carbene + alcohol trapping products (i.e. **188**) detectable by GCMS clearly indicates that, in contrast to the previous systems studied (**141** and **176**), cyclization of **184** produces the exocyclic vinylcarbene (**186**) with total regioselectivity (Scheme 66).

b) Thermolysis of **183** *in the presence of benzylidenemalononitrile: [3+2] Cycloaddition*

It has been demonstrated, first by Boger and co-workers,[85,86,92,97,132,133] and later by Nakamura and co-workers,[102] that π-delocalized 3,3-dioxyvinylcarbenes behave as highly efficient 1,3-dipoles in their reactions with benzylidenemalononitrile, and other analogous electron-deficient olefins, to yield substituted cyclopentenone ketals. The regioselective formation of the exocyclic π–delocalized vinylcarbene **186** prompted us to investigate the possibility of trapping this vinylcarbene with an appropriate olefin in a [3+2] cycloaddition reaction.

Thermolysis of **183** (toluene / reflux) in the presence of benzylidenemalononitrile at a low concentration led to the clean formation of a diastereomeric mixture of **189** and **190** (ratio 45 : 55) which were isolated by chromatography in a combined yield of 81 % (Scheme 68). This tandem sequence, involving an intramolecular carbene cyclization followed by an intermolecular [3+2] cycloaddition, leads to the rapid and efficient formation of an interesting bicyclic ring system which may be useful as a precursor in organic synthesis.

Scheme 68



183 **186** **189** **190**

81 %

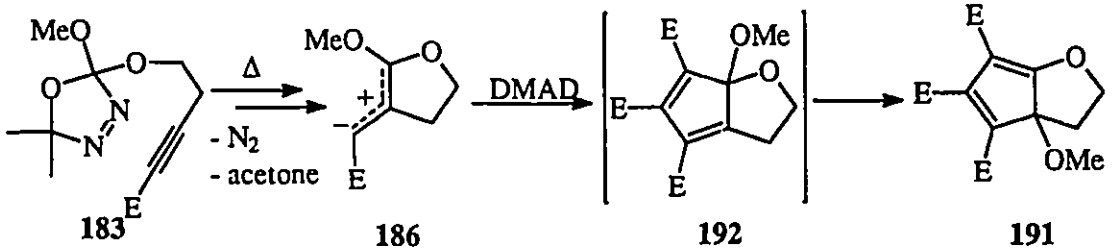
E = CO_2Me

c) Thermolysis of **183** *in the presence of DMAD: [3+2] Cycloaddition*

The thermolysis (toluene / reflux) of oxadiazoline **183** in the presence of DMAD at low concentration also led to the construction of an interesting bicyclic product (**191**) which was isolated in 30 % yield (Scheme 69). The formation of this product is attributed to an initial [3+2] cycloaddition between the intermediate vinylcarbene **186** and DMAD to give **192**, followed by a 1,5-methoxy[134] shift (Scheme 69). The ^{1}H NMR spectrum of the crude thermolysis product indicated that **191** was the major product (> 80 %) of this reaction. The fact that **191** was isolated in only up to 30 % yield suggests that it must have partially decomposed during chromatography. No evidence for the initial [3+2] cycloadduct (**192**) could not be detected (< 3 %) in the crude thermolysis product, therefore the 1,5-shift is facile under the reaction conditions (refluxing toluene) and greatly favors the formation of **191**.

In contrast to the above result, Boger and Brotherton reported that the generation of a π–delocalized 3,3-dioxyvinylcarbene in the presence of DMAD failed to give a [3+2] adduct.[86] The ester substituent may possibly play a role in the successful cycloaddition of **186** with DMAD.

Scheme 69



183 **186** **192** **191**

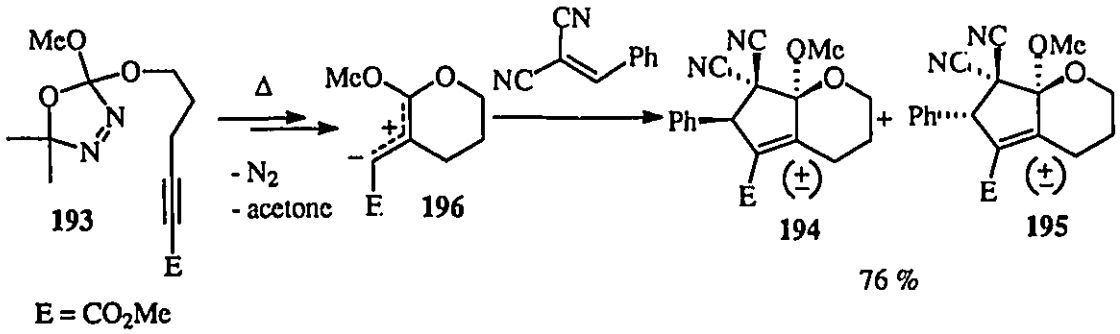
E = CO_2Me 30 %

2.4.3 Ester Substituent: Extension of the Tether

a) Thermolysis of **193** *in the presence of benzylidenemalononitrile: [3+2] Cycloaddition*

Extension of the alkyne tether by one methylene unit was found not to alter the observed chemistry of the oxadiazoline. Oxadiazoline **193** was prepared from the unsubstituted oxadiazoline (**123i**) in the same manner as oxadiazoline **183** (Scheme 67). The thermolysis of oxadiazoline **193** (toluene / reflux) in the presence of benzylidenemalononitrile (low concentration) led to the clean formation of diastereomeric adducts **194** and **195** (46:54 ratio), which can be attributed to a [3+2] cycloaddition between 3,3-dioxyvinylcarbene **196** and the olefin. The adducts were isolated by chromatography in a combined yield of 76 % (Scheme 70). The diastereomers in this case were separable.

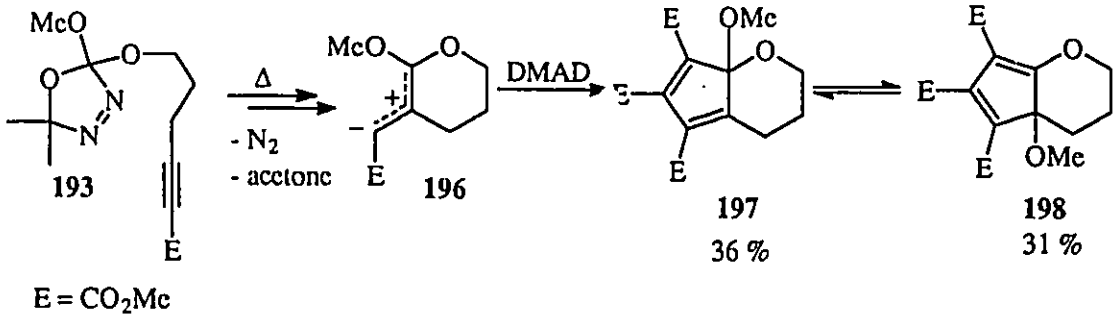
Scheme 70



b) Thermolysis of **193** *in the presence of DMAD: [3+2] Cycloaddition*

In contrast to the above thermal reaction of **183** with DMAD (Scheme 70) which gave a single cycloadduct (**191**), the thermolysis of oxadiazoline **193** in the presence of DMAD gave a mixture of two isomeric cycloadducts, **197** and **198**, which were found to be in a 55 : 45 ratio as estimated from the ^{1}H NMR spectra of the crude thermolysis product (Scheme 71). These cycloadducts were separated by chromatography in 36 % and 31 % yield, respectively.

Scheme 71



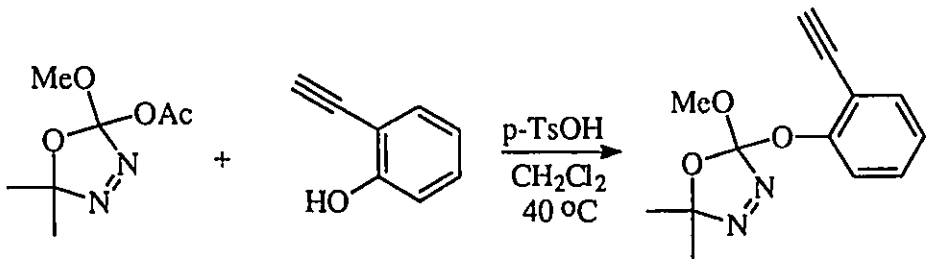
The formation of cycloadduct **197** can be attributed to a [3+2] cycloaddition between the intermediate π–delocalized vinylcarbene (**196**) and DMAD. And cycloadduct **198**, a product analogous to **191**, is derived from **197** by a thermal 1,5-methoxy shift.[134] Heating a pure sample of either **197** or **198** at 110 °C for 12 hours gave a mixture of **197** and **198** in the same ratio as that observed for the crude thermolysis product. This result indicates that, in contrast to the formation of **191**, the 1,5-methoxy shift that gives **198** is

an equilibrium process with K ≡ 0.8 (Scheme 71), and that equilibrium is established during the thermolysis.

2.5 Thermolysis of Oxadiazolines 199 and 210 : Synthesis of Novel Benzofuran Systems

Aryloxymethoxy substituted oxadiazoline **199** was prepared by an acid catalyzed exchange reaction between the acetoxymethoxyoxadiazoline **132** and ortho-hydroxyphenylacetylene in CH_2Cl_2 (Scheme 72). The *ortho*-hydroxyphenylacetylene was prepared according to the procedure reported by Prey and Pieh.[135] For the exchange to proceed at a reasonable rate, p-toluenesulfonic acid had to be used and the solution was refluxed.

Scheme 72



132 **199**

This oxadiazoline was prepared in order to investigate whether the carbene resulting from thermolysis (**200**) would undergo an intramolecular cyclization onto the tethered alkyne moiety and, if so, whether the resulting vinylcarbene would be formed regioselectively as observed for **141**, **176**, **186**, or **196** (vide supra). The geometry of the initially formed aryloxymethoxycarbene **200** is considerably different from that of **141**, **176**, **186**, or **196**, since the tether now consists of four atoms (from oxygen to the terminal

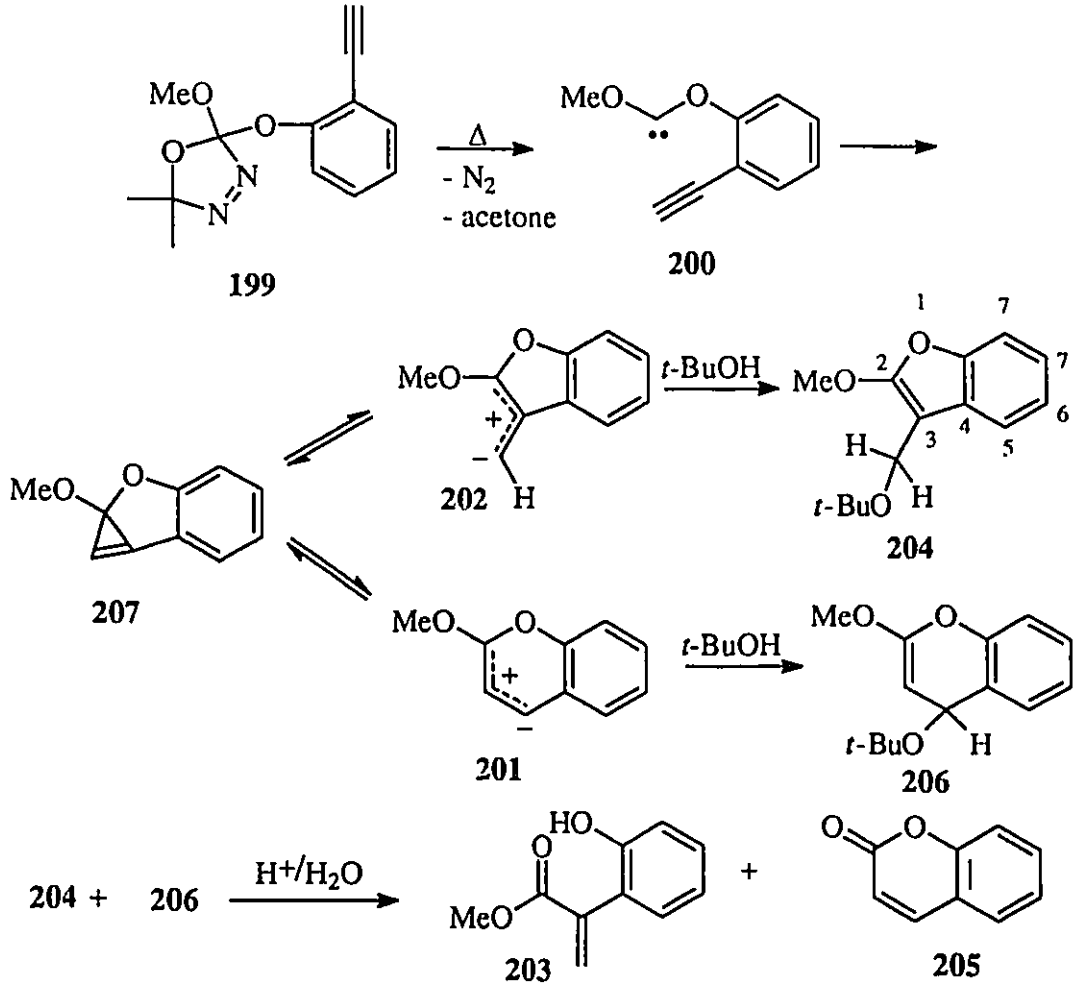
alkyne carbon atom) that are coplanar. In addition, the electronic properties of both the carbene and the alkyne are considerably different from those of **141** because of the presence of the aromatic ring.

2.5.1 Thermolysis of 199 in the Presence of t-BuOH

Thermolysis (refluxing toluene) of oxadiazoline **199** in the presence of *tert*-butyl alcohol at a low concentration gave one major product with the mass of one carbene unit plus the alcohol. This composition was inferred from the mass spectra (GCMS) of the crude thermolysis product. Attempted purification of this product by chromatography or by distillation led to decomposition. The sensitivity of this product was not surprising since the expected product from either the endocyclic (**201**) or the exocyclic (**202**) 3,3-dioxyvinylcarbene is a ketene acetal, a class of compounds that are prone to hydrolysis or polymerization.[127,128] Consequently, the crude thermolysis product was intentionally hydrolyzed (p-TsOH / H_2O) to give a stable compound that could be purified by chromatography (Scheme 73). The major product obtained from hydrolysis was isolated in 40 % yield and was shown to have the structure of **203** on the basis of spectral data. The formation of **203** was attributed to hydrolysis of **204**, which is derived from an O-H insertion reaction of the exocyclic vinylcarbene **202** with the alcohol. The presence of **204** was later confirmed based on the spectroscopic data of the crude thermolysis mixture. Therefore, in contrast to **141** which cyclizes to give an endocyclic π–delocalized 3,3-dioxyvinylcarbene (**142**), the cyclization of **200** seems to give primarily the exocyclic vinylcarbene **202**. In retrospect, analysis of the ^{1}H NMR spectra and GCMS trace of the crude hydrolysis mixture also showed evidence of coumarin[136] (**205**), which is likely

obtained from hydrolysis of **206**. The formation of **206** can be attributed to trapping of the endocyclic vinylcarbene **201** with *tert*-butyl alcohol. The ratio of **203** : **205** was estimated to be approximately 5 : 1 by ^{1}H NMR spectroscopy indicating a moderately high preference for the exocyclic vinylcarbene **202** which may be formed either *via* regioselective ring opening of cyclopropenone ketal **207** as illustrated, or *via* direct regioselective intramolecular attack of the carbene onto the internal alkyne carbon.

Scheme 73

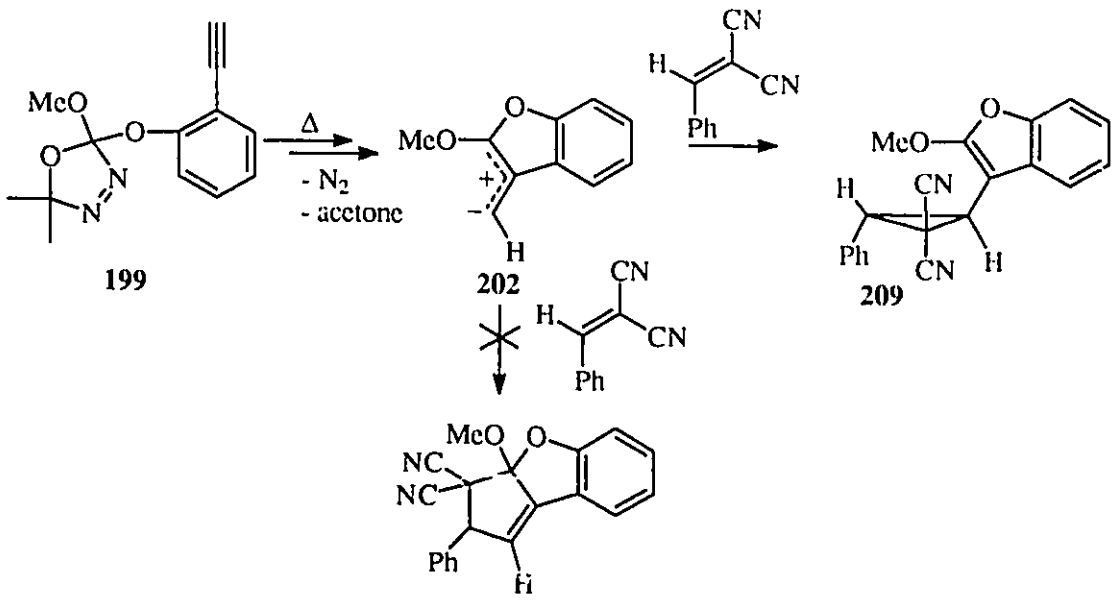


2.5.2 Thermolysis of 199 and 210 in the Presence of Benzylidenemalononitrile: [1+2] Cycloaddition

The preferential generation of an exocyclic π–delocalized 3,3-dioxyvinylcarbene **202**, upon thermolysis of oxadiazoline **199**, raises the possibility of capturing the major vinylcarbene **202** in a [3+2] cycloaddition with a highly electron-deficient olefin such as benzylidenemalononitrile. This cycloaddition would lead to the formation of a novel functionalized tricyclic benzofuran ring system **208** (Scheme 74).

Thermolysis of oxadiazoline **199** in the presence of benzylidenemalononitrile in low concentration led to the formation of one major product in 67 % yield. This product had the mass (by e.i. mass spectrometry) expected for **208**. Surprisingly, only a single diastereomer was formed. The ^{1}H NMR and ^{13}C NMR spectra of this product, on the other hand, were not consistent with the structure of **208**. Most significantly, in the ^{1}H NMR spectra, two doublets corresponding to two methine protons were too far up field to be consistent with the structure of **208** and, in addition, the ^{13}C NMR spectra displayed a resonance at high field (δ: 14.4 ppm) which could not be assigned to a carbon of **208**. This product was later confirmed to have the structure **209** based on comparison of the ^{1}H and ^{13}C NMR spectra of this product with those of a close analog (**211**, *vide infra*) whose structure was unambiguously determined by single crystal X-ray diffraction.

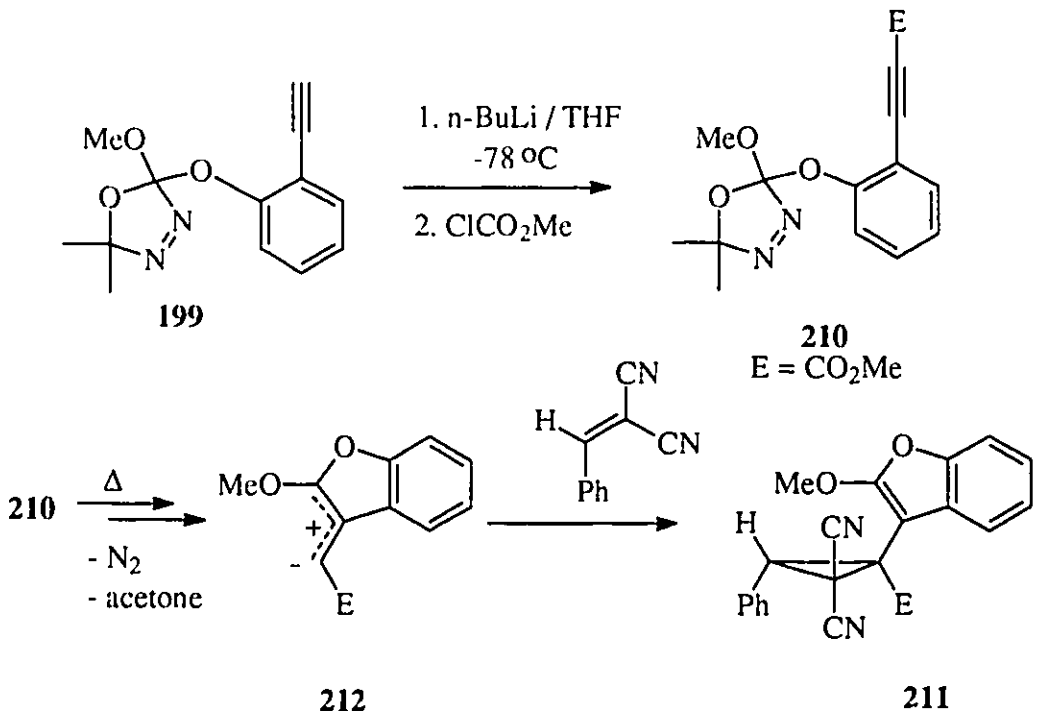
Scheme 74



199 **202** **209** **208**

The formation of **209** is highly unusual since the reaction of a 3,3-dioxyvinylcarbene with benzylidenemalononitrile, or related olefins, has been shown to give [3+2] cycloadducts in every case studied by our group and also by others[85,86,92,97,102,132,133] (*vide supra*). There has been no evidence in support of formation of a [1+2] cycloadduct. Of further interest is the fact that **209** was formed with *trans* stereoselectivity on the cyclopropane ring.

Scheme 75

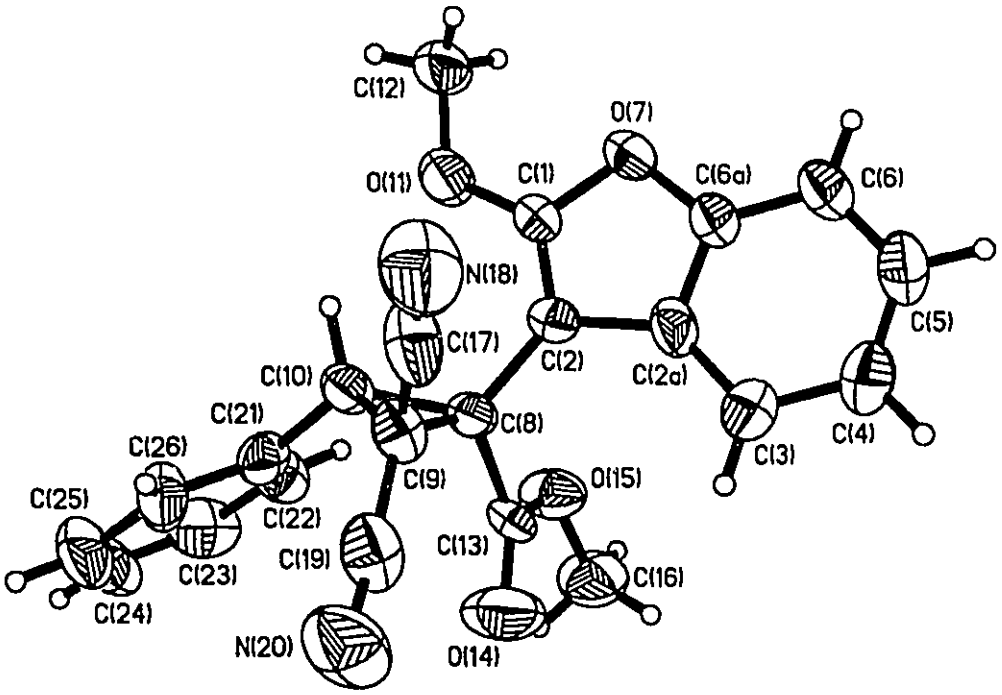


An ester substituted analog of **209** was prepared in order to investigate whether the ester group may have played a role in facilitating the [3+2] cycloaddition of **186** or **196** with benzylidenemalononitrile. The ester substituted oxadiazoline **210** was prepared from **199** by deprotonation of the alkyne moiety with n-butyllithium, to form the corresponding acetylide, followed by treatment of the acetylide with methylchloroformate (Scheme 75).

Thermolysis of **210** in the presence of benzylidenemalononitrile in low concentration led to the formation of one major product (**211**) which has NMR spectra closely resembling those of **209** (Scheme 73). This product was isolated in 37 % yield and its structure was determined by single crystal X-ray diffraction (Figure 12). The formation of **211** can be attributed to a [1+2] cycloaddition of the intermediate 3,3-

dioxyvinylcarbene (**212**), and similar to the formation of **209**, only one stereoisomer was obtained, in which the benzofuran and the phenyl groups are *trans*.

Figure 12: X-Ray Structure of **211**



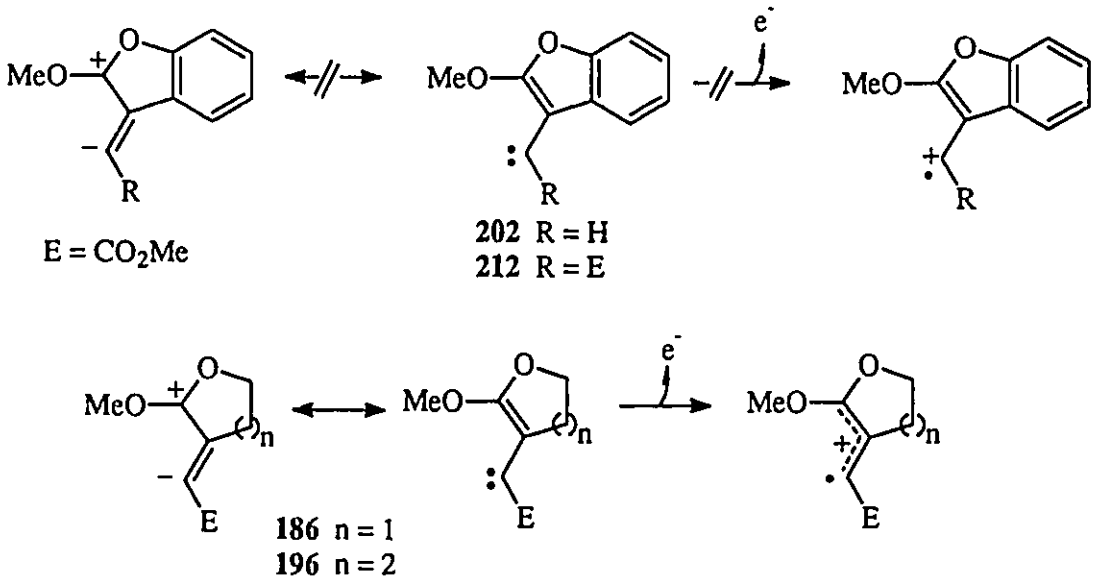
The stereochemistry observed for both **209** and **211** can be rationalized simply on the basis of steric effects. The transition state for the [1+2] cycloaddition where the benzofuran moiety of the vinylcarbene is *syn* with respect to the phenyl group of the olefin suffers greater steric hindrance than if the two groups are *anti*.

The fact that both of the vinylcarbenes **202** and **212** undergo a [1+2] cycloaddition and not a [3+2] cycloaddition with benzylidenemalononitrile is of significant interest. As mentioned previously, the [3+2] cycloaddition is the exclusive pathway for the reaction of

π–delocalized 3,3-dialkoxyvinylcarbenes with olefins with geminal electron-withdrawing groups.

The different behavior of vinylcarbenes **202** and **212** in comparison to other 3,3-dioxyvinylcarbenes such as **186** and **196** may be rationalized by the fact that **202** and **212** have less 1,3-dipolar character and are therefore more likely to behave as typical localized carbenes. The reduced 1,3-dipolar character may stem from two possible sources. First, π–donation into the formally vacant carbene p-orbital is reduced because of the inherently poorer electron donating ability of an aryloxy substituent in comparison to an alkoxy substituent. Secondly, benzofuran is a ten π-electron aromatic ring system and both **202** and **212** lose some aromatic stabilization in the canonical 1,3-dipolar form (Scheme 76).

Scheme 76



As a result of the poorer π-electron delocalization of carbenes **202** and **212**, a single electron transfer from the carbene to the olefin which, according to Boger is

required for a [3+2] cycloaddition, would result in a radical cation that is less stabilized than the corresponding radical cation from systems which have two alkoxy groups (i.e. **186** or **196**) (Scheme 76). Consequently, the reason that **202** and **212** undergo a [1+2] cycloaddition, instead of a [3+2] cycloaddition, with benzylidenemalononitrile is likely because of the inability of these carbenes to transfer an electron to the olefin, and therefore provides support for Boger's proposed mechanism for the [3+2] cycloadditions. Nevertheless, the fact that these vinylcarbenes (**202** and **212**) undergo facile reaction with the highly electron-deficient olefin implies that these carbenes still have pronounced nucleophilic character.

The thermolysis of **199** or **201** in the presence of a low concentration of DMAD produces a complex mixture of products. This clearly indicates the dramatically different nature of vinylcarbenes **202** and **212** in comparison to vinylcarbenes **186** and **196**, which undergo a [3+2] cycloaddition with DMAD.

2.5.3 Vinylcyclopropane Rearrangement Of Adducts 209 and 211

The vinylcyclopropane rearrangement in simple unsubstituted systems has been extensively studied.[137] This transformation has also been exploited in a number of synthetic applications for the construction of substituted cyclopentenes.[138-140]

In theory, cycloadducts **209** and **211** have the possibility of undergoing a vinylcyclopropane rearrangement. This rearrangement may possibly provide the interesting ring system which was initially expected from the possible [3+2] cycloaddition

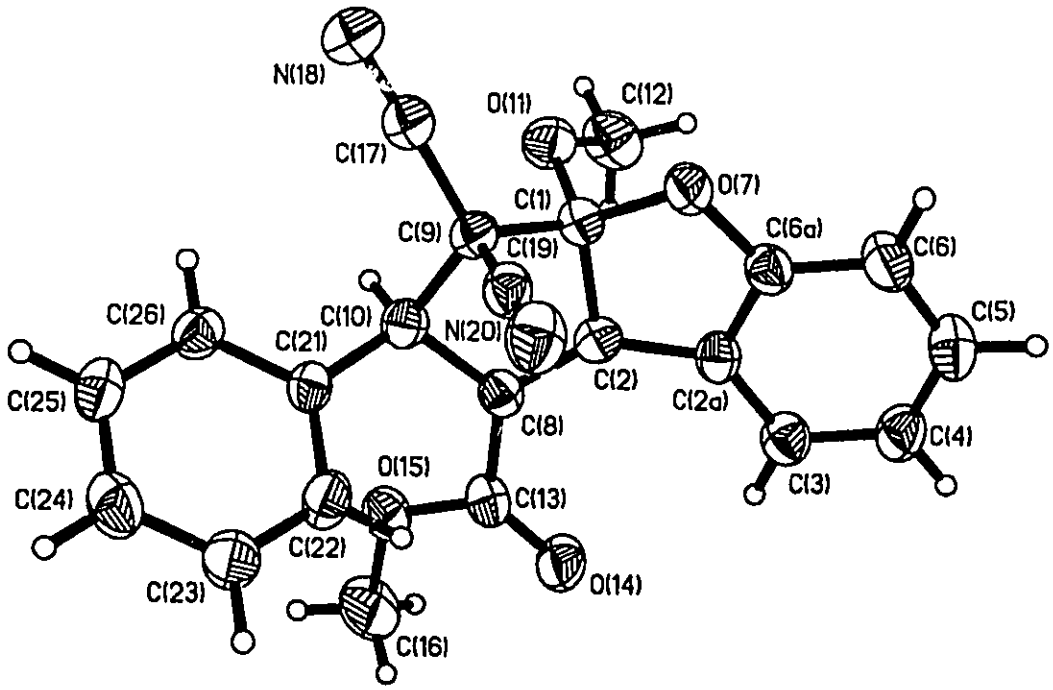
of vinylcarbenes **202** or **212** with benzylidenemalononitrile. In contrast to the desired rearrangement, Boger and Brotherton have shown that cyclopropane ketene acetals such as **76** (Introduction), which are closely related to **209** and **211**, do not undergo rearrangement even at temperatures as high as 200 °C. Nevertheless adducts **209** and **211** may be more likely than **76** to undergo the vinylcyclopropane rearrangement because of the presence of the two electron-withdrawing cyano groups on the cyclopropane ring, which would be expected to stabilize a possible zwitterionic or biradical intermediate. If this proposed rearrangement proceeds, the fact that **209** and **211** are diastereomerically pure adds a further dimension to this investigation, whether that rearrangement proceeds diastereoselectively.

Initially, heating a sample of **211** (toluene/sealed tube) at 150 °C in an oil bath for four days led to the formation of a mixture of products, in addition to a significant amount of unreacted vinylcyclopropene **211** (≈ 40 %). The major product (≈ 25 %) was found to have a mass (by high resolution mass spectrometry) that corresponds to the mass of **211** plus an extra oxygen atom. This product could not be firmly identified by NMR spectroscopy and, although it is a solid, attempts to grow crystals of satisfactory quality for X-ray determination failed. The additional oxygen atom is likely derived from molecular oxygen since the sample was not degassed prior to heating.

The above reaction was repeated, however this time the sample was first degassed. It was found that **211** was indeed converted to the expected product (**212**) by a vinylcyclopropane rearrangement, as inferred from the spectroscopic data and later confirmed by single crystal X-ray diffraction (Figure 10). The reaction proceeded very

cleanly; however, even after four days at 150 °C, the conversion was about 50 % complete.

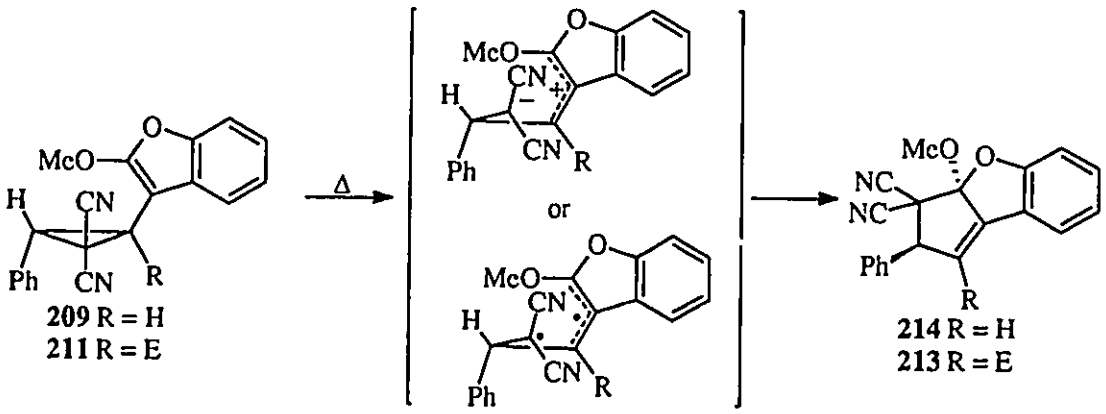
Figure 13: X-Ray Structure of **213**



Of particular interest was the fact that only a single diastereomer was obtained which indicates that the vinylcyclopropane rearrangement proceeds in a totally stereoselective manner. Specifically, the closure of a possible dipolar or zwitterionic intermediate in this rearrangement proceeds with π-facial selectivity (Scheme 77) or alternatively, the rearrangement proceeds in a totally concerted manner. In any case, this two step approach, involving an initial [1+2] cycloaddition to give a cyclopropane ketene

acetal followed by a vinylcyclopropane rearrangement results in the totally diastereoselective formation of a very interesting ring system (**213**).

Scheme 77



Cyclopropane ketene acetal **209** was also shown to undergo a vinylcyclopropane rearrangement, albeit more slowly, under similar conditions. After four days at 150 °C, the conversion was about 33 % complete. The rearrangement in this case also proceeds diastereoselectively to provide **214**.

Conclusion

Oxadiazolines are a highly efficient thermal source of dioxycarbenes that display a number of very desirable advantages over previously known dioxycarbene precursors. Both the "lead tetraacetate oxidation method" and the "acetoxy exchange method" provide simple and very convenient approaches to a large variety of different

dioxyoxadiazolines. Moreover, these dioxycarbene precursors are ideally suited for the investigation of the intramolecular cyclizations of dioxycarbenes.

As demonstrated by the groups of Boger, and of Nakamura, 3,3-dioxyvinylcarbenes are a very interesting and synthetically useful class of reactive intermediates. We have shown that both endocyclic and exocyclic 3,3-dioxyvinylcarbenes can be selectively generated *in situ* by the intramolecular reaction of a dioxycarbene with a tethered triple bond. The regioselectivity of vinylcarbene formation was shown to be completely controlled by the nature of the alkyne substituent.

For the situation in which the alkyne substituent is H or Me, lower ring strain may be responsible for the highly regioselective generation of the endocyclic vinylcarbene over the exocyclic vinylcarbene. However, when the alkyne substituent is an ester, electronic stabilization of the vinyl anion/carbene moiety in the exocyclic vinylcarbene overrides stabilization from ring strain in the endocyclic vinyl carbene, to result in the highly regioselective formation of the exocyclic vinylcarbene.

The generation of an endocyclic vinylcarbene was shown to result in an interesting cascade of reactions, which begin with initial reaction of the vinylcarbene with acetone, to provide a complex novel tricyclic ring system. The proposed mechanism of this interesting cascade of reactions was firmly established by a number of labeling experiments as well as by the capture of key intermediates.

The generation of an exocyclic π–delocalized vinylcarbene allows efficient [3+2] cycloaddition with an appropriate olefin or alkyne, for the rapid construction of novel

bicyclic products. This sequence is mechanistically very interesting and also synthetically useful.

In one example, generation of a unique exocyclic 3,3-dioxyvinylcarbene in the presence of an electron-deficient olefin, benzylidenemalononitrile, led to an unexpected [1+2] cycloadduct. This reaction provides support for Boger's proposed single electron transfer mechanism for the [3+2] cycloaddition of 3,3-dioxyvinylcarbenes with highly electron-deficient olefins.

Chapter 3: EXPERIMENTAL

3.1 General Methods. NMR spectra were recorded on a Bruker DRX-500, AM-500, AC-300, or AC-200 spectrometer. Chemical shifts for ^{1}H NMR spectra were measured using TMS (δ = 0), C_6H_6 (δ = 7.15) , or $CHCl_3$ (δ = 7.24) an internal reference, while ^{13}C-NMR spectra were referenced to the chloroform-*d* triplet (δ = 77.0) or benzene-d_6 triplet (δ = 128.0). Mass spectra were recorded on a ZAB-E double-focusing mass spectrometer or on a Hewlett Packard MSD GCMS. FTIR spectra were obtained with a Bio-Rad, FTS-40 instrument. Benzene, toluene, and THF were distilled from sodium benzophenone ketyl, and dichloromethane was distilled from calcium hydride. Chromatography solvents (EtOAc and hexanes) were distilled before use. All reactions were carried out under a nitrogen atmosphere unless specified otherwise. A Rigaku AFC6R diffractometer, with Cu rotating anode, was used to determine the structure of **140**, **211** and **213**.

Preparation of Carbomethoxyhyrazone of acetone (129): Methyl hydrazino-carboxylate (8.0 g, 0.089 mol) was dissolved in acetone (16.0 g, 0.28 mol). Anhydrous sodium sulfate was added to the reaction mixture to remove water produced during the condensation. After stirring overnight at room temperature, the mixture was filtered and

the excess acetone was evaporated in vacuo to give **129** (9.75 g, 0.075 mol) of satisfactory purity in 84 % yield. White solid, mp 78 - 81 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.85 (s, 3H), 2.06 (s, 3H), 3.84 (s, 3H), 7.62 (bs, 1H).

General procedure for the preparation of 2-oxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines by lead tetraacetate (LTA) oxidation: Preparation of 123h: Solid LTA (95% purity, 14.0 g, 0.030 mol) was added slowly with stirring to an ice-cooled solution of 3-butyn-1-ol (8.6 g, 0.12 mol) and the methoxycarbonyl hydrazone of acetone (**129**) (4.0 g, 0.031 mol) in dichloromethane (100 mL). Increments of oxidant were small enough to keep the solution temperature below 10 °C. After overnight stirring at room temperature, the precipitate was removed by gravity filtration and the organic filtrate was washed with aqueous sodium bicarbonate solution (5%) before it was dried over magnesium sulphate. Evaporation of the solvent left a crude oil that was chromatographed on a silica column (24:1 hexane / EtOAc) to afford **123h** (2.2 g, 0.011 mol) as a colourless oil in 37% yield. IR (CCl_4) cm^{-1}: 3300 (≡CH), 3030-2840 (C-H), 2110 (C≡C), 1580 (N=N). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.52 (s, 3H), 1.53 (s, 3H), 1.94 (t, ^{4}J=2.7 Hz, 1H), 2.49 (dt, ^{3}J = 7.2 Hz, ^{4}J = 2.7 Hz, 2H), 3.42 (s, 3H), 3.76 (dt, ^{3}J = 7.2 Hz, ^{2}J = - 9.3 Hz, 1H), 3.84 (dt, ^{3}J = 7.2 Hz, ^{2}J = -9.3 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 19.9, 24.0, 24.2, 51.9, 62.8, 69.7, 80.4, 119.4, 136.7; MS (e.i.) m/z: 167, 129 (100%), 111, 97, 73, 59 (molecular ion not observed); MS (c.i., NH_3) m/z: 216 $(M + NH_4)^+$; MS (HR) m/z: 129.0685, calcd. for $C_5H_9N_2O_2$ (M - $OCH_2CH_2C{\equiv}CH$), found 129.0664; Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.52; H, 7.12; N, 14.14. Found: C, 54.32; H, 7.22; N, 13.75.

Preparation of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (132). To an ice cooled heterogeneous mixture of LTA (95% purity, 171 g, 366 mmol) and acetic acid (2 mL) in CH_2Cl_2 (160 mL) was added a solution of the carbomethoxy hydrazone of acetone (42 g, 325 mmol) in CH_2Cl_2 (100 mL). The addition was done slowly by means of a fitted separatory funnel and the mixture was stirred with a mechanical stirrer and continuously purged with N_2. Following addition of the hydrazone, the ice-bath was removed and the mixture was allowed to warm slowly to room temperature with continued stirring (*ca* 1 hour). The mixture was then filtered (Buchner funnel / aspirator), and washed with dilute (4 %) bicarbonate. The organic layer was then collected and the aqueous layer was extracted (2 x 20 mL) with methylene chloride. The combined organic extracts were then dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo gave a mixture of **132** and a single impurity (**133**) in a ratio of 75 : 25. These products were obtained in a combined yield of 90 %. The impurity **133** is an acyclic isomer of the oxadiazoline **132**. Purification of the oxadiazoline is possible by slow bulb to bulb distillation (O.3 mm Hg, 60 °C pot temperature) but separation it is not required and the mixture of **132** and **133** can be used in the subsequent reactions.

2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (132). FTIR (NaCl cell, CCl_4) cm^{-1}: 2993, 2951, 2849, 1832, 1771, 1715, 1462, 1443, 1380, 1369, 1260, 1214, 1208, 1180, 1158, 1085, 1061, 1013, 981, 924, 910, 851, 625, 561; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.51 (s, 3H), 1.62 (s, 3H), 2.10 (s, 3H), 3.58 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 19.7, 21.7, 24.2, 52.6, 122.3, 134.0, 166.4; MS (e.i.) m/z: 129, 117, 73, 59, 43 (100%) (molecular ion not observed); MS (c.i., NH_3) m/z: 206 $(M+NH_4)^+$, 189 $(M+H)^+$.

Methyl 2,3-diaza-4-methyl-4-acetoxypent-2-enoate, 133. FTIR (NaCl cell, CCl_4) cm^{-1}: 2997, 2957, 1776, 1464, 1437, 1368, 1261, 1241, 1164, 1044, 1020, 940, 908, 870, 607, 572; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.62 (s, 6H), 2.11 (s, 3H), 3.98 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 21.7, 24.2, 54.8, 101.7, 161.8, 169.1; MS (e.i.) m/z: 129, 101, 73, 59, 43 (100%) (molecular ion not observed); MS (c.i., NH_3) m/z: 206 $(M + NH_4)^+$.

Typical procedure for acetoxy exchange: Preparation of 123h: To a 75 : 25 mixture of **132** and **133** (3.11 g, 12.4 mmol of **132**) in CH_2Cl_2 (50 mL) was added 3-butyn-1-ol (0.87 g, 12.4 mmol) and acetic acid (*ca* 0.5 mL). The resulting solution was allowed to stand at room temperature for 48 hours. The solution was then stirred with aqueous NaOH for 1 hour to selectively hydrolyze **133**. Extraction with CH_2Cl_2, drying of the combined organic layers over $MgSO_4$, and evaporation of the solvent left **123h** (2.12 g,10.7 mmol) in 86 % yield as a colorless oil which was analytically pure by ^1H NMR and GC. Alternatively, after the exchange reaction, the mixture of **123h** and **133** can be purified by chromatography (5% EtOAc / hexanes) to give **123h** in 88 % yield.

2,2-Dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123a. FTIR (NaCl cell, CCl_4) cm^{-1}: 2992, 2949, 2916, 2846, 1459, 1445, 1382, 1368, 1263, 1214, 1144, 1108, 1076, 1031, 983, 915, 899, 853; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 3.45 (s, 6H); ^{13}C-NMR δ(50.3 MHz, $CDCl_3$) δ: 23.7, 51.5, 118.8, 137.0; MS (e.i.) m/z : 132, 129, 105, 91, 90, 75, 74, 73, 59 (100%), 43 (molecular ion not observed); MS (c.i., NH_3) m/z : 178 $(M+NH_4)^+$; 94 % yield.

2-Ethoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123b. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.03 (t,^{3}J = 7.1 Hz, 3H), 1.25 (s, 3H), 1.26 (s, 3H), 3.26 (s, 3H), 3.65 (q, ^{3}J = 7.1 Hz, 1H), 3.71 (q, ^{3}J = 7.1 Hz, 1H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 15.2, 23.9, 24.0, 51.6, 60.5, 118.7, 137.9. MS (e.i.) m/z: 146, 125, 105 (100%), 77 (molecular ion not observed); MS (c.i., NH_3) m/z: 175 $(M+H)^+$; 90 % yield.

2-Methoxy-2-(1-propoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123c. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.93 (t, ^{3}J = 7.3 Hz, 3H), 1.54 (s, 6H), 1.62 (m, 2H), 3.46 (s, 3H), 3.63 (t, ^{3}J = 6.6 Hz, 1H), 3.70 (t, ^{3}J = 6.6 Hz, 1H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 10.3, 22.6, 23.9, 51.6, 66.13, 118.7, 137.0. MS (e.i.) m/z: 185, 167, 149, 129, 112, 97, 81, 69 (100%), 57 (molecular ion not observed); MS (c.i., NH_3) m/z: 206$(M+NH_4)^+$, 189 $(M+H)^+$; 92 % yield.

2-Methoxy-2-(1-methylethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123d. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.23 (s, 3H), 1.26 (s, 3H), 1.54 (d, 6H), 3.41 (s, 3H), 4.23 (m, 1H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.3, 23.5, 23.9, 51.5, 68.4, 118.3, 137.3. MS (e.i.) m/z: 160, 129, 118, 101, 77, 73, 59 (100%), 43 (molecular ion not observed); MS (c.i., NH_3) m/z: 189 $(M+H)^+$; 74 % yield.

2-(1-Butoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123e. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.81 (t, ^{3}J = 7.2 Hz, 3H), 1.31-1.24 (m, 2H), 1.42 (s, 6H), 1.52-1.44 (m,

2H), 3.49 (s, 3H), 3.65-3.49 (m, 2H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 13.8, 18.9, 23.7, 23.8, 31.2, 51.4, 64.1, 118.5, 136.9. MS (e.i.) m/z : 129 (molecular ion not observed); MS (c.i., NH_3) m/z: 220 $(M+H)^+$; 82 % yield.

2-Methoxy-2-(1,1-dimethylethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123f. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.41 (s, 9H, $C(CH_3)_3$), 1.51 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 3.32 (s, 3H, OCH_3); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.7, 24.1, 30.0, 51.4, 78.8, 118.4, 137.5; MS (e.i.) m/z: 185, 172, 145, 129, 116 (100%), 99 (molecular ion not observed); MS (c.i., NH_3) m/z: 203 $(M+H)^+$; 67 % yield.

2-(2,2,2-Trifluoroethoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123g. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.54 (s, 3H), 1.60 (s, 3H), 3.43 (s, 3H), 3.89 (q, $^3J_{HF}$ = 8.5 Hz, 1H), 3.90 (q, $^3J_{HF}$ = 8.5 Hz, 1H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.7, 24.0, 52.1, 62.0 (q, $^2J_{CF}$ = 36 Hz), 120.8, 128.7 (q, $^1J_{CF}$ = 275 Hz, CF_3,). MS (e.i.) m/z: 200, 197, 159, 158, 143, 142, 141, 139, 129, 127, 83, 59, 43, 42, 41 (molecular ion not observed); MS (c.i., NH_3) m/z: 246 $(M+NH_4)^+$; 84 % yield.

2-Methoxy-5,5-dimethyl-2-(4-pentyn-1-oxy)-Δ^3-1,3,4-oxadiazoline 123i. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.50 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.81 (tt, ^3J = 6.2 Hz, ^3J = 6.9 Hz, 2H, CH_2), 1.91 (t, ^4J = 2.7 Hz, 1H, C≡CH), 2.26 (dt, ^3J = 6.9 Hz, ^4J = 2.7 Hz, 2H, CH_2), 3.42 (s, 3H, CH_3O), 3.74 (dt, ^3J = 6.2 Hz, ^2J = -9.7 Hz, 1H, OCH_2), 3.83 (dt, ^3J = 6.2 Hz, ^2J = -9.7 Hz, 1H, , OCH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.0, 24.0, 24.1,

28.4, 51.8, 63.0, 68.7, 83.3, 119.1, 136.9; MS (e.i.) m/z: 181 (M^+ - OCH_3, 2 %), 129 (M^+ - $O(CH_2)_3C{\equiv}CH$, 10 %), (molecular ion not observed); MS (c.i., NH_3) m/z: 230 $(M+NH_4)^+$; 78 % yield.

2-Methoxy-2-phenoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123j. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.27 (s, 3H), 1.56 (s, 3H), 3.61 (s, 3H), 7.33-7.12 (m, 5H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.2, 23.8, 52.1, 120.2, 121.3, 124.2, 128.9, 136.4, 151.9; MS (e.i.) m/z: 191, 179, 153, 129 (100%), 105, 94, 77 (molecular ion not observed); MS (c.i., NH_3) m/z: 240 $(M+NH_4)^+$. Anal: for $C_{11}H_{14}N_2O_3$, calcd. : C59.45, H 6.35, N 12.61; found: C 59.24, H 6.43, N 12.70; 61 % yield.

2-(4-Cyanophenoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123k. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.46 (s, 3H), 1.84 (s, 3H), 3.53 (s, 3H), 7.35 (d, ^3J = 8.0 Hz, 2H), 7.62 (d, ^3J = 8.0 Hz, 2H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.7, 23.8, 52.4, 107.2, 118.4, 120.5, 121.4, 133.4, 135.8, 155.5; MS (e.i.) m/z: 216, 160, 129 (100%), 102, 73, 56 (molecular ion not observed); MS (c.i., NH_3) m/z: 265 $(M+NH_4)^+$, 248 $(M+H)^+$; 67 % yield.

2-Methoxy-2-(4-methoxyphenoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 123l. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.20 (s, 3H), 1.50 (s, 3H), 3.62 (s, 3H), 3.76 (s, 3H), 6.80 (d, J = 9.1 Hz, 2H), 7.08 (d, J = 9.1 Hz, 2H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.3, 24.1, 52.3,

55.3, 113.9, 120.1, 123.2, 136.8, 145.1, 156.6; MS (e.i.) m/z: 221, 205, 149 (100%), 135, 129, 123, 95, 73, 56 (molecular ion not observed); 68 % yield.

Thermolysis of 123h. A solution of **123h** (2.0150 g, 10.177 mmol) in 100 mL of toluene blanketed with dry N_2 was refluxed for 24 h. Following the thermolysis, the solvent was removed with a rotary evaporator and the residue was purged further of volatiles, using a sublimation apparatus kept at 65 °C / 0.05 Torr. When no more material collected on the cold surface, the brown residue (1.2743 g) was examined by ^{1}H NMR spectroscopy, which showed that it was primarily **140**

Passage of the crude **140** through a short column of silica (30% EtOAc / hexane) gave, after evaporation of the solvent, a colorless oil. Dissolution of the oil in toluene and chilling of the solution in the refrigerator afforded crystalline **140** (1.0567 g, 3.747 mmol) in 74% yield.

Liquid collected on the cold surface of the sublimation apparatus was subjected to centrifugal chromatography (2 mm silica plate, Chromatotron apparatus, 25% EtOAc / hexane) which afforded ester **139** (0.087 g, *ca* 5%).

Similar thermolyses on a smaller scale were carried out in benzene using the sealed tube method. For example, a solution of **123h** (0.3112 g, 1.57 mmol) in benzene (15.6 mL) was flame sealed into a glass tube of 100 mL volume, after degassing at 0.1 Torr by three freeze-pump-thaw cycles. The tube was then immersed in an oil bath operating at 110 ± 0.1 °C for 30 h before it was cooled and opened. **Caution:** Pressure from N_2 released in the thermolysis must be taken into account in choosing sample size and vessel

volume. Workup as described above for larger scale reactions gave the same results, as judged by ^{1}H NMR spectroscopy of the crude product.

(1α, 1aα, 3aα, 6aα, 6bα)-(±)-Methyl-1a-ethenyloctahydro-6a-methoxy-2,2-dimethyl-3,6-dioxacyclobut[*cd*]indene-1-carboxylate, 140. White solid, mp 85.5 - 87.3 °C; IR (CCl_4) cm^{-1}: 3080 (=C-H), 3040-2800 (C-H), 1740 (C=O), 1637 (C=C). ^{1}H NMR (500 MHz, C_6D_6) δ: 0.83 (s, 3H), 1.26 (s, 3H), 1.35 (m, $^2J_{4\alpha,4\beta}$ = -14.6 Hz, $^3J_{4\alpha,5\beta}$ = 12.1 Hz, $^3J_{4\alpha,5\alpha}$ = 4.9 Hz, $^3J_{3a,4\alpha}$ = 3.1 Hz, 1H, H-4$_\alpha$), 1.41 (m, $^2J_{4\alpha,4\beta}$ = -14.6 Hz, $^3J_{4\beta,5\beta}$ = 2.5 Hz, $^3J_{4\beta,5\alpha}$ = 2.1 Hz, $^3J_{3a,4\beta}$ = 2.8 Hz, 1H, H - 4β), 2.51 (d, $^3J_{3a,6b}$ = 7.2 Hz, 1H, H-6b), 3.14 (s, 3H, ether CH_3), 3.40 (s, 3H, ester), 3.60 (m, $^2J_{5\alpha,5\beta}$ = -12.0 Hz, $^3J_{5\alpha,4\alpha}$ = 4.9 Hz, $^3J_{4\beta,5\alpha}$ = 2.1 Hz, 1H, H-5), 3.88 (m, $^3J_{3a,6b}$ = 7.2 Hz, $^3J_{3a,4\alpha}$ = 3.1 Hz, $^3J_{3a,4\beta}$ = 2.8 Hz,1H, H-3a), 3.96 (s, 1H, H-1), 3.99 (m, $^3J_{4\alpha,5\beta}$ = 12.1 Hz, $^2J_{5\alpha,5\beta}$ = -12.0 Hz, $^3J_{4\beta,5\beta}$ = 2.5 Hz, 1H, H-5β), 5.02 (dd, $^3J_{AX}$ = 17.3 Hz, $^2J_{AB}$ = -1.7 Hz, 1H, H-A), 5.21 (dd, $^3J_{BX}$ = 10.7 Hz, $^2J_{AB}$ = -1.7 Hz, 1H, H-B), 6.42 (dd, $^3J_{AX}$ = 17.3 Hz, $^3J_{BX}$ = 10.7 Hz, 1H, H-X); ^{13}C NMR (125 MHz, C_6D_6) δ: 21.5(-)(CH_3), 22.9(-)(CH_3), 26.8(+)(C-4), 43.1(-)(C-6b), 48.8(-)(OCH_3), 48.9(-)(C-1), 50.8 (-)(OCH_3), 56.2 (+)(C-1a), 59.0 (+)(C-5), 70.2 (-)(C-3a), 83.1 (+)(C-2), 96.3 (+)(C-6a), 114.9 (+)($\underline{C}H_2$=CH), 135.1 (-)(CH_2=$\underline{C}$H), 168.8 (+)(CO); MS (e.i.) m/z: 282 (M^+, 12%), 251(M^+-OCH_3, 8%), 223 (M^+-$C_2H_3O_2$, 40%), 135 (100%), 113 (100%). The molecular structure of **140** was secured by means of single crystal X-ray diffraction.

(E)-Methyl-3-ethenyl-4-hydroxy-4-methylpent-2-enoate (139). Compound **139** was obtained as an oil. Attempts to grow a crystal failed. UV (EtOH) (λ_{max} 271 nm, ε=1,900); IR(CCl_4) cm^{-1}: 3610 (br, OH), 3060 - 2820 (CH), 1728 (CO); ^1H NMR (500 MHz, C_6D_6) δ: 0.91 (s, 1H, OH), 1.11 (s, 6H), 3.40 (s, 3H), 5.21 (m, $^2J_{AB}$ = -1.8 Hz, $^3J_{AX}$ = 12.0 Hz, 1H, H-A), 5.44 (m, $^2J_{AB}$ = -1.8 Hz, $^3J_{BX}$ = 18.0 Hz, 1H, H-B), 6.18 (s, 1H, H-2), 7.15 (m, $^3J_{AX}$ = 12.0 Hz, $^3J_{BX}$ = 18.0 Hz, 1H, H-X); ^{13}C NMR (125 MHz, C_6D_6) δ: 29.6 (C-5), 50.8 (C-4), 72.7 (CH_3O), 115.8 ($\underline{C}H=CH_2$), 120.6 ($CH=\underline{C}H_2$), 132.5 (C-2), 160.6 (C-3), 167.0 (CO); MS (e.i.) m/z: 170 ($M^{+\cdot}$, 12%), 155 (M^+-CH_3, 5%), 139 (M^+-CH_3O, 13%), 111 (M^+-$C_2H_3O_2$, 17%), 59 (100%). NOE: irradiation at the geminal dimethyl frequency caused enhancement of signal intensities at δ = 5.44 (H_B) and at δ = 6.18 (H-2).

Thermolysis of 123h in the presence of acetone-d_6. The sealed tube/benzene method described above was used, with initial concentrations of 0.1 M **123h** and 0.4 M acetone-d_6, 99% labeled. Isolated **140** showed reduced signal intensities, in the ^1H NMR spectrum, for the methyl singlets suggesting *ca* 80% incorporation of acetone-d_6 from solution. The mass spectrum showed (m/z) 288: 282 = 87:13, in satisfactory agreement with the result from NMR spectroscopy.

Thermolysis of 123h in the presence of cyclopentanone. A solution of **123h** (0.1700 g, 0.8586 mmol) and cyclopentanone (0.850 g, 10.1 mmol) in toluene (10 mL) was refluxed for 30 h. Evaporation of most of the solvent and centrifugal chromatography of the residue (2 mm silica plate, Chromatotron apparatus), using ethyl acetate (30%) in hexanes

for elution, afforded **149**, (0.079 g, 60%) as a viscous oil. ^{1}H NMR (300 MHz, C_6D_6) δ: 1.31-1.47 (m, 8H, 6H, cyclopentyl + H-4α and H-4β), 1.64-1.71 (m, 2H, cyclopentyl), 2.49 (d, $^3J_{3a,6b}$ = 7.2 Hz, H-6b), 3.14 (s, 3H, ether CH_3), 3.39 (s, 3H, ester CH_3), 3.62 (m, $^2J_{5\alpha,5\beta}$ = -11.6 Hz, $^3J_{5\alpha,4\alpha}$ = 4.7 Hz, $^3J_{5\alpha,4\beta}$= 2.2 Hz, 1H, H-5α), 3.81 (m, $^3J_{3a,6b}$ = 7.3 Hz, $^3J_{3a,4\alpha}$ = 2.9 Hz, $^3J_{3a,4\beta}$ = 2.9 Hz, 1H, H-3a), 3.95 (s, 1H, H-1), 4.04 (m, $^3J_{4\alpha,5\beta}$ = 11.6 Hz, $^2J_{5\alpha,5\beta}$ = -11.6 Hz, $^3J_{4\beta,5\beta}$ = 3.5 Hz, 1H, H-5β), 5.14 (m, $^3J_{A,X}$ = 17.3 Hz, $^2J_{A,B}$ = -1.8 Hz, 1H, H-A), 5.25 (m, $^3J_{B,X}$ = 10.7 Hz, $^2J_{A,B}$ = -1.8 Hz, 1H, H-B), 6.51 (m, $^3J_{A,X}$ = 17.3 Hz, $^3J_{B,X}$ = 10.7 Hz, 1H, H-X); ^{13}C NMR (75 MHz, C_6D_6) δ: 24.6, 25.8, 26.9, 33.1, 33.2, 43.2 (C-6b), 48.8 (OMe), 50.7 (C-1), 50.8 (OMe), 55.0 (C-1a), 59.1 (C-5), 70.5 (C-3a), 95.4 (C-2), 96.6 (C-6a), 115.0 (C-10), 135.3 (C-9), 169.0 (CO); MS (GCMS, e.i.) m/z: 308 (M^+, 15%), 277 (M^+-OCH_3, 2%), 249 (M^+-$C_2H_3O_2$, 35%), 113 (100%).

Preparation of 123h-d_1. Oxadiazoline **123h** (0.400 g, 2.02 mmol) was added to D_2O (10 mL) together with six pellets (*ca* 0.6 g) of KOH. The heterogeneous mixture was stirred vigorously for 3 h before dichloromethane (10 mL) was added for extraction. The organic layer was dried with $MgSO_4$ and the solvent was taken off with a rotary evaporator. Oxadiazoline **123h**-d_1 was obtained in quantitative yield. The ^{1}H NMR spectrum was identical to that for **123h**, except for a missing triplet at 1.94 ppm and a triplet, instead of a doublet of triplets, at 2.49 ppm.

Thermolysis of 123h-d_1. The sealed tube/benzene method, described above, was used and the isolated major product was examined by ^{1}H NMR spectroscopy and by mass

spectrometry. The ^{1}H NMR spectrum showed clearly the absence of signals for H-1 and H-6b and the removal of one coupling for the signal from H-3a, with respect to the spectral data for **140** (above). In the mass spectrum, the molecular ion signal was at m/z 284, corresponding to **140**-d_2.

Thermolysis of 123h-d_1 in the presence of 139. Oxadiazoline **123h**-d_1 (0.05 g, 0.03 mmol) was refluxed for 30 h in toluene (0.5 mL) in the presence of **139** (0.010 g, 0.051 mmol). The product was not isolated but the crude reaction mixture was analyzed by GCMS which showed that **140** had been formed (retention time) and that it consisted of d_1 and d_2 species in the ratio 46:54, as judged from the relative intensities of the signals at m/z 283 and 284.

Thermolysis of 123h in the presence of *t*-butyl alcohol (0.015 M). A solution of oxadiazoline **123h** (0.2052 g, 1.036 mmol) and *t*-butyl alcohol (0.222 g, 3.0 mmol) in toluene (200 mL) was refluxed for 30 h. Removal of most of the solvent, and spectroscopy of the residue (^{1}H NMR, ^{13}C NMR, and GCMS), showed that it consisted primarily of **150**: ^{1}H NMR (500 MHz, C_6D_6) δ: 1.11 (s, 9H), 1.47 (m, $^2J_{5\alpha,5\beta}$ = -13.8 Hz, $^3J_{6\alpha,5\beta}$ = 5.2 Hz, $^3J_{5\beta,4}$ = 2.9 Hz, $^3J_{6\beta,5\beta}$ = 2.4 Hz, $^4J_{5\beta,3}$ = 1.2 Hz, 1H, H-6β), 1.62 (m, $^2J_{5\alpha,5\beta}$ = -13.8 Hz, $^3J_{6\beta,5\alpha}$ = 11.9 Hz, $^3J_{5\alpha,4}$ = 4.3 Hz, $^3J_{6\alpha,5\alpha}$ = 3.8 Hz, 1H, H-5α), 3.23 (s, 3H, OCH_3), 3.856 (m, $^3J_{4,3}$ = 4.9 Hz, $^4J_{5\beta,3}$ = 1.2 Hz, 1H, H-3), 3.862 (m, $^2J_{6\alpha,6\beta}$ = -10.4 Hz, $^3J_{6\alpha,5\beta}$ = 5.2 Hz, $^3J_{6\alpha,5\alpha}$ = 3.8 Hz, $^4J_{6\alpha,4}$ = 1.0 Hz, 1H, H-6α), 3.95 (m, $^3J_{4,3}$ = 4.9 Hz, $^3J_{5\alpha,4}$ = 4.3 Hz, $^3J_{5\beta,4}$ = 2.9 Hz, $^4J_{6\alpha,4}$ = 1.0 Hz, 1H, H-4), 4.12 (m, $^3J_{6\beta,5\alpha}$ = 11.9 Hz, $^2J_{6\alpha,6\beta}$ = -

10.4 Hz, $^3J_{6\beta,5\beta}$ = 2.4 Hz, 1H, H-6β); ^{13}C NMR (75 MHz, C_6D_6) δ: 28.7(-)(Me_3), 32.2(+)(C-5), 54.2(-)(CH_3O), 61.2 (-)(C-4), 63.8(+)(C-6), 72.7(+)($\underline{C}Me_3$), 74.2(-)(C-3), 161.6(+)(C-2); MS (e.i.) m/z: 186 ($M^{+\cdot}$, 4%), 171 (M^+ - CH_3, 1%), 129 (M^+ - C_4H_9, 4%), 113 (M^+ - C_4H_9O, 100%). The compound is very sensitive to moisture and attempts to isolate a pure sample failed.

Thermolysis of 123h in presence of *t*-butyl alcohol (0.5 M). A solution of **123h** (0.100 g, 0.505 mmol) and *t*-butyl alcohol (0.40 g, 5.4 mmol) in benzene (10 mL) was heated in a sealed tube at 100 °C for 30 h. Evaporation of the solvent and excess *t*-butyl alcohol left a residue that was *ca* 90 % **151** by ^{1}H NMR spectroscopy: ^{1}H NMR (200 MHz, $CDCl_3$ δ: 1.26(s, 9H), 1.95 (*t*, ^4J = 2.7 Hz, 1H), 2.46 (dt, ^3J = 6.9 Hz, ^4J = 2.7 Hz, 2H), 3.28 (s, 3H), 3.635 (*t*, ^3J = 6.9 Hz, 1H), 3.643 (*t*, ^3J = 6.9 Hz, 1H), 5.31 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.78 ($C\underline{C}H_2$), 28.61 (($CH_3)_3$), 50.45 (CH_3O), 60.72 (OCH_2), 69.22 ($\underline{C}(CH_3)_3$), 74.57 (C≡$\underline{C}$H), 81.41 ($\underline{C}$≡CH), 109.36 (HCO_3); MS (GCMS, e.i.) m/z: 186 ($M^{+\cdot}$, 1%), 171 (M^+- CH_3, 1%), 155 (M^+ - OCH_3, 3%), 117 (M^+ - C_4H_5O, 3%), 113 (M^+ - C_4H_9O, 57%), 57 ($C_4H_9^+$, 100%).

Thermolysis of oxadiazoline 123h in the presence of DMAD: A solution of oxadiazoline **123h** (1.0013 g, 5.06 mmol, 0.051 M) and DMAD (1.50 g, 10.56 mmol, 0.11 M) in benzene (100 mL) was sealed in a 250 mL glass tube after three freeze-pump-thaw cycles. The sample was placed in an oil bath operating at 110 ± 0.1 °C for 24 hours. Following the thermolysis, the sample was cooled, and the solvent evaporated in vacuo.

Centrifugal chromatography (Chromatotron, 4 mm plate, 10 - 30 % EtOAc / hexanes) of the crude reaction mixture yielded **156** (27 %), **157** (10 %), **158** (2 %), and **159** (1 %).

Thermolysis of **123h** (0.2242 g, 1.13 mmol, 0.0038 M) in the presence of DMAD (0.51g, 3.59 mmol, 0.012 M) in toluene (300 mL) was conducted by refluxing the mixture under a blanket of dry N_2 for 24 hours to give **156** (21 %), **157** (6 %), and **159** (9 %) after chromatographic purification. And similarly, thermolysis of **123h** (0.1036 g, 0.52 mmol, 0.0021 M) in the presence of DMAD (0.0809 g, 0.57 mmol, 0.0023) in refluxing toluene (250 mL) for 24 hours gave only **159** in 20 % yield after purification.

156, Note: spectral data are those of a 1:1 diastereomeric mixture. ^{1}H NMR (200 MHz, C_6D_6) δ: 1.69 (t, ^{4}J=2.7 Hz, 1H, C≡CH), 1.75 (t, ^{4}J=2.7 Hz, 1H, C≡CH), 2.33 (dt, ^{3}J=6.7 Hz, ^{4}J=2.7 Hz, 2H, CH_2), 2.37 (dt, ^{3}J=6.7 Hz, ^{4}J=2.7 Hz, 2H, CH_2), 3.15 (s, 3H, CH_3O), 3.24 (s, 3H, CH_3O), 3.35 (s, 3H, CH_3O) , 3.36 (s, 3H, CH_3O) , 3.37 (s, 3H, CH_3O) , 3.38 (s, 3H, CH_3O) , 3.40 (s, 3H, CH_3O), 3.88 (t, ^{3}J=6.7 Hz, 2H, OCH_2), 3.91 (t, ^{3}J=6.7 Hz, 2H, OCH_2); ^{13}C NMR (50 MHz, C_6D_6) δ: 20.0 (CH_2), 51.6 (CH_3O), 52.3 (CH_3O), 52.5 (CH_3O), 52.7 (CH_3O), 52.8 (CH_3O), 62.8 (OCH_2), 62.9 (OCH_2), 70.0 (C≡C-H), 78.3 (C≡C), 79.3 (C≡C), 80.7 (C≡C), 100.6 (C-5), 123.6 (C-2), 136.6 (C-4), 141.1 (C-3), 153.0 (C=O), 160.0 (C=O), 161.6 (C=O); MS (e.i.) m/z (rel. intensity): 365 (M^+ - OCH_3, 10), 337 (M^+ - CO_2CH_3, 100), 281 (21), 157 (38); MS (c.i., NH_3) m/z: 414 $(M + NH_4)^+$.

157: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.68 (t, ^{4}J=2.7 Hz, 1H, C≡C-H), 2.35 (dt, ^{3}J=6.7 Hz, ^{4}J=2.7 Hz, 2H, CH_2), 3.30 (s, 3H, CH_3O), 3.35 (s, 6H, CH_3O), 3.41 (s, 6H, CH_3O), 3.82 (t, ^{3}J=6.7 Hz, 2H, OCH_2); ^{13}C NMR (50 MHz, C_6D_6) δ: 20.3 (CH_2), 52.0 (CH_3O), 52.2 (2 x CH_3O), 52.3 (2 x CH_3O), 52.7 (CH_3O), 63.2 (OCH_2), 70.0 (C≡CH), 80.7 (C≡CH), 112.1(C-1), 138.5 (C-2), 141.2 (C-4), 162.1 (2 x C=O), 162.4 (2 x C=O); MS (e.i.) m/z (rel. intensity): 396 (M^+, 8), 365 (M^+ - OCH_3, 15), 337 (M^+ - CO_2CH_3, 35), 307 (63), 253 (48); MS (c.i., NH_3) m/z: 414 $(M + NH_4)^+$, 397 $(M + H)^+$.

158: ^{1}H NMR (200 MHz, C_6D_6) δ: 1.45 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.69 (t, ^{4}J=2.6 Hz, 1H, C≡C-H), 2.40 (dt, ^{3}J=7.1 Hz, ^{4}J=2.6 Hz, 2H, CH_2), 3.26 (s, 3H, CH_3O), 3.35 (s, 3H, CH_3O), 3.36 (s, 3H, CH_3O), 3.87 (t, ^{3}J=7.1 Hz, 1H, OCH_2), 3.88 (t, ^{3}J=7.1 Hz, 1H, OCH_2); MS (GCMS, e.i.) m/z (rel. intensity): 297 (M^+ - CH_3, 27 %), 281 (M^+ - CH_3O, 30 %), 243 (M^+ - $OCH_2CH_2C{\equiv}CH$, 100 %), 211 (33), 179 (83), 137 (27).

(E)-Dimethyl-3-carbomethoxy-4-etheneyl-hexa-2,4-diene-1,6-dicarboxylate, 159: ^{1}H NMR (500 MHz, C_6D_6) δ: 3.27 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 5.23 (d, $^3J_{A,X}$ = 11.0 Hz, $^2J_{A,B}$ = 0 Hz, 1H, H_A), 5.57 (d, $^3J_{B,X}$ = 17.7 Hz, $^2J_{A,B}$ = 0 Hz, 1H, H_B), 5.85 (s, 1H, C=CH), 5.99 (s, 1H, C=CH), 7.82 (dd, $^3J_{A,X}$ = 11.0 Hz, $^3J_{B,X}$ = 17.7 Hz, 1H, H_X); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 51.6 (CH_3O), 52.2 (CH_3O), 52.8 (CH_3O), 119.9 (=C-H_x), 124.8 (C-2), 124.8 (C-5), 131.2 (H_2C=C), 146.0 (C-4), 148.4 (C-3), 164.7 (C=O), 165.5 (C=O), 166.5 (C=O); MS (e.i.) m/z (rel. intensity): 254 (M^+,

4), 223 (M^+ - OCH_3, 10), 195 (M^+ - CO_2CH_3, 100), 163 (17); MS (c.i., NH_3) m/z: 272 $(M + NH_4)^+$, 255 $(M + H)^+$.

Attempted intramolecular Diels-Alder reaction of 157. A solution of **157** (89.9 mg, 0.227 mmol) in toluene (15 mL) was prepared. This solution was sealed in a 50 mL tube and placed in an oil bath operating at 130 ± 0.1 °C for 30 hours. Following evaporation of the solvent in vacuo, centrifugal chromatography of the crude reaction mixture (Chromatotron, 1 mm plate, 10 - 30 % EtOAc / hexane) yielded three major products **A**, **B**, and **C** in 12, 26, and 10 % yields, respectively. These products could not be identified based on their spectral data.

Unknown product A: ^{1}H NMR (200 MHz, C_6D_6) 2.20 (ddd, ^{2}J= 17.0 Hz, ^{3}J= 11.3 Hz, ^{3}J= 10.5 Hz, 1H, CH_2) , 2.88 (ddd, ^{2}J= 17.0 Hz, ^{3}J= 6.7 Hz, ^{3}J= 2.0 Hz, 1H, CH_2), 3.21 (s, 3H, CH_3O), 3.23 (s, 3H, CH_3O), 3.37 (s, 3H, CH_3O), 3.50 (s, 3H, CH_3O), 3.51 (m, 1H, OCH_2), 3.56 (s, 3H, CH_3O), 3.72 (m, 1H, OCH_2), 6.12 (s, 1H, CH); MS(e.i.), *m/z* (rel. intensity): 365 (M^+ - OCH_3, 10), 337 (M^+ - CO_2CH_3, 100), 321 (8), 263 (9), 149 (7); MS (c.i., NH_3) m/z: 414 $(M + NH_4)^+$, 397 $(M + H)^+$

Unknown product B: ^{1}H NMR (200 MHz, C_6D_6) 1.51 (m, 1H, CH_2) , 1.71 (m, 1H, CH_2), 3.21 (s, 3H, CH_3O), 3.24 (s, 3H, CH_3O), 3.36 (s, 3H, CH_3O), 3.48 (s, 3H, CH_3O), 3.60 (m, 2H, OCH_2), 3.83 (s, 3H, CH_3O), 3.84 (s, 1H, CH); ^{13}C NMR (50 MHz, C_6D_6) δ: 26.5, 39.8, 47.7, 51.5, 51.8, 52.3, 58.1, 59.0, 71.9, 102.3, 112.2, 128.5, 142.0, 164.4,

165.9, 167.1, 167.8, 172.0. MS(e.i.), *m/z* (rel. intensity): 365 (M^+ - OCH_3, 10), 337 (M^+ - CO_2CH_3, 83), 309 (22), 263 (100).

Unknown product C: ^{1}H NMR (200 MHz, C_6D_6) 1.43 (ddd, ^{2}J= 12.9 Hz, ^{3}J= 7.7 Hz, ^{3}J= 4.7 Hz, 1H, CH_2) , 1.83 (ddd, ^{2}J= 12.9 Hz, ^{3}J= 8.4 Hz, ^{3}J= 8.4 Hz, 1H, CH_2), 3.21 (s, 3H, CH_3O), 3.32 (s, 3H, CH_3O), 3.36 (s, 3H, CH_3O), 3.39 (s, 3H, CH_3O), 3.62 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 3.86 (m, 2H, OCH_2), 6.59 (s, 1H, CH); ^{13}C NMR (50 MHz, C_6D_6) δ: 35.6, 51.2, 51.7, 52.0, 52.7, 53.3, 57.1, 59.2, 72.7, 101.8, 119.1, 130.0, 141.2, 155.2, 164.7, 165.1, 165.3, 167.2, 170.4. MS(e.i.), *m/z* (rel. intensity): 396 (M^+, 11), 365 (M^+ - OCH_3, 15), 338 (18), 337 (M^+ - CO_2CH_3, 100), 263 (55).

Thermolysis of oxadiazoline 123h in the presence of methylpropiolate at high concentration: A solution of oxadiazoline **123h** (0.2061 g, 1.04 mmol, 0.052 M) and methylpropiolate (1.50 g, 10.56 mmol, 0.11 M) in toluene (100 mL) was blanketed with dry N_2 and refluxed for 21 hours. Following evaporation of the solvent in vacuo, centrifugal chromatography (2 mm plate, 10 - 20 % EtOAc / hexane) of the crude reaction mixture yielded (E)-Dimethyl-4-(3-butynoxy)-4-methoxy-hept-2-ene-5-yne-1,7-dicarboxylate (**170**) (0.0808 g, 0.289 mmol) in 28 % isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.96 (t, ^{4}J = 2.6 Hz, 1H, C≡C-H), 2.34 (dt, ^{4}J = 2.6 Hz, ^{3}J = 6.8 Hz, 2H, CH_2), 3.29 (s, 3H, OCH_3), 3.62 (dt, ^{3}J = 6.8 Hz, ^{2}J = -9.2 Hz, 1H, OCH_2), 3.64 (dt, ^{3}J = 6.8 Hz, ^{2}J = -9.2 Hz, 1H, OCH_2), 3.74 (s, 3H, OCH_3), , 3.76 (s, 3H, OCH_3), 6.31 (d, ^{3}J = 15.7 Hz, 1H, C=C<u>H</u>E), 6.73 (d, ^{3}J = 15.7 Hz, 1H, <u>H</u>C=CE) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ:

19.6 (CH_2), 51.8 (CH_3O), 51.9 (CH_3O), 53.0 (CH_3O), 69.7 (C≡CH), 77.4 (C≡CE), 80.3 (C≡CH), 80.5 (C≡CE), 95.2 (OCO), 125.3 (C=CE), 142.1 (C=CE), 152.9 (C=O), 165.7 (C=O); MS (e.i.) m/z: 265 (M^+ - CH_3, 1 %), 249 (M^+ - CH_3O, 8 %), 221 (M^+ - CO_2CH_3, 10 %), 211 (M^+ - $OCH_2CH_2C{\equiv}CH$, 100 %), MS (c.i., NH_3) m/z: 298 $(M + NH_4)^+$.

Thermolysis of oxadiazoline 123h in the presence of methylpropiolate at low concentration: A solution of oxadiazoline **123h** (0.1262 g, 0.64 mmol, 0.0032 M) and methylpropiolate (0.11 g, 1.31 mmol, 0.065 M) in toluene (200 mL) was blanketed with dry N_2 and refluxed for 23 hours. GCMS analysis of the crude thermolysis product indicated the formation of two major products with of the mass 196. Following evaporation of the solvent in vacuo, centrifugal chromatography (1 mm plate, 5 - 10 % EtOAc / hexane) of the crude reaction mixture yielded **173** (0.0264 g, 0.13 mmol) in 21 % isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.96 (m, ^2J = - 18.0 Hz, ^3J = 5.4 Hz, ^3J = 3.3 Hz, ^4J = 1.6 Hz, 1H, allylic CH_2), 2.29 (m, ^2J = - 18.0 Hz, ^3J = 8.6 Hz, ^3J = 7.3 Hz, ^3J = 2.6 Hz, ^4J = 2.6 Hz, 1H, allylic CH_2), 3.43 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.82 (m, 2H, OCH_2), 5.76 (ddd, ^3J = 10.1 Hz, ^4J = 2.6 Hz, ^4J = 1.6 Hz, 1H, HC=CHCH$_2$), 6.07 (ddd, ^3J = 10.1 Hz, ^3J = 2.6 Hz, ^3J = 5.4 Hz, 1H, HC=CHCH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.8 (CH_2), 51.2 (CH_3O), 52.9 (CH_3O), 58.9 (OCH_2), 75.2 (C≡CE), 83.0 (C≡CE), 91.7 (OCO), 126.5 (HC=CHCH$_2$), 129.3 (HC=CHCH$_2$), 153.4 (C=O); MS (GCMS, e.i.) m/z: 181 (M^+ - CH_3, 3 %), 165 (M^+ - CH_3O, 100 %), 137 (M^+ - CO_2CH_3, 7 %), 113 (M^+ - C≡C-E, 17 %), 107 (54 %), 77 (60 %). The other major product from this reaction, which decomposes upon chromatography, is most likely to be ketene acetal **174**.

MS (GCMS, e.i.) m/z: 196 ($M^{+\cdot}$, 34 %), 181 (M^+ - CH_3, 7 %), 165 (M^+ - CH_3O, 11 %), 149 (56 %), 137 (M^+ - CH_3O, 56 %), 77 (100 %).

Thermolysis of 2-methoxy-5,5-dimethyl-2-(3-pentynoxy)-Δ^3-1,3,4-oxadiazoline (175). A solution of 2-methoxy-5,5-dimethyl-2-(3-pentynoxy)-Δ^3-1,3,4-oxadiazoline (**175**) (361 mg, 1.7 mmol) in 80 mL of dry benzene was prepared. At atmospheric pressure, 40 mL of benzene was then distilled from this solution to remove adventitious water by azeotropic distillation. The solution was then sealed into a 100 mL glass tube after degassing at 0.1 Torr. by three freeze-pump-thaw sequences. The tube was then immersed into an oil bath operating at 110 ± 0.1 °C for 20 hours before it was cooled and opened. The crude reaction mixture was concentrated in vacuo to yield a yellow oil (258 mg). Spectroscopy of the residue showed that it consisted primarily (> 90 %) of (E)-methyl-3-ethenyl-4-(5,6-dihydro-2-methoxy-3-methyl-2H-pyran-4-oxy)-2,4-dimethylpent-2-enoate (**181**). The spectral data below are those of the crude thermolysis product, which was primarily (> 90 %) **181** ^{1}H NMR (500 MHz, C_6D_6) δ: 1.14 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.4 - 1.7 (m, complex, 2H, H-5'a and H-5'b), 1.83 (s, 3H, CH_3 on C-3'), 2.22 (d, ^{5}J = 1.7 Hz, 3H, CH_3 on C-2), 3.35 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.82 (m, $^2J_{6'a,6'b}$ = - 10.2 Hz, $^3J_{5'a,6'a}$ = 3.7 Hz, $^3J_{5'b,6'a}$ = 3.7 Hz, $^4J_{4',6'a}$ = 1.2 Hz, 1H, H-6'a), 3.98 (m, $^3J_{4',5'a}$ = 6.9 Hz, $^3J_{4',5'b}$ = 6.9 Hz, $^3J_{4',6'a}$ = 1.2 Hz, 1H, H-4'), 4.04 (m, $^2J_{6'a,6'b}$ = - 10.2 Hz, $^3J_{5'a,6'b}$ = 12.5 Hz, $^3J_{5'b,6'b}$ = 2.3 Hz, 1H, H-6'b), 4.88 (dd, $^3J_{BX}$ = 10.9 Hz, $^2J_{AB}$ = 2.3 Hz, 1H, H-B), 5.10 (dd, $^3J_{AX}$ = 17.2 Hz, $^2J_{AB}$ = 2.3 Hz, 1H, H-A), 6.25 (m, $^3J_{AX}$ = 17.2 Hz, $^3J_{BX}$ = 10.9 Hz, $^5J_{X,}$

$_{Me}$ = 1.7 Hz, 1H, H-X). ^{13}C NMR (75 MHz, C_6D_6) δ: 13.2 (CH_3), 17.8 (CH_3), 26.6 (CH_3), 27.8 (CH_3), 31.5 (CH_2), 51.1 (OCH_3), 54.9 (OCH_3), 63.6 (C-6'), 67.3 (C-4'), 76.8 (C-4), 83.5 (C-3'), 116.9 (CH_2=$\underline{C}$H), 130.7 (C-2), 139.0 ($\underline{C}H_2$=CH), 146.2 (C-2'), 155.5 (C-3), 172.0 (C=O); MS (e.i.) m/z: 310 (M^+, 58 %), 295 (M^+ - CH_3, 18 %), 279 (M^+ - CH_3O, 9 %), 279 (M^+ - CO_2CH_3, 37 %),168 (82 %),143 (100 %), MS (c.i., NH_3) m/z: 311 $(M + H)^+$. Attempts to purify this product by chromatography led to hydrolysis of the ketene acetal moiety to give (E)-methyl-3-ethenyl-4-(tetrahydro-4*H*-pyran-4-oxy-2-one)-2,4-dimethylpent-2-enoate (**182**) as the major isolated hydrolysis product. ^{1}H NMR of **182** (500 MHz, C_6D_6) δ: 0.97 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.17 (d, ^3J = 7.0 Hz, 3H, CH_3 on C-3'), 1.19 - 1.26 (m, complex, 1H, H-5'), 1.55 (m, ^2J = -14.2, ^3J = 8.5, ^3J = 5.6 Hz, ^3J = 5.6 Hz, 1H, H-5'), 2.05 (dq, ^3J = 7.0 Hz, ^3J = 4.3 Hz, 1H, H-3'), 2.10 (d, ^5J = 1.7 Hz, 3H, CH_3 on C-2), 3.34 (s, 3H, OCH_3), 3.36 (m, complex, 1H, H-4'), 3.51 (m, $^2J_{6'a,6'b}$ = - 11.5 Hz, $^3J_{5'a,6'a}$ = 5.1 Hz, $^3J_{5'b,6'a}$ = 8.5 Hz, 1H, H-6'a), 3.90 (m, $^2J_{6'a,6'b}$ = - 11.5 Hz, $^3J_{5'a,6'b}$ = 11.5 Hz, $^3J_{5'b,6'b}$ = 5.8 Hz, 1H, H-6'b), 4.88 (dd, $^3J_{BX}$ = 10.9 Hz, $^2J_{AB}$ = 2.2 Hz, 1H, H-B), 5.03 (dd, $^3J_{AX}$ = 17.2 Hz, $^2J_{AB}$ = 2.2 Hz, 1H, H-A), 6.16 (m, $^3J_{AX}$ = 17.2 Hz, $^3J_{BX}$ = 10.9 Hz, $^5J_{X,Me}$ = 1.7 Hz, 1H, H-X). ^{13}C NMR (50 MHz, C_6D_6) δ: 12.9 (CH_3), 17.9 (CH_3), 26.1 (CH_3), 27.3 (CH_3), 29.7 (CH_2), 41.1 (C-4'), 51.2 (OCH_3), 64.5 (C-6'), 68.8 (C-4'), 77.7 (C-4), 83.5 (C-3'), 117.3 (CH_2=$\underline{C}$H), 131.1 (C-2), 138.6 ($\underline{C}H_2$=CH), 145.0 (C-3), 172.0 (C=O), 172.4 (C=O); MS (e.i.) m/z: 296 (M^+, 25 %), 281 (M^+ - CH_3, 5 %), 265 (M^+ - CH_3O, 13 %), 238 (9 %), 168 (100 %), MS (c.i., NH_3) m/z: 314 $(M + NH_4)^+$, 297 $(M + H)^+$.

2-Methoxy-2-(4-methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (183). A stirred solution of **123h** (764 mg, 3.9 mmol) in dry THF was cooled at -78 °C under nitrogen for 30 minutes. A 1.6 M solution of n-butyllithium in hexanes (2.4 mL, 3.8 mmol) was then added dropwise. This solution was stirred at -78 °C for 1 hour before addition of methylchloroformate (0.75 mL, 9.8 mmol). The reaction mixture was allowed to reach room temperature overnight with the cooling bath left in place. Water (25 mL) was then cautiously added and most of the THF was then removed from the aqueous solution by rotary evaporation. The aqueous residue was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried over anhydrous Na_2SO_4, and then concentrated in vacuo. Chromatography (Chromatotron, 4 mm plate, 10 % EtOAc / hexanes) gave **183** as a yellow oil in 76 % yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.54 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.67 (t, ^{3}J=6.9 Hz, 2H, CH_2), 3.43 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3O), 3.88 (dt, ^{3}J=6.9 Hz, ^{2}J= -9.7 Hz, 1H, ^{1}H of CH_2O), 3.96 (dt, ^{3}J=6.9 Hz, ^{2}J= -9.7 Hz, 1H, ^{1}H of CH_2O); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.9 (CH_3), 23.6 (CH_3), 23.9 (CH_2), 51.6 (CH_3O), 52.3 (CH_3O), 61.4 (CH_2O), 73.6 (E$\underline{C}$≡C), 85.2 (EC≡$\underline{C}$), 119.3 (C5), 136.4 (C2), 153.5 (C=O); MS (c.i., NH_3) m/z: 274 $(M + NH_4)^+$.

Thermolysis of 2-methoxy-2-(4-methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (183) in the presence of *tert*-butyl alcohol. A solution of 2-methoxy-2-(4-methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**183**) (119 mg, 0.47 mmol) in 130 mL of dry toluene was prepared. At atmospheric pressure,

20 mL of the toluene was then distilled off from this solution to remove adventitious water by azeotropic distillation. *Tert*-butyl alcohol (90 mg , 1.2 mmol) was added and the solution was refluxed under a nitrogen atmosphere for 20 hours. Concentration of this solution in vacuo gave an oil. The spectral data of the residue indicated that it was primarily (> 80 %) methyl-2-*tert*-butoxy-2-(2-methoxy-4,5-dihydro-3-furanyl)-ethanoate (**187**). ^{1}H NMR (500 MHz, C_6D_6) δ: 1.32 (s, 9H, $(CH_3)_3$), 2.85 (m, $^{2}J_{4'\alpha,4'\beta}$ = -19.4 Hz, $^{3}J_{4'\alpha,5'\beta}$ = 7.9 Hz, $^{3}J_{4'\alpha,5'\alpha}$ = 7.9 Hz, $^{4}J_{2,4'\alpha}$ = 2.9 Hz, 1H, H-4'α), 2.99 (m, $^{2}J_{4'\alpha,4'\beta}$ = -19.4 Hz, $^{3}J_{4'\beta,5'\beta}$ = 6.1 Hz, $^{3}J_{4'\beta,5'\alpha}$ = 8.1 Hz, $^{4}J_{2,4'\beta}$ = 2.8 Hz, 1H, H-4'β), 3.09 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.61 (m, $^{2}J_{5'\alpha,5'\beta}$ = - 8.0 Hz, $^{3}J_{4'\alpha,5'\beta}$ = 8.1 Hz, $^{3}J_{4'\beta,5'\beta}$ = 6.1 Hz, 1H, H-5'β), 3.64 (m, $^{2}J_{5'\alpha,5'\beta}$ = - 8.0 Hz, $^{3}J_{4'\alpha,5'\alpha}$ = 5.8 Hz, $^{3}J_{4'\beta,5'\alpha}$ = 7.9 Hz, 1H, H-5'α), 6.26 (dd, $^{4}J_{2,4'\beta}$ = 2.8 Hz, $^{4}J_{2,4'\alpha}$ = 2.9 Hz, 1H, H-2); ^{13}C NMR (75 MHz, C_6D_6) δ: 30.2 (+)(C-4'), 30.3(-)($(CH_3)_3$), 49.6 (-)(CH_3O), 50.8 (-)(CH_3O), 64.1 (+)(C-5'), 64.2 (+)($\underline{C}(CH_3)_3$), 76.7(+)(C-3'), 114.0 (-)(C-2), 158.9 (+)(C-2'), 167.0 (+)(CO);

Typical [3+2] cycloaddition with dimethylacetylene dicarboxylate (DMAD). Thermolysis of 2-methoxy-2-(4-methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (183) in the presence of DMAD. A solution of **183** (180 mg, 0.71 mmol) in dry toluene (180 mL) was prepared. At atmospheric pressure, 20 mL of the toluene was then distilled off to remove adventitious water by azeotropic distillation. DMAD (140 mg, 0.99 mmol) was added before the solution was refluxed for 20 hours. Following concentration in vacuo, the crude thermolysis product was purified by chromatography (Chromatotron, 2 mm plate, 10 - 20 % EtOAc / hexanes) to give the

[3+2] cycloadduct **191** as a yellow oil in 29 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.18 (m, ^{2}J= - 13.2 Hz, ^{3}J= 10.7 Hz, ^{3}J= 7.7 Hz, 1H, CH_2), 2.50 (m, ^{2}J= - 13.2 Hz, ^{3}J= 4.1 Hz, 1H, CH_2), 3.23 (s, 3H, ether CH_3O), 3.73 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 4.99 (m, ^{2}J= - 8.4 Hz, ^{3}J= 7.7 Hz, 1H, OCH_2), 5.38 (m, ^{2}J= - 8.4 Hz, ^{3}J= 10.7 Hz, ^{3}J= 7.7 Hz, ^{3}J= 4.1 Hz, 1H, OCH_2); ^{13}C NMR (125 MHz, C_6D_6) δ: 34.5 (+)(C-3), 51.1 (-)(CH_3O), 51.2 (-)(CH_3O), 51.9 (-)(CH_3O), 52.3 (-)(CH_3O), 86.0 (+)(OCH_2), 91.0 (+)($CH_3O\underline{C}O\underline{C}H_2$), 101.3 (C-8), 118.5 (+)(C-6), 153.3 (+)(C-7), 161.3 (+)(2 x C=O), 164.5 (+)(C=O), 183.6 (+)(C-4) Assignment of $CH_3O\underline{C}OCH_2$ was based on a two and three bond ^{1}H- ^{13}C correlation (HETCOR) NMR experiment which shows correlation of the resonance at 91.0 ppm to the ether OCH_3 hydrogens. In addition, assignment of E-C=$\underline{C}OCH_2$ was based on the fact the resonance at 183.6 ppm showed a correlation with a proton of both OCH_2 and CH_2. MS(e.i.), *m/z* (rel. intensity) 312 (M^+, 100), 297 (M^+ - CH_3, 7), 281 (M^+ - OCH_3, 47), 269 (27), 253 (M^+ - CO_2CH_3, 59), 221 (55), 84 (100); MS(HR) m/z: 312.0845 calcd. for $C_{14}H_{16}O_8$ (M^+), found 312.0844.

Typical [3+2] cycloaddition with benzylidenemalononitrile. Thermolysis of 2-methoxy-2-(4-methoxycarbonyl-3-butyn-1-oxy)-5,5-dimethyl-Δ^{3}-1,3,4-oxadiazoline (183) in the presence of benzylidenemalononitrile. A solution of **183** (136 mg, 0.53 mmol) and benzylidinemalononitrile (90 mg, 0.58 mmol) in 150 mL dry toluene was

prepared. At atmospheric pressure, 20 mL of the toluene was then distilled off from this solution to remove adventitious water by azeotropic distillation before the solution was refluxed for 20 hours. Following concentration in vacuo the crude thermolysis product was purified by chromatography (Chromatotron, 1 mm plate, 5 - 15 % EtOAc / hexanes) to give the [3+2] cycloadducts **189** and **190** as a 54 : 46 mixture of diastereomers in 81 % combined yield. The spectral data are of a 54 : 46 diastereomeric mixture of cycloadducts. ^{1}H NMR of **189** and **190** with approximate integrations based on a 1 : 1 ratio (300 MHz, $CDCl_3$) δ: 2.78 - 3.09 (m, 2H, allylic CH_2) , 3.22 - 3.45 (m, 2H, allylic CH_2), 3.50 (s, 3H, CH_3O), 3.54 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 3.76 (s, 3H, CH_3O), 4.45 - 4.57 (m, 2H, OCH_2), 4.62 - 4.75 (m, 2H, OCH_2), 5.05 (d, ^{5}J= 1.8 Hz, 1H, benzylic CH), 5.21 (dd, ^{5}J= 1.6 Hz, ^{5}J= 4.7 Hz, 1H, CH), 7.29 - 7.46 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.4 (2 x CH_2), 48.8 ($C(CN)_2$), 51.1 ($C(CN)_2$), 51.8 (CH_3O), 52.0 (CH_3O), 52.4 (CH_3O), 53.2 (CH_3O), 62.2 (CPh), 64.2 (CPh), 74.2 (CH_2O), 74.5 (CH_2O), 111.0 (OCO), 111.3 (OCO), 111.8 (CN), 114.0 (CN), 114.8 (CN), 116.0 (CN), 126.9, 127.6, 128.2, 128.6, 128.7, 129.1, 129.2 (8 x aryl C's + 2 C=CE), 155.1 (C=CE), 155.5 (C=CE), 162.9 (C=O), 163.3 (C=O); MS(e.i.), *m/z* (rel. intensity): 324 (M^+, 100), 309 (M^+ - CH_3, 3), 293 (M^+ - OCH_3, 8), 265 (M^+ - CO_2CH_3, 35), 237 (24), 205 (44), 111 (71); MS(HR) m/z: 324.1110 calcd. for $C_{18}H_{16}N_2O_4$ (M^+), found 324.1100.

2-Methoxy-2-[5-methoxycarbonyl-4-pentyn-1-oxy]-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (193). A stirred solution of 2-methoxy-5,5-dimethyl-2-(4-pentyn-1-oxy)-Δ^3-1,3,4-oxadiazoline **123i** (1.00 g, 4.7 mmol) in dry THF (50 mL) was cooled at -78 °C for

30 minutes under nitrogen. A 1.6 M solution of n-butyllithium in hexanes (3.3 mL, 5.2 mmol) was then added dropwise. This solution was stirred at -78 °C for 1 hour before addition of methylchloroformate (1.0 mL, 12 mmol). The reaction mixture was allowed to reach room temperature overnight with the cooling bath left in place. Water (25 mL) was then added cautiously and most of the THF was evaporated from the aqueous mixture by rotary evaporation. The aqueous residue was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried over anhydrous Na_2SO_4 and then concentrated in vacuo. Chromatography (Chromatotron, 4 mm plate, 10 % EtOAc / hexanes) gave **193** as an oil in 60 % yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.49 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.84 (m, ^{3}J=7.2 Hz, ^{3}J=6.5 Hz, ^{3}J=6.0 Hz, 2H, CH_2), 2.41 (t, ^{3}J=7.2 Hz, 2H, CH_2), 3.38 (s, 3H, CH_3O), 3.70 (s, 3H, CH_3O), 3.71 (dt, ^{2}J= -9.9 Hz, ^{3}J=6.5 Hz, 1H, 1H of OCH_2), 3.80 (dt, ^{2}J= -9.9 Hz, ^{3}J=6.0 Hz, 1H, 1H of OCH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.4 (CH_2), 23.9 (CH_3), 24.1 (CH_3), 27.6 (CH_2), 51.8 (CH_3O), 52.5 (CH_3O), 62.8 (CH_2O), 73.2 (E<u>C</u>≡C), 88.4 (EC≡<u>C</u>), 119.2 (C-5), 136.9 (C-2), 154.0 (C=O); MS(e.i.) (rel. intensity) m/z: 239 (M^+ - OCH_3, 3), 169 (5), 239 (M^+ - $O(CH_2)_3C{\equiv}C$-E, 15), 125 (65), 93 (68), 59 (100); MS (c.i., NH_3) m/z: 288 $(M + NH_4)^+$.

Thermolysis of 2-methoxy-2-[5-methoxycarbonyl-4-pentyn-1-oxy]-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (193) in the presence of benzylidenemalononitrile. The typical procedure for [3+2] cycloaddition with benzylidenemalononitrile (above) was followed. Thermolysis of 2-methoxy-2-[5-methoxycarbonyl-4-pentyn-1-oxy]-5,5-dimethyl-Δ^3-1,3,4-

oxadiazoline (**30**) (134 mg, 0.50 mmol) in the presence of benzylidenemalononitrile gave **31** and **32** in a ratio of 55 : 45. These products were separated by chromatography (Chromatotron, 2 mm plate, 5 - 10 % EtOAc / hexanes) in a combined yield of 76 %.

Spectral data of 194.[141] FTIR (NaCl) cm^{-1}: 2980 - 2849, 1724, 1456, 1438, 1281, 1252, 1051; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.83 - 1.93 (m, 2H, CH_2), 2.60 (m, ^2J= - 15.1 Hz, ^3J= 10.2 Hz, ^3J= 8.0 Hz, ^5J= 2.2 Hz, 1H, allylic CH_2), 3.49 (m, ^2J= - 15.1 Hz, ^3J= 3.9 Hz, ^3J= 3.9 Hz, ^4J= 1.7 Hz, 1H, allylic CH_2), 3.53 (s, 3H, CH_3O), 3.62 (s, 3H, CH_3O), 3.86 (m, ^2J= - 10.7 Hz, ^3J= 8.5 Hz, ^3J= 6.2 Hz, 1H, OCH_2), 4.09 (m, ^2J= - 10.7 Hz, ^3J= 3.2 Hz, ^3J= 3.2 Hz, ^4J= 1.7 Hz, 1H, OCH_2), 4.71 (d, ^5J= 1.7 Hz, 1H, allylic CH), 7.26 - 7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.2 (CH_2), 25.0 (CH_2), 48.0 ($C(CN)_2$), 50.4 (CH_3O), 52.0 (CH_3O), 58.6 (CPh), 64.7 (CH_2O), 108.8 (OCO), 111.9 (CN), 114.5 (CN), 127.1, 128.7, 129.0, 134.8 (phenyl C's + C=CE), 149.9 (C=CE), 163.5 (C=O); MS(e.i.), *m/z* (rel. intensity): 338 (M^+, 70), 323 (M^+ - CH_3, 3), 307 (M^+ - OCH, 22), 279 (M^+ - CO_2CH_3, 23), 273 (100), 247 (32), 219 (35), 125 (87); MS (HR) m/z: 338.1267 calcd. for $C_{19}H_{18}N_2O_4$ (M^+), found 338.1265.

Spectral data of 195.[141] FTIR (NaCl) cm^{-1}: 2965 - 2848, 1724, 1456, 1437, 1280, 1255, 1048; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.90 - 2.12 (m, 2H, CH_2), 2.53 (m, ^2J= - 13.9 Hz, ^3J= 12.5 Hz, ^3J= 6.0 Hz, ^5J= 3.5 Hz, 1H, allylic CH_2), 3.48 (m, ^2J= - 13.9 Hz, ^3J= 6.0 Hz, ^3J= 4.0 Hz, ^4J= 2.0 Hz, 1H, allylic CH_2), 3.56 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 3.94

(m, ^{2}J= - 11.5 Hz, ^{3}J= 11.7 Hz, ^{3}J= 3.2 Hz, 1H, OCH_2), 4.11 (m, ^{2}J= - 11.5 Hz, ^{3}J= 4.8 Hz, ^{3}J= 1.8 Hz, ^{4}J= 2.0 Hz, 1H, OCH_2), 4.80 (d, ^{5}J= 3.5 Hz, 1H, allylic CH), 7.13 - 7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.8 (2 x CH_2), 50.9 ($C(CN)_2$), 49.3 (CH_3O), 51.8 (CH_3O), 58.2 (CPh), 64.9 (CH_2O), 108.7 (OCO), 111.3 (CN), 113.7 (CN), 126.7, 128.3, 128.9, 129.1 (phenyl C's + C=CE), 150.3 (C=CE), 163.7 (C=O); MS(e.i.), *m/z* (rel. intensity): 338 (M^+, 80), 323 (M^+ - CH_3, 5), 307 (M^+ - OCH_3, 22), 279 (M^+ - CO_2CH_3, 26), 273 (100), 247 (39), 219 (31), 125 (100); MS(HR) m/z: 338.1267 calcd. for $C_{19}H_{18}N_2O_4$ (M^+), found 338.1247.

Thermolysis of 2-methoxy-2-[5-methoxycarbonyl-4-pentyn-1-oxy]-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (193) in the presence of DMAD. The typical procedure for [3+2] cycloaddition with DMAD (above) was followed. Thermolysis of 2-methoxy-2-[5-methoxycarbonyl-4-pentyn-1-oxy]-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**193**) (133 mg, 0.49 mmol) in the presence of DMAD gave two products **197** and **198** in a ratio of 53 : 47. These products were isolated by chromatography (Chromatotron, 1 mm plate, 10 - 20 % EtOAc / hexanes) in 36 and 31 % yields respectively. Heating either one of the two isolated isomeric cycloadducts (**197** or **198**) led to a 53 : 47 mixture of the two.

Spectral data of 197. ^{1}H NMR (300 MHz, C_6D_6) δ: 1.16 - 1.34 (m, 2H, CH_2), 2.06 (m, 1H, allylic CH_2), 3.03 (s, 3H, CH_3O), 3.28 (s, 3H, CH_3O), 3.33 (m, 1H, allylic CH_2), 3.36

(s, 3H, CH_3O), 3.39 (m, 1H, OCH_2), 3.71 (s, 3H, CH_3O), 3.81 (m, 1H, OCH_2); ^{13}C NMR (50 MHz, C_6D_6) δ: 24.9 (CH_2), 28.8 (allylic CH_2), 50.9 (CH_3O), 51.4 (2 x CH_3O), 52.1 (CH_3O), 61.5 (OCH_2), 105.8 ($CH_3O\underline{C}OCH_2$), 123.2 (vinyl C), 132.3 (vinyl C), 147.7 (vinyl C), 161.4 (C=O), 162.6 (C=O), 163.1 (C=O), 165.2 (E-C=$\underline{C}CH_2$); MS(e.i.), *m/z* (rel. intensity): 326 (M^+, 100), 311 (M^+ - CH_3, 11), 295 (M^+ - OCH_3, 80), 283 (17), 267 (M^+ - CO_2CH_3, 82), 235 (50); MS(HR) m/z: 326.1002 calcd. for $C_{15}H_{18}O_8$ (M^+), found 326.1001.

Spectral data of 198. ^1H NMR (500 MHz, C_6D_6) δ: 1.01 (m, ^2J = -17.4 Hz, ^3J = 6.1, ^3J = 4.7, ^3J = 4.2, 1H, CH_2), 1.26 - 1.35 (m, 3H, 2H of CH_2 and 1H of allylic CH_2), 2.72 (m, ^2J= - 15.3 Hz, ^3J= 9.6 Hz, ^3J= 4.7 Hz, 1H, 1H of allylic CH_2), 3.49 (s, 3H, CH_3O), 3.54 (s, 3H, CH_3O), 3.76 (m, ^2J= - 10.5 Hz, ^3J= 6.1 Hz, ^3J= 2.4 Hz, 1H, OCH_2), 5.33 (m, ^2J= - 10.5 Hz, ^3J= 11.5 Hz, ^3J= 4.2 Hz, 1H, OCH_2); ^{13}C NMR (50 MHz, C_6D_6) δ: 17.2 (CH_2), 27.1 (CH_2), 51.1 (2 x CH_3O), 52.0 (CH_3O), 52.2 (CH_3O), 68.0 (OCH_2), 83.7 ($CH_3O\underline{C}CH_2$), 105.3, 121.7, 150.1 (3 vinyl C's), 161.4 (C=O), 161.9 (C=O), 165.5 (C=O), 175.0 (O$\underline{C}$=C); MS(e.i.), *m/z* (rel. intensity): 326 (M^+, 79), 311 (M^+ - CH_3, 11), 295 (M^+ - OCH_3, 52), 283 (14), 267 (M^+ - CO_2CH_3, 100), 235 (60); MS(HR) m/z: 326.1002 calcd. for $C_{15}H_{18}O_8$ (M^+), found 326.1002.

Preparation of *ortho*-hydroxy phenyl acetylene: This compound was prepared according to the procedure reported by Prey and Pieh.[135] A solution of 2,3-benzofuran (5.89 g, 49.9 mmol), containing finely cut sodium (3.30 g, 143.5 mmol) in pyridine (50 g)

was refluxed under a blanket of nitrogen for four hours. After cooling to room temperature, pyridine (20 mL) and water (30 mL) were slowly added to the "tar like" mixture. The excess 2,3-benzofuran was extracted with ether (30 mL) from the aqueous pyridine solution. The aqueous pyridine solution was acidified to a pH of 2 using dilute HCl and the free phenol was then extracted (3 x 20 mL) with ether. The combined organic extracts were washed once with dilute HCl (20 mL) and once with water (20 mL). Upon drying the organic layer with Na_2SO_4 and concentrating in vacuo the title compound (3.54 g, 30.0 mmol) of high purity was obtained in 61 % yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.43 (s, 1H, C≡CH), 4.75 (br, OH), 6.90 (m, 1H, $^3J_{5,4}$ = 7.4 Hz, $^3J_{5,6}$ = 7.7 Hz, $^4J_{5,3}$ = 1.2 Hz, H-5), 6.93 (dd, 1H, $^3J_{4,3}$ = 8.3 Hz, $^4J_{3,5}$ = 1.2 Hz, H-3), 7.25 (m, 1H, $^3J_{4,3}$ = 8.3 Hz, $^3J_{5,4}$ = 7.4 Hz, $^4J_{4,6}$ = 1.7 Hz, H-4), 7.37 (dd, 1H, $^3J_{6,5}$ = 7.7 Hz, $^4J_{4,6}$ = 1.7 Hz, H-6); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 78.4 (C≡CH), 84.0 (C≡CH), 108.3 (C-1), 114.8 (C-4), 120.2 (C-3), 130.8 (C-5), 132.2 (C-6), 157.4 (C-2); MS (GCMS, e.i.) m/z: 118 ($M^{+\cdot}$, 80 %), 90 (90 %), 89 (100 %), 75 (2 %), 74 (4 %).

Preparation of 2-(2-Ethynylphenoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (199). A solution of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**132**) (70 % pure) (1.60 g, 5.96 mmol of oxadiazoline), *ortho*-hydroxy phenyl acetylene (0.70 g, 5.93 mmol), and p-toluene sulfonic acid (0.10 g) in CH_2Cl_2 (50 mL) was refluxed for 48 hours before dilute KOH (5 %, 10 mL) was added. The mixture was stirred for one hour followed by extraction (3 x 20 mL) with CH_2Cl_2. After drying the combined organic extracts with Na_2SO_4 and concentrating in vacuo the titled compound was obtained as a

yellow oil upon chromatography (Chromatotron, 4 mm plate, 10 % EtOAc / hexanes) in 37 % yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.29 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.22 (s, 1H, C≡CH), 3.64 (s, 3H, OCH_3), 7.01 - 7.47 (m, 5H, phenyl H's); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.4 (CH_3) , 24.1 (CH_3), 52.6 (CH_3O), 79.5 (C≡CH), 81.5 (C≡CH), 116.0 (aryl C), 120.8 (C-5), 121.2 (aryl C), 124.1 (aryl C), 129.6 (aryl C), 133.7 (aryl C), 136.7 (C-2), 153.0 (aryl C); MS (GCMS, e.i.) m/z: 218 (M^+ - N_2, 1 %), 215 (M^+ - CH_3O, 1 %), 203 (4 %), 160 (M^+ - C_3H_6O - N_2, 15 %), MS (c.i., NH_3) m/z: 264 $(M + NH_4)^+$, 247 $(M + H)^+$.

Thermolysis of 199 in the presence of *tert*-butyl alcohol. A solution of 2-(2-Ethynylphenoxy)-2-methoxy-2,2-dimethyl-Δ^3-1,3,4-oxadiazoline (**199**) (0.235 g, 0.957 mmol) and *tert*-butyl alcohol (0.26 g, 3.5 mmol) in dry toluene (100 mL) was refluxed for 24 hours. Analysis of the crude thermolysis mixture (0.1985 g) by ^{1}H NMR indicated that it consisted mainly of 3-Methyl(*tert*-butoxy)-2-Methoxy-2,3-benzofuran (**204**). Note: This compound is sensitive to moisture and attempts to isolate a pure sample failed. Therefore these spectral data are of the crude thermolysis product which is primarily (> 80 % by ^{1}H NMR) **204**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 9H, Me_3), 4.04 (s, 3H, CH_3O), 4.43 (s, 2H, CH_2O), 7.09 (m, $^3J_{6,7}$ = 7.5 Hz, $^3J_{7,8}$ = 7.4 Hz, $^4J_{5,7}$ = 1.6 Hz, 1H, H-7), 7.16 (m, $^3J_{5,6}$ = 7.5 Hz, $^3J_{6,7}$ = 7.5, $^4J_{6,8}$ = 1.4 Hz, 1H, H-6), 7.25 (dd, 1H, $^3J_{7,8}$ = 7.4 Hz, $^4J_{6,8}$ = 1.8 Hz, H-8), 7.25 (dd, 1H, $^3J_{5,6}$ = 7.5 Hz, $^4J_{5,7}$ = 1.6 Hz, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.6 (Me_3), 53.2 ($O\underline{C}H_3$), 58.6 ($O\underline{C}H_2$), 73.1 ($\underline{C}Me_3$), 82.5 (C-3), 91.2 (C-2), 110.0 (C-8), 118.7 (C-6), 121.8 (C-4), 122.9 (C-5), 129.9 (C-7), 159.1 (C-9);

Methyl 2-(2-hydroxyphenyl)propenoate (203) To the crude thermolysis product (0.058 g) consisting of mainly **202** was added para-toluene sulfonic acid (0.010 g) in water (0.10 mL). The solution was stirred for 1.5 hours at room temperature before it was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were then dried over Na_2SO_4 and concentrated in vacuo. Chromatography (1 mm plate, 10 % EtOAc/hexanes) yielded **203** (0.0152 g) in 40 % yield. ^{1}H NMR analysis of the crude hydrolysis mixture revealed that **205** was also formed. The ratio of **203** to **205** was estimated to be approximately 5 : 1 by ^{1}H NMR . ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.85 (s, 3H, OCH_3), 5.89 (d, 1H, ^2J = 1.3, H-3), 6.42 (d, 1H, ^2J = 1.3, H-3), 6.89 (m, 1H, $^3J_{5',6'}$ = 7.9 Hz, $^3J_{4',5'}$ = 7.3 Hz, $^4J_{3',5'}$ = 1.2 Hz, H-5'), 6.92 (dd, 1H, $^3J_{3',4'}$ = 7.1 Hz, $^4J_{3',5'}$ = 1.2 Hz, H-3'), 7.12 (dd, 1H, $^3J_{5',6'}$ = 7.9 Hz, $^4J_{4',6'}$ = 1.8 Hz, H-6'), 7.25 (m, 1H, $^3J_{4',5'}$ = 7.3 Hz, $^3J_{3',4'}$ = 7.1 Hz, $^4J_{4',6'}$ = 1.8 Hz, H-4'), 7.50 (bs, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 53.0 (CH_3O), 117.8 (C-3), 120.7 (C-2), 124.7 (C-1'), 130.3, 130.4, 130.7 (C-6', C-5, C-4'), 139.4 (C-3'), 153.6 (C-1'), 169.7 (C=O).

Thermolysis of 199 in the presence of benzylidenemalononitrile. A solution of 2-(2-Ethynylphenoxy)-2-methoxy-2,2-dimethyl-Δ^3-1,3,4-oxadiazoline (**199**) (36 mg, 0.53 mmol) and benzylidenemalononitrile (90 mg, 0.58 mmol) in 150 mL dry toluene was prepared. At atmospheric pressure, 20 mL of the toluene was then distilled off from this solution to remove adventitious water by azeotropic distillation before the solution was refluxed for 20 hours. Following concentration in vacuo the crude thermolysis product

was purified by chromatography (Chromatotron, 1 mm plate, 5 - 15 % EtOAc / hexanes) to give **209** in 67 % yield. This product was recrystalized in hexanes/EtOAc. Slow crystallization at room temperature gave excellent quality crystals. White solid, mp 141 - 142 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.42 (d, ^3J = 8.7 Hz, 1H, allylic CH), 3.89 (d, ^3J = 8.7 Hz, 1H, benzylic CH), 4.14 (s, 3H, CH_3O), 7.16 - 7.91 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.4 ($\underline{C}(CN)_2$), 29.8 (allylic $\underline{C}H$), 38.7 (benzylic $\underline{C}H$), 58.4 ($O\underline{C}H_2$), 83.2 (C-3), 110.7 (C-8), 112.5 ($\underline{C}N$), 113.6 ($\underline{C}N$), 117.3 (C-6), 122.6 (C-5), 123.8 (C-7), 128.4 (C-4), 129.1, 129.4, 130.6, 134.5 (phenyl C's),147.9 (C-2), 159.9 (C-9); MS(e.i.), *m/z* (rel. intensity): 314 (M^+, 13), 237 (M^+ - Ph, 5), 154 (100), 127 (50), 103 (55) , 91 (80); MS(HR) m/z: 314.1055 calcd. for $C_{20}H_{14}O_2N_2$ (M^+), found 314.1057.

Preparation of 2-[2-(methylpropiolate)-phenoxy]-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (210). A stirred solution of 2-(2-Ethynylphenoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline **199** (500 mg, 2.0 mmol) in dry THF (30 mL) was cooled at -78 °C for 60 minutes under nitrogen. A 2.4 M solution of n-butyllithium in hexanes (0.85 mL, 2.0 mmol) was then added dropwise. This solution was stirred at -78 °C for 1 hour before addition of methylchloroformate (0.5 mL, 6 mmol). The reaction mixture was allowed to slowly reach room temperature overnight with the cooling bath left in place. Water (15 mL) was then cautiously added and the THF was removed in vacuo by rotary evaporation. The aqueous residue was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried over anhydrous Na_2SO_2 and then concentrated in vacuo. Chromatography (Chromatotron, 4 mm plate, 10 - 15 % EtOAc / hexanes) gave **210** as an

oil in 40 % yield. FTIR (NaCl, neat) cm^{-1}: 2991, 2954, 2916 (C-H), 2227 (C≡C), 1714 (C=O); ^1H NMR (200 MHz, $CDCl_3$) δ: 1.28 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 7.06 - 7.54 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.3 (CH_3) , 24.1 (CH_3), 52.7 (2 coincidental CH_3O), 82.6 (alkyne C), 84.1 (alkyne C), 113.8 (C-5), 121.1, 121.6, 124.4, 131.6, 134.4 (5 aromatic C), 136.6 (C-2), 153.9 (aromatic C), 154.3 (C=O); MS (e.i.) m/z: 273 (M^+ - CH_3O, 6 %), 235 (5 %), 217 (18 %), 203 (20 %), 185 (20 %), 173 (30 %), 159 (18 %), 145 (16 %), 129 (M^+ - $C_{10}H_7O_2$, 100 %), MS (c.i., NH_3) m/z: 322 $(M + NH_4)^+$.

Thermolysis of 2-[2-(2-carbomethoxyethynyl)-phenoxy]-2-methoxy-5,5-dimethyl-Δ³-1,3,4-oxadiazoline (210) in the presence of benzylidenemalononitrile. A solution of 2-[2-(2-carbomethoxyethynyl)-phenoxy]-2-methoxy-5,5-dimethyl-Δ³-1,3,4-oxadiazoline (154 mg, 0.63 mmol) and benzylidenemalononitrile (100 mg, 0.65 mmol) in 150 mL dry toluene was prepared. At atmospheric pressure, 20 mL of the toluene was then distilled off from this solution to remove adventitious water by azeotropic distillation before the solution was refluxed for 20 hours. Following concentration in vacuo the crude thermolysis product was purified by chromatography (Chromatotron, 1 mm plate, 5 - 15 % EtOAc / hexanes) to give a single major product (99.7 mg, 0.41 mmol) **211** in 37 % yield as a solid. This product was recrystalized in hexanes/EtOAc. Slow crystallization at room temperature gave x-ray quality crystals. White solid, mp 188 - 190 °C; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.60 (s, 3H, CH_3O), 3.89 (s, 1H, benzylic CH), 4.20 (s, 3H, CH_3O), 7.16 - 7.50 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.5 ($\underline{C}(CN)_2$), 40.0 (allylic CH), 42.5

(benzylic CH), 58.4 (OCH_3), 58.4 (OCH_3), 85.2 (C-3), 110.9 (C-8), 111.1 (CN), 113.5 (CN), 117.4 (C-6), 122.8 (C-5), 124.1 (C-7), 127.8 (C-4), 128.6, 129.1, 129.3 (phenyl C's), 147.9 (C-2), 160.7 (C-9), 164.8 (C=O). MS(e.i.), *m/z* (rel. intensity): 372 (M^+, 58), 357 ($M^+ - CH_3$, 8), 313 ($M^+ - CO_2CH_3$, 100), 297 (20); MS(HR) m/z: 372.1110 calcd. for $C_{22}H_{16}O_4N_2$ (M^+), found 372.1106.

Attempted vinylcyclopropane rearrangement of 211 - sample not degassed: A solution of vinyl cyclopropane **211** (15.6 mg, 0.041 mmol) in toluene (14 mL) was prepared. At atmospheric pressure, 10 mL of the toluene was then distilled off from this solution to remove adventitious water by azeotropic distillation. The solution was then transferred to a 50 mL glass tube which was sealed before placing in an oil bath operating at 150 ± 0.1 °C for four days. Following thermolysis, the sample was cooled and then concentrated in vacuo. The ^1H NMR spectrum of the crude indicated that in addition to unreacted **211** there were a few other products. In addition to recovered **211**, the major product was the only one that could be successfully isolated by chromatography (Chromatotron, 2 mm plate, 10 - 20 % EtOAc / hexane). This product was a white powder and had a mass 15.9949 a.m.u. more than the expected product from vinylcyclopropane rearrangement. The structure of this product could not be determined based on spectroscopic data and attempts to grow crystals suitable for X-ray analysis failed. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.65 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 4.93 (s, 1H, CH), 7.10 - 7.60 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 50.0, 53.0, 56.0, 72.2, 110.9, 111.3, 122.7, 123.4, 126.7, 129.0, 129.6, 129.8, 130.1, 132.0, 132.5, 152.9, 167.4.

MS(e.i.), *m/z* (rel. intensity): 382 (M^+, 15), 357 (M^+ - OCH_3, 12), 323 (11) , 297 (18) , 269 (11), 243 (19), 121 (31), 105 (20), 91 (100); MS(HR) m/z: 388.1059 calcd. for $C_{22}H_{16}O_5N_2$ (M^+), found 388.1053.

Vinylcyclopropane rearrangement of 211: A solution of vinyl cyclopropane **211** (18.7 mg, 0.049 mmol) in toluene (20 mL) was prepared. At atmospheric pressure, 10 mL of the toluene was then distilled off from this solution to remove adventitious water by azeotropic distillation. The solution was then transferred to a 50 mL glass tube, degassed by three freeze-pump-thaw cycles, and then sealed before placing in an oil bath operating at 150 ± 0.1 °C for four days. Following thermolysis, the sample was cooled and then concentrated in vacuo. The ^1H NMR spectrum of the crude indicated that about 50 % of **211** had been converted to **213**. Chromatography (Chromatotron, 4 mm plate, 10 - 15 % EtOAc / hexanes) gave **213** as a white powder in approx. 40 % yield and the unreacted **211** was recovered. Very slow crystallization of **213** in EtOAc / hexanes at room temperature yielded crystals which were suitable for analysis by X-ray diffraction. White solid, mp 217 - 218 °C; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.31 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O), 5.30 (s, 1H, benzylic CH), 7.11 - 7.55 (m, 8H), 8.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 51.9 (OCH_3), 53.4 (OCH_3), 54.4 ($C(CN)_2$), 62.9 (allylic/ benzylic CH), 110.4, 110.8, 111.5, 112.2, 114.8, 118.9, 122.5, 127.2, 128.6, 128.8, 128.9, 129.2, 129.4, 133.8, 135.1, 150.4, 163.2, 165.5 (C=O). MS(e.i.), *m/z* (rel. intensity): 372 (M^+, 8), 313 (M^+ - CO_2CH_3, 28), 141 (29) , 84 (30); MS(HR) m/z: 372.1183 calcd. for $C_{22}H_{16}N_2O_4$ (M^+), found 372.1112.

Vinylcyclopropane rearrangement of 209: A solution of vinyl cyclopropane **209** (36.6 mg, 0.117 mmol) in toluene (20 mL) was prepared. At atmospheric pressure, 10 mL of the toluene was then distilled off from this solution to remove adventitious water by azeotropic distillation. The solution was then transferred to a 50 mL glass tube, degassed by three freeze-pump-thaw cycles, and then sealed before placing in an oil bath operating at 150 ± 0.1 °C for four days. Following thermolysis, the sample was cooled and then concentrated in vacuo. The ^{1}H NMR spectrum of the crude indicated that about 33 % of **209** had been converted to **214**. The product was not isolated however the formation of **214** was inferred on the basis of the crude ^{1}H NMR spectra. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.85 (s, 3H, CH_3O), 5.22 (d, ^{3}J = 1.9 Hz,1H, benzylic CH), 6.36 (d, ^{3}J = 1.9 Hz,1H, alkene CH), 7.15 - 8.05 (m, 9H).

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Appendix

Table 3. Crystal data and structure refinement for **140**

Empirical formula	$C_{15}H_{22}O_5$	
Formula weight	282.33	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 14.438(5) Å	α = 90 °
	b = 8.697(5) Å	β = 98.44(4) °
	c = 11.964(7) Å	γ = 90 °
Volume, Z	1486.0(13) $Å^3$, 4	
Density (calculated)	1.262 Mg/m^3	
Absorption coefficient	0.776 mm^{-1}	
F(000)	608	
Crystal size	0.26 x 0.11 x 0.06 mm	
θ range for data collection	3.09 ° to 54.99 °	
Limiting indices	$-16 \leq h \leq 16, -9 \leq k \leq 9, -13 \leq l \leq 13$	
Reflections collected	1977	
Independent reflections	1865 [R(int) = 0.0521]	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1806 / 0 / 268	
Goodness-of-fit on F^2	1.010	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0456, wR2 = 0.1077	
R indices (all data)	R1 = 0.1895, wR2 = 0.1644	
Extinction coefficient	0.0016(3)	
Largest diff. peak and hole	0.174 and -0.214 e. $Å^{-3}$	

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **140**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(3)	3844(2)	7692(3)	2272(3)	52(1)
O(6)	1341(2)	7834(4)	1907(3)	59(1)
O(7)	1936(4)	2870(5)	1289(4)	98(2)
O(8)	1343(3)	4659(4)	87(3)	68(1)
O(9)	1104(2)	5555(4)	2710(3)	62(1)
C(1A)	3156(3)	5368(6)	2667(4)	43(1)
C(1)	2368(3)	5545(6)	1625(4)	42(1)
C(2)	4096(3)	6087(6)	2445(4)	47(1)
C(3A)	3259(4)	8109(6)	3103(5)	52(2)
C(4)	2663(4)	9461(7)	2678(6)	65(2)
C(5)	1968(5)	9044(7)	1660(6)	66(2)
C(6A)	1793(3)	6493(6)	2375(4)	48(1)
C(6B)	2678(3)	6679(6)	3254(4)	44(1)
C(7)	1882(4)	4176(7)	1020(5)	52(1)
C(8)	782(5)	3491(10)	-595(7)	91(3)
C(9)	3273(4)	3811(6)	3218(5)	50(2)
C(10)	3155(5)	3451(9)	4233(6)	73(2)
C(11)	4447(5)	5553(9)	1379(6)	63(2)
C(12)	4860(4)	5919(8)	3464(6)	61(2)
C(13)	612(6)	6233(14)	3570(7)	86(3)

Table 5. Bond lengths [Å] and angles [deg.] for **140**.

O(3)-C(3a)	1.442(6)	C(2)-C(1a)-C(1)	112.0(4)
O(3)-C(2)	1.450(5)	C(6b)-C(1a)-C(1)	88.2(3)
O(6)-C(6a)	1.412(5)	C(7)-C(1)-C(6a)	116.6(4)
O(6)-C(5)	1.447(6)	C(7)-C(1)-C(1a)	122.4(4)
O(7)-C(7)	1.180(6)	C(6a)-C(1)-C(1a)	88.9(3)
O(8)-C(7)	1.332(6)	O(3)-C(2)-C(11)	106.5(5)
O(8)-C(8)	1.469(8)	O(3)-C(2)-C(12)	110.1(5)
O(9)-C(6a)	1.389(5)	C(11)-C(2)-C(12)	110.6(5)
O(9)-C(13)	1.459(8)	O(3)-C(2)-C(1a)	101.8(3)
C(1a)-C(9)	1.504(7)	C(11)-C(2)-C(1a)	115.5(5)
C(1a)-C(6b)	1.552(7)	C(12)-C(2)-C(1a)	111.8(5)
C(1a)-C(2)	1.552(6)	O(3)-C(3a)-C(4)	109.1(5)
C(1a)-C(1)	1.568(6)	O(3)-C(3a)-C(6b)	105.3(4)
C(1)-C(7)	1.511(7)	C(4)-C(3a)-C(6b)	112.4(5)
C(1)-C(6a)	1.546(6)	C(3a)-C(4)-C(5)	111.5(5)
C(2)-C(11)	1.512(8)	O(6)-C(5)-C(4)	111.9(6)
C(2)-C(12)	1.527(7)	O(9)-C(6a)-O(6)	106.9(4)
C(3a)-C(4)	1.501(8)	O(9)-C(6a)-C(6b)	15.0(4)
C(3a)-C(6b)	1.526(7)	O(6)-C(6a)-C(6b)	118.3(4)
C(4)-C(5)	1.526(7)	O(9)-C(6a)-C(1)	108.8(4)
C(6a)-C(6b)	1.540(7)	O(6)-C(6a)-C(1)	117.8(4)
C(9)-C(10)	1.290(7)	C(6b)-C(6a)-C(1)	89.4(4)
C(3a)-O(3)-C(2)	107.7(4)	C(3a)-C(6b)-C(6a)	114.9(4)
C(6a)-O(6)-C(5)	114.5(4)	C(3a)-C(6b)-C(1a)	104.9(4)
C(7)-O(8)-C(8)	117.0(5)	C(6a)-C(6b)-C(1a)	89.7(4)
C(6a)-O(9)-C(13)	114.2(6)	O(7)-C(7)-O(8)	122.7(5)
C(9)-C(1a)-C(6b)	119.5(4)	O(7)-C(7)-C(1)	128.3(5)
C(9)-C(1a)-C(2)	113.1(4)	O(8)-C(7)-C(1)	109.0(5)
C(6b)-C(1a)-C(2)	103.9(4)	C(10)-C(9)-C(1a)	127.6(6)

Symmetry transformations used to generate equivalent atoms:

Table 6 Anisotropic displacement parameters ($A^2 \times 10^1$) for **140.**

The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U 11	U22	U33	U23	U13	U12
O(3)	43(2)	45(2)	70(3)	2(2)	11(2)	-1(2)
O(6)	47(2)	57(2)	73(3)	-2(2)	1(2)	14(2)
O(7)	139(4)	53(3)	90(3)	-2(3)	-21(3)	-12(3)
O(8)	66(2)	70(3)	61(3)	-9(2)	-9(2)	-8(2)
O(9)	45(2)	73(2)	68(3)	-3(2)	15(2)	-9(2)
C(1a)	36(3)	47(3)	43(3)	-1(3)	-1(2)	7(3)
C(1)	39(3)	40(3)	44(3)	0(3)	0(3)	-3(2)
C(2)	39(3)	46(3)	57(3)	6(3)	9(3)	0(2)
C(3a)	44(3)	46(3)	63(4)	-4(3)	1(3)	0(3)
C(4)	59(4)	47(4)	90(5)	-6(4)	11(4)	-6(3)
C(5)	66(4)	40(3)	89(5)	6(4)	-1(4)	5(4)
C(6a)	39(3)	49(3)	56(4)	-8(3)	10(3)	2(3)
C(6b)	40(3)	54(3)	37(3)	2(3)	6(3)	-3(3)
C(7)	46(3)	63(4)	46(4)	-7(3)	4(3)	1(3)
C(8)	74(5)	110(6)	80(6)	-19(5)	-14(4)	-33(5)
C(9)	53(3)	46(4)	51(4)	4(3)	4(3)	6(3)
C(10)	84(5)	70(5)	66(5)	21(4)	14(4)	6(4)
C(11)	55(4)	66(5)	73(5)	2(4)	23(4)	4(4)
C(12)	44(3)	69(5)	66(4)	-6(4)	-7(3)	1(4)
C(13)	61(4)	131(8)	68(5)	-8(5)	21(5)	2(5)

Table 7 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **140**.

	x	y	z	U(eq)
H(1)	2615(33)	6262(57)	985(41)	76(17)
H(3A)	3710(32)	8284(54)	3885(43)	68(16)
H(4A)	2998(34)	10289(62)	2512(40)	63(18)
H(4B)	2333(40)	9677(69)	3318(52)	101(24)
H(5A)	1595(29)	9854(51)	1429(35)	40(15)
H(5B)	2310(40)	8623(65)	940(52)	103(23)
H(6B)	2575(30)	6536(53)	4029(39)	51(15)
H(8A)	484(74)	4107(123)	-1147(87)	218(29)
H(8B)	321(69)	3185(128)	-278(91)	218(29)
H(8C)	1237(70)	3014(120)	-911(89)	218(29)
H(9)	3517(31)	3123(52)	2784(38)	43(15)
H(10A)	2923(42)	4236(71)	4719(51)	105(25)
H(10B)	3273(41)	2355(74)	4453(51)	96(21)
H(11A)	3957(37)	5718(59)	783(46)	69(20)
H(11B)	4646(40)	4393(76)	1378(48)	98(22)
H(11C)	4968(38)	6167(59)	1260(43)	73(19)
H(12A)	5123(44)	4845(79)	3511(50)	107(24)
H(12B)	4647(32)	6222(56)	4199(45)	63(17)
H(12C)	5393(41)	6608(67)	3375(47)	84(20)
H(13A)	185(54)	6909(90)	3190(64)	133(35)
H(13B)	328(67)	5337(119)	3758(78)	192(52)
H(13C)	1075(70)	6500(114)	4185(89)	203(48)

Table 8. Crystal data and structure refinement for **211.**

Empirical formula	$C_{22} H_{16} N_2 O_4$
Formula weight	372.37
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system	monoclinic
Space group	Cc
Unit cell dimensions	a = 10.237(2) Å $\alpha = 90^\circ$
	b = 16.925(3) Å $\beta = 107.48(3)^\circ$
	c = 11.594(2) Å $\gamma = 90^\circ$
Volume, Z	1916.0(7) $Å^3$, 4
Density (calculated)	1.291 Mg/m^3
Absorption coefficient	0.741 mm^{-1}
F(000)	776
θ range for data collection	5.23 to 59.99 deg.
Limiting indices	$-11 \le h \le 11, 0 \le k \le 18, -12 \le l \le 12$
Crystal size	.19 x .12 x .09 mm
Reflections collected	2723
Independent reflections	2721 [R(int) = 0.0223]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2718 / 2 / 254
Goodness-of-fit on F^2	1.186
Final R indices [$I>2\sigma(I)$]	R1 = 0.0776, wR2 = 0.1641
R indices (all data)	R1 = 0.1222, wR2 = 0.1962
Absolute structure parameter	-0.4(6)
Extinction coefficient	0.0015(2)
Largest diff. peak and hole	0.195 and -0.172 e. $Å^{-3}$

Table 9. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **211**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(7)	7268(5)	125(2)	1602(4)	52(1)
O(11)	7952(7)	-1096(3)	2448(5)	79(2)
O(14)	4276(6)	-2317(4)	-1459(6)	86(2)
O(15)	4095(5)	-1700(3)	173(5)	58(1)
N(18)	9301(9)	-1311(5)	-882(9)	91(3)
N(20)	6396(10)	-3038(5)	-2620(8)	91(3)
C(1)	7277(8)	-677(4)	1479(7)	48(2)
C(2)	6546(6)	-935(4)	383(6)	41(2)
C(2a)	5963(7)	-229(4)	-317(6)	44(2)
C(3)	5141(8)	-70(5)	-1472(7)	59(2)
C(4)	4845(9)	725(5)	-1794(7)	65(2)
C(5)	5361(9)	1326(5)	-992(9)	71(2)
C(6)	6163(8)	1179(4)	169(8)	58(2)
C(6a)	6461(7)	401(4)	492(7)	47(2)
C(8)	6272(7)	-1761(4)	-54(5)	38(2)
C(9)	7243(7)	-2130(4)	-714(6)	43(2)
C(10)	7255(7)	-2399(4)	549(6)	40(2)
C(12)	8808(9)	-716(5)	3500(7)	66(2)
C(13)	4769(7)	-1961(4)	-552(6)	44(2)
C(16)	2641(7)	-1825(5)	-208(8)	73(3)
C(17)	8371(10)	-1661(5)	-814(8)	63(2)
C(19)	6693(9)	-2644(5)	-1774(8)	58(2)
C(21)	6834(7)	-3229(4)	765(6)	42(2)
C(22)	5927(8)	-3349(4)	1407(6)	53(2)
C(23)	5614(10)	-4125(5)	1670(7)	70(3)
C(24)	6219(11)	-4756(5)	1302(8)	75(3)
C(25)	7128(10)	-4631(5)	656(8)	73(3)
C(26)	7450(8)	-3868(4)	403(7)	59(2)

Table 10. Bond lengths [Å] and angles [deg.] for **211**.

O(7)-C(1)	1.365(8)	C(2A)-C(2)-C(8)	125.1(6)
O(7)-C(6a)	1.384(8)	C(3)-C(2A)-C(6A)	119.5(6)
O(11)-C(1)	1.333(8)	C(3)-C(2A)-C(2)	136.5(7)
O(11)-C(12)	1.424(8)	C(6A)-C(2A)-C(2)	104.0(5)
O(14)-C(13)	1.185(8)	C(2A)-C(3)-C(4)	117.7(7)
O(15)-C(13)	1.314(8)	C(5)-C(4)-C(3)	121.4(7)
O(15)-C(16)	1.436(8)	C(6)-C(5)-C(4)	121.6(7)
N(18)-C(17)	1.144(11)	C(6A)-C(6)-C(5)	117.3(7)
N(20)-C(19)	1.149(10)	C(6)-C(6A)-O(7)	126.6(7)
C(1)-C(2)	1.340(9)	C(6)-C(6A)-C(2A)	122.4(7)
C(2)-C(2a)	1.467(9)	O(7)-C(6A)-C(2A)	111.0(6)
C(2)-C(8)	1.484(9)	C(2)-C(8)-C(10)	119.2(5)
C(2a)-C(3)	1.377(10)	C(2)-C(8)-C(13)	114.1(6)
C(2a)-C(6a)	1.410(9)	C(10)-C(8)-C(13)	118.7(5)
C(3)-C(4)	1.406(11)	C(2)-C(8)-C(9)	117.6(6)
C(4)-C(5)	1.372(12)	C(10)-C(8)-C(9)	60.0(4)
C(5)-C(6)	1.372(11)	C(13)-C(8)-C(9)	116.7(5)
C(6)-C(6a)	1.377(10)	C(17)-C(9)-C(19)	112.0(6)
C(8)-C(10)	1.499(9)	C(17)-C(9)-C(10)	117.8(6)
C(8)-C(13)	1.511(9)	C(19)-C(9)-C(10)	121.0(6)
C(8)-C(9)	1.556(9)	C(17)-C(9)-C(8)	117.8(6)
C(9)-C(17)	1.435(11)	C(19)-C(9)-C(8)	120.5(6)
C(9)-C(19)	1.472(11)	C(10)-C(9)-C(8)	58.1(4)
C(9)-C(10)	1.529(9)	C(8)-C(10)-C(21)	124.2(6)
C(10)-C(21)	1.512(9)	C(8)-C(10)-C(9)	61.8(4)
C(21)-C(22)	1.368(10)	C(21)-C(10)-C(9)	120.9(6)
C(21)-C(26)	1.379(10)	O(14)-C(13)-O(15)	125.0(7)
C(22)-C(23)	1.406(11)	O(14)-C(13)-C(8)	124.5(7)
C(23)-C(24)	1.365(13)	O(15)-C(13)-C(8)	110.5(6)
C(24)-C(25)	1.376(12)	N(18)-C(17)-C(9)	177.5(9)
C(25)-C(26)	1.385(11)	N(20)-C(19)-C(9)	172.8(9)
C(1)-O(7)-C(6a)	105.0(6)	C(22)-C(21)-C(26)	119.8(7)
C(1)-O(11)-C(12)	120.7(5)	C(22)-C(21)-C(10)	120.1(6)
C(13)-O(15)-C(16)	116.6(6)	C(26)-C(21)-C(10)	119.9(6)
O(11)-C(1)-C(2)	128.7(6)	C(21)-C(22)-C(23)	119.5(8)
O(11)-C(1)-O(7)	117.4(6)	C(24)-C(23)-C(22)	120.6(9)
C(2)-C(1)-O(7)	113.8(7)	C(23)-C(24)-C(25)	119.6(8)
C(1)-C(2)-C(2a)	106.1(6)	C(26)-C(25)-C(24)	120.1(9)
C(1)-C(2)-C(8)	128.7(6)	C(25)-C(26)-C(21)	120.4(8)

Symmetry transformations used to generate equivalent atoms:

Table 11. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **211.**

The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
O(7)	64(3)	33(3)	49(3)	-3(2)	0(2)	-6(2)
O(11)	111(5)	41(3)	54(3)	-1(3)	-24(3)	3(3)
O(14)	64(4)	97(5)	85(4)	-48(4)	3(3)	-3(3)
O(15)	43(3)	65(3)	63(3)	-14(3)	13(3)	-13(3)
N(18)	79(5)	79(6)	129(8)	20(5)	50(5)	-6(5)
N(20)	131(7)	81(5)	65(5)	-21(5)	38(5)	1(5)
C(1)	52(4)	30(4)	51(5)	-4(4)	-2(3)	0(4)
C(2)	39(4)	34(4)	44(4)	-1(3)	3(3)	-8(3)
C(2a)	44(4)	31(4)	56(5)	10(3)	17(4)	-2(3)
C(3)	52(5)	54(5)	59(5)	-1(4)	1(4)	9(4)
C(4)	72(6)	56(6)	59(5)	20(4)	7(4)	8(5)
C(5)	70(6)	44(5)	90(7)	15(5)	11(5)	12(4)
C(6)	58(5)	34(4)	77(6)	6(4)	14(4)	-7(4)
C(6a)	45(4)	33(4)	58(5)	4(3)	10(3)	-2(3)
C(8)	46(4)	29(3)	32(4)	0(3)	3(3)	-5(3)
C(9)	56(4)	37(4)	42(4)	4(3)	24(4)	2(3)
C(10)	48(4)	31(4)	41(4)	-3(3)	11(3)	-5(3)
C(12)	81(6)	46(5)	52(5)	-3(4)	-9(4)	-6(4)
C(13)	51(4)	23(3)	48(4)	-8(3)	2(4)	-7(3)
C(16)	44(5)	78(6)	94(7)	-15(5)	14(4)	-13(4)
C(17)	72(6)	45(5)	83(6)	17(4)	38(5)	11(4)
C(19)	83(5)	51(5)	50(5)	9(4)	32(4)	12(4)
C(21)	44(4)	42(4)	37(4)	11(3)	6(3)	-2(3)
C(22)	76(6)	40(4)	44(4)	5(3)	18(4)	-5(4)
C(23)	87(6)	68(6)	52(5)	14(4)	15(5)	-24(5)
C(24)	116(8)	37(5)	63(6)	-1(4)	11(6)	-10(5)
C(25)	98(7)	36(5)	80(7)	8(4)	18(6)	7(4)
C(26)	62(5)	45(5)	67(6)	6(4)	16(4)	16(4)

Table 12. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **211**.

	x	y	z	U(eq)
H(3A)	4793(8)	-475(5)	-2020(7)	70
H(4A)	4288(9)	847(5)	-2568(7)	78
H(5A)	5162(9)	1846(5)	-1241(9)	85
H(6A)	6493(8)	1587(4)	715(8)	70
H(10A)	8046(7)	-2204(4)	1195(6)	48
H(12A)	9220(9)	-1106(5)	4101(7)	99
H(12B)	8270(9)	-360(5)	3815(7)	99
H(12C)	9513(9)	-426(5)	3295(7)	99
H(16A)	2257(7)	-1611(5)	386(8)	110
H(16B)	2453(7)	-2381(5)	-294(8)	110
H(16C)	2240(7)	-1567(5)	-969(8)	110
H(22B)	5521(8)	-2921(4)	1667(6)	64
H(23A)	4990(10)	-4209(5)	2097(7)	85
H(24A)	6017(11)	-5267(5)	1488(8)	91
H(25A)	7527(10)	-5059(5)	388(8)	88
H(26A)	8086(8)	-3786(4)	-13(7)	70

Table 13. Crystal data and structure refinement for **213**.

Empirical formula	$C_{22} H_{16} N_2 O_4$	
Formula weight	372.37	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 13.219(3) Å b = 9.5354(12) Å c = 15.031(2) Å	a = 90 ° b = 98.050(12) ° g = 90 °
Volume, Z	1876.1(6) Å 3, 4	
Density (calculated)	1.318 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	776	
Crystal size	0.25 x 0.25 x 0.50 mm	
(range for data collection	1.92 ° to 24.99 °	
Limiting indices	$-1 \leq h \leq 15, -1 \leq k \leq 11, -17 \leq l \leq 17$	
Reflections collected	4255	
Independent reflections	3305 [R(int) = 0.0632]	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3305 / 0 / 254	
Goodness-of-fit on F^2	0.873	
Final R indices [I>2s (I)]	R1 = 0.0482, wR2 = 0.1060	
R indices (all data)	R1 = 0.0798, wR2 = 0.1162	
Extinction coefficient	0.0037(11)	
Largest diff. peak and hole	0.167 and -0.209 $e.Å^{-3}$	

Table 14. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **213**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(7)	6081(1)	2692(2)	7132(1)	40(1)
O(11)	7157(1)	4503(2)	6841(1)	45(1)
O(14)	4197(1)	7153(2)	7957(1)	51(1)
O(15)	5623(1)	8271(2)	8558(1)	44(1)
N(18)	9000(2)	3576(3)	8523(2)	57(1)
N(20)	6194(2)	2618(2)	9459(1)	48(1)
C(1)	6473(2)	4058(2)	7394(2)	35(1)
C(2)	5555(2)	4965(2)	7449(1)	31(1)
C(2a)	4699(2)	4246(2)	6932(1)	33(1)
C(3)	3676(2)	4567(3)	6645(1)	39(1)
C(4)	3050(2)	3518(3)	6241(2)	44(1)
C(5)	3423(2)	2182(3)	6137(2)	48(1)
C(6)	4435(2)	1837(3)	6417(2)	44(1)
C(6a)	5049(2)	2887(2)	6802(1)	34(1)
C(8)	5792(2)	5995(2)	8045(1)	31(1)
C(9)	7060(2)	4187(2)	8358(2)	33(1)
C(10)	6868(2)	5807(2)	8550(1)	32(1)
C(12)	6734(2)	4873(3)	5937(2)	52(1)
C(13)	5106(2)	7179(2)	8182(1)	35(1)
C(16)	5017(2)	9501(3)	8687(2)	65(1)
C(17)	8153(2)	3838(3)	8432(2)	39(1)
C(19)	6576(2)	3295(3)	8978(2)	35(1)
C(21)	7052(2)	6137(2)	9539(1)	30(1)
C(22)	6277(2)	6117(3)	10070(2)	41(1)
C(23)	6486(2)	6381(3)	10975(2)	48(1)
C(24)	7468(2)	6655(3)	11370(2)	48(1)
C(25)	8246(2)	6686(3)	10858(2)	41(1)
C(26)	8041(2)	6420(2)	9946(2)	36(1)

Table 15. Bond lengths [Å] and angles [deg] for **213**.

C(1)-O(11)	1.379(3)	C(2A)-C(2)-C(1)	105.9(2)
C(1)-O(7)	1.436(3)	C(3)-C(2A)-C(6A)	119.0(2)
C(1)-C(2)	1.502(3)	C(3)-C(2A)-C(2)	135.4(2)
C(1)-C(9)	1.549(3)	C(6A)-C(2A)-C(2)	105.3(2)
C(2)-C(8)	1.337(3)	C(4)-C(3)-C(2A)	118.2(2)
C(2)-C(2A)	1.451(3)	C(5)-C(4)-C(3)	121.0(2)
C(2A)-C(3)	1.395(3)	C(4)-C(5)-C(6)	122.0(2)
C(2A)-C(6A)	1.399(3)	C(6A)-C(6)-C(5)	116.4(2)
C(3)-C(4)	1.393(3)	C(6)-C(6A)-O(7)	123.0(2)
C(4)-C(5)	1.383(3)	C(6)-C(6A)-C(2A)	123.4(2)
C(5)-C(6)	1.385(3)	O(7)-C(6A)-C(2A)	113.5(2)
C(6)-C(6A)	1.365(3)	C(6A)-O(7)-C(1)	105.8(2)
C(6A)-O(7)	1.398(3)	C(2)-C(8)-C(13)	124.2(2)
C(8)-C(13)	1.480(3)	C(2)-C(8)-C(10)	111.2(2)
C(8)-C(10)	1.526(3)	C(13)-C(8)-C(10)	124.5(2)
C(9)-C(17)	1.471(3)	C(17)-C(9)-C(19)	109.3(2)
C(9)-C(19)	1.472(3)	C(17)-C(9)-C(1)	114.3(2)
C(9)-C(10)	1.599(3)	C(19)-C(9)-C(1)	110.0(2)
C(10)-C(21)	1.505(3)	C(17)-C(9)-C(10)	112.5(2)
O(11)-C(12)	1.439(3)	C(19)-C(9)-C(10)	110.4(2)
C(13)-O(14)	1.203(3)	C(1)-C(9)-C(10)	100.0(2)
C(13)-O(15)	1.327(3)	C(21)-C(10)-C(8)	118.5(2)
O(15)-C(16)	1.449(3)	C(21)-C(10)-C(9)	111.9(2)
C(17)-N(18)	1.138(3)	C(8)-C(10)-C(9)	100.6(2)
C(19)-N(20)	1.139(3)	C(1)-O(11)-C(12)	116.4(2)
C(21)-C(22)	1.385(3)	O(14)-C(13)-O(15)	124.8(2)
C(21)-C(26)	1.391(3)	O(14)-C(13)-C(8)	123.5(2)
C(22)-C(23)	1.372(3)	O(15)-C(13)-C(8)	111.6(2)
C(23)-C(24)	1.374(3)	C(13)-O(15)-C(16)	115.6(2)
C(24)-C(25)	1.369(3)	N(18)-C(17)-C(9)	177.5(3)
C(25)-C(26)	1.384(3)	N(20)-C(19)-C(9)	179.2(2)
O(11)-C(1)-O(7)	110.8(2)	C(22)-C(21)-C(26)	118.4(2)
O(11)-C(1)-C(2)	117.4(2)	C(22)-C(21)-C(10)	122.4(2)
O(7)-C(1)-C(2)	106.0(2)	C(26)-C(21)-C(10)	119.1(2)
O(11)-C(1)-C(9)	104.7(2)	C(23)-C(22)-C(21)	120.4(2)
O(7)-C(1)-C(9)	116.2(2)	C(22)-C(23)-C(24)	120.7(2)
C(2)-C(1)-C(9)	101.9(2)	C(25)-C(24)-C(23)	119.9(2)
C(8)-C(2)-C(2A)	142.9(2)	C(24)-C(25)-C(26)	119.7(2)
C(8)-C(2)-C(1)	110.1(2)	C(25)-C(26)-C(21)	120.9(2)

Symmetry transformations used to generate equivalent atoms:

Table 16. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **213**. The anisotropic displacement factor exponent takes the form:
$-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
C(1)	34(1)	34(1)	39(1)	-5(1)	6(1)	-2(1)
C(2)	30(1)	32(1)	31(1)	3(1)	4(1)	2(1)
C(2a)	35(1)	35(1)	29(1)	1(1)	1(1)	-2(1)
C(3)	39(1)	41(1)	35(1)	0(1)	-1(1)	2(1)
C(4)	35(1)	49(2)	45(1)	-2(1)	-5(1)	0(1)
C(5)	49(2)	45(2)	47(2)	-6(1)	-6(1)	-9(1)
C(6)	49(2)	35(1)	46(1)	-8(1)	-2(1)	-1(1)
C(6a)	36(1)	35(1)	31(1)	-3(1)	0(1)	1(1)
O(7)	36(1)	35(1)	48(1)	-10(1)	-1(1)	3(1)
C(8)	35(1)	30(1)	30(1)	-1(1)	6(1)	-3(1)
C(9)	28(1)	33(1)	38(1)	-2(1)	4(1)	1(1)
C(10)	32(1)	29(1)	35(1)	1(1)	6(1)	-4(1)
O(11)	41(1)	58(1)	39(1)	-4(1)	12(1)	-3(1)
C(12)	65(2)	53(2)	40(1)	1(1)	16(1)	-4(2)
C(13)	41(2)	31(1)	32(1)	0(1)	-1(1)	-1(1)
O(14)	37(1)	45(1)	66(1)	-11(1)	-8(1)	8(1)
O(15)	46(1)	30(1)	55(1)	-9(1)	5(1)	-2(1)
C(16)	71(2)	36(2)	87(2)	-17(2)	6(2)	9(2)
C(17)	36(1)	37(1)	45(1)	-6(1)	4(1)	0(1)
N(18)	37(1)	62(2)	72(2)	-12(1)	3(1)	7(1)
C(19)	33(1)	31(1)	38(1)	-1(1)	-3(1)	2(1)
N(20)	50(1)	37(1)	55(1)	4(1)	1(1)	-5(1)
C(21)	29(1)	27(1)	33(1)	1(1)	1(1)	-3(1)
C(22)	33(1)	47(2)	40(1)	0(1)	2(1)	-8(1)
C(23)	43(1)	64(2)	37(1)	-4(1)	10(1)	-9(1)
C(24)	53(2)	58(2)	31(1)	-5(1)	0(1)	-2(2)
C(25)	35(1)	40(1)	44(1)	0(1)	-6(1)	-2(1)
C(26)	31(1)	32(1)	44(1)	1(1)	6(1)	-1(1)

Table 17. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **213**.

	x	y	z	U(eq)
H(3A)	3419(2)	5471(3)	6724(1)	47
H(4A)	2360(2)	3716(3)	6034(2)	53
H(5A)	2976(2)	1488(3)	5867(2)	58
H(6A)	4687(2)	927(3)	6345(2)	53
H(10A)	7345(2)	6374(2)	8246(1)	38
H(12A)	7279(2)	5169(3)	5609(2)	78
H(12B)	6250(2)	5633(3)	5950(2)	78
H(12C)	6389(2)	4065(3)	5641(2)	78
H(16A)	5459(2)	10238(3)	8964(2)	98
H(16B)	4512(2)	9267(3)	9074(2)	98
H(16C)	4674(2)	9822(3)	8110(2)	98
H(22A)	5603(2)	5921(3)	9810(2)	49
H(23A)	5953(2)	6373(3)	11328(2)	57
H(24A)	7604(2)	6822(3)	11992(2)	57
H(25A)	8916(2)	6887(3)	11125(2)	49
H(26A)	8578(2)	6431(2)	9597(2)	43