Mechanistic Studies on the Reactions of Dialkoxycarbenes with Carbonyl Compounds

by

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Abstract

Syntheses of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**) were performed from either lead (IV) acetate or iodobenzene diacetate oxidation of the carbomethoxy hydrazone of acetone (**200**) in methanol. The synthesis of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) was achieved by lead (IV) acetate oxidation in dichloromethane solvent. The synthesis of **51** from substitution by methanol on 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) was also performed. Synthesis of 2-methoxy-5,5-dimethyl-2-(2,2,2-trifluoroethoxy)-Δ^3-1,3,4-oxadiazoline (**210**) was achieved by substitution by 2,2,2-trifluoroethanol on 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**).

Thermolyses of **51** and **210** in the presence of a variety of cyclic anhydrides **215** yield the products **216**. Dialkoxycarbene reactions with unsymmetrically substituted anhydrides have been shown to occur preferentially at the most electron deficient carbonyl group. Competition studies between substituted maleic anhydrides show a preference for carbene attack on the most electron deficient anhydride. On the basis of these studies, the mechanism for the formation of **216** is believed to occur by inital attack of the dialkoxycarbene onto the carbonyl group of the anhydride.

Thermolyses of **51** and **210** in the presence of benzoyl cyanide **122b** and benzoyl fluoride **122c** were found to yield the products **127b-e**. The mechanism of

formation of these compounds was also attributed to initial attack of dialkoxycarbene onto the carbonyl group. In keeping with literature results, dimethoxyoxadiazoline **51** was found to react with benzoyl chloride (**122a**) to yield methyl benzoylformate (**125**). Thermolysis of **51** in the presence of benzalphthalide (**224**) was found to yield the product **225**. The results are discussed in terms of the mechanism of the 1,2-group migration common to all these reactions and those of dialkoxycarbene addition to anhydrides.

Reaction of **51** with 9-fluorenone (**230**) and coumarin (**231**) yield products from intramolecular methoxy migration. The mechanism was established by deuterium and ^{18}O labelling experiments. This mechanism involves the intermediacy of an oxirane **235**. Although **235** can be identified in the reaction mixture after shortened thermolysis times it does not survive attempts at isolation.

N-Phenylmaleimide (**270**) was found to intercept dimethoxycarbene (**10**) to give a cyclopropane product **271**. The regiochemistry of addition to maleimide and maleic anhydride was examined by *ab initio* molecular orbital calculations. The computational results reflect the observed sense of regioselectivity only when higher level basis sets employing polarization functions are used to calculate the energies.

Thermolyses of **51** and **210** in the presence of the stable 1,2-bisketene **292** yielded products of overall [4 + 1] addition of the dialkoxycarbene to the π-system of the bisketene. This result is in keeping with dialkoxycarbene addition to the less hindered side of the bisketene.

Thermolyses of dimethoxyoxadiazoline **51** in the presence of β-dicarbonyl compounds **302a-d** yield the products of formal insertion of the carbene into the C–H bond of the keto tautomer. The presence of the enol tautomers of these compounds is expected to be substantial on the basis of literature values for the equilibrium constants in benzene. The results indicate that the reaction is likely to proceed through O–H insertion of the dialkoxycarbene through an ion pair intermediate. This is fitting for the mechanism of O–H insertion for nucleophilic carbenes.

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Chapter 1

Introduction

Carbenes are compounds which possess a neutral divalent carbon atom. The unusual electronic, structural, and synthetic properties imparted upon a divalent carbon atom have made carbenes of interest to nearly all fields of chemistry. Speculation as to the intermediacy of carbenes in a variety of reactions started early in the 20th century and they have been firmly recognized as reactive intermediates since Herzberg detected methylene by microwave spectroscopy in 1959.[1]

From the volumes of information known about carbene chemistry, only a small fraction has been devoted to the study of nucleophilic carbenes. As we shall see below, nucleophilic carbenes are those which, by virtue of their substituents, have the ability to be charge donors in reactions with other molecules. Many researchers have tried to describe the structure and reactions of carbenes using molecular orbital treatments. The following section describes some of the important theories used to account for the observed properties of nucleophilic carbenes.

1.1 Electronic Structure

Gaspar and Hammond have used a simple picture of the bonding in a carbene to explain many features of the carbene's molecular and electronic structure.[2] Carbon has the $1s^2\ 2s^2\ 2p_x^1\ 2p_y^1$ electronic configuration. The $1s^2$ electrons are not involved in bonding which leaves four available electrons (Figure 1). A carbene such as methylene has only two substituents each of which require the use of one electron on the carbon atom for formation of a bond. The arrangement of hydrogen atoms around the divalent carbon atom dictates how the atomic orbitals and the valence electrons are used. At one extreme, it is possible to envision a geometry in which methylene is a linear molecule (H–C–H bond angle = 180°, see Figure 1). The unhybridized atomic orbitals of carbon are not suitable for bonding two substituents in a linear arrangement. Hybridization of one of the 2p orbitals with the 2s orbital is necessary in order to achieve two sp hybridized orbitals with a 180° orientation with respect to each other. These orbitals will overlap with the 1s orbitals of hydrogen to form the C–H bonds. The remaining electrons on carbon occupy the two degenerate, non-bonding, pure p orbitals. Hund's rule dictates that when degenerate orbitals are available for bonding, that the molecule will adopt the configuration with the greatest number of unpaired electrons. Linear methylene should, therefore, adopt a triplet electronic configuration. At another geometrical extreme, one can imagine a methylene molecule with perpendicular H–C–H bonds (bond angle = 90°, see Figure 1). The unhybridized atomic orbitals of carbon can support the bonding of two

substituents in this geometry. The $2p_x$ and $2p_y$ orbitals are used for bonding the two hydrogen 1s orbitals. The 2s and $2p_z$ orbitals of carbon remain as non-bonding orbitals of greatly different energy. The 2s orbital is much lower in energy and, thus, the remaining electrons on carbon will be paired in the 2s orbital and the ground state will be singlet.

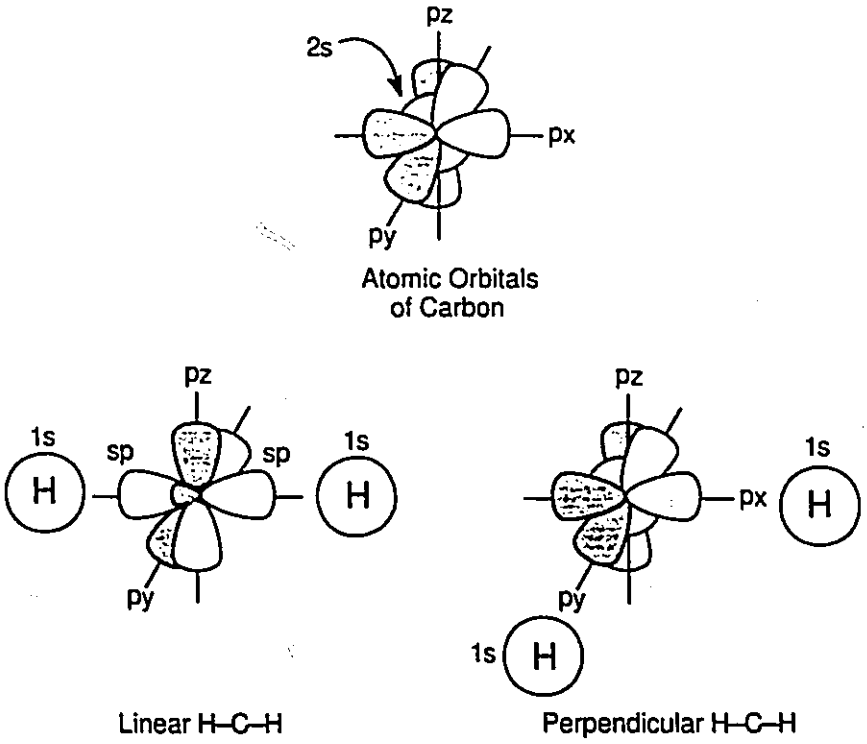


Figure 1

Thus, the linear molecule has a triplet structure with pure p non-bonding orbitals and the bent molecule has a singlet structure with one pure s and one pure p non-bonding orbital. In reality, most carbenes have neither the linear nor the perpendicular geometry. For these carbenes, the lowest energy geometry is achieved

by hybridization of two p orbitals with the s orbital (sp^2 hybridization). From the two extreme cases described above, it is clear that the result of bending the molecule from 180° is an increase in the s-character of the non-bonding orbital which resides in the plane being formed by the H–C–H atoms. The orbital with partial s-character is lower in energy with respect to the pure p orbital. It is evident, then, that the triplet state will favour a H–C–H bond angle greater than that favoured by the singlet state (Figure 2). The singlet state will become the ground state when the energy gained by placing both electrons in the lower energy orbital becomes greater than the energy needed to overcome the electron-electron repulsion which occurs upon placing two electrons in the same spatial orbital. Thus, there will be a critical angle at which the energy of the two electronic states will become the same—angles greater than this critical angle will correspond to triplet ground states while smaller angles will correspond to singlet ground states.

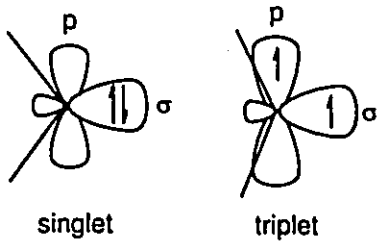
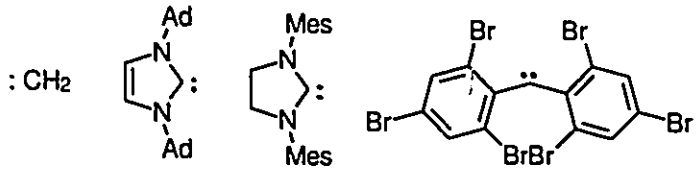


Figure 2

1.2 Substituent Effects

The effect of carbene substituents is the most important means by which the organic chemist can control the properties of carbenes. An understanding of substituent effects is therefore at the heart of carbene chemistry. Substituents can affect the multiplicity of the ground state, the thermodynamic stability of the carbene, and the reactivity of the carbene in chemical reactions. Carbene reactivity can span a vast range as illustrated by the carbenes **1**-**4**. The simplest carbene, methylene **1**, was referred to as 'the most indiscriminate reagent known in organic chemistry' based on its insertion into the C–H bond of simple hydrocarbons.[3] At the other extreme are the stable, crystalline, amino-substituted singlet carbenes (**2** and **3**, Scheme 1) first isolated by Arduengo and co-workers.[4-6] Tomioka and co-workers have generated the stable, crystalline triplet carbene **4**.[7] In these examples, the substituents control the multiplicity of the ground state and are the source of the remarkable stability of these carbenes.



1 triplet **2** singlet **3** singlet **4** triplet

Ad = adamantyl Mes = mesityl

Scheme 1

There is substantial qualitative information available on the effect of substituents on carbenes. Carbenes can generally be grouped into one of several categories based on the type of substituent. Heteroatom substituents increase the stability of the singlet state by donating electron density into the formally unoccupied p orbital on the carbenic centre.[2,8-12] Conjugatively withdrawing groups such as vinyl, cyano and carbonyl groups tend to stabilize the triplet state of the carbene.[2,12,13] Aryl carbenes, unless substituted by heteroatoms, generally have triplet ground states.[12,14] Substituents which are electropositive with respect to carbon, such as silicon, lithium, and boron, tend to stabilize the triplet state.[8,11,15] The effects of substituents on the properties of carbenes has been well studied theoretically.[2,8-11,13-24]

A simple model to predict the effect of a variety of substituents on a carbene is detailed in the excellent review by Gaspar and Hammond.[2] We have seen already (Figure 1) the description of the molecular orbitals of methylene and how they change with geometry. We can examine the effect of substitution on the carbene centre by the same process.

There are two processes by which a substituent can stabilize a carbene. In the first case, a linear carbene can be envisioned with a substituent which has one lone pair. This lone pair will align itself with one of the degenerate orbitals of the carbene. The interaction of the lone pair with the p orbital on carbon will result in loss of the degeneracy of the two p orbitals. As illustrated in Figure 3 the result of the orbital interaction is the formation of a π orbital between the heteroatom and the carbene

centre. The energy of the remaining p orbital on carbon is not affected by the interaction with the lone pair, although it now holds the electrons of the carbene (and hence it is labeled as σ). VSEPR theory predicts a linear geometry to be high in energy since the carbene has two ligands and a lone pair. This unfavorable geometry partially offsets the stabilization afforded by the lone pairs of the heteroatom. As we have seen in Figure 1, bending of the H–C–X bond increases the s character in the σ orbital and lowers the energy of the occupied orbital. Thus, stabilization of the carbene occurs on bending. No matter how low the σ orbital falls in energy on bending, the multiplicity will be singlet since four electrons are being used. A triplet state can be achieved in this case only if the σ and π* orbitals are of similar energy.

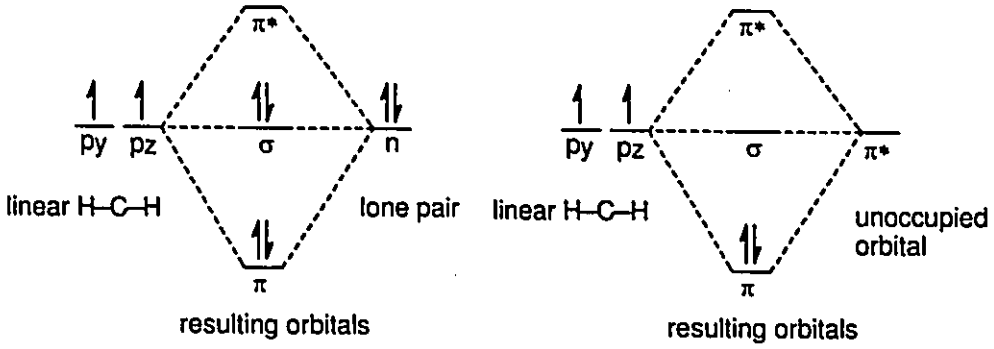


Figure 3

The second scenario occurs when the carbene substituent has unoccupied orbitals (Figure 3). The unoccupied orbital again interacts with one of the p orbitals on the carbene resulting in the formation of a π bond from the substituent to the carbene. The resulting orbital holds the electrons from the carbene. The energy of

the σ orbital (which is empty in this instance) remains unchanged until bending of the H–C–X bond occurs which stabilizes the σ orbital. In this instance, the relative energies of the π and σ orbitals determines the multiplicity of the ground state. If bending stabilizes the σ orbital so that it is comparable to the π orbital, the multiplicity will become triplet.

An interesting possibility arises if there is a cyano substituent on the carbene. The cyano substituent has two unoccupied orbitals with the same geometry (orthogonal) as the carbene p orbitals (Figure 4). In this case, the orbital interactions yield two stabilized, degenerate molecular orbitals. The multiplicity of the carbene from this simple picture must be triplet. The effect of the energies upon bending of the carbene is more complicated in this case. As the molecule bends, one of the p orbitals on the linear carbene grows in s character which, at relatively small bending angles, will not greatly affect the prediction of a triplet ground state.

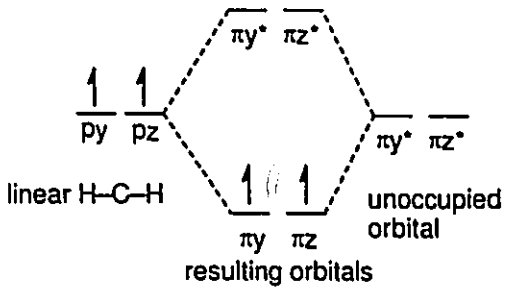


Figure 4

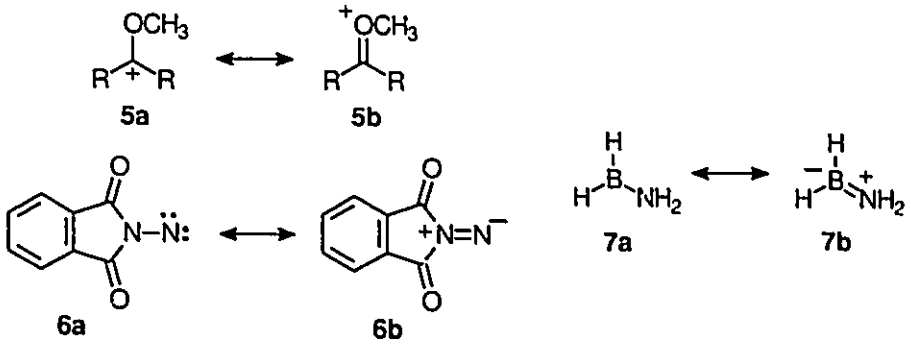
The above molecular orbital treatment is fairly simplistic, but the trends presented are backed up by more detailed theoretical calculations. Studies have been

made of the energies of the singlet and triplet states of a variety of substituted carbenes as the bond angle is changed.[8,12] In the most recent study, semi-empirical calculations which are supported by *ab initio* calculations are used to quantify the trends described above as well as others. Hydroxycarbene is a triplet at large bond angles but a singlet near the known ground state angle of ~110°. Dihydroxycarbene is a ground state singlet over almost all bond angles with a known ground state angle that is again ~110°. Cyanocarbene is found to have a linear triplet ground state; the triplet is lower in energy except at very small bond angles.

An important result of the interaction of a lone pair on an α-substituent with the carbene centre is a raising of the energy of the LUMO of the carbene. The π* orbital of the carbene is the LUMO in this case (Figure 3). The result of orbital interaction between a low-lying unoccupied orbital on an α-substituent and the filled orbital on the carbon atom of the carbene is the lowering of the HOMO energy. The HOMO of the carbene in this case is the π orbital (Figure 3). In general terms, the HOMO of a carbene is designated as the σ orbital and the LUMO is designated as the p orbital (see Figure 2).

Of course, the ability of heteroatomic substituents to stabilize electron-deficient centres is well established in other systems. The stabilizing effect is generally represented by partial double bond character between the heteroatom and the electron deficient centre or as one or more resonance structures. The effects of oxygen substituents on cations such as **5** (Scheme 2) are well known.[25] Amino

substituents are known to possess a stabilizing effect on nitrenes[26-28]—in fact, amino nitrenes such as **6** are often referred to as 1,1-diazenes which are simply resonance structures of the nitrenes (Scheme 2). Amino- and oxysubstituted boranes such as **7** are also known to be stabilized with respect to the unsubstituted varieties.[29] These stabilizing interactions are represented in Scheme 2. The charges follow the valence bond representations of the structures and not the charge density on the particular atoms.



Scheme 2

Frontier orbital theory can describe the effect of substituents on the chemical properties of the carbene. Carbenes possessing substituents which are good π donors (such as nitrogen or oxygen) are dominated by the stabilizing effect of the lone pair and hence have increased LUMO energies. For instance, dimethoxycarbene (**8**) is very highly stabilized (ΔE_{st} = 79.8 kcal/mol) and is calculated to have ε(HOMO) = –10.81 and ε(LUMO) = 4.09 eV.[10] Carbenes possessing substituents which are poorer π donors but highly electronegative (such as halogens) have lowered HOMO energies

(electronegativity can be pictured as an unoccupied orbital in Figure 3). For instance, difluorocarbene (9) is also highly stabilized (ΔE_{st} = 62.8 kcal/mol) with ε(HOMO) = –13.38 and ε(LUMO) = 1.89 eV.[10]

Frontier molecular orbital theory predicts how the molecular orbitals of two species interact during a chemical reaction. Generally, the interaction is thought of as a transfer of electron density from an occupied orbital of one reacting species into an unoccupied orbital of the other reacting species. The sense of the charge transfer is that which corresponds to the lowest energy separation between HOMO and LUMO. For instance, the interaction of a carbene with an alkene or other molecule can occur in two possible modes. Either the carbene acts as an electron acceptor from the alkene or as an electron donor to the alkene. The former constitutes an electrophilic interaction with respect to the carbene and the latter constitutes a nucleophilic interaction.

The frontier orbital energies are critical in assessing the philicity of the carbene. In a model reaction of a carbene with a simple alkene, one can demonstrate the effect of orbital energies on philicity. Orbital energies obtained from Rondan et al.[10] are shown in Figure 5. The dominant interaction between (dimethylamino)methoxycarbene and ethylene (bold line on left of Figure 5) will be between the carbene σ and the alkene π*. The lone pairs on the oxy and amino substituents disfavour the electrophilic interaction by raising the LUMO energy (as in Figure 3). Conversely, the dominant interaction between difluorocarbene and

ethylene (bold line on right of Figure 5) will be between the carbene p and the alkene π. In this case, the electronegativity of the fluorine substituents disfavours the nucleophilic interaction by lowering the HOMO energy (as in Figure 3). Despite their opposite carbenic philicity, it should be reiterated that both are highly stabilized carbenes relative to methylene (ΔE_{st} = 93.4 and 62.8 kcal/mol respectively).

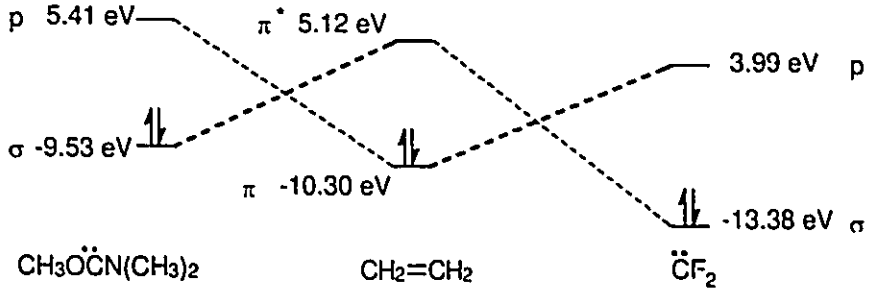


Figure 5

As the alkene is varied—made either more electron rich or deficient—the HOMO and LUMO of the alkene will change. This in turn will alter the degree of orbital interaction between carbene and alkene. For carbenes which have very high LUMO energies, the HOMO(carbene)–LUMO(alkene) interaction will be dominant with a wide range of alkenes—these carbenes are called nucleophilic carbenes. For carbenes which have very low HOMO energies, the LUMO(carbene)–HOMO(alkene) interaction will be dominant with a wide range of alkenes—these carbenes are called electrophilic carbenes. There is also a less common class of carbenes which have HOMO and LUMO energies such that changes in the alkene can result in a change in the dominant orbital interaction—these carbenes are called ambiphilic carbenes. Since

carbenes have an unfilled valence octet, they are inherently electrophilic. Nucleophilicity is bestowed only onto carbenes substituted with groups which strongly stabilize the development of positive charge on the carbene carbon atom in the transition state.

The frontier orbital symmetries can also explain the geometrical factors associated with approach of a carbene to an alkene.[30,31] Figure 6 shows the simple frontier molecular orbital representation of ethylene and methylene. Figure 6a shows the approach of methylene perpendicular to the molecular plane of the alkene. In this instance, one can see that the orbital interactions σ(HOMO)–π*(LUMO) and π(LUMO)–p(HOMO) are both non-bonding in nature as imposed by the symmetry of the orbitals of the system. Figure 6b shows the approach of methylene parallel to the molecular plane of the double bond. Here, interactions are bonding in nature. In this orientation, the orbital symmetry of the molecules show that both σ(HOMO)–π*(LUMO) and p(LUMO)–π(HOMO) are now bonding interactions.

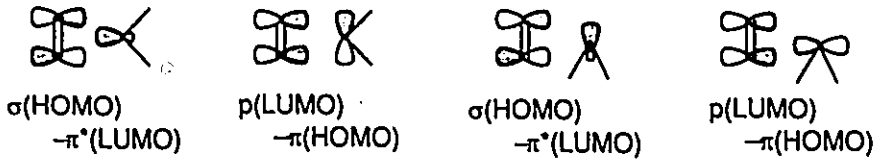


Figure 6

These observations suggest that there are important consequences for the relative geometry of the approaching species. The parallel approach seems to be favourable on orbital symmetry grounds. The final product, however, has a

completely perpendicular geometry (cyclopropane). It is not surprising, therefore, that the geometry of the transition state would be at some intermediate stage. Rondan et al.[10] have found that the calculated transition states for cyclopropanation of a variety of carbenes to ethylene possess a geometry which is intermediate between the parallel approach and the geometry of the cyclopropane.

The major consequence of the increased thermodynamic stabilization of carbenes upon substitution with heteroatoms is a lower reactivity of these carbenes towards all reactions. Thus rate constants for bimolecular and unimolecular reactions are expected to decrease as the stability of the carbene is increased. One illustration of this effect is a compilation by Moss of the rates of reaction of carbenes with pyridine to form observable pyridinium ylides.[32] The rates of reactions of simple alkyl or aryl carbenes with pyridine are generally diffusion controlled.[33] More stabilized carbenes show reduced rates for ylide formation. These rate constants decrease far below the diffusion controlled level, for instance, methoxyphenylcarbene and methoxymethylcarbene react with pyridine with rate constants of only 6.6×10^5 and 1.2×10^5 $M^{-1}s^{-1}$ respectively.

The increased selectivity of carbenes as they become substituted with carbene stabilizing groups has been the basis of Moss' Carbenic Selectivity Index.[34-36] This index is a means to predict and correlate quantitatively the chemical properties of carbenes by means of an easily measurable quantity. Moss proposed that the relative rates for reaction of dichlorocarbene with a variety of simple methyl substituted

alkenes be used as an arbitrary standard against which the selectivity of all other carbenes could be measured. Determination of a selectivity index is easily accomplished since relative rates for the reactions of carbenes with a variety of substrates can be readily obtained by using competition reactions and analyzing the product mixtures. Thus, simply by measuring the relative rate for reaction of a test carbene with the standard alkenes, a comparison of the selectivity of dichlorocarbene with that of the test carbene can be made.

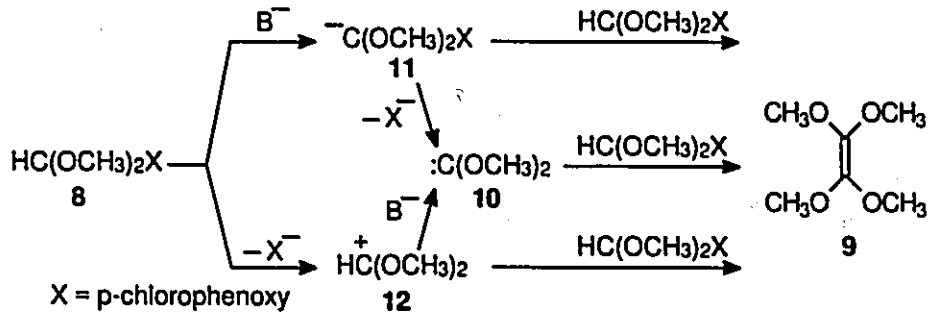
1.3 Dialkoxycarbene Generation

The generation of dialkoxycarbenes is aided by the relatively high thermodynamic stability of these reactive intermediates. For this reason, carbene generation from a variety of substrates has been achieved. Dialkoxycarbenes are generally produced through thermodynamically favourable cycloreversion reactions initiated either thermally or photochemically. Base catalyzed α-elimination to yield dialkoxycarbenes is also readily achieved, however, these techniques are unsuitable for many purposes and tend to be less useful for mechanistic studies.

1.3.1 Dialkoxycarbenes from α-Elimination

α-Elimination is one of the most common methods for the generation of dichlorocarbene and dibromocarbene.[28] In a similar manner, one might expect that

dimethoxycarbene should be generated from treatment of an orthoformate with strong base. This methodology was investigated by Scheeren et al. [37] who found that treatment of dimethyl p-chlorophenyl orthoformate (**8**) with sodium hydride yielded tetramethoxyethene (**9**). Formation of dimethoxycarbene (**10**) in this system is complicated, however, by several competing processes as described in Scheme 3.[37] The intermediates **10**, **11**, or **12** may be generated in these systems. As illustrated in Scheme 3, any or all of these intermediates may be responsible for the formation of tetramethoxyethene. For this reason, dimethoxycarbene generation is ambiguous in these systems and α-elimination is not a suitable technique for studies in which the identity of the reactive intermediate must be clearly established.



Scheme 3

α-Elimination of acetic acid from substituted methyl acetate derivatives has also been used as a source of dimethoxycarbene.[38] Dimethoxymethyl and diethoxymethyl acetate (**13** and **14**, not illustrated) when thermolyzed in the gas phase generate dimethoxycarbene (**10**) and diethoxycarbene (**15**). Methyl acetate was

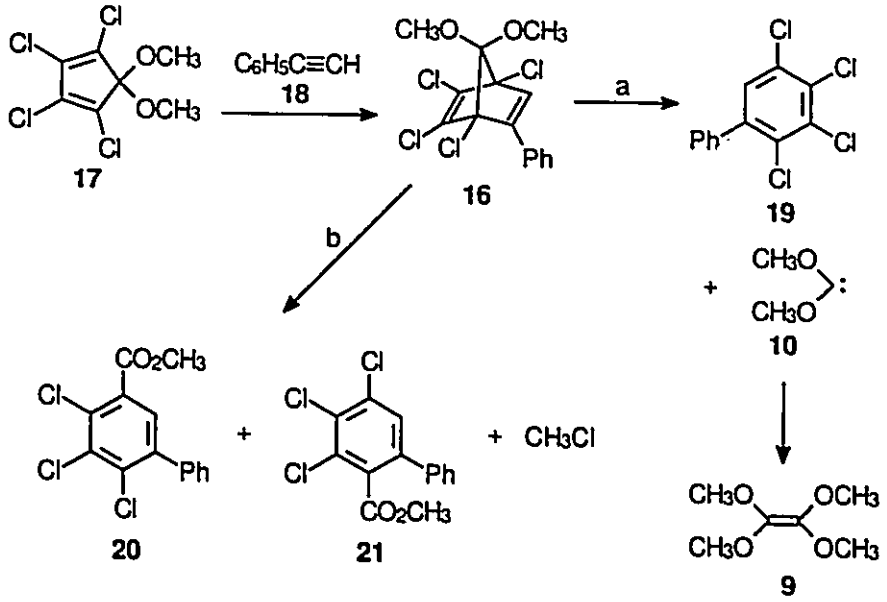
observed in the reactions of **13** and ethyl propionate was formed in reactions of **14**. These products may have arisen from 1,2-alkyl migration in the dialkoxycarbene.

While the use of α-elimination chemistry to generate dioxycarbenes (or carbene equivalents) is of synthetic value because if its ease and low cost, there are several serious limitations. Generation of asymmetric dioxycarbenes is generally not possible due to difficulties in generating orthoformate systems with two or more different oxygen substituents. The harshly basic conditions required for the generation of carbenes from orthoformates also tend to be incompatible with the strongly electrophilic traps for the carbenes.

1.3.2 Dialkoxycarbenes from Cycloreversion

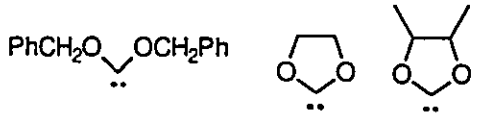
In 1964, Hoffmann[39] and Lemal[40] both developed the thermal decomposition of 1,2,3,4-tetrachloro-7,7-dimethoxy-5-phenylnorbornadiene **16** as the first major source of dimethoxycarbene (**10**). Cycloaddition of the cyclopentadiene **17** and phenyl acetylene (**18**) readily yields this dialkoxycarbene precursor. R. W. Hoffmann developed this class of compounds as a practical and synthetically viable route to dimethoxycarbene and other dialkoxycarbenes.[41] As demonstrated in Scheme 4 (path a), thermolysis of the norbornadienone ketal **16** yields dimethoxycarbene (**10**) which dimerizes to tetramethoxyethene (**9**) in the absence of a good carbene trap. The thermal [4 + 1] cycloreversion to give dimethoxycarbene is driven by formation of the aromatic tetrachlorobiphenyl **19**. This byproduct must be removed before the carbene

derived products can be isolated. Additionally, a side reaction occurs (path b) which yields the biphenyl products **20** and **21**. Further aspects of the thermal decomposition of the norbornadienone ketals and other compounds were reviewed by Hoffmann.[42]



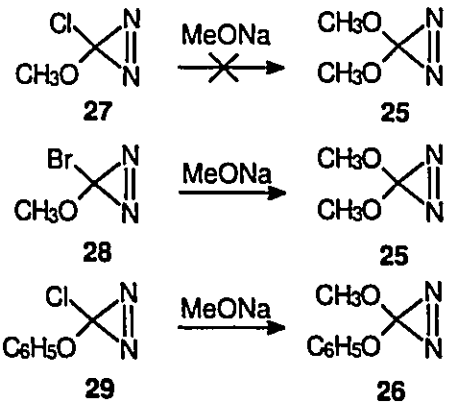
Scheme 4

Hoffmann successfully used the 7,7-dimethoxynorbornadiene **16** to study a wide spectrum of dimethoxycarbene chemistry. Much of the earlier results and a discussion of thermal cycloreversions as routes to carbene generation are summarized in a 1971 review by Hoffmann.[41] This review reports the generation of dibenzyloxycarbene **22** and the cyclic carbenes **23** and **24** from appropriate norbornadiene precursors.



22 23 24

Use of Hoffmann's precursor was the best route to dimethoxycarbene until the publication by Moss and co-workers in 1988 of the synthesis of 3,3-dimethoxydiazirine (**25**) by diazirine exchange.[43] The synthesis of 3,3-dimethoxydiazirine was preceded by the synthesis of 3-methoxy-3-phenoxydiazirine (**26**) by a similar route (Scheme 5).[44] Synthesis of **25** was first attempted from the chlorodiazirine **27**,[44] but gave poor results. Exchange using the bromodiazirine **28**, however, was more successful.[43] Methoxy substitution on the chlorodiazirine **29** was successful in generating the diazirine **26**.[44]



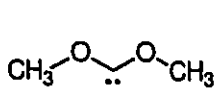
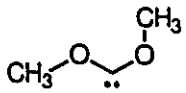
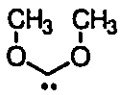
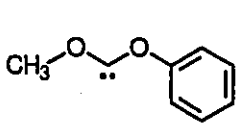
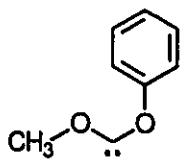
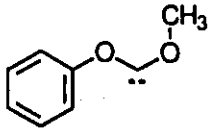
Scheme 5

Diazirines were the first photochemical source of dioxycarbenes and provided the first opportunity for direct observation of the carbene. Moss and co-workers used nanosecond laser flash photolysis techniques to record the UV spectrum of

dimethoxycarbene in pentane (λ_{max} = 255 nm, $\tau_{1/2}$ = 2 ms).[43] The carbene in this case was directly observable without the need for probe techniques such as interception with pyridine.[33] Photolysis of dimethoxydiazirine, which was trapped in a 3-methylpentane matrix at 77 K, revealed a stable species with a UV spectrum (λ_{max} = 255 nm) similar to the transient UV spectrum obtained upon solution phase photolysis. The heat of formation of dimethoxycarbene has also been experimentally determined from photoacoustic calorimetry studies to be – 61 ± 4.5 kcal/mol.[45]

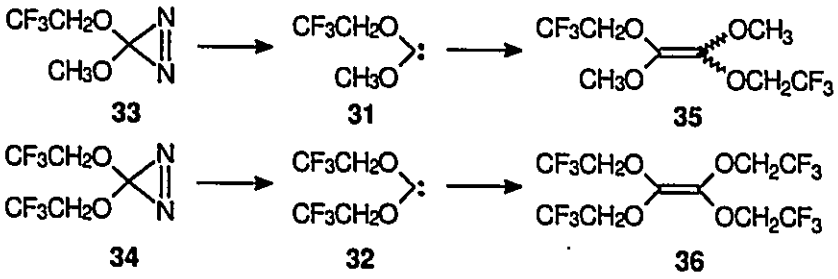
Moss and co-workers have examined the structures of dimethoxycarbene **10** and methoxyphenoxycarbene **30** using *ab initio* calculations. The alkoxy substituents can give rise to three geometries with at least C_s symmetry. These are the W, S and U configurations which are calculated to have relative energies of 0, 1.56, and 21.34 kcal/mol respectively. The W and S configurations are separated by a barrier

Table 1. Calculated Structures, Energies, and Orbital Energies of Dimethoxycarbene **10** and Methoxyphenoxycarbene **30**.

			
E_{rel} (kcal/mol)	0	1.56	21.34
ε (HOMO), eV	-10.62	-10.38	-9.64
ε (LUMO), eV	4.34	4.49	4.35
			
E_{rel} (kcal/mol)	1.27	2.18	0
ε (HOMO), eV	-10.78	-10.64	-10.49
ε (LUMO), eV	3.33	4.29	3.35

estimated to lie 15.8 kcal/mol above the W conformation.[43] It should be noted that a transition state for the rotation was not obtained for this system—a geometry optimization was performed with one methyl group constrained to lie perpendicular to the plane of the molecule. The HOMO and LUMO energies of the isomers are indicated in Table 1. The W and two S isomers of methoxyphenoxycarbene **30** are also shown with relative energies indicated. The greater steric bulk of this carbene is reflected in the lower energy conformations being in the S geometry.

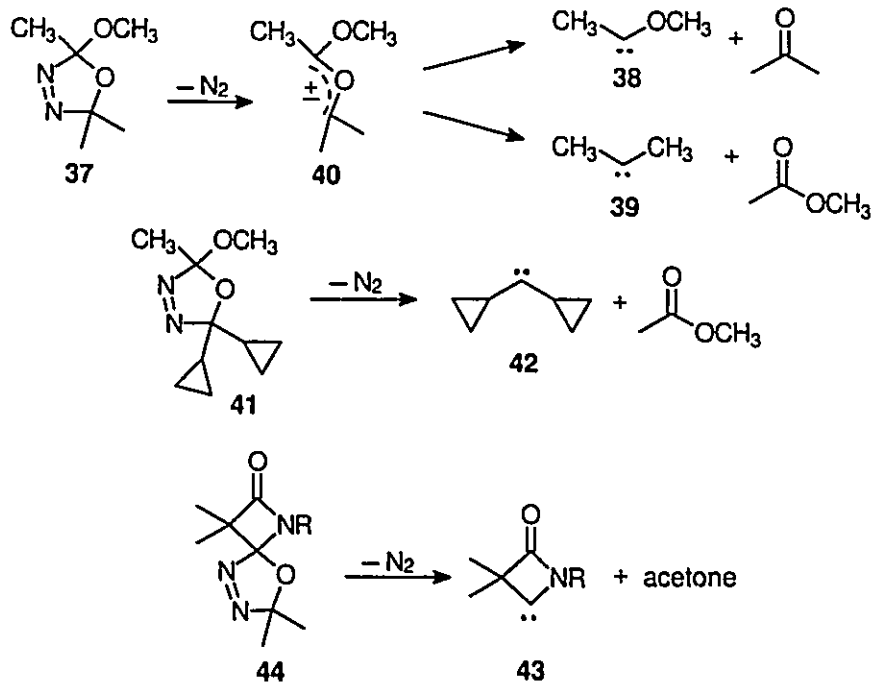
Only a few other dialkoxycarbenes have been generated from diazirine precursors. Methoxy(2,2,2-trifluoroethoxy)carbene (**31**) and bis-(2,2,2-trifluoroethoxy)carbene (**32**) have been generated from thermolysis of the appropriately substituted diazirines **33** and **34** (Scheme 6).[46] Formation of carbene dimers **35** and **36** indicated that carbenes were intermediates in the reaction.



Scheme 6

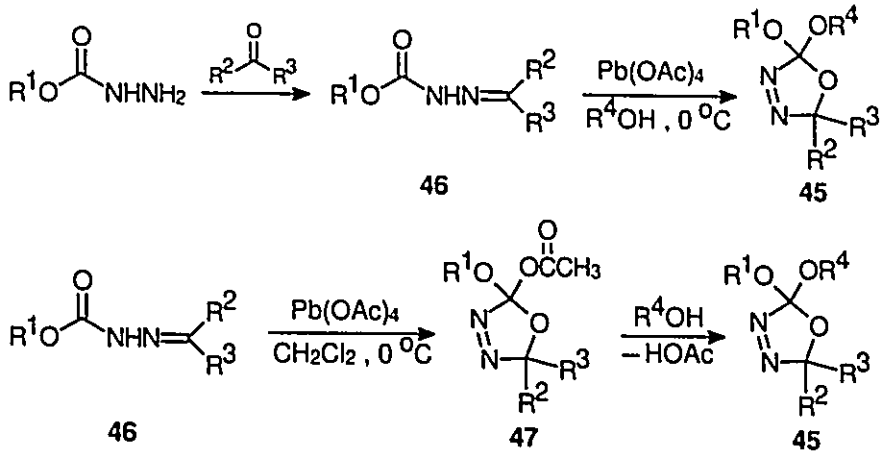
Oxadiazolines have been developed more recently by Warkentin and co-workers as a source of stabilized carbenes. A variety of carbenes can be generated from the thermolysis of Δ^3-1,3,4-oxadiazolines. Bekhazi and Warkentin have studied

2-methoxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (**37**) and found products consistent with generation of both methoxymethylcarbene (**38**) and dimethylcarbene (**39**) (Scheme 7).[47,48] This was rationalized in terms of competition between two pathways for fragmentation of the carbonyl ylide (**40**) resulting from loss of nitrogen. A greater selectivity was achieved in the thermolysis of the dicyclopropyl oxadiazoline **41** which yielded dicyclopropylcarbene (**42**).[49] Selective generation of β-lactamylidenes **43** was achieved by El-Zoghbi and Warkentin from the thermolysis of β-lactam spiro-fused oxadiazolines **44** (Scheme 7).[50-53]



Scheme 7

In 1992, Warkentin and co-workers reported the generation of dialkoxycarbenes from solution phase thermolysis of 2,2-dialkoxy-5,5-dialkyl-Δ^3-1,3,4-oxadiazolines **45**. The synthesis of dialkoxyoxadiazolines from lead(IV) acetate oxidation of alkoxycarbonyl hydrazones **46** has made a variety of substituted dioxyoxadiazolines available (Scheme 8).[54] Additionally, a very versatile method for the preparation of oxadiazolines from alcohol substitution on 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**47**) has been described, Scheme 8.[55]

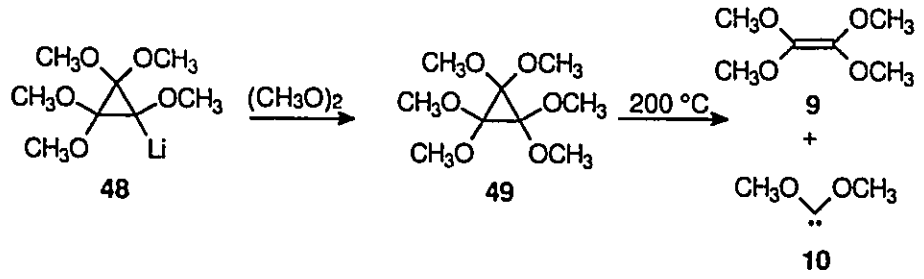


Scheme 8

The synthesis of a wide variety of oxadiazolines and the generation of a number of substituted dialkoxycarbenes have been achieved in the Warkentin group.[54-59] Oxadiazolines have many advantages over other thermal sources of oxycarbenes. A versatile assortment of oxadiazolines has been prepared. They are shelf stable for extended periods, and they generate carbenes at reasonable temperatures. The side products of thermolysis do not interfere in the isolation of the products and there are few problems with competing decomposition pathways. One of the largest limitations of oxadiazolines is that photochemical dialkoxycarbene generation has not been possible from this carbene source.

Another source of dimethoxycarbene from thermal cycloreversion is known. Treatment of lithiopentamethoxycyclopropane **48** with dimethyl peroxide yields hexamethoxycyclopropane **49** which has been shown by Moss and Cox to yield

dimethoxycarbene (**10**) upon thermolysis at 200 °C (Scheme 9).[60] Dimethoxycarbene is the only dialkoxycarbene that has been generated in this fashion.



Scheme 9

1.4 Chemistry of Dioxycarbenes

1.4.1 Carbene Rearrangements in the Gas Phase

The most versatile method for the study of oxycarbenes in the gas phase is by generation of the carbene in the dilute gas phase of the mass spectrometer. The radical cations of oxycarbenes are usually thermodynamically and kinetically stable entities which occur as fragment ions in the mass spectra of some types of compounds. Neutralization-reionization mass spectrometry (NRMS) is a technique in which electron transfer to the radical cation of the carbene can yield fast-moving neutral carbenes in the gas phase.[61] Reionization of the carbene can be affected by collisions with a reionizing gas. If the neutral carbene is stable within the time frame of the neutralization-reionization experiment (~1 μs) reionization should yield at least small amounts of the radical cation of the carbene—these ions are referred to as

'survivor' ions since the atom connectivity has survived neutralization. If the neutral carbene is inherently unstable, reionization will reveal only rearrangement or fragmentation products. The NRMS experiment, therefore provides evidence for the persistence of the neutral carbene with a lifetime of at least 1 μs. NRMS is particularly well suited to the study of the gas phase chemistry of oxycarbenes.

To complement experimental investigations, quantum mechanical investigations of carbene properties are often performed. Not only can quantum mechanical calculations support the experimental observations, but they can also probe higher energy reaction pathways which may not be experimentally observable. In this way, carbene chemistry may be more fully explored with the reliability of some experimental verification. Small reactive intermediates such as simple carbenes are conveniently studied by *ab initio* quantum mechanical calculations. The calculations generally best reflect the properties of the molecules in the gas phase which is convenient for comparison to gas phase results from mass spectrometry.

1,2-Hydrogen rearrangements are typical carbene reactions.[13,28,62,63] In the simplest case, methylcarbene undergoes a facile rearrangement to ethylene which can be thought of as an intramolecular C–H insertion. The 1,2-H rearrangement of a carbene has often been referred to as a 'hydride' shift.[13,62] This makes reference to the geometry of the migrating group which, in the case of H-migration from a methyl group, is thought to occur perpendicular to the plane of the carbene (Figure 7). The hydrogen atom migrates with the pair of electrons from the σ bond to the empty p

orbital of the carbene (Figure 7). This is supported by theoretical calculations which yield transition states with geometries in which the hydrogen atom bridges the migration origin and terminus in a position perpendicular to the molecular plane.[17]

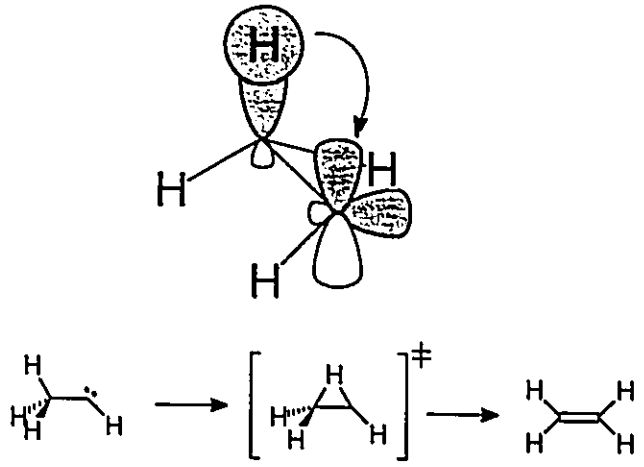


Figure 7

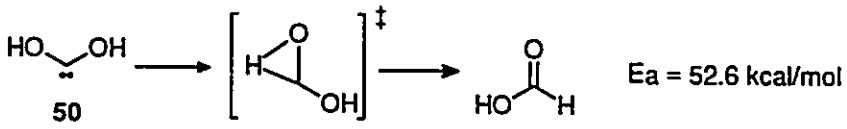
The barrier for the 1,2-H shift in most carbenes is extremely low which makes direct studies of simple alkyl carbenes difficult. Recent theoretical studies by Evanseck and Houk[17] found that the calculated height of the barrier for rearrangement of methylcarbene was strongly dependent on the basis set used for the calculation. On the basis of their highest level calculations, they proposed a tiny barrier to rearrangement of methylcarbene (0.6 kcal/mol using the MP4/6-311G** + ZPVE//MP2/6-31G* level of theory). Similar values have been determined experimentally from internal competition studies[64,65] and laser flash photolysis studies.[33]

Heteroatom substituents on the carbene centre are expected to raise the barrier for rearrangement because of the known effect of heteroatoms to stabilize the carbene.[10,34,35] As the ground state stability of the carbene increases, the height of the barrier for any rearrangement of the carbene is expected to increase correspondingly. The effect of substituents on the barrier for intramolecular C–H insertion has been systematically explored by Evanseck and Houk using high level ab initio calculations.[17]

Solution phase rearrangements of dialkoxycarbenes are not often observed. The barriers for 1,2-alkyl shifts are quite high and thus the rate of dimerization of the carbene in solution is usually faster than the rate of the rearrangement. Gas phase studies where the carbene concentration is extremely low provide the best information concerning the intramolecular chemistry of dioxycarbenes.

The parent dioxycarbene is dihydroxycarbene (**50**). This species has been well studied theoretically.[8,9,11,15,23,66-70] It has been proposed as an intermediate in the gas phase decarboxylation of oxalic acid.[71-74] The barrier to rearrangement of dihydroxycarbene to formic acid has been calculated to be 53 kcal/mol using a basis set at the DZP SCF level (Scheme 10).[69] Unlike the geometry predicted for methylcarbene, the geometry of this transition state was found to have C_s symmetry with the hydrogen migrating in the plane of the molecule. A rotational barrier of 30.1 kcal/mol and a singlet-triplet energy gap of 39.7 kcal/mol were also calculated for dihydroxycarbene using a DZP basis set.[70] The high rotational barriers are consistent

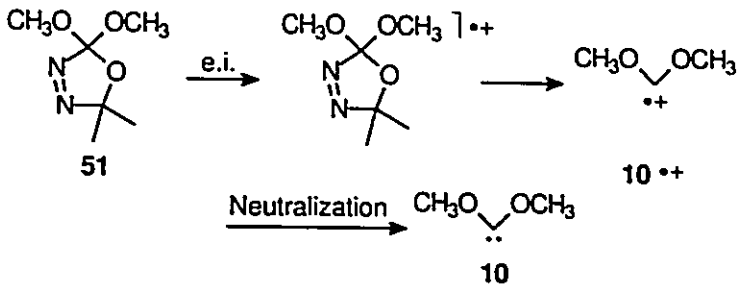
with a large degree of double bond character between the oxygen substituent and the carbene carbon atom.



Scheme 10

Several experimental studies and one theoretical study of 1,2-alkyl shifts in oxycarbenes are available. Dimethoxycarbene (**10**) was first generated under pyrolytic conditions by Hoffmann and a product from the pyrolysis was methyl acetate which was thought to result from 1,2-methyl migration of dimethoxycarbene.[75] No theoretical investigation into the size of the barrier or the geometry of the transition state for this rearrangement has been published.

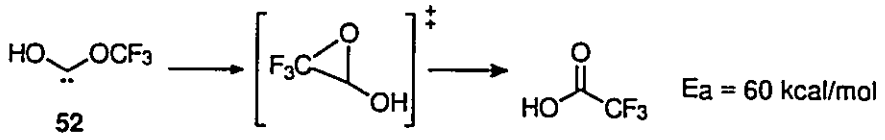
Terlouw et al. have examined 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**) in an attempt to determine if the carbene can be generated from reionization of the cation radical of dimethoxycarbene ($\mathbf{10}^{\bullet+}$)(Scheme 11).[76] The electron ionization mass spectrum of dimethoxyoxadiazoline shows an ion with m/z 74 which corresponds to the mass of dimethoxycarbene. Collisionally induced dissociation (CID) experiments on this ion showed that the structure of the ion corresponds to the radical cation of dimethoxycarbene, and NRMS studies have shown that the neutral dimethoxycarbene is a viable species in the gas phase.



Scheme 11

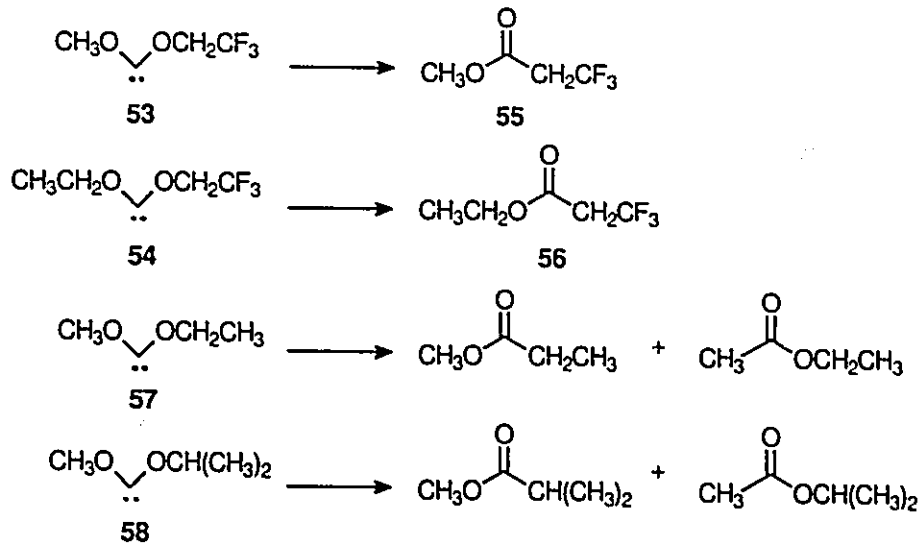
Gas phase pyrolysis experiments using the 7,7-norbornadienone ketal precursor **16** have been performed, but only methyl acetate, presumably resulting from rearrangement of the carbene, was found at high pyrolysis temperatures.[77] Evidence for dimethoxycarbene was not found. Terlouw and co-workers examined the pyrolysis of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**) and found direct evidence for formation of dimethoxycarbene.[76] The dimethoxycarbene could be generated only in a mixture with either precursor oxadiazoline (at pyrolysis temperature ≈ 360 °C) or methyl acetate (at pyrolysis temperature ≈ 510 °C). Again, these experiments confirmed the presence of dimethoxycarbene as a species with substantial lifetime in the gas phase.

The energy of the transition state for 1,2-CF_3 migration of hydroxy(trifluoromethoxy)carbene (**52**) to trifluoroacetic acid has been calculated to lie 60 kcal/mol above the carbene at the PMP4/6-31G* + ZPVE//UHF/6-31G* level (Scheme 12).[78] Like dihydroxycarbene (**50**) the geometry of the transition state was found to be consistent with migration of the CF_3 group in the plane of the molecule.



Scheme 12

Terlouw and co-workers have continued to examine the rearrangement chemistry of dialkoxycarbenes in the gas phase of the mass spectrometer.[58] Evidence for the intermediacy of methoxy(2,2,2-trifluoroethoxy)carbene (**53**) and ethoxy(2,2,2-trifluoroethoxy)carbene (**54**) in the pyrolysis experiments was found by detection of the esters **55** and **56** from carbene rearrangement (Scheme 13). These carbenes were not directly detected as neutrals in these experiments since the rearrangement of the carbene was very facile. Ethoxymethoxycarbene (**57**) and isopropoxymethoxycarbene (**58**) were detected in mixtures with the rearrangement products (Scheme 13). The rearrangement products could be characterized by their CID mass spectra.[58] Attempts to generate these carbenes from neutralization of the radical cation of the carbene were foiled by interferences from reionization of other high mass fragments.



Scheme 13

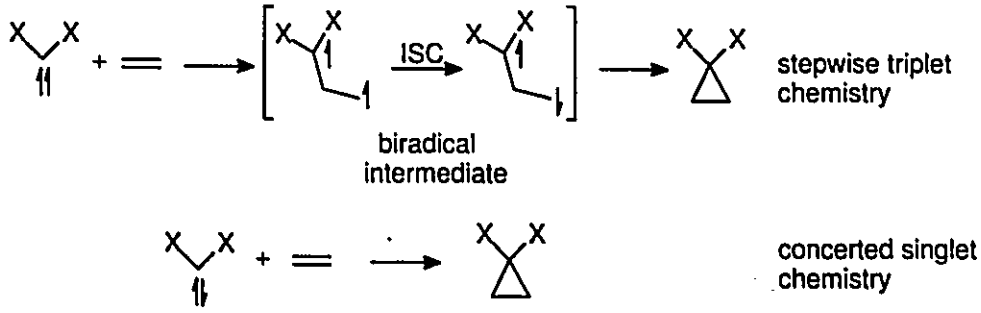
Rearrangement of **53** and **54** exclusively by 2,2,2-trifluoroethyl migration was observed. This is in keeping with migration of the alkyl group with the electrons from the breaking C–O bond. The preferential rearrangement of **57** and **58** by ethyl and isopropyl migrations, respectively, is more difficult to rationalize, but the authors suggest that the results are in keeping with the greater polarizability of the larger alkyl groups.

1.4.2 Addition of Dioxycarbenes to Double Bonds

The typical alkenes used in carbene trapping studies are not effective as traps for the highly nucleophilic and unreactive dialkoxycarbenes. Although some exceptions are known, simple alkyl substituted alkenes are in most cases totally

unreactive towards dioxycarbenes. In most concentration ranges, the presence of an electron withdrawing group (phenyl, ester, cyano, halogen) is generally required before the rate of addition becomes greater than the rate for dimerization or other intramolecular chemistry.

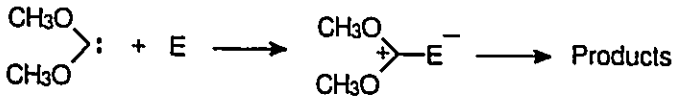
The observation of stepwise or concerted addition of carbenes to substrates is frequently used as an indication of the reactive state of the carbene and is the basis of the Skell-Woodworth Rules.[79] Triplet carbenes generally undergo stepwise reactions yielding a biradical intermediate (Scheme 14). The intermediate undergoes intersystem crossing from the triplet to the singlet manifold before forming product. Singlet carbenes generally undergo concerted reactions since the need for intersystem crossing is eliminated.



Scheme 14

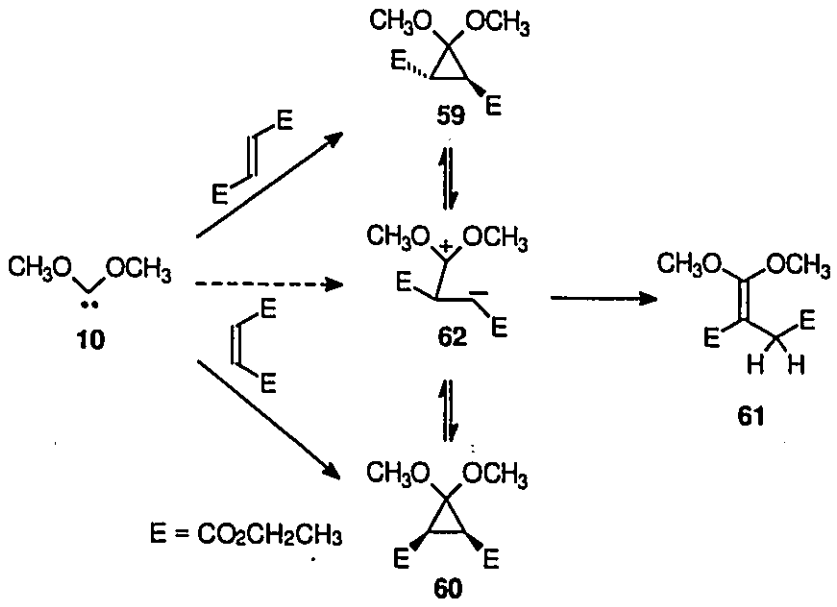
Carbenes with oxygen or nitrogen substituents on the carbene present a third possibility—stepwise, ionic reactions. Nucleophilic attack of such a carbene on an electrophilic substrate (E) should yield a heteroatom stabilized carbocation (Scheme 15). It is also important to note that because of the low reactivity of such carbenes,

the substrate is generally highly activated with electron withdrawing groups. The result is an ionic intermediate which is stabilized by both electron donating and electron withdrawing groups. As we shall see, the chemistry of strongly nucleophilic carbenes often involves the intermediacy of dipolar intermediates of this sort.



Scheme 15

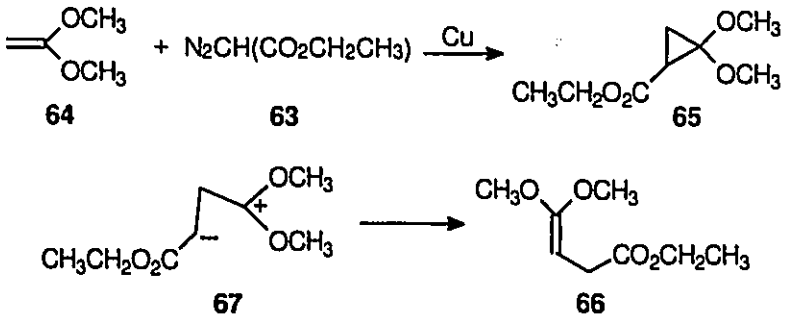
Among the additions of dimethoxycarbene (**10**) to simple double bonds studied by Hoffmann was the reaction with the electron deficient alkenes diethyl maleate and diethyl fumarate.[80] Rather than the traditional cyclopropane products (**59** and **60**), the



Scheme 16

rearranged products **61** were found exclusively in these reactions (Scheme 16). This is rationalized in terms of a thermally unstable cyclopropane product which is in an equilibrium with the dipole **62**. Proton migration yields the observed product.

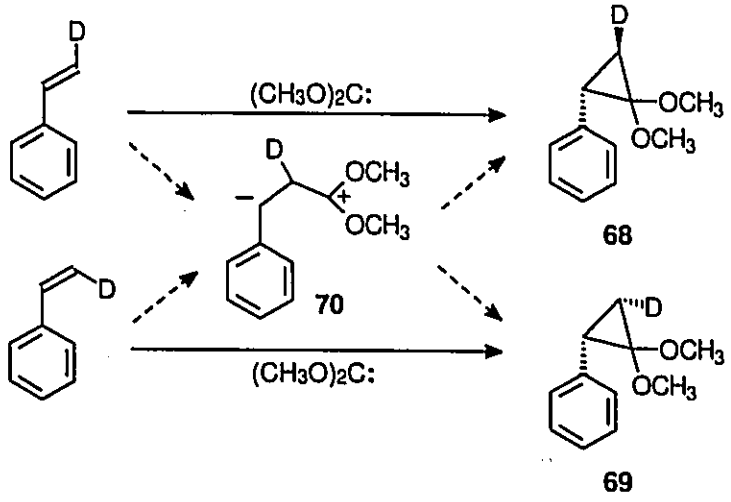
The argument for the instability of **59** and **60** is supported by the observations of Graziano and Scarpati. Similar cyclopropane products can be isolated from the copper catalyzed addition of **63** to the dimethyl ketene acetal **64** (Scheme 17).[81-83] Quantitative conversion of the cyclopropane product **65** to **66** was found upon heating to 130 °C for 4 hours.[84] The rearrangement was postulated to proceed through a dipolar intermediate such as **67**.



Scheme 17

The results of Hoffmann for the addition of dimethoxycarbene to maleate and fumarate bear upon one of the most contentious issues in nucleophilic carbene chemistry. In this instance, does dimethoxycarbene add by a concerted mechanism followed by opening of the unstable product (solid arrows in Scheme 16) or by a stepwise addition of the carbene to generate the dipole **62** as the first formed intermediate (dashed arrow in Scheme 16)?

Moss and Huselton tried to answer this question by examining the stereochemistry of the addition of dimethoxycarbene generated from **16** (7,7-dimethoxynorbornadienone ketal) to β-deuteriostyrene (Scheme 18).[85] The addition of dimethoxycarbene to *cis*- and *trans*-β-deuteriostyrene yields the cyclopropane products **68** and **69** which result from addition with retention of the stereochemistry of the double bond. This indicates that reaction of **10** does not yield the dipolar intermediate **70** (dashed lines in Scheme 18) which would result in loss of stereochemistry.

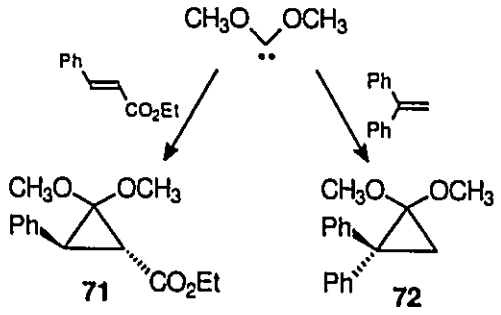


Scheme 18

While the results of Moss and Huselton demonstrate that cyclopropanation of styrene with dimethoxycarbene inherently proceeds by a concerted mechanism, the question of the sense of addition of **10** to maleate and fumarate remains unanswered. The presence of the ester groups should favour the stepwise path over the concerted

pathway since there is greater polarization of the charge in the transition state leading to the ionic intermediate.

Other cyclopropanations have been studied by Hoffmann.[80] Addition of dimethoxycarbene to ethyl cinnamate and 1,1-diphenylethene yield the cyclopropane products **71** and **72** as shown in Scheme 19. Interestingly, Hoffmann reports some substrates to which additions of dimethoxycarbene did not proceed well. These include N-phenylmaleimide, maleic anhydride and di*methyl* fumarate.

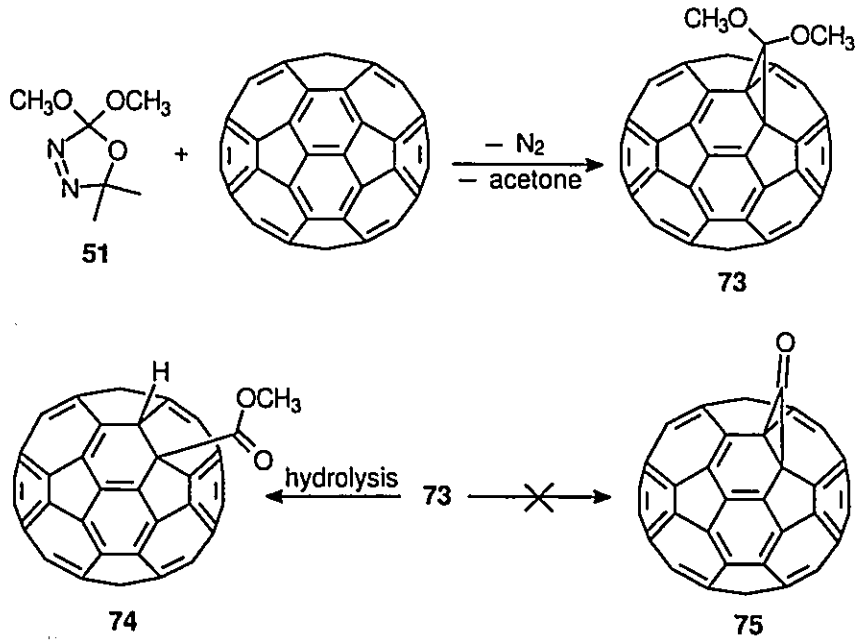


Scheme 19

The high stabilization energy of dialkoxycarbenes makes them quite unreactive. This has been verified by determination of the absolute rate constants for reactions of dimethoxycarbene with alkenes. Moss has generated dimethoxycarbene from laser flash photolysis of 3,3-dimethoxydiazirine (**25**). 2-Chloroacrylonitrile and acrylonitrile quench the transient signal of dimethoxycarbene **10** with $k_{abs} = 5.0 \times 10^5$ and 10^3 $M^{-1}s^{-1}$ respectively. The relative values of these rate constants reflect the known greater electrophilicity of 2-chloroacrylonitrile in carbene reactions.[86] For comparison, absolute rate constants for reaction of the more reactive

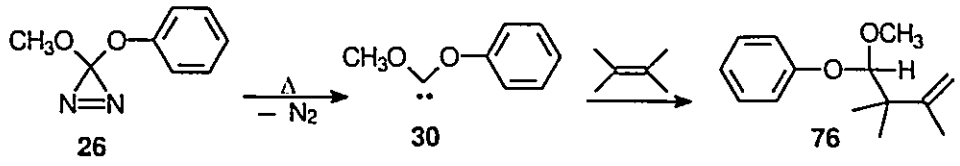
methoxymethylcarbene **38** with the same alkenes are $k_{abs} = 4.9 \times 10^7$ and 1.5×10^6 $M^{-1}s^{-1}$.[87] Tetramethylethene did not quench dimethoxycarbene which is in keeping with the expected properties of this highly stabilized nucleophilic carbene.

Two studies of the thermolysis of the dimethoxyoxadiazoline **51** in the presence of buckminsterfullerene (C_{60}) have reported an adduct of dimethoxycarbene and C_{60} with the structure **73** (Scheme 20).[88,89] The π system of the fullerene is quite electrophilic and thus was expected to be a good trap for dimethoxycarbene. The methanofullerene adduct originates from addition of the carbene across a [6,6] ring juncture which is in keeping with the higher double bond character in the [6,6] junctures compared to the [5,6] ring junctures.[90] Wudl and co-workers hydrolyzed the cyclopropanone ketal and obtained the methyl ester **74** (Scheme 20). All attempts to hydrolyze the ketal to the cyclopropanone **75** proved unsuccessful.



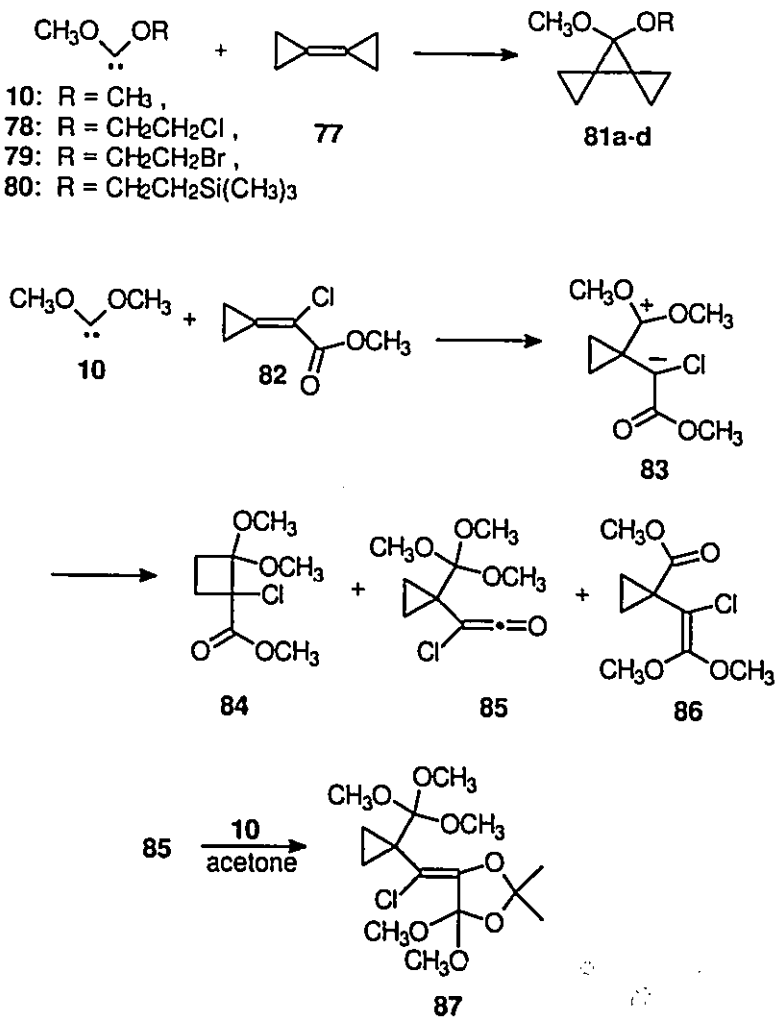
Scheme 20

Methoxyphenoxycarbene **30** also forms cyclopropane products with methyl acrylate, acrylonitrile and 2-chloroacrylonitrile.[44] These products were obtained upon thermolysis of the diazirine **26** in the presence of the appropriate alkene. A product **76** was also isolated from the thermolysis of methoxyphenoxycarbene in the presence of tetramethylethene (Scheme 21). The origin of this product is uncertain—it is not a product from simple addition to the double bond. Competition studies showed a reactivity order of 1 : 28 : 870 for tetramethylethene, acrylonitrile and 2-chloroacrylonitrile respectively.[44,86]



Scheme 21

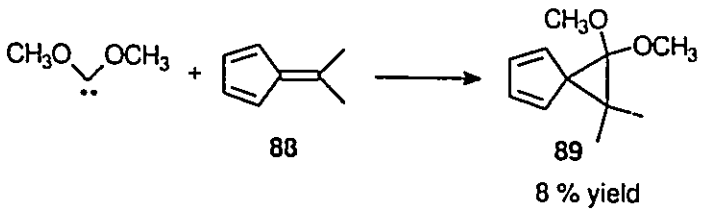
A wide variety of dialkoxycarbenes have been generated by de Meijere et al. for studies of their reactions with strained alkenes.[59] Dicyclopropylidene **77** acts as an efficient trap for dimethoxycarbene **10**, (2-chloroethoxy)methoxycarbene **78**, (2-bromoethoxy)methoxycarbene **79** and methoxy(2-(trimethylsilyl)ethoxy)carbene **80** to yield the spirocyclic compounds **81a-d** (Scheme 22). These carbenes are all generated from the appropriate oxadiazoline precursors prepared by the procedures developed by Warkentin and co-workers.[55] Reaction of dimethoxycarbene **10** with methyl 2-chloro-2-cyclopropylideneacetate **82** was also performed. A complex mixture of products was observed which could be rationalized in terms of reactions of the dipolar intermediate **83** from attack by dimethoxycarbene. The products arise from rearrangements of **83** by ring expansion (to give **84**), methoxy transfer (to give **85**), and methyl transfer (to give **86**). Another product **87** seems to arise from sequential addition of a second carbene and a molecule of acetone to the ketene **85** (for a related example see section 1.4.5). The acetone arises from the thermolysis of dimethoxyoxadiazoline. Whenever possible, the structures of the products were identified by X-ray crystallographic techniques.



Scheme 22

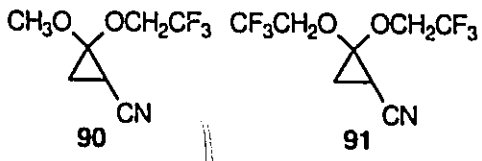
A simple alkene with which dimethoxycarbene **10** is known to react is 6,6-dimethylfulvene (**88**).[91] Moss et al. have shown that dimethoxycarbene generated from thermolysis of the 7,7-dimethoxynorbornadienone ketal **16** in neat **88** affords the adduct **89** in poor yield (Scheme 23). The addition of dimethoxycarbene is

regioselective in keeping with the larger LUMO coefficient on the exocyclic double bond of 6,6-dimethylfulvene.



Scheme 23

Moss and co-workers generated the trifluoroethoxy substituted carbenes **31** and **32** in the presence of acrylonitrile. Carbene addition to the alkene cleanly afforded the cyclopropane adducts **90** and **91**.[46] They also report formation of adducts of these carbenes with methyl acrylate.



Although the cyclopropanation reaction is among the most studied of carbene reactions, only two studies have used modern theoretical methods to address the mechanism of formation of cyclopropanes by dioxycarbenes. The most notable one is the 1980 study by Rondan, Houk and Moss.[10] Calculations were performed on the [2 + 1] cycloaddition of a variety of carbenes onto ethylene. Among the transition states calculated was that for the addition of dihydroxycarbene **50** to ethylene (Figure 8). The activation barrier for the addition was found to be 45 kcal/mol using the 4-31G

basis set and the reaction was found to be exothermic by 18 kcal/mol. The geometry of the transition state indicated a late transition state (i.e. closer to a cyclopropane geometry) compared to other less stabilized carbenes. This is in keeping with the greater stability (and hence higher activation energy) of dihydroxycarbene compared to other carbenes. Mulliken population analyses even suggest that the charge transfer in the transition state is towards the alkene by 0.06 electrons which reflects the nucleophilic character of the carbene. The results for dihydroxycarbene conform to those for the other carbenes calculated in this study.[10]

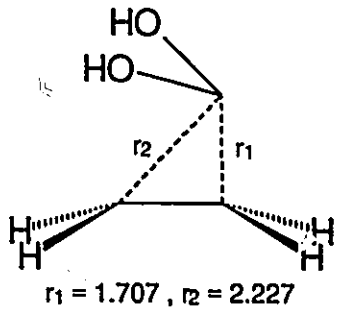


Figure 8

Bertran and co-workers used the STO-3G basis set to locate the transition states for addition of the nucleophilic carbenes dihydroxycarbene and diaminocarbene to substituted alkenes.[92] This is an important consideration since, although theoretically interesting, the addition of these carbenes to ethylene is not observed experimentally. All transition states in this study were found to possess geometries indicating a concerted reaction of the carbene to form a cyclopropane product (Figure 9). As expected, addition of the nucleophilic dihydroxycarbene **50** to acrolein was

found to occur with a transition state indicating addition of the carbene preferentially towards the unsubstituted carbon of the alkene. The degree of charge transfer was also determined in the transition state and found to be 0.143 electrons toward the alkene. This is in keeping with the greater electrophilicity of acrolein compared to ethylene (see above). It is interesting to note that the addition of dihydroxycarbene to hydroxyethene is predicted by these calculations to occur preferentially to the unsubstituted carbon atom of the alkene. In addition, the charge transfer in the transition state was calculated to be 0.106 electrons towards the carbene. These results are in keeping with an electrophilic interaction between dihydroxycarbene and hydroxyethene. The calculations suggest the possibility of some ambiphilic character for dihydroxycarbene. While this is surprising, it is not in conflict with the known chemistry of dioxycarbenes, which does not contain information on reactions with strongly electron rich alkenes. No information was presented on the possibility of addition of the dihydroxycarbene to acrolein in a stepwise fashion. The possible addition of dihydroxycarbene to the C=O bond of the acrolein was also not studied.

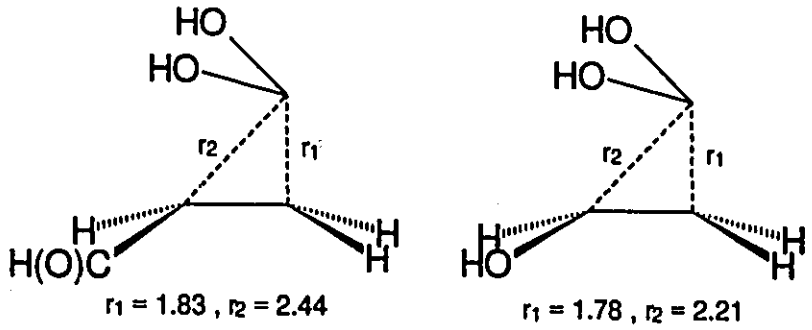


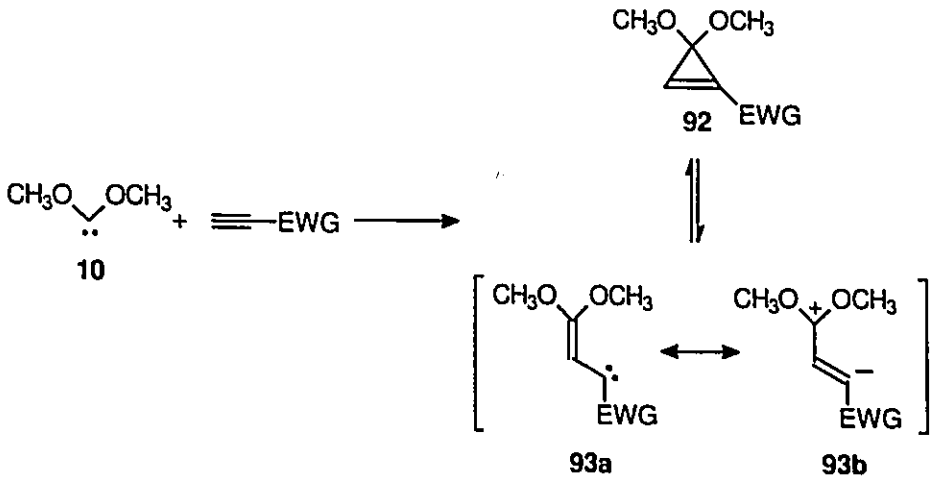
Figure 9

The two studies detailed above are informative but in some ways leave questions unanswered. The possible addition of dioxycarbenes in a step-wise fashion was not investigated. Such additions should be possible given an alkene sufficiently electrophilic to stabilize this type of a transition state. Bertran and co-workers studied both 'inward' and 'outward' transition states for the addition of methylene to the ethylene. The transition states represented in Figure 8 and Figure 9 are inward transition states. Outward transition states are those in which the carbene substituents point away from the alkene carbon atom with the longest bond length (r_2 in Figure 9). Bertran found that the inward transition states were lower in energy than the outward.[93] On the strength of this information, the outward transition states seem to have been dropped from consideration in the later work.[92] Unfortunately, these transition states would be those expected from stepwise addition to the double bond and their investigation is warranted. The basis sets employed in both studies, while adequate at the time, do not include polarization functions or diffuse functions on carbon which would be important for the energies of the carbenes, transition states, and any intermediates derived from stepwise addition.

1.4.3 Addition of Dialkoxycarbenes to Triple Bonds

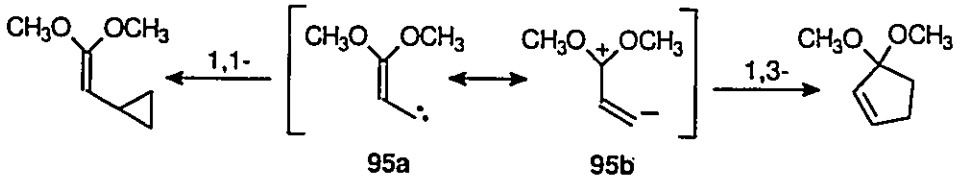
Activated triple bonds also serve as good dialkoxycarbene traps. The presence of electron withdrawing groups on the cyclopropenone ketal tends to decrease the thermal stability of the products. The ester substituted compound **92** is unstable at

room temperature and opens readily to the vinyl carbene.[95] The thermal lability of this compound can be attributed to the high strain energy and the presence of both anion and cation stabilizing groups on the molecule. Thus, the cyclopropenone ketals which would typically result from addition of dimethoxycarbene onto an activated alkyne are generally unstable with respect to the 3,3-dimethoxyvinylcarbene **93** (Scheme 24).



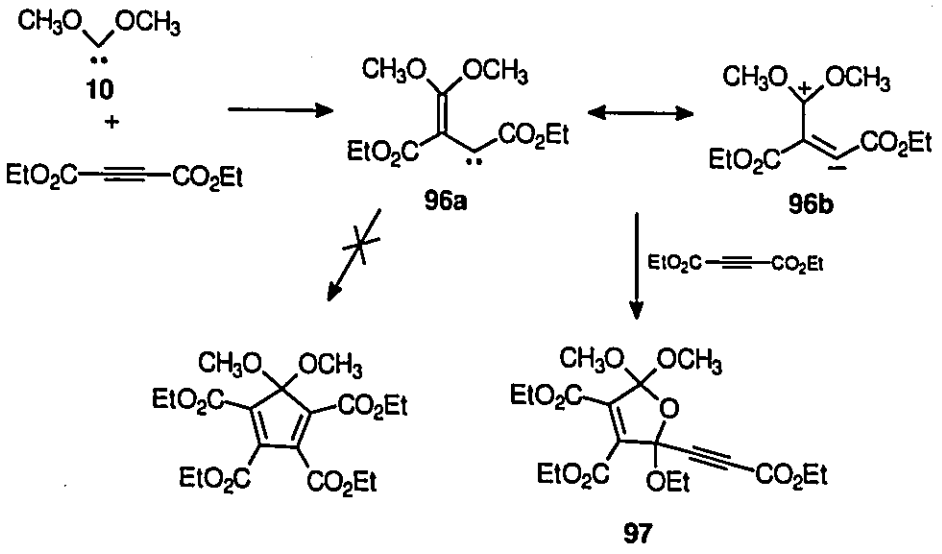
Scheme 24

Dimethoxycyclopropenone ketals have been synthesized by a non-carbene route and characterized by Boger. The variety without substitution on the vinyl carbons is relatively stable at room temperature.[96] Heating in refluxing benzene (~20 hr.) opens the cyclopropenone ketal to the vinyl carbene **95** which can act as either a 1,3- or 1,1-dipole in dipolar cycloaddition reactions with a variety of electron deficient dipolarophiles to yield either vinyl cyclopropane or cyclopentene type products (Scheme 25).[96-99]



Scheme 25

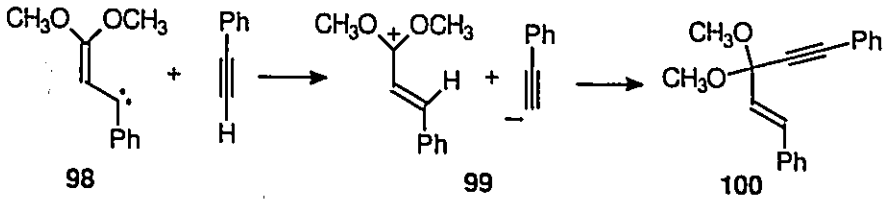
The addition of dimethoxycarbene to diethyl acetylenedicarboxylate was studied by Hoffmann.[80] Carbene addition yielded the vinyl carbene **96** which underwent cycloaddition across the C=O bond of a second molecule of the alkyne to yield the product **97** (Scheme 26). Cycloaddition of the vinyl carbene **96** across the C≡C of the alkyne to yield a cyclopentadiene product was not reported.



Scheme 26

The addition of dimethoxycarbene (**10**) to phenylacetylene proceeds by a different route (Scheme 27).[80] Addition to the terminal end of the alkyne again yields

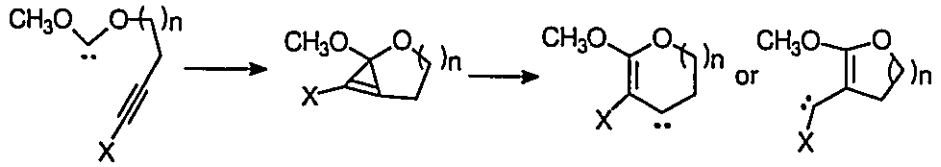
a vinyl carbene (**98**), but in this case the carbene abstracts the acidic alkyne proton from a second molecule of phenylacetylene to yield the ion pair **99** which collapses to yield the product **100**.



Scheme 27

Kassam and Warkentin have examined the intramolecular reaction of dialkoxycarbenes with tethered alkyne groups.[56] Reaction of the dialkoxycarbene to the alkyne occurred to yield either the exocyclic or endocyclic vinyl carbene depending upon the substitution on the alkyne and the chain length (Scheme 28). The cyclopropenone ketal, similar to those studied by Boger, was postulated to be an unobserved intermediate in the reaction. The vinyl carbenes were subsequently trapped by precedented cycloaddition reactions and O–H insertion reactions. (3-Butynoxy)methoxycarbene (**101a**, X = H, n = 1) yields products only from the 6-endo vinyl carbene **102a**.[56] Substitution of an ester group (**101b**, X = CO_2CH_3, n = 1) on the terminal position of the alkyne reverses this trend such that the ester stabilized exocyclic vinyl carbene **103b** is produced.[100] Lengthening the alkyl chain leads to products resulting from the six-membered exocyclic vinyl carbenes **103c** and **103d** (X

= H, n = 2 and X = CO_2CH_3, n = 2) hence avoiding the seven-membered cyclic vinyl carbene.



101a: n = 1, X = H
b: n = 1, X = CO_2CH_3
c: n = 2, X = H
d: n = 2, X = CO_2CH_3

104 **102** **103**

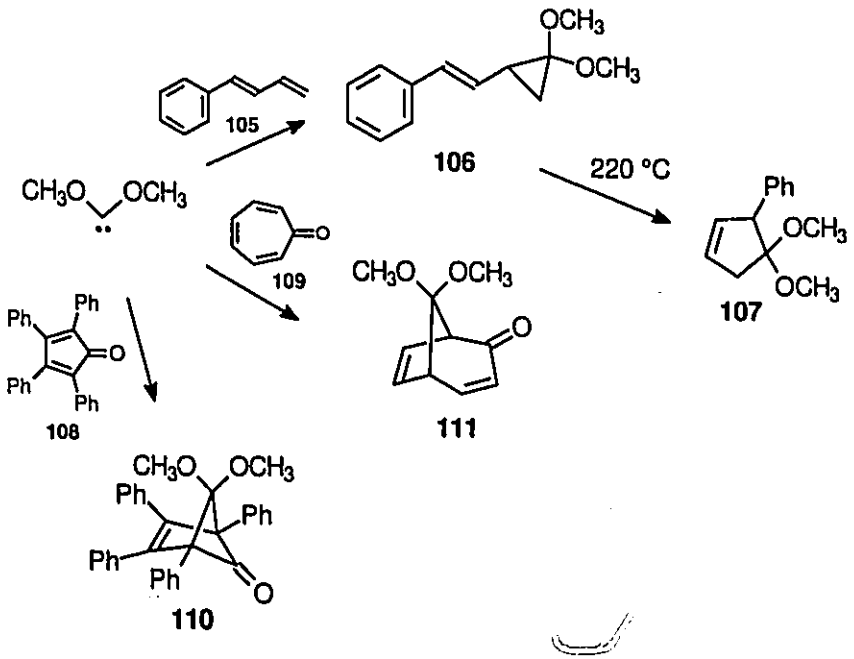
Scheme 28

Smith studied the nature of the cyclization of **101a** to **102a** using semi-empirical calculations.[101] Kassam and Warkentin proposed the intermediacy of the cyclopropenone ketal **104a** between the acyclic dialkoxycarbene and the dialkoxyvinylcarbene (Scheme 28). Smith proposed that such an intermediate may be unnecessary. A transition state corresponding to formation of the vinylcarbene by 6-endo cyclization of the carbene to the alkyne was located using the PM3 Hamiltonian. The calculated activation barrier for the formation of **102a** from **101a** (Scheme 28) by a direct mechanism is 17.6 kcal/mol. This value is lower than the relative energies of the transition state leading to formation of **104a** (27 kcal/mol) or the minimum corresponding to **104a** (25.6 kcal/mol). Conversion of **104a** to **102a** requires another 9.2 kcal/mol in activation energy. Smith therefore favoured a stepwise cyclization of the carbene to the tethered alkyne over a mechanism involving concerted cyclopropene formation. The barriers to interconversion of the isomers suggests that

equilibration of the intermediates may be possible. The relative energies of **102a** and **104a** derived from the calculations suggest that the vinyl carbene may be the most populated species at equilibrium.

1.4.4 Addition of Dialkoxycarbenes to Dienes/Heterodienes

The addition of carbenes to conjugated systems is closely related to the additions to alkenes. The major complication arises from a possible competition between 1,2-addition and 1,4-addition of the carbene to the diene. Hoffmann examined a variety of dienes in an attempt to investigate the general trends in dialkoxycarbene chemistry.[102] His results are summarized in Scheme 29.



Scheme 29

The reaction of dimethoxycarbene **10** with 1-phenylbutadiene **105** to give the [2 + 1] product **106** is similar to the adduct of dimethoxycarbene with styrene studied by Hoffmann[80] and Moss.[85] The rearrangement of the [2 + 1] adduct to the cyclopentene **107**, which is the expected product from [4 + 1] addition, suggests that rearrangements of this sort are possible but occur at a much higher temperature.

The mechanism for the [4 + 1] cycloaddition of dimethoxycarbene to tetraphenylcyclopentadienone (**108**) and tropone (**109**) to yield **110** and **111** is uncertain (Scheme 29).[102] These reactions can occur by either a concerted [4 + 1] addition of the carbene to the diene or a stepwise addition involving initial [2 + 1] cycloaddition of the carbene followed by vinyl cyclopropane rearrangement of the initial product. While the vinyl cyclopropane rearrangement in the case of **106** above occurs only at much higher temperatures, the initial [2 + 1] adducts may be less stable in the cases of addition to tropone and tetraphenylcyclopentadienone. Similar [4 + 1] cycloadditions of silylenes to dienes have been shown to proceed by a stepwise mechanism.[103-105] The orbital symmetry of the [4 + 1] addition to both dienes is similar as illustrated by the orbital diagrams[106] of tropone and fulvene in Figure 10 (arrows indicate position of addition—fulvene was used as a model for tetraphenylcyclopentadienone).

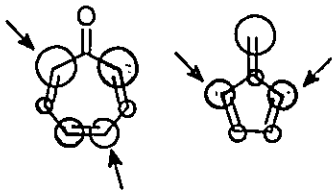
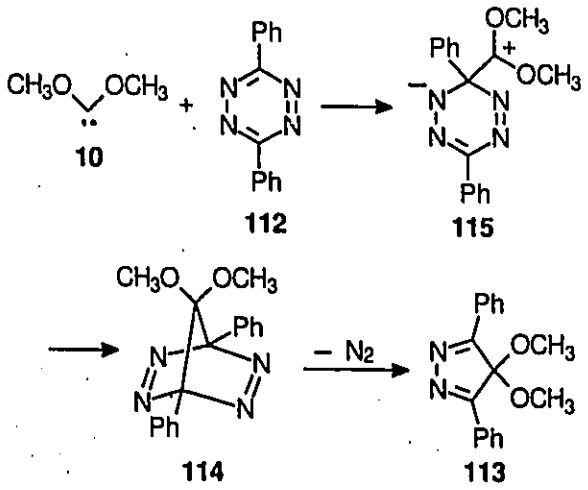


Figure 10

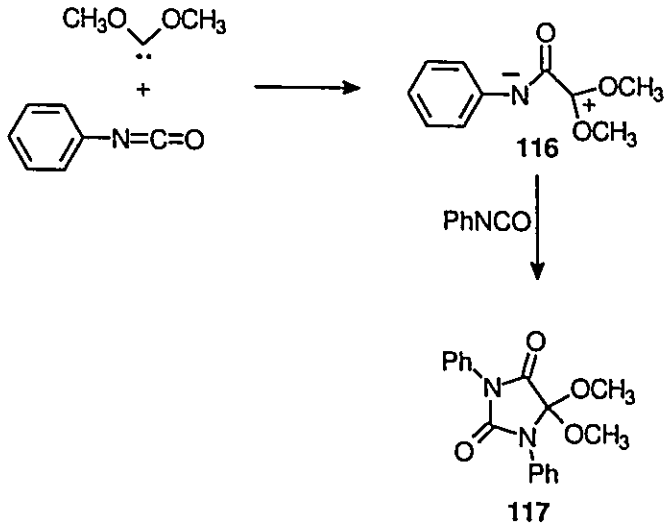
Seitz and co-workers studied the addition of dimethoxycarbene generated from the 7,7-dimethoxynorbornadiene **16** to a variety of substituted tetrazines such as **112** (Scheme 30).[107] The observed product is the pyrazole **113** which has arisen directly from loss of molecular nitrogen from **114**. The bridged product **114**, in turn, must arise from a [4 + 1] cycloaddition of dimethoxycarbene to the tetrazine. The cycloaddition likely arises from stepwise addition of the carbene onto the heterodiene to give the ionic intermediate **115** which cyclizes to give the initial product **114**.



Scheme 30

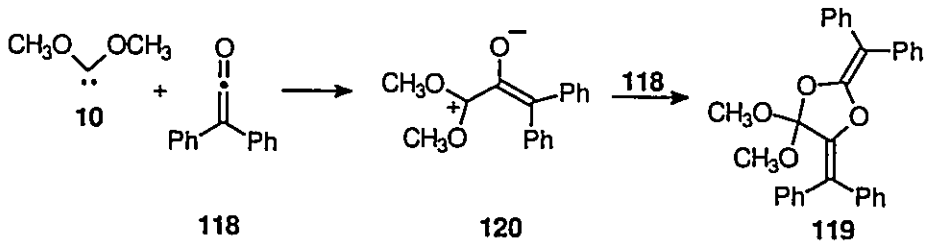
1.4.5 Addition of Dialkoxycarbenes to Cumulated Double Bonds

The reaction of dimethoxycarbene with isocyanates is one of the most studied dialkoxycarbene reactions.[41] Phenyl isocyanate reacts with dimethoxycarbene (Scheme 31) to yield a dipolar intermediate (**116**) which undergoes a cycloaddition across the N=C bond of a second molecule of phenyl isocyanate to yield the cyclic product **117** with excellent regioselectivity.[108] Hoffmann also studied the reaction of dimethoxycarbene with a variety of isocyanates and isothiocyanates. Isothiocyanates react with dimethoxycarbene to yield the analogous thio substituted product. By employing competition studies between substituted aryl isocyanates, Hoffmann was able to make a Hammett correlation which has a ρ value of + 2.0. This result indicates that negative charge is developed on the nitrogen of the isocyanate in the transition state. This, of course, is in keeping with a mechanism featuring nucleophilic attack of dimethoxycarbene onto the isocyanate.



Scheme 31

Hoffmann has also used diphenylketene **118** as a carbene trap. Thermolysis of the norbornadienone ketal precursor **16** in the presence of diphenylketene yields the 2:1 adduct **119** (Scheme 32). This compound presumably results from addition of dimethoxycarbene to the sp hybridized carbon to yield the intermediate **120**. This dipolar species undergoes a dipolar cycloaddition with another molecule of diphenylketene to generate the observed product **119**. An example of dimethoxycarbene addition to a more complicated ketene is described above (Scheme 22).



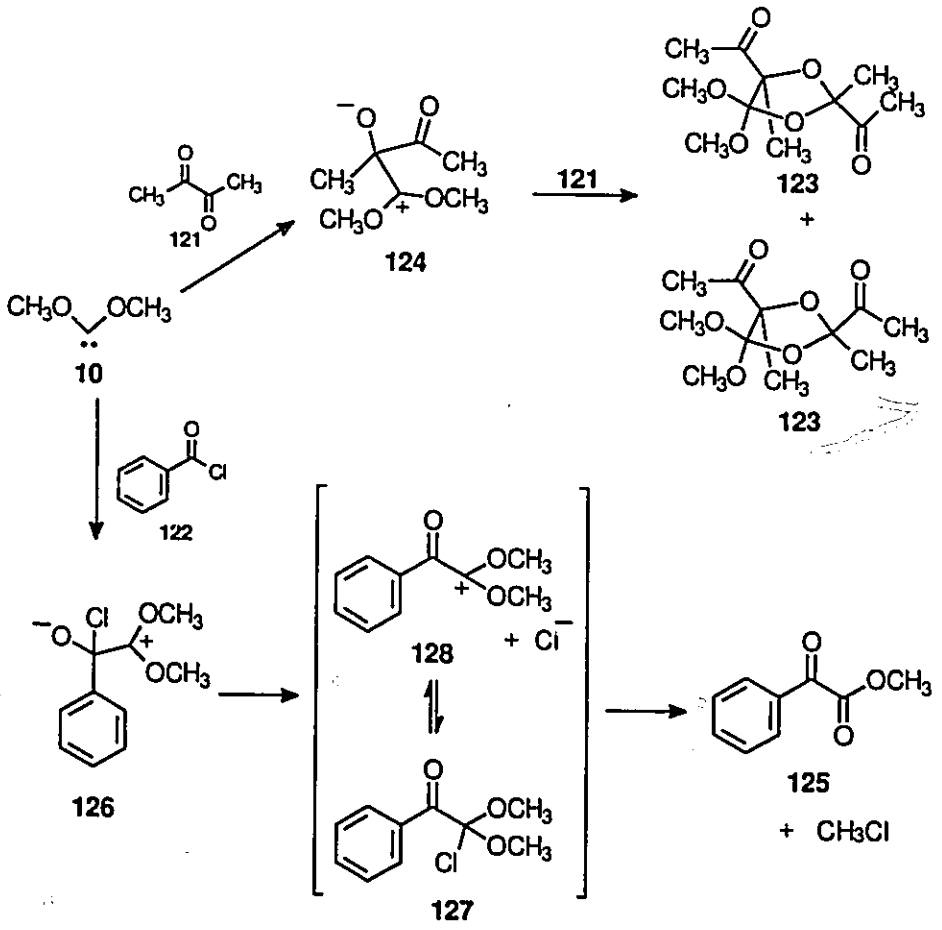
Scheme 32

1.4.6 Addition of Dialkoxycarbenes to Carbonyl Compounds

Carbene addition to a carbonyl group is the heteroatomic equivalent of the cyclopropanation reaction. The addition of nucleophilic carbenes to carbonyl groups is significantly different from addition to alkene double bonds in that the oxygen of the carbonyl group lends itself to formation of ionic intermediates. In typical solution chemistry, the addition of nucleophiles to carbonyl groups tends to proceed through a tetrahedral intermediate which is either protonated to give an alcohol or collapses, causing overall substitution.[109] It is not surprising to see stabilized tetrahedral intermediates in the chemistry of dialkoxycarbenes with carbonyl groups. Hoffmann studied the addition of dimethoxycarbene to biacetyl (**121**) and benzoyl chloride (**122**) and found products suggestive of carbene addition.

Biacetyl yielded two isomeric products which are adducts of dimethoxycarbene (**10**) with two molecules of biacetyl (Scheme 33). The diastereomeric products **123** can be rationalized in terms of nucleophilic attack of dimethoxycarbene to yield the

tetrahedral intermediate **124** which adds to a second molecule of biacetyl across the carbonyl bond. Benzoyl chloride yielded methyl benzoylformate (**125**) as the major product. The mechanism of the formation of **125** was not investigated further. Presumably, **125** arose from a mechanism similar to that proposed in Scheme 33. Attack of dimethoxycarbene gave the tetrahedral intermediate **126** which rearranged to form either **127** or **128**. The products **127** and **128** are likely to be in equilibrium. The ion pair **128** decomposes by demethylation of the cation by chloride ion to give **125**.

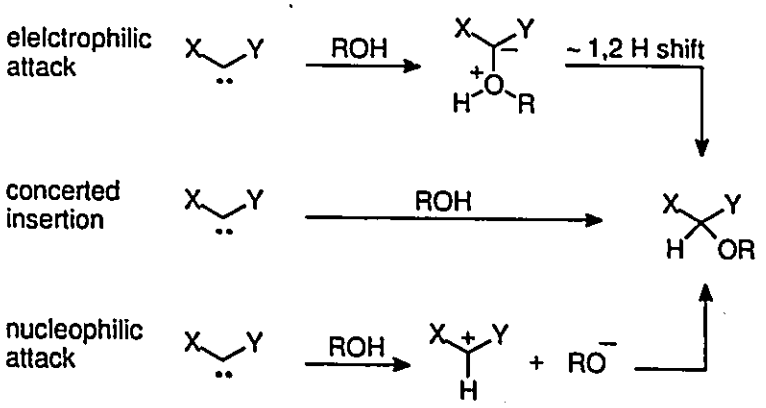


Scheme 33

1.4.7 Bond Insertion Reactions of Dialkoxycarbenes—O–H Insertion

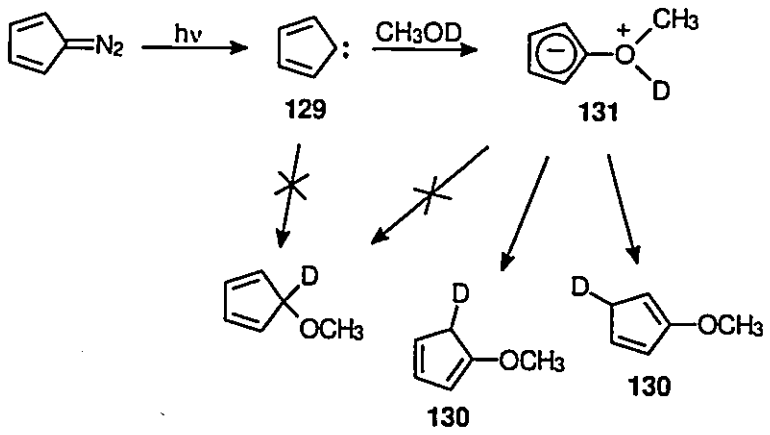
The mechanism of the insertion of nucleophilic carbenes into O–H bonds to yield ethers has been well studied. A detailed review by W. Kirmse of the mechanistic features of O–H insertions of carbenes has recently appeared.[110] There are three mechanisms generally attributed to carbene O–H insertions. Electrophilic carbenes

are most often associated with initial formation of an oxygen ylide by electrophilic attack of the carbene on the oxygen atom of the alcohol. Hydrogen migration from the ylide gives the ether product. Nucleophilic carbenes are most often associated with a mechanism involving proton abstraction by the carbene to generate an ion-pair intermediate which can collapse to yield the ether. Concerted insertion has earned the least support experimentally. The three mechanisms are pictured in Scheme 34.



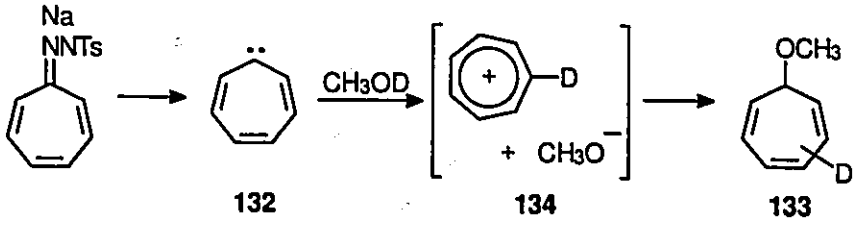
Scheme 34

The role of intermediates in the insertion into O–H bonds has been confirmed with the use of deuterium labelling. Cyclopentadienylidene (**129**) reacts with ROD to yield methoxycyclopentadiene isomers **130** with the deuterium scrambled between the two vinyl positions of the cyclopentadiene ring (Scheme 35).[111] The deuterium is not found on the sp^3 carbon atom to which the methoxy group is bound. This electrophilic carbene presumably reacts through an oxygen ylide **131**.



Scheme 35

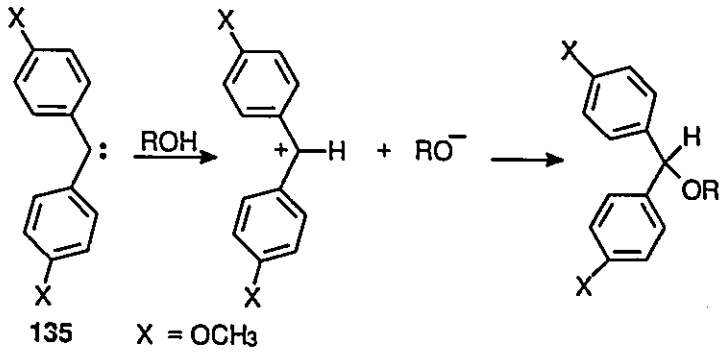
Cycloheptatrienylidene **132** reacts with ROD to yield methoxycycloheptatriene isomers **133**, with the deuterium distributed statistically among the various ring positions (Scheme 36).[111] The ratio of deuterated isomers is consistent with the formation of the ion-pair intermediate **134** which can collapse onto any of the ring positions.



Scheme 36

For nucleophilic carbenes, very strong evidence for the intermediacy of ion pairs exists from the direct detection of the cations by laser flash photolysis studies. Protonation of photogenerated diarylcarbenes by hydroxylic compounds has been

shown to yield diarylmethyl cations which can be observed as intermediates.[112-114] Electron donating substituents on the aromatic rings [as in bis(4-methoxyphenyl)carbene **135**, Scheme 37] tend to enhance the efficiency of the carbocation formation[112,113] as well as to increase their lifetimes in solution.[112]



Scheme 37

Moss studied the O–H insertion of dimethoxycarbene (**10**) into methanol.[115] Photochemical generation of **10** from 3,3-dimethoxydiazirine (**25**) in the presence of methanol cleanly gives trimethylorthoformate in > 90 % yield. Generation of the carbene in a laser pulse allows the rate constant for quenching of the intermediate to be determined. The absolute rate constant for quenching by oligomeric methanol is $6.36 \pm 0.39 \times 10^6$ $M^{-1}s^{-1}$. A primary kinetic isotope effect (k_H/k_D) of 3.3 ± 0.5 was measured for the O–H insertion by obtaining second order rate constants for reaction with methanol and methanol-d_4. For comparison, the rate constant for reaction of methoxymethylcarbene with oligomeric methanol is $7.0 \pm 0.82 \times 10^9$ $M^{-1}s^{-1}$—a rate constant which is near the limit of diffusion-controlled reactions.[116]

Insertion of dimethoxycarbene into the more acidic and reactive O–H group of acetic acid was also studied.[115] The rate constant for quenching of dimethoxycarbene by AcOH was $2.91 \pm 0.13 \times 10^9$ $M^{-1}s^{-1}$ which gave k_H/k_D near unity. Since the rate of reaction of dimethoxycarbene with acetic acid was controlled by diffusion, a reliable isotope effect could not be measured for this system.

Rate constants for reactions of dimethoxycarbene with other alcohols were measured by Du *et al.* again from photolysis of the diazirine.[45] Rate constants for O–H insertion range from 10^4 to 10^9 $M^{-1}s^{-1}$ (Table 2). The authors found a Brønsted correlation between the pKa of the hydroxylic compound and the rate constant for the O–H insertion.

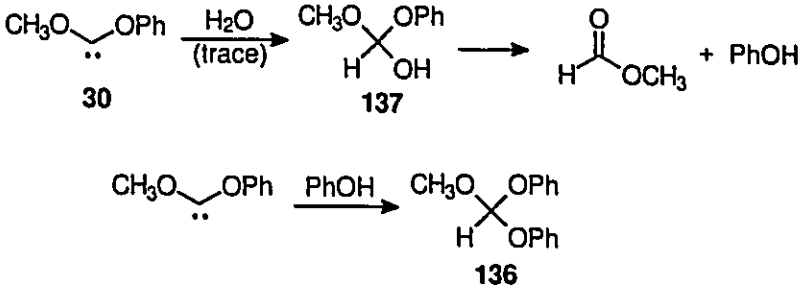
Table 2. Rate Constants for Insertion of Dimethoxycarbene (**10**) into the O–H Bond of Hydroxylic Substrates

Substrate	pKa (H_2O)	k_q ($M^{-1}s^{-1}$), 25 °C
CH_3CH_2OH	15.90	3.2×10^4
CH_3OH	15.54	8.8×10^4
$ClCH_2CH_2OH$	14.31	9.1×10^5
FCH_2CH_2OH	14.20	2.3×10^6
F_3CCH_2OH	12.37	6.3×10^7
$(CF_3)_2CHOH$	9.30	6.7×10^8
CH_3COOH	4.76	2.4×10^9

The information from the laser flash photolysis studies (above) indicates that the mechanism for O–H insertion is in keeping with initial proton abstraction to give an intermediate ion pair which collapses to yield the orthoformate products. The large primary kinetic isotope effect and Brønsted correlation both suggest that proton

transfer is important in the transition state for the insertion. The lower reactivity of dimethoxycarbene compared to other carbenes is also consistent with the greater thermodynamic stability of dialkoxycarbenes compared to most other carbenes.

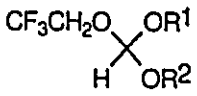
Products from insertion of methoxyphenoxycarbene **30** into O–H bonds have been observed as side products in the thermolysis of the 3-methoxy-3-phenoxydiazirine **26** in pentane.[44] The orthoformate product **136** resulting from insertion of **30** into the O–H bond of phenol was isolated (Scheme 38). Phenol presumably comes from reaction of methoxyphenoxycarbene with water in the reaction mixture to yield the unstable hemiacetal **137** which decomposes with loss of phenol.



Scheme 38

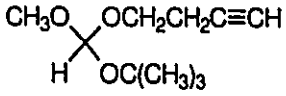
Generation of carbenes **31** and **32** (from the appropriate diazirine precursors) in methanol and trifluoroethanol afforded appropriate orthoformates.[46] Dimethyl (2,2,2-trifluoroethyl) orthoformate (**138**) was formed from reaction of **31** with methanol. Methyl bis-(2,2,2-trifluoroethyl) orthoformate (**139**) was isolated from thermolysis of **31** in the presence of trifluoroethanol and from thermolysis of **32** in the

presence of methanol. Tris-(2,2,2-trifluoroethyl) orthoformate (**140**) was isolated from reaction of **32** with trifluoroethanol.



138: $R^1 = R^2 = CH_3$
139: $R^1 = CH_3$, $R^2 = CH_2CF_3$
140: $R^1 = R^2 = CH_2CF_3$

Insertion of dimethoxycarbene generated from 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**) into the O–H bond of phenol has been reported by Warkentin and co-workers.[54] Kassam and Warkentin have also reported insertion of (3-butyn-1-oxy)methoxycarbene **101a** into the O–H bond of *t*-butanol to afford the chiral orthoester *tert*-butyl 3-butynyl methyl orthoformate (**141**) in ~90 % yield.

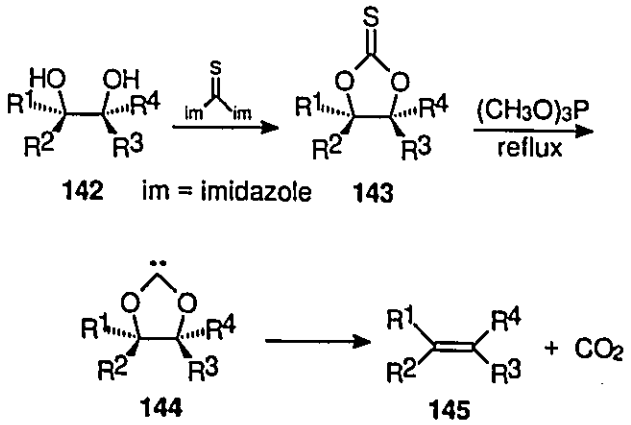


141

1.4.8 Fragmentations of Oxycarbenes

One of the most familiar uses of dialkoxycarbenes is in the Corey-Winter alkene synthesis.[117] This procedure involves generation of alkenes from fragmentation of a cyclic dialkoxycarbene. Conversion of a vicinal diol **142** into a cyclic thiocarbonate such as **143** can be accomplished by treatment with 1,1-thiocarbonyldiimidazole. Desulfurisation of the thiocarbonate with triphenylphosphine

yields the cyclic dialkoxycarbene intermediate **144** (Scheme 39). These carbenes are known to undergo a rapid extrusion of carbon dioxide to yield alkene **145** with retention of the configuration of the thiocarbonate. The reaction is driven by the thermodynamically favourable formation of carbon dioxide.

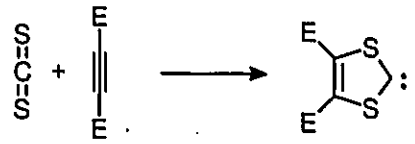


Scheme 39

Fragmentations of cyclic dialkoxycarbenes have been studied theoretically. The activation barriers to fragmentation of the cyclic dioxycarbenes **146** and **147** were calculated by Sauers.[118] He found a transition state which suggested a concerted fragmentation of the carbenes to carbon dioxide and ethylene. Based on the calculated barriers to fragmentation, the saturated carbene is expected to fragment readily (E_a = 11.3 kcal/mol) while the unsaturated carbene is expected to be considerably more stable (E_a = 30.1 kcal/mol). Both calculations were performed using the QCISD(T)//MP2/6-31G** level of theory.

146 147

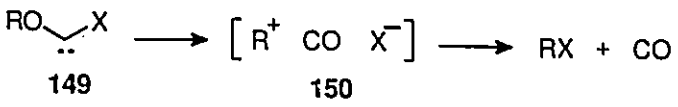
Although the fragmentation of dioxycarbenes is irreversible, this type of reaction can proceed in reverse. Cyclic dithiocarbenes such as **148** can be generated by heating carbon disulfide with an appropriate alkyne (Scheme 40).[119] The dioxycarbene equivalent of this is the cycloaddition of alkynes to carbon dioxide. Such reactions have never been reported probably owing to the greater thermodynamic stabilization of carbon dioxide compared to carbon disulfide.



E = CO_2CH_3 **148**

Scheme 40

Another fragmentation characteristic of oxycarbenes is outlined in Scheme 41. A variety of oxycarbenes **149** have been found to fragment according to this general scheme.[120-125] The net reaction is an extrusion of carbon monoxide, but there is significant evidence that the reaction proceeds through the ion pair shown **150**. Moss has studied the stereochemistry of this fragmentation in some detail, but to this date, there are no examples of *di*alkoxycarbenes undergoing fragmentation in this manner.



Scheme 41

1.5 Objective

The preceding Chapter gives a comprehensive review of the current state of research into dialkoxycarbene chemistry. The new research described in the later sections of this work has three objectives. First, to develop the use of dialkoxyoxadiazolines (see section 1.3) as convenient, thermal sources of dialkoxycarbenes. Second, to survey new chemistry of dialkoxycarbenes in order to identify new carbene reactions and obtain mechanistic information on these reactions. Third, to develop the reactions of dialkoxycarbenes with carbonyl groups in order to explore the mechanistic and synthetic value of the reactions.

It is inevitable that many of the issues described in this Introduction will arise in our further research. In particular, the question of concerted versus stepwise mechanisms for carbene reactions and the extensive involvement of ionic intermediates in these reactions will figure prominently in the new discussions to come.

Chapter 2

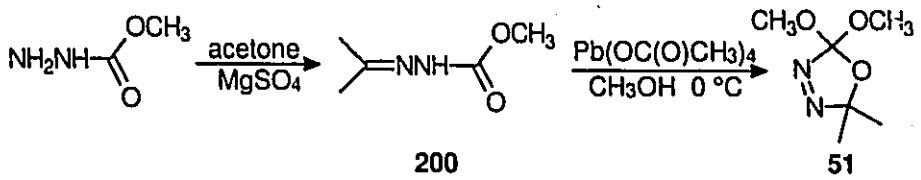
Results and Discussion

The reactions of dialkoxycarbenes with carbonyl compounds have proven to be a rich area of study. The work described in this Chapter has identified and characterized a variety of new reactions and mechanistic pathways. These studies have provided important experimental data which have facilitated attempts to determine how and why dialkoxycarbenes react with carbonyl compounds.

2.1 Synthesis of Oxadiazolines

The convenient generation of dialkoxycarbenes is critical for the study of their chemistry. A convenient, general method for dialkoxycarbene generation has been developed using Δ^3-1,3,4-oxadiazolines. There are several routes to the synthesis of 2,2-dialkoxy-5,5-dialkyl-Δ^3-1,3,4-oxadiazolines which have been explored. Each method uses the appropriate hydrazone and an oxidative cyclization to yield the five-membered heterocycle.

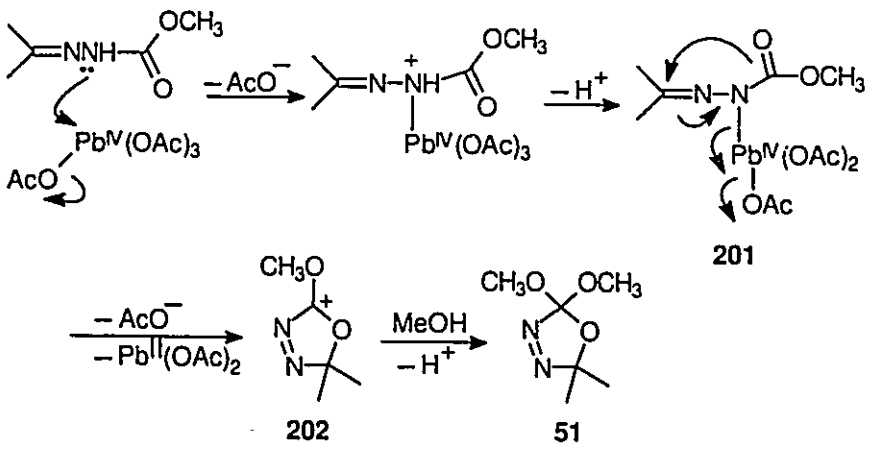
The oxidative cyclization of hydrazones and semicarbazones using lead (IV) acetate has been well studied in the literature.[126] This reagent has been used in the synthesis of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**). The reaction of the methoxycarbonyl hydrazone of acetone **200** in methanol solvent with 1.05 equivalents of lead (IV) acetate (Scheme 42)[54] is an efficient method for the synthesis of **51**. The method is easily performed, has wide applicability to the synthesis of other oxadiazolines, and is suited to large scale syntheses. The disadvantages include the high price of lead(IV) acetate and the high toxicity of the lead(II) acetate byproduct. With some substrates, lead (IV) acetate oxidation can give low yields of oxadiazolines and can be incompatible with substrates which are sensitive to strong oxidants. Neither of these issues are problematic for the synthesis of **51**, however.



200 **51**

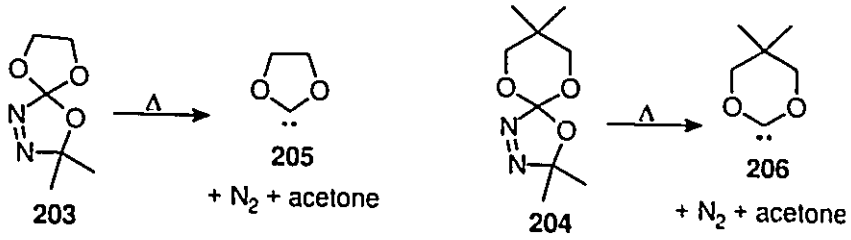
Scheme 42

The mechanism of the oxidative cyclization is believed to proceed in the manner described in Scheme 43.[126,127] The mechanism is initiated by complexation of the lead to the nitrogen of the hydrazone to give the organometallic **201**. Cyclization is accompanied by loss of the metal which is now at the Pb^{II} oxidation state. Interception of the cation **202** with a molecule of solvent yields 2,2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**).



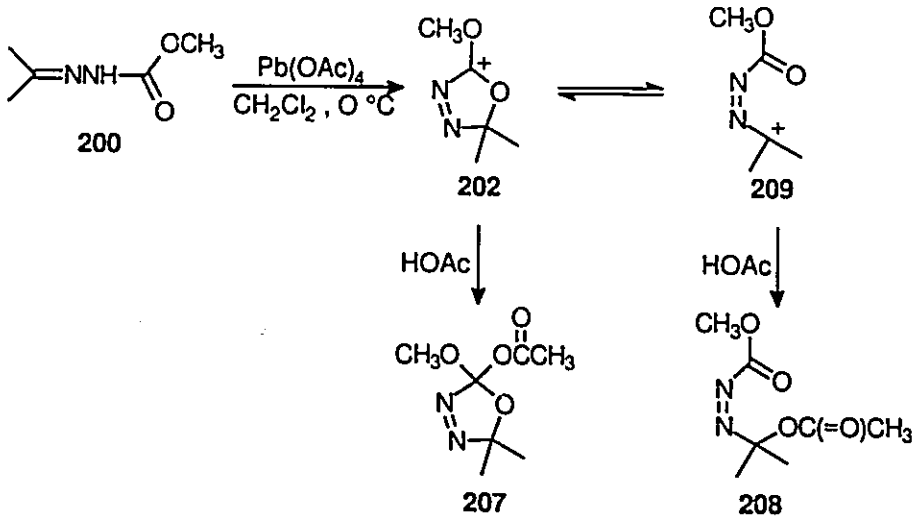
Scheme 43

Previous research on the synthesis of dioxyoxadiazolines using lead (IV) acetate oxidation has been performed by Warkentin and co-workers. The synthesis of **51** and its thermolysis to generate dimethoxycarbene was the focus of the Honours Chemistry thesis of T. Tadey.[128] Thermolysis of **51** was shown to yield tetramethoxyethene (**9**) which results from dimerization of two carbene units. Preliminary results were also obtained from some simple trapping studies which were performed using phenol and other established carbene traps. In addition, the generation of cyclic dioxycarbenes from thermolysis of Δ^3-1,3,4-oxadiazolines was the focus of the M.Sc. thesis of B. Jose.[129] This work involved the synthesis of spirocyclic dioxyoxadiazolines **203** and **204** which, upon thermolysis, yielded carbenes **205** and **206** (Scheme 44). Carbene **205** is of the type that is generated during a Corey-Winter alkene synthesis[117] (see Chapter 1). Trapping studies showed that the thermolysis of dioxyoxadiazolines was a viable means of generating dioxycarbenes.



Scheme 44

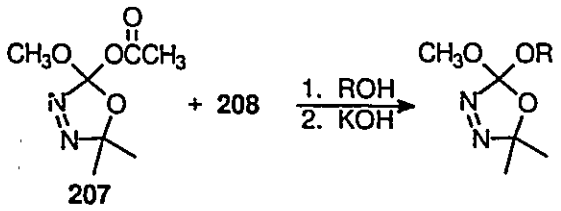
A closely related method for the synthesis of dioxyoxadiazolines has been developed which involves the use of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) as a common precursor to a variety of oxadiazolines. The results of this work have been published in the Journal of the American Chemical Society[55] and some of the results are detailed below. Synthesis of **207** is readily achieved by the reaction of lead (IV) acetate with hydrazone **200** in a non-hydroxylic solvent such as methylene chloride (Scheme 45). The synthesis of oxadiazolines containing acetoxy groups has been performed previously.[130] The mechanism of the oxidative cyclization is presumably very similar to that proposed in Scheme 43 with the exception that the cation **202** is trapped by a molecule of acetic acid. There is a competing reaction, however, which is the formation of the acyclic isomer **208** which may arise from trapping by acetic acid of an acyclic cation **209** (Scheme 45). Under a variety of conditions, the ratio of oxadiazoline to acyclic isomer is 2:1.



Scheme 45

The acetoxyoxadiazoline **207** was found to be unstable in the presence of hydroxylic compounds. Warkentin and co-workers[55] have shown that substitution of a variety of alcohols and phenols for the 2-acetoxy group of the oxadiazoline **207** yielded the appropriate dioxyoxadiazolines in good yields. The synthesis of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) and the demonstration of its ability to undergo substitution with simple alcohols was developed by K. Kassam.[131] For simple alcohols, addition of the alcohol to a solution of **207** in CH_2Cl_2 results in formation of the dialkoxyoxadiazoline after standing overnight. The acyclic isomer **208**, which is inert towards hydroxylic compounds, can be easily removed after the reaction of **207** by treatment of the reaction mixture with KOH. Stirring overnight in the presence of KOH followed by workup (sodium bicarbonate extraction) results in hydrolysis of the acyclic isomer and removal of the hydrolysis

products (Scheme 46). In many cases, further purification is not necessary. This synthetic route to oxadiazolines is highly advantageous in that a variety of oxadiazolines can be generated under very mild conditions from a common cyclized precursor.

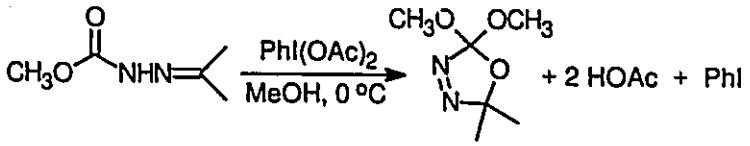


Scheme 46

The acetoxy exchange method has been used for the synthesis of oxadiazolines which cannot be synthesized from the traditional lead (IV) acetate oxidation. 2-Methoxy-5,5-dimethyl-2-(2,2,2-trifluoroethoxy)-Δ^3-1,3,4-oxadiazoline (**210**) cannot be synthesized from oxidative cyclization of **200** in the presence of 2,2,2-trifluoroethanol (TFE). The reason for this is that the alcohol reacts with the lead (IV) salt probably because the alcohol is sensitive to oxidation. The acetoxy exchange route to dioxyoxadiazolines is particularly well suited for the synthesis of **210**. 2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) reacts cleanly at room temperature with 2,2,2-trifluoroethanol (R = CH_2CF_3 in Scheme 46) in methylene chloride solvent to produce cleanly the oxadiazoline **210** in 84 % yield.

Lead (IV) acetate oxidation has proven to be of great utility for the preparation of oxadiazolines. Other oxidants, however, are also known to give

oxadiazolines upon oxidative cyclization of hydrazones. Dimethoxyoxadiazoline **51** has been prepared by oxidation of **200** with iodobenzene diacetate in methanol solution. This was achieved using the general method developed by Yang and Dai for the synthesis of monoalkoxyoxadiazolines (Scheme 47).[132] Oxidation with iodobenzene diacetate is the best route to **51** that has been examined. The yield was nearly quantitative as shown by NMR analysis of the product before chromatography. However, chromatography over neutral alumina to remove iodobenzene led to some decomposition and reduced the yield to 75%.



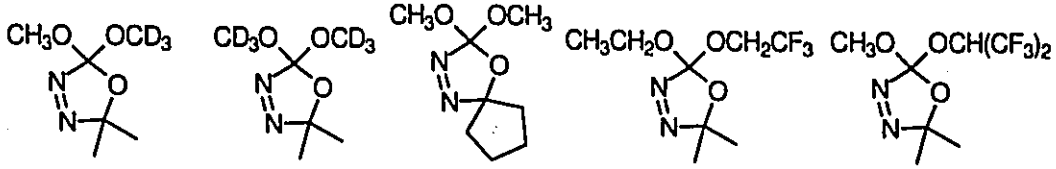
200 **51**

Scheme 47

The synthesis of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline **(207)** by iodobenzene diacetate oxidation in methylene chloride solvent was attempted, but the results were disappointing. The yields of the acetoxy oxadiazoline **207** were low and the acyclic isomer **208** tended to predominate over the oxadiazoline. Attempts were made to optimize the reaction conditions but these failed. The addition of extra acetic acid to the reaction mixture did not increase the yield. Changing the solvent in which the oxidation was performed to tetrahydrofuran or ether decreased both the overall yield and the proportion of **207** to **208**.

Electrochemical oxidation is another possible route to the synthesis of oxadiazolines. Generation of oxadiazolines from electrochemical oxidation is appealing since it avoids the use of the toxic lead oxidants. Chiba and Okimoto[133] successfully synthesized dimethoxyoxadiazoline **51** by electrochemical oxidation of **200** in methanol containing sodium acetate as an electrolyte. They found that the technique was adequate for oxadiazolines with one alkoxy group at the 2-position, but the yield for the 2,2-dialkoxyoxadiazoline **51** was quite low. Therefore, this technique is not promising as an alternative synthesis of **51** or related compounds.

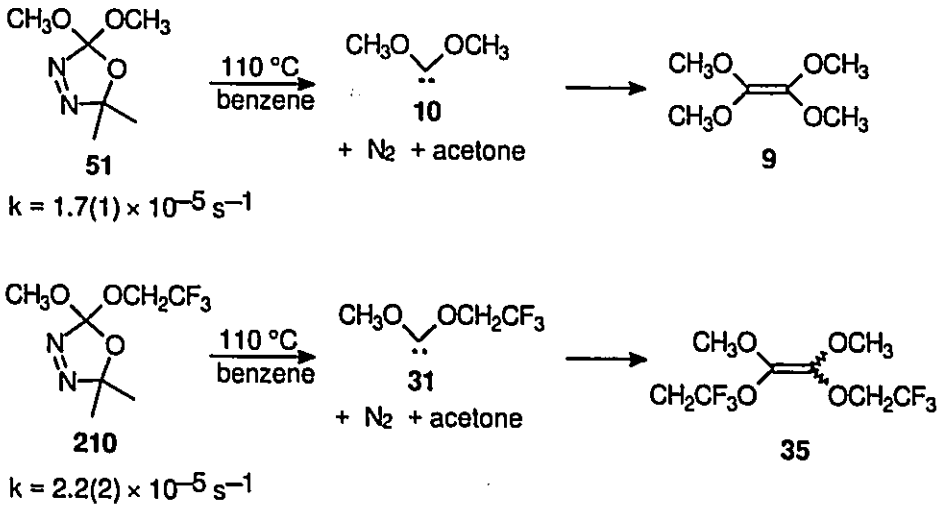
Combinations of the techniques described above are powerful tools for the synthesis of 2,2-dialkoxy-5,5-dialkyl-Δ^3-1,3,4-oxadiazolines. Oxadiazolines with a wide variety of substituent groups can potentially be synthesized. Substituents at the 5-position of the oxadiazoline are readily incorporated by the appropriate choice of ketone. The alkoxy groups can be altered by either appropriate choice of hydrazone or alcohol depending on each situation. Oxadiazolines that have been synthesized by these techniques are shown below and their syntheses are detailed in Chapter 4.



methoxy-d_3-**51** dimethoxy-d_6-**51** **211** **212** **213**

2.1.1 Carbene Generation

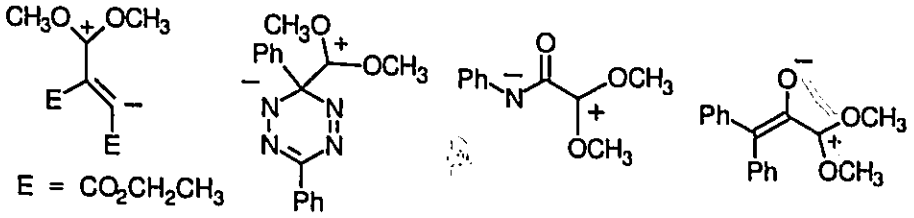
The decomposition of dimethoxyoxadiazoline **51** and methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** at 100 °C was monitored by NMR spectroscopy using p-xylene as an internal standard. The intensity of the methoxy singlet decreased with first-order kinetics (**51**: $k = 1.7(1) \times 10^{-5}\ s^{-1}$; **210**: $k = 2.2(2) \times 10^{-5}\ s^{-1}$). The generation of dialkoxycarbenes **10** and **31** upon thermolysis of the oxadiazolines in benzene is evidenced by the formation of acetone and carbene dimer (Scheme 48). Tetramethoxyethene (**9**) and 1,2-bis(trifluoroethoxy)-1,2-dimethoxyethene (**35**) were formed—the latter in a 1:1 ratio (by uncorrected GC analysis) of *E* and *Z* isomers.



Scheme 48

2.2 Trapping of Dialkoxycarbenes with Cyclic Anhydrides

As illustrated in Chapter 1, the chemistry of dioxycarbenes has become a focus of interest for both physical organic and theoretical chemists. From the known chemistry of dimethoxycarbene, it has become evident that these singlet carbenes have a tendency to react via stepwise ionic mechanisms. For instance, Hoffmann[80,102,108,134,135] and Seitz [107] found numerous products which could only be rationalized as arising from zwitterionic intermediates. Several examples which were discussed in Chapter 1 are compiled in Scheme 49 (for more information, the scheme numbers refer to Chapter 1). These intermediates formally arise from nucleophilic attack of dimethoxycarbene onto the carbene trap.



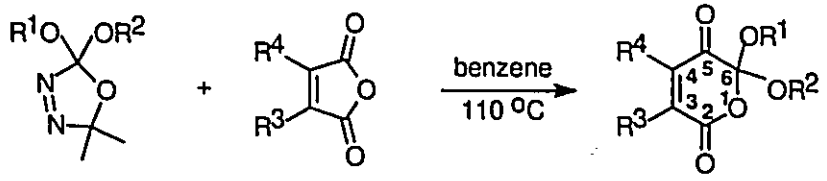
96 Scheme 26 **115** Scheme 30 **116** Scheme 31 **120** Scheme 32

Scheme 49

The convenience of 2,2-dioxyoxadiazolines as thermal precursors of dioxycarbenes[54] provides us with the opportunity to investigate some new chemistry of these interesting reactive intermediates. While some of the chemistry of dimethoxycarbene (**10**) and methoxy(2,2,2-trifluoroethoxy)carbene (**31**) (see Chapter 1) has been investigated, anhydrides have never been used as dialkoxycarbene traps.

Hoffmann, in fact, reports that maleic anhydride did not yield a product of trapping of dimethoxycarbene with this electrophilic reagent.[80] The reactions of two dialkoxycarbenes with a series of cyclic anhydrides **215** to afford the novel products of ring expansion **216** have been studied. This work has been published in Leibigs Annalen by Pole and Warkentin.[57]

Table 3. Yields of Carbene Insertion Products **216** based on Oxadiazolines **51** and **210**.



51: $R^1 = R^2 = CH_3$, **215** **216**

210: $R^1 = CH_3$,
$R^2 = CH_2CF_3$

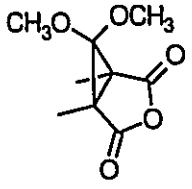
216 ($R^1 = CH_3$)	R^2	R^3	R^4	Yield (%)
a	CH_3	H	H	40
b	CH_2CF_3	H	H	46
c,d[a, b]	CH_3	CH_3 , H		81
e,f[a, b]	CH_2CF_3	CH_3 , H		60
g	CH_3	CH_3	CH_3	75
h	CH_2CF_3	CH_3	CH_3	68
i	CH_3	Cl	Cl	60
j	CH_2CF_3	Cl	Cl	45
k,l[a, b]	CH_3	Br, H		43
m,n[a, b]	CH_2CF_3	Br, H		36
o	CH_3	$-(CH_2)_4-$		40
p	CH_2CF_3	$-(CH_2)_4-$		25
q	CH_3	$-(CH=CCl-CCl=CH)-$		60
r,s[a]	CH_3	$-(CH=CH-C(NO_2)=CH)$		44

[a] Yield determined on the mixture. [b]Identity of these isomers is indicated in Scheme 50.

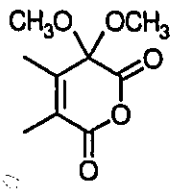
Dimethoxycarbene (**10**) and methoxy(2,2,2-trifluoroethoxy)carbene (**31**) were generated by thermolysis of 2,2-dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines **51** and **210**. In a typical trapping experiment, dialkoxyoxadiazoline and one equivalent of anhydride **215** were dissolved in dry benzene at a concentration of 0.05-0.1 mol/L. The solution was heated in a sealed tube at 110 °C for 20 hours using a constant temperature oil bath. The trapping products observed (**216**) formally arise from the insertion of dialkoxycarbene into the carbonyl carbon–anhydride oxygen bond. The yields of carbene insertion products (based on oxadiazoline) for a variety of anhydrides are given in Table 3. Yields were determined by NMR spectroscopy of an aliquot of the reaction mixture to which a known amount of an internal standard had been added after the thermolysis.

The products were characterized by analysis of their ^{1}H- and ^{13}C-NMR spectra, electron impact and chemical ionization mass spectra, and infrared spectra. The results match those expected for compounds of the general type **216**. The dimethoxycarbene adducts for the symmetrical anhydrides show a single methoxy signal in both the ^{1}H and ^{13}C NMR spectrum. This excludes the isomer **217** as a possible structure. For the case of **216a**, the ^{13}C chemical shift of the CO-$\underline{C}$(OR)$_2$ (C-6) carbon (δ = 109), the difference in the chemical shifts of the carbonyl groups [δ = 161 for the lactone carbonyl (C-2) and δ = 186 for the ketone carbonyl (C-5)], and the similarity in the chemical shifts of the vinyl carbons (δ = 140 and 142) suggest the assignment of **216**, rather than **218**, as the structure of the product. Similar

arguments can be made for the other products of carbene insertion (see Table 4). Some products from trapping of methoxy(2,2,2-trifluoroethoxy)carbene (**31**) were analyzed by ^{19}F-NMR and showed a triplet at $\delta = -79$ (referenced to $CFCl_3$) similar to the triplet of the oxadiazoline **210** ($\delta \sim -74.6$ ($^3J_{HF} = 8.4$ Hz)). The mass spectra of the products did not show a molecular ion which is, in general, consistent with the presence of a *gem*-dialkoxy fragment in the product **216**.[136] Primary neutral losses of 31 ($CH_3O^{\bullet}$) and 59 ($CH_3O^{\bullet}$ + CO) were observed for the adducts from dimethoxycarbene. The lack of an observable molecular ion precluded determination of the exact mass of the molecular ions of the compounds. The compounds **216g** and **216i**, however, showed small $[M + H]^+$ ions in the e.i. mass spectra upon which satisfactory exact mass determinations were performed. Elemental analysis of some of these compounds was attempted, but the results were unsatisfactory. The sensitivity of these compounds towards hydrolysis makes them unstable as neat compounds for long periods of time.



217



218

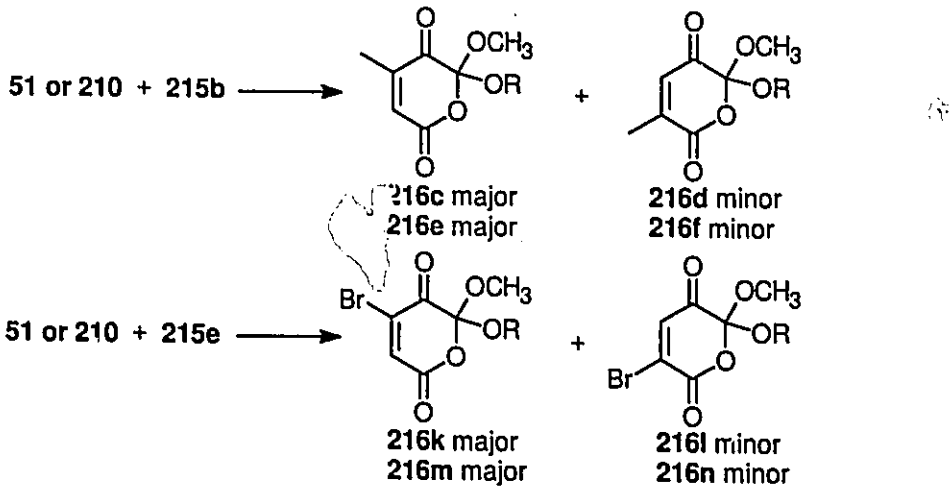
The use of unsymmetric anhydrides as carbene traps provided the opportunity to investigate how the carbene selects between non-equivalent anhydride carbonyl groups (Scheme 50). Methylmaleic anhydride **215b** reacted with dimethoxycarbene **10** to give the isomer **216c** with a preference of 3.0:1 and with methoxy(2,2,2-trifluoroethoxy)carbene **31** to favour **216c** in a 2.6:1 ratio. Bromomaleic anhydride **215e** reacted with **10** in a ratio of 4.5:1 in favour of **216k**, and with **31** to favour **216m** in a 3.8:1 ratio. The assignments of the major and minor isomers were based on the NMR spectrum of the mixture. It is well established that the ^{13}C proton

Table 4. Spectroscopic Data for Products of Trapping of Dimethoxycarbene (**10**) and Methoxy(2,2,2-trifluoroethoxy)carbene (**31**) with Anhydrides **215**.

	^{13}C-NMR (ppm)[a]					FTIR (cm^{-1})[b]		^{1}H-NMR (ppm)[c]
216	C-5	C-2	C-4	C-3	C-6	C=O		OCH_3
a	185.1	160.1	136.9	134.9	109.8	1766	1741	3.47
b	183.7	158.9	137.0	134.9	108.5	1778	1742	3.50
c	186.1	160.0	147.2	130.4	109.3	1765	1733	3.37
d	185.4	161.3	145.9	133.1	109.3	1765	1733	3.37
e	184.8	158.8	147.5	130.4	108.2	1769	1735	3.41
f	184.0	160.3	146.2	133.2	109.0	1769	1735	3.41
g	186.0	161.5	141.9	139.8	109.3	1756	1726	3.35
h	184.6	160.5	142.2	140.1	108.3	1764	1728	3.48
i	177.3	154.7	140.9	139.0	109.5	1778	1749	3.50
j	176.1	153.5	141.0	139.1	109.5	1784	1750	3.54
k	179.1	158.0	136.4	135.5	109.3	1829	1769	3.48
l	182.6	156.1	138.0	134.8	111.3	1829	1769	3.48
m	178.0	156.1	136.3	135.4	108.0	1799	1766	3.48
n	181.2	155.1	138.1	134.7	107.6	1799	1766	3.48
o	185.8	161.5	143.7	141.8	109.3	1755	1727	3.44
p	184.4	160.2	143.9	142.0	108.2	1764	1728	3.48
q	182.9	159.8	140.7[d]	140.2[d]	111.0	1770	1746	3.46

[a] $CDCl_3$, referenced to the triplet of $CDCl_3$ at 77.0 ppm; [b] FTIR spectra taken in the gas phase; [c] $CDCl_3$, referenced to $CHCl_3$ at 7.24 ppm; [d] Highest frequency aromatic signals.

coupled spectra of α,β-unsaturated esters and ketones show a larger vicinal ($^3J_{C=O,\ H}$) than geminal ($^2J_{C=O,\ H}$) coupling between the carbonyl carbon and the vinyl protons.[137,138] A gated proton decoupling pulse sequence was used to generate the ^{13}C proton-coupled NMR spectra of the products from thermolysis of **51** and **210** with **215b** and **e**. Each sample contained the two trapping products as well as remaining anhydride. In both cases, the ester carbonyl groups showed small couplings in the major products (**216c** and **k**) and the ketone carbonyl groups showed a larger splitting. Additionally, the ketone carbonyl of **216c** and **e** showed a vicinal coupling to the methyl group which was absent in the minor product **216d**. This is consistent with the structure of the major product being that from attack of the dialkoxycarbene with the carbonyl group adjacent to the substituent.



Scheme 50

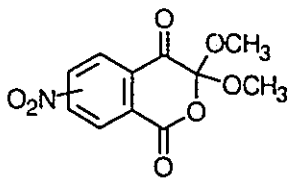
The observed selectivity can be accounted for by a preference for attack of the dialkoxycarbene at the most electron deficient carbonyl carbon of the anhydride. The methyl group of methylmaleic anhydride is also conjugatively donating (by hyperconjugation) to the distant carbonyl group. In the case of bromomaleic anhydride, the bromine is most inductively withdrawing from the adjacent carbonyl group while weakly donating, conjugatively, to the distant carbonyl group. The results observed are in keeping with attack of the carbene on the most electrophilic carbonyl group. The preference for attack of the carbene adjacent to the substituent indicates that electronic considerations are strong enough to overcome any steric factors associated with such attack. This was not the case in another study in the literature in which the addition of a Wittig reagent to these anhydrides was found to give products from the sterically favoured attack at the distant carbonyl group.[139]

The dialkoxycarbene reaction with unsymmetric anhydrides may provide a means of measuring the selectivity of nucleophilic carbenes. This is of substantial importance since the experimental measurement of a selectivity index for dialkoxycarbenes has not been achieved. Carbene selectivity is measured by competition reactions between alkyl substituted olefins such as tetramethylethene, isobutene and 2-butene. Since dimethoxycarbene is unreactive towards these alkenes, the only values which are available for the selectivity indices of nucleophilic carbenes are extrapolated from trends with electrophilic carbenes. A method for the direct

measurement of selectivities for nucleophilic carbenes would be of great general interest for carbene chemists.

The internal competition between unsymmetric anhydrides may provide a means of measuring the selectivity of carbenes. The results above are promising. Methoxy(2,2,2-trifluoroethoxy)carbene (**31**) shows a lower selectivity towards both methylmaleic anhydride **216b** and bromomaleic anhydride **215e** than dimethoxycarbene (**10**). This is in keeping with the results of Moss and co-workers. They have found that the electron withdrawing effect of the trifluoromethyl group makes trifluoroethoxy-substituted carbenes more reactive and less selective than the analogous methoxy-substituted carbenes.[32,140] This is in accord with the decreased ability of the trifluoroethoxy oxygen to stabilize the carbene.

For 4-nitrophthalic anhydride **215h**, the carbene must select between the carbonyl group para and the carbonyl group meta to the nitro substituent. The observation that dimethoxycarbene reacts to yield a 1:1 mixture of products (by uncalibrated GC/MSD integration) is roughly in keeping with the similarity in the σ_p and σ_m values for the nitro substituent (σ_p = 0.78, σ_m = 0.71, σ_p/σ_m = 1.10). Although the study of other monosubstituted phthalic anhydrides would be useful for the further characterization of these reactions, such substrates are difficult to synthesize and are not available commercially.



216r, s

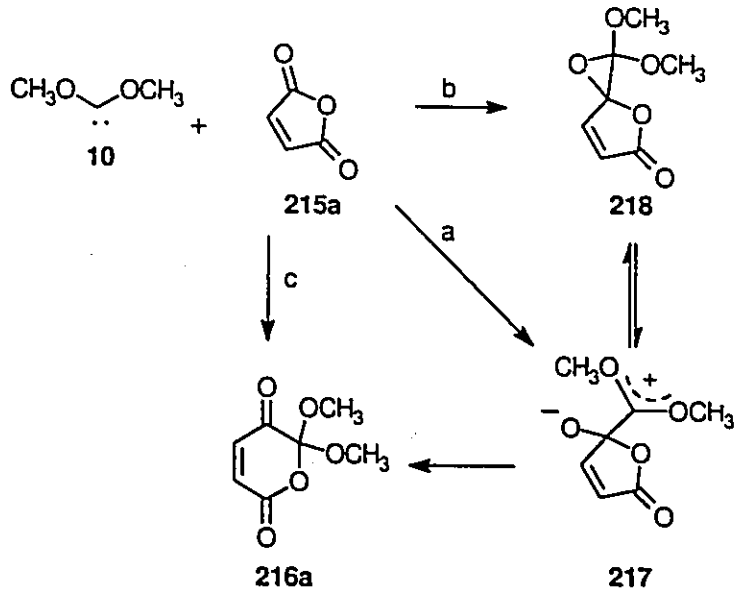
A competition study between maleic (**215a**) and dimethylmaleic anhydride (**215c**) was performed. Results of a thermolysis of oxadiazoline **51** performed in the presence of three equivalents each of maleic (**215a**) and dimethylmaleic (**215c**) anhydrides showed a 5.6:1 preference for attack of dimethoxycarbene on maleic anhydride over dimethylmaleic anhydride. Donation of electron density by the methyl groups of **215c** decreases the reactivity of this anhydride.

The nucleophilicity of dimethoxycarbene was also tested by means of a competition experiment between dimethylmaleic (**215c**) and dichloromaleic (**215d**) anhydrides. Dimethoxyoxadiazoline **51** was thermolyzed in the presence of a five-fold excess of a 1:1 molar mixture of dichloromaleic and dimethylmaleic anhydrides. Analysis of the product mixture by ^{1}H NMR, GC/FID, and GC/MSD did not show an observable signal for the product of trapping with dimethylmaleic anhydride. Based on the sensitivity of GC and GC/MS, the reaction of dimethoxycarbene occurred with > 100:1 preference for the more electron deficient dichloromaleic anhydride. This experiment supports a mechanism involving nucleophilic attack of dimethoxycarbene on the carbonyl carbon of the anhydride.

The products **216a-s** are interesting structures which are derived, formally, from the insertion of a masked carbonyl group into the basic anhydride framework. Reports of compounds of this sort in the literature have not been found. Similar carbonyl carbon—anhydride oxygen insertion products were observed from the reaction of isocyanides with trifluoroacetic anhydride.[141] There is some precedent for the insertion of nucleophilic carbenes α- to a carbonyl group. The reaction of dimethoxycarbene with benzoyl chloride has been studied by Hoffmann (see Chapter 1, Scheme 33).[80]

Perhaps the most characteristic reaction of a nucleophile is addition to carbonyl carbon to yield a tetrahedral intermediate. Of the possible mechanisms for formation of **216**, nucleophilic attack of the carbene at the carbonyl carbon atom to generate a tetrahedral, dipolar intermediate **217** is most likely (path a, Scheme 51). The stepwise nature of the reaction is precedented by many of the reactions studied by Hoffmann and others (see Chapter 1). The dipole **217** can rearrange to **216** by a 1,2-migration of the carboxylate group in either a concerted or stepwise manner. While a direct insertion mechanism (path c) would arrive at **216a**, it is unlikely that the observed high selectivity for dichloromaleic anhydride over dimethylmaleic anhydride could result from a mechanism in which the carbonyl carbon remains sp^2 hybridized throughout. Although not observed, the formation of the oxirane **218** as an intermediate is an important consideration. It could arise either by a concerted but asynchronous carbene addition to the carbonyl group (path b) or by a reversible

closure of **217** to **218** in competition with rearrangement of **217** to **216a**. Our experimental results thus far cannot distinguish between these mechanistic possibilities.

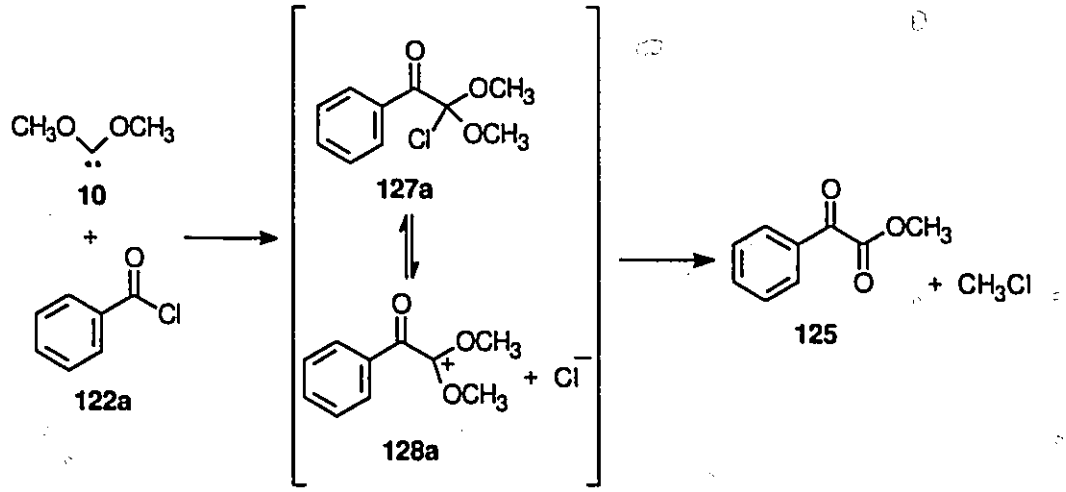


Scheme 51

2.3 The Mechanism of Intramolecular 1,2-Shifts from a Tetrahedral Intermediate

2.3.1 Reaction of Dialkoxycarbenes with Benzoyl Cyanide and Fluoride

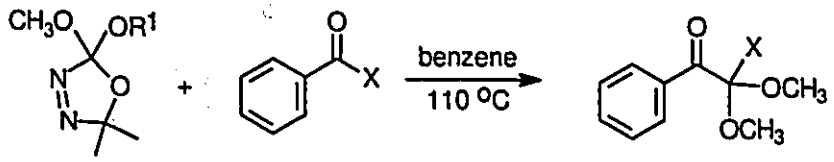
There are few examples of the addition of dialkoxycarbenes to carbonyl groups (see Chapter 1). Hoffmann has studied the reaction of dimethoxycarbene (**10**) with benzoyl chloride (**122**, Scheme 52).[80] The product observed in this reaction was methyl benzoylformate (**125**) which presumably arose from decomposition of the initially formed product (**127a**) which was not detected.



Scheme 52

The study by Hoffmann leaves many issues unaddressed. For instance, it is not clear that **127a** is the initial product in the reaction. If it can be shown that **127a** is formed, it would be of interest to establish the source of its instability. Additionally, since the product **127a** bears some noteworthy similarities to the products observed from the insertion of dialkoxycarbenes into anhydrides, it is desirable to investigate any possible common mechanistic features that the reactions may share.

Thermolyses of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**) and 2-methoxy-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**210**) in the presence of benzoyl cyanide (**122b**) and fluoride (**122c**) at 110 °C were performed. The products from these reactions (**127b-e**) result from insertion of dialkoxycarbene (**10** and **31**) into the bond between the carbonyl and the X substituent (X = Cl, CN, F). Evidence for the formation of methyl benzoylformate **125** in these reactions was not found. The products of dimethoxycarbene with **122b** and **c** were isolated by preparative GC and distillation, respectively.



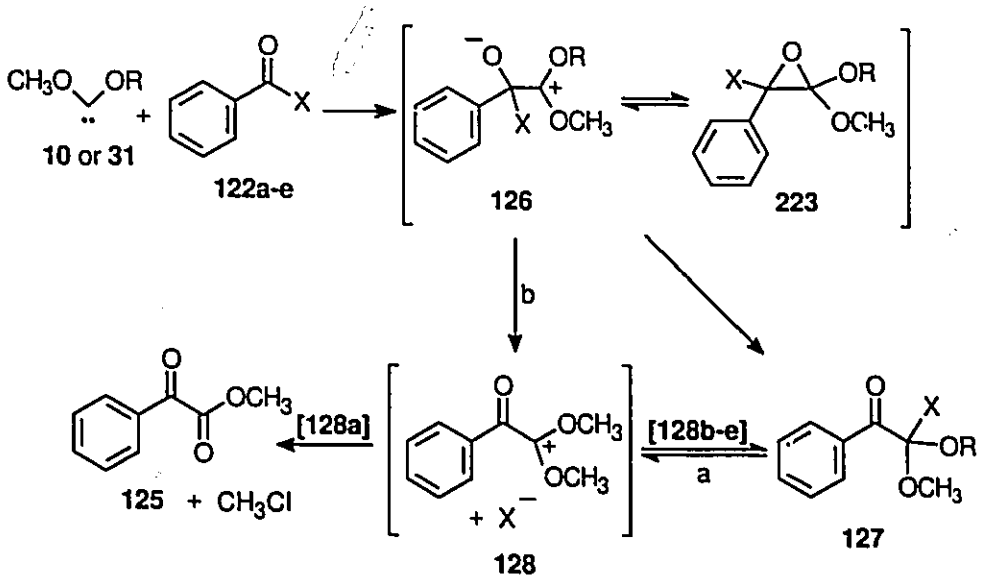
51: $R^1 = CH_3$
210: $R^1 = CH_2CF_3$

122b: X = CN
c: X = F

127b-e

Scheme 53

The structures of the products **127b-e** are closely analogous to the structures of the products from insertion of **10** and **31** into the anhydrides **215**. There is increasing evidence to suggest that the mechanism involves attack of the carbene on the carbonyl carbon of the benzoyl compound to generate a zwitterionic tetrahedral intermediate (**126**, Scheme 54) in either a direct fashion or via the oxirane **233**. The zwitterion **126** is probably in equilibrium with the oxirane **223**, although no direct evidence of this exists. The tetrahedral intermediate **126** collapses with migration of the X group to the cationic centre to yield **127**.



Scheme 54

Benzoyl fluoride and cyanide yield only the insertion product **127** whereas benzoyl chloride yields methyl benzoylformate **125** as the only observed product.[80] The formation of methyl benzoylformate most likely involves ion pair **128** (Scheme

54). The ion pair can be formed either from ionization of the insertion product **127** (path a, Scheme 54) or by fragmentation of the tetrahedral intermediate **126** (path b, Scheme 54).

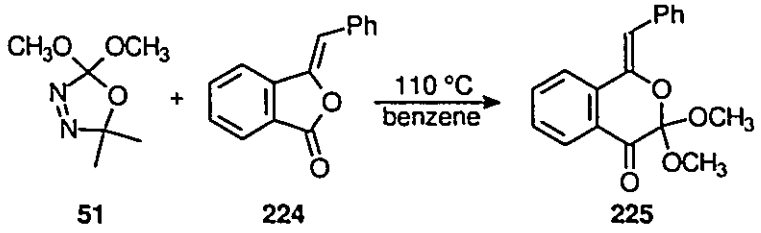
It is possible to distinguish between these two pathways. If the mechanism suggested by path b was operative for the carbene insertion, then products **125** and **127** must be formed by competitive reactions of the ion pair **128**. In this scenario, the product distribution should be controlled by the nucleophilicity of the X^- group. The experimental results do not support this mechanism since CN^- is a stronger nucleophile than Cl^- and yet **125** is formed only when X = Cl^-.[109] Formation of **128b** or **c** should efficiently yield **125** as the major product.

Alternatively, path a involves formation of **125** from ionization of **127** and should be controlled by the leaving group ability of the X substituent. This prediction fits better with the observed results since fluoride and cyanide are poorer leaving groups compared to chloride. For these reasons, a concerted mechanism for the 1,2-X shift (**126** → **127**) is considered to be more likely. This is likely to be true of all three X included in this study and for the previously reported 1,2-acyloxy shifts that occur during reactions of dialkoxycarbenes with cyclic anhydrides.

2.3.2 Reaction of Dimethoxycarbene with Benzalphthalide

Additional support for the conclusions made above came from a study of the reaction of dimethoxycarbene with benzalphthalide (**224**). Dimethoxyoxadiazoline

(**51**) was thermolyzed for 20 hours in the presence of a 2-fold excess of benzalphthalide. Radial chromatography of the reaction mixture yielded a product identified as **225** in 23 % isolated yield based on oxadiazoline (Scheme 55). The product results formally from insertion of the dimethoxycarbene into the C—O bond adjacent to the carbonyl group.

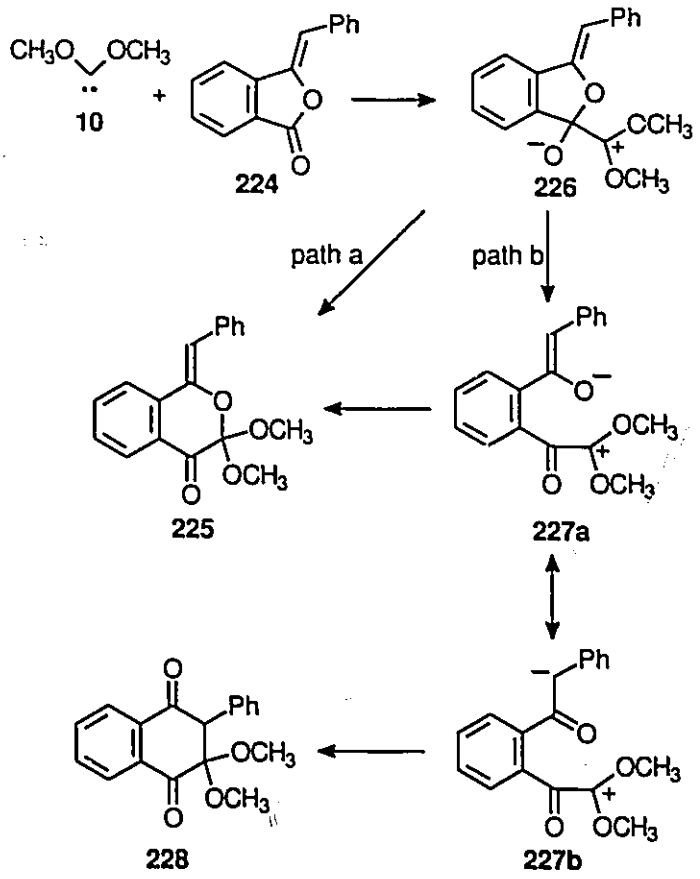


51 **224** **225**

Scheme 55

The adduct of dimethoxycarbene (**10**) with benzalphthalide **224** is structurally similar to the product of trapping with anhydrides already reported (see section 2.2). A similar mechanism can be inferred for formation of **225** from attack of **10** on the carbonyl carbon of **224** to give the zwitterion **226** (Scheme 56). Rearrangement of **226** by a 1,2-shift of the enolic oxygen yields **225**. The observation of this product suggests that rearrangement from **226** to **225** proceeds via a concerted 1,2-shift (path a). A stepwise rearrangement (path b) would generate an enolate **227**. It was shown that enolates of this sort give products from alkylation at carbon rather than oxygen (see section 2.7) and thus should give at least some **228**, and perhaps even be the major product of trapping. Neither **228** nor products resulting from carbene addition to the double bond of benzalphthalide were observed.

The results of these studies give new insights into the mechanism of insertion of dialkoxycarbenes into the carbonyl carbon–X bond where X = OC(=O)R, Cl, CN, F, or $OC(=CR_2)R$.



Scheme 56

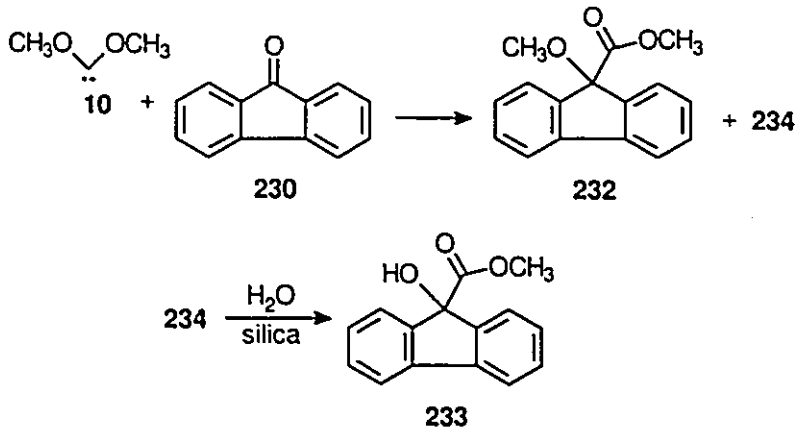
2.4 Rearrangement Reactions of a Tetrahedral Intermediate

2.4.1 Reaction of Dimethoxycarbene with Fluorenone and Coumarin

Reactions of dialkoxycarbenes with other carbonyl compounds have been studied. A fascinating mechanistic puzzle was discovered from the reaction of dimethoxycarbene (**10**) with the carbonyl group of 9-fluorenone (**230**) and coumarin (**231**).

Thermolysis of dimethoxyoxadiazoline **51** for 24 hours at 110 °C in the presence of a 2-fold excess of fluorenone (**230**, Scheme 57), yielded an adduct identified as methyl 9-methoxyfluorene-9-carboxylate, **232**. The adduct was isolated by radial chromatography (10% ethyl acetate in hexanes, 4mm silica plate). During chromatography, a product identified as methyl 9-hydroxyfluorene-9-carboxylate (**233**) was also isolated. The product **232** had two methoxy singlets in the ^{1}H NMR spectrum ($\delta(CDCl_3)$ = 2.87 and 3.57). The chemical shifts of these singlets are unexpectedly low, but they (and the other NMR data) are in reasonable agreement with the spectra of this compound reported by Johnston *et al.*[142] The 9,9-disubstitution must cause the methoxy groups of the ester and ether to lie largely over the magnetic shielding cone of the aromatic ring. The presence of a carbonyl group is evident from the ^{13}C NMR spectrum ($\delta(CDCl_3)$ = 171.2), and the e.i. mass spectrum shows ions at m/z 254 $[M]^+$ and 195 $[M - CO_2CH_3]^+$, consistent with structure **232**

(Scheme 57). It is clear that **233** is not a primary carbene derived product and must have arisen from hydrolysis of some unidentified carbene derived product **234**



Scheme 57

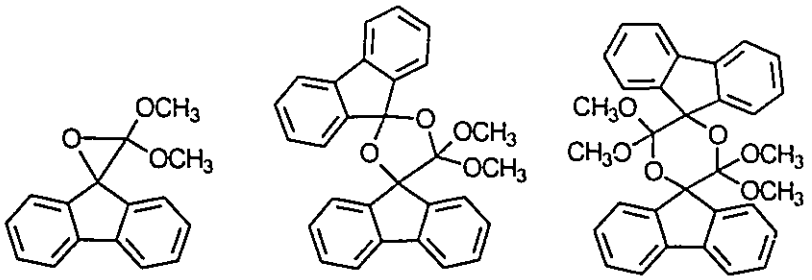
Analysis of the GC and GC/MS spectra of the crude reaction mixture revealed signals for the excess fluorenone and the product **232**, but a signal for **233** was not observed. However, **233** isolated by chromatography over silica clearly gave a signal by GC and GC/MS. This is strong evidence that **233** is not present in the crude reaction mixture. It is likely that a thermally sensitive species may not survive gas chromatographic separation (oven temperature > 200 °C during sample elution). It is possible, therefore, that a peak for such a species will not be detected. Other products which could arise from carbene derived chemistry were not evident in the GC trace of the crude reaction mixture. Clearly, however, there must be some other product **234** which upon chromatography yielded the hydrolysis product **233**. This species which was not detected during GC must be the source of **233**.

Analysis of the ^{1}H-NMR spectrum of the crude reaction mixture revealed signals matching those for the isolated product **232**. The yield by NMR was 24 % based on oxadiazoline. In addition to the methoxy signals of **232**, a single methoxy resonance was detected at δ = 3.56. Since, as discussed above, this signal cannot be attributed to **233**, this species must be the species **234**. Making the assumption that the compound contains two equivalent methoxy signals, the yield of **234** by NMR can be calculated to be 10 % based on oxadiazoline.

It is possible only to speculate upon the identity of the product **234**. A likely theory is that the species **234** is the source of the product **232**. Addition of dimethoxycarbene to the carbonyl group of fluorenone could yield a species which builds up in concentration. Continued heating of this species may yield the product **232**. As a test of this theory, one would expect that at short thermolysis times a greater proportion of **234** compared to **232** would be present. Additionally, further thermolysis of the sample past the 24 hours required to thermolyze the oxadiazoline should decrease the amount of **234** compared to **232**.

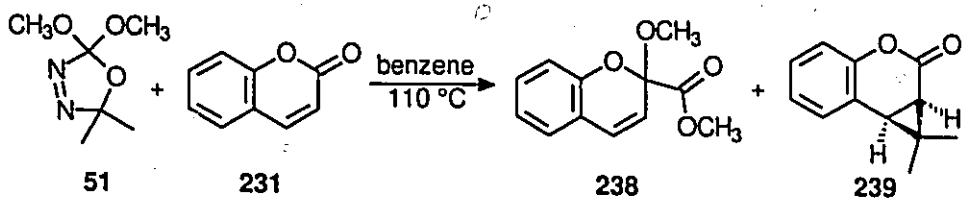
A thermolysis of **51** in the presence of **230** for 6 hours at 110 °C was performed. The ^{1}H-NMR of the crude reaction mixture (with solvent and volatiles removed and an internal standard added) showed a signal for **51** and a single methoxy signal (δ = 3.51) of approximately equal integration to the methoxy signal of the remaining oxadiazoline. The spectrum correlates very well (except in relative intensities) with the spectrum of the crude reaction mixture after 20 hours. This

methoxy singlet was assigned to the product **234** . Methoxy signals for **232** at this short thermolysis time were very small in comparison to those for **234** (20 % of the total thermolysis products). The yield by NMR of **232** was 10 % and of **234** was 39 % based on the measured 70 % decomposition of the oxadiazoline. A ^{13}C-NMR spectrum was obtained on the mixture. Since the signals for **51**, **230**, and **232** are known, the signals for the product **234** could be identified in the mixture. In addition to a signal at δ = 52.9 corresponding to a methoxy group, signals at 74.9 and 105.1 ppm were noted in the spectrum. In addition, the number of aromatic signals in the spectrum of the crude suggested that there was only one magnetically distinct fluorene fragment in the structure of **234**. Although inconclusive, these details are roughly in keeping with what would be expected from the ^{13}C-NMR spectrum of the oxirane **235**. The product **234** does not survive gas chromatography or silica gel chromatography, and thus further characterisation of **234** was not possible. The chemistry of **235** is also expected to fit with the observed high reactivity of this species towards hydrolysis. Other possible products include the adduct **236** which may have arisen from reaction of the dipoles **247** or **250** (see below) with fluorenone or the product **237** from coupling of dipoles. These products do not fit the NMR data as well as the oxirane **235**, however. Species **236** does not fit the ^{13}C-NMR information suggesting that the product has only one magnetically distinct fluorenone ring. The central six membered ring of species **237** is not expected to give rise to equivalent methoxy signals.



235 236 237

Coumarin (**231**) is a cyclic α,β-unsaturated ester which has the potential for trapping dimethoxycarbene by addition to either the C=C bond or the C=O bond. Dimethoxyoxadiazoline **51** was thermolyzed at 110 °C for 24 hours in the presence of a 5-fold excess of coumarin. The reaction was carried out in either sealed tubes with benzene solvent or under reflux in toluene. A product of this reaction (~ 15% isolated yield based on oxadiazoline) was isolated by radial chromatography and identified as **238** (Scheme 58). A very minor second product was isolated by radial chromatography and was identified as the cyclopropane **239**.

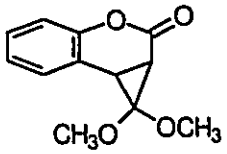


51 231 238 239

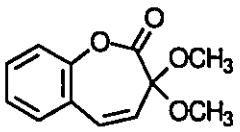
Scheme 58

The product **238** was characterised by means of its ^{1}H and ^{13}C NMR, IR, and mass spectra. Importantly, the product retained the vinyl signals of coumarin in both the ^{1}H and ^{13}C NMR spectra. These signals were shifted significantly to lower

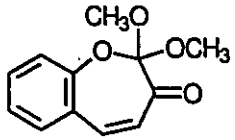
frequency ($\delta(CDCl_3)$ H_4 = 6.840 H_3 = 5.848) indicative of the loss of conjugation to the carbonyl group of coumarin. The long-range coupling in coumarin ($^5J_{4,8}$ = +0.65 Hz)[143] was also intact in the product ($^5J_{4,8}$ = 0.9 Hz) which lends support for retention of the coumarin skeleton in the product. The product is clearly not consistent with a cyclopropane structure such as **240**. Spectroscopy clearly shows a carbonyl group in the IR (1750 cm^{-1}) and in the ^{13}C-NMR ($\delta(CDCl_3)$ = 167.7). The e.i. mass spectrum shows $[M - OCH_3]^+$ at m/z 189 as the highest mass ion with $[M - CO_2CH_3]^+$ at m/z 161 as the base peak. The methoxy signals in the ^{1}H NMR spectrum were very different in chemical shift ($\delta(CDCl_3)$ = 3.843 and 3.311), the higher frequency signal corresponding to the methoxy group of an ester. Structures such as **241** or **242** corresponding to ring expansion were not consistent with the spectroscopic data. The proposed structure **238** clearly fits the spectroscopic data.



240



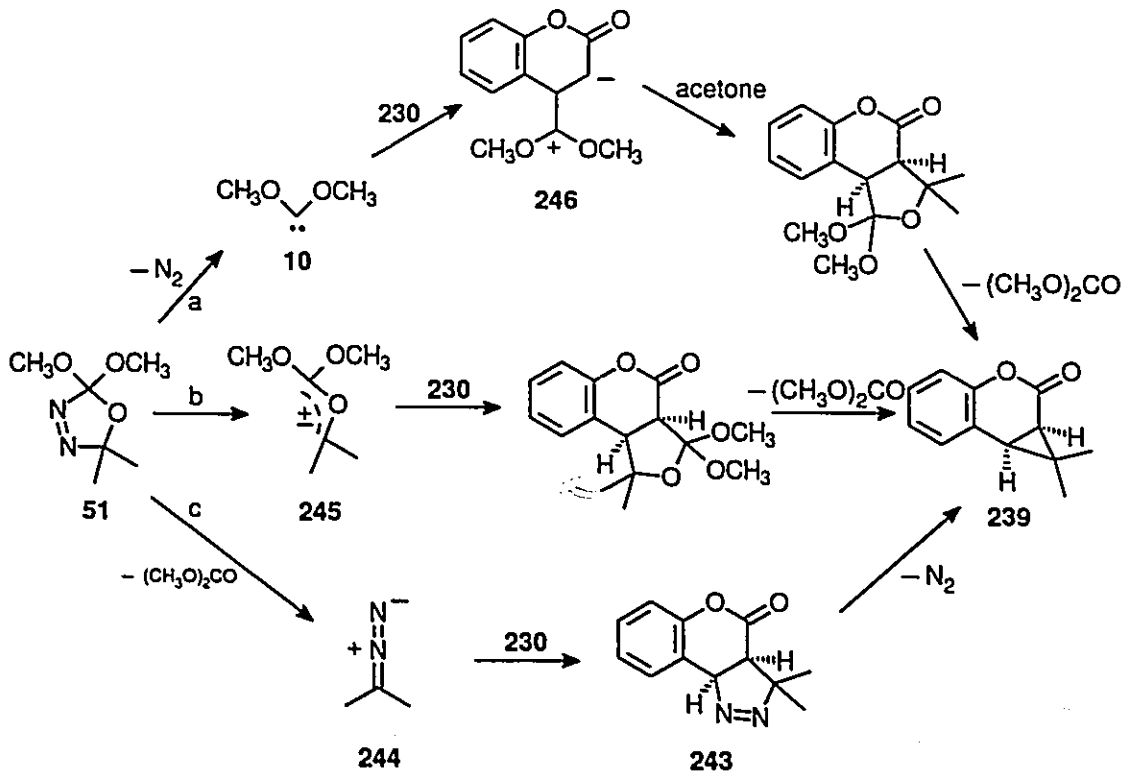
241



242

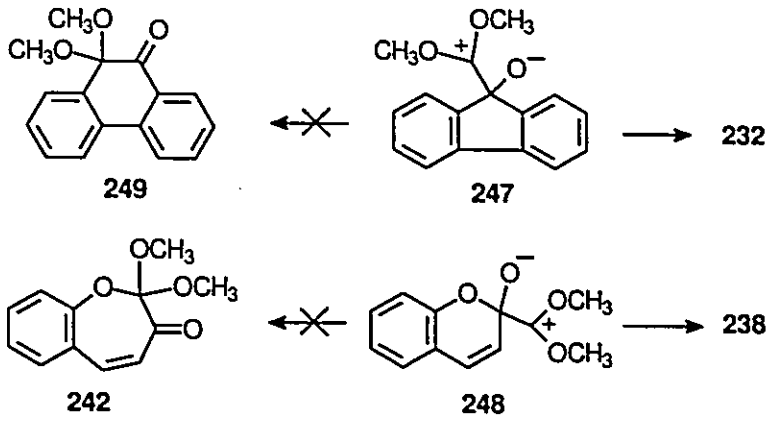
The product **239** was characterised by its mass spectrum and ^{1}H-NMR spectrum. The ^{1}H-NMR clearly shows the cyclopropyl hydrogens and the two distinct methyl groups. A ^{1}H-NMR spectrum of the crude reaction mixture from which the solvent had been removed, showed signals for the methoxy groups of **238** (23 % yield by NMR and based on oxadiazoline), but < 5 % of any other product with methyl groups. Thus, the product **239** is very minor, even in the crude reaction mixture. The

source of **239** is not clear. Of the many possibilities, the simplest—addition of dimethylcarbene to the C=C bond of coumarin—is the least likely. The extremely efficient 1,2-H migration of dimethylcarbene would make any intermolecular trapping of the carbene virtually impossible. Other likely scenarios are illustrated in Scheme 59. The fact that adducts such as **243** from 2-diazopropane (**244**) are not seen in other reactions of dimethoxycarbene with electron deficient traps would suggest that path c is unlikely. The formation of the carbonyl ylide **245** (path b) from loss of nitrogen from the oxadiazoline has some precedent,[48] but not for the oxadiazoline **51**. Path a which involves trapping of the zwitterion **246** with a molecule of acetone is also a possible route to the observed product. Our results at this time cannot distinguish among these possibilities.



Scheme 59

Other instances of reaction of dimethoxycarbene with the carbonyl group of a simple ketone (such as fluorenone) or a simple ester (such as coumarin) are not known. Formation of **232** and **238** from reaction of dimethoxycarbene with fluorenone and coumarin, respectively, are the result of carbenic attack on the carbonyl group followed by rearrangement. Addition of dimethoxycarbene (**10**) to the electron deficient carbonyl groups of **230** and **231** are likely to generate the dipoles **247** and **248** respectively.



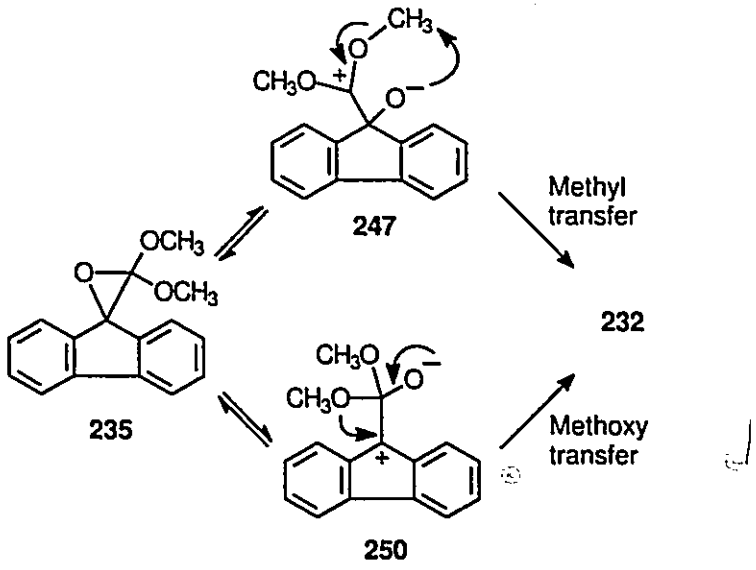
Scheme 60

The intermediates **247** and **248** are similar to those postulated in the previously reported reaction of dialkoxycarbenes with anhydrides (Scheme 51, above). The anhydrides reacted by collapse of the initially formed tetrahedral intermediate with 1,2-migration of a carboxylate group. The dipoles **247** and **248**, however, do not rearrange by a 1,2-migration. Ring expansion to a seven-membered ring **242** is not as favourable due to the high strain involved in creating a seven-membered ring (Scheme 60). Rearrangement of the zwitterion **247** by aryl group migration to give **249** is apparently not a favourable pathway in this system either (Scheme 60).

2.4.2 Isotopic Labelling Studies on the Formation of 232

There are two possible methods of group transfer to obtain **232** which are illustrated in Scheme 61—similar possibilities exist for production of the coumarin product **238**. Intramolecular methyl transfer in the dipole **247** can yield directly the

observed product. The zwitterion **247** is probably in equilibrium with the oxirane **235** and possibly the isomeric zwitterion **250**. 1,2-Methoxy transfer from **250** can directly yield **232**.

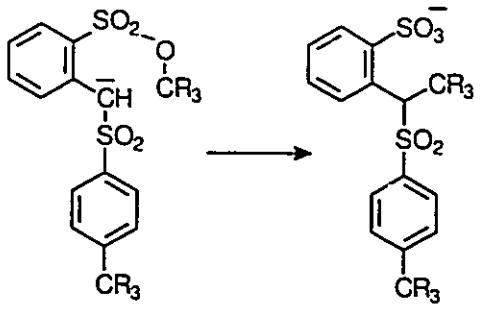


Scheme 61

Using the classification method developed by Baldwin,[144] one would classify the direct intramolecular methyl transfers of **247** and **248** to **232** and **238** as 5-*endo-tet* rearrangements. *Endo-tet* rearrangements are disfavoured for all ring sizes considered by the Baldwin Rules. The reasoning behind the rule is that the methyl transfer is an S_Ni reaction (i represents the fact that the reaction is intramolecular) which is essentially an intramolecular S_N2 reaction on the methyl group. The transition state of such a reaction requires a linear geometry between the nucleophile,

methyl carbon atom and the leaving group. This geometry is impossible to achieve even with fairly large ring sizes.

Methyl transfers of this sort are known in the literature, but they tend to occur in a bimolecular sense. Eschenmoser and co-workers have used isotopic labelling to examine methyl transfers from **251** to **252** (Scheme 62). A crossover experiment was employed in which the reaction was performed with 50% deuterated (R = D in Scheme 62) and 50% non-deuterated (R = H) precursor. On the basis of the observation of scrambling of the labels between the deuterated and non-deuterated compounds, they concluded that intramolecular rearrangement is disfavoured compared to a bimolecular reaction.[145] The geometry required for the *endo-tet* rearrangement transition state cannot be attained even in rings with up to seven atoms.[144] King and McGarrity used similar techniques to examine methyl transfers from **253** to **254** through 8-membered transition states. Even with the larger ring size, they did not find any evidence for intramolecular methyl transfer.[146]



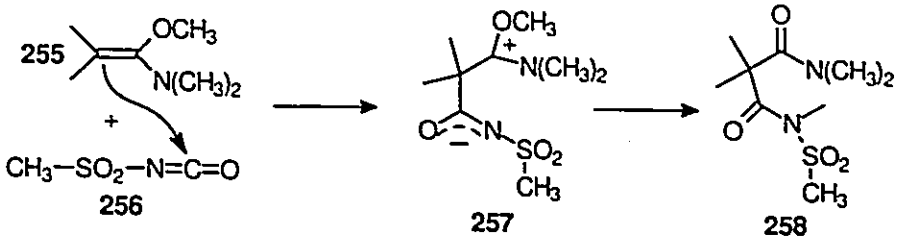
251 **252**

$(CR_3)_2N[CH_2]_4SO_2OCR_3 \longrightarrow (CR_3)_3\overset{+}{N}[CH_2]_4S\overset{-}{O}_3$

253 **254**

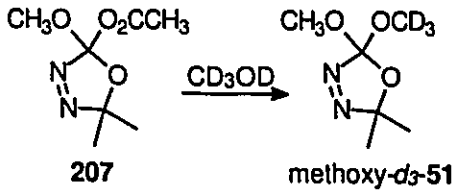
Scheme 62

Methyl transfers in dipolar species were studied by Shaumann and co-workers. These studies are important since the ionic intermediates studied by Shaumann are more similar to the intermediates **247** and **248** than those in the studies of Eschenmoser and King. Addition of ketene *O,N*-acetals[147] **255** to sulfonyl isocyanate **256** yields the 1,4-dipole **257** (Scheme 63). The dipoles undergo formal *O*→*N* methyl shifts to give the products **258**. Cross-over experiments in which scrambling of the label was observed confirmed that the rearrangement of the 1,4-dipoles **257** by methyl transfer was an intermolecular process. Similar chemistry has been studied by Shaumann from the reaction of sulfonyl isocyanates with N-alkylimidocarbonates.[148]



Scheme 63

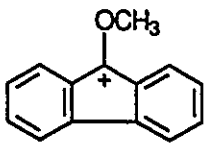
In the study of the reaction of dimethoxycarbene with fluorenone and coumarin, an attempt was made to distinguish between intramolecular methyl transfer, intermolecular methyl transfer and methoxy transfer by using isotopic labelling studies. The trideuterated dimethoxyoxadiazoline **51**-d_3 was prepared from exchange of the acetoxymethoxyoxadiazoline **207** with methanol-d_4 (Scheme 64).[55] A purely intramolecular rearrangement of zwitterions **247** or **248** should produce product with only one deuterated methoxy group. A purely bimolecular rearrangement, on the other hand, will result in 25% non-deuterated, 50% trideuterated and 25% hexadeuterated product (assuming a statistical distribution and ignoring any isotope effects on the rearrangement).



Scheme 64

The product from reaction of dimethoxycarbene with coumarin, **238**, does not have a molecular ion in either the e.i. or c.i. (NH_3) mass spectrum. The loss of $CH_3O^{\bullet}$ in these mass spectra prevents convenient determination of the degree of label crossover by analysis of the mass spectrum of the product. The product of fluorenone with dimethoxycarbene, however, has a molecular ion in both the e.i. and c.i. mass spectra. Thermolysis of trideuterated dimethoxyoxadiazoline **51**-d_3 in the presence of fluorenone under the same conditions as used previously yielded product which was found to have retained the isotopic distribution of the oxadiazoline in the molecular ion region. The observation that isotopic crossover does not occur is consistent with the formation of the product solely through an intramolecular rearrangement.

The possibilities of either intramolecular methyl transfer or methoxy transfer remain. The two mechanisms remaining can be resolved by ^{18}O labelling of the oxygen atom of fluorenone. The mass spectrum of the unlabelled product has a base peak at m/z 195 which corresponds to the ion **259** from loss of CO_2CH_3. The methyl transfer mechanism should retain the label in the m/z 195 ion while the methoxy transfer mechanism should lose the label. Analysis of the e.i. mass spectrum of the product should, therefore, distinguish between the two mechanisms.



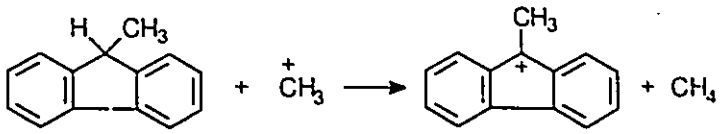
259

Fluorenone labelled with ^{18}O on the carbonyl was prepared by a literature method. A sample of 50% $H_2{}^{18}O$ was obtained from Prof. J. K. Terlouw.[149] Fluorenone with 42% ^{18}O was obtained by this method. Reaction of dimethoxycarbene with the labelled compound afforded labelled ^{18}O-**232**. The $^{16}O/^{18}O$ ratio of the molecular ion was 2.1:1 while the ratio of the fragment ion **259**was found to be 66:1. This corresponds to complete incorporation of the label onto the ester portion of the product **232**.

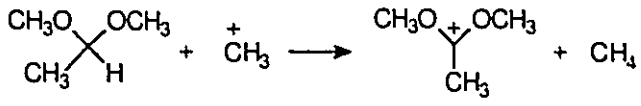
These labelling results conclusively show that the mechanism of group transfer to form **232** proceeds exclusively by methoxy transfer. The mechanism disfavoured by the Baldwin rules is eschewed in favour of methoxy transfer. A necessary consequence of these results is that the oxirane **235** must be an intermediate in the reaction. This is of considerable importance since this is the first evidence collected to suggest that an oxirane is an intermediate in the addition of dimethoxycarbene to a carbonyl group. As discussed earlier, the oxirane **235** can be identified in the crude reaction mixture. The identification of **235** and its requirement as an intermediate in the mechanism support each other. By analogy to the results of dimethoxycarbene addition to fluorenone, the mechanism for formation of **235** from addition of dimethoxycarbene (**10**) to coumarin (**231**) is likely proceed to by intramolecular methoxy transfer.

The dipoles **247** and **250** are both possible intermediates in the reaction of dimethoxycarbene with fluorenone. The data thus far do not provide any information on the relative stabilities of the two species. In most of the examples described in sections 2.2 and 2.3, the dipole formed formally from addition of dimethoxycarbene to the carbonyl group is the most stable since the cationic portion is stabilised by the electron donating methoxy groups. However, since the cationic portion of the dipole **250** is a fluorenyl cation, it is possible that this intermediate could be as stable or more stable than **247**.

Cationic stabilisation energies have been calculated to assess the relative stabilities of fluorenyl cations and dimethoxymethyl cations. Since the dipoles **247** and **250** both have similar anionic portions, the cationic portion of the dipole was modelled as a means of gauging the relative energies of the two dipoles. The isodesmic equations in Scheme 65 were used to assess the stabilisation energy (E_{st}) of 9-methylfluorenyl cation and 1,1-dimethoxyethyl cation relative to methyl cation.



AM1					E_{St} (kcal/mol)
ΔH_f (kcal/mol)	50.517	252.355	241.542	−8.777	70.107



AM1					
ΔH_f (kcal/mol)	−103.105	252.355	78.123	−8.777	79.704

Scheme 65

The enthalpies of formation of the species were calculated using the AM1 Hamiltonian in the Spartan computational package.[150] The stabilisation energies of the cations under study relative to methyl cation were calculated by the negative of the enthalpy of reaction for the isodesmic reaction (Scheme 65). The stabilisation energy of the 1,1-dimethoxyethyl cation is 9.8 kcal/mol greater than the stabilisation energy of the 9-methylfluorenyl cation. On the basis of these calculations, the dipole **247** is favoured relative to **250**. Thus, in an equilibrium between **247**, **235**, and **250**, the dipolar species **247** is expected to predominate over the dipolar species **250**.

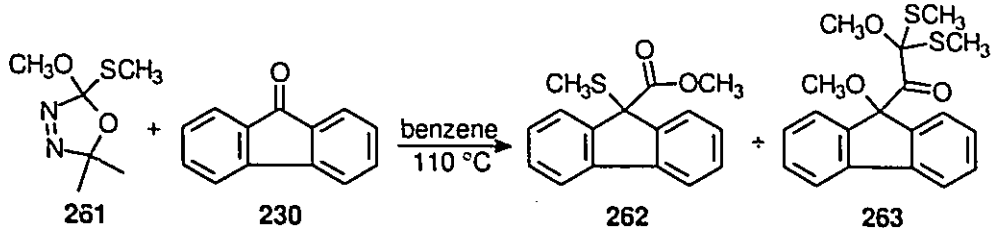
Also of interest is the regioselectivity for carbene attack on coumarin. Carbene addition to carbonyl is difficult to rationalize given the reported formation of the cyclopropane product from reaction of dimethoxycarbene (**10**) with ethyl cinnamate.[80] Under the conditions used in our studies, dimethoxycarbene generated from **51** reacts with ethyl cinnamate to yield the cyclopropane **71** (see Chapter 1,

Scheme 19). The spectral data of the observed product conforms to those expected for the known compound. Monocyclic cyclopropanes such as **71** are known to open to a zwitterion similar to those discussed in Chapter 1, Scheme 16.[84]

In cyclic systems the additional ring strain should facilitate ring opening. Thus, the cyclopropane formed between coumarin and dimethoxycarbene **10** would very likely be thermally unstable to the reaction conditions employed in this study. It is possible, therefore, that cyclopropanation is the kinetically favoured process, but is reversible under the reaction conditions. Alternatively, the ring strain may increase the barrier for the addition to the double bond until it is prohibitively high compared to carbonyl addition.

2.4.3 Reaction of Methoxy(thiomethyl)carbene with Fluorenone

In addition to the reaction of dimethoxycarbene with fluorenone, the reaction of methoxy(thiomethyl)carbene (**260**) with the carbonyl group of fluorenone was studied. Methoxy(thiomethyl)carbene has been shown by H. T. Er and J. Warkentin to result from thermolysis of 2-methoxy-2-thiomethyl-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**261**).[151,152] Heating a solution of **261** in the presence of fluorenone (**230**) at 110 °C for 20 hours yields two products identified as **262** and **263** (Scheme 66).



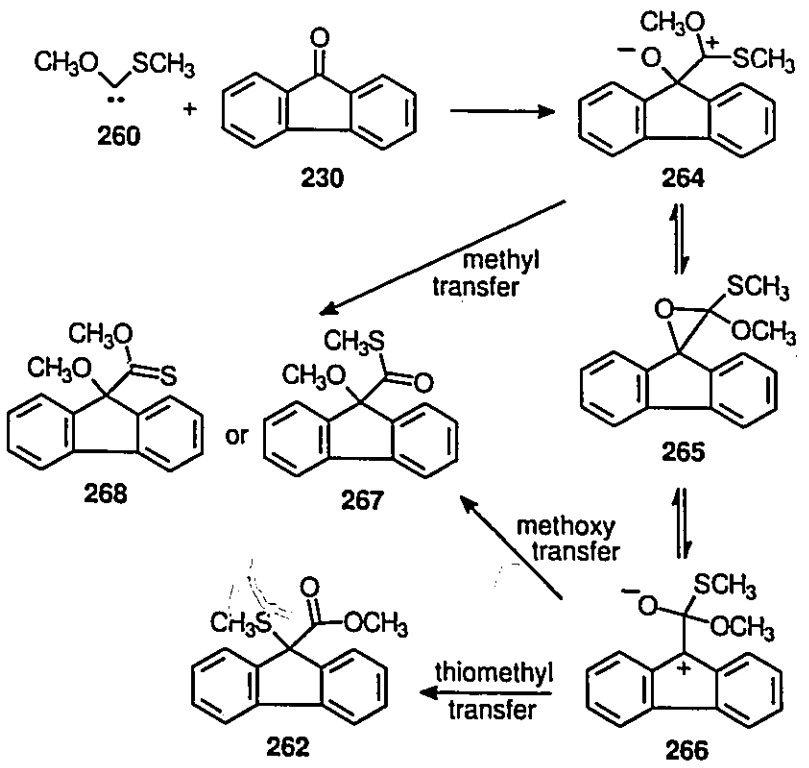
Scheme 66

The identity of **262** was established by its mass spectrum and ^{1}H-NMR and ^{13}C-NMR spectra. The compound was separated by radial chromatography, but co-eluted with fluorenone. The product **262** was characterized as a mixture by NMR by subtracting the known signals for fluorenone. The ^{1}H-NMR spectrum of the mixture shows a singlet at 3.66 ppm corresponding to a methoxy group and at 1.56 ppm corresponding to a thiomethyl group. The chemical shift of the methoxy group is in keeping with the ester methoxy of the dimethoxycarbene adduct with fluorenone **232**. The ^{13}C-NMR spectrum also contains signals at 12.3, 53.0, and 62.6 ppm corresponding to the thiomethyl, methoxy, and C-9 carbon atoms respectively. The mass spectrum has a molecular ion and shows losses of both thiomethylcarbonyl at m/z 195 and methoxycarbonyl at m/z 211. Based on analogy to the mass spectrum of **232**, the loss of thiomethylcarbonyl was not expected for the structure **262**. This ion must arise from a more complicated rearrangement involving initial loss of thiomethyl (fragment at m/z 223) followed by an extrusion of carbon monoxide.

The product **263** was identified based on its mass, ^{1}H-NMR and ^{13}C-NMR spectra. Isolation of the product was possible by radial chromatography. The ^{1}H-

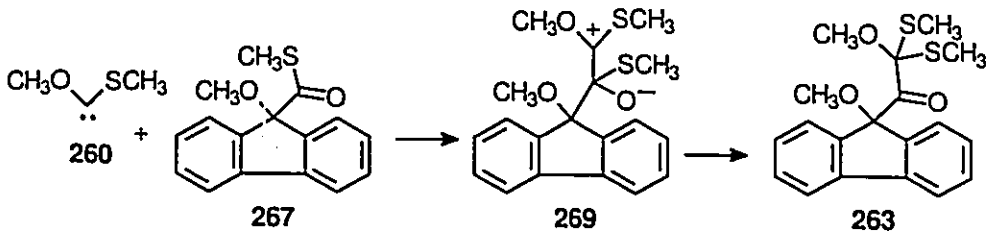
NMR of the product showed two methoxy signals and one thiomethyl signal. The mass spectrum of the product showed that the product was an adduct of one molecule of fluorenone with two units of the carbene. The ^{13}C-NMR of the compound also was in keeping with the product **263**.

The origin of the two products **262** and **263** can be rationalized in terms of competition between thiomethyl transfer and methyl transfer. The product **262** is analogous to the product **232** in the reaction of dimethoxycarbene with fluorenone. The initially formed zwitterion **264** closes to the oxirane **265** and reopens to the isomeric dipole **266** (Scheme 67). This dipole is readily set up for competitive migration of the methoxy and thiomethyl groups to the cationic centre. Thiomethyl migration is expected to be far faster than methoxy migration because of the greater stability of the sulfur anion. This is demonstrated by the greater acidity of RSH (pKa = 10-11) compared to ROH (pKa = 15).[109] The product **262**, thus, is expected over the product of methoxy transfer **267**. The preferential migration of thiomethyl groups over methoxy groups in the reactions of similar tetrahedral intermediates has been observed in our lab by D. L. Reid.[153]



Scheme 67

The product **263** must arise from reaction of methoxy(thiomethyl)carbene **(260)** with the initial product **267**. Attack on the thioester **267** results in the formation of a tetrahedral intermediate **269** which collapses with migration of the thiomethyl group to yield **263** (Scheme 68). The thioester **267** was not isolated from the reaction mixture. Reaction of the carbene with a primary product is reasonable when the primary product contains a functional group which is more reactive towards the carbene than the initial carbene trap. The thioester **267** is expected to be a more reactive carbonyl group than the carbonyl group of fluorenone **230** and thus can be expected to compete for dimethoxycarbene.



Scheme 68

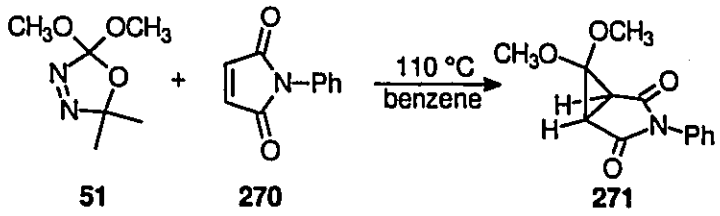
The origin of **267**, in turn, is of some interest. There are two possible pathways for formation of **267** as illustrated in Scheme 67. Either methyl transfer from the dipole **264** or methoxy transfer from **266** could yield **267**. As discussed previously, however, methoxy transfer from **266** is not expected to be competitive with thiomethyl migration. Additionally, methyl transfer from **264** would be expected to yield **268** rather than **267** (Scheme 67) since the thioalkyl group would be expected to be more susceptible to nucleophilic attack. Although intramolecular methyl transfer is disfavoured by the Baldwin Rules, the order of the reaction has not been established with this system—intermolecular and intramolecular methyl transfers must be considered.

2.5 The Regiochemistry of Dimethoxycarbene Reaction with α,β-Unsaturated Carbonyl Compounds

The study of other cyclic α,β-unsaturated carbonyl compounds as dialkoxycarbene traps is of significant interest. A variety of maleic anhydrides,

coumarin, and benzalphthalide have been studied above. Each of these compounds have C=C bonds conjugated to the carbonyl groups. The regiochemistry of dimethoxycarbene addition to coumarin is discussed above. These compounds have shown a preference for attack at the carbonyl group rather than Michael addition to the C=C bond. The study of other related systems in which Michael addition is preferred by dialkoxycarbenes may allow us to speculate on the factors controlling the regiochemistry of carbene addition to these compounds in general.

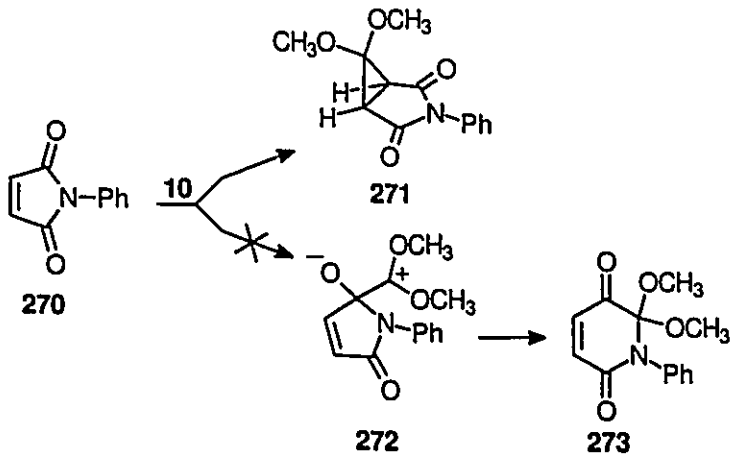
To this end, N-phenylmaleimide (**270**) was studied and was also found to be a good trap for dimethoxycarbene (**10**). Despite the structural similarity of the maleimide to maleic anhydride, formation of the analogous product was not observed with **270**. The structure of the product of carbene addition to **270** was the cyclopropane **271** resulting from [2 + 1] cycloaddition of the carbene onto the double bond (Scheme 69). The analogous cyclopropane product was not observed in the case of addition of dimethoxycarbene to maleic anhydride. It is interesting to recall that in Hoffmann's original work on the chemistry of dimethoxycarbene, he reports that adducts of **10** with maleic anhydride and N-phenylmaleimide were not observed.[80]



51 **270** **271**

Scheme 69

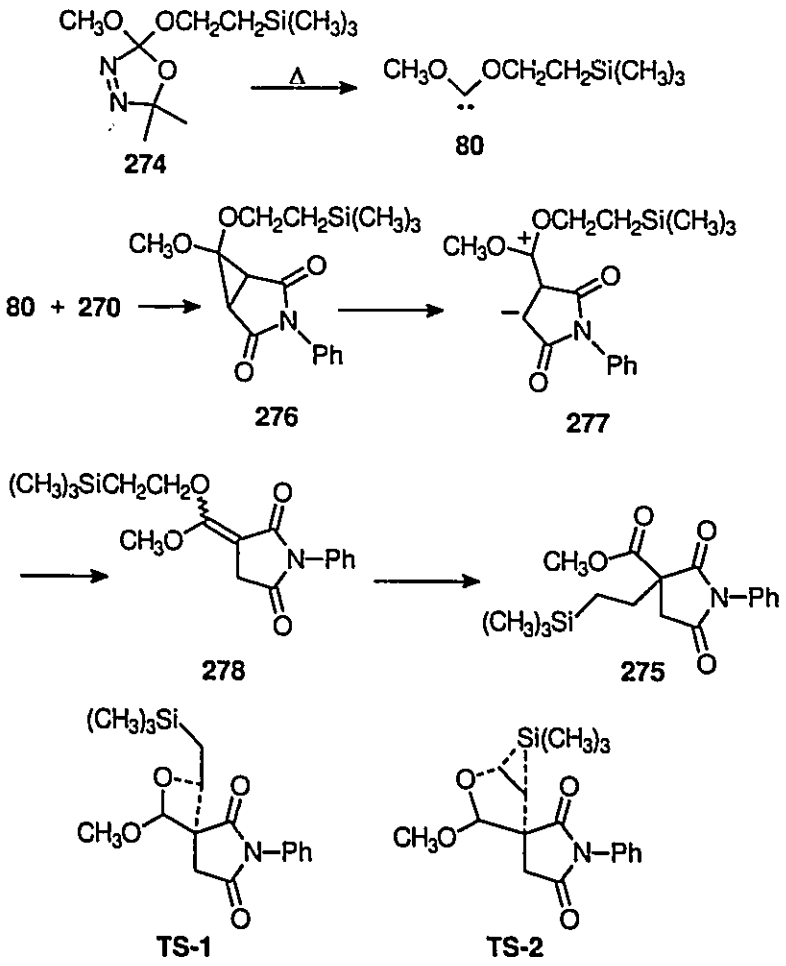
The reaction of **10** with N-phenylmaleimide is the only instance of dimethoxycarbene addition to the C=C bond of a cyclic α,β-unsaturated carbonyl compound that has been found. The carbonyl groups of N-phenylmaleimide are deactivated compared to those of maleic anhydride which is certain to decrease the rate of addition of **10** to the carbonyl group of **270**. Carbonyl addition should yield the zwitterion **272** which could rearrange by a 1,2-N shift to give the ring expanded product **273** (Scheme 70). Evidence of this type of process was not observed in this system.



Scheme 70

Related results have been obtained by Pole, Sharma, and Warkentin for the reaction of methoxy(2-trimethylsilylethoxy)carbene (**80**) with N-phenylmaleimide (**270**).[154] A product from the thermolysis of the oxadiazoline **274** in the presence of **270** was isolated by P. K. Sharma and was found to have the structure **275** (Scheme 71). This is clearly not a primary product. It must arise from addition of the

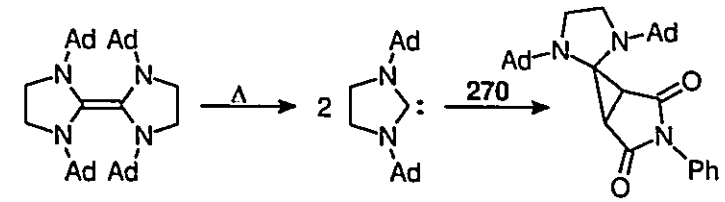
dialkoxycarbene to the C=C bond of the maleimide to yield **276** which is similar to that which occurred in the addition of dimethoxycarbene to **270**. As discussed in Chapter 1, the initial cyclopropane product is often unstable[84] and in this case **276** would be expected to open to the zwitterion **277** and rearrange by a proton migration to give the ketene acetal **278**. Based on the structure of **275**, the ketene acetal must have undergone a further rearrangement of the β-silylalkyl group to give **275** (Scheme 71). The mechanism of this last migration is speculated to be either a 1,3-alkyl transfer with a transition state such as TS-1 or a 2,3-Wittig-type migration involving a silicon 'bridged' transition state, TS-2. The transition states for both mechanisms feature a silyl stabilised cationic fragment and an enolate-like anionic fragment. Evidence for bridging in β-silylethyl cations is known in the literature.[155-157]



Scheme 71

A product similar to the cyclopropane **271** was found in the literature for the reaction of the tetraaminoethene **279** with N-phenylmaleimide (**270**). Thermolysis of **279** in the presence of **270** yields the product **280** which is formally the result of addition of the diaminocarbene **281** across the double bond of the maleimide (Scheme 72).[158] The intermediacy of the free carbene in this case is uncertain, but the structure

of the product is analogous to those observed for the chemistry of dimethoxycarbene (**10**) and methoxy(2-trimethylsilylethoxy)carbene (**80**).



279 **281** **280**

Ad = 1-adamantyl

Scheme 72

Overall, carbene addition to α,β-unsaturated carbonyl groups can be described in terms of two competing rates—the rate of carbonyl addition and the rate of Michael addition. It has been observed that most nucleophiles attack α,β-unsaturated carbonyl compounds with a preference for one pathway over the other. These selectivities are often explained in terms of the frontier molecular orbitals of the system.

In Fleming's book,[106] an interpretation of the regioselectivity of nucleophilic addition to α,β-unsaturated carbonyl compounds was provided in terms of two competing considerations—frontier orbital overlap and electrostatic attraction. Nucleophilic dimethoxycarbene (**10**) should be sensitive to the coefficients of the LUMO of the substrate. Maleic anhydride and N-phenylmaleimide, however, both have the majority of the LUMO density on the C=C double bond (see Figure 11) and yet their chemistry towards dimethoxycarbene is very different. The addition of dimethoxycarbene to the carbonyl group of a variety of maleic anhydrides cannot

readily be explained in terms of frontier orbital overlap alone. Clearly some consideration must be given to the electrostatic attractions as well.

According to the principal of hard and soft acids and bases (HSAB),[159] the reactions of nucleophiles and electrophiles are controlled to different extents by either electrostatic attraction or orbital overlap. Those species for which reactions are dominated by electrostatic forces are referred to as being 'hard' and those which are dominated by orbital overlap are referred to as being 'soft'. The principal of HSAB states that hard nucleophiles prefer to react with hard electrophiles and soft nucleophiles prefer to react with soft electrophiles.

By this definition, hard nucleophiles will preferentially react with α,β-unsaturated carbonyl compounds at the carbonyl group while soft nucleophiles will tend to attack in a Michael sense. Thus, dimethoxycarbene is acting as a hard base in its reaction with maleic anhydride and a soft base in its reaction with N-phenylmaleimide. Since both modes of attack are observed, the regiochemistry seems to be controlled by a combination of orbital overlap and electrostatic attractions. It seems reasonable that orbital overlap dominates the chemistry of dimethoxycarbene (soft base) until electrostatic attractions to the carbonyl group become very strong. The reaction of dimethoxycarbene as a hard base is atypical since an uncharged nucleophile tends to be soft. For example, carbenes such as dichlorocarbene or the Simmons-Smith reagent tend to display the properties of a soft electrophile.[106]

In order to attempt to answer some of the questions surrounding the regiochemistry of dimethoxycarbene addition to α,β-unsaturated carbonyl compounds, quantum mechanical calculations have been performed on the ground and transition states involved in these reactions. The results described here are preliminary, but show promise that *ab initio* quantum mechanical calculations may be of use in addressing some of the issues raised above.

The reaction of dihydroxycarbene with maleic anhydride and maleimide has been studied as a model reaction using the RHF/3-21G basis set available in the Spartan computational package.[150] Frontier orbital co-efficients have been calculated for maleic anhydride and maleimide and are shown in Figure 11. Geometry optimizations have been performed on the three conformations of dihydroxycarbene (the W, S, and U conformers). Transition states have been calculated for the reaction of dihydroxycarbene with the C=O and C=C bonds of both maleic anhydride and maleimide. The transition states are shown below (**TS-A**, **B**, **C**, and **D**). The transition states have been characterized by a frequency analysis which revealed one imaginary vibrational frequency corresponding in magnitude and in direction to the reaction co-ordinate.

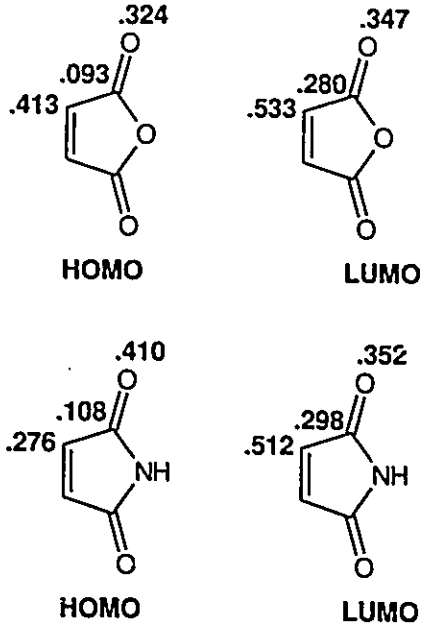
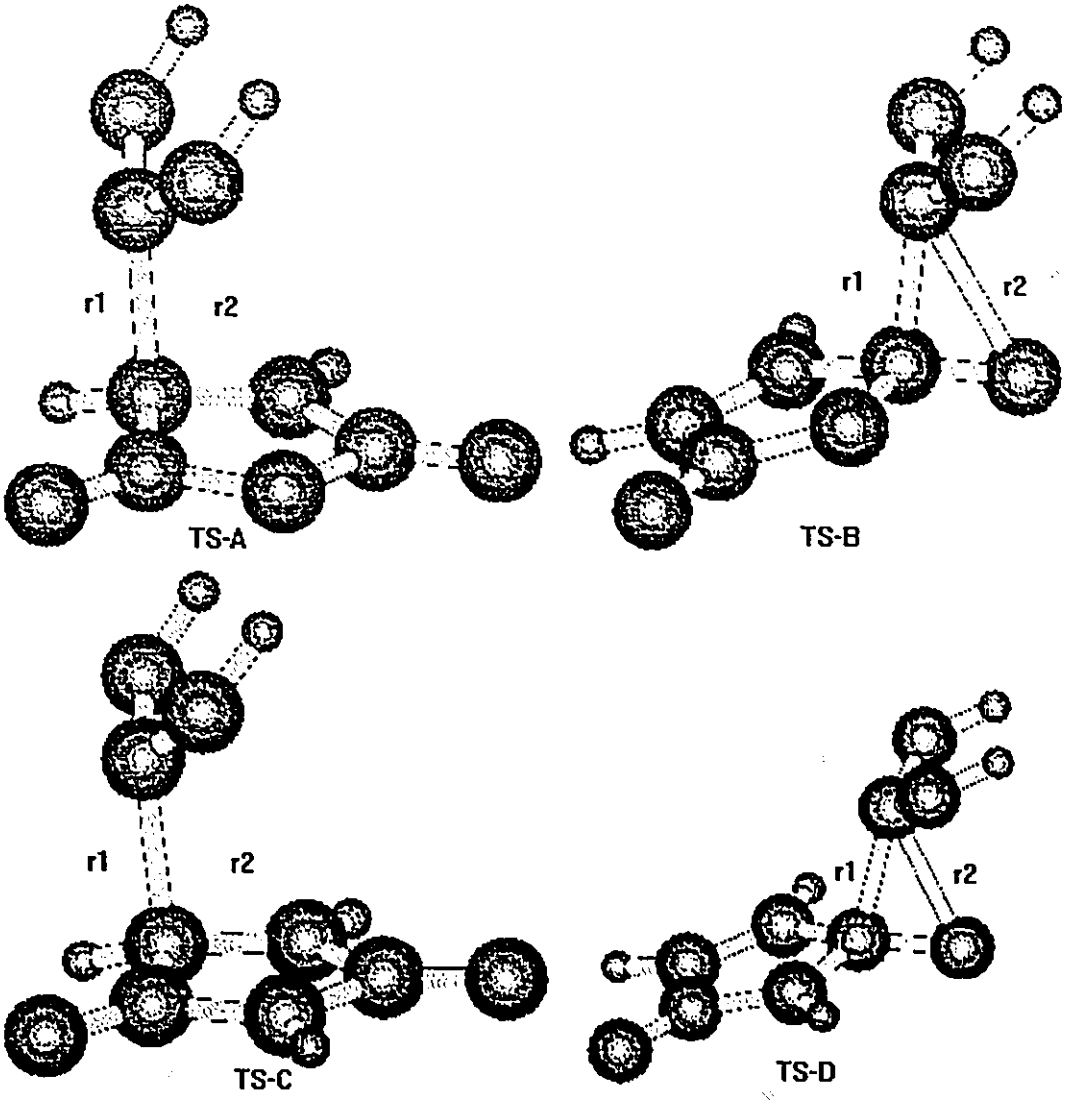


Figure 11

As expected from previous studies,[10,92] the transition states are unsymmetric for addition of dihydroxycarbene to both the C=C and C=O double bonds. Table 5 shows the distances r^1 and r^2 which are defined as the distances from the carbene carbon atom to the nearest and farthest atom, respectively, of the double bond. The degree of asynchronicity in the transition state can be assessed by examining the difference in r^1 and r^2.



The geometries of the transition states **A-D** suggest that bonds from the carbene carbon atom to both atoms of the double bond have been formed for both carbonyl and olefin addition. The transition states for dihydroxycarbene addition to the C=O bonds are more synchronous than addition to the C=C bonds. **TS-B** and **TS-D** show shorter bond lengths with the carbonyl carbon atom than with the oxygen atom. This is in keeping with a nucleophilic reaction of the carbene with the carbonyl

group. The formation of both bonds in the transition state—even if the formation is non-synchronous as observed here—is indicative of a concerted addition of dihydroxycarbene to the double bonds in this study. These results support the idea of an asynchronous, but concerted, nucleophilic attack of the carbene onto both the alkene and carbonyl double bonds.

Table 5. Calculated Transition State Bond Lengths and Energies for Reactions of Dihydroxycarbene with Maleic Anhydride and Maleimide

Species	Basis Set	r^1 (Å)	r^2 (Å)	Energy (hartrees)	ZPVE (kcal/mol)	Corrected Energies (hartrees)
215a	3-21G			-375.1035	38.036	-375.044
270	3-21G			-355.3996	46.797	-355.327
50-W	3-21G			-187.6377	21.770	-187.604
50-S	3-21G			-187.6412	21.597	-187.607
50-U	3-21G			-187.6245	20.684	-187.592
TS-A	3-21G	1.86	2.50	-562.7000	60.045	-562.606
TS-A	6-311G*			-566.0127		-565.919
TS-B	3-21G	1.72	2.17	-562.6940	59.824	-562.601
TS-B	6-311G*			-566.0176		-565.924
TS-C	3-21G	1.85	2.44	-542.9923	68.789	-542.885
TS-C	6-311G*			-546.1855		-546.078
TS-D	3-21G	1.76	2.04	-542.9836	68.290	-542.877
TS-D	6-311G*			-546.1831		-546.076

The energies of the reactants and transition states were calculated and are tabulated in Table 5. Zero-point vibrational energies are also tabulated for each of the compounds studied. The total energy of the molecules are corrected for their zero-point vibrational energy and these values are also tabulated. Single point calculations were performed on the four transition states **A-D** using the RHF/6-311G* basis set. The energies from these calculations are also tabulated.

The relative energies of the transition states should reflect the experimentally observed regioselectivity. Thus the transition state for carbonyl addition to maleic anhydride should be lower in energy than that for alkene addition and the transition state for alkene addition to maleimide should be lower in energy than that for carbonyl addition. From the RHF/3-21G results in Table 5, the transition state energies show that the transition state for reaction of dihydroxycarbene with the alkene of maleic anhydride is lower in energy than that for carbonyl addition by 3.55 kcal/mol (difference in corrected energies from Table 5 × 627.5 kcal/mol·hartree). The transition state for reaction of dihydroxycarbene with the alkene of maleimide is also lower in energy than that for carbonyl addition by 4.97 kcal/mol. Thus, the calculated results for dimethoxycarbene addition to maleic anhydride are not in agreement with the experimental results.

The preference for alkene addition to maleimide is larger than the preference for alkene addition to maleic anhydride. This is in keeping with the experimental observation that addition to the alkene of maleimide is preferred over addition to the double bond of maleic anhydride.

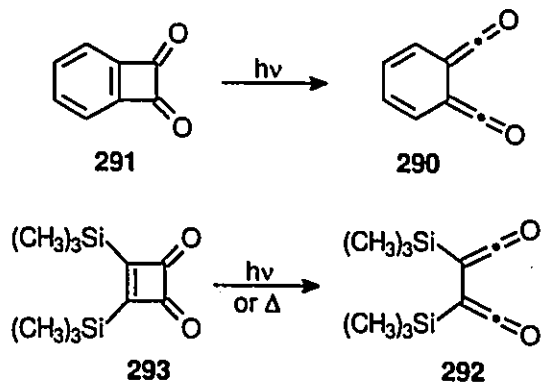
A possible reason for the discrepancies in the energies is that the level of theory employed was not sufficient to represent the transition states of these species. We've explored this likely possibility. The transition states **A-D** for these reactions are likely to be highly polarized and probably possess partial ionic character. It is likely, therefore that a basis set which includes polarization functions on the first row

elements would better describe the energy of the transition states.[160,161] Due to the computational limitations involved in performing high level calculations on such large molecules, full geometry optimizations at a higher level were not possible. Single point calculations were performed using the RHF/6-311G* basis set on the geometries optimized using the RHF/3-21G basis set. The single point energies for the transition states are tabulated in Table 5. The energy differences provide results in better keeping with the observed regiochemistry. The transition state for carbonyl addition to maleic anhydride is now 3.11 kcal/mol lower in energy than alkene addition and the transition state for alkene addition to maleimide is 1.48 kcal/mol lower in energy than carbonyl addition. It should be noted that the differences observed in the relative energies, although experimentally significant, are small from a computational point of view and thus may be subject to significant computational errors.

It is also important to note that the larger basis set used may cause geometrical changes for the same reasons given for the changes observed in the relative energies. It is difficult to draw strong conclusions from the single point calculations described above. It is reassuring, however, that the RHF/3-21G calculations yield results which reflect reasonable geometrical parameters for the ground and transition states of these reactions. Further work is necessary to resolve the difficulty in using the relative energies of the transition states as a means to predict regioselectivity.

2.6 Addition of Dimethoxycarbene to 1,2-Bisketenes

A 1,2-bisketene is a highly reactive carbonyl compound which is composed of two ketene groups conjugated to each other. Bisketenes such as **290** are known from the photolysis of benzocyclobutenediones **291** (Scheme 73).[162,163] As with most ketenes, species such as these are highly reactive intermediates. Recently, Tidwell and coworkers at the University of Toronto have synthesized silicon-substituted 1,2-bisketenes such as **292** from thermolysis of the cyclobutenedione **293** and found that the bisketenes are stable compounds at room temperature in an inert atmosphere (Scheme 73).[164,165]



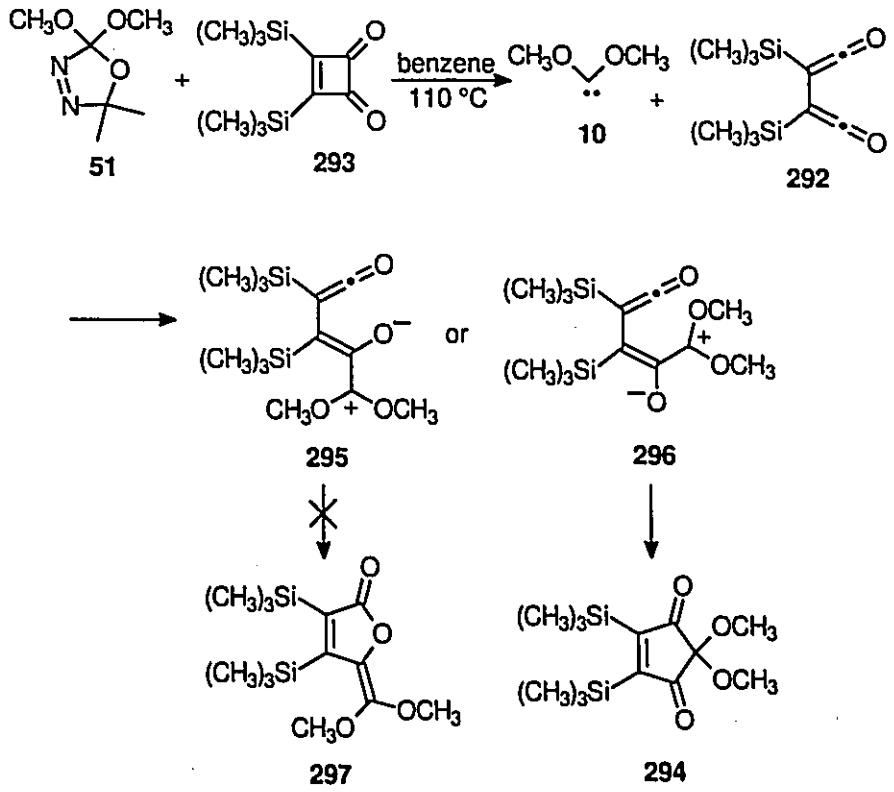
Scheme 73

Since ketenes have strongly electrophilic carbonyl groups, they are expected to react readily with nucleophiles such as dimethoxycarbene (**10**). Thermolysis of dimethoxyoxadiazoline **51** in the presence of the dione **293** should generate the bisketene **292** and dimethoxycarbene (**10**) together in the thermolysis vessel.

A co-thermolysis of dimethoxyoxadiazoline **51** and **293** (a sample of which was provided by T. T. Tidwell) in benzene solvent was performed at 110 °C for 20 hours in a sealed tube. It was possible to isolate a single product (62 % yield) from the reaction which had spectral data corresponding to the structure **294**. The spectral data showed one methoxy signal and one $(CH_3)_3Si$ signal in the ^{1}H-NMR spectrum. One vinyl signal, one carbonyl signal and one $(CH_3)_3Si$ signal were also apparent in the ^{13}C-NMR spectrum. The mass spectrum contained a molecular ion which was used to measure the exact mass of the compound. Tidwell and co-workers had also made this compound independently from another source. The spectral characteristics matched those obtained by Tidwell[166] which provided further support for the structure.

The product **294** is the product of formal [4 + 1] cycloaddition of dimethoxycarbene to the 1,2-bisketene. Based on several precedents from Tidwell and co-workers, the reaction is probably not a concerted [4 + 1] cycloaddition.[166] The addition of dimethoxycarbene most likely occurs onto the sp-hybridized carbon atom of one of the ketene groups to yield an ionic species. As shown in Scheme 74, this zwitterion can exist as two geometrical isomers **295** and **296**. The product **294** results from closure of **296** to yield the product of overall [4 + 1] addition to the bisketene. The isomeric zwitterion **295** should close to yield the methylenecyclopentene **297**, but evidence for this product was not found in the analysis of the reaction mixture. The formation of zwitterion **295** or **296** is controlled

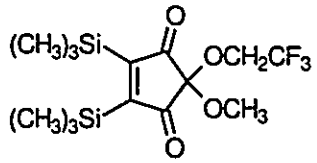
by steric factors. Attack of the carbene onto the sp-hybridized carbon atom can occur *syn* to either the trimethylsilyl group (to give **295**) or the ketene group (to give **296**). In keeping with studies of other reactions of these 1,2-bisketenes, the trimethylsilyl group is bulkier than the ketene group and thus ionic intermediates resulting from attack of nucleophiles adjacent to the ketene group are preferred.[166]



Scheme 74

The reaction of methoxy(2,2,2-trifluoroethoxy)carbene **31** with the 1,2-bisketene **292** was also attempted. A co-thermolysis of methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** and **293** in benzene solvent was performed at 110 °C

for 20 hours in a sealed tube. GC and GC/MS analysis of the reaction mixture indicated that the reaction mixture was far more complicated than the previous reaction. A product **298** which is analogous in structure to **294** was isolated in 10 % yield.



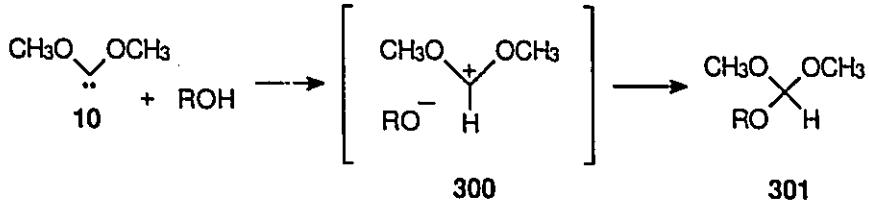
298

The reaction of **10** and **31** with **292** is demonstrative of another type of carbene addition to carbonyl groups. The formation of a zwitterionic intermediate is again featured in the reaction mechanism. In this instance, however, the anionic portion of the zwitterion is conjugated to the remaining π-system which results in the formation of cyclic products such as **294**.

2.7 Reaction of Dimethoxycarbene with Activated Methylene Compounds

Investigations of the reactions of carbenes with alcohols and phenols has resulted in a better understanding of the mechanistic processes involved in insertion of carbenes into the O–H bond.[110] As discussed in Chapter 1, significant evidence exists to support the idea that nucleophilic carbenes such as dimethoxycarbene (**10**, Scheme 75) abstract the O–H proton of alcohols to generate an ion pair (**300**) which collapses

to yield an orthoformate **301**. The measurement of absolute rate constants for the reaction of dimethoxycarbene with a variety of alcohols has revealed a correlation between the carbene quenching rate constant and the pKa of the alcohol.[45] Additionally, a large primary deuterium kinetic isotope effect (k_H/k_D = 3.3) has been measured for the insertion of dimethoxycarbene into the O–H bond of methanol.[115]

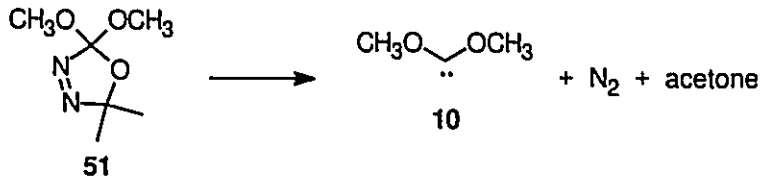


Scheme 75

Since proton abstraction by the carbene produces the anion and cation in intimate contact, the ion pair **300** is classified as a contact ion pair. Proton abstraction by a carbene is an excellent method for the generation of ion pairs of this sort. The spectroscopic detection of the cationic intermediates resulting from protonation of other carbenes has been achieved using laser flash photolysis.[112,114,167,168]

Reports of addition of nucleophilic carbenes to compounds with a high enol content have not appeared. Deprotonation of an enol by a nucleophilic carbene should yield an enolate and a stabilized carbocation. Collapse of this ion-pair should then be possible on either the oxygen or the carbon of the enolate.

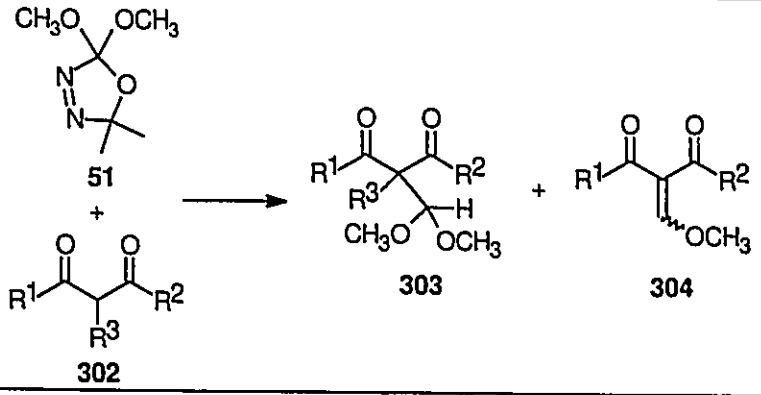
The dimethoxycarbene precursor 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**, Scheme 76)[54] was used to generate dimethoxycarbene (**10**) in the presence of several β-dicarbonyl compounds **302a-d.** A solution of dimethoxyoxadiazoline (0.05 M) in dry benzene was prepared containing one equivalent of a β-dicarbonyl compound. The solution was sealed in a resealable thermolysis tube and heated in a thermostated oil bath at 110 °C for 20 hours.

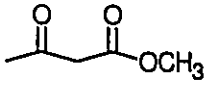
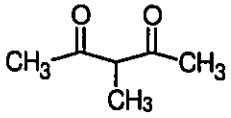
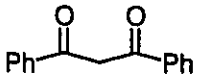
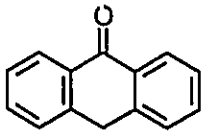


Scheme 76

The major products (**303**, Table 6) arose, formally, from carbene insertion into the C–H bond of the keto tautomer of **302a-d.** In the cases of **302a** and **b**, the reaction mixture also contained the products **304a** and **304b** which arose from elimination of methanol from, respectively, **303a** and **303b**. Product **304b** was a mixture of *E*- and *Z*-isomers in roughly equal proportions. The reaction mixture from trapping with **302c** contained no such product because the methyl group at R^3 blocked elimination. The ratio of initial trapping products (**303**) to products of methanol loss (**304**) was 2.2:1 and 4.7:1 respectively for 2,4-pentanedione and methyl acetoacetate. Yields based on oxadiazoline for the carbene-derived products are given in Table 6.

Table 6. Yields of Products of Dimethoxycarbene Trapping **303a-d**, **304a-b**, and **306** with Activated Methylene Compounds **303a-d** and **305**.



Compound	Trap	Product	Yield[a]
302a		**303a** **304a**	17 8
302b		**303b** **304b** (E,Z isomers)	29 14
302c		**303c**	26
302d		**303d**	56
305		**306**	30

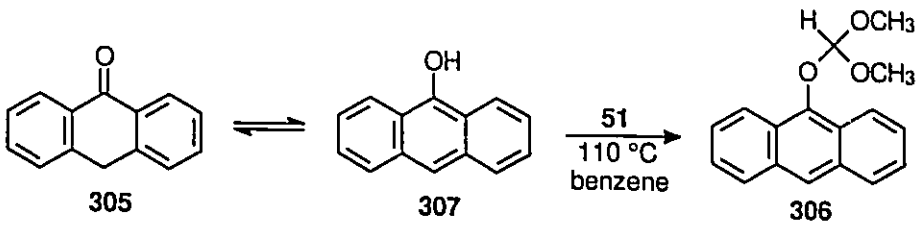
[a] Yield by NMR and based on oxadiazoline.

The crude samples from trapping with **302a-c** were analyzed directly by GC and GC/MSD. The products of carbene trapping were further characterized by NMR spectroscopy. The reaction products resulting from trapping with **302a-c** were purified by removal of the solvent and the excess β-dicarbonyl compound under

vacuum. Reaction mixtures containing more than one product were characterized as a mixture. The product from carbene trapping by **302d** was identified by ^{1}H-NMR spectroscopy on the reaction mixture which contained excess trap. A relatively pure sample of **303d** was obtained by conducting a thermolysis with a three-fold excess of oxadiazoline **51**. This caused the total conversion of **302d** to product **303d**.

The mixtures resulting from trapping of **10** by **302a** and **b** could be converted entirely to the products of methanol loss by adding pyridine (5 μl in 25 mL) and reheating the mixture to 110 °C for 20 hours. It should be noted that addition of pyridine prior to thermolysis (so that it is present during carbene generation) resulted in a very low yield of any carbene-derived products, probably because of some reaction of the carbene with pyridine.[33]

Similar methods were used to examine the trapping of **10** with anthrone **305**. Solutions of 0.05 M oxadiazoline and one equivalent of anthrone **305** were heated at 110 °C for 20 hours. The reaction mixture revealed a single anthrone-derived product **306** which results formally from insertion of dimethoxycarbene into the O–H bond of 9-anthranol (**307**), the enol tautomer of anthrone (Scheme 77). The yield of **306** was measured on a sample to which a single drop of pyridine had been added to the thermolysis tube prior to thermolysis in order to facilitate tautomerization to the anthrone to the enol tautomer.

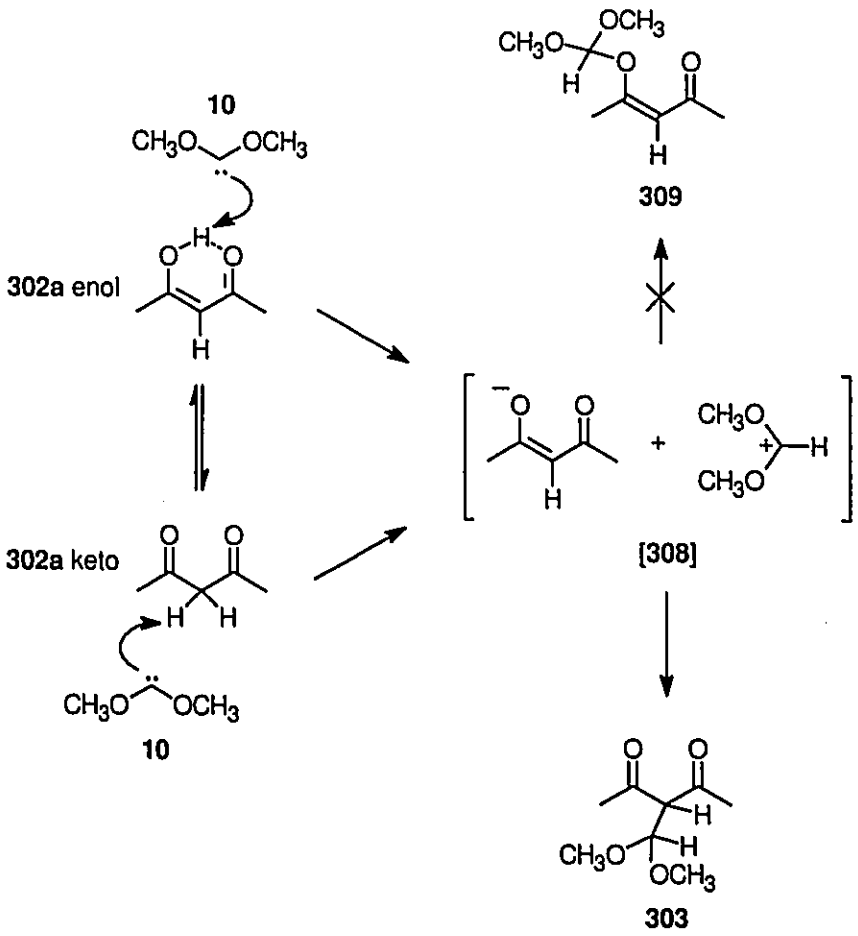


Scheme 77

Trapping studies with other β-dicarbonyl compounds were carried out. Methyl cyanoacetate (**302e**), malononitrile (**302f**) and dimethyl malonate (**302g**) all proved to be ineffective agents for trapping of dimethoxycarbene. Although similar conditions were used in order to investigate trapping of **10** by **302e-g**, only minor amounts of likely products of trapping could be detected in the GC/MSD traces of the crude reaction mixtures. Addition of various amounts of pyridine seemed to have little effect on the trapping efficiency of **302e-g**.

Since carbonyl compounds **302** exist in an equilibrium with their enolic forms, there are two pathways, both involving proton abstraction, to achieve overall C–H insertion (Scheme 78). As discussed above, there is a body of evidence to suggest that the insertion reactions of dialkoxycarbenes are stepwise in nature and progress through an ion-pair intermediate. For example, proton abstraction from the keto form of **302a** should yield an ion-pair intermediate **308**. Collapse of the ion-pair on the carbon of the enolate yields the observed product (**303**). Proton abstraction from the enol form of **302a** should yield the same ion pair **308** which should collapse again to

yield **303**. Evidence was not found in any of the systems studied for a product of structure **309** which would arise from *O*-alkylation of the enolate.



Scheme 78

The observation of the predominance of *C*-alkylation is in keeping with the greater thermodynamic stability of **303** compared to **309**. The stability of the *C*-alkylation product compared to that of the *O*-alkylation product, is seen in the greater bond energy of a carbonyl group compared to a simple double bond (difference of ca.

25 kcal/mol). Our studies cannot distinguish between thermodynamically or kinetically controlled mechanisms. The alkylation can occur with a preference for *C*-alkylation such as that observed for soft electrophiles such as alkyl iodides which tend to react with enolates at carbon.[106] Alternatively, the formation of **309** from the ion pair **308** may be a kinetically preferred, reversible process which ultimately gives the thermodynamically favoured *C*-alkylation product **303**.

Tautomerisation equilibrium constants and pKa's of some of the carbonyl compounds are presented in Table 7. Although the equilibrium enol contents of β-dicarbonyl compounds are substantially increased in non-polar solvents, the uncatalyzed rate for tautomerisation of **302a-d** and **305** could possibly be quite slow. The presence of the enolic form of **302a** and **b** was confirmed by ^{1}H-NMR spectroscopy in a benzene-d_6 solution which had been freshly prepared from the pure compounds at approximately the concentration of the thermolysis experiments. The characteristic hydrogen bonded proton appears as a broad signal (δ = 16.16) in the case of **302a** and as a sharp singlet (δ = 12.62) in the case of **302b**. Clearly, there is a significant enol content in the carbene traps being used even without special attempts to achieve preequilibration.

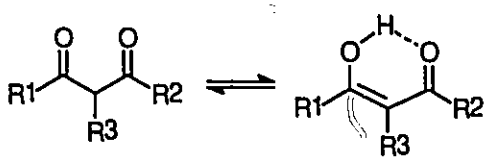


Table 7. Physical properties of carbonyl compounds **302a-f.**

Compound	K_T[a]	pKa
302a	14.7[b]	9[e]
302b	0.26[b]	11[e]
302c	0.67[c]	—
302d	22.8[c]	—
302e	—	9[e]
302f	—	13[e]
305	0.0025[d]	—

[a] Equilibrium constant for tautomerisation; K_T = [enol]/[keto]. [b] in benzene-d_6, from Ref. 169. [c] in $CDCl_3$ at 40 °C, from Ref. 170. [d] in toluene-d_8, from Ref 169. [e] from Ref. 171.

These results seem to favour a mechanism in which proton abstraction from the enol is the source of the ion-pair intermediate. In the cases of **302a-d**, the high enol content is ideal for the well precedented abstraction of a proton from an O–H bond, in this case from the enol form of **302a-d**. The active methylene compounds containing at least one ketone functional group tend to have high enol contents. The enol content at equilibrium seems to be more important for successful carbene trapping than the pKa of the carbon acid. This reinforces the conclusion that proton abstraction occurs from the enol. For instance, the pKa of methyl cyanoacetate and 2,4-pentanedione are similar, yet the former is a poor carbene trap while the latter is an efficient trap.

The mechanism of the loss of methanol is of some interest. The synthesis of these compounds from the action of trimethylorthoformate and acetic anhydride on β-dicarbonyl compounds has been known for over a century. The mechanism of the formation of these compounds in the reaction mixtures studied here has been probed

using **302a** as a model. After thermolysis, the GC trace of the reaction mixture showed that **303a** and **304a** were present in a 1:1 ratio of intensities. The reaction mixture from **302a** was reheated at 130 °C for 20 hours without causing a significant change in the GC trace of the mixture. Thus the product of methanol loss does not arise as a consequence of the thermal instability of the initially formed product.

The complete conversion of **303a** and **b** to **304a** and **b** can be catalyzed by reheating the sample in the presence of pyridine. The 1:1 ratio of **303a** to **304a** is thus not indicative of equilibration during the reaction. The **304a** must come from a process related to the presence of the carbene intermediate.

Our interpretation of these results invokes rapid proton transfers between the ion pair intermediate **308**, the β-dicarbonyl compound **302**, and the initial product **303**. Thus, the enolate anion of the ion pair, for example, can abstract a proton from **303** to induce the loss of methoxide to give **304**. Methoxide then acts as a chain carrier, either by direct abstraction from **303** or through formation of enolate from **302**. These ions can also serve to catalyze the tautomerisation of keto-**302** to enol-**302**.

The observation of the trapping of the enolic form of anthrone is significantly different from those mentioned above in that exclusive *O*-alkylation of the enolate is observed. The lower enol content of **305** is presumably sufficient to trap the carbene which is generated over the course of 20 hours. The addition of a drop of pyridine accelerates the known slow rate of tautomerisation of anthrone in non-polar solvents

and thus replenishes the enol as it is consumed in the reaction.[172-175] The predominance of *O*-alkylation must be either the result of a increased thermodynamic stability of the *O*-alkylation product over the *C*-alkylation product or a reduced rate for the reverse reaction of the *O*-alkylation product. The former may be true if the steric congestion of the *C*-alkylation product is significantly greater than that of the *O*-alkylation product. The latter may be true if the enolate of anthrone is less thermodynamically stabilized than the enolate of 2,4-pentanedione. These factors have not been further studied and thus the two possibilities cannot be distinguished with confidence.

The reactions of dimethoxycarbene with the activated methylene compounds studied here have suggested that dimethoxycarbene can react by abstraction of a proton from an enol. A contact ion pair in which the anion is enolic is generated and ultimately collapses to generate the observed products.

Chapter 3

Conclusions and Summary

The reactions of carbenes with olefinic double bonds is a characteristic reaction of these reactive intermediates. The formation of cyclopropanes from these reactions is very important from both a mechanistic and synthetic point of view. Section 1.4.2 details many of the important reactions of dialkoxycarbenes with C=C bonds.

A heteroatomic equivalent of the cyclopropanation reaction is the addition of carbenes to carbonyl groups. The two reactions are both [2 + 1] cycloaddition of the carbene with the π-system of the double bond. The reactions of dialkoxycarbenes with carbonyl groups have not been well studied to this point. A study has been conducted of the addition of nucleophilic dialkoxycarbenes to the carbonyl groups of a variety of compounds and the results bear upon many of the important issues raised in the study of carbene reactions with olefins. Our studies have allowed us to

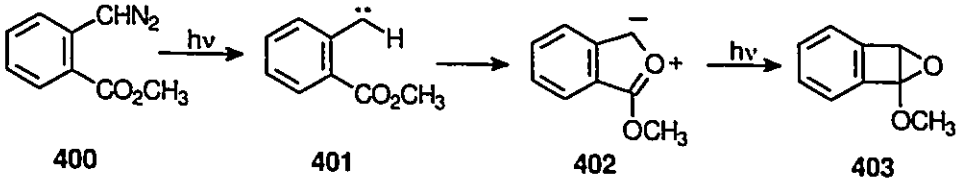
understand better how and why these reactions occur as well as to understand better the properties of these carbenes in general.

3.1 Mechanism of Carbene Addition to Carbonyl Compounds

The reactions of electrophilic carbenes with carbonyl compounds have a long history in carbene chemistry.[176,177] The intermediacy of carbonyl ylides in these reactions has been established by extensive trapping studies with alkenes,[176] by direct observation in cold matrices,[178] and by detection through spectroscopic means.[179-183] In these studies it has been established that the initially formed intermediate is the carbonyl ylide. The ring openings of oxiranes to carbonyl ylides (and the reverse) have been studied in detail[177] and are generally photochemically initiated reactions. Thus, concerted formation of the oxirane followed by ring opening to the carbonyl ylide is unlikely to occur thermally under these conditions.

This is supported experimentally. The generation of carbene **401** by photolysis (350 nm) of **400** in an Ar matrix at 10 K yields the carbonyl ylide **402** (Scheme 79).[180] Evidence for formation of the oxirane **403** under these conditions was not found. Only further photolysis (350 nm) of the carbonyl ylide **402** results in ring closure to the oxirane **403**. The reaction is reversible—formation of the carbonyl ylide from photolysis (254 nm) of the oxirane was found. Thus, it is clear that the initial reaction of a carbene with a carbonyl compound occurs to yield the carbonyl ylide. The direct

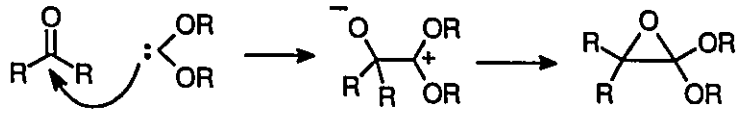
formation of carbonyl ylides in the addition of dichlorocarbenes to aromatic ketones[181] and aldehydes[182,183] has also been demonstrated.



400 401 402 403

Scheme 79

The complementary addition of nucleophilic carbenes to carbonyl groups has not been so well investigated. Stepwise nucleophilic addition of a carbene to a carbonyl group should yield the tetrahedral intermediate **404** (Scheme 80). Unlike ring closure of the carbonyl ylide, ring closure of the tetrahedral intermediate **404** to the oxirane **405** is expected to be thermally facile. Thus, studies to distinguish between stepwise and concerted carbene addition are made far more difficult. While the intermediacy of the dipole **404** has been firmly established by trapping studies (see section 1.4.6), it is not clear if this is a primary or secondary product.

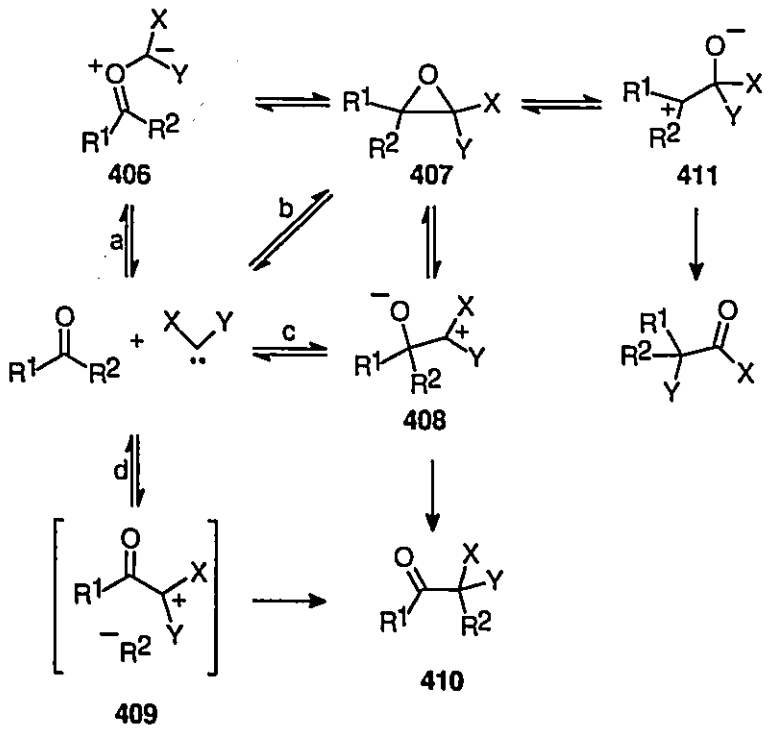


404 405

Scheme 80

The addition of carbenes to carbonyl compounds can proceed through various pathways. These pathways are represented by the series of general reactions shown

in Scheme 81. In the study of the addition of dialkoxycarbenes to carbonyl compounds detailed in this work, an investigation of each of these mechanistic possibilities was attempted in order to provide evidence to support or refute them. The goal has been to simplify the complex mechanistic picture shown in Scheme 81.



Scheme 81

The products in Scheme 81 are representations of all the products of carbonyl addition studied in sections 2.2, 2.3 and 2.4 of this work. Four mechanisms (paths a-d) for the initial interaction of the dialkoxycarbene and the carbonyl group are illustrated in Scheme 81. Path a represents electrophilic addition of the carbene to the carbonyl group to yield the carbonyl ylide **406**, path b represents concerted addition

to yield the oxirane **407**, path c represents nucleophilic addition to yield a tetrahedral intermediate **408** and path d represents an S_N2 mechanism on the sp^2 carbon atom to yield the ion pair **409**. Other mechanisms are possible but are thought to be less likely and are not considered in this analysis. Unlike carbene reactions with alkenes,[184-189] evidence for the formation of a dipole-dipole complex between the carbene and carbonyl group has never been uncovered in these reactions. Radical addition via a triplet state of the carbene is considered unlikely because of the very large singlet-triplet energy gap of dimethoxycarbene.

Our studies of addition of dialkoxycarbenes to carbonyl groups strongly indicate that the addition of the carbene occurs in a nucleophilic sense. First, only carbonyl groups which are very reactive towards nucleophilic attack are found to operate as efficient dialkoxycarbene traps. Second, internal and external competition reactions between substituted anhydrides indicate that the relative rate constants for attack of the dialkoxycarbene on the carbonyl group are greatest for the most electron deficient carbonyl groups. Third, despite the fact that the carbene trap is in most cases expected to be a very good trap for carbonyl ylides, in none of the studies that we have performed was evidence found for formation of any products derived from a carbonyl ylide. Fourth, reaction by path a yields the observed product **410** only by a very circuitous route; we cannot determine any driving force to justify the operation of such a complex mechanism.

Based on the above arguments, the product **410** is formed from a pathway which involves nucleophilic attack of the carbene onto the carbonyl group. We can conclude that the formation of products in the reactions that we have studied does not proceed through a mechanism such as path a in Scheme 81.

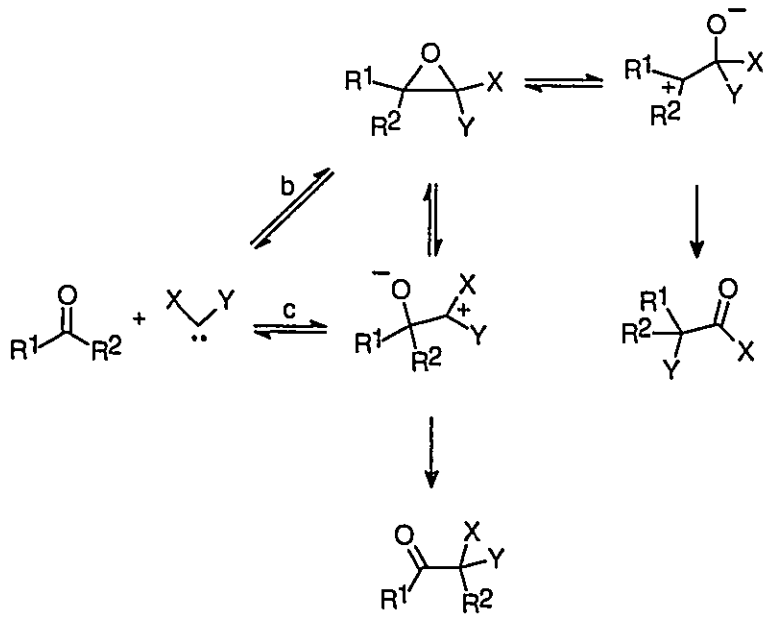
The results of these studies cannot distinguish between pathways b and c as illustrated in Scheme 81. Both pathways will feature nucleophilic attack of the dialkoxycarbene onto the carbonyl group. Distinction between these pathways is in some ways trivial since the oxirane **407** and dipole **408** are likely to be in a rapid equilibrium. It is unreasonable that the dipole **408** would exist with a significant lifetime without simply closing to the oxirane. The results of the reaction of dimethoxycarbene with fluorenone (see section 2.4) provides evidence that the dipole **408** must close to the oxirane and open in the other sense to the dipole **411** in order to achieve the observed product.

Furthermore, formation of the ion pair **409** has been refuted in our studies of the reactions of dialkoxycarbenes with benzoyl cyanide and benzalphthalide (see section 2.3). These results also allow us to conclude that pathway d (Scheme 81) for the initial addition of the carbene to the carbonyl compound is not valid. The S_N2 reaction on a carbonyl group has been well studied theoretically[190-192] and are supported experimentally.[193-200]

The 1,2-migration of the R^2 group of **408** to the cationic centre to yield **410** (Scheme 81) bears similarities to a Wolff rearrangement.[109] There are two

mechanisms possible for this 1,2-shift. The first mechanism involves a concerted 1,2-migration and the second involves formation of the ion pair **409** followed by ion pair collapse to yield **410**. The results in section 2.3 suggest that the concerted mechanism is favoured in the reaction of dialkoxycarbenes with benzoyl cyanide and benzalphthalide. We can conclude that the ion pair **409** is not formed. Likewise, the ion pair in the rearrangement of **411** is not expected to be an intermediate.

Based on these conclusions, a simplified mechanistic scheme can be proposed for the addition of dialkoxycarbenes to carbonyl groups (Scheme 82). One major ambiguity remains unanswered; we cannot distinguish between concerted and stepwise carbene addition. Computational results (section 2.5) indicate that the transition states for dihydroxycarbene additions to the carbonyl groups of maleic anhydride and maleimide involve substantial bonding to both the carbon and oxygen atoms. The transition states for addition of the carbene to the carbonyl groups of both species show a geometry indicative of concerted, nucleophilic addition. These calculations are preliminary, however, and must be further refined before conclusions can be made with confidence.



Scheme 82

3.2 Regioselectivity of Dialkoxycarbene Addition to α,β-Unsaturated Carbonyl Compounds

The reactions of dialkoxycarbenes with various substituted maleic anhydrides, coumarin, benzalphthalide and N-phenylmaleimide provide opportunities to study the regiochemistry of carbene addition to carbonyl compounds with extended conjugation. Carbonyl addition and Michael addition (addition to the alkene) are both possible modes of attack on α,β-unsaturated carbonyl compounds. Of the reactions studied in this work, only N-phenylmaleimide yields a cyclopropane product from Michael

addition of dimethoxycarbene to the α,β-unsaturated carbonyl π-system. A variety of maleic anhydrides, on the other hand, yield only products from attack of the carbene at the carbonyl carbon atom of the anhydride.

We have examined the factors determining the regioselectivity of dialkoxycarbene addition to N-phenyl maleimide, maleic anhydride, coumarin and benzalphthalide. Two factors seem to dictate the regioselectivity. The first is the electrophilicity of the carbonyl group. Anhydrides are known to be more reactive towards nucleophilic attack than maleimides. They are also more reactive than maleate esters which are known to react with dimethoxycarbene to yield cyclopropane derived products (see Chapter 1). A competition between the two modes of attack determines the product distribution. It is possible that some systems will yield products from attack at both the carbonyl and alkene groups.

Coumarin is a cyclic α,β-unsaturated ester which reacts with dimethoxycarbene only at the carbonyl group. It is difficult to propose a large difference in the electrophilicity of the carbonyl group of coumarin compared to that of ethyl cinnamate. A second factor must contribute to the observed regiochemistry. This second factor is likely to be the strain energy of the cyclopropane product. A high strain energy will tend to disfavour attack at the alkene moiety of coumarin compared to attack on the carbonyl group. Similar arguments can be made for the cyclopropane products derived from dimethoxycarbene addition to maleic anhydrides although, in this case, we expect that the dominant interaction is the activation of the

carbonyl group of the anhydride. The cyclopropane derived from attack of dimethoxycarbene onto the C=C bond of benzalphthalide will be a strained spirocyclic cyclopropane with one acyloxy and two alkoxy substituents.

It is likely then, that the subtle regioselectivity of dialkoxycarbene addition to α,β-unsaturated carbonyl compounds is controlled by a combination of the electrophilicity of the carbonyl group and the strain energy of the cyclopropane product.

3.3 [4 + 1] Cycloaddition of Dialkoxycarbenes and Bisketenes

The reaction of dimethoxycarbene **10** and methoxy(2,2,2-trifluoroethoxy)carbene **31** with the 1,2-bisketene **292** is representative of a different type of carbonyl group addition. Since the carbene attack occurs at an sp hybridized carbon atom, the anionic end of the zwitterionic intermediate is conjugated to the rest of the molecule. This results in cyclization products rather than the rearrangement products seen in the other studies.

Our results show that 1,2-bisketenes are good traps for dialkoxycarbenes. In addition, the trapping gives interesting products which are formally the result of [4 + 1] cycloaddition of the dialkoxycarbene across the π-system of the bisketene. The observed products can be rationalized in terms of predominance of the sterically preferred attack of carbene onto the ketene group.

3.4 Dimethoxycarbene Reaction with β-Dicarbonyl Compounds

It has been known for many years that the reaction of organometallics with β-dicarbonyl compounds is severely complicated by the destruction of the organometallic by deprotonation of the acidic β-dicarbonyl compound.[171] In this reaction, proton transfer is faster than the desired addition to a carbonyl group of the β-dicarbonyl compound. The reaction of dimethoxycarbene with β-dicarbonyl compounds follows the same trend. Our studies suggest that the reaction proceeds by proton abstraction by the carbene from the enol of the β-dicarbonyl compound to yield an ion pair intermediate. The observation of net C–H insertion is the result of ion pair collapse onto the carbon of the enolate by either a thermodynamically or kinetically controlled mechanism.

3.5 Summary and Perspective

The study of organic reaction mechanisms is at the heart of understanding organic chemistry. The emphasis of this project has been to explore new aspects of the chemistry of dialkoxycarbenes and examine the mechanistic puzzles discovered.

New features of both the carbene reactions and the subsequent rearrangements of the intermediates have been uncovered. Complex mechanisms of rearrangement are characteristic features of this area of chemistry. We have found conclusive evidence for the mechanisms of a variety of these reactions and have found that these studies evoke many of the same questions that are evoked with the reactions of other nucleophiles with carbonyl groups.

Carbenes have proven important to many aspects of chemistry. The addition of carbenes to alkenes is the most commonly used route to cyclopropanes[13,28,36,109,201,202] and other strained molecules.[63,203-207] Carbenes and carbenoids (carbenes which are co-ordinated to a metal) are used in a great number of synthetic methodologies.[63,176,208,209] Polymers containing repeating carbene units have been synthesized[210,211] and found to possess unusual electronic properties as a result of the unusual electronic structure of the carbene. Thiamine (Vitamin B_1) in its deprotonated form is a carbene which undergoes reactions characteristic of a nucleophilic carbene.[212-214] The Corey-Winter alkene synthesis is commonly used for the stereospecific formation of alkenes from the extrusion of CO_2 from cyclic carbonates through dialkoxycarbene intermediates.[117]

Our study of the reactions of dialkoxycarbenes with carbonyl compounds is important to many areas of organic chemistry. From the standpoint of organic synthesis, we have been able to make a variety of molecules with functional groups which are difficult to make in any other way. Dialkoxycarbenes can be used to

perform unique synthetic transformations on readily available starting materials. When incorporated into a molecule, the dialkoxycarbene produces a carbon atom at the ketone oxidation state. This carbon atom can be translated as a protected carbonyl group in the product which would be useful in the further elaboration of a synthesis. In addition, carbene reactions often entail complex rearrangements of great interest for physical organic chemistry and the chemical properties and molecular structures of the carbenes, dipoles, ylides, oxiranes, and ion pairs which have been shown to be intermediates in these reactions are of interest to all chemists.

Although the application of the reactions studied in this work to a general synthetic methodology has not been attempted, there is potential for the synthesis of important new compounds or materials using dialkoxycarbene chemistry. Thus, it is with considerable interest that progress is awaited in further chemistry of dialkoxycarbenes.

Chapter 4

Experimental

4.1 Synthesis of Oxadiazolines

Syntheses of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**).

Procedure A: Lead (IV) acetate oxidation of **200** in methanol solvent.

The methoxycarbonylhydrazone of acetone (**200**) (20g, 1 eq) was dissolved in 250mL of methanol and cooled with stirring in an ice bath to near 0°C. Solid lead (IV) acetate (70g, 1.05 eq) was then added to the flask over five minutes. The mixture was kept stirring in the ice bath for 30 minutes, the bath was removed, the reaction mixture allowed to warm to room temperature and then it was left stirring overnight. KOH pellets (5 g) were added to the reaction mixture which was allowed to stir overnight again. The methanol was then removed using a rotary evaporator. Water

(200 mL) was added to precipitate the lead salts. This mixture was extracted with dichloromethane (200 mL, 3 times) and dried with anhydrous $MgSO_4$. Evaporation gives the crude oxadiazoline **51**. Crude **51** was distilled (~50°C at 0.1 mmHg) to give oxadiazoline in 50 % yield from the hydrazone. The product was stored for long periods at room temperture without any sign of decomposition.

Procedure B: Synthesis of **51** by methanol substitution on acetoxyoxadiazoline **207**.

A general procedure is given since this procedure has been performed on both small and large scales. Amounts as small as 50 mg or as large as 40 g of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) have been successfully converted to dimethoxyoxadiazoline (**51**) using this procedure. 2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) (1 eq, a mixture of oxadiazoline **207** and acyclic impurity **208**) was dissolved in dichloromethane (oxadiazoline concentration ~ 0.2 mol/L) with methanol (5 eq). A few drops of acetic acid was generally added at this point to the reaction mixture. This was generally not necessary but was often found to accelerate the exchange reaction. The mixture was allowed to sit at room temperature overnight. The formation of dimethoxyoxadiazoline **51** and the reaction of acetoxyoxadiazoline **207** can be followed easily by GC for optimization of the yield. When the exchange was complete, KOH pellets were added and the reaction mixture was stirred at room temperature overnight. Formation of a light yellow

precipitate on the surface of the KOH pellets was indication that the hydrolysis of the acyclic isomer was occuring. If the stirring was stopped momentarily, the precipiate would settle revealing the nearly colourless solution which indicated the complete removal of the acylic isomer. Water was added to the reaction mixture and the organic phase extracted. Another extraction with 4% sodium bicarbonate was performed on the dichloromethane layer before drying with anhydrous $MgSO_4$. Evaporation of the dichloromethane yielded crude dimethoxyoxadiazoline **51** which could be purified further by distillation (~50°C at 0.1 mmHg). Yield: 94% from **207**.

Procedure C: Preparation of **51** from iodobenzene diacetate oxidation of **200**

The methoxycarbonylhydrazone of acetone (20g) was dissolved in 250mL of methanol and the solution was cooled with stirring in an ice bath to near 0°C. A slurry of iodobenzene diacetate (50g) in methanol was added with stirring to the reaction mixture. Iodobenzene diacetate was prepared by a literature procedure.[1] When the iodobenzene diacetate had fully dissolved (usually about 10 minutes), the reaction mixture was removed from the ice bath and the solvent removed by rotary evaporation. Since the reaction of the iodobenzene diacetate with the hydrazone was very fast, dissolving the reactant became the slow step of the reaction. The crude product was dissolved in dichloromethane and extracted with sodium bicarbonate to remove acetic acid. This afforded a mixture of iodobenzene and oxadiazoline which

was separated by column chromatography (alumina; hexanes). Unoptimized yield: 18.5g (75%). Chromatography seemed to cause some hydrolysis of the product since the yield (by NMR) was nearly quantitative before chromatography.

2,2-Dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**). FTIR (CCl_4, NaCl cell) cm^{-1}: 2992, 2949, 2916, 2846, 1459, 1445, 1382, 1368, 1263, 1214, 1144, 1108, 1076, 1031, 983, 915, 899, 853; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 3.45 (s, 6H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.7, 51.5, 118.8, 137.0; MS (e.i.) m/z : 132 [M – OCH_3]$^+$, 129 [M – OCH_3]$^+$, 105, 91, 90, 75, 74, 73, 59 (100%), 43 (molecular ion not observed); MS (c.i., NH_3) m/z : 178 [M + NH_4]$^+$.

Synthesis of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) and methyl 2,3-diaza-4-methyl-acetoxypent-2-enoate (**208**).

The methoxycarbonylhydrazone of acetone (**200**, 20g, 1 eq) was dissolved in 250mL of dichloromethane and the solution was cooled with stirring in an ice bath to near 0°C. Once cooled, solid lead (IV) acetate (70g, 1.05 eq) was added to the flask over five minutes. After stirring at ice temperature for 30 minutes, the bath was removed and the reaction mixture allowed to warm to room temperature where it was left stirring for about 4 hours or until the free-flowing lead diacetate salts have clearly precipitated. The mixture was then extracted with sodium bicarbonate to remove acetic acid and the lead salts. The solution was dried with anhydrous $MgSO_4$ and the

solvent was evaporated. The crude product was a mixture of ~66% oxadiazoline **207** and ~34% of the acyclic impurity **208**. This mixture can be stored for long periods in a refrigerator.

2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**). 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; ^{1}H-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 (**208**). FTIR (CCl_4, NaCl cell) cm^{-1}: 2997, 2957, 1776, 1464, 1437, 1368, 1261, 1241, 1164, 1044, 1020, 940, 908, 870, 607, 572; ^{1}H-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.) mz: 129 $[M - C_2H_3O_2]^+$, 101, 73, 59, 43 (100%) (molecular ion not observed); MS (c.i., NH_3) m/z: 206 $[M + NH_4]^+$.

Synthesis of 2-methoxy-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**210**) from acetoxy exchange.

2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) (1 eq, a mixture of oxadiazoline and acyclic impurity) was dissolved in dichloromethane with trifluoroethanol (5 eq) and a few drops of acetic acid were added. This was left overnight at room temperature. Formation of methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** and reaction of acetoxyoxadiazoline **207** could be easily followed by GC for optimization of the yield. When exchange was complete, KOH pellets were added to the reaction mixture which was stirred at room temperature overnight. When the acyclic impurity had hydrolyzed, water was added to the reaction mixture and and extraction was performed. A further extraction of the organic layer was performed with sodium bicarbonate. Drying of the organic layer with $MgSO_4$ and evaporation of the dichloromethane yielded crude methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** which was purified further by distillation (~30°C at 0.1 mmHg). Yield: 84% from acetoxyoxadiazoline **210**.

2-Methoxy-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**210**). ^{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); ^{1}H-NMR (200 MHz, C_6H_6) δ: 1.13 (s, 6H, CH_3), 3.02 (s, 3H, OCH_3), 3.89 (dq, $^3J_{HF}$ = 8.6 Hz, 1H, OCH_2CF_3), 3.90 (dq, $^3J_{HF}$ = 8.6 Hz, 1H, OCH_2CF_3); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.7, 24.0, 52.1, 62.0 (q, $^2J_{CF}$ = 36 Hz), 120.8, 123.2 (q, $^1J_{CF}$ = 275 Hz, CF_3,), 135.9 (C_2); ^{19}F-NMR (471 MHz, $CDCl_3$) δ: −74.594 (t, $^3J_{HF}$ = 8.4 Hz). 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 $[M + NH_4]^+$, 129 $[M - OCH_3]^+$ (100%).

Synthesis of 2-(1,1,1,3,3,3-hexafluoroisopropoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**213**) from a Substitution Reaction on Acetoxyoxadiazoline **207**.

2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**207**) (1 eq, a mixture of oxadiazoline and acyclic impurity) was dissolved in dichloromethane with hexafluoroisopropanol (5 eq) and a few drops of acetic acid added. This was allowed to sit at room temperature overnight. Formation of oxadiazoline **213** and reaction of acetoxyoxadiazoline **207** was followed easily by GC for optimization of the yield. When exchange was complete, KOH pellets were added to the reaction mixture which was stirred at room temperature overnight. When the acyclic impurity was hydrolyzed, water was added to the reaction mixture and an extraction of the organic layer performed. Drying and evaporation of the dichloromethane yields crude hexafluoroisopropoxymethoxy oxadiazoline which can be purified further by distillation (~40°C at 0.1 mmHg).

2-(1,1,1,3,3,3-Hexafluoroisopropoxy)-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**213**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.06 (s, 3H, CH_3), 1.109 (s, 3H, CH_3), 2.858 (s, 3H, OCH_3), 4.971 (m, 1H, $OC\underline{H}(CF_3)_2$); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 23.5; 23.8, 52.4 (OCH_3), 70.0 (q, $O\underline{C}H_2CF_3$, $^2J_{CF}$ = 35 Hz), 122.0 (C_5), 135.6 (C_2); ^{19}F-

NMR (471 MHz, $CDCl_3$) δ: −73.472 (m). MS (e.i.) m/z 227, 195, 104 (molecular ion not observed); GC/MS (e.i.) m/z 268 $[M - N_2]^+$, 265 $[M - OCH_3]^+$, 227, 207, 187, 151, 133, 129 $[M - OCH(CF_3)_2]^+$, 113, 73, 69 (100%), 59, 43; MS (c.i.) m/z 314 $[M + NH_4]^+$, 270, 253, 223, 129 (100%).

Preparation of 2-methoxy-5,5-dimethyl-2-(trideuteromethoxy)-Δ^3-1,3,4-oxadiazoline [(*methoxy-d_3*)-**51**].

To a solution of acetoxyoxadiazoline **207** in methylene chloride was added methanol-d_4. The solution was left stirring overnight to allow the exchange to occur. Pellets of KOH were then added and the solution was stirred overnight again to remove the acyclic isomer **208**. The resulting mixture was extracted with sodium bicarbonate and the organic layer was dried with anhydrous $MgSO_4$. Mass spectral analysis of the oxadiazoline showed that the deuterium incorporation had proceeded to give 95 % (*methoxy-d_3*)-**51**. The remaining 5 % was identified as the unlabelled compound. The unlabelled compound may have arisen as a result of adventitious water which is known[2] to yield **51** from hydrolysis of **207**.

Preparation of the methoxycarbonylhydrazone of cyclopentanone

The methoxycarbonylhydrazone of cyclopentanone was prepared by refluxing a benzene solution of methyl hydrazinocarboxylate and cyclopentanone with a Dean-Stark trap until the azeotropic distillation of water had stopped. The solvent was removed by rotary evaporation. Excess cyclopentanone was removed by pumping with a higher vacuum (1 mmHg). The crude hydrazone was recrystallized from hexanes:benzene (white crystals, m.p. 76-78°C).

Methoxycarbonylhydrazone of cyclopentanone. FTIR (CCl_4, NaCl cell) cm^{-1}: 3389, 3241, 3129, 2965, 2874, 1765, 1727, 1706, 1500, 1454, 1362, 1310, 1206, 1072, 1037. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.81 (m, 4H), 2.26 (bt, 2H, ^3J = 6.9 Hz), 2.47 (bt, 2H, J = 7.3 Hz), 3.84 (s, 3H, OCH_3), 8.10 (bs, 1H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 24.6, 24.6, 27.0, 33.2, 52.8 (b, CH_3O), 163.3 (C=O). MS (e.i.) m/z 155, 124, 102, 97, 84, 76, 67, 59.

Synthesis of 2,2-dimethoxy-5,5-(tetramethylene)-Δ^3-1,3,4-oxadiazoline (**211**).

The methoxycarbonylhydrazone of cyclopentanone (10g, 1 eq) was dissolved in 150mL of methanol and cooled with stirring in an ice bath to near 0°C. Once cooled, solid lead (IV) acetate (30g, 1.05 eq) was added to the flask over five minutes. After stirring at ice temperature for 30 minutes, the bath was removed and the reaction mixture allowed to warm to room temperature where it was left stirring overnight. The next day, KOH pellets (5 g) were added and the reaction mixture was allowed to

stir overnight again. The methanol was then removed using a rotary evaporator. Water (200 mL) was added to precipitate the lead salts. This mixture was extracted with dichloromethane (200 mL, 3 times) and dried with anhydrous $MgSO_4$. Evaporation gaves crude oxadiazoline **211** which was distilled (~55°C at 0.1 mmHg) to give colourless oxadiazoline. Yield: 75% from hydrazone. The product can be stored for long periods at room temperature.

2,2-Dimethoxy-5,5-(tetramethylene)-Δ^3-1,3,4-oxadiazoline (**211**). FTIR (CCl_4, NaCl cell) cm^{-1}: 3009, 2974, 2950, 2878, 2847, 1572, 1442, 1329, 1235, 1158, 1076, 1038, 1013, 946, 915, 904, 624, 543, 476. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.90 (m, 6H), 2.20 (m, 2H), 3.4 (s, 6H, OCH_3); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 24.8, 35.1, 51.4 (OCH_3), 127.6 (C_5), 136.7 (C_2). MS (e.i.) m/z 155 $[M - OCH_3]^+$, 99, 91, 90, 86, 84 (100%); MS (c.i., NH_3) $[M + NH_4]^+$ = 204, $[M + H]^+$ = 187, 155 $[M - OCH_3]^+$ (100%), 108, 99, 86. UV (hexanes) nm: 200-250, 290-340.

Synthesis of 2-acetoxy-2-ethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline and ethyl 2,3-diaza-4-methyl-acetoxypent-2-enoate.

The ethoxycarbonylhydrazone of acetone was prepared by stirring ethyl carbazate overnight in an acetone solution containing anhydrous $MgSO_4$ as a dessicant. Filtration and evaporation of the solvent yields hydrazone of sufficient quality to use without further purification. The ethoxycarbonylhydrazone of acetone (10g, 1 eq)

was dissolved in 250 mL of dichloromethane and cooled with stirring in an ice bath to near 0°C. Once cooled, solid lead (IV) acetate (32g, 1.05 eq) was added to the flask over five minutes. After stirring in the ice bath for 30 minutes, the bath was removed and the reaction mixture allowed to warm to room temperature where it was left stirring for about 4 hours or until the free-flowing lead diacetate salts had clearly precipitated. The mixture was extracted with sodium bicarbonate to remove acetic acid and the lead salts. The solution was dried with anhydrous $MgSO_4$ and the solvent evaporated. The crude product was a mixture of ~66% oxadiazoline and ~34% of the acyclic impurity.

2-Acetoxy-2-ethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.24 (t, 3H, ^3J = 7.2 Hz), 1.62 (s, 6H, $C(\underline{C}H_3)_2$), 2.06 (s, 3H, CH_3CO_2, overlapping with signal from acyclic isomer), 3.89 (m, 2H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 15.0, 22.4, 24.1, 24.4, 61.4, 100.4, 133.8, 166.4. MS (e.i.) m/z (%): 143 $[M - CH_3CO_2]^+$ (5), 71 (4), 59 (29), 43 (100).

Ethyl 2,3-diaza-4-methyl-acetoxypent-2-enoate. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.37 (t, 3H, ^3J = 7.1 Hz), 1.48 (s, 6H), 2.06 (s, 3H, CH_3CO_2, overlapping with signal from cyclic isomer), 4.38 (q, 2H, ^3J = 7.1 Hz). MS (e.i.) m/z (%): 101 (40), 59 (35), 43 (100).

Synthesis of 2-ethoxy-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline **(212)**.

2-Acetoxy-2-ethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (3 g, mixture of oxadiazoline and acyclic impurity, see preparation described above) was dissolved in dichloromethane (25 mL) with 2,2,2-trifluoroethanol (2 g) and acetic acid (0.5 mL) added. The mixture was allowed to sit at room temperature overnight. Formation of ethoxy(2,2,2-trifluoroethoxy)oxadiazoline **212** and reaction of the 2-acetoxy-2-ethoxyoxadiazoline can be followed easily by GC for optimization of yields. When the exchange was complete, KOH pellets were added and the reaction mixture was stirred at room temperature overnight. When the acyclic impurity was hydrolyzed, water was added and the organic layer was extracted. Drying of the organic layer and evaporation of the dichloromethane yielded crude ethoxy(2,2,2-trifluoroethoxy)oxadiazoline **212** which was suitable for use without further purification.

2-Ethoxy-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**212**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.22 (t, 3H, ^3J = 7.0 Hz), 1.48 (s, 3H), 1.54 (s, 3H), 4.127 (q, 1H, $^3J_{HF}$ = 8.4 Hz, OCH_2CF_3), 4.136 (q, 1H, $^3J_{HF}$ = 8.4 Hz, OCH_2CF_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.8 ($\underline{C}H_3CH_2O$), 23.7, 24.0, 60.9 (OCH_3), 61.9 (q, $^2J_{CF}$ = 37 Hz, $O\underline{C}H_2CF_3$), 120.4 (C_5), 135.7(C_2); ^{19}F-NMR (471 MHz, $CDCl_3$) δ: –74.553 (t, $^3J_{HF}$ = 8.5 Hz). MS (e.i.) m/z 214 $[M - N_2]^+$, 197 $[M - OCH_2CH_3]^+$, 172, 156, 145, 143, 141, 125, 111, 83, 69, 59, 43.

Synthesis of 2-(trideuteromethoxy)-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (*methoxy-d_3*-**210**).

2-Acetoxy-2-(trideuteromethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline was prepared according to the following procedure. Methyl carbazate-d_3 was prepared by adding CD_3OD (3 eqiv.) to 1,1'-carbonyldiimidazole (1 eqiv.) in CH_2Cl_2 solvent, letting stand for two hours, and then adding hydrazine monohydrate (10 equiv.) and letting stand overnight. Evaporation of the solvent and higher vacuum removal of excess hydrazine yielded methyl carbazate-d_3 which was used without further purification. Simply dissolving the carbazate in acetone in the presence of a desiccant ($MgSO_4$) and allowing to stand overnight yielded the labelled (methoxycarbonyl)hydrazone of acetone. Oxidation and exchange were achieved exactly analogous to the procedure detail above for the unlabelled molecule. The *methoxy-d_3*-**210** thus obtained was suitable for use without further purification.

2-(Trideuteromethoxy)-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (methoxy-d_3-**210**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.49 (s, 3H), 1.55 (s, 3H), 4.13 (q, OCH_2CF_3, 1H, $^3H_{HF}$ = 8.4), 4.14 (q, OCH_2CF_3, 1H, $^3J_{HF}$ = 8.4 Hz); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 23.7 (CH_3), 24.0 (CH_3), 61.9 (q, $O\underline{C}H_2CF_3$, $^2J_{CF}$ = – 36 Hz), 120.8, 123.2 (q, $^1J_{CF}$ = 277 Hz), 128; ^{19}F-NMR (471 MHz, $CDCl_3$) δ: –1.588 (t, $^3J_{HF}$ = 8.4 Hz). MS (e.i.) m/z: 203 $[M - N_2]^+$, 197 $[M - OCD_3]^+$, 167, 162, 161, 146, 145, 142, 141, 132 $[M - OCH_2CF_3]^+$, 127, 83, 62 (100%).

Synthesis of 2,2-bis(trideuteromethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (*dimethoxy-d_6*-**51**).

Dimethylcarbonate-d_6 was prepared by treatment of a solution of 1,1'-carbonyldiimidazole (2.2 g) in dichloromethane (50 mL) with methanol-d_4 (1 g). Pyridine (0.5 mL) was added to catalyze the reaction. The mixture was allowed to stand at room temperature overnight. Hydrazine monohydrate (5.5 g) was added along with enough absolute ethanol to keep the reaction mixture homogeneous. The mixture was again allowed to stir overnight at room temperature. The solvent and excess hydrazine were distilled to yield crude trideuteromethyl hydrazinocarboxylate. (Note: it was important to remove efficiently the hydrazine or acetone azine will contaminate the product.) To the residue was added acetone and anhydrous $MgSO_4$. The mixture was again allowed to stand overnight. Filtration and evaporation yielded crude (trideuteromethoxy)carbonylhydrazone of acetone. The preparation of 2-acetoxy-2-(trideuteromethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline was similar to that described below for the unlabelled compound. Procedure B for the synthesis of dimethoxyoxadiazoline **51** (see above for the unlabelled oxadiazoline) was followed for the preparation of 2,2-bis(trideuteromethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (*dimethoxy-d_6*-**51**) from the acetoxy(trideuteromethoxy)oxadiazoline except that methanol-d_4 was used in a two fold excess and the reaction mixture was warmed

slightly with hot tap water to facilitate exchange. The exchange reaction was followed by GC to ensure optimization of the yield.

4.2 Reaction of Dialkoxycarbenes with Cyclic Anhydrides

Typical thermolyses were performed with an oxadiazoline concentration between 0.05 and 0.10 M in dry benzene and one equivalent of anhydride. Samples were sealed in a resealable thermolysis tube and heated to 110 °C for 20 hours. A full procedure is given for the preparation and purification of **216g** below. The scale of these reactions can be varied between 0.01 g (sealed in an NMR tube) to 1 g (sealed in a thermolysis tube) of oxadiazoline. 1,4-Dimethoxybenzene was added in known concentration to an aliquot of the reaction mixture and the yield of products **216a-s** were then obtained by ^{1}H-NMR spectroscopy. GC calibrations were also performed using 1,4-dimethoxybenzene as the calibration standard.

The crude reaction mixtures were analyzed by GC/FID, GC/MSD and GC/FTIR. The products, which are orthoesters with one oxy group being a carboxylate, are not stable to silica gel chromatography. As alternatives, several methods were used to increase product purity. A concentrated solution of trap and product could, in many cases, be separated by preparative gas chromatography. Often, thermolyses at a 3:1 oxadiazoline:trap ratio resulted in samples which were fairly free of excess anhydride (this method usually worked best for the dimethoxy products). In

the case of **216q**, when a mixture of **215g** and **216q** in benzene solution was stirred vigourously with aqueous sodium carbonate (two phase system), selective hydrolysis of **215g** occurred to yield a mixture enriched in **216q**. When purification was attempted, purity was measured by GC/FID analysis (integration of the spectra after the solvent peak) and expressed as the percentage of the product in the total, **%(216)**. The difference between this value and 100 % was accounted for by remaining anhydride or small amounts of other impurities.

The products **216** are not stable as neat liquids as they are highly susceptible to hydrolysis. For this reason, attempts to obtain elemental analyses were unsuccessful. Isolation of the products of trapping was not always possible and spectroscopic analyses (^{1}H, ^{13}C, ^{19}F-NMR, MS, FTIR) were often most efficiently performed on the crude reaction mixtures. After removing solvent and any volatiles generated, the crude thermolysis mixtures showed signals from the unreacted anhydride and the desired product. GC/FID analysis of the crude reaction mixtures provided a method for indicating how "cleanly" (i.e. to give only one trapping product) the reaction had proceeded. The result is expressed as the sum of the total % integration belonging to the remaining anhydride and the product **%(215+216)**. This value was highest for products of trapping of dimethoxycarbene; the difference from 100 % was distributed over many small peaks in the GC traces. The crude mixtures resulting from thermolysis of 2-methoxy-2-(2,2,2-trifluoroethoxy)oxadiazoline had several minor

side-products which were detectable in the GC/FID and GC/MSD traces. These compounds were not characterized.

Unless otherwise stated for the particular compound, ^{1}H and ^{13}C-NMR: Bruker AC-200. ^{19}F-NMR: Bruker AC-300. Gas phase FT-IR: Hewlett-Packard HP-5890 gas chromatograph connected to a Bio-Rad FTS-40 FT-IR with a Bio-Rad GC/C 32 GC interface. MS(CI): VG Analytical ZAB-E double focusing mass spectrometer.

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of Maleic Anhydride (**215a**).

The maleic anhydride for production of **216a** and **216b** was purified by distillation (b.p. = 196-200 °C, lit b.p.[3] = 197-9 °C) at atmospheric pressure using tetrachloroethane to remove any water from the system by azeotropic distillation. Reaction of **51** with **215a** according to the general procedure described above gave **216a**. Yield: 40 % by NMR and based on oxadiazoline; %(**215+216**) = 91 %. The compound was purified by preparative scale GC.

6,6-Dimethoxy-2H-pyran-2,5-(6H)-dione (**216a**). FTIR (gas phase) ν (cm^{-1}): 3019 (bw), 2963 (m), 2859 (w), 1766 (s), 1741 (s), 1263 (m), 1197 (s), 1175 (m), 1087 (s), 1052 (m), 959 (s). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.47 (s, 6H, $C(OC\underline{H}_3)_2$), 6.79 (d, 1H, ^{3}J = 15.6 Hz, 3-H), 6.84 (d, 1H, ^{3}J = 15.6 Hz, 4-H). ^{13}C-NMR (50.3 MHz,

$CDCl_3$) δ: 51.6 ($C(O\underline{C}H_3)_2$), 109.8 (C-6), 134.9 (C-3), 136.9 (C-4), 160.1 (C-2), 185.1 (C-5). MS (e.i.) m/z (%): 141 $[M - OCH_3]^+$ (7), 113 $[M - CO_2CH_3]^+$ (100), 99 (18), 85 (40), 82 (75), 74 (15), 59 (100), 54 (87), 53 (20); MS (c.i., NH_3) m/z (%): 173 $[M + H]^+$ (100).

Thermolysis of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** in the presence of Maleic Anhydride (**215a**).

Reaction of **210** with **215a** according to the general procedure described above gave **216b**. Yield: 46 % by NMR and based on oxadiazoline; %(**215+216**) = 60 %. The compound was purified by preparative scale GC.

6-(2,2,2-Trifluoroethoxy)-6-methoxy-2H-pyran-2,5-(6H)-dione (**216b**). FTIR (gas phase) ν (cm^{-1}): 3025 (bw), 2967 (w), 2863 (w), 1778 (m), 1742 (m), 1295 (m), 1256 (m), 1188 (s), 1090 (m), 1060 (w), 982 (m). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.50 (s, 3H, OCH_3), 4.12 (m, 2H, $O\underline{C}H_2CF_3$), 6.84 (d, 1H, ^3J = 13.9 Hz, 3-H), 6.89 (d, 1H, ^3J = 13.9 Hz, 4-H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 52.5 ($C(O\underline{C}H_3)_2$), 61.2 (q, $^2J_{CF}$ = – 36.9 Hz, $O\underline{C}H_2CF_3$), 108.5 (C-6), 122.9 (q, $^1J_{CF}$ = 277 Hz, $\underline{C}F_3$), 134.9 (C-3), 137.0 (C-4), 158.9 (C-2), 183.7 (C-5). MS (e.i.) m/z (%): 209 $[M - OCH_3]^+$ (2), 181 $[M - CO_2CH_3]^+$ (64), 167 (10), 153 (10), 142 (7), 141 $[M - OCH_2CF_3]^+$ (3), 127 (6), 113 $[M - CO_2CH_2CF_3]^+$ (81), 99 (10), 85 (18), 83 (85), 82 (95), 69 (16), 59

(65), 54 (100), 53 (20); MS (c.i., NH_3) m/z (%): 258 $[M + NH_3]^+$ (45), 241 $[M + H]^+$ (100).

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of Methylmaleic Anhydride (**215b**).

The methylmaleic anhydride for production of **216c-f** was purified by vacuum distillation. Reaction of **51** with **215b** according to the general procedure described above gave **216c** and **d** in a 3.0:1 ratio by GC/MSD. Yield (**216c** + **216d**): 81 % by NMR and based on oxadiazoline. ^{13}C-NMR coupling constants were measured on the resulting mixture of isomers by a gated $^{13}C[^1H]$ decoupling technique. This technique provides the ^{13}C proton coupled NMR spectrum while allowing nuclear Overhauser enhancement (nOe) of the signals.

6,6-Dimethoxy-4-methyl-2H-pyran-2,5-(6H)-dione (**216c**) and *6,6-Dimethoxy-3-methyl-2H-pyran-2,5-(6H)-dione* (**216d**). Mixture of **216c** and **216d**: FTIR (gas phase) ν (cm^{-1}): 2963 (w), 1765 (s), 1733 (m), 1261 (m), 1197 (s), 1171 (m), 1064 (m), 969 (m). Major isomer, **216c**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.99 (d, 3H, ^4J = 1.6 Hz, CH_3), 3.37 (s, 3H, OCH_3), 6.6 (3-H, obscured by excess anhydride); ^{13}C-NMR (50.3 MHz (75.5 MHz for J_{CH} measurement), $CDCl_3$) δ: 14.7 (CH_3), 51.4 ($C(O\underline{C}H_3)_2$), 109.3 (C-6), 130.4 (dq, $^1J_{CH}$ = 171 Hz, $^4J_{C,\ methyl\text{-}H}$ = 6 Hz, C-3), 147.2 (q, $^2J_{C,\ methyl\text{-}H}$ = – 6.4 Hz, C-4), 160.0 (d, $^2J_{CH}$ = – 3.2 Hz, C-2), 186.1 (dq, $^3J_{C,\ 3\text{-}H}$ = 14

Hz, $^{3}J_{C\text{-}5,\ methyl\text{-}H}$ = 3.7 Hz, C-5). MS (e.i.) m/z (%): 155 $[M - OCH_3]^+$ (5), 127 $[M - CO_2CH_3]^+$ (85), 113 (4), 99 (70), 96 (55), 74 (12), 69 (30), 68 (100), 67 (10), 59 (90), 53 (15), 40 (50), 39 (95). Minor isomer, **6d**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.11 (obscured by excess anhydride), 3.37 (s, 3H, OCH_3), 6.6 (4-H, obscured by excess anhydride); ^{13}C-NMR (50.3 MHz (75.5 MHz for J_{CH} measurement), $CDCl_3$) δ: 18.0 (CH_3), 51.4 ($C(O\underline{C}H_3)_2$), 109.3 (C-6), 133.1 (dq, $^{1}J_{CH}$ = 169 Hz, $^{4}J_{C,\ methyl\text{-}H}$ = 6 Hz, C-4), 145.9 (C-3), 161.3 (C-2), 185.4 ($|^{2}J_{CH}| < 1$ Hz, C-5). MS (e.i.) m/z (%): 155 $[M - OCH_3]^+$ (4), 127 $[M - CO_2CH_3]^+$ (100), 113 (5), 99 (25), 96 (50), 74 (12), 69 (20), 68 (75), 67 (10), 59 (80), 40 (35), 39 (75).

Thermolysis of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** in the presence of Methylmaleic Anhydride (**215b**).

Reaction of **210** with **215b** according to the general procedure described above gave **216e** and **f** in a 2.6:1 ratio by GC/MSD integration. Yield of **216e** + **216f**: 60 % by NMR and based on oxadiazoline; %(**215**+**216**) = 50 %. ^{13}C-NMR coupling constants were measured on the resulting mixture of isomers by a gated $^{13}C[^{1}H]$ decoupling technique.

6-(2,2,2-Trifluoroethoxy)-6-methoxy-4-methyl-2H-pyran-2,5-(6H)-dione (**216e**) and *6-(2,2,2-Trifluoroethoxy)-6-methoxy-3-methyl-2H-pyran-2,5-(6H)-dione* (**216f**). Mixture of **216e** and **216f**: FTIR (gas phase) ν (cm^{-1}): 3004 w), 2967 (w), 1769 (m),

1735 (m), 1644 (w), 1452 (w), 1419 (w), 1345 (w), 1294 (m), 1182 (s), 1072 (w), 1009 (w), 983 (m), 889 (w). Major isomer, **216e**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.00 (d, 3H, ^4J = 1.4 Hz, CH_3), 3.411 (s, 3H, OCH_3), 4.0 (m, 2H, OCH_2CF_3), 6.59 (q, 1H, ^4J = 1.9 Hz, 3-H); ^{13}C-NMR (50.3 MHz (75.5 MHz for J_{CH} measurement), $CDCl_3$) δ: 14.8 (CH_3), 52.2 ($C(O\underline{C}H_3)_2$), 61.0 (q, $^2J_{CF}$ = – 37 Hz, $O\underline{C}H_2CF_3$), 108.2 (C-6), 122.9 (tq, $^1J_{CF}$ = 277 Hz, $^2J_{CH}$ = – 4.8 Hz, $OCH_2\underline{C}F_3$), 130.4 (dq, $^1J_{CH}$ = 172 Hz, $^3J_{C,\,methyl\text{-}H}$ = 6.2 Hz, C-3), 147.5 (dq, $^2J_{C,\,3\text{-}H}$ = – 1.3 Hz, $^2J_{C,\,methyl\text{-}H}$ = – 6.6 Hz, C-4), 158.8 (d, $^2J_{CH}$ = – 3.0 Hz, C-2), 184.8 (dq, $^3J_{C,\,3\text{-}H}$ = 11.8 Hz, $^3J_{C\text{-}5,\,methyl\text{-}H}$ = 4.2 Hz, C-5). MS (e.i.) m/z (%): 223 $[M - OCH_3]^+$ (1), 195 $[M - CO_2CH_3]^+$ (35), 167 (56), 155 $[M - OCH_2CF_3]^+$ (2), 142 (3), 139 (5), 127 $[M - CO_2CH_2CF_3]^+$ (51), 99 (9), 96 (59), 83 (62), 69 (29), 68 (100), 59 (45), 40 (45), 39 (67). Minor isomer, **216f**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.12 (d, 3H, ^4J = 1.4 Hz, CH_3), 3.405 (s, 3H, OCH_3), 4.0 (m, 2H, OCH_2CF_3), 6.6 (obscured by excess anhydride); ^{13}C-NMR (50.3 MHz (75.5 MHz for J_{CH} measurement), $CDCl_3$) δ: 19.8 (CH_3), 52.2 ($C(O\underline{C}H_3)_2$), 61.1 (q, $^2J_{CF}$ = – 37 Hz, $O\underline{C}H_2CF_3$), 109.0 (C-6), 122.9 (tq, $^1J_{CF}$ = 277 Hz, $^2J_{CH}$ = – 4.8 Hz, $OCH_2\underline{C}F_3$), 133.2 (dq, $^1J_{CH}$ = 170 Hz, $^3J_{C,\,methyl\text{-}H}$ = 5.9 Hz, C-4), 146.2 (q, $^2J_{C,\,methyl\text{-}H}$ = – 7.1 Hz, C-4), 160.3 (dq, $^3J_{C,\,4\text{-}H}$ = 12.5 Hz, $^3J_{C\text{-}2,\,methyl\text{-}H}$ = 4.5 Hz, C-2), 184.0 (s, $^2J_{C,\,4\text{-}H}$ < 1 Hz, C-5). MS (e.i.) m/z (%): 223 $[M - OCH_3]^+$ (1), 195 $[M - CO_2CH_3]^+$ (48), 167 (26), 155 $[M - OCH_2CF_3]^+$ (1), 142 (4), 139 (4), 127 $[M - CO_2CH_2CF_3]^+$ (71), 99 (11), 96 (56), 83 (67), 68 (100), 67 (14), 59 (46), 40 (41), 39 (67).

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of Dimethylmaleic Anhydride (**215c**).

Dimethylmaleic anhydride for production of **216g** and **216h** was obtained from Aldrich and used as received. Dimethoxyoxadiazoline **51** (0.20g) and dimethylmaleic anhydride (**215c**, 0.16 g) were dissoved in benzene (25 mL) in a glass thermolysis tube equiped with a J. Young teflon stopcock. The mixture was sealed in the tube using the stopcock and placed in an oil bath at 110 °C for 20 hours. The solvent was removed by rotatory evaporation to yield 0.23 g of a mixture of anhydride and carbene trapping product. The mixture was injected onto a packed GC column (OV-17, 6', isothermal @ 140 °C) and the entire second peak (product **216g**, 30 minute retention time) was collected. The mass collected was 0.038 g which was found to be ~70% pure by GC/FID analysis. Higher purity collection (up to ~95% with corresponding reduction in mass) was possible if only the heart of the peak was collected. Collected yield: 10% based on oxadiazoline. The NMR yield was obtained by taking 0.5 mL of the crude reaction mixture and 0.5 mL of a stock solution of 1,4-dimethoxybenzene (0.05 M in benzene). The solvent was removed from the mixture by rotatory evaporation and integration of the methoxy signals of the standard and the product were measured. Yield: 75 % by NMR and based on oxadiazoline; %(**215+216**) = 88 %. Larger-scale thermolyses were performed in sealed tubes or under reflux with toluene solvent. Product for characterization was

isolated by preparative gas chromatography (%(**216**) = 96 %). Subjection of the reaction mixture to the thermolysis conditions for an additional 24 hours did not show product decomposition.

6,6-Dimethoxy-3,4-dimethyl-2H-pyran-2,5-(6H)-dione (**216g**). FTIR (gas phase) ν (cm^{-1}): 3019 (w), 2964 (m), 2857 (w), 1756 (s), 1726 (m), 1388 (w), 1234 (s), 1178 (s), 1119 (w), 1081 (s), 1008 (m), 980 (m). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.94 (q, 3H, ^5J = 0.8 Hz, CH_3), 2.06 (q, 3H, ^5J = 0.8 Hz, CH_3), 3.35 (s, 6H, $C(OCH_3)_2$); ^{1}H-NMR (300 MHz, C_6D_6) δ: 1.48 (q, 3H, ^5J = 1.1 Hz, CH_3), 1.62 (q, 3H, ^5J = 1.1 Hz, CH_3), 3.20 (s, 3H, OCH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 11.9, 15.0, 51.5, 109.3 (C-6), 139.8 (C-3), 141.9 (C-4), 161.5 (C-2), 186.0 (C-5). MS (e.i.) m/z (%): 169 $[M - OCH_3]^+$ (4), 141 $[M - CO_2CH_3]^+$ (75), 113 (50), 110 (60), 91 (6), 82 (45), 59 (50), 54 (100); MS (c.i., NH_3) m/z (%): 218 $[M + NH_4]^+$ (15), 201 $[M + H]^+$ (100). High resolution MS (e.i.) $[M + H]^+$ found: 201.079; calculated: 201.076.

Thermolysis of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** in the presence of Dimethylmaleic Anhydride (**215c**).

Reaction of **210** with **215c** according to the general procedure described above gave **216h**. Yield: 30 % by NMR and based on oxadiazoline; %(**215+216**) = 84 %. Product for characterization was isolated by preparative gas chromatography (%(**216**) = 74 %).

6-(2,2,2-Trifluoroethoxy)-3,4-dimethyl-6-methoxy-2H-pyran-2,5-(6H)-dione, (**216h**). FTIR (gas phase) ν (cm^{-1}): 3024 (b), 2965 (w), 2862 (b), 1764(s), 1728 (m), 1454 (w), 1389 (w), 1295 (m), 1230 (m), 1182 (s), 1073 (m), 1006 (m), 970 (w). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.04 (q, 3H, ^5J = 1.1 Hz, CH_3), 2.16 (q, 3H, ^5J = 1.1 Hz, CH_3), 3.48 (s, 3H, OCH_3), 4.10 (m, 2H, $OC\underline{H}_2CF_3$); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 12.0, 15.1, 52.2, 61.2 (q, $O\underline{C}H_2CF_3$, $^2J_{CF}$ = – 36.6 Hz), 108.3, 123.0 (q, CF_3, $^1J_{CF}$ = 277 Hz), 140.1, 142.2, 160.5, 184.6; ^{19}F-NMR (282.4 MHz, $CDCl_3$, referenced to $CFCl_3$ at 0 ppm) δ: – 78.781 (t, $^3J_{HF}$ = 8.8 Hz, $OCH_2C\underline{F}_3$). MS (e.i.) m/z (%): 237 $[M - OCH_3]^+$ (2), 209 $[M - CO_2CH_3]^+$ (45), 181 (35), 169 $[M - OCH_2CF_3]^+$ (2), 153 (5), 141 (56), 113 (10), 110 (40), 83 (60), 82 (35), 54 (100); MS (c.i., NH_3) m/z (%): 286 $[M + NH_4]^+$ (75), 269 $[M + H]^+$ (10).

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of Dichloromaleic Anhydride (**215d**)

Dichloromaleic anhydride for production of **216i** and **216j** was obtained from Fluka and was recrystallized from toluene before use. Reaction of **51** with **215d** according to the general procedure described above gave **216i**. Yield: 60 % by NMR and based on oxadiazoline; %(**215+216**) = 90 %. The use of toluene as the thermolysis solvent resulted in the production of an unwanted side product. **216i** for characterization was isolated by preparative gas chromatography (%(**216**) = 76 %). Subjection of the

reaction mixture to the thermolysis conditions for an additional 24 hours did not show any product decomposition.

3,4-Dichloro-6,6-dimethoxy-2H-pyran-2,5-(6H)-dione (**216i**). FTIR (gas phase) ν (cm^{-1}): 3026 (w), 2965 (m), 2860 (w), 1778 (s), 1749 (m), 1580 (m), 1456 (w), 1304 (w), 1197 (s), 1179 (s), 1153 (s), 1060 (m), 1049 (m), 985 (m), 963 (m), 832 (m). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.50 (s, 6H, OCH_3); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 52.4, 111.0, 139.0, 140.9, 154.7, 177.3. MS (e.i.) m/z (%, intensity of lowest m/z isotopomer): {209, 211, 213} (2), {181, 183, 185} (40), {150, 152, 154} (30), {133, 135} (80), {122, 124, 126} (40), {94, 96, 98} (50), {87, 89} (100), 59 (50); MS (c.i., NH_3) m/z (%, intensity of lowest m/z isotopomer): {258, 260, 262} $[M + NH_4]^+$ (5), {241, 243, 245} $[M + H]^+$ (100), {207, 209, 211} (20). High resolution MS (e.i.) $[M + H]^+$ found: 240.961; calculated: 240.967.

Thermolysis of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** in the presence of Dichloromaleic Anhydride (**215d**).

Reaction of **210** with **215d** according to the general procedure described above gave **216j**. Yield: 45 % by NMR and based on oxadiazoline; %(**215**+**216**) = 75 %. Product for characterization was isolated by preparative gas chromatography (%(**215**) = 69 %).

3,4-Dichloro-6-(2,2,2-trifluoroethoxy)-6-methoxy-2H-pyran-2,5-(6H)-dione (**216j**). FTIR (gas phase) ν (cm^{-1}): 2968 (w), 1784 (m), 1750 (m), 1579 (m), 1295 (m), 1190 (s), 1071 (w), 982 (m). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.54 (s, 3H, OCH_3), 4.15 (m, 2H, $OC\underline{H}_2CF_3$); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 53.1, 61.7 (q, $O\underline{C}H_2CF_3$, $^{2}J_{CF}$ = – 37.5 Hz), 109.5, 122.5 (q, $^{1}J_{CF}$ = 278 Hz, $\underline{C}F_3$), 139.1, 141.0, 153.5, 176.1. ^{19}F-NMR (282.4 MHz, $CDCl_3$. referenced to $CFCl_3$ at 0 ppm) δ: –78.673 (t, $^{3}J_{HF}$ = 8.2 Hz, $OCH_2C\underline{F}_3$). MS (e.i.) m/z (%, intensity of lowest m/z isotopomer): 277 [M – OCH_3] (< 1), {249, 251, 253} [M – CO_2CH_3]$^{+}$ (20), 229 (4), {201, 203} (70), {181, 183, 185} (30), {150, 152, 154} (35), {122, 124, 126} (50), {93, 95, 97} (45), {87, 89} (100).

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of Bromomaleic Anhydride (**215e**).

Bromomaleic anhydride (**215e**) for the production of **216k-n** was obtained from Aldrich and purified by vacuum distillation prior to use. Reaction of **51** with **215e** according to the general procedure described above gave **216k** and **1** in a 4.5:1 ratio by GC/MSD integration. Yield: 43 % by NMR and based on oxadiazoline; %(**215+216**) = 86 %. Coupling constants were measured on the resulting mixture of isomers by a gated ^{13}C[^{1}H] decoupling technique.

4-Bromo-6,6-dimethoxy-2H-pyran-2,5-(6H)-dione (**216k**) and *3-Bromo-6,6-dimethoxy-2H-pyran-2,5-(6H)-dione* (**216l**). Mixture of **216k** and **216l**: FTIR (gas phase) ν (cm $^{-1}$): 2969 (w), 1829 (s), 1769 (m), 1621 (w), 1297 (w), 1233 (m), 1192 (s), 1033 (w), 909 (m). MS (c.i., NH_3) m/z (%, intensity of lowest m/z isotopomer): {268, 270} $[M + NH_4]^+$ (15), {251, 253} $[M + H]^+$ (100). Major product, **216k**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.48 (s, 6H, OCH_3), 7.27 (s, 1H, 3-H); ^{13}C-NMR (50.3 MHz (75.5 MHz for J_{CH} measurement), $CDCl_3$) δ: 52.00, 109.3, 135.5 (d, $^1J_{CH}$ = 179 Hz), 136.4 (d, $^2J_{CH}$ = – 5 Hz), 158.0 (d, $^2J_{CH}$ = – 1.4 Hz), 179.1 (d, $^3J_{CH}$ = 8.4 Hz). MS (c.i.) m/z (%, intensity of lowest m/z isotopomer): {219, 221} $[M - OCH_3]^+$ (2), {191, 193} $[M - CO_2CH_3]^+$ (24), {160, 162} (32), {132, 134} (42), {131, 133} (4), 127 (60), {104, 106} (42), 99 (27), 69 (8), 59 (29), 53 (100), 29 (18). Minor product, **216l**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.43 (s, 6H, OCH_3), 7.27 (s, 1H, 4-H); ^{13}C-NMR (50.3 MHz (75.5 MHz for J_{CH} measurement), $CDCl_3$) δ: 51.95 (OCH_3), 111.3, 134.8 (d, $^2J_{CH}$ = – 5 Hz), 138.0 (d, $^1J_{CH}$ = 176 Hz), 156.1, 182.6 ($^2J_{CH}$ < 1 Hz). MS (c.i.) m/z (%, intensity of lowest m/z isotopomer): {219, 221} $[M - OCH_3]^+$ (4), {191, 193} $[M - CO_2CH_3]^+$ (66), {160, 162} (42), {132, 134} (57), 127 (3), {104, 106} (69), 99 (67), 69 (13),59 (62), 53 (100), 29 (24).

Thermolysis of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** in the presence of Bromomaleic Anhydride (**215e**).

Reaction of **210** with **215e** according to the general procedure described above gave **216m** and **n** in a 3.8:1 ratio by GC/MSD integration. Yield: 36 % by NMR and based on oxadiazoline; %(**215**+**216**) = 70 %. Coupling constants were measured on the resulting mixture of isomers by a gated $^{13}C[^{1}H]$ decoupling technique.

4-Bromo-6-(2,2,2-trifluoroethoxy)-6-methoxy-2H-pyran-2,5-(6H)-dione (**216m**) and *3- Bromo-6-(2,2,2-trifluoroethoxy)-6-methoxy-2H-pyran-2,5-(6H)-dione* (**216n**). Mixture of **216m** and **216n**: FTIR (gas phase) ν (cm^{-1}): 2974 (w), 1799 (w), 1766 (m), 1294 (m), 1187 (s), 1124 (w), 989 (w). Major product, **216m**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.48 (s, 3H, OCH_3), 4.1 (m, 2H, OCH_2CF_3), 7.30 (s, 1H, 3-H). ^{13}C-NMR (50.3 MHz (75.5 MHz for J_{CH} measurement), $CDCl_3$) δ: 52.7 (OCH_3), 61.3 (q, $^{2}J_{CF}$ = – 37 Hz, $O\underline{C}H_2CF_3$), 108.0 (C-6), 122.6 (q, $^{1}J_{CF}$ = 277 Hz, OCH_2CF_3), 135.4 (d, $^{1}J_{CH}$ = 179 Hz), 136.3 (d, $^{2}J_{CH}$ = – 5 Hz), 156.8 (d, $^{2}J_{CH}$ = – 2.2 Hz), 178.0 (d, $^{3}J_{CH}$ = 8.8 Hz). MS (e.i.) m/z (%, intensity of lowest m/z isotopomer): {287, 289} $[M - OCH_3]^+$ (< 1), {259, 261} $[M - CO_2CH_3]^+$ (18), {231, 233} (1), {219, 221} $[M - OCH_2CF_3]^+$ (1), 195 (66), {191, 193} $[M - CO_2CH_2CF_3]^+$ (20), 179 (3), 167 (15), {160, 162} (55), 143 (3), {132, 134} (67), {104, 106} (44), 83 (50), 69 (17), 59 (17), 53 (100), 33 (8), 29 (10). Minor product, **216n**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.48 (s, 3H, OCH_3), 4.1 (m, 2H, OCH_2CF_3), 7.31 (s, 1H, 4-H). ^{13}C-NMR (50.3 MHz (75.5 MHz for J_{CH} measurement), $CDCl_3$) δ: 52.7 (OCH_3), 61.2 (q, $^{2}J_{CF}$ = – 37 Hz, $O\underline{C}H_2CF_3$), 107.6 (C-6), 122.6 (q, $^{1}J_{CF}$ = 277 Hz, OCH_2CF_3), 134.7 (d, $^{2}J_{CH}$ = – 5 Hz), 138.1 (d, $^{1}J_{CH}$ = 177 Hz), 155.1, 181.2 ($^{2}J_{CH}$ < 1 Hz). MS (e.i.) m/z (%, intensity

of lowest m/z isotopomer): {287, 289} $[M - OCH_3]^+$ (< 1), {259, 261} $[M - CO_2CH_3]^+$ (40), {231, 233} (3), {219, 221} $[M - OCH_2CF_3]^+$ (2), 195 (2), {191, 193} $[M - CO_2CH_2CF_3]^+$ (60), 179 (5), 167 (27), {160, 162} (71), 143 (< 1), {132, 134} (84), {104, 106} (65), 83 (73), 69 (23), 59 (34), 53 (100), 33 (11), 29(11).

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of Tetrahydrophthalic Anhydride (**215f**).

Tetrahydrophthalic anhydride for the production of **216o** and **216p** was obtained from Aldrich and used as received. Reaction of **51** with **215f** according to the general procedure described above gave **216o**. Yield: 40 % by NMR and based on oxadiazoline; %(**215+216**) = 97 %.

6,6-Dimethoxy-3,4-tetramethylene-2H-pyran-2,5-(6H)-dione (**216o**). FTIR (gas phase) ν (cm^{-1}): 3018 (w), 2958 (m), 2874 (w), 2855 (w), 1756 (s), 1727 (m), 1256 (w), 1219 (m), 1207 (m), 1172 (s), 1075 (w), 999 (m), 977 (m). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.7 (m, 4H), 2.4 (m, 4H), 3.44 (s, 6H, $C(OCH_3)_2$); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 20.2, 20.6, 22.0, 24.9, 51.4, 109.3, 141.6, 143.5, 161.2, 185.6. MS (c.i.) m/z (%): 195 (2), 167 (45), 136 (25), 108 (45), 80 (40), 79 (100); MS (c.i., NH_3) m/z (%): 227 $[M + H]^+$ (100).

Thermolysis of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** in the presence of Tetrahydrophthalic Anhydride (**215f**).

Reaction of **210** with **215f** according to the general procedure described above gave **216p**. Yield by NMR: 25 % based on oxadiazoline. Product for characterization was isolated by preparative gas chromatography (%(**215**) = 69 %).

6-(2,2,2-Trifluoroethoxy)-6-methoxy-3,4-tetramethylene-2H-pyran-2,5-(6H)-dione (**216p**). FTIR (gas phase) ν (cm $^{-1}$): 3024 (w), 2959 (m), 2876 (w), 1764 (s), 1728 (m), 1293 (m), 1180 (s), 1155 (m), 1126 (w), 1075 (w), 995 (m). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.8 (m, 4H), 2.5 (m, 4H), 3.48 (s, 3H, OCH_3), 4.10 (m, 2H, OCH_2CF_3); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 20.2, 20.6, 22.2, 25.1, 52.1, 61.2 (q, $^{2}J_{CF}$ = – 36 Hz, OCH_2CF_3), 108.2, 122.9 (q, $^{1}J_{CF}$ = 278 Hz, $\underline{C}F_3$), 142.0, 143.9, 160.2, 184.6. ^{19}F-NMR (282.4 MHz, $CDCl_3$, referenced to $CFCl_3$ at 0 ppm) δ: –78.840 (t, $^{3}J_{HF}$ = 8.2 Hz, $OCH_2C\underline{F}_3$). MS (e.i.) m/z (%): 263 (< 1), 235 (18), 195 (< 1), 179 (3), 167 (24), 136 (24), 108 (45), 83 (19), 80 (37), 79 (100), 77 (27), 52 (18).

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of 4,5-Dichlorophthalic Anhydride (**215g**).

The 4,5-dichlorophthalic anhydride for production of **216q** was obtained from Aldrich and used as received. Reaction of **51** with **215g** according to the general procedure

described above gave **216q**. Yield: 60 % by NMR and based on oxadiazoline; %(**215+216**) = 94 %. Isolation was performed by stirring the crude reaction mixture with a heterogeneous aqueous sodium carbonate solution overnight. Selective hydrolysis of **215g** yielded a sample enriched in **216q**.

6,7-Dichloro-3,3-dimethoxy-2-oxa-2,3-dihydronaphthoquinone (**216q**). FTIR (gas phase) ν (cm^{-1}): 3095 (w), 3022 (w), 2963 (w), 2857 (w), 1770 (m), 1746 (m), 1587 (w), 1261 (s), 1174 (w), 1050 (m), 1004 (w), 967 (w). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.46 (s, 6H, OCH_3), 8.05 (s, 1H, aromatic), 8.20 (s, 1H, aromatic); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 51.9, 111.0, 127.4, 128.8, 130.0, 132.4, 140.2, 140.7, 159.8, 182.9. MS (e.i.) m/z (%, intensity of lowest m/z isotopomer): {259, 261, 263} (< 1), {231, 233, 235} (45), {217, 219, 221} (10), {200, 202, 204} (25), {173, 175, 177} (32), {172, 174, 176} (100), {145, 147, 149} (20), {144, 146, 148} (60), {109, 111} (40), 74 (35); MS (c.i., NH_3) m/z 291 $[M + H]^+$ (100).

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of 4-Nitrophthalic Anhydride (**215h**).

4-Nitrophthalic anhydride for production of **216r** and **216s** was obtained from Aldrich and used as received. Reaction of **51** with **215h** according to the general procedure described above gave **216r** and **s** in a 1.0:1 ratio by GC/MSD integration. Yield: 44 % by NMR and based on oxadiazoline; %(**215+216**) = 87 %.

3,3-Dimethoxy-6-nitro-2-oxa-2,3-dihydronaphthoquinone (**216r**) and *3,3-Dimethoxy-7-nitro-2-oxa-2,3-dihydronaphthoquinone* (**216s**). First isomer: MS (e.i.) m/z (%): 236 [M – OCH_3]$^+$ (<1), 208 [M – CO_2CH_3]$^+$ (56), 194 (10), 177 (42), 162 (27), 150 (42), 149 (100), 134 (9), 119 (8), 104 (19), 103 (70), 75 (85), 74 (44), 63 (9). Second isomer: MS (e.i.) m/z (%): 236 [M – OCH_3]$^+$ (<1), 208 [M – CO_2CH_3]$^+$ (55), 194 (6), 177 (43), 162 (31), 150 (42), 149 (100), 134 (9), 119 (10), 104 (20), 103 (70), 75 (95), 74 (45), 63 (10).

4.3 The Mechanism of Intramolecular 1,2-Shifts from a Tetrahedral Intermediate

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of Benzoylcyanide (**122b**).

A solution containing 0.0089g of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**), 0.006g of p-xylene (internal NMR integration standard) and 0.031g of benzoyl cyanide (**122b**) was dissolved in 0.5 mL benzene-d_6 and degassed, sealed in an NMR tube and heated at 110 °C for 22 hours in a constant temperature oil bath. The yield of **127b** (40% based on oxadiazoline) was determined by NMR integration of the product's methoxy signal versus the methyl signal of p-xylene. Larger-scale thermolyses were also performed in sealed tubes. Product for characterization was

isolated by preparative gas chromatography. Subjection of the reaction mixture to the thermolysis conditions for an additional 24 hours showed no product decomposition.

2-Cyano-2,2-dimethoxyacetophenone (**127b**). FTIR (gas phase) ν (cm $^{-1}$): 3078 (w), 3018 (w), 2955 (m), 2850 (w), 2241 (C≡N) (w), 1717 (C=O) (s), 1602 (w), 1452 (w), 1278 (w), 1202 (m), 1191 (m), 1147 (s), 1101 (s), 1075 (s), 1014 (m), 988 (m), 879 (m). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.58 (s, 6H, $C(OCH_3)_2$), 7.46 (t (fine coupling also), 2H, H_{meta}), 7.62 (t (fine coupling also), 1H, H_{para}), 8.17 (d (fine coupling also), 2H, H_{ortho}): ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 53.6 (OCH_3), 101.8 ($\underline{C}(OCH_3)_2$), 112.8 ($\underline{C}N$), 128.6, 130.4, 134.6, 187.6 (C=O). MS (e.i.) m/z (%): 179 $[M - CN]^+$ (2), 174 $[M - OCH_3]^+$ (3), 146 $[M - C_2H_3O_2]^+$ (6), 105 $[C_6H_5CO]^+$ (100), 100 $[(CH_3O)_2CCN]^+$ (9), 77 $[C_6H_5]^+$ (62), 51 (24), 50 (9).

Thermolysis of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** in the presence of Benzoylcyanide (**122b**).

A solution was prepared containing 0.29 g (0.05 M) of 2-methoxy-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**210**) and 0.16 g (0.05 M) of benzoyl cyanide (**122b**) dissolved in 25 mL benzene. The solution was sealed in a tube, and heated at 110 °C for 22 hours in a constant temperature oil bath. Analyses of the reaction mixture by GC, GC/MS and GC/FTIR were used to characterize the product.

2-Cyano-2-methoxy-2-trifluoroethoxyacetophenone (**127c**). FTIR (gas phase) ν (cm^{-1}): 3078 (w), 2959 (w), 2854 (w), 2242 (C≡N) (w), 1720 (C=O) (m), 1601 (w), 1585 (w), 1452 (w), 1421 (w), 1293 (m), 1186 (s), 1147 (m), 1111 (m), 1026 (m), 1026 (w), 986 (w), 885 (w). MS (e.i.) m/z (%): 247 $[M - CN]^+$ (1), 242 $[M - OCH_3]^+$ (<1), 214 (1), 174 $[M - OCH_2CF_3]^+$ (3), 168 (4), 146 (3), 105 $[C_6H_5CO]^+$ (100), 83 $[CF_3CH_2]^+$ (8), 77 $[C_6H_5]^+$ (56), 51 (19).

Thermolysis of Dimethoxyoxadiazoline **51** in the presence of Benzoylfluoride (**122c**).

A solution containing 0.0089g of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, 0.006g of p-xylene (internal NMR integration standard) and 0.035g of benzoyl fluoride was dissolved in 0.5 mL benzene-d_6, degassed, sealed in an NMR tube and heated at 110 °C for 22 hours in a constant temperature oil bath. The yield of **127d** (60% based on oxadiazoline) was determined by NMR integration of the product's methoxy signal versus the methyl signal of p-xylene. Subjection of the reaction mixture to the thermolysis conditions for an additional 24 hours did not show product decompostion. Attempted purification by preparative gas chromatography caused decomposition of the product. The product was isolated by distilling (0.2 mmHg) the solvent and excess benzoyl fluoride from the reaction mixture.

2-Fluoro-2,2-dimethoxy-acetophenone (**127d**). FTIR (gas phase) ν (cm^{-1}): ^{1}H-NMR (300 MHz, C_6D_6) δ: 3.24 (s, 6H, OCH_3), 7.02-7.15 (m, 3H, aromatic), 8.21-8.24 (m,

2H, aromatic); ^{13}C-NMR (75.5 MHz, C_6D_6) δ: 51.2, (other signals obscured by signals from benzene) 187.6, 203.7; ^{19}F-NMR (282.4 MHz, C_6D_6) δ: -99.07 (s). MS (e.i.) m/z (%): 179 $[M - F]^+$ (4), 167 $[M - OCH_3]^+$ (10), 151 (3), 105 $[PhCO]^+$ (85), 93 $[(CH_3O)_2CF]^+$ (85), 77 (100), 59 (30), 51 (50), 50 (20).

Thermolysis of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** in the presence of Benzoylfluoride (**122c**).

A solution was prepared containing 0.29 g (0.05 M) of 2-methoxy-2-(2,2,2-trifluoroethoxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**210**) and 0.16 g (0.05 M) of benzoyl fluoride (**122c**) dissolved in 25 mL benzene. The solution was sealed in a tube, and heated at 110 °C for 22 hours in a constant temperature oil bath. Analyses of the reaction mixture by GC, GC/MS and GC/FTIR were used to characterize the product.

2-Fluoro-2-methoxy-2-trifluoroethoxyacetophenone (**127c**). FTIR (gas phase) cm^{-1}: 3076 (w), 2969 (w), 2869 (w), 1722 (m), 1603 (w), 1453 (w), 1418 (w), 1296 (m), 1182 (s), 1014 (w), 916 (m). MS (e.i.) m/z (%): 226 $[M]^+$ (« 1), 247 $[M - F]^+$ (< 1), 235 $[M - OCH_3]^+$ (< 1), 227 (< 1), 185 (2), 167 $[M - OCH_2CF_3]^+$ (5), 161 $[CF_3CH_2OC(OCH_3)F]^+$ (100), 105 $[PhCO]^+$ (90), 83 $[CF_3CH_2]^+$ (37), 79 (12), 77 $[Ph]^+$ (80), 51 (34) 50 (9).

Reaction of Dimethoxyoxadiazoline **10** with Benzoyl Chloride **127a**.

A solution was prepared containing 0.12 g of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**) and 0.11 g of benzoyl chloride (**122a**) dissolved in 25 mL benzene. The solution was sealed in a tube, and heated at 110 °C for 22 hours in a constant temperature oil bath. Analyses of the reaction mixture by GC and GC/MS were used to characterize the product. An authentic sample of methyl benzoylformate (**9**) was obtained (Aldrich) and used to firmly match the mass spectra.

Methyl benzoylformate, **9**. MS (e.i.) m/z (%): 136 $[M - CO]^+$ (4), 105 $[M - CO_2CH_3]^+$ (100), 77 $[Ph]^+$ (72), 51 (33), 50 (15).

Thermolysis of Dimethoxyoxadiazoline **51** in the Presence of Benzalphthalide (**224**).

Dimethoxyoxadiazoline (**51**, 0.20 g) and two equivalents of benzalphthalide (**224**, 0.28 g) were dissolved in 25 mL of benzene and sealed in a thermolysis tube and heated for 20 hours at 110 °C. The reaction mixture was concentrated and separated by radial chromatography (silica; 2% ethyl acetate/hexanes) as a band following the fluorescent benzalphthalide band. Increasing the solvent polarity narrowed the gap between the product and excess trap. Isolated yield of **225**: 23 % based on oxadiazoline. NMR yield: 40 % based on oxadiazoline.

2-Benzylidene-6,6-dimethoxy-3,4-benzo-2H-pyran-5-(6H)-one (**225**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.49 (s, 6H, OCH_3), 6.73 (s, 1H, vinyl), 7.4-7.2 (m, 4H, aromatic), 7.59 (td, 1H, J = 7.7 Hz, J = 1.4 Hz, aromatic), 7.9-7.8 (m, 3H, aromatic), 8.05 (dd, 1H, J = 7.8 Hz, J = 1.2 Hz, aromatic); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 51.4 (OCH_3), 108.6 ($\underline{C}(OCH_3)_2$), 112.2 (–O–C=$\underline{C}$H–), 127.2, 127.4, 127.6, 128.4, 128.6, 129.5, 134.2, 134.2, 135.2, 145.0 (–O–$\underline{C}$=CH–), 185.1 (C=O). MS (e.i.) m/z (%): 296 $[M]^+$ (19), 265 $[M - OCH_3]^+$ (19), 251 (5), 237 $[M - CO_2CH_3]^+$ (6), 222 (69), 205 (39), 194 (18), 193 (15), 179 (64), 178 (20), 177 (28), 165 (100), 163 (23), 152 (15); MS (c.i., NH_3) m/z (%): 314 $[M + NH_4]^+$ (5), 297 $[M + H]^+$ (< 5), 265 $[M - OCH_3]^+$ (100). Exact mass: found ($C_{18}H_{16}O_4$): 296.1053, calc. ($C_{18}H_{16}O_4$): 296.1049.

4.4 Rearrangement Reactions of a Tetrahedral Intermediate

Thermolysis of Dimethoxyoxadiazoline **51** in the Presence of Fluroenone (**230**).

Dimethoxyoxadiazoline **51** (0.20 g) and two equivalents of 9-fluorenone **230** (0.45 g) were dissolved in 6 mL of benzene and sealed in a thermolysis tube and heated for 20 hours at 110 °C. The reaction mixture was concentrated and separated by centrifugal chromatography (silica; hexanes/ethyl acetate). The product **232** was isolated as a band following fluorenone. The product **233** was also isolated as a second band

following both **230** and **232**. The crude reaction mixture was analyzed by NMR using an internal standard added after the thermolysis. The isolated product **233** was not found in the reaction mixture. The product identified as **234** was identified in the crude mixture. Yields for **232** of 24 % and for **234** of 10 % were obtained based on oxadiazoline. Analysis of the reaction mixture after a thermolysis time of 6 hours revealed yields for **234** of 39% and for **232** of 10 % determined by NMR of the crude reaction mixture. These yields accounted for only 70 % decomposition of the oxadiazoline with this truncated reaction time.

Methyl 9-methoxy-fluorene-9-carboxylate (**232**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.87 (s, 3H, OCH_3), 3.57 (s, 3H, CO_2CH_3), 7.29 (m, 2H, aromatic), 7.40 (m, 2H, aromatic), 7.50 (m, 2H, aromatic), 7.65 (m, 2H, aromatic); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 51.7, 52.7, 88.4, 120.2, 124.6, 128.0, 129.9, 141.5, 171.2. MS (e.i.) m/z (%): 254 (5%), 223 (2%), 195 (100%), 180 (35%); MS (c.i., NH_3) m/z (%): 272 [M + NH_4]$^+$ (40%), 242 (45%), 240 (100%). m.p. = 118-120 °C, lit. m.p. = 125 °C.[4]

Methyl 9-hydroxyfluorene-9-carboxylate (**233**). MS (e.i.) m/z (%): 240 [M]$^+$ (8), 195 (13), 181 [M – $C_2H_3O_2$]$^+$ (100), 152 (28); MS (c.i.,NH_3) m/z (%): 258 [M + NH_4]$^+$ (100). Exact mass ($C_{15}H_{12}O_3$): found 240.0792, calc. 240.0786.

9-(Dimethoxymethylene)fluorene oxide (234). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.57 (two OCH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 52.9 (OCH_3), 74.9 (C-9), 105.1 [$\underline{C}(OCH_3)_2$], 119.9, 125.2, 127.5, 129.6, 138.1, 141.4.

Reaction of Dimethoxyoxadiazoline **51** with Coumarin **231**

Dimethoxyoxadiazoline **51** (0.20 g) and coumarin (**231**) (0.97 g) were dissolved in 25 mL of benzene and sealed in a thermolysis tube and heated for 20 hours at 110 °C. The reaction mixture was concentrated and the products separated by radial chromatography (silica; hexanes/ethyl acetate) as a band running ahead of the excess coumarin. Hydrolysis of the product was not apparent on the silica. Isolated yield: 20% based on oxadiazoline.

2-Methoxy-2-carbomethoxy-2H-1-benzopyran (**235**). FTIR (CCl_4, NaCl cell) cm^{-1}: 3505, 3025, 2990, 2945, 2825, 1750 (C=O), 1640 (C=C), 1455, 1235, 1170, 1110, 1035, 895. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.31 (s, 3H), 3.84 (s, 3H), 5.85 (d, 1H, ^3J = 9.8 Hz), 6.84 (d, 1H, ^3J = 9.8 Hz), 7.28-6.92 (m, 4H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 51.1 ($^1J_{CH}$ = 144 Hz), 53.1 ($^1J_{CH}$ = 148 Hz), 97.7, 116.2 ($^1J_{CH}$ = 162 Hz, $^2J_{CH}$ = – 7.6 Hz), 118.5 ($^1J_{CH}$ = 171 Hz), 118.9, 122.0 ($^1J_{CH}$ = 163 Hz, $^2J_{CH}$ = – 7.8 Hz), 127.1 ($^1J_{CH}$ = 160.3), 128.7 ($^1J_{CH}$ = 164 Hz, $^2J_{CH}$ = – 5.5 Hz), 130.1 ($^1J_{CH}$ = 162 Hz, $^2J_{CH}$ = – 8.9 Hz), 151.2, 167.7. MS (e.i.) m/z (%): 189 $[M - OCH_3]^+$ (15), 161 $[M - C_2H_3O_2]^+$ (100), 146 (12), 118 (40).

7,7-Dimethoxy-3-oxa-4,5-benzobicyclo[4.1.0]hept-4-ene-2-one (**236**).

0.936 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.11 (d, 1H, ^3J = 7.5 Hz, H-3), 2.42 (d, 1H, ^3J = 7.5 Hz, H-4), 6.9-7.3 (aromatic). MS (c.i., NH_3) m/z (%): 206 $[M + NH_4]^+$ (100), 189 $[M + H]^+$ (32).

Reaction of Methoxy(trideuteromethoxy)oxadiazoline (*methoxy-d_3*)-**51** with Fluorenone (**230**).

Trideuterated oxadiazoline (*methoxy-d_3*)-**51** was prepared from the reaction of methanol-d_4 with acetoxyoxadiazoline **207** using the procedure described above (see section 4.1). A solution was prepared containing 0.20 g of (*methoxy-d_3*)-**51** and 0.45 g of fluorenone (**230**) dissolved in 6 mL of benzene. The solution was heated at 110 °C in a constant temperature oil bath for 24 hours. The reaction mixture was separated as before by radial chromatography and the fraction corresponding to labelled **232** was analyzed by mass spectrometry.

(*methoxy-d_3*)-**51**. MS (c.i., NH_3) m/z (%): 184 $[M\text{-}d_6 + NH_4]^+$ (< 1), 181 $[M\text{-}d_3 + NH_4]^+$ (100), 178 $[M\text{-}d_0 + NH_4]^+$ (5).

232-d_3. MS (c.i.) m/z (%): 260 $[M\text{-}d_6]^+$ (0), 257 $[M\text{-}d_3]^+$ (100), 254 $[M\text{-}d_0]^+$ (9)

Reaction of Dimethoxyoxadiazoline **51** with ^{18}O-Fluorenone (^{18}O-**230**).

Labelled fluorenone was prepared according to the procedure of Proctor et al.[3] 0.093 g of fluorenone was dissolved in 4 mL benzene, 4 mL methanol, 1 μL HCl, and 50 μL $H_2{}^{18}O$ (50 atom % ^{18}O). The solution was placed in a sealed tube and heated at 80 °C for 18.5 hours. The solvents were removed by distillation and the solid remaining was subjected to reduced pressure in order to pump off all excess solvent. A solution was then prepared of 0.041 g of **51** and 0.046 g of ^{18}O-**230** dissolved in 1 mL of benzene. The solution was then heated in a sealed tube at 110 °C for 24 hours. GC/MS analysis of the reaction mixture revealed that the product **232** had incorporated the oxygen label (^{18}O-**232**).

Methyl 9-methoxyfluorene-9-carboxylate-[^{18}O] (^{18}O-**232**). MS (e.i.) m/z (% intensity of lowest m/z isoptomer): {254, 256} $[M]^+$ (2), 195 $[M - CO_2CH_3]^+$ (100), 180 (70), 163 (15), 152 (36).

Reaction of Methoxy(thiomethyl)carbene (**257**) with Fluorenone (**230**).

A solution was prepared containing 0.11 g of methoxy(thiomethyl)oxadiazoline **258** and 0.24 g fluorenone dissolved in 3 mL of benzene. The solution was then heated in a sealed tube at 110 °C for 24 hours. GC/MS analysis of the reaction mixture revealed a single product peak which corresponded in mass to an adduct of one carbene unit with the fluorenone. The reaction mixture was separated by radial chromatography (10 % ethyl acetate/hexanes). The product **259** was found to co-

elute with fluorenone and thus was not obtained as a pure compound. The product **260** was found to separate as a band following fluorenone.

Methyl 9-thiomethyl-9H-fluorenone-9-carboxylate (**259**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.56 (s, 3H, SCH_3), 3.66 (s, 3H, OCH_3), aromatic; ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 12.3, 53.0. 62.6, 170.4, 193.6. MS (e.i.) m/z (%): 270 $[M]^+$ (36), 223 (46), 211 (43), 195 (100), 180 (42), 165 (24), 164 (32), 163 (42), 152.

9-Methoxy-9-(methoxy(bis(thiomethyl))acetyl)-fluorene (**260**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.78 (s, 6H, two SCH_3), 3.55 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 7.27 (td, 2H, J = 7.6 Hz, 1.3 Hz), 7.40 (td, 2H, J = 7.4 Hz, 1.1 Hz), 7.66 (dd, 2H, J = 7.3 Hz, 0.6 Hz), 8.16 (d, 2H, J = 7.6 Hz); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 14.9, 52.6, 52.7, 101.8, 119.1, 126.6, 128.6, 129.4, 141.9, 170.0. MS (e.i.) m/z (%): 313 $[M - SCH_3]^+$ (100), 281 (4), 266 (20), 254 (12), 222 (15), 211 (20), 180 (15), 164 (18), 137 $[CH_3OC(SCH_3)_2]^+$ (98), 121 (18); MS (c.i., NH_3) m/z (%): 329 $[M - OCH_3]^+$ (78), 313 $[M - SCH_3]^+$ (100).

4.5 The Regiochemistry of Dimethoxycarbene Reaction with α,β-Unsaturated Carbonyl Compounds

Reaction of Dimethoxyoxadiazoline **51** with N-Phenylmaleimide (**270**).

Dimethoxyoxadiazoline (**51**, 0.20 g) and N-phenylmaleimide (**10**, 0.22 g) were dissolved in benzene and sealed in a thermolysis tube. The solution was heated to 110 °C for 20 hours in a constant temperature oil bath. Evaporation of the solvent yielded a mixture of N-phenylmaleimide **10** and the cyclopropane product **17**. Yield: 40 % by NMR and based on oxadiazoline.

6,6-Dimethoxy-3-aza-3-phenylbicyclo[3.1.0]hexan-2,4-dione (**271**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.89 (s, 2H, CH), 3.40 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 7.2-7.5 (m, aromatic); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 33.3 (d, $^{1}J_{CH}$ = 183 Hz, CH), 54.3 (q, $^{1}J_{CH}$ = 144 Hz, OCH_3), 96.4 ($\underline{C}(OCH_3)_2$), 126.3, 128.0, 128.2, 128.8, 170.1 (C=O). MS (e.i.) m/z (%): 247 $[M]^+$ (7), 232 $[M - CH_3]^+$ (2), 216 (3), 202, 201, 188, 173, 144, 128 $[M - PhNCO]^+$ (100), 119 (7), 113 (35), 99 (50), 91 (16), 59 (34), 55 (41).

4.6 Addition of Dialkoxycarbenes to 1,2-Bisketenes

Reaction of Dimethoxyoxadiazoline **51** with 2,3-bis(trimethylsilyl)-1,4-butadiene-1,4-dione (**292**).

A solution containing 0.06 g of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**51**) and 0.08 g of 3,4-bis(trimethylsilyl)cyclobut-3-ene-1,2-dione (**293**) dissolved in 12.5 mL of benzene was heated at 110 °C for 20 hours. Since the rate of formation of

the 1,2-bisketene **292** is faster than the rate of formation of the dimethoxycarbene **10**, there must have been sufficient 1,2-bisketene formed to serve as a good carbene trap. The reaction mixture was analyzed by GC, GC/MS, and GC/FTIR. GC/MS revealed a product with the mass of an adduct of one carbene unit with the bisketene. Evaporation of the solvent yielded (0.09 g) of crude mixture of product and 2,3-bis(trimethylsilyl)buta-1,3-diene-1,4-dione. The mixture was chromatographed by eluting through a small tube of silica gel using 10% ethyl acetate in hexanes to yield 0.07 g of the product **294** (Isolated yield: 62 % based on oxadiazoline). A small amount of 3,4-bis(trimethylsilyl)maleic anhydride was found in the reaction mixture which is known to result from the reaction of the 1,2-bisketene with atmospheric oxygen.[6]

4,5-bis(trimethylsilyl)-2,2-dimethoxycyclopent-4-ene-1,3-dione (**294**). FTIR (gas phase) cm^{-1}: 2957 (m), 2910 (w), 2848 (w), 1753 (w), 1714 (s), 1258 (m), 1196 (w), 1090 (s), 1051 (w), 977 (w), 858 (s), 777 (w). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.31 (s, 18H, $Si(CH_3)_3$), 3.50 (s, 6H, OCH_3); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 200.1 (C=O), 173.4 (vinyl), 85.5 ($\underline{C}(OCH_3)_2$), 51.3 (OCH_3), 0.12 ($Si(CH_3)_3$). MS (e.i.) m/z 300 $[M]^+$ (24 %), 285 $[M - CH_3]^+$ (25 %), 272 $[M - CO]^+$ (27 %), 257 (42 %), 242 (8 %), 226 (17 %), 155 $[Me_3Si\text{-}C{\equiv}C\text{-}SiMe_2]^+$ (100 %), 125 (83 %), 97 (28 %), 89 (25 %), 73 $[(CH_3)_3Si]^+$ (82 %), 59 (26 %), 45 (19 %); MS (c.i., NH_3) m/z 318 $[M + NH_4]^+$ (100 %), 301 $[M + H]^+$ (62 %). Exact mass ($C_{13}H_{24}O_4Si_2$): calculated = 300.1213, found = 300.1221.

Reaction of Methoxy(2,2,2-trifluoroethoxy)oxadiazoline **210** with 2,3-bis(trimethylsilyl)-1,4-butadiene-1,4-dione (**292**).

A solution containing 0.08 g of methoxy(2,2,2-trifluoroethoxy)oxadiazoline (**210**) and 0.08 g of 3,4-bis(trimethylsilyl)cyclobut-3-ene-1,2-dione (**293**) dissolved in 12.5 mL of benzene was heated at 110 °C for 20 hours. Analysis of the reaction mixture by GC and GC/MS revealed that the reaction mixture was contained many more products than the analogous reaction with dimethoxyoxadiazoline **51**. GC/MS revealed a product with the mass of an adduct of one carbene unit with the bisketene. An aliquot of the mixture was chromatographed by centrifugal chromatography on silica gel using 10% ethyl acetate in hexanes. The reaction mixture was separated by chromatography to give 0.003 g of the product **294**. Yield: 10 %. A small amount of 3,4-bis(trimethylsilyl)maleic anhydride was again found in the reaction mixture.[6]

4,5-bis(trimethylsilyl)-2,2-dimethoxycyclopent-4-ene-1,3-dione (**294**). FTIR (gas phase) cm^{-1}: 2992 (w), 2961 (m), 2910 (w), 1753 (m), 1714 (s), 1458 (w), 1419 (w), 1291 (m), 1259 (m), 1177 (s), 1099 (s), 1072 (m), 961 (w), 857 (s), 780 (w). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.33 (s, 18H, $Si(CH_3)_3$), 3.53 (s, 3H, OCH_3), 4.25 (q, ^3J = 8.7 Hz, 2H, OCH_2CF_3); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 0.07 ($Si(CH_3)_3$), 51.9 (OCH_3), 60.9 (q, $^2J_{HF}$ = 51 Hz, CH_2CF_3), 85.0, 174.0, 198.6 (C=O). MS (e.i.) m/z

(%) 368 $[M]^+$ (18), 353 $[M - CH_3]^+$ (20), 340 $[M - CO]^+$ (12), 325 (8), 310 (4), 269 (6), 257 (22), 226 (35), 170 (20), 155 $[Me_3Si\text{-}C{\equiv}C\text{-}SiMe_2]^+$ (100), 125 (64), 97 (30), 73 (100); MS (c.i., NH_3) m/z (%) 386 $[M + NH_4]^+$ (100). Exact mass ($C_{14}H_{23}F_3O_4Si_2$): calculated = 368.1087, found = 368.1087.

4.7 Reaction of Dimethoxycarbene with Activated Methylene Compounds

Typical thermolyses were performed with an oxadiazoline concentration between 0.03 and 0.10 M in dry benzene and one equivalent of trap. Samples were sealed in a resealable thermolysis tube and heated in a constant temperature oil bath at 110 °C for 20 hours. The crude reaction mixtures were analyzed by GC/MSD and GC/FTIR. The ketal **303** and enol ether **304** products are not stable to chromatography. Excess trap in the cases of **302a-c** could be removed under vacuum. This yielded samples which could be analyzed by ^1H- and ^{13}C-NMR spectroscopy without the spectra being obscured by excess trap. In the case of **302d** and **305** thermolyses at a 2-3:1 oxadiazoline:trap ratio resulted in samples which were fairly free of excess trap.

The products **303** and **304** are not stable as neat liquids as they are highly susceptible to hydrolysis. In the cases where isolation of the products of trapping was

not possible, spectroscopic analyses (^{1}H, ^{13}C, MS, FTIR) were most efficiently performed on the crude reaction mixtures.

Unless otherwise stated for the particular compound, ^{1}H and ^{13}C-NMR spectra were obtained with a Bruker AC-200 NMR spectrometer. Gas phase FT-IR: Hewlett-Packard HP-5890 gas chromatograph connected to a Bio-Rad FTS-40 FT-IR with a Bio-Rad GC/C 32 GC interface. MS(EI): HP-5890 Series II gas chromatograph with a 5971A mass selective detector. MS(CI): VG Analytical ZAB-E double focusing mass spectrometer.

Reaction of Dimethoxyoxadiazoline **51** with 2,4-Pentanedione **302a**.

A solution was prepared containing 0.13 g dimethoxyoxadiazoline **51** and 0.09 g of 2,4-pentanedione **302a** dissolved in 25 mL of benzene. The solution was sealed in a thermolysis tube and heated at 110 °C for 20 hours. The solvent and excess **302a** were removed under reduced pressure to give 0.05 g of a mixture of **303a** and **304a**. ^{1}H-NMR analysis of the mixture shows a mixture of 2.3:1 **303a**:**304a**. Total yield of carbene derived products = 25 % by NMR and based on oxadiazoline.

3-(Dimethoxymethyl)-2,4-pentanedione (**303a**). FTIR (gas phase) cm^{-1}: 3005 (w), 2961 (m), 2944 (m), 2844 (w), 1718 (s), 1444 (w), 1363 (m), 1284 (w), 1199 (m), 1120 (s), 1084 (s). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.17 (s, 6H, $COCH_3$), 3.31 (s, 6H, OCH_3), 4.01 (d, 1H, ^3J = 8.4 Hz, $(CH_3CO)_2C\underline{H}$), 4.94 (d, 1H, ^3J = 8.4 Hz,

$(CH_3O)_2\underline{C}H)$; ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ: 30.2 ($\underline{C}H_3CO$), 54.5 (OCH_3), 71.5 ($(COCH_3)_2\underline{C}H$), 103.1 ($\underline{C}H(OCH_3)_2$), 200.7 (C=O). MS (e.i.) m/z (%): 143 [M – OCH_3]$^+$ (4), 131 [M – CH_3CO]$^+$ (28), 127 (12), 101 (51), 85 (100), 83 (14), 75 [$(CH_3O)_2CH$]$^+$ (82), 69 (10), 55 (10), 47 (25), 43 (94).

3-(Methoxymethylene)-2,4-pentanedione (**304a**). FTIR (gas phase) cm^{-1}: 3017 (w), 2950 (w), 2856 (w), 1700 (s), 1610 (s), 1444 (w), 1369 (w), 1278 (s), 1191 (w), 1133 (s), 1066 (w), 995 (s), 958 (w). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.24 (s, 3H, $COCH_3$), 2.30 (s, 3H, $COCH_3$), 3.96 (s, 3H, OCH_3), 7.53 (s, 1H, vinyl); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 29.1 (CH_3), 32.0 (CH_3), 63.5 (OCH_3), 122.2 (vinyl), 166.9 (vinyl), 197.0 (C=O), 197.8 (C=O). MS (e.i.) m/z (%): 142 [M]$^+$ (5), 127 [M – CH_3]$^+$ (61), 85 (100), 69 (5), 43 (55); MS (c.i., NH_3) m/z (%): 160 [M + H]$^+$ (10), 143 [M + NH_4]$^+$ (100).

Conversion of **303a** to **304a** by the Addition of Pyridine.

Dimethoxyoxadiazoline **51** (0.10 g) and 2,4-pentanedione **302a** (0.07 g) were dissolved in 12.5 mL of benzene and sealed in a thermolysis tube. After thermolysis at 110 °C for 20 hours, 0.33 g of pyridine was added to the thermolysis tube and the mixture heated again for 20 hours. Conversion of the initial trapping product was found to be complete. The only product detectable by GC/MSD was **304a**. 0.03 g of

product was isolated. Addition of pyridine before the thermolysis of the oxadiazoline gives a low yield of products of carbene trapping.

Reaction of Dimethoxyoxadiazoline **51** with Methyl Acetoacetate (**302b**).

A solution was prepared containing 0.14 g of dimethoxyoxadiazoline **51** and 0.09 g of methyl acetoacetate **302b** dissolved in 25.0 mL of benzene. The solution was sealed in a thermolysis tube and heated at 110 °C for 20 hours. Removal of the solvent and excess **302b** yielded 0.08 g of a mixture of **303b** and **304b**. ^{1}H-NMR analysis of the mixture shows a mixture of 4.7:1 **303b**:**304b**. Total yield of carbene derived products = 43 % by NMR and based on oxadiazoline.

Methyl 2-(dimethoxymethyl)-3-oxobutanoate (**303b**). FTIR (gas phase) cm^{-1}: 3004 (w), 2962 (m), 2845 (w), 1765 (s), 1737 (s), 1441 (w), 1364 (m), 1299 (w), 1195 (s), 1138 (m), 1117(s), 1094 (s), 989 (w). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.23 (s, 3H, $C\underline{H}_3CO$), 3.35 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.69 (s, 3H, $CO_2C\underline{H}_3$), 3.84 (d, 1H, ^3J = 8 Hz), 4.91 (d, 1H, ^3J = 8 Hz); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 30.3 ($\underline{C}H_3CO$), 52.4 ($CO_2\underline{C}H_3$), 55.0 ($O\underline{C}H_3$), 55.2 ($O\underline{C}H_3$), 63.2 ($CO\underline{C}HCO$), 103.2 ($\underline{C}(OCH_3)$), 166.7 ($\underline{C}O_2CH_3$), 199.8 ($\underline{C}OCH_3$). MS (e.i.) m/z (%): 147 [M – CH_3CO]$^+$ (< 1%), 143 (10), 131 (14), 117 (30), 115 (6), 101 (5), 85 (100), 75 (85), 69 (14), 59 (11), 47 (17), 43 (37).

E,Z-Methyl 2-(methoxymethylene)-3-oxobutanoate (**304b**). FTIR (gas phase) cm $^{-1}$: 3025 (w), 2955 (m), 2856 (w), 1736 (s), 1708 (s), 1615 (s), 1441 (m), 1374 (m), 1287 (s), 1267 (s), 1196 (s), 1140 (s), 1079 (m), 997 (m). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.25 (s, 3H, CH_3CO), 2.30 (s, 3H, CH_3CO), 3.67 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.92 (s, 3H, CO_2CH_3), 3.94 (s, 3H, CO_2CH_3), 7.50 (s, 1H, vinyl), 7.51 (s, 1H, vinyl); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 28.5 ($COCH_3$), 31.5 ($COCH_3$), 51.6 (CO_2CH_3), 51.7 (CO_2CH_3), 63.5 (OCH_3), 63.6 (OCH_3), 113.2 (vinyl), 114.0 (vinyl), 165.4 (C=O), 165.6 (vinyl), 165.8 (C=O), 166.7 (vinyl), 195.0 (C=O), 196.5 (C=O). MS (e.i.) m/z (%): 158 $[M]^+$ (4), 143 $[M - CH_3]^+$ (58), 127 $[M - OCH_3]^+$ (17), 85 (43), 75 (100), 69 (15), 43 (37); MS (c.i., NH_3) m/z (%): 176 $[M + NH_4]^+$ (10), 159 $[M + H]^+$ (100).

Conversion of **303b** to **304b** by the Addition of Pyridine.

Dimethoxyoxadiazoline **51** (0.10 g) and methyl acetoacetate **302b** (0.08 g) were dissolved in 12.5 mL of benzene and sealed in a thermolysis tube. After thermolysis at 110 C for 20 hours, 0.33 g of pyridine was added to the thermolysis tube and the mixture heated again for 20 hours. Conversion of the initial trapping product was found to be complete. The only product detectable by GC/MSD was **304b**. 0.06 g of product was isolated. Addition of pyridine before the thermolysis of the oxadiazoline gives a low yield of products of carbene trapping.

Reaction of Dimethoxyoxadiazoline **51** with 3-Methyl-2,4-pentanedione **302c**.

A solution was prepared containing 0.20 g of dimethoxyoxadiazoline **51** and 0.14 g of 3-methyl-2,4-pentanedione **302c** dissolved in 25.0 mL of benzene. The solution was sealed in a thermolysis tube and heated at 110 °C for 20 hours. Removal of the volatiles under vacuum yielded clean **303c**. The yield was determined by the removal of an aloquot of the reaction mixture and the addition of an internal NMR standard. Yield of **303c** = 26 % by NMR and based on oxadiazoline.

3-Methyl-3-(dimethoxymethyl)-2,4-pentanedione (**303c**). FTIR (gas phase) cm^{-1}: 3002 (m), 2959 (b), 2943 (b), 2840 (m), 1712 (s), 1451 (b), 1360 (m), 1193 (m), 1110 (s), 1091 (s), 963 (w). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.38 (s, 3H, CH_3), 2.09 (s, 6H, $(C\underline{H}_3CO)_2C$). 3.49 (s, 6H, $(C\underline{H}_3O)_2C$), 4.90 (s, 1H, $C\underline{H}(CH_3)$); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 13.3 ($\underline{C}H_3$), 27.3 ($\underline{C}H_3CO$), 58.6 ($C(O\underline{C}H_3)_2$), 71.8 ($\underline{C}H(CH_3)$), 107.8 ($\underline{C}(OCH_3)_2$), 204.7 ($CH_3\underline{C}O$). MS (e.i.) m/z (%): 145 (13), 115 (36), 114 (15), 99 (100), 97, (8), 75 (57), 47 (17), 43 (76).

Reaction of Dimethoxyoxadiazoline **51** with Dibenzoylmethane **302d**.

A solution was prepared containing 0.12 g of dimethoxyoxadiazoline **51** and 0.19 g of dibenzoylmethane **302d** dissolved in 25.0 mL of benzene. The solution was sealed in

a resealable thermolysis tube and heated at 110 °C for 20 hours. Removal of the solvent yielded 0.24 g of a mixture of product **303d** and excess **302d**. Pure product was obtained by performing another thermolysis in which an excess of oxadiazoline was used in order to completely converted **302d** to product. A solution of **51** (0.15 g) and **302d** (0.08 g) in 25.0 mL of benzene was prepared and sealed in a resealable thermolysis tube. After thermolysis and solvent removal 0.14 g of product was obtained (50 % yield based on oxadiazoline).

2-(Dimethoxymethyl)-1,3-diphenyl-1,3-propandione (**303d**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.4 (s, 6H, $C(OC\underline{H}_3)_2$), 5.32 (d, 1H, ^3J = 7.9 Hz), 5.71 (d, 1H, ^3J = 7.9 Hz), 7.35 (m, 4H, aromatic), 7.48 (m, 2H, aromatic), 7.94 (m, 4H, aromatic); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 56.7, 61.1, 106.2, 128.1, 128.6, 133.3, 136.5, 192.0. MS (e.i.) m/z (%): 267 $[M - OCH_3]^+$(5), 193 $[M - C_6H_5CO]^+$ (40), 105 $[C_6H_5CO]^+$ (60), 77 $[C_6H_5]^+$ (25), 75 $[(CH_3O)_2CH]^+$ (100).

Reaction of Dimethoxyoxadiazoline **51** with Anthrone (**305**).

A solution was prepared containing 0.12 g of dimethoxyoxadiazoline **51** and 0.15 g of anthrone **305** dissolved in 25.0 mL of benzene with one drop of pyridine. The solution was sealed in a resealable thermolysis tube and heated at 110 °C for 20 hours. Removal of the solvent yielded 0.19 g of a mixture of product and excess anthrone. Pure product was obtained by performing another thermolysis in which an

excess of oxadiazoline was used which completely converted the anthrone to product. A solution of 0.15 g of **51** and 0.11 g of **305** in 25.0 mL of benzene with two drops of pyridine was prepared and sealed in a resealable thermolysis tube. After thermolysis and solvent removal 0.17 g of product was obtained (68 % yield based on oxadiazoline).

9-((Dimethoxy)methoxy)anthracene, **13**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.54 (s, 6H, $C(OC\underline{H}_3)_2$), 5.74 (s, 1H, $C\underline{H}(OCH_3)_2$), 7.45 (m, 2H, aromatic), 7.5 (m, 2H, aromatic), 7.95 (m, 2H, aromatic), 8.23 (s, 1H, 10-H), 8.50 (m, 2H, aromatic); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 51.3 ($C(O\underline{C}H_3)_2$), 116.4 ($\underline{C}(OCH_3)_2$), 122.9, 123.1, 125.2, 125.3, 128.0, 132.0, 146.4. MS (e.i.) m/z (%): 268 $[M]^+$ (2), 237 $[M - OCH_3]^+$ (9), 221 (5), 193 (38), 165 (71), 164 (18), 163 (31), 139 (12), 115 (5), 75 (100), 63 (5), 47 (30).

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