CARBENES AND RADICALS FROM BENZYLOXY Δ^3-1,3,4-OXADIAZOLINES

By

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Δ^3-1,3,4-OXADIAZOLINES

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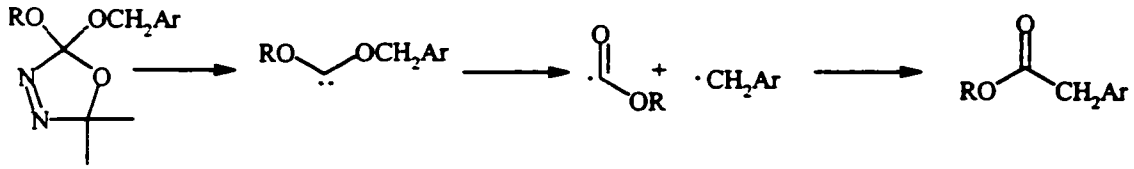
Abstract

Recently, dialkoxycarbenes bearing the appropriate carbene substituents have been reported to fragment to radical pairs at moderate temperatures (110°C). This dissertation investigates the fragmentation of dialkoxycarbenes bearing one or two benzyloxy groups to a radical pair or a diradical. Δ^3-1,3,4-Oxadiazolines, which are established precursors of dialkoxycarbenes, were utilized to generate the benzyloxycarbenes.

Dialkoxycarbenes bearing one of two benzyloxy substituents fragment to an alkoxycarbonyl and a benzyl radical and subsequent radical coupling afford phenylacetates, Scheme I. The rate constant for this fragmentation is estimated to be 10^7 s^{-1}. Utilizing benzyloxy(*p*-substituted-benzyloxy)carbenes the substituent effects on the fragmentation were studied. A preference for the cleavage to the benzyl group bearing the electron-withdrawing group was observed and this suggests that the transition state for fragmentation of benzyloxycarbenes is quite polar.

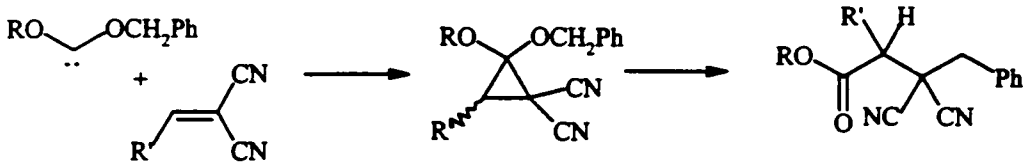


R =CH_3, CH_2Ph

Scheme I

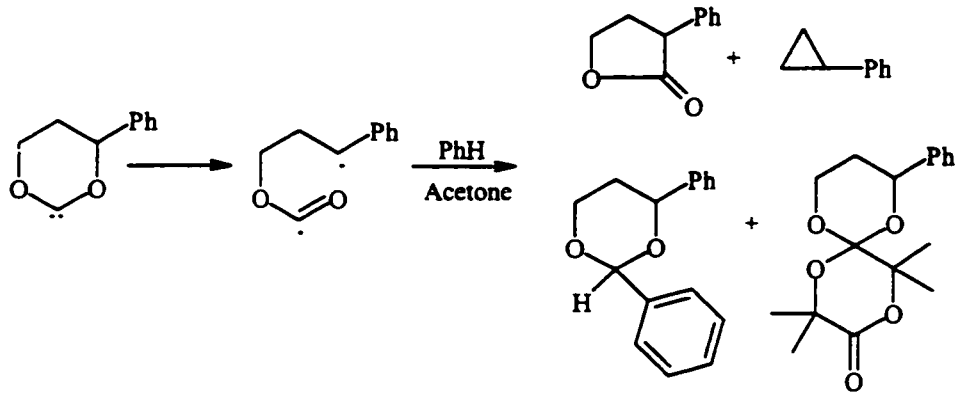
After establishing the homolysis of benzyloxycarbenes to radical pairs in solution, carbene traps were used to determine if these carbenes underwent intermolecular

reactions with alkenes in competition with carbene fragmentation. Alkenes bearing two cyano groups (methylidenemalononitriles) were cyclopropanated by the benzyloxycarbenes followed by rearrangement of the cyclopropanes, Scheme II. Alkenes bearing substituents that are less electron withdrawing, such as phenyl and ester groups did not react with benzyloxycarbenes. Fragmentation of these carbenes was faster than their addition of the carbene to the alkenes and products from radical coupling and radical additions to the double bonds were detected.



Scheme II

The chemistry of a six-membered-ring dioxycarbene, 1,3-dioxa-4-phenyl-cyclohex-2-ylidene, was also studied. Fragmentation of 1,3-dioxa-4-phenyl-cyclohex-2-ylidene affords a diradical and some unique chemistry of this diradical was observed. Along with typical diradical chemistry, such as coupling, novel products from the intermolecular homolytic aromatic substitution of the diradical onto benzene and reaction of the diradical with acetone were isolated, Scheme III. Intermolecular reactions of diradicals are rare and coupling and disproportionation dominate. The unusual reactivity of this diradical is assumed to be related to the conformation in which it is born.



Scheme III

Acknowledgements

I owe Prof. John Warkentin my deepest gratitude for providing me with an enjoyable and stimulating work environment. His patience and encouragement over the past four years is appreciated. I would also like to thank my committee members Profs. Bell and McGlinchey for offering helpful insight and support throughout the thesis.

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List of Abbreviations

AHC	alloxy(hydroxy)carbene
CI	chemical ionization
DMAD	dimethyl acetylenedicarboxylate
DMB	1,4-dimethoxybenzene
EI	electron impact
FID	flame ionization detector
GC	gas chromatography
HMBC	heteronuclear multiple bond correlation
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
KIE	kinetic isotope effect
LUMO	lowest unoccupied molecular orbital
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
ROESY	rotating frame Overhauser enhancement spectroscopy
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy

Chapter 1

Introduction

Reactive intermediates are an important aspect of chemistry. Most chemical reactions involve reactive intermediates (C*) during the conversion of reactants (A) to products (B, equation 1).

$$A \longrightarrow C^* \longrightarrow B \qquad (1)$$

In organic chemistry the four most common carbon-centered reactive intermediates are, carbocations, carbanions, free radicals and carbenes. Carbocations, carbanions and free radicals are trivalent species and are either charged or neutral (Figure 1), whereas carbenes are divalent and neutral. Carbenes have been recognized intermediates since the early 20th century. Methylene ($:CH_2$), the simplest carbene was first observed experimentally in 1959 by microwave spectroscopy.[1]

Figure 1: Organic reactive intermediates

1.1 Electronic Configuration of Carbenes

Carbenes are neutral carbon-centered divalent intermediates with four bonding and two non-bonding electrons. Unlike most molecules carbenes have two low lying electronic states that are energetically accessible, a singlet and a triplet.[2] A linear carbene would have two non-bonding orbitals that are identical, but experimental and theoretical results have shown that methylene is bent. Therefore, carbenes are generally thought of as sp^2 hybridized with two non-degenerate, non-bonding orbitals, an in-plane sp^2 orbital (σ), and a perpendicular *p*-orbital. Arrangement of the non-bonding electrons into these orbitals dictates the spin state of the carbene. The singlet electronic configuration has two electrons paired in the σ-orbital with the higher energy *p*-orbital vacant. Triplet carbenes have one electron in a σ-orbital and the other in a *p*-orbital and these two electrons have parallel spins. Figure 2 shows the two electronic configurations for carbenes.

Triplet Carbene Singlet Carbene

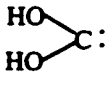
Figure 2: Singlet and triplet states of carbenes

Methylene is the simplest carbene and its electronic structure has been thoroughly examined since the 1930's.[2] Experimentally,[3] and theoretically,[4] it has been determined that methylene is a triplet in its ground state and has a H-C-H bond angle of 130°. Singlet

methylene has a H-C-H bond angle of 102° and is approximately 10 kcal mol^{-1} higher in energy than the triplet.

Substituents affect the singlet-triplet gap (ΔE_{ST}) of carbenes.[5] Increasing the size of the carbene substituents from hydrogen to bulky alkyl groups causes steric effects, which in turn affect the multiplicity of the carbene. These bulky substituents favour large carbene bond angles; for example, diadamantylcarbene has a triplet ground state with a carbene bond angle of 152°.[6] Alternatively, cyclic carbenes with a considerable amount of angle strain have bond angles closer to 100° and the singlet ground state is lower in energy.[7] For example, cyclobutylidene has a carbene bond angle of 96.1° and the singlet state is favoured by 5.4 kcal mol^{-1}.[8] As the size of the ring increases in these cycloalkylidenes the singlet becomes destabilized with respect to the triplet.[9] Secondly, substituents that are more electronegative than carbon decrease the *p*-character of the non-bonding σ-orbital; therefore these carbenes have singlet ground states.[10,11] Substituents with electron pairs (O, N, F, S) donate electron density to the virtual *p*-orbitals of singlets; thereby increasing the stability of the singlet state.[12,13] The singlet-triplet gap (ΔE_{ST}) was found to be 79.4 kcal mol^{-1} for imidazolin-2-ylidene (**1**), a diaminocarbene.[14] Oxygen substituents also stabilize the singlet with respect to the triplet. For example, singlet dihydroxycarbene (**2**)[10d] is 19 kcal mol^{-1} lower in energy than the triplet, and singlet dimethoxycarbene[13] (**3**) was calculated to be 24 kcal mol^{-1} more stable than the triplet.

1



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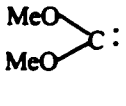


3

On the other hand substituents that are more electropositive than carbon (Li, B, Si) stabilize the triplet state of a carbene.[11] Carbenes with electron-withdrawing groups, such as aryl,[15] vinyl,[16] cyano,[7] and carbonyl[7] groups also have triplet ground states.

1.2 Singlet *versus* Triplet Reactivity

Singlet and triplet carbenes have different reactivities. Skell and Woodworth[17] developed a method for distinguishing between these two spin states based on the cyclopropanation of double bonds. In general triplet carbenes tend to react as diradicals. However, singlet carbenes can react *via* a concerted mechanism. Singlet dimethylcarbene reacted with *cis*-2-butene by a concerted mechanism yielding a cyclopropane in which the stereochemistry was conserved (Figure 3a). Alternatively, triplet carbenes cannot react with alkenes in a concerted fashion as a result of spin conservation, and add stepwise (Figure 3b). After addition of the carbene to the alkene intersystem crossing to the singlet diradical must occur before closure, allowing for bond rotation, as a result *cis*- and *trans*-cyclopropanes are formed. Figure 3 shows this difference in stereochemistry for the reactions of singlet and triplet dimethylcarbene.

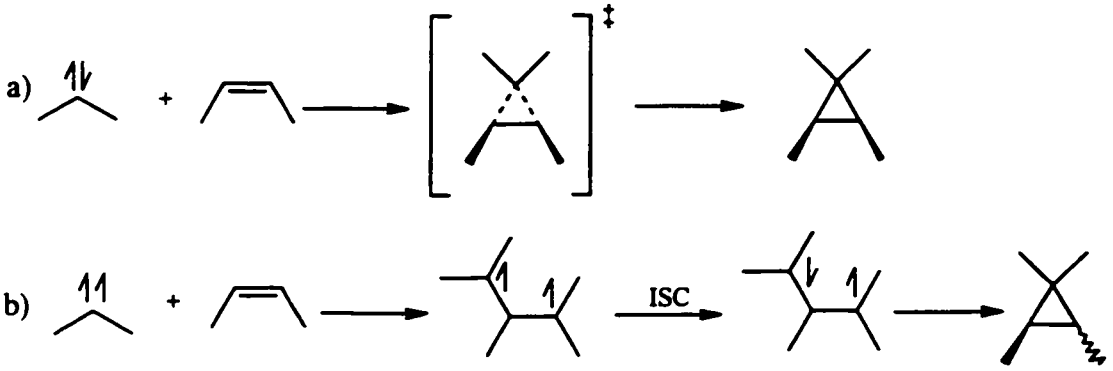


Figure 3: Addition of singlet and triplet dimethylcarbene to *cis*-2-butene

Triplet states of dioxycarbenes lie approximately 24 kcal mol^{-1} above the singlet states, indicating that the triplet states are not largely populated and do not contribute to the reactivity of dioxycarbenes. Dioxycarbenes react as singlets and are the focus of this dissertation.

1.3 Electrophilic *versus* Nucleophilic Reactivity of Singlet Carbenes

Carbenes have six valence electrons and are isoelectronic with carbocations. Thus, singlet carbenes are expected to react as electrophiles. In the 1950's Skell[18] and Doering[19] reacted dichlorocarbene ($:CCl_2$) and dibromocarbene ($:CBr_2$) with a set of alkenes and observed that these carbenes reacted selectively within the series. Increasing rate constants were observed as the substitution on the alkene increased, suggesting that the transition state was similar to that of electrophilic bromination of alkenes. Therefore $:CBr_2$ and $:CCl_2$ are electrophilic carbenes. With improved methods for carbene generation an expanse of carbenes are available for determining their "philicity."[20] Since

the 1970's a large collection of carbenes have been identified as electrophiles, nucleophiles or ambiphiles.

Moss and his co-workers,[21] utilizing a free energy relationship (equation 2), have developed a "carbene selectivity spectrum" in which the position of the singlet carbene on this spectrum reflects its "philicity." The "carbene selectivity index" (m_{CXY}) is a measure of the relative reactivities of carbenes with alkenes.[22,20,21]

$$m_{CXY} = -1.10\Sigma_{X,Y}\sigma_R^{+} + 0.53\Sigma_{X,Y}\sigma_I^{+} - 0.31 \qquad (2)$$

Relative rates of addition for a given carbene (:CXY) to a set of alkenes are plotted against the relative rates for addition of dichlorocarbene ($:CCl_2$) to the same set of alkenes. A log-log correlation gives a slope of m_{CXY}; ambiphiles have a m_{CXY} of approximately 1.5 and nucleophilic carbenes have a m_{CXY} greater than 2.2. The dependence of m_{CXY} on σ_R and σ_I allows for the calculation of the "philicity" of unknown carbenes.[21] For example, the calculated m_{CXY} for dimethoxycarbene (**3**) is 2.2, which indicates that it is nucleophilic. Experimentally, it has been determined that dimethoxycarbene (**3**) is indeed nucleophilic as it adds primarily to electron deficient alkenes, such as styrene, diethyl malonate, ethyl cinnamate,[23] acrylonitrile, chloroacrylonitrile, and methyl acrylate.[24] Dimethoxycarbene (**3**) does not add to electron rich alkenes such as cyclohexene.[25,26] Ambiphilic carbenes have been observed experimentally and include, MeOCCl,[27] MeOCPh,[28] and MeCOMe.[29]

Moss' selectivity spectrum can be understood using a frontier molecular orbital approach (FMO). The carbene's expressed "philicity" is determined by the differential orbital interaction between the Lowest Unoccupied Molecular Orbital (LUMO) and

Highest Occupied Molecular Orbital (HOMO) of either the carbene or the alkene at the transition state as shown in Figure 4.

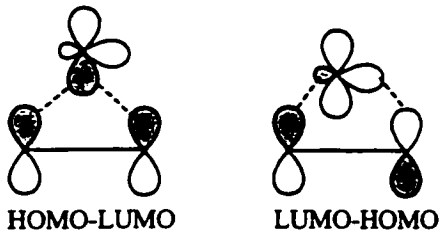


Figure 4: Molecular orbital (MO) interactions for a carbene with an alkene

For electrophilic carbenes the dominant interaction is between the LUMO of the carbene (vacant *p*-orbital) and the HOMO of the alkene (π). Contrarily, for nucleophilic carbenes the principal interaction is between the HOMO of the carbene (filled σ) and the LUMO of the alkene (π^*). For ambiphilic carbenes both of these interactions are important (Figure 5).[21]

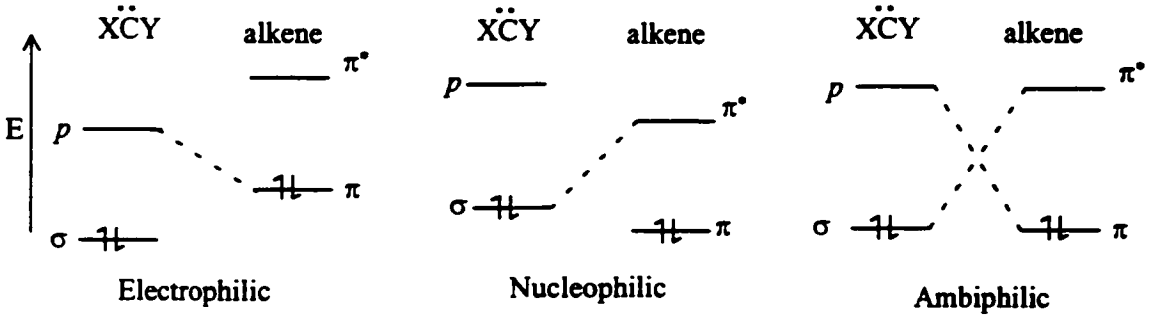


Figure 5: HOMO - LUMO interactions for electrophilic, nucleophilic, and ambiphilic carbenes with an alkene

Energies of the carbene *p*- and σ-orbitals are readily available from *ab initio* calculations and the alkene π and π^* molecular orbital energies are available from spectroscopy.[21] Substituents on both the alkene and the carbene affect the HOMO and LUMO energies.

As the alkene becomes more electron rich the energy of the HOMO (π) increases. Alternatively, the energy of the LUMO (π^*) decreases as the alkene becomes more electron deficient.[30] Electron donating substituents on the carbene raise the energy of the LUMO (*p*) and the carbene is nucleophilic. Electrophilic carbenes with electronegative groups that are poor electron donors (F, Cl, Br) lower the LUMO (*p*) of the carbene.[31]

In general, electrophilic carbenes add to electron rich alkenes with increasing rates as the electron density of the alkene increases. Nucleophilic carbenes add to alkenes with increasing rates as the alkene becomes more electron deficient. Ambiphilic carbenes have high affinities for both electron rich and electron poor alkenes, but add poorly to alkenes with intermediate π-electron density.[21]

Ab initio calculations support the use of the FMO approach discussed above. Addition of methylene (CH_2) to ethylene with a C_{2v} symmetric transition state is forbidden according to the Woodward-Hoffmann rules for cycloadditions.[32] Therefore, attack of a carbene on ethylene has C_s symmetry (Figure 6).[33]

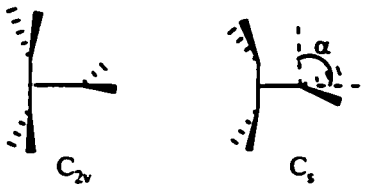


Figure 6: Transition states for approach of a carbene to ethylene

Ab initio calculations indicated a two-phase process for the addition of a carbene to an alkene. Firstly, an electrophilic phase occurs in which there is maximum overlap between the filled π-orbital of ethylene with the virtual carbene *p*-orbital. A second nucleophilic

phase follows this electrophilic phase in which the carbene lone pair is involved in bonding.[31] The reactivity of singlet carbenes towards alkenes is reflected in the energy of activation (E_a). The transition state for the addition of an electrophilic carbene to an alkene is early and approximates the first or electrophilic phase. Alternatively, addition of a nucleophilic carbene to an alkene has a late transition state and resembles the second or nucleophilic phase.[31]

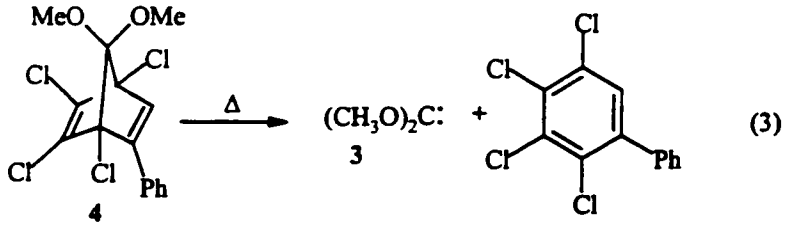
Utilizing *ab initio* calculations, Houk described the addition of methylene to ethylene in terms of the carbene tilt angle (α, Figure 6). Since reaction of an electrophilic carbene with an alkene has an early transition state the carbene approaches the alkene with greater π-bonding and a tilt angle of 0° would be expected. On the other hand, a nucleophilic carbene approaches the alkene with greater σ-bonding as a result of its late transition state. Thus, the tilt angle for nucleophilic carbenes should be closer to 90°. Computationally, dimethoxycarbene, a nucleophilic carbene, has a tilt angle of 58° and dichlorocarbene and difluorocarbene, which are electrophilic carbenes, have a tilt angle less than 45°.[31]

1.4 Generation of Dioxycarbenes

1.4.1 Thermolysis of Norbornadienone Ketals

A dioxycarbene was first generated in 1935;[34] nevertheless, a convenient source of dioxycarbenes was not discovered until 1964.[25,35,36] At that time, Hoffmann and Lemal

independently reported that cycloelimination of substituted norbornadienone ketal, **4**, leads to dimethoxycarbene (**3**) and tetrachlorobiphenyl (equation 3). These systems are attractive because the combination of aromatization with the relief of ring strain provides a considerable driving force.[26]



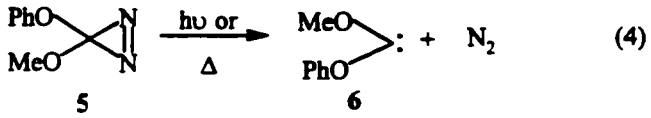
4 (3)

A wide variety of dioxycarbenes can be produced using this method, but undesirable biphenyl products are formed which interferes with the isolation of carbene derived products.[37]

1.4.2 Decomposition of Diazirines

Diazirines are established thermal and photochemical precursors to carbenes[38] but they were not used to produce dioxycarbenes until 1987. Moss and co-workers developed the first photochemical source of dioxycarbenes. 3-Methoxy-3-phenoxydiazirine (**5**),[39] synthesized using the diazirine exchange method,[40] yielded methoxy(phenoxy)carbene (**6**) either photochemically or thermally (equation 4). Dimethoxycarbene was also generated by this method.[24] Thermal and photochemical decompositions of diazirines are clean and they are well suited for the direct observation of carbenes, making them convenient for kinetic studies. One limitation with using diazirines as sources for dioxycarbenes is that

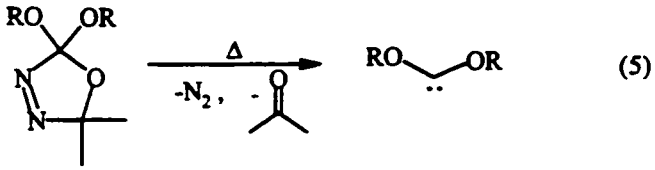
they are hazardous compounds, generally available only in dilute solutions,[41] and therefore they are not convenient for synthetic work.



5 6 (4)

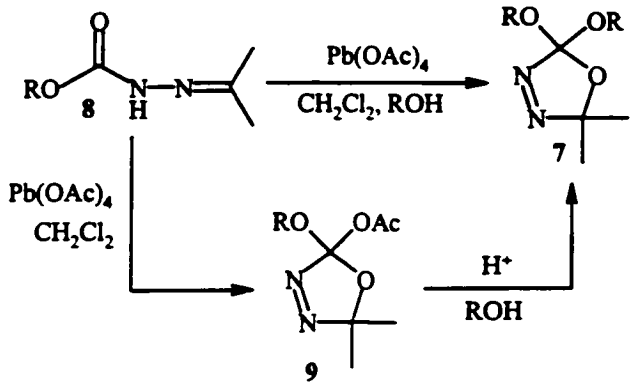
1.4.3 Thermolysis of Δ^3-1,3,4-Oxadiazolines

Warkentin and co-workers developed Δ^3-1,3,4-oxadiazolines as precursors for dioxycarbenes.[42,43] Upon thermolysis dioxy oxadiazolines lose nitrogen and acetone to yield the dioxycarbene (equation 5).



(5)

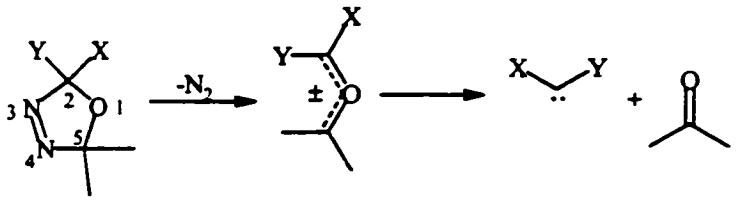
Oxadiazolines **7** are synthesized by the lead(IV) acetate oxidation of the (alkoxycarbonyl)-hydrazones of acetone (**8**) in the presence of the desired alcohol.[44,45] Convenient preparations of substituted oxadiazolines may also be achieved by exchange of the acetoxy group in 2-acetoxy-2-alkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines (**9**) with an alcohol, Scheme 1.[46]



Scheme 1

A wide variety of oxadiazolines have been prepared, and they are known to be shelf stable for long periods. Carbenes can be generated at reasonable temperatures and the side products of the thermolysis (N_2 and acetone) do not interfere with the isolation of products.[46]

Thermolysis of oxadiazolines involves a stepwise mechanism in which nitrogen is first lost to form a carbonyl ylide. Subsequent fragmentation of this ylide yields acetone and the carbene (equation 6).

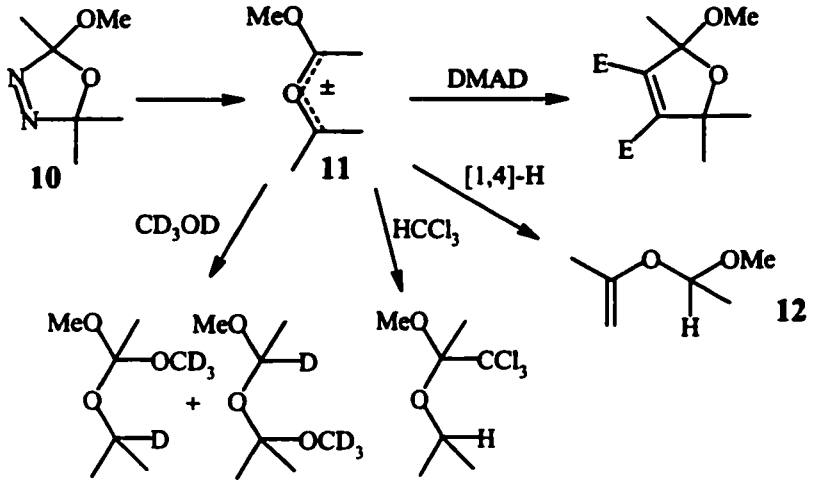


(6)

Substituent effects for the decomposition of 2-aryl-2-methoxy-Δ^3-1,3,4-oxadiazolines were consistent with a concerted loss of nitrogen from the oxadiazoline.[47] An enhancement in the thermolysis rate constant was observed when the *para* substituent was electron-withdrawing. Therefore, C2 becomes more electron-rich as nitrogen is lost from the oxadiazoline, which is consistent with an ylide-like transition state. Similarly, an

increase in the thermolysis rate constant was observed for the decomposition of 2-aryloxy-2-phenoxy oxadiazolines as the *para* substituent became more electron-withdrawing. This enhancement is also consistent with the involvement of a carbonyl ylide intermediate in the decomposition of oxadiazolines.[48]

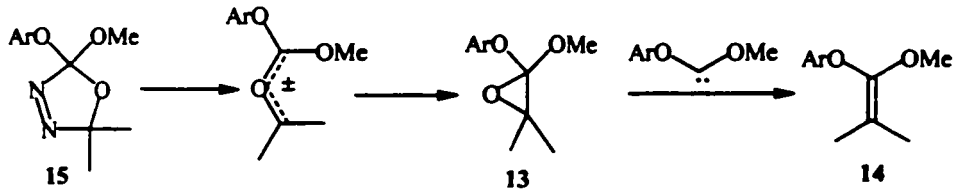
Evidence for the involvement of carbonyl ylide intermediates in the decomposition of oxadiazolines has been obtained from the thermolysis of 2-methyl-2-methoxy oxadiazoline (**10**). Carbonyl ylide **11** was trapped with deuterated methanol,[49] alkenes (*cis*-dichloroethylene, 2,5-norbornadiene),[50] dimethyl acetylenedicarboxylate (DMAD), acetone,[51] and chloroform,[52] Scheme 2. Enol ether **12** was also formed from a [1,4]-sigmatropic shift in **11**.



Scheme 2

Confirmation for the involvement of carbonyl ylide intermediates in the thermolysis of dialkoxy oxadiazolines has been challenging. Smith has calculated that a carbonyl ylide is not an intermediate in the decomposition of 2,2-dimethoxy-5,5-

dimethyl-Δ^3-oxadiazoline. Rather, formation of the carbene and acetone occurs simultaneously with loss of nitrogen from the oxadiazoline.[53] Warkentin and Couture observed oxirane **13** and ketene acetal **14** from the thermolysis of aryloxy methoxy oxadiazoline **15**. Their formation was best rationalized to be from the carbonyl ylide (equation 7).[54]

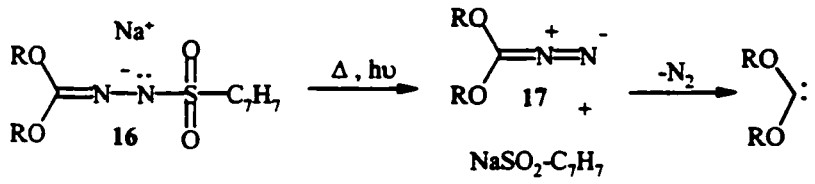


(7)

The proposed mechanism involves closure of the carbonyl ylide to an oxirane, **13**, and subsequent oxygen abstraction by a second molecule of carbene generates the ketene acetal, **14**. Deoxygenation of oxiranes has been observed with dimethoxycarbene.[55,56] Ketene acetals were also detected from the thermolysis of diaryloxy oxadiazolines.[48] Observation of these ketene acetals suggests that carbonyl ylides are intermediates in the decomposition of dialkoxy and diaryloxy oxadiazolines.

1.4.4 Decomposition of *p*-Tosylsulfonylhydrazones

A variety of oxy-[57,58,59] and dioxycarbenes[60,61,62] have been produced from *p*-tosylsulfonylhydrazones. Tosylhydrazone salts, **16**, decompose photochemically[63] or thermally to give first the diazo compounds, **17**, which under aprotic conditions lose nitrogen to yield carbenes (equation 8).



Dioxy- and oxycarbenes are commonly formed from the pyrolysis of the tosylhydrazone salts and not from photolysis. High temperatures (158 - 310°C) were required for the decomposition of tosylhydrazone salts and many of the carbenes generated fragmented at those temperatures. Fragmentations of these and other carbenes are discussed in Section 1.5.2.1.

1.5 Chemistry of Nucleophilic Carbenes

In the following sections the chemistry of nucleophilic carbenes will be discussed.[64] Main emphasis will be on dioxycarbenes, which will provide the required background for Chapter 2.

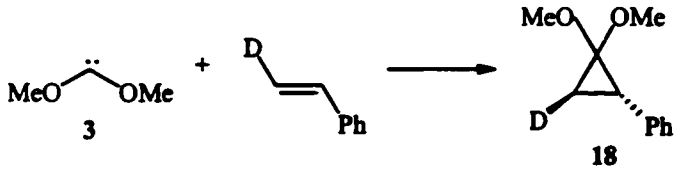
1.5.1 Intermolecular Reactions

1.5.1.1 Addition of Nucleophilic Carbenes to Alkenes

A well-known reaction of carbenes is the cyclopropanation of alkenes. Nucleophilic carbenes add poorly to electron rich alkenes as discussed in Section 1.3. Early experiments revealed that dimethoxycarbene (3) failed to react with cyclohexene, a commonly used carbene trap.[25,26] Moss observed increasing rate constants for the addition

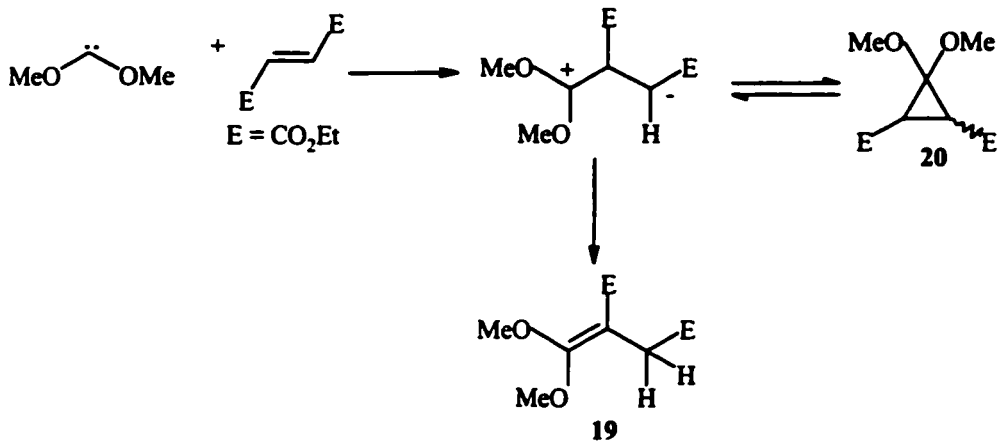
of dimethoxycarbene (3) to tetramethylethylene, acrylonitrile and chloroacrylonitrile ($<10^3$, $\sim10^3$ and 5 x 10^5 $M^{-1}s^{-1}$),[24] suggesting that an electron-withdrawing group is required to activate the alkene towards attack by nucleophilic carbenes.

Dimethoxycarbene (3) reacted with electron deficient alkenes, such as, styrene, 1,1-diphenylethylene, methyl acrylate, ethyl cinnamate and acrylonitrile,[23,24] yielding cyclopropanes. Utilizing β-deuteriostyrenes, Moss proposed a concerted mechanism for the carbene addition, since the cyclopropanation occurred with retention of stereochemistry (equation 9).[65]



(9)

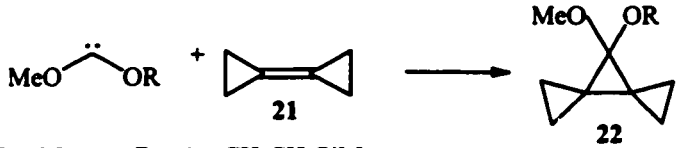
On the other hand, Hoffmann discovered that the reaction of dimethoxycarbene (3) with diethyl fumarate and diethyl maleate yielded the ketene acetal and not the expected cyclopropanes.[23] Scheme 3 shows the reaction between dimethoxycarbene (3) and diethyl fumarate affording ketene acetal **19**, and not cyclopropane **20**. A stepwise mechanism is proposed in which the dipolar intermediate is in equilibrium with cyclopropane **20**. Formation of **19** is a result of a [1,2]-proton shift in the dipolar intermediate.



Scheme 3

Dimethoxy- and dialkoxycarbenes add to many electrophilic alkenes yielding cyclopropanes and other novel compounds. The mechanism of cyclopropanation appears to be concerted with β-deuteriostyrenes but as Hoffmann observed, the mechanism may actually involve a dipolar intermediate that closes to give the cyclopropane. Several examples of the reactions of dialkoxycarbenes with electron deficient alkenes will be discussed in the following section.

Strained alkenes, for example bicyclopropylidene, (**21**) are attacked by dialkoxycarbenes yielding triangulanes, **22** (equation 10).[66]

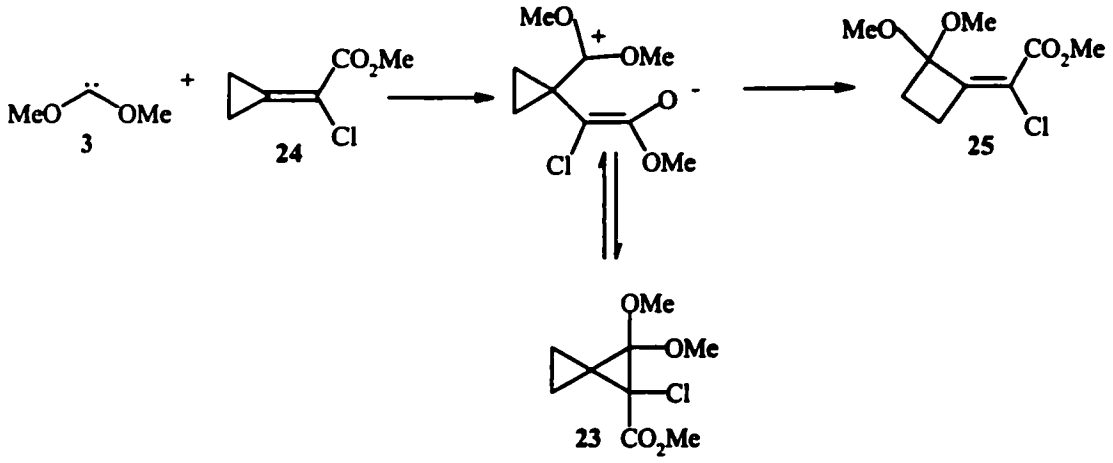


R = Me, *tert*-Bu, Ac, $CH_2CH_2SiMe_3$
CH_2CH_2Cl, CH_2CH_2Br

(10)

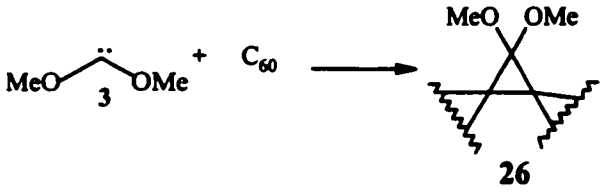
Spiro compound **23**, was not observed from the addition of dimethoxycarbene (**3**) to methylenecyclopropane **24**.[66] Ring expansion of the dipolar intermediate yielded **25** as the

major product along with other products proposed to be formed *via* the dipolar intermediate, Scheme 4.



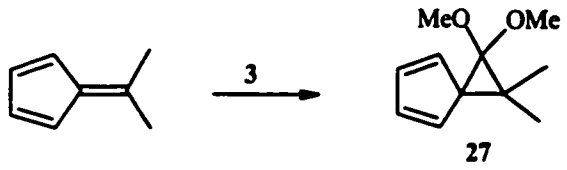
Scheme 4

Addition of carbenes to C_{60} is a method for functionalizing the carbon skeleton of C_{60}.[67] Dimethoxycarbene[68,69] (**3**) added to the electrophilic double bonds of C_{60} synthesizing a methanofullerene, **26** (equation 11). Reaction of dimethoxycarbene occurred exclusively with the double bonds at the 6,6-ring juncture.



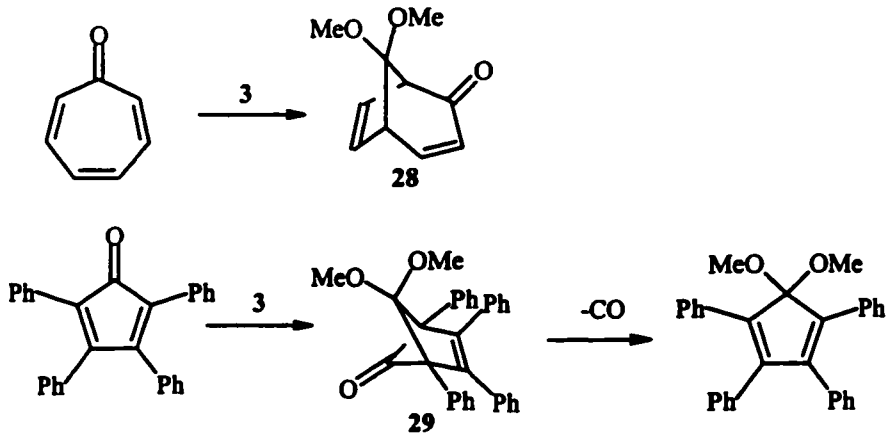
(11)

Nucleophiles react with 6,6-dimethylfulvene at the exocyclic double bond. However, electrophiles react at the endocyclic double bond. The nucleophilicity of dimethoxycarbene (**3**) was indicated by its exclusive addition to the exocyclic double bond of 6,6-dimethylfulvene generating the spiro compound **27** (equation 12).[70]



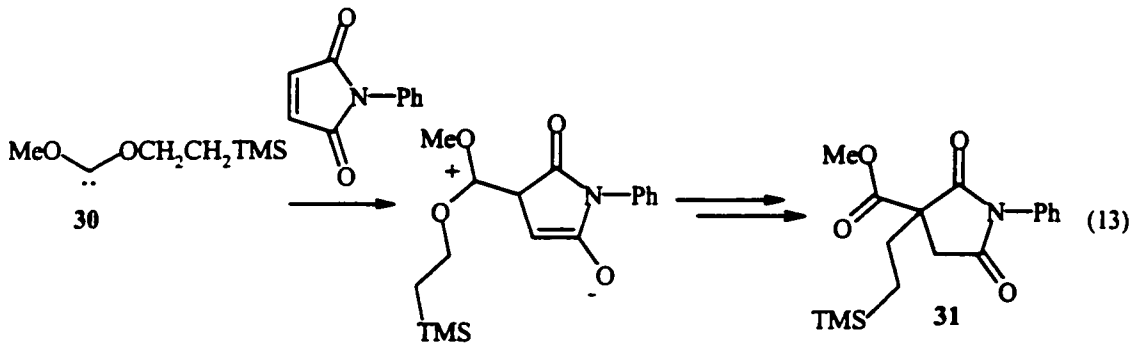
(12)

1,4-Additions were observed from the reaction of dimethoxycarbene (**3**) with dienes.[71] Dimethoxycarbene (**3**) added to tetraphenylcyclopentadienone and tropone yielding the bicyclic compounds **28** and **29** as shown in Scheme 5.

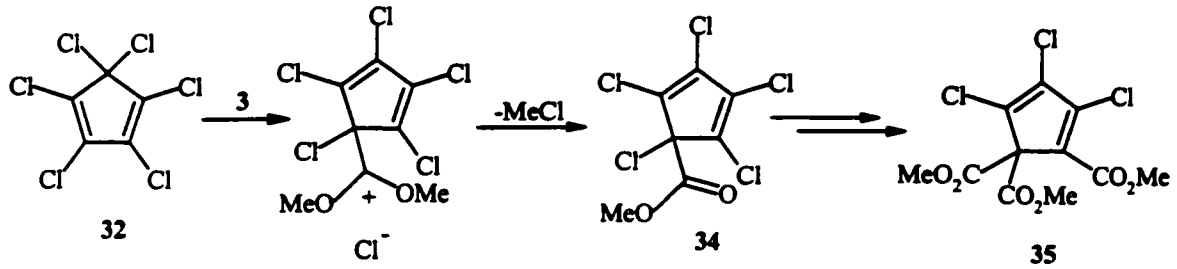


Scheme 5

N-Phenylmaleimide is cyclopropanated by dimethoxycarbene (**3**),[64b] but methoxy[(2-trimethylsilyl)ethoxy]carbene (**30**) attacked *N*-phenylmaleimide yielding **31**. Formation of **31** is hypothesized to be from the rearrangement of a dipolar intermediate (equation 13).[72]

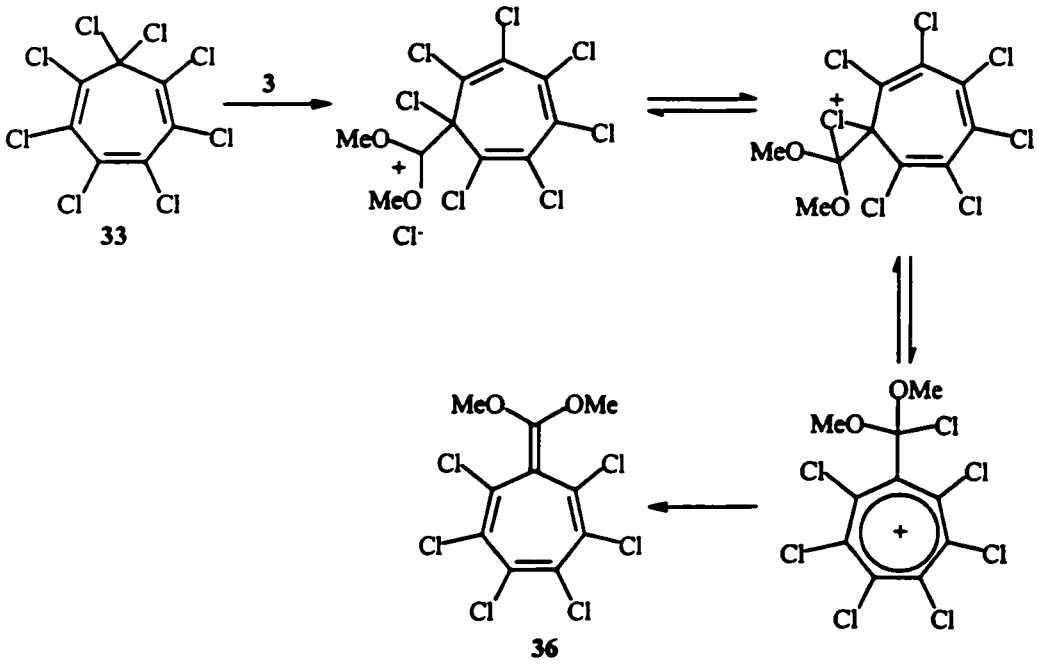


Dimethoxycarbene (3) also reacted with perchlorinated cyclic olefins, hexachlorocyclopentadiene (32), octachlorocycloheptatriene (33), and octachlorobicyclo[3.2.0]heptadiene.[73] A Michael-like addition of dimethoxycarbene to 32 was proposed followed by dechloromethylation to form 34. This process was repeated two more times to yield triester 35, Scheme 6.



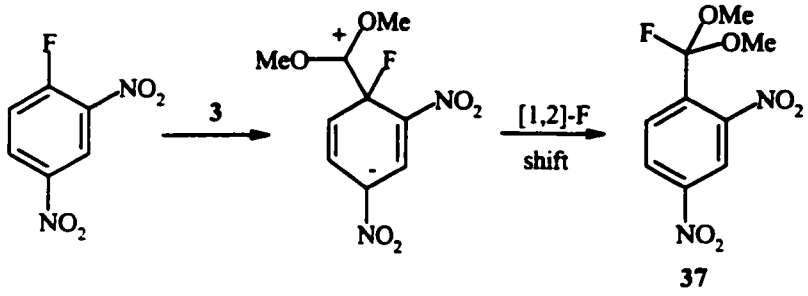
Scheme 6

Similarly, dimethoxycarbene attacked octachloroheptatriene (33) by first a Michael-like addition. However, in this case the intermediate dechlorinated to form the ketene acetal 36, Scheme 7.



Scheme 7

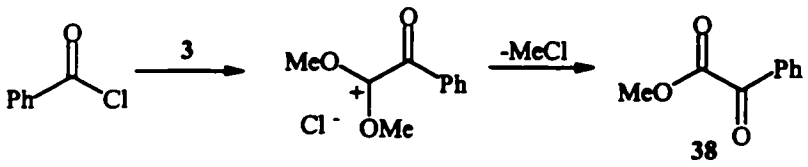
Dimethoxycarbene (3) has also been observed to displace fluoride from aromatic rings, resulting in nucleophilic aromatic substitution (equation 14).[74] The reaction is postulated to proceed with nucleophilic attack of the carbene on the aromatic ring followed by a [1,2]-fluoride migration leading to 37.



(14)

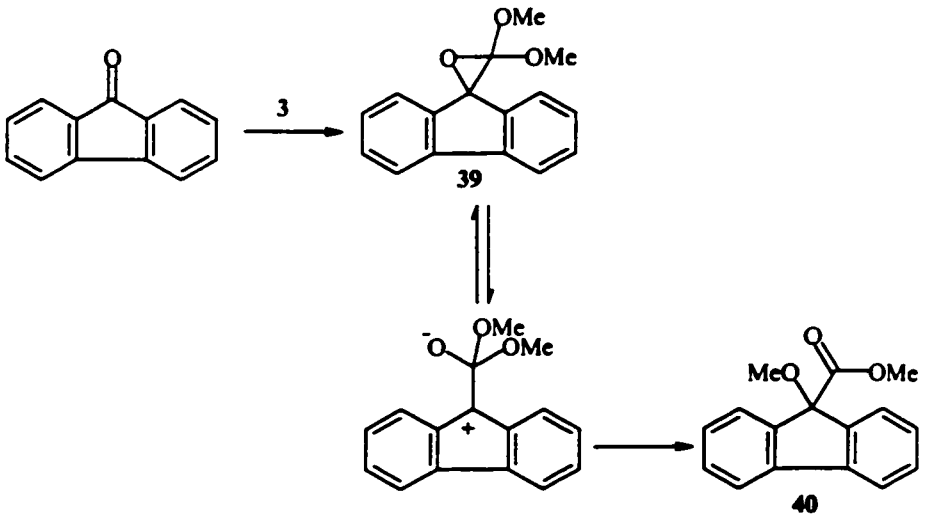
1.5.1.2 Reactions of Nucleophilic Carbenes with Carbonyl Groups (C=O)

Dioxycarbenes add to electron deficient alkenes and are considered nucleophiles. Carbonyl groups are attacked by nucleophiles at the electrophilic carbonyl carbon. Since dioxycarbenes are nucleophiles they should also add to carbonyl groups. Two research groups have independently investigated the reaction of dioxycarbenes with various compounds containing carbonyl groups. Hoffmann was the first to examine the reaction of dimethoxycarbene (**3**) with carbonyl groups using benzoyl chloride. Hoffmann proposed that dimethoxycarbene (**3**) initially attacks the carbonyl carbon followed by loss of chloride. The carbocation generated can then demethylate producing **38** (equation 15).[23]



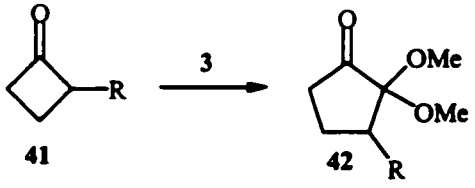
(15)

Pole and Warkentin established that the addition of dimethoxycarbene (**3**) to fluorenone yielded a 2,2-dialkoxyoxirane, **39**.[75] Oxirane **39** is postulated to be in equilibrium with the dipole, which rearranges by a methoxy transfer to produce **40**, Scheme 8. Dimethoxycarbene (**3**) can add to the carbonyl group either stepwise or by a direct [2+1] cycloaddition. This was the first evidence of the involvement of an oxirane intermediate in the addition of a dioxycarbene to a carbonyl group.



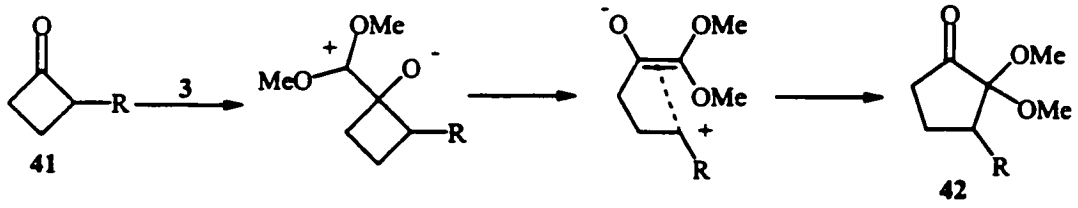
Scheme 8

Warkentin and Venneri have demonstrated that dimethoxycarbene (3) also adds to strained cyclic carbonyl compounds.[76] Reaction of dimethoxycarbene (3) with strained cyclic ketones **41** resulted in ring expansion producing mono acetals of β-dicarbonyl compounds **42** (equation 16).



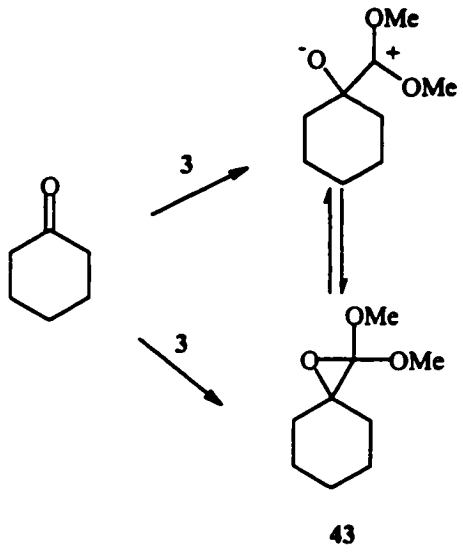
(16)

The preferred migration of the carbon bearing the substituent suggests that the transition state may have enolate character and that the migrating group moves with cationic character, Scheme 9.



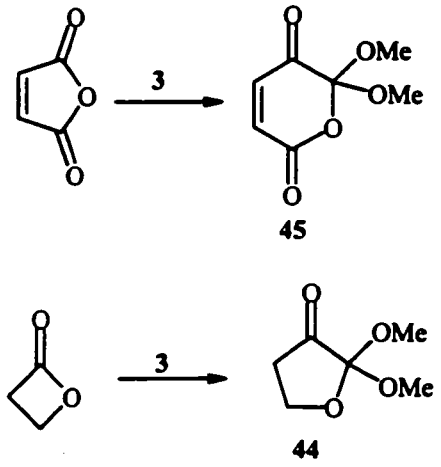
Scheme 9

Addition of dimethoxycarbene to cyclohexanone yielded an oxirane (**43**) and the product resulting from ring expansion was not detected.[77] Attack of the carbene onto the carbonyl group can either be concerted or stepwise. Concerted addition of the carbene gives the oxirane directly, whereas stepwise addition first gives the zwitterionic intermediate that then collapses to the oxirane, Scheme 10.



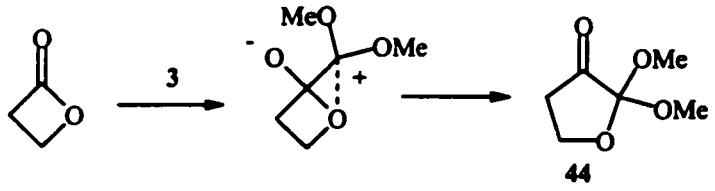
Scheme 10

Ring expansion products, **44** and **45**, were detected from the reaction of dimethoxycarbene (**3**) with strained lactones[76] and anhydrides,[78] Scheme 11. In both cases the carbene inserted between the carbonyl carbon and the α-oxygen.



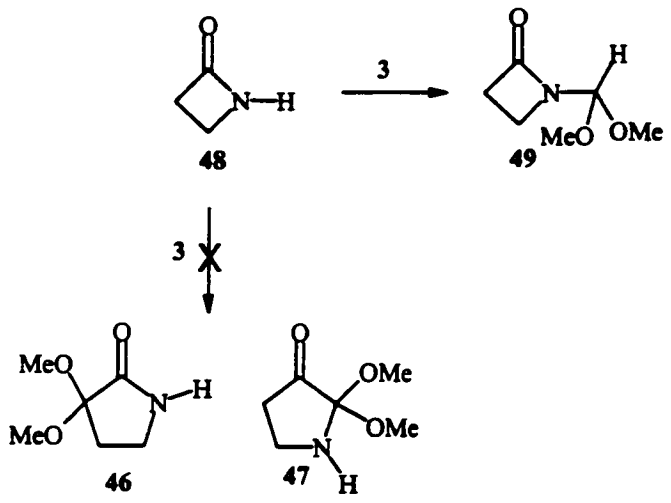
Scheme 11

The mechanism for the ring expansion of lactones and anhydrides is different from that for the ring expansion of the cyclic ketones. In this case the ring oxygen must interact with the developing positive charge as the carbene bonds to the carbonyl carbon. Warkentin and Venneri proposed a bicyclic transition state with a new bond forming between the carbene and the α-oxygen, Scheme 12.[76]



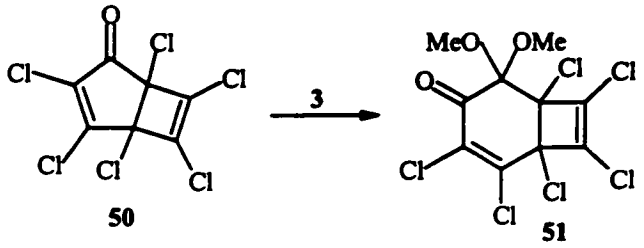
Scheme 12

Ring expansion products, **46** and **47**, were not detected from the reaction of dimethoxycarbene (**3**) with the strained lactam azetidinone, **48**. Rather, the product (**49**) from insertion of dimethoxycarbene into the N-H bond was observed, Scheme 13. Failure of dimethoxycarbene to react with the lactam carbonyl group is attributed to its reduced electrophilicity due to resonance.



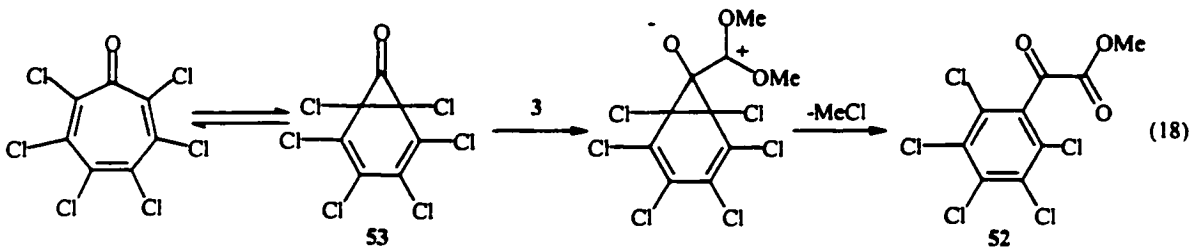
Scheme 13

Dimethoxycarbene (**3**) also attacked hexachlorobicyclo[3.2.0]-hept-3,6-dien-2-one (**50**) yielding **51** from ring expansion (equation 17).[73]



(17)

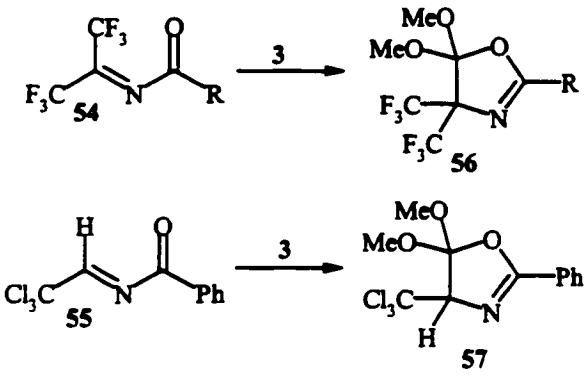
Alternatively, a ring contraction product, **52**, was observed from the addition of dimethoxycarbene (**3**) with hexachlorotropone. Hexachlorotropone is expected to exist in equilibrium with noracaradienone (**53**) and a mechanism is postulated in which initial attack of dimethoxycarbene (**3**) onto the carbonyl group of noracaradienone generates a zwitterionic intermediate. Loss of methyl chloride from the dipolar intermediate produces **52** (equation 18).



(18)

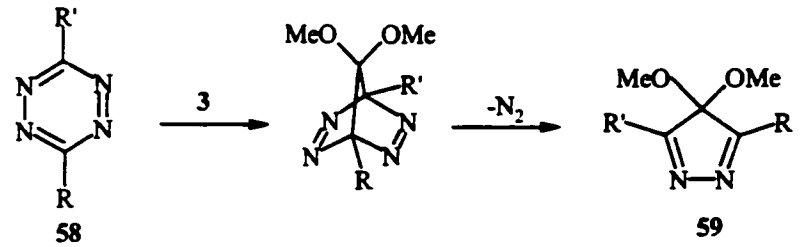
1.5.1.3 Reactions of Nucleophilic Carbenes with Imines (C=N)

Reaction of dimethoxycarbene (**3**) with conjugated imines, **54** and **55** yielded the five-membered ring heterocycles, **56** and **57**, Scheme 14. Hoffmann proposed that dimethoxycarbene adds to these imines by a [1 + 4] cycloaddition.[79]



Scheme 14

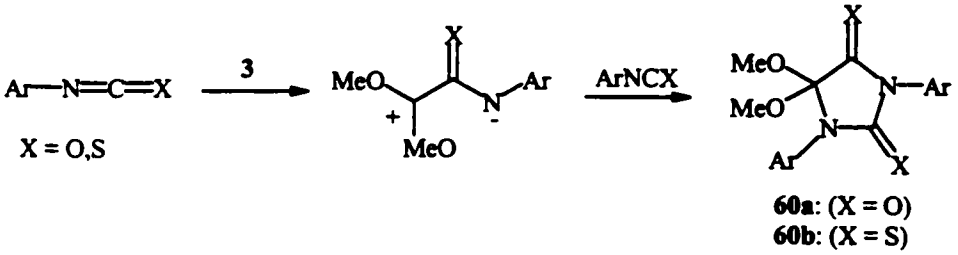
Similarly, a [1 + 4] cycloaddition was observed for the reaction of dimethoxycarbene (**3**) with substituted tetrazines, **58**. A bicyclic intermediate was presumably formed initially and it lost nitrogen to generate the heterocycle, **59** (equation 19).[80]



(19)

1.5.1.4 Reactions of Nucleophilic Carbenes with Heterocumulenes

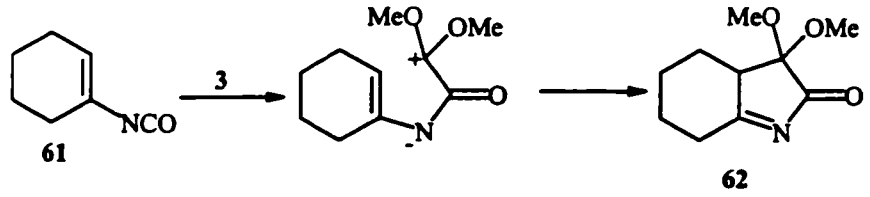
Heterocumulenes contain an electrophilic carbon which is attacked by nucleophilic carbenes, yielding 1:2 adducts and novel heterocycles. Dimethoxycarbene (**3**) added to two equivalents of aryl isocyanates or aryl isothiocyanates to form the 1:2 adducts, 5,5-dimethoxyhydantoins, **60a**, or 5,5-dimethoxydithiohydantoins, **60b**, Scheme 15.[81,82] Dimethoxycarbene (**3**) is expected to initially attack the electrophilic carbon of the heterocumulene to generate a zwitterionic intermediate. This dipolar intermediate undergoes a cycloaddition with another molecule of heterocumulene to produce the final heterocycle.[82]



Scheme 15

1:2 Adducts were also detected from the reaction of diamino- and amino(thio)carbenes with aryl isocyanates and aryl isothiocyanates.[83]

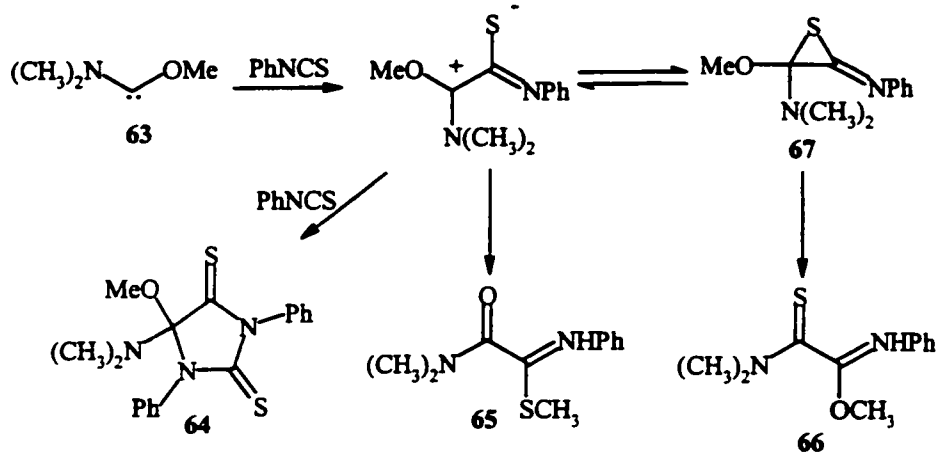
The zwitterionic intermediate formed from the reaction of a dioxycarbene with isocyanates or isothiocyanates can potentially be trapped with other dipolarophiles. Rigby and co-workers have utilized an isocyanate with a double bond (**61**) capable of intramolecular cycloaddition with the formed dipole affording **62** (equation 20).[84]



(20)

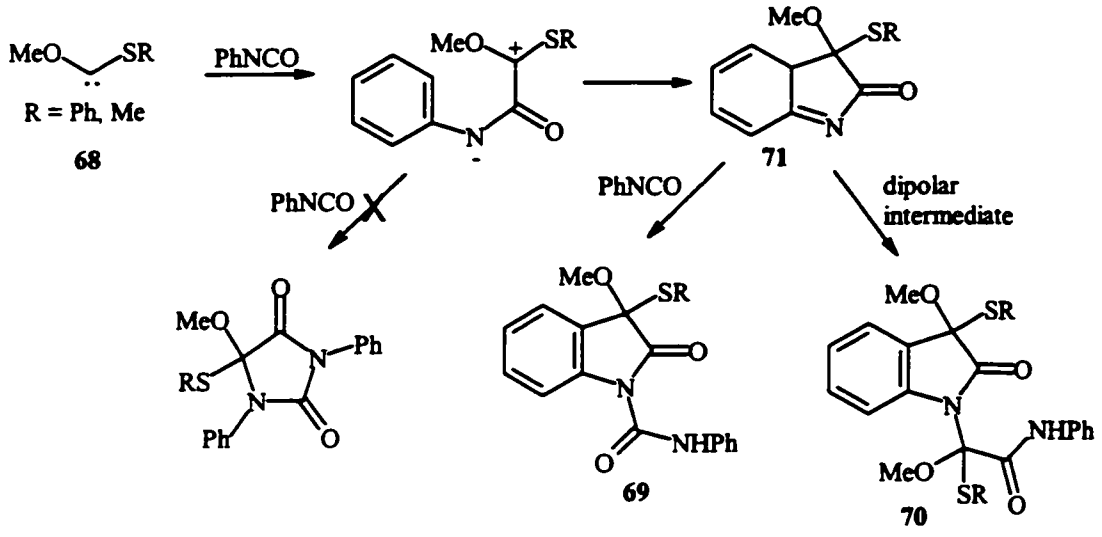
By exploiting chiral carbenes, Rigby and co-workers have synthesized complex molecules with a high level of asymmetric induction.[85]

(Dimethylamino)methoxycarbene (**63**) added to two molecules of aryl isocyanate generating the 1:2 adduct.[86] Alternatively, **63** reacted with an aryl isothiocyanate to give the expected 1:2 adduct **64** and two additional products **65** and **66**. Scheme 16 outlines the proposed mechanism. Attack of **63** onto the isothiocyanate yields a dipolar intermediate. Ring closure of the dipolar intermediate gives thiirane **67**, which undergoes ring-opening in the opposite direction to afford **66**. Inter- or intramolecular methyl transfer in the dipolar intermediate produces **65**.



Scheme 16

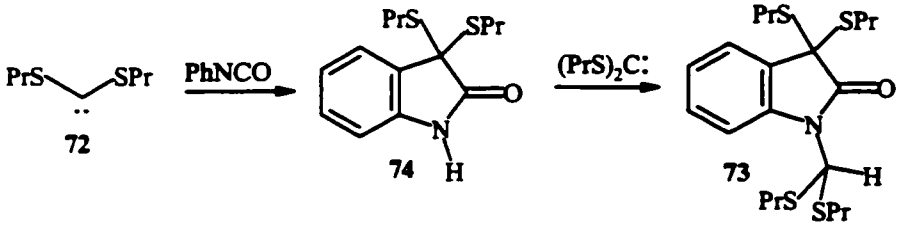
Reaction of methoxy(alkylthio)carbenes **68** with phenyl isocyanate yielded isatins **69** and **70** and not the expected 1:2 adduct, Scheme 17.[87] Carbene **68** presumably adds to phenyl isocyanate to give the dipolar intermediate, which collapses to produce a non-aromatic intermediate **71**. Either another molecule of isocyanate reacts with the intermediate to form **69** or the intermediate reacts with the dipole to give **70**.



Scheme 17

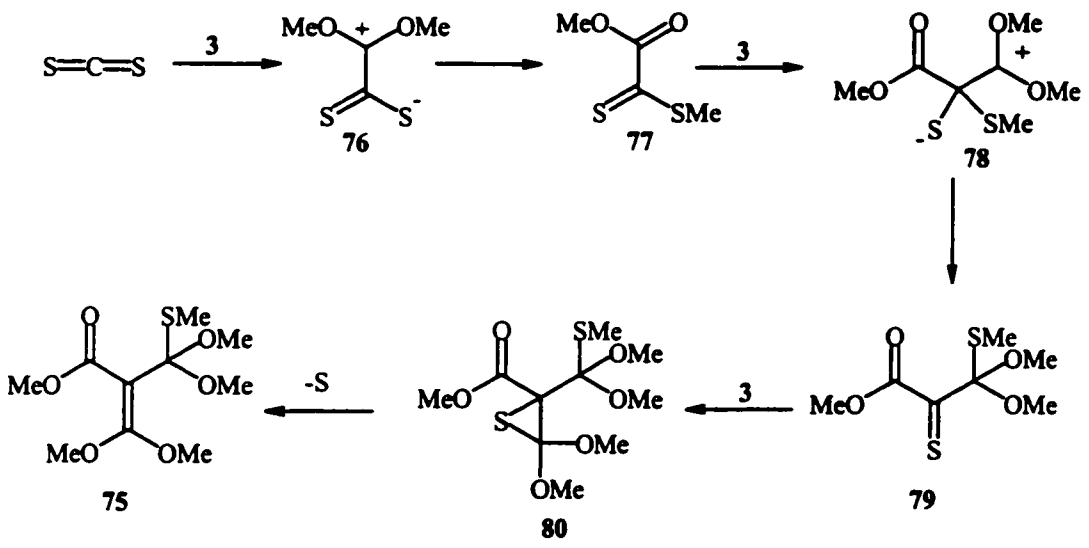
The dipolar intermediate generated from the attack of **68** onto phenyl isocyanate was proposed to be less stable then its analogue from dimethoxycarbene. As a consequence intramolecular ring closure was fast and the 1:2 adducts were not observed.[87]

Correspondingly, di(alkylthio)carbene **72** added to phenyl isocyanates yielding isatin product **73**, by a similar mechanism.[88] However, in this case carbene **72** adds to the phenyl isocyanate initially generating **74**, which undergoes carbene insertion into the N-H bond (equation 21). Rigby has also observed the addition of bis(alkylthio)carbenes to vinyl isocyanates.[89]



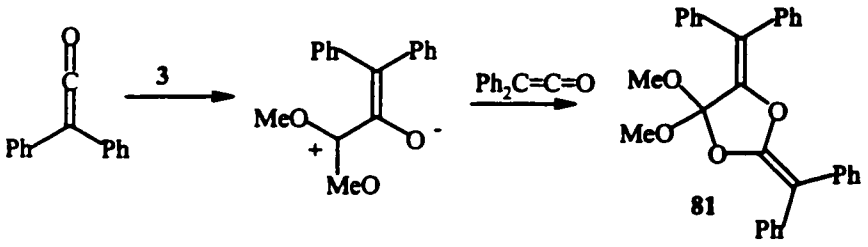
(21)

Three molecules of dimethoxycarbene (**3**) reacted with the carbon disulphide (CS_2) yielding the 3:1 adduct, **75**, Scheme 18.[90] It was postulated that initial attack of dimethoxycarbene (**3**) onto the electrophilic carbon of CS_2 gave the intermediate **76**, which underwent a methyl migration producing **77**. Attack of another molecule of **3** onto intermediate **77** generated **78**. Intermolecular methyl transfer in the dipolar intermediate **78** formed **79**. A third molecule of **3** reacted with **79** to give the thiirane **80**. Finally, **80** lost sulfur to yield the 3:1 adduct **75**.



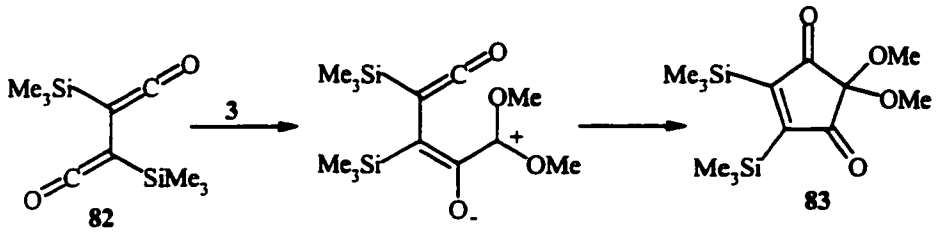
Scheme 18

Ketenes also react with dioxycarbenes yielding 1:2 adducts. Reaction of dimethoxycarbene (**3**) with two molecules diphenylketene afforded the 1:2 adduct, **81** (equation 22). Dimethoxycarbene (**3**) presumably adds initially to electrophilic carbon of diphenylketene generating a zwitterionic intermediate. Cycloaddition with another molecule of diphenylketene produces **81**.[23]



(22)

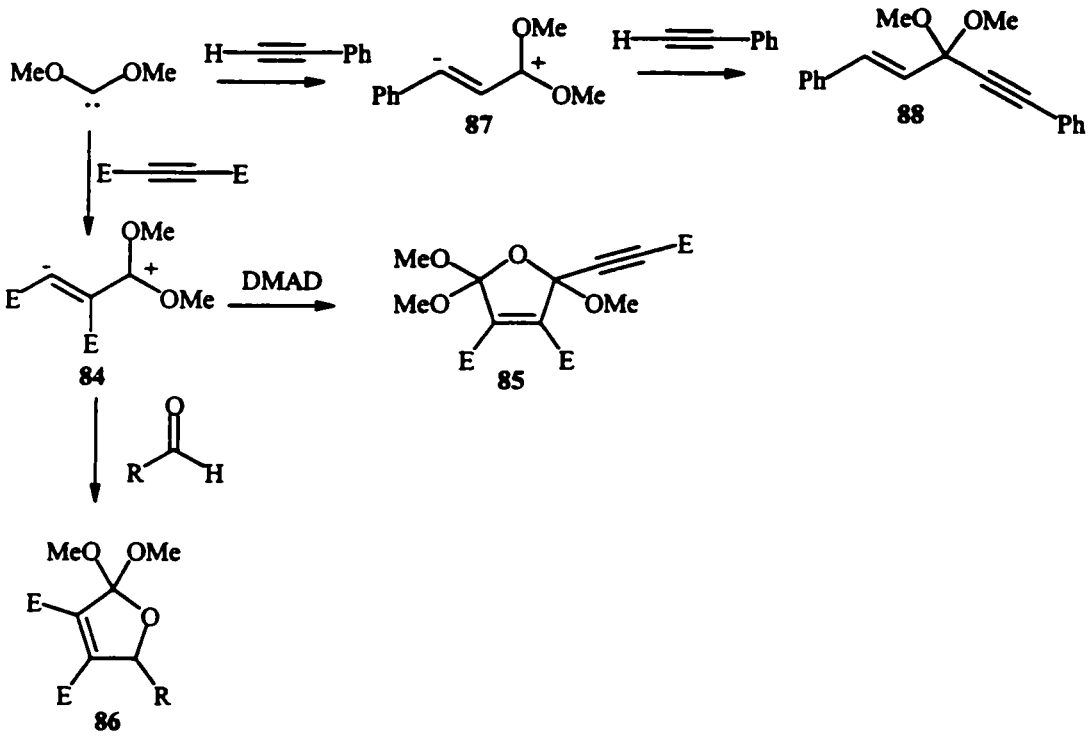
Similarly, dimethoxycarbene (**3**) reacted with bisketene **82**, yielding **83** (equation 23).[91]



(23)

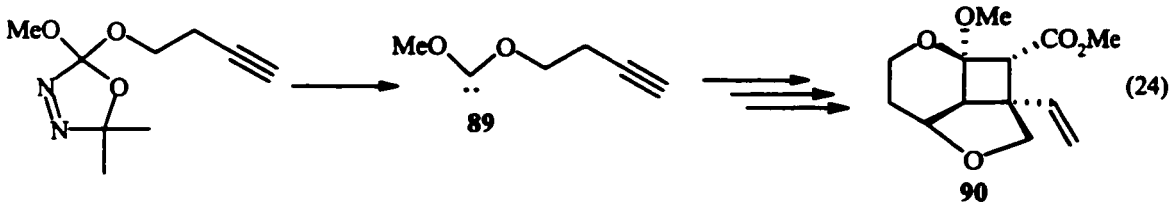
1.5.1.5 Reactions of Nucleophilic Carbenes with Alkynes

Electron deficient alkynes such as dimethyl acetylenedicarboxylate (DMAD) and diphenylacetylene react with dialkoxycarbenes.[23,72] Addition of dimethoxycarbene (**3**) to these alkynes is postulated to generate a dipolar intermediate, Scheme 19. Evidence for a dipolar intermediate was established when **84** was trapped with another molecule of DMAD, producing **85**.[72] Recently, dipolar intermediate **84** has been trapped with aldehydes (and quinones) generating **86**.[92] Alternatively, the zwitterionic intermediate **87** from the reaction of dimethoxycarbene (**3**) with phenylacetylene must abstract the acidic alkyne proton from another molecule of phenylacetylene producing an ion pair. Collapse of the ion pair yields **88**.



Scheme 19

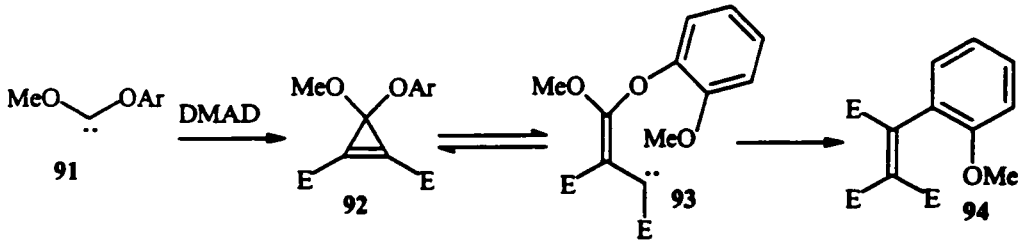
Kassam and Warkentin have synthesized a series of complex molecules utilizing a carbene with a tethered triple bond (equation 24).[93,94,95] For example, dialkoxycarbene **89** generated from the corresponding oxadiazoline attacked the alkyne intramolecularly. Attack of the carbene was followed by a cascade of reactions, which generated **90**.[93]



(24)

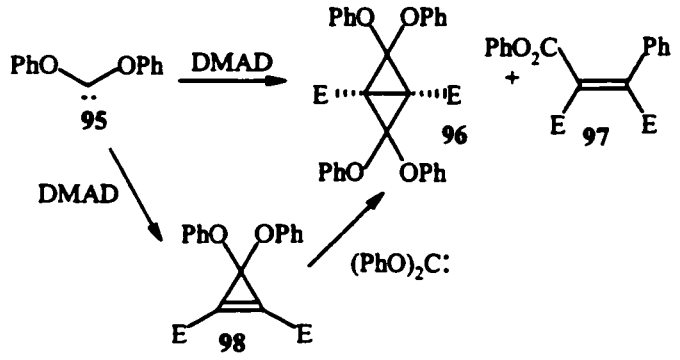
Diaryloxy- and aryloxycarbenes reacted with DMAD yielding a product from *ipso* aromatic substitution (equation 25).[96,97,98,48] Warkentin and Lu proposed a pathway in which aryloxy(methoxy)carbene **91** attacks DMAD producing cyclopropene **92**, which exists in equilibrium with the vinylcarbene, **93**. The vinylcarbene undergoes *ipso*

aromatic substitution to afford **94**.[96] Mono-substituted diaryloxycarbenes provided insight for the mechanism for the *ipso* aromatic substitution step.[97] Electron-withdrawing substituents in the *para* position increased the migratory aptitude of the aryl group while an electron donating substituent decreased it. Preferred migration of the aryl group containing the electron-withdrawing substituent suggests the mechanism involves nucleophilic attack of the vinyl carbene onto the aryl group.



(25)

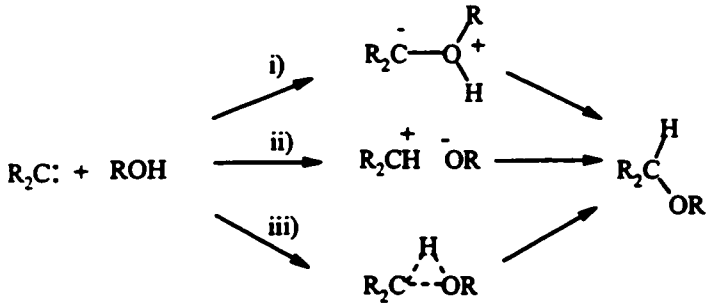
Interestingly, reaction of diphenoxycarbene (**95**) with DMAD gave a bicyclo[1.1.0]butane, **96**, along with the product from *ipso* aromatic substitution, **97**.[98,48] Bicyclo[1.1.0]butane **96** presumably arises from the addition of a second molecule of diphenoxycarbene to the cyclopropene **98**, Scheme 20. Observation of **96** suggests that a cyclopropene intermediate is involved in the formation of **97**.



Scheme 20

1.5.1.6 Insertion of Nucleophilic Carbenes into O-H Bonds

Three possible mechanisms are available for the insertion of singlet carbenes into O-H bonds:[99] i) Electrophilic attack of the carbene at oxygen followed by proton transfer, ii) protonation of the carbene to give an ion pair, which collapses to the product, and iii) a concerted insertion, Scheme 21.

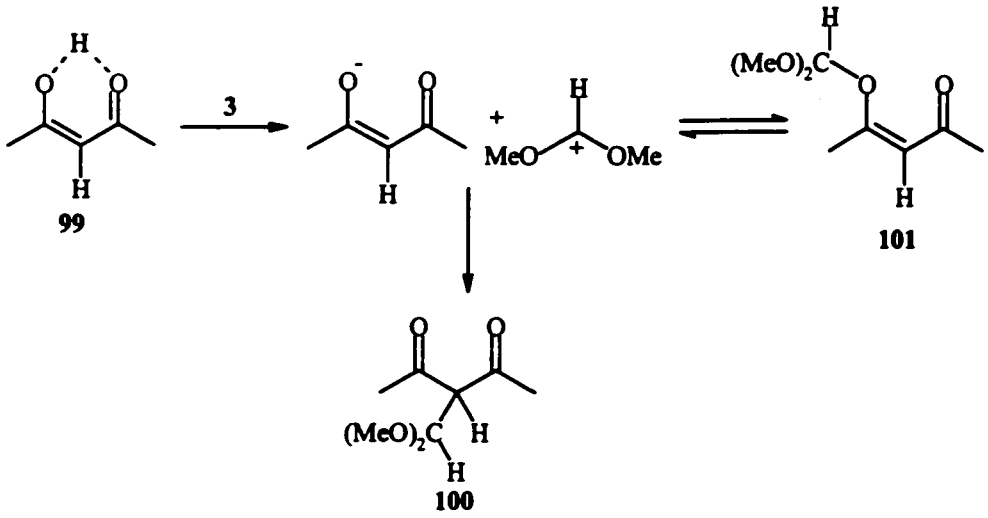


Scheme 21

Moss investigated the reaction of dimethoxycarbene (**3**) with methanol and discovered a large primary kinetic isotope effect (KIE = 3.3),[100] which was consistent with either pathway ii) or iii). Dimethoxycarbene (**3**) also reacted with a series of alcohols (1M ROH in CH_3CN) with rate constants that increased with decreasing p*K*a values of the alcohols. For example, the pseudo-first order rate constants for decay of dimethoxycarbene at ambient temperatures were 3.2 x 10^4 s^{-1} in ethanol (p*K*a = 15.90) and 6.7 x 10^8 s^{-1} in hexafluoroispropyl alcohol (p*K*a = 9.30).[101] The Brønsted coefficient (α = -0.66) from the reaction of dimethoxycarbene with the alcohol series also suggests a substantial degree of proton transfer between the carbene and the alcohol at the transition state. [101] It is suspected that dioxycarbenes like dimethoxycarbene (**3**) react primarily by

pathway ii). Carbocation intermediates have been detected by laser flash photolysis for the reaction of singlet carbenes with alcohol.[102,103]

Couture and Warkentin have demonstrated that dimethoxycarbene deprotonates enol **99** and collapse of the ion pair leads to **100**, or **101**, Scheme 22.[104] *C*-alkylation predominates over *O*-alkylation because **100** has a greater thermodynamic stability then **101**.



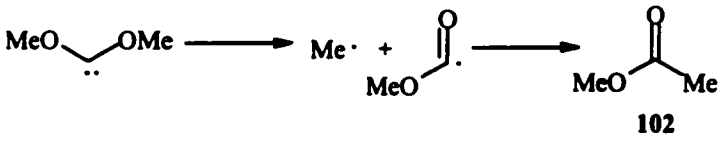
Scheme 22

1.5.2 Intramolecular Reactions

1.5.2.1 Homolysis of Dioxycarbenes

Evidence for fragmentation of dioxy- and oxycarbenes generated from the pyrolysis of tosylhydrazone salts (160°-175°) has been acquired.[57,60,105] Carbon monoxide, methane, and hydrogen gas were detected from methoxymethylene. These products were postulated to be derived from the fragmentation of methoxymethylene to carbon monoxide, methyl radicals, and hydrogen atoms.[57] Oele observed analogous products from the gas phase pyrolysis of methoxymethylene.[105] Similarly, diethoxycarbene decomposed to carbon dioxide and ethyl radicals.[60,105]

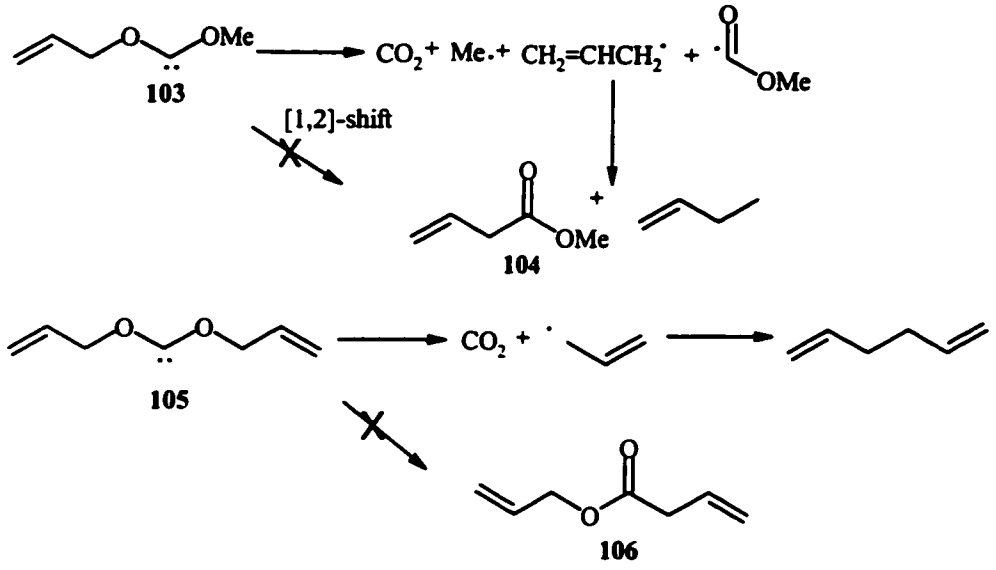
Hoffmann reported that dimethoxycarbene (3), produced in the gas phase at high dilution from the corresponding substituted norbornadienone ketal, yielded methyl acetate (**102**). Hoffmann hypothesized that this apparent rearrangement proceeded *via* methyl and methoxycarbonyl radicals, which coupled to form methyl acetate (equation 26).[36b,37a] Lemal also predicted the homolysis of dimethoxycarbene as a result of the detection of methylacetate, and CO_2.[106]



102 (26)

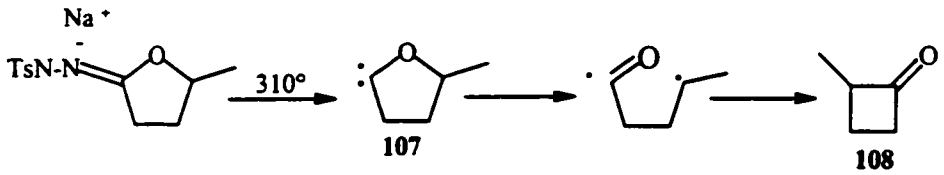
Pyrolysis of dibenzyl norbornadienone ketal in vacuo generated dibenzyloxycarbene, which produced benzyl formate and toluene, suggesting fragmentation of the carbene.[26]

Fragmentation of allyloxy(methoxy)- and di(allyloxy)carbene was observed in the gas phase pyrolysis (250°) of the corresponding substituted norbornadienone ketals.[107] Allyloxy(methoxy)carbene (**103**) decomposed to CO_2, methyl and allyl radicals. Additionally, methoxycarbonyl radicals were formed which coupled with allyl radicals to yield the apparent rearrangement product, **104**, Scheme 23. For the pyrolysis of di(allyloxy)carbene (**105**) only CO_2 and dimers of allyl radicals were observed. Product, **106**, from the apparent rearrangement was not detected, Scheme 23. Consequently, both allyloxy(methoxy)- and di(allyloxy)carbene fragment to radical pairs and subsequent radical coupling yields the products. Ester **104** was proposed to be a result of this radical coupling and not from the concerted [1,2]- and [2,3]-rearrangements of allyloxy(methoxy)carbene (**103**).



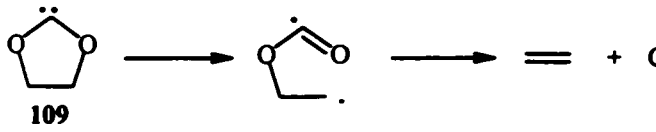
Scheme 23

Cyclic oxycarbenes **107** from the pyrolysis of tosylhydrazone salts were postulated to decompose to diradicals.[58,108,109] Subsequent ring closure of the diradical resulted in ring contraction and formation of ketone **108** (equation 27).



(27)

Ethylene and carbon dioxide (CO_2) were produced from the cycloreversion of cyclic dioxycarbene, **109**, generated from the tosylhydrazone salt. Stereochemistry was not retained in alkenes formed from the fragmentation of substituted cyclic dioxycarbenes. Thus, a stepwise mechanism to a diradical with subsequent loss of CO_2 to yield the alkenes was suggested.[61,62]

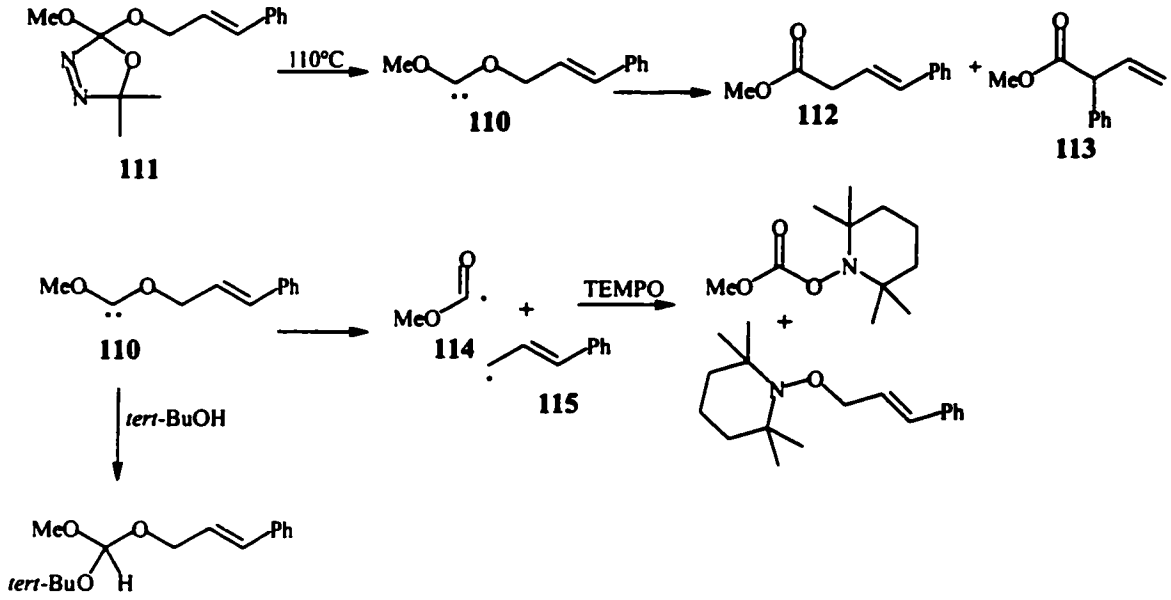


(28)

Corey and Winter have utilized the cycloreversion of five-membered ring dioxycarbenes to generate alkenes stereospecifically from diols.[110] Decomposition of cyclic thiocarbonates in refluxing triethylphosphite over 70-80° yielded alkenes with retained stereochemistry. Retention of stereochemistry of the olefins suggests a concerted loss of CO_2 from the dioxycarbene. *Ab initio* (MP2/6-31G*) calculations suggested that the concerted loss of CO_2 from cyclic dioxycarbenes is possible.[111] However, the authors did not calculate the corresponding asynchronous decomposition. Earlier computations at the

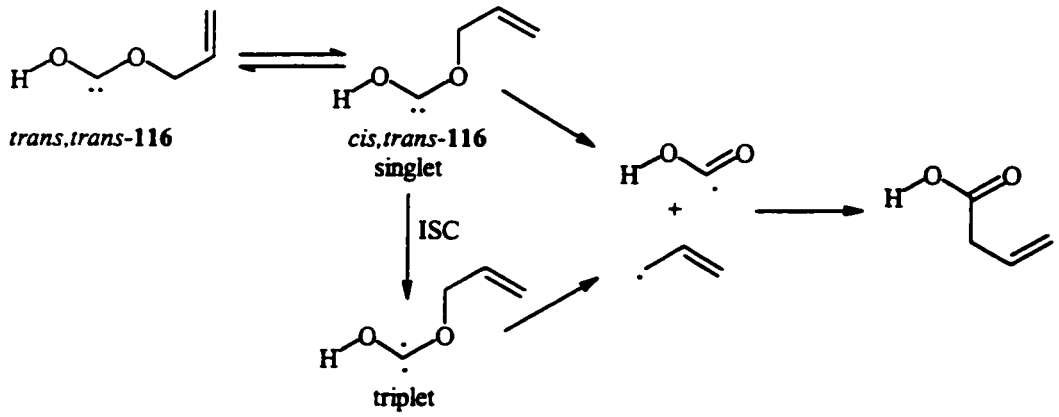
RHF/4-31G level of theory on these cyclic dioxycarbenes predicted that fragmentation to the diradical is lower in energy then the concerted loss of CO_2.[112]

Recently, Warkentin and Venneri have established the homolysis of cinnamyloxy(methoxy)carbene, **110**.[113] Thermolysis of 2-cinnamyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline, **111** yielded the esters **112** and **113**. Esters **112** and **113** could have arisen from either [1,2]- or [2,3]-rearrangements. Nevertheless, Warkentin and Venneri were able to trap both the carbene **110** and radical intermediates **114** and **115** from the thermolysis of **111**, Scheme 24. Trapping both carbene and radical intermediate demonstrated that **110** fragmented in solution, similarly to allyloxy(methoxy)carbene generated in the gas phase.[107] Fragmentation of cinnamyloxy(methoxy)carbene (**110**) to a radical pair followed by radical coupling afforded esters **112** and **113**. This was the first evidence for the fragmentation of dioxycarbenes in solution at low temperatures.



Scheme 24

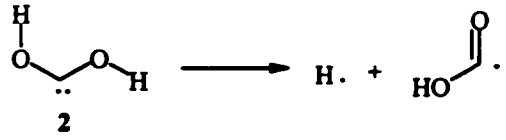
Calculations at the B3LYP/6-31+G* level of theory determined the thermodynamics for the homolysis of allyloxy(hydroxy)carbene, (**116**).[114] Scheme 25 outlines the possible pathways for the homolysis of allyloxy(hydroxy)carbene (**116**).



Scheme 25

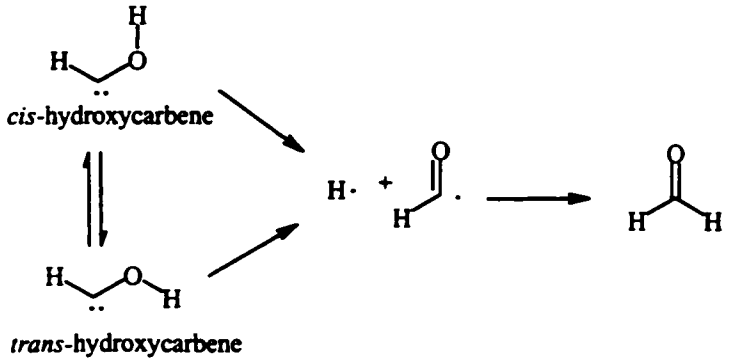
Intersystem crossing from the singlet to the triplet is possible and β-scission could occur form triplet allyloxy(hydroxy)carbene. However, the singlet-triplet gap was determined to be 26 kcal mol^{-1} for allyloxy(hydroxy)carbene,[114] which is similar to the singlet-triplet gaps obtained for both dihydroxycarbene and dimethoxycarbene.[10d,13,115,116,117] Therefore the triplet state is not sufficiently populated to be the principal pathway for homolysis. Fragmentation of singlet allyloxy(hydroxy)carbene (**116**) was calculated to occur predominately from the *cis,trans* conformer of **116**. Allyl and hydroxycarbonyl radicals lie 11.4 kcal mol^{-1} above *cis,trans*-**116** and a transition state was not found for the homolysis. The *cis,trans* conformer of **116** lies 2.4 kcal mol^{-1} above *trans,trans* conformer of **116**, which is the ground state conformer of **116**; the barrier for their interconversion is 14.3 kcal/mol.[114]

Feller *et al.* calculated at the RHF/DZP level of theory, that the hydroxycarbonyl and hydrogen radicals from the fragmentation of dihydroxycarbene (**2**, equation 29), lie 43 kcal mol^{-1} above the *cis,trans* conformer.[118] A small additional barrier for homolysis of dihydroxycarbene was found, approximately 3 kcal mol^{-1}. Saito and co-workers also calculated the fragmentation of dihydroxycarbene to hydrogen and hydroxycarbonyl radicals and found that the radicals lie ~83 kcal mol^{-1} above dihydroxycarbene.[119] It was suggested that the barriers for simple scission reactions are equal to the heats of formation for the radicals without any additional barrier.



2 (29)

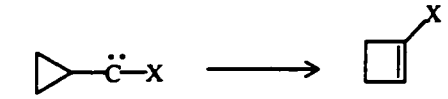
Reid and Hernández-Trujillo have examined the homolysis of hydroxycarbene at the CAS and MRCI levels of theory, Scheme 26.[120] A transition state was found for the homolyis of *trans*-hydroxycarbene, but not for the fragmentation of *cis*-hydroxycarbene. Despite the barrier for formation of radicals from *trans*-hydroxycarbene, homolysis of the ground state singlet is viable.



Scheme 26

1.5.2.2 [1,2]-Rearrangements of Nucleophilic Carbenes

Dialkylcarbenes rearrange rapidly *via* a [1,2]-hydrogen shift to give an alkene. Alkyl migrations are promoted by ring strain and substituents on the carbene (equation 30).[121] Alkyl migrations of nucleophilic carbenes are uncommon as substitution of electron donating substituents increases the activation energy substantially, therefore slowing down the rearrangement.[122]



(30)

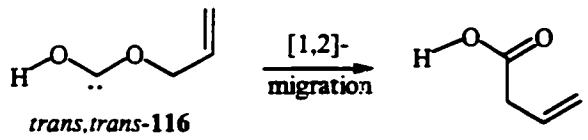
Moss investigated the [1,2]-hydrogen shift in methoxy-substituted carbenes.[123] Methoxy(methyl)carbene gave only 8% of the expected alkene from a [1,2]-hydrogen shift. Methoxy(neopentyl)carbene did not undergo a [1,2]-hydrogen shift. Moss estimated the rate constant for the [1,2]-hydrogen shift for methoxy(methyl)carbene to be 10^3 s^{-1}.[123]

Methoxy(2,2,2-trifluoroethoxy)carbene (**117**) was generated from 2-methoxy-5,5-dimethyl-2-(2,2,2-trifluoroethoxy)-Δ^3-1,3,4-oxadiazoline by very low vapour pressure pyrolysis (VLVP) at 430°.[124] Methoxy-(2,2,2-trifluoroethoxy)carbene isomerized to methyl 3,3,3-trifluoropropionate (**118**) *via* a [1,2]-trifluoroethyl migration (equation 31). Migration of the methyl group was not observed, indicating that negative charge develops on the migrating group, similar to [1,2]-hydrogen shifts in alkyl carbenes.[122] The trifluoromethyl group stabilizes the build up of negative charge.

117 **118** (31)

The [1,2]-hydrogen shift in dihydroxycarbene to yield formic acid has been explored computationally.[115,125,126,127] *Ab initio* calculations gave a barrier of 38 kcal mol^{-1} for the [1,2]-hydrogen shift in the *trans,trans*-conformer of dihydroxycarbene using MP4(SDQT)/6-31G**//RHF/6-31G**.[115] Similarly, a barrier of 52.6 kcal mol^{-1} was obtained at the DZP level of theory.[125] The [1,2]-hydrogen shift of dihydroxycarbene occurs in-plane, analogous to the [1,2]-hydrogen shift in carbanions, and is destabilized by the anti-aromatic 4-electron cyclic transition state.[118] Rearrangements of hydroxycarbene have been computed, and occur in-plane with a barrier of ~36 kcal mol^{-1}.[128,129,130]

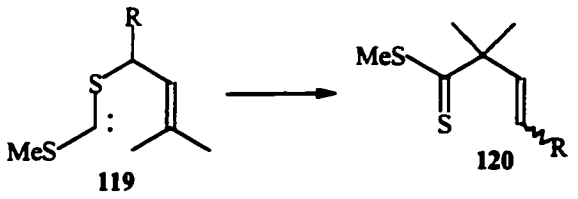
Computations on the [1,2]-alkyl shifts of dialkoxycarbenes have been carried out.[131,132] At the PMP4/6-31G*//UHF/6-31G* level of theory the barrier for the [1,2]-alkyl shift in F_3COCOH was found to be ~60 kcal mol^{-1}. The migration of the trifluoromethyl group occurred out of plane.[131] The barrier for the [1,2]-allyl shift in allyloxycarbene was calculated to be 42.5 kcal mol^{-1} at the MINDO/3 level.[132] Reid obtained similar results for the [1,2]-allyl shift in the *trans,trans* conformer of allyloxy(hydroxy)carbene (**116**, equation 32).[114] The barrier to the [1,2]-allyl migration in **116** was determined to be 41.9 kcal mol^{-1} at the B3LYP/6-31+G* level of theory. Migration of the allyl group in **116** occurred out-of-plane by 52°.[114]



trans,trans-**116** (32)

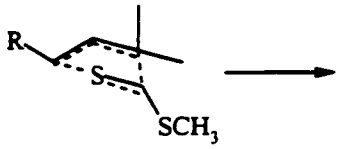
1.5.2.3 [2,3]-Sigmatropic Rearrangements of Nucleophilic Carbenes

[2,3]-Sigmatropic rearrangements have been observed for nucleophilic carbenes. γ-Unsaturated dithiocarbenes **119** undergo [2,3]-sigmatropic rearrangements to give dithioesters, **120** (equation 33).[133]



119 **120** (33)

Substituents in the β-position lead exclusively to the trans dithioester.[134] This phenomenon is rationalized with a five-membered ring "folded envelope" transition state in which the alkyl group ends up pseudoequatorially (equation 34).



trans-**120** (34)

Calculations on the [2,3]-sigmatropic shift in allyloxycarbene at the MINDO/3 level gave a barrier of 31.5 kcal mol^{-1}. The transition state was product like, although attempts were not made to optimize the transition state.[132] Reid found a barrier of 20 kcal mol^{-1} for the [2,3]-sigmatropic rearrangement of allyloxy(hydroxy)carbene (**116**) at the B3LYP/6-31G* level of theory.[114] A lower barrier to the [2,3]-sigmatropic shift versus

the [1,2]-shift is expected because the transition state is aromatic with six π-electrons for the [2,3]-shift.

1.6 OBJECTIVES

Dioxy- and other nucleophilic carbenes have been studied over the past five decades. Homolytic fragmentation of dioxycarbenes at moderate temperatures (110°C) is an emerging field of carbene chemistry. The driving force for the homolysis of dialkoxycarbenes should be the formation of a stabilized radical. Therefore carbenes bearing one or two benzyloxy groups should fragment to an alkoxycarbonyl radical and a benzyl radical. One objective was to prepare precursors of benzyloxy- and di(benzyloxy)carbenes in order to study carbene fragmentation. The oxadiazoline system was chosen because they are established precursors to dioxycarbenes.

The initial target was to study the homolysis of benzyloxy(methoxy)carbene to a radical pair. A subsequent objective was to generate carbenes bearing two benzyloxy groups (benzyloxy(*p*-substituted-benzyloxy)carbenes), to take advantage of the internal competition that would exist for the cleavage of the carbene to form either a *p*-substituted-benzyl or an unsubstituted-benzyl radical. Utilizing *para*-substituents that vary from electron donating to electron-withdrawing the affect of the *para* substituent on the fragmentation might be determined.

Dialkoxycarbenes attack electron deficient alkenes and insert readily into alcohol O-H bonds as discussed in the Introduction. In the second part of this thesis the objective was to determine if these common intermolecular reactions of dialkoxycarbenes could

compete with homolysis of the benzyloxycarbenes. Alkenes can potentially trap both the carbene and the radicals from thermolysis of benzyloxy oxadiazolines, depending on the rate of fragmentation of the carbene. Analysis of the products from the thermolysis of benzyloxy oxadiazolines in the presence of alkenes substituted with electron-withdrawing groups (cyano, phenyl and ester) should provide insight into this competition.

Reid and Hernández-Trujillo did not find a barrier for the homolysis of singlet *cis*-hydroxycarbene, when the hydrogen and carbene lone pair were *anti*.[120] Based on these computational results the fragmentation of a six-membered ring benzyloxy carbene should be facile, since the benzyloxy group is held *anti* to the carbene lone pair. Homolysis of this six-membered ring carbene should afford a diradical upon homolysis. If the fragmentation of the carbene to the diradical were efficient then the chemistry of the diradical might be studied.

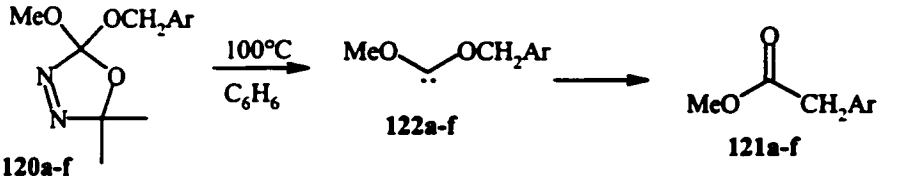
Chapter 2

Results and Discussion

2.1 Chemistry of Benzyloxymethoxy Oxadiazoline[135]

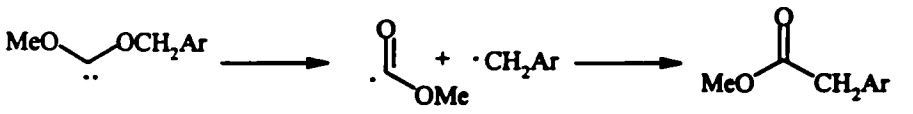
The homolysis of singlet carbenes to radicals in solution is a relatively unexplored aspect of carbene chemistry. Trapping both radicals and carbenes from the thermolysis of cinnamyloxymethoxy oxadiazoline, **111**,[113] was the first example of carbene fragmentation in solution at moderate temperatures. Warkentin and Venneri were first to establish the oxadiazoline → carbene → radicals pathway. The driving force for the fragmentation of cinnamyloxy(methoxy)carbene (**110**) was the formation of a stabilized cinnamyl radical. Consequently, other dioxycarbenes should fragment in this manner if they contain the appropriate carbene substituent.

El-Saidi synthesized a series of benzyloxymethoxy oxadiazolines, **120a-f**, which upon thermolysis yielded methyl arylacetates, **121a-f**, as the major products.[136] Methyl arylacetates, **121a-f**, were proposed to be from the rearrangement of benzyloxy(methoxy)carbenes, **122a-f**, (equation 35).

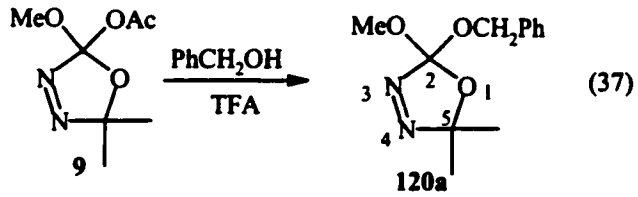


a: Ar = C_6H_5 **b**: Ar = *p*-$MeOC_6H_4$; **c**: Ar = *p*-MeC_6H_4;
d: Ar = *p*-ClC_6H_4; **e**: Ar = *p*-$F_3CC_6H_4$; **f**: Ar = *p*-$O_2NC_6H_4$

However, esters **121a-f** may have been produced from fragmentation of benzyloxy(methoxy)carbenes, **122a-f**, to methoxycarbonyl and benzyl radicals, followed by radical coupling (equation 36). The first section sets out to determine the mechanism for the formation of methyl arylacetates, **121a-f**, from oxadiazolines **120a-f** using benzyloxymethoxy oxadiazoline, **120a**, as a model.



Benzyloxymethoxy oxadiazoline, **120a**, was prepared from the acid catalyzed exchange reaction of benzyl alcohol with 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**9**, equation 37) . Benzyloxymethoxy oxadiazoline, **120a**, was identified by its characteristic ^{13}C NMR shifts at 119.3 (C5) and 136.6 (C2) ppm.[42] An AB quartet was observed for the diastereotopic benzylic protons in the ^1H NMR spectrum.

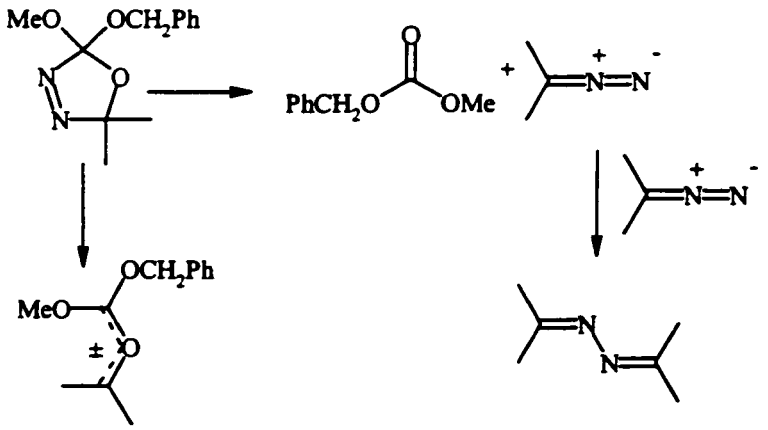


Thermolysis of **120a** was carried out in degassed benzene at 110°C for 24 hours. The product mixture from the thermolysis of **120a** was not examined in detail but methyl

phenylacetate (**121a**, 42%) was identified as the major product. Acetone azine, benzyl methyl carbonate and bibenzyl (4.3%) were also detected. The yields of methyl phenylacetate (**121a**) and bibenzyl were determined from ^{1}H NMR spectroscopy, using *p*-xylene as an internal standard. Unusually long spin lattice relaxation times (T_1) are obtained for the thermolysis mixtures, due to the absence of oxygen. Oxygen is referred to as a paramagnetic relaxation agent, which reduces the relaxation times of nuclei.[137] Spin lattice relaxation time (T_1) is the time it takes for the system to return to equilibrium after a pulse; if insufficient time is left between pulses then the integration is inaccurate. The T_1 for the thermolysis mixture, measured using an inversion-recovery pulse sequence,[138] showed that the acetone proton signal had the longest relaxation time (T_1 > 18 s). Ideally in quantitative NMR, five to ten times the T_1 is used as a relaxation delay, in this case a relaxation delay of five minutes was used. *p*-Xylene was chosen as the internal standard because the methyl signals did not overlap with any of the reactant or product signals. Radicals are known to attack benzylic hydrogens, however, the concentration of *p*-xylene was merely 0.016 M. ^{1}H NMR spectra of the commercially available authentic samples were run in C_6D_6 and referenced to *p*-xylene and used to identify the components of the crude thermolysis mixture in the ^{1}H NMR spectrum.

Methyl phenylacetate (**121a**) is a product from the apparent rearrangement of the carbene. Bibenzyl was formed from the coupling of two benzyl radicals. Detection of bibenzyl is suggestive that methyl phenylacetate is produced *via* radical coupling. Benzyl methyl carbonate was a result of competitive decomposition of oxadiazoline **120a**.[139] In competition with extrusion of nitrogen from the oxadiazoline to afford the carbonyl ylide,

the oxadiazoline fragments to benzyl methyl carbonate and 2-diazopropane. Subsequent reaction of 2-diazopropane with another molecule of itself yields acetone azine, Scheme 27.

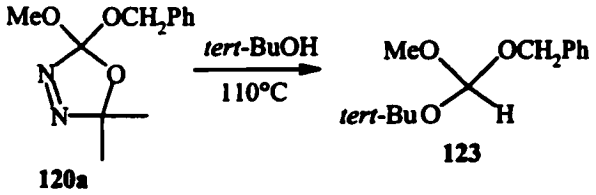


Scheme 27

Detection of bibenzyl was inadequate evidence to establish the mechanism. Therefore both the carbene and the radicals were trapped. Carbenes readily insert into alcohol O-H bonds with rate constants of approximately 10^9 $M^{-1}s^{-1}$ at ambient temperatures (Section 1.5.1.6).[103] An alcohol was utilized to trap benzyloxy(methoxy)carbene (**122a**) and confirm its involvement in the proposed mechanism. Trapping radicals with a stable nitroxyl radical is commonly employed as a radical clock. Stable nitroxyl radicals do not undergo chain reactions; they exclusively trap carbon-centered radicals and prevent subsequent radical reactions.[140] The coupling of stable nitroxyl radicals with carbon radicals is a fast reaction, with a rate constant of approximately 10^9 $M^{-1}s^{-1}$ at ambient temperatures. Stable nitroxyl radical trapping shows

little sensitivity to the stability of the radicals being trapped. A stable nitroxyl radical was utilized as a radical trap to establish radical intermediates from the thermolysis of **120a**.

Carbene trapping experiments were carried out using *tert*-butyl alcohol as the carbene trap. *tert*-Butyl alcohol was chosen because it is readily dried and is easily removed after completion of the thermolysis as a result of its low boiling point. Thermolysis of **120a** in the presence of *tert*-butyl alcohol (0.5M) yielded orthoformate **123** as the major product (61%) and benzyl methyl carbonate as a minor product (10%, equation 38). Therefore thermolysis of the benzyloxymethoxy oxadiazoline affords benzyloxy(methoxy)carbene.

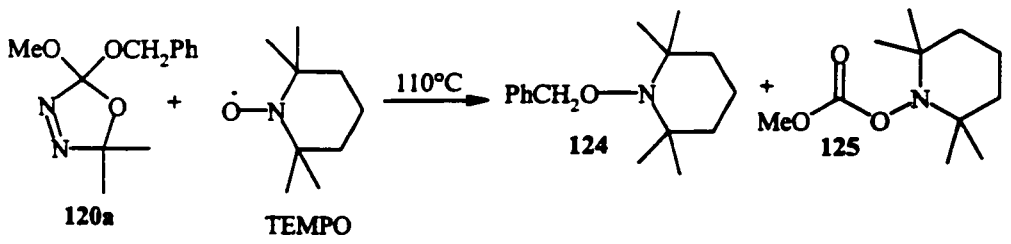


120a **123** (38)

To confirm the involvement of benzyl and methoxycarbonyl radicals in the formation of the methyl phenylacetate (**121a**), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was utilized as a radical trap. TEMPO was chosen because it traps carbon-centered radicals efficiently, does not react with any of the starting materials or known products, and does not undergo any self-reactions or unimolecular decomposition.[141] The rate constant for benzyl radical trapping with TEMPO is approximately 1.0×10^8 $M^{-1}s^{-1}$ at 18°C.[142] Trapping radicals with TEMPO is a reversible process, and dissociation of TEMPO adducts with secondary radicals begins at 120°C.[141] Dissociation of the TEMPO adducts was not a concern for the results obtained in this study, because the concentration

of TEMPO was 0.5 M and if any dissociation occurred coupling with another TEMPO would be more likely then coupling with another radical.

Thermolysis of benzyloxymethoxy oxadiazoline, **120a**, was carried out in a solution of TEMPO (0.5M) in benzene at 110°C for 24 hours. Benzyloxy-2,2,6,6-tetramethyl-1-piperidine (**124**) was isolated and methyl 1-(2,2,6,6-tetramethylpiperdinyl) carbonate (**125**) was detected in the gas chromatograph/mass spectrum (GC/MS) trace and in the ^{1}H NMR spectrum of the crude mixture of products (equation 39).



(39)

The crude product mixture from the thermolysis was not examined in detail but the gas chromatograph (GC) trace indicated that methyl phenylacetate was also produced. Comparison of the peak areas from the GC/MS trace revealed that methyl phenylacetate, **124**, and **125** were formed in equal amounts (**120a**:**124**:**125**; 1.2:1:1). The failure to trap all of the radicals from the fragmentation of benzyloxy(methoxy)carbene (**122a**) may suggest a competitive [1,2]-rearrangement of the carbene. Reid has calculated that the [1,2]-rearrangement of singlet allyloxy(hydroxy)carbene to be higher in energy than its homolysis (Section 1.5.2.2). The barrier to the [1,2]-allyl shift in allyloxy(hydroxy)carbene was calculated to be 41.9 kcal mol^{-1} at the B3LYP/6-31+G* level of theory.[114] Homolysis of singlet allyloxy(hydroxy)carbene occurs from the *cis,trans*-conformer and the allyl and hydroxycarbonyl radicals lie 11.3 kcal mol^{-1} above

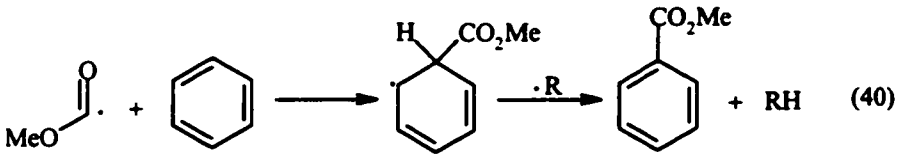
the *cis,trans*-conformer (Scheme 24 in Section 1.5.2.1). The *trans,trans*-conformer of allyloxy(hydroxy)carbene is the lowest energy conformer and interconversion with the *cis,trans*-conformer has a barrier of 14.3 kcal mol^{-1}. These DFT calculations predict that homolysis of singlet allyloxy(hydroxy)carbene is the dominant pathway for ester formation, not rearrangement.[114]

Homolysis of singlet benzyloxy(methoxy)carbene (**122a**) results in formation the methoxy carbonyl and benzyl radicals as a singlet pair. Rate constants for radical coupling are dependent on the method of radical generation. Radical pairs are produced as singlets or triplets as a result of spin conservation. The rate for the coupling of triplet radical pairs is dependent on the rate for intersystem crossing (ISC), whereas, the rate for coupling of singlet radical pairs depends on their orientation in solution.[143] Radical coupling reactions of diffusely separated radicals occur at the diffusion controlled limit (k_c = 8 x 10^9 $M^{-1}s^{-1}$).[144] For example, the rate constant for the coupling of two benzyl radicals is 1.8 x 10^9 $M^{-1}s^{-1}$ in benzene.[145] As a result singlet radical pairs born inside the solvent cage are expected to couple with rate constants greater than 10^9 $M^{-1}s^{-1}$. TEMPO trapping cannot compete with in-cage coupling of singlet pairs. Therefore, TEMPO catches diffusely separated radical pairs.

Trapping of the benzyloxy(methoxy)carbene (**122a**) with *tert*-butyl alcohol was faster than its fragmentation to radicals. Therefore, it was possible to estimate the rate constant for fragmentation of benzyloxy(methoxy)carbene (**122a**). The rate constant for trapping (p-$OMeC_6H_4)_2C$: with *tert*-butyl alcohol is 0.4 x 10^9 $M^{-1}s^{-1}$ at ambient temperatures,[103] hence the rate constant at 110°C is predicted to be 10^9 $M^{-1}s^{-1}$. Methyl

phenylacetate was not detected in the thermolysis of **120a** with *tert*-butyl alcohol (0.5M). Assuming that the limit for detection of methyl phenylacetate by NMR is 2% the product ratio for **123**:**121a** is predicted to be 98:2. Utilizing the above information the upper limit for the rate constant for fragmentation of **122a** is approximately 10^7 s^{-1}.

Trapping benzyl and methoxycarbonyl radicals with TEMPO provided evidence that benzyloxy(methoxy)carbene (**122a**) fragments to radicals. In the absence of TEMPO benzyl radicals coupled to form bibenzyl (~ 4%). Thus, methoxycarbonyl radicals must have also been produced in approximately the same yield (8%). What was the fate of the methoxycarbonyl radicals? Two methoxycarbonyl radicals could couple to form dimethyl oxalate. Abstraction of a hydrogen by methoxycarbonyl radical from a hydrogen source is possible, thus forming methyl formate. The volatile products from the thermolysis were not examined and methyl formate was not identified. GC analysis of the crude product mixture from the thermolysis of **120a** in the absence of added traps revealed that methyl benzoate (3%) was produced. Formation of methyl benzoate is explained in terms of homolytic aromatic substitution (equation 40).

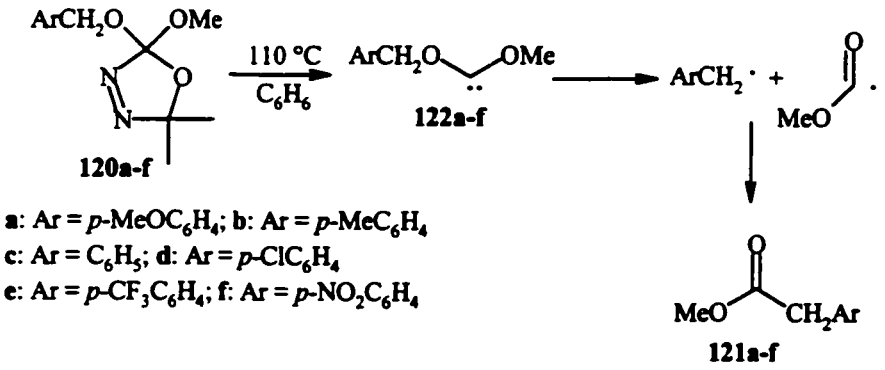


(40)

Homolytic aromatic substitution has been observed with phenyl[146] and alkyl radicals.[147] One example of homolytic substitution with methoxycarbonyl radicals exists in the literature. Methoxycarbonyl radicals generated from dimethyl azodicarboxylate afforded methyl benzoate (13%).[148] Homolytic aromatic substitution can be a reversible reaction

since a bimolecular hydrogen abstraction step is required to form the final product.[149] As a result most homolytic aromatic substitutions occur with low yields.

Trapping of both radical and carbene intermediates from benzyloxymethoxy oxadiazoline **120a**, establishes that methyl arylacetates, **121a-f**, are formed from fragmentation of benzyloxy(methoxy)carbenes, **122a-f**, followed by coupling of methoxycarbonyl and benzyl radicals, Scheme 28. This is the second example of the oxadiazoline → carbene → radicals pathway.

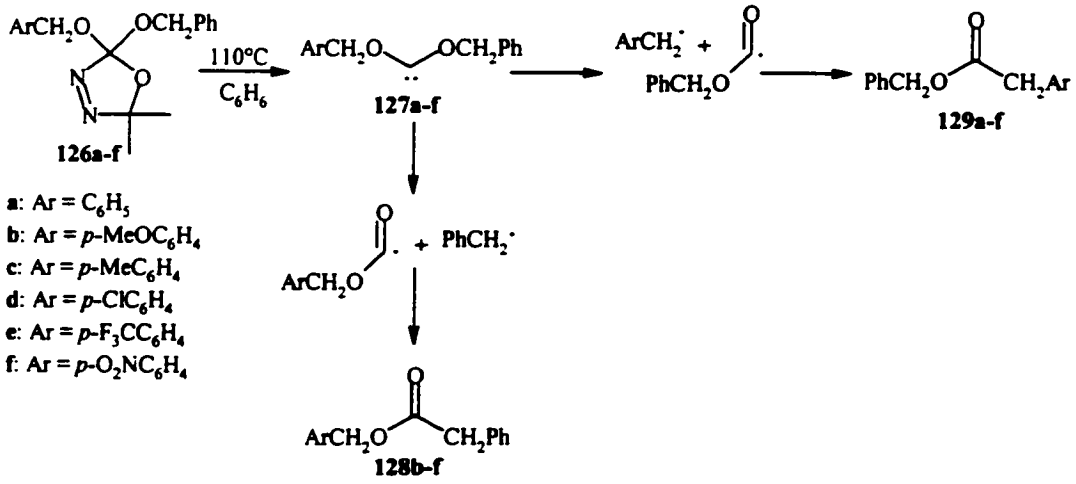


Scheme 28

2.2 Chemistry of Di(benzyloxy) Oxadiazolines[150]

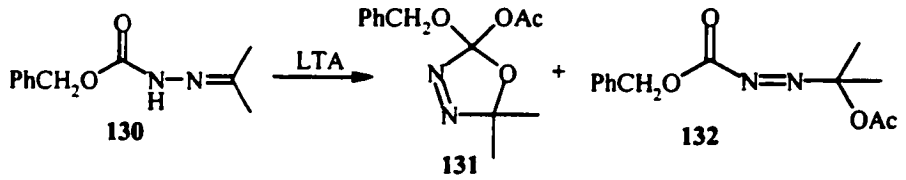
The yields of esters from oxadiazolines **120a-f** were below 50% and inferences on the effect of the *para* substituent on the fragmentation of benzyloxy(methoxy)carbenes, **122a-f**, could not be made. In order to make the substituent effects independent of the ester yields, a series of di(benzyloxy) oxadiazolines, **126a-f**, were synthesized as precursors to di(benzyloxy)carbenes, **127a-f**. Internal competition exists in carbenes **127a-f**; the carbene can either fragment to a benzyl radical and a *p*-substituted-

benzyloxycarbonyl radical, or a *p*-substituted-benzyl radical and a benzyloxycarbonyl radical, Scheme 29. Subsequent coupling of the radicals should afford phenylacetates **128a-f** and **129a-f**. 2,2-Dibenzyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**126a**) was chosen as a model system to confirm the involvement of radicals in the fragmentation of carbenes **127a-f**.



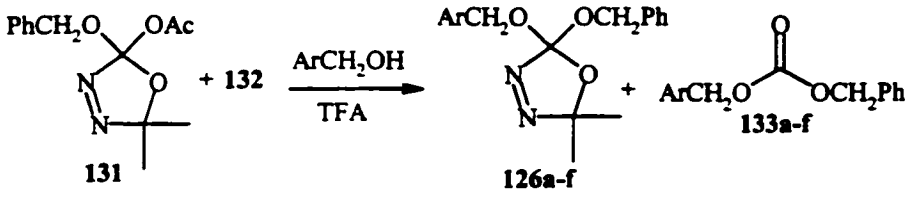
Scheme 29

Oxidation of the benzyloxycarbonyl hydrazone of acetone (**130**) with lead(IV) acetate (LTA) afforded a mixture of 2-acetoxy-2-benzyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**131**) and the acyclic by-product **132** (**131**:**132** = 60:40, equation 41).



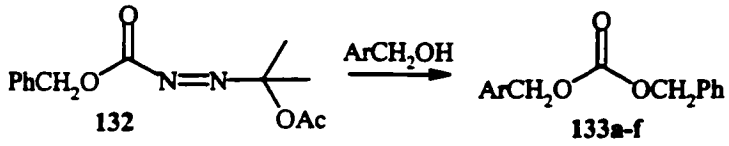
(41)

Acid catalyzed exchange of the appropriate benzyl alcohol for the acetoxy group in 2-acetoxy-2-benzyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**130**) afforded di(benzyloxy) oxadiazolines, **126a-f**, with yields between 40% and 80% (equation 42).



(42)

Acetoxy benzyloxy oxadiazoline, **131**, was not purified before the exchange reaction because the acyclic by-product is removed by washing the reaction mixture with a strong base (10% NaOH) after completion of the exchange. Two by-products were formed during the exchange reaction, *p*-substituted-benzyl acetate and carbonates, **133a-f**. *p*-Substituted benzyl acetates were probably formed from the acid catalyzed esterification of acetic acid with the appropriate benzyl alcohol, and the formation of carbonates, **133a-f**, is proposed to be from the attack of the appropriate benzyl alcohol on the acyclic by-product **132** (equation 43).



(43)

^{1}H NMR spectroscopy was used to monitor the exchange reaction for synthesis of **126a**. The AB quartet for the diastereotopic benzylic hydrogens at 4.93 ppm disappeared and a new one appeared at 4.85 ppm after one hour. If the exchange was left longer than one hour, the amount of dibenzyl carbonate (**133a**) and benzyl acetate increased substantially. After one hour enough carbonate was produced that it could not be removed by chromatography. All samples of oxadiazolines **126a-f** for thermolysis contained a minor amount of carbonate, **133a-f**. Carbonate is a common by-product from the

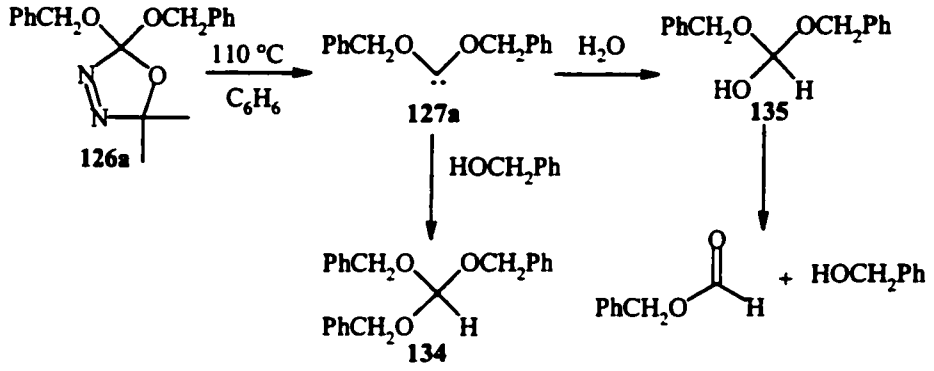
thermolyses of oxadiazolines, and its presence in the starting material does not affect the results obtained.

Disappearance of the methyl signals of di(benzyloxy) oxadiazolines **126a** and **126f** by ^{1}H NMR spectroscopy was used to determine their rates of decomposition. The rate constant for decomposition was 8.8 x 10^{-5} s^{-1} for **126a** and 7.9 x 10^{-5} for **126f**. The relatively small differences in the rate constants suggest that the thermolysis of di(benzyloxy) oxadiazolines is relatively insensitive to the *para* substituent. An enhancement in the rate of decomposition for aryloxy(phenoxy) oxadiazolines was observed when one of the substituents was electron-withdrawing (*p*-CN), indicating that the decomposition involves a carbonyl ylide intermediate.[48] An opposite effect was observed for the decomposition of **126a** and **126f**, but the difference is not large enough to discount the stepwise mechanism. Also in the case of **126f**, the substituent is insulated from the oxygen atom by a methylene group, and factors other than the stability of the carbonyl ylide may affect the thermolysis rate.

Thermolysis of **126a** in benzene at 110°C for 24 hours yielded bibenzyl (14%), benzyl phenylacetate (**129a**, 29%), dibenzyl carbonate (**133a**, 6%[i]), acetone (88%), benzyl formate (22%) and tribenzyl orthoformate (**134**, 19%). Yields for each of the products were determined from ^{1}H NMR spectroscopy using 1,4-dimethoxybenzene (DMB) as the internal standard. A three minute relaxation delay was used to improve the accuracy of the integration. 1,4-Dimethoxybenzene was an appropriate internal standard, as its proton signals did not overlap with any of the product signals. Products from the thermolysis of

126a were identified in the ^{1}H NMR spectrum by comparison to the crude ^{1}H NMR spectra of authentic compounds run in C_6D_6 and referenced to 1,4-dimethoxybenzene.

Additional dibenzyl carbonate (**133a**) was formed from the competitive fragmentation of the oxadiazoline giving 2-diazopropane and carbonate.[139] Observation of bibenzyl is most likely an indicator that benzyl phenylacetate **129a** arose from the coupling of a benzyl radical with a benzyloxycarbonyl radical. The yield of benzyl phenylacetate (**129a**) was low due to the presence of water. Adventitious water, like the alcohols mentioned in the Introduction, traps the carbene efficiently forming a hemiorthoformate, **135**, which decomposes to benzyl alcohol and benzyl formate. The liberated benzyl alcohol traps carbene **127a** and affords tribenzyl orthoformate (**134**), Scheme 30. Confirmation for the identity of **134** was obtained from thermolysis of **126a** in the presence of benzyl alcohol, which yielded tribenzyl orthoformate (**134**, 81%).



Scheme 30

Additional evidence for the involvement of carbene intermediates was obtained from the trapping of dibenzyloxycarbene (**127a**) with *tert*-butyl alcohol. Thermolysis of

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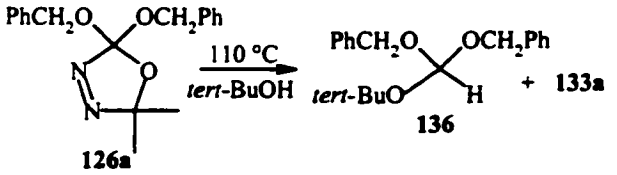
[1] The yield of **133a** does not include the 4.6% present initially.

126a in the presence of *tert*-butyl alcohol yielded orthoformate **136** (43%) and dibenzyl carbonate (**133a**, 3%, equation 44). Detection of orthoformate **136** confirms the involvement of di(benzyloxy)carbenes **127a-f** in the thermolysis of di(benzyloxy) oxadiazolines, **126a-f**.



(44)

Increasing the concentration of *tert*-butyl alcohol consequently increased the amount of orthoformate **136**, at the expense of benzyl phenylacetate (**129a**), Figure 7. The plot indicates that the yields of orthoformate and esters are interdependent; therefore the carbene is a precursor to the radicals.

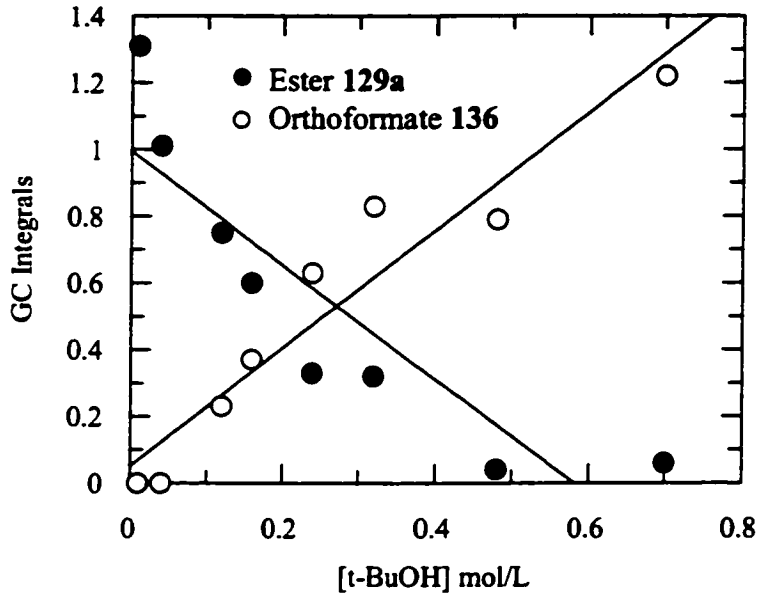
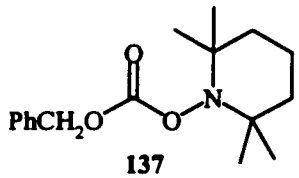


Figure 7: Dependence of the yields of **129a** and **136** on the *tert*-butyl alcohol concentration

A radical trapping experiment using TEMPO confirmed that the formation of **129a** involved radical intermediates. Thermolysis of **126a** was carried out in a degassed solution of TEMPO (1.0M) in benzene at 110°C for 24 hours. Product yields were determined by GC analysis using a flame ionization detector (FID), and corrections were made to the peak areas for the effective carbon numbers. A FID detector is a carbon counter and the peak area is proportional to number of carbons, but the presence of functional groups in the analyte affects the detector response.[151] Authentic samples were co-injected with the thermolysis product mixture to identify each component of the mixture. One concern with using the GC to determine the yield of **124** was its reversible thermal dissociation. The injector temperature was 200°C, or 75°C greater than the reported temperature (125°C) at which **124** begins to dissociate.[152] Authentic **124** was used for a control experiment to estimate the percent of decomposition of **124** during GC analysis. TEMPO adduct **124** was synthesized independently from the thermolysis of *tert*-butyl peroxide in a solution of toluene containing TEMPO. Adduct **124** was dissolved in benzene along with the internal standard 1,4-dimethoxybenzene (DMB). The ratio of DMB to **124** was determined to be 3.86:1 from the integration of the ^{1}H NMR spectrum. This solution was then injected into the GC, and using corrected peak areas, the ratio of DMB to **124** was found to be 3.78:1. These results indicate that there was very little, if any, loss of **124** during GC analysis.

Products from the thermolysis of **126a** in the presence of TEMPO were benzyl formate (18%), benzyl phenylacetate (**129a**, 13%), **124** (18%), dibenzyl carbonate (**133a**, 18%), and tribenzyl orthoformate (**134**, 42%). The high yield of tribenzyl orthoformate

(**134**) indicates the presence of water. Benzyl radicals were trapped with TEMPO affording adduct **124**. Analogous coupling of benzyloxycarbonyl radicals with TEMPO to produce **137** was not detected. The failure to trap benzyloxycarbonyl radicals is a result of the large rate constant for decarboxylation (k_{CO_2}) of the benzyloxycarbonyl radical, which was estimated from Arrhenius parameters to be 1 x 10^9 s^{-1} at 110°C.[153]



137

Benzyl phenylacetate (**129a**) and **124** were produced in almost equal amounts. The dependence of the yields of benzyl phenylacetate (**129a**) and **124** on the TEMPO concentration was determined using uncorrected peak areas from the GC/MS trace. Table 1 shows that increasing the concentration of TEMPO did not have a significant effect on the ratio of benzyl phenylacetate (**129a**) to **124**, which was approximately one at all concentrations. Failure to trap all the radicals might be attributed to a competitive [1,2]-rearrangement of the carbenes. However, Reid has calculated the barrier to a [1,2]-allyl shift in allyloxy(hydroxy)carbene to be higher than that for the homolysis of singlet allyloxy(hydroxy)carbene.[114] Therefore a likely explanation for the invariance of **129a** and **124** on the concentration of TEMPO is that dibenzyloxycarbene (**127a**) fragments to a singlet radical pair. TEMPO cannot compete with in-cage coupling but it traps the stabilized benzyl radicals even at the lowest concentration of TEMPO (0.01M). Therefore

the ratio of **124**:**129a** is independent of TEMPO concentration and is determined by the rate of coupling and the separation of the radical pairs.

Table 1: Relative yields of **124** and **129a**

[TEMPO] (M)	**124**	**129a**	Ratio (**124**:**129a**)
0.01	1.1	0.91	1.2
0.02	1.0	0.75	1.3
0.04	0.89	0.52	1.7
0.08	0.99	1.06	0.93
0.16	0.63	0.57	1.1
0.32	0.73	0.71	1.0

Thermolyses of **126b-f** were carried out in degassed deuterated benzene (C_6D_6) in flame sealed NMR tubes, which were heated at 110°C for 24 hours. Absolute yields of the esters **128b-f** and **129b-f** from the thermolyses of **126b-f** are listed in Table 2 and were determined from ^{1}H NMR spectroscopy using *p*-xylene as an internal standard, with a five minute relaxation delay. Authentic samples of **128b-f** and **129b-f** were synthesized from the corresponding phenyl acetyl chlorides using the appropriate benzyl alcohol. The ^{1}H NMR spectra of the authentic compounds were run in C_6D_6 and referenced to *p*-xylene and used to identify esters **128b-f** and **129b-f** in the ^{1}H NMR spectra of the crude thermolysis mixtures. For the thermolysis of **126b**, the methylene signals of isomers **128b** and **129b** were not suitably resolved in the ^{1}H NMR spectra using deuterated benzene, and the C_6D_6 was removed and replaced with CCl_4. Evaporation of the solvent resulted in loss of the internal standard and the absolute yields for **128b** and **129b** were not determined.

Table 2: Absolute yields for esters **128b-f** and **129b-f**

	% Yield of **128**	% Yield of **129**	**129:128**
b	--	--	1.0
c	9	10	0.94
d	27	11	2.3
e	30	10	3.0
f	26	2	11.4

The magnitude and sense of the selectivity of the fragmentation of the carbene is reflected in the relative yields of esters **128b-f** and **129b-f**, Table 2. The yields of esters **129b-f** are proportional to the rate of fragmentation of the carbene to a *p*-substituted benzyl radical (k_X) and the yields of esters **128b-f** are proportional to the rate of fragmentation of the carbene to a benzyl radical (k_H). A linear free energy relationship can be constructed using the product ratios (**129:128**) and σ constants, (equation 45).

$$\log \mathbf{129/128} = \rho\,\sigma \qquad (45)$$

A correlation between the logarithms of the product ratios (**129:128**) with σ^- substituent constants was found ($\rho_{(PhH,\ 110°C)} = 0.7$), Figure 8.

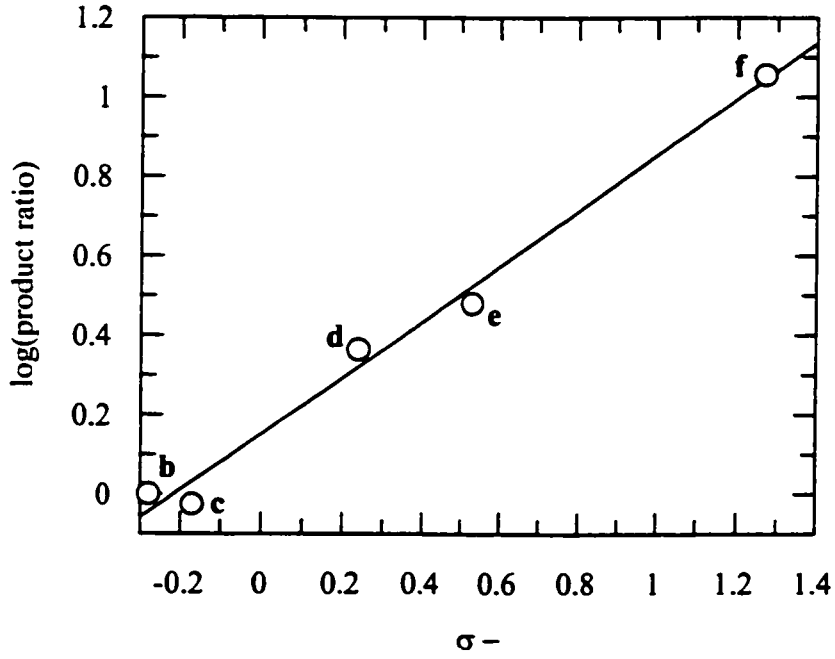


Figure 8: Correlation between the logarithms of the product ratios of esters **128b-f** and **129b-f** with σ^- substituent constants.

The correlation suggests that transition state for the fragmentation of di(benzyloxy)carbenes (**127a-f**) is lower in energy if electron density increases at the carbon becoming the benzylic fragment and decreases at the carbene carbon. Therefore the transition states for the homolysis of di(benzyloxy)carbenes (**127a-f**) are quite polar, Figure 9.

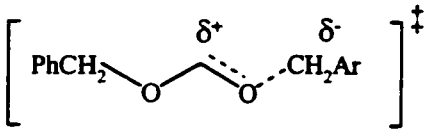


Figure 9: Transition state for the fragmentation of di(benzyloxy)carbenes **127a-f**

Reid and Hernández-Trujillo analyzed the electronic properties for the homolysis of hydroxycarbene at the CAS and MRCI levels of theory. They observed electron density

changes in the conversion of both *cis*- and *trans*-hydroxycarbene to a hydrogen atom and an acyl radical in which the carbon loses electron density to the leaving hydrogen.[120] Reorganization of electron density for the homolysis of hydroxycarbene supports the observed enhancement for loss of the benzyl group containing the electron-withdrawing *para* substituent in di(benzyloxy)carbenes (**127a-f**).

Along with esters **128b-f** and **129b-f**, the thermolyses of **126b-f** gave a complex mixture of products as a result of the *para* substituent; two formates, two orthoformates and three bibenzyls were detected in the GC trace. Table 3 shows the ratios of the formates, bibenzyls and orthoformates from the thermolysis of **126b-e** determined from GC analysis.

Table 3: Ratios of the formates, bibenzyls and orthoformates from the thermolysis of **126b-e**

	126b: Ar = $MeOC_6H_4$	**126c**: Ar = MeC_6H_4	**126d**: Ar = ClC_6H_4	**126e**: Ar = $CF_3C_6H_4$
$PhCH_2O(CO)H$	1.0	1.0	1.0	1.0
$ArCH_2O(CO)H$	0.8	0.4	1.5	1.6
$(PhCH_2)_2$	1.0	1.0	1.0	1.0
$ArCH_2CH_2Ph$	1.8	1.8	1.7	1.9
$(ArCH_2)_2$	0.4	0.9	0.69	0.7
$(PhCH_2O)_2(ArCH_2O)CH$	0.4	1.1	1.0	1.0
$(PhCH_2O)(ArCH_2O)_2CH$	1.0	1.0	1.0	1.0

Inspection of the ratios for the two formates and three orthoformates suggest that there is not a preference for cleavage of the benzyloxy group containing the *para* substituent *versus* the unsubstituted benzyloxy group in the hemiorthoformate produced from the trapping **127b-f** with water. The bibenzyls were formed in the expected ratio in which the

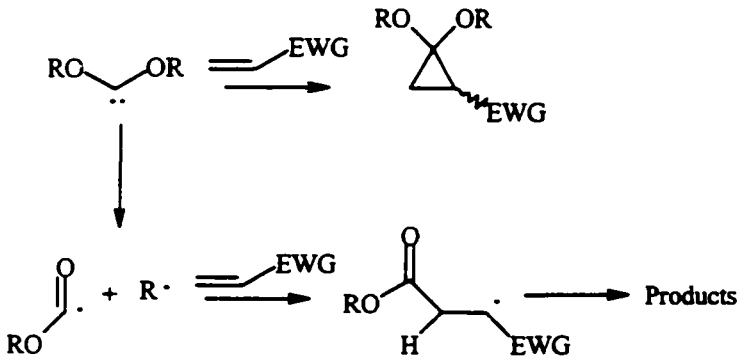
asymmetric bibenzyl was formed in the highest yield and the two symmetrical bibenzyls were formed in lower yields.

In summary, di(benzyloxy) oxadiazolines **126a-f** afford both carbenes and radicals upon thermolysis, and the benzyloxycarbonyl and benzyl radicals formed couple to yield esters **128a-f** and **129a-f**. Computations suggest that the homolysis of singlet dialkoxycarbenes is possible and esters **128a-f** and **129a-f** were not formed from competitive [1,2]-alkyl shifts. Fragmentation of di(benzyloxy)carbenes is sensitive to the *para* substituent, which supports the computational finding that there is reorganization of the electron density for the homolysis of hydroxycarbene. The homolysis of di(benzyloxy)carbenes is the third example of carbene fragmentation in solution at moderate temperatures.

2.3 Reactions of Benzyloxycarbenes with Alkenes[154]

Dioxycarbenes add to electron deficient alkenes with increasing rates as the alkene becomes more electron deficient (Section 1.5.1.1). Similarly, carbon-centered alkyl radicals add to alkenes with faster rates as the electron-withdrawing ability of the substituent on the alkene increases.[155] In the previous sections (Section 2.1 and 2.2) the homolysis of benzyloxycarbenes **122a-f** and **127a-f** was established. Fragmentation of benzyloxycarbenes occurs with a rate constant of approximately 10^7 s^{-1}. Alkenes can potentially trap either the carbene or radicals from the thermolysis of **120a** and **126a** depending on both the rate of carbene addition to the alkene and the rate of fragmentation

of the carbenes. If homolysis of the carbene is faster than trapping the carbene with the alkene, radical derived products should be formed. Alternatively, if carbene trapping is faster than fragmentation of the carbene, a cyclopropane should be produced, Scheme 31.

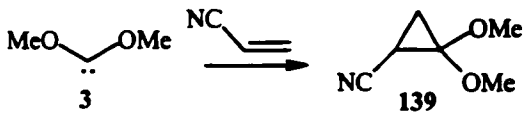


Scheme 31

Five alkenes were used to trap the carbene or radical intermediates from the thermolysis of **120a** and **126a**, benzylidenemalononitrile (**138**), (1-ethoxyethylidene)malononitrile, 1,1-diphenylethylene, diethyl benzalmalonate and dimethyl benzalmalonate.

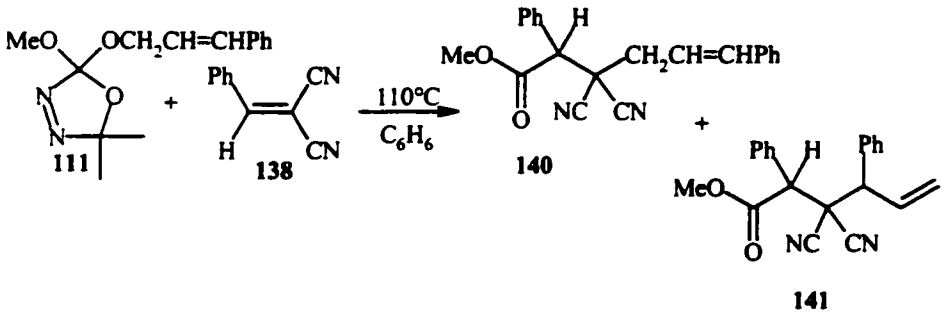
2.3.1 Thermolysis of **120a** and **126a** in the Presence of Benzylidenemalononitrile (**138**)

Cyano substituents are electron-withdrawing groups and should activate the alkene towards attack by a carbene. Moss and co-workers have shown that dimethoxycarbene (**3**) adds to acrylonitrile affording cyclopropane **139** (equation 46).[14] Benzylidenemalononitrile (**138**) is also an electron deficient alkene as a result of the geminal dicyano substituents and the phenyl group. Therefore the addition of benzyloxycarbenes to benzylidenemalononitrile is expected to be facile.



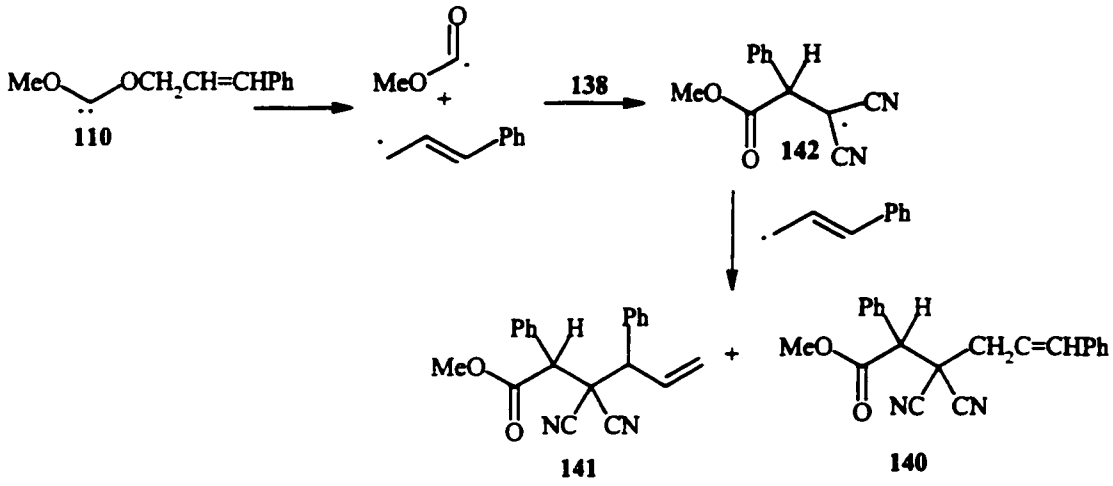
(46)

Venneri and Warkentin investigated the chemistry of cinnamyloxy(methoxy)carbene (**110**) with benzylidenemalononitrile (**138**).[156] Thermolysis cinnamyloxymethoxy oxadiazoline, **111**, in the presence of benzylidenemalononitrile (**138**) afforded esters, **140** and **141** (equation 47).



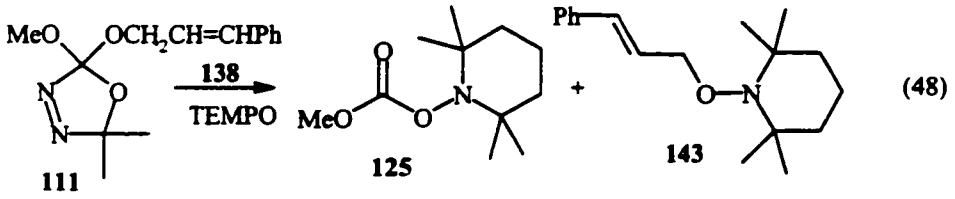
(47)

Venneri proposed the following mechanism for the formation of esters **140** and **141** based on the result that cinnamyloxy(methoxy)carbene (**110**) fragments to a radical pair. The methoxycarbonyl radical adds first to **138** and the resulting radical **142** couples with a cinnamyl radical forming esters **140** and **141** (Scheme 32). Precedence exists for the addition of alkoxycarbonyl radicals to alkenes.[157] However, the radical addition of small molecules to an alkene proceeds *via* chain reactions in which there is an initiation step followed by chain propagating steps.[158] A high yielding regiospecific radical addition followed by selective coupling with cinnamyl radicals was unexpected and novel.



Scheme 32

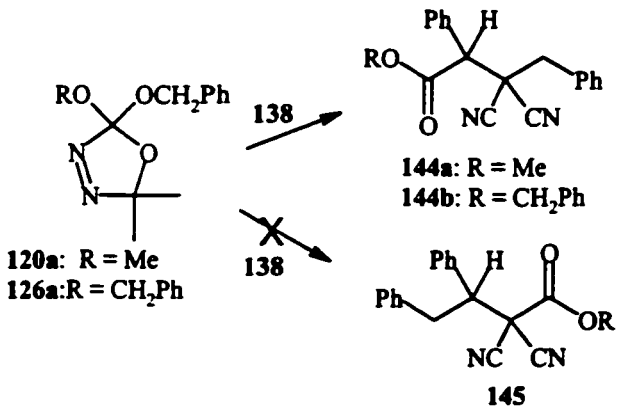
To provide insight into the mechanism, cinnamyloxymethoxy oxadiazoline, **111**, was thermolyzed in the presence of both TEMPO and benzylidenemalononitrile.[156] Esters **140** and **141** were not detected from the thermolysis, rather, TEMPO adducts **125** and **143** were isolated (equation 48). Addition of TEMPO terminated radical reactions and the failure to detect esters **140** and **141** suggested that the proposed mechanism was correct.



(48)

The generality of this reaction was examined using benzyloxycarbenes **122a** and **127a** that have also been established to fragment to radicals (Section 2.1 and 2.2). Thermolysis of **120a** and **126a** in the presence of benzylidenemalononitrile (**138**, 0.17M) afforded esters **144a** and **144b** in 48% and 37% yields (isolated) respectively, Scheme 33.

Addition of the fragments was regioselective as **144a** and **144b** were the major products and **145** was not detected.

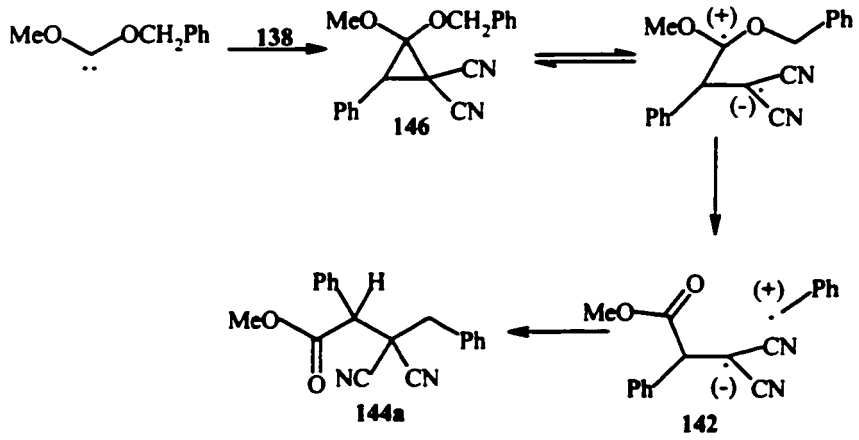


Scheme 33

Isolation of **144b** was unexpected because a previous attempt to trap benzyloxycarbonyl radicals from the thermolysis of **126a** in the presence of TEMPO was unsuccessful. Failure to trap benzyloxycarbonyl radicals with TEMPO was attributed to the large rate constant for decarboxylation of benzyloxycarbonyl radicals, which was estimated to be $1 \times 10^9\ s^{-1}$ at 110°C.[153] Intramolecular addition of alkoxycarbonyl radicals to double bonds is slow ($k_a \sim 10^5\ s^{-1}$)[153] in comparison to the rate of decarboxylation of benzyloxycarbonyl radicals. Therefore, intermolecular addition of a benzyloxycarbonyl radical to the benzylidenemalononitrile does not seem reasonable and the mechanism proposed by Venneri is unlikely.

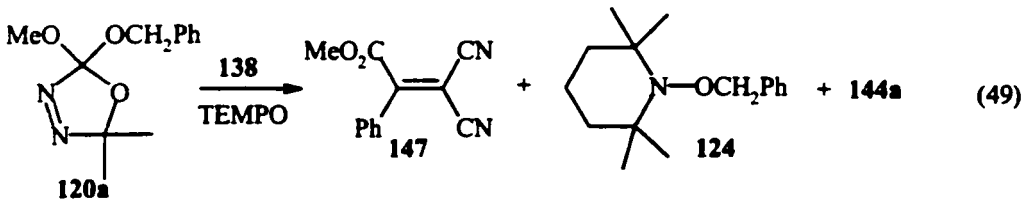
An alternative mechanism is proposed in which the carbene adds first to the double bond to produce a cyclopropane **146**, which exists in equilibrium with its ring-opened counterpart, Scheme 34. The diradical or dipolar intermediate could then fragment to give the radical or ion pair, which can couple to give the product. Heterolytic

thermal ring-opening of 1,1-dialkoxycyclopropanes has been established,[159,160] and cyclopropanes with vicinal withdrawing and donor groups undergo ring-opening more readily.[159,161] Cyclopropane **146** has two geminal withdrawing groups (cyano) and two geminal electron donating alkoxy groups. Consequently, ring-opening should be facile and occur with selective cleavage of the bond between the donor and acceptor groups. Selective cyclopropane ring cleavage results in regioselective ester formation.



Scheme 34

Thermolysis of **120a** in the presence of TEMPO (0.2M) and benzylidenemalononitrile (0.15M) was carried out to provide information about the mechanism. Ester **144a** was produced as the major product along with two additional products, **124** and a product from disproportionation **147** (equation 49). Adduct **125** formed from the trapping of methoxycarbonyl radicals with TEMPO was not detected.



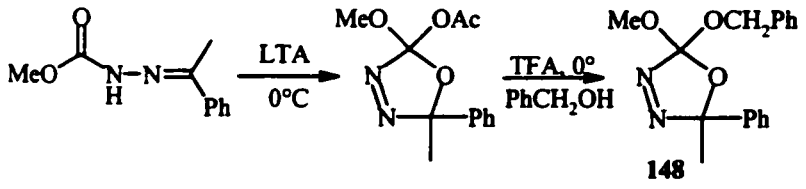
(49)

The inability to suppress the yield of **144a** indicates that the mechanism cannot be the one proposed by Venneri, as the addition of TEMPO should terminate radical reactions. Methoxycarbonyl radicals are not expected to add to benzylidenemalononitrile in competition with TEMPO trapping as the rate constant (k_a)[153] for the intramolecular addition of alkoxycarbonyl radicals to alkenes is approximately 10^5 s^{-1} and the rate constant for TEMPO trapping is approximately 10^9 s^{-1} at ambient temperatures.[140] Therefore the mechanism proposed in Scheme 34 is reasonable. Observation of **124** indicates that cyclopropane **146** undergoes homolytic ring-opening to a diradical that fragments to the radical pair, which couple to give product. Homolytic ring-opening of cyclopropane **146** is an alternative to heterolytic cyclopropane ring-opening proposed in references 159, 160 and 161. Baldwin observed a correlation between the thermal enantiomerization of cyclopropanes and radical stabilization energies, suggesting that homolytic ring-opening is feasible.[162] Product **147** is a result of disproportionation of radical **142** with either TEMPO or a benzyl radical.

Thermolysis of cinnamyloxymethoxy oxadiazoline **111** in the presence of both TEMPO (0.2M) and benzylidenemalononitrile (0.1M) was re-investigated. GC/MS revealed that the disproportionation product **147** was the major product along with TEMPO adducts **125** and **143**. Esters **140** and **141** were detected as minor products from the thermolysis. Observation of **147** is indicative that cinnamyloxy(methoxy)carbene **110** also adds to benzylidenemalononitrile followed by cyclopropane rearrangement. In this case both methoxycarbonyl and cinnamyl radicals were trapped by TEMPO forming **125** and **143**. Trapping of both methoxycarbonyl and cinnamyl radicals suggests that

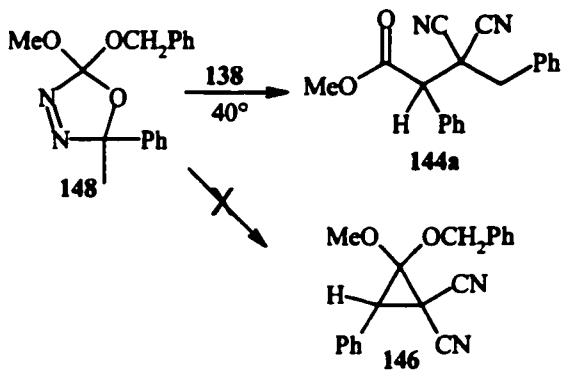
homolysis of **110** is faster than that of the benzyloxycarbenes, **122a** and **127a**. Alternatively, addition of **110** to benzylidenemalononitrile may be slower, but that is less likely.

Homolytic ring-opening of **146** occurred thermally and detection of cyclopropane **146** was not likely at 110°C. Production of the carbene at lower temperatures could result in the observation of the cyclopropane in the NMR spectrum. Békhazi synthesized phenyl substituted oxadiazolines and determined that the rate constant for their decomposition was approximately 10^{-5} at 40°C.[47] Synthesis of 2-benzyloxy-2-methoxy-5-methyl-5-phenyl-Δ^3-1,3,4-oxadiazoline (**148**, two diastereomers) was achieved by the route outlined in equation 50. Oxadiazoline **148** decomposes at room temperature making purification difficult. Thermolysis of **148** was enhanced and yielded benzyloxy(methoxy)carbene (**122a**) at 40°C. The rate constant for decomposition was determined to be 7.7 x 10^{-5} at 40°, whereas decomposition of **120a** had a rate constant of 2.35 x 10^{-5} s^{-1} at 100°C.



148 (50)

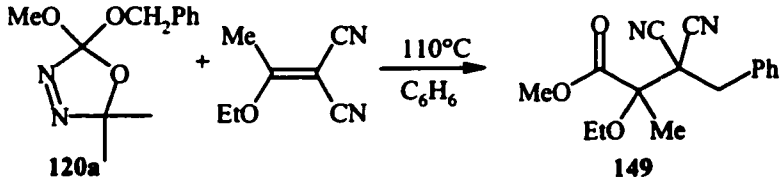
Thermolysis of **148** in the presence of benzylidenemalononitrile (**138**) in the NMR probe at 40°C did not result in the observation of cyclopropane **146**, rather ester **144a** was detected, Scheme 35. Therefore homolytic cleavage of the cyclopropane **146** occurs at temperatures close to ambient.



Scheme 35

2.3.2 Thermolysis of **120a** in the Presence of (1-Ethoxyethylidene)malononitrile

To determine if benzyloxycarbenes add to other methylidenemalononitriles as a result of the geminal cyano groups, **120a** was thermolyzed in the presence of (1-ethoxyethylidene)malononitrile (0.17M), which yielded ester **149** (equation 51). Isolation of ester **149** indicates that benzyloxy(methoxy)carbene (**122a**) also adds to (1-ethoxyethylidene)malononitrile and that addition is followed by radical rearrangement to yield ester **149**.



(51)

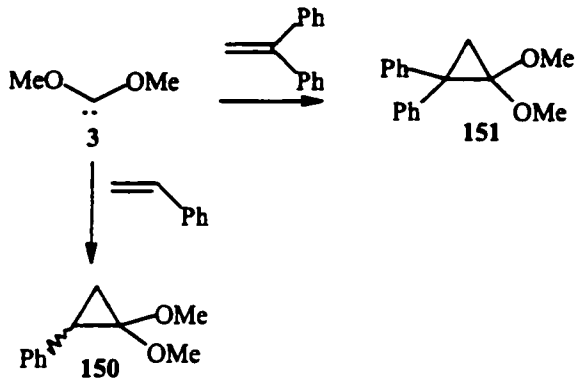
The regiochemistry of **149** was confirmed by 2-dimensonal NMR. A Heteronuclear Multiple Bond Correlation (HMBC) experiment showed a correlation between the methyl proton at 2.23 ppm and the carbonyl carbon at 172.6 ppm. HMBC

shows two and three bond (^3J) correlations between a proton (^{1}H) and a carbon (^{13}C).[163] If **149** had the opposite regiochemistry a correlation would not be observed between the carbonyl group and the methyl protons in the ^{1}H NMR spectrum. Formation of **149** again requires selective cleavage between the vicinal withdrawing and donating groups of the intermediate cyclopropane.

Benzyloxycarbenes add to benzylidenemalononitrile and (1-ethoxyethylidene)malononitrile yielding a cyclopropane, which ring-opens to the diradical. Cleavage occurs exclusively between the vicinal withdrawing and donating groups. Subsequent rearrangement of the diradical yields esters **144a**, **144b**, and **149**. The above two examples establish the addition of benzyloxycarbenes to methylidenemalononitriles. In order to assess the requirement for the geminal cyano groups, three alkenes with other geminal electron-withdrawing groups were utilized as potential carbene traps, 1,1-diphenylethylene, diethyl benzalmalonate and dimethyl benzalmalonate.

2.3.3 Thermolysis of **120a** in the Presence of 1,1-Diphenylethylene

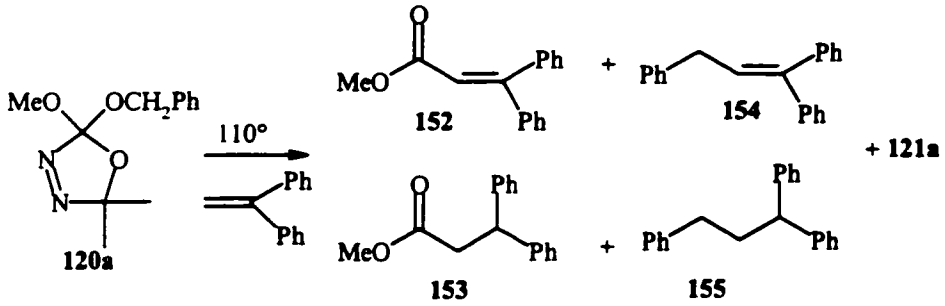
Moss and Hoffmann have independently shown that dimethoxycarbene (**3**) adds to styrene[65,23] and 1,1-diphenylethylene[23] to generate the corresponding cyclopropanes **150** and **151**, Scheme 36. The yield of the cyclopropanation was moderate, approximately 35%.



Scheme 36

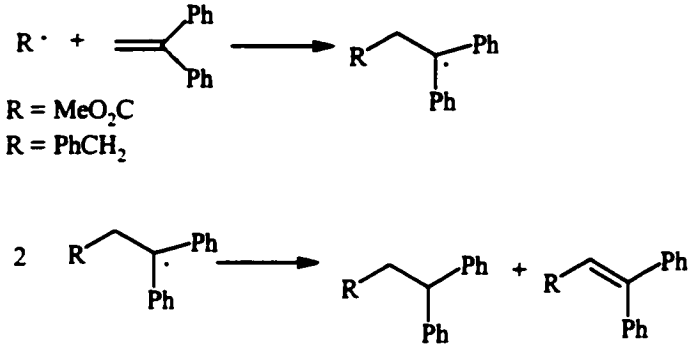
Based on the results of Hoffmann and Moss a cyclopropane or a product from the analogous ring-opening should be detected upon thermolysis of benzyloxymethoxy oxadiazoline, **120a**, in the presence of 1,1-diphenylethylene and styrene. The reaction of benzyloxy(methoxy)carbene (**122a**) with styrene was unsuccessful because the thermolysis of **120a** was carried out at 110°C, which is close to the temperature in which styrene begins to autopolymerize.[164]

Thermolysis of **120a** in the presence of 1,1-diphenylethylene (0.17M) yielded a complex mixture of products, Scheme 37.



Scheme 37

The product mixture was not examined in detail but products **152**, **153**, **154**, **155** and methyl phenylacetate (**121a**) were identified with the aid of authentic samples. Authentic **154** was synthesized by the dehydration of 1,1,3-triphenylpropanol and subsequent catalytic hydrogenation of **154** afforded **155**. Esters **152** and **153** were isolated from the thermolysis mixture. Product ratios were determined from GC analysis and were, **121a**, 3.3; methyl 3,3-diphenylpropanoate (**153**), 1.2; methyl 3,3-diphenylpropenoate (**152**), 1.0; 1,1,3-triphenylpropane (**155**), 1.2; 1,1,3-triphenylpropene (**154**), 1.1. The products from the thermolysis of **120a** in the presence of 1,1-diphenylethylene indicate a radical mechanism and not initial cyclopropanation of the double bond by the carbene. Methyl phenylacetate (**121a**) was a result of in-cage coupling of methoxycarbonyl and benzyl radicals; products **152**, **153**, **154** and **155** were derived from addition of a methoxycarbonyl or benzyl radical to the 1,1-diphenylethylene followed by disproportionation, Scheme 38. A combination of both steric effects and the stability of the newly formed radical could contribute to the regioselectivity.[165] Disproportionation can be between equivalent and non-equivalent radicals.

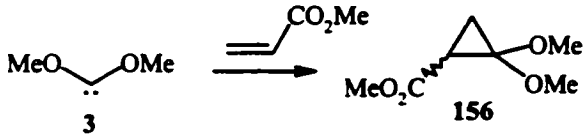


Scheme 38

Benzyloxycarbenes do not add to 1,1-diphenylethylene at a concentration of 0.17M. The rate of fragmentation of the carbene far exceeds the rate of addition of the carbene to the alkene. Therefore a complex mixture of products was observed from radical addition to the alkene followed by disproportionation.

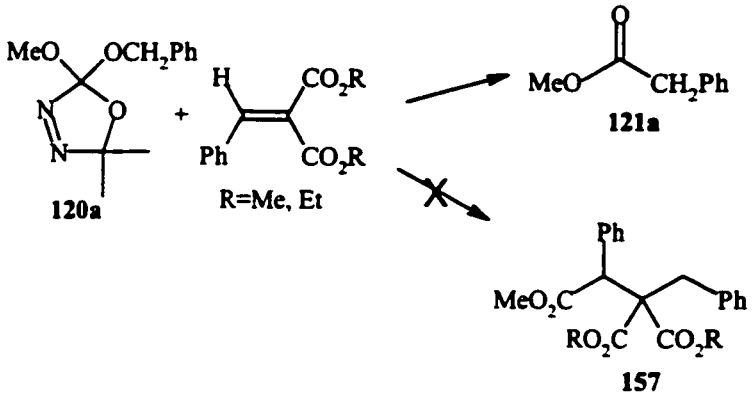
2.3.4 Thermolysis of **120a** in the Presence of Dimethyl and Diethyl Benzalmalonate

Diethyl and dimethyl benzalmalonate are electron deficient alkenes in which the two cyano groups in benzylidenemalononitrile have been replaced with two ester groups. Moss and Hoffmann have independently observed the addition of dimethoxycarbene to methyl acrylate,[24] diethyl fumarate, diethyl maleate and ethyl cinnamate.[23] Addition of dimethoxycarbene to methyl acrylate yielded cyclopropane **156** (equation 52).[24]



3 **156** (52)

It is expected that these benzalmalonates would behave similar to benzylidenemalononitrile (**138**) in which the benzyloxycarbenes should cyclopropanate the double bond, followed by rearrangement of the cyclopropane. Thermolysis of **120a** in the presence of diethyl benzalmalonate (0.16M) yielded methyl phenylacetate (**121a**) as the major product. Product **157** from cyclopropanation of the double bond followed by subsequent ring-opening, was absent (Scheme 39).



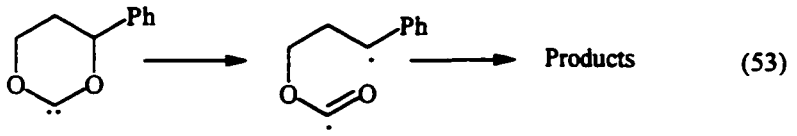
Scheme 39

Steric interactions between the two ethoxy groups may have caused the ester groups to be twisted out of the plane of the double bond thus reducing the electron-withdrawing affect created by geminal ester groups. The thermolysis was repeated utilizing dimethyl benzalmalonate (0.16M) in which steric effects should be smaller. Methyl phenylacetate was again the major product and the GC/MS trace indicated that the product from cyclopropanation followed by ring-opening was absent. The product mixture was not examined any further. These two reactions indicate that the rate of fragmentation of benzyloxycarbenes is faster than their addition to benzalmalonates.

Alkenes that have been shown to trap dimethoxycarbene (3), for example, 1,1-diphenylethylene[23] and ester substituted alkenes,[24,23] do not trap benzyloxycarbenes and products are observed that are derived from radical reactions. Hence, the fragmentation of benzyloxycarbenes to radicals is faster than carbene addition to these alkenes. It appears that the geminal cyano groups are imperative for fast addition of benzyloxycarbenes to alkenes.

2.4 Chemistry of Cyclic Dioxycarbenes

Fragmentation of benzyloxy(methoxy)- and di(benzyloxy)carbenes to a radical pair has been established as described in Section 2.1 and 2.2. Alternatively, a diradical would be formed from the homolysis of carbene **158** in which the benzyloxy group is tethered to the methoxy group (equation 53).

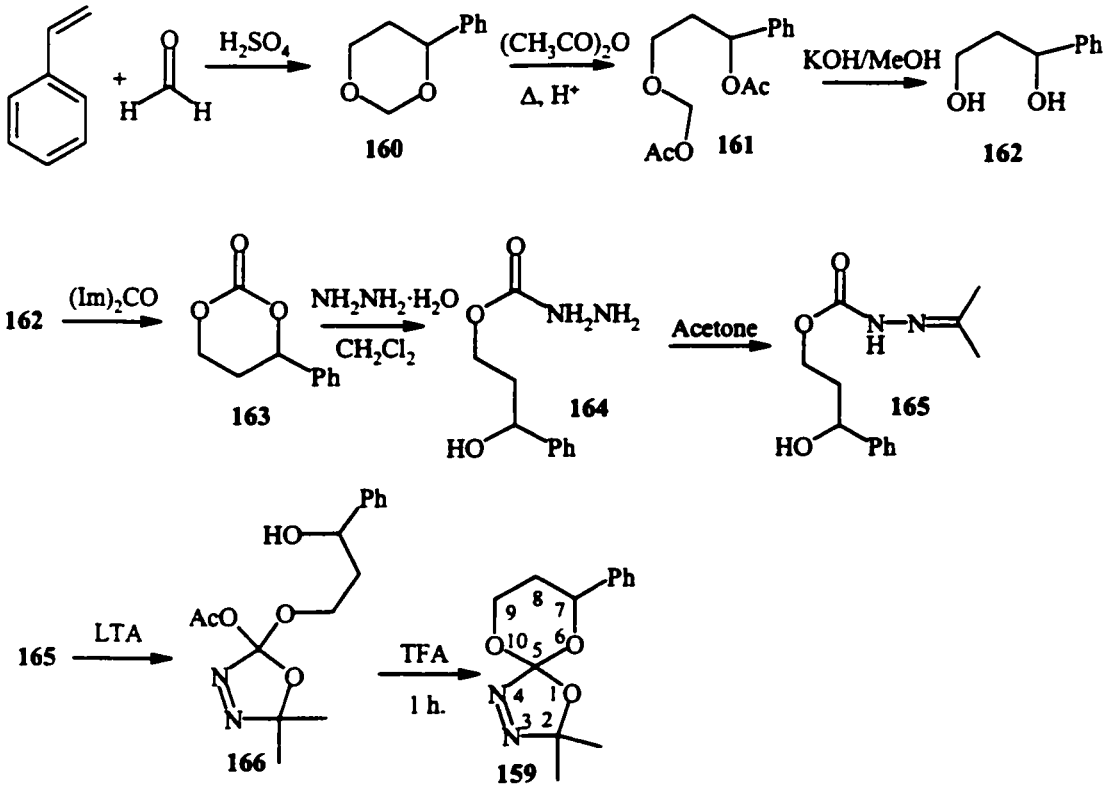


158 (53)

Computations by Reid, on the homolysis of singlet allyloxy(hydroxy)carbene, revealed that a barrier was not expected when the leaving group was *anti* to the carbene lone pair. Therefore, homolysis occurred from the *cis,trans*-conformer of allyloxy(hydroxy)carbene (Section 1.5.2.1, Scheme 25). Similarly, Reid and Hernández-Trujillo did not find a barrier for the homolysis of singlet *cis*-hydroxycarbene, when the hydrogen and carbene lone pair were *anti* (Section 1.5.2.1, Scheme 26).[120] Based on these computational results fragmentation of **158** to a diradical should be facile, since the benzyloxy group is held *anti* to the carbene lone pair. The chemistry of 1,3-dioxa-4-phenyl-cyclohex-2-ylidene (**158**) was studied utilizing spiro oxadiazoline **159** as the precursor.

Spiro oxadiazoline **159** was synthesized by the multi-step synthesis outlined in Scheme 40. Ring-opening of 4-phenyl-1,3-dioxane (**160**) with acetic anhydride was regioselective affording exclusively **161**. Saponification of **161** yielded the 1-phenyl-1,3-propanediol (**162**). Utilizing 1,1'-carbonyldiimidazole as a phosgene equivalent, carbonate

163 was synthesized from propanediol **162**. Hydrazinolysis of **163** in a heterogeneous solution of hydrazine in dichloromethane yielded insoluble white crystals of **164**. Both regioisomers of **164** were obtained if the hydrazinolysis was carried out in a homogenous solution using methanol (MeOH) as the solvent.



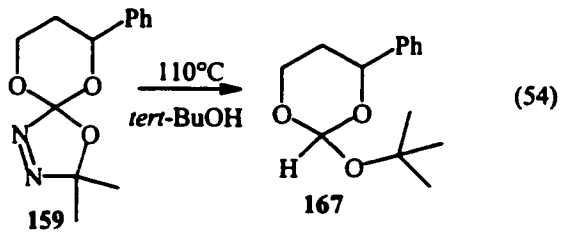
Scheme 40

Oxidation of hydrazone **165** with lead(IV) acetate (LTA) over 2 days yielded the acetoxy compound **166**. Cyclization of **166** to **159** was unsuccessful under the oxidation conditions. Failure to cyclize **166** to **159** was unexpected because the intramolecular capture of the intermediate cation by the tethered alcohol should have been faster than the bimolecular capture of acetic acid to form **166**. In order to cyclize **166** to spiro

oxadiazoline **159**, trifluoroacetic acid was added to the residue obtained after aqueous work-up of the oxidation reaction mixture. Two diastereomers were obtained in a 1:1 ratio. Characteristic C5 and C2 chemical shifts at 119 ppm and 140 ppm were observed in the ^{13}C NMR spectra, which confirmed the identity of **159**.[42] Characteristic axial and equatorial coupling constants (*J*) were observed for the 1,3-dioxane ring protons indicating that the ring was intact.

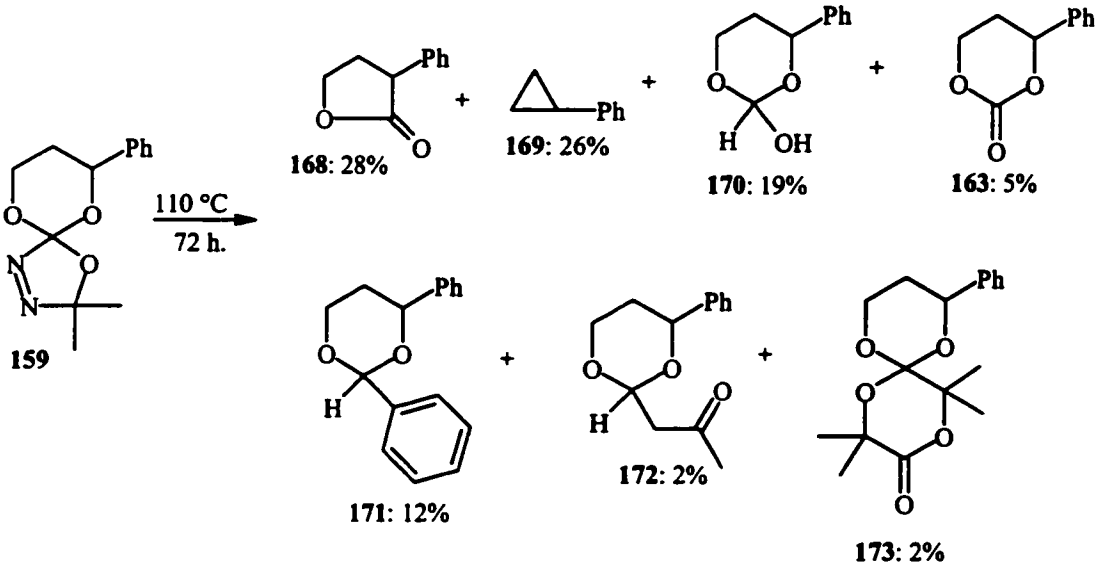
Preliminary analysis of the product mixture from the thermolysis of **159** at 110°C for 24 hours by NMR spectroscopy revealed that some of **159** remained. By means of NMR experiments the rate constant for decomposition of **159** was estimated to be 1.5 x 10^{-5} s^{-1} and its half-life was approximately 13 hours. The long half-life for the decomposition of **159** indicated that **159** needed to be thermolyzed for a minimum of 72 hours. Alternatively, the rate constant for decomposition of dibenzyloxy oxadiazoline **126a** was determined to be 8.7 x 10^{-5} s^{-1} at 110°C, with a half-life of two hours. Differences in these two rate constants may be due to the six-membered ring. As the oxadiazoline loses nitrogen and the carbonyl ylide carbons become sp^2 hybridized, the six-membered ring resists opening of the angle and as a result decomposition is slow.

Thermolysis of **159** in the presence of *tert*-butyl alcohol afforded orthoformate **167** (equation 54). Trapping the carbene with *tert*-butyl alcohol confirms that the thermolysis of oxadiazoline **159** yields carbene **158** upon thermolysis. Two diastereomers of **167** were obtained in a 3:1 ratio in which the *cis* isomer is expected to be the major product.



(54)

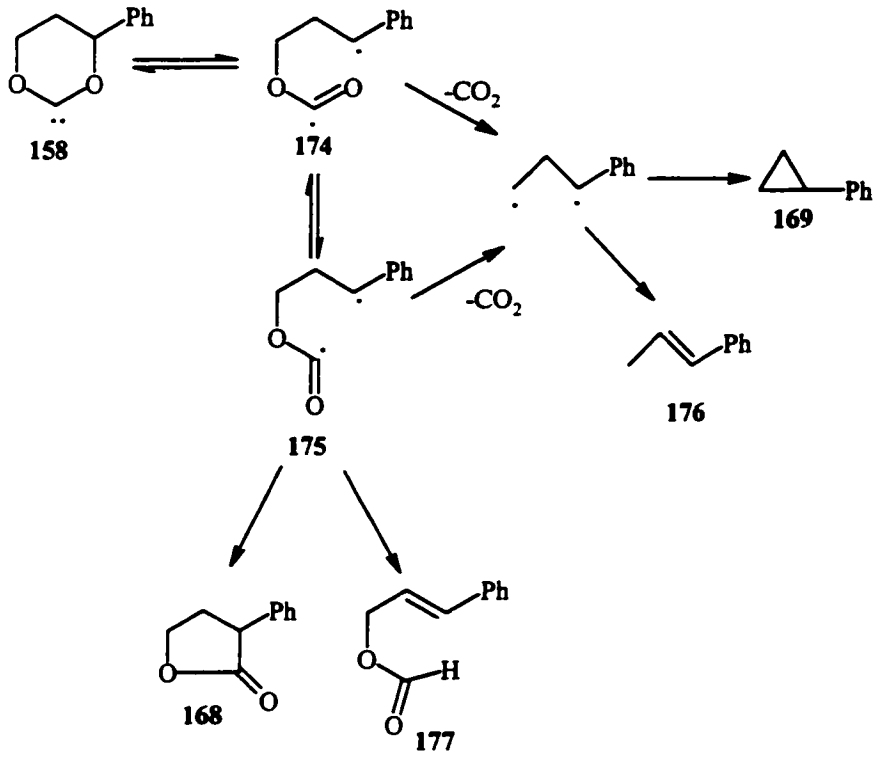
Thermolysis of **159** in degassed benzene at 110°C for 72 hours afforded a complex mixture of products, Scheme 41.



Scheme 41

Product yields from the thermolysis of **159** were determined by GC analysis of the crude thermolysis mixture using 1,4-dimethoxybenzene (DMB) as the internal standard. Each GC injection was repeated three times to minimize any errors. The areas for each peak were corrected using the response factors for the flame ionization detector (FID).[151] Identification of the products was achieved by co-injection with authentic samples, which were purchased from Aldrich or purified from the crude thermolysis mixture and fully characterized.

Major products from the thermolysis of **159** were α-phenyl-γ-butyrolactone (**168**) and phenylcyclopropane (**169**), which are rationalized from the homolysis of **158** followed by chemistry of the diradical, Scheme 42. Homolysis occurs from singlet **158** and the diradical is born as a singlet as a result of spin conservation. The diradical is produced in conformation **174** and must rotate to conformation **175** before it can couple to form **168**. Decarboxylation can occur from both conformations of the diradical.



Scheme 42

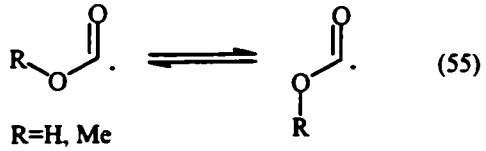
1-Phenylpropene (**176**) and 3-phenylpropenyl formate (**177**) from disproportionation of the diradicals were not detected. Failure to observe **177** is not surprising as 1,5-diradicals generated from the photolysis of α-(o-tolyl)acetophenone exclusively cyclize to indanol.[166] Similarly, for the 1,5-diradical, 2,6-diphenylheptan-2,6-

diyl, cyclization predominates over the [1,4]-hydrogen shift (coupling : disproportionation = 7:1).[167] Therefore, disproportionation is not anticipated to compete with cyclization of **175**. Similarly, formation of phenylcyclopropane is expected to dominate over the [1,2]-hydrogen shift in the diradical produced from the decarboxylation of **174** or **175**. [1,2]-Hydrogen shifts in 1,3-diradicals, to produce propenes, have been observed from the pyrolysis of 1,1-dimethyl-2,2-d_2-cyclopropane.[168]

Since lactone **168** and phenylcyclopropane (**169**) were formed in approximately equal amounts the rate constants for cyclization (k_c) and decarboxylation (k_{CO_2}) are expected to be similar at 110°C. The rate constant for decarboxylation can be estimated from the product ratio (RCH_3:RCH_2OCHO = 38:25) for the hydrogen abstraction from $HSnBu_3$ (0.025M) by a primary alkoxycarbonyl radical *versus* its decarboxylation.[169] Utilizing the rate constant (k_H) for the reaction of primary alkoxycarbonyl radicals with $HSnBu_3$ ($k_H = 1.77 \times 10^6\ M^{-1}s^{-1}$ at 110°C, extrapolated from Arrhenius parameters),[153] the rate of decarboxylation is estimated to be $6.8 \times 10^4\ s^{-1}$. Therefore, the upper limit for cyclization of **174** is $10^5\ s^{-1}$. The rate constant for cyclization is smaller than expected, considering that the diradical is formed as a singlet.

An explanation for this slower rate constant for the cyclization of the diradical to **168** may be a result of the barrier to rotation about the O-CO bond. In order for the diradical to couple to give lactone **168**, rotation about the O-CO bond of the diradical from conformation **174** to **175** must occur, Scheme 42. Previous computations modelled the isomerization of hydroxycarbonyl radical (equation 55). Three pathways were used to

model this isomerization, rotation about the HOCO dihedral angle, and in-plane inversions of the HOC or OCO angles.[170] From these calculations the authors were able to estimate that the rotational transition state was approximately 6.7 kcal mol^{-1} above the *cis*-hydroxycarbonyl radical and approximately 24 kcal mol^{-1} lower in energy than the in-plane pathway.

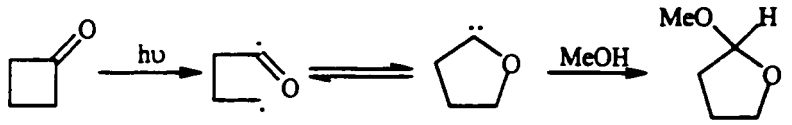


R=H, Me (55)

Reid modelled the rotational barrier for the methoxycarbonyl radical at both B3LYP and MP2 levels of theory.[171] Rotation of the *cis*-methoxycarbonyl radicals occurs with a barrier of 8.0 kcal mol^{-1} and 8.9 kcal mol^{-1} at the B3LYP/6-31+G* and MP2(FC)/6-31+G* levels of theory. The rotational barrier for the *trans*-methoxycarbonyl radicals was 0.5 kcal mol^{-1} and 0.1 kcal mol^{-1} higher in energy than that of the *cis* conformer at B3LYP and MP2(FC), respectively. Consideration was given to rotations of the O-CO bond only because the barrier to rotations about alkyl single bonds is much smaller, approximately 4 kcal mol^{-1}.[172] These computational results suggest that the isomerization of conformer **174** to **175** may be slow. Consequently, the cyclization of **174** to lactone is also slow. That cyclization would be fast if the 1,5-diyl was born in conformation **175**, because radical-radical coupling reactions occur with small barriers and with rate constants approximately 10^9 s^{-1}.[144]

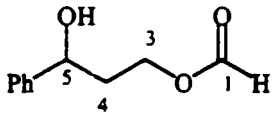
Closure of diradical **174** to carbene **158** in Scheme 42 is speculative. The barrier to recoupling of the diradical cannot be large, since the diradical is born in conformation

174. Photolysis of cyclobutanones generates a 1,4-diradical that couples at the carbonyl oxygen to yield an oxycarbene. These oxycarbene intermediates have been trapped by methanol (equation 56).[173] Therefore, reclosure of diradical **174** to regenerate carbene **158** is reasonable.

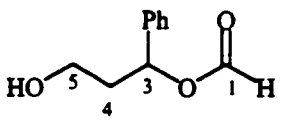


(56)

After chromatography of the product mixture from the thermolysis of **159** a compound was isolated that had a GC retention time different from that of the signals in the GC trace of the crude mixture. A proton signal at 8.1 ppm in the ^{1}H NMR spectrum suggested this compound was formate, **178** or **179**.

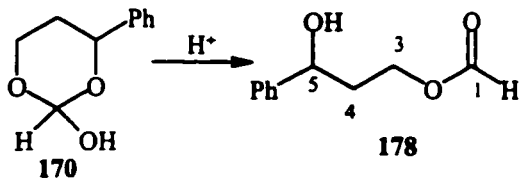


178



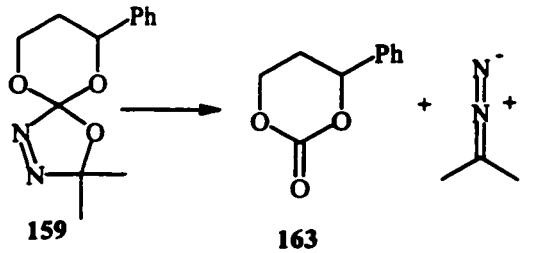
179

By a 2-dimensional NMR Heteronuclear Multiple Bond Correlation (HMBC) experiment the regiochemistry of the formate was determined to be that of **178**. A ^3J correlation was observed between the carbonyl carbon and the methylene protons at position 3. A formate was also detected from the thermolysis of dibenzyloxy oxadiazoline **126a**. Benzyl formate was proposed to result from the decomposition of hemiorthoformate **135** (Section 2.2, Scheme 30). Similarly, carbene **158** must insert into the O-H bond of water generating hemiorthoformate **170**. Upon chromatography **170** hydrolyzes exclusively to **178** (equation 57).



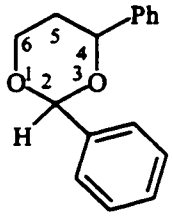
170 178 (57)

Two diastereomers of **170** should have been formed but they were not resolved on the GC. Hemiorthoformate **170** survived the thermolysis conditions unlike hemiorthoformate **135**. The stability of hemiorthoformate **170** is attributed to its sugar-like structure. Competitive decomposition of spiro oxadiazoline **158**, afforded **163** and 2-diazopropane (equation 58).[139]



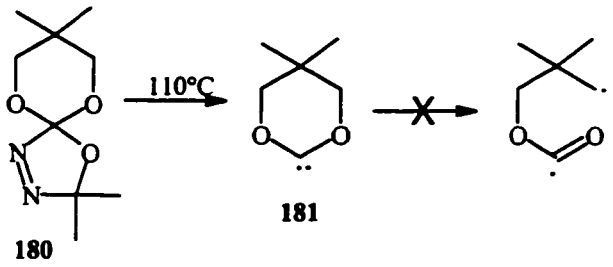
159 163 (58)

Product **171** appeared to originate from the insertion of carbene **158** into a C-H bond of benzene. The identity of **171** was determined from NMR analysis and was confirmed by comparison with the ^{1}H NMR of an authentic sample. Authentic **171** was synthesized by means of the acid catalyzed protection of benzaldehyde with 1-phenyl-1,3-propanediol. Two diastereomers of **171** were isolated from the crude thermolysis product mixture (3:1), in which the major isomer is expected to be the thermodynamic isomer, *cis*-2,4-diphenyl-1,3-dioxane.



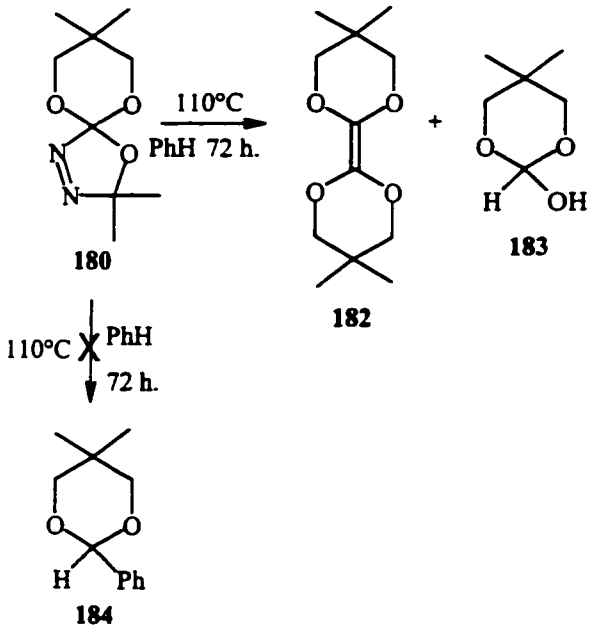
171

Literature precedence for the insertion of dioxycarbenes into benzene is not available. Dimethoxycarbene has been shown to undergo *ipso* aromatic substitution on Sanger's reagent, but the yield was low (Section 1.5.1.1, equation 14).[74] Insertions of dioxycarbenes into C-H bonds have also not been observed. Evidence for the insertion of diaminocarbenes into the C-H bond of alkynes and of sulphones has been reported.[174] The unusual reactivity of **158** might be related to the *cis,cis*-conformation to which it is constrained. Reid has calculated the energy of *cis,cis*-allyloxy(hydroxy)carbene to be 11.7 kcal mol^{-1} higher than that of the *trans,trans*-conformer.[114] Raising the ground state energy of the carbene and not the energy of the transition state might reduce the barrier to insertion of the carbene into C-H bonds. Analogous 1,3-dioxa-cyclohex-2-ylidenes should yield similar C-H insertion products if the formation of **171** is dependent on the geometry of the carbene. To provide further insight into the mechanism for the formation of **171**, spiro oxadiazoline **180** was synthesized. Thermolysis of spiro oxadiazoline **180** affords carbene **181**, which cannot fragment, as a stabilized diradical would not be formed (equation 59).



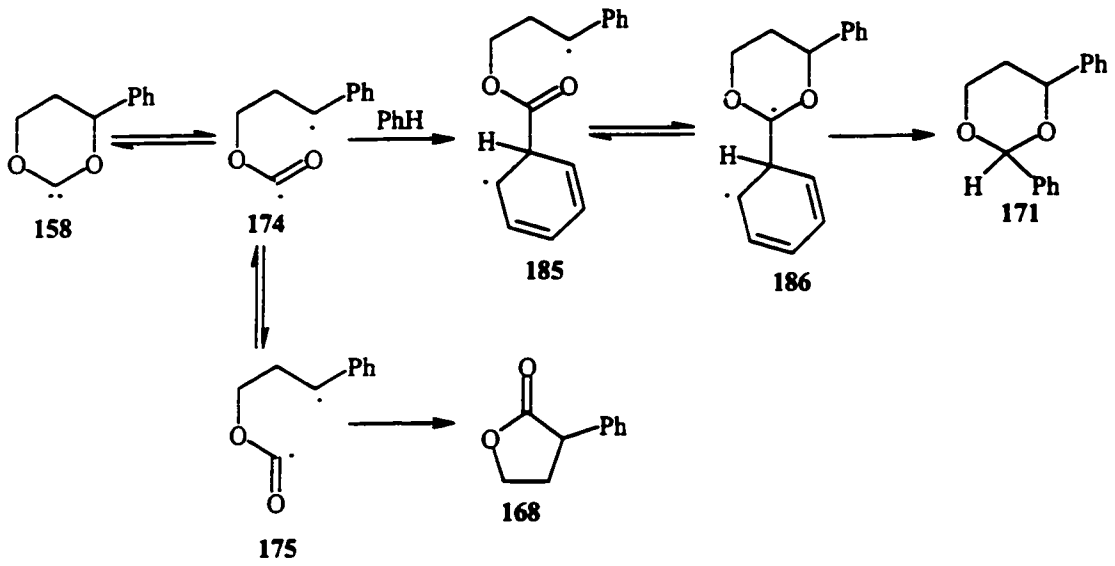
180 181 (59)

Synthesis of spiro oxadiazoline **180** was achieved by a route analogous to that in Scheme 40, except that neopentyl glycol is commercially available and its synthesis was not required. Thermolysis of **180** in degassed benzene afforded two major products, carbene dimer **182** (28%) and hemiorthoformate **183** (21%), Scheme 43. Dimerization is a common reaction of dimethoxycarbene in the absence of traps.[24] Isolation of carbene dimer confirms that carbene **181** does not fragment. By GC analysis of the thermolysis product mixture, using authentic **184** as a reference, it was determined that **184** from insertion of carbene **181** into benzene was not present. Failure to observe **184** suggests that **171** cannot be produced from insertion of carbene **158** into a C-H bond of benzene.



Scheme 43

An alternative mechanism is proposed for the formation of **171** based on the analogy that methyl benzoate has been produced from the homolytic aromatic substitution of methoxycarbonyl radicals onto benzene.[148] Methyl benzoate was also formed during the thermolysis of benzyloxymethoxy oxadiazoline **120a** (Section 2.1, equation 40) in which the methoxycarbonyl radicals were generated from the homolysis of benzyloxy(methoxy)carbene (**122a**). Scheme 44 outlines the proposed mechanism in which the diradical attacks benzene followed by a sequence of intramolecular reactions. The net result of this pathway is homolytic aromatic substitution of the diradical onto benzene, which affords **171**.[175]



Scheme 44

One example of homolytic aromatic substitution with alkoxycarbonyl radicals[148] has been reported in the literature, implying that the substitution is too slow to be useful. The reaction is slow overall because it can be reversible[149] and formation of the final product requires a bimolecular hydrogen transfer step. In the case of diradical **185** an intramolecular step competes with reversal and that could enhance the rate of aromatic substitution. Closure of the diradical to oxygen of the carbonyl group affords diradical **186**. 6-*Endo* closures of diradicals have not been reported, but 6-*endo* cyclization of a radical onto the oxygen of a carbonyl group has been observed.[176] An allyl radical, generated from the β-scission of an oxyl radical, added to the oxygen of the carbonyl group to form a tetrahydropyranyl radical.[176] 6-*Endo* cyclizations of carbon-centred radicals to double bonds have also been reported.[177,178,179] The final step in the mechanism is a [1,2]-hydrogen shift to yield **171**. Radicals do not undergo hydrogen transfers but [1,2]-hydrogen transfers in 1,3-diyls are common.[168] [1,2]-Hydrogen

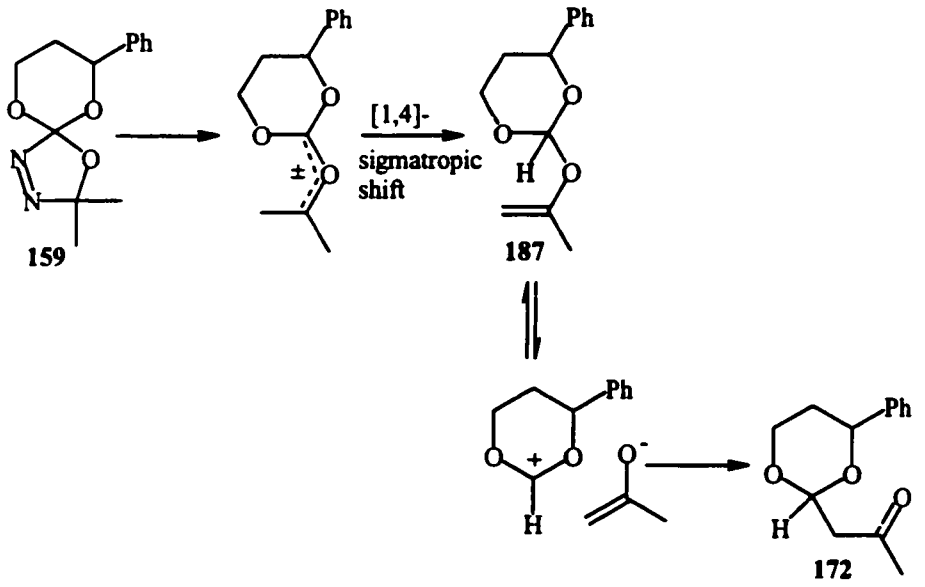
migrations in 1,3-diradicals are under kinetic control and therefore both diastereomers of **171** should have been obtained. Two diastereomers of **171** were isolated by chromatography in a ratio of 3:1. It cannot be certain that the diastereomer ratio was 3:1 before purification as the two diastereomers of **171** were not resolved on the GC. Aromatization of **186** should also provide a considerable driving force towards the formation of **171**.

The mechanism at first glance seems unlikely because the diradicals have the option to decarboxylate or undergo cyclization. Coupling and decarboxylation of radicals are reactions that are normally considered to be fast.[144,153] In order for the diradical to couple to give lactone **168**, rotation about the O-CO bond of the diradical from conformation **174** to **175** must occur, Scheme 44. The barrier to rotation about the O-CO bond of methoxycarbonyl radicals was calculated by Reid to be approximately 9 kcal mol^{-1} at MP2(FC)/6-31+G* level of theory.[171] The large barrier to rotation about the O-CO bond of diradical **174** results in a slower rate constant for cyclization of the diradical to lactone **168**. Therefore attack of the diradical onto benzene can compete with cyclization and decarboxylation of the diradical.

The rate constant for the addition of alkoxycarbonyl radicals to benzene is unknown. However, utilizing the product ratio obtained from the thermolysis of **159** one can be estimated. Decarboxylation and coupling of the diradical occurred with yields that were twice as high as that for **171** from the attack of the diradical on benzene. The rate constant for decarboxylation (k_{CO_2}) of a primary alkoxycarbonyl radical was estimated to

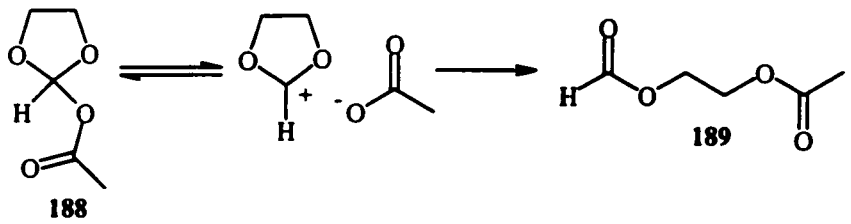
be 6.8 x 10^4 s^{-1} (p. 88). Since the rates of decarboxylation and coupling are approximately two times that for diradical attack on benzene then $2k_{CO_2} \sim k_{benzene}$[Benzene]. The concentration of benzene is approximately 10 M, and therefore the rate constant for attack of the diradical onto benzene is 3.4 x 10^3 $M^{-1}s^{-1}$ or about 10^3 s^{-1} at 110°C.

Thermolysis of **159** afforded two unexpected minor products, **172** (2%) and **173** (2%), Scheme 41. The net reaction for the formation of **172** appears to be insertion of the carbene into the C-H bond of acetone. Acetone is liberated during the decomposition of the oxadiazoline, but insertions of dioxycarbenes into C-H bonds have not been observed. The yield of **172** remained constant when **159** was thermolyzed in the presence of added acetone (1.1M), thus confirming that **172** was not produced from the insertion of the carbene **158** into the C-H bond of acetone. A more likely explanation would be a reaction of the carbonyl ylide, Scheme 45.



Scheme 45

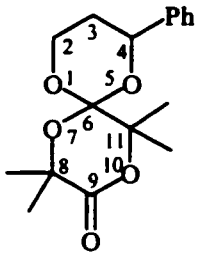
A [1,4]-sigmatropic shift in the carbonyl ylide yielding **187** is proposed in Scheme 45. [1,4]-Sigmatropic shifts have been observed for trimethylmethoxy carbonyl ylides, from the decomposition of methylmethoxy oxadiazoline,[180,49-52] and other carbonyl ylides,[181,182] although subsequent rearrangement did not occur. Cleavage of **187** affords an ion pair and collapse of this ion pair yields **172**. A model system, 2-acetoxy acetal **188**, provides precedence for the proposed mechanism.[183] Thermolysis of acetal **188** at 120°C yielded diester **189**. Diester **189** probably arose from the reversible dissociation of acetal **188** to an ion pair. Subsequent nucleophilic substitution by the acetate at carbon yields diester **189** (equation 60).



(60)

Formation of the ion pairs from both **187** and **188** is most likely reversible. However, for the ion pair from **187**, collapse to carbon is irreversible affording **172**. Isolation of **172** is consistent with the involvement of a carbonyl ylide intermediate in the decomposition of dialkoxy oxadiazolines (Section 1.4.3). Observation of **172** contradicts the computational results from Smith in which he concluded that acetone is lost simultaneously with the extrusion of nitrogen from dimethoxy oxadiazoline.[53]

One diastereomer of **173** was obtained from chromatography and its structure was determined by NMR analysis. The proton signals in the ^{1}H NMR spectrum had coupling constants characteristic of axial and equatorial protons, which indicated that the 1,3-dioxane ring was still intact. A Nuclear Overhauser Effect (NOE) experiment confirmed that this ring was in a chair conformation with the phenyl group equatorial. Saturation of the signal from the axial proton at C2 gave an enhancement of the axial proton signal at C4 and the equatorial proton signal at C3.



173

The chemical ionization mass spectrum gave a $(M+H)^{+}$ peak at 307 m/z, indicating that the second six-membered ring had the elemental composition $C_7H_{12}O_3$. In the ^{13}C NMR spectrum a carbon had a chemical shift characteristic of a carbon connected to three oxygens (C6). Four methyl signals were observed in the ^{1}H spectrum, and the 2-D NMR

HMBC experiment exhibited a ^{3}J correlation between two methyl signals at 1.48 ppm and 1.50 ppm with C6. Hence, the quaternary carbon bearing these two methyl groups is connected to C6. The other two methyl signals at 1.53 ppm and 1.56 ppm signals had a ^{3}J correlation with the C=O group in the HMBC, consequently they are adjacent to the carbonyl group. The chemical shift of the carbonyl carbon was approximately 170 ppm, which is characteristic of an ester group and not a ketone. Although, two fragments, C6-$C(CH_3)_2$-O and O-$C(CH_3)_2$-C=O, were identified from analysis of the HMBC experiment, the connectivity of these two fragments could not be determined from the HMBC experiment.

Rotating Frame Overhauser Enhancement SpectroscopY (ROESY) confirmed the connectivity of the fragments in the second six-membered ring, by showing cross-peaks for the protons that are dipolar coupled. Transfer of magnetization through space occurs between nuclei that are separated by less than 4 Å.[184] In the ROESY spectrum a correlation was observed between the axial proton at C4 and a methyl signal at 1.56 ppm and the methyl signal at 1.53 ppm exhibited a correlation with the axial proton at C2. Therefore, the oxygen at position 7 is axial, and C11 is equatorial. The two methyl signals at 1.48 ppm and 1.50 ppm did not show a correlation with any of the ring protons, confirming that they are attached to equatorial C11 and are too far away from the ring protons to show an Overhauser effect (Figure 10).

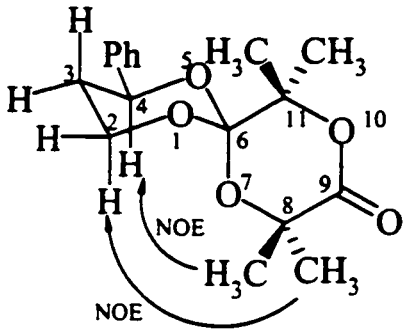
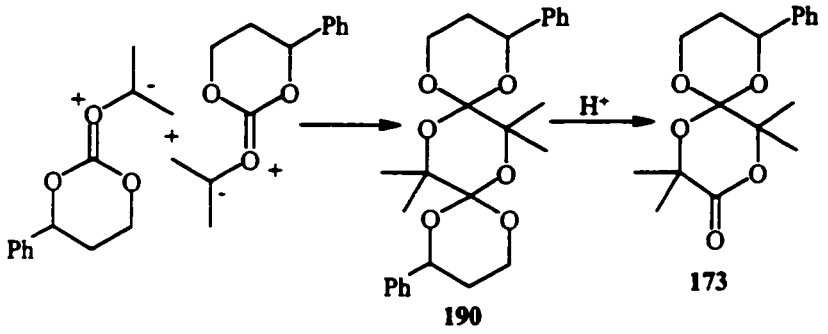


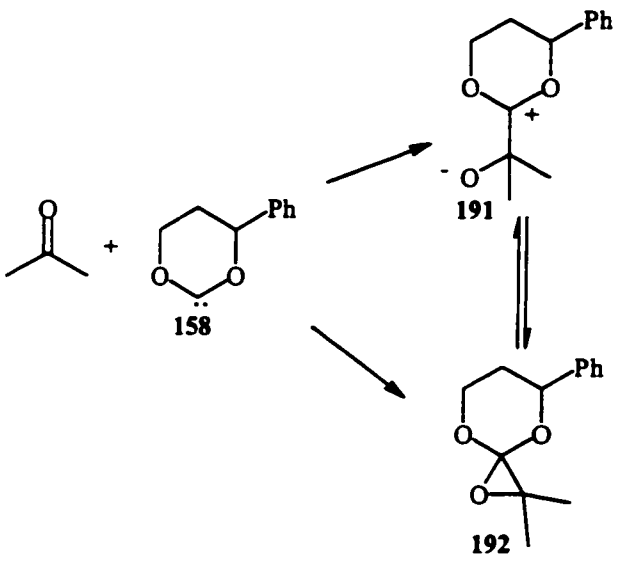
Figure 10: NOE's of the methyl signals of **173** in the ROESY spectrum

Compound **173** appears to originate from the dimerization of two carbonyl ylides followed by partial hydrolysis of **190** (equation 61). The dimerization of two carbonyl ylides is unlikely because the decomposition of oxadiazoline **159** is slow ($t_{1/2}$ = 13 h at 110°C) and therefore their maximum concentration is low.



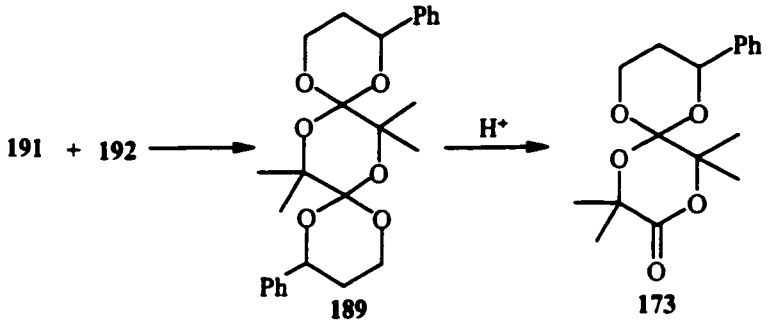
(61)

Alternatively, **190** could be formed from the dimerization of two oxiranes. An oxirane could be formed either form the closure of the carbonyl ylide or from the addition of carbene **158** to acetone. Addition of carbene **158** to acetone can either be stepwise to form the dipole **191** or concerted to afford oxirane **192** directly, Scheme 46.



Scheme 46

Attack of carbene **158** onto acetone is not unreasonable, as oxiranes have been observed from the reaction of dimethoxycarbene (**3**) with carbonyl groups (Section 1.5.1.2).[77,78] An oxirane has been isolated from the reaction of dimethoxycarbene (**3**) with cyclohexanone,[77] and another has been detected by NMR spectroscopy from the reaction of dimethoxycarbene with fluorenone.[78] Reaction between dipole **191** and oxirane **192** followed by partial hydrolysis leads to **173** (equation 62).

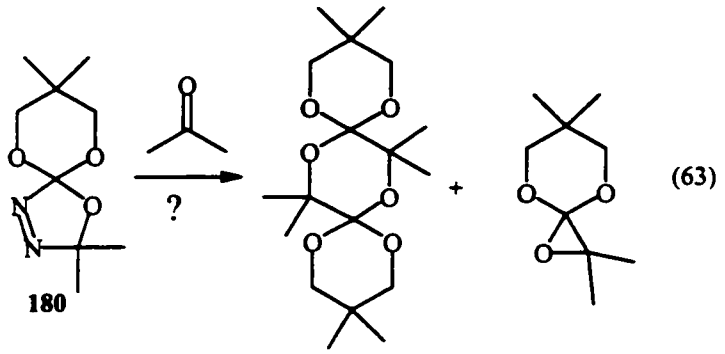


(62)

Thermolysis of **158** was then repeated in the presence of added acetone (1.1M) to determine the dependence of the yield of **173** on the acetone concentration. GC analysis

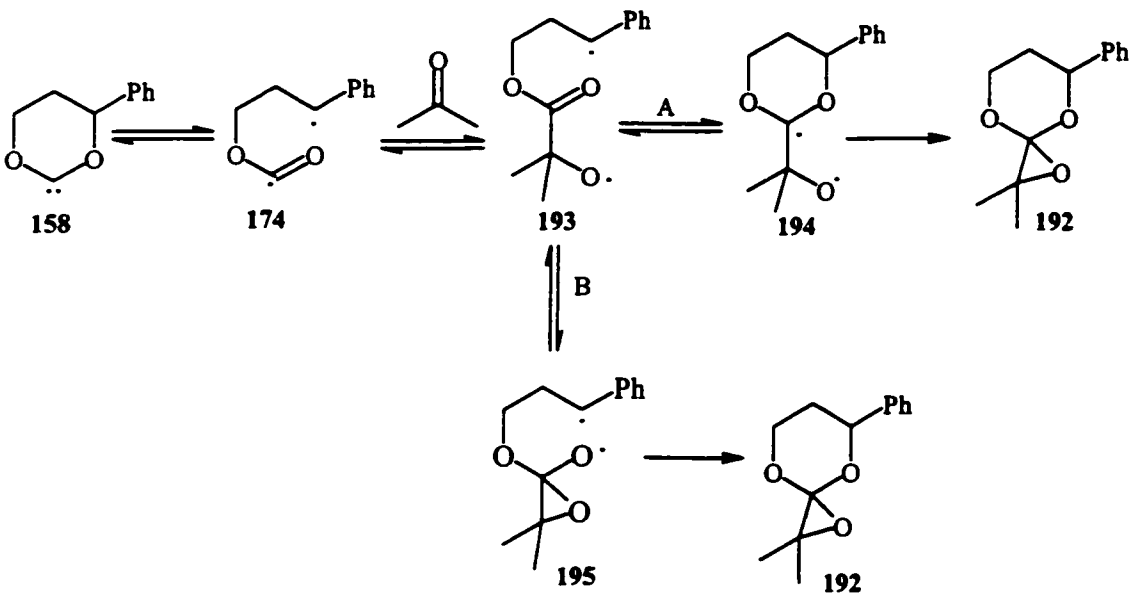
of the crude mixture indicated that **173** had become the major product (28%), and that the yields of lactone **168** and phenylcyclopropane **169** had dropped dramatically to approximately 5%. The yields of **171**, **172** and carbonate **163** remained unchanged. Accordingly, the formation of **173** was dependent on the concentration of acetone. The dependence of the yield of **173** on the concentration of acetone suggests that carbene **158** adds to acetone to form a dipole or oxirane.

To provide further evidence that 1,3-dioxa-cyclohex-2-ylidenes attack the carbonyl group of acetone, spiro oxadiazoline **180** was thermolyzed in the presence of acetone (1.8M). Detection of either a dialkoxyoxirane or an analogous oxirane dimer was expected if carbene **181** reacted with acetone (equation 63).



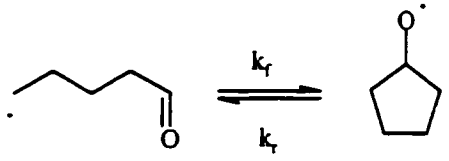
180 (63)

Analysis of the thermolysis mixture by GC indicated that there were only two products from the thermolysis of **180**, carbene dimer **182** and **183**. Failure to detect a product derived from the reaction of carbene **181** with acetone suggested that the proposal that the carbene **158** attacks that carbonyl group of acetone was incorrect. An alternative mechanism is proposed in which the oxirane is produced from attack of diradical **174** onto the carbonyl group of acetone, Scheme 47.



Scheme 47

Reactions of diradicals with ketones have not been reported but radical additions to ketones have.[185] The addition of the diradical to acetone is expected to be reversible as oxyl radicals readily undergo β-scission reactions.[186] Beckwith determined that the rate constant for the reverse reaction (k_r = 4.7 x 10^8 s^{-1}) in equation 64 is larger than that for the forward reaction (k_f = 8.7 x 10^5 s^{-1}) at 80°C.[187]



(63)

Two pathways are available for the collapse of diradical **193**. Pathway A involves 6-*endo* cyclization of diradical **193** followed by radical coupling of the oxyl radical to form the oxirane. In pathway B the oxyl radical can add to the carbonyl group followed

by radical coupling to form the six-membered ring. Precedence exists for the 6-*endo* cyclization of diradical **193**[176] but both pathways are possible.

The final step of the mechanism is reasonable, as oxiranes presumably exist in equilibrium with their ring-opened dipoles.[76,77,78] Attack of the dipole onto the oxirane generates a product with the correct regiochemistry. Partial hydrolysis of **190** most likely occurred during work up because the concentration of water during the thermolysis should be low. The small amount of water present initially reacts with carbene **158** affording the hemiorthoformate, **170**.

The chemistry of **159** is unique; products derived from a carbonyl ylide, carbene and a diradical have been isolated. The major pathway for carbene **158** is homolysis to the diradical giving **168**, **169** and **171** as the major products. Diradicals rarely undergo intermolecular reactions and the isolation of **171** and **173** provides evidence for a diradical reaction with benzene and acetone. The unique reactivity of the diradical could be related to its conformation or the barrier to rotation of the O-C-O portion of the diradical. Isolation of the minor compound **172** provides evidence for the involvement of carbonyl ylides in the decomposition of dialkoxy oxadiazolines. The complex mixture of products from the thermolysis of **159** establishes the oxadiazoline → carbonyl ylide → carbene → radical pathway for benzyloxycarbenes, **120a-f**, **126a-f** and **159**.

Chapter 3

Summary

The chemistry of benzyloxy oxadiazolines is very rich. Upon thermolysis they yield benzyloxycarbenes, which fragment to a radical pair or a diradical. Studying benzyloxymethoxy oxadiazoline initially confirmed that changing the carbene substituent to a benzyloxy group could promote carbene fragmentation. Trapping of both radical and carbene intermediates from benzyloxymethoxy oxadiazoline establishes that methyl arylacetates are formed from fragmentation of benzyloxy(methoxy)carbenes followed by coupling of a methoxycarbonyl and benzyl radicals. Since trapping of the carbenes with *tert*-butyl alcohol competes with fragmentation the rate constant for this fragmentation could be estimated to be $10^7 s^{-1}$.

Di(benzyloxy) oxadiazolines also afforded both carbenes and a radical pair upon thermolysis. Phenylacetates were formed from the coupling of the benzyloxycarbonyl and benzyl radicals. A preference was observed for the cleavage of the carbene to a benzyl radical bearing an electron-withdrawing group. A correlation with the logarithms of the product ratio with $\sigma^{\cdot}$ substituent constants was found ($\rho_{110°C} = 0.7$) suggesting that the transition state is quite polar, in the sense that electron density increases at the carbon becoming the benzylic radical and decreases at the carbene carbon. The sensitivity of the

fragmentation to the *para* substituent supports the computational finding that there is reorganization of the electron density for the homolysis of hydroxycarbene.[120]

Thermolysis of benzyloxy oxadiazolines **120a** and **126a** in the presence of electron deficient alkenes trapped both carbene and radical intermediates. Benzyloxycarbenes add to alkenes bearing geminal cyano groups (methylidenemalononitriles) yielding a cyclopropane, which ring-opens to the diradical. Cleavage of the cyclopropane occurs exclusively between the vicinal withdrawing and donating groups. Subsequent rearrangement of the diradical affords esters. Alkenes such as, 1,1-diphenylethylene and ester substituted alkenes, that have been shown to trap dimethoxycarbene (**3**) do not trap benzyloxycarbenes and products are observed that are derived from radical reactions. Hence, addition of the carbene to these alkenes cannot compete with the fragmentation of benzyloxycarbenes to radicals. The geminal cyano groups are necessary for fast addition of benzyloxycarbenes to alkenes.

Thermolysis of spiro oxadiazoline **159** yielded products derived from a carbonyl ylide, carbene and a diradical. The major pathway for cyclic carbene **158** is homolysis to the diradical. Subsequent coupling and decarboxylation of the diradical yielded a lactone and phenylcyclopropane as the major products. Diradicals rarely undergo intermolecular reactions and the isolation of 2,4-diphenyl-1,3-dioxane (**171**) and spiro compound **173** is the first evidence that intermolecular diradical reactions can occur in moderate yields. The unique reactivity of the diradical could be related its conformation to which it is born and the barrier to rotation of the O-C-O portion of the diradical (~8 kcal mol^{-1}). Isolation of the minor compound **172** provides evidence for the involvement of carbonyl ylides in

the decomposition of dialkoxy oxadiazolines. The complex mixture of products from the thermolysis of **159** establishes the oxadiazoline → carbonyl ylide → carbene → radical pathway for benzyloxycarbenes.

Thermolysis of spiro oxadiazoline **180**, on the other hand, afforded a cyclic carbene that could not fragment to a diradical. Products were isolated that were derived from dimerization of two carbenes and a hemiorthoformate from the reaction of the carbene with water.

Chapter 4

Experimental

NMR spectra were recorded on a Bruker AV-200, AV-300 or AV-500 spectrometer and the spectrometer field strength is specified for each spectrum. Chemical shifts for ^1H NMR spectra are reported in ppm and are referenced to the residual solvent resonances ($CHCl_3$, 7.24 ppm, C_6HD_5, 7.15 ppm; CD_2HOD, 4.76 ppm), unless otherwise stated. ^{13}C NMR spectra are also reported in ppm and referenced to the solvent peaks ($CDCl_3$, 77.0 ppm; C_6D_6, 128.0 ppm). Melting points were obtained on a Thomas Hoover capillary melting point apparatus, and are not corrected. Mass spectra were obtained on a ZAB-E double focusing mass spectrometer or on a Hewlett Packard MSD GC/MS (5971A) and peak heights are reported as their intensity relative to the base peak. Radial chromatography was performed using a Chromatotron (7942T, Harrison Research, Inc.), with silica-coated plates (thickness: 1 mm, 2 mm or 4 mm). The GC/FID utilized was a Varian Vista Series 6000 chromatograph equipped with a J&W DB-1 megabore 0.53 mm i.d. column (flowrate 15 mL/min) and flame ionization detector (FID). Peak areas were obtained with a Hewlett Packard 3390A integrator.

Thermolyses were carried out in benzene distilled from either CaH_2 or sodium and stored over molecular sieves (4 Å). Solutions of the oxadiazolines (0.1 M) required for

the thermolyses were sealed into thermolysis tubes. The tubes were evacuated using the freeze-pump-thaw cycle, which was repeated three times before sealing. After sealing the tubes were placed in a constant temperature oil bath preheated to 110°C for either 24 or 72 hours, depending on the oxadiazoline.

4.1 Synthesis and Thermolysis of Benzyloxymethoxy Oxadiazoline (**120a**)

Synthesis of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4- oxadiazoline (**9**):

The methoxycarbonyl hydrazone of acetone (10g, 0.076 mol) dissolved in dichloromethane (CH_2Cl_2, 86 mL) was added dropwise under nitrogen to a cooled solution of lead(IV) acetate (38g, 0.076 mol) in dichloromethane (86 mL). After addition of the hydrazone, the ice bath was removed and the solution was stirred for 2 hours. After 2 hours the solution had become heterogeneous and the mixture was filtered through Celite to remove the precipitated lead diacetate. The filtrate was washed twice with water (25 mL) and once with 5% sodium bicarbonate (25 mL), and the dichloromethane layer was dried over magnesium sulphate. After filtration the solvent was removed by rotary evaporation. The resultant yellow oil was a mixture of oxadiazoline **9** and the acyclic isomer (63:37).

2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4- oxadiazoline: Yellow oil; yield 65%; ^{1}H NMR(200 MHz, $CDCl_3$) δ(composite spectrum) **9**: 1.59 (s, 6H), 2.07 (s, 3H), 3.55 (s, 3H); **acyclic isomer**: 1.48 (s, 6H),2.06 (s, 3H), 3.94 (s, 3H); ^{13}C NMR(50 MHz, $CDCl_3$)

δ(composite spectrum): 20.4, 21.1, 21.4, 22.3, 23.9, 24.2, 52.3, 54.6, 101.5, 122.0 (C5), 133.8 (C2), 161.6, 166.2 168.9.

Synthesis of 2-benzyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**120a**):

Benzyl alcohol (1.53g, 14.1 mmol) and trifluoroacetic acid (0.01 mL) were added to a solution of crude 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (2g, 11.0 mmol) in dichloromethane (50 mL). After 48 hours, 10% NaOH was added and the heterogeneous mixture was stirred for another hour. After one hour the aqueous layer was removed and the dichloromethane was washed twice with water (15 mL). The dichloromethane solution was then dried with magnesium sulphate and the solvent was removed by rotary evaporation. The crude reaction mixture was then purified by radial chromatography (10% EtOAc in hexanes).

2-Benzyloxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (120a): Pale yellow oil; yield 35%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.48 (s, 3H), 1.51 (s, 3H), 3.43 (s, 3H), 4.68 (d, ^2J = -11.5 Hz, 1H), 4.78 (d, ^2J = -11.5 Hz, 1H), 7.24 - 7.27 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 23.9, 24.0, 51.9, 66.6, 119.3 (C5), 127.7, 127.8, 128.3, 136.6 (C2), 137.1.

Thermolysis of **120a**:

Benzyloxymethoxy oxadiazoline **120a** (22.7 mg, 0.096 mmol) was dissolved in deuterated benzene (C_6D_6) containing *p*-xylene (1μL, 0.0087 mmol) as an internal standard. The resultant solution was flame sealed into a NMR tube and heated for 24 hours as described above. Product yields were calculated from the NMR spectrum, which was referenced to the methyl groups of *p*-xylene at 2.10 ppm. To ensure accurate

integration, a relaxation delay of 5 minutes was used as a result of the long T_1 for the acetone signal (T_1 > 18 s). Methyl benzoate was detected in the GC trace after NMR analysis, by co-injection with an authentic sample of methyl benzoate.

Methyl phenylacetate (122c): Yield 42%; ^{1}H NMR(500 MHz, C_6D_6) δ: 3.22 (s, 3H), 3.29 (s, 2H). *Bibenzyl:* Yield 4.3%; ^{1}H NMR(500 MHz, C_6D_6) δ: 2.71 (s). *Benzyl methyl carbonate:*[188] Yield 12%; ^{1}H NMR(500 MHz, C_6D_6) δ: 3.28 (s, 3H), 4.91 (s, 2H).

Thermolysis of **120a** in the presence of *tert*-butyl alcohol:

A solution of benzyloxymethoxy oxadiazoline, **120a** (205 mg, 0.86 mmol) and dry *tert*-butyl alcohol (606 mg, 9.1 mmol) in benzene (17.4 mL) was sealed into a thermolysis tube and heated for 24 hours. Unreacted *tert*-butyl alcohol and the solvent were removed by rotary evaporation after thermolysis.

Benzyl tert-butyl methyl orthoformate (123): Yield 61%; ^{1}H NMR(200 MHz, C_6D_6) δ: 1.26 (s, 9H), 3.21 (s, 3H), 4.60 (s, 2H), 5.36 (s, 1H), 7.03 - 7.15 (m, 5H); ^{13}C NMR(50 MHz, C_6D_6) δ: 28.81 (CH_3), 49.83 (OCH_3), 65.11 (CH_2), 73.94 (CMe_3), 109.53 (orthoformyl), 127.50, 128.48, 128.65, 139.01; MS (EI) *m/z*: 193 ($(M-31)^+$, 17), 181 (61), 151 ($(M-73)^+$, 36), 91 (100). *Benzyl methyl carbonate:* Yield 10%.

Thermolysis of **120a** in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO):

A solution of benzyloxymethoxy oxadiazoline **120a** (0.2074 g, 0.878 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (0.547 g, 3.5 mmol) in benzene (17.5 mL) was sealed into a thermolysis tube and the tube was heated for 24 hours. Solvent and volatile products were removed by rotary evaporation and excess TEMPO was removed

using the low pressure vacuum pump. The product mixture was separated by radial chromatography (10% EtOAc in hexanes). 1-Benzyloxy-2,2,6,6-tetramethyl-1-piperidine **124**, was isolated and methyl 1-(2,2,6,6-tetramethyl-1-piperidinyl) carbonate **125** was identified in the crude by GC/MS and ^{1}H NMR.

1-Benzyloxy-2,2,6,6-tetramethyl-1-piperidine (**124**):[189] Yield 12%; ^{1}H NMR(200 MHz, C_6D_6) δ: 1.17 (s, 6H), 1.28 (s, 6H), 1.28 - 1.49 (m, 6H), 4.89 (s, 2H), 7.08 - 7.35 (m, 5H); ^{13}C NMR(50 MHz, C_6D_6) δ: 17.45, 20.36, 33.31, 39.99, 79.31, 127.76, 128.52, 128.28, 138.72; GC/MS (EI) *m/z*: 247 (M^+, 1), 156 (100), 91 (45). *Methyl 1-(2,2,6,6-tetramethylpiperidinyl) carbonate, **125**:* ^{1}H NMR(200 MHz, C_6D_6): 1.15 (s, 6H), 1.21 (s, 6H), 1.24-1.77 (m, 6H), 3.48 (s, 3H); GC/MS (EI) *m/z*: 215 (M^+, 3), 200 ((M-15), 100), 83 (76), 55 (84).

4.2 Synthesis and Thermolyses of Di(benzyloxy) Oxadiazolines (**126a-f**)

Synthesis of benzyl hydrazinocarboxylate:[190]

A solution of ether (72 mL) and benzyl chloroformate (10.0 mL, 0.071 mol) was added slowly (*ca.* 1 h) to a cooled solution (-5 °C) of hydrazine monohydrate (16.8 mL, 0.33 mol) and ether (10.0 mL). After addition, the ice bath was removed and stirring was continued for 1 hour. A white precipitate, formed during the reaction, dissolved upon the addition of water. The ether layer was separated and washed three times with water (25 mL) before it was dried with magnesium sulphate. The solvent was removed by rotary evaporation.

Benzyl hydrazinocarboxylate:[190] White solid; yield 82%; mp 65-66°C; lit[191] mp 67-70°C; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 3.74 (s, 2H, NH_2), 5.12 (s, 2H, CH_2O), 6.12 (s, 1H, NH), 7.3 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 67.34 (CH_2), 128.21, 128.34, 128.57, 136.03, 155.55 (C=O); MS (EI) *m/z*: 166 (M^+, 1), 122 (9), 91 (100), 65 (9); MS (CI, NH_3), *m/z*: 184 ($(M+NH_4)^+$, 33), 167 ($(M+H)^+$, 100), 123 (12), 108 (21), 91 (62).

Synthesis of the benzyloxycarbonyl hydrazone of acetone (**130**):

Benzyl hydrazinocarboxylate (7.55 g, 0.045 mol) was dissolved in acetone (40 mL). Magnesium sulphate (5g) was added and the reaction mixture was stirred overnight. The magnesium sulphate was removed by vacuum filtration and the solvent was removed by rotary evaporation leaving a white solid.

*Benzyloxycarbonyl hydrazone of acetone (**130**):*[192] White solid; yield 82%; mp 75-77°C, lit.[192] mp 85°C; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.76 (s, 3H), 2.00 (s, 3H), 5.21 (s, 2H), 7.34 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 16.08, 25.28, 67.33 (CH_2), 128.31, 128.41, 128.52, 135.98, 151.14 (C=N), 154.80 (C=O); MS (EI) *m/z*: 206 (M^+, 1), 91 (100), 65 (10), 49 (22); MS (CI, NH_3) *m/z*: 207 ($(M+H)^+$, 100), 91 (32).

Synthesis of 2-acetoxy-2-benzyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**131**):

Hydrazone **130** (7.15g, 0.037 mol) was dissolved in dichloromethane (70 mL) and added dropwise to a solution of lead(IV) acetate (28.0g, 0.106 mol) in dichloromethane (60 mL) under nitrogen. After the addition of the hydrazone solution the mixture was stirred for two hours. The heterogeneous mixture was filtered through Celite and the dichloromethane was washed once with water (25 mL) and twice with 5% sodium

bicarbonate (25 mL). After drying with magnesium sulphate the dichloromethane was evaporated leaving a yellow oil which was a mixture of **131** and **132** (60:40).

2-Acetoxy-2-benzyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (131) and 132: Yellow oil; yield 58%; ^{1}H NMR(200 MHz, $CDCl_3$) δ(composite spectrum), **131**: 1.52 (s, 3H). 1.67 (s, 3H), 2.10 (s, 6H), 4.91 (d, ^2J = -8.6 Hz, 1H, CH_2Ph), 4.99 (d, ^2J= -8.6 Hz, 1H, CH_2Ph), 7.2 - 7.5 (m, 5H); **132**: 1.63 (s, 6H, $C(CH_3)_3$), 5.37 (s, 2H, CH_2), 7.2 - 7.5 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$) δ(composite spectrum): 20.51, 21.39, 22.45, 24.12, 24.47, 25.27, 67.51, 69.96, 122.47 (C5), 136.08 (C2), 127.89, 128.10, 128.45, 128.71, 128.79, 133.68, 134.15, 166.45.

Synthesis of di(benzyloxy) oxadiazolines **126a-f**:

The appropriate benzyl alcohol (0.48 g, 4.4 mmol) was added to a solution of crude **131** (1.0 g, 3.7 mmol, **131:132** = 60:40,) in dichloromethane (30 mL). Trifluoroacetic acid (0.096 mL, 1.25 mmol) was added last to the reaction mixture and the solution was stirred for approximately 1 hour. Aqueous 10% NaOH (35 mL) was added after completion of the reaction and the mixture was stirred for another hour. The dichloromethane layer was separated, washed twice with water (15 mL), dried over magnesium sulphate and the solvent was removed by rotary evaporation. The oxadiazolines were purified using radial chromatography (100% hexanes).

2,2-Dibenzyloxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (126a): Pale yellow oil; yield 35%; ^{1}H NMR(300 MHz, C_6D_6) δ: 1.30 (s, 6H), 4.80 (d, ^2J = -11.6 Hz, 2H), 4.91 (d, ^2J = -11.6 Hz, 2H), 7.06 - 7.41 (m, 10H); ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.57 (s, 6H). 4.76 (d, ^2J = -

11.4 Hz, 2H), 4.86 (d, ^2J = -11.4 Hz, 2H), 7.30 - 7.35 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.1, 66.9, 119.6 (C5), 127.8, 127.9, 128.4, 136.7, 136.2.

2-Benzyloxy-2-(4-methoxybenzyloxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline ***(126b)****:* Yellow oil; yield 53%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.59 (s, 6H), 3.79 (s, 3H), 4.72 (d, ^2J = -11.2 Hz, 1H), 4.78 (d, ^2J = -11.5 Hz, 1H), 4.83 (d, ^2J = -11.2 Hz, 1H), 4.88 (d, ^2J = -11.5 Hz, 1H), 6.86 (d, ^3J = 8.62 Hz, 2H) 7.29 - 7.33 (m, 7H); ^{1}H NMR(200 MHz, C_6D_6) δ: 1.23 (s, 3H), 1.25 (s, 3H), 3.27 (s, 3H), 4.72 - 4.92 (m, 4H), 6.69 (d, ^3J = 6.6 Hz, 2H), 6.71 - 7.25 (m, 7H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 24.01, 55.14, 66.56, 66.69, 113.71, 119.32 (C5), 127.67, 128.27, 128.67, 129.45, 136.66 (C2), 159.31; MS (EI) *m/z*: 191 (3), 163 (51), 121 (100), 91 (87), 84 (24), 43 (24); MS (CI, NH_3) *m/z*: 260 (4), 163 (20), 121 (100), 108 (23), 65 (8), 43 (12).

2-Benzyloxy-2-(4-methylbenzyloxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline ***(126c)****:* Clear oil; yield 41%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.59 (s, 6H), 2.35 (s, 3H), 4.74 (d, ^2J = -11.0 Hz, 1H), 4.83 (d, ^2J = -11.0 Hz, 2H), 4.89 (d, ^2J = -11.4 Hz, 1H), 7.14 - 7.35 (m, 9H); ^{1}H NMR(300 MHz, C_6D_6) δ: 1.24 (s, 2H), 1.25 (s, 3H), 2.09 (s, 3H), 4.73 - 4.94 (m, 4H), 6.90 - 7.28 (m, 9H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 21.09, 24.04, 66.72, 119.37 (C5), 127.71, 127.84, 128.29, 128.99, 133.56, 136.55 (C2), 136.67; MS (EI) *m/z*: 181 (3), 105 (95), 91 (100), 43 (10); MS (CI, NH_3) *m/z*: 274 (3), 147 (8), 122 (18), 105 (100), 91 (53).

2-Benzyloxy-2-(4-chlorobenzyloxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline ***(126d)***: Pale yellow oil; yield 80%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 6.56 (s, 6H), 4.74 (d, ^2J = -11.6 Hz, 2H), 4.84 (d, ^2J = -11.6 Hz, 2H), 7.24 - 7.34 (m, 9H); ^{1}H NMR(300 MHz, C_6D_6) δ: 1.21

(s, 3H), 1.22 (s, 3H), 4.57 (d, ^2J = -11.8 Hz, 1H), 4.66 (d, ^2J = -11.8 Hz, 1H), 4.68 (d, ^2J = -11.6 Hz, 1H), 4.78 (d, ^2J = -11.6 Hz, 1H), 6.88 (d, ^3J = 8.6 Hz, 2H), 7.00 - 7.12 (m, 5H), 7.21 (d, ^3J = 8.6 Hz, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 24.00, 24.07, 66.02, 66.78, 119.63 (C5), 127.69, 127.8, 128.36, 128.48, 129.03, 133.61, 135.19, 136.47 (C2), 136.47; MS (EI) *m/z*: 239 (1), 237 (3), 203 (3), 195 (4), 169 (3), 167 (10), 127 (15), 125 (44), 105 (12), 91 (100); MS (CI, NH_3) *m/z*: 296 (2), 294 (5), 144 (4), 142 (12), 127 (11), 125 (33), 91 (100).

2-Benzyloxy-2-(4-trifluoromethylbenzyloxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline ***(126e):*** Clear oil; yield 68%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.48 (s, 3H), 1.49 (s, 3H), 4.64 (d, ^2J = -11.5Hz, 1H), 4.71 (d, ^2J = -13.9 Hz, 1H), 4.75 (d, ^2J = -13.9 Hz, 1H), 4.84 (d, ^2J = -11.5 Hz, 1H), 7.15 - 7.24 (m, 5H), 7.35 (d, ^3J = 8.0 Hz, 2H), 7.50 (d, ^3J = 8.0 Hz, 2H); ^{1}H NMR(300 MHz, C_6D_6) δ: 1.26 (s, 6H), 4.60 - 4.82 (m, 4H), 6.97 - 7.26 (m, 9H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 24.00, 24.12, 65.96, 66.87, 119.33 (C5), 125.33, 127.61, 127.72, 127.97, 128.40, 136.43 (C2), 136.64; ^{19}F NMR(282 MHz, $CDCl_3$, ref. CCl_3F) δ: -62.80 (s); MS (EI) *m/z*: 249 (2), 229 (2), 159 (56), 133 (57), 91 (100); MS (CI, NH_3) *m/z*: 328 (2), 176 (9), 159 (18), 108 (42), 91 (100).

2-Benzyloxy-2-(4-nitrobenzyloxy)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline ***(126f):*** Yellow oil; yield 56%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.57 (s, 3H), 1.59 (s, 3H), 4.71 (d, ^2J = -11.4 Hz, 1H), 4.79 (d, ^2J = -11.4 Hz, 1H), 4.88 (d, ^2J = -13.1 Hz, 1H), 4.97 (d, ^2J = -13.1 Hz, 1H), 7.24 - 7.32 (m, 5H), 7.47 (d, ^3J = 8.6 Hz, 2H), 8.16 (d, ^3J = 8.6 Hz, 2H); ^{1}H NMR(300 MHz, C_6D_6) δ: 1.23 (s, 6H), 4.53 - 4.72 (m, 4H), 6.82 (d, ^3J = 8.8 Hz, 2H),

7.00 - 7.21 (m, 5H), 7.74 (d, ^3J = 8.8 Hz, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 23.89, 24.11, 65.46, 66.85, 119.96 (C5), 123.48, 127.64, 127.73, 127.96, 128.36, 136.24, 136.48 (C2), 144.19, 147.36; MS (EI) *m/z*: 137 (13), 136 (95), 91 (100), 49 (24), 43 (16); MS (CI, NH_3) *m/z*: 254 (2), 153 (13), 136 (24), 107 (60), 91 (100), 60 (16).

Thermolysis of **126a-f**:

A solution of dibenzyloxy oxadiazoline, **126a**, (15.9 mg, 0.05mmol) containing 4.6% of dibenzyl carbonate and 1,4-dimethoxybenzene (1.0 mg, 0.0072 mmol) as an internal standard, in benzene-d_6 (0.54 mL) was flame sealed into a NMR tube. The NMR tube was heated for 24 hours and product yields were determined from ^{1}H NMR spectroscopy, using a relaxation delay of 3 min.

Acetone: Yield 88%; ^{1}H NMR(200 MHz, C_6D_6) δ: 1.61 (s). *Bibenzyl:* Yield 14%; ^{1}H-NMR(200 MHz, C_6D_6) δ: 2.78 (s, 4H), 7.02 - 7.20 (m, overlap with other signals); GC/MS (EI) *m/z*: 182 (M^+, 26), 91 (100), 65 (13). *Benzyl phenylacetate:*[193] Yield 29%; ^{1}H NMR(200 MHz, C_6D_6) δ: 3.38 (s, 2H), 4.96 (s, 2H), 7.02 - 7.20 (m, overlap with other signals); GC/MS (EI) *m/z*: 226 (M^+, 1), 91 (100), 65 (10). *Dibenzyl carbonate:*[194] Yield 6%; ^{1}H NMR(200 MHz, C_6D_6) δ: 4.98 (s, 4H), 7.02 - 7.20 (m, overlap with other signals), GC/MS (EI) *m/z*: 180 (33), 151 (26), 107 (60), 91 (100), 79 (48), 65 (29). *Tribenzyl orthoformate:*[195] Yield 19%; ^{1}H NMR(200 MHz, C_6D_6) δ: 4.66 (6H), 5.46 (s, 1H), 7.02 - 7.20 (overlap with other signals); GC/MS (EI), m/z: 197 (9), 181 (10), 107 (10), 91 (100). *Benzyl formate:*[196] Yield 22%; ^{1}H NMR(200 MHz, C_6D_6) δ: 4.91 (2H), 7.02 - 7.20 (m, overlap with other signals), 7.60 (1H).

For the thermolysis of **126b-f**, *p*-xylene was used as the internal standard and yields of **128** and **129** were determined from ^{1}H NMR spectroscopy using a 5 minute relaxation delay. Chemical shifts (CH_2CO, ppm) in C_6D_6 used for the measurement of the relative yields of **128b-f** and **129b-f** are listed below (**128b** and **129b** in CCl_4).

p-xylene, 2.10; **128b**, 3.52; **129b**, 3.48; **128c**, 3.32; **129c**, 3.34; **128d**, 3.29; **129d**, 3.12; **128e**, 3.31; **129e**, 3.14; **128f**, 3.31; **129f**, 3.06.

Synthesis of benzyl arylacetates **129a-f**:

The required arylacetyl chloride (0.061 g, 6.4 mmol) was dissolved in benzene (5 mL) and added slowly to a solution of benzyl alcohol (0.16 g, 0.8 mmol) in pyridine (0.2 mL, 2.3 mmol), which was cooled in an ice bath. After addition, stirring was continued for one hour. The benzene layer was washed twice with water (5 mL), and dried with magnesium sulphate. After filtration and evaporation of the benzene, the ^{1}H NMR spectrum was recorded in both C_6D_6 (referenced to the p-xylene methyl signal at 2.10 ppm) and $CDCl_3$.

*Benzyl phenylacetate (**129a**)*:[193] Pale yellow oil; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 3.60 (s, 2H), 5.03 (s, 2H), 7.08 - 7.29 (m, 10H); ^{1}H NMR(300 MHz, C_6D_6) δ: 3.40 (s, 2H), 4.97 (s, 2H), 7.09 - 7.22 (m, 10H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 41.33, 66.61, 128.18, 128.54, 129.27, 135.83, 171.39 (C=O); ^{13}C NMR(75 MHz, C_6D_6) δ: 41.35, 66.42, 128.2, 128.3, 128.7, 129.6, 134.5, 170.92 (C=O); GC/MS (EI) *m/z*: 226 (M^+, 1), 91 (100), 65 (10).

*Benzyl 4-methoxyphenylacetate (**129b**)*:[197,198,199] Clear oil; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 3.59 (s, 2H), 3.78 (s, 3H), 5.10 (s, 2H), 6.84 (d, ^3J = 8.6 Hz, 2H), 7.16 - 7.30 (m, 7H); ^{1}H

NMR(300 MHz, C_6D_6) δ: 3.23 (s, 3H), 3.32 (s, 2H), 4.92 (s, 2H), 6.68 (d, ^3J = 8.7 Hz, 2H), 7.00 - 7.08 (m, 7H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 40.43, 55.26, 66.55, 114.00, 128.10, 128.51, 130.30, 132.29, 172.93 (C=O).

*Benzyl 4-methylphenylacetate (**129c**)*:[200] Clear oil; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 3.63 (s, 2H), 5.13 (s, 2H), 7.10 - 1.33 (m, 9H); ^{1}H NMR(300 MHz, C_6D_6) δ: 2.02 (s, 3H), 3.34 (s, 2H), 4.90 (s, 2H), 6.87 - 7.12 (m, 10H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 21.03, 40.91, 66.53, 128.09, 128.49, 129.24, 130.83, 135.92, 136.70, 171.57 (C=O); MS (EI) *m/z*: 240 (M^+, 25), 193 (13), 181 (16), 105 (100), 91 (76); MS (CI, NH_3) *m/z*: 258 ($(M+NH_4)^+$, 13), 241 ($(M+H)^+$, 5), 216 (79), 108 (51), 91 (100).

*Benzyl 4-chlorophenylacetate (**129d**)*:[199] Orange oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 3.60 (s, 2H), 5.10 (s, 2H), 7.16-7.32 (m, 9H); ^{1}H NMR(300 MHz, C_6D_6) δ: 3.13 (s, 2H), 4.88 (s, 2H), 6.76 (d, ^3J = 8.4 Hz, 2H), 6.79 - 7.15 (m, 7H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 40.52, 66.69, 128.09, 128.24, 128.49, 130.60, 132.25, 133.04, 170.91 (C=O); MS (EI) *m/z*: 262 ($^{37}M^+$, 3), 260 ($^{35}M^+$, 10), 181 (10), 127 (24), 125 (60), 91 (100), 65 (16), 63 (10); MS (CI, NH_3) *m/z*: 280 ($(^{37}M+NH_4)^+$, 18), 278 ($(^{35}M+NH_4)^+$, 55), 125 (44), 108 (49), 91 (100), 80 (42); HRMS calculated for $C_{15}H_{13}O_2{}^{35}Cl$: 260.0604, found: 260.0603.

*Benzyl 4-trifluoromethylphenylacetate (**129e**):* Clear oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 3.71 (s, 2H), 5.13 (s, 2H), 7.28 - 7.35 (m, 5H) 7.38 (d, ^3J = 8.1 Hz, 2H), 7.56 (d, ^3J = 8.1 Hz, 2H); ^{1}H NMR(300 MHz, C_6D_6) δ: 3.13 (s, 2H), 4.88 (s, 2H), 6.76 (d, ^3J = 8.0 Hz, 2H), 6.79 - 7.15 (m, 7H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 29.69, 66.95, 125.48, 125.55, 128.24, 128.38, 128.54, 128.61, 129.37, 129.71, 135.61, 137.84, 170.55 (C=O); ^{19}F NMR

(282 MHz, $CDCl_3$, ref. CCl_3F) δ: -62.82 (s); MS (EI) *m/z*: 294 (M^+, 3), 181 (8), 159 (5), 108 (21), 91 (100), 650(10); MS (CI, NH_3) *m/z*: (($M+NH_4$)$^+$, 5), 159 (5), 108 (21), 91 (100); HRMS calculated for $C_{16}H_{13}O_2F_3$: 294.0867, found: 294.0872.

Benzyl 4-nitrophenylacetate (129f): Yellow solid; mp 73-75°C, lit.[201] mp 90-92°C; ^1H NMR(300 MHz, $CDCl_3$) δ: 3.76 (s, 2H), 5.14 (s, 2H), 7.29 - 7.35 (m, 5H), 7.43 (d, ^3J = 8.7 Hz, 2H), 8.16 (d, ^3J = 6.6 Hz, 2H); ^1H NMR(300 MHz, C_6D_6) δ: 3.03 (s, 2H), 4.27 (s, 2H), 4.86 (s, 2H), 6.66 (d, ^3J = 8.7 Hz, 2H), 6.93 - 7.07 (m, 5H), 7.69 (d, ^3J = 8.7 Hz, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 40.96, 67.14, 123.73, 126.97, 128.61, 130.29, 135.35, 141.12, 169.98; MS (EI) *m/z*: 271 (M^+, 8), 136 (8), 91 (100), 65 (9); MS (CI, NH_3) *m/z*: 289 (($M+NH_4$)$^+$, 6), 271 (M^+, 3), 135 (10), 108 (9), 91 (100); HRMS calculated for $C_{15}H_{13}NO_4$: 271.0845, found: 271.0827.

Synthesis of *p*-substituted benzyl phenylacetates **128b-f**:

A solution of phenylacetyl chloride (0.51 g, 3.0 mmol) in benzene (5 mL) was added slowly to a cooled solution of the appropriate arylmethanol (0.4 g, 3.0 mmol) in pyridine (0.5 mL, 9.0 mmol). After one hour the benzene solution was washed twice with water and dried with magnesium sulphate. Benzene was removed with a rotary evaporator. Some of the esters were purified by radial chromatography (10% EtOAc in hexanes). ^1H NMR spectra were obtained in both $CDCl_3$ and in C_6D_6 (reference to *p*-xylene methyl signal at 2.10 ppm).

4-Methoxybenzyl phenylacetate (128b):[197,198] Orange oil; ^1H NMR(300 MHz, $CDCl_3$) δ: 3.61 (s, 2H), 3.77 (s, 2H), 5.04 (s, 2H), 6.83 - 6.87 (m, 2H), 7.20 - 7.28 (m, 7H); ^1H

NMR(300 MHz, C_6D_6) δ: 3.20 (s, 3H), 3.32 (s, 2H), 4.89 (s, 2H), 6.65 (d, ^3J = 8.7 Hz, 2H), 7.00 - 7.10 (m, 7H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 41.28, 55.17, 66.37, 113.56, 126.97, 127.93, 128.46, 129.19, 129.89, 133.90, 159.55, 171.39 (C=O); MS (EI) *m/z*: 256 (M^+, 21), 121 (100), 91 (37); MS (CI, NH_3) *m/z*: 256 (8), 138 (8), 121 (100).

*4-Methylbenzyl phenylacetate (**128c**)*:[200] Clear oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 6.65 (s, 2H), 5.08 (s, 2H) 7.13 - 7.31 (m, 9H); ^{1}H NMR(300 MHz, C_6D_6) δ: 2.00 (s, 3H), 3.32 (s, 2H), 4.91 (s, 2H) 6.85 - 7.12 (m, 9H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 21.16, 41.36, 66.57, 127.06, 128.27, 128.55, 129.21, 129.27, 132.89, 133.95, 138.03, 171.41; MS (EI) *m/z*: 240 (M^+, 16), 209 (5), 105 (100), 91 (46), 65 (12); MS (CI, NH_3) *m/z*: 258 ($(M+NH_4)^+$, 26), 154 (16), 105 (100), 91 (34), 65 (5).

*4-Chlorobenzyl phenylacetate (**128d**)*: Red oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 3.63 (s, 2H), 5.05 (s, 2H), 7.17 - 7.29 (m, 9H); ^{1}H NMR(300 MHz, C_6D_6) δ: 3.29 (s, 2H), 4.69 (s, 2H), 6.73 (d, ^3J = 8.4 Hz, 2H), 6.93 - 7.12 (m, 7H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 41.23, 65.64, 127.10, 128.52, 128.62, 129.17, 133.67, 134.29, 171.19 (C=O); MS (EI) *m/z*: 262 ($^{37}M^+$, 3), 260 ($^{35}M^+$, 8), 127 (29), 125 (87), 91 (100), 65 (18), 51 (5); MS (CI, NH_3) *m/z*: 280 (($^{37}M + NH_4)^+$, 18), 278 (($^{35}M+NH_4)^+$, 55), 260 (M^+ , 5), 184 (42), 125 (100), 108 (19), 91 (39); HRMS calculated for $C_{15}H_{13}O_2{}^{35}Cl$: 260.0604, found: 260.0603.

*4-Trifluoromethylbenzyl phenylacetate (**128e**)*: ^{1}H NMR(300 MHz, $CDCl_3$) δ: 3.66 (s, 2H), 5.14 (s, 2H), 7.22 - 7.29 (m, 5H), 7.35 (d, ^3J = 8.0 Hz, 2H), 7.55 (d, ^3J = 8.1 Hz, 2H); ^{1}H NMR(300 MHz, C_6D_6) δ: 3.31 (s, 2H), 4.69 (s, 2H), 6.80 (d, ^3J = 8.0 Hz, 2H), 7.00 - 7.12 (m, 5H), 7.20 (d, ^3J = 8.1 Hz, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 4.21, 65.45,

125.40, 127.17, 127.87, 128.53, 129.17, 133.53, 139.76, 171.06 (C=O); ^{19}F NMR (282 MHz, $CDCl_3$) δ: -62.89 (s); MS (EI) *m/z*: 294 (M^+, 8), 159 (60), 109 (18), 91 (100), 65 (33), 49 (82); MS (CI, NH_3) *m/z*: 312 ($(M+NH_4)^+$, 90), 272 (8), 176 (16), 159 (18), 108 (71), 91 (100); HRMS calculated for $C_{16}H_{13}O_2F_3$: 294.0868, found: 294.0858.

*4-Nitrobenzyl phenylacetate (**128f**):* Yellow solid; mp 52-55 °C; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 3.67 (s, 2H), 5.18 (s, 2H), 7.22 - 7.32 (m, 5H), 7.37 (d, ^3J = 8.6 Hz, 2H), 8.13 (d, ^3J = 8.1 Hz, 2H); ^{1}H NMR(300 MHz, C_6D_6) δ: 3.31 (s, 2H), 4.60 (s, 2H), 6.63 (d, ^3J = 8.7 Hz, 2H), 7.01 - 7.12 (m, 5H), 7.68 (d, ^3J = 8.8 Hz, 2H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 41.18, 64.90, 123.65, 127.26, 128.06, 129.16, 133.38, 143.03, 147.59, 170.93 (C=O); MS (EI) *m/z*: 271 (M^+, 5), 136 (5), 106 (3), 91 (100), 65 (10); MS (CI, NH_3) *m/z*: 289 ($(M+NH_4)^+$, 8), 271 (M^+, 2) 135 (11), 108 (10), 91 (100), 65 (6). HRMS calculated for $C_{15}H_{13}NO_4$: 271.0845, found: 271.0861.

Synthesis of dibenzyl carbonate **133a**:

Benzyl alcohol (1.5 g, 13 mmol) and pyridine (0.98 g, 12.3 mmol) were dissolved in 60 mL of dichloromethane. A solution of 1,1'-carbonyldiimidazole (1 g, 6.1 mmol) in dichloromethane (20 mL) was added slowly (ca. 1 hour) under nitrogen. The solution was stirred overnight, washed once with water, twice with 5% HCl, and once with brine. The dichloromethane layer was dried with magnesium sulphate; after filtration the dichloromethane was removed by rotary evaporation. Dibenzyl carbonate was purified by radial chromatography (10% EtOAc in hexanes).

Dibenzyl carbonate (133a):[194] White solid; yield 6.6%; mp 28-29°C, lit.[194] mp 27.3-29.1°C; ^{1}H NMR(200 MHz $CDCl_3$) δ: 5.09 (s, 4H), 7.13 - 7.37 (m, 10H); ^{1}H NMR(200 MHz, C_6D_6) δ: 4.94 (s, 4H), 7.04 - 7.17 (m, 10H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 69.58, 128.21, 128.47, 135.13, 154.99 (C=O); MS (EI) *m/z*: 180 (4), 151 (5), 107 (32), 91 (100), 79 (32), 65 (14), 51 (11); MS (CI) *m/z*: 260 ($(M+NH_4)^+$, 100), 243 ($(M+H)^+$, 10), 198 (26), 181 (32), 108 (73), 91 (72).

Synthesis of tribenzyl orthoformate:

Dibenzyloxy oxadiazoline **126a** (30.3 mg, 0.11 mmol), containing 9% carbonate, benzyl alcohol (60.6 mg, 0.56 mmol), and the internal standard (1,4-dimethoxybenzene, 3.6 mg, 0.026 mmol) were dissolved in benzene (1 mL). The solution was flamed sealed into an NMR tube and heated at 110 °C for 24 h. Product yields were determined by ^{1}H NMR using a 3 minute relaxation delay. Column chromatography of the crude with 10% EtOAc in hexanes yielded purified tribenzyl orthoformate.

Tribenzyl orthoformate (134):[195] Yield 81%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 4.66 (s, 6H), 5.43 (s, 1H), 7.24 - 7.35 (m, 15H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 66.33, 111.51, 127.71, 127.88, 128.41, 137.46. *Dibenzyl carbonate (133a):* 17%.

Synthesis of benzyl formate:

Benzyl alcohol (2.16g, 0.02 mol), ethyl formate (1 g, 0.013 mol) and a catalytic amount of H_2SO_4 were dissolved in benzene (10mL) and heated at 50°C for 24 hours. After cooling the solution was washed with 10% NaOH (10 mL) and brine (10mL). Benzyl formate was purified by radial chromatography (10%, EtOAc in hexanes).

Benzyl formate:[196] ^{1}H NMR(200 MHz, $CDCl_3$) δ: 4.60 (s, 2H), 7.23 - 7.43 (m, 5H), 8.13 (s, 1H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 65.64, 128.32, 128.48, 128.62, 135.19, 160.71 (C=O)

Thermolysis of **126a** in the presence of *tert*-butyl alcohol:

Dibenzyloxy oxadiazoline, **126a** (224 mg, 0.72 mmol), dry *tert*-butyl alcohol (1.69 g, 22.9 mmol) and 1,4-dimethoxybenzene (10.1 mg, 0.07 mmol) were dissolved in benzene (28 mL). The resultant solution was sealed into a resealable thermolysis tube and heated for 24 hours. Solvent and *tert*-butyl alcohol were removed by rotary evaporation after the thermolysis.

Dibenzyl tert-butyl orthoformate (135): Yield 43%; ^{1}H NMR(200 MHz, C_6D_6) δ: 1.19 (s, 9H), 4.74 (s, 4H), 5.62 (s, 1H), 7.13 - 7.43 (m, 10H); ^{13}C NMR(50 MHz, C_6D_6) δ: 28.8 (CH_3), 65.1 (CH_2), 74.2 (CMe_3), 108.8 (orthoformyl), 127.5, 127.9, 128.5, 138.9.

Dibenzyl carbonate (133a): Yield 3 %.

Thermolysis of **126a** in the presence of TEMPO:

A solution of dibenzyloxy oxadiazoline, **126a** (275 mg, 0.88 mmol), 2,2,6,6-tetramethyl-1-piperdinyloxy (TEMPO, 551 mg, 3.53 mmol) and 1,4-dimethoxybenzene (12.8 mg, 0.075 mmol) in dry benzene (18 mL) were sealed into a thermolysis tube and heated for 24 hours. After 24 hours the solution was injected into the GC and the products from the thermolysis were identified by co-injection of authentic samples of each product.

1-Benzyloxy-2',2',6',6'-tetramethyl-1-piperidine (124): Yield 18%. *Benzyl phenylacetate (128a):* Yield 13%. *Dibenzyl carbonate (133a)*: Yield 18%. *Tribenzyl orthoformate (134):* Yield 42%. *Benzyl formate*: Yield 18%.

Synthesis of 1-benzyloxy-2',2',6',6'-tetramethyl-1-piperidine (**124**):

A solution of *tert*-butylperoxide (BOOB, 2.0 g, 13.0 mmol) and TEMPO (1.47 g, 9.4 mmol) in toluene (20mL) was sealed into a thermolysis tube and heated at 110°C for 69 hours. BOOB and toluene were removed by rotary evaporation and the resultant crude mixture was purified using column chromatography (silica) with 100% hexanes. *1-Benzyloxy-2,2,6,6-tetramethyl-1-piperidine (124):*[189] Yield 1.5 g; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.17 (s, 6H), 1.28 (s, 6H), 1.49 - 1.53 (m, 6H), 4.85 (s, 2H), 7.35 - 7.39 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 17.09, 20.26, 33.07, 39.70, 59.97, 78.71, 127.25, 127.39, 128.20, 138.30; GC/MS (EI) *m/z*: 247 (M^+, 1), 156 (100), 91 (45).

Thermolysis rate constants for **126a** and **126f**:

The appropriate di(benzyloxy) oxadiazoline **126a** or **126f** (0.05 mmol) and p-xylene (1 μL, 0.008 mmol) were dissolved in benzene-d_6 (0.54 mL) and flame sealed into a NMR tube. At appropriate intervals, the sealed tube was removed from the constant temperature oil bath (110°C) and the 200 MHz ^{1}H NMR spectra were obtained. Corrections were not made to account for the period in which the tube was outside the oil bath.

First order decomposition rates were obtained from the plot of $\ln(I_o/I_f)$ *versus* time, where I and I_0 are the normalized integrals for the methyl signal at δ = 1.3 ppm at time t and t_0. Raw data and plots are contained in the Appendix.

4.3 Reactions of Benzyloxycarbenes with Alkenes

Thermolysis of **120a** in the presence of **138:**

A solution of benzyloxymethoxy oxadiazoline **120a** (106 mg, 0.45 mmol) and benzylidenemalononitrile (**138**, 130 mg, 0.84 mmol) in benzene (5 mL) was sealed into a thermolysis tube, which was then heated for 24 hours. Benzene was removed by distillation and the crude residue was purified by radial chromatography (30% EtOAc in hexanes) to afford **144a**. Methyl phenylacetate was not detected.

Methyl 3,3-dicyano-2,4-diphenylbutanoate (**144a**): White solid; yield 49% (isolated); mp 127-128°C; ^{1}H NMR(200 MHz, C_6D_6) δ: 2.77 (d, ^2J = -13.6 Hz, 1H), 2.85 (d, ^2J = -13.6 Hz, 1H), 3.15 (s, 3H), 3.67 (s, 1 H), 6.99 - 7.11 (m, 6H), 7.19 - 7.23 (m, 2H), 7.30 - 7.34 (m, 2H); ^{13}C NMR(50 MHz, C_6D_6) δ: 41.59, 42.89, 52.42, 56.03, 114.25, 114.69, 128.29, 128.84, 128.98, 129.39, 129.78, 130.69, 131.52, 132.26, 168.90; IR (CCl_4) cm^{-1}: 1746s; MS (EI) *m/z*: 305 ($(M+H)^+$, 1), 150 (78), 121 (27), 91 (100), 65 (22); HRMS: calculated for $C_{19}H_{17}N_2O_2$: 305.1290, found: 305.1297.

Thermolysis of **126a** in the presence of **138:**

Thermolysis of a solution of dibenzyloxy oxadiazoline **126a** (102.3 mg, 0.33 mmol) and benzylidenemalononitrile (**138**, 106.9 mg, 0.69 mmol) in benzene (5 mL) for

24 hours gave a mixture that was partially separated by radial chromatography (30% EtOAc in hexanes). The fractions collected were purified by further chromatography (30% EtOAc in hexanes) to collect a fraction rich in benzyl 3,3-dicyano-2,4-diphenylbutanoate. Re-chromatography of that fraction, with 100% hexanes as eluent, gave pure benzyl 3,3-dicyano-2,4-diphenylbutanoate.

Benzyl 3,3-dicyano-2,4-diphenylbutanoate (**144b**): Yellow oil; yield 37% (isolated); ^{1}H NMR(200 MHz, $CDCl_3$) δ: 3.24 (s, 2H), 3.96 (s, 1H), 5.15 (d, ^{2}J = -12.0 Hz, 1H), 5.31 (d, ^{2}J = -12.0 Hz, 1H), 7.24 - 7.41 (m, 15H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 41.57, 42.59, 55.46, 68.05, 113.77, 114.07, 128.61, 128.74, 128.86, 128.93, 129.32, 129.39, 129.83, 130.33, 130.67, 131.42, 134.48, 168.05; IR (CCl_4) cm $^{-1}$: 2252w, 1740s; MS (EI) *m/z*: 381 ($(M+H)^+$, 3), 245 (7), 226 (3), 91 (100), 65 (11); HRMS: calculated for $C_{25}H_{21}N_2O_2$: 381.1603, found: 381.1604.

Thermolysis of **120a** in the presence of **138** and TEMPO:

A solution of **120a** (112.9 mg, 0.48 mmol), **138** (113.9 mg, 0.74 mmol), and TEMPO (188.9 mg, 1.21 mmol) in benzene (5 mL) was thermolyzed for 24 hours. Separation of the crude product mixture by radial chromatography (30% EtOAc in hexanes) gave a fraction containing mainly methyl 3,3-dicyano-2,4-diphenylbutanoate, which was chromatographed again with 100% hexanes as eluent to give methyl 3,3-dicyano-2,4-diphenylbutanoate (**144a**) and methyl 3,3-dicyano-2-phenylpropenoate (**147**). GC analysis indicated that benzyl radicals were caught with TEMPO to afford **124**.

Methyl 3,3-dicyano-2,4-diphenylbutanoate (144a): Yield 26%. *Methyl 3,3-dicyano-2-phenylpropenoate (147):* Yellow oil; yield 2.6%; ^{1}H NMR (200 MHz, C_6D_6) δ: 3.18 (s, 3H), 6.82 - 6.86 (m, 5H); MS (EI) *m/z*: 212 (M^+, 70), 197 (89), 153 (73), 127 (100), 100 (35), 77 (89), 51 (92); HRMS: calculated for $C_{12}H_8N_2O_2$: 212.0586, found: 212.0583.

Synthesis of methoxycarbonyl hydrazone of acetophenone:[202]

Methyl hydrazinocarboxylate (10.5 g, 0.12 mol) and acetophenone (13.4 g, 0.12 mol) were added to a 250 mL-round bottom flask containing benzene (125 mL) and ethanol (10 mL). A Dean Stark apparatus was attached to the flask and the solution was refluxed for 12 hours. The ethanol and benzene were then removed by distillation.

Methoxycarbonyl hydrazone of acetophenone: White solid; yield 86%; mp 125-126°C; ^{1}H NMR(200 MHz, $CDCl_3$) δ(ppm): 2.19 (s, 3H), 3.83 (s, 3H), 7.30 - 7.34 (m, 3H), 7.68 - 7.72 (m, 2H), 8.31 (s, 1H); ^{13}C NMR(50 MHz, $CDCl_3$) δ(ppm): 12.94, 52.92, 126.24, 128.26, 128.09, 137.97, 148.82, 154.83. MS (EI) *m/z*: 192 (M^+, 100), 133 (19), 118 (29), 104 (45), 92 (63), 77 (69); MS (CI, NH_3) *m/z*: 193 ($(M+H)^+$, 100); HRMS: calculated for: $C_{10}H_{12}N_2O_2$: 192.0898, found: 192.0889.

Synthesis of 2-acetoxy-2-methoxy-5-methyl-5-phenyl-Δ^3-1,3,4-oxadiazoline:

The methoxycarbonyl hydrazone of acetophenone (10 g, 0.052 mmol) in dichloromethane (20 mL) was added slowly to a cold solution of lead(IV)acetate (24.0 g, 0.05 mol) in dichloromethane (100 mL). After addition of the hydrazone the mixture was stirred for 7 hours at 0°C. The heterogeneous mixture was filtered through Celite and washed twice with cold water (150 mL) and twice with cold 5% $NaHCO_3$ (150 mL). After

the dichloromethane layer was dried with $MgSO_4$, evaporation of dichloromethane afforded a yellow oil, which was a mixture of two diastereomers (6:1) and the acyclic by-product (oxadiazoline:acyclic = 56:43).

2-Acetoxy-2-methoxy-5-methyl-5-phenyl-Δ^3-1,3,4-oxadiazoline: Yellow oil; yield 74%; ^{1}H NMR(200 MHz, $CDCl_3$) δ(composite spectrum): Major diastereomer: 1.91 (s, 3H), 2.14 (s, 3H), 3.47 (s, 3H), 7.33 - 7.57 (m, 5H). Minor diastereomer: 1.96 (s, 3H), 3.63 (s, 3H), 7.33 - 7.57 (m, 5H). Acyclic isomer: 1.98 (s, 3H), 3.95 (s, 3H), 7.33 - 7.57 (m, 5H).

Synthesis of 2-benzyloxy-2-methoxy-5-methyl-5-phenyl-Δ^3-1,3,4-oxadiazoline (**148**):

Crude acetoxy oxadiazoline (1.0 g, 4.0 mmol) and benzyl alcohol (0.84 g, 7.7 mmol) were dissolved in dichloromethane (30 mL) at 0°C. Trifluoroacetic acid (3 drops) was added to the solution and the mixture was stirred at 0°C for 6 hours. After 6 hours 10% NaOH was added to the flask and the mixture was stirred for two hours at 0°C. The dichloromethane layer was washed twice with water (15 mL) and dried over $MgSO_4$. Evaporation of the dichloromethane afforded a crude oxadiazoline, which was purified on a silica gel column using 100 % hexanes. The first fraction collected was then re-purified on a silica gel column using 100% toluene. Two diastereomers of **148** were obtained in an 8:1 ratio.

*2-Benzyloxy-2-methoxy-5-methyl-5-phenyl-Δ^3-1,3,4-oxadiazoline (**148**, major diastereomer):* ^{1}H NMR(300 MHz, $CDCl_3$) δ: 1.80 (s, 3H), 3.37 (s, 3H), 4.90 (d, 1H, ^2J = -11.5 Hz), 4.98 (d, 1H, ^2J = -11.5 Hz), 7.29 - 7.43 (m, 9H); ^{13}C NMR(75 MHz, $CDCl_3$) δ:

28.74, 52.33, 57.09, 121.48, 125.14, 127.83, 127.93, 128.47, 128.58, 136.70, 138.44, 138.32.

Thermolysis of **148**:

Oxadiazoline **148** (28.5 mg, 0.09 mmol) and 1,4-dimethoxybenzene (1.1 mg, 0.008 mmol) were dissolved in benzene-d_6 (0.5 mL) and flame sealed into a NMR tube. At appropriate intervals, the sealed tube was removed from the constant temperature oil bath (40°C) and the 300 MHz ^{1}H NMR spectra were obtained. Corrections were not made to account for the period in which the tube was outside the oil bath.

First order decomposition rates were obtained from the plot of $\ln(I_o/I_f)$ *versus* time, where I and I_0 are the normalized integrals for the methyl signal at $\delta = 1.80$ ppm at time t and t_0. Raw data and plots are contained in the Appendix.

A solution of **148** (14 mg, 0.047 mmol), benzylidenemalononitrile (15 mg, 0.097) and *tert*-butylbenzene (1μL, 0.0006 mmol) in benzene (0.5 mL) was flame sealed into a NMR tube. Thermolysis of **148** was carried out in the 300 MHz NMR spectrometer (probe temperature = 40°C). ^{1}H NMR spectra were taken every 30 minutes. Peaks that were characteristic for cyclopropane **146** were not observed in the proton spectra.

Thermolysis of **120a** in the presence of (1-ethoxyethylidene)malononitrile:

A solution of **120a** (109.75 mg, 0.46 mmol) and (1-ethoxyethylidene)-malononitrile (113.7 mg, 0.84 mmol) in benzene (5mL) was sealed and heated for 24 hours. The crude ester was separated by means of radial chromatography (20% EtOAc in hexanes) and it was purified by re-chromatography with 100% hexanes as eluent. The

regiochemistry of the product was determined by HMBC. A ^3J correlation was observed between the ^{13}C signal at 172.65 ppm and the methyl proton signal at 2.23 ppm.

Methyl 3,3-dicyano-2-ethoxy-2-methyl-4-phenylbutanoate (149): Yellow oil; yield 17% (isolated); ^1H NMR(500 MHz, $CDCl_3$) δ: 1.29 (t, ^3J = 7.0 Hz, 3H), 2.23 (s, 3H), 3.30 (s, 3H), 3.50 (dq, ^2J = -9.6 Hz, ^3J = 7.0 Hz, 1H), 3.55 (dq, ^2J = -9.6 Hz, ^3J = 7.0 Hz, 1H), 4.53 (d, ^2J = -11.7 Hz, 1H), 4.56 (d, ^2J = -11.7 Hz, 1H), 7.31 - 7.34 (m, 1H), 7.34 - 7.37 (m, 4H); ^{13}C NMR(125 MHz, $CDCl_3$) δ: 14.62, 19.40, 50.43, 59.29, 65.48, 90.45, 111.38, 112.15, 127.95, 128.39, 128.71, 136.02, 172.65; MS (EI) *m/z*: 287 ($(M+H)^+$, 3), 179 (12), 151 (16), 91 (100); HRMS: calculated for $C_{16}H_{19}N_2O_3$: 287.1396, found: 287.1381.

Thermolysis of **120a** in the presence of 1,1-diphenylethylene:

A solution of **120a** (100 mg, 0.42 mmol) and 1,1-diphenylethylene (152 mg, 0.84 mmol) in benzene (5 mL) was heated at 110°C for 24 hours. The crude reaction mixture was analyzed GC by co-injection with authentic compounds. The compounds identified, and their relative amounts from integration of the GC traces, are listed below.

Methyl phenylacetate (120a): 3.3 parts; *methyl 3,3-diphenylpropanoate (153)*:[203] 1.2 parts; *methyl 3,3-diphenylpropenoate (152)*:[204] 1.0 part; *1,1,3-triphenylpropane (155)*: 1.2 parts; *1,1,3-triphenylpropene (154)*: 1.1 parts.

Synthesis of reference samples **155** and **154**:

1,1,3-Triphenylpropene (**154**) was synthesized from reaction of phenyl magnesium bromide with ethyl hydrocinnamate to yield 1,1,3-triphenylpropanol.

Dehydration of the alcohol afforded 1,1,3-triphenylpropene.[205] 1,1,3-Triphenylpropane (**155**) was synthesized by catalytic hydrogenation of crude 1,1,3-triphenylpropene.

1,1,3-Triphenylpropanol: ^{1}H NMR(200 MHz, $CDCl_3$) δ: 2.18 (s, 1H, OH), 2.56 (s, 4H), 7.12-7.43 (m, 15H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 30.24, 43.94, 78.15, 125.77, 125.992, 126.87, 127.10, 127.19, 128.18, 128.36, 128.70, 129.98, 131.49, 142.31, 146.81; ^{1}H NMR(200 MHz, C_6D_6) δ: 1.62 (s, 1H), 2.35 - 2.44 (m, 2H), 2.56 - 2.5 (m, 2H), 7.0 - 7.45 (m, 15H). *1,1,3-Triphenylpropene (**154**):* ^{1}H NMR(200 MHz, C_6D_6) δ: 3.36 (d, ^3J = 7.6 Hz, 2H), 6.19 (t, ^3J = 7.6Hz, 1H) 7.0 - 7.36 (m, 15H). *1,1,3-Triphenylpropane (**155**):* ^{1}H NMR(200 MHz, $CDCl_3$) δ: 2.52 - 2.59 (m, 2H), 2.70 - 2.77 (m, 2H), 4.08 (t, ^3J = 7.7 Hz, 1H).

Methyl 3,3-diphenylpropenoate (**152**) and methyl 3,3-diphenylpropanoate (**153**) were isolated together from the appropriate thermolysis experiment and a composite spectrum was obtained which agreed well with the sum of the individual spectra in the literature. The mixture was used for co-injection onto the GC column.

^{1}H NMR(200 MHz, $CDCl_3$) δ(composite spectrum), **152**:[204] 3.49 (s, 3H), 6.36 (s, 1H), 7.09 - 7.36 (m, 5H); **153**:[203] 3.05 (d, ^3J = 7.9 Hz, 2H), 3.60 (s, 3H), 4.54 (t, ^3J = 7.9 Hz, 1H), 7.09 - 7.36 (m, 5H).

Thermolysis of **120a** in the presence of diethyl benzalmalonate

A solution of **120a** (84.7 mg, 0.359 mmol) and diethyl benzalmalonate (19.8 mg, 0.80 mmol) in 5 mL of benzene was heated for 24 hours at 110°C. Analysis by GC/MS indicated that there were many products and that methyl phenylacetate was the major one.

A component with a mass appropriate for the adduct of methoxycarbonyl and benzyl radicals with diethyl benzalmalonate ($C_{23}H_{26}O_6$) was absent. The reaction mixture was not analyzed further.

Synthesis of dimethyl benzalmalonate:

Dimethyl benzalmalonate was synthesized using a literature procedure.[206] Dimethyl malonate (10g, 0.075 mol) and benzaldehyde (9.5 g, 0.09 mol) were dissolved in 20 mL of benzene. Piperidine (1 mL) was added last to the solution, a Dean Stark head was attached to the flask and the solution was refluxed at 135°C overnight. Benzene was removed by distillation, the pressure was then reduced to 1mm Hg and pure dimethyl benzalmalonate was collected between 130-140°C. lit.[207] bp 168°/10mm Hg.

Dimethyl benzalmalonate: ^{1}H NMR(200 MHz, $CDCl_3$) δ: 3.82 (s, 6H), 7.37 (s, 5H), 7.75 (s, 1H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 52.62, 125.48, 128.84, 129.34, 130.65, 132.73, 142.88, 164.44, 167.06.

Thermolysis of **120a** in the presence of dimethyl benzalmalonate:

A solution of **120a** (115.6 mg, 0.49 mmol) and dimethyl benzalmalonate (18.06 mg, 0.82 mmol) in benzene (5 mL) was heated as described above. Analysis by GC/MS indicated that the major product was methyl phenylacetate. A compound with a mass appropriate for the adduct of methoxycarbonyl and benzyl radicals with dimethyl benzalmalonate ($C_{21}H_{22}O_6$) was absent. The product mixture was not analyzed further.

4.3 Synthesis and Thermolysis of Spiro Oxadiazolines **159** and **180**

Synthesis of 4-phenyl-1,3-dioxane (**160**):[208]

A solution of styrene (100 g, 0.96 mol), 37 % aqueous formaldehyde (200 mL, 2.5 mol), and sulphuric acid (conc. 8.0 mL, 0.14 mol) was refluxed for 7 hours. After cooling, the solution was washed twice with benzene (160 mL) and the combined benzene layers were then washed twice with water (250 mL). Benzene was removed by distillation at atmospheric pressure (80 °C); the pressure was then reduced to 2mm Hg, and 4-phenyl-1,3-dioxane was collected between 96-130 °C (lit[208] bp 94-95mm Hg).

4-Phenyl-1,3-dioxane (160): Clear oil; yield 57%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.71 (m, 1H), 2.10 (ddd, ^3J = 4.9 Hz, ^3J = 12.2 Hz, ^3J = 12.4 Hz, ^2J = -12.4, 1H), 3.87 (ddd, ^3J = 2.5 Hz, ^3J =11.8 Hz, ^2J = -11.8 Hz, 1H), 4.19 (dd, ^3J = 4.8 Hz, ^2J = -11.4 Hz, 1H), 4.64 (dd, ^3J = 2.5 Hz, ^2J = -11.2 Hz, 1H), 4.89 (d, ^2J = -6.3 Hz, 1H), 5.22 (d, ^2J = -6.3 Hz, 1H), 7.26 - 7.39 (m, 5H).

Synthesis of 1,5-diacetoxy-4-oxa-1-phenylpentane (**161**):[209]

4-Phenyl-1,3-dioxane (**160**, 80 g, 0.49 mol) was dissolved in acetic anhydride (138 mL, 1.46 mol), concentrated HCl (1 mL) was added, and the solution was heated to 80°C for 20 hours. The solution was cooled, neutralized with 10% NaOH (as determined by universal litmus paper), and washed twice with ether (50 mL). The ether layer was dried with magnesium sulphate. After vacuum filtration the ether was removed by rotary evaporation.

*1,5-Diacetoxy-4-oxa-1-phenylpentane (**161**):* Orange oil; yield 83%; ^{1}H NMR(500 MHz, $CDCl_3$) δ: 1.87 (s, 3H), 1.90 - 1.96 (m, 1H), 1.99 (s, 3H), 2.05 - 2.12 (m, 1H), 4.01 - 4.06 (m, 1H), 4.13 - 4.18 (m, 1H), 4.65 (m, 1H), 5.01 (d, ^{3}J = 2.6 Hz, 1H), 5.28 (d, ^{3}J = 2.6 Hz, 1H), 7.24 - 7.32 (m, 5H); ^{13}C NMR(125 MHz, $CDCl_3$) δ: 20.49, 20.60, 36.70, 60.80, 78.01, 86.81, 126.36, 127.82, 128.35, 140.81, 170.17, 170.58; MS (EI) *m/z*: 206 (1), 177 (4), 163 (3), 146 (17), 133 (6), 117 (29), 107 (25), 91 (6), 77 (8), 43 (100); MS (CI, NH_3) *m/z*: 284 ($(M+NH_4)^+$, 28), 177 (100), 146 (17), 117 (95), 75 (4).

Synthesis of 3-phenyl-1,3-propanediol (**162**):[210]

A saturated solution of KOH in methanol (30 mL) was added slowly to a solution of 1,5-diacetoxy-4-oxa-1-phenylpentane (**161**, 15.62 g, 0.058 mol) in ether (10 mL). After stirring the solution for 3 hours, it was neutralized with 5% HCl. The aqueous/methanol layer was extracted twice with ether (30 mL). Distillation of the crude product at 0.5mm Hg, afforded racemic 3-phenyl-1,3-propanediol, which was collected at 119°C (lit.[211] bp 117-118°C at 0.25 mmHg).

*1-Phenyl-1,3-propanediol (**162**):* Clear oil; yield 54%; ^{1}H NMR(200 MHz, MeOH-d_4) δ: 1.68 - 1.91 (m, 2H), 3.62 - 3.41 (m, 2H), 4.83 (dd, ^{3}J = 2.6 Hz, ^{3}J = 5.4 Hz, 1H), 7.22 - 7.52 (m, 5H); ^{13}C NMR(50 MHz, MeOH-d_4) δ: 42.71, 65.50, 75.92, 126.73, 128.20, 129.40, 146.33; ^{1}H-NMR(200 MHz, $CDCl_3$) δ: 1.86 (m, 2H), 3.76 (m, 2H), 4.83 (dd, ^{3}J = 4.7 Hz, ^{3}J = 7.9 Hz, 1H), 7.22 - 7.52 (m, 5H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 40.34, 60.44, 73.08, 125.55, 127.25, 128.25, 144.19; MS (EI) *m/z*: 152 (M^+, 14), 133 (9), 105

(50), 107 (100), 91 (16), 79 (78), 51 (23), 43 (16); MS (CI, NH_3) *m/z*: 170 ($(M+NH_4)^+$, 21), 152 (100), 135 (56), 117 (86), 91 (16).

Synthesis of cyclic carbonates:[212,213]

A solution of 1,1'-carbonyldiimidazole (3.51 g, 0.022 mol) in dichloromethane (100 mL) was added dropwise (*ca.* 1 hour) to a solution of the appropriate 1,3-propanediol (0.021 mol) and triethylamine (0.054 mol) in dichloromethane (180 mL). After stirring overnight, the solution was washed three times with 5% HCl (250 mL), and once each with water (250 mL) and brine (250 mL). The dichloromethane layer was dried over magnesium sulphate and after filtration the solvent was removed by rotary evaporation.

2-Oxo-4-phenyl-1,3-dioxane (163): White crystals (recrystallized from EtOH); yield 70%; mp 53-54 °C; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 2.20 - 2.38 (m, 2H), 4.46 - 4.51 (m, 2H), 5.51 (dd, ^3J = 3.8 Hz, ^3J = 9.6 Hz, 1H), 7.26 - 7.44 (m, 5H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 29.42, 66.87, 80.15, 125.67, 127.83, 129.0, 137.90, 148.77 (C=O); MS (EI) *m/z*: 178 (M^+, 12), 117 (82), 104 (100), 91 (11), 77 (51), 56 (48), 51 (36); MS (CI, NH_3) *m/z*: 196 ($(M+NH_4)^+$, 100), 179 ($(M + H)^+$, 30), 134 (9), 117 (89), 104 (8); HRMS: calculated for $C_{10}H_{10}O_3$: 178.0629, found: 178.0657.

Neopentyl carbonate:[214] White solid; yield 54%; mp 88-93°C, lit.[214] mp 109°C ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.11 (s, 6H), 4.06 (s, 4H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 21.20, 28.54, 77.62, 148.30; MS (EI) *m/z*: 131 ($(M+H)^+$, 15), 86 (11), 71 (38), 56 (100), 41 (90); MS (CI, NH_3) *m/z:* 148 ($(M+NH_4)^+$, 100), ($(M+H)^+$, 40).

Hydrazinolysis of cyclic carbonates:

Hydrazine monohydrate (7.1 mL, 0.15 mol) was added to a solution of the appropriate cyclic carbonate (0.022 mol) in dichloromethane (70 mL) under nitrogen. Stirring was continued for 2 hours and the water layer was removed. Evaporation of the solvent yielded the hydrazinocarboxylate. For the synthesis of **164**, the product was insoluble in dichloromethane and the white crystals were filtered from the solution.

(3-Hydroxy-3-phenylpropoxy)carbonyl hydrazine (164): White solid; yield 77%; mp 138-139°C; ^{1}H NMR(200 MHz, MeOH-d_4) δ: 1.92 (m, 2H), 4.00 - 4.12 (m, 2H), 4.66 (m, 1H), 7.17 - 7.26 (m, 5H); ^{13}C NMR(50 MHz, MeOH-d_4) δ: 39.50, 63.39, 71.73, 126.93, 128.38, 129.38, 145.96, 160.69 (C=O); MS (EI) *m/z*: 192 (7), 134 (9), 118 (11), 117 (100), 91 (11), 79 (16), 57 (11), 43 (12); MS (CI, NH_3) *m/z*: 211 ($(M+H)^+$, 3), 193 (100), 152 (13), 135 (8), 117 (100), 105 (8), 76 (11), 69 (19), 43 (52).

(3-Hydroxy-2,2-dimethylpropoxy)carbonyl hydrazine: White solid; yield 81%; mp 68-70°C ; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 0.86 (s, 6H), 3.25 (s, 2H), 3.91 (s, 2H), 5.66 (bs, 1H), 6.61 (bs, 1H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 21.49, 36.96, 67.89, 70.47, 159.65; MS (EI) *m/z*: 163 ($(M+H)^+$, 1), 84 (19), 76 (22), 56 (79), 41 (100); MS (CI, NH_3) *m/z*: 180 ($(M+NH_4)^+$, 48), 163 ($(M+H)^+$, 96), 148 (51), 122 (48), 105 (16), 69 (24), 52 (100); HRMS calculated for $C_6H_{15}N_2O_3$: 163.1082, found: 163.1092.

Synthesis of hydrazones:

The appropriate hydrazinocarboxylate (5.23 mmol) was dissolved in dichloromethane (10 mL), along with acetone (1 mL). After the hydrazinocarboxylate had

dissolved, Na_2SO_4 (0.24 g, 1.4 mmol) was added, and the mixture was stirred for 2 hours. The Na_2SO_4 was removed by filtration and the solvent was removed by rotary evaporation.

(3-Hydroxy-3-phenylpropoxy)carbonyl hydrazone of acetone (165): White solid; yield 60%; mp 109-110°C; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 1.82 (s, 3H), 2.03 (s, 3H), 2.07 - 2.11 (m, 2H), 4.24 - 4.27 (m, 1H), 4.45 - 4.53 (m, 1H), 4.81 (dd, ^3J = 4.2 Hz, ^3J = 4.5 Hz, 1H), 7.27 - 7.38 (m, 5H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 16.24, 25.49, 38.62, 63.30, 71.36, 125.89, 127.69, 128.64, 144.10, 151.30, 154.45; MS (EI) *m/z*: 251 ($(M+H)^+$, 1), 144 (15), 117 (100), 91 (17), 72 (38), 56 (31), 43 (38); MS (CI, NH_3) *m/z*: 251 ($(M+H)^+$, 29), 233 (23), 193 (48), 117 (100), 99 (12), 72 (19). HRMS: calculated for $C_{13}H_{19}N_2O_3$: 251.1395, found: 251.1382.

(3-Hydroxy-2,2-dimethylpropoxy)carbonyl hydrazone of acetone: Clear oil; yield 100%; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 0.87 (s, 6H), 1.83 (s, 3H), 1.99 (s, 3H), 3.28 (s, 2H), 3.98 (s, 2H), 7.96 (bs, 1H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 16.50, 21.55, 25.33, 36.70, 68.31, 70.96, 152.29, 155.02; MS (EI) *m/z*: 203 ($(M+H)^+$, 100), 117 (55), 72 (83); MS (CI, NH_3) *m/z*: 203 ($(M+H)^+$, 100); HRMS calculated for $C_9H_{19}N_2O_3$: 203.1395, found: 203.1414.

Synthesis of spiro oxadiazolines **159** and **180**:

A solution of lead(IV) acetate (4.43 g, 10.0 mmol) in dichloromethane (25 mL) was cooled in an ice bath, under nitrogen. The appropriate carbonyl hydrazone of acetone (0.004 mol) dissolved in dichloromethane (5 mL) was added dropwise over 1 hour. After addition stirring was continued for two days. The heterogeneous mixture was filtered

through Celite, washed four times with 5% $NaHCO_3$ (25 mL), and dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was re-dissolved in dichloromethane (20 mL). Trifluoroacetic acid (0.01 mL) was added and the reaction was monitored with TLC. After 90 minutes the reaction was complete and the solution was washed with 10% NaOH and dried over $MgSO_4$. Removal of the solvent yielded the crude oxadiazolines, which were purified using radial chromatography (10 % EtOAc in hexanes).

3,4-Diaza-2,2-dimethyl-7-phenyl-1,6,10-trioxaspiro[5.4]dec-3-ene (159): White solid, two diastereomers (1:1); yield 38%; ^{1}H NMR(300 MHz, $CDCl_3$) δ (composite spectrum): 1.48 (s, 3H), 1.52 (s, 3H), 1.53 (s, 6H), 1.90 - 2.03 (m, 2H), 2.18 - 2.39 (m, 2H), 4.23 - 4.31 (m, 2H), 4.35 (ddd, ^3J = 3.5 Hz, ^3J = 11.3 Hz, ^2J = -11.3 Hz, 1H) 4.81 (ddd, ^3J = 2.8 Hz, ^3J = 11.8 Hz, ^2J = -11.9 Hz, 1H), 5.24 (dd, ^3J = 3.1 Hz, ^3J = 11.6 Hz, 1H), 5.73 (dd, ^3J = 2.7 Hz, ^3J = 11.6 Hz, 1H), 7.23 - 7.40 (m, 10H); ^{13}C NMR(75 MHz, $CDCl_3$) δ (composite spectrum): 24.49, 24.62, 31.74, 31.92, 63.02, 65.16, 74.62, 77.09, 119.81, 120.44, 125.92, 128.18, 128.54, 133.93, 140.21; MS (EI) *m/z*: 162 (1), 116 (72), 117 (100), 104 (12), 91 (19), 65 (3), 43 (19); MS (CI, NH_3) *m/z*: 260 (1), 196 (19), 179 (3), 117 (100), 91 (3).

3,4-Diaza-2,2,8,8,-tetramethyl-1,6,10-trioxaspiro[5.4]dec-3-ene (180): Pale yellow solid (recrystallized from EtOH); yield 31%; mp 120-121°C; ^{1}H NMR(200 MHz, $CDCl_3$) δ: 0.99 (s, 3H), 1.21 (s, 3H), 1.52 (s, 6H), 3.74 (d, ^2J = -11.0 Hz, 2H); 4.23 (d, ^2J = -11.0 Hz, 2H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 21.83, 22.60, 24.62, 29.81, 74.98, 119.84, 133.63; MS (CI, NH_3) *m/z*: 218 ($(M+NH_4)^+$, 17), 193 (34), 148 (100), 131 (66).

Thermolysis of **159** in the presence of *tert*-butyl alcohol:

Oxadiazoline **159** (27.4 mg, 0.11 mmol) and *tert*-butyl alcohol (82.2 mg, 1.1 mmol) were dissolved in 2 mL of benzene and flamed sealed into a thermolysis tube. The tube was heated for 72 hours at 110°C in a preheated oil bath. Two diastereomers of **167** were obtained in a ratio of 3:1. The crude sample was not purified but the signals corresponding to the major diastereomer were identified.

2-tert-Butoxy-4-phenyl-1,3-dioxane (167): Yield 76%; ^{1}H NMR(500 MHz, C_6D_6) δ: 1.59 (s, 9H, CH_3), 1.48 - 1.73 (dm, 1H H5eq.), 1.96 (ddd, ^{3}J = 5.0 Hz, ^{3}J = 12.6 Hz, ^{3}J = 12.4 Hz, ^{2}J = -12.4 Hz, 1H, H5ax.), 3.36 - 3.5 (m, 1H, H6ax.), 3.57 (dd, ^{3}J = 1.4 Hz, ^{3}J = 4.0 Hz, ^{2}J = -11.0 Hz, 1H, H6eq.), 5.32 (dd, ^{3}J = 2.4 Hz, ^{3}J = 11.7 Hz, 1H, H4ax.), 7.03 - 7.37 (m, 5H); ^{13}C NMR(125 MHz, C_6D_6) δ: 28.74 (CH_3), 33.77, 58.32, 69.44, 77.13 (CMe_3), 105.21 (orthoformyl), 125.91, 128.08, 128.32, 142.90; MS (EI) *m/z*: 152 (6), 134 (31), 107 (100), 79 (84), 59 (14), 51 (30); MS (CI, NH_3) *m/z*: 196 (8), 179 (8), 152 (24), 134 (17), 117 (100), 105 (19).

Thermolysis of **159**:

Oxadiazoline **159** (0.1515 g, 0.61 mmol), and the internal standard 1,4-dimethoxybenzene (0.0205 g, 0.148 mmol) in benzene (6mL) were sealed into a thermolysis tube heated, which was heated at 110°C for 72 hours. The crude mixture was injected into the GC/FID to determine the product yields. The peak areas were corrected for the detector response.[151] Products were identified by co-injection of authentic

compounds; the remainder of the mixture was separated by radial chromatography (100% hexanes).

Phenylcyclopropane (169): Yield 26%; MS(EI) *m/z*: 118 (M^+, 54), 117 (100), 115 (48), 91 (74), 77 (22), 63 (38), 39 (33).

2-Oxo-4-phenyl-1,3-dioxane (163): Yield 5%.

α-*Phenyl-γ-butyrolactone (168)*:[215,216] Yield 28%; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 2.44 (dddd, ^3J = 8.2 Hz, ^3J = 9.2 Hz, ^3J = 10.1 Hz, ^2J = -12.6 Hz, 1H), 2.71 (dddd, ^3J = 3.4 Hz, ^3J = 6.8 Hz, ^3J = 9.1 Hz, ^2J = 12.6 Hz, 1H), 3.80 (dd, ^3J = 9.7 Hz, ^3J = 9.9 Hz, 1H), 4.34 (ddd, ^3J = 6.7 Hz, ^3J = 9.1 Hz, ^2J = -9.1 Hz, 1H), 4.46 (ddd, ^3J = 3.4 Hz, ^3J = 8.2 Hz, ^2J = -9.1 Hz, 1H), 7.27 - 7.40 (m, 5H); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 31.62, 45.54, 66.56, 127.71, 127.98, 129.00, 136.79, 177.43; MS (EI) *m/z*: 162 (M^+, 22), 117 (100), 103 (16), 91 (48), 77 (24), 63 (14), 51 (15); HRMS: calculated for $C_{10}H_{10}O_2$: 162.0680, found: 162.0675.

2-Hydroxy-4-phenyl-1,3-dioxane (170): Yield 19%; MS(EI) *m/z*: 163 ($(M-OH)^+$, 1), 133 (2), 117 (100), 105 (30), 91 (20), 77 (39), 43 (63).

3-Hydroxy-3-phenylpropyl formate (178): ^{1}H NMR(300 MHz, $CDCl_3$) δ: 2.02 - 2.19 (m, 2H), 4.23 (ddd, ^3J = 5.9 Hz, ^3J = 5.7 Hz, ^3J = 5.7 Hz, ^2J = -11.3 Hz, 1H), 4.43 (ddd, ^3J = 5.9 Hz, ^3J = 5.7 Hz, ^3J = 5.7 Hz, ^2J = -11.3 Hz, 1H), 4.83 (dd, ^3J = 5 Hz, ^3J = 7.6 Hz, 1H), 7.07 - 7.36 (m, 5H), 8.08 (s, 1H). ^{13}C NMR(75 MHz, $CDCl_3$) δ: 37.93, 61.27, 71.31, 125.85, 128.04, 128.80, 143.90, 161.22; MS (EI) *m/z*: 180 (M^+, 3), 163 (4), 152 (7), 134

(52), 107 (96), 91 (20), 79 (100), 51 (21), 43 (17); HRMS: Calculated for $C_{10}H_{12}O_3$: 180.0786, found: 180.0778.

2-(2-Oxopropyl)-4-phenyl-1,3-dioxane (172): Yield 2%; ^{1}H NMR(500 MHz, $CDCl_3$) δ: 1.70 (ddd, ^3J = 2.5 Hz, ^3J = 3.5 Hz, ^2J = -13.4 Hz, 1H, H5eq.), 1.99 (dddd, ^3J = 4.6 Hz, ^2J = -13.3 Hz, ^3J = 11.9 Hz, ^3J = 11.9 Hz, 1H, H5ax.), 2.22 (s, 3H), 2.84 (d, ^3J = 5.1 Hz, 2H), 3.94 (ddd, ^3J = 2.6Hz, ^3J = 11.7 Hz, ^2J = -11.9 Hz, 1H, H6ax.), 4.20 (ddd, ^3J = 1.3 Hz, ^3J = 4.9 Hz, ^2J = -11.5 Hz, 1H, H6eq.), 4.72 (dd, ^3J = 2.5 Hz, ^3J =11.4 Hz, 1H, H4ax.), 5.17 (t, ^3J = 5.1 Hz, 1H), 7.28 - 7.4 (m, 5H); ^{13}C NMR(125 MHz, $CDCl_3$), δ: 31.51, 33.17, 49.33, 67.02, 78.93, 99.06, 125.95, 127.98, 128.61, 141.492, 205.21; MS (CI, NH_3) *m/z*: 238 ($(M+NH_4)^+$, 25), 221 ($(M+H)^+$, 58), 187 (31), 152 (30), 135 (44), 117 (100), 91 (14), 78 (10), 43 (14).

8,8,11,11-Tetramethyl-2-phenyl-1,5,7,10-tetraoxa-9-oxospiro[5.5]undecane (173): Yield 2%; ^{1}H NMR(500 MHz, C_6D_6) δ: 1.15 (dddd, ^3J = 1.5 Hz, ^3J = 2.6 Hz, ^3J = 2.6 Hz, ^2J = -13.4 Hz, 1H, H3eq.), 1.48 (s, 3H, H11'), 1.50 (s, 3H, H11'), 1.53 (s, 3H, H8'), 1.56 (s, 3H, H8'), 1.62 (dddd, ^3J = 4.9 Hz, ^3J = 11.7, ^3J = 12.9 Hz, ^2J = -13.1 Hz, 1H, H3ax.), 3.41 (ddd, ^3J = 1.6 Hz, ^3J = 4.9 Hz, ^2J = -11.1 Hz, 1 H, H4eq.), 3.97 (ddd, ^3J = 2.5 Hz, ^3J = 12.8 Hz, ^2J = -11.1 Hz, 1H, H4ax.), 5.00 (dd, ^3J = 2.7 Hz, ^3J = 11.7 Hz, 1H, H2ax.), 7.08 - 7.12 (m, 5H); ^{13}C NMR(125 MHz, C_6D_6) δ: 24.07 (C11'), 24.20 (C11'), 28.58 (C8'), 28.72 (C8'), 32.47 (C3), 60.34 (C4), 71.65 (C2), 76.74 (C11), 84.16 (C8), 109.07 (C6), 128.85, 128.39, 128.15, 141.42, 171.06 (C=O); MS (EI) *m/z*: 204 (4), 179 (4), 117 (100),

104 (18), 70 (70), 43 (37); MS (CI, NH_3) *m/z*: 307 ($(M+H)^+$, 18), 134 (18), 117 (100), 70 (32); IR (NaBr, neat): 1738 cm^{-1}.

2,4-Diphenyl-1,3-dioxane (171): Yield 12%; ^1H NMR(500 MHz, $CDCl_3$) δ: 1.81 (ddd, ^3J = 2.5 Hz, ^3J = 4.0 Hz, ^2J = -13.4 Hz, 1H, H5eq.), 2.14 (dddd, ^3J = 4.9 Hz, ^2J = -13.4 Hz, ^3J = 12.2 Hz, ^3J = 11.9 Hz, 1H, H5ax.), 4.14 (ddd, ^3J = 2.5 Hz, ^3J = 11.9 Hz, ^2J = -11.9 Hz, 1H, H6ax.), 4.37 (ddd, ^3J = 1.3 Hz, ^3J = 4.9 Hz, ^2J = -11.5 Hz, 1H, H6eq.), 4.92 (dd, ^3J = 2.6 Hz, ^3J = 11.4 Hz, H4ax.), 5.73 (s, 1H), 7.28 - 7.58 (m, 10H); ^{13}C NMR(125 MHz, $CDCl_3$) δ: 33.63 (C5), 67.48 (C6), 79.29 (C4), 101.79 (C2), 126.03, 126.38, 127.89, 128.38, 128.59, 128.95, 138.88, 141.86; MS (EI) *m/z*: 239 ($(M-H)^+$, 1), 134 (7), 117 (61), 105 (100), 78 (35), 77 (82), 51 (32).

Thermolysis of **159** in the presence of acetone:

A solution of oxadiazoline **159** (0.1684 g, 0.679 mmol) in acetone (0.5 mL) and benzene (5.5 mL) was sealed into a thermolysis tube and heated for 72 hours. After thermolysis the internal standard 1,4-dimethoxybenzene (6.8 mg, 0.1218 mmol) was added to the solution. The crude solution was injected to the GC/FID for determination of product yields.

Phenylcyclopropane (169): Yield 4%. *α-Phenyl-γ-butyrolactone (168)*: Yield 5%. *2-Hydroxy-4-phenyl-1,3-dioxane (170)*: 21%. *2-(2-Oxopropyl)-4-phenyl-1,3-dioxane (172)*: Yield 2%. *8,8,11,11-Tetramethyl-2-phenyl-1,5,7,10-tetraoxa-9-oxospiro[5.5]undecane (173)*: Yield 28%. *2,4-Diphenyl-1,3-dioxane (171)*: Yield 13%; *2-Oxo-4-phenyl-1,3-dioxane (163)*: Yield 7%.

Thermolysis of **180**:

A solution of oxadiazoline **180** (317.9 mg, 11.58 mmol) in benzene (15 mL) was sealed into a thermolysis tube and heated for 72 hours at 110°C. After thermolysis cumene (17 μL, 0.12 mmol) was added as the internal standard. Product yields were determined from the GC/FID trace. Products **182** and **183** were isolated from the preparatory GC (OV-17, 6ft x ¼ inch, flowrate 40 mL/min).

2-Hydroxy-5,5-dimethyl-1,3-dioxane (183): Yield 21%; ^{1}H NMR(200 MHz, C_6D_6) δ: 1.02 (s, 3H), 1.76 (s, 3H), 3.13 (d, ^{2}J = -10.6 Hz, 2H), 3.81 (d, ^{2}J = -10.6 Hz, 2H), 5.97 (s, 1H). *Carbene dimer (182):* Yield 28%; ^{1}H NMR(300 MHz, C_6D_6) δ: 0.67 (s, 12H), 3.43 (s, 8H); ^{13}C NMR(75 MHz, C_6D_6) δ: 21.86, 30.95, 78.36, 136.69; MS (EI) *m/z*: 229 ($(M+H)^+$, 4), 191 (8), 161 (13), 132 (32), 115 (92), 69 (100), 56 (78). HRMS calculated for $C_{12}H_{21}O_4$: 229.1439, found: 229.1453.

Thermolysis of **180** in the presence of acetone:

A solution of oxadiazoline **180** (317.9 mg, 11.58 mmol) in acetone (1 mL) and benzene (6.5 mL) was sealed into a thermolysis tube and heated for 72 hours at 110°C. After thermolysis cumene (17 μL, 0.12 mmol) was added as the internal standard. Product yields were determined from the GC/FID trace.

2-Hydroxy-5,5-dimethyl-1,3-dioxane (183): Yield 20%. *Carbene dimer (182):* Yield 30%.

Synthesis of authentic **173** and **184**:[217]

p-Toluenesulfonic acid (0.5 g, 2.9 mmol) was added to a solution of the appropriate 1,3-propanediol (0.032 mol) and benzaldehyde (3.4 g, 0.036 mol) in

dichloromethane (50 mL). The solution was stirred overnight before it was washed with $NaHCO_3$ (10mL) and the dichloromethane layer was dried over Na_2SO_4. The residue obtained was purified by column chromatography (silica, 10% EtOAc in hexanes).

cis-*2,4,-Diphenyl-1,3-dioxane (171):* ^{1}H NMR(200 MHz, $CDCl_3$) δ: 1.83 (m, 1H, H5eq.), 2.18 (dddd, ^3J = 4.9 Hz, ^3J = 12.2 Hz, ^3J = 12.2 Hz, ^2J = -12.3 Hz, H5ax.), 4.16 (ddd, ^3J = 2.3 Hz, ^3J = 11.8 Hz, ^3J = -11.8 Hz, 1H H6ax.), 4.40 (ddd, ^3J = 1.0 Hz, ^3J = 4.5 Hz, ^2J = -11.4 Hz, 1H, H6eq.), 4.98 (dd, ^3J = 2.4 Hz, ^3J = 11.2 Hz, 1H, H4ax.) 5.77 (s, 1H), 7.33 - 7.66 (m, 10H); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 33.49, 67.34, 79.13, 101.62, 126.28, 125.93, 127.79, 128.29, 128.48, 128.87, 141.73, 138.73; MS (EI) *m/z*: 240 (M^+, 8), 192 (9), 134 (18), 118 (60), 105 (100), 77 (60), 51 (36); MS (CI, NH_3) *m/z*: 258 ($(M+NH_4)^+$, 41), ($(M+H)^+$, 41), 124 (24), 52 (100); HRMS calculated for $C_{16}H_{16}O_2$: 240.1150, found: 240.1167.

5,5-dimethyl-2-phenyl-1,3-dioxane (184): ^{1}H NMR(200 MHz, $CDCl_3$) δ: 0.82 (s, 3H), 1.35 (s, 3H), 3.68 (d, ^2J = -10.8 Hz, 2H), 3.82 (d, ^2J = -10.8 Hz, 2H,), 5.44 (s, 1H,); ^{13}C NMR(50 MHz, $CDCl_3$) δ: 21.87, 23.07, 30.21, 77.63, 101.76, 126.18, 128.28, 128.86, 138.55; MS (EI) *m/z*: 192 (M^+, 100), 115 (28), 107 (85), 77 (60), 56 (97); MS (CI, NH_3) *m/z*: 210 $(M+NH_4)^+$ 55), 193 ($(M+H)^+$, 100).

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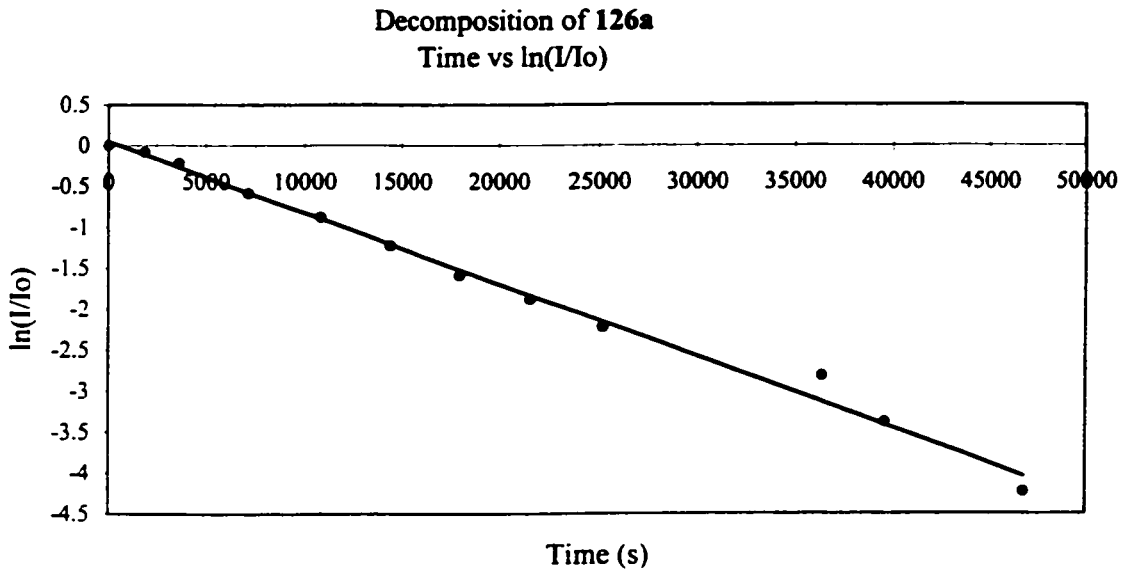
Appendix

Rate of Decomposition for **126a** at 110°

Time (s)	ln I/I_o
0	0
1800	-0.082
3600	-0.2181
7200	-0.586
10800	-0.8827
14400	-1.2309
18000	-1.5942
21600	-1.8847
25200	-2.2243
36400	-2.8199
39600	-3.3801
46800	-4.2346

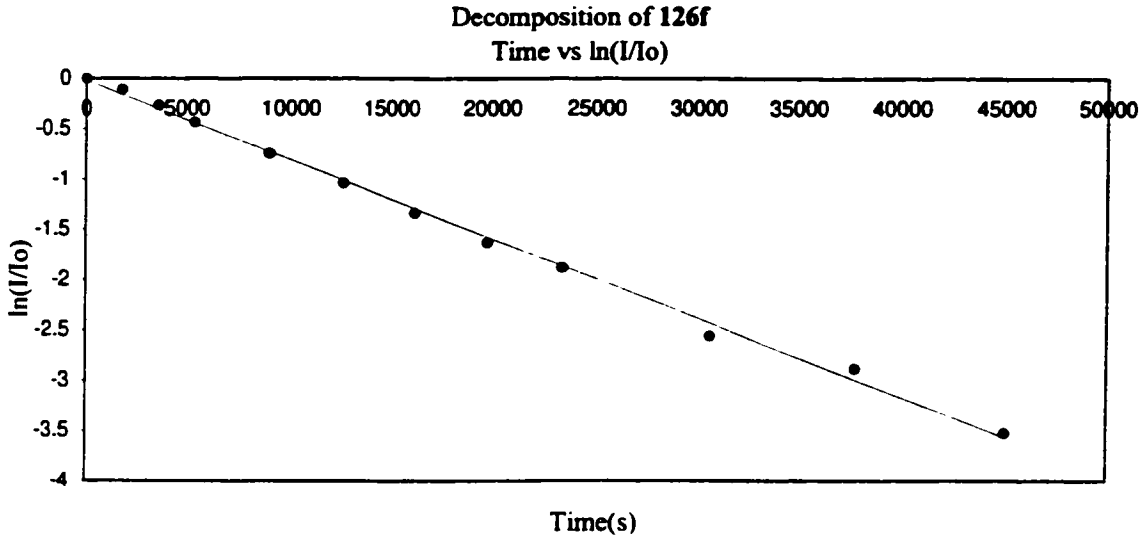
Regression Analysis	
Observations	12
R^2	0.9915
Slope	-8.7×10^{-5}
k^{110} (s^{-1})	8.7×10^{-5}
$t_{1/2}^{110}$ (h)	2



Rate of Decomposition for **126f** at 110°

Time (s)	ln (I/I_o)
0	0
1800	-0.1109
3600	-0.2676
5400	-0.439
9000	-0.7468
12600	-1.0411
16200	-1.3405
19800	-1.6348
23400	-1.8843
30600	-2.5635
37800	-2.8887
45000	-3.5249

Regression Analysis	
Observations	9
R^2	0.997
Slope	-7.9×10^{-5}
k^{110} (s^{-1})	7.9×10^{-5}
$t_{1/2}^{110}$ (h)	2



Rate of Decomposition for the major diastereomer of **148** at 40°

Time (s)	$\ln(I/I_o)$
0	0
900	-0.09728
1800	-0.17044
2700	-0.15049
3600	-0.40704
5400	-0.38561
7200	-0.58777
9000	-0.73159
10800	-0.86319
12600	-1.09108
14400	-1.16059
16200	-1.27153
18000	-1.52494
19800	-1.73799
23400	-1.80193
25200	-1.97455
28800	-2.16425
32400	-2.45331

Regression Analysis	
Observations	18
R^2	0.9957
Slope	-7.7×10^{-5}
k^{110} (s^{-1})	7.7×10^{-5}
$t_{1/2}^{110}$ (h)	3