# Heterocycles Derived from Heteroatom-Substituted Carbenes

Ying Cheng*,‡ and Otto Meth-Cohn*,§

*Department of Chemistry, Beijing Normal University, Beijing 100875, China, and Chemistry Department, Sunderland University, Sunderland, SR1 3SD, United Kingdom*

*Received August 6, 2003*

## Contents



* E-mail: ycheng2@bnu.edu.cn.
‡ Beijing Normal University. Phone: 861062205558. Fax: 861062202075.
§ Sunderland University. E-mail: otto.meth-cohn@sunderland.ac.uk.

## 1. Introduction

Carbenes are viewed classically as electron-deficient intermediates, capable of addition to alkenes, C−H insertion, and reaction with heteroatom lone pairs to yield ylides. However, the reactivity of carbenes is strongly influenced by the electronic properties of their substituents. If one or two heteroatoms (e.g., O, N, or S) are directly bonded to the carbene carbon atom, the electronic delocalization of the lone pair can compensate for the electronic deficiency at the carbene and could cause the nature of the carbene to change from electrophilic to nucleophilic. Carbenes can thus be divided into electrophilic carbenes, nucleophilic carbenes, and ambiphilic carbenes.

Nucleophilic carbenes tend to be unreactive toward electron-rich double bonds but can add to electronically deficient unsaturated compounds. One intriguing feature of nucleophilic carbenes is their unpredictable annulations with such unsaturated electrophiles, and many novel heterocycles have been derived from these annulation reactions. The nucleophilic character of diheteroatom-substituted carbenes offers opportunities for constructing functionally rich heterocyclic compounds and has therefore attracted considerable attention in recent years.

Although the most important application of electrophilic carbenes in organic synthesis is the cyclopropanation of alkenes, many monoheteroatom-substituted electrophilic carbenes have also been used in constructing heterocyclic compounds.

This review will focus on those reactions which afford heterocyclic products via a heteroatom-substituted carbene intermediate. However, reactions yielding heterocyclic compounds from alkylhalocarbenes and dihalocarbenes (e.g., the conversion of pyrroles to pyridines with chloroform and a base) are long known and can be found in earlier reviews.[1,2] Also in earlier reviews, the generation of heteroatom-substituted carbenes,[3,4] their stability,[4,5] reactivity, and reactions[3−8] as well as their application in organometallic catalysis[9] have been covered. This review is organized as follows: In section 2, mono-

10.1021/cr030604w CCC: $48.50 
Published on Web 03/06/2004

Ying Cheng was born in 1961 in Anhui, China. She studied chemistry at Fudan University and received her M.Sc. degree in 1986. She received her Ph.D. degree at the University of Sunderland, U.K., under the guidance of Professor Otto Meth-Cohn in 1999. Since 2000, she has been Professor of Organic Chemistry at Beijing Normal University. Her research interests include the chemistry of ambiphilic and nucleophilic carbenes and new synthetic methods for the novel heterocyclic compounds and natural compounds.

Professor Otto Meth-Cohn is now retired but still mildly chemically active. He has published over 250 papers, edited and written numerous book and major reference works, and enjoyed a lifetime in heterocyclic chemistry, mostly as an academic (Salford and Sunderland Universities, National Chemical Research Labs, South Africa) but with bouts in industry (e.g., Sterling Organica) also. Current passions also include mountain walking, cycling, bridge, painting in watercolors, reading, gardening, and extensive traveling.

heteroatom-substituted carbenes will be discussed, following the periodic order of the heteroatom substituents. Diheteroatom-substituted carbenes are reviewed in section 3 in the same sequence. The substrates with which the carbenes react are also dealt with in their periodic sequence, i.e., alkene, alkyne, ketene, imine, iminium salts, nitrile, isonitrile, isocyanate, isothiocyanate, carbonyl, thiocarbonyl, etc.

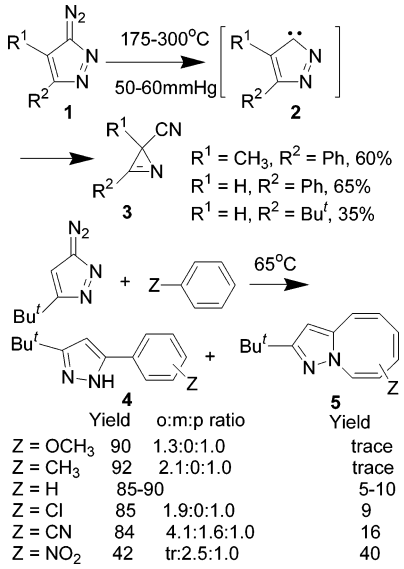
## *2. Heterocycles from Carbenes Bearing One Heteroatom Substituent*

### 2.1. Nitrogen-Substituted Carbenes

Nitrogen-substituted carbenes can be divided according to the hybridization of the nitrogen atom bonding to the carbene center. Monoamidocarbenes and azocarbenes, for example, behave as electrophilic carbenes. Like other classical electrophilic carbenes, these carbenes prefer inserting into C−H bonds or attacking electron-rich double bonds and heteroatom functions, such as nitrogen, oxygen, and sulfur. On the other hand, aminocarbenes are prone to behave as nucleophiles.

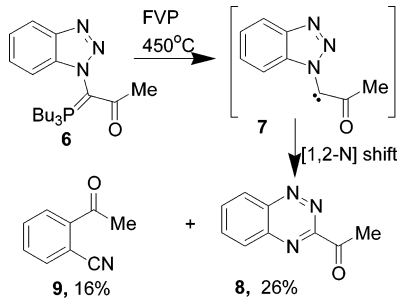
Pyrolysis of 3-diazopyrazoles **1** at 174−300 °C and at 60 mmHg led to the formation of a transient azocarbene intermediate **2**, which rearranged to give 2-cyano-2*H*-azirines **3** in moderate yields. Thermolysis of **1** in the presence of substituted benzenes afforded substitution products **4** of the benzenes by carbenes as the major products, accompanied to a small extent by ring expansion to give pyrazoloazocines **5**. It was found that electron donors in the benzene ring facilitated formation of substituted phenylpyrazoles, whereas electron-withdrawing groups enhance ring expansion to pyrazolo[1,5-a]azocines **5** (Scheme 1).[10,11]

**Scheme 1**




In the flash-vacuum pyrolysis of a range of α-benzotriazolyl-*β*-oxophosphorus ylides **6**, only one example resulted in extrusion of *n*-$Bu_3P$ to give 3-acetyl-1,2,4-benzotriazine **8** and *o*-cyanoacetophenone **9**. The products apparently derived from [1,2-*N*]-rearrangement of the initially formed acetylbenzotriazolylcarbene **7** (Scheme 2).[12]

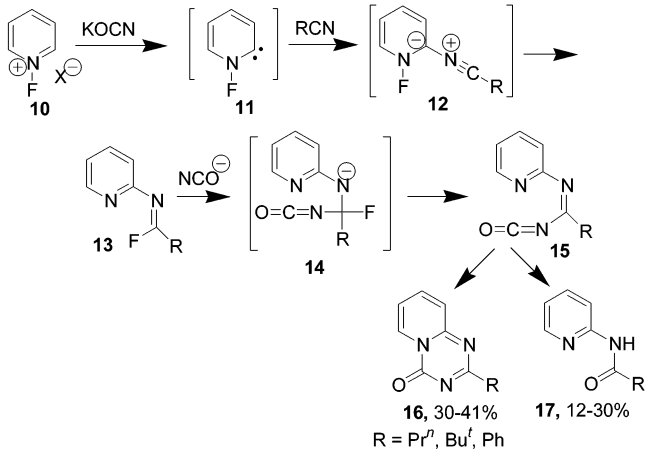
**Scheme 2**




When *N*-fluoropyridinium salts **10** were treated with cyanate ion at −10 °C in the presence of a nitrile, pyridotriazinones **16** were isolated as the major products in 30−41% yields. A mechanism for

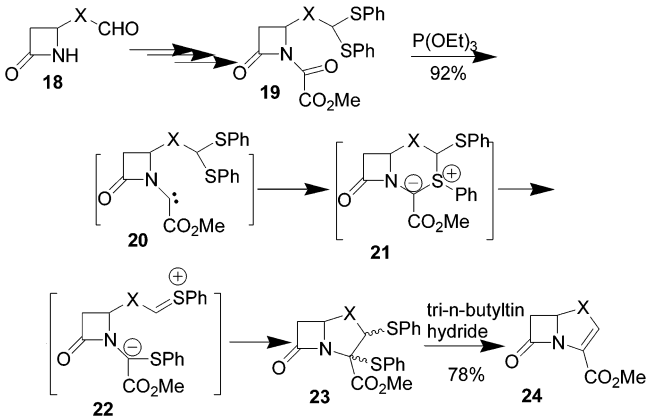
the formation of the pyridotriazinones **16** and the minor product amides **17** was proposed involving the addition of *N*-fluoroaminocarbene **11** to the nitrile, rearrangement of the fluoride **12**, addition of cyanate ion to the fluoroimine **13,** and cyclization. Supporting this mechanism was the observation of the fluoroimine **13** in the GC-MS analysis (Scheme 3).[13]

**Scheme 3**



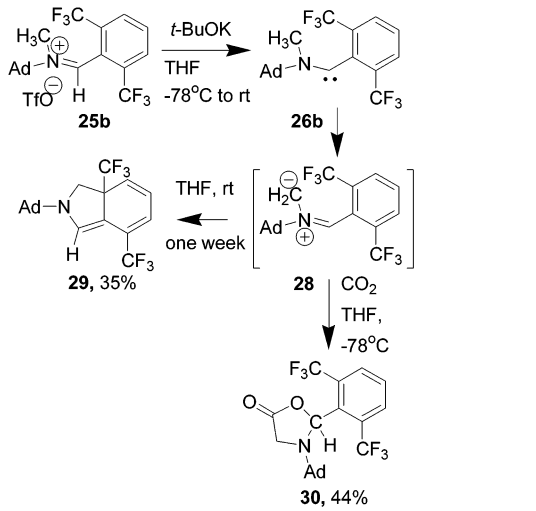

Penems and carbapenems have attracted great interest due to their potential as antimicrobial agents. One method for the construction of the penem and carbapenem ring system employed an oxalimide cyclization, which involved the intramolecular attack of an amidocarbonylcarbene to the sulfur atom of a thioacetal **20** as a key step (Scheme 4).[14]

**Scheme 4**




Although many stable diaminocarbenes have been prepared and isolated since the first example reported by Arduengo in 1991,[15] stable monoaminocarbenes were unknown until 2001. Bertrand and co-workers prepared and isolated the first examples, stable aminoarylcarbenes **26a**,**b** by deprotonation of the corresponding iminium salt **25a**,**b**. The reactivities of these two aminocarbenes are quite different. While **26a** was stable for days in solution at −50 °C, it underwent an intramolecular C−H insertion reaction at room temperature within a few hours. On the other hand, **26b** was stable for months in the solid state but isomerized within several days in tetrahydrofuran solution to afford a novel isoindole **29** in 35% yield. The isoindole **29** most likely resulted from the azomethine ylide **28**, which could indeed be trapped by carbon dioxide, yielding a [1,3]-dipolar cycloadduct **30**. The ylide **28** is in equilibrium with carbene **26b** via the action of *t*-BuOH or traces of water in the system (Scheme 5).[16,17]

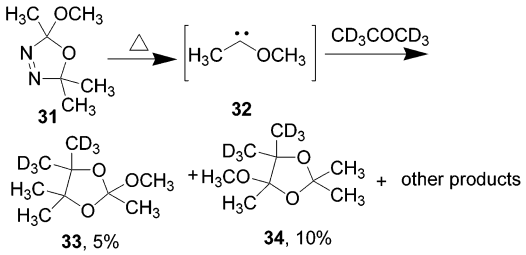
**Scheme 5**




## 2.2. Oxygen-Substituted Carbenes

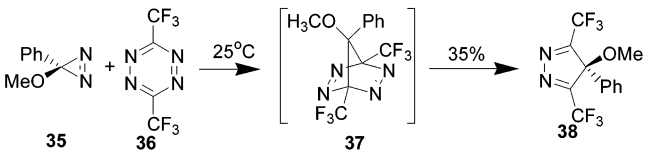
Monooxycarbenes have received relatively little attention. Methoxymethylcarbene **32** was captured by $d_6$-acetone to form ketals **33** and **34** along with ethyl acetate and other products (Scheme 6).[18] Meth-

**Scheme 6**




oxyphenylcarbene derived from the diazirine **35** was found to be ambiphilic.[19] It attacked the highly electron-deficient tetrazine **36** to form an isopyrazole **38** via [4 + 1]-cycloaddition followed by [4 + 2]-cycloreversion (Scheme 7).[20]

**Scheme 7**

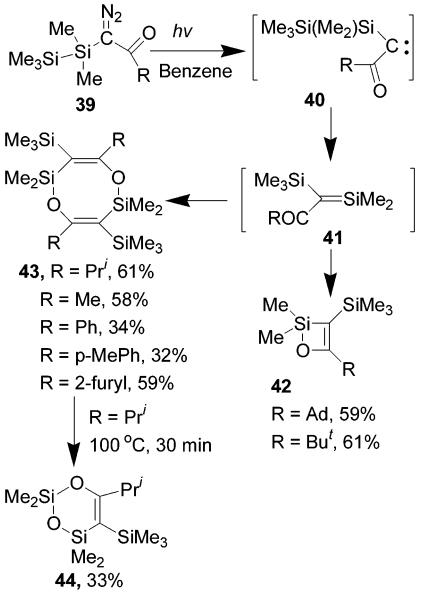



## 2.3. Silicon-Substituted Carbenes

The thermolysis or irradiation of silanyldiazoacetate or -diazoketone is an efficient method for the generation of silylcarbenes. Many novel silicon-containing heterocycles have been obtained from these silylcarbenes intermediates, particularly by Maas and co-workers. For example, a range of pentamethyldisilanyldiazomethyl ketones **39** have been irradiated.[21−23] It was found that in benzene solution,

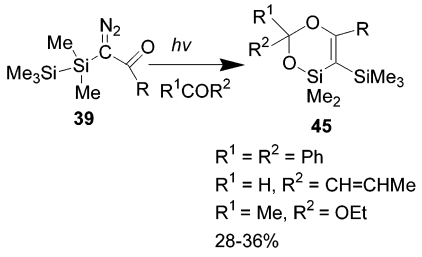
the photolysis of **39** containing a bulky substituent at the carbonyl led to the formation of 1-oxa-2-silacyclobut-3-enes **42.** On the other hand, the ketones **39** bearing a small group afforded 1,5-di-oxa-2,6-disilacycloocta-3,7-dienes **43**, which gave 1,3-dioxa-2,4-disilacyclohex-5-ene **44** on prolonged heating. Both of these product types can be accounted for by way of the acyl(disilanyl)carbenes **40** and acylsilenes **41** (Scheme 8). Some such silenes have been trapped

**Scheme 8**



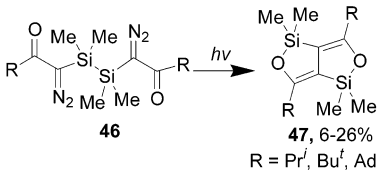

in a matrix.[24] If the same photolysis reactions were carried out in the presence of an aldehyde, ketone, or ester, 1,3-dioxa-4-silacyclohexenes **45** were formed from the [4 + 2]-cycloaddition of acylsilenes at the carbonyl group (Scheme 9).[25]

**Scheme 9**



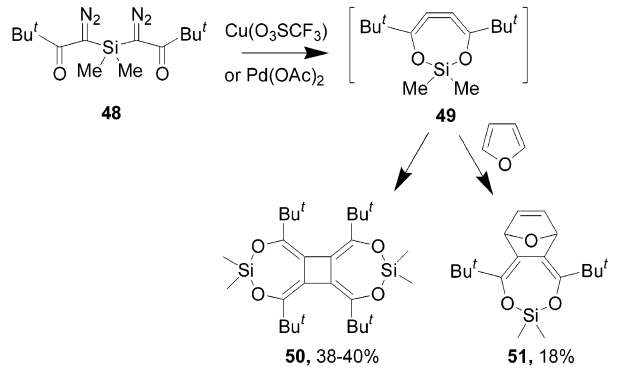

Photolysis or catalytic decomposition of bissilanyldiazomethyl ketones **46** lead to the formation of 4,8-disubstituted 3,7-dioxa-2,6-disilabicyclo[3.3.0]-octa-4,8-dienes **47** in 6−26% yields (Scheme 10).[26]

**Scheme 10**



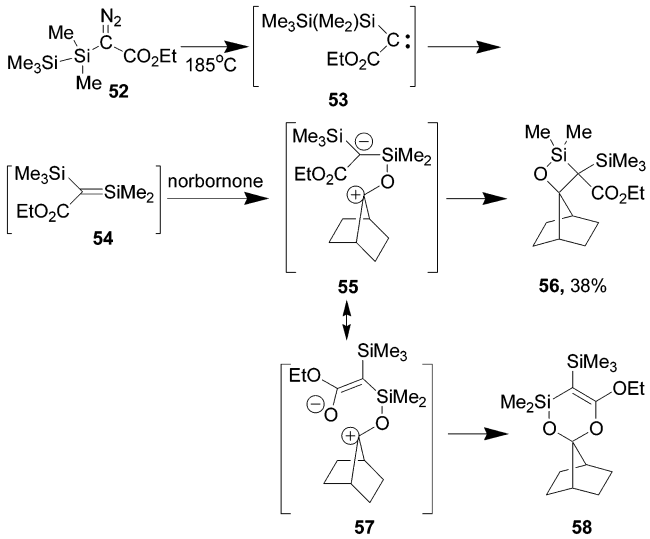

A silyl-substituted biscarbene or biscarbenoid was generated from bis(diazocarbonyl)silane **48** in the presence of copper triflate or palladium acetate. It probably exists as a cyclic cumulene triene intermediate **49**. The cyclic triene could be trapped by furan or dimerized to give the [4]-radialene **50** (Scheme 11).[27]

**Scheme 11**



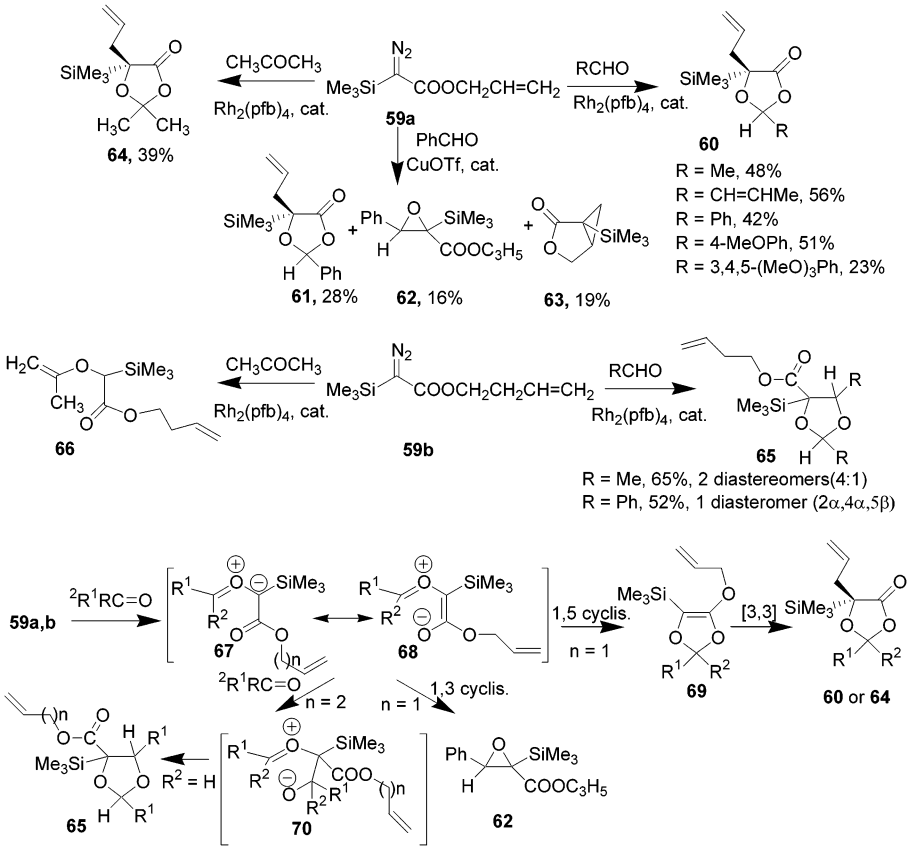

Ando and co-workers studied the co-thermolysis of pentamethyldisilanyldiazoacetate **52** with norbornone at 185 °C. They isolated a 1:1 adduct of the silaethylene **54** to norbornone in 38% yield. They assigned this compound as 2-silaoxetane **56**, which was formed from zwitterionic intermediate **55** generated from the addition of silaethylene to norbornone.[28] Barton and Hussmann reexamined this adduct, and on the basis of its abnormal IR and $^{13}$C NMR data, they formulated the product as the ketene acetal **58**, derived from the cyclization of the zwitterion **57** (Scheme 12).[29]

**Scheme 12**




The reactions of allyl or 3-butenyl α-diazo-α-(trimethylsilyl)acetates **59a**,**b** with aldehydes or acetone under catalysis of rhodium perfluorobutyrate or copper triflate afforded several different types of products.[30] When the interaction of allyl α-diazo-α-(trimethylsilyl)acetates **59a** with an aldehyde was carried out in the presence of rhodium perfluorobutyrate, the only isolated products were the [1 + 1]-adducts, 5-allyl-5-trimethylsilyl-1,3-dioxolan-4-ones **60**. If the same reaction was catalyzed by copper triflate, three heterocyclic compounds (**61**−**63**) were obtained. When **59a** reacted with acetone catalyzed

**Scheme 13**



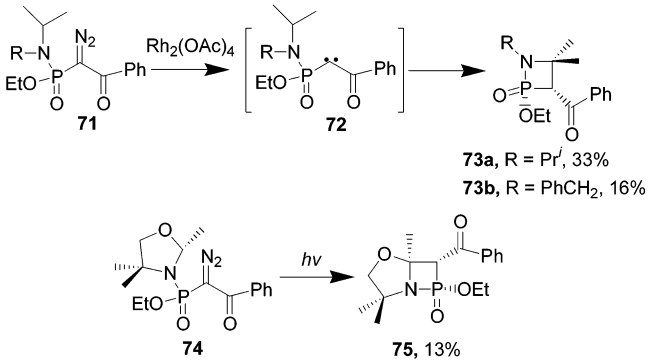

by rhodium perfluorobutyrate, the same type of 1,3-dioxolan-4-one **64** was produced. In contrast, the reactions of 3-butenyl α-diazo-α-(trimethylsilyl)acetates **59b** with aldehydes under the catalytic action of rhodium perfluorobutyrate yielded a [1 + 2]-cyclic acetal **65**. The same diazo compound gave an acyclic compound **66** with acetone under the same conditions. The formation of these heterocycles can be explained by electrophilic attack of the silylcarbonylcarbenes on the carbonyl oxygen leading to the ketone ylide **67**.[31] [1,5]-Cyclization followed by [3,3]-sigmatropic rearrangement of **67** then affords **60** or **64**. On the other hand, [1,3]-cyclization of **67** gives the three-membered ring product **62**. When the intermediate **67** reacted with another molecule of aldehyde, the acetal **65** was obtained (Scheme 13).

## 2.4. Phosphorus-Substituted Carbenes

Photolytic or rhodium-catalyzed decomposition of *N,N*-dialkyl-substituted α-diazo-*β*-ketophosphonamidates **71** generated carbene or carbenoid intermediates, which inserted into the α-C−H bond of the N-alkyl group leading to the formation of 1,2-azaphosphetidines **73a**,**b** and **75** in low yields.[32] Both **73a** and **73b** were formed diastereoselectively, in a ratio of about 10:1 in favor of the (*Sp, Rc)* relative configuration (Scheme 14).

The short-lived benzoylphosphene**78**, generated photochemically from (diazophenacyl)diphenylphosphine oxide **76** via a [1,2]-phenyl shift of the phosphorylcarbene intermediate **77**, undergoes [4 + 2]-cy-

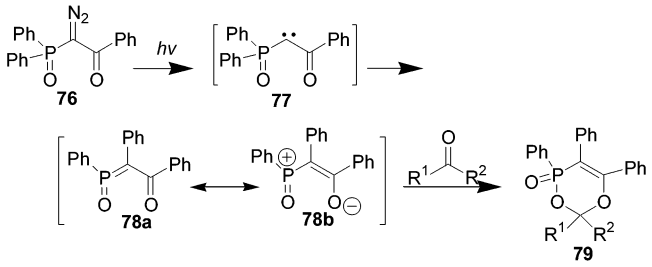
**Scheme 14**




cloaddition with ketones or aldehydes affording 1,3,4$\lambda^5$-dioxaphosphorins **79** (Scheme 15).[33] The structure of dioxaphosphorin derived from acetaldehyde was determined unambiguously by X-ray crystallography.[34]

The photolysis of (diazobenzyl)diphenylphosphane oxide **80** in the presence of aldehydes or ketones behaves differently to that of the carbonyl analogue **76**. The short-lived phosphene **83** reacted in a [2 + 2]-cycloaddition with aromatic aldehydes yielding 1,2$\lambda^5$-oxaphosphetanes **84**. With α,*β*-unsaturated ketones or aldehydes, the initially formed oxaphosphetanes **85** or **88** underwent a partial or complete fragmentation to the 1,3-butadienes **86** or **89**. In addition, the reactions between the phosphene and α,*β*-unsaturated ketones also led to the [4 + 2]-cycloadducts 1,2$\lambda^5$-oxaphosphorin **87**. The existence of the phosphorylcarbene was proved by the adduct **82** it formed with benzene (Scheme 16).[35,36]

**Scheme 15**



$R^1 = R^2 = Ph$, 14%; $R^1 = R^2 = CH_3$, 45%
$R^1 = CH_3$, $R^2 = Ph$, 23%; $R^1$ $R^2$ = cyclohexyl, 59%
$R^1 = CH_3$, $R^2 = t$-Bu, 40%; $R^1 = CH_3$, $R^2 = H$, 27%
$R^1 = CCl_3$, $R^2 = H$, 15%;
$R^1 = CH{=}CHCH_3$, $R^2 = H$, 45%
$R^1 = CH{=}CHPh$, $R^2 = H$, 32%

## *3. Heterocycles from Carbenes Bearing Two Heteroatom Substituents*

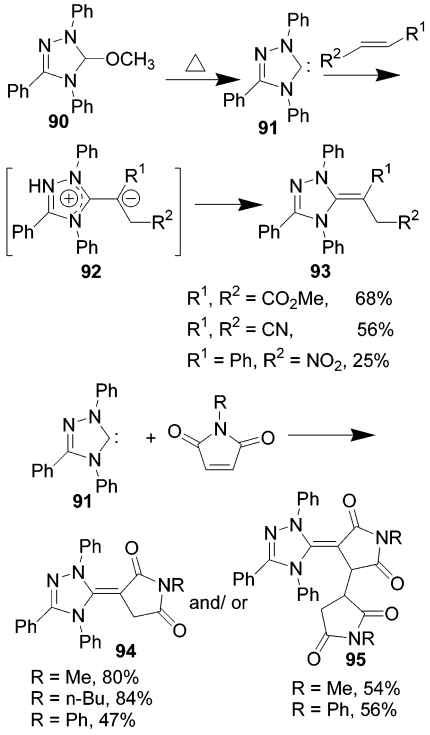
### 3.1. Dinitrogen-Substituted Carbenes

Diaminocarbenes are the most prolifically studied group of carbenes, particularly the heterocyclic examples, some examples of which are isolable and stable.[4,6]

#### *3.1.1. Addition to Carbon–Carbon Double Bonds*

Diaminocarbenes are generally nucleophilic but weakly reactive. However, in only a few cases were they reported to attack electron-deficient carbon−carbon double bonds. These reactions were anomalous in not giving rise to cyclopropanes. For example, the stable diaminocarbene, 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene **91**, added to the double bonds of the methyl fumarate or maleate, fumaronitrile, and nitrostyrene leading to the formation of the 5-methylenetriazolines **93** in good yields. Depending upon the reaction conditions, the reactions of **91** with maleic imides formed methylenetriazolines **94** and/or **95**. The formation of the 1:2 adducts **95** became more significant with an excess of the imide (Scheme 17).[37]

**Scheme 17**



R = Me, 80%
R = n-Bu, 84%
R = Ph, 47%

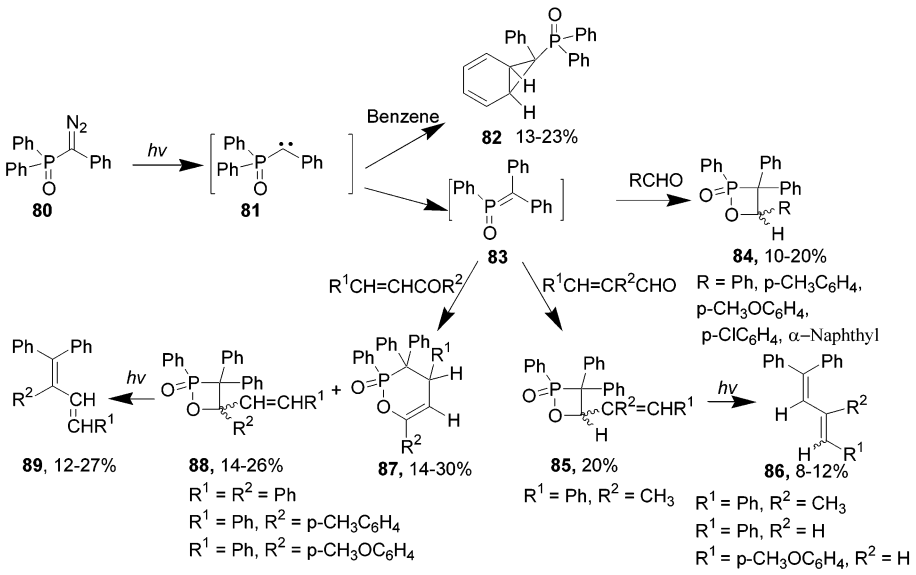
R = Me, 54%
R = Ph, 56%

*N*,*N*-Dimethylaminobenzotriazolylcarbene **97**,[38] generated from deprotonation of the iminium salt **96**, was trapped with *trans*-dibenzoylethylene yielding 4-benzoyl-5-(dimethylamino)-2-phenylfuran **99** (13%) and 3-benzotriazolyl-4-benzoyl-2-phenylfuran **100** (6%). The formation of these phenylfuran derivatives can be readily explained by a [1 + 4]-cycloaddition of carbene **97** to dibenzoylethylene (Scheme 18).

#### *3.1.2. Addition to Carbon–Carbon Triple Bond*

The addition of the stable diaminocarbene triazol-5-ylidene **91** to the triple bond of dimethyl acetylene-

**Scheme 16**



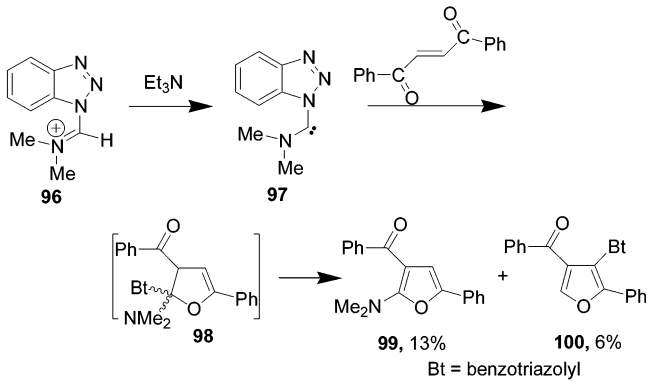
**88**, 14-26%
$R^1 = R^2 = Ph$
$R^1 = Ph$, $R^2 = p\text{-}CH_3C_6H_4$
$R^1 = Ph$, $R^2 = p\text{-}CH_3OC_6H_4$

**84**, 10-20%
R = Ph, $p\text{-}CH_3C_6H_4$, $p\text{-}CH_3OC_6H_4$, $p\text{-}ClC_6H_4$, α–Naphthyl

**85**, 20%
$R^1 = Ph$, $R^2 = CH_3$

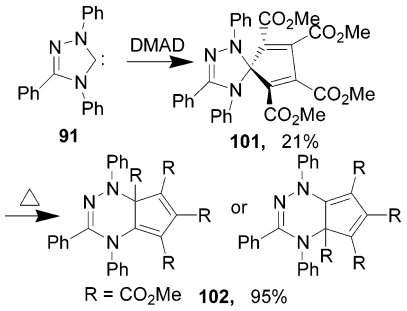
**86**, 8-12%
$R^1 = Ph$, $R^2 = CH_3$
$R^1 = Ph$, $R^2 = H$
$R^1 = p\text{-}CH_3OC_6H_4$, $R^2 = H$

**Scheme 18**




dicarboxylate was followed by subsequent 1,3-dipolar cycloaddition of the dipolar intermediate to a second molecule of DMAD producing a spiro compound **101**. The spiro system **101** was unstable and rearranged on heating to give the bicyclic compound **102** (Scheme 19).[37] Distinction between the two alternative struc-

**Scheme 19**




tures of the bicyclic systems by NMR was not possible.

Very recently, Nair and co-workers reported an interesting multicomponent reaction of N-heterocyclic carbenes with DMAD together with aldehydes.[39] The reaction of the 1,3-dimesityl imidazolin-2-ylidene **105** (generated in situ by deprotonation of 1,3-dimesityl-imidazolinium chloride **103** with sodium hydride) with DMAD and substituted benzaldehyde led to the formation of 2-oxymaleate derivatives **104** in good yields. Initial attack of the aldehyde by the carbene followed by the conjugate addition of the resulting enaminol **107** to the alkyne accounted for the products (Scheme 20).

In contrast, using the corresponding unsaturated N-heterocyclic carbene, the same components reacted in reverse order. Thus, 1,3-dimesitylimidazol-2-ylidene **110** afforded furanone derivatives **109** on stirring with DMAD and substituted benzaldehydes at room temperature. The formation of the furanones involved initial nucleophilic addition of carbene to the DMAD to form a zwitterion **111**, which attacked the aldehyde and then cyclized at the ester carbonyl (Scheme 21).

### 3.1.3. Addition to Ketene

Ketenes react efficiently with nucleophiles, but their reaction with carbenes has been barely studied. Very recently, the N-heterocyclic carbene **115**, generated from thermolysis of 2-trichloromethyl-1,3-imidazolidine **114**, was shown to participate in efficient [4 + 1]-cycloaddition reactions with (trialkylsilyl)vinylketenes **116** producing highly substituted cyclopentenones.[40] The type of products depended on the structures of the vinyl double bond (Scheme 22).

### 3.1.4. Addition to Carbon–Nitrogen Double Bonds

Although electrophilic carbenes do not add to iminium double bonds, the diaminocarbene **115** derived from the bis-diphenylimidazolidinylene **120** readily reacted with an iminium salt **121** leading to a highly strained spiro intermediate **122**, which rearranged into a pyridinium salt **124** (Scheme 23).[41]

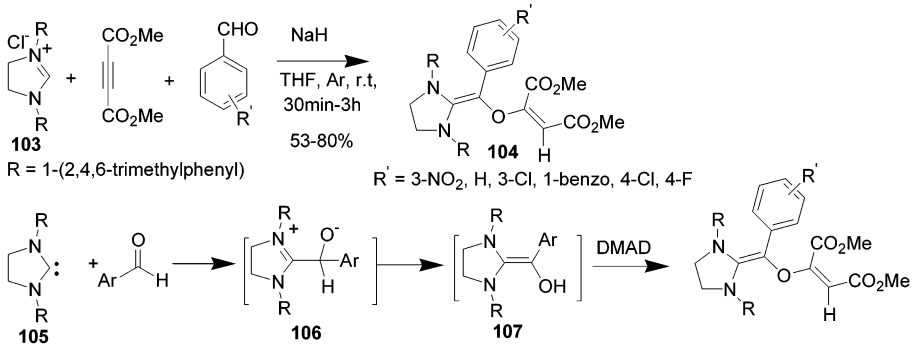
### 3.1.5. Addition to Tetrazines

As with the ambiphilic oxyphenylcarbene mentioned in section 2, *N*-heterocyclic carbenes react with tetrazines to form isopyrazole derivatives via [4 + 1]-cycloaddition followed by [4 + 2]-cycloreversion. The outcome of these reactions depended upon the substituents on the tetrazines. As expected, both the reactions of 1,2,4-triphenyltriazol-5-ylidene **91**[37] and 1,3-diphenylimidazol-2-ylidene **115**[42] with 3,6-diphenyltetrazine afforded the spirocyclic system **126** and **127** in excellent yields (Scheme 24). However, the reactions between the 1,3-diarylimidazol-2-ylidene and 3,6-dimethylthiotetrazine **130** or bis(trifluoromethyl)tetrazine **36** are not as efficient as those above. While the spirocycles **131** were formed in moderate yields from the former tetrazine, in the latter case chiral tetracyclic compounds **133** were produced with high diastereoselectivity via the further cyclization of the spirocycles (Scheme 25).[43]

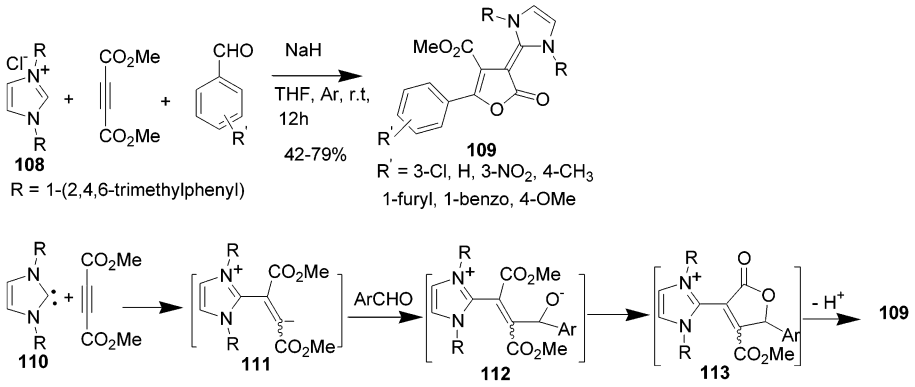
### 3.1.6. Addition to Isocyanates and Isothiocyanates

A recent study[44] showed that N-heterocyclic diaminocarbenes, derived from 2-trichloromethyl-1,3-imi-

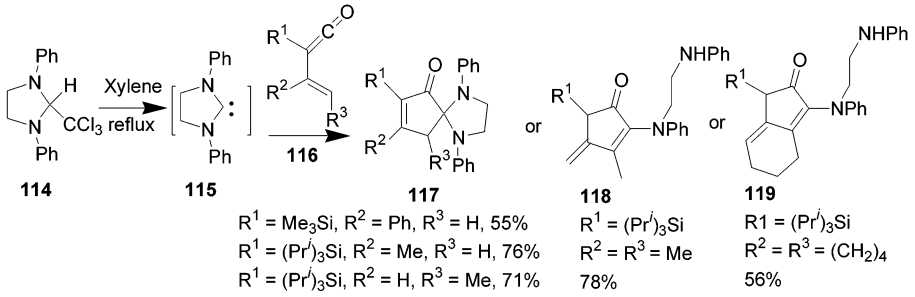
**Scheme 20**



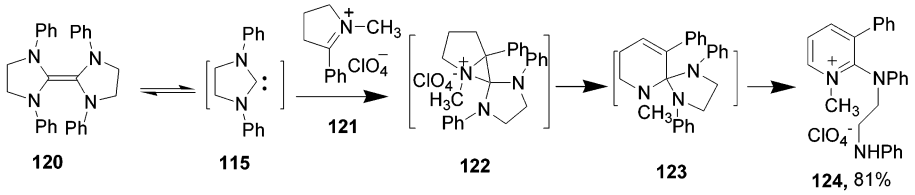
**Scheme 21**



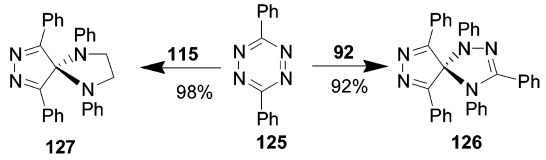

**Scheme 22**




**Scheme 23**




**Scheme 24**

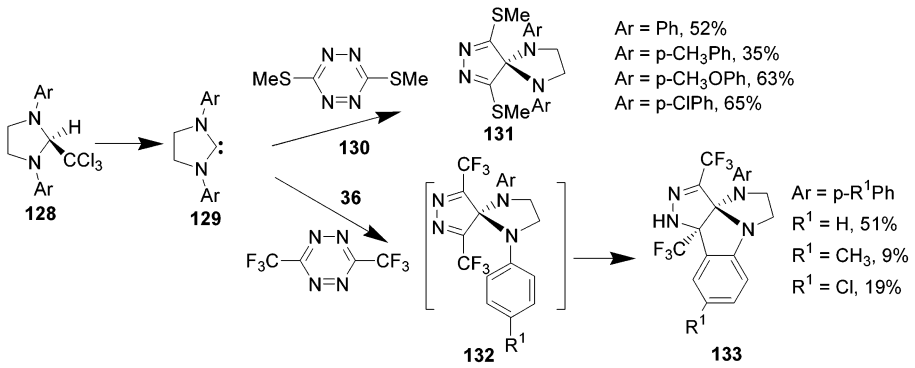



dazolidines **114** and **145**, undergo [4 + 1]-cycloadditions with vinyl isocyanates to afford hydroindolones in moderate yields. No further insertion of the carbene into the N−H bond of the hydroindolone was observed in all cases, probably due to the significant steric hindrance in the vicinity of the carbene center.

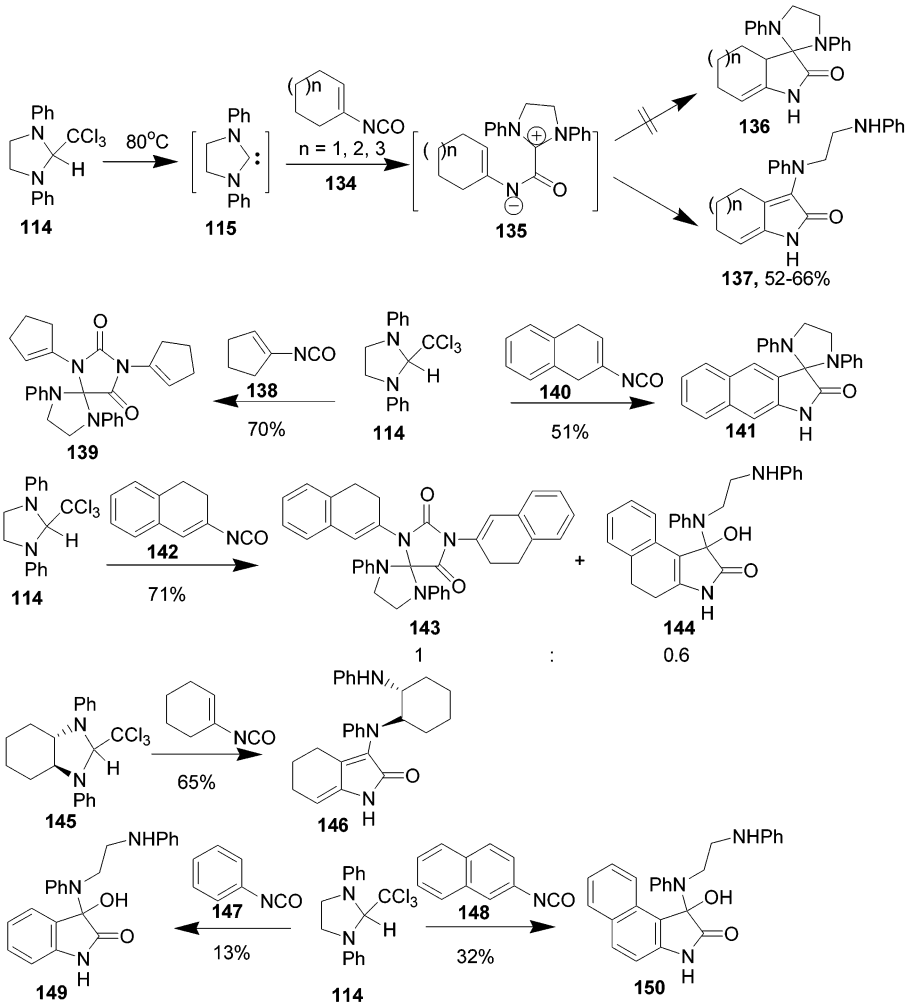
Another distinctive feature of the reaction is the production of an enamine **137** rather than the alternative aminal **136** in most instances. The minor carbinolamine **144** isolated from benzocyclohexenyl isocyanate became the major product type in the reactions of both phenyl and naphthyl isocyanates with the same carbene, giving **149** and **150,** respectively. A possible mechanism for the production of the carbinolamines is the trapping of the intermediate iminium ion with water present in the reaction mixture (Scheme 26).

The earliest reports of the interaction of nucleophilic carbenes with isocyanates were those of Hoff-

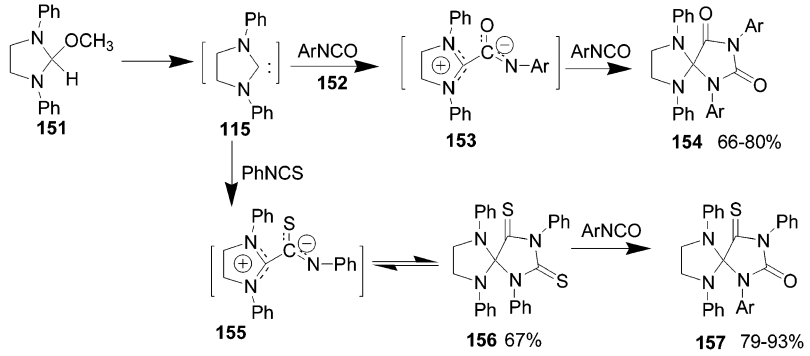
**Scheme 25**



**Scheme 26**



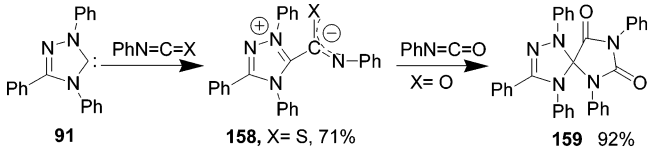
**Scheme 27**



mann and co-workers.[45] 1,3-Diphenylimidazolidinylidene **115**, which was generated by α-elimination of 2-methoxydiphenylimidazolidine **151**, added to 2 mol of aryl isocyanates or phenyl isothiocyanate to yield spiro hydantoins **154** or dithiohydantoins **156** in good yields. When the dithiohydantoins **156** reacted with isocyanates, the monothiohydantoins **157** were obtained. These results confirmed the product **156** was in equilibrium with its dipolar precursor **155** (Scheme 27).

The dipolar adduct **158** of stable diaminocarbene triazol-5-ylidene **91** to phenyl isothiocyanate was isolated in high yield. However, the similar intermediate from phenyl isocyanate was not isolable even

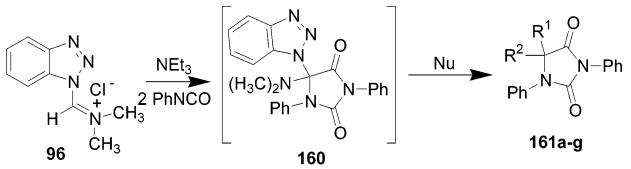
**Scheme 28**



using an excess of the carbene but underwent a second addition to phenyl isocyanate to form the spiro hydantoin **159** in excellent yield (Scheme 28).[37]

The existence of *N*,*N*-dimethylaminobenzotriazolylcarbene **97**[38] was evidenced by deprotonation of the iminium salt **96** in the presence of phenyl isocyanate. The reaction of carbene **97** with isocyan-

**Scheme 29**




**a**, Nu = $H_2O$; $R^1$,$R^2$ = O; 67%
**b**, Nu = propylamine; $R^1$,$R^2$ = propylimino; 54%
**c**, Nu = $NEt_4SH$; $R^1$ = H, $R^2$ = H; 35%
**d**, Nu = MeOH; $R_1$ = $(CH_3)_2NH$, $R^2$ = MeO; 57%
**e**, Nu = Morpholine, $R^1$ = $(CH_3)_2NH$, $R^2$ = N-morpholinyl; 48%
**f**, Nu = $NaBH_4$, $R^1$ = $(CH_3)_2NH$, $R^2$ = H; 51%
**g**, Nu = EtMgBr, $R^1$ = $(CH_3)_2NH$, $R^2$ = Et; 56%

ate took place in the typical 1:2 cycloaddition manner. However, imidazolidinedione **161a** was isolated instead of the expected 5-(dimethylamino)-5-benzotriazolyl-1,3-diphenylhydantoin **160**. The formation of imidazolidinedione **161a** was explained by hydrolysis of the benzotriazolyl group on workup. Quenching this reaction with different nucleophiles proved to be a one-pot synthesis of various 5-substituted hydantoins **161b**−**g** in moderate yields (Scheme 29).

### *3.1.7. Addition to Phosphaalkynes*

Recently, the reactivity of N-heterocyclic carbenes toward phosphaalkynes was examined.[46−48] The behavior of two N-heterocyclic carbenes, *N*,*N*′-bis(2,2-dimethylpropyl)benzimidazolin-2-ylidene **162** and 1,3,4,5-tetramethylimidazol-2-ylidene **168**, toward *tert*-butylphosphaalkyne **163a** or diisopropylaminophosphaalkyne **163b** proved to be quite different.

The reactions of carbenes **162** or **168** with *tert*-butylphosphaalkyne **163a** were complete after 2 days at room temperature and afforded the triphosphole derivatives **166** or **169** in 92% or 68% yield, respectively. The structure of **166** was established unequivocally by X-ray crystal structure analysis, while compound **169** was characterized by comparison of the NMR data with those in the literature. The same product, **169**, was also obtained by treating carbene **168** with 2,4,6-tri-*tert*-butyl-1,3,5-triphosphabenzene, a reversible trimer of the phosphaalkyne.[49]

Under comparable conditions, the reaction between **162** and **163b** took only 15 min, during which time the air-sensitive 1,2,3-triphosphetene **167** crystallized out as the sole product (90%).

The formation of the two triphospholes, **166** and **169**, and 1,2,3-triphosphetene **167** was accounted for by the nucleophilic addition of the carbenes to the carbon atoms of the phosphaalkyne triple bond. By contrast, **168** attacked the phosphorus atom of the phosphaalkyne **163b** and formed a new aminophosphorus carbene intermediate **170**, which underwent a C−H insertion into the adjacent *N*-methyl group to form the bicyclic product **171** in good yield (Scheme 30).

## 3.2. Nitrogen, Oxygen-Substituted Carbenes

As with diaminocarbenes, this is a well-studied carbene type.

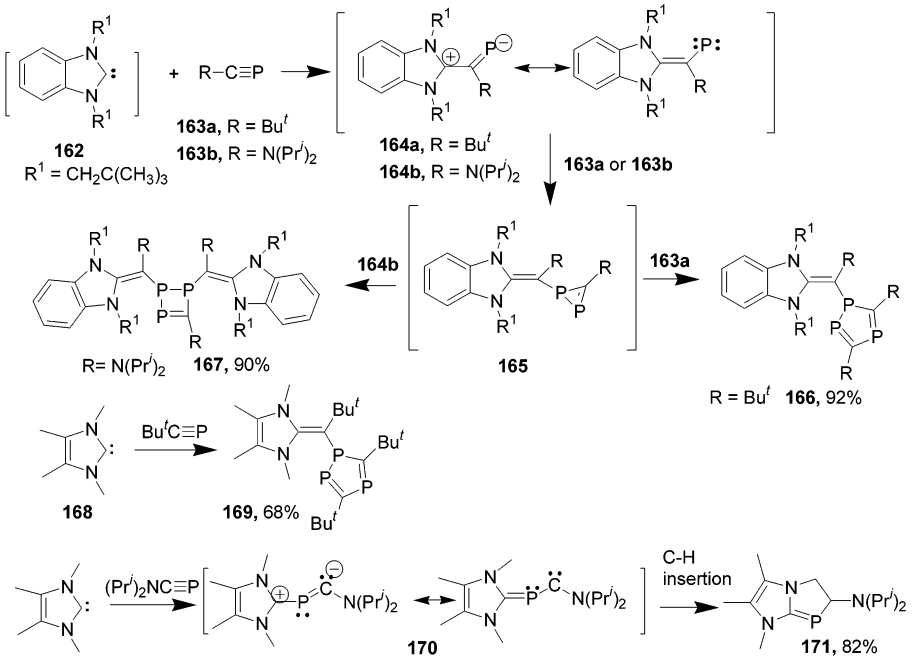
### *3.2.1. Addition to Carbon–Carbon Triple Bonds*

The most efficient method for the generation of cyclic aminooxycarbenes is the thermolysis of 2-alkoxy-2-amino-1,3,4-oxadiazolines **172**. *N*-Acyloxazolidinylcarbenes[50,51] added to the triple bond of methyl propiolate or dimethyl acetylenedicarboxylate to form oxazolinyl-substituted esters **173** as the major product. In the latter reaction this was accompanied by minor amounts of the dihydrofuran **174**. The esters **173a** and **173c** decomposed during chromatographic purification (Scheme 31).

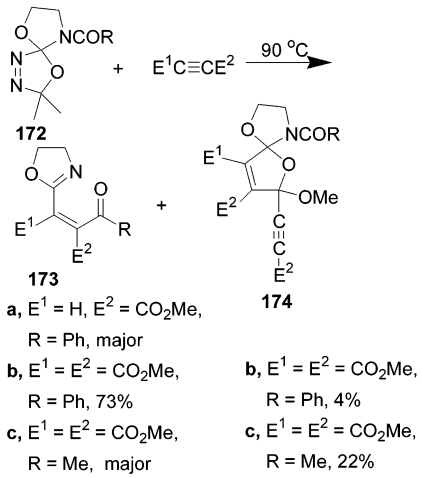
### *3.2.2. Addition to Tetrazines*

Amide acetals are useful precursors of acyclic aminooxycarbenes. By heating a mixture of *N*,*N*-

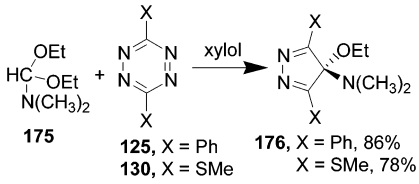
**Scheme 30**



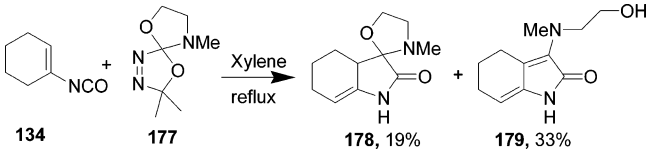
**Scheme 31**




**Scheme 32**




**Scheme 33**




dimethylformamide diethylacetal and diphenyltetrazine or bis(methylthio)tetrazine in xylene, 4-(dimethylamino)-4-ethoxy-3,4-bis(methylthio)-4*H*-pyrazoles **176** were obtained in good yield by way of [1 + 4]-addition and nitrogen elimination (Scheme 32).[20,52]

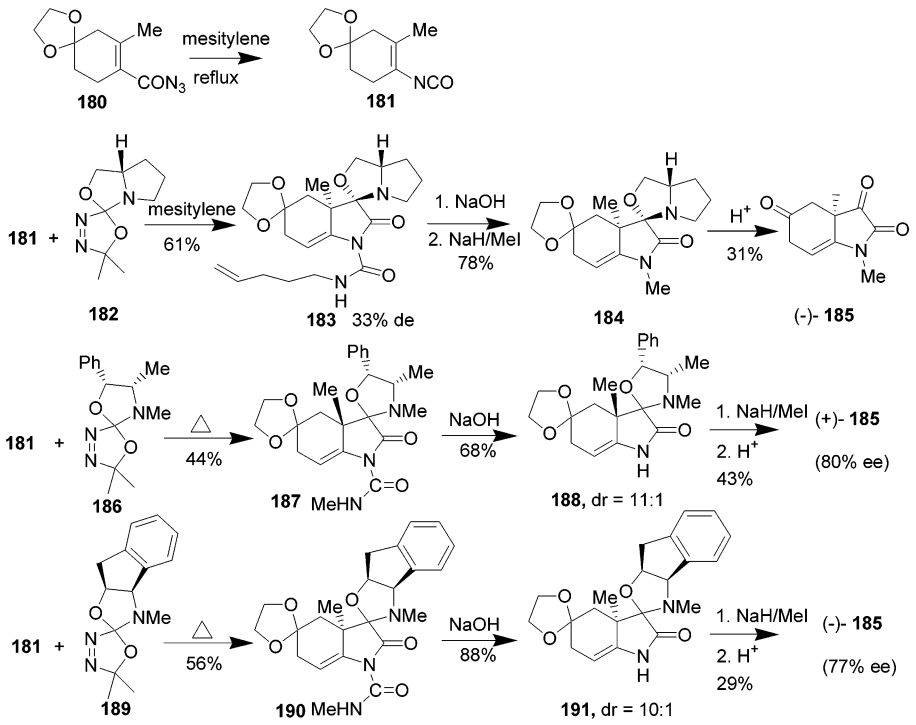
### *3.2.3. Addition to Isocyanates or Isothiocyanate*

When heated at 100 °C in toluene, the reaction of the *N*-methyloxazoline-derived aminooxycarbene with cyclohexenyl isocyanate gave a complex mixture of products. However, performing the same reaction in refluxing xylene resulted in two 1:1 adducts, the hydroindolones **178** and **179** (Scheme 33).[53]

To form the hydroindolone ring with asymmetric induction, the reaction between chiral carbenes and vinyl isocyanates has been investigated.[54] Although the asymmetric induction of chiral aminooxycarbenes precursor **182** was disappointing, encouraging diastereomeric excesses were obtained from chiral oxadiazolines **186** and **189**. Interestingly, while the dextrorotatory product was preferentially formed from the carbene precursor **186**, the levorotatory compound was produced in excess with comparable efficiency by using **189** as the chiral agent. The ultimate synthetic utility of this methodology was dependent upon the ease of removal of the chiral auxiliary from the initial cycloadduct. It proved readily removable hydrolytically, giving, for example, the enantiomerically pure hydroisatin **185** (Scheme 34).

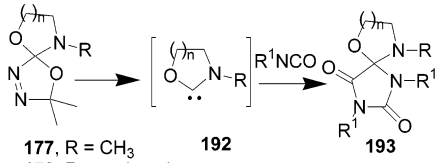
Almost 40 years ago, Hoffmann's group studied the activities of dimethylaminomethoxycarbene toward aryl isocyanates or phenyl isothiocyanate. They found that dimethylaminomethoxycarbene proved to be much more reactive toward aryl isocyanates, giving hydantoins in high yields. By contrast, dithiohydantoins were formed in very low yield.[55] Thirty years later, Warkentin and co-workers systematically investigated the reactions between the cyclic aminooxycarbenes **192**[50−52] and methyl or phenyl isocy-

**Scheme 34**



anate. All the reactions examined gave the spiro hydantoins **193** in moderate to good yields (Scheme 35).

**Scheme 35**

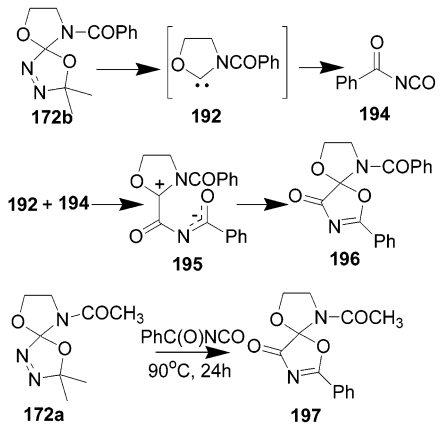


**177**, R = $CH_3$ **192** **193**
**172**, R = carbonyl

| | |
|---|---|
| n = 1, R = $CH_3$, $R^1$ = Ph | 27% |
| n = 1, R = $CH_3$, $R^1$ = $CH_3$ | 44% |
| n = 1, R = C(O)$CH_3$, $R^1$ = Ph | 87% |
| n = 1, R = C(O)Ph, $R^1$ = Ph | 76% |
| n = 1, R = C(O)C($CH_3$)=$CH_2$, $R^1$ = Ph | 72% |
| n = 2, R = C(O)Ph, $R^1$ = $CH_3$ | 78% |

In thermolyses[56] of *N*-benzoyl spiro-fused 2-alkoxy-2-amino-1,3,4-oxadiazoline **172b**, an unstable white solid was obtained. Purification by radial chromatography proved impossible, and it did not survive GC. However, it was possible to identify it as the spiro heterocycle **196** by use of IR, NMR, and mass spectroscopies**.** The formation of **196** presumably arose from nucleophilic attack of the carbene **192** on benzoyl isocyanate **194** (itself generated from the carbene), followed by cyclization of the dipolar intermediate **195**. In support of this mechanism, thermolyses of *N*-acetyl-2-alkoxy-2-amino-1,3,4-oxadiazoline **172a** with benzoyl isocyanate gave another unstable compound **197**, the spectroscopic data of which was similar to that of **196** (Scheme 36).

**Scheme 36**



## 3.3. Nitrogen, Sulfur-Substituted Carbenes

### *3.3.1. Addition to Tetrazines*

The chemistry[57] of singlet cyclic aminothiocarbenes, typified by 3-methyl-2,3-dihydro-1,3-benzothiazole-2-ylidene **199**, is much more complex than that of its analogues mentioned above. The carbenes are generally obtained by elimination of HX from a 2-X-substituted benzothiazoline, X being, for example, CN, piperidino, etc.

From the reaction of aminothiocarbene **199** with bis-trifluoromethyl-substituted tetrazine **36** or with bis(methylthio)-substituted tetrazine **130**, two different types of pyrazolobenzothiazine **201** or **203** were isolated, respectively. The formation of these two tricyclic compounds was explained by [1,5]-sigmatropic rearrangement of the thiazole sulfur atom of the spiro intermediates **200**.

By contrast, the reaction of the carbene **199** derived from cyano- or piperidinobenzothiazoline **198a**,**b** with diphenyltetrazine was different from the above and also dependent upon the carbene precursor (Scheme 37). Clearly this area needs further study.

Hoffmann[45] and co-workers compared the reactions of aryl isocyanates with aminothiocarbene **199** and diaminocarbene **115**. Although the reactions between these two carbene types and isocyanates followed the same course, their reactivities proved to be quite different. In contrast to the reactions between diaminocarbene **115** and aryl isocyanates or phenyl isothiocyanate, which gave hydantoins or dithiohydantoin in similar yields, the aminothiocarbene **199** were much more reactive toward aryl isocyanates than with phenyl isothiocyanate and formed hydantoins in 60−74% yields but only afforded 18% of dithiohydantoin. This result was paralleled by the action of aminooxycarbenes with isocyanates.[55]

The 2-thiadiazolidinylidene aminothiocarbenes **208**, derived by deprotonation of 1,3,4-thiadiazolium salts **207**, were trapped with aromatic isocyanates leading to the formation of the spiro heterocycles **209** in good yields (Scheme 38).[58]

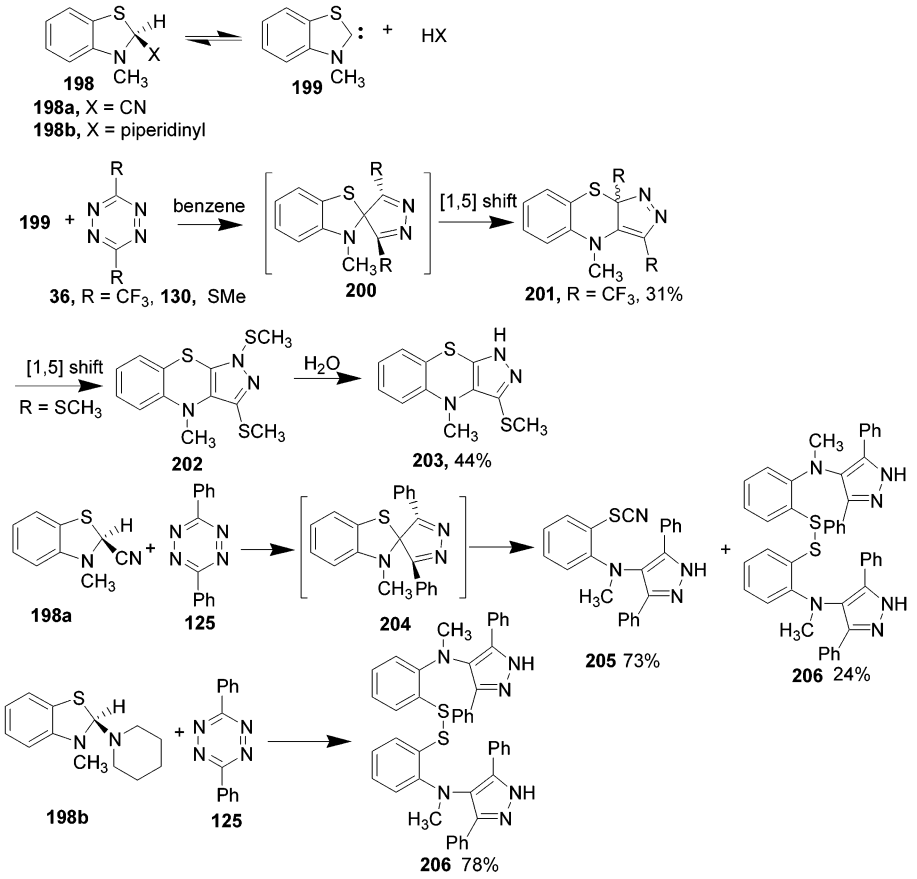
## 3.4. Nitrogen, Chlorine-Substituted Carbenes

The aminochlorocarbene intermediates were first mentioned by Böhme's group in his examination of the deprotonation of Vilsmeier reagents with Hünig's base.[59] They isolated the *sym*-dimethylaminodichloroethene and -diphenylaminodichloroethene, which were considered to be the dimers of dimethylaminochlorocarbene and diphenylaminochlorocarbene, and investigated the substitution reaction of these novel ethenes by nucleophiles.

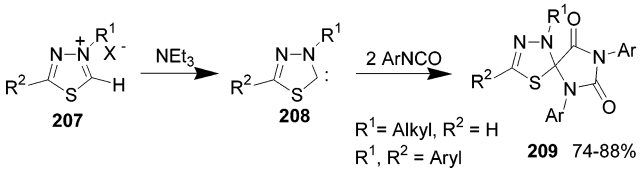
In 1996, during a study of the interaction of Vilsmeier reagents with *N*,*N*-dimethylanilines, we isolated minor amounts of the supposed dimers **213** of the arylaminochlorocarbenes **212** (actually, they are the product of reaction of the carbene with the Vilsmeier reagent), together with indolo[3,2-b]quinolinium salts **214**, 2,2-bisindoles **215,** and isatins **216** (Scheme 39).[60] Further studies utilizing Hünig's base in place of the anilines allowed efficient formation of each of these products.

The indolo[3,2-b]quinolinium salts **214** were shown to derive from the further interaction of the dimers **213** with Vilsmeier's reagents by isolating the same products from the reactions of the 'dimers' and the Vilsmeier reagents. The indolo[3,2-b]quinolinium salts **214** could be further converted into indolo[3,2-b]quinoline **217** or indoloquinolone **218** by ready demethylation or hydrolysis (Scheme 40).[61] The bisindoles **215** could also be argued to be products of the interaction of the dimers with Vilsmeier's reagents.[61] However, in a more recent study, it was shown that treatment of the dimer with acid formed the bisindole.[62]

**Scheme 37**



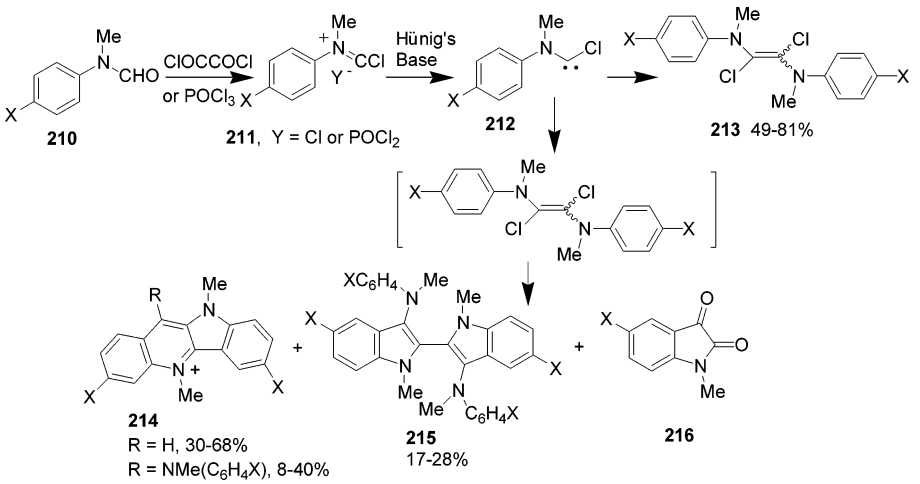

**Scheme 38**



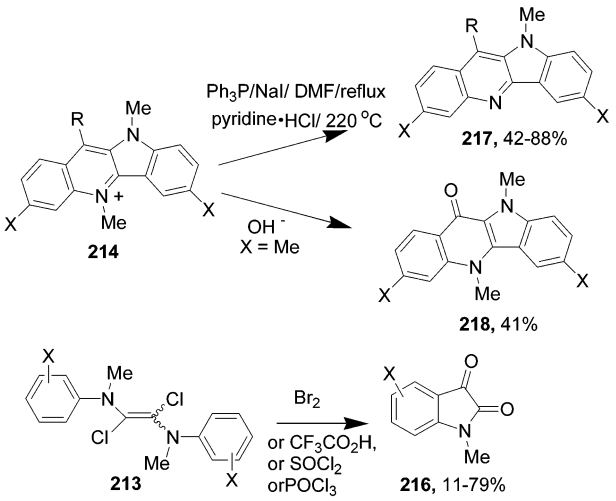

The formation of the isatins **216** was shown to be due to the action of an electrophile on the dimers, and this discovery has resulted in a simple, efficient route to isatins. The optimal electrophile proved to be bromine (Scheme 40).[63] Recently, we also discovered that these unstable arylaminochlorocarbene dimers could be prepared in good yields at low temperature and that they cyclized to give 2-chloro-3-arylaminoindoles **219** at high temperature (Scheme 41).[64]

To study the reactivity of arylaminochlorocarbenes themselves rather than their derived dimers and find new applications of them in construction of novel heterocycles, we have now developed a method for their construction that avoided their being trapped by Vilsmeier reagent. This has allowed, for example, the intermolecular reaction of arylaminochlorocarbenes **212** with diethyl acetylenedicarboxylate. For example, arylaminochlorocarbenes bearing an electron-donating group on the phenyl ring, such as methoxy

**Scheme 39**



**Scheme 40**




or methyl, reacted to form quinolines **225**, the 1:2 adducts of carbenes to diethyl acetylenedicarboxate (Scheme 42).[65]

The similar halogen-substituted phenylaminochlorocarbenes **226** preferred to add to oxalyl chloride and yielded benzo[1,4]diazepines **236** under the same conditions. The diazepines were formed optimally from the arylaminochlorocarbenes and oxalyl chloride by using an excess of oxalyl chloride and in the absence of DEAD (Scheme 43).[65,66]

## 3.5. Dioxygen-Substituted Carbenes

### *3.5.1. Addition to Carbon–Carbon Double or Triple Bonds*

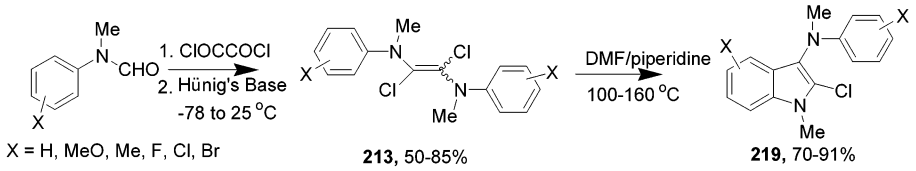
The additions of dimethoxycarbene **245** to cyclopropylmethylene-1-carboxylates **238** gave 1,3-dioxolane **240** together with 1,1-dimethoxycyclobutanes **239.** The products were derived from the dipolar intermediate **246**, generated by nucleophilic attack of the dimethoxycarbene at the carbon−carbon double bond of cyclopropylmethylene-1-carboxylates **238** (Scheme 44).[67]

The cyclization of (alkynyl-1-oxy)-alkoxycarbenes has been extensively studied by Warkentin's group.[68−70] The (alkynyl-1-oxy)methoxycarbenes **250**, generated by thermolysis of the corresponding oxadiazoline precursors **249**, cyclized by carbene attack of the C−C triple bond, leading to a new carbene. The endocyclic or exocyclic 3,3-dialkoxyvinylcarbenes **252** or **254** apparently form by way of the highly strained dialkoxycyclopropene **251**.

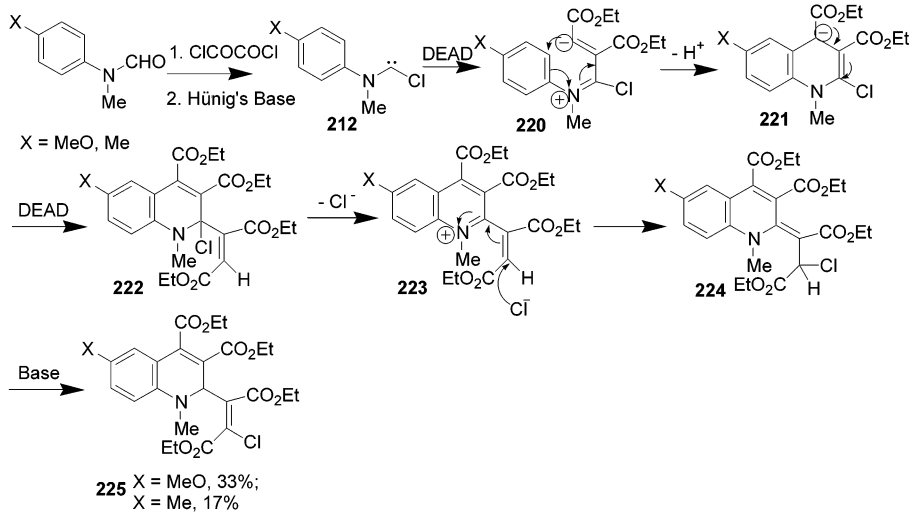
It was found that the alkyne substituent controlled the regioselectivity of the dialkoxycarbene cyclization. A hydrogen or methyl substituent led to formation of the endocyclic vinylcarbene, while an ester substituent preferred exocyclic carbene formation. The 3,3-dialkoxyvinylcarbene **252** and **254** can be trapped by an alcohol, which afforded pyrans **253** or furans **255** (Scheme 45).[69,70] 3,3-Dialkoxyvinylcarbenes behave as highly efficient 1,3-dipoles in their reactions with electron-deficient olefins.[71] Thermolysis of the oxadiazoline precursors **249c** and **249d** in the presence of benzylidenemalononitrile or DMAD led to exocyclic vinylcarbenes which underwent [3 + 2]-cycloaddition with benzylidenemalononitrile or DMAD to form bicyclic heterocycles **256**−**260** in good yields (Scheme 46).[69]

If the oxadiazoline **249a**[68] was heated in toluene for 30 h alone, a very strained tricyclic cyclobutanone ketal **264** was formed in 74% yield. A mechanism was postulated including addition of 3,3-dioxyvinylcarbene to acetone as a key step. The intermediate **252a** reacted with the acetone, formed earlier in the

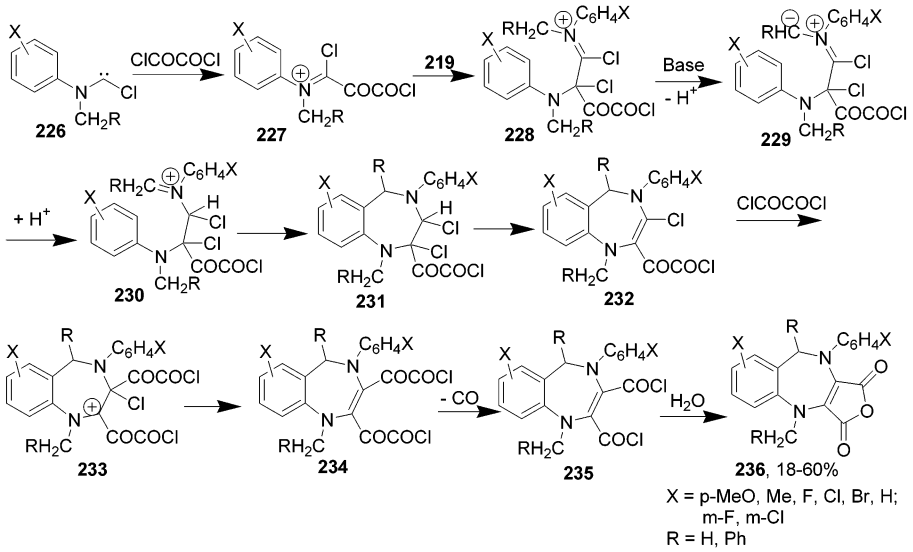
**Scheme 41**



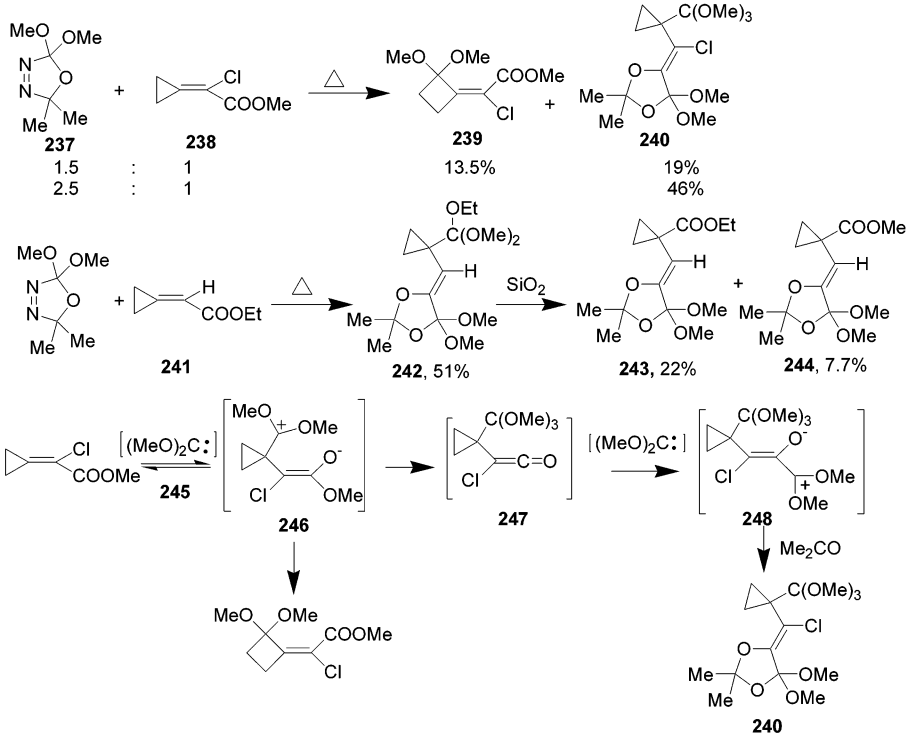

**Scheme 42**



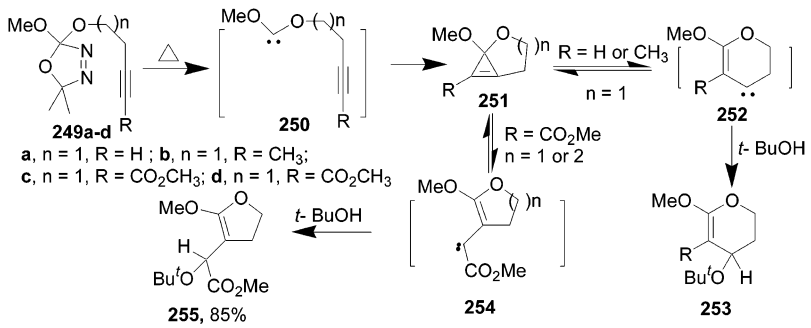
**Scheme 43**




**Scheme 44**

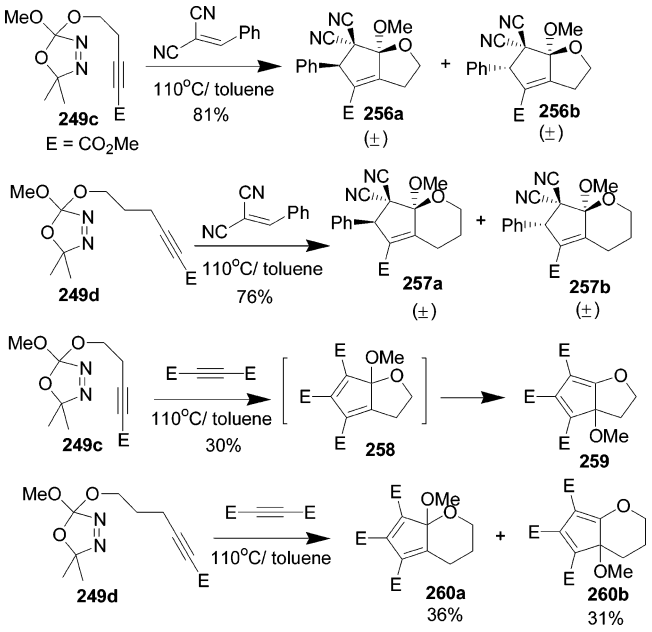



**Scheme 45**



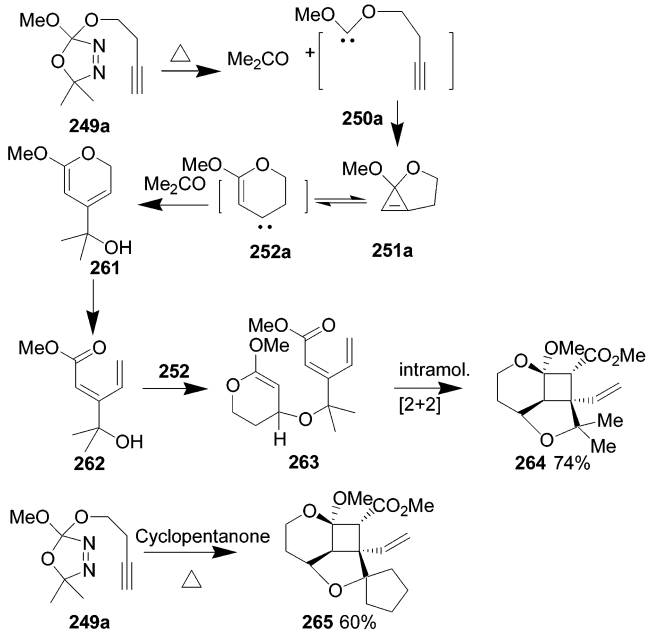

decomposition of **249a**, to afford alcohol **261** and then **262**. The dienone **262** reacted rapidly with carbene **252a** to give **263** by OH insertion. The intramolecular [2 + 2]-cycloaddition between the electron-rich enediol diether and the α,β-unsaturated ester group of **263** produced tricyclic compound **264**.

**Scheme 46**




The thermolysis of **249a** in the presence of a large excess of cyclopentanone afforded the spirocyclic product **265** (60%), which supported the trapping of carbene **252a** by acetone (Scheme 47).

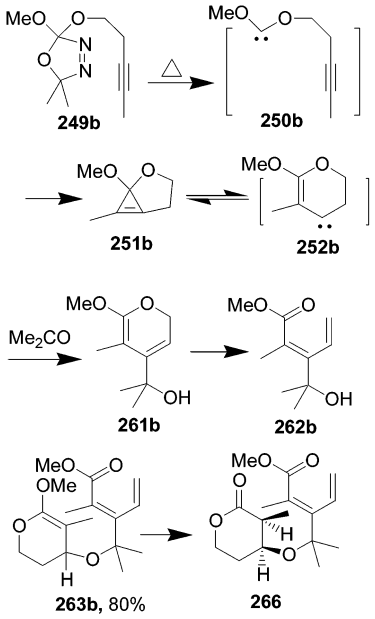
**Scheme 47**




Interestingly, the methyl-substituted analogue **249b** of **249a** did not produce a tricyclic compound under the same conditions.[69] Upon thermolysis of **249b** in benzene, only one identifiable product was found, shown to be the ketene acetal **263b**. As further evidence of the structure, **263b** was hydrolyzed to give lactone **266** (Scheme 48). The isolation of **263b** gave powerful support for the mechanism illustrated in Scheme 47.

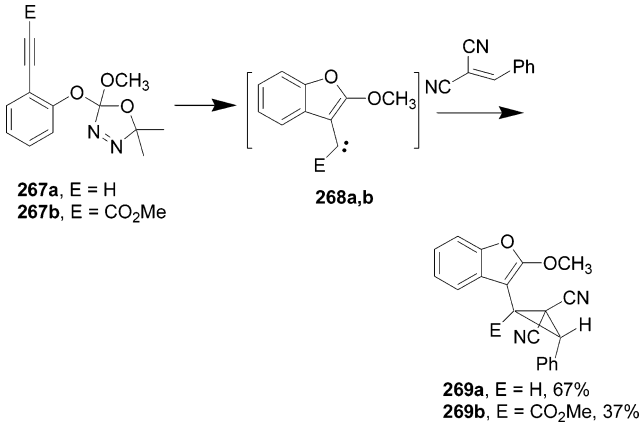
The aryloxymethoxy analogues of **249**[70] are strikingly different from those reported above. Thermolysis of aryloxymethoxy-substituted oxadiazolines **267a** or **267b** in the presence of benzylidenemalononitrile

**Scheme 48**




led to the formation of one major product **269** in 67% or 37%, respectively (Scheme 32). The structures of the products **269a** and **269b** were assigned by spectroscopy data and X-ray crystallography of the latter compound and shown to be classical carbene-derived cyclopropanes. They were formed by the addition of an exocyclic vinylcarbene to the benzylidenemalononitrile double bond. Presumably the vinylcarbenes **268** have less 1,3-dipole character than their dialkoxy analogues and therefore are more likely to behave as typical localized carbenes to give [1 + 2]-adducts with alkenes (Scheme 49).

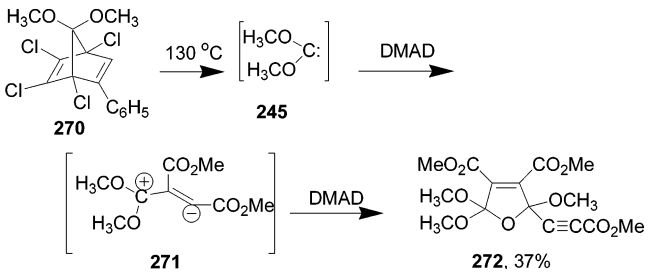
**Scheme 49**




The first study of the addition of nucleophilic carbenes to acetylenedicarboxylate was the pioneering work of Hoffmann in 1974.[72] From the reaction of the dimethoxycarbene **245**, derived from precursor **270**, with dimethyl acetylenedicarboxylate, a dihydrofuran **272** was obtained in 37% yield. The formation of **272** can be explained by nucleophilic addition of the carbene to DMAD and followed by 1,3-dipolar addition of the dipolar intermediate **271** with the carbonyl group of DMAD (Scheme 50).

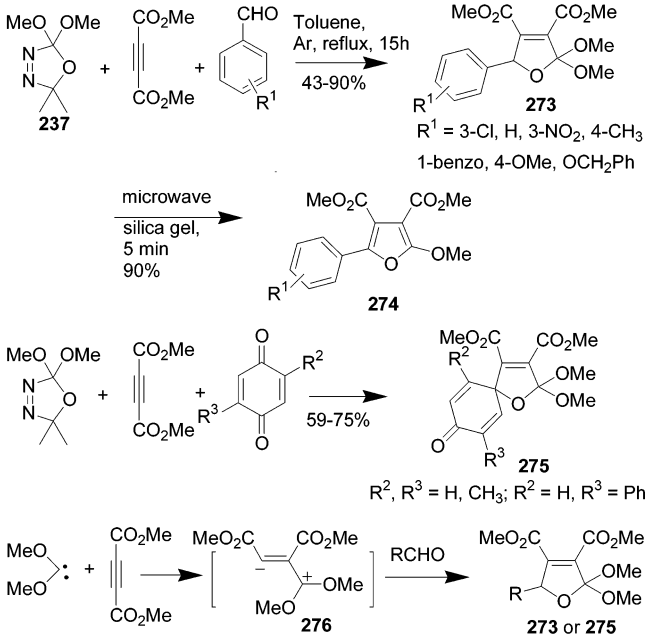
The multicomponent reactions of dimethoxycarbene with DMAD together with aldehydes or quinone

**Scheme 50**



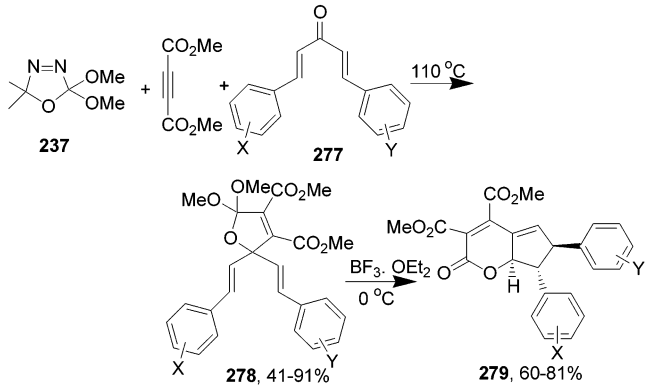

bears some relationship to the similar reactions of 1,3-dimesitylimidazol-2-ylidene **110** illustrated in Scheme 21. The dimethoxycarbene attacked the triple bond of DMAD leading to a zwitterionic intermediate **276**. Cycloaddition of the zwitterion to the carbonyl group afforded dihydrofuran derivatives **273** and **275** (Scheme 51).[73]

**Scheme 51**



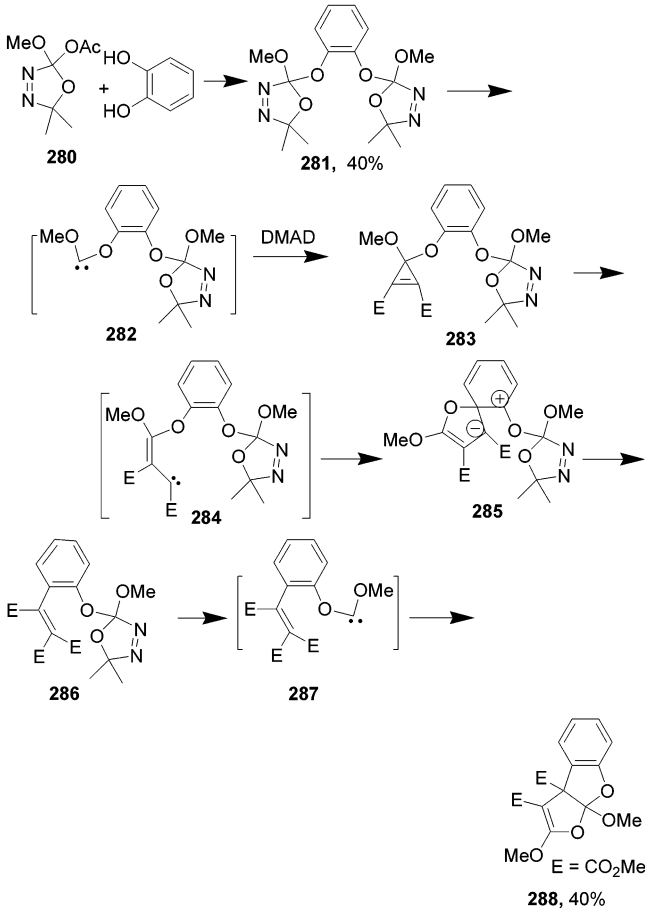

The *gem*-divinyldihydrofuran **278**, obtained in high yield from the cyclization of dimethoxycarbene with DMAD and the carbonyl groups of dienones **277**, have been used in the synthesis of bicyclic lactones **279** via an interrupted Nazarov reaction (Scheme 52).[74]

**Scheme 52**




Bis(oxadiazoline) **281**,[75] prepared from oxadiazoline **280** and catechol, reacted with dimethyl acetylenedicarboxylate upon heating in benzene to afford dihydrofuranobenzofuran **288**. A mechanism was proposed involving the nucleophilic addition of dioxycarbene **282** to DMAD, *ipso* aromatic substitution by the vinylcarbene **284**, followed by an intramolecular [4 + 1]-cycloaddition of the second dioxycarbene **287** with the unsaturated ester group (Scheme 53).

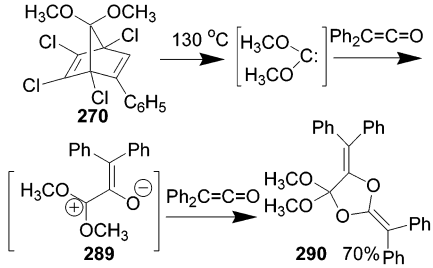
**Scheme 53**




### 3.5.2. Addition to Ketenes

In the 1970s, Hoffmann and co-workers found that dimethoxycarbene, generated by thermolysis of 7,7-dimethoxynorbornadienes **270**, yielded a 1:2 adduct **290** with diphenylketene (Scheme 54).[72]

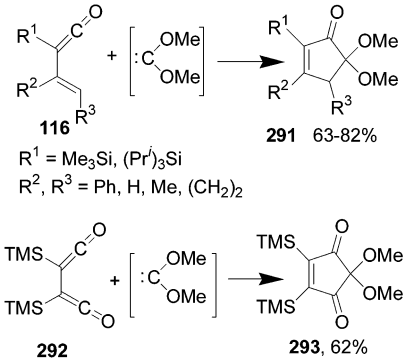
**Scheme 54**




The chemistry is quite different in the reaction of dimethoxycarbene with silyl-substituted ketenes. It

was shown that the dimethoxycarbene participated in efficient [4 + 1]-cycloadditions with (trialkylsilyl)-vinylketenes **116** or bis(trimethylsilyl)ketene **292** producing dimethoxycyclopentenones **291**[40] or dimethoxycyclopentenedione **293**, respectively (Scheme 55).[76] The formation of **291** and **293** also involves different types of silyl-substituted ketenes.

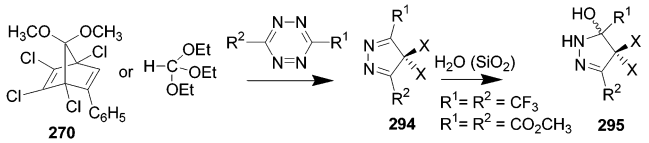
**Scheme 55**




### 3.5.3. Addition to Tetrazines

Seitz and co-workers studied the reactions between dialkoxycarbenes and various 3,6-substituted-1,2,4,5-tetrazines. It was found that the dimethoxy- and diethoxycarbene underwent [4 + 1]-cycloaddition with tetrazines, followed by a [4 + 2]-cycloreversion to afford isopyrazoles **294** or **295** in good yields (Scheme 56).[20,52]

**Scheme 56**



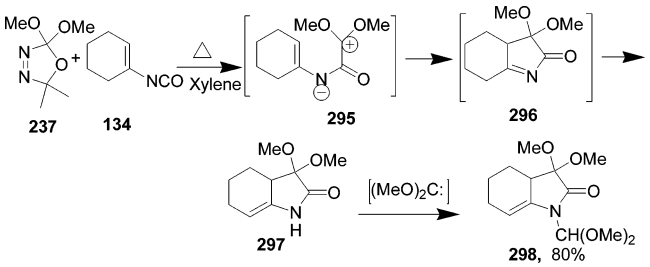

**294a** X = Y = $OCH_3$, $R^1$= $R^2$ = Ph, 85%
**294b** X = Y = $OCH_3$, $R^1$= $R^2$ = $SCH_3$, 80%
**294c** X = Y = $OCH_3$, $R^1$= $N(CH_3)_2$, $R^2$ = $SO_2CH_3$, 79%
**294d** X = Y = $OCH_3$, $R^1$= $N(CH_3)_2$, $R^2$ = $SCH_3$, 75%
**294e** X = Y = $OCH_2CH_3$, $R^1$= $R^2$ = Ph, 88%
**294f** X = Y = $OCH_2CH_3$, $R^1$= $R^2$ = $SCH_3$, 71%
**294a** X = Y = $OCH_3$, $R^1$= $R^2$ = $CF_3$,88%
**294a** X = Y = $OCH_3$, $R^1$= $R^2$ = $CO_2CH_3$,34%

### 3.5.4. Addition to Isocyanates

The reactions between dioxycarbenes and diaminocarbenes with vinyl isocyanates are somewhat different. The former reactions normally yield 2:1 adducts, while the latter were found to follow the 1:1 addition mode.

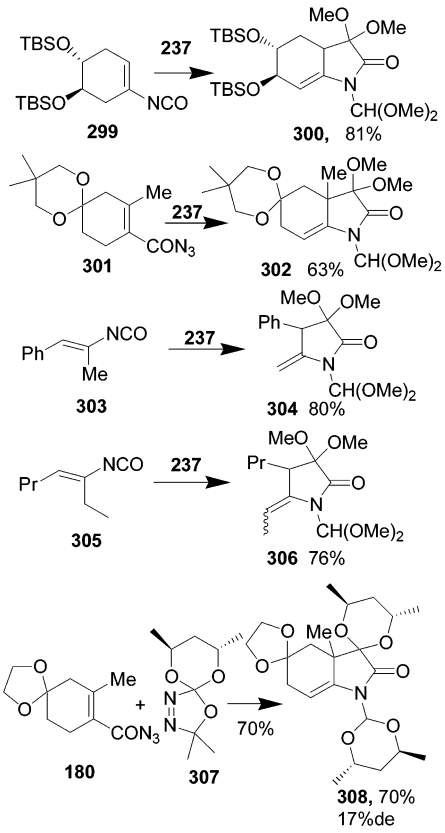
Heating of 1-isocyanatocyclohexene **134**[53] with an excess of dimethoxycarbene precursor, 2,2-dimethoxy-1,3,4-oxadiazoline **237**, afforded the hydroindolone **298** in good yields (Scheme 57). It is presumed that the hydroindolone was formed from the nucleophilic addition of dimethoxycarbene to the vinyl isocyanate N*C*O carbon, followed by cyclization. The subsequent addition of a second equivalent of carbene occurs via an NH insertion. This mechanism was supported by the isolation of N-unsubstituted hydroindolone **297**

**Scheme 57**




in low yield when a stoichiometric amount of **237** was utilized. Structurally elaborate vinyl isocyanates or acyl azides had been used in this [1 + 4]-cyclization and afforded good yields of hydroindolone products (Scheme 58).[53,54] This process was subsequently

**Scheme 58**



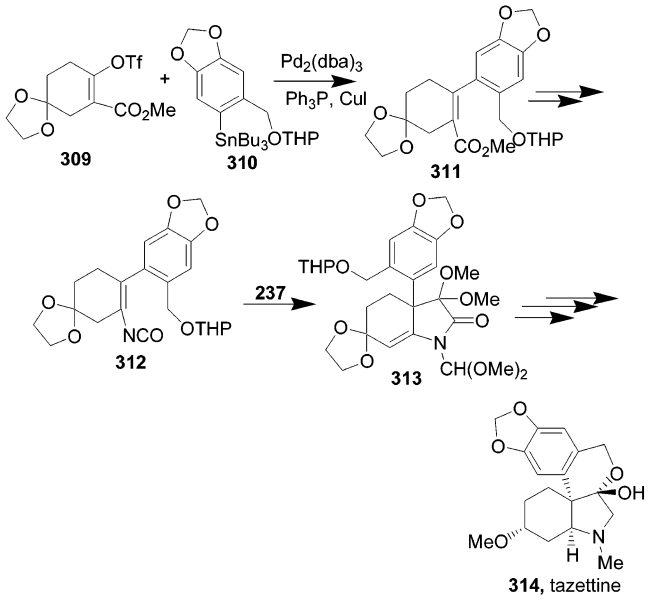

exploited as the key transformation in a total synthesis of the alkaloid tazettine (Scheme 59).[77]

The reactions between dialkoxycarbenes and aryl isocyanates or benzoyl isocyanate followed the same reaction pattern as that of aminooxycarbenes illustrated in Schemes 33 and 34. Thus, dimethoxycarbenes added to two molecules of aryl isocyanates affording 5,5-dimethoxy-1,3-diarylhydantoins **315** in 65−80% yields,[78,79] while with benzoyl isocyanate, dimethoxycarbene reacted to give 2-phenyl-4,4-dimethoxyoxazolone **316** as the major product (Scheme 60).[56]

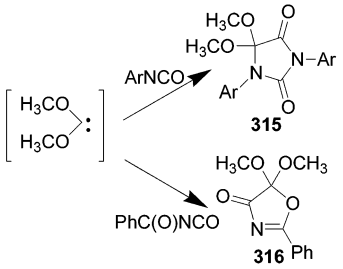
### 3.5.5. Addition to Cyclic Anhydrides

Dialkoxycarbenes[80] have been found to insert into the carbon−oxygen bond of anhydrides **317**, producing 2*H*-pyran-2,5-(6*H*)-diones **318** in moderate yields

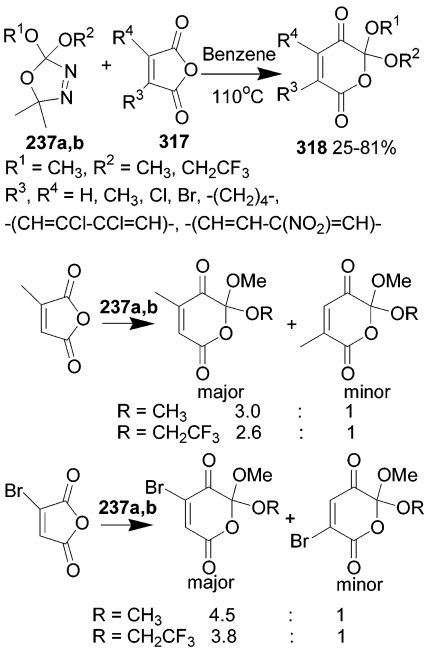
**Scheme 59**




**Scheme 60**




**Scheme 61**



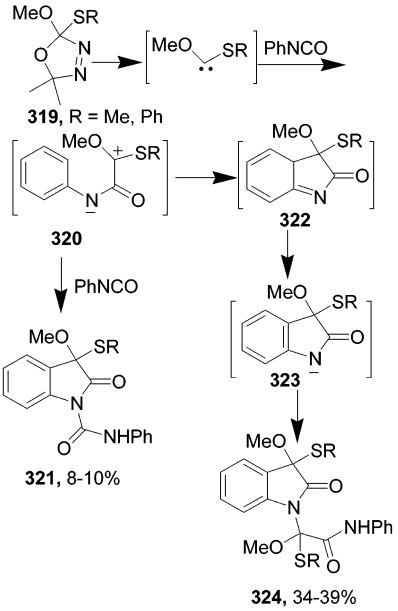

(Scheme 61). When unsymmetrical anhydrides were used as carbene traps, the major products were those in which the carbene attacked the more electron-deficient carbonyl carbon of the anhydride. For example, the bromine of bromomaleic anhydride is inductively electron withdrawing from the adjacent carbonyl group but conjugatively donating to the distant carbonyl group. The methyl group of methylmaleic anhydride is also conjugatively (by hyperconjugation) electron donating to the distant carbonyl group.

## 3.6. Oxygen, Sulfur-Substituted Carbenes

### *3.6.1. Addition to Isocyanates*

As described above, diamino-, aminoalkoxy-, or dialkoxycarbenes form hydantoin analogues by addition to phenyl isocyanate. However, it was found that the alkylthio- and phenylthiomethoxycarbenes, generated from oxadiazolines **319**, yield oxindoles **321** and **324** with phenyl isocyanate (Scheme 62).[81] The

**Scheme 62**

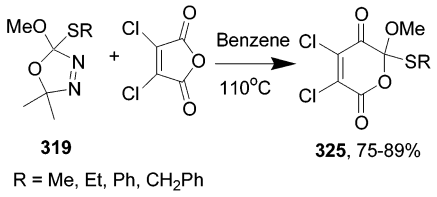



different outcome from these two types of reactions can be explained by the different stability of the dipolar intermediates. The less stable intermediate preferred to undergo intramolecular cyclization rather than intermolecular addition to another molecule of isocyanate.

### *3.6.2. Addition to Cyclic Anhydrides*

Thio-oxycarbenes react with dichloromaleic anhydride in a similar way as dioxycarbenes, leading to the pyran-2,5-diones **325** in high yields (Scheme 63).[81]

**Scheme 63**




## 3.7. Oxygen, Halogen-Substituted Carbenes

The reactivity of alkoxyhalocarbenes toward alkenes, alkynes, and alcohols has been studied experi-

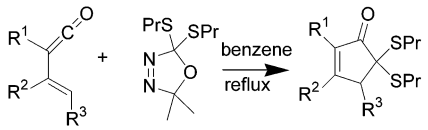
mentally and theoretically. It was found that the alkoxychlorocarbene,[82,83] chlorophenoxycarbene,[84] fluoromethoxycarbene,[85] and fluorophenoxycarbene[86] were ambiphilic carbenes, which added to both electron-rich and electronic-deficient double bonds to form cyclopropanes. However, no useful examples of the application of alkoxyhalocarbenes in construction of heterocycles have yet appeared.

## 3.8. Disulfur-Substituted Carbene

### *3.8.1. Addition to Ketene*

Dithiocarbenes and dioxycarbenes behave similarly toward vinylketenes. When a mixture of bis(propylthio)oxadiazoline **326** and (trialkylsilyl)vinylketenes **116** was heated in benzene, bis(propylthio)cyclopentenones **327** were formed in high yields (Scheme 64).[40]

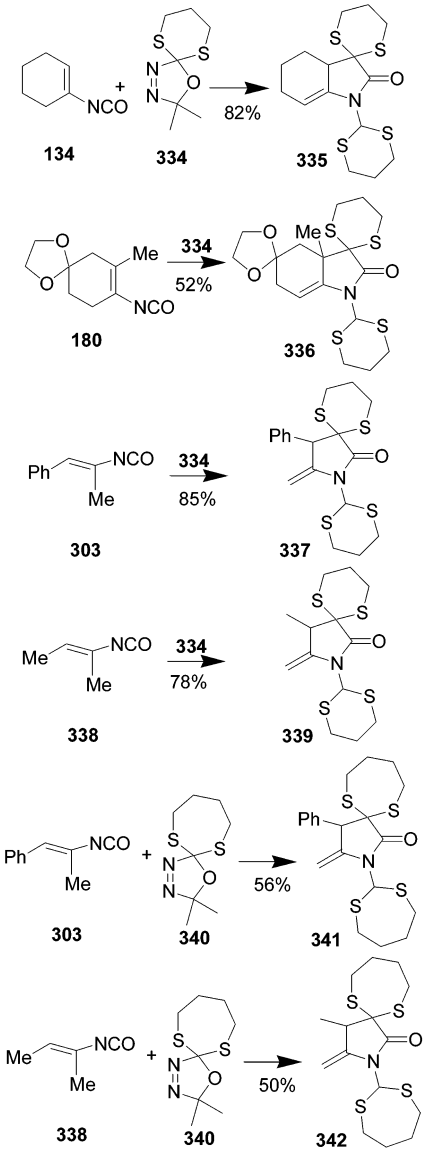
**Scheme 64**




### *3.8.2. Addition to Vinyl Isocyanates*

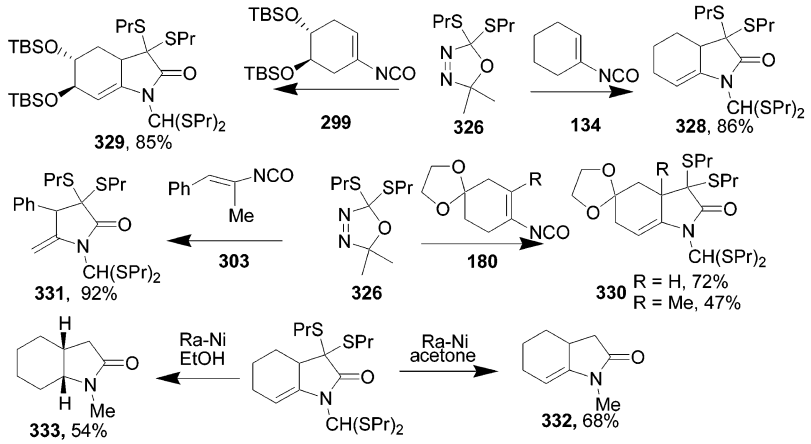
The reactions of bis(propylthio)carbene or cyclic dithiocarbenes[87,88] with vinyl isocyanates followed the same style as the dimethoxycarbenes and yielded dipropylthio-substituted hydroindolones **328**−**331** or spiro dithiohydroindolones **335**−**342** in good to excellent yield**s** (Schemes 65 and 66). The compound **328** was reduced to *N*-methyl-2-hydroindolones **332** or **333**, a motif found in many alkaloid targets such as in the crinine and erythrina families. Interestingly, when a large excess of oxadiazoline (10 equiv) was heated with the vinyl isocyanate, the reaction followed an unexpected pathway to deliver an alternative 2:1 adduct **343** or **344**. These abnormal 2:1 adducts were believed to arise from the competitive addition of a second equivalent of carbene to the initial dipolar 1:1 adduct prior to ring closure (Scheme 67).

**Scheme 66**

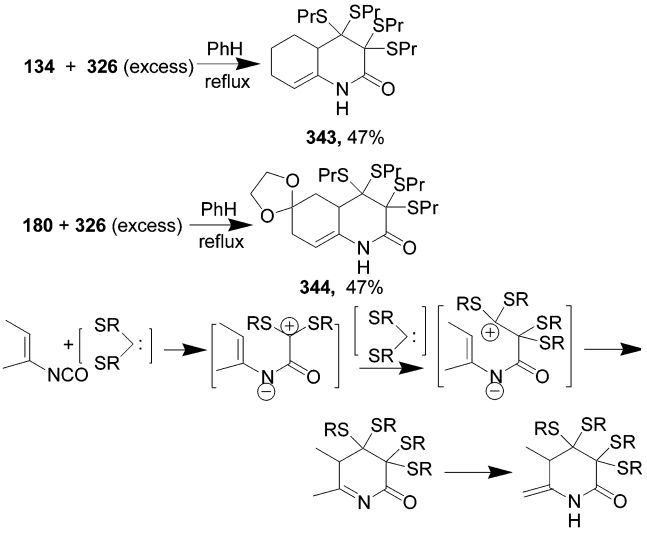



The *cis*-3*a*-aryloctahydroindole nucleus is a structural feature found in the *amaryllidaceae* and *scele-*

**Scheme 65**

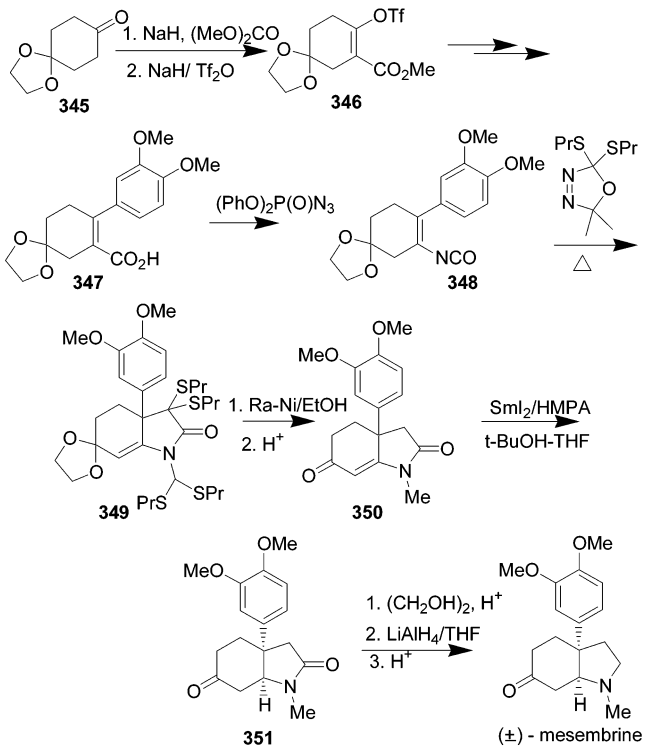


**Scheme 67**



*tium* alkaloids. The [4 + 1]-cycloaddition of bis-(alkylthio)carbenes with vinyl isocyanates provided a efficient method to generate this skeleton and therefore has been used in the total synthesis of (±)-mesembrine (Scheme 68).[89]

**Scheme 68**

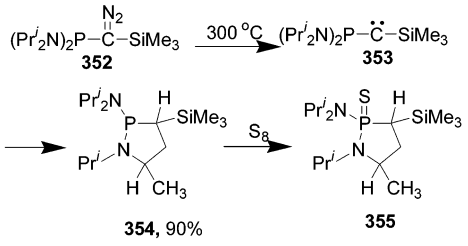


## 3.9. Phosphorus, Silicon-Substituted Carbenes

Photolysis of the phosphinosilyldiazo derivative **352** afforded the stable intermediate **353**, whose carbene character has been exemplified by its insertion into a carbon−nitrogen bond to form a mixture of four diastereoisomers of azaphospholidines **354** in 90% yield (Scheme 69).[90]

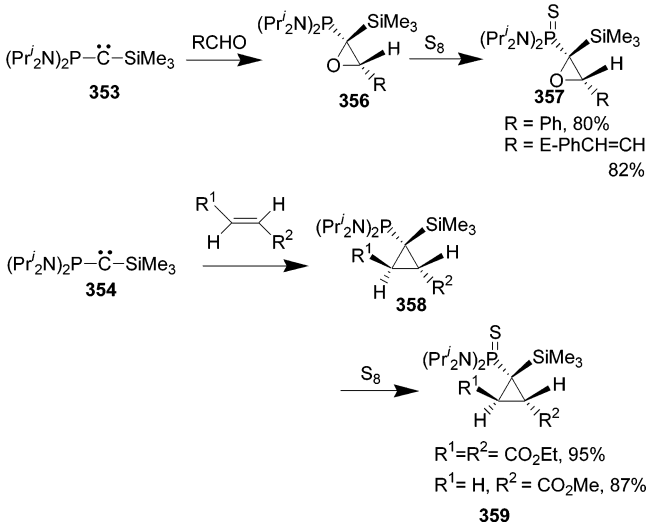
Further evidence for its carbene character was the formation of an oxirane with carbonyl groups and cyclopropanation with alkenes. Carbene **353** did not

**Scheme 69**



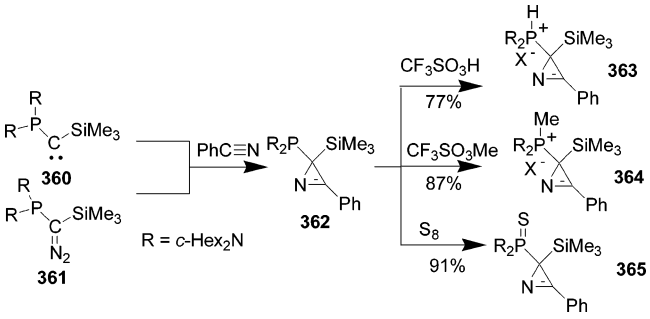
react with acetone but readily added to benzaldehyde and cinnamaldehyde, affording oxiranes **356**, which were isolated as **357** after treatment with elemental sulfur in 80−82% yields. The nucleophilicity of carbene **353** was shown in its reaction with alkenes. The carbene **353** did not add to alkyl-substituted alkenes but readily added to electrophilic olefins (Scheme 70).[91]

**Scheme 70**



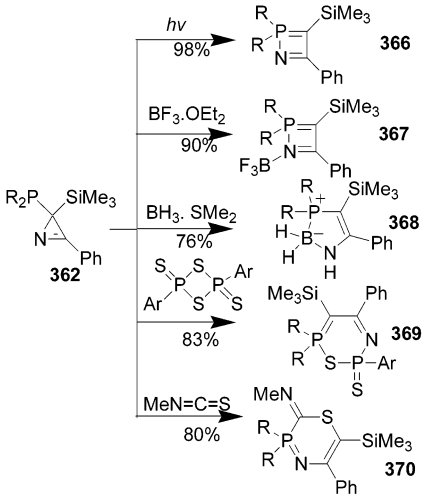
The stable (phosphino)(silyl)carbene,[92] [bis(dicyclohexylamino)phosphino]trimethylsilylcarbene **360,** reacted with benzonitrile leading to the corresponding 2-phosphino-2*H*-azirine **362** in 85% yield (Scheme 71). A stepwise mechanism, involving the initial

**Scheme 71**

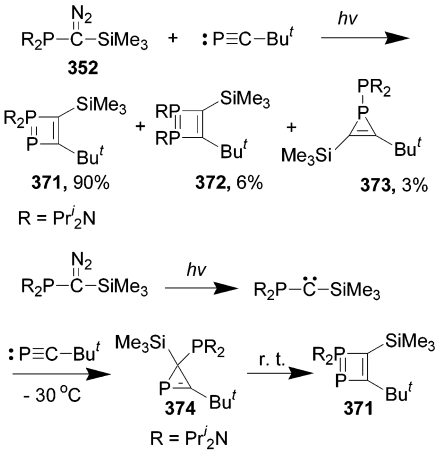


nucleophilic attack of the carbene at the carbon atom of the nitrile leading to a 1,3-dipole, or a concerted [1 + 2]-cycloaddition of carbene to the nitrile could be a reasonable pathway to the azirine. The azirine is a useful building block and formed various heterocycles **367**−**370** by treatment with different Lewis acids (Scheme 72).

**Scheme 72**

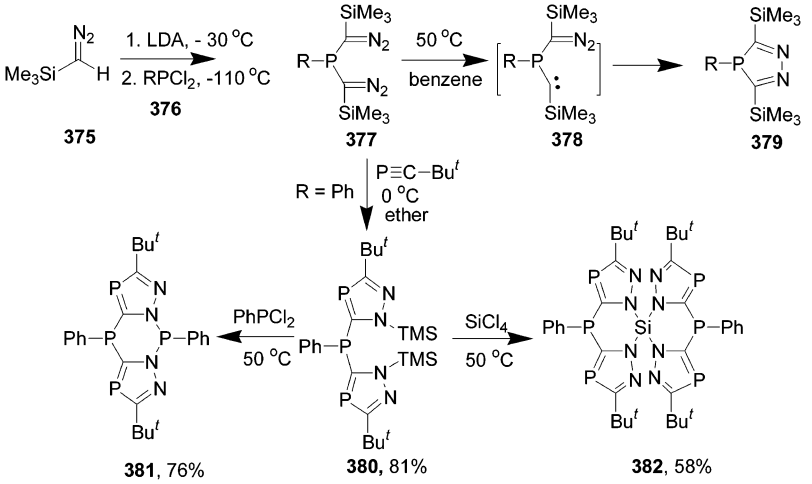



**Scheme 73**




The photolysis of [bis(diisopropylamino)phosphino]-(trimethylsilyl)diazomethane **352** in the presence of *tert*-butylphosphaalkyne afforded the 1$\lambda^5$,2$\lambda^3$-diphosphete **371** in 90% yield.[93] It was shown that the precursor of the diphosphete **371** was 2-phosphino-*2H*-phosphirene **374**, by reaction of $\lambda^3$-phosphinocarbene **353** with phosphaalkyne at lower temperature. The 2-phosphino-*2H*-phosphirene **374** rearranged into 1$\lambda^5$,2$\lambda^3$-diphosphete **371** quantitatively at room temperature (Scheme 73).[94]

**Scheme 74**




On thermal treatment, the bis(diazomethyl)phosphanes **377** (prepared by lithiation of diazo(trimethylsilyl)methane **375** followed by coupling with dichlorophosphanes **376**) eliminated nitrogen and were converted into the highly air-sensitive 4*H*-1,1,4-diazaphospholes **379**. Phosphinocarbenes **378** were assumed to be responsible for the ring closure. At lower temperature, the *P*-phenyl-substituted bis-(diazomethyl)phosphanes **377** underwent a double, regiospecific [3 + 2]-cycloaddition with phosphaalkyne and a subsequent [1,5]-sigmatropic TMS shift to give rise to the bis(diazaphopholyl)phosphane **380.** The latter compound **380** was condensed with dichlorophosphane or tetrachlorosilane resulting in the novel tricyclic compound **381** or the spiro compound **382**, respectively (Scheme 74).[95]

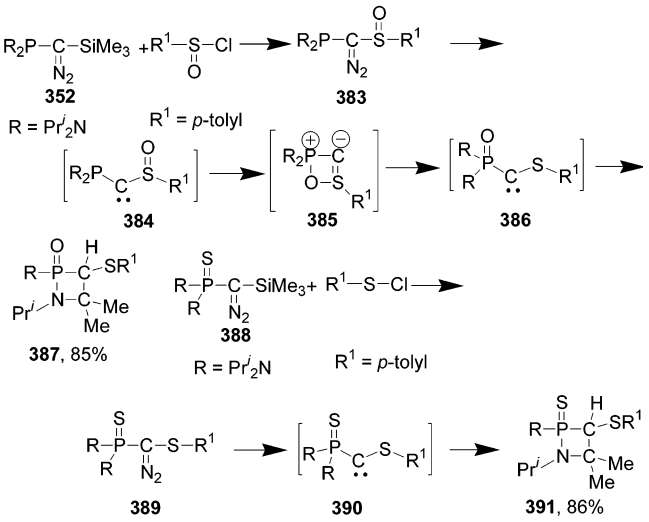
## 3.10. Phosphorus, Sulfur-Substituted Carbenes

Diazo derivatives are classical precursors of carbenes. The bis(diisopropylamino)phosphanyl](trimethylsilyl)diazomethane **352** has been shown to react with an acyl chloride with elimination of trimethylchlorosilane to form the corresponding substituted diazo compound.[96] In an attempt to prepare [bis(diisopropylamino)phosphanyl](*p*-tolylsulfinyl)-diazomethane **383** by treatment of the silylated diazo compound **352** with *p*-toluenesulfinyl chloride, the evolution of nitrogen was observed and the 2-oxo-1,2$\lambda^5$-azaphosphetane **387** was obtained in 85% yield along with a quantitative amount of trimethylchlorosilane after workup. The same product was also obtained from the reaction of **352** and *p*-toluenesulfonyl chloride in 80% yield. Similarly, the reaction between the [bis(diisopropylamino)thioxophosphoranyl](trimethylsilyl)diazomethane **388** and *p*-toluenesulfanyl chloride yielded 2-thioxo-1,2$\lambda^5$-azaphosphetane **391** in 86% yield (Scheme 75).[97] The structure of **391** was finally determined by X-ray crystallography. The formation of azaphosphetane **387** or **391** was proposed, derived from the insertion of (phosphoranyl)(sulfanyl)carbene **386** or **390** into the C−H bond of an isopropyl substituent.

## 3.11. Diphosphorus-Substituted Carbenes

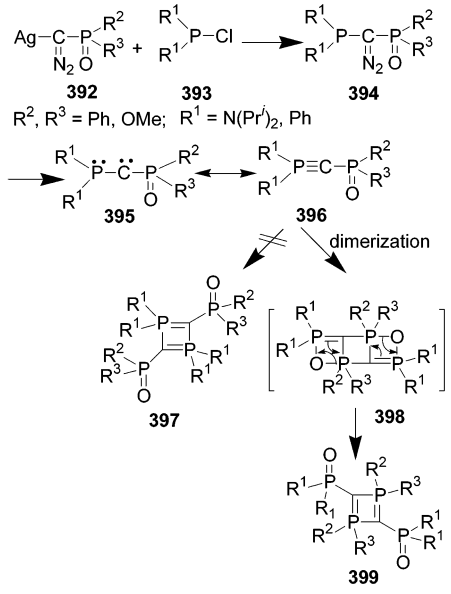
In 1986, the Regitz[98] group reported a simple one-pot reaction of silver diazo compounds **392** with

**Scheme 75**



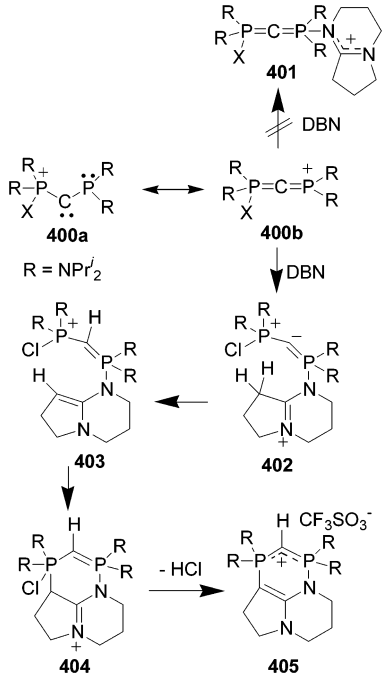
chlorophosphines **393**, from which the $\lambda^5$-1,3-diphosphetes **399** were isolated as high-melting crystals. In the first step of this one-pot reaction, the phosphinodiazo compounds **394** were formed and then decomposed spontaneously forming the phosphinocarbene **395**, which can also be represented by a $\lambda^5$-phosphaalkyne **396**. Instead of [2 + 2]-cycloaddition leading to the $\lambda^5$-1,3-diphosphetes **397** or carbene dimerization to olefins, the phosphaalkynes dimerized to give $\lambda^5$-1,3-diphosphetes **399** in which endocyclic and exocyclic phosphorus atoms have apparently interchanged their substituents. The structure of **399** ($R^1 = N(i\text{-}Pr)_2$, $R^2 = R^3 = Ph$) was ascertained beyond doubt by X-ray crystallography (Scheme 76).

**Scheme 76**



Although the synthesis and spectroscopic characterization of the (phosphino)(*P*-chlorophosphonio)-carbene **400** had been achieved in solution, isolation of this compound was unsuccessful. To isolate the carbene−DBN adduct, an excess of DBN was added to a dichloromethane solution of **400** at −78 °C. Surprisingly, a novel tricyclic carbodiphosphorane compound **405** was obtained in 50% yield after purification of the crude reaction mixture. The product was apparently formed from the 1,3-dinucleophilic attack of DBN on the (phosphino)(phosphonio)-carbene (Scheme 77).[99] The X-ray diffraction study

**Scheme 77**



showed that there is a weak interaction of the triflate anion with the methylene proton but not with either of the phosphorus centers.

## 4. Conclusion

Compared to the chemistry of typical carbon- or halogen-substituted carbenes, which have been extensively investigated, the chemistry of heteroatom-substituted carbenes is considerably more diverse and complex. Although much of the work is new and has been attracting considerable attention in recent years, there remains much to be explored in this fascinating area. No doubt, heteroatom-substituted carbenes will become increasingly important building blocks in constructing novel heterocycles in coming years.

## 5. Acknowledgments

We thank the National Natural Science Foundation of China and the Excellent Young Teachers Program of MOE, PRC, for financial support of this work.

## 6. References

(1) Kostikov, R. R.; Khlebnikov, A. F. *Khim. Geterotsikl. Soedin.* **1976**, *11*, 1443.
(2) Khlebnikov, A. F.; Novikov, M. S.; Kostikov, R. R. *Adv. Heterocycl. Chem.* **1996**, *65*, 93.
(3) Warkentin, J. *Adv. Carbene Chem.* **1998**, *2*, 245.
(4) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162.
(5) Arduengo, A. J., III *Acc. Chem. Res.* **1999**, *32*, 913.
(6) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.
(7) Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58.

(8) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15.
(9) Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1290.
(10) Magee, W. L.; Shechter, H. *J. Am. Chem. Soc.* **1977**, *99*, 633.
(11) Magee, W. L.; Shechter, H. *Tetrahedron Lett.* **1979**, *49*, 4697.
(12) Aitken, R. A.; Fairhurst, I. M.; Ford, A.; Milne, P. E. Y.; Russell, D. W.; Whittaker, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1517.
(13) Kiselyov, A. S.; Strekowski, L. *Tetrahedron Lett.* **1994**, *35*, 207.
(14) Kametani, T.; Chu, S.-D.; Itoh, A.; Wang, T.-C.; Nakayama, A.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1988**, 544.
(15) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.
(16) Solé, S.; Gornitzka, H.; Schoeller, W. W.; Bourissou, D.; Bertrand, G. *Science* **2001**, *292*, 1901.
(17) Cattoën, X.; Solé, S.; Pradel, C.; Gornitzka, H.; Miqueu, K.; Bourissou, D.; Bertrand, G. *J. Org. Chem.* **2003**, *68*, 911.
(18) Békhazi, M.; Warkentin, J. *J. Am. Chem. Soc.* **1983**, *105*, 1289.
(19) Moss, R. A.; Shen, S.; Hadel, L. M.; Kmiecik-Lawrynowicz, G.; Wlostowska, J.; Krog-Jespersen, K. *J. Am. Chem. Soc.* **1987**, *109*, 4341.
(20) Kümmell, A.; Seitz, G. *Tetrahedron Lett.* **1991**, *32*, 2743.
(21) Sekiguchi, A.; Ando, W. *J. Am. Chem. Soc.* **1984**, *106*, 1486.
(22) Maas, G.; Schneider, K.; Ando, W. *J. Chem. Soc., Chem. Commun.* **1988**, 72.
(23) Schneider, K.; Daucher, B.; Fronda, A.; Maas, G. *Chem. Ber.* **1990**, *123*, 589.
(24) Sekiguchi, A.; Sato, T.; Ando, W. *Organometallics* **1987**, *6*, 2337.
(25) Maas, G.; Alt, M.; Schneider, K.; Fronda, A. *Chem. Ber.* **1991**, *124*, 1295.
(26) Maas, G.; Fronda, A. *J. Organomet. Chem.* **1990**, *398*, 229.
(27) Maas, G.; Fronda, A. *Angew. Chem.* **1989**, *101*, 1750.
(28) Ando, W.; Sekiguchi, A.; Sato, T. *J. Am. Chem. Soc.* **1982**, *104*, 6830.
(29) Barton, T. J.; Hussmann, G. P. *Organometallics* **1983**, *2*, 692.
(30) Alt, M.; Maas, G. *Chem. Ber.* **1994**, *127*, 1537.
(31) Liu, M. T. H.; Soundrarajan, N.; Anand, S. M.; Ibata, T. *Tetrahedron Lett.* **1987**, *28*, 1011.
(32) Afarinkia, K.; Cadogan, J. I. G.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1992**, 285.
(33) Regitz, M.; Illger, W.; Maas, G. *Chem. Ber.* **1978**, *111*, 705.
(34) Maas, G.; Regitz, M.; Illger, W. *Chem. Ber.* **1978**, *111*, 726.
(35) Regitz, M.; Eckes, H. *Chem. Ber.* **1980**, *113*, 3303.
(36) Regitz, M.; Eckes, H. *Tetrahedron* **1981**, *37*, 1039.
(37) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Liebigs Ann.* **1996**, 2019.
(38) Katritzky, A. R.; Cheng, D.; Leeming, P.; Ghiviriga, I.; Hartshorn, C. M.; Steel, P. J. *J. Heterocycl. Chem.* **1996**, *33*, 1935.
(39) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665
(40) Rigby, J. H.; Wang, Z. *Org. Lett.* **2003**, *5*, 263.
(41) Moehrle, H.; Dwuletzki, H. *Arch. Pharm. (Weinheim, Ger.)* **1987**, *320*, 298.
(42) Moehrle, H.; Dwuletzki, H. *Chem.-Zeit.* **1987**, *111*, 9.
(43) Frenzen, G.; Kümmell, A.; Meyer-Dulheuer, C.; Seitz, G. *Chem. Ber.* **1994**, *127*, 1803.
(44) Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289.
(45) Hoffmann, R. W.; Hagenbruch, B.; Smith, D. M. *Chem. Ber.* **1977**, *110*, 23.
(46) Hahn, F. E.; Wittenbecher, L.; Van, D. L.; Fröhlich, R.; Wibbeling, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 2307.
(47) Hahn, F. E.; Van, D. L.; Moyes, M. C.; Fehren, T.; Fröhlich, R.; Würthwein, E.-U. *Angew. Chem., Int. Ed.* **2001**, *40*, 3144.
(48) Hahn, F. E.; Van, D. L.; Wittenbecher, L.; Moyes, M. C.; Fehren, T.; Fröhlich, R.; Würthwein, E.-U. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1863.
(49) Clendenning, S. B.; Hitchcock, P. B.; Nixon, J. F.; Nyulászi, L. *Chem. Commun.* **2000**, 1305.
(50) Couture, P.; Terlouw, J. K.; Warkentin, J. *J. Am. Chem. Soc.* **1996**, *118*, 4214.
(51) Couture, P.; Warkentin, J. *Can. J. Chem.* **1997**, *75*, 1281.
(52) Gerninghaus, C.; Kümmell, A.; Seitz, G. *Chem. Ber.* **1993**, *126*, 733.
(53) Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.* **1996**, *118*, 12848.
(54) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 2473.
(55) Reiffen, M.; Hoffmann, R. W. *Chem. Ber.* **1977**, *110*, 37.
(56) Couture, P.; Warkentin, J. *Can. J. Chem.* **1997**, *75*, 1264.
(57) Imming, P.; Kümmell, A.; Seitz, G. *Heterocycles* **1993**, *35*, 299.
(58) Haug, E.; Kantlehner, W.; Hagen, H.; Speh, P.; Brauner, H.-J. *Liebigs Ann. Chem.* **1988**, 605.
(59) Böhme, H.; Sutoyo, P. *Tetrahedron Lett.* **1981**, *22*, 1671.
(60) Cheng, Y.; Goon, S.; Meth-Cohn, O. *Chem. Commun.* **1996**, 1395.
(61) (a) Cheng, Y.; Goon, S.; Meth-Cohn, O. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1619. (b) Cheng, Y. Ph.D. thesis, 1999, pp 104−109.
(62) Cheng, Y.; Yang, H. Unpublished results, 2002.
(63) Meth-Cohn, O.; Goon, S. *Tetrahedron Lett.* **1996**, *37*, 9381.
(64) Cheng, Y.; Zhan, Y.-H.; Guan, H.-X.; Yang, H.; Meth-Cohn, O. *Synthesis* **2002**, *16*, 2426.
(65) Cheng, Y.; Yang, H.; Meth-Cohn, O. *Chem. Commun.* **2003**, 90.
(66) Cheng, Y.; Yang, H.; Meth-Cohn, O. *Org. Biomol. Chem.* **2003**, *1*, 3605.
(67) Meijere, A.; Kozhushkov, S. I.; Yufit, D. S.; Boese, R.; Haumann, T.; Pole, D. L.; Sharma, P. K.; Warkentin, J. *Liebigs Ann.* **1996**, 601.
(68) Kassam, K.; Warkentin, J. *J. Org. Chem.* **1994**, *59*, 5071.
(69) Kassam, K.; Warkentin, J. *Can. J. Chem.* **1997**, *75*, 120.
(70) Kassam, K.; Venneri, P. C.; Warkentin, J. *Can. J. Chem.* **1997**, *75*, 1256.
(71) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695.
(72) Hoffmann, R. W.; Lilienblum, W.; Dittrich, B. *Chem. Ber.* **1974**, *107*, 3395.
(73) Nair, V.; Bindu, S.; Balagopal, L. *Tetrahedron Lett.* **2001**, *42*, 2043.
(74) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821.
(75) Lu, X.; Warkentin, J. *Tetrahedron Lett.* **1999**, *40*, 1483.
(76) Colomvakos, J. D.; Egle, I.; Ma, J.; Pole, D. L.; Tidwell, T. T.; Warkentin, J. *J. Org. Chem.* **1996**, *61*, 9522.
(77) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664.
(78) Hoffmann, R. W.; Reiffen, M. *Chem. Ber.* **1977**, *110*, 49.
(79) El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. *J. Am. Chem. Soc.* **1992**, *114*, 8751.
(80) Pole, D. L.; Warkentin, J. *Liebigs Ann.* **1995**, 1907.
(81) Er, H.-T.; Pole, D. L.; Warkentin, J. *Can. J. Chem.* **1996**, *74*, 1480.
(82) Smith, N. P.; Stevens, I. D. R. *J. Chem. Soc., Perkin Trans. II* **1979**, 1298.
(83) Moss, R. A.; Fedorynski, M.; Shieh, W.-C. *J. Am. Chem. Soc.* **1979**, *101*, 4736.
(84) Moss, R. A.; Perez, L. A.; Wlostowska, J.; Guo, W.; Krogh-Jespersen, K. *J. Org. Chem.* **1982**, *47*, 4177.
(85) Du, X.-M.; Fan, H.; Goodman, J. L.; Kesselmayer, M. A.; Krogh-Jespersen, K.; LaVilla, J. A.; Moss, R. A.; Shen, S.; Sheridan, R. S. *J. Am. Chem. Soc.* **1990**, *112*, 1920.
(86) Moss, R. A.; Kmiecik-Lawrynowicz, G.; Krogh-Jespersen, K. *J. Org. Chem.* **1986**, *51*, 2168.
(87) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1999**, *64*, 1766.
(88) Rigby, J. H.; Laurent, S.; Dong, W.; Danca, M. D. *Tetrahedron* **2000**, *56*, 10101.
(89) Rigby, J. H.; Dong, W. *Org. Lett.* **2000**, *2*, 1673.
(90) Igau, A.; Grützmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463.
(91) Igau, A.; Baceiredo, A.; Trinquier, G.; Bertrand, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 621.
(92) Piquet, V.; Baceiredo, A.; Gornitzka, H.; Dahan, F.; Bertrand, G. *Chem. Eur. J.* **1997**, *3*, 1757.
(93) Armbrust, R.; Sanchez, M.; Réau, R.; Bergsträsser, U.; Regitz, M.; Bertrand, G. *J. Am. Chem. Soc.* **1995**, *117*, 10785.
(94) Sanchez, M.; Réau, R.; Marsden, C. J.; Regitz, M.; Bertrand, G. *Chem. Eur. J.* **1999**, *5*, 274.
(95) Regitz, M.; Keller, H. *Tetrahedron Lett.* **1988**, *29*, 925.
(96) Baceiredo, A.; Bertrand, G.; Majoral, J.-P.; El Anba, F.; Manuel, G. *J. Am. Chem. Soc.* **1985**, *107*, 3945.
(97) Sicard, G.; Grützmacher, H.; Baceiredo, A.; Fischer, J.; Bertrand, G. *J. Org. Chem.* **1989**, *54*, 4426.
(98) Keller, H.; Mass, G.; Regitz, M. *Tetrahedron Lett.* **1986**, *27*, 1903.
(99) Dyer, P.; Guerret, O.; Dahan, F.; Baceirdo, A.; Bertrand, G. *J. Chem. Soc., Chem. Commun.* **1995**, 2339.

CR030604W