Reactions in the conjugated 'ene–ene–yne' manifold: five-membered ring fragmentation and ring formation *via* coarctate/pseudocoarctate mechanisms

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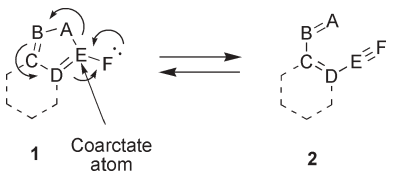
The fragmentation of a 5-membered heteroaromatic ring to afford a conjugated ene–ene–yne skeleton, and the corresponding reverse process, cyclization of the hetero-ene–ene–yne motif to generate a variety of heterocyclic systems, are the subject of this review. These synthetically useful reactions, which proceed through a coarctate/pseudocoarctate mechanistic pathway, are unique in that they involve the generation of either a carbene or nitrene intermediate, and provide access to hard to obtain heterocyclic or ene–ene–yne structures. While fragmentation of heteroaromatic rings containing a exocyclic carbene or nitrene has been well documented in the literature for over 40 years, the use of hetero-ene–ene–yne precursors to synthesize heterocycles is a relatively new approach that is generating much interest in the literature. This review highlights both the synthetic and mechanistic aspects of these unique reactions.

1. Introduction

This review focuses upon the fragmentation of 5-membered heterocyclic rings (*e.g.*, **1**) to afford conjugated ene–ene–yne systems (*e.g.*, **2**) and the corresponding reverse process, namely cyclization of the ene–ene–yne motif (Scheme 1). Fragmentation is achieved by the generation of an electron deficient atom, *e.g.*, a carbene or nitrene, exocyclic to the heterocyclic core. This is usually achieved *via* thermal or photolytic decomposition of azido or diazo species, causing the ring to open into a conjugated ene–ene–yne structure. Treatment of this structure either thermally, photochemically, or by transition metal catalysis causes the formation of the 5-membered ring and an exocyclic carbene/nitrene, which can be intercepted by a trapping agent.

Both the forward (ring formation) and the reverse (ring fragmentation) reactions are synthetically useful transformations. Several important heterocyclic systems are easily attainable in high yields *via* the ring closing methodology. The only limits to this reaction are the ease with which the desired 'ene–ene–yne' core can be assembled and optimal



Scheme 1 Generic 'coarctate' reaction.

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cyclization conditions determined. Conversely, the ring-opening reaction permits access to highly conjugated structures that are otherwise synthetically challenging to construct. The 'ene–ene–yne' systems that result from fragmentation are often unstable, reactive intermediates. Nonetheless, their careful study can yield novel molecular structures, elucidate new mechanistic pathways, and provide ample fodder for both experimental and theoretical chemists alike.

In 1994, after completing a systematic classification of about 80,000 reactions, particularly those involving carbenes and nitrenes, Herges determined that reactions involving a 5-membered aromatic ring with an exocyclic carbene (*e.g.*, **1**), among others, fell under a previously undescribed class of concerted reactions.[1,2] Herges contended that the transition states of these complex reactions are formally derived from pericyclic reactions, and hence proceed through a Hückel aromatic transition state *via* a constriction in the orbital topology. Herges called these reactions *coarctate* (meaning compressed or constricted). Although true coarctate reactions are concerted, they cannot be considered pericyclic because bond making and bond breaking do not occur in a cyclic fashion, *i.e.*, the forming or reacting carbene is exocyclic to the 5-membered ring. Coarctate reactions can be identified on a visual inspection of starting materials or products by the 'coarctate atom', the atom at which two bonds are made and two bonds are broken.

A quintessential example discussed by Herges is the fragmentation of 2-furfurylcarbene (**4a**), elegantly discovered and analyzed by Hoffman and Shechter.[3–6] Upon loss of N_2 from diazo **3**, **4a** undergoes stereoselective ring opening to afford *cis*-2-penten-4-ynal (**5**, Scheme 2). Herges contended that the small activation barrier and consistent stereochemistry could be explained by a stabilized coarctate transition state (TS). Birney correlated the difference between pericyclic/pseudopericyclic reactions to certain coarctate reactions.[7]

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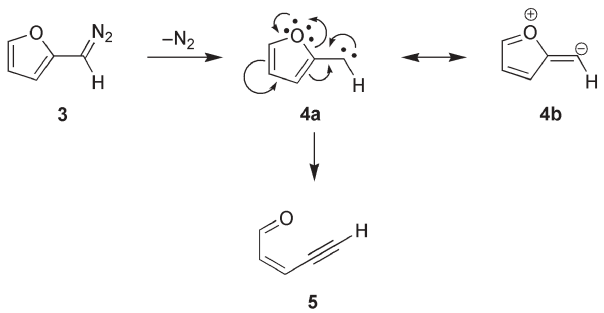


Scheme 2 'Pseudocoarctate' ring-opening of 2-furfurylcarbene.

Among pericyclic reactions there are special cases where reactions do not proceed through cyclic aromatic transition states. In these examples the cyclic delocalization of the electrons is disrupted due to orthogonal orbitals at the atoms where bond formation is occurring, as originally identified by Lemal *et al.*[8] and expanded upon by Birney and co-workers.[9–13] For a pericyclic reaction to exhibit a truly aromatic TS, there must be some degree of distortion from planarity in the TS. Consequently, pseudopericyclic reactions can be recognized by planar transition states that are neither aromatic nor antiaromatic because they lack a loop of interacting orbitals. Applied to 2-furfurylcarbene, the disconnection in the loop of interacting orbitals can be recognized easily on paper if the 2-furfurylcarbene resonance structure is drawn so that the out of plane π-orbitals are in the same orientation as the products (**4a** → **4b**); thus, it would be expected that the TS is planar. Also, because of the involvement of one of the lone pair of oxygen, the reaction is not truly concerted, which is a requirement of a purely coarctate cyclization. For both 'pseudo' mechanisms the reaction barriers are often very low because electron–electron repulsion derived from cyclic overlap of orbitals is not inherent. Density functional theory (DFT) analysis of furfurylcarbene ring opening showed that the geometric structure for the TS was indeed planar with a low barrier to ring opening and hence the cyclization, analogous to pseudopericyclic, should be termed pseudocoarctate.[7,14] For a reaction to be considered truly coarctate, there must be some distortion from planarity in the TS. Otherwise, the in plane σ-bond would not be able to overlap with the out of plane π-system, which is required for bond formation.

The 'pseudo' term primarily is employed when heteroatoms are involved, where bond forming or bond breaking occurs due to the interaction of the in-plane lone pair with the in plane σ-bond, therefore inhibiting a true compressed loop of interacting orbitals and resulting in a planar transition state. However, without detailed theoretical analysis of each ene–ene–yne conjugated system, it cannot be determined unequivocally whether or not ring formation or fragmentation proceeds through a coarctate or pseudocoarctate pathway.[15–17] Also, several of the ene–ene–yne cyclizations included herein are transition metal catalyzed, further complicating the analysis of the exact mechanism, such as the exact nature of the TS and the concerted nature of the reaction. Hence, in light of this, our review will focus only upon the synthetic and experimental mechanistic aspects of

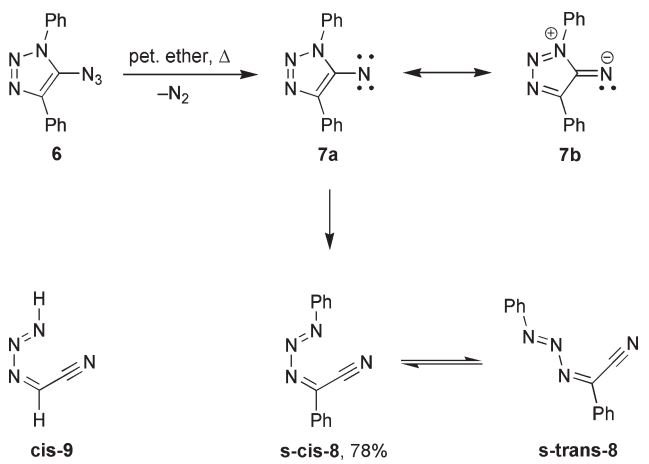
these ring-opening and ring-closing reactions. It should be noted that while the ring fragmentation reactions have been studied for over 40 years, the cyclizations are a relatively new interest that is generating numerous papers. This review strives to encompass all aspects of these unusual reactions.

2. Ring fragmentation reactions

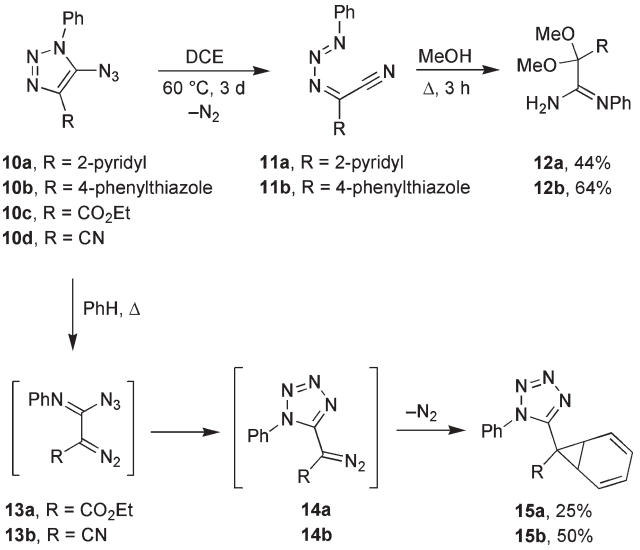
2.1 Triazoles

The first account of this unusual ring cleavage was reported by Smith *et al.* during their investigations into the reactivity of azidotriazoles.[18] This group synthesized 1,4-diphenyl-5-azido-1,2,3-triazole (**6**) with the intent of learning more about the factors that determine the preferred site of cyclization of decomposing azides (Scheme 3). Thermal decomposition of azide **6** was accompanied by concomitant loss of N_2, however, with none of the expected products resulting from known azide chemistry. Instead, a brilliant red product (**s-*cis*-8**) was obtained in 78% isolated yield.[19] Interestingly, the IR spectrum of the product did not show a strong nitrile stretch around 2200 cm^{-1}. Although the authors originally postulated that in solution **s-*cis*-8** was in equilibrium with the highly stabilized 1,2,3-triazole nitrene **7b**, it was proven *via* X-ray crystallography[20] that conformational isomer **s-*trans*-8** was the product in the solid state. In addition, molecular orbital calculations of ***cis*-9** at the HF/6–31 g(d) level corroborate the spectroscopic results, as the calculations predicted a very weak IR transition for the C≡N stretching mode.[21]

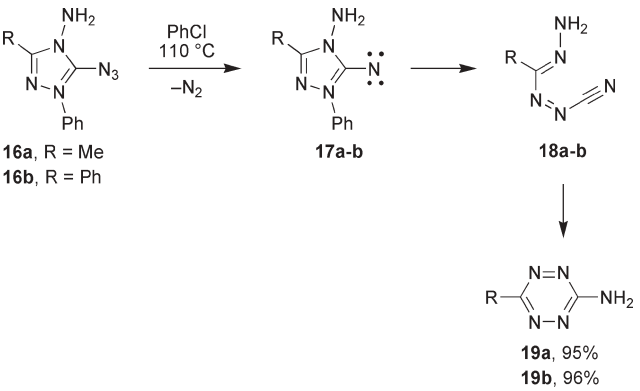
L'abbe and coworkers explored the effect substitution had on the overall reactivity of the azido-1,2,3-triazole core, with product formation being dependent upon the electronegativity of the group at the C-4 position. Inclusion of a phenyl (*e.g.*, **6**) or aromatic heterocycle (*e.g.*, **10a,b**) at C-4 facilitated ring opening to furnish azo-imine-nitriles **11a–b** (Scheme 4).[22,24–27] The resultant nitriles, however, were unstable and reacted further with MeOH to afford acetamidines **12a–b** in moderate yield. Incorporation of a carbomethoxy (**10c**) or nitrile (**10d**) at C-4 resulted in a Dimroth-type rearrangement,[23] giving the isomeric tetrazole-diazo compounds **14a–b** by way of diazo **13a–b**.[24–27] Loss of dinitrogen resulted in [2 + 1] cycloaddition to the benzene



Scheme 3 Ring fragmentation of nitrene **7a**.



Scheme 4 Reactions of azidotriazoles **10a–d**.

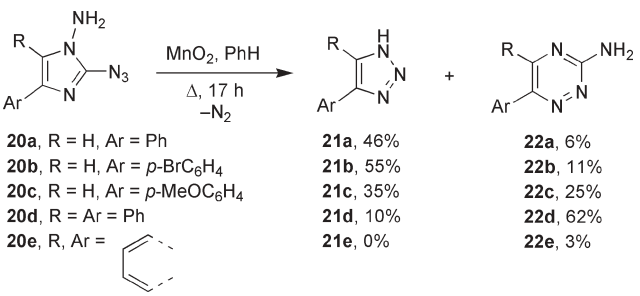


Scheme 5 Ring opening of azidotriazoles **16a–b**.

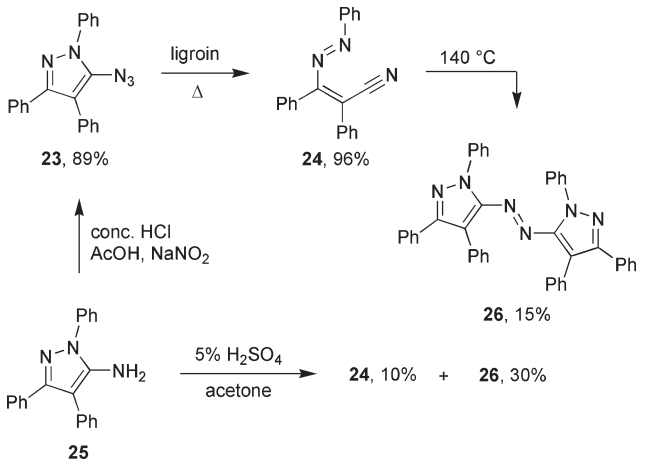
solvent to yield dienes **15a–b**. Analogous rearrangements were also observed with 5-azido-1,2,3-thiadiazoles.[28]

This unique methodology was also viable for other isomeric triazoles. Ring opening of azidotriazoles **16a–b** afforded the unstable open-chain products **18a–b** *via* nitrenes **17a–b** (Scheme 5). Attack at the nitrile C-atom by the primary amine followed by tautomerization gave the explosive tetrazines **19a–b** in excellent yields.[29]

Similar reactivity was observed upon MnO_2 oxidation of aryl 1,2-diaminoimidazoles **20a–e** (Scheme 6). The resultant cyanoimine intermediates underwent further rearrangement to



Scheme 6 Ring opening/rearrangement of imidazoles **20a–e**.



Scheme 7 Reactivity of pyrazole **23**.

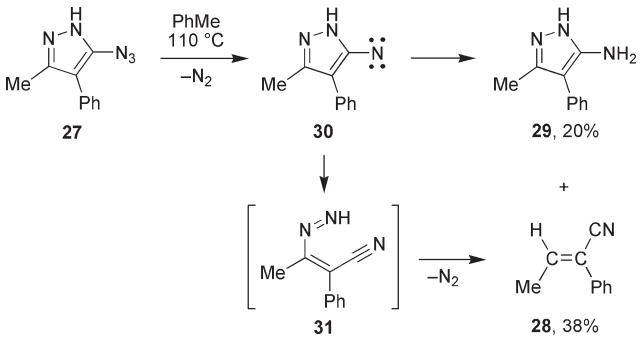
give a mixture of triazoles **21a–e** and regioisomeric triazines **22a–e**.[30,31] Changing from a nitrene to carbene functionality in the α position does not give rise to any ring opened products, but rather resulted in solvent incorporation at the carbene.[32–34] Even in cases where there was no carbene trap (*i.e.*, hexafluorobenzene as the solvent) no products derived from ring opening were detected.

2.2 Pyrazoles

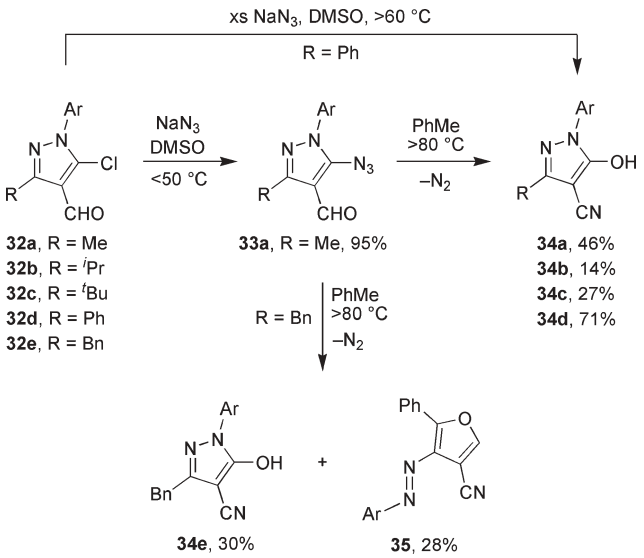
Analogous to their work with triazoles, Smith *et al.* investigated azidopyrazole **23** in their quest to synthesize a suitably stabilized nitrene or carbene.[35] The N-1 Ph-substituted pyrazole **23** decomposed at 50 °C losing one molar equivalent of N_2 to form the deep red azo-ene-nitrile **24** in excellent yield (Scheme 7). Compound **24** was considerably more stable thermally than nitrile **8**, likely due to the additional phenyl ring attached to the alkene backbone. The parent aminopyrazole **25** also rearranged *via* addition of dilute acid to afford **24** accompanied by formation of nitrene dimer **26** containing reformed pyrazole rings. It can be rationalized in an oxidizing environment, a nitrene/nitrenoid is formed followed by either facile ring-opening or nitrene dimerization. Heating ring-opened nitrile **24** to 140 °C also produced dimer **26** in modest amounts. The latter result clearly demonstrates the ease with which the ring-opened and ring-closed forms can interconvert.

Pyrazole **27**, with no substituents at the N-1 position, also underwent ring-opening to give alkene **28** along with reduced aminopyrazole **29** in 38% and 20% yield, respectively (Scheme 8).[36] Presumably due to the lack of a more stabilized nitrene intermediate, elevated temperatures were required (*ca.* 110 °C) for ring-opening of **30**. The expected imine-ene-nitrile **31** was presumably formed, but was unstable under the reaction conditions and thus lost an additional equivalent of N_2 to furnish **28**.

If a reactive carbonyl functionality such as an aldehyde is incorporated into the azidopyrazole moiety at C-4 (*e.g.*, **33a**), generated *in situ* from chlorides **32a–e**, ring-opening is immediately followed by a ring-closing reaction to afford nitrile-substituted pyrazoles **34a–e** in moderate to good yield (Scheme 9).[37–39] In certain cases (R = Bn), the azo-ene-nitrile ring-opened product could undergo subsequent ring-closure to



Scheme 8 Ring-opening of pyrazole **27**.



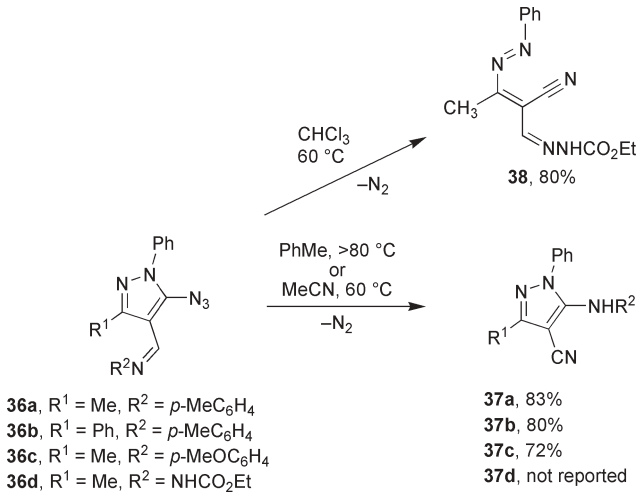
Scheme 9 Ring-opening/rearrangements of *in situ* generated pryrazoles **33a–e**.

afford uniquely substituted phenylazofuran **35** in addition to pyrrole **34e**; however, conditions for the optimization of either product were not explored.[40]

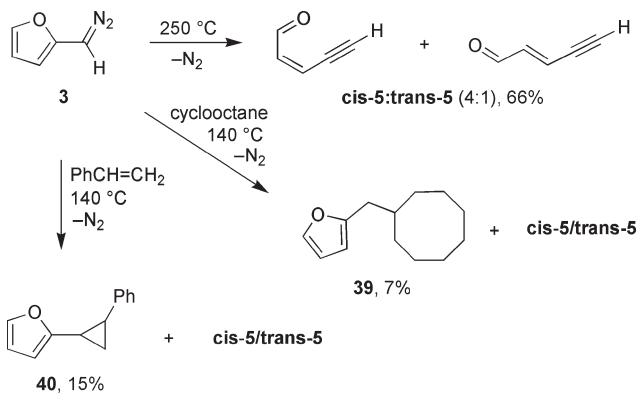
4-Imino-5-azidopyrazoles (**36a–d**) also undergo thermal ring-opening and ring-closing reactions to afford rearranged aminopyrazoles **37a–c** in very good yield (Scheme 10). Ester **36d** is much more thermolabile to azido decomposition; under certain conditions the reaction progress can be stopped at azo **38**, thus supporting the theorized tandem ring-opening/ring-closing mechanism.[37]

2.3 Furans

An extensively studied core in the class of ring-opening reactions is the thermal decomposition of the 2-furfurylcarbene system. Originally investigated by Hoffman and Shechter,[6] 1-diazo-1-(2-furyl)methane **3** can undergo thermally-induced reorganization (250 °C, 0.5 mm) to afford a 4 : 1 mixture of *cis*/*trans*-2-penten-4-ynals (**5**) in 66% combined yield (Scheme 11). The two isomers could be stored at −78 °C but rapidly decomposed at room temperature. Although *cis* and *trans* isomers of **5** are produced, the rearrangement is nonetheless stereoselective, with formation of the *trans* isomer attributed to facile *cis*→*trans* isomerization at the elevated



Scheme 10 Reactions of 4-imino-5-azidopyrazoles **36a–d**.

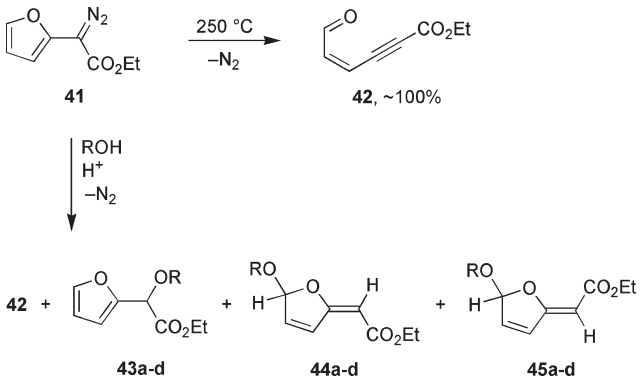


Scheme 11 Reactivity of diazo **3**.

temperatures required for diazo decomposition. The stereospecificity of this reaction was later confirmed by Sander *et al.* utilizing low temperature matrix isolation spectroscopy.[41] Further experiments utilizing carbene traps supported the existence of a carbene intermediate. Thermal diazo decomposition in cyclooctane and styrene afforded the C–H insertion (**39**) and [2 + 1] cycloaddition (**40**) products respectively, albeit in very low yields (7% and 15%, respectively). Ring-opening of 1-diazo-1-(2-furyl)ethane is so facile that it even outcompetes the usually favorable 1,2-C–H shift, with only 3% formation of the respective propenylfuran.[4,6] A number of substituted derivatives of **3**, prepared from the sodium salts of furfuryltosylhydrazones,[3] have also been studied and yielded analogous results.[4]

Similar to **3**, ethyl (2-furyl)diazoacetate (**41**) undergoes ring fragmentation at 250 °C to generate ene-yne-al **42** (Scheme 12).[3,5] Compound **41** also undergoes cationic decomposition either thermally or by Ag(I) or Cu(I) catalysis with acetic acid or alcohols to afford, in addition to **42**, products resulting from 1,1- (furans **43a–d**) and 1,5-addition (isomeric dihydromethylene-furans **44a–d** and **45a–d**) of the nucleophilic solvent medium (Scheme 12, Table 1). In the case where R = Ac, **44a** is unstable and isomerizes to **43a**.

Due to the high propensity for ring fragmentation, the parent 2-furfurylcarbene **4a** is not observable in low

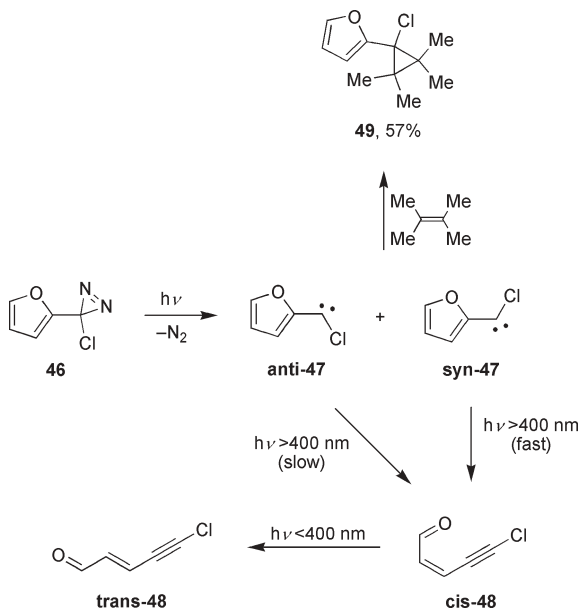


Scheme 12 Carbenic and cationic decomposition of ester **41**.

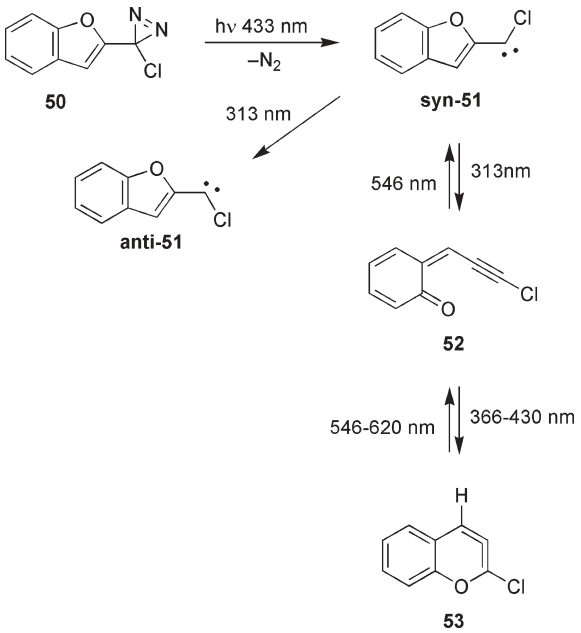
Table 1 Decomposition of **41** in hydroxylic solvents in Scheme 12

Entry	OR	Conditions	**42**[a]	**43**[a]	**44**	**45**
1	**a**	AcOH	0%	46%	54%	0%
2	**a**	$AcOH/CH_2Cl_2$	20%	15%	57%	0%
3	**b**	MeOH	34%	15%	28%	31%
4	**b**	MeOH/TsOH	0%	16%	44%	20%
5	**b**	$MeOH/AgNO_3$	0%	11%	25%	65%
6	**b**	MeOH/CuCl	0%	95%	trace	trace
7	**b**	$MeOH/NiCl_2$	32%	18%	32%	18%
8	**c**	EtOH	64%	12%	24%	0%
9	**c**	EtOH/TFA	22%	16%	46%	15%
10	**d**	^{i}PrOH	95%	trace	trace	0%
11	**d**	^{i}PrOH/TsOH	0%	7%	53%	40%

temperature matrixes.[41] Sheridan and Khasanova have studied a Cl-substituted analogue in detail starting from diazirine **46** (Scheme 13).[14] Photolysis of **46** in an N_2 matrix afforded chlorocarbenes ***synlanti*-47**, which were observable in the IR spectrum (their respective line spectra assigned by DFT calculations). The *syn* isomer proved to be the more reactive, opening upon further photolysis to give ***cis*-48**. Subsequent irradiation of ***cis*-48** at $\lambda < 400$ nm facilitated *cis*→*trans*



Scheme 13 Reactions of carbene **47**.



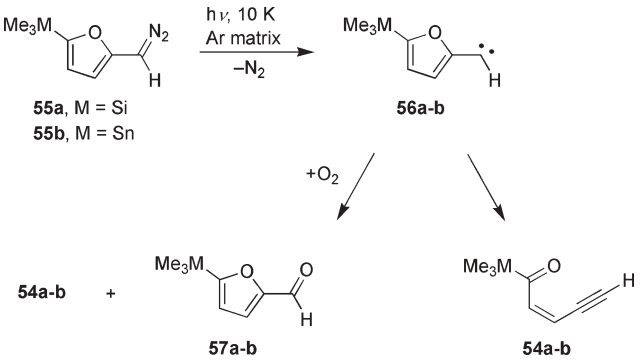
Scheme 14 Reactions of carbene **51**.

isomerization. The successful detection of **47** was attributed to stabilization of the singlet carbene by the chlorine atom, which resulted in less facile ring opening. This hypothesis was corroborated by a DFT analysis which compared a number of different substituents α to the carbene and their effect on carbene stability.[42] The increased stability of **47** was also verified experimentally as carbene trapped products (*i.e.*, **49**) were isolated in significantly higher yields (*ca.* 50% higher) than for the parent furylcarbene.

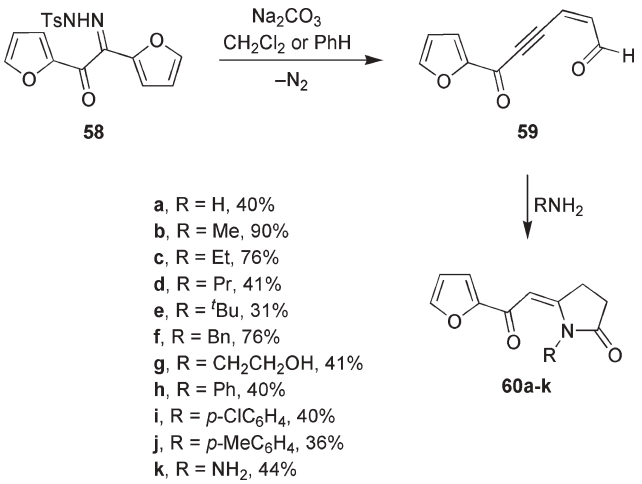
In addition to stabilization by the α-chloro substituent, Sheridan investigated the stabilizing effects of benzannulation by preparing benzofuran analogue **50** (Scheme 14). When subjected to low temperature photolysis, facile ring-opening of **50** afforded highly stabilized carbene ***synlanti*-51**, which could be selectively interconverted between the carbene and the novel didehydrobenzopyran **53** by way of ring-opened **52**.[43] The facile interchange between these species was monitored by IR and UV-vis spectroscopy and corroborated by DFT computations, which suggested that the various reactive intermediates all lie fairly close in energy.

Novel acylsilane **54a** and acylstannane **54b** have been prepared by furfurylcarbene ring-opening of **55a–b**, and have been analyzed both computationally and spectroscopically in a low temperature Ar matrix.[45] Even at 10 K carbenes **56a–b** were too unstable to be observed by IR spectroscopy. If the matrix was doped with 5% O_2, furaldehydes **57a–b** were formed along with **54a–b**. The ring-opened products, however, were not fully characterized due to their high rate of decomposition at ambient temperatures (Scheme 15).

Furfurylcarbene ring fragmentation is a sufficiently facile reaction that it has synthetic practicality. Treatment of tosylhydrazone **58** with mild base results in ring-opening to generate unstable acetylenic aldehyde **59** (Scheme 16).[44] This intermediate in turn can be intercepted by a variety of primary amines to afford pyrrolidinones **60a–k** in moderate to excellent yield.

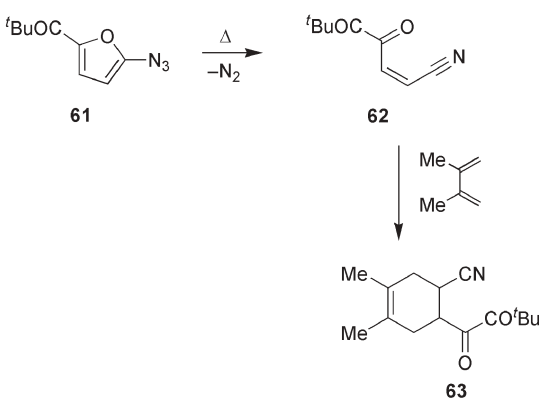


Scheme 15 Reactions of carbenes **56a–b**.

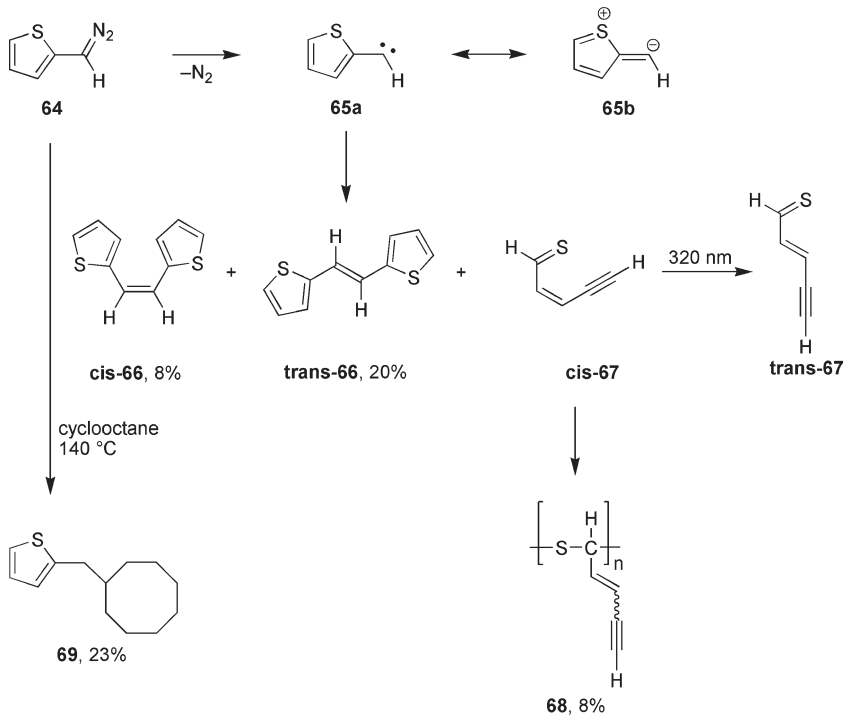


Scheme 16 Formation of pyrrolidinones **60a–k**.

Replacement of the diazoalkane moiety attached to the furan ring with an azide group (*e.g.*, **61**), followed by thermal decomposition, furnishes the corresponding furylnitrene, in which ring opening remains a facile reaction pathway (Scheme 17).[46,47] The resultant nitrile **62** could be fully characterized, but similar to **5** and **59** was thermally unstable and underwent facile *cis* to *trans* isomerization followed by decomposition over several days at room temperature. Nitrile **62**, however, was stable enough to undergo Diels–Alder cyclization at ambient temperature with 2,3-dimethyl-1,3-butadiene to afford adduct **63**, as the authors claim, in very good yield.



Scheme 17 Reactions of azide **61**.



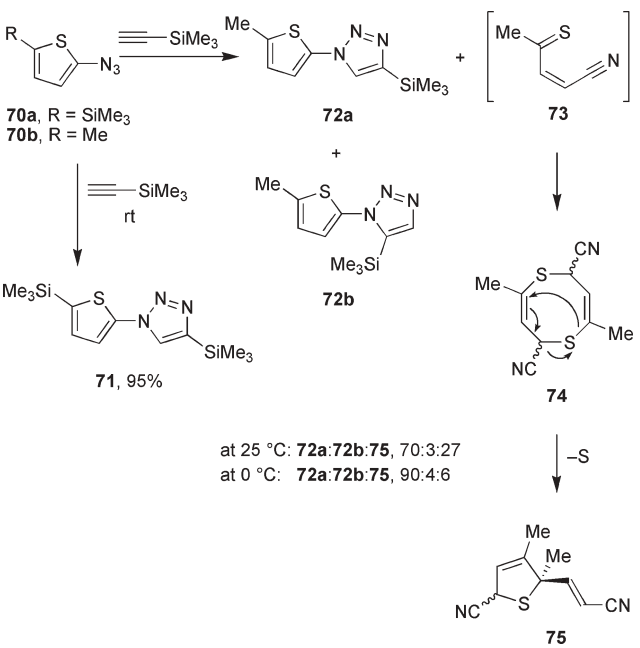
Scheme 18 Reactions of carbene **65**.

2.4 Thiophenes

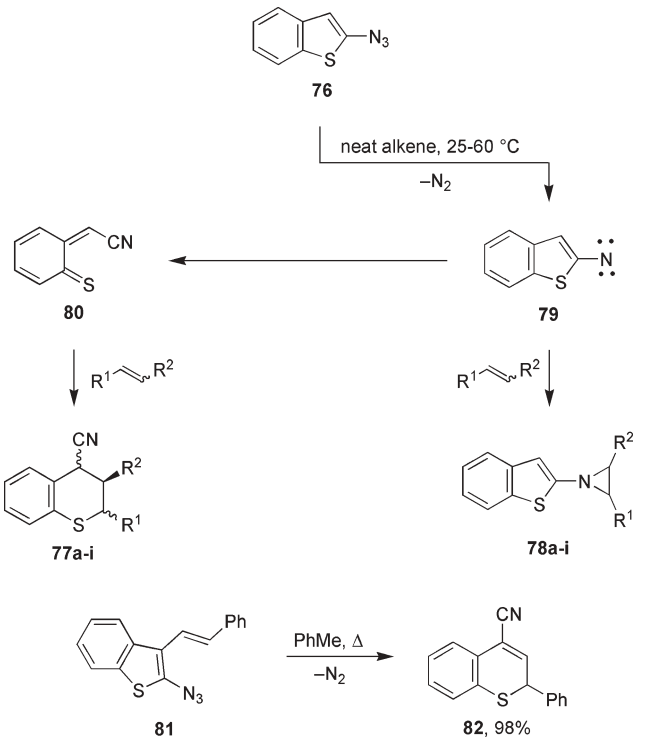
The pyrolysis of the structurally analogous 2-azothiophene **64** was also investigated by Hoffman and Shechter (Scheme 18).[4] In comparison to the furan ring system, carbene (**65a**) is significantly more stable due to the greater ability of sulfur to accept a positive charge in relation to oxygen, stabilizing resonance form **65b**; hence, the C–S single bond is not as easily broken, resulting in a longer lived intermediate. This intermediate preferentially dimerizes to yield ***cis/trans*-66**, whereas carbene–carbene dimerization of 2-furfurylcarbene **4a** so far has not been documented in the literature. Low yields of **68** were also obtained, attributed to ring-opening of **65**, followed by facile oligomerization of **67** under the reaction conditions due to the predilection of thioaldehydes to oligomerize. Carbene **65** could also be trapped with cyclooctane to give C–H insertion adduct **69**. Albers and Sander found that thermolysis of **64** followed by trapping of the product in an Ar matrix resulted in formation of ***cis*-67**, which upon irradiation ($\lambda > 320$ nm) gave a mixture of ***cis*** and ***trans*-67**.[48] A mixture of ***cis/trans*-67** could also be obtained directly by photolysis of **64**.

The enhanced stabilization of 2-methylenethiophenes,[49,50] 2-azidothiophenes,[51] and 2-azidobenzo[*b*]thiophenes[52] has been utilized to prepare the respective cyclopropyl- or aziridyl-substituted thiophenes. Formation of the cyclopropanes and aziridines presumably occurs *via* [2 + 1] cycloaddition, although aziridine formation could be a result of alkene/azido 1,3-dipolar cycloaddition followed by extrusion of N_2. Whereas 2-azido-5-trimethylsilylthiophene **70a** is quite stable and at 50 °C the only product obtained is the 1,3-dipolar cycloadduct **71**, under analogous conditions 2-azido-5-methylthiophene **70b** more readily decomposes, giving products resulting from both ring-opening (**75** *via* **73** then dimer **74**) and [2 + 3] cycloaddition (Scheme 19). Temperatures below ambient more stringently favored formation of the 1,3-dipolar cycloaddition products **72a–b**.[53,54] 2-Azidoselenophenes were also shown to be significantly stable to ring opening in opposition to 2-azidofurans.[55]

Thermal ring cleavage of 2-azidobenzo[*b*]thiophene **76** in the presence of a variety of alkenes has been utilized for the synthesis of thiochromans **77** (Scheme 20);[54] however, due to the increased stabilization of the resultant nitrene (**79**),



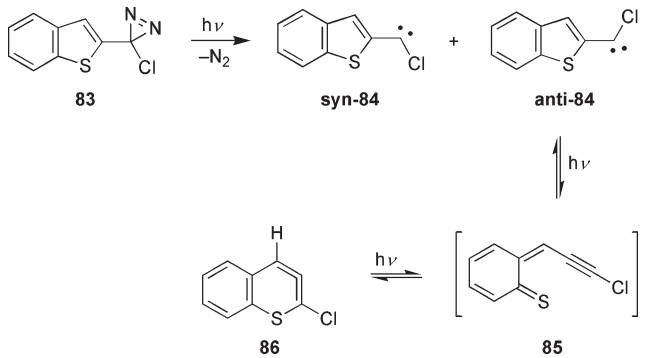
Scheme 19 Reactions of azides **70a–b**.



Scheme 20 Ring cleavage of 2-azidobenzo[*b*]thiophenes **76** and **81**.

products arising from both [2 + 1] cycloaddition (**78**) and the desired ring-opened Diels–Alder adducts (**77** *via* **80**) were formed.[56] Product ratios could be manipulated thermally (Table 2, entries 8–9 *vs.* 10–11), with aziridine formation favored at ambient temperatures and thiochroman formation favored at elevated temperatures due to the increased propensity for ring fragmentation. Incorporation of an alkene into the benzothiophene ring system as in **81** results in virtually quantitative isolated yield of the electrocyclization adduct **82**.[57] *o*-Azidobithienyls reportedly underwent ring opening in the expected fashion but resulted in unidentified, uncharacterized products.[58]

Analogous to the benzofuranylchlorocarbene system, Sheridan investigated benzothiophenylchlorocarbene **84** as another system for spectroscopic detection of transient electron deficient species (Scheme 21).[59] Irradiation of diazirine **83** in a low temperature matrix generated ***syn*-84** and ***anti*-84**. Selective irradiation at $\lambda > 350$ nm favors



Scheme 21 Reactions of carbene **84**.

formation of allene **86** by way of intermediate alkynylchloride **85**. Irradiation at shorter wavelengths ($\lambda < 300$ nm) drives the reaction back towards carbenes **84**, and the two can be selectively interconverted.

2.5 Other ring opening reactions

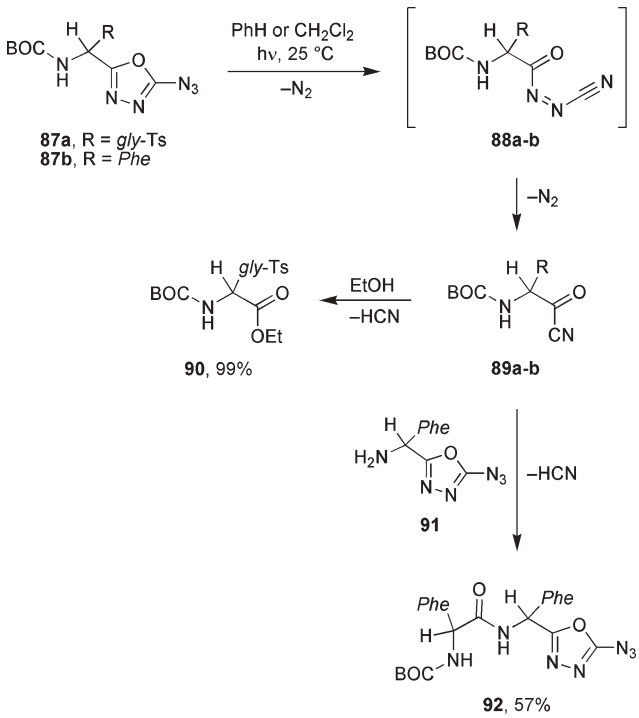
A variety of other nitrene and methylene substituted heterocycles have been synthesized that undergo ring fragmentation to afford the conjugated ene–ene–yne moiety. Woodward utilized the photolytic ring opening of 5-azidooxadiazoles **87a–b** *via* reactive azo **88** as a method for peptide synthesis (Scheme 22).[60] Loss of an additional equivalent of N_2 from **88** gave acylnitrile **89**, which was susceptible to nucleophilic attack. In the presence of EtOH, ester **90** was formed in excellent yield. Addition of functionalized amino acid **91** to acylnitrile **89b** generated the amide linkage in dipeptide **92** in moderate yield.

Thermolysis of azoisoxazoles **93** and azooxazoles **94** has been investigated (Scheme 23, Table 3). While the expected ring-opened products **95** and **96** (*via* tautomerization of **97**) were obtained from **93**, two additional products, nitrile **98** and ketone **99**, were isolated that could not be attributed to ring-opening of carbene **100**. In the case of isomeric oxazole **94**, only nitrile **101** and ketone **102** were generated. Pyrolysis of **93** and **94** at *ca.* 300–350 °C resulted in fragmentation products **98–99** and **101–102**, respectively, which are theorized to arise from ring expansion to the allenic systems **103** (for **93**).[61] Carbene intermediate **100** can be intercepted as the [2 + 1] cycloaddition product with styrene (**104**) in low yield; however, even at 145 °C, fragmentation to **98a** and **99a**

Table 2 Yields of the thermal reaction of 2-azidobenzothiophene **76** with alkenes at rt

Entry	Cmpd	R^1	R^2	Thiochroman **77**	Aziridine **78**
1	**a**	H	H	22%	75%
2	**b**	H	CN	10%	85%
3	**c**	H	CO_2Me	3%	90%
4	**d**	H	$SiMe_3$		93%
5	**e**	Me[a]	Me	47%	*trans*-25% + *cis*-10%
6	**e**	Me[b]	Me	*cis*/*cis*-22% + *cis*/*trans*-22%	*trans*-17% + *cis*-16%
7	**f**	CO_2Et	CO_2Et		*trans*-85%% + *cis*-9%
8	**g**	Me[a]	CO_2Me	35%	*trans*-48%
9	**h**	Me[b]	CO_2Me	*cis*/*cis*-29% + *cis*/*trans*-15%	*trans*-11% + *cis*-34%
10	**g**[c]	Me[a]	CO_2Me	*trans*/*trans*-81%	*trans*-14%
11	**h**[c]	Me[b]	CO_2Me	*cis*/*cis*-38% + *cis*/*trans*-30%	*trans*-1% + *cis*-4%

[a] *Trans* isomer. [b] *Cis* isomer. [c] Reaction carried out at 60 °C.



Scheme 22 Ring opening of 5-azidooxadiazoles **87a–b**.

remained the predominant pathway. Analogous to ring expansion of phenylmethylenes *via* cyclopropene intermediates to yield stabilized 6π-electron arylidenes, the 6-membered

Table 3 Yields of the fragmentation products of **93a–c** and **94a–c** at 300–350 °C

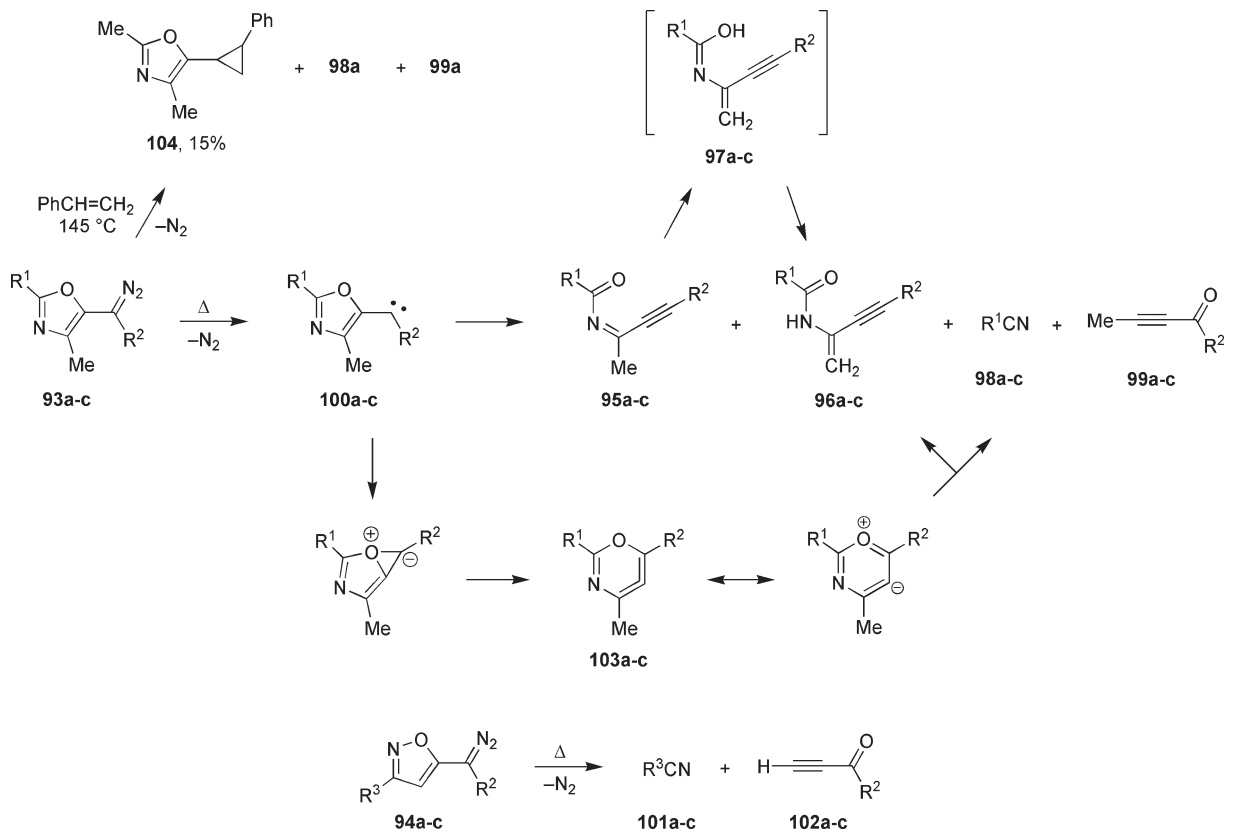
Sm	R^1	R^2	R^3	**95**	**96**	**98**	**99**	**101**	**102**
93a	Me	H		48%[a]		18%	9%		
93b	Me	Me		9%	17%	25%	18%		
93c	Ph	Me		13%	8%	26%	18%		
94a		H	Me					25%	17%
94b		H	Et					27%[b]	19%[b]
94c		Ph	Me						

[a] Reported combined yield for **95** and **96**. [b] Isolated, but yield not reported.

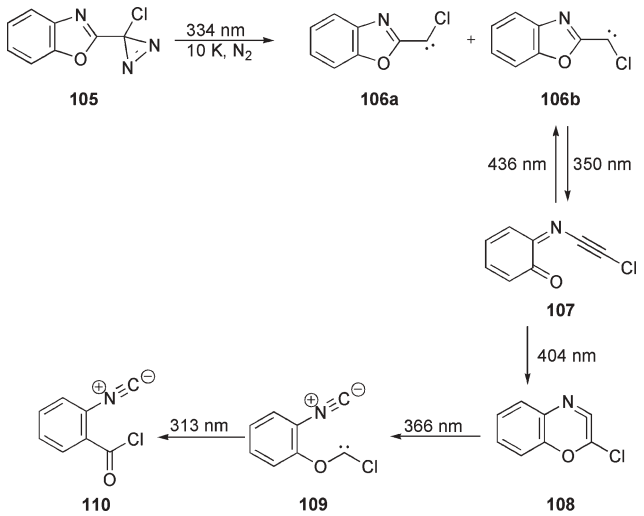
heteroaryl-allenic intermediates had been postulated for these systems but not previously encountered.[4]

Photolysis of benzoxazole **105** in a nitrogen matrix at 334 nm was found to generate ***syn***- and ***anti*-106**, which could subsequently be ring-opened to give quinoimine **107** (Scheme 24).[62] By alternating the irradiation wavelength between 350 nm and 436 nm, it is possible to switch between **106** and **107** several times. Irradiation of **107** at 404 nm resulted in ring-closing to give cyclic ketenimine **108**. Compound **108** was not stable and fragmented to give phenoxycarbene **109**, which could also be obtained by photolysis of **108** at 366 nm. When subjected to 313 nm light, **108** rearranged to acid chloride **110**.

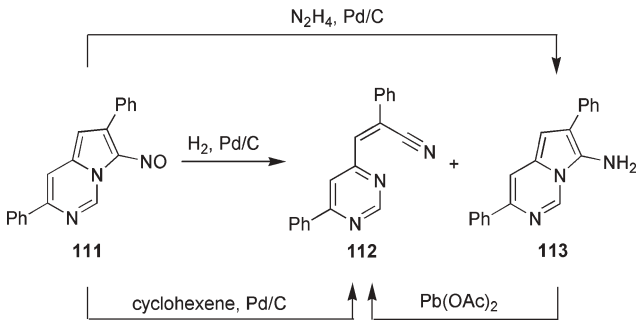
Attempted hydrogenation of a nitroso group α to a bridgehead nitrogen in the pyrrolopyrimidine **111** resulted in high yields of ring-opened pyrimidines **112** and only trace amounts of the expected amine **113** (Scheme 25).[63] Aminopyrimidine **113** could be synthesized from **111** *via* hydrogenation with



Scheme 23 Ring fragmentation of azoisoxazoles **93** and azooxazoles **94**.



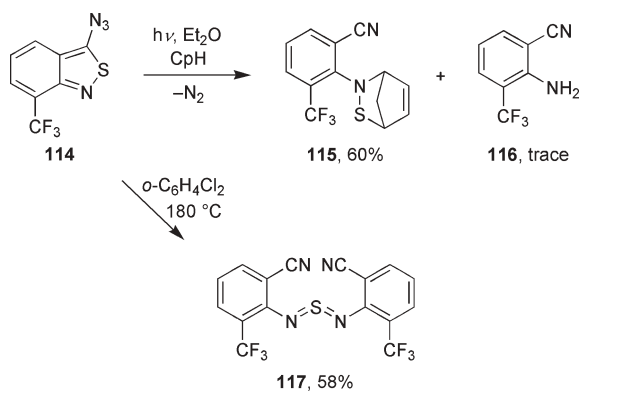
Scheme 24 Photolysis of benzoxazole **105**.



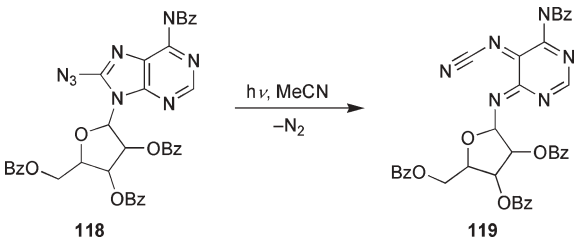
Scheme 25 Reactions of pyrrolopyrimidine **111**.

N_2H_4 on Pd/C, and treatment of **113** with $Pb(OAc)_2$ yielded **112**. Alternatively, using cyclohexene and Pd/C could be used to selectively prepare **112** from **111**.

2-Azidobenzoisothiazole **114** undergoes thermolytic or photolytic ring opening to afford the otherwise very difficult to obtain nitrosothiols, which can undergo cyclization with alkenes to afford intermolecular Diels–Alder adduct **115** along with trace amounts of decomposition product **116** (Scheme 26).[64,65] Alternatively, nitrosothiol dimerization generates thiodiimide **117**.



Scheme 26 Reactions of 2-azidobenzoisothiazole **114**.



Scheme 27 Ring-opening of azide **118**.

In the search for molecules suitable for photoaffinity labeling, Platz and coworkers investigated 8-azidoadenosine derivatives.[66] The perbenzoylated ribose analog **118**, when subjected to laser photolysis, underwent ring-opening to afford what the authors attribute to **119** (Scheme 27). Although a full computational analysis was performed on the ring opening of **118**, full structural characterization was not performed due to the inherent instability of the resultant diazoquinodimethane **119**.

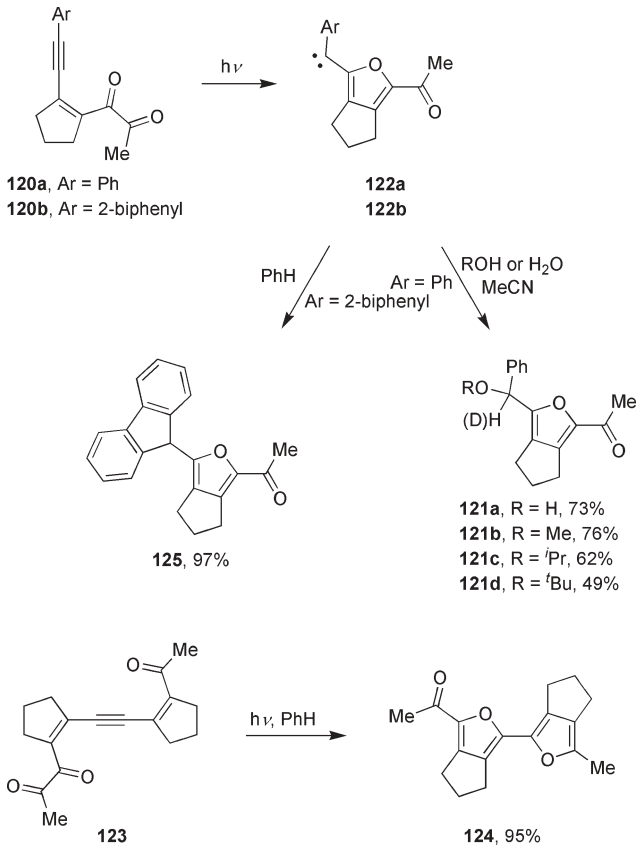
3. Ring formation reactions

3.1 Carbonyl-ene-yne

Until the mid-1990s, 5-membered heterocyclic carbene or nitrene intermediates were primarily a result of decomposition reactions, which as outlined in the previous section generally afforded either ring-opened products and/or heterocycles *via* trapping of the electron deficient center. Generating such intermediates and using them in ring forming reactions, however, was unrecognized as a viable method for heterocycle synthesis.

In their quest to develop novel radical generating systems to act as photochemical DNA cleavers, Saito *et al.* serendipitously discovered in 1995 that α-diketones conjugated with an ene-yne motif (**120a**,**b**) undergo photolytic cyclization in aqueous conditions to give O–H insertion benzylfuran product **121a** in modest yield (Scheme 28).[67] Subsequent optimization afforded both aqueous and alcoholic carbene-trapped furan products in very good yields (**121a–d** *via* carbene **122a**).[68] Photolysis in deuterated solvents led to deuterium incorporation specifically at the benzylic position. The resultant carbenes generated by this method were quite versatile and could induce cyclization of diketone **123** to give bisfuran **124** in excellent yield.[68,69] Alternatively, if a biphenyl moiety was incorporated as in **120b**, carbene **122b** could undergo intramolecular C–H insertion to furnish fluorene **125** in near quantitative yield.[69] The key to successful furan ring synthesis under the photolytic conditions employed was the α-diketone structural motif.

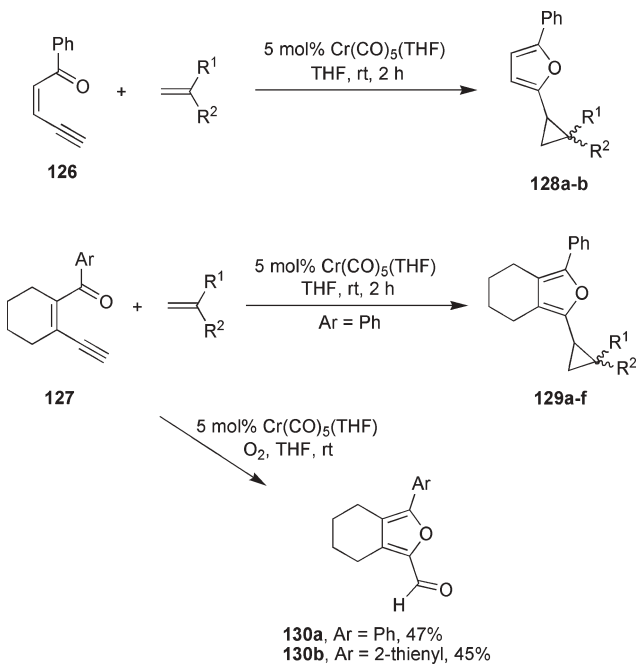
The catalytic use of transition metal complexes to afford more stable carbene intermediates has greatly expanded the synthetic viability of the ketone-ene-yne cyclization, leading to a variety of fused aromatic ring systems.[70] For example, 5 mol% $Cr(CO)_5(THF)$ readily induces cyclization of **126** and **127** to yield stable (2-furyl)carbene-Cr complexes (Scheme 29). The carbenoids can be intercepted by a variety of alkenes to furnish the corresponding cyclopropanes **128a–b** and **129a–f** in very good yields with varying ratios of *cis : trans* (Table 4),[71,72] or trapped with molecular oxygen[73] to afford furfuraldehydes



Scheme 28 Photolytic cyclization of ene-yne-diones **120** and **123**.

130a–b.[74] Rh salts can also be employed as a carbene stabilizer for the cyclization of **127** (Table 4, entry 9).

In the presence of allyl sulfides, the resultant carbenes of the cyclization of **131a–c** undergo C–C bond formation to yield



Scheme 29 Cyclization of ene-yne-ones **126–127**.

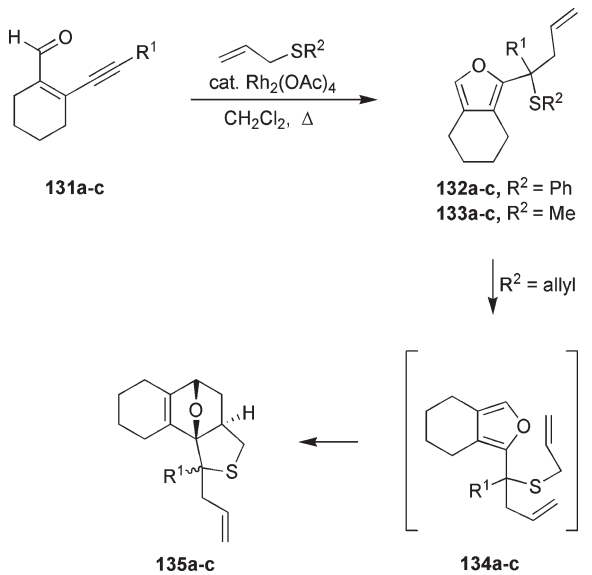
Table 4 Yields and products in the cyclization of **126–127**

Entry	Sm	R^1	R^2	Pdt, Yield (*cis : trans*)
1	**126**	OEt	OEt	**128a**, 82% (NA)
2	**126**	H	O^{t}Bu	**128b**, 63% (76:24)
3	**127**	H	O^{t}Bu	**129a**, 90% (60 : 40)
4	**127**	OEt	OEt	**129b**, 99% (NA)
5	**127**	$OSiMe_3$	Ph	**129c**, 83% (66 : 34)
6	**127**	H	Ph	**129d**, 85% (74 : 26)
7	**127**	Et	Et	**129e**, 54% (NA)
8	**127**	$–OCH_2CH_2CH_2–$		**129f**, 90% (*endo* only)
9	**127**[a]	H	O^{t}Bu	**129a**, 99% (90 : 10)

[a] 2.5 mol% $Rh_2(OAc)_4$ in THF, rt.

furans **132a–c** and **133a–c** *via* the Doyle–Kirmse reaction (Scheme 30, Table 5).[75] If diallyl sulfide was employed to generate the intermediate furans **134a–c**, the authors obtained excellent yields of the intramolecular Diels–Alder adducts **135a–c**.

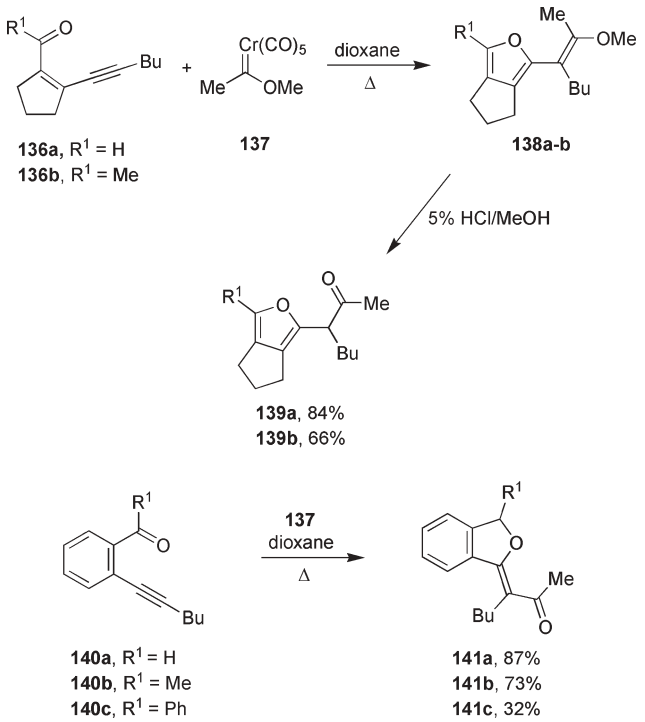
Cyclization of **136a–b** promoted by Fischer carbene **137** provided enol ethers **138a–b**; subsequent acidolysis furnished furans **139a–b** in good overall yield (Scheme 31).[76] Benzaldehyde **140a**, acetophenone **140b**, or benzophenone **140c** all exhibited similar reactivity, affording isobenzofurans which then tautomerized to the corresponding ketones **141a–c** in modest to very good yields.[77]



Scheme 30 Cyclization of ene-yne-als **131a–c**.

Table 5 Yields from tandem cyclization/Doyle–Kirmse reaction of ene-yne-als **131**

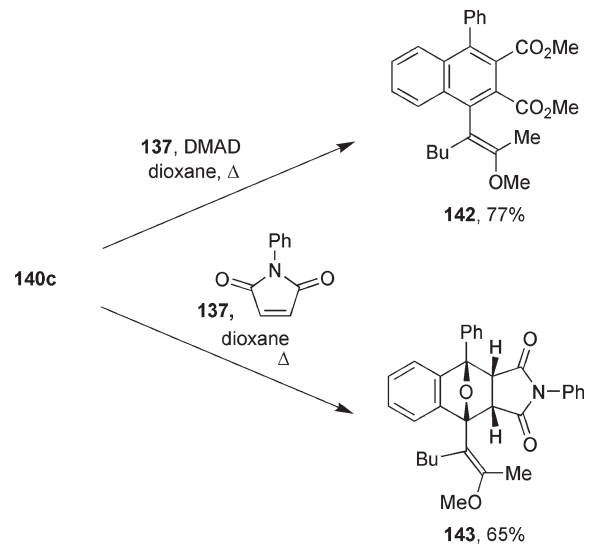
Sm	R^1	R^2	Pdt, Yield
131a	Bz	Ph	**132a**, 98%
131b	Ac	Ph	**132b**, 94%
131c	CO_2Me	Ph	**132b**, 83%
131a	Bz	Me	**133a**, 77%
131b	Ac	Me	**133b**, 72%
131c	CO_2Me	Me	**133c**, 91%
131a	Bz	Allyl	**135a**, 92%
131b	Ac	Allyl	**135b**, 80%
131c	CO_2Me	Allyl	**135c**, 90%



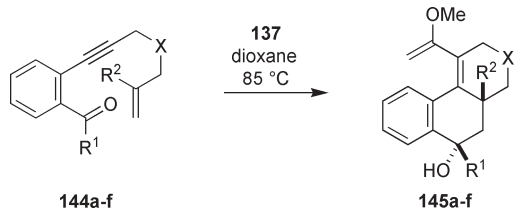
Scheme 31 Cyclization of ene-yne-carbonyls **136** and **140**.

The initially formed isobenzofurans, although quite unstable, are still useful synthetic intermediates and readily undergo intermolecular Diels–Alder cyclizations. For example, reaction of **140c** with **137** in the presence of DMAD or *N*-phenylmaleimide provided cycloadducts **142** or **143**, respectively, in very good yield (Scheme 32).[77]

Intramolecular Diels–Alder reactions with isobenzofurans can be accomplished by tethering an alkene to the alkyne moiety, as in **144a–f**, to afford hydrophenanthrene derivatives **145a–f** by way of an oxanorbornene ring (Scheme 33, Table 6).[78] The alkene for tandem cyclization/intramolecular Diels–Alder can also be incorporated into the system *via* the



Scheme 32 Cyclization/Diels–Alder reactions of **140c**.



Scheme 33 Cyclization/Diels–Alder reactions of **144a–f**.

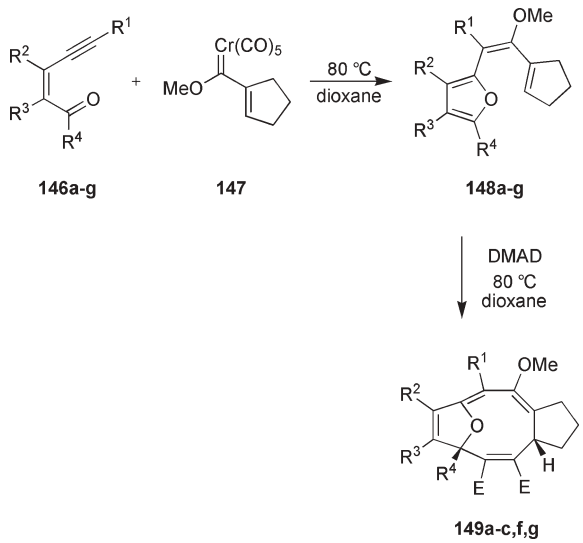
Table 6 Yields of the tandem cyclization/intramolecular Diels–Alder reaction of **144**

Entry	R^1	R^2	X	Yield **145**
a	H	H	CH_2	60%
b	H	H	O	37%
c	Me	H	O	34%[a]
d	H	H	$C(CO_2Me)_2$	51%
e	H	Me	$C(CO_2Me)_2$	60%
f	H	H	NTs	56%

[a] Accompanied by 13% yield of a Pauson–Khand by-product.

Fischer carbene complexes.[79] *o*-Alkynylbenzamides undergo the expected tandem cyclization/intramolecular Diels–Alder when an alkene is incorporated into the Fischer carbene compound or into the benzamide moiety.[80] Incorporation of a nitrile into the Fischer carbene complex allows for tandem isobenzofuran formation/intramolecular aza-Diels–Alder to form quinoline derivatives.[81] Although the reactivity of the carbonyl-ene-yne system with Cr Fischer carbene complexes is versatile, the reactions sometimes suffer from low yields, formation of multiple products, and the requirement of stoichiometric amounts of Cr reagents.

The synthesis of furan-bridged 10-membered rings is attained through the [8 + 2] cycloaddition of dienylfurans and DMAD.[82] Upon reaction of carbonyl **146a–f** with α,β-unsaturated Fischer carbene complex **147** and DMAD, macrocycles **149a–c,f,g** were obtained in good yields (Scheme 34). Furan **148** could be isolated; however, the yields for macrocycle formation were slightly better when the one-pot



Scheme 34 Cyclization/cycloaddition reactions of **146a–g**.

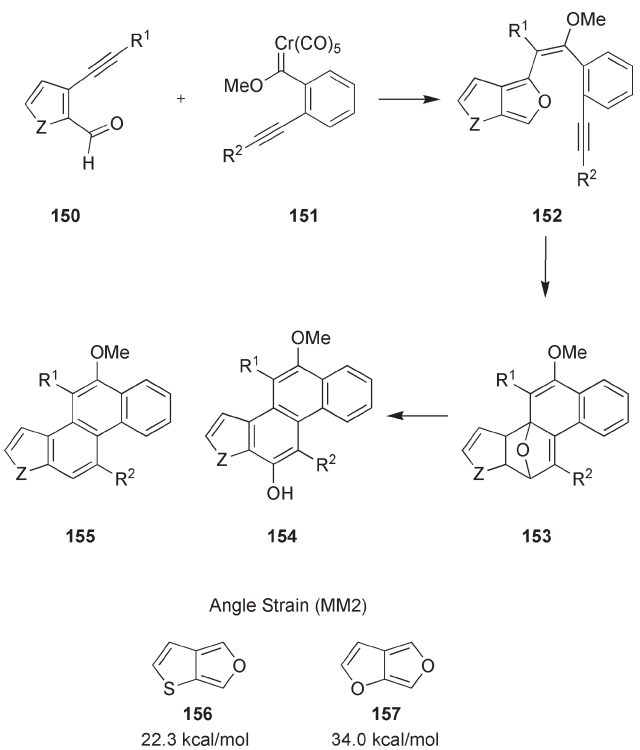
Table 7 Cyclization/cycloaddion reactions of **146a–g**

Entry	R^1	R^2	R^3	R^4	**148**	**149**
a	Bu	$-CH_2CH_2CH_2-$		H		64%[a]
b	Bu	$-CH_2CH_2CH_2-$		H	78%	78%[b]
c	Bu	$-CH_2CH_2CH_2-$		Me		58%[a]
d	Bu	Ph	H	H	72%	0%[b]
e	Bu	^{t}Bu	H	H	74%	0%[b]
f	H	^{t}Bu	H	H		62%[a]
g	$SiMe_3$	H	H	H		60%[a]

[a] Yield for one-pot reaction involving furan formation and [8 + 2] cycloaddition. [b] Yield for [8 + 2] cycloaddition only.

reaction was performed (Table 7, entries 1 and 2). It was noted that **146d**,**e** yielded only the dienylfuran, and none of the macrocycle. This is attributed to the large substituent groups preventing the furan from attaining a confirmation required for cycloaddition. This tandem cyclization/cycloaddition is also possible using *o*-ethynylphenyl-carbonyl compounds as the cyclization precursor.[83]

Through the tandem cyclization/carbene trapping/cycloaddition of furan- or thiophene- based carbonyl-ene-yne systems, it is possible to quickly construct polyaromatic compounds that contain one heteroatom. In the study of 3-alkynyl-2-formylheteroaromatic systems, Zhang and Herndon found conditions that allowed for the synthesis of two new phenyl rings in a one-pot two-step reaction.[84] Treatment of **150** with *o*-alkynylphenyl carbene complex **151** resulted in the formation of a furan ring and coupling with the carbene complex (Scheme 35). Furan **152** is set up to do an intramolecular Diels–Alder reaction to form two new 6-membered rings (**153**), which upon ring opening of the furan rearomatizes to yield **154**. The reaction proceeded at higher yields with the



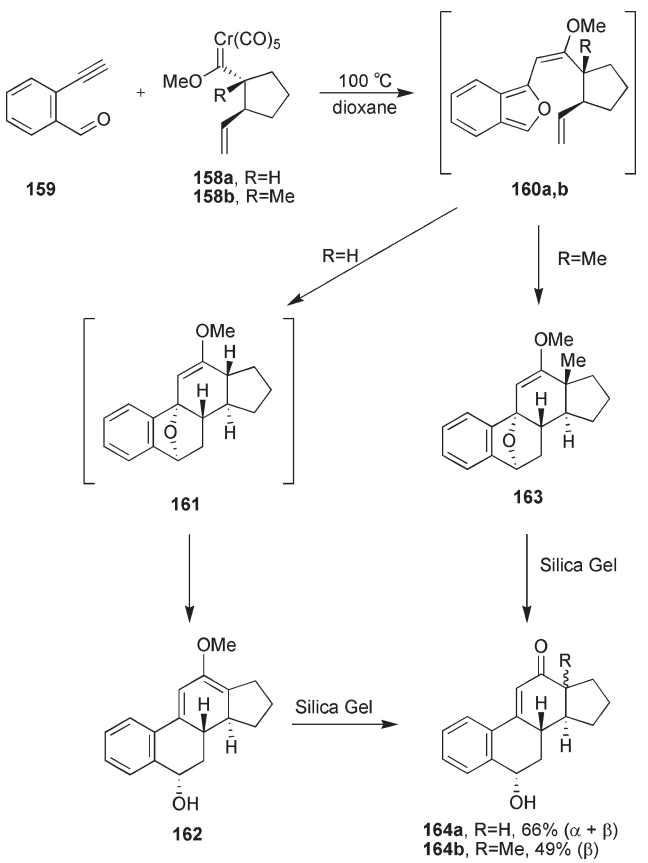
Scheme 35 Synthesis of annulated phenanthrenes **154** and **155**.

Table 8 Cyclizations of **150** to annulated phenanthrenes **154** and **155**

Entry	Z	R^1	R^2	**154**	**155**
a	S	H	$SiMe_3$	63%	21%
b	O	H	$SiMe_3$	6%	56%
c	S	H	Ph	9%	57%
d	O	H	Ph	0%	60%
e	O	Bu	Ph	0%	88%

thiophene core, and when diphenylacetylene Cr carbene complexes were used (R^2 = Ph), deoxygenated **155** was recovered (Table 8). This was postulated to arise from the insertion of a CO ligand from the chromium complex into the furan ring to give a diene lactone, which upon Diels–Alder/retro Diels–Alder would eliminate CO_2. The cyclization was found to proceed predominantly when the thiophene starting material was used, and this is believed to arise from the lower strain energy for the furan intermediate **156** *vs*. **157** (Scheme 35) This preference for 5-membered heterocycles to favor diene lactone formation under these reaction conditions has been used by Herndon in the synthesis of a cadinene natural product.[85]

Coupling of 2-ethynylbenzaldehyde with 2-alkenylcyclopentylcarbene-chromium complexes resulted in the formation of the steroid ring skeleton.[86] Using a general synthesis for the formation of the carbene complexes, Herndon and co-workers were able to synthesize several different steroids. Reaction of Cr-carbene complexes **158a,b** with benzaldehyde **159** resulted in the formation of isobenzofurans **160a,b** (Scheme 36). Compound **160a** can then undergo a Diels–Alder reaction to

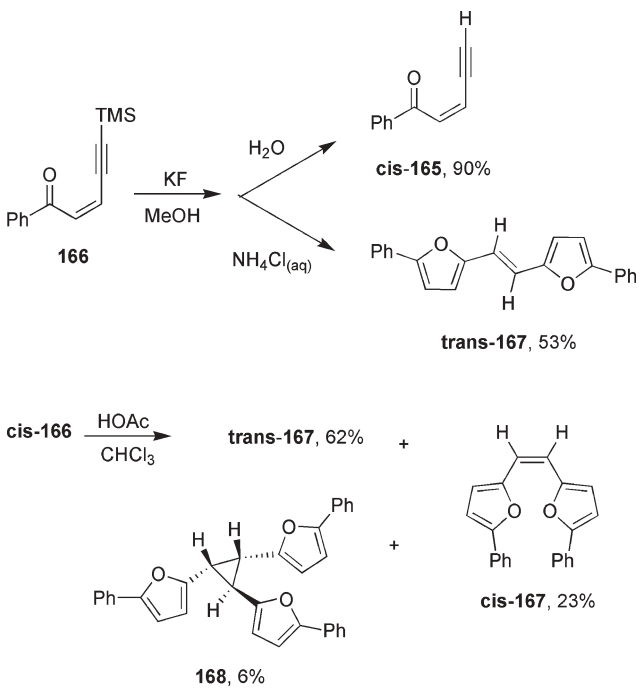


Scheme 36 Synthesis of steroid compounds **164a,b**.

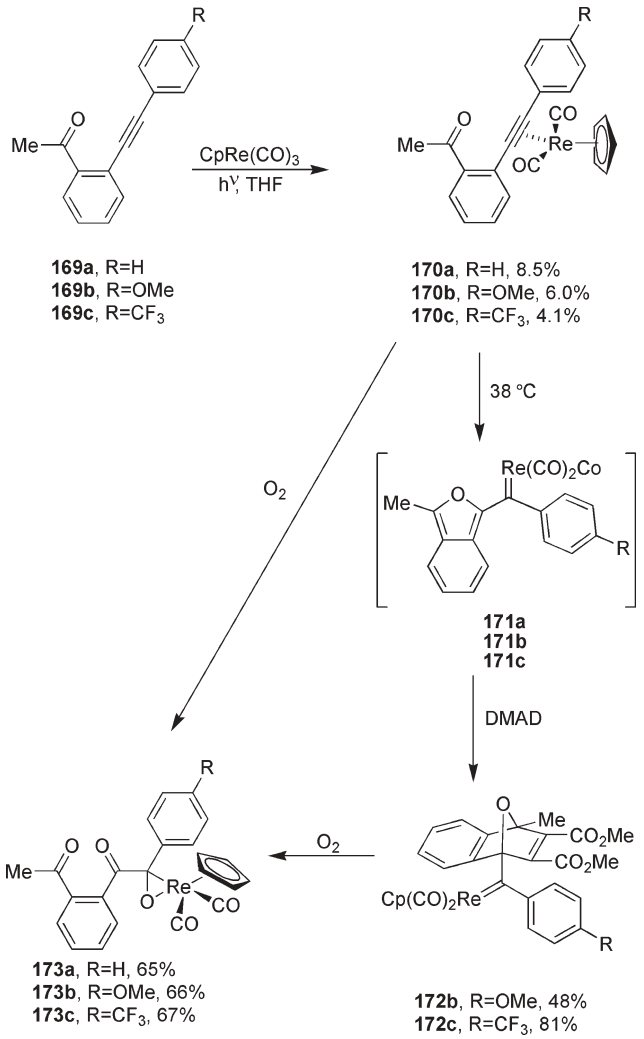
give **161**, which was found to be unstable and underwent ring-opening to afford steroid **162**. Hydrolysis of the labile methoxy group was accomplished with silica gel chromatography to give **164a**. When the methylated carbene complex **158b** was used, the Diels–Alder product **163** was isolable and could be converted to the steroid *via* silica gel chromatography. In the case where R = H, the product was recovered as a mixture of diastereomers in a 66% yield. Switching to a methyl resulted in 49% yield of a single diastereomer, and if a cyclohexyl carbene was used the yield jumped to 75%.

In their quest to synthesize novel alkynylcarbene rhenium complexes, Casey *et al.* discovered that the carbonyl-ene-yne system **165** was susceptible to acid-catalyzed cyclization.[87] Aqueous work-up following fluoride ion desilylation of **166**, at neutral pH, resulted in a 90% yield of the expected ene-yne-one ***cis*-165**. Work-up under slightly acidic conditions resulted in formation of the 1,2-difurylethylene ***trans*-167** as the only product in 53% isolated yield (Scheme 37). Intentional acid promoted cyclization of ***cis*-165** in AcOH resulted in a good combined yield of the furyl dimers ***cis*/*trans*-167** along with a small amount of the unique trifurylcyclopropane **168**. Although the products could be theorized to arise from carbene–carbene dimerization and subsequent [2 + 1] cyclo-addition of ***cis*** or ***trans*-167**, the reaction conditions do not support this hypothesis. Cyclization is facile in AcOH under ambient conditions without addition of transition metals, suggesting a different mechanism of cyclization than that encountered by Shechter *et al.*[3–6]

Still desiring to observe Re-alkyne complexes, Casey *et al.* moved to *o*-alkynylphenyl ketone derivatives **169a–c**, postulating that the decreased aromatic nature of isobenzofuran *versus* that of furan would lead to slower ring closing rates and allow for the detection of the uncyclized complexes.[88] Upon irradiating $CpRe(CO)_3$ in THF and subsequent treatment with



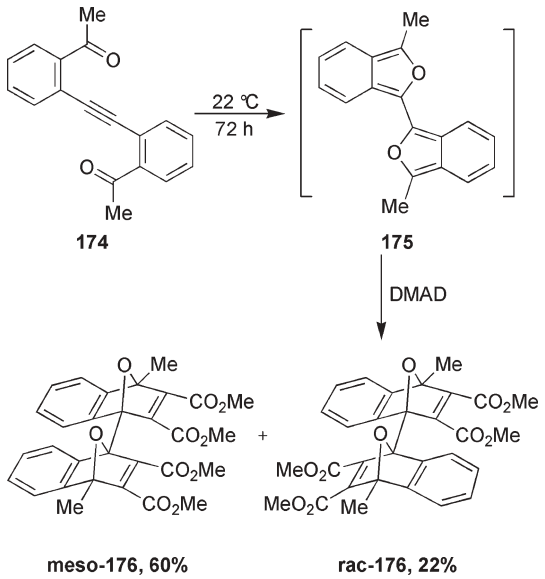
Scheme 37 Acid-catalyzed cyclization of ***cis*-166**.



Scheme 38 Reactions Re-alkyne complex **170a–c**.

169a–c, Re-alkyne complexes **170a–c** were isolated but in very poor yields (4–8%, Scheme 28). This is attributed to (1) incomplete photolysis of the Re starting material and (2) facile formation of Re-carbene complexes that arise from ring cyclization. Conversion of **170a–c** to the corresponding isobenzofuran carbene–Re complex **171** was achieved by heating to 38 °C. While the products were found to be too sensitive to isolate, monitoring the reaction by ^{13}C NMR spectroscopy indicated the formation of a carbene (δ 245.0 ppm). The isobenzofuran complex could undergo Diels–Alder reaction with DMAD to give Re-carbene **172**, which was sufficiently stable to afford crystals suitable for X-ray crystallography. When **172** was exposed to air, the complex rapidly disappeared and was replaced by diketone **173**. Alkyne complex **170** slowly converted also to **173** upon exposure to air over 100 h.

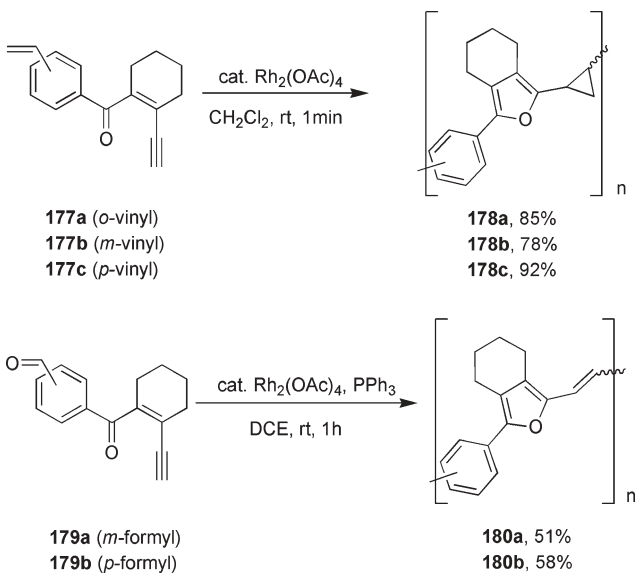
Double cyclization was obtained by linking two of the phenyl ketones together with an acetylene unit.[89] Alkyne **174** (Scheme 39) is obtained by the Sonogashira cross-coupling of *o*-iodoacetophenone with trimethylsilylacetylene, deprotection with KF followed by a second Sonogashira with *o*-iodoaceto-phenone. However, if this product remained in solution



Scheme 39 Bis-cyclization/Diels–Alder reaction of **174**.

overnight, an insoluble product formed which was theorized to be bis-isobenzofuran **175**. Dissolving **174** in neat DMAD and stirring under a N_2 atmosphere for 3 d gave cycloadducts ***meso*-176** and ***rac*-176** in 60% and 22% yields, respectively. These results confirm that **174** does indeed undergo a bis-cyclization to give **175**, which then undergoes double Diels–Alder reaction to give **176** as an isolable product.

The unique transition metal catalyzed cyclization of the carbonyl-ene-yne system coupled with the ability of carbenes to undergo [2 + 1] cycloaddition with an incorporated alkene has been utilized to synthesize novel furylcyclopropyl polymers (Scheme 40).[90] $Rh_2(OAc)_4$-catalyzed cyclization/polymerization of **177a–c** afforded the cyclopropyl-linked polymers **178a–c** in very good yield and decent molecular weight distribution. The UV/vis data, however, were the same for both the polymer and the monomer. The extent of conjugation



Scheme 40 Polymerization of **177** and **179**.

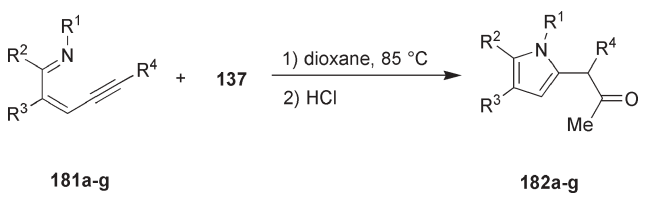
across the polymers could be increased (and hence alter the optical properties of the polymer) *via* a modified Wittig-type condensation with an attached benzaldehyde functionality as in **179a–b** and the *in-situ* formed (2-furyl)phosphorus ylide to form C=C linked furyl polymers (**180a–b**) in moderate yield. Subsequently, with an increase in the conjugation across the polymer due to the alkene linkages, the λ_{max} underwent a bathochromic shift of 150 nm in relation to the cyclopropyl linked polymer.

3.2 Imine-ene-yne

In comparison to the carbonyl-ene-yne system, there are few examples in the literature utilizing the imine-ene-yne conjugated system to synthesize pyrroles. Following their work with Fischer carbene complexes, Herndon and co-workers prepared pyrroles **182a–g** in moderate to good yield from the corresponding imine-ene-yne system **181a–g** in conjunction with **137** (Scheme 41, Table 9).[91] The best results were obtained with *N,N*-dimethylhydrazo imines while *N*-tosylimine and *N*-benzylimine were much less effective at cyclizing to the pyrrole (entries b and c).

Rhodium proved to be a very efficient catalyst for the cyclization of differently *N*-substituted imines for the synthesis of (2-cyclopropyl)pyrroles. Utilizing only 2.5 mol% of $Rh_2(OAc)_4$ to induce cyclization of **183a–c**, a variety of differently functionalized alkenes could be employed as carbenoid traps resulting in (2-cyclopropyl)pyrroles **184a–i** in varying ratios of *cis : trans* (Scheme 42, Table 10).[92] The resultant products were unstable and purification on silica was accompanied by lowered yields. Florisil, however, proved to be a viable chromatographic stationary phase and facilitated *cis*/*trans* isomerization with the *trans* isomer the major product after purification in each case. Following cyclopropanation of **183a**, pyrrolinone **185** could be synthesized in very good yield (but no diastereoselectivity) by heating with dilute acid.

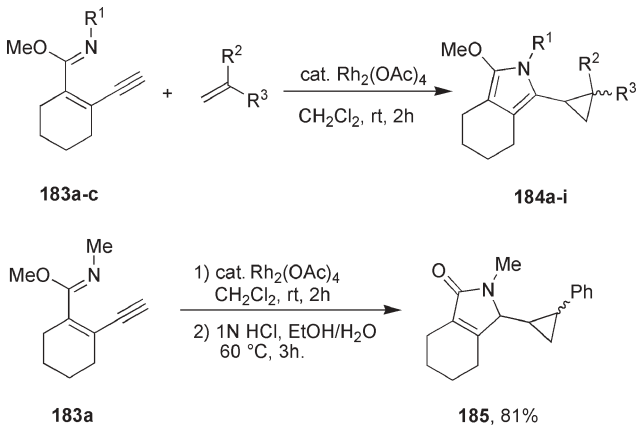
The imine-ene-yne system **186a–h** also afforded pyrroles. Cyclization with 5 mol% $TpRuPPh_3(MeCN)_2PF_6$ [Tp = tris(1-pyrazolyl)borate] in the presence of 1.5 equiv. H_2O gave 2-(hydroxymethyl)pyrroles **187a–h** in very good yield



Scheme 41 Cyclization/acidolysis reactions of **181**.

Table 9 Synthesis of pyrroles *via* coupling of Fischer carbene complexes with **181**

Entry	R^1	R^2	R^3	R^4	Yield (**182**)
a	NMe_2	Ph	H	Bu	62%
b	Ts	Ph	H	Bu	37%
c	Bn	Ph	H	Bu	9%
d	NMe_2	Bu	H	Bu	64%
e	NMe_2	H	H	Bu	70%
f	NMe_2	$-(CH_2)_4-$		Bu	36%
g	NMe_2	H	Allyl	Bu	64%

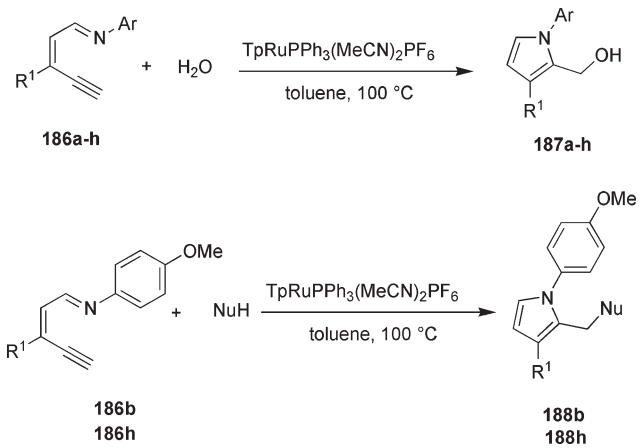


Scheme 42 Cyclization reactions of **183** and subsequent acidolysis.

Table 10 Synthesis of 2-cyclopropylpyrroles **183**

Entry	R^1	R^2	R^3	Yield (*cis*/*trans*)[a] (**184**)
a	Me	H	Ph	100% (74 : 26)
b	Me	H	Ph	82% (4 : 96)[b]
c	Me	Me	Ph	98% (59 : 41)
d	Me	H	O^{t}Bu	90% (10 : 90)
e	Me	OEt	OEt	100% (NA)
f	Me	$OSiMe_3$	Me	88% (76 : 24)
g	Allyl	H	Ph	99% (68 : 32)
h	Ph	H	Ph	99% (55 : 45)
i	^{t}Bu	H	Ph	18%[c,d]

[a] Without purification. [b] Isolated yield after purification on florisil. [c] Isolated yield after purification on SiO_2. [d] Ratio of *cis : trans* not reported.



Scheme 43 Cyclization reactions of **186** with H_2O and nucleophiles.

(Scheme 43, Table 11).[93] A variety of other alcohols and amines were also able to add across the carbene *via* either O–H insertion or N–H insertion to afford the alkoxy- or amino-pyrroles **188b,h** (Scheme 43, Table 12).

3.3 Azo-ene-nitrile

There is a singe example from the literature prior to the mid 1990s where an azo-ene-yne was utilized in the synthesis of the heterocyclic 2-phenyl-2*H*-indazole system.[94] 2-(Cyanophenyl) phenyldiazene **189** could be successfully cyclized in the

Table 11 Catalytic cyclization of imine-ene-yne **186** with H_2O

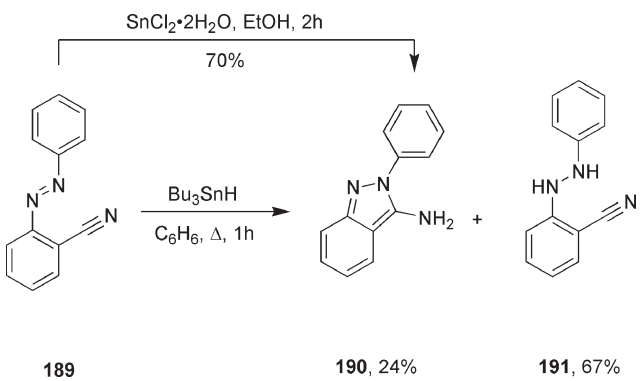
Entry	R^1	Ar	Yield (**187**)
a	Me	Ph	78%
b	Me	*p*-$MeOC_6H_4$	80%
c	Pr	Ph	80%
d	Pr	*p*-$MeOC_6H_4$	84%
e	Bu	Ph	85%
f	Bu	*p*-$MeOC_6H_4$	84%
g	Hex	Ph	82%
h	Hex	*p*-$MeOC_6H_4$	87%

Table 12 Catalytic cyclization of **186b** and **186h** with alcohols and amines

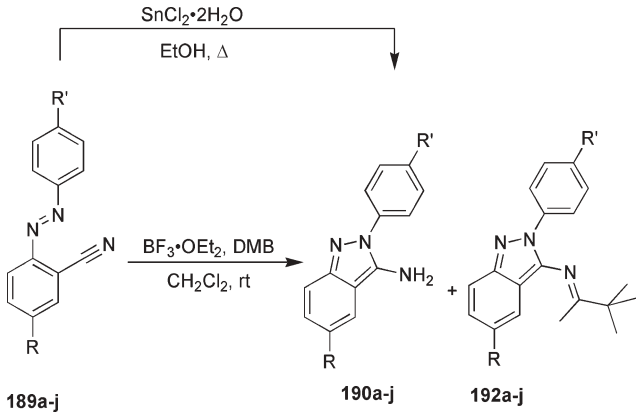
Entry	sm	NuH	Yield (**188**)
a	**186b**	MeOH	86%
b	**186b**	^{i}BuOH	82%
c	**186b**	CH_2=$CHCH_2OH$	86%
d	**186b**	^{i}PrOH	78%
e	**186b**	$PhNH_2$	68%
f	**186b**	PhMeNH	74%
g	**186h**	MeOH	89%
h	**186h**	PhMeNH	81%

presence of the two electron reductant $SnCl_2{\cdot}2H_2O$ (Scheme 44). This mechanism occurs presumably *via* reduction of the intermediate nitrene, followed by addition of two protons from the solvent to afford 3-amino-2-phenylisoindazole **190** in 70% yield. Similar results were obtained during the reduction of diazene **189** to its corresponding hydrazo compound utilizing Bu_3SnH. Along with the expected hydrazo compound **191** (67%), isoindazole **190** (24%) was also isolated.[95]

A more thorough investigation into the cyclization of substituted **189** mediated by $SnCl_2{\cdot}2H_2O$ as well as other Lewis acids was recently reported.[96] Treating **189a–j** with either $SnCl_2{\cdot}2H_2O$ or $BF_3{\cdot}OEt_2$ afforded two different products that were both derived from five-membered ring formation, furnishing either **190a–j** or **192a–j** (Scheme 45, Table 13). Interestingly, employing 2,3-dimethyl-2-butene (DMB) as a nitrene trap yielded **192**, where the Lewis acid bound nitrene behaves more like a nitrenium ion. The trap, when captured by the nitrenium, then undergoes a 1,2-methyl shift to yield imine **192a–j**.



Scheme 44 Sn-promoted reactivity of **189**.



Scheme 45 BF_3 and $SnCl_2$ mediated cyclization of **190a–j** or **192a–j**.

Table 13 Isolated yields for the cyclizations of **189a–j**

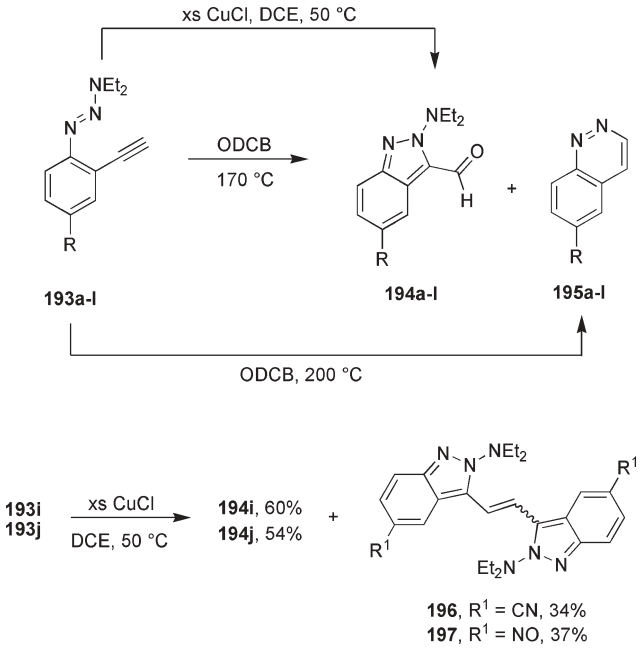
Entry	R	R′	**190**[a]	**192**[a]	**192**[b]
a	H	H	84%	16%	95%
b	^{t}Bu	H	94%	NA[c]	87%
c	Me	H	90%	5%	95%
d	Cl	H	95%	NA[c]	94%
e	OMe	H	72%	27%	74%
f	OMe	Br	79%	9%	76%
g	OMe	F	70%	27%	79%
h	OMe	CO_2Me	89%	4%	84%
i	OMe	CN	63%	30%	94%
j	OMe	NO_2	78%	22%	80%

[a] $BF_3{\cdot}OEt_2$ mediated reaction. [b] $SnCl_2{\cdot}2H_2O$ mediated reaction. [c] Amine not isolated if imine yield was >90%.

3.4 Azo-ene-yne

Our laboratory has been extremely successful in utilizing the conjugated azo-ene-yne system for the synthesis of a variety of uniquely substituted isoindazoles. For example, *o*-ethynyltriazenes **193a–l** are exceptional because they exhibit two different cyclization pathways depending on the reaction conditions, affording either isoindazolecarbaldehydes **194** or cinnolines **195** exclusively (Scheme 46). Treating **193** with excess CuCl, a known carbene stabilizer, furnishes the isoindazolecarbenes which are then subsequently trapped with molecular oxygen in high yields.[97] In the absence of copper, a mixture of **194** and **195** is obtained at 170 °C in *o*-dichlorobenzene (ODCB) (Table 14).[98] Increasing the temperature to 200 °C resulted in complete conversion to the cinnolines in excellent yields. When strongly electron donating groups are present, however, isoindazoles **194k,l** are the only products encountered under all reaction conditions attempted.[97] With strong electron withdrawing substituents on **193**, carbene dimerization, affording alkenes **196** and **197**, is a competitive side reaction at 50 °C.[99] Dimer formation could be suppressed if the reactions were run at room temperature.

The intermediacy of carbenes was confirmed by intermolecular [2 + 1] cycloaddition to give the cyclopropane **198** in 65% yield (Scheme 47).[16] Analogous to Saito's work, incorporation of a biphenyl moiety as in **199** afforded fluorene **200** in 55% yield *via* intramolecular C–H insertion (Scheme 47).[16]

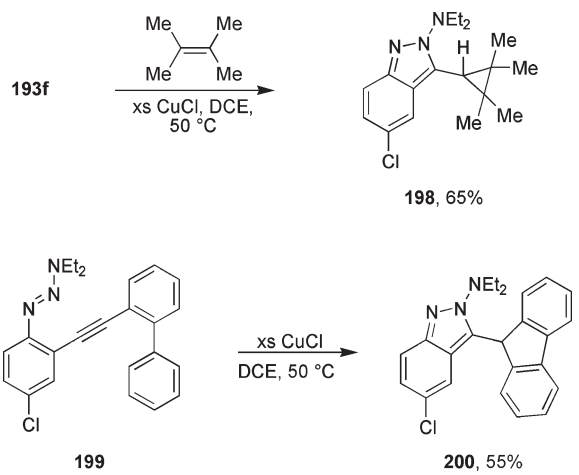


Scheme 46 Cyclization reactions of **193**.

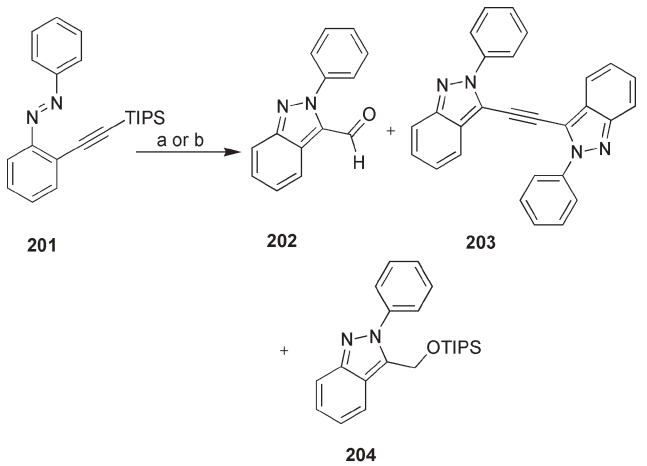
Table 14 Yields of the cyclization of triazenes **193**

Entry	R	Isoindazole[a,b] (**194**)	Cinnolines[a,c] (**195**)
a	H	55% [95%]	35% (99%)
b	Me	20% [90%]	51% (97%)
c	^{t}Bu	22% [96%]	61% (98%)
d	C≡CH	36% [91%]	39% (83%)
e	Br	15% [98%]	70% (98%)
f	Cl	14% [95%]	58% (97%)
g	F	25% [94%]	35% (90%)
h	CO_2Me	63% [83%][d]	28% (96%)
i	CN	50% [85%][d]	45% (98%)
j	NO_2	60% [78%]	25% (93%)
k	OMe	85% [98%]	0% (0%)
l	OAc	89% [86%]	0% (0%)

[a] Yield at 170 °C. [b] Yield of CuCl-promoted reaction in brackets. [c] Yield at 200 °C in parentheses. [d] Reaction run at rt.



Scheme 47 Carbene trapping reactions of **193f** and **199**.



a) 1) TBAF, THF/MeOH, rt 2) CuX, DCE, 0 °C

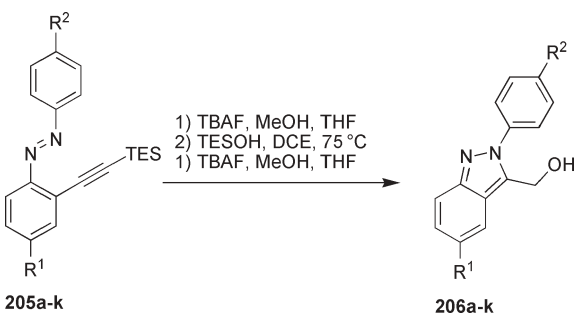
b) 1) TBAF, THF/MeOH, rt 2) DCE, 75 °C

	202	203	204
CuCl	10%	11%	9%
$CuCl_2$	39%	4%	3%
$Cu(OAc)_2$	5%	5%	3%
No Cu salt	0%	0%	61%

Scheme 48 Product distribution of the cyclization reactions of **201**.

Replacement of the diethylamino group by a phenyl unit results in a diazene (*e.g.*, **201**) which is amenable to facile cyclization, presumably due to the extended conjugation across the molecule and subsequent stabilization of the carbene. The deprotected *o*-ethynyldiazenes are quite unstable and decompose rapidly upon standing at room temperature; hence, fluoride-promoted desilylation of the alkyne must be followed immediately by either Cu or thermally induced cyclization. Under copper-promoted cyclization conditions a mixture of three products was obtained in 13–46% yield – the expected isoindazolecarbaldehyde **202**, the alkyne dimerized/cyclized bis-isoindazole **203**, and the residual TIPSOH-trapped isoindazole **204** (Scheme 48).[15] When thermal anaerobic conditions were employed, **204** was formed as a single product in 61% yield.

Optimization of the reaction resulted in stringent deprotection/cyclization/deprotection conditions utilizing the TES-protected alkynes **205** and TESOH as the carbene trap to afford a variety of differently substituted isoindazole-alcohols **206** in very good yield for the three synthetic steps (Scheme 49, Table 15).[15] To the best of our knowledge this is the first



Scheme 49 Deprotection/cyclization/deprotection reactions of **205**.

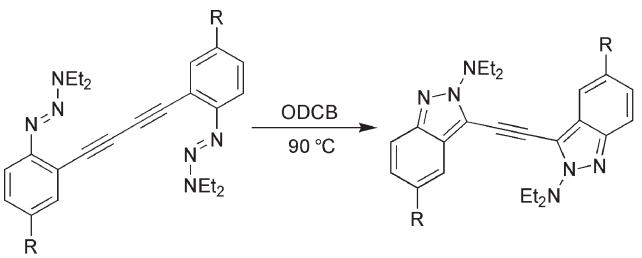
Table 15 Yields of the cyclization of diazenes **205**

Entry	R^1	R^2	**206**[a]
a	H	H	75%
b	Me	H	80%
c	^{t}Bu	H	79%
d	Cl	H	82%
e	C≡CH	H	80%
f	OMe	H	79%
g	OMe	Br	79%
h	OMe	F	78%
i	OMe	CO_2Me	72%
j	OMe	CN	73%
k	OMe	NO_2	54%

[a] Overall yield for three synthetic steps.

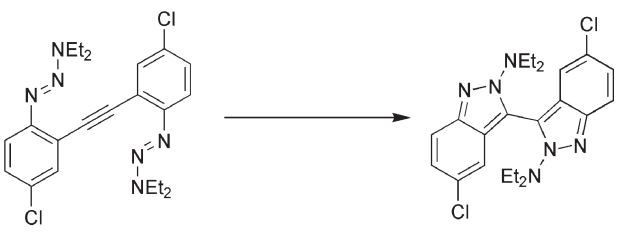
example of a coarctate cyclization that does not require a carbene stabilizer, Lewis acid catalyst or photochemical irradiation to induce cyclization.

Linking two phenyldiazenes or triazenes with either a mono- or diacetylene unit allows for the synthesis of bis-isoindazole systems *via* double cyclization.[17] Butadiyne-linked triazenes **207a–f** were obtained using Eglinton homocoupling conditions on monoyne **193**. Carbene stabilizers were not necessary to induce cyclization to **208**, which proceed in excellent yields simply by heating **207** in ODCB to 90 °C (Scheme 50).[17] These cyclizations were found to proceed even in the solid state over several months of refrigeration. Monoyne **209** could cyclize to the corresponding bis-isoindazole **210**, but required higher temperatures and/or carbene stabilizers to induce cyclization (Scheme 50). Interestingly, heating **207a–f** and **209** in excess



207a, R=H
207b, R=^{t}Bu
207c, R=Cl
207d, R=NO_2
207e, R=CN
207f, R=OMe

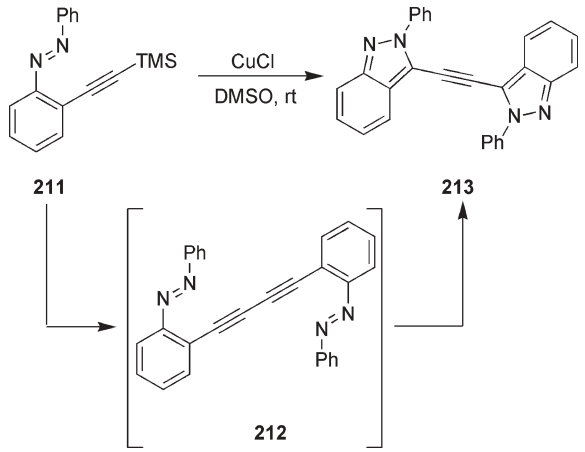
208a, R=H, 98%
208b, R=^{t}Bu, 99%
208c, R=Cl, 97%
208d, R=NO_2, 97%
208e, R=CN, 98%
208f, R=OMe, 87%



209 **210**

MeOH, CuCl, 125 °C	98%
PrOH, 200 °C	100%
DMB, CuCl, DCE, rt	98%
DMB, PrOH, 200 °C	97%

Scheme 50 Bis-cyclizations of diyne **207a–f** and monoyne **209**.

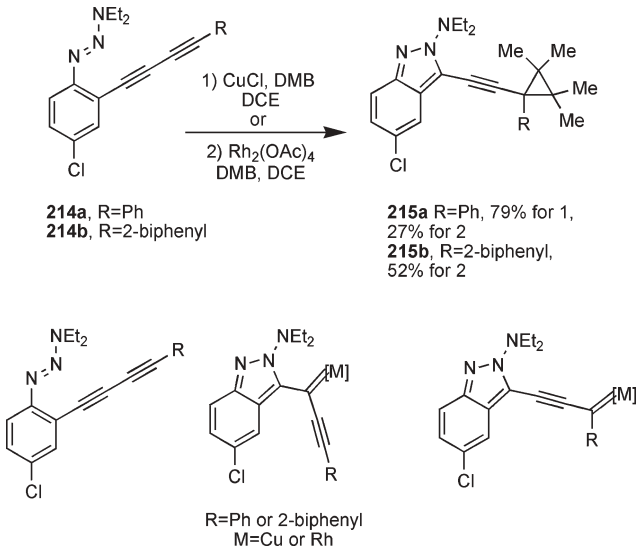


Scheme 51 Tandem homocoupling/bis-cyclization of diazene **211**.

DMB or protic solvents produced only **208a–f** or **210**; no products arising from carbene trapping were observed.

Synthesis of the butadiene-like diazene was attempted by subjecting **211** to a variety of homocoupling methods; however, the recovered material was identified as cyclized **213** (Scheme 51). Uncyclized dimer **212** was never isolated under any reaction conditions, and the cyclization only occurred in moderate yields. DFT computations suggest that both triazene systems cyclize *via* two-step processes, with relatively low activation barriers and short lived carbene intermediates. Alternatively, the diazenes (ethyne-linked cyclization was not attempted experimentally, only computationally) were found to go through a concerted, synchronous mechanism with 12 (monoyne) or 16 (diyne) bonds being made and broken simultaneously.

It was anticipated that replacing the second phenyltriazene moiety of **207** with either a phenyl or biphenyl would induce cyclization and allow the migration of the resulting carbenoid down the alkyne chain to be observed. Treatment of **214a,b** with either CuCl or $Rh_2(OAc)_4$ and DMB resulted in the cyclization of the triazene and migration of the intermediate carbenoid; [2 + 1] cycloaddition to DMB afforded isoindazoles **215a,b** as the only products (Scheme 52).[100] In both cases, cyclization was followed by migration and cycloaddition, with no observation of products arising from an unmigrated carbenoid. Surprisingly, **214b** did not undergo C–H insertion as had been seen with other carbene-biphenyl systems (*e.g.*, **199** to **200**). Additionally, if the reaction was carried out in the absence of DMB, no C–H insertion was observed.

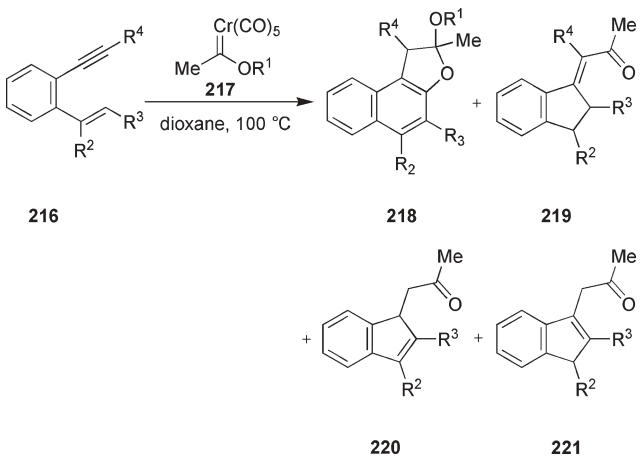


Scheme 52 Cu and Rh induced ring formation and carbenoid migration of triazenes **214a,b**.

3.5 Other cyclizations

The all-carbon ene–ene–yne system has been studied by Herndon and Zhang as a method to synthesize indenes and indanes through the coupling of *o*-ethynylstyrene derivatives **216** with Fischer carbene complexes **217** (Scheme 53).[101] Similar to other systems where five- or six-membered rings could be assembled depending on reaction conditions, it was shown that enhancing the nucleophilicity of the alkene while using electron deficient carbene complexes resulted in optimal formation of indene/indane species. If methoxy containing carbene species were employed, silica gel chromatography resulted in the deprotection and tautomerization of the intermediate enol ether. It was proposed that the indane formation proceeded *via* a 1,5-hydride shift, and suppression of this could favor indene production. This was achieved by using silyl groups which upon desilyation afforded indenes **220** and **221** in moderate to good yields depending on the location of the original silyl group (Table 16).

The serendipitous discovery that the ketone-imine-yne system could undergo cyclization to afford the corresponding 5-membered oxazole was reported by Kerwin and Feng.[102] Their work was initially motivated by an interest in the aza-Bergman rearrangement of conjugated 3-azaenediynes. Under the acidic reaction conditions employed, however, a portion of deprotected **223** was converted from the yne-imine to acyl-imine **224** which then underwent facile cyclization to afford methyleneoxazole **225** (Scheme 54). Carbene **225** subsequently underwent [2 + 1] cycloaddition with 1,4-cyclohexadiene to afford cyclopropane **226** in 35% yield along with nitrile **227** in



Scheme 53 Synthesis of indenes **220** and **221** from styrenes **216** and Ficher carbenes **217**.

Table 16 Yields for the cyclization of **216** to indenes **220** and **221**

Entry	R^1	R^2	R^3	R^4	Yield **217**	Yield **218**	Yield **219**	Yield **220**
a	Me	H	H	H	28%	26%	—	—
b	$-(CH_2)_2Cl$	H	H	H	8%	54%	—	—
c	Ph	H	H	H	13%	66%	—	—
d	Me	Me	H	H	—	3%	73%	—
e	Me	Me	H	$SiMe_3$ (H)[a]	—	5%	76%	—
f	Me	Ph	H	H	—	—	89%	—
g	Me	H	Me	H	40%	—	—	39%
h	Me	Me	Me	$SiMe_3$ (H)[a]	—	—	40%	12%
i	Me	O $SiMe_3$	H	$SiMe_3$ (H)[a]	—	—	79%	—

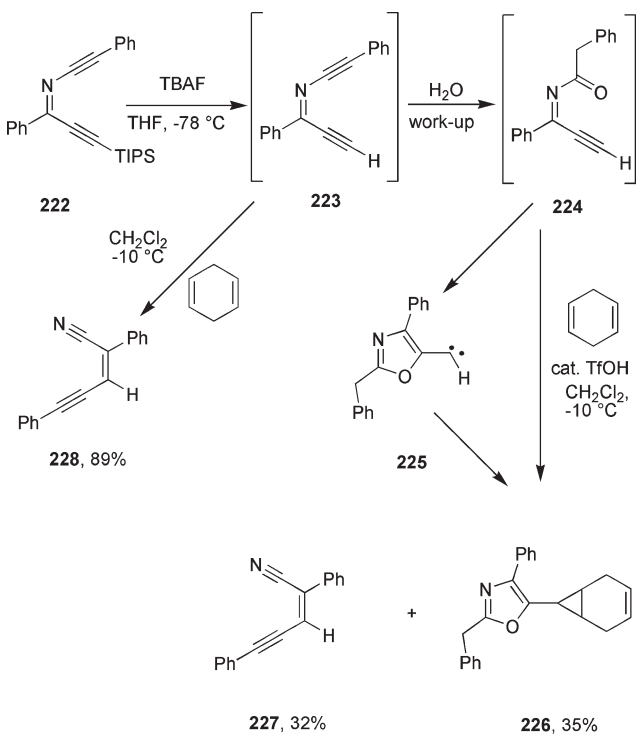
[a] Substituent in parentheses refers to final R^4 after desilyation from enol ether hydrolysis.

32% yield. In the absence of acid, nitrile **228** was isolated in 89% yield.

4. Conclusions

The ring opening reactions of 5-membered carbene or nitrene substituted heterocycles have been extensively studied in the literature. A variety of unstable and often unattainable functionalities can be synthesized in this manner and further utilized in the synthesis of novel heterocyclic compounds. In addition, their study is paramount to understanding the fundamental reactivity of the electron deficient carbene and nitrene moieties and their inherent propensities to undergo further rearrangement, solvent incorporation, or dimerization.

As the tools that organic chemists possess have greatly expanded over the last 20 years, particularly with the incorporation of organometallic chemistry into everyday practice, the ene–ene–yne conjugated system has also become an ideal skeleton for the construction of a variety of heterocycles. The number of publications on these types of ene–ene–yne cyclizations has risen sharply over the past few years and will likely continue to be a viable method for many years to come. The variety of 5-membered heterocycles that can be accessed with this methodology is only limited by the synthesis of the hetero-ene–ene–yne precursors. Once prepared, all that is needed is determination/optimization of the appropriate cyclizing agent and reaction conditions.



Scheme 54 Aza-Bergman rearrangement and hydrolysis/cyclization reaction of **222**.

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