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SYNTHETIC ASPECTS OF DIELS–ALDER CYCLOADDITIONS WITH HETERODIENOPHILES

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CONTENTS

1. INTRODUCTION

The Diels–Alder reaction is clearly one of the most useful synthetic methods in organic chemistry. This statement is supported by the appearance of several hundred publications annually dealing with both preparative[1] and mechanistic[2] aspects of this father of cycloaddition reactions. The vast majority of the work reported in this area has dealt with additions of conjugated 1,3-dienes with ethylenic and acetylenic dienophiles to produce carbocyclic systems. However, it has been known for decades that reactive species can be generated in which one or both of the dienophile carbon atoms have been replaced by hetero atoms, and that cycloadditions of these systems with conjugated dienes give entry to a variety of 6-membered heterocyclic compounds.[3,4] Unlike the all-carbon Diels–Alder reaction, the heterodienophile variation has received little systematic study and it is safe to say that until recently it has remained but a curiosity to the practicing synthetic chemist. Relatively few applications of this type of methodology to synthesis of complex molecules have been described to date. The apparent unwillingness of synthetic groups to exploit hetero Diels–Alder chemistry may be due in part to a lack of extensive data which complicates the task of incorporating such cycloadditions into sophisticated synthetic strategies.

Furthermore, a dearth of substantial mechanistic information exacerbates the situation and often precludes rational synthetic planning. It seems that hetero Diels–Alder reactions may run the gamut from the "usual" concerted/non-synchronous mechanism[2] to those which are clearly stepwise, dipolar events. In the former processes, polar-like transition states may well be involved.[5] Although frontier molecular orbital theory (FMO) has been invoked to rationalize some of the available experimental information,[6,7] little application of this theory to the bulk of existing data has appeared.

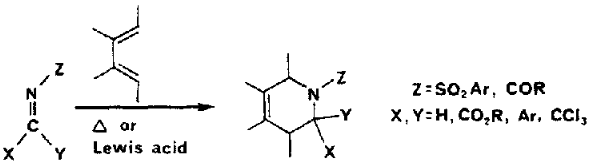
A comprehensive review of Diels–Alder cycloaddition reactions with heterodienophiles appeared in 1967, covering the literature through about 1965.[3] Other less complete reviews,[4] some dealing with specific sub-areas, have appeared since then (*vide infra*). It is the aim of this Report to critically survey the more important recent developments in this area with particular emphasis on potential synthetic applications. No attempt has been made to present an exhaustive review of the literature. Duplication and overlap with existing reviews has been minimized, and our primary intent has been to update earlier summaries.

2. C–N DIENOPHILES

A. *Imines*

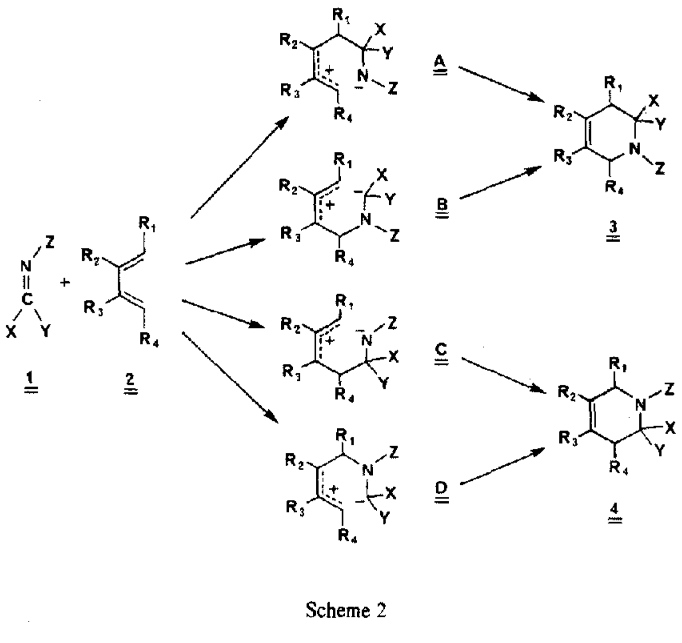
The use of imines as the dienophilic components of [4+2]-cycloaddition reactions was thoroughly reviewed in 1967[8] and was recently updated in 1979.[9]

Not all imino compounds are effective dienophiles. Simple Schiff bases have proven to be unreactive in [4+2]-cycloadditions unless exceptionally reactive dienes such as quinone methides are employed.[10,11] Electron deficient imines, however, provide more reliable reaction partners. In particular, N-sulfonylimines and N-acylimines add to many 1,3-dienes in good yields affording tetrahydropyridines (Scheme 1). Such cycloadditions can be effected either thermally or under Lewis acid catalysis. A relatively large number of examples exist of cycloadditions with these sorts of imines where substituents X/Y are usually hydrogen, aryl, trichloromethyl and/or carboxyl groups.[8,9] Such highly electrophilic imines are often unstable, and in the large majority of cases have been generated *in situ* from a more stable precursor (*vide infra*).



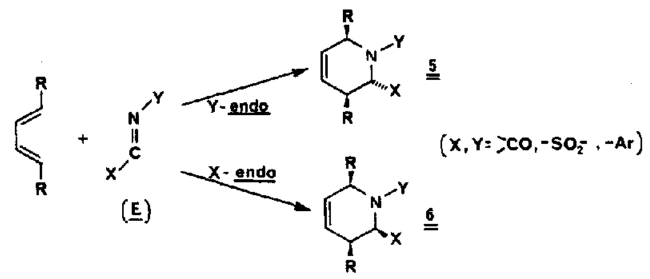
Scheme 1

Addition of an imine **1** to an unsymmetrical diene **2** can, in principle, give two regioisomeric adducts **3** and **4**. In fact, imino Diels–Alder reactions show an excellent regioselectivity comparable to all-carbon systems.[12] The simple empirical model shown in Scheme 2 can be effective in qualitatively predicting the major regioisomer in most unsymmetrical systems. If one considers the relative stability of the four possible dipolar "transition states" or "intermediates" **A–D** for cycloaddition of an N-acyl- or N-sulfonylimine with an unsymmetrical diene, one finds that the major product is derived from the most stable of these four possibilities. It should be emphasized that such a model may actually be little more than a mnemonic, since mechanistic data concerning these cycloadditions is scarce at present.



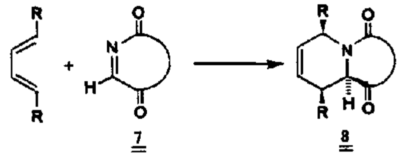
Scheme 2

Imino Diels–Alder reactions also show excellent stereoselectivity and some generalizations can be made. It appears from available data[13] that acyclic imines probably react via their (*E*)-isomers in most cases. However, many of the useable electron deficient imino dienophiles cannot be easily isolated. Also, the facile thermal (Z)/(E) isomerization in these systems and nitrogen lone pair inversion in the adducts results in loss of information about the geometry of the reacting imine. Thus, it has been impossible to unambiguously establish the nature of the reacting imino species. Scheme 3 outlines the stereochemical consequences of addition of an acyclic (E)-imine to a substituted diene. If the nitrogen substituent (Y) is *endo* in the transition state product **5** will be formed. Similarly, if the carbon substituent (X) is *endo*, product **6** will result. In general, π-substituents (e.g. carbonyl, sulfonyl, aryl) on nitrogen appear to be better *endo* directors than equivalent substituents on the carbon terminus of the dienophile.[13] Thus, adducts of type **5** predominate. The reason for this effect is not yet fully understood.[13]



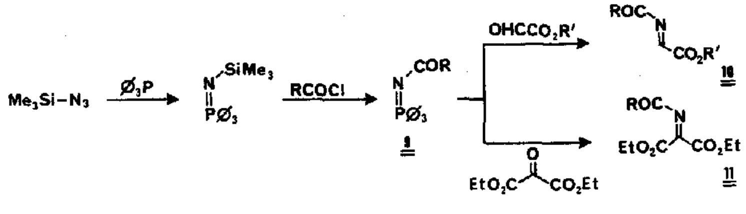
Scheme 3

The situation is more easily rationalized in the case of cyclic imines such as **7** (Scheme 4). Imine geometry here is, of course, unambiguous. The stereochemical outcome of this cycloaddition is easily predictable since both carbonyl groups of **7**, as anticipated, direct *endo*, and adduct **8** is the predominant product in these cases.[9,14]



Scheme 4

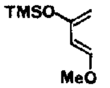
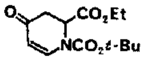
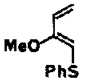
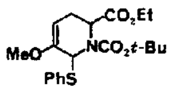
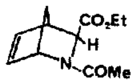
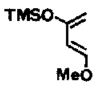
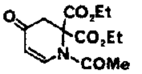
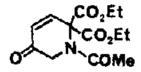
Recent work by Jung *et al.*[15] exemplifies many of the points outlined above. N-Acylimines **10** and **11** were prepared by aza-Wittig reactions of **9** as shown in Scheme 5.[16] Compound **11** was an isolable oil, whereas **10** was generated and used *in situ*. Acyl imines with several different R and R′ groups were prepared by variations of this approach.



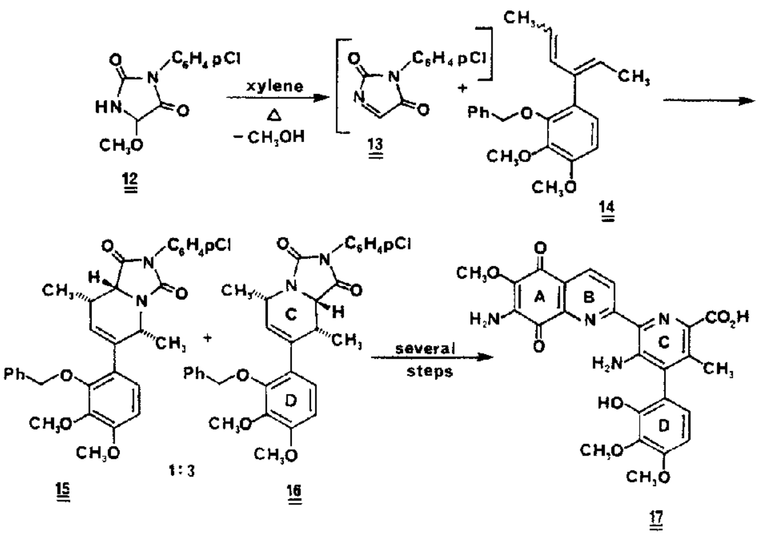
Scheme 5

A number of Diels–Alder cycloadditions were carried out with imines **10** and **11** using a few reasonably complex dienes under thermal conditions. Some typical examples are listed in Table 1. Note that in entries (1) and (2) only single regioisomers of predictable structure (Scheme 2) were found. The reaction in entry (4) gave a 3:1 mixture of regioisomers reflecting a near equivalence of the respective reaction transition states or intermediates (*cf.* **B** and **C** in Scheme 2 if R_1 = OMe, R_3 = OTMS). A single stereoisomer was produced in the reaction shown in entry (3). This product can be explained by assuming that the **E** form of imine **10** reacts *via* a transition state having the nitrogen carbonyl group *endo*, and thus the carboethoyl group assumes an *exo* position in the adduct.

Table 1. Cycloadditions of N-acylimines and dienes

Entry	Dienophile	Diene	Product(s)	Reaction Conditions	Yield(%)
(1)	10 (R=tBu; R'=Et)			(1) ϕH/Δ/15h (2) $H_3O^{\oplus}$	84
(2)	10 (R=tBu; R'=Et)			ϕH/Δ/12h	56
(3)	10 (R=Me; R'=Et)			DME/Δ/15h	81
(4)	11 (R=Me)			(1) 140°/2h (2) $H_3O^{\oplus}$	45
			+ 		15

Weinreb and coworkers have used an imino Diels–Alder reaction in construction of the C/D ring system of the antitumor antibiotic streptonigrin (**17**).[17,18] Methoxyhydantoin **12**,[14] on heating in xylene, produces unstable imine **13** which reacts with diene **14** to afford a 1:3 mixture of adducts **15** and **16** (Scheme 6). The stereochemistry of these adducts,[18] along with the regiochemistry of the major product

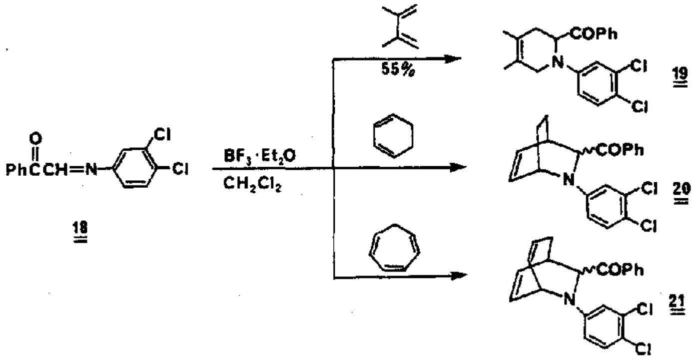


Scheme 6

16, were predictable based upon the generalizations noted above in Schemes 2 and 4. Interestingly, although diene **14** was a mixture of *cis*- and *trans*-disubstituted double bond isomers, only the *trans* compound was reactive in the cycloaddition. The desired adduct **16** was converted in a series of steps to streptonigrin (**17**).

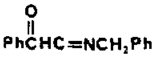
Diels–Alder reactions with N-acyl- and N-sulfonylimines are presently the most thoroughly studied cycloadditions of this type, but a wide variety of other imino compounds are known to participate as dienophiles.[8,9] However, little systematic study of these miscellaneous imines has appeared, and it should be emphasized here that the structural factors which make a C=N compound a useable dienophile have not yet been fully established.

A few examples of cycloadditions with N-aryl imines exist[19,20] and it appears that for sufficient reactivity a second electron withdrawing group must be present. For example, McKay and Proctor[19] have reported that imine **18** reacted with several dienes under $BF_3{\cdot}Et_2O$ catalysis (but not thermally, even under high pressure) to afford Diels–Alder adducts (Scheme 7). These workers have apparently not

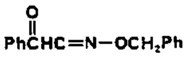


Scheme 7

established the stereochemistry of adducts **20** and **21**, although one might anticipate that the *exo* carbonyl forms would be the kinetic products of the last two additions.[13] It was also reported that imines **22** and **23** were unreactive as dienophiles even in the presence of $BF_3{\cdot}Et_2O$.

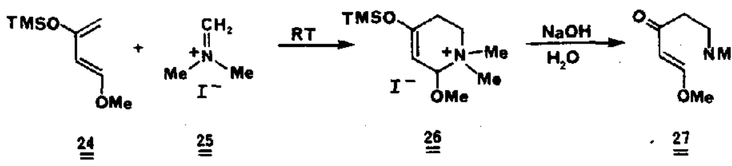

$\mathrm{Ph}\overset{O}{\overset{\|}{C}}\mathrm{HC{=}NCH_2Ph}$

22

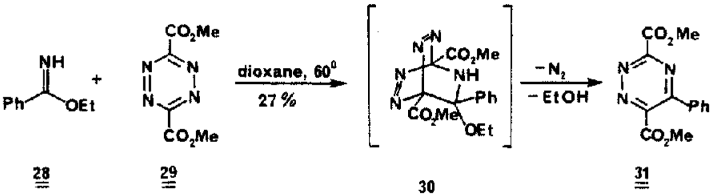

$\mathrm{Ph}\overset{O}{\overset{\|}{C}}\mathrm{HC{=}N{-}OCH_2Ph}$

23

It has been known for a number of years that simple iminium salts will react as dienophiles.[8,9] A recent example of this type of cycloaddition was reported by Danishefsky *et al.*[21] who found that diene **24** reacted with Eschenmoser's salt (**25**) to afford **26**. Cleavage of **26** with aqueous sodium hydroxide afforded a 95% overall yield of the interesting Mannich base **27**.



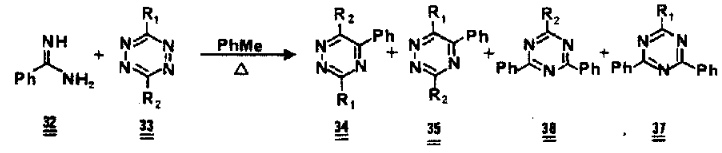
A few rare examples exist of electron rich imino ethers,[22] imino chlorides[8] and amidines[23] acting as dienophiles. These reactions are apparently not general, and are successful only with certain special electron deficient dienes. Condensation of imino ether **28** with tetrazine **29** afforded a low yield of triazine **31**, presumably formed *via* adduct **30** (Scheme 8).[22]



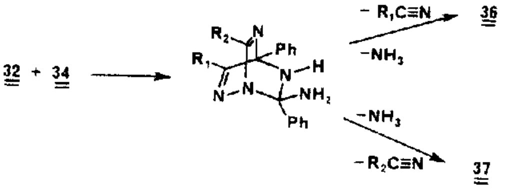
Scheme 8

In a related series,[23] amidine **32** was found to combine with several disubstituted tetrazines to yield a variety of heterocyclic products derived from initially formed Diels–Alder adducts. The results of this study are outlined in Table 2. *as*-Triazines **34** and **35** clearly arise *via* a Diels–Alder addition of **32** and **33**, producing a bicyclic intermediate like **30**. The s-triazines **36** and **37** have been shown to arise by further Diels–Alder reactions of excess amidine **32** with as-triazines **34** and **35**, respectively, as depicted in Scheme 9.

Table 2. Synthesis of as-triazines and s-triazines

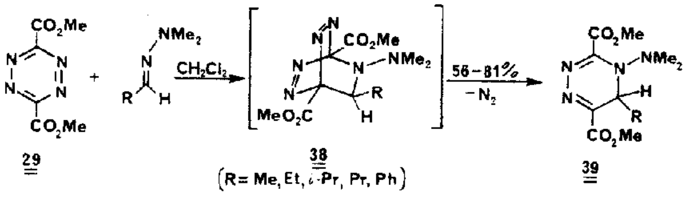


Entry	R_1	R_2				
(1)	2-pyridyl	2-pyridyl	33%		5%	
(2)	ϕ	ϕ	34%		-	
(3)	ϕ	2-pyridyl	7.5%	30%	28%	6%
(4)	ϕ	Me	-	70%	-	7%
(5)	2-pyridyl	Me	-	35%	-	-



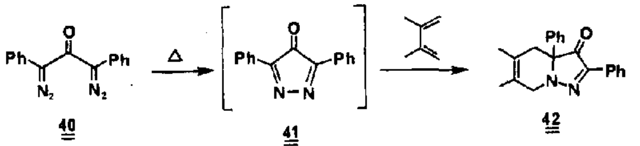
Scheme 9

Aldehyde dimethyl hydrazones have also been reported to add in Diels–Alder fashion to tetrazine **29** to give compounds such as **39** in good yields.[24,25] Bicyclic compound **38** is presumably an intermediate in these reactions but was not actually observed. Interestingly, ketone hydrazones react with **29** *via* their enamine tautomers, giving diazenes as products, and not structures of type **39**.



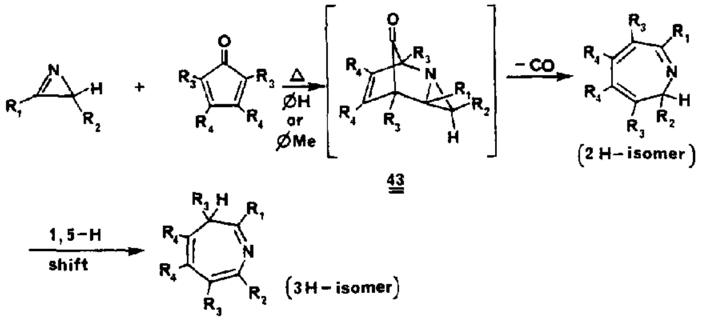
Scheme 10

Trost and Whitman[26] have generated the hydrazone **41** *via* thermolysis of *bis*-diazoketone **40** (Scheme 11). This reactive species was trapped with 2,3-dimethylbutadiene to afford adduct **42** in 85% yield.



Scheme 11

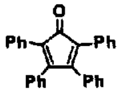
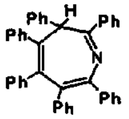
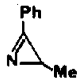
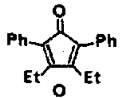
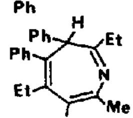
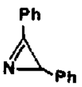
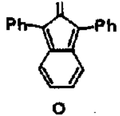
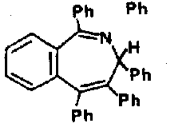
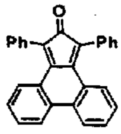
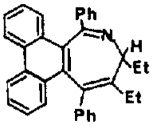
A series of rather interesting imino Diels–Alder reactions have been carried out over the past several years with 1-azirines as dienophiles.[27] Many examples have been published of thermal cycloadditions of substituted 1-azirines to cyclopentadienones as outlined in Scheme 12.[28,29] Bicyclic adducts of type **43**



Scheme 12

were never isolated but under the reaction conditions lost carbon monoxide to initially give 2H-azepines. These compounds are capable of undergoing a thermally allowed 1,5-hydrogen shift, affording the isomeric 3H-azepines. Some typical examples of this reaction are indicated in Table 3.[28] Hassner and

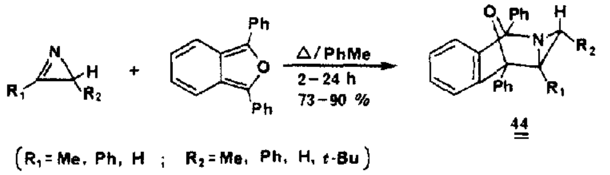
Table 3. Thermal addition of 1-azirines to cyclopentadienones

Azirine	Cyclopentadienone	Product	Reaction Conditions	Yield(%)
			toluene/Δ/ 4 days	61
			toluene/Δ	66
			xylene/Δ/10h	63
			toluene/Δ/ 2 days	90

Anderson[28a] have also examined the regiochemistry of addition of 1-azirines to unsymmetrical cyclopentadienones. Suffice it to say here that these reactions gave varying mixtures of isomeric 3H-azepines depending upon the nature of the substituents on diene and dienophile. These results have been rationalized in terms of possible electronic and steric factors influencing the cycloaddition.

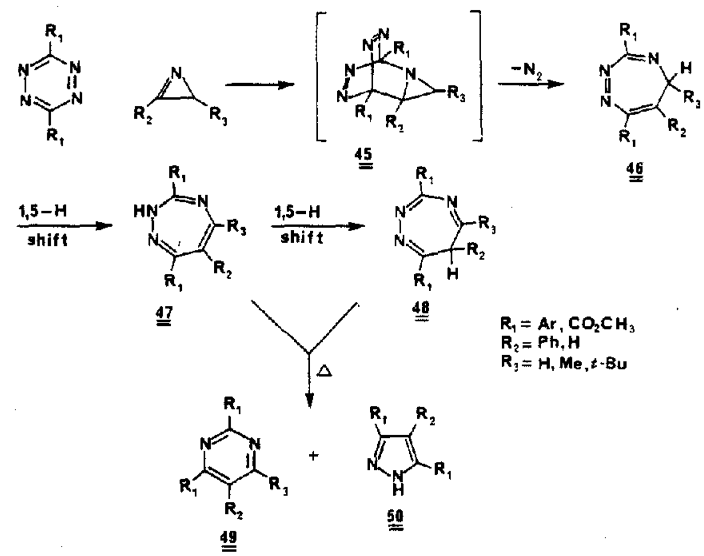
1-Azirines also add smoothly to diphenyl isobenzofuran to afford *exo* bicyclic adducts of structure **44**

(Scheme 13).[29] The *exo* selectivity has been explained on the basis of unfavorable secondary orbital interactions in the *endo* transition state.[29a]



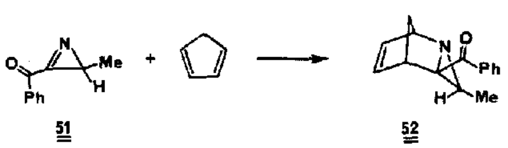
Scheme 13

Several groups have reported on the reactions of 1-azirines with s-tetrazines.[30] The nature of the products of this sort of reaction is dependent upon the structures of the azirine and tetrazine used, and upon the reaction conditions. The primary product from the cycloaddition (Scheme 14) is probably the triazepine **46**, presumably formed through the intermediacy of **45**. However, **46** can rearrange by a 1,5-hydrogen shift to **47** and another such shift would afford **48**. In addition, these triazepines can further rearrange to afford pyrimidines **49** and/or pyrazoles **50**.

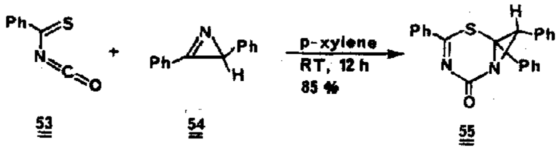


Scheme 14

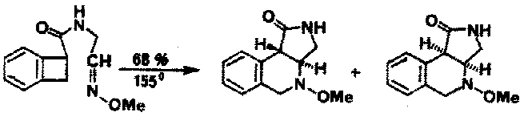
1-Azirines with alkyl or aryl substituents apparently do not add to simple 1,3-dienes other than those described above. However, it has been reported that the benzoyl azirine **51** does combine with cyclopentadiene, affording *endo* adduct **52**.[31]



Finally, Nair and Kim[32] have shown that 1-azirines such as **54** will undergo [4+2]-cycloaddition reactions with thiobenzoyl isocyanate (**53**) to yield structures such as **55**, which rearrange to some interesting heterocyclic systems.

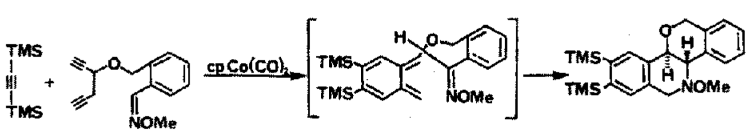


The recent flurry of activity in the area of intramolecular Diels–Alder chemistry[33] has spilled over to a limited extent into the hetero variation of the reaction. The initial example of an intramolecular imino Diels–Alder reaction was described by Oppolzer,[10] who found that upon heating benzocyclobutene **56** a mixture of tricyclic adducts **57** and **58** resulted. This cycloaddition proceeds through a thermally generated quinone methide which is a powerful enough diene to react with an oximino dienophile.



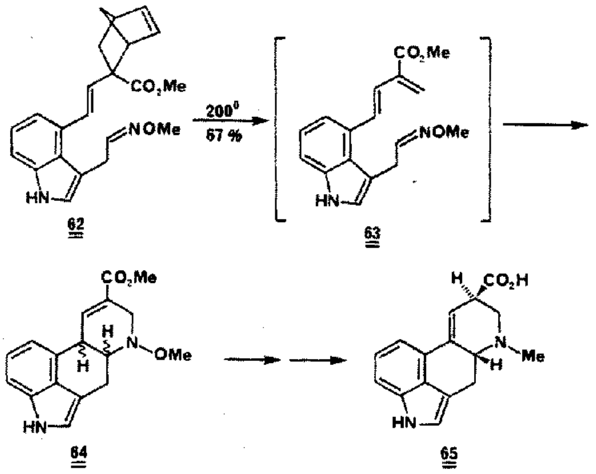
56 57 58

An elegant variation of this sort of intramolecular cycloaddition was recently reported by Funk and Vollhardt.[34] Co-oligomerization of *bis*-trimethylsilylacetylene with diyne **59** under mild conditions catalyzed by cyclopentadienylcobalt dicarbonyl gave a 45% isolated yield of *trans*-fused tetracyclic compound **61**. It appears that quinone methide **60** is an intermediate in this process, and cycloaddition occurs through an *exo* transition state leading exclusively to the stereochemistry observed in **61**. A similar stereochemical situation probably applies in conversion of **56** to **57**, but the *trans* isomer apparently epimerizes thermally to **58** under the cyclization conditions.[10]



59 60 61

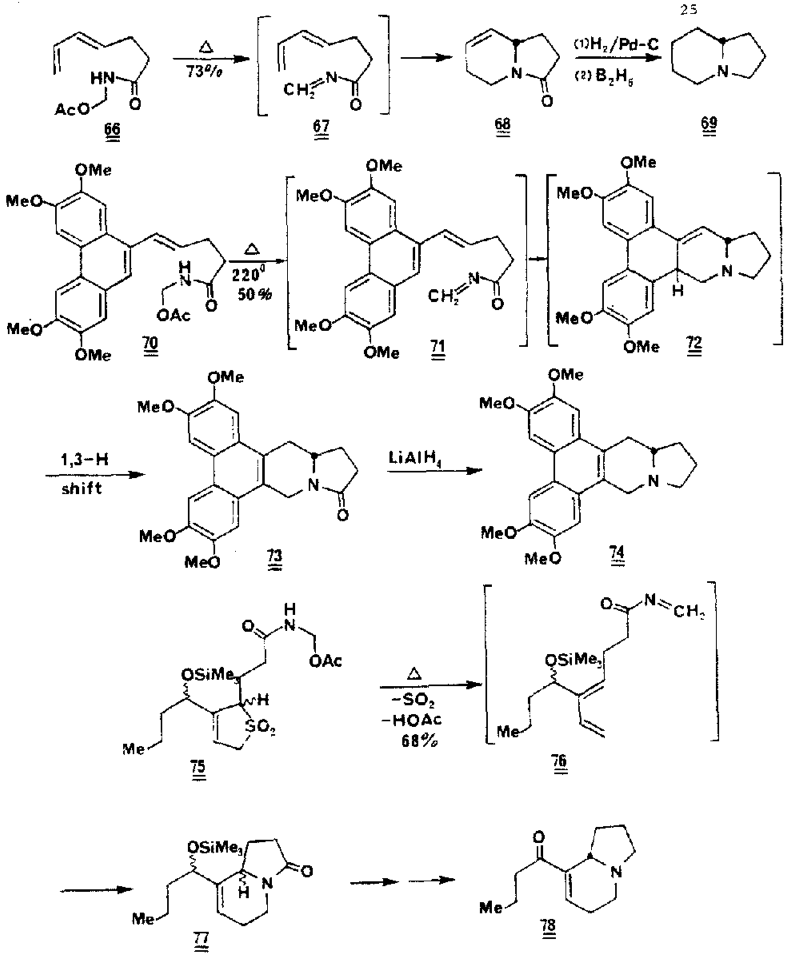
Oppolzer *et al.*[35] have devised a clever new total synthesis of lysergic acid (**65**) which has as its key step an intramolecular imino Diels–Alder reaction (Scheme 15). Compound **62** was prepared and was slowly added to refluxing trichlorobenzene. A retro-Diels–Alder reaction occurred liberating cyclopentadiene and affording diene **63** which cyclized to give tetracyclic indole **64** as a 3:2 mixture of diastereomers. Three additional steps served to convert **64** to (±)-lysergic acid (**65**). Of particular interest here is the fact that oximes are not normally reactive dienophiles, and clearly the intramolecularity of the conversion of **63**–**64** is crucial to the success of this transformation.[33]



Scheme 15

Recently, Weinreb *et al.*[36] have successfully explored the possibility of using intramolecular imino

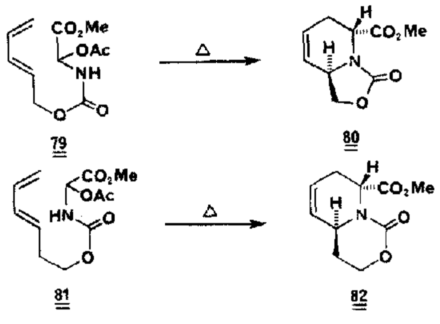
Diels–Alder reactions in total synthesis of some indolizidine alkaloids, namely δ-coniciene (**69**), tylophorine (**74**) and elaeokanine-A (**78**) (Scheme 16).



Scheme 16

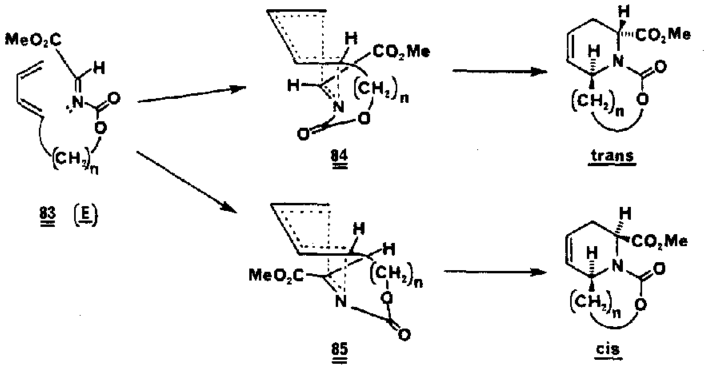
Short contact pyrolysis of diene **66** afforded a good yield of bicyclic lactam **68** which is believed to have formed *via* Diels–Alder cycloaddition of intermediate N-acylimine **67**. Similarly, heating **70** at 220° in bromobenzene (sealed tube) led to a 50% yield of the pentacyclic tylophorine precursor **73**, presumably formed through intermediates **71** and **72**. Finally, entry was gained to the ring system of elaeokanine-A (**78**) by short contact pyrolysis of **75** to afford bicyclic lactam **77** as a mixture of diastereomers. Thermal chelotropic elimination of SO_2 and loss of acetic acid from **75** was postulated to occur, affording intermediate dieneacylimine **76** which cyclized to **77**.

Weinreb *et al.* have also recently probed the stereochemistry of some intramolecular imino Diels–Alder cycloadditions.[37] Cyclizations of the type shown in Scheme 17 were found to be totally



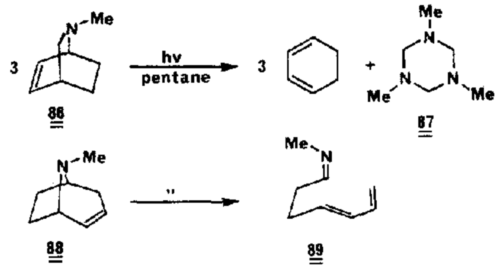
Scheme 17

stereoselective (much more so than intermolecular analogs[13]) and produced only the bicyclic isomers having the *trans* relationship of hydrogens adjacent to the ring nitrogen. This also appears to be a general phenomenon in other related systems.[37,38] A rationale is depicted in Scheme 18. It would seem that the reacting imino dienophile in these cases, formed from **79** and **81** by thermal elimination of acetic acid, must be the (E)-isomer **83**. An explanation based upon an intermediate (Z)-imine was considered untenable.[37b] Imine **83** can in principle cyclize *via* either transition state **84** or **85**, providing the *trans* or *cis* bicyclic compounds, respectively. However, the exclusive production of the *trans* adducts indicates that transition state **84** is favored over **85** by at least 3 kcal/mol. This result is in accord with the generalization (*vide supra*) for the intermolecular imino reaction, which stated that N-π-substituents are usually the controlling *endo* directors (see Scheme 3).[13] It is not clear why **84** is better than **85** nor is it evident why these intramolecular reactions are so highly stereoselective relative to similar intermolecular cases. Probably some subtle steric or conformational effects are adding to the selectivity.



Scheme 18

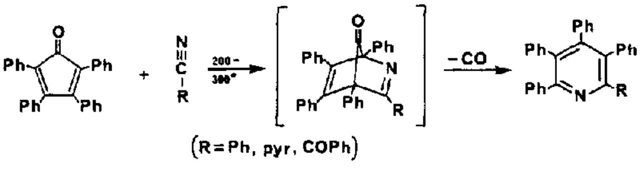
Our final note on imino Diels–Alder chemistry is a report that the retro reaction can be effected by photolysis of some adducts at 185 nm.[39] Thus, irradiation of **86** produced cyclohexadiene and imine trimer **87** (Scheme 19). Similarly, photolysis of tropidine (**88**) gave imino-diene **89** in 52% yield. This final example raises the intriguing question as to whether the forward reaction of **89** to **88** might be achieved in some manner.



Scheme 19

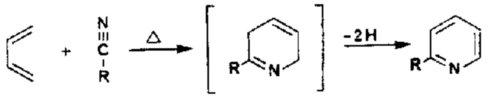
B. *Nitriles*

The ability of nitriles to act as Diels–Alder dienophiles has been known since 1935 when Dilthey discovered that tetracyclone reacted with several nitriles at high temperatures to afford substituted pyridines as outlined in Scheme 20.[40] This subject has been reviewed a few times since then,[41–43] but a number of recent developments are worthy of note here.

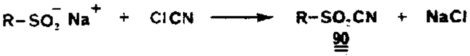


Scheme 20

One of the features of Diels–Alder reactions with nitriles which have made them unattractive dienophiles is the requirement of extremely high reaction temperatures (200–500°)[41] for cycloaddition. Under these extreme conditions, the initial dihydropyridine reaction products of nitriles and acyclic 1,3-dienes invariably oxidize to the corresponding pyridines (Scheme 21). However, it has been found recently that sulfonyl cyanides **90** will react with a variety of cyclic and acyclic dienes under much milder conditions.[44,45] These sulfonyl nitriles are readily prepared by reaction of a sodium sulfinate with cyanogen chloride (Scheme 22).



Scheme 21

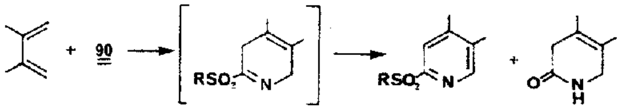


$$R{-}SO_2^-\,Na^+ + ClCN \longrightarrow \underset{\mathbf{90}}{R{-}SO_2CN} + NaCl$$

(R = aryl, benzyl, alkyl)

Scheme 22

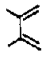
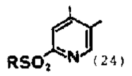
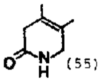
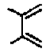
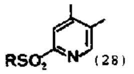
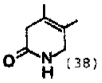
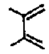
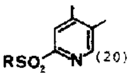
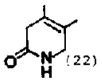
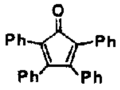
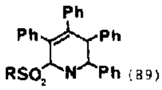
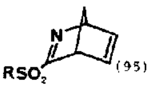
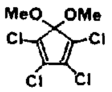
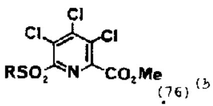
Cycloaddition of sulfonyl nitriles with dienes affords an initial dihydropyridine **91**, which under the reaction conditions is oxidized to pyridine **92** or is hydrolyzed *in situ* by a trace of moisture to give lactam **93** (Scheme 23). Table 4 contains some typical examples of cycloadditions reported to date. One



91 **92** **93**

Scheme 23

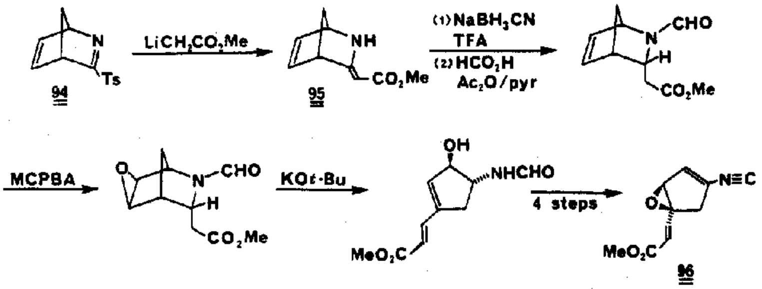
Table 4. Cycloadditions of sulfonylcyanides and 1,3-dienes

R-SO$_2$CN	Diene	Product(s) (yield, %)	Reaction conditions[a]
R=pMeC$_6$H$_4$		 (24)  (55)	60h/20°
R=pMeC$_6$H$_4$		 (28)  (38)	2h/72°
R=C$_6$H$_5$CH$_2$		 (20)  (22)	20h/20°
R=pMeC$_6$H$_4$		 (89)	45 min/175°
R=pMeC$_6$H$_4$		 (95)	30 min/RT
R=pClC$_6$H$_4$		 (76)[b]	10h/150°

(a) reactions were run neat in excess diene

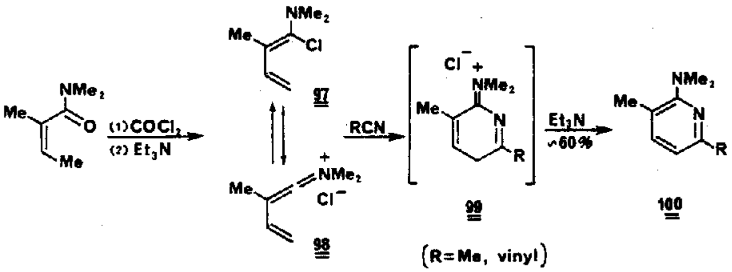
(b) see ref. 45 for an explanation of formation of this product would think that with further work experimental conditions might be developed to cleanly provide either pyridines **92** or compounds in the dihydro oxidation state (e.g. **91**, **93**).

A nice total synthesis of the isonitrile fungal metabilite **96** has been achieved using bicyclic adduct **94**, prepared from tosyl cyanide and cyclopentadiene.[46,47] The synthetic route is depicted in Scheme 24. One key step in this work was the coupling of **94** with lithio methyl acetate to yield intermediate **95**.



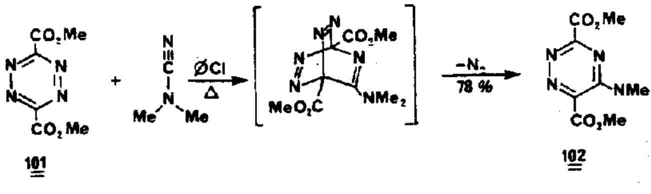
Scheme 24

Ghosez[48] has recently prepared so called "push-pull" dienes of type **97**/**98** (Scheme 25). These dienes are electrophilic enough to react at low temperatures with unactivated, electron rich nitriles affording adducts **99**, which tautomerize to amino pyridines **100**. This method would seem to offer a rather nice approach to synthesis of certain substituted pyridines.



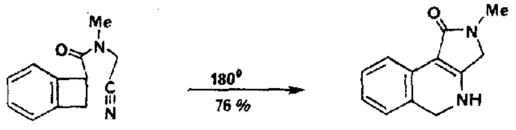
Scheme 25

Tetrazine **101** is also sufficiently electrophilic to combine with N-substituted cyanamides to afford triazenes **102** in good yield[49] (Scheme 26).

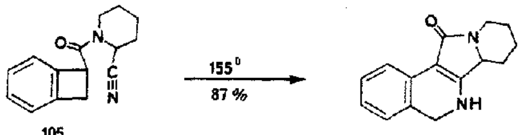


Scheme 26

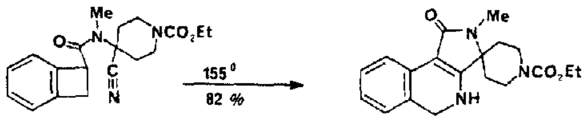
Only a few scattered examples exist of intramolecular Diels–Alder cycloadditions of nitriles. Oppolzer[10] has synthesized the benzocyclobutene-nitriles **103**, **105** and **107** and found that upon pyrolysis they were transformed into isoquinoline derivatives **104**, **106** and **108**, respectively, in excellent yields. Quinone methides are, of course, assumed to be the dienes in these cycloadditions.



103 **104**

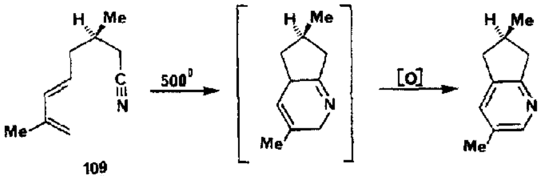


105 **106**



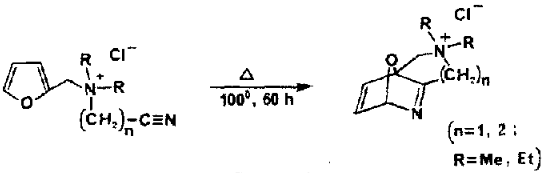
107 **108**

A rather sketchy report has appeared describing synthesis of pyridine **110** by thermal intramolecular cycloaddition of diene-nitrile **109**.[50] Unfortunately, neither yields nor a detailed account of reaction conditions are contained in this paper.



109 **110**

A furan has been reported as the diene in some intramolecular [4+2]-cycloadditions of nitriles (Scheme 27).[51]

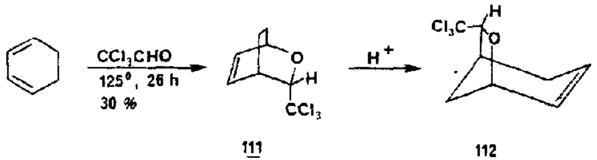


Scheme 27

3. C–O DIENOPHILES

Certain types of carbonyl compounds are capable of acting as dienophiles in [4+2]-cycloadditions. In general, only very electrophilic carbonyl groups are highly reactive, and thus most simple aryl and alkyl aldehydes and ketones cannot be used under "normal" reaction conditions (*vide infra*). More useful dienophiles are formaldehyde, chloral, ketomalonates, glyoxylates and various fluorinated ketones. Relatively little can be added to existing reviews[52] since there has been surprisingly little activity in this area in recent years.

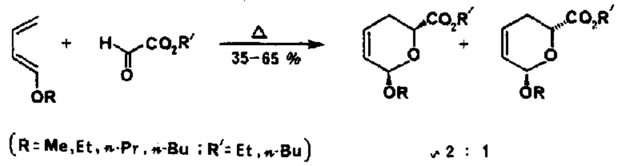
The Diels–Alder adduct of cyclohexadiene and chloral[53] has recently been established to have the *endo* configuration **111**.[54] In order for this cycloaddition to be at all reproducible it was necessary to exclude all moisture and conduct the reaction in vacuum. Adduct **111** is extremely acid labile, rearranging rapidly to isomer **112**. It was suggested that similar rearrangements may occur in other adducts of cyclohexadiene and carbonyl compounds.[55c]



111 **112**

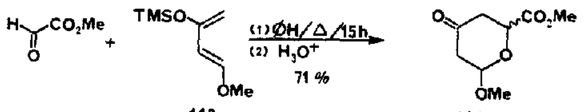
Glyoxylate esters have been reported to add to a number of electron-rich dienes.[15,55,56] In particular, alkoxydienes have proven to be excellent substrates for cycloaddition.

Thermal additions of a number of alkoxybutadienes and glyoxylate esters have been conducted and alkoxydihydropyrans have been isolated.[55a] In all cases a mixture of *cis* (*endo*) and *trans* (*exo*) products were obtained in about a 2:1 ratio, although these ratios were slightly solvent dependent[55b] (Scheme 28).



Scheme 28

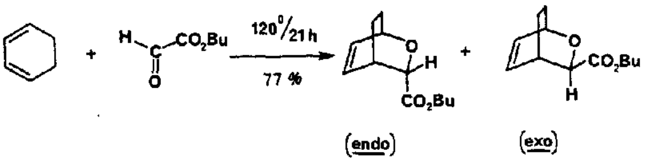
Jung *et al.*[15] recently observed that methyl glyoxylate adds to diene **113** to afford, after hydrolysis, a good yield of pyranone **114** as a 1:1 mixture of *cis* and *trans* stereoisomers.



113 114

The above additions of glyoxylates with unsymmetrical dienes appear to be completely regioselective. As has been pointed out by Fleming,[6] FMO theory can be used to rationalize these results. Regiochemistry is presumably controlled here by the interaction of HOMO of the diene and the LUMO of the carbonyl compound.

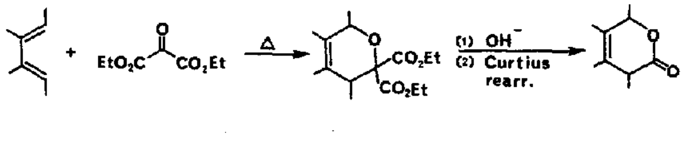
Butyl glyoxylate also reacts smoothly with cyclohexadiene, affording a 9:1 mixture of the *endo* and *exo* adducts, respectively (Scheme 29).[55c]



Scheme 29

In an extensive series of papers Jurczak *et al.*[57] have examined asymmetric induction in the Diels–Alder reactions of a number of dienes with several optically active esters of glyoxylic acid. Cycloadditions were run at atmospheric pressure[57a] and at high pressures (6–10 kbar).[57c,e,f] In summary, asymmetric induction using glyoxylate esters of optically active menthol, borneol, 2-octanol, and 2,2-dimethyl-3-heptanol gave optical yields of only 0.4–13% at atmospheric pressure, depending upon the solvent used. At high pressures, optical yields of adducts with R(–)-menthyl glyoxylate esters were somewhat better (1–21%) depending upon diene, solvent and pressure. Jurczak has proposed a mechanistic model to account for these results.[57d,f]

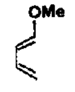
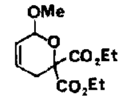
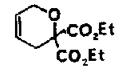
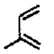
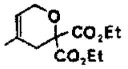
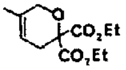
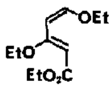
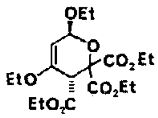
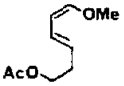
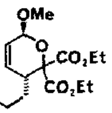
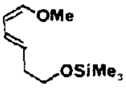
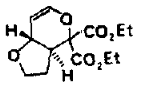
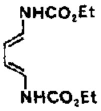
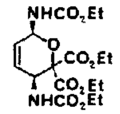
Diethyl ketomalonate (**115**) has been shown to be a good carbonyl dienophile affording adducts of type **116** upon reaction with 1,3-dienes (Scheme 30).[54a,58,59] Several typical reactions are listed in Table 5.



115 116 117

Scheme 30

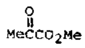
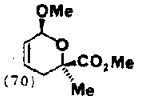
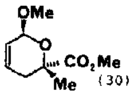
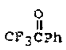
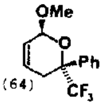
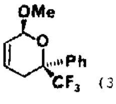
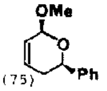
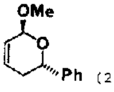
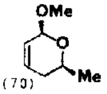
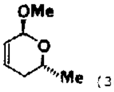
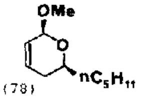
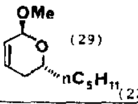
Table 5. Reactions of diethyl ketomalonate (**115**) with 1,3-dienes

Diene	Product(s) (ratio)	Reaction conditions	Yield (%)	(ref.)
		80°/1.5h	52	(54*a*)
		130°/4h	63	(58)
	  (11:1)	130°/4h	64	(58)
		50°/6h	54	(59*a*)
		ϕH/115°/60h 8.5kbar/60°/48h	51 98	(59*a*)
		80°/72h	43	(59*a*)
		80°/44h	34	(59*b*)

Ruden and Bonjouklian have suggested that **115** might serve as the synthetic equivalent of carbon dioxide, which itself does not react as a dienophile.[58] They have found that adducts **116** can in fact be transformed *via* a Curtius sequence to β,γ-unsaturated lactones **117**.

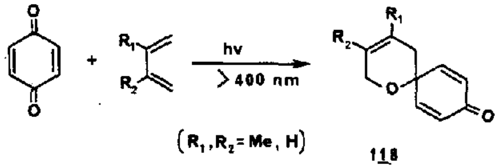
A recent paper by Jurczak *et al.*[60] gives hope that the scope of carbonyl dienophile cycloadditions might be broadened if reactions are carried out under ultra-high pressures. 1-Methoxybutadiene was found to add smoothly at ~20 kbar to several aldehydes and ketones which are normally not good dienophiles (Table 6). It is yet to be demonstrated, however, that other dienes will react as well. Some of

Table 6. High pressure induced cycloadditions of trans-1-methoxybutadiene and carbonyl compounds[60]

Carbonyl compound	Products (%)		Pressure (kbar)	Temperature (°C)	Yield (%)
 $\mathrm{Me\overset{O}{\overset{\|}{C}}CO_2Me}$	 (70)	 (30)	20.0	50°	85
 $\mathrm{CF_3\overset{O}{\overset{\|}{C}}Ph}$	 (64)	 (36)	19.5	20°	81
PhCHO	 (75)	 (25)	19.5	50°	80
MeCHO	 (70)	 (30)	20.0	65°	62
n-C_5H_{11}CHO	 (78)	 (29) (22)	20.0 23.5	65° 20°	28 16

the adducts listed in Table 6 have been used in short total syntheses of two δ-lactone insect pheromones.[61]

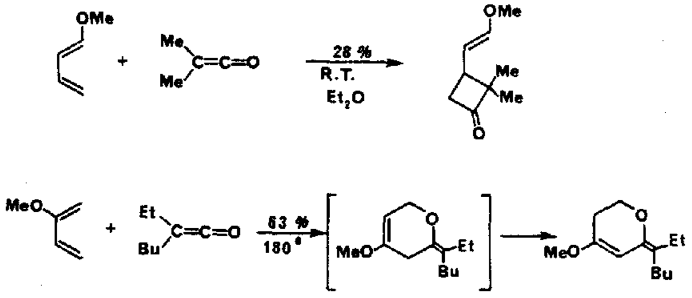
Several years ago Barltrop and Hesp[62] described the photoinduced Diels–Alder reactions of benzoquinone and three simple acyclic1,3-dienes to afford spiroadducts **118** (Scheme 31). It was suggested that a stepwise mechanism with a diradical intermediate was operating in this process.



118

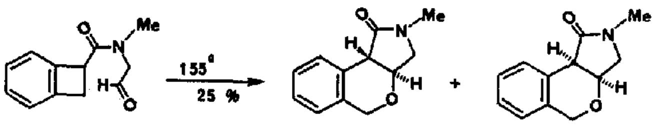
Scheme 31

Upon occasion, ketene carbonyls can act as dienophiles. However, other cycloaddition pathways (such as [2+2] addition) are usually preferred and this Diels–Alder reaction is certainly not of general utility. Scheme 32[63] indicates how relatively small structural changes in reactants can affect the nature of the cycloaddition products.



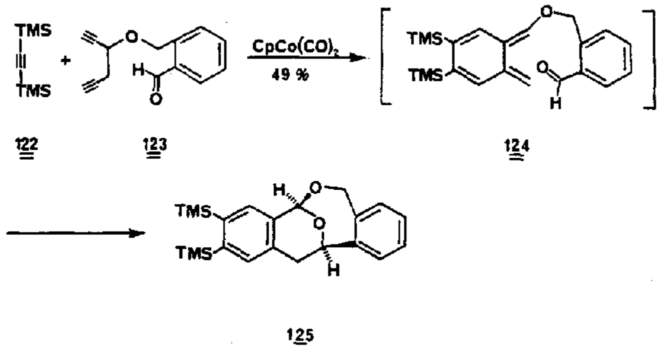
Scheme 32

A few rare instances of intramolecular carbonyl Diels–Alder cyclizations exist.[64] Oppolzer[10] found that aldehyde **119** upon heating afforded a 25% yield of adducts **120** and **121**.



119 120 121

Using their cobalt catalyzed oligomerization method, Funk and Vollhardt[34] discovered that condensation of **122** and **123** afforded the bridged adduct **125** (Scheme 33). Interestingly, the quinone methide

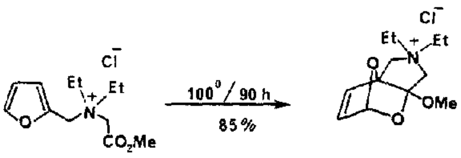


125

Scheme 33

intermediate **124** in this case undergoes cyclization with the opposite regiochemistry relative to Oppolzer's system **119**. Whether this is due to the nature of the bridging chain between diene and dienophile, or to some sort of polar interaction is not clear. From the product stereochemistry it is clear, however, that **124** must cyclize *via* an *endo*-phenyl transition state.

The intramolecular cycloaddition of furan-ester **126** was reported several years ago to yield tricyclic compound **127**.[51] To our knowledge this is the only example to date of a simple ester carbonyl group acting as a dienophile.



126 127

4. C–S DIENOPHILES

Brief reviews of the Diels–Alder reaction involving thiocarbonyl dienophiles have previously appeared.[52a,65] There has been a significant amount of work published in the past dozen years and thiocarbonyl groups of all kinds appear to be highly reactive as dienophiles—much more so than the corresponding carbonyl compound.

Thioketones of various types are well documented as effective dienophiles[66–68] and a representative listing of cycloadditions is contained in Table 7. In general, it appears that thioketones add to most

Table 7. Condensations of thioketones with 1,3-dienes

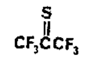
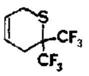
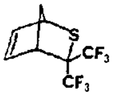
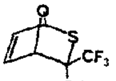
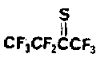
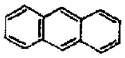
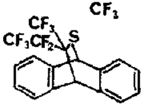
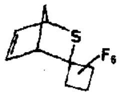
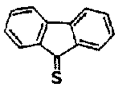
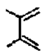
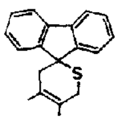
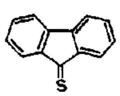
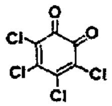
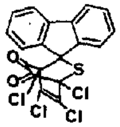
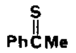
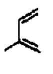
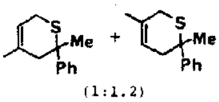
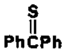
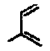
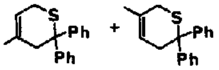
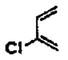
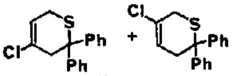
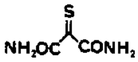
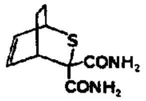
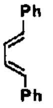
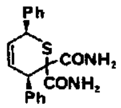
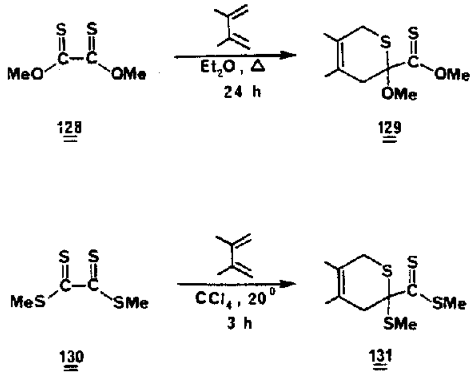
Thioketone	Diene	Adduct(s) (ratio)	Reaction Conditions	Yield(%)	Ref
 $CF_3C(=S)CF_3$			-78°	90	(66*a*)
"			-78°	85	(66*a*)
"			-78°	73	(66*a*)
 $CF_3CF_2C(=S)CF_3$			0°	95	(66*a*)
					(66*c*)
			RT	84	(66*a* 67*b*)
			-5°	82	(67*a*,*b*)
 $PhC(=S)Me$		 (1:1.2)	RT/2days	100	(67*d*)

Table 7. (*Contd*)

Thioketone	Diene	Adduct(s) (ratio)	Reaction Conditions	Yield(%)	Ref
 $\overset{S}{\overset{\|}{PhCPh}}$		 (1.5:1)	RT/10h	100	(67*d*)
"		 (1:1.8)	RT/10h	100	(67*d*)
			25°	60	(68)
"			25°	40	(68)

dienes in high yield at exceptionally low temperatures to afford stable adducts.[69] Very little has been done towards establishing the regiochemical selectivity of thioketone additions to unsymmetrical dienes, and the few such entries in Table 7 indicate that mixtures were obtained.[67d] The stereochemistry of thioketone cycloadditions has not been probed to date either. It has been reported that Diels-Alder cycloadditions of thioketones can also be photochemically induced.[67c,e]

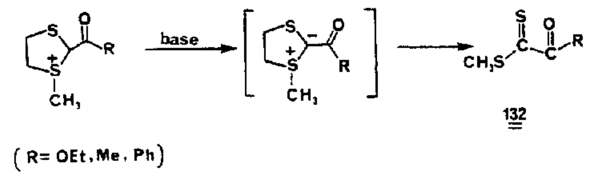
Thiooxalates **128** and **130** have been found to form [4+2]-cycloaddition products **129** and **131**, respectively (Scheme 34). Yields in both cases were reported to be quantitative. Interestingly, **128** and **130** can also act as heterodienes, and will add to many dienophiles.



Scheme 34

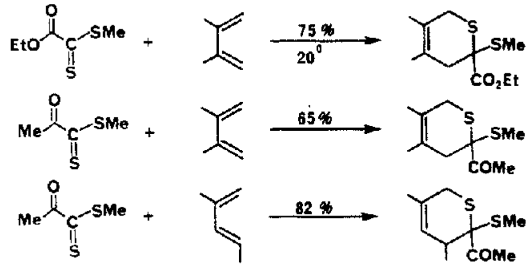
Vedejs *et al.*[71] have developed a clever method for generation of thiooxalate derivatives **132** by the dithiolanium ylide cycloreversion shown in Scheme 35.

Thiocarbonyl compounds **132** were not isolated, but were trapped as formed by 1,3-dienes to afford



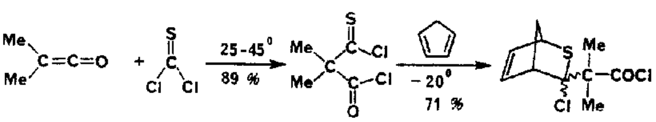
Scheme 35

good yields of Diels–Alder adducts (Scheme 36). 1,3-Dimethylbutadiene gave only a single regioisomer (>98%) having the structure shown. This regiochemistry is in line with that found in cycloadditions of some cyanothioformamides with unsymmetrical dienes (*vide infra*).



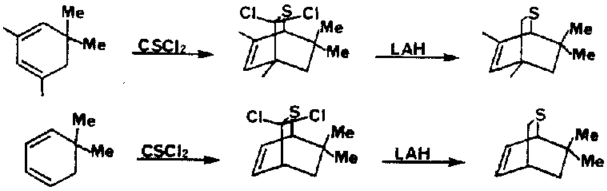
Scheme 36

In 1981 Martin *et al.*[72] reported that thiophosgene reacts with dimethylketene to yield **133**. This thioacid chloride combines rapidly with cyclopentadiene, leading to adduct(s) **134**.



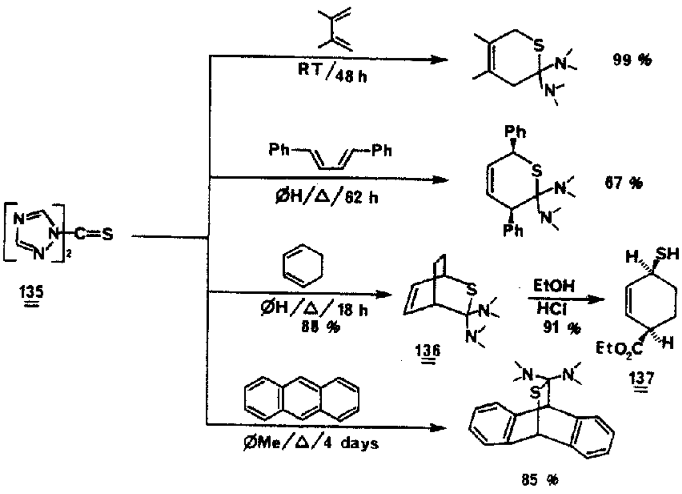
133 **134**

Thiophosgene has proven to be a generally useful thiocarbonyl dienophile,[73] and reacts cleanly with cyclopentadiene[66a,73b], cyclohexadienes[73c], 1,4-diphenylbutadiene[70a] and anthracene[73d] to give the expected dichlorosulfide adducts. In cases with unsymmetrically substituted cyclohexadienes, as shown in Scheme 37 only the single regioisomers indicated were formed.[73c] Reduction of various thiophosgene Diels–Alder adducts with lithium aluminum hydride affords the corresponding sulfides,[67a,73] thus giving products equivalent to thioformaldehyde adducts.



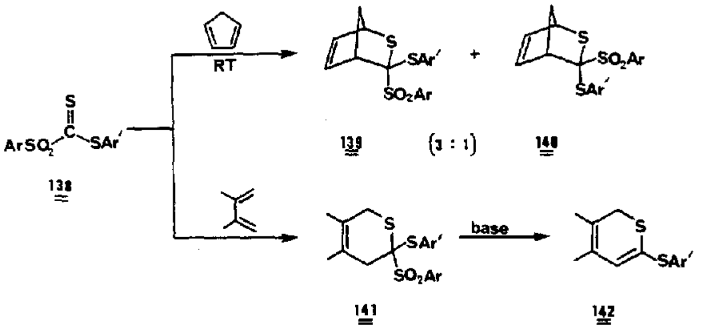
Scheme 37

Larson and Harpp[74] have prepared the *bis*-triazole **135** and found that it undergoes cycloaddition with 1,3-dienes to afford stable adducts in high yields (Scheme 38). These adducts, upon treatment with ethanolic HCl, are converted to *cis*-mercaptoesters (see **136**→**137**).



Scheme 38

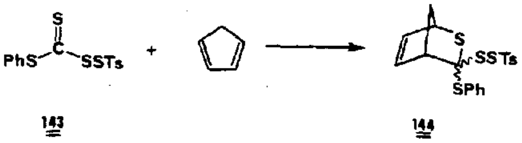
Trithiocarbonate S,S-dioxides **138** are also reactive thiocarbonyl dienophiles (Scheme 39).[75] Addition of **138** to cyclopentadiene afforded a high yield of a 3:1 mixture of the *endo* and *exo* adducts **139** and **140**, respectively. The corresponding adducts with acyclic dienes are unstable, and readily eliminate aryl sulfinic acids to provide thiopyrans (see **141**→**142**).



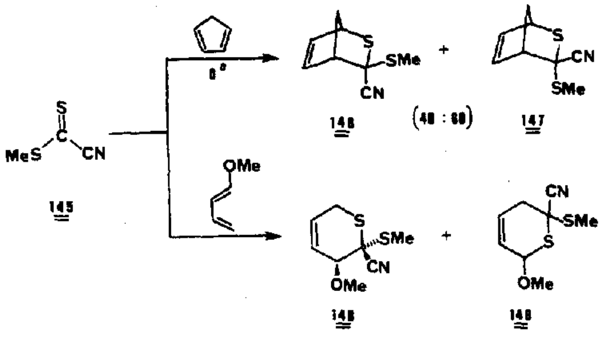
(Ar = p-tolyl, p-Cl phenyl ; Ar' = phenyl, p-Cl phenyl)

Scheme 39

Similarly, trithiocarbonate derivative **143** is a dienophile and reacts with cyclopentadiene to give adduct(s) **144**.[76]

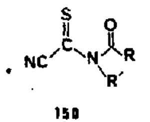


Vyas and Hay[77] reported that methyl cyanodithioformate (**145**) will function as a dienophile (Scheme 40). Addition of **145** to cyclopentadiene gave a quantitative yield of *exo* and *endo* adducts **146** and **147** in a 40:60 ratio. When 1-methoxybutadiene was used, sulfide **148** was the major reaction product along with traces (<20%) of regioisomer **149** which was not characterized fully. The *endo*-cyano stereochemistry shown was established for **148** by extensive NMR studies. An interesting point here is that the regiochemistry of addition of 1-methoxybutadiene and **145** is opposite to that normally preferred in carbonyl [4+2]-cycloadditions (*vide supra*).



Scheme 40

Similarly, cyanothioformamides of type **150** were shown to be reactive thiocarbonyl dienophiles, and additions to several dienes have been described.[78]

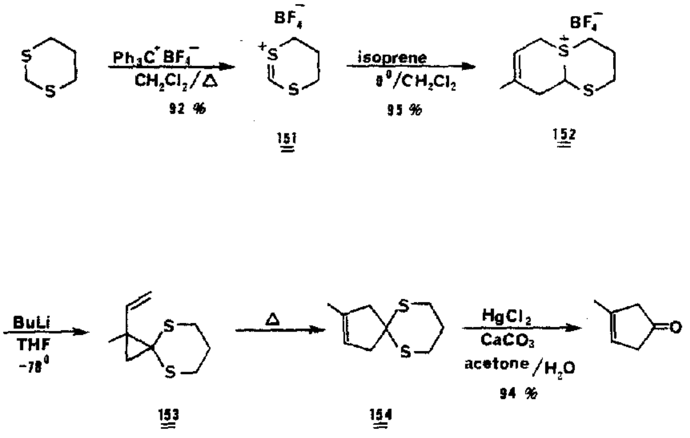


150

R = CF_3, CH_3, Ph

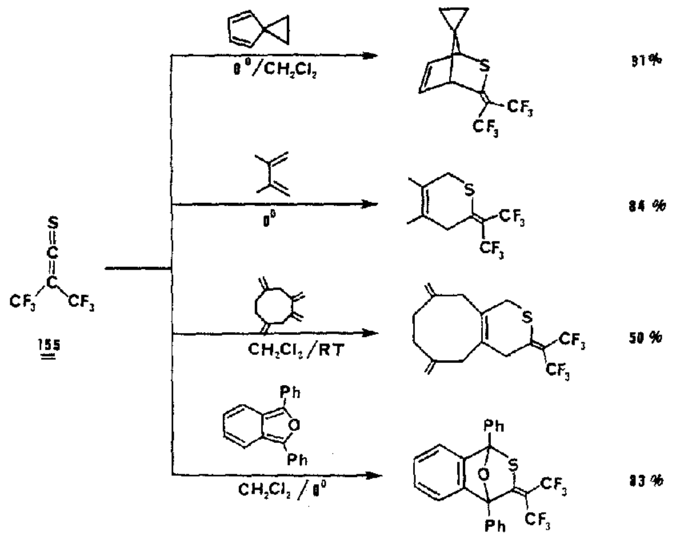
R' = Ph, Aryl, Me

A rather interesting route to cyclopentenones has been developed by Corey and Walinsky[79] (Scheme 41) which uses dithienium salt **151** as a dienophile in the initial step. This species adds regioselectively to isoprene, leading to adduct **152**. Addition of **151** to 2,3-dimethylbutadiene and butadiene was also reported. Compound **152**, on treatment with butyllithium at low temperature, gave vinyl cyclopropane **153**, which thermally rearranged to provide cyclopentenone dithioketal **154**, and subsequently a cyclopentenone.



Scheme 41

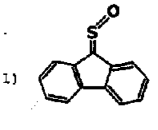
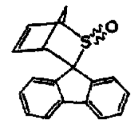
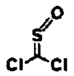
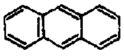
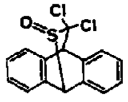
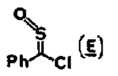
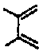
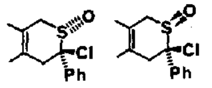
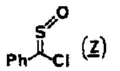
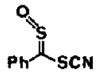
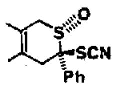
Although monomeric thioketenes are generally highly unstable, Raasch has found that *bis*-trifluoromethyl thioketene (**155**) is stable enough to handle, and that it is an excellent dienophile.[66c,80] Some typical results are depicted in Scheme 42.



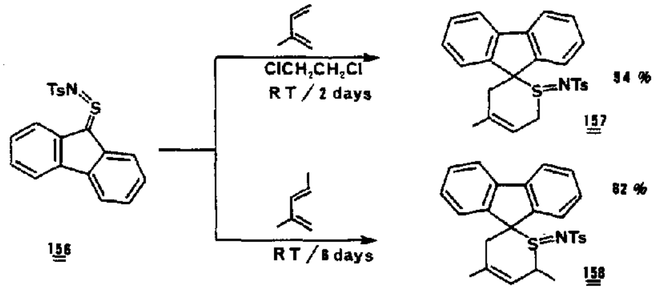
Scheme 42

Sulfines represent another type of cumulene which can act as heterodienophiles. Zwanenburg *et al.*[81] have synthesized several different types of sulfines and examined the reactions of these species with a number of 1,3-dienes. Some of their results are listed in Table 8. The product of addition of thiofluorene S-oxide and cyclopentadiene (entry (1)) is unstable and the *exo*:*endo* ratio changes with time. It is therefore not clear whether the kinetic product of the reaction is *exo* or *endo*. The mixtures of stereoisomers in entries (3) and (4) are probably due to an equilibration process occurring during the reaction, or upon workup. The $\Delta S^{\neq}$ values were measured for these two reactions, and were found to be −15 and −20 eu, respectively. Such parameters are indicative of a concerted cycloaddition mechanism.

Table 8. Cycloadditions of sulfines and 1,3-dienes[81]

Entry	Sulfine	Diene	Product(s) (ratio)	Reaction conditions	Yield (%)
(1)			 (exo:endo=4:1)	ΦH/RT	48
(2)				ΦH/36h	75
(3)			 (67 : 12)	RT/2 days	79
(4)		"	(18 : 70)	RT/7 days	88
(5)		"		20°/4 days	79

The related thione S-imide 156 reacts with acyclic dienes to afford Diels–Alder products.[82] With isoprene and 1,3-dimethylbutadiene, only regioisomers 157 and 158, respectively, were produced (Scheme 43). Cyclopentadiene, on the other hand, afforded a product of a 1,3-dipolar addition, *not* a Diels–Alder adduct.

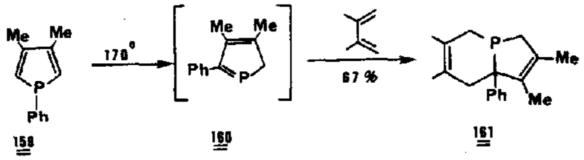


Scheme 43

5. MISCELLANEOUS C-X DIENOPHILES

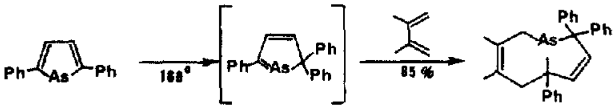
A. *Phospholes* (*X*=*P*)

It was recently reported that on heating phosphole 159 in the presence of excess 2,3-dimethylbutadiene adduct 161 could be isolated in excellent yield.[83] It was postulated that the transient 2H-phosphole 160 was the dienophile in this case.



B. *Arsoles* (X=As)

On heating arsole **162** in the presence of 2,3-dimethylbutadiene, adduct **164** was isolated.[84] In this case arsole **163** is believed to be the reacting species.



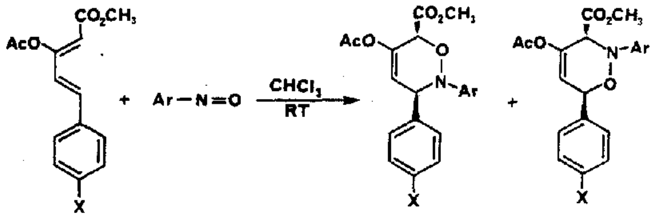
162 **163** **164**

6. N–O DIENOPHILES

Nitroso compounds of various structural types have been widely utilized as Diels–Alder dienophiles, and the subject has been comprehensively reviewed several times.[85–88] In general, the material covered in this section has not been included in the previous reviews.

Kresze *et al.* have studied cycloadditions of aryl nitroso compounds and 1,3-dienes in considerable depth,[87,89] and much insight has been gained about the scope and mechanism of this sort of cycloaddition. Some of the more recent work in this area (cited below) is representative of the field.

In 1973 Kresze and Hartner[90] found that substituted dienes of type **165** will add to several substituted aryl nitroso compounds to afford a mixture of dihydro-1,2-oxazines **166** and **167**. The ratio of regioisomers **166** and **167**, as can be seen in Scheme 44, is dependent upon the nature of substituents in diene and dienophile. A rationalization for this effect has been offered by Kresze in a series of papers,[87,89] and essentially involves a consideration of the relative stabilization of dipolar transition states by electron donating and withdrawing aryl substituents.

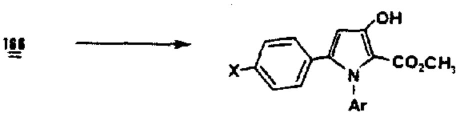


165 **166** **167**

		% of mixture	
X = H	Ar = Ph	76	24
H	pClPh	68	32
H	pNO$_2$Ph	54	46
H	2,4-(NO$_2$)$_2$Ph	31	69
MeO	Ph	62	38

Scheme 44

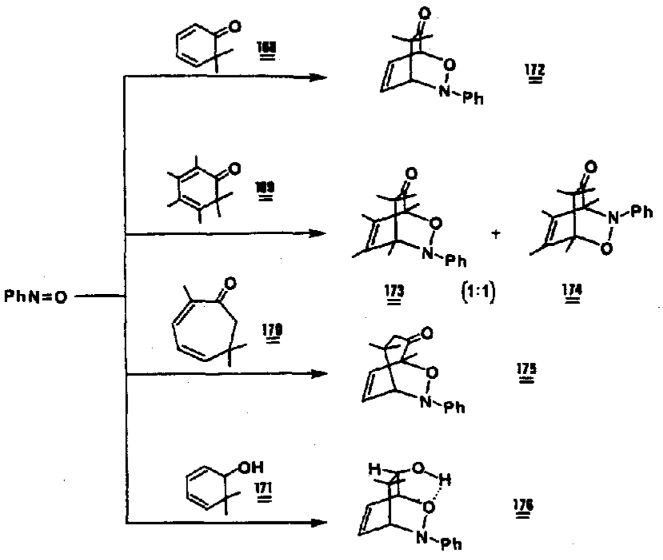
Adducts such as **166** have some synthetic utility, and are readily converted to hydroxypyrroles **168**



168

upon chromatography on silica gel. Other adducts related to **166** are known to also produce pyrroles.[87]

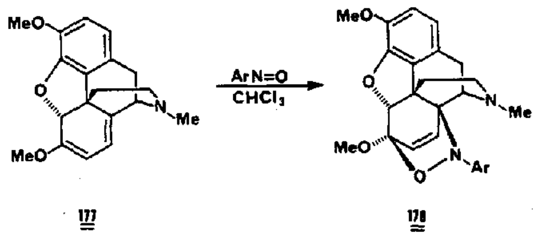
Recently, Hart *et al.*[91] have added nitrosobenzene to several dienones and dienols and their results are summarized in Scheme 45. Additions to dienones **168** and **170** produced only adducts **172** and **175**,



Scheme 45

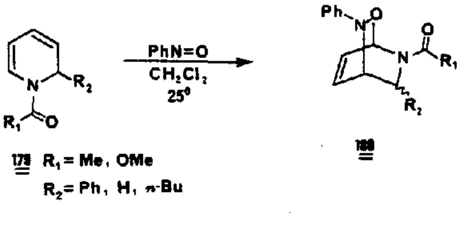
respectively. This regioselectivity can be rationalized by FMO theory if one considers the interaction of the dienone HOMO and the LUMO of nitrosobenzene.[6] The regiochemistry and syn-selectivity of the reaction with dienol **171** yielding **176** may be due to hydrogen bonding in the transition state for cycloaddition. The lack of regioselectivity of the reaction with permethyldienone **169** yielding **173** and **174** is somewhat puzzling, but may be due to steric factors.

Nitrosobenzenes have been reported to add to thebaine (**177**) at room temperature to afford Diels–Alder adducts **178** in high yields.[92] These reactions are reversible at ambient temperatures. Electron



withdrawing p-aryl substituents diminished dissociation, and the opposite effect was observed for electron donating substituents.

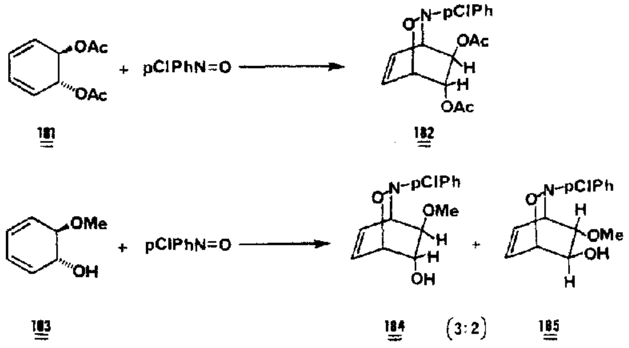
N-Acyldihydropyridines **179** will also combine with nitrosobenzene to give Diels–Alder adducts **180** (Scheme 46).[93] Only the regioisomer shown was produced in these reactions. The stereochemistry of R_2



Scheme 46

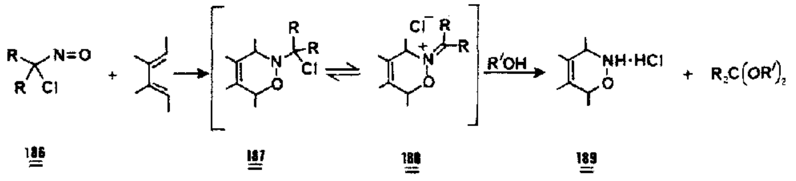
has not been established, although the products are single isomers at this center. The regiochemistry of this cycloaddition is in accord with the predictions of FMO theory.[6]

Kresze *et al.*[94] have added p-chloronitrosobenzene to dienes **181** and **183** (Scheme 47). In the former case, only adduct **182** was formed. In the latter addition, a 3:2 mixture of isomeric adducts **184** and **185** were produced. It is not easy to explain these stereochemical results. Based upon Hart's work (*vide supra*)[91] one would have expected the *syn*-hydroxy isomer **185** to be the major product of the second cycloaddition.



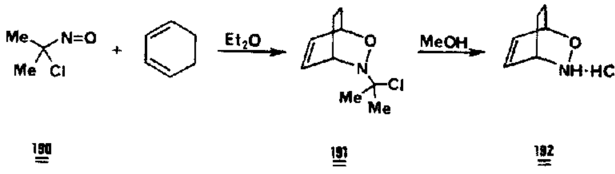
Scheme 47

It has been known for many years[95] that α-chloronitroso compounds **186** react with 1,3-dienes to yield unstable adducts **187**/**188**. If these reactions are run in alcoholic solvent, the product actually isolated is the dihydro-1,2-oxazine **189** (Scheme 48).



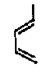
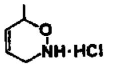
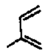
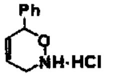
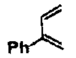
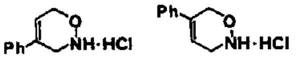
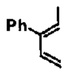
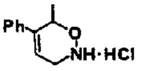
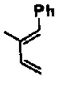
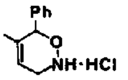
Scheme 48

Thus, addition of chloronitroso compound **190** to cyclohexadiene in ether gave unstable adduct **191**, which when dissolved in methanol afforded dihydrooxazine **192**.[96]



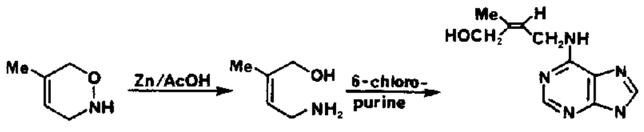
The regiochemistry of the addition of α-chloronitroso compounds has recently been investigated,[97] and the results are listed in Table 9. In general, the orientational preferences are in accord with those observed using aryl nitroso compounds.[87] An exception is the case of isoprene, which gives the opposite selectivities with chloronitroso compounds and nitrosobenzene. It was suggested that steric factors are important in cycloadditions with chloronitroso compounds, and that the large alkyl group on nitrogen will approach the least bulky end of the diene. However, such an argument does not satisfactorily explain the differing results with 2-substituted butadienes (i.e. isoprene and 2-phenylbutadiene).

Table 9. Addition of 1-chloro-1-nitrosocyclohexane to unsymmetrical 1,3 dienes

Diene	Adduct(s) (ratio)	Reaction conditions[a]	Yield (%)
		0°/96h	47
	 (80:20)	RT/48h	32
		RT/5h	53
	 (70:30)	RT/1h	58
		0°/72h	33
		0°/24h	73

(a) Reactions were run in φH/EtOH or Et_2O/EtOH

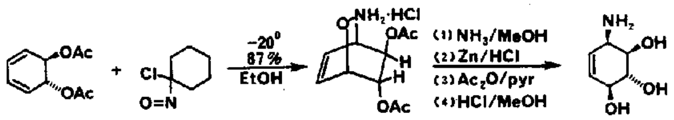
Leonard *et al.* have used the major adduct **193** from isoprene cycloaddition to a chloronitroso compound in a total synthesis of the cell division stimulant *cis*-zeatin (**194**) (Scheme 49).[98]



193 **194**

Scheme 49

Kresze *et al.* utilized the adducts of α-chloronitroso compounds and various cyclohexadienes in syntheses of some inosamine derivatives.[99] For example, konduramin-Fl (**197**) has been synthesized as depicted in Scheme 50. Interestingly, addition of 1-chloro-1-nitrosocyclohexane to diene **195** gave only adduct **196**. Just why this is so is not clear.

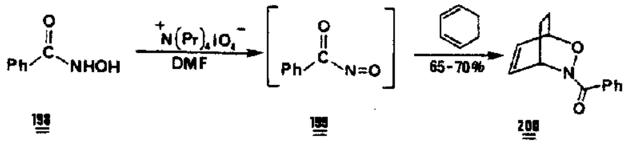


195 **196** **197**

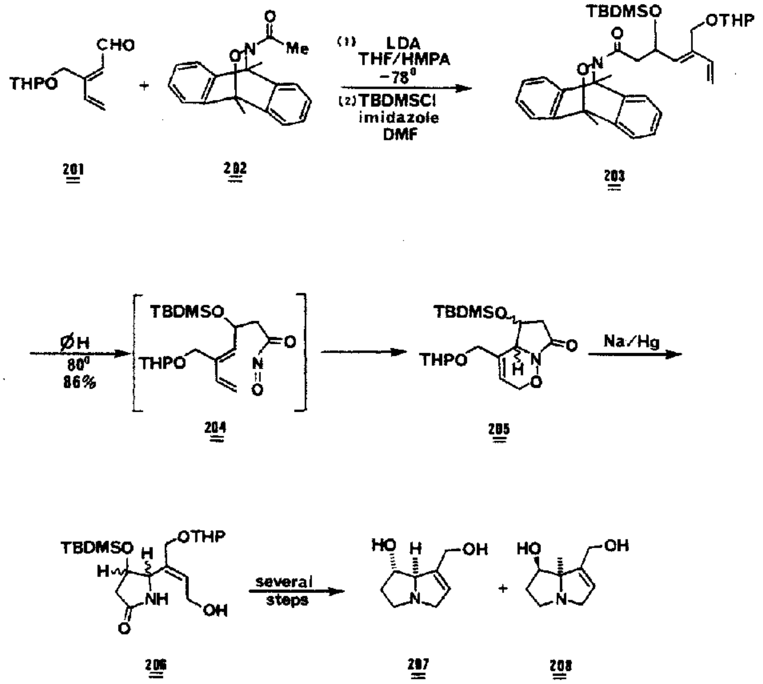
Scheme 50

In the past few years Kirby has discovered that electron deficient acylnitroso and cyanonitroso compounds can be readily generated, and that these species are excellent dienophiles. A review of this subject appeared in 1977.[88,100]

This methodology has been elegantly applied by Keck *et al.* in a new approach to alkaloid synthesis.[101a] For example, slow addition of benzohydroxamic acid (**198**) to tetrapropylammonium periodate in DMF in the presence of cyclohexadiene gave adduct **200**. Acylnitroso compound **199** is presumably the reacting species here.



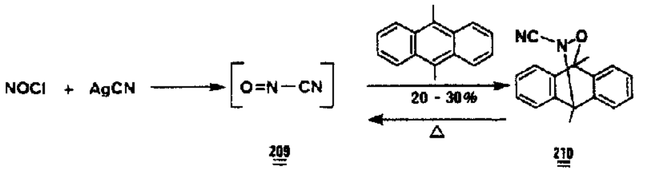
Keck has also utilized an intramolecular variation of the acylnitroso cycloaddition in a total synthesis of the necine bases heliotridine (**207**) and retronecine (**208**) (Scheme 51).[101b,c] Aldehyde **201** was



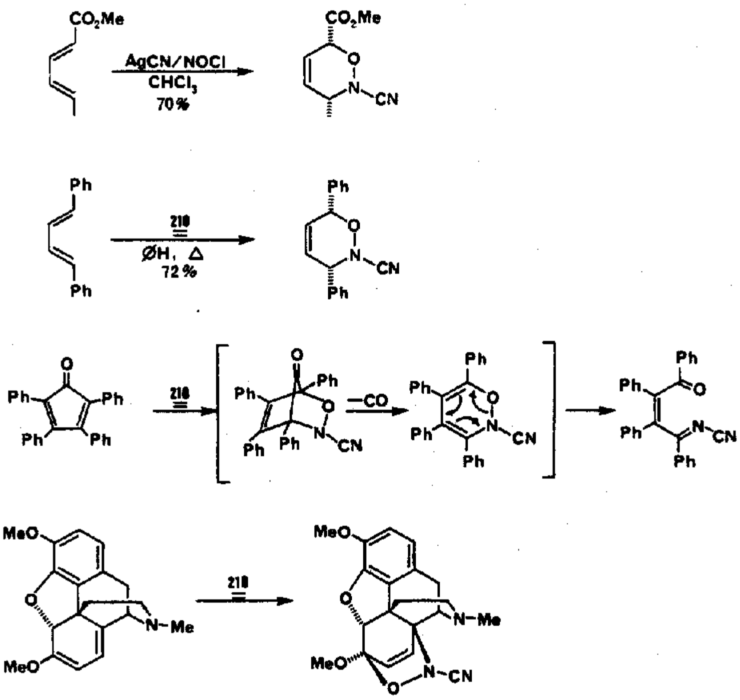
Scheme 51

condensed with the carbanion derived from deprotonation of **202** to afford, after hydroxyl protection, compound **203**. Heating **203** in benzene caused a retro Diels–Alder reaction[88] to occur, giving intermediate acylnitroso compound **204**, which underwent intramolecular cycloaddition to give 205 as a 1.3:1 mixture of diastereomers. Reductive cleavage of the N–O bond of **205** led to lactams **206** which were converted to heliotridine and retronecine in a few steps.

Kirby has recently published the details of his work with nitrosyl cyanide (**209**).[102] This species can be generated from nitrosyl chloride and silver cyanide, and can be trapped *in situ* by several dienes. However, it seems that it is often cleaner and more convenient to use 9,10-dimethylanthracene adduct **210** as a latent source of nitrosylcyanide.

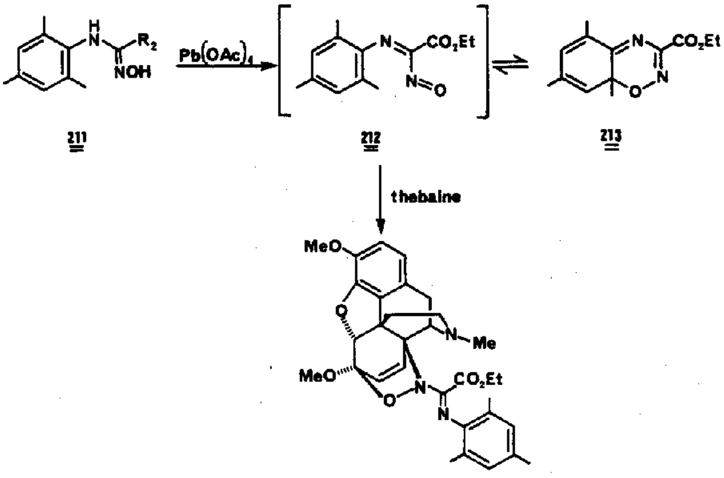


Several examples of Diels–Alder reactions with nitrosyl cyanide are shown in Scheme 52. Orientation of addition to unsymmetrical dienes generally corresponds to that of aryl- and chloroalkylnitroso compounds.



Scheme 52

The iminonitroso compound 212 has been generated by oxidation of 211.[103] This material reversibly cyclizes to 213, and the nitroso intermediate can be trapped by thebaine to afford Diels–Alder adduct 214. Related nitroso compounds can also be formed and trapped where the ortho aromatic positions are not blocked by methyl groups (Scheme 53).

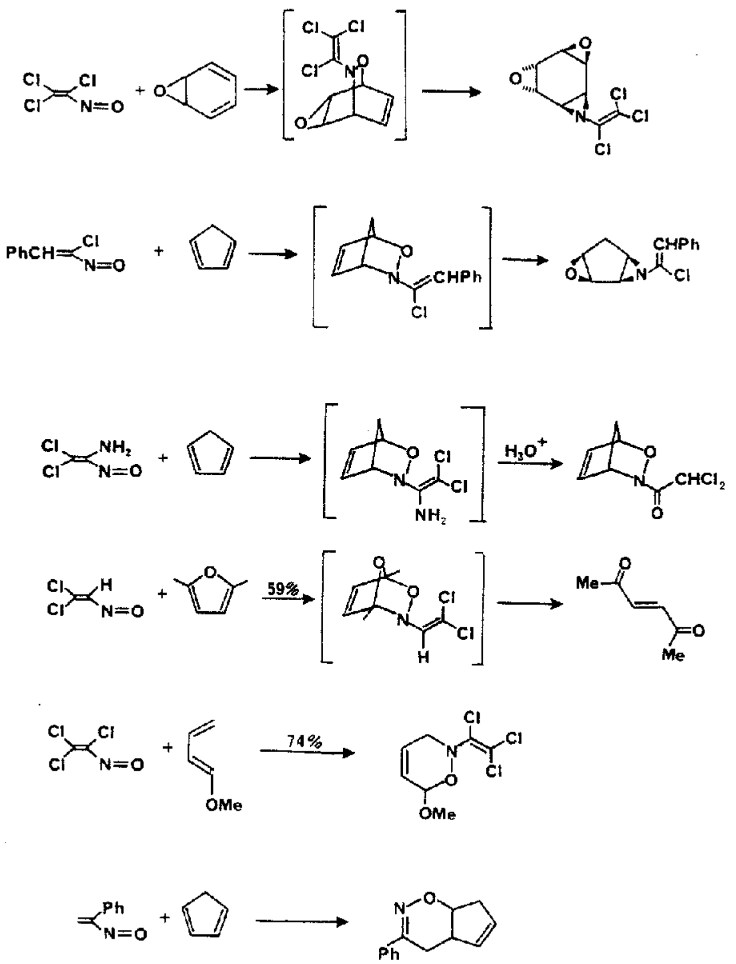


Scheme 53

Some work has recently appeared on the synthesis and reactions of vinylnitroso compounds.[104,105] These compounds are capable of acting either as dienes or as nitroso dienophiles, but their reactivity is crucially dependent upon their structure. In general, if the vinylnitroso system **216** contains any β-substituents, the compounds will react as dienophiles; if there is no β-substituent, the system acts as the 4π component of a Diels–Alder reaction, and will react with dienophiles.

Vinylnitroso compounds **216** are generally unstable and are generated *in situ* by base treatment of α-haloximes **215**. These dienophiles will react with various dienes to initially produce the usual type of nitroso Diels–Alder adducts, but in many cases these compounds rearrange to epoxyepimines. The examples depicted in Scheme 54 show some of the many types of reactions of these systems can undergo.[104,105]

215 216

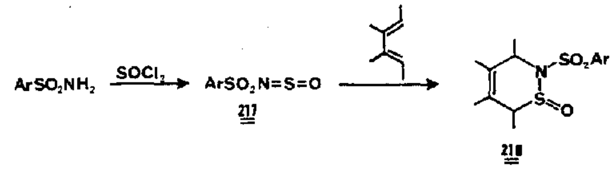


Scheme 54

7. N–S DIENOPHILES

Cycloaddition reactions using imines of sulfur dioxide as dienophiles are well documented in previous reviews.[106–108] There has been relatively little work in this area in the past decade, and thus existing reviews serve to cover the large majority of literature on N–S dienophiles.

The most thoroughly studied dienophiles of this class are N-sulfinylsulfonamides **217**, prepared from aryl sulfonamides and thionyl chloride (Scheme 55).[108,109] These sulfinyl compounds add readily to

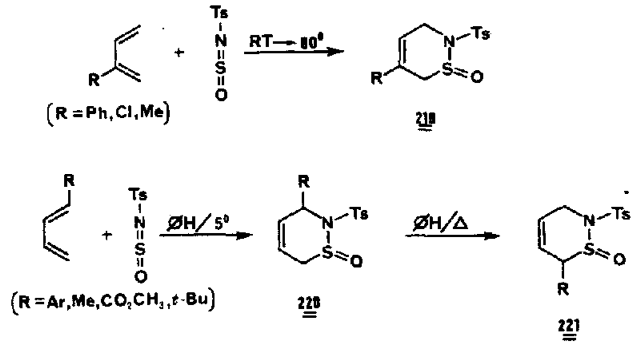


Scheme 55

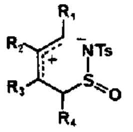
conjugated dienes at low temperatures to afford adducts of type **218**. These cycloadditions are often reversible at higher temperatures (*vide infra*).

Kresze and Wagner have studied the orientation of addition of **217** to unsymmetrical dienes and have found that the reaction is highly stereoselective.[110] 2-Substituted dienes react with N-sulfinyltoluenesulfonamide to give thermally-stable adducts of structure **219**. 1-Substituted dienes react at low temperature to cleanly afford adducts **220**. These adducts are thermally unstable, and at higher temperatures give what is apparently the thermodynamic isomer **221**, presumably *via* a retro Diels–Alder pathway.

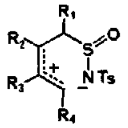
The regiochemistry of the kinetic products of addition might be rationalized by considering two dipolar species **222** and **223**. Clearly the kinetic adducts in Scheme 56 are derived from the more stable of the two forms (see Scheme 2).



Scheme 56

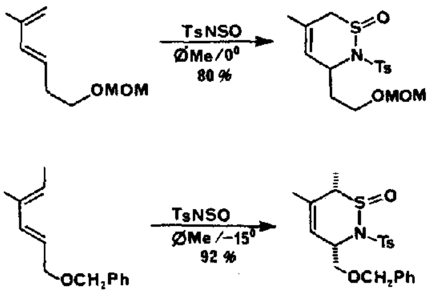


222



223

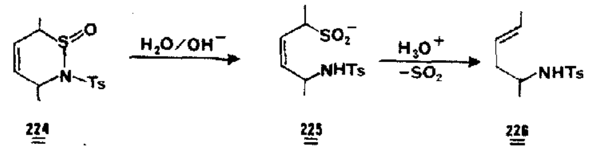
The regiochemistry of addition of sulfinylimines to complex dienes can likewise be rationalized by considering such dipolar forms. The two additions shown in Scheme 57 are totally regioselective, and the structures of the products were predicted using this approach.[111]



Scheme 57

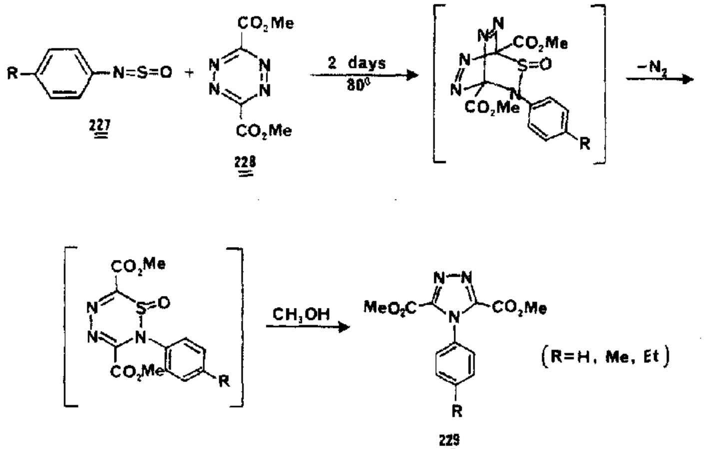
In an elegant mechanistic study, Mock and Nugent[112] have presented compelling evidence that Diels–Alder cycloadditions of arylsulfinylsulfonamides are, in fact, non-concerted processes, and that forms **222** and **223** represent true reaction intermediates rather than dipolar transition states.

A number of reactions have been reported for the products of sulfinylsulfonamide Diels–Alder reactions.[113] One of the more interesting is shown in Scheme 58 and involves hydrolysis of adduct **224** to sulfinate **225**, which upon acidification suffers loss of SO_2 by a retro-ene reaction, yielding **226**. This appears to be a general reaction of these ring systems. Mock has recently investigated the mechanism and stereochemistry of this retro-ene process.[113b]



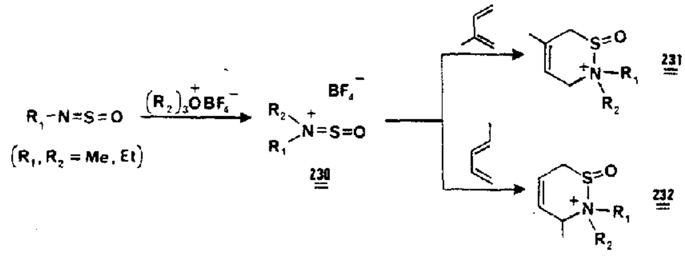
Scheme 58

N-Sulfinylaniline derivatives are well known as Diels–Alder dienophiles[106,107] but relatively little use has been made of these species in recent years.[114,115] One recent example of this type of cycloaddition (Scheme 59) involved addition of **227** to tetrazine **228** to yield triazoles **229**.[114]



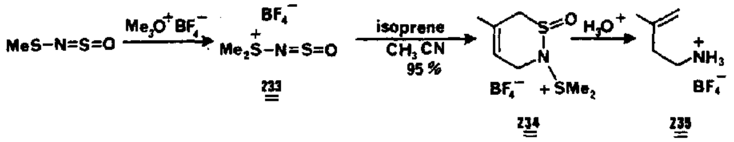
Scheme 59

Generally, sulfinylimines derived from alkyl amines are not good dienophiles.[106] However, Kresze *et al.*[116] have synthesized alkyl-N-sulfinylimmonium salts such as **230** (Scheme 60) and found that these species are excellent dienophiles. Additions of **230** to isoprene and piperylene were regioselective and afforded adducts **231** and **232**, respectively. Similar results were obtained with charged sulfinyl com-



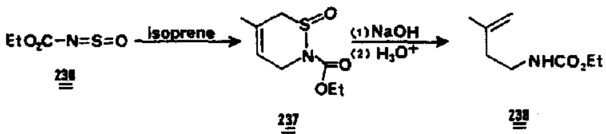
Scheme 60

pound **233** (Scheme 61) to give adducts like **234**. Hydrolysis of **234** gave unsaturated amine **235** *via* the retro-ene process described above.



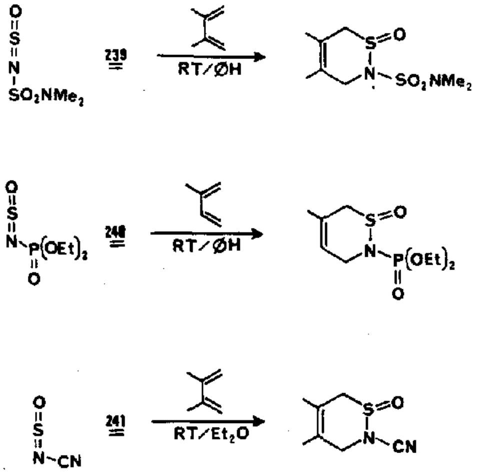
Scheme 61

A few scattered reports describing cycloadditions of N-sulfinylcarbamates have appeared.[115,117] Thus, isoprene and **236** reacted at room temperature to afford adduct **237**, which upon hydrolysis produced carbamate **238** (Scheme 62).



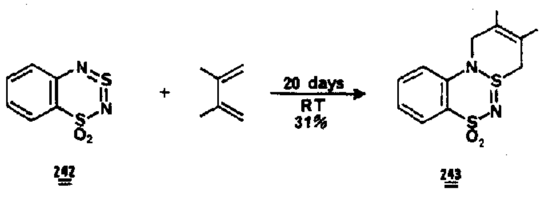
Scheme 62

Other miscellaneous sulfinyl compounds have been used as dienophiles including dialkylsulfinylsulfamides **239**,[118] dialkylsulfinylphosphoramidates **240**,[117d,119] and thionylcyanamid (**241**)[120] (Scheme 63).

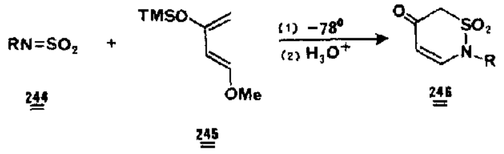


Scheme 63

Several *bis*-imines of sulfur dioxide are also effectively used as dienophiles.[107,121] For example, compound **242** reacted with 2,3-dimethylbutadiene to give adduct **243**.[121c]

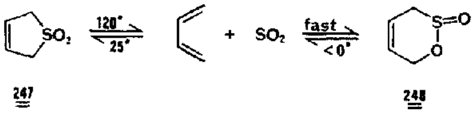


A few examples have been described of apparent Diels–Alder reactions with imines derived from sulfur trioxide.[122] Sulfonylimines are quite reactive in a [2+2]-manner with alkenes, but their ability to act as authentic dienophiles is yet to be established. Sulfonyl imines **244** (R = Me, iPr) do react with diene **245** to give, after hydrolysis, adducts **246**. However, product formation *via* a true [4+2]-cycloaddition process may not be occurring here.[122]



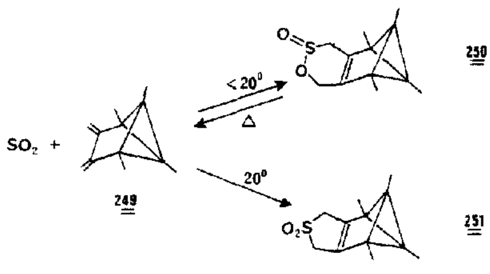
8. S–O, S–S AND Se–O DIENOPHILES

Cycloaddition reactions of dienes with sulfur dioxide, unlike its imino derivatives, usually produce dihydrothiophene dioxides **247** rather than Diels–Alder adducts **248**. Durst[123] has shown that 3,6-dihydrooxathiin-2-oxide (**248**) is the kinetic product of reaction of SO_2 with 1,3-dienes but is thermally unstable and undergoes a retro-Diels–Alder reaction to butadiene and SO_2. A thermodynamically favorable addition then occurs producing stable adduct **247** (Scheme 64). Thus, the apparent inability of SO_2 to form Diels–Alder adducts is not one of reactivity, but of product instability.



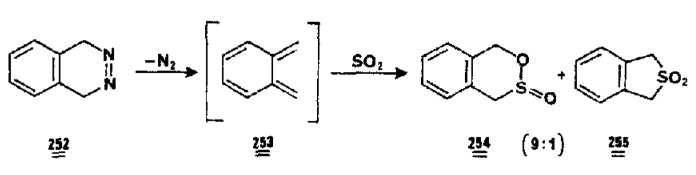
Scheme 64

Hogeveen and Heldeweg have found a rare example of a Diels–Alder reaction with sulfur dioxide where the oxathiin adduct is reasonably stable.[124] Addition of SO_2 to diene **249** at low temperature yielded adduct **250** as the kinetic product. At temperatures above 20° products resulting from the dihydrothiophene **251** were observed (Scheme 65).

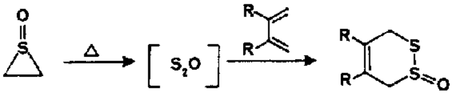


Scheme 65

In a recent experiment, Durst has shown that oxathiins are in fact the kinetic products of SO_2-diene reactions.[125] Quinone methide **253** was generated from diazocompound **252** and was found to react with sulfur dioxide to afford a 9:1 mixture of **254** and **255**, respectively. This ratio reflects the fact that formation of **254** has a $\Delta\Delta G^{\neq}$ of about 12 kcal/mole lower than that for formation of **255**.



In some related work, Dodson *et al.* have generated disulfur monoxide (S_2O) by pyrolysis of thiirane oxide (**256**) and found that this species is trapped by conjugated dienes to give Diels–Alder products of type **257** (Scheme 66).[126]

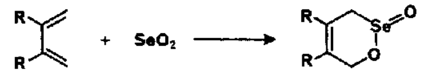


256 **257**

(R= β-naphthyl, Ph)

Scheme 66

Mock and McCausland have established that the products of cycloaddition of dienes and selenium dioxide have seleninic ester structures **258**.[127]

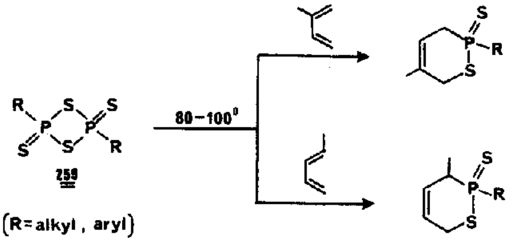


(R= alkyl, aryl) **258**

9. P–S DIENOPHILES

Various phosphorous containing compounds are capable of acting as heterodienophiles.[128–130]

Phosphonodithioic anhydrides **259** react regioselectively with unsymmetrical dienes to give Diels–Alder adducts.[128] For example, isoprene and piperylene combine with **259** to afford **260** and **261**, respectively (Scheme 67). Yields with most dienes are in the 70–90% range. It was suggested [128c] that a biradical mechanism is most consistent with the regiochemical results.

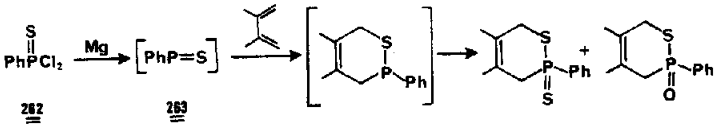


259 **260** **261**

(R=alkyl, aryl)

Scheme 67

It has been proposed that phosphinothioylidene **263**, formed by magnesium reduction of **262**, can be trapped by 2,3-dimethylbutadiene to yield adduct **264** (Scheme 68).[129] Compound **264** was not isolated but



262 **263** **264** **265** **266**

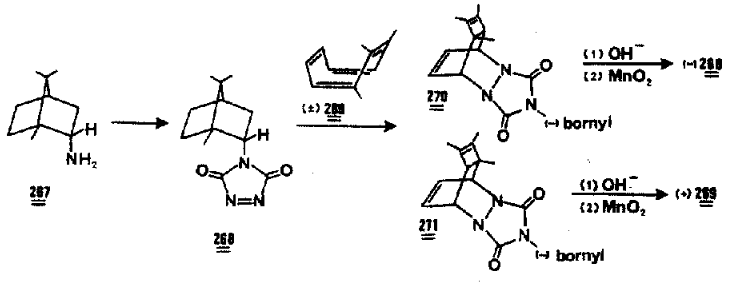
Scheme 68

compounds **265** and **266** were. It was postulated that these species were produced during the workup procedure. However, this interpretation has been questioned.[128b]

10. N–N DIENOPHILES

The use of azo compounds in Diels–Alder reactions has been known for over fifty years and various types of cyclic and acyclic azo dienophiles have been widely used in organic synthesis. The subject has been thoroughly reviewed several times and relatively little in the way of exceptionally new azo dienophiles and/or novel applications has appeared recently.

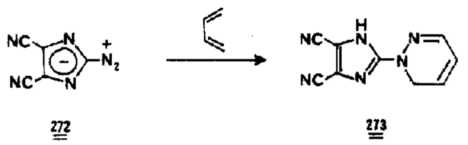
Triazoline dienes have been routinely used as azo dienophiles for many years,[133] and a complete listing of every application is well beyond the scope of this review.[134] In a more interesting recent example, Paquette has synthesized the chiral triazoline dione **268** from (−)-bornyl amine **267** (Scheme 69).[135]

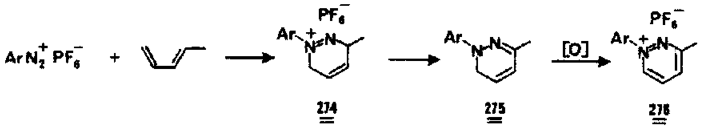


Scheme 69

Addition of **268** to racemic trimethylcyclooctatetrene **269** afforded separable diastereomeric adducts **270** and **271**. These compounds were then converted back to the optically active forms of **269**.

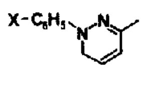
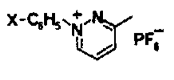
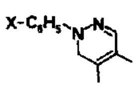
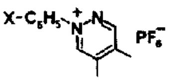
The observation that diazodicyanoimidazole (**272**) added to butadiene to afford a Diels–Alder adduct **273**[136a] led Sheppard *et al.* to reexamine the reaction of aryl diazonium salts and conjugated dienes.[136b] It was found that certain diazonium salts do react with electron rich dienes to afford pyridazines (Scheme 70). In general, it appears that electron deficient diazonium salts are the best dienophiles. The results of this study are outlined in Table 10.



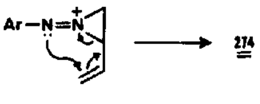


Scheme 70

Table 10. Cycloaddition of 1,3-dienes and substituted aryldiazonium hexafluorophosphates

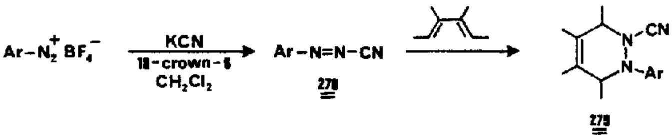
Diene	Product	Isolated yield of pyridazine(%) (X=) H	p-Cl	m-F	p-F	p-NO₂
		-	-	-	-	73
		trace	26	-	-	-
		-	-	-	-	79
		42	60	52	72	-

It was suggested that the formation of the observed products could be rationalized by assuming that a concerted [4+2]-cycloaddition occurs to yield **274** (a non-concerted, dipolar cycloaddition step would not give the observed regiochemistry). Loss of a proton from **274** would afford dihydropyridazines **275**. In all cases except the p-NO_2 ones, these dihydro compounds are rapidly oxidized (air?) to the pyridazines **276**. An alternative mechanism which cannot be completely ruled out is that an aziridinium species **277** is the initial reaction product, and it, by a [2,3]-sigmatropic rearrangement, produces dihydropyridazine **274**.

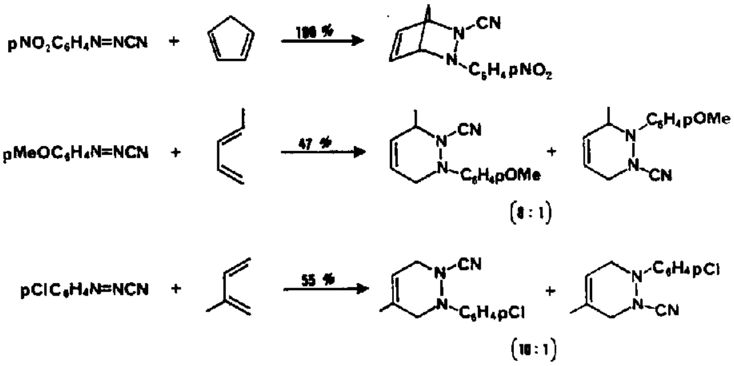


277

Ahern and Gokel[137] have found that arenediazocyanides **278** are effective dienophiles. These compounds are prepared by addition of cyanide to diazonium salts in the presence of 18-crown-6. Addition



of **278** to a number of dienes gave good yields of adducts **279**. A few representative examples of this cycloaddition are given in Scheme 71.



Scheme 71

CONCLUSION

In this review we have attempted to describe recent advances in [4+2]-cycloadditions using the major types of heterodienophiles. Emphasis was placed on representative material published within the past dozen years, and for descriptions of earlier studies the reader should see the reviews cited. Cycloaddition reactions with singlet oxygen have been omitted because of space limitations, and since this subject has been excellently reviewed numerous times.[3,138] Also, more esoteric dienophiles, such as boron imides[139] and silylenes[140], have not been included in the discussion since the synthetic utility of these species seems somewhat limited at present.

As can be seen from the work cited, heterodienophiles allow construction of many types of interesting 6-membered ring heterocycles. Many of these systems can be subsequently used in synthesis of other types of heterocyclic molecules. The cycloadditions whith these dienophiles often show excellent regio- and stereo-selectivity, although examples of reactions with the more complex types of dienes which have become available in recent years are still rare. In a few instances, intramolecular cycloadditions of heterodienophiles have been studied, but again, these cases are rare.

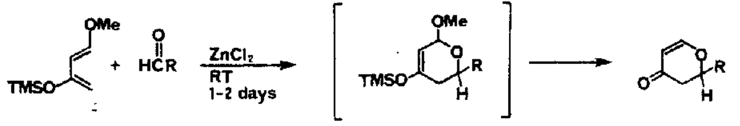
We hope that by pointing out the potential of cycloadditions with heterodienophiles, as well as some of the limitations, the methodology will find wider application by the synthetic community.

ADDENDUM

Since submission of the original manuscript some significant results have been reported involving cycloadditions of carbonyl dienophiles.

Danishefsky *et al.* have discovered that highly oxygenated 1,3-dienes react with various types of aldehydes under Lewis acid catalysis to afford γ-pyrones possibly derived from Diels–Alder adducts.[141] Thus, diene **280** reacted under mild conditions with the different aldehydes shown in Table 11 to afford 2,3-dihydro-γ-pyrones **282** in generally good yields. Intermediate **281** might be the initial product of the reaction, but was not isolated when using $ZnCl_2$ as catalyst. It was noted that possible reaction intermediates were detected in cycloaddition experiments involving BF_3 catalysis, but no details were given.

Table 11. Diels–Alder synthesis of 2,3-dihydro-γ-pyrones **282**

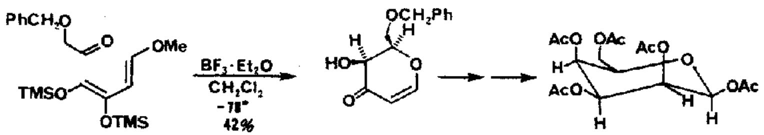


280 **281** **282**

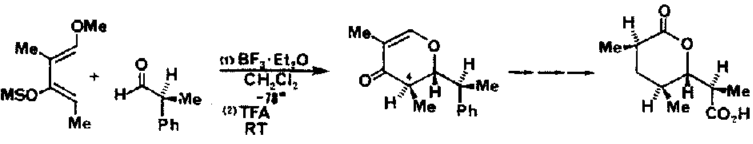
R	Yield of **282** (%)
CH_2OCH_2Ph	87
CH_2SPh	70
CHNHCbz	80
Ph	65
pNO_2Ph	58
$oOCH_3Ph$	58
CH_3	17
CH_2CH_3	48
$CH(CH_3)_2$	43
$CH_2CH(CH_3)_2$	37

Some elegant applications of this methodology to natural product syntheses have also been described. For example, diene **283** combined with benzyloxyacetaldehyde to afford adduct **284**, which was subsequently converted to talose derivative **285**. Diene **286** underwent cycloaddition with chiral aldehyde **287** under the conditions shown to yield pyrone **288** and its C-4 epimer (4.3:1 ratio, 95%). Compound **288** was efficiently transformed to the Prelog–Djerassi lactone **289**.

Snider and Phillips[142] have very cleverly combined two consecutive ene-reactions with a carbonyl Diels–Alder cycloaddition to produce pyran **296**, which has previously been used by Kozikowski[143] in total synthesis of pseudomonic acid (**297**). Thus, 1,5-diene **290** underwent dimethylaluminum chloride

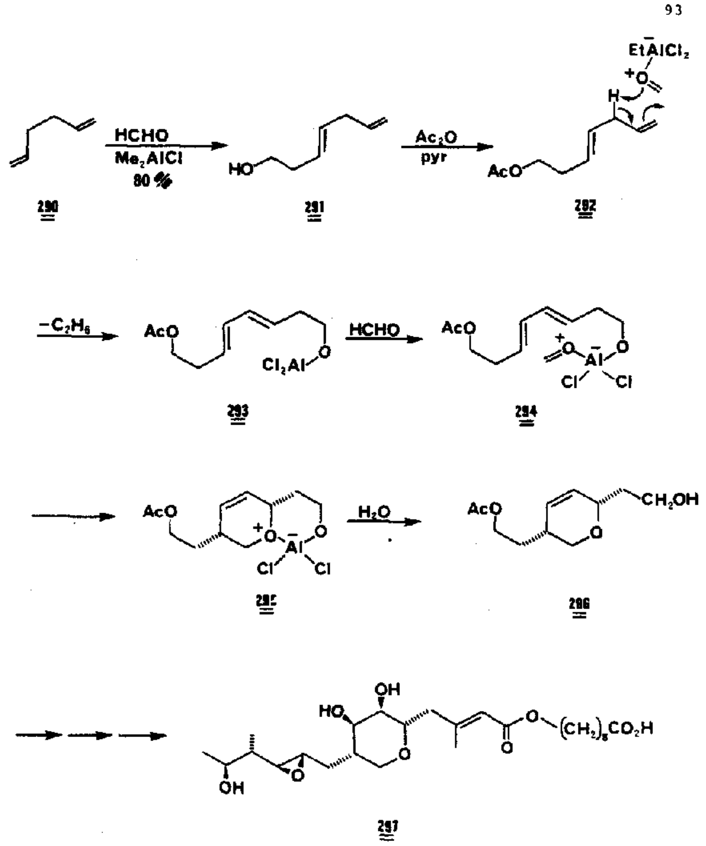


283 **284** **285**



286 **287** **288** **289**

catalyzed ene-reaction with formaldehyde to afford **291** (Scheme 72) as a 8:1 mixture of *trans*:*cis*



Scheme 72

isomers (80%). Isomers were not separated since the *cis* compound did not undergo the subsequent Diels–Alder reaction. Treatment of derived acetate **297** with ethyl aluminum dichloride and formaldehyde in CH_2Cl_2/CH_3NO_2 (12 h, 25°) gave a 35–40% yield of adduct **296**. This transformation presumably involves initial ene-reaction of **292** to give **293** which reacted with formaldehyde to produce complex **294**. A "quasi" intramolecular Diels–Alder cycloaddition then ensued which led to **295**. Hydrolysis of aluminum complex **295** gave the desired pyran **296**, identical with material prepared by the Kozikowski group.[143]

Acknowledgment—We are grateful to the National Institutes of Health and the National Science Foundation for support of the research of SMW which has been included in this Report.

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[1] For reviews see *inter alia* [a]A. S. Onishchenko, *Diene Synthesis*. Israel Program for Scientific Translation, Jerusalem (1964); [b]H. Wollweber, *Diels–Alder Reaktion*. Thieme Verlag, Stuttgart (1972).

[2] J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **19**, 779 (1980) and refs. cited.

[3] J. Hamer (Ed.), *1,4-Cycloaddition Reactions*. Academic Press, New York (1967).

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