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Small Ring Compounds in Organic Synthesis V

Volume Editor: A. de Meijere

With contributions by
A. Brandi, F. M. Cordero,
A. Goti, T. Hirao

With 5 Figures and 48 Tables

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Small Ring Compounds in Organic Synthesis IV

Preface

Ten years have passed since the first volume on "Small Ring Compounds in Organic Synthesis" was published within the series Topics in Current Chemistry (Vol. 133), and three more volumes have appeared in the meantime (Vol. 135, 144, 155). Wouldn't that be enough?

Although this collection of reviews by individual authors, who are themselves actively engaged in research with the use of small ring compounds in Organic Synthesis, has not been and is not intended to be comprehensive, the field is developing at such a rate that coverage of new topics appears highly appropriate. The importance of small ring chemistry can be estimated from the fact that a forthcoming volume of Houben-Weyl "Methods of Organic Chemistry" on three- and four-membered carbocyclic compounds only covering the literature of the last 25 years will comprise over 5000 pages. Extraordinary new natural products have been discovered which contain fatty acid analogues with four and even five adjecent cyclopropyl groups. Just to name a single type of cyclopropane derivative, a recent survey has uncovered 91 pharmaceutically important compounds which contain a cyclopropylamine substructure. Clearly, the answer to the above question is "No".

The two articles in this current volume describe recent developments with small ring compounds which have not been compiled in such a context before. *T. Hirao* discusses selective transformations initiated by transition derivatives in the construction of functionally substituted five-, six- and seven-membered rings as well as open-chair compounds. Cycloadditions onto methylene- and alkylidene-cyclopropane derivatives, described by *A. Goti, F. M. Cordero* and *A. Brandi*, not only yield products with spirocyclopropane moieties which can be desirable as such or as potential mimics of gem-dimethyl groupings, but also intermediates which can undergo further transformations with ring-opening of the cyclopropane units.

The authors, the editor and the publisher of this and a few more forthcoming Topics on "Small Ring Compounds in Organic Synthesis" intend to provide a service to the research community and hope that these books will generate more and fresh interest in this fascinating chemistry.

Göttingen, February 1996 Armin de Meijere

Cycloadditions onto Methylene- and Alkylidenecyclopropane Derivatives

Andrea Goti, Franca M. Cordero and Alberto Brandi

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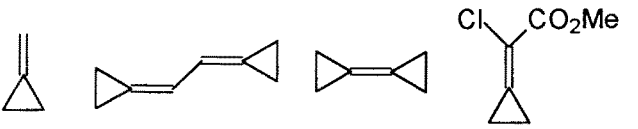
List of Symbols and Abbreviations

BCP	Bicyclopropylidene
COD	Cyclooctadiene
CSI	Chlorosulfonylisocyanate
MCP	Methylenecyclopropane
MCPBA	*m*-Chloroperbenzoic acid
NMO	*N*-Methylmorpholine *N*-oxide
PKR	Pauson Khand Reactions
PTAD	4-Ph-1, 2, 4,-triazoline-3, 5-dione
SET	Single electron transfer
TCNE	Tetracyanoethylene
TMANO	Trimethylamine *N*-oxide
TMM	Trimethylenemethane

Alkylidenecyclopropanes are a peculiar class of olefinic compounds characterized by a high ring strain, but at the same time a sufficient stability to permit their use in organic synthesis. The strain associated with the structure of these compounds is in general responsible for the good reactivity of the carbon-carbon double bond, even in sterically encumbered substrates. The key role of these compounds in organic synthesis resides in the exclusive, and by far the most useful, possibility of the introduction of a cyclopropyl ring in a more complex molecule through reactions onto the exocyclic double bond. For this reason the investigations on the synthesis and reactivity of these compounds has exploded in the last decade. This article will deal with all the reactions which involve the exocyclic double bond of alkylidenecyclopropanes in cycloaddition processes. Albeit most of the reactions are true pericyclic cycloaddition processes, also those reactions which lead to cycles by stepwise processes will be reported with comments on the mechanism.

1 Introduction

Methylene- and alkylidenecyclopropanes are highly strained molecules, but at the same time most of them are surprisingly stable to allow their use in many synthetic applications. Being multifunctional reagents with high energy, they offer enormous potential in organic syntheses that has been only partially disclosed in the last decades.



1 2 3 4

The parent methylenecyclopropane (MCP) (**1**) [1] is a highly volatile compound (bp 11 °C) which can be prepared in multigram quantities and is commercially available. Numerous efficient and straightforward syntheses of the different types of methylene- and alkylidenecyclopropanes have appeared in the literature and the matter has been reviewed by Binger and Büch [2]. In the last decade other selective syntheses have been developed which gave easy access to compounds containing specific substitution patterns [3], to optically active derivatives [4], or more sophisticated derivatives like dicyclopropylideneethane (**2**) [5], bicyclopropylidene (BCP) (**3**) [6] and chloromethoxy carbonylmethylenecyclopropane (**4**) [7].

The highly strained nature of methylene- and alkylidenecyclopropanes has been evidenced by spectroscopic measurements and X-ray analysis. The presence of the exocyclic double bond imposes a lengthening of the C(2)-C(3) bond as a result of an increase of the C(2)-C(1)-C(3) angle (compared to cyclopropane). This structural feature is reflected in a typical reactivity of these compounds which is a thermal or transition metal catalysed [3 + 2] cycloaddition with alkenes. This chemistry, usually referred to as "TMM chemistry", has been the object of many studies and thoroughly reviewed by Binger and Büch [2] and Trost [8].

The second large group of reactions is characterised by the elaboration of the exocyclic double bond. This chemistry is particularly interesting because it allows the incorporation of a cyclopropyl ring in a more complex molecule, to take advantage of its peculiar feature as a reactive three-carbon functional group.

Among these reactions, the cycloadditions play a central role because of their general application, and for the unequalled property of the possible introduction of two new carbon-carbon or carbon-heteroatom bonds in the same step or process.

Despite the study of cycloadditions to alkylidenecyclopropanes being far from fully exploited, the results accumulated in the literature are enough for a comprehensive review which will present the state of the art. The present review will deal with all the processes of cycloadditions, without discriminating between the nature, concerted or stepwise, of the processes. It will cover those reactions which involve exclusively the exocyclic double bond of methylenecyclopropane and alkylidenecyclopropanes in the formation of three-, four-, five- and six-membered rings.

2 Six-Membered Ring

2.1 Diels-Alder Reactions

2.1.1 Alkylidenecyclopropanes as Dienophiles

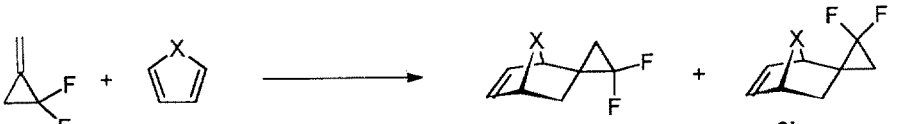
Examples of the use of alkylidenecyclopropanes as dienophiles are very limited in the literature. Moreover, the few examples reported deal with rather sophisticated substrates such as 2,2-difluoromethylenecyclopropane, diarylmethylenecyclopropanaphthalenes, bicyclopropylidene and (diacylmethylene)cyclopropanes.

MCP (**1**) is not known to undergo [4 + 2] cycloadditions. The substitution of two, or more, ring protons with fluorine atoms, however, seems to improve dramatically the dienophilic reactivity of the exocyclic double bond. 2,2-Difluoromethylenecyclopropane (**5**) is a quite reactive dienophile in Diels-Alder cycloadditions. With cyclopentadiene (**6**) and furan (**7**), it formed two isomeric adducts (Scheme 1) [9]. In both cases the adduct with the *endo* CF_2 group is the major isomer.

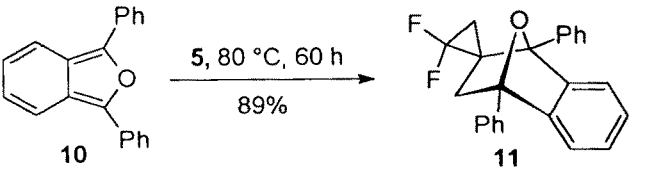
Diphenylisobenzofuran (**10**) reacted with **5** to give only the *endo* isomer **11** (Scheme 2) [9].

Butadiene (**12**) was less reactive than the cyclic dienes and its reaction with **5** required 7 days at 110 °C to produce **13** (Scheme 3) [9]. No formation of [2 + 2] cycloadducts was observed in the above reactions of **5**.

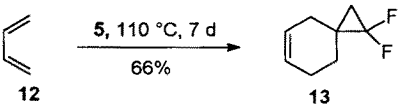
Although diarylmethylenecyclopropabenzenes react in [4 + 2] cycloadditions at the 'cyclopropene' bridge bond [10a], diarylmethylenecyclopropa[*b*]-naphthalenes **14** react readily across the exocyclic double bond [10b]. The



Scheme 1



Scheme 2



Scheme 3

primary adduct was not observed, but only rearrangement products were isolated. The principal factor responsible for the product formation in these reactions is the relief of strain in the spirocyclic cycloproparenyl intermediate **15**, which provides either ring-expanded or ring-opened products. The diphenyl derivative **14a** when treated with diphenylisobenzofuran (**10**) in refluxing toluene for several days gave **16a** in 55% yield [10] (Table 1). Similarly, **14b** and **14c** provided the cyclobutarenes **16b, c** in 32 and 42% yields, respectively. No cycloaddition to the internal, strained 'cyclopropene' bridge bond is observed despite the fact that parent cyclopropabenzene provides many of such examples [10a].

The formation of compound **16** likely involves an initial [4 + 2] cycloaddition across the exocyclic double bond to give the highly strained spirocycloproparene **15** which relieves the ring strain by rearrangement with concomitant ring expansion to **16**.

Reaction rates and yields increase upon using a hydrophilic solvent. The cycloaddition of **10** to **14a** is essentially complete in a few hours when performed in ethylene glycol and gave **16a** in higher yield (62%) [10b].

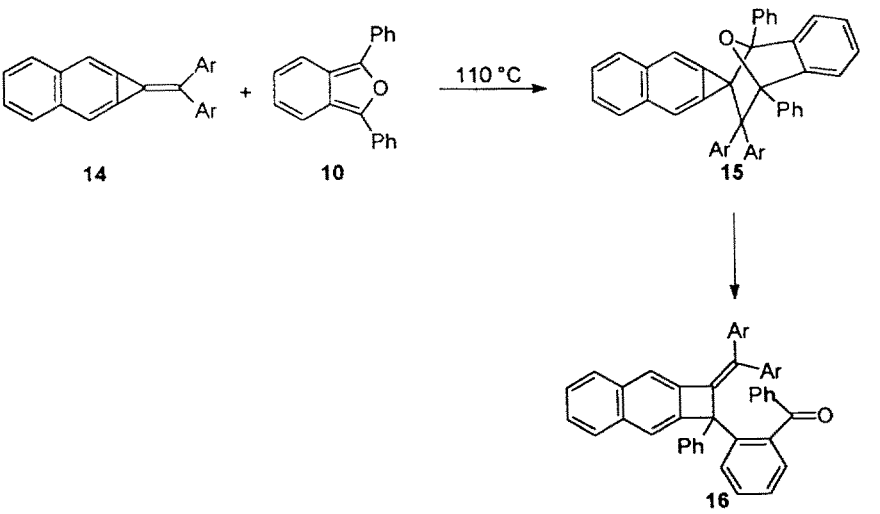
The reactions of **14** with α-pyrone (**17**) were carried out at 110 °C and gave the rearranged compound **19** [10b] (Table 2).

The reaction proceeds analogously via a formal [4 + 2] cycloaddition to give the highly strained adduct **18**. This intermediate quickly rearranges, via the cleavage of the cycloproparenyl σ-bond, to give the cyclopentanone **19**. Once again, a dramatic increase in both yield and reaction rate was observed when ethylene glycol was employed as the solvent (Table 2, entry 1).

Another strained alkylidenecyclopropane, 2-methylbicyclo[3.1.0]hex-1-ene (**21**), formed by cyclization of the carbenoid generated from dibromide **20** at 0 °C gave, in the presence of an excess of 1, 3-diphenylisobenzofuran (**10**), a very small amount (5%) of a 2:1 mixture of diastereoisomeric Diels-Alder adducts **22** (Scheme 4) [11a]. The parent furan does not capture **21** even when used as solvent for the carbenoid cyclization.

Analogues *endo* and *exo* cycloadducts have been observed in the reactions of cyclopentadiene (**6**) with **21** or methoxybicyclo[3.1.0]hex-1-ene (**23**) (Scheme 5) [11].

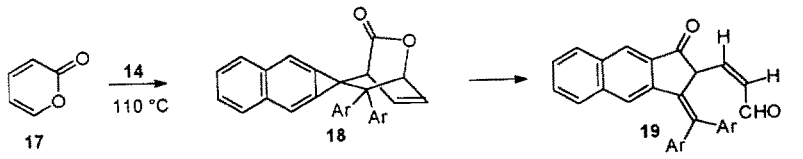
Table 1. Reactions of diarylalkylidenecyclopropanes **14** with diphenylisobenzofuran (**10**) [10]



Entry	Reagent	Ar	Product	Yield (%)[a]
1	**14a**	Ph	**16a**	55 (62)[b]
2	**14b**	C_6H_4OMe-*p*	**16b**	32
3	**14c**	$C_6H_4CF_3$-*m*	**16c**	42

[a] Toluene, 110 °C, several days
[b] Ethylene glycol, 110 °C, ~7 h

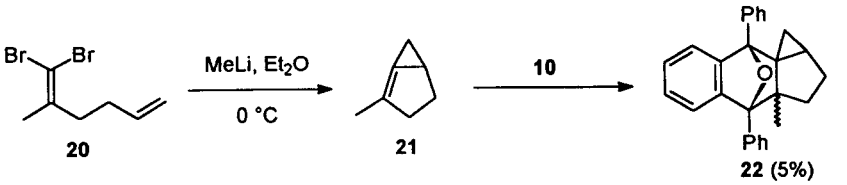
Table 2. Reactions of diarylalkylidenecyclopropanes **14** with α-pyrone (**17**) [10]



Entry	Reagent	Ar	Product	Yield[a] (%)
1	**14a**	Ph	**19a**	50 (11)[b]
2	**14b**	C_6H_4OMe-*p*	**19b**	25
3	**14c**	$C_6H_4CF_3$-*m*	**19c**	16

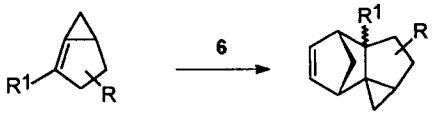
[a] Ethylene glycol, 110 °C, 12 h
[b] Toluene, 110 °C, several days

Whereas the parent MCP (**1**) is not reported to give [4 + 2] cycloadditions, bicyclopropylidene (**3**) has been shown to give Diels-Alder adducts. Bicyclopropylidene (**3**) is a unique olefin, combining the structural features of a tetrasubstituted ethylene and two methylenecyclopropane units. The central



20 **21** **22 (5%)**

Scheme 4

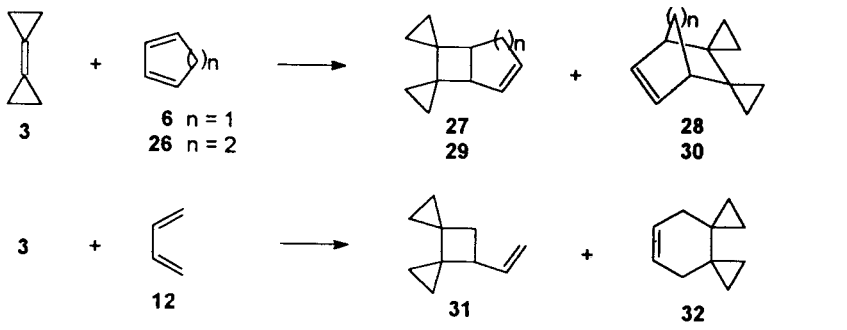


21 R = H, R^1 = Me **24** (2 stereoisomers)
23 R = OMe, R^1 = H **25** (4 stereoisomers)

Scheme 5

$C(sp^2)=C(sp^2)$ bond imparts properties which more closely resemble those of the central double bond in butatriene than of the one in a simple tetrasubstituted ethylene [12]. For this reason, bicyclopropylidene (**3**) undergoes cycloadditions with 1,3-dienes, and these showed an interesting dependence on the structure of the diene. Whereas cyclopentadiene (**6**) gave the [4 + 2] cycloadduct **28** exclusively, 1,3-cyclohexadiene (**26**) and 1,3-butadiene (**12**) led to mixtures of the [4 + 2] and [2 + 2] cycloadducts, with the proportion of the [2 + 2] adduct increasing respectively [13] (Table 3).

Table 3. Cycloadditions of bicyclopropylidene (**3**) to 1,3-dienes **6**, **26** and **12** in the presence of traces of hydroquinone [13]



Entry	Diene	Reaction conditions T (°C)	time (h)	Products (rel yields, %) [2 + 2]	[4 + 2]	Total yields[a] %
1	**6**	150	10		**28** (> 97)	16[b]
2	**26**	170	11	**29** (78)	**30** (22)	50
3	**12**	180	12	**31** (92)	**32** (8)	54

[a] Based on GLPC-isolated amounts
[b] In this reaction **3** was not consumed completely (50%)

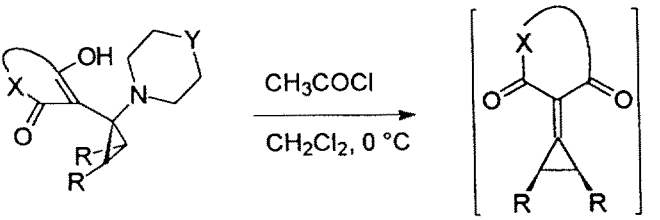
The observation that the overwhelming product from the cycloaddition of **3** to 1,3-butadiene (**12**) is a cyclobutane derivative **31** and the proportion of the [4 + 2] adduct increases in the order **12** < **26** ≪ **6** is in accord with the increasing diene reactivity in this series. Whereas cyclopentadiene readily combines with most dienophiles at low temperatures, 1,3-butadiene, mainly owing to its predominant *s-trans* conformation, enters into [4 + 2] cycloadditions only at elevated temperatures.

Electron-withdrawing substituted alkylidenecyclopropanes were more extensively studied.

(Diacylmethylene)cyclopropanes (**34**) generated from the corresponding aminocyclopropanes **33** and acetylchloride (Scheme 6) are highly reactive intermediates and can be trapped by dienes such as 2,3-dimethylbutadiene (**35**), pentadiene **36** and isoprene (**37**) yielding the Diels-Alder products **38–40** [14] (Table 4).

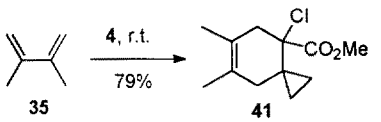
Pentadiene **36** and isoprene (**37**) gave with **34a** exclusively the regioisomers **39** and **40**, respectively. Bicyclic methylenecyclopropanes **34a** and **34b** gave stereospecifically the isomers **38a** and **38b** deriving from the attack on the convex face of the methylenenorcarane **34a** (or **34b**). The reaction yields were generally good, but obtained with an excess of the diene. Only **34c** gave **38c** in 85% yield in the presence of only one molar equivalent of diene **35** [14].

2-Chloro-2-cyclopropylideneacetate (**4**) is one of the most studied and reactive dienophiles. It reacts readily with open-chain dienes, like 2,3-dimethylbutadiene (**35**), at room temperature to yield **41** (79%) (Scheme 7) or Danishefsky diene **42** to give exclusively the regioisomer **43** [15] (Scheme 8).



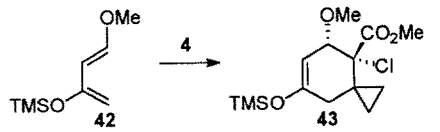
33 Y = O, CH_2 **34**

Scheme 6



35 **41**

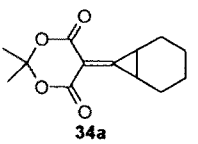
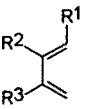
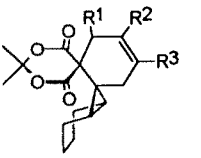
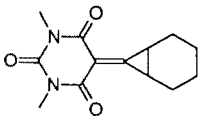
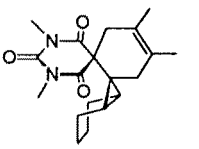
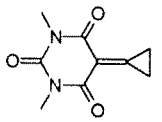
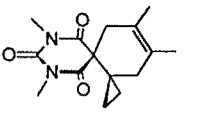
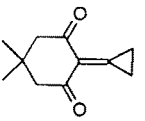
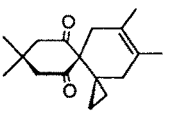
Scheme 7



42 **43**

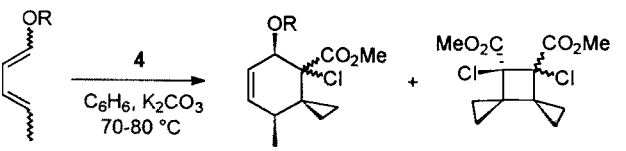
Scheme 8

Table 4. Cycloadditions of (diacylmethylene)cyclopropanes (**34**) to 1,3-dienes **35**, **36**, and **37**

Entry	Alkylidene cyclopropanes	Dienes	Reaction conditions	Cycloadducts (yield %)
	 **34a**		20 °C, 3 h	
1		**35** R^1 = H, R^2 = Me, R^3 = Me		**38a** (77)
2		**36** R^1 = Me, R^2 = H, R^3 = H		**39** (43)
3		**37** R^1 = H, R^2 = H, R^3 = Me		**40** (61)
4	 **34b**	**35**	20 °C, 3 h	 **38b** (74)
5	 **34c**	**35**	50 °C, 20 h	 **38c** (85)
6	 **34d**	**35**	50 °C, 20 h	 **38d** (73)

On the other hand, 1-ethoxy-1,3-pentadiene (**44a**) and 1-(trimethylsilyloxy)-1,3-pentadiene (**44b**), as mixtures of four isomers, gave low yields of **45a** and **45b** [16], respectively, besides a complex mixture of products including *cis* and *trans*-**46**, head-to-head dimers of **4** [7a, 17] (see Sect. 4.1.1) (Scheme 9).

Cyclopropylideneacetate **4** reacted with 1,2-bis(ethylidene)cyclohexane **47** to give a 60% yield of the octahydronaphthalene **48** [18] (Scheme 10).

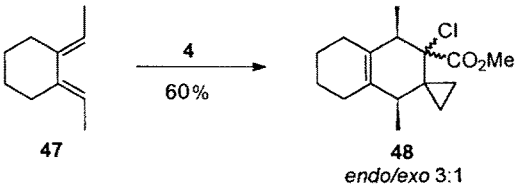


44a R = Et
44b R = $SiMe_3$

45a (18%)
45b (12%)

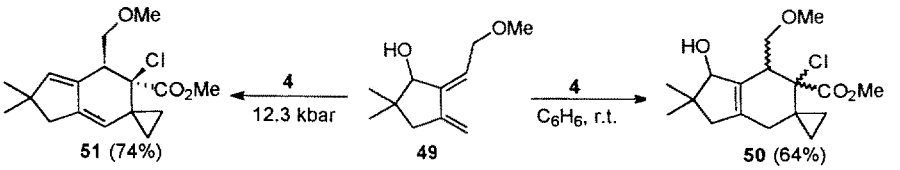
46

Scheme 9



47 48
endo/exo 3:1

Scheme 10



51 (74%) 49 50 (64%)

Scheme 11

The dimethylenecyclopentane **49** readily added to **4** under stirring in benzene at room temperature to give three diastereoisomers of **50**, all of which had the expected regiochemistry. At room temperature and 12.3 kbar, the dehydrated product **51** was also obtained in 74% yield [17] (Scheme 11).

A new synthetic approach to the antibacterial and cytotoxic sesquiterpene Illudin M and structurally related sesquiterpenes could be based on the good regioselectivity observed in these cycloadditions [17, 18].

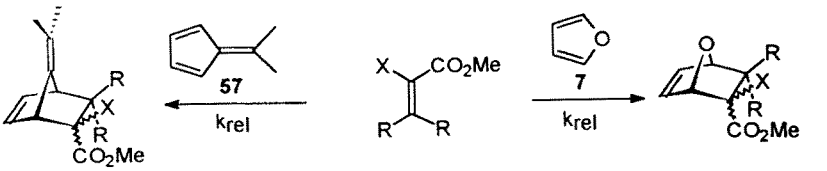
2-Hetero substituted 2-cyclopropylideneacetates are ring-strain activated acrylates, highly reactive dienophiles in Diels-Alder reactions, but also powerful Michael acceptors. The reactivity of these compounds is enhanced by the same strain release in the Diels-Alder cycloadditions as well as in the 1,4-additions, and indeed the borderline between tandem Michael-cyclization and Diels-Alder-type cycloaddition is not well defined in many cases.

The relative reactivities of several of these 2-hetero substituted 2-cyclopropylideneacetates **4** and **53–55** as well as of the parent 2-cyclopropylideneacetate **52** and acrylates **56a–d** towards 6,6-dimethylfulvene (**57**) and furan (**7**) were determined by competition experiments [17, 19] (Table 5). The *endo/exo* selectivity is low, but usually still higher than for simple acrylic esters.

Methyl 2-chloro-2-cyclopropylideneacetate (**4**) was readily prepared in two steps from ethylene and tetrachlorocyclopropene [7], and reacted with 4-methylcyclohexa-1,3-dien-2-ol trimethylsilyl ether (**62a**) at 60 °C to give a complex mixture containing about equal amounts of both regioisomeric adducts **63a, 64a** besides the tricyclic ketoester **65a** after acidic workup (Schemes 12 and 13) [15]. Each regioisomer was a mixture of *endo* and *exo*-diastereomers. The trimethylcyclohexadiene **62b** yielded, after 2 days at 100 °C and acidic work-up, the tricyclic ketoester **65b** as the main product (Schemes 12 and 13) [15].

When treated with lithium cyclohexadienolates **68**, generated from the corresponding cyclohexenones **66** with lithium diisopropylamide (LDA) or from

Table 5. Relative rates of reaction of cyclopropylideneacetates **4**, **52–55** and selected acrylic esters **56a–d** with **57** and **7** [17, 19]



58 R = $(CH_2)_2$
59 R = H, Me

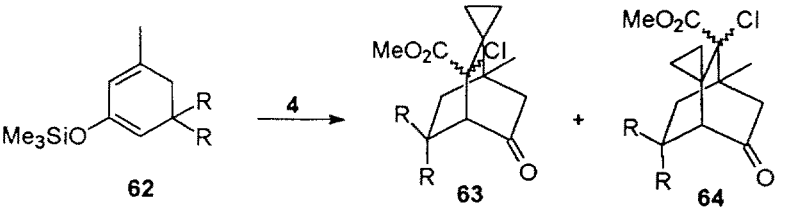
4, **52-55** R = $(CH_2)_2$
56 R = H, Me

60 R = $(CH_2)_2$
61 R = H, Me

Entry	Cpd.	R, R	X	Product[b]	Relative rates (*endo*/*exo*[a])	Product[c]	Relative rates (*endo*/*exo*[a])
1	**52**	CH_2–CH_2	H	**58a**	17 (1.8)	**60a**	4 (5.6)
2	**53**	CH_2–CH_2	F	**58b**	–	**60b**	3 (0.5)
3	**4**	CH_2–CH_2	Cl	**58c**	355 (1.3)	**60c**	16 (1.4)
4	**54**	CH_2–CH_2	Br	**58d**	–	**60d**	16 (1.1)
5	**55**	CH_2–CH_2	N_3	**58e**	–	**60e**	27 (2.8)
6	**56a**	H, H	H	**59a**	~1 (1.3)	**61a**	1 (1.3)
7	**56b**	$=CH_2$	H	**59b**	51 (2.1)	**61b**	–
8	**56c**	CH_3, CH_3	H	**59c**	≪[d]	**61c**	≪[d]
9	**56d**	CH_3, CH_3	Cl	**59d**	≪[d]	**61d**	≪[d]

[a] The *endo*/*exo* designation relates to the position of the CO_2Me group
[b] [4 + 2] Cycloaddition to 6,6-dimethylfulvene (**57**)
[c] [4 + 2] Cycloaddition to furan (**7**)
[d] Relative amount of product too small for detection

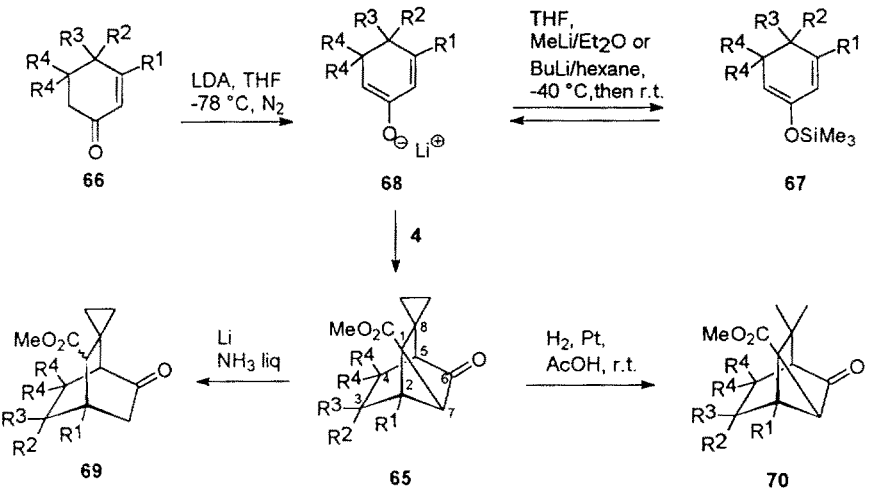
the enol trimethylsilyl ethers **67** with methyllithium or butyllithium, **4** underwent smoothly and completely regio- and stereoselective additions with subsequent γ-elimination to give the tricyclic γ-ketoesters **65** (Scheme 13) in good to excellent yields (Table 6) [15, 20]. With the exception of the addition of the unsubstituted cyclohexadienolate **68d**, the yields of cycloadducts are in the range of those from other acrylates [21] and better than those from α-bromocrotonate [22]. It is especially noteworthy that methyl 3,3-dimethylacrylate does not react with any of the cyclohexadienolates **68**. The addition of the considerably more reactive cyclopropylideneacetate **4**, however, can be utilized to achieve the same goal by subsequent catalytic hydrogenation [23] as was demonstrated with the adducts **65a** and **65e**. When hydrogenated over PtO_2 in acetic acid, compound **65e** cleanly gave the *gem*-dimethyl derivative **70e** (56%), while **70a** obtained from **65a** (67% crude) partially underwent further hydrogenation under these conditions (Scheme 13) [15]. The skeletal three-membered ring in **65** can be reductively opened between C1 and C7 with lithium in liquid ammonia to produce the bicyclo[2.2.2]octane derivative **69** [22b]. Thus, **4** can be used as a reactive multifunctional building block to construct bi- and tricyclic skeletons of a variety of terpenoidic natural products.



62 63 64

a R = H
b R = Me

Scheme 12



66 68 67

69 65 70

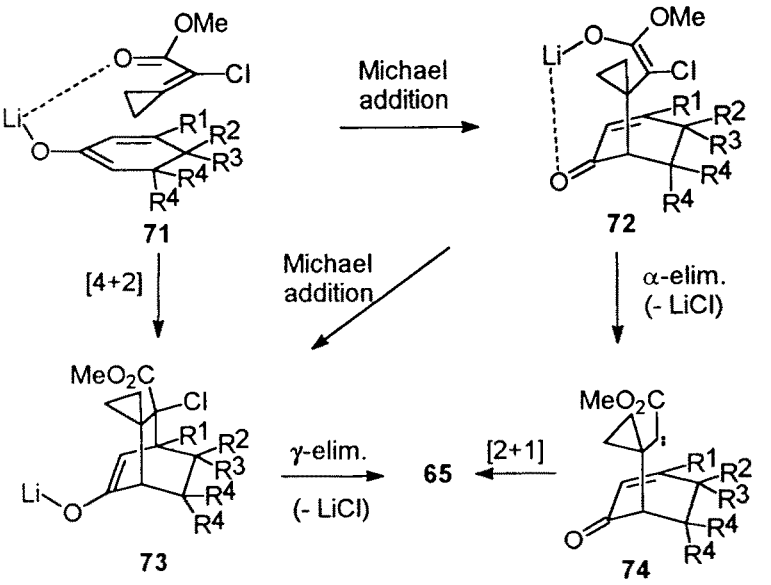
Scheme 13

Table 6. Tricyclic ketoesters **65** from **4** and lithium cyclohexadienolates **68** (see Scheme 13) [15, 20]

Entry	Cpd.	R^1	R^2	R^3	R^4	Yield [%]	(Method[a])	Isolation[b]
1	**65a**	CH_3	H	H	H	68	(II)	A, B
2	**65b**	CH_3	H	H	CH_3	75	(II)	B
3	**65c**	H	CH_3	CH_3	H	52	(II)	B
4	**65d**	H	H	H	H	34	(I)	B
5	**65e**	$-(CH_2)_2CH(OBu^t)-$		CH_3	H	79/94	(I/II)	B

[a] I. **66**, LDA, THF, − 78 °C; II: **67**, THF, MeLi/Et_2O or BuLi/hexane, − 40 °C, then r.t.
[b] A: Recrystallization; B: Kugelrohr distillation

Mechanistically, the formation of the tricyclic products **65** from **68** and **4** can be rationalized in three different ways (Scheme 14). It can be initiated by a sequence of two Michael additions starting from a preoriented complex **71** to give predominantly **73** via **72** with a chloro substituent *anti* to the enolate

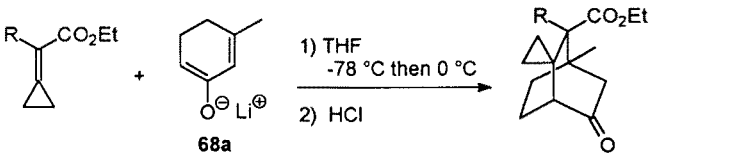


Scheme 14

moiety, so that subsequent γ-elimination can occur. The compound **73** with the proper configuration at C2 could also be formed by a concerted [4 + 2] cycloaddition of the dienophile **4** to the electron-rich diene **68** with the typical *endo* selectivity of a Diels-Alder reaction. If the first Michael addition of **68** to **4** were faster than the concerted cycloaddition, the intermediate **72** could also α-eliminate the chloride ion to yield a carbomethoxy carbene **74**, which subsequently undergoes an intramolecular chelotropic addition to give **65**.

The kinetic dienolate **68a** also reacted with the non-heterosubstituted cyclopropylideneacetates **52b** and **75** to give the *endo* bicyclo[2.2.2]octanes **69a** and **76**, respectively (Scheme 15) [24].

The reactivity of ethyl cyclopropylideneacetate (**52b**) has been exploited by Spitzner and Sawitzki in a new (formal) total synthesis of the diterpene (+)-isoeremolactone **80** (Scheme 16) [25]. The key step of the synthesis is the addition of the enantiomerically pure dienolate **78** to the reactive acrylate **52b**, to give a single isomer **79** in 92% yield.

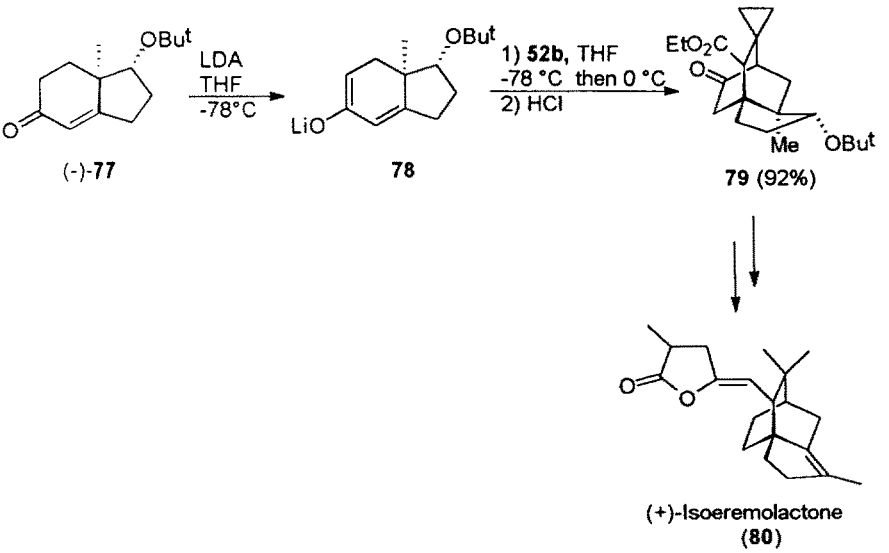


52b R = H
75 R = Me

68a

69a R = H (61%)
76 R = Me (79%)

Scheme 15



Scheme 16

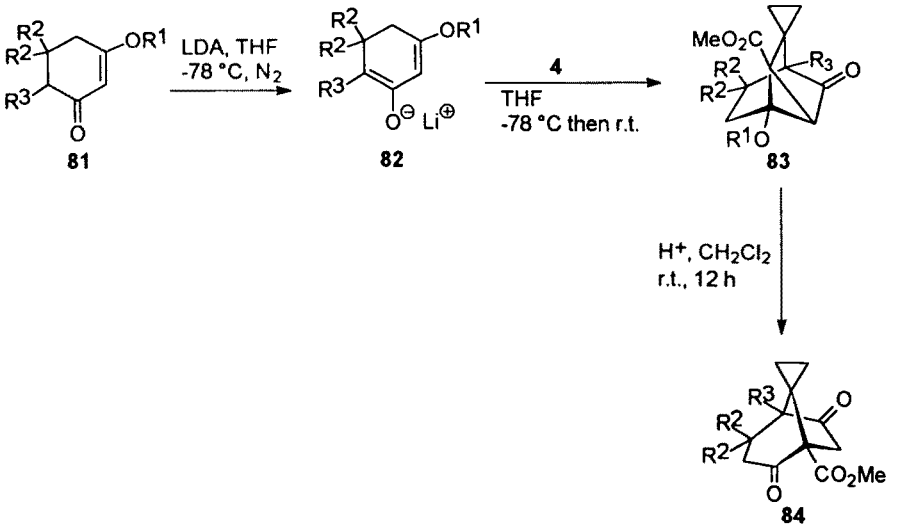
A large number of lithium 1-alkoxycyclohexadienolates **82** generated from the corresponding 3-alkoxycyclohex-2-enones **81** with LDA reacted with the 2-chloro-acrylate **4** to give the tricyclic γ-ketoesters **83** in good yields (Table 7) [26, 15]. The stereochemical control of the reaction could not be achieved with a chiral auxiliary in the alkoxy group of **81** (R^1 = (+)-menthyl), as a 1.1:1 mixture of diastereomeric products **83h** was obtained (entry 8). Treatment of the tricyclic γ-ketoesters **83** with an acid (e.g. aqueous HCl, CF_3COOH, *p*-TsOH) in dichloromethane affords the spirocyclopropanated 2,6-dioxobicyclo[3.2.1]octane-1-carboxylates **84** in excellent yields (Table 7) [26, 15].

Cyclopentadiene (**6**) added to **4** at room temperature. The reaction was complete within 5 h and gave a mixture of *endo/exo*-**86a** in 90% yield. The 2-phenylthio derivative **85** (X = SPh) showed similar reactivity, while the unsubstituted compound **52** reacted more slowly (Table 8) [15, 17].

Furans react readily with **4** in [4 + 2] cycloadditions, but the reactivity depends on the nature of the heterocyclic diene. Whereas the parent furan (**7**) reacts with neat **4** affording excellent yields of a 1.4:1 *endo/exo* mixture of cycloadducts **60c** (entry 3, Table 5) [16], and 2-methylfuran (**87a**) afforded the corresponding *endo*-**88a** and *exo*-**88a** as a 1.5:1 mixture in 76% yield, 2,5-dimethylfuran (**87b**) reacted much more slowly, and after 120 h gave only 5% conversion to *endo/exo*- **88b** (2:1) (Table 9).

This low reactivity of **88b** is probably due to the steric influence of the second methyl group at C-5, which interacts with the cyclopropyl ring of **4** thereby elevating the energy of the transition state. Only upon heating at 60 °C was the

Table 7. 2-Alkoxy-6-oxotricyclo [3.2.1.0] octane-1-carboxylates **83** from alkoxycyclohexadienolates **82** and methyl 2-chloro-2-cyclopropylideneacetate (**4**), and their transformation to 2,6-dioxobicyclo-[3.2.1]octane-1-carboxylates **84** [26, 15]

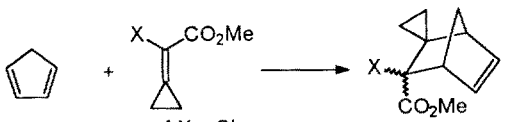


Entry	Starting material	R^1	R^2	R^3	Product	Yield[a] (%)	Product	Yield (%)
1	**81a**	Me	H	H	**83a**	59	**84a**	98
2	**81b**	Et	H	H	**83b**	60	**84b**	98
3	**81c**	Me	Me	H	**83c**	86	**84c**	91
4	**81d**	Et	Me	H	**83d**	58	**84d**	93
5	**81e**	*i*-Pr	Me	H	**83e**	71	**84e**	95
6	**81f**	*n*-Bu	Me	H	**83f**	72	**84f**	94
7	**81g**	allyl	Me	H	**83g**	66	**84g**	93
8	**81h**	(+)-menthyl	Me	H	**83h**	67[b]	**84h**	–
9	**81i**	*n*-Bu	Me	allyl	**83i**	58	**84i**	99
10	**81l**	Bz	H	H	**83l**	92	**84l**	–
11	**81m**	$SiMe_3$	H	H	**83m**	–	**84m**	32

[a] Isolated yield of pure product after recrystallization or flash chromatography
[b] Diastereomeric ratio 1.1:1

reaction complete within 12 h (Table 9) [16]. The corresponding cycloadducts *endo*-**88c** and *exo*-**88c** of 2-methoxyfuran (**87c**), formed in 1.2:1 ratio, turned out to be extremely hydrolysable. They apparently underwent facile hydrolytic cleavage and decomposition on silica gel or alumina to give a complex mixture of products. 2-Methyl-5-(trimethylsilyloxy)furan (**87d**) underwent smooth Diels-Alder reaction with **4** at room temperature to give all the four possible cycloadducts *endo*-**88d**, *exo*-**88d**, *endo*-**89d** and *exo*-**89d** in 8:2:1:0.5 ratio (Table 9), also prone to estensive hydrolytic decomposition on purification by silica gel chromatography.

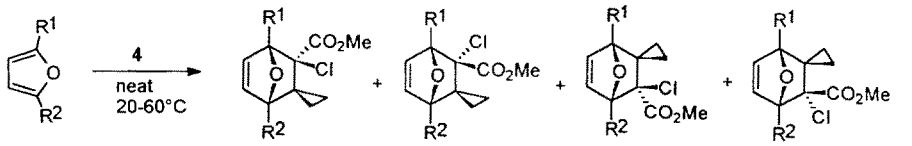
Table 8. Diels-Alder additions of cyclopentadiene (**6**) with 2-cyclopropylideneacetates **4**, **85**, and **52**



6 **4** X = Cl; **85** X = SPh; **52** X = H **86**

Entry	X	Reaction conditions	Product	Product ratio *endo/exo*	Yield (%)
1	**4** Cl	r.t., 5 h	**86a**	2.8	90
2	**85** SPh	r.t., 3 h	**86b**	1.4	81
3	**52** H	r.t., 4 d	**86c**	3.2	84

Table 9. Diels-Alder additions of furans **87a–e** to methyl 2-chloro-2-cyclopropylideneacetate (**4**) [16]



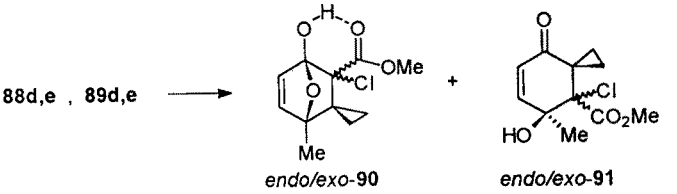
87 *endo*-**88** *exo*-**88** *endo*-**89** *exo*-**89**

Entry	Furan	R^1	R^2	Temp	Time	Yield[a]	Product ratio[b]			
	87			(°C)	(h)	(%)	*endo*-**88**[c]	*exo*-**88**[c]	*endo*-**89**[c]	*exo*-**89**[c]
1	**a**	Me	H	20	100	76	1.5	1	–	–
2	**b**	Me	Me	60	12	72	2	1	–	–
3	**c**	OMe	H	20	32	25 (95)[d]	1.2	1	–	–
4	**d**	$OSiMe_3$	Me	20	140	8.6 (81)[e]	8	2	1	0.5
5	**e**	OMe	Me	20	120	48 (78)[e]	10	3	1	0.3

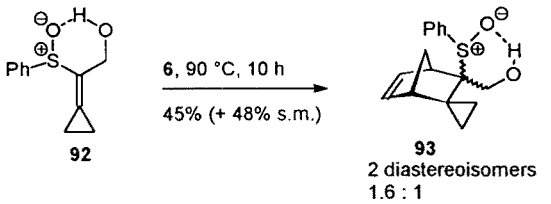
[a] Combined yields of isolated products, based on consumed **4**
[b] Taken from ^{1}H-NMR spectra of crude products
[c] *endo/exo* ratio refers to CO_2Me group
[d] Yield of crude product, purity 95%
[e] Yield of mixture of isomers

Reaction mixtures of isomeric cycloadducts from furans **87d** and **87e** gave, after purification by column chromatography on both silica gel and neutral alumina, mixtures of diastereomeric hydrolysed products **90** and **91** (Scheme 17) [16].

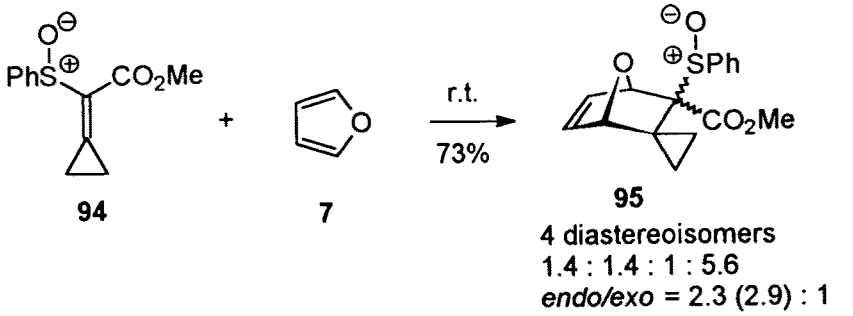
Hydrolysis was avoided by addition of triethylamine (3–5%) to the eluent for chromatography. Compounds *endo/exo*-**88e** and *endo/exo*-**89e** were separated without decomposition in this way. Attempts to enhance the *endo* selectivity by



Scheme 17



Scheme 18



Scheme 19

performing the reaction between **87e** and **4** in the presence of various Lewis acids failed. Experiments carried out with furan (**7**) and **4** under high pressure (8–10 kbar) also did not indicate a significant increase in *endo* selectivity.

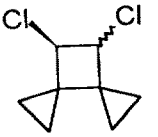
The major isomers *endo*-**88d** and *endo*-**88e** have been transformed to a potential intermediate for the synthesis of the antitumor sesquiterpene Illudin M [16–19].

The hydroxymethyl-substituted phenylsulfoxide **92**, also as the optically active (*R*) enantiomer, added to cyclopentadiene (**6**) at 90 °C to give a mixture of two diastereoisomers **93** in 1.6:1 ratio (Scheme 18) [19].

The 2-phenylsulfinylester **94**, which had been prepared in racemic form, rapidly cycloadded to furan (**7**) at room temperature, albeit with low stereoselectivity [19]. The effect of Lewis acids on the stereoselectivity of the cycloaddition has not been tested (Scheme 19).

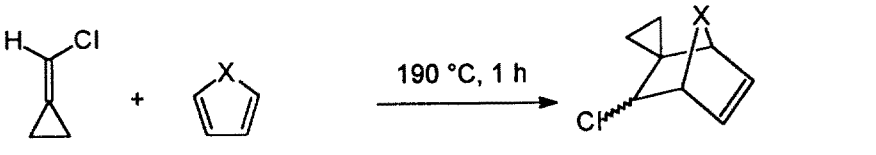
At 190 °C, chloromethylenecyclopropane (**96**) underwent [4 + 2] cycloaddition reactions in the presence of a large excess of cyclopentadiene (**6**), furan (**7**) and 1,3-cyclohexadiene (**26**) to give the *endo* and *exo* **97**, **98** and **99**, respectively (Scheme 20) [27].

Without a large excess of 1,3-diene the formation of *cis* and *trans*-head-to-head dimer **100** competed. The composition of the reaction mixture depends on the reaction time. *Endo/exo* ratio for **97** dropped from 98:2 to 22:78 after 5 h heating at 190 °C. This equilibration probably takes place by a reversal of the [4 + 2] cycloaddition [27].



100

2,3-Dimethylbutadiene (**35**) and chloromethylenecyclopropane (**96**) gave a much more complex mixture of products **102**, **103** and **104** on heating at 190 °C for 1 h, the former two presumably arising from the [4 + 2] cycloaddition product **101** (Scheme 21) [27].

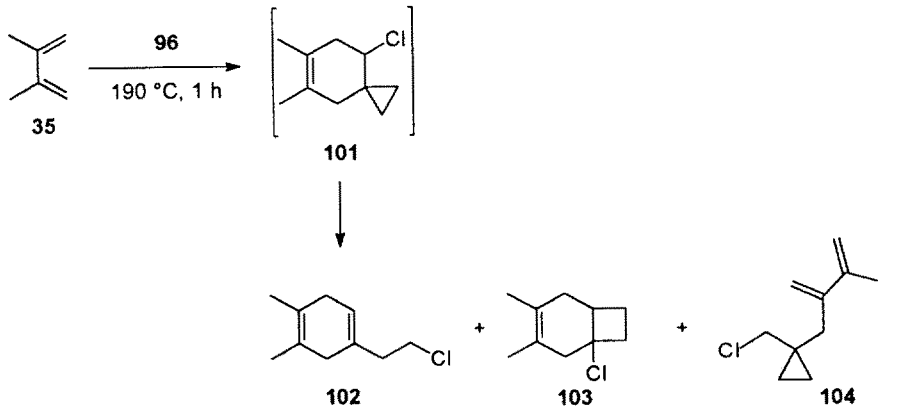


96

6 X = CH_2
7 X = O
26 X = CH_2CH_2

97 X = CH_2
98 X = O
99 X = CH_2CH_2

Scheme 20



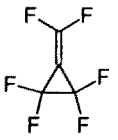
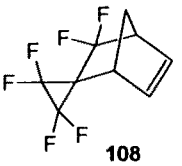
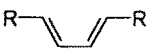
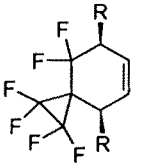
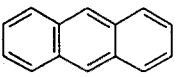
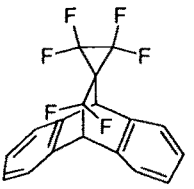
Scheme 21

Compounds **102** and **103** are products of cyclopropylcarbinyl rearrangements under the reaction conditions, and compound **104** is the product of an "ene reaction". Relative reactivities of **96** with furan (**7**), 2,3-dimethylbutadiene (**35**), 1,3-cyclohexadiene (**26**) and cyclopentadiene (**6**) were estimated to be 1:2.5:2.5:50, respectively [27].

Although tetrafluoroethylene and other 1,1-difluoroalkenes readily undergo thermally-induced [2 + 2] dimerization, perfluoromethylenecyclopropane (**105**) does not dimerize on heating at 150 °C for 24 h [28]. On the other hand, it readily undergoes [4 + 2] cycloaddition reactions (Table 10) [29].

Cyclopentadiene (**6**) reacted with **105** at 0 °C to give **108** (entry 1). At 100 °C, butadiene (**12**) afforded **109** (entry 2). No [2 + 2] cycloadduct was formed in either reaction. Perfluoromethylenecyclopropane (**105**) failed to react with *cis,cis*- or *cis,trans*-2,4-hexadiene at 100 °C, although **110** was readily formed from *trans,trans*-2,4-hexadiene (**106**) under these conditions [29] (entry 3). Anthracene (**107**) added to **105** at 100 °C. The dienophilicity of **105** is exceptional when compared with the reactivity of simple fluoroolefins, such as perfluoroisobutylene, which require 150 and 200 °C to undergo cycloaddition to cyclopentadiene [30] and anthracene, respectively.

Table 10. Cycloadditions of perfluoromethylenecyclopropane (**105**) to dienes **6**, **12**, **106**, and **107**

Entry	Perfluoromethylene cyclopropane	Dienes	Reaction temperature	Cycloadducts
1	 **105**	 **6**	0 °C	 **108**
2	**105**	 **12** R = H	100 °C	 **109** R = H
3	**105**	**106** R = Me	100 °C	**110** R = Me
4	**105**	 **107**	100 °C	 **111**

2.1.2 Alkylidenecyclopropanes as Dienes

Although 1,1-disubstituted-1,3-dienes are quite unreactive in the Diels-Alder reaction, allylidenecyclopropanes exhibit a good reactivity especially toward activated dienophiles. The strain present in the alkylidenecyclopropane moiety is responsible for the reactivity enhancement observed in these compounds. The literature concerning the parent diene and few analogs until 1984 has been thoroughly reviewed by Krief [31]. Since then, some other examples of variously-substituted allylidenecyclopropane reacting as dienes in [4 + 2] cycloadditions were published.

Diels-Alder reactions of 2-(trimethylsilyloxy)allylidenecyclopropane (**112**) with electrophilic dienophiles gives 3-silyloxy spiro[2.5]oct-2-enes or the corresponding hydrolysis compounds spiro[2.5]octan-3-ones (Tables 11 and 12) [32].

While doubly activated dienophiles gave moderate to good yields under thermal conditions (Table 11), mono activated alkenes such as cyclohexenone (**123**) failed to react at temperatures up to 150 °C but underwent cycloaddition under Lewis-acid catalysis even if with poor yields (Table 12, entries 1–3) [32].

More substituted and unactivated dienophiles such as 3-acetoxy-2-methylcyclopentenone, did not react with **112** even in the presence of BF_3 etherate. 4-Acetylspiro[2.1.2.3]decen-9-one (**128**) could also be isolated under these con-

Table 11. Cycloadditions of **112** to doubly activated dienophiles

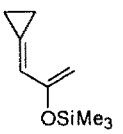
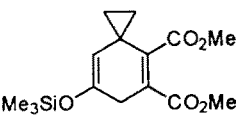
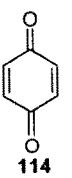
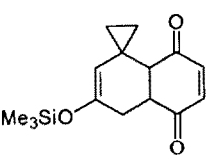
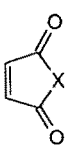
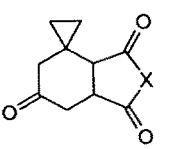
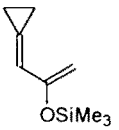
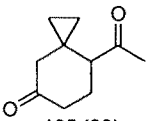
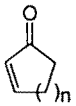
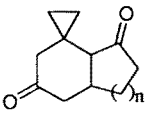
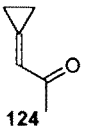
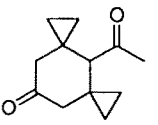
Entry	Allylidene cyclopropanes	Dienophiles	Reaction conditions	Cycloadducts (yield %)
1	 **112**	 **113**	benzene 110 °C 12 h	 **117** (67)
2	**112**	 **114**	CH_2Cl_2 25 °C, 6 h	 **118** (40)
3	**112**	 **115** X = O	C_6H_6, 130 °C, 24 h	 **119** X = O (68)
4	**112**	**116** X = N-Ph	C_6H_6, 120 °C, 22 h	**120** X = N-Ph (30)

Table 12. Cycloaddition of **112** to mono activated dienophiles

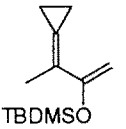
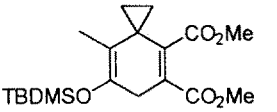
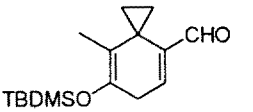
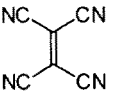
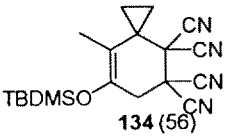
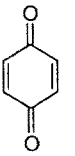
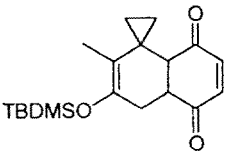
Entry	Allylidene cyclopropanes	Dienophiles	Reaction conditions	Cycloadducts (yield %)
1	 **112**	 **121**	1) CH_2Cl_2 $BF_3{\cdot}Et_2O$, r.t. 2) H_2O	 **125** (30)
2	**112**	 **122** n = 1	1) CH_2Cl_2 $BF_3{\cdot}Et_2O$, r.t. 2) H_2O	 **126** n = 1 (10)
3	**112**	**123** n = 2		**127** n = 2 (30)
4	**112**	 **124**	ether $BF_3{\cdot}Et_2O$	 **128** (56)

ditions (Table 12, entry 4). The product, apparently, results from hydrolysis of **112** to the cyclopropylidene ketone **124** and its further cycloaddition to **112** [32].

The related 1-methyl-2-*t*-butyldimethylsilyloxy allylidenecyclopropane (**129**) reacted with activated dienophiles at ambient temperature or even below (Table 13, entries 2–4) to give moderate to good yields of the corresponding [4 + 2] cycloadducts **133–135**. Only dimethyl acetylenedicarboxylate (**113**) required heating to 110 °C to give good yields of the adduct **132** (Table 13, entry 1) [32]. Adduct **135** from *p*-quinone (entry 4) tends to oxidize by purification on silica gel in the air.

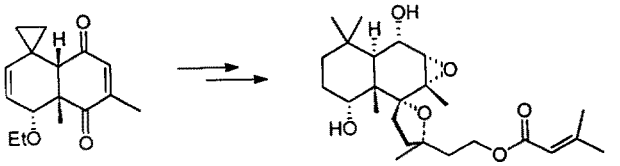
(*E*)-3-(Ethoxy)-allylidenecyclopropane (**136a**) readily underwent Diels-Alder reaction with activated dienophiles under mild conditions (Table 14) [33]. Only one regioisomer was formed with unsymmetrically substituted dienophiles such as methyl maleic anhydride (**137**), and quinones **138–141** (entries 2 and 3–6). All the cycloadducts **143–147** derive from an *endo* approach between the two reagents. Two site-isomers were obtained in 96:4 ratio with 3-isopropyl-6-methyl-*p*-quinone (**141**) (entry 6) and the high site-selectivity observed in this

Table 13. Cycloaddition of **129** to activated dienophiles

Entry	Allylidene cyclopropanes	Dienophiles	Reaction conditions	Cycloadducts (yield %)
1	 **129**	 **113**	benzene 110 °C 12 h	 **132** (70)
2	**129**	 **130**	neat 0° C 30 min	 **133** (45)
3	**129**	 **131**	CH_2Cl_2 25 °C 30 min	 **134** (56)
4	**129**	 **114**	CH_2Cl_2 25 °C 6 h	 **135** (39)

case is probably due to the different steric hindrance of the isopropyl group compared to the methyl on the *p*-quinone in the *endo* transition state [33]. The cycloaddition of acetoxy derivative **136b** with **139** also occurred regiospecifically and gave only the *endo* cycloadduct **148** (entry 7) [34].

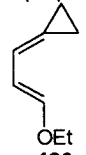
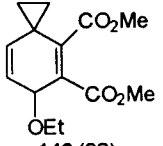
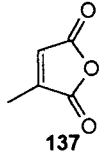
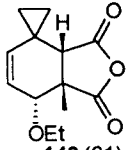
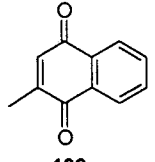
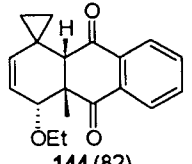
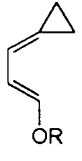
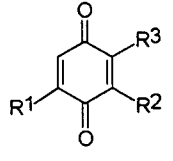
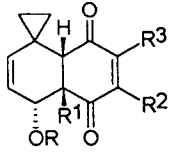
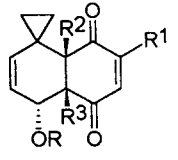
The bicyclic adduct **145** was prepared on a large scale (100 g) and used as key intermediate in the total synthesis of the racemic diterpene Erigerol (Scheme 22) [35].



145 (±)Erigerol

Scheme 22

Table 14. Diels-Alder cycloadditions of **136a, b** to activated dienophiles

Entry	Allylidene cyclopropanes	Dienophiles	Reaction conditions	Cycloadducts (yield %)
1	 **136a**	 **113**	DME 24 h, 50 °C	 **142** (32)
2	**136a**	 **137**	DME 24 h, 50 °C	 **143** (61)
3	**136a**	 **138**	DME 24 h, 50 °C	 **144** (82)
			**a.** DME, 24 h, 50 °C or **b.** benzene, 24 h, 150 °C hydroquinone (traces)	 + 
4	**136a** R = Et	**139** $R^1 = R^2 = Me$, $R^3 = H$	**a**	**145** (92)
5	**136a** R = Et	**140** $R^1 = R^2 = R^3 = Me$	**a**	**146** (84)
6	**136a** R = Et	**141** $R^1 = Me$, $R^2 = H$, $R^3 = i$Pr	**a**	**147a** (80)
7	**136b** R = Ac	**139** $R^1 = R^2 = Me$, $R^3 = H$	**b**	**148** (38)

4	**136a** R = Et	**139** $R^1 = R^2 = Me$, $R^3 = H$	**a**	**145** (92)	(-)
5	**136a** R = Et	**140** $R^1 = R^2 = R^3 = Me$	**a**	**146** (84)	(-)
6	**136a** R = Et	**141** $R^1 = Me$, $R^2 = H$, $R^3 = i$Pr	**a**	**147a** (80)	**147b** (3)
7	**136b** R = Ac	**139** $R^1 = R^2 = Me$, $R^3 = H$	**b**	**148** (38)	(-)

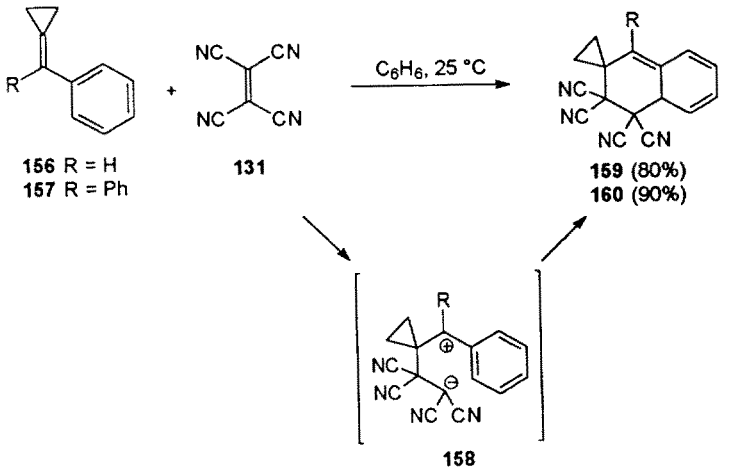
2,3-Tetramethyleneisobutenylidenecyclopropane (**149**) reacted with maleic anhydride (**115**) and *N*-phenylmaleimide (**116**) to give predominantly the ene product **153** which undergoes further [4 + 2] cycloaddition to **154** with dienophile (Table 15, entries 1 and 2) [35]. To a minor extent, **149** also underwent a [1,3]-sigmatropic rearrangement to **151**, followed by cycloaddition, to produce **152**, along with [2 + 2] cycloaddition products **155** across the exocyclic double bond. The 1:2 adducts **154** and 1:1 adducts **155** were produced as a couple of stereoisomers. 2-Ethoxyisobutenylidenecyclopropane (**150**) underwent only the ene reaction followed by cycloaddition of the intermediate diene **153** (R^1 = H, R^2 = OEt, X = NPh) with **116** to give two stereoisomers of general structure **154** (R^1 = H, R^2 = OEt, X = NPh) in 1:1 ratio (Table 15, entry 3). Compound **150** showed to be less reactive toward **116** than **149**, as, under the same conditions under which the reaction of **149** went to completion, the consumption of **116** was only partial (Table 15) [36].

While 2-arylsubstituted methylenecyclopropanes reacted with tetracyanoethylene (**131**, TCNE) to give [3 + 2] adducts, i.e. methylenecyclopentanes [37], via cleavage of the cyclopropyl C–C bond, benzylidenecyclopropanes **156** and **157** behaved as dienes toward TCNE (Scheme 23).

Benzylidenecyclopropane (**156**) and diphenylmethylenecyclopropane (**157**) reacted rapidly with TCNE to afford **159** and **160**, respectively, in good yields. Since the reaction rate is highly dependent on the solvent polarity, the cycloadditions of **156** and **157** with TCNE were rationalized as stepwise reactions involving the dipolar ions **158** (Scheme 23) [37].

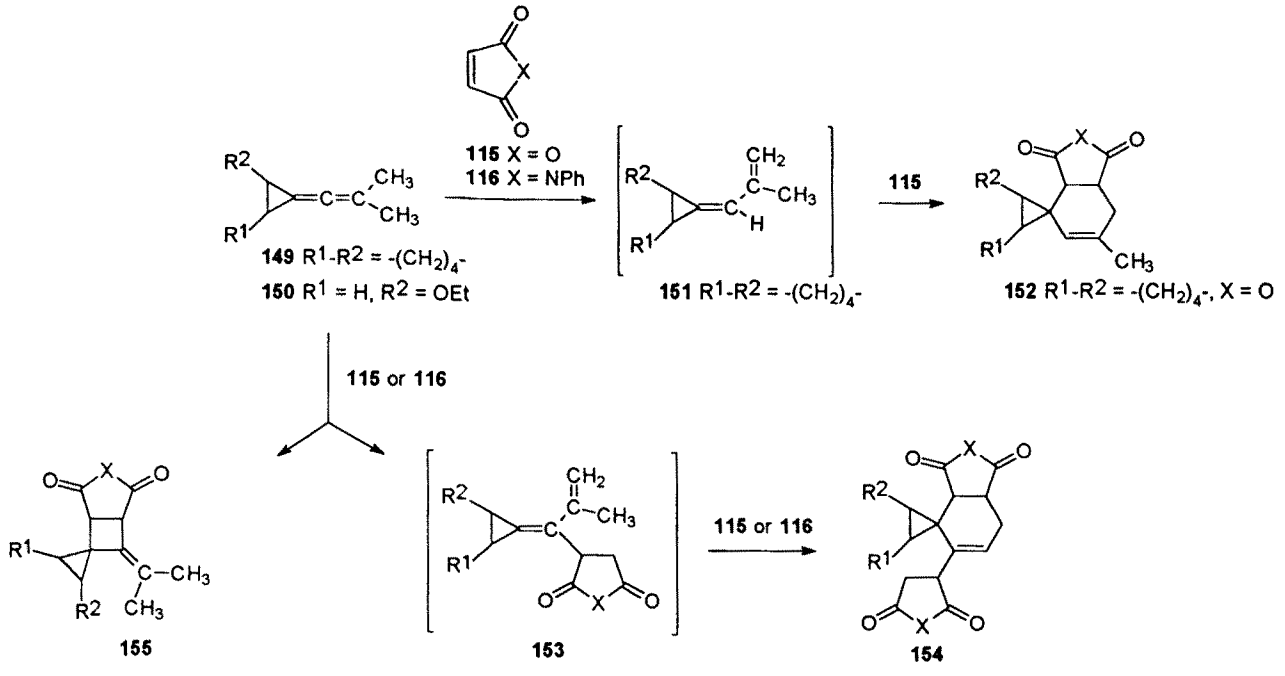
The formation of **160** as an undetectable intermediate in the reaction of **157** and TCNE in toluene at 120 °C had been previously hypothesized [38].

Dicyclopropylideneethane (**2**) is a reactive diene in Diels-Alder reactions, despite the steric congestion at its bonding centers. Relief of the strain appears to contribute to the enhanced reactivity of **2** which underwent cycloaddition with



Scheme 23

Table 15. Reactions of **149** and **150** with maleic anhydride (**115**) and *N*-phenylmaleimide (**116**)



Entry	R^1	R^2	X	React. conds.	154	155	152
1	$-(CH_2)_4-$		O	toluene 160 °C, 48 h	two stereoisomers in ~1:2 ratio (~ 70%)	two isomers in ~1:4 ratio (~ 15%)	(~5–10%)
2	$-(CH_2)_4-$		NPh	toluene, 160 °C, 30 h	two stereoisomers[a]	two isomers	(in traces)
3	H	OEt	NPh	toluene, 160 °C, 48 h[b]	two stereoisomers in 1:4 ratio	–	–

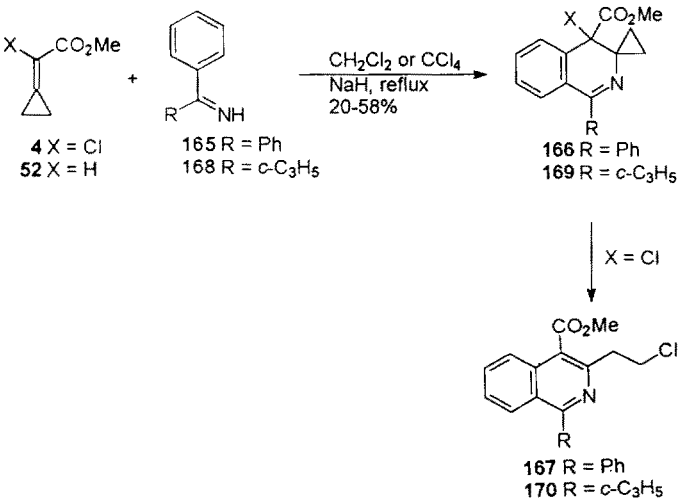
[a] The 1:2 adducts represent an estimated 90% of the total products
[b] Analysis by NMR indicated consumption of ~40% of **116**

dimethyl acetylenedicarboxylate (**113**) and *N*-phenylmaleimide (**116**) in benzene at reflux to give the dispiro[2.2.2.2]decadiene and decene derivatives **161** and **162**, respectively (Table 16, entries 1–3). The addition of TCNE (**131**) to **2** proceeded smoothly at room temperature in dichloromethane to afford the [4 + 2] cycloadduct **163** in 43% yield together with a 25% yield of the [2 + 2] adduct **164** [39]. It has been shown that some [2 + 2] adducts of TCNE to 1,3-butadienes quite readily rearrange to the corresponding cyclohexene derivatives [40]. Compound **164**, however, showed no tendency to isomerize to **163** under the reaction conditions. Therefore, the observed product distribution is a kinetically controlled result. The formation of the [2 + 2] adduct **164** is in contrast to the results of Paquette et al., who carried out the reaction in carbon tetrachloride and isolated **163** in 27% yield, but none of the tetracyanocyclobutane derivative **164** [5]. Cycloaddition of TCNE (**131**) to unsaturated compounds is generally accepted as a two-step process with formation of a zwitterion [40, 41], hence accelerated in polar solvents. The observed difference in the product compositions may be accounted for, at least partly, by the solvent polarity effect.

2.2 Hetero Diels-Alder

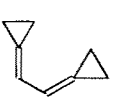
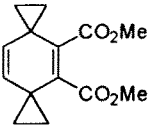
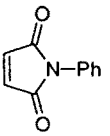
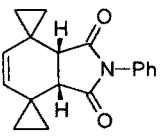
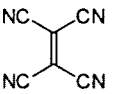
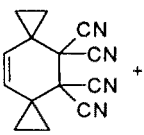
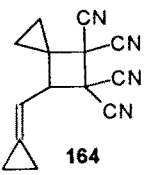
2.2.1 Alkylidenecyclopropanes as Dienophiles

(Diphenylmethylene)amine (**165**) reacted with 2-chlorocyclopropylideneacetate (**4**) in aprotic, dry solvents, to give the isoquinoline **167** (R = Ph) in one shot (up to 53%) [17]. The analogous reaction between **165** and **52** led to the spiroadduct **166** (R = Ph, X = H). Cyclopropylphenylketimine **168** gave with **4** the isoquinoline **170** (R = *c*-C_3H_5) (Scheme 24).



Scheme 24

Table 16. Cycloadditions of **2** to activated dienophiles

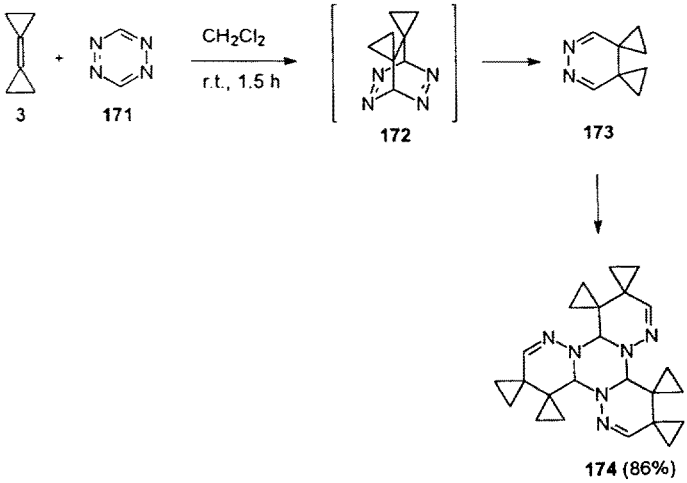
Entry	Allylidene cyclopropanes	Dienophiles	Reaction conditions	Cycloadducts (yield %)
	 **2**	 **113**		 **161**
1			C_6H_6, 80 °C, 2 h	(35)
2			C_6H_6, 80 °C, 12 h	(12)
3	**2**	 **116**	C_6H_6, 80 °C, 12 h	 **162** (74)
	2	 **131**		 **163** +  **164**
4			CH_2Cl_2, r.t., 4 d	(43) (25)
5			CCl_4, r.t., 2 d	(27) (-)

1,2,4,5-Tetrazine (**171**) and its derivatives are electron-deficient cycloaddends, which undergo [4 + 2] cycloadditions with inverse electron demand. When bicyclopropylidene (**3**) was added to a dichloromethane solution of **171**, its red color disappeared within 1.5 h at room temperature. The white crystalline product isolated in 86% yield turned out to be a mixture of at least two stereoisomeric compounds **174**, trimers of the 8,9-diazadispiro[2.0.2.4]deca-7,9-diene (**173**) evidently formed via the normal [4 + 2]-cycloadduct **172** after nitrogen extrusion (Scheme 25) [13b].

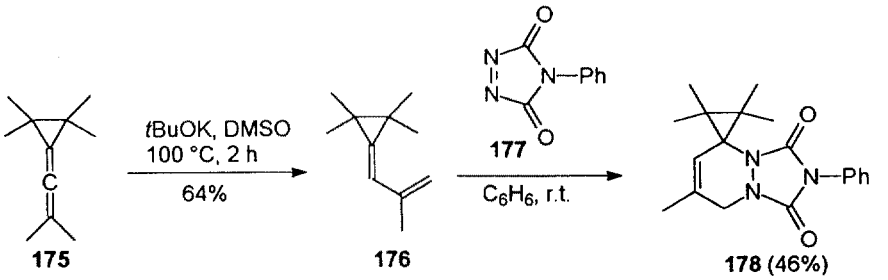
Apparently, **3** undergoes [4 + 2] cycloadditions with inverse electron demand more readily than normal Diels-Alder reactions (see Sect. 2.1.1). This is in accord with the high lying HOMO of bicyclopropylidene [12]. Several attempts to trap the monomeric **173**, which should be in equilibrium with **174** [42], as a cycloadduct with a second molecule of **3** were unsuccessful even at elevated temperatures in chloroform (70 °C) or toluene-d_8 (150 °C) [13b].

2.2.2 Alkylidenecyclopropanes as Dienes

Two examples of [4 + 2] cycloadditions of allylidene cyclopropanes with heteroenes have been previously reported in Krief's review [31]. Only a few other examples have been studied more recently.



Scheme 25



Scheme 26

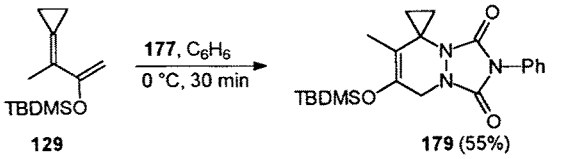
2-Methyl-3-(tetramethylcyclopropylidene)propene (**176**), obtained by isomerization of allene **175** with potassium *tert*-butoxide, added to 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD, **177**) at room temperature to give the Diels-Alder adduct **178** in 46% yield (Scheme 26) [43].

The 2-(trimethylsilyloxy)allylidenecyclopropane **129** underwent a facile cycloaddition to the same dione **177** to form the cycloadduct **179** in 55% yield [32] (Scheme 27).

Benzylidenecyclopropane (**156**) reacted rapidly with **177** to form the 2:1 adduct **181** (Scheme 28), the formation of which was explained as occurring via the primary adduct **180** [44].

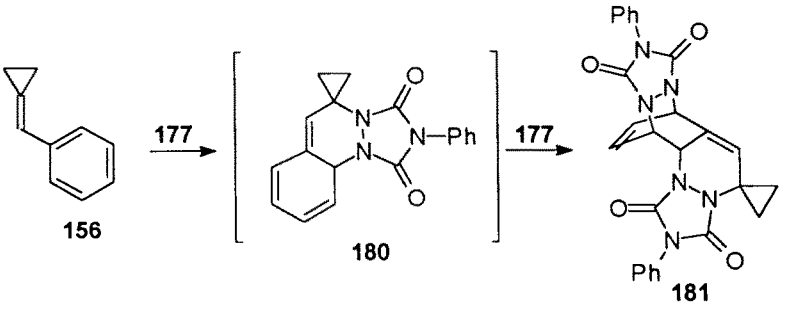
The reaction of dicyclopropylideneethane (**2**) with PTAD (**177**) was instantaneous at room temperature in benzene and the adduct **182** was obtained in 90% yield (Scheme 29) [39].

When *N*-methyltriazolinedione **183** was added to **2** in chloroform at − 60 °C, a rapid reaction occurred as judged by the immediate disappearance of the pink color of the dienophile. Surprisingly, however, the yield of isolated



129 **179** (55%)

Scheme 27



156 **180** **181**

Scheme 28

2 **177** R = Ph C_6H_6, r.t. **182** (90)
183 R = Me $CHCl_3$, -60 °C then r.t. **184** (17)

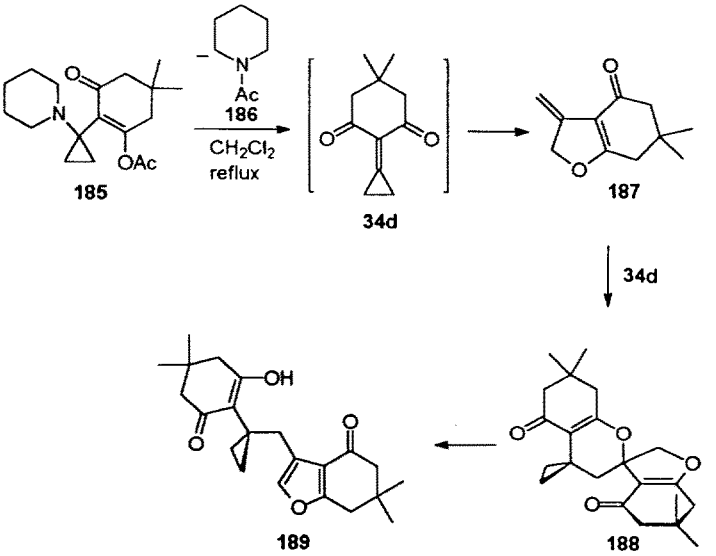
Scheme 29

urazole **184** was quite low (17%) after chromatography on neutral alumina. No other recognizable substance could be isolated (Scheme 29) [5].

The [4 + 2] cycloaddition of enones and electron-rich olefins is a well-known method for the synthesis of pyrane derivatives [45]. Methylenecycloalkanediones [46] have also been used extensively for this purpose.

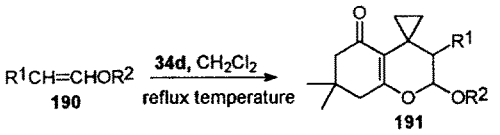
The highly reactive cyclopropylidenedimedone (**34d**), generated in situ from acetylated (piperidinocyclopropyl)dimedone **185** was trapped by [4 + 2] cycloaddition with electron-rich alkenes. Without a trapping reagent **34d** rearranged to methylenefuran **187**, which is able to trap a second molecule of **34d** by a [4 + 2] cycloaddition leading to **188**. A β-elimination generating an aromatic furan ring eventually gives **189** by simple heating in dichloromethane (Scheme 30). The pure spiro compound **188** could be isolated in 44% yield; upon further heating, **188** isomerized quantitatively to the furan **189** [47].

When **34d** was generated in the presence of enol ethers **190**, [4 + 2] cycloadducts **191a–c** were isolated [47] (Table 17). The cycloadducts **191b** and **191c** proved to be pure stereoisomers, with the two heterocyclic ring systems *cis* connected.



Scheme 30

Table 17. Cycloadditions of cyclopropylidenedimedone **34d** to enolethers **190a–c**

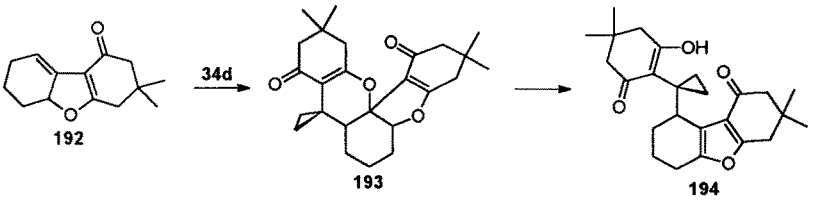


Entry	Enolether	R^1	R^2	Time (h)	Product	Yield (%)
1	**190a**	Me	Et	3	**191a**	64
2	**190b**	$-(CH_2)_2-$		5	**191b**	48
3	**190c**	$-(CH_2)_3-$		5	**191c**	38

Reacting with the methylene dihydrofuran derivative **192** as trapping reagent, **34d** gave rise to a mixture of [4 + 2] cycloadduct **193** and furan **194**, which could be separated and obtained in 25% and 37% yields, respectively. Upon further heating, **193**, whose configuration has not been determined, isomerized completely to the more stable **194** (Scheme 31) [47].

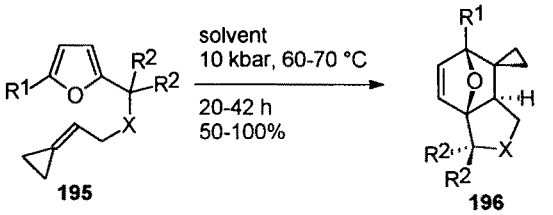
2.3 Intramolecular Cycloadditions

The furfuryl derivatives **195**, with an allyl ether (X = O) or allylamine (X = NMe) type chain linked to a methylenecyclopropane moiety, readily



Scheme 31

Table 18. Intramolecular Diels-Alder reactions under high pressure of furfuryl-substituted alkylidenecyclopropanes **195**

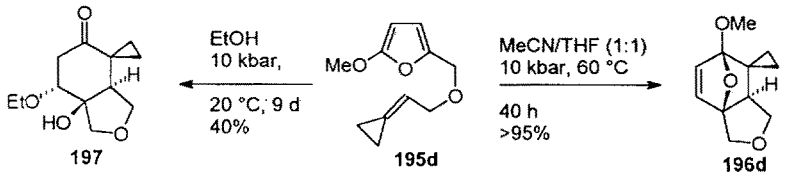


Entry	Starting material	X	R^1	R^2	Product	Yield (%)
1	**195a**	O	H	H	**196a**	> 95
2	**195b**	O	H	Me	**196b**	> 95
3	**195c**	O	Me	H	**196c**	74
4	**195d**	O	OMe	H	**196d**	> 95
5	**195e**	NMe	H	H	**196e**	50
6	**195f**	NMe	H	=O	**196f**	55

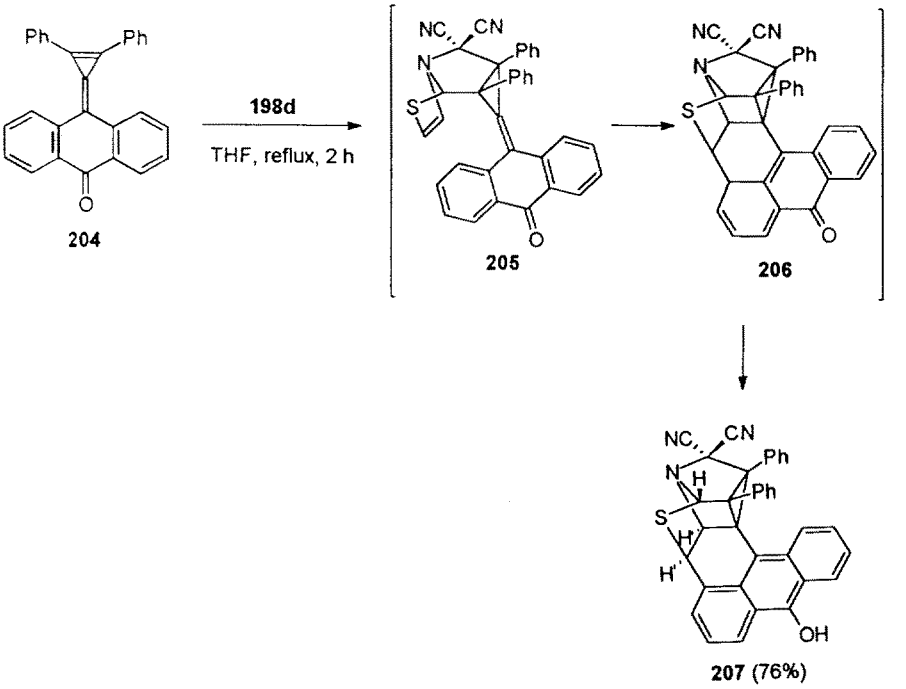
undergo intramolecular Diels-Alder reactions at 10–12 kbar to yield spirocyclopropane-annulated tricyclic structures **196** with excellent yields and diastereoselectivity (Table 18) [48].

At ambient pressure, **195a** did not undergo intramolecular [4 + 2] cycloaddition even at temperatures up to 150 °C. The use of Lewis acids to promote the Diels-Alder reactions was of marginal success only. In contrast, on exposing the furan derivatives **195** to high pressure (10 kbar) in 0.1–0.5 mol l^{-1} solutions at 60–70 °C, a clean cycloaddition took place (Table 18).

While most reactions proceeded cleanly in the solvent mixture acetonitrile/tetrahydrofuran (1:1), allyl ether **195a** showed the cleanest reaction in ethanol, containing 4% of water, with the highest yield up to 100%. The allylamide **195f** in acetonitrile/tetrahydrofuran tended to react more slowly, but still cleanly, in contrast to the allylamine **195e**, which gave a lower 50% yield of **196e**. The transformation of allylamine **195e** was also attempted in ethanol or in dichloromethane, but always gave rise to complex mixtures of products of high polarity. In an attempt to cyclize the 5-methoxyfuran derivative **195d** in ethanol under 10 kbar pressure at room temperature, the bicyclic ketone **197** was



Scheme 32



Scheme 33

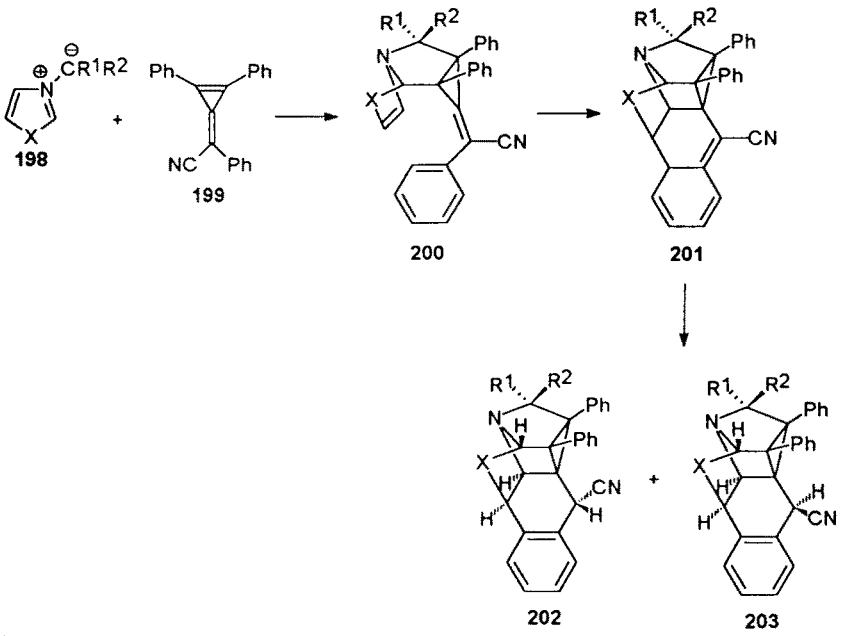
isolated instead of the expected tricyclic system **196d**. However, in acetonitrile/tetrahydrofuran at 60 °C, **196d** was obtained in virtually quantitative yield (Scheme 32) [48].

Activation parameters for the intramolecular cycloaddition of **195a** have been determined by means of on-line infrared spectroscopy under high pressure [48].

Pentacylic cage compounds **202** were synthesized through a double cycloaddition reaction to methylenecyclopropene **199**, which involves an intermolecular 1,3-dipolar cycloaddition of **198** on the *endo* double bond to give **200** followed by an intramolecular Diels-Alder reaction between a benzylidenecyclopropane moiety and an ene function (Table 19) [49].

The reaction of the imidazolium methylides **198a, b** with **199** proceeded stereo- and regioselectively forming the *endo* [3 + 2] cycloadducts **200** which

Table 19. Reactions of imidazolium, thiazolium and pyridinium *N*-methylides **198** with benzylidenecyclopropene **199** [49]



Entry	Ylide 198	X	R^1	R^2	Reaction conditions			Products (Yield%)	
					Solvent	Temp.	Time	202	203
1	**a**	NMe	CN	CN	EtOH	Reflux	24 h	**a** (36)	(–)
2	**b**	NMe	CO_2Et	CO_2Et	THF	Reflux	3 h	**b** (90)	(–)
3	**c**	S	H	COPh	THF	Reflux	3 h	**c** (51)	**c** (31)
4	**d**	S	CN	CN	THF	r.t.	4 d	**d** (51)	**d** (36)
5	**e**	CH=CH	CN	CN	Xylene	Reflux	67 h	**e** (80)	(–)
6	**f**	CH=CH	CO_2Et	CO_2Et	C_6H_6	Reflux	69 h	**f** (89)	(–)
7	**g**	CH=CH	H	CO_2Me	C_6H_6	Reflux	48 h	**g** (40)	(–)
8	**h**	CH=CH	H	CO_2Et	C_6H_6	Reflux	42 h	**h** (57)	(–)
9	**i**	CH=CH	H	COPh	C_6H_6	Reflux	24 h	**i** (67)	(–)

then cycloadded to give the primary adducts **201**. Aromatization to the benzene ring afforded the cage compounds **202a, b** (entries 1–2).

When the reaction of thiazolium *N*-phenacylide **198c** with **199** was carried out at room temperature, the *endo*-[3 + 2] adduct **200c** could be isolated in 79% yield. Upon heating in THF under reflux for 3 h, **200c** was transformed into two stereoisomeric cage compounds **202c** and **203c** (entry 3). On the other hand, the *N*-dicyanomethylide **198d** in THF at room temperature gave directly the two isomeric cage compounds **202d** and **203d** (entry 4) [49b].

Pyridinium *N*-methylides **198e–i** also gave the corresponding cage compounds **202e–i** as the sole product when refluxed in the appropriate solvent (entries 5–9) [49c].

The reaction of the thiazolium *N*-methylide **198d** with the methylenecyclopropene **204** in refluxing THF for 2 h gave a 76% yield of the cage compound **207** (Scheme 33) [49b].

Imidazolium, thiazolium and pyridinium ylides **198** also react with the acylmethylenecyclopropenes **208–210** to give the analogous heterocyclic cage compounds **212** (Table 20).

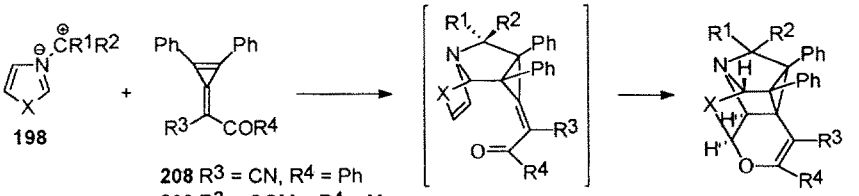
The imidazolium methylides **198a, b** required reflux in EtOH or THF to give the compounds **212a, b** (entries 1–2) [49a], whereas for thiazolium **198d** and pyridinium *N*-methylides **198f, g** room temperature was sufficient to give the corresponding cage compounds **212d–f** and **212h, i** in quantitative or good yield, respectively (entries 4–6, 8–9) [50, 49c].

3 Five-Membered Ring

3.1 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloadditions are the most general method for the synthesis of five-membered heterocycles [51]. Various easily available and efficient 1,3-dipolar reagents are able to react with double or triple bonds to afford many different classes of structurally differentiated, selectively substituted heterocycles

Table 20. Reactions of imidazolium, thiazolium and pyridinium *N*-methylides **198** with methylenecyclopropenes **208, 209** and **210** [49a, 50, 49c]



Entry	Ylide	X	R^1	R^2	Reagent	R^3	R^4	Reaction conditions			Products **212** (Yield%)
								Solvent	Temp.	Time	
1	**198a**	NMe	CN	CN	**208**	CN	Ph	EtOH	Reflux	29 h	**a** (76)
2	**198b**	NMe	CO_2Et	CO_2Et	**208**	CN	Ph	THF	Reflux	2 h	**b** (99)
3	**198c**	S	H	COPh	**209**	COMe	Me	THF	Reflux	2 h	**c** (93)
4	**198d**	S	CN	CN	**209**	COMe	Me	THF	r.t.	4 d	**d** (94)
5	**198d**	S	CN	CN	**208**	CN	Ph	THF	r.t.	6 d	**e** (100)
6	**198d**	S	CN	CN	**210**	CN	OEt	THF	r.t.	6 d	**f** (96)
7	**198e**	CH=CH	CN	CN	**208**	CN	Ph	Xylene	Reflux	3 d	**g** (16)
8	**198f**	CH=CH	CO_2Et	CO_2Et	**208**	CN	Ph	C_6H_6	r.t.	6 d	**h** (60)
9	**198g**	CH=CH	H	CO_2Me	**208**	CN	Ph	C_6H_6	r.t.	2 d	**i** (49)

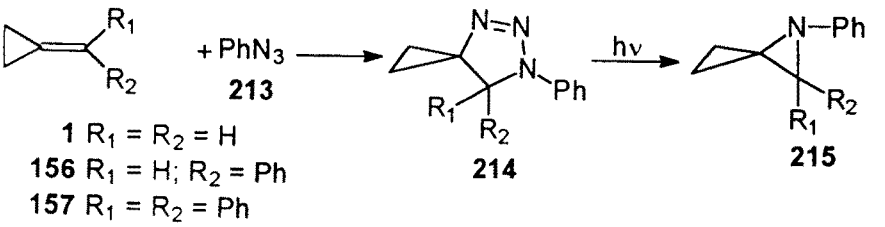
containing one, two, or three heteroatoms. The extension of this methodology to methylene- or alkylidenecyclopropane dipolarophiles gives a unique entry to spirocyclopropane-anellated heterocycles. Such compounds are, by themselves, capable of considerable biological activity [52], or, combining the heteroatom functionality and the strained cyclopropane ring, are the candidates for synthetically useful selective transformations [8]. Examples of 1,3-dipolar cycloadditions to alkylidenecyclopropanes are limited to dipoles like azides, diazoalkanes, nitrones, ozone, nitrile oxides, and nitrile ylides, and will be as such systematically reviewed.

3.1.1 Azides

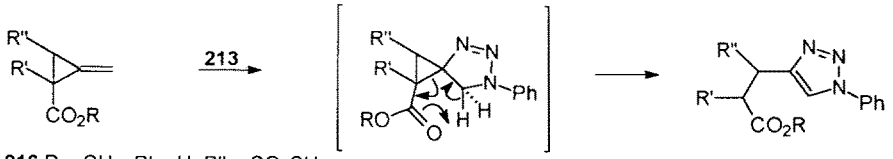
The reaction of methylenecyclopropane with azides is the earliest 1,3-dipolar cycloaddition reported so far on this system [53, 54].

In a study aimed at the synthesis of the *N*-substituted azaspiropentane ring system **215**, MCP (**1**) was allowed to react at 25 °C with phenylazide (**213**) to give a single regioisomeric triazoline **214** in 68% yield (Scheme 34). The cycloaddition was highly regioselective, but little effort was spent by the authors in ascertaining the structure, because of no practical consequence to the final reaction product. The structure assignment was based by the authors upon the general observation that the substituent-bearing nitrogen of phenyl azide ordinarily bonds to the olefinic carbon best able to bear positive charge [55, 56]. Further irradiation of methylene chloride solutions of **214** at 0 °C with a mercury lamp gives 1-phenyl-azaspiro[2.2]pentanes **215** (Scheme 34).

A different result was obtained in the cycloaddition to methylenecyclopropanes **216–218** bearing alkoxycarbonyl substituents on the cyclopropyl ring. In this instance, 1,2,3-triazoles **220** isomeric with the triazolines **219** were formed in the reaction [57]. The formation of triazoles **220** is rationalised by the intermediate formation of triazolines **219**, which are unstable under the reaction conditions and undergo a rearrangement to the aromatic triazoles via a hydrogen transfer that probably occurs with the assistance of the proximal ester carbonyl (Scheme 35). The formation of triazoles **220** also confirms the regiochemistry of the cycloaddition for the methylene unsubstituted methylenecyclopropanes, still leaving some doubt for the substituted ones **156** and **157**.

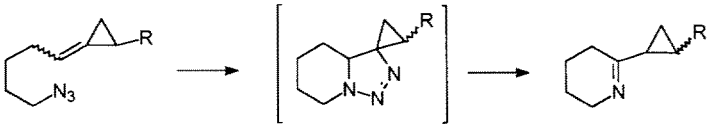


Scheme 34



216 R = CH_3; R' = H; R'' = CO_2CH_3
217 R = CH_2CH_3; R' = R'' = H
218 R = CH_2CH_3; R' = CH_3; R'' = H

Scheme 35



221 R = H
222 R = CH_3

224 R = H (66%)
225 R = CH_3 (60%)

Scheme 36

An intramolecular version of an azide cycloaddition of **221** and **222** provided cyclopropylimines **224** and **225** via formation of triazoline **223** followed by extrusion of nitrogen with concomitant 1,2-hydrogen shift (Scheme 36) [58]. The cyclization was found to be solvent dependent: polar solvents such as DMF gave the best yields, whereas benzene gave several side products.

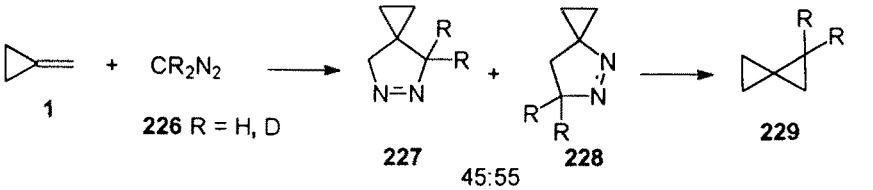
3.1.2 Diazoalkanes

In a study aimed at elucidating the mechanism of the thermal decomposition of spiropentane **229**, the two regioisomeric pyrazolines **227** and **228** were obtained in high yield by allowing a solution of MCP (**1**) and diazomethane (**226**) (or diazomethane-d_2) in diethylether to stand at 3 °C for three weeks (Scheme 37) [59].

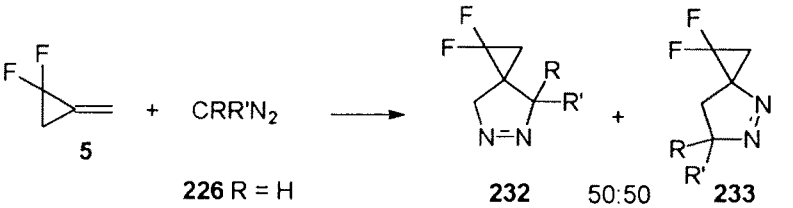
The regioisomer **228** deriving from the attack of diazomethane carbon on the CH_2 end of MCP's double bond is slightly preferred in the cycloaddition. That the regiochemical outcome is a result of steric factors is apparent from the reaction of diazoalkanes **226**, **230**, and **231** with 2,2-difluoromethylenecyclopropane (**5**) (Scheme 38). Diazomethane (**226**) gives a 1:1 mixture of the two regioisomers **232** and **233**, whereas diphenyl diazomethane (**231**) gives exclusively compound **237** [60].

The approach of the two reagents at the transition state seems to be influenced by the substituents on diazoalkane in the more hindered transition state **B** (Fig. 1).

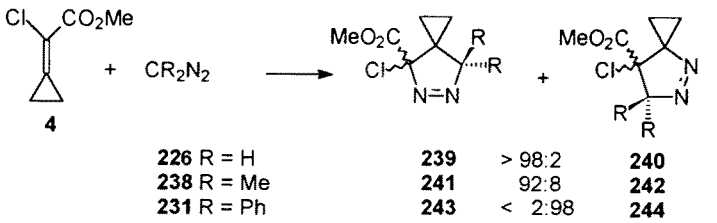
Despite a similar reversal of regioselectivity is also observed in the cycloadditions of diazoalkanes **226**, **238**, and **231** to methoxycarbonyl methylenecyclopropane **4** (Scheme 39), the result cannot be ascribed only to steric effects in this case [61]. A difference in dipolar character of dipoles **226** and **231** is also able to justify the result.



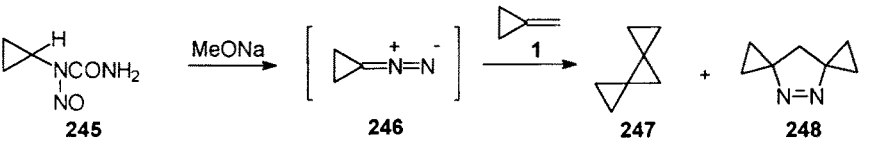
Scheme 37



Scheme 38



Scheme 39



Scheme 40

Fig. 1. TS trajectories for the regioisomeric approaches of MCP and diazoalkanes

Recently, diazocyclopropane (**246**) was synthesized from cyclopropyl *N*-nitroso urea (**245**) and its reaction with **1** has been studied. The cycloaddition gave a mixture of the unique primary adduct **248** together with the [3]-triangulane (**247**) derived from N_2 extrusion (Scheme 40) [62].

3.1.3 Nitrones

The cycloadditions of nitrones to alkylidenecyclopropanes are, by far, the most studied reactions of this class. The first example reported in the literature refers to the cycloaddition of *N*-(phenylaminooxoethylidene)aniline *N*-oxide (**249**) to 2,2-dimethylmethylenecyclopropane (**250**). The authors report about the formation of a single 5-spirocyclopropane fused regioisomer **251** (Scheme 41) [63].

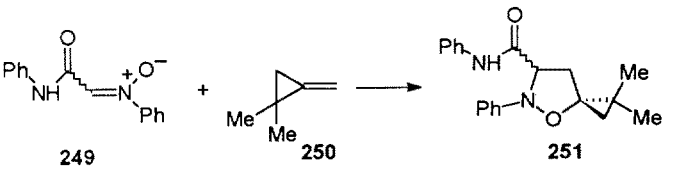
The impulse to the study of these cycloadditions came from the discovery that 5-spirocyclopropane isoxazolidines (or isoxazolines) undergo a thermal rearrangement resulting in the production of selectively substituted tetrahydro- (or dihydro) pyrid-4-ones (Scheme 42) [64]. In particular, cyclic nitrones gave ultimately *N*-bridgehead bicyclic ketones, molecular skeleton of many alkaloid families [65].

The cycloaddition of nitrones to the parent MCP (**1**) was found to give generally mixtures of the regioisomeric 5-spirocyclopropane **254a** and 4-spirocyclopropane **254b** isoxazolidines in ratios ranging from 2:1 up to >20:1 (Table 21). Only the six-membered ring nitrone **257** gave a good 9:1 regioisomeric ratio (entry 3).

The major adduct from *C*,*N*-diphenyl nitrone (**265**) and **1** could not be isolated, as the 5-spirocyclopropaneisoxazolidine **266** underwent rearrangement under the reaction conditions, also affording the uncommon rearrangement product benzazocine **269** (Scheme 43) [66].

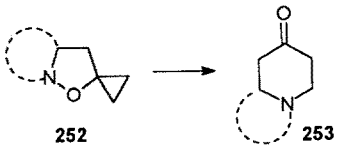
The unexpected regiochemical outcome of the cycloaddition gave rise to a complete study of the factors influencing the regioselectivity, inasmuch as 4-spirocyclopropane isoxazolidines are unable to undergo the useful thermal rearrangement.

The influence of substituents on regioselectivity was studied by using a model nitrone 3,4-dihydro-2,2-dimethyl-2*H*-pyrrole 1-oxide (DMPO, **256**) with different alkylidenecyclopropanes substituted with phenyl (**156**), electron-releasing (**270** and **271**) and electron-withdrawing groups (**52**, **272** and **4**) [67,



249 250 251

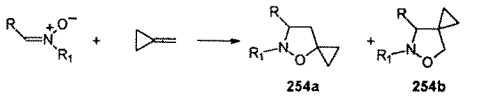
Scheme 41

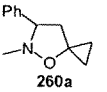
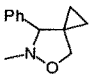
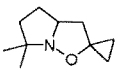
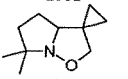
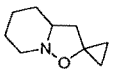
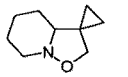
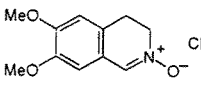
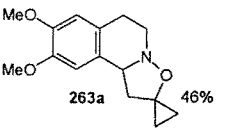
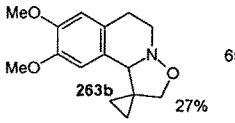
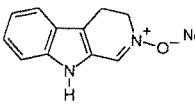
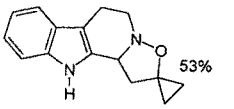
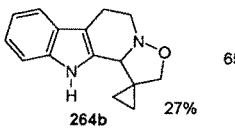


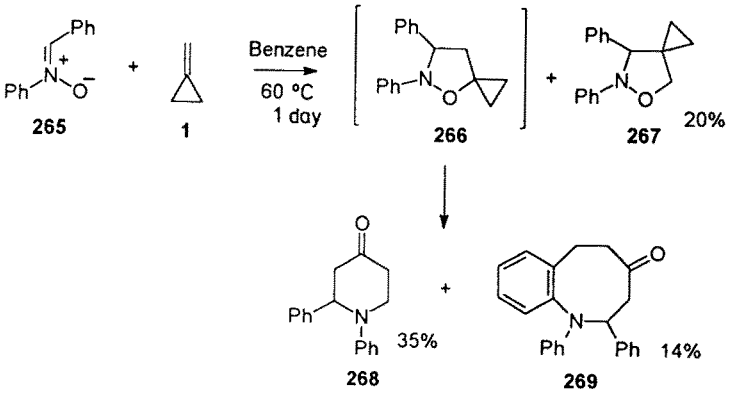
252 253

Scheme 42

Table 21. Cycloadditions of nitrones to MCP **1**



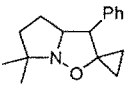
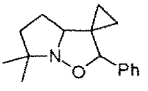
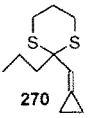
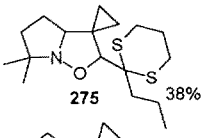
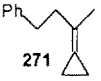
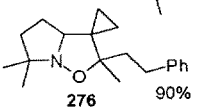
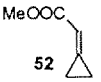
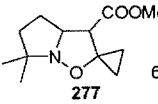
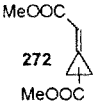
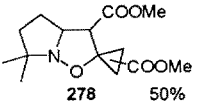
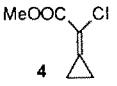
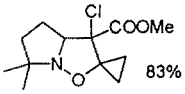
Entry	Nitrone	Reaction conditions	5-Spirocyclopropane isoxazolidine		4-Spirocyclopropane isoxazolidine	Ref.
1	 **255**	Neat, 60 °C, 5 days	 **260a**	83% 70:30	 **260b**	65a
2	 **256**	Neat, 60 °C, 2 days	 **261a**	86% 65:35	 **261b**	65a
3	 **257**	Neat, 60 °C, 2 days	 **262a**	69% 90:10	 **262b**	65a
5	 **258**	CH_2Cl_2, 45 °C, 3 days	 **263a** 46%		 **263b** 27%	65b
6	 **259**	Neat, 70 °C, 2 days	 **264a** 53%		 **264b** 27%	65b



Scheme 43

68]. Aryl or alkyl substituents on the exocyclic double bond steer the regioselectivity towards the formation of isoxazolidine-4-spirocyclopropanes **274–276** (Table 22, entries 1–3). A complete reversal of regioselectivity to **277–279** was observed in the reactions of methoxycarbonyl substituted methylenecyclo-

Table 22. Regioselectivity of the cycloadditions of nitrone **256** to alkylidenecyclopropanes substituted with phenyl, electron-releasing and electron-withdrawing groups [67, 68]

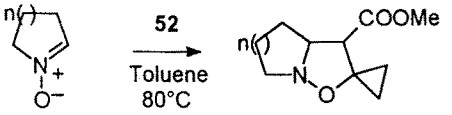
Entry	Reaction conditions	Methylene-cyclopropane	5-Spirocyclopropane isoxazolidine		4-Spirocyclopropane isoxazolidine
1	Benzene, 80 °C 15 h	 **156**	 **273**	61% 1:19	 **274**
2	Toluene, 110 °C 45 h	 **270**	-		 **275** 38%
3	Toluene, 110 °C 13 h	 **271**	-		 **276** 90%
4	Benzene, 50 °C 40 h	 **52**	 **277** 65%		-
5	Benzene, r.t., 90 h	 **272**	 **278** 50%		-
6	Benzene, r.t., 12 h	 **4**	 **279** 83%		-

propanes **52**, **272** and **4** (entries 4–6). The chloro derivative **4**, in addition to regioselectivity, also shows high reactivity (entry 6) [68].

The same regioselectivity was observed in the cycloaddition of nitrones **257** and **280** to cyclopropylideneacetate **52** (Scheme 44) [69].

These experimental findings, as well as earlier data on alkylidenecyclopropanes, clearly disclose a peculiar effect of a cyclopropylidene system both on reaction rates and regioselectivity. In fact, the parent MCP as well as its derivatives exhibit a high reactivity in 1,3-dipolar cycloadditions with nitrones. In contrast, the related open chain isobutene and its derivatives are well known to enter 1,3-dipolar cycloadditions sluggishly [51c–d, 70]. For example, there is no chance to obtain a cycloadduct from **256** and an open chain trialkyl or tetraalkylethylene, as was obtained in the reaction of **256** with **270** and **271**.

As for the regioselectivity of the nitrone cycloaddition to MCP and its alkyl or aryl derivatives, a tendency of the three-membered ring to end up at the 4-position of the final isoxazolidine ring clearly emerges from the experimental findings. This result is particularly noteworthy if compared to regiospecific formation of the 5,5-disubstituted isoxazolidines in the reactions of nitrones, not



n=1 **280** **281** 64%
n=2 **257** **282** 78%

Scheme 44

only with open chain 1,1-disubstituted ethylenes, but also with methylenecyclobutane [70, 71]. Moreover, the regiospecificity of the reaction of **256** with **270** and **271**, with formation of a 4-spirocyclopropane derivative, clearly reflects the different effect of the three-membered ring moiety as compared to open chain alkyl substituents.

Steric effects play a role in promoting regiospecificity, in particular in the case of **271**. A cyclopropylidene moiety certainly exhibits a lower steric requirement than an isopropylidene system; consequently, compound **276** is sterically less congested than its regioisomer and it is quite reasonable to assume that this difference is also experienced at the transition state leading to them. However, the whole of regiochemical data of the reactions of nitrones with MCP and its alkyl and aryl derivatives seems to suggest that there is an inherent "electronic" effect in methylenecyclopropanes which promotes formation of the 4-spiro regioisomer. This tendency of MCP to give rise to reversal of regiochemistry has also been observed in the cycloaddition to diazoalkanes (see Sect. 3.1.2).

The regiochemical data of the reactions of nitrone **256** with methoxycarbonyl derivatives **52** and **272** are the same as observed in the reactions of the related methyl 3,3-dimethylacrylate with nitrones, that is regiospecific formation of the 4-methoxycarbonyl adduct [72].

MO calculations both at the semiempirical (C-INDO and MNDO) and ab initio level (STO-3G) were carried out in order to investigate whether or not there is any peculiar feature of the MOs of methylenecyclopropane which could open the way to an explanation of the reactivity and the regiochemistry of the reactions of this dipolarophile and its derivatives [67b]. It is well known that angle strain in a dipolarophile can affect its reactivity and that this effect is not properly accounted for by PMO approach [72, 73]. It has been observed that a decrease in angle strain on going from educts to adducts induces an increase in reaction rate [74]. Consequently, the higher reactivity of methylenecyclopropane compared with 1,1-dialkylethylenes may well simply reflect a decrease in angle strain of the cyclopropylidene system along the reaction coordinate, and there is no cogent need to look for additional effects. However, the effect of angle strain on regioselectivity is not a common observation. MO calculations (at least at that level of theory) fail to differentiate the effect of a cyclopropylidene system from that of alkyl substituents, and therefore, to rationalize the experimental results. In fact, all these calculations show that polarization of HOMO and LUMO in methylenecyclopropane is very similar to that in methylenecyc-

lobutane and isobutylene. Moreover, alkylidenecyclopropanes exhibit a substantially unpolarized double bond in striking contrast with experimental data [67b]. The analysis of the transition states carried out with semiempirical (AM1) and ab initio level (STO 3-21G), if it was able to find a 1.8 Kcal/mole difference in favor of the transition state leading to the 4-spirocyclopropane isoxazolidine for 2,2-dimethylmethylenecyclopropane, was unable to predict the lack of regioselectivity with MCP [75].

To explain the regiochemical outcome of the reaction, another rationale approach could be undertaken. There is still ample debate among theoretical chemists about concertedness or unconcertedness of pericyclic reactions [76–78]. Adding fire to the debate, the cycloaddition can be assumed to take place through an *asymmetric polarized transition state* where charge separation assumes higher importance. If this is true, transition states that are able to stabilize the separate charges will be preferred. If we consider all the possible transition states with charge separation (Fig. 2) for the cycloaddition to methylenecyclopropane derivatives, it is apparent that **TS-B**, which holds a negative charge on a cyclopropyl carbon, and **TS-D**, which bears a positive charge α to a cyclopropyl ring, are more stabilized than the regioisomeric **TS-A** and **TS-C**. They both lead to the formation of 4-spirocyclopropane isoxazolidines. When R is an electrondonating group the stabilization is much higher, leading to the exclusive formation of 4-spirocyclopropane isoxazolidines.

For electronwithdrawing substituted methylenecyclopropanes (R = EWG) the stabilization of the negative charge by the EWG group as in **TS-A** justifies the high regioselectivity observed.

The role of steric effect in determining the regioselectivity is also evident on the nitrone side. The remarkable difference in regioselectivity between the cycloadditions of nitrone **256** and nitrone **283** to **285** (Table 23, entries 1–2) is a tangible proof [65c]. Since the small difference between the two nitrones should only slightly affect the frontier orbital parameters, a steric effect must play an important role at the transition state. The second methyl in nitrone **256** points right towards the approaching methylenecyclopropane in the transition state, thus hindering the approach that leads to the 5-spiro regioisomer more than the other regioisomeric mode. The six-membered ring nitrone **257** again gives an excellent regioselectivity in the cycloaddition (entry 4).

An effective steric effect on regioselectivity is observed with ketonitrones. These give predominantly, or exclusively, 5-spiro regioisomers because of the

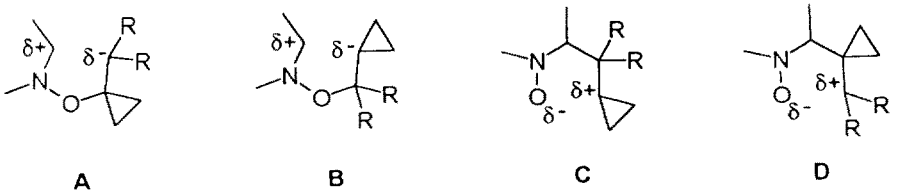
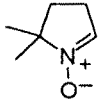
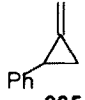
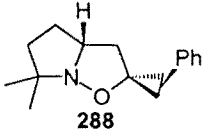
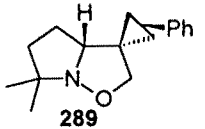
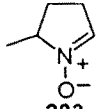
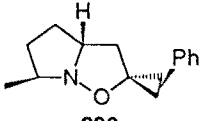
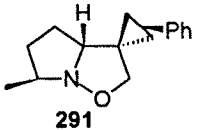
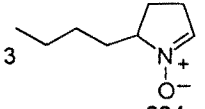
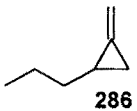
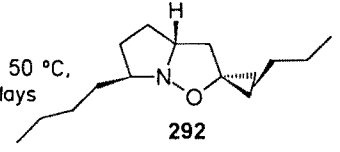
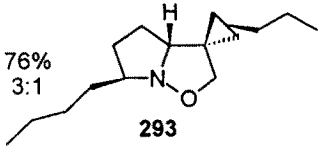
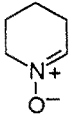
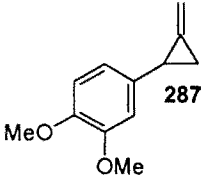
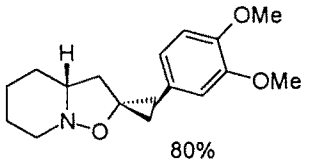


Fig. 2. Polar TS for the cycloaddition of nitrones to alkylidenecyclopropanes

Table 23. Cycloadditions of nitrones to ring-substituted methylenecyclopropanes

Entry	Nitrone	Methylene-cyclopropane	Reaction conditions	5-Spirocyclopropane isoxazolidine		4-Spirocyclopropane isoxazolidine	Ref.
1	 **256**	 **285**	neat, r.t, 15 days	 **288**	76% 2:1	 **289**	65c
2	 **283**	**285**	neat, r.t, 15 days	 **290**	90% 5:1	 **291**	65c
3	 **284**	 **286**	benzene, 50 °C, 15 days	 **292**	76% 3:1	 **293**	65c
4	 **257**	 **287**	CH_2Cl_2, r.t, 4 days	 80% **294**	–		65b

effect of the second substituent on the nitrone carbon which hinders the approach leading to 4-spiro regioisomers (Table 24) [79].

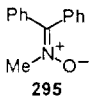
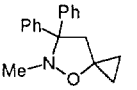
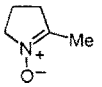
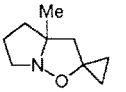
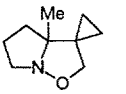
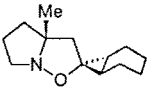
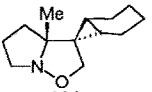
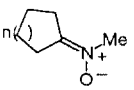
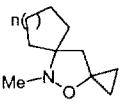
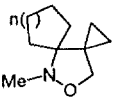
The symmetric nature of bicyclopropylidene (**3**) eludes the regioisomeric question in cycloadditions with nitrones (Scheme 45).

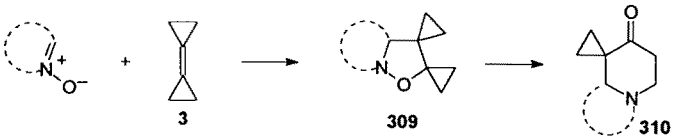
The overall process from **3** gives straightforward access to α-spirocyclopropyl heterocyclic ketones **310** [80], some of which display interesting DNA cleaving activity [80c]. The reaction conditions can be properly controlled in order to isolate the primary adducts **314–320** (Table 25). The cycloaddition to methoxycarbonyl substituted bicyclopropylidene **311** with **256** gave a mixture of the four possible regioisomeric and stereoisomeric *anti*-adducts **320** (see later) (entry 7).

The ease with which nitrones undergo cycloadditions to a tetrasubstituted olefin like **3** must be related to the high energy of the HOMO of the dipolarophile (see Sect. 2.1.1). This factor renders comparable the reactivity of BCP (**3**) and MCP (**1**), which has a lower lying HOMO, despite the less steric hindrance of **1**.

The cycloadditions of nitrones to methylenecyclopropanes **285–287** (Table 23), **299** (Table 24, entry 3), and **311** (Table 25, entry 7) substituted on the ring occur with very high diastereofacial selectivity. Nitrone **256** gives with 1-methylene-2-phenylcyclopropane (**285**) a mixture of four isomers in a 2:2:1:1 ratio

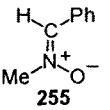
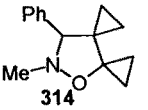
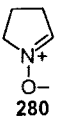
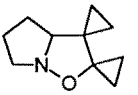
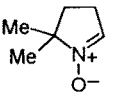
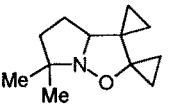
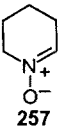
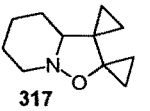
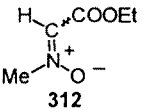
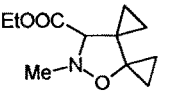
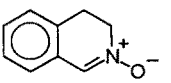
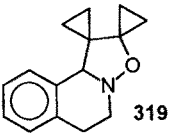
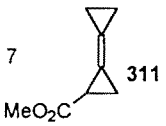
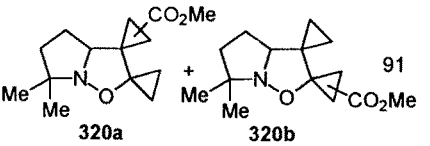
Table 24. Cycloadditions of ketonitrones to methylenecyclopropanes

Entry	Nitrone	Methylene-cycloprropane	Reaction conditions	5-Spirocyclopropane isoxazolidine		4-Spirocyclopropane isoxazolidine
1	 **295**	 **1**	Benzene, 80 °C, 2 days	 **300**		–
2	 **296**	**1**	Benzene, 80 °C, 7 days	 **301**	78% 5.5:1	 **302**
3	**296**	 **299**	Toluene, 80 °C, 7 days	 **303**	41% 4:1	 **304**
4 5	 **297** n = 1 **298** n = 2	**1**	Benzene, 80 °C, 1 day	 **305** n = 1 **307** n = 2	42% 6:1 40% 6:1	 **306** n = 1 **308** n = 2



Scheme 45

Table 25. Cycloadditions of nitrones to biocyclopropylidenes **3** and **311**

Entry	BCPs	Nitrone	Reaction conditions	Cycloadducts	Yield%
1	 **3**	 **255**	Benzene, 60 °C, 30 days	 **314**	93
2	**3**	 **280**	Benzene, r.t, 20 days	 **315**	42
3	**3**	 **256**	Benzene, r.t., 7 days	 **316**	80
4	**3**	 **257**	Benzene, 60 °C, 7 days	 **317**	37
5	**3**	 **312**	THF, r.t., 11 days	 **318**	39
6	**3**	 **313**	Benzene, r.t., 10 days	 **319**	73
7	 **311**	**256**	Benzene, r.t., 18 days	 **320a** **320b**	91

(Table 23, entry 1) identified as two pairs of 5-spirocyclopropanepyrrolo-isoxazolidines **288a** and **288b** and 4-spirocyclopropanepyrrolo-isoxazolidines **289a** and **289b**. The more regioselective nitrone **257** gives only two diastereoisomers **294a, b** in almost 1:1 ratio (Table 23, entry 4). The same diastereoselectivity is observed when a substituent is also present on the nitrone ring, as in nitrones **283** and **284** (Table 23, entries 2–3). Again, of the eight possible diastereoisomers expected for each regioisomer, only two are obtained, those derived from an *anti-anti* Transition State [65b, c] (Fig. 3).

The nitrone and the substituted methylenecyclopropane approach, in each of the two possible regioisomeric arrays, away from the nitrone substituent and away from the methylenecyclopropane substituent. The most favoured *anti-anti* Transition State produces the observed major diastereoisomers [81,65c]. The only two isomers formed, for each regioisomeric mode, must derive from *anti-anti exo* and *anti-anti endo* approaches. No *exo-endo* selectivity is generally observed, as a consequence of the strong preference for the *anti* approach towards the substituent on the cyclopropyl ring.

In the overall cycloaddition-rearrangement process [64], the {C-3}-{C-8a} relative stereochemistry of the indolizidinone obtained by rearrangement of the isoxazolidine derives from the cycloaddition step and is not affected during the rearrangement. This allowed the control of two out of three chiral centers in a synthetic protocol for a synthesis of the amphibian alkaloid (±)-Gephyrotoxin 223AB (Scheme 46) [65c].

When optically pure nitrones **321** and **322** were used, the stereoselective addition gave rise to enantiopure 5-spiro isoxazolidines with very good yield, regio- and diastereoselectivity (Table 26). The stereoselectivity of the cycloaddition of L-tartaric acid derived nitrones **321** depends on the size of the hydroxyl protecting group, going from 5:1 to 12:1 on passing from benzyl to TBDPS group [82]. Again, the alkoxy group most proximal to the nitrone functionality steers the *anti* approach of the dipolarophile. Monohydroxylated nitrone **322**, derived from L-malic acid, gives results even more stereoselective, as *syn* product cannot be observed [83].

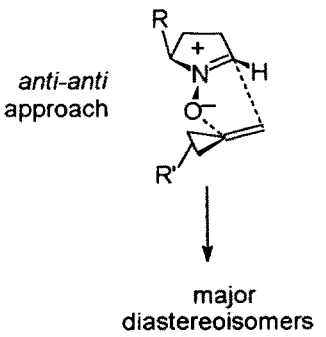
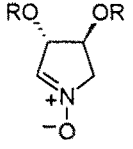
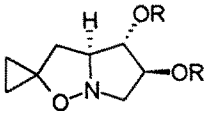
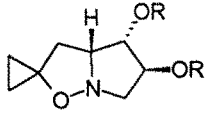
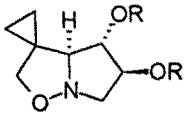
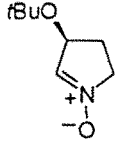
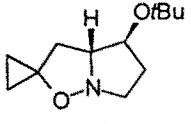
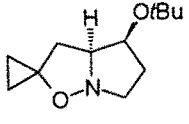
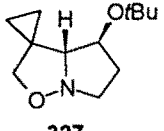
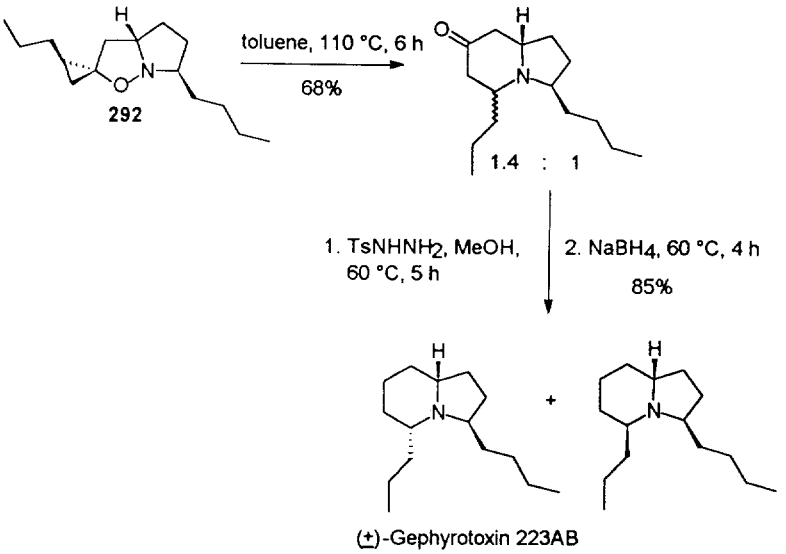


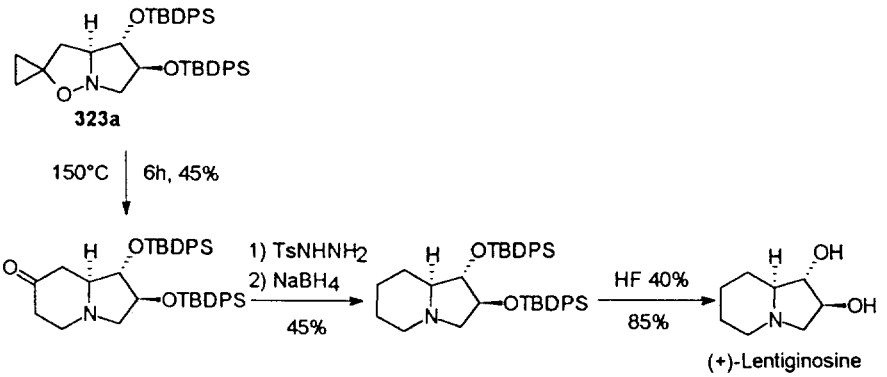
Fig. 3. Preferred TS trajectory for the cycloaddition of 5-substituted pyrroline *N*-oxides to ring-substituted methylenecyclopropanes

Table 26. Stereoselective cycloadditions of chiral nitrones **321** and **322** to **1**

Entry	Nitrone	Reaction conditions	5-Spirocyclopropane isoxazolidine		4-Spirocyclopropane isoxazolidine	Ref.
			anti-adduct	*syn*-adduct		
			 **323**	 **324**	 **325**	
1	**321a** R = TBDPS	35 °C, 8 days	78%	6%	9%	82
2	**321b** R = TBDMS	35 °C, 11 days	70%	10%	8%	84
3	**321c** R = Bn	40 °C, 7 days	73%	15%	8%	82
4	 **322**		 **326**		 **327**	
		r.t., 7 days	60%	–	10%	83



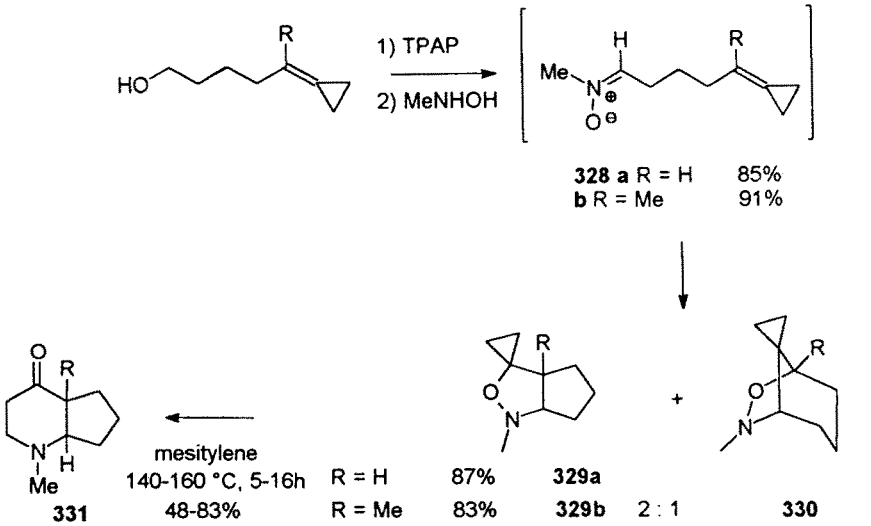
Scheme 46



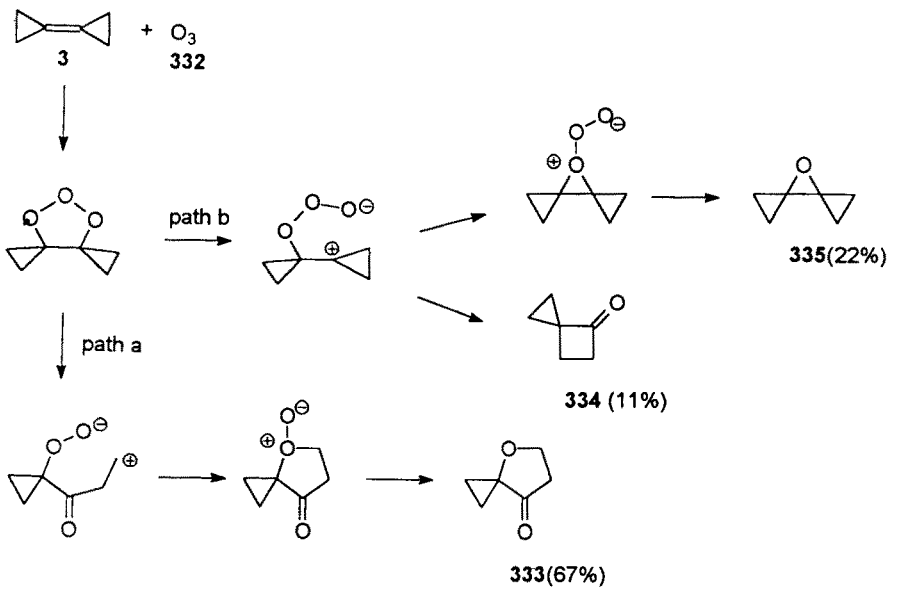
Scheme 47

Hydroxylated nitrones **321** and **322** afford, by subsequent thermal rearrangement of the adducts, a straightforward approach to polyhydroxylated indolizidines, inhibitors of glycosidases. The total synthesis of (+)-Lentiginosine is representative of the process (Scheme 47) [82].

The cyclopropylidene nitrones **328** readily give an intramolecular cycloaddition with a preferred regioisomery opposite to that of the intermolecular reaction. When R = H, the "fused" isomer **329a** is the only compound isolated in good yield. When R = Me, 30% of the "bridged" isomer **330** is also formed by the effect of a steric repulsion of the methyl group at the transition state. Both "fused" isomers **329a, b** readily rearranged to 4-azahydrindan-7-ones **331** (Scheme 48) [85].



Scheme 48



Scheme 49

3.1.4 Ozone

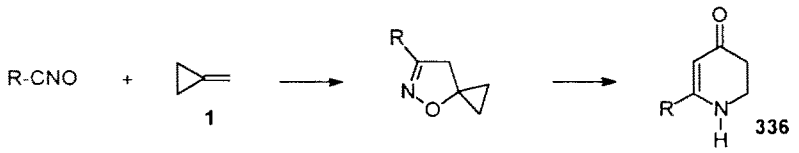
Ozone (**332**) generally combines with alkenes in a 1,3-dipolar fashion giving the so-called primary ozonides which recombine to 1,2,4-trioxolanes (ozonides). Its reaction with the parent MCP (**1**) is not known, whereas it reacts readily at

– 78 °C with BCP (**3**) most likely for the preferred interaction of the high lying HOMO of BCP with the low lying LUMO of ozone.

The reaction gave only the rearrangement products **333** and **334**, and the side product **335**, as expected from the reactivity of alkylidenecyclopropane derivatives (Scheme 49). Compound **333** might arise from the O–O bond cleavage followed by the rearrangement of a cyclopropyloxy cation to an oxoethyl cation (Scheme 49, path a). Spiro-hexanone **334** could arise from a different fragmentation of ozonide C–O bond and further cyclopropyloxy-cyclobutanone rearrangement (Scheme 49, path b). Oxirane **335** can eventually derive from the same path b or from other side processes [13b].

3.1.5 Nitrile Oxides

Nitrile oxides are very reactive dipoles which, apart a few members, need to be prepared in situ for their tendency to dimerize to furoxans [86]. This behaviour represents a limit to their use with alkylidenecyclopropanes that is only in part compensated by their reactivity. The cycloadditions of several nitrile oxides with alkylidenecyclopropanes were extensively studied in connection with the rearrangement process leading to dihydropyrid-4-ones **336** [64, 87].



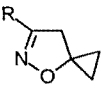
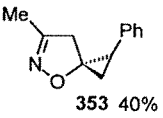
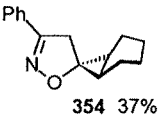
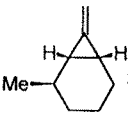
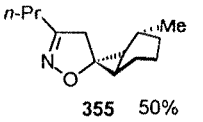
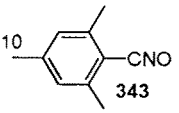
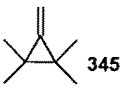
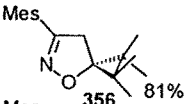
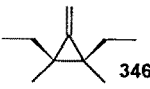
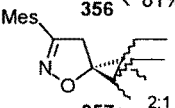
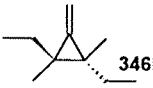
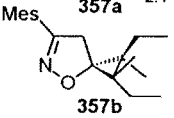
A positive feature of the reaction is that nitrile oxides are more regioselective, in cycloadditions to methylenecyclopropanes, compared to nitrones. Only traces (up to 5%) of the 4-spirocyclopropane regioisomers are generally observed with methylenecyclopropanes unsubstituted on the exocyclic double bond. The yields are only moderate, but higher with more stable nitrile oxides (Table 27, entries 5, 6, 10–12).

In addition, high diastereoselectivity is observed when substituents are present on the cyclopropane ring. Only the depicted diastereomers are detected (Table 27, entries 7–9) as a result of the preferred approach of the dipole from the less hindered face of the dipolarophile ("anti" approach). The *cis*-diethyl substituted methylenecyclopropane **346a** (Table 27, entry 11), gave quantitatively a 2:1 mixture of diastereomeric isoxazolines **357a** with nitrile oxide **343**, the major being that one deriving from the attack of the nitrile oxide from the side of the less bulky methyl groups [90].

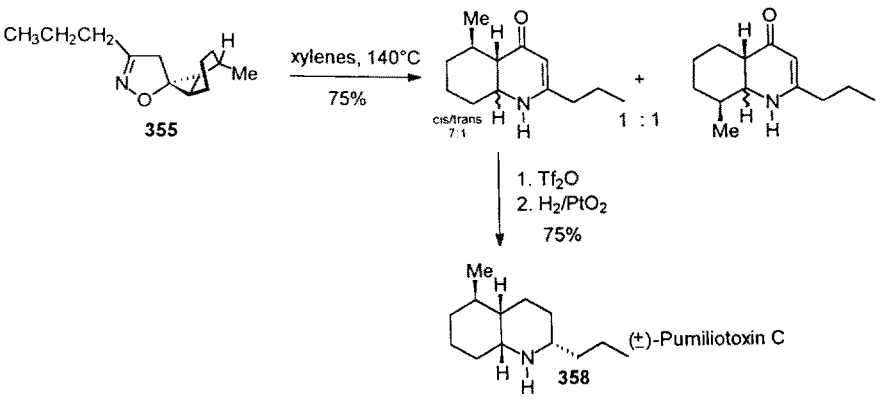
The isoxazoline **355** (Table 27, entry 9) served as precursor for the total synthesis of the amphibian alkaloid (±)-Pumiliotoxin C **358** (Scheme 50) [89].

The question of regioselectivity of the cycloaddition with alkylidenecyclopropanes was also addressed, in analogy with nitrones, and afforded somewhat different results (Table 28) [91, 67b].

Table 27. Cycloadditions of nitrile oxides **337–343** to methylenecyclopropanes

Entry	Nitrile oxide	Methylene-cyclopropane	5-Spirocyclopropane isoxazolidine	Reaction conditions	Ref.
	R-CNO	 **1**			
1	**337** R = Me		**347** 35%	Et_2O, 0 °C-r.t., 16 h	87
2	**338** R = *n*-Pr		**348** 72%	Et_2O, r.t., 3 days	88
3	**339** R = CO_2Me		**349** 50%	$CHCl_3$, r.t., 5 days	64
4	**340** R = $PhCH_2$		**350** 36%	Et_2O, 0 °C-r.t.,12 h	87
5	**341** R = Ph		**351** 72%	Et_2O, 0 °C-r.t.,12 h	87
6	**342** R = α-Naphthyl		**352** 68%	Et_2O, 0 °C-r.t., 20 h	64
7	MeCNO **337**	 **285**	 **353** 40%	C_6H_6, 80 °C, 1 h-r.t., 12 h	87
8	PhCNO **341**	 **299**	 **354** 37%	Et_2O, 0 °C-r.t., 1 h	87
9	*n*-PrCNO **338**	 **344**	 **355** 50%	C_6H_6, r.t., 16 h	89
10	 **343**	 **345**	 **356** 81%	Et_2O, 80 °C, 24 h	90
11	**343**	 **346a**	 **357a** 2:1	C_6D_{12}, 50 °C, 2 days	90
12	**343**	 **346b**	 **357b**	C_6D_{12}, 50 °C, 2 days	90

Albeit nitrile oxides are more regioselective than nitrones towards MCP, in cycloadditions with alkylidenecyclopropanes they show a lower regiocontrol than nitrones. The same trend, however, on passing from electron-donating to electron-withdrawing substituents is observed. Benzylidenecyclopropane (**156**) gives (entry 1, Table 28) only a 1:4 mixture (compared with 1:19 with nitrone



Scheme 50

Table 28. Cycloadditions of nitrile oxides **337** and **341** to alkylidenecyclopropanes [91, 67b]

Entry	Reaction conditions	Nitrile oxide	Methylene cyclopropane	5-Spirocyclopropane isoxazoline		4-Spirocyclopropane isoxazoline
1	Benzene, 80 °C 1 h	MeCNO **337**	Ph, **156**	Me, Ph, N, O **359**	50% 1 : 4	Me, N, O, Ph **360**
2	Toluene, 110 °C 1 h	**337**	Ph, **271**	–		Me, N, O, Ph **361** 65%
3	Benzene, r.t. 17 h	PhCNO **341**	MeOOC, **52**	Ph, CO_2Me, N, O **362**	53% 3 : 1	Ph, N, O, CO_2Me **363**
			MeOOC, MeOOC, **272**	R, CO_2Me, N, O, CO_2Me		R, CO_2Me, N, O, CO_2Me
4	Benzene, r.t., 24 h	**341**		R = Ph **364** 3.4	15%	1 **365**
5	Benzene, 80 °C 1 h	**337**		R = Me **366**		**367**
				80°C ↓ R, CO_2Me, N, O, CO_2Me		
				R = Ph **368** 37%		
				R = Me **369** 45%		

256) of regioisomeric isoxazolines **359** and **360**. The carbomethoxymethylene-cyclopropane (**52**) (entry 3) gives a mixture of isoxazolines **362** and **363** in a 3 : 1 ratio with inverted regioselectivity as in nitrones, but 25% of 4-spiroregioisomer formed, in sharp contrast with the nitrone result and also with the outcome of

the cycloaddition with methyl 3,3-dimethylacrylate [72c]. The two divergent results cannot be easily explained and testify to the uncertainty about the "cyclopropylidene effect" on regioselectivity. The cycloadducts **364** and **366** from **272** are not thermally stable (entries 4–5, Table 28) and undergo a cyclopropyl ring opening with aromatization to the isoxazole ring to afford **368** and **369** (see Sect. 3.1.1).

A wide range of aliphatic nitrile oxides **370a–k** and **372a–e**, variously functionalized on the side chain, were added to MCP and its derivatives, on the route for the synthesis of functionalized dihydropyridones (Tables 29 and 30) [92].

Reaction yields and regioselectivity were comparable, or better, than those obtained with more simple nitrile oxides. Examples of the use of an optically active (*R*)-4-chloro-valeronitrile *N*-oxide for the synthesis of non-racemic isoxalines **371d** and **371e** are also reported [93].

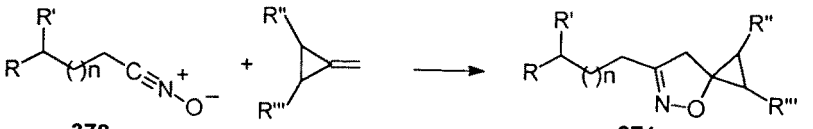
Halide substituted isoxazolines **371a–f** gave bicyclic dihydropyridones **374** after rearrangement. Methoxycarbonyl substituted isoxazolines **371g–k** gave the lactams **375**, whereas carbonyl substituted isoxazolines **373a–e** gave pyrroles **376** (Scheme 51).

The process has been applied to the synthesis of a Δ^9-19-nor-10-azatestosterone **378** by cycloaddition of nitrile oxide **377** to MCP followed by thermal rearrangement of the adduct (Scheme 52) [94].

Adducts **380–383** of nitrile oxides to highly hindered bicyclopropylidene (**3**) can be obtained, despite the lower reactivity of the tetrasubstituted double bond which reduces the yields favoring the dimerization of reactive nitrile oxides (Table 31, entries 1–2) [80a, b].

Better yields were obtained with the stable mesitonitrile oxide (**343**) which enables the cycloaddition at higher temperature (entry 3). In the reaction of **341**

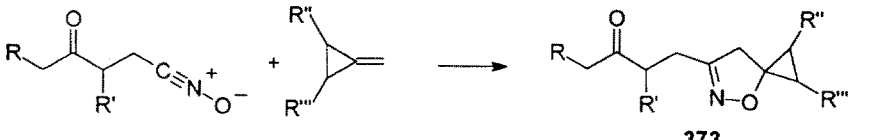
Table 29. Cycloadditions of nitrile oxides **370** to methylenecyclopropanes **1**, **285**, and **299**



370 **371**

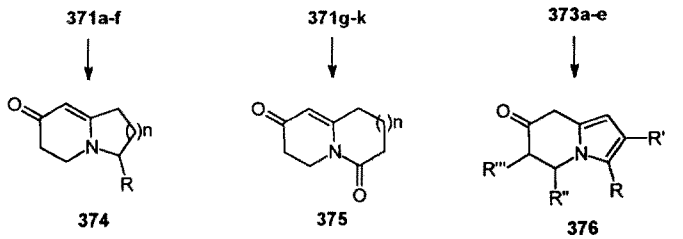
Entry	MCPs	Isoxazoline	R	R'	n	R''	R'''	Yield%
1	**1**	**371a**	H	Cl	1	H	H	52
2	**1**	**371b**	H	Br	2	H	H	46
3	**1**	**371c**	H	Br	3	H	H	56
4	**1**	**371d**	CH_3	Cl	1	H	H	62
5	**285**	**371e**	CH_3	Cl	1	Ph	H	68
6	**299**	**371f**	CH_3	Cl	1	$-(CH_2)_4-$		53
7	**1**	**371g**	CO_2Me	CO_2Me	0	H	H	68
8	**1**	**371h**	CO_2Me	H	0	H	H	67
9	**1**	**371k**	CO_2Me	CO_2Me	1	H	H	70

Table 30. Cycloadditions of nitrile oxides **372** to methylenecyclopropanes **1**, **285**, and **299**



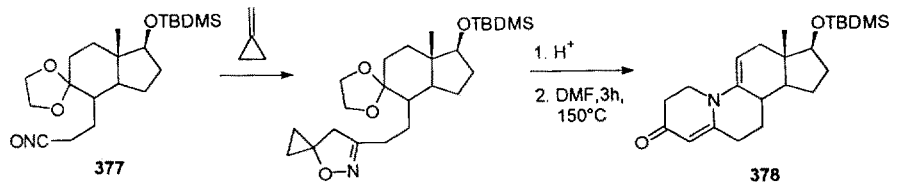
372 **373**

Entry	MCPs	Isoxazoline	R	R′	R″	R‴	Yield%
1	**1**	**373a**	H	H	H	H	63
2	**285**	**373b**	H	H	Ph	H	51
3	**299**	**373c**	H	H	$-(CH_2)_4-$		42
4	**1**	**373d**	$-(CH_2)_3-$		H	H	72
5	**285**	**373e**	$-(CH_2)_3-$		Ph	H	41



374 **375** **376**

Scheme 51



377 **378**

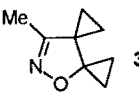
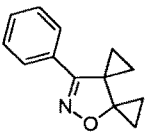
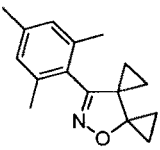
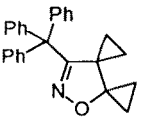
Scheme 52

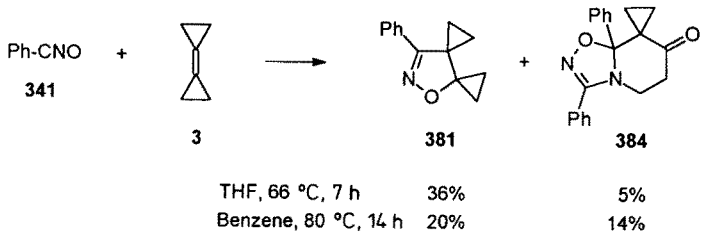
with **3**, in addition to the isoxazoline **381**, another cycloadduct **384** was isolated in small quantity (5%). Its formation depended on the reaction conditions, increasing with the increase of the temperature and reaction time (Scheme 53).

Compound **384** derived from the reaction of two molecules of benzonitrile oxide (**341**) with one of BCP (**3**). Its formation can be explained with the cycloaddition of a second molecule of **341** to the isoxazoline **381** to give the isoxazolidine **385**, which undergoes a thermal rearrangement to **384** (Scheme 54).

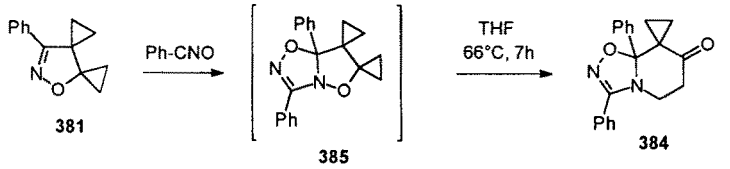
The bis(spirocyclopropane)isoxazolines **381** and **382** undergo a thermal rearrangement at much higher temperature than isoxazolidines (see Sect. 3.1.3), to afford the furo[2,3-*c*]pyridines **386** (Scheme 55) [80b].

Table 31. Cycloadditions of nitrile oxides to bicyclopropylidene (3)

Entry	Nitrile oxide	Reaction conditions	Cycloadduct	Yield%
1	Me-CNO **337**	Diethylether, 20 °C, 7 days	 **380**	<10
2	Ph-CNO **341**	THF, 66 °C, 7 h	 **381**	36
3	2,4,6-Me_3-C_6H_2-CNO **343**	Toluene, 110 °C, 48 h	 **382**	67
4	Ph_3C-CNO **379**	Toluene, 110 °C, 7 days	 **383**	17



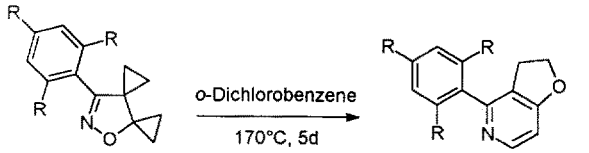
Scheme 53



Scheme 54

3.1.6 Nitrile Ylides

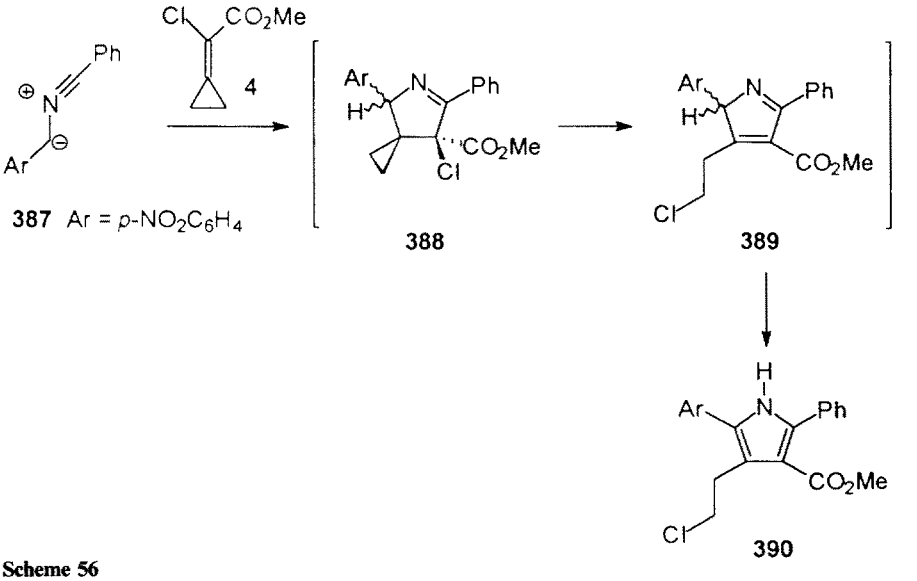
The reaction of 1-phenyl-3-*p*-nitrophenylnitrile ylid (**387**) to methylenecyclopropane **4** is the sole reported example of cycloaddition of this dipole type. The only product isolated from the reaction was the pyrrole **390**, which arose via **389**,



R = H **381**
R = Me **382**

R = H **386a** 44%
R = Me **386b** 44%

Scheme 55



Scheme 56

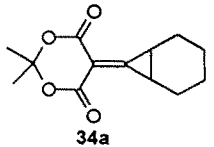
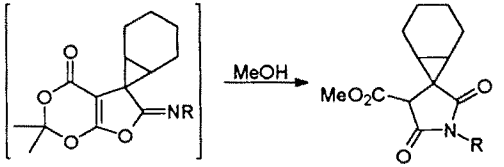
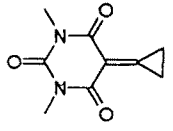
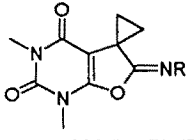
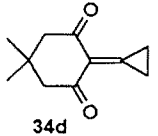
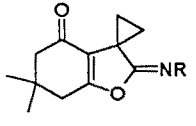
formed in turn from the primary cycloadduct **388**, by a cyclopropylcarbinyl-homoallyl rearrangement (Scheme 56) [61].

3.2 [4 + 1] Cycloadditions

The only examples dealing with [4 + 1] cycloadditions of alkylidenecyclopropanes involve the additions of isonitriles to diacylmethylenecyclopropanes.

The unstable 2-cyclopropylidene-1,3-cycloalkanediones **34a, c, d** were trapped in situ by isocyanides **391** to give [4 + 1] cycloadducts under mild reactions conditions to afford 3-spirocyclopropane furans or pyrroles (Table 32) [95]. In the case of **34a**, the primary cycloaddition products **392** and **394** decomposed very easily to give the stable pyrrolidindiones **393** and **395**, respectively, as a single stereoisomer, upon addition of methanol (entries 1–2). Compounds **34c** and **34d** gave the expected adducts in moderate to good yields (Table 32, entries 3–7).

Table 32. Cycloadditions of isocyanides **391** with 2-cyclopropylidene-1,3-cycloalkanediones **34a, c, d**

Entry	2-Cyclopropylidene-1,3-cycloalkanediones	Isocyanides	Reaction conditions	Products (yield %)
	 **34a**	C≡N–R	CH_2Cl_2 0 °C, 1 h then 20 °C, 12 h	
1		**391a** R = Ph		**392** R = Ph **393** R = Ph (54)
2		**391b** R = 4-MeOC$_6$H$_4$		**394** R = 4-MeOC$_6$H$_4$ **395** R = 4-MeOC$_6$H$_4$ (64)
	 **34c**		CH_2Cl_2 0 °C, 30 min then 20 °C, 1.5 h	
3		**391a** R = Ph		**396** R = Ph (54)
4		**391c** R = CH_2Ts		**397** R = CH_2Ts (43)
	 **34d**		CH_2Cl_2 20 °C, 24 h	
5		**391a** R = Ph		**398** R = Ph (70)
6		**391c** R = CH_2Ts		**399** R = CH_2Ts (64)
7		**391d** R = *t*Bu		**400** R = *t*Bu (73)

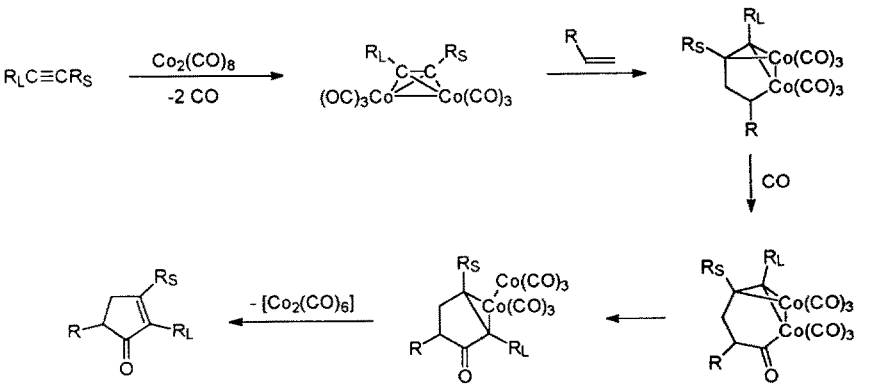
3.3 Pauson-Khand Reactions

The Pauson-Khand reaction (PKR) [96] consists of the synthesis of cyclopentenones by reaction of an alkene with a dicobalthexacarbonyl complexed alkyne (Scheme 57) and has recently emerged as one of the methods of choice for the obtainment of five-membered carbocyclic rings [97]. Its unique atom connectivity, which involves the two unsaturated carbons of the reagents and the carbon atom of a carbon monoxide ligand of cobalt usually in a regioselective manner (Scheme 57), has brought to refer to PKR as a [2 + 2 + 1] cycloaddition.

Initially, the synthetic utility of the process was compromised by the necessity of severe conditions (heating of reagents in hydrocarbon solvents over several hours) and the resulting low yields. Recently, it has been found that the reaction can be greatly improved in both rates and yields by addition of tertiary amine oxide [98] or DMSO [99], and by immobilizing the reagents on adsorbents and carrying out the reaction in dry state conditions [100], or by using ultrasound activation [101]. A further impulse to the application of the PKR in organic synthesis is expected to be brought about by recently established catalytic protocols, which employ $Co_2(CO)_8$ or other cobalt complexes as catalysts under CO pressure [102].

3.3.1 Intermolecular Pauson-Khand Reactions

Intermolecular PKRs proceed especially easily with strained alkenes, e.g., norbornene, norbornadiene, and cyclobutene [97]. Nevertheless, highly strained MCP gave unsatisfactory results when reacted at 20 °C in hexane with acetylene, propyne, or phenylacetylene, both in terms of yields (10–15%) and of regioselectivity of the attack to the ethylenic bond (ca. 1 : 1) [100a, 103]. The reagents were consumed, but extensive tar formed and no variation in reaction conditions was successful.



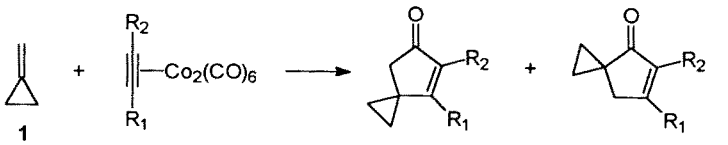
Scheme 57

The [2 + 2 + 1] cycloaddition of MCP (**1**) with several alkynes was greatly improved by carrying out the reaction at 50 °C in dry state conditions after having adsorbed the reagents on SiO_2 (Table 33) [100a, 103], conditions which have been previously demonstrated useful for intramolecular PKRs [100b–c]. Successively, the reaction has been extended to the use of disubstituted and functionalized alkynes and of different adsorbents (Table 33) [100a, 104].

In these conditions, the cycloaddition gave good yields and displayed interesting regioselectivity features, similar to those observed for different alkenes [97]. Indeed, it was completely regioselective towards the alkyne component, producing only 2-substituted derivatives from terminal alkynes **402–408** (entries 2–12) and placing the larger substituent α to carbonyl from the unsymmetrically disubstituted alkyne **410** (entry 14). The regioselectivity with respect to MCP depended on the solid support used, but fell typically in the range 3–6:1 in the case of acetylene (**401**) and monosubstituted alkynes **402–408** (entries 1–12), with the prevalent isomer bearing the spirocyclopropane moiety β to carbonyl [100a, 103, 104]. On the other hand, α-spirosubstituted products were formed exclusively in cycloadditions with internal alkynes **409–410** (entries 13 and 14) [100a, 104].

No example of [2 + 2 + 1] intermolecular cycloaddition involving substituted MCPs has been reported so far.

Table 33. Pauson-Khand reactions of methylenecyclopropane (**1**)



1 **401-410** **411-420a,b**

Entry	R_1	R_2	Alkyne	Conditions		Products	Yield (%)	**a:b** ratio
				Support	t (h)			
1	H	H	**401**	SiO_2	2	**411**	46	6:1
2	H	CH_3	**402**	SiO_2	2	**412**	64	4.9:1
3	H	CH_3	**402**	Al_2O_3	2	**412**	77	5:1
4	H	CH_3	**402**	$MgO \cdot SiO_2$	0.5	**412**	53	2.5:1
5	H	CH_3	**402**	zeolite NaX	2	**412**	81	2.3:1
6	H	Ph	**403**	SiO_2	3	**413**	79	4.4:1
7	H	*c*-C_3H_5	**404**	zeolite NaX	1.5	**414**	67	3:1
8	H	$CH{=}CH_2$	**405**	zeolite NaX	1	**415**	25	> 20:1
9	H	$C(Me){=}CH_2$	**406**	zeolite NaX	2	**416**	59	3:1
10	H	$C(Me){=}CH_2$	**406**	zeolite H-ZSM	0.5	**416**	69	5.5:1
11	H	CH_2OMe	**407**	zeolite NaX	1	**417**	79	5:1
12	H	$C(OH)Me_2$	**408**	SiO_2	6	**418**	47	3:1
13	Et	Et	**409**	zeolite NaX	4	**419**	54	< 1:20
14	Me	$SiMe_3$	**410**	zeolite NaX	2	**420**	81	< 1:20

3.3.2 Intramolecular Pauson-Khand Reactions

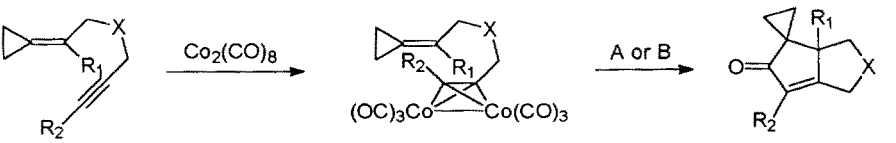
The intramolecular version of the PKR has attracted much more synthetic interest, leading to valuable bicyclic systems and being more general and viable [97]. Particularly, 1,6-enynes have been extensively used for the construction of the bicyclo[3.3.0]octane [105], cyclopenta[*c*]furan [106], or cyclopenta[*c*]pyrrole [107] skeletons in a single step.

Salaün and de Meijere's groups have applied successfully the intramolecular PKR on 1-cyclopropylidene-1,6-enynes **421–426** (Table 34) [108], accessible via the Pd(0) catalysed alkylation of stabilized carbanions with 1-vinylcyclopropanes 1-substituted with leaving groups [3a, 109].

The intermediate hexacarbonyldicobalt complexes **427** can be isolated, but the best results were obtained by carrying out the cycloaddition step by the addition of trialkylamine *N*-oxides [98] directly in the reaction mixture. Whereas trisubstituted [110] or tetrasubstituted [111] alkenes have been found unreactive or have given poor yields in intramolecular PKRs, the alkylidenecyclopropanes **421–426**, including the tetrasubstituted **424** (entry 5) react smoothly [108], thus assessing the importance also in this kind of reaction of the methylenecyclopropane as terminal group, for its high strain energy content. This is confirmed by the inertness of the isopropylidene analogue of **421** in the same reaction conditions. Finally, it should be noted that sulfonyl substitution at C4 was not tolerated under the reaction conditions, since compound **434** gave only the elimination product in low yield (Scheme 58) [108].

Due to the interest of the accessible bicyclic systems in the field of natural products as potential precursors of terpenes, and to exploit the potentiality of

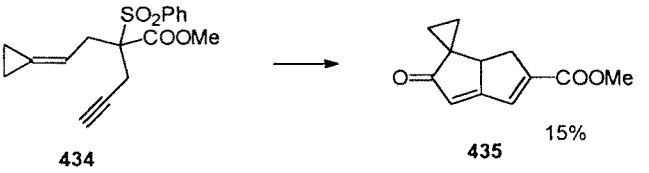
Table 34. Intramolecular Pauson-Khand reactions of alkylidenecyclopropanes **421–426**



421-426 **427** **428-433**

Entry	R_1	R_2	X	Enyne	Conditions	Product	Yield (%)
1	H	H	$C(COOMe)_2$	**421**	A[a]	**428**	73
2	H	H	$C(COOMe)_2$	**421**	B[b]	**428**	87
3	H	Me	$C(COOEt)_2$	**422**	B[b]	**429**	75
4	H	$SiMe_3$	$C(COOMe)_2$	**423**	A[a]	**430**	35
5	Me	H	$C(COOMe)_2$	**424**	A[a]	**431**	64
6	H	H	NTs	**425**	B[b]	**432**	80
7	H	H	CHCOOMe	**426**	B[b]	**433**	73

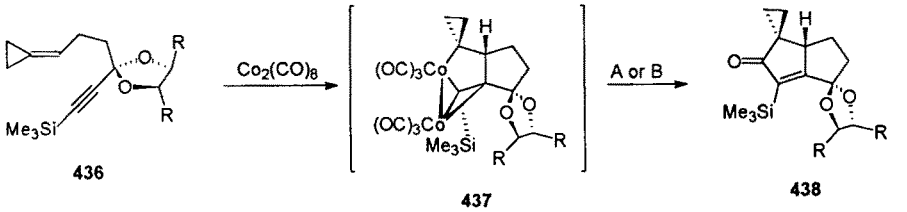
[a] 1. Flash Chromatography; 2. NMO (3 eq), Ar, rt, 10 h
[b] TMANO (5 eq), O_2, rt, 14 h



434 435

Scheme 58

Table 35. Diastereoselective intermolecular PKR of enynes **436a–c**



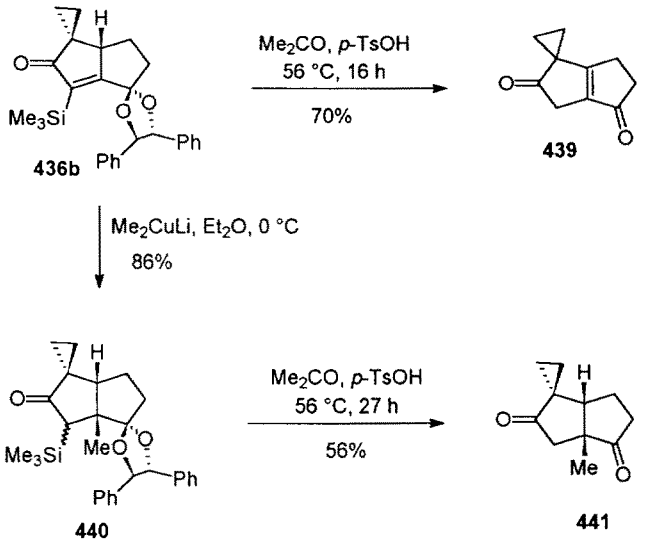
436 437 438

Entry	R	Enyne	Yield (%)	Products	Diastereoisomeric ratio
1	Me	**436a**	63	**438a**	2:1
2	Ph	**436b**	69	**438b**	5:1
3	*c*-Hex	**436c**	76	**438c**	6.4:1

the reaction, attempts for inducing asymmetry in the [2 + 2 + 1] cycloaddition have been performed [112]. Some examples of PKR with asymmetric induction had been previously reported, either by using chiral catalysts [113] or chiral auxiliaries in both intramolecular [114] and intermolecular [115] versions.

C_2-Symmetric chiral diols were chosen as auxiliaries to synthesize chiral ketals **436a–c** from the corresponding α-acetylenic ketones (Table 35) [112]. The basis for the choice of the auxiliaries and their positioning α to the alkyne rests on the mechanistic rationalization of the PKR, assuming that formation of intermediate would be favored for steric reasons. Indeed, enynes **436a–c** gave the intramolecular PKR in good yield and fair diastereoselectivity with bulky R groups (Table 35, only the major diastereoisomer reported) [112]. The use of the corresponding desilylated terminal alkynes led to almost no stereoselectivity and also to low yields of bicyclic products. Once again the presence of the methylenecyclopropyl terminator is essential: enynes without this end group reacted poorly, albeit with nearly the same diastereoselectivity, even at 110 °C.

In order to establish the bridgehead carbon configuration with certainty and to demonstrate the usefulness of the method, desilylation and deprotection of **438b** in acidic conditions have been performed. Since they are accompanied by double bond migration and loss of chirality, a dimethylcuprate alkylation has been carried out before acid hydrolysis (Scheme 59) [112].



Scheme 59

4 Four-Membered Ring

4.1 [2 + 2] Cycloadditions to C=C Bonds

Normal monoalkenes are known to undergo only two types of pericyclic reactions, namely the [π2s + π2a] and [π2s + π4s] modes. Nevertheless, thermal cyclodimerizations of alkenes are rare, because the orbital symmetry conservation rules preclude a concerted [π2s + π2s] reaction and the [π2s + π2a] transition state is energetically unfavorable. Some peculiar olefins, such as fluoroalkenes, undergo a facile thermal cyclodimerization, which has been explained by a stepwise mechanism involving diradical intermediates which are stabilized by the fluoro substituents. Several methylenecyclopropane derivatives behave in an entirely analogous manner, giving head-to-head dimers upon heating. The role of the cyclopropane ring on the high propensity of methylenecyclopropanes to undergo cyclodimerizations and thermal [2 + 2] cycloadditions is not fully understood as yet. In view of the considerable double bond character of the cyclopropane ring, as evidenced by its chemical behavior and explained by the various theoretical models describing its bonding properties, it is probably more appropriate to draw parallels between methylenecyclopropanes and allenes, as the latter compounds likewise cyclodimerize readily.

4.1.1 Cyclodimerization

Due to their tendency to dimerize in different thermal conditions, the formal [2 + 2] cycloaddition reaction of methylenecyclopropane derivatives and their

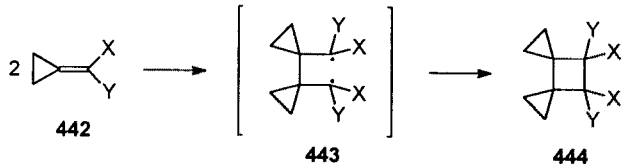
congeners **442** has been one of the first investigated. The reaction generates dispirocyclobutane derivatives **444** deriving from a cyclodimerization in a head-to-head fashion and occurs most likely, at least in the majority of cases, via a stepwise mechanism involving diradical intermediates **443** (Scheme 60). Indeed, the thermal [π2s + π2s] cycloaddition is forbidden on the basis of the Woodward-Hoffmann symmetry orbital selection rules, and, additionally, the allowed [π2s + π2a] topological interaction would require too much energy in order to twist the C=C double bond.

Methylenecyclopropane itself undergoes the cyclodimerization at elevated temperatures (200–250 °C) to give predominantly the head-to-head dimer **445** vs its head-to-tail isomer **446** (Scheme 61) [116, 117], albeit in poor yield.

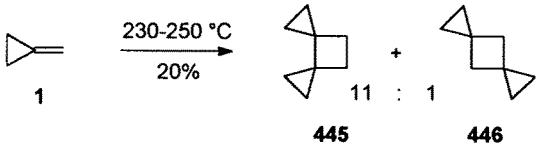
The cyclodimerization reaction is not a general one and appears to be very sensitive to the substitution at both the cyclopropane carbons and the *exo* double bond. Indeed, alkylidenecyclopropanes do not undergo the reaction [117, 118], apart from bicyclopropylidene and cyclobutylidenecyclopropane [117]. 2,2-Disubstituted methylenecyclopropanes are equally unreactive towards cyclodimerization since they rather isomerize (225 °C) to the corresponding alkylidenecyclopropanes [119], which do not dimerize even upon heating at 250 °C for long reaction times [117]. Diphenylmethylenecyclopropane undergoes rearrangement to 1-phenyl-3,4-dihydronaphthalene rather than dimerization at temperatures above 190 °C [120].

The only notable exception is regarding the very strained alkylidenecyclopropanes **21**, which are believed to be formed "in situ" as elusive intermediates and cannot be either isolated or even detected (Scheme 62) [121, 122, 11a].

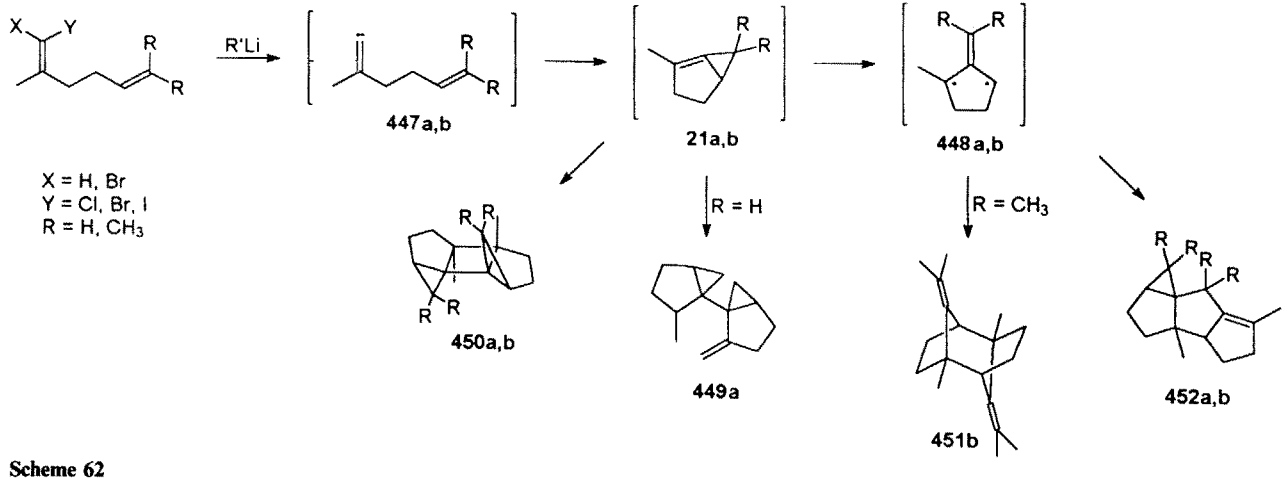
Depending on the substitution and on the temperature at which the vinyl carbenoid **447** is generated, the main products of the reaction are different dimers [121, 122, 11a]. The formal [2 + 2] cycloadduct **450b** prevails at low temperature (< − 50 °C) when R=CH_3 (**450b**:**452b** 9:1), while apparently higher temperatures favor the ring-opening of the three membered ring to



Scheme 60



Scheme 61


X
Y
R
R
R'Li
447a,b
21a,b
448a,b
X = H, Br
Y = Cl, Br, I
R = H, CH3
R = H
R = CH3
450a,b
449a
451b
452a,b

Scheme 62

a trimethylenemethane 1,3-diyl species **448b** which is responsible for the formation of products **451b** and **452b** by reaction with itself and with **21b**, respectively [121, 122, 11a]. However, it has been proposed that formation of species **452** at low temperature occurs via a concerted $[\pi + \sigma]$ pathway, without involvement of TMM intermediates [122, 11a]. At 0 °C, with $R = CH_3$, the cyclodimer **450b** is the minor product, besides the prevalent TMM dimer **451b**. In the case of the terminal olefin (R = H), the product **449a** deriving from an ene reaction between two molecules of **21a** is also formed. In this case, the products of the reaction are **450a**, **452a**, and **449a** in a 1:5:2.5 ratio, independent of temperature in the range − 90 to 0 °C [122, 11a]. This result has been interpreted in terms of a higher rate of concerted processes when the encumbering methyl groups are removed [122, 11a].

When heated at 190 °C, 1'-halo- **96** and **453** (Table 36, entries 1 and 2) and ethoxymethylenecyclopropane (**454**) (entry 3) gave the head-to-head dimerization in good yield as a mixture of cis and trans isomers, with the latter slightly prevailing [27].

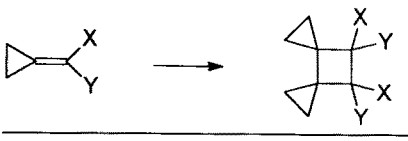
(Dichloromethylene)cyclopropane (**455**) (entry 4) undergoes the cyclodimerization in milder conditions to afford the corresponding dispirooctane **459** in good yield [117, 118a], while (difluoromethylene)cyclopropane (**456**) required higher temperatures to afford the cyclodimer **460** in low yield (entry 5) [9].

In contrast, perfluoromethylenecyclopropane (**105**) failed to give any thermal dimerization (cesium fluoride promotes its dimerization, but not in a [2 + 2] fashion) [29], while tetrafluoroethylene and other 1,1-difluoroalkenes readily undergo thermal [2 + 2] dimerization [123].

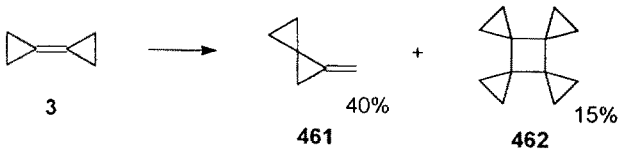
Upon heating to 210 °C, bicyclopropylidene (**3**) gives a 5.2:3.3:1 mixture of **461** and **462**, together with unreacted **3** (Scheme 63) [6a].

All the reported cyclodimerization reactions can be rationalized on the basis of Scheme 60, proceeding through the more stable diradical formed by head-to-head coupling, the driving force for the process being the energy gain due to the

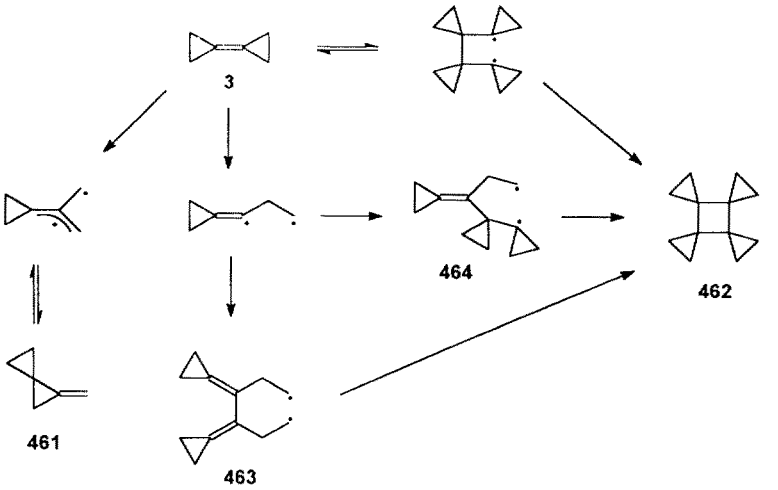
Table 36. Cyclodimerization of 1'-substituted methylenecyclopropanes **96** and **453–456**



Entry	X	Y	MCPs	Conditions		Product	Yield	Diastereomeric ratio	Reference
				T (°C)	t (h)				
1	H	Cl	**96**	190	2	**100**	80	47:53	27
2	H	Br	**453**	190	2	**457**	67	47:53	27
3	H	OEt	**454**	190	2	**458**	83	43:57	27
4	Cl	Cl	**455**	110	8	**459**	100		117
5	F	F	**456**	320	3.5	**460**	30		9



Scheme 63



Scheme 64

release of ring strain [6a, 13]. The formation of the diradical intermediate accounts for the occurrence of diastereoisomers from 1'-substituted methylenecyclopropanes (Table 36, entries 1–3). However, a more complex mechanistic picture is required to account for the formation of **461** from BCP (Scheme 64).

The reported proposed sequence also offers two additional alternative mechanisms for the cyclodimerization of BCP (**3**), involving either intermediate **463** or **464** [6a, 13b]. However, they appear less likely, requiring successive three-membered ring fissions and formations. Alternatively, a thermally allowed concerted [$\pi 2s + \pi 2a + \sigma 2a$] pericyclic reaction involving the Walsh type molecular orbital of cyclopropane [124] has been proposed (Fig. 4) [13b].

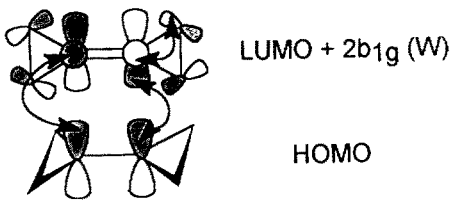


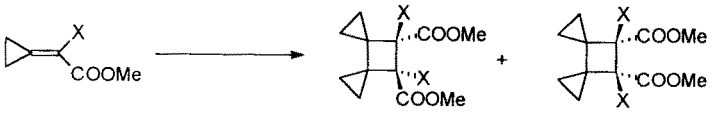
Fig. 4. Orbital interactions for the [$\pi 2s + \pi 2a + \sigma 2a$] pericyclic dimerization of BCP

Methyl 2-chloro-2-cyclopropylidenacetate (**4**) cleanly and quantitatively dimerizes at 120 °C to afford a 1:1 mixture of cis and trans dispirooctane **46** diastereoisomers (Scheme 65, X = Cl) [7, 20].

Apparently, the dimerization of **4** is considerably more facile than that of MCP or BCP, resembling those of (dichloromethylene)cyclopropane (**455**) and "radicophilic" olefins with a capto-dative substitution pattern [125], some of which are known to cyclodimerize even at room temperature. Indeed, the capto-datively substituted methylenecyclopropane **85** undergoes the homodimerization at 60 °C (Scheme 65) [126].

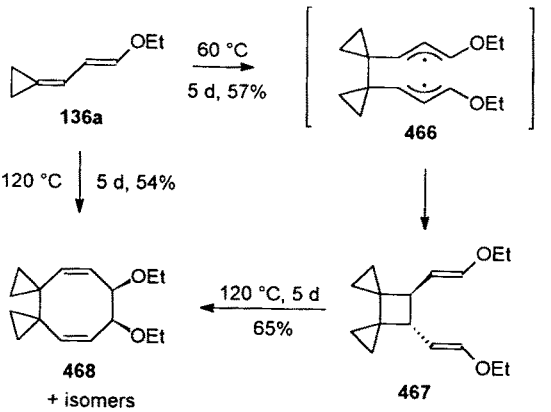
In all the latter cases the easier dimerization reaction is connected with the particular stability of the intermediate diradical species. This is also the reason for the recently found facile dimerization of the 1-donor substituted allylidenecyclopropane **136a** (Scheme 66) [127]. Allylidenecyclopropane **136a** cyclodimerizes to the expected cyclobutane **467** in very mild thermal conditions, due to the stabilization of the intermediate **466**. At higher temperature (120 °C) both **136a** and **467** give a more complex mixture of products, with the cyclooctadiene dimer **468** being the prevailing one (Scheme 66) [127].

Recently, it has been reported a cyclodimerization of an allylidenecyclopropane **470** occurring at a very low temperature (− 78 °C or − 90 °C) [128].



X = Cl	**4**	120 °C, 15 h, 100%	**46a**	1	:	1	**46b**
X = SPh	**85**	60 °C, 9 h, 56%	**465a**	1.3	:	1	**465b**

Scheme 65



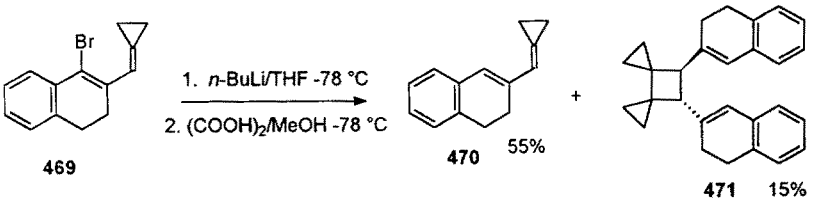
Scheme 66

However, the cyclodimer **471** is produced as a side-product during the preparation of the parent allylidenecyclopropane **470** from the corresponding 1-bromoallylidene derivative **469** by a metalation-protonation procedure (Scheme 67).

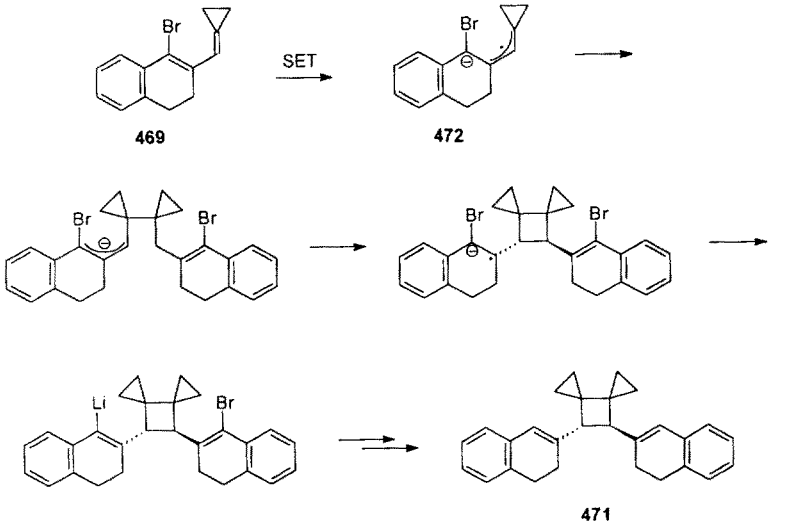
Therefore, it has been considered that the formation of the dimer involves a mechanism different to the simple head-to-head radical coupling of the parent monomer. As suggested by the authors, it is likely that the overall mechanistic sequence is initiated by the radical-anion **472** of compound **469** formed by a single electron transfer (SET) process, which is the first stage of the bromine-lithium exchange (Scheme 68) [128].

Albeit the transition metal catalysed reactions of methylenecyclopropane derivatives have already been thoroughly reviewed [2], it should be noted here that the cyclodimerization of these compounds can also be achieved by catalysis with Ni or Co complexes. The regioselectivity of the process is surprising and opposed to that of the thermal reaction, giving dispiro[2.1.2.1]octane derivatives (Scheme 69) [2].

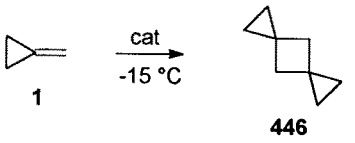
The process, which must involve initial π-bonding of the double bond of methylenecyclopropane to the metal, proceeds apparently via the intermediate



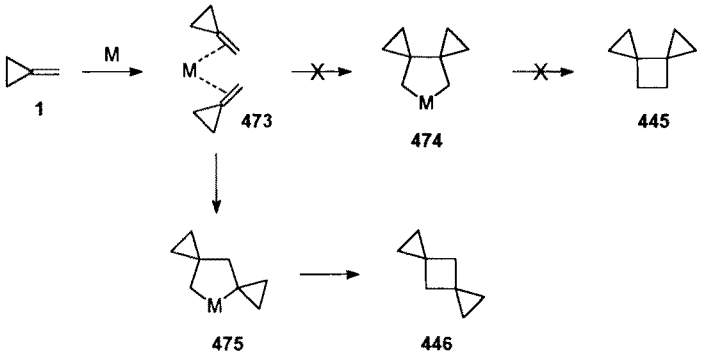
Scheme 67



Scheme 68



Scheme 69

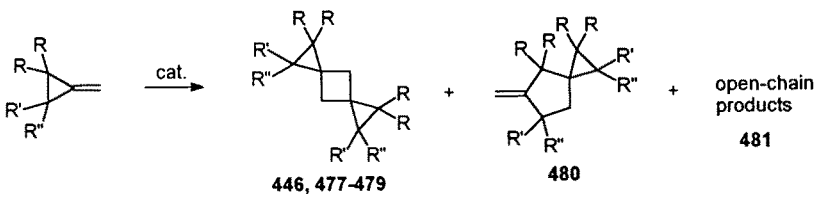


Scheme 70

475, instead of the expected **474**, probably due to steric reasons (Scheme 70) [129, 2].

Anyway, the catalysed process is not a clean one, generally also affording five-membered ring **480** and open-chain products **481**, as the result of the cyclopropane ring-opening of one or both the methylenecyclopropane addends (Table 37) [116, 130, 2].

Table 37. Metal catalysed dimerization of methylenecyclopropanes **1**, **250**, **345**, and **476**



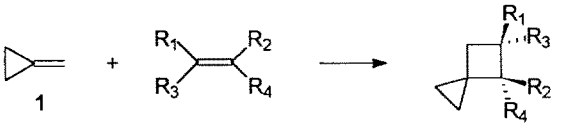
Entry	R	R′	R″	MCPs	Catalyst	Tot. yield%	Dispirooctane	Prod. ratio
1	H	H	H	**1**	$Ni(cod)_2$	50	**446**	20:80:0
2	H	CH_3	H	**476**	$Ni(cod)_2$	25	**477**	40:60:0
3	H	H	H	**1**	$Ni(cod)_2$/dialkyl fumarate	80	**446**	5:95:0
4	H	CH_3	H	**476**	$Ni(cod)_2$/dialkyl fumarate	85	**477**	11:89:0
5	H	CH_3	CH_3	**250**	$Ni(0)/PEt_3$	92	**478**	29:40:31
6	H	CH_3	CH_3	**250**	$Ni(0)/P(iPr)(tBu)_2$	86	**478**	76:5:19
7	CH_3	CH_3	CH_3	**345**	$Ni(0)/PEt_3$	86	**479**	21:0:79
8	CH_3	CH_3	CH_3	**345**	$Ni(0)/P(iPr)(tBu)_2$	82	**479**	0:0:100
9	CH_3	CH_3	CH_3	**345**	$Ni(0)/P(C_6H_{11})_3$	59	**479**	59:0:41

4.1.2 Codimerization

The reactivity of methylenecyclopropanes with olefins, as exemplified by the following examples, is also governed by subtle structural factors, which are able to steer the outcome of the reaction towards different products arising from alternative mechanistic pathways.

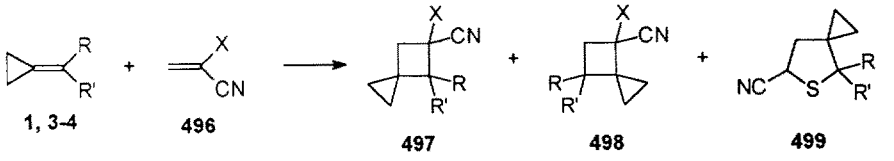
MCP (**1**) has been codimerized with several different types of compounds containing C=C double bonds (Tables 38, 39, and 40).

Table 38. [2 + 2] Cycloadditions of MCP (**1**)



Entry	R_1	R_2	R_3	R_4	Alkene	Conditions		Product	Yield (%) (diast. ratio)	Ref.
						T (°C)	t (h)			
1	F	F	F	F	**482**	175	12	**488**	56	131
2	H	H	O–CO–O		**483**	hν, 15	48	**489**	60	132a
3	Cl	Cl	O–CO–O		**484**	hν, 20	48	**490**	90	132b
4	H	H	NAc–CO–NAc		**485**	hν, −70	63	**491**	74	132b
5	H	H	CO–O–CO		**115**	hν, 20	48	**492**	50	132b
6	H(Me)	Me(H)	CO–O–CO		**137**	hν, 20	48	**493a, b**	71 (55:45)	132b
7	Me	Me	CO–O–CO		**486**	hν, 15	48	**494**	96	132b
8	Cl	Cl	CO–O–CO		**487**	hν, 15	48	**495**	77	132b

Table 39. [2 + 2] Cycloadditions of MCPs with capto-dative olefins **496**

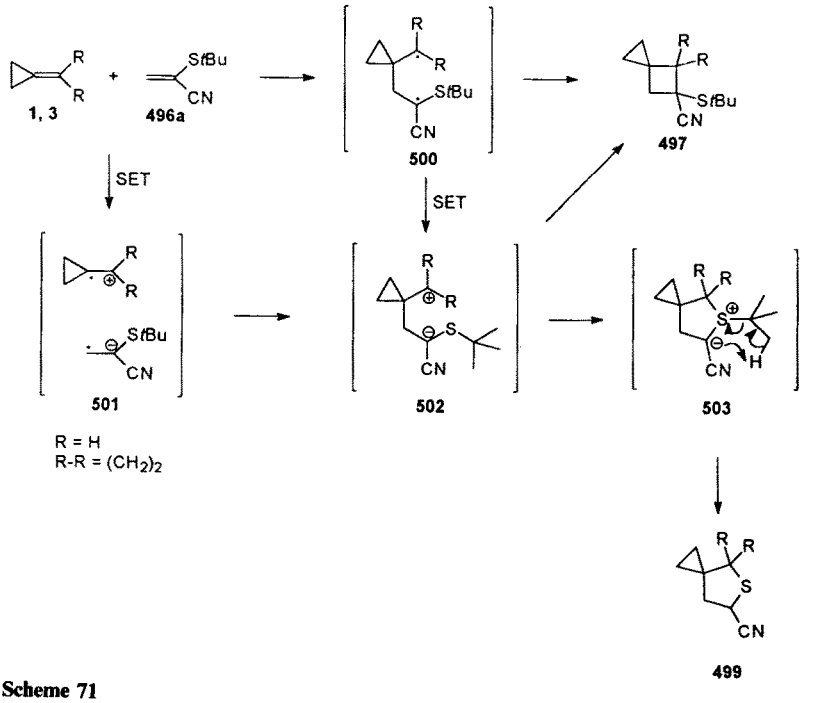


Entry	R	R'	MCP derivative	X	Alkene	Conditions		497 (%)	498 (%)	499 (%)
						T (°C)	t (h)			
1	H	H	**1**	S*t*Bu	**496a**	150	24	20		25
2	$(CH_2)_2$		**3**	S*t*Bu	**496a**	100	40	34		24
3	Cl	COOMe	**4**	S*t*Bu	**496a**	100	40	43	20	
4	H	H	**1**	SPh	**496b**				tars	
5	H	H	**1**	OMe	**496c**				tars	
6	H	H	**1**	$N[(CH_2)_2]_2O$	**496d**				tars	
7	$(CH_2)_2$		**3**	OMe	**496c**	130	96	59		
8	$(CH_2)_2$		**3**	$N[(CH_2)_2]_2O$	**496d**			tars		

The first [2 + 2] cycloaddition of methylenecyclopropane which has been reported involves the use of tetrafluoroethylene (**482**) (Table 38, entry 1) [131], an olefin having a high tendency to give cycloadditions in a [2 + 2] fashion, which are considered to occur in a two-step process involving diradical intermediates. In the same article, the author reports unsuccessful attempts to react methylenecyclopropane with maleic anhydride or acrylonitrile [131].

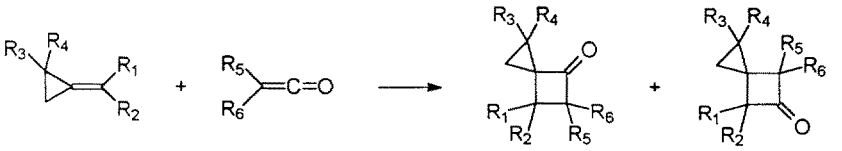
[2 + 2] Cycloadducts have been successively obtained by reaction of MCP with maleic anhydride (**116**) and a number of related electron-deficient alkenes (**137, 486, 487**) under photolytic conditions in the presence of a sensitizer (Table 38, entries 5–8) [132b]. Analogous cycloadditions in mild conditions with high yields have also been performed with electron-donor substituted alkenes, such as vinylene carbonates **483** and **484** and the imidazolinone **485** (entries 2–4) [132]. In the case of the unsymmetrical anhydride **137** (entry 6), an almost equimolar mixture of both the possible regioisomers has been obtained [132b]. In all these cases the reaction has also been proposed to occur via diradical intermediates formed from the reaction of **1** with the alkene in its excited triplet state [132].

Two other [2 + 2] cycloadditions on methylenecyclopropane have been carried out with particular alkenes. The first one is the reaction with the capto-datively substituted olefin **496a**, which affords the spirohexane cycloadduct **497a** in modest yields (Table 39, entry 1) [126]. The low yield is partially



Scheme 71

Table 40. [2 + 2] Cycloadditions of MCPs with ketenes **508–510**



Entry	MCPs	R_1	R_2	R_3	R_4	Ket.	R_5	R_6	Prod.	Yield (%)	Reg. ratio	Ref.
1	**1**	H	H	H	H	**508**	Me	Me	**511**		50:50	133
2	**250**	H	H	Me	Me	**508**	Me	Me	**512**	65	55:45	134
3	**504**	H	H	Me	Et	**508**	Me	Me	**513**	70	44:56	134
4	**3**	$(CH_2)_2$		H	H	**509**	H	Cl	**514**	63		13b
5	**3**	$(CH_2)_2$		H	H	**510**	Cl	Cl	**515**	59		13b
6	**505**	$(CH_2)_5$		H	H		Et, Ph, Cl				100:0	135
7		H, Me, Ph	Me, Ph	H	H		Et, Ph, Cl				100:0	135
8		H, Me, Ph, *c*-C_3H_5,	Me, Ph, *c*-C_3H_5, *p*-MeOPh	H	H	**510**	Cl	Cl		13–68	100:0	136
9	**453**	H	Br	H	H	**510**	Cl	Cl	**516**		100:0	137
10	**506**	H	$SiMe_3$	H	H	**510**	Cl	Cl	**517**		> 1	138
11[a]	**507a–c**	H	H	H	MMe_3	**510**	Cl	Cl	**518**	55–60	0:100	138

[a] M = Si, Ge, Sn

due to the parallel formation of an undesired product deriving from a formal loss of isobutene and possessing the structure of spiro(tetrahydrothiophene)-cyclopropane **499a**. An analogous result occurs from the reaction of the same capto-dative olefin **496a** with BCP (**3**) (entry 2). The rationale proposed for the outcome of these reactions is depicted in Scheme 71 [126].

The formation of the regular [2 + 2] cycloadducts **497** is explained by the usual route with the intervention of diradical intermediates **500**, which are also able to account for the observed regioselectivity. In order to explain the formation of the tetrahydrothiophene by-products **499**, a concurrent SET mechanism has been reasonably suggested, taking into account the electronic nature of the reacting olefins. The SET step could occur either at the level of the starting reactants or of the diradical intermediate **500**, leading to a radical-ion pair **501** and to a zwitterionic intermediate **502**, respectively. Finally, a preferred cyclization by attack of the more nucleophilic sulfur atom and loss of isobutene from **503** gives the ultimate spiroheptane by-products **499**. The same SET route could also be invoked for the formation of the [2 + 2] cycloadducts **497** by closure of the four membered ring at the level of the dipolar intermediate **502** [126]. The SET mechanism seems to be suppressed when the methylenecyclopropane **4** with two electron-withdrawing groups is employed; however, in this case the reported anomalous production of two regioisomers **497c** and **498c**, each one as a single diastereomer, has not been rationalized. The use of more rapidly dimerizing or less reactive capto-dative olefins **496b–d** is unsatisfactory, giving

rise to intractable mixtures, apart from the reaction of BCP (**3**) with the alkene **496c** (entry 7) [126].

The last [2 + 2] cycloaddition performed onto methylenecyclopropane itself consists of the use of ketene derivatives, particularly of dimethylketene **508** (Table 40, entry 1) [133]. The result is an almost equimolar mixture of the two possible regioisomers **511**, albeit no yield has been reported. Anyway, the particular reactivity of methylenecyclopropane was confirmed, since it was found to be around 15 times more reactive than isobutene [133]. The scarce regioselectivity of this cycloaddition was confirmed by the reactions of the same ketene **508** with 2,2-disubstituted methylenecyclopropanes (entries 2 and 3) [134]. BCP has also been shown to be reactive towards chloro-substituted ketenes **509** and **510**, affording the expected cycloadducts **514** and **515** in mild conditions (entries 4 and 5) [13b].

When methylenecyclopropanes substituted at the double bond were reacted, the cycloaddition turned out to be regiospecific, affording only the cyclobutanones α-spirocyclopropane substituted (entries 6–9) [2, 135–137]. The reaction with diphenylketene also furnished tetrahydronaphthalene derivatives [2, 135]. The reaction between dichloroketene (**510**) and methylenecyclopropanes mono or disubstituted at the double bond with alkyl, aryl, cyclopropyl, or bromine, invariably gave only the 5,5-dichlorospiro[2.3]hexan-4-one regioisomers (entries 8–9) [136, 137]. When a silyl group is the substituent at the *exo* double bond in methylenecyclopropane **506**, the reaction still gives the same regioisomer of **517** as the predominant product, but loses its specificity (entry 10) [138]. In contrast, when the metal subtituent (M = Si, Ge, Sn) is on the ring carbon atom (**507a–c**) the dichloroketene cycloaddition gains regiospecificity, affording only the opposite 4,4-dichlorospiro[2.3]hexan-5-ones **518a–c** as a mixture of diastereoisomers [138].

All these reactions can be interpreted on the basis of thermally allowed [π2s + π2a] cycloadditions considering the tendency of ketenes to react easily in an antarafacial fashion (Figure 5) and their very rare involvement in nonconcerted cycloadditions. However, the observed orientation of addition and the effect of the different substituents might imply that the transition states **A** and/or **B** are characterized by some degree of partial bonding which gives them a substantial dipolar character (Fig. 5), as suggested by Isaacs and Stanbury [133]. Such a type of transition state would be able to account for the regiospecificity found with methylenecyclopropanes substituted at the double bond [2, 135–137] with formation of the more stable TS **A** favored over its regioisomeric **B**, albeit steric factors cannot be ruled out.

The substitution of the exo-methylene hydrogen atoms of MCP with halogens seems to favor the [2 + 2] cycloaddition reaction by stabilizing the intermediate diradical. Indeed, chloromethylenecyclopropane (**96**) reacts with acrylonitrile (**519**) to give a diastereomeric mixture of spirohexanes in good yield (Table 41, entry 2) [27], but was unreactive towards styrene and *cis*-stilbene. Anyway, it reacted with dienes (2,3-dimethylbutadiene, cyclopentadiene, cyclohexadiene, furan) exclusively in a [4 + 2] fashion (see Sect. 2.1.1) [27], while its

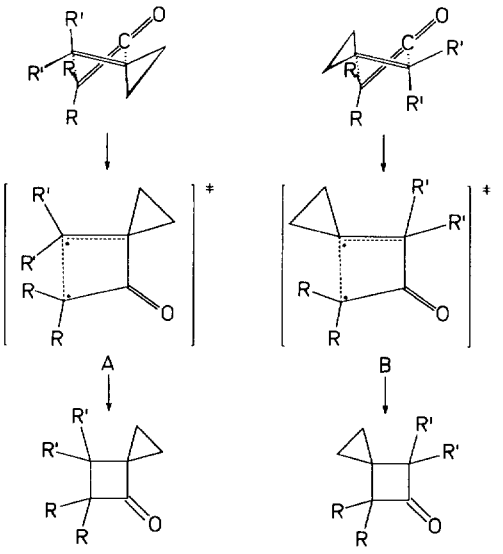
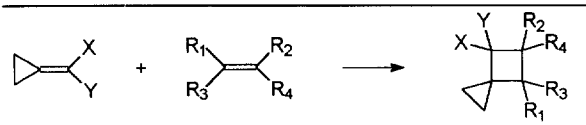


Fig. 5. Regioisomeric pathways in the [2 + 2] cycloaddition of ketenes to alkylidenecyclopropanes

Table 41. [2 + 2] Cycloadditions of 1'-halo-substituted methylenecyclopropanes **96**, **455** and **456**



Entry	X	Y	MCP	R1	R2	R3	R4	Alkene	Conditions		Product	Yield (%)	Ref.
									T (°C)	t (h)			
1	Cl	Cl	**455**	H	H	H	$CH{=}CH_2$	**12**	80	60	**521**	84	139
2	H	Cl	**96**	H	H	H	CN	**519**	196	2	**522**	85 (56:44)	27
3	F	F	**456**	H	H	H	$CH{=}CH_2$	**12**	110	168	**523**	42	9
4	F	F	**456**	H	H	CH_2	$CH{=}CH$	**6**	115	96	**524**	45	9
5	F	F	**456**	F	Cl	F	Cl	**520**	115	96	**525**	45	9

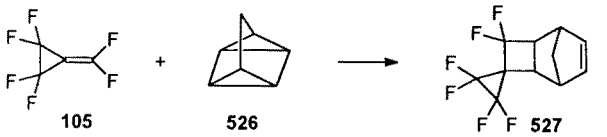
congener dichloromethylenecyclopropane (**455**) afforded with butadiene (**12**) only the [2 + 2] adduct (entry 1) [139]. Similarly, difluoromethylenecyclopropane (**456**) afforded with butadiene (entry 3) and even with cyclopentadiene (entry 4) exclusively the [2 + 2] cycloadducts **523** and **524**, albeit in low yield [9].

In contrast, perfluoromethylenecyclopropane (**105**) gave with butadiene and other dienes exclusively the [4 + 2] cycloadducts (see Sect. 2.1.2) [29]. Moreover, it failed to give any [2 + 2] cycloaddition, either with itself and with styrene or acrylonitrile at 150–175 °C. The only product formally deriving from

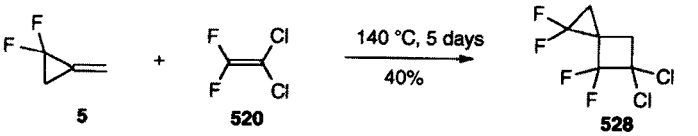
a [2 + 2] cycloaddition to norbornadiene is **527**, actually obtained from the reaction with quadricyclane (**526**) (Scheme 72) [29]. The report caused some confusion in the literature, since the paper erroneously described its formation as derived from the reaction with "quadricyclene" [29], albeit the author repeatedly affirmed that no [2 + 2] cycloaddition to perfluoromethylene was successful, and it has since been reported that "perfluoromethylenecyclopropane readily undergoes a [2 + 2] cycloaddition with quadricyclene" [27].

Finally, both difluoromethylenecyclopropane (**456**) (Table 41, entry 5) and its isomer 2,2-difluoro-methylenecyclopropane (**5**) (Scheme 73) gave a [2 + 2] cycloaddition with 1,1-dichloro-2,2-difluoroethylene (**520**), but the latter required more drastic conditions. Compound **5** reacted with dienes similarly to perfluoromethylenecyclopropane, affording exclusively [4 + 2] cycloadducts (see Sect. 2.1.1) [9].

The rationalization for the different behavior of the various substituted methylenecyclopropanes has been ascribed to the balance of three major factors connected with their reactivity: (1) exothermicity of double bond opening, (2) accommodation of the odd electrons on the potential biradical, and (3) ease of approach of reactants in formation of the initial new bond [139, 29]. All the methylenecyclopropane derivatives accommodate the first two factors, with increasing substitution and the presence of conjugating substituents on the reacting alkene favoring the [2 + 2] cycloaddition pathway. The comparison of reactivities of the fluorinated MCPs **5**, **105**, and **456** furnishes some elucidation. The behavior of difluoromethylenecyclopropane (**456**) is consistent with the general observation that fluorinated ethylenes are very poor dienophiles [140], but are reactive [2 + 2] addends [123]. The anomalous behavior of perfluoromethylenecyclopropane (**105**) and, partially, of 2,2-difluoromethylenecyclopropane (**5**) has been ascribed to the third factor, as a result of steric repulsion from the cyclopropane ring fluorine toward incoming cycloaddend at the site of initial bond formation [9, 29, 30, 141]. Finally, MCPs undergo thermal [2 + 2] cycloadditions mainly because of their highly strained double bonds. This



Scheme 72



Scheme 73

reactivity can be markedly enhanced by sterically modest radical-stabilizing substituents, but any geminal substituents on the ring carbons markedly decrease biradical [2 + 2] reactivity. Fluorine substituents on the vinyl carbon modestly increase [2 + 2] reactivity, while allylic fluorine substituents on the ring dramatically increase Diels-Alder reactivity, probably due to the strong inductive effect by the fluorine atoms [9].

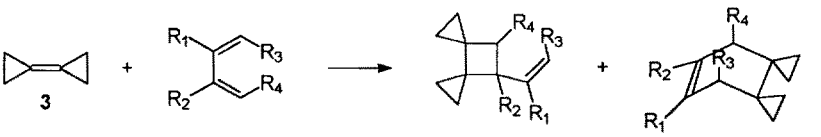
The cycloadditions of BCP to dienes are generally less selective, with the [2 + 2] to [4 + 2] ratio strongly depending on the diene structure (Table 42) [13].

Thus BCP seems to follow two competitive pathways in the cycloaddition with dienes: (i) a stepwise diradical process giving the [2 + 2] adduct, or (ii) a concerted pathway giving the [4 + 2] adduct. Accordingly, the proportion of the latter increases with the reactivity of diene in Diels-Alder reactions. Conversely, the reaction with 2,3-dicyanobutadiene (**529**), generated in situ by electrocyclic ring-opening of 1,2-dicyanocyclobutene [142], furnishes selectively the [2 + 2] cycloadduct **530** (Table 42, entry 4) due to the presence of substituents able to stabilize the diradical intermediate [13b].

BCP is unreactive towards electron-rich olefins, but reacts smoothly with a series of electron-deficient alkenes (Table 43) [13b, 143].

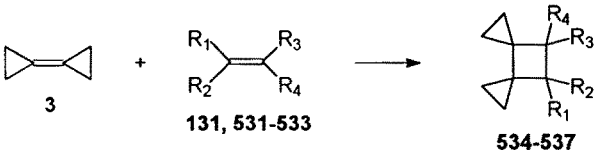
The cycloadditions in entries 1–3 are still believed to occur via a diradical stepwise pathway, as confirmed by obtaining a thermodynamic 78:22 *trans/cis* mixture of dispirooctanes **536** from *trans*-dicyanoethylene (**533**) (entry 3) [13b, 143]. The cycloaddition to tetracyanoethylene (**131**) in the absence of oxygen gives only low yields of the [2 + 2] adduct, due to the simultaneous formation of products **542** and **543** (Scheme 74) [13b]. Still, the formation of the cyclobutanes **537** and **542** is noteworthy, since the reactions of TCNE with phenyl substituted MCPs exclusively afford methylenecyclopentane derivatives [37, 144]. The reaction is thought to occur via dipolar intermediates **539–541** formed after an initial SET process (Scheme 74) [13b]. The occurrence of intermediates **540** and **541** has been confirmed by trapping experiments [13b].

Table 42. Cycloadditions of BCP (**3**) with dienes **6, 12, 26,** and **529**

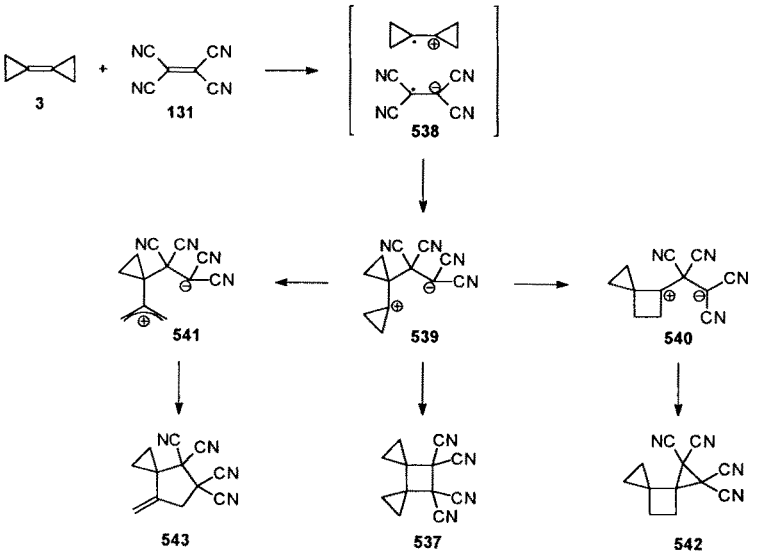


Entry	R_1	R_2	R_3	R_4	Diene	Conditions		Products		Yield (%)	Ratio
						T (°C)	t (h)	[2 + 2]	[4 + 2]		
1	H	H	H	H	**12**	180	12	**31**	**32**	54	92:8
2	H	H	CH_2		**6**	150	10		**28**	16	0:100
3	H	H	$(CH_2)_2$		**26**	170	11	**29**	**30**	50	78:22
4	CN	CN	H	H	**529**	140	8	**530**		28	100:0

Table 43. [2 + 2] Cycloadditions of BCP (3) with electron-deficient alkenes **131**, and **531–533**



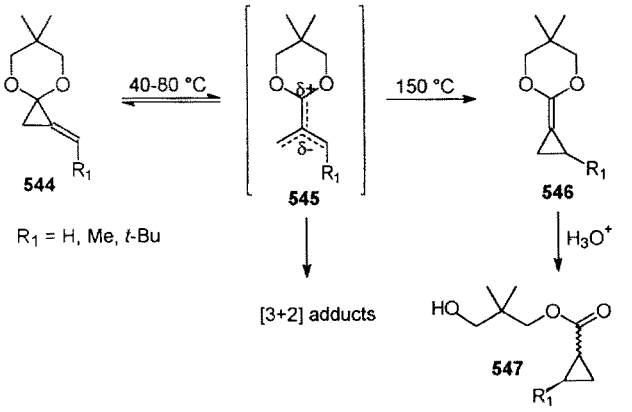
Entry	R_1	R_2	R_3	R_4	Alkene	Conditons		Product	Yield (%)	Diast. ratio
						T (°C)	t (h)			
1	H	Cl	Cl	Cl	**531**	180	96	**534**	18	
2	H	H	H	CN	**532**	190	2	**535**	98	
3	H	CN	CN	H	**533**	190	2	**536**	57	78:22
4	CN	CN	CN	CN	**131**	60	0.5	**537**	18	



Scheme 74

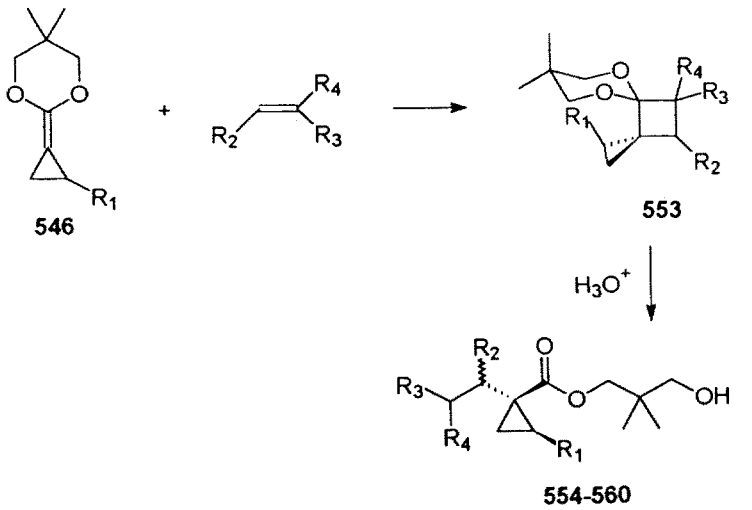
Very recently, [2 + 2] cycloadditions with alkenes activated by electron-with drawing groups have been performed on the double bond of methylenecyclopropanes exo-substituted with two electron-donating groups, e.g., dimethyleneketene acetals **546** (Scheme 75, Table 44) [145].

Dimethyleneketene acetals **546** are easily available by a thermolytic rearrangement of methylenecyclopropanone ketals **544**, in turn prepared from the corresponding cyclopropenone ketals [146a]. The thermolysis is a two-step process, involving the reversible formation of a dipolar TMM intermediate **545** [146b], followed by the irreversible production of stable **546** at higher temperature (Scheme 75) [145].



Scheme 75

Table 44. [2 + 2] Cycloadditions of ketene acetals **546**

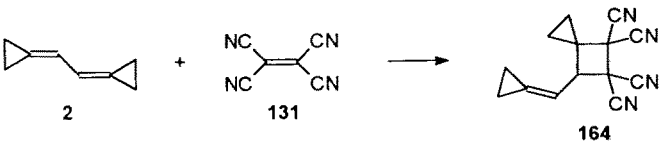


Entry	R_1	MCP	R_2	R_3	R_4	Alkene	Conditions		Product	Yield
							T (°C)	t (h)		(%)
1	H	**546a**	H	H	COOMe	**56a**	rt	12	**554**	54
2	H	**546a**	CH_2CH_2CO		H	**122**	40	23	**555**	56
3	H	**546a**	Me	COOEt	COOEt	**548**	rt	7	**556**	94
4	H	**546a**	Ph	CN	CN	**549**	rt	2	**557**	91
5	H	**546a**	COOMe	H	COOMe	**550**	40	1	**558a**	98 (0:100)[a]
6	H	**546a**	COOMe	COOMe	H	**551**	40	3	**558b, a**	81 (17:83)[a]
7	Me	**546b**	Ph	CN	CN	**549**	rt	4	**559**	91
8	H	**546a**		C_{60}		**552**	rt	20	**560**	67(67,100)[b]

[a] Diastereomeric ratio
[b] Yields of the two steps

Compounds **544** had previously been employed for the thermal [3 + 2] cycloaddition to C=C [146] and C=O [147] double bonds via the occurrence of intermediates **545**. Dimethyleneketene acetals **546** undergo acidic hydrolysis to the corresponding carboxylic esters **547** with some degree of selectivity (Scheme 75) [145]. Moreover, they are able to undergo [2 + 2] cycloadditions with electron-deficient alkenes **56a, 122,** and **548–551** at room temperature or by heating at 40 °C (Table 44, entries 1–7) [145]. Since the adducts **553** give, under acidic hydrolysis, the carboxylic esters **554–560**, rather than the expected spirohexanones, the whole reaction sequence has been utilized for the synthesis of the formal Michael addition products **554–560** of the ketene acetals **546** to the reacting olefins, a reaction type previously unavailable (Table 44) [145]. The cycloadducts **553** have been only spectroscopically characterized without isolation, since hydrolytically unstable, except in the case of the adducts of Buckminster-fullerene C_{60} (**552**) (entry 8) and to an alkyne derivative (see Sect. 4.2). The reactions of **546a** with dimethyl fumarate (**550**) and maleate (**551**) (entries 5 and 6) indicated that the [2 + 2] cycloaddition proceeds in a stepwise manner. Indeed, while the former reaction took place stereospecifically, the latter provided a cis/trans mixture, with the amount of trans isomer increasing with the heating time. The example in entry 7 shows that the cycloaddition occurs completely stereoselectively, with the reacting alkene approaching the ketene acetal exclusively from the face of the double bond *anti* with respect to the substituent on the cyclopropane ring, according to the 1,3-dipolar cycloadditions to substituted MCPs (see Sect. 3.1.3). This stereochemical information is maintained in the successive hydrolysis product **559**. The cycloaddition to fullerene C_{60} **552** (Table 44, entry 8), which occurs with perispecificity and regiospecifically on a 6,6-juncture, is remarkable not only for the chemical and biological relevance of fullerene derivatives, but also for highlighting once again the crucial dependence of MCPs reactivity on their strain. Indeed, the corresponding nonstrained equivalent *O*-TMS ketene acetal of methyl isobutyrate is completely inert towards C_{60} even under high pressure (9 Kbar) [145].

Other sporadic examples of [2 + 2] cycloadditions of olefins on the exo double bond of structurally more complex MCPs, such as methylenecyclopropenes, allylidene-, and alkenylidenecyclopropanes, have been reported. Thus, dicyclopropylideneethane (**2**) reacted with TCNE (**131**) to give the [2 + 2] adduct **164** as a minor product, together with the prevalent [4 + 2] adduct **163** (Scheme 76) [39]. The same reaction in a different solvent had been previously reported to furnish exclusively the Diels-Alder product (see Sect. 2.1.2) [5].



2 131 164

Scheme 76

Compound **561**, albeit inert towards dimethyl acetylenedicarboxylate, also reacted promptly with TCNE to give the spirohexene derivative **562** (Scheme 77) [148].

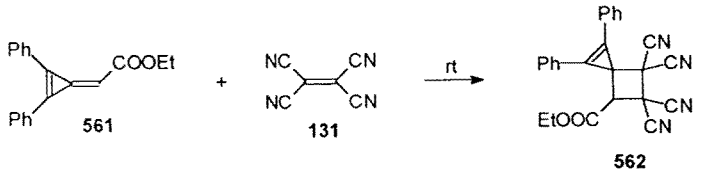
Two alkenylidene derivatives **149** and **563** have been reacted with several electron-deficient alkenes (Table 45) [36, 149].

The allene **149** gave by reaction with maleic anhydride (entry 1) and *N*-phenylmaleimide (entry 2) the [2 + 2] adducts **155a, b** as mixtures of two diastereoisomers [36]. Nevertheless, their chemical yield was very low and competitive reactions, mostly [4 + 2] cycloadditions on a rearranged allylidenecyclopropane and on a primary 1 : 1 adduct derived from an ene reaction (see Sect. 2.1.2), prevailed. Allenes **149** and **563** cycloadded to tetracyano- and 1,1-bistrifluoromethyl-2,2-dicyanoethylene (Table 45, entries 3–6) also selectively at the cyclopropyl substituted double bond in order to remove most of the ring strain [149a].

Complete regio- and stereoselectivity have also been reported for the cycloaddition of the same allene **563** to dichlorodifluoroethylene (entry 7) [149b], with a proposed stepwise mechanism initiated by a radical attack of the alkene on the face of the C1-C4 double bond opposite to the phenyl group, which is consistent with the high degree of facial selectivity exhibited by **563** in other reactions [150]. The intermediate diradical should then collapse to the final product before extensive inversion and rotation around C–C bonds. This reaction also gave 32% of **570** as a by-product, which was produced quantitatively by increasing the reaction temperature (Scheme 78) [149b]. Its formation is accounted for by a preliminary thermally induced rearrangement of **563** to the dimethylenecyclopropane **571** via TMM diradicals [151], followed by [2 + 2] cycloaddition of the alkene **520** on the less hindered double bond of **571** *anti* to the phenyl. According to the observed reactivity of MCP (**1**), the alkenylidenecyclopropane **563** did not react with maleic anhydride, giving on heating exclusively the rearranged **571** [36].

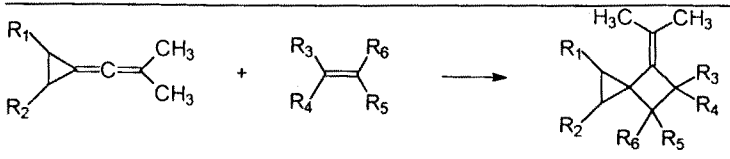
As in the case of dimerizations, MCP derivatives are known to undergo metal-catalysed [2 + 2] codimerizations with other alkenes in a few cases [2]. The examples are limited to strained olefins, such as norbornadiene (**572**) (Scheme 79) [152] and cyclobutene (**574**) (Scheme 80) [153], and to alkyl acrylates (Table 46) [154] and always compete with the alternative [3 + 2] addition of TMM species.

Catalysis by nickel is essential for the formation of [2 + 2] adducts via nickelacyclopentane intermediates [129], since the use of palladium invariably

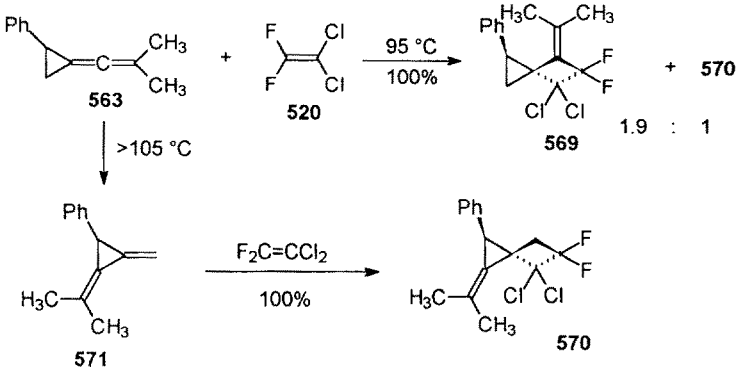


Scheme 77

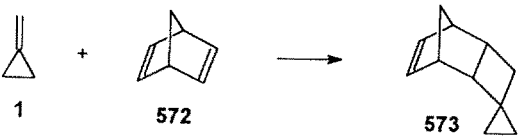
Table 45. Cycloadditions of alkenylidenecyclopropanes **149** and **563**, with electron-deficient alkenes



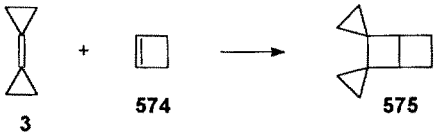
Entry	R_1	R_2	MCP	R_3	R_4	R_5	R_6	Alkene	Conditions		Product	Yield (%)	Ref.
									T (°C)	t (h)			
1	$(CH_2)_4$		**149**	H	COOCO		H	**115**	160	48	**155a**	15 (4:1)	36
2	$(CH_2)_4$		**149**	H	CONPhCO		H	**116**	160	30	**155b**	< 10 (2 diast.)	36
3	$(CH_2)_4$		**149**	CN	CN	CN	CN	**131**			**565**		149a
4	$(CH_2)_4$		**149**	CN	CN	CF_3	CF_3	**564**			**566**		149a
5	H	Ph	**563**	CN	CN	CN	CN	**131**			**567**		149a
6	H	Ph	**563**	CF_3	CF_3	CN	CN	**564**			**568**	(2 diast.)	149a
7	H	Ph	**563**	F	F	Cl	Cl	**520**	95	312	**569**	60	149b



Scheme 78

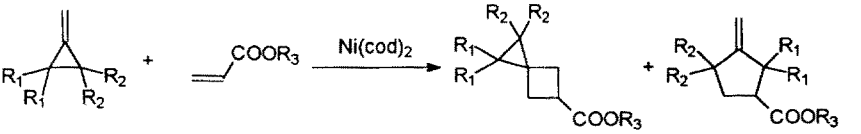


Scheme 79



Scheme 80

Table 46. Metal-catalysed cycloadditions of methylenecyclopropanes **1**, **250** and **345** to alkyl acrylates **56a** and **576**



Entry	R_1	R_2	MCP	R_3	Acrylate	Yield	Spirohexane (%)	Methylene-cyclopentane	Ratio
1	H	H	**1**	Me	**56a**	90		**580**	0:100
2	H	Me	**250**	Me	**56a**	67	**577**	**581**	18:82
3	H	Me	**250**	*t*Bu	**576**	71	**578**	**582**	40:60
4	Me	Me	**345**	Me	**56a**	75	**579**		100:0

gives only the [3 + 2] addition [2, 155]. Substitution on the cyclopropane ring is also important, since unsubstituted and monosubstituted MCPs gave only the [3 + 2] addition, while di- and tetrasubstituted derivatives also gave [2 + 2] adducts, whose amount increased with increasing the number of substituents (Table 46) [154].

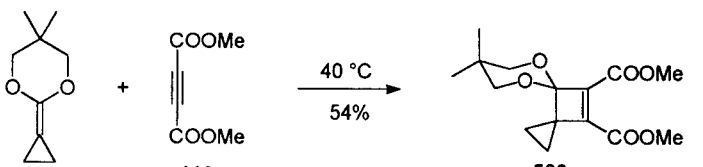
In the case of dimethylmethylenecyclopropane (**250**) (entries 2 and 3) a mixture of cis and trans spirohexanes was formed, but the reaction was in all cases completely regioselective.

4.2 [2 + 2] Cycloadditions to C≡C Bonds

Only rare examples of [2 + 2] cycloadditions involving MPCs and C≡C triple bonds have been reported. As already mentioned, the dimethyleneketene acetal **546a** reacted with dimethyl acetylenedicarboxylate (**113**) to give a stable adduct **583** with respect to hydrolysis, which could be isolated (Scheme 81) [145].

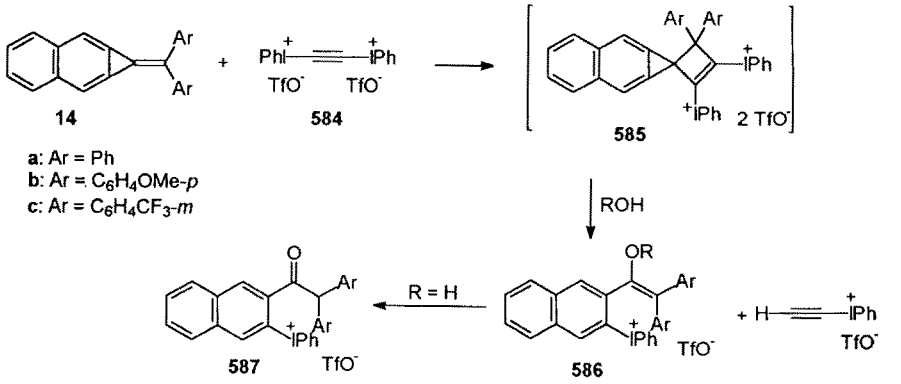
Diarylmethylenecyclopropa[*b*]naphthalenes **14**, unlike their benzene parent counterparts which give cycloaddition reactions at the "cyclopropene" bridge bond [10a], react on the exo double bond in Diels-Alder cycloadditions (see Sect. 2.1.1) [10b]. The reactions of **14** with the highly electron-deficient acetylenic(phenyl)iodonium triflate **584** give products **586a** and **587**, which are believed to derive from unstable primary [2 + 2] cycloadducts **585** (Scheme 82) [10b].

Finally, alkenylidenecyclopropanes **175** and **563** have been found to be reactive towards activated acetylenes **113** and **588** (Table 47) [156]. Several features of these reactions are remarkable. The reaction never gives cyclopropane ring-opened products and is highly regioselective with respect to both the cycloaddends: only in one case (entry 1) an attack on the double bond far from the cyclopropane ring occurs to give **593**, and attack of the unsymmetrical alkyne **588** gives only one of the possible regioisomers. Formation of spiroproducts **589–592** is favored by the higher relief of ring strain. With the monosubstituted alkenylidenecyclopropane **563** only one diastereoisomer **591** is formed in the reaction with **113**, that resulting from the attack on the face *anti* to the phenyl substituent, while the related adduct **592a** was again the prevalent one from **588** [156].



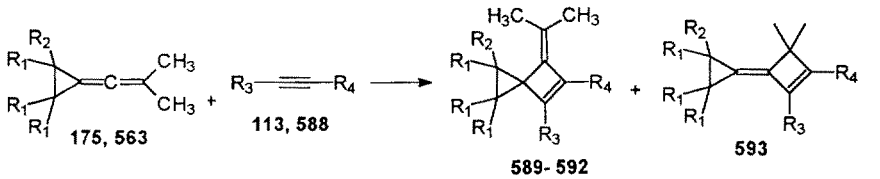
546a 113 583

Scheme 81



Scheme 82

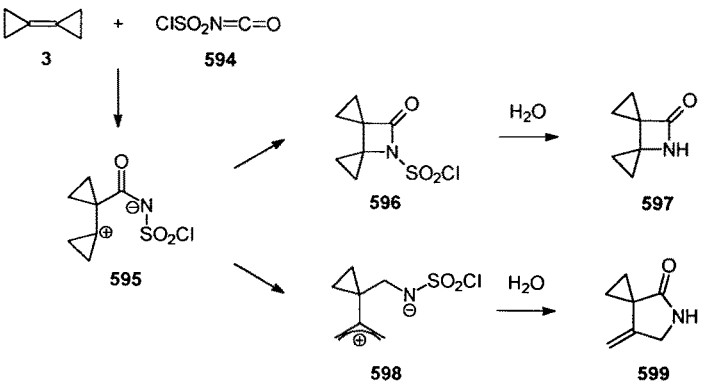
Table 47. [2 + 2] Cycloadditions of alkenylidenecyclopropanes **175** and **563** with alkynes **113** and **588**



Entry	R_1	R_2	MCP	R_3	R_4	Alkyne	Conditions T (°C)	t (h)	Yield (%)	Products	Ratio
1	Me	Me	**175**	CO_2Me	CO_2Me	**113**	90	19	43	**589, 593**	65:35
2	Me	Me	**175**	CN	Cl	**588**	70	12	33	**590**	100:0
3	H	Ph	**563**	CO_2Me	CO_2Me	**113**	100	29	39	**591**	100:0 (1 diast.)
4	H	Ph	**563**	CN	Cl	**588**	80	20	62	**592a, b**	100:0 (2 diast., 61:39)

4.3 [2 + 2] Cycloadditions to C=X Bonds

The only successful [2 + 2] cycloaddition reported so far involving an MCP derivative and a carbon-heteroatom double bond is the reaction of BCP (**3**) with chlorosulfonylisocyanate (CSI) (**594**) [13b, 143]. CSI is a typical [2 + 2] cycloaddend with most alkenes, but has been demonstrated to be also involved in stepwise cycloadditions via polar intermediates [157]. The reaction of BCP and CSI gives the [2 + 2] cycloadduct **596** only as a minor product, besides the major [3 + 2] adduct **599** (Scheme 83) [13b, 143]. Therefore, it has been reasonably suggested that both products derive from a common dipolar intermediate **595**, formed by nucleophilic attack of BCP on the electron-deficient carbon of CSI (Scheme 83) [13b].



Scheme 83

The formation of the β-lactam derivative **597** remains an isolated case. For example, several alkenylidenecyclopropanes react with CSI and toluenesulfonylisocyanate, but [2 + 2] adducts are formed only by attack on the double bond not linked to the cyclopropane ring; when this bond is attacked only products derived from cyclopropane ring opening are formed [158].

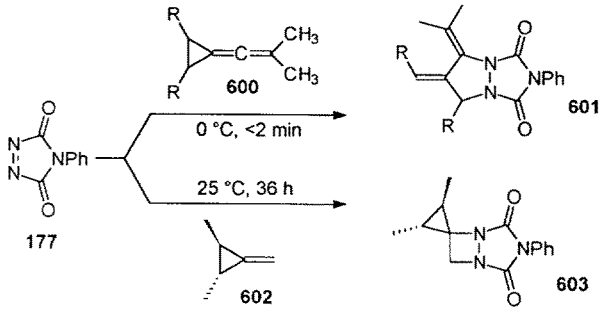
4.4 [2 + 2] Cycloadditions to X=Y Bonds

The N=N double bond of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**177**) is undoubtedly the most studied heteroatom-heteroatom multiple bond involved in reactions with MCPs.

PTAD reacts with MCP derivatives in a variety of modes of addition to C=C double bonds, depending on the structural features of the reacting MCPs. For example, it reacts with allylidene- and benzylidenecyclopropanes giving [4 + 2] cycloadditions (see Sect. 2.1.2), with alkylidenecyclopropanes giving ene reactions [44], and with BCP giving products probably deriving from an initial [2 + 1] cycloaddition (see Sect. 5.2) [13b].

PTAD reacts very rapidly with alkenylidenecyclopropanes **600** attacking only the cyclopropylidene substituted double bond, but exclusively with ring-opening giving [3 + 2] cycloadducts **601** (Scheme 84) [44, 159]. Finally, it gives the [2 + 2] adduct **603** by reaction with 2,3-trans-dimethylmethylenecyclopropane (**602**), albeit reacting much more slowly (Scheme 84) [44, 159b].

The only other X=Y bond involved in additions to MCP derivatives is the S=O double bond of sulfur trioxide. Actually, the reactions of MCP (**1**) and BCP (**3**) with SO_3 afford exclusively the γ-sultones **608** and **609** (Scheme 85) [160], formal products of [3 + 2] additions of TMM species to S=O double bond. However, by analogy with larger methylene- and cycloalkylidenecycloalkane derivatives which give stable β-sultones at low temperature, it is presumed that



Scheme 84

Scheme 85

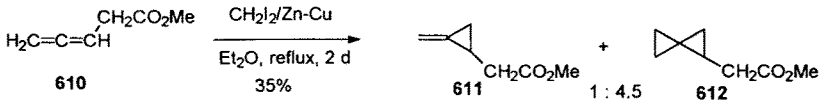
the initial products are unstable spirocyclopropane-β-sultones **604** and **605** formed by [2 + 2] addition, which isomerize to dipolar species **606** and **607** that eventually give the final products **608** and **609** (Scheme 85) [160].

5 Three-Membered Ring

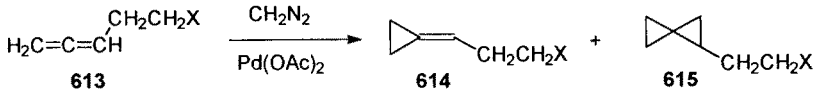
5.1 Carbene (or Carbenoid) Additions

The earlier examples of [2 + 1] cycloaddition of a carbene (or carbenoid) on the double bond of alkylidenecyclopropanes to yield spiropentane derivatives were observed as undesired side reactions in the synthesis of alkylidenecyclopropanes through the addition of a carbene to a substituted allene [161]. In some cases the spiropentane derivative was obtained as the major product [161a, c] especially when a large excess of the carbene reagent was used. For example, when methyl 3,4-pentadienoate (**610**) was treated with a ten-fold excess of methylene iodide and zinc-copper couple the two products **611** and **612** were isolated in 1:4.5 ratio (Scheme 86) [161a].

Diazomethane in the presence of palladium acetate gave with allenes **613** a similar mixture of methylenecyclopropanes **614** and spiropentanes **615**. In contrast to Simmons-Smith reagent, diazomethane prefers to add to the less substituted allenic double bond (Scheme 87) [162].

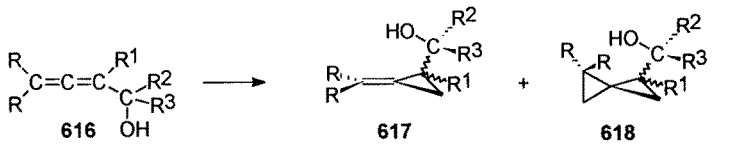


Scheme 86



X = OH, Br, OAc, OTs

Scheme 87



Scheme 88

The cyclopropanation of α-allenic alcohols **616** gave methylenecyclopropanes **617a, b** and spiropentanes **618a, b** in different proportions depending on the carbenoid reagent used (Scheme 88) [163, 4b].

The use of an excess (3 equivalents) of the Simmons-Smith reagent gave exclusively the spiropentane derivatives **618** in 60–70% yield [163a]. In contrast, not even trace amounts of these products were observed by using samarium-dihalomethane as the carbene source [4b].

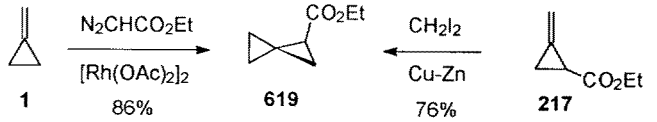
The use of carbene additions to MCP derivatives has lately become a general strategy for obtaining spiropentanes and higher spiranic triangulanes.

The rhodium acetate catalyzed addition of ethyl diazoacetate to MCP (**1**) gave spiropentane **619** in high yield (Scheme 89) [6e]. The same compound **619** was obtained in lower yield by a Simmons-Smith reaction to methylenecyclopropane **217** [164].

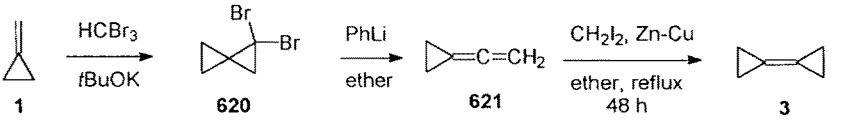
Gem-dibromospiropentane (**620**), obtained by the reaction of MCP with dibromocarbene, was used in the synthesis of BCP (**3**) (Scheme 90) [6a]. The reaction of the intermediate vinylidenecyclopropane **621** with a large excess of Simmons-Smith reagent gave exclusively BCP (**3**), but using modified Simmons-Smith procedures the [3]-triangulane (**247**) was also obtained in small yield (Scheme 91) [165].

The same triangulane **247** was also obtained by direct cyclopropanation of methylenecyclopropane **461** (Scheme 92) [166].

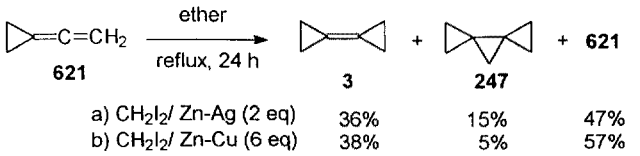
Thermally generated perchlorovinyl carbene **623** reacted with MCP (**1**) to give the spiropentane derivative **624** in modest yield (Scheme 93) [167].



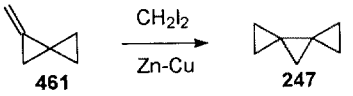
Scheme 89



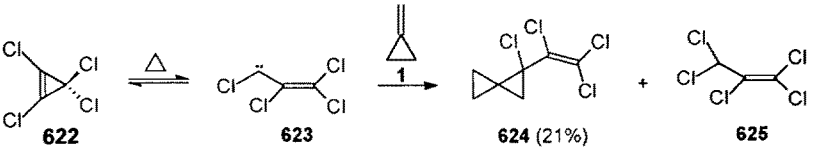
Scheme 90



Scheme 91



Scheme 92



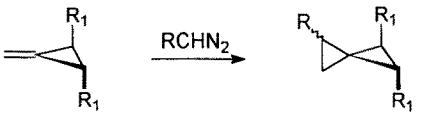
Scheme 93

Several optically active spiropentanes were obtained by carbene addition to chiral methylenecyclopropanes (Table 48) [168, 169].

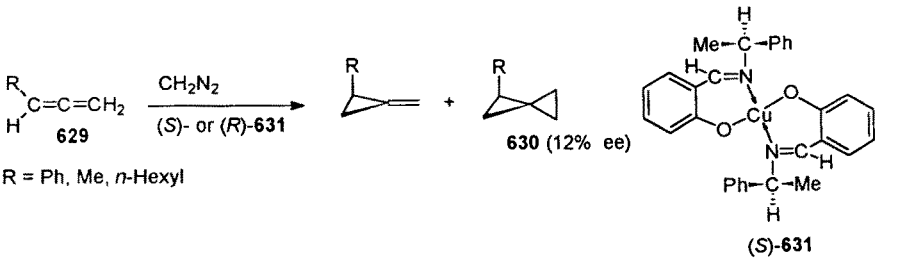
An asymmetric synthesis of the spiropentanes **630**, albeit with low enantiomeric excess, was achieved by the reaction of allenes **629** with diazomethane in the presence of an optically pure copper (II) chelate complex (*R*) or (*S*)-**631** (Scheme 94) [170].

Fitjer and Conia have synthesized the unbranched [3]- **247** and [4]-triangulane **632** and tricyclopropylidene ([3]-rotane, **633**) starting from BCP (**3**) (Scheme 95) [171]. The reaction of BCP (**3**) with the *N*-nitrosourea **245** is related to the analogous reaction with MCP (**1**) reported to give the pyrazoline [3 + 2] adduct (see Sect. 3.1.2).

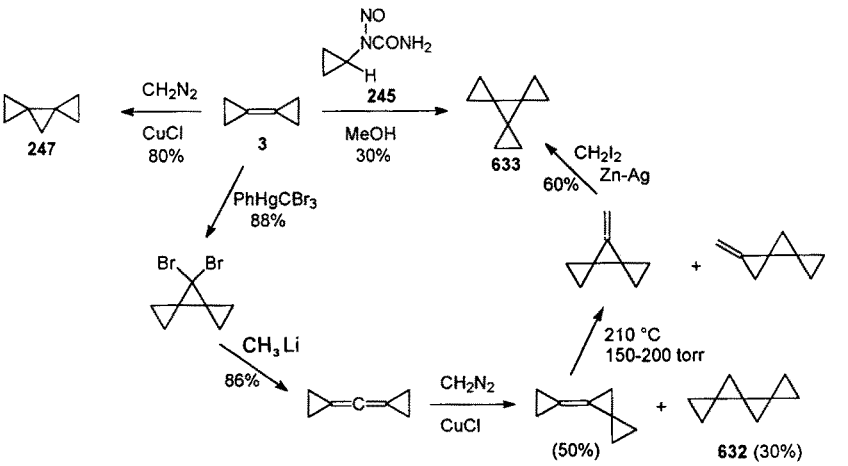
Table 48. Carbene additions to optically active methylenecyclopropanes



Entry	R_1	MCP	R	Products	Yield %
1	Me	(−)-**602**	H	(+)-**626**	35
2	COOMe	(−)-**216**	COOEt	(+)-**627a**, (+)-**627b**	60
3	COOMe	(+)-**216**	H	(−)-**628**	65

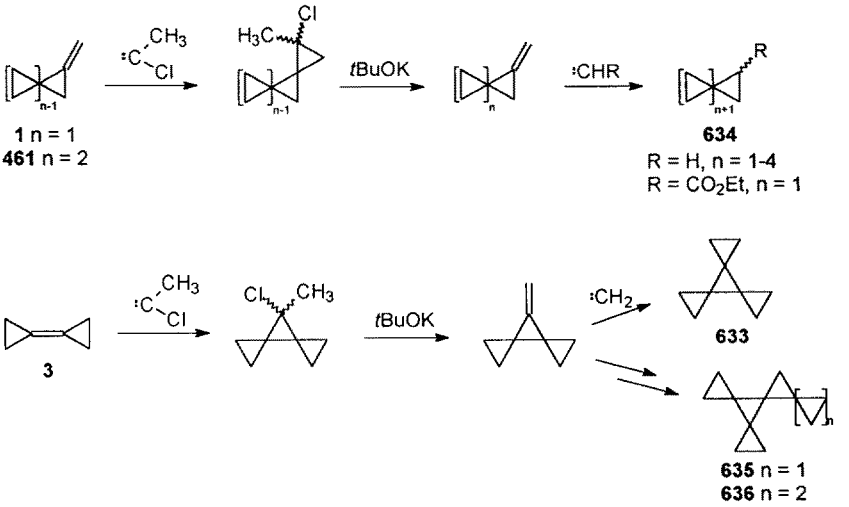


Scheme 94



Scheme 95

The synthetic procedure described by Arora and Binger [1b] to prepare **461** was extensively applied to the synthesis of unbranched **634** [172, 6e] and branched **633**, and **635**−**636** [173, 172b] triangulanes. The sequence is based on the addition of a chloromethyl carbene to an appropriate methylenecyclo-



Scheme 96

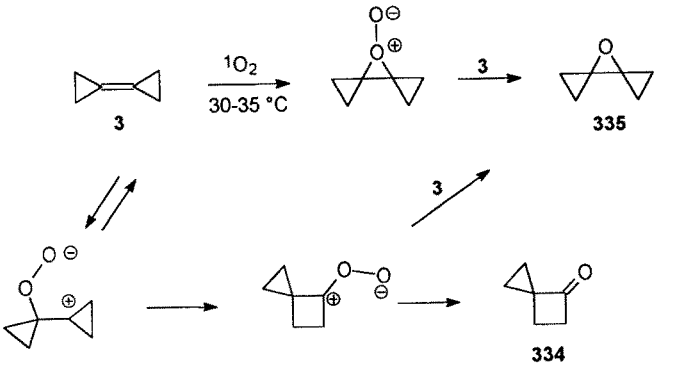
propane followed by dehydrochlorination with *tert*-butoxide and final cyclopropanation of the resulting methylenetriangulane (Scheme 96).

New procedures, in addition to the previous one, were developed to obtain higher branched triangulanes [174].

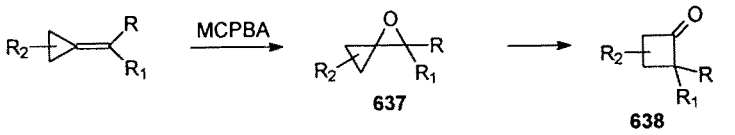
5.2 Heteroatom Additions

Methylenecyclopropanes are rather sluggish towards singlet oxygen oxidations [175, 13b], and common epoxidation with peracids also proceeds much more slowly than that of methylenecycloalkane homologues [176]. The rate of epoxidation has been correlated to π-orbital energies, implying that the scarce reactivity of MCP (**1**), and its derivatives, is due to the scarce interaction of LUMO of $^1O_2$ with the low lying HOMO of **1** [176]. For this reason BCP (**3**) behaves in a markedly different way with respect to MCP (see Sects. 2.1.1, 2.2.1, 3.1.3, 3.1.4, 4.1, 4.2), reacting readily with photochemically generated singlet oxygen at 30–35 °C (Scheme 97) [13b]. A 6:10 mixture of spiroheptanone **334** and bicyclopropylidene epoxide **335** (see Sect. 3.1.4) was obtained in these conditions. It is interesting to note that MCP did not react under these conditions, neither did BCP with $^3O_2$ [13b].

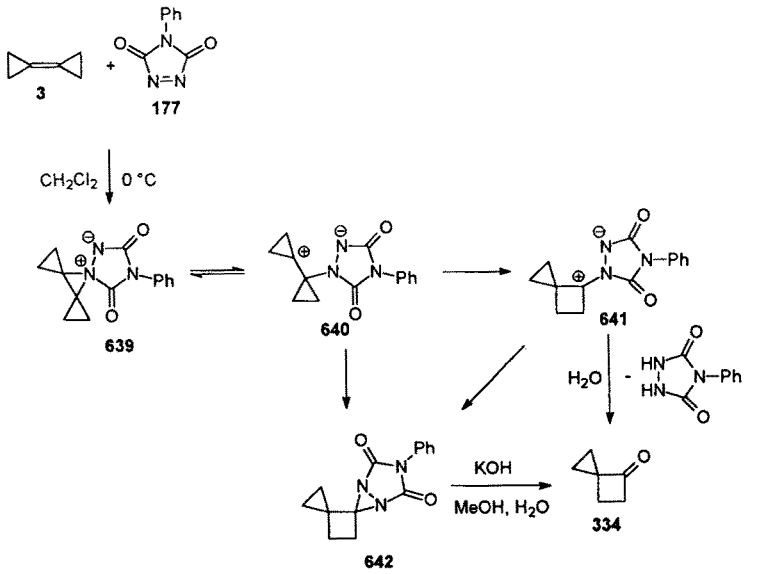
The same epoxide **335** was easily obtained in mild conditions (0 °C, 5 min) by *m*-chloroperbenzoic acid oxidation [13b]. Epoxidation of alkylidenecyclopropanes by *m*-chloroperbenzoic acid has been greatly exploited as a route to the synthesis of cyclobutanones **638** via the well known ring expansion of oxaspiropentanes **637** (Scheme 98) [176, 177, 8].



Scheme 97



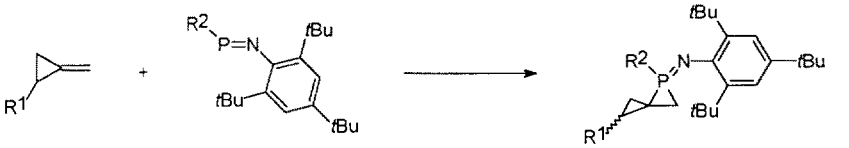
Scheme 98



Scheme 99

Two [2 + 1] additions of heteroatoms other than oxygen to MCP derivatives have been reported.

The first one regards the addition of a nitrogen atom of PTAD (**177**) to BCP (**3**), giving an aziridinium cation adduct, which is only postulated as intermedi-



1 R_1 = H
285 R_1 = Ph

643 R_2 = Et
644 R_2 = Me

Et_2O, rt, 12 h
n-hexane, rt, 3 d

645 46%
646 60:25:15

Scheme 100

ate in the formation of the final product of the reaction **642** or **334** (Scheme 99) [13b]. When the reaction is carried out in CH_2Cl_2 the only product formed in 83% yield is **642**, which is believed to derive from the dipolar intermediate **640**, in analogy to the cycloaddition of TCNE to BCP (see Sect. 4.1.2). Alkaline hydrolysis of **642** gives the spirohexanone **334**. This product is the only one formed (76% yield) when the reaction is carried out in wet acetone, via intermediate **641** formed by a cyclopropylmethyl to cyclobutyl rearrangement (Scheme 99).

The only reported example of [2 + 1] cycloaddition to methylenecyclopropanes involving phosphorus consists in the addition of iminophosphanes **643** and **644** to **1** and **285**. The reaction was carried out at room temperature, and readily gave iminophosphaspiro[2.2]pentanes **645** and **646** in moderate yields (Scheme 100) [178]. The major diastereoisomer of **646** selectively crystallized (38% yield) from the reaction mixture and its structure was confirmed by X-ray analysis [178]. This diastereoisomer derived from the attack of the exocyclic double bond by phosphorus on the opposite side of the phenyl substituent.

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Selective Transformations of Small Ring Compounds in Redox Reactions

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Reductive and oxidative transformations of small ring compounds form the basis of a variety of versatile synthetic methods which include functionalization and carbon skeleton construction. Redox mechanisms of organotransition metal compounds play an important role in inducing or catalyzing specific reactions. Another useful route in this area is based on one-electron redox reactions. The redox tautomerism of dialkyl phosphonate also contributes to the efficiency of the reductive transformation of small ring compounds. This review summarizes selective transformations which have a high potential for chemical synthesis.

1 Introduction

Strained small ring compounds are useful in providing carbon-skeleton building blocks via ring cleavage or enlargement, which is of synthetic potential as described in the previous volumes of this series. From this point of view, various methods have been developed for selective ring transformations, including nucleophilic and electrophilic ones [1, 2].

Such manipulation mostly depends on the characteristics of the ring structures and their functional groups. It might be necessary to introduce functional groups selectively into small ring systems, but the direct functionalization of ring carbon atoms is rather difficult. Thus the availability of functionalized ring compounds is an important factor.

Redox reactions are considered as being able to provide versatile and efficient methods for bringing about ring transformations. Transition metal complexes in particular are able to induce or catalyze oxidative or reductive transformations of small ring compounds. Organometallics, such as metallacycles derived by the insertion of metal atoms into rings, are involved as key intermediates in many cases, allowing subsequent functionalization or carbon–carbon bond formation.

Another important class of redox reactions is referred to as one-electron transfer. One of the most useful procedures is based on a one-electron redox reaction of a metal complex. The radicals concomitantly generated by both oxidation and reduction are envisaged as being versatile intermediates in unique ring transformations.

This review surveys recent developments in the selective transformation of small ring compounds via redox reactions, which furnish a variety of valuable methods of synthesis.

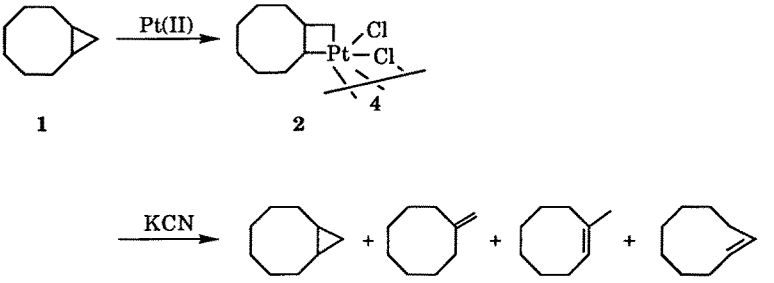
2 Ring Rearrangement via Metallacycles

2.1 Cyclopropanes

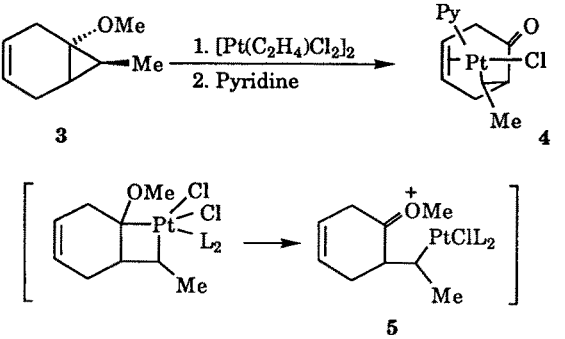
The transition-metal induced rearrangement of strained cyclopropanes is mostly caused by inserting metal atoms into a three-membered ring, thus producing metallacycles and/or η^3-allyl metal complexes. Tipper reported the first example of the metallacycles obtained from $[Pt(C_2H_4)Cl_2]_2$ [3]. The stereospecific addition of cyclopropanes has been investigated from both mechanistic and synthetic view points [4].

The platinacyclobutane **2** derived from the *cis*-disubstituted cyclopropane **1** is isolated and characterized as shown in Scheme 1 [5]. (Scheme 1)

An electron-releasing methoxy group enhances the regioselective insertion of platinum into a cyclopropane ring of **3** to form the complex **4**, suggesting the stabilization of the incipient cation **5** with the methoxy group [6]. This result is in contrast to complexation to only the olefinic moiety of bicyclo[4.1.0]hept-3-ene under identical conditions. (Scheme 2)



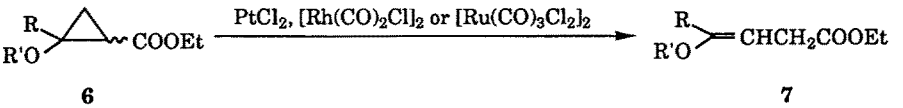
Scheme 1



Scheme 2

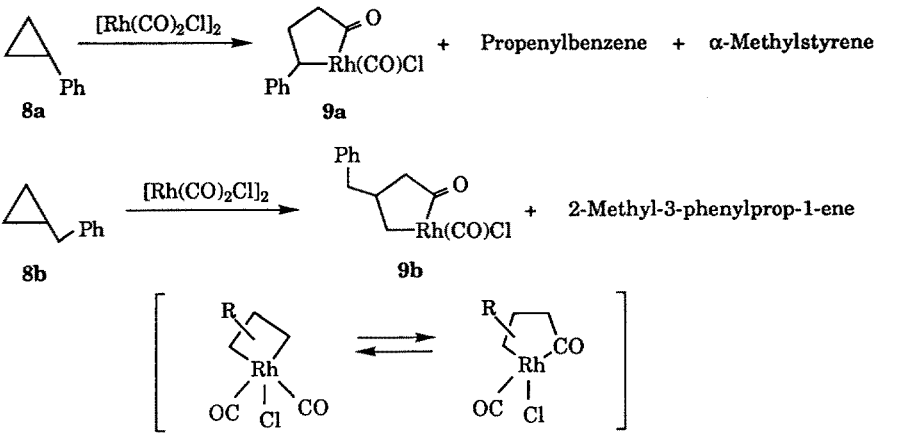
The alkoxycyclopropane **6**, bearing the ethoxycarbonyl group, is converted to the ring-opened vinyl ether **7** [7]. (Scheme 3)

The $[Rh(CO)_2Cl]_2$-induced ring fission of substituted cyclopropanes **8a–b** affords the rhodium complexes **9a–b** via carbonylation [8]. The regioselectivity of carbonyl group insertion depends on the substituent. Reduction with $NaBH_4$ leads to the corresponding alcohol. (Scheme 4)



6 **7**

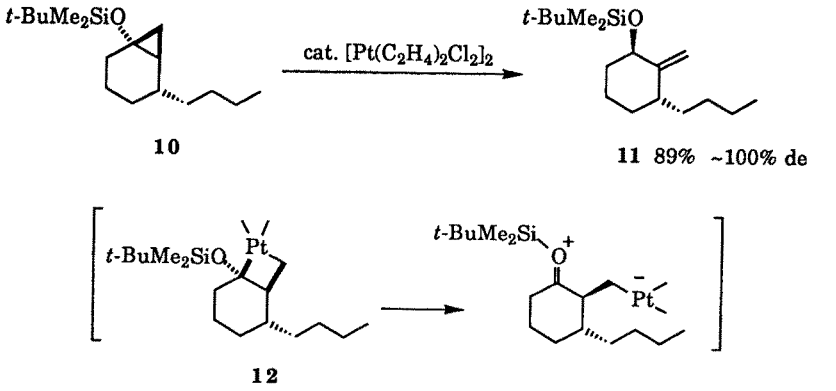
Scheme 3



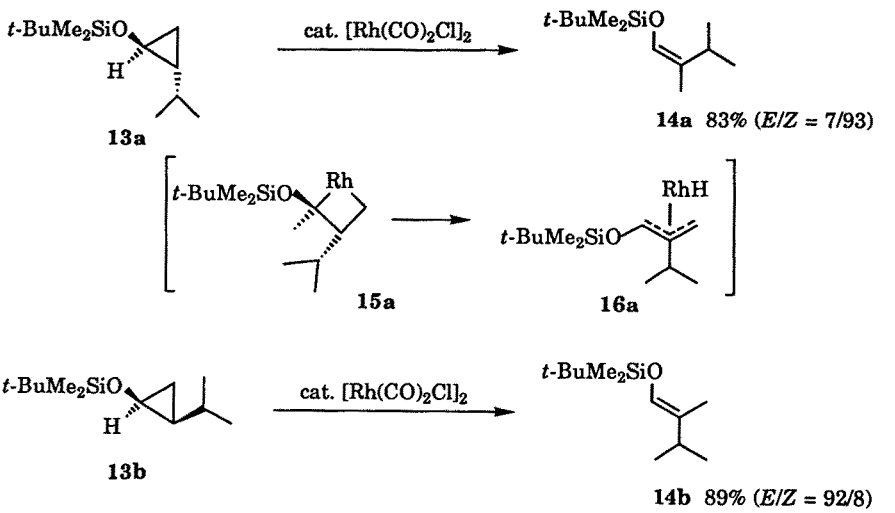
Scheme 4

Catalytic rearrangement of cyclopropanes to olefins is generally less accessible and only a few reactions have been reported so far. The cyclopropane **10**, bearing the silyloxy group, is regioselectively transformed to the allyl silyl ether **11** with Zeise's dimer catalyst [9]. It is worth noting that the bond fission occurs diastereoselectively via the 2-siloxyplatinacyclobutane intermediate **12**. ZnI_2 also induces a similar transformation, but with less efficiency. (Scheme 5)

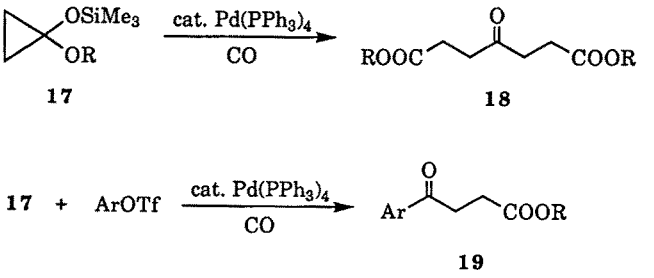
On the other hand, the use of $[Rh(CO)_2Cl]_2$ as a catalyst results in ring opening of the siloxycyclopropanes **13** to the silyl enol ethers **14** with high stereoselectivity [10]. The 2-siloxyrhodacyclobutane **15a** is proposed to undergo β-elimination to give π-allylrhodium **16a** followed by reductive elimination to the silyl enol ether **14a**. 1-Trimethylsiloxybicyclo[n.1.0]alkanes serve as β-metallo-carbonyl compounds via desilylation with a variety of transition metals [11]. The palladium-catalyzed reaction of the siloxycyclopropanes **17** under carbon monoxide in chloroform provides a route to the 4-keto pimelates **18**. In the presence of aryl triflates, the 1,4-dicarbonyl compounds **19** are



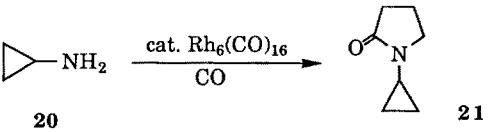
Scheme 5



Scheme 6



Scheme 7



20 21

Scheme 8

produced in HMPA. On the other hand, the use of vinyl triflates leads to acyloxycyclopropanes instead. The similar transformation occurs in the palladium-catalyzed acylation with acid chlorides [12]. 1-Allyloxy-1-siloxycyclopropanes are rearranged by Pd(II) salts to give a mixture of Δ^2-, Δ^3-, and Δ^4-hexenoic acids [13]. (Scheme 6 and 7)

Lactam ring formation is observed in the rhodium-catalyzed ring-opening carbonylation of cyclopropylamine **20** to *N*-cyclopropylpyrrolidone **21** (Scheme 8) [14]. (Scheme 8)

2.2 Vinylcyclopropanes

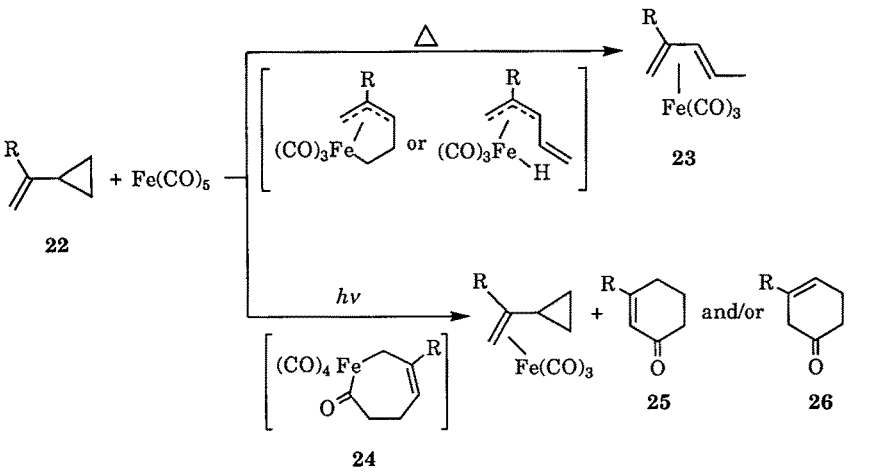
Substitution of cyclopropane rings with the alkenyl group permits unique ring transformations based on metal coordination interaction with four π-electrons. The transition-metal-induced ring-opening rearrangement also results in the formation of metallacycles. Further elaboration is attained by insertion and reductive elimination.

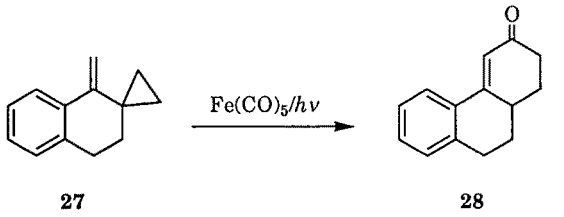
With the low-valence iron pentacarbonyl, vinylcyclopropanes **22** are thermally transformed to the diene π-complexes, the (1,3-*trans*-pentadiene)iron carbonyl complexes **23**, through bond fission, 1,2-hydrogen shift, and stereoselective coordination [15]. (Scheme 9)

1,1-Dicyclopropylethylene **29** does not behave as a six π-electron ligand, producing the diene π-complex **31** via ring opening and carbonylation together with the similar π-complex **30** as mentioned above [16]. The complex **30** is not a precursor to **31**. (Scheme 10)

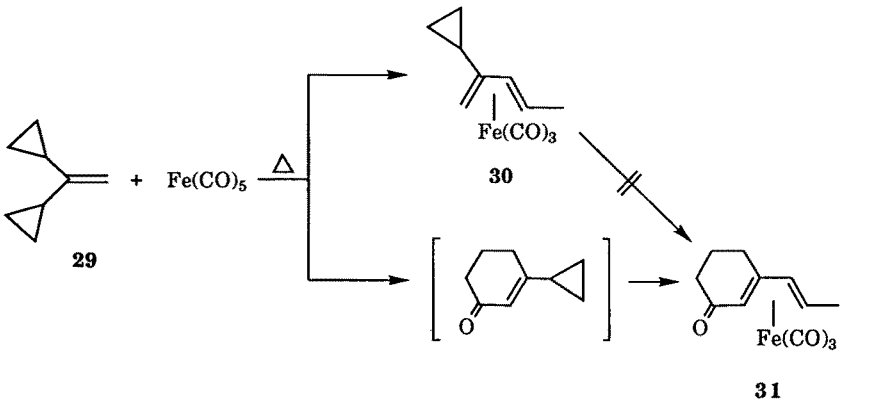
Carbonyl insertion is preferentially observed in the photoinduced reaction of **22** to give the cyclohexenones **25** and **26** as shown in Scheme 9 [17]. The acyl complex **24** is involved as an intermediate. The cyclohexenone formation appears to be susceptible to conformational effect, as observed in the facile rearrangement of **27** to **28**.

The photoinduced 1,7-cycloaddition of carbon monoxide across the divinylcyclopropane derivative **32** yields the two cyclic dienyl ketones **34**, via the ferracyclononadiene intermediate **33** [18]. (Scheme 11)
cyclopentene rearrangement. The dienylcyclopropane **35** is capable of forming the complex **36**, followed by ring enlargement to **37** [19]. 1,1-Dicyclopropylethylene **29** is also converted to the 1-cyclopropyl-1-cyclopentene **38**. The additional functionality of vinylcyclopropanes is necessary to serve as a π-donor





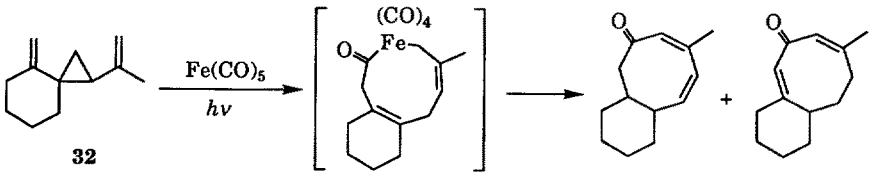
Scheme 9



Scheme 10

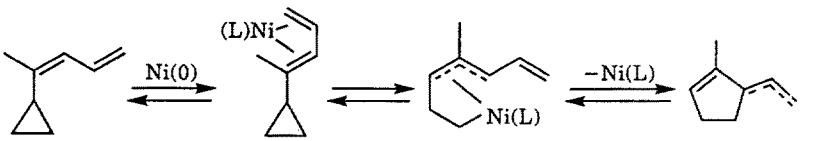
for these rearrangement reactions. The absence of such a functionality only results in fragmentation to dienes. (Scheme 12)

The 1:1 complex of *cis*-divinylcyclopropane **39** with bisethylenehexafluoroacetonatorhodium(I) $[Rh(C_2H_4)_2(acacF_6)]$ rearranges to the cyclo-

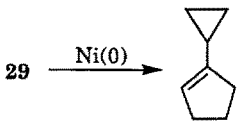


32 33 34

Scheme 11

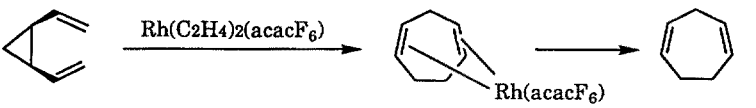


35 36 37



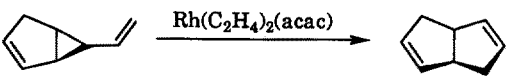
38

Scheme 12



39 40

Scheme 13



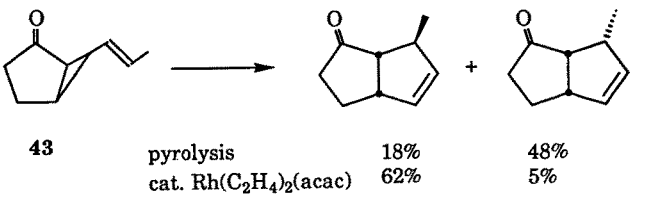
41 42

Scheme 14

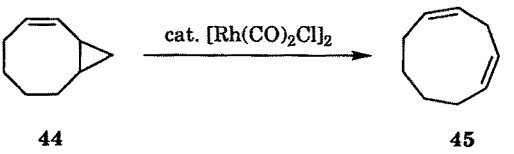
hepta-1,4-diene complex **40** at 65 °C. In contrast, the bis-π-allylrhodium complex is produced in the case of the *trans*-isomer [20]. (Scheme 13)

endo-6-Vinylbicyclo[3.1.0]hex-2-ene **41** forms an intermediate complex with $Rh(C_2H_4)_2(acac)$ to give bicyclo[3.3.0]octa-2,6-diene **42** (Scheme 14) [21]. The $Rh(C_2H_4)_2(acac)$-catalyzed rearrangement of **43** favors the exo-diastereomer [22]. (Scheme 14 and 15)

$[Rh(CO)_2Cl]_2$ catalyzes the ring enlargement of bicyclo[6.1.0]non-2-ene **44** to give **45** [23]. The reaction path is thought to involve initial coordination of



Scheme 15

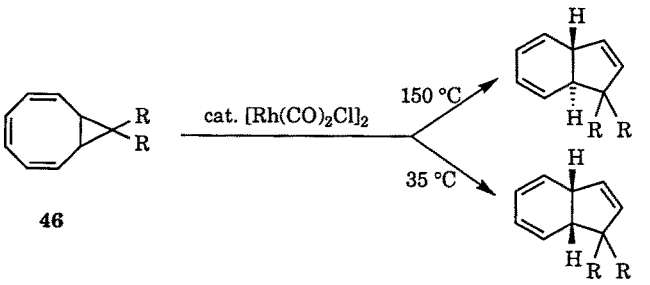


Scheme 16

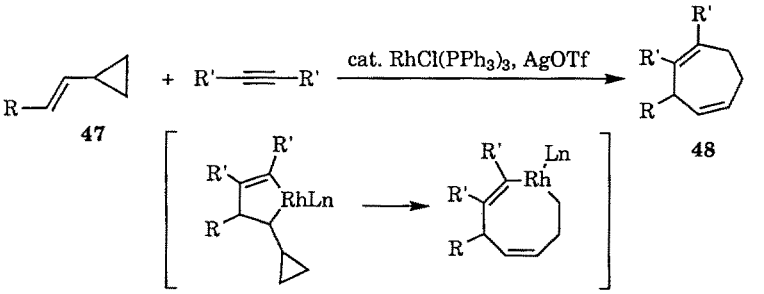
the vinyl moiety with rhodium(I) and stereospecific *cis*-β-hydride elimination from a metallacyclic allylrhodium(III) alkyl intermediate. Starting from 1,1-dimethyl-2-vinylcyclopropane, 1-phenyl-2-vinylcyclopropane, 1-ethoxycarbonyl-2-vinylcyclopropane, and 7-vinylbicyclo[4.1.0]heptane, the corresponding 1,3-dienes are produced predominantly or exclusively. (Scheme 16)

The bicyclo[6.1.0]nonatriene **46** is transformed to the 8,8-dihydroindene on treatment with a catalytic amount of $[Rh(CO)_2Cl]_2$ [24]. The stereoselectivity depends on the reaction temperature. [5 + 2]cycloaddition of vinylcyclopropanes **47** with alkynes is catalyzed by $RhCl(PPh_3)_3$ in the presence of silver triflate to give seven-membered rings **48** [25]. (Scheme 17 and 18)

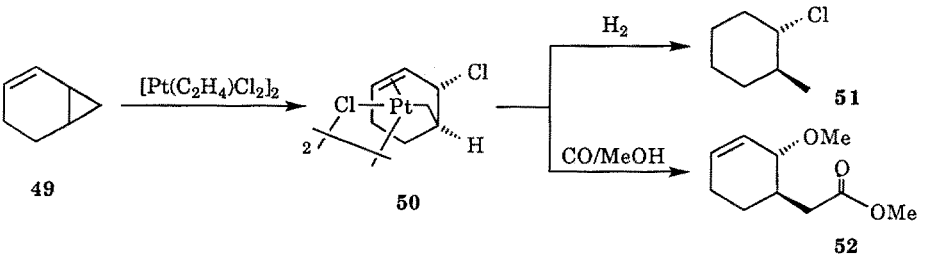
Treatment of the olefin **49** with Zeise's dimer leads to the chloroplatination complex **50** [26]. The addition adduct **50** is hydrogenated stereospecifically to the *trans*-disubstituted chlorocyclohexane **51**. The insertion of carbon monoxide into **50**, in the presence of methanol, yields the ester **52** stereoselectively.



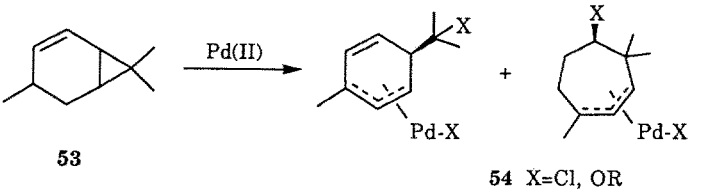
Scheme 17



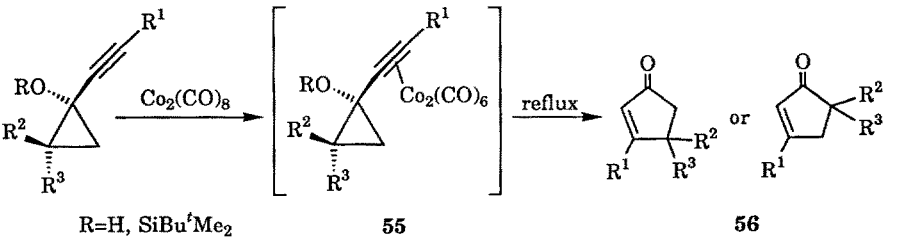
Scheme 18



Scheme 19



Scheme 20



Scheme 21

A similar ring-opening metallation is observed with bicyclo[3.1.0]hex-2-ene and bicyclo[5.1.0]oct-2-ene. The olefin **49** undergoes ring enlargement with $Fe_2(CO)_9$ to form the corresponding π-allyl and η^4-diene complexes [27]. *trans*-Palladation of **53** results in the formation of the π-allyl complexes **54** [28]. (Scheme 19 and 20)

Cyclopropane ring cleavage is also observed in the case of zirconocene η^2-alkene and η^2-imine complexes with adjacent cyclopropane rings to give η^3-allyl, η^3-azaallyl, and η^1-enamine complexes [29].

Hexacarbonyldicobalt-complexed 1-(1-alkynyl)cyclopropanols **55** rearrange to give the 2-cyclopenten-1-ones **56** in good yields (Scheme 21). In the case of 2-substituted 1-alkynylcyclopropanol derivatives, rearrangement is conformationally controlled to give 4- or 5-substituted 2-cyclopenten-1-ones regioselectively [30]. It has been suggested that oxidative addition of a cobalt species to the cyclopropane ring yields the metallacyclic intermediate. The regioselectivity depends on the feasibility of this insertion. (1,2-Propadienyl)cyclopropanols are similarly converted to 1,4-hydroquinones [31]. (Scheme 21)

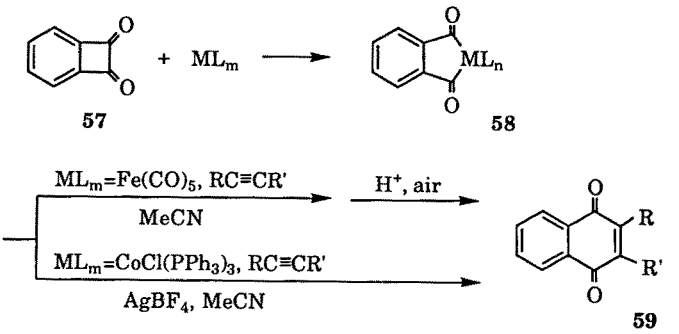
2.3 Cyclobutenediones and Cyclobutenones

Strained ring compounds undergo insertion of a low-valence metal complex to give metallacycles and the cycloaddition of metallacycles has a potential in synthesis, as described above. This method is useful in ring transformations of cyclobutenediones and cyclobutenones.

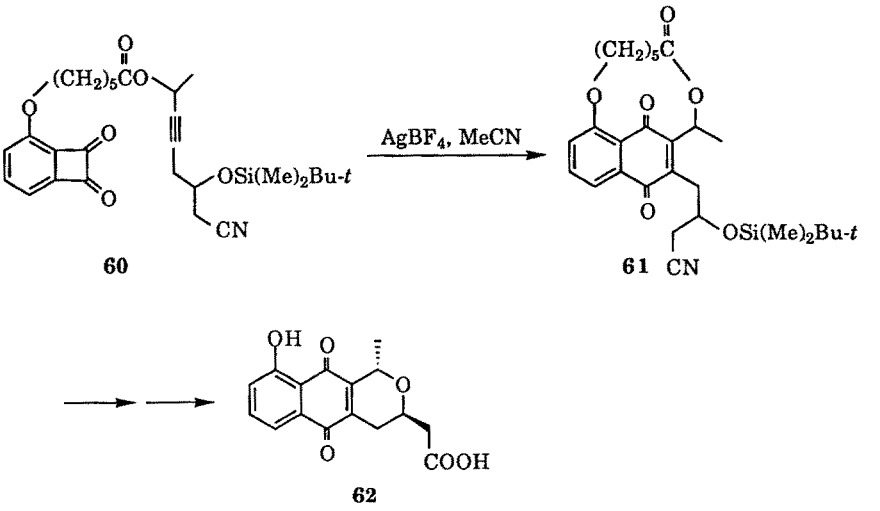
Benzocyclobutenedione **57** is transformed to the phthaloylmetal complex **58** by treatment with $Fe(CO)_5$, $RhCl(PPh_3)_3$, and $CoCl(PPh_3)_3$. The phthaloyliron complex **58** (M=Fe) reacts with alkynes, and subsequent acidification under air then gives the naphthoquinone **59**. The cyclization of the phthaloylcobalt **58** (M=Co) with alkynes requires $AgBF_4$-activation [32]. (Scheme 22)

This reaction is applied to the intramolecular regioselective cyclization of the 3-alkoxybenzocyclobutenedione **60** to **61**, a precursor of nanaomycin A **62** [33]. (Scheme 23)

The benzoquinone **66** is similarly prepared by the regioselective cycloaddition of **64**, derived from **63**. The cyclization reaction is based on the electronic effect of the substituent of **65** [34]. The maleoylcobalt complex **67**, substituted by PPh_3, is unreactive towards terminal alkynes. The reaction course is altered

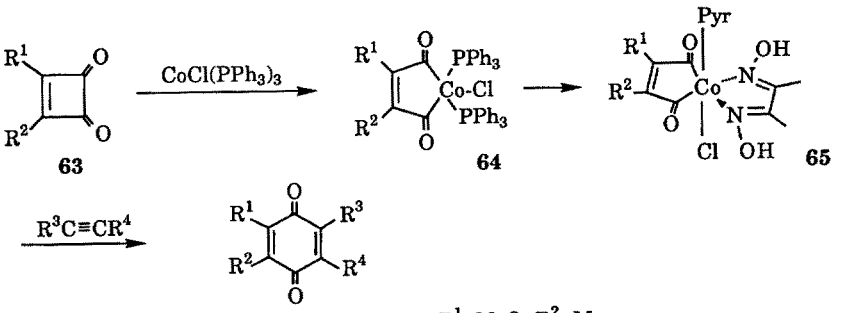


Scheme 22



60 61 62

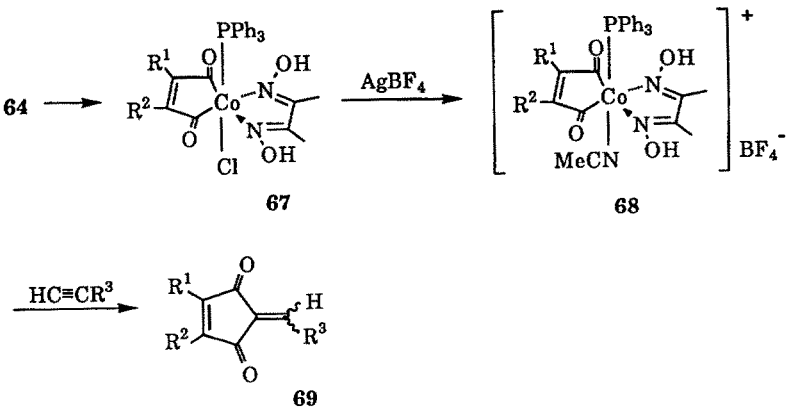
Scheme 23



63 64 65

66 e.g. R^1=MeO, R^2=Me

Scheme 24



67 68 69

Scheme 25

by treatment with $AgBF_4$; a terminal alkyne unexpectedly serves as a vinylidene tautomer in the cyclization involving the cationic complex **68**, yielding the 5-alkylidenecyclopentenedione **69** [35]. Retarded quinone formation allows this tautomerization. (Scheme 24 and 25)

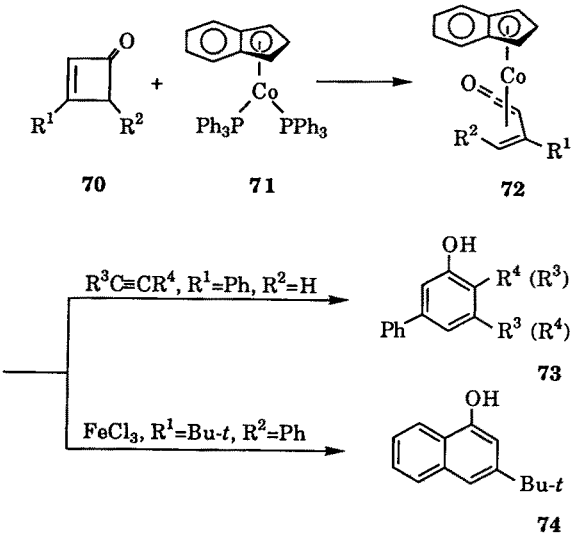
The cyclobutenone **70** is transformed to the η^4-vinylketene complex **72** with $(\eta^5$-indenyl)$Co(PPh_3)_2$ **71**. The vinylketene complex **72** undergoes cyclization with alkynes to produce the corresponding phenols **73**. $FeCl_3$ oxidation of the (2-phenylvinyl)ketene complex, however, leads to the naphthol **74**. A catalytic synthesis of phenols via the vinylketene intermediates **72** is achieved by the use of $Ni(COD)_2$ as a catalyst [36]. (Scheme 26)

The rearrangement of **70** to vinylketenes is thermally possible [37]. A variety of cyclobutenones are prepared by the transition-metal-induced carbon–carbon bond formation, which elevates the synthetic utility of their ring enlargement.

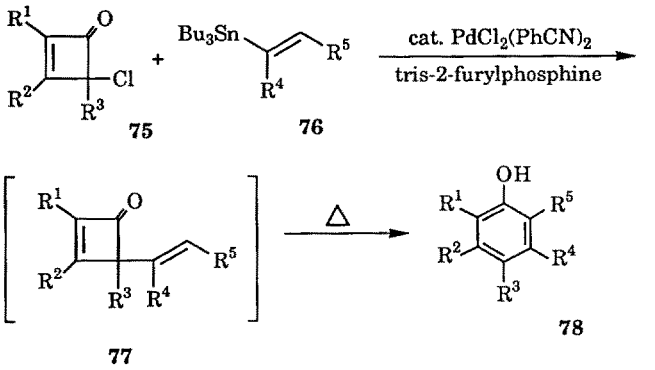
2,3-Disubstituted 4-chloro-2-cyclobutenones **75** undergo the palladium-catalyzed cross-coupling reaction with vinyl- and arylstannanes **76** or vinylzirconium reagents to give the 4-R_{unsat}-2-cyclobutenones **77**. Without isolation, these cyclobutenones **77** are rearranged to the substituted phenols **78** on thermolysis [38]. Application of this method to the stannylated heteroaromatics **79** provides a synthetic route to the aromatic benzoheterocycles **80** [39]. (Scheme 27 and 28)

The use of the stannylquinones **81** results in the regioselective formation of 1,4-naphthoquinones or 9,10-anthraquinones **82** [40]. Highly-oxygenated angularly-fused polycyclic aromatic compounds are prepared by the ring enlargement [41]. (Scheme 29)

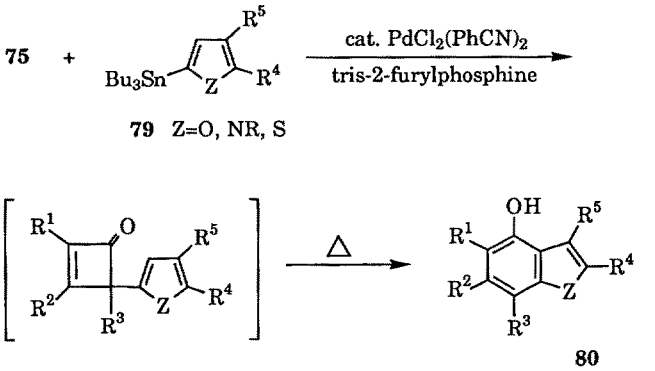
The coupling reaction of **75** with 3-(tributylstannyl)-3-cyclobutene-1,2-dione 2-ethylene acetal **83** is also catalyzed by $PdCl_2(PhCN)_2$, giving the benzo-



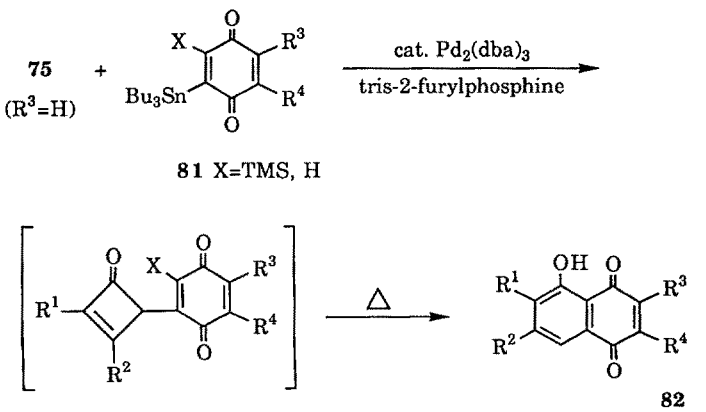
Scheme 26



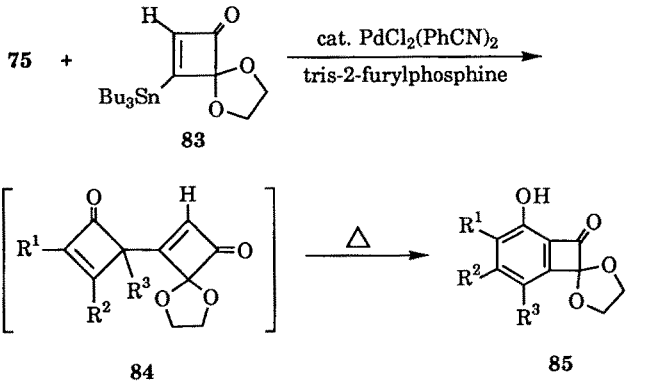
Scheme 27



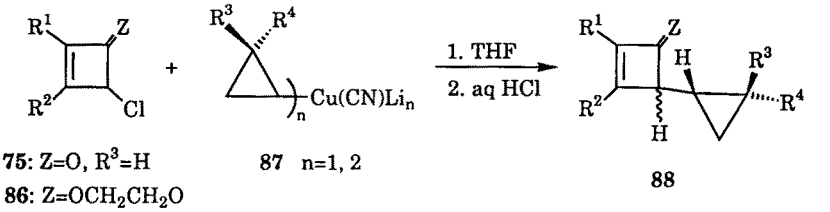
Scheme 28



Scheme 29

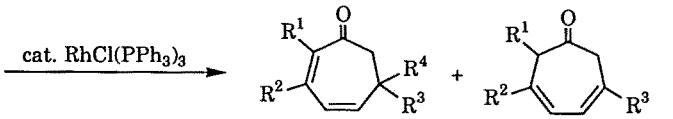


Scheme 30

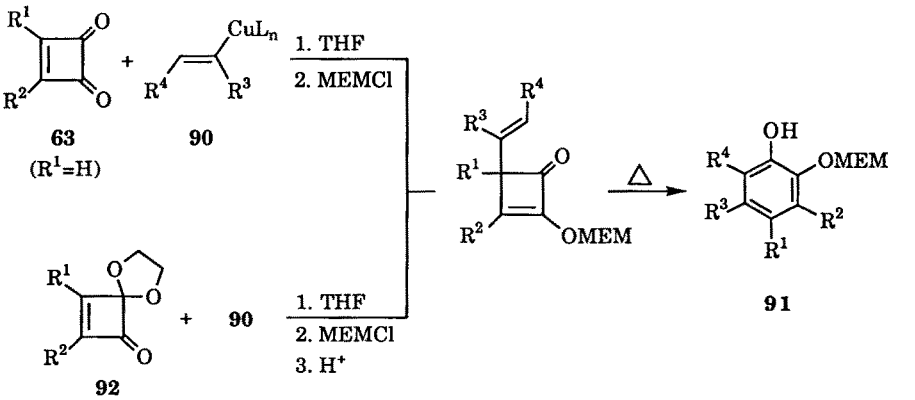


75: Z=O, R^3=H
86: Z=OCH_2CH_2O

87 n=1, 2



Scheme 31



Scheme 32

cyclobutenedione monoacetal **85**. The 3-(1-oxo-2-cyclobuten-4-yl)-3-cyclobutene-1,2-dione 2-ethylene acetal **84** is similarly involved as an intermediate, which is susceptible to thermal rearrangement to **85** [42]. (Scheme 30)

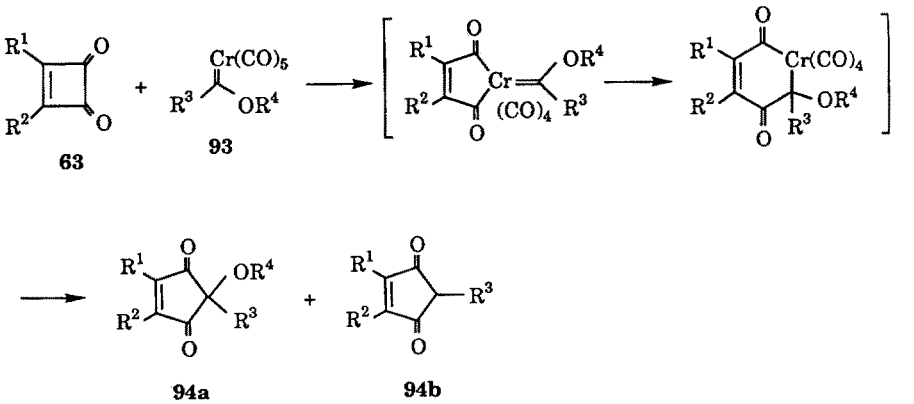
The coupling reaction of the cyclopropylcuprates **87** with the 4-chlorocyclobutenones **75** or their ethylene acetals **86** is useful for preparing the 4-cyclopropyl-2-cyclobutenones **88**. The ring fission of **88** to the cycloheptadienones **89** is performed by a Rh(I)-catalyst. The less substituted cyclopropane ring bond is cleaved selectively. Cyclooctadienones are obtained by using 4-cyclobutyl-2-cyclobutenones [43]. (Scheme 31)

Conjugate addition of vinyl-, aryl-, heteroarylcuprates **90** to the cyclobutenedione **63**, followed by in situ protection with (methoxyethoxy)methyl chloride of the enolates, provides a method for synthesizing substituted catechol derivatives **91** [44]. Regiocontrolled synthesis is achieved by using cyclobutenedione monoacetals **92** as starting substrates. (Scheme 32)

3-(Tributylstannyl)-3-cyclobutene-1,2-diones and 4-methyl-3-(tributylstannyl)-3-cyclobutene-1,2-dione 2-ethylene acetals undergo the palladium/copper-catalyzed cross coupling with acyl halides, and palladium-catalyzed carbonylative cross coupling with aryl/heteroaryl iodides [45]. The coupling reaction of alkenyl(phenyl)iodonium triflates is also performed by a palladium/copper catalyst [46].

3 Ring Rearrangement via Carbene Complexes

Carbene complexes are versatile intermediates in ring construction [47]. The insertion of alkoxycarbenechromium complexes **93** into cyclobutenediones **63** leads to the ring-expanded cyclopentenediones **94** as shown in Scheme 33 [48].



Scheme 33

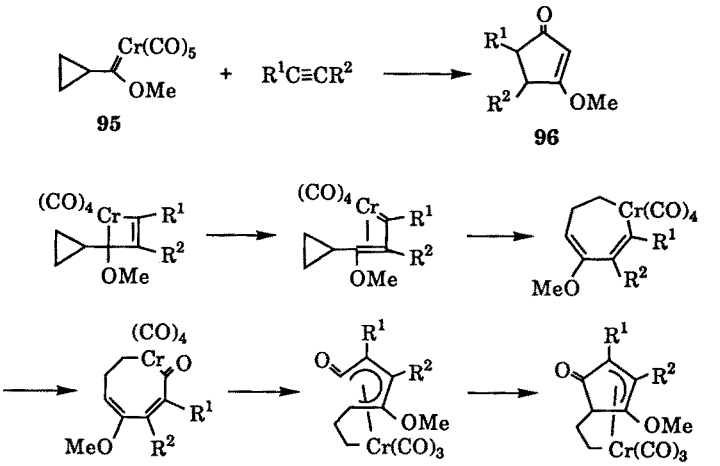
The similar insertion of **93** into 1,2-diphenylcyclopropenone results in cyclobutenones or *o*- and *p*-alkoxyphenols [49]. In the reaction of **93** with 1-alkynylcyclobutenols, 2-alkenyl-4-cyclopentene-1,3-diones are obtained via alkyl shift-ring expansion [50]. (Scheme 33)

The presence of a cyclopropyl moiety in the carbene complexes makes them useful for synthesis. The cyclopropylcarbene complexes **95** undergo a cycloaddition reaction with alkynes to give the cyclopentenones **96** [51]. The reaction course is explained as being metallacyclopentene fragmentation. (Scheme 34)

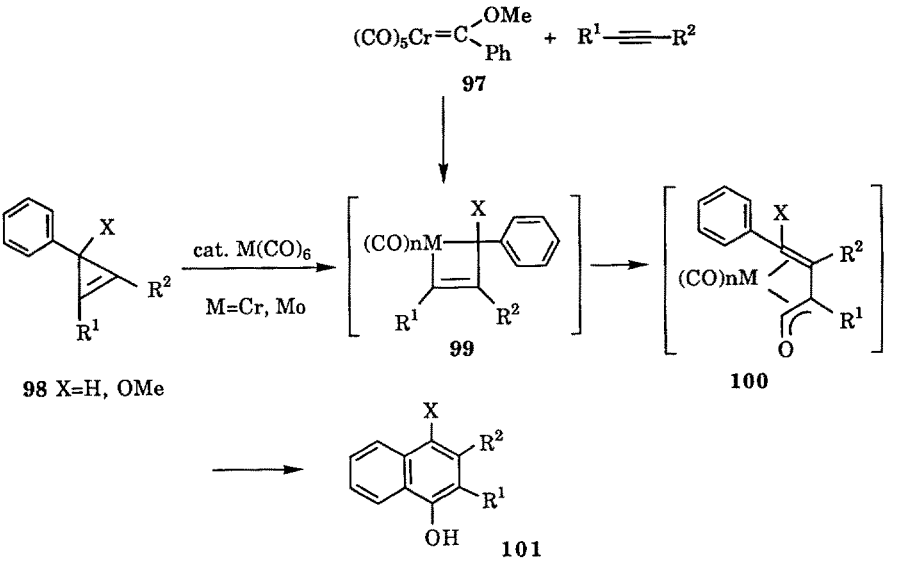
Cycloaddition of the carbene chromium complexes **97** with CO incorporation provides a versatile method for naphthol synthesis, in which the metallacyclic intermediates **99** are involved [47]. An alternative entry to **101** is achieved by metal carbonyl-catalyzed rearrangement of the cyclopropenes **98** via the same metalla-cyclobutenes **99** and vinylketene complexes **100** [52]. $Mo(CO)_6$ shows a higher activity than $Cr(CO)_6$ and $W(CO)_6$. The vinylketene complex **103** is formed by the regioselective ring cleavage of 1,3,3-trimethylcyclopropene **102** with an excess of $Fe_2(CO)_9$ [53]. (Scheme 35 and 36)

The intramolecular addition of alkynyl-substituted α-diazoketones is catalyzed by $Rh_2(OAc)_4$ to give transient cyclopropenes, which spontaneously rearrange to vinylogous α-keto carbene intermediates for further carbon-skeleton transformations [54].

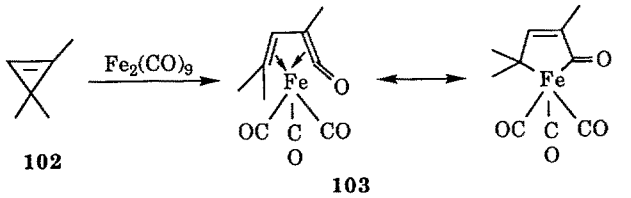
The Rh(II)-catalyzed isomerization of isolated cyclopropenes has been investigated. Starting from phenyl-substituted cyclopropenecarboxylates **104**, a furan ring is formed [55, 56]. In the case of alkyl-substituted derivatives ones, the dienoate and methylidenecyclopentane derivatives, **105** and **106**, are obtained [55]. A mechanism involving vinylcarbene complexes is able to account for these rearrangements. Regioselective electrophilic attack by the bulky Rh(II) catalyst *trans* to the cyclopentenone ring of **107** and *ipso* to the smaller group



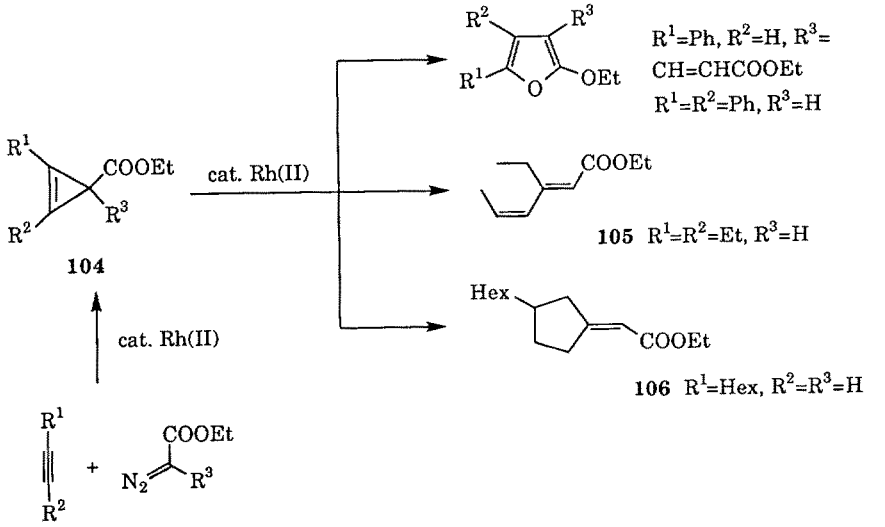
Scheme 34



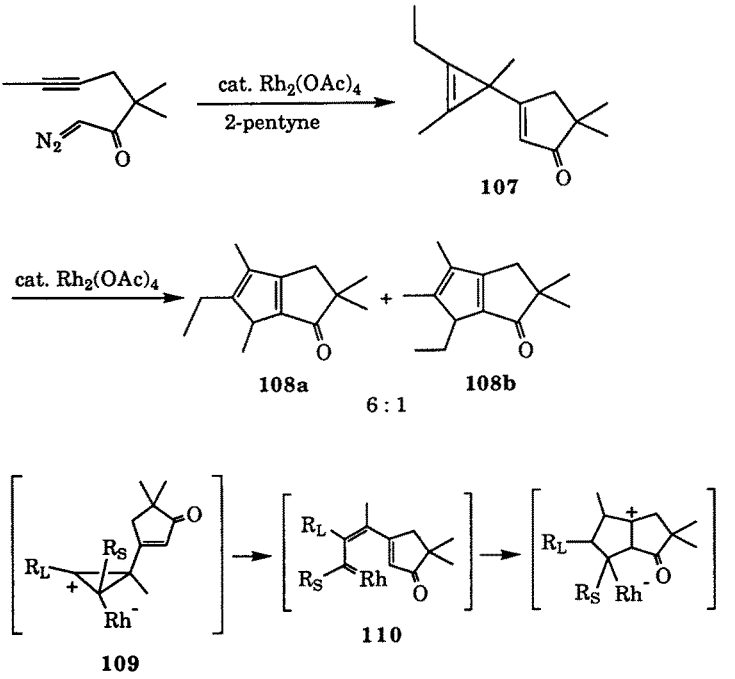
Scheme 35



Scheme 36



Scheme 37



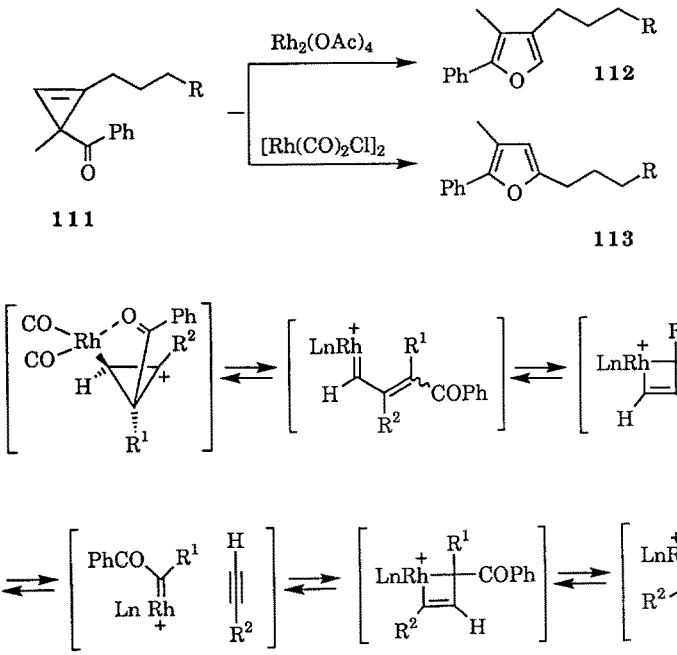
Scheme 38

yields **109**. Ring opening of **109** to the carbene complex **110** explains the predominant formation of **108a** [57]. (Scheme 37 and 38)

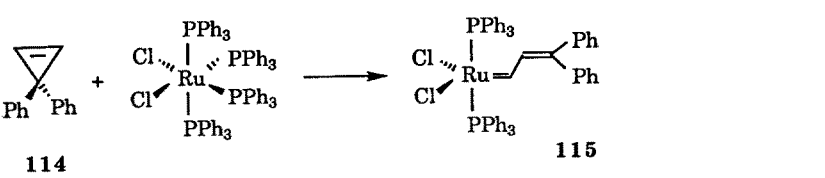
The selective cleavage of the less substituted σ-bond of **111** is also observed to give **112**. A pronounced alternative of the ring-opening reaction is performed using a Rh(I) catalyst, producing the regioisomeric furan **113** [58]. Scheme 39 accounts for the reaction path. The rhodium vinylcarbene intermediates undergo intermolecular alkyne insertion to give substituted phenols [59]. (Scheme 39)

Cyclopropenes with high strain are readily transferable [60] as mentioned above. Ring opening of 3,3-diphenylcyclopropene **114** with $RuCl_2(PPh_3)_n$ ($n = 3, 4$) forms the carbene complex **115** quantitatively. The ruthenium complex **115** reacts with methylenecyclopropane and methylenecyclobutane, and serves as a ring-opening methathesis polymerization catalyst. The analogous vinylcarbene complexes $(Cp_2M(PMe_3)(=C(H)CH=CPh_2)$ (M = Ti, Zr) have also been prepared [61]. The use of $(Cp^*RuCl)_4$ results in the bridging vinylcarbene complex **116**, which catalyzes dimerization to the triene **117** [62]. (Scheme 40 and 41)

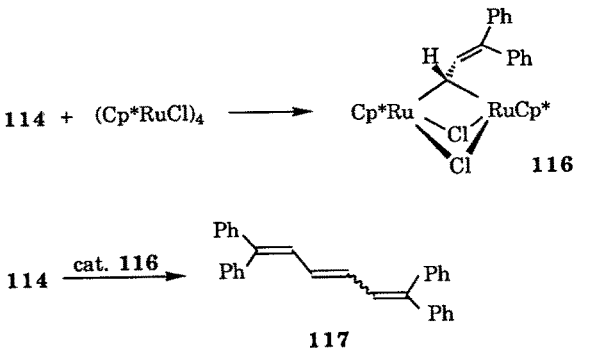
Cycloaddition of cyclopropenes is catalyzed by transition metal complexes. 1-Methylcyclopropene **118** undergoes a facile $PdCl_2(PhCN)_2$-catalyzed cyclodimerization to dimethyltricyclo[3.1.0.$0^{2,4}$]hexanes **119**. In contrast, cyclotrimerization of 3,3-dimethylcyclopropene **120** occurs in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give hexamethyl-*trans*-σ-trishomobenzene **121**



Scheme 39



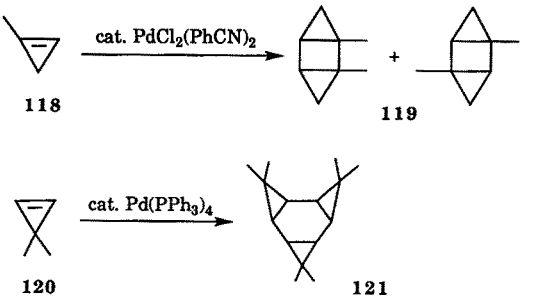
Scheme 40



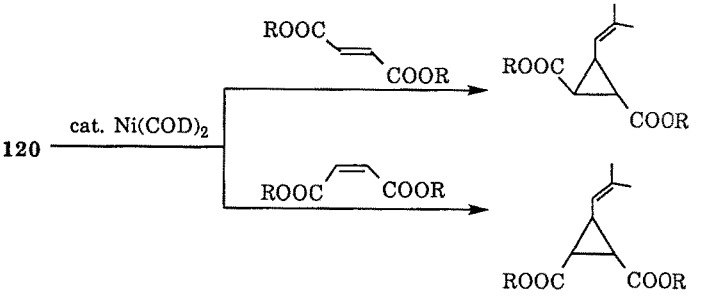
Scheme 41

[63]. Stereospecific codimerization of **120** with diethyl fumarate and maleate is accomplished by the $Ni(COD)_2$ catalyst as shown in Scheme 43 [64]. (Scheme 42 and 43)

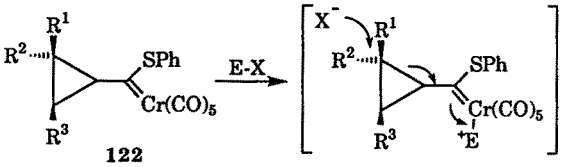
1,5-Addition of halogens and pseudohalogens to the cyclopropylthiocarbene chromium complexes **122** affords the 1,4-dihalo-1-phenylthio-1-alkenes **123** stereoselectively [65]. Electrophilic halogen is likely to activate the carbene complexes, followed by the homo-Michael addition of halide anion. (Scheme 44)



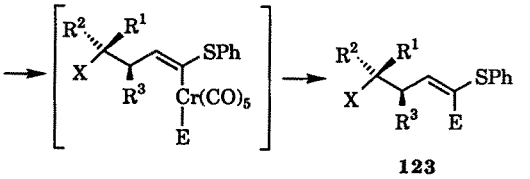
Scheme 42



Scheme 43



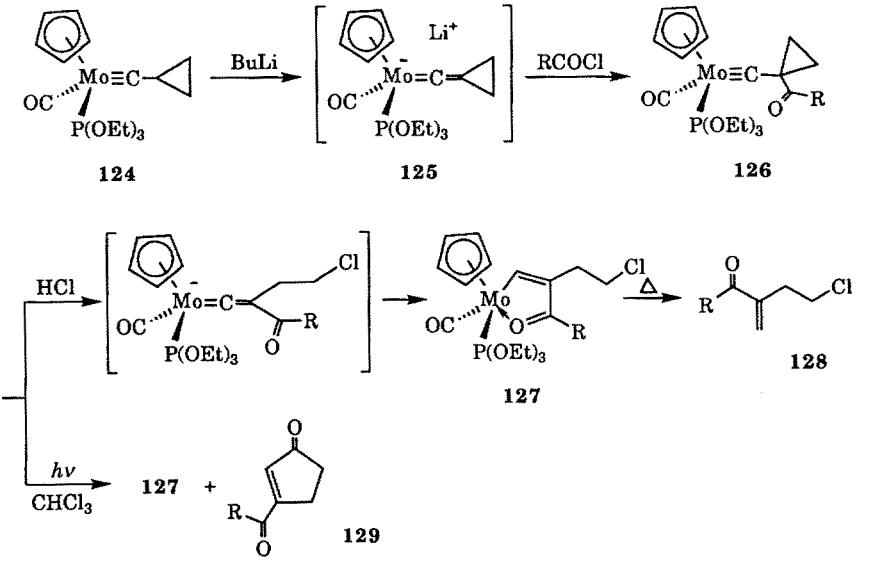
E-X: I_2, Br_2, PhSeCl



123

Scheme 44

Deprotonation of the cyclopropylcarbyne molybdenum complex **124** with BuLi generates the anionic vinylidene complex **125**. Electrophilic attack with acid chlorides or chloroformates occurs at the β-carbon to give the acylcyclopropylcarbyne complex **126**. The complex **126** undergoes nucleophilic ring opening in the presence of chloride to yield oxometallacycle **127**. Thermal degradation leads to the α,β-unsaturated ketone **128**. In the photooxidation of **126** in chloroform, the 3-acylcyclopentenone **129** is produced via carbonylation. Ring opening of **126** can also be achieved by other nucleophiles such as aniline and thiophenol [66]. Addition of HCl to the cyclopropylcarbyne complex results in the formation of the diene complex [67]. (Scheme 45)



Scheme 45

4 Ring Transformation via π-Allyl Complexes

π-Allyl complexes are very important intermediates in organic syntheses. Versatile reactions have been developed utilizing the characteristics of small ring compounds.

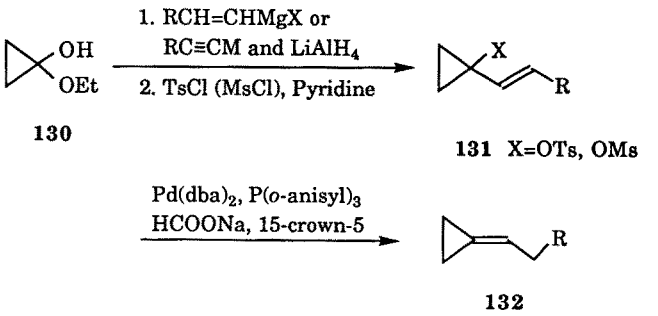
1-Ethenylcyclopropyl tosylates **131** and 2-cyclopropylideneethyl acetates **133**, readily available from the cyclopropanone hemiacetals **130**, undergo the regioselective Pd(0)-catalyzed nucleophilic substitution via the unsymmetrical 1,1-dimethylene-π-allyl complexes. For example, reduction with sodium formate affords a useful route from **131** to the strained methylenecyclopropane derivatives **132**. The regioselective attack of the hydride is caused by the sterically

bulky ligand [68]. This overall process represents an alternative to the Wittig reaction.

The stabilized anion **134** also attacks the terminal vinylic position of **131** exclusively to give cyclopropylideneethyl derivatives **135**, which are synthetically useful building blocks [69]. The use of chiral phosphanes as ligands leads to optically active methylenecyclopropane derivatives. (Scheme 47)

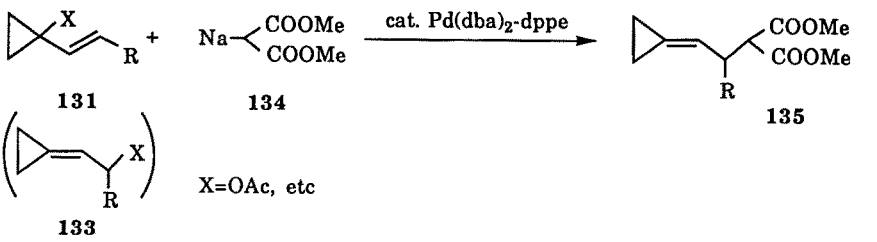
1-Azido-1-alkenylcyclopropanes **136**, convenient precursors of 2,3-methanoamino acids, are formed regioselectively in the azidation. On the other hand, the amination with dibenzylamin occurs exclusively on the less-substituted allylic end (Scheme 48) [70].

Three-component coupling of methylenecyclopropane **137** with iodobenzene or 2-bromopropene and malonate anion is catalyzed by a palladium(0)



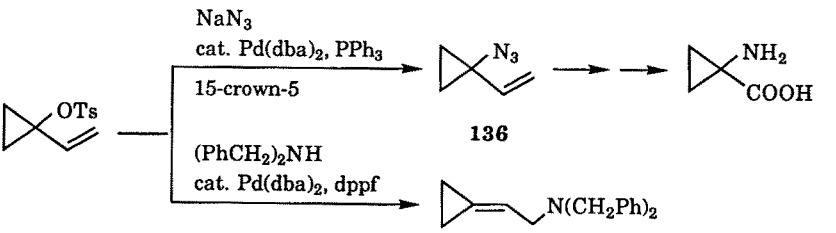
130 **131** X=OTs, OMs **132**

Scheme 46



131 **134** **135** **133**

Scheme 47



136

Scheme 48

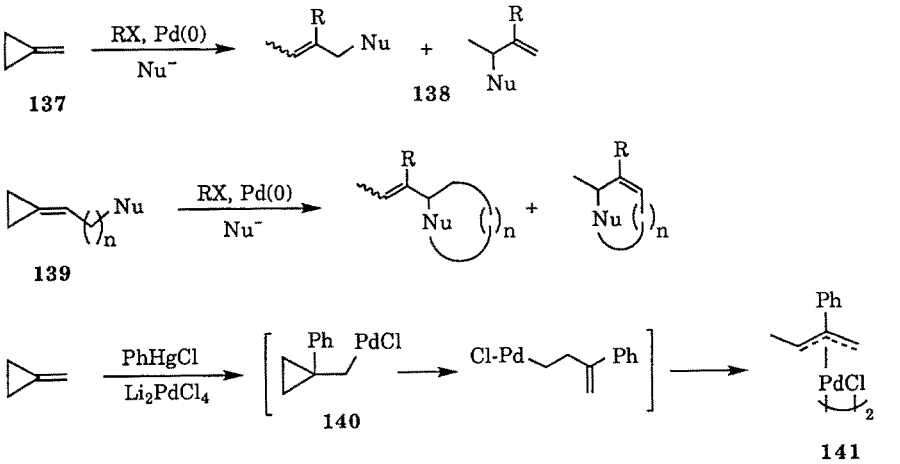
complex giving the ring-opened olefin **138**. The stoichiometric reaction supports the notion that the π-allylpalladium intermediate **141** is involved, resulting from rearrangement of the intially formed α-cyclopropanic σ-palladium species **140**. This method is applied to the intramolecular cyclization of **139** [71]. (Scheme 49)

The dienyl cyclopropane **142**, bearing two electron-withdrawing groups, is rearranged to the ring-enlarged cyclopentene **143** on treatment with a catalytic amount of $Pd(PPh_3)_4$ [72]. Asymmetric rearrangement is performed by the nickel catalyst and chiral phosphine ligand [73]. (Scheme 50)

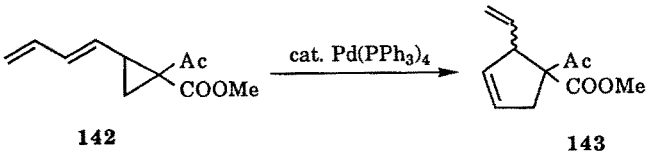
The vinylcyclopropane **144**, bearing two electron-withdrawing groups, undergoes the intermolecular palladium-catalyzed [3 + 2]cycloaddition reaction of the π-allylpalladium intermediate **145** with α,β-unsaturated esters or ketones to provide a useful method for forming the cyclopentane ring of **146** [74]. (Scheme 51)

$Pd(PPh_3)_4$ catalyzes the ring expansion of the vinyloxaspirohexane **147** in the presence of *p*-nitrophenol to yield the 2-ethylidenecyclopentanone **149** [75]. The π-allylpalladium complex **148** is an intermediate in rearrangement. (Scheme 52)

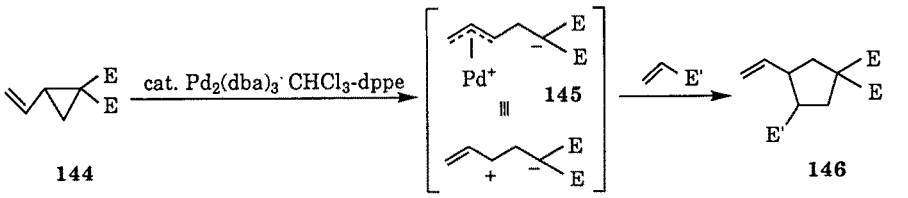
The nickel-catalyzed cross coupling of cyclopropyl Grignard reagents with benzylic dithioacetals gives substituted dienes via regioselective ring opening to homoallylnickel intermediates [76].



Scheme 49

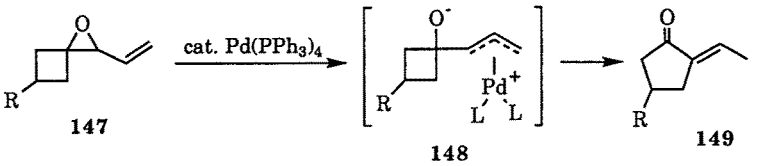


Scheme 50



E, E'= electron-withdrawing group

Scheme 51



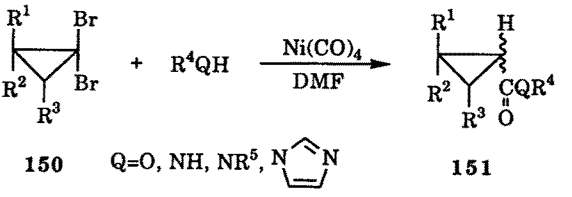
Scheme 52

5 Reductive Transformation of Halocyclopropanes

5.1 Transition Metal Enolates

Direct attachment of a functional group to the carbon atoms of the cyclopropane ring is fairly difficult. *gem*-Dibromocyclopropanes are readily available through the addition of dibromocarbene to olefinic compounds. Their synthetic versatility is reviewed in a previous volume of this series [77]. Substitution of the bromide with the aid of nucleophilic organometallics to form a new carbon–carbon bond has been investigated [78].

Metal carbonyls in a low oxidation state are able to induce the carbonylative transformation. Reductive carbonylation of the *gem*-dibromocyclopropanes **150** is realized by treatment with nickeltetracarbonyl in an alkanol to give the alkyl cyclopropanecarboxylates **151** with reduction of another bromide [79]. Amines, phenol, and imidazole can also be used instead of alcohols. (Scheme 53)

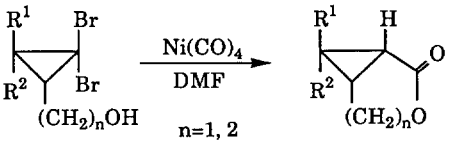


Scheme 53

The *gem*-dibromocyclopropanes **152** bearing a hydroxyalkyl group, prepared by the addition of dibromocarbene to allylic or homoallylic alcohols, undergo an intramolecular reductive carbonylation to the bicyclic lactones **153**. bicyclic lactone derived from prenyl alcohol is an important precursor for the synthesis of *cis*-chrysanthemic acid. (Scheme 54)

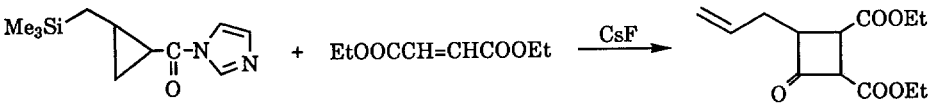
CsF induces the ring-opening cyclization of the thus obtained 1-[2-(trimethylsilylmethyl)cyclopropylcarbonyl]imidazole **154** with diethyl fumarate or diethyl maleate to give the cyclobutanone **155** [80]. The facile ring fission of **154** also occurs in the presence of $BF_3 \cdot OEt$ with the formation of the corresponding γ,δ-unsaturated carboxylic acid. (Scheme 55)

The course of the reductive carbonylation reaction is considered to involve intially the alkoxycarbonyl complex **156**, which attacks **150** to form the nickel enolates **157** followed by protonation [81]. (Scheme 56)



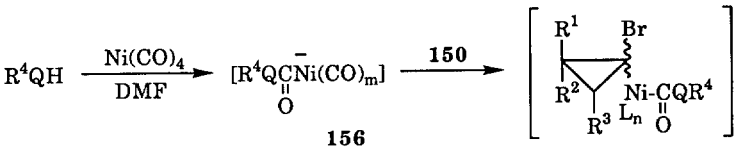
152 **153**

Scheme 54

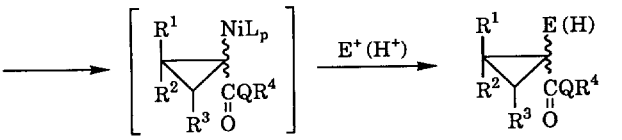


154 **155**

Scheme 55



156

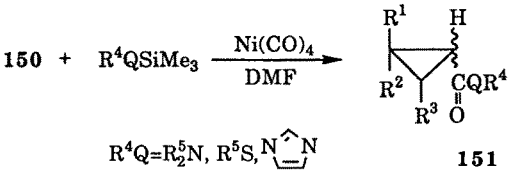


157

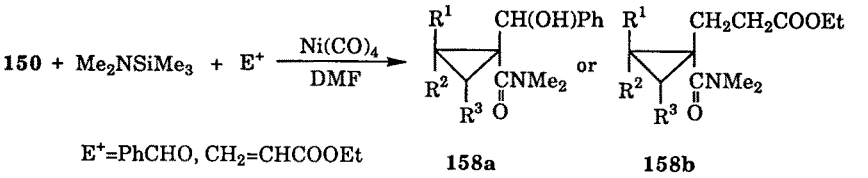
Scheme 56

It is supposed that the nickel enolate intermediate **157** reacts with electrophiles rather than with protons. The successful use of trimethylsilyl-substituted amines (Scheme 57) permits a new carbon–carbon bond to be formed between **157** and electrophiles such as benzaldehyde and ethyl acrylate. The adduct **158** is obtained stereoselectively only by mixing nickel tetracarbonyl, the *gem*-dibromocyclopropane **150**, dimethyl(trimethylsilyl)amine, and an electrophile [82]. *gem*-Functionalization on a cyclopropane ring carbon atom is attained in this four-component coupling reaction. Phenyl trimethyl silylsulfide serves as an excellent nucleophile to yield the thiol ester, which is in sharp contrast to the formation of a complicated product mixture starting from thiols instead of the silylsulfide [81]. (Scheme 58)

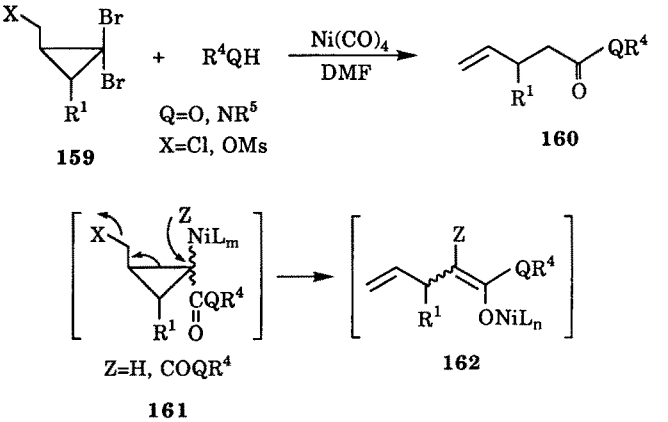
The carbonylation reaction of the *gem*-dibromocyclopropanes **159** bearing the chloromethyl group leads via ring-opening to the γ,δ-unsaturated carboxylic



Scheme 57



Scheme 58



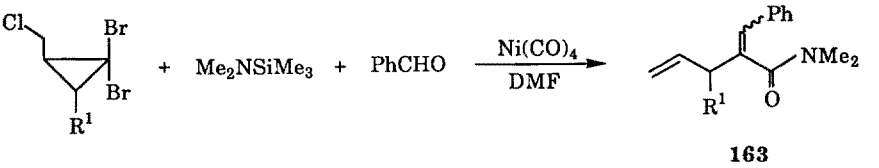
Scheme 59

acid derivatives **160**. The mesyloxy group is also used instead of the chloride for this transformation. In the nickel enolate intermediate **161**, the subsequent attack of the alkoxycarbonyl moiety or hydride possibly explains the ring rearrangement with removal of the chloro or mesyloxy group to form another nickel enolate **162** [83]. Since the starting *gem*-dibromocyclopropanes **159** are derived from dibromocarbene and allylic chlorides or alcohols, these transformations provide a useful procedure for formal substitution with the ester enolate at the γ-position. (Scheme 59)

With dimethyl(trimethylsilyl)amine, the nickel enolate **162** is capable of reacting with benzaldehyde to produce the condensation product **163** (Scheme 60).

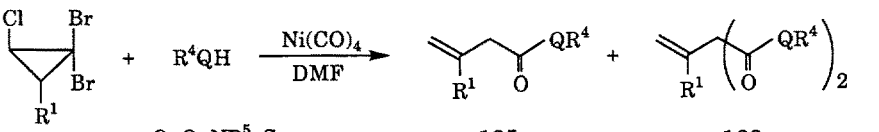
The 1-chloro-2,2-dibromocyclopropanes **164** similarly undergo the nickel-carbonyl-induced ring-opening carbonylation with an amine or an alcohol to give the β,γ-unsaturated carboxylic acid derivatives **165** and the dicarboxylic acid ones **166** [84]. The mechanism described above appears to be operating; this is supported by the four-component condensation to **167**. (Scheme 61 and 62)

Another example for *gem*-functionalization is demonstrated in the reaction with disulfides. The tandem sulfenylation and carbonylation to 1-alkylthiocyclopropanecarbothioates **168** are realized, indicating that disulfides can serve both as nucleophiles and electrophiles [81]. (Scheme 63)



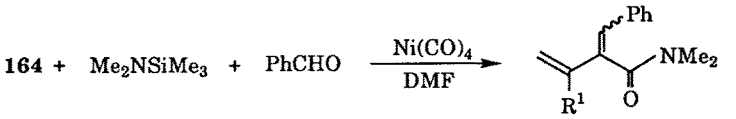
163

Scheme 60



164 Q=O, NR^5, S **165** **166**

Scheme 61

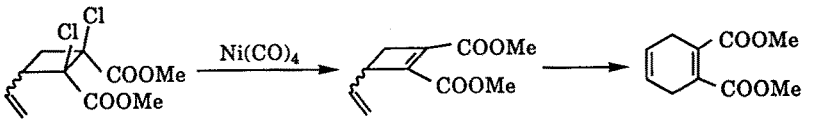


167

Scheme 62

168

Scheme 63



169 170 171

Scheme 64

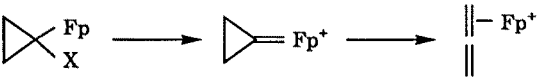
Ironcarbonyl induces a similar reductive carbonylation of **150** with sodium methoxide [85]. A catalytic cycle is formed by using $CoCl_2$ and $Ni(CN)_2$ as catalysts under phase-transfer conditions [86].

Upon treatment with nickeltetracarbonyl, dimethyl 3-vinyl-1,2-dichlorocyclobutane-1,2-dicarboxylate **169** is rearranged, to dimethyl 1,4-cyclohexadiene-1,2-dicarboxylate **171** with concomitant loss of the chlorine atoms [87]. Reduction to dimethyl 3-vinylcyclobutene-1,2-dicarboxylate **170** is involved in the initial step. (Scheme 64)

5.2 Transition Metals σ-Bonded to Cyclopropanes

Transition metals **172** σ-bonded to cyclopropanes, substituted on the α-carbon with a halogen atom, are interesting intermediates for cyclopropylidene complexes **173** or allene ones **174** [88]. The former complexes are also supposed to be precursors of the above-mentioned nickel enolates. (Scheme 65)

Treatment of 1,1-dichloro-2,3-diphenylcyclopropane **175a** with Fp^- results in reduction to the monochlorocyclopropane **176a** rather than substitution. Under typical phase-transfer conditions, the reaction leads to the bridging



172 173 174

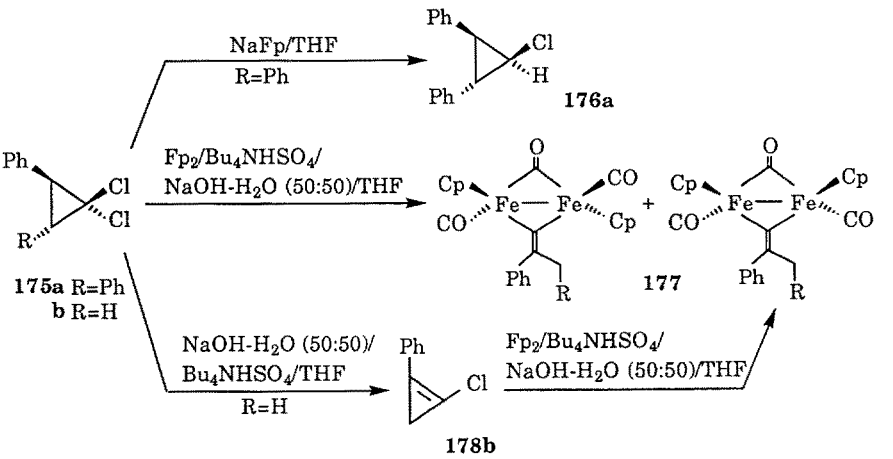
Fp=CpFe(CO)$_2$

Scheme 65

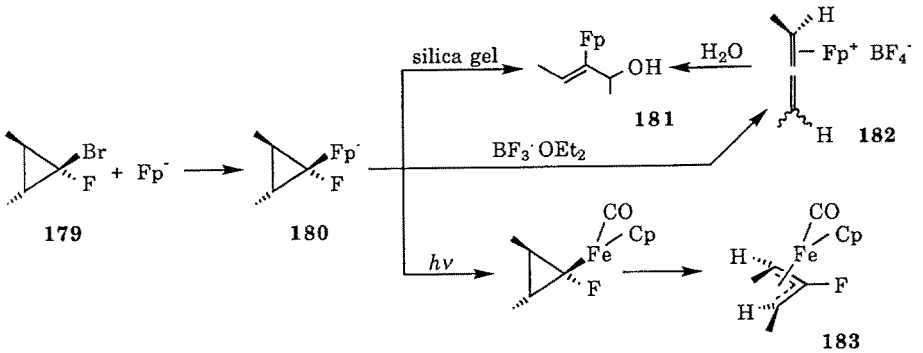
vinylidene dimer complexes **177**. 1-Chloro-2-phenylcyclopropene **178b** is initially formed as illustrated in Scheme 66 [89]. In the case of the *gem*-dibromocyclopropanes, the only isolated product is Fp_2 without formation of the corresponding σ-complexes. (Scheme 66)

Because of the exceptional C–F bond strength, the successful preparation of α-halocyclopropyl σ-complexes is realized by substitution of 1-bromo-1-fluoro-*trans*-2,3-dimethylcyclopropane **179** with Fp^- [90]. Silica gel column chromatography of the thus obtained σ-complex **180** results in ring opening to the alcohol **181** as a single stereoisomer. The allene complex **182** is produced by treatment with $BF_3 \cdot OEt_2$, indicating that **181** is derived from **182** and water. The π-allyl complex **183** is formed by photolysis via a disrotatory process.

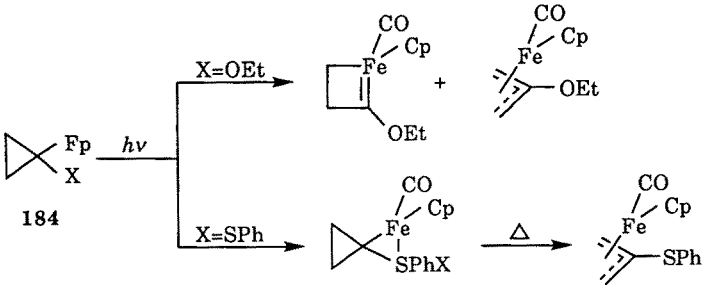
The α-alkoxy and α-phenylthio cyclopropyl Fp-σ-complexes **184** (Scheme 67) are similarly obtained by direct substitution of the corresponding bromide on the ring with Fp^-. Photolysis yields the rearranged complexes [91]. (Scheme 68)



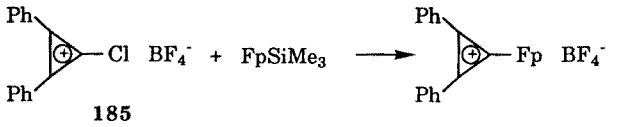
Scheme 66



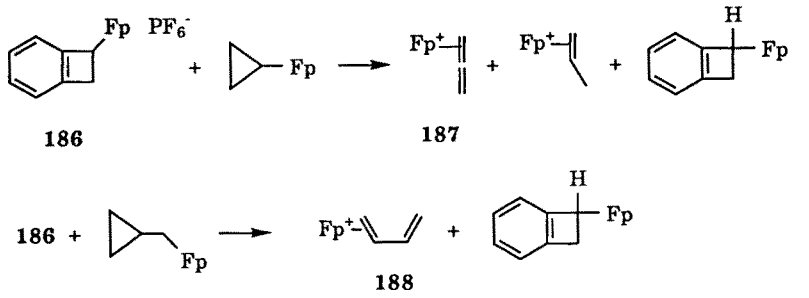
Scheme 67



Scheme 68



Scheme 69



Scheme 70

A carbon-iron bond is also formed by the reaction of the cyclopropenium salt **185** with dicarbonyl(η^5-cyclopentadienyl)(trimethylsilyl)iron [92]. (Scheme 69)

In the reaction with benzocyclobutenylidene-η^5-cyclopentadienyliron(II) hexafluorophosphate **186**, $CpFe(CO)_2R$ (R=cyclo-C_3H_5, CH_2-cyclo-C_3H_5) is converted to the allene and butadiene complexes, **187** and **188**, respectively [93]. (Scheme 70)

5-Oxo-4-oxaspiro[2.3]hexanes are rearranged in the presence of a copper catalyst to give 2(5*H*)-furanones and 2(3*H*)-furanones [94].

5.3 Reduction with Dialkyl Phosphonate

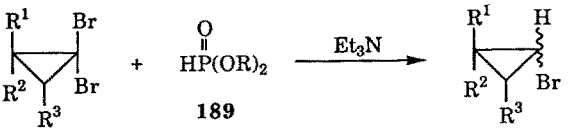
Reduction of *gem*-dibromocyclopropanes has been achieved by a variety of reducting agents to give either monobromocyclopropanes or cyclopropanes,

depending on their redox potential [77]. A combination of dialkyl phosphonate **189** (commercially named dialkyl phosphite) and triethylamine is effective for reducing organic halides, as exemplified by the monodebromination of the *gem*-dibromocyclopropanes **150** to the corresponding monobromocyclopropanes **190** with considerably high stereoselectivity [95]. The reducting capability of pentavalent dialkyl phosphonate is attributed to trivalent dialkyl phosphite via redox tautomerism. This redox property has been applied to Atherson-Todd phosphonation. A similar mechanism is operating in the reduction system consisting of dialkyl phosphonate and triethylamine. The monodebromination reaction is also carried out in liquid ammonia solution [96]. (Scheme 71)

The 1-bromo-1-chlorocyclopropanes **191** are reduced to the corresponding chlorocyclopropanes **192** selectively although *gem*-dichlorocyclopropanes do not undergo reduction with dialkyl phosphonate and triethylamine [97]. (Scheme 72)

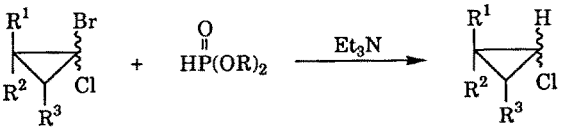
The reduction reaction of the 1,1-dibromo-2-trimethylsilyloxycyclopropanes **195**, however, results in ring fission and stereoselective deconjugation to (*E*)-β,γ-unsaturated carbonyl compounds **197** [98]. The α-bromo α,β-unsaturated carbonyl compounds **196**, which are obtained from **195** by pyrolysis, treatment with acid [99] or more smoothly with diethyl phosphonate, are involved in the initial step of the ring rearrangement. Reductive deconjugation of **196** is accomplished by treatment with dialkyl phosphonate and triethylamine to give **197** stereoselectively in good yields. The α-bromo β,γ-unsaturated carbonyl compounds generated from the dienol isomers of **196** are considered to be reduced to **197** using dialkyl phosphonate and triethylamine. Such a reduction is performed in the selective conversion of α,p-dibromoacetophenone to *p*-bromoacetophenone.

1,1-Dibromo-2-trimethylsilyloxycyclopropanes **195** and α-bromo α,β-unsaturated carbonyl compounds **196** are readily prepared by the addition of



150 **189** **190**

Scheme 71



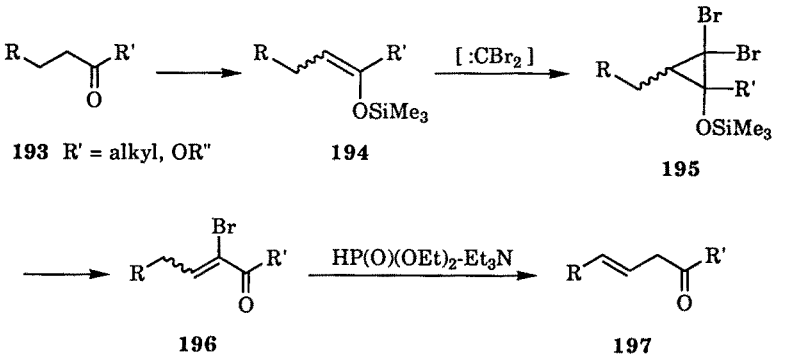
191 **192**

Scheme 72

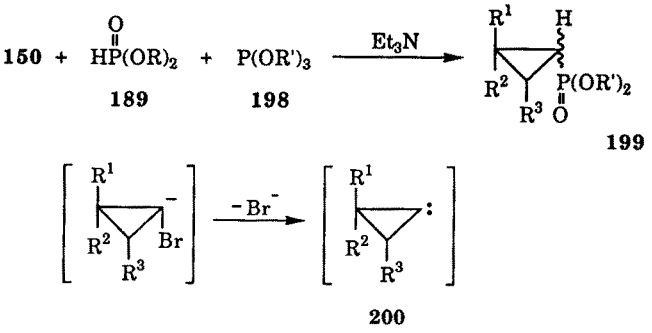
dibromocarbene to the silyl enol ethers or silyketene acetals **194**. A combination of this with the reductive deconjugation provides a versatile synthetic method for introducing a carbon–carbon double bond at the β,γ-position with one-carbon homologation of the starting carbonyl compounds **193** [100, 101]. Since β,γ-unsaturated carbonyl compounds are readily transformed to γ-hydroxy or γ-oxo α,β-unsaturated carbonyl compounds, the method has been applied to the synthesis of the naturally occurring compounds, recifeiolide [102], pyrenophorin [100], and patuolide A [103].

The presence of trialkyl phosphite **198** in the above mentioned reduction of the *gem*-dibromocyclopropanes **150** with dialkyl phosphonate and triethylamine alters the reaction course. Dialkyl cyclopropanephosphonates **199** are produced via reductive phosphonation [104]. Trialkyl phosphite participates in the carbon-phosphorous bond formation. It is supported by the exclusive formation of diisopropyl cyclopropylphosphonate in the phosphonation reaction with diethyl phosphonate and triisopropyl phosphite. (Scheme 74)

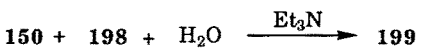
A similar transformation is also performed by treatment of **150** with trialkyl phosphite, triethylamine, and water since dialkyl phosphonate is generated by hydrolysis of trialkyl phosphite (Scheme 75). The use of deuterium oxide



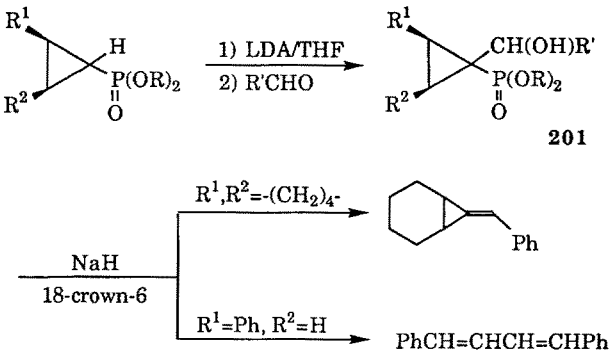
Scheme 73



Scheme 74



Scheme 75



Scheme 76

gives the allylphosphonate as a favored product via ring opening, suggesting the involvement of the cyclopropylidene intermediate **200** in the formation of the carbon-phosphorus bond [105]. (Scheme 75)

The cyclopropylphosphonate anion undergoes the stereoselective addition reaction with aldehydes [106]. Although the Wittig-Horner elimination is not observed at this stage, the olefinic compounds are produced by treatment of the adduct alcohols **201** with NaH in the presence of 18-crown-6 as illustrated in Scheme 76.

6 Transformation via One-Electron Transfer

Radicals are versatile synthetic intermediates. One of the efficient procedures for radical generation is based on one-electron oxidation or reduction with transition metal compounds. An important feature is that the redox activity of transition metal compounds can be controlled by appropriate ligands, in order to attain chemoselectivity in the generation of radicals. The application to small ring compounds provides useful methods for organic syntheses. Reductive transformation are first reviewed here.

6.1 Reduction

One-electron reduction of organic halides is convenient for generating radicals. *gem*-Dibromocyclopropanes are reduced by such a system [77]. Using an excess of MoH_2Cp_2, stereoselective debromination is successful, possibly because of

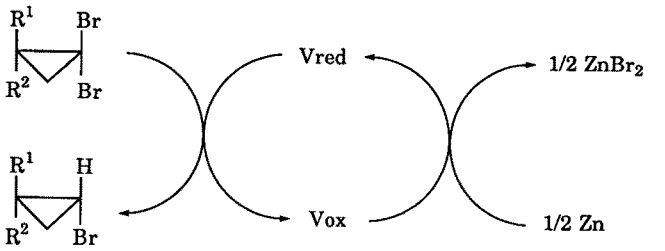
steric crowding at the molybdenum site [107]. A radical chain mechanism is implied, involving monodebromination with $\cdot MoHCp_2$ or $\cdot MoXCp_2$.

Vanadium compounds in a low oxidation state are known to be effective for inducing one-electron reduction. The highly stereoselective monodebromination of *gem*-dibromocyclopropanes proceeds with the help of a low-valent vanadium species generated from vanadium(III) chloride and zinc in dimethoxyethane in cooperation with diethyl phosphonate or triethyl phosphite [108]. This system is extended to a catalytic reaction induced by VCl_3 or $CpV(CO)_4$ as shown in Scheme 77.

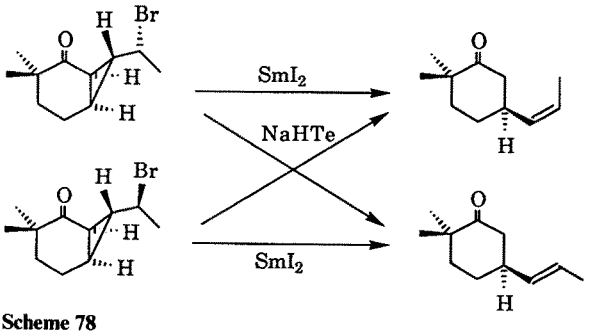
Reduction of chiral cyclopropyl halides using SmI_2 has been investigated [109]. Cyclopropylogous bromoketones undergo reductive ring cleavage to give (*E*)- or (*Z*)-2,2-dimethyl-5-(1-propenyl)cyclohexanone diastereoselectively as illustrated in Scheme 78 [110]. The reducing agents, SmI_2 and NaHTe, work in an opposing and complementary sense. (Scheme 78)

SmI_2-induced one-electron transfer permits radical ring-opening reaction of the cyclopropyl ketone **202** [111]. The regioselectively generated radical enolate **204**, via ring-opening of **203**, is trapped by electrophiles such as allyl bromide and acetyl chloride [112]. Intramolecular cyclization with a pendant chain possessing an unsaturated radicophilic acceptor yields **205**. (Scheme 79 and 80)

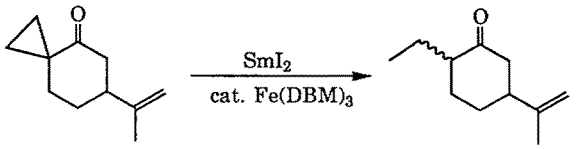
In the presence of AIBN, tributyltin hydride is an excellent dehalogenating reagent for generating radicals. The bromoalkylcyclobutanone **206** undergoes reductive ring expansion to give, via the annealed alkoxy radical, the *cis*-fused bicycle **207** stereospecifically as the major product [113]. (Scheme 81)



Scheme 77

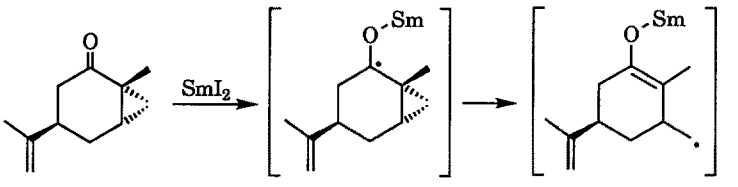


Scheme 78

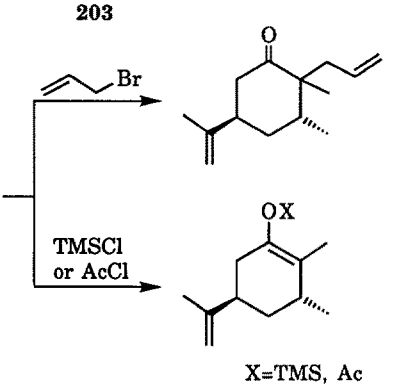


202

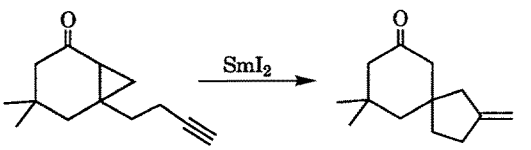
Scheme 79



203 **204**



X=TMS, Ac

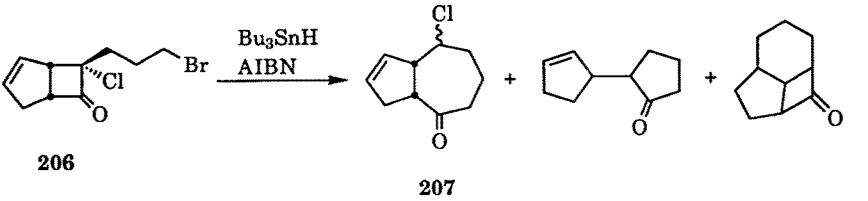


205

Scheme 80

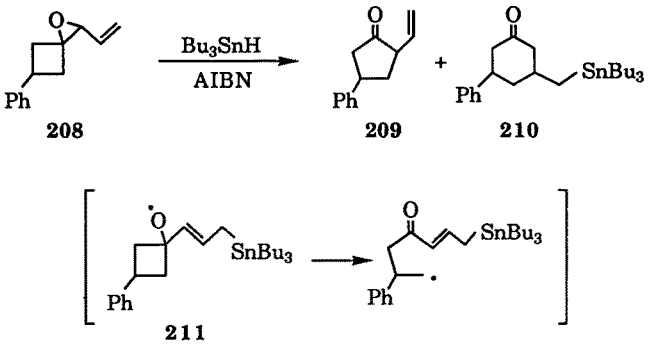
Ring cleavage of the vinyloxaspirohexane **208** to the alkoxy radical **211** followed by radical recyclization leads to ring expansion to the cyclic ketones **209** and **210** [114]. (Scheme 82)

Intramolecular radical cyclization of methylenecyclopropanes accompanies ring rearrangement [115]. In the case of (methylenecyclopropyl)propyl radicals, 5-*exo*-cyclization is observed as illustrated in Scheme 83, but 6-*exo*- and 7-*endo*-cyclizations occur with (methylenecyclopropyl)butyl radicals, depending on the substituent. (Scheme 83)



206 207

Scheme 81



208 209 210 211

Scheme 82

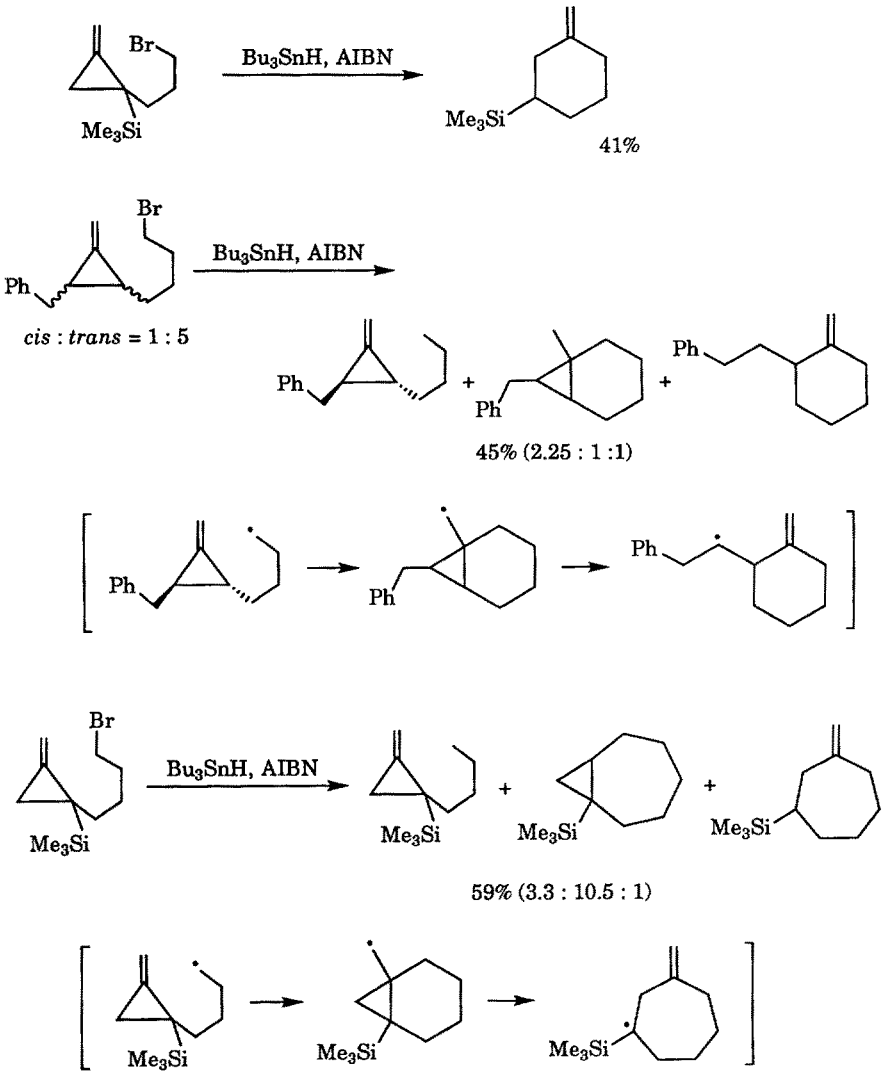
The trimethylsilyl ethers **212** of four-membered 1-alkenyl-1-cyclobutanols rearrange to the ring-expanded β-mercuriocyclopentanones **213**. These can be converted into the α-methylenecyclopentanones **214** through elimination or further expanded by one-carbon atom into cyclohexanones **215** via the Bu_3SnH-mediated free radical chain reactions [116]. A similar radical intermediate is suggested to be involved in the ring expansion of α-bromomethyl-β-keto esters [117]. (Scheme 84)

Cyclopropylmercury bromide **216** is reduced with $NaBH_4$ to yield the corresponding pyramidal σ-radical, which undergoes a carbon–carbon bond forming reaction with an olefin **217**, bearing electron-withdrawing groups, to yield **218** [118]. The organomercury compound **220** derived from ring-opening of the siloxycyclopropane **219** with $Hg(OAc)_2$ is similarly reduced to the radical, which adds to methyl vinyl ketone [119]. (Scheme 85 and 86)

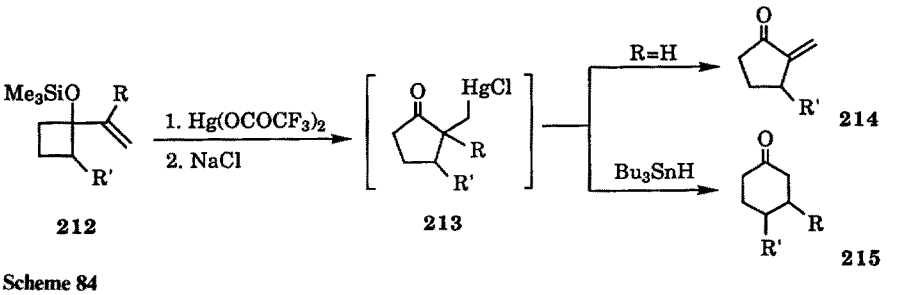
6.2 Oxidation

The complementary method for generating radicals is one-electron oxidation using transition metal compounds.

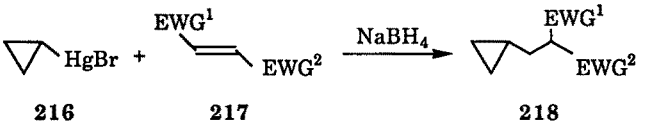
In addition to ionic ring transformation with transition metals [11], 1-trimethylsiloxybicyclo[n.1.0]alkanes undergo one-electron oxidation. Oxida-



Scheme 83

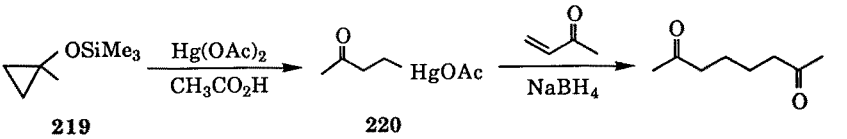


Scheme 84



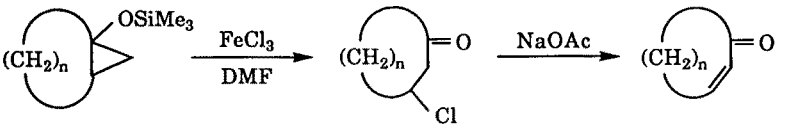
216 **217** **218**

Scheme 85



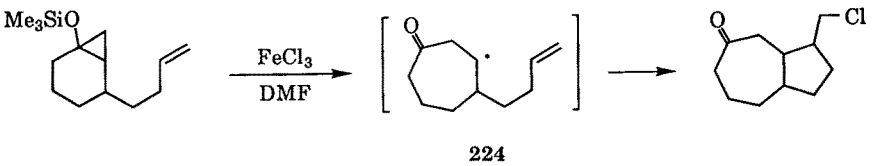
219 **220**

Scheme 86



221 **222** **223**

Scheme 87



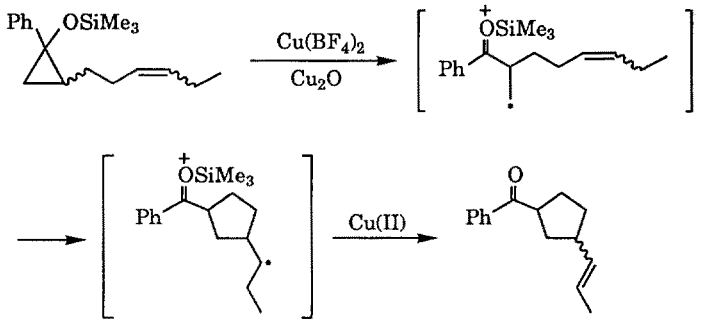
224

Scheme 88

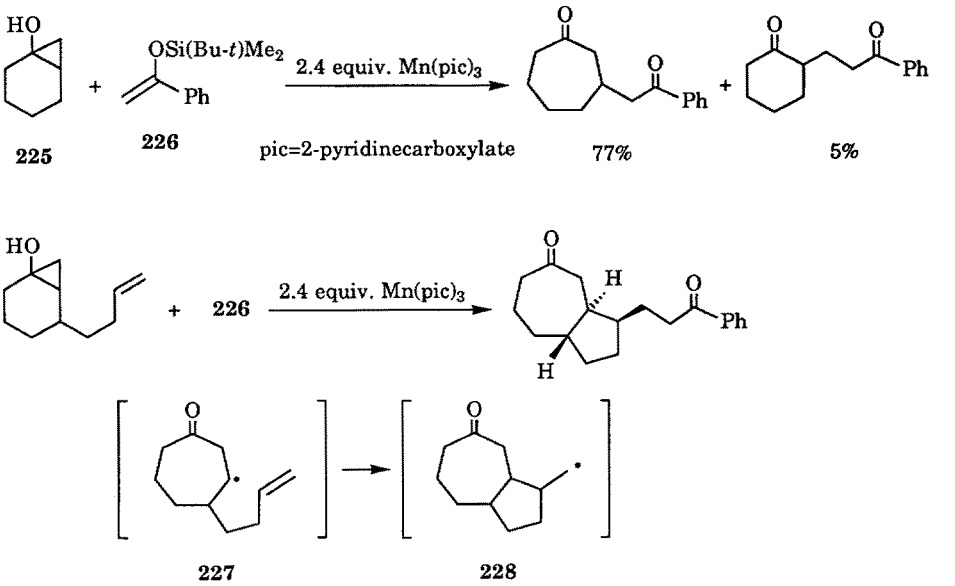
tion of **221** with iron(III) chloride leads, via regioselective ring enlargement, to the β-chlorocycloalkanones **222** [120]. The radical intermediates are considered to be generated in situ. Further treatment with sodium acetate gives the α,β-unsaturated cyclic ketones **223**. (Scheme 87)

This reaction is extended to the intramolecular ring closure of the intermediate radical **224** with olefinic or trimethylsilylacetylenic side chains [121]. $Cu(BF_4)_2$ is also effective as an oxidant (Scheme 89) [122]. Conjugate addition of Grignard reagents to 2-cyclopenten-1-one followed by cyclopropanation of the resulting silyl enol ethers gives the substituted cyclopropyl silyl ethers, which are oxidized to 4-substituted-2-cyclohexen-1-ones according to the above-mentioned method [123]. (Scheme 88 and 89)

A similar ring expansion has been reported in the oxidation of cyclopropanol **225** with manganese(III) tris(2-pyridinecarboxylate) to generate the β-keto radical, which is allowed to add to the silyl enol ether **226** [124]. The



Scheme 89

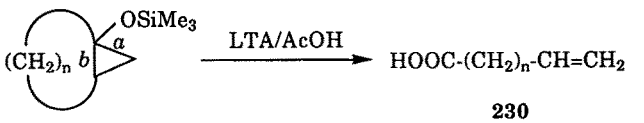


Scheme 90

radical **228** obtained by the intramolecular cyclization of **227** also reacts with various radical-trapping reagents including electron-rich olefins and diphenyl diselenide. (Scheme 90)

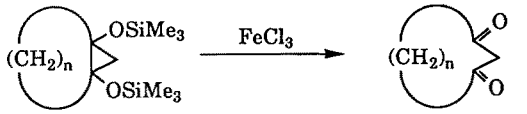
Oxidation of trimethylsiloxycyclopropanes with $AgBF_4$ results in the formation of 1,6-diketones [125]. Lead(IV) tetraacetate, which is able to oxidize a cyclopropane ring [126], induces the fragmentation of both the *a* and *b* bonds of **229** in acetic acid to give the olefinic carboxylic acids **230** [127]. (Scheme 91)

The bis(trimethylsiloxy)bicyclo[n.1.0]alkane **231** undergoes the $FeCl_3$-induced ring expansion to the cycloalkane-1,3-dione **232**. This method has been applied to the synthesis of macrocyclic tetraketones [128]. (Scheme 92)



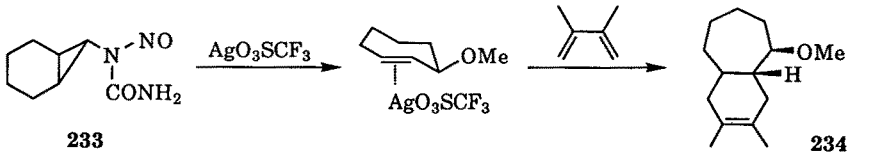
229 230

Scheme 91



231 232

Scheme 92



233 234

Scheme 93

The ring-opening of the cyclopropane nitrosourea **233** with silver triflate followed by stereospecific [4 + 2]cycloaddition yields **234** [**129**]. (Scheme 93)

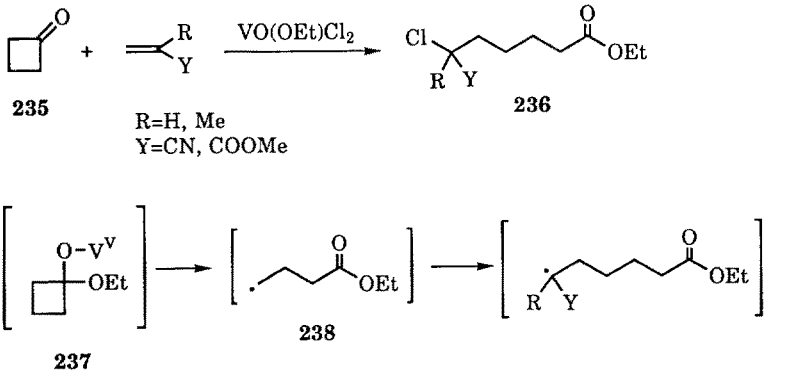
Oxovanadium(V) compounds, $VO(OR)X_2$, are revealed to be Lewis acids with one-electron oxidation capability. These properties permit versatile oxidative transformations of carbonyl and organosilicon compounds as exemplified by ring-opening oxygenation of cyclic ketones [130], dehydrogenative aromatization of 2-cyclohexen-1-ones [131], allylic oxidation of α,β-unsaturated carbonyl compounds [132], decarboxylative oxidation of α-amino acids [133], oxidative desilylation of silyl enol ethers [134], allylic silanes, and benzylic silanes [135].

Oxidation of cyclobutanone **235** with more than 2 equivalents of $VO(OEt)Cl_2$ leads to ring-opening addition to an olefin bearing an electron-withdrawing group to give **236** [136]. Alkyl 4-chlorobutyrate is obtained in the absence of an olefin. The radical intermediate **238** is considered to be generated by one-electron oxidation of the alkoxide intermediate **237**. This carbon-carbon bond forming reaction is facilitated by the presence of $CuCl_2$.

Addition of alkyllithium to cyclobutanones and transmetallation with $VO(OEt)Cl_2$ is considered to give a similar alkoxide intermediates, which are converted to either the γ-chloroketones **239** or the olefinic ketone **240** depending on the substituent of cyclobutanones. Deprotonation of the cationic species, formed by further oxidation of the radical intermediate, leads to **240**. The oxovanadium compound also induces tandem nucleophilic addition of silyl enol ethers and oxidative ring-opening transformation to produce 6-chloro-1,3-diketones and 2-tetrahydrofurylidene ketones. (Scheme 95)

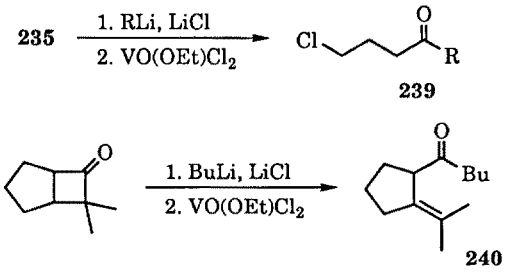
Olefinic cyclobutanols are oxidized using $Mn(OAc)_3 \cdot 2H_2O$ in ethanol to give the corresponding tertiary radicals, which undergo 6-*endo*- or 5-*exo*-cyclization to form the corresponding radicals as shown in Scheme 96 [137]. Ring-opening carbonylation of cyclobutanols is induced by one-electron oxidation with lead tetraacetate under carbon monoxide [138]. 4-Hydroxy-2-cyclobutenones are oxidized with lead tetraacetate to give 5-acetoxy-2(5*H*)-furanones via acyl radicals [139]. (Scheme 96)

The oxidation of 2,2-dichloro-3-cyclobuten-1-ones **241** with $VO(OR)Cl_2$ results in the regioselective formation of alkyl 2,4,4-trichloro-3-butenoates **242** with chlorination at the α-position of **243** [140]. (Scheme 97)



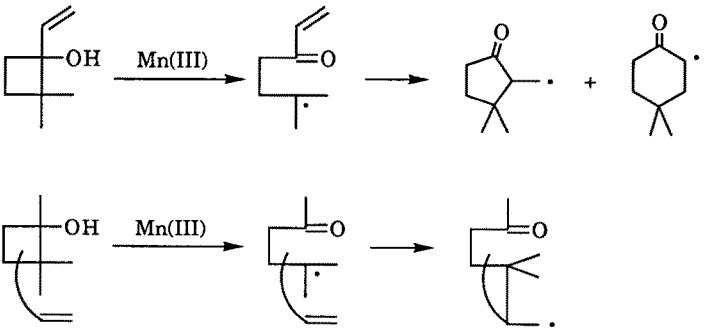
235 **236** **237** **238**

Scheme 94

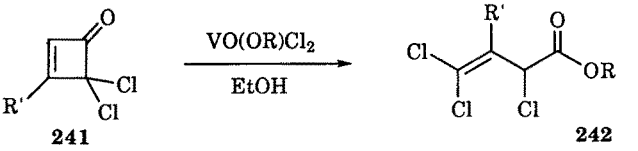


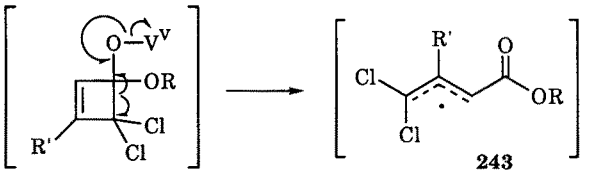
235 **239** **240**

Scheme 95



Scheme 96



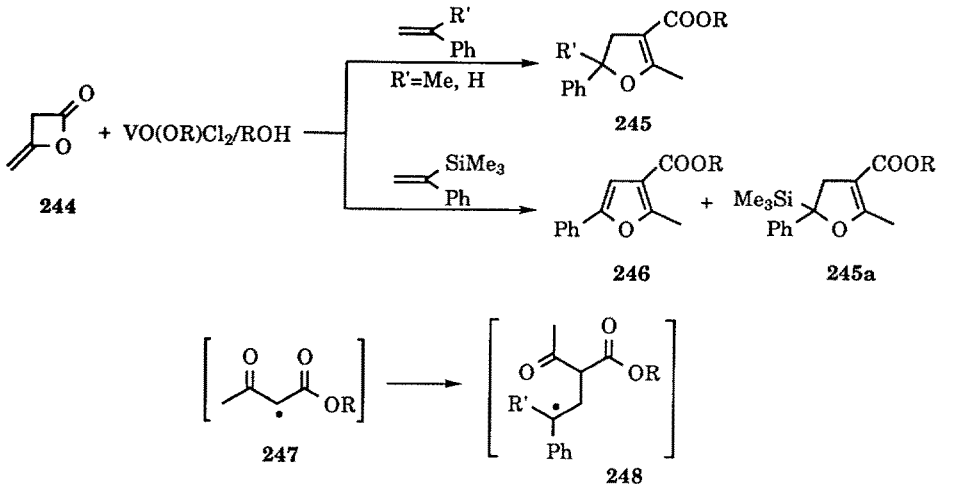


Scheme 97

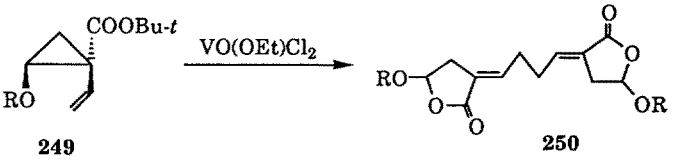
The ring-opening cycloaddition of diketene **244** with styrenes is performed by $VO(OR)Cl_2$, giving 3-alkoxycarbonyl-2-methyl-5-phenyl-4,5-dihydrofurans **245** [141]. Desilylative aromatization to the furan **246** is observed starting from α-trimethylsilylstyrene. The radical **247**, generated by ring opening of **244**, is capable of forming a new carbon–carbon bond with styrenes to yield **248**. The carbon–silicon bond of the thus obtained furan **245a** is oxidatively cleaved by $VO(OR)Cl_2$. 1,1,3,3-Tetramethylcyclobutan-2,4-dione undergoes the $VO(OEt)Cl_2$-induced oxidative ring cleavage to 4-chloro-3-oxo-2,2,4-trimethylpentanoate and 3-oxo-2,2,4-trimethyl-4-pentenoate [142]. (Scheme 98)

Oxidation of the 2-alkoxycyclopropanecarboxylate **249** bearing both donor and acceptor substituents with $VO(OEt)Cl_2$ leads to dimerization to the α-ethylidenebutyrolactone **250** [143]. (Scheme 99)

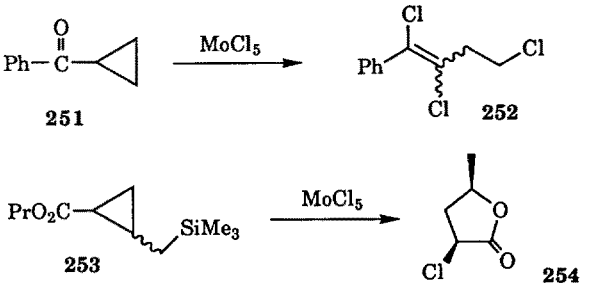
$MoCl_5$ promotes the ring-opening transformations of cyclopropyl ketones. Cyclopropyl phenyl ketone **251** is converted to 1-phenyl-1,2,4-trichloro-1-butene **252**. Desilylative lactonization of propyl 2-(trimethylsilylmethyl)cyclopropanecarboxylate **253** yields *cis*-2-chloro-4-pentanolide **254** stereoselectively [144]. (Scheme 100)



Scheme 98



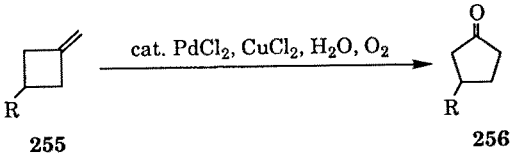
Scheme 99



Scheme 100

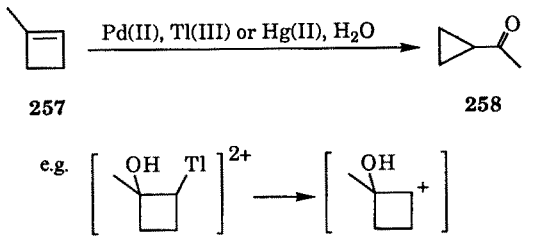
7 Oxidative Functionalization with Transition Metals

The palladium(II)-catalyzed hydroxylation of the methylenecyclobutane **255** in the presence of water results in ring enlargement to the corresponding cyclopentanones **256** [145]. (Scheme 101)



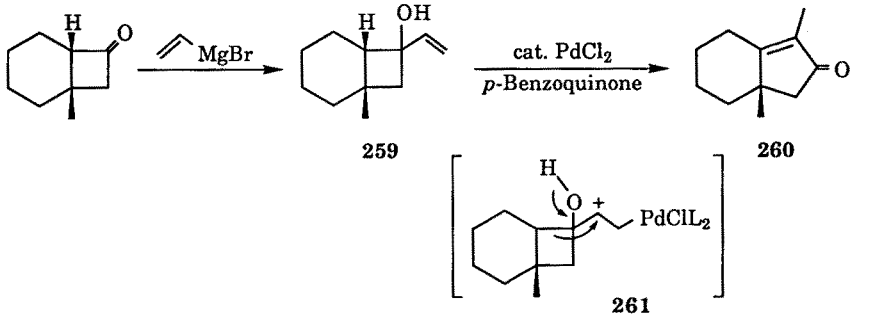
255 256

Scheme 101



257 258

Scheme 102



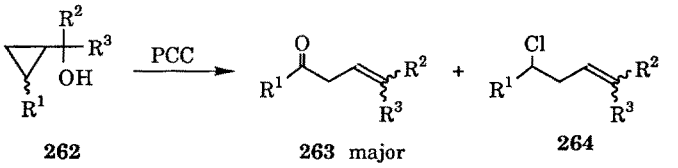
259 260 261

Scheme 103

Metal ions such as thallium(III), mercury(II), and palladium(II) in aqueous solution oxidize 1-methylcyclobutene **257** to cyclopropyl methyl ketone **258**. A mechanism involving the carbonium ion is operating [146]. (Scheme 102)

The 2-cyclopenten-1-one **260** is produced by treatment of the 1-vinyl-1-cyclobutanol **259** with $PdCl_2(PhCN)_2$ and *p*-benzoquinone [147]. Oxidative ring expansion takes place in the intermediate **261**. 1-(1-Alkynyl)-4-methoxy-4-methyl-2-cyclobutenols also undergo the palladium-catalyzed ring expansion to give 4-alkoxy-5-alkylidenecyclopentenones [148]. (Scheme 103)

Oxidative rearrangement of the *tertiary*-cyclopropylcarbinol **262** using PCC leads to the β,γ-unsaturated ketone **263** and halide **264** [149]. (Scheme 104)



262 263 major 264

Scheme 104

8 Conclusion

In view of the extensive and fruitful results described above, redox reactions of small ring compounds provide a variety of versatile synthetic methods. In particular, transition metal-induced redox reactions play an important role in this area. Transition metal intermediates such as metallacycles, carbene complexes, π-allyl complexes, transition metal enolates are involved, allowing further transformations, for example, insertion of olefins and carbon monoxide. Two-electron- and one-electron-mediated transformations are complementary to each other although the latter radical reactions have been less thoroughly investigated.

Some other reviews may also help the reader's understanding [2]. One useful reaction, which is not described here but which was already reviewed in the last volume of this series [60, 150], is the transition metal-catalyzed [3 + 2]cycloaddition of methylenecyclopropanes.

transition metal compounds and the construction of efficient redox systems may be expected to present a conceptually novel approach to organic synthesis, which will be of considerable importance in the future.

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