# Heterocycles from Alkylidenecyclopropanes

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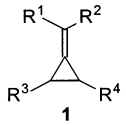
## I. Introduction

Heterocyclic compounds, which represent almost two-thirds of all the known organic compounds, include some of the most significant for human beings. It is not surprising, therefore, that this class of compounds has received special attention by chemists of different origin to provide selective synthetic access to the enormous variety of structural features typical of this class.

The scope of this review is to collect and analyze the methods that make use of strained alkylidenecyclopropanes[1] (ACPs) **1** to produce heterocyclic compounds. Doing this, we are confident of making a useful contribution to the organic chemistry community because, despite the huge literature already available on these rather sophisticated olefins, their employment in the synthesis of heterocyclic compounds has been only barely examined before and it is time to propose a comprehensive review that will present the state of the art.

**Chart 1**




**1**

Alkylidenecyclopropanes **1**, including the parent compound methylenecyclopropane (MCP, **2**), are highly strained molecules, but at the same time, most of them are so stable that they can be used in many synthetic applications. The high energy incorporated in these compounds, associated with a large structural differentiation available, confers an enormous potential in organic syntheses that has been only partially disclosed in the past decades.[2]

Numerous efficient and straightforward syntheses of different types of alkylidenecyclopropanes have appeared in the literature, and the matter has been thoroughly reviewed.[1]

The most typical reactivity of alkylidenecyclopropanes is their involvement in cycloaddition reactions.[3,4] In fact, as strained alkenes, they can be substrates for Diels−Alder or 1,3-dipolar cycloadditions. Moreover, an alkylidenecyclopropane is a synthetic equivalent of trimethylenemethane (TMM), a reactive species that, due to the work of Binger[4] and Trost,[5] can be considered an all-carbon 1,3-dipole. The synthesis of heterocycles using these processes essentially rests on the use of reactive partners containing one or more heteroatoms. A high molecular diversity is realized through the many possible combinations and will be analyzed accordingly. Dealing with cycloaddition processes, we will avoid any discrimination between the concerted or stepwise nature of the processes, only mentioning this difference during the discussion. To limit the analysis, only examples in which the heteroatom is directly involved in the reacting moiety will be taken into account and not in rings fused or linked to the reacting moiety.

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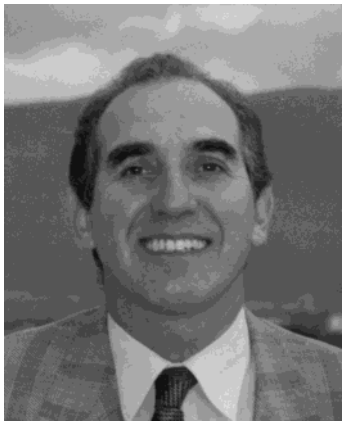

Alberto Brandi was born in Florence in 1951. He received a doctorate in chemistry in 1975 from the University of Florence, became a CNR fellow in 1978, and in 1980 was Ricercatore Universitario at the Department of Organic Chemistry of University of Florence. From 1982 to 1984 he was a NATO fellow with Professor Barry M. Trost at the University of Wisconsin—Madison and from 1987 to 1990 was Associate Professor at the University of Basilicata-Potenza. In 1990, he returned to the University of Florence, where in 1994 he became Professor of Organic Chemistry in the Faculty of Science. From 2001, he has been head of the Department of Organic Chemistry "U. Schiff" of the University of Florence. Recent research interests include the chemistry of strained heterocycles spiro-fused with small rings, stereoselective 1,3-dipolar cycloadditions of enantiopure nitrones for asymmetric syntheses of alkaloids and biologically active aza-heterocycles, and synthesis of peptidomimetics.

Stefano Cicchi, born in Firenze in 1963, is a researcher at the Organic Chemistry Department of the University of Firenze. He received his Laurea in chemistry in 1989 from the University of Firenze and in 1992 his doctoral degree in synthetic organic chemistry with work on 1,3-dipolar cycloaddition reactions of nitrones with phosphinylalkenes. He was CNR fellow from 1993 to 1995 with Dr. Claudio Bianchini (ICCOM-CNR, Firenze). He spent a research period in the laboratories of Prof. Bernd Giese (Basel, Switzerland, 1991) and Prof. Pedro Merino (Zaragoza, E, 2002). His research interests concern new synthetic methods and strategies for the synthesis of heterocycles with biological activity, the synthesis and study of new dendrimeric materials, and the chemistry of small rings.

The reader can mentally make this logical variation extending the ample possibilities offered by the chemistry for the synthesis of heterocyclic compounds.

## *II. Heterocycles from [4+2] Cycloadditions*

Despite the large body of Diels−Alder cycloadditions in organic synthesis, alkylidenecyclopropanes are still underestimated as valuable partners in these reactions. A recent review gives an overview of the known literature.[3] Even less is, therefore, produced

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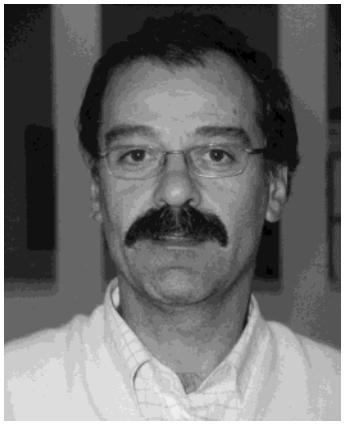


Andrea Goti was born in Firenze, Italy, in 1957. He studied at the University of Firenze, where he earned his doctoral degree in chemistry in 1982, under the supervision of Professor F. De Sarlo. He was a CNR Postdoctoral Fellow at Princeton University with Professor M. F. Semmelhack (1987) and a Vigoni Visiting Researcher at the Georg-August University of Göttingen (Germany) with Professor A. de Meijere (1994). From 1985 to 1998 he was a Researcher at the Consiglio Nazionale delle Ricerche, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni (CSCEA) in Firenze. In 1998, he was appointed Associate Professor at the University of Firenze, where he was nominated Full Professor (Professore Straordinario) in 2002. His current research projects focus on stereoselective organic synthesis based on 1,3-dipolar cycloaddition chemistry, synthetic applications of organometal derivatives, synthesis of biologically active natural and non-natural products, new oxidation methods, and green chemistry.

in the field of heterocyclic chemistry. In principle, alkylidenecyclopropanes can both behave as dienophiles or, when properly substituted, as dienes to afford heterocycles, and the two aspects will be addressed separately.

### A. Alkylidenecyclopropanes as Dienophiles

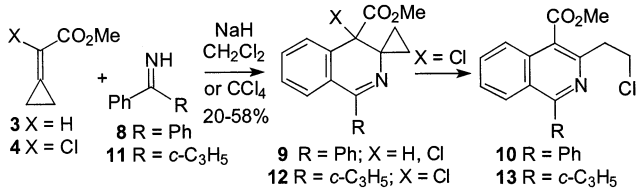
#### *1. Intermolecular Cycloadditions*

The parent methylenecyclopropane (**2**), according to its limited use as a dienophile in Diels−Alder

cycloadditions,[6] is not known to undergo hetero [4+2] cycloadditions. Examples of the use of alkylidenecyclopropanes as dienophiles are also very limited in the literature and refer mainly to more sophisticated substrates such as cyclopropylideneacetates **3** and **4**, bicyclopropylidene (**5**), 2-cyclopropylideneimidazolidine **6,** or 2,2-difluoromethylenecyclopropane (**7**).

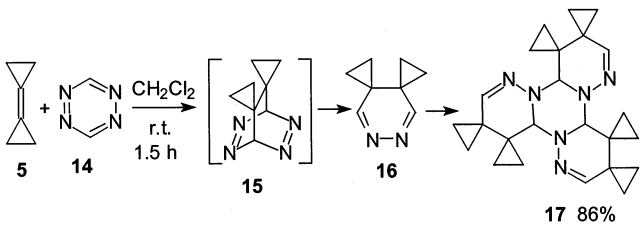
The hetero Diels−Alder cycloaddition of imines **8** and **11** with 2-chlorocyclopropylideneacetate (**4**) gave directly the isoquinolines **10** (R = Ph) and **13** (R = *c*-$C_3H_5$) (up to 58%), respectively.[7] The driving force of aromatization facilitates the cyclopropylmethyl chloride/homoallyl chloride rearrangement. When the chloride is absent, the spirocyclopropane product **9** (R = Ph, X = H), derived from dehydrogenation of the primary adduct, can be isolated (Scheme 1).

**Scheme 1**




Bicyclopropylidene[8] (**5**), in contrast to the parent MCP (**2**), gives [4+2] cycloadditions very easily. **5** is a unique olefin, combining the structural features of a tetrasubstituted ethylene and two methylenecyclopropane units.[9] The central C=C bond imparts properties that more closely resemble those of the central double bond in butatriene than of that in a simple tetrasubstituted ethylene. Apparently, **5** undergoes [4+2] cycloadditions with inverse electron demand more readily than normal Diels−Alder reactions,[3] in accord with its high-lying HOMO.[9,10] 1,2,4,5-Tetrazine (**14**) and its derivatives as electron-deficient cycloaddends undergo cycloadditions with **5** very smoothly at room temperature. The colorless crystalline product isolated in 86% yield is a mixture of at least two stereoisomeric compounds **17**, trimers of the 8,9-diazadispiro[2.0.2.4]deca-7,9-diene (**16**) evidently formed via the normal [4+2]-cycloadduct **15** after nitrogen extrusion (Scheme 2).[11] Several

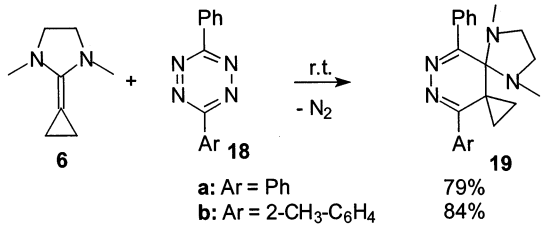
**Scheme 2**




attempts to trap the monomeric **16**, which should be in equilibrium with **17**,[12] as a cycloadduct with a second molecule of **5** were unsuccessful even at high temperatures in chloroform (70 °C) or toluene-$d_8$ (150 °C).[11]

The highly reactive 2-cyclopropylideneimidazolidine **6** reacts rapidly at room temperature with diaryl-substituted 1,2,4,5-tetrazines **18** to give the dispiro products **19** via a two-step hetero Diels−Alder reaction followed by elimination of nitrogen. The unsymmetrically substituted tetrazine **18b** afforded the single regioisomer **19b** in 84% yield (Scheme 3).[13]

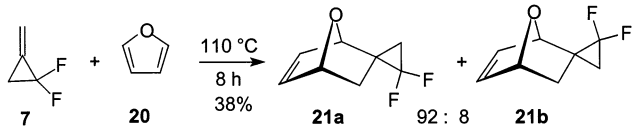
**Scheme 3**




Apart from these three examples of hetero Diels−Alder, all the other examples refer to the use of furans or thiophene *S*-oxides as dienes.

The substitution of two, or more, ring protons of MCP with fluorine atoms seems to improve dramatically the dienophilic reactivity of the exocyclic double bond. 2,2-Difluoromethylenecyclopropane (**7**) is quite a reactive dienophile in Diels−Alder cycloadditions[14] and with furan (**20**) is able to form spirofused heterocyclic adducts (Scheme 4). The endo/exo selec-

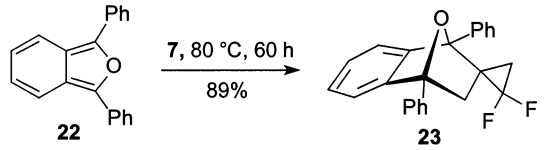
**Scheme 4**




tivity of the $CF_2$ is in favor of the endo adduct, and it is larger for furan compared to cyclopentadiene, probably to minimize dipolar interactions, in the transition state, between oxygen and fluorine.

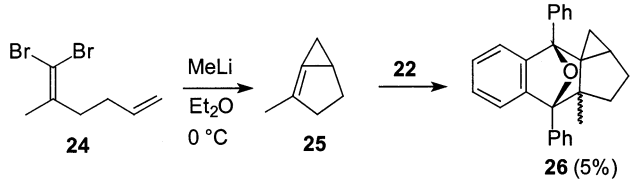
Analogously, diphenylisobenzofuran **22** reacted with **7** to give only the endo isomer **23** (Scheme 5).[14]

**Scheme 5**




The highly strained alkylidenecyclopropane 2-methylbicyclo[3.1.0]hex-1-ene (**25**), formed by cyclization of the carbenoid generated from dibromide **24** at 0 °C, gave, in the presence of an excess of 1,3-diphenylisobenzofuran (**22**), a very small amount (5%) of a 2:1 mixture of diastereoisomeric Diels−Alder adducts **26** (Scheme 6).[15] The parent furan (**20**)

**Scheme 6**

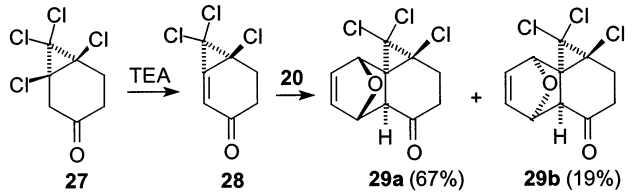



does not capture **25** even when used as solvent for the carbenoid cyclization.

Dehydrochlorination of the bicycloheptanone **27** afforded the unstable alkylidenecyclopropane **28**,

which was trapped by furan (**20**) to give the diastereomeric adducts **29a** and **29b** in 78:22 ratio (Scheme 7).[16]

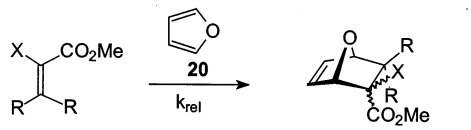
**Scheme 7**




Alkylidenecyclopropanes substituted with electron-withdrawing groups were more extensively studied because of their higher reactivity. 2-Hetero-substituted 2-cyclopropylideneacetates, as ring-strained activated acrylates, are highly reactive dienophiles in Diels–Alder reactions but are also powerful Michael acceptors. The reactivity of these compounds is enhanced by the same strain release both in Diels–Alder cycloadditions and in 1,4-additions, and indeed the borderline between tandem Michael addition–cyclization and Diels–Alder cycloaddition is not well-defined in many cases.

The relative reactivities of several of these 2-hetero-substituted 2-cyclopropylideneacetates **4** and **30**–**32** as well as of the parent 2-cyclopropylideneacetate **3** and acrylate **33** toward furan (**20**) were determined by competition experiments[7a] (Table 1). The endo/exo selectivity is low but in accordance with that of simple acrylic esters.

**Table 1. Relative Rates of Reaction of Cyclopropylideneacetates 3, 4, and 30–32 and Acrylic Ester 33 with 20**




**3, 4, 30-32** R,R = $(CH_2)_2$
**33** R = H

**34** R,R = $(CH_2)_2$
**35** R = H

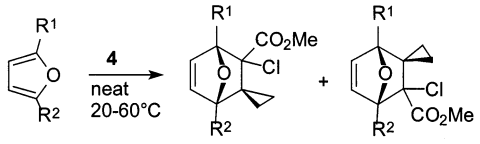
| entry | cpd | R, R | X | product | relative rates (endo/exo[a]) |
|---|---|---|---|---|---|
| 1 | **3** | $CH_2$–$CH_2$ | H | **34a** | 4 (5.6) |
| 2 | **30** | $CH_2$–$CH_2$ | F | **34b** | 3 (0.5) |
| 3 | **4** | $CH_2$–$CH_2$ | Cl | **34c** | 16 (1.4) |
| 4 | **31** | $CH_2$–$CH_2$ | Br | **34d** | 16 (1.1) |
| 5 | **32** | $CH_2$–$CH_2$ | $N_3$ | **34e** | 27 (2.8) |
| 6 | **33** | H, H | H | **35** | 1 (1.3) |

[a] The endo/exo designation relates to the position of the $CO_2Me$ group.

The diastereomeric Diels–Alder adducts **34a**–**34d** were isolated in yields ranging from 43 to 72%. The unstable azido derivative **32** did not add to furan under thermal conditions but afforded *endo/exo*-**34e** in 16% yield under 10 kbar pressure.[17]

Furans react readily with **4** in [4+2] cycloadditions, but the reactivity depends on the substitution pattern of the heterocyclic diene. Whereas the parent furan (**20**) reacts with neat **4** at 45 °C affording excellent yields (90%) of a 1.4:1 endo/exo mixture of cycloadducts **34c** (Table 1, entry 3),[18] and 2-methylfuran (**36a**) afforded the corresponding *endo*-**37a** and *exo*-**37a** as a 1.5:1 mixture in 76% yield (Table 2, entry 1), 2,5-dimethylfuran (**36b**) reacted much more slowly and, after 120 h, gave only 5% conversion to *endo/exo*-**37b** (2:1) (Table 2, entry 2).

**Table 2. Diels–Alder Additions of Furans 36a–e to Methyl 2-Chloro-2-cyclopropylideneacetate (4)**



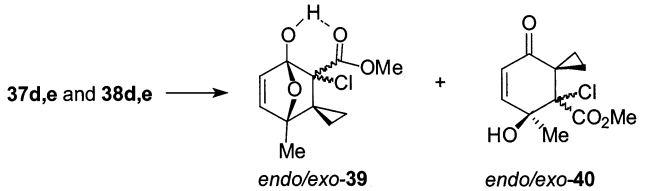

**36** **37** **38**

| | | | | | product ratio[b] | | | |
|---|---|---|---|---|---|---|---|---|
| entry | **36** | $R^1$ | $R^2$ | yield[a] (%) | *endo*-**37**[c] | *exo*-**37**[c] | *endo*-**38**[c] | *exo*-**38**[c] |
| 1 | **a** | Me | H | 76 | 1.5 | 1 | | |
| 2 | **b** | Me | Me | 72 | 2 | 1 | | |
| 3 | **c** | OMe | H | 25 (95)[d] | 1.2 | 1 | | |
| 4 | **d** | $OSiMe_3$ | Me | 8.6 (81)[d] | 8 | 2 | 1 | 0.5 |
| 5 | **e** | OMe | Me | 48 (78)[d] | 10 | 3 | 1 | 0.3 |

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

The added methyl group in **36b** probably interacts with the cyclopropyl ring of **4**, increasing the energy of the transition state. Only upon heating at 60 °C was the reaction complete within 12 h (Table 2).[18] The corresponding cycloadducts *endo*-**37c** and *exo*-**37c** of 2-methoxyfuran (**36c**), formed in 1.2:1 ratio, turned out to be extremely hydrolyzable. 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 (**36d**) underwent smooth Diels–Alder reaction with **4** at room temperature to give all four possible cycloadducts *endo*-**37d**, *exo*-**37d**, *endo*-**38d**, and *exo*-**38d** in 8:2:1:0.5 ratio (Table 2), but extensive hydrolytic decomposition occurred as well on purification by silica gel chromatography. Mixtures of diastereomeric hydrolyzed products **39** and **40** (Scheme 8)[18] were also obtained from cycloadducts

**Scheme 8**

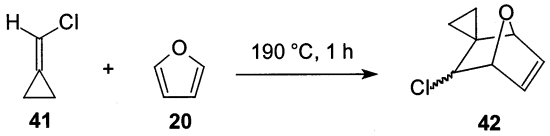



of furans **36d** and **36e** on purification by column chromatography on both silica gel and neutral alumina. The hydrolysis was avoided by addition of triethylamine (3–5%) to the eluent for chromatography. and compounds *endo/exo*-**37e** and *endo/exo*-**38e** could be separated without decomposition in this way. Attempts to enhance the endo selectivity by performing the reaction between **36e** and **4** in the presence of various Lewis acids failed. Experiments

carried out with furan (**20**) and **4** under high pressure (8−10 kbar) also did not indicate a significant increase in endo selectivity. The major isomers *endo*-**37d** and *endo*-**37e** have been transformed to a potential intermediate for the synthesis of the antitumor sesquiterpene illudin M.[7a,18,19]

Chloromethylenecyclopropane (**41**) is much less reactive than **4** and underwent [4+2] cycloaddition reactions at 190 °C in the presence of a large excess of furan (**20**) to give mixtures of *endo*- and *exo*-**42** (Scheme 9).[20]

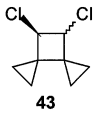
**Scheme 9**




**41** **20** **42**

Without a large excess of 1,3-diene, the formation of cis and trans head-to-head dimer **43** competed. The composition of the reaction mixture depends on the reaction time, as an equilibration by a reversal of the [4+2] cycloaddition is likely to take place.[20]

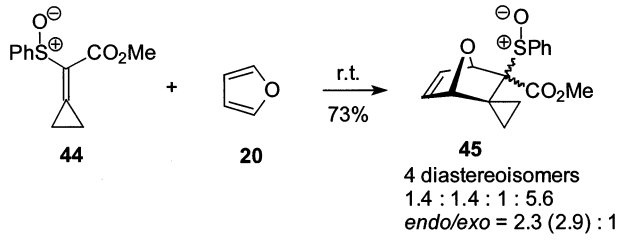
**Chart 2**




**43**

The 2-phenylsulfinyl ester **44**, which had been prepared in racemic form, rapidly cycloadded to **20** at room temperature, albeit with low stereoselectivity (Scheme 10).[21]

**Scheme 10**




**44** **20** **45**

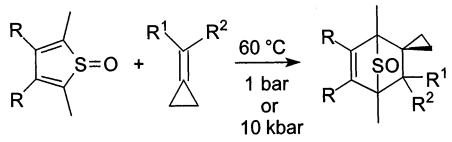
4 diastereoisomers
1.4 : 1.4 : 1 : 5.6
*endo/exo* = 2.3 (2.9) : 1

Thiophene *S*-oxides **46** react readily with ACPs with one or two electron-withdrawing groups on the exocyclic position to give only one diastereoisomer **49** (Table 3).[22]

Bicyclopropylidene (**5**) showed a low reactivity toward heterocyclic dienes **46a** and **46b** at ambient pressure but afforded cycloadducts **49e** and **49f** under high pressure (10 kbar) (Table 3).[22] The Wittig olefination of cyclopropanone hemiacetal **51** with stabilized phosphoranes **50** was used to generate in situ monosubstituted alkylidenecyclopropanes, which were trapped by thiophene derivatives **46** (Table 4).[22]

Other examples of Diels−Alder reactions involving cyclopropylideneacetates **3** and **4** in Pd-catalyzed domino processes aimed at the synthesis of heterocycles are reported in section VIII.

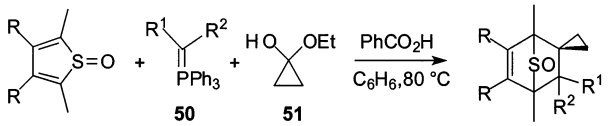
**Table 3. Diels−Alder Additions of Thiophene *S*-Oxides 46 to Methylenecyclopropanes 3−5, 47, and 48**




**46** **3-5, 47, 48** **49**

| | | | | | | | yield (%) | |
|---|---|---|---|---|---|---|---|---|
| entry | | R | | $R^1$ | $R^2$ | | 1 bar | 10 kbar |
| 1 | **46a** | Bn | **4** | $CO_2Me$ | Cl | **49a** | 60 | 92 |
| 2 | **46b** | $CH_2C_6H_4$-*p*-*t*Bu | **47** | $CO_2Et$ | H | **49b** | 85 | |
| 3 | **46a** | Bn | **48** | $CO_2H$ | H | **49c** | 50 | |
| 4 | **46c** | Br | **3** | $CO_2Me$ | H | **49d** | 67 | |
| 5 | **46b** | $CH_2C_6H_4$-*p*-*t*Bu | **5** | -$(CH_2CH_2)$- | | **49e** | | 48 |
| 6 | **46a** | Bn | **5** | -$(CH_2CH_2)$- | | **49f** | | 43 |

**Table 4. Diels−Alder Additions of Thiophene *S*-Oxides 46 to in Situ-Generated ACPs**




**46** **50** **51** **49**

| entry | | R | | $R^1$ | $R^2$ | | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **46b** | $CH_2C_6H_4$-*p*-*t*Bu | **50a** | COPh | H | **49g** | 90 |
| 2 | **46a** | Bn | **50b** | $COC_6H_4$-*p*-Cl | H | **49h** | 91 |
| 3 | **46a** | Bn | **50c** | COMe | H | **49i** | 52 |
| 4 | **46a** | Bn | **50d** | CN | H | **49j** | 71 |
| 5 | **46d** | $C_6H_4$-*p*-OMe | **50e** | $CO_2Et$ | H | **49k** | 67 |

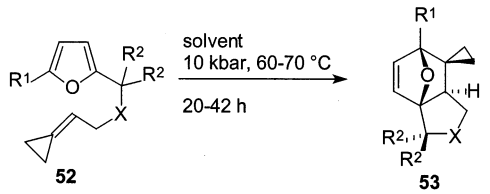
### *2. Intramolecular Cycloadditions*

The furfuryl derivatives **52**, with an allyl ether (X = O) or allylamine (X = NMe) type chain linked to an ACP moiety, readily undergo intramolecular Diels−Alder reactions at 10−12 kbar to yield spirocyclopropane-annelated tricyclic structures **53** in excellent yields and with high diastereoselectivity (Table 5).[23]

At ambient pressure, **52a** 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 only marginally successful. In contrast, on exposing the furan derivatives **52** to high pressure (10 kbar) in 0.1−0.5 M solutions at 60−70 °C, a clean cycloaddition took place (Table 5).

While most reactions proceed cleanly in the solvent mixture acetonitrile/tetrahydrofuran (1:1), allyl ether **52a** showed the cleanest reaction in ethanol containing 4% of water, with the highest yield up to 100%. The allylamide **52f** in acetonitrile/tetrahydrofuran reacted more slowly, similarly to the allylamine **52e**, both giving lower yield of products **53e** and **53f** (Table 5, entries 5 and 6). The transformation of allylamine **52e** was also attempted in ethanol or in dichloromethane but always gave rise to complex mixtures

**Table 5. Intramolecular Diels−Alder Reactions under High Pressure of Furfuryl-Substituted ACPs 52**

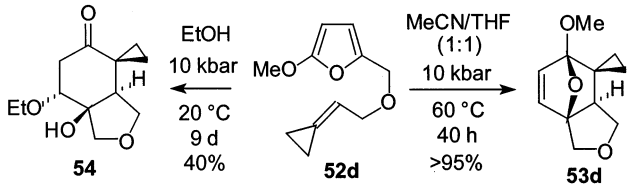



52 53

| entry | starting material | X | $R^1$ | $R^2$ | product | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **52a** | O | H | H | **53a** | >95 |
| 2 | **52b** | O | H | Me | **53b** | >95 |
| 3 | **52c** | O | Me | H | **53c** | 74 |
| 4 | **52d** | O | OMe | H | **53d** | >95 |
| 5 | **52e** | NMe | H | H | **53e** | 50 |
| 6 | **52f** | NMe | H | =O | **53f** | 55 |

of products of high polarity. In an attempt to cyclize the 5-methoxyfuran derivative **52d** in ethanol under 10 kbar pressure at room temperature, the bicyclic ketone **54** was isolated instead of the expected tricyclic system **53d**. However, in acetonitrile/tetrahydrofuran at 60 °C, **53d** was obtained in virtually quantitative yield (Scheme 11).[23]

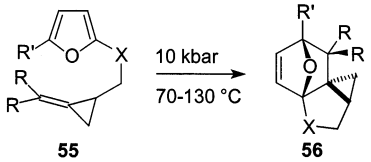
**Scheme 11**




54 52d 53d

A number of bicyclopropylidene and methylenecyclopropane derivatives linked with furan units underwent an intramolecular cycloaddition under high pressure (Table 6).[24]

**Table 6. Intramolecular Diels−Alder Reactions under High Pressure of Furfuryl-Substituted ACPs 55**




55 56

| entry | 55 | X | R, R | R′ | 56 | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **a** | $CH_2$ | $CH_2-CH_2$ | H | **a** | 32 |
| 2 | **b** | $CH_2$ | $CH_2-CH_2$ | OMe | **b** | >95 |
| 3 | **c** | $CH_2O$ | $CH_2-CH_2$ | H | **c** | 42−46 |
| 4 | **d** | $Si(Me)_2O$ | $CH_2-CH_2$ | H | **d** | 83 |
| 5 | **e** | $CH_2$ | H, H | H | **e** | 82 |
| 6 | **f** | $CH_2O$ | H, H | H | **f** | 47−50 |
| 7 | **g** | $Si(Me)_2O$ | H, H | H | **g** | 25 |

All the intramolecular Diels−Alder reactions of tethered ACP derivates **52** and **55** proceeded with complete diastereoselectivity.[23,24]

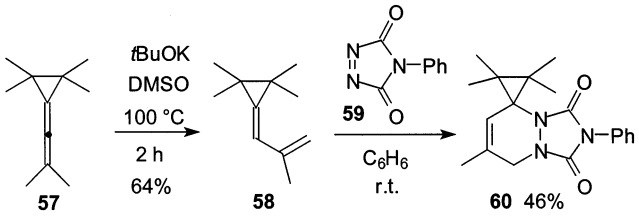
## B. Alkylidenecyclopropanes as Dienes

### *1. Intermolecular Cycloadditions*

Allylidenecyclopropanes exhibit a good reactivity as dienes, especially toward activated dienophiles higher than 1,1-disubstituted-1,3-dienes, which are quite unreactive in Diels−Alder reactions. Likely, the strain present in the alkylidenecyclopropane moiety is responsible for the reactivity enhancement observed in these compounds. The reaction has led to polycyclic compounds with complex structures.[3,25] Cycloadditions leading to heterocycles are more limited.

2-Methyl-3-(tetramethylcyclopropylidene)propene (**58**), obtained by isomerization of allene **57** with potassium *tert*-butoxide, added to 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD, **59**) at room temperature to give the Diels−Alder adduct **60** in 46% yield (Scheme 12).[26]

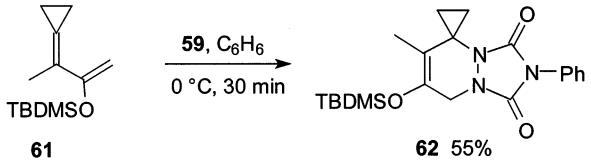
**Scheme 12**




57 58

The 2-(*tert*-butyldimethylsilyloxy)allylidenecyclopropane **61** underwent a facile cycloaddition to the same dione **59** to form the cycloadduct **62** in 55% yield[27] (Scheme 13).

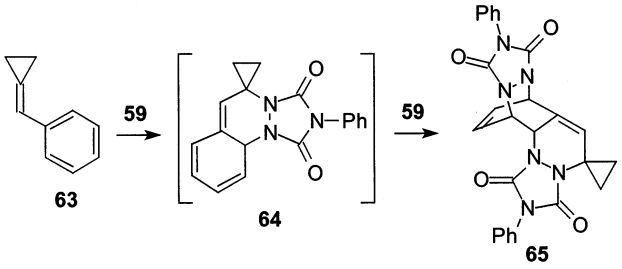
**Scheme 13**




61

Benzylidenecyclopropane (**63**) reacted rapidly with **59** to form the 2:1 adduct **65** (Scheme 14). The formation of **65** was proposed to occur via the primary adduct **64**.[28]

**Scheme 14**

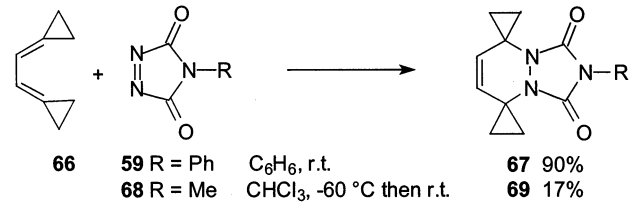



63 64 65

The reaction of bis(cyclopropylidene)ethane (**66**) with PTAD (**59**) was instantaneous at room temperature in benzene, and the adduct **67** was obtained in 90% yield (Scheme 15).[29]

When *N*-methyltriazolinedione **68** was added to **66** 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 urazole **69** was quite low (17%) after chromatography on neutral alumina. No other recognizable substance could be isolated (Scheme 15).[30]

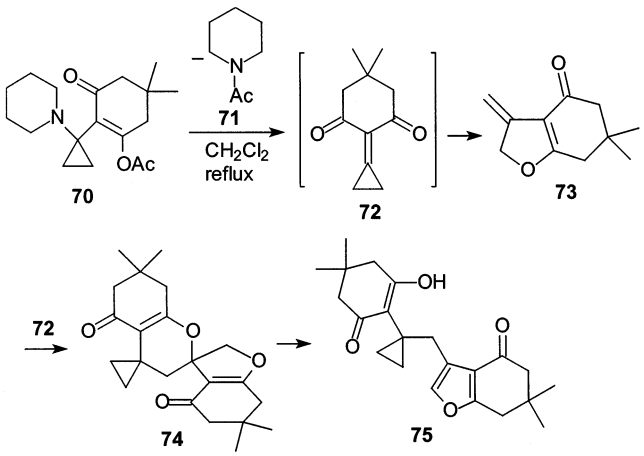
**Scheme 15**




The [4+2] cycloaddition of enones and electron-rich olefins is a well-known method for the synthesis of pyran derivatives.[31] Methylenecycloalkanediones[32] have also been used extensively for this purpose.

The highly reactive cyclopropylidenedimedone **72**, generated in situ from acetylated (piperidinocyclopropyl)dimedone **70**, was trapped by [4+2] cycloaddition with electron-rich alkenes and alkynes. Without a trapping reagent, **72** rearranged to **73**, which is able to trap a second molecule of **72** by a [4+2] cycloaddition leading to **74**. A $\beta$-elimination generating an aromatic furan ring gives eventually **75** by simple heating in dichloromethane (Scheme 16). The pure spiro compound **74** could be isolated

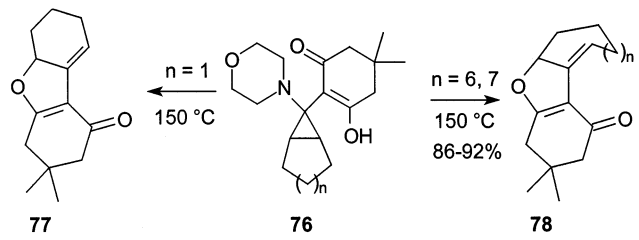
**Scheme 16**




in 44% yield; upon further heating, **74** isomerized quantitatively to the furan **75**.[33]

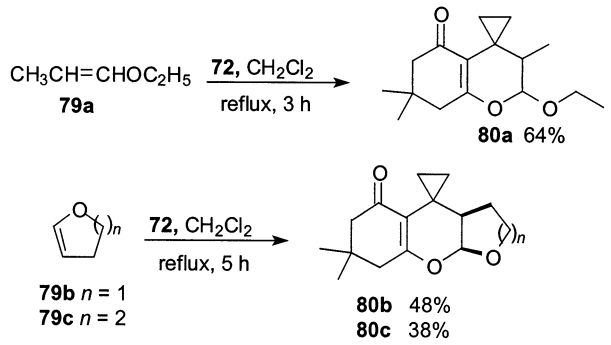
When the cyclopropane is fused with a cycle, the thermal rearrangement produces a tricyclic furan with ring enlargement of the fused cycle (Scheme 17).[34]

**Scheme 17**



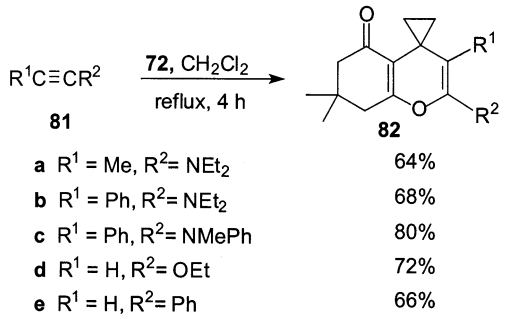

When **72** was generated in the presence of enol ethers **79**, [4+2] cycloadducts **80a**−**c** were isolated in good to moderate yields (Scheme 18).[33] The cycloadducts **80b** and **80c** proved to be formed as a single stereoisomer, with the two heterocyclic ring systems being cis-fused.

**Scheme 18**



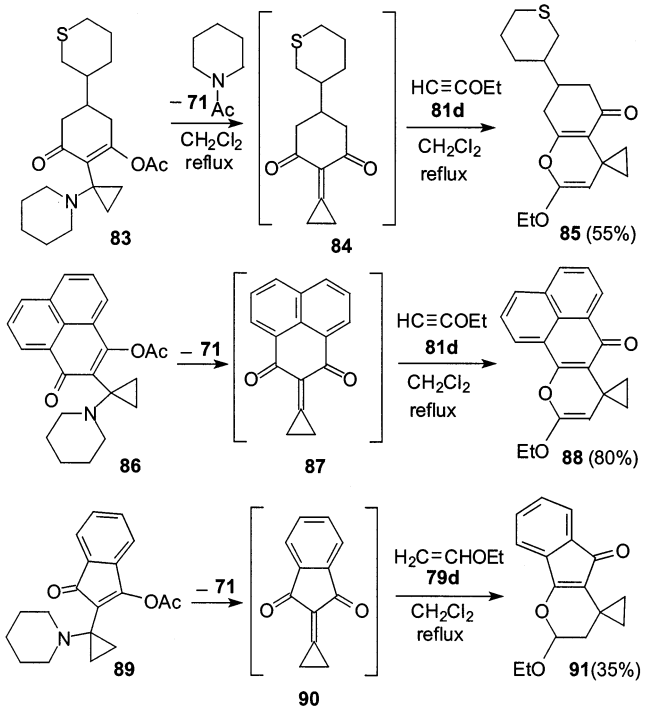

Cyclopropylidenedimedone **72** was trapped in a [4+2] cycloaddition also by the addition of ynamines **81a**−**81c**, ynether **81d**, and phenylacetylene (**81e**) to give cycloadducts **82a**−**82e** in good yields (Scheme 19).[35]

**Scheme 19**



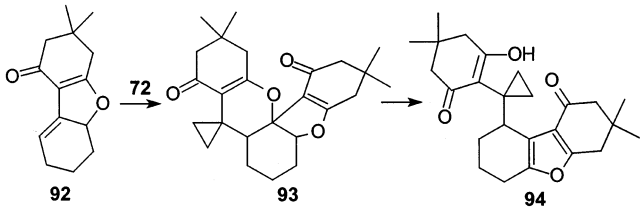

Analogously, 2-cyclopropylidene-1,3-diones **84**, **87**, and **90** generated by deamination of **83**, **86**, and **89**, respectively, reacted with ethoxyacetylene (**81d**) or ethyl vinyl ether (**79d**) to afford adducts **85**, **88**, and **91** (Scheme 20).[35]

**Scheme 20**



When reacting with the methylenedihydrofuran derivative **92** as trapping reagent, **72** gave rise to a mixture of [4+2] cycloadduct **93** and furan **94**, which could be separated and obtained in 25 and 37% yields, respectively. Upon further heating the adduct **93**, with an unknown configuration, isomerized completely to the more stable product **94** (Scheme 21).[33]

**Scheme 21**




### *2. Intramolecular Cycloadditions*

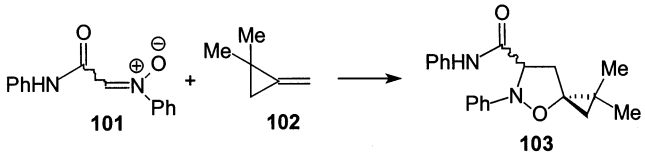
Alkylidenecyclopropanes **99**, obtained by an intermolecular 1,3-dipolar cycloaddition of imidazolium, thiazolium, and pyridinium ylides **95** on the endo cyclopropene double bond of alkylidenecyclopropenes **96**−**98**, are prone to undergo an intramolecular hetero Diels−Alder reaction to give heterocyclic cage compounds **100** (Table 7).[36] The imidazolium methylides **95a,b** required reflux in EtOH or THF to give compounds **100a,b** (entries 1 and 2), whereas for thiazolium **95d** and pyridinium *N*-methylides **95f,g**, room temperature was already sufficient to give the corresponding cage compounds **100d**−**f** and **100h,i** in quantitative or good yields, respectively (entries 4−6, and 8 and 9).

## *III. Heterocycles from [3+2] Cycloadditions*

## A. Nitrones

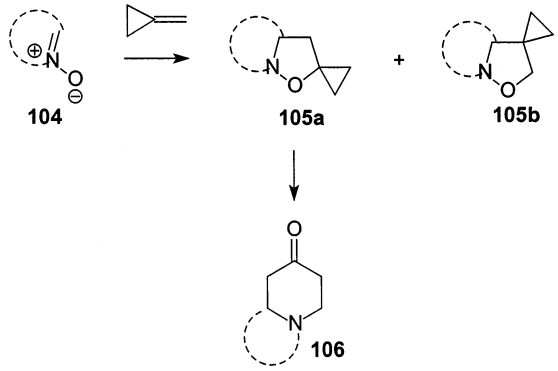
The cycloaddition of a nitrone to an alkylidenecyclopropane is able to produce a spirocyclopropane isoxazolidine heterocycle in a regio- and stereoselective manner. The rich chemistry associated with this kind of heterocyclic ring, originating from the easy cleavage of the N−O bond followed by further chemical transformations, makes these reactions among the most studied of this class. The first example reported was the cycloaddition of *N*-(phenylamino-oxoethylidene)aniline *N*-oxide (**101**) to 2,2-dimethylmethylenecyclopropane (**102**) which gave a single 5-spirocyclopropane fused regioisomer **103** (Scheme 22).[37]

**Scheme 22**



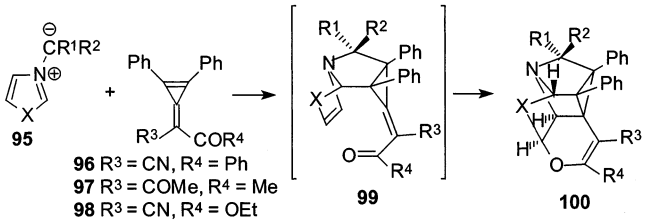

The strong driving force to the study of these cycloadditions came from the discovery that 5-spirocyclopropane isoxazolidines **105a** (or the related isoxazolines) undergo thermal rearrangement resulting in the production of substituted tetrahydro- (or dihydro-) pyrid-4-ones **106**. In particular, cyclic nitrones gave ultimately N-bridgehead bicyclic ketones with the molecular skeleton found in many compounds of alkaloid families (Scheme 23).[38−41]

**Scheme 23**




The cycloaddition of nitrones to MCP (**2**) gives generally a mixture of the regioisomeric 5-spiro-

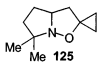
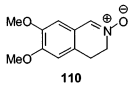
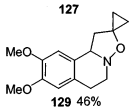
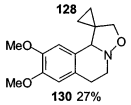
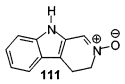
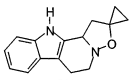
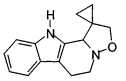
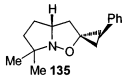
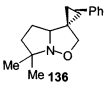
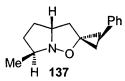
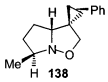
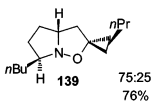
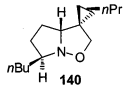
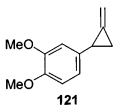
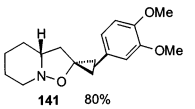
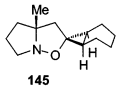
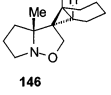
**Table 7. Reactions of Imidazolium, Thiazolium, and Pyridinium *N*-Methylides 95 with Alkylidenecyclopropenes 96−98**




| entry | ylide | X | $R^1$ | $R^2$ | reagent | $R^3$ | $R^4$ | products **100** yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **95a** | NMe | CN | CN | **96** | CN | Ph | **a** (76) |
| 2 | **95b** | NMe | $CO_2Et$ | $CO_2Et$ | **96** | CN | Ph | **b** (99) |
| 3 | **95c** | S | H | COPh | **97** | COMe | Me | **c** (93) |
| 4 | **95d** | S | CN | CN | **97** | COMe | Me | **d** (94) |
| 5 | **95d** | S | CN | CN | **96** | CN | Ph | **e** (100) |
| 6 | **95d** | S | CN | CN | **98** | CN | OEt | **f** (96) |
| 7 | **95e** | CH=CH | CN | CN | **96** | CN | Ph | **g** (16) |
| 8 | **95f** | CH=CH | $CO_2Et$ | $CO_2Et$ | **96** | CN | Ph | **h** (60) |
| 9 | **95g** | CH=CH | H | $CO_2Me$ | **96** | CN | Ph | **i** (49) |

cyclopropane **105a** and 4-spirocyclopropane **105b** isoxazolidines in a ratio ranging from >20:1 to 2:1 (Table 8).

**Table 8. Cycloadditions of Nitrones to MCPs**

| entry | nitrone | MCP | 5-spirocyclopropane isoxazolidine | | 4-spirocyclopropane isoxazolidine | Ref. |
|---|---|---|---|---|---|---|
| 1 |  **107** |  **2** |  **123** | 70:30 83% |  **124** | 39 |
| 2 |  **108** | **2** |  **125** | 65:35 86% |  **126** | 39 |
| 3 |  **109** | **2** |  **127** | 90:10 69% |  **128** | 39 |
| 4 |  **110** | **2** |  **129** 46% | |  **130** 27% | 39 |
| 5 |  **111** | **2** |  **131** 53% | |  **132** 27% | 39 |
| 6 |  **112** | **2** |  **133** | 67:33 76% |  **134** | 42 |
| 7 | **108** |  **119** |  **135** | 67:33 76% |  **136** | 40 |
| 8 |  **113** | **119** |  **137** | 83:17 90% |  **138** | 40 |
| 9 |  **114** |  **120** |  **139** | 75:25 76% |  **140** | 40 |
| 10 | **109** |  **121** |  **141** 80% | | – | 39 |
| 11 |  **115** | **2** |  **142** | | – | 43 |
| 12 |  **116** | **2** |  **143** | 85:15 78% |  **144** | 43 |
| 13 | **116** |  **122** |  **145** | 80:20 41% |  **146** | 43 |
| 14 |  **117** $n = 1$ | **2** |  **147** $n = 1$ | 42% 86:14 |  **148** $n = 1$ | 43 |
| 15 | **118** $n = 2$ | | **149** $n = 2$ | 40% 86:14 | **150** $n = 2$ | 43 |

The role of steric effects in determining the regioselectivity on the nitrone side is evident. The remarkable difference in regioselectivity between the cycloadditions of nitrones **108** and **109** with **119** (Table 8, entries 7 and 8) is tangible proof.[40] Since the small difference between the two nitrones should only slightly affect the frontier orbital parameters, a steric effect must play an important role in the transition state. The second methyl group in nitrone **108** points toward the approaching methylenecyclopropane in the transition state, thus hindering the approach that leads to the 5-spiro regioisomer (TS A, Chart 3). The six-membered-ring nitrone **109** exhibits excellent regioselectivity in the cycloaddition (Table 8, entries 3 and 10), because the approach of MCP leading to the 4-spirocyclopropane regioisomer is somewhat hindered by the vicinal axial hydrogen (TS B, Chart 3).

**Chart 3. Selected Transition States for Cycloadditions of MCP to Five-Membered Nitrone (TS A), Six-Membered Nitrone (TS B), and Ketonitrone (TS C), Showing Unfavorable Steric Interactions**




Also, ketonitrones **115**−**118** give predominantly, or exclusively, 5-spiro regioisomers (Table 8, entries 11−15), due to a similar effect of the second substituent on the nitrone carbon atom (TS C, Chart 3).[43]

The cycloadditions of nitrones to methylenecyclopropanes **119**−**122** substituted on the ring (Table 8, entries 7−10 and 13) occur with high diastereofacial selectivity. The same diastereoselectivity is observed when a substituent is present on the nitrone ring, as in nitrones **113** and **114** (Table 8, entries 8 and 9). The favored approach of the nitrone and the substituted methylenecyclopropane, in each of the two possible regioisomeric transition states, is opposite from the nitrone substituent and from the methylenecyclopropane substituent. The most favored anti−anti transition state produces the observed diastereoisomers (Chart 4). The only two

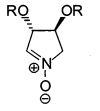
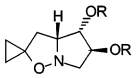
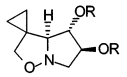
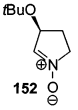
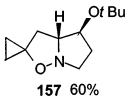
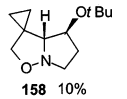
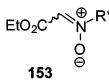
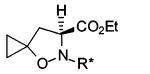
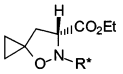
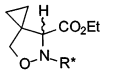
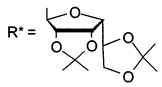
**Chart 4**




isomers formed, for each regioisomeric mode, must derive either from an anti−anti exo or anti−anti endo approach, where the exo/endo notation has been extended to the substitution at the cyclopropane ring carbon. The control of exo−endo selectivity is generally absent, as a consequence of the strong preference for the anti approach toward the substituent on the cyclopropyl ring.

The highly stereoselective addition of optically pure nitrones **151**−**153** gives rise to enantiopure 5-spirocyclopropane isoxazolidines in good yield (Table 9). The stereoselectivity of the cycloaddition of L-tartaric acid-derived nitrones **151a**−**d** depends on the size of the hydroxyl protecting group, ranging between 5:1 and 12:1 on passing from benzyl to TBDPS group.[44]

**Table 9. Stereoselective Cycloadditions of Chiral Nitrones 151−153 to 2**

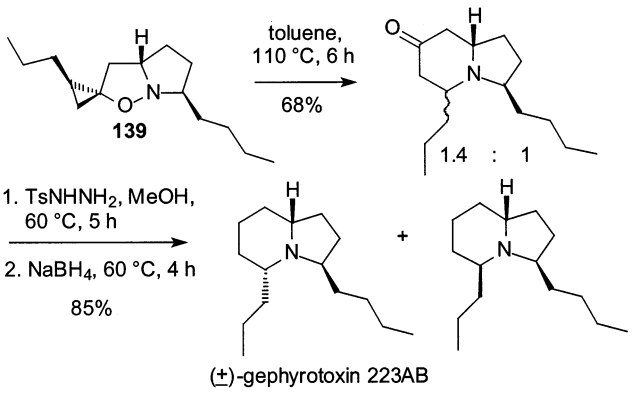
| entry | nitrone | 5-spirocyclopropane isoxazolidine *anti*-adduct | 5-spirocyclopropane isoxazolidine *syn*-adduct | 4-spirocyclopropane isoxazolidine | Ref. |
|---|---|---|---|---|---|
| |  |  **154** |  **155** |  **156** | |
| 1 | **151a** R = TBDPS | 78% | 6% | 9% | 44 |
| 2 | **151b** R = *t*Bu | 64% | 8% | 4% | 42 |
| 3 | **151c** R = TBDMS | 70% | 10% | 8% | 47 |
| 4 | **151d** R = Bn | 73% | 15% | 8% | 44 |
| 5 |  **152** |  **157** 60% | |  **158** 10% | 45 |
| 6 |  **153** |  **159** 53% |  **160** 17% |  **161** 16% | 46 |
| | R* =  | | | | |

Again, the alkoxy group most proximal to the nitrone functionality drives the anti approach of the dipolarophile. The reaction of monohydroxylated nitrone **152**, derived from L-malic acid, shows an even greater stereoselection, as the syn product is not even observed.[45] Ethoxycarbonyl-substituted nitrone **153** forms 5-spirocyclopropaneisoxazolidines **159** and **160** in a lower stereoselectivity (3:1), but this is rather likely a result of the *Z*/*E* configurational equilibrium of the nitrone.[46]

The configuration of stereocenters, introduced in isoxazolidines with the cycloaddition step, is not affected during the thermal rearrangement,[41] and the overall cycloaddition/rearrangement process has been applied to the synthesis of natural products.

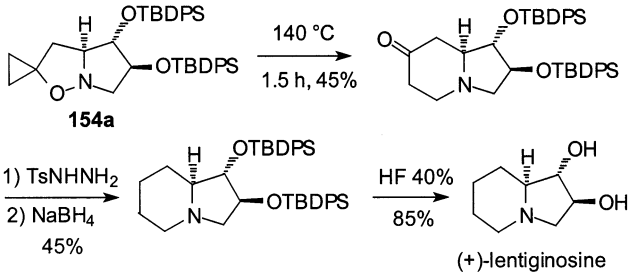
The indolizidine amphibian alkaloid (±)-gephyrotoxin 223AB was synthesized from **139** with the control of two out of three stereogenic centers (Scheme 24).[40]

**Scheme 24**



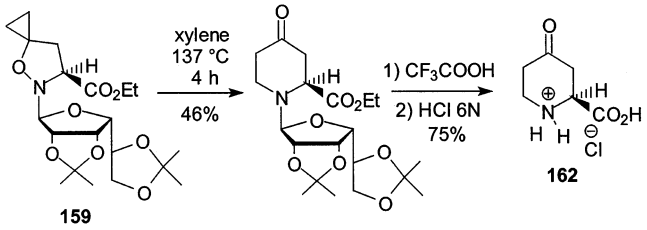

Hydroxylated nitrones **151** and **152** afford, by subsequent thermal rearrangement of the adducts, a straightforward approach to polyhydroxylated indolizidines, inhibitors of glycosidases. The total synthesis of (+)-lentiginosine is representative of the strategy (Scheme 25).[44]

**Scheme 25**




Isoxazolidine **159** has been employed for a straightforward synthesis of the rare amino acid (2*S*)-4-oxopipecolic acid as its hydrochloride salt **162** (Scheme 26).[46]

**Scheme 26**



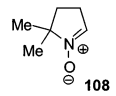
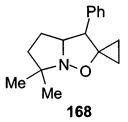
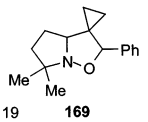
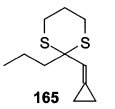
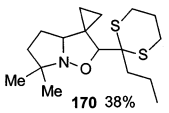
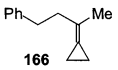
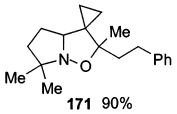
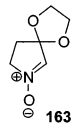
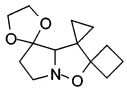
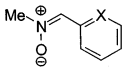
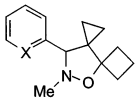

The good reactivity of MCPs, together with the low regioselectivity, is rather unexpected on the grounds of a simple analysis of literature data of nitrone cycloadditions. In fact, the related isobutene and its derivatives are well known to undergo 1,3-dipolar cycloadditions sluggishly.[48] Thus, there is no chance to obtain a cycloadduct from **108** and a trialkyl or tetraalkylethylene. On the other hand, the behavior of MCPs contrasts with that of 1,1-disubstituted ethylenes,[49,50] and also with methylenecyclobutane,[51] which form 5,5-disubstituted isoxazolidines in the reactions with nitrones in a complete regioselective fashion. These experimental findings clearly disclose a peculiar effect of a cyclopropylidene system both on reaction rates and on regioselectivity.

The tendency of the three-membered ring to end up at the 4-position of the final isoxazolidine ring clearly emerges from the cycloadditions to ACPs. Nitrone **108** with alkyl-substituted ACPs **165** and **166** gives exclusively the 4-spirocyclopropane isoxazolidines **170** and **171** (Table 10, entries 2 and 3).[52] When the substituent is phenyl (entry 1), only 5% of the 5-spirocyclopropane isoxazolidine is formed. Particularly remarkable is the regioselectivity of cycloaddition to cyclopropylidenecyclobutane (Table 10, entries 4−6).[53]

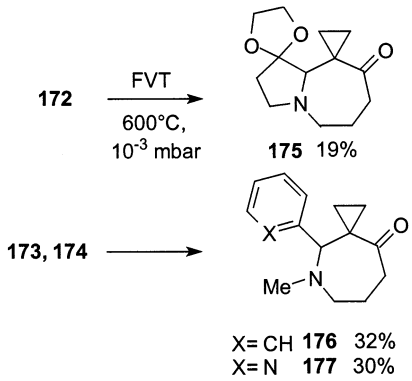
The spirocyclobutane isoxazolidines **172**−**174** gave the azepinones **175**−**177** in moderate yield (Scheme 27) by thermal rearrangement under flash vacuum thermolysis (600 °C, $10^{-3}$ mbar),[53] in analogy with a thermal rearrangement observed previously for the nitrone cycloadducts to methylenecyclobutanes.[51]

When electronic effects exerted by electron-withdrawing groups are involved, and this is the case in ACPs **3**, **4**, **47**, **183**, **184**, and **182**, a complete reversal

**Table 10. Cycloadditions of Nitrones to ACPs with Alkyl and Phenyl Groups**

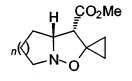
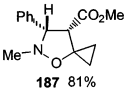
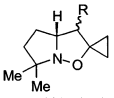
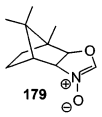
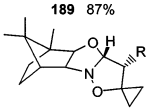
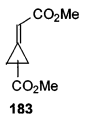
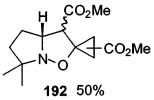
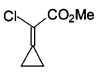
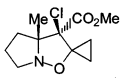
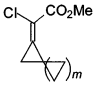
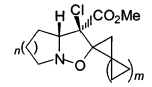
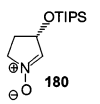
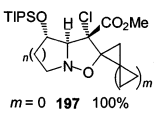
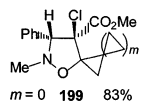
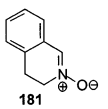
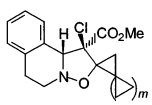
| entry | nitrone | ACP | 5-spirocyclopropane isoxazolidine | 4-spirocyclopropane isoxazolidine | Ref. |
|---|---|---|---|---|---|
| 1 |  **108** |  **63** |  **168** 1 : 19 61% |  **169** | 52 |
| 2 | **108** |  **165** | – |  **170** 38% | 52 |
| 3 | **108** |  **166** | – |  **171** 90% | 52 |
| 4 |  **163** |  **167** | – |  **172** 48% | 53 |
| |  | **167** | |  | |
| 5 | **107** X= CH | | – | X= CH **173** 47% | 53 |
| 6 | **164** X= N | | – | X= N **174** 85% | 53 |

**Scheme 27**




of regioselectivity is observed, in agreement with the conjugate nucleophilic attack nature of the nitrone cycloaddition (Table 11). Moreover, this regioselectivity is the same as that observed in the reactions of the related methyl 3,3-dimethylacrylate with nitrones, namely, total regioselective formation of the 4-methoxycarbonyl adduct.[57] The high regioselectivity of these dipolarophiles is also accompanied, as expected, by a higher reactivity. Apart from cyclopropylidenechloroacetates **4** and **184**, the diastereoselectivity of the cycloadditions is only moderate and is clearly the result of an interplay of secondary orbital interactions that favor an endo approach of the EWG group and steric hindrance imposed by nitrone substituents. In cyclopropylidenechloroacetates **4** and **184**, the competition between a chloro and a methoxycarbonyl group favors the methoxycarbonyl group in the endo position for all endocyclic nitrones (Table 11, entries 9−14, 17, and 18), and the exo position for the acyclic (*Z*)-*C*-Ph,*N*-Me nitrone **107** (entries 15−16). Meaningful is the comparison of diastereoselectivity of the carbomethoxy- and the

**Table 11. Cycloadditions of Nitrones to Cyclopropylidene Acetates 3, 4, 47, 183, and 184 and Cyclopropylidene Acetonitrile 182**

| entry | nitrone | cyclopropylidene acetate | 5-spirocyclopropane isoxazolidine[a] | *endo* (EWG)/ *exo* ratio | Ref. |
|---|---|---|---|---|---|
| |  |  **3** |  | | |
| 1 | *n*=1 **178** | | *n*=1 **185** 64% | 68 : 32 | 54 |
| 2 | *n*=2 **109** | | *n*=2 **186** 78% | 70 : 30 | 54 |
| 3 |  **107** | |  **187** 81% | 47 : 53 | 55 |
| 4 |  **108** |  **3** R = $CO_2Me$ |  **188** 65% | 33 : 67 | 58 |
| 5 | | **182** R = CN | **189** 87% | 80 : 20 | 58 |
| |  **179** |  **47** R = $CO_2Et$ |  **190** 54% | 83 : 17 | 58 |
| 7 | | **182** R = CN | **191** 84% | 88 : 12 | 58 |
| 8 | **108** |  **183** |  **192** 50% | 50 : 35 : 15 | 53 |
| 9 |  **116** |  **4** |  **193** 83% | 100 : 0 | 56 |
| | |  |  | | |
| 10 | **178** | *m* = 0 **4** | *n* = 1; *m* = 0 **194** 65% | 100 : 0 | 63 |
| 11 | **178** | *m* = 1 **184** | *n* = 1; *m* = 1 **195** 70% | 100 : 0 | 63 |
| 12 | **109** | *m* = 0 **4** | *n* = 2; *m* = 0 **196** 100% | 55 : 45 | 56 |
| |  **180** | |  | | |
| 13 | | *m* = 0 **4** | *m* = 0 **197** 100% | 84 : 16 | 56 |
| 14 | | *m* = 1 **184** | *m* = 1 **198** 100% | 86 : 14 | 56 |
| | | |  | | |
| 15 | **107** | *m* = 0 **4** | *m* = 0 **199** 83% | 16 : 84 | 63 |
| 16 | **107** | *m* = 1 **184** | *m* = 1 **200** 68% | 0 : 100 | 63 |
| |  **181** | |  | | |
| 17 | | *m* = 0 **4** | *m* = 0 **201** 91% | 100 : 0 | 63 |
| 18 | | *m* = 1 **184** | *m* = 1 **202** 93% | 100 : 0 | 63 |

[a] Major diastereoisomer displayed.

cyano-substituted methylenecyclopropane (Table 11, entries 4 and 5). The small cyano group, despite its tendency toward lower endo selectivity in cycloadditions, when compared to the ester group, gives a much higher 4:1 (vs 1:2) endo selectivity with nitrone **108**.[58]

The regiochemical data of the reactions of nitrones with MCP and its alkyl and aryl derivatives seem to suggest that there is an inherent "electronic" effect in methylenecyclopropanes that promotes formation of the 4-spiro regioisomer. This tendency of MCP to give this "reversed" regiochemistry has also been observed in the cycloaddition to diazoalkanes.[3]

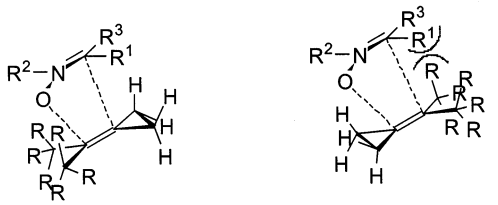
MO calculations, at both the semiempirical and the ab initio levels, aimed at investigating any inherent feature of the MOs of MCP able to explain the reactivity and the regiochemistry of the reactions of this dipolarophile and its derivatives, were carried out.[52b,53] Angle strain in a dipolarophile can affect its reactivity, but it is well known that the PMO approach cannot give a correct explanation of this effect.[57,59] Certainly it has been observed that a decrease in angle strain in the cycloaddition process induces an increase in reaction rate.[60] Therefore, the higher reactivity of methylenecyclopropane compared to 1,1-dialkylethylenes may be explained with the considerable decrease in angle strain of the cyclopropylidene moiety along the reaction coordinate without the necessity of looking for other electronic effects.

The same argument, however, does not apply to an explanation of the observed regioselectivity. HOMO and LUMO energies and atomic orbital coefficients for nitrone **178** and ACPs **2**, **167**, and 2,2-dimethylmethylenecyclopropane (**102**) were calculated by ab initio (up to the STO 6-311G level) [52b,53] and DFT methods.[53] The calculated $\Delta E$ values between the frontier orbitals for different approaches of reactants cannot justify the observed regioselectivities. The polarization of atomic orbitals in alkylidenecyclopropanes or cyclobutylidenecyclopropane (**167**), although indicating the correct regioselectivity, appears too small to be significant to explain the regioselectivity observed in the experiments. On the other hand, the polarization of HOMO and LUMO in methylenecyclopropane **2** is very similar to that in isobutylene, again in contrast to what would be expected from the experimental data. The ab initio[52b] and DFT[53] analyses of the transition states of **102** and **167** cycloadditions, respectively, were able to find a difference of 1.8 kcal/mol (STO 3-21G level),[61] for **102** and less than 1 kcal/mol (at the STO 6-311G level)[53] for **167**, in favor of the transition state leading to the 4-spirocyclopropane isoxazolidines, but were not able to predict the lack of regioselectivity shown by MCP (**2**).[52]

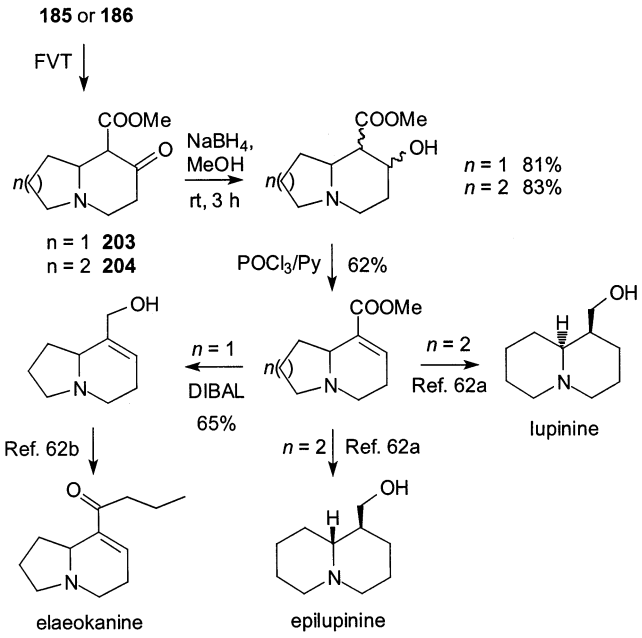
Considering the nature of substituents and the results of the calculations, steric effects must play a role in promoting this regioselectivity. A cyclopropylidene moiety is certainly less sterically demanding than an isopropylidene system, or than a puckered cyclobutylidene moiety, and it is quite reasonable to assume that this difference leads to an appreciable effect in the transition state. The greater steric bulk of any other substituent relative to the cyclopropyl group with its smaller bond angle favors the transition state that has the bulkier side of the dipolarophile close to the less sterically congested oxygen end of the nitrone and thus leads to the 4-spirocyclopropane isoxazolidine.

The adducts of methyl cyclopropylideneacetate (**3**), **185**, and **186** (Table 11, entries 1 and 2) rearranged thermally under FVT to indolizidinones **203** and quinolizidinones **204**, respectively. The compounds were employed in the formal syntheses of the alkaloids (±)-lupinine, (±)-epilupinine, and (±)-elaeokanine A (Scheme 28).[54,62]

**Chart 5. Two Possible Transition Structures for the 1,3-Dipolar Cycloaddition of a Nitrone to an ACP**

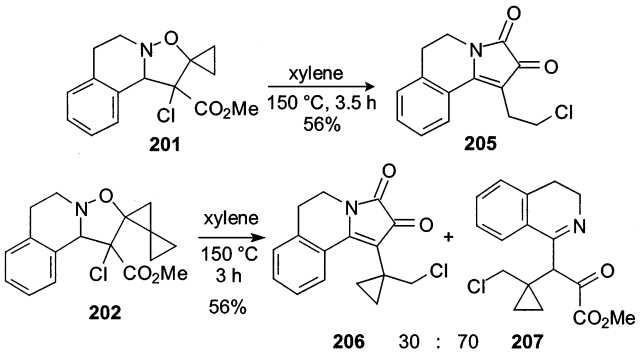


**Scheme 28**




Isoxazolidines **201** and **202** (Table 11, entries 17 and 18) turned out to be quite stable at temperatures below 100 °C. When heated at 150 °C in xylene, they underwent a novel reaction to α-ketolactam **205** or to a mixture of α-ketolactam **206** and the open-chain derivative **207**, respectively (Scheme 29).[63]

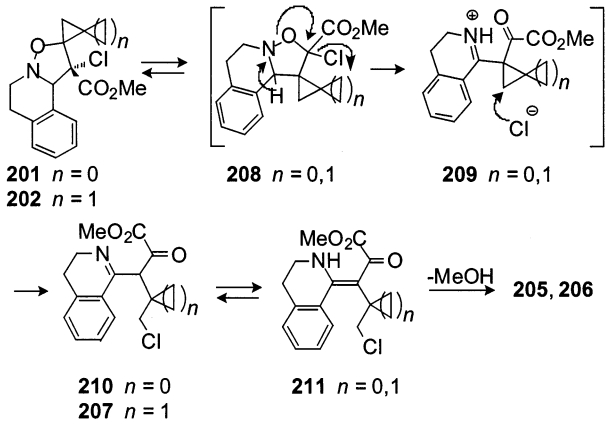
**Scheme 29**




The formation of compounds **205**−**207** can be rationalized by assuming that the primary cycloadducts **201** and **202** undergo a cycloreversion−cycloaddition[64] sequence leading to the regioisomeric 4-spirocyclopropaneisoxazolidines **208**, which undergo a sequential ring opening followed by nucleophilic attack of chloride on the (bis)acceptor-substituted cyclopropane ring in **209**, to form the α-ketoesters **210** and **207**, the latter of which was in fact

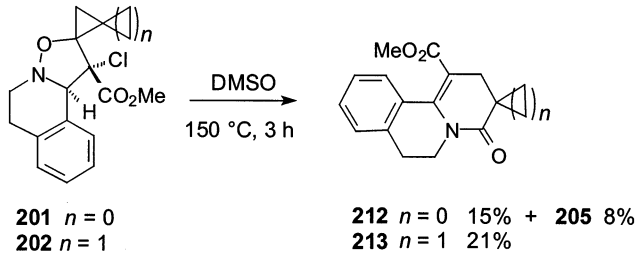
isolated. The enamine tautomers **211** then undergo cyclization with loss of methanol to α-ketolactams **205** and **206** (Scheme 30).[63]

**Scheme 30**



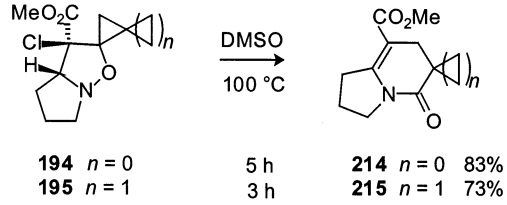

When the thermal rearrangement of isoxazolidines **201** and **202** was carried out in DMSO at 150 °C, a completely different reaction pathway was observed. Although decomposition of the starting materials predominated, the benzoquinolizinones **212** and **213** were isolated in 15 and 21% yield, respectively (Scheme 31). Benzoquinolizinone **212** was obtained as an inseparable mixture together with the ketoamide **205** (8%).[63]

**Scheme 31**



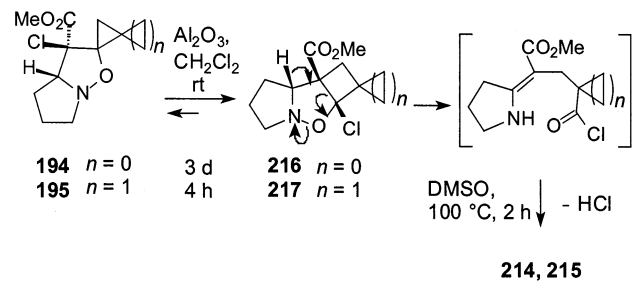

The origin of the new products became clear after the rearrangements of the cycloadducts from pyrroline *N*-oxide (**178**) and *C*-phenyl-*N*-methylnitrone (**107**) (Table 11, entries 10, 11, 15, and 16) were studied. When the isoxazolidines **194** and **195** were heated at 110 °C in toluene, complex mixtures of products were obtained. However, again by heating **194** and **195** in the more polar DMSO at 100 °C, a clean and fast reaction occurred to give the hexahydroindolizin-5-ones **214** and **215** in 83 and 73% yield, respectively (Scheme 32).[63,65]

**Scheme 32**




The study of the process, and the apparent influence of the polar solvent, revealed the formation of the cyclobutane-annelated isoxazolidine **216** and **217**, by treatment with the mildly Lewis acidic $Al_2O_3$ in $CH_2Cl_2$. The process is another example of the cyclopropylmethyl chloride/cyclobutyl chloride equilibration (Scheme 33).

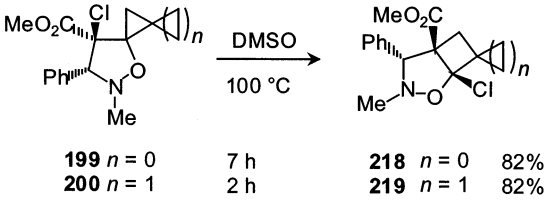
**Scheme 33**




When heated in DMSO, **216** and **217** gave quantitatively the same indolizidin-5-ones **214** and **215** that were formed from the isoxazolidines **194** and **195**. The indolizidin-5-ones **214** and **215** must form by a ring-enlargement process that is triggered by the abstraction of the bridgehead proton (Scheme 33).[63]

Surprisingly, isoxazolidines **199** and **200** gave in DMSO the crystalline cyclobutane-annelated isoxazolidines **218** and **219**, compounds quite stable toward further thermal rearrangement. An X-ray crystal structure analysis of **218** was carried out (Scheme 34).[63]

**Scheme 34**

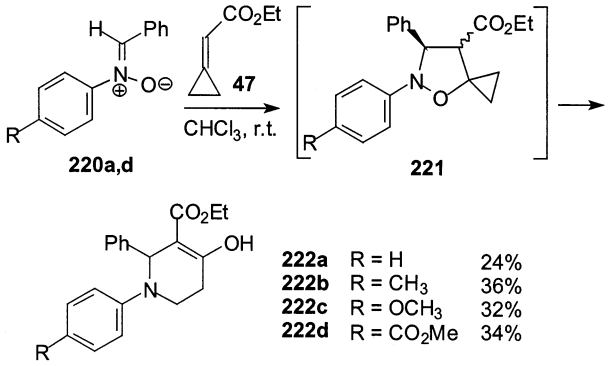



*N*-Aryl-substituted isoxazolidines **221** cannot be isolated, because they undergo the thermal rearrangement at a temperature lower than necessary for the cycloaddition to occur. This facile thermal rearrangement depends on the nature of the nitrone **220**. The *N*-aryl substituent must facilitate the N−O bond cleavage by stabilizing the forming radical species.[66] The effect is enhanced by electron-donating substituents on the *N*-aryl ring, and it is hampered by electron-withdrawing groups, suggesting a polar contribution in the homolytic cleavage of the N−O bond.[67] DFT calculations confirmed the experimental data giving an activation energy that is lower by about 17 kcal/mol for *N*-aryl-substituted isoxazolidines than for *N*-alkyl isoxazolidines.[68] In the cycloaddition with cyclopropylideneacetate **47**, the products **222** are obtained in moderate yields at room temperature (Scheme 35).[67]

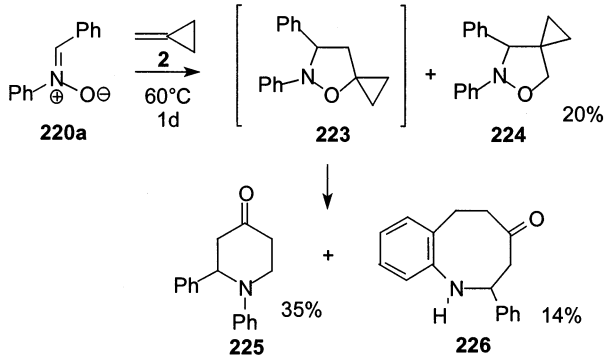
The benzazocine **226** was produced in moderate yield besides the tetrahydropyridone **225**, in the rearrangement of **223** by closure of the diradical delocalized on the *N*-aryl ring followed by H-shift (Scheme 36).[66]

Methylenespiropentane **227** and methylenedispiroheptane **228** react with nitrones like methylenecy-

**Scheme 35**




**Scheme 36**




clopropane, affording similar mixtures of regioisomeric compounds. Adducts of **227** are obtained as a mixture of endo/exo stereoisomers.[69]

**Chart 6**


The further rearrangement of spiropentane (or spiroheptane) isoxazolidines **229** interestingly gives selectively the spirocyclopropanetetrahydropyridones **230**, ruling out any alternative cyclopropylmethyl radical/homoallyl radical reaction pathway leading to **231** (Scheme 37 and Table 12).[70]

A priori, the symmetric nature of bicyclopropylidene (**5**) circumvents any regioisomeric problem in cycloadditions with nitrones. Therefore, the overall process becomes very efficient for the synthesis of spirocyclopropanetetrahydropyridones **241** (Scheme 38).

The higher boiling point of bicyclopropylidene (100 °C), compared to methylenecyclopropane (11 °C), allows one to run the two-step cycloaddition/rearrangement process in "one pot", and these conditions usually give a better total yield. A large variety of structurally differentiated α-spirocyclopropane heterocyclic ketones **241** has been obtained (Table 13).[71] Some of these compounds have displayed the ability of cleaving a supercoiled DNA plasmid,[72] probably due to the presence of the α-spirocyclopropane ketone functionality, in analogy to the naturally occurring cytotoxic compounds illudine and ptaquiloside. The most active compounds were shown to be **256** and

**Scheme 37**

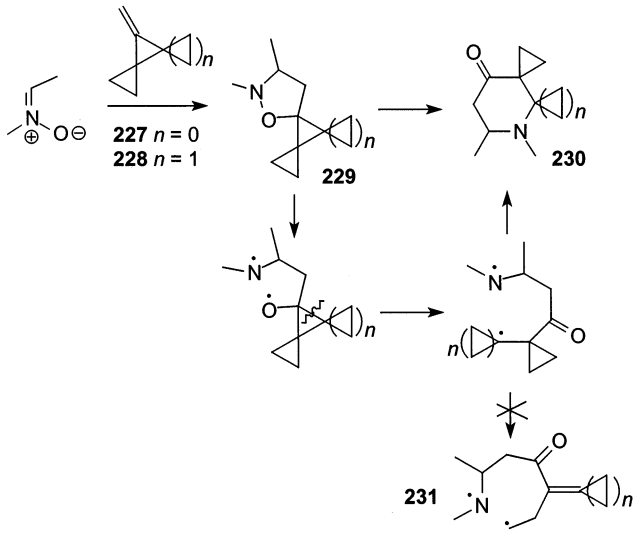
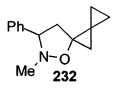
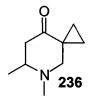
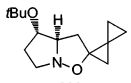
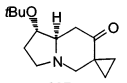
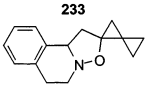
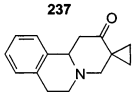
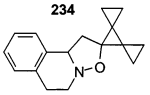
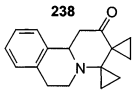
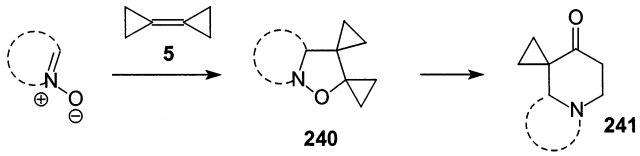



**Table 12. Cycloadditions of Nitrones to Methylenespiropentane (227) and Methylenedispiroheptane (228)**

| entry | nitrones | alkene | cycloadduct | rearrangement product | % yield of "one pot" reactions" (Calc. for two steps) | Ref. |
|---|---|---|---|---|---|---|
| 1 | **107** | **227** |  **232** |  **236** | 28 (19) | 70 |
| 2 | **152** | **227** |  **233** |  **237** | 22 (22) | 69b,70 |
| 3 | **181** | **227** |  **234** |  **238** | 29 (13) | 69a,70 |
| 4 | **181** | **228** |  **235** |  **239** | 19 (17) | 70 |

**Scheme 38**




**253**. Interestingly, a structure/activity relationship study has shown that the isomeric compounds **237** and **238** possess virtually no activity.[70]

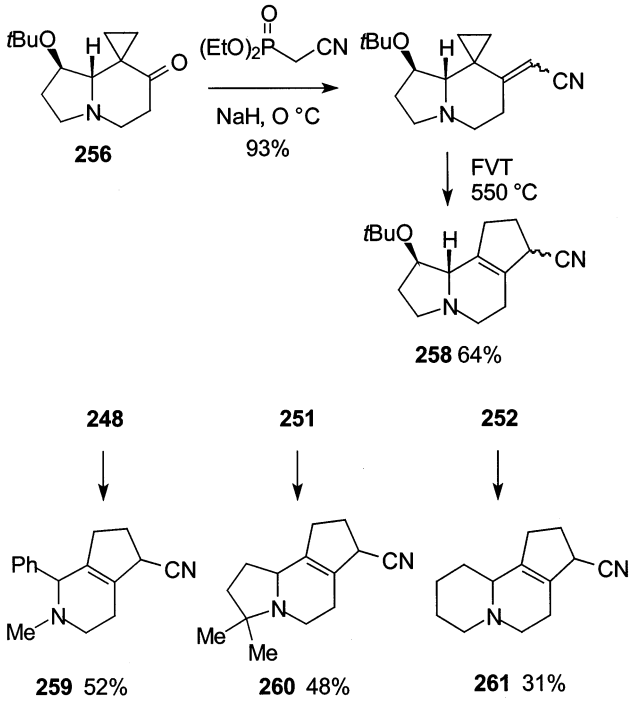
Spirocyclopropanated heterocyclic ketones **256**, **248**, **251**, and **252** were transformed further to the cyclopentene-anellated heterocycles **258**−**261**, respectively, by Wadsworth−Emmons olefination followed by thermal vinylcyclopropane−cyclopentene rearrangement in moderate to good yields (overall 31−60%) (Scheme 39).[73]

*N*-Phenyl-substituted nitrones **220** gave with bicyclopropylidene a more efficient domino cycloaddition/rearrangement process than methylenecyclopropane itself (Scheme 36) and led similarly to a mixture of rearrangement products, but with a much higher yield, particularly of the azocinones **264** (Scheme 40).[74]

**Table 13. Cycloadditions/Rearrangement of Nitrones with Bicyclopropylidene (5)**

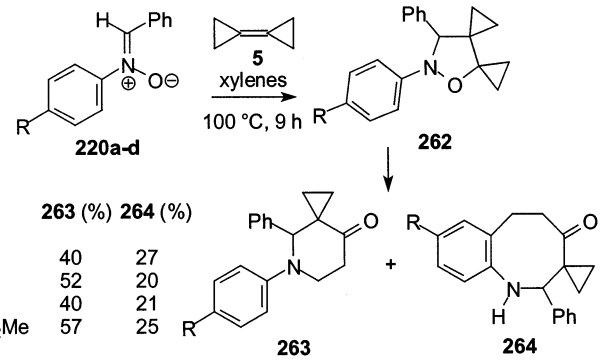
| Entry | Nitrone | Cycloadducts | Rearrangement products | % yield of "one pot" reactions (Calc. for two steps) | Ref. |
|---|---|---|---|---|---|
| 1 | **107** R = Ph | **242a** | **248** | 61 (58) | 71 |
| 2 | **153** R = $CO_2Et$ | **242b** | **249** | 54 (48) | 71 |
| 3 | **178** R = H | **243a** | **250** | – (25) | 71 |
| 4 | **108** R = Me | **243b** | **251** | 80 (61) | 71 |
| 5 | **109** | **244** | **252** | 48 (25) | 71 |
| 6 | **181** R = H | **245a** | **253** | 73 (36) | 71 |
| 7 | **110** R = OMe | **245b** | **254** | 31 (21) | 70 |
| 8 | **112** | **246** | **255** | 65 (43) | 70 |
| 9 | R = H **152** | **247a** | **256** | 64 (64) | 70 |
| 10 | R = O*t*Bu **151b** | **247b** | **257** | 62 ( – ) | 70 |

**Scheme 39**

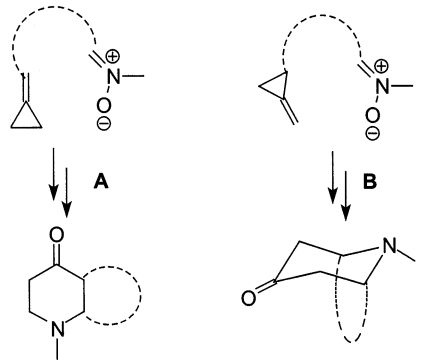



The construction of a nitrone functionality tethered to a methylenecyclopropane moiety allows the cycloaddition/rearrangement process to be run in an intramolecular fashion. In principle, two different strategies can be followed (Scheme 41): (i) route A, where the chain connecting the nitrone functionality and the MCP is linked through the exomethylene

**Scheme 40**




**Scheme 41**



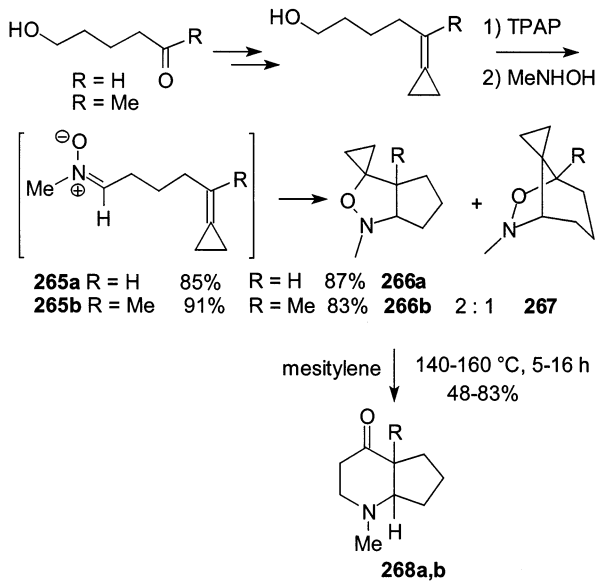

carbon; (ii) route B, where the chain is connected to the cyclopropane ring, leading to bridged heterocycles. Despite its viability, route B has been neglected to date because of the lower regioselectivity expected in the cycloaddition step. On the other hand, route A has been exploited for the synthesis of azahydrindane and pyrrolo[3,4-*b*]pyrido skeletons, also in enantiopure form.[75,76]

The cyclopropylidene nitrones **265a,b**, obtained by Wittig olefination from the corresponding hydroxyketones or hydroxyaldehydes, followed by standard transformation of the alcoholic functionality to the nitrone, undergo readily an intramolecular cycloaddition with a regioselectivity opposite to that of the intermolecular reaction. The three-carbon connecting chain favors the fused ring closure over the bridged one, just the opposite of what may be expected from comparison with the intermolecular process. Only sterically exacting substituents on the exocyclic double bond in **265b** (R = Me) steer the reaction to the formation of 30% of the "bridged" isomer **267**. Both "fused" isomers **266a,b** readily rearrange to 4-azahydrindan-7-ones **268** (Scheme 42).[75]

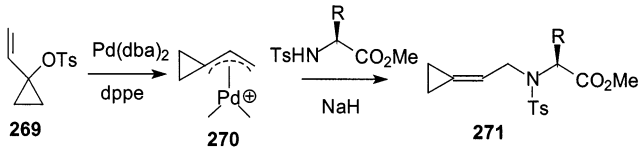
One of the best methods for the synthesis of alkylidenecyclopropanes is the palladium(0)-catalyzed nucleophilic substitution of 1-tosyloxy-1-vinylcyclopropane (**269**).[77] Several optically pure alkylidenecyclopropanes **271** were synthesized in high yields by this method using *N*-tosylamino esters as nucleophiles (Scheme 43).[76]

The glycolic ester anion also works as an excellent nucleophile. The alkylidenecyclopropanes were transformed into the corresponding nitrones without loss of optical purity, except in the case of the phenylglycine derivative. The alkylidenecyclopropane ni-

**Scheme 42**

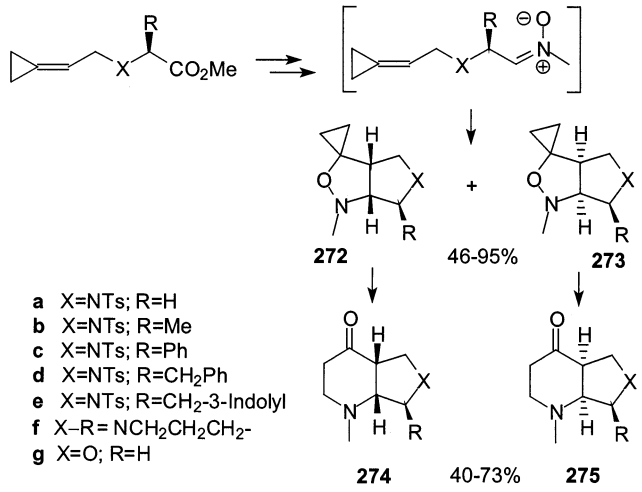



**Scheme 43**



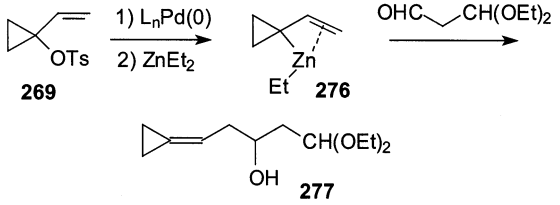

trones underwent smooth in situ intramolecular cycloaddition with a stereoselectivity that was moderate with most substituted substrates but complete with phenylglycine and proline derivatives. The spirocyclopropane isoxazolidines **272** and **273** were then transformed by selective thermal rearrangements into octahydro-2*H*-pyrrolo[3,4-*b*]pyridin-7-ones **274a**−**f**, **275a**−**f**, and octahydrofuro[3,4-*b*]pyridin-7-one (**274g**, **275g**), compounds with ring skeletons of biologically active natural and non-natural products (Scheme 44).[76]

**Scheme 44**



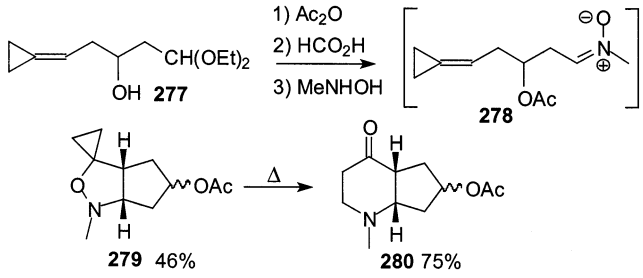

The electrophilic nature of the $\pi$-allyl palladium complex **270** can be easily inverted to a nucleophilic character by reaction with diethylzinc. The formation of $\sigma$- or $\pi$-1,1-dimethyleneallylzinc complexes **276**, resulting from an alkyl−allyl ligand exchange, was considered to explain this umpolung (Scheme 45).[78]

**Scheme 45**




Addition of **276** to 3,3-diethoxypropanal provided 5-cyclopropylidene-1,1-diethoxy-3-hydroxypentane (**277**) (Scheme 45). Its nitrone derivative **278** underwent intramolecular cycloaddition to provide a 1:1 mixture of spirocyclopropane isoxazolidines **279**, which then were transformed into octahydropyrindin-4-ones **280** (Scheme 46).[79]

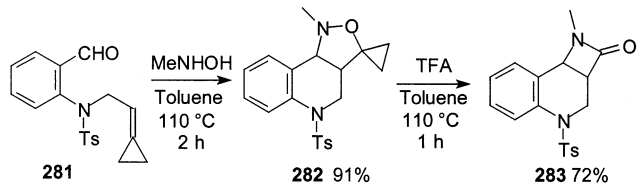
**Scheme 46**




By using a chiral acylating auxiliary, moderate enantioselectivity can be achieved in the cycloaddition process.[79]

Recently, the chemistry of spirocyclopropane isoxazolidines has been enriched by another selective process. By heating **282** in the presence of a protic acid, a ring contraction accompanied by extrusion of ethylene leads to the formation of $\beta$-lactam **283** (Scheme 47).[80]

**Scheme 47**

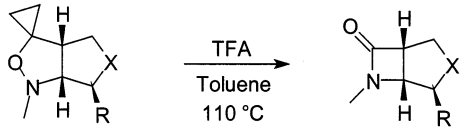



This chemoselective process nicely complements the rearrangement to tetrahydropyridones. The isoxazolidines **272b**, **272e**, **284**, and **279**, employed in the cycloaddition/thermal rearrangement process, gave the corresponding $\beta$-lactams **285**−**288** as well in good yields by simple addition of TFA or TsOH to the heated solution (Scheme 48).

## B. Nitrile Oxides

3-Substituted 5-spirocyclopropane isoxazolines **290**, the partially unsaturated analogues of compounds derived from cycloadditions of nitrones to methylenecyclopropanes, were obtained by cycloadditions of nitrile oxides **289** to **2**. These experiments were carried out in connection with the study of applying

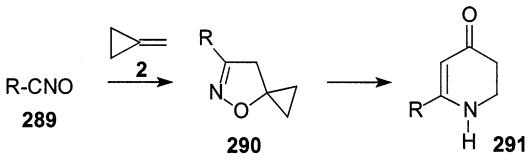
**Scheme 48**




| | | | | |
|---|---|---|---|---|
| **272b** | R = Me | X = NTs | **285** | 60% |
| **272e** | R = $CH_2$-3-Indolyl | X = NTs | **286** | 63% |
| **284** | R = *i*-Pr | X = NTs | **287** | 57% |
| **279** | R = H | X = CHOAc | **288** | 76% |

the rearrangement process to the synthesis of dihydropyrid-4-ones **291** (Scheme 49).[41] Nitrile oxides are

**Scheme 49**




very reactive dipoles, most of which need to be prepared in situ because of their tendency to easily dimerize to furoxans.[81] This behavior, only in part compensated by their reactivity, has represented a limit to their broader use in reactions with alkylidenecyclopropanes.

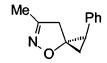
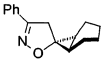
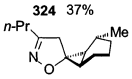
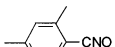
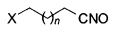
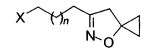
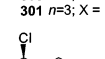
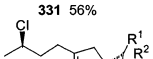
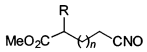
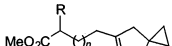
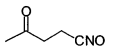
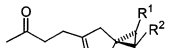
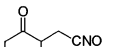
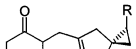
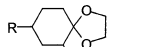
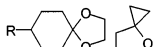
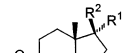
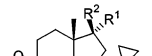
One positive feature in the synthesis of 5-spirocyclopropane isoxazolines is that nitrile oxides are more regioselective in cycloadditions to methylenecyclopropanes compared to nitrones. Only traces (up to 5%) of the 4-spirocyclopropane regioisomers are generally observed with methylenecyclopropanes unsubstituted at the exocyclic double bond. The yields of cycloadditions vary from good to moderate and refer generally, apart from those with aromatic nitrile oxides (Table 14, entries 5, 6, 8, and 10−12), to the use of nitrile oxides prepared in situ by different standard procedures, such as by isocyanate-mediated dehydration of nitro compounds or by triethylamine-mediated dehydrochlorination of chloroximes.[81]

The presence of substituents on the cyclopropane ring produces only the diastereomers resulting from the preferred approach of the dipole from the less hindered face of the dipolarophile (anti approach) (Table 14, entries 7−9, 17, 18, 23, 24, and 26). The *cis*-diethyl-substituted methylenecyclopropane **315** (Table 14, entry 11)[84] gave quantitatively a 2:1 mixture of diastereomeric isoxazolines **327** with nitrile oxide **298**, the major being that one derived from the attack of the nitrile oxide from the side of the less bulky methyl groups.

The isoxazoline **325** (Table 14, entry 9) was employed for a total synthesis of the amphibian alkaloid (±)-pumiliotoxin C(**348**) (Scheme 50).[83]

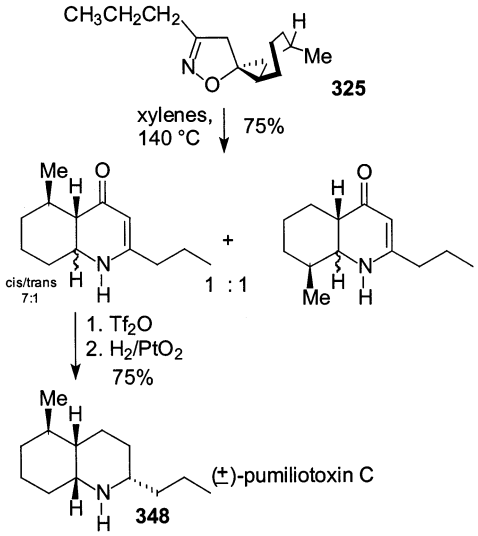
Numerous aliphatic nitrile oxides **299**−**312** (Table 14, entries 13−31), functionalized on the side chain with halide, methoxycarbonyl, and keto groups were added to MCP and its derivatives, en route to functionalized N-bridgehead bicyclic dihydropyridones.[85−89] The reaction yields and regioselectivities were generally good, even better than those obtained with simpler nitrile oxides. Optically active (*R*)-4-chlorovaleronitrile *N*-oxide (**302**) (entries 16−18) gave

**Table 14. Cycloadditions of Nitrile Oxides to MCPs**

| entry | nitrile oxide | methylene-cyclopropane | 5-spirocyclopropane isoxazolidine | Ref. |
|---|---|---|---|---|
| | R-CNO |  **2** |  | |
| 1 | **292** R = Me | | **317** 35% | 82 |
| 2 | **293** R = *n*Pr | | **318** 72% | 3 |
| 3 | **294** R = $CO_2$Me | | **319** 50% | 41 |
| 4 | **295** R = $CH_2$Ph | | **320** 36% | 82 |
| 5 | **296** R = Ph | | **321** 72% | 82 |
| 6 | **297** R = α-Naphthyl | | **322** 68% | 41 |
| 7 | **292** |  **119** |  **323** 40% | 82 |
| 8 | **296** |  **122** |  **324** 37% | 82 |
| 9 | **293** |  **313** |  **325** 50% | 83 |
| 10 |  **298** |  **314** $R^1 = R^2 = R^3$ = Me |  **326** 81% | 84 |
| 11 | | **315** $R^1 = R^2$ = Et; $R^3$ = Me | **327** 100% 2:1 | 84 |
| 12 | | **316** $R^1 = R^3$ = Et; $R^2$ = Me | **328** 100% | 84 |
| |  | **2** |  | |
| 13 | **299** *n*=1; X = Cl | | **329** 52% | 85 |
| 14 | **300** *n*=2; X = Br | | **330** 46% | 85 |
| 15 | **301** *n*=3; X = Br | | **331** 56% | 85 |
| 16 |  **302** |  **2** $R^1 = R^2$ = H |  **332** 73% | 86 |
| 17 | | **119** $R^1$ = Ph; $R^2$ = H | **333** 75% | 86 |
| 18 | | **122** $R^1 = R^2 = -(CH_2)_4-$ | **334** 53% | 86 |
| |  | **2** |  | |
| 19 | **303** *n*=0; R = $CO_2$Me | | **335** 68% | 85 |
| 20 | **304** *n*=0; R = H | | **336** 67% | 85 |
| 21 | **305** *n*=1; R = $CO_2$Me | | **337** 70% | 85 |
| 22 |  **306** |  **2** $R^1 = R^2$ = H |  **338** 63% | 87 |
| 23 | | **119** $R^1$ = Ph; $R^2$ = H | **339** 51% | 87 |
| 24 | | **122** $R^1 = R^2 = -(CH_2)_4-$ | **340** 42% | 87 |
| 25 |  **307** |  **2** R = H |  **341** 72% | 87 |
| 26 | | **119** R = Ph | **342** 41% | 87 |
| |  | **2** |  | |
| 27 | **308** R = H | | **343** 73% | 88 |
| 28 | **309** R = $CH_2CONHtBu$ | | **344** 58% | 88 |
| |  | **2** |  | |
| 29 | **310** $R^1$ = H; $R^2$ = OTBDMS | | **345** 88% | 89 |
| 30 | **311** $R^1 = R^2 = OCH_2CH_2O$ | | **346** 40% | 89 |
| 31 | **312** $R^1$ = H; $R^2$ = CONH*t*Bu | | **347** 50% | 89 |

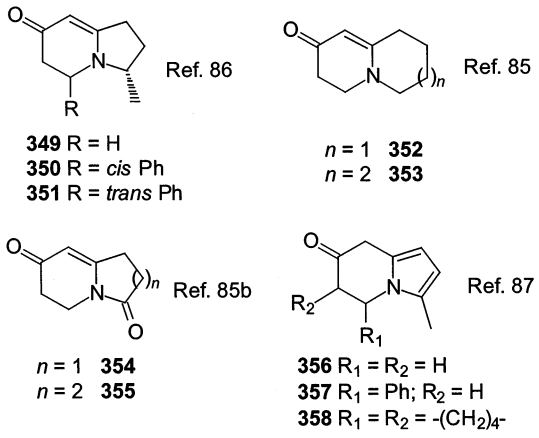
nonracemic isoxazolines **332**−**334**, which were transformed selectively by thermal rearrangement into indolizinones **349**−**351** (Chart 7).[86] Bromo-substituted isoxazolines **330**−**331** (Table 14, entries 14 and 15) gave quinolizinone **352** and pyrido[1,2-*a*]azepinone **353** (Chart 7) with lower selectivity besides other isomers.[85] Methoxycarbonyl-substituted isoxazolines **335**−**337** (Table 14, entries 19−21) gave the lactams **354** and **355** (Chart 7),[85] whereas carbonyl-substituted isoxazolines **338**−**340** (Table 14, entries

**Scheme 50**



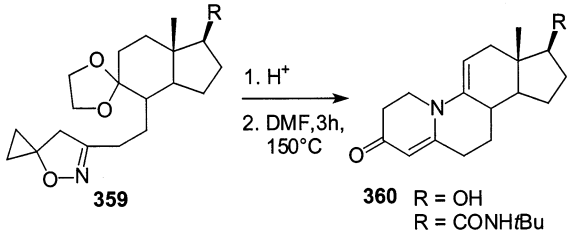

22−24) gave pyrroles **356**−**358** by condensation and H-shift with aromatization of the five-membered ring (Chart 7).[87]

**Chart 7. N-Bridgehead Heterocycles Synthesized by Thermal Rearrangement of 5-Spirocyclopropane Isoxazolines**



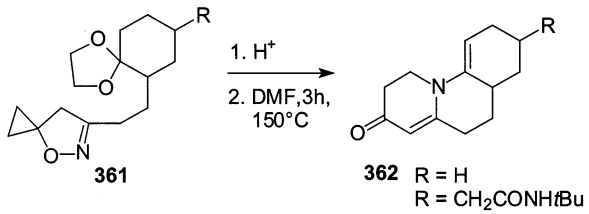

Isoxazolines **345**−**347** (Table 14, entries 29−31) have been used as key intermediates by Guarna[89] for the synthesis of $\Delta^9$-19-nor-10-azatestosterones **360** belonging to a novel class of inhibitors of human steroid 5α-reductases (Scheme 51).

**Scheme 51**



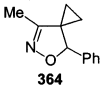
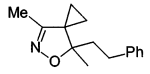
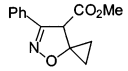
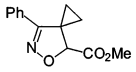
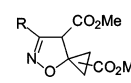
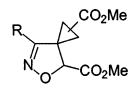
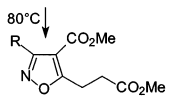

The isoxazolines **343**−**344** (Table 14, entries 27 and 28) were transformed by Guarna et al.[88] into octahydrobenzo[*c*]quinolizin-3-ones **362**, which showed strong inhibitory activity toward 5α-reductases as well (Scheme 52).

**Scheme 52**




The study of the regioselectivity of the cycloaddition of nitrile oxides with alkylidenecyclopropanes was carried out in analogy and comparison with the cycloaddition of nitrones, affording somewhat different results (Table 15).[90,52b]

**Table 15. Cycloadditions of Nitrile Oxides 292 and 296 to ACPs**

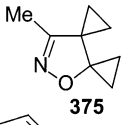
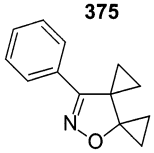
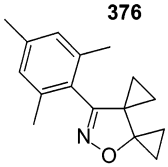
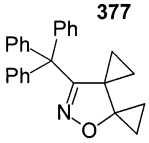
| entry | nitrile oxide | methylene cyclopropane | 5-spirocyclopropane isoxazoline | 4-spirocyclopropane isoxazoline |
|---|---|---|---|---|
| 1 | MeCNO **292** |  **63** |  **363** | 50% 1 : 4  **364** |
| 2 | **292** |  **163** | – |  **365** 65% |
| 3 | PhCNO **296** |  **3** |  **366** | 53% 3 : 1  **367** |
| 4 | **296** |  **180** |  **368** | 15% 3.4 : 1  **369** |
| 5 | **292** | | **370** | **371** |
| | | | 80°C  **372** 37% **373** 45% | |

Although nitrile oxides appear more regioselective than nitrones toward MCP, in cycloadditions with ACPs substituted with EDG or EWG, they show a slightly lower regioselectivity than nitrones (Table 15, entries 1, 3, and 4). The differences, however, are too small to allow any conclusive explanation about the different behavior of the two 1,3-dipoles and about the "cyclopropylidene effect" on the regioselectivity of the reactions.

The thermally unstable cycloadducts **368** and **370** generated from **180** (Table 15, entries 4 and 5) undergo a cyclopropyl ring opening with aromatization to afford the isoxazoles **372** and **373**.[52b,90]

Compared with nitrones, the cycloadditions of nitrile oxides to bicyclopropylidene **5** give much poorer results, because the tetrasubstituted nature of the alkene, with its low reactivity, lets the dimerization of nitrile oxides become a competing reaction. Low yields of adducts were obtained with acetonitrile oxide (**292**) or benzonitrile oxide (**296**) (Table 16, entries 1 and 2).[71b] Only stable, bulky nitrile oxides give satisfactory yields of adducts (Table 16, entry 3), as the cycloaddition could be carried out at higher temperature without the risk of added dimerization of the nitrile oxides. Nevertheless, when the steric

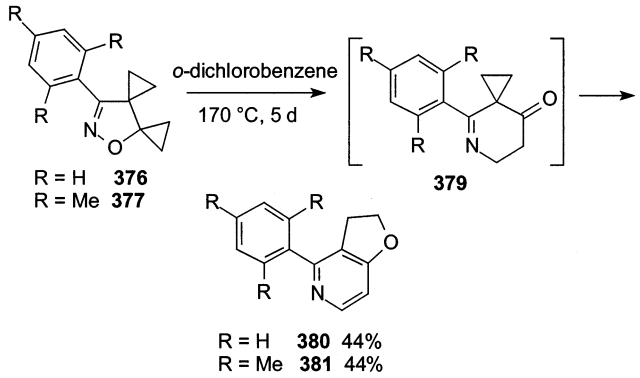
**Table 16. Cycloadditions of Nitrile Oxides to Bicyclopropylidene (5)**

| Entry | Nitrile oxide | Cycloadduct | Yield (%) |
|---|---|---|---|
| 1 | Me-CNO **292** |  **375** | <10 |
| 2 | Ph-CNO **296** |  **376** | 36 |
| 3 | 2,4,6-$Me_3$-$C_6H_2$-CNO **298** |  **377** | 67 |
| 4 | $Ph_3C$-CNO **374** |  **378** | 17 |

demand increases too much, the reactivity drops (Table 16, entry 4).[71b]

The process is of scant utility for the synthesis of spirocyclopropane heterocycles, because in the thermal rearrangement of these isoxazolines, not only the spirocyclopropane vicinal to the oxygen undergoes ring opening but also the second spirocyclopropane experiences a ring enlargement. Under concomitant aromatization, furo[1,2-*c*]pyridines **380** and **381** were formed (Scheme 53).[71b]

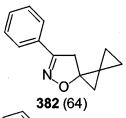
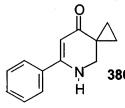
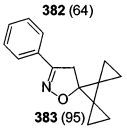
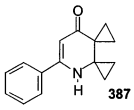
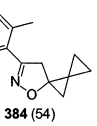
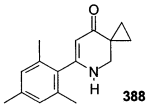
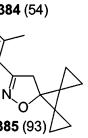
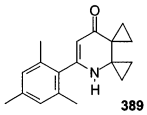
**Scheme 53**




The higher temperature required for the thermal rearrangement is responsible for this uncommon reactivity (Scheme 53).[71b]

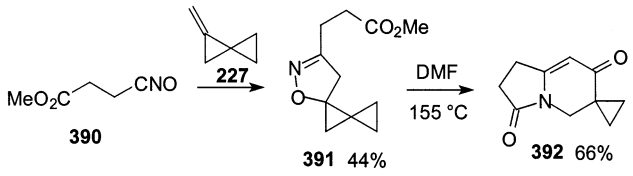
On the other hand, the synthesis of spirocyclopropane aza heterocycles from nitrile oxides proceeds very efficiently when methylenespiropentane (**227**) or methylenedispiroheptane (**228**) are used as dipolarophiles. The much higher regioselectivity in the reaction of nitrile oxides with these alkenes, accompanied by the highly selective thermal rearrangement of the adducts, leads to very efficient syntheses of spirocyclopropane- or bis(spirocyclopropane)dihydropyridone structures **386**−**389** (Table 17).[70]

**Table 17. Cycloadditions of Nitrile Oxides 296 and 298 to 227 and 228**

| Entry | Nitrile oxide | MCP | Cycloadduct (% Yield) | Rearrangement product (% Yield) |
|---|---|---|---|---|
| 1 |  **296** |  **227** |  **382** (64) |  **386** (70) |
| 2 | **296** |  **228** |  **383** (95) |  **387** (92) |
| 3 |  **298** | **227** |  **384** (54) |  **388** (53) |
| 4 | **298** | **228** |  **385** (93) |  **389** (73) |

The 3-methoxycarbonylpropionitrile oxide (**390**) affords with methylenespiropentane (**227**) a straightforward two-step synthesis of the spirocyclopropane indolizindione **392** (Scheme 54).[70]

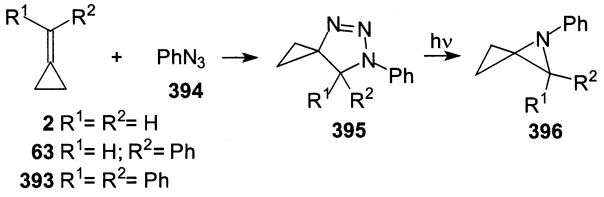
**Scheme 54**




## C. Azides

The reaction of methylenecyclopropane with azides is the first 1,3-dipolar cycloaddition reported with this system.[60b,91,92] In a study aimed at the synthesis of the *N*-substituted azaspiropentane ring system **396**, MCP (**2**) was allowed to react at 25 °C with phenyl azide (**394**) to give a single regioisomeric triazoline **395** in 68% yield (Scheme 55). The cyclo-

**Scheme 55**

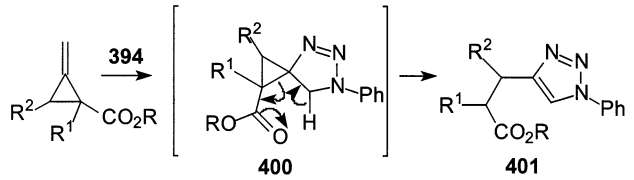



addition was highly regioselective, but the authors spent little effort on ascertaining the structure of **395**, because it has no consequence on the final reaction product **396**. The structure assignment was based upon the general observation that the substituted nitrogen of phenyl azide ordinarily binds to the olefinic carbon that is able to bear positive charge.[93,94] Further irradiation of solutions of **395** in methylene chloride at 0 °C with a mercury lamp gives 1-phenylazaspiro[2.2]pentanes **396** (Scheme 55).

A different result was obtained in the cycloaddition to methylenecyclopropanes **397**−**399** bearing alkoxycarbonyl substituents on the cyclopropyl ring. In this

instance, 1,2,3-triazoles **401** isomeric with the triazolines **400** were formed in the reaction.[95] The formation of triazoles **401** is rationalized with the intermediate formation of triazolines **400**, 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 56). The formation of triazoles **401** also confirms the

**Scheme 56**

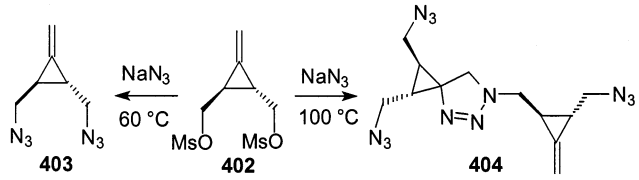



**397** R = Me; $R^1$ = H; $R^2$ = $CO_2Me$
**398** R = Et; $R^1$ = $R^2$ = H
**399** R = Et; $R^1$ = Me; $R^2$ = H

regiochemistry of the cycloaddition with methylenecyclopropanes unsubstituted at the methylene group, while leaving some doubt as to the regiochemistry in the case of substituted **63** and **393**.

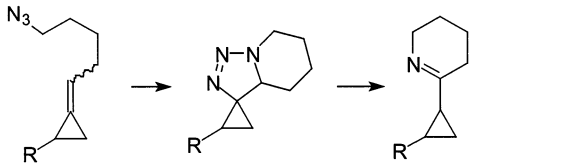
The dimesylate **402** reacted with sodium azide in DMF at 60 °C to give the corresponding diazide **403** in 84% isolated yield. When the same reaction was performed at 100 °C a 1,3-dipolar cycloaddition of **403** to the double bond of a second molecule occurred to give triazoline **404** in 62% yield (Scheme 57).[96]

**Scheme 57**




An intramolecular version of an azide cycloaddition to ACPs is provided by **405** and **406**, which form cyclopropylimines **408** and **409** via formation of triazoline **407** followed by extrusion of nitrogen with concomitant 1,2-hydrogen shift (Scheme 58).[97] The

**Scheme 58**

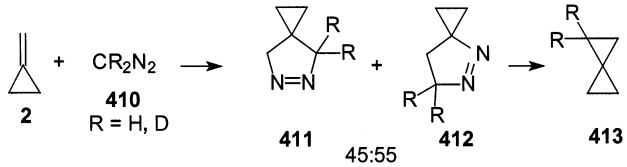



cyclization was found to be solvent dependent: polar solvents such as DMF gave the best yields, whereas benzene led to the formation of several side products.

## D. Diazoalkanes

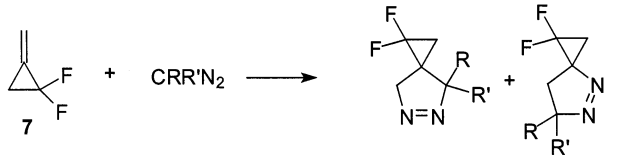
To carry out a study aimed at elucidating the mechanism of the thermal decomposition of spiropentane **413**, the two regioisomeric pyrazolines **411** and **412** were synthesized in high yield by allowing a solution of MCP (**2**) and diazomethane (**410**) (or diazomethane-$d_2$) in diethyl ether to stand at 3 °C for three weeks (Scheme 59).[98]

**Scheme 59**




The regioisomer **412** derived from the attack of the diazomethane carbon on the $CH_2$ end of MCP's double bond is slightly preferred in the cycloaddition. The regiochemical outcome is a result of steric factors as shown by the reaction of diazoalkanes **410**, **414**, and **415** with 2,2-difluoromethylenecyclopropane (**7**) (Scheme 60). Diazomethane (**410**) gives a 1:1 mixture

**Scheme 60**

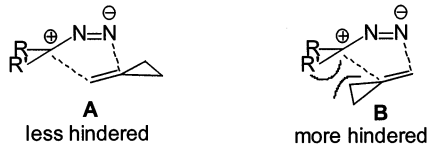



| | | | |
|---|---|---|---|
| **410** R = R' = H | **416** | 50:50 | **417** |
| **414** R = H; R' = CH=$CH_2$ | **418** | 35:65 | **419** |
| **415** R = R' = Ph | **420** | 0:100 | **421** |

of the two regioisomers **416** and **417**, whereas diphenyldiazomethane (**415**) gives exclusively compound **421**.[99]

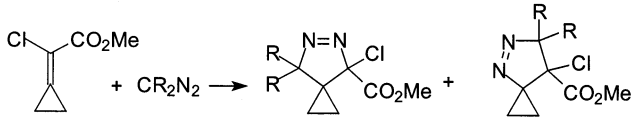
The approach of the two reagents seems to be influenced by the steric demand of substituents on the diazoalkane which disfavor mainly the transition state **B** (Chart 8).

**Chart 8. TS Trajectories for the Regioisomeric Approaches of MCP and Diazoalkanes**




The steric effect must be overwhelmed by an electronic effect in the cycloadditions of diazoalkanes **410**, **422**, and **415** to ACP **4** (Scheme 61).[100]

**Scheme 61**

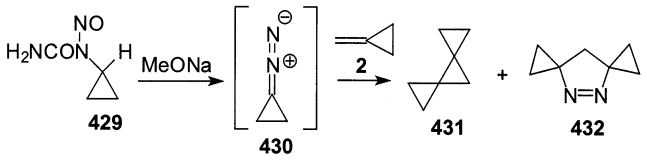



| | | | |
|---|---|---|---|
| **410** R = H | **423** | >98:2 | **424** |
| **422** R = Me | **425** | 92:8 | **426** |
| **415** R = Ph | **427** | < 2:98 | **428** |

Compound **430** was synthesized from cyclopropyl *N*-nitrosourea (**429**), and its reaction with **2** has been studied. The cycloaddition gave a mixture of the

unique primary adduct **432** together with the [3]-triangulane (**431**) derived from $N_2$ extrusion (Scheme 62).[101]

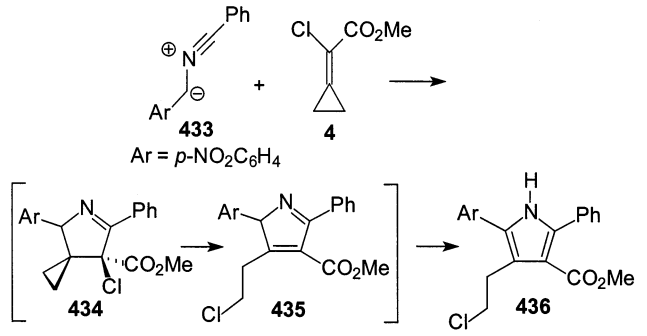
**Scheme 62**



## E. Nitrile Ylides

The reaction of 1-phenyl-3-*p*-nitrophenylnitrile ylide (**433**) to ACP **4** is the sole reported example of a cycloaddition of this dipole type. The only product isolated from the reaction was the pyrrole **436**, which arose from **435**, formed in turn from the primary cycloadduct **434**, by a cyclopropylcarbinyl−homoallyl rearrangement (Scheme 63).[100]

**Scheme 63**

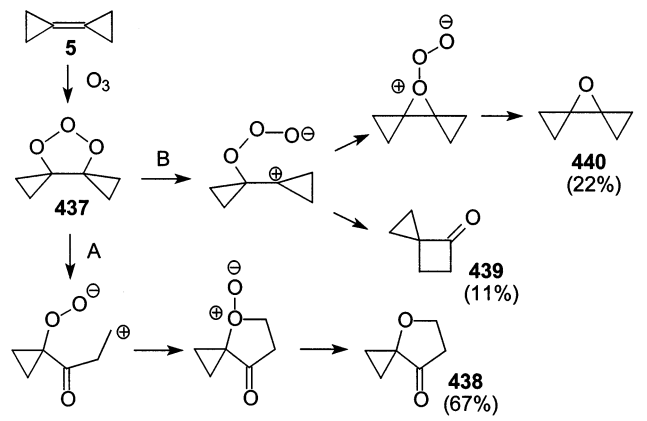


## F. Ozone

Ozone generally combines with alkenes in a 1,3-dipolar fashion giving the so-called primary ozonides, which rearrange to 1,2,4-trioxolanes (ozonides). Its reaction with the parent MCP (**2**) is not known, whereas it reacts readily at −78 °C with BCP (**5**), most likely because of the preferred interaction of the high-lying HOMO of BCP with the low-lying LUMO of ozone.

The reaction gave the products **438** and **439**, derived from opening of a cyclopropyl ring, and **440**, as expected from the reactivity of alkylidenecyclopropane derivatives (Scheme 64). Compound **438**

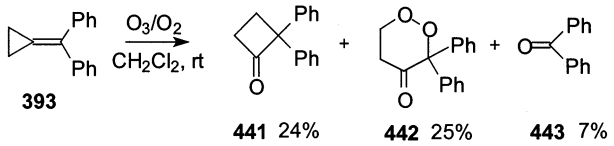
**Scheme 64**



might arise from the O−O bond cleavage followed by the rearrangement of a cyclopropyloxy cation to an oxoethyl cation (Scheme 64, path A). Spirohexanone **439** could arise from a different fragmentation of ozonide C−O bond and further cyclopropyloxy−cyclobutanone rearrangement (Scheme 64, path B). Oxirane **440** can eventually derive from the same path B or from other side processes.[10]

The reaction of diphenylmethylenecyclopropane (**393**) with ozone was recently described by Beck to afford, in mixtures with cyclobutanone **441** and benzophenone (**443**), the peroxide **442** (Scheme 65).[102]

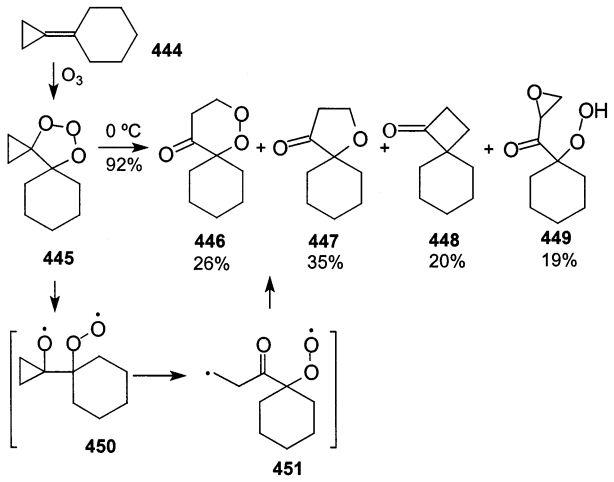
**Scheme 65**



The authors suggested a single electron-transfer mechanism, rather than a 1,3-dipolar cycloaddition, for this reaction.

The ozonolysis of cyclopropylidenecycloalkanes afforded mixtures of compounds in which, in the case of cyclohexylidenecyclopropane (**444**), the main product was the spirocyclic oxaketone **447**. The authors suggested a radical fragmentation of the primary ozonide **445** to **450** and subsequent rearrangement of the cyclopropyl group to afford diradical **451**, which evolved to **446** and **447** (Scheme 66).[103]

**Scheme 66**



## G. Trimethylenemethane Chemistry

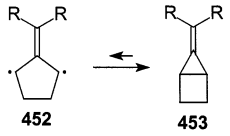
The behavior of ACPs as trimethylenemethane (TMM) species, consisting, in a general sense, of a cyclopropane ring opening and reaction of the formed $C_4$ unit at the 1,3-termini, will be discussed in this chapter.

### *1. Thermal- and Photochemical-Induced Reactions*

TMM diradicals are short-lived intermediates, which more conveniently are generated thermally from diazenes by $N_2$ extrusion. The parent TMM has been isolated in a matrix at low temperature: it is stable for several months at the boiling temperature of liquid nitrogen (−196 °C) and it has been charac-

terized as a triplet diradical in its ground state.[104] At higher temperatures, these species undergo rapid ring closure by radical coupling to alkylidenecyclopropanes. This reaction hampers the use of transiently generated TMM diradicals as a three-carbon unit in [3+2] cycloadditions. Only when their lifetime is greatly enhanced by structural factors that disfavor ring closure to ACPs can they participate in cycloadditions with electron-deficient alkenes.[105] The most notable and studied examples regard diradicals of type **452** (Scheme 67), where intramolecular cycliza-

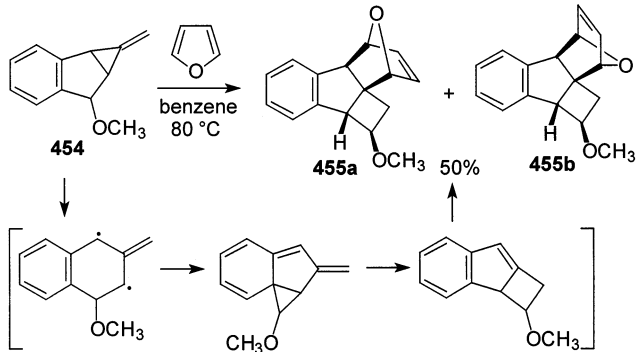
**Scheme 67**




tion to the corresponding ACPs **453** is relatively less favored by the strain energy of the 5-alkylidenebicyclo-[2.1.0]pentane system. An equilibrium occurs between these compounds and the 1,3-diyl species, which makes possible in this case the generation of diradical TMMs by thermal treatment of the corresponding ACPs at viable temperatures.

Depending on the structure of the substrate, the formed diradical can evolve in different ways or can be trapped. From a related 6-methylenebicyclo[3.1.0]-hexene derivative **454**, Berson obtained the diastereomeric oxabicyclo adducts **455** by trapping the unstable indene derivative (which otherwise undergoes cyclodimerization), formed from the primary diradical intermediate, in a Diels−Alder cycloaddition with furan (Scheme 68).[106]

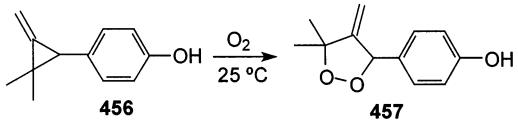
**Scheme 68**




Other ACP derivatives, which are able, for structural reasons, to stabilize the 1,3-diyl form, were found to react smoothly with $O_2$ through the diradical species to afford 1,2-dioxolanes.

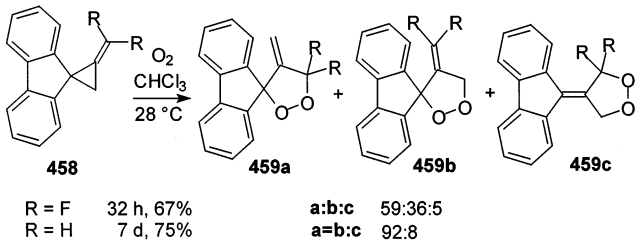
The presence of a 4-hydroxyphenyl group confers to **456** a remarkable reactivity since it is rapidly and quantitatively transformed by atmospheric oxygen to dioxolane **457** (Scheme 69).[107]

**Scheme 69**




Fluorene-substituted ACPs **458** also gave endocyclic peroxides **459a**−**c** when molecular oxygen was passed through a solution of **458** in $CHCl_3$ at room temperature (Scheme 70).[108] The fluorene group plays

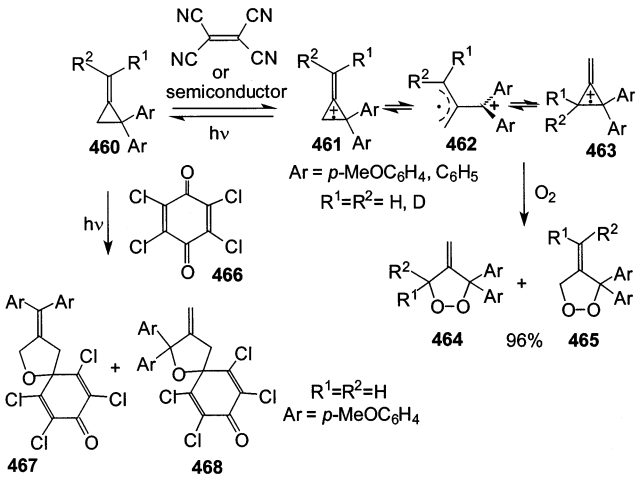
**Scheme 70**




a critical role, since no reaction has been observed with the closely related diphenyl-substituted ACPs under thermal conditions.

However, substituted methylenecyclopropanes **460** can react with oxygen when photoirradiated in the presence of TCNE or of a semiconductor via the bisected radical cation **462** to afford dioxolanes **464** and **465**. Better results are obtained with electron-donating substituents, which stabilize the cation (Scheme 71).[108,109] If the irradiation is performed in

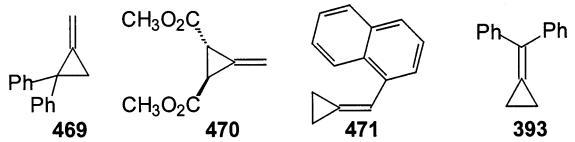
**Scheme 71**




a thoroughly deaerated solution in the presence of chloranil (**466**), two different products, **467** and **468**, derived from a [3+2] cycloaddition to the C=O double bond can be isolated.[110]

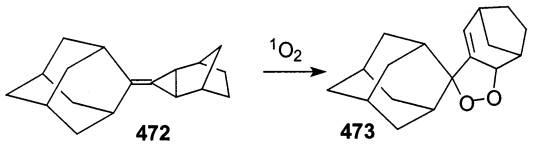
Simple ACPs such as **469**−**471** and **393** (Chart 9) are inert toward singlet oxygen, and some derivatives react very slowly. This can be explained, in part, both by the low energy of the LUMO of the MCP and by the absence of an allylic proton, with the exclusion of the cyclopropyl hydrogens, to perform an "ene" reaction.[111]

**Chart 9. ACPs Inert toward Singlet Oxygen**



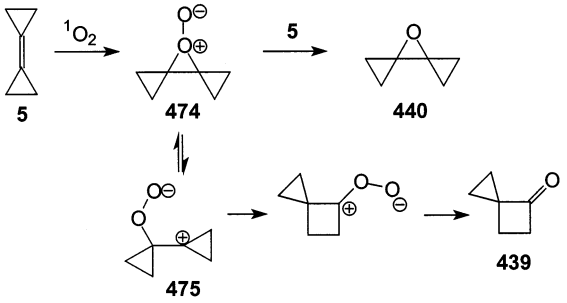
During mechanistic studies on the reaction of singlet oxygen with substituted alkylidenecyclopropanes, adamantyl derivatives were synthesized[112] as in the case of **472**, which afforded dioxolane **473** in 80% isolated yield (Scheme 72).[113]

**Scheme 72**




Bicyclopropylidene (**5**) with its high-energy HOMO reacted smoothly with singlet oxygen to afford epoxide **440** and ketone **439**, in a combined yield of 76% and in a ratio of 6:10. The mechanistic pathways to these compounds start from the perepoxide **474** (Scheme 73).[11] Perepoxide **474** can react with another

**Scheme 73**



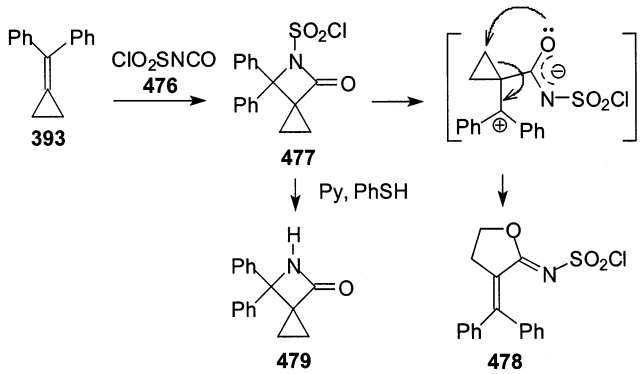

molecule of bicyclopropylidene to afford epoxide **440**. Alternatively, cleavage to zwitterion **475** and cyclopropylmethyl to cyclobutyl rearrangement affords ketone **439**.

Some ACP derivatives react with electrophiles giving products deriving from cyclopropane ring opening through stabilized carbocations. With appropriate electrophiles that allow reclosure reactions, the product is the result of a formal cycloaddition reaction, with the ACP functioning as a TMM-type 1,3-dipolar fragment. Concerning heterocycle formation, good electrophiles are heterocumulenes, e.g., *N*-chlorosulfonylisocyanate (CSI, **476**) and sulfur trioxide. CSI behaves as a typical [2+2] cycloaddend with most alkenes, but it has been demonstrated to be also involved in stepwise cycloadditions via polar intermediates.[114] The additions of CSI with both alkylidene and alkenylidenecyclopropanes have been studied in detail by several authors.[115−121]

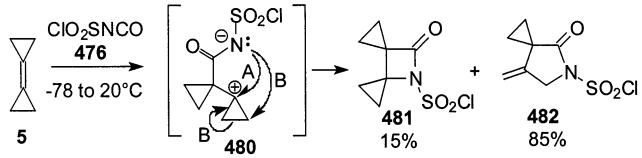
Diphenylmethylenecyclopropane (**393**) reacts with CSI (**476**) to afford the iminolactone **478** (Scheme 74).[116] A careful analysis of the reaction demonstrated that the $\beta$-lactam **477** was a labile intermediate since a prompt reduction of **477** with pyridine/thiophenol allowed the isolation of lactam **479**.[117]

Bicyclopropylidene (**5**) reacts with CSI to give only small amounts of the $\beta$-lactam **481**, while the main product is the $\gamma$-lactam **482** (Scheme 75). This finding is best explained in terms of a 1,4-zwitterionic intermediate **480**, which predominantly cyclizes with a concomitant cyclopropyl-to-allyl opening of its cationic end group (route B).[118]

**Scheme 74**

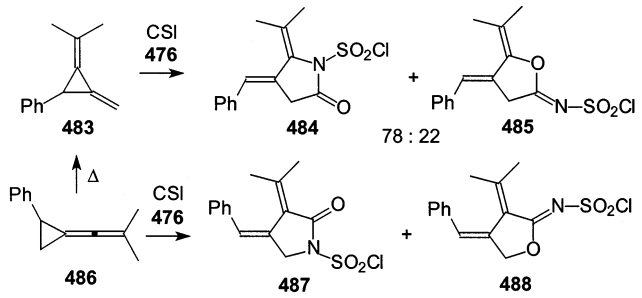



**Scheme 75**




The formation of the $\beta$-lactam derivative **481** remains an isolated case. For example, the bis(alkylidene)cyclopropane **483**, which can be prepared by thermal rearrangement of isopropenylidenecyclopropane **486**,[119] gives the regioisomeric adducts **484** and **485** in a 78:22 ratio in the reaction with CSI (Scheme 76).[120] It is interesting to note that the

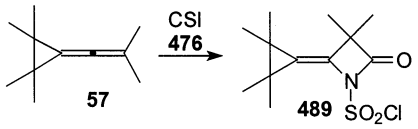
**Scheme 76**




analogous reaction with **486** produced, besides smaller amounts of other constitutional isomers, two other regioisomers **487** and **488**,[121] which are stable, in sharp contrast to the reported instability of **484** and **485**.

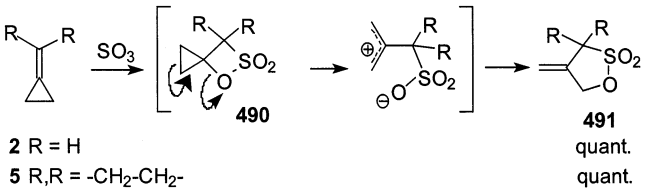
Moreover, the reaction of CSI with alkenylidenecyclopropanes is extremely sensitive to substitution of the cyclopropyl ring and also of the allene moiety. Thus, the electrophilic attack can occur at both C=C double bonds. Reaction of CSI with the fully substituted alkenylidenecyclopropane **57** occurrs exclusively at the double bond away from the cyclopropane in a [2+2] fashion to afford cleanly lactam **489** (Scheme 77).[121]

**Scheme 77**



The addition of sulfur trioxide to MCP (**2**) and BCP (**5**) afforded the corresponding $\gamma$-sultones **491**, moderately stable at room temperature (Scheme 78).

**Scheme 78**

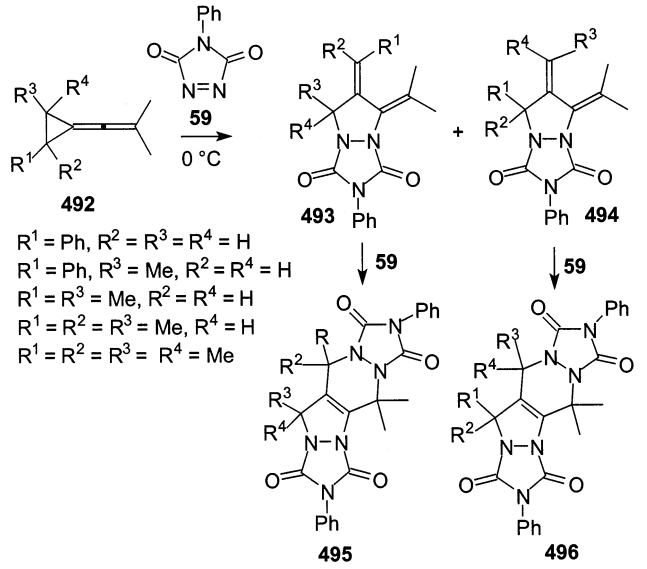



These adducts are supposed to originate from the isomerization of initially formed $\beta$-sultones **490**.[122]

PTAD (**59**) reacts with MCP derivatives in a variety of modes of addition to the C=C double bond, depending on the structural features of the reacting MCPs. Thus, it reacts with allylidene- and benzylidenecyclopropanes in [4+2] cycloadditions (see section II.B.1), with alkylidenecyclopropanes it undergoes ene reactions[28] or [2+2] cycloadditions (see section V), and with BCP it gives products probably derived from an initial [2+1] cycloaddition (see section VI).

With alkenylidenecyclopropanes **492**, PTAD (**59**) reacts very rapidly attacking only the cyclopropylidene-substituted double bond, but exclusively with ring opening, giving [3+2] cycloadducts **493** and **494** (Scheme 79).[28,123] The dienes **493** and **494** in most

**Scheme 79**

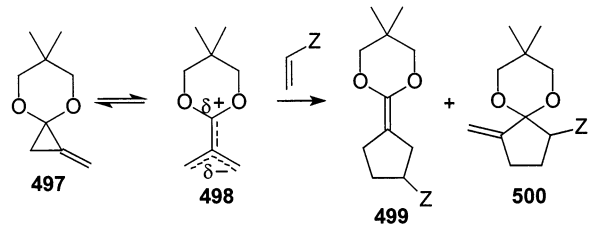



cases react further with PTAD in a hetero Diels–Alder mode to form the 2:1 adducts **495** and **496**, respectively.

Although **483** and other highly substituted ACP derivatives react as nucleophiles in some reactions, behaving ultimately as latent 1,3-dipoles, they are still considered precursors of diradical TMMs, reacting also with radicals and undergoing ring opening by homolytic C–C bond cleavage under thermal conditions.

Only recently, Nakamura and co-workers have collected evidence for the occurrence of discrete dipolar TMM intermediates from *gem*-dialkoxy-substituted MCPs and ACPs under thermolytic conditions.[124] Compound **497** undergoes a degenerate rearrangement, which has been evidenced by isotopic and chemical labeling at the exo methylene carbon atom, at temperatures as low as 40 °C (Scheme 80).[125]

**Scheme 80**




This rearrangement occurs through the zwitterionic intermediate **498**, whose nucleophilic character is demonstrated by reaction with electron-poor alkenes in [3+2] cycloadditions producing functionalized cyclopentane derivatives **499** and **500**.[126] Analogous reactions take place with electron-deficient alkynes.[127] The intermediate TMM **498** is rather inert to triplet $O_2$, being converted only slowly to an unstable 1,2-dioxolane by passing $O_2$ to a toluene solution of **497**, heated at 80 °C.[125] This property allows synthetically simpler procedures, since reactions of **497** and related compounds need not be carried out under rigorous exclusion of oxygen. The regioselectivity of the reaction with alkenes depends on the electron-withdrawing properties of the *Z* group(s), with groups of moderate potency giving selectively the regioisomer **499** and more potent groups usually affording a mixture of **499** and **500** with the latter isomer prevailing (Scheme 80).[128] This different outcome of the reaction has been interpreted on the basis of a mechanistic switch from a concerted pathway with regular alkenes to a stepwise mechanism with strongly electron-deficient alkenes, initiated by a SET from **498** to the alkene that forms an intermediate radical anion. This hypothesis is supported by the contrasting stereochemical data collected in the two cases with *Z* and *E* 1,2-disubstituted and trisubstituted alkenes: cyclopentylidene acetals of type **499** are formed essentially with stereochemical preservation[126,129] while considerable loss of stereochemical information occurs in the formation of methylenecyclopentanone ketals **500**, obtained as mixtures of diastereomers.[128]

Nakamura and co-workers have also investigated extensively the reactivity of MCP **497** and its substituted congeners toward carbon–heteroatom double bonds and have found that additions to carbonyl compounds and imines represent a useful and practical way for the synthesis of oxygen and nitrogen heterocycles, respectively. Under simple thermal conditions, both aromatic and aliphatic aldehydes and ketones react with **497** to give mainly $\alpha$-methylene-$\gamma$-lactone ketal derivatives **501**, together with small amounts of the regioisomeric alkylidenetetrahydrofurans **502** (Scheme 81).[130] The scope of the reaction is well represented by the examples in Table 18. The regioselectivity of the reaction is always synthetically useful, varying from excellent for aliphatic carbonyl derivatives to fairly good for aromatic

**Scheme 81**

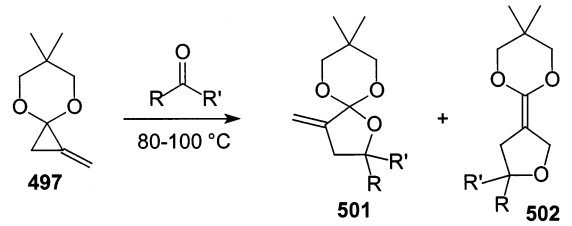
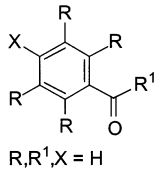
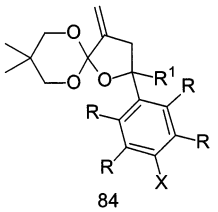
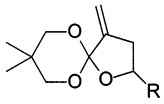
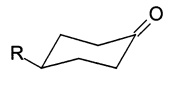
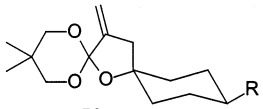


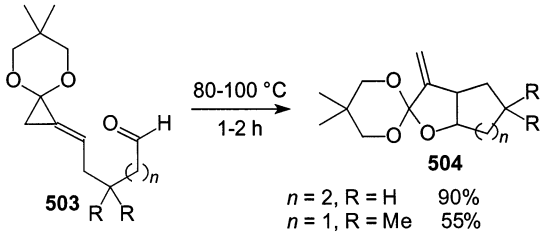

**Table 18. Reactions of MCP 497 with Carbonyl Derivatives**

| Entry | Aldehyde or ketone | Major product (% Yield) | 501:502 Ratio |
|---|---|---|---|
| |  |  | |
| 1 | R,R$^1$,X = H | 84 | 89:11 |
| 2 | R,R$^1$ = H, X = OMe | 82 | 87:13 |
| 3 | R,R$^1$ = H, X = Cl | 81 | 87:13 |
| 4 | R,X = F, R$^1$ = H | 75 | 92:8 |
| 5 | R,X = H, R$^1$ = Me | 81 | 93:7 |
| |  |  | |
| 6 | R = $n$C$_5$H$_{11}$ | 84 | 96:4 |
| 7 | R = $t$Bu | 86 | 96:4 |
| |  |  | |
| 8 | R = H | 56 | 96:4 |
| 9 | R = $t$Bu | 81 | 98:2 |

ones. The product from entry 9 consisted of two diastereomers in a 4:1 ratio, the major being the O,$t$Bu-trans derivative. This reaction required prolonged reaction times, but its rate was enhanced under high pressure.[130]

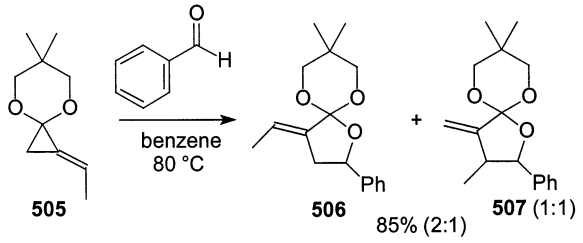
Recently, an intramolecular version of the process has been studied (Scheme 82).[131] Bicyclic-fused methylenedihydrofuranone ketals **504** were obtained from **503** in short reaction times with complete regioselectivity but negligible diastereoselectivity (~1.2:1).

**Scheme 82**



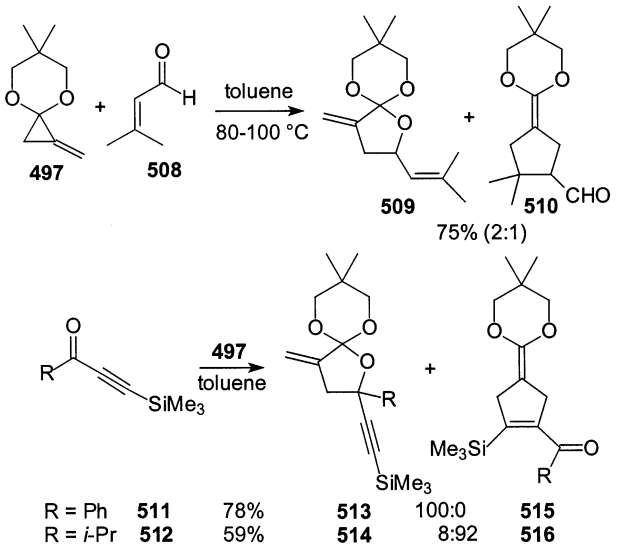

The regioselectivity observed in the addition of benzaldehyde to the ethylidenecyclopropane **505** has been explained in terms of steric effects in the initial attack of dipolar TMM intermediate to the carbonyl carbon. Alkylidenefuranone ketal **506**, derived from attack of the less hindered methylene carbon, was the prevalent adduct (Scheme 83).[124,130]

**Scheme 83**




With α,β-unsaturated carbonyl compounds, competition between addition at C=O and C=C double (or triple) bond has been observed. While the addition to alkenyl ketones occurs only at the C=C bond, the addition to the corresponding aldehydes gives a mixture of adducts stemming from C=C and C=O addition. The heterocyclic derivative is most abundant, when the C=C bond is sterically congested, such as in aldehyde **508** (Scheme 84).[130] Since alkynes

**Scheme 84**

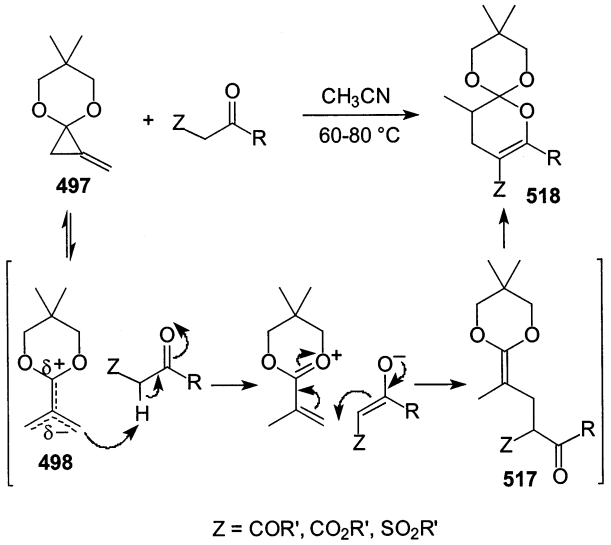



are less reactive toward MCP **497** than alkenes, acetylenic ketone **511** resulted predominantly in addition to the C=O double bond with formation of furan adduct **513** (Scheme 84).[127] However, this reaction showed an interesting dichotomy, since the ratio was almost completely reversed toward the alkylidenecyclopentene **516** in the case of the starting compound **512**, where the carbonyl group is sterically and electronically deactivated. Furthermore, addition of **512** is highly solvent-dependent: in acetonitrile, the ratio **514**/**516** increased to 57:43.[127] This solvent effect is consistent with a stepwise mechanism for addition at C=O, with formation of a polar intermediate occurring faster in a polar solvent than the concerted addition to the triple bond. Reactions of **497** in $CH_3CN$ gave small amounts (3−10%) of adducts even to the C=O group of acetylenic methyl esters.

With β-diketones and related compounds, the [3+2] cycloadduct to C=O has also been observed in a few cases. However, the acidity of the doubly activated methylene group now offers an alternative and competitive reaction pathway. This new reaction pathway usually becomes dominant and ultimately

leads to the formation of structurally diverse oxygen heterocycles, namely, dihydropyranone ketals **518**, formally derived from a [3+3] cycloaddition (Scheme 85).[132] Ketene acetals of structure **517**, precursors of

**Scheme 85**




**518**, have been isolated instead of the pyranones with certain active methylene substrates. Examples in Table 19 illustrate the viability and the scope of this method for the synthesis of dihydropyran-2-one ketals and the competition with the [3+2] cycloaddition to C=O.[132]

Early attempts to synthesize pyrrolidinone derivatives by means of the analogous [3+2] cycloaddition to simple imines were unsuccessful.[130] However, it has been found recently that **497** reacts thermally with more electron-deficient C=N double bonds, such as those of *O*-alkyloximes[133] and *N*-tosyl- and methoxycarbonylimines,[134] to produce the desired five-membered azaheterocycles. Interestingly, *O*-alkyloximes and *N*-tosylimines show opposite regiochemical preference, making the process synthetically more useful since structurally different products become available. Cycloadditions with *O*-alkyloximes **519a** occur at the chemically equivalent termini of TMM **498**, in analogy to cycloadditions with alkenes and alkynes. Consequently, ketene acetal-substituted pyrrolidines **520** are the primary cycloadducts which, upon acidic hydrolysis, are precursors to pyrrolidinecarboxylic acid esters **521** (Scheme 86 and Table 20).[133] Conversely, cycloadditions to *N*-tosyl- and *N*-acylimines **519b** display the same regioselectivity as those to carbonyl derivatives, with the heteroatom linking to the acetal carbon atom. Lactam acetals **522** are then produced primarily, which can be converted to $\gamma$-amino acids **523** on hydrolysis (Scheme 86 and Table 21).[134]

The reactions with *O*-alkyloximes **519a** represent a useful synthesis of pyrrolidine derivatives by [3+2] cycloaddition, an alternative to the azomethine ylide−alkene dipolar cycloaddition. The reaction requires quite high temperatures and prolonged reaction time; however, it can be facilitated by high pressure (10 kbar). *O*-Alkyloximes derived from aromatic aldehydes are good substrates for the reaction, as com-

**Table 19. Reactions of MCP 497 with Active Methylene Compounds**

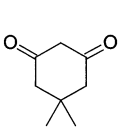
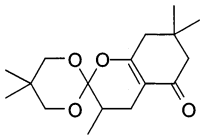
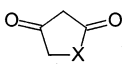
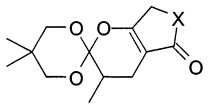
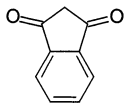
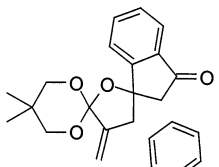
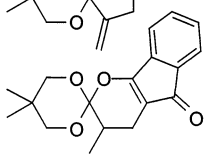
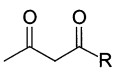
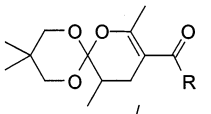
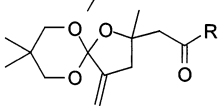
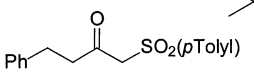
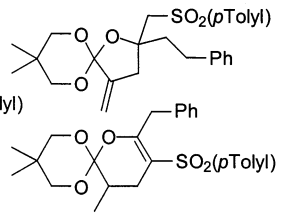
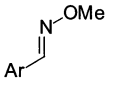
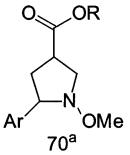
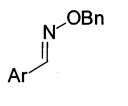
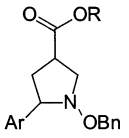
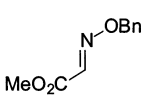
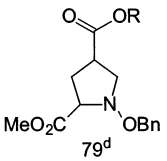
| Entry | Active methylene compound | Products | Yield % |
|---|---|---|---|
| 1 |  |  | 90 |
| 2 |  X = $CH_2$ |  | X = $CH_2$ 90 |
| 3 | X = O | | X = O 91 |
| 4 |  |   | 52 <10 |
| 5 |  R = Me |  | R = Me 65 R = OMe 52 |
| 6 | R = OMe |  | R = Me 10 R = OMe 17 |
| 7 |  |  | 44 10 |

**Table 20. Reactions of MCP 497 with O−Alkyl Oximes**

| Entry | Oxime | Pyrrolidine (% Yield) [R = $CH_2C(CH_3)_2CH_2OH$] |
|---|---|---|
| |  |  |
| 1 | Ar = $C_6H_5$ | 70[a] |
| 2 | Ar = *p*-$MeOC_6H_4$ | 70[b] |
| 3 | Ar = 2-Furyl | 90[c] |
| |  |  |
| 4 | Ar = *p*-$ClC_6H_4$ | 99[c] |
| 5 | Ar = 3-Pyridyl | 66[c] |
| 6 |  |  79[d] |

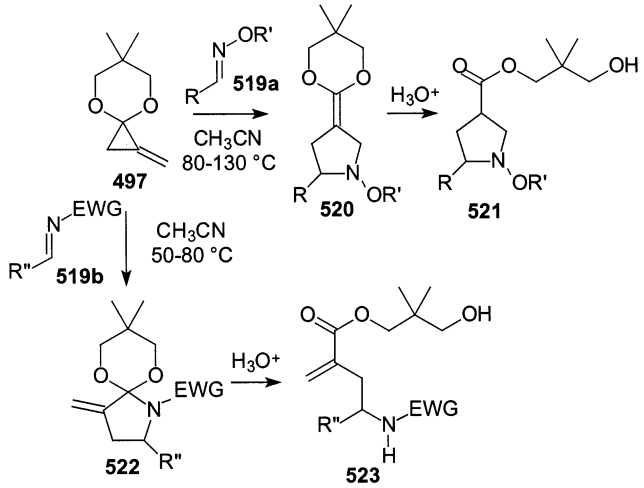
[a] At 120−130 °C. [b] In $CH_2Cl_2$ at 10 kbar pressure. [c] At 100 °C. [d] At 80 °C.

**Table 21. Reactions of MCP 497 with *N*-Tosylimines and *N*-Methoxycarbonylimines**

| Entry | Imine | Adduct (% Yield) |
|---|---|---|
| 1 | R = Ph | 92[a] |
| 2 | R = 2-Furyl | 89[a] |
| 3 | R = *t*Bu | 86[a] |
| 4 | | 85[a] |
| 5 | R = Ph | 77 |
| 6 | R = 2-Furyl | 78 |

[a] The yield refers to the corresponding open-chain γ-aminoester obtained after mild hydrolysis.

**Scheme 86**

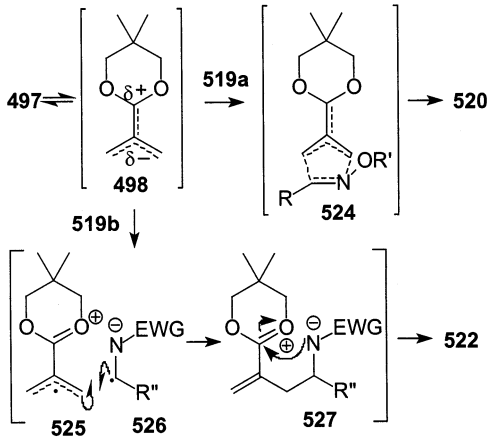



pared with aliphatic ones, which react only under high pressure and afford complex mixtures of products. A reaction rate depending on the electron deficiency of the C=N bond has been observed for *C*-aryloximes (Table 20): *p*-chlorobenzaldehyde oxime (entry 4) reacted at lower temperature than benzaldehyde oxime (entry 1), while the *p*-methoxy substituted gave addition only under high pressure (entry 2). The more electron-deficient glyoxylate oxime reacted fast at 80 °C, providing an efficient route to proline derivatives (entry 6).[133] *O*-Methyloximes and *O*-benzyloximes performed equally well. However, a strong dependence of reactivity on the configuration of the oxime has been reported: (*E*)-oximes are much more reactive than their *Z* isomers, with the latter being converted only partially and with low yields. In this respect, *O*-benzyloximes are to be preferred to *O*-methyloximes, as they are obtained from the corresponding aldehydes generally with a higher *E*/*Z* ratio (~9:1 vs 7:3). The pyrrolidine products are obtained as diastereomeric mixtures, with a cis/trans ratio of ~2:1.[133]

*N*-Tosyl and *N*-methoxycarbonylimines react much faster than *O*-alkyloximes, requiring lower temperatures and shorter reaction times (2−12 h). Tosylimines afford lactam acetal derivatives (Table 21) with complete regioselectivity and in excellent yield. The yields reported in entries 1−4 refer to the γ-aminoesters, since the primary cycloadducts are rather sensitive to acids and are more conveniently isolated as open-chain derivatives, from which the deprotected lactams can be regenerated on prolonged acid treatment.[134] Steric effects do not play an important role, since additions to imines derived from hindered aldehydes (entry 3) and even from ketones (entry 4) perform equally well. The major limitation rests in the failure of imines bearing hydrogens on the α-carbons to undergo cycloaddition; instead, deprotonation by the intermediate TMM **498** occurs. *N*-Methoxycarbonylimines are also able to participate in this cycloaddition (entries 5 and 6), but with a slightly lower regioselectivity and formation of small amounts (3−13%) of ketene acetal pyrrolidines, which account for the lower yield in the lactam derivative.[134]

The contrasting regiochemical outcome of the additions of **497** to oximes and imines has been attributed to different mechanisms followed (Scheme 87). *O*-Alkyloximes **519a** and intermediate **498** would

**Scheme 87**

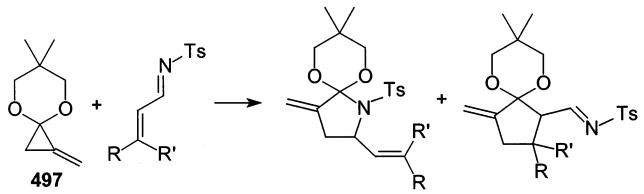



cycloadd in a concerted manner through TS **524**. The observed rate enhancement under high-pressure conditions and 67-fold rate difference for (*E*)- versus (*Z*)-oximes are in agreement with the highly ordered TS of a concerted cycloaddition.[133] Conversely, with the more electron-deficient C=N double bond of tosylimines **519b**, a SET mechanism from **498** would initially take place, generating the radical cation **525** and the radical anion **526**. From these intermediates a stepwise cycloaddition occurs, which accounts for the observed regioselectivity with formation of products **522**.[134]

The issue of chemoselectivity at a C=C or C=N double bond in the reaction of **497** with α,β-unsatur-

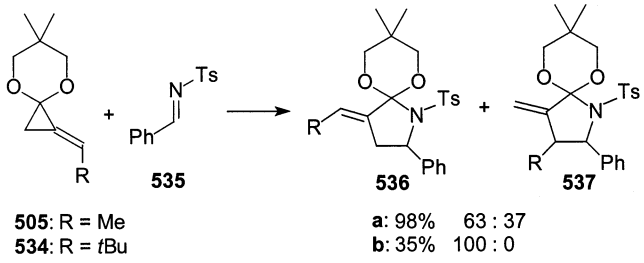
ated tosylimines **528** and **529** has also been addressed. The cycloaddition takes place predominantly at the C=N double bond, but formation of cyclopentanes **532** and **533** cannot be excluded even with sterically congested C=C double bonds as in **529** (Scheme 88).[134] However, the regioselectivity concerning MCP **497** is the same as in the addition to C=N and opposite to that usually observed in the addition to alkenes, suggesting that also for the minor product the single-electron pathway is followed.

**Scheme 88**



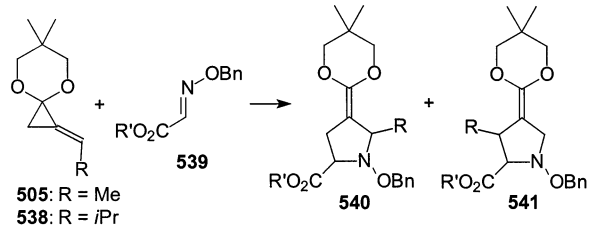

Cycloadditions to C=N double bonds of substituted ACPs **497** have also been studied. These reactions pose a further regiochemical issue originating from the nonequivalence of the terminal carbons of the TMM species. Thus, reaction of ACP **505** (90% *E*) with the tosylimine **535** derived from benzaldehyde gave the two regioisomers **536a** and **537a** in a 2:1 ratio (Scheme 89). The selectivity derives from initial formation of the new C−C bond at the less hindered position of an unsymmetric TMM radical cation related to **525**. Accordingly, ACP **534** (>98% *E*) gave exclusively the regioisomer **536b**. Compounds **536** are formed as single *E*-diastereoisomers.[134]

**Scheme 89**




Cycloadditions to *O*-alkyloximes are much more sensitive to substitution at the reacting TMM species. Oximes derived from aryl aldehydes are inert even toward ACP **505**. Only the more reactive oximes stemming from glyoxylic acid cycloadd to ACPs **505** and **538**, affording highly substituted proline derivatives (Table 22).[133] All the possible isomers, i.e., two regioisomers with each one as a mixture of two diastereoisomers, were obtained from the reaction of **505** with methyl ester **539**, with little regioselectivity and virtually no diastereoselectivity (Table 22, entry 1, cis/trans ratios evaluated after hydrolysis of the primary adducts). However, on increasing the bulkiness of the substituents, either of the intermediate TMM or the glyoxal derivative, both regio- and stereoselectivity increased as well. Best results in terms of selectivity were obtained by combining the most hindered ACP **538** and *tert*-butyl ester of **539**

**Table 22. Reactions of MCP 505 and 538 with *O*-Benzyl Oximes**

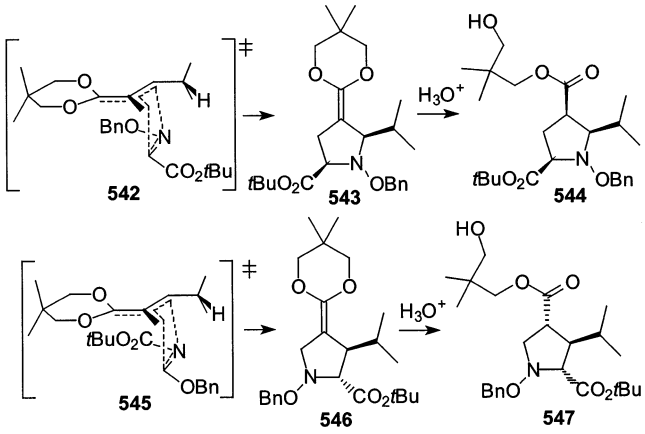



| entry | ACP | 539, R′ | yield (%) | 540:541 | *cis*/*trans*[a]-540 | *trans*/*cis*[a]-541 |
|---|---|---|---|---|---|---|
| 1 | **505** | Me | 81 | 70:30 | 68:32 | 49:51 |
| 2 | **505** | *t*Bu | 99 | 82:12 | 77:23 | 57:43 |
| 3 | **538** | Me | 81 | 78:22 | 71:29 | >96:4 |
| 4 | **538** | Ph | 41 | 77:23 | 52:48 | 61:39 |
| 5 | **538** | 2,6-$Me_2C_6H_3$ | 83 | 44:56 | 93:7 | >95:5 |
| 6 | **538** | 2,4,6-$tBu_3C_6H_2$ | 41 | 88:12 | 94:6 | >95:5 |
| 7 | **538** | $CHPh_2$ | 71 | 83:17 | >95:5 | 93:7 |
| 8 | **538** | *t*Bu | 89 | 90:10 | >97:3 | >96:4 |

[a] Evaluated after hydrolysis of the primary adducts to the corresponding esters.

(entry 8). These reagents afforded a 9:1 regioisomeric mixture of **543** and **546**, both as single diastereoisomers, but with opposite relative stereochemistry, cis for **543** and trans for **546** (Scheme 90). Again, the small solvent effects and the results observed confirm the concertedness of the reaction. Products **543** and **546** can be easily accommodated on the basis of cyclic TS **542** and **545**, respectively, with concurrent formation of the incipient bonds. When the R group of the ACP is bulky, the TS having substituents on the oxime pointing toward R are much higher in energy. Therefore, only TS like **542** and **545**, which account for the observed stereoselectivities, are available for the formation of regioisomers **543** and **546**, respectively, especially with bulky ester groups. Acidic hydrolysis of adducts **543** and **546** also occurred with high diastereoselectivity, affording pyrrolidine dicarboxylates **544** and **547** in a completely controlled manner, making the process extremely useful from a synthetic point of view (Scheme 90).[133]

**Scheme 90**

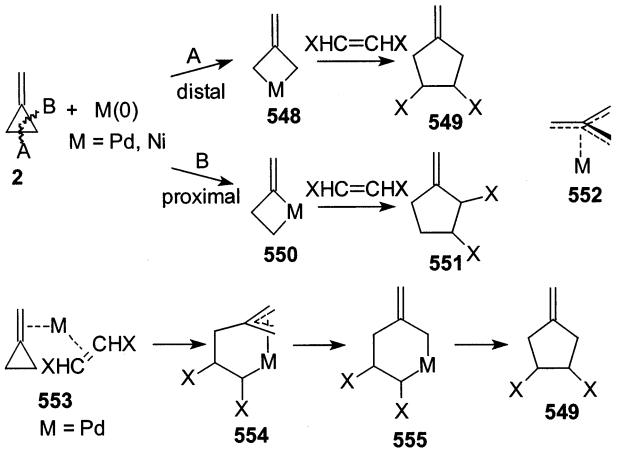



### 2. Metal-Induced Reactions

Due to the pioneering studies of Noyori and Binger, it has been known for long time that ACPs are able

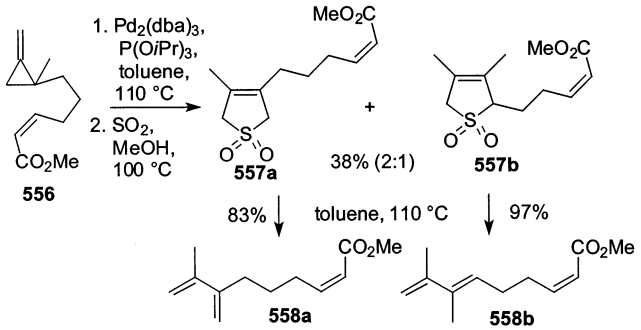
to participate in [3+2] cycloaddition reactions with alkenes under catalysis of $d^{10}$ metal species (Ni(0) or Pd(0)) to give alkylidenecyclopentanes.[135] The regiochemistry of the reaction depends on a number of factors, mainly on the nature of the metal and ligands, the presence and type of substituents on the ACP, and the nature of the alkene, and involves the cleavage of the distal (with respect to the C=C double bond) or the proximal cyclopropane C−C bond (Scheme 91, routes A and B, respectively). Generally,

**Scheme 91**




Pd catalysts favor distal cleavage, while Ni catalysts behave in a more subtle way and give predominantly proximal cleavage with MCP, but increasingly distal cleavage on added substitution on the cyclopropane. The two regiochemical options can be interpreted on the basis of formation of metallacyclobutane intermediates **548** and **550**, albeit $\eta^4$-TMM metal complexes **552** have been invoked in some occasions. However, the actual mechanism of the reaction seems to be more complex, and mechanistic studies and theoretical ab initio MO calculations[136] suggest that, at least with Pd catalysts, distal cleavage occurs from a complex **553** with both double bonds coordinated to the metal and gives a $\pi$-allyl−Pd complex **554**, which is transformed into a palladacyclohexane **555**, which eventually affords the final product **549** by reductive elimination. However, involvement of palladacyclobutane intermediates cannot be completely ruled out and they are often quoted, since they represent a practical tool for easier rationalization of the results. In any case, it is now generally accepted that, in contrast to the Pd-catalyzed [3+2] cycloadditions starting from silylmethylallyl acetates, developed by Trost,[137] where zwitterionic TMM−Pd complexes are generated,[138] $d^{10}$ metal-catalyzed [3+2] cycloaddition reactions of ACPs do not involve transition metal complexes of the TMM type. The different mechanisms account for the profound differences between the two methods in both reactivity and outcome of the reaction. However, independent of the mechanisms involved, both methods have been used profusely in organic synthesis in the last two decades and have emerged as really useful procedures for the construction of cyclopentane skeletons. Many excellent reviews on the subject are available.[4,124b,139] Much more limited are the examples in which these methods are used for synthesizing heterocycles: those employing ACPs are discussed below.

**Scheme 92**




The intramolecular variant of the metal-catalyzed [3+2] cycloaddition of ACPs with alkenes or alkynes, introduced by independent studies from Motherwell's and Nakamura's groups,[140] has also been studied extensively and constitutes a useful extension for the construction of homocyclic fused rings, i.e., pentalene and indane systems. During one of these studies, Motherwell and Binger found that MCP **556** is reluctant to cycloadd intramolecularly, affording a complex mixture of products, whose spectroscopical data were suggestive of a different metal-mediated reaction, namely, ring opening to its diene isomers. Indeed, treatment of the mixture with $SO_2$ gave the isomeric sulfolenes **557**, from which the precursor dienes **558** could be regenerated on heating (Scheme 92).[141]

The intramolecular [3+2] cycloaddition of ACPs might serve for the synthesis of bicyclic heterocycles simply by placement of a heteroatom in the chain connecting the two reactive moieties. By this strategy, Lautens has achieved a highly stereocontrolled synthesis of fused tetrahydrofurans **563** by linking MCP carbinols **560** with propargyl or allyl functions via the oxygen atom.[142] The starting MCP-substituted alcohols **560** have been synthesized by completely regioselective Sm-directed cyclopropanation of allenic alcohols **559**, which, in several cases, also displayed good to excellent levels of diastereoselectivity (Scheme 93).[143] Relative stereochemistry in MCPs **560** has

**Scheme 93**

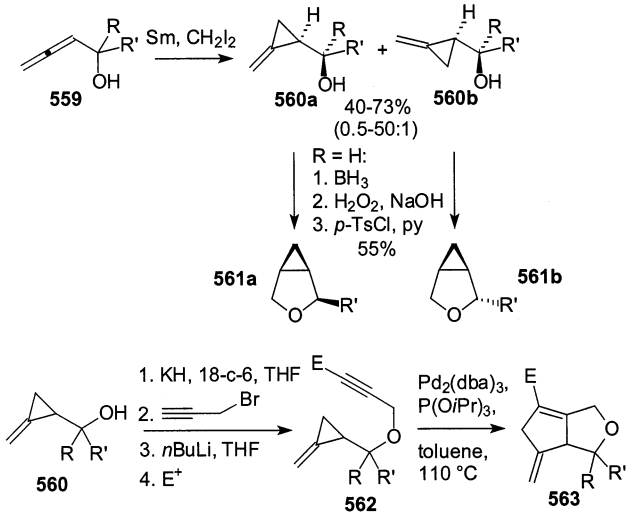
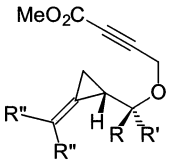
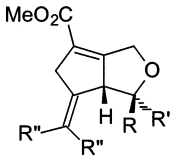
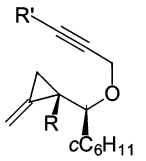
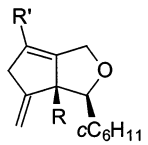
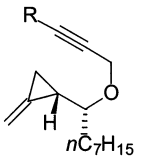
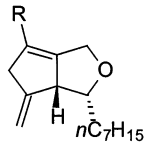


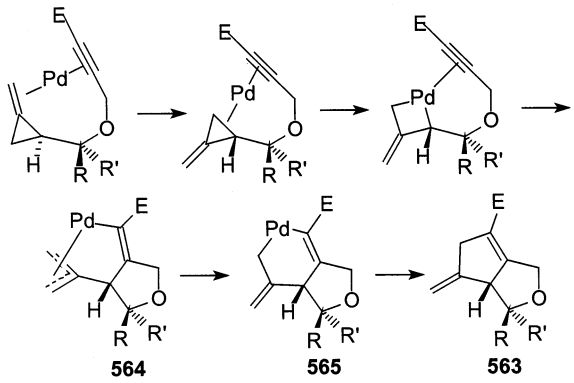
**Table 23. Palladium-Catalyzed [3+2] Intramolecular Cycloadditions of ACP Alkynes**

| Entry | ACP | Adduct (% Yield) |
|---|---|---|
| |  |  |
| 1 | R = *c*C$_6$H$_{11}$, R' = R" = H | 75 |
| 2 | R = R" = H, R' = *c*C$_6$H$_{11}$ | 72 |
| 3 | R = *n*C$_7$H$_{15}$, R' = R" = H | 71 |
| 4 | R = R" = H, R' = *n*C$_7$H$_{15}$ | 83 |
| 5 | R-R' = (CH$_2$)$_5$, R" = H | 68 |
| 6 | R = *c*C$_6$H$_{11}$, R' = H, R" = *n*Pr | 58 |
| |  |  |
| 7 | R = OMe, R' = CO$_2$Me | 75 |
| 8 | R = Me, R' = CO$_2$Me | 43 |
| 9 | R = H, R' = CH$_2$OH | 85 |
| 10 | R = H, R' = CH$_2$OTBDMS | 100 |
| 11 | R = H, R' = COMe | 92 |
| 12 | R = H, R' = TMS | 46 |
| |  |  |
| 13 | R = TBDMS | 40 |
| 14 | R = SiMe$_2$Ph | 40 |

been ascertained by their two-step conversion into cyclopropane-fused tetrahydrofurans **561**, which represents a practical entry to these peculiar bicyclic systems from MCPs, albeit not a direct one.[142b] The [3+2] intramolecular cycloaddition of the ACP moiety to C−C triple bond catalyzed by palladium complexes [Pd$_2$(dba)$_3$/P(O*i*Pr)$_3$ or Pd(PPh$_3$)$_4$] was successful within a broad range of substituents. It occurred in a highly stereoselective manner to afford, with complete retention of configuration at the stereogenic cyclopropyl carbon atom, compounds of type **563**, which can serve for further synthetic elaborations (Table 23).[142c] The relative stereochemistry of the adducts has been proven unequivocally by an X-ray crystal structural analysis of the product obtained from entry 9, which was identical to that from entry 1 after reduction with DIBAL-H.

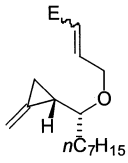
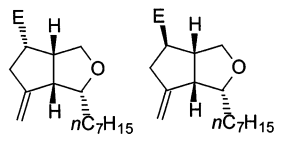
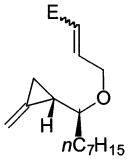
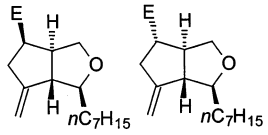
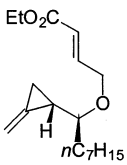
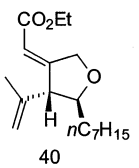
The proposed mechanistic sequence shown in Scheme 94 accounts for the observed retention of stereochemistry, since both insertion and carbopalladation steps occur with retention. Moreover, this mechanism is in agreement with the higher reactivity of electron-deficient alkynes, which supports initial coordination of the C≡C bond, and with deuterium-labeling experiments, which showed the equivalence of the two terminal allyl carbon atoms, advocating the formation of a $\pi$-allyl−Pd complex **564**, a rapidly equilibrating methylenepalladacyclohexene **565**, or both.[142c]

**Scheme 94**




Analogous intramolecular cycloadditions to electron-deficient alkenes occurred in refluxing toluene but required higher amounts of Pd catalysts and longer reaction times. With C=C double bonds, two new stereogenic centers are formed in the cycloaddition and high stereocontrol was achieved at the bridgehead carbon atom, which depends on the relative stereochemistry of the preexisting stereocenters; i.e., different diastereoisomers exhibit complementary facial selectivity in the addition to the alkene (Table 24, cf. entries 1−6 vs 7−11).[142d] This behavior is

**Table 24. Palladium-Catalyzed [3+2] Intramolecular Cycloadditions of MCP Alkenes**[a]

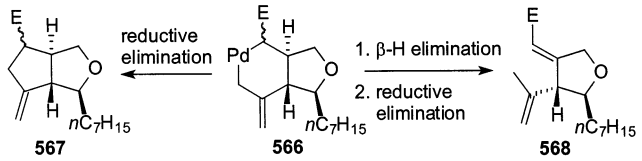
| Entry | MCP (Alkene Configuration) | Catalyst | Products [% Yield (ratio)] |
|---|---|---|---|
| |  | |  |
| 1 | E = CO$_2$Et (*E*) | A | 78 (100:0) |
| 2 | E = CO$_2$Et (*E*) | B | 53 (100:0) |
| 3 | E = CO$_2$Et (*Z*) | A | 75 (100:0) |
| 4 | E = COMe (*E*) | A | 81 (100:0) |
| 5 | E = SO$_2$Ph (*E*) | A | 60 (0:100) |
| 6 | E = CN (*Z*/*E* 1:2) | A | 92 (50:50) |
| |  | |  |
| 7 | E = CO$_2$Et (*E*) | A | 87 (50:50) |
| 8 | E = CO$_2$Et (*E*) | B | 95 (65:35) |
| 9 | E = CO$_2$Et (*Z*) | A | 83 (50:50) |
| 10 | E = SO$_2$Ph (*E*) | A | 86 (80:20) |
| 11 | E = CN (*Z*/*E* 1:4) | A | 91 (40:60) |
| 12 |  | C |  40 |

[a] Catalysts: (A) Pd(PPh$_3$)$_4$ (10−20%). (B) Pd$_2$(dba)$_3$/P(O*i*Pr)$_3$ (30%), 4-Å MS. (C) Pd$_2$(dba)$_3$/P(OiPr)$_3$ (37%).

independent of the stereochemistry at the double bond (entries 1−3 and 7−9). The level of stereocontrol exerted on the carbon atom bearing the electron-

withdrawing group is highly dependent on the type of diastereoisomeric MCP. The anti diastereoisomers, with the exception of MCP in entry 6, gave a single product, but with opposite stereochemistry in the case of the sulfone in entry 5 with respect to ester and ketone (entries 1−4). Conversely, the syn diastereoisomers always gave mixtures of products with low, if any, selectivity (entries 7−11). The most notable feature of this process is the high-yield formation of unusual trans-fused [3.3.0]bicyclic systems in entries 7−11. Albeit the observed selectivities cannot be rationalized easily, the formation of trans-fused products has been related likely to trans-fused methylenepalladacyclohexane intermediate precursors **566** (Scheme 95). However, the TS for the

**Scheme 95**



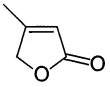
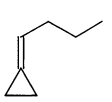
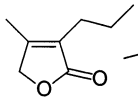
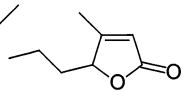
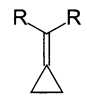
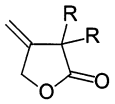
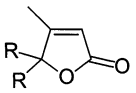

reductive elimination to methylenecyclopentane **567** is expected to be of high energy and competition with $\beta$-hydride elimination becomes viable (Scheme 95). This happened in the reaction of the ester catalyzed by $Pd_2(dba)_3$, which afforded diene **568** (entry 12). Generally, for the formation of the bicyclic adducts, $Pd(PPh_3)_4$ was found to be the most satisfying catalyst.[142d]

While the metal-catalyzed [3+2] cycloaddition to C−C unsaturated bonds has been thoroughly studied and applied in synthesis, general procedures for the corresponding additions to unsaturated carbon−heteroatom moieties, which would afford heterocycles in the newly formed ring, have been disclosed only very recently (see below), in contrast to the cycloaddition using TMM generated according to Trost's method, where additions to C=O[144] and C=N[145] double bonds had been carried out much earlier. The only exception were the additions to heterocumulenes, i.e., to the C=O bond of $CO_2$ and the C=N bond of keteneimines.

The Pd-catalyzed additions of ACPs to $CO_2$ (40 atm) in benzene at 130 °C were first studied by Inoue (Table 25, entries 2−5, 8, and 9).[146] The best catalytic systems were found to be $Pd(dba)_2/PPh_3$ and Pd(diphos)$_2$, which gave opposite regioselectivity in the resulting $\gamma$-lactone products (Table 25, entries 4, 5, 8, and 9). Later studies by Binger on other ACP substrates, including MCP, demonstrated that the process is affected by side reactions, namely. co-oligomerization due to subsequent additions of other ACP units to the butenolides,[147] which account for the low yields. Although it was possible to obtain the $\gamma$-butenolide from MCP (entry 1) in good yields, after extensive optimization studies, in DMF at 165 °C under 40 bar of $CO_2$ and with the use of the ($\eta^3$-allyl)-($\eta^5$-cyclopentadienyl)Pd/$PPh_3$ catalyst,[147] the shortcomings connected with this method prevent its application to substituted derivatives.

Binger also observed that MCP and its substituted derivatives **569** undergo Pd [$Pd(PPh_3)_4$ 0.7−3.5%] or

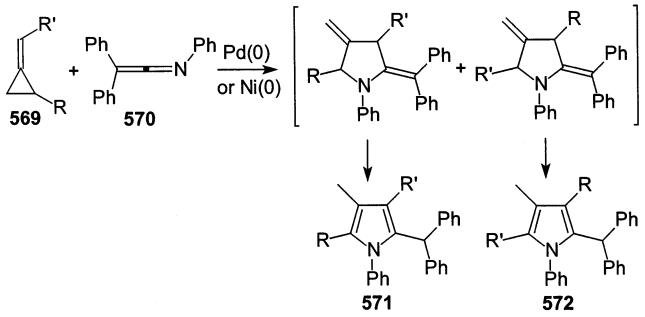
**Table 25. Palladium-Catalyzed [3+2] Additions of ACPs with $CO_2$[a]**

| Entry | ACP | Catalyst | Products (% Yield) | |
|---|---|---|---|---|
| 1 |  | A |  80 | |
| |  | |  |  |
| 2 | | B | 38 | 29 |
| 3 | | C | 14 | 12 |
| |  | |  |  |
| 4 | R = Me | D | 31-69 | 0-8 |
| 5 | R = Me | C | trace | 48 |
| 6 | R = Me | A | 13 | 18 |
| 7 | R = Ph | A | 0 | 18 |
| 8 | R-R = $(CH_2)_5$ | D | 32 | trace |
| 9 | R-R = $(CH_2)_5$ | C | 5 | 21 |

[a] Catalysts: (A) ($\pi$-allyl)(Cp)Pd/$PPh_3$. (B) $Pd(PPh_3)_4$. (C) Pd(diphos)$_2$. (D) $Pd(dba)_2/PPh_3$.

Ni [$Ni(cod)_2$ 1−5%/$P(OPh)_3$] catalyzed addition to the C=N double bond of triphenylketeneimine **570** where the C=C bond is not affected (Scheme 96 and Table

**Scheme 96**




26).[148] The addition affords pyrroles **571** and **572** or pyrrolines derived from isomerization of the primary *exo*-methylene adducts in good yields. However, the process appears to be limited to this type of ketene imine, since addition of MCP to diphenylketene-*N*-methylimine gave a cyclopentenone imine derived from the cycloaddition to the C=C double bond.[148]

It is only thanks to recent efforts from Yamamoto's group[139g] that a more general access to methylenetetrahydrofuran and methylenepyrrolidine derivatives has become available by metal-catalyzed [3+2] cycloadditions of ACPs to aldehydes[149] and imines,[150] respectively. The reaction of ACPs with aromatic aldehydes is completely regioselective, affording moderate to good yields of methylenetetrahydrofurans when carried out at 120 °C for 5−32 h in the absence of solvent and with $Pd(PPh_3)_4$ (2%) and $Bu_3PO$ (4%) as catalysts (Table 27).[149] With THF the reaction is less efficient, and different palladium catalysts and ligands are also ineffective or less satisfying. With unsymmetrically substituted ACPs, the addition

**Table 26. Palladium-Catalyzed [3+2] Additions of ACPs with Keteneimine 570**

| Entry | ACP | Products (% Yield) | |
|---|---|---|---|
| 1 | R = R' = H | 96 | |
| 2 | R = Me, R' = H | 44 | 31 |
| 3 | R = H, R' = Me | 46 | 31 |
| 4 | R = Me | 93 | |
| 5 | R-R = $(CH_2)_5$ | 91-94 | |

**Table 27. Palladium-Catalyzed [3+2] Additions of ACPs with Aldehydes**

| Entry | ACP | Aldehyde | Product (% Yield) |
|---|---|---|---|
| 1 | R = R' = *n*Bu | Ar = 2-Furyl | 75 |
| 2 | R = R' = *n*Bu | Ar = (5-Me)-2-Furyl | 65 |
| 3 | R = R' = *n*Bu | Ar = 3-Furyl | 51 |
| 4 | R = R' = *n*Bu | Ar = 2-Thienyl | 64 |
| 5 | R = R' = *n*Bu | Ar = (3,4-$OCH_2O$)$C_6H_3$ | 43 |
| 6 | R = R' = *n*Bu | Ar = *p*-$MeOC_6H_4$ | 38 |
| 7 | R = R' = *n*Hex | Ar = 2-Furyl | 71 |
| 8 | R-R = $(CH_2)_5$ | Ar = (5-Me)-2-Furyl | 77 |
| 9 | R = $CH_2CH_2Ph$, R' = Me | Ar = 2-Furyl | 86 |
| 10 | R = $CH_2CH_2Ph$, R' = H | Ar = 2-Furyl | 42 |

showed almost no diastereoselectivity (~1.15:1, Table 27, entries 9 and 10). As to the scope of the reaction, an MCP substituted at the cyclopropyl ring was reported to give no cycloaddition at all. Benzaldehydes bearing electron-donating substituents (entries 5 and 6) gave less satisfactory results than the heteroaromatic ones. No information was given about the behavior of structurally different aldehydes.

*N*-Tosylimines were found to give [3+2] cycloaddition reactions with ACPs at 120 °C in toluene after 9−24 h under catalysis of $Pd(PPh_3)_4$ (5%) and $Ph_3PO$ (10%) and afforded, also with high regiochemical control, methylenepyrrolidines in good to excellent yields (Table 28).[150] The reaction is strongly affected by the nature of catalyst, ligands, and solvent. THF, DMF, dioxane, and acetonitrile gave moderate yields of adducts, while addition did not occur at all in $CH_2Cl_2$. $Pd(dba)_2/PPh_3$ was less efficient, while $Pd_2(dba)_3{\cdot}CHCl_3$ and $Pd(PPh_3)_2Cl_2$ were ineffective. Other ligands [$PPh_3$, $Bu_3PO$, P(*o*-tolyl)$_3$] performed well, but bidentate ligands inhibited the addition. Cycloaddition to nonsymmetric substrates (entry 9) was unselective (1.3:1). The reaction showed a similar efficiency with aromatic aldehyde-derived tosylimines substituted with both electron-donating and electron-withdrawing groups (Table 28, entries 3−6). Interestingly, the imine from pivalaldehyde

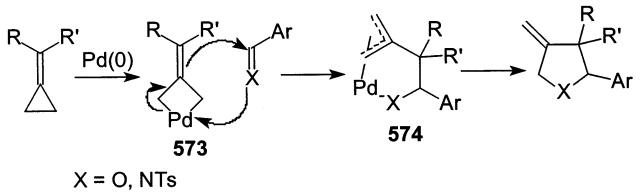
**Table 28. Palladium-Catalyzed [3+2] Additions of ACPs with *N*-Tosylimines**

| Entry | ACP | *N*-Tosylimine | Product (% Yield) |
|---|---|---|---|
| 1 | R = R' = *n*Bu | Ar = 2-Furyl | 89 |
| 2 | R = R' = *n*Bu | Ar = 2-Thienyl | 91 |
| 3 | R = R' = *n*Bu | Ar = (3,4-$OCH_2O$)$C_6H_3$ | 93 |
| 4 | R = R' = *n*Bu | Ar = *p*-$MeC_6H_4$ | 91 |
| 5 | R = R' = *n*Bu | Ar = *p*-$MeOC_6H_4$ | 94 |
| 6 | R = R' = *n*Bu | Ar = *p*-$F_3CC_6H_4$ | 88 |
| 7 | R = R' = *n*Hex | Ar = 2-Furyl | 88 |
| 8 | R-R = $(CH_2)_5$ | Ar = 2-Furyl | 91 |
| 9 | R = $CH_2CH_2Ph$, R' = Me | Ar = 2-Furyl | 71 |
| 10 | | | 57 |

was also able to give the addition, albeit affording the adduct in lower yields after 3 days, but showed opposite regiochemical preference in the formation of the alkylidenepyrrolidine (Table 28, entry 10).[150]

The results of the palladium-catalyzed cycloaddition to aldehydes and tosylimines have been rationalized according to a common mechanistic sequence analogous to that reported in Scheme 94, initiated with formation of a palladacyclobutane **573** by cleavage of the distal cyclopropane C−C bond (Scheme 97).

**Scheme 97**

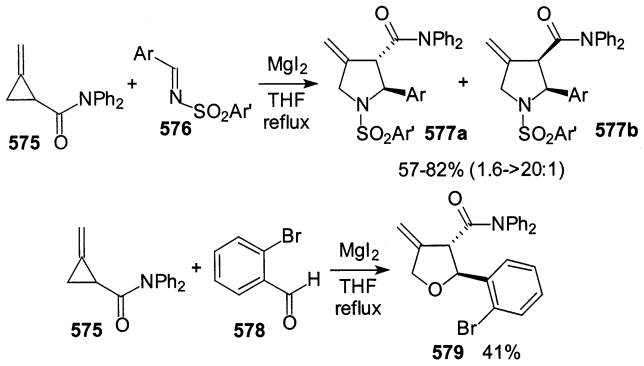



This intermediate, a $\sigma$-allyl-type Pd complex, would then instigate a nucleophilic attack with allylic inversion at the C=X bond to afford the $\pi$-allyl intermediate **574**, which eventually leads to the final heterocyclic product.[149,150] The inversion of regiochemistry observed in the addition to the pivalaldehyde-derived imine might originate from excessive steric hindrance which would steer the addition to occur via a preferred attack from the α- rather than the $\gamma$-carbon atom of intermediate **573**.[150]

Lautens has recently described a Mg-mediated approach to similar *N*-sulfonyl methylenepyrrolidines utilizing a different concept.[151] The work was inspired from previous results from Carreira,[152] who demonstrated that cyclopropanecarboxylic acid derivatives behave as homo-Michael acceptors,[153] affording pyrrolidines in the presence of aldimines. Treatment of diphenylamide **575** with aromatic *N*-sulfonylaldimines **576** and a stoichiometric amount of $MgI_2$ brought the formation of methylenepyrrolidines **577**

in good yields and a diastereoselectivity from poor to excellent in favor of the trans isomer (Scheme 98

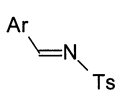
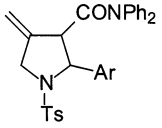
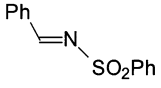
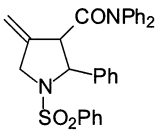
**Scheme 98**




and Table 29).[151] The reaction worked efficiently with both electron-deficient and electron-rich arylimines (Table 29, entries 1−8). Concerning the stereoselectivity, the presence of any substituent at the ortho position of the aryl substituent proved to furnish the trans isomer exclusively (Table 29, entries 5−8). It was found that stoichiometric $MgI_2$ was not strictly necessary: the reaction occurred also with 10−30 mol % of the salt without any loss in yields. 2-Bromobenzaldehyde (**578**) was also able to participate in the reaction, affording the methylenetetrahydrofuran **579** in 41% yield (Scheme 98). However, the reactions with aromatic aldehydes are less general and give more complex mixtures of products. No reaction occurred with aliphatic aldehydes or aliphatic sulfonylaldimines. Although the products **577** and **579** derive formally from a [3+2] cycloaddition, the reaction is actually a novel domino cyclization via a bifunctional vinylogous enolate intermediate generated in situ from the monoactivated MCP **575** by means of $MgI_2$ and follows a ring-opening − enolate addition−ring-closing pathway (see below).

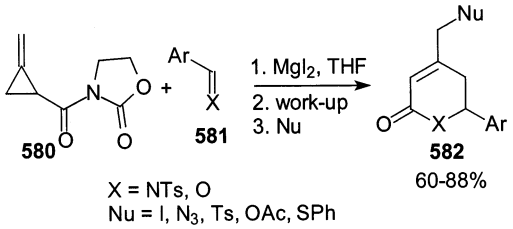
The nature of the methylenecyclopropanecarboxylic acid derivative proved to be extremely critical for both

**Table 29. $MgI_2$-Mediated Reactions of Diphenylamide 575 with *N*-Sulfonylimines**

| Entry | *N*-Sulfonylimine | Product [% Yield (*trans*:*cis* ratio)] |
|---|---|---|
| |  |  |
| 1 | Ar = *p*-$F_3CC_6H_4$ | 65 (1.6:1) |
| 2 | Ar = *p*-$O_2NC_6H_4$ | 57 (2.2:1) |
| 3 | Ar = *p*-$BrC_6H_4$ | 85 (2.3:1) |
| 4 | Ar = *p*-$MeOC_6H_4$ | 78 (5.3:1) |
| 5 | Ar = *o*-$F_3CC_6H_4$ | 81 (>20:1) |
| 6 | Ar = *o*-$BrC_6H_4$ | 71 (>20:1) |
| 7 | Ar = 2,4-$Cl_2C_6H_3$ | 78 (>20:1) |
| 8 | Ar = 2,4-$Me_2C_6H_3$ | 82 (>20:1) |
| 9 |  |  81 (4.1:1) |

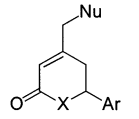
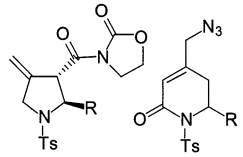
aspects of reactivity and outcome of the reaction. Indeed, the corresponding ethyl ester was unreactive toward either imines or aldehydes, while the phenylamide and diethylamide derivatives, in contrast to their diphenylamide analogue, gave complex mixtures of products with both substrates. Replacement of the diphenylamide group for a more electron-withdrawing oxazolidinone in imide **580** with the aim of increasing reactivity and employing milder reaction conditions not only was successful but resulted, unexpectedly, in steering the reaction toward the formation of completely different six-membered heterocyclic products **582** (Scheme 99 and Table 30).[151]

**Scheme 99**




The imide **580** reacted very quickly with *N*-tosyl-4-bromobenzaldimine and a stoichiometric amount of $MgI_2$ in refluxing THF affording a $\delta$-lactam bearing an allylic iodo substituent and lacking the oxazolidinone group as the exclusive product (Table 30, entry 1). Since the resulting iodides were unstable to chromatography on silica, the products of the reactions were usually isolated after displacement of the iodide with nucleophiles (Table 30, entries 2−15). The reaction was already successful at room temperature but required 1 equiv of $MgI_2$. The scope of the reaction is very broad: aryl aldimines (Table 30,

**Table 30. $MgI_2$ Mediated Reactions of Imide 580 with *N*-Tosylimines and Carbonyl Derivatives[a]**

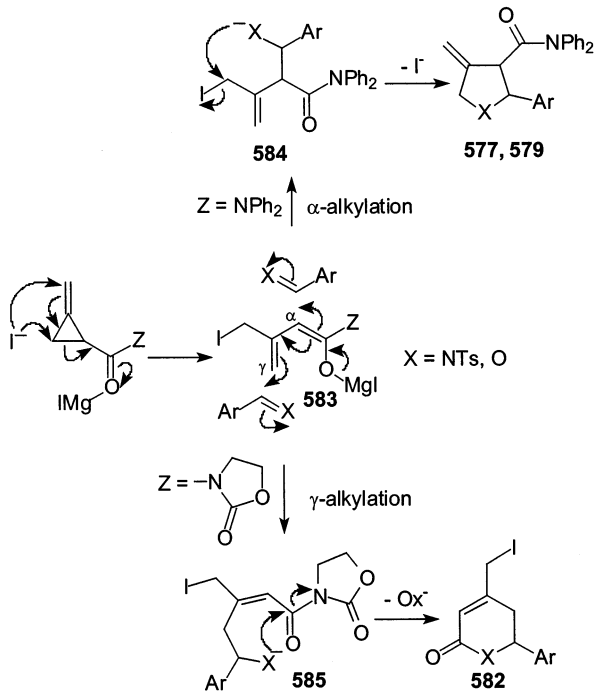
| Entry | Imine or Aldehyde | Method, Nu | Products (% Yield) |
|---|---|---|---|
| |  | |  |
| 1 | X = NTs, Ar = *p*-$BrC_6H_4$ | A, I | 60 |
| 2 | X = NTs, Ar = *p*-$BrC_6H_4$ | B, $N_3$ | 78 |
| 3 | X = NTs, Ar = $C_6H_5$ | B, $N_3$ | 81 |
| 4 | X = NTs, Ar = *o*-$F_3CC_6H_4$ | A, Ts | 75 |
| 5 | X = NTs, Ar = 2,4-$Me_2C_6H_3$ | B, OAc | 72 |
| 6 | X = O, Ar = $C_6H_5$ | B, $N_3$ | 88 |
| 7 | X = O, Ar = *o*-$BrC_6H_4$ | B, SPh | 67 |
| 8 | X = O, Ar = *p*-$O_2NC_6H_4$ | A, OAc | 71 |
| 9 | X = O, Ar = (3,4-$OCH_2O$)$C_6H_3$ | B, Ts | 65 |
| 10 | X = O, Ar = 2,4-$Cl_2C_6H_3$ | A, $N_3$ | 74 |
| |  | |  |
| 11 | R = *n*Pr | B, $N_3$ | 72 (6.2:1) 11 |
| 12 | R = *n*Pr | C, $N_3$ | 66 (4.5:1) 8 |
| 13 | R = *n*Pr | D, $N_3$ | 0 23 |
| 14 | R = *c*Hex | B, $N_3$ | 31 (>20:1) 34 |
| 15 | R = *c*Hex | D, $N_3$ | 0 40 |

[a] Methods: (A) reflux, 1 h. (B) 0 °C to room temperature, 3 h. (C) $MgI_2$ (30 mol %), rt, 7 h. (D) reflux, 10 min.

entries 1−5), aromatic aldehydes (Table 30, entries 6−10), and even alkyl aldimines (Table 30, entries 11−15) are good substrates for the reaction. In the latter case, the reaction gave mixtures of methylenepyrrolidines and lactams and the bulky imine from pivalaldehyde did not react. Aliphatic aldehydes were also unreactive. The outcome of the reactions with aliphatic *N*-tosylimines was strongly affected by the temperature. At room temperature, formation of methylenepyrrolidines was favored: as in the case of amide **575**, a preference for the trans diastereoisomers has been observed (Table 30, entries 11, 12, and 14). On the other hand, no pyrrolidine was found when the reaction was performed in refluxing THF: the α,β-unsaturated δ-lactams were obtained in modest yields as major products under these conditions (Table 30, entries 13 and 15), apart from byproducts.[151]

The divergent results of these additions to MCPs **575** and **580** have been interpreted on the basis of a common-type magnesium dienolate intermediate **583** which is formed initially by $MgI_2$-induced cyclopropane ring opening (Scheme 100).[151] A nucleophilic

**Scheme 100**



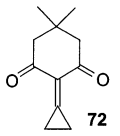
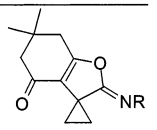
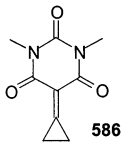
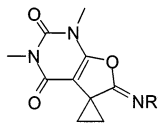
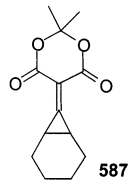
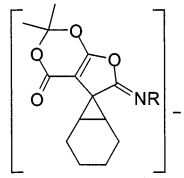
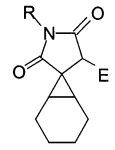

attack of **583** to the C=N or C=O double bond then occurs with complete and opposite regioselectivity: the dienolate derived from diphenylamide **575** alkylates through the α-carbon atom to give intermediate **584**, that from oxazolidinone **580** through the γ-carbon to produce intermediate **585** (Scheme 100). Intermediate **584** eventually leads to the methylenepyrrolidines **577** by a 5-exo-tet cyclization and displacement of iodide. In principle, two options are possible for the further reaction of intermediate **585** due to the properties of oxazolidinone as a good leaving group, i.e., a 6-exo-trig cyclization with displacement of the oxazolidinone or a 5-exo-tet cyclization with displacement of iodide and formation of five-membered heterocycles. According to the experimental results, the former one must be highly favored since δ-lactams (or lactones) **582** are obtained exclusively. An alternative hetero Diels−Alder process of magnesium dienolate **583** with imines or aldehydes would also account for formation of the products and cannot be excluded completely.

## IV. Heterocycles from [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 **72**, **586**, and **587** can be trapped in situ by isocyanides **588** to give [4+1] cycloadducts under mild reaction conditions to afford 3-spirocyclopropane furans or pyrroles (Table 31).[154] The primary cycload-

**Table 31. Cycloaddition of Isocyanides 588 with 2-Cyclopropylidene-1,3-cycloalkanediones 72, 586, and 587**

| Entry | ACP | Isocyanide | | Product (% yield) |
|---|---|---|---|---|
| 1 |  **72** | C≡N−R | |  |
| 2 | | **588a** | | **589a** (70) |
| 3 | | **588b** | | **589b** (64) |
| | | **588c** | | **589c** (73) |
| 4 |  **586** | **588a** | |  |
| 5 | | **588b** | | **590a** (54) |
| | | | | **590b** (43) |
| 6 |  **587** | **588a** |  **591a** |  **592a** (54) |
| 7 | | **588d** | **591d** | **592d** (64) |

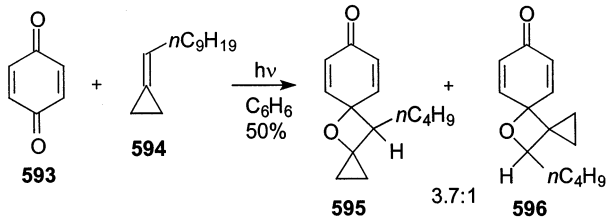
**a:** R = Ph; **b:** R = $CH_2Ts$; **c:** R = *t*Bu; **d:** R = 4-$MeOC_6H_4$; E = $CO_2Me$

dition products **591a** and **591d** rearranged, upon addition of methanol, to the stable pyrrolidindiones **592a** and **592d**, which were isolated as a single stereoisomer (entries 6 and 7). The expected adducts **589** and **590** from **72** and **586,** respectively, were obtained in moderate to good yields (Table 31, entries 1−5).

## V. Heterocycles from [2+2] Cycloadditions

A single example of [2+2] addition of an alkylidenecyclopropane to a C=O double bond has been reported. The Paternò−Büchi reaction of 1,4-benzoquinone **593** with **594** proceeded with moderate regioselectivity by irradiation of a degassed solution of reagents. Oxetanes **595** and **596** were obtained in a 3.7:1 ratio and in 50% yield (Scheme 101).[155]

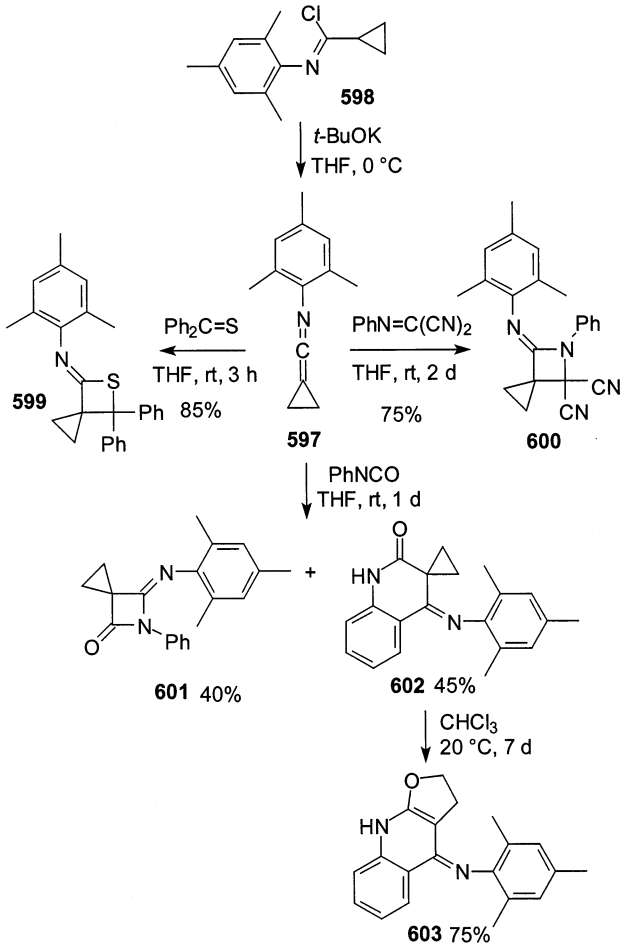
**Scheme 101**




4-Spirocyclopropane $\beta$-lactam derivatives have been obtained by reaction of alkylidenecyclopropanes and CSI (**476**) but only in small amounts (see section III.G.1, Scheme 74).

Ketene imine **597**, generated by treatment of cyclopropylformimidoyl chloride **598** with potassium *tert*-butoxide, was trapped in situ with suitable reactants to afford spiro-fused four-membered heterocycles. In particular, thiobenzophenone and *N*-(dicyanomethylene)aniline added in a [2+2] fashion to the C=C double bond of **597** to give the corresponding spiro derivatives **599** and **600**, respectively (Scheme 102).[156] In addition, **597** reacted with phenyl

**Scheme 102**




isocyanate to give a mixture of the [2+2] and [4+2] adducts **601** and **602**, respectively. After several days, a solution of the 3-spirocyclopropane quinolinone **602** in $CHCl_3$ converted into the furo[2,3-*b*]quinoline **603** (Scheme 102).

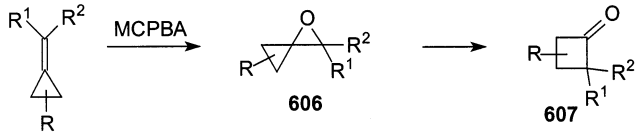
PTAD (**59**) reacted slowly with 2,3-*trans*-dimethylmethylenecyclopropane (**604**) affording the [2+2] adduct **605** (Scheme 103).[28,123b]

**Scheme 103**


## VI. Heterocycles from [2+1] Cycloadditions

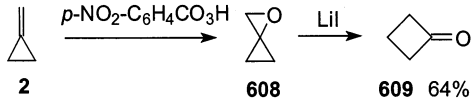
Epoxidation of alkylidenecyclopropanes to afford oxaspiropentanes **606** is a reaction that has been studied by several authors. The epoxidation has been performed with peracetic,[157] peroxybenzimidic,[158] *m*-chloroperbenzoic (MCPBA),[159] and *p*-nitroperbenzoic acids.[160] The synthetic utility of this procedures lies in the easy acid-catalyzed rearrangement of oxaspiropentanes to cyclobutanones **607** (Scheme 104).

**Scheme 104**



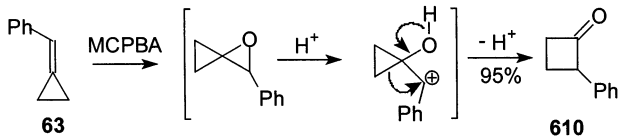

For example, cyclobutanone (**609**) was obtained in good yield by the treatment of oxaspiropentane (**608**) with LiI (Scheme 105).[160]

**Scheme 105**




This acid-catalyzed rearrangement can be very fast and hamper the isolation of the oxaspiropentane. The rearrangement was proposed to proceed through the formation of an α-oxycyclopropylcarbinyl cation, which undergoes a pinacolic rearrangement to generate a cyclobutanone. The presence of a cyclopropyl substituent, and potentially of another stabilizing substituent, such as the phenyl group in **63**, enhances its formation. Treatment of benzylidenecyclopropane (**63**) with an excess of MCPBA afforded only the cyclobutanone **610** in almost quantitative yield (Scheme 106).[160c] The same reactivity was shown by

**Scheme 106**

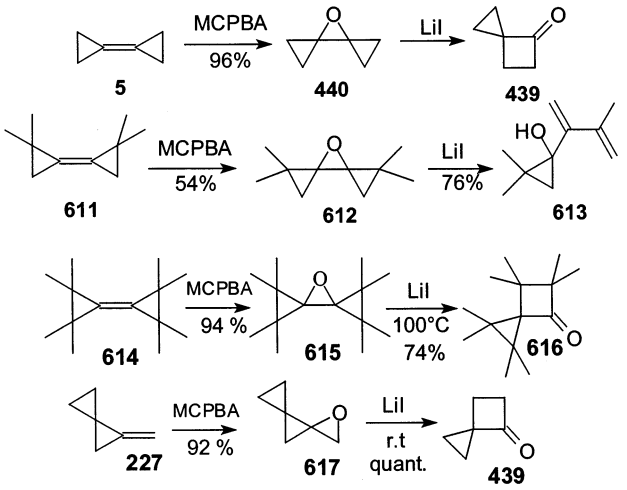



cyclohexylidenecyclopropane. The rates of epoxidation of methylenecyclopropanes are remarkably lower than those of their methylenecycloalkane homologues, their reactivity being correlated to the $\pi$-orbital energy.[159a]

Again bicyclopropylidene (**5**) revealed itself as a unique reagent, since it readily reacted with MCPBA in the presence of sodium carbonate at 0 °C to afford

the corresponding epoxide **440**, which was found to be fairly stable, reacting at 75 °C with LiI to give the expected spiro[2.3]hexan-4-one (**439**).[161] Also, tetramethyl-substituted bicyclopropylidene **611** afforded a stable epoxide, which, however, rearranged to dienol **613** probably for steric reasons (Scheme 107).[159a] Permethylbicyclopropylidene (**614**) was oxi-

**Scheme 107**

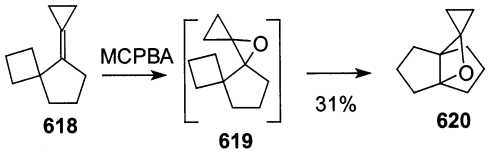



dized with MCPBA to the corresponding epoxide **615**, which was revealed as remarkably stable since it isomerized to **616** only by heating at 100 °C with LiI. Conversely, epoxide **617** isomerized at room temperature to afford quantitatively **439**.[162]

As a general rule, oxaspiropentanes that evolve to a secondary carbocation are more stable than fully substituted oxaspiropentanes that generate a more stable tertiary carbocation.[158a]

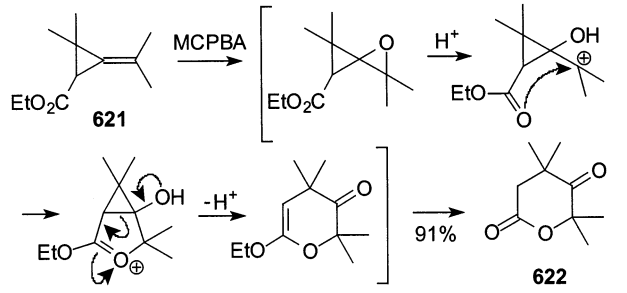
Such a rule can account for the unexpected result of the epoxidation of alkene **618**, which upon treatment with MCPBA afforded the oxetane **620** as the main product (Scheme 108).[163]

**Scheme 108**




The presence of other substituents can drive the rearrangement along different pathways. ACP **621**, upon oxidation with MCPBA, afforded the ketolactone **622**, after trapping of the cationic center by the ester functionality (Scheme 109).[160c]

**Scheme 109**

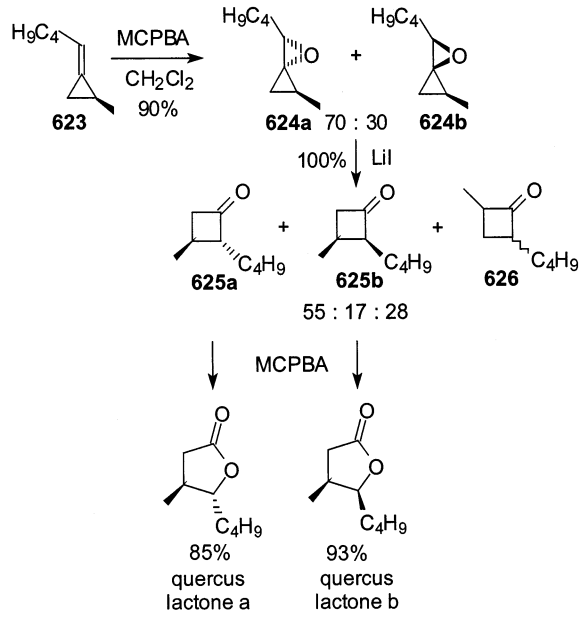



The treatment of allylidenecyclopropanes with MCPBA afforded exclusively substituted cyclobutanones.[164]

Generally, the use of buffered solutions ($NaHCO_3$,[165] $Na_2HPO_4$[166]) can suppress the rearrangement.[167] Dimethyldioxirane, which circumvents the presence of acids, is a convenient reagent for the synthesis of oxaspiropentanes.[168]

Several oxaspiropentane derivatives have been synthesized using this methodology[169] and have found application in the synthesis of natural products and analogues, often without isolation of the intermediate.[170] Examples of a diastereoselective epoxidation of an enantiopure ACP[171] have been reported. Salaün used the epoxidation of ACP **623** to obtain epoxides **624**, which were transformed into the corresponding cyclobutanones **625**, intermediates in the synthesis of naturally occurring quercus lactones (Scheme 110).[172]

**Scheme 110**

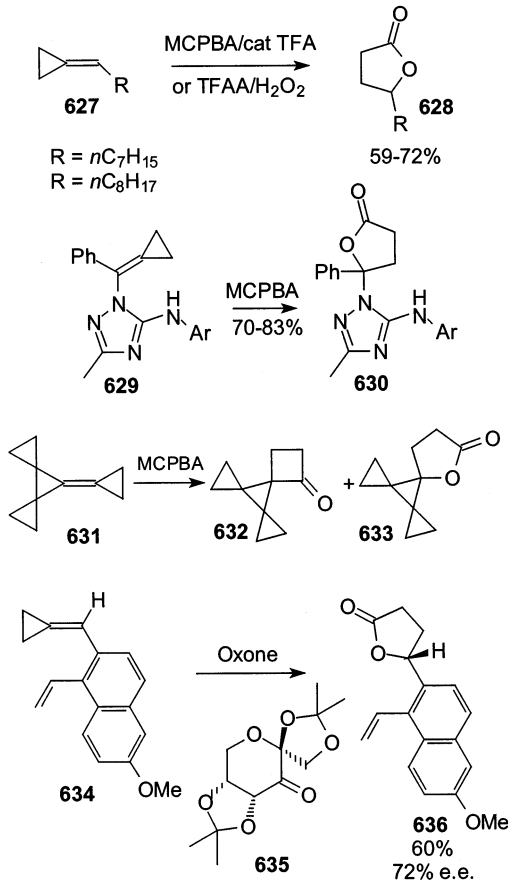



Since MCPBA is the oxidant for both oxidation steps, its use in large excess led to a cascade reaction that converted directly ACPs **627**, **629**, **and 631** to $\gamma$-butyrolactones **628**, **630**, and **633** via cyclobutanone formation and Baeyer−Villiger oxidation (Scheme 111).[162,173] The same transformation can be achieved with the use of in situ-generated trifluoroperacetic acid.[173b] The enantioselective version of such a process was developed using Shi's catalyst **635** (Scheme 111).[174] Chiral nonracemic lactones **628** were also synthesized from ACPS **627** by a stepwise procedure employing a Sharpless asymmetric AD followed by ring enlargment with preservation of the stereochemical information.[173b,175]

Examples of enantioselective epoxidation of alkylidenecyclopropanes using the Jacobsen catalyst[170b] or via the Katsuki−Sharpless reaction,[170d,e] although without isolation of the oxaspiropentanes, have been reported.

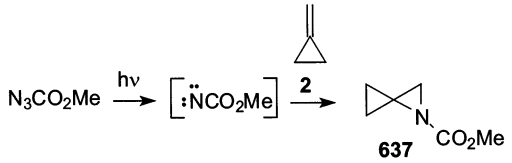
A few [2+1] additions of heteroatoms other than oxygen to MCP derivatives have been reported. Azaspiropentane **637** was prepared in 35% yield

**Scheme 111**




through a concerted addition of the singlet nitrene generated by photolysis of methyl azidoformate to the exocyclic bond of MCP (**2**) (Scheme 112).[60b]

**Scheme 112**

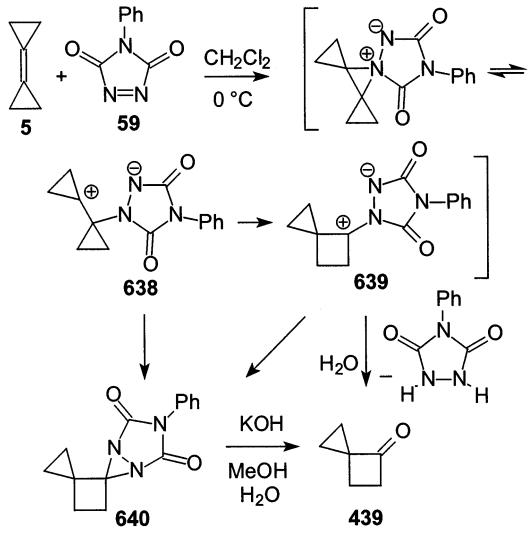



The addition of a nitrogen of PTAD (**59**) to BCP (**5**) gave an aziridinium cation adduct, which is only postulated as an intermediate in the formation of the final reaction products **640** and **439** (Scheme 113).[11] When the reaction is carried out in $CH_2Cl_2$, the only product formed in 83% yield was **640**, which is believed to derive from the dipolar intermediate **638**. Alkaline hydrolysis of **640** gave the spirohexanone **439**. This product is the only one formed (76% yield) when the reaction is carried out in wet acetone (Scheme 113).

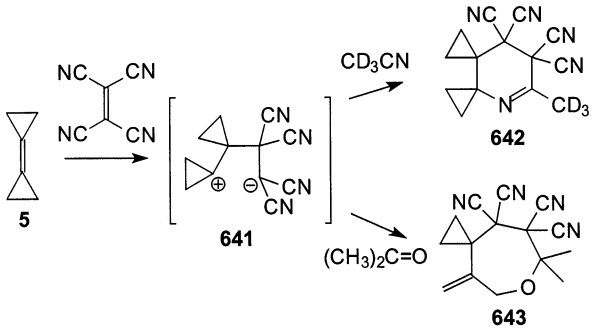
The intermediacy of the zwitterion **641**, an analogue of **638**, was evidenced also in the reaction of BCP (**5**) with tetracyanoethylene (TCNE) (Scheme 114).[118] The reaction afforded two different heterocyclic derivatives **642** and **643** depending on the type of solvent employed.

A reported example of a [2+1] cycloaddition to methylenecyclopropanes involving phosphorus consists of the addition of iminophosphanes **644** to **2** and **119**. The reaction was carried out at room tempera-

**Scheme 113**

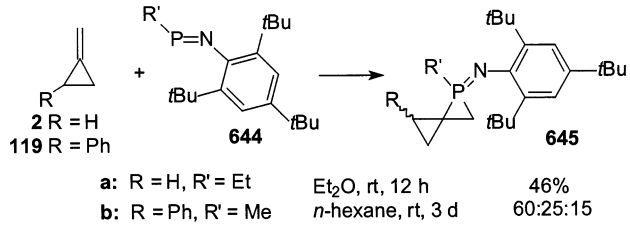



**Scheme 114**




ture and gave readily iminophosphaspiro[2.2]pentanes **645** in moderate yields (Scheme 115).[176] The major

**Scheme 115**



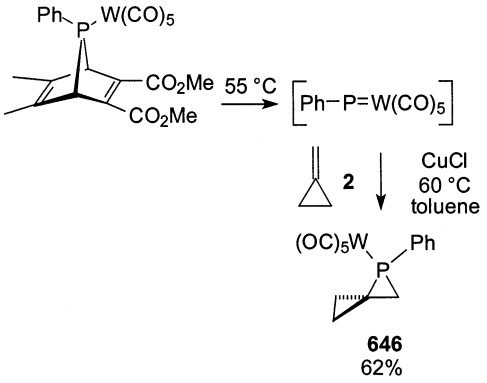

diastereoisomer of **645b** selectively crystallized (38% yield) from the reaction mixture and its structure, confirmed by an X-ray analysis,[176] proved that it derived from the attack of phosphorus on the opposite side of the phenyl substituent.

Finally, MCP (**2**) reacted with the phosphinidene complex $PhPW(CO)_5$ to give (1-phenyl-1-phosphaspiro-[2.2]pentane)pentacarbonyltungsten (**646**) in 62% yield (Scheme 116).[177] The molecular structure of **646** was determined by single-crystal X-ray analysis.

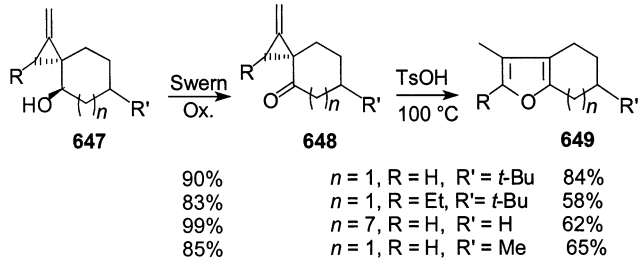
## *VII. Heterocycles from Thermal Rearrangements of Alkylidenecyclopropanes*

MCP derivatives **648**, substituted with a carbonyl group, rearrange upon heating and under acid catalysis to afford fused 3-methylfurans **649** (Scheme 117).[178]

**Scheme 116**

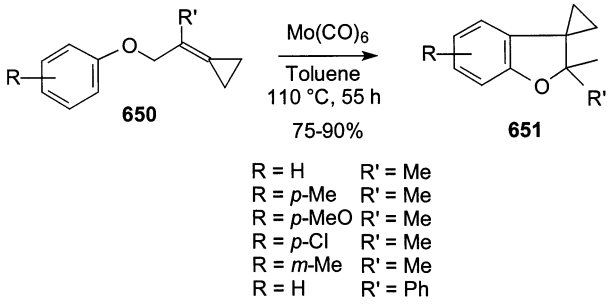



**Scheme 117**




A new example of Claisen rearrangement followed by a cyclization reaction has been reported with cyclopropylidenephenoxy derivatives **650** that, upon heating with a catalytic amount of $Mo(CO)_6$, afforded dihydrobenzofurans **651** (Scheme 118).[179]

**Scheme 118**

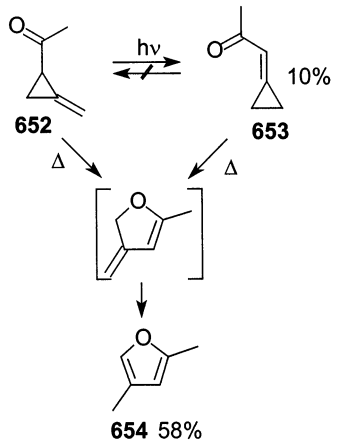



The photochemical and thermal rearrangements of 2-acetylmethylenecyclopropane **652** were studied. While irradiation of **652** caused only the irreversible, low-yielding, isomerization to ketone **653**, heating of **652** or **653** afforded 2,4-dimethylfuran **654** (Scheme 119).[180] These results can be rationalized both with a concerted mechanism following orbital symmetry conservation rules and with a diradical mechanism.

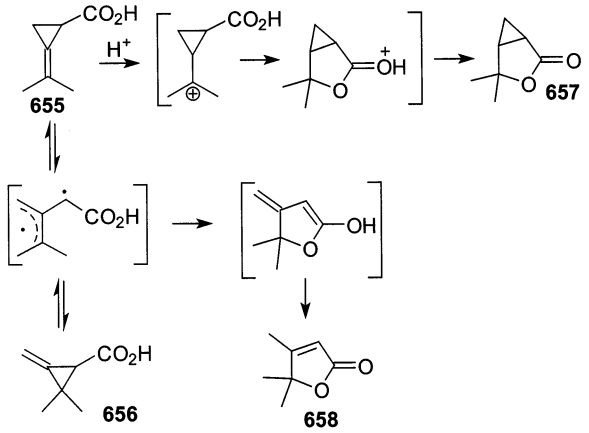
Also dimethyl-substituted methylenecyclopropanecarboxylic acids **655** and **656** undergo thermal rearrangements to afford lactones **657** and **658**. Pyrolysis of both acids gave mixtures of lactones in different ratios depending on the starting material.[181] Acid **655** afforded lactones **657** and **658** in 7:1 ratio while **656** afforded **657** and **658** together with **655** in a 1:7:2 ratio, respectively (Scheme 120).

Cyclopropane-fused lactones **660**, analogues to **657,** but bearing a bromo atom on the bridged carbon, were obtained by treatment of methylenecyclopropanecarboxylic acids **659** with $Br_2$ (Scheme 121).[182]

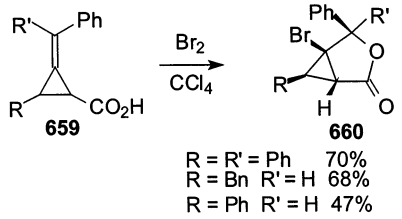
**Scheme 119**




**Scheme 120**

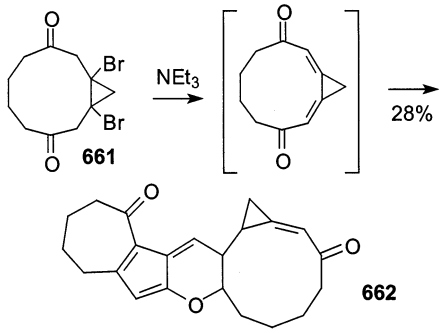



**Scheme 121**




A pentacyclic fused ring system was obtained starting from the bicyclic dibromoundecanone **661** that, upon treatment with triethylamine, afforded the polycyclic compound **662** (Scheme 122).[183]

**Scheme 122**



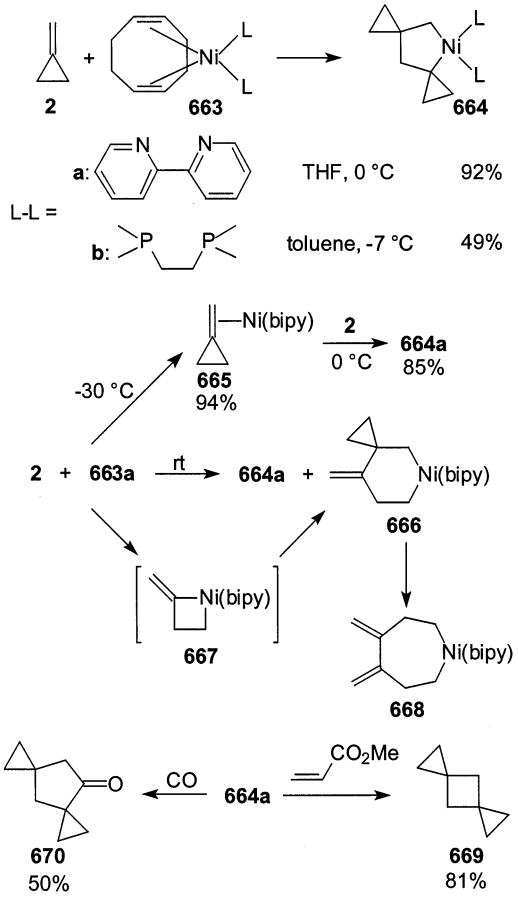

## *VIII. Heterocycles from Metal-Mediated Reactions*

Metallacycles of different sizes have been postulated as reactive intermediates during the course of

both the palladium- and nickel-catalyzed [3+2] TMM-type cycloaddition of MCPs (methylenemetallacyclobutanes and cyclohexanes)[135,139] and the nickel-catalyzed [2+2] cyclodimerization and cyclocodimerization reactions (nickelacyclopentanes).[4] Several metallacycles of the proposed types have been isolated as stable compounds by reacting MCP or its derivatives with stoichiometric amounts of model nickel complexes or different metal complexes.

Nickelacyclopentanes **664** have been prepared from MCP (**2**) by Binger by use of chelating ligands that are able to stabilize the nickelacycle intermediates (Scheme 123).[184] These are crystalline compounds

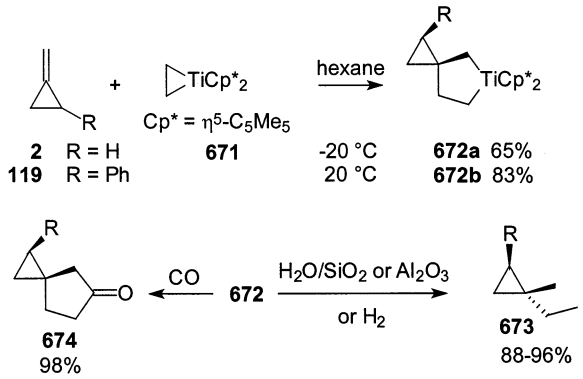
**Scheme 123**




stable in the solid state under argon. However, the products obtained are strongly dependent upon the reaction conditions. At low temperature, only the alkene complex **665**, corresponding to $\eta^2$-MCP complexes postulated as the primary intermediates in [3+2] metal-catalyzed reactions, was isolated in high yields. This olefin complex gave the nickelacyclopentane **664a** when treated at 0 °C in the presence of MCP. At room temperature, MCP reacted with the bipyridyl complex **663a** to give a mixture of the same nickelacyclopentane **664a** and a methylenenickelacyclohexane **666**, besides traces of two regioisomers of **666**.[184a] Since **664a** is slowly converted at room temperature into a regioisomer of **666** rather than into **666**, this compound is believed to originate from the unstable methylenenickelacyclobutane **667**. After longer reaction times, **666** undergoes a methylcyclopropyl−homoallyl rearrangement to **668**. From these stable nickelacycles, the catalytic cycles involved in MCP transformations can be envisioned. For example, reductive elimination of Ni from complex **664a** in the presence of a large excess of methyl acrylate gave in high yield spirooctane **669**, the product of the nickel-catalyzed cyclodimerization. With CO, **664a** furnished the bis(spirocyclopropane)cyclopentanone **670**.

Early transition metals are well known to promote the oxidative coupling of unsaturated C−C bonds. Thus, metallacyclopentane derivatives are obtained from two molecules of alkenes.[185] These metallacycles are usually unstable, not isolable species, which may decompose through two main alternative pathways: a $\beta$-hydrogen elimination followed by reductive elimination to give an alkene or a $\beta$-carbon−carbon fission which leads ultimately to the starting alkenes. Thus, an equilibrium is established between the alkene components plus the metal species and the metallacycle: this equilibrium may lie on the side of the metallacycle in the case of alkenes with large energy content, which may release part of their strain energy. Takaya took advantage of this concept in order to synthesize stable titanacyclopentanes from MCP (Scheme 124).[186] MCPs **2** and **119** reacted with

**Scheme 124**

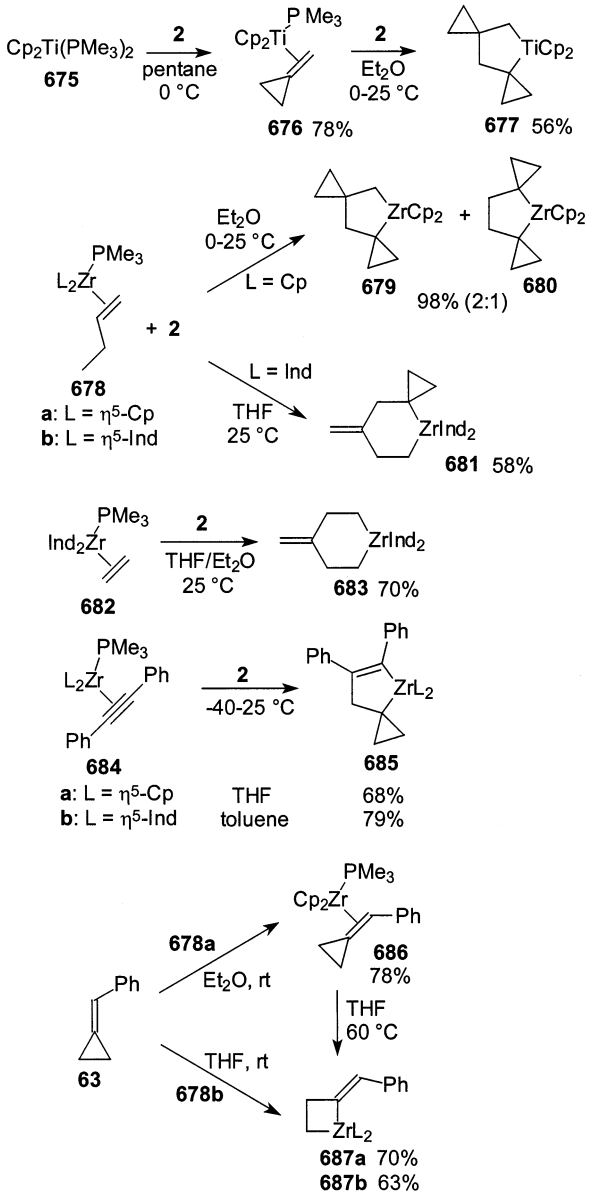



**671** to give the titanacyclopentanes **672** in good yields, while 2,2-diphenylmethylenecyclopropane was unreactive under the same conditions and isomerized to an open-chain diene at elevated temperatures. Compounds **672** have considerable stability, undergoing thermal decomposition only under forcing conditions: at 200 °C, they rearranged to isomeric dienes and alkenes. Highly efficient and stereocontrolled syntheses of substituted cyclopropanes **673** and spiro-fused bicycloheptanones **674** via titanacyclopentanes **672** have been performed (Scheme 124).[186]

Binger has now extended this study by reacting different complexes of Ti and Zr with MCP (**2**) and benzylidenecyclopropane (**63**).[187] Reaction of 1 equiv of MCP (**2**) with Ti complex **675** gave the $\eta^2$-alkene complex **676**, which with excess MCP was converted into titanacyclopentane **677**. On the other hand, the reactions of **675** with 2,2-diphenylmethylenecyclopropane (**469**) and benzylidenecyclopropane (**63**) stopped at the stage of the alkene complex. The course of the reactions of excess MCP with analogous Zr complexes **678** is highly dependent on the type of ligands available for the metal. Complex **678a** be-

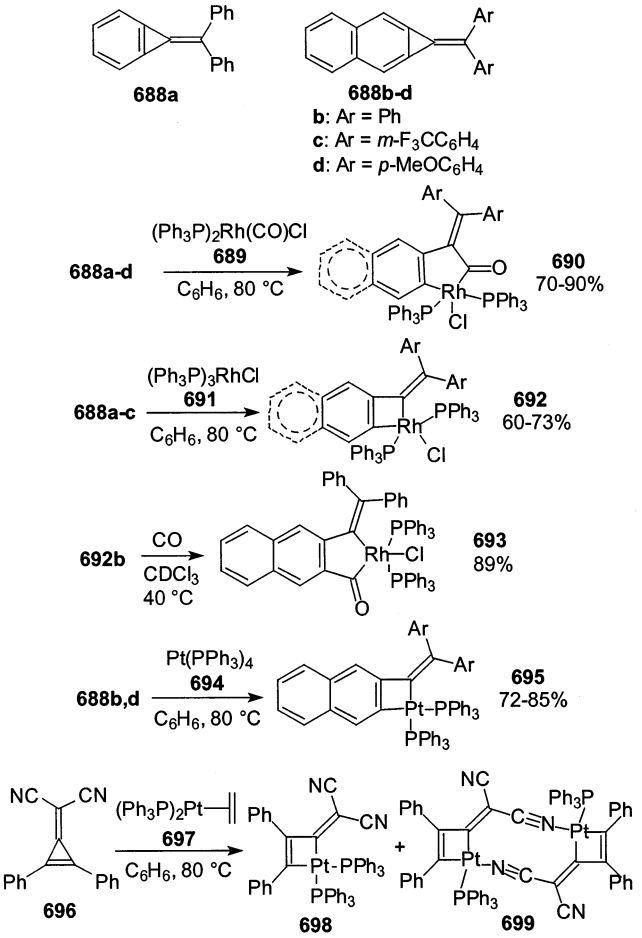
haved analogously to the Ti complex **675**, albeit regioselectivity was lost, affording a mixture of zirconacyclopentanes **679** and **680**, while the indenyl complex **678b** gave directly the methylenezirconacyclohexane **681**. Since conversion of **679** into the analogue of **681** was ruled out, **681** should arise from an intermediate where proximal C−C bond cleavage of MCP had occurred. No alkene complex was isolated in any case in these reactions. Similar divergent behavior has been observed in the co-cyclodimerization of MCP with alkene and alkyne complexes **682** and **684**: the latter gave spiro-cyclized zirconacyclopentenes **685** and the former the methylenezirconacyclohexane **683**. The zirconium complexes **678** were also able to react with benzylidenecyclopropane (**63**), affording in this case benzylidenezirconacyclobutanes **687**, which derive from cleavage of the proximal C−C bond of **63** (Scheme 125).[187]

**Scheme 125**




Alkylidenecycloproparenes gave a similar cyclopropane ring cleavage with formation of rhodium(I) or platinum(0) methylenemetallacyclobutanes, which may undergo subsequent insertion reactions (Scheme 126).[188]

**Scheme 126**

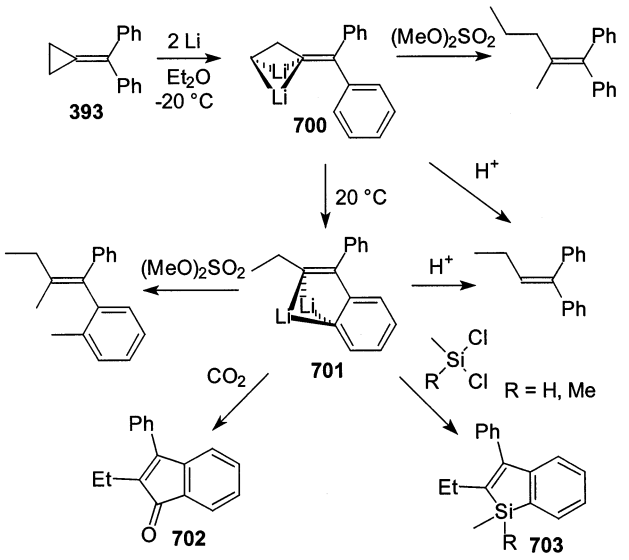



For example, compounds **688** reacted with the rhodium−carbonyl complex **689** to give the rhodaindanones **690**, derived from cyclopropane ring opening and CO insertion, in high yield (70−90%). With Wilkinson's catalyst (**691**), the reaction stopped at the stage of rhodacyclobutarenes **692**. Interestingly, **692b** reacted with CO at 40 °C to furnish exclusively the cyclic acylrhodium **693**, regioisomer of **690b**, derived from CO insertion with cleavage of the weaker C−Rh bond. At higher temperatures (70 °C), a 5:1 mixture of **693** and **690b** was obtained. Analogous reactions of **688b,d** were observed with $Pt(PPh_3)_4$ (**694**), which afforded alkylideneplatinacyclobutarenes **695**. All the above metallacycles were isolated as air-stable solids.[188a] A similar behavior had been recorded previously in the reaction of dicyanomethylenecyclopropene **696** with the Pt−olefin complex **697**, which gave the dicyanomethyleneplatinacyclobutene **698** and the dimeric compound **699** (Scheme 126).[189]

Bond cleavage of the proximal C−C cyclopropane bond of MCP and some of its derivatives has also been observed when these were treated with lithium powder, where a 1,3-dilithio intermediate was formed.[190] With diphenylmethylenecyclopropane (**393**) and other benzylidenecyclopropanes, the 1,3-dilithio intermediate **700**, initially formed at −20 °C, underwent at room temperature an uncommon 1,6-proton

shift to give a more stable dilithio intermediate **701** (Scheme 127).[191] On the basis of spectroscopic experi-

**Scheme 127**

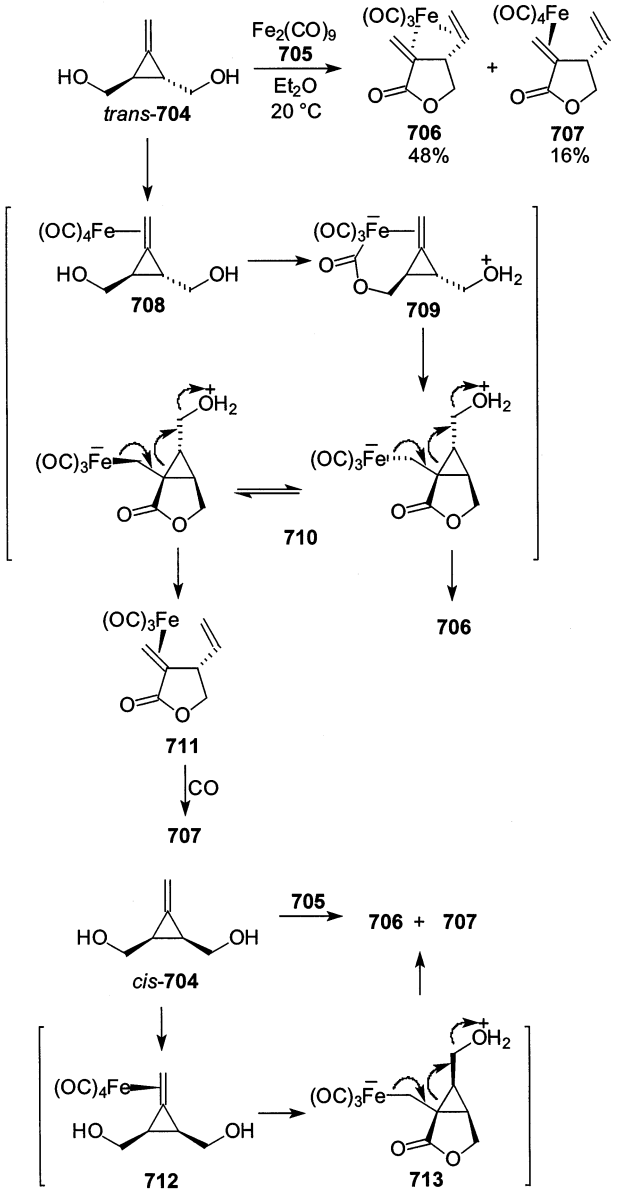



ments, these dilithio species are presumed to exist as doubly bridged compounds. The higher stability of **701** is then ascribed to a preference for 1,4-dilithio bridges versus 1,3-dilithio bridges in **700**, in addition to the preference for an $sp^2$ C−Li species rather than for an $sp^3$ C−Li species. The proposed structures for **700** and **701** are in agreement with the products of their hydrolysis and methylation reactions with dimethyl sulfate. Furthermore, intermediate **701** gave indanone **702** with $CO_2$ and the benzo-fused silacycles **703** when reacted with dichlorosilanes.[191]

Formation of more usual oxa and aza heterocycles has been observed during metal-promoted stoichiometric or catalytic reactions of ACPs; however, apart from the already discussed [3+2] cycloadditions of intermediates of the TMM type, these reactions have mostly remained at the stage of sporadic examples rather than of a diligent study in order to establish useful preparative methods.

As already stated, the first step in most metal-catalyzed processes involving ACPs, including [3+2] cycloaddition reactions, is considered to be a $\pi$-coordination of the C=C double bond to the metal to give $\eta^2$-alkene−metal intermediates analogous to **665** (Scheme 123).[4] Accordingly, numerous $\eta^2$-alkylidenecyclopropane−metal complexes have been prepared and isolated by treatment of MCPs with metal derivatives of Fe(0), Ni(0), Pd(0), and other metals.[192] While the complexes of Ni are able to participate in formal cycloaddition reactions,[184a] as shown in Scheme 123, those of Fe are usually either too stable to easily undergo further transformations[192a,b] or take different pathways, such as rearrangements with ring opening to Fe−diene[192d] or to Fe−TMM[192d,193] complexes. With MCP substrates suitably substituted to undergo intramolecular reaction with the complexed metal, other possibilities arise, as in the case of bis(hydroxymethyl)methylenecyclopropanes **704**, which gave the two vinylmethylenebutyrolactone−iron complexes **706** and **707** by treatment with diiron nonacarbonyl (**705**) (Scheme 128).[194] The same nonconju-

**Scheme 128**

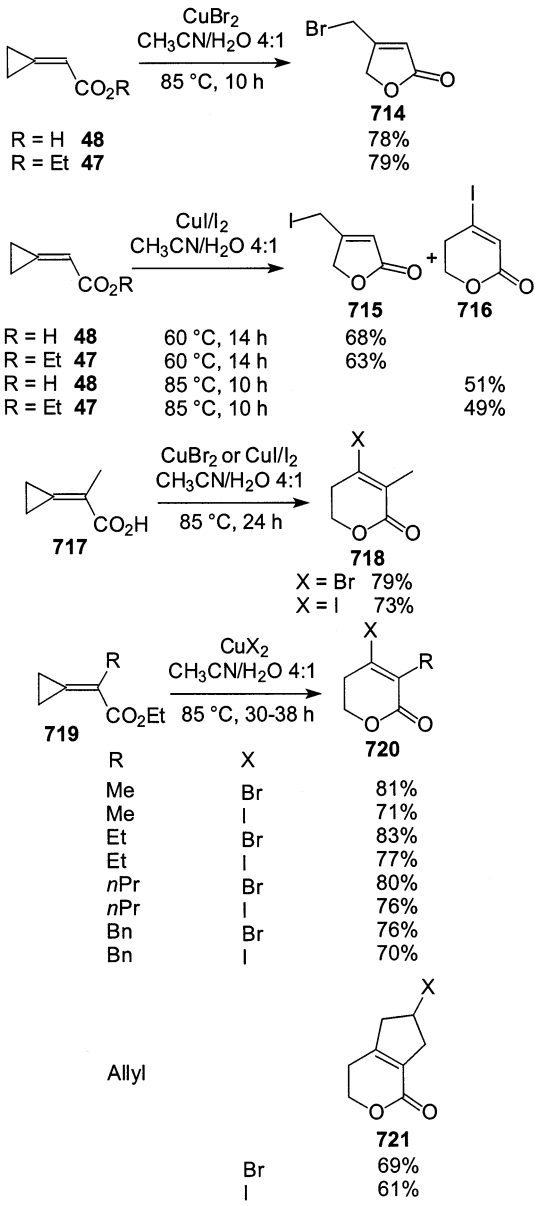



gated 1,4-diene and monoalkene complexes **706** and **707**, respectively, which isomerized to more stable conjugated 1,3-dienetricarbonyliron complexes by heating in $Et_2O$,[195] were obtained from both the trans and cis isomers of **704**. The reaction has been proposed to occur via preliminary coordination of the starting MCP *trans*-**704** to give complex **708**, which undergoes intramolecular insertion of CO and C=C double bond to afford the alkyl−iron species **710**. This intermediate evolves through cyclopropane ring opening and elimination of water. The face of the alkene coordinated by iron depends on which conformation of **710** the elimination occurs, that, in turn, determines the formation of the final products **706** and, after addition of CO, **707** (Scheme 128). According to the proposed mechanism, the yield of **707** increased under CO atmosphere. This mechanism is also able to explain the formation of optically active products starting from nonracemic *trans*-**704**, since one of the stereogenic carbons is not affected during all the course of the reaction and the formation of

the same products **706** and **707** from *cis*-**704** through intermediates **712** and **713** (Scheme 128).[194]

Recently, Huang and Zhou have reported the synthesis of a series of five- and six-membered lactones mediated by Cu(II) salts based on a related approach.[196] The starting materials were cyclopropylideneacetic acids and the corresponding esters, already embodying the carboxylic moiety that gives the intramolecular nucleophilic attack on the $\pi$-complexed ACP, which perform equally well in the reaction (Scheme 129).

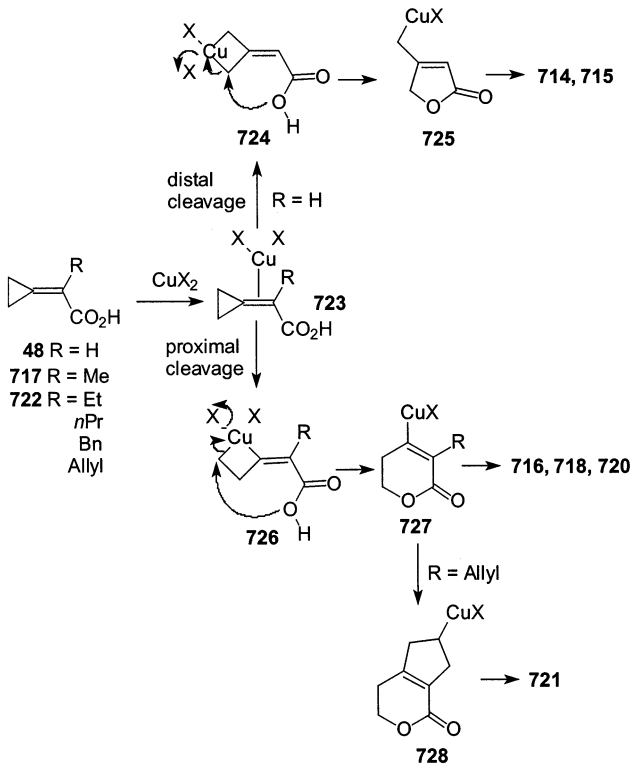
**Scheme 129**




Cyclopropylideneacetic acid (**48**) and its ethyl ester **47** gave the bromomethyl-$\gamma$-butenolide **714** when reacted with $CuBr_2$ (Scheme 129). With $CuI/I_2$, an interesting dichotomy was observed: the corresponding iodobutenolide **715** was the sole product when the reaction was carried out at 60 °C, while at 85 °C the iodopyranone **716** was uniquely obtained. A mixture of the two products was afforded at intermediate temperatures, with the pyranone being favored on increasing the temperature. On the contrary, pyranone formation has not been observed in the reaction with $CuBr_2$ under any conditions. However, when $\alpha$-substituted cyclopropylideneacetic acid **717** and esters **719** were employed in the same reaction, only pyranone derivatives **718**−**721** were obtained, independently on the halide used. In this case, a reaction temperature of 85 °C was necessary, no reaction occurring at 60 °C.[196]

Apparently, the observed selectivities depend on which cyclopropane C−C bond is cleaved preferentially in the intramolecular nucleophilic attack to the copper complex **723**, according to the proposed mechanism (Scheme 130).[196] Cleavage of the distal bond

**Scheme 130**

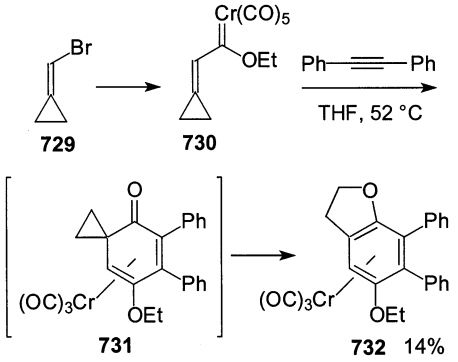



affords five-membered lactones **714** and **715**, while cleavage of the proximal bond gives pyranones **716**, **718**, and **720**, albeit no effort of rationalization has been made in order to understand the effects of temperature, subtitution, and halide used on the preferred mode of cleavage. The mechanism in Scheme 130 is also able to account for the formation of bicyclic pyranone **721** when an allyl-substituted cyclopropylidene acetate was used: the intermediate **727** (R = Allyl) undergoes a carbocupration at the terminal C=C double bond to give the copper intermediate **728**, precursor of **721**.

The $\eta^6$-$Cr(CO)_3$ complex of dihydrobenzofuran **732** has been obtained in low yield by a Dötz reaction of chromium carbene **730**, prepared in turn from bromomethylenecyclopropane (**729**). The final step of this reaction is the acylcyclopropane ring expansion of the intermediate **731** (Scheme 131).[197]

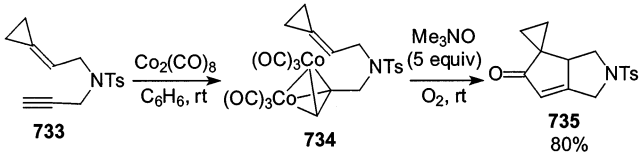
de Meijere and Salaün have found that the terminal cyclopropane moiety in cyclopropylidenealkynes is able to greatly enhance the efficiency of the

**Scheme 131**



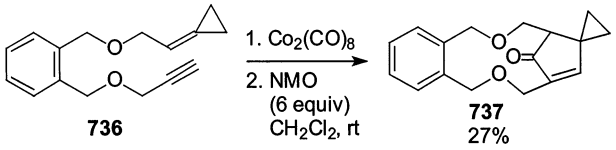

intramolecular Pauson−Khand reaction of enynes, since analogous isopropylidene substrates were found to be totally unreactive.[198] One of the substrates included in this study, the enyne **733**, containing a nitrogen atom in the chain connecting the reactive unsaturated groups, allowed tricyclic pyrrolidine **735** to be accessed in high yield from the Co−alkyne complex **734** under promotion of the reaction by trimethylamine *N*-oxide (Scheme 132).[198]

**Scheme 132**




The complete regioselectivity observed in this reaction is probably dictated by the length of the chain, since intermolecular Pauson−Khand reactions with MCP were shown to be less selective and gave preferentially the opposite regioisomer, having the spirocyclopropane situated in $\beta$ to the ketone.[199] Indeed, it has been published recently in the course of a broader study aimed at the synthesis of medium-sized cyclic compounds by means of *N*-methylmorpholine *N*-oxide (NMO)-promoted intramolecular Pauson−Khand reaction, that **736** with a longer linkage gave exclusively the dioxaundecane **737**, albeit in modest yield (Scheme 133).[200] Thus, a complete

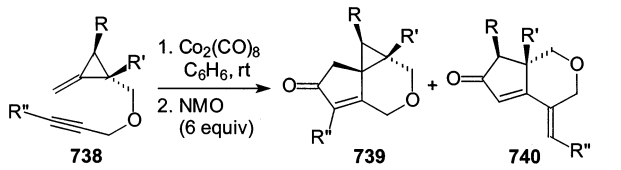
**Scheme 133**




reversal of the regioselectivity from the fused to the bridged bicyclic adduct was observed. Interestingly, the related unsubstituted terminal alkene gave in similar yields a mixture of the bridged and fused adducts with almost no selectivity.

Motherwell has studied more systematically the intramolecular Pauson−Khand reaction for a series of MCPs possessing an ethereal tether with the cycle rather than to the exo double bond (Table 32).[201] With mono- and 1,2-disubstituted MCPs **738a,b**, the reaction followed a regular course and afforded the expected fused tricyclic compounds **739a,b** as the

**Table 32. Intramolecular Pauson−Khand Reactions of MCPs 738**[a]

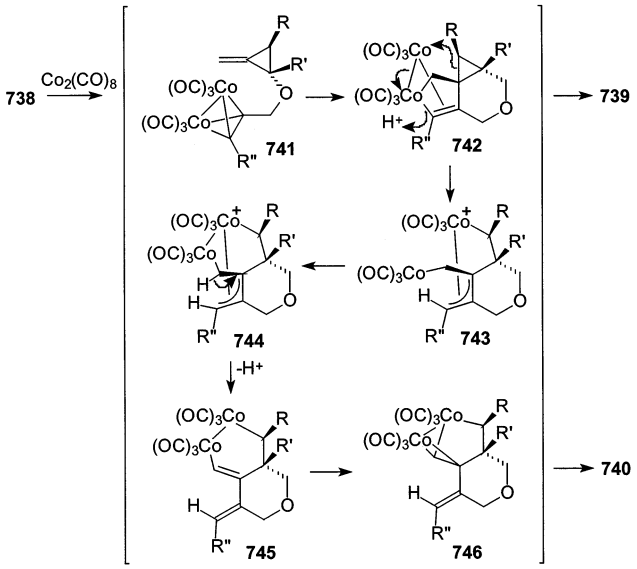



| entry | enyne | conditions | products (% yield) 739 | 740 |
|---|---|---|---|---|
| 1 | **a**: R = R′ = R″ = H | A | 41 | |
| 2 | **b**: R = $n$C$_9$H$_{19}$, R′ = R″ = H | A | 38 | |
| 3 | **c**: R = R″ = H; R′ = Me | A | | 51 |
| 4 | **c** | B | 44 | 12 |
| 5 | **d**: R = Et, R′ = Me, R″ = H | A | | 47 |
| 6 | **d** | C | 20 | 26 |
| 7 | **e**: R = Et, R′ = Me, R″ = SiMe$_3$ | A | 10 | 40 |
| 8 | **e** | D | 28 | 28 |

[a] Conditions: (A) C$_6$H$_6$, reflux. (B) THF, rt. (C) C$_6$H$_6$, rt. (D) THF, reflux.

only products (entries 1 and 2). However, when enynes **738c**−**e**, having a *gem*-methyl group at the cyclopropane carbon bearing the linked chain, were reacted under the same conditions, structurally different compounds were isolated as the exclusive or predominant product (entries 3, 5, and 7). These compounds were assigned structures **740c**−**e**, which still possess a bicyclic skeleton with a cyclopentenone fused to a tetrahydropyran nucleus but lack the cyclopropane ring. This indicated that an unusual rearrangement had occurred; furthermore, the two carbon atoms of the alkyne were not included in the cyclopentenone ring. The authors proposed these products as originating from a common intermediate **742** of the standard Pauson−Khand reaction, which then evolved through a different pathway with cyclopropane ring opening due to extra strain imposed by the presence of the methyl group (Scheme 134).[201] By

**Scheme 134**



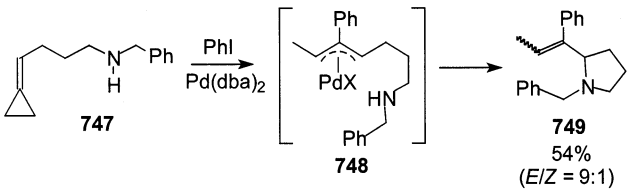

using milder reaction conditions, a coordinating solvent such as THF, or both, it was possible to force

the reaction to follow, at least in part, the pathway of a normal Pauson−Khand reaction and to give also tricyclic products **739c−e** (entries 4, 6, and 8). In both compounds **739** and **740**, the stereochemistry of the starting MCP **738** was preserved and furthermore **739** was formed with complete stereoselectivity.

The full realm of palladium-catalyzed reactions has emerged during the past decade as an impressively powerful tool for the synthesis of complex organic molecules. Particularly, cleverly designed substrates have been demonstrated to be able to increase enormously their structural complexity in a single chemical operation by combining reactions that may occur subsequently in a domino-type sequence of events[202] starting from a Pd-catalyzed process.[203] ACPs are optimal substrates for participating in Pd-catalyzed domino processes for several reasons: (i) the high reactivity of the exo C=C double bond allows them to easily undergo carbopalladation, hydropalladation, and heteroatom−palladation reactions, as well as many other different types of reactions due to strain relief upon addition; (ii) the high-lying HOMO of ACPs makes them good ligands for transition metals;[204] (iii) the intermediates derived from Pd−X addition to the C=C double bond are quite reluctant to undergo $\beta$-H elimination, a major pathway for the termination of a reaction cascade, due to the unfavorable formation of strained compounds (cyclopropenes or ACPs); (iv) the presence of a strained cyclopropane moiety directly linked to Pd, or to the α-carbon, allows different mechanistic courses to be viable by ring opening with formation of allyl− or homoallyl−Pd complexes. For these reasons, several reaction sequences involving ACPs and palladium catalysts have been recently designed and executed for assembling complex molecules, particularly mono- and polynuclear carbocyclic compounds.[205] In contrast, the examples of similar formations of heterocyclic compounds are limited.

The catalytic carbopalladation of alkylidenecyclopropanes **747** bearing a nucleophilic group leads to cyclic compounds **749** resulting from an intramolecular addition to the intermediate $\pi$-allyl−palladium complex **748** (Scheme 135).[206]

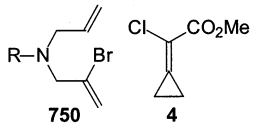
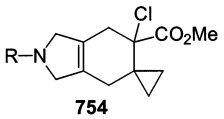
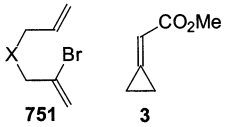
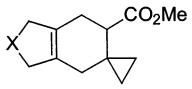
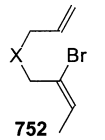
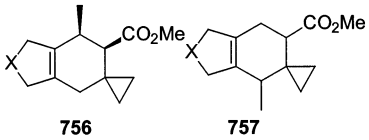
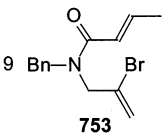
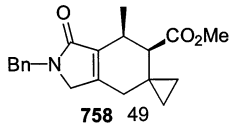
**Scheme 135**




Under similar Heck-type reaction conditions, however, the cyclopropane ring remains intact if the alkylidenecyclopropane or the alkyl−Pd intermediates, derived from carbopalladation of the exo C=C bond, find favorable competing pathways. Thus, de Meijere has used ACPs in domino intramolecular Heck−intermolecular Diels−Alder reactions either as dienophiles[205c,e] or as precursor of the intermediate conjugate diene[203b,205e] for the cycloaddition process.

When a nitrogen or an oxygen atom was included in the chain connecting the two alkenes to be joined

**Table 33. Domino Heck−Diels−Alder Reactions of 1,6-Dienes with ACPs 3 and 4**

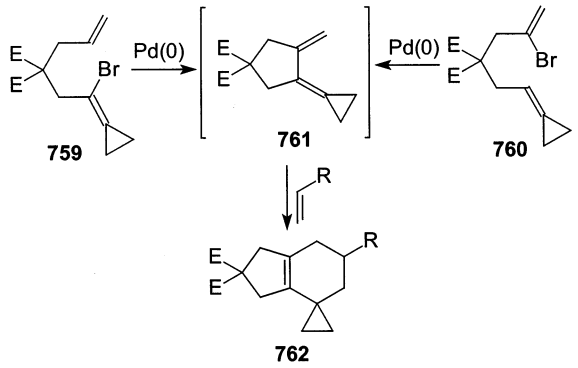
| Entry | Diene | ACP | Products (% Yield) |
|---|---|---|---|
| |  |  |  |
| | **750** | **4** | **754** |
| 1 | R = CHO | | 45 |
| 2 | R = Ac | | 69 |
| 3 | R = Boc | | 43 |
| 4 | R = Ts | | 44 |
| |  |  |  |
| | **751** | **3** | **755** |
| 5 | X = N-CHO | | 41 |
| 6 | X = O | | 31 |
| |  | **3** |  |
| | **752** | | **756** **757** |
| 7 | X = N-Bn | | 11.1:1[a] 40 (91:9) |
| 8 | X = O | | 6.6:1[a] 41 (89:11) |
| |  | **3** |  |
| 9 | **753** | | **758** 49 |

[a] Major diastereoisomer shown.

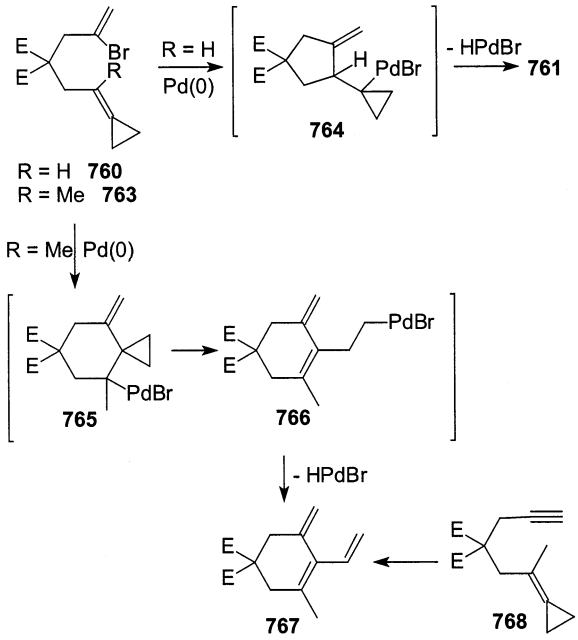
in the Heck reaction (e.g., in **750−753**), hexahydroisoindole and isobenzofuran systems were the final products of the domino process. The reactions were performed at 80−85 °C in acetonitrile with a 2-fold excess of dienophile in the presence of $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), and $Ag_2CO_3$ (1.25 equiv). With cyclopropylideneacetates **3** and **4** as dienophiles, the process afforded the spiro-fused tricyclic compounds **754−758** (Table 33).[207] With unsymmetrical dienes, the Diels−Alder reaction showed high regioselectivity, with preferential formation of isomers **756** and **758** with the methyl substituent distal to the cyclopropane ring (entries 7−9). The major regioisomers were also obtained with considerable diastereofacial selectivity, with the predominant stereoisomers being those shown in structures **756** and **758**, possessing the substituent on the six-membered ring in a cis relationship.

In these domino processes, ACPs have also been introduced in the diene moiety, either as a starter (in **759**) or as a terminator (in **760**) in the Heck reaction (Scheme 136).[203b,205e] Several spiro-fused cyclopropanehydrindanes **762** were obtained by this way as exclusive products derived from a completely regioselective Diels−Alder reaction of the intermediate diene **761**, formed in turn by regioselective Heck reactions. Especially noteworthy is the regioselectivity of the carbopalladation step from **760**, occurring with such an orientation that Pd is attached to the cyclopropane carbon atom in **764** and subsequent $\beta$-H elimination occurs exclusively from the carbon out-

**Scheme 136**



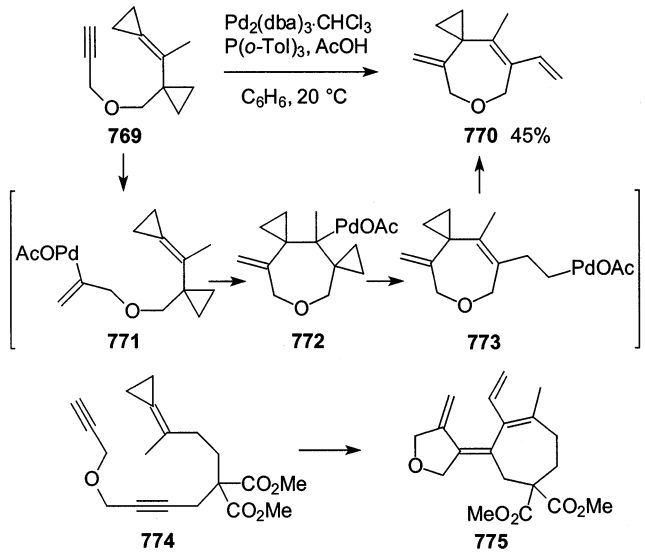

**Scheme 137**




side the cyclopropane in order to avoid formation of more strained cyclopropenes (Scheme 137).

However, when the exo C=C double bond of ACPs is a tetrasubstituted one as in **763**, the reaction takes a different course, affording cross-conjugated trienes (dendralenes, e.g., **767**) in which cyclopropane ring opening has occurred (Scheme 137).[205d] The same and related dendralenes were also obtained starting from enynes (e.g., **768**) under Trost cycloisomerization[208] conditions or under Heck conditions with a starter iodoarene. The mechanism proposed for the formation of these products considered a reversal of the regioselectivity in the initial carbopalladation step, with formation of a cyclopropylcarbinyl−Pd species **765** that preferred to rearrange to the homoallyl−Pd complex **766** with cyclopropane ring opening[209] rather then completing the Heck reaction with the $\beta$-H elimination. To ascertain this mechanism, the enyne **769** was subjected to the cycloisomerization reaction conditions and furnished the spiro-fused oxepane **770** in 45% yield (Scheme 138).[205d] After initial hydropalladation of **769** to alkenyl−Pd **771**, the further carbopalladation to **772** with the proposed regiochemistry was proven by the subsequent rearrangement, which occurred preferentially with ring opening of the cyclopropane closer to oxygen to give

**Scheme 138**

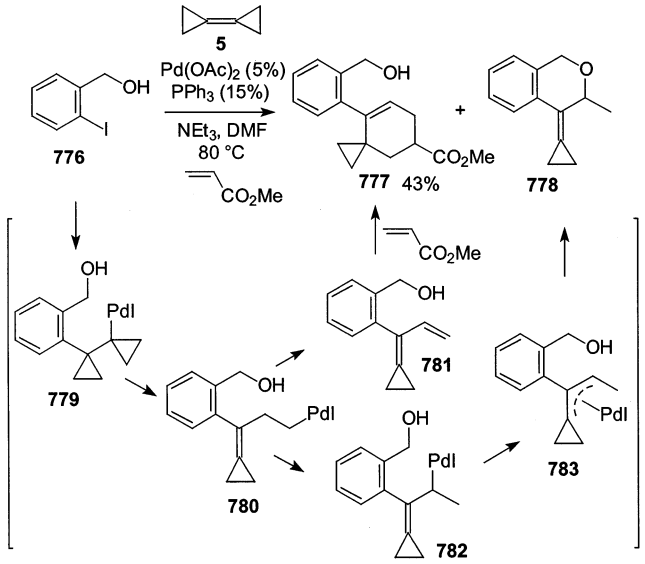



**773** and eventually the final heterocyclic product **770** by $\beta$-H elimination. This process can be applied to the synthesis of products of increased molecular complexity by extending the number of single steps involved in the domino sequence, as demonstrated by the synthesis of the tetrahydrofuran tetraene **775** from the enediyne **774** with the same reagents under high dilution (Scheme 138).[203b]

The scope of this process has been significantly extended by applying the Pd-mediated addition−rearrangement−elimination sequence in an intermolecular fashion using BCP (**5**).[205d] BCP revealed an exceptionally reactive acceptor alkene, even better than styrene and methyl acrylate, toward alkenyl and aryl palladium species. When BCP undergoes the carbopalladation reaction, Pd is placed in such a position to give rearrangement with ring opening of one of the two cyclopropane rings. The final products are therefore conjugated ACP dienes (from aryl−Pd) or cross-conjugated ACP trienes (from alkenyl−Pd), which are prompt to undergo subsequent Diels−Alder cycloadditions. Several mono- and polynuclear carbocyclic compounds have subsequently been synthesized by intermolecular Heck−intermolecular Diels−Alder domino sequences employing BCP.[203b,205d] With the aryl iodide **776** bearing a nucleophilic oxygen atom, the heterocyclic side product **778** has been obtained together with the product of the Heck−Diels−Alder process **777** (Scheme 139).[203b] The origin of benzopyranylidenecyclopropane **778** has been sought in a homoallyl−Pd **780** to allyl−Pd **782** rearrangement that competes with the $\beta$-H elimination to diene **781** and gives a $\pi$-allyl−Pd intermediate **783** prone to undergo nucleophilic attack with the observed regiochemistry, according to well-precedented reactions reported for similar substrates.[77] However, this reaction pathway has been reported only in connection with the formation of a byproduct; its optimization with suppression (or limitation) of the elimination reaction might open the way to a new synthesis of heterocyclic ACPs.

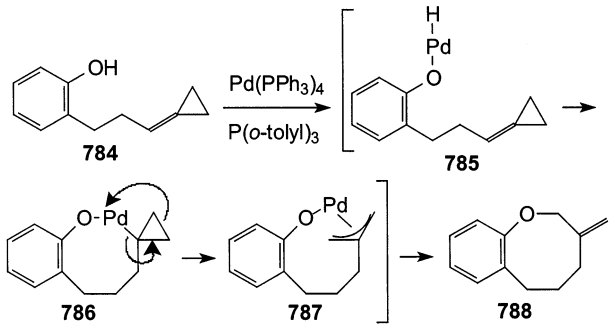
A similar internal nucleophilic attack on the allyl−Pd intermediate **787** has been proposed in order to

**Scheme 139**




account for the formation of the methylenebenzooxocane **788** from the ACP **784** under palladium catalysis (Scheme 140).[210] In this case, the $\pi$-allyl complex

**Scheme 140**




**787** originates from distal C−C bond cleavage of the cyclopropyl−Pd **786**. The overall process consists of a palladium-catalyzed hydroalkoxylation of the C=C double bond of ACP **784** and is initiated by oxidative addition of Pd(0) to the O−H bond to give **785**, which undergoes subsequent intramolecular hydropalladation to afford **786**.

Recently, Yamamoto investigated extensively the palladium-catalyzed intermolecular hydroalkoxylation,[210,211] hydroamination,[212] and hydrocarbonation[213] reactions of alkylidenecyclopropanes.[139g] Among the latter, hydrocarbonations employing heteroaromatic compounds deserve to be reported here, although the heterocyclic nucleus is already present in the substrate and not formed during the reaction. However, their generality with respect to the heterocycle and broad scope makes the process useful for the synthesis of allylated heteroaromatics. The reactions of furan, thiophene, pyrrole, and thiazole derivatives **790**−**793**, including benzofuran and benzothiophene, with ACPs **789** catalyzed by tetrakis(triphenylphosphine)palladium(0) have been reported to afford regioselectively the allylated heterocycles **794**−**800** deriving from cyclopropane ring opening (Scheme 141 and Tables 34−36).[214]

The reaction conditions were optimized for the hydrofurylation reaction: both the reported catalyst

**Scheme 141**

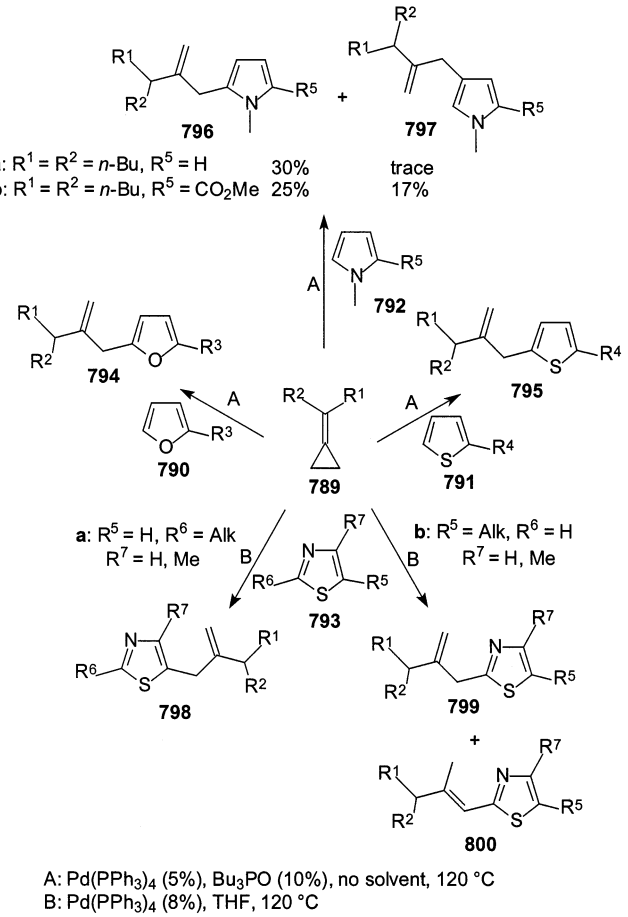
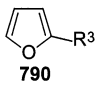
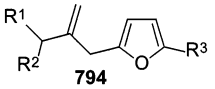
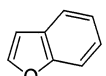
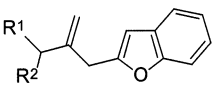



**Table 34. Palladium-Catalyzed Allylation of Furans with ACPs 789**[a]

| Entry | ACP | Furan | Adduct (% Yield) |
|---|---|---|---|
| |  789 |  790 |  794 |
| 1 | $R^1 = R^2 = n$Bu | $R^3$ = H | 77 |
| 2 | $R^1 = R^2 = n$Bu | $R^3$ = Me | 70 |
| 3 | $R^1 = R^2 = n$Bu | $R^3 = nC_5H_{11}$ | 70 |
| 4 | $R^1 = R^2 = n$Bu | $R^3 = CO_2Et$ | 77 |
| 5 | $R^1$ = Me, $R^2 = CH_2CH_2Ph$ | $R^3$ = Me | 68 |
| 6 | $R^1$ = Me, $R^2$ = cHex | $R^3$ = Me | 74 |
| 7 | $R^1$-$R^2 = (CH_2)_5$ | $R^3$ = Me | 65 |
| 8 | $R^1$ = H, $R^2 = CH_2CH_2Ph$ | $R^3$ = Me | 43 |
| | |  801 |  802 |
| 9 | $R^1 = R^2 = n$Bu | | 63 |
| 10 | $R^1$ = Me, $R^2 = CH_2CH_2Ph$ | | 35 |

[a] Major diastereoisomer shown.

and ligand were essential for the allylation to occur. Other catalysts [$Pd_2(dba)_3 \cdot CHCl_3$, $Pd(OAc)_2$, $Pt(PPh_3)_4$] did not promote the reaction at all, while ligands other than tributylphosphine oxide gave unsatisfactory results. Several furans and ACPs were employed (Scheme 141 and Table 34), but substitution on the cyclopropane ring seems not to be tolerated, since 2-(2-phenylethyl)methylenecyclopropane

**Table 35. Palladium-Catalyzed Allylation of Thiophenes with ACPs 789**

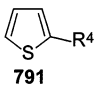
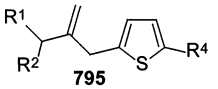
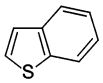
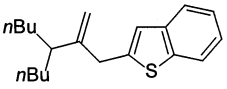
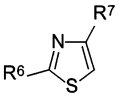
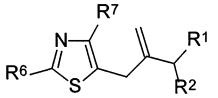
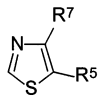
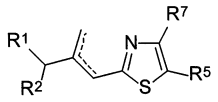
| Entry | ACP | Thiophene | Adduct (% Yield) |
|---|---|---|---|
| |  |  |  |
| | **789** | **791** | **795** |
| 1 | $R^1 = R^2 = n$Bu | $R^4$ = H | 53 |
| 2 | $R^1 = R^2 = n$Bu | $R^4$ = Me | 49 |
| 3 | $R^1 = R^2 = n$Bu | $R^4 = CO_2Et$ | 66 |
| 4 | $R^1 = R^2 = n$Hex | $R^4 = CO_2Et$ | 66 |
| | |  |  |
| 5 | $R^1 = R^2 = n$Bu | **803** | **804** 58 |

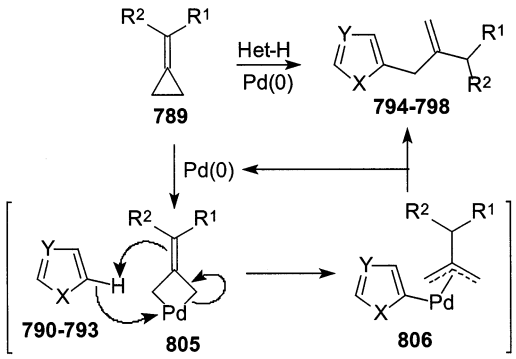
**Table 36. Palladium-Catalyzed Allylation of Thiazoles with ACPs 789**

| Entry | ACP | Thiazole | Adduct (% Yield) | |
|---|---|---|---|---|
| |  |  |  | |
| | **789** | **793a** | **798** | |
| 1 | $R^1 = R^2 = n$Bu | $R^6 = i$Bu, $R^7$ = H | 77 | |
| 2 | $R^1 = R^2 = n$Hex | $R^6 = i$Bu, $R^7$ = H | 65 | |
| 3 | $R^1$ = H, $R^2 = nC_7H_{15}$ | $R^6 = i$Bu, $R^7$ = H | 19 | |
| 4 | $R^1 = R^2 = n$Bu | $R^6$ = Et, $R^7$ = Me | 20 | |
| | |  |  | |
| | | **793b** | **799** | **800** |
| 5 | $R^1 = R^2 = n$Bu | $R^5$ = Me, $R^7$ = H | 37 | 3 |
| 6 | $R^1$ = Me, $R^2 = (CH_2)_2CO_2Et$ | $R^5$ = Me, $R^7$ = H | 46 | 9 |
| 7 | $R^1 = R^2 = n$Bu | $R^5 = R^7$ = Me | 16 | 19 |
| 8 | $R^1 = R^2 = n$Bu | $R^5 = (CH_2)_2OMe$, $R^7$ = Me | 25 | 11 |

was unreactive.[214] For all the heterocycles studied, the best conditions were found to be the use of neat ACP with a 5-fold excess of heteroaromatic, 5 mol % of catalyst, and 10 mol % of ligand, with the exception of the thiazoles, where THF was used as solvent in the presence of 8 mol % of catalyst and no ligand. Furans **790** and thiophenes **791** were allylated exclusively at the 2-position (Scheme 141 and Tables 34 and 35); the unsubstituted furan and thiophene also gave small amounts of 2,5-(bis)allylated derivatives besides the major monoallylated compound (Tables 34 and 35, entries 1). *N*-Methylpyrroles **792** reacted sluggishly to afford moderate yields of adducts **796** and **797** where competition with the allylation at the 3-position arose (Scheme 141). Thiazoles **793a** reacted preferentially at the 5-position to give adducts **798**; when this position was occupied by an alkyl group as in compounds **793b**, allylation at the 2-position occurred to afford adducts **799** and their conjugated isomers **800** (Scheme 141 and Table 36). The following order of reactivity was observed: furan > thiophene ≈ thiazole (5-position) > thiazole (2-position) ≈ *N*-methylpyrrole.[214]

For the mechanism of the reaction, the authors are inclined to favor an initial oxidative addition of Pd(0) into the distal cyclopropane C−C bond with formation of methylenepalladacyclobutanes **805** (Scheme 142). This hypothesis is in contrast with

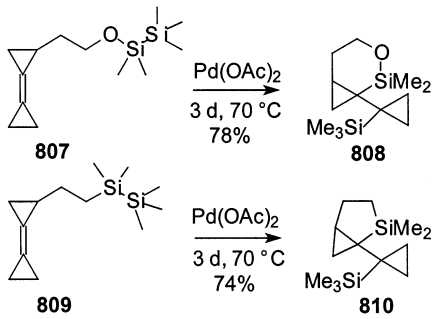
**Scheme 142**




their proposal on hydroalkoxylation and amination reactions where insertion of Pd into the Het−H bond is envisioned (see Scheme 140) and is justified by the lower acidity of protons attached to carbon atoms. Then, the palladacyclobutane intermediates **805** react as $\sigma$-allylmetals with the heteroaromatics **790**−**793** to give the $\pi$-allyl complexes **806**, and eventually, reductive elimination leads to the final compounds **794**−**798** and to regeneration of Pd(0).[214] This mechanism is supported by the isolation of a diene derived from an isomerization with ring opening, when ACP **789** ($R^1$ = H, $R^2 = CH_2CH_2Ph$) was subjected to the reaction conditions, and, in contrast, also by the recovery of unaltered substrates in the reaction of furans with diphenylacetylene.

Due to the high reactivity of the bicyclopropylidene moiety, it was possible to obtain siloxa- and silaheterocycles **808** and **810** through an intramolecular palladium-catalyzed addition of disilanes **807** and **809**, respectively, to the C=C double bond (Scheme 143).[215] In these cases, the silasilylation reaction

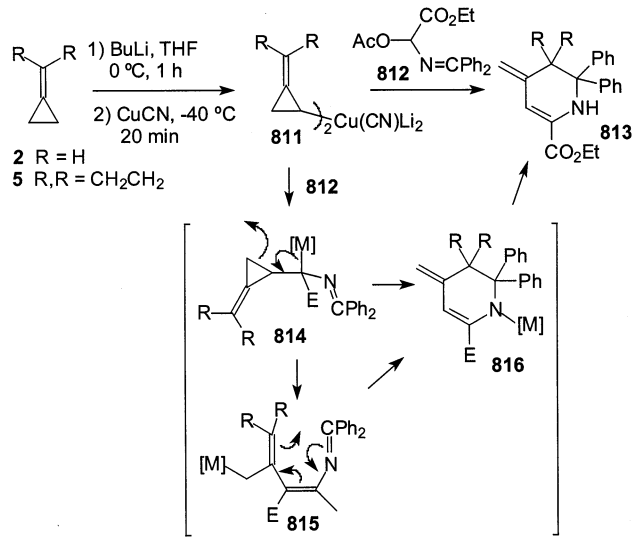
**Scheme 143**




occurred with preservation of both cyclopropane rings.

Organocopper reagents **811** derived from bicyclopropylidene (**5**) and methylenecyclopropane (**2**) reacted with the electrophilic glycine equivalent **812** to afford 4-methylene-1,2,3,4-tetrahydropyridine derivatives **813** (Scheme 144).[216] Formally, this reaction can be described as a [3+3] cycloaddition and may proceed through a fast cyclopropylmethyl to but-3-enyl rearrangement of the normal coupling product **814** to **815**. Then, the cyclization to **816** could be viewed as a 6$\pi$−electrocyclization of **815**. Alterna-

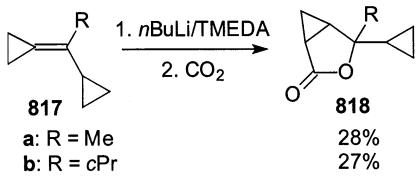
**Scheme 144**




tively, the concerted cyclization and rearrangement of **814** could lead directly to **816**, the metalated form of the final compound **813**.

Cyclopropyl-substituted ACPs **817** gave the cyclopropane-fused lactones **818** in modest yields by a deprotonation followed by carboxylation (Scheme 145).[217]

**Scheme 145**




## *IX. Heterocycles from the Nucleophilic Addition to Alkylidenecyclopropanes*

Chloro(cyclopropylidene) acetates are much better Michael acceptors than any other 3,3-disubstituted acrylates. This is partly due to the strain release on increasing the p character of hybridization upon nucleophilic addition but is also related to the presence of the α-chloro substituent.[7a] Furthermore, the multifunctionality of these compounds makes them versatile tools in synthesis, as was demonstrated by the one-pot synthesis of several different heterocycles using phase-transfer catalysis (Scheme 146).

The kind of product obtained critically depended on the nature of the base employed.[100] Treatment of 2-chloro-2-cyclopropylideneacetate (**4**) with a primary amine afforded unstable Michael adducts that, in situ, upon addition of a second equivalent of amine and a stronger base, such as NaH, evolved to 1-azaspiropentane-2-carboxylic amides **819** (Table 37).[218]

The reaction of **4** with lithium benzylamide (0.5 equiv) afforded via a Michael−Michael ring closure (MIMIRC) mechanism, in which two molecules of **4** are employed, lactam **820** with three cyclopropyl rings (Scheme 147).[219]

Again **4**, and substituted derivatives **821**, reacted with carboxamides under basic conditions to afford, through a domino process involving a Michael addition followed by an intramolecular nucleophilic substitution, 4-spirocyclopropane-annelated oxazoline-carboxylates **822** (Table 38). The reaction was performed on a wide number of aliphatic and aromatic carboxamides in yields ranging from 24 to 77%. The reaction proceeded with good stereoselectivity using substituted cyclopropyl derivatives (entries 16−22).[220]

Aliphatic and aromatic thiocarboxamides also underwent Michael additions to **4** and **821** under basic conditions, by attack of the sulfur atom on the electrophilic carbon of the cyclopropylidene acetates and afforded 5-spirocyclopropane-annelated thiazoline-4-carboxylates **823**, generally in good yields (Table 39).[221]

**Scheme 146**

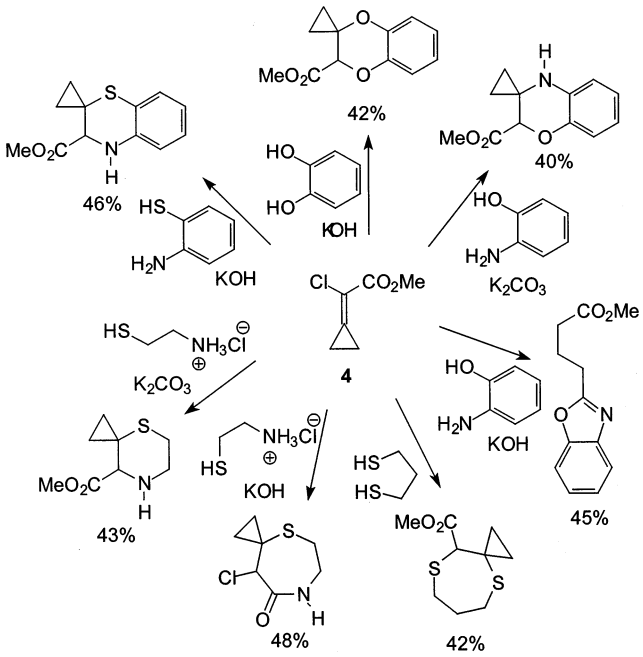
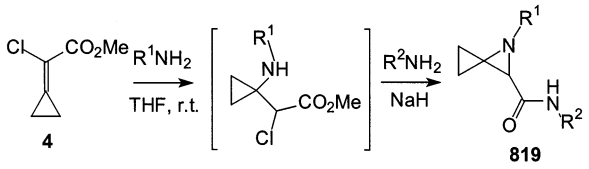



**Table 37. Synthesis of Azaspiropentane-2-carboxylic Acid Amides 819 by Reactions of Chlorocyclopropylidene Acetate 4 with Amines**




| entry | $R^1$ | $R^2$ | product **819** | d.r. |
|---|---|---|---|---|
| 1 | Bn | Bn | **a** | |
| 2 | *p*-$MeOC_6H_4CH_2$ | *p*-$MeOC_6H_4CH_2$ | **b** | |
| 3 | Bn | *p*-$MeOC_6H_4CH_2$ | **c** | |
| 4 | Bn | (*S*)-$CH(CH_3)C_6H_5$ | **d** | 1.1:1 |
| 5 | (*S*)-$CH(CH_3)C_6H_5$ | Bn | **e** | 1.6:1 |
| 6 | Bn | H | **f** | |

**Scheme 147**

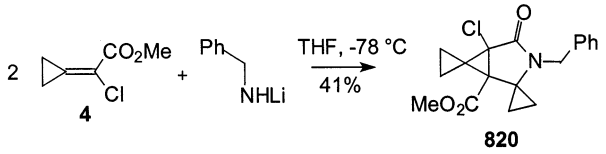
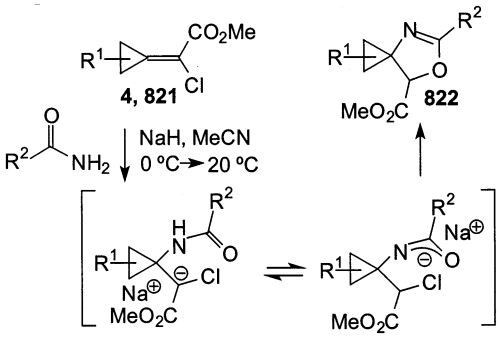


**Table 38. Synthesis of 4-Spirocyclopropane-Annelated Oxazoline Carboxylates 822 by Reaction of Chlorocyclopropylidene Acetates 4 and 821a,b with Carboxamides**




| entry | ACP | $R^1$ | $R^2$ | 822 | yield (%) | d.r. |
|---|---|---|---|---|---|---|
| 1 | **4** | H | Ph | **a** | 60 | |
| 2 | | H | 3-$C_5H_4N$ | **b** | 38 | |
| 3 | | H | 2-$C_4H_3O$ | **c** | 49 | |
| 4 | | H | *p*-CN−$C_6H_4$ | **d** | 74 | |
| 5 | | H | *o*-Me-$C_6H_4$ | **e** | 70 | |
| 6 | | H | *m*-Me-$C_6H_4$ | **f** | 58 | |
| 7 | | H | *p*-Me-$C_6H_4$ | **g** | 50 | |
| 8 | | H | *m*-F−$C_6H_4$ | **h** | 75 | |
| 9 | | H | *p*-Br−$C_6H_4$ | **i** | 73 | |
| 10 | | H | *o*-$NO_2$−$C_6H_4$ | **j** | 47 | |
| 11 | | H | *p*-$NO_2$−$C_6H_4$ | **k** | 47 | |
| 12 | | H | *o*-Cl−$C_6H_4$ | **l** | 77 | |
| 13 | | H | *p*-Cl−$C_6H_4$ | **m** | 68 | |
| 14 | | H | *o*-I−$C_6H_4$ | **n** | 72 | |
| 15 | | H | *m*-I−$C_6H_4$ | **o** | 49 | |
| 16 | **821a** | Et | Ph | **p** | 56 | 9:1 |
| 17 | | Et | *o*-Me-$C_6H_4$ | **q** | 68 | 17:1 |
| 18 | | Et | *o*-I−$C_6H_4$ | **r** | 55 | 17:1 |
| 19 | | Et | *p*-$NO_2$−$C_6H_4$ | **s** | 40 | 2:1 |
| 20 | | Et | *m*-F−$C_6H_4$ | **t** | 46 | 7:1 |
| 21 | | Et | 3-$C_5H_4N$ | **u** | 25 | 5:1 |
| 22 | **821b** | $(CH_2)_2OBn$ | *p*-$NO_2$−$C_6H_4$ | **v** | 41 | 2:1 |
| 23 | **4** | H | Me | **w** | 6 | |
| 24 | | H | Et | **x** | 24 | |
| 25 | | H | *n*-Pr | **y** | 24 | |
| 26 | | H | *t*-Bu | **z** | 24 | |

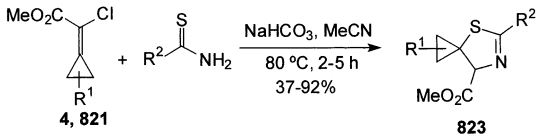
Recently, it was demonstrated that amidines **824** can start a domino process in which, after a nucleophilic attack, the presence of a good leaving group allows a series of rearrangements that afford cyclobutene-annelated pyrimidones **825** (Scheme 148).[222]

## X. Heterocycles from Radical Cyclizations

The exo C=C double bond of ACPs has also been reacted with radical species. The initial attack is often followed by cyclopropane ring opening; however, that is not the rule. The radical species derived from the initial reaction then give the final products by hydrogen capture or evolve into other species in a radical cascade sequence. A few of these reactions led to the synthesis of heterocyclic compounds, when the radical addition to C=C has been performed in an intramolecular fashion, either by attack of a heteroatom-centered radical or by attack of a carbon-centered radical connected to the ACP with a chain containing a heteroatom.

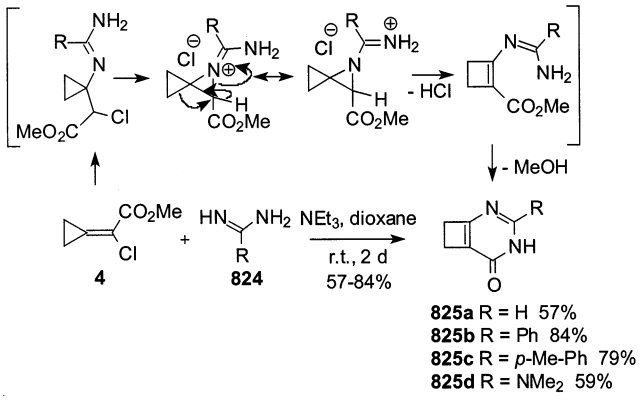
An early example of the former type was the addition of the aminyl radical generated from ACP chloroamine **826**, which gave unexpectedly the cyclopropane-fused piperidine **827** (Scheme 149).[223]

**Table 39. Synthesis of 5-Spirocyclopropane-Annelated Oxazoline Carboxylates 823 by Reaction of Chlorocyclopropylidene Acetates 4 and 821a−c with Thiocarboxamides**



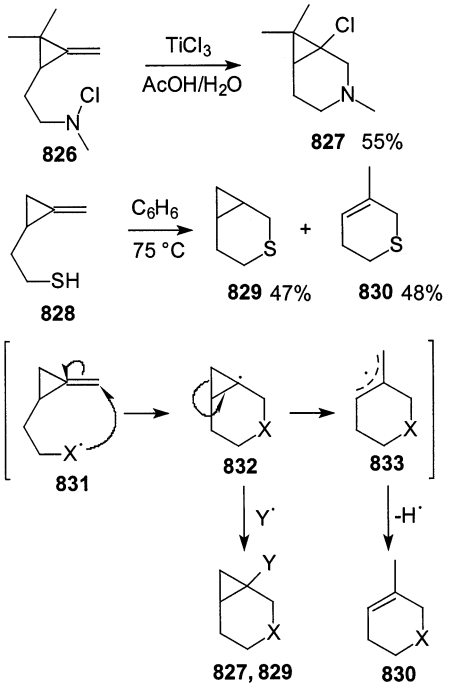

| entry | ACP | $R^1$ | $R^2$ | prdct 823 | yield (%) | d.r. |
|---|---|---|---|---|---|---|
| 1 | **4** | H | Ph | **a** | 86 | |
| 2 | | H | Me | **b** | 73 | |
| 3 | | H | *p*-Br−$C_6H_4$ | **c** | 85 | |
| 4 | | H | *p*-*t*Bu-$C_6H_4$ | **d** | 77 | |
| 5 | | H | *p*-MeO−$C_6H_4$ | **e** | 92 | |
| 6 | | H | *p*-Me-$C_6H_4$ | **f** | 68 | |
| 7 | | H | *p*-F−$C_6H_4$ | **g** | 67 | |
| 8 | | H | 2-$C_4H_3S$ | **h** | 53 | |
| 9 | | H | $NMe_2$ | **i** | 49 | |
| 10 | | H | NMePh | **j** | 37 | |
| 11 | | H | $O(CH_2CH_2)_2N$ | **k** | 39 | |
| 12 | **821c** | Me | Ph | **l** | 51 | 1.2:1 |
| 13 | | Me | Me | **m** | 52 | 1.9:1 |
| 14 | | Me | *p*-MeO−$C_6H_4$ | **n** | 72 | 1.2:1 |
| 15 | **821a** | Et | Ph | **o** | 58 | 2.1:1:1 |
| 16 | | Et | Me | **p** | 78 | 1.7:1:1 |
| 17 | | Et | *p*-Br−$C_6H_4$ | **q** | 52 | 9.3:1.5:1 |
| 18 | | Et | *p*-*t*Bu-$C_6H_4$ | **r** | 66 | 2.3:1.1:1 |
| 19 | **821b** | $(CH_2)_2$-OBn | Ph | **s** | 52 | 2:1 |
| 20 | | $(CH_2)_2$-OBn | Me | **t** | 77 | 1.1:1 |

**Scheme 148**

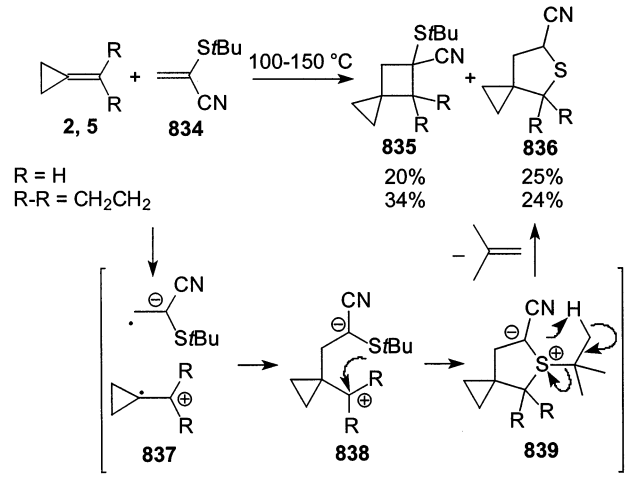



Analogously, the sulfide **828** afforded thiabicyclo[4.1.0]heptane **829** together with thiopyran **830**.[224] The formation of six-membered heterocycles **827** and **829** must derive from a 6-endo-trig cyclization of the primary radicals **831.** This leads to the bridgehead radical **832,** which gives the products **827** and **829** by capture of Cl and H radicals, respectively, or rearranges to the allyl radical **833** precursor of sulfide **830**. The cyclization of **831** is anomalous, since 5-hexenyl radicals, both carbon- and heteroatom-centered, normally undergo a favored 5-exo-trig cyclization according to Baldwin's rules. The normal behavior has always been observed, also in the cyclization of ACP carbon-centered radicals (see below). The 5-exo-trig cyclization would be expected to lead to (different) cyclopropane ring-opened products through a cyclopropylmethyl radical.

**Scheme 149**



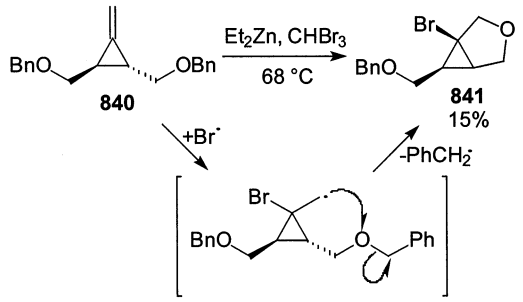

**Scheme 150**




Sulfur heterocycles **836** have been obtained in modest yields by reaction of MCP (**2**) and BCP (**5**) with the capto-dative alkene **834**, besides the desired spirocyclopropane-substituted [2+2] adducts **835** (Scheme 150).[225] The formation of tetrahydrothiophenes **836** has been explained by an initial SET step to the radical ion species **837**, followed by coupling to the dipolar intermediates **838**, which then undergo intramolecular nucleophilic attack of the thioether and finally results in the loss of isobutene.

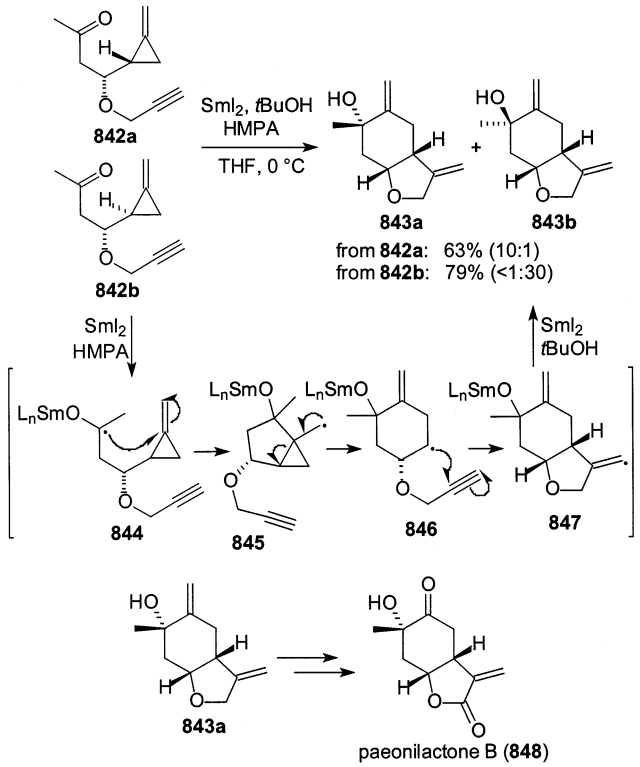
During a study aimed at the synthesis of spirocyclopentane derivatives as intermediates of potential antiviral carbocyclic nucleosides, it has been observed that 2,3-disubstituted MCPs when reacted with a $Et_2Zn/CHBr_3$ system gave products derived from a formal addition of bromoform to the C=C double bond, probably by radical mechanism, rather than from the expected [2+1] addition of a zinc carbenoid. In the single case of MCP **840**, due to the presence of the benzyloxy groups, the oxabicyclohexane **841** has been isolated, the formation of which has been explained by the addition of a bromo radical, formed in the reaction mixture, followed by an intramolecular cyclization and C−O bond fission with displacement of a benzyl radical (Scheme 151).[226]

**Scheme 151**




During the past decade, Kilburn and co-workers have studied extensively the radical cyclizations of MCPs,[227] including examples where the C=C double bond of MCPs takes part in a radical cascade process,[228] for the synthesis of polynuclear fused and spiranic carbocyclic compounds. Recently, these studies have been extended to MCP substrates possessing both a ketone and a propargyl ether or an allyl ether functionality on the side chain, with the purpose of synthesizing monoterpenes of the paeonilactone family, natural products with analgesic properties extracted from the root of *Paeonia albiflora* Pallas. The synthetic strategy considered a radical cascade sequence promoted by $SmI_2$[229] with the ketone being the starter and the terminal alkyne or alkene the terminator. MCPs **842** were synthesized from MCP (**2**) by metalation, addition to an aldehyde, and final derivatization of the alcohol. Both diastereoisomers **842a** and **842b** reacted with $SmI_2$ (2.2 equiv) in THF in the presence of HMPA as a ligand and *t*BuOH, to afford a mixture of diastereomeric perhydrobenzofurans **843** in different ratio (Scheme 152).[230] It is noteworthy that the two diastereomeric MCPs **842a** and **842b** showed high and opposite preference for formation of **843a** and **843b**, respectively, allowing access to both stereoisomeric series. In absence of HMPA, the reaction was very poor, while replacement of HMPA with the less coordinating DMPU required a large excess of $SmI_2$ and gave lower yields, besides significantly reducing the diastereomeric ratio (from **842a**). The observed diastereofacial preferences have been ascribed to different conformational preferences for the TS derived from the two diastereoisomers of **842**. Mechanistically, the reaction consists of a sequence of radical additions: the initially generated ketyl radical **844** adds to the exo C=C double bond of MCP in a 5-exo-trig fashion. This preferred mode of cyclization has been observed to be exclusive for all additions of 5-pentenyl-type radicals to MCPs, with the only exceptions being the aminyl and thiyl radicals shown in Scheme 149. The generated cyclopropylmethyl radical **845** undergoes a rapid rearrangement to the homoallyl radical **846**, which eventually initiates the last addition to the alkyne to give the alkenyl radical **847**, precursor of the final product. The promotion of such a radical cascade by $SmI_2$ is remarkable, as competiting reduc-

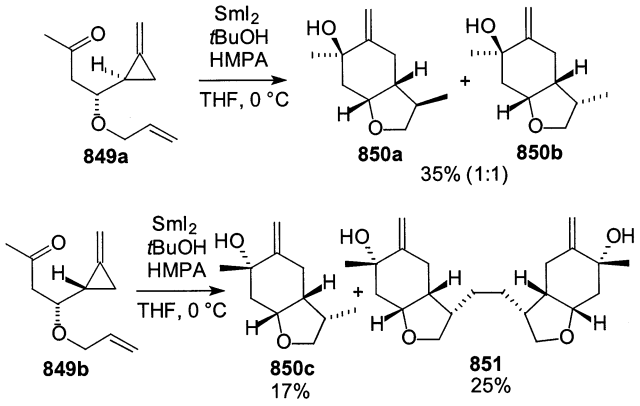
**Scheme 152**




tion could be possible for each radical intermediate. Compound **843a** was successfully converted into the target paeonilactone B (**848**) (Scheme 152).[230]

The study was then extended to analogous MCP alkenes **849** in order to investigate the diastereoselectivity affordable in the construction of a fourth stereogenic center, i.e., that at the tetrahydrofuran ring derived from the last addition to the vinyl group, and simultaneously to synthesize a key intermediate of paeonilactone A (Scheme 153).[230b,231] The reactions

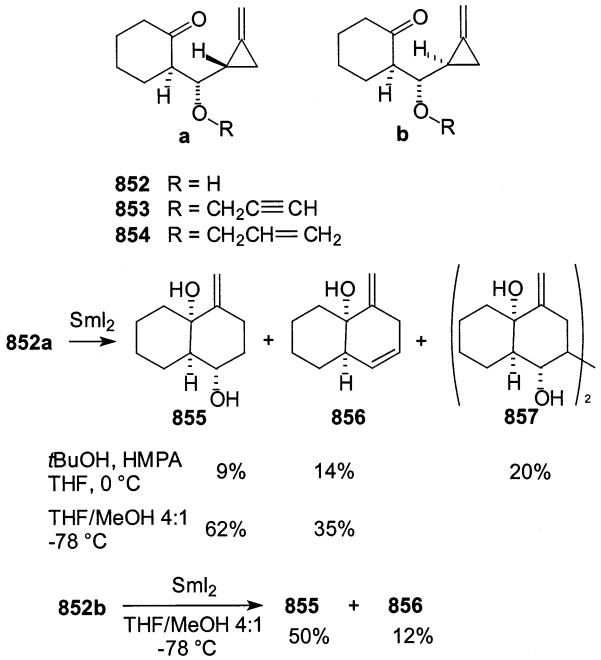
**Scheme 153**




of MCPs **849a** and **849b** showed the same high stereocontrol as their alkyne congeners (Scheme 152), where the bridgehead and carbinol stereocenters are concerned, but divergent behavior with regard to the additional center. While **849a** gave exclusively the two cyclic ethers **850a,b** but without any selectivity, reaction of **849b** was completely stereoselective, leading to a single bicyclic product **850c** together with the dimer **851**, which still possessed the same relative configuration as **850c** at all stereogenic centers in both portions of the molecule. Interestingly, only dimeric *meso*-**851** was detected and isolated, showing that dimerization occurs only between two opposite enantiomers. In this case, the alkyl radical generated with complete stereoselectivity in the last addition of the radical cascade must have an unusually high lifetime under the reaction conditions, which allows it to couple with another (enantiomeric) radical rather than being reduced to the organosamarium compound.

The complexity of the studied system was increased by including the ketone in a cyclohexanone framework, in such a way as to access tricyclic ethers with the eudesmane sesquiterpenoid lactones skeleton. Thus, MCPs **852**−**854** were synthesized and subjected to the $SmI_2$-promoted cascade reaction (Scheme 154).[232] The reaction was tested initially with free

**Scheme 154**

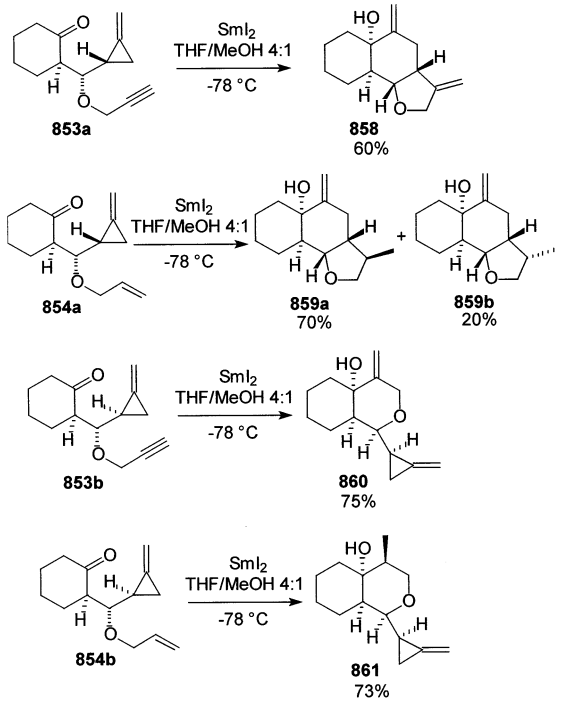



alcohols **852** that showed the feasibility of the process also with the cyclohexanone moiety. However, the outcome of the reaction was strongly dependent on the conditions employed. The conditions developed in the previous studies with MCP **849a** gave the expected decalin framework, but the desired diol **855** only in low yield, together with dimer **857** and diene **856**, derived respectively from radical coupling and from elimination of hydroxide ion from the intermediate anion, which competes with protonation. Similarly, a poor reaction was obtained with **852b**. When only THF was used without any additive at 0 °C, **852a** gave just the reduction of the ketone to the corresponding cyclohexanol. The best conditions were found by performing the reaction at low temperature in THF/MeOH 4:1, which afforded only the diol **855** and the elimination product **856** in high combined yields from either **852a** or **b** (Scheme 154).[232]

With these results, reactions of propargyl ethers **853** and allyl ethers **854** were accomplished with the two systems THF/MeOH and THF/*t*BuOH/HMPA,

always at low temperature. Although the former conditions proved in all cases more satisfactory, the outcome did not differ substantially except in a single case. The $SmI_2$-promoted reactions of ethers **853a** and **854a** furnished the desired tricyclic ethers **858** and **859**, respectively, in good yields with complete diastereocontrol at the four bridgehead stereogenic carbons and a fair 3.5:1 preference concerning the fifth stereocenter formed from MCP **854a** (Scheme 155).[232] Interestingly, the ratio was inverted in

**Scheme 155**

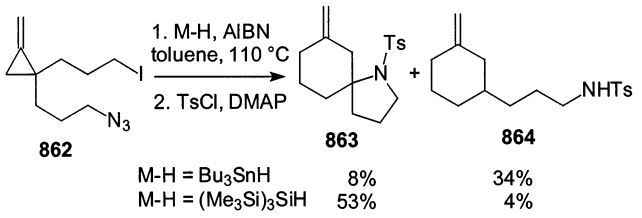



*t*BuOH/HMPA to 10:1 in favor of **859b** over **859a**, albeit they were obtained in lower yield. This result was interpreted with a switch from a preferred chelated to a nonchelated intermediate in the last cyclization. In contrast, the MCPs of the other diastereomeric series, **853b** and **854b**, furnished only bicyclic ethers **860** and **861**, respectively, still in good yield and complete stereoselectivity over all four and five stereocenters. Apparently, compounds **860** and **861** originate from a truncated cascade, where the exo C=C double bond of MCP is unable to participate and thus the ketyl radical cyclizes in a 6-exo fashion to the propargyl or allyl unsaturation. The different behavior of the two diastereomeric series has been ascribed to different conformational preferences of the initially generated ketyl radical.[232]

Also, Kilburn has synthesized aza heterocycles via intramolecular radical cyclizations of MCPs, employing either a nitrogen end group in the cascade or substrates containing a nitrogen atom in the connecting chain.

The MCP iodoazide **862** was reacted with tin and silicon hydride initiators of radical chain reactions in order to access, after trapping of the resulting amine by tosylation, spiro-fused bicycles **863** (Scheme 156).[233] With tributyltin hydride, the main product was, however, the monocyclic tosylamine **864**, derived from reduction of azide prior to its intervention in

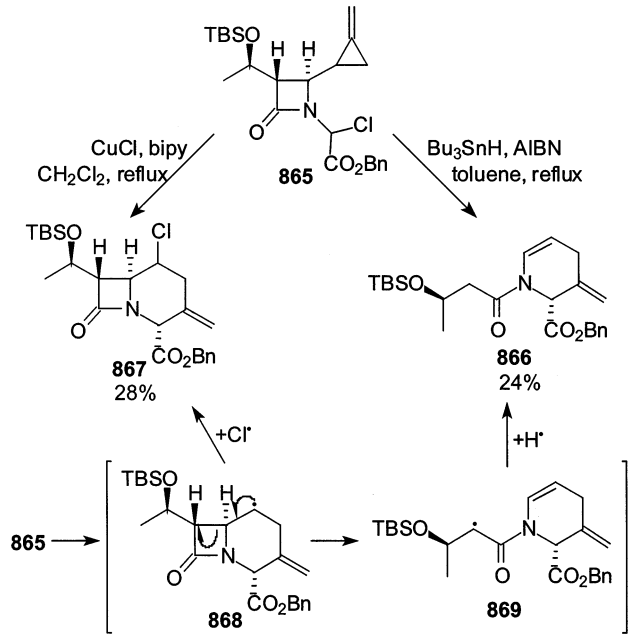
**Scheme 156**




the radical cascade sequence. As previously observed in radical reactions with azides,[234] this inconvenience could be overcome by the use of more chemoselective tris(trimethylsilyl)silane.

The second approach regards methylenecyclopropyl-substituted azetidinones, with the purpose of synthesizing new polycyclic $\beta$-lactam derivatives. The appropriate substrates were accessed by coupling of methylenecyclopropylcuprate with a preformed 4-acetoxyazetidinone and a subsequent elaboration of the coupling product to place suitably the reacting moieties for an intramolecular cascade and finally subjected to radical reaction conditions.[235] The azetidinone **865** reacted with tributyltin hydride to give only piperidine **866** in low yield, with the chain corresponding to the opened four-membered ring (Scheme 157). On the other hand, the use of CuCl/bipyridine

**Scheme 157**

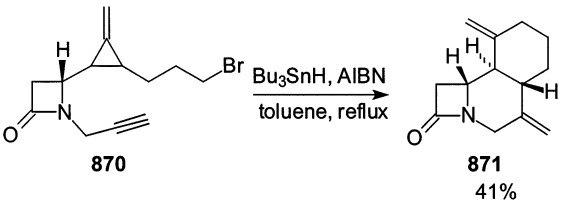



under atom-transfer conditions allowed access to the carbacephem structure of **867** as a single diastereoisomer (of unknown stereochemistry at the chloro-bearing carbon atom), albeit in modest yield. Both products **866** and **867** may derive from a common methylenecyclohexyl radical intermediate **868**, formed by the general sequence shown in Scheme 152, which follows a different fate: rearrangement with ring opening to **869** and quenching in the first case, capture of a chlorine radical in the second.[235]

The MCP **870** took part in a radical cascade sequence similar to those initiated by $SmI_2$ described for MCP ketones. Homolytic cleavage of the C−Br

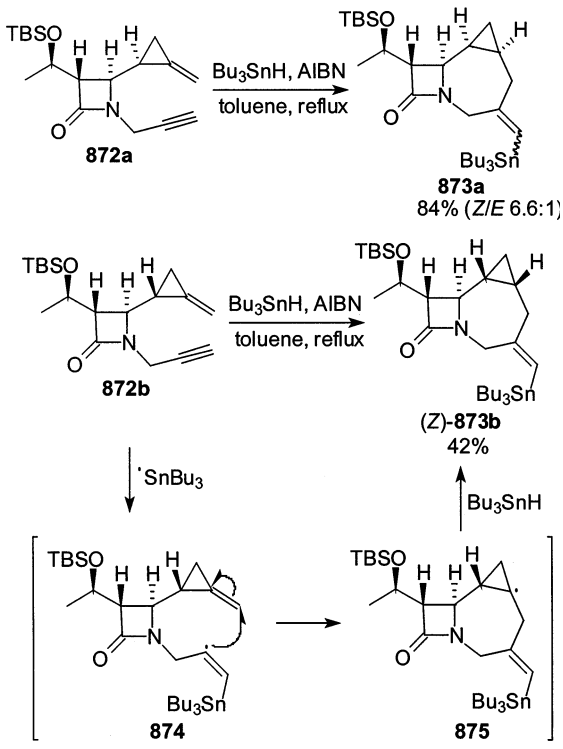
bond is now the starting event of the sequence, which leads exclusively to the new tricyclic $\beta$-lactam **871**, with a trans ring fusion of the six-membered rings, as the final product (Scheme 158).[235]

**Scheme 158**




Conversely, radical reactions of diastereomeric MCPs **872**, initiated by the addition of a tributyltin radical to the alkyne, gave tricyclic $\beta$-lactams **873** containing an intact fused cyclopropane ring (Scheme 159).[235] The alkenyl radical initially generated, e.g.,

**Scheme 159**




**874**, in this case cyclizes through a preferred 7-endo-trig mode to a bicyclic bridgehead radical **875**, precursor of the isolated products **873**. While MCP **872b** reacts with complete stereocontrol affording only (*Z*)-**873b**, **872a** gives, with a fair preference for the *Z* diastereoisomer, a *Z*/*E* diastereomeric mixture, which leads to one methylenecycloheptane by destannylation.

## XI. Conclusions

ACPs represent a largely accessible class of compounds involved in numerous and selective synthetically useful transformations, most of them described in the present review. From a rapid overview of the literature in the field, it appears evident that the synthesis of heterocyclic compounds has been only occasionally investigated by researchers, despite the large body of results already accumulated. Therefore, many possibilities exist for the development of new strategies leading to heterocyclic compounds starting from ACPs. The peculiar reactivity of such compounds is, moreover, able to furnish results that would be achievable from other starting materials only with difficulty. In particular, the strain energy associated to ACPs allows one to carry out sequential synthetic transformations, in a domino fashion, without the use of added reagents and catalysts. It is of general belief that these domino processes are important for the development of a more environmentally friendly synthetic organic chemistry. Several of these processes have been already developed, and we paid particular attention to them during the review. Hopefully, also with this contribution, we can instigate a multitude of new examples of uses of ACPs in domino reactions in the synthesis of heterocyclic compounds.

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