Synthesis of Methylene- and Alkylidenecyclopropane Derivatives†

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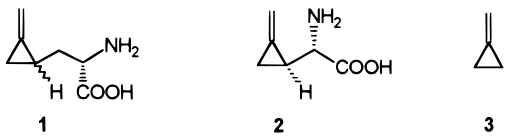
I. Introduction

Energy associated with highly strained molecules limits their application in synthetically useful strategies, yet, on associating energy with sufficiently stable molecules usable in a laboratory, these very same molecules become important new tools for molecular construction. Over the last decade, the case of methylenecyclopropane derivatives applied to synthetic transformations has brought about mounting interest in the scientific world. The attractive feature of these compounds is their surprising stability, accompanied by a high level of strain, conferring on them an otherwise unattainable chemical reactivity.

A perception of the stability of these compounds is provided by the amino acids hypoglycine (**1**)[1] and methylenecyclopropylglycine (**2**)[2] (Chart 1), natural

Chart 1



1 **2** **3**

compounds that have been isolated, the former from the unripe fruit of the ackee tree *Blighia sapida*, and the latter from the kernels of litchi fruits. Both compounds display powerful biological activity: **1** is responsible for Jamaican vomiting sickness, while **2** causes hypoglycemia in mice and fasted rats.[3−5] The parent methylenecyclopropane (**3**),[6] a stable volatile olefin (bp 11 °C), can be stored in a sealed tube for several years without decomposition, and it is also commercially available (Fluka, Merck). On the other

† Abbreviations: MCP, methylenecyclopropane; ACP, alkylidenecyclopropane; BCP, bicyclopropylidene; TMM, trimethylenemethane.

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Alberto Brandi was born on January 21, 1951, in Firenze, Italy. He received his Doctor degree in 1975 at the University of Firenze under the supervision of Professor Francesco De Sarlo. From September 1978 to October 1987 he served as Ricercatore Universitario at the University of Firenze. From September 1982 to January 1984 he worked as a postdoctoral fellow with Professor Barry M. Trost at the University of Wisconsin—Madison. In 1987 he was appointed Professore Associato at the University of Basilicata. In 1990 he returned to the University of Firenze where he was appointed as Professore Ordinario (Full Professor) in 1994. His current research interests include the use of 1,3-dipolar cycloadditions of strained molecules and thermal rearrangements for the synthesis of alkaloids and *N*-bridgehead aza heterocycles, and asymmetric synthesis of compounds of biological interest as glycosidase inhibitors, peptidomimetics, and DNA cleaving agents.

Andrea Goti was born in Firenze, Italy, in 1957. He studied at the University of Firenze, where he earned his Doctor degree in Chemistry in 1982, under the supervision of Professor F. De Sarlo. He was a C.N.R. 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). Since 1985 he has been appointed at the Consiglio Nazionale delle Ricerche, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni (CSCEA) in Firenze, where he is currently a Researcher. Since 1995–96 he has been "Professore a Contratto" in Organic Chemistry at the University of Firenze. His current research projects focus on stereoselective organic synthesis based on 1,3-dipolar cycloaddition chemistry, synthesis of biologically active natural and nonnatural products, new oxidation methods, and synthetic applications of organotransition metal complexes.

hand, the reactivity of these compounds is remarkable, such as in cycloaddition reactions and "trimethylenemethane" chemistry, which have recently been extensively reviewed.[7,8]

The growing interest in the chemistry of these compounds has in its turn stimulated the development of alternative approaches to their skeleton, aimed at selectively introducing structural and chemical diversification. These synthetic efforts have been only partially reviewed in the past,[8−10] and a more updated and comprehensive analysis of all the synthetic methods is highly appropriate.

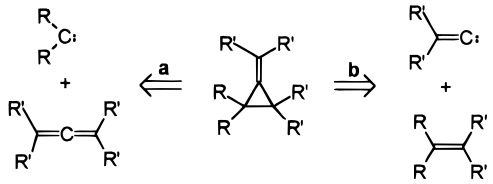
This review intends to collect systematically the widespread knowledge regarding synthetic methods for this class of compounds, focusing particularly on the most recent achievements in this field. The emphasis will be more on the synthetic side, rather than on the mechanistic one, in order to furnish the synthetic organic chemists planning to use these reactive tools with a full picture of the whole body of the materials available nowadays. The material has been organized so as to differentiate methods using the formation of the cyclopropane ring from methods using an already formed cyclopropane ring. Reaction processes are reported, therein, disregarding the nature of the substrate. A chapter has been dedicated to the growing chemistry of optically active methylenecyclopropane derivatives. The review, including addenda, covers the literature up to the most part of 1997.

II. Formation of the Cyclopropane Ring

A. Additions

Among addition reactions, carbene (or carbenoid) addition to unsaturated compounds is undoubtedly the most useful preparative way. It is one of the first general methods thoroughly applied for the assembly of the alkylidenecyclopropane moiety, with reports appearing since the early 1960s. Two variants can be employed: (a) addition of generated carbenes to allenes, or (b) addition of alkylidenecarbenes to olefins (Scheme 1).

Scheme 1

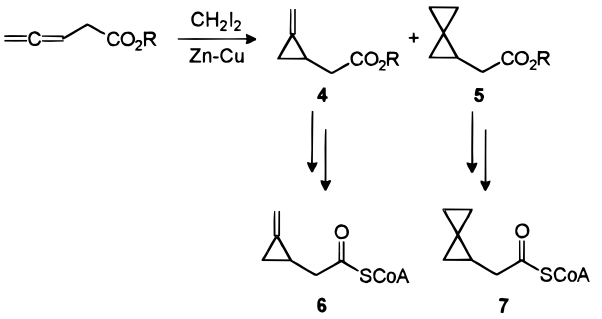


1. Carbene Additions to Allenes

The addition of variously substituted carbenes or carbenoid systems, generated in several different ways, to cumulenes has been extensively applied to the synthesis of alkylidenecyclopropanes.

MCPs can be accessed by addition of the simple unsubstituted carbene to allenes. Shortly after the discovery and application to simple olefins of the Simmons−Smith method, the first of these syntheses[11] has been accomplished on methyl 3,4-pentadienoate to gain a mixture of **4** and **5** (R = Me) (Scheme 2), with the relative amount of the spiro derivative increasing with the excess of the methylenation reagent. The same synthesis from the corresponding ethyl allenylacetate has been repeated recently, on the way to the synthesis of racemic methylenecyclopropaneacetic acid (MCPA, **4** (R = H)) and spiropentaneacetic acid (SPA, **5** (R = H)) and their coenzyme A derivatives **6** and **7** (Scheme 2).[12] All these compounds displayed strong inhibitory effects on fatty acid metabolism, MCPA-CoA (**6**) and

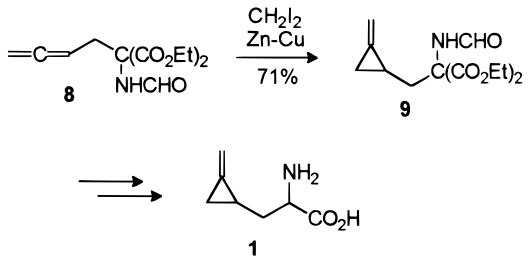
Scheme 2



SPA-CoA (**7**), presumably being the bioactive species. The (*R*)-MCPA-CoA enantiomer is the metabolite of (+)-hypoglycine A (**1**) responsible for Jamaican vomiting sickness by inactivating acyl-CoA dehydrogenases.[3−5]

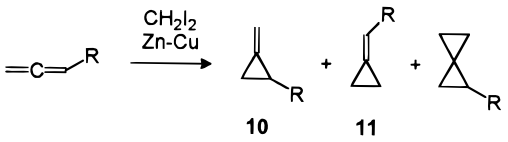
The Simmons−Smith reagent has also been successfully used for a direct synthesis of racemic hypoglycine A (Scheme 3).[13]

Scheme 3



The formation of spiropentane derivatives is general and cannot normally be avoided, even by using a slight excess of the Simmons−Smith reagent. While in all the previously reported examples cyclopropanation at the substituted double bond prevailed to afford MCPs, simple monosubstituted allenes have been reported to give almost equal amounts of MCP and ACP derivatives **10** and **11** in low yields, the formation of spiro compounds always being a major drawback (Scheme 4).[14]

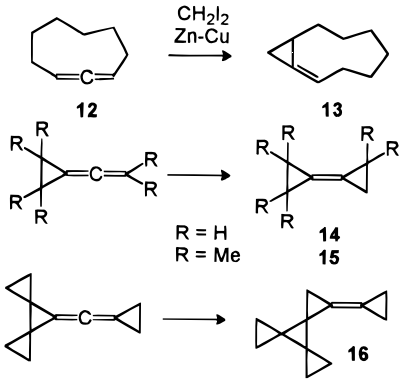
Scheme 4



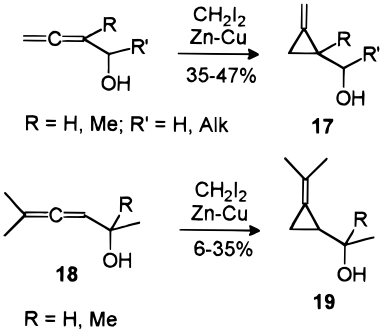
The Simmons−Smith reagent also permitted monocyclopropanation of 1,2-cyclononadiene (**12**) to the ACP **13**[15] and of vinylidenecyclopropane and higher alkenylidenecyclopropanes to BCP derivatives **14**−**16**[16] (Scheme 5).

Monocyclopropanation of α-allenic alcohols by the Simmons−Smith reagent proceeded regiospecifically at the double bond close to the hydroxy group (Scheme 6), even in the case of 1,1,3-trisubstituted allenes **18**.[17,18] This finding is in agreement with the observed increase of rate of the Simmons−Smith reaction assisted by vicinal hydroxy groups. However, double cyclopropanation giving spiropentane carbinols usually represents the main process and

Scheme 5



Scheme 6

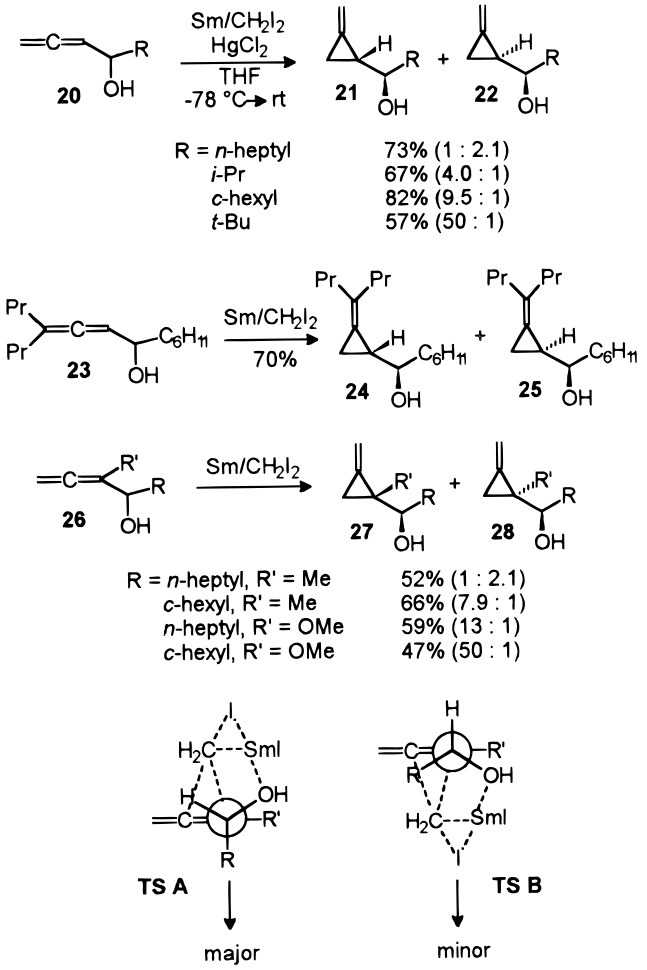


cannot be avoided even at low conversions, so that methylenecyclopropane carbinols are only obtained in moderate yields and with scarce diastereoselectivity (1:1 to 4:1).

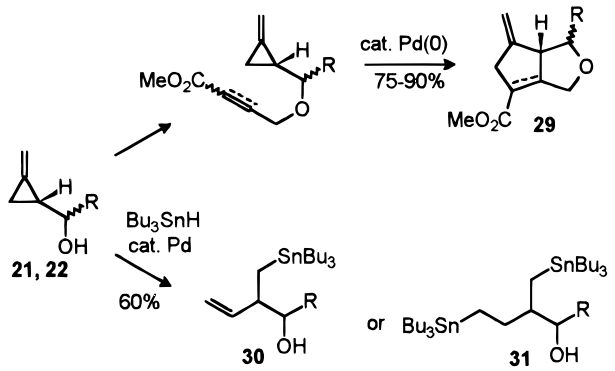
In order to gain selectivity and make the process synthetically useful, Lautens and co-workers have recently explored a large number of cyclopropanation procedures by methylene carbenoids to α-allenic alcohols. The Molander cyclopropanation procedure employing Sm and methylene iodide (or CH_2ClI) in THF, proved to be highly selective, providing ACP alcohols with the exclusion of double cyclopropanation (Scheme 7),[19,20] as expected on the basis of the need of a free allylic hydroxyl moiety for effectiveness of the method. A detailed study of the diastereoselectivity of the cyclopropanation reaction has been carried out using a variation of the substituents at both ends of the allene and especially at the hydroxyl-bearing carbon atom. Useful selectivities (up to 50:1) are obtained with bulky alkyl substituents at this carbon and the results have been interpreted on the basis of a preferred "outside Houk model" **TS A** (Scheme 7). The same cyclopropanation method has also been used to obtain enantiomerically enriched methylenecyclopropanic alcohols (see section V.B)[19] and deuterated methylenecyclopropanes by replacing the methylenation reagent with CD_2I_2.[21]

MCPs **21** and **22** have been utilized for the synthesis of bicyclic cyclopentanotetrahydrofurans **29** by transition metal-catalyzed intramolecular [3 + 2] cycloaddition reactions[20−23] and for the synthesis of homoallylic alcohols **30** or bis(stannylated) compounds **31** by ring-opening hydrostannylation with different catalysts[24] (Scheme 8). The replacement of $HgCl_2$ in this Sm-mediated cyclopropanation procedure by different activating agents has recently been

Scheme 7



Scheme 8



studied. A semicatalytic amount of chlorosilanes (TMSCl, TBDMSCl) has been found effective in the addition and, in some cases, it has showed a marked influence on stereoselectivity.[25] Titanium isopropoxide, albeit less effective in activating the metal, gave an even higher selectivity.[25]

The methylene carbene for cyclopropanation of allenes has also been generated by decomposition of diazomethane. Photochemical decomposition in the presence of allene gave MCP itself in a 60% yield without the formation of spiropentane or insertion products.[26] More recently, Cu_2Cl_2-catalyzed decomposition of diazomethane served for the cyclopropanation of two bis-allenic compounds **32**, which resulted in the formation of all possible mono- and

Scheme 9

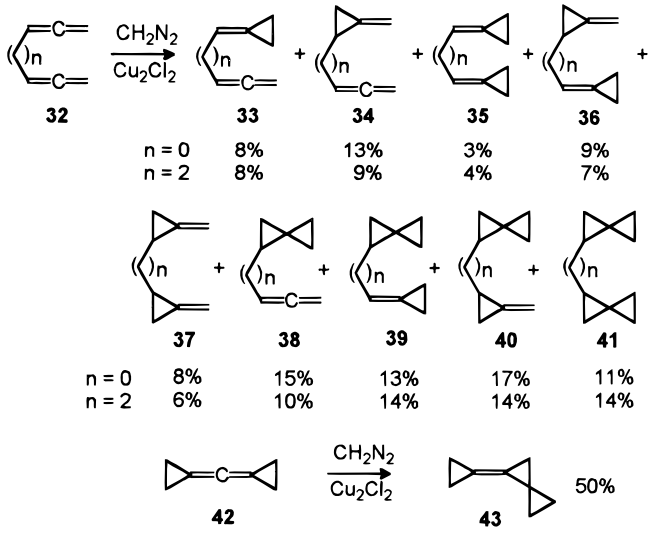
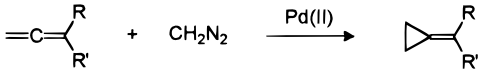


Table 1. Palladium-Catalyzed Methylenation of Allenes



entry	R	R′	yield (%)	ref
1	H	Bu	67	30
2	H	Ph	35	30
3	H	CH_2CH_2OH	not reported	32
4	H	CH_2CH_2Br	70	32
5	H	CH_2CH_2OAc	90	32
6	H	CH_2CH_2OTs	78	32
7		$(CH_2)_2$	rearranges	31
8		$(CH_2)_3$	70	30
9		**12** → **13**	70	30

polycyclopropanated derivatives (Scheme 9).[27,28] In the case of biallenyl ($n = 0$), formation of both the possible diastereoisomers in about equimolar amounts has been reported for derivatives **37**, **40**, and **41**.[27] In contrast, the same reaction on dicyclopropylidenmethane **42** furnished the monoadduct **43** in 50% yield.[29]

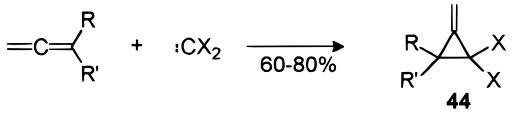
Better results in terms of selectivity have been achieved by reacting diazomethane and allene derivatives in the presence of Pd(II) catalysts. Under these conditions the reactivity could be modulated in order to obtain good yields of ACPs, with only a limited formation of double addition products (Table 1).[30−32] The addition occurs at the less substituted terminus. Formation of bicyclopropylidene from vinylidenecyclopropane (entry 7) is only postulated as a reactive intermediate complex, which gives ring-opened products under the reaction conditions.[31]

The cyclopropanation of allenes by monohalo- and dihalocarbenes to give the corresponding halogen-substituted ACPs is the most studied reaction of this type and has been applied for a long time. It usually gives good yields of products and is not affected by double cyclopropanation of allenes. Indeed, the formation of spiropentanes has been reported only in a few cases and at a minor extent.[33−36] Thus, this reaction has also been employed as an alternative to the use of methylene carbenoids, since the bromides

can be effectively reduced by Bu_3SnH[17,37] or Na/MeOH[38,39] (see section IV.C).

The cyclopropanation of allene itself gives poor results,[40−42] but the addition of dichloro- or dibromocarbene generated in several ways (base-induced elimination from CHX_3 or trihaloacetate, thermal decomposition of phenyl(trihalomethyl)mercury or trichloromethyltrifluorosilane) to 1,1-disubstituted allenes afforded MCPs **44** in high yields (Scheme 10).[17,36,37,39,43−50]

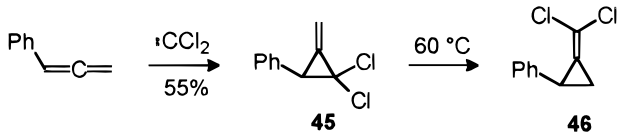
Scheme 10



X = Cl, Br; R, R' = Alk, Ar

The addition occurs selectively at the substituted double bond, providing that the reaction is carried out at moderate temperatures. At higher temperatures, different ACPs can be detected, as a result of a rearrangement via TMM species (see section IV.E). The temperatures required for this transformation are usually high, but they depend on the substituents. Aryl substituents facilitate the isomerization and easily rearrange under the reaction conditions.[47] For example, 1,1-dichloro-2-methylene-3-phenylcyclopropane (**45**) derived by addition of dichlorocarbene to phenylallene rearranges to **46** at 60 °C (Scheme 11).[51]

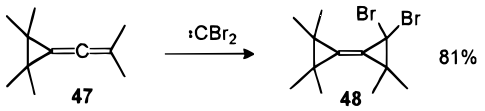
Scheme 11



Contrary to phenylallene, alkyl monosubstituted allenes gave mixtures of cyclopropanation products at the substituted and unsubstituted double bonds, with the former prevailing (from 2:1 to 3:1).[35b,52]

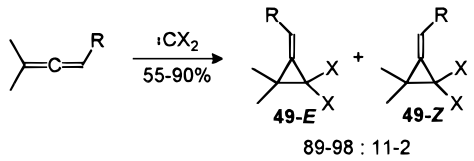
Symmetrically 1,3-substituted and tetrasubstituted allenes gave monocyclopropanated products in 65−85% yields.[34,37,53,54] With (isopropylidenemethylene)-cyclopropane **47**, dibromocarbene gave exclusively bicyclopropylidene **48** in high yield (Scheme 12).[50]

Scheme 12



Trialkyl-substituted allenes gave cyclopropanation exclusively at the more substituted double bond, affording two diastereomeric ACPs (Scheme 13).[37,43,46,52] The isomer **49-*E*** is largely preferred, and its amount increased with the dimension of R, as a result of steric hindrance presented by this substituent on the approaching carbene.[52] Contrary to cyclopropanation by methylene carbenoids, dibromocarbene addition to 1,1-dimethyl-3-(1-hydroxy)ethylallene occurred, as expected, only at the more substituted double bond.[38] An analogous selectivity in the formation of *E* isomer has been observed in the addition of dibromocarbene to isopropyltrimethylallene, which anyway occurred at both double bonds.[55] Conversely, triphenylallene gave with dichlorocarbene the product of monoaddition at the less substituted double bond in 40−57% yield.[36,56]

Scheme 13



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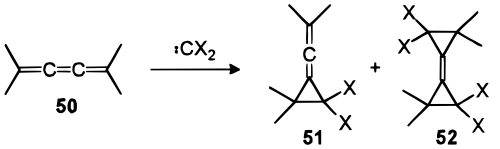
X = Cl, Br; R = Me, Et, *i*-Pr

When reacted with tetramethylbutatriene **50**, dichlorocarbene produced alkenylidenecyclopropane **51** and bicyclopropylidene **52** (X = Cl) in 65 and 16% yields, respectively, while dibromocarbene gave a complex mixture from which the product of double cyclopropanation was isolated (Scheme 14).[34]

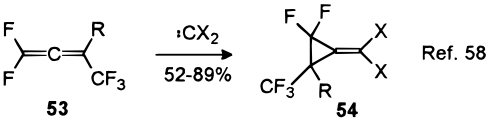
Scheme 14



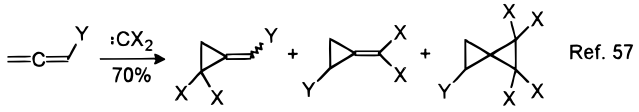
X = Cl, Br

An alkylidenecyclopropane rearrangement occurring in uncommonly mild conditions must be invoked in order to rationalize the outcome of the additions of dichloro- and difluorocarbene (generated by thermal decomposition of perfluorocyclopropane or hexafluoropropylene oxide) to allene, fluoroallene, and perfluoroallenes (Scheme 15).[57−58] Difluorocarbene

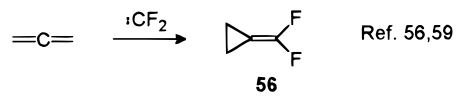
Scheme 15



X = Cl, F; R = CF_3, C_3F_7



X = F, Y = H
X = Cl, Y = F



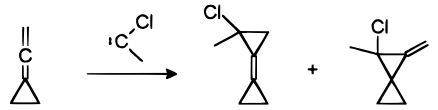
is not expected to react at the perfluoroalkyl-substituted end of the allene **53**, which is inactivated for both steric and electronic reasons. On the other hand, ACPs **54** (X = Cl) and **56** cannot be the primary products of carbene addition and the formation of spiro compounds of type **57** cannot be explained as well. It is likely, therefore, that additions occur at the fluorine-substituted end of **53** and at the unsubstituted terminus of fluoroallene, followed by re-

arrangement of adducts to the final products. Support of this conclusion comes from the observation that difluorosubstitution in 2,2-difluoromethylenecyclopropane, obtained analogously by the addition of difluorocarbene to allene, lowers considerably the activation energy for the rearrangement.[57a,59]

A similar effect is brought about by substitution with sulfides: 2-(thiophenyl)isopropylidenecyclopropane was obtained as the only product after heating at 120 °C the addition product of (phenylthio)carbene to 1,1-dimethylallene. The alkylidenecyclopropyl sulfide was oxidized to the corresponding sulfone and both compounds have been employed in thiyl-catalyzed [3 + 2] cycloaddition reactions.[60,61]

Additions of chloro- and bromocarbene to allene[62,63] and of methylchlorocarbene to allene[64] and 1,1-dimethylallene[48] have been performed and always gave methylenecyclopropanes in low yields. 2-Chloro- and 2-bromomethylenecyclopropane have been used as intermediates for the synthesis of methylenecyclopropene.[62,63] Methylchlorocarbene has also been added to vinylidenecyclopropane: in this case both the possible monocyclopropanation products were formed, with prevalence of an addition to the unsubstituted terminus (Scheme 16).[64] The addition

Scheme 16



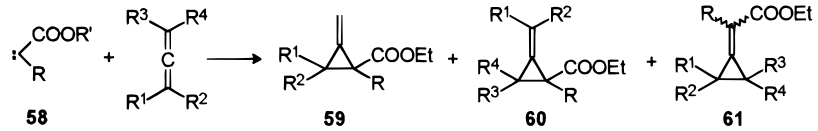
of the generated fluoro(dichlorofluoromethyl)carbene to allene furnished the monoadduct in 98% yield.[65]

The outcome of the addition of carbenes **58** substituted with ester groups to unsymmetrically substituted allenes is strongly dependent on the mode of generation of the carbene from the corresponding diazo compounds (Table 2).

Mixtures of regioisomers are usually obtained when the carbenes are generated by photolysis (with or without the presence of a sensitizer) or by copper-catalyzed decomposition.[52,68] Products of methylenecyclopropane rearrangement (see section IV.E) have also been identified in some instances.[68] Phenyl(ethoxycarbonyl)- and methyl(ethoxycarbonyl)carbene generated by irradiation gave exclusively the product of addition at the less substituted double bond of 1,1-dimethylallene, but the other regioisomer prevailed at low temperature.[68] Also, (ethoxycarbonyl)carbene and bis(methoxycarbonyl)carbene gave exclusively products **60** ($R^3 = R^4 = H$) by addition to 1,1-disubstituted allenes, when thermally generated at 100 °C under rhodium acetate catalysis.[69,71] These findings have been discussed on the basis of a balance of kinetic and thermodynamic effects in the methylenecyclopropane rearrangements, with addition to the more substituted position being kinetically favored.[68,71] Very recently, phenyl(methoxycarbonyl)carbene generated in several diverse conditions has been reacted with enantioenriched and racemic (in presence of a chiral rhodium catalyst) 1,3-dimethylallene.[72]

The 9-fluorenylcarbene generated from the corresponding diazo derivative has been reacted with allene to give the desired MCP adducts in poor yields.[73] The addition reactions of arylcarbenes to 1,1-dimethylallene have been extensively studied by Creary during the last two decades.[68,74] The regiochemistry of the addition contrasts with the behavior

Table 2. Cyclopropanation of Allenes by Ester-Substituted Carbenes

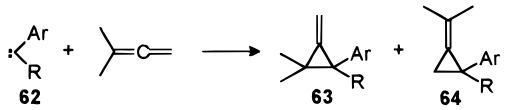


58 59 60 61

							yield (%)			
entry	R	R′	R^1	R^2	R^3	R^4	**59**	**60**	**61**	ref
1	H	Me	H	H	H	H	47			66
2	H	Et	H	H	H	H	33			66
3	H	Bu	H	H	H	H	18			66
4	H	Et	Pr	H	H	H	2			52
5	H	Et	Bu	H	H	H	8	4		52
6	H	Me	Ph	H	H	H	61[a]			67
7	H	Et	Me	Me	H	H	33	1.5		52
8	H	Et	Me	Me	H	H	13	10.5	1.5[a]	68
9	H	Et	Me	Me	H	H	22.5	25	3.5[a]	68
10	H	Et	Me	Me	H	H	6.5	21.5	12[a]	68
11	H	Et	Me	Me	H	H		38		69
12	H	Et		$(CH_2)_2$	H	H		*b*		70
13	H	Et	Me	Me	Me	H	26	2[a]		52
14	H	Et	Me	Me	Me	Me	37−40			52,53
15	Me	Et	Me	Me	H	H		38		68
16	Ph	Et	Me	Me	H	H		92		68
17	CO_2Me	Me	H	$SiMe_3$	H	H		33[c]		71
18	CO_2Me	Me	Me	Me	H	H		85		69
19	CO_2Me	Me	Me	$SiMe_3$	H	H		79[c]		71
20	CO_2Me	Me	Bu	$SiMe_3$	H	H		80[c]		71

[a] Mixture of diastereoisomers. [b] The only product (yield not reported). [c] *E* isomer only.

Scheme 17



R = H, Ar = Ph, *p*-XC_6H_4 (X = Me, OMe, Cl, F, Br, CF_3, CO_2Me, CN, NO_2, SMe, $SiMe_3$, *t*-Bu, $PO(OEt)_2$, SOMe, SO_2Me, $PS(OEt)_2$, NMe_2, $SnMe_3$, $CH=CH_2$, Ph, $C(CH_3)=CH_2$, *c*-C_3H_5, CH_2SiMe_3, CO_2Et), *m*-XC_6H_4 (X = Cl, OMe, F, Me, CF_3, CN, NO_2, $SiMe_3$, $PO(OEt)_2$, SMe, SOMe, SO_2Me, $PS(OEt)_2$), 1-naphthyl, 3,5-$Cl_2C_6H_3$, 3,5-$Me_2C_6H_3$, 4-pyridyl, 3-pyridyl, 2,6-$Me_2C_6H_3$, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-pyrenyl

R = CO_2Et, Ar = Ph, *p*-XC_6H_4 (X = Me, F, OMe, SMe, CO_2Et, SOMe, SO_2Me, *c*-C_3H_5, CH_2SiMe_3, CF_3)

R = Ar = Ph

R = $PO(OEt)_2$, Ar = Ph

R = Me, Ar = Ph, *p*-$CF_3C_6H_4$

R = OMe, Ar = Ph, *p*-$CF_3C_6H_4$

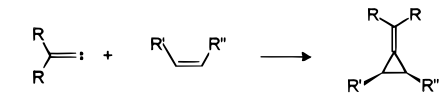
R = CF_3, Ar = Ph, *p*-XC_6H_4 (X = CO_2Et, SO_2Me, SMe, OMe, NMe_2)

R = OMe, Ar = *m*-$CF_3C_6H_4$

of the ester-substituted carbenes. Indeed, a general preference for cyclopropanation at the more substituted double bond is observed with arylcarbenes **62** (Scheme 17). However, the regiochemistry is strongly dependent on the mode of generation of the carbene species and on the substituents at the aromatic ring. The arylcarbene species have been generated by $E1_{CB}$ reaction of the corresponding arenemethyl chlorides (or bromides) and by photolytic decomposition of the parent diazo compound, either directly or benzophenone sensitized, or, in a few instances, copper catalyzed. The additions usually give a mixture of isomers **63** and **64** in fair to good yields. The results have shown that singlet carbenes add preferentially to the more substituted bond of 1,1-dimethylallene to give MCPs **63**, while triplet carbenes add with lower regioselectivity, often furnishing predominantly the thermodynamically preferred ACPs **64**, probably via an intermediate trimethylenemethane species. Singlet monoarylcarbenes add to 1,1-dimethylallene with a selectivity which increases with the electron-donor ability of the substituent, which implies that such substituents stabilize the singlet state. The regiochemical results suggested also that many carbenes reacted in the singlet state even when the triplet state is the initially generated one. On the basis of these generalizations, the regiochemistry of this reaction has been proposed as a probe for determination of carbene multiplicity.[74a]

A Fischer-type carbene complex, i.e., benzylidenepentacarbonyl tungsten, reacted with 1,1-dimethyl- and phenylallene to form in ~35% yield the corresponding methylenecyclopropane pentacarbonyl tungsten complexes, which gave quantitatively the free MCPs by treatment with Et_4NBr.[75] The addition occurred exclusively at the substituted double bond and with phenylallene gave, remarkably, only *cis*-2,3-diphenylmethylenecyclopropane.

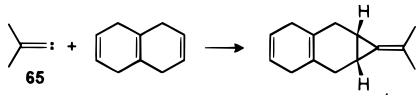
Table 3. Cyclopropanation of Mono- and Disubstituted Alkenes by Symmetric Alkylidenecarbenes



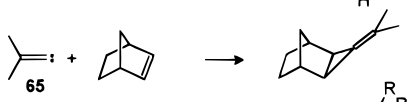
R = Me, Et, CH_2Ph, $(CH_2)_5$;
R' = CO*t*-Bu, Ph, C_6H_4*p*-Me, C_6H_4*p*-Cl, C_6H_4*p*-Br, *n*-C_5H_{11}, *n*-C_6H_{13}, OEt, OMe, OPh, OCOMe, Et, $CH=CH_2$, CH_2SiMe_3, $SiMe_3$;
R" = H — Ref. 78-90

R = Me, Et, $(CH_2)_5$, $(CH_2)_4$, $(CH_2)_2CH(t\text{-Bu})(CH_2)_2$, *c*-Pr, Cl, F, $CH_2N(Ts)CH_2$, $CH_2N(Bn)CH_2$;
R'-R" = $(CH_2)_n$ (n = 2-6), $O(CH_2)_3$, $CH_2CH=CH$, $CH_2CH=CHCH_2$
R = R' = R" = Me — Ref. 15,77,78,80, 81,83,85-88,91-98

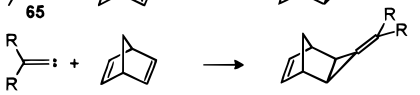
R = Me, $(CH_2)_5$; R' = Me; R" = *i*-Pr — Ref. 80a,89,95b,99

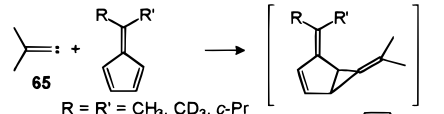


Ref. 80a

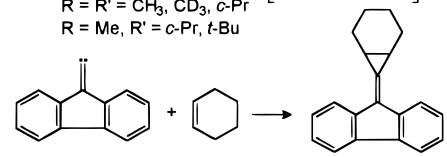


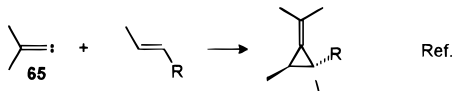
Ref. 78,85


R = Me, $(CH_2)_5$
Ref. 94,100

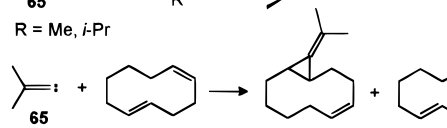


R = R' = CH_3, CD_3, *c*-Pr
R = Me, R' = *c*-Pr, *t*-Bu
Ref. 101,102,77

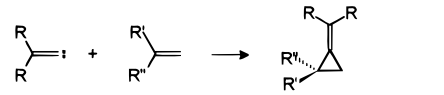

Ref. 103



R = Me, *i*-Pr
Ref. 78,80a,85,89,99



Ref. 76

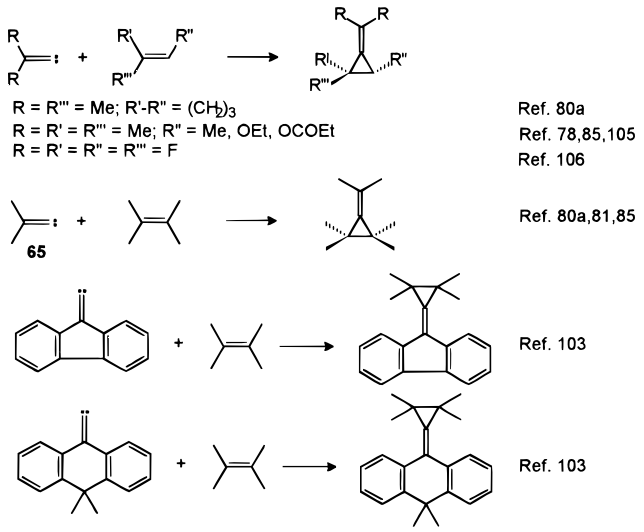

R = Me, Et; R' = Me, Ph; R" = Me, Ph
Ref. 78,83,85,104

2. Alkylidenecarbene Additions to Alkenes

Investigations on the reaction of alkylidenecarbenes with alkenes have been carried out for more than 30 years. Most of the work on the subject has been focused on mechanistic and theoretical aspects, e.g., to determine the intermediacy of an alkylidenecarbene species and its nature (carbenoid or carbenic, multiplicity, etc.),[76] rather than on a synthetic perspective. However, many procedures able to furnish good yields of a variety of rather unusual ACPs have been developed, so that this method can be synthetically very useful (Tables 3−7).

When symmetrically disubstituted alkylidenecarbenes (Tables 3−5) and/or 1,2-symmetrically disubstituted alkenes (Table 6) are employed, a single

Table 4. Cyclopropanation of Tri- and Tetrasubstituted Alkenes by Symmetric Alkylidenecarbenes



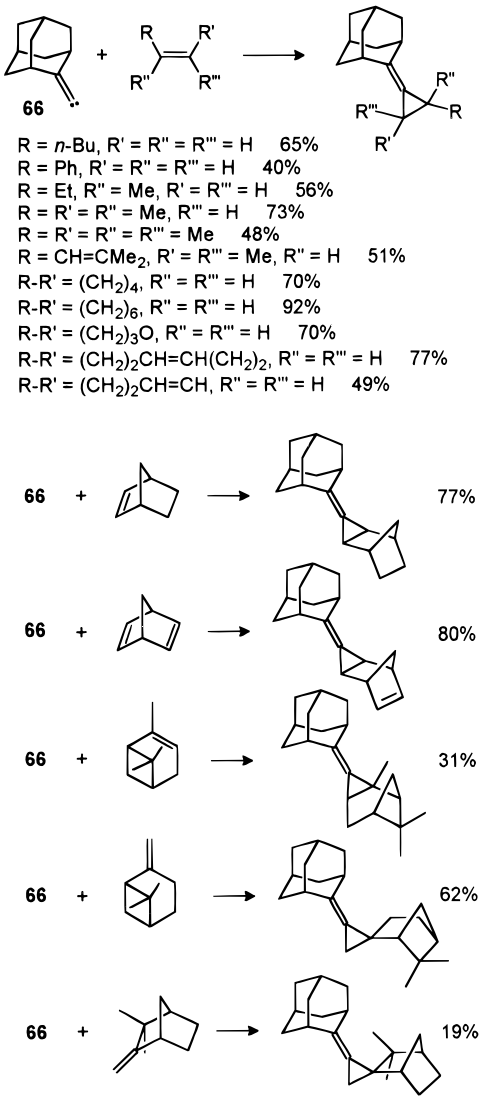
monoadduct was obtained in the cycloaddition, with the stereochemistry at the alkene double bond preserved. Only recently, in a single case, an ACP derived by addition of a second alkylidenecarbene-carbene equivalent to the primary adduct has been observed.[77] The addition of unsymmetric alkylidenecarbenes to alkenes not symmetrical with respect to the double bond gave mixtures of both the possible stereoisomers, in proportions primarily controlled by steric factors (Table 7).

The alkylidenecarbene species have been generated by a great variety of methods, most of which have already been reviewed in detail.[76] The majority of these methods consists of 1,1-eliminations from substituted alkenes, either base, thermally, or photochemically induced, depending on the nature of the starting substrate. Alkenyl halides,[93] 1,1-dihalides,[82,78,88] triflates,[83,76] 1-trimethylsilyl-1-halides,[87] 1-trimethylsilyl-1-triflates,[76,86] phenyliodonium salts,[89] and triphenylbismuthonium salts[90] have been used as suitable starting materials for the base-induced generation of dialkyl-substituted alkylidene carbenes. Simple haloalkenes usually fail to furnish convenient yields of ACPs;[82] however, peculiar substrates, e.g., (bromomethylene)adamantane (Table 5),[107] were able to cycloadd olefins very efficiently. With all the other starting materials, methods able to give fair to almost quantitative yields have been developed.

Another broad family of substrates are able to produce the desired alkylidenecarbene species by decomposition of intermediate diazoalkenes or vinyldiazonium ions.[76] *N*-Nitrosooxazolidones,[80a,94a] *N*-nitroso-*N*-acetyl-1,2-amino alcohols,[94a,80b] (tosylazo)-alkenes[76,86] and peculiar, stable vinylamines[103] have served this scope. A method for the direct production of alkylidenecarbenes from the corresponding ketones by treatment with dialkyl diazomethylphosphonate (DAMP) and bases with intervention of intermediate diazoalkenes has also been developed,[95a,b,111] and has found recently new synthetic applications.[97,109,98]

Other less general methods are also available. Isopropylidenecarbene **65**, generated by thermolysis

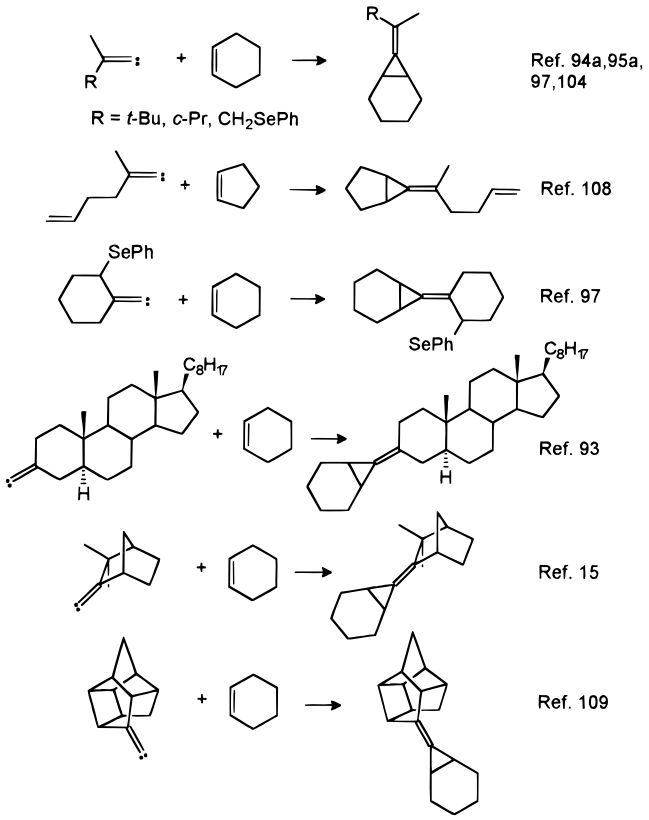
Table 5. Cyclopropanation of Alkenes by Adamantylidenecarbene[107]



of bis(1-bromo-2-methylpropenyl)mercury in the presence of diphenylmercury, gave good yields of adducts to alkenes.[81] 2,2-Diphenyl-1-isopropylidenecyclopropane and 9-isopropylidenebicyclo[6.1.0]nonane decompose photolytically to give dimethylvinylidenecarbene, which has been trapped with alkenes.[112,95c] Dichloro- and difluorovinylidene carbenes have also been generated photochemically by decomposition of [(perchlorovinyl)phenyl]mercury[91] and trifluoroethylene[106] or difluoropropadienone,[96] respectively, and trapped with alkenes.

The intramolecular version of alkylidenecarbene trapping by alkenes has also been addressed, mainly due to the pioneering work of Köbrich,[113] later studied in deeper mechanistic details by Berson[114,108] (Table 8). The generated bicyclic systems, having a bridgehead double bond, have been found to be stable enough to be characterized when the larger ring is a six- or seven-membered one. In contrast, compounds **67** and **68** were not stable and gave dimers, which formation has been proposed to occur via TMM species.[113a,108,114b] Intramolecular trapping of the proposed intermediate **69**, deriving from reaction of molecular carbon with cyclooctatetraene, to give the

Table 6. Cyclopropanation of Symmetric Alkenes by Unsymmetric Alkylidenecarbenes



unstable species **70** on the way of naphthalene formation, has been invoked in order to rationalize the observed labeling pattern in the final product when carbon vapor enriched in ^{13}C was used.[115]

3. Alkylidenecarbene Additions to Cumulenes

Alkylidenecarbenes have been added to allenes to afford, albeit generally in low yields, interesting 1,2-dialkylidenecyclopropanes (Scheme 18).[116,80a,104] Tetramethylbutatriene **71** has also been used as carbenophile: a mixture of four out of the possible ACP mono- **72**, **73** and diadducts **74**, **75** was formed,

Scheme 18

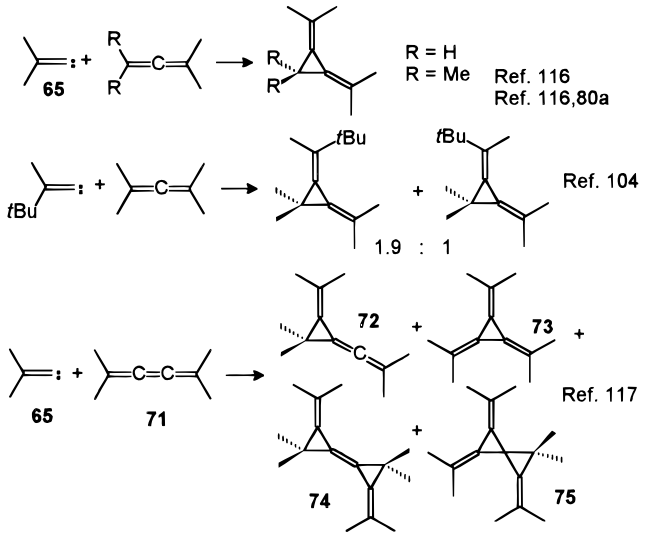
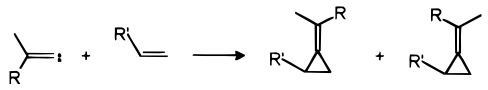
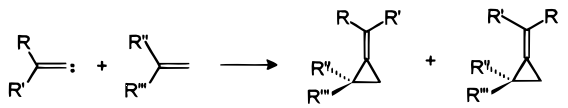


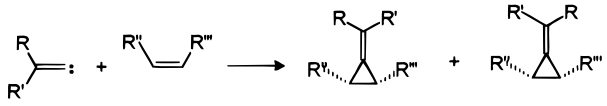
Table 7. Cyclopropanation of Unsymmetric Alkenes by Unsymmetric Alkylidenecarbenes



entry	R	R′	yield (%)	ratio	ref
1	Et	*t*-Bu	48	2	55
2	*i*-Pr	*t*-Bu	59	3	55
3	*t*-Bu	*t*-Bu	28	9	55
4	*i*-Pr	Et		2.1	110
5	*t*-Bu	Et		4.3	110
6	*i*-Pr	OEt		3	110
7	*t*-Bu	OEt		11.5	110
8	*i*-Pr	Ph		3.9	110
9	*t*-Bu	Ph		250	110



entry	R	R′	R″	R‴	yield (%)	ratio	ref
10	Me	Et	Me	Me	67−74	1.3	83,55
11	Me	*i*-Pr	Me	Me	74	1.5	55
12	Me	*t*-Bu	Me	Me	15	2	55
13	Me	*t*-Bu	Ph	Ph	14	0:100	104
14	$(CH_2)_4CH(SePh)$		$(CH_2)_5$		31	3.3	97



entry	R	R′	R″−R‴	yield (%)	ratio	ref
15	Me	$(CH_2)_2CH{=}CH_2$	$CH{=}CHCH_2$			108
16	$(CH_2)_4CH(SePh)$		$O(CH_2)_3$	99	2	97

among which the interesting skeleton of the [3]radialene **73** emerged (Scheme 18).[117,118] 1-Alkylidene-2-vinylidenecyclopropanes, such as **72**, have also been obtained by addition of vinylidenecarbenes to allenes.[116,82]

Aryl-substituted [3]radialenes were obtained in poor to moderate yields by cyclooligomerization of copper or nickel alkylidenecarbenoids.[119,118]

4. Carbene Additions to Alkynes

The related isopropylidenecarbene addition to alkynes gave unstable methylenecyclopropenes which could be trapped *in situ* by enophiles (see section IV.B.1) or stabilized as cyclopropenylium ions.[120] However, the reaction with 1-phenylpropyne **76** afforded directly only the dimethylenecyclopropane **77** (Scheme 19),[120] which formation might be explained

Scheme 19

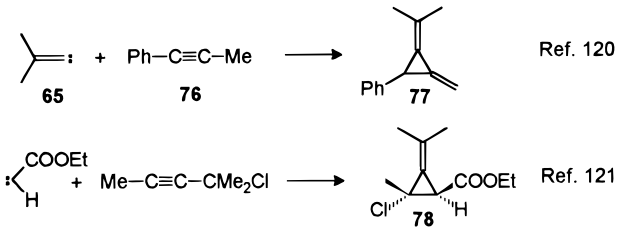
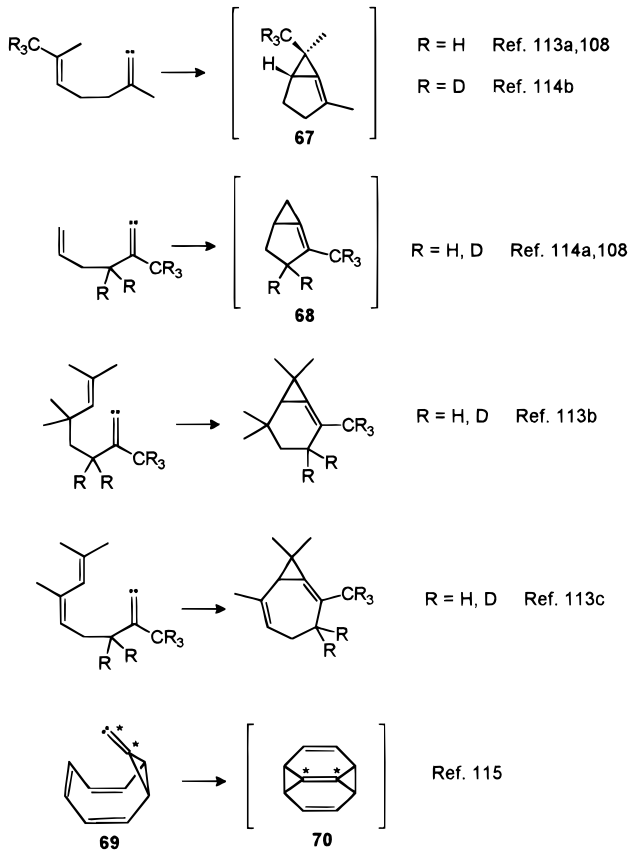


Table 8. Intramolecular Cyclopropanations by Alkylidenecarbenes



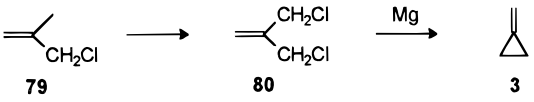
either by addition to phenylallene formed by base-catalyzed isomerization of the alkyne or by isomerization of the intermediate methylenecyclopropene formed after addition to the triple bond. As a matter of fact, the analogous formation of ACP **78** by addition of (ethoxycarbonyl)carbene to 4-chloro-4-methylpent-2-yne (Scheme 19)[121] has been assessed to derive from thermal isomerization of the intermediate cyclopropene by chlorine migration.

B. Eliminations

1. Eliminations of HX, XX, and XY Groups

The first synthesis of MCP **3** has been achieved by dechlorination with magnesium of 3-chloro-2-(chloromethyl)-1-propene (**80**) in THF with a yield of 17%. The starting dichloride was obtained by chlorination of methallyl chloride (**79**) (Scheme 20).[6]

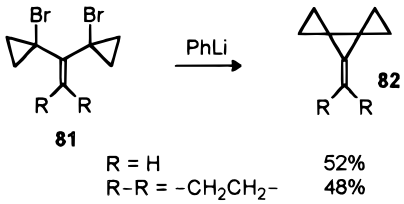
Scheme 20



The yield (30%) and the purity (99%) of **3** was later improved using the same methodology.[122] Methylene- and cyclopropylidenedispiroheptane have been successfully synthesized by this method (Scheme 21).[123,124]

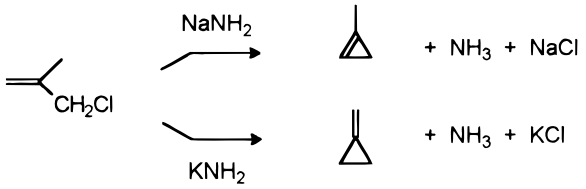
Only later Binger reported a new synthesis of **3** that started directly from methallyl chloride **79** by

Scheme 21



treatment with a strong base. The base counterion plays an important role in the nature of products formed, as $NaNH_2$ gives the cyclopropene derivative, whereas KNH_2 gives MCP (Scheme 22).[125]

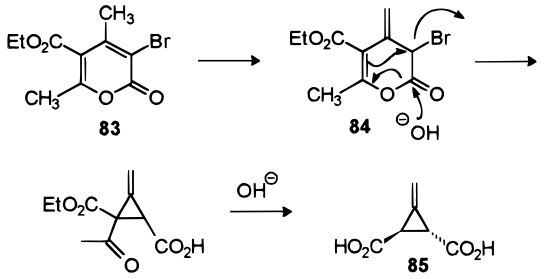
Scheme 22



Caubere has, then, slightly modified the procedure using a complex base system (*t*-BuOK/$NaNH_2$).[126] The synthesis has been also described in detail by Conia and coworkers in *Organic Syntheses*.[127] A chloromethylallyl sulfone gave, by treatment with 2 equiv of BuLi, a dianion which could be alkylated to afford sulfonyl substituted MCPs in 35−55% yield.[128]

The synthesis of the famous Feist's acid **85**, now commercially available, has been achieved by a similar displacement of a particular allyl bromide **84** obtained by bromination of the ethyl ester of isodehydroacetic acid (Scheme 23).[129]

Scheme 23

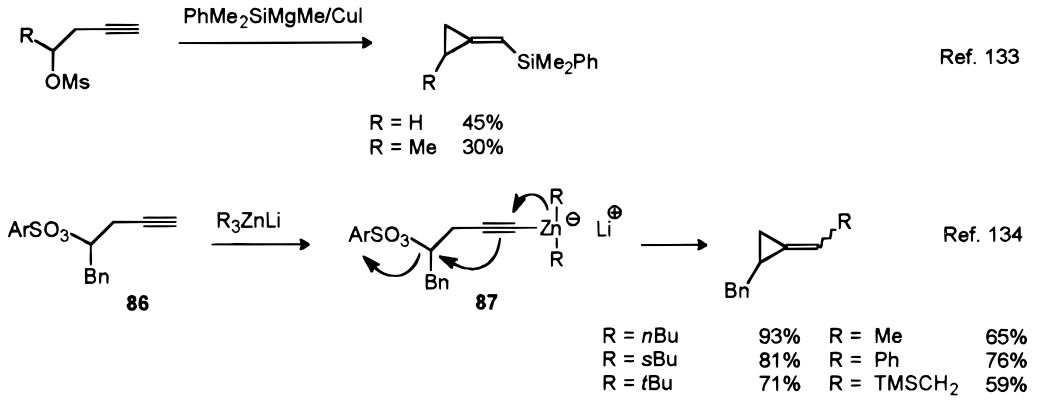


Treatment of bromoalkenes with bases (KO*t*-Bu) is not as effective as the previous treatments with allyl bromides, producing always mixtures of elimination products besides ACPs and MCPs.[15,130]

The double Michael addition of malonate on trichloronitroethylene followed by double HCl elimination produced a functionalized ACP in 34% yield.[131] Lithioalkenes undergo cyclization to ACPs or MCPs with an appropriate leaving group in the homoallylic position.[5d,132] The nucleophilic alkene can be also produced from an alkyne by addition of an organometallic reagent (Scheme 24).[133] With the organozinc-substituted alkynes **87** the cyclization by displacement of an homoallylic sulfonate occurs with concomitant alkylation on the exocyclic double bond (Scheme 24).[134]

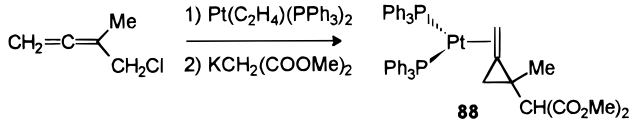
A Pt π-complexed MCP **88** has been isolated by treatment of 4-chloro-3−methylbuta-1,2-diene with

Scheme 24



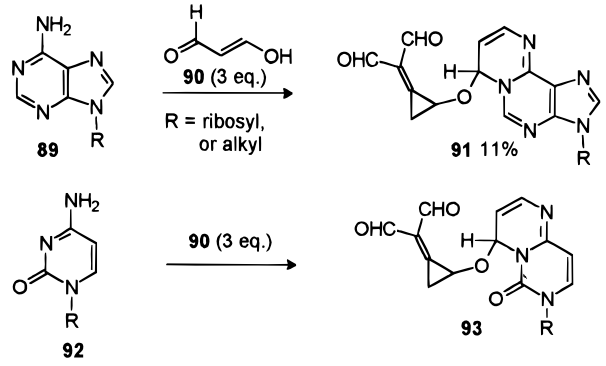
$Pt(C_2H_4)(PPh_3)_2$ followed by nucleophilic addition of potassium malonate (Scheme 25).[135]

Scheme 25



An unique synthesis of intriguing nucleobase substituted bis(formyl)MCPs **91** and **93** was obtained by treatment of nucleosides with excess of malonodialdehyde (**90**). The formation of ACPs occurs by elimination of water to give the final products, deriving from addition of 3 equiv of malonodialdehyde (Scheme 26).[136]

Scheme 26

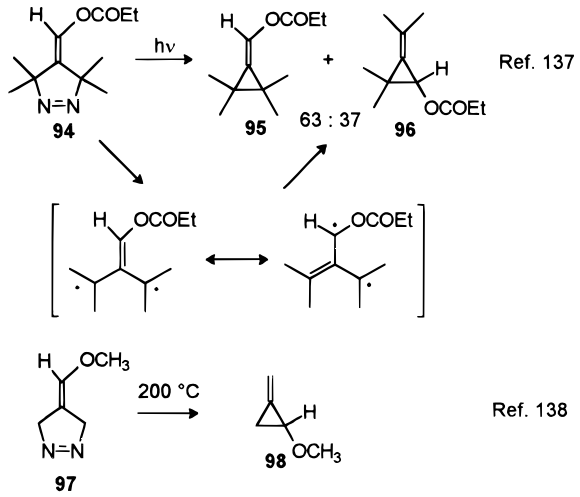


2. Eliminations of N_2 from Pyrazolines

The first synthesis of MCPs and ACPs from pyrazolines by extrusion of N_2 goes back to 1964, when Day synthesized a 3:2 mixture of the propionate esters **95** and **96** by photolysis (Hanovia medium-pressure mercury lamp) of the pyrazoline **94** (Scheme 27).[137] Only shortly later another group showed that thermolysis at 200 °C of (methoxymethylene)pyrazoline **97** furnished exclusively 2-(methoxymethylene)cyclopropane **98** in 72% yield (Scheme 27).[138] The required pyrazolines were generally synthesized by diazoalkane cycloaddition to allenes.

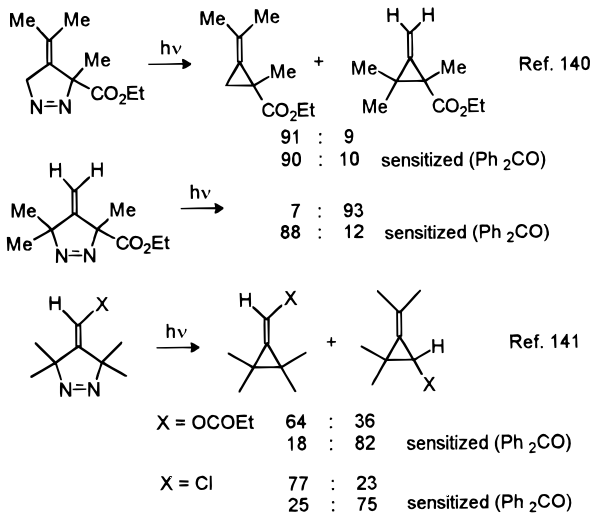
The formation of a mixture of isomers in the thermal or photochemical extrusion of N_2 is justified by the occurrence of a diradical resonating species (TMM diradical), although the results of irradiations

Scheme 27



generally show that the carbon skeletons of the precursor pyrazolines are mostly conserved during the reaction.[139−141] The more substituted ACP derivatives are the most favored under benzophenone-sensitized photolysis, as well as by thermal isomerization (Scheme 28).[139,140,142]

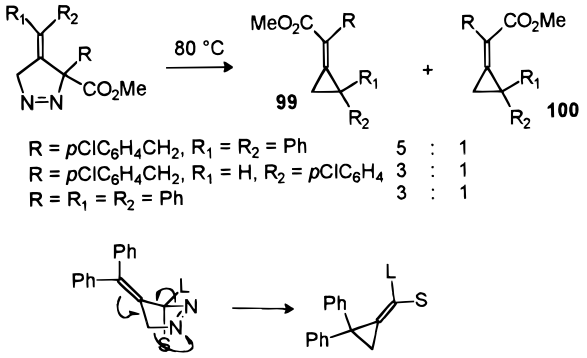
Scheme 28



The stereochemical outcome of the nitrogen extrusion has been studied carefully. It has been shown that the less stable *Z* ACP **99** is formed by effect of a

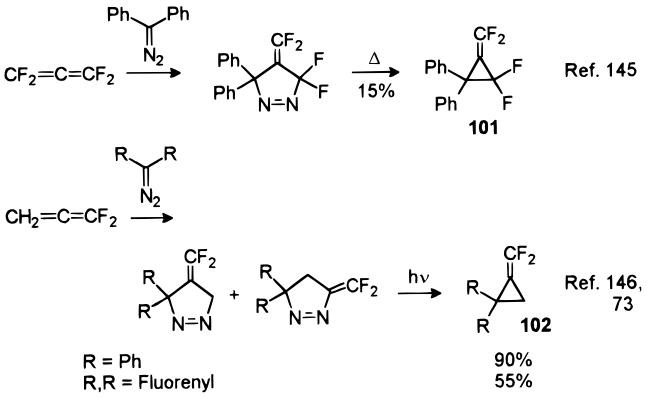
thermolysis of the pyrazoline in a preferred conformation having the bulkiest substituent in a pseudoequatorial position. This leads to the preferential formation of the sterically less stable ACPs **99** (Scheme 29).[143]

Scheme 29



Another study of the stereochemistry of the thermolysis of 4-alkylidene-1-pyrazolines, making use also of deuterated derivatives, showed the time dependence of the composition of the isomeric mixtures.[144] Fluorinated allenes gave fluorinated ACPs **101**−**102** by this process (Scheme 30).[145,146,73]

Scheme 30

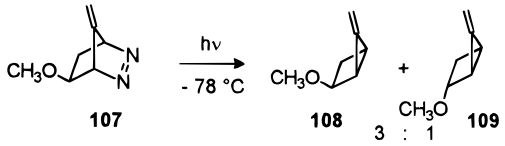


A phosphorylated MCP was synthesized in 47% yield starting from a phosphorylated allene.[147]

Another general method for the synthesis of pyrazolines, direct precursors of MCP by N_2 extrusion, consists of the bis(nucleophilic) substitution of *sym*-dicarbethoxy hydrazine **104** with a dibromoallyl derivative **103**, followed by decarboxylation and oxidation with HgO[144b,148] or chlorine[149a] of the intermediate pyrazolidine **105** (Scheme 31).

Several alkyl-substituted MCPs and ACPs were synthesized by this method.[148−151] In one case the methylene pyrazoline **106** was obtained from a pyrazolidinone by Wittig olefination.[150] In another single case the pyrazoline **107** was obtained by reaction of a TMM diradical with diazodicarboxylate followed by decarboxylation and oxidation. By using this method, the thermally very unstable 2-methoxy-5-methylenebicyclo[2.1.0]pentanes **108** and **109** were synthesized (Scheme 32).[152]

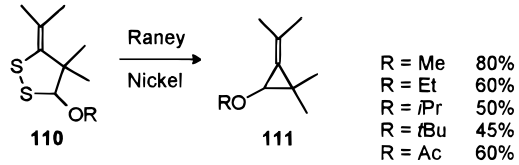
Scheme 32



3. Miscellaneous Eliminations

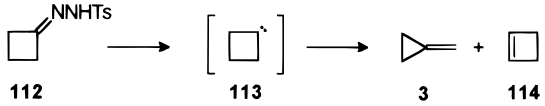
An example of sulfur "extrusion" mediated by Raney nickel from methylenedithiolanes **110** is reported to give ACPs in moderate to good yields (Scheme 33).[153]

Scheme 33



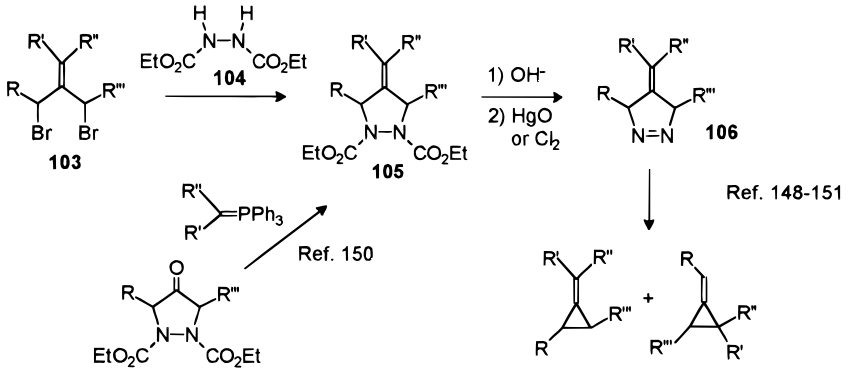
Ring contraction to give MCPs by thermal or photochemical means is a typical reaction of cyclobutylidenes.[154,155] These very reactive species can be generated by thermal decomposition of cyclobutanone tosylhydrazones **112** at temperatures generally above 150 °C; ring contraction then occurs to give MCP **3** as the major product together with cyclobutene **114** (Scheme 34).

Scheme 34



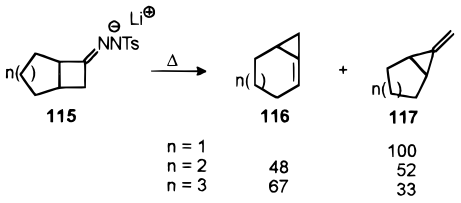
Geminal dihalogeno cyclobutanes have been also transformed into MCPs in high yield by treatment

Scheme 31



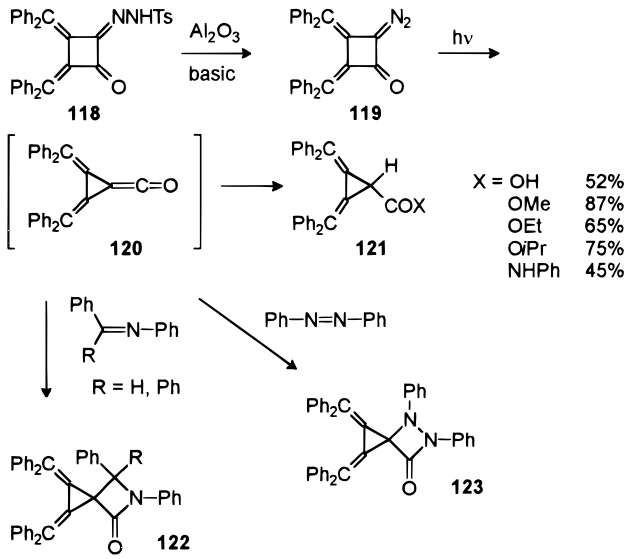
with MeLi at −78 °C.[156] Laser-driven thermolysis of spirohexane produced MCP through the formation of cyclobutylidene **113**.[157] The cyclobutylidene ring contraction has been barely used as a method for the synthesis of MCP **3** or its simple derivatives.[53,158] More widespread has been the study of bicyclic fused cyclobutylidenes which gave bicyclic MCPs, not as the exclusive isomers, and occasionally as intermediates for further transformations.[158−162] Pyrolysis of the dry lithium salts of fused cyclobutylhydrazones **115** at 120−180 °C and 0.1 mmHg produced mixtures of endocyclic ACPs **116** and exocyclic ACPs **117**. Only the cyclopentane derivative gave exclusively a bicyclic MCP (Scheme 35).[163]

Scheme 35



Irradiation of a 2-diazo-3,4-bis(diphenylmethylene)-cyclobutanone (**119**) in water, alcohols or aniline as solvents produced the bis(diphenylmethylene)cyclopropanes **121** in good yields through a ketene species **120**. Irradiation in the presence of imines or azobenzene produces the ketene adducts **122** and **123**, respectively (Scheme 36).[164]

Scheme 36

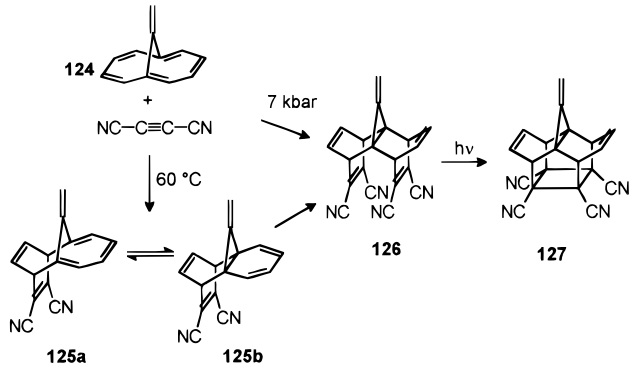


C. Rearrangements

Only a few, peculiar reactions have been reported to give MCP or ACP derivatives by rearrangement of compounds not containing a cyclopropane ring. Formation of MCPs in low yields, among several isomers, has been detected in the photochemical reaction of 1,3,5-trienes[165,166] and of 3-methyl-1,2-dihydronaphthalene,[167] still through an intermediate triene. Their formation has been rationalized to occur via a sigmatropic 1,5-hydrogen shift from the triene having the *Z* configuration at the central double bond.[167]

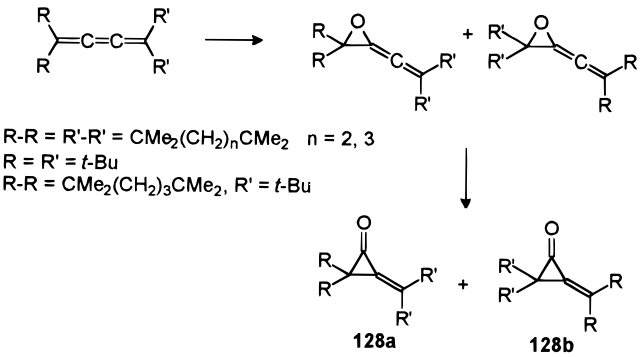
Compound **125** has been obtained, albeit in very low yield, by cycloaddition of the annulene **124** to dicyanoethylene (Scheme 37).[168] The resulting adduct **125**, as appears from spectral data, is an almost equimolar mixture of the valence isomers **125a** and **125b**. Therefore, the methylenecyclopropane **125b** can be seen as formed from isomerization of the primary adduct **125a**, although it is questionable if it can arise directly from the MCP tautomer of **124**. The high pressure reaction gave two 2:1 adducts, one of which was the adduct **126** (11% yield), as confirmed by its facile intramolecular cycloaddition to the interesting cage compound **127**.[168]

Scheme 37



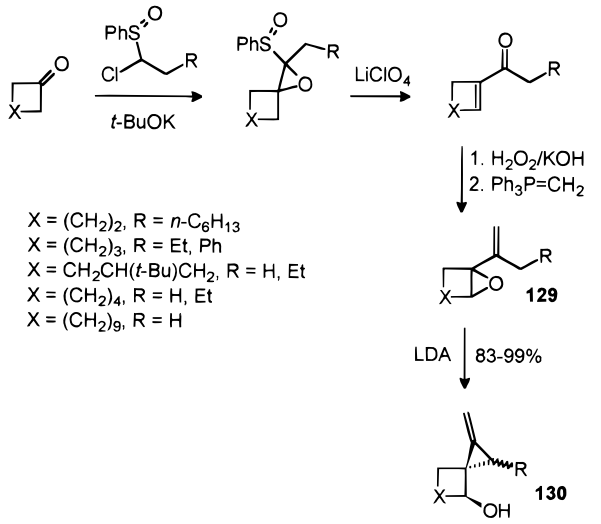
MCPBA oxidation of highly strained 1,2,3-trienes in CH_2Cl_2 or biphasic system gave alkylidenecyclopropanones **128** by rearrangement of the primarily formed unsaturated epoxides (Scheme 38),[169,170] in analogy to the behavior of allenes. Products could be isolated in elevated yields (81−97%), in spite of their tendency to decarbonylate easily to allenes.

Scheme 38



Finally, methylenecyclopropanes spirocyclized to cycloalkane systems **130** have been obtained in high yield by base-induced rearrangement of bicyclic epoxides **129**, prepared in turn from the corresponding cycloalkanones by the sequence reported in Scheme 39.[171] The final isomerization, by base-catalyzed epoxide opening,[5d] represents a peculiar example of a general preparative method of ACPs by elimination reactions, which has been discussed in the preceding section II.B.1.

Scheme 39



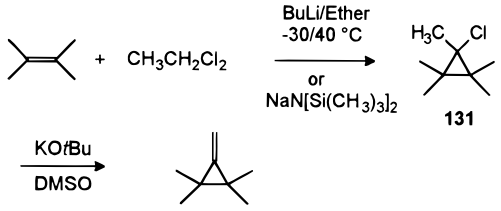
III. From Preformed Cyclopropanes

A. Eliminations

1. Eliminations of HX Groups (X = Halides)

The formal elimination of a hydrohalic acid from a preformed substrate containing a cyclopropyl ring is one of the most common processes for the synthesis of MCPs and ACPs. The success of this strategy derives from the availability of starting materials, easily obtained from halocarbene chemistry. The pioneering work of Binger[8a,172] has shown the generality and simplicity of the method (Scheme 40).

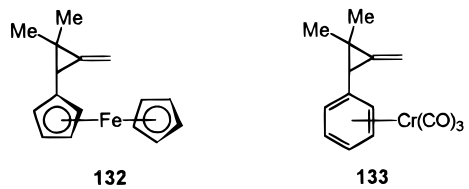
Scheme 40



The chlorocarbene obtained by treatment of 1,1-dichloroethane with a strong base reacts readily with an alkene (multisubstitution of the alkene favors the reaction) to give the methyl−chloro-substituted cyclopropane **131**, that undergoes HCl elimination by KO*t*-Bu in DMSO.

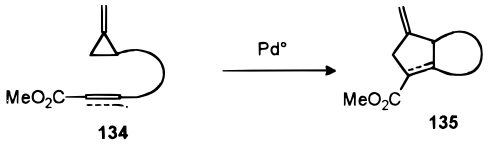
The method has been utilized for the construction of various alkyl-,[5a,64,172−180] aryl-,[172,181] and alkoxy-substituted[178] MCPs. It has been applied nicely also to the synthesis in good yields of ferrocene **132** and chromium tricarbonyl-derived **133** MCPs (Scheme 41).[74i]

Scheme 41



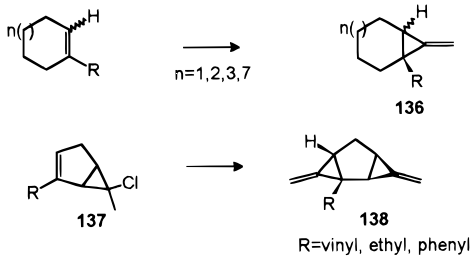
By this method, Motherwell and Binger have recently synthesized numerous MCPs of general structure **134** to be employed in intramolecular additions mediated by Pd^0 (Scheme 42).[182]

Scheme 42



With cyclic alkenes as the starting material, fused bicyclomethylenecyclopropanes **136** are readily obtained (Scheme 43).[172,183−186]

Scheme 43

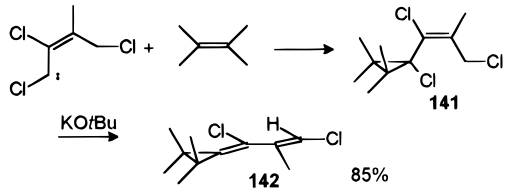


Tricyclic dimethylenecyclopropanes **138** were accordingly synthesized to study the stereochemical outcome of a metastable intermediate under thermal rearrangement conditions.[187]

A wide range of interesting mono- and dimethylenetriangulanes **140** were synthesized by repeating applications of this methodology (Table 9).

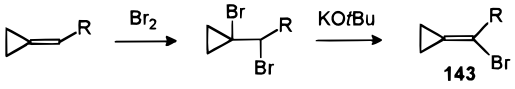
HCl 1,4-elimination from **141** afforded allylidenecyclopropanes **142** in high yield (Scheme 44).[191]

Scheme 44



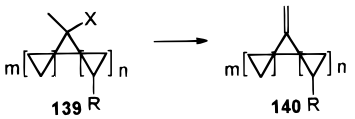
α-(Halomethylene)cyclopropanes **143** have been obtained by halogen addition to a preformed methylenecyclopropane followed by HX elimination (Scheme 45),[173,192−195] or by elimination after a carbene insertion.[196] 2-Methoxycarbonyl derivatives were synthesized in this way.[197,198]

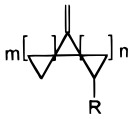
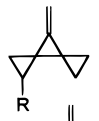
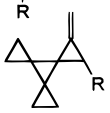
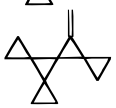
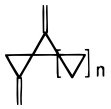
Scheme 45



The other most frequently used method of preparing the 1-halo-1-methylcyclopropane derivatives **131** consists in the halogen−metal exchange of a *gem*-dihalocyclopropane **144**, followed by alkylation and

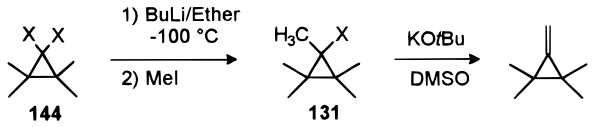
Table 9. Synthesis of Linear and Branched Methylenetriangulanes



		yield%	Ref.
	R=H, m=0, n=1	62-80	172,188a
	R=H, m=0, n=4	82	188b
	R=H, m=2, n=2	55	188e
	R=CH_2OTHP, m=0, n=1	76	188d
	R'=H, R = H	75	188a
	R'=H, R = CH_2OMe	78	188e
	R'=H, R = CH_2OTHP	82	188e
	R'=CH_2OTHP, R=H	80	188d
	R = H	75	188b
	R = CH_2OMe	81	188e
	R = CH_2OTHP	76	188e
	R = H	86	188a,189
	R = nC_7H_{15}	80	190
	R = CH_2OTHP	63	188c
	R = H	85-70	188c,188e
	R = CH_2OMe	78	188e
	R = CH_2OTHP	78	188e
		82	188c,188e
		56	188e
	n=0	20-25	188d
	n=1	45	70,188c
	n=0	40-50	188d
	n=1	40	188c
		45	188d

HX elimination under the same conditions (Scheme 46).[199]

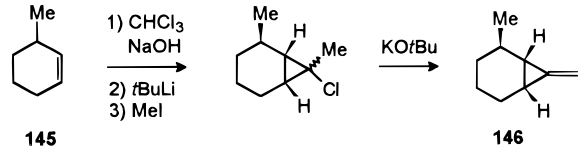
Scheme 46



Several alkyl-,[199b] aryl-,[199,200] and thio-substituted[201] and fused bicyclic[186b,199,202,203] methylenecyclopropanes have been obtained in this way. This methodology is preferred over the previous one when starting alkenes are prone to isomerization with strong bases as in the 3-methylcyclohexene (**145**) used to synthesize the methylenenorcarane derivative **146** (Scheme 47).[186b,203]

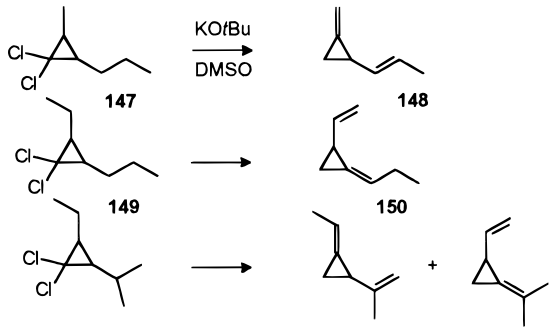
When a *gem*-dihalo dialkyl-disubstituted cyclopropane is treated with excess KO*t*-Bu in DMSO, methylene- or alkylidenecyclopropanes can derive from double HX elimination followed by an allylic

Scheme 47



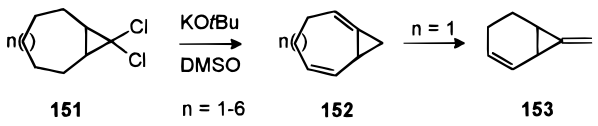
hydrogen shift. The process in general lacks selectivity, unless substituents on the cyclopropyl ring, like in **147** and **149**, steer the HX elimination (Scheme 48).[204−208]

Scheme 48



When the *gem*-dihalocyclopropane is ring fused, as **151**, bicyclo[*n*.1.0]alkenes (or endocyclic alkylidenecyclopropanes) **152** are obtained preferentially (Scheme 49).[205a]

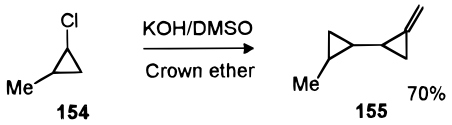
Scheme 49



When $n = 1$ the primary *endo*-methylenecyclopropane rearranges to the *exo*-methylenecyclopropane **153** with ring contraction (Scheme 49).[209] Also monochlorocyclopropanes give the same process.[210,211]

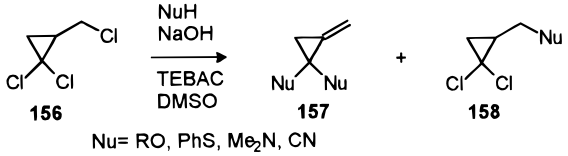
The same process with 1-methyl-2-chlorocyclopropane **154** in the presence of a crown ether has led to the formation of cyclopropylmethylenecyclopropane **155** in good yields (Scheme 50).[212]

Scheme 50



When the elimination is carried out in the presence of a nucleophile (alcohol, thiol, or amine) the formation of the methylenecyclopropane is accompanied by nucleophilic substitution. Products of simple substitution **158** are always isolated along with the methylenecyclopropanes **157** (Scheme 51).[213] The process

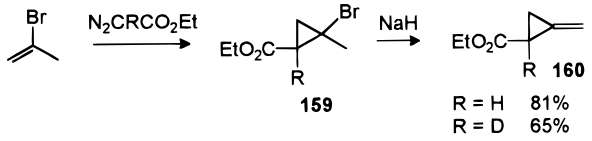
Scheme 51



is likely to occur through the intermediate formation of methylenecyclopropenes (see section IV.B.1).

The synthesis of methylenecyclopropanecarboxylate esters **160** was readily achieved by HBr elimination of the cyclopropyl bromide **159** obtained by carbene addition to 2-bromopropene (Scheme 52).[4,214]

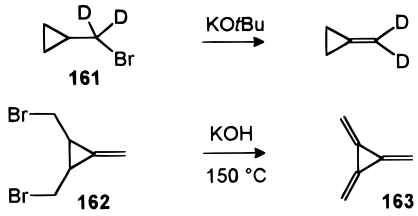
Scheme 52



By using this method a deuterated carbene allowed the synthesis of a deuterated derivative.[215] The process has been extensively applied to the synthesis of hypoglycine A derivatives (see section V.B).

Eliminations of cyclopropylcarbinyl halogenides **161** are less common, but also effective in the synthesis of MCPs.[216−218] The remarkably stable trimethylenecyclopropane **163**, the simplest member of the class of radialenes,[118] has been synthesized in this way (Scheme 53).[219] A formal triple elimination

Scheme 53

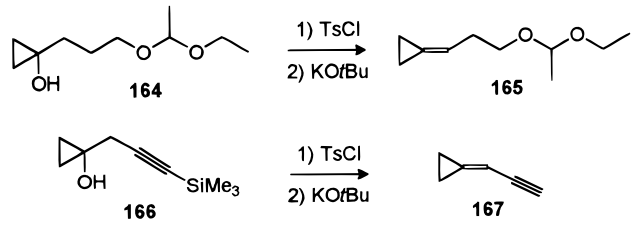


of HCl accounts for the formation of a related electron-donor-substituted [3]radialene in a process which employs hexachlorocyclopropane as the starting material.[220]

2. Eliminations of HY Groups (Y ≠ Halides)

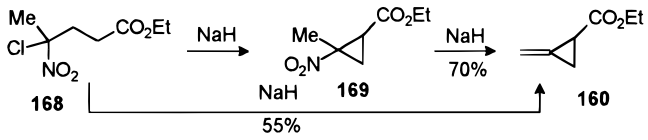
The same trimethylenecyclopropane **163** has been prepared by pyrolysis of tris-quaternary ammonium hydroxides[221,222] or tris-acetates analogues.[223] Trimethylammonium substituted cyclopropanes under basic conditions gave smoothly in high yields α-azido or α-silyloxy cyclopropylideneacetates.[224] Base-catalyzed elimination of tosylates worked efficiently (Scheme 54).[225]

Scheme 54



Simple dehydration with sulfuric acid or P_2O_5 of a tricyclopropylcarbinol failed to give a MCP, and a dialkoxydiphenylsulfurane as a dehydrating agent was required.[226] Elimination of nitrous acid with NaH from 2-methyl-2-nitrocyclopropanecarboxylate **169** was also reported to give **160** (Scheme 55).[227] The

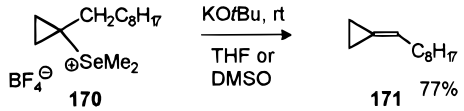
Scheme 55



MCP can be also formed in the same conditions in "one pot" from the cyclopropane precursor **168**.

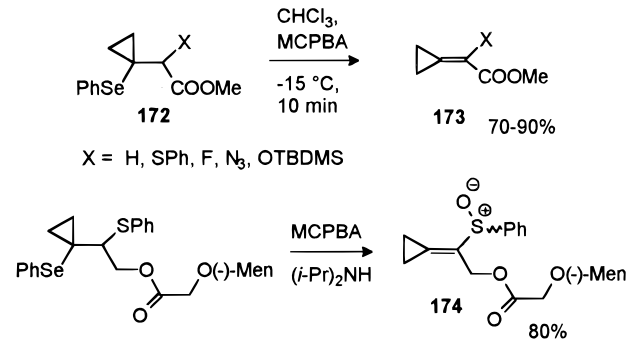
Much more widespread is the utilization of selenides or sulfides to run the elimination reaction. The work in this field has been completely reviewed.[9] Krief has shown that elimination of methylselenonium salts **170** is preferred over selenoxide elimination for the synthesis of alkylidenecyclopropanes (Scheme 56).[228]

Scheme 56



Phenyl selenoxide elimination from **172** served, however, for the synthesis of a variety of modified cyclopropylideneacetates **173** (Scheme 57).[224,229]

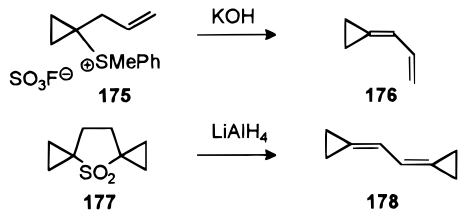
Scheme 57



Chiral hydroxymethyl−phenylsulfinyl-disubstituted alkylidenecyclopropanes could be prepared via the corresponding menthyloxyacetates **174** obtained by this method.[229c]

Base-catalyzed elimination of the sulfonium salt **175**[230] and reductive elimination of SO_2 from the sulfolane **177**[231] afforded examples of diene derivatives **176** and **178**, respectively (Scheme 58).

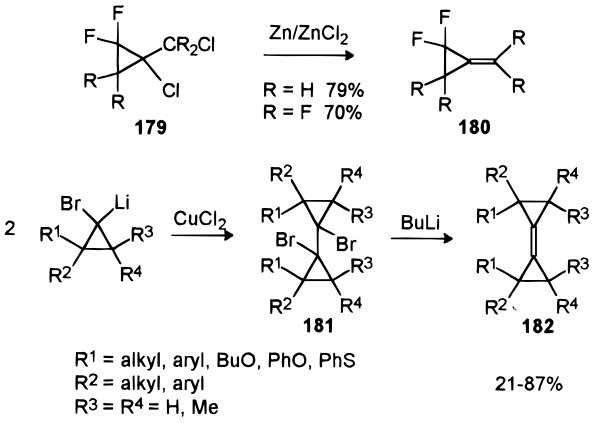
Scheme 58



3. Eliminations of XY Groups

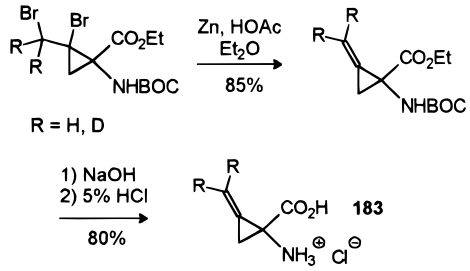
The formal elimination of a halogen molecule has been carried out on compound **179** with good yields by the couple $Zn/ZnCl_2$ in refluxing dioxane or DMSO,[232,233] or from **181** by a Li−halogen exchange[234] (Scheme 59).

Scheme 59



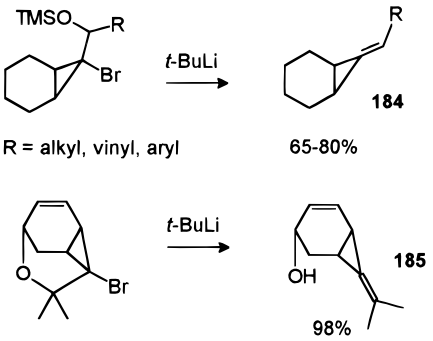
This procedure has been used for a new synthesis of 1-amino-2-methylenecylopropane-1-carboxylate (methylene-ACC) **183** and its deuterated analogue, useful in the study of the mechanism of action of ACC deaminase enzyme (Scheme 60).[235]

Scheme 60



The successful formal elimination of BrOR by *t*-BuLi or Mg has been also reported (Scheme 61).[236−238]

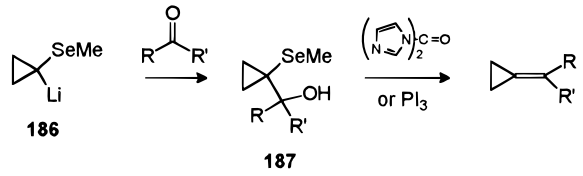
Scheme 61



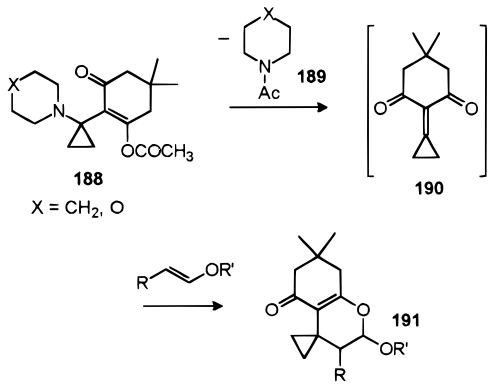
The starting materials for these processes where obtained from 1-bromo-1-lithiocyclopropanes by reaction with aldehydes or ketones. 1-(Methylseleno)-1-lithiocyclopropanes can be used for the same scope in a similar way. The formal elimination of MeSeOH from **187** with carbonyldiimidazole or phosphorus triiodide gave alkylidenecyclopropanes in 58−75% yield (Scheme 62).[239]

The 1,4-elimination of acetylpiperidine or morpholine **189** by thermal decomposition of α-amino-α-dimedone cyclopropane derivatives **188** has been widely used by Vilsmaier for the in situ formation of cyclopropylidenedimedone **190** which undergoes [4 + 2] cycloadditions with enol ethers to give adducts **191** (Scheme 63).[240]

Scheme 62



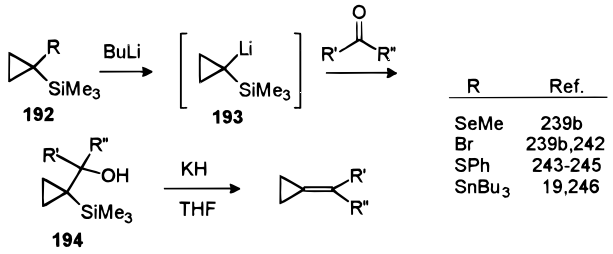
Scheme 63



4. Peterson Eliminations and Related Reactions

The base-mediated elimination of Me_3SiOH of silyl-substituted cyclopropanes[241] is among the most used and convenient methods for the synthesis of ACPs. It has been applied to a variety of structurally differentiated alkylidenecyclopropanes. Several methods have been used, differing in the mode of formation of the 1-(trimethylsilyl)-1-lithiocyclopropane key precursors. Krief[239b] reported the first example of this methodology, immediately followed by a Japanese group,[242] obtaining the key precursor **193** from an α-(methylseleno)- or an α-bromo(trimethylsilyl)-cyclopropane (Scheme 64).

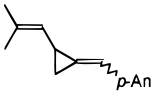
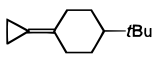
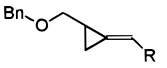
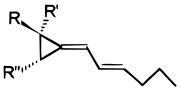
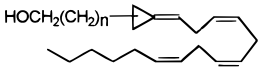
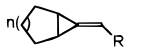
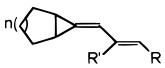
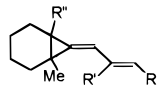
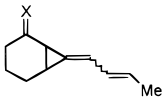
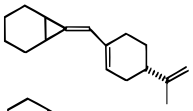
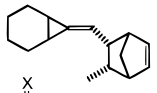
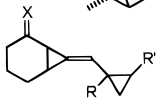
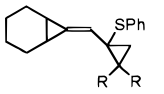
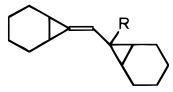
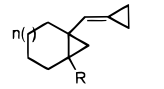
Scheme 64



Cohen and co-workers obtained this precursor from α-(phenylthio)silanes (R = SPh), which in turn originated from cyclopropanone thioketals. The reductive lithiation is carried out conveniently with electron-transfer reagents like lithium naphthalenide or 1-(dimethylamino)naphthalenide (LDMAN).[243−245,247] In all these cases the *β*-hydroxy silane **194** is obtained by reaction of the lithio derivative with aldehydes or ketones. The Peterson elimination has proven to be facile and reliable with different substrates. The reaction conditions usually require a simple stirring of the *β*-hydroxy silane in THF with KH at room temperature. Many monocyclic and bicyclic alkylidene- and allylidenecyclopropanes were obtained by this method in good to excellent yields (Table 10).

Recently, the *β*-hydroxy silane was obtained by reaction of 1-(diphenylmethylsilyl)cyclopropane-

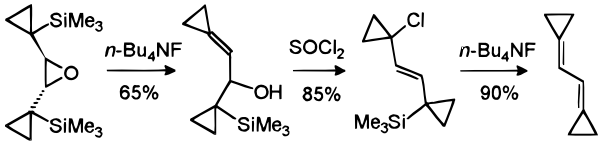
Table 10. Alkylidenecyclopropanes Synthesized by Peterson Elimination

Entry		Yield (%)	Ref.
1	 R = *n*-Dec R' = H	76	239b
2	R = *p*-An R' = H	85	243
3	R = R' = *n*-Bu	76	248
4	R = R' = Ph	81	248
5	 R = *n*-Non R' = Me	78	239b
6		95	243
7		86	243
8	 R = Ph	56	242
9	R = CH=CHC$_3$H$_7$	46	242
10	 R = R' = R'' = H	67	244
11	R = R'' = Me R' = H	71	239b
12	R = R' = Me R'' = H	76	239b
13	 n = 1, 2	41	250
14	 n = 1 R = C$_5$H$_{11}$	78	244,245
15	n = 2 R = C$_5$H$_{11}$	80-100	239b,243,244
16	n = 1 R = Furyl	86	244,245
17	n = 2 R = Furyl	78	244,245
18	n = 1 R = *p*-An	62	244,245
19	n = 2 R = *p*-An	79	244,245
20	n = 2 R = Ph	55	242
21	 n = 1 R = Me R' = H	76	244,247
22	n = 2 R = Me R' = H	45-85	242,244,247
23	n = 1 R = *n*-Pr R' = H	76	244,245
24	n = 2 R = *n*-Pr R' = H	81	244,245
25	n = 1 R = *i*-Pr R' = H	78	244,245
26	n = 2 R = *i*-Pr R' = H	82	244,245
27	n = 1 R = Ph R' = H	77	244,245
28	n = 2 R = Ph R' = H	81	244,245
29	n = 1 R = H R' = Me	79-95	244,243
30	n = 2 R = H R' = Me	86-100	244,243
31	n = 2 R = SPh R' = H	93	245
32	 R = Me R' = H R'' = H	99	244,245
33	R = H R' = Me R'' = H	74	244,245
34	R = H R' = Me R'' = Me	79	244,245
35	 X = O	90	245,247
36	X = CH$_2$	99	245
37		6-73	244,245
38		73	244
39	 X = H,H R = R' = H	91	251
40	X = H,H R = Me R' = H	81	251
41	X = H,H R = OEt R' = H	70	251
42	X = H,H R = H R' = SPh	79	251
43	X = O R = R' = H	89	251
44	 R = R = H	82	251
45	R = R = Me	70	251
46	 R = H	82	251
47	R = SPh	72	251
48	 n = 1 R = H	92	251
49	n = 2 R = OMe	85	251

carboxylate with organometallic alkylating agents, and elimination was carried out with KO*t*-Bu (Table 10, entries 3 and 4).[248]

With the β-hydroxy silane **196**, obtained by the opening of the epoxysilane **195**, Peterson elimination failed. Treatment with thionyl chloride produced the 1,4-chlorosilane **197** which underwent fluoride-catalyzed elimination of Me_3SiCl to give the interesting diene **178** (Scheme 65).[249]

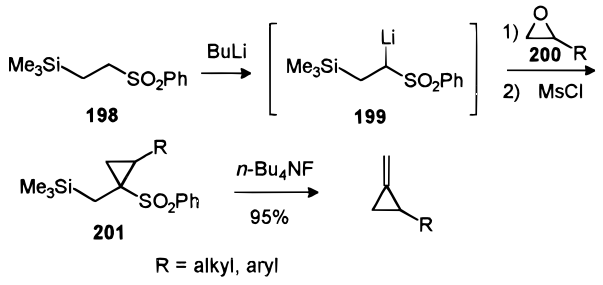
Scheme 65



Lautens applied the same procedure for elimination (1, $SOCl_2$; 2, *n*-Bu_4NF) to β-hydroxy silanes in his synthesis of chiral MCPs (see section V.B).[19,20,246]

Removal of phenylsulfonyl and trimethylsilyl from α-(phenylsulfonyl)-β-(trimethylsilyl)cyclopropanes by tetra-*n*-butylammonium fluoride is another related convenient synthesis of MCPs that has recently appeared. 1-(Phenylsulfonyl)-2-(trimethylsilyl)ethane **198** is easily converted by BuLi to the 1-lithio derivative **199** which, by reaction with epoxides **200** followed by mesylation, affords cyclopropanes **201** in 45−75% overall yields. Elimination occurs smoothly in THF at 65 °C to give MCPs in excellent yields (Scheme 66).[252] The epoxide group was also replaced by a cyclic sulfate with success.[253]

Scheme 66



This methodology has been applied conveniently to a new enantioselective formal synthesis of hypoglycine (**1**) (see section V.B).[254]

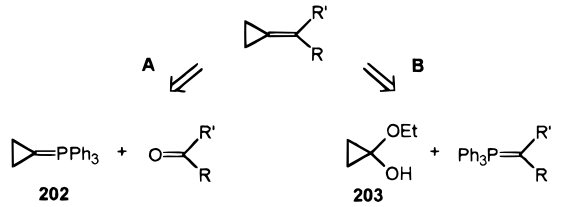
B. Wittig Olefinations and Related Reactions

1. Wittig Olefinations

The Wittig olefination has been extensively used for the synthesis of diversely functionalized methylene- and alkylidenecyclopropanes.

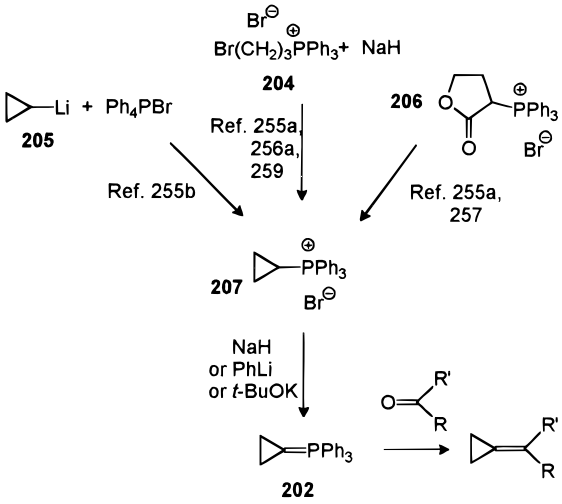
The retrosynthetic analysis under Wittig conditions provides the two possible routes A and B for the formation of the double bond (Scheme 67). By far,

Scheme 67



route A, employing cyclopropylidene phosphorane **202**, has been the most utilized by researchers, because of the unavailability of cyclopropanone and the low reactivity of its synthetic equivalent cyclopropanone hemiacetal **203**. The first applications of route A in the literature were reported approximately simultaneously by three different groups[255−257] whose approaches differed exclusively in the preparation of the precursor phosphonium salt **207** (Scheme 68).

Scheme 68

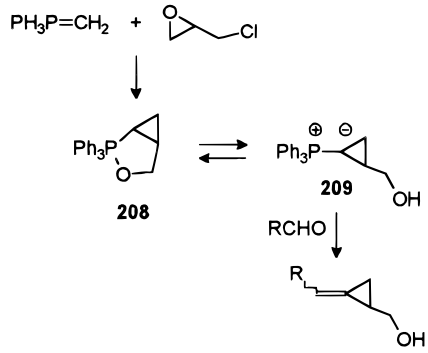


The most commonly used method employs 3-bromotriphenylphosphonium bromide (**204**) as the precursor in a "two step" or "one step" process to produce the ylide **202**.[255b,256b] Reflux in tetrahydrofuran for several hours is generally required for the completion of the reaction. The yields of ACPs range between 45 and 80%, being slightly higher for the "one step" procedure.[256b] Ketones and aromatic aldehydes seem to give comparable results, although enolizable aldehydes cannot survive the reaction conditions. A great improvement in the reaction yields has been found by using 10 mol % of an additive phase-transfer catalyst, TDA-1 (tris[2-(2-methoxyethoxy)ethyl]-amine).[258] More recently, the process was further improved with the use of less expensive bases and shorter reaction times.[259]

An interesting method for the synthesis of methylene- or alkylidenecyclopropane carbinols via Wittig olefination was developed by Le Corre (Scheme 69).[260]

The intermediate ylide **209**, in equilibrium with the oxaphosphole **208**, was formed by sequential nucleophilic substitution/cyclization of methylenephosphorane with epichlorohydrin. A slight change of the

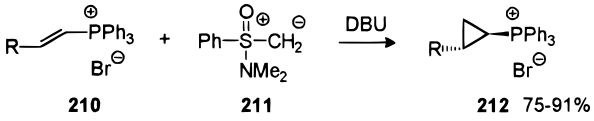
Scheme 69



reaction conditions (solvent and base) brought about the formation of isomeric alkylidenecyclobutanols.[261] The method has found application in the synthesis of optically active (methylenecyclopropyl)carbinols (see section V.B).[260b,261b]

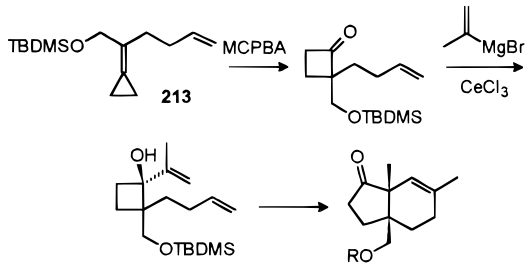
A new synthesis of cyclopropyl phosphonium salts **212**, to be employed in the process, by reaction of vinyl phosphonium salts **210** with sulfoxonium ylides **211** has recently appeared (Scheme 70).[262]

Scheme 70



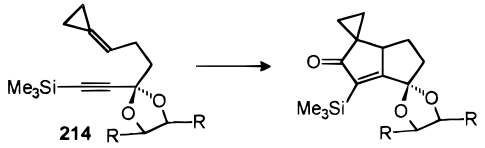
The olefination through ylide **202** has found many applications in various synthetic strategies.[28,173,194,260a,263−275] Conia's group has synthesized many α-cyclopropylidene aldehydes and ketones by this method.[276] Fukumoto has used alkylidenecyclopropanes **213** obtained by this method for the synthesis of diversely functionalized cyclobutanones on the route to alkylated cyclopentanones (Scheme 71).[277]

Scheme 71



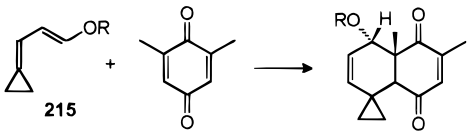
de Meijere and Salaün have used cyclopropylidenes **214** obtained via this procedure for an intramolecular Pauson−Khand reaction (Scheme 72).[278]

Scheme 72



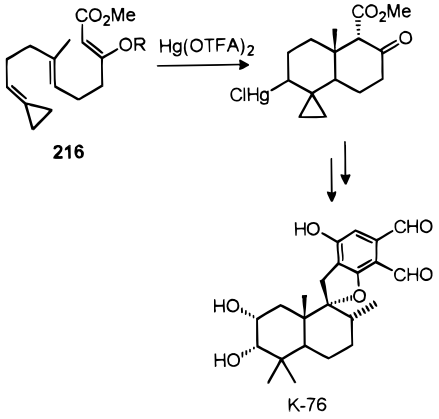
3-Alkoxyprop-2-enylidenecyclopropanes **215** were used in the synthesis of a precursor of forskolin (Scheme 73).[279,280] The fungal metabolite K-76 with

Scheme 73



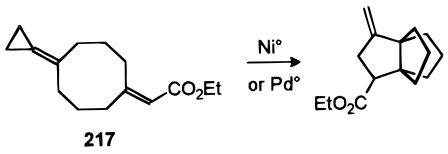
high antiinflammatory activity has been synthesized through an electrophile-induced polyene cyclization of the alkylidenecyclopropane **216** as a key step (Scheme 74).[281]

Scheme 74



Similar ACPs, also as tritiated derivatives, were used to study the mechanism of inactivation of monoterpene cyclases.[282] [3.3.3]Propellanes were synthesized by transannular cycloaddition of olefinic methylenecyclopropanes **217** obtained by Wittig olefinations (Scheme 75).[283]

Scheme 75



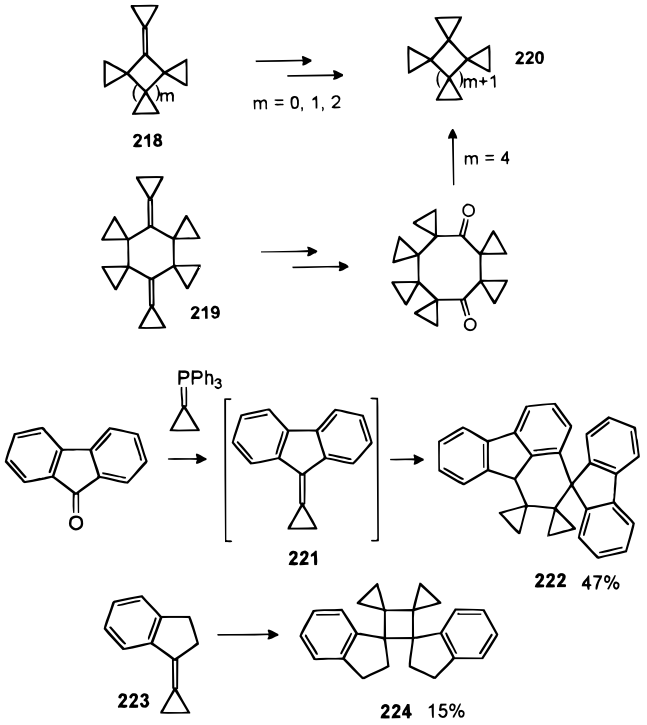
Cyclopropylidene-polyspiroalkanes **218** and **219** were synthesized by this method as a route to [*n*]rotanes **220** (Scheme 76).[284]

The reaction of cyclopropylidenetriphenylphosphorane with fluorenone, surprisingly, did not provide the expected ACP **221**, but the compound **222**, a product of [4 + 2] cycloaddition between two molecules of **221**, apparently unstable and very reactive in those conditions (Scheme 76).[285]

On the other hand, an analogous ACP **223** obtained from indanone could be isolated and slowly underwent dimerization, however to the head-to-head [2 + 2] adduct **224** (Scheme 76).[285]

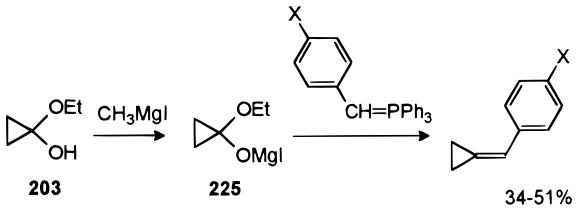
Cyclopropanone, although spectroscopically detected at low temperature in inert solvents,[286] is not sufficiently stable to permit useful synthetic applications according to route B (Scheme 67). However, the hemiacetal **203** can provide a convenient source of the parent ketone. The hemiacetal can be conveniently prepared in large scale from ethyl 3-chloropropanoate. The first attempt to employ the hemiacetal in a Wittig-type process to produce ACPs was carried out by Salaün's group, but cyclohexylidene-

Scheme 76



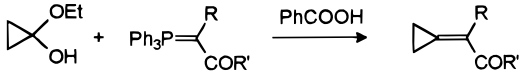
phosphorane failed to give the alkylidenecyclopropane with **203**. However, its magnesium salt **225**, obtained by treatment of **203** with methylmagnesium iodide, gave with benzylidenephosphoranes the products of Wittig reaction in 34−51% yield (Scheme 77).[225,287]

Scheme 77



The hemiacetal **203** was later found to give directly Wittig reactions with stabilized ylides in the presence of benzoic acid as catalyst (Scheme 78).[280,288−290] A

Scheme 78

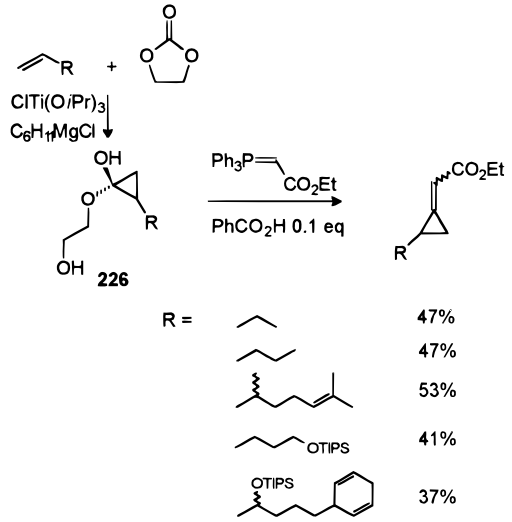


	Yield%	Ref.
R = Br R' = OBn	40	288
R = H R' = OMe	44	266
R = H R' = OEt	87	280
R = H R' = OBn	49	291
R = H R' = OMenthyl	55	280
R = H R' = OCyclohexyl-2-Ph	22	292
R = Me R' = OEt	64-74	280,290
R = Et R' = OEt	57	290
R = Pent R' = OEt	25	290
R = Ph R' = OEt	14	290
R = H R' = Me	40	280

large series of alkoxycarbonylmethylenecyclopropanes, also chiral,[289,292] have been synthesized accordingly.

Recently, a new synthesis of the intermediate cyclopropanone hemiacetals **226** by reductive coupling of a terminal olefin with ethylene carbonate mediated by titanium alkoxide has been reported (Scheme 79).[293]

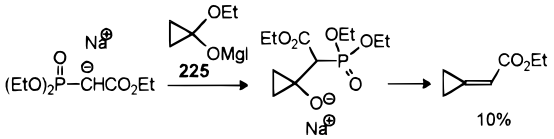
Scheme 79



2. Wadsworth–Emmons and Horner–Wittig Olefinations

The Wadsworth−Emmons process for olefination was applied for the first time with the carbanion of phosphonoacetate, but gave with the magnesium salt **225** only a 10% yield of cyclopropylideneacetate (Scheme 80).[225]

Scheme 80



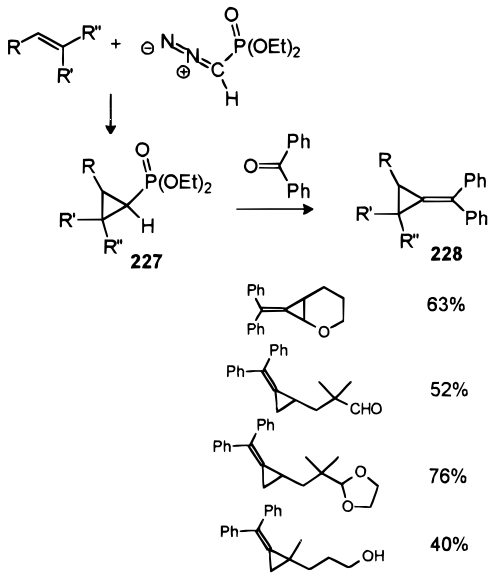
Much better results gave the other disconnective alternative (route A, Scheme 67) starting from cyclopropylphosphonates. These were extensively used by Motherwell in a cyclopropanation/Wadsworth−Emmons strategy for the synthesis of (diphenylmethylene)cyclopropanes **228** (Scheme 81).[294]

The Horner−Wittig methodology has provided good yields of ACPs starting from cyclopropyldiphenylphosphine oxide **229** (Scheme 82).[295]

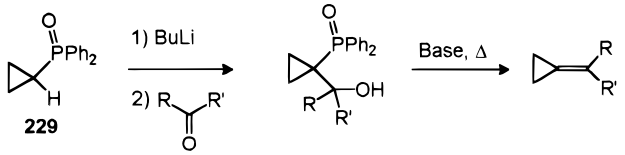
3. Wittig-Related Reactions

Olefinations with cyclopropyl phosphonium ylides, silanes, and selenides have shown high utility for the production of methylene- and alkylidenecyclopropanes, but all the processes did prove not to work with readily enolizable carbonyls or with esters. A recent study has solved this problem by applying titanocene chemistry (Scheme 83).[296] The method is of quite general application: the bis(cyclopropyl)-titanocene **230** smoothly reacts with aldehydes, ketones, and esters via a titanacarbene species. Esters gave only slightly lower yields of the products (55−71%) compared to carbonyl compounds (55−90%).

Scheme 81

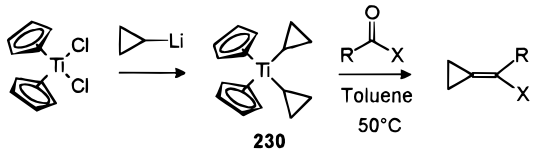


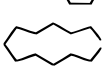
Scheme 82



R = H R' = Ph	96%	72%
R = H R' = C_7H_{15}	78%	47%
R = CH_3 R' = Ph	76%	84%
R = Ph R' = Ph	65%	92%
R = R' = CH_3	86%	18%
R = R' = -$(CH_2)_5$-	68%	61%
R = R' = C_4H_9	83%	77%

Scheme 83



R = Ph X = H	90%
R = Ph X = Me	87%
R = Ph X = Ph	82%
R = Ph X =	55%
R =  X = H	55%
R−X = 	75%
	70%
	85%
R = H X = OBu	71%
R = Me X = $O(CH_2)_{11}Me$	65%
R = CD_3 X = $O(CH_2)_{11}Me$	55%
R−X = 	67%

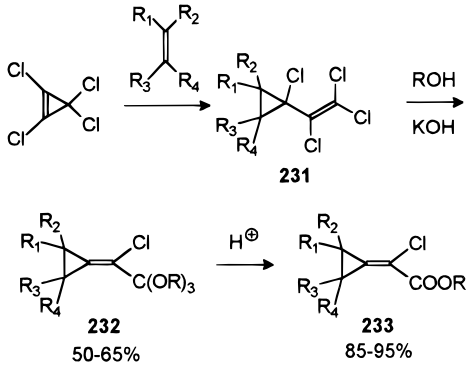
C. Reactions with Double Bond Shift

1. Nucleophilic Displacements

The synthesis of chloro(cyclopropylidene)acetates is the most representative among the syntheses of

MCPs and ACPs occurring by nucleophilic displacement. The contribution of de Meijere's group to this chemistry has been decisive since the earliest discovery, also with some degree of serendipity, that 1-chloro-1-(trichlorovinyl)cyclopropanes **231** afford orthoesters **232** by treatment with potassium hydroxide and methanol (Scheme 84). The starting

Scheme 84

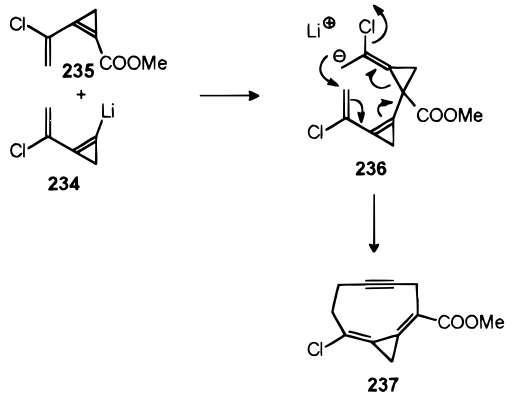


cyclopropanes are readily accessible from olefins and tetrachlorocyclopropene. On acid-catalyzed hydrolysis the orthoesters **232** are transformed into the esters **233**.[297]

The cyclopropylideneacetates have been employed in many synthetic strategies, already extensively reviewed.[229,298] The most significant are with regard to the use in Michael-type and Diels−Alder processes for the synthesis of spirocyclopropane-annelated bicyclic and tricyclic skeletons,[297a,299−301] of spirocyclopropane-annelated heterocycles,[302,303] and of cyclopropyl β-amino acids.[291,304]

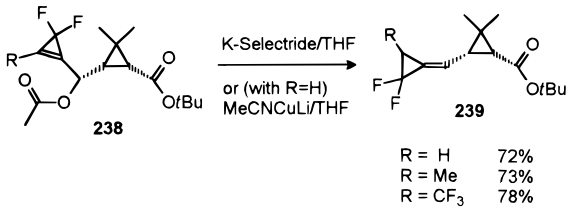
Nucleophilic displacements of substituted cyclopropenes have been reported to lead to MCPs and ACPs. The cyclic (bismethylenecyclopropane **237** has been synthesized by nucleophilic displacement of the vinylcyclopropenyllithium derivative **234** on vinylcyclopropene **235** (Scheme 85).[305]

Scheme 85



β-Cyclopropylidene ethanols were obtained in low yield by treatment with aqueous carbonate of 1-chloro- or 1-bromospiropentanes,[306] and difluorocyclopropene carbinol acetates **238** were transformed into difluorocyclopropylidenes **239**, new insecticidal pyrethroids, by K-Selectride or methylcyanocuprate in good yields (Scheme 86).[307]

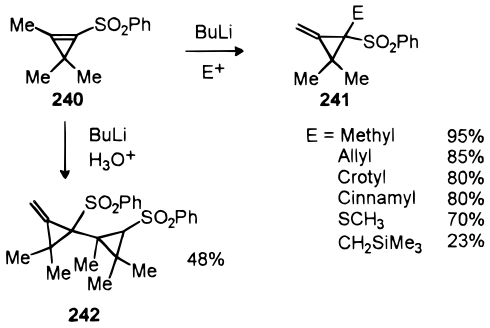
Scheme 86



2. Electrophilic Substitutions

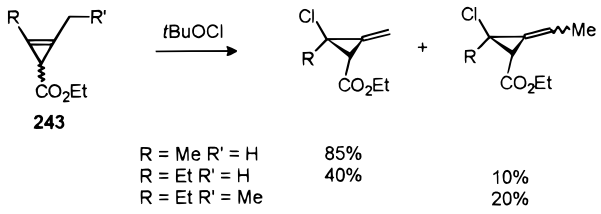
Cyclopropenes can produce MCPs and ACPs also by electrophilic substitution. The benzensulfonyl-substituted cyclopropene **240** gave, by treatment with BuLi and quenching with an electrophile, good yields of benzenesulfonyl-substituted MCPs **241** (Scheme 87).[308]

Scheme 87



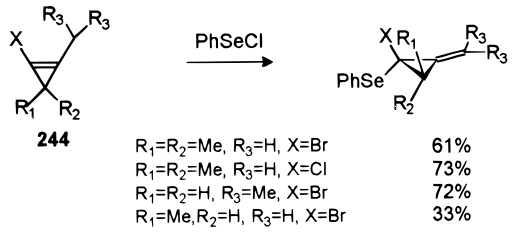
When the treatment with base was followed by aqueous workup, the dimer **242** was obtained in 48% yield. Dialkyl-disubstituted cyclopropenes **243** gave with *t*-BuOCl chloro-substituted MCPs and ACPs. With unsymmetrical cyclopropenes mixtures of substitution products result (Scheme 88).[309]

Scheme 88



Benzeneselenylation of halocyclopropenes has afforded substituted MCPs and ACPs in good yield (Scheme 89).[310]

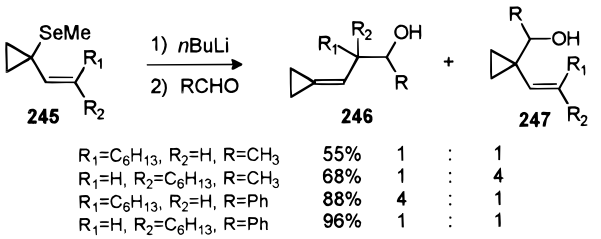
Scheme 89



Reaction of vinyl cyclopropyl selenides with aldehydes as electrophiles has led to the formation of

cyclopropylidene alcohols **246** together with their cyclopropylcarbinol isomers **247** (Scheme 90).[311]

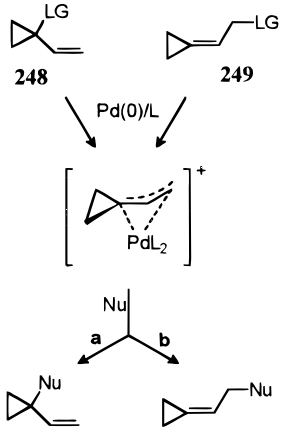
Scheme 90



3. Through Transition Metal Allyl Complexes

Palladium-catalyzed transformations of allylic substrates has gained a wide applicability in organic synthesis. The extension of this chemistry to vinylcyclopropanes **248** or to cyclopropylideneethane derivatives **249** has led, through the intermediate π-allylpalladium complexes, to a very general and convenient synthesis of highly functionalized ACPs in good to excellent yield (Scheme 91).[312,313]

Scheme 91

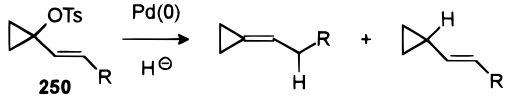


Several leaving groups were tested for the reaction (LG = Cl, MeCOO, MeOCOO, TsO, MsO, TfaO): in general, better leaving groups increased the reactivity. Compounds **248** and **249** showed similar reactivity with identical regioselectivity, depending exclusively on the ligand and the nucleophile used. Tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] and bis(dibenzylideneacetone)palladium/1,2-bis(diphenylphosphino)ethane [$Pd(dba)_2$/dppe] are the two most used catalysts, the second giving generally better results. A variety of soft carbon nucleophiles (stabilized carbanions) gave substitutions to the terminal position of the π-allyl system with good to excellent yields (route b, Scheme 91, Table 11), in contrast to hard nucleophiles, which added preferentially to the cyclopropane terminus (route a, Scheme 91).[313]

A series of oxygen and nitrogen nucleophiles also reacted with 1-ethenylcyclopropyl tosylate in the presence of Pd(0) and gave cyclopropylideneethyl substitution products in high yields (Table 12).[313] Sodium azide, however, gave nucleophilic attack to the cyclopropyl carbon.[320]

Another efficient synthetic method consists of the Pd(0)-catalyzed reduction of (1-alkenyl) cyclopropyl esters **250** (Scheme 92).[322] The reduction products

Scheme 92

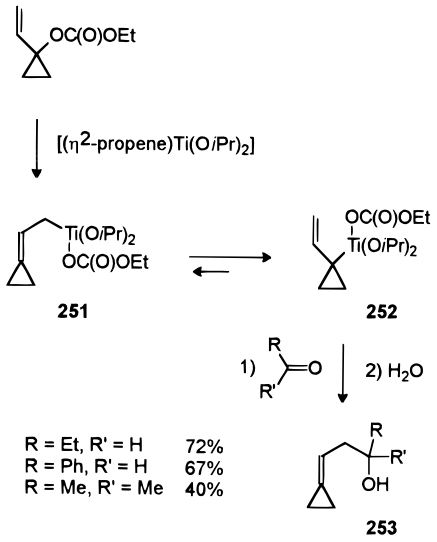


are highly dependent on the hydride sources and the ligands on palladium. Use of sodium formate/15-crown-5 as the hydride source and $Pd(OAc)_2/PPh_3$ as catalyst gave the best yield of ACPs.

ACPs were formed in mixtures together with normal adducts in Pd complexed TMM cycloaddition reactions from 2-(1-(trimethylsilyl)-1-cyclopropyl)allyl pivalates.[323]

Titanium σ-allyl complexes can undergo the same protocol for the synthesis of ACPs via their reaction with carbonyl compounds. Vinylcyclopropyl carbonate reacts with [(η^2-propene)Ti(O*i*-Pr)$_2$], readily generated from [Ti(O*i*-Pr)$_4$] and *i*-PrMgBr, to give mainly the vinylcyclopropyltitanium compound **252**. The less hindered cyclopropylidene titanium compound **251** seems to be disfavored by the strain of the alkylidenecyclopropane fragment. Subsequent reaction of **252** with carbonyl compounds gives ACPs **253** in good yields by nucleophilic attack with allylic shift (Scheme 93).[324]

Scheme 93



4. Singlet Oxygen Insertions

The reaction of singlet oxygen with vinylcyclopropane derivatives has been extensively studied in parallel by Conia and Frimer groups and produces

Table 11. Alkylidenecyclopropanes Synthesized from Vinylcyclopropanol Derivatives via Allylpalladium Complexes

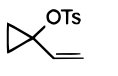
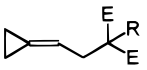
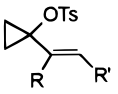
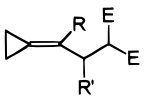
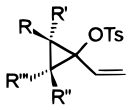
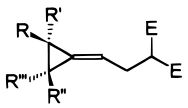
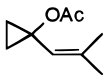
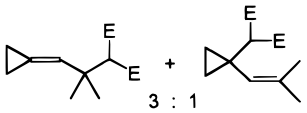
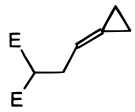
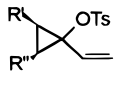
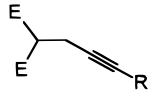
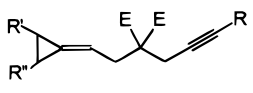
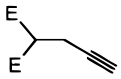
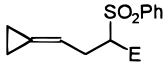
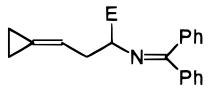
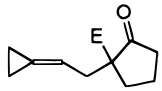
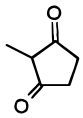
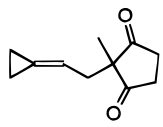
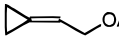
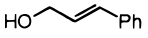
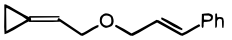
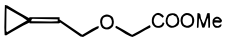
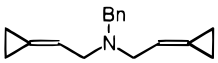
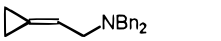
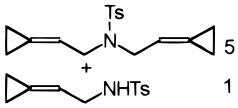
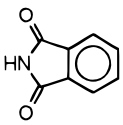
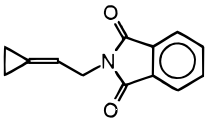
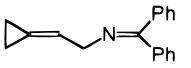
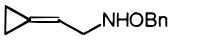
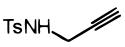
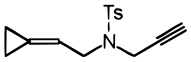
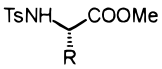
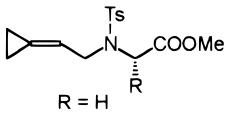
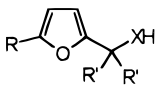
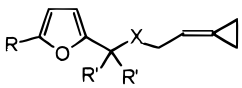
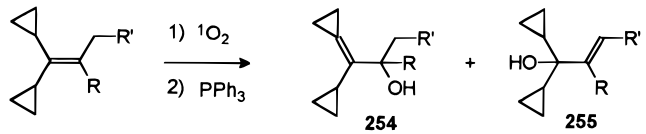
Entry				Yield (%)	Ref.
					
1		E = COOR	R = H	86	313,312a
2			R = Me	82	313,312a
3			R = Allyl	91	313,312a
					
4			R = Me, R' = H	81	313,312b
5			R = H, R' = Me	89	313,312b,229c
6			R = H, R' = Ph	94	313,312b,229c
					
7			R = Me, R' = R'' = R''' = H	68	314
8			R = TMS, R' = R'' = R''' = H	91	314
9			R = $TMSCH_2$, R' = R'' = R''' = H	86	314
10			R = R'' = Me, R' = R''' = H	65	314
11			R = R''' = Me, R' = R'' = H	67	314
12			R = R' = R'' = R''' = Me	65	314
13			 3 : 1	33	313, 312b
14				91	313, 312a
					
15			R = R' = R'' = H	91	313, 312a
16			R = Me, R' = R'' = H	75	315
17			R = TMS, R' = R'' = H	35	315
18			R = H, R' = R'' = Me	72	316
19			R = R'' =H, R' = TMS	64	316
20			R = R'' =H, R' = OEt	75	316
21				91	315
22				92	313,312a
23	"			87	313,312b,317
24	"			93	313,312a
25	"			72	313,312a

Table 12. Heteroatom-Substituted Alkylidenecyclopropanes Synthesized from Vinylcyclopropanol Derivatives via Allylpalladium Complexes

Entry				Yield (%)	Ref.
1		KOAc, 18-crown-6		80	312b,313
2	"			95	312b,313
3	"			87	319
4	"	$BnNH_2$		75	320
5	"	Bn_2NH		85	320
6	"	$TsNH_2$		75	312b,313
7	"			65	312b,313
8	"			95	320
9	"	NH_2OBn		84	320
10	"			80	315
	"				
11			R = H	83	318
12			R = Me	72	318
13			R = Bn	70	318
14			R = Ph	86	319
15			R = 3-Indolyl-CH_2	92	319
					
16			X = O, R = R' = H	96	321
17			X = O, R = H R' = Me	66	321
18			X = O, R = Me R' = H	86	321
19			X = O, R = OMe, R' = H	73	321
20			X = NMe, R = R' = H	94	321
21			X = NMe, R = H, R' = =O	95	321

hydroxy-substituted ACPs **254** after reduction of the intermediate hydroperoxides by triphenylphosphine. The dye-sensitized photooxygenation is not, however, regioselective with simple vinyl cyclopropanes, because of competing hydrogen abstraction from a cyclopropyl or an alkyl group, and give mixtures of ACPs **254** and cyclopropylcarbinols **255** (Scheme 94).[268,325,326]

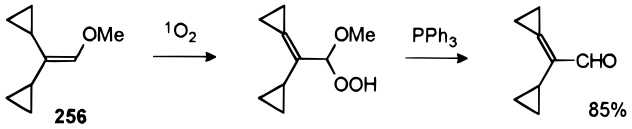
Scheme 94



R = R' = H	60-75%	:	25-40%
R = Me R' = H	35-37%	:	63-65%
RR' = CH_2	100%	:	0%
RR' = $(CH_2)_2$	100%	:	0%
RR' = $(CH_2)_3$	27%	:	73%
RR' = $(CH_2)_4$	75%	:	25%

Enol ethers **256** give a much higher regioselectivity, probably due to a different mechanism of photooxygenation (Scheme 95).[276d,325b,327]

Scheme 95

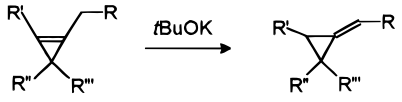


D. Isomerizations and Rearrangements

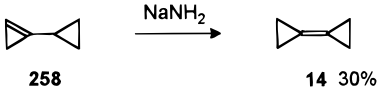
1. Base-Catalyzed Isomerizations

Isomerizations of alkylcyclopropenes to ACPs is a well-documented method for the synthesis of these compounds, because, owing to a relief in ring strain, the compounds with an exocyclic double bond are thermodynamically more stable (by 6−10 kcal/mol) than those with the double bond in the endocyclic position. Alkyl groups in alkyl-substituted cyclopropenes **257** proved acidic enough to give the isomerization in the presence of *t*-BuOK as the base (Scheme 96).[328−334]

Scheme 96



		Ref.
$R=(CH_2)_6CH_3$ R'=H		328a
$R=CH_2OCH_3$ R'=H		328a
$R=CH(CH_3)OH$ R'=H		328b
$R=CH_3$ $R'=C_2H_5$ R''=H R'''=CO_2Et	80%	330
R=R'=H R''=R'''=CH_3	80%	331
R=H R'=CH_3 R''=R'''=CH_3	50%	331
R=H R'=$COOCH_3$ R''=R'''=CH_3	66%	331
R=R''=H R'=CH_3 R'''=CH_2OH	70%	332
R=R''=H R'=CH_2CH_3 R'''=CH_2OH	70%	332
R=R''=H R'=$C(CH_3)_3$ R'''=CH_2OH	70%	332
R=R'=H R''-R'''=$OCH_2C(CH_3)_2CH_2O$	73%	333

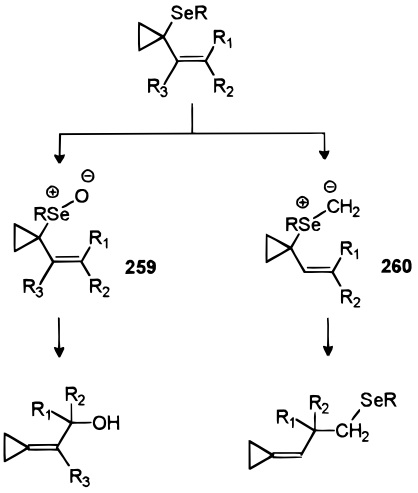


Treatment of 1-cyclopropylcyclopropene (**258**) with $NaNH_2$ led to the formation of bicyclopropylidene **14** in 30% yield.[335] Endobicyclic ACPs were formed from isomerization of bicyclic cyclopropenes.[205a] The deprotonation with *tert*-butyllithium of BHT ester of cyclopropanecarboxylic acid or *S*-*tert*-butyl esters of cyclopropanethiocarboxylic acids gave the corresponding lithium enolates that were used for X-ray crystal structure analysis.[336] Finally, a cyclopropylidenemolybdenum carbene complex was obtained by treatment with BuLi of a cyclopropyl carbene complex.[337]

Cyclopropyl selenoxides **259** or selenonium ylides **260**, generated from the corresponding salts, gave ACPs by base-mediated sigmatropic rearrangements (Scheme 97).[338] Sulfonium salts give the same isomerization as selenonium salts with comparable yields.[338]

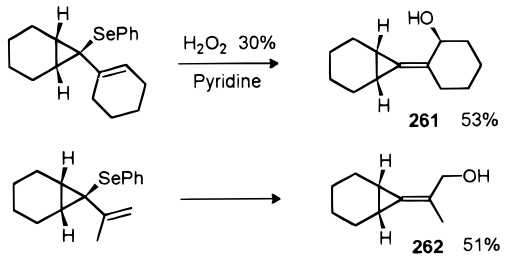
Hydroxylated methylenenorcaranes **261** and **262** were obtained in fair yields via selenoxide sigmatropic rearrangement (Scheme 98).[97]

Scheme 97



R_1=H, R_2=C_6H_{13}, R_3=H	75%	R=CH_3, R_1=H, R_2=C_6H_{13}	85%
R_1=H, R_2=C_6H_{13}, R_3=Ph	70%	R=CH_3, R_1=H, R_2=C_6H_{13}	70%
R_1=C_8H_{17}, R_2=C_8H_{17}, R_3=H	75%	R=Ph, R_1=H, R_2=H	60%
R_1=R_2=-$(CH_2)_3$-, H, R_3=H	80%	R=Ph, R_1=H, R_2=C_6H_{13}	67%
R_1=H, R_2=C_5H_{11}, R_3=H	77%	R=CH_3, R_1=CH_3, R_2=C_6H_{13}	85%
R_1=H, R_2=C_5H_{11}, R_3=C_6H_{13}	92%		

Scheme 98



2. Thermal and Photolytic Isomerizations

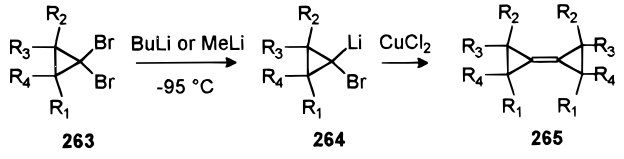
Thermal isomerizations are also found to give ACPs, but are much more limited in scope. By heating at 265 °C, a trichlorospirohexane gave an allylidenecyclopropane in 70% yield.[339] Several [1.1.1]-propellanes gave dimethylenecyclopropanes in a flow system at 430 °C.[205a,340] 1-Phosphinoyl-1-cyclopropyl-3-(*o*-alkynylphenyl)allenes gave the isomeric phosphinoyl ACPs at much lower temperature (80−100 °C) in 52−68% yield.[341] An ACP intermediate is hypothesized in the thermal Brook rearrangement of (1-diphenylmethylsilyl)cyclopropanecarboxylate.[248] A tricylic diazo ketone, in the presence of dimethylamine, gave an aminoacryloyl-MCP under photolysis.[342]

E. Carbene Dimerizations

A large series of symmetrically substituted bicyclopropylidenes were synthesized by a common method consisting of a dimerization of cyclopropyl carbenes catalyzed by $CuCl_2$. The carbene precursors were synthesized by metal−halogen exchange of *gem*-dibromocyclopropanes **263** (Scheme 99).[234,343−346]

The reaction is essentially a "one pot" reaction; lithium−bromo exchange occurs at −95 °C, followed by treatment with $CuCl_2$ (10 mol %) at low temper-

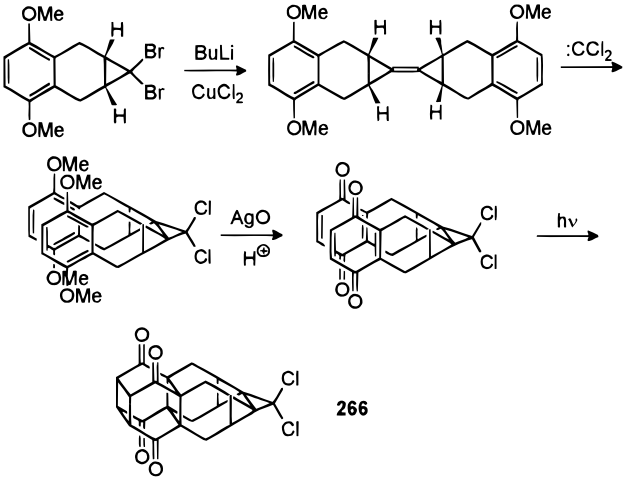
Scheme 99



		Ref.
R_1=PhCH$_2$, R_2=R_3=R_4=H	87%	234
R_1=R_4=H, R_2-R_3=-(CH$_2$)$_4$-	87%	234
R_1=R_4=H, R_2=Me, R_3=Et	65%	234
R_1-R_2=-(CH$_2$)$_4$-, R_3=R_4=H	85%	234
R_1-R_2=-CH$_2$CHORCHORCH$_2$-, R_3=R_4=H	58%	345
R_1=R_2=R_3=R_4=Me	30%	234
R_1=Ph, R_2=R_3=R_4=H	50%	234
R_1=R_4=H, R_2=Me, R_3=Ph	75%	234
R_1=R_4=H, R_2=Ph, R_3=Ph	60%	234
R_1=BuO, R_2=R_3=R_4=H	21%	234
R_1-R_2=-O-(CH$_2$)$_3$-, R_2=R_3=R_4=H	26%	234
R_1=PhO, R_2=R_3=R_4=H	56%	234
R_1=PhS, R_2=R_3=R_4=H	44%	234
R_1=PhSCH$_2$, R_2=R_3=R_4=H	86%	344
R_1=PhCH$_2$SCH$_2$, R_2=R_3=R_4=H	59%	344
R_1=*i*-PrSCH$_2$, R_2=R_3=R_4=H	48%	344
R_1=*c*-HexSCH$_2$, R_2=R_3=R_4=H	67%	344

ature and workup at room temperature. The yields depend on the substrates and range from poor to excellent (20−87%). Mixed couplings between different carbenoids are possible, but led to mixture of products. The diastereoselectivity with monosubstituted cyclopropanes is poor, and mixtures of all the possible diastereoisomers are obtained. One of these bicyclopropylidenes has been utilized for the synthesis of a tubelike cage compound **266** (Scheme 100).[346] A successive mechanistic study on the mode

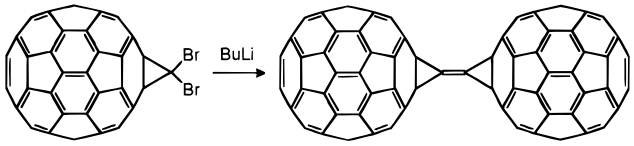
Scheme 100



of formation of cyclopropyl "carbene dimers" suggests that these products arise by elimination from an intermediate vicinal bromo lithio species rather than by an effective dimerization process.[346b]

A synthesis of a C_{60} fullerene bicyclopropylidene has been recently attempted with this method. The compound **268** was not isolated but clearly detected with a MALDI-TOF mass spectrometric analysis (Scheme 101).[347]

Scheme 101



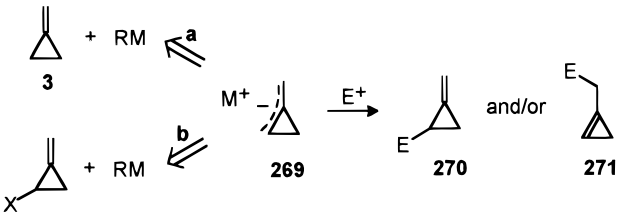
IV. From Preformed Methylene- and Alkylidenecyclopropanes

A. Functionalizations via Organometals

1. At the Cyclopropane Ring

The functionalization of MCPs by addition of electrophiles to the delocalized anion **269** (Scheme 102)

Scheme 102

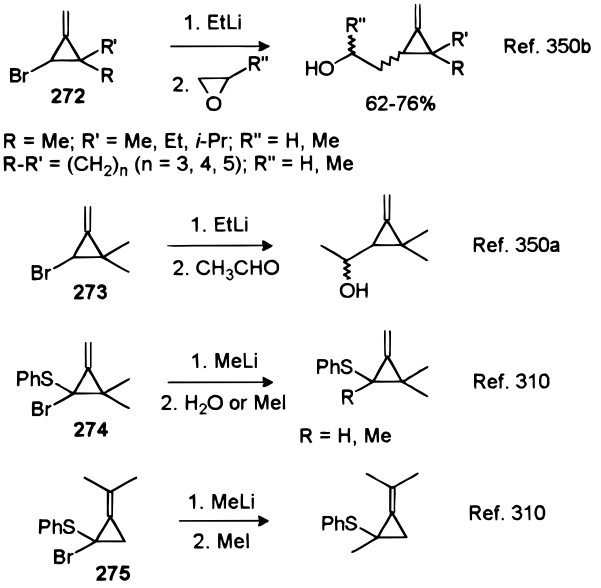


represents a straightforward and viable route for the synthesis of derivatives substituted at the cyclopropane ring. Indeed, the electrophiles add preferentially to ring allylic positions in order to give the less strained compounds **270**. Cyclopropene derivatives **271** have been detected or isolated in only a few cases.[348,349]

The reactive intermediate allylic metal species can derive either from the metalation reaction of a simple MCP derivative (route a) or from the metal−halogen exchange of a 1-halo-2-methylenecyclopropane (route b, X = halide). Albeit procedure a is more direct and has found more applications, procedure b has been the first one to be studied chronologically. This is due to the early synthesis of 1-bromo-2-methylenecyclopropanes accomplished by dibromocarbene addition to allenes and subsequent reduction with Bu_3SnH (see section II.A.1). The lithium salts obtained after treatment of 1-bromo-2-methylenecyclopropanes **272** and **273** with EtLi have been alkylated by oxiranes and acetaldehyde, respectively (Scheme 103).[350] Recently, Baird has used this method for the functionalization of geminal bromo thiophenyl ACPs **274** and **275** (Scheme 103), easily obtained by benzenesulfenyl chloride addition to bromocyclopropenes.[310]

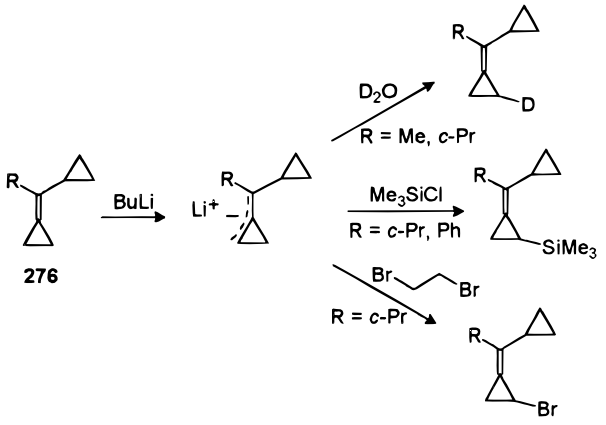
The high acidity of the ring protons of MCP, necessary for the development of route a in Scheme 102, was observed more than 20 years ago by Harris and co-workers, who profitted for the obtainment of polydeuterio MCP by deuterium exchange with DMSO-d_6 at 25 °C.[351] Later, tetradeuterio MCP was used by Noyori in order to gain evidence for the involvement of a TMM species in the nickel catalyzed [3 + 2] addition.[352]

Scheme 103



The earlier applications by use of the metalation procedure have been accomplished by Russian workers on cyclopropylidene cyclopropane derivatives **276** (Scheme 104). The subsequent functionalization

Scheme 104

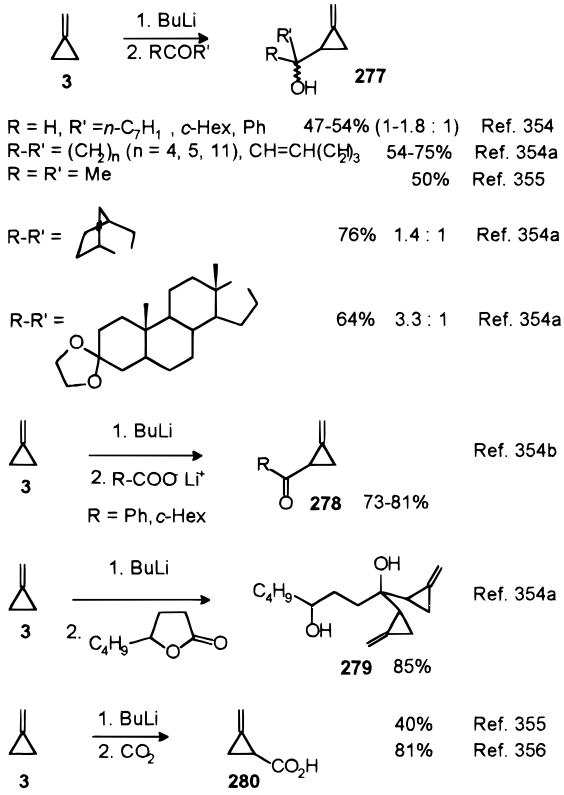


occurred regioselectively at the allylic positions of the cyclopropane ring possessing the exo double bond.[353]

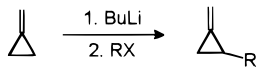
Only relatively recently MCP itself has been used as a substrate in the metalation route, first by Thomas and Binger, who studied the addition to carbonyl compounds[354] and the silylation/alkylation reaction,[348] respectively. The addition reactions of methylenecyclopropyl lithium to C=O bond are reported in Scheme 105. Methylenecyclopropyl carbinols **277** and **279** were obtained in moderate to good yields from aldehydes or ketones and one lactone, respectively. Additions to lithium carboxylates gave ketones **278** in excellent yields. Addition to CO_2 gave methylenecyclopropane carboxylic acid **280**.

Heteroatom substitution and monoalkylation by alkyl halides and oxirane give usually moderate yields of the corresponding 2-substituted MCP derivatives (Scheme 106). The tetradeuterated derivative of 2-(2-methylenecyclopropyl)ethanol **281**,[216] as well as the ^{13}C- and ^{14}C-labeled analogues obtained by alkylation to labeled oxirane,[362] were used by

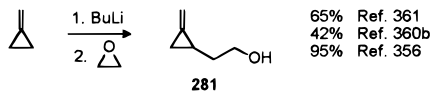
Scheme 105



Scheme 106



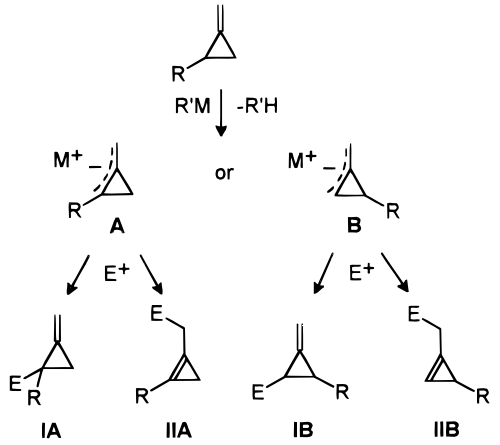
R	X	Yield (%)	Reference
$SiMe_3$	Cl	72	348
$SiMe_2Cl$	Cl	36	356
$GeMe_3$	Cl	27	357
$SnMe_3$	Cl	53	355
$SnBu_3$	Cl	30	358
i-Bu	Br	40	355
$CH_2CH=CH_2$	Br		359
$CH_2CMe=CH_2$	Cl	30	359
CH_2Ph	Br	44	360a
$(CH_2)_3OTHP$	Br	55	360b
$(CD_2)_2OH$	Br		216



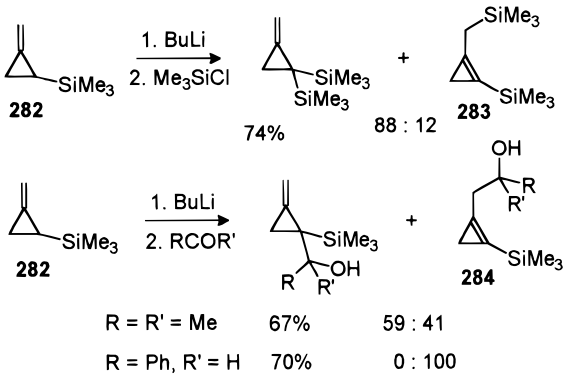
Baldwin to access variously labeled (2-methylenecyclopropyl)acetyl-CoA derivatives for mechanistic studies related to the biological activity of hypoglycine A (**1**).

The same procedure applied to substituted MCPs might in principle afford four different types of products, deriving from the two allyl anions **A** and **B** (Scheme 107). Again, functionalization at the cyclopropane ring prevails. Products of type **IIA**, **283** and **284**, have been isolated only from 2-(trimethylsilyl)methylenecyclopropane **282** in the silylation and addition to carbonyls of the corresponding anion (Scheme 108).[348] These products have been proposed to originate from an electron-transfer mechanism.

Scheme 107



Scheme 108

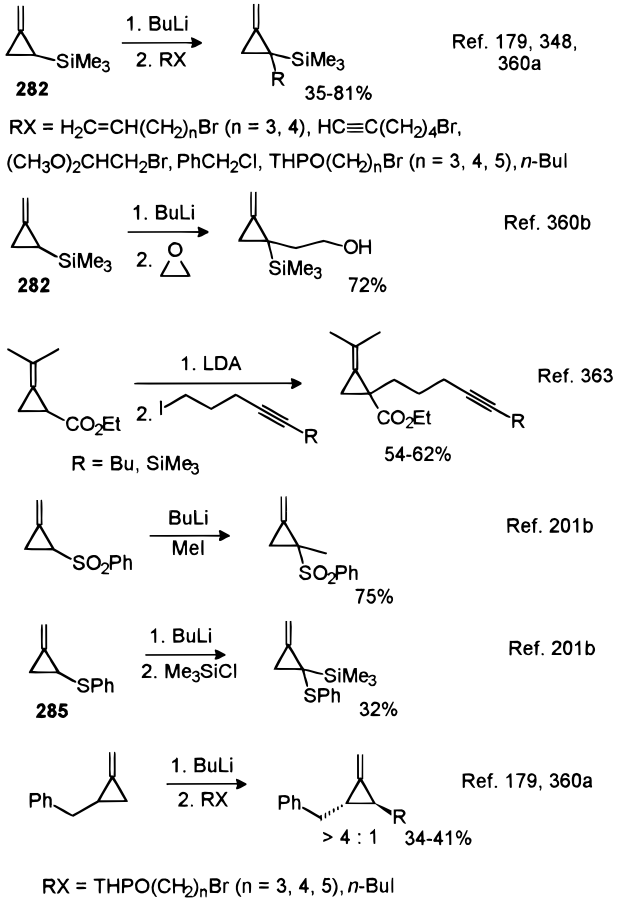


Alkylation of the anions generated from 2-substituted MCPs occurred exclusively at the ring carbon atoms to afford products **IA** or **IB**, generally in a regiospecific manner, depending on the ability of the substituent R in stabilizing an adjacent negative charge (Scheme 107). Trimethylsilyl, ester and sulfonyl groups direct the alkylation at the α position by stabilizing anion **A**, while alkyl groups favor the formation of *β* alkylation products (Scheme 109). The low yield obtained from the thiophenyl derivative **285** is ascribed to a competitive elimination to methylenecyclopropene followed by butyl addition at the *endo* double bond (see section IV.B.1).[201b]

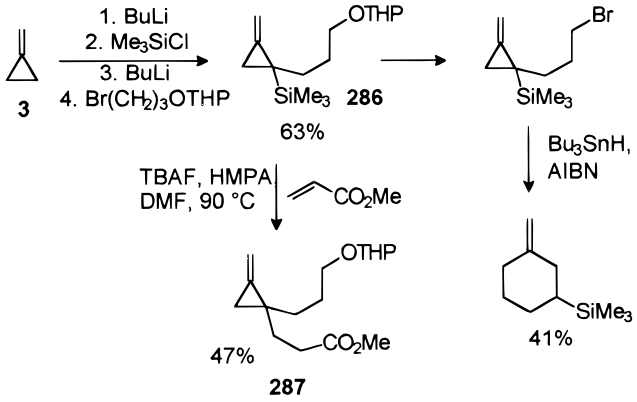
Most of the compounds reported in Scheme 109 have been actually prepared more conveniently by a one-pot sequential double alkylation procedure starting from MCP. For example, Kilburn and coworkers have synthesized in such a way 2,2- and 2,3-disubstituted MCPs employed in a synthetic strategy involving the MCP ring opening and cyclization through radicals (Scheme 110).[179,360b] Geminal dialkyl-disubstituted MCP **287** for this process have also been prepared by regioselective generation of the anion α to the alkyl group from 2-alkyl-2-trimethylsilyl MCP **286** followed by Michael addition to acrylates (Scheme 110).[364]

The metalation/alkylation procedure has been recently extended to the synthesis of substituted BCP derivatives.[349,356,365] BCP (**14**) and the symmetrically substituted 7-cyclopropylidenedispiro[2.0.2.1]heptane **288** gave excellent yields of the expected substitution products (Scheme 111), while unsymmetrical BCPs

Scheme 109



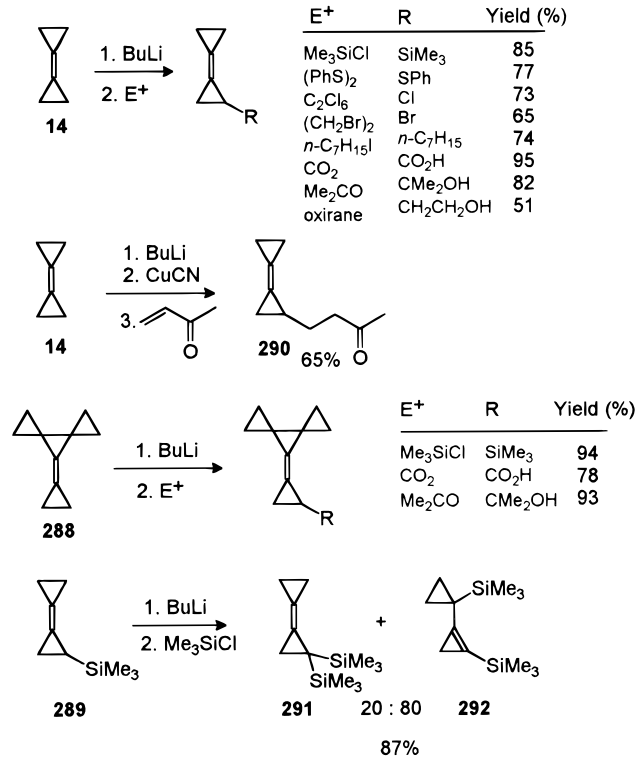
Scheme 110



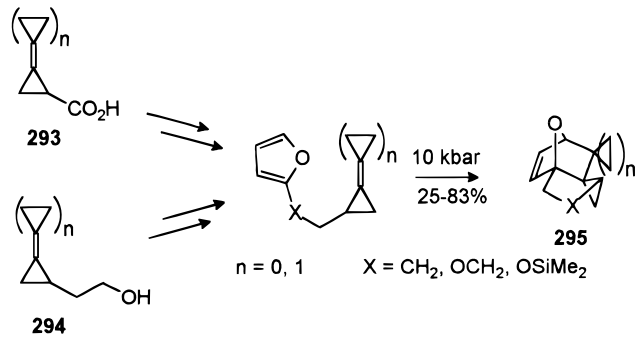
gave mixtures of silylated derivatives still in good yields, but with very little selectivity.[349] Reaction of a lower order BCP cyanocuprate with methyl vinyl ketone afforded the desired conjugate addition product **290** in good yield (Scheme 111).[365] Trimethylsilyl BCP **289** gave bis(silylated) compounds **291** and **292** in analogy to the MCP homologue, but with a reversed ratio (Scheme 111),[349] reflecting the smaller difference of strain energy between the products in this case.

BCPs **293** and **294** ($n = 1$, Scheme 112) and their MCP analogues ($n = 0$) have been utilized by de Meijere and co-workers for the synthesis of interesting penta- or tetracyclic heterocycles **295** by means of intramolecular Diels−Alder reactions to furan derivatives under high pressure.[356]

Scheme 111



Scheme 112



2. At the Exocyclic Double Bond

Although much less interest has been focused to the functionalization at the exo double bond of ACP derivatives, it has been shown that it is possible to generate the vinyl carbanion from (bromomethylene)-cyclopropane (**296**) and to react it with different electrophiles (Scheme 113).

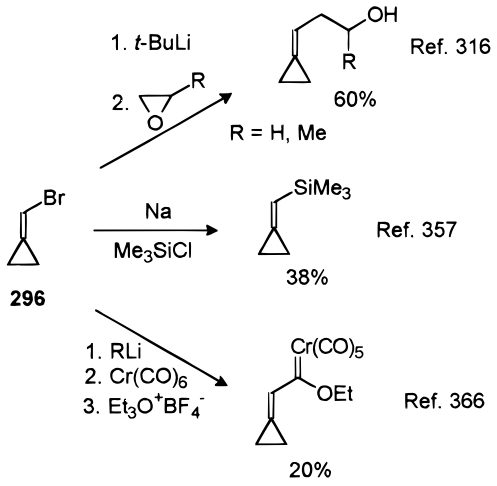
ACPs have also been obtained from cross-coupling type reactions from (bromomethylene)cyclopropanes (Scheme 114).

Tin-substituted derivatives **298** have been obtained by metalation of the oxazolidinone **297** at the vinylic position (Scheme 115).[367]

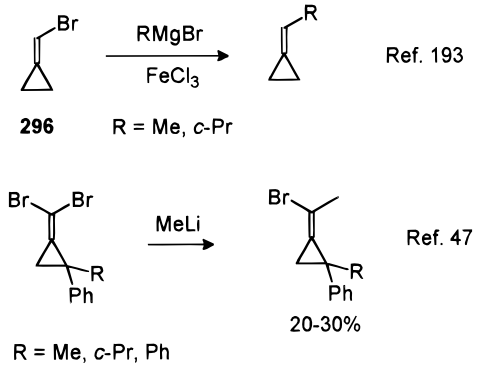
ACPs have recently been synthesized by reaction of homopropargylic sulfonates with triorganozincates (see section II.B.1). The reaction has been proposed to involve an intermediate cyclopropylidene alkylzinc reagent **299**, which indeed has been trapped by an electrophilic reagent. The overall process constitutes a straightforward access to variously functionalized ACPs (Scheme 116).[134]

Allylidenecyclopropanes **301** have been synthesized by reaction of vinylidenecyclopropanes **300** with

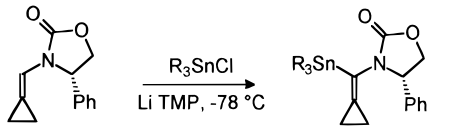
Scheme 113



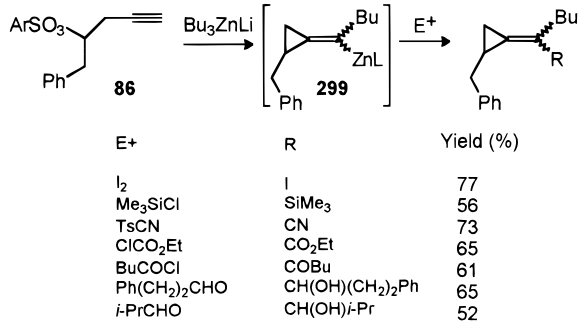
Scheme 114



Scheme 115

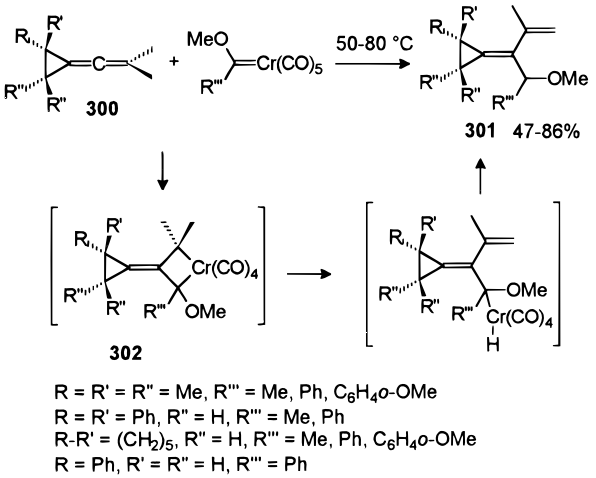


Scheme 116



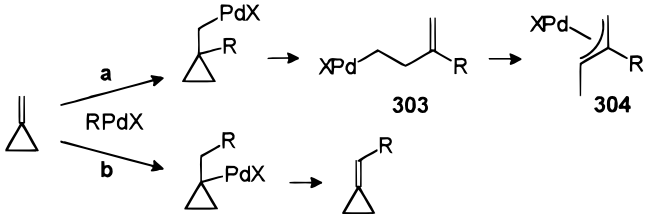
Fischer chromium (and molybdenum) carbene complexes (Scheme 117).[368] The reaction outcome has been interpreted to derive from initial formation of a chromium metallacyclobutane species **302** by addition on the dimethyl-disubstituted double bond, followed by β-hydride elimination and final reductive elimination. Products with *E* configuration at the double bond result from attack of the carbene from the less hindered side, while the stereoselectivity with a vinylidenecyclopropane monosubstituted at the ring is low (2:1).[368]

Scheme 117



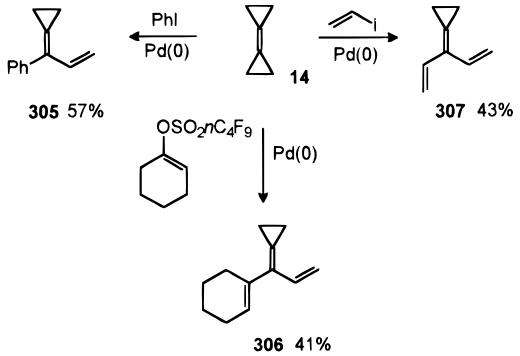
ACP derivatives have found several applications in palladium chemistry, reacting under various conditions in the presence of different reagents and Pd(II) or Pd(0) catalysts. In most cases, they undergo ring-opening reactions, as in the case of [3 + 2] cycloadditions in the presence of alkenes and in chloropalladation of MCP.[8a] Carbopalladation of ACP derivatives may follow two different routes, depending on the regiochemistry of the addition of organopalladium species to the double bond (Scheme 118).

Scheme 118

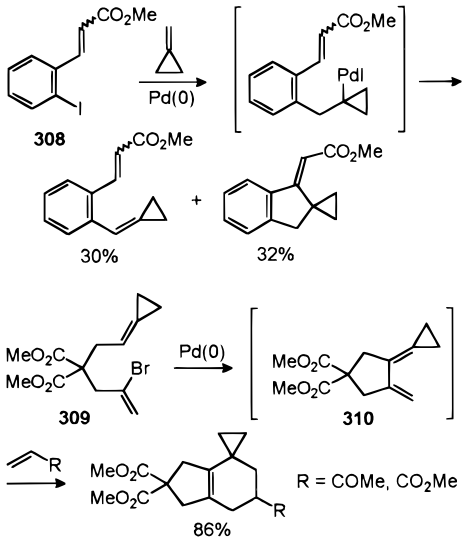


Usually, route a, with Pd bonding at the 1′-position, is preferred; in this case, a ring opening occurs to give a σ-homoallyl Pd complex **303**, which in turn rearranges to a π-allyl complex **304**.[369,370] In the presence of nucleophiles, products of attack to all the intermediates have been isolated.[175,267] Allylidenecyclopropanes **305**−**307** have been successfully synthesized by this route by using BCP as acceptor in Heck-type reactions (Scheme 119).[274] The terminal vinyl moiety is presumably formed by β-hydride

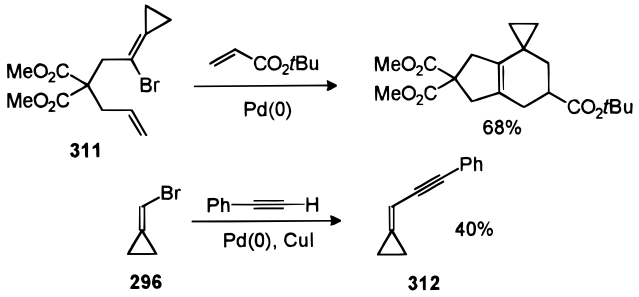
Scheme 119



Scheme 120



Scheme 121



elimination from a homoallyl complex of type **303**. The interesting dendralene systems obtained were reacted subsequently in Diels−Alder reactions.[274]

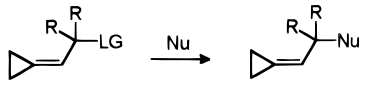
In some cases, different results have been obtained by employing ACPs in Heck conditions, which can be rationalized in terms of a preference for the alternative regiocontrol in the addition followed by β-hydride elimination (route b, Scheme 118). This was the case of the addition of iodocynnamate **308** to **3** under Pd catalysis[371] and of the intramolecular Heck reaction−Diels−Alder cycloaddition domino process started from **309**,[372] which occurred through the formation of diene **310** (Scheme 120). Formation of ACPs in low yield in the acryloxypalladation of MCP has been ascribed to an analogous mechanism.[373]

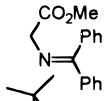
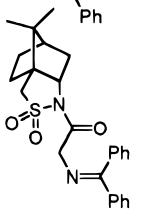
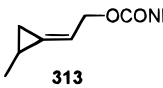
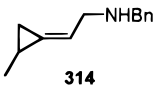
(1-Bromoalkylidene)cyclopropanes have also recently been used as starters for Pd-catalyzed functionalizations (Scheme 121). The same diene **310** has been generated from a bromo ACP **311** and used in a Diels−Alder cycloaddition.[372] (Bromomethylene)-cyclopropane (**296**) gave the enyne **312** by means of a Sonogashira−Castro reaction with phenylacetylene.[358]

3. At the Allylic Position

As already mentioned in section III.C.3, the ACP synthesis developed in Salaün's and de Meijere's groups worked either by using vinylcyclopropanes or ACPs containing a suitable allylic leaving group as starting reagent (see Scheme 91).[313] Reactions car-

Table 13. Alkylidenecyclopropanes Synthesized from Cyclopropylideneethanol Derivatives via Allylpalladium Complexes

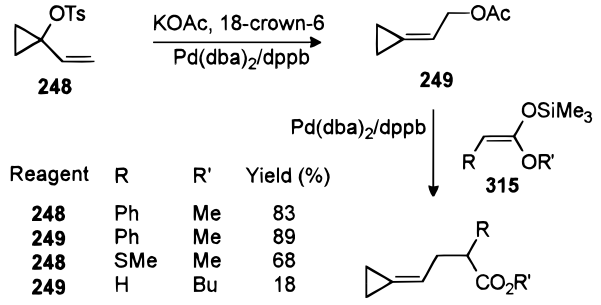


entry	R	LG	NuH	Yield (%)	Ref.
1	H	OCOMe	$CH_2(CO_2Et)_2$	85	313
2	H	OCO_2Me	$CH_2(CO_2Me)_2$	76	313
3	H	$OC(=NH)CCl_3$	"	100	374
4	Me	OCOMe	"	84	313
5	H	OCO_2Me		76	313
6	H	OCO_2Et		66 (d.e. >90%)	317
7	 313		 314	74	320

ried out on ACPs having an acetate or carbonate leaving group are reported in Table 13. In the last entry, the carbamate leaving group of **313** already contained the nucleophile benzylamine, which was freed by decarboxylation, to afford the allylbenzylamine **314**.

The (cyclopropylidene)ethyl acetate **249** was also able to undergo nucleophilic attack by silylketene acetals **315** under Pd(0) catalysis to afford ACPs (Scheme 122).[229c] In contrast, vinylcyclopropane to-

Scheme 122

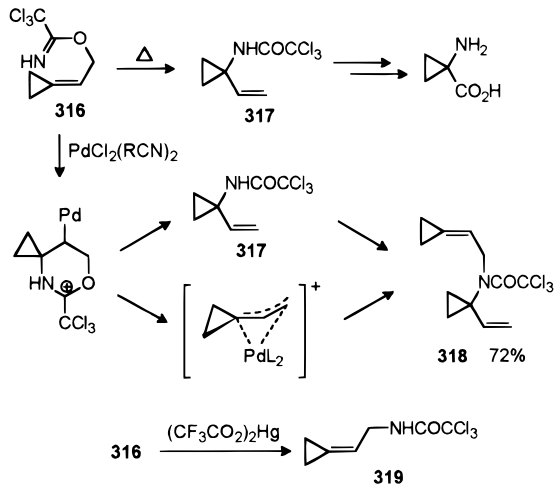


Reagent	R	R'	Yield (%)
248	Ph	Me	83
249	Ph	Me	89
248	SMe	Me	68
249	H	Bu	18

sylate **248** did not give this reaction under the same conditions, but it reacted when potassium acetate and 18-crown-6 were added to induce its preliminary conversion to derivative **249** in situ.

The trichloroacetimidate **316** has been subjected to a thermolytic aza-Claisen rearrangement en route to the synthesis of cyclopropane amino acids. In the attempt to catalyze the rearrangement, reactions with several metal derivatives have been performed

Scheme 123



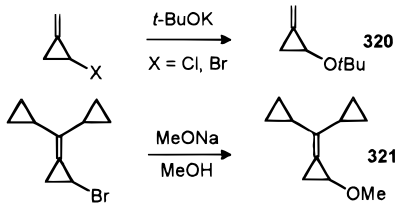
(Scheme 123).[374] Palladium(0) proved to be inefficient, but formed the π-allyl complex, as proved by attack of nucleophiles (Table 13, entry 3). Catalysis by Pd(II) salts gave product **318**, presumably arising from attack of **317** to the π-allyl complex, formed as well in the reaction (Scheme 123). Indeed, protection at nitrogen furnished the desired rearranged products. Finally, the anti-aza-Claisen ACP derivative **319** was obtained by the use of mercury salts.[374]

B. Additions

1. To Methylenecyclopropenes

Addition of nucleophiles to unstable methylenecyclopropenes, generated in situ as reactive intermediates, is an useful route to the synthesis of 2-heterosubstituted MCPs. In this way, 2-*tert*-butoxymethylenecyclopropane **320** has been obtained from the corresponding halo derivatives by an elimination−addition sequence,[62,63] and the methoxy derivative **321** has been synthesized analogously[375] (Scheme 124). The same elimination−addition sequence on

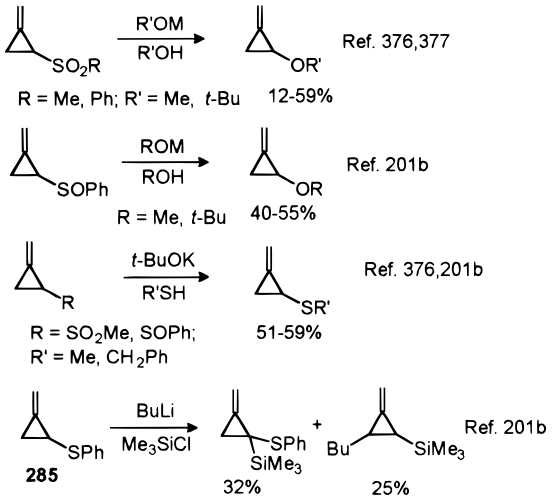
Scheme 124



gem-dihalo MCPs gave double nucleophilic addition,[213a] or, with equimolar amounts of base and after hydrolysis, cyclopropenones.[54]

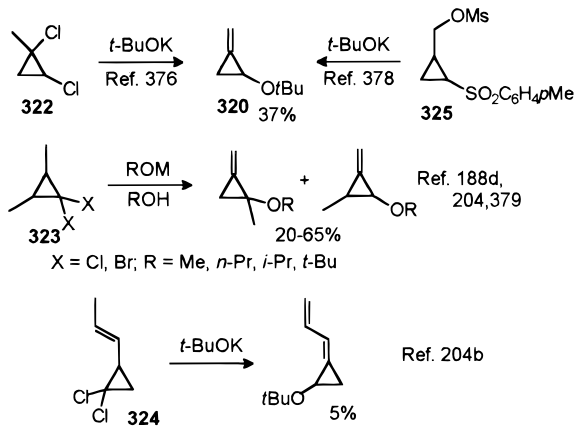
The same procedure is also effective on sulfur-substituted MCPs (Scheme 125). Obtainment of butyl-substituted MCP in addition to the expected silylated compound was explained with an elimination from **285**, followed by nucleophilic addition of the butyl carbanion.[201b]

Scheme 125



Since the base of choice for the elimination reaction is potassium *tert*-butoxide as in the synthesis of ACPs by elimination from halocyclopropanes (see section III.A.1), dihalocyclopropanes can be used directly in this synthesis by a double elimination−nucleophilic addition sequence. Both 1,2-dihalo- **322** and *gem*-dihalocyclopropanes **323** and **324** gave the reaction (Scheme 126),[376] which occurred also by replacing the

Scheme 126

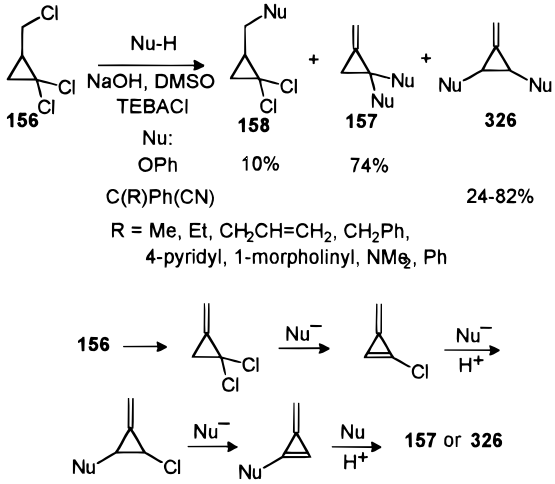


leaving groups with the sulfonyl mesylate, like in **325**.[378]

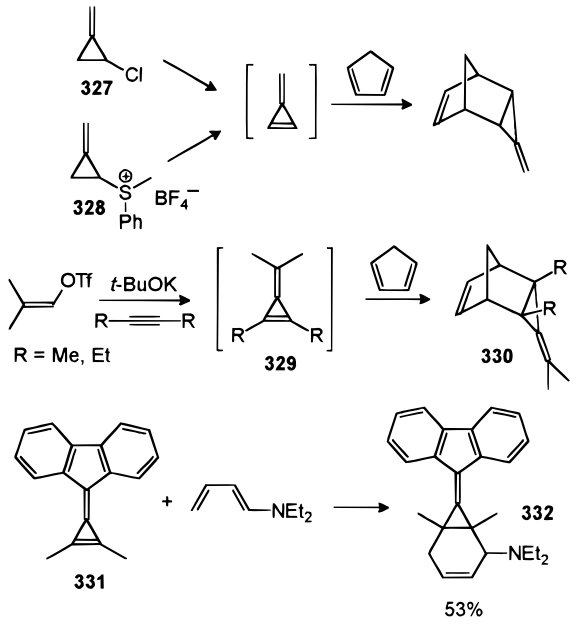
Effective methods for the obtainment of products **157** or **326**, deriving from double nucleophilic addition to trichlorocyclopropane **156**, have been developed by Jonczyk and co-workers (see section III.A.1) (Scheme 127).[213a,d] The overall process is supposed to involve two methylenecyclopropene species and the regiochemistry of the final addition depends on the different ability of the nucleophile to stabilize a developing adjacent negative charge.

Bicyclic fused ACPs have been synthesized by Diels−Alder cycloadditions to the endocyclic double bond of methylenecyclopropenes (Scheme 128). This method has been used for detection of methylenecyclopropene itself, generated by elimination from the chloro derivative **327**[62] or the sulfonium salt **328**,[201b] by trapping with cyclopentadiene. Tetraalkyl-

Scheme 127



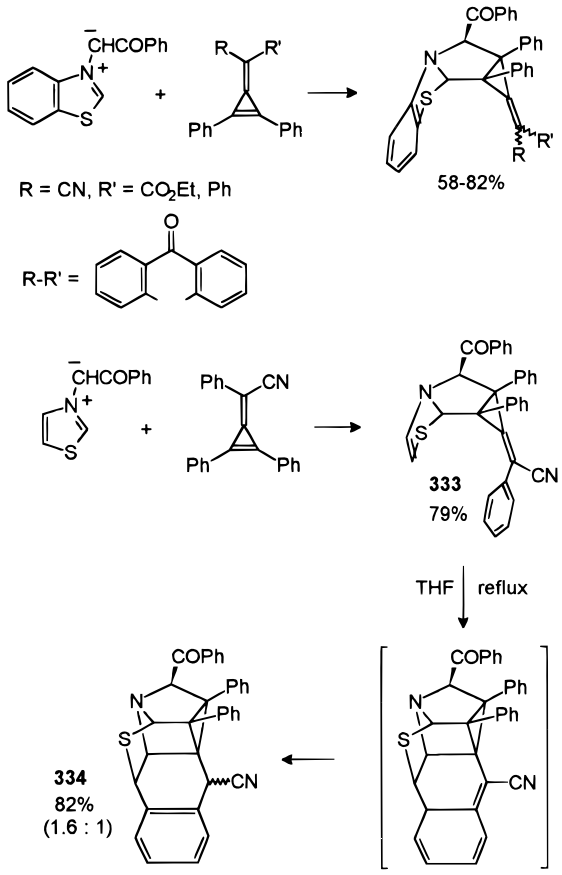
Scheme 128



tetrasubstituted methylenecyclopropenes **329**, generated by addition of alkylidene carbenes to alkynes, have been trapped analogously to afford cycloadducts **330** in excellent yields.[120] Endo adducts were exclusively obtained in these cycloadditions. The stable substituted calicene **331** was reacted with an aminodiene to afford the conjugated ACP **332**.[380]

Reactions of stabilized methylenecyclopropenes with 1,3-dipoles have also been carried out and usually give products whose formation has been interpreted with an initial cycloaddition to the endocyclic double bond to give unstable primary adducts that readily rearrange.[381] A few examples of stable [3 + 2] cycloadducts by reaction of benzothiazolium or thiazolium *N*-methylides with methylenecyclopropenes have been reported (Scheme 129).[382a,b] The adduct **333** gave an intramolecular [4 + 2] cycloaddition by refluxing in THF affording the cage compound **334**.[382b] Related cage compounds were directly obtained in reactions with other thiazolium *N*-methylides,[382b,c] and with pyridinium *N*-methylides[383] and imidazolium *N*-methylides.[384]

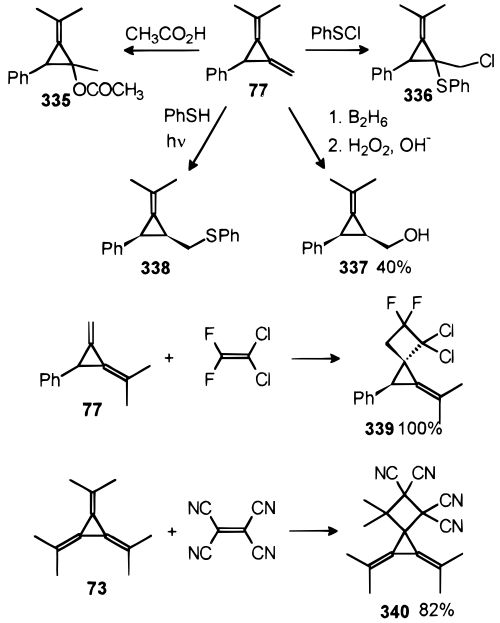
Scheme 129



2. To Polyalkylidenecyclopropanes

Electrophilic additions to the less substituted double bond of the bis-ACP **77** occurred to give small amounts of products **335** and **336** (Scheme 130),[385] in addition to major ring-opened compounds. The hydroboration−oxidation gave the alcohol **337**, together with rearranged products deriving from hydroboration of the other double bond and radical addition of thiophenol also produced the 2,3-disubstituted ACP **338** (Scheme 130).[385] [2 + 2] cycloadditions of dichlorodifluoroethylene to **77**[386] and of TCNE to the radialene derivative **73**[118] afforded the corresponding monoadducts **339** and **340** in excellent yields (Scheme 130).

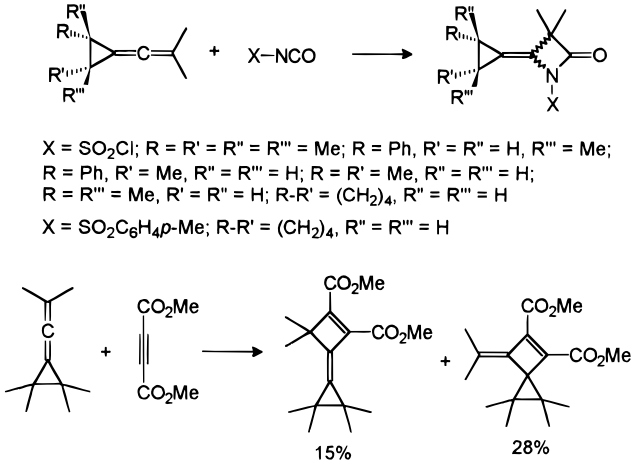
Scheme 130



3. To Alkenylidenecyclopropanes

Isopropenylidenecyclopropanes **300** underwent electrophilic additions to afford mostly ring-opened products; however, in a few cases small amounts of ACPs, arising through an intermediate vinyl cation, have been identified.[387,388] The same compounds gave bicyclic products via [2 + 2] cycloadditions at the dimethyl-disubstituted double bond with reactive isocyanates (Scheme 131).[387−389] Alkenylidenecyclopropanes gave [2 + 2] adducts also with alkynes, but at the cyclopropane-substituted double bond preferably. Only dimethyl acetylenedicarboxylate gave a mixture of both adducts by reaction with **47** (Scheme 131).[390]

Scheme 131



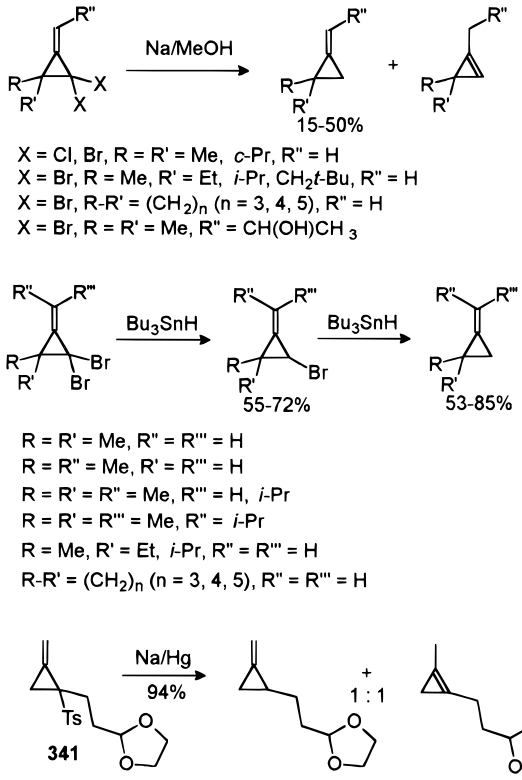
C. Reductions

The reduction of *gem*-dihalo derivatives to the corresponding ACPs can be carried out with alkali metals in alcohol (Scheme 132).[18a,35a,38] Minor amounts (~10%) of isomeric cyclopropenes are usually obtained by this method. A more efficient way to perform the same transformation from dibromides consists in their treatment with *n*-Bu_3SnH;[37,55] with this reagent, a stepwise reduction with obtainment also of the monobromide can be carried out (Scheme 132).[37,45,48] A single example of a reduction of a 2-tosyl MCP **341**, which afforded a roughly equimolar mixture of the corresponding MCP and its isomeric methylcyclopropene, has also been reported (Scheme 132).[128b] Catalytic hydrogenation of a methylenecyclopropene over Rh on alumina afforded low yields of the ACP derivative.[54]

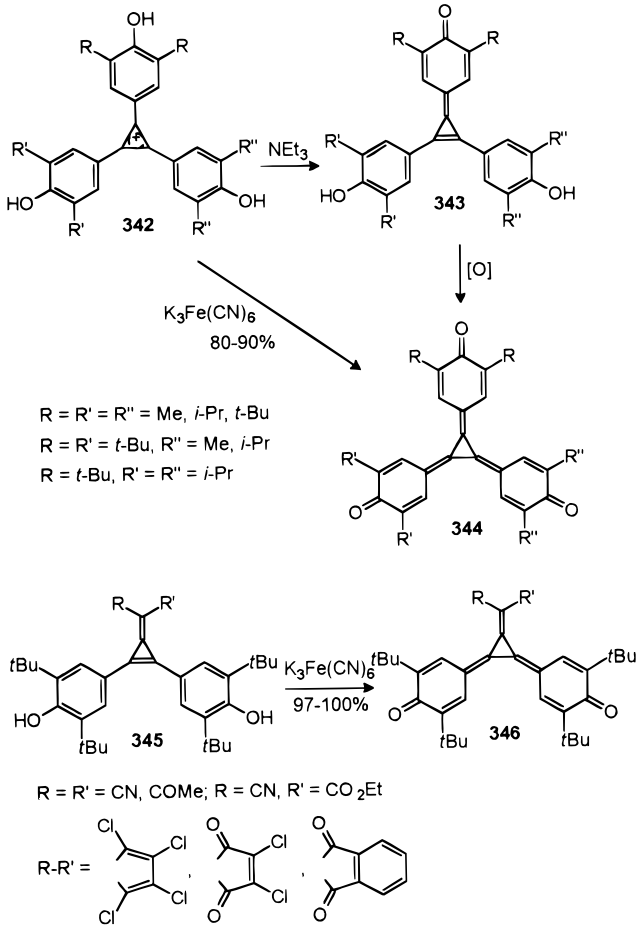
D. Oxidations

Triquinocyclopropanes **344**, peculiar compounds having the [3]radialene skeleton,[118] were obtained by oxidation of diarylquinocyclopropenes **343**, in turn accessible by deprotonation of the corresponding cyclopropenium salts **342** (Scheme 133).[391] Best results were achieved by directly treating the salts

Scheme 132



Scheme 133



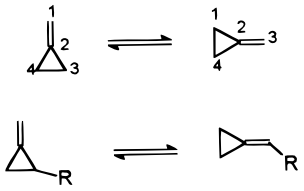
342 with alkaline aqueous potassium hexacyanoferrate. Analogous compounds in which one, two, or all of the three benzoquinone moieties are replaced by anthraquinone or other quinoid systems have been accessed by this way.[391b−f] Related alkylidenediquinocyclopropanes **346** were analogously synthesized from the corresponding diarylcyclopropenes **345** (Scheme 133).[392]

The syntheses of hexacyano- and hexakis(methoxycarbonyl)[3]radialene,[393,118] and of a silyl-substituted hexaethynyl[3]radialene[394] are also based on the oxidation of the corresponding dianions in the final key step of a process started with the reaction of tetrachlorocyclopropene with carbanions.

E. Rearrangements

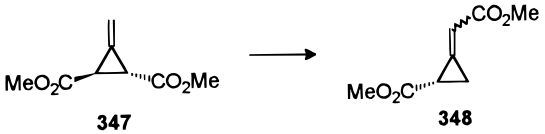
The thermal MCP (or ACP) rearrangement (Scheme 134), several examples of which have already been

Scheme 134



encountered and evidenced along the text, consists in a [1,3]-sigmatropic transformation between two ACPs. It was firstly recognized by Ettlinger in 1952,[395] who assigned the correct structures to Feist's acid dimethyl ester **347** and its isomerization product **348** (Scheme 135), previously observed in the early 1930s.[396]

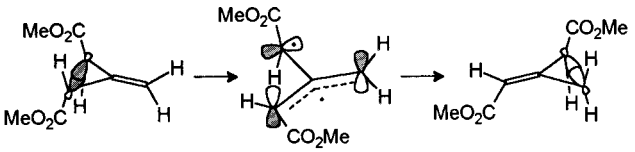
Scheme 135



Some years later, Ullman found that the products of this rearrangement were in fact a couple of diastereoisomers[129] and that the rearrangement of the chiral ester occurred with retention of optical activity.[397] On the mechanistic side, this finding ruled out the occurrence of an intermediate planar diradical or dipolar species. A lot of investigation followed these earlier reports, in order to elucidate the mechanism of this well-recognized archetypical molecular rearrangement, whose discussion is above the scope of the present review, some aspects of which have already been discussed in previous reviews.[398] This rearrangement has been found to be a general process, which occurs with the most diverse derivatives, including a degenerate rearrangement on MCP itself.[399] Detailed studies on labeled[217,351,399b] and chiral nonracemic substrates[161,217,399c−402] and on the kinetics[218,351,399b,403−405] of the rearrangement have also been carried out. The unifying mechanism, able to explain the mass of collected data, most widely accepted with a few exceptions, and supported also by theoretical studies,[406−408] involves the formation of orthogonal diradical intermediates with the "pivot" carbon, i.e., the one which experiences the [1,3]-shift

to the exocyclic carbon atom, migrating with net inversion of configuration and suprafacial utilization of the allyl moiety (Scheme 136).[217,218,399c,400] Re-

Scheme 136

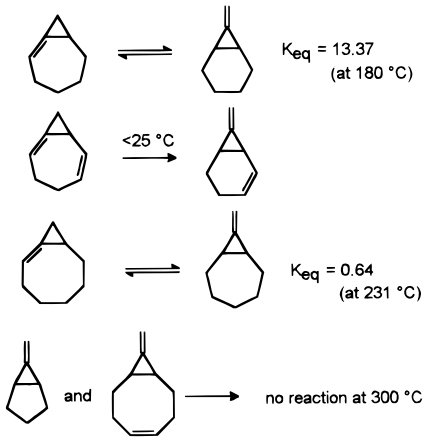


cently, the X-ray crystallographic structure determination of methylenecyclopropane-2-carboxamide has shown that the molecule in its ground state exhibits significant distortion from an idealized geometry in a manner consonant with the stereochemical preferences observed in the MCP rearrangements.[409]

Consistent with the above interpretation is the greatly reduced barrier to isomerization in the presence of radical-stabilizing substituents such as halogens[18a,35a,41,44b,47,49,58,59,206,208,233,410,411] or aryl groups,[51,68,74b,75] as already pointed out. This makes the rearrangement synthetically useful for the obtainment of the thermodynamically more stable ACP derivatives. Creary has investigated the effects on rearrangement rates of substituents on both aryl ring and cyclopropane carbon within a broad series of aryl-substituted MCPs (Scheme 17) and proposed, on the basis of his results, this rearrangement as an useful probe for determination of free-radical substituent effects.[68,74b−i]

When fused bicyclic MCPs are involved in the rearrangement, the relative stability of MCP and ACP derivatives is strongly dependent on the ring size and the presence of further unsaturations in the larger ring (Scheme 137).[158c,161,163,202,209,412] Difference

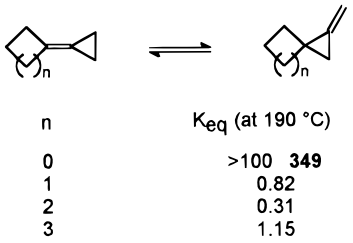
Scheme 137



in stability may become so relevant that the rearrangement occurs at unusually low temperatures[158c] or, when both products are unstable, the intermediate TMM diradicals give mostly dimerization.[413]

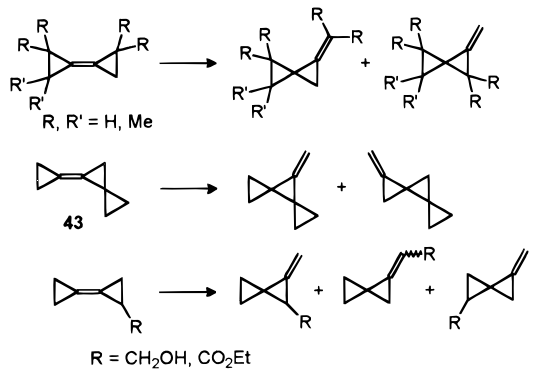
Cyclopropylidenecycloalkanes undergo a similar thermal rearrangement at high temperatures. At the equilibrium, the ACP derivatives usually prevail over their spiranic MCP isomers (Scheme 138).[414]

Scheme 138



Additional ring strain in BCP is the factor which determines complete reversal of the equilibrium to methylenespiropentane **349**,[16a] which has a lower energy strain content of about 12 kcal/mol. The same difference operates in substituted BCPs (Scheme 139).[16c,29,410,414−416] A similar rearrangement has been

Scheme 139



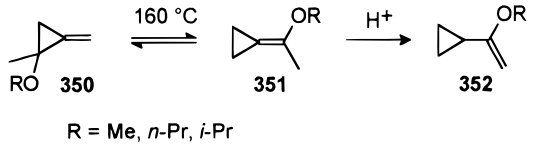
observed in a substituted adamantylidenecyclopropane.[107]

The photochemically induced MCP rearrangement has also been investigated,[95c,216,229b,268,417−419] albeit more sparely. Comparison of the obtained results, substantially different and often less satisfying from a synthetic point of view, with those of thermolysis suggested that photolysis involves excited states of TMM which are not accessible in the thermal reaction.[419,420]

Base-catalyzed MCP rearrangements have also been recorded, among which *cis* to *trans* isomerization of Feist's acid derivatives (and their iron tetracarbonyl complexes) is remarkable.[421]

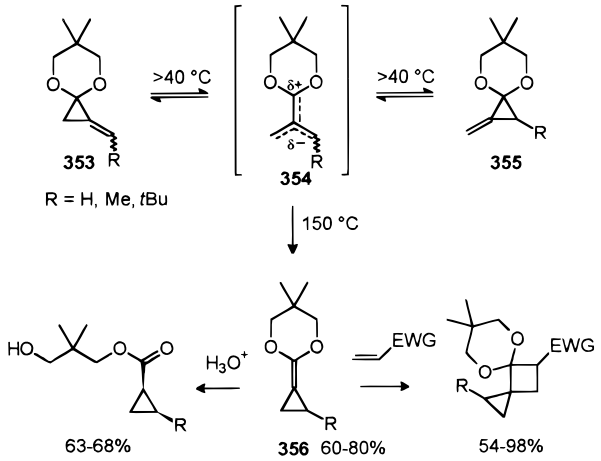
The rearrangement of alkoxy-substituted MCPs **350** deserves some further comments. 2-Isopropoxy-2-methyl-MCP was reported to undergo an unusual thermal rearrangement to give almost quantitatively the enol ether **352**.[204a] Further investigations proved that the product derived from an acid-catalyzed isomerization of the ACP **351** formed by the usual reversible rearrangement (Scheme 140).[378]

Scheme 140



gem-Dialkoxy ACPs **353** were found to isomerize at low temperature (40−100 °C) in a reversible manner, as shown by isotope and chemical labeling

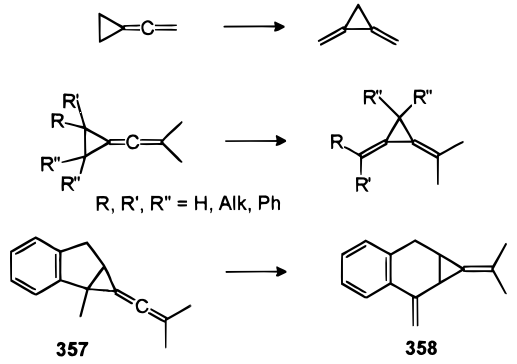
Scheme 141



of the *exo*-methylene position (Scheme 141).[422] For example, the equilibrium ratio of **353**−***E***, **353**−***Z***, and **355** (R = Me) at 100 °C was determined as 62:30:8. In this case, it has been suggested that rearrangement occurs through the dipolar TMM intermediate **354**. At higher temperature, these compounds isomerized irreversibly to dimethylene ketene acetals **356**, which undergo hydrolysis to cyclopropanecarboxylates (mainly *cis*) and [2 + 2] cycloadditions with alkenes, alkynes, azodicarboxylates, and [60]fullerene (Scheme 141).[423]

A thermal rearrangement analogous to the one previously described occurs with vinylidenecyclopropane[424] and a series of isobutenylidenecyclopropanes to give, often as the exclusive products, dimethylenecyclopropane and its corresponding dimethyl derivatives, respectively (Scheme 142).[16c,82,386,410,425−427]

Scheme 142



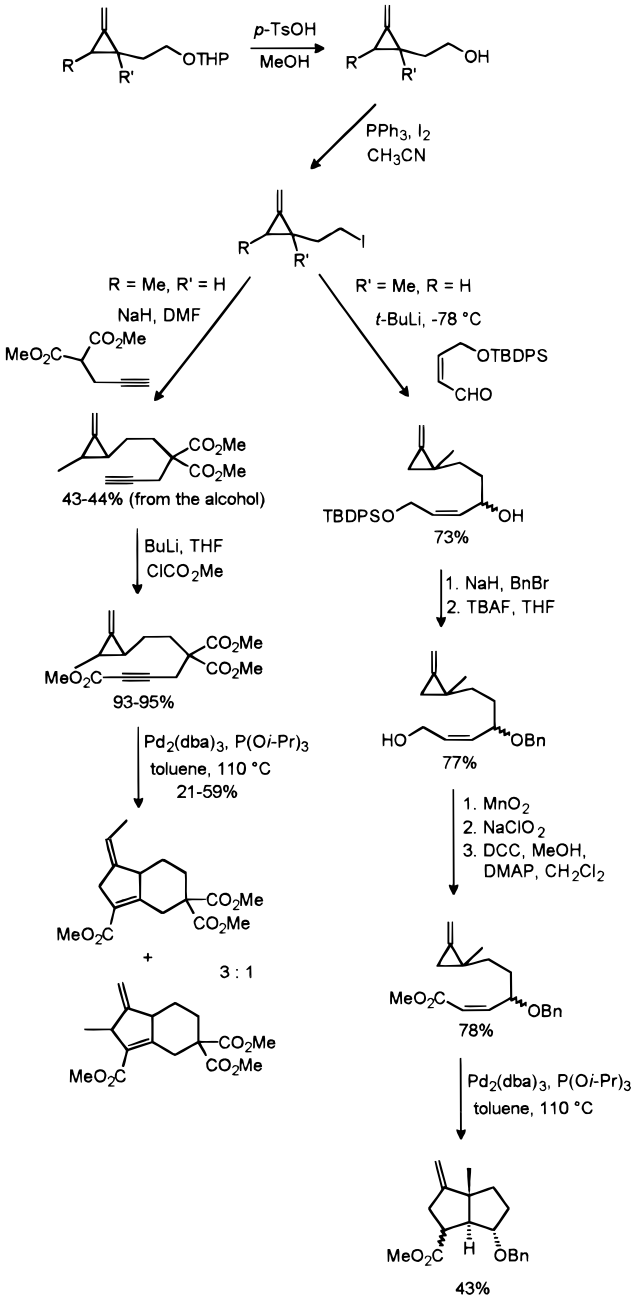
An unusual rearrangement was displayed by the fused alkenylidenecyclopropane **357** which gave exclusively the ACP **358** by heating in refluxing benzene (Scheme 142).[428]

A different rearrangement from alkenylidenecyclopropanes occurred under catalysis of strong bases, or in peculiar cases by thermolysis, to give allylidenecyclopropanes which were trapped or evolved into other products.[429,387,430]

F. Functional Group Interconversions away from the Methylenecyclopropane Moiety

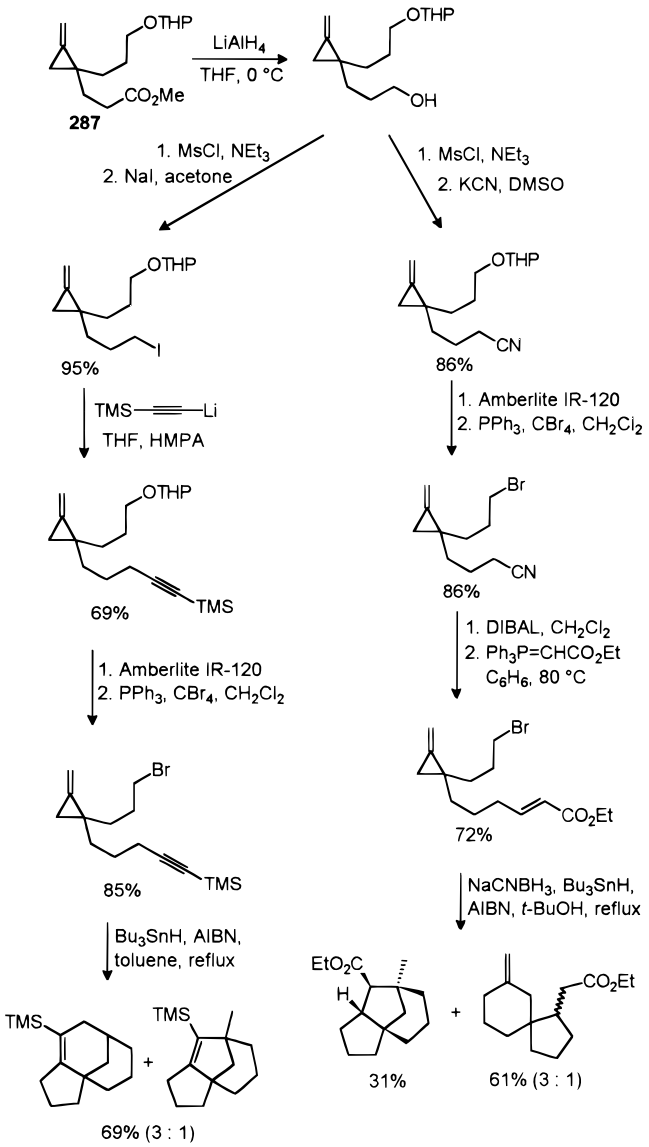
The elevated strain energy content of ACPs makes the cyclopropylidene system rather unstable from a thermodynamic point of view; therefore, it is reactive under thermal conditions or when catalysis by transition metals is employed. However, at low or room temperature these molecules are surprisingly stable on the kinetic side and the cyclopropylidene moiety is able to survive the most diverse reaction conditions. This feature allows a large variety of manipulations to be carried out on MCPs and ACPs for transformation of functionalities without affecting the cyclopropylidene nucleus.

Scheme 143



Reactions with catalytic or stoichiometric amounts of strong acids (HCl,[5d,13,313,249b] H_2SO_4,[4a,265] HIO_4,[182] CF_3COOH,[380] AcOH,[313] *p*-TsOH,[182,431] PPTS,[225] $Me_3O^+BF_4^-$,[201a,377] strongly acidic resins,[297c,360] silica gel[276b−d]) and bases (NaOH,[13,66,215,313,432] KOH,[298a,433] LiOH,[5d] MeONa,[432] *t*-BuOK,[32] NaH,[215,252b,372,374] KH,[20] *n*-BuLi,[20,434] *t*-BuLi,[182] LDA,[435] LiTMP,[267] K_2CO_3,[4a,c,281] *i*-Pr_2NEt,[182] NEt_3,[12,272,436] NH_3[433]) have been per-

Scheme 144



formed. Alkylations of carbonyl and carboxyl functionalities directly linked to the cyclopropane ring or in the side chains can be achieved by the use of Grignard[260b,276e,294b,437,438] or alkyllithium[332,354b,356,418,437,438] reagents. Aryllithium and -magnesium reagents have also been formed by metal−halogen exchange on the aryl group linked to the MCP moiety and they were able to give metal−metal exchange with trimethyl borate and mercuric chloride.[74f] Cyclopropyl Grignard reagents have been obtained from the corresponding cyclopropyl bromides *gem*-disubstituted to the cyclopropylidene moiety and used in coupling reactions.[123] Halogenations on alcohols and carboxylic acids in the chains have been carried out by the use of different agents, e.g., $SOCl_2$,[17,439] PBr_3,[220,281,282] Br_2/PPh_3,[267,372,414] I_2/PPh_3,[356] $(COCl)_2$.[11,433] The use of powerful oxidizing (CrO_3/H_2SO_4,[4a,215,253,261b,361] CrO_3/py,[18b,332,350,401] PCC,[253,294b] MnO_2,[276e,282,313,438] $NaClO_2$,[182] $NaIO_4$,[201a,377] oxalyl chloride/DMSO,[171b,260b,283,313] TPAP/NMO,[273] DDQ,[440] H_2O_2,[201a,376,377] MCPBA,[74c,g] oxone,[60,180] DMDO,[229c] *t*-BuOOH[439]) and reducing ($LiAlH_4$,[4a,18b,70,214,215,220,252b,265,273,313,330,332,356,382a,400,401,414,433,437,441] $NaBH_4$,[282,437] DIBAL[4a,215,252b,261b,312a,320,372,442]) systems is generally compatible with the presence of cyclopropylidene functionalities. Functional group interconversions aside from the cyclopropane ring, e.g., mesylation,[215] tosylation,[5d,214,400] nucleophilic substitutions of halides and sulfonates,[215,400] Wittig and related reactions,[283] esterification,[302,312a,361] thioesterification,[5a,12,14a,c,361,443] and amidation[441] of carboxylic acid or chlorides, usually occur without any inconvenient. Finally, thermolytic group eliminations have also been carried out successfully in some cases.[164,380]

This broad compatibility has allowed long reaction sequences to be carried out on MCP and ACP derivatives in order to assemble the desired reactive functionalities attached to the cyclopropylidene system, as exemplified by recent work from Motherwell's[180,182,294c] (Scheme 143) and Kilburn's[360,364,435] (Scheme 144) groups, who used the synthesized ACPs for intramolecular transition metal-catalyzed [3 + 2] cycloadditions and radical cascade ring-closure reactions, respectively.

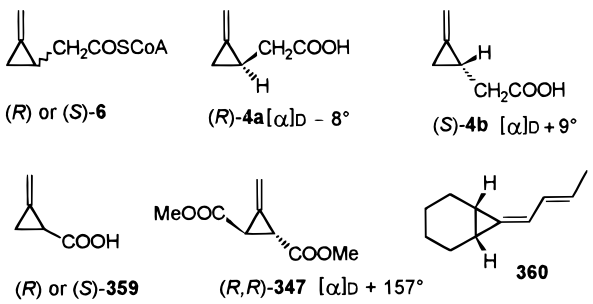
V. Optically Active Methylene- and Alkylidenecyclopropanes

In this section are reported the examples, indeed very few, of the synthesis of optically active MCPs and ACPs by resolution or asymmetric synthesis, disregarding the cases where optical purity is introduced by covalently bonded chiral auxiliaries. Several examples of this type, nevertheless, have been reported throughout the review.

A. By Resolution

The studies on hypoglycine A and its mechanism of action in causing Jamaican vomiting sickness has stimulated the synthesis of chiral optically pure, in both enantiomeric forms, 2-methylenecyclopropaneacetic acid **4** (MCPA), which, as a coenzyme A thioester **6**, is the metabolite directly responsible for hypoglycine toxicity. Syntheses of racemic MCPA from active esters provided diastereomeric mixtures of MCPA-CoA,[5a] also tritiated on the cyclopropyl ring.[4c] The single enantiomers were obtained, however, by esterification of optically pure MCPA **4** obtained from resolution of the racemic acid chloride with (*R*)-(−)-2-phenylglycinol. The diastereomeric amides were separated by HPLC and hydrolyzed in dioxane/aqueous sulfuric acid to give (*R*) **4a** and (*S*)-MCPA **4b** with high optical purity (Scheme 145).[4a,5b,215]

Scheme 145

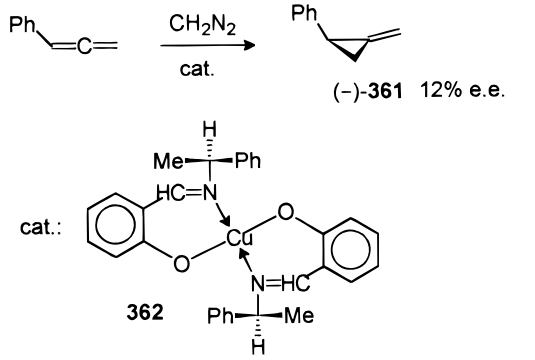


Only a few other examples of resolution are reported (Scheme 145). 2-Methylenecyclopropane carboxylic acid **359** was resolved with cinchonidine.[444] Feist's acid was recently resolved using quinine and analyzed as the dimethyl ester, to give (*R*,*R*)-(+) enantiomer **347** with more than 99% ee.[445] Cohen achieved the resolution of a β-silyl allylic alcohol, precursor of the ACP **360** by Peterson elimination, by destructive asymmetric epoxidation that gave the material with 45% ee.[247]

B. By Asymmetric Synthesis

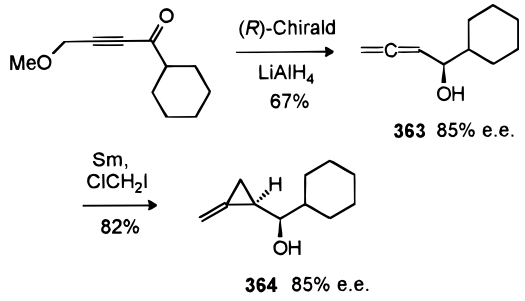
The first example of asymmetric synthesis of optically active MCPs was reported by Noyori and Nozaki who performed the cyclopropanation of phenylallene with diazomethane catalyzed by the chiral copper complex **362**.[446,447] The asymmetric induction was, however, very poor. It was only 12% ee for the phenyl-substituted MCP **361** (Scheme 146).

Scheme 146



Only very recently has Lautens found a much more efficient route to enantiomerically enriched MCPs and ACPs by cyclopropanation of chiral allenic alcohols promoted by samarium (Scheme 147).[19,20,246]

Scheme 147



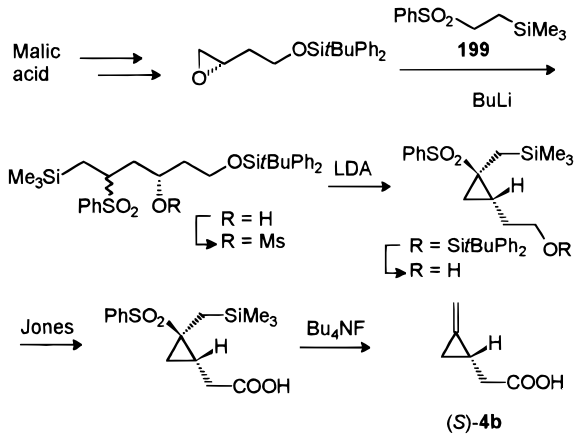
The chiral allene **363** was obtained by enantioselective reduction of the ynone with $LiAlH_4$/Darvon alcohol (Chirald), followed by hydride displacement of the propargylic methoxy group. The cyclopropanation occurs with complete retention of optical purity, complete diastereoselectivity, affording enantiomerically enriched MCP **364** in very good yield. Enantiomeric excesses of roughly 25% ee have been obtained in the addition of singlet and triplet (methoxycarbonyl)phenylcarbene to enantioenriched 1,3-dimethylallene.[72] A chiral rhodium catalyst [dirhodium(II) tetrakis(methyl-2-pyrrolidone-5(*R*)-carboxylate)] in the reaction of racemic 1,3-dimethylallene was not able to provide any transfer of chirality to the products.[72]

A chiral tricyclic bis-MCP was synthesized from 6-chloro-6-methylbicyclo[3.1.0]hexan-2-one.[187a]

Amino acids can be incorporated in ACP structures to give chiral ACPs with high optical purity by means of palladium(0) chemistry. An iminoglycine derivative, made chiral by amidation with Oppolzer's camphorsultam, produced optically pure cyclopropylidenealanine by C-alkylation to cyclopropyl-π-allyl palladium complex (see Table 13, entry 6).[317] *N*-Tosyl amino acid esters gave, by nucleophilic nitrogen attack to the same π-allyl palladium complex, chiral ACP derivatives in very good chemical and optical yield (see Table 12, entries 11−15).[318] Malonate alkylation of the π-allyl palladium complex in the presence of BINAP gave ACPs with 50% ee (see Table 11, entries 5 and 6).[229c]

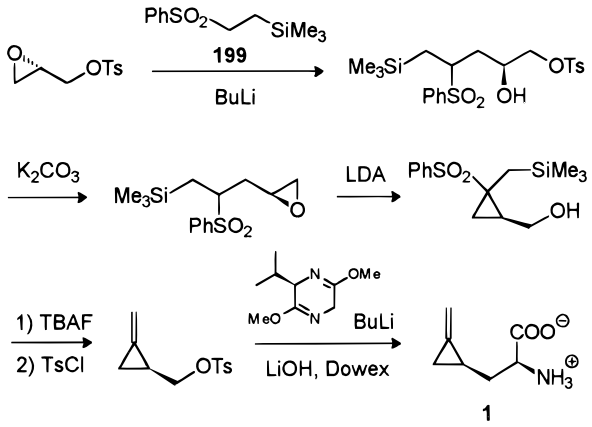
Many synthetic efforts have been devoted to the synthesis of chiral MCPs related to hypoglycine (**1**) or to MCP-substituted acetic acid (**4**).[3−5] Wicha developed a synthesis of the *S* enantiomer of **4b** starting from malic acid as the chiral source (Scheme 148).[254]

Scheme 148



Baldwin developed a similar protocol for the synthesis of hypoglycine A (**1**) starting, however, from optically pure glycidol as the chiral precursor (Scheme 149).[5c]

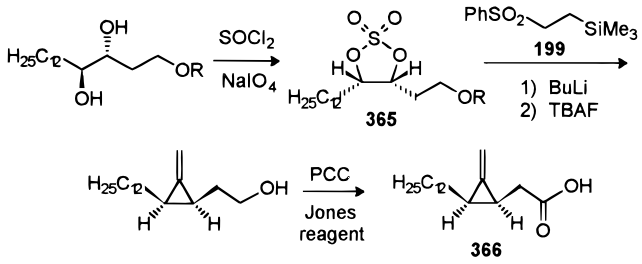
Scheme 149



Simultaneously, the synthesis of a dodecyl−MCP-substituted acetic acid **366** was achieved by a process

which utilizes the cyclic sulfate **365** as the compound to be opened by the same carbon nucleophile **199** (Scheme 150).[253]

Scheme 150

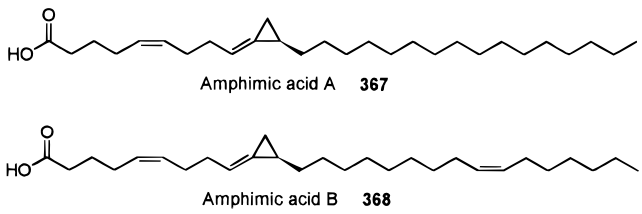


VI. Addenda

The literature on MCP and its derivatives has flourished also during the first part of 1997 confirming the vitality of this field of research. Several reports have been published covering all aspects of the chemistry of MCP and its derivatives, from theoretical[448] to mechanistic[449] and applicative.[450−453]

Noteworthy, two novel natural products possessing a cyclopropylidene moiety, amphimic acids A (**367**) and B (**368**) (Scheme 151), were isolated from the

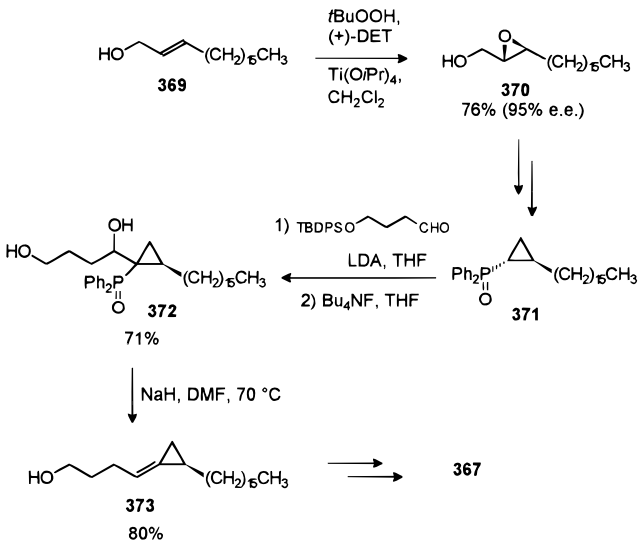
Scheme 151



Australian sponge *Amphimedon* sp.[454] These compounds are unsaturated C_{28} fatty acids and inhibit DNA topoisomerase I.

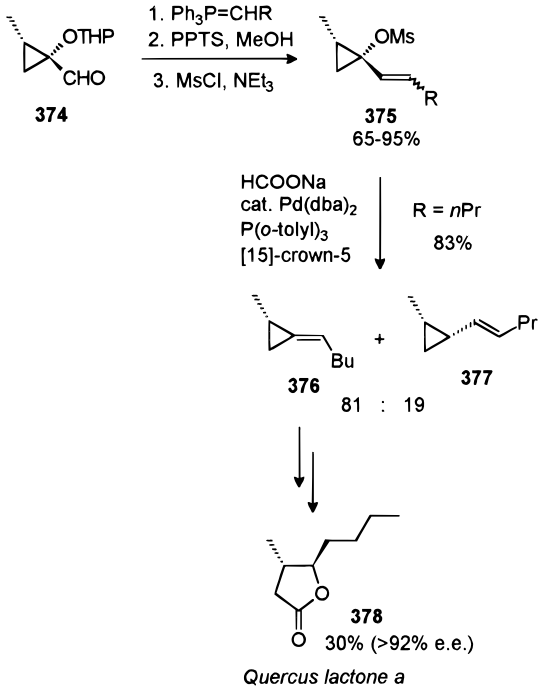
The enantioselective synthesis of amphimic acid A (**367**) was performed for confirmation of the proposed structure and determination of its absolute configuration (Scheme 152). Sharpless epoxidation of allyl alcohol **369** to epoxide **370** which was later converted to the cyclopropane **371**, was the source of stereochemical differentiation. Reaction of the carbanion of **371** with protected 4-hydroxybutyraldehyde provided a diastereomeric mixture of β-hydroxy phosphine oxides **372**, which gave the ACP **373** by base-induced Horner elimination (Scheme 152). The acid **367** was finally obtained by standard transformations, including Swern and chlorite oxidations and a Wittig reaction, which did not interfere with the ACP moiety.[454]

Scheme 152



For the synthesis of new optically active ACPs **376** Salaün has applied the palladium(0)-catalyzed hydrogenolysis of 1-(1-alkenyl)cyclopropyl sulfonates (see section III.C.3).[455] The process employed highly enantioenriched (>95% ee) cyclopropanecarbaldehydes **374**, which gave the required diastereoisomeric allyl mesylates **375** by Wittig reaction, deprotection and mesylation (Scheme 153). The Pd-catalyzed reduction with sodium formate produced ACPs **376** and alkenylcyclopropanes **377**, with a regioisomeric ratio strongly dependent on the bulkiness of the added phosphine ligands, ranging from 47:53 for dppe to 81:19 for P(*o*-tolyl)$_3$.[455] ACP **376** has been used for a synthesis of *Quercus lactone a* **378** (and its epimer *b*) by epoxidation, LiI-induced rearrangement, and final Baeyer−Villiger oxidation (Scheme 153).[456]

Scheme 153

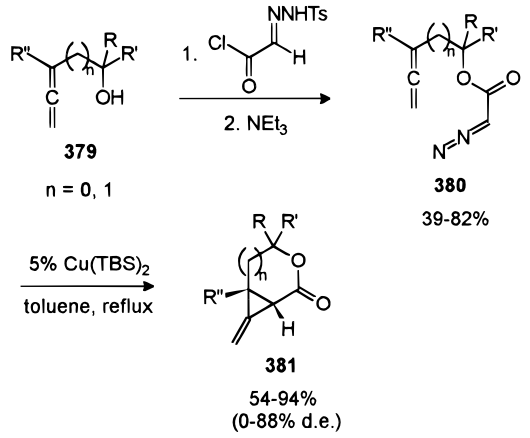


Several papers reported the synthesis of new ACP derivatives, sometimes via unprecedent procedures, which will be exposed below.

Lautens has prepared substituted methylenecyclopropyl lactones **381** by a regioselective intramolecular cyclopropanation of diazoacetates **380**, available in turn from allenic alcohols **379** (Scheme 154).[457]

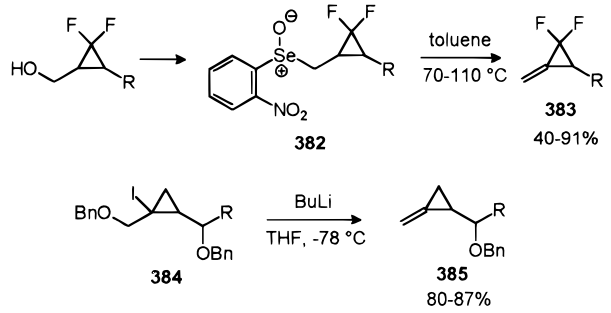
gem-Difluoro-disubstituted MCPs **383** were obtained in good yield by selenoxide elimination from the corresponding cyclopropanes **382** (Scheme 155).[458] Interestingly, the same reaction failed when performed on the related cyclopropanes lacking the fluoro substituents, while it has success with the

Scheme 154



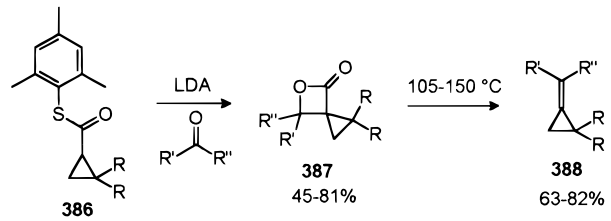
selenoxide directly linked to cyclopropane (see section III.A.2). Compounds **383** behave as good Michael acceptors, in contrast to their analogs **385**, prepared by elimination from the iodo derivative **384** (Scheme 155).[458]

Scheme 155



Danheiser has conceived a novel elimination route to ACPs by thermolysis of α-spirocyclopropyl *β*-lactones.[459] The whole process represents an efficient two-step synthesis of ACPs starting from *S*-mesityl cyclopropanecarboxylic thiol esters **386**. The corresponding enolates were reacted with ketones to afford the *β*-lactones **387**, which underwent cycloreversion to ACPs **388** when subjected to heating (Scheme 156).[459] The use of the *S*-mesityl thiol esters is a clue

Scheme 156

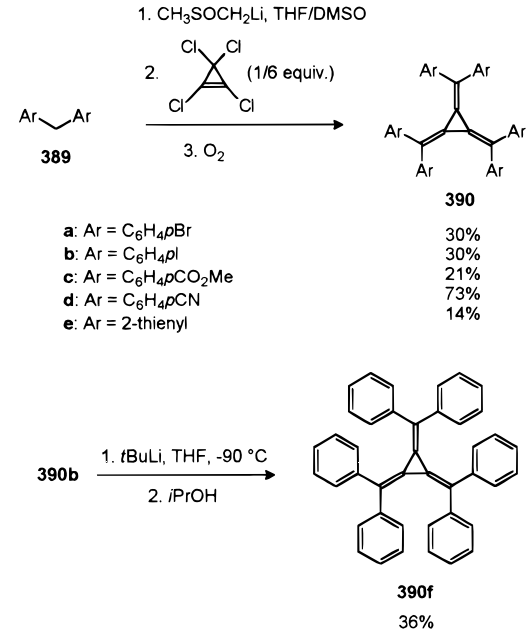


for the success of the method. The hindrance of the substituent at sulfur suppresses self-condensation in favor of the reactivity of the strained enolate intermediate.

On the way to a new methylenecyclopropene synthesis, Billups has obtained new trimethylsilyl-substituted bromomethylenecyclopropanes by dibromocarbene addition to trimethylsilylallene followed by partial reduction.[460] The synthesis of a variety of cyclopropylidene aryloxy derivatives has been performed by using the Wittig reaction under McMurry's conditions (see section III.B.1).[461] With the same method, an enantiopure ACP starting from D-gliceraldehyde has also been synthesized.[462] A symmetrically substituted bis-silylpropyl ACP was obtained in 75−80% yield by Rh(I)-catalyzed hydrosilylation of (dicyclopropylmethylene)cyclopropane.[451]

Several hexaaryl[3]radialenes **390** have been synthesized by Oda in moderate to good yields from the corresponding diarylmethanes **389** (Scheme 157).[463]

Scheme 157



The process represents an extension of the method based on reaction of tetrachlorocyclopropene with active methylene compounds followed by oxidation (see section IV.D). For this reason, electron-withdrawing aryl substituents gave the best results, while diphenylmethane failed to give the reaction. However, the previously unknown hexaphenyl[3]radialene **390f** was obtained from its *p*-iodo derivative **390b** by halogen−metal exchange/protonation (Scheme 157).[463]

VII. References

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