Syntheses of *gem*-Dihalocyclopropanes and Their Use in Organic Synthesis

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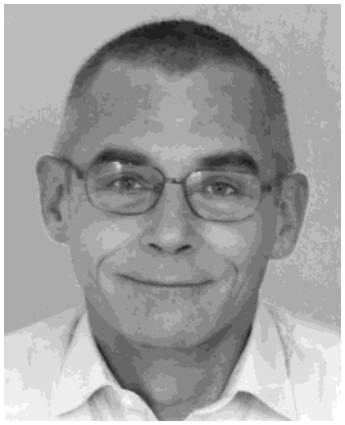

Michał Fedoryński was born in 1946 in Bydgoszcz, Poland. He received his M.Sc. (1969) and Ph.D. (1974) degrees from the Warsaw University of Technology. His Ph.D. dissertation was on dihalocarbene chemistry, supervised by Professor Mieczysław Mąkosza. In 1974, he joined the faculty of the Warsaw University of Technology. In 1979, he spent 15 months as a postdoc with Professor Robert A. Moss, Rutgers University, New Brunswick, NJ, where he worked on ambiphilic carbene chemistry. In 1985, he worked for 6 months as a visiting researcher at the same institution. His research interests include phase-transfer catalysis and the chemistry of carbanions and dihalocarbenes.

I. Introduction

gem-Dihalocyclopropanes play an important role in organic synthesis. They are valuable substrates for the preparation of monohalocyclopropanes, cyclopropanes, cyclopropenes, benzocyclopropenes, bicyclobutanes, allenes and cumulenes, cyclopentane and cyclopentadiene derivatives, and many other hydrocarbon systems, both unsubstituted and possessing useful functional groups. One of the reasons for the intensive research into syntheses using *gem*-dihalocyclopropanes as substrates is their exceptional availability. In a now classic paper from 1954, Doering and Hoffmann showed that dichlorocarbene generated from chloroform in an α-elimination process under strictly anhydrous conditions adds to alkenes with the formation of *gem*-dichlorocyclopropane derivatives.[1] To date, the addition of dihalocarbenes to alkenes is the most important and, in fact, the only synthetic route to *gem*-dihalocyclopropanes. After 1954 many different methods for generating dihalocarbenes were developed. However, these methods each had disadvantages which limited their usefulness, and as a result, *gem*-dihalocyclopropanes were not intensively used in synthesis.

α-Elimination of a hydrogen halide molecule from a haloform remains the most important and the most frequently used method for generating dihalocarbenes. However, in 1969 Mąkosza showed that α-elimination as well as addition of dichlorocarbene to an alkene can be performed in a two-phase system using concentrated aqueous NaOH as a base in the presence of a quaternary ammonium salt (quat) acting as a phase-transfer catalyst.[2] This work had a tremendous impact on the chemistry of carbenes and also promoted and facilitated the application of *gem*-dihalocyclopropanes as substrates for further transformations.

There are numerous reviews covering the chemistry of dihalocarbenes and the use of *gem*-dihalocyclopropanes in organic synthesis. The Houben-Weyl monographs[3−5] are fundamental references that discuss the subject in full up to the year 1995. Weyer-

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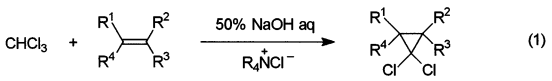
stahl,[6] Kostikov,[7] and Banwell[8] reviewed the synthetic applications of *gem*-dihalocyclopropanes up until 1990. Other papers will be referred to in the appropriate sections.

There are also numerous reviews and books which to some extent deal with the phase-transfer catalysis (PTC) methods of producing carbenes and *gem*-dihalocyclopropanes.[9−16] It seems, however, that, despite the indisputable advantages of this method in comparison with more traditional methods, a considerable portion of the chemical community does not appreciate its relevance or use it to its full advantage.

In this review I will discuss methods for the synthesis of *gem*-dihalocyclopropanes that have withstood the test of time, and that have illustrated the usefulness of this class of compounds as starting materials in organic synthesis. The literature covered is from 1995 up to the begining of 2002. References to the earlier literature are contained within the works referenced here. The text is divided into three parts and begins with an introduction to the PTC method. This is intentional, because understanding the reaction mechanism in a two-phase system will, without doubt, enable a more effective utilization of it. We then have an appeal for wider application of this method. Finally, the syntheses and applications of *gem*-dihalocyclopropanes will be discussed.

II. Phase-Transfer Catalysis in the Chemistry of Dihalocarbenes

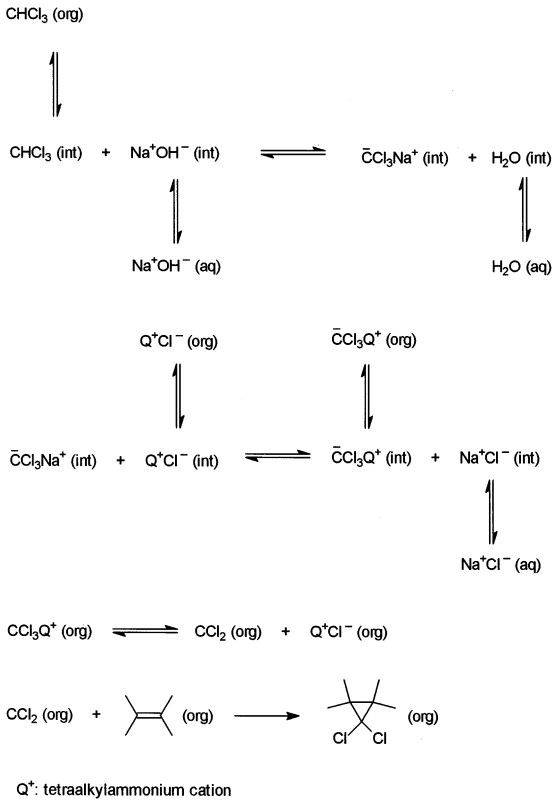
Generation of dichlorocarbene in a PTC system occurs when concentrated aqueous NaOH is stirred with chloroform in the presence of a catalytic amount of lipophilic tetraalkylammonium (TAA) salt. In the presence of alkenes, *gem*-dichlorocyclopropane derivatives are formed (eq 1).



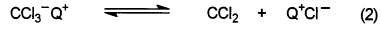
(1)

Usually high yields of the *gem*-dichlorocyclopropanes are obtained, even from alkenes of low nucleophilicity. Hydrolysis of the carbene does not proceed to a significant extent, even though the reaction of the carbene with water and hydroxide anions is known to proceed at a high rate,[17] and despite the fact that these reactions are carried out in the presence of a great excess of aqueous NaOH. These results indicate that there is very little contact between the dihalocarbene and the water and hydroxide anions in the PTC system. This and other observations led Mąkosza in 1974 to formulate an interfacial mechanism to account for the generation of dichlorocarbene in a catalytic two-phase system.[18] According to his proposal, which is now commonly accepted, in the two-phase system consisting of chloroform with an alkene and concentrated aqueous NaOH, deprotonation of the chloroform occurs in the interfacial region. Trichloromethyl anions produced as sodium salts undergo ion exchange with the TAA salt (or other sources of organic cations, such as alkali-metal cations complexed with crown ethers) to give lipophilic ion pairs. These ion pairs enter the organic phase, where they dissociate reversibly to form dichlorocarbene. The catalyst is recovered in this process. The dichlorocarbene then adds to the alkene, giving a *gem*-dichlorocyclopropane derivative. Since the carbene is actually formed in an anhydrous medium (the organic phase) which does not contain hydroxide anions or water, its hydrolysis is minimal (Scheme 1).

Scheme 1



Trichloromethyl carbanions can also dissociate to dichlorocarbenes in the interfacial region, where they hydrolyze to form chloride and formate anions. However, this hydrolysis is a prevented process because the resulting chloride anions are less hydrophilic than hydroxide anions and therefore preferentially occupy the interfacial region. This shifts the equilibrium between the dichlorocarbene and the trichloromethyl anion to the left. On the other hand, in the absence of a catalyst, the dichlorocarbene cannot react with an alkene in the interfacial region, where it is surrounded by chloride anions. The most important difference between the reactions of dichlorocarbene generated in PTC systems and reactions carried out under classical conditions, for instance using potassium *tert*-butoxide as a base for α-elimination, is that in the first case all the components of the equilibrium (eq 2)



(2)

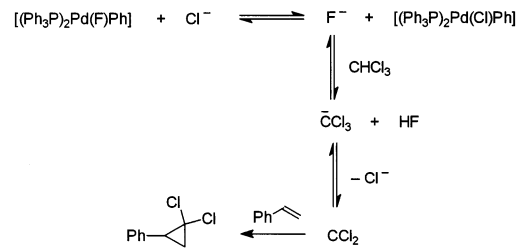
are soluble in the reaction medium, so the process is really reversible.

As a consequence, dichlorocarbene can undergo even very slow reactions with good yields. Additionally, the organic phase does not contain anything

other than the carbene precursor, the carbene acceptor (an alkene), and the catalyst. The base and water are confined to the aqueous phase; therefore, the carbene is not consumed by competing processes.

In this context, recent papers by Grushin, which indirectly support Mąkosza's mechanism, are worth noting.[19,20] Grushin developed an efficient method for generating highly basic and nucleophilic "naked" fluoride anions in a ligand-exchange reaction between the palladium fluoride complex $[(Ph_3P)_2Pd(F)Ph]$ and $[Ph_3P{=}N{=}PPh_3]^+Cl^-$. When the naked fluoride was generated in chloroform, the solution remained stable for days at room temperature. Upon addition of styrene, the naked fluoride disappeared rapidly and 1,1-dichloro-2-phenylcyclopropane was formed in good yield. Thus, it would appear that all the equilibria among chloroform, its anion, and dichlorocarbene in homogeneous solution are shifted to the right only when the carbene is irreversibly trapped by an alkene (Scheme 2).

Scheme 2



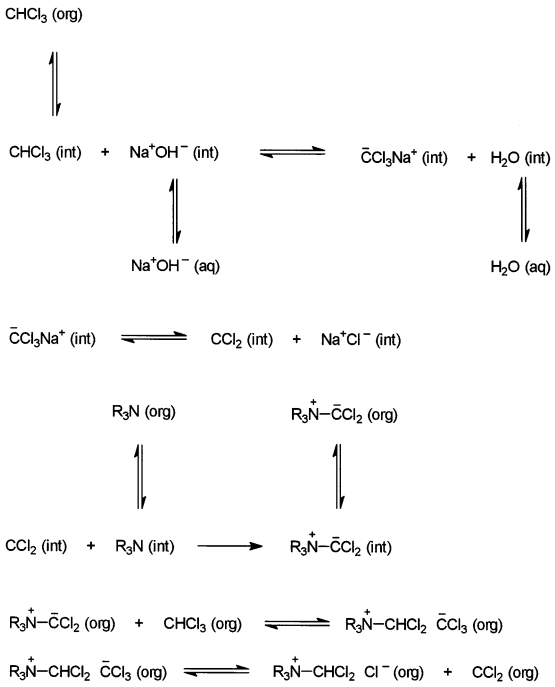
Other experimental observations also strongly support the mechanistic picture given above. The most important are the following.

(a) The rate of chloroform consumption in the two-phase system depends on the nucleophilicity of an alkene.[21] For example, in the presence of the very unreactive 3,3-dimethylbut-1-ene more than half of the chloroform consumed was hydrolyzed, whereas with active 2-methylbut-2-ene only 4% hydrolysis occurred.

(b) In the presence of an alkene the hydrolysis of the chloroform primarily proceeds at the beginning of the reaction, when there is a great excess of the alkene present relative to the generated dichlorocarbene. This is contrary to what would be expected on the basis of a stoichiometric approach, in which the hydrolysis should occur at the end of the reaction, when there is only a very small excess of alkene present.[22] This means that when chloride anions are present in the system in small quantities, hydrolysis of the carbene is the dominant process, whereas the accumulation of chloride anions produced during the formation and hydrolysis of the carbene protects it from hydrolysis. Indeed, when a sodium hydroxide solution saturated with sodium chloride was used to generate the carbene, hydrolysis was substantially diminished.

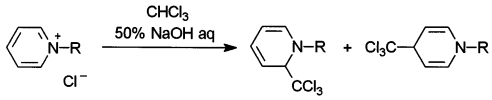
(c) The generation of dichlorocarbene in the interfacial region is confirmed by the observation that some trialkylamines efficiently catalyze the generation of dichlorocarbene.[23] Because trialkylamines are very active nucleophiles, they react with the carbene in the interfacial region to form ammonium ylides,

Scheme 3



which then enter the organic phase, where they act as bases in deprotonating the chloroform, thus producing carbene in the organic phase (Scheme 3).[24]

(d) Mąkosza et al. recently found that the reaction of some *N*-alkylpyridinium salts with chloroform, when carried out in the presence of concentrated aqueous NaOH, proceeds by a fast addition of trichloromethyl anions to positions 2 and 4 of the pyridinium ring to form the corresponding adduct in high yield (eq 3).[25]



(3)

R = Ph_2CH, 92%

On the other hand, treatment of these salts with concentrated aqueous NaOH in toluene or chlorobenzene results in their rapid decomposition, obviously via the formation of unstable adducts of hydroxide anions. These results rule out the formation of tetraalkylammonium hydroxide ion pairs as a path for generating trichloromethyl anions and confirms the interfacial generation of trichloromethyl anions as the pathway operating in the PTC system.

The mechanism of dichlorocarbene formation in the PTC system that is discussed above can be extended to all other dihalocarbenes, and indicates that the main function of the catalyst is to supply lipophilic cations which are able to form lipophilic ion pairs with trihalomethyl anions. This implies that the structure of the catalyst will not have a significant effect on the reaction course or dihalocarbene activity, provided that the catalyst is lipophilic enough. Indeed, competition experiments using different alkenes demonstrated that the selectivity of dichlorocarbene is independent of the catalyst used, within experimental error.[26] This means that kinetically free dichlorocarbene is involved in the processes discussed. On the other hand, there are many examples

reported where the catalyst structure strongly influences the direction of carbenic PTC reactions, such as in reactions of the carbene with electrophilic alkenes, allylic bromides, and enol esters. (For reviews, see refs 22 and 27−29.) This indicates that the general mechanism for the generation of dihalocarbenes discussed above is probably somewhat oversimplified, and undoubtedly needs further investigation. Fortunately, these observations, which will be discussed in later sections, generally increase the applicability of PTC in carbene reactions.

The material in section III is divided for reasons of clarity, according to the type of halogen atoms in the *gem*-dihalocyclopropane molecule. The most important methods for preparing *gem*-dihalocyclopropanes will be presented, followed by examples taken from papers published within the last seven years, or earlier if necessary. The influence of the alkenes' functional groups on dihalocarbene addition to their double bonds will also be discussed.

III. Syntheses of gem-Dihalocyclopropanes

III.1. *gem*-Dichlorocyclopropanes

All the important practical methods of synthesizing *gem*-dichlorocyclopropanes consist of the addition of dichlorocarbene to an appropriate alkene. The following methods are used for generating the dichlorocarbene.

(1) α-Elimination of hydrogen chloride from chloroform. Currently, PTC is most often used for this purpose, but *t*-BuOK is also sometimes used despite the rather low yields of addition products that are generally obtained with unreactive alkenes (for earlier examples see refs 3, 4, 30, and 31). The reaction of chloroform with oxirane in the presence of a TAA salt (for a review, see ref 32) is essentially not used at present.

(2) Reaction of ethyl trichloroacetate with sodium methoxide.[33] Because the mixed carbonate rather than the alcohol is formed as the byproduct in this reaction, there is no need to use sterically hindered alkoxides.

(3) Thermal decomposition of sodium trichloroacetate.[34] These reactions are carried out in DME at 80 °C. With alkenes of low reactivity, a large excess of the carbene precursor is required. The use of chloroform instead of DME as a solvent in the presence of a catalytic amount of a TAA salt is also recommended.[35]

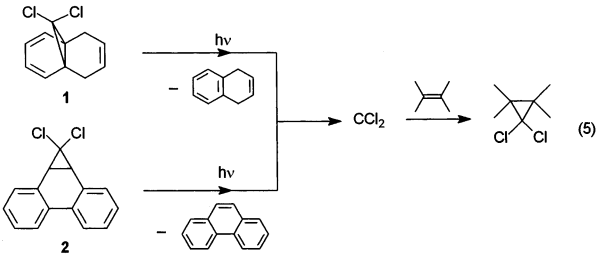
(4) Thermal decomposition of trihalomethyl(phenyl)mercury. Trichloro- or bromodichloromethyl(phenyl)mercury is used for this purpose (for a review, see ref 36). This method is very efficient, and permits the preparation of *gem*-dichlorocyclopropanes from base-sensitive alkenes or alkenes of low reactivity in good yields.

Recently, Suslick et al. found that photolysis of dichlorocarbene (and other carbene) complexes of the metalloporphyrin $Fe(TPP)CCl_2$ (TPP = 5,10,15,20-tetraphenylporphyrinate), using light in the visible or UV range, liberates the dichlorocarbene, which then can be captured by alkenes in high yields (eq 4).[37,38]

$$Fe(TPP)CCl_2 \xrightarrow[\text{benzene}]{h\nu} Fe(CTPP) + CCl_2 \quad (4)$$

alkene, *gem*-dichlorocyclopropane yield (%): cyclohexene, 82; cyclooctene, 80; styrene, 80; hex-1-ene, 79

Selectivity data, obtained from competition experiments using this method, were the same as those obtained for dichlorocarbene generated using the chloroform/*t*-BuOK system. This indicates that the photochemical reaction generates free carbene. This method, although of no practical value, should be very useful in physicochemical investigations of dichlorocarbene, especially since the potentially best precursor for this purpose, 3,3-dichlorodiazirine, is still unknown. (For a review of diazirines in carbene chemistry, see ref 39.) Until now, physicochemical studies of dichlorocarbene were performed using compounds **1** and **2** as the carbene precursors. Their photolysis yields dichlorocarbene, which can be captured by alkenes (eq 5).[40,41]

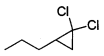
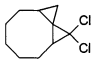
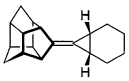
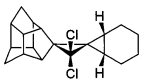
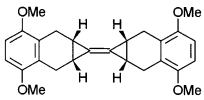
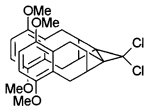
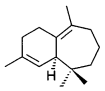
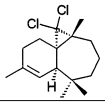


(5)

Other recently described methods, such as (a) the lithiation of diethyl trichloromethyl phosphonate in the presence of an alkene,[42] (b) the decomposition of trimethylsilyl trichloroacetate under the influence of potassium fluoride in the presence of a quat or crown ether,[43] (c) the use of alumina impregnated with potassium fluoride as a base for α-elimination in the presence of a quat as a catalyst,[44] (d) the reaction of chloroform and magnesium with alkenes,[45] (e) the reaction of carbon tetrachloride with reduced titanium in the presence of alkenes,[46] and (f) the reaction of chloroform with butyllithium in the presence of alkenes,[47] do not offer advantages over the methods presented earlier, and have not found practical application in recent years, or have been only rarely used.

A great majority of the reactions of alkenes with chloroform described in the last seven years were performed in a PTC system. The *t*-BuOK/$CHCl_3$ system for generating dichlorocarbene was also frequently used, and other methods were occasionally applied. Quite often the method used for generating dichlorocarbene is not mentioned, especially in reactions of simple alkenes. The generation of dichlorocarbene by classical methods in the presence of alkenes usually yields very reproducible results. Procedures for most of the important methods can be found in the Houben-Weyl monographs.[3,4] The yields of PTC reactions, as reported by different authors for the same reactions carried out under very similar conditions, sometimes differ substantially. This is probably the result of heterogeneity within the system. Vigorous stirring in these reactions is very important; hence, mechanical rather than mag-

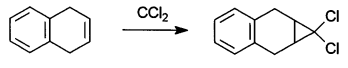
Table 1. Examples of Dichlorocarbene Addition to Alkenes

Substrate	Carbene precursor	Product	Yield (%)	Ref.
	$CHCl_3$ 50% NaOH TEBA		91	57
	$CHCl_3$ NaOH solid TEBA hexane		82	60
	$CHCl_3$ 50% NaOH TEBA		75	65
	Cl_3CCO_2Et NaOMe		91	95
	$CHCl_3$ NaOH solid TEBA CH_2Cl_2		50	55

netical stirrers should be used, especially for reactions carried out on a large scale. The use of trialkylamines as catalysts, instead of quats, surprisingly has not found wide application. The most popular catalysts used in PTC reactions are benzyltriethylammonium chloride (TEBA) or tetrabutylammonium bromide (TBAB). However, in some recent papers, more sophisticated catalysts are advocated, such as 2-benzylidene-*N*,*N*,*N*,*N*′,*N*′,*N*′-hexaethylpropane-1,3-diammonium dihalides, $PhCH{=}C[CH_2N^+(C_2H_5)_3X^-]_2$,[48−50] or poly(ethylene glycol)-supported tetrakisammonium salts[51] (the so-called multisite catalysts). However, the benefits associated with their usage are usually overestimated, especially when the difficulties associated with their syntheses are taken into account.

General problems connected with these reactions are discussed in refs 3 and 4 and in references therein. The cycloaddition of dichlorocarbene to unsaturated hydrocarbons is a stereospecific process that preserves the configuration of the alkene in the products. Dichlorocarbene is an electrophilic species, so more highly substituted alkenes react more quickly with it. As a rule, 1,1-disubstituted alkenes react at a higher rate than 1,2-disubstituted alkenes, straight-chain (*Z*)-alkenes react faster than the corresponding *E* isomers, and cyclic (*E*)-alkenes are more reactive than the corresponding *Z* isomers.

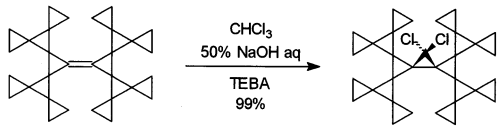
Many examples of *gem*-dichlorocyclopropanes prepared by the addition of dichlorocarbene to unsaturated compounds have appeared recently.[52−82] Some recent examples of reactions of unsaturated hydrocarbons with dichlorocarbene are collected in Table 1. The superiority of the PTC method is illustrated in eq 6.



(6)

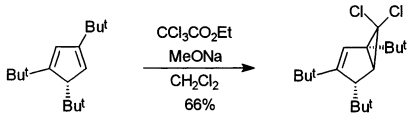
$CHCl_3$/TEBA, 50% NaOH	81%[59]
$CHCl_3$/t-BuOK	27%[83]
CCl_3CO_2Na	47%[84]

The addition of dichlorocarbene to cyclopropylidene-type hydrocarbons occurs in high yields, and the products are useful intermediates in spiroannulated cyclopropane syntheses (eq 7).[61]



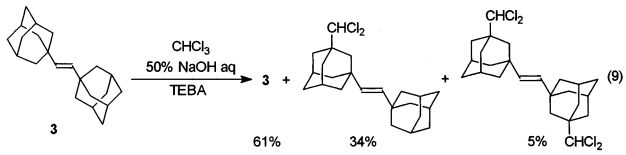
(7)

The addition of dichlorocarbene to cycloalkenes with four- and five-membered rings leads to bicycloalkane derivatives, which very often cannot be isolated and undergo further transformations.[56,62] However, using carefully chosen conditions, it is possible in some cases to isolate the primary adducts in high yields[68] (eq 8).[52]



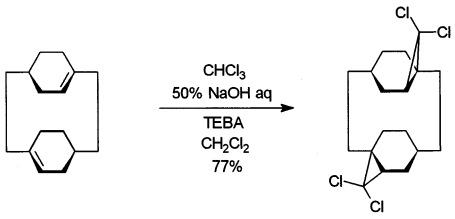
(8)

When working with hydrocarbons containing allylic double bonds or tertiary carbon−hydrogen bonds, one should take into account the possibility that the carbene may insert into a carbon−hydrogen bond, especially when trihalomethyl(phenyl)mercury compounds are the carbene precursors. In the case of caged molecules or alkenes which are highly hindered in the vicinity of the double bond, the insertion sometimes becomes a dominant or exclusive process (eq 9).[53]



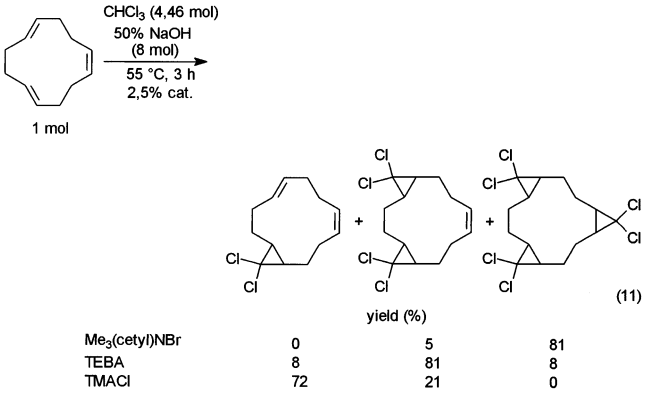
(9)

The addition of dichlorocarbene to open-chain and cyclic unconjugated dienes and polyenes can result in mono- or polyaddition products. Generally, when the carbene precursor is used in excess, more polyaddition occurs, so it is possible to control the reaction course to some extent by changing the ratio of carbene precursor to polyene.[55,60] PTC conditions strongly favor polyaddition[54,63] (eq 10).[66]



(10)

On the other hand, in an earlier paper, Dehmlow found that the course of the addition of PTC-generated dichlorocarbene to unconjugated di- and polyenes, when carried out under identical conditions, depended strongly on the catalyst used.[85] With lipophilic quats, di- or polyaddition occurred, while monoaddition products were obtained in high yields with tetramethylammonium (TMA) salts (eq 11).



(11)

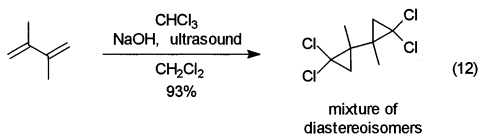
This result is rather surprising because it is unlikely that TMA salts can be good PT catalysts. Sasson et al. found that, in the 50% aqueous NaOH/benzene/catalytic (TMA)Br two-phase system, after vigorous stirring and phase separation, the ammonium salt was present in the aqueous phase![86]

It is not clear whether the TMA salt influences the selectivity of the process. One could surmise that higher conversions of the diene or polyene in reactions carried out in the presence of this catalyst could primarily yield polyaddition products.

We have investigated the changes in the amounts of the diene ((*Z*,*Z*)-cycloocta-1,5-diene) and its reaction products as a function of the quantity of dichlorocarbene consumed by cycloaddition processes.[22] Assuming that mono- and diadditions of the carbene to the diene are consecutive reactions, we found that when the process is carried out in the presence of TEBA, dichlorocarbene adds to the diene and to its monoadduct at the same rate. In the presence of (TMA)HSO_4, the double bond in the monoadduct reacts at a rate 7 times slower than the double bond of the diene. High yields of the monoaddition product from reactions with TMA as the catalyst can be attributed to the reduced rate of attack by dichlorocarbene on the double bond in the monoadduct, which occurs for reasons that are as yet unclear. Definitely, these processes occur in the interfacial region rather than in the bulk of the organic phase.

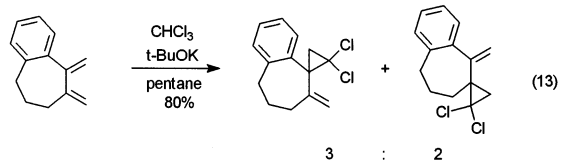
Similar monoaddition results were obtained using the 4-*tert*-butylcalix[6]arene derivative as a catalyst in the presence of solid KOH.[87]

Conjugated dienes undergo monocyclopropanation more readily than do unconjugated dienes, since the remaining double bond is deactivated after the addition of the first molecule of dichlorocarbene. However, the synthesis of diadducts from the addition of dichlorocarbene to conjugated dienes is also possible. Sonication of the reaction mixtures was recently recommended for this purpose (eq 12).[63]



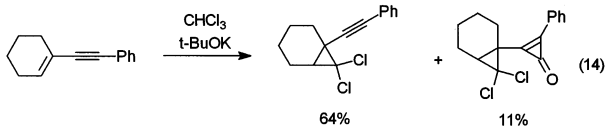
(12)

The PTC system is suitable for the synthesis of either mono- or diadducts, while the *t*-BuOK/$CHCl_3$ method allows the monoadducts to be obtained, often in high yields (eq 13).[74]



(13)

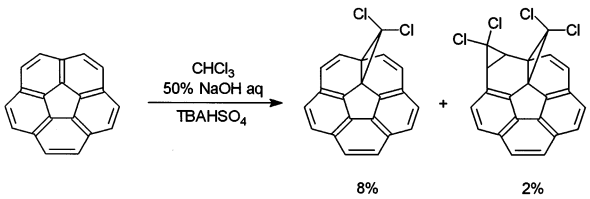
Dichlorocarbene usually adds to the double bond of enynes, whether conjugated or unconjugated.[88] Sometimes a small percentage of the carbene adds to phenyl-substituted enyne triple bonds (eq 14).[89]



(14)

Aromatic hydrocarbons, due to specific stabilization of the π electron systems, are not very susceptible to reactions with carbenes. Only very active carbenes, such as methylene or alkoxycarbonyl carbene, react with benzene. Dichlorocarbene is less reactive, so it can react only with compounds such as alkylnaphthalenes, indenes, or phenanthrene and its derivatives, where the extended conjugated system reduces the loss of aromatization energy following addition. The adducts initially formed often rearrange and then undergo addition of another molecule of carbene.

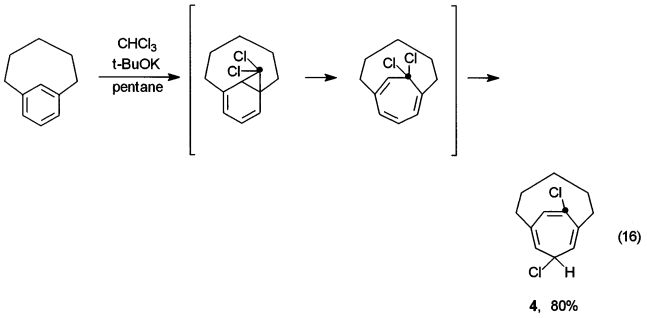
Contrary to expectations, the dichlorocyclopropanation of corannulene occurs first at the radial double bond, even though this disrupts the cyclic conjugation in two benzene rings, rather than in only one as would happen if cyclopropanation initially occurred at the rim (eq 15).[73] An explanation is given, based on HOMO−corannulene and LUMO−carbene calculations and considerations of possible transition states for dichlorocarbene addition to corannulene.



(15)

Of particular interest are the reactions of dichlorocarbene with metacyclophanes. Dichlorocarbene adds to the formal anti-Bredt double bond of the aromatic ring of [5]metacyclophane, affording cycloheptatriene **4**.[75] Experiments with labeled carbon atoms and computational studies strongly support the mechanism for this transformation presented in eq 16. The initially formed dichlorocarbene adduct undergoes electrocyclic ring opening followed by a rapid suprafacial [1,5] sigmatropic chlorine migration, leading to **4**.

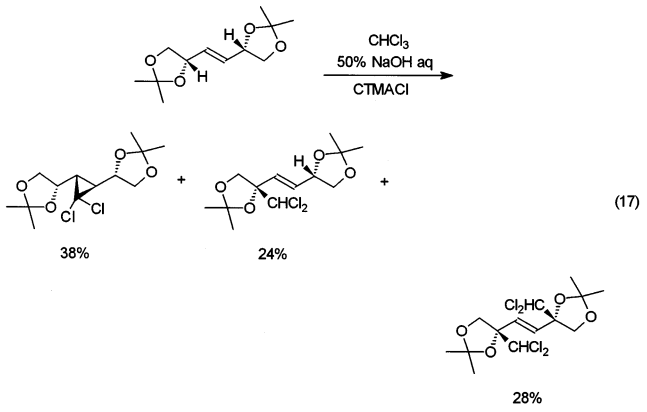
The presence of substituents such as halogens,[74,90−92] silicon[93,94] ether or acetal linkages,[95−103] esters,[70,101,104] cyano,[101] and phosphine oxide,[105−107] which are remote from the double bond in the alkene molecule, does not influence the dichlorocarbene addition reaction. It is worth noting that ethyl or methyl esters are usually not hydrolyzed under PTC conditions (see, for instance, ref 108). In some cases the insertion



(16)

4, 80%

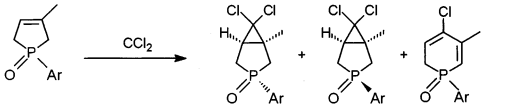
of dichlorocarbene into the C−H bond of cyclic vinyl or allyl ethers competes with cycloaddition (eq 17).[97]



(17)

38% 24% 28%

Interestingly, the course of the reaction of dihydrophosphole oxide **5** with dichlorocarbene depends strongly on the kind of dichlorocarbene precursor used and on the structure of the aromatic substituent connected to the phosphorus atom. When Ar was 2,4,6-triisopropylphenyl, compounds **6**−**8** were formed in the PTC system. Using sodium trichloroacetate in chloroform as the carbene source, in the presence of a quat, isomer **7** was formed exclusively (eq 18).[106] The reason for this selectivity is not clear. For Ar = 2,4,6-trimethylphenyl, only a mixture of the carbene addition products **6** and **7** was formed in high yield in the PTC system.[107]



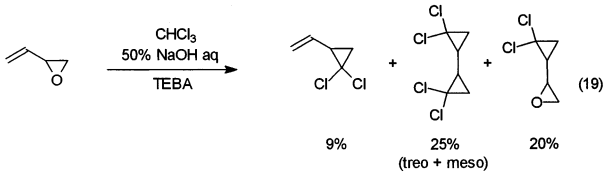
(18)

		6	7	8
Ar = 2,4,6-(i-Pr)$_3$C$_6$H$_2$	$CHCl_3$/TEBA/NaOH aq	42%	10%	48%
	CCl_3CO_2Na/TEBA/$CHCl_3$	–	47%	–
Ar = 2,4,6-Me$_3$C$_6$H$_2$	$CHCl_3$/TEBA/NaOH aq	60%	24%	–

Unsaturated secondary amines with allyl substituents, or those having double bonds further removed from the nitrogen atom, undergo formylation under PTC conditions. The dichlorocarbene addition can occur only after the *N*-formyl derivative is formed.

Epoxides are as a rule deoxygenated by dichlorocarbene, and the alkene formed adds another molecule of the carbene (eq 19).[109]

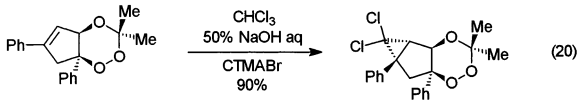
However, there are examples of reactions with unsaturated epoxides in which the oxirane moiety is



(19)

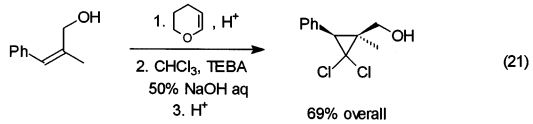
9% 25% (treo + meso) 20%

preserved.[110] The peroxide moiety in peroxides containing double bonds withstand dichlorocarbene cycloaddition reactions under PTC conditions (eq 20).[111]



(20)

In the case of unsaturated alcohols, the hydroxy group (or the corresponding oxyanion, generated under basic conditions) may compete with the double bond for reaction with the dichlorocarbene. The nature of the final product depends on the structure of the unsaturated alcohol and on the reaction conditions. Allyl alcohol, for instance, does not form the corresponding dichlorocyclopropane. When bromodichloromethyl(phenyl)mercury is the carbene precursor, allyl chloride, allyl formate, and other products are formed.[112] Under PTC conditions, tris-(allyloxy)ethane (20%), 1,1-dichloro-2-chloromethylcyclopropane (6%), allyl chloride, and other products are formed.[113] Allyl alcohols substituted at the double bond form *gem*-dichlorocyclopropanes in varying yields, while unsaturated alcohols with the double bond further removed from the hydroxy group form cyclopropanes, usually in good yields. However, unsaturated alcohols sometimes form byproducts which make separation of the main product difficult and are therefore often protected, usually by acetal protecting groups (eq 21),[114] before the addition of carbene. This approach ensures good yields of cyclopropanes.[114]



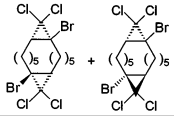
(21)

69% overall

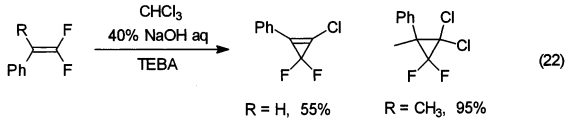
Vinyl halides are less reactive toward dichlorocarbene than are unsubstituted alkenes, particularly if they contain more than one halogen atom connected to the double bond. In these cases PTC usually works well, but Seyferth's procedure for the generation of dichlorocarbene gives the best results. In the case of tri- and tetrachloroethene, only the latter method leads to good yields of the products.[115] Moreover, the PTC system should not be used in reactions with di- or trichloroethene, because explosive chloro- or dichloroacetylene, respectively, is generated under these conditions.[116,117] Haloalkenes substituted by an alkyl or aryl group form appropriate trihalocyclopropanes using PTC or other methods.[118−125] Some examples are presented in Table 2.

1,1-Difluoro-2-arylethenes possessing α-hydrogen atoms add dichlorocarbene, but the dichlorodifluorocyclopropane formed undergoes in situ *β*-elimination

Table 2. Examples of Dichlorocarbene Addition to Vinyl Halides

Substrate	Carbene precursor	Product	Yield (%)	Ref.
	$CHCl_3$, TEBA 50% NaOH		22	119
	$CHCl_3$, TEBA 50% NaOH		50	119
	$CHCl_3$, TEBA 50% NaOH		64	119
	$CHCl_3$, CH_2Cl_2 cetrimide 50% NaOH		29	118
	$CHCl_3$, TBAB 50% NaOH		84	122
	$CHCl_3$, TEBA NaOH solid sonication		71	123
	Cl_3CCO_2Na DMF		50	120

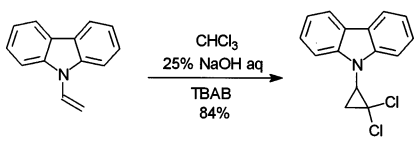
to form stable 1-aryl-2-chloro-3,3-difluorocyclopropenes (eq 22).[124]



(22)

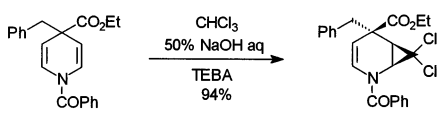
Vinyl ethers[126−131] and sulfides form appropriate *gem*-dichlorocyclopropanes, usually in good yields. It would appear that the formation of cyclopropane from the latter is a multistep process, beginning with the formation of a sulfonium ylide which then undergoes rearrangement and cyclization. Vinyl selenides[132] also react satisfactorily, as do vinylsilanes.[133] Trimethylsilyl enol ethers are very sensitive to aqueous conditions; thus, PTC cannot be used with them. However, *tert*-butyldimethylsilyl derivatives withstand these conditions.[134] The use of ethyl trichloroacetate/MeONa in the latter case also gives good results.[135] Some examples are given in Table 3.

Enamines form *gem*-dichlorocyclopropanes, usually in high yields, although these products are often unstable[136] (eq 23).[137]



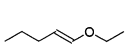
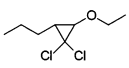
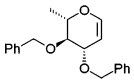
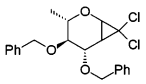
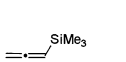
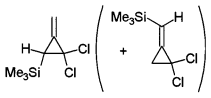
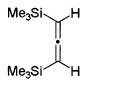
(23)

N-Benzoyldihydropyridine derivatives form stable adducts, also usually in high yields (eq 24).[138] Many earlier examples of reactions of nitrogen heterocycles with dichlorocarbene, which frequently produced *gem*-dichlorocyclopropanes, are collected in ref 4.



(24)

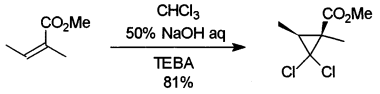
Table 3. Examples of Addition of Dichlorocarbene to Vinyl Ethers and Silanes

Substrate	Carbene precursor	Product	Yield (%)	Ref.
	$CHCl_3$ Et_3BuNCl 50% NaOH		79	127
	$BrCCl_3$ MeLi, −78°C		78	126
	$CHCl_3$, TEBA 50% NaOH		95	129
	$PhHgCBrCl_2$ benzene reflux		78	133
	$PhHgCBrCl_2$ benzene reflux		75	162

In the equilibrating system depicted in eq 2, electrophilic alkenes can react with trichloromethyl anions to form Michael-type adducts, or with dichlorocarbene to form *gem*-dichlorocyclopropane derivatives, or they may form a mixture of products.

gem-Dichlorocyclopropane derivatives are unambiguously formed from electrophilic alkenes only if the Seyferth method (thermal decomposition of trichloromethyl(phenyl)mercury, which does not include trichloromethyl anion formation) is used for carbene generation. The course of the reaction of electrophilic alkenes with chloroform in the presence of a base depends on what kind of electron-withdrawing group is present and on what substituents are connected to the double bond. If the PTC method is used, it additionally depends on the kind of catalyst used. Because most of these reactions were performed in PTC systems, we will limit further discussion to this system.

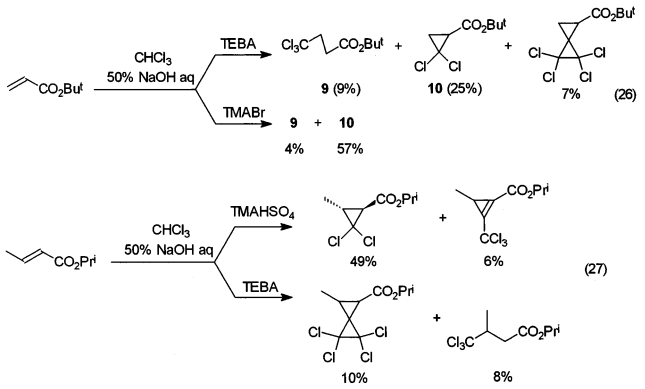
α-Substituted, α,*β*-disubstituted, or α,*β*,*β*-trisubstituted acrylic esters form *gem*-dichlorocyclopropanes independently of the kind of catalyst used, as shown in eq 25.[139]



(25)

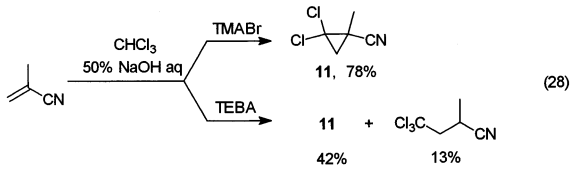
In the presence of TEBA, methyl and ethyl acrylates form chain products via Michael addition.[140] *tert*-Butyl acrylate[141] and acrylates that are *β*-substituted or *β*,*β*-disubstituted[142] usually form mixtures of products in which the tetrachlorospiropentane derivative is present. The latter results from further transformations of the initially formed *gem*-dichlorocyclopropane. On the other hand, unsubstituted and *β*-substituted or *β*,*β*-disubstituted acrylic esters form dichlorocyclopropane derivatives with good selectivity when a TMA salt is used as the catalyst, and in the presence of a large excess of chloroform[141,143,144] (eqs 26[143,144] and 27[142,143]).

Because TMA cations are small, $CCl_3^-TMA^+$ ion pairs are rather tight and inactive, and as a result the trichloromethyl anion does not react with the

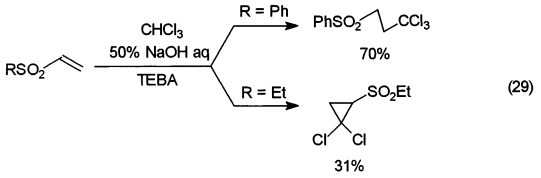


Michael acceptor. However, the $CCl_3^-TMA^+$ ion pair may reside much further from the boundaries of the interfacial region than does the $Na^+CCl_3^-$ ion pair, and can dissociate there to dichlorocarbene, which slowly adds to the electrophilic alkene. An alternative explanation, suggested by a reviewer, is that the $TMA^+CCl_3^-$ ion pairs are less stable than other $TAA^+CCl_3^-$ species and decompose to the hard−hard ion combination (TMA)Cl and dichlorocarbene before a Michael reaction can occur.

The direction of the reaction of α,β-unsaturated nitriles with chloroform under PTC conditions depends on the structure of the nitrile and to some extent on the kind of catalyst. In the presence of TEBA, acrylonitrile[140] and its 3-substituted derivatives[140] exclusively gave Michael adducts, (*E*)-2-phenyl-2-butenenitrile added dichlorocarbene,[145] and methacrylonitrile formed a mixture of chain and cyclic products.[142] When TMA was the catalyst, methacrylonitrile formed only the cyclopropane product in high yield (eq 28).[143]

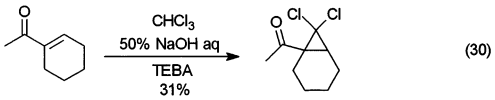


The reactions of α,β-unsaturated sulfones with chloroform, when carried out under PTC conditions, yield products which depend on the type of substitutent on the sulfonyl group (eq 29).[139,146]

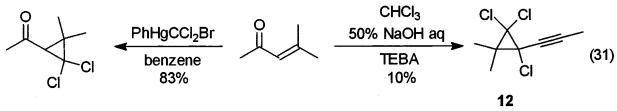


The use of a TMA salt in the reaction of phenyl vinyl sulfone with chloroform does not change the direction of the reaction.[143] Cyclic vinyl and allyl sulfones add dichlorocarbene under PTC conditions.[147]

Suitably substituted vinyl ketones, especially those with an alkyl group in the α position, undergo addition of dichlorocarbene under PTC conditions; however, the yields are often low, as shown, for example, in eq 30.[148]

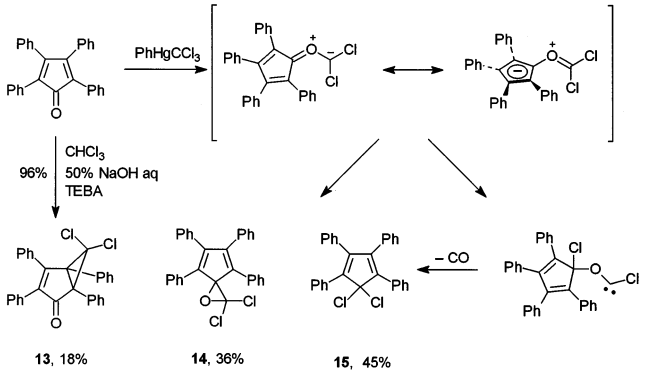


It seems that Seyferth's method should be a good choice for synthesizing the addition products of dichlorocarbene and vinyl ketones in high yields. Unfortunately, there are only a few examples of reactions of these compounds with dichlorocarbene generated from trichloromethyl(phenyl)mercury.[149] Mesityl oxide forms the desired *gem*-dichlorocyclopropane in good yield using the Seyferth precursor.[149] Under PTC conditions compound **12** is formed in low yield (eq 31);[142] however, the mechanism of this latter reaction is not known.

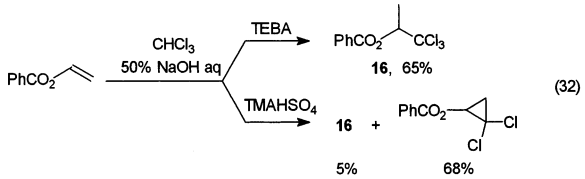


Tetraphenylcyclone forms monoadduct **13** with PTC-generated dichlorocarbene.[150] When trichloromethyl(phenyl)mercury was used as the carbene source, a mixture of products **13**−**15** was formed, possibly via the carbonyl ylide (Scheme 4).[151] However, the formation of **15** via a 1,4-cycloaddition of dichlorocarbene and the extrusion of carbon monoxide from the adduct cannot be excluded.[152]

Scheme 4

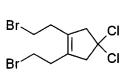
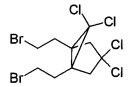
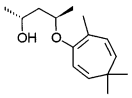
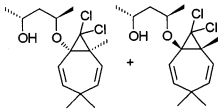
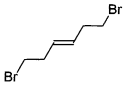
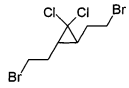
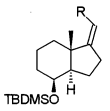
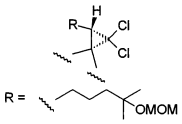
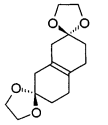
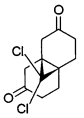
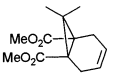
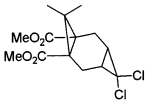
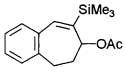
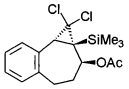
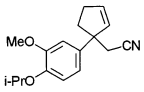
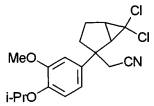
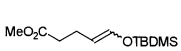
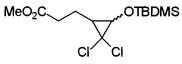
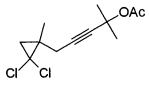
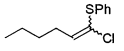
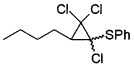
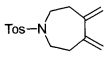
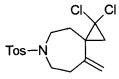
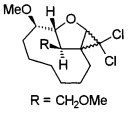


Aldehyde enol esters yield products derived from the formal addition of trichloromethyl anion to them in the presence of TEBA.[153] This process consists of the hydrolytic generation of aldehyde, addition of the trichloromethyl anion to the carbonyl group, and O-acylation of the adduct by an enol ester.[154] In the presence of a TMA salt and a large excess of chloroform, a mixture of formal addition and cyclopropane products is formed, in which the latter prevails (eq 32).[153]



Ketone-derived enol esters add dichlorocarbene exclusively, often in high yields.[153,155] Selected ex-

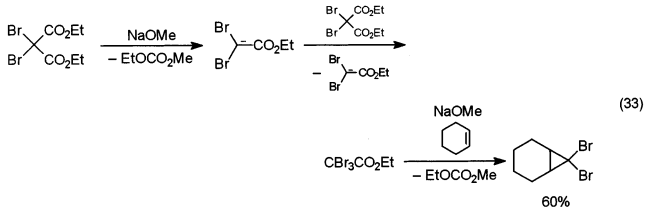
Table 4. Examples of Dichlorocarbene Addition to Alkenes Containing Various Functional Groups

Substrate	Carbene precursor	Product	Yield (%)	Ref.	Substrate	Carbene precursor	Product	Yield (%)	Ref.
	$CHCl_3$ cetrimide 50% NaOH		89	91		$CHCl_3$, TEBA NaOH aq	 2.3 : 1	100	134
	$CHCl_3$ PTC		78	126					
	$CHCl_3$ TBAHS NaOH solid		82	163		1. $CHCl_3$ TEBABr 50% NaOH 2. HCl/MeOH		84	102
	CCl_3CO_2Na glyme/diglyme		63	156		$CHCl_3$ cetrimid 50% NaOH		81	104
	$CHCl_3$, TEBA 50% NaOH		89	157		$CHCl_3$, TEBA 50% NaOH		50	160
	$CHCl_3$ t-BuOK hexane		45	167		$CHCl_3$, TEBA 50% NaOH CH_2Cl_2		75	159
	$CHCl_3$, TEBA NaOH solid		98	158		$CHCl_3$ t-BuOK benzene		69	161
	$CHCl_3$, TBAB 50% KOH	 R = CH_2OMe	> 60	131					

amples of *gem*-dichlorocyclopropanes formation from alkenes substituted by two (or more) different functional groups[156−167] are presented in Table 4.

III.2. *gem*-Dibromocyclopropanes

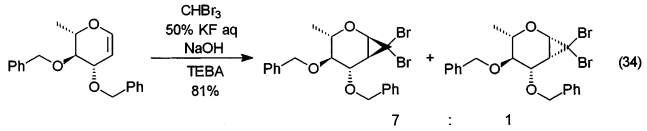
gem-Dibromocyclopropanes are, as a rule, more active than the corresponding *gem*-dichloro compounds; therefore, *gem*-dibromocyclopropanes are very valuable substrates in organic synthesis. The most important and convenient method for their preparation is the addition of dibromocarbene to an alkene. Two methods for the generation of dibromocarbene are presently in common use: base-induced α-elimination of hydrogen bromide from bromoform and thermal decomposition of tribromomethyl(phenyl)mercury. The latter allows the preparation of *gem*-dibromocyclopropanes, even from electrophilic alkenes, in good yields. It is also used with highly deactivated or base-sensitive alkenes. However, the high cost and toxicity of this carbene precursor limit its wide application. For the α-elimination process, *t*-BuOK in a hydrocarbon solvent and phase-transfer catalysis are commonly used methodologies. Other methods are seldom used if at all. Dibromocarbene was generated in a photolytic reaction from an iron porphyrinate complex and was captured by a series of alkenes (see section III.1).[37,38] Mebane et al. found recently that the reaction of diethyl dibromomalonate with sodium methoxide when carried out in cyclohexene yields 7,7-dibromonorcarane in 60% yield.[168] The key step in this reaction is a bromophilic attack on diethyl dibromomalonate by a dibromoethoxycarbonyl carbanion, which in turn is formed from the reaction of diethyl dibromomalonate and methoxide ion (eq 33).



(33)

Dibromocarbene is the most reactive dihalocarbene. Its cycloaddition to unsaturated hydrocarbons and alkenes possessing functional groups proceeds rapidly. Many examples of these reactions have been published in the last seven years.[52,56,61,63,64,71,73,90,94−96,100,104,118,119,125,129,133,134,151,159,166,169−238] Determination of the optimal conditions for the reaction of dibromocarbene with alkenes possessing functional groups is often not an easy task, especially under PTC conditions. The mechanistic details of the PTC generation of dibromocarbene have been less thoroughly investigated than those of dichlorocarbene reactions. Due to the high reactivity of dibromocarbene, its hydrolysis proceeds to a greater extent than does that of chloroform under these conditions. In the case of unreactive alkenes, small amounts of tarry materials are often formed, making separation of the product difficult. However, after some experimenta-

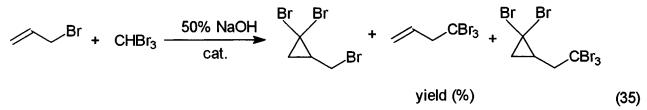
tion conditions can be found which ensure high yields of products. One possible approach to performing PTC addition of dibromocarbene to alkenes has been overlooked by chemists: Nagarajan et al. obtained only tarry material in the reaction of glucal with bromoform in the presence of 50% aqueous NaOH and TEBA. However, the use of a large excess of potassium fluoride solution and small amounts of alkali instead of concentrated aqueous NaOH permitted the preparation of *gem*-dibromocyclopropane in high yield (eq 34).[129]



Because of the high activity of dibromocarbene, its PTC reactions can be carried out at low temperatures (up to −80 °C) with solid potassium hydroxide as a base. Its reactions with gaseous alkenes can be conveniently carried out this way.[239] Sonication of the reaction mixture is sometimes recommended. The yields of cyclopropanes increase if a small quantity of ethanol is added to a reaction mixture,[240] although the mode of action of this additive is not clear. Tertiary amines have not found wide application as catalysts,[241] although sometimes they are used as a second catalyst in conjunction with a quat.

All the general rules governing the addition of dichlorocarbene to alkenes which are discussed in section III.1 are applicable to the analogous reactions with dibromocarbene. However, some points deserve comment.

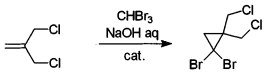
Allylic halides, particularly bromides, besides 1,1-dibromocyclopropane derivatives furnish the products of alkylation of the tribromomethyl anion and sometimes the products of their further transformations (elimination products, carbene addition products, etc). The ratio of the products depends on the reaction conditions, the structure of the allyl halide, and the type of catalyst.[242,243] The latter dependence is illustrated in eq 35.[243]



		yield (%)	
TEBA	40	25	18
benzo-15-crown-5	56	5	9
Ph_4AsCl	7	82	9
TMACl	42	3	7

TMA salt favors dibromocarbene addition; however, long reaction times are often required to reach satisfactory yields. The synthesis of the dibromocarbene adduct of 3-chloro-2-(chloromethyl)propene is a good illustration of the necessity of optimizing the bromoform process as carried out under PTC conditions in particular cases. This reaction was thoroughly investigated[244−251] because the product is an important substrate for the syntheses of bicyclobutane. Almost all the procedures described suffer from serious disadvantages, such as low yields of product,[244−246,251] poor reproducibility,[247] and tedious separation.[244−246,248,249] Of all the methods described,

Scheme 5

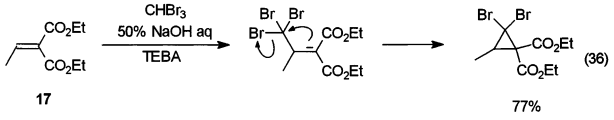


$CHBr_3$/alkene ratio	NaOH concentration	NaOH/alkene ratio	solvent	catalyst	additives	Time	Temp.	Yield (%)	Ref.
1.0	36%	3.1	CH_2Cl_2	TMABr	EtOH, cat.	40 h	r. t.	25	250
2.0	50%	9.7	—	dibenzo-18-crown-6	pinacol, cat.	4 days	40°C	60–80	248,249
1.02	50%	4.7	CH_2Cl_2	$PhNMe_3Cl$	EtOH, cat.	40 h	r. t.	37%	244,245
2.12	50%	9.4	CH_2Cl_2	TEBA	EtOH, cat.	24 h	r. t.	29–31	246
2.5	44%	9.9	—	aliquat	—	2 days	40°C	70	247
2	55%	13.3	CH_2Cl_2	TMABr	—	20 h	50°C	75	251

the one in which a TMA salt is used as a catalyst and concentrated aqueous NaOH as a base ensures the highest yield and is very easy to work up.[251] Since 3-chloro-2-(chloromethyl)propene is a disubstituted alkene, it reacts faster than does allyl chloride (Scheme 5).

Electrophilic alkenes often react with bromoform under PTC conditions differently than they do with chloroform. Methacrylonitrile with TEBA as a catalyst forms the *gem*-dibromocyclopropane derivative exclusively and in high yield,[252] whereas, with chloroform under similar conditions, both chain and cyclic products are formed in moderate yield.[142]

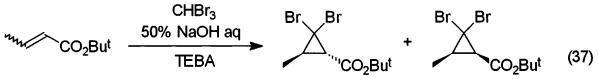
Very often *gem*-dibromocyclopropane formation from electrophilic alkenes is a result of the addition of a tribromomethyl anion followed by cyclization, rather than direct dibromocarbene addition (eq 36).[253]



17 77%

Compound **17** when reacted with chloroform forms only tarry material.

Differentiation between direct carbene addition and the process in which Michael addition of a trihalomethyl anion is followed by cyclization can be made on the basis of investigations into the stereochemical course of the reaction. For instance, (*E*)-*tert*-butyl crotonate adds dibromocarbene stereospecifically, while the *Z* isomer forms a mixture of geometrical isomers.[144] The *E* isomer's product is undoubtedly a result of tribromomethyl anion addition and subsequent intramolecular cyclization (eq 37).



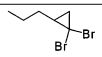
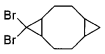
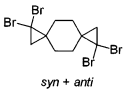
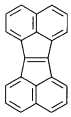
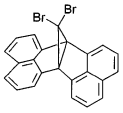
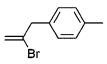
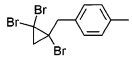
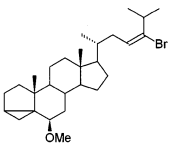
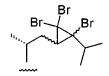
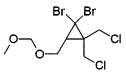
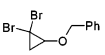
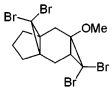
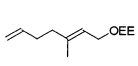
E 34%
Z 42% 5%

Selected recent examples of *gem*-dibromocyclopropane syntheses are collected in Table 5.

III.3. *gem*-Difluorocyclopropanes

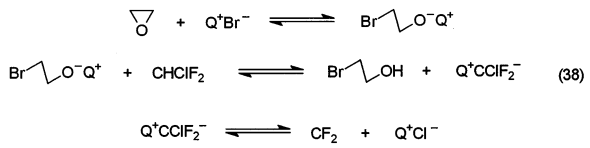
The simplest approach to the synthesis of *gem*-difluorocyclopropanes—the reaction of difluorohalomethane with a base in the presence of an alkene—unfortunately does not work satisfactorily, despite the fact that many base/solvent systems (such as CH_3Li, *t*-BuOK, NaOH/tetraglyme, and concentrated aqueous NaOH with a PT catalyst) were tested. The only exception is the Buddrus method, in which

Table 5. Examples of Dibromocarbene Addition to Unsaturated Hydrocarbons and Functionalized Alkenes

Substrate	Carbene precursor	Product	Yield (%)	Ref.
	$CHBr_3$, TEBA 50% NaOH		95	207
	$CHBr_3$, t-BuOK pentane		81	170 174
	$CHBr_3$, t-BuOK pentane		65	71
	$CHBr_3$ NaOH, TBAB CH_2Cl_2		79	193
	$CHBr_3$, t-BuOK		57 73	199 203
	$CHBr_3$ cetrimide 50% NaOH CH_2Cl_2		79	205
	$CHBr_3$, TEBA 50% NaOH EtOH cat.	 *syn + anti*	56	209
	$CHBr_3$ cetrimide 50% NaOH CH_2Cl_2		80	180 231
	$CHBr_3$, TEBA 50% NaOH CH_2Cl_2 EtOH cat.		87	196
	$CHBr_3$ cetrimide 50% NaOH EtOH cat.		61	125
	$CHBr_3$, TEBA 50% NaOH CH_2Cl_2		69	216
	$CHBr_3$ cetrimide 50% NaOH		19	215
	$CHBr_3$, TEBA 50% NaOH		67	219
	$CHBr_3$, TEBA 50% NaOH sonication	 23(*R*), 24(*R*) 23(*S*), 24(*S*) + 	52 12	179
	$CHBr_3$, TEBA NaOH solid sonication		86	172
	$CHBr_3$ NaOH $PhMe_3NCl$		30	187
	$CHBr_3$, TEBA 50% NaOH		55	220
	$CHBr_3$, TEBA 50% NaOH		38	225
	$CHBr_3$, TEBA 50% NaOH		68	226
	1. $CHBr_3$, TEBA 50% NaOH 2. H^+ $CHBr_3$ cetrimide		67	212

Substrate	Carbene precursor	Product	Yield (%)	Ref.
	38% NaOH Et_3N cat. CH_2Cl_2 $CHBr_3$, TEBA		99	199
	50% NaOH EtOH cat. CH_2Cl_2		68	176
	$CHBr_3$ t-BuOK pentane		93	178 230
	$CHBr_3$ t-BuOK pentane		72	189
	$PhHgCBr_3$ benzene		25	225
	$CHBr_3$, TEBA 50% NaOH		74 85	230
	$CHBr_3$, TBAB 25% NaOH		61	137
	$CHBr_3$ t-BuOK pentane		93	195
	$CHBr_3$ cetrimide 50% NaOH		41	217
	$CHBr_3$ cetrimide 50% NaOH		50	217
	$CHBr_3$, TEBA 50% NaOH		89 80 92	203 232 231
	$CHBr_3$, TEBA 50% NaOH benzene	 2 : 1	81	211
	$CHBr_3$ t-BuOK pentane		85	182
	$CHBr_3$, TEBA 50% NaOH CH_2Cl_2		> 56	221
	$CHBr_3$ PTC	 95 : 5	24	227
	$CHBr_3$, TEBA 50% NaOH		49	233
	$CHBr_3$, TEBA NaOH CH_2Cl_2		91	228

chlorodifluoromethane is treated with oxirane (or chloromethyloxirane), with a TAA salt as the catalyst, in the presence of an alkene.[254] The haloform is deprotonated by the halohydrin anion, which is formed by the ring opening of the oxirane by the halide ion (eq 38).

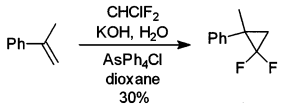


(38)

This is a very efficient method (although it fails in the case of 1-alkenes or 1-haloalkenes), which is attributed to the concentration of the base (alkoxide) being low and never exceeding that of the catalyst. However, rather harsh conditions (the reaction mixture is heated in an autoclave at ~140 °C) preclude wide application of this method. In fact, during the last seven years we could not find a report of its application for the synthesis of *gem*-difluorocyclopropanes.

Difluorocarbene generated in the PTC system from chlorodifluoromethane in the presence of aqueous NaOH, aqueous KOH, or a solid base, and with TAA salt as a catalyst, does not undergo cycloaddition to alkenes. Weyerstahl obtained the difluorocarbene adduct of tetramethylethylene in 1% yield under the conditions mentioned above.[255] The rates of deprotonation of the chlorodifluoromethane and the rates of dissociation of the resulting carbanion to form difluorocarbene are similar. This indicates that the chlorodifluoromethyl anion is a very short lived species and cannot be transferred from the interfacial region, where it is formed, into the organic phase. Difluorocarbene is therefore formed in the interfacial region and undergoes fast hydrolysis.

Surprisingly, difluorocarbene can be captured by nucleophilic alkenes in the PTC system, if it is generated from chlorodifluoromethane by the action of concentrated KOH in dioxane in the presence of tetraphenylarsonium chloride as a catalyst. However, the yields of *gem*-difluorocyclopropanes are modest and seldom exceed 30% (eq 39).[256]

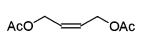
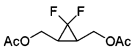
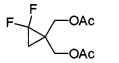
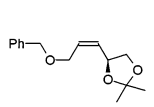
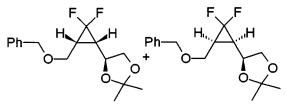
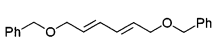
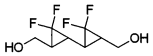
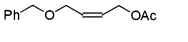
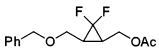
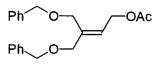
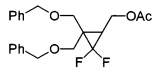
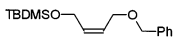
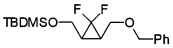
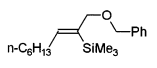
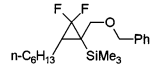
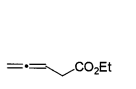
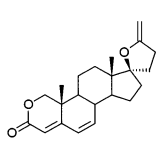
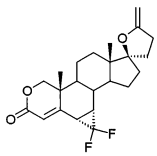


(39)

It is possible that the reversible reaction between the tetraphenylarsonium cation and chlorodifluoromethyl anion that leads to the pentacoordinated arsenic compound stabilizes the latter and permits its transportation into the bulk of the organic phase.

Because of the aforementioned difficulties, many other methods for generation of difluorocarbene were elaborated. They are described in an excellent review by Brahms and Dailey in 1996[257] and also in the Houben-Weyl monographs in 1989[3] and 1997,[4] and will be mentioned here only briefly. The most important methods for the preparation of *gem*-difluorocyclopropanes based on difluorocarbene (or carbenoid) addition to an alkene are the following.

Table 6. Examples of Addition of Difluorocarbene Generated from Sodium Chlorodifluoroacetate to Alkenes

Substrate	Product(s)	Yield (%)	Ref.
		80	266
		74	265
	 1.4 : 1	94	273
		66[a]	268
		83	271
		75	261
		95	262
		98	263
 1 : 1		22	272
		64	267

[a] Overall yield after debenzylation.

(1) Decomposition of alkali-metal chlorodifluoroacetates in the presence of an alkene.

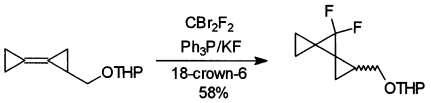
Historically this was the first example of the addition of difluorocarbene to alkenes.[258] A sodium salt is most often used, and must be thoroughly dried. Usually reactions are performed by refluxing sodium chlorodifluoroacetate with the alkene in diglyme or triglyme, sometimes in the presence of 18-crown-6 as a catalyst. Difluorocarbene generated in this way does not undergo addition to alkenes of low reactivity. An excess of the difluorocarbene precursor is necessary to obtain good yields of the products. During the last seven years this method has been the one most often used.[259−273] Recent examples of these reactions are presented in Table 6.

(2) Alkali-metal halide mediated cleavage of methyl chlorodifluoroacetate in the presence of an alkene.

Lithium chloride complexed with HMPA or KF in the presence of 18-crown-6 is commonly used for this purpose.[274] Good yields of *gem*-difluorocyclopropanes were only obtained with electron-rich alkenes.

(3) Reaction of dibromodifluoromethane with triphenylphosphine, potassium fluoride, and an alkene.

In this process, bromodifluoromethyl(triphenyl)-phosphonium bromide is initially formed and then reacts with the fluoride ion to release difluorocarbene.[275] The presence of catalytic amounts of 18-crown-6 increases the yields of *gem*-difluorocyclopropanes.[276] 1,2-Disubstituted alkenes react unsatisfactorily, whereas tetra-, tri-, and *gem*-disubstituted alkenes afford *gem*-difluorocyclopropanes in good yields. These reactions can be run at room temperature; however, at least double the amount of triphenylphosphine and dibromodifluoromethane must be used to obtain good yields[277] (eq 40).[103]

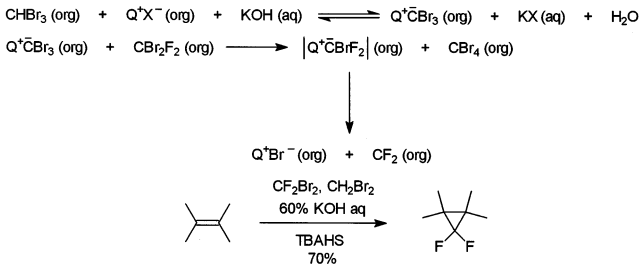


(40)

(4) Reaction of dibromodifluoromethane with dibromo- or tribromomethane and an alkene under PTC conditions.

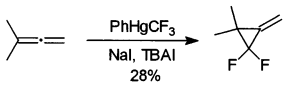
As was mentioned earlier, difluorocarbene generated from chlorodifluoromethane under PTC conditions cannot undergo cycloaddition reactions with alkenes because it is hydrolyzed at the phase boundary. It was shown, however, that difluorocarbene can be generated in a PT-catalyzed system via the halophilic reaction of tribromo-[278] or dibromomethyl[279] carbanions with dibromodifluoromethane. These carbanions, which are produced after the deprotonation of bromoform (or methylene bromide) at the phase boundary, enter the organic phase in the form of lipophilic ion pairs with the catalyst cation. These ion pairs undergo halophilic reactions with dibromodifluoromethane to form carbon tetrabromide (or bromoform) and the ion pair $CBrF_2^-NBu_4^+$, which then splits into TBAB and difluorocarbene. The latter can react with alkenes, giving *gem*-difluorocyclopropane derivatives (Scheme 6). This method is limited to nucleophilic alkenes, but it is so simple to perform that it can be recommended as the method of choice in these cases.

Scheme 6



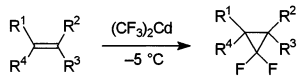
(5) Decomposition of organometallic reagents substituted with a trifluoromethyl group in the presence of an alkene.

The decomposition of trifluoromethyl(phenyl)mercury, induced by sodium iodide at 80 °C (refluxing benzene), permits the preparation of *gem*-difluorocyclopropanes in good yields, even from electron-deficient alkenes (for a review, see ref 280). Despite the many advantages of this method (almost any functional group can be present in the alkene, and good yields are obtained even with deactivated alkenes), it is seldom used[281,282] (eq 41),[281] because trifluoromethyl(phenyl)mercury is not commercially available and its synthesis is complicated.



(41)

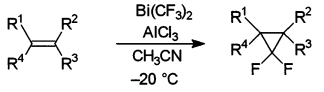
Trifluoromethyl derivatives of tin, cadmium, silicon, bismuth, and phosphorus are also used as sources of difluorocarbene. Usually they require rather high reaction temperatures (100−200 °C), with some important exceptions. Bis(trifluoromethyl)cadmium, which is readily available from diethylcadmium and trifluoroiodomethane, decomposes quantitatively in the presence of alkenes at −5 °C in noncoordinating, low-polarity solvents such as chloroform or dichloromethane to form *gem*-difluorocyclopropanes and cadmium fluoride.[283] With less active alkenes, such as allyl bromide, dimerization of the difluorocarbene is observed (eq 42).



(42)

cyclohexene, hex-1-ene, *trans*-butene, *cis* and *trans* stilbene; yields > 95%

Tris(trifluoromethyl)bismuth, when treated with $AlCl_3$ at −20 °C, liberates difluorocarbene which can be trapped with alkenes in good yields[284] (eq 43).



(43)

isobutene (75%), cyclohexene (40%), styrene (60%), 2,3-dimethylbuta-1,3-diene (75%, monoadduct)

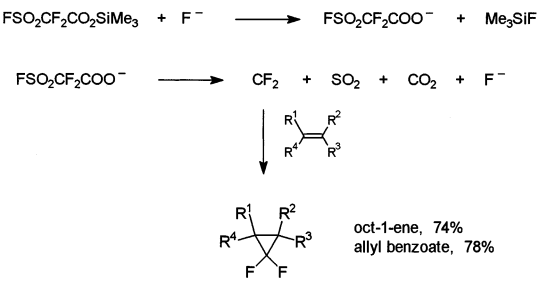
(6) Thermal decomposition of trifluoro(trifluoromethyl)oxirane in the presence of alkenes.

Heating a mixture of oxirane and an alkene at ∼200 °C in an autoclave leads to the production of *gem*-difluorocyclopropane derivatives, even in the case of alkenes of low activity.[285] The reaction conditions substantially limit the wide application of this method. Recently, this reaction was used for the preparation of some perfluoroalkylcyclopropanes.[286]

(7) Reduction of dibromodifluoromethane in the presence of an alkene. Dibromodifluoromethane treated with zinc in THF (in the presence of a catalytic amount of iodine) generates free difluorocarbene, which can be captured by nucleophilic alkenes in good yields.[287] With *cis*- and *trans*-but-2-ene, 1-hexene, or cyclohexene the yields did not exceed 7%. This room temperature reaction permits the preparation of *gem*-difluorocyclopropanes under very mild conditions. Difluorodiiodomethane does not undergo this reaction with zinc.[288]

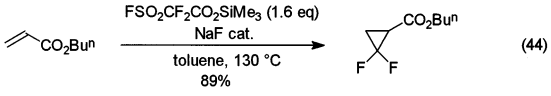
(8) Decomposition of trimethylsilyl fluorosulfonyldifluoroacetate (TFDA). Recently, Dolbier et al. reported a new, very efficient method for the preparation of *gem*-difluorocyclopropanes from both nucleophilic and electrophilic alkenes.[289] It consists of a chain process decomposition of the title compound in the presence of an alkene and a catalytic amount of sodium fluoride at ∼105 °C (Scheme 7).

Scheme 7



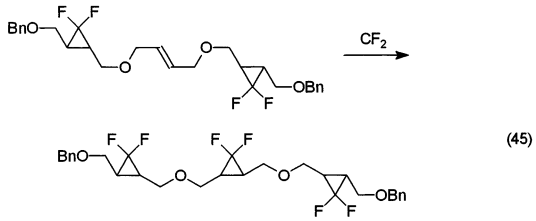
TFDA can be obtained from trimethylsilyl chloride and fluorosulfonyldifluoroacetic acid in 78% yield.

This method allows for the preparation of *gem*-difluorocyclopropanes in high yield, even from acrylic ester (eq 44),[289] and unboubtedly will be used for synthesizing cyclopropanes, which until now were not available.



(44)

A comparison of this method and that using sodium chlorodifluoroacetate as the difluorocarbene source shows the superiority of the former reaction (eq 45).[259]

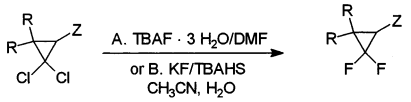


(45)

$ClCF_2CO_2Na$ (50 eq), diglyme, 180 °C, 54%
$FSO_2CF_2CO_2SiMe_3$ (10 eq), NaF cat., toluene, 105 °C, 72%

Alternative methods for synthesizing functionalized *gem*-difluorocyclopropanes, which do not proceed by the addition of difluorocarbene to an alkene, are described below.

gem-Difluorocyclopropanes substituted with an electron-withdrawing group can be synthesized from the corresponding *gem*-dichlorocyclopropanes (which in turn are available from electrophilic alkenes and dichlorocarbene generated in the PTC system in the presence of tetramethylammonium salt; see section III.1) via their reaction with TBAF in DMF or KF and TBAHS in an acetonitrile/water mixture (eq 46).[290] This process takes place via consecutive elimination−addition steps.

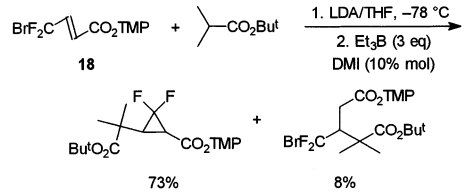


(46)

Z = CO_2Bu^t, CO_2Pr^i, SO_2Ph, COPh; R = H, Me

This method is very simple; however, a strong electron-withdrawing group and an α hydrogen atom must be present in the substrate. Yields of the products do not exceed 50%. 1,1-Dichloro-2-cyanocyclopropane was destroyed under the reaction conditions.

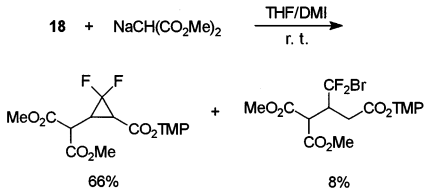
Taguchi's method consists of the reaction of (*E*)-4-bromo-4,4-difluorocrotonate **18** with the lithium enolate of an ester or amide in the presence of triethylborane (for a short review, see ref 291). It involves a Michael addition of the enolate to the crotonate **18**, followed by an intramolecular substitution in which triethylborane acts as a radical initiator for cleaving the CF_2–Br bond (eq 47).[292] Simple Michael addition products are formed as byproducts in amounts that depend on the solvent used.



(47)

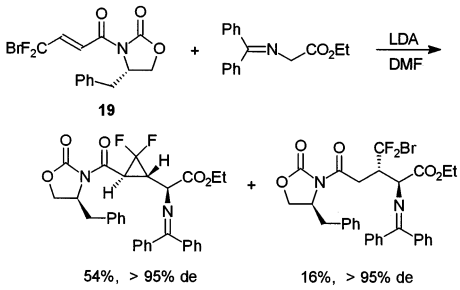
TMP = 2,4,6-$Me_3C_6H_2$; DMI = 1,3-dimethyl-2-imidazolidinone

Compound **18** reacts similarly with carbanions derived from active methylene compounds such as malonic ester (eq 48).[292]



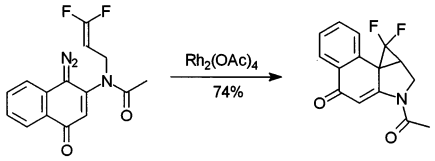
(48)

Asymmetric syntheses of *gem*-difluorocyclopropanes using **18** and a chiral carbanion precursor[293] or the chiral acceptor **19** and *N*-(diphenylmethylidene)glycinate[294] (however, see ref 260) were also studied, providing good results (eq 49).[294]



(49)

Inter- or intramolecular additions of carbenes to 1,1-difluoro-1-alkenes lead to *gem*-difluorocyclopropanes (eq 50).[295]

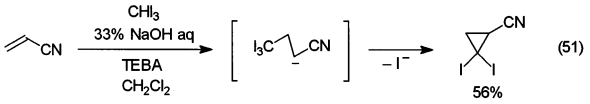


(50)

In the former case, however, only 1,1-difluoro-1-alkenes which do not possess a *β*-hydrogen atom can be used in the reaction with PTC-generated dichlorocarbene. Otherwise, stable 1,1-difluorocyclopropene derivatives are formed in high yields (see section III.1).

III.4. *gem*-Diiodocyclopropanes

gem-Diiodocyclopropanes are rather unstable compounds. Therefore, the number of papers reporting their synthesis is limited. The treatment of iodoform with a base in the presence of alkenes is the only method used for the preparation of these compounds. Phase-transfer catalysis[296,297] or a *t*-BuOK/*t*-BuOH/light petroleum system[298] was used for this purpose. The formation of *gem*-diiodocyclopropanes from unsaturated hydrocarbons proceeds via the addition of diiodocarbene to the double bond,[299] whereas electrophilic alkenes (such as acrylonitrile and methyl methacrylate) form appropriate cyclopropanes via an addition−elimination mechanism (eq 51).[297]



(51)

In both cases, under PTC conditions, significant amounts of tetraiodoethene are formed. Phenyl vinyl sulfone and diethyl vinyl phosphonate do not react with iodoform under these conditions.

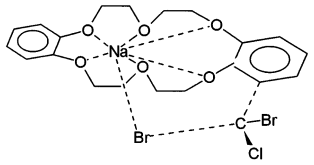
The reaction of corannulene with diiodocarbene generated from iodoform in a PTC system proceeds analogously to that with dichlorocarbene[73] (see section III.1).

III.5. Mixed *gem*-Dihalocyclopropanes

III.5.1. gem-Bromochlorocyclopropanes

The α-elimination of hydrogen chloride from dibromochloromethane and the thermal decomposition of dibromochloromethyl(phenyl)mercury in the presence of alkenes are presently used to prepare *gem*-bromochlorocyclopropanes. Potassium *tert*-butoxide is most often used as a base for the α-elimination. This method ensures good product yields with high selectivities. The formation of other *gem*-dihalocyclopropanes does not occur under these conditions. In this system, equilibrations among trihalomethyl anions, halogen anions, and bromochlorocarbene do not occur, or are at least seriously curtailed, because potassium derivatives of trihalomethyl anions and potassium halides are not soluble in the reaction medium. In the PTC system, the yields and purity of the products depend strongly on the kind of catalyst used, and on the nucleophilicity of the alkene. With typical quats such as TEBA or TBAB mixtures of all three possible dihalocyclopropanes are formed.[252] This result is not surprising because the dissociation of a dibromochloromethyl anion to bromochlorocarbene and its reactions with halogen anions are truly reversible processes in this system. Such equilibrations take place although the relative order of dissociation of halide anions from trihalomethyl anions is Br > I > Cl. Of course, such mixtures of dihalocyclopropanes are difficult to separate, so these reactions are not preparatively useful. In the presence of dibenzo-18-crown-6 as a catalyst, the synthesis of *gem*-bromochlorocyclopropanes in a PTC system proceeds, within a narrow range of experimental conditions, in good yields and selectivity, even from 1-alkenes.[300] 3,5-Di-*tert*-butylbenzo-15-crown-5 and 3,3′,5,5′-tetra-*tert*-butyldibenzo-18-crown-6 behave similarly[301] as do TMA salts. However, under comparable reaction conditions, TMA salts produce very low conversions. Other crowns behave like typical TAA phase-transfer catalysts. The presence of dibenzo-18-crown-6 in the system probably prevents to some extent the equilibria mentioned,[302] for reasons which are as yet unknown. Dehmlow postulated the formation of an "ion pair carbene complex", **20** (Scheme 8), as an explanation for the dibenzo-18-crown-6 specificity.[302]

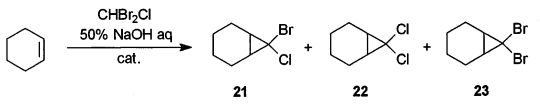
Scheme 8



20

Complexation of the electrophilic bromochlorocarbene with the benzo substitutent and with the $Br^{-}\cdots Na^{+}\cdots$crown unit stabilizes the carbene and bromide ion more effectively than is seen in other PTC systems. In this way, halide exchange is suppressed by **20** and the transfer of bromochlorocarbene to alkene becomes competitive. However, other benzocrowns such as benzo-18-crown-6 behave similarly to typical TAA salts. With unreactive alkenes such as *tert*-butylethene, even in the presence of dibenzo-18-crown-6, equilibration between the carbanions and the carbenes takes place, leading to a mixture of three dihalocyclopropanes in low yield.[302] A comparison of catalysts in the bromochlorocyclopropanation of cyclohexene under PTC conditions is shown in Scheme 9.[301]

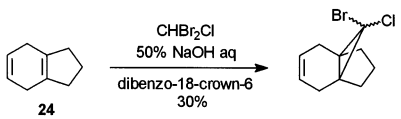
Scheme 9



21 **22** **23**

catalyst	ratio 21	22	23	Yield, %
benzo-15-crown-5	68.5	25.1	6.4	71
3,5-di-t-butylbenzo-15-crown-5	96.4	3.6	0	75
dibenzo-18-crown-6	96.2	3.2	0.4	63
3,3',5,5'-tetra-t-butyldibenzo-18-crown-6	97.5	2.5	0	46
TMACl	97.8	2.2	0	22
TEBA	50.8	40.8	8.2	56

Recent examples of syntheses of *gem*-bromochlorocyclopropane derivatives include the addition of bromochlorocarbene to styrene,[237,303] phenyl vinyl sulfide,[303] some alkenes with halogen atoms removed from the double bond,[90,236,304,305] and the bicyclic diene **24** (eq 52).[306]



24

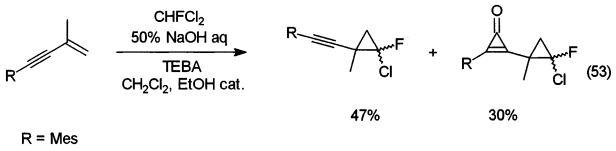
(52)

III.5.2. gem-Chlorofluorocyclopropanes

gem-Chlorofluorocyclopropanes are prepared via the addition of chlorofluorocarbene to alkenes. The

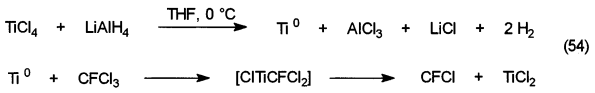
reactivity and selectivity of this carbene are between those of difluoro- and dichlorocarbene. Its addition to alkenes is stereoselective, predominantly forming the isomers with the chlorine atom *cis* or *endo* to the alkyl group or to the second ring, respectively. The chlorofluorocarbene is most often generated by the following.

(a) α-Elimination of HCl from dichlorofluoromethane. In a PTC variant of this reaction, concentrated KOH in the presence of 18-crown-6 is most often used,[307−310] while quats behave similarly. Chain and cyclic unsaturated hydrocarbons, allylic alcohols and halides, vinyl ethers, ketene acetals, alkenes with a trimethylsilyl group further removed from the double bond, and many other unsaturated compounds were cyclopropanated under these conditions (for examples, see ref 4). With conjugated enynes, the chlorofluorocarbene often adds not only to the double bond (as dichlorocarbene usually does; see section III.1), but also, to a significant extent, to a triple bond. The resulting chlorofluorocyclopropenes hydrolyze to the corresponding cyclopropenones under the reaction conditions (eq 53).[311]

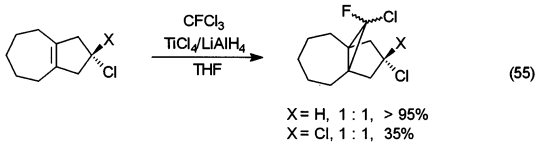


t-BuOK was used as a base for the generation of chlorofluorocarbene from dichlorofluoromethane, especially for additions to enamines[312] and trimethylsilyl enol ethers.[313] Appropriate *gem*-chlorofluorocyclopropanes are usually unstable and undergo further transformations.

(b) Reduction of trichlorofluoromethane by zerovalent titanium species. This process occurs according to eq 54.



In the presence of alkenes, vinyl ethers, *N*-vinyl amides, and other compounds, *gem*-chlorofluorocyclopropanes are formed in moderate to excellent yields.[314,315] The reaction conditions are mild. Recently, this method was used for the syntheses of tri-[236] and tetrahalopropellanes[305] (eq 55).

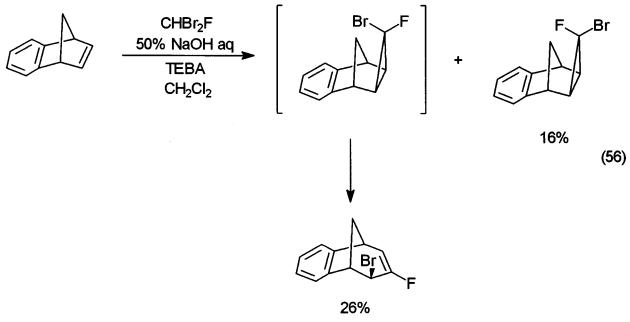


(c) Thermal decomposition of dichlorofluoromethyl(phenyl)mercury. This is a very efficient method for the synthesis of *gem*-chlorofluorocyclopropanes. The reactions are performed in boiling benzene or in glyme, in the presence of sodium iodide, which cuts the reaction time significantly.[316]

Other methods for generating chlorofluorocarbene for alkene addition reactions, such as the reaction of trichlorofluoromethane with magnesium,[317] or the reaction of ethyl dichlorofluoroacetate with sodium methoxide,[318] have not been recently used.

III.5.3. gem-Bromofluorocyclopropanes

gem-Bromofluorocyclopropanes are often unstable; thus, despite their potential usefulness in organic synthesis, there is a limited amount of information available concerning their synthesis and applications. For the preparation of *gem*-bromofluorocyclopropanes, the reaction of dibromofluoromethane and a base (aqueous NaOH/TAA catalyst[319,320] or *t*-BuOK) with an alkene, or the thermal decomposition of dibromofluoromethyl(phenyl)mercury in the presence of an alkene,[321] is used. The mercury precursor is rather unstable, which allows the addition of bromofluorocarbene to alkenes, including electrophilic ones, to be performed even at room temperature or at 80 °C within a very short time. Recently, a series of alkylidene-*gem*-bromofluorocyclopropanes was obtained from the corresponding allenes and dibromofluoromethane with *t*-BuOK as a base.[322] The same method was used for the preparation of trihalopropellanes (see section III.5.2).[236] It is worth noting that the addition of bromofluorocarbene, which is generated from dibromofluoromethane under PTC conditions, to benzonorbornadiene[323] or bicyclo[3.2.0]hept-6-ene[324] affords unrearranged bromofluorocyclopropane in addition to the *exo*-bromofluoro ring-opened product (eq 56).[323]

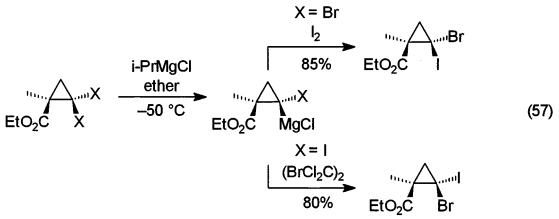


III.5.4. gem-Haloiodocyclopropanes

Fluoro- and chloroiodocyclopropanes were obtained by generation of the appropriate dihalocarbene in a PTC system from diiodofluoromethane[325] or chlorodiiodomethane,[296] respectively, followed by its addition to alkenes. Yields did not exceed 20% in the first case, but were good in the second.

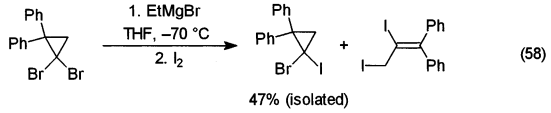
Dibromoiodomethane and bromodiiodomethane, when treated with a concentrated NaOH solution in a PTC system in the presence of alkenes, form mixtures of all three possible dihalocyclopropanes.[326] Thus, there is no convenient method for the preparation of *gem*-bromoiodocyclopropanes via the addition of bromoiodocarbene to alkenes.

Knochel et al. described the syntheses of configurationally stable, ester-functionalized cyclopropylmagnesium reagents, which react stereoselectively with electrophiles, including iodine or 1,2-dibromotetrachloroethane,[327] to produce *gem*-bromoiodocyclopropane derivatives (eq 57).



(57)

In a similar approach, Baird synthesized 1-bromomagnesio-1-bromo-2,2-diphenylcyclopropane and the corresponding *gem*-bromoiodocyclopropane derivative[328] (eq 58).



(58)

IV. Applications of gem-Dihalocyclopropanes in Organic Synthesis

Numerous possible applications of *gem*-dihalocyclopropanes in organic synthesis were mentioned in the Introduction. These compounds can undergo various transformations, in which the integrity of the cyclopropane ring is preserved or ring opening takes place. In general, the introduction of two geminal halogen substituents to the cyclopropane ring results in a lengthening of the bond opposite the halogen-bearing carbon atom and in the shortening of the adjacent bonds, as compared to those in the parent hydrocarbon. As a consequence, if the ring opening occurs during the reaction, it is most often the C2−C3 bond which is broken. (Theoretical aspects of the reactivity and properties of cyclopropanes are reviewed in refs 329 and 330 and references therein.)

In the following sections, the transformations of *gem*-dihalocyclopropanes which are the most important for synthesis are presented. General information is illustrated by recent examples, or older examples if necessary.

IV.1. Reductive Dehalogenation of *gem*-Dihalocyclopropanes

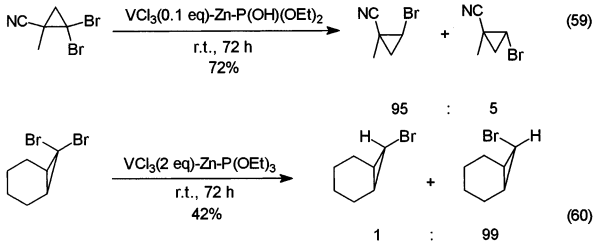
The addition of dihalocarbene to an alkene and subsequent transformation of the *gem*-dihalocyclopropane formed into a monohalogenated or completely dehalogenated cyclopropane derivative is, as a rule, a more efficient and easier method for the preparation of these classes of compounds than is their direct synthesis via the addition of a monohalocarbene or methylene to an alkene, or by the Simmons−Smith cyclopropanation of an alkene.

The removal of one or both of the halogens in a *gem*-dihalocyclopropane can be accomplished using a variety of reagents. Tributyltin hydride[114,130,166,183,188,189,196,197,209,229,331−333] (usually in the presence of an initiator, such as AIBN), lithium aluminum hydride,[59,64,128,129,334−336] and alkali metals in protic solvents[60,61,71,134,163,181] were recently most often used for this purpose. Alkali metals (lithium or sodium) in liquid ammonia,[104,337] alkyllithium[203,207] followed by treatment with an alcohol, potassium dimethyl phosphite,[338] Grignard reagents,[328] diethyl phosphite in the presence of triethylamine,[339] sodium dimethyl sulfoxide in DMSO,[340] low-valent vanadium and diethyl phosphonate or triethyl phosphite,[341] hydrazine hydrate and Raney nickel,[342] and photochemical[54,343,344] methods also have been frequently used.

With lithium aluminum hydride, either partial or complete dehalogenation of *gem*-dichloro- and dibromocyclopropanes is possible, depending on the molar ratio of the reactants and on the reaction temperature. Tributyltin hydride behaves similarly in the reactions with *gem*-dibromocyclopropanes, whereas monodehalogenation usually occurs with *gem*-dichlorocyclopropanes. With sodium in liquid ammonia only the fully reduced compounds are obtained. Diethyl phosphite in the presence of triethylamine converts *gem*-dibromocyclopropanes selectively to monobromo compounds. With other reducing agents it is usually possible to obtain monohalogenated compounds in good yields; however, the chemoselectivity sometimes is low.

The ease of dehalogenation follows the order I > Br > Cl > F; therefore, *gem*-bromochlorocyclopropanes are reduced to chlorocyclopropanes and *gem*-fluorohalocyclopropanes to fluorocyclopropanes.

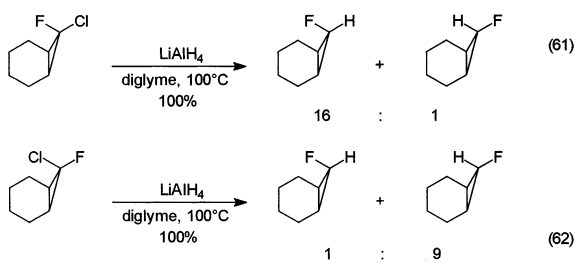
The *cis*/*trans* or *exo*/*endo* ratio of monoreduction products depends on many, usually complex, factors. Radical tributyltin hydride reductions lead most often to a mixture of stereoisomers, in which the *endo* isomer frequently predominates, while reductions with sodium dimethyl sulfoxide lead predominantly to *exo* isomers. Potassium dimethyl phosphite reduces *gem*-dibromocyclopropanes stereoselectively to *exo* isomers. Reduction with low-valent vanadium/diethyl phosphonate proceeds with very high selectivity; however, the yields of the isolated products are variable (eqs 59 and 60).[341]



(59)

(60)

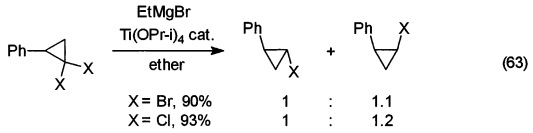
The stereochemistry of the reductions of fluorochlorocyclopropanes with tributyltin hydride depends on the ability of the substituents to stabilize a radical center. Reductions of these compounds with lithium aluminum hydride proceed with high stereoselectivity, predominantly with retention of configuration (eqs 61 and 62). These classical experiments are discussed in detail in refs 7 and 8.



(61)

(62)

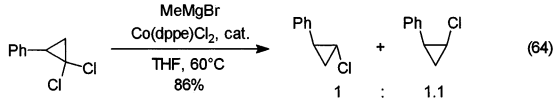
Treatment of *gem*-dibromo- and dichlorocyclopropanes with ethylmagnesium bromide in the presence of a catalytic amount of titanium isopropoxide in ether at room temperature results in the formation of monohalocyclopropanes in high yields; however, the *exo*/*endo* selectivity is low[345−347] (eq 63).[345] Nonhalogenated products can be obtained from *gem*-dibromocyclopropanes using an excess of Grignard reagent.



(63)

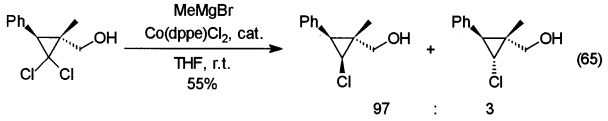
It seems that this is one of the most efficient and effective methods for converting *gem*-dibromocyclopropanes into the corresponding monobromides. The mechanism of this reaction is not fully understood at present. Many observations are consistent with a radical mechanism; however, two-electron processes cannot be excluded.[347]

Similar monodechlorination results were obtained for *gem*-dichlorocyclopropanes using methylmagnesium bromide or *tert*-butylmagnesium chloride and the catalyst $Co(dppe)Cl_2$[348,349] (eq 64).[348]



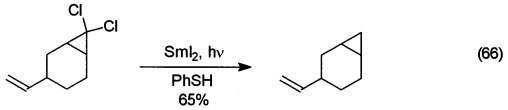
(64)

gem-Dihalocyclopropanes bearing a neighboring hydroxymethyl group underwent highly stereoselective reductions, giving *anti*-monochlorides.[348] A chelation-controlled pathway may be responsible for this stereoselectivity (eq 65).



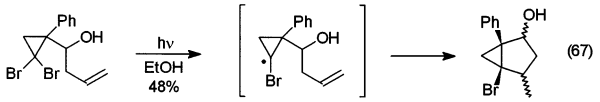
(65)

gem-Dichlorocyclopropanes form the corresponding cyclopropanes upon irradiation with visible light in the presence of samarium iodide.[54] This reaction proceeds via cyclopropyl radicals, which are formed by the reduction of the *gem*-dichlorocyclopropane with samarium iodide. These radicals abstract hydrogen from the benzenethiol. At least a 4-fold excess of SmI_2 is necessary to ensure good yields of the cyclopropanes (eq 66).



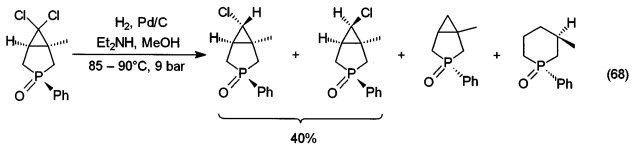
(66)

Phenyl-*gem*-dibromocyclopropanes which are irradiated with visible light while in ethanol furnish monobromo compounds in moderate to excellent yields.[343] The formation of cyclopropyl radicals in this process was recently demonstrated by trapping them in the intramolecular reaction shown in eq 67.[344]



(67)

The catalytic hydrogenation of *gem*-dihalocyclopropanes usually proceeds with the opening of the three-membered ring.[350] Using carefully chosen conditions, partial preservation of the cyclopropane ring is often possible (eq 68).[351]

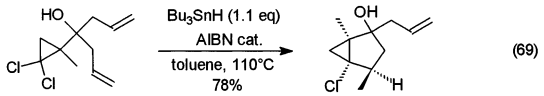


(68)

Selected examples of reductions of *gem*-dihalocyclopropanes are collected in Table 7.

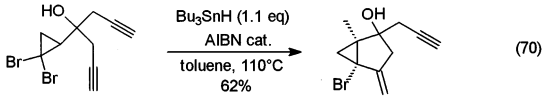
IV.2. Radical Cyclizations and Additions of *gem*-Dihalocyclopropanes

Halocyclopropyl radicals, generated from *gem*-dihalocyclopropane derivatives in the reaction with tributyltin hydride and AIBN as an initiator, can enter into inter- or intramolecular addition reactions.[212,352,353] Alkenes and alkynes containing a properly located *gem*-dihalocyclopropyl substituent were transformed into the corresponding bicyclo[3.1.0] products (eq 69).[352]



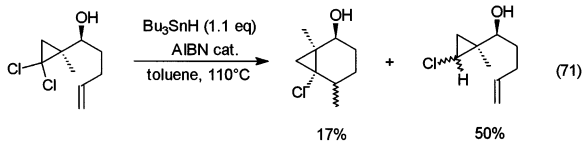
(69)

The cyclizations occurred with high stereoselectivity in a 5-*exo*-trig manner; 6-*endo*-trig products were not formed. New *exo*-methyl groups were formed *trans* to the adjacent chloro substituent with high stereoselectivity. Similarly, *gem*-dibromocyclopropyl alkynes underwent 5-*exo*-dig-type regioselective cyclizations in good yields (eq 70).[352]



(70)

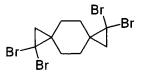
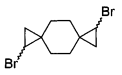
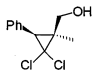
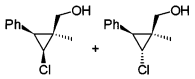
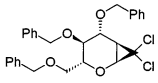
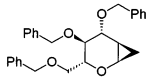
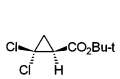
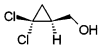
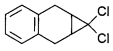
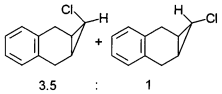
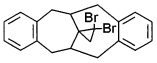
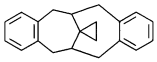
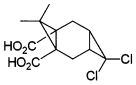
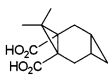
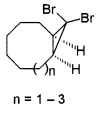
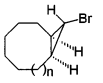
6-*exo*-Trig cyclizations were also observed in the reactions of appropriate *gem*-dichlorocyclopropyl alkenes, although the cyclic products were often accompanied by products from the reduction of chlorine (eq 71).[352]



(71)

Suitably functionalized *gem*-dibromocyclopropanes **25** undergo stereocontrolled bifurcating-type radical cyclizations, leading to tricyclic 5-*exo*-trig and transannular compounds **26**, with only trace amounts of other stereoisomers being obtained (eq 72).[212]

Table 7. Examples of Reductive Dehalogenation of *gem*-Dihalocyclopropanes

Substrate	Reducing agent	Product	Yield (%)	Ref.
	Bu_3SnH		76	209
	Bu_3SnH		76	332
	Bu_3SnH AIBN cat.	 1 : 1.7	67	114
	Bu_3SnH		77	183
	Bu_3SnD		89	188
	Bu_3SnH AIBN cat.		78	129
	$LiAlH_4$		major	336
	DIBAL		90	
	$LiAlH_4$	 3.5 : 1	85	59
	$LiAlH_4$	 *Z*/*E* = 1.16	51	334
	$LiAlH_4$		60	335
	$LiAlH_4$		83	64
	Na/EtOH		40	181
	Li/t-BuOH		75	71
	Na/NH_3		73	104
 n = 1 – 3	$NaCH_2SOCH_3$ DMSO		41–75	340
	t-BuMgCl $Co(dppe)Cl_2$		76	349
	1. BuLi –110°C 2. EtOH	 *Z*/*E* = 3 : 97	89	207
	$(EtO)_2POH$ Et_3N	 *Z*/*E* = 1 : 3	94	339
	NH_2NH_2 Ni-Raney KOH/EtOH	 *Z*/*E* = 2	86	342

Intermolecular radical additions of 2,3-*cis*-disubstituted *gem*-dibromocyclopropanes to electrophilic

25 **26** (72)

R^1 = OH, R^2 = allyl 43%
$R^1 = R^2$ = H 32%

alkenes proceed with high stereoselectivity via *exo* attack, to give the products in moderate yields (Scheme 10).[353]

Scheme 10

R^1	R^2	Z	Yield (%)	*exo*/*endo*
$(CH_2)_4$		CN	59	99.5 : 0.5
		CO_2Me	35	99.5 : 0.5
$(CH_2)_6$		CN	52	97 : 3
		CO_2Me	40	97 : 3
$SiMe_3$	H	CN	35	99 : 1

Similar reactions of monosubstituted *gem*-dibromocyclopropanes proceed with moderate stereoselectivities, with the exception of the reactions of 2-trimethylsilyl derivatives (Scheme 10).

IV.3. Halogen–Metal Exchange and Further Reactions of 1-Halo-1-metallocyclopropanes

Halogen−metal exchange between *gem*-dihalocyclopropanes and alkyllithium leads to cyclopropylidene lithium halocarbenoids. These compounds are quite stable at low temperatures (∼−100 °C) and can react with electrophiles such as alkyl halides,[176,184,205,354] trimethylsilyl or stannyl chlorides, carbon dioxide,[355] aldehydes,[356,357] acid chlorides, ketones,[205] and iminium salts to form the appropriate products of substitution at the C1 carbon atom. Some recent examples are given below (eqs 73[205] and 74[355]).

(73)

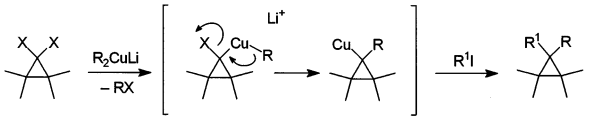
(74)

Intramolecular alkylations of lithium halocarbenoids lead to polycyclic ring systems[172,187,249,358,359] (eq 75).[249]

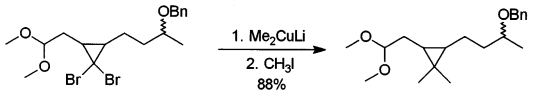
(75)

Both of the halogen atoms in *gem*-dihalocyclopropanes can be replaced to yield *gem*-disubstituted cyclopropanes. The reaction of *gem*-dihalocyclopropanes with dialkyl cuprates or higher order cuprates,[190,191,360−362] trialkyl zincates,[363] trialkyl man-

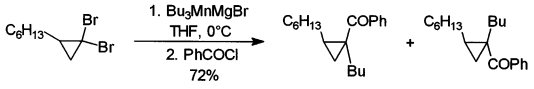
ganates[364] (which can be prepared in situ from Grignard reagents or alkyllithium and magnesium chloride)[365] or trialkyl magnesates[204] affords alkylated cyclopropylmetals, which undergo alkyl migration as the halogen anion is eliminated, and then react further with various electrophiles to furnish doubly alkylated cyclopropane derivatives (eqs 76, 77,[190] 78,[364] and 79[204]).



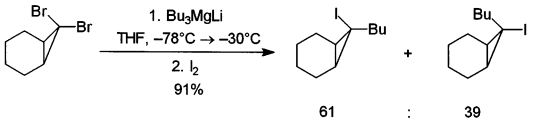
(76)



(77)



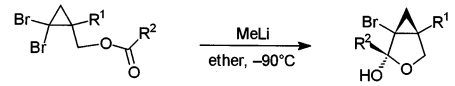
(78)



(79)

The reaction of 1,1-dibromo-2-phenylcyclopropane with dilithium tetramethyl zincate followed by oxidation of the resulting cyclopropyl zincate by $VO(OEt)_2Cl_2$ leads to substitution of one or both of the bromides by a methyl group.[366]

The reactions of *gem*-dibromocyclopropanes possessing an ester functionality with methyllithium at −90 °C proceed as an intramolecular trapping of lithium bromocyclopropane by an ester carbonyl group to form five-membered rings with high stereoselectivity[210,367] (eq 80).[367]



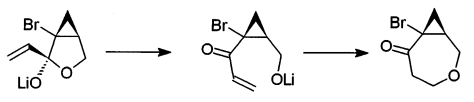
(80)

27

R^1 = H, Me; R^2 = Me, Pr, Ph 46 – 82%

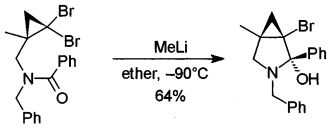
These five-membered ring products could be the result of a stereoselective metal−halogen exchange, leading to the *syn*-lithium ester, or of the formation and equilibration of two isomeric lithiobromides, where only one isomer cyclizes.

When R^1 = H and R^2 = vinyl in **27**, the hemiacetal which is initially formed undergoes ring opening to a keto alcohol. This keto alcohol then undergoes Michael cyclization with the formation of a bicyclic ketone (eq 81).[210,367]



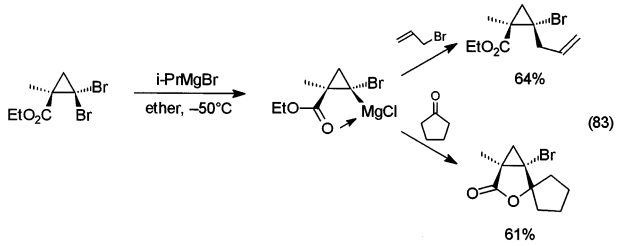
(81)

The reactions of 2-acylaminomethyl-1,1-dibromocyclopropanes with methyllithium proceed similarly (eq 82).[210,368]



(82)

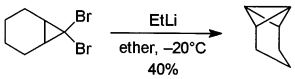
Knochel recently described the stereoselective formation of the *cis*-magnesium carbenoid from 1,1-dibromo-2-ethoxycarbonyl-2-methylcyclopropane and isopropylmagnesium bromide in diethyl ether at −50 °C. This species was trapped stereoselectively by several electrophiles[327] (see also section III) (eq 83).



(83)

Reaction of *gem*-dihalocyclopropanes with alkyllithiums at temperatures above −80 °C results in the formation of cyclopropylidenes. The most common reaction of this active intermediate is isomerization to the corresponding allene. This synthetically valuable reaction has been the subject of many reviews and therefore will not be discussed here. When allene formation is impossible, the cyclopropylidene can react in a variety of ways, usually with preservation of the three-membered ring. It can undergo intramolecular insertion into C−H bonds, especially those adjacent to oxygen or nitrogen, intermolecular insertion into C−H bonds of the solvent, dimerization, and intra-[173,369−371] and intermolecular addition to the double bond.

The ratio of products obtained depends strongly on the alkyllithium used, temperature, solvent, and so forth. Under carefully chosen conditions, the preparation of a particular product in reasonable yield is often possible (eq 84).[369]



(84)

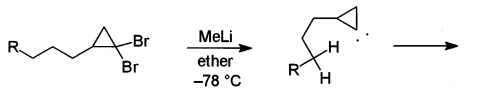
gem-Dibromo(vinyl)cyclopropanes, when placed under these conditions, can undergo a vinylcyclopropylidene to cyclopentadiene isomerization (the Skattebol rearrangement) (eq 85).

(85)

All of these processes are synthetically very useful.

Brinker investigated the stereo- and regioselectivity of the C−H insertion reactions of cyclopropylidenes **28**−**30**, which are generated from appropriate *gem*-dibromocyclopropanes and methyllithium at −78 °C.[208] In each case the main products formed were the corresponding allenes, but bicyclo[3.1.0]hexanes were also formed as a result of 1,5 C−H insertions. The chemoselectivities of the allene formation versus the C−H insertion were similar for

all of the compounds investigated, indicating that the double bond in the cyclopropylidene **28** does not activate the insertion reaction. However, it appears that it does influence the *syn*/*anti* selectivity (eq 86).

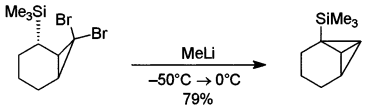


(86)

		syn		*anti*	(*syn* + *anti*)		*allene*
28	R = vinyl	86	:	14	11	:	89
29	R = allyl	70	:	30	7	:	93
30	R = n-propyl	60	:	40	16	:	84

The presence of a double bond favors the formation of *syn*-insertion products. The authors suggest that the extent of interaction between the lithium substituent and the double bond could be responsible for the observed stereoselectivity, because the activated complexes for the *syn*- and *anti*-insertions are different. If this is true, it is likely that carbenoids, rather than free carbenes, are the active species in these reactions.

Cyclopropylidenes generated from *gem*-dibromobicycloalkanes containing a trimethylsilyl substituent insert preferentially into C−H bonds activated by the trimethylsilyl group, leading to highly strained cyclopropyl systems in good yields (eq 87).[235]



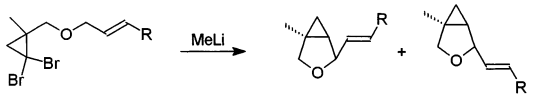
(87)

The *gem*-dibromocyclopropane **31**, which is derived from an acyclic alkene, reacts similarly (eq 88),[235] but the less substituted **32** forms the allene product exclusively (eq 89).[235]

31 (88)

32 (89)

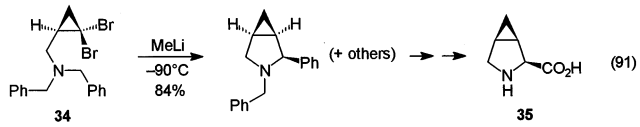
Allyl ethers **33** react with methyllithium at −90 to −70 °C to give a mixture of 3-oxabicyclo[3.1.0]-hexane derivatives, in which the exo isomer predominates, and is obtained in good yields (eq 90).[232,372]



33 (90)

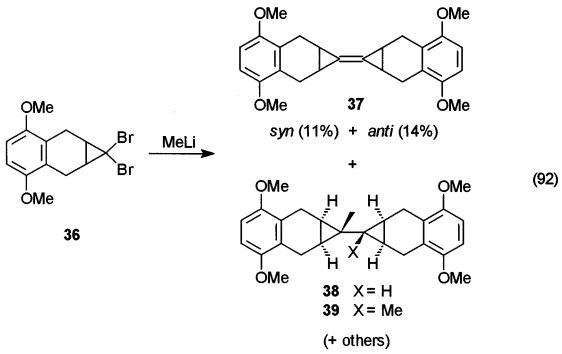
R = H, 73%	17	:	1	
R = Ph, 41%	7	:	1	

The product of the intramolecular insertion of a single enantiomer of the cyclopropylidene derived from **34** into the C−H bond adjacent to the nitrogen was used in the synthesis of enantiomerically pure methanoproline **35** (eq 91).[373]



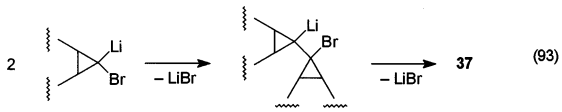
34 **35** (91)

Banwell found that treatment of a *gem*-dibromocyclopropane, **36**, with methyllithium at −80 °C led to a complicated mixture of products, among them the *syn*- and *anti*-cyclopropylidene dimers **37**, along with compounds **38** and **39** (eq 92).[224]



(92)

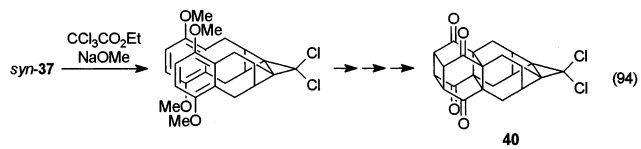
The formation of cyclopropylidene dimers can occur via a direct reaction of two molecules of the halolithium carbenoid, with simultaneous extrusion of two molecules of lithium bromide, or via a stepwise formation of the intermediate β-halobicyclopropyllithium, followed by an E1cb elimination reaction (eq 93).



(93)

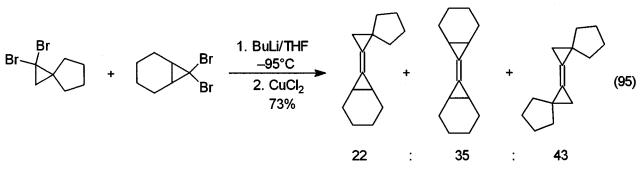
Compounds **38** and **39** can arise from further reactions of the initially formed β-halobicyclopropyllithium derivative with methyl bromide. After methylation, the product containing the bromine substituent undergoes a bromine-for-lithium exchange with methyllithium. The carbanion thus formed would lead to **38** after protonation or to **39** after reaction with another methyl bromide molecule. This very interesting result suggests that cyclopropylidene dimers may be formed via a β-halocyclopropyllithium species, but the question remains unresolved.

The addition of dichlorocarbene to the *syn*-cyclopropylidene dimer **37** results in the formation of the tricyclane derivative, which was used in the synthesis of the tubelike molecule **40** (eq 94).[95]



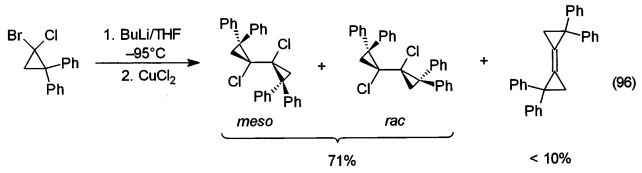
(94)

The yields obtained for cyclopropylidene dimers derived from *gem*-dibromocyclopropanes can be significantly improved by using alkyllithium and a catalytic amount of $CuCl_2$.[58,220] Mixed couplings between two different carbenoids are also possible (eq 95).[220]



(95)

1-Chloro-1-lithiocyclopropanes derived from *gem*-bromochlorocyclopropanes react with $CuCl_2$ to give mixtures of oxidative coupling products and the carbene dimers (eq 96).[303]

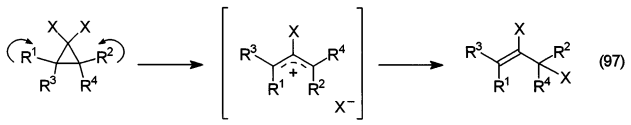


(96)

IV.4. Thermal Reactions of *gem*-Dihalocyclopropanes

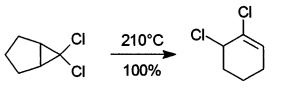
Thermal rearrangements of *gem*-dihalocyclopropanes have been discussed in detail in many reviews.[6−8] The basic rules governing these transformations will be described here, and will be illustrated with examples taken from the recent literature.

Most often the first step in the thermal rearrangement of *gem*-dihalocyclopropanes consists of a concerted, disrotatory, electrocyclic ring opening at the C2−C3 bond and a concomitant ionization of a carbon−halogen bond. The allylic cation thus formed is then captured by the halide counterion, or can undergo proton elimination to form a 1,3-diene. The latter process is especially favored in the presence of a base (eq 97).

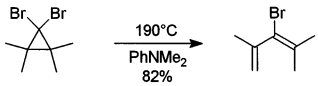

(97)

The ease with which a *gem*-dihalocyclopropane rearranges depends on stereochemical factors, the stability of the allyl cation, the lability of the halogen, and, in the case of bi- or polycyclic compounds, the size of the ring fused to the *gem*-dihalocyclopropane moiety. The thermal isomerization of dihalocyclopropanes is facilitated by the presence of alkoxy, alkyl, and aryl substituents on the three-membered ring. Likewise the thermal isomerization of bi- and polycyclic systems is facilitated by an *endo* leaving halogen substituent. Since *endo* derivatives lead to *cis*-substituted allyl cations and *exo* derivatives to *trans*-substituted allyl cations, only *exo* derivatives of a large ring system can undergo facile rearrangement in bicyclic systems.

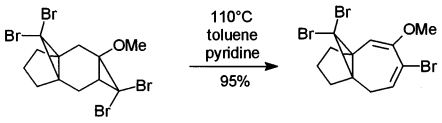
Thermal rearrangements of strained bicyclic systems are particularly facile reactions. In fact, as was mentioned in section III, often isolation of the addition products from the reaction of dihalocarbene with cyclic, less-than-six-membered alkenes is not possible because of their rapid isomerization.[202,374,375] Some recent examples of thermal reactions of *gem*-dihalocyclopropanes[376] are given below (eqs 98,[68] 99,[177] and 100[226]).



(98)

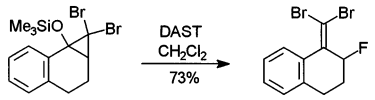


(99)



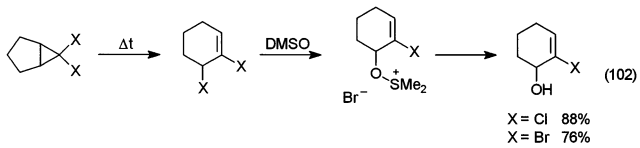
(100)

Allylic fluorides were prepared via the cleavage of tertiary *gem*-dibromocyclopropylsilyl ethers with diethylaminosulfur trifluoride (DAST). This reaction proceeds through an allylic fluoro cation[377] (eq 101).



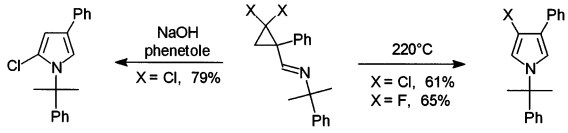
(101)

2-Halo-2-cycloalkenols were prepared by heating some *n*,*n*-dihalobicyclo[*n*-3.1.0]alkanes in DMSO.[378] Intermediate 1,*n*-dihalocycloalkenes were formed and underwent nucleophilic attack by DMSO, followed by a Pummerer rearrangement and hydrolytic decomposition (eq 102).



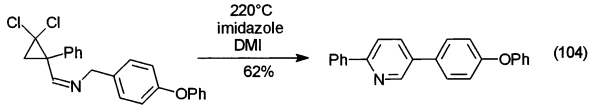
(102)

The thermolysis of *N*-*tert*-alkyl- and *N*-aryl-2,2-dihalocyclopropanecarboxaldimines gives *tert*-alkyl- or aryl-substituted 3-halopyrroles, respectively (eq 103).[145] An ionic mechanism for chloropyrrole formation is proposed, while a homolytic pathway is proposed for fluoro derivatives. Basic additives (6 molar equivalents) lead to 2-chloropyrroles via a 1,2 bond cleavage of the cyclopropane ring.



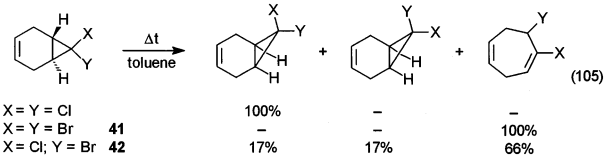
(103)

If the carbon atom on the imino nitrogen posseses a hydrogen substituent, thermolysis of the compound leads to 2-phenylpyridine derivatives. Recently, this approach was applied for the synthesis of ter-, quarter-, and quinquearyls possessing a pyridine ring.[99] The presence of imidazole (6 molar equivalents) and 1,3-dimethyl-2-imidazolidinone (DMI) as the solvent was essential for obtaining the product free of the chloro derivative (eq 104).

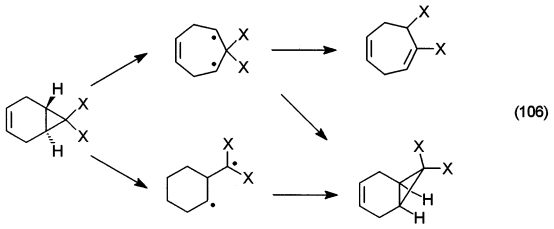


(104)

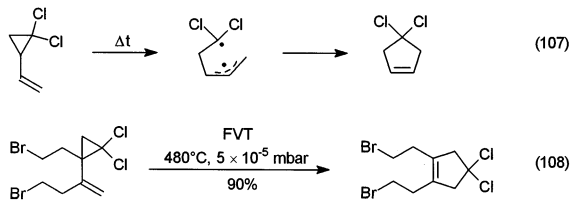
The course of the thermal rearrangement of 7,7-dihalo-*trans*-bicyclo[4.1.0]hept-3-enes, which are prepared via multistep syntheses, depends strongly on the type of halogen atom present (eq 105).[90]



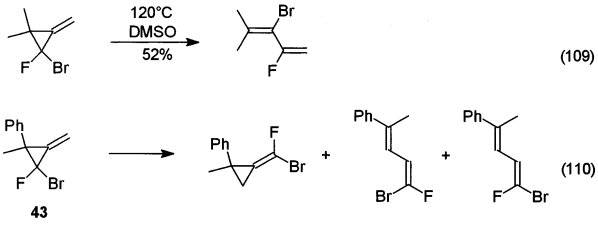
Solvent polarity (among solvents such as deuterated nitromethane, acetonitrile, or methanol) does not significantly affect the relative rate constants for these reactions. Isomerizations of **41** and **42** carried out in nucleophilic solvents lead to the cycloheptadiene products regardless of the solvents' polarities. These results indicate that ionic intermediates are not present in the reactions investigated. It is therefore more likely that the disrotatory ring opening of *trans*-fused cyclopropanes leads to strained *cis*−*trans*-alkyl cations within seven-membered rings. A likely mechanism for this reaction involves radical cleavage of either the bridgehead or a bond peripheral to the three-membered ring. Subsequent ring closure within the resulting biradicals would lead to *cis*-fused isomers, while a 1,2 shift of the bromine atom in the intermediate formed by cleavage of the bridgehead bond would produce cycloheptadiene products (eq 106).



Thermal rearrangements of *gem*-dihalo(vinyl)-cyclopropanes to dihalocyclopentenes, especially under conditions of flash vacuum pyrolysis, occur via diradical intermediates (eq 107). This transformation is of great practical value and is used as a key step in the syntheses of many products[74,161] (eq 108).[91]

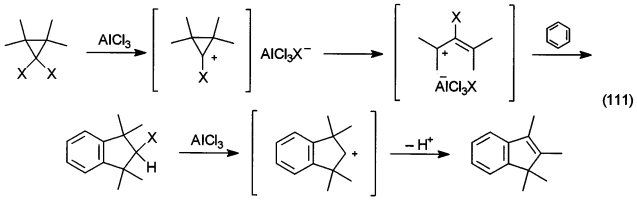


2-Bromo-2-fluoroalkylidenecyclopropanes undergo thermal rearrangement in polar solvents to form 3-bromo-2-fluoro-1,3-butadienes. The reaction proceeds through a polar transition state (eq 109).[322] Isomerization of **43**, which contains an aromatic substituent connected to a cyclopropane ring, leads to a mixture of products, probably via biradical intermediates (eq 110).[322]

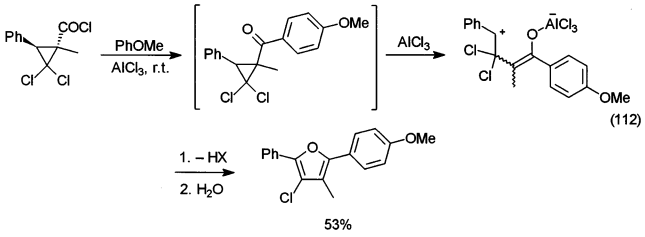


IV.5. Reactions of *gem*-Dihalocyclopropanes in the Presence of Lewis Acids

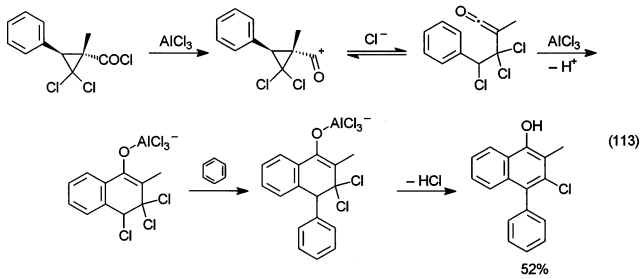
In the presence of Lewis acids such as $AlCl_3$ and $FeCl_3$, *gem*-dichlorocyclopropanes undergo ring opening to produce the chloroallyl cation, which can react with aromatic hydrocarbons in a Friedel−Crafts-type reaction. Classical Buddrus[379] and Skattebol[380] syntheses of indene derivatives are examples of this process (eq 111).



3-Aryl-2,2-dichlorocyclopropanecarbonyl chlorides react with anisole in the presence of $AlCl_3$, producing 2,5-diaryl-3-chlorofurans in a one-pot reaction.[381] Independently prepared 3-aryl-2,2-dichlorocyclopropyl ketones react similarly (eq 112).

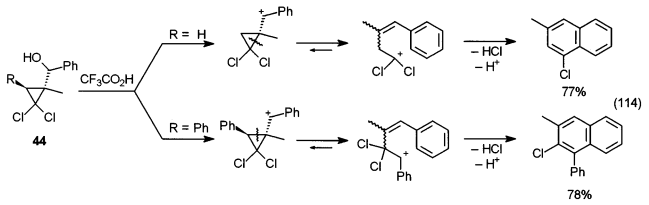


With less active arenes, intramolecular cyclization of 3-aryl-2,2-dichlorocyclopropane carbonyl chlorides proceeds faster than their intermolecular coupling with the arene, resulting in the formation of 4-aryl-3-halo-1-naphthols (eq 113).[382,383]

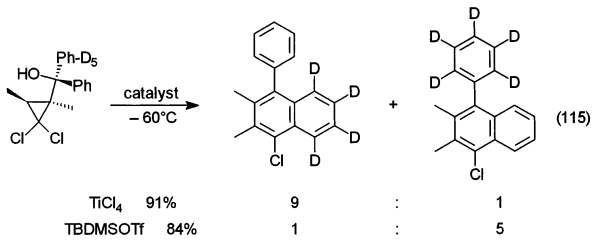


Aryl(*gem*-dichlorocyclopropyl)methanols **44**, when treated with acids, lead to 1- or 2-chloronaphthalenes in good yields and selectivity. Which product is obtained is dictated by the preferential formation of the more stable cationic intermediate (eq 114).[139]

Interestingly, (*gem*-dichlorocyclopropyl)diarylmethanols undergo highly regiocontrolled benzannulation

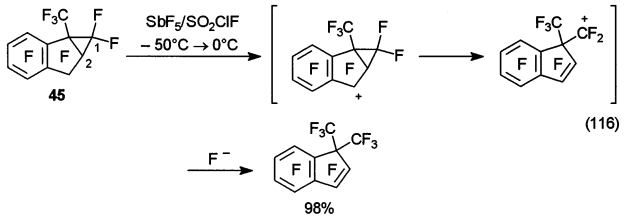


to α-arylnaphthalenes, depending on the catalyst used (eq 115).[384]

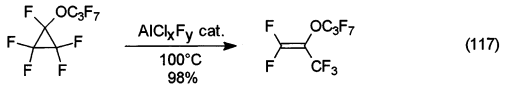


The authors propose that a chelation mechanism is followed when the catalyst is $TiCl_4$, while a nonchelation mechanism is in operation when the catalyst is silyl triflate.

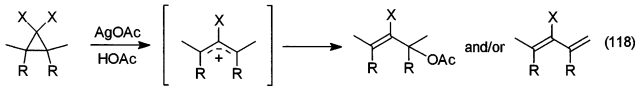
The perfluoro compound **45** undergoes C1−C2 bond cleavage in the presence of SbF_5/SO_2ClF to form the isomeric perfluoromethylindene derivative (eq 116).[385]



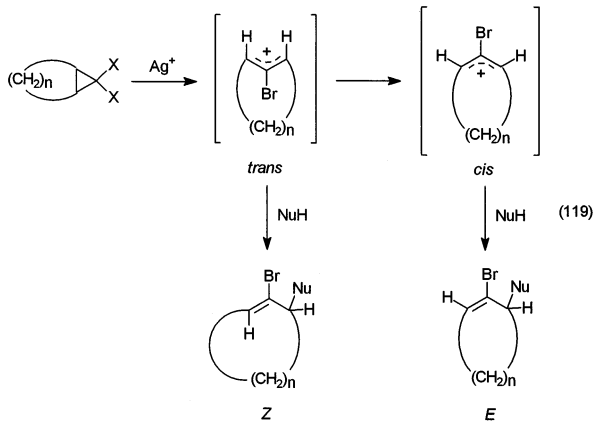
Isomerizations of perfluorocyclopropane derivatives are catalyzed by aluminum chlorofluoride[386] (which is prepared by the reaction of $CFCl_3$ with $AlCl_3$) (eq 117).



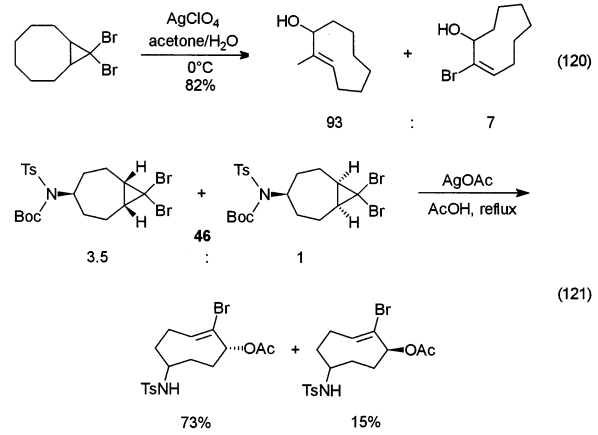
Silver salts, which are also Lewis acids, promote the dissociation of the carbon−halogen bond in *gem*-dihalocyclopropanes, resulting in disrotatory electrocyclic ring opening of the three-membered ring and the formation of the allylic cation. However, with silver salts this process occurs under much milder conditions than do the thermal reactions. The allylic cation thus formed can be trapped by the anion of the silver salt or by a nucleophilic solvent, or it can eliminate a proton or other group to give a diene (eq 118).



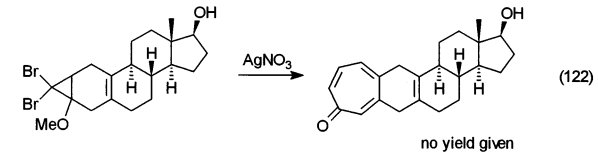
The stereochemistry of the products of silver ion induced reactions of ring-fused *gem*-dihalocyclopropanes is discussed in detail in Banwell's review.[8] The stereochemical outcome depends mostly on the size of the ring fused to the three-membered ring containing the *gem*-dihalo functionality (eq 119).



When $n = 3$ or 4 in a *gem*-dihalobicyclo[*n*.1.0.]-alkane, the reaction proceeds via removal of an *endo*-halogen to form the *cis* allylic cation, and finally, the *E* product. When $n \geq 5$, *E* and/or *Z* products are obtained. In this case the *trans* cation is formed initially, because the *exo*-halogen is more accessible to the silver ion. The *trans* cation then can be captured by a nucleophile to give the *Z* product, or it can isomerize to the *cis* isomer, which is subsequently captured by a nucleophile and forms the *E* product. The solvolyses of 9,9-dibromobicyclo[6.1.0]nonane and of a 3.5:1 mixture of *exo*- and *endo*-**46** are good examples of these reactions[170,174,182] (eqs 120[174] and 121[182]).

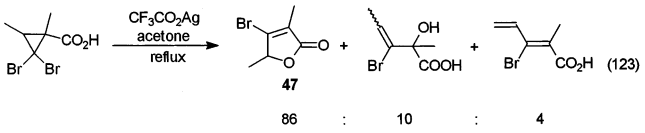


Solvolysis of alkoxydihalocyclopropanes promoted by silver salts leads to α,β-unsaturated ketones. This approach was recently used for the synthesis of the tropone skeleton (eq 122).[194]



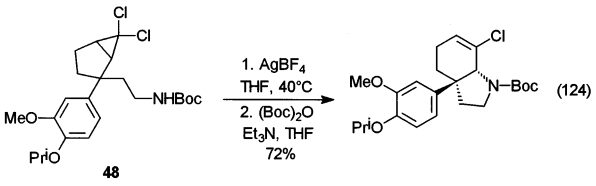
gem-Dibromocyclopropane derivatives possesing a nucleophilic center in the molecule undergo ring-opening reactions that lead to intramolecular cyclizations of the allylic cation. The example given below (eq 123) also shows the importance of the solvent

properties in influencing the silver ion assisted ring opening of *gem*-dihalocyclopropane derivatives.[387]

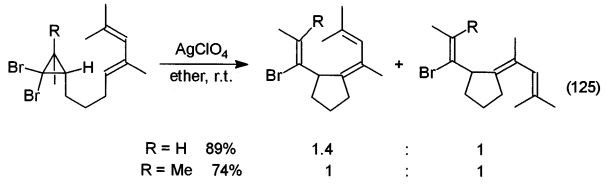


In acetone, hexafluoro-2-propanol, and *tert*-butyl alcohol, lactone **47** was formed as the main product (isolated in 62% yield when the reaction was carried out in acetone). In other solvents (for example, methanol or trifluoroacetic acid) complicated mixtures of products were formed, in which the amount of **47** did not exceed 50%. These results were discussed on the basis of the nucleophilicity, polarity, and hydrogen-bonding ability of the solvents.

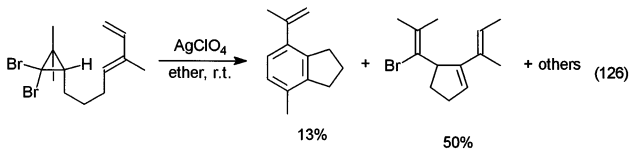
Electrocyclic ring opening of the epimeric *gem*-dichlorocyclopropane derivative **48**, initiated by silver tetrafluoroborate, and subsequent allyl cation cyclization was used for the synthesis of crinine-type alkaloids (eq 124).[160]



In some cases, allyl cations generated from *gem*-dibromocyclopropanes containing a diene unit undergo cyclization to form trienic cyclopentane derivatives (eq 125).[223]

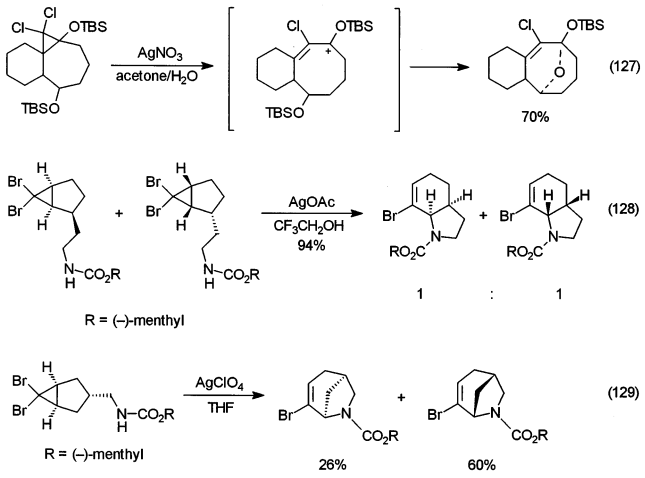


Interestingly, analogous *gem*-dibromocyclopropanes that do not contain *gem*-dimethyl groups in the diene unit produce, among other things, the formal Diels–Alder product, as a result of allyl cation cyclization (eq 126).[223] The authors speculate that the steric hindrance caused by the *gem*-dimethyl groups is responsible for preventing further cyclization in the former case.

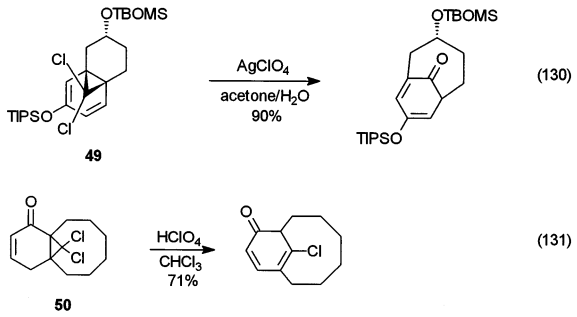


Silver ion assisted cleavage followed by intramolecular trapping of the allyl cation has been used for the syntheses of many heterocyclic compounds (eqs 127,[135] 128,[213] and 129[211]).

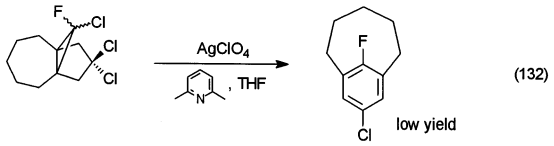
The treatment of propellane-type compounds **49** and **50** with $AgClO_4$[102] or $HClO_4$,[58] respectively,



produces troponophanes in high yields (eqs 130[102] and 131[58]).



A general method for the synthesis of [5]metacyclophanes has been elaborated by Bickelhaupt. This method consists of the reaction of tetrahalopropellanes with silver perchlorate in the presence of lutidine. A recent example is given in eq 132.[305]



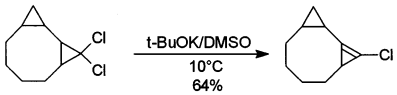
IV.6. Transformations of *gem*-Dihalocyclopropanes into Cyclopropene Derivatives

gem-Dihalocyclopropanes can be easily transformed into the corresponding halocyclopropenes (for a review, see ref 388). Depending on their structure and the method by which they were synthesized, these strained molecules sometimes can be isolated[60,122,389] or trapped by an appropriate reagent, often as their Diels–Alder adducts,[133,214,221,390,391] or can undergo a plethora of further transformations.[392] Many of these reactions are of great importance in organic synthesis.

The following methods are used for converting *gem*-dihalocyclopropanes into cyclopropenes.

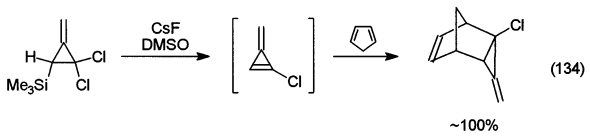
(a) 1,2-Dehydrohalogenation. *gem*-Dihalocyclopropane derivatives containing one or more hydrogen atoms on the cyclopropyl ring undergo dehydrohalogenation in the presence of base to produce the corresponding halocyclopropenes. This reaction is facilitated by electron-withdrawing substituents on

the cyclopropane ring. The halocyclopropene derivatives thus formed can be isolated in some instances[60] (eq 133), but usually react further.



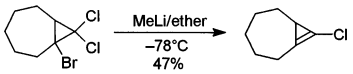
(133)

(b) Dehalosilylation. *gem*-Dihalocyclopropanes containing a trialkylsilyl group on the cyclopropyl ring eliminate a trialkylsilyl halide molecule when reacted with fluoride ions.[162,164,390,393−397] Tetrabutylammonium fluoride and cesium fluoride are the most commonly used sources of fluoride. This is a very clean and efficient method for the synthesis of cyclopropenes (eq 134).[133]



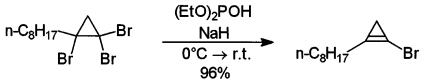
(134)

(c) 1,2-Dehalogenation. *gem*-Dihalocyclopropanes containing additional halogen atoms on the cyclopropane ring form halocyclopropenes when reacted with alkyllithium[118,122,156,169,171,214,215,217,218,221,231,234,391,398−402] (eq 135).[122]



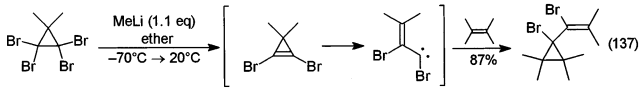
(135)

1,1,2-Tribromocyclopropanes also can be debrominated with a dialkyl phosphite and trialkylamine or sodium hydride to form 1-bromocyclopropenes (eq 136).[389]



(136)

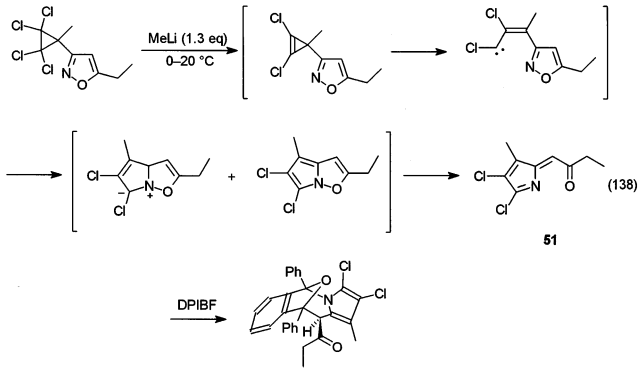
In the absence of a nucleophile, cyclopropenes which are formed in situ from *gem*-dihalocyclopropanes can rearrange to vinylcarbenes. These carbenes then can be trapped by an alkene, thus allowing the preparation of vinylcyclopropane derivatives (eq 137).[217]



(137)

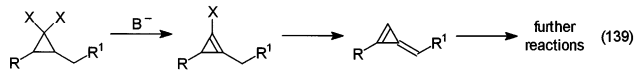
1,1,2,2-Tetrachlorocyclopropanes with an attached isoxazole ring, when treated with MeLi, form intermediate vinylcarbenes which react intramolecularly to yield the final products (eq 138).[398] Unstable **51** was trapped as a [6+4] cycloadduct with diphenylisobenzofuran (DPIBF).

If the substituent attached to the double bond at the cyclopropene ring allows hydrogen migration, rearrangement to the corresponding methylenecyclopropene occurs. This is often followed by further base-catalyzed reactions, depending on the structure



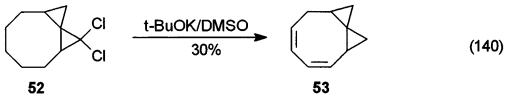
(138)

of the hydrocarbon framework in the methylenecyclopropene (eq 139).



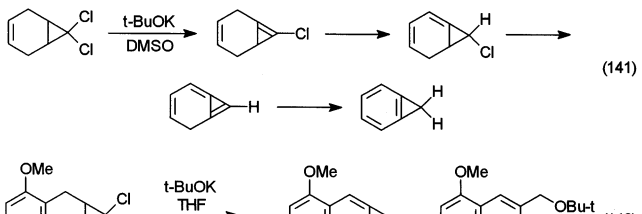
(139)

Dehydrohalogenation of the tricyclic *gem*-dichlorocyclopropane **52** with *t*-BuOK/DMSO led to diene **53**.[60] This diene was formed after repeated double bond migration. Because of the presence of the spirocyclopropane fragment, the reaction was not accompanied by skeletal rearrangement (eq 140).

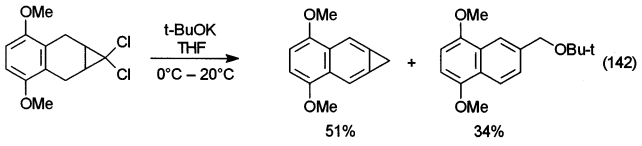


(140)

Stabilization of the cyclopropene may occur if its double bond can become part of an aromatic system. This possibility has potentially interesting mechanistic ramifications. Dihalonorcarene derivatives, when treated with a strong base such as *t*-BuOK/DMSO, form benzocyclopropenes (the Billups reaction, eq 141; for a review, see ref 403), which are thermally stable yet highly reactive compounds (eq 142).[98]



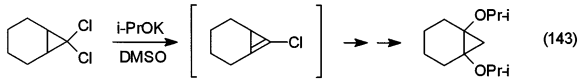
(141)



(142)

If the base used for the dehydrohalogenation of a *gem*-dihalocyclopropane is a strong nucleophile, or if an even stronger nucleophile is present in the reaction mixture, the initially formed halocyclopropene can add the base or nucleophile to its strained carbon−carbon double bond. The addition of a base or nucleophile to a halocyclopropene (usually derived from a bicyclic *gem*-dihalocyclopropane) that does not possess an electron-withdrawing substituent occurs at the nonhalogenated sp^2 carbon and usually is followed by a second elimination−addition reaction or/and other transformations. The classic reaction of dichloronorcarane with potassium isopropoxide, in

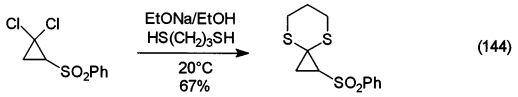
which diisopropoxynorcarane is formed as a main product, serves as an example of this process[404] (eq 143).



(143)

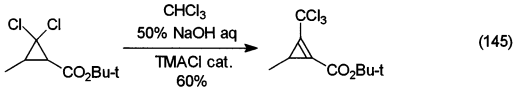
Unfortunately, this type of transformation has not been extensively studied in recent years, despite its synthetic potential.

An electron-withdrawing group attached to the *gem*-dihalocyclopropyl ring facilitates the elimination of hydrogen halide in the presence of a base, and also promotes the addition of a nucleophile to a halogen-containing sp^2 carbon atom in the resulting halocyclopropene. Usually, a second elimination−addition follows this reaction, leading to a formal overall substitution of both halogen atoms[405] (eq 144).



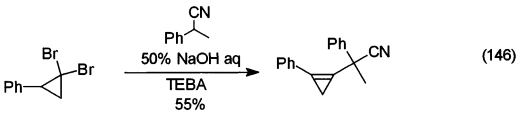
(144)

In some cases the intermediates in these processes can be isolated[143] (eq 145).[144]



(145)

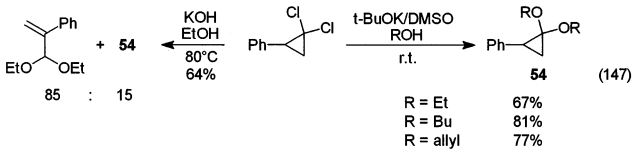
2-Phenylalkanenitriles react with 1,1-dibromo-2-phenylcyclopropane in the PTC system to produce 1,2-disubstituted cyclopropene derivatives, although in moderate yields (eq 146).[406]



(146)

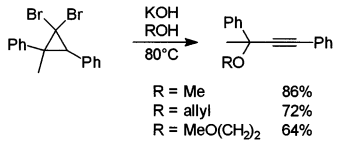
The cyclopropene double bond in the product is probably insufficiently polarized by the phenyl group to promote further addition of the 2-phenylalkanenitrile anion. The lack of further addition is not due to steric reasons, since the sterically crowded diphenylacetonitrile carbanion substitutes for both chlorine atoms in 1,1-dichloro-2-phenylsulfonylcyclopropane.[141]

gem-Dihalophenylcyclopropanes react with alcohols or phenols in the presence of *t*-BuOK/DMSO at room temperature to form phenylcyclopropanone ketals.[407] The use of solid KOH as a base under more forced conditions (100 °C) led to mixtures of **54** and 2-phenylpropenal acetals in ratios that depended on the kind of alcohol present and the nature of the substituents on the cyclopropane ring (eq 147).[407] The 2-phenylpropenal acetal resulted from cyclopropene−vinylcarbene isomerization and subsequent reaction with an alcohol.



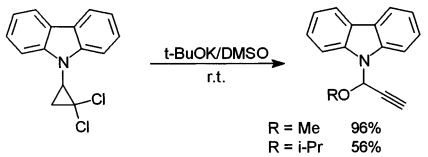
(147)

More highly substituted *gem*-dibromocyclopropanes usually react with alcohols in the presence of KOH to form complicated mixtures of products. However, in some cases propargyl ethers are formed exclusively,[408] possibly via a halocyclopropene intermediate. This intermediate undergoes heterolytic cleavage of a carbon−halogen bond with simultaneous C2−C3 bond breaking, leading to a substituted propargyl cation (eq 148).



(148)

Propargyl ethers were also obtained from *N*-*gem*-dichlorocyclopropyl-substituted carbazole, phenothiazine, phenoxazine, and alcohols, in the presence of *t*-BuOK/DMSO (eq 149).[409]

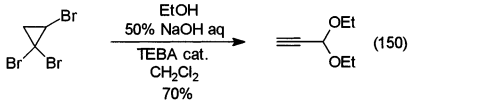


(149)

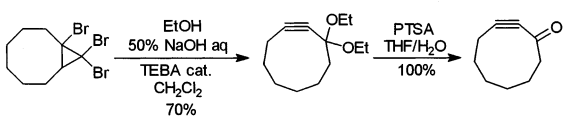
Recently Sydnes has shown that 1,1,2-trihalocyclopropanes treated with concentrated aqueous NaOH and an excess of alcohol in the presence of a catalytic amount of a quaternary ammonium salt, i.e., under PTC conditions, undergo various transformations which are believed to occur through the initial formation of a *gem*-dihalocyclopropene by dehydrohalogenation (for a review, see ref 410). It would appear that it is the quat salt of the alkoxide, and not NaOH or sodium alkoxide, which acts as a very strong base under these conditions[411] to deprotonate the substrate, as long as the substrate does not contain an electron-withdrawing or phenyl group. Substituted 1,1,2-trihalocyclopropanes transform into acetylenic alkyl acetals and/or acetylenic alkyl ketals under the conditions described.[119] A possible mechanism for the formation of these products is presented in Scheme 11.[119,410]

The corresponding products are formed from 1,1,2-tribromo-3-methylcyclopropane in the same yield and proportion.

The acetal/ketal ratio depends on the nature of the substituents attached to the ring, on the kind of alcohol used, and on the reaction conditions.[119,219] Very often regioselective ring opening is possible. This makes these reactions synthetically very useful (eqs 150[119] and 151[216]).

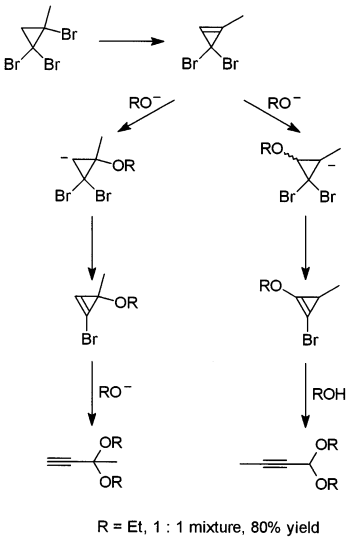


(150)

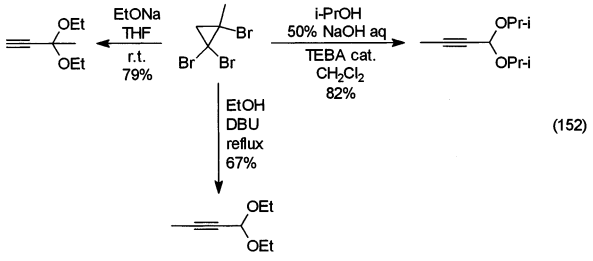


(151)

Scheme 11



It has been shown that acetal formation is favored by alcohol addition to the intermediate cyclopropene, whereas the ketal is predominantly formed by an alkoxide ion attack on the same intermediate. This and other observations have led to elaboration of the reaction conditions under which selective formation of different types of products is possible (eq 152).[412]

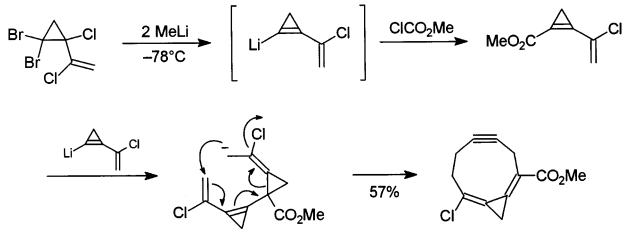


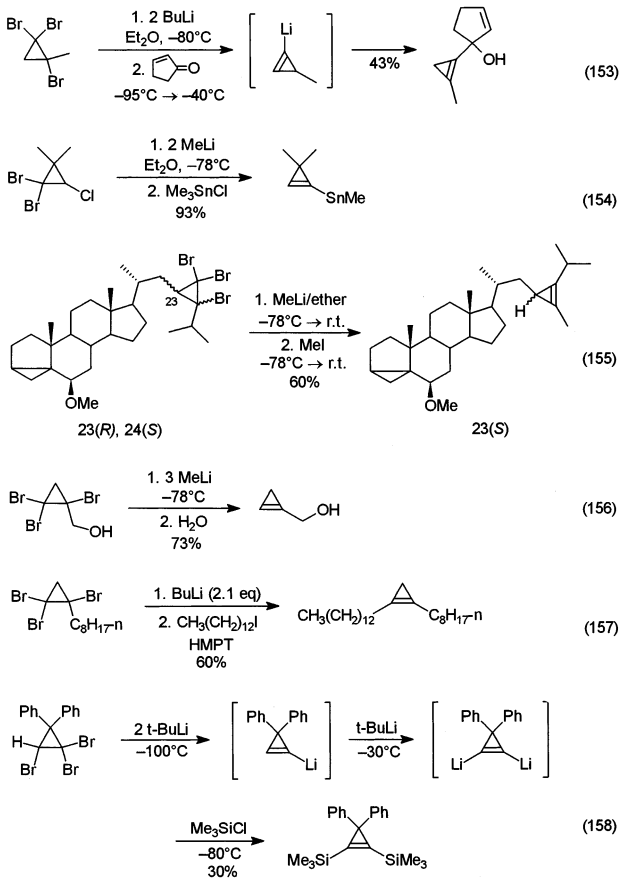
(152)

Halocyclopropenes obtained by method c, i.e., using MeLi for the dehalogenation, often react with a second equivalent of MeLi to give the 1-lithiocyclopropene derivative. These compounds can undergo many valuable reactions such as protonation, addition to a carbonyl group,[231] alkylation,[218,221,234] silylation,[215,221] or stannylation.[399] Some examples are given in eqs 153,[231] 154,[399] 155,[234] 156,[221] 157,[218] and 158.[215]

The very unusual reaction of 1-lithio-2-(1-chlorovinyl)cyclopropene with methylchloroformate leads to cyclononadienyne **55**.[118] One possible route to the formation of this product is shown in Scheme 12.

Scheme 12



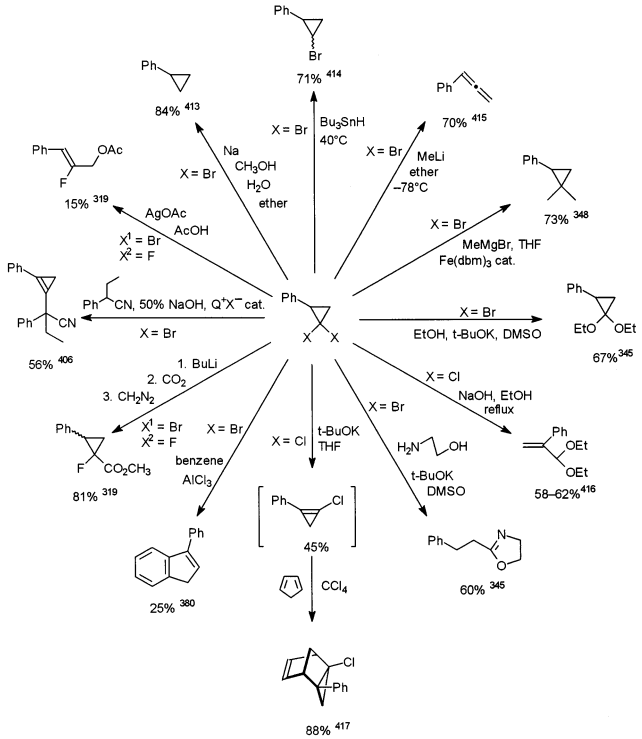


This example shows that the reactions of lithiocyclopropenes have great synthetic possibilities, which have yet to be explored.

V. Summary

In this short review I show that syntheses of *gem*-dihalocyclopropane derivatives can be accomplished

Scheme 13



by several highly efficient procedures, among which the phase-transfer catalytic method is the method of choice. The general concept of PTC and its basic mechanistic features were discussed, along with its major benefits and advantages in the chemistry of dihalocarbenes and *gem*-dihalocyclopropanes. Because *gem*-dihalocyclopropanes are readily available, they have found wide application as substrates for the syntheses of many classes of compounds, which are often not easy to obtain using other starting materials. The main types of *gem*-dihalocyclopropane transformations that have been described in recent years were discussed. These transformations demonstrate the importance of *gem*-dihalocyclopropanes in organic synthesis. Some transformations of 1,1-dihalo-2-phenylcyclopropanes (which are produced by the PTC reactions in yields exceeding 90%) are shown in Scheme 13 to illustrate the importance of this type of reaction.

VI. Note Added in Proof

Additional recent work has been published on the syntheses of *gem*-dichlorocyclopropanes and their use in organic synthesis.[418]

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