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Additional and Supplementary Volumes to the 4th Edition

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(HOUBEN-WEYL)

ADDITIONAL AND SUPPLEMENTARY VOLUMES TO THE 4TH EDITION

EDITORIAL OFFICE

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GEORG THIEME VERLAG STUTTGART · NEW YORK

VOLUME E 17c

CARBOCYCLIC THREE- AND FOUR-MEMBERED RING COMPOUNDS

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Preface

Methods of Organic Chemistry – or synonymously Houben-Weyl – would be severely incomplete in this decade without the coverage of small ring chemistry. The first, and only, Houben-Weyl volume on Carbocyclic Three- and Four-membered Ring Compounds was published 25 years ago. Until that time small ring chemistry was, in the main, considered a domain for mechanistic and physical organic investigations, although many of the basic preparative methods had already been developed and the majority of important transformations thoroughly studied and reasonably well understood. Nevertheless, the notion, which started to evolve slowly in the sixties, of small ring compounds being useful and, frequently, uniquely applicable building blocks for other carbocyclic and also acyclic organic skeletons, has only since fully matured.

Quite a number of cyclopropane and cyclobutane derivatives have gained importance in their own right. For instance, the cyclopropyl group has turned out to be an essential feature in natural and non-natural products with insecticidal, cytostatic, various plant physiological, as well as antiinfective, activities and has, therefore, entered the realm of industrially applied chemistry. A recent survey listed 191 pharmaceutically important compounds containing an aminocyclopropane substructure, the best known example being the widely used broad-spectrum antibiotic Ciprofloxacin.

Yet the discovery of new types of natural small ring compounds continues. For example, a few years ago an antibiotic natural product with an unusual fatty acid side chain containing four adjacent cyclopropyl groups was described, and more recently, a similar compound with five adjacent, and a total of six, cyclopropyl groups has been reported. The vast progress in the development of stereoselective synthetic methodology (see Houben-Weyl Volume E21) has also brought about new methods for stereoselective cyclopropanations, and this has gone hand in hand with efforts towards enantioselective total syntheses of cyclopropyl-group-containing natural and non-natural products. So far these developments have only scratched the surface, as most of these methods are still hampered by severe constraints, and so the race goes on.

In view of this progress, it appeared to be time to publish an up-to-date comprehensive treatment of the methods of preparation and transformation of carbocyclic three- and four-membered-ring compounds. Certainly, the access to cyclopropane derivatives via carbene additions to alkenes, which represents one of the most general methods, has been covered – albeit from a different perspective – in the Houben-Weyl volume on Carbenes (E19b), and cross-references are frequently made to Houben-Weyl E19b in the corresponding sections of this volume. Yet this earlier volume cannot even be considered to be a comprehensive summary of the methods for the synthesis of cyclopropanes, let alone of the preparations and transformations of cyclopropenes, cyclopropanes, cyclopropenones and triafulvenes, all of which are covered here.

Twenty five years ago, all of the material on cyclopropane and cyclobutane chemistry was compiled by two single authors, which at the time must have been a truly Herculean task. Nowadays, this would simply be impossible. Thus, Houben-Weyl E17 has come to life only through the joint efforts of more than 60 authors, some of whom have invested a lot of their time with major contributions. An estimated 20,000

publications were read and evaluated, well over 13,000 references actually being quoted in the three-membered-ring sections alone. An editorial staff of 6 native speakers took care to make the presentation uniform and polish the language, especially of the non-native English writing authors. All the art work was redrawn by a group of 4.

The editor is indebted to all the authors, the editorial staff and the artists for the fruitful collaboration which made this book possible. We all hope that this handbook will serve the chemical community well and will become an indispensable reference tool for those engaged in Synthetic Organic Chemistry.

Göttingen, August 1996 Armin de Meijere

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Volume E 17c

B. Transformations

1. Elimination Reactions

M. S. BAIRD

1,2-Elimination in cyclopropanes will lead to the preparation of a cyclopropene if the 1,2-bond is endocyclic or a methylenecyclopropane if it is exocyclic; these reactions are covered in Sections 2.A.1.1.1. and 1.A.5.2.2., respectively. 1,1-Eliminations leading to cyclopropylidenes are covered in Houben-Weyl, Vol. E19b, pp 391–511.

2. Ring-Opening Reactions

2.1. Addition Reactions

2.1.1. Nonactivated Cyclopropanes

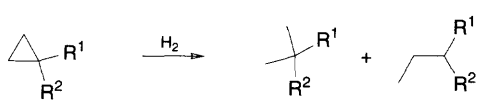
S. VON ANGERER

2.1.1.1. Reductive Ring Fission

2.1.1.1.1. Hydrogenolysis

Alkyl-substituted cyclopropanes are cleaved preferentially at the least substituted bond by catalytic hydrogenation. This observation is in agreement with theoretical considerations that favor the C–C bond opposite to the substituent as the cleavage site due to the weakly electron-donating effect of the alkyl substituent.[1] With a C–C double bond or other cyclopropyl groups in the molecule, however, the preferred mode of ring opening can be different (*vide infra*).[2] Electron-withdrawing groups, such as a carbonyl function, result in the cleavage of the adjacent bond (see Section 2.1.3.1.). Mono- and 1,1-disubstituted cyclopropanes react with hydrogen in the presence of a noble metal catalyst such as palladium, platinum or rhodium to give geminal dimethyl groups, such as in **1**, or tertiary alkyl substituents, such as in **3**.[1–6]

When benzylcyclopropane was hydrogenolyzed in the presence of platinum a substantial proportion of the alkyl derivative with a reduced aromatic ring was obtained. With a palladium catalyst derivative **2e** became the main product with the phenyl ring retained.[3]



1 **2**

1,2	R^1	R^2	Reaction Conditions	Yield[a] (%)		Ref
				1	**2**	
a	C_6H_{13}	H	Pd/C, EtOH	95	5	3
b	Me	Me	Pd/C, MeOH or Pt, HOAc, 0 °C 10–24 h	n.r.	–	1
c	Me	1-adamantyl	Pt_2, HOAc, 50 °C/3 atm	96	–	4
d	CH_2OH	CH_2OH	Pd/C, EtOH, 185 atm, 24 h	n.r.	–	1,2
e	Bn	H	Pd/C, EtOH	25	75	3

[a] n.r. = not reported.

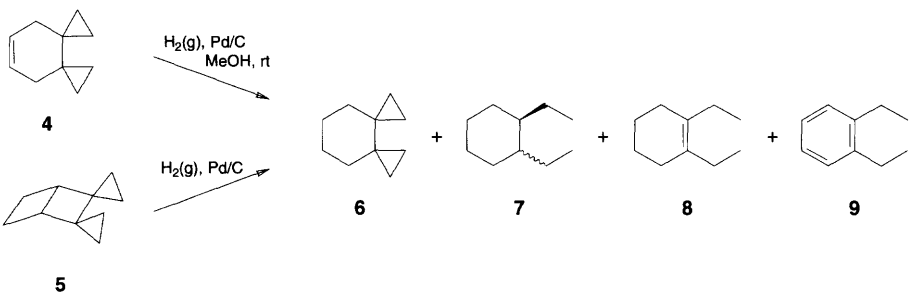
for references see p 1982

3

n	m	R	Reaction Conditions	Yield (%)	Ref
3	3	–	H_2(g), Rh/C, 60 °C/100 atm	58	6
2	3	CH_2-*t*-Bu	H_2(g), PtO_2, HOAc	92	5

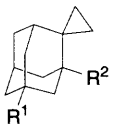
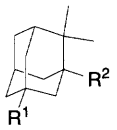
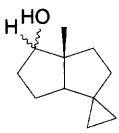
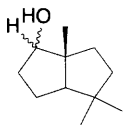
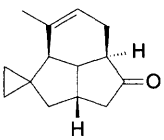
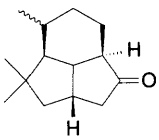
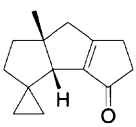
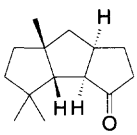
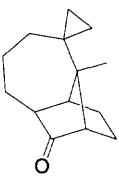
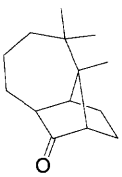
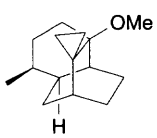
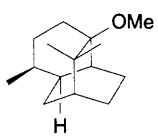
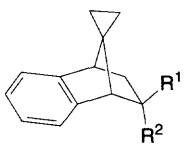
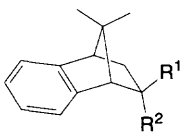
Spirocyclopropanes usually behave as 1,1-dialkylcyclopropanes and yield cyclic structures with geminal dimethyl substituents (see Table 1).[4,7–14] The introduction of a geminal dimethyl fragment via a spirocyclopropane has frequently been used in the synthesis of natural products such as $\Delta^{9(12)}$-capnellene,[8] longifolene,[12,13], patchouli alcohol,[10] seychellene,[10] and pentalenene.[9]

Exceptions were dispiro[2.0.2.4]dec-8-ene (**4**) and dispiro{cyclopropane-1,2′-bicyclo[2.2.0]hexane-3′,1″-cyclopropane} (**5**) in which both three-membered rings were opened to ethyl groups.[15]



Substrate	Yield (%)			
	6	**7**	**8**	**9**
4	45	32	7	16
5	8	84	–	7

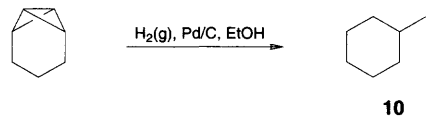
Table 1. 1,1-Dialkylcyclopropanes from Spirocyclopropanes

Substrate	R^1	R^2	Reaction Conditions	Product	Yield (%)	Ref
	H	H	H_2(g), PtO_2, HOAc, 50 °C/3 atm		–	4
	H	H	H_2(g), PtO_2, HOAc		85	7
	OH	H	H_2(g), PtO_2, HOAc		85	7
	H	OH	H_2(g), PtO_2, HOAc		83	7
			H_2(g), Pt, HOAc, rt		–	8
			H_2(g), Pt, HOAc, 3 atm		96	9
			H_2(g), PtO_2, HOAc, 60 °C/3 atm		60	14
			H_2(g), PtO_2, HOAc, 25 °C, 18 h		96	12, 13
			H_2(g), PtO_2, NaOAc, HOAc, rt, 40 min		83	10
	R^1	R^2				
	H	OH	H_2(g), PtO_2, HOAc, 10 d		100	11
	OH	H	H_2(g), PtO_2, HOAc, 10 d		8[a]	11

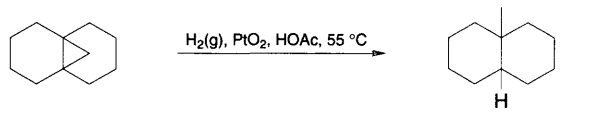
[a] Additionally the derivative R^1 = OAc; R^2 = H was obtained in 79% yield.

for references see p 1982

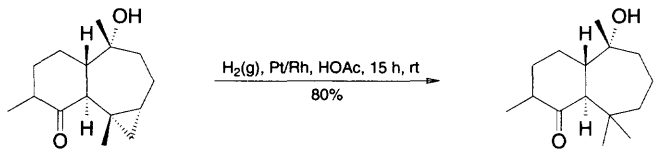
In analogy to the mono-alkylated cyclopropanes annulated cyclopropanes gave methylated cyclic products **10**,[17] **11**,[16] and **12**[18] upon catalytic hydrogenolysis.



10

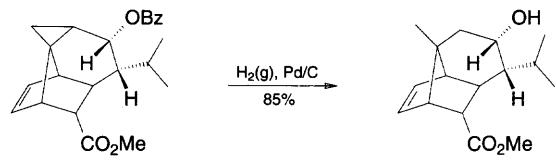


11 (*cis*/*trans*) 1 : 1



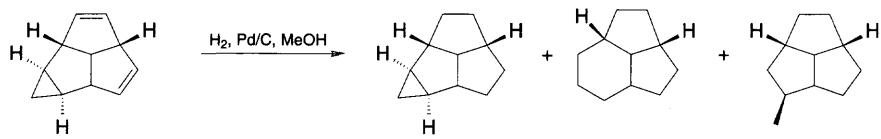
12

In polycyclic systems with a bicyclo[2.2.1]heptane group generally the six-membered ring was retained and the cyclopropane ring opened to give a methyl group, i.e. formation of **13**.[19]

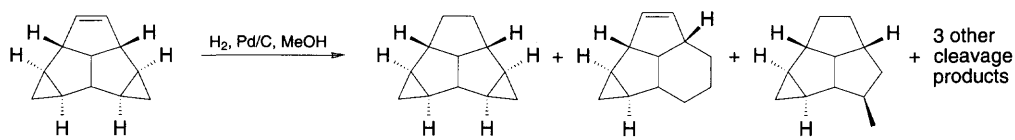


13

In bi- and oligocyclic systems the cleavage reaction can also take a different course depending on the preferred mode of adsorption of the molecule on the catalyst surface. For example, in *exo*-homotriquinacene, **14** and **15** and in hexacyclo[4.4.0.0^{2,10}.0^{4,8}.0^{7,9}]decane (diademane), both types of cyclopropane C–C bonds were cleaved by hydrogenation in the presence of palladium on charcoal.[20]



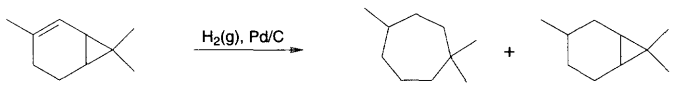
14 16% 33% 51%



15 27% 16% 10% 13%

Hydrogenation of 3,7,7-trimethylbicyclo[4.1.0]hept-2-ene in ethanol gave a 1 : 1 mixture of ring-opened product **16** and ring-retained product **17** both with the double bond reduced.[21] In

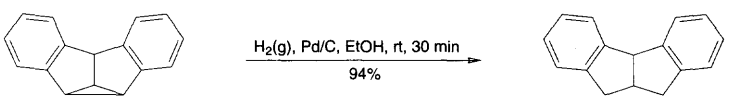
propionic acid only the monocyclic derivative **16** was obtained. It is apparent that ring opening can only occur simultaneously with or after the reduction of the double bond.



16 **17**

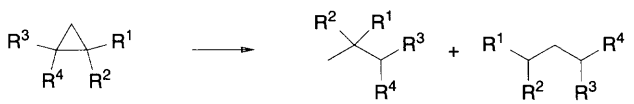
Conditions	Product
EtOH, 20 °C	**16**/**17** 1 : 1
$EtCO_2H$, 96 °C	**16**

The cyclopropane ring in dibenzannulated tricyclo[3.3.0.$0^{2,8}$]octa-3,6-diene was opened to give the symmetric bicyclo[3.3.0]octadiene skeleton **18**.[22]



18

Recently, various methyl-substituted cyclopropanes have been used as test substrates for some novel hydrogenation catalysts such as palladium(0),[23] nickel(0),[24,25] copper(0),[26] and rhodium(0) on silica gel.[27] Although the ratio of cleavage products **19** and **20** was dependent on the experimental conditions, especially on the hydrogen pressure, the main product was usually formed by the cleavage of the least substituted C–C bond in the ring. In further studies, the cyclopropane ring was opened by treating it with deuterium gas in the presence of iridium(0) on alumina.[28] When methyl- or 1,1-dimethylcyclopropane was used the deuterium label was found at the unsubstituted carbon atoms.



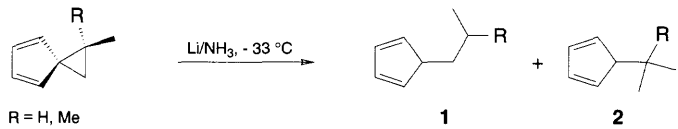
19 **20**

R^1	R^2	R^3	R^4	Catalyst	Product	Ref
H	H	H	H	Ni/NaX, zeolite	–	25
Et	H	H	H	Pd/silica gel	**19**	23
Me	H	H	Me	Pd/silica gel	**19**	23
Me	Me	Me	Me	Pd/silica gel	**19**	23
Me	H	H	Me	Rh/silica gel	**19**	27
Me	Me	H	H	Ni/silica gel	**19** + **20**	24
Me	Me	H	H	Cu	**19** + **20**	26
Me	H	Me	H	Cu	**19** + **20**	26
Me	H	H	Me	Cu	**19** + **20**	26
Me	Me	Me	Me	Cu	**20**	26
Me	Me	Me	Me	Rh/silica gel	**19** + **20**	27

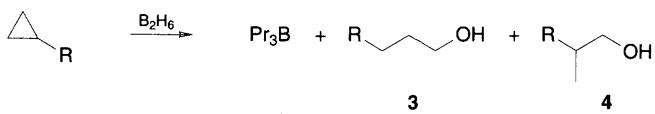
for references see p 1982

2.1.1.1.2. Reactions with Hydride Complexes

An example of the reduction of a nonactivated cyclopropane by lithium in liquid ammonia is the reduction of 1-methyl- and 1,1-dimethylspiro[2.4]hepta-4,6-diene. Either cyclopropane bond at the spiro center was cleaved to give alkyl-substituted cyclopentadienes **1** and **2**.[29]



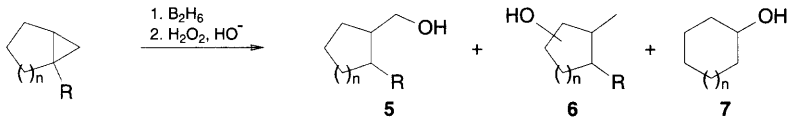
In the 1950s, it was reported that the reaction of cyclopropane with lithium aluminum hydride gave tripropylaluminum.[30] However, this result was not verified.[31] The reaction of cyclopropane in the vapor phase with diborane to monoalkylcyclopropanes was shown to be fairly regioselective, the products being derived from addition of the hydride to the most-substituted carbon atom, and the boron to the least-substituted carbon atom.[31] With butyl-, pentyl- and octylcyclopropanes after oxidative workup the linear primary alcohols **3** were obtained as the major products together with small quantities of the 2-methyl derivatives **4**.



R	Conditions	Yield[a] (%)			Ref
		Pr_3B	**3**	**4**	
H	rt, months or 80–100 °C	n.r.	–	–	32
Bu	106 °C, 1.5 h	–	90	5	31
C_5H_{11}	110 °C, 1 h	–	90	10	31
C_8H_{17}	86 °C, 15 min	–	81	9	31

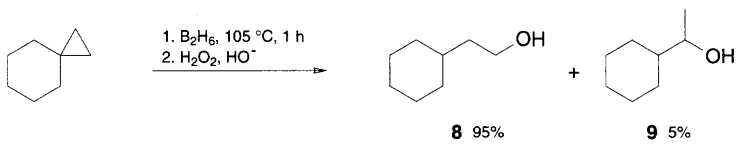
[a] n.r. = not reported.

The reaction of bicyclo[4.1.0]heptane with diborane and subsequent treatment with hydrogen peroxide produced predominantly cyclohexylmethanol (**5b**) in high yield.[31] Under modified experimental conditions small amounts of isomeric methylcyclohexanol (**6b**) and cycloheptanol (**7b**) were isolated. In contrast to the hydroboration of alkenes, the cyclopropane cleavage reaction is inhibited by ethereal solvents such as diethyl ether, tetrahydrofuran or 2-methoxyethyl ether. Bicyclo[3.1.0]hexane reacted with diborane in a similar fashion to give mainly cyclopentylmethanol (**5a**).[31] The reaction of 1-methylbicyclo[4.1.0]heptane gave a mixture of *cis*- and *trans*-(2-methylcyclohexyl)methanol (**5c**) in an initial ratio of 60 : 40. Spiro[2.5]octane reacted with diborane to yield only products derived from scission at the spiro carbon. The main product was 2-cyclohexylethanol (**8**).[31]

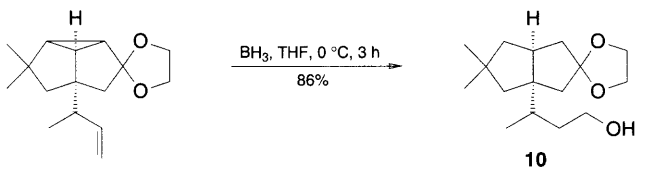


5–7	R	n	Conditions	Yield (%)		
				5	6	7
a	H	1	93 °C, 1 h	92	trace	8
b	H	2	sealed tube, 100 °C, 22 h	96	trace	trace
c	Me	2	106 °C, 1 h	97[a]	–	–

[a] (*cis*/*trans*) 6 : 4.

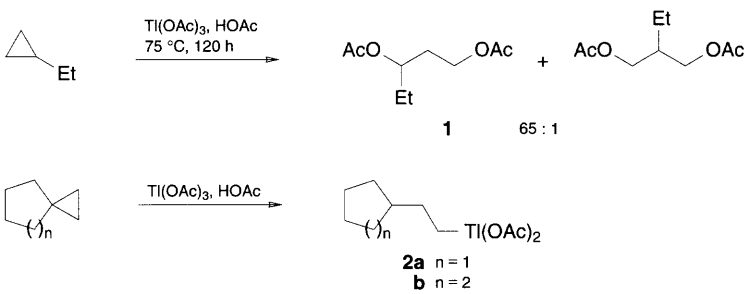


In the 7,7-dimethyltricyclo[3.3.0.0^{2,8}]octane system, the use of diborane resulted in hydrogenolytic cleavage of the most strained cyclopropane bond giving **10**.[33]



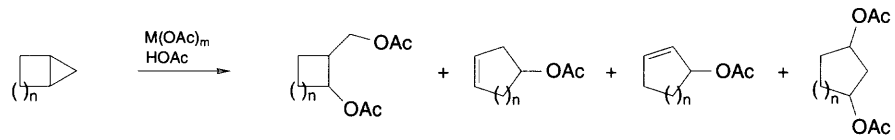
2.1.1.2. Oxidative Ring Fission

Due to the ring strain, the cyclopropane ring can be opened when treated with oxidizing agents such as lead(IV) acetate or thallium(III) acetate at elevated temperatures. The cleaved C–C bond is initially replaced by an acetoxy group and a hydroxy function which is subsequently acetylated. In ethylcyclopropane, the bond next to the substituent was cleaved almost exclusively on reaction with thallium(III) acetate giving 1,3-diacetoxypentane (**1**) as the major product.[34] An analogous result was observed for spiro[2.4]heptane (**2a**) and spiro[2.5]octane (**2b**) which incorporate a cyclopropane group.[35]



for references see p 1982

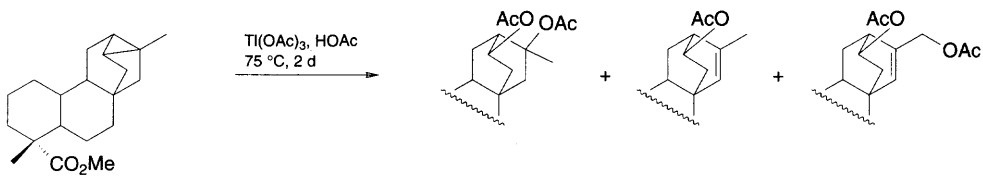
When bicyclic compounds **3** with cyclopropane rings were oxidized with thallium(III) acetate or lead(IV) acetate the cleavage of both types of C–C bonds was observed together with secondary elimination products. It has been observed that, as the ring size increased from bicyclo[2.1.0]pentane (**3a**) to bicyclo[3.1.0]hexane (**3b**) and to bicyclo[4.1.0]heptane (**3c**), cleavage of the bond between the bridgehead and the methylene increased at the expense of cleavage of the bond between the two bridgeheads due to the strain on the C–C bridge.[36,37] Thallium(III) acetate was the more selective agent.[36] In a mechanistic study, kinetics of this oxidative ring-opening reaction were determined.[35]



3 **4** **5** **6** **7**

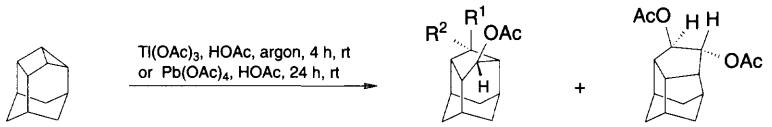
3–7	n	M(OAc)m	Temp, Time	Yield (%)				Ref
				4	**5**	**6**	**7**	
a	1	$Pb(OAc)_4$	25°C, 24 h	–	36	25	39	36
		$Tl(OAc)_3$	25°C, 60 h	–	27.5	22.5	50	35, 36
b	2	$Pb(OAc)_4$	75°C, 26 h	24.5	27	24	24.5	36, 37
		$Tl(OAc)_3$	75°C, 62 h	46	25	20	9	35, 36
c	3	$Pb(OAc)_4$	75°C, 60 h	69	11.5	9	7.5	36, 37
		$Tl(OAc)_3$	25°C, 82 h	91	3	trace	6	32, 34–36

Treatment of *ent*-trachyloban-19-oate **8** with thallium(III) acetate in acetic acid resulted in cleavage of the most strained bond of the three-membered ring to afford the corresponding diacetate together with elimination products.[38]



8 18% 10% 6%

The oxidative cleavage of the central C–C bond of the bicyclo[2.1.0]pentane fragment in pentacyclo[5.3.1.$0^{2,6}$.$0^{3,5}$.$0^{4,9}$]undecane (**9**) with thallium(III) acetate and lead(IV) acetate was used for the introduction of functional groups into noriceane (tetracyclo[5.3.1.$0^{2,6}$.$0^{4,9}$]undecane).[39] The oxidation reaction yielded two unrearranged diacetates **10** with different configuration and a rearrangement product **11** due to the formation of a bridgehead carbenium ion as intermediate. The preferred orientation of the acetoxy groups depended on the oxidizing agent: *endo,exo* for thallium(III) acetate and *exo,exo* for lead(IV) acetate.



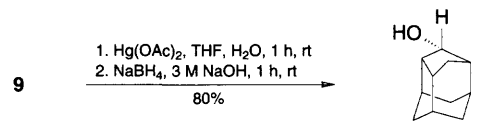
9

endo,exo-**10** $R^1 = H$, $R^2 = OAc$
exo,exo-**10** $R^1 = OAc$, $R^2 = H$

11

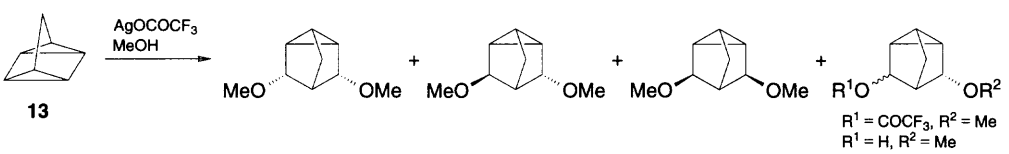
Reagent	Yield (%)		
	endo,exo-**10**	*exo,exo*-**10**	**11**
$Tl(OAc)_3$	40	4	18
$Pd(OAc)_4$	20	40	20

Mercury(II) acetate also underwent addition across this particular bond of **9** and gave *endo*-tetracyclo[5.3.1.$0^{2,6}$.$0^{4,9}$]undecan-3-ol (**12**) in excellent yield following the reduction of the primary adduct with sodium borohydride.[39] The *endo*-product suggests the intervention of a 1,3-bridged metal ion in these reactions.



12

Silver(I) ions generally catalyze the rearrangement of strained polycyclic systems which contain cyclopropane groups. It was shown, however, that silver(I) cleaved one or two of the strained cyclopropane bonds in quadricyclane (**13**) in an oxidation reaction. A complex mixture was obtained on treatment of quadricyclane (**13**) with silver(I) trifluoroacetate. The main addition products contained two oxygen functions and one intact cyclopropane ring.[40]



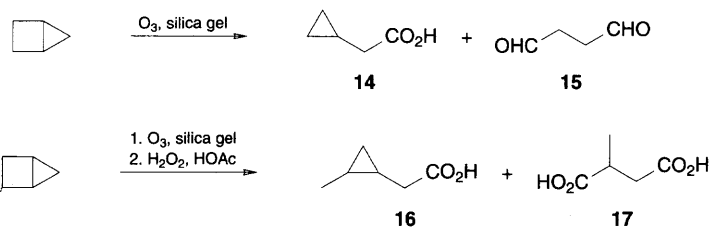
13

$R^1 = COCF_3$, $R^2 = Me$
$R^1 = H$, $R^2 = Me$

Although the cyclopropane ring and the C–C double bond have many similarities in their chemical properties, a cyclopropane ring, in contrast to the double bond, is stable towards ozone; an exception is found when additional strain is put on one of the cyclopropane bonds. Highly strained bicyclo[2.1.0]pentane reacted with ozone adsorbed on silica gel to give a 2 : 5 mixture of cyclopropaneacetic acid (**14**) and butanedial (**15**), the formation of **15** can be rationalized as cleavage of all three cyclopropane bonds.[41] Analogously, *exo*- and *endo*-2-methylbi-

for references see p 1982

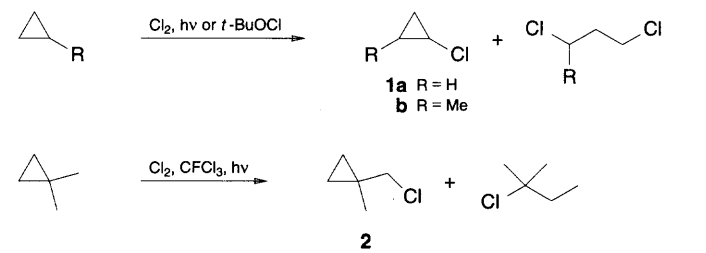
cyclo[2.1.0]pentane gave 2-methylbutanedioic acid (**17**) as the main product after workup with hydrogen peroxide.[41] Cleavage of all three cyclopropane bonds by ozone was also observed in methyl-substituted bicyclobutanes.[41]



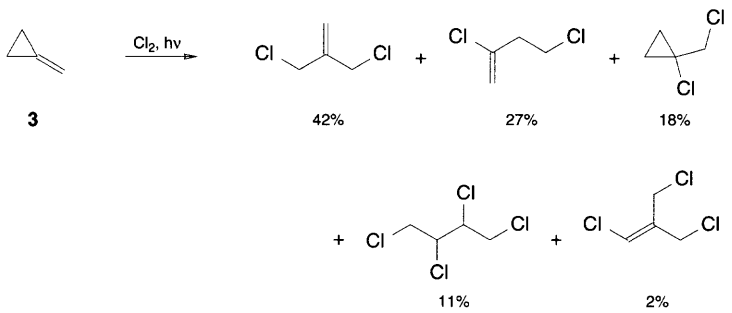
2.1.1.3. Reactions with Radicals

The ring-opening reaction of the cyclopropyl radical cation has been the subject of a number of theoretical[42,43] and spectroscopic[44,45] studies. The addition of radicals to cyclopropane resulting in ring opening can proceed by two mechanisms: (1) by a type of substitution reaction in which the C–C bond is cleaved on the attack of the radical; (2) by hydrogen abstraction, C–C bond cleavage, and capture of a reactive species such as a halogen atom. In the latter mechanism, the capture reaction can occur prior to cleavage to yield substituted cyclopropanes.

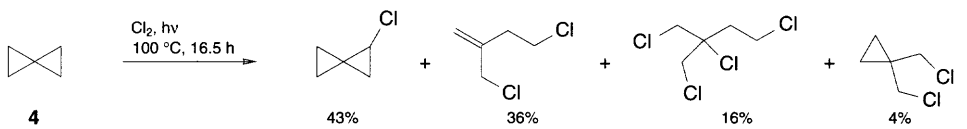
Photochlorination of cyclopropane gave chlorocyclopropane (**1a**) and 1,3-dichloropropane.[46] The latter was the major product at low temperature.[46,47] Photochlorination with *tert*-butyl hypochlorite gave mostly chlorocyclopropane (**1a**).[46] Methylcyclopropane reacted with chlorine to give predominantly 1-chloro-2-methylcyclopropane (**1b**), but small amounts of acyclic products such as 2-chlorobutane, 1,3-dichlorobutane, and 1,3-dichloro-2-methylpropane were also obtained.[46,48] With *tert*-butyl hypochlorite 4-chlorobut-1-ene was isolated as the only acyclic product. Photochlorination of 1,1-dimethylcyclopropane in trichlorofluoromethane at0 °C gave the chloromethylcyclopropane derivative **2** in 67% yield after immediate workup.



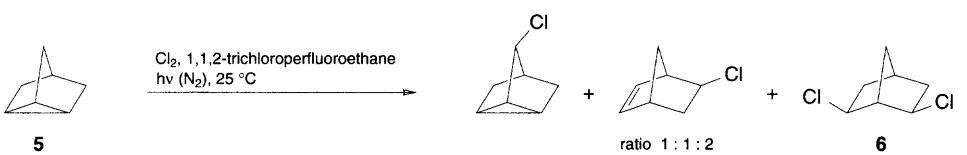
The increased strain in methylenecyclopropane, which is relieved on ring opening, makes the cyclic bonds more liable to cleavage than methylcyclopropane. Photochlorination of methylenecyclopropane (**3**) in the liquid phase produced a mixture of several addition products including 3-chloro-2-chloromethylprop-2-ene (42%), 2,4-dichlorobut-1-ene (27%), 1-chloro-1-chloromethylcyclopropane (18%), 1,2,3,4-tetrachlorobutane (11%), and 1,3-dichloro-2-chloromethylprop-1-ene (2%).[49]



Spiropentane (**4**), which can be considered as a homomethylenecyclopropane, reacted under irradiation with chlorine in the vapor phase to give a mixture of four compounds. Main products were chlorospiropentane (43%) and 4-chloro-2-chloromethylbut-1-ene (36%) together with 1,2,4-trichloro-2-chloromethylbutane (16%) and 1,1-bis(chloromethyl)cyclopropane (4%) whose proportions were dependent on the irradiation conditions.[50] The latter was formed almost exclusively when the photochlorination reaction was carried out in the liquid phase, but also when the vapor phase chlorination was performed in the dark.[50]

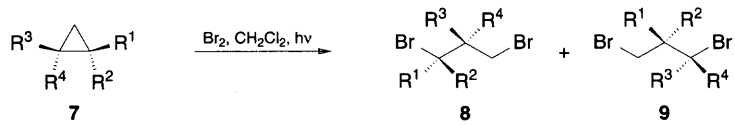


Photochlorination of tricyclo[2.2.1.$0^{2,6}$]heptane (nortricyclane, **5**) gave two substitution products and the addition product *exo,exo*-2,6-dichlorobicyclo[2.2.1]heptane (**6**) in which one of the cyclopropane bonds was cleaved.[51] The steric orientation of the halogen atoms suggests an inversion of configuration at the carbon atoms is involved.



A number of methyl- and ethyl-substituted cyclopropanes **7** were brominated under conditions that guaranteed a radical reaction pathway (irradiation at $-78\,^{\circ}C$ in dichloromethane).[48] Methylcyclopropane (**7a**) underwent exclusive cleavage of the bond next to the substituent to give a quantitative yield of 1,3-dibromobutane (**8a**). Analogous results were obtained with ethylcyclopropane (**7b**) and 1,1-dimethylcyclopropane (**7c**). In 1,2-dimethylcyclopropane (**7d**) the bond between the substituted and the nonsubstituted carbon atom was cleaved. Higher substituted cyclopropanes **7e** and **7f** showed a similar reaction course.[48]

for references see p 1982

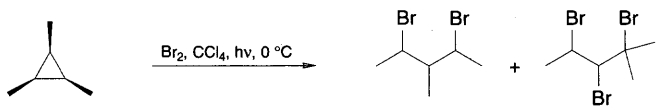


7 8 9

7–9	R^1	R^2	R^3	R^4	Temp (°C), Time (min)	Yield (%)	
						8	**9**
a	Me	H	H	H	−78, 8	100	–
b	Et	H	H	H	0, 2	100	–
c	Me	Me	H	H	−78, –	90	–
d	Me	H	Me(H)[a]	H(Me)[a]	−78, 10	100[b]	–
e	Me	Me	Me	H	−78, 5	83	7
f	Me	Me	Me	Me	−78, 3	–	100

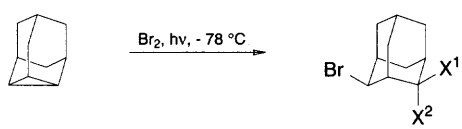
[a] *cis* or *trans*.
[b] (1*S*,2*S*/1*S*,2*R*) 1 : 1.

In a stereochemical study, it was shown that the free radical ring cleavage of all-*cis*-1,2,3-trimethylcyclopropane (**10**) by bromine proceeded with inversion of configuration at one center and by nonstereospecific reaction at the other center.[52] Equal amounts of (*S*)-*meso*-2,4-dibromo-3-methylpentane and *dl*-2,4-dibromo-3-methylpentane were obtained by this reaction. The reaction of the corresponding *trans* derivative was much slower than that of the all-*cis* compound.



10 70% 10%

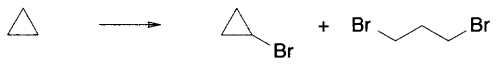
Photobromination of 2,4-dehydroadamantane (**11**) at −78 °C yielded a mixture of two dibromoadamantanes with axial, equatorial (a,e) and equatorial, equatorial (e,e) orientations of the halogen atoms.[48]



11

(a,e) X^1 = H, X^2 = Br 68%
(e,e) X^1 = Br, X^2 = H 32%

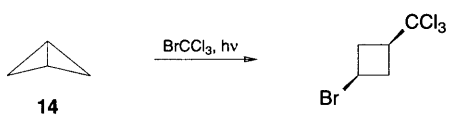
The products of halogenation reactions by radical mechanisms often depend on the source used for the generation of halogen radicals. In photochlorination reactions, the use of *tert*-butyl hypochlorite results predominantly in ring-retained products whereas chlorine at low temperature preferentially opens the cyclopropane ring. A similar observation was made in the bromination reaction. Photolysis of cyclopropane in the presence of *N*-bromosuccinimide yielded almost exclusively bromocyclopropane (**12**) whereas using bromine as the reagent gave only 1,3-dibromopropane (**13**).[53] It is thought that the bromine atom cleaved the C – C bond whereas in the reaction with *N*-bromosuccinimide the competing succinimide radical abstracted the hydrogen followed by the capture of a bromine atom.



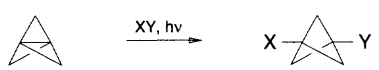
12 **13**

Reagent	Yield (%)	
	12	**13**
Br_2, hv, 0 °C	0	100
NBS	98	2

Highly strained systems such as bicyclobutane (**14**) and [1.1.1]propellane (**15**) readily underwent addition of bromotrichloromethane across the central bond by a radical mechanism.[54] Benzoyl peroxide catalyzed a number of addition reactions to the extremely strained central bond of [1.1.1]propellane (**15**). Examples were acetaldehyde, cyanogen bromide, deuteriochloroform, diphenyl disulfide, diphenyl diselenide, iodine, and *tert*-butyl hypochlorite.[54] Radical chain addition of various organic disulfides to [1.1.1]propellanes (**15**), initiated by 2,2'-azobis(isobutyronitrile) gave the normal adducts across the strained central bond and homologs that contained two or more bicyclo[1.1.1]pentane moieties.[55]



14



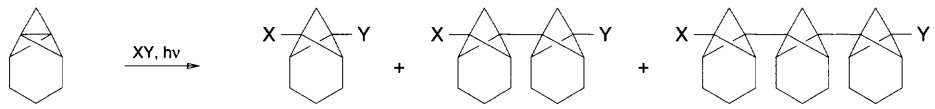
15

X	Y	Reagent	X	Y	Reagent
Br	CCl_3	$BrCCl_3$	SPh	SPh	$(PhS)_2$, Et_2O, pentane
Ac	CH(OH)Me	MeCHO, BzOOH	SePh	SePh	$(PhSe)_2$, Et_2O, pentane
Br[a]	CN[a]	BrCN, BzOOH, pentane	I	I	I_2, pentane
D	$CDCl_3$	$CDCl_3$, BzOOH	O-*t*-Bu	Cl	*t*-BuOCl

[a] The main product was a dimer.

Similar addition reactions were observed with the bridged [1.1.1]propellane system tetracyclo[5.1.0.0^{1,6}.0^{2,7}]octane (**16**) when reacted with diethyl ether, carbon tetrachloride, bromochloromethane, iodomethane, *tert*-butyl bromide, benzyl bromide and tri(butyl)tin hydride.[56]

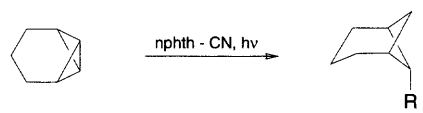
for references see p 1982



16 **17** **18** **19**

16–19	X	Y	Reagent	Yield (%)		
				17	18	19
a	CH(OEt)Me	H	Et_2O	13	12	5
b	Cl	Cl_3	CCl_4	54	4	–
c	Br	CH_2Cl	$BrCH_2Cl$	31	–	–
d	I	Me	MeI, 40 °C, 12 h	25	–	–
e	I	Et	EtI, 50 °C, 17 h	35	–	–
f	Br	*t*-Bu	*t*-BuBr, DBPO, 80 °C	36	–	–
g	Br	Bn	BnBr, DBPO	50	–	–
h	$SnBu_3$	H	Bu_3SnH, Et_2O, rt	72	–	–
i	H	H	1. Li, Et_2NH, 14 h, reflux 2. H_2O	63	–	–

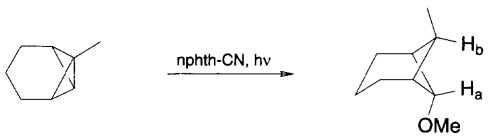
Addition following a radical mechanism can also be achieved by generating radicals by homolytic fission of a cyclopropane bond followed by reaction with other components such as the solvent. When the tricyclo[4.1.0.$0^{2,7}$]heptane system **20** was irradiated in the presence of a photosensitizer such as naphthalene-1-carbonitrile (nphth-CN) the central bond of the bicyclobutane moiety was cleaved and nucleophiles were added across the original bond.[57] In the absence of nucleophiles dimerization and loss of hydrogen occurred. The formation of this product can be rationalized by attack of the radical formed by the photolysis of the most strained cyclopropane bond at the bridgehead of the bicyclobutane fragment in a second molecule. This assumption was supported by the results from studies with tricyclo[4.1.0.$0^{2,7}$]heptanes bearing methyl substituents at the relevant bridgehead atoms.[58, 59]



20 **21**

21	R	Conditions	Yield (%)	Ref
a	OMe	MeOH, KOH	100	57, 59
b	OH	KOH, H_2O, THF	91	57
c	CN	ICN, KCN, MeCN, 18-crown-6 CF_3CH_2OH	91	57

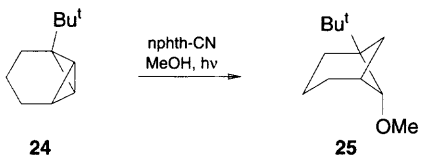
Irradiation of a methanolic solution of 1-methyltricyclo[4.1.0.$0^{2,7}$]heptane (**22**) in the presence of naphthalene-1-carbonitrile gave 6-methoxy-7-methylbicyclo[3.1.1]heptane (**23a**, 93%, isolated yield 56%).[58, 59] In an aqueous system, the corresponding hydroxy derivative **23b** was isolated in 70% yield. The orientation of addition was anti-Markovnikov and the substituents were located in the less hindered positions. The same bond was cleaved when the 2-*tert*-butyl derivative **24** was submitted to this reaction. With two methyl substituents, i.e. **26**, a mixture of two stereoisomers **27A,B** and a dehydrogenated product **28** was obtained whose formation could be explained by the occurence of a tertiary carbon radical.[58]



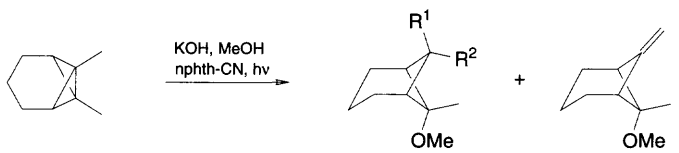
22 23

23	R	Conditions	Yield (%)	Ref
a	OMe	MeOH, 10 h	93	58, 59
b	OH	KOH, H_2O, THF	90	58
c[a]	OMe	MeOD, 10 h	93	58

[a] For H_b = D.



24 25

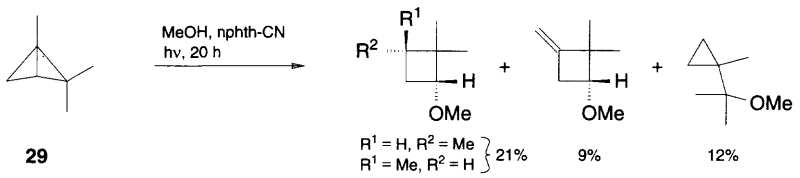


26

27 A R^1 = Me, R^2 = H 32%
B R^1 = H, R^2 = Me 7%

28 40%

In a similar fashion 1,2,2-trimethylbicyclobutane (**29**) reacted in methanol under irradiation in the presence of naphthalene-1-carbonitrile to give three products that corresponded to those obtained with dimethylated tricyclo[4.1.0.0^{2,7}]heptane system.[59] In addition, cleavage of the bond between the quaternary carbon atoms was observed.



29

R^1 = H, R^2 = Me
R^1 = Me, R^2 = H } 21%

9%

12%

As byproducts stereoisomeric adducts of the reduced photosensitizer (1,2-dihydronaphthalene-1-carbonitrile) to cyclobutanes were found.[59]

2.1.1.4. Reactions with Electrophiles

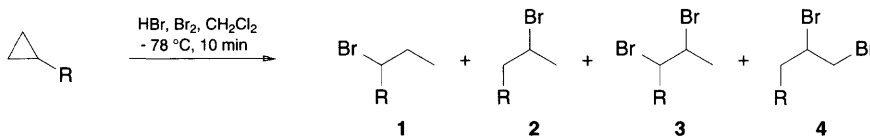
Although cyclopropanes are far less reactive than alkenes, they can be opened by various electrophiles including protic acids, bromine, chlorine, mercury(II) salts and acetyl chloride. The ring-cleavage processes of cyclopropanes by electrophiles were studied with the aid of ab initio molecular orbital[60] and other calculations.[61] Early studies assumed that traditional

for references see p 1982

open carbocations were formed. More recent data from bromination reactions suggested the formation of intermediates with location of the electrophile across an edge or at a corner of cyclopropane.[62]

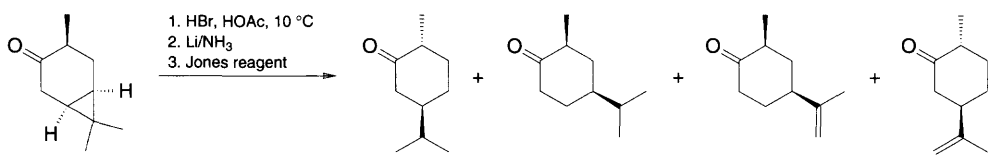
2.1.1.4.1. Acids

Hydrogen bromide underwent rapid addition to methylcyclopropane in the presence of bromine to give predominantly 2-bromobutane (**1a**, 50% yield). A small amount (10%) of disubstituted butanes **3a** and **4a** was also isolated. A 100% excess of bromine over the cyclopropane was added in order to convert alkene products into dibromides. The reaction was carried out in the dark to avoid radical reactions of bromine. A similar result was obtained with ethylcyclopropane.[63] *cis*- and *trans*-1,2-Dimethylcyclopropane gave a mixture of four isomeric bromopentanes in 76% and 89% yield, respectively, on treatment with hydrogen bromide/bromine at −78 °C.[63]



1–4	R	Yield (%)				Ref
		1	2	3	4	
a	Me	50	–	4	6	63, 87
b	Et	29	1	7	–	63

Treatment of (−)-*cis*-caran-4-one (**5**), in which the cyclopropane fragment is separated from the activating carbonyl function by a methylene group, with dry hydrogen bromide in acetic acid gave a mixture of bromo derivatives which were reduced with lithium in liquid ammonia to avoid decomposition. The products were characterized as ketones following Jones oxidation.[64] The cleavage of the cyclopropane bond occurred without preference for one of the cyclopropane bonds outside of the cyclohexane ring.



The ring-opening reaction of 5β,10β-methylene-bridged steroids, e.g. **6**, with hydrogen halides gave access to angular methyl groups in position 10. The presence of a carbonyl group at C3 rendered the system susceptible to dehydrohalogenation reactions with formation of an α,β-unsaturated ketone structure.[65]