Three-Membered-Ring-Based Molecular Architectures†

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1. Introduction

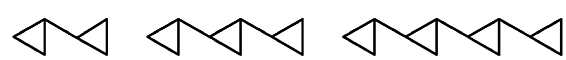
The chemistry of three-membered rings has come a long way in the 120 odd years, since the first cyclopropane derivatives were synthesized by William Henry Perkin in Munich in the laboratory of the eminent chemist Adolf von Baeyer.[1] At that time, only some five- and mainly six-membered rings had been found in natural products, and nobody would have anticipated that cyclopropanes are actually abundant in nature. In his book “Terpenes and Camphor”, Otto Wallach, another eminent chemist of his time, in 1909 already summarized the chemistry of terpene hydrocarbons like sabinene and thujene in which he identified carbocyclic three-membered rings.[2] Chrysanthemic acid, which was identified by Staudinger and Ruzicka in 1924,[3] was probably the first natural product containing a cyclopropane moiety that exhibited an important biological activity. Ever since, the number of newly discovered cyclopropane natural products has been increasing from year to year, and so has been their complexity.[4] This indicates that the three-membered carbocycle, despite its significant ring strain, attributed to it as early as 1885 by Adolf von Baeyer,[5] can be formed rather easily. In fact, the ring closure of a 1,3-difunctional three-carbon unit leading to a cyclopropane is more favored entropically than that of a corresponding five- or six-carbon unit. Most of the simple cyclopropane derivatives are actually prepared by such 1,3-elimination reactions.[6,7] A great advance in the synthesis of cyclopropanes was initiated with the discovery of carbene additions to alkenes in 1955,[8] and it is mainly due to the rapid development of carbene chemistry in the second half of the last century,[7,9] but also to new photochemical and other strikingly simple transformations leading to three-membered carbocycles, that almost any kind of structure appears to be achievable in cyclopropane chemistry nowadays.[10,11] This article is intended to review the wonderful world of molecular assemblies containing more than one cyclopropane ring. Not only have such compounds been prepared in the laboratory out of scientific curiosity, but strikingly even Nature puts forward some of the most unusual structures containing several cyclopropane moieties.

† Dedicated to Professor Emanuel Vogel, who greatly encouraged A.d.M. during his first endeavors in cyclopropane chemistry.

2. Linear Aggregates of Cyclopropane Rings

2.1. 1,2-Linked Oligocyclopropyl Systems

Bicyclopropyl (**1**) is to be regarded as the first member of a series of analogous hydrocarbons consisting of 1,2-connected cyclopropane moieties, the next higher analogues being tercyclopropane (**2**), quatercyclopropane (**3**), and so on.



1 **2** **3**

The first synthesis of **1** was accomplished in 1952 by Slabey, who performed a Wurtz-type coupling by treating cyclopropyl chloride (**4**) with elemental lithium (Scheme 1). Along with the reduction product cyclopropane and halogen-containing byproducts, bicyclopropyl (**1**) was formed in 10−12% yield.[12] With sodium, the yield of **1** was significantly lower. Other methods for the preparation of **1** rely on carbene addition to double bonds in either 1,3-butadiene (**6**)[13,14] or vinylcyclopropane (**7**)[14] or reductive 2-fold ring closure of tetrakis(bromomethyl)ethane (**5**).[13d,14]

Initially, bicyclopropyl (**1**) was tested as a potential high-energy fuel;[12] later studies were concerned with its structure and conformations. From IR and Raman spectra of **1** in the liquid and solid state, Lüttke et al. concluded that **1** adopts the *s-trans* conformation in the solid state and that a second

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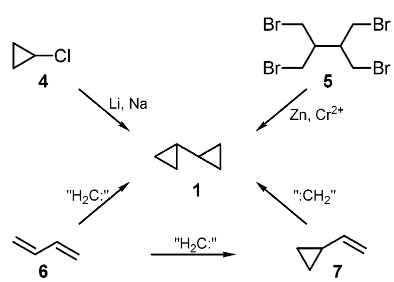
Armin de Meijere, born 1939, studied chemistry in Freiburg and Göttingen, receiving a doctoral degree (Dr. rer. nat.) in 1966 in Göttingen, completing postdoctoral training at Yale University in 1967–1969, and receiving Habilitation in 1971 in Göttingen. He was appointed full professor of organic chemistry in Hamburg, 1977–1989 and ever since has been in Göttingen. He was visiting professor at the University of Wisconsin, the IBM Research Laboratories, the Technion in Haifa, Israel, Princeton University, the Universities of Aix-Marseille III, Paris-Sud, Orsay, Rennes, Toulouse, Bordeaux, Firenze, the Ecole Normale Supérieure, Paris, the Universities of Florida at Gainesville and Colorado at Boulder, Indian Institute of Science in Bangalore, University of Santiago de Compostela, Spain. His awards and honors include German Merit Foundation (Studienstiftung des Deutschen Volkes), “Dozentenstipendium” of the Fonds der Chemischen Industrie, member of the Norwegian Academy of Sciences, Alexander von Humboldt-Gay Lussac prize, member of the Braunschweigische Wissenschaftliche Gesellschaft, Honorary Professor of St. Petersburg State University in Russia, Fellow of the Japan Society for the Promotion of Science, Paul Tarrant Distinguished Lecturer at the University of Florida, Lady Davis Distinguished Visiting Professor at the Technion in Haifa, the Merck-Eurolab Distinguished Lecturer of the French Chemical Society, Novartis Lecturer, Parke-Davies Lecturer, Adolf von Baeyer Medal of the German Chemical Society, and Editor or member of the editorial board of a number of scientific journals, periodicals and books including *Chemical Reviews*, *Synlett*, and *Chemistry—A European Journal*. His scientific achievements have been published in over 630 original publications, review articles, and book chapters. His current research interests include the development of new small ring building blocks and their application in the syntheses of natural and non-natural compounds, new highly strained polycyclic compounds and organometallic complexes with interesting properties, and applications of organometallic complexes and catalysts in organic synthesis.

Sergei I. Kozhushkov was born in 1956 in Kharkov, USSR. He studied chemistry at Lomonosov Moscow State University, where he obtained his doctoral degree in 1983 under the supervision of Professor N. S. Zefirov and performed his “Habilitation” in 1998. From 1983 to 1991, he worked at Moscow State University and then at Zelinsky Institute of Organic Chemistry. In 1991, he joined the research group of Professor A. de Meijere (Georg-August-Universität Göttingen, Germany) as an Alexander von Humboldt Research Fellow; since 1993 he has worked as a Research Associate, since 1996 he has held a position of a Scientific Assistant, and since 2001 a permanent position as a Senior Scientist at the University of Göttingen. His current research interests focus on the chemistry of highly strained small ring compounds. From 2003–2006, he won six awards from InnoCentive, Inc.

Heiko Schill was born in 1976 in Aurich, Germany. He studied chemistry at the Georg-August University of Göttingen, Germany, and was a member of the Studienstiftung des deutschen Volkes (German Merit Foundation) until he obtained his degree of Diplomchemiker in 2002. He obtained his doctoral degree (Dr. rer. nat) in 2005 under the supervision of Professor A. de Meijere and was employed as a research and teaching assistant until 2006. He currently occupies a postdoctoral position in the group of Professor C. M. Williams at the University of Queensland, Australia.

Scheme 1



conformer had to be present in the liquid.[15] Electron diffraction studies disclosed gaseous **1** to consist of about 40% of the *s-trans* conformer ($\varphi = 180°$) in a shallow potential energy well with a width of $\pm 80°$ and 60% of a *gauche* conformer with a torsional angle of $\varphi = 35-40°$ (Figure 1).[16] An X-ray crystal structure analysis of **1** proved that the *s-trans* conformer was the only one present in the crystal and that the amplitudes of vibration of the molecules in the crystal were not unusually large at the observation temperature of -100 °C.[17] The central bond in **1** was found to be significantly shorter than both types of the cyclopropane bonds (Figure 1).[17]

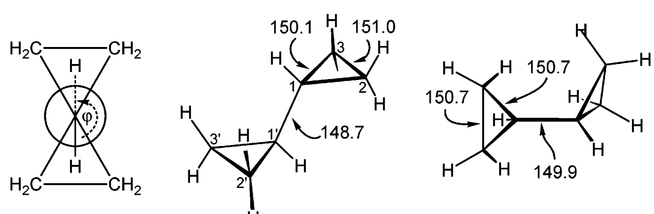
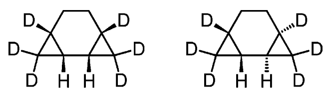


Figure 1. The conformation and structure of bicyclopropyl (**1**) in the crystal: left, definition of torsional angle φ; middle, structural parameters obtained from X-ray analysis; right, structural parameters obtained from electron diffraction.

In a second gas-phase electron diffraction (GED) study of bicyclopropyl (**1**),[18] the conformer distribution was 47.5% *s-trans* and 52.5% *gauche* ($\varphi = 48.7°$) corresponding to an energy difference of less than 500 cal/mol in favor of the *s-trans* conformer.[18]

Since conformer distributions cannot very accurately be determined by the GED method, the energy difference between the two conformers as determined for the liquid phase by Lüttke et al. is significantly more reliable.[14] By integrating two representative bands in the IR spectrum of **1** at different temperatures, the energy difference was found to be 150 ± 15 cal/mol in favor of the *gauche* conformer. This was confirmed by a study of the temperature dependence of the $^3J_{H,H}$ coupling constants between the two methine protons in **1** as determined in the ^{13}C satellites of 2,2,3,3,2′,2′,3′,3′-octadeuteriobicyclopropyl. Using *cis*- (*cis*-**8**) and *trans*-tricyclo[5.1.0.0^{2,4}]octane (*trans*-**8**) as well as substituted



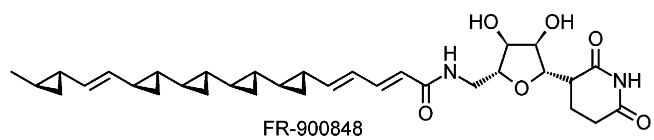
cis-**8** *trans*-**8**

bicyclopropyls as conformationally constrained analogues of **1** to experimentally calibrate the Karplus equation for the torsional angle dependence of this vicinal coupling constant, the torsional angle of the *gauche* conformer was estimated as $\varphi = 53.8°$,[19] and the energy difference between the *gauche* and *s-trans* conformer was found to be 143−177 cal/mol in favor of the *gauche* conformer slightly depending on the assumptions made for the analysis.[14] These results were confirmed once more by a Raman spectroscopic study by Bernstein et al. on **1** in all three phases. Solid **1** consists solely of the *s-trans* conformer, and in both the liquid and the gas phase, the *gauche*-**1** is more stable by 188 ± 10 cal/mol (liquid) and 91 ± 28 cal/mol (gas phase).[20] Finally in 1981, a normal coordinate analysis was conducted by Lüttke et al. thus completing the studies of the vibrational spectra of **1**.[15]

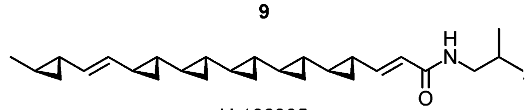
Another question of interest with regard to bicyclopropyl (**1**) was the nature of the central C(1)−C(1′)-bond. Since sp^2-hybrid orbitals are involved in the exocyclic bonds of a cyclopropane, and similarities between alkenes and cyclopropanes in terms of chemical behavior were well-known, certain effects of conjugation between the two cyclopropyl groups of **1** were searched for. The conformational analyses (see above) did not disclose a preference for the *s-trans* conformer, which would allow for maximum overlap of the corresponding Walsh-type orbitals (the *s-cis* conformation, which would be equally suited to achieve maximum overlap, should suffer strongly from repulsive van-der-Waals interactions of the eclipsed hydrogen atoms). Since both 1,3-butadiene (by 2.1 kcal/mol) and vinylcyclopropane (by 1.1 kcal/mol) adopt such preferred conformations benefitting from conjugation, the shortened central bond in **1** was believed to be due to the sp^2-like hybridization of the carbon atoms only and not to any extent to conjugation in this molecule.[21] However, this does not preclude a strong electronic interaction between two cyclopropyl groups. In fact, Klessinger et al. first assigned the bands in the He(I)-photoelectron spectrum (PE) of **1** and deduced an almost identical degree of orbital splitting ($\Delta I_{as} = 2.3-2.5$ eV) compared with that in 1,3-butadiene ($\Delta I_{as} = 2.45$ eV).[22] The assignment of the ionization events was subsequently challenged by Gleiter and Paquette et al., who predicted broad and featureless bands for the non-rigid *s-trans* conformer and attributed the bands with almost the same orbital splitting ($\Delta I_{as} = 2.0-2.3$ eV) to the more or less rigid *gauche* conformer.[23]

A detailed study employing X-ray crystal structure analysis of bicyclopropyl (**1**) was conducted by Nijveldt et al. in 1988. They tried to identify the effects of the putative conjugation by highly precise structure determinations of cyclopropane, vinylcyclopropane, and **1**.[24] Whereas typical effects of conjugation, such as preference for the bisected conformation, increase of the electron density around the central bond, and decrease (increase) of the length of the central (double) bond, were indeed found in vinylcyclopropane, the obtained geometrical data for **1** gave no conclusive evidence for conjugation.[24c]

With the isolation of the oligocyclopropane FR-900848 **9** from the fermentation broth of *Streptoverticillium fervens* HP-891,[25] the focus in research on bicyclopropyl (**1**) and the higher analogues **2** and **3** began to shift from a more theoretical interest in structures and conformations to useful methodology for stereoselective syntheses of such compounds. The natural product **9** displayed pronounced activity



FR-900848
9



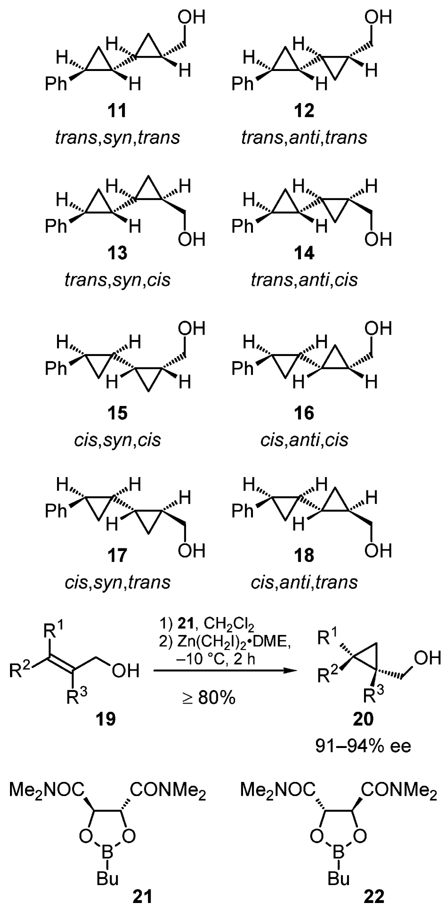
U-106305
10

against filamentous fungi, such as *Aspergillus niger*, while not having any adverse effects on either Gram-positive or Gram-negative bacteria nor non-filamentous fungi such as *Candida albicans*. It was therefore considered as a possible lead structure in the development of novel antifungal therapeutics targeted against *Aspergillus fumigatus*, a human pathogen responsible for significant morbidity and also mortality in immunosuppressed patients, suffering, for example, from AIDS. The constitution of **9** was elucidated by scientists at the Fujisawa company by combined NMR and degradation studies.[25] However, the absolute configuration of the central quatercyclopropane moiety as well as the configuration of the isolated cyclopropane and of the double bond between these two units had not been established.

The structure elucidation required stereoselective syntheses of cyclopropylmethanols and bicyclopropylmethanols as model compounds for comparison with authentic samples and with synthetic intermediates. As a first example, all eight diastereomers of (phenylbicyclopropyl)methanol **11**−**18** were prepared by Zercher et al.[26]

Many more such model compounds including ter- and quatercyclopropanes and also higher analogues were synthesized in a stereoselective manner. The advances in this area have been reviewed recently.[27] Most of these syntheses relied on the stereoselective cyclopropanation of allyl alcohols employing tartrate-derived dioxaborolanes as chiral nonbonded auxiliaries (Scheme 2).[28] Although originally just reported for the auxiliary derived from the (+)-isomer of

Scheme 2



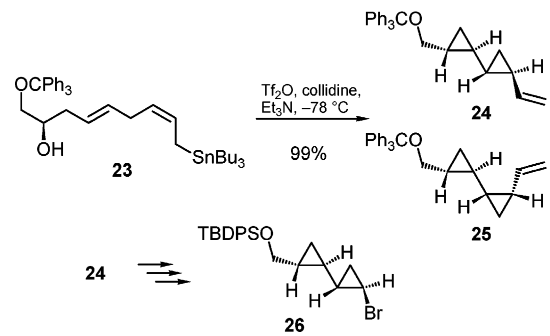
tartaric acid diamide **21**, the adverse configuration could be obtained with its enantiomer **22**. This and other methods of stereoselective cyclopropanations have been reviewed recently.[29]

Two total syntheses of **9** by Barrett et al.[30] and Falck et al.[31] and a formal synthesis by Zercher et al.[32] have been reported. These have also been reviewed in detail by Pietruszka.[27]

A few years after the isolation of FR-900848, another oligocyclopropyl-endowed natural product, U-106305 **10**, was isolated from the fermentation broth of *Streptomyces* sp. UC-11136. This compound turned out to be a cholesteryl ester transfer protein (CETP) inhibitor.[33] The constitution of this natural product was established through NMR and mass spectrometric studies, suggesting all double bonds to be (*E*) and all cyclopropane rings to be *trans* configured.[33] However, because the absolute configuration had not been established for any of the stereogenic centers, there were 64 different isomers to be considered. The configuration of the natural product was established independently by Barrett et al.,[34] who synthesized a product that was identical with the natural compound, and by Charette et al.,[35] who prepared the enantiomer of the natural product. The reader is referred to the recent review of Pietruszka for detailed information on these syntheses.[27]

Very recently, a new approach to enantiopure bicyclopropyl building blocks, mimicking the biosynthetic pathway to many cyclopropane-containing natural products,[4b] by solvolysis of the tin-substituted skipped dienyl homoallyl triflate generated in situ from the alcohol **23** was presented by White et al. (Scheme 3).[36] A 3.7:1:1 mixture of three enantiopure diastereomers was obtained in virtually quantitiative yield. After further elaboration of the obtained mixture, the major isomer could be isolated and was identified by X-ray structure analysis of the resulting analogue as the *trans*,*anti*,*trans*-isomer **24**. One of the minor isomers also gave suitable crystals and was found to be derived from the *trans*,*anti*,*cis*-isomer **25**. The last missing isomer was presumably *trans*,*syn*,*cis*-configured. It was also possible to transform the vinylbicyclopropyl **24** into the intermediate **26**, which was used by Falck et al. in their total synthesis of FR-900848.[31] This methodology is superior in terms of obtained yields, but unfortunately not in terms of selectivity, to a related protocol using silicon-substituted substrates as reported by Taylor et al.[37] With a very similar precursor, a 1:1 mixture of the *trans*,*anti*,*trans*-isomer and *trans*,*syn*,*trans*-isomer was obtained in 69% yield without showing evidence for the formation of any *cis*-configured byproducts.[37] An overview over this field of research has been published recently.[38]

Scheme 3



The biosynthesis of U-103605 **10** has been elucidated by feeding experiments.[33] After feeding ^{13}C-labeled *S*-adenosylmethionine, significantly enhanced NMR signals of the methylene carbons of all cyclopropane moieties were detected. The incorporation of labeled [1-^{13}C]- or [2-^{13}C]-acetate and the pattern of the labels within the backbone of the fatty acid side chain disclosed that a polyketide biosynthetic pathway must lead to an oligounsaturated precursor, which is subsequently cyclopropanated. Although the biosynthesis of FR-900848 had not been studied, it was assumed to proceed along the same lines as that of U-103605, since both natural products are produced by related microorganisms and both show a remarkable structural resemblance.[34]

However, according to very recent results of Oikawa et al., no ^{13}C-label is incorporated into FR-900848 after feeding of [1-^{13}C]- or [1,2-$^{13}C_2$]-acetate.[39] On the other hand, administration of D-[U-$^{13}C_6$]-glucose or [1,3-$^{13}C_2$]-glycerol led to incorporation of ^{13}C into the backbone of the fatty acid side chain as well as into the aminonucleoside moiety. The pattern of the isotopic labeling nevertheless still suggested a polyketide mechanism. Apparently, the necessary acetyl-CoA is built up after glycolysis rather than by the normal utilization of acetate.

The structural parameters of molecules with repetitive units such as oligocyclopropanes are highly interesting, but usually cannot be easily determined. In the case of oligocyclopropanedimethanols, some partially contradicting X-ray structures have been published. Barrett et al. found for the all-*syn*,*trans*-tercyclopropanedimethanol **27**, an intermediate in

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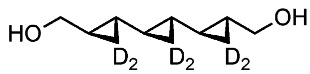


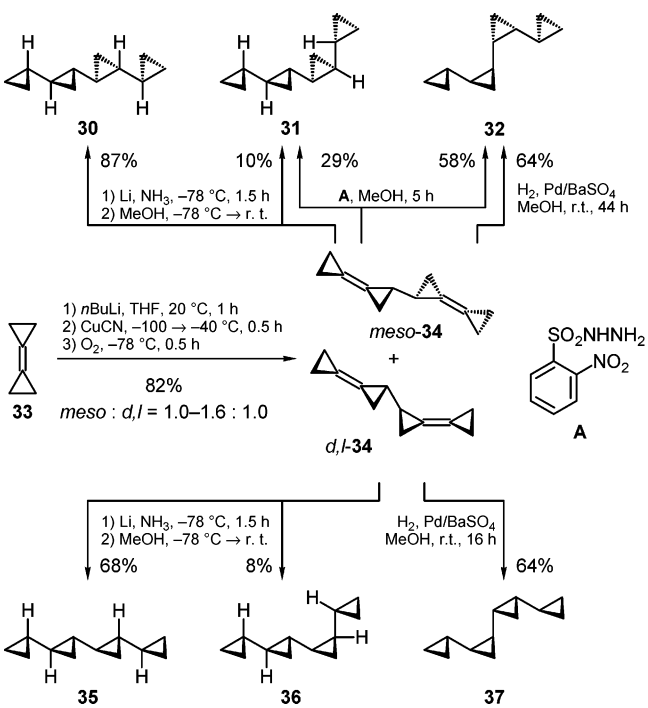
28

29

their total synthesis of U-103605, interunit dihedral angles of +49.7° and −58.6° between two adjacent cyclopropane moieties, which breaks the symmetry for the prevailing conformation in the solid state.[40] In contrast to these findings, the crystal structure of all-*syn*,*trans*-quinquecyclopropanedimethanol **29** shows all interunit dihedral angles as corresponding to (+)-*gauche*.[35] To resolve these putative contradictions, which may be due to packing effects, an NMR study on the partially deuterated all-*syn*,*trans*-tercyclopropanedimethanol **28** in combination with quantum chemical calculations was undertaken.[41] The interunit dihedral angles were both found to be +40° causing the molecule to assume a helical conformation in accordance with the crystal structure published by Charette et al.[35]

All six diastereomeric unsubstituted quatercyclopropanes have been obtained by oxidative coupling of bicyclopropylidene (**33**) to give *meso*- (*meso*-**34**) and *d*,*l*-bis(bicyclopropylidenyl) (*d*,*l*-**34**), which subsequently were reduced either under Birch conditions with diimine or by catalytic hydrogenation to give quatercyclopropanes **30**−**32** and **35**−**37** (Scheme 4).[42] The geometrical parameters of **30** and **32** in

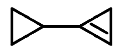
Scheme 4



the solid state could be determined by X-ray structure analyses. In both isomers, the central bicyclopropyl unit was found to be *s-trans* oriented, whereas the outer bicyclopropyl moieties adopt *gauche* conformations.[42] In order to be able to study the conformational behavior in solutions, fully deuterated analogues of the bis(bicyclopropylidenyl)s *meso*-[D_{14}]-**34** and *d*,*l*-[D_{14}]-**34** were subjected to Birch reduction conditions giving the analogues of the *trans*,*trans*-diastereomers **30** and **35** and the *cis*,*trans*-isomers **31** and **36** in which all hydrogens except those explicitly given in Scheme 4 were replaced by deuterium.[42] In this way, the conformations of the outer bicyclopropyl moieties could be deduced by determining the vicinal coupling constants $\langle ^3J_{H,H} \rangle$ for the remaining methyne hydrogens and comparing them with the value obtained for bicyclopropyl (**1**). In **30**, the *gauche* conformation for the outer bicyclopropyl moieties is more strongly preferred than in bicyclopropyl (**1**) itself. Judged by the $\langle ^3J_{H,H} \rangle$ values, the predominance of this conformation decreases on going from **30** via **35** and **31** to **36**. These results were corroborated by calculations of the enthalpies of formation.[42]

2.2. Oligocyclopropenyl Systems

The highly sensitive 1-cyclopropylcyclopropene (**38**),



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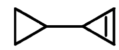

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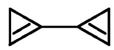

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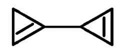

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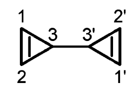
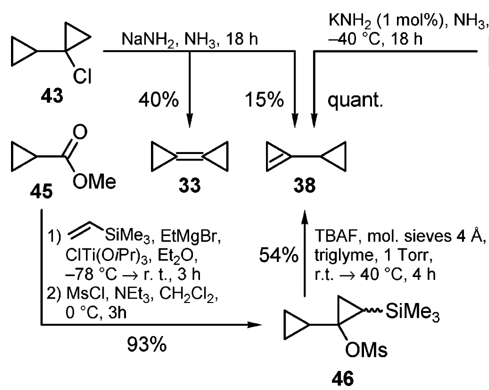


42

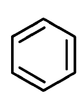
3-cyclopropylcyclopropene (**39**), and the doubly unsaturated bicyclopropenyl isomers **40**−**42** are all related to bicyclopropyl (**1**). 1-Cyclopropylcyclopropene (**38**) was first obtained by potassium amide-mediated dimerization of unsubstituted cyclopropene (**44**) (Scheme 5).[43] Other methods for

Scheme 5



the preparation of **38** rely on elimination reactions of appropiately substituted bicyclopropyls. Thus, Conia et al. reported the dehydrohalogenation of 1-chloro-1-cyclopropylcyclopropane (**43**) with sodium amide to yield a mixture of the kinetically favored product **38** and the more stable isomer bicyclopropylidene (**33**), which arises from **38** by a base-catalyzed rearrangement (Scheme 5).[44] Finally, a Peterson-type elimination of the 1-mesyloxy-2-trimethylsilylbicyclopropyl (**46**) gave **38** in preparatively useful yields (Scheme 5).[45] The isomeric 3-cyclopropylcyclopropene (**39**) was obtained by an ene-type dimerization of cyclopropene (**44**) in solution.[46]

Among the three bicyclopropenyls, especially the 3,3′-isomer **42** has been studied extensively, because it is one of the five conceivable valence isomers of benzene, **47**−**51**.[47]



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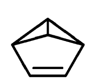

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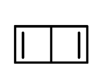

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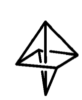

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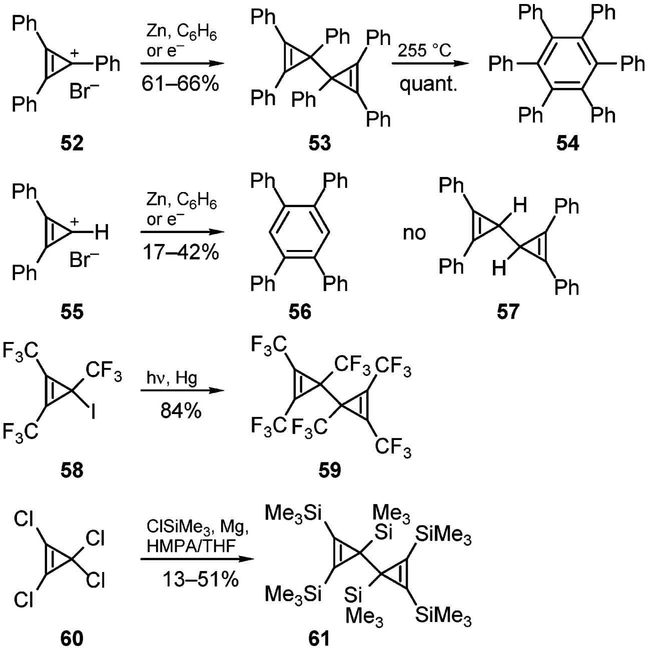
Benzvalene **48** and prismane **50**, which also contain two three-membered carbocycles (see below), as well as "Dewar-benzene" **49**, have been prepared in the last decades,[48] and "benz-Möbius-stripane" **51** most probably cannot exist.

Incidentally, the first substituted representative of any of these isomers ever prepared was hexaphenyl-3,3′-bicyclopropenyl (**53**), whereas the parent **42** was the last of the unsubstituted valence isomers to be isolated. Breslow et al. obtained **53** by reduction of the corresponding cyclopropenylium bromide **52** with zinc (Scheme 6).[49] Upon heating **53** to its melting point, it rearranges to hexaphenylbenzene (**54**) quantitatively within a few seconds.[49]

Scheme 6

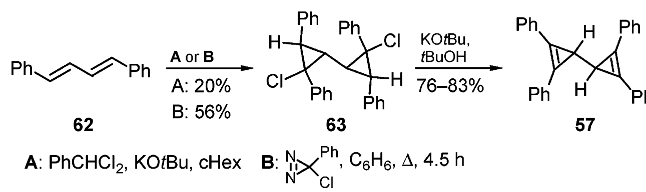


A number of differently substituted analogues were prepared by similar methods. Reduction of ethyl diphenylcyclopropenylium salts with zinc yielded 3,3′-bicyclopropenyls, in which the three-membered rings are connected at the phenyl-bearing carbons.[50] A systematic study on *n*-propyl- and phenyl-substituted cyclopropenylium salts showed that chromium(II) as a reducing agent led to the same selectivity and that phenyl substituents accelerated the reaction significantly.[51] Reductive dimerization of diphenylcyclopropenylium bromide (**55**) with zinc failed to give any isolable tetraphenyl-3,3′-bicyclopropenyl (**57**), but yielded 1,2,4,5-tetraphenylbenzene (**56**) directly.[50] Hexakis(trifluoromethyl)bicyclopropenyl (**59**) could be obtained by photolysis of 3-iodo-1,2,3-tris(trifluoromethyl)cyclopropene (**58**) in the presence of mercury.[52] The synthesis of hexakis(trimethylsilyl)-3,3′-bicyclopropenyl (**61**) by reaction of tetrachlorocyclopropene (**60**) with magnesium in the presence of chlorotrimethylsilane was published independently by two groups.[53] Differently substituted silyl derivatives are accessible in the same fashion.[53a]

Another feasible access to 3,3′-bicyclopropenyls is by electrochemical reduction of cyclopropenylium salts. Electrolysis of **52** at a voltage corresponding to the first wave measured by cyclic voltammetry (−0.7 V vs SCE) afforded the dimer **53**, but when diphenylcyclopropenylium bromide (**55**) was reacted under the same conditions, only 1,2,4,5-tetraphenylbenzene (**56**) was obtained.[54] Hexaphenylbicyclopropenyl (**53**) was also prepared along other routes from triphenylcyclopropenylium salts.[55] The synthesis of hexakis(trimethylsilyl)-3,3′-bicylopropenyl (**61**) was also accomplished by electrochemical reduction.[56]

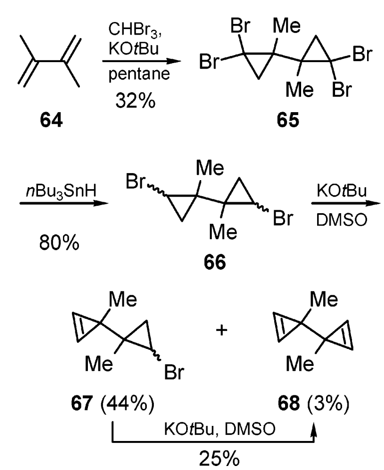
1,1′,2,2′-Tetraphenyl-3,3′-bicyclopropenyl (**57**) could be obtained by 2-fold chlorophenylcarbene addition to 1,4-diphenyl-1,3-butadiene (**62**) and subsequent 2-fold dehydrochlorination with potassium *tert*-butoxide (Scheme 7).[50,57]

Scheme 7



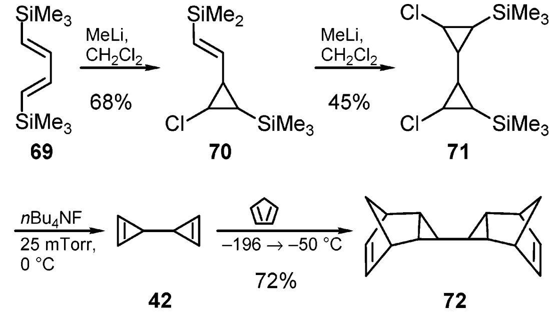
A similar approach actually led to 3,3′-dimethylbicyclopropenyl **68**. Although an attempted Hofmann degradation of 1,1′-dimethyl-2,2′-bis(trimethylammonio)bicyclopropyl diiodide failed,[58] the dehydrobromination of a mixture of stereoisomeric 2,2′-dibromo-1,1′-dimethylbicyclopropyl (**66**), prepared by tributyltin hydride reduction of the tetrabromide **65**, yielded the desired bicyclopropenyl **68**, albeit in a very low yield (3%).[59] The major product was the (bromocyclopropyl)cyclopropene **67**, which, after isolation, could be converted to **68** in a yield of 25% (Scheme 8).[59]

Scheme 8



The unsubstituted parent hydrocarbons **41** and **42** were first prepared in 1989 by chlorocarbene addition to 1,4-bis(trimethylsilyl)-1,3-butadiene (**69**) followed by vacuum gas−solid reaction (VGSR) with tetrabutylammonium fluoride (Scheme 9). When the receiving cold trap was

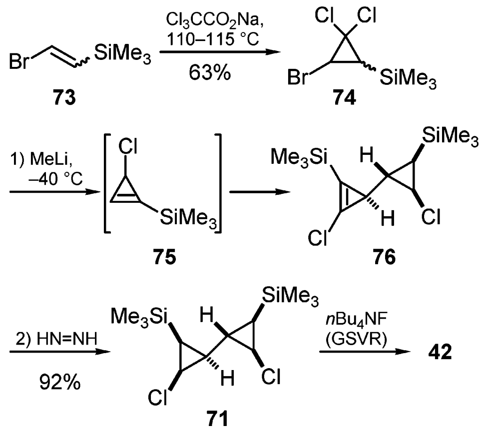
Scheme 9



charged with cyclopentadiene, the Diels−Alder adduct **72** resulting from **42** was obtained.[60] Although already announced in 1989, the generation of **40** was only published in 1994.[61]

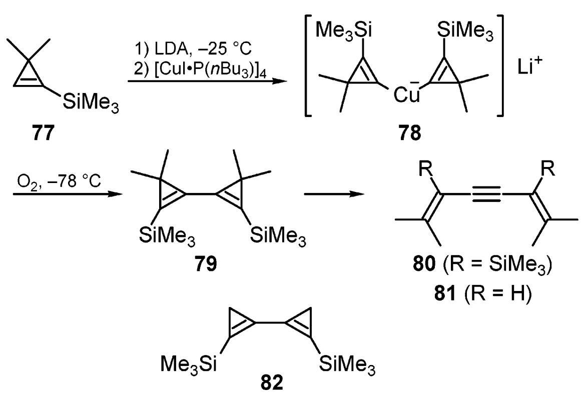
A higher yielding preparation of **42** utilized an ene reaction between 1-chloro-3-trimethylsilylcyclopropene **75** and subsequent diimine reduction to furnish **71** in a one-pot process (Scheme 10).[62]

Scheme 10



The first example of a 1,1′-bicyclopropenyl was reported by Szeimies et al.[63] Lithiation of 3,3′-dimethyl-1-trimethylsilylcyclopropene (**77**), its tranformation to the cuprate **78**, and oxidative coupling of the two cyclopropenyl moieties afforded the 2,2′-bis(trimethylsilyl)-1,1′-bicyclopropenyl (**79**) in 30% overall yield (Scheme 11).

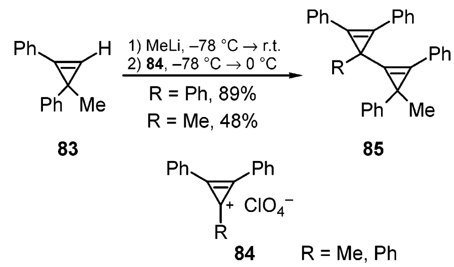
Scheme 11



The trimethylsilyl groups proved to be essential for the survival of this compound. Attempted desilylation with cesium fluoride led to isomerization to **81**. Under flash vacuum pyrolysis conditions, upon heating in ethereal solutions, or upon exposure to silver tetrafluoroborate, **79** also isomerized to **80**.[63] The yield of **79** was improved to 57% using slightly modified conditions. The synthesis of the 2,2′-bis(trimethylsilyl)-1,1′-bicyclopropenyl (**82**) was also accomplished under these modified conditions, but only in 5% yield.[64]

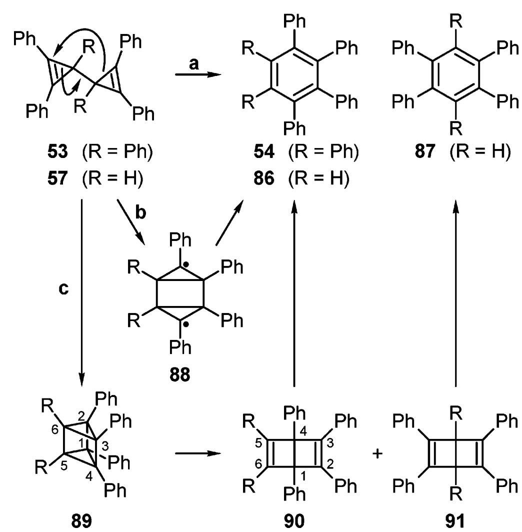
Examples of 1,3′-bicyclopropenyls **85** have been realized by Padwa et al.[65] by deprotonation of 3-methyl-1,3-diphenylcyclopropene **83** with methyllithium and subsequent reaction of the lithio compound with cyclopropenylium salts **84** (Scheme 12).

Scheme 12



The most prominent reactions of the bicyclopropenyls are thermal and photochemical isomerizations to benzene derivatives, as was first reported by Breslow et al.[49] Later on, the same authors suggested three different mechanistic possibilities.[50] The "direct" pathway (a) requires simultaneous breaking of two single bonds and formation of a single and a double bond. Along route (b), homolytic cleavage of one π-bond yields a diradical with a new single bond. The third pathway, (c), involves the prismane intermediate **89**, which requires a sequence of [2 + 2] cycloaddition, [2 + 2] cycloreversion, and further rearrangement of a Dewar benzene to a benzene derivative (Scheme 13).

Scheme 13

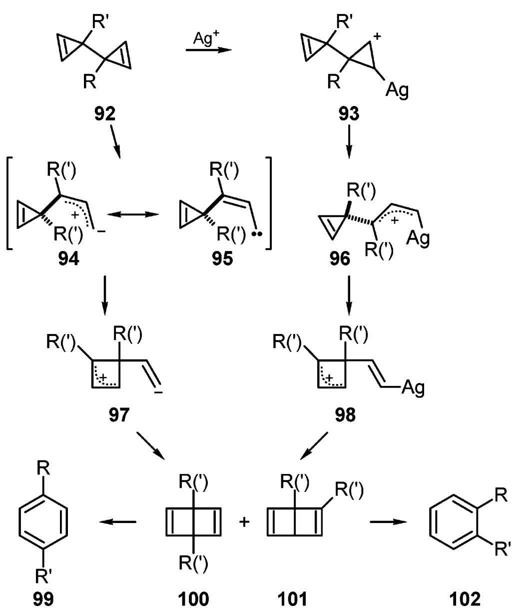


All three of these proposed mechanisms hold as long as the uniformly substituted bicyclopropenyl **53** is concerned. However, the thermolysis of the nonuniformly substituted **57** yielded 1:10 (135 °C) and 1:3.5 (300 °C) mixtures of 1,2,3,4-tetraphenylbenzene (**86**) and its 1,2,4,5-isomer **87**. The authors concluded that these products could only have been formed along path (c), because in the common prismane intermediate **89** (R = H), the [2 + 2] cycloreversion can take place by cleavage either of the C3−C6 and C4−C5 bonds to give the Dewar benzene **90** (R = H) or of the C2−C6 and C1−C5 bonds leading to the Dewar benzene **91** (R = H). The latter compound subsequently rearranges to 1,2,4,5-tetraphenylbenzene (**87**).

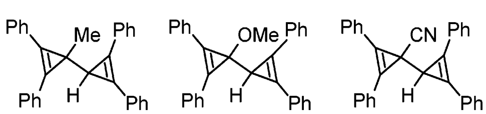
Weiss et al. found a silver salt-promoted rearrangement of the bicyclopropenyl **57** to the Dewar benzene **91** (R = H).[66] Analogous results were reported by Bickelhaupt et al. on the 3,3′-dimethyl-3,3′-bicyclopropenyl (**68**).[67] However, apart from the expected 1,4-dimethyl-substituted Dewar benzene **100**, the unexpected 1,2-derivative **101** was found along with the rearrangement products, *p*-xylene and *o*-xylene.

Weiss et al. proposed a new mechanistic rationalization, which reconciled all known results.[68] After an initial cycloreversion of one cyclopropene moiety to give the vinylcarbene **94** and ensuing cyclopropenylmethyl to cyclobutenyl cation rearrangement, ring closure would form a Dewar benzene, **100** or **101**, which, in turn, can rearrange to the benzene derivatives. The silver salt-promoted reaction should follow a similar route. Addition of a silver cation to a double bond in **92** and ring opening of the thus formed silver-substituted cyclopropyl cation **93** would give the correspondingly substituted allyl cation **96**, which would also undergo ring enlargement to **98** and then ring closure to a Dewar benzene derivative (Scheme 14).

Scheme 14



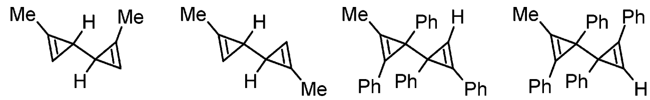
Donor substituents as in **103** and **104** accelerate the rearrangement, whereas electron-withdrawing substituents as in **105** completely prevent it.[69]



103 **104** **105**

The intermediacy of a prismane in the photochemical rearrangement of 3,3′-bicyclopropenyl was ruled out by Weiss et al.[70] Silver salt-catalyzed rearrangement of **103** furnishes a Dewar benzene of type **100**, which in turn gives a prismane upon irradiation. The succeeding reactions of this prismane should be the same regardless of its mode of generation, and thus photolysis of a bicyclopropenyl and the corresponding Dewar benzene should yield the same product mixture, if a prismane were an intermediate. However, photolysis of the bicyclopropenyl **103** furnished the benzene derivatives with the hydrogen and methyl groups in *ortho*- and *meta*-positions, whereas photolysis of the Dewar benzene gave the *ortho* and *para* analogues without any *meta* product.[70]

A thermal or photochemical Cope rearrangement proceeding via a diradical intermediate was proposed to explain the interconversion of bicyclopropenyls **68** and **103** with their isomeric counterparts (**106** and **107** in the case of **68**, **108** and **109** in the case of **103**).[71,72]

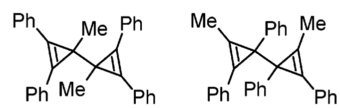


106 **107** **108** **109**
(*d*,*l*) (*meso*)

Bergman et al. carefully analyzed the proportions of all three xylenes obtained upon gas-phase thermolysis of bicyclopropenyl **68** and the diastereomers **106** and **107**. Judging from reaction rates and product distributions at low conversion, the authors concluded that the first step of the isomerization ought to be the ring opening of one of the cyclopropenes, ring enlargement, ring closure to a Dewar benzene, and finally its isomerization to the benzenes.[73,74]

The behavior of photochemically generated radical cations of 3,3′-dimethyl-3,3′-bicyclopropenyl **68** was studied by Abelt and Roth.[75] Based on the results of chemically induced dynamic nuclear polarization (CIDNP) experiments, they postulated a dimethylbenzvalene **111** to be formed from the

110 **111**



112 **113**

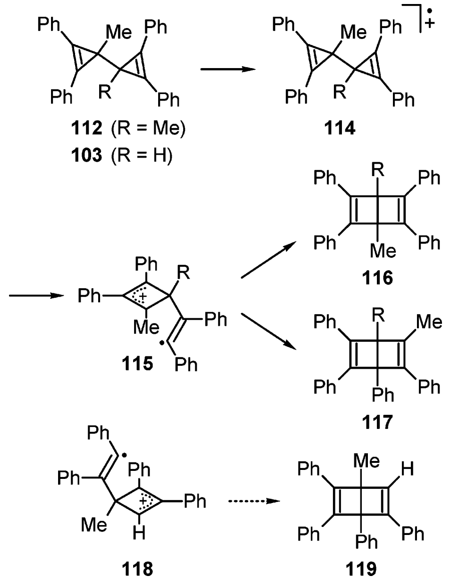
initially generated tricyclo[3.1.0.0^{2,4}]hexane radical cation **110** during the aromatization to *ortho*- and *para*-xylenes. This is in marked contrast to the mechanistic proposals for the other types of isomerization. Similar results have been published by Padwa et al. based on studies of photochemically generated radical cations from bicyclopropenyls **116** and **117**, although they did not propose a benzvalene intermediate.[57]

More recently, Ikeda et al. reinvestigated the photoinduced electron-transfer reactions of bicyclopropenyls **112** and **103**.[76] According to their mechanistic proposal, the initial radical cation **114** should undergo ring enlargement analogously to the mechanism proposed for the thermal or silver-catalyzed rearrangement by Weiss et al.[68] and Bergman et al.[74] The new cyclobutenyl radical cation **115** undergoes ring closure to either of the two Dewar benzene radical cations, which subsequently experience back electron transfer to give **116** or **117** (Scheme 15).

Alternatively, **118** could have been formed from **103**, but **119**, which ought to have been formed from **118**, was not observed, apparently because **115** (R = H) is energetically favored over **118**.

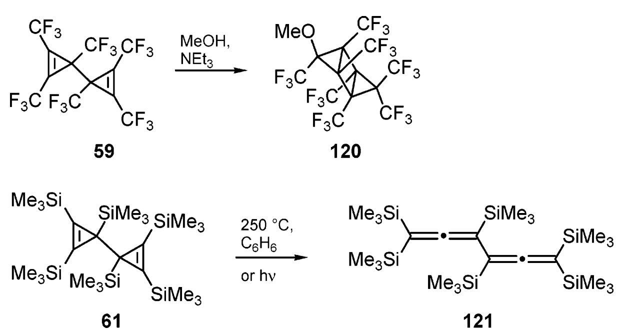
Hexakis(trifluoromethyl)-3,3′-bicyclopropenyl (**59**) is somewhat remarkable in its reactivity. Although it cleanly rearranges to the expected hexakis(trifluoromethyl)benzene on heating, its half-life is longer than 2 h at 360 °C,[52] whereas the hexaphenyl analogue **53** rearranged completely within a few seconds at 255 °C.[49] Greenberg et al., in a combined theoretical and calorimetric study, found that trifluoromethyl groups do not stabilize or destabilize thermodynamically

Scheme 15



strained and unsaturated compounds, but kinetically stabilize such molecules due to steric encumbrance.[77] Upon irradiation of **59**, a complex mixture of valence isomers was formed.[52] Interestingly, a very facile addition of methanol onto **59** led to 2-methoxyhexakis(trifluoromethyl)tricyclo[3.1.0.0^{2,4}]hexane (**120**) (Scheme 16).[52]

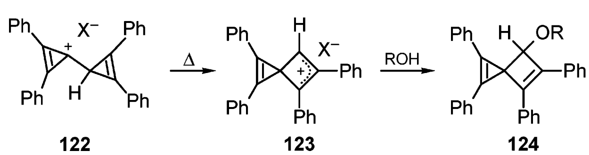
Scheme 16



Hexakis(trimethylsilyl)-3,3′-bicyclopropenyl (**61**) also exhibited a unique reactivity, because it did not thermally or photochemically rearrange to hexakis(trimethylsilyl)benzene but to hexakis(trimethylsilyl)hexa-1,2,4,5-tetraene (**121**).[53a]

Weiss et al. also studied the rearrangement of cyclopropenylcyclopropenylium cation **122** derived from the methoxy-substituted **104** or the hydroxy analogue. Instead of the expected Dewar benzene cation, they found, after quenching the rearranged cation with methanol or water, the spirohexadiene derivative **124**, which proved to be stable under the reaction conditions and also stable toward silver cations (Scheme 17).[78]

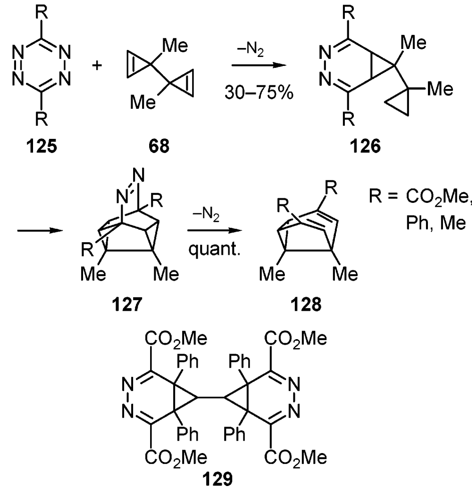
Scheme 17



An unexpected rearrangement of the tetraphenylbicyclopropenyl **57** was found upon exposure to nonacarbonyldiiron to give a complex of 2,3,5,7-tetraphenyl-2,4,6-cycloheptatriene η^4-coordinated to an $Fe(CO)_3$ fragment.[79]

Dimethylbicyclopropenyl **68** was reported to react with symmetrically disubstituted tetrazines **125** to yield tetrasubstituted semibullvalenes **128**. The proposed intermediate diazasnoutene **127** could not be isolated (Scheme 18). An

Scheme 18



analogous reaction with the tetraphenylbicyclopropenyl **57** led to the 1:2 adduct **129** with two linked diazanorcaradiene units.[80]

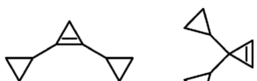
Such [4 + 2] cycloadditions of 3,3′-bicyclopropenyls were also performed with triazines,[81] α-pyrons,[81] 1,3,4-oxadiazoles,[82] and unsymmetrically substituted tetrazines.[83]

Interesting rearrangements of 3,3′-bicyclopropenyl as a valence isomer of benzene have also triggered a number of theoretical investigations. Castenmiller and Buck were the first to report on results of semiempirical MINDO/3 and ab initio calculations at the STO-3G level of theory for various structures on the $C_6H_5^+$ potential energy surface.[84] Greenberg and Liebman calculated relative energies of the unsubstituted and various monosubstituted valence isomers of benzene at the STO-3G level of theory, including several conformations for the bicyclopropenyls.[85]

Calculations at the RHF/STO-3G level of theory[86] predicted a slight (190 cal/mol) preference for the *s-trans* conformer of 2,2′,3,3,3′,3′-hexamethyl-1,1′-bicyclopropenyl. For unsubstituted 3,3′-bicyclopropenyl, detailed rotational profiles have been obtained at the RHF/STO-3G and RHF/4-31G level of theory.[87] In close analogy to bicyclopropyl, a *gauche* ($\varphi = 45°$) and the *s-trans* conformer ($\varphi = 180°$) differ in energy only by a small margin (100 cal/mol) but in favor of the latter. These calculations also disclosed a pronounced "through-bond" $\pi-\pi$ interaction in all studied conformations,[87] and these interactions have been confirmed by photoelectron spectroscopy.[88] According to an X-ray crystallographic determination, the unsubstituted 3,3′-bicyclopropenyl (**42**) adopts the *s-trans* conformation in the crystal. The He(I)-PE spectrum of **42** could be best interpreted by assuming a 2:1 mixture of the *s-trans* and *gauche* conformers.[61]

At the RMP2/6-31G* level of theory using homodesmic reactions, the heat of formation for benzvalene (**48**) (90.2 kcal/mol) was calculated to be lower than that for Dewar benzene (**49**) (94.0 kcal/mol), while those for prismane (**50**) and 3,3′-bicyclopropenyl (**42**) were found to be close to each other around 137 kcal/mol.[89] Using isodesmic reactions and an atomization scheme, the heats of formation were recalculated with several G2- and CBS-based ab initio methods.[90] Independently, the same approach was used at the G2 level of theory by another group on a larger set of molecules.[91] Both groups reported very good agreement for the calculated enthalpy of formation of benzene with the experimental value and predicted the calculated heats of formation at this level of theory to be quite reliable (1−3 kcal/mol off) in general. The former group later also used the G3 ab initio method to recalculate the heats of formation. Whereas the G3 method proved to be superior when the atomization scheme was applied, it did not give significantly better results when used together with the isodesmic bond separation scheme.[92]

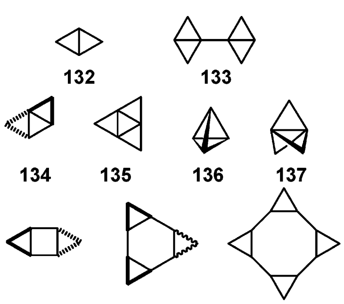
Only two higher oligocyclopropyl systems containing a cyclopropenyl group have been reported. Schipperjin et al. obtained not only 1-cyclopropylcyclopropene (**38**) when treating cyclopropene (**44**) with alkali metal amides (see Scheme 5) but also 1,2-dicyclopropylcyclopropene (**130**) in 40% yield when using 1.2 equiv of sodium amide.[43] The 3,3-dicyclopropylcyclopropene (**131**) will be discussed in section 2.4.



130 **131**

2.3. Fused Systems

Interesting cyclopropane assemblies also arise by consecutive 1,2-fusion of cyclopropane rings to cyclopropane itself (structures **132**−**137**) or to larger carbocycles (structures **138**−**140**).



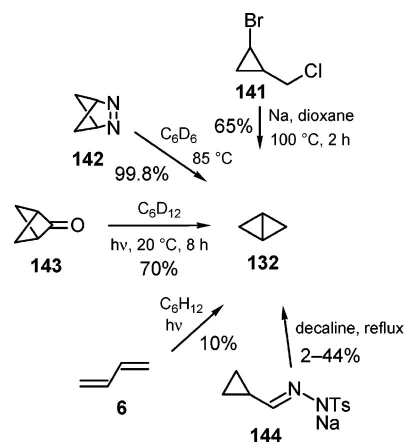
132 **133** **134** **135** **136** **137** **138** **139** **140**

Naturally, the strain energies of these compounds differ drastically; in fact, on going from **132** to **137**, some or all of the cyclopropane bonds become more and more "bent",[93] and [1.1.1]propellane **137** has two inverted[94] carbon atoms. For all these hydrocarbons the total strain energy (SE) of the molecule significantly exceeds the sum of SE's of its components. Thus, for bicyclo[1.1.0]butane (**132**) SE_{exp} = 66.5 versus $\sum 2SE_{cyclopropane}$ = 56.3,[95] for tricyclo[2.1.0.0^{1,3}]pentane (**134**) SE_{calcd} = 134.7[96] versus $\sum 3SE_{cyclopropane}$ = 84.4,[95] for tricyclo[1.1.0.0^{2,4}]butane (tetrahedrane, **136**) SE_{calcd} = 132.8[95,97] (140.8[98a,b]) versus $\sum 4SE_{cyclopropane}$ = 112.5,[95] and for [1.1.1]propellane (**137**) SE_{calcd} = 104.2[98a,b] (98.2[98c]) versus $\sum 3SE_{cyclopropane}$ = 84.4[95] kcal/mol. As a consequence of this increased ring strain, going along with a change in hybridization, the cyclopropane derivatives **132**−**137** show a pronounced tendency to undergo ring-opening reactions as well as enhanced C−H acidities.[99]

On the other side, the changes in hydridization on going from **138** to **140** are less significant, and the total SEs of tricyclo[3.1.0.0^{2,4}]hexane (**138**), tetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane (**139**), and pentacyclo[9.1.0.0^{2,4}.0^{5,7}.0^{8,10}]dodecane (**140**) only slightly differ from the sums of SEs of their constituting monocycles [e.g., **138** SE_{calcd} = 83.1[100] versus $\sum SE_{cycl}$ = 83.2;[95] *cis*-**139** (*cis*-[1.1.1]-tris-σ-homobenzene) SE_{calcd} = 85.6[95,101] versus $\sum SE_{cycl}$ = 85.7 kcal/mol[3]]. The latter, however, still remains elusive[102] but has been estimated to undergo a very facile [$\sigma^2_s + \sigma^2_s + \sigma^2_s$] cycloreversion (see below)[103] with an activation enthalpy of $\Delta H^{\ddagger}$ = 23.4−25.8 kcal/mol.[104]

The histories, preparations, and chemical transformations of bicyclobutane (**132**),[105] tetrahedrane (**136**),[106] [1.1.1]-propellane (**137**),[107] and tetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane (**139**),[108] as well as of their functional derivatives, have been reviewed in various contexts. The parent hydrocarbon **132** has been prepared from different C_4-building blocks in several ways (Scheme 19), such as intramolecular reductive ring closure in (2-bromocyclopropyl)methyl chloride (**141**),[109] thermally induced extrusion of nitrogen from the bicyclic diazo compound **142**,[110a] photochemical decarbonylation of the bicyclic ketone **143**,[110b] photochemical bicyclization of 1,3-butadiene (**6**),[111] and thermal fragmentation of the sodium salt of cyclopropanecarboxaldehyde tosylhydrazone **144**.[112]

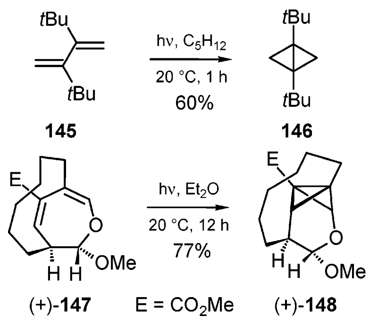
Scheme 19



Unfortunately, the simplest approach by photolysis of 1,3-butadiene (**6**)[105c,111] produces cyclobutene mainly and the parent bicyclobutane (**132**) only in traces. Therefore, this transformation is mostly of theoretical interest,[113] but Hopf et al.[114a] have shown that direct irradiation (450 W Hg high-pressure lamp) of 2,3-di-*tert*-butylbuta-1,3-diene (**145**) in dilute solution yields 1,3-di-*tert*-butylbicyclo[1.1.0]butane (**146**) as the only photoproduct (60% after 60 min) (Scheme 20). Under similar conditions, the enantiomerically pure bridged dihydrooxepine (+)-**147** is stereoselectively transformed to the enantiomerically pure bridged bicyclobutane derivative (+)-**148** in 77% yield (Scheme 20).[114b]

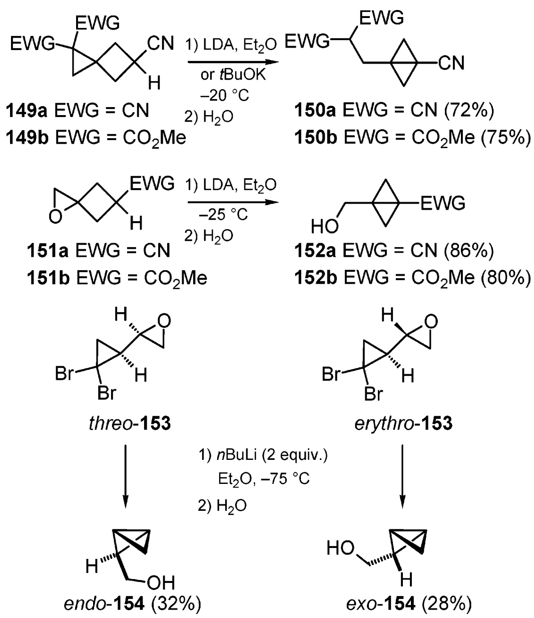
The preparation of functionally substituted bicyclobutanes has been reviewed comprehensively.[105d−f] Among the established methods, the ones in which the central bond of the bicyclobutane moiety was closed by intramolecular anion-induced nucleophilic ring opening of a carbo- or heterocyclic[115] three-membered ring spiroannelated in the 3-position of an acceptor-substituted cyclobutane fragment (Scheme 21), have experienced some further development. Thus, treatment of the acceptor-substituted spirohexanes **149**[116a,b] or their oxa

Scheme 20



analogues **151**[116c] with a strong base furnished the bicyclobutane derivatives **150** or **152** in 72−86% yields. In a modified approach originally developed by Gaoni,[115a] dibromooxabicyclopropyls *threo*-**153** and *erythro*-**153** upon treatment with *n*-butyllithium stereoselectively afforded (bicyclobutyl)methanols *endo*-**154** and *exo*-**154**, respectively, albeit in moderate yields (32 and 28%, respectively) (Scheme 21).[117]

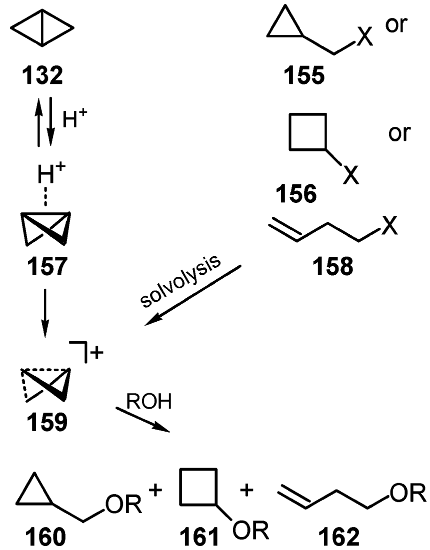
Scheme 21



The bonding and spectroscopic properties of bicyclobutane have been studied extensively in the past,[105,118] but they keep attracting attention.[119] As disclosed from its vibrational spectra,[120] unsubstituted bicyclobutane (**132**) itself contains two undistorted cyclopropane rings [bond length 1.498(3) vs 1.499(1) Å in unsubstituted cyclopropane itself[24]], which are fused with an interplanar angle of 122.7(5)°; however, these parameters are rather sensitive to the position and nature of added substituents.[120b] Thus, in *endo,endo*-bicyclobutane-2,4-dimethanol dimesylate, the central C−C bond is elongated to 1.512 Å, and the interplanar angle was found to be 128.2°.[120c] The barrier of inversion for **132** was calculated to be 47−50 kcal/mol,[121a] but it can be significantly lowered by electron-withdrawing substituents in the 1,3-positions.[121b]

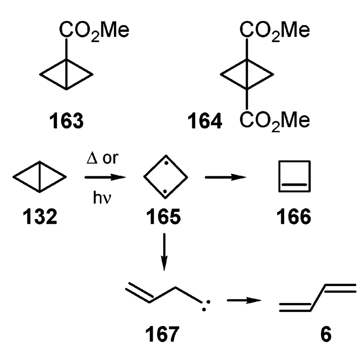
The main chemical feature of bicyclobutane and its derivatives (and in this respect it is very similar to [1.1.1]-propellane (**137**), see below) is their pronounced tendency to undergo reactions with cleavage of the central bond upon attack of electrophiles, nucleophiles, and radicals.[105] Thus, upon protonation, bicyclobutane (**132**, C_4H_6) initially yields the edge-protonated species **157**,[122] which forms the bicyclobutonium cation ($C_4H_7^+$) **159** (Scheme 22).[123] No wonder that bicyclobutanes undergo facile acid-catalyzed C−C bond cleavage at pH values as high as 4.[93a] Attack of an external nucleophile onto **159** leads to the products **160**−**162** in different ratios depending on the substituents. Because the same intermediate **159** can also be produced under solvolysis conditions from compounds of types **155**, **156**, or **158**, the reactions of bicyclobutanes with electrophiles[105a] yield products that are analogous to those derived from cyclopropylmethyl, cyclobutyl, and homoallyl carbocations.[124] Yet, cyclobutane derivatives usually are the main products resulting from reactions of bicyclobutanes with electrophiles,[105a] nucleophiles,[105d] and radicals.[125] From a practical point of view, the observed regioselective anion- and radical-induced central bond opening of methyl bicyclobutane-1-carboxylate (**163**) and dimethyl bicyclobutane-1,3-dicarboxylate (**164**) in polymerization reactions has triggered a broadened investigation, and the polymers resulting from the bicyclobutanes **163** and **164** have been termed "new materials for the 21st century".[126,127]

Scheme 22

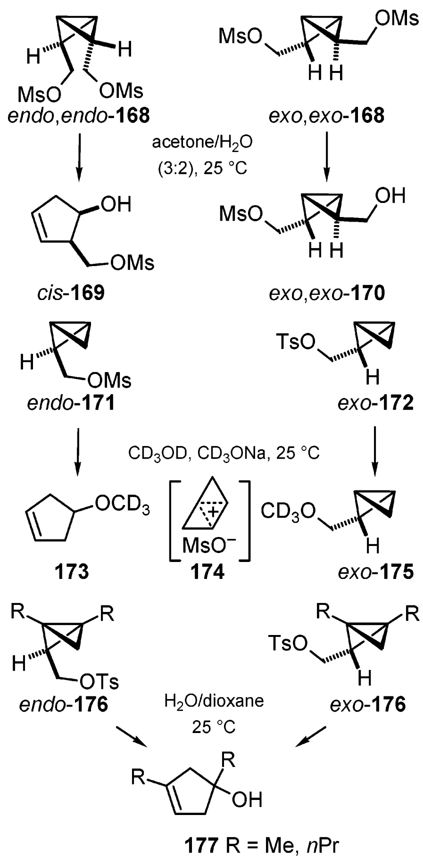


Thermolysis (200 °C), as well as photolysis, of bicyclobutane (**132**) or substituted bicyclobutanes also leads to an initial breakage of the central bond; in the absence of external reactive species, the 1,3-diradical intermediate **165**[128] rearranges to give a mixture of cyclobutene (**166**) and 1,3-butadiene (**6**) (or a complex mixture of their substituted analogues) (Scheme 23).[105c]

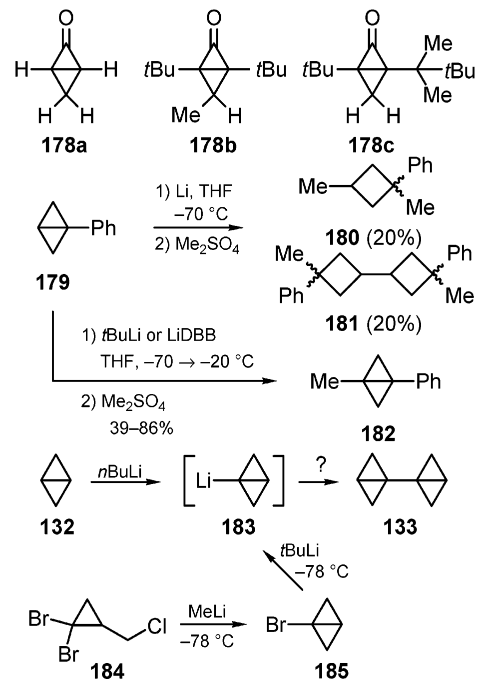
Scheme 23



Scheme 24



Scheme 25



A bicyclobutyl moiety can participate in reactions of an adjacent cationic center in different ways. Thus, solvolysis of *endo*,*endo*-**168** in 40% aqueous acetone gave mainly mesylate of *cis*-(2-hydroxycyclopent-4-ene-1-yl)methanol (*cis*-**169**), while the solvolysis of *exo*,*exo*-**168** proceeded about 8 times more slowly and afforded unrearranged product *exo*,*exo*-**170** exclusively (Scheme 24).[120d]

The monomesylate *endo*-**171**, under solvolytic conditions, reacted at a very similar rate as cyclopropylmethyl mesylate to yield the rearranged product **173** exclusively but about a thousand times faster than the tosylate *exo*-**172**,[117] which underwent substitution of the tosylate group with complete retention of the *exo*-bicyclo[1.1.0]but-2-ylmethyl skeleton in *exo*-**175**. A computational study of the nature of the intermediate bicyclo[1.1.0]but-2-ylcarbinyl cations, in each case at the B3LYP level of theory, disclosed the cation derived from *exo*-**172** to be a local energy minimum, while the cation from *endo*-**171** was found to be only a transition structure that is immediately converted into the nonclassical cyclopent-3-en-1-yl cation (**174**) by a Wagner−Meerwein rearrangement.[117] Alkyl groups at the 1- and 3-positions of *endo*- and *exo*-**172** stabilize such a cation when derived from *exo*-**172** so that the same product **177** is formed upon solvolysis of both *endo*- and *exo*-**176**.[117,129]

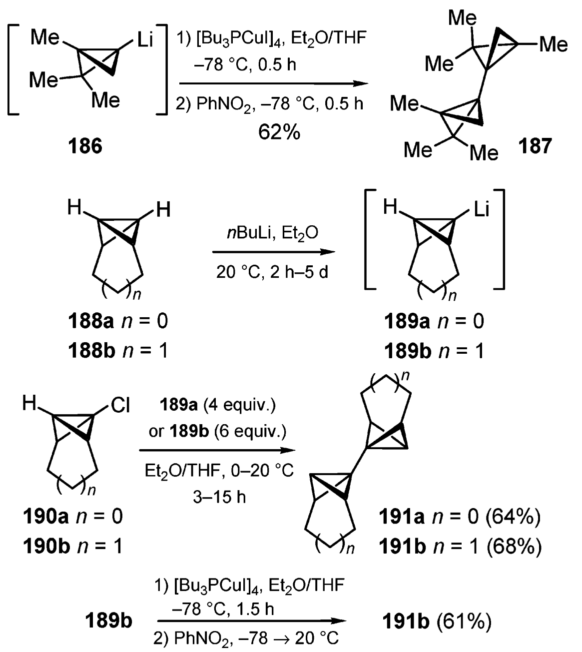
As in the case of tetrahedrane (**136**) (see below), bulky substituents at the bridgehead positions can kinetically stabilize otherwise unstable derivatives of bicyclobutane (**132**). Thus, while the unsubstituted bicyclobutanone **178a** remains elusive, its di-*tert*-butyl (**178b**) and 3-*tert*-butyl-1-(dimethylneopentyl) (**178c**) derivatives (Scheme 25) turned out to be stable enough to be analyzed by X-ray diffraction.[130] The latter revealed the central C1−C3 bond to be extremely long [1.691(5) Å].

Another interesting piece of chemistry of bicyclobutanes results from their enhanced C−H acidity.[99] Indeed, while phenylbicyclobutane **179** is reduced by metallic lithium across the central bond to give 1,3-dilithio-1-phenylcyclobutane, which could be methylated with dimethyl sulfate to yield the dimethylcyclobutane **180** and the dimethylbicyclobutyl derivative **181**, treatment of **179** with *tert*-butyllithium or lithium di-*tert*-butylbiphenyl (LDBB) led to deprotonation, and subsequent methylation produced the bicyclobutane derivative **182** in 39% and 86% yield, respectively (Scheme 25).[131] Analogously, deprotonation of **132** with *n*-butyllithium led to the potentially useful lithiobicyclobutane **183**, which so far was obtained from (dibromocyclopropyl)methyl chloride **184** along a route similar to the one applied in the preparation of [1.1.1]propellane (see below) (Scheme 25).[132] Whereas bis(bicyclo[1.1.0]butyl) **133**, which in principle should be accessible by oxidative dimerization of **183**, is still elusive, the dimer **187** obtained in 62% yield from the lithiotrimethylbicyclobutane **186** as a mixture of two diastereomers turned out to be kinetically more stable (Scheme 26).[133]

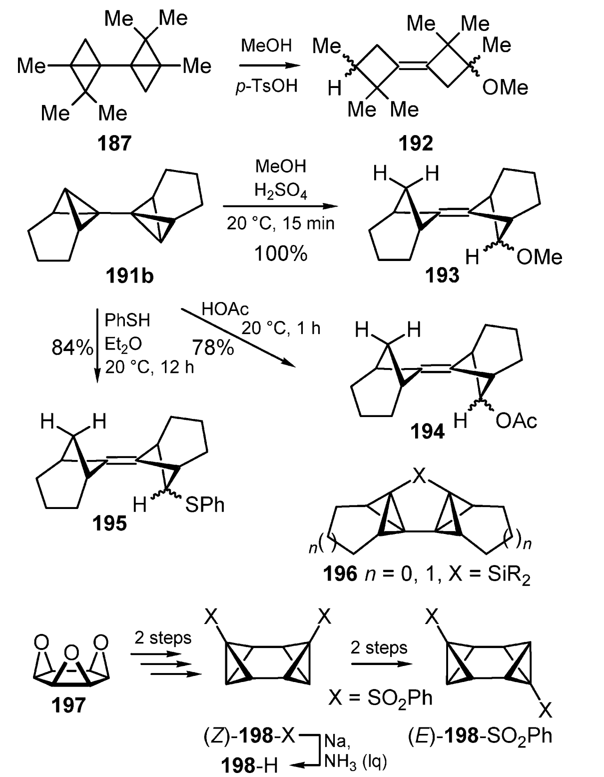
The same procedure could be applied to the lithiated trimethylene-bridged bicyclobutane **189b** to give the corresponding bis(bicyclobutyl) **191b** in 61% yield. The lithiobicyclobutanes **189a**,**b** could also be directly coupled with the corresponding chlorides **190a**,**b** to furnish the dimethylene- and trimethylene-bridged bi(bicyclo[1.1.0]butyl)s **191a**,**b** in good yield.[134a,b] However, the latter procedure required a 4−6-fold excess of the lithiobicyclobutane **189**, while the oxidative coupling of the cuprates derived from **189** is significantly more efficient.[134b] Presumably, the coupling of Grignard reagents derived from **189** under catalysis with [1,2-bis(diphenylphosphanyl)ethane]nickel dichloride or certain iron complexes[134c,d] would be even more efficient, yet this approach has not been elaborated in detail.

Bis(bicyclo[1.1.0]butyl)s of this type [and also bis-(tetrahedranyl), see below] represent interesting cases with respect to bond theory because they are examples of conjugation in formally saturated systems. As a result, the

Scheme 26



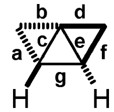
Scheme 27



bond between the two bicyclobutyl moieties should be shortened to 1.467 Å, as calculated at the 6-31G* level of theory for the hypothetical parent hydrocarbon **133**.[135a] Indeed, X-ray crystal structure analyses of the derivatives **191a**,**b** disclosed the bond between the two bicyclobutyl moieties to be shortened [1.445(3) Å], while the central bonds in the bicyclobutane fragments were found to be lengthened [1.547(2) Å].[135b] These data are in accord with the results of DFT computations (1.456 vs 1.534 Å)[136] and indicate that these molecules in the ground state should be predisposed for reorganizations. Thus, while breakage of the central bond in bicyclobutane (**132**) to form the cyclobutyl 1,3-diradical **165** (Scheme 23) is endothermic by ca. 41 kcal/mol,[133] opening of both central bonds in **133** is endothermic by only ca. 25 kcal/mol. As expected, the known derivatives of **133** are highly reactive toward electrophiles. For example, methanol under acid catalysis undergoes a 1,4-type addition across the two central bonds in **187** to yield the adduct **192**.[133] An analogous behavior toward electrophiles was reported for compounds **191a**,**b** (Scheme 27).[134b]

On the other hand, either of the two remaining bridgehead positions in **191a**,**b** can be deprotonated again and the lithiated species transformed to 2-fold bridged bis(bicyclo-[1.1.0]butyl)s of type **196a**,**b** (Scheme 27).[137] An interesting tetrahydrodimer of bicyclobutane, octabisvalene **198**-H, was prepared in three steps from 3,6,9-trioxatetracyclo[6.1.0.0^{2,4}.0^{5,7}]-nonane (*cis*-trioxatrishomobenzene) (**197**) via the bis(phenylsulfonyl) derivative (*Z*)-**198**-SO_2Ph; the latter and the $(CH)_8$ hydrocarbon **198**-H exhibited enhanced C,H acidity and other remarkable chemical properties.[138]

Fusion of a third cyclopropane ring to any of the outer edges in bicyclobutane (**1**) leads to the extremely strained tricyclo[2.1.0.0^{1,3}]pentane (**134**), an isomer of [1.1.1]propellane (**137**). The preferred symmetry of **134** with a pyramidally tetracoordinated carbon atom was predicted to be C_1 and not C_2, as might be expected.[139] This hydrocarbon has attracted a good deal of attention, and a number of theoretical studies have been published (see Table 1).



134

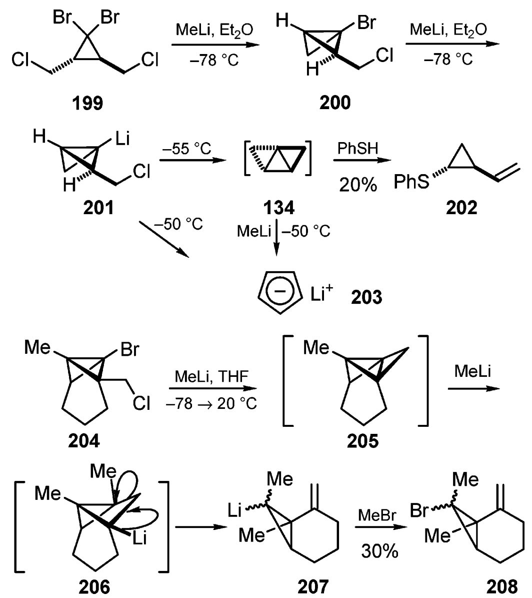
All of these indicate that the structure **134** is a minimum on the C_5H_6 energy hypersurface but comes along with a strain energy of 134.7−143 kcal/mol, that is, 26.9−28.6 kcal/mol per carbon atom, which makes it one of the most highly strained of all known organic compounds. No wonder that tricyclopentane **134** has never been isolated in pure form, but could only be detected as an intermediate independently by two research groups. Wiberg et al.[140] demonstrated that the reaction of *trans*-1,1-dibromo-2,3-bis(chloromethyl)-cyclopropane (**199**) with methyllithium at −78 °C initially leads to the unstable 1-bromo-2-(chloromethyl)bicyclo[1.1.0]-butane (**200**) (12% yield upon attempted isolation), which, in turn, furnished 1-lithio-2-(chloromethyl)bicyclobutane (**201**) (Scheme 28). The latter reacts at −50 °C to afford lithium cyclopentadienide (**203**). At −55 °C, however, **201** forms an unstable compound, which eventually reacts further with methyllithium to yield **203**, but it could also be trapped with thiophenol to give (2-vinylcyclopropyl) phenyl sulfide (**202**). This trapping experiment as well as the observed signals in the ^{13}C NMR spectrum of the reaction mixture prior to trapping served as evidence that this intermediate possesses the structure of tricyclopentane **134**.

In a similar attempt with the bridged bromo(chloromethyl)-bicyclobutane **204**, the results were even more disappointing, since the bromine−lithium exchange took place only at ambient temperature. However, the formation of the final product **208** was assumed to proceed via the bridged tricyclopentane **205** as an intermediate, which (like [1.1.1]-propellane[107]) adds one additional equivalent of methyllithium across one of its most highly strained bridgehead−bridgehead single bonds to give lithiobicyclo[2.1.0]pentane **206** (Scheme 28), and the latter, after isomerization to **207**

Table 1. Computed Strain Energies (SE) and Geometric Parameters of Tricyclo[2.1.0.0[1,3]]pentane (134)

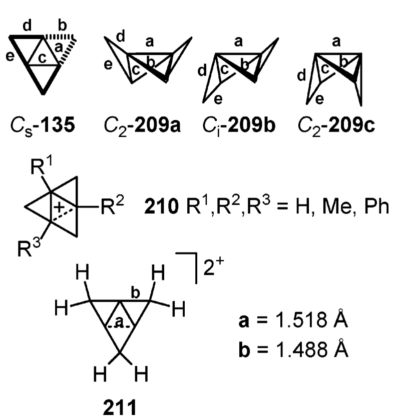
method of computation	SE (kcal/mol)	bond lengths [Å]							ref
		a	b	c	d	e	f	g	
B3LYP/6-31G*	134.7		1.485	1.456	1.489	1.515			96
MP2/6-311+G(2d,p)// MP2/6-31G(d)	139.9								139
MP2/6-31G*	143	1.534	1.492	1.446	1.486	1.577	1.505	1.497	140
B3LYP/6-31G*				1.454		1.519			141
MP2/6-31G*	137.2		1.484	1.491	1.485	1.483		1.536	142
MP2/6-31G*		1.534	1.492	1.446	1.486	1.577	1.505	1.497	143

Scheme 28



and metal−halogen exchange, furnished **208** as a 2.5:1 mixture of diastereomers.[144] Interestingly, the cation derived from **134** was predicted by computations to be relatively stable.[145]

Apart from several preparations of trishomocyclopropenyl cations of type **210** in superacidic media,[146] no experimental



studies directed toward the tetracyclic hydrocarbons **135** and **209** have been published up to now. DFT computations at the B3LYP level of theory predict an enhanced stability for the aromatic planar dication **211** ($C_6H_6^{2+}$) with essentially normal lengths of the cyclopropane-type carbon−carbon bonds.[147]

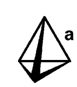
Computations at the B3LYP, MP2, and CCSD(T) levels of theory predict that tetracyclo[3.1.0.0[1,3].0[3,5]]hexane (**135**) and its isomers **209** are energetically high-lying isomers of benzene on the C_6H_6 potential energy surface (Table 2).

Table 2. B3LYP-Computed Strain Energies (SE) and Geometric Parameters of Tetracyclohexanes 135 and 209

hydrocarbon	SE (kcal/mol)	bond lengths [Å]					ref
		a	b	c	d	e	
135	171.3	1.346	1.517	1.861	1.498	1.530	148
135	174.4	1.343	1.517	1.860	1.498	1.527	149a
209b	143.3	1.913	1.460	1.506	1.556	1.476	148
209c	171.3	1.684	1.524	1.440	1.523	1.526	148

Further computations[141] (B3LYP/6-31G*) predicted for **209a** the length of bond a = 1.680 Å and for **209b** a = 1.793 Å; however, **209b** was found to be more stable by 25.5 kcal/mol, and no local minimum was found on the C_6H_6 energy hypersurface for a structure related to **209c**. Consequently, **135** and **209c** are ca. 80 kcal/mol higher in energy than, for example, [3]radialene and 150−160 kcal/mol higher in energy than benzene. The activation energy for the first step in the rearrangement of **135** to [3]radialene was computed to be only ca. 10 kcal/mol,[149a] which might be high enough to isolate **135** in a low-temperature matrix. However, probably only the tetracycle **209b** or the thermodynamically more stable heteroanalogues[149b] may be reasonable targets for a synthetic chemist.

Linking the two methylene moieties in bicyclobutane (**132**) by a carbon−carbon bond formally leads to the esthetically appealing T_d-tricyclo[1.1.0.0[2,4]]butane (tetrahedrane) (**136**).



136

Practically, however, the unsubstituted **136** ought to be unachievable since according to earlier computations, this molecule should have at least twice the strain energy of **132** and be unstable with respect to fragmentation into two acetylene molecules with an exothermicity of 70−100 kcal/mol.[150] Because "nothing is more practical than a good theory" (V. I. Lenin), almost all theoretically oriented chemists considered the computation of this hydrocarbon as a debt of honor. The results of a representative fraction of these studies are summarized in Table 3.

Some chemical properties of **136** have also been predicted by computations. Thus, tetrahedrane (**136**) should have a similar acidity as water, and its deprotonation should yield a stable anion, as predicted at the B3LYP/6-311++G** level of theory.[163] On the other hand, in the gas phase **136** should form a stable complex with hydrogen chloride.[122] The radical cation of tetrahedrane should rearrange to the cyclobutadiene radical cation at 0 K with an activation energy of 4.3 kcal/mol.[164] Even the thermochemical properties of oligonitrotetrahedranes as "potential novel energetic materials" have been predicted applying modern computational methods.[158a,160]

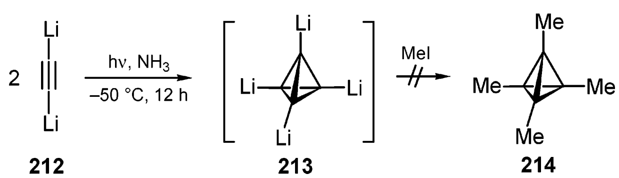
Table 3. Computed Geometric Parameters, Enthalpy of Formation, and Strain Energies (SE) of T_d-Tricyclo[1.1.0.0^{2,4}]butane (Tetrahedrane, 136)

method of computation	a [Å]	ΔH_f°(kcal/mol) (kcal/mol)	SE (kcal/mol)	ref
SCF/4-31G	1.482	129.3	137.0	151
SCF/DZ+D	1.460	134.0	142.6[a]	152
SCF/3-21G	1.489			153
G2		127.4	136.3	154
G2(MP2)		126.6	135.2[a]	155
various	1.463−1.493[b]	114.7−134.7[c]	123.3−143.3[a]	156
B3LYP/6-311+G(3df,2p)		124.2	132.8[a]	97
B3LYP/6-31G	1.473	143.4	152.0[a]	157
B3LYP/6-31G	1.494	125.1	133.7[a]	157
CBS-Q	1.469−1.490[d]	128.4	137.0[a]	158
G3(MP2)/B3LYP		129.9	136.5	159
B3LYP/aug-cc-pvdz	1.485			160
BLYP/TZP	1.488	141.6	150.2[a]	161
B3LYP/6-31G(d)	1.479	132.2	140.8[a]	162

[a] Derived from the calculated ΔH_f° and applying strain-free increments from ref 95. [b] Range as computed applying 24 ab initio and 24 DFT methods. [c] Range as computed applying 7 ab initio and 22 DFT methods. [d] Range as computed applying eight different methods.

A number of attempts to prepare **136** or its derivatives had been undertaken before the first success was achieved. Initially, unsubstituted tetrahedrane (**136**) was only proved to be a short-lived intermediate in several reactions. This conclusion was made on the basis of the observed redistribution of a ^{13}C label in acetylene molecules resulting from fragmentation of **136**.[165] In 1978, Schleyer et al. described the synthesis of tetralithiotetrahedrane (**213**) by photolysis of dilithium diacetylide (**212**),[166a] and 1 year later the methylation of **213** was erroneously claimed to have yielded isolable tetramethyltetrahedrane (**214**) (Scheme 29).[166b] However, the tetrahedrane **214** turned out to be as unstable as the parent hydrocarbon **136**.[167] A recently published extended examination of the C_4Li_4 potential energy surface at the B3LYP/6-31G(d) level of theory demonstrated that the isomer tetralithiotetrahedrane (**213**) is indeed a local minimum, which, however, lies higher in energy and should be unstable thermodynamically, while it might be a kinetically stable form.[168]

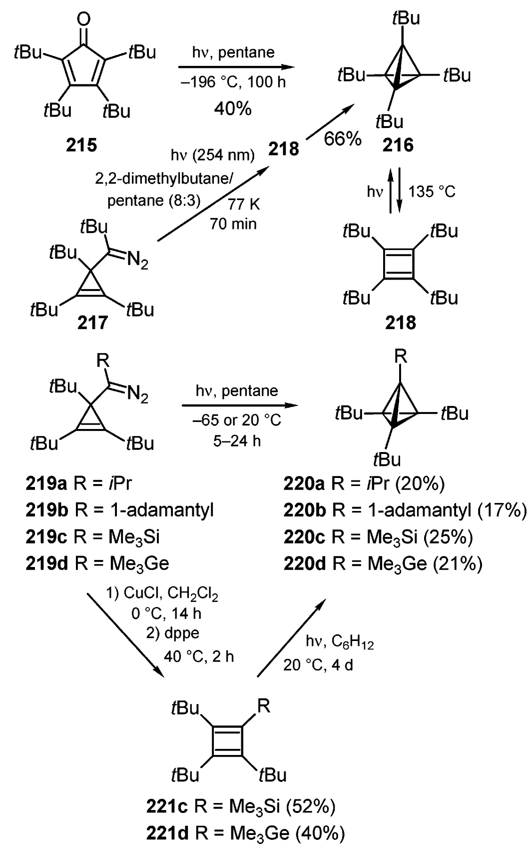
Scheme 29



Also in 1978, Maier et al. reported the first preparation of a really stable tetrahedrane derivative, tetra-*tert*-butyltetrahedrane (**216**), by low-temperature photolysis of tetra-*tert*-butylcyclopentadienone (**215**) (Scheme 30).[169] Substantial quantities of di-*tert*-butylacetylene were also detected. The four bulky substituents in **216** significantly retard both its fragmentation into two acetylene fragments and thermal reorganization into tetra-*tert*-butylcyclobutadiene (**218**). The latter transformation has an activation energy of 26 kcal/mol, and in addition, **218** can be converted back into **216** photochemically.

Since these results were reviewed,[106b,c] further progress has been made by Maier et al. Thus, a new more convenient and efficient approach to **216** by photochemical decomposition of appropriately substituted (3-cyclopropenyl)diazomethane derivatives of type **217** has been developed (Scheme 30).[170] By this method, a few other monoalkyl-substituted tri-*tert*-butyltetrahedranes (**220a**,**b**) have been obtained, albeit

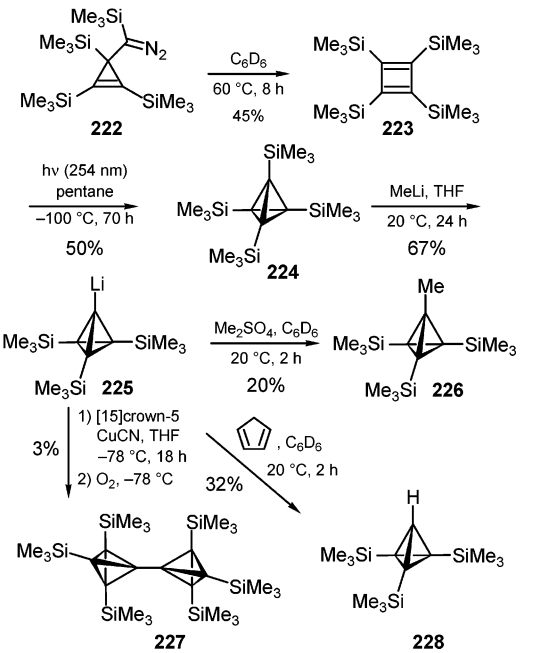
Scheme 30



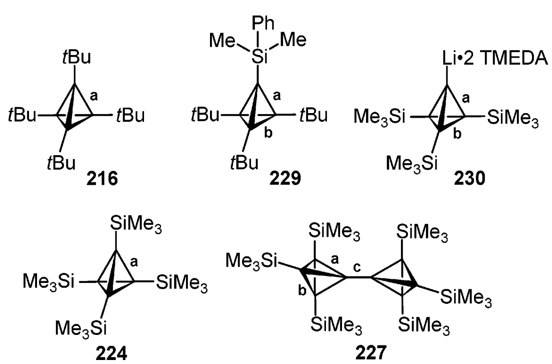
in lower yields. The single less bulky substituent in **220a** drastically changes its chemical behavior, as it can be converted irreversibly into the corresponding cyclobutadiene derivative both thermally and photochemically. Upon prolonged heating, compounds **220a**,**b** undergo fragmentation into two acetylene units.[170c]

In contrast to this, the attempted photochemical transformation of the heterosubstituted diazo compounds **219c**,**d** into the corresponding tetrahedranes **220c**,**d** did not succeed. But Cu(I)-catalyzed decomposition of **219c**,**d** followed by photochemical isomerization of the resulting cyclobutadienes **221c**,**d** did afford the heterosubstituted tri-*tert*-butyltetrahedranes **220c**,**d**, in moderate yields (Scheme 30).[171] Several $R^1R^2R^3$Si-substituted tri-*tert*-butyltetrahedrane derivatives were prepared along this route,[171] while in the preparation of tetrakis(trimethylsilyl)tetrahedrane (**224**) (23% yield over two steps, Scheme 31), the transformation of the corresponding cyclopropenyldiazomethane **222** into tetrakis(trimethylsilyl)cyclobutadiene **223** was achieved thermally.[172] However, none of the known methods proved to be successful for the preparation of perfluoroalkyl-substituted tetrahedranes.[173]

Scheme 31



Tetrakis(trimethylsilyl)tetrahedrane (**224**) is of special interest for several reasons. First, it turned out to be thermally stable up to 300 °C.[172] Computations at the B3LYP/6-31G(d) level of theory disclosed that bulky substituents at the corners stabilize the tetrahedrane skeleton not only kinetically but also thermodynamically by 17.1 kcal/mol for **216** and



by 76.7 kcal/mol for **224**.[172b] Second, treatment of **224** with excess methyllithium in THF at ambient temperature furnished tris(trimethylsilyl)tetrahedryllithium **225** as a colorless solid in 67% yield (Scheme 31). This lithium derivative is sensitive to air and moisture but thermally stable,[174a] and it reacts with dimethyl sulfate as well as cyclopentadiene to produce the tetrahedrane derivatives **226** and **228**, respectively, in 20% and 32% yield, respectively. These tetrahedranes also turned out to be surprisingly thermally stable up to 100 °C. The oxidative coupling of **225** via a cuprate complex (Scheme 31) afforded hexakis(trimethylsilyl)tetrahedranyltetrahedrane (**227**) in 3% isolated yield after HPLC separation.[174b]

The structural parameters of several stable tetrahedranes were determined by X-ray diffraction (see Table 4). Thus,

Table 4. Geometric Parameters of Substituted Tetrahedranes as Determined by X-ray Crystal Structure Analyses

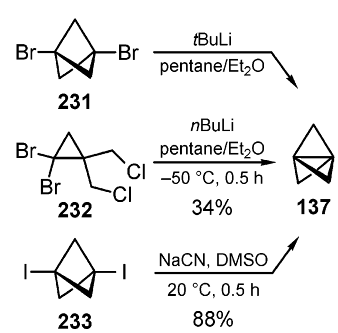
	average bond length [Å]			
compound	*a*	*b*	*c*	ref
216	1.497(5)			175
229	1.470(6)	1.514(7)		171c
230	1.543(2)	1.499(2)		174a
224	1.502(4)			172b
227	1.521(2)	1.484(2)	1.436(3)	174b

enforced by the restricted rotation of the *tert*-butyl groups, tetrahedrane **216** only possesses T and not T_d symmetry.[175] In the derivative **229**, the tetrahedrane skeleton is distorted to C_s symmetry, and the presence of the $SiMe_2Ph$ group obviously leads to an elongation of those tetrahedrane bonds that originate from the silyl-substituted position.[171c] Similar effects were observed in tetrahedranes **224**, **227**, and **230**. Especially remarkable, however, is the drastic shortening of the central bond c in hexakis(trimethylsilyl)tetrahedranyltetrahedrane (**227**),[174b] which, as described above for bis(bicyclobutyl) derivatives, indicates a strong conjugation effect between two formally saturated systems.[176]

The gas-phase basicity of tetra-*tert*-butyltetrahedrane (**216**) was determined by FT−ion cyclotron resonance (ICR) mass spectrometry to be 274.0 ± 2.4 kcal/mol, making **216** one of the strongest bases reported so far.[177] The radical cation generated from **216** cannot even be detected, because it immediately rearranges to the corresponding cyclobutadienyl radical cation.[178] Similarly, the electrochemical oxidation of tri-*tert*-butyl(trimethylsilyl)tetrahedrane (**220c**) proceeds irreversibly by one-electron transfer at $E_{pa} = +0.40$ V with immediate fast (on the cyclic voltammetry time scale) rearrangement of the radical cation of **220c** to the radical cation of the corresponding cyclobutadiene.[179]

Tricyclo[1.1.1.0[1,3]]pentane (**137**) (so-called [1.1.1]propellane) in which three cyclopropane rings are fused across the same single bond, was first prepared in 1982 from 1,3-dibromobicyclo[1.1.1]pentane (**231**) by Wiberg et al. (Scheme 32).[180] This synthesis was of principal importance, but it had more theoretical than practical significance, because the starting material **231** was and is not readily available.

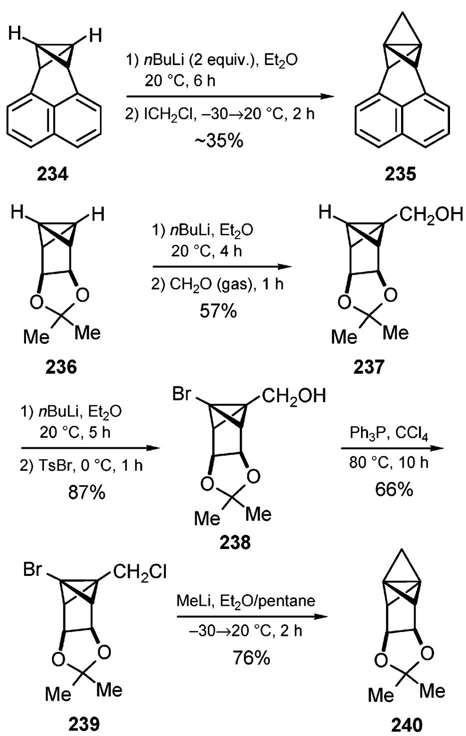
Scheme 32



The real breakthrough was achieved by Szeimies et al. only 3 years later.[181] Upon treatment of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (**232**), which can be easily prepared by dibromocarbene addition onto commercially available 3-chloro-2-(chloromethyl)propene with *n*-butyllithium, [1.1.1]propellane (**137**) was obtained in 34% yield. By replacing *n*-butyllithium with methyllithium[182] and modifying the reaction conditions, it was possible to increase the yield up to 70% and to make **137** isolable.[183] Nowadays, **137** is almost a commodity chemical in synthetic organic chemistry and is used widely for the preparations of mono- and disubstituted derivatives of bicyclo[1.1.1]pentane like **231**. While neat **137** is rather unstable, it can cleanly be converted into stable 1,3-diiodobicyclo[1.1.1]pentane (**233**), from which **137** can be recovered in very high yield;[184] thus, **233** can be regarded as a long-term storage form of [1.1.1]-propellane **137**.

Another methodology developed by Szeimies et al. [185a] makes use of the enhanced C−H acidity of the bridgehead hydrogen atoms in bicyclobutane (**132**) (see above) and is applied mainly for the preparation of substituted and bridged [1.1.1]propellanes. Thus, naphthotetracyclo[5.1.0.0^{1,6}.0^{2,7}]oct-3-ene (**235**) was prepared recently in one step from the corresponding bicyclobutane derivative **234** (Scheme 33).[185b] However, a four-step sequence must be applied for the preparation of the propellane derivative **240** (Scheme 33, 25% overall yield), because the 2-fold deprotonation of **236** occurred to an extent of less than 20%.[185b]

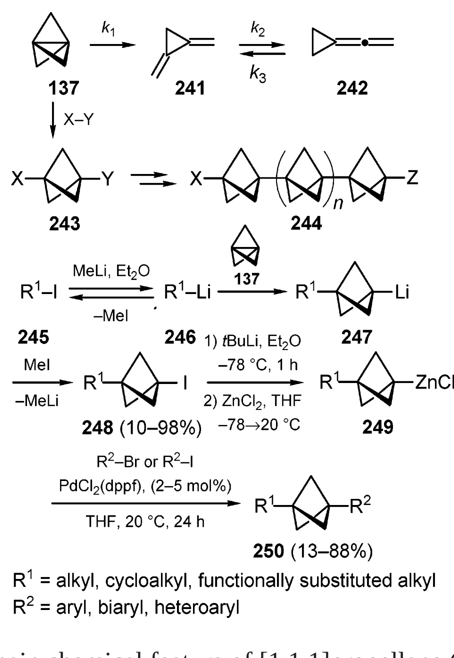
Scheme 33



The physical and chemical properties of [1.1.1]propellane (**137**) have probably been reviewed more frequently than those of other strained hydrocarbons.[107] Therefore, in the current context only the main principal statements are repeated, and an update on the last excellent review by Michl et al. is presented.[107a] Structural properties of **137**, as well as of substituted [1.1.1]propellanes, experimentally determined with various methods, have all been summarized in ref 107a (for additional more recent results see also ref 186). The external bond lengths in the parent **137** (1.512−1.555 Å) have been found to be significantly longer than those in unsubstituted cyclopropane itself (1.499(1) Å),[120b] yet the central bond in **137** (1.593−1.605 Å) is much longer. This is in line with the results of recent MP2/6-311G** computations (1.523 vs 1.607 Å), while the DFT (B3LYP/6-311G**) as well as MP2/cc-pVTZ method slightly underestimate these distances (1.519 vs 1.576 Å).[187] Experimentally determined electron density distributions in [1.1.1]propellane derivatives indicate the presence of bent bonds and excess electron density in the region outside of the inverted[94] bridgehead carbon atoms, while the electron density between these carbons is slightly less than would correspond to the sum of contributions from two spherically symmetrical neutral atoms.[186,188]

[1.1.1]Propellane **137** has been estimated to have a strain energy of 104.2[98a,b] or 98.2[98c] kcal/mol, compared with 66.5 kcal/mol[3] for bicyclo[1.1.1]pentane (**132**) and 28.1 kcal/mol for cyclopropane.[3] The first ionization event of **137** is at an unusually low energy for a saturated hydrocarbon (IE = 9.74 eV).[189] It should be pointed out that there is no easy way to release strain from **137**: breakage of the central C−C bond releases less than a third of the total strain energy,[190] and breakage of a peripheral C−C bond is symmetry-forbidden.[107a] No doubt, the relatively high stability of the parent **137** is quite surprising. Thus, while **137** polymerizes spontaneously in the liquid phase at temperatures above 0 °C, it can be stored as a solid in liquid nitrogen, and diluted solutions of **137** in ether may be stored in a refrigerator for several days. At elevated temperatures (200−450 °C), **137** in the gas phase rearranges to dimethylenecyclopropane (**241**) and the latter then thermally undergoes further reorganization to ethenylidenecyclopropane (**242**) (Scheme 34);[191] in the range 204−244 °C, the Arrhenius activation parameters of this rearrangement were determined as $\log(A/s^{-1}) = 14.02 \pm 0.23$ and $E_a = 39.66 \pm 0.52$ kcal/mol.[191a] The activation barrier was also computed at the CCSD(T)/6-311G(2d,p)//MP2/6-311G(2d,p) level of theory to be 40.0 kcal/mol.

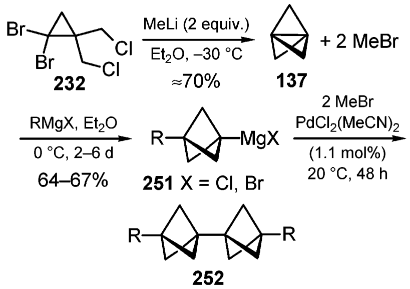
Scheme 34



The main chemical feature of [1.1.1]propellane (**137**) and its derivatives is that they undergo smooth additions of anionic, radical, and electrophilic species across the central bond to produce disubstituted derivatives of type **243** of bicyclo[1.1.1]pentane (Scheme 34).[107]

The latter have found ever increasing applications in synthetic organic chemistry. For example, they can be transformed into linear rod-like[192] oligomers, so-called staffanes **244**,[107a,b] used as mesogenic units in liquid crystalline compounds,[193] used as stiff linkers between fluorophore and photochromic units,[194] used as trigonal or tetragonal connectors for the construction of large molecular assemblies,[195] etc. Thus, the initial step in the synthesis of liquid crystalline compounds was an addition of aliphatic and some aromatic Grignard reagents to [1.1.1]propellane (**137**) to give the corresponding 3-substituted bicyclo[1.1.1]pent-1-ylmagnesium reagents in 13−99% yield, as well as methyllithium-catalyzed addition of alkyl iodides **245** to **137** to produce iodides **248** (Scheme 34). The latter, after transformation into zinc derivatives **249**, were coupled with different aryl, biaryl, and heteroaryl halides under $PdCl_2$(dppf) catalysis to produce the mesogenic scaffolds **250** in 13−88% yield.[193] Similar results were obtained from bicyclo[1.1.1]pent-1-ylmagnesium reagents **251** under $NiCl_2$(dppe) catalysis. Bis(acetonitrile)palladium(II) chloride turned out to be the best catalyst for the preparation of symmetrically 3,3′-dialkyl- and 3,3′-diaryl-substituted [2]staffanes **252** from 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (**232**) in 53−60% yield for the coupling step (Scheme 35).[183c]

Scheme 35

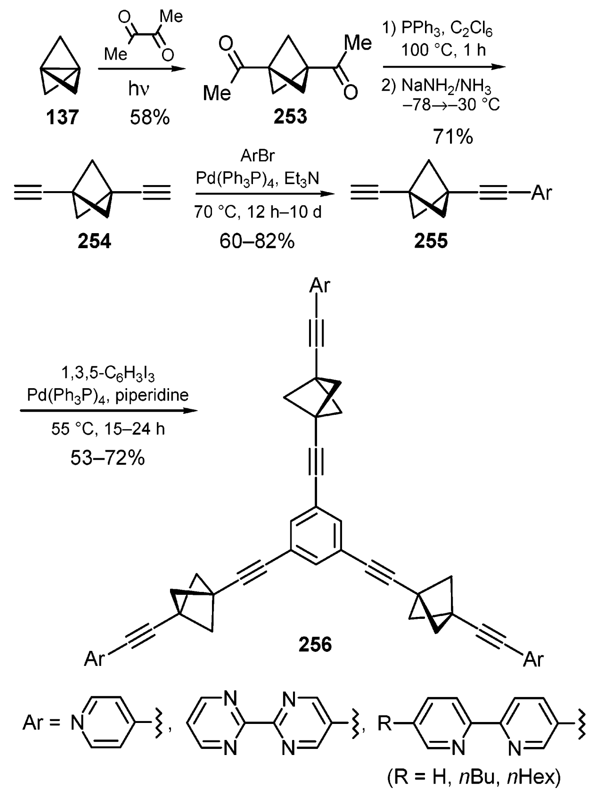


R	*t*Bu	c-C_6H_{11}	iPr	c-C_5H_9	Ph	*p*Tol
Yield (%)	57	51	57	60	53	59

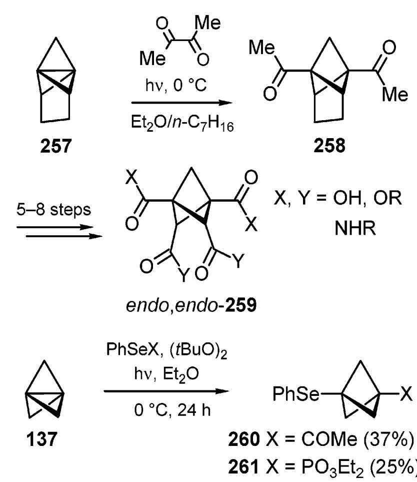
“One-pot” mode in this particular case is not only a facilitation of the procedure, but also a necessary condition for success, as the final coupling proceeds only in the presence of methyl bromide generated in the first step.

The synthesis of trigonal or tetragonal connectors of the type **256** for the construction of large molecular assemblies with metal centers[195] was initiated with a radical addition of diacetyl across the central bond in **137** to produce 1,3-diacetylbicyclo[1.1.1]pentane (**253**), which was converted into the explosive 1,3-diethynylbicyclo[1.1.1]pentane (**254**) in 71% yield (Scheme 36). One of the termini of the latter was coupled with an aryl bromide applying copper-free Pd-catalyzed cross-coupling conditions for the terminal alkynyl units to aryl halides to give the extended terminal acetylene **255**, 3 equiv of which were then coupled with 1,3,5-triiodobenzene furnishing a trigonal connector **256** in 53−72% yield (Scheme 36). The corresponding tetragonal connectors were obtained by cross-coupling of **255** with 1,2,4,5-tetraiodobenzene. The same initial step, photochemically induced radical addition of diacetyl across the central bond in propellane **257**, was used in a multistep preparation of functionally tetrasubstituted bicyclo[1.1.1]pentane derivatives *endo*,*endo*-**259** (Scheme 37);[196] however, the overall yields in these syntheses were rather low because of the low yield upon oxidation of diketone **258** to the corresponding diacid by haloform reaction (25%). The radical addition of organoselenium reagents to [1.1.1]propellane (**137**) (which was tested along a route to amino acids with a bicyclo[1.1.1]pentane framework) turned out to be low-yielding as well (Scheme 37).[197]

Scheme 36



Scheme 37

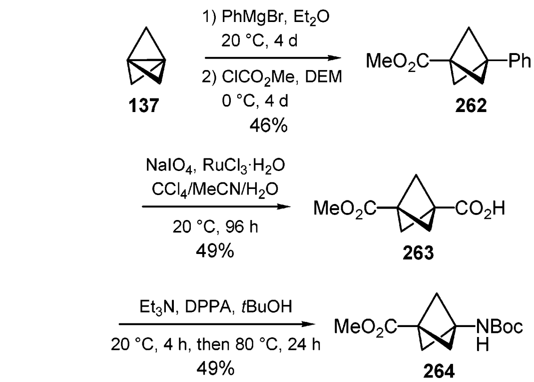


The protected 3-aminobicyclo[1.1.1]pentane-1-carboxylic acid **264**, which can be considered as a rigid analogue of 4-aminobutyric acid, was recently prepared by Curtius degradation of the monoester **263**, which, in turn, was obtained from [1.1.1]propellane (**137**) by the addition of phenylmagnesium bromide followed by ethoxycarbonylation with ethyl chloroformate and oxidative cleavage of the phenyl group in 23% overall yield (Scheme 38).[198] Radical addition onto **137** was also used as a key step in the synthesis of (bicyclo[1.1.1]pent-1-yl)amine.[199]

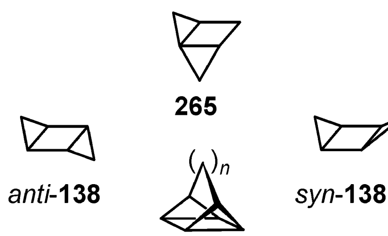
Among further perspectives, the most intriguing one probably is the intensively discussed potential application of staffanes **244** produced from [1.1.1]propellanes, as molecular rotors in molecular sized machinery, which is an important part of nanotechnology.[200]

1,2-Fusion of cyclopropane rings to two neighboring edges of cyclobutane formally leads to the yet elusive tricyclo-[3.1.0.0^{1,3}]hexane **265**.[141] The calculated strain energy of this

Scheme 38



compound strongly exceeds the sum of SEs of the cyclobutane and the two cyclopropane rings (SE_{calcd} = 112.9 kcal/mol[96] versus $\sum SE_{cycl}$ = 83.2[95]). However, the SE per carbon atom in **265** (18.8 kcal/mol) is less than that in [1.1.1]propellane (**137**) (20.8 kcal/mol[98a,b]).



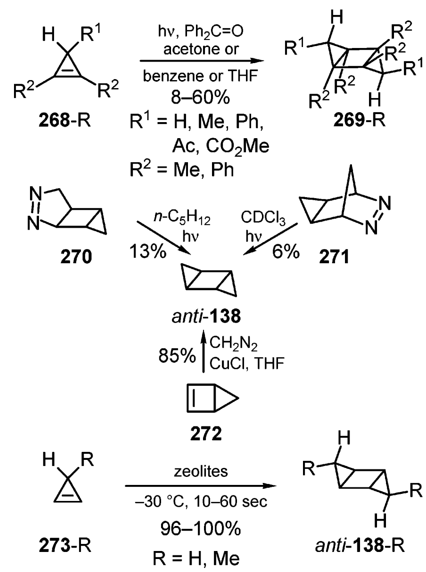
266 *n* = 0 ([3]prismane)
267 *n* = 1 (quadricyclane)

In contrast to this, compounds with two cyclopropane rings fused to two opposite edges of cyclobutane, that is, tricyclo[3.1.0.0^{2,4}]hexane (*anti*-**138**), in which the SE virtually corresponds to the sum of SEs of its constituting monocycles (SE_{calcd} = 83.1[100] versus $\sum SE_{cycl}$ = 83.2[95]), are well-known and reasonably stable. Moreover, bridged derivatives of *syn*-**138**, namely, [3]prismane **266**[201] and especially quadricyclane **267**,[202] have been studied extensively. The photochemical isomerization of norbornadiene to **267** or derivatives thereof, followed by catalyzed exothermal back transformation has been investigated as a potential storage system for solar energy.[202] The unbridged *syn*-tricyclo[3.1.0.0^{2,4}]hexane (*syn*-**138**) should be thermodynamically less stable than *anti*-**138** by 20.7 kcal/mol.[203]

Hexasubstituted tricyclo[3.1.0.0^{2,4}]hexanes **269**-R were prepared first by photochemical dimerization of trisubstituted cyclopropenes **268**-R in 8−60% yield[204] and presumably obtained as *trans*-configured compounds (see, however, refs 204a,d) (Scheme 39). The parent hydrocarbon *anti*-**138** was initially obtained by photolytic decomposition of the isomeric diazo compounds **270** and **271**, however, in low yields.[205] Interestingly, *syn*-**138** was not formed from **271**.[205b]

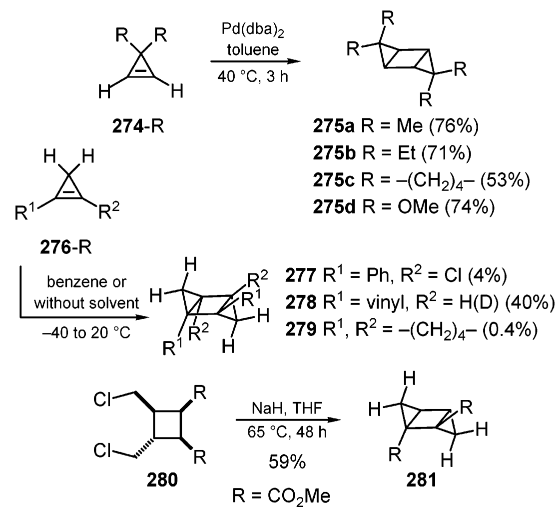
The hydrocarbon *anti*-**138** was obtained in much better yield (85%) by CuCl-catalyzed cyclopropanation of bicyclo[2.1.0]pent-2-ene (**272**),[206] yet by far the best approach to the parent *anti*-**138** and the dimethyl derivative *anti*-**138**-Me is by dimerization of cyclopropene **273**-H or its methyl derivative **273**-Me in the presence of zeolites, which furnished *anti*-**138** and *anti*-**138**-Me in virtually quantitative yield (Scheme 39).[207] 1,3,3-Trisubstituted cyclopropene derivatives did not dimerize under these conditions. On the other hand, cyclodimerization of 3,3-dialkylcyclopropenes

Scheme 39

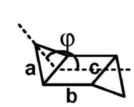


274-R catalyzed by [bis(dibenzylideneacetone)palladium or bis(1,5-cyclooctadiene)palladium] in the absence of phosphine ligands furnished 3,3,6,6-tetraalkyltricyclo[3.1.0.0^{2,4}]hexanes **275** in high yields (Scheme 40),[208a−c] while nickel catalysts were less efficient.[208d] In several rare cases, 1,2-disubstituted cyclopropenes **276**-R underwent spontaneous thermal [2 + 2] dimerization to afford dichlorodiphenyl-(**277**),[209] 1,2-divinyl- (**278**),[210] or pentacyclic (**279**)[211] tricyclo[3.1.0.0^{2,4}]hexanes (Scheme 40). At last, dimethyl *anti*-tricyclo[3.l.0.0^{2,4}]hexane-l,2-dicarboxylate (**281**) was prepared by 2-fold γ-dehydrochlorination in dimethyl 3,4-bis(chloromethyl)cyclobutane-1,2-dicarboxylate **280** (Scheme 40).[212]

Scheme 40



Hybridization features in *anti*-**138** have been studied in great detail theoretically, as well as by ^{13}C NMR spectroscopy.[213] Computed and experimentally determined geometric parameters of *anti*-**138** so far (see Table 5; for geometries



anti-**138**

Table 5. Computed and Experimentally Determined Geometric Parameters of *anti*-Tricyclo[3.1.0.0^{2,4}]hexane (*anti*-138)

method	average bond length [Å] a	b	c	φ	ref
4-21G	1.516	1.520	1.521	109.6	215
MM2	1.503	1.545	1.511	129.0	216
4-21G	1.512	1.547	1.504		216
MM3	1.504	1.549	1.513	113.8	217
GED	1.508(23)[a]	1.508(23)[a]	1.508(23)[a]	113.0	218

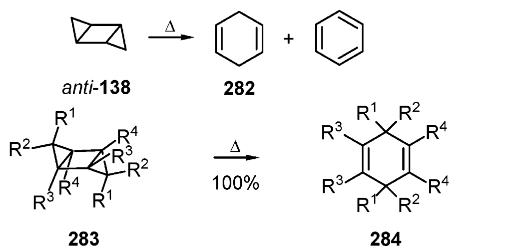
[a] Only the mean carbon−carbon bond length, averaged over both three- and four-membered rings, was reported in this gas-phase electron diffraction (GED) study.

of diradicals and ions derived from **138**, see also ref 214) leave some questions open.

Neither have the exact bond lengths in *anti*-**138** been obtained by a gas-phase electron diffraction (GED) study,[218] nor have computations at a sufficiently high level of theory been performed.

As far as the chemical properties of *anti*-**138** and its derivatives are concerned, only their thermal reorganizations to 1,4-cyclohexadiene (**282**) and its derivatives have been investigated in great detail (Scheme 41). Thus, in the temperature range 170−200 °C, *anti*-**138** provides **282**, which contains 6−11% of benzene.[206] The Arrhenius parameters for this rearrangement were determined to be log $A = 13.70 \pm 0.01$ and $E_a = 36.75 \pm 0.03$ kcal/mol. Thermolysis of *anti*-**138** at low pressure proceeds exothermally ($\Delta\Delta H_f^\circ = 41.6$ kcal/mol) to give thermally excited 1,4-cyclohexadiene (**282**).[219] The latter gave unexcited **282** by collisions or decomposed to give benzene and hydrogen. The activation barrier at 186.4 °C was determined to be 37.0 kcal/mol. Rearrangements of substituted tricyclo[3.1.0.0^{2,4}]hexanes **283** proceed quantitatively, however, at different temperatures depending on the substituents. As a rule, 3,6-disubstituted tricyclo[3.1.0.0^{2,4}]hexanes are more stable, and unsaturated substituents in the 1-, 2-, 4-, and 5-positions facilitate the rearrangement (Scheme 41; for orbital pictures of this rearrangement see also ref 213d).

Scheme 41

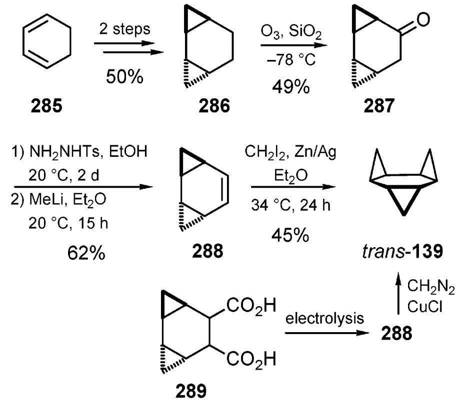


Compound	283a	278	277	275d	281	275a	283b	283c
R^1	H	H	H	OMe	H	Me	Ph	CO_2Me
R^2	H	H	H	OMe	H	Me	Ph	CO_2Me
R^3	Ph	vinyl	Ph	H	CO_2Me	H	Ph	Ph
R^4	Ph	H(D)	Cl	H	CO_2Me	H	Ph	Ph
T [°C]	15	20	100	110	190	200	230	230
Ref.	204d	210	209	208c	212	208a	204d	204d

Such a rearrangement can also be catalyzed; at least the rearrangement of tricyclo[3.1.0.0^{2,4}]hexane-1,2-dimethanol (**283**, $R^1 = R^2 = R^3 =$ H; $R^4 = CH_2OH$) under catalysis with $AgBF_4$ has been reported as well.[212]

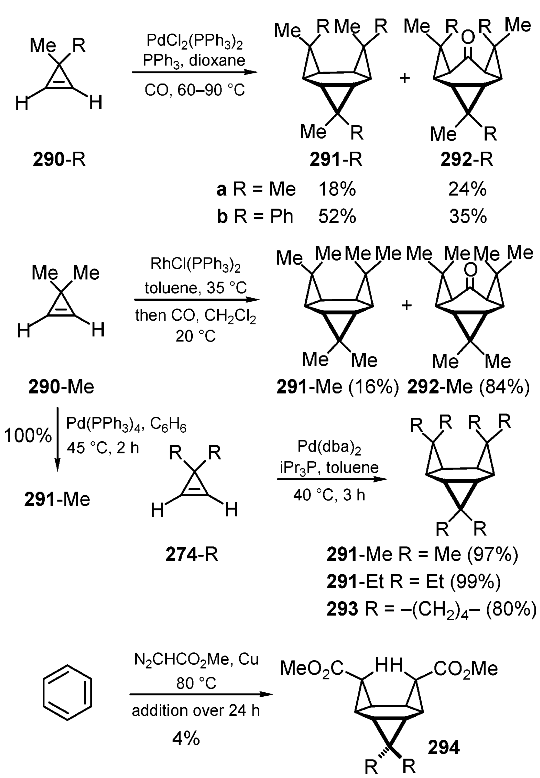
1,2-Fusion of three cyclopropanes to every second edge in cyclohexane formally leads to the *cis* and *trans* isomers of tetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane (tris-σ-homobenzene, **139**). The isomers are diastereomeric and have roughly the same strain energy of 85.6 kcal/mol,[95,101] which is virtually the same value as the sum of SEs of three cyclopropanes and a cyclohexane (85.7 kcal/mol[95]). Whereas the unsubstituted *trans*-**139** turned out to be relatively stable, the parent *cis*-**139** still remains elusive.[102] Hydrocarbon *trans*-**139** was obtained by cyclopropanation of tricyclo[5.1.0.0^{4,6}]oct-2-ene (**288**) applying Müller−Gaspar−Roth[220a] or Simmons−Smith[220b] protocols (Scheme 42). The tricyclooctene **288**, in turn, was prepared in five steps (15% overall yield) from cyclohexa-1,3-diene (**285**)[220b] or by electrolysis of the not easily available tricyclooctanedicarboxylic acid **289**.[220a]

Scheme 42



The most straightforward approach to hexaalkyl-substituted *trans*-**139** of type **291** would be by selective trimerization of dialkylcyclopropenes **290**-R. Indeed, in the carbonylation reactions of 3,3-dimethyl- (**290**-Me) and 3-methyl-3-phenylcyclopropene (**290**-Ph) in the presence of rhodium[221a] or palladium catalysts,[221b] tetracycles **291**-R were isolated, however, in low to moderate yields, while trimerization of 3,3-dimethylcyclopropene (**290**-Me) catalyzed by tetrakis(triphenylphosphine)palladium afforded *trans*-3,3,6,6,9,9-

Scheme 43

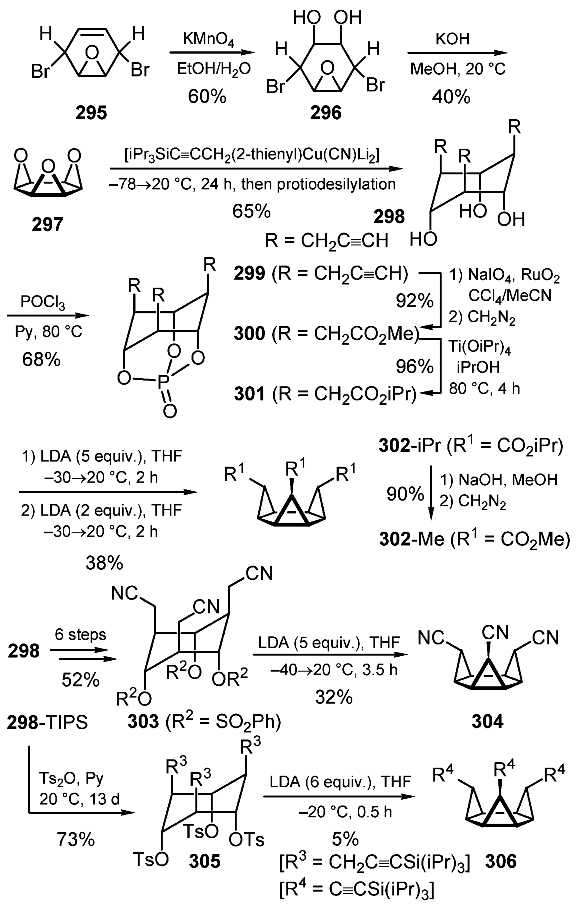


hexamethyl[1.1.1]-tris-σ-homobenzene (**291**-Me) quantitatively[222] (Scheme 43).

It is remarkable that the same catalyst that led to cyclodimerization of 3,3-dialkylcyclopropenes **274**-R to 3,3,6,6-tetraalkyltricyclo[3.1.0.0^{2,4}]hexanes **275** (Scheme 40) in the presence of phosphine ligands (triisopropylphosphine proved to be best) causes virtually quantitative trimerization of **290**-R ($\equiv$ **274**-R) into **291**-R (Scheme 43).[208a,b] Another possible "shotgun" preparation of functionally substituted *trans*-tris-σ-homobenzenes of the type **294**, that is, by direct 3-fold cyclopropanation of benzene with methyl diazoacetate, turned out to be of low efficiency (Scheme 43),[223a] while the analogous attempted 3-fold cycloaddition of dichlorocarbene was not successful at all.[223a]

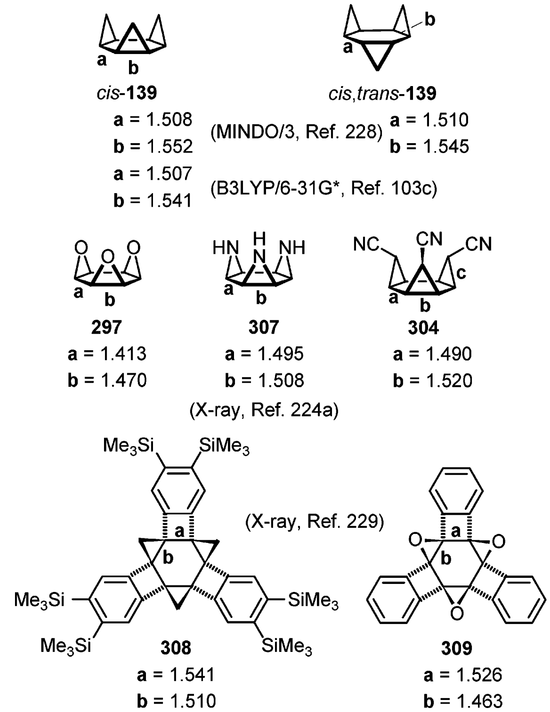
Prinzbach et al.[224] demonstrated that electronegative substituents on the cyclopropane rings can efficiently stabilize *cis*-[1.1.1]-tris-σ-homobenzene derivatives, and they synthesized a series of such compounds starting from *cis*-trioxatris-σ-homobenzene **297**, which, in turn, was prepared from 3,6-dibromo-5,6-epoxycyclohexene (**295**) in 24% overall yield (Scheme 44).[225]

Scheme 44



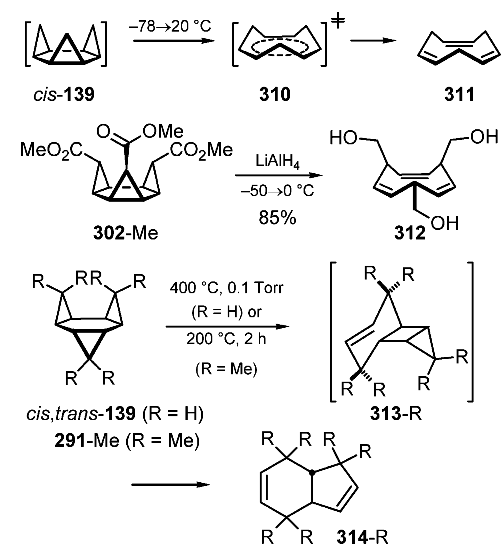
The principal steps in these elaborate preparations were the stereoselective ring opening of **297** with the weakly basic mixed cyanocuprate of lithiated tris(isopropylsilyl)-protected propyne and fixation of the all-axial orientation of the six substituents on the flexible cyclohexane precursor **298** by bridging the three hydroxy groups in the form of the adamantoid orthophosphates **299**–**301** (Scheme 44).[226] Successful application of this strategy led to the preparation of *cis*-tris-σ-homobenzenes **302**-iPr, **302**-Me, **304**, and **306** in 15%, 13%, 11%, and 2.5% overall yield, respectively.[227]

Computed as well as experimetally determined bond lengths [Å] in the six-membered rings of hydrocarbons *cis*-**139** and *trans*-**139** clearly demonstrate that these molecules



are predisposed to undergo [$\sigma^2_s + \sigma^2_s + \sigma^2_s$] cycloreversions[103] with opening of all three cyclopropane rings, because the bonds between the rings are shorter, while the ones within the cyclopropane rings are longer than normal. Indeed, the elusive *cis*-**139** would easily undergo the [$\sigma^2_s + \sigma^2_s + \sigma^2_s$] cycloreversion to give *cis*,*cis*,*cis*-cyclonona-1,4,7-triene **311** upon attempted preparation (Scheme 45).[102] For this rearrangement $\Delta H^{\ddagger} = 23.4-25.8$ and $E_a = 24.0-36.4$ kcal/mol were estimated from kinetic studies of structurally related cage hydrocarbons with *cis*-tris-σ-homobenzene moieties[104] [computed values $\Delta H^{\ddagger} = 23 \pm 3$ kcal/mol (most probable value as taken from a comparison of values obtained with 15 computational methods applied to this peculiar case);[103a] $E_a = 36.3$ kcal/mol (MINDO/3)[228] or 22.0 kcal/mol (B3LYP/6-31G)[103c]].

Scheme 45

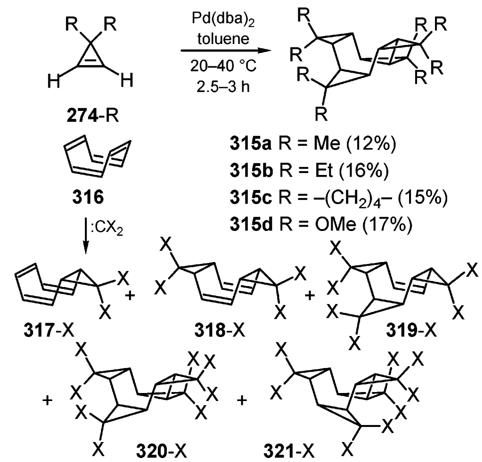


The anomalously facile cleavage of all three cyclopropane rings in *cis*-**139** was rationalized in terms of through-bond interactions involving the breaking σ-bonds and the neighboring groups.[103d,230] In contrast to this, the *cis*-tris-σ-homobenzenes **302**-R, **304**, and **306** rearrange to the corresponding cyclononatriene derivatives only above 180 °C and *cis*-trioxatris-σ-homobenzene **297** even above 200 °C.[224a] The importance of electronic influences of substituents is best illustrated by the fact that 3-fold reduction of tris(methoxycarbonyl)-*cis*-tris-σ-homobenzene **302**-Me to tris(hydroxymethyl)-*cis*-tris-σ-homobenzene, that is, transformation of the three electron-withdrawing into electron-donating substituents, is accompanied by immediate [$\sigma^2_s + \sigma^2_s + \sigma^2_s$] cycloreversion, occurring at 0 °C, so that the 3,6,9-tris(hydroxymethyl)cyclonona-1,4,7-triene (**312**) was the only isolated product (85% yield) (Scheme 45).[226] In contrast to this, two derivatives of all-*cis*-[2.1.2.1.2.1]hexaannulane **308** and a heteroanalogue **309** turned out to be relatively stable.[229] Thus, the triepoxide **309**, like benzenetriepoxide **297**, could be heated to 180 °C before it underwent rearrangement with [$\sigma^2 + \sigma^2 + \sigma^2$] cycloreversion of the heptacyclic core structure.

According to MINDO/3-calculations,[228] *trans*-tris-σ-homobenzene (*trans*-**139**) structurally is also predisposed to such a cycloreversion with a computationally predicted $E_a = 48.3$ kcal/mol, and this structural predisposition is also in line with X-ray crystal structural data of its hexamethyl derivative **291**-Me (a = 1.480−1.485 Å, b = 1.515 Å).[231] Indeed, rearrangement of *trans*-**139**[219,232] follows first-order kinetics with the Arrhenius parameters $\log(A/s^{-1}) = 13.39$ and $E_a = 41.9 \pm 0.9$ kcal/mol. However, under the drastic reaction conditions, the expected initially stereoselectively formed *cis*,*trans*,*trans*-cyclonona-1,4,7-triene underwent intramolecular [2 + 2] cycloaddition across the two strained *trans*-configured double bonds to yield *trans*-tricyclo[4.3.0.0^{7,9}]non-3-ene (**313**-H) (Scheme 45), which immediately underwent further rearrangement in its bicyclo[2.1.0]pentane moiety to eventually furnish *trans*-bicyclo[4.3.0]nona-3,7-diene (**314**-H). This mechanism was proved by carbon labeling in the starting material *trans*-**139**.[232] In the case of the hexamethyl-*trans*-tris-σ-homobenzene **291**-Me, the thermal rearrangement apparently proceeded along the same route but at a lower temperature so that the hexamethyl-*trans*-tricyclononene **313**-Me could be isolated.[232,233]

Among the fused systems listed at the start of this section, pentacyclo[9.1.0.0^{2,4}.0^{5,7}.0^{8,10}]dodecane (**140**) appears to be the most scarcely investigated one. Thus, among the 28 known derivatives of **140**, 18 are crystalline, yet not a single X-ray crystal structure analysis has been published up to now. All stereochemical relationships in these molecules were derived on the basis of molecular symmetries obtained from analyses of their NMR spectra. There are two general synthetic approaches to **140** and its derivatives. As in the case of tricyclo[3.1.0.0^{2,4}]hexane (**138**) and tetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane (**139**), the first one is based upon cyclooligomerization reactions of cyclopropene derivatives. Thus, in the palladium-catalyzed cyclodimerization of 3,3-dialkylcyclopropenes **274**-R [bis(dibenzylideneacetone)palladium or bis(1,5-cyclooctadiene)palladium] in the absence of phosphine ligands, as discussed above (Scheme 40), the corresponding cyclotetramers, 3,3,6,6,9,9,12,12-octaalkylpentacyclo[9.1.0.0^{2,4}.0^{5,7}.0^{8,10}]dodecanes **315** are also formed as byproducts, albeit in low yields (12−17%, Scheme 46).[208a−c] However, compounds **315** can easily be separated from the major products, the tricyclo[3.1.0.0^{2,4}]hexanes **275**.

Scheme 46



The second general approach to **140** and substituted derivatives thereof is by consecutive cyclopropanation of cyclooctatetraene (**316**).[234−238] In all cases, the products **320** and **321** of 4-fold cyclopropanation (Scheme 46 and Table 6) are formed in very low yields, if at all. The only possibility to increase these yields is to repeat the cyclopropanations on the mono-, bis-, and triscyclopropanated compounds **317**−**319**. Thus, dibromocyclopropanation of **318**-Br furnished **319**-Br (14%) and **320**-Br (1.3%); dibromocyclopropanation of **319**-Br afforded **320**-Br in 7% yield.[237] Treatment of **318**-CO_2Me with 3 equiv of dimethyl diazomalonate did result in the formation of **320**-CO_2Me (1% yield).[238] In most cases, the tetraadducts predominantly are the *trans*,*cis*,*trans*-configured derivatives **320**; however, upon 4-fold cyclopropanation with the sterically less demanding methylene transfer reagent diazomethane, the *cis*,*cis*,*trans* tetraadduct **321**-H was formed in slightly higher yield than the *trans*,*cis*,*trans* isomer.[234]

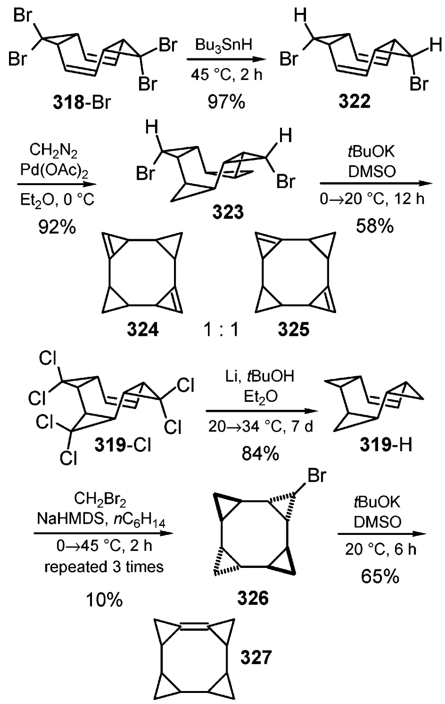
Table 6. Consecutive Cyclopropanation of Cyclooctatetraene (316) under Different Conditions

X	conditions	317 (%)	318 (%)	319 (%)	320 (%)	321 (%)	ref
H	CH_2N_2, CH_2Cl_2, CuCl, −10 to 0 °C	13	26	36	7	10	234
Me	Me_2CBr_2, *n*BuLi, Et_2O, −78 to 20 °C, 13 h	*a*	*a*	*a*	16	*a*	235
Cl	$CHCl_3$, TEBACl, C_6H_6, 50% NaOH, 20 °C, 16 h	22	25	10	3		236
Br	$CHBr_3$, TEBACl, 50% NaOH, 20 °C, several days	38	25	0.8	0.3	*a*	237
CO_2Me	N_2=C(CO_2Me)$_2$, CCl_4, [Rh(OAc)$_2$]$_2$, 10 h	32	9[b]	0.4	0	0	238

[a] Not reported. [b] Mixture of two diastereomers.

Little is known about chemical transformations of the substituted derivatives **320**-X. Halogen−metal exchange in **320**-Br proceeds mainly with attack on the *endo*-bromine atoms, while tributyltin hydride removes the *exo*-oriented bromines with a certain degree of stereoselectivity.[237] Such a reductive removal of two bromine substituents from the bis adduct **318**-Br was used in the preparation of the unstable cyclopropene derivatives **324** and **325**, which were obtained as an inseparable 1:1 mixture by 2-fold dehydrobromination of the dibromopentacyclo[9.1.0.0^{2,4}.0^{5,7}.0^{8,10}]dodecane (**323**) (52% overall yield in three steps, Scheme 47).[239]

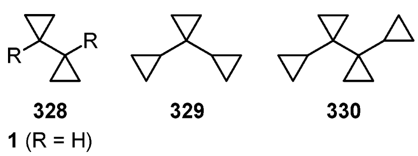
Scheme 47



In contrast to this, dehydrobromination of the monobromide **326** under the same conditions furnished the reasonably stable cyclic bicyclopropylidene derivative **327** in 65% yield (Scheme 47).[240] The bromide **326** was prepared in two steps from the tris adduct **319**-Cl; unfortunately, though, the monobromocarbene addition onto the double bond in tetracyclo[8.1.0.0^{2,4}.0^{5,7}]undec-8-ene (**319**-H) gave **326** in only 10% yield (Scheme 47).

2.4. 1,1-Linked Oligocyclopropyl Systems

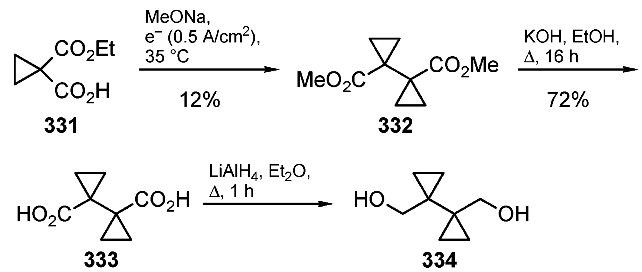
Bicyclopropyl (**1**) (see section 2.1) can be considered not only as the simplest member of the 1,2-connected oligocyclopropanes but also as the first in the series of 1,1-connected analogues **328**−**330** and the like. This classification is especially appropriate for the 1,1′-disubstituted derivatives **328** (R ≠ H) of **1**.



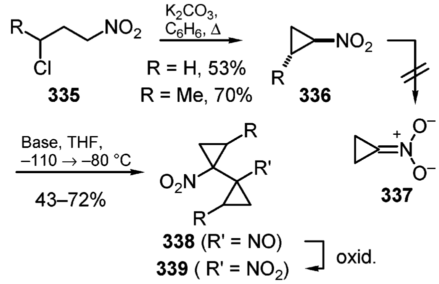
The first 1,1′-disubstituted derivatives, the diester **332** and the diacid **333**, were obtained by Kolbe electrolysis of the monoester of 1,1-cyclopropanedicarboxylic acid **331** and subsequent saponification (Scheme 48).[241,242] The dissociation constants of **333** as an example of a sterically encumbered succinic acid derivative were measured.[243] The reduction of the diacid **333** with lithium aluminum hydride furnished the diol **334**, the intramolecular hydrogen-bonding properties of which were studied by IR spectroscopy and compared with those of a number of different 1,2- and 1,4-diols (Scheme 48).[244]

The accesses to 1,1′-dinitrobicyclopropyl (**339**) and 1-nitro-1′-nitrosobicyclopropyl (**338**) are mechanistically closely related (Scheme 49).[245] Upon deprotonation of nitrocyclopropane derivates **336** with strong bases (LDA, ^{n}BuLi, KHMDS) at low temperatures, only radical dimerization products could be obtained, although a variety of different electrophiles were employed to trap the putative *aci*-nitro anion **337**. Most probably, the nitro-substituted radical is formed more rapidly by a one-electron transfer as indicated by the detection of long-lived paramagnetic species by ESR spectroscopy. In their crystals, both **338** and **339** adopt *gauche* conformations.[245]

Scheme 48

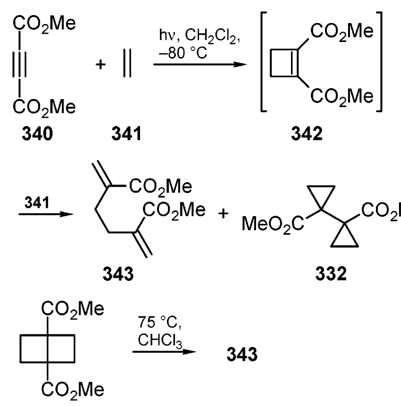


Scheme 49



The photochemically induced reaction of ethylene (**341**) with dimethyl acetylenedicarboxylate (**340**) furnished a 9:1 mixture of dimethyl 2,5-dimethyleneadipate (**343**) and the diester **332** in 63% yield (Scheme 50).[246,247] The adipate **343** must arise from dimethyl 1,4-bicyclo[2.2.0]hexanedicarboxylate (**344**), the expected product of a 2-fold [2 + 2] cycloaddition of ethylene (**341**) to the alkyne **340**. Indeed, an authentic sample of **344** gave **343** upon heating at 75 °C.[246,247]

Scheme 50



A variety of other 1,1′-disubstituted bicyclopropyls have been prepared by cyclopropanation of 1,3-butadiene derivatives (Scheme 51, Table 7). Quantitative protiodesilylation of the bissilyl ether **346** was accomplished by heating in methanol (Scheme 51).[257] The (cyclopropylcyclopropyl)silyl ethers **347**−**349** could be cleaved in the same way in over 95% yield,[249] whereas their treatment with methanolic NaOH

Scheme 51

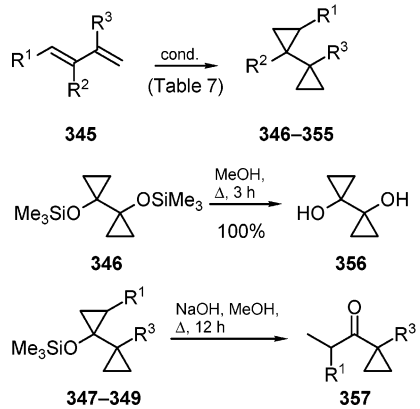


Table 7. 1,1′-Disubstituted 1,1′-Bicyclopropyls by Cyclopropanation of 1,3-Butadiene Derivatives

compd	R^1	R^2	R^3	cond.[a]	yield (%)	ref
346	H	$OSiMe_3$	$OSiMe_3$	A	78	248
347	H	$OSiMe_3$	H	A	90	249
348	H	$OSiMe_3$	Me	A	90	249
349	Me	$OSiMe_3$	H	A	90	249
350	H	Ph	Ph	B	11	250
351	H	CO_2Me	CO_2Me	A	55	251
352	H	CN	CN	C	*b*	252
353	H	Me	Me	D	*b*	253
353	H	Me	Me	E	15	254
354	H	$Ph_2P(O)$	$Ph_2P(O)$	F	39	255
355	H	F	Me	E	11	256

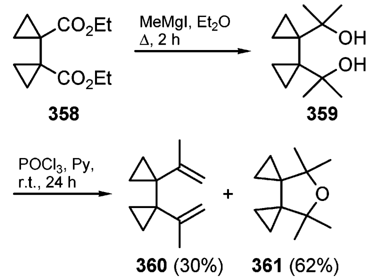
[a] Condition A: (1) CH_2I_2, Zn(Ag) couple, Et_2O, 1 h; (2) butadiene, Δ; (3) pyridine, 0 °C, 1 h. Condition B: (1) $CHCl_3$, aq NaOH, PTC; (2) Na, MeOH, Et_2O, 0 °C, 2 h. Condition C: (1) CH_2N_2, THF/Et_2O, rt; (2) toluene, 100 °C, 1 h. Condition D: CH_2N_2, CuCl, 20 °C. Condition E: CH_2N_2, $Pd(OAc)_2$, Et_2O or $PhCH_3$, −5 °C. Condition F: (1) Me_3SOI, NaH, DMSO, 1 h; (2) butadiene, DMSO, 70 °C, 2 h. [b] Not reported.

solution (12 h, reflux) afforded the corresponding cyclopropylketones **357** in over 95% yield (Scheme 51).[249] The bis(diphenylphosphinoxy) derivative **354** was reduced to the 1,1′-bis(diphenylphosphinyl)bicyclopropyl, which was used as a ligand in various low-valent metal complexes.[255] The latter was also transformed into the corresponding sulfur and borane adducts.

In the crystal, 1,1′-diphenylbicyclopropyl **350** exists in an *s-trans* conformation,[258] just like the parent compound **1** (see above). In contrast, the preferred conformation of the dinitrile **352** in the crystal is *gauche* with a torsional angle $\varphi = 58°$.[259] Based on He(I)-photoelectron spectroscopic evidence in the gas phase, 1,1′-dimethylbicyclopropyl (**353**) exists predominantly in a *gauche* conformation; no indication of the *s-trans* conformer could be found.[23b] This conformational behavior of **353** was confirmed by a gas-phase electron diffraction study.[253] A *gauche* conformation with a torsional angle $\varphi = 139°$ was found as the prevalant orientation of the unligated 1,1′-bis(diphenylthiophosphinyl)bicyclopropyl obtained from **354**.[255] This is different from all other *gauche* conformers of bicyclopropyl derivatives, which have torsional angles of less than 100°.

1,1′-Diisopropenylbicyclopropyl **360** was the first substituted derivative of a 1,1′-divinyl-substituted bicyclopropyl. It was prepared in two steps in 30% overall yield (Scheme 52) starting from the diester **358** (prepared analogously to

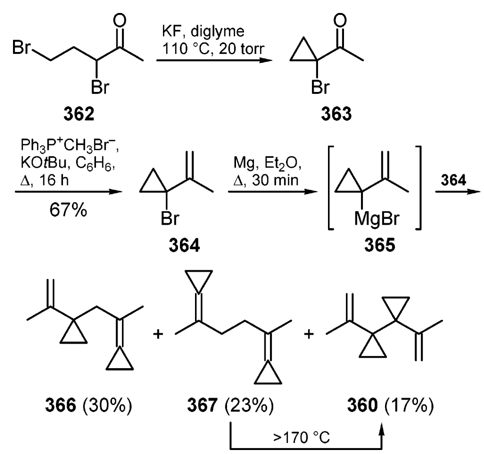
Scheme 52



332, see Scheme 48). The diene **360** was fully cyclopropanated to yield 1,1‴-dimethylquatercyclopropane.[260]

It also proved to be possible to obtain **360** by a Wurtz-type coupling of the Grignard reagent **365**, which in turn was obtained from 1-bromocyclopropyl methyl ketone (**363**) after Wittig alkenation with triphenylmethylenephosphorane to give **364**.[261] It was not possible to directly brominate cyclopropyl methyl ketone to prepare **363**; instead a base-induced cyclization of 1,3-dibromopropyl methyl ketone (**362**) was applied (Scheme 53).[262] The coupling of **365** with **364** gave not only **360** but also **366** and **367**, the latter of which could be transformed into **360** by a thermally induced Cope rearrangement (Scheme 53).[261]

Scheme 53

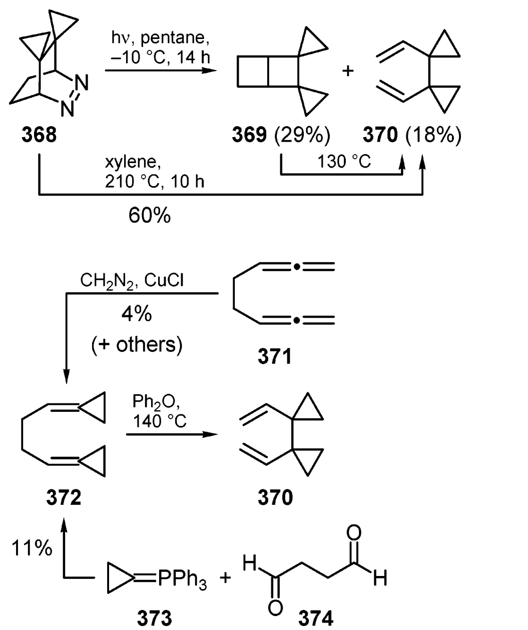


The unsubstituted 1,1′-divinylbicyclopropyl **370** was obtained by photochemical or thermal decomposition of the azo compound **368**, as well as by thermal rearrangement of dispirocyclopropanebicyclo[2.2.0]hexane **369** formed from **368** along with **370** upon photolysis [or by nickel(0)-catalyzed [2 + 2] cycloaddition of cyclobutene to bicyclopropylidene (see below, section 3.4.)] (Scheme 54).[263,264]

The diene **370** is also formed in the thermally induced Cope rearrangement of 1,4-biscyclopropylidenebutane **372**, which was obtained either along with other products by 2-fold cyclopropanation of 1,2,6,7-octatetraene (**371**) with diazomethane in the presence of copper(I) chloride in 4% yield or more selectively in 11% yield by Wittig alkenation of succinic dialdehyde **374** with triphenylcyclopropylidenephosphorane **373** (Scheme 54).[265] Heating of **372** leads cleanly to **370** (Scheme 54), and the activation parameters of this rearrangement have been determined experimentally to be $\log(k/s^{-1}) = 9.57 - (26.2 \pm 0.7)$ kcal/mol/(RT ln 10).[266]

A computational study employing a specifically tailored force field predicted the *s-trans* conformer to be energetically favored for bicyclopropyl (**1**) itself and for 1,1′-difluorobicyclopropyl, whereas for 1,1′-dichloro-, 1,1′-dibromo-, and

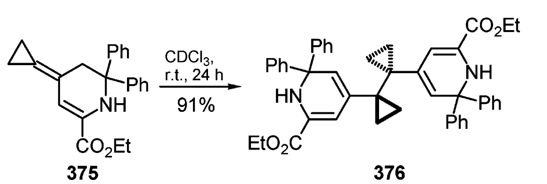
Scheme 54



1,1′-diiodobicyclopropyl, *gauche* conformers with torsional angles of $\varphi = 82-95°$ were computed to have lower energies.[267] The MM2- and MM3-force fields have also been modified to give better agreements with energies and geometries of bicyclopropyls and other cyclopropyl compounds.[216,217]

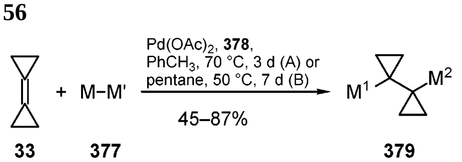
The 1,1′-bis(dihydropyridyl)bicyclopropyl **376** was formed as a mixture of two rotamers by an interesting dimerization of the 4-cyclopropylidene-1,4,5,6-tetrahydropyridine **375**. These rotamers could be separated by column chromatography, indicating that the rotational barrier around the central single bond in **376** is extraordinarily high (Scheme 55).[268] The C_2-symmetric (minor) rotamer depicted in Scheme 55 exhibited a *gauche* conformation ($\varphi = 53.4°$) for its bicyclopropyl moiety in the crystal.[268]

Scheme 55



Several 1,1′-dimetalated bicyclopropyls were prepared from bicyclopropylidene **33** by palladium-catalyzed addition of disilanes and silylstannanes **377** across the double bond of **33** in moderate to very good yields (Scheme 56).[269]

Scheme 56

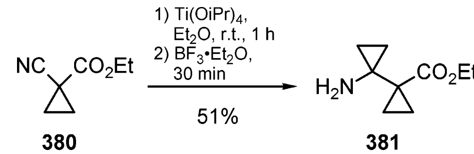


378 = 1,1,3,3-tetramethylbutylisonitrile

Cpd.	M–M'	Cond.	M^1	M^2	Yield (%)
a	$Me_3Si-SiMe_3$	A	$SiMe_3$	$SiMe_3$	77
b	$Me_3Si-SiPh_3$	A	$SiMe_3$	$SiPh_3$	87
c	$Me_3Si-SnBu_3$	B	$SiMe_3$	$SnBu_3$	45
d	$Me_3Si-SnMe_3$	B	$SiMe_3$	$SiMe_3$	68

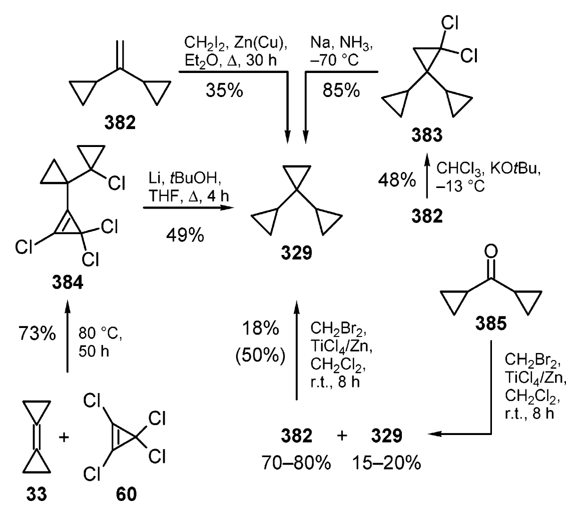
The interesting protected β-amino acid ethyl 1-(1′-aminocyclopropyl)cyclopropanecarboxylate (**381**) was obtained in one step by the titanium-mediated reductive cyclopropanation of the cyano group in ethyl 1-cyanocyclopropanecarboxylate (**380**) (Scheme 57).[270]

Scheme 57



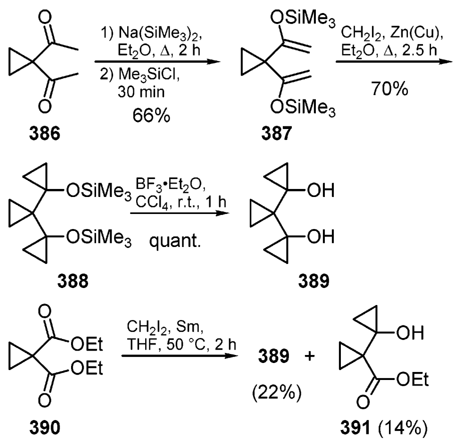
The unsubstitued 1,1-linked tercyclopropane, 1,1-dicyclopropylcyclopropane (**329**) was prepared for the first time by Simmons–Smith cyclopropanation of 1,1-dicyclopropylethene (**382**) in modest yield (Scheme 58).[271] Addition of dichlorocarbene, generated from chloroform with potassium *tert*-butoxide, to **382** and subsequent reduction with sodium in liquid ammonia was reported to produce **329** in an overall yield of 41% (Scheme 58).[272] Better yields in dihalocyclopropanations can be obtained under phase-transfer conditions (e.g., see Table 8). A third preparative alternative starts with the chloro–ene reaction of tetrachlorocyclopropene (**60**) with bicyclopropylidene (**33**). Reduction of the obtained isomer **384** of the primary adduct with lithium and *tert*-butyl alcohol furnished **329** in 36% overall yield.[273] The bicyclopropyl moiety in **384** has been shown to adopt the *gauche* conformation ($\varphi = 55°$) in the crystal.[273] Methylenation of dicyclopropyl ketone **385** with dibromomethane in the presence of titanium(IV) chloride and zinc yielded not only the expected 1,1-dicyclopropylethene (**382**) but also the tercyclopropane **329** as a side product. Treatment of **382** under the same conditions also gave **329** in about the same yield (50% based on converted starting material) along with 65% of recovered **382** (Scheme 58).[274]

Scheme 58



The only known 1,1′-disubstituted tercyclopropanes are the diol **389** and derivatives thereof. The diol **389** was first prepared from 1,1-diacetylcyclopropane (**386**). Transformation to the bissilylenol ether **387** and its subsequent cyclopropanation gave the trimethylsilyl-protected diol **388** in reasonable yield (Scheme 59). Protiodesilylation was accomplished in quantitative yield by treatment with boron trifluoride etherate.[275,276] A one-pot procedure leading to diol **389** was established by Imamoto et al.; treatment of the

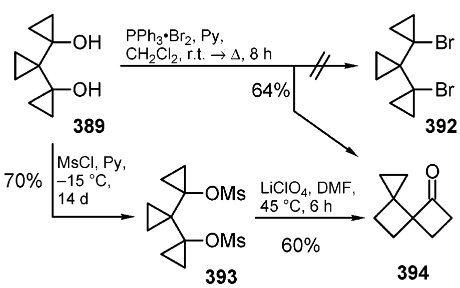
Scheme 59



diester **390** with diiodomethane and samarium furnished the desired diol **389** directly in 22% yield along with 14% of ethyl hydroxybicyclopropylcarboxylate **391** (Scheme 59).[277,278]

Whereas an attempted conversion of the diol **389** to the dibromide **392** produced dispiro[2.0.3.2]nona-5-one **394**, transformation to the dimesylate **393** succeeded. The latter was conceived as a possible precursor to [3]rotane **683** (see section 3.3). However, **393** could not be transformed into the dibromide **392** either, and an attempted electrochemical reduction led to the same ketone **394** again, even without passing an electric current through the solution (Scheme 60). This skeletal transformation is brought about by a cascade of two consecutive cyclopropylmethyl to cyclobutyl cation rearrangements.[275,276]

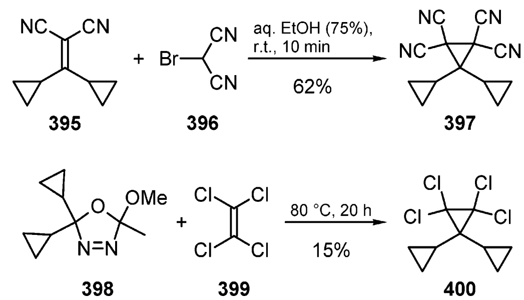
Scheme 60



The first analogue of **329** with substituents on the central ring, the tetracyano derivative **397**, was obtained by a modification of the so-called Wideqvist reaction (Scheme 61). Compound **397** could not be obtained under the classical conditions for this reaction, that is, in situ generation of the alkylidenemalodinitrile **395** from 1 equiv of bromomalodinitrile **396** and a corresponding carbonyl compound in the presence of iodide.[279] The same substitution pattern could be achieved by addition of dicyclopropylcarbene generated by thermal decomposition of the methoxyoxadiazoline **398** to tetrachloroethene (**399**) (Scheme 61).

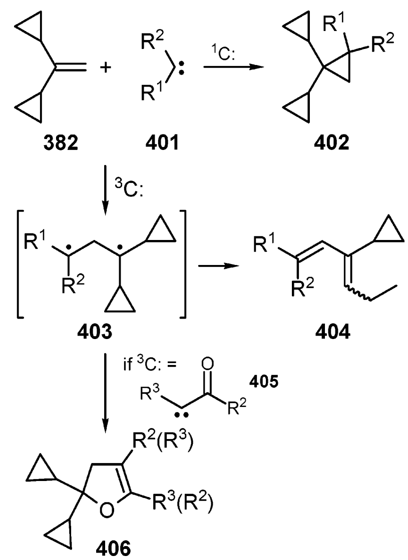
Other derivatives of **329** with substituents on the central ring were prepared by addition of various carbenes **401** to 1,1-dicyclopropylethene (**382**). The applied carbenes included carbonyloxyalkyl-, bis(alkoxycarbonyl)-, and dihalocarbenes (Scheme 62, Table 8). 1,1-Dicyclopropylethene (**382**) has also been proposed as a tool to detect the spin state of carbenes. Generation of the carbene in the presence of **382** should lead to substituted tercyclopropanes **402**, if the reaction proceeds by a way of a concerted cheletropic transformation as supposed to occur with singlet carbenes.

Scheme 61



On the other hand, if the reaction proceeds via diradical intermediates, which are proposed for reactions with triplet carbenes, ring-opened products of type **404** should be obtained as a consequence of the very fast cyclopropylmethyl to homoallyl radical rearrangement in the intermediate **403** (Scheme 62). While clearly displaying the expected behavior in the reactions with singlet and triplet 9-fluorenylidene[280,281] and singlet methoxycarbonylcarbene (entry 6, Table 8),[282] the reaction with triplet methoxycarbonylcarbene (entry 7) yielded only very small amounts of the rearranged product of type **404**,[282] which renders **382** as a probe for carbene spin states useless for highly reactive carbenes. In the special case that R^2 comprises a carbonyl function, ring closure of the intermediate diradical to the dihydrofuran **406** was observed (entries 8, 9).[283]

Scheme 62

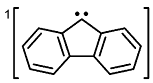
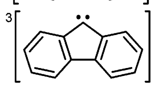
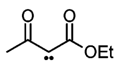
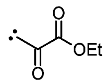


The addition of dichlorocarbene to differently substituted oligocyclopropylalkenes has also been used to assess the limits of this reaction with regard to the steric encumbrance in the starting alkenes.[217]

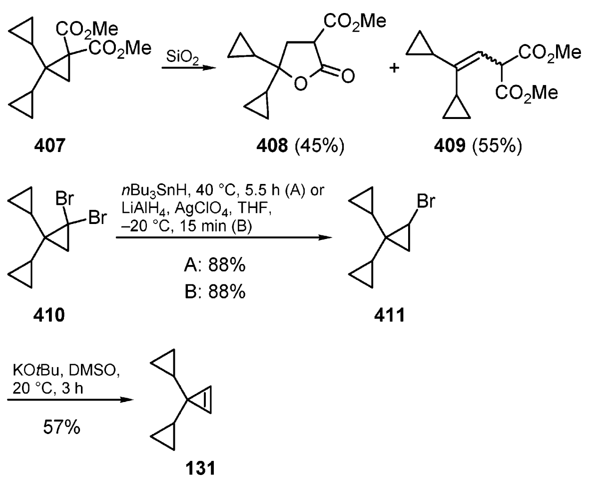
Some of the carbene adducts of **382** undergo interesting transformations; for example, the diester **407** (entry 3, Table 8) was easily converted to the γ-lactone **408**, along with the ring-opening product **409**, upon exposure to silica gel (Scheme 63).[288]

Reduction of the dibromide **410** (entry 10, Table 8) either with tributylstannane (A)[286] or with lithium aluminum hydride in the presence of 1 mol % silver perchlorate (B),[289] furnished the monobromide **411** in 88% yield, which was dehydrobrominated to yield 3,3-dicyclopropylcyclopropene (**131**) (Scheme 63).[286] Apart from this, the dihalo derivatives **383** and **410** have also been used to prepare 2-cyclopropyl-

Table 8. Carbene Addition to 1,1-Dicyclopropylethene 382

Entry	Carbene **401** R^1R^2C	Yield **402** (%)	Yield **404** (%)	Yield **406** (%)	Ref.
1	Cl_2C:	48, 71 (**383**)	–	–	272,284
2	$EtO_2C(H)C$:	59, 89	–	–	272,283
3	$(MeO_2C)_2C$:	88, 79	–	–	285,283
4		57	6	–	280,281
5		5	16	–	280,281
6	$^1[MeO_2C(H)C:]$	17–56	–	–	216
7	$^3[MeO_2C(H)C:]$	44	2–4	–	216
8		–	–	86	283
9		–	–	59	283
10	Br_2C:	57–65	–	–	286
11	MeClC:	44	–	–	287

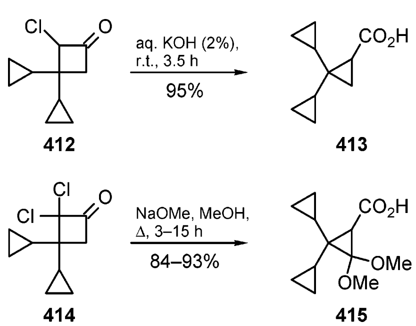
Scheme 63



3-halobuta-1,3-dienes, either by heating[290] or by silver-assisted solvolysis.[291]

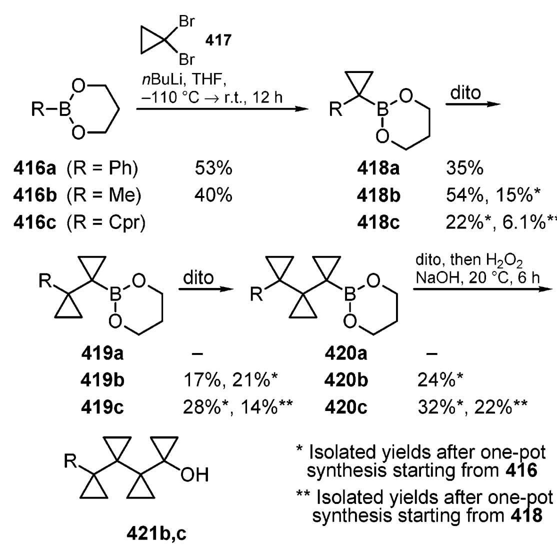
The acid **413** and the substituted derivative **415** have been obtained by a Favorsky-type ring-contracting rearrangement of chlorocyclobutanones **412** and **414**, respectively, which in turn were synthesized by [2 + 2] cycloaddition of mono- and dichloroketene to 1,1-dicyclopropylethene **382** (Scheme 64).[292,293]

Scheme 64



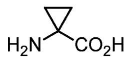
Eventually, the synthesis of 1-hydroxy-substituted 1,1-linked ter- (**420b** and **419c**), quater- (**420c**), and quinquecyclopropanes (**421c**) was achieved applying the so-called Matteson homologation.[294,295] Starting from trimethylenephenylboronate **416a** (R = Ph), 2-fold insertion of in situ generated bromolithiocyclopropane by bromine–lithium exchange on dibromocyclopropane **417** with *n*-butyllithium at −110 °C furnished trimethylene 1′-phenylbicyclopropylboronate **419a** (R = Ph) in 19% overall yield (Scheme 65).[296] Further homologation using the same protocol did not succeed. With the methylboronate **416b**, however, two further homologation steps succeeded to give **421b** (Scheme 65).[296] The simultaneous synthesis of **419b**, **420b**, and **421b** could also be accomplished using a one-pot protocol, according to which the reaction mixture was cooled again prior to addition of another batch of dibromocyclopropane and *n*-butyllithium and was slowly warmed to room temperature, in 15%, 21% and 24% overall yield, respectively.[296] Starting from the cyclopropyl- (**416c**) or the bicyclopropyl boronate (**418c**), the quinquecyclopropane **421c** could be obtained according to the one-pot protocol in 32% and 22% overall yield, respectively, along with **419c** and **420c** (Scheme 65).[296] Treatment of the boronic esters with hydrogen peroxide under basic conditions furnished the free hydroxyoligocyclopropanes from these.

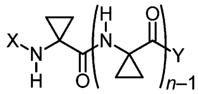
Scheme 65

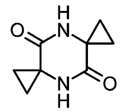


In the crystal, the quatercyclopropyl 3,5-dinitrobenzoate derived from **421b** adopts a helical conformation in which all bicyclopropyl moieties are *gauche* oriented. The same is true for the quinquecyclopropyl ester derived from **421b**. The helical structure, which is due to the *gauche* conformation of the bicyclopropyl moieties, was also reproduced in optimized geometries obtained at the B3LYP/6-31G* level of theory.[296]

A large number of different cyclopropyl-endowed amino acids have been synthesized during the last decades.[297,298] Many of these compounds exhibit interesting chemical and biological activities, but do not fall into the scope of this review, because they contain only a single cyclopropane moiety. However, oligohomopeptides **423** consisting of 1-aminocyclopropanecarboxylic acid (ACC, Ac_3c, methanoalanine, **422**) must be considered as containing a number of 1,1-disubstituted cyclopropane moieties. Cyclopropyl groups in amino acids, when incorporated into peptides,


422-H

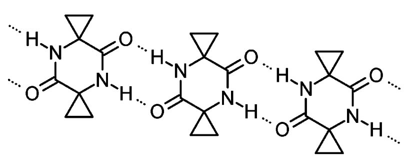

423


424

restrict the conformational flexibility of the peptide chains and can thus enforce specific secondary structures of peptides, which can be used for fine tuning the receptor-binding properties or modifying their biological activities in general.

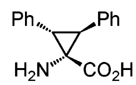
In a series of papers, Toniolo et al. in 1989 published results of extensive structural studies, applying X-ray diffraction, NMR, IR spectroscopy, and force-field calculations, on oligopeptides of type **423** ranging from monomers to tetramers ($n = 1-4$) bearing different groups on the N- (X = H, Ac, 4-Br−Bz, Boc, Fmoc, Z) and on the C-terminus (OMe, OH, NHMe).[299−302] Whereas the dimers are too short to show the typical behavior of the longer peptides and simply adopt more or less extended conformations, the trimers and tetramers folded into type I β-bends and (distorted) 3_{10} helices. Judging from their results, the authors propose single ACC residues in a peptide to favorably occupy both corners of either type I or type III β-bends or the right corner of a type II β-bend.[302] The six-membered ring of the diketopiperazine **424**, the cyclic dimer of **422**, was found to be almost perfectly planar in the crystal.[300]

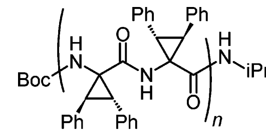
Diketopiperazines that have a symmetrical substitution pattern with one hydrogen-bond donor and one acceptor on each side of the molecule should therefore be able to form long tape-like aggregates in the crystal. Indeed, in a systematic study on 13 symmetrically substituted diketopiperazines, **424** among seven others gave suitable crystals for X-ray structure analysis and was indeed found to form the expected tape-like aggregate **425**. Five of the studied compounds, including **424**, formed linear tapes. However, **424** was the only diketopiperazine among these in which not all tapes were aligned with their long axis parallel: stacks of parallel tapes were “zippered” together with a diagonal tape.[303]


425

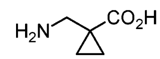
Homopeptides of type **423** (X = Ac, Y = NHMe, $n = 5-13$) have also been used as model compounds in the evaluation of an extended AMBER force field, which had been parametrized for the cyclopropane ring before. These calculations predicted for all peptides a 3_{10} helix to be the preferred conformer. During the parametrization, several data sets obtained at different levels of theory (AM1, HF, MP2, MP4, and B3LYP) were compared with the experimentally obtained geometrical parameters of the cyclopropane system, showing the AM1 and B3LYP computations to give the best results. Although no structural data on longer homooligomers of ACC **422** are available for comparison with the computational results, these are in line with the studies on the smaller peptides.[304]

In all X-ray studies on oligomers of ACC **422**, right-handed as well as left-handed helices had been found due to the achiral nature of ACC. The dipeptide **427** and the tetrapeptide **428** of 1-amino-*trans*-2,3-diphenylcyclopropanecarboxylic acid (**426**), in which C_α is not, but the two C_β atoms are stereogenic centers, in a crystal structure analysis as well as NMR studies displayed strong biases to fold into right-handed type III β-turns (for **427**) or a right-handed 3_{10} helix (for **428**).[305,306]


426


427 (n = 1)
428 (n = 2)

The β-amino acids 1-(aminomethyl)cyclopropanecarboxylic acid (**429**) and (1-aminocyclopropyl)acetic acid (**430**) are the simplest cyclopropyl-containing β-amino acids. Seebach et al. obtained oligomers **431** (n = 2, 3, 4, and 6)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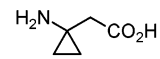
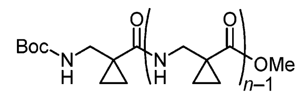

430

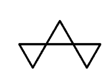

431

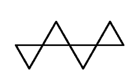
of **429** and studied their structures in the crystals as well as in solution employing IR and NMR spectroscopy. Based on the geometrical parameters obtained, a model using idealized torsional angles was proposed for the oligomers of **429**, which shows a stair-like aggregation featuring eight-membered H-bonded ring substructures.[307] The β-alanine analogue 2-(1-aminocyclopropyl)acetic acid (**430**) so far has not been employed in the preparation of homooligopeptides.[308]

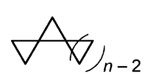
2.5. Spiroannelated Systems—Linear Triangulanes and Heteroanalogues

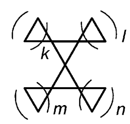
Spiroannelation of two or more cyclopropane rings in a molecule is accompanied by an additional increase in strain and causes changes in the electronic structure. This leads to remarkable changes in physical and chemical properties. The simplest member of this family, spiropentane (**432**), has about

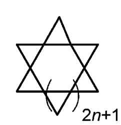

432


433


434


435

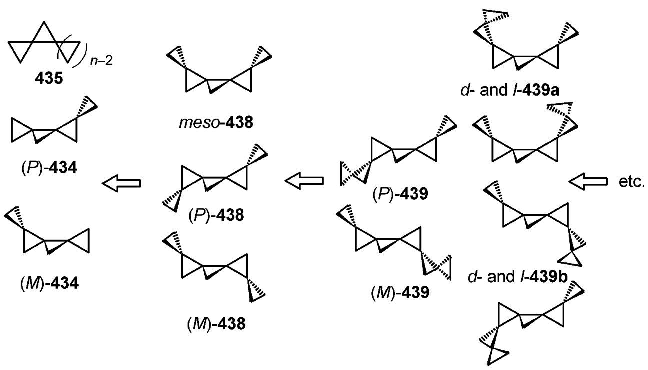

436


437

110 years of history,[309] while the hydrocarbons consisting of three (**433**)[248,276,310] and four (**434**)[276,311] spiroannelated cyclopropane units have been known for the past 35 years. Eventually such hydrocarbons, which consist of spiroannelated cyclopropane rings only, were termed [n]triangulanes.[312] The whole class of triangulanes can be subdivided into three subclasses according to their structure: the unbranched (or linear) [n]triangulanes (UTs or LTs) **435**, the branched [n]-triangulanes (BTs) **436**, and cyclic [n]triangulanes (CTs) **437**. Thus, spiropentane (**432**), according to this definition, is unbranched [2]triangulane ([2]UT).

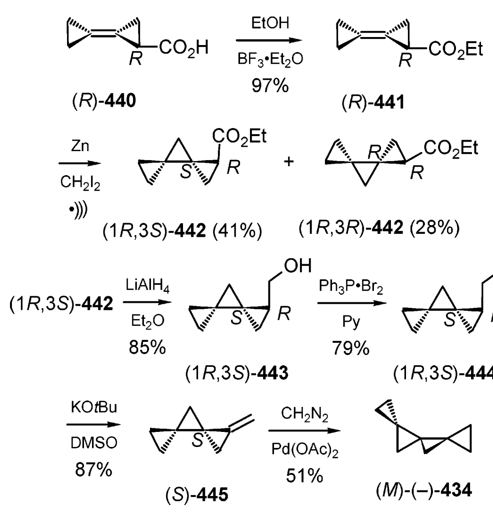
The major achievements in the chemistry of such hydrocarbons have been reviewed exhaustively not long ago.[313] Since then, the efforts in this field have been focused on the synthesis of higher unbranched [n]triangulanes in enantiomerically pure form. The stereochemical features of unbranched [*n*]triangulanes **435** have been thoroughly analyzed.[312] According to this, the number of stereoisomers grows rapidly with an increasing number of three-membered rings, and many of the diastereomers of higher [*n*]triangulanes ($n \geq 4$) are chiral. Thus, attachment of a fourth spirocyclopropane ring to the achiral molecule of dispiro-[2.0.2.1]heptane ([3]UT) **433** will lead to two enantiomeric [4]UTs, (*M*)- and (*P*)-**434** (Scheme 66). Essentially, the C_2-symmetric molecule of **434** with its completely rigid and thereby mutually orthogonal cyclopropane rings is a section of a helix, and therefore, the stereochemical descriptors for helices can logically be applied for **434** and extended unbranched [*n*]triangulanes **438**, **439**, etc., **435** ($n \geq 7$).

Scheme 66



The first enantiomerically pure unbranched [4]triangulane, (*M*)-(−)-trispiro[2.0.0.2.1.1]nonane (**434**),[314] was prepared starting from racemic bicyclopropylidenecarboxylic acid, *rac*-**440**.[315] The optical resolution of *rac*-**440** with dehydroabietylamine furnished (*S*)-(+)-**440** and (*R*)-(−)-**440**. The ethyl ester (*R*)-**441** of the latter was cyclopropanated to give ethyl (1*R*,3*R*)- and (1*R*,3*S*)-[3]triangulane-1-carboxylates, (1*R*,3*R*)-**442** and (1*R*,3*S*)-**442** (Scheme 67).

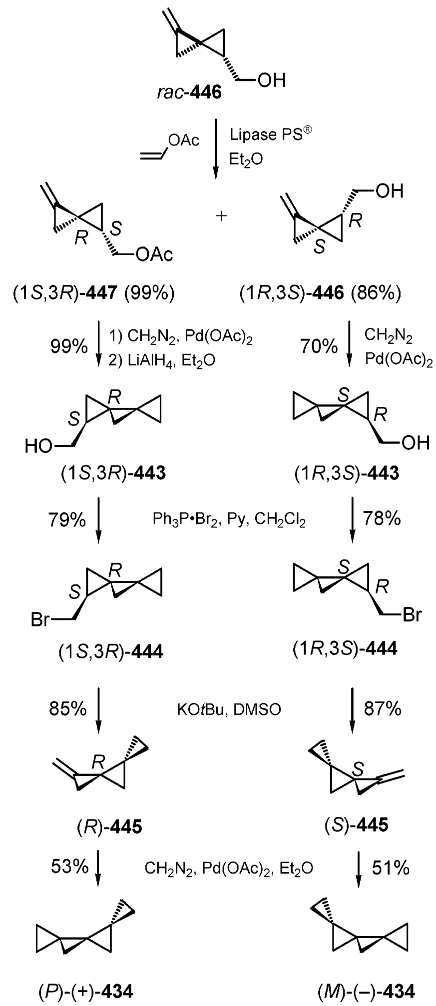
Scheme 67



The (1*R*,3*S*)-**442** was converted into (*M*)-(−)-**434** with an enantiomeric excess of 99% by reduction to the alcohol (1*R*,3*S*)-**443**, its conversion to the bromide (1*R*,3*S*)-**444**, and subsequent dehydrobromination to (*S*)-1-methylene[3]-triangulane (*S*)-**445**, followed by cyclopropanation (6% overall yield starting from *rac*-**440**).[314,316]

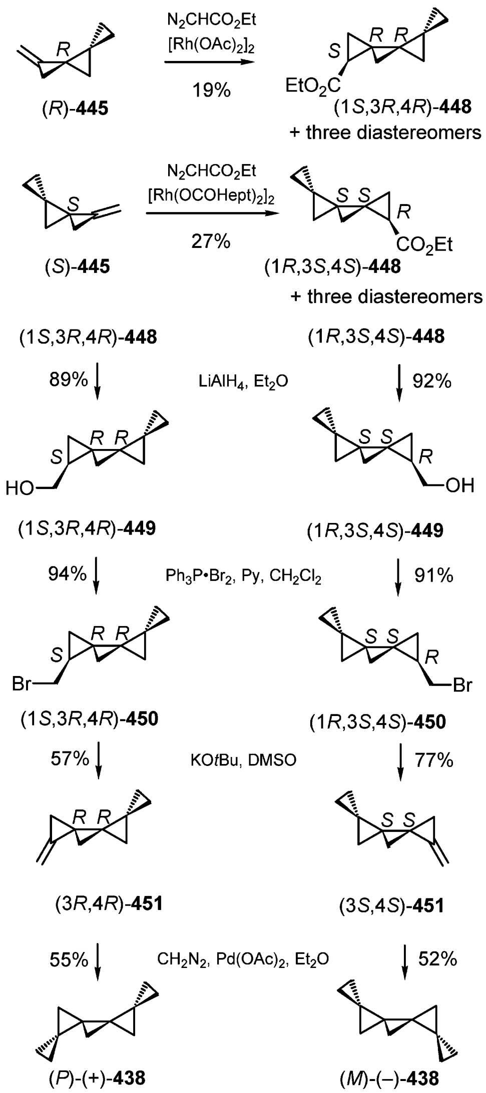
A more efficient and less laborious approach to the enantiomerically pure [3]triangulanylmethanols (1*S*,3*R*)-**443** and (1*R*,3*S*)-**443** was by means of an enantioselective enzymatic acylation in ≥100 g quantities of the racemic alcohol *rac*-**446** catalyzed by Lipase PS (*Pseudomonas sp*) (Scheme 68).[317] From these alcohols (1*S*,3*R*)-**443** and (1*R*,3*S*)-**443**, the enantiomerically pure triangulanes (*P*)-**434** and (*M*)-**434** were prepared by a set of routine transformations (Scheme 68), which had previously been applied to prepare the [4]triangulanes (*M*)-**434** and (*P*)-**434** in 35% and 21% overall yield, respectively, starting from the alcohol *rac*-**446**, with enantiomeric excesses of ≥96%.[316]

Scheme 68



Since the position of the methylene group in methylene-[3]triangulanes (*R*)-**445** and (*S*)-**445** predetermines any further extension of the helix, these alkenes were used for the preparation of enantiomerically pure [5]triangulanes (*P*)-**438** and (*M*)-**438** (Scheme 69). Thus, the addition of ethoxycarbonylcarbene, generated by decomposition of ethyl diazoacetate in the presence of dirhodium tetraoctanoate, onto (*R*)-**445** and (*S*)-**445**, furnished the enantiomerically pure esters (1*S*,3*R*,4*R*)-(+)-**448** and (1*R*,3*S*,4*S*)-(−)-**448** in 19% and 27% isolated yield, respectively, which were isolated by simply distilling off the other three diastereomers in each case over a concentric-tube column. The enantiomerically pure esters **448** were transformed to the enantiomerically pure [5]triangulanes (*P*)-**438** and (*M*)-**438** in four standard steps. Thus, reduction with lithium aluminum hydride followed by treatment with the triphenylphosphane/bromine reagent and then dehydrobromination with potassium *tert*-butoxide gave methylene[4]triangulanes (*3R,4R*)-**451** and (*3S,4S*)-**451** in 48% and 64% overall yield, respectively. Cyclopropanation of the latter under the conditions mentioned above furnished the enantiomerically pure (*M*)-(−)- and (*P*)-(+)-[5]triangulane (*M*)-(−)-**438** and (*P*)-(+)-**438** in 55% and 52% yield, respectively, after gas chromatographic separation in the last step (Scheme 69), corresponding to a 5% and 9%, respectively, overall yield from the methylene[3]triangulanes (*R*)-**445** and (*S*)-**445**, respectively, with an enantiomeric excess of ≥94% for both.[316]

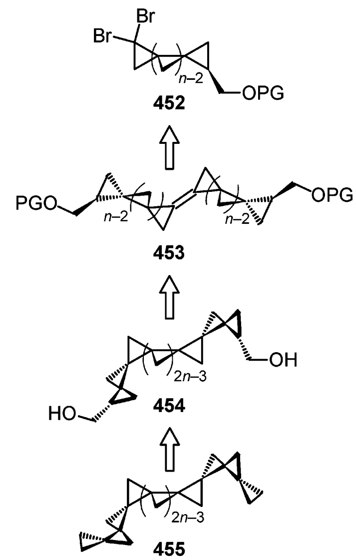
Scheme 69



However, because of the rapidly growing number of possible stereoisomers of these [*n*]triangulanes with increasing *n*, for example, the family of [9]triangulanes consists of 4 *meso*-diastereomers and 16 pairs of enantiomers,[312] and the fact that upon each addition of a monosubstituted cyclopropanating reagent onto a methylene[*n*]triangulane, two new stereogenic centers are created, any linear synthesis such as the one discussed for the enantiomerically pure [4]- and [5]triangulanes would face severe problems of separation en route to higher [*n*]triangulanes.

Therefore new, more convergent routes to (*M*)-(−)- and (*P*)-(+)-[*n*]triangulanes **455** with odd *n* ≥ 7 starting from appropriate α,*ω*-difunctional chiral building blocks were elaborated (Scheme 70). This strategy consists of dehalogenative coupling of the 1-bromo-1-lithiocyclopropanes generated from protected (*ω*,*ω*-dibromotriangulanyl)methanol **452** in the presence of cupric chloride according to the method of Neuenschwander et al.[318] followed by Müller−Gaspar−Roth cyclopropanation[319] of the central double bond in the bicyclopropylidene derivative **453** and final transformation of the terminal hydroxymethyl groups in **454** into terminal cyclopropane rings applying the sequence of routine methods mentioned above.

Scheme 70

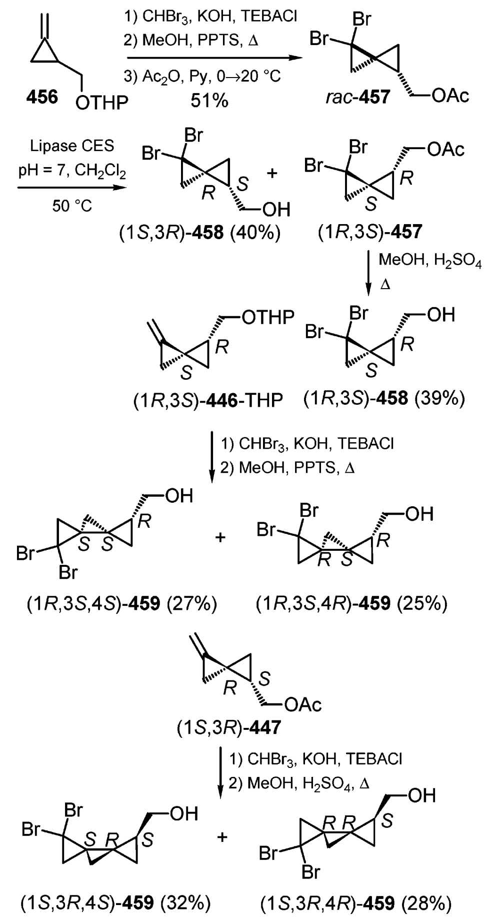


The actual starting materials were prepared as shown in Scheme 71. Thus, highly diastereoselective dibromocarbene addition onto 2-[(2-methylenecyclopropyl)methoxy]tetrahydropyran (**456**) followed by reprotection and enantioselective enzymatic deacylation with Lipase CES furnished [(1*S*,3*R*)- and (1*R*,3*S*)-4,4-dibromospiropent-1-yl]methanol [(1*S*,3*R*)-**458** and (1*R*,3*S*)-**458**] with an *anti*-arrangement of their hydroxymethyl and dibromomethylene groups in 20% overall yield for each. On the other hand, THP protection of the above-described enantiomerically pure alcohol (1*R*,3*S*)-**446** followed by dibromocyclopropanation of (1*R*,3*S*)-**446**-THP or acetate (1*S*,3*R*)-**447**, deprotection, and separation of diastereomers afforded enantiomerically pure (5,5-dibromodispiro[2.0.2.1]heptyl)methanols (1*R*,3*S*,4*S*)-**459** and (1*S*,3*R*,4*R*)-**459** in 27% and 28% yield, respectively.

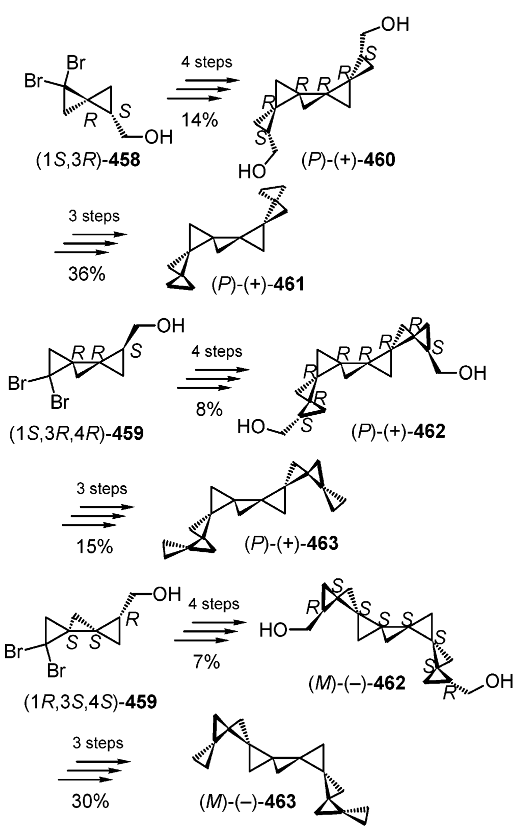
The convergent assembly of the chiral building blocks (1*S*,3*R*)-**458**, (1*R*,3*S*,4*S*)-**459**, and (1*S*,3*R*,4*R*)-**459** in seven simple steps according to the newly developed strategy discussed above furnished the continuously helical [7]- and [9]triangulanes (*P*)-(+)-**461**,[320] (*M*)-(−)-**463**,[321] and (*P*)-(+)-**463**,[320,321] respectively, in 5%, 2%, and 1% overall yield, respectively (Scheme 72).

Monoprotection of one hydroxymethyl terminus in (*M*)-(−)-**460** [prepared analogously to (*P*)-(+)-**460**] followed by transformation of the hydroxymethyl group in (*M*)-(−)-**460**−THP into a cyclopropane moiety and of the tetrahydropyranyloxymethyl group in the resulting (*M*)-(−)-**464** into a double bond (in three steps each) afforded methylene[6]-triangulane (*M*)-(−)-**465** (Scheme 73). The latter was subjected to the established set of transformations − dibromocyclopropanation, diastereomer separation, dehalogenative coupling, diastereomer separation, and cyclopropanation of the central double bond in (*E*)- and (*Z*)-**467** − to furnish two bent and one straight rod-like [15]triangulanes (*R*,*R*)-(−)-

Scheme 71

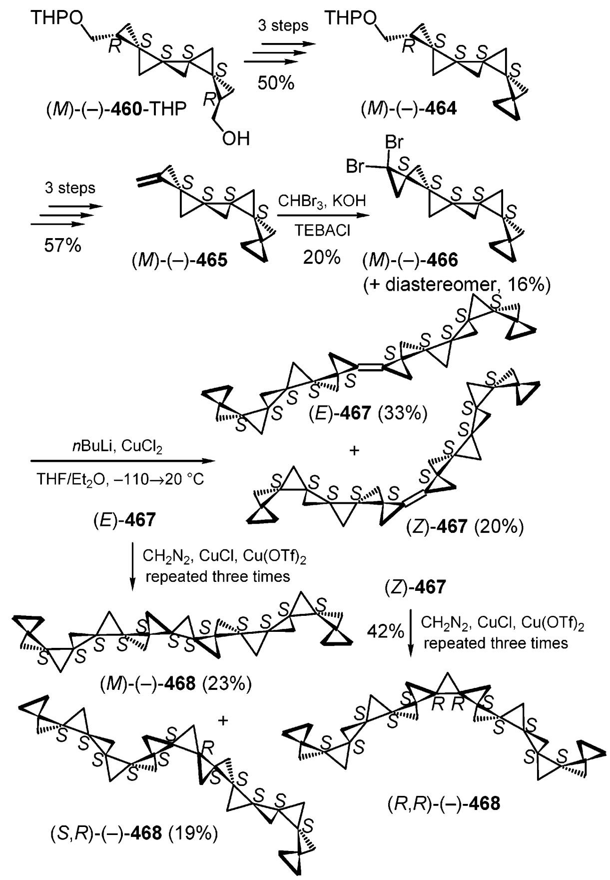


Scheme 72



468, (*S*,*R*)-(−)-**468**, and (*M*)-(−)-**468**, which could be separated and characterized by X-ray crystal structure analyses (Scheme 73).[320]

Scheme 73



The latter essentially set the new record for unbranched [*n*]triangulanes. The widths between the outermost hydrogen atoms in (*S*,*R*)-**468**, (*R*,*R*)-**468**, and (*M*)-**468** were found to be 17.3, 13.5, and 21.1 Å, respectively, and the widths between the outermost carbon atoms are 16.4, 11.6, and 19.5 Å, respectively.

The whole family of enantiomerically pure σ-[*n*]helicenes (*P*)-**434** and (*M*)-**434** (σ-[4]helicenes), (*M*)-(−)-**438** and (*P*)-(+)-**438** (σ-[5]helicenes), (*P*)-(+)-**461** (σ-[7]helicene), as well as both the σ-[9]helicenes (*M*)-(−)-**463** and (*P*)-(+)-**463**, and the σ-[15]helicene (*M*)-(−)-**468** do not display any absorption in the ordinarily accessible vis/UV spectral range (800−200 nm). However, they have remarkably high specific rotations even at 589 nm, which increase drastically on going to shorter wavelengths, indicating that these compounds must have Cotton effects with extremely large amplitudes in the optical rotatory dispersion (ORD) below 200 nm (Table 9).

Comparison of the values of $[\alpha]_D^{20}$ for the now known five enantiomerically pure σ-[*n*]helicenes − (*M*)-(−)-**434** (−192.7),[314] (*P*)-(+)-**438** (+373.0),[316] (*P*)-(+)-**461** (+672.9),[320] (*P*)-(+)-**463** (+909.9),[321] and (*M*)-(−)-**468** (−1302.5)[320,321] − indicates a drastic and continuous increase of the specific rotation with an increasing number of three-membered rings (cf. ref 322). This increase goes beyond that to be expected with increasing molecular weights (Figure 2). Interestingly, the values of $[\alpha]_D^{20}$ normalized with respect to the number of spiroannelated cyclopropanes exceeding $n = 3$ for the achiral [3]triangulane ($n - 3$), decrease steadily with an increasing number *n*.

The decreasing incremental value $[\alpha]_D^{20}/(n - 3)$ ($\Delta[\alpha]$) for each added spirocyclopropane ring starting from the achiral

Table 9. Comparison of the Measured (in $CHCl_3$) and DFT/SCI-Computed Specific Rotations of Enantiomerically Pure [*n*]Triangulanes

compd (*n*)	λ [nm]	$[\alpha]_D^{20}$ measured	$[\alpha]_D^{20}$ computed[a]	ref
(*M*)-(−)-**434**	589	−192.7	−217.9	
(4)	546	−229.7	−264.0	314
	436	−400.2	−407.8	
	365	−648.2	−576.7	
(*P*)-(+)-**438**	589	+373.0	+394.9	
(5)	546	+445.2	+508.1	316
	436	+777.4	+791.9	
	365	+1264.0	+1080.3	
(*P*)-(+)-**461**	589	+672.9	+879.5	320, 321
(7)	546	+802.8	+1054.4	
	436	+1404.5	+1873.1	
	365	+2290.8	+3165.2	
(*P*)-(+)-**463**	589	+909.9	+1006.5	
(9)	546	+1087.1	+1192.8	320, 321
	436	+1907.0	+2010.7	
	365	+3119.4	+3145.5	
(*M*)-(−)-**468**	589	−1302.5	−2419.9	
(15)	546	−1556.6	−2875.5	320, 321
	436	−2738.7	−4904.8	
	365	−4493.4	−7804.1	

[a] All computed values were adjusted by substracting a constant value to account for effects of solvent−solute interactions, which currently cannot be taken into account computationally.

[3]triangulane (dispiro[2.0.2.1]heptane) exhibits virtually a linear dependence on the number of the rings with a regression line $\Delta[\alpha] = 223.32 - 7.72n$ and a correlation coefficient $r = 0.999$. The extrapolation of this line intersects the baseline at $n = 29$, which means that the specific rotation, normalized with respect to the number ($n - 3$) of three-membered rings added to the achiral [3]triangulane, for higher enantiomerically pure helical [*n*]triangulanes ($n \geq 29$) would not increase any more. Although it has never been interpreted in this way, the same phenomenon can be observed for the π-[*n*]helicenes, for which the intersection with the baseline already occurs around $n = 15$ (Figure 2).

In contrast to the large number of all-carbon triangulanes, far fewer compounds of this type are known that contain a heteroatom, most probably because the three-membered heterocycles are more reactive.[313a] Some progress, however, has also been achieved in the field of heteroanalogues of unbranched triangulanes. Thus, the previously unknown 1-oxa[3]triangulane (**470**) was prepared from methylene-spiropentane (**469**) in the usual way (Scheme 74);[324] however, **470** appeared to be much less stable than the isomeric 7-oxa-[3]triangulane (**471**),[313a,324] which had been obtained from bicyclopropylidene **33**.

More progress has been made during the past decade toward phosphatriangulanes. Thus, after the first preparation of phosphaspiropentane in 1993,[325] a series of novel, highly stable linear mono- and diphospha[*n*]triangulanes, **473**, **474**, **475**, **477**, and **480**, were synthesized recently in high yields

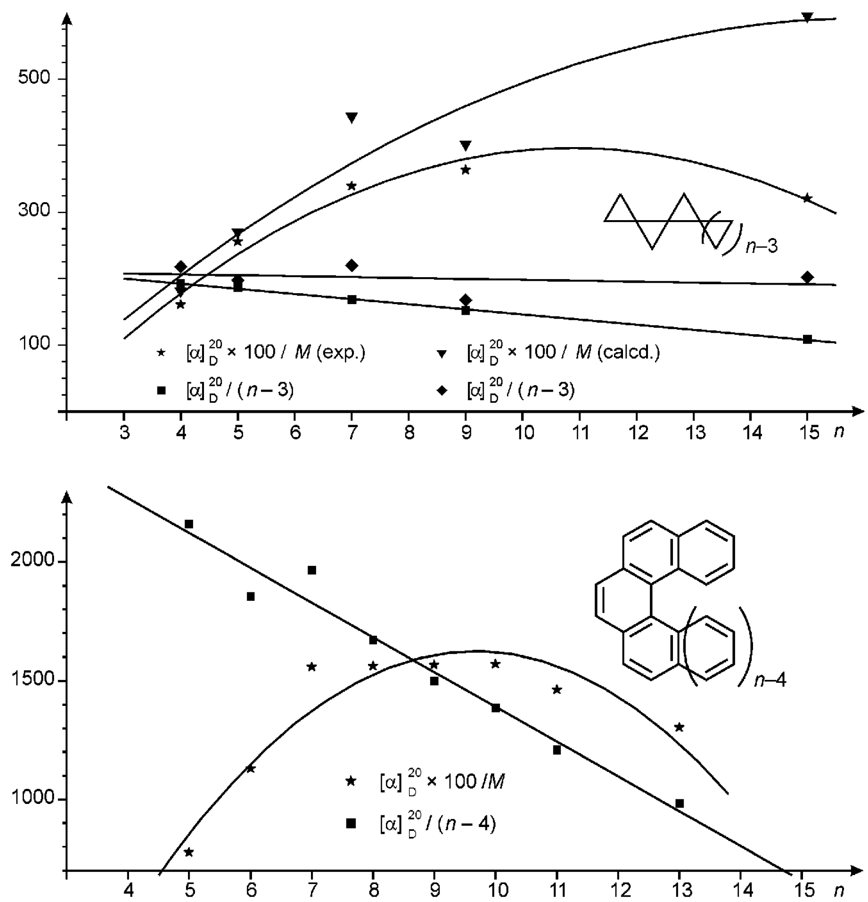
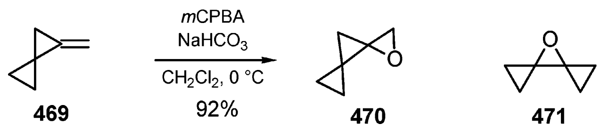


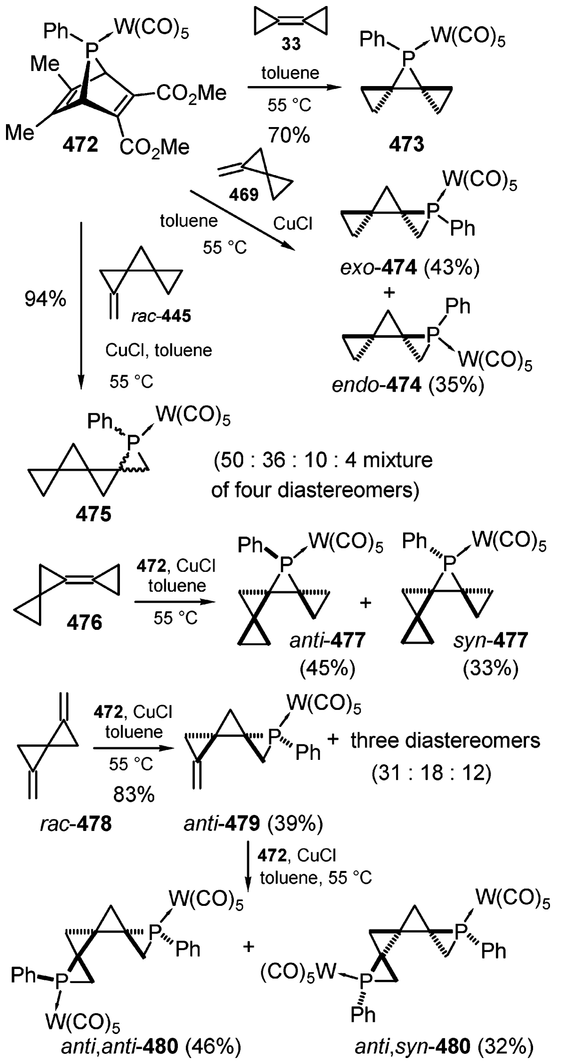
Figure 2. Dependence of specific rotations of enantiomerically pure helical [*n*]triangulanes ("σ-[*n*]helicenes") normalized with respect to molecular weights (■, experimentally determined values; ◆, computed values) and to the number of spiroannelated cyclopropanes (★, experimentally determined values; ▼, computed values) on the number of spiroannelated cyclopropane rings (top) in comparison with analogous experimentally determined values for π-[*n*]helicenes (bottom).[323]

Scheme 74



by phosphinidene addition to bicyclopropylidene (**33**), methylenetriangulanes **469** and *rac*-**445**, spirocyclopropanated bicyclopropylidene **476**, and dimethylenespiropentane *rac*-**478**, respectively (Scheme 75). The phosphinidene was generated by thermal[326] or CuCl-catalyzed[327] decomposition of the substituted 7-phosphanorbornadiene **472**. The effect of spirofusion on the electronic properties of these esthetically appealing phosphacycles is apparent from single-crystal X-ray structure analyses, which revealed a tightening of the phosphirane ring on spirocyclopropanation.

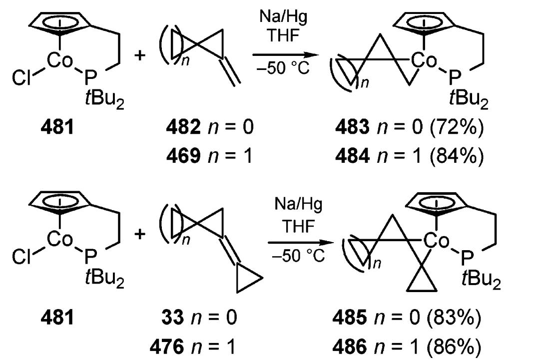
Scheme 75



However, whereas the [*n*]triangulane hydrocarbons possess a significant excess strain of 8.6 kcal/mol per spirocarbon,[313a,328] the corresponding strain increment for phospha[3]triangulane **473** was estimated to be only 5.2 kcal/mol per spirocarbon.[326]

Treatment of {η^5:η^1[2-(di-*tert*-butylphosphanyl-*P*)ethyl]-cyclopentadienyl}cobalt(I) chloride (**481**) with methylenecyclopropane (**482**) or bicyclopropylidene (**33**), as well as with their spirocyclopropanated analogues methylenespiropentane (**469**) or cyclopropylidenespiropentane (**476**), in the presence of sodium amalgam at −50 °C furnished the stable cobalt complexes **483**, **485**, **484**, and **486**, respectively, in 72%, 83%, 84%, and 86% isolated yield, respectively[329] (Scheme 76).

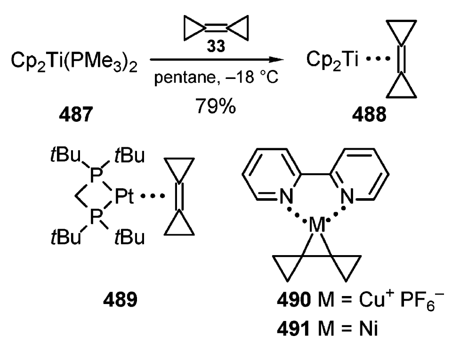
Scheme 76



The compounds **483**, **484**, and **485** are thermally stable up to 109, 145, and 160 °C, respectively, as was determined by differential thermal analysis (DTA)-thermogravimetry (TG) analysis. The X-ray crystal structure analyses of such complexes as well as the NMR spectroscopic data of all complexes disclose them as linear cobalta[*n*]triangulanes.[329]

In spite of being a tetrasubstituted alkene, bicyclopropylidene (**33**) turned out to be a remarkably good ligand not only for cobalt but also for titanium, platinum, copper, and nickel. Thus, treatment of $(Cp)_2Ti(PMe_3)_2$ (**487**) with 1.16 equiv of **33** in pentane gave (η^2-bicyclopropylidene)(bis-η^5-cyclopentadienyl)titanium(II) **488** in 79% yield as a green solid (Scheme 77).[329a] Stable complexes of platinum(0) (**489**),[330] copper(I) (**490**),[331] and nickel(0) (**491**)[332] with a bicyclopropylidene ligand have also been obtained (Scheme 77).

Scheme 77



The complexes **489**,[330] **490**,[331] and **491**[332] have been fully characterized by X-ray crystal structure analyses, which show that the bicyclopropylidene ligand in all of them is remarkably bent out-of-plane at both termini of the double bond; that is, these complexes are further examples of 7-metalla-[3]triangulanes.

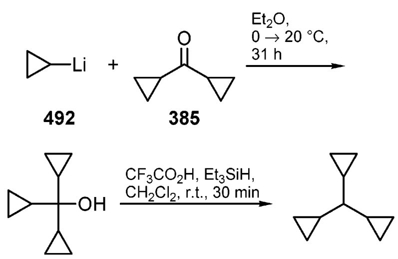
3. Branched Aggregates of Three-Membered Rings

3.1. Oligocyclopropyl-Substituted Alkanes, Alkenes, and Alkynes

With modern cyclopropanation methodologies available, a large variety of differently functionalized aliphatic compounds containing two or more isolated cyclopropyl moieties can be synthesized without problems. Very often, alkenes serve as starting materials and are cyclopropanated according to a broad variety of well-established protocols. In addition to these, esters[333] and *N*,*N*-dialkylcarboxamides,[334,335] nitriles,[334a,b] ketocarbonyl groups,[336] and eneamines[337] can be converted into variously substituted cyclopropanes. Depending on the functionalities present in the precursor, the appropriate protocol for the cyclopropanations must be chosen. The synthesis of alkanes with more than two cyclopropanes attached to the same carbon is more challenging.

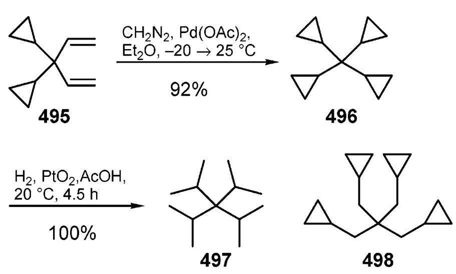
Tricyclopropylmethane **494** was first described by Hart et al. without giving any experimental details.[338] A synthesis by addition of cyclopropyllithium **492**, generated in situ from bromocyclopropane and lithium sand, to dicyclopropylketone **385** to form tricyclopropylmethanol **493**[339] and its subsequent reduction with triethylsilane and trifluoroacetic acid (Scheme 78) was described by Tremper et al.[340] Alternatively, the alcohol **493** can be reduced with aluminum chloride−lithium aluminum hydride (80% yield).[341]

Scheme 78



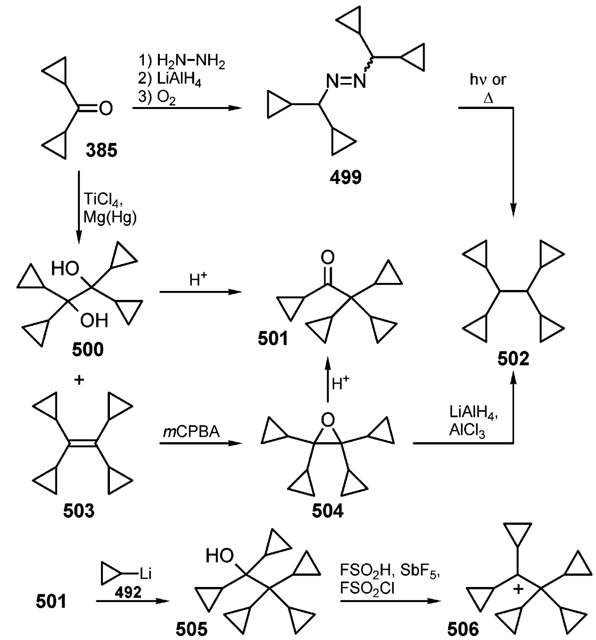
Tetracyclopropylmethane **496** had been elusive until 2001, despite the reported syntheses of several other percyclopropylated main group element compounds. Eventually, **496** was prepared by repeated addition of $Pd(OAc)_2$ to a solution of dicyclopropyldivinylmethane (**495**) and diazomethane in ether (Scheme 79).[342,343] According to an X-ray diffraction study, the hydrocarbon **496** adopts an S_4-symmetrical conformation in the crystal.[342] Catalytic hydrogenation of **496** furnished the previously unknown tetraisopropylmethane (**497**) in quantitative yield (Scheme 79). This even more sterically crowded hydrocarbon assumes a D_{2d}-symmetric conformation, which, according to computations, is not much different geometrically and energetically from the corresponding S_4-symmetric conformation.[342] The dynamics of the conformational changes of these highly congested hydrocarbons have been studied by NMR spectroscopy.[343] Tetrakis(cyclopropylmethyl)methane (**498**) was synthesized along the same lines as tetracyclopropylmethane (**496**).[344]

Scheme 79



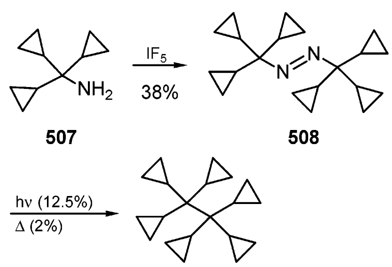
Tetracyclopropylethane **502** was prepared along two different routes by Timberlake et al. (Scheme 80).[345] The ketone **501** had been used before to generate the pentacyclopropylethyl cation by addition of cyclopropyllithium **492** to **501** and treatment of the resulting alcohol with FSO_3H-SbF_5/FSO_2Cl (1:1).[345,346] Pentacyclopropylethane itself has not been described in the literature.

Scheme 80



Hexacyclopropylethane (**509**), however, had been obtained 19 years earlier by photolysis of hexacyclopropylazomethane (**508**),[347,348] which in turn was prepared by oxidative dimerization of tricyclopropylmethylamine **507** with iodine pentafluoride (Scheme 81).[349] Thermolysis of **508** also gave **509**, yet in only 2% yield.[347,348] Hexacyclopropylethane **509** was used to study the influence of steric crowding on the ease of single-bond homolysis.[347,348,350]

Scheme 81

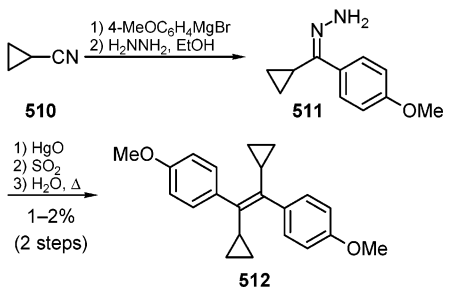


Cyclopropyl-substituted alkenes have mainly been studied with respect to their physical properties and mechanistic aspects of various alkene transformations. The first substituted dicyclopropylethene **512** was prepared in 1960 with an overall yield of 1−2% (Scheme 82).[351]

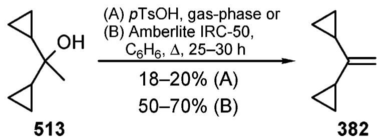
Unsubstituted 1,1-dicyclopropylethene **382** could be obtained by dehydration of the tertiary alcohol **513** (Scheme 83).[352] The originally reported procedure employed distillation of **513** over *p*-toluenesulfonic acid and gave rise to up to 20% of **382**. Better yields could be obtained by dehydration of **513** in the presence of strongly acidic cation exchange resins with azeotropic removal of water.[272]

A few years later, Maercker generated cyclopropylmethylenetriphenylphosphorane **515** from the phosphonium salt prepared from cyclopropylmethyl bromide and triphenylphos-

Scheme 82

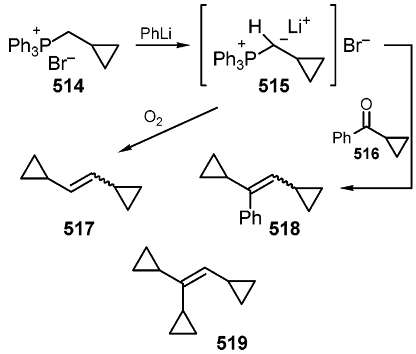


Scheme 83

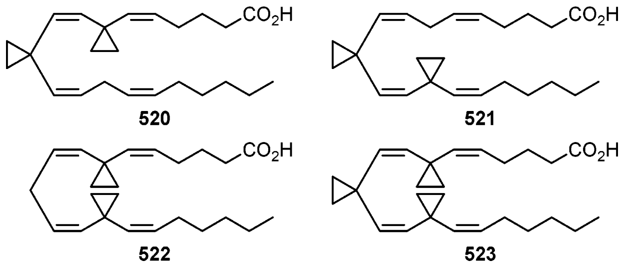


phine. The reactions of this phosphonium ylide with alkylcyclopropylketones led to substituted dicyclopropylethenes like **518**, whereas air oxidation furnished unsubstituted 1,2-dicyclopropylethene **517** (Scheme 84).[353]

Scheme 84



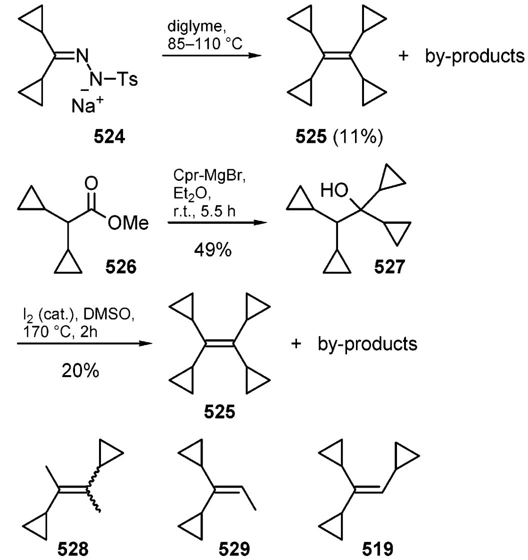
Wittig olefinations of appropriate carbonyl compounds with methylenetriphenylphosphorane and with **515** were used to prepare 1,1- (**382**),[354] *cis*-1,2- (*cis*-**517**), and *trans*-1,2-dicyclopropylethene (*trans*-**517**), as well as tricyclopropylethene (**519**).[355,356] The mixture of diastereomeric *cis*-**517** and *trans*-**517** could be separated by vapor-phase chromatography. Although dicyclopropylmethylenephosphoranes can be generated from the corresponding quaternary phosphonium salts, and these do indeed react with aldehydes (e.g., benzaldehyde) to give trisubstituted ethenes, the attempted preparation of tetrasubstituted ethenes from ketones in this manner did not succeed.[356] Wittig reactions have also been employed to obtain di- and tricyclopropanated analogues **520**−**523** of arachidonic acid, which have been suspected



to show modulatory effects within the arachidonic acid cascade, including lipoxygenase inhibition.[357]

The synthesis of tetracyclopropylethene **525** was first accomplished, albeit in low yield (11%) among an array of several side products, by dimerization of dicyclopropylcarbene, which was generated by thermal decomposition of the dicyclopropylketone 4-toluenesulfonylhydrazone sodium salt **524** (Scheme 85).[355,356] A slightly more productive synthesis was elaborated by Hanack et al., who added cyclopropylmagnesium bromide to methyl 2,2-dicyclopropylacetate **526** to furnish tetracyclopropylethanol **527**, which in turn could be dehydrated by treatment with iodine in DMSO to give 20% of **525** along with (mainly ring-opened) side products (Scheme 85).[358] The same methodology was used toward the preparation of (*E*/*Z*)-1,2-dicyclopropyl-2-butene (**528**), 1,1-dicyclopropylpropene (**529**), and tricyclopropylethene (**519**).[359]

Scheme 85



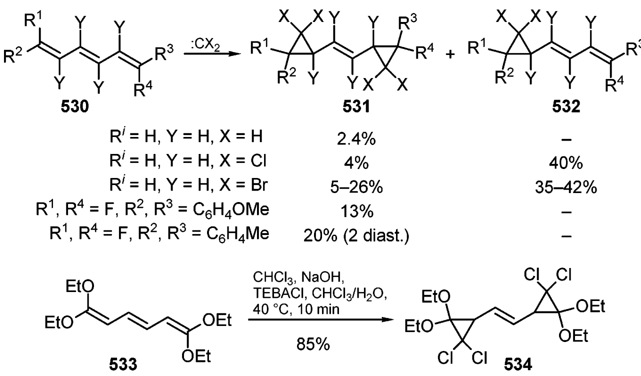
Cyclopropyl-substituted ethenes can also efficiently be prepared by reductive dimerization (McMurry coupling) of cyclopropylketones. Applying different methods to generate the low-valent titanium species, several groups synthesized 1,1- and 1,2-dicyclopropyl- as well as tetracyclopropylethenes.[360−363]

1,2-Dicyclopropylethenes have also been obtained by the addition of carbenes or carbenoids to 1,3,5-hexatrienes.[364−368] In many cases, the terminal double bonds are cyclopropanated selectively, and the second cyclopropanation (especially with dihalocarbenes) is much slower than the first one, which causes low yields of the bisadducts (Scheme 86).[367] However, in special cases, for example, the 2-fold cyclopropanation with dichlorocarbene of **533**, endowed with particularly electron-rich terminal double bonds, the bisadduct **534** was formed in very good yield (Scheme 86).[365] In other cases, mixtures of regioisomers were obtained.[365]

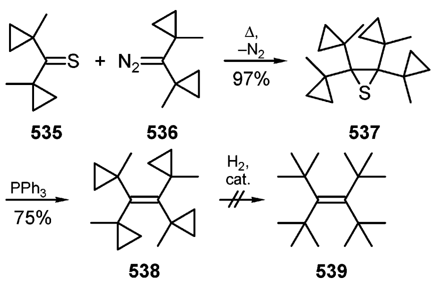
The ethylene derivative **538**, being the sterically most encumbered alkene ever synthesized, was prepared by thermal decomposition of the thiadiazoline formed by thermal [2 + 3] cycloaddition of **535** and **536** and subsequent sulfur extrusion from the resulting thiirane **537** (Scheme 87).[369] The attempted catalytic hydrogenation of **538** to yield tetrakis(*tert*-butyl)ethene (**539**) proved to be unsuccessful, just as the attempted direct synthesis of this latter compound **539** along the same lines.

Other methods for the preparation of cyclopropyl-substituted ethenes include the Ramberg−Bäcklund reaction

Scheme 86

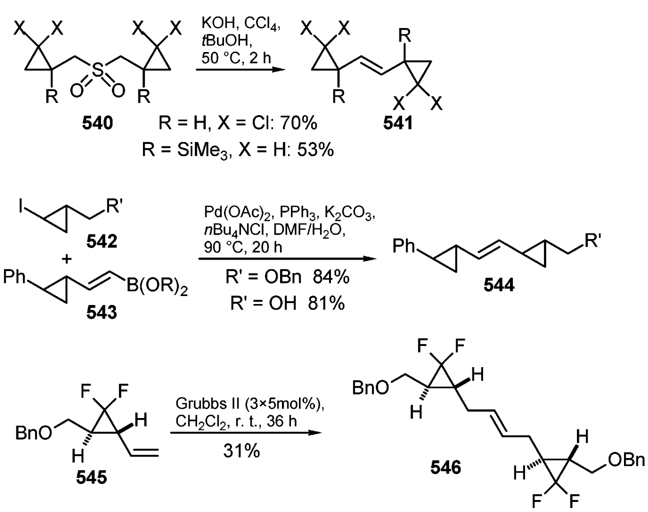


Scheme 87



(Scheme 88),[370] Suzuki-type cross-coupling reactions of iodocyclopropanes with vinylcyclopropylboronic acids (Scheme 88, $B(OR)_2$ = catecholboranyl),[371] and alkene metathesis (Scheme 88).[372]

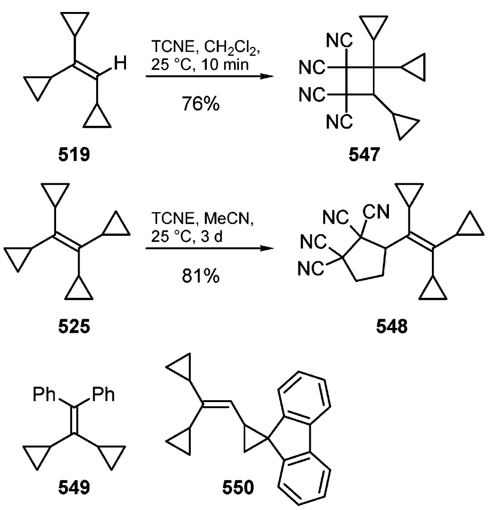
Scheme 88



All of these alkenes possess electron-rich double bonds, which is mirrored in their physical properties and their chemical behavior. The ionization energies as measured by He(I)-photoelectron spectroscopy steadily decrease on going from 1,1-dicyclopropyl- (**382**, 8.80 eV) via 1,2-dicyclopropyl- (**517**, *cis* 8.50 eV, *trans* 8.40 eV) to tricyclopropylethene (**519**, 8.00 eV) and finally tetracyclopropylethene (**525**, 7.90 eV).[373] Studies of the rate constants of carbene additions onto the double bonds of these compounds show two mutually counteracting influences by an increasing number of cyclopropyl substituents. On one hand, they accelerate the reaction by their electron-donating effect, while on the other hand, they retard the reactions by their steric shielding of the double bond. This became especially evident for tri- and tetracyclopropylethene.[284,374,375]

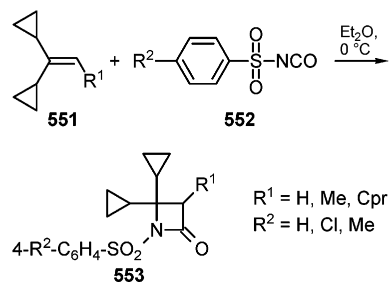
Di- (**517**) and tricyclopropylethenes such as **519** undergo thermal cycloadditions with electron-deficient alkenes. One of the best studied cyclophiles in this context is tetracyanoethene (TCNE). As early as 1970, Nishida et al. reported the formation of tetracyanocyclobutanes such as **547** from **519**.[376] Shortly thereafter, the same group found a markedly different mode of reaction for tetracyclopropylethene (**525**) with insertion of TCNE into one of the cyclopropyl rings leading to the tetracyanovinylcyclopentane derivative **548** (Scheme 89).[377,378]

Scheme 89



Not only do other tetrasubstituted cyclopropylethenes such as 1,1-dicyclopropyl-2,2-diphenylethene (**549**) react in the same way to yield the corresponding five-membered ring products, but also the spirofluorenyl compound **550**, a trisubstituted alkene,[379,380] and even *cis*- (*cis*-**517**) and *trans*-1,2-dicyclopropylethene (*trans*-**517**) with TCNE give rather high yields of this type of product (Scheme 89).[381] In the latter case, the selectivity can be influenced by the polarity of the solvent.[381] For the [2 + 2] pathway, the reactivity is mostly influenced by the steric demands of the substituents around the double bond and the substitution pattern (1,1-dicyclopropylethylene **382** reacts faster than the 1,2-disubstituted **517**).[382,383] Effenberger et al. reported on [2 + 2] cycloadditions of TCNE and sulfonylisocyanates onto cyclopropylethenes, which corroborated these findings (Scheme 90).[384]

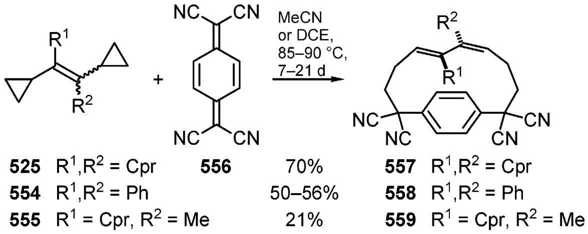
Scheme 90



The reactions of alkenes **525**, **554** and **555** bearing at least two cyclopropyl substituents, with tetracyanoquinodimethane (TCNQ) **556** provided an easy access to [10]paracyclophanediene derivatives **557**−**559** (Scheme 91).[385,386]

Cyclopropylethenes have also been applied to study the mechanism of singlet oxygen reactions with alkenes[387] and

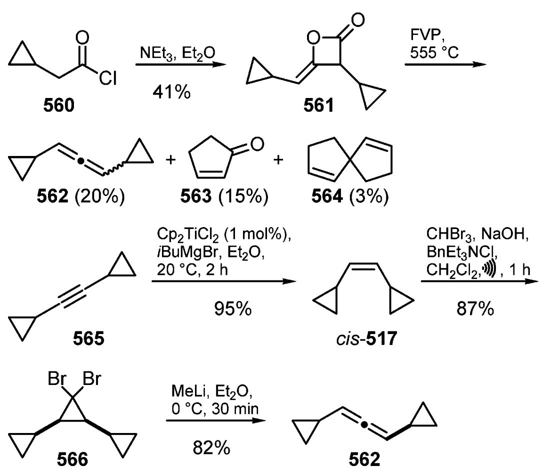
Scheme 91



the epoxidation of alkenes with various peroxides in the presence of porphyrin complexes of iron, manganese, and chromium as models to elucidate the mechanism of the oxidation of alkenes by cytochrome P-450.[388−392] In these studies, and in the one of Brandt et al. on the chromium−salen-mediated epoxidation,[393] cyclopropylethenes were used in order to probe for radical intermediates, which would rapidly undergo ring opening of adjacent cyclopropyl groups.

1,3-Dicyclopropylpropadiene (**562**) was first reported in 1975 by Berkowitz et al.[394] Upon treatment of cyclopropylacetyl chloride **560** with triethylamine, the cyclopropylketene dimer **561** was obtained, and this upon flash vacuum pyrolysis furnished **562** in 20% yield along with side products and polymeric material (Scheme 92).

Scheme 92

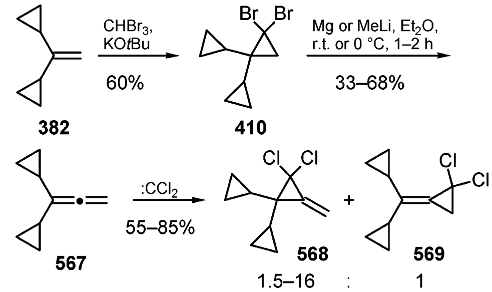


A more productive synthesis, by which **562** became accessible in three steps in 68% overall yield from dicyclopropylethyne (**565**) via *cis*-1,2-dicyclopropylethene (*cis*-**517**) and its dibromocarbene adduct **566** was developed in 2003 (Scheme 92).[395]

1,1-Dicyclopropylpropadiene (**567**) was obtained by several groups by sequences of dibromocyclopropanation of 1,1-dicyclopropylethene (**382**) and subsequent reaction of the resulting dibromocyclopropane **410** with metallic magnesium or methyllithium, that is, by the so-called Doering−Moore−Skattebøl reaction (Scheme 93).[396−398]

Although dihalocarbene additions to unsymmetrically substituted propadienes usually occur preferentially at the less substituted double bond, addition of dichlorocarbene to **567** was found to give predominantly the adduct to the C(1)−C(2) double bond **568** (Scheme 93).[396−398] The ratio of the regioisomeric adducts depended on the protocol for the generation of the dichlorocarbene. Addition of fluorenylidene only occurred at the unsubstituted C(2)−C(3) double bond, albeit in low yields (13−19%).[399] This supports the predictions of Creary, according to which singlet carbenes should

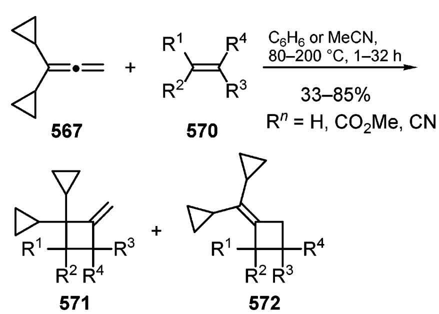
Scheme 93



attack the C(1)−C(2) bond and triplet carbenes the C(2)−C(3) double bond in 1,1-disubstituted propadienes.[400]

Propadienes are well-known to undergo thermal [2 + 2] cycloadditions. In accord with the conservation of orbital symmetry rules, these reactions occur stepwise to nonstereospecifically give cyclobutanes of types **571** and **572** upon reaction of **567** with differently substituted, activated alkenes **570**.[401,402] The ratio of the two products depended on the structure of the alkene **570** employed and on the polarity of the solvent. Whereas most 1,2-disubstituted alkenes gave predominantly products of type **572**, irrespective of the solvent employed (C_6H_6 or MeCN), the ratio **572** to **571** was lower for 1,1-disubstituted alkenes and varied with the two solvents. In these cases, an acceleration of the reaction in polar solvents was observed (Scheme 94).[401,402]

Scheme 94

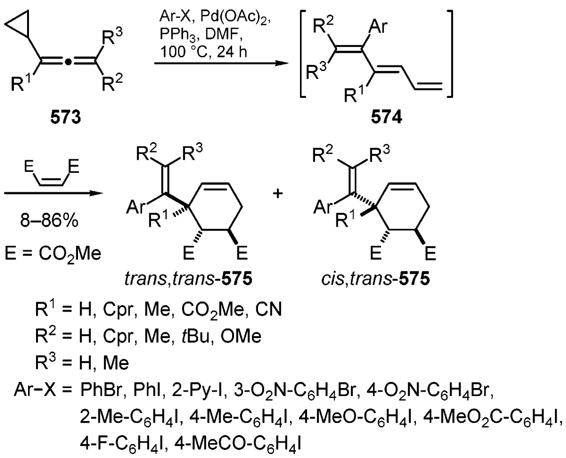


Domino Heck−Diels−Alder processes employing cyclopropyl-substituted allenes **573** as Heck-coupling partners furnished 3,4,5-trisubstituted cyclohexene derivatives **575**, derived from the intermediate 1,3,5-hexatrienes **574** (Scheme 95). Originally, these reactions were developed only for 1,3-dicyclopropylpropadiene (**562**) with different aryl halides and dienophiles,[395,403] but later they were extended to a larger number of differently substituted propadienes including the 1,1-dicyclopropyl derivative **567** (≡ **573**, R^1 = Cpr, R^2,R^3 = H) (Scheme 95).[404]

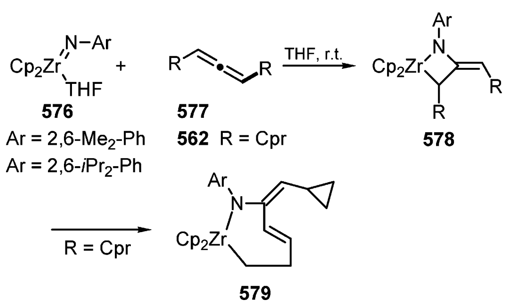
In a recent study, 1,3-dicyclopropylpropadiene (**562**) was used as a probe for radical intermediates in the isomerization of azametallacyclobutanes **578** formed by the reaction of 1,3-disubstituted allenes with imidozirconium complexes **576** (Scheme 96).[405] Indeed, an (*E*)-zirconacycloheptene **579** instead of the usual azazirconacyclobutane **578** could be isolated and characterized by X-ray crystal structure analysis. This method can be used to obtain enantioenriched allenes **577** by employing enantioenriched zirconium complexes **576** and subsequent liberation of the isomerized **577** by treatment of the azazirconacyclobutanes **578** with allene.[405]

Reactions of propargylic alcohols with chlorodiarylphosphines in the presence of organic bases yield phosphorylpropadienes.[406] Dibromocarbene addition to the phosphoryl-

Scheme 95

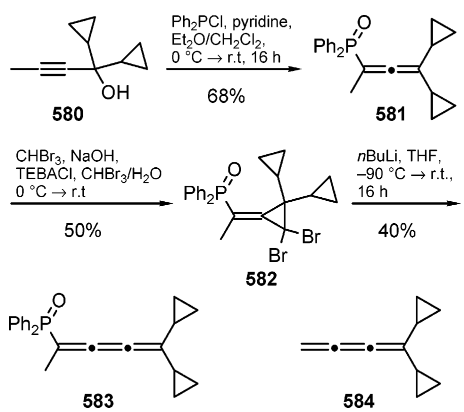


Scheme 96



propadiene **581**, prepared along this route, regioselectively furnished the adduct **582**, which could be subjected to the Doering−Moore−Skattebøl rearrangement to afford butatriene **583** (Scheme 97).[407,408] The thermally unstable parent compound **584** had been obtained previously by Kostikov et al. by treatment of the corresponding dibromocyclopropane obtained from 1,1-dicyclopropylpropadiene (**567**) with methyllithium.[409]

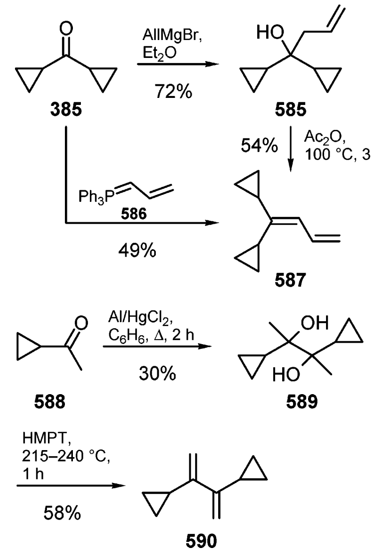
Scheme 97



Several oligocyclopropylated 1,3-butadienes are known. The first reported example is 1,1-dicyclopropyl-1,3-butadiene (**587**), which was obtained from dicyclopropylketone (**385**) either by addition of allylmagnesium bromide and subsequent dehydration of the resulting homoallylalcohol **585**[410−412] or, as reported later, by Wittig olefination of **385**[413] with allylidenetriphenylphosphorane (Scheme 98).

The synthesis of 2,3-dicyclopropylbuta-1,3-diene (**590**) was accomplished by dehydration of the diol **589**, which was obtained by pinacol reduction of cyclopropyl methyl ketone

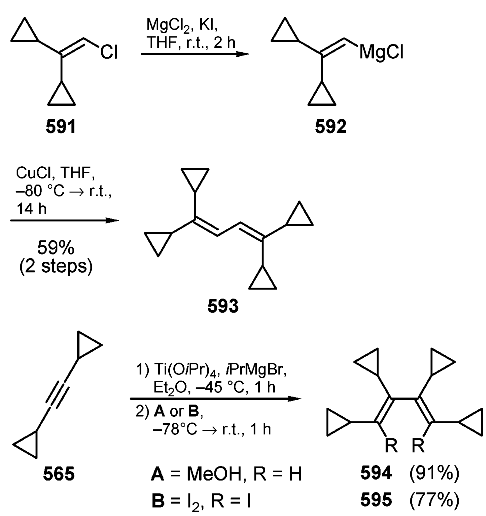
Scheme 98



588 with aluminum amalgam (Scheme 98).[414] The diol **589** can be prepared in higher yield (60%) by reductive coupling of **588** with Ti(0) species generated from titanium(IV) chloride and magnesium.[415]

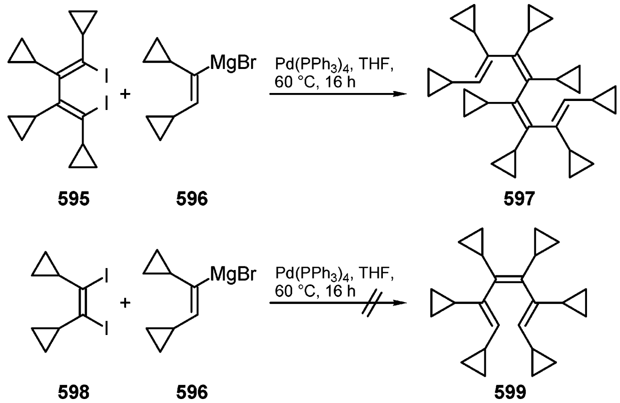
Tetracyclopropyl-1,3-butadiene (**593**), as reported by Nishida et al. was obtained by copper-promoted coupling of 2,2-dicyclopropylvinylmagnesium chloride **592** (Scheme 99).[380] (*E*,*E*)-1,2,3,4-Tetracyclopropylbuta-1,3-diene (**594**) and the (*Z*,*Z*)-1,4-diiodo-1,2,3,4-tetracyclopropylbuta-1,3-diene (**595**) could be prepared from dicyclopropylacetylene (**565**), adopting protocols of Sato et al.[416] to generate an intermediate 2,3,4,5-tetracyclopropyltitanacyclopentadiene, which, upon quenching with either water or iodine, gave **594** and **595**, respectively, in good to excellent yields (Scheme 99).[417]

Scheme 99



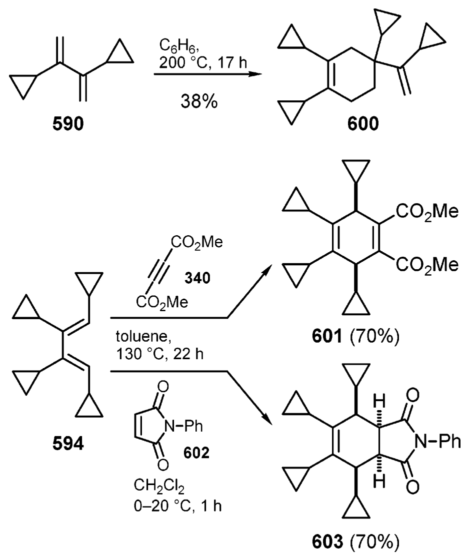
Diiodination of dicyclopropylethyne (**565**) following a protocol of Liu et al. afforded (*Z*)-1,2-dicyclopropyl-1,2-diiodoethene (**598**), albeit in a rather low yield of 32%.[417] Both diiodo compounds **595** and **598** were subjected to a Pd-catalyzed $C_{sp^2}-C_{sp^2}$ coupling with (*E*)-1,2-dicyclopropylethenylmagnesium bromide **596** in order to obtain (*E*,*Z*,*Z*,*E*)-1,2,3,4,5,6,7,8-octacyclopropylocta-1,3,5,7-tetraene (**597**) and (*E*,*Z*,*E*)-1,2,3,4,5,6-hexacyclopropylhexa-1,3,5-triene (**599**), respectively. While **597** was produced as an unseparable mixture with other products, as proved by mass spectrometry, **599** could not be detected (Scheme 100).[417]

Scheme 100



Whereas 1,1-dicyclopropyl-1,3-butadiene (**587**), according to an earlier report, failed to undergo a Diels−Alder reaction,[411] the 2,3-isomer **590** underwent Diels−Alder dimerization to yield **600** (38%), along with 47% of some polymeric material.[75] 1,2,3,4-Tetracyclopropylbutadiene (**594**) smoothly reacted both with dimethyl acetylenedicarboxylate (**340**) and *N*-phenylmaleimide (**602**) to afford the corresponding Diels−Alder adducts **601** and **603** in good yields (Scheme 101).[417]

Scheme 101



The first synthesis of dicyclopropylethyne (**565**) was accomplished by Köbrich et al. applying a Fritsch−Buttenberg−Wiechell rearrangement of the carbenoid generated from **591**, which was obtained by a Wittig-type olefination of dicyclopropyl ketone (**385**) (Scheme 102).[418,419] An alternative synthesis of **565** started with the Reformatsky reaction of methyl 3-bromopropionate with dicyclopropylketone to furnish the dicyclopropylhydroxypropionic acid (**604**), and the latter was converted in four steps to 5,5-dicyclopropyl-3-nitrosooxazolidone (**605**), which, upon treatment with a base, gave **565** (Scheme 102).[420]

Two other approaches started from cyclopropylmethyl cyclopropyl ketone **609** which was obtained from a reaction of cyclopropanecarbonyl chloride with 4-trimethylsilylbutene and subsequent cationic cyclization. The ketone **609** was either transformed into the *gem*-dichloride **606**, which yields dicyclopropylethyne (**565**) by 2-fold dehydrohalogenation or by conversion to the selenadiazole **611** and its fragmentation upon treatment with *n*-butyllithium at low temperature (Scheme 102).[421]

Eventually, **565** was prepared in three steps from sodium acetylide and 1-bromo-3-chloropropane **608** via 5-chloro-1-pentyne (**607**) and 1,8-dichlorooct-4-yne (**610**)[422,423] or, even shorter, in two steps from commercially available cyclopropylacetylene (**613**) via 1-cyclopropyl-2-(3-chloropropyl)-acetylene (**612**) (Scheme 102).[417]

Cyclopropylacetylene (**613**) also was converted in four steps to 1-cyclopropyl-2-(1-methylcyclopropyl)acetylene (**615**) in 5% overall yield (Scheme 103).[424] A series of variously substituted dicyclopropylethynes **618** were prepared by Nefedov et al. by addition of halo(cyclopropylalkynyl)-carbenes, generated in situ by treatment of 1-cyclopropyl-2-(dihalomethyl)acetylenes **616** with potassium hydroxide in the presence of triethylbenzylammonium chloride (TEBACl) in dichloromethane or potassium *tert*-butoxide in hexane to correspondingly substituted alkenes (Scheme 103).[425,426]

Bis(1-methylcyclopropyl)acetylene (**621**) was obtained from 2,5-dimethylhexa-1,5-diene-3-yne (**619**) by 2-fold addition of dichloro- or dibromocarbene and subsequent reductive dehalogenation of the bis(dihalocyclopropyl)-acetylenes **620**-X with lithium and *tert*-butyl alcohol in up to 45% overall yield (Scheme 104).[427]

Compound **621** could also be obtained by 2-fold methylation of dicyclopropylacetylene (**565**) (see below, Scheme 113).[428] Hydrogenation of **565** using a Lindlar catalyst gave (*Z*)-dicyclopropylethene ((*Z*)-**517**), which was contaminated with small amounts of (*E*)-**517** as well as ring-opening products.[418,419] Reduction with diimine furnished (*Z*)-**517** contaminated with a considerable amount of dicyclopropylethane,[419] and reduction with lithium aluminum hydride yielded (*E*)-**517**, which was contaminated with a small amount each of (*Z*)-**517** and **565**.[419]

1,4-Dicyclopropylbuta-1,3-diyne (**622**) was prepared in good yields starting either from cyclopropylethyne (**613**)[429] or 1-trimethylsilyl-2-cyclopropylethyne (**623**)[430] by copper-mediated oxidative coupling (Scheme 105).

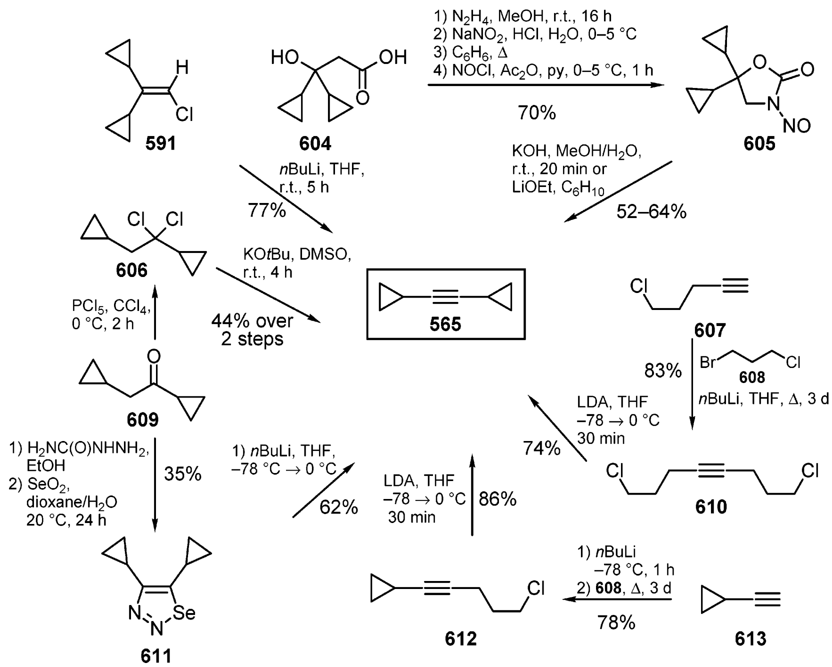
The observed reaction mode upon deprotonation of dicyclopropylethyne (**565**) in the propargyl position with alkyllithium reagents and subsequent quenching with electrophiles to yield products of type **625** only was taken to indicate the unimportance of the allenic structure **624b** (Scheme 106).[431,432] This assumption was confirmed by NMR spectroscopic evidence obtained by two groups.[433,434]

Although metalated cyclopropanes usually are regarded as configurationally stable, the 1-alkynyl-1-lithiocyclopropanes apparently undergo rapid inversion as indicated by the equivalence of the two pairs of diastereotopic protons on the cyclopropane ring in the ^1H NMR spectra.[432,435]

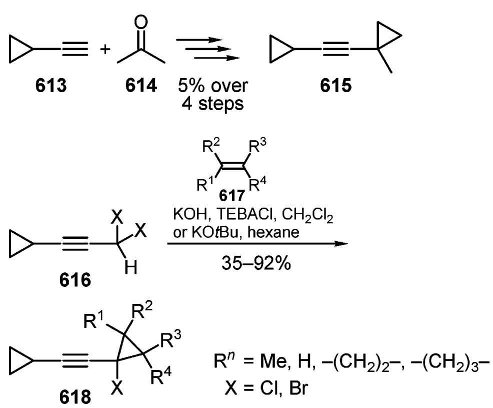
Employing mixtures of *n*- or *tert*-butyllithium and tetramethylethylenediamine (TMEDA), dilithiation of **565** could be affected, and the resulting bislithiated compound could be isolated and trapped with electrophiles to yield bis(1′-substituted) derivatives of **565**.[431,432]

Exposure of halo derivatives **625e**,**f** to organolithium reagents led to smooth halogen−metal exchange to give **624**.[432] Interestingly, however, when the chloride **625f** was treated with phenyllithium, the reaction set in only at temperatures as high as 0 °C and gave, along with the cyclopropyl(1-phenylcyclopropyl)ethyne (**626**), products of

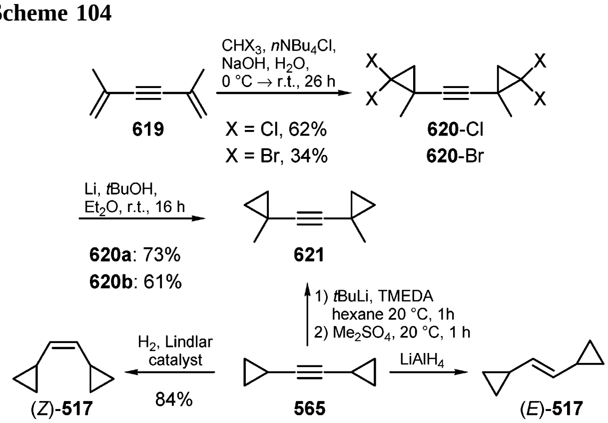
Scheme 102



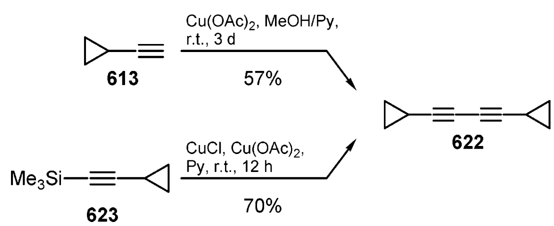
Scheme 103



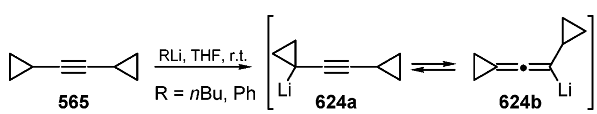
Scheme 104

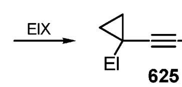


Scheme 105



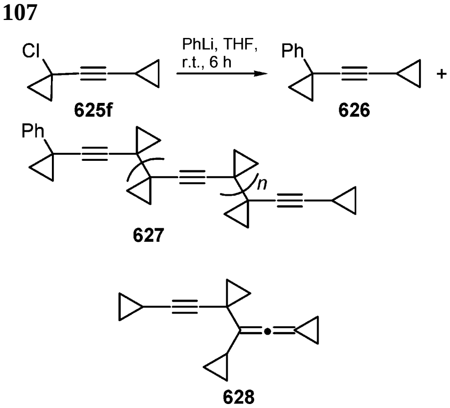
Scheme 106





625	ElX	El	Yield (%)
a	CO_2, H^+	CO_2H	73
b	Me_3SiCl	$SiMe_3$	73
c	*n*BuCl	*n*Bu	73
d	BrCN	CN	10
e	BrCN	Br	62
e	TsBr	Br	48
f	TsCl	Cl	52

Scheme 107

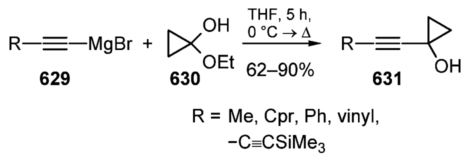


type **627** with two, three and even more dicyclopropylethyne moieties ($n = 0-3$) (Scheme 107).[436] Employing magnesium for the metalation of the bromo derivative **625e**, the product **628** containing an allenic moiety was obtained along with the purely acetylenic compound **627** ($n = 0$) in about the same amount (~20−40%).[437]

As early as 1976 first computations at the SCF/STO-3G level of theory predicted only a very low barrier for the internal rotation of the cyclopropyl groups in dicyclopropylethyne (**565**).[438] This assumption was consolidated by analyses of IR spectra by Schrumpf et al.[439] and Mohaček et al.[440] The latter also set out to establish the different solid phases of **565** by means of IR spectroscopy.[441] Using a combination of quantum-chemical calculations (up to MP2/6-31G*) and electron diffraction methods, Dakkouri et al. finally estimated the barrier to rotation in **565** in the gas phase to be about 365 cal/mol.[442]

Among a series of terminally substituted ethynylcyclopropanols, Salaün et al. also prepared 1-(cyclopropylethynyl)-cyclopropanol **631** (R = Cpr) starting from magnesium acetylides **629** and the cyclopropanone hemiacetal **630** in good yields (Scheme 108). The solvolysis rates of the tosylates prepared from the alcohols **631** indicated that the cation resulting from **631** (R = Cpr) must be particularly well stabilized.[443,444]

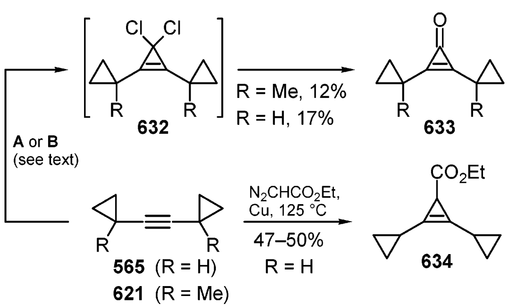
Scheme 108



Heating of dicyclopropylethyne (**565**) with carbonyliron complexes furnished an array of unsaturated cyclopropyl-containing compounds. Furthermore, cyclopropenes can be obtained by cyclopropanation of **565**. Apart from the two examples outlined below, the majority of the studies connected with these reactivities will be treated in the next section.

Dehmlow et al. obtained 2,3-dicyclopropylcyclopropenones (**633**) via the dichlorocarbene adducts **632**. For **621** (R = Me), cyclopropanation under phase-transfer conditions (chloroform/conc. NaOH soln./TEBACl, method A) proved to be effective, whereas in the case of **565** (R = H), $CHCl_3$/KO*t*Bu (method B) was used, but the yields of the cyclopropenones **633** obtained after hydrolysis were low in both cases (Scheme 109).[445]

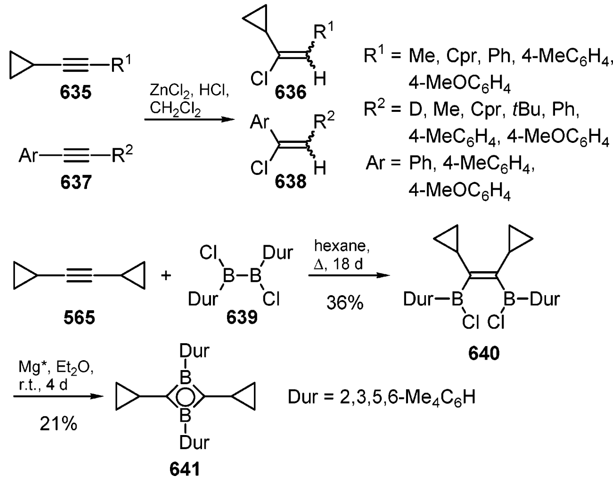
Scheme 109



Copper-mediated addition of ethyl diazoacetate to **565** was reported to give ethyl 2,3-dicyclopropylcyclopropene-1-carboxylate (**634**), which could be hydrolyzed to the corresponding acid in 70–75% yield (Scheme 109).[446]

Dicyclopropylethyne (**565**) has been converted to a number of model compounds in studies directed at comparing the influence of cyclopropyl and other alkyl or aryl substituents on the stability of, for example, vinyl cations,[447] the precursors (**636** and **638**) of which were prepared by addition of HCl to the correspondingly substituted cyclopropylalkynes **635**. 2,4-Dicyclopropyl-1,3-dihydro-1,3-diboret (**641**) was obtained from **565** in two steps in about 8% overall yield (Scheme 110).[448] As opposed to other 1,3-dihydro-1,3-diborets, the distance between C(2) and C(4) is significantly longer in **641** owing to a significantly reduced 1,3-interaction between them due to the outstanding donor abilities of the cyclopropyl groups.

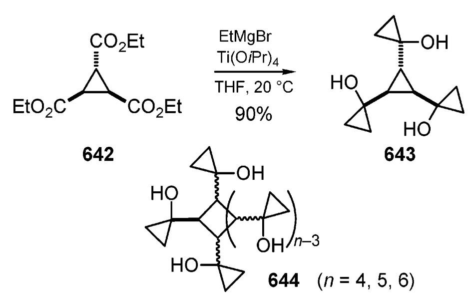
Scheme 110



3.2. Oligocyclopropyl-Substituted Carbo- and Heterocycles

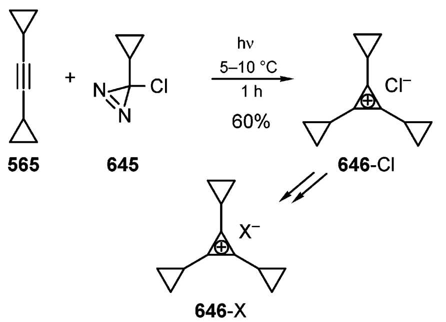
Because cyclopropyl substituents are known to more efficiently stabilize a carbocation than even a phenyl or a vinyl group,[449] preparation and properties of structurally interesting oligocyclopropyl-substituted saturated and especially unsaturated carbocycles are still intriguing and always coming along with a bonding theoretical aspect. Thus, *trans*-1,2,3-tris(1-hydroxycyclopropyl)cyclopropane {3′-(1-hydroxycyclopropyl)-[1,1′;2′,1″]tercyclopropane-1,1″-diol} (**643**) was synthesized applying the reductive titanium-mediated cyclopropanation[333] of triethyl *trans*-cyclopropanetricarboxylate **642** (Scheme 111). In the crystal, the triol **643** shows pronounced differences in the cyclopropane bond lengths, which are induced by the different orientations of the substituents.[450] The corresponding analogues **644** with larger rings ($n = 4, 5, 6$) have not yet been reported but should, in principle, be accessible by the same methodology.

Scheme 111



All known oligocyclopropyl-substituted small- and medium-sized unsaturated rings have been prepared from the same starting material, dicyclopropylacetylene (**565**) (see previous section). Thus, the parent tricyclopropylcyclopropenylium chloride **646**-Cl was obtained by cheletropic addition of cyclopropylchlorocarbene generated by photolysis of cyclopropylchlorodiazirine (**645**) to **565** (Scheme 112).[451−453] The chloride **646**-Cl was then transformed into other salts **646**-X [X = BF_4^-,[451] SbF_6^-,[453] tris(7*H*-dibenzo[*c*,*g*]fluorenylidenemethyl)methide ion ($C_{67}H_{39}^-$),[454a] *tert*-butylfulleride ($tBuC_{60}^-$),[454b] etc.]. The tricyclopropylcyclopropenylium cation in these salts **646**-X turned out to be the most stable in the series of

Scheme 112



trialkyl-substituted cyclopropenylium cations; only heteroatom substituents exceed the stabilizing power of three cyclopropyl groups.[451,452] The pK_{R^+} value of tricyclopropylcyclopropenylium cation (9.47) tops that of the triisopropyl derivative (6.4) by 3 orders of magnitude.[454a]

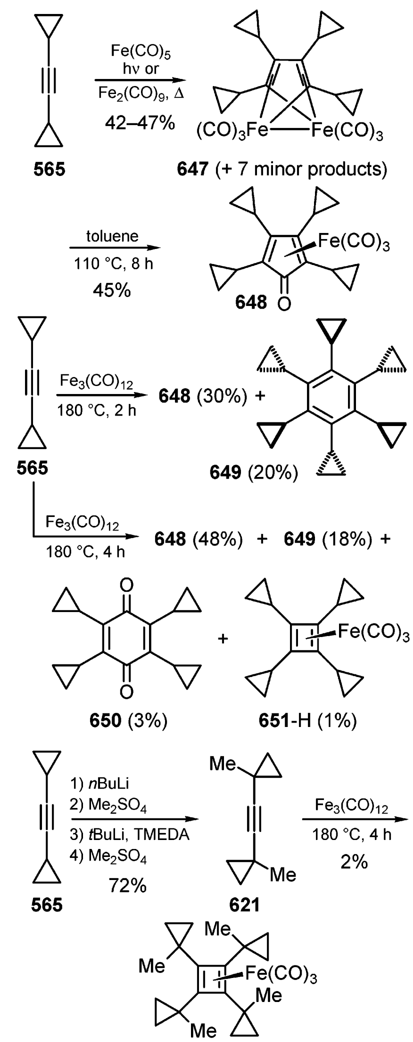
Dicyclopropylacetylene (**565**) reacts with different carbonyl iron complexes under various conditions to produce oligocyclopropyl-substituted five- and six-membered unsaturated carbocycles (Scheme 113). Thus, heating or irradiation of **565** with $Fe_2(CO)_9$ or $Fe(CO)_5$, respectively, produced the dinuclear complex **647** in 47% and 42% yield, respectively, along with seven minor products. Heating of **647** in toluene furnished tricarbonyl(tetracyclopropylcyclopentadienone)iron (**648**) in 45% yield.[455] The latter was prepared directly from **565** by heating with $Fe_3(CO)_{12}$ at 180 °C in 30% yield along with hexacyclopropylbenzene (**649**) (20% yield).[456] In the crystal, **649** disclosed an unusual conformation of D_{3d} symmetry in which the cyclopropyl substituents are alternatingly oriented up and down with respect to the central six-membered ring (Scheme 113); thus no conjugative interaction between the six cyclopropyl groups and the π-system of the aromatic ring is possible.[457] For comparison, in 1,2-diisopropyl-3,4,5,6-tetracyclopropylbenzene, which was prepared by cotrimerization of diisopropylacetylene and dicyclopropylacetylene (**565**) under catalysis with Hg[Co(CO)$_4$]$_2$, the four cyclopropyl groups adopt the same conformation with $C_{ar}-C_{ar}-C_{cycl}-H$ torsional angles close to 90°, whereas the two isopropyl groups maintain a bisected orientation.[458]

Upon careful reinvestigation of the thermal reaction of **565** with $Fe_3(CO)_{12}$ under almost the same conditions as previously reported[456] (4 h of heating), the known[455] tetracyclopropyl-*p*-benzoquinone (**650**) (3%) and the previously unknown tricarbonyl(tetracyclopropylcyclobutadiene)iron (**651**-H) (1%), along with the previously described products **648** (48%) and **649** (18%), were isolated (Scheme 113).[459]

Under the same conditions, the reaction of bis(1-methylcyclopropyl)ethyne (**621**) with $Fe_3(CO)_{12}$ yielded neither any of the peralkylated cyclopentadienone complex nor the corresponding benzene or benzoquinone derivatives. The sole product that could be isolated, as a crystalline yellow material in 2% yield, was the tricarbonyl[tetrakis(1-methylcyclopropyl)cyclobutadiene]iron (**651**-Me), as proved by an X-ray crystal structure analysis.[459] The complex **651**-Me constitutes the bulkiest metal-complexed peralkylated cyclobutadiene ever obtained.

Upon liberation from its tricarbonyliron complex **648**, tetracyclopropylcyclopentadienone undergoes rapid [4 + 2] cyclodimerization to the highly congested 1,2,4,5,6,7,8,9-octacyclopropyltricyclo[5.2.1.0^{2,6}]deca-4,8-diene-3,10-dione (**652**) (Scheme 114), which was characterized by an

Scheme 113

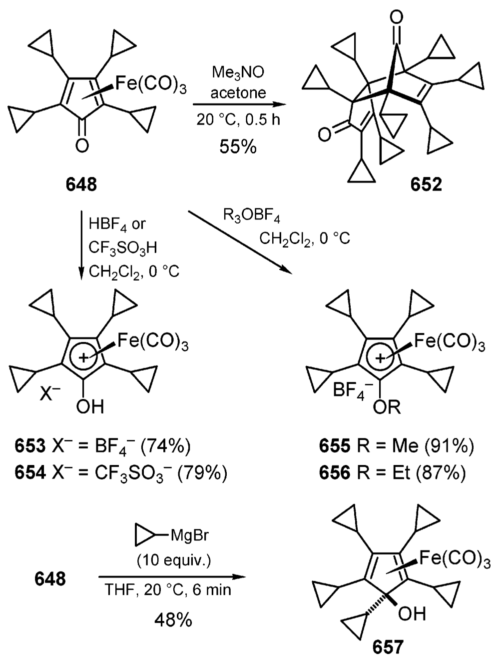


X-ray crystal structure analysis.[460] Alkylation of **648** with R_3OBF_4 (R = Me, Et) as well as protonation with HBF_4 or CF_3SO_3H afforded the remarkably stable cationic alkoxy- and hydroxy-substituted tricarbonyl(tetracyclopropylcyclopentadienyl)iron complexes **653**−**656** in high yields (74−91%, Scheme 114). X-ray crystal structural data for **653** and **654**, as well as NMR and IR spectroscopic evidence for all four complexes **653**−**656**, indicate that their positive charges predominantly rest on the tricarbonyliron fragments.[423]

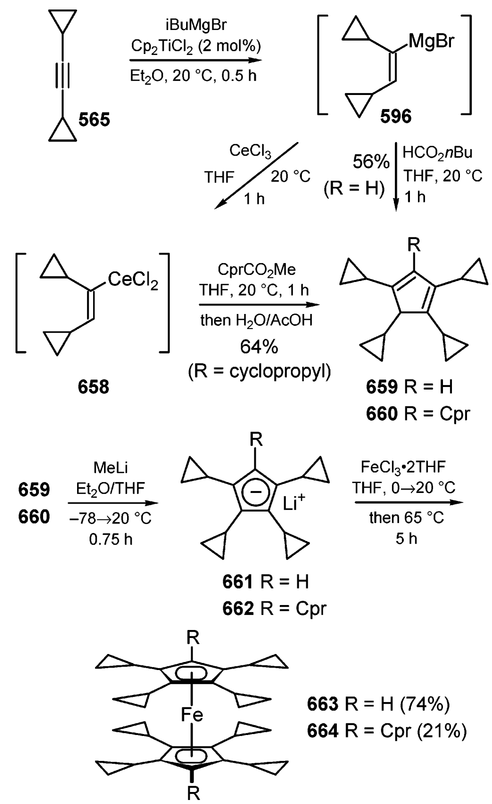
Treatment of **648** with cyclopropylmagnesium bromide gave the tricarbonyl(pentacyclopropylcyclopentadienyl)iron complex **657** in 48% yield (Scheme 114); the latter, however, turned out to be unstable at ambient temperature, and attempted generation of the cationic tricarbonyl(pentacyclopropylcyclopentadienylium)iron complex from **657** by treatment with trifluoromethanesulfonic acid in dichloromethane at 0 °C was unsuccessful.[460]

Intuitively, one would be inclined to predict that five cyclopropyl groups attached to the antiaromatic cyclopentadienyl cation might be able to let the system overcome the instability caused by its antiaromaticity. The parent cyclopentadienyl cation, its pentachloro derivative, and the pentaisopropyl-substituted compound have all been generated at low temperatures (78 and 115 K) and shown by electron spin resonance (ESR) spectroscopy to exist as triplet

Scheme 114



Scheme 115



species.[461a] Although only two of the five cyclopropyl substituents around the cyclopentadienyl cation core in a pentacyclopropylcyclopentadienyl cation adopt the proper orientation for their acting as electron donors, as predicted by a simple AM1 calculation, the two should exert a unique stabilizing effect according to DFT and Hartree−Fock computations at the BLYP/3-21G and HF/3-21G levels of theory.[461] Experimental and computational evidence predict that the elusive antiaromatic pentacyclopropylcyclopentadienyl cation should be a reasonably long-lived singlet species.[461b]

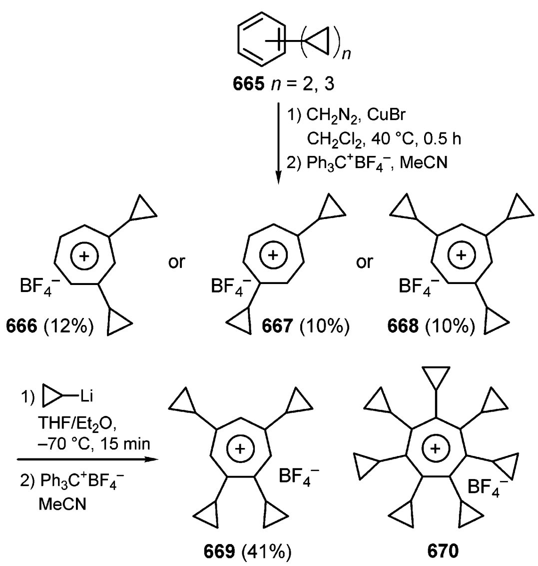
Tetra- (**659**) and pentacyclopropylcyclopentadiene (**660**), two new donor-substituted ligands for metal complexes, were both prepared from dicyclopropylacetylene (**565**) applying the protocol of Sato et al. for hydromagnesiations of alkynes.[462] Thus, by treatment with isobutylmagnesium bromide in the presence of titanocene dichloride (2 mol %) in diethyl ether, **565** was transformed to 1,2-dicyclopropylethenylmagnesium bromide (**596**), which, when added to a solution of butyl formate in THF, gave 1,2,4,5-tetracyclopropylcyclopentadiene (**659**) right away in 56% yield (Scheme 115).[423]

In order to obtain **660**, the solution of **596** in diethyl ether was first combined with a slurry of cerium(III) chloride in tetrahydrofuran; then methyl cyclopropanecarboxylate was added to the formed **658** at ambient temperature. After optimization of all parameters, workup of such a reaction mixture with aqueous acetic acid (6:1) gave pentacyclopropylcyclopentadiene (**660**) in 64% yield (Scheme 115).

Upon treatment with an ethereal solution of methyllithium, both cyclopropyl-substituted cyclopentadienes **659** and **660** in THF were quantitatively deprotonated to the corresponding cyclopentadienides **661** and **662**, respectively (Scheme 115). Treatment of the solutions of the latter with solutions of iron(III) chloride in THF yielded 1,1′,2,2′,3,3′,4,4′-octacyclopropyl- (**663**) and decacyclopropylferrocene (**664**) in 74% and 21% yield, respectively; the structures of both ferrocenes were established by X-ray crystal structure analyses.[423]

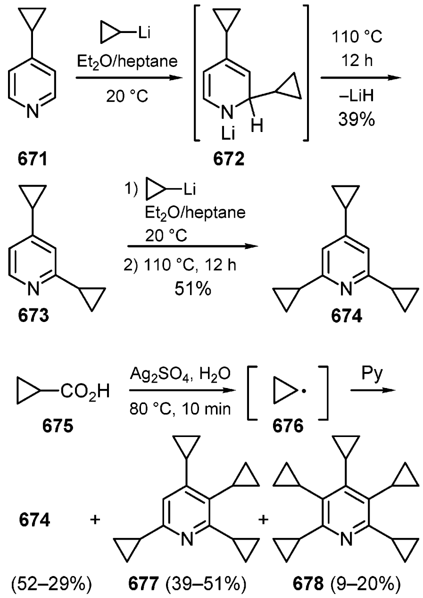
Two, three, and four cyclopropyl groups in oligocyclopropyltropylium tetrafluoroborates **666**−**669**, which were prepared from appropriately cyclopropyl-substituted benzene derivatives (Scheme 116),[463] have been shown to stabilize the cycloheptatrienyl cation tremendously, raising the pK_{R^+} from 7.5−7.6 to 8.7 and even 9.1, respectively. It is remarkable that the fourth cyclopropyl group in 1,2,4,6-tetracyclopropyltropylium cation **669**, although necessarily adjacent to one of the other three, still enhances the stability significantly. One might therefore envisage that the unknown heptacyclopropylcycloheptatrienyl cation **670** would be even more stable.

Scheme 116



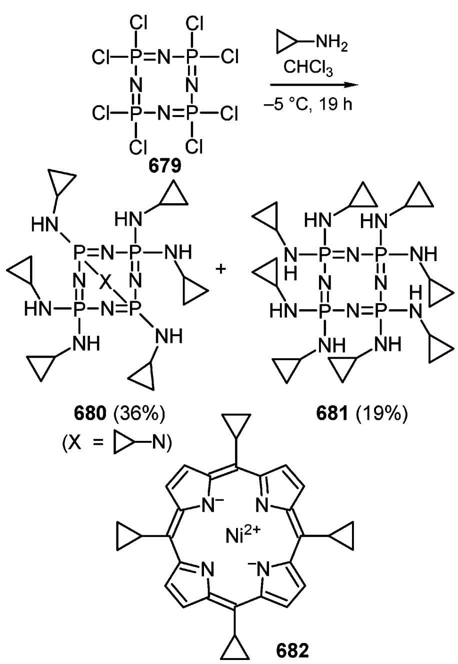
Several oligocyclopropyl-substituted heterocyclic compounds have also been reported. Thus, consecutive attachment of cyclopropyl groups onto 4-cyclopropylpyridine (**671**) by two sequences of nucleophilic addition of cyclopropyllithium followed by thermal elimination of lithium hydride from the intermediate lithium dicyclopropyldihydropyridide (**672**) and the corresponding trisubstituted dihydropyridide furnished 2,4,6-tricyclopropylpyridine (**674**) in 20% overall yield (Scheme 117).[464]

Scheme 117



Pyridines **677** and **678** with four and five cyclopropyl groups, respectively, have been obtained in moderate yields by attack on pyridine of cyclopropyl radicals generated in situ from cyclopropanecarboxylic acid by oxidation with silver sulfate (Scheme 117). This approach was efficient also for other mono- and bicyclic nitrogen heterocycles related to pyridine.[464]

Scheme 118

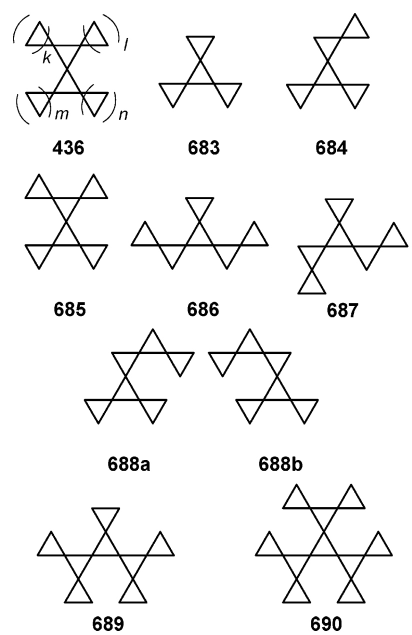


Some oligocyclopropyl-substituted highly symmetric heterocyclic compounds, for example, various tetra(cyclopropylamino)porphyrins were prepared by alkylation of cyclopropylamine.[465] Another example is octakis(cyclopropylamino)cyclotetraphosphazatetraene **681** (Scheme 118), which was prepared in 19% yield from cyclopropylamine and the tetrachloro derivative **679** along with the bicyclic heptakis(cyclopropylamino) derivative **680** (36%).[466]

Two tetracyclopropylporphyrin complexes, nickel(II) 5,10,15,20-tetra(cyclopropyl)porphyrin (**682**) and the closely related iron(III) complex, were synthesized to study the lowest energy nonplanar deformations of the porphyrin macrocycle by X-ray crystal structure analysis[467a] and the ground-state electron configuration of such complexes.[467b]

3.3. Branched Triangulanes and Heteroanalogues

The simplest and most highly symmetrical member in the family of branched triangulanes (BTs) **436**, [3]rotane **683**, was first prepared by Conia et al. in 1973.[310e,311,468] [3]Rotane **683** is the only possible branched [4]triangulane ([4]BT); higher rotanes[469] cannot be called triangulanes. The stereochemical features of branched triangulanes **436** have not been analyzed as thoroughly as those of the unbranched ones.[312,470] It is apparent that the number of possible stereoisomers of branched [*n*]triangulanes does not grow as rapidly with an increasing number (*n*) of three-membered rings as that of the unbranched [*n*]triangulanes. Thus, [5]BT **684** is the only possible branched [5]triangulane, and the family of [6]BTs **685**−**688** consists of three *meso*-diastereomers, **685**−**687**, as well as one pair of enantiomers **688**. For comparison, the family of [5]UTs consists of one *meso*-diastereomer and one pair of enantiomers, and that of [6]UTs has three pairs of enantiomers.

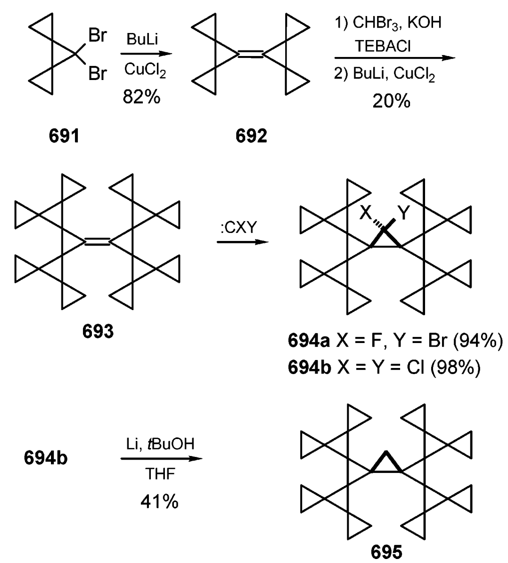


The simplest branched triangulane of type **436** was prepared along several routes.[313] For the construction of a branched triangulane framework such as **684**−**687**, uncomfortably complicated multistep preparations were initially used, but these strategies were replaced by the highly convergent building block method in which two building blocks of comparable size were combined to form the final BT molecule. The C_{3h}-symmetric [10]BT, the perspirocyclopropanated [3]rotane **690**, was prepared in this way,[318f,471] and **690** remained the absolute record for branched [*n*]-triangulanes[472] until the year 2000, when the preparations and physical and chemical properties of this family of hydrocarbons were exhaustively reviewed.[313a]

The most recent approach to BTs is essentially an extension of the building block method based upon the efficient dehalogenative dimerization of bromocoppercyclopropylidenoids generated from dibromotriangulanes with *n*-butyllithium in the presence of cupric chloride according to the method of Neuenschwander et al.[318] (see Section 2.5).

It is spectacular that this new method could also successfully be applied to 7,7-dibromodispiro[2.0.2.1]heptane (**691**), the dibromocarbene adduct of bicyclopropylidene (**33**), to yield the perspirocyclopropanated "second-generation" bicyclopropylidene **692** (82% isolated yield) making this exotic hydrocarbon, a superbicyclopropylidene, which had previously been prepared along a tedious 14-step sequence,[318f,473] easily available in preparatively useful multigram quantities (Scheme 119).[318f,474] It is even more spectacular that the dibromocarbene adduct of **692**[471] can be reductively "dimerized" again to give the "supersuperbicyclopropylidene" or "third-generation" bicyclopropylidene **693** (17% overall from **691**). The addition of dihalocarbenes onto this alkene yielded the dihalo[15]BTs **694a** and **694b** with unique structural features[318f] in virtually quantitative yields, and reductive dechlorination of the latter furnished C_{2v}-[15]triangulane **695**, the largest BT known up to now.

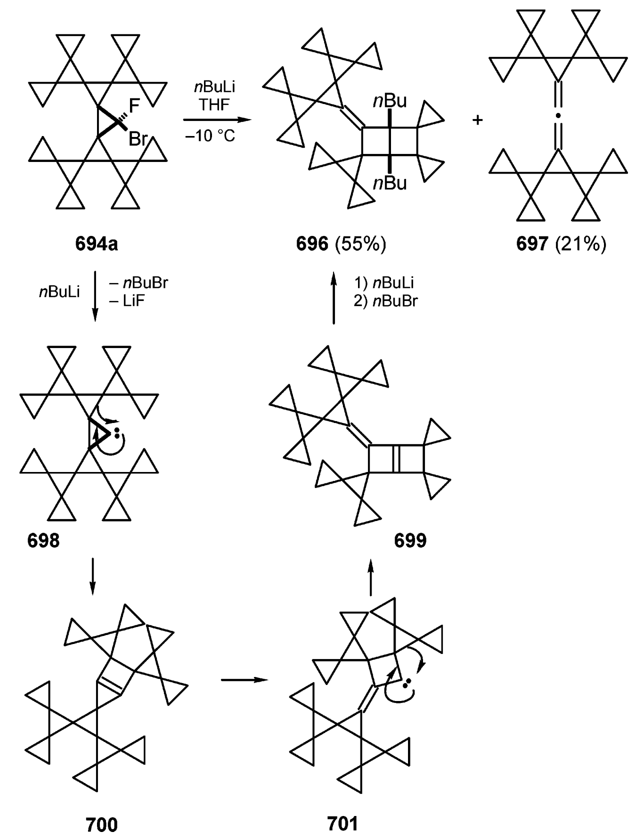
Scheme 119



Increasing the number of three-membered rings in BTs drastically changes the reactivity. Thus, upon treating **694a** with *n*-butyllithium, the allene **697** resulting from the well-known Doering−Moore−Skattebøl ring opening,[475] which is common for dibromocyclopropanes and lower dibromotriangulanes,[313a] was obtained as the minor product only, while the major product **696**, containing a bicyclo[2.2.0]hexane moiety (Scheme 120), resulted from a remarkable skeletal rearrangement and incorporation of two *n*-butyl groups.

This unusual transformation has been rationalized to proceed with a cyclopropylcarbene to cyclobutene ring enlargement in the initially formed cyclopropylidene intermediate **698**. The excessively strained bicyclo[2.1.0]pent-1(4)-ene intermediate **700** then undergoes opening of its cyclopropene to a vinylcarbene unit, and this is followed by a cyclopropylcarbene to cyclobutene rearrangement in the intermediate **701**. The resulting bicyclo[2.2.0]hex-1(4)-ene

Scheme 120

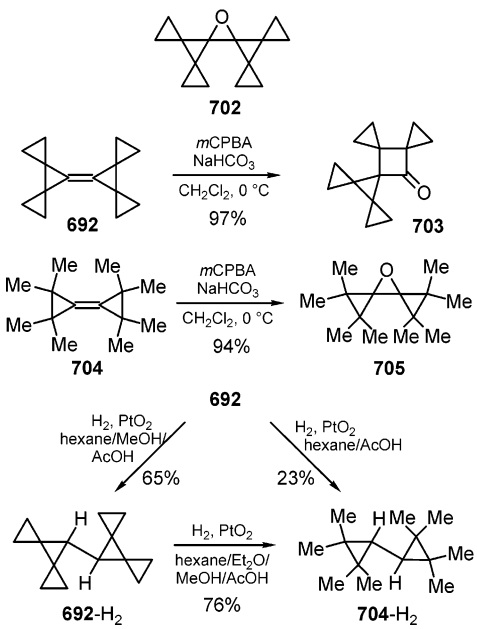


699 with its highly strained bridgehead−bridgehead double bond then adds a molecule of *n*-butyllithium, and the bridgehead lithium derivative finally reacts with the initially formed *n*-butyl bromide to give **696**.

As far as heteroanalogues of branched triangulanes are concerned, the result in an earlier communication[473] reporting the successful preparation of the oxa[7]triangulane **702** by epoxidation of perspirocyclopropanated bicyclopropylidene **692** with *m*-chloroperbenzoic acid (*m*CPBA) was reinvestigated, and an X-ray crystal structure analysis of the product revealed the real structure as that of the cyclobutanone **703**,[324] while the analogous permethylated bicyclopropylidene **704** afforded the corresponding octamethyloxa[3]triangulane **705** in 94% yield under identical conditions (Scheme 121). Under appropriate conditions (PtO_2, hexane/MeOH/AcOH), the perspirocyclopropanated bicyclopropylidene (**692**) can be subjected to catalytic hydrogenation to yield perspirocyclopropanated bicyclopropyl **692**-H_2 without ring opening.[318f] Under slightly harsher conditions (PtO_2, Hexane/AcOH), hydrogenolytic ring opening of all four spirocyclopropane groups occurs along with hydrogenation of the double bond to yield permethylated bicyclopropyl **704**-H_2 (Scheme 121). The latter is also formed from **692**-H_2 under slightly modified conditions (PtO_2, hexane/Et_2O/MeOH/AcOH).[318f]

An interesting influence of the number of spiroannelated three-membered rings on the reactivity was also observed for the branched higher phospha[*n*]triangulanes (Scheme 122).[327b,476] Thus, heating of the perspirocyclopropanated bicyclopropylidene **692** with the substituted 7-phosphanorbornadiene **472** at 100 °C afforded the perspirocyclopropanated 7-phosphadispiro[2.0.2.1]heptane **706**, a phospha[7]triangulane, in 88% yield (Scheme 122). On the other hand, the results of the CuCl-catalyzed reactions obviously depend on the number and positions of spiroannelated

Scheme 121



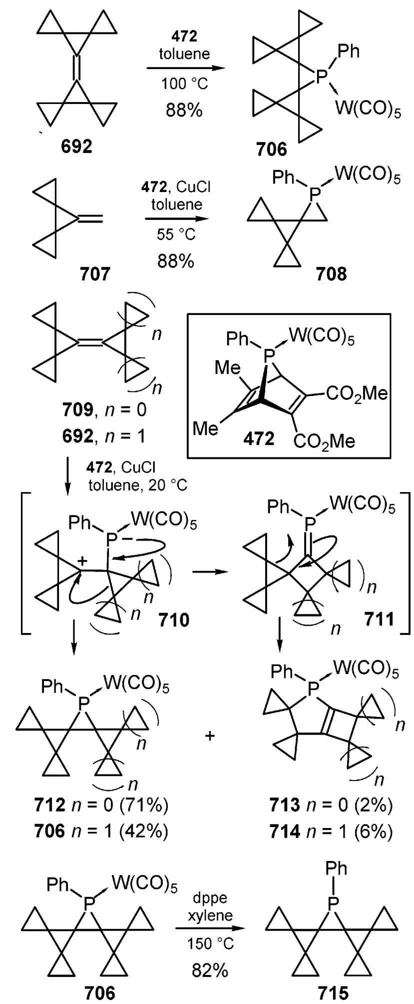
cyclopropane rings. While 7-methylene[3]triangulane **707** afforded phospha[3]rotane **708** in 88% yield, the 2-fold (**709**) and 4-fold (**692**) spirocyclopropanated bicyclopropylidenes already reacted at room temperature instead of the usual 55−60 °C, but the yields of the branched phosphatriangulanes were significantly lower (Scheme 122).

Moreover, along with phospha[5]- (**712**) and phospha[7]-triangulanes (**706**), which were obtained in 71% and 42% yield, respectively, complex mixtures of byproducts were formed, from which the rearranged products **713** and **714** were isolated in 2% and 6% yield, respectively. It is believed[327,476] that, in contrast to the thermally induced cheletropic addition of phosphinidene R−P═W(CO)$_5$, the bulkier [PhP(Cl)W(CO)$_5$]-Cu-L is more sensitive to steric constraints and probably reacts stepwise via the intermediate zwitterions **710**. The latter are capable of undergoing not only ring closure to give phosphatriangulanes **712** and **706** but also the well-known cyclopropylmethyl to cyclobutyl cation ring enlargement[477] to form intermediates **711**, which, after a subsequent [1,3]-sigmatropic shift, afford the 2-phosphabicyclo[3.2.0]heptenes **713** and **714**.

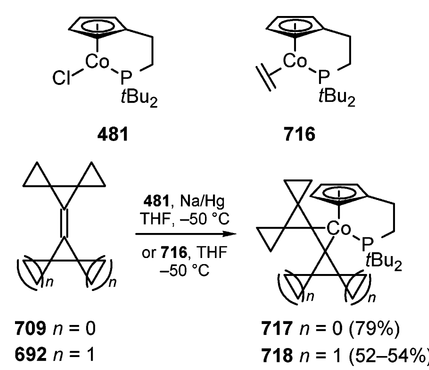
It is noteworthy that an increasing number of spiroannelated cyclopropane rings leads to an increasing thermal stability of the uncomplexed branched phospha[*n*]triangulanes. Thus, the stabilizing W(CO)$_5$ group could be removed from **706** by direct ligand exchange in refluxing xylene (150 °C!) with (Ph$_2$PCH$_2$)$_2$ (dppe) to give the unprotected 7-phenylphospha[7]triangulane **715** in 82% yield as the sole product (Scheme 122).[476]

The new stable branched cobalta[5]- (**717**) and cobalta-[7]triangulanes (**718**) have also recently been prepared either by treatment of {η^5:η^1[2-(di-*tert*-butylphosphanyl-*P*)ethyl]-cyclopentadienyl}cobalt(I) chloride (**481**) with spirocyclopropanated bicyclopropylidenes **709** and **692** in the presence of sodium amalgam at −50 °C or by ligand exchange of the ethene complex {η^5:η^1[2-(di-*tert*-butylphosphanyl-*P*)ethyl]-cyclopentadienyl}-(η^2-ethene)cobalt(I) (**716**) (Scheme 123) and completely characterized by X-ray crystal structure analyses.[329b]

Scheme 122



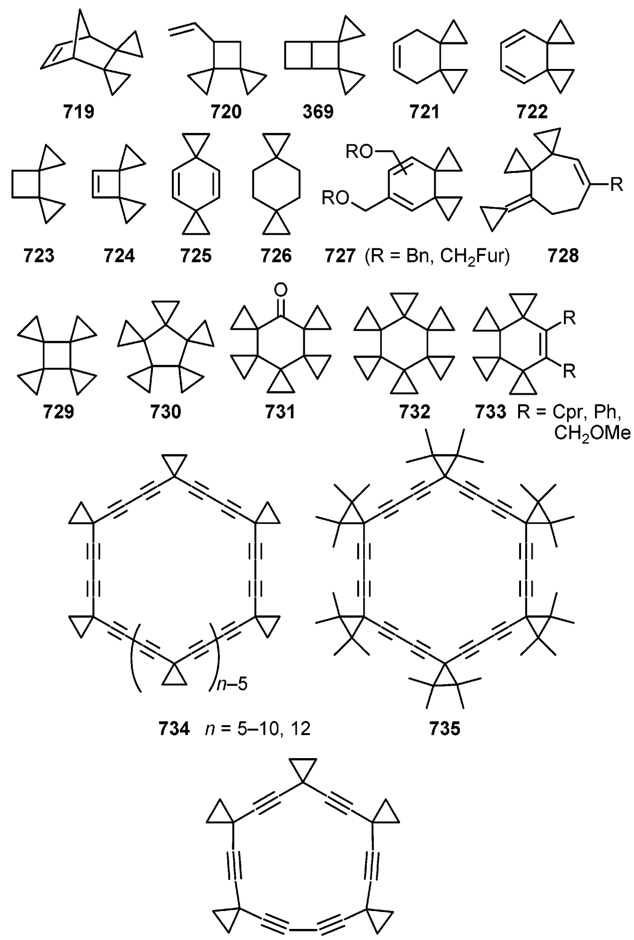
Scheme 123



3.4. Oligospirocyclopropanated Carbo- and Heterocycles

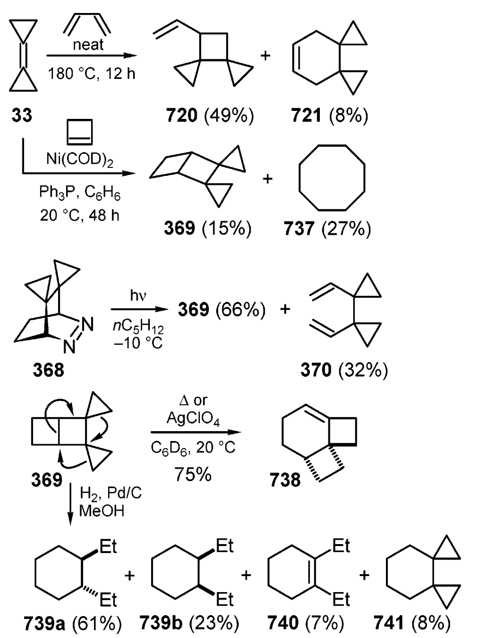
Quite a few cyclic hydrocarbons and their derivatives with more than one spiroannelated cyclopropane moiety (e.g., **369**, **719**−**736**) have been prepared in the last 35 years.

Both of the two isomeric hydrocarbons, 7-vinyldispiro-[2.0.2.2]octane (**720**) and dispiro[cyclopropane-1,2′-bicyclo-[2.2.0]hexane-3′,1′′-cyclopropane] (**369**), as well as dispiro-[2.0.2.4]dec-8-ene (**721**), all containing two adjacent spirocyclopropanes, can be prepared from the same synthetic precursor, bicyclopropylidene (**33**),[478,479] by thermally[264] or catalytically[263] induced [2 + 2] or [4 + 2] cycloadditions, respectively (Scheme 124). Alternatively, **369** was prepared



by photolysis of the bisspirocyclopropanated 2,3-diazabicyclo-[2.2.2]oct-2-ene (**368**) (Scheme 54).[263,264] This approach, at first sight, looks more productive, but the precursor has to be prepared along a 12-step synthetic route, whereas cyclobutene and bicyclopropylidene can be obtained in 8 steps altogether.

Scheme 124



Upon heating at 200−250 °C, the bicyclo[2.2.0]hexane derivative **369** underwent [2 + 2] cycloreversion to 1,1′-divinylbicyclopropyl (**370**), which was also obtained as a byproduct in the photolysis of **368**. Under silver-salt catalysis, **369** rearranged at ambient temperature, apparently in a cascade of cyclopropylcarbinyl to cyclobutyl cation rearrangements, to yield the interesting chiral cyclohexene-annelated spiro[3.3]heptane **738**.[263,264] Catalytic hydrogenation of **369** proceeded with addition across the central single bond in the bicyclo[2.2.0]hexane moiety and predominant concomitant opening of a proximal bond in each of the two adjacent spirocyclopropanes (Scheme 124).[480]

Thermally induced [2 + 2] cycloadditions of mono- and disubstituted methylenecyclopropanes **742** can also be applied for the assembly of various dispiro[2.0.2.2]octane skeletons **743** (Scheme 125 and Table 10). For unsymmetrical methylenecyclopropanes **742** ($R^1 \neq R^2$), however, the reaction yields mixtures of diastereomers.

Scheme 125

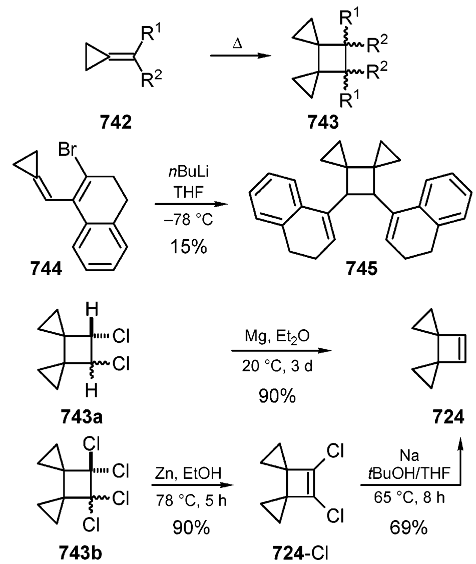
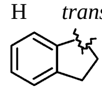


Table 10. Cyclodimerization of Substituted Methylenecyclopropanes 742

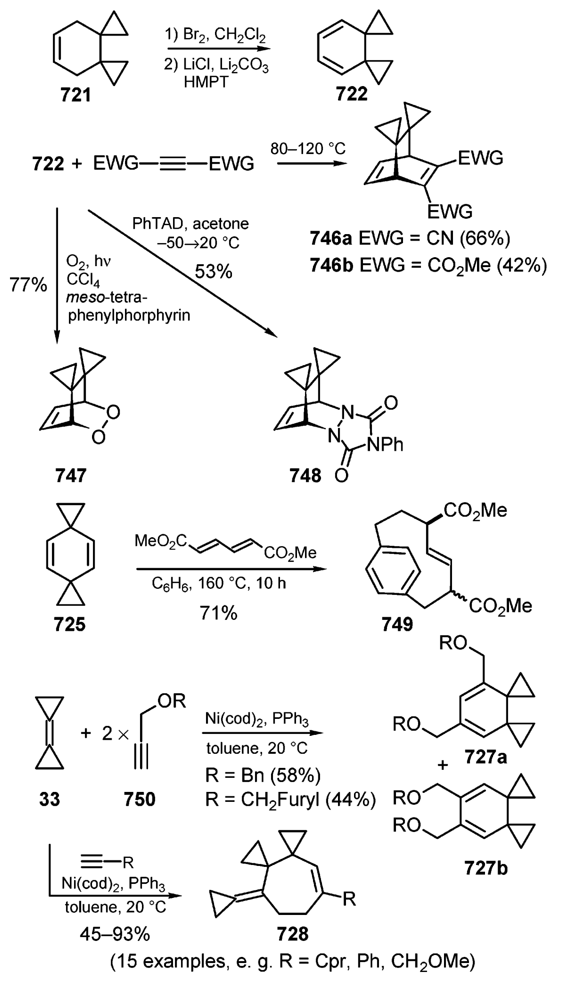
R^1	R^2	conditions	yield (%)	ref
H	H	200−245 °C, 48 h	20	481
Me	Me	200−245 °C, 80 h	0	481
−(CH2)3−		210 °C, 4 h	high[a]	481
F	F	312 °C, 3.5 h	30	482
Cl	Cl	110 °C, 8 h	100	481, 483
Cl	CO_2Me	120 °C, 15 h	100	484
H	Cl	188 °C, 2 h	80	485
H	OEt	192 °C, 2 h	87	485
H	*trans*-EtOCH═CH−	50−60 °C, 3−5 d	60	486
		−25 °C, 24 h	31	487

[a] Not reported.

Treatment of the methylenecyclopropane derivative **744** with *n*-butyllithium at low temperature furnished the interesting cyclodimer **745**. The latter must have been formed by cyclodimerization of the intermediate anion radical initially formed in the bromine−lithium exchange, and subsequent 2-fold protonation.[488] By treatment with magnesium in diethyl ether, the dimer *cis*,*trans*-**743a** (R^1 = H, R^2 = Cl) was converted into the interesting dispiro[2.0.2.2]oct-7ene (**724**), in 90% yield,[485] while from **743b** ($R^1 = R^2$ = Cl) hydrocarbon **724** was prepared in two steps (60% overall yield)[481] (Scheme 125). The dispirooctene **724** proved to be remarkably stable to unimolecular thermal decomposition but very prone to polymerization at room temperature, even in dilute solution[481] (see, however, ref 485). The electrophilic additions onto **724** proceed predominantly with retention of its dispiro[2.0.2.2]octane skeleton.[485]

Dispiro[2.0.2.4]dec-8-ene (**721**) was converted by addition of bromine and 2-fold dehydrobromination into dispiro-[2.0.2.4]deca-7,9-diene (**722**). On a multigram scale, **721** was obtained in five steps starting with a Diels−Alder addition of tetraethyl ethenetetracarboxylate to butadiene.[489] In the molecule of **722**, an *s-cis*-butadiene, two vinylcyclopropanes, and one bicyclopropyl moiety are uniquely combined.[490] Upon heating at 140 °C or upon flash vacuum pyrolysis at 400 °C, **722** rearranged with opening of both three-membered rings to yield tetralin (28%) and mainly *o*-ethylstyrene (72%). As an *s-cis*-fixed 1,3-diene, it disclosed an enhanced reactivity toward a variety of dienophiles including singlet oxygen and *N*-phenyltriazolinedione (Scheme 126).[491]

Scheme 126



The most interesting feature of dispiro[2.2.2.2]deca-4,5-diene (**725**), which was prepared in four steps from 2,5-dimethylenecyclohexane-1,4-diol (18% overall yield),[492a,c] is its thermal [8 + 4] cycloaddition with conjugated dienes across both three-membered rings to form [8]paracyclophanes of the type **749** (Scheme 126).[492b,c]

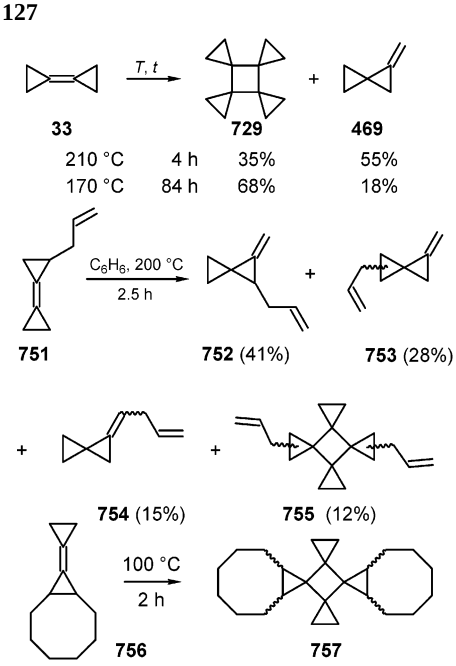
The saturated analogue of **725**, dispiro[2.2.2.2]decane (**726**), was prepared mainly for comparison of its He(I)-PE spectrum with that of **725**,[493] and this comparison led to the conclusion that the spirocyclopropane moieties in **725** transmit the electronic interaction between the two double bonds far better than CH_2 and CMe_2 groups.

Under nickel(0) catalysis [Ni(cod)$_2$, PPh_3, toluene, rt], two molecules of propargyl benzyl ether and one of bicyclopropylidene (**33**) underwent cocyclization to yield two isomeric derivatives of dispiro[2.0.2.4]deca-7,9-diene, **727a** and **727b** (ratio 2:1), whereas many other terminal alkynes including propargyl methyl ether under the same conditions gave moderate to high yields of 7-cyclopropylidenedispiro[2.0.2.5]-undec-10-ene derivative **728** by cocyclization of one molecule of the alkyne with two molecules of **33**, one of which reacted with ring opening (Scheme 126).[494]

The higher [*n*]rotanes ($n = 4, 5, 6$),[495,496] like [3]rotane **683** mentioned above, are esthetically appealing, highly symmetrical molecules, which can be considered as cyclic oligomers of cyclopropylidene. The syntheses, structures, conformations, and dynamics of the [4]- (**723**), [5]- (**730**), and [6]rotanes (**732**) have attracted considerable interest[242,251,497] after the first preparations of [4]rotane (**723**)[260,498] and [5]rotane (**730**)[499] in 1969. The series was completed in 1976 by the synthesis of [6]rotane.[499a,d,500]

Undoubtedly, the most convenient approach to [4]rotane **729** is by thermal [2 + 2] dimerization of bicyclopropylidene (**33**) (Scheme 127). This dimerization is known to proceed by heating hydrocarbon **33** either neat or in solutions in closed vessels at temperatures above 160 °C, and it is competing with the isomerization of **33** to methylenespiropentane **469**. The ratio of **729** to **469** depends on the reaction conditions employed. Several rationalizations of this surprisingly efficient [2 + 2] cycloaddition, which according to orbital symmetry conservation rules should not be a concerted reaction, have been published over the years.[260,479a,501]

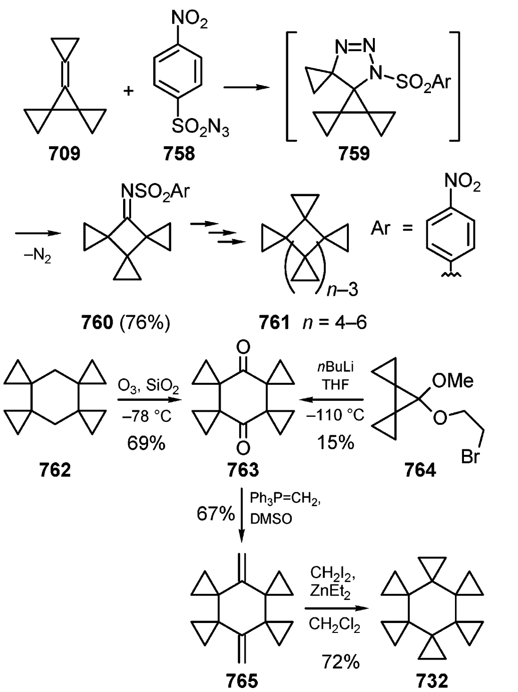
Scheme 127



In most cases, substituted bicyclopropylidenes such as **751** upon heating gave complex mixtures of products like **752**−**755** (Scheme 127).[501a] However, formation of a single product **757** was observed when 9-cyclopropylidenebicyclo-[6.1.0]nonane **756** was heated at 100 °C (Scheme 127); unfortunately, no stereochemical details have been reported for **757**.[502]

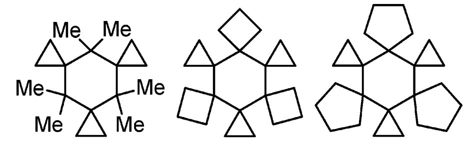
[5]Rotane (**730**) and [6]rotane (**732**) can be prepared by the same general approach to [*n*]rotanes **761** ($n = 4, 5, 6$),[499] starting with the 1,3-dipolar cycloaddition of *p*-nitrobenzenesulfonyl azide (**758**) onto 7-cyclopropylidenedispiro[2.0.2.1]heptane (**709**) followed by hydrolysis of the imine **760** after fragmentative rearrangement of **759**, Wittig olefination with cyclopropylidenetriphenylphosphorane, and several repetitions of the previous four steps. While this approach is still the only one known for **730**, [6]rotane **732** can be prepared more conveniently in two steps from tetraspiro[2.0.2.1.2.0.2.1]tetradecane-7,14-dione (**763**),[500] which can be obtained along two different routes (Scheme 128).[500,503] Two-fold methylenation and subsequent cyclopropanation of the resulting **765** furnishes **732** in 48% overall yield.[500]

Scheme 128



Computations at sufficiently high levels of theory recently disclosed that D_{4h}-[4]rotane **729** and higher even-numbered [*n*]rotanes like [6]rotane **732** do not necessarily have degenerate HOMOs. Accordingly, the radical cations of **729** and **732**, in contrast to those derived from D_{3h}-[3]rotane **683** and [5]rotane **730**, retain the full symmetry of the parent neutral hydrocarbons.[504] As a consequence, the radical cations of **729** and **732** should have longer lifetimes, and their symmetric structures should be detectable, at least at low temperatures.[505] This has indeed been proved for the radical cation of **729**.

The conformations and dynamic conformational behavior of higher [*n*]rotanes are of special interest. X-ray crystal structure analyses established the conformations of **730** and **732** in the solids.[505,506] In solution, however, [6]rotane **732** is especially intriguing as an example of a completely substituted cyclohexane, the conformations and dynamic behavior of which are dominated by strong nonbonding interactions. As a consequence, an unusual accumulation of anomalies was observed for such compounds.[507] Thus, while cyclohexanes normally adopt a chair conformation, and the free energy of activation for the chair-to-chair interconversion seldom exceeds 11.9 kcal/mol,[508] [6]rotane **732** was the first per(cyclo)alkylated cyclohexane for which the chair-to-chair interconversion was frozen at room temperature in solution. Its barrier of inversion (21.3 ± 0.2 kcal/mol)[509] was the highest of any cyclohexane derivative known at the time of publication. However, the conformational behavior of "mixed" [*n*]rotanes **766**−**768** with alternating spirocyclopropanes and



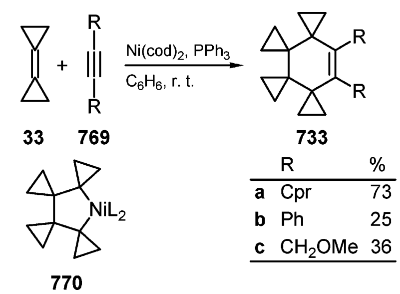
766 **767** **768**

gem-dimethyl groups or larger spiroannelated rings are even more remarkable.[510]

Thus, while hexamethyltrispiro[2.1.2.1.2.1]dodecane (**766**) is one of the rare examples of a cyclohexane with a pure twist-boat conformation ($\Delta G^{\ddagger}_{(TB/TB)} = 4.7$ kcal/mol), the hydrocarbons **767** as well as **768** are examples for cyclohexanes equilibrating between a chair and a twist-boat conformation with $\Delta G^{\ddagger}_{(C/C)} = 22.0$ and 16.1 kcal/mol, respectively.

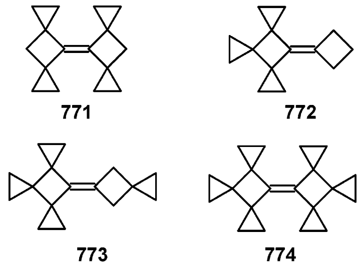
A remarkably simple and efficient access to 13,14-dicyclopropyltetraspiro[2.0.2.0.2.0.2.2]tetradec-13-ene (**733a**) has recently been uncovered. Upon treatment of a 2:1 mixture of bicyclopropylidene (**33**) and dicyclopropylacetylene **769**-Cpr (≡ **565**) in benzene solution with bis(cyclooctadiene)nickel in the presence of triphenylphosphine at 20 °C, **733a** was obtained in 73% yield. In the context of other nickel(0)-catalyzed cocyclizations of **33** with alkynes (see above), the formation of **733a** (Scheme 129) must be interpreted to proceed via the tetraspirocyclopropanated nickelacyclopentane **770**, but without a cyclopropylcarbinylmethyl to homoallylmetal rearrangement as described above. Other 13,14-disubstituted tetraspirotetradecadecenes **733b**,**c** were prepared from **33** and symmetrically disubstituted acetylenes as well, albeit in lower yields (25% and 36%, respectively). In the crystal, **733a** adopts a twist-chair conformation.[511]

Scheme 129



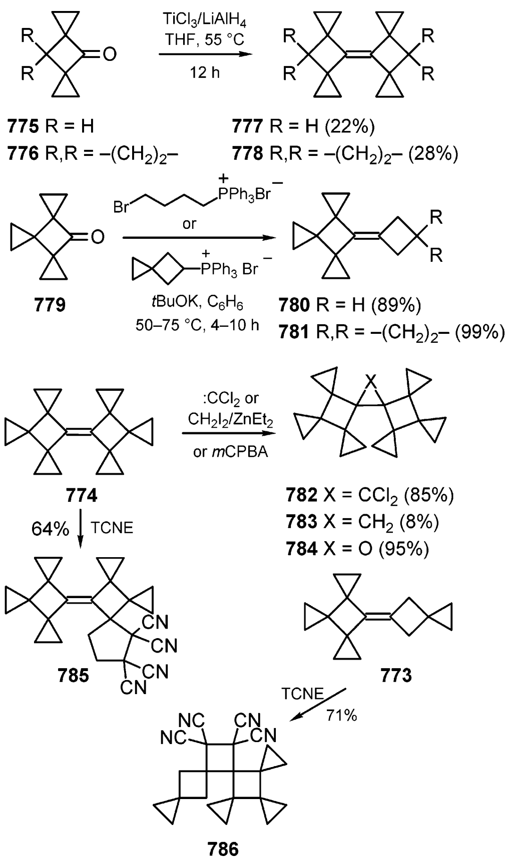
	R	%
a	Cpr	73
b	Ph	25
c	CH_2OMe	36

Spirocyclopropanated bicyclobutylidenes such as **771**−**774** are closely related to [4]rotane **729**.[512] The four spirocyclopropanated hydrocarbons **771**−**774** were prepared in 22%, 28%, 89%, and 98% yield, respectively, by McMurry coupling of the corresponding spirocyclopropanated cyclobutanones **775** and **776** (to yield **777** and **778**, respectively) or Wittig olefination of perspirocyclopropanated cyclobutanone **779** (to give **780** and **781**) (Scheme 130).[512] The successive attachment of spirocyclopropane moieties onto the bicyclobutylidene core led to a significant bathochromic shift of the UV absorption maximum by 12 and 17 nm, respectively, for each added pair of β- and α-spirocyclopropane groups. As taken from the He(I)-PE spectra of these bicyclobutylidenes, the effect of spirocyclopropanation upon their π-ionization energies (π-IE$_v$) was found to be almost additive,



leading to a lowering of 0.05 eV per any additional β-spirocyclopropane, and 0.28−0.22 eV per each additional α-spirocyclopropane group, indicating an increasing nucleophilicity of the double bonds in this series of tetrasubstituted alkenes.

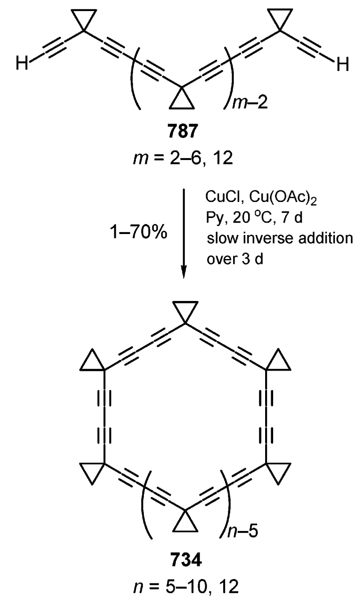
Scheme 130



The structures of the parent bicyclobutylidene and the perspirocyclopropanated bicyclobutylidene **774** were determined by X-ray crystallography, which disclosed considerable steric congestion around the double bond in **774**. In accordance with this congestion, **774** did undergo addition of dichlorocarbene, epoxidation with *m*-chloroperbenzoic acid, and cyclopropanation with $CH_2I_2/ZnEt_2$ (85%, 95%, and 8% yield, respectively) but did not add the more bulky dibromocarbene. The reaction of **774** with tetracyanoethylene proceeded smoothly but led to the formal [3 + 2] cycloadduct **785** across the proximal single bond of one of the inner cyclopropane rings (Scheme 130).[512]

Even more spectacular than [*n*]rotanes are the "expanded" analogues **734** in which all carbon−carbon single bonds between two cyclopopane moieties in the [*n*]rotanes are replaced with butadiyne moieties.[513] A reasonable approach to macrocycles of type **734** has been established employing oxidative coupling with the $CuCl/Cu(OAc)_2$/pyridine system of one, two, or more open-chain dehydrooligomers of 1,1-diethynylcyclopropane (Scheme 131),[514] and the success then depended on the availability of appropriate building blocks for the corresponding acyclic dehydrooligomers **787**.[513a]

Scheme 131

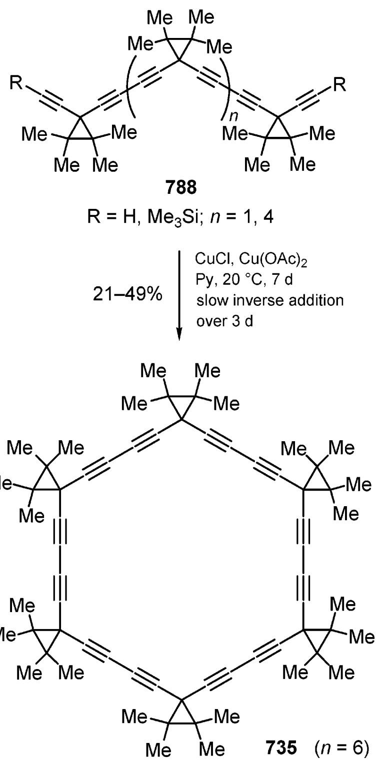


The whole family of these "expanded" [*n*]rotanes **734**,[514] as well as selected acyclic building blocks for them,[515] were investigated in great detail by X-ray crystallography. However, despite quite interesting structural features having been disclosed, these investigations have not revealed any bond length equalization that might be due to cyclic delocalization, as all the bond lengths observed for the macrocyclic expanded [*n*]rotanes **734** were virtually the same as those in their parent subunits. Thus, for these compounds there is no indication of significant homoconjugation in the hexayne macroring (cf. ref 516).

All of these compounds are extremely high-energy molecules, and thus all of the "expanded" [*n*]rotanes **734** are remarkably sensitive toward shock. Even when struck a bit too hard with a spatula, a pestle, or a falling ball, they went off with a flame and yielded a cloud of black soot.[514] The composition of the black soot formed in such destructive processes is of special interest. For example, not only amorphous carbon and graphite, but also ordered tube- and onion-type carbon layers along with the evolution of methane and hydrogen gas have been detected upon an analogous explosive thermal decomposition of a cyclic oligoyne with aromatic connectors.[517] However, only amorphous carbon with small graphitic areas was found in the explosion products of the butadiyne-expanded [*n*]rotanes **734**, and traces of C_{60}-fullerene were detected by mass spectrometry after the explosion of exp-[6]rotane **734** ($n = 6$).[518] A more detailed investigation of the thermal behavior of these "exploding" [*n*]rotanes by differential scanning calorimetry (DSC) measurements was performed for exp-[6]rotane **734** ($n = 6$) and its permethylated analogue **735**.[518,519] The latter was prepared by two- or one-component assemblies similar to **734** ($n = 6$) using a modified Glaser-coupling protocol (Scheme 132).[518]

This study revealed that slow decomposition of exp-[6]-rotane **734** ($n = 6$) already starts at 100 °C, and an explosive quantitative decomposition sets on at 154 °C with an energy release of $\Delta H_{decomp} = 478$ kcal/mol. The permethylated exp-

Scheme 132



[6]rotane **735** is thermally less labile, and its decomposition is moderated with an onset at 135 °C and a maximum decomposition rate at 194.5 °C with $\Delta H_{decomp} = 285$ kcal/mol. For example, ΔH_{decomp} of the well-known explosive hexogen (1,3,5-trinitro-1,3,5-triazacyclohexane, RDX) determined under similar experimental conditions was only 143 kcal/mol. Applying an evolved gas analysis (EGA) technique to the thermal decomposition of **734** ($n = 6$) and **735** in different heatable optical cells with rapid scan FT-IR spectroscopy monitoring, the formation of only methane, ethylene, and acetylene could be detected in the case of **734** ($n = 6$), and the only gaseous product evolved upon the decomposition of permethyl-exp-[6]rotane **735** ($n = 6$) was tetramethylethylene. The latter fact leads one to conclude that the spirocyclopropane moieties in these expanded [*n*]-rotanes fragment only externally and leave carbene moieties behind.[518,519]

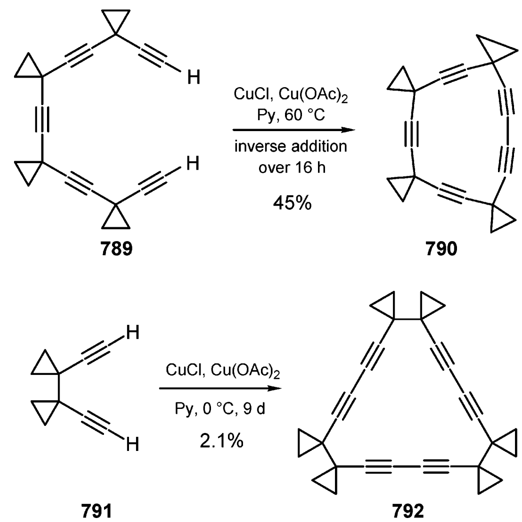
Unfortunately, all attempts to synthesize the perspirocyclopropanated analogues of the so-called [*n*]pericyclynes,[520] that is "expanded" [*n*]rotanes **734**, in which all single carbon−carbon bonds between two cyclopropane fragments are replaced with simple ethyne moieties, were unsuccessful.[513a]

The closest analogue to such spirocyclopropanated [*n*]-pericyclynes ever prepared is the cyclic pentayne **790**, which can be considered as a perspirocyclopropanated [5]pericyclyne lacking one spirocyclopropane linkage. It was obtained by intramolecular acetylene−acetylene coupling of the acyclic unprotected pentayne **789** under oxidative conditions (Scheme 133).[521]

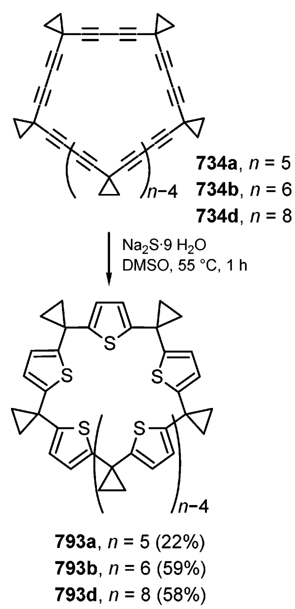
The "half-expanded" (with diacetylene moieties) [6]rotane **792** could be prepared under similar conditions by a "shotgun" approach, that is, by dehydrotrimerization of the diyne **791**, albeit in a yield of only 2.1% (Scheme 133).[429]

The "exploding" [*n*]rotanes **734** react with $Na_2S{\cdot}(H_2O)_9$ under strongly basic conditions (KOH/DMSO) within 1 h to produce the corresponding macrocycles **793** in surprisingly good yields (up to 59% for $n = 6$, Scheme 134).[430] The relatively low isolated yield of the [5.5]-macrocycle **793a** was caused by its instability. These macrocycles with alternating thiophene and spirocyclopropane rings are essentially a new family of [*n*]rotanes expanded with thiophene moieties. In the crystal, the macrocycle of **793b** adopts a chair-like conformation with a center of inversion (overall S_6-symmetry), in which the two cyclopropyl groups on each thiophene unit are alternatingly almost bisected and perpendicular in their orientation. This unusual conformation with three sulfur atoms above and three below the equatorial plane of the macrocycle probably results as an energetic compromise between the mutual repulsion of the sulfur atoms and a maximum conjugation between the cyclopropane and thiophene fragments.

Scheme 133

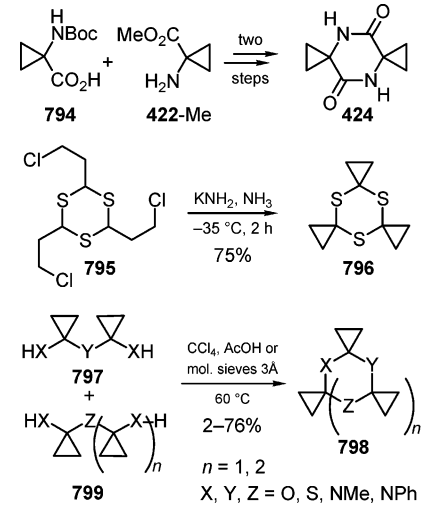


Scheme 134



Among the known heteroanalogues of expanded [*n*]-rotanes, the simplest one is 4,9-diazadispiro[2.2.2.2]decane-5,10-dione, the bisspirocyclopropanated diketopiperazine **424**, which was prepared from 1-aminocyclopropanecarboxylic acid (ACC, **422**)[522] (Scheme 135, details are not given) and investigated by X-ray crystallography.[303] The central ring in **424** was found to be almost planar; the hydrogen-bonding interactions between diketopiperazine moieties dominate the packing arrangement of these molecules in the crystal (see also Section 2.4).

Scheme 135



4,8,12-Trithiatrispiro[2.1.2.1.2.1]dodecane (**796**), the cyclic trimer of thiocyclopropanone is the first member of a larger family of [*n*]rotanes **798** expanded with heteroatoms, which all are essentially cyclic oligomers of cyclopropanone, cyclopropanethione, and cyclopropanimine, respectively. Compound **796** was prepared by 3-fold γ-dehydrochlorination of compound **795** with potassium amide in 75% yield (Scheme 135).[523] Later on, a general approach to compounds of type **798** by condensation of cyclopropanone derivatives **797** and **799** was elaborated (Scheme 135).[524] This method allows one to prepare [3]- and [4]rotanes **798** ($n = 1, 2$) expanded with heteroatoms with all possible combinations of X, Y, and Z in 2−76% yields.

A variety of spirocyclopropane-annelated tetrahydropyridinones of type **803** and **804**, which can be considered as heterocyclic analogues of [*n*]rotanes, have been synthesized by 1,3-dipolar cycloaddition/thermal rearrangement (so-called Brandi−Guarna reaction[525]) of nitrones to cyclopropylidenespiropentane (**476**) and 7-cyclopropylidenedispiro[2.0.2.1]-heptane (**709**) in good yields (Scheme 136 and Table 11).[526] Some such compounds showed interesting biological activities in cleaving a DNA plasmid.[527]

Scheme 136

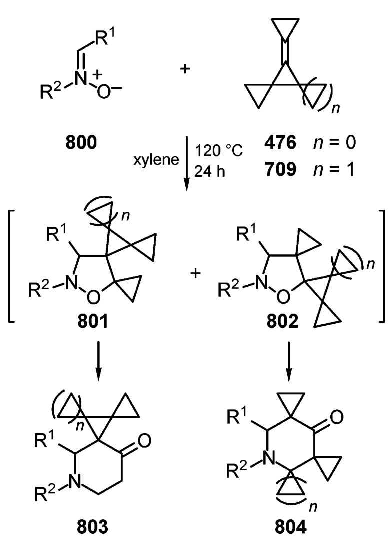
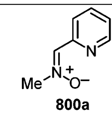
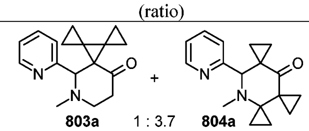
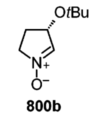
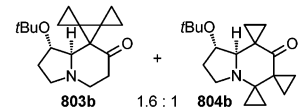
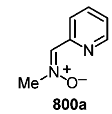
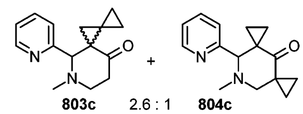
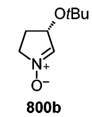
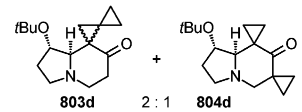


Table 11. Spirocyclopropane-Annelated Tetrahydropyridones 803/804 from Spirocyclopropanated Bicyclopropylidenes 709 and 476 and Nitrones by One-Pot Sequences of 1,3-Dipolar Cycloadditions and Thermal Rearrangements[526]

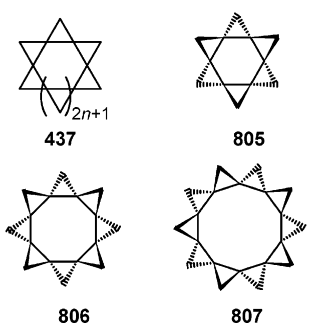
Entry	Nitrone	Alkene	Products (ratio)	Total Yield [%]
1		**709**		68
2		**709**		77
3		**476**		72
4		**476**		80

3.5. Cyclic Triangulanes

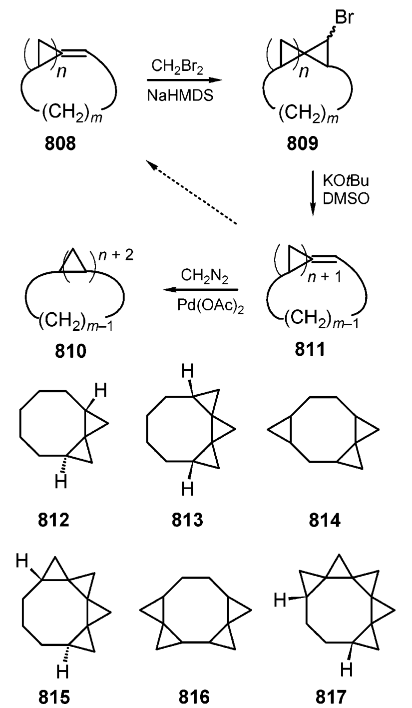
The [*n*]cyclotriangulanes (CTs) **437** remain elusive, because no successful preparation of any CT has ever been reported. Yet two statements can be made without any experimental support: (i) any cyclic triangulane must have an even number of annelated three-membered rings and a planar central ring;[313a,101] (ii) according to various calculations, [8]CT **806** would be the most realistic and straightforward synthetic target,[101,528,529] although [10]CT **807** and [6]CT ("Davidane") **805** should not be impossible despite their excessive strain energies due to the additional angle distortion in their spiropentane subunits. However, no workable concepts to prepare [8]CT **806** and [10]CT **807** have been published so far.

A conceived approach to cyclic triangulanes was by bromocyclopropanation with bromocarbene of a cycloalkene **808** ($n = 0$) to a bromobicyclo[*m*.1.0]alkane **809** ($n = 0$), followed by dehydrobromination and isomerization to a ring-annelated methylenecyclopropane **811** ($n = 0$) (Scheme 137).[530] With this product, the same sequence of transformations can be repeated over and over again. A final simple methylenation of any bridged methylenetriangulane **811** ($n \geq 0$) would lead to the corresponding ring-annelated triangulane **810** ($n \geq 0$).

This multistage strategy was probed starting from cyclooctene, cycloocta-1,4-diene, and cyclooctatetraene furnishing ring-annelated triangulanes **812**−**817** with up to five spirolinked cyclopropane rings (Scheme 137). However, the



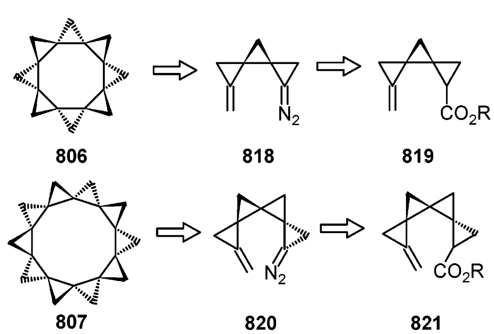
Scheme 137



application of this approach to complete the construction of [*n*]cyclotriangulanes has not been reported; therefore, it is an open question, whether cyclic triangulanes can be obtained along this pedestrian route, as the more highly cyclopropanated bridged methylene[*n*]triangulanes **811** and the intermediate cyclopropene derivatives en route to them are so reactive that they add *tert*-butyl alcohol under the conditions of dehydrobromination with potassium *tert*-butoxide in DMSO.[530]

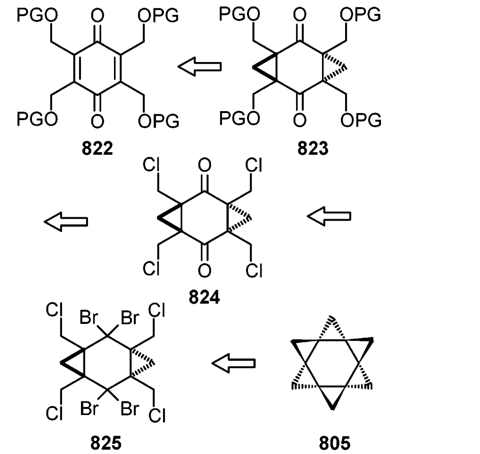
The most highly convergent syntheses would be by dimerization of in situ generated carbenes from, for example, chiral diazomethylenetriangulanes **818** and **820**, respectively (Scheme 138). These would not have to be enantiomerically pure, because both enantiomers upon dimerization would yield the same achiral CTs **806** and **807**, respectively. Anyway, a feasible access to the appropriate precursors **819** and **821** even in enantiomerically pure form has recently been elaborated.[314,316,320,321]

Scheme 138

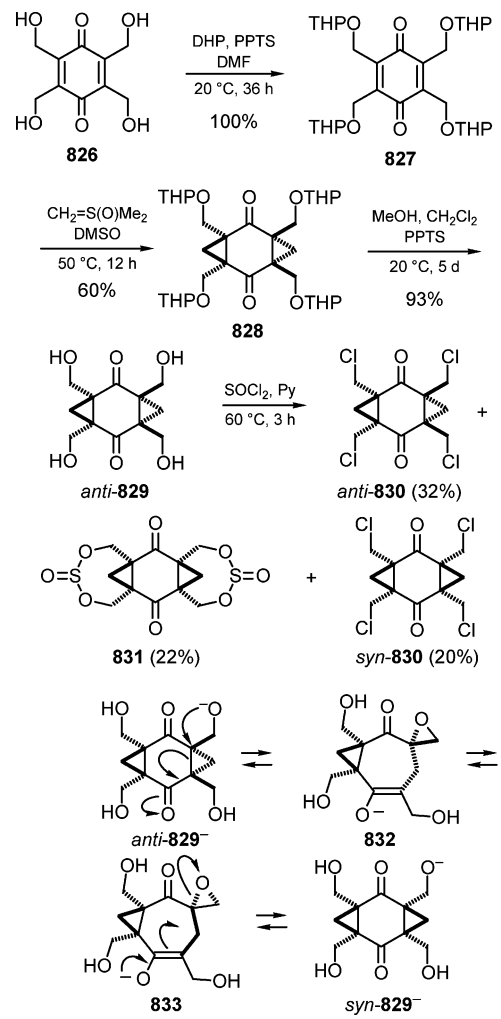


A conceivable synthetic approach to Davidane **805** was envisaged based on a *trans*-selective 2-fold cyclopropanation of functionally tetrasubstituted quinones of type **822**, which would set the stage for the correct geometry of the target. After several transformations, which turned out to be realizable (Scheme 139), a 4-fold cyclization of the tetrabromotetra(chloromethyl)tricyclo[5.1.0.0^{3,5}]octane **825** by treatment with an alkyllithium reagent, in close analogy to that applied in the high-yielding preparation of the extremely strained [1.1.1]propellane,[107a] might lead to the hydrocarbon **805**.

Scheme 139



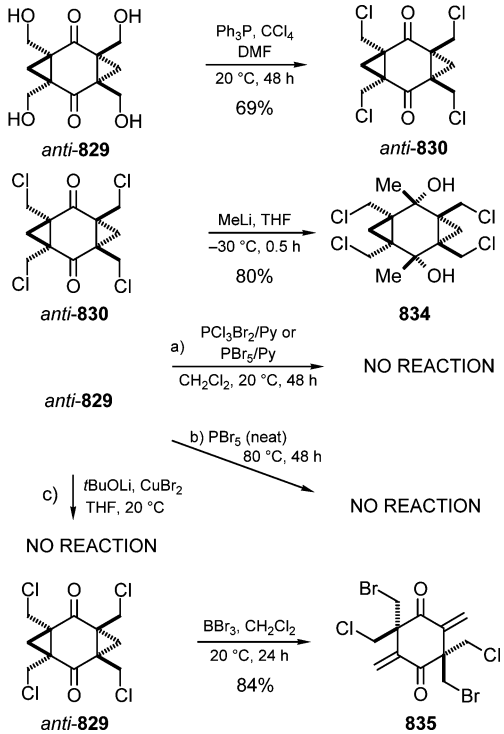
Scheme 140



According to this strategy,[531] the known tetra(hydroxymethyl)-1,4-benzoquinone (**826**)[532] was completely protected and subjected to 2-fold cyclopropanation with the sulfur ylide from trimethylsulfoxonium iodide[533] to give, after deprotection, tetra(hydroxymethyl)-*anti*-tricyclo[5.1.0.0^{3,5}]octane (*anti*-**829**) with the appropriate configuration in 56% overall yield

(Scheme 140). An attempted transformation of the latter to the corresponding tetra(chloromethyl)tricyclooctane with thionyl chloride/pyridine afforded a mixture of the products *anti*-/*syn*-**830** and **831**, two of which, *syn*-**830** and **831**, turned

Scheme 141



out to have the wrong configuration. Presumably, a base-induced isomerization of *anti*-**829** via intermediates **832** and **833** (Scheme 140) occurred under these conditions analogously to a reported case (cf. ref 534). However, chlorination with the triphenylphosphine/carbon tetrachloride reagent furnished the tetrachloride *anti*-**830** as the sole product (Scheme 141).

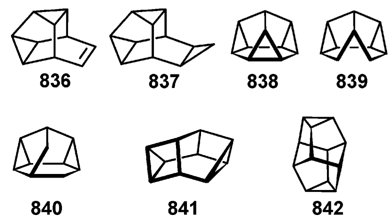
The carbonyl groups in *anti*-**830** do react with methyllithium to give the tricyclic diol **834** as a single diastereomer. However, the carbonyl groups turned out to be completely resistant toward transformation to *gem*-dibromo derivatives both with classical (entries a, b) and modern[535] (entry c) reagents (Scheme 141), while application of boron tribromide led to opening of both cyclopropane rings to yield **835**. The structures of almost all of these tricyclic intermediates were rigorously proved by X-ray crystallography.[536]

4. Cage Structures with Three-Membered Rings

4.1. Cages Incorporating Three-Membered Rings

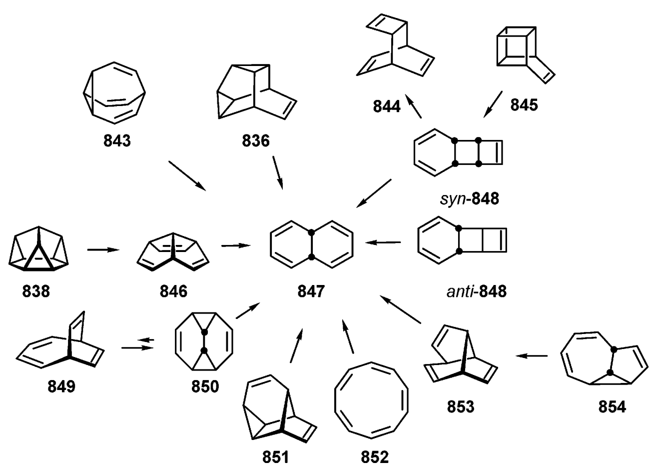
A number of cage hydrocarbons **836**−**842** incorporating two or even three cyclopropane moieties have been prepared and found to have interesting properties. The bridged trishomobarrelene **837** is known as its *gem*-dichloro derivative only.[537a]

Bullvalene (**843**), snoutene (**836**), and diademane (**838**) have one common feature: they all are members of the $(CH)_{10}$ hydrocarbon family[538] and as such are characterized by multiple rearrangements that they can undergo to other members of the same family (Scheme 142).[539] These rearrangements can be initiated either thermally, photochemically, or under metal catalysis. The thermodynamic sink of



all interconversions of $(CH)_{10}$ hydrocarbons apparently is *cis*-9,10-dihydronaphthalene (**847**), which is formed by thermal rearrangement from bullvalene (**843**), lumibullvalene (**853**), isobullvalene (**854**), and isolumibullvalene (**851**), from bicyclo[4.2.2]decatetraene (**849**) and its intramolecular Diels−Alder adduct **850**, from pentacyclo[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]dec-9-ene (**845**, basketene) and tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene (**844**, Nenitzescu's hydrocarbon), from hexacyclo-[4.4.0.0^{2,4}.0^{3,9}0^{5,7}.0^{8,10}]decane (**838**, diademane) and triquinacene (**846**), and from the *syn*- and *anti*-tricyclo[4.4.0.0^{2,5}]decatrienes (**848**), all-*cis*-cyclodecapentaene (**852**), and pentacyclo-[4.4.0.0^{2,4}.0^{3,8}.0^{5,7}]dec-9-ene (**836**, snoutene).

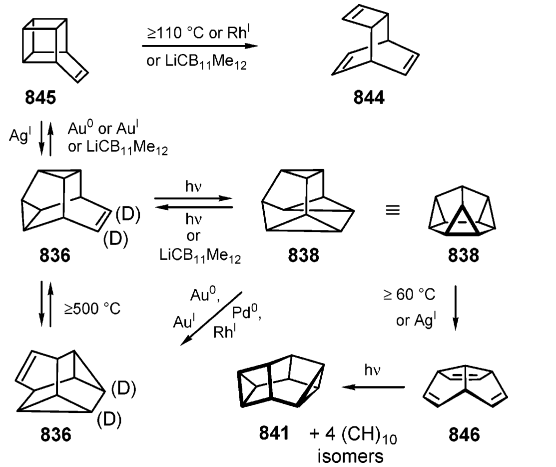
Scheme 142



Many of these interconversions do not directly lead to **847**; for example, basketene (**845**) is known to rearrange to Nenitzescu's hydrocarbon **844** upon heating[540] and under rhodium(I)[541] catalysis, while under silver(I) catalysis, it rearranges to snoutene (**836**).[541,542] In the presence of gold (Au^0 or Au^I), however, snoutene (**836**) rearranges to basketene (**845**),[543] a fact that apparently has to do with the relative stabilities of the intermediate metal complexes. Upon heating to 500 °C, snoutene (**836**) undergoes an interesting automerization, as detected by appropriate labeling, which interchanges the two vinylic with the two cyclopropylic methyne positions.[544] When irradiated with UV light, snoutene (**836**) reversibly rearranges to diademane (**838**).[220b,545] Thermally[104,546] and under silver(I)[547] or copper(I)[547] catalysis, diademane (**838**) rapidly rearranges to triquinacene (**846**), and this in turn undergoes photochemical isomerization to hexacyclo(4.4.0.0^{2,4}.0^{3,10}.0^{5,8}.0^{7,9})decane (**841**, barettane), along with four other $(CH)_{10}$ hydrocarbons (Scheme 143).[548] Diademane (**838**) also underwent isomerization to snoutene (**836**) under Au^0, Au^I, Pd^0, or Rh^I catalysis.[547] Alternatively, barettane **841** was obtained from the bistosylhydrazone of tetracyclo[5.2.1.0^{2,6}.0^{4,8}]decane-5,10-dione by 2-fold deprotonation with butyllithium and subsequent thermolysis.[548]

The recently reported new catalyst for pericyclic rearrangements, $LiCB_{11}Me_{12}$, provoked diademane (**838**) to undergo a rapid isomerization to snoutene (**836**) as well as

Scheme 143

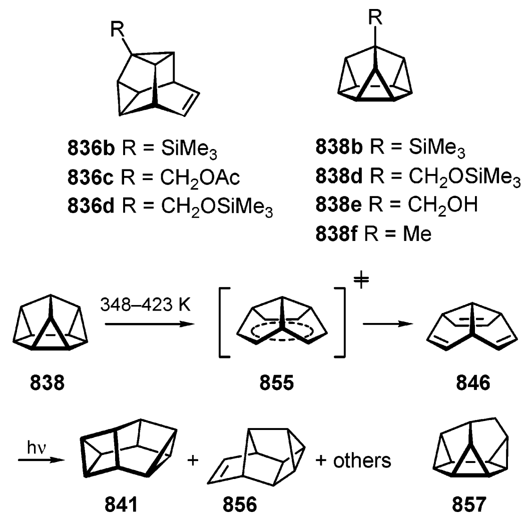


basketene (**845**) to yield Nenitzescu's hydrocarbon **844** (Scheme 143).[549]

Because work on $(CH)_{10}$ hydrocarbons has drastically slowed down during the last two decades, the goal as formulated in 1981, "The heats of formation of all these compounds, as well as activation parameters for their rearrangements, must be determined in order to construct a meaningful energy surface",[539a] is still far away. Although 24 isomers of the 93 theoretically possible $(CH)_{10}$ valence isomers[538] are known, only the enthalpies of formation ΔH_f°(g) of bullvalene (**843**) (79.7 kcal/mol)[550] and snoutene (**836**) (72.4 ± 0.9 kcal/mol)[551] had been reported some time ago, yet in the latter case the purity of the sample was only 97.5%. Values of 83.7 and 73.6 kcal/mol have been calculated for isobullvalene (**854**) and lumibullvalene (**853**), respectively, but only with the MM2 force-field method.[552] More recently, bullvalene (**843**) and triquinacene (**846**) have been calculated at various higher levels of theory.[553]

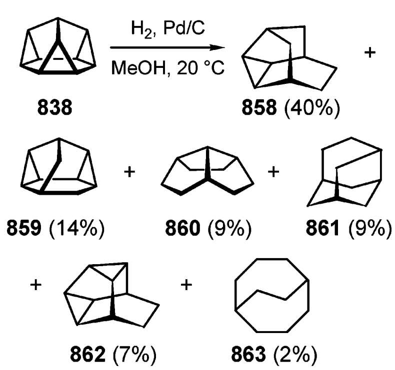
Some progress has recently also been made in terms of experimental values in that the enthalpies of formation [ΔH_f°(g)] of triquinacene (**846**),[554] basketene (**845**),[555] and snoutene (**836**)[555] were determined by measuring their heats of combustion in a microcalorimeter and found to be 57.51 ± 0.70, 110.2 ± 0.5, and 78.4 ± 0.3 kcal/mol, respectively. The latter value is 5.95 kcal/mol higher than the one reported for a less pure sample,[551] while the newly determined enthalpy of formation of triquinacene (**846**) is about 4 kcal/mol higher than that previously reported, but coincides with values computed by ab initio and density functional theory methods. As a consequence, the previously derived homoaromatic stabilization energy (claimed to be 4.5 kcal/mol) from enthalpy of hydrogenation measurements does not really exist for **846**.[554] In addition, the enthalpies of isomerization of **845** to **844**[555] and of **838** to **846**[554] have been measured by differential scanning calorimetry (DSC) to be −20.7 ± 0.3 and −29.4 ± 0.3 kcal/mol, respectively, with enthalpies of activation of 28.6 ± 0.1 and 28.4 ± 0.2 kcal/mol, respectively. From these experimentally obtained data, the values of the strain energies (SE) for the hydrocarbons **836**, **838**, **843**, **844**, **845**, and **846** were estimated to be 78.4, 86.9, 37.0, 44.6, 110.3, and 14.5 kcal/mol, respectively. The obtained strain energies and derived heats of isomerization to 9,10-dihydronaphthalene (**847**) do not in any way correlate with either the activation energies for the thermal isomerizations of these $(CH)_{10}$ hydrocarbons or the structural features determined experimentally for bullvalene (**843**),[556] basketene (**845**),[555] and trimethylsilylsnoutene (**836b**, Scheme 144)[557] or computationally (DFT at the B3LYP/6-311+G* level) for unsubstituted snoutene (**836**).[555]

Scheme 144



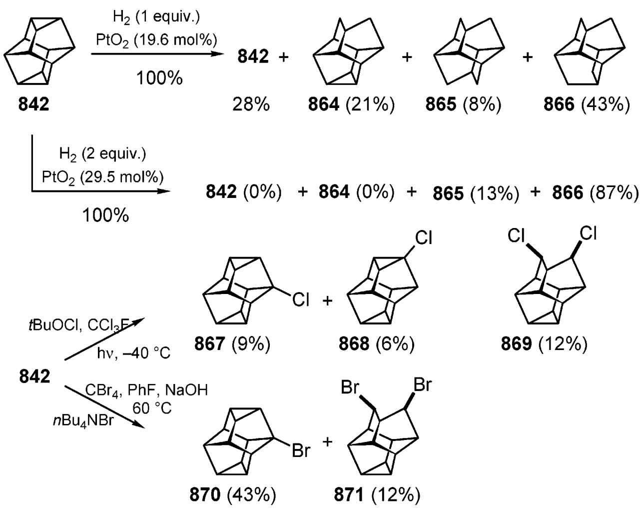
Surprisingly, the X-ray crystal structure analysis of 6-hydroxymethyldiademane (**838e**) disclosed a pronounced alternation of the bond lengths in the six-membered ring,[557] with 1.494(4) between and 1.539(4) Å within the three cyclopropane moieties, which is in close agreement with computations at different levels of theory.[557,558] This corroborates a predisposition in the ground state of the tris-σ-homobenzene skeleton of this molecule to undergo a facile [$\sigma^2_s + \sigma^2_s + \sigma^2_s$] cycloreversion to the triquinacene skeleton as observed for the parent diademane **838** (with the transition structure **855** of the same C_{3v}-symmetry as the starting material **838** and the product **846**), its derivatives **838b**−**f**, and other tris-σ-homobenzene derivatives, for example, homodiademane **857**[545a,546b] (Scheme 144). On the other hand, upon catalytic hydrogenation of **838**, a complex mixture of di-, tetra- and hexahydro derivatives was formed, and its relative composition was independent of the progress of the hydrogenation; the main products, secosnoutane (**858**) and 2,4,6,9-tetradehydroadamantane (**859**, pentacyclo-[$4.4.0.0^{2,10}.0^{3,5}.0^{4.8}$]decane[559]), were formed by cleavage of one of the shorter [1.502(4) Å] cyclopropane bonds (Scheme 145).[547] The so-called stabilomer in the family of $C_{10}H_{16}$ hydrocarbons, adamantane, was not detected. Not surprisingly, hydrogenolysis of barettane **841** furnished a single product formed by cleavage of the central single bonds in its two bicyclo[2.1.0]pentane moieties.[220b,548]

Scheme 145



The D_{3d}-symmetric *p*-[$3^2.5^6$]octahedrane **842**,[560] a $(CH)_{12}$ hydrocarbon that corresponds to a cubane with two opposite corners truncated, possesses a strain energy of 83.7 kcal/mol, or 4.7 kcal/mol per C−C bond, as computed at the B3LYP/6-311+G* level of theory.[561] This is significantly higher than that of the structurally related $(CH)_{16}$ [D_{4d}]-decahedrane (75.4 kcal/mol, 3.1 kcal/mol per C−C bond) and $(CH)_{20}$ [I_h]-dodecahedrane (51.5 kcal/mol, 1.7 kcal/mol per C−C bond).[562] However, despite its strain, **842** is kinetically quite stable as it does not decompose until above 180 °C, and computationally it was determined to be the thermodynamically most stable of all $(CH)_{12}$ isomers.[553,561] Catalytic hydrogenation of **842** led to consecutive opening of the two cyclopropane rings to give [C_2]-bissecooctahedrane (pentacyclo[$6.4.0.0^{2,6}.0^{3,11}.0^{4,9}$]dodecane), **866**) as the major product (Scheme 146).

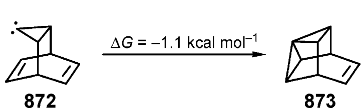
Scheme 146



Because the barriers for an S_R2 attack of radicals on a carbon atom of one of the cyclopropane fragments are ca. 10 kcal/mol higher than those for hydrogen atom abstraction (B3LYP/6-31G*), some radical reactions of **842** proceeded with complete retention of its carbon skeleton. Thus, the chlorination of **842** with *tert*-butyl hypochlorite gave a mixture of 1- and 2-chlorooctahedranes **867** and **868** (ratio 3:2). Bromination of **842** with carbon tetrabromide under phase-transfer catalytic (PTC) conditions (^{n}Bu$_4$NBr/NaOH) selectively gave 1-bromooctahedrane **870** in 43% isolated yield (Scheme 146).[561]

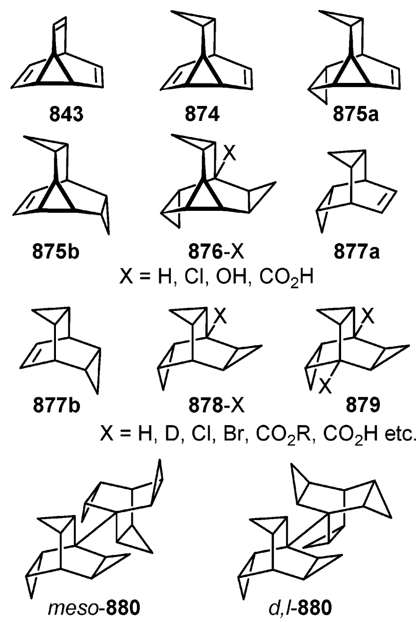
At least one further development in the chemistry of oligocyclic aliphatic molecules with three-membered rings may be directed toward uncharged molecules with a pyramidally tetracoordinated carbon atom. Thus, recent B3LYP/6-31G(d) and MP2 calculations predict interactions between the divalent carbon and one double bond in tricyclo[$3.2.2.0^{2,4}$]nona-6,8-dien-3-ylidene (**872**). The carbene **872** should easily form the kinetically more stable pentacyclo[$4.3.0.0^{2,9}.0^{3,8}.0^{7,9}$]non-4-ene (**873**) (Scheme 147), which comprises a pyramidally tetracoordinated carbon atom.[563]

Scheme 147



4.2. Cages and Half-Cages with Annelated Three-Membered Rings

Strained oligocyclic molecules with three-membered rings are not only attractive from an esthetical point of view but also challenging targets for organic chemists to probe various concepts of structure−reactivity relationships.[201a,564] The golden age of such hydrocarbons as **843** and **874**−**880** was in the 1960s−1980s, and most of the preparations, as well as the main peculiarities of such hydrocarbons, that is, bonding properties,[565] strain and its implications,[165c,566] and chemical transformations, have been reviewed several times.[539,567,568]

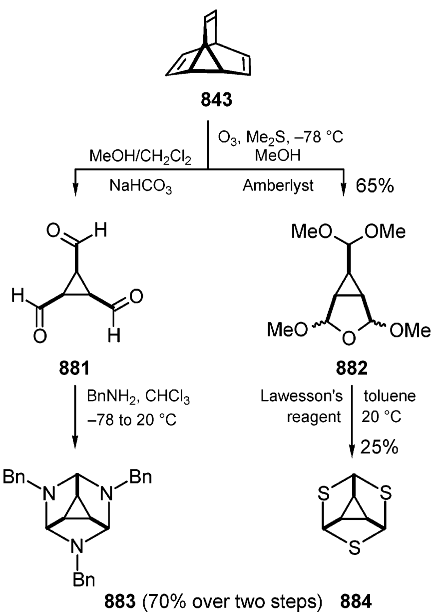


Among such structures, the propeller-shaped cage-like molecules trishomobullvalene **876** (X = H) and trishomobarrelene **878** (X = H) constitute interesting test cases for the ever advancing theoretical models that computations of chiroptical properties can be based upon.[567] Regrettably, the work on such hydrocarbons has drastically slowed during the last two decades, yet it has seen a bit of a renaissance in recent years. For example, for tricyclo[$3.3.2.0^{2,8}$]deca-3,6,9-triene (bullvalene) **843**, "the compound of 1 209 600 different faces",[539a,569] new computational[570] and experimental[571] studies of the degenerate Cope rearrangement in it and its analogues as well as structure and bonding properties have recently been reported.[572] In addition, **843** has recently used as a starting material for the preparation of the functionally all-*cis*-1,2,3-trisubstituted cyclopropane derivatives **881** and **882** (Scheme 148).[573,574]

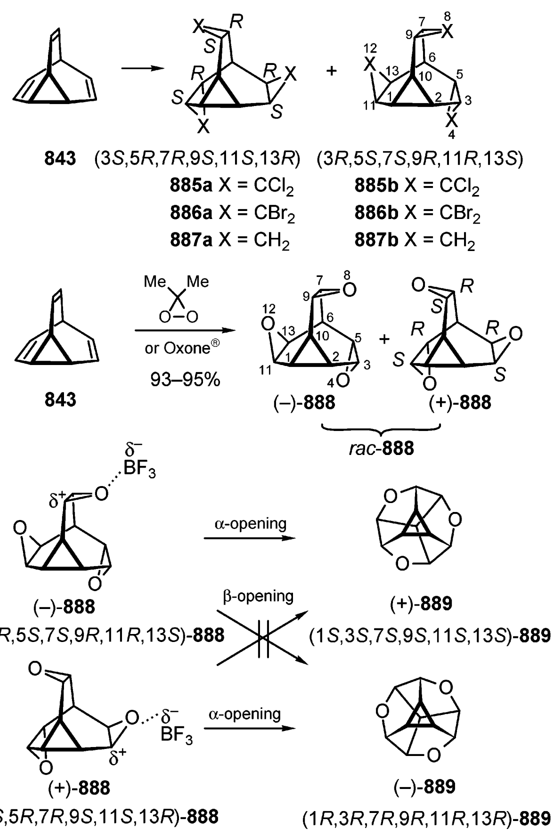
The latter were used without purification for the syntheses of the C_{3v}-symmetrical triaza- (**883**)[573a] and trithia[3]-peristylane (**884**),[573b] which were obtained in 70% and 16% overall yield, respectively. These novel aza- and thiabowls display unprecedented supramolecular architectures in the solid state.

Apart from this, bullvalene **843** turned out to be a particularly suitable starting material for the preparation of such molecules as homobullvalene **874**, bishomobullvalene **875a**,**b**, and trishomobullvalene **876**. Thus, 3-fold dihalocyclopropanation[237,537] and 3-fold cyclopropanation[575] of **843** led to the rigid C_3-symmetrical helical molecules **885**−**887**, which can be left- or right-handed propellers (Scheme 149).[200,576]

Scheme 148



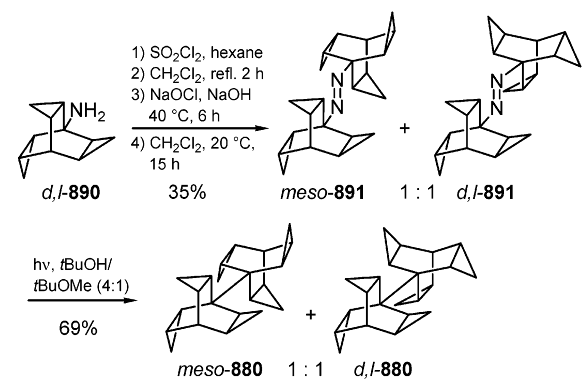
Scheme 149



While carbocyclic homobullvalenes **874**−**876** have been extensively reviewed,[567] less has been reported about their heteroanalogues. The recently published[577] epoxidation of bullvalene (**843**) with dimethyldioxirane or with a neutralized solution of Oxone gave the racemic trisepoxide *rac*-**888** in 93−95% isolated yield (Scheme 149). The two enantiomers of **888** were separated by preparative HPLC and exhibited specific rotations of $[\alpha]_D^{25} = +160$ and $[\alpha]_D^{25} = -157$; the absolute configuration of (−)-**888** was determined by anomalous X-ray diffraction and turned out to be (3*R*,5*S*,7*S*,9*R*, 11*R*,13*S*), and this could also be reproduced by DFT computations at the TD-B3LYP/6-31+G(d,p)//BLYP/6-31+G(d) level of theory. Upon treatment with $BF_3{\cdot}Et_2O$ at −78 °C, the trisepoxide *rac*-**888** rearranges with retention of the skeletal three-membered carbocycle to give the cage trisether *rac*-**889**, the enantiomers of which were separated by preparative HPLC on a chiral column and exhibited specific rotations of $[\alpha]_D^{25} = +49$ and $[\alpha]_D^{25} = -46$. The absolute configuration of (−)-**889** was determined by anomalous X-ray diffraction to be (1*R*,3*R*,7*R*,9*R*,11*R*,13*R*). Especially remarkable is the fact that the acid-catalyzed isomerization of the enantiomerically pure (+)-**888** proceeded without racemization to give exclusively (−)-**889**, and (−)-**888** provided only (+)-**889**. Thus, this isomerization occurs with ring opening of the three C−O bonds in the epoxide moieties in the α-position relative to the three-membered carbocycle rather than in the *β*-position.

In contrast to homobullvalenes **874**−**876**, homobarrelenes **877a**,**b** and **878**-H are achiral molecules, but bridgehead-substituted trishomobarrelenes **878**-X (X ≠ H) are chiral (see review in ref 567), and bi(trishomobarrelenyl) **880** exists in two diastereomeric forms, *meso*- and *d,l*-**880** (Scheme 150).

Scheme 150

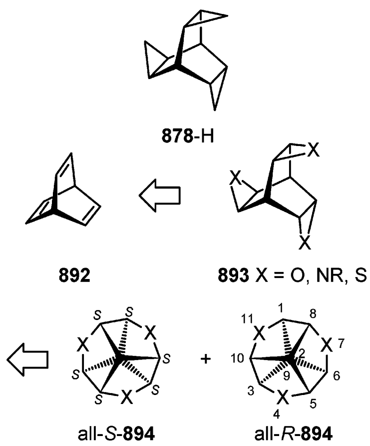


A 1:1 mixture of *meso*- and *d,l*-**880** was obtained in 69% yield upon photolysis of the azo compounds *meso*-**891**/*d,l*-**891** (1:1) in a 4:1 mixture of *tert*-butyl alcohol and *tert*-butyl methyl ether. The azo compounds *meso*-**891**/*d,l*-**891** were prepared from the bridgehead amine *d,l*-**890**, obtained by aminolysis of the corresponding chloride,[578] via the sulfonylbis(trishomobarrelenyl)amide. The *meso* diastereomer, *meso*-**880**, crystallized from a pentane solution of the *meso*-**880**/*d,l*-**880** mixture, and it was fully characterized by an X-ray crystal structure analysis. The enantiomers of *d,l*-**880** could be separated by high-pressure liquid chromatography on a chiral column and disclosed specific rotations $[\alpha]_D^{26} = 266$ ($CHCl_3$, $c = 2.96$ mg/mL).[578]

Heteroanalogues of trishomobarrelenes possess an additional interesting feature: trioxatrishomobarrelene **893** (X = O), the trisepoxide of barrelene **892**,[579] is an achiral molecule just like the hydrocarbon **878**-H (Scheme 151), but the rearrangement product of **893**, [D_3]-trioxatrishomocubane[580] **894** (X = O), is chiral. However, 4-oxa-[581] and 4,7,-11-trioxatrishomocubanes[579] had previously been synthesized in racemic form only and in low or at best moderate yields, respectively.

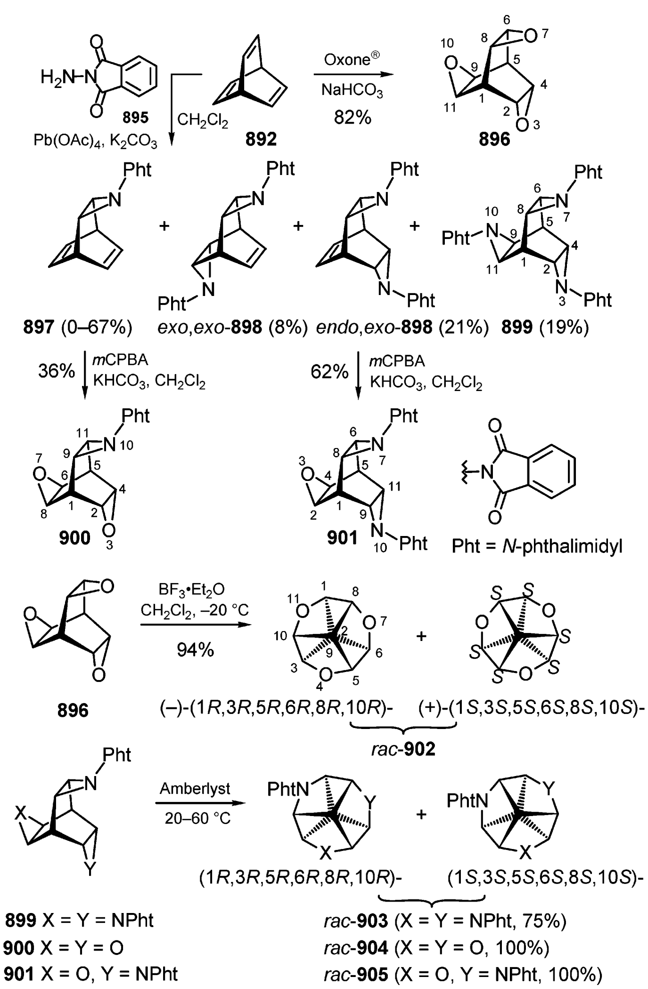
A recent revisit to this area[582] showed that epoxidation of barrelene (**892**) with a neutralized solution of Oxone gave the trisepoxide **896** in 82% isolated yield, while aziridination of **892** with phthalimidonitrene generated in situ by lead tetraacetate oxidation of *N*-aminophthalimide (**895**) gave a mixture of mono- (**897**), bis- (**898**) and trisaziridine (**899**) in different proportions depending on the number of repeti-

Scheme 151



tions of this aziridination and the excesses of reagents used (Scheme 152).

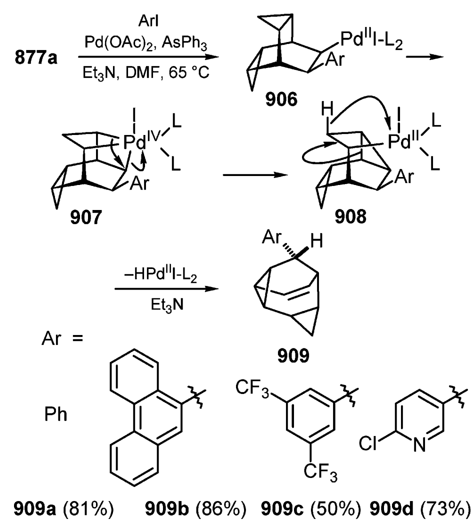
Scheme 152



Epoxidation of **897** and *endo*,*exo*-**898** with buffered *m*-chloroperbenzoic acid furnished the azadioxatrishomobarrelene **900** and diazaoxatrishomobarrelene **901** in 36% and 62% yield, respectively. Upon treatment with $BF_3{\cdot}Et_2O$ at −20 °C (for **896**) or with the strongly acidic ion-exchange resin Amberlyst 15 at ambient or elevated temperatures (for **899**−**901**), these triheterotrishomobarrelenes rearrange to give the 4,7,11-triheterotrishomocubanes, propeller-shaped highly symmetrical chiral molecules *rac*-**902**−**905** derived from barrelene, in 75−100% yields. The enantiomeric pairs of trioxa- (**902**) and triazatrishomocubane (**903**) were separated by preparative HPLC on chiral columns. Compound **902** exhibited specific rotations of $[\alpha]_D^{25} = +196$ and $[\alpha]_D^{25} = -173$, which slightly exceed the specific rotation of the carbocyclic [D_3]-trishomocubane ($[\alpha]_D^{25} = 155-165$ in different solvents, as reported by several research groups[567,583]). The triaza analogue **903** had $[\alpha]_D^{25} = +30$ and $[\alpha]_D^{25} = -28$. The geometry of *rac*-**903** and the absolute configurations of (−)-**902** and (+)-**903** were determined by X-ray crystallography. According to these, (−)-**902** and (+)-**903** possess the same (1*R*,3*R*,5*R*,6*R*,8*R*,10*R*)-configuration.

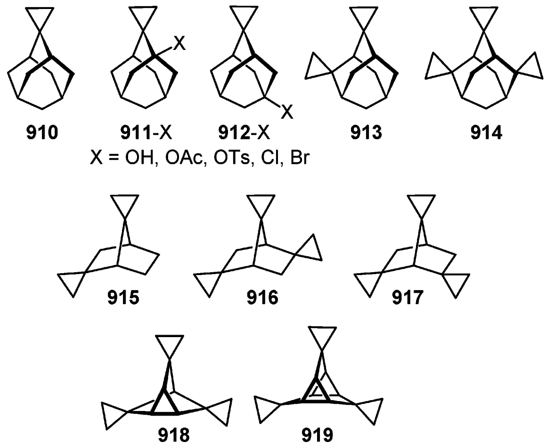
The recently published π,σ-domino-Heck arylations,[584] which proceed cleanly with the *endo*,*exo*- (**877a**) but not with the *exo*,*exo*-bishomobarrelene (**877b**), convincingly demonstrate how important the relative configuration of such strained oligocyclic molecules with three-membered rings can be for their reactivity (Scheme 153).[585] Thus, treatment of **877a** with aryl iodides under the optimized conditions for hydroarylations of bicyclic alkenes [$Pd(OAc)_2$, $AsPh_3$, NEt_3, HCO_2H, DMF, 65 °C][585] surprisingly led to the formation of previously unknown 9-arylhomobarbaralanes **909** (barbaralane[570,572b] ≡ tricyclo[3.3.1.0^{2,8}]nona-3,6-diene) in 50−86% yield; the straightforward product of a hydroarylation across the double bond in **877a** was not even formed in traces. This new carbopalladation of a conformationally fixed allylcyclopropane moiety with subsequent rearrangement of the resulting (cyclopropylethyl)palladium subunit in **906** into a new one in **908** via the palladium(IV) intermediate **907** obviously cannot take place on the diastereomeric **877b**, as the double bond in the latter is shielded on both sides.

Scheme 153



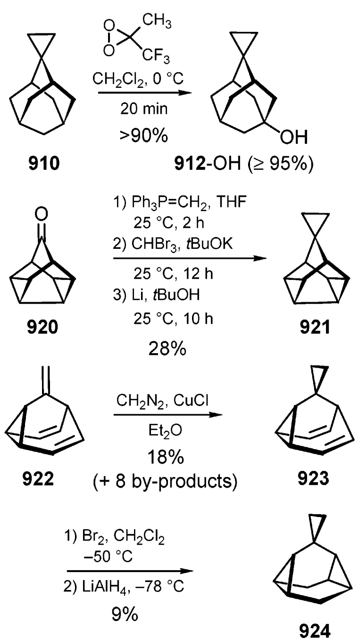
4.3. Cages with Spiroannelated Three-Membered Rings

Surprisingly, in contrast to cage molecules with 1,2-annelated cyclopropane rings, the knowledge on cage compounds with spiroannelated three-membered rings is rather limited. The molecules that were studied in most detail are spiro(cyclopropane-1,2′-adamantane) (**910**)[586] and its functional 1′- and 4′-derivatives **911**[587,588] and **912**.[588,589a] The former[586] and **911**-OH[587−589a] were prepared by Simmons−Smith cyclopropanation of the corresponding 2-methylene-



adamantanes. Most conveniently **912**-OH can be prepared by direct regioselective functionalization of **910** applying methyl(trifluoromethyl)dioxirane (Scheme 154).[589b] In this peculiar case, both α-bridgehead tertiary C−H's become deactivated by the proximal cyclopropyl moiety positioned in the unfavorable "eclipsed" (perpendicular) orientation.

Scheme 154



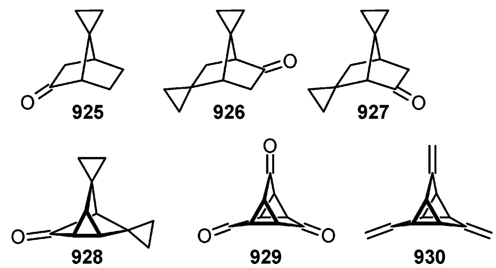
Bis- **913** and trisspirocyclopropanated adamantanes **914** have not yet been prepared, but bis- **915** and trisspirocyclopropanated norbornanes **916** and **917**, nortricyclane **918**, and triasterane **919** are known compounds.[590]

The influence of the spirocyclopropane moiety upon the solvolysis rates is the most remarkable feature of compounds **911**-X (X = OTs, Cl, Br). Since the cyclopropane ring in **911**-X is conformationally locked in such a way that its Walsh bonding orbitals are perpendicular relative to the bonding orbital of the leaving groups and the developing "empty" orbitals, the solvolyses of **911**-X are retarded by a factor of 10^3 compared with the corresponding unsubstituted adamantyl bridgehead derivatives. This is due to the electron-withdrawing inductive effect of the sp^2-like carbon atoms in a cyclopropane ring.[588] Spiro(cyclopropane-1,2′-adamantane) (**910**) was used as a model compound in the study of remote hyperconjugation effects.[591]

The 9-spirocyclopropanepentacyclo[4.3.0.0^{2,4}.0^{3,8}.0.^{5,7}]-nonane (**921**) was prepared from homocuneone **920** by Wittig methylenation followed by dibromocyclopropanation and reductive debromination in 28% overall yield (Scheme 154).[592]

The preparation of triasterane-3-spirocyclopropane **924** from 9-methylenebarbaralane **922** was less efficient, because two low-yielding steps led to a 1.6% overall yield only.[593] Both hydrocarbons **921** and **924** were used as model compounds in the investigation of intricate electronic effects by He(I)-photoelectron spectroscopy. Thus, the lower first ionization energy of **921** in comparison with that of the model 7-spirocyclopropanenorbornane (9.6 eV) was attributed to a through-space interaction.[592]

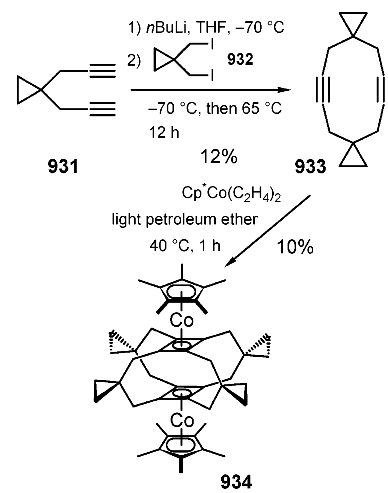
The spirocyclopropanated norbornanes **915**−**917**, nortricyclane **918**, and triasterane **919** were all prepared from the corresponding ketones **925**−**927** and triasteranetrione **929**,



respectively, by Wittig methylenation and subsequent cyclopropanation.[590a] The crystal structures of the triasterane derivatives **929**, **930**, and **919** were determined by X-ray diffraction.[590b] All of these hydrocarbons **915**−**919** were used to study through-space and through-bond electronic interactions by He(I)-PE spectroscopy.[590a]

The reaction of 1,1-bis(iodomethyl)cyclopropane (**932**) with dilithio-1,1-bispropargylcyclopropane afforded the bis-spirocyclopropanated cyclodecadiyne **933** in 12% yield (Scheme 155).[594]

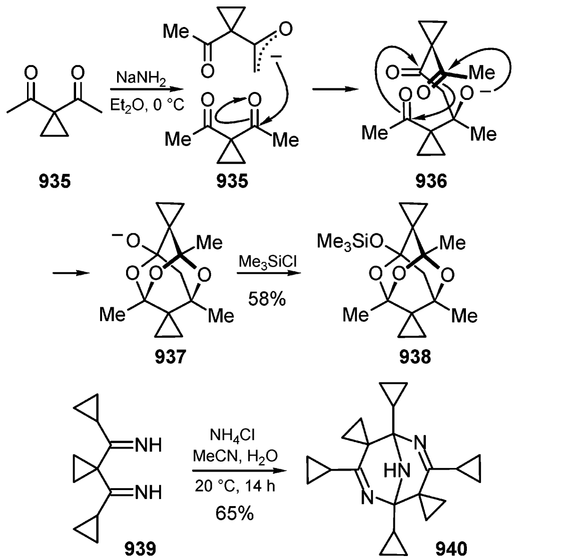
Scheme 155



In the crystal, **933** adopts a chair conformation like a cyclohexane, but expanded with two ethyne moieties with a distance of 3.003 Å between the latter. With Cp*Co(C_2H_4)$_2$, two molecules of **933** undergo cocyclization to form tetrakisspirocyclopropanated cyclobutadiene-superphane **934** stabilized as a bis(pentamethylcyclopentadienyl)cobalt complex with a distance of 2.900 Å between the complexed cyclobutadiene moieties (Scheme 155).[594]

A couple of interesting heteroanalogues of cage molecules with spiroannelated three-membered rings has also been reported. Thus, treatment of 1,1-diacetylcyclopropane (**935**)[595] with sodium amide leads to the formation of the unique trioxaadamantane with two spiroannelated cyclopropanes, 1′-trimethylsilyloxy-3′,5′,7′-trimethyldispiro[cyclopropane-1,9′-(2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decane)-10′,1′′-cyclopropane] (**938**),[596a] the structure of which was confirmed by X-ray diffraction[596b] (Scheme 156).

Scheme 156



Presumably, the initially generated enolate of **935** attacks the carbonyl group of a second molecule of **935** to form the intermediate **936**. Two consecutive intramolecular aldol reactions lead to the cage hemiacetal oxyanion **937**, which is trapped by trimethylsilyl chloride to yield **938**.

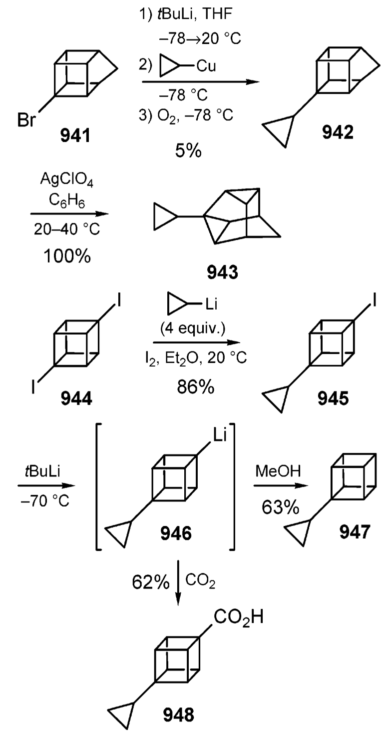
The second example, 1,3,5,7-tetracyclopropyl-2,6,9-triazadispiro(bicyclo[3.3.1]nona-2,6-diene-4,1′:8,1′′-dicyclopropane) (**940**) concerns a hybrid structure of the examples discussed in this and those in the next section. The bisspirocyclopropanated triazabicyclo[3.3.1]nonadiene **940** was obtained in 65% yield by self-condensation of the diimine **939** under the action of ammonium chloride (Scheme 156).[597] Magnesium chloride and trifluoroacetic acid also initiate the formation of **940**, but only in 18% and 15% yield, respectively. The structure of **940** was also confirmed by X-ray crystallography.

4.4. Cages with Three-Membered Ring Substituents

Cage molecules with three-membered ring substituents can be prepared along principally different routes. It is obvious that cyclopropyl moieties can be attached to a preexisting oligocyclic skeleton by substitution or by transformation of other functional substituents. Alternatively, multiple cyclization of an oligocyclopropyl-substituted subunit can lead to a more complex oligocyclopropyl-substituted framework.

According to the first approach, cyclopropylhomocubane **942** was prepared by air oxidation of the mixed cuprate in situ generated from homocubyl bromide **941** and cyclopropylcopper; however, the yield after purification by preparative gas chromatography was only 5% (Scheme 157).[598] Upon treatment with silver perchlorate, cyclopropylhomocubane **942** smoothly and quantitatively rearranged to give cyclopropylnorsnoutane **943**[598] (Scheme 157).

Scheme 157

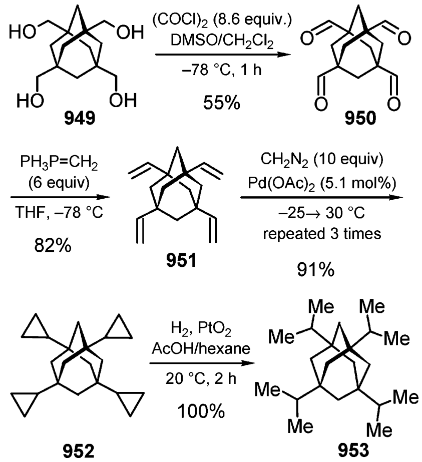


On the other hand, treatment of 1,4-diiodocubane (**944**) with 4 equiv of cyclopropyllithium in the presence of iodine gave 4-cyclopropylcubyl iodide (**945**) in much better yield (86%) (Scheme 157).[599] Lithiation of **945** by treatment with *tert*-BuLi furnished the intermediate lithiocyclopropylcubane **946**. Protonation of the latter afforded cyclopropylcubane **947**, a stable material under ordinary conditions, in 63% yield after purification by preparative gas chromatography,[599] while reaction of **946** with carbon dioxide gave the corresponding acid **948** in essentially the same yield (62%) (Scheme 157).[600] Both transformations of **944** to **947** and to **948** could be performed in single-pot operations. The acid **948** was used for the preparation of [(4-cyclopropylcubyl)methyl]lamine, which was shown to be a time-dependent, irreversible inhibitor of monoamine oxidase B.[600]

It is obvious that the introduction of multiple cyclopropyl substituents by such methods will be difficult or at best proceed with very low yields. It ought to be more efficient to transform appropriate functional substituents preexisting on the skeleton into cyclopropyl moieties. Thus, 1,3,5,7-tetracyclopropyladamantane (**952**) was obtained by 4-fold cyclopropanation of 1,3,5,7-tetraethenyladamantane (**951**) with diazomethane catalyzed by palladium(II) acetate (91% yield) (Scheme 158).[601] The tetraene **951** was prepared in two steps, Swern oxidation and Wittig olefination, from the known 1,3,5,7-tetrakis(hydroxymethyl)adamantane (**949**) in 45% overall yield. Hydrogenolysis of **952** over a platinum catalyst furnished 1,3,5,7-tetraisopropyladamantane (**953**) in quantitative yield.

An X-ray crystal structure analysis of the tetravinyl derivative **951** revealed an approximately C_2-symmetric conformation in the solid state at 150 K.[601] However, no well-defined orientation was detected for the cyclopropyl groups in **952**; in fact, the molecules were severely disordered even

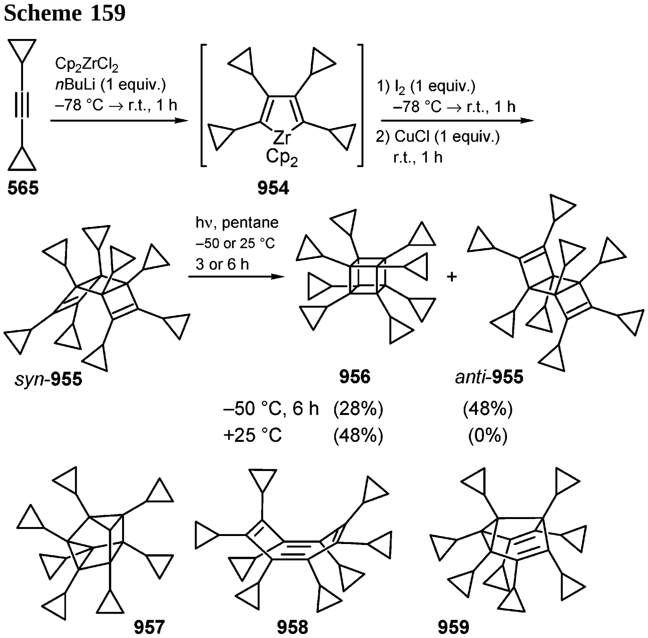
Scheme 158



at 30(1) K, and attempts to detect restricted rotation by NMR spectroscopy at very low temperature[602] also were unsuccessful. In contrast to this, X-ray crystal structure analysis of the tetraisopropyl derivative **953** revealed an S_4-symmetric conformation for this hydrocarbon at 203 K.[601]

A single yet outstanding example of the second approach to an oligocyclopropyl-substituted cage molecule has been realized very recently.[603] *syn*-1,2,3,4,5,6,7,8-Octacyclopropyltricyclo[4.2.0.0^{2,5}]octa-3,7-diene (*syn*-**955**) was prepared from dicyclopropylacetylene in up to 68% yield adopting a well-established protocol for the cyclodimerization of internal alkynes. Irradiation of *syn*-**955** in pentane solution at +25 °C gave octacyclopropylcubane (**956**) in 48% yield (Scheme 159).[603] The structure of **956** was confirmed by X-ray crystal structure analysis. The high efficiency with which **956** is formed by a photochemically initiated intramolecular [2 + 2] cycloaddition is quite remarkable. Higher temperatures apparently favor the formation of **956**, because irradiation of *syn*-**955** at −50 °C predominantly gave *anti*-**955** along with **956**. Octamethyl- and octaethylcubane had been obtained previously by irradiation of the corresponding *syn*-tricyclooctadienes, yet in only 1% and 2% yield, respectively. In the case of *syn*-**955**, not even a trace of octacyclopropylcuneane (octacyclopropylpentacyclo[4.2.0.0^{2,4}.0^{3,8}.0^{5,7}]octane, **957**) was isolated after the irradiation, although cuneanes are normally the main products in such transformations.[604,605] It is also remarkable that in this particular case the isomerization of *syn*-**955** to *anti*-**955**[605] appears to be irreversible, because no traces of either **956** or *syn*-**955** were found after irradiation of *anti*-**955** under the same conditions.[603]

Scheme 159



Octacyclopropylcubane **956** is a remarkably stable hydrocarbon. Upon heating at 250 °C, **956** rearranges with a half-life of approximately 3 h to yield octacyclopropylcyclooctatetraene (**958**), which further decomposes at this temperature. Apparently, the eight cyclopropyl groups around the cubane cage kinetically stabilize the molecule. This cubane **956**, in contrast to the parent compound, is also stable toward $[Rh(COD)Cl]_2$ which causes cubane itself to isomerize to *syn*-tricyclooctadiene. Treatment of **956** with silver perchlorate and silver tetrafluoroborate, which catalyze the isomerization of other cubanes to cuneanes or semibullvalenes (cf. refs 606 and 607), did not lead to **957** or **959** but left **956** unchanged. Upon heating at 250 °C, both *syn*- and *anti*-**955** rearranged to octacyclopropylcyclooctatetraene (**958**), the structure of which was proved by X-ray crystallography.

5. Conclusion

Although the first molecules with more than one three-membered carbocycle are more than 50 years old, it is modern synthetic methodology as well as advanced analytical tools that have brought the design of unusual and fascinating molecular assemblies with multiple cyclopropane rings to full blossom. While a vast array of different architectures have already been realized, the current overview definitely will not constitute the end of this development. In view of the unique physical and chemical properties of the cyclopropane moieties, this design tool will always be used to create new assemblies with interesting features. As the authors of this review, at least we are convinced that the "molecular world" would be poorer without three-membered rings.

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