Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis†

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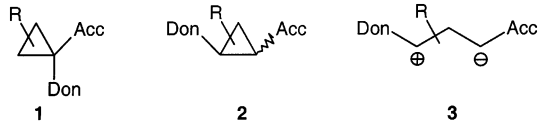
† Dedicated to Professor Klaus Hafner on the occasion of his 75th birthday.

I. Introduction and Scope of This Review

For quite some time cyclopropane derivatives have been more than laboratory curiosities, but they are frequently employed as versatile building blocks in organic syntheses.[1] Apt activation of the strained three-membered ring is mandatory for this purpose, and generally, electron-donating or -accepting substituents are involved in their reactions to make polar processes more favorable. Ring cleavage or ring enlargement may then occur under relatively mild conditions. Only (formal) pericyclic reactions such as vinylcyclopropane−cyclopentene[2] or divinylcyclopropane−cycloheptadiene[3] rearrangements in principle proceed without additional activating substituents. Nevertheless, synthetically useful versions of these reactions most frequently involve precursor cyclopropanes containing functional groups that often facilitate the rearrangement and allow further transformations of the products obtained.

Cyclopropane derivatives substituted by donor and acceptor groups are particularly suitable for synthetic applications, since electronic effects of these substituents guarantee activation of the cyclopropanes and a high versatility of the products after ring cleavage. In this review *geminally* donor−acceptor-substituted cyclopropanes **1** (Scheme 1) will not be treated, since

Scheme 1



substituents do not act in a synergic manner, and therefore, only few examples for their synthetic use are known. This account will only deal with *vicinally* donor−acceptor-substituted cyclopropanes **2** that serve as 1,3-dipolar synthon **3** in many synthetically valuable transformations.[4] Since the two charges of synthon **3** are in 1,3-relationship, many reactions employing **2** may be regarded as processes involving

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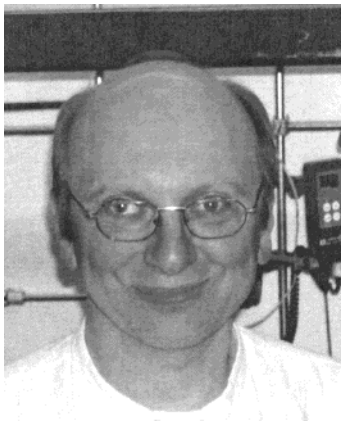
Hans-Ulrich Reissig was born in Helmbrechts, Germany, in 1949. He studied chemistry at the Ludwig-Maximilians-Universität München, where he received the diploma in 1975 and the doctoral degree in 1978, working under the direction of Rolf Huisgen on 1,3-dipolar cycloadditions. For postdoctoral studies he spent one year as Nato Fellow with Edward Piers at the University of British Columbia, Vancouver, being involved for the first time in cyclopropane chemistry and cuprate reactions. He began independent research on donor–acceptor-substituted cyclopropanes as Liebig Fellow at the Universität Würzburg (mentor Siegfried Hünig) and finished his habilitation in 1984. He was appointed Privatdozent and granted with Heisenberg and Winnacker Fellowships. In 1986, he joined the Technische Hochschule Darmstadt as associate professor, and from 1993 to 1999 he held a chair of organic chemistry at the Technische Universität Dresden. He has been full professor at the Freie Universität Berlin since 1999 and is member of the editorial board of *European Journal of Organic Chemistry*. The scientific achievements have been published in over 200 original publications. He is interested in many areas of synthetic organic chemistry, including cyclopropane chemistry and heterocyclic chemistry. The main efforts of his current research are the stereoselective construction of carbocycles and heterocycles with biological activity, including natural products.

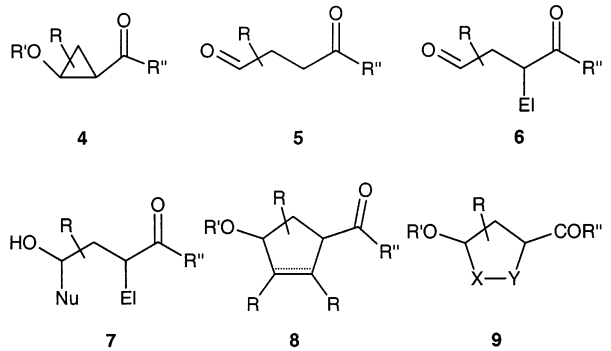


Reinhold Zimmer was born in Wiesbaden, Germany, in 1959. He studied chemistry at the Technische Hochschule Darmstadt and graduated in 1988. From 1988 to 1990 he carried out his Ph.D. research under the guidance of Hans-Ulrich Reissig at the same university, being involved in hetero-Diels–Alder reactions and the chemistry of 1,2-oxazines. From 1992 to 1994 he worked as a Karl-Landsteiner Fellow with Maximilian A. Grassberger at the Sandoz Research Institute in Vienna, Austria, on modifications of FK 506 and ascomycins. From 1994 to 2000 he worked as a research associate with Hans-Ulrich Reissig at the Technische Universität Dresden. In 1998, he spent two months as a short-time lecturer (DAAD exchange program) in the Department of Chemistry at the Indian Institute of Technology in Kanpur, India. In 2000, he moved to the Freie Universität Berlin, continuing his collaboration with Hans-Ulrich Reissig.

a formal *umpolung of reactivity* and, therefore, often provide products not easily available by alternative methods.[5]

Aminocyclopropanes—including aminocyclopropanes with acceptor substituents—will be treated in an individual review of this issue[6] and our report therefore emphasizes oxygen functions as donor substituents. The acceptor groups applied in the majority of examples are carbonyl groups, and therefore, most of the donor−acceptor cyclopropanes (abbreviated as D−A cyclopropanes) can be described by general structure **4** (Scheme 2). Their simplest and

Scheme 2



most frequently applied ring cleavage affords products of type **5**, which are very useful intermediates due to the 1,4-distance of the two carbonyl groups. Ring-opening reactions under incorporation of apt electrophiles deliver compounds such as **6**, whereas transformations including nucleophiles and electrophiles furnish compounds **7**. (Formal) [3+2] cycloadditions of **4** with multiple bond systems can afford five-membered carbocycles and heterocycles of general structure **8** or **9**.

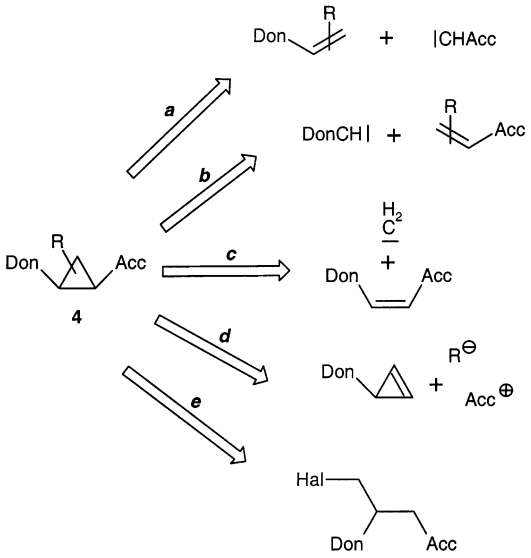
Acceptor substituents other than carbonyl groups, such as cyano, oxazolinyl, sulfonyl, or phosphonyl, are occasionally found in D−A cyclopropanes, and synthetic applications are relatively rare. These compounds will be discussed either together with closely analogous carbonyl compounds or separately in section IV. With respect to other donor substituents such as phenylthio or (trialkyl/aryl)silylmethyl, a few examples will also be provided in section IV.

Since a rather comprehensive review about D−A cyclopropanes appeared in 1988, we now concentrate on new developments and applications of this very versatile class of small-ring compounds.[7] However, fundamental processes will be repeated here when they are required for understanding new reactions.

II. Synthesis of D–A Cyclopropanes

Cyclopropanes are most frequently prepared by additions of carbenes or their equivalents to alkenes.[8] This is also true for syntheses of D−A cyclopropanes **2**, which are very often accessible by addition of an acceptor-substituted carbene—usually generated from a diazocarbonyl compound—to electron-rich olefins (pathway a). The complementary approach (pathway b) combines a donor-substituted carbene (equivalent) with an electron-deficient alkene, and the methylenation of donor−acceptor olefins is also conceivable (pathway c) (Scheme 3). These rather straightforward (formal) [2 + 1] cycloadditions are supplemented by

Scheme 3



different methods such as additions to cyclopropenes (pathway d) and/or intramolecular S_N reactions of suitably substituted substrates (pathway e).

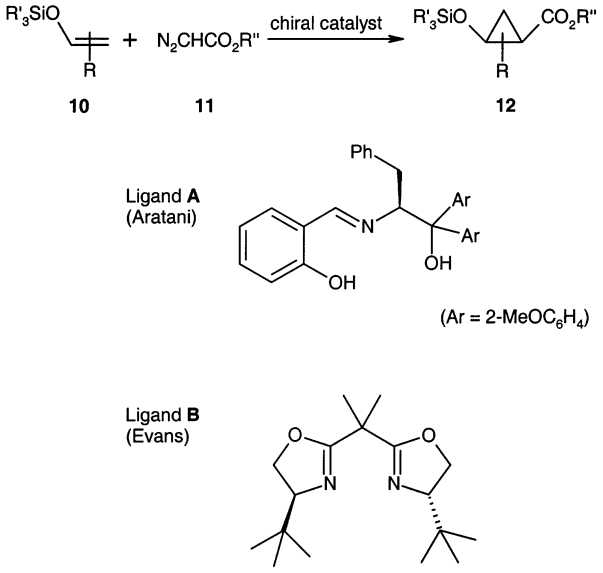
All these reactions have been well-known for many years and only new, synthetically useful developments such as efficient intramolecular and highly enantioselective versions as well as the use of Fischer carbene complexes will be described in this account. The most convenient source of carbene equivalents are diazoalkanes, which decompose in the presence of metal catalysts and furnish reactive carbene complexes (carbenoids) able to undergo smooth additions to olefins.[9] For synthesis of D−A cyclopropanes, acceptor-substituted diazoalkanes (mostly diazocarbonyl compounds) are very suitable starting materials, and their additions to electron-rich olefins are generally efficient. Although not relevant for most synthetic applications of D−A cyclopropanes which involve ring cleavage, cis/trans-selectivity of cyclopropane formation is frequently poor. Few new methods are dealing with this problem and provide reasonable solutions.

A. Enantioselective Reactions of Diazoalkanes Using Chiral Catalysts

Whereas asymmetric cyclopropanation of simple olefins such as styrene has been achieved with high efficiency and selectivity,[10] the corresponding enantioselective syntheses of D−A cyclopropanes are still a challenge. Systematic studies were performed with structurally typical silyl enol ethers **10** and diazoacetates **11** in the presence of various metal catalysts containing chiral ligands such as **A** (Aratani's ligand) or **B** (Evans' ligand) (Scheme 4).[11−17]

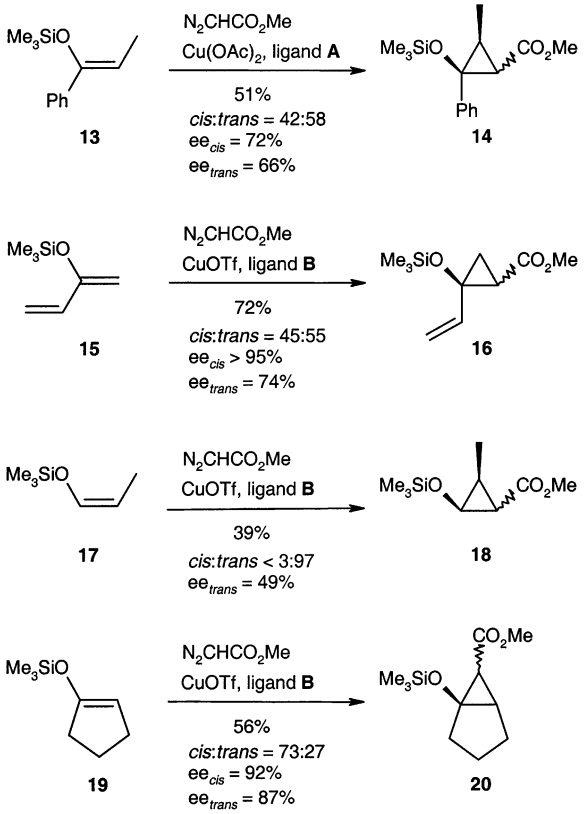
Although very high enantiomeric excesses for **12** could be obtained in singular examples by application of the appropriate catalyst, it must be noted that a satisfactory general solution cannot be presented so far. The size of the group R″ of the diazo component seems to have only minor influence on the enantioselectivity of the cyclopropanation but a considerable

Scheme 4



effect on the cis/trans-selectivity. Di- and trisubstituted silyl enol ethers containing a phenyl group were most efficiently converted into cyclopropanes in the presence of Aratani's Schiff base **A**, whereas the otherwise extremely successful Evans' bisoxazoline ligand **B**[18] gave good to excellent enantioselectivities only for 1,1-disubstituted and cyclic enol ethers. Scheme 5 presents typical examples where good

Scheme 5



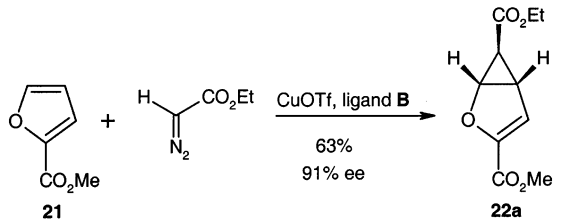
enantioselectivities were recorded. The objective of obtaining high diastereoselectivity (cis/trans-selectivity) *and* enantioselectivity could so far not be attained. With ligand **B**, synthetically most

valuable D−A cyclopropanes such as **18** were formed with high trans-selectivity, but the ee was only 49%. On the other hand, Pfaltz obtained both diastereomers of bicyclic product **20** with high ee values, but the diastereoselectivity was only in the range of 3:1.

A study comparing several chiral copper catalysts with various bisoxazoline ligands reported cyclopropanation of vinyl acetate with diazoacetates, which was achieved with moderate cis/trans-selectivity and enantiomeric excesses in the range of 60−88%.[19] Chiral carbene complexes were alternatively generated from sulfonium ylides in the presence of chiral Cu(I) or Rh(II) catalysts. Cyclopropanations of silyl enol ethers proceeded with moderate to low cis/trans-selectivity and modest enantioselectivity. A copper−semicorrin complex induced the highest enantiomeric excess of 64%, which was the same as that obtained with the diazoacetate as precursor.[20]

Reactions of furan derivatives with diazoacetates in the presence of Evans' bisoxazoline copper catalyst and similar complexes provided bicyclic D−A cyclopropanes in good yield, excellent diastereoselectivity, and good to very good enantioselectivity. As an example, methyl furan-2-carboxylate **21** furnished product **22a** in 91% ee, which could be increased up to 99% ee by one recrystallization (Scheme 6).[21] With

Scheme 6

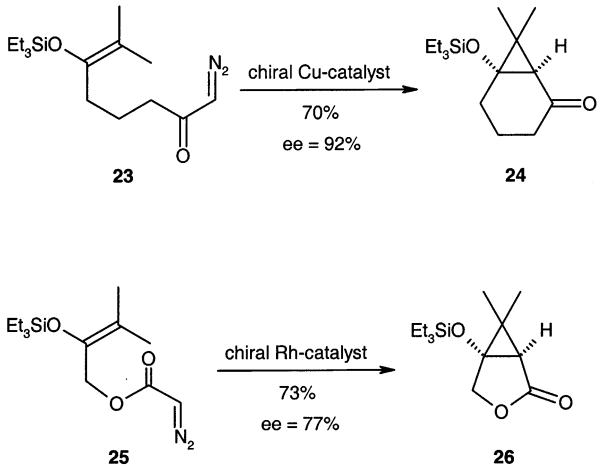


a related aza(bisoxazoline) copper catalyst, a slightly higher ee was recorded; however, the yields with this type of catalyst were inferior. Dihydrofuran derivatives of type **22a** are very valuable starting materials for further synthetic applications (see Schemes 27, 47, and 146).

D−A cyclopropanes have also been prepared by intramolecular cyclopropanations in an enantioselective manner. Due to geometric constraints, formation of only one diastereomer is possible, and therefore, substrate **23** was efficiently converted into bicyclic D−A cyclopropane **24** with 92% ee employing a chiral bisoxazoline copper catalyst (Scheme 7). In contrast, this type of catalysts was not very stereoselective for diazo compound **25** as starting material, but a chiral rhodium complex was more successfully employed in this case and furnished cyclopropane **26** with 77% ee. Both compounds were required for an approach to the phorbol CD-ring skeleton.[22]

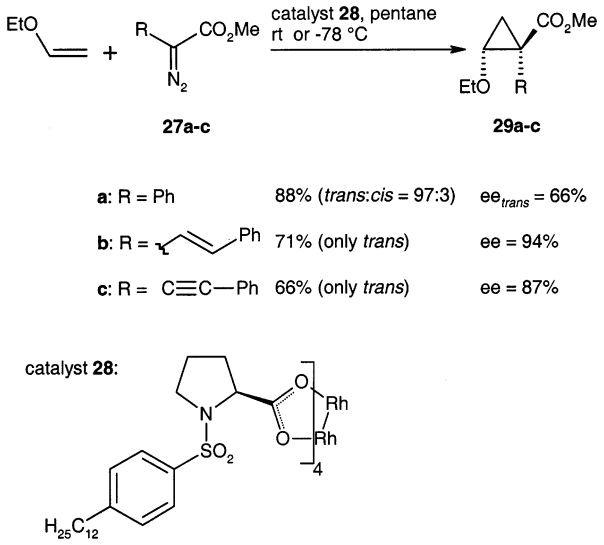
Chiral rhodium catalysts, which have most successfully been employed for cyclopropanations of simple olefins, are generally not very efficient for enantioselective formation of D−A cyclopropanes. However, a series of rhodium(II) prolinate derivatives such as **28** has been shown to act as very good catalysts for enantioselective cyclopropanation of enol

Scheme 7



ethers with diazoacetates **27a−c** bearing unsaturated substituents. Diazophenylacetate **27a** and ethyl vinyl ether furnished D−A cyclopropane **29a** in excellent yield and trans/cis-selectivity; however, the induced ee was only 66% (Scheme 8).[23] Styryl-

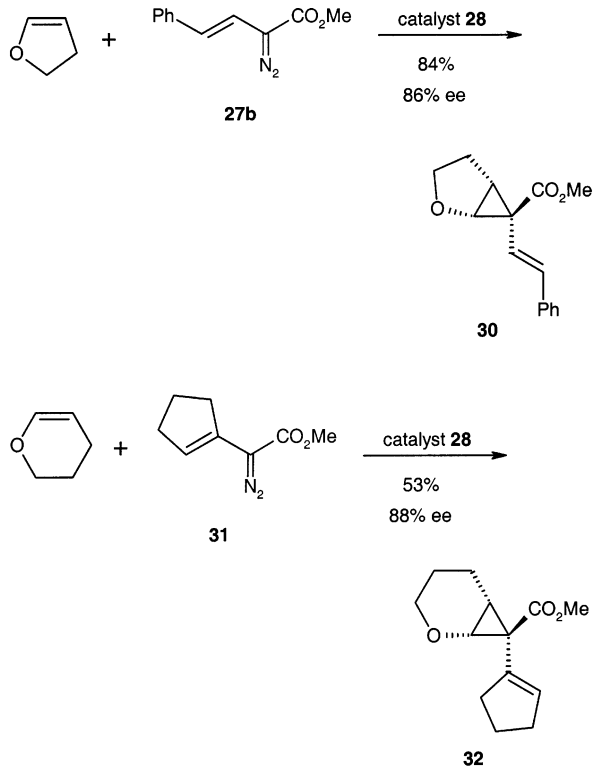
Scheme 8



substituted diazoacetate **27b** and the corresponding alkynyl-substituted diazo compound **27c** afforded D−A cyclopropanes **29b** and **29c** with very good ee of 94 and 87%, respectively.[24] A novel rhodium catalyst containing bridging prolinate ligands was also investigated. It increased the ee of compound **29a** to 79% ee, but decreased that of **29b** to 87%. These observations demonstrate that catalyst tuning is still mainly a matter of trial and error.[25]

Cyclic enol ethers such as 2,3-dihydrofuran and dihydropyran were also suitable substrates for highly enantioselective cyclopropanations with alkenyl-substituted diazoacetates **27b** and **31**. In the presence of catalyst **28**, the diastereoselectivities were excellent and enantiomeric excesses were close to 90% (Scheme 9).[26] Products **30** and **32** were used for Lewis acid-promoted ring enlargements to enantio-enriched cyclopentene derivatives (see Scheme 30).

Scheme 9

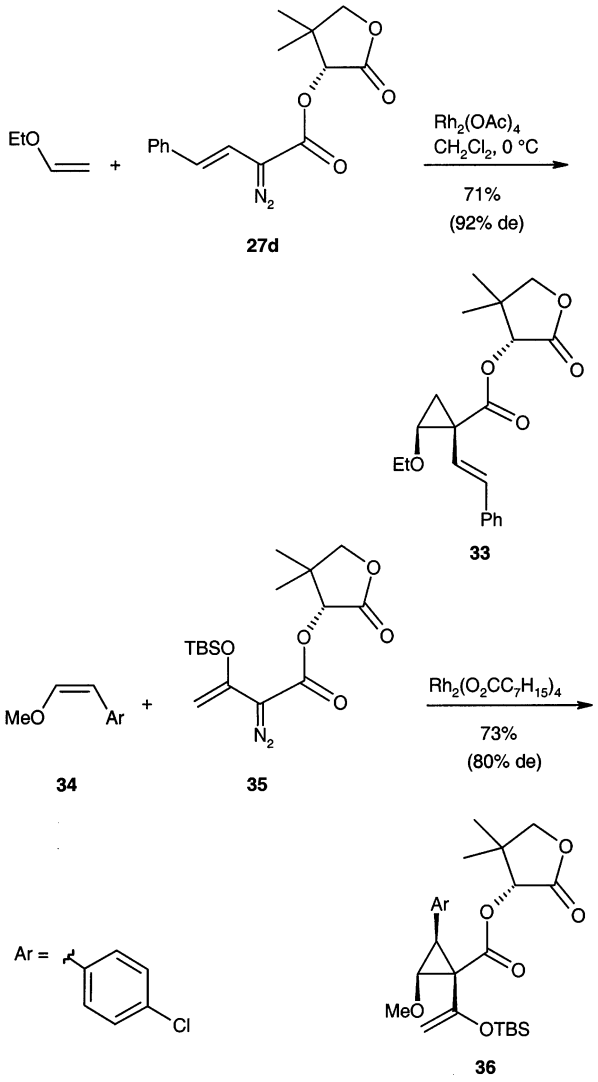


B. Asymmetric Cyclopropanations with Diazo Alkanes Using Chiral Auxiliaries

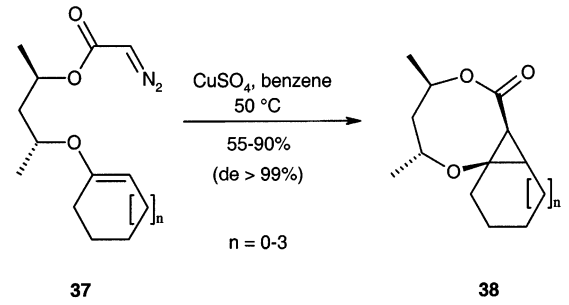
Stereoselective intermolecular cyclopropanations of enol ethers bearing carbohydrate auxiliaries with methyl diazoacetate were only moderately successful.[27] Chiral auxiliaries at the diazoacetate part were more efficient. Rhodium acetate-catalyzed reaction of compound **27d** containing (*R*)-pantolactone as auxiliary with ethyl vinyl ether gave D−A cyclopropane **33** with a diastereomeric excess of 92% (Scheme 10).[28] The related diazoacetate **35** and enol ether **34** furnished vinylcyclopropane **36** with a diastereomeric excess of 80%.[29]

Intramolecular reactions with substrates **37** incorporating (*R*,*R*)-2,4-pentanediol as chiral linker between the enol ether and the diazo part provided the respective diastereomerically pure D−A cyclopropanes **38** (Scheme 11). Some of them were transformed into highly enantio-enriched ring-opened products.[30]

Scheme 10



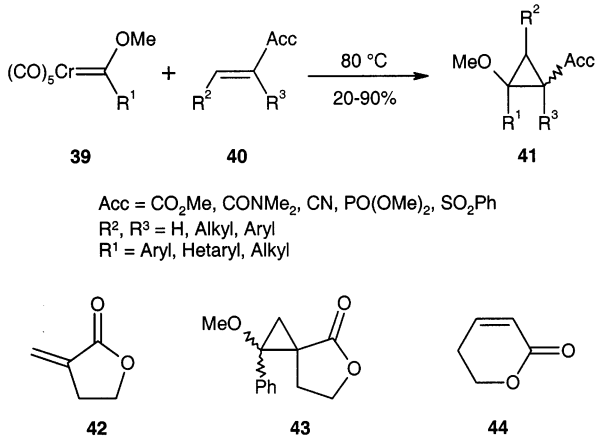
Scheme 11



C. Synthesis of D–A Cyclopropanes by Use of Fischer Carbene Complexes

One of the first reactions performed with Fischer carbene complexes was the transfer of carbene ligands to electron-deficient alkenes leading to formation of D−A cyclopropanes (pathway b, Scheme 3).[31] Given the large synthetic potential of this class of cyclopropanes, the scope and limitations of this transformation were systematically investigated. Chromium carbene complexes **39** were reacted with a variety of acceptor-substituted olefins **40** and provided the corresponding D−A cyclopropanes **41** in moderate to excellent yields (Scheme 12). In several cases acyclic byproducts were isolated, which most likely arise from ring opening of the D−A cyclopropanes **41**.[32,33] Diastereoselectivity, yield, and formation of these side products strongly depend on the substitution pattern, the best results being obtained with aryl-substituted carbene complexes and alkenes just bearing the acceptor group ($R^2 = R^3 = H$). Interestingly, only olefins capable of adopting a cisoid conformation of the C−C double bond and the acceptor group undergo the cyclopropanation reaction. Thus, unsaturated lactone **42** and complex **39** ($R^1 = Ph$) furnished the expected D−A cyclopropane **43** in good yield, whereas lactone **44** did not react at all with this carbene complex.

Scheme 12

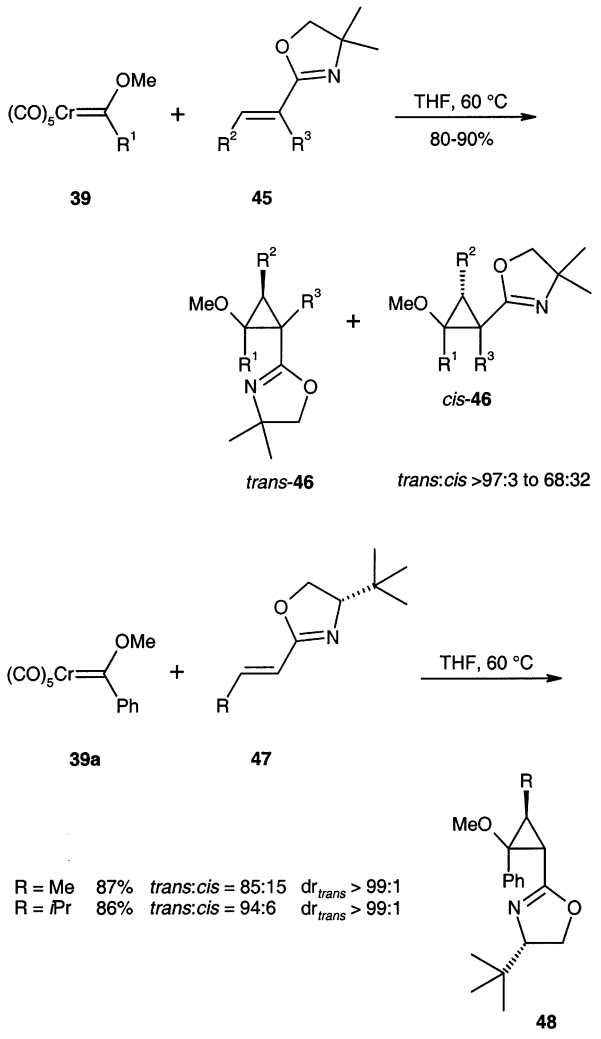


For certain unsaturated nitriles, a remarkable competition between cyclopropanation and CH-insertion reaction has been observed, which depends on the solvent employed.[34] Chromium cyclopropylcarbene complexes and electron-deficient olefins furnished several cyclopropyl-substituted D−A cyclopropanes.[35] Whereas tungsten carbene complexes turned out to be much less reactive and provided only low yields of D−A cyclopropanes, the less stable molybdenum carbene complexes have successfully been applied for syntheses of D−A cyclopropanes, in particular with complexes bearing alkyl carbene ligands.[36] A low-temperature carbene transfer was achieved by irradiation at 0 °C, providing good yields of D−A cyclopropanes similar to those depicted in Scheme 12.[37]

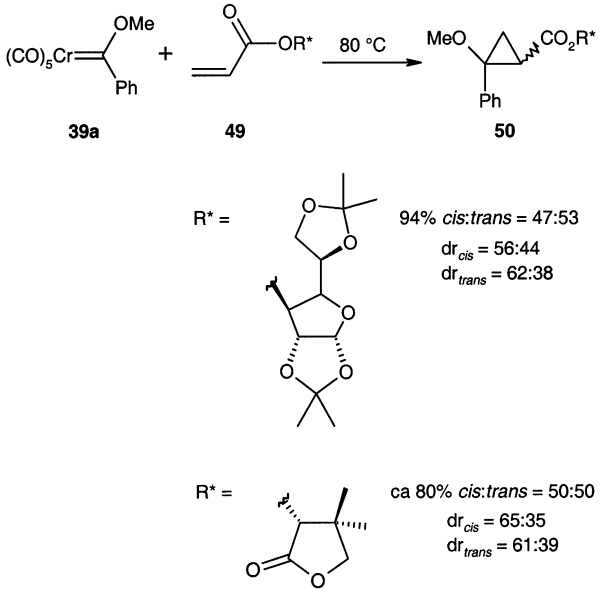
Most interestingly, thermal reactions of chromium carbene complexes **39** with alkenyl-substituted oxazolines **45** as electron-deficient olefin components proceed with good to excellent trans-selectivity (Scheme 13). The corresponding D−A cyclopropanes **46** were isolated in good yield, and the trans:cis ratio ranges from >97:3 to 68:32. This high diastereoselectivity was further exploited by use of chiral alkenyl-substituted oxazolines **47** as precursor olefins. They combine with carbene complex **39a** with excellent diastereofacial selectivity, which is induced by the oxazoline auxiliary. The diastereomeric excess for major trans-isomers of **48** is >99:1.[38]

Reactions of parent chromium carbene complex **39a** with acrylates **49a,b** bearing chiral auxiliaries (diacetone glucose or (*R*)-pantolactone) afforded the corresponding D−A cyclopropanes **50a,b** in good yields but very moderate diastereoselectivities (Scheme 14).[39]

Scheme 13



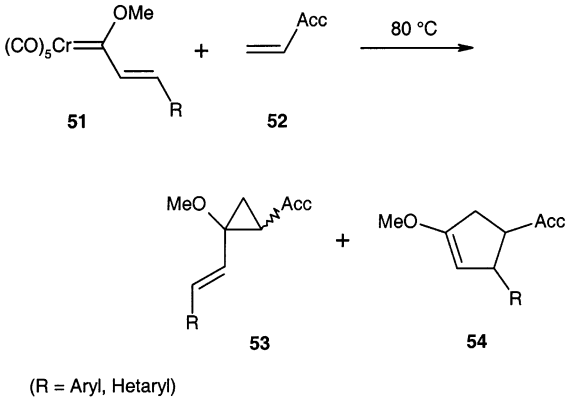
Scheme 14



An enantiopure tricarbonyldiphosphinoxymolybdenum carbene complex bearing a chiral phosphorus ligand was thermally reacted with acrylonitrile and provided the expected D−A cyclopropane in excellent yield. However, the enantiomeric ratio for the major trans-isomer was only in the range of 2:1.[40]

Carbene-transfer reactions of alkenylcarbene complexes **51** to alkenes **52** furnished alkenyl-substituted D−A cyclopropanes **53** and cyclopentene derivatives **54** (Scheme 15). The ratio of the two isomeric products remarkably depends on substituents Acc and R.[41] For carbene complexes **51** with the strongly electron-donating group R = 2-(*N*-methylpyrrolyl), a striking effect of the solvent polarity was detected: while only cyclopropanes **53** were isolated in unpolar solvents such as cyclohexane, use of acetonitrile led

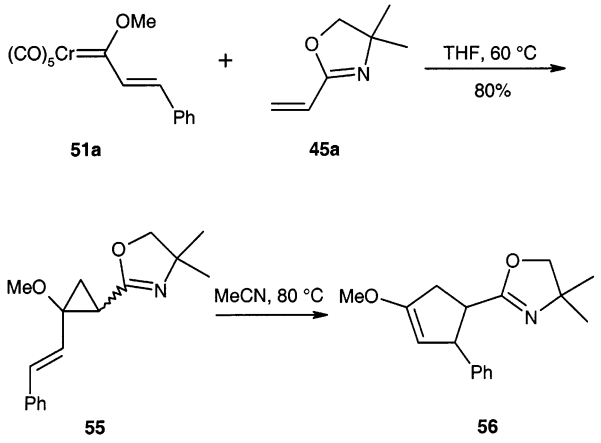
Scheme 15



to exclusive formation of cyclopentene derivatives **54**. Since **53** did not rearrange under the reaction conditions applied, compounds **54** were assumed to be directly generated from the starting materials and not via **53** by vinylcyclopropane–cyclopentene rearrangement (see section III.B).[42]

However, it was demonstrated that closely related alkenyl-substituted oxazolinylcyclopropanes **55** are intermediates during formation of cyclopentene derivatives **56** (Scheme 16). Reaction of carbene com-

Scheme 16

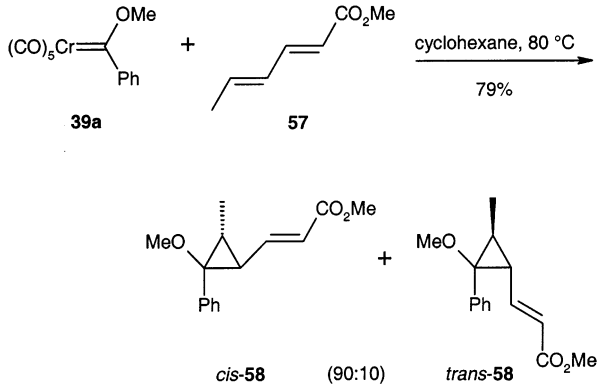


plex **51a** with alkene **45a** in THF at 60 °C provided vinylcyclopropane derivative **55**, and heating of this compound to 80 °C in acetonitrile caused rearrangement to cyclopentene derivative **56**. Rearrangement of separated diastereomers **55** gave cyclopentene **56** with an identical diastereomer ratio, which was interpreted in favor of 1,5-zwitterions as intermediates.[43]

Thermal reactions of Fischer carbene complexes with electron-deficient 1,3-dienes open an alternative route to alkenyl-substituted D–A cyclopropanes. These transformations proceed with surprisingly high regioselectivity strongly favoring the "remote" double bond of the 1,3-diene. As a typical example, reaction of carbene complex **39a** with diene ester **57** provided cyclopropane **58** with good yield and with much higher diastereoselectivity than simple olefins (Scheme 17).[44] A similar behavior was found for cyclic diene esters.[45]

Several of these D–A vinylcyclopropanes underwent rearrangements to functionalized cyclopentene

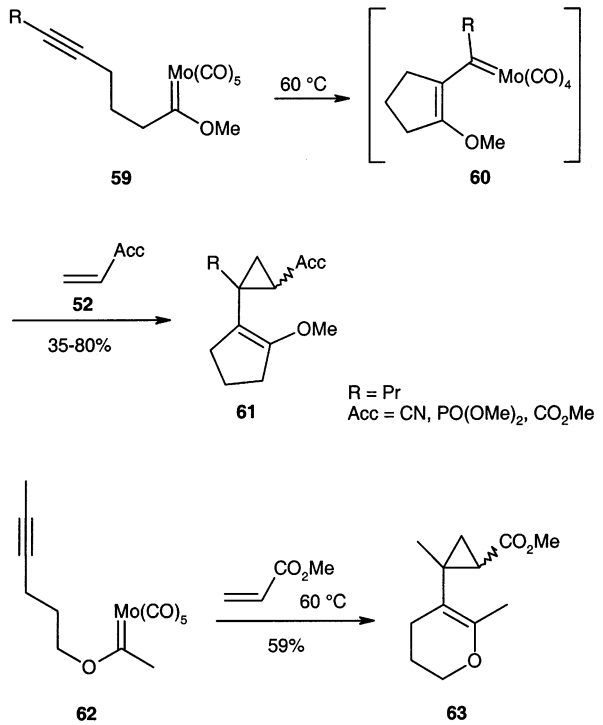
Scheme 17



derivatives at temperatures as low as 150 °C, if dimethyl formamide was used as solvent. Again, 1,5-zwitterionic intermediates seem to be most likely for this process.[46] Thermal reaction of alkenyl-substituted Fischer carbene complexes with 1,3-dienes provided 1,4-cycloheptadiene derivatives (see section III.E.1), since the intermediate divinylcyclopropanes can undergo a subsequent Cope rearrangement. In certain cases these reactions are complicated by an unusual carbene–ligand metathesis, which then leads to preferential formation of cyclopentene derivatives.[47]

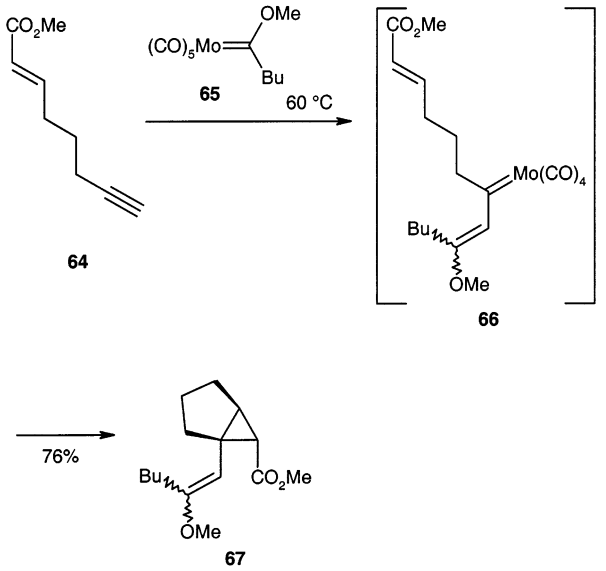
An intriguing approach to D–A cyclopropanes via Fischer carbene complexes was introduced by Harvey, who combined the well-known insertion reactions of these complexes and alkynes with cyclopropanation reactions. As an example, intramolecular reaction of compound **59** first generated alkenyl-substituted carbene complex **60**, which was trapped with electron-deficient olefins **52** to furnish cyclopropanes **61** in moderate to good yield but poor diastereoselectivity (Scheme 18). In a similar fashion,

Scheme 18



the complementary substituted complex **62** provided dihydropyranyl-substituted cyclopropane **63** in good yield.[48] An alternative intramolecular version involves reactions of enynes such as **64** with molybdenum carbene complex **65** (Scheme 19). Insertion of the alkyne moiety into the carbene metal bond furnished a new complex **66**, which underwent an intramolecular cyclopropanation to provide D−A cyclopropane **67**. The scope and limitations of this pathways to D−A cyclopropanes are not known.[49]

Scheme 19

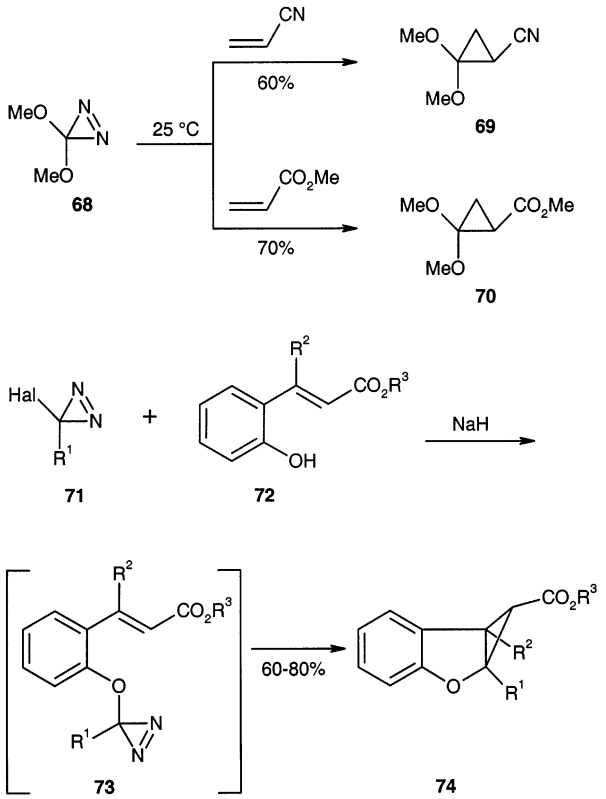


D. Other Methods Leading to D–A Cyclopropanes

Diazirines are constitutional isomers of diazo alkanes and may also be used as carbene source for cyclopropanation reactions. Of particular interest are alkoxy-substituted diazirines, which deliver nucleophilic carbenes capable to react with electron-deficient olefins. Although this approach is of limited synthetic value, a few typical examples are presented in Scheme 20. Whereas thermal reaction of 3-methyl-3-methoxydiazirine or 3-phenyl-3-methoxydiazirine in the presence of alkenes such as acrylonitrile or methyl acrylate provided only very low yields of the corresponding D−A cyclopropanes, the more nucleophilic carbene generated from 3,3-dimethoxydiazirine (**68**) reacted with these olefins in acceptable yields.[50] Thus, reactions of **68** with acrylonitrile or methyl acrylate furnished D−A cyclopropanes **69** and **70**. However, carbene precursor **68** must be generated at low temperature and decomposes at room temperature, which restricts the scale of these reactions and their synthetic value. The olefins must be used in excess to efficiently trap the generated nucleophilic carbene.

An intramolecular version of this [2 + 1] cycloaddition with nucleophilic carbenes was reported by Vasella et al.[51] The required precursor **73** was generated by reaction of 3-halo-3-alkyl(aryl)diazirines **71** with *o*-hydroxycinnamates **72** in the presence of sodium hydride. Intermediate diazirines **73** spontaneously decomposed to afford homobenzofurans **74** in good yields. D−A cyclopropane derivatives of

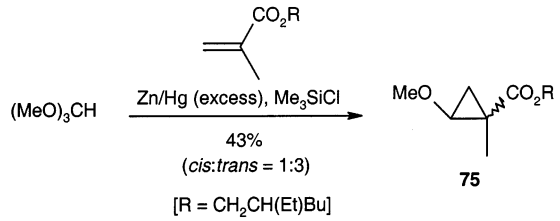
Scheme 20



carbohydrates were also prepared with diazirines as intermediates (see section V.A).

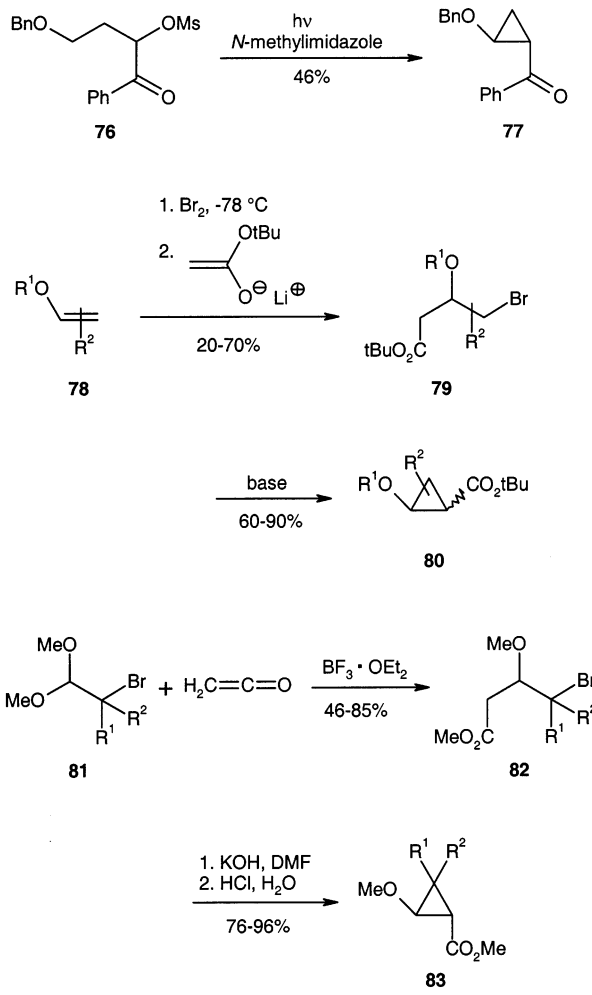
Alkoxycyclopropanes were synthesized by employing an orthoformate as source for a (zinc)carbenoid. Treatment of trimethyl orthoformate with zinc in the presence of trimethylchlorosilane and alkenes provided the expected cyclopropanes. An alkyl methacrylate as olefin furnished the expected D−A cyclopropane **75** in moderate yield and diastereoselectivity (Scheme 21).[52]

Scheme 21



A novel and highly diastereoselective photochemical cyclization leading to cyclopropanes also allows synthesis of D−A cyclopropanes as demonstrated by the conversion of **76** into **77** (Scheme 22).[53] A versatile synthesis of *tert*-butyl 2-alkoxycyclopropanecarboxylates **80** involved bromination of enol ethers **78** at low temperature, followed by reaction with the lithium enolate of *tert*-butyl acetate. Intermediates **79** could be cyclized by base treatment, furnishing the desired D−A cyclopropanes **80** in good yield and trans-selectivity.[54] A similar intramolecular S_N2 reaction of compounds **82** provided cyclopropane derivatives **83** in good yields and mainly as trans-isomers. Here the crucial precursor **82** was prepared

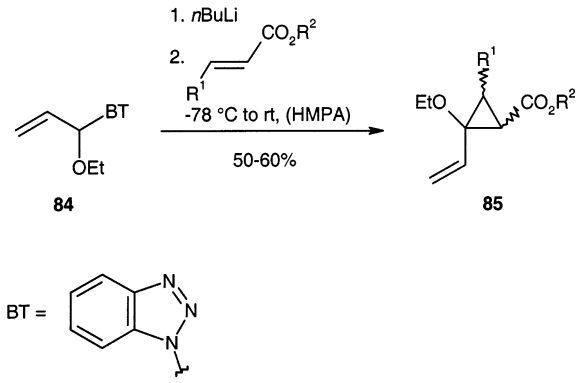
Scheme 22



from easily available α-bromoacetals **81** and ketene in the presence of borontrifluoride etherate.[55]

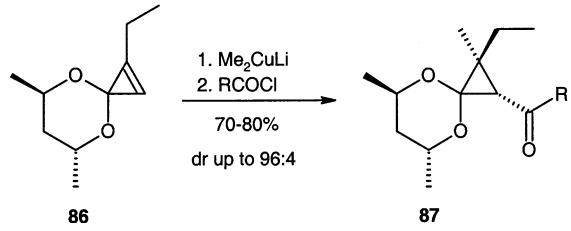
A supplementary cyclization mode was reported by Katritzky et al., who lithiated benzotriazole derivative **84** and trapped the generated allyllithium species with α,β-unsaturated esters. During warm up the intermediate underwent cyclization and furnished vinylcyclopropane derivatives **85** in moderate yield as a 1:1 mixture of cis/trans-isomers (Scheme 23).[56]

Scheme 23



Additions of cuprates to 3,3-dialkoxy-substituted cyclopropenes furnish copper intermediates that may be trapped by electrophiles. This elegant method also led to highly diastereoselective construction of D−A cyclopropanes of type **87**. When chiral cyclopropene derivative **86** was treated with lithium dimethyl cuprate and subsequently quenched with acid chlorides as electrophiles, the addition products **87** were formed in good yield (Scheme 24). The diastereo-

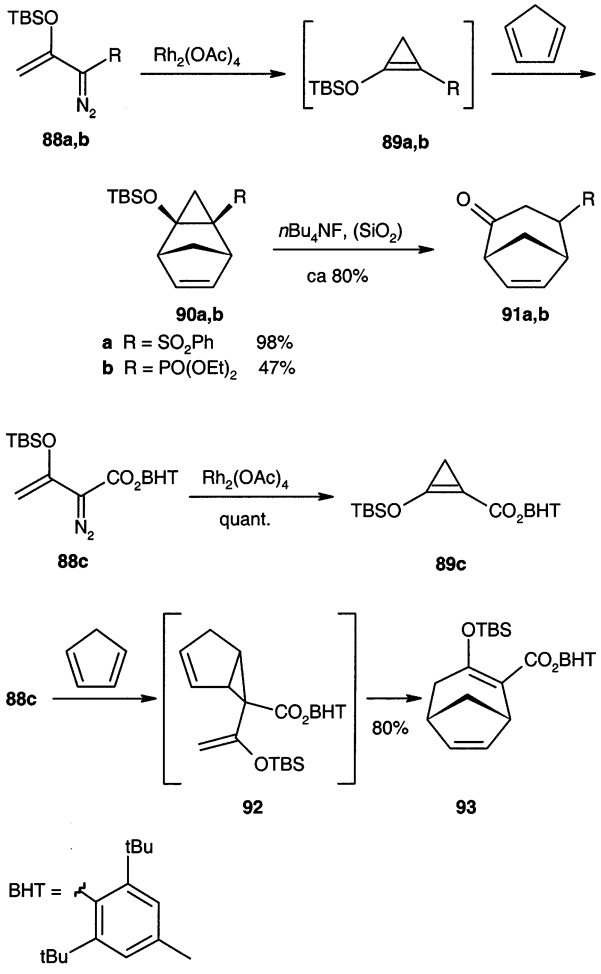
Scheme 24



selectivity with respect to the chiral auxiliary is very high, and therefore, acid-induced ring cleavage of **87** furnished 1,4-dicarbonyl compounds with high enantiopurity.[57] The scope and limitations of this modular and highly stereoselective methods are so far unknown.

A second unique approach to D−A cyclopropanes involves the intermediacy of donor−acceptor substituted *cyclopropenes*. These were generated by rhodium-catalyzed decomposition of vinyl-substituted diazo compounds **88a,b**, leading to the intermediates **89a,b** (Scheme 25). They are trapped by cyclopenta-

Scheme 25



diene in a Diels−Alder reaction to furnish the tricyclic D−A cyclopropanes **90a,b** in moderate to excellent yields, which can be cleaved by fluoride treatment to provide the bicyclic compounds **91a,b** in good yield (for ring cleavage of D−A cyclopropanes see section III.C.1).[58] With the related diazoacetate **88c** bearing a sterically demanding ester group, the corresponding donor−acceptor-substituted cyclopropene **89c** could actually be isolated and characterized. Interestingly, decomposition of **88c** in the presence of cyclopentadiene did not provide an adduct analogous to **90a,b** but product **93**. Its formation may be interpreted as a tandem cyclopropanation−Cope process with vinylcyclopropane **92** as intermediate (see section III.E.1).

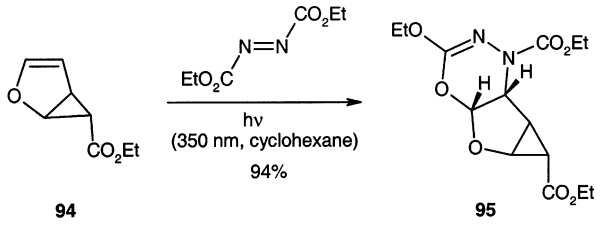
III. Synthetic Methods Based on D–A Cyclopropanes

Most synthetic applications employing D−A cyclopropanes explore one of the ring cleavage modes described in the Introduction; however, examples are known that involve modifications at the D−A cyclopropane core without ring opening. The resulting products may be used for further synthetic explorations typical for D−A cyclopropanes.

A. Methods without Cleavage of the Cyclopropane Ring

Cyclopropanation of furan with ethyl diazoacetate, which occurs with high diastereoselectivity, makes available bicyclic compound **94**. This product undergoes a [4 + 2] cycloaddition with diethyl azodicarboxylate, furnishing a new tricyclic D−A cyclopropane **95** in high yield (Scheme 26).[59]

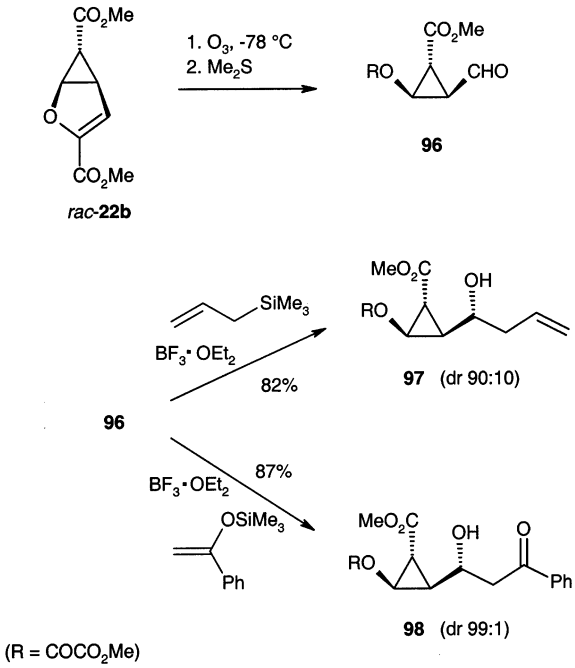
Scheme 26



Ozonolysis of bicyclic compounds such as (*rac*)-**22b** afforded trisubstituted D−A cyclopropanes **96** (Scheme 27). Additions of nucleophiles, such as allyl silane or silyl enol ethers, to aldehyde **96** in the presence of Lewis acid occurred with excellent diastereoselectivity. In agreement with the Felkin−Anh model, they provide a variety of new D−A cyclopropanes such as **97** and **98**.[60] These compounds are useful intermediates for further synthetic transformations. Since cyclopropanation of furan derivatives was also performed in the presence of chiral catalysts, starting materials **22** are also accessible in highly enantioenriched form (see Scheme 6).

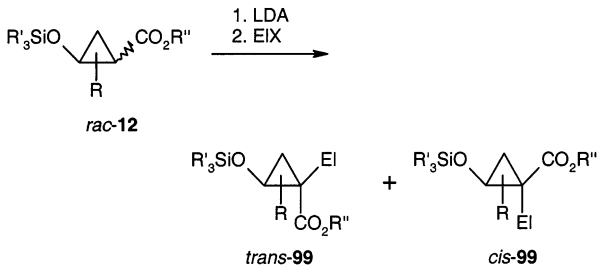
An extremely useful reaction of D−A cyclopropanes involves their substitution α to the acceptor group, allowing introduction of new (reactive) moieties. For this purpose, siloxycyclopropanecarboxylates **12** were the most suitable precursor compounds. Deprotonation with bases such as LDA followed by reaction of

Scheme 27



the enolate with the required electrophile ElX generally yielded the expected products **99** in good yields and very often with excellent diastereoselectivity under preference of *trans*-**99** (Scheme 28). The prin-

Scheme 28

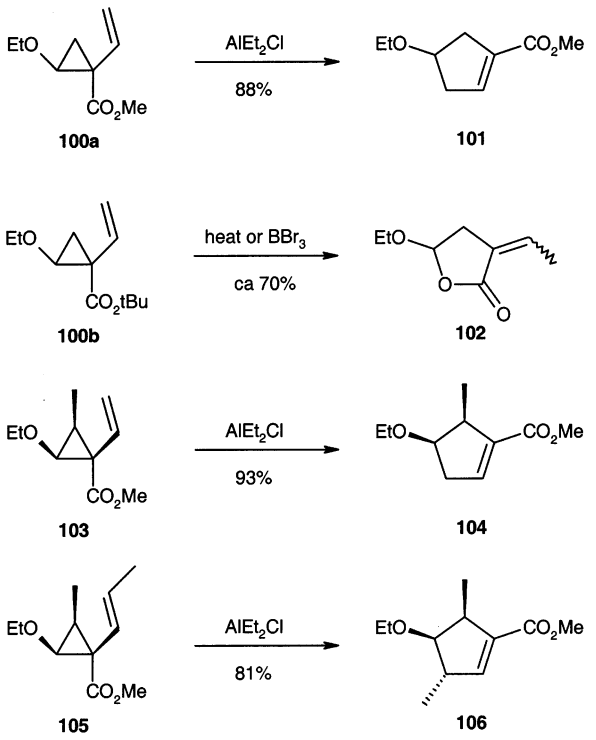


cipal reaction and the interpretation of the stereoselectivity has earlier been described in detail. Meanwhile, it has frequently and reliably been applied to the construction of synthetically important intermediates, as demonstrated in the subsequent paragraphs.[61,7]

B. Transformations by (Formal) Pericyclic Reactions

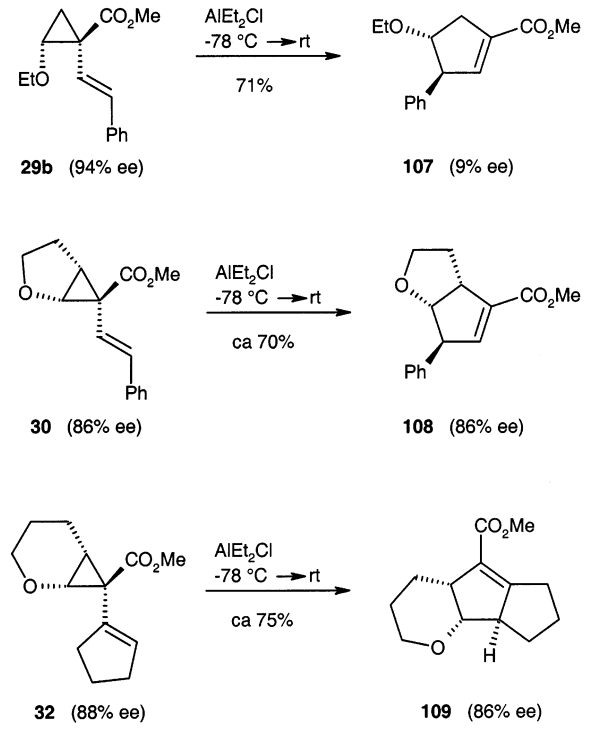
The vinylcyclopropane−cyclopentene rearrangement remains a mechanistically striking and synthetically very useful reaction for the preparation of five-membered ring systems (Scheme 29).[2] An interesting new variation was reported with vinylcyclopropanes **100a,b**, where the result strongly depends on the ester substituent. Treatment of methyl ester **100a** with diethylaluminum chloride led to the expected cyclopentene derivative **101**, whereas *tert*-butyl ester **100b** underwent an unusual rearrangement to α-ethylidenebutyrolactone **102** formed as an *E*/*Z*-mixture of isomers.[62] Vinylcyclopropanes **103** and **105** with additional substituents revealed a remarkably high stereoselectivity of the rearrangement, leading to cyclopentene derivatives **104** and **106**.[63]

Scheme 29



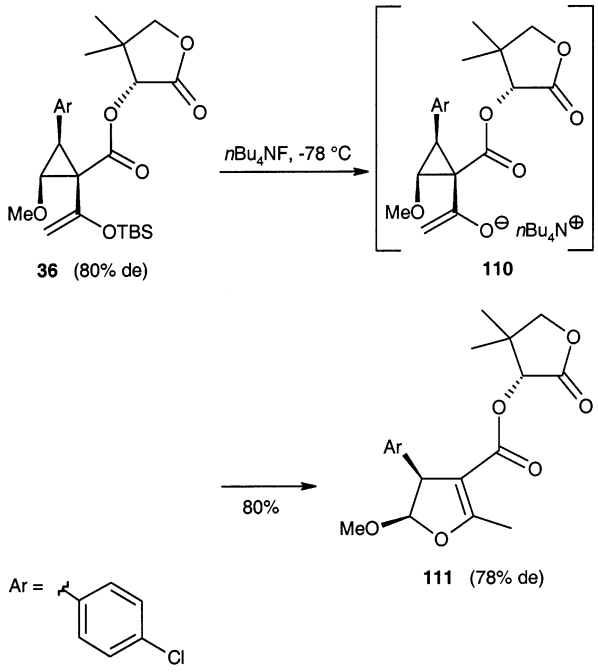
When these diethylaluminum chloride-assisted ring enlargements were performed with enantioenriched vinylcyclopropanes **29b**, **30**, and **32**, the first precursor almost completely lost its chiral information during transformation into **107**, whereas **30** and **32** were converted into cyclopentene derivatives **108** and **109**, essentially without decrease of the enantiopurity (Scheme 30).[26]

Scheme 30



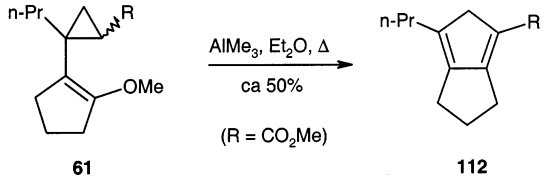
An anion-accelerated vinylcyclopropane–cyclopentene rearrangement was investigated with arylsubstituted cyclopropane **36** as precursor (Scheme 31). Its treatment with fluoride furnished **111** in good yield and without loss of diastereomeric purity. Here, enolate **110** is the intermediate that can undergo the ring enlargement at surprisingly low temperature.[26]

Scheme 31



Similar reaction conditions were employed when cyclopentenyl-substituted cyclopropane **61** (see Scheme 18) was rearranged into a bicyclic compound **112** (Scheme 32). Treatment of **61** with an excess of

Scheme 32

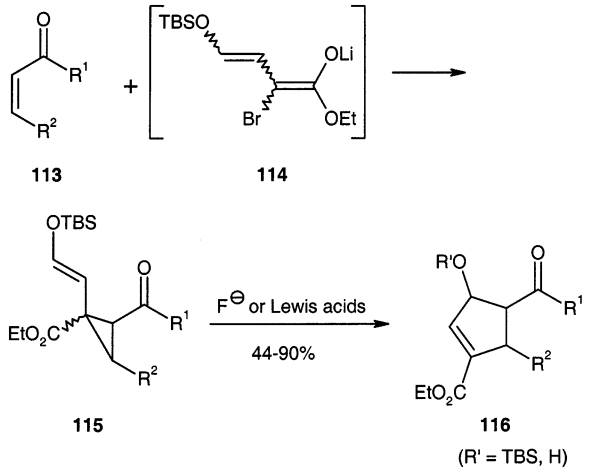


trimethylaluminum at 32 °C caused a Lewis acid-assisted vinylcyclopropane–cyclopentene rearrangement, followed by elimination of methanol, providing **112** in moderate yield.[64]

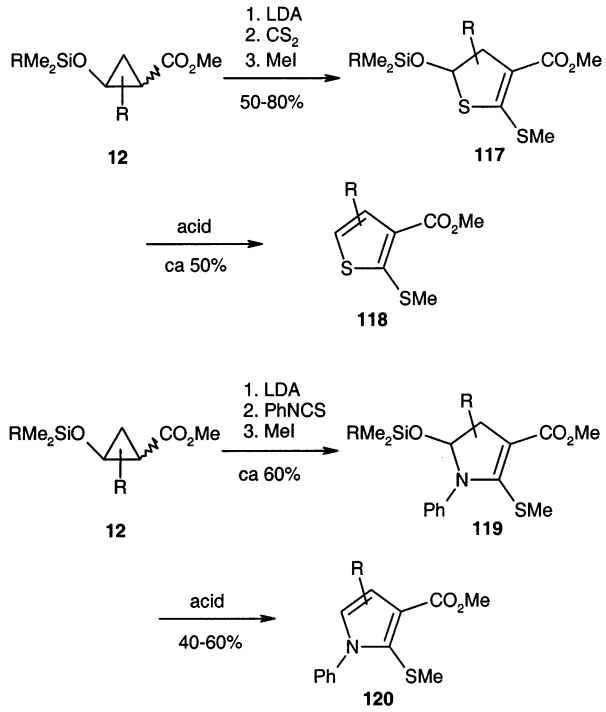
Addition of lithium enolate **114** derived from γ-siloxy-α-bromocrotonate to cyclic enones **113** furnished vinylcyclopropanes **115**, which may be regarded as vinylogous D–A cyclopropanes (Scheme 33). Their treatment with fluoride reagents or Lewis acids provided the corresponding annulated cyclopentene derivatives **116**. The stereoselectivity of the reactions involved is only moderate.[65]

D–A cyclopropanes were precursors for the synthesis of several five-membered heterocycles involving a related ring expansion step. Thus, siloxycyclopropanecarboxylates **12** furnished dihydrothiophene derivatives **117** in good yield, when treated with LDA followed by addition of carbon disulfide and methyl iodide (Scheme 34). It was suggested that the ring-expansion step occurs as an anion-accelerated 1,3-sigmatropic rearrangement.[66] Similarly, D–A cyclo-

Scheme 33



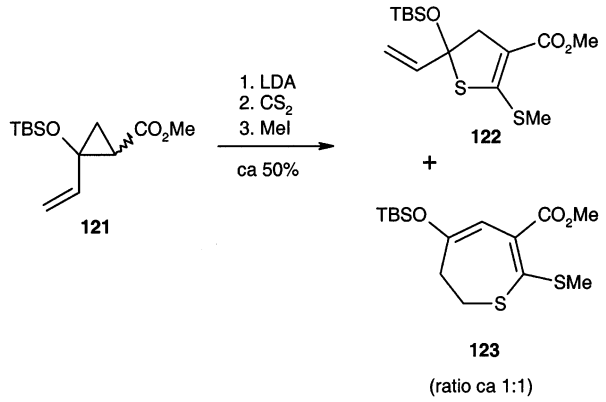
Scheme 34



propanes **12** provided dihydropyrrole derivatives **119** when the cyclopropane enolate was trapped with phenyl isothiocyanate and methyl iodide.[67] Several of the dihydrothiophene or dihydropyrrole derivatives underwent an (Lewis) acid-induced elimination to afford the corresponding aromatic thiophene or pyrrole systems **118** and **120**. In connection with these experiments, density functional calculations were performed investigating the 1,3-sigmatropic rearrangements of certain vinylcyclopropanes and their hetero analogues.[68]

Vinyl-substituted D−A cyclopropane **121** is an interesting case in these reactions. The analogous sequence employing carbon disulfide and methyl iodide as electrophiles provided a 1:1 mixture of dihydrothiophene derivative **122** and isomeric dihydrothiepine **123** (Scheme 35). In this example, a competition between the (formal) 1,3-sigmatropic and 3,3-sigmatropic rearrangements occurs, and this probably reflects the diastereoselectivity of the enolate reaction: when it accepts carbon disulfide cis to the alkenyl group, a system is generated that can undergo the 3,3-sigmatropic reaction, whereas the other diastereomer (alkenyl and C=S trans) is only capable to rearrange in a 1,3-sigmatropic fashion. The primary product of the 3,3-sigmatropic rearrangement apparently suffers subsequent double bond shift, providing **123** with conjugated diene moiety. Other alkenyl-substituted siloxycyclopropanes similar to **121**, but bearing substituents at the alkenyl group, only formed dihydrothiophene derivatives. Furthermore, reaction of deprotonated **121** with phenyl isothiocyanate and methyl iodide gave only dihydropyrrole derivatives (see Scheme 34). Apparently, a delicate balance of steric and electronic effects determines the selectivity of these reactions.[69]

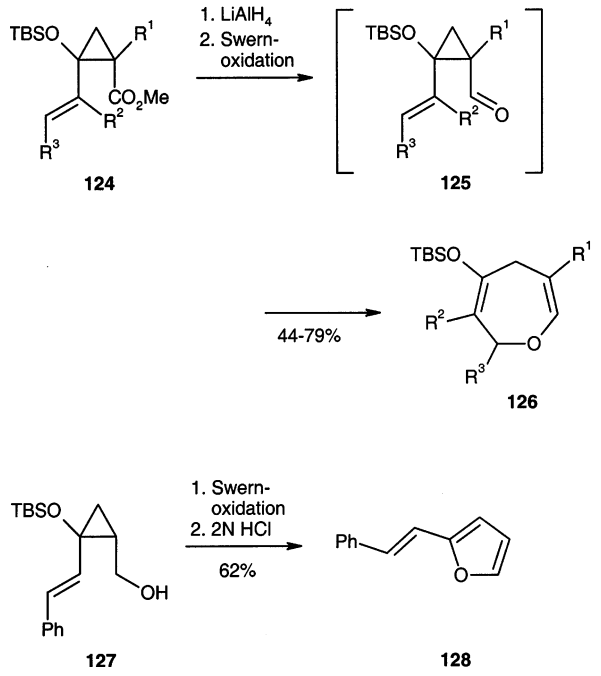
Scheme 35



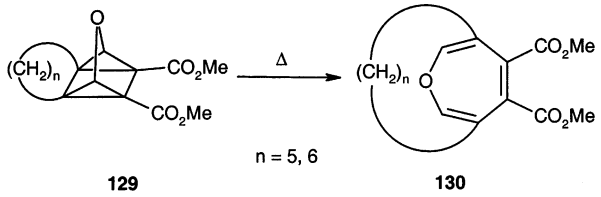
3,3-Sigmatropic rearrangements of divinylcyclopropanes to cycloheptadiene derivatives belong to the most important reactions for construction of seven-membered carbocycles.[3] This principle was also applied to the synthesis of heterocyclic compounds.[70] Not surprisingly, D−A cyclopropanes may be used as precursors for preparation of functionalized seven-membered heterocycles (see formation of **123** in Scheme 35). Starting with siloxycyclopropanecarboxylates **124**, reduction of the methoxycarbonyl group and subsequent Swern oxidation to aldehydes **125** provide a system that very easily undergoes a 3,3-sigmatropic rearrangement, furnishing the 2,5-dihydrooxepines **126** in good overall yield (Scheme 36). For several of these oxepine derivatives **126**, an acid- or base-catalyzed ring contraction to the corresponding 5-alkenyldihydrofuran derivatives was observed. When oxidized to the aldehyde and then treated with acid, cyclopropanes such as **127** bearing an aryl or an electron-donating group at the alkenyl substituent furnished furan derivatives such as **128**.[71] A DFT study on the vinylcyclopropanecarbaldehyde to 2,5-dihydrooxepine hetero-Cope-type rearrangement and on related reactions was performed in connection with these experiments.[72]

Special examples were described by Tochtermann et al., who investigated oxaquadricyclan derivatives incorporating two D−A cyclopropane units. By thermolysis, compounds **129** rearrange to bridged oxepine derivatives **130** (Scheme 37). X-ray analyses and semiempirical calculations were executed to study the properties of precursor compounds **129**.[73]

Scheme 36

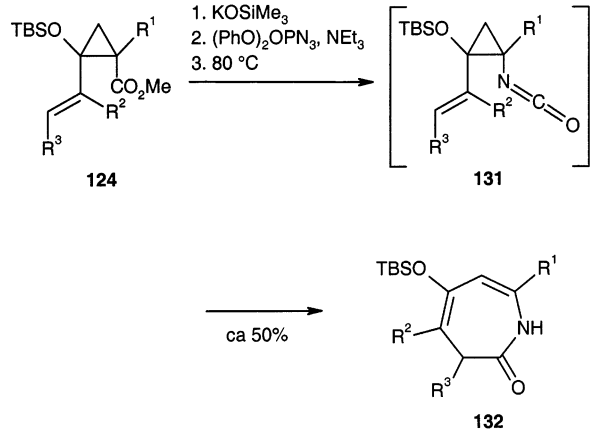


Scheme 37



A straightforward entry to 1,3-dihydroazepin-2-one derivatives **132** was developed by transforming the above-mentioned vinyl-substituted siloxycyclopropanecarboxylates **124** into the corresponding vinylcyclopropyl isocyanates **131** (Scheme 38). Saponifi-

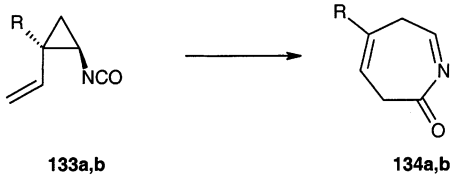
Scheme 38



cation of **124** with potassium trimethylsilanolate followed by treatment with diphenyl phosphorazidate provided the acyl azides as intermediates that rearranged to the crucial isocyanates **131** by heating to 80 °C. These underwent immediate 3,3-sigmatropic rearrangement to seven-membered heterocycles that after a proton shift finally delivered azepin-2-ones **132** in satisfactory overall yield.[74]

DFT calculations (B3LYP/6-31G*) on the reaction **133** → **134** revealed that the reaction enthalpy is dramatically more exothermic when R is a hydroxy group that simulates the siloxy substituent of **131** (Scheme 39). According to these results, the activation energy is only slightly decreased when going from **133a** to **133b**, but the calculated barriers reveal that the rearrangement to seven-membered rings should occur at relatively low temperatures.[75]

Scheme 39



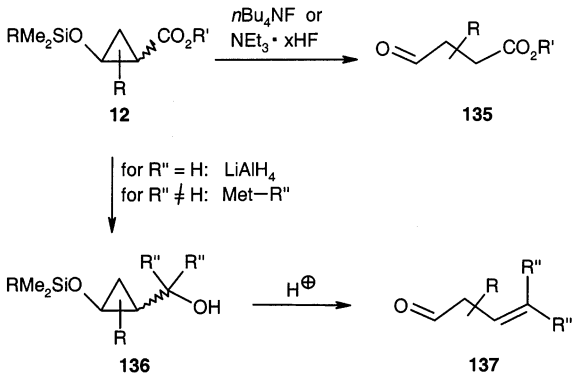
	R	$\Delta H_o^{\#}$ (kJ/mol)	ΔH_o (kJ/mol)
a	H	74.2	-44.2
b	OH	71.7	-61.7

C. Ring Cleavage of D–A Cyclopropanes and Isolation of the Primary Products

1. Reactions of D–A Cyclopropanes with Brönstedt and Lewis Acids or Fluoride Reagents

Ring opening of D−A cyclopropanes with acids, which may be classified as a strain-driven retro-aldol reaction, generally provides 1,4-dicarbonyl compounds and derivatives thereof. It is the most frequently employed synthetic application of this class of small ring compounds. The first fundamental results were reported by Wenkert et al.[4] Many synthetically useful variations have meanwhile been reported, where siloxy-substituted cyclopropanecarboxylates **12** turned out to be particularly versatile intermediates (Scheme 40). These are cleaved under

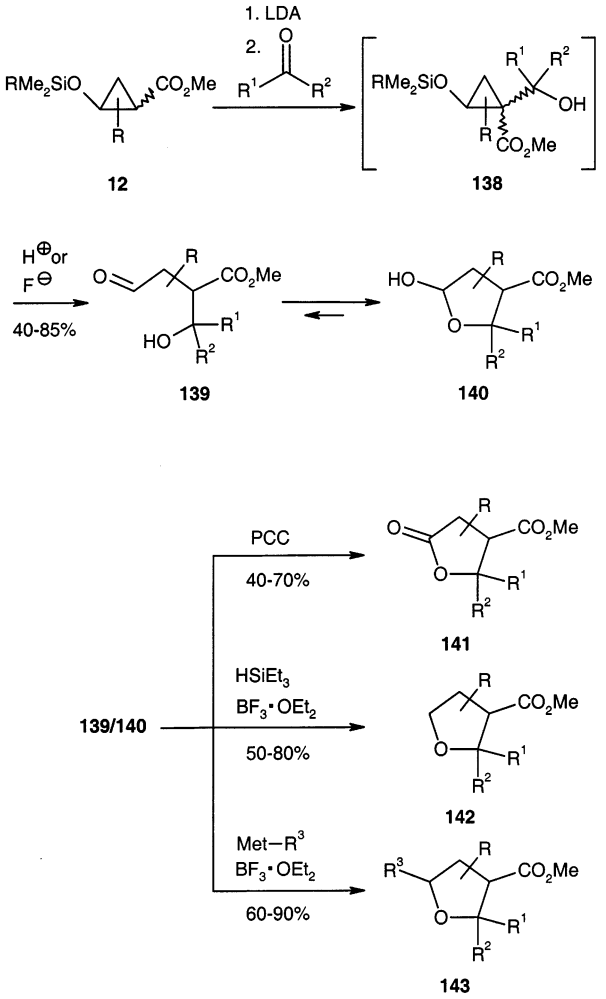
Scheme 40



very mild conditions either with tetra-*n*-butylammonium fluoride and related salts or with triethylamine hydrofluorides to provide the γ-oxo esters **135**.[76] A less frequently applied alternative mode of ring cleavage first converts the ester function of **12** into an alcohol group and then treats the resulting **136** with acid, which provides the β,γ-unsaturated carbonyl compounds **137**.[77]

By treatment with LDA, siloxycyclopropanecarboxylates **12** were converted into the corresponding enolates, which can efficiently be trapped with a variety of carbonyl compounds (Scheme 41). The

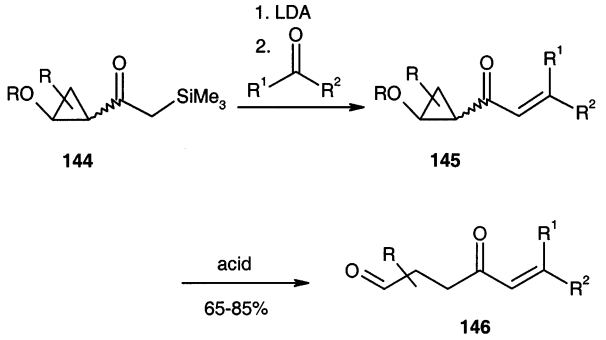
Scheme 41



produced substituted siloxycyclopropanes **138** were transformed into ring-cleaved compounds by treatment with fluoride or acid. The resulting functionalized 1,4-dicarbonyl compounds **139** are in equilibrium with γ-lactols **140**, which were transformed into paraconic esters **141** by oxidation with PCC.[78] Even more possibilities were offered by Lewis acid-promoted reactions of γ-lactols **140** with nucleophiles. Reactions with triethylsilane provided tetrahydrofurans **142** in excellent yields, and a variety of organometallic reagents could be used to transform **140** into highly substituted furan derivatives **143**. The C−C bond formation usually occurs with very good stereoselectivity.[79]

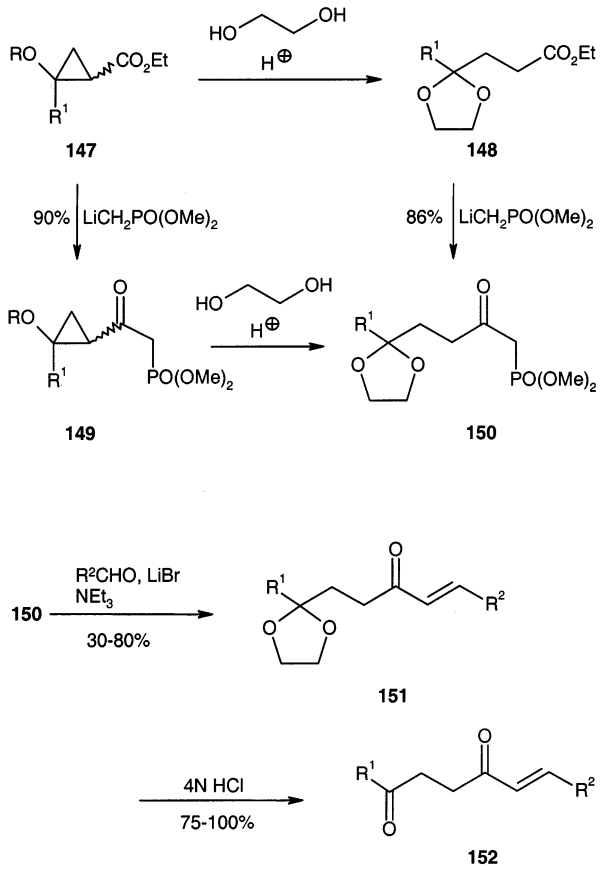
Cyclopropanation of enol ethers with 1-diazo-3-trimethylsilyl-2-propanone in the presence of copper(II) acetylacetonate or rhodium(II) acetate gave D−A cyclopropanes of type **144**, which could be converted into new cyclopropyl substituted enones **145** by Petersen olefination (Scheme 42). Intermediates **145** were ring-opened by acid treatment and provided 1,4-dicarbonyl compounds **146** incorporating an enone unit.[80] A second approach to compounds

Scheme 42



such as **152** uses a Horner−Emmons olefination of phosphonates **150**, which were obtained by straightforward steps from D−A cyclopropane **147** (Scheme 43).[81]

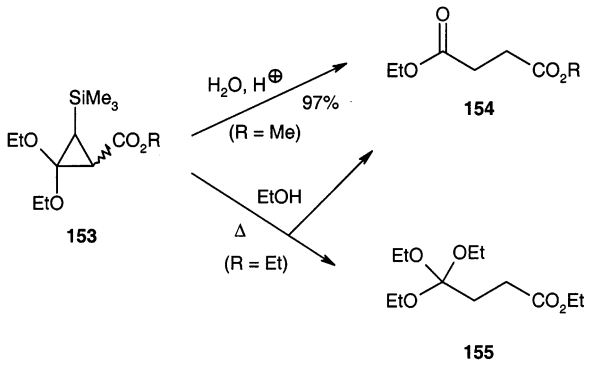
Scheme 43



A further example involves trimethylsilyl-substituted D−A cyclopropanes **153**, which were prepared in good yield by rhodium(II) acetate-catalyzed reaction of methyl or ethyl diazoacetate with the corresponding trimethylsilylketene dialkylacetal. Whereas **153**, when treated with aqueous acid, furnished diester **154** in ethanol, it provided a mixture of diester **154** and ortho ester **155** (Scheme 44). Both reaction conditions induced complete desilylation of the compounds involved.[82]

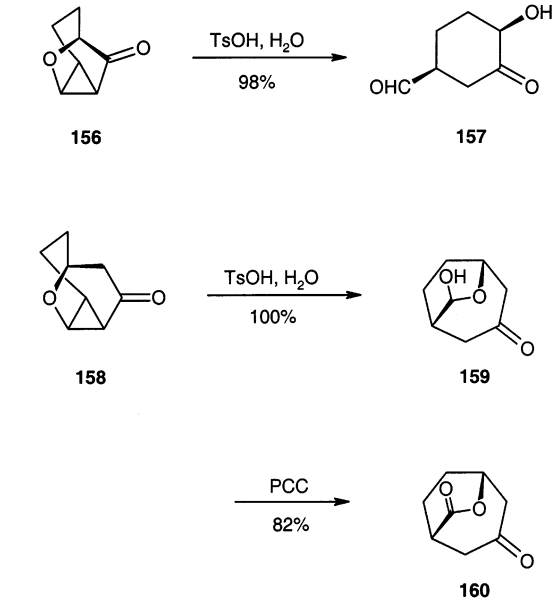
Intramolecular cyclopropanation of 2-substituted 3,4-dihydropyrans bearing diazoketone moieties smoothly furnished tricyclic D−A cyclopropanes such as **156** and **158**, which were cleaved by treatment with aqueous acid to provide, in stereo-

Scheme 44



selective fashion, either dicarbonyl compounds such as **157** or—because of the larger ring sizes favoring acetalization—the corresponding lactol **159** (Scheme 45). This latter intermediate could be oxidized em-

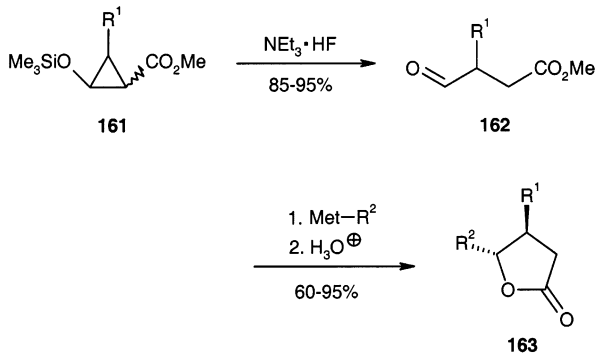
Scheme 45



ploying pyridinium chlorochromate and finally furnished bicyclic lactone **160** in good yield.[83]

The preparation of rather sensitive, and otherwise difficult to access, β-formyl esters **162** was efficiently achieved by ring cleavage of the corresponding siloxycyclopropanecarboxylates **161** (Scheme 46).[84,85] Treatment with fluoride reagents afforded 1,4-dicarbonyl compounds **162**, which were required for a systematic study of chelate-controlled stereo-

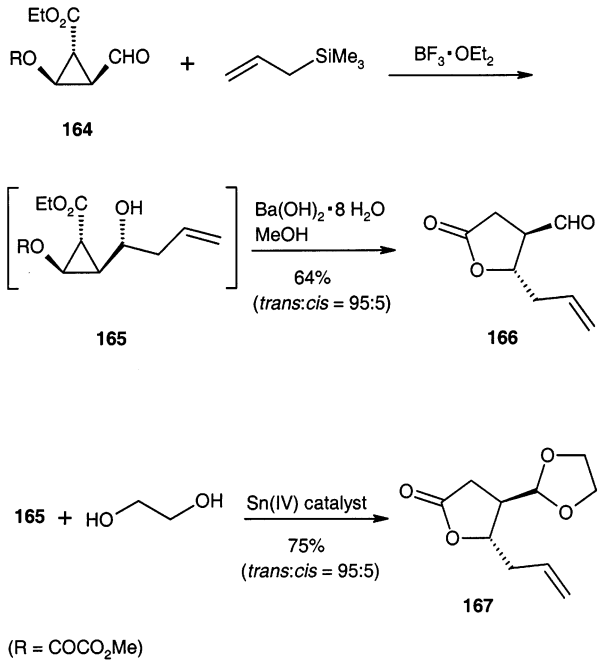
Scheme 46



selective additions of various organometallic compounds such as allyl silanes, silyl enol ethers, cuprates, and Grignard reagents. This reaction sequence finally provided a broad range of highly substituted γ-lactones **163**, which were usually formed with good to excellent preference of trans-substituted compound.[86]

The highly diastereoselective addition of nucleophiles, e.g. allyl silanes, to cyclopropyl aldehydes such as **164** has already been illustrated in Scheme 27. Without purification, products **165** were smoothly converted into functionalized γ-lactones **166** or **167**. Base-assisted cyclopropane ring cleavage and recyclization led to aldehyde **166**. Alternatively, ring opening followed by reaction with 1,2-ethanediol employing Otera's tin(IV) catalyst provided acetal **167** in good yields. The reactions depicted in Scheme 47 were performed with optically pure starting material **164** (see Scheme 6) and therefore led to enantiopure products **166** and **167**.[21]

Scheme 47

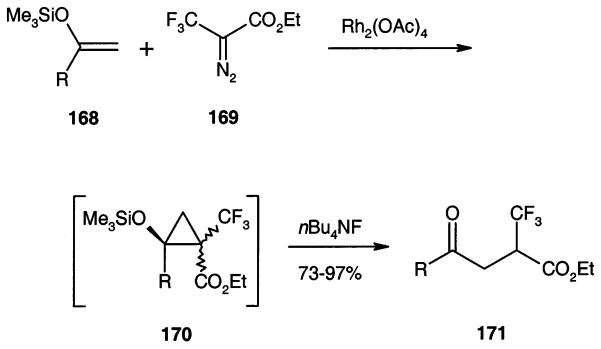


(R = $COCO_2Me$)

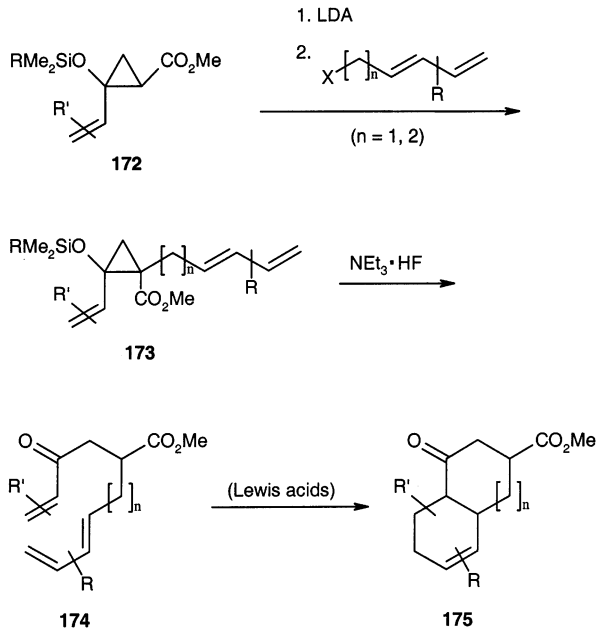
Diazoacetate **169** with a trifluoromethyl group allowed preparation of fluorinated γ-keto esters **171** in good yields. Cyclopropanation of silyl enol ethers **168** with **169** under standard conditions provided intermediate D–A cyclopropanes **170**, which were not isolated but directly converted in γ-keto esters **171** by fluoride treatment (Scheme 48).[87]

Functionalized enones **174** were synthesized for applications in intramolecular Diels–Alder reactions. The corresponding vinyl-substituted siloxycyclopropanes **172** were equipped with the required dienyl substituent by deprotonation and alkylation with the appropriate electrophile (Scheme 49). Ring opening of **173** furnished enones **174**, which in part immediately underwent the intramolecular [4 + 2] cycloaddition to bicyclic compounds **175**. In other cases, heating or treatment with Lewis acid was required to promote the Diels–Alder reaction to **175**.[88]

Scheme 48



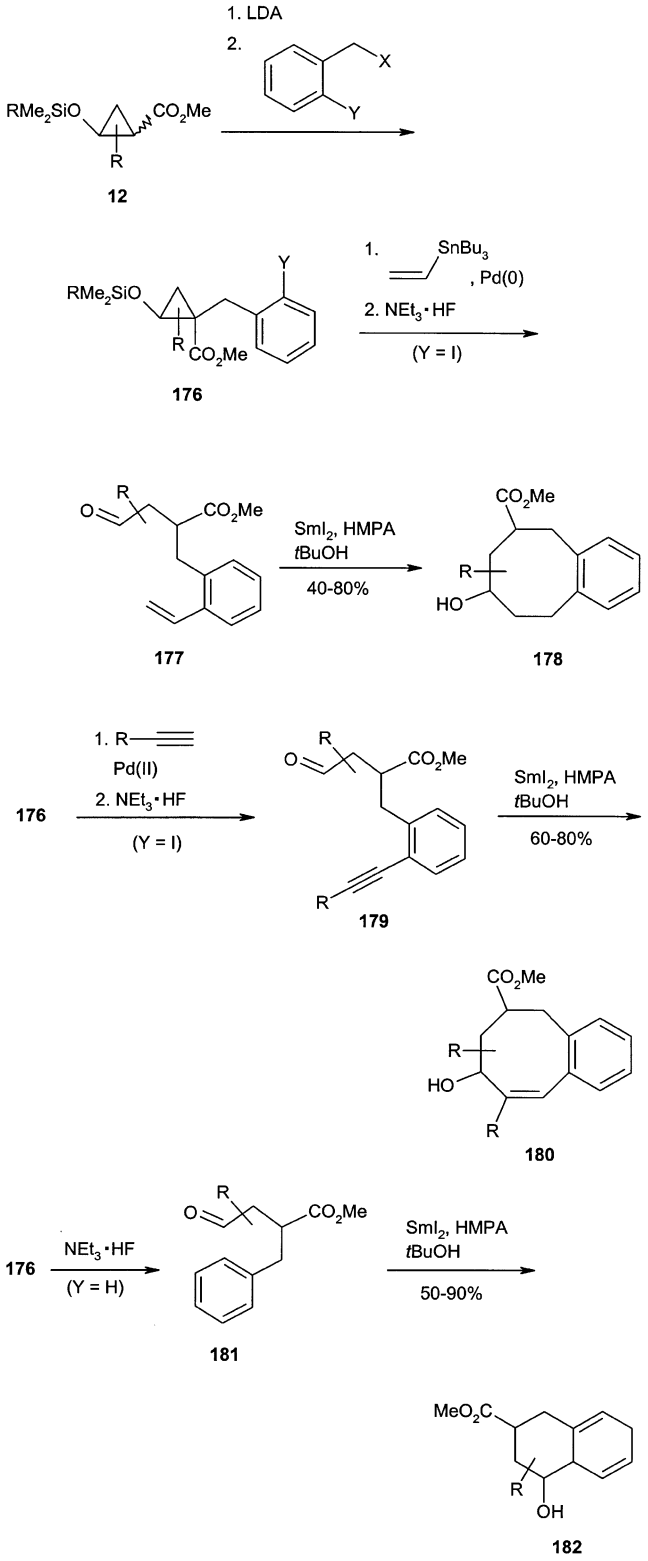
Scheme 49



Siloxycyclopropanecarboxylates **12** were extremely useful and versatile starting materials for the construction of compounds investigated in novel samarium(II)-induced cyclization processes (Scheme 50). Reaction of deprotonated siloxycyclopropanes **12** with appropriate benzyl halides provided the crucial intermediates **176**. The aryl group was further equipped with alkenyl or alkynyl substituents by palladium-catalyzed processes. All these intermediates were ring-opened under mild conditions with fluoride reagent to furnish styrene derivatives **177**, aryl alkynes **179**, or benzyl-substituted 1,4-dicarbonyl compounds **181**. Treatment of these compounds with samarium diiodide in the presence of HMPA and *tert*-butyl alcohol afforded either benzannulated cyclooctane derivatives **178** and cyclooctenes **180** or, most surprisingly, hexahydronaphthalenes **182**. These cyclizations, which involve ketyls as reactive intermediates, generally proceed with very high diastereoselectivities.[89−91]

Treatment of 3-alkoxycyclohexenones **183** with LDA generated a dienolate that underwent cascade cycloadditions with 2-chloro-2-cyclopropylideneacetate **184** and smoothly provided polycyclic compounds such as **185** (Scheme 51). These incorporate a D−A cyclopropane core activated by two acceptor groups. Acid-promoted ring cleavage of **185** or of the

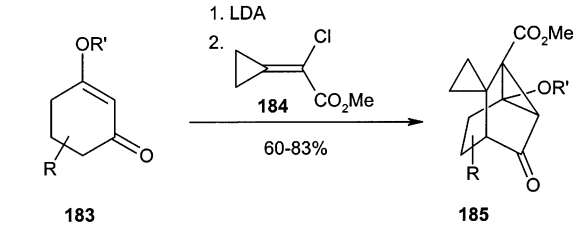
Scheme 50



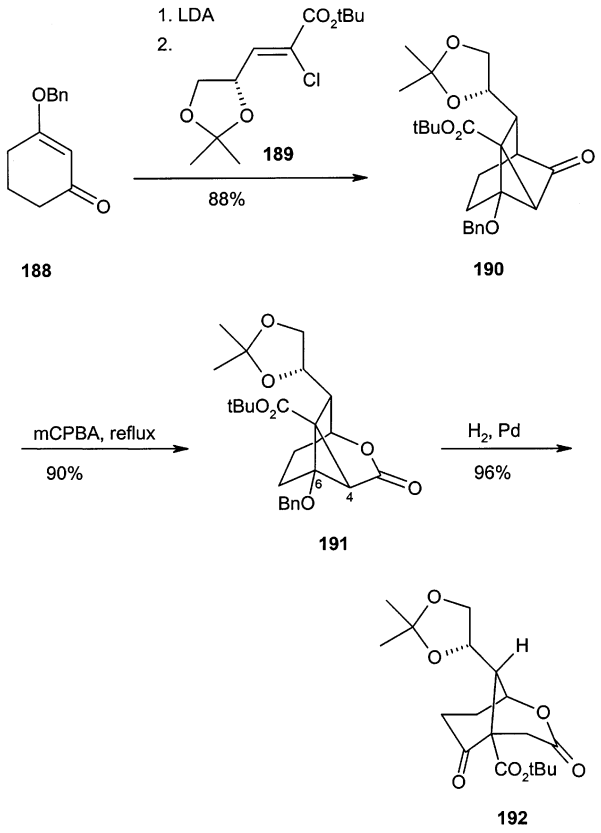
intermediate obtained after Wittig olefination furnished bicyclo[3.2.1]octane derivatives **186** or **187** in excellent yields.[92] Apparently, the bond activated by the alkoxy group and the carbonyl group is cleaved with high regioselectivity in these compounds.

Enantiopure polycyclic compounds were obtained when glyceraldehyde-derived Michael acceptor **189** was combined with the dienolate generated from **188** (Scheme 52). The resulting product **190** could be

Scheme 51



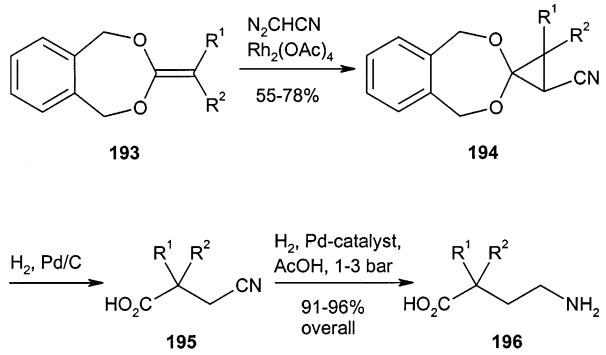
Scheme 52



transformed into lactone **191** by Baeyer–Villiger oxidation, and hydrogenolysis finally afforded bicyclic lactone **192** with excellent regioselectivity. The C-4, C-6 bond of the cyclopropanol generated by hydrogenolysis of **191** seems to have a stronger interaction with the lactone carbonyl group than with the ester substituent, which causes selective cleavage of this bond. Lactone **191** and similar compounds were also used as starting materials for other transformations, leading to interesting enantiopure polycyclic compounds.[93]

A very mild method for ring cleavage employs generation of free cyclopropanols by hydrogenolysis of benzylic ethers. As an example, D–A cyclopropanes **194**, which were easily available from ketene acetals **193** and diazoacetonitrile, underwent smooth ring cleavage via the cyclopropanol when it was reduced with hydrogen in the presence of Pd/C (Scheme 53). Products **195** were further transformed

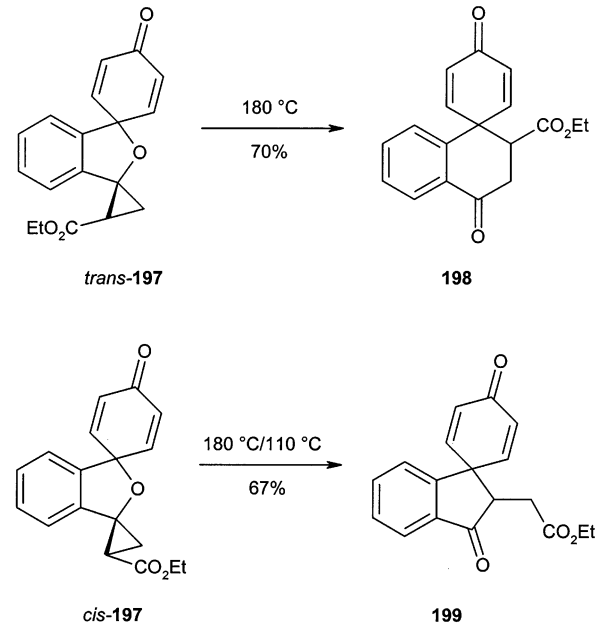
Scheme 53



into γ-amino acids **196** by reduction of the nitrile group, usually under slightly enforced conditions. This sequence was also exploited for synthesis of specifically deuterated γ-amino acids.[94]

An exceptional case of thermal rearrangement of D–A cyclopropanes to γ-keto esters was reported by Swenton et al.[95] Depending on the configuration of the tetracyclic starting material **197**, constitutionally different products were isolated (Scheme 54). Heating

Scheme 54

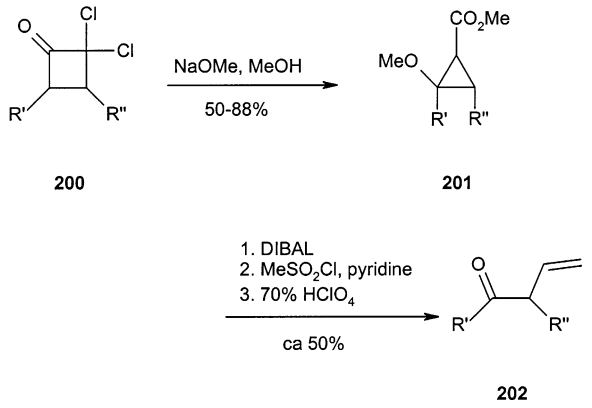


of *trans*-**197** provided tetralone derivative **198**, while similar treatment of *cis*-**197** afforded indanone **199** in moderate yield. The latter process, which occurs also at temperatures as low as 110 °C, was explained by cyclopropane ring cleavage providing a stabilized intermediate (probably a 1,3-zwitterion) followed by

1,2-H-shift and 1,3-rearrangement to indanone **199**. In contrast, this kind of cyclopropane cleavage is less favorable for *trans*-**197**, and therefore, a competing cleavage was proposed furnishing a phenoxy−cyclopropoxy radical pair. Cyclopropane ring opening and reclosure to the six-membered ring afforded tetralone derivative **198**.

The well-known ring contraction of dichlorocyclobutanones **200**, which were easily available by dichloroketene additions to olefins, was exploited to prepare various bicyclic D−A cyclopropanes **201** (Scheme 55). These were converted into the corresponding α-vinyl ketones **202** by DIBAL reduction and subsequent elimination.[96]

Scheme 55

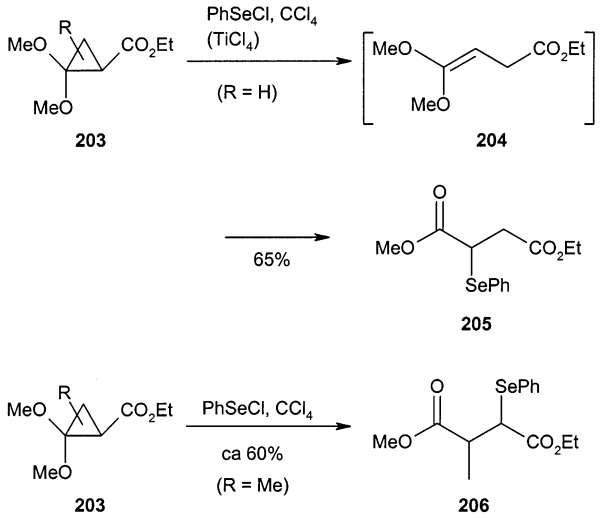


200 201 202

2. Reactions with Other Electrophiles and Oxidations

Many examples exist that involve reaction of D−A cyclopropanes with electrophilic reagents, including oxidizing agents. Ring-opening bromination, selenenylation, and sulfenylation of siloxycyclopropanecarboxylates were reported earlier.[97] Closely related reactions of ethyl 2,2-dimethoxycyclopropanecarboxylates **203**, in the presence or absence of $TiCl_4$, were studied more recently (Scheme 56). The parent

Scheme 56

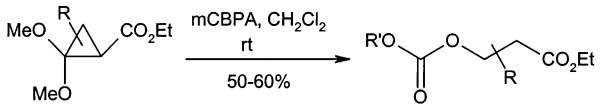


203 204 205 203 206

compound **203** (R = H) provided the selenenylated ester **205**, the formation of which was explained by a Lewis acid-catalyzed rearrangement of **203** to ketene acetal **204**, followed by reaction with the electrophilic selenium compound. If the D−A cyclopropane **203** bears additional alkyl substituents R, the direct reaction of benzeneselenenyl chloride occurs, furnishing the expected products **206**. Detailed investigations concerning the stereoselectivity of this process leading to **206** were performed.[98] Related observations were made when sulfenyl chlorides were reacted with compounds **203**.[99] Oxidation of the selenenylated or sulfenylated diesters with hydrogen peroxide and elimination furnished the corresponding unsaturated esters. D−A cyclopropanes **203** may also be cleaved by oxidation with ruthenium tetroxide or lead tetraacetate; however, these reactions are synthetically less valuable.[100]

Oxidative cleavage reactions of D−A cyclopropanes of type **203** using *m*-CPBA proceed in a more complicated fashion and provide β-hydroxycarboxylic acid derivatives **207** (Scheme 57). The suggested mechanism involves acid-catalyzed ring opening, formation of a peroxy ester, and a Baeyer−Villiger-type rearrangement.[101]

Scheme 57



203 207

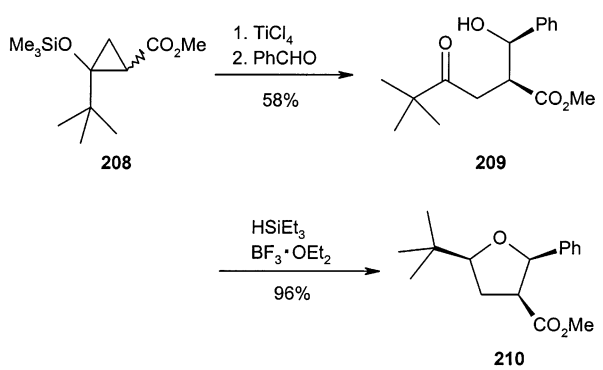
(R' = Me or Ph-m-Cl)

3. Reactions with Electrophilic Double Bonds

Reactions of D−A cyclopropanes with electrophilic double bonds usually require assistance of Lewis acids and provide either acyclic or cyclic compounds. The latter are formed by formal cycloadditions or by cyclization of an intermediate. Many examples were performed with carbonyl compounds as electrophiles, furnishing products under formation of one C−C bond or under conversion into tetrahydrofuran derivatives.

Reactions of siloxycyclopropanecarboxylates with carbonyl compounds as electrophiles in the presence of Lewis acids occur under ring cleavage and C−C bond formation. The activation of D−A cyclopropane **208** with $TiCl_4$ generates a highly reactive titanoxycyclopropane, which by reaction with benzaldehyde stereoselectively provided addition product **209** (Scheme 58). Similar transformations with other

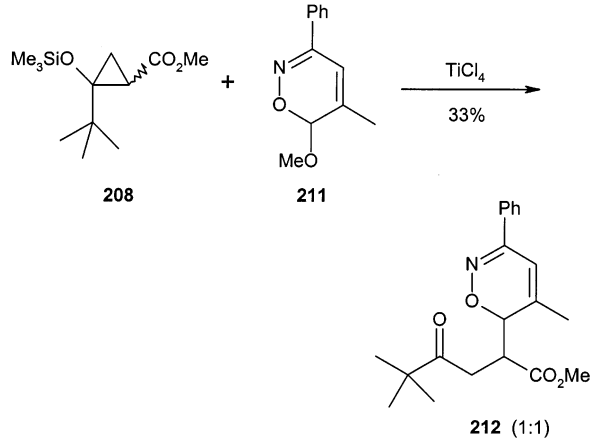
Scheme 58



208 209 210

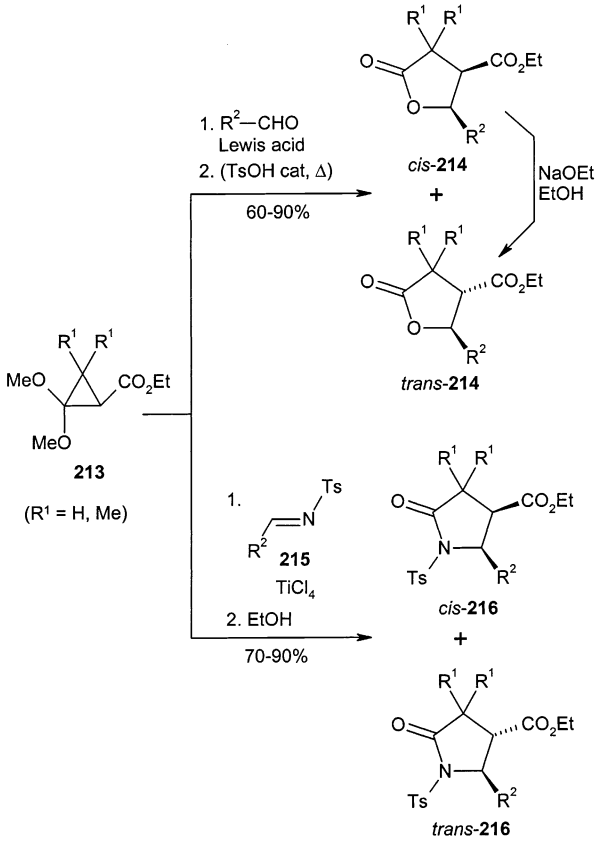
carbonyl compounds were also reported. Subsequent Lewis acid-assisted reactions of adducts such as **209** with silylated nucleophiles (e.g. triethylsilane) provided highly substituted tetrahydrofuran derivatives such as **210**.[102] A rather particular electrophile is an azapyrylium ion that was generated by $TiCl_4$ treatment of 6*H*-1,2-oxazine **211**. It combines with D−A cyclopropane **208** under formation of substituted heterocycle **212** as 1:1 mixture of two diastereomers (Scheme 59).[103]

Scheme 59



Reactions of D−A cyclopropane **213** with aldehydes in the presence of Lewis acid after acidic workup furnished the corresponding γ-lactones **214** with good to excellent cis-selectivity (Scheme 60). The diastereoselectivity is strongly dependent on the aldehyde and the Lewis acid applied, $TiBr_4$ and $SnBr_4$

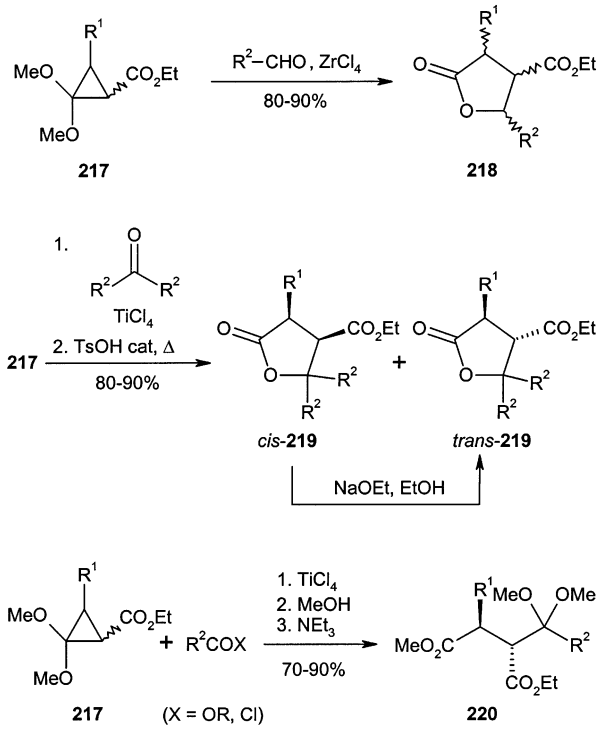
Scheme 60



being the best promotors. Base-catalyzed equilibration provided the more stable *trans*-**214** in good yield. Similar observations were reported for unsymmetrical ketones. The results were explained as aldol type reactions with O-metalated ketene acetals as crucial intermediates.[104] Excellent cis-selectivities and good yields were also obtained for the $TiCl_4$-assisted addition of **213** to *N*-tosyl aldimines **215**. Sodium ethoxide-catalyzed epimerization of *cis*-**216** to *trans*-**216** was complicated by ring opening of the γ-lactam to the corresponding esters.[105]

Similarly, D−A cyclopropanes of type **217** were combined with aldehydes, affording the corresponding γ-lactones **218** as mixtures of four diastereomers, generally with predominance of cis−trans-isomers (Scheme 61). After treatment with base this mixture

Scheme 61

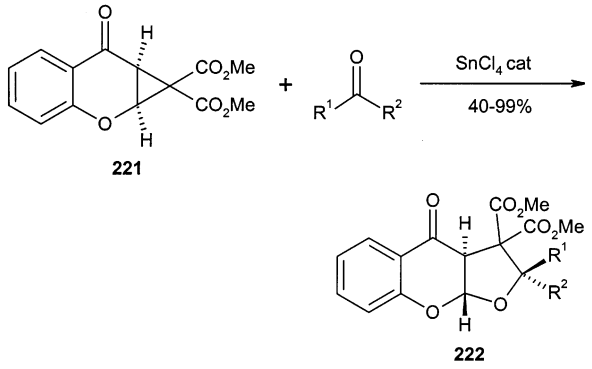


almost exclusively provided trans−trans-isomers of **218**. This approach to trisubstituted γ-lactones was exploited for the synthesis of several natural products with β-carboxy-γ-lactone substructure.[106] Cyclopropane **217**, $TiCl_4$, and symmetrical ketones furnished the expected γ-lactones **219** with high cis-selectivity. Again, base treatment induced smooth isomerization to provide trans-substituted γ-lactones *trans*-**219** in good yields.[107] A $TiCl_4$-promoted Claisen-condensation type reaction transformed D−A cyclopropane **217** and carboxylic acid derivatives into acetals **220** in good yield and excellent anti-selectivity.[108]

Addition of Lewis acid-activated aldehydes and ketones to methanochromanone **221** resulted in smooth formation of the corresponding formal [3 + 2] cycloadducts **222**; the diastereoselectivity of this process was reported to be very high (Scheme 62).[109]

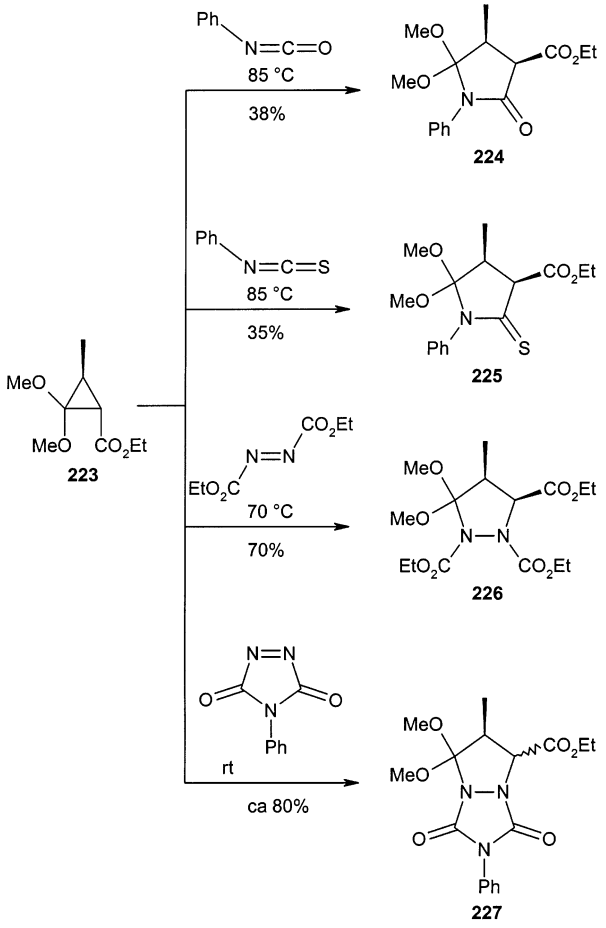
Ethyl 2,2-dimethoxycyclopropanecarboxylates of the general structure **203** were reacted with several compounds containing electrophilic double bonds.

Scheme 62



Heating of derivative **223** with phenyl isocyanate provided the expected cycloaddition product **224** (Scheme 63).[110] Similarly, phenyl isothiocyanate and

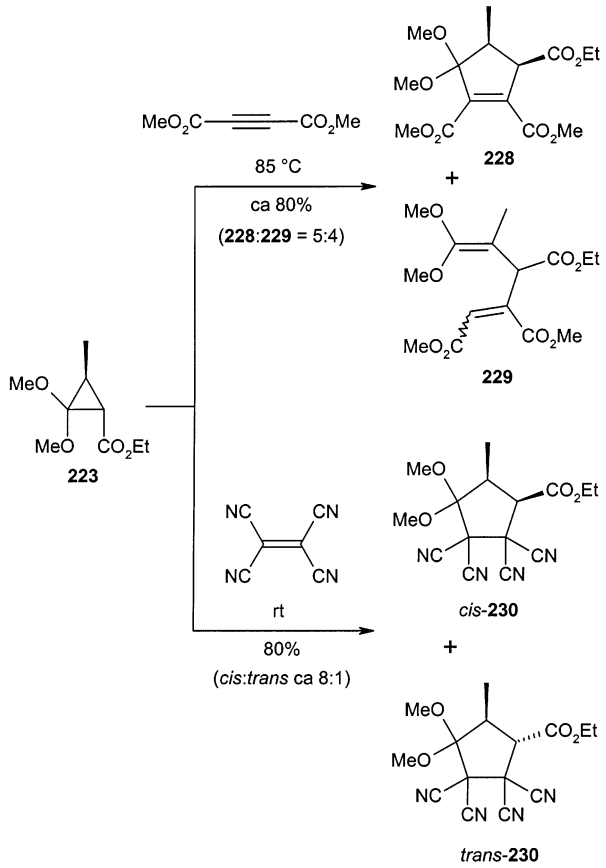
Scheme 63



223 furnished pyrrolidine derivative **225** in moderate yield.[111] In both [3 + 2] cycloadditions the heterocyclic products were accompanied by several other components. This was not the case for the thermal reactions of **223** with diethyl azodicarboxylate and 4-phenyl-1,2,4-triazole-3,5-dione, which cleanly provided the expected cycloadducts **226** and **227**.[112] Whereas formation of **226** proceeded with high diastereoselectivity, as already observed for **224** and **225**, cycloadduct **227** was obtained as a mixture of cis/trans-isomers, the ratio depending slightly on the polarity of the solvent used. Compound **227** was rather sensitive and easily hydrolyzed to provide an acyclic diester.

Heating of **223** with dimethyl acetylenedicarboxylate afforded a 5:4 mixture of the cycloadduct **228** and acyclic ketene acetal **229**.[113] All these experiments are compatible with a mechanism involving an attack of the electrophilic multiple bond to the nucleophilic cyclopropane **223** as the first step. The charges of intermediate 1,5-zwitterions are nicely stabilized by substituents. The stereochemical outcome of the reactions requires *inversion of configuration* at the ethoxycarbonyl-bearing cyclopropane carbon, which is attacked by the electrophile. The 1,5-zwitterions then undergo a ring closure, affording cycloadducts **224**−**228**. In contrast, Graziano et al. interpreted the reaction of **223** with tetracyanoethylene as a symmetry-allowed [$_{\pi}2_{s}+_{\sigma}2_{a}$] pathway directly leading to [3+2] cycloadducts.[114] Formation of **230** proceeds with high though not perfect stereoselectivity, since small amounts of *trans*-**230** were also isolated. Although the solvent polarity has little influence on the outcome of this cycloaddition, this may also occur via 1,5-zwitterions such as the other cycloadditions summarized in Scheme 64.[115] Several of the reactions were not only performed with D−A cyclopropane **223** but also with similarly substituted compounds of general structure **203**, which afforded analogous results.

Scheme 64



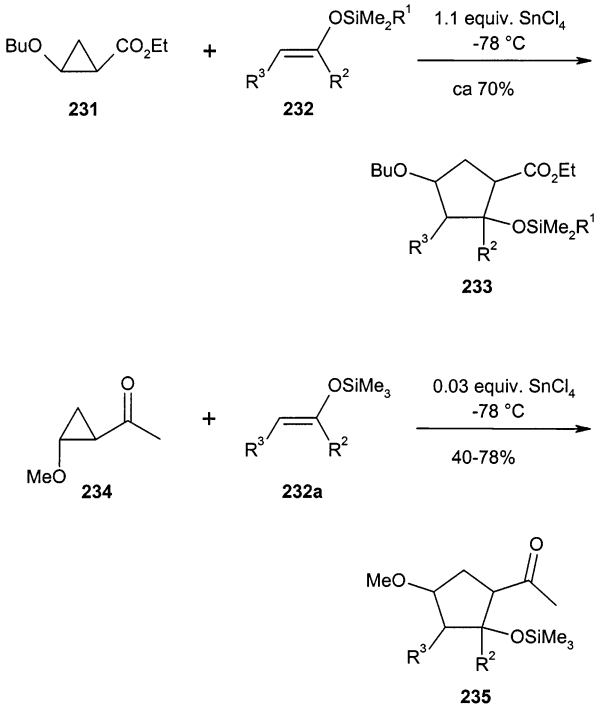
4. Reactions with Nucleophiles Including Formal Cycloadditions

Whereas electrophiles generally attack D−A cyclopropanes at the carbon bearing the acceptor group, nucleophiles react with the cyclopropane carbon

connected with the donor substituent (see Scheme 2 of the Introduction). Usually this latter process is also promoted by Lewis acids, which coordinate at the acceptor substituent and thus lead to ring cleavage and development of an electrophilic center capable of combining with the nucleophile.

A formal [3 + 2] cycloaddition was possible starting from D−A cyclopropane **231** and silyl enol ethers **232**, which upon treatment with 1.1 equiv of $SnCl_4$ provided the corresponding cyclopentane derivatives **233** as mixtures of diastereomers (Scheme 65). The

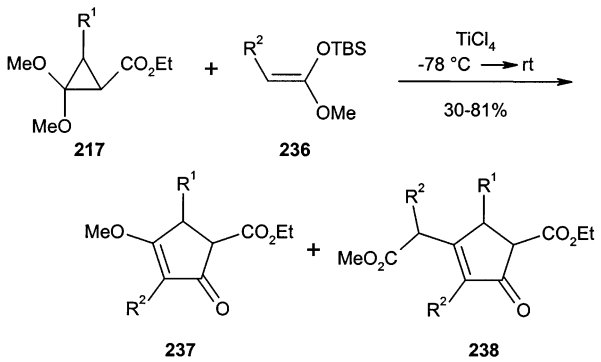
Scheme 65



analogous reaction was observed with cyclopropyl ketone **234**, which furnished cyclopentyl ketones **235** in moderate to good yields. Here catalytic quantities of the Lewis acid were sufficient. The products **233** and **235** served as versatile starting materials that afforded cyclopentene and cyclopentadiene derivatives by base-assisted elimination.[116]

A similar reaction mode was observed when D−A cyclopropane **217** was combined with ketene silyl acetals **236** in the presence of $TiCl_4$ (Scheme 66). A subsequent elimination was inevitable, which led to

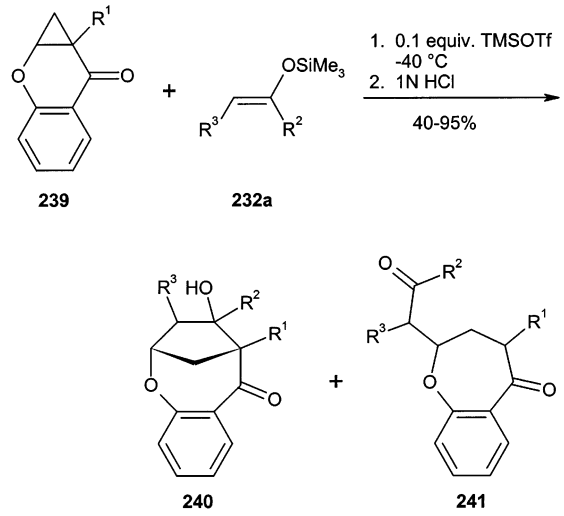
Scheme 66



cyclopentene derivatives **237**. In several examples an additional substitution product **238** was formed that incorporates a second equivalent of the nucleophilic olefin.[117]

If substituents R^1−R^3 at both components were not too bulky, reaction of 2,3-methanochromanones **239** with silyl enol ethers **232a** in the presence of 10% of trimethylsilyltriflate provided formal [3 + 2] cycloadducts **240** (Scheme 67). Otherwise dicarbonyl compounds **241** were isolated as major or exclusive products.[118]

Scheme 67



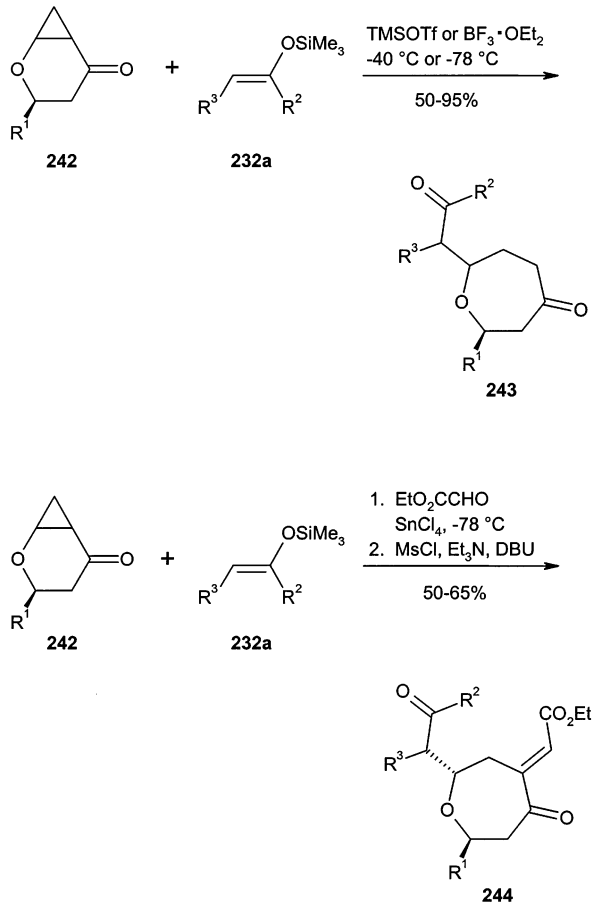
This reaction mode was observed when cyclopropapyranone **242** and silyl enol ethers **232a** or ketene silyl acetals were activated by BF_3, trimethylsilyltriflate, or $SnCl_4$. The resulting 4-oxepanone derivatives **243**—formed mainly as trans-isomers—were isolated in moderate to good yield.[119] The Lewis acid-promoted reaction of cyclopropapyranones **242** with silyl enol ethers **232a** could be extended to a three-component reaction by introducing ethyl glyoxylate to the mixture. Subsequent elimination gave trisubstituted 4-oxepanones **244** with an *exo*-alkylidene group. The intermediate enolate derived from the D−A cyclopropane **242** was trapped by the aldehyde in an aldol reaction. All four stereoisomers of **244** were formed, the isomer depicted in Scheme 68 being isolated as the major component.[120]

Cyclopropanedicarboxylate **245** was treated with $TiCl_4$ and several allyl silanes **246**, providing a mixture of the formal [3 + 2] cycloadducts **247** and the acyclic component **248** (Scheme 69). The ratio of these two products strongly depended on the bulkiness of the silyl substituents: with allyltrimethylsilane, **248** was the major product, whereas cyclopentane derivative **247** was formed exclusively with allyltriisopropylsilane as the nucleophilic component.[121] Similar observations were made with methanochromane **239** (Scheme 67).

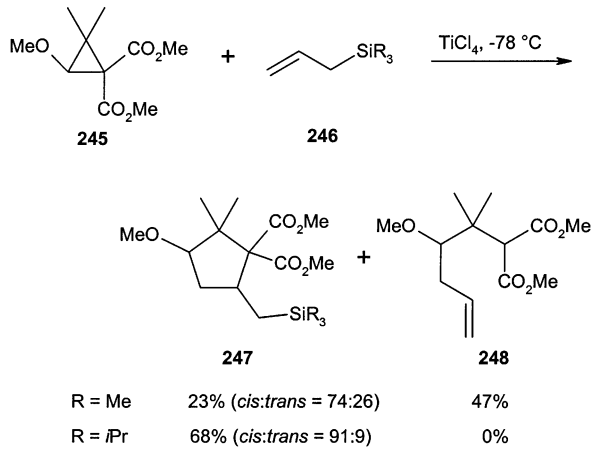
5. Reactions with Radicals Including Polymerizations

Surprisingly, only a few reactions of D−A cyclopropanes involving radicals as intermediates are

Scheme 68



Scheme 69

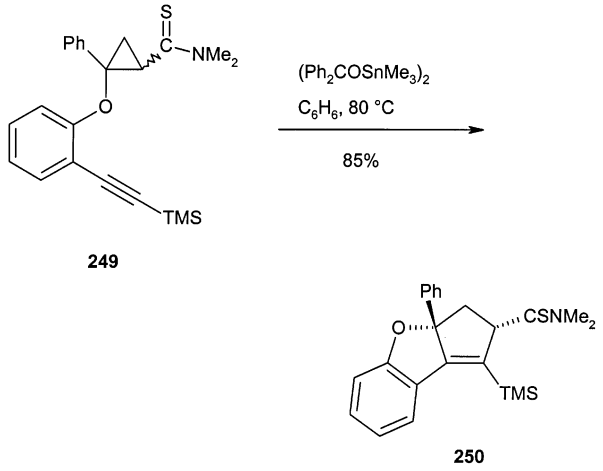


R = Me	23% (*cis*:*trans* = 74:26)	47%
R = *i*Pr	68% (*cis*:*trans* = 91:9)	0%

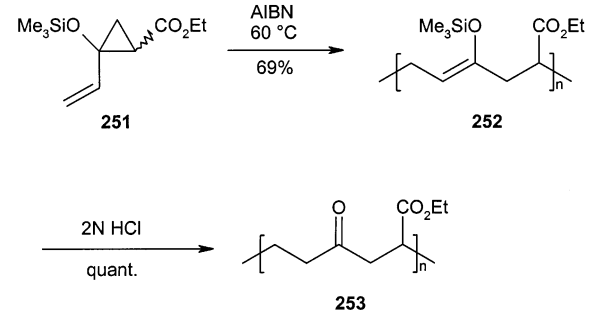
known. Transformation of cyclopropyl thioamide **249** into tricyclic product **250**—representing the skeleton of the natural product rocaglamide—starts with a trimethyltin radical-induced cyclopropane cleavage followed by addition of the resulting benzylic radical to the triple bond and readdition of the vinyl radical to form the cyclopentene derivative **250** (Scheme 70). The process constitutes an overall [3 + 2] cycloaddition.[122]

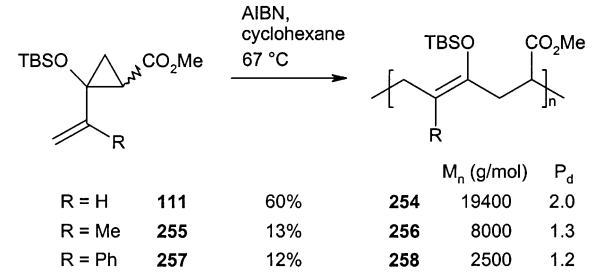
Endo et al. reported a novel AIBN-induced ring-opening polymerization of ethyl 2-siloxy-2-vinylcyclopropanecarboxylate **251** providing the respective poly(silyl enol ether) **252** in good yield and with

Scheme 70



Scheme 71





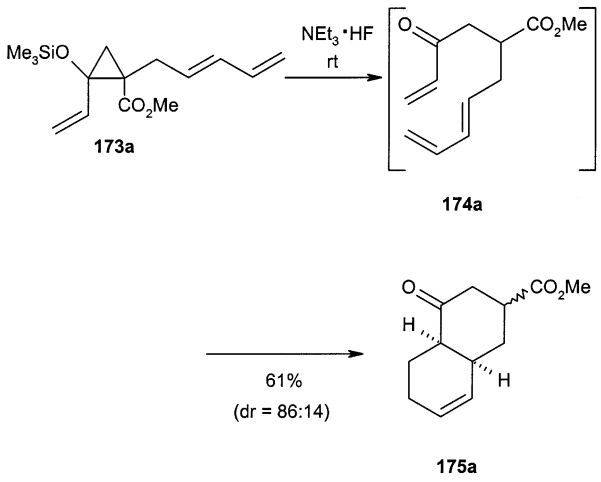
				M_n (g/mol)	P_d
R = H	**111**	60%	**254**	19400	2.0
R = Me	**255**	13%	**256**	8000	1.3
R = Ph	**257**	12%	**258**	2500	1.2

moderate molecular weights (M_n up to 10 440 g/mol) (Scheme 71). The product could be converted into polyketo esters **253** by treatment with acid or fluoride.[123] The related methyl esters **111**, **255**, and **257**, which provide more stable polymeric *tert*-butyldimethylsilyl enol ethers **254**, **256**, and **258**, were investigated in more detail.[124] Whereas the parent compound **111** furnished the expected poly(enol ether) **254** in reasonable yield and with relatively high molecular weights (19 400 g/mol in solution and up to 42 000 g/mol, when the polymerization was performed without solvent), the higher substituted vinylcyclopropanes **255** and **257** gave the polymers **256** and **258** in low yield only and with drastically decreased M_n values. Therefore, this approach to poly(silyl enol ethers) and subsequently to polyketo esters seems to be rather limited, since monomers **111** or **251** were the only precursors giving moderate molecular weights.

D. Combined Cleavage and Transformation to Advanced Products, Sequential Reactions, Multicomponent Reactions

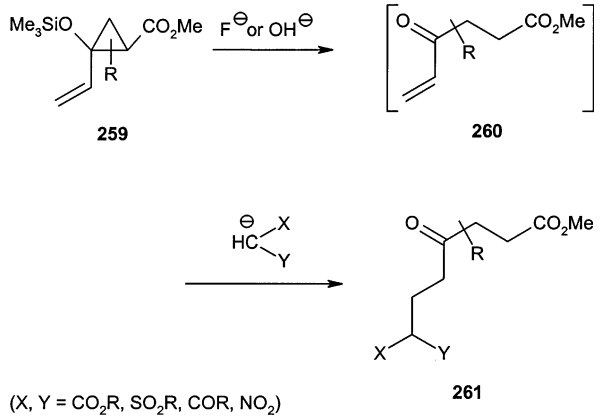
Generation of reactive enone esters of type **174** from alkenyl-substituted siloxycyclopropanecarboxylates **173** was already presented in section III.C (see Scheme 49). The resulting compounds are very useful starting materials for intramolecular Diels–Alder reactions. In case of compound **173a**, ring cleavage to **174a** was immediately followed by stereoselective intramolecular cycloaddition, leading to bicyclic compound **175a** in moderate yield and diastereoselectivity (Scheme 72).[88]

Scheme 72



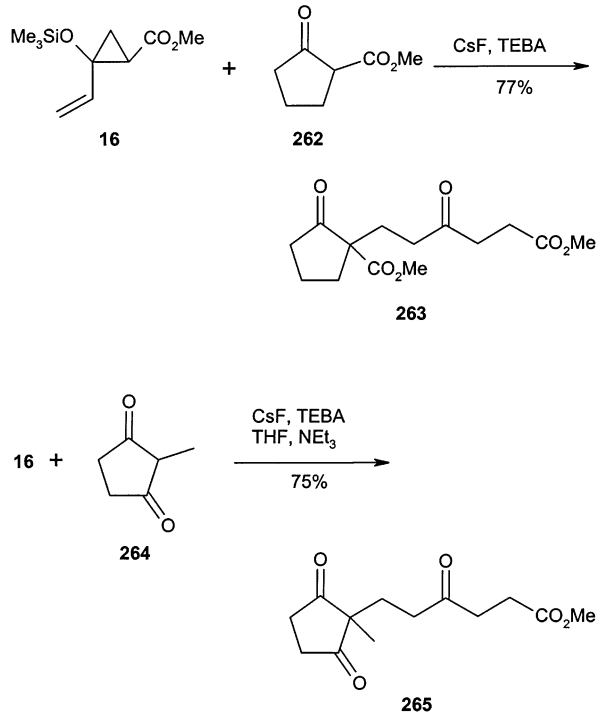
Enones **260**, generated by ring opening of alkenyl-substituted siloxycyclopropanes **259**, were also efficiently trapped by CH-acidic compounds (Scheme 73). They undergo Michael additions, affording the

Scheme 73

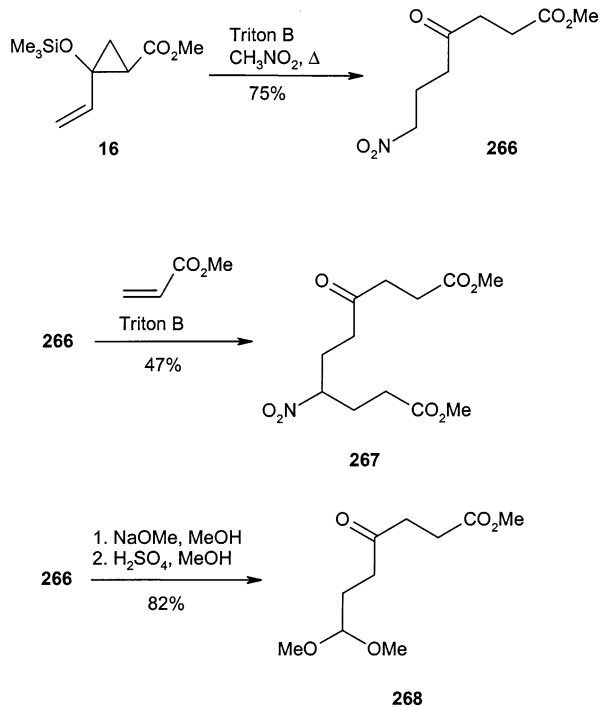


expected polyfunctionalized compounds **261**. Two examples are shown in Scheme 74: cesium fluoride-promoted reactions of vinylcyclopropane **16** with the two cyclic ketones **262** and **264** in the presence of triethylbenzylammonium chloride (TEBA) led to tetracarbonyl compounds **263** and **265** in good yield.[125] Adducts of vinylcyclopropanes of general structure **259** with nitroalkanes served as particularly versatile intermediates for a variety of subsequent reactions. Parent vinylcyclopropane **16** and nitromethane provided Michael adduct **266** in high yield, which could

Scheme 74



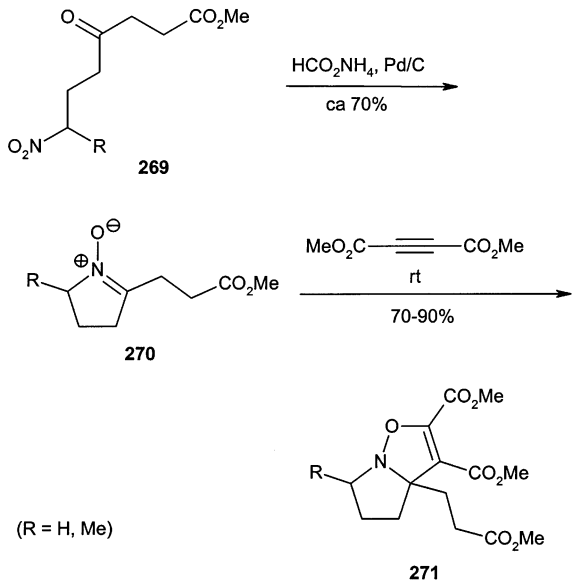
Scheme 75



be further substituted to diester **267** by a second 1,4-addition to methyl acrylate (Scheme 75).[126,127] By Nef reaction intermediate **266** was also converted into acetal **268**. Similar transformations of other polyfunctionalized nitro compounds obtained via this route produced building blocks for prostaglandins or the antibiotic macrolide pyrenophorin (see section V.E, Scheme 143).[128]

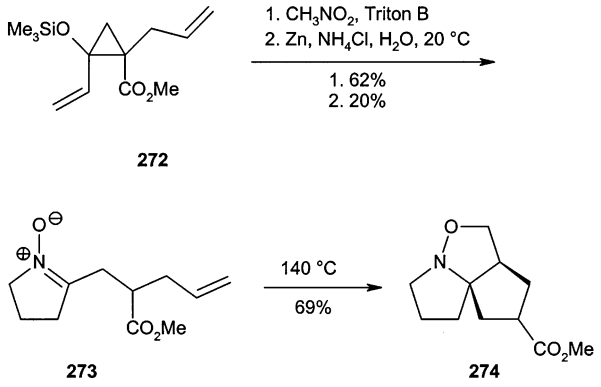
By use of ammonium formate and Pd/C as catalyst, nitroalkane adducts of type **269** were efficiently converted into cyclic nitrones **270**, which undergo 1,3-dipolar cycloadditions to functionalized isoxazole

Scheme 76



derivatives (Scheme 76). Thus, reaction of **270** with dimethyl acetylenedicarboxylate furnished bicyclic products **271** in good yield. Monosubstituted alkenes as dipolarophiles gave mixtures of regio- and stereoisomeric isoxazolidines. Intramolecular cycloaddition of nitrone **273** afforded a good yield of tricyclic compound **274** as a 55:45 mixture of diastereomers. The ultimate starting material in this sequence was siloxycyclopropane **16**, which was allylated to provide compound **272** with the required dipolarophilic side chain. Whereas its ring cleavage combined with Michael addition of nitromethane proceeded without problems, nitrone **273** had to be generated by the less efficient zinc/ammonium chloride method (Scheme 77).[129]

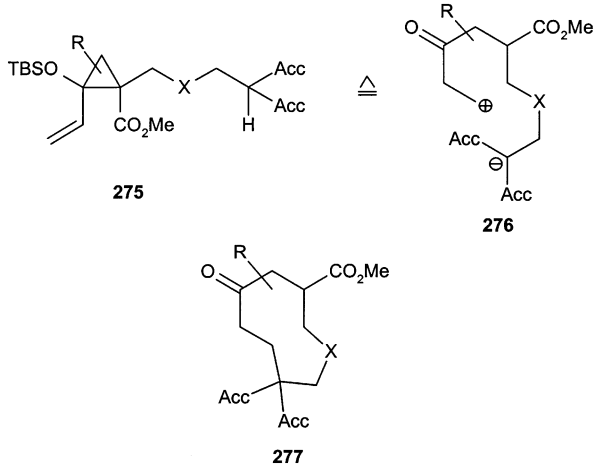
Scheme 77



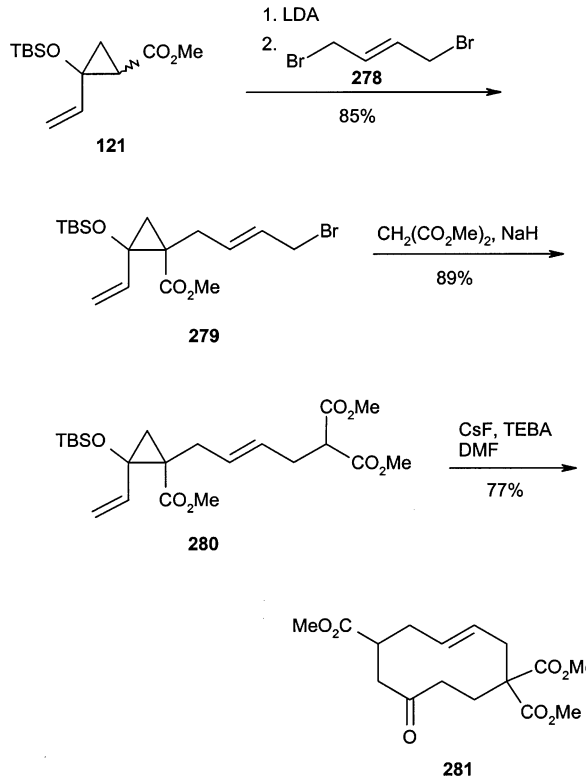
Trapping of siloxycyclopropane-derived enones may also be achieved in an intramolecular fashion. This concept uses suitably substituted alkenylcyclopropanes **275** as equivalent of a 1,n-dipolar synthon **276** (Scheme 78). Apt reaction conditions should lead to the intramolecular Michael adducts **277**. This approach worked nicely and allowed synthesis of a variety of highly functionalized medium- and large-ring compounds in a highly flexible modular fashion.[130,131]

Precursor **280** of cyclodecenone derivative **281** was prepared as illustrated in Scheme 79. Deprotonation

Scheme 78



Scheme 79

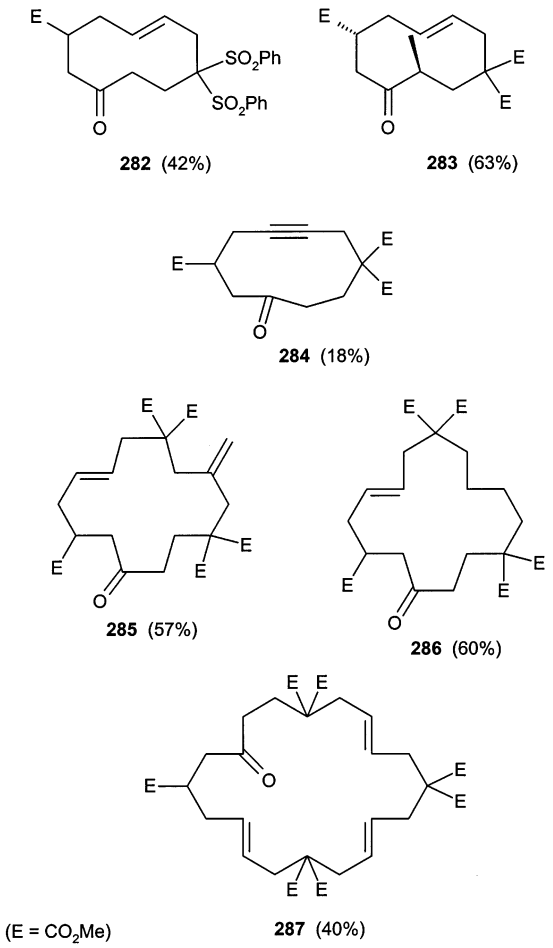


and alkylation of siloxycyclopropane **121** with a reactive dibromide **278** led to building block **279** in good yield, which was further equipped with the required pronucleophilic moiety by base-assisted reaction with dimethyl malonate, giving crucial precursor **280** in excellent overall yield. Its exposure to cesium fluoride under high-dilution conditions induced the anticipated ring-opening/ring-closure cascade reaction, affording the desired cyclodecenone derivative **281** in surprisingly high yield. Performing this reaction without dilution led to formation of **281** in only 11% yield, with the corresponding dimer as major product (24% yield). Even low amounts (8%) of the trimer could be isolated.[131]

In a similar fashion, other pronucleophilic units replacing the dimethyl malonate moiety, different spacer elements, and other siloxycyclopropane derivatives were examined. Intermediates **279** and **280**

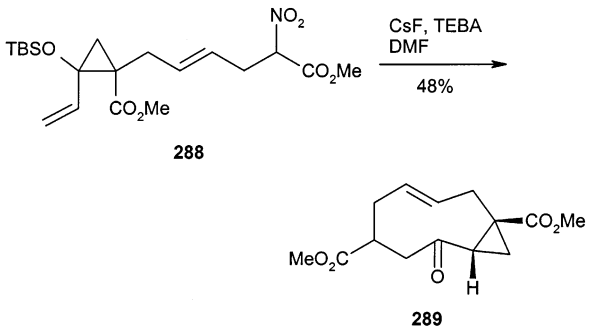
were also used for the construction of extended cyclization precursors required for syntheses of large-ring compounds. Typical products **282**−**287** are collected in Scheme 80; the recorded yields refer to the crucial ring-opening/cyclization step with cesium fluoride under high dilution.[131,132]

Scheme 80



With D−A cyclopropane **288** bearing a nitro ester side chain, an unusual transformation into bicyclic compound **289** was observed (Scheme 81). Here the

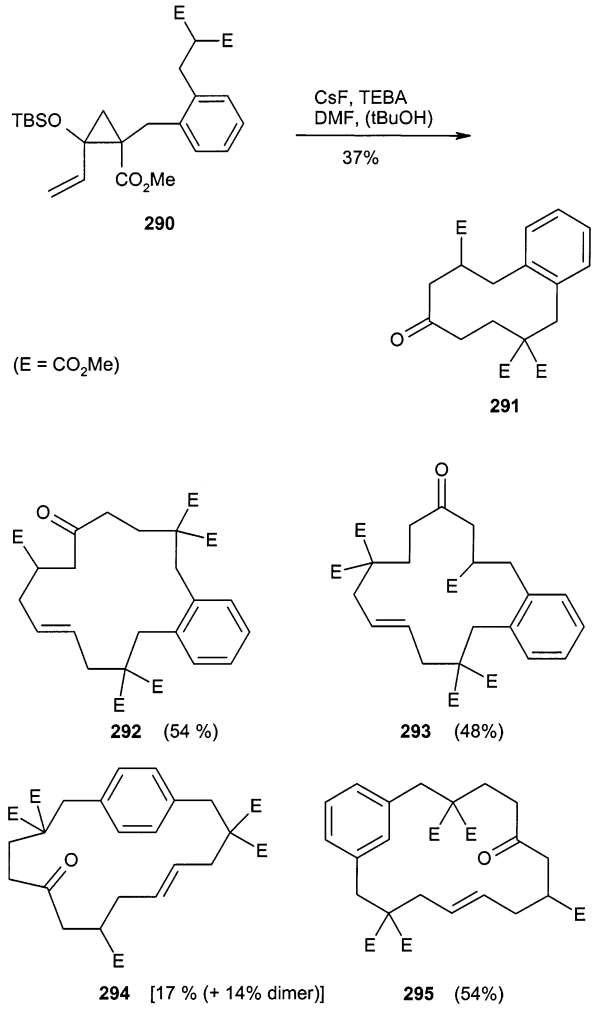
Scheme 81



ring-opening/ ring-closure cascade was apparently followed by a second ring closure with the nitrite anion as leaving group forming the new cyclopropane ring of **289**.[131]

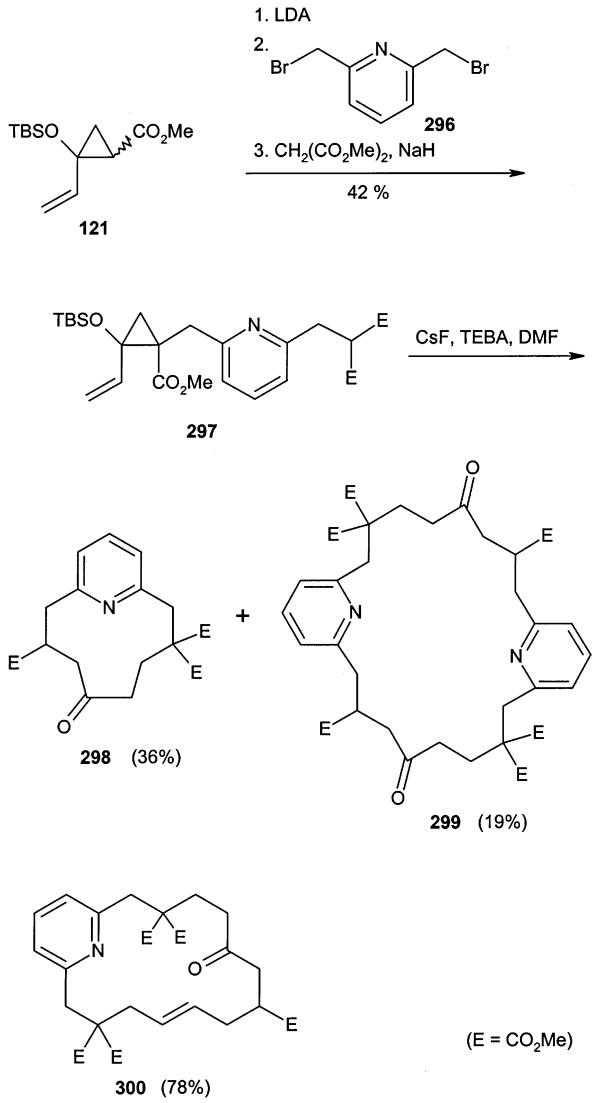
Only in instances did introduction of aromatic rings into the spacer unit of the precursor cyclopropanes allow conversion into large-ring compounds. While ortho-substituted precursor **290** could be transformed into benzannulated cyclodecanone derivative **291** in 37% yield, the corresponding meta- and para-substituted compounds afforded only dimeric macrocycles in low yield. However, introduction of a second spacer element made the ring closure again more efficient. Macrocycles **292**−**295**, which may also be classified as functionalized cyclophane derivatives, were isolated in moderate to good yields, as indicated in Scheme 82.[133]

Scheme 82

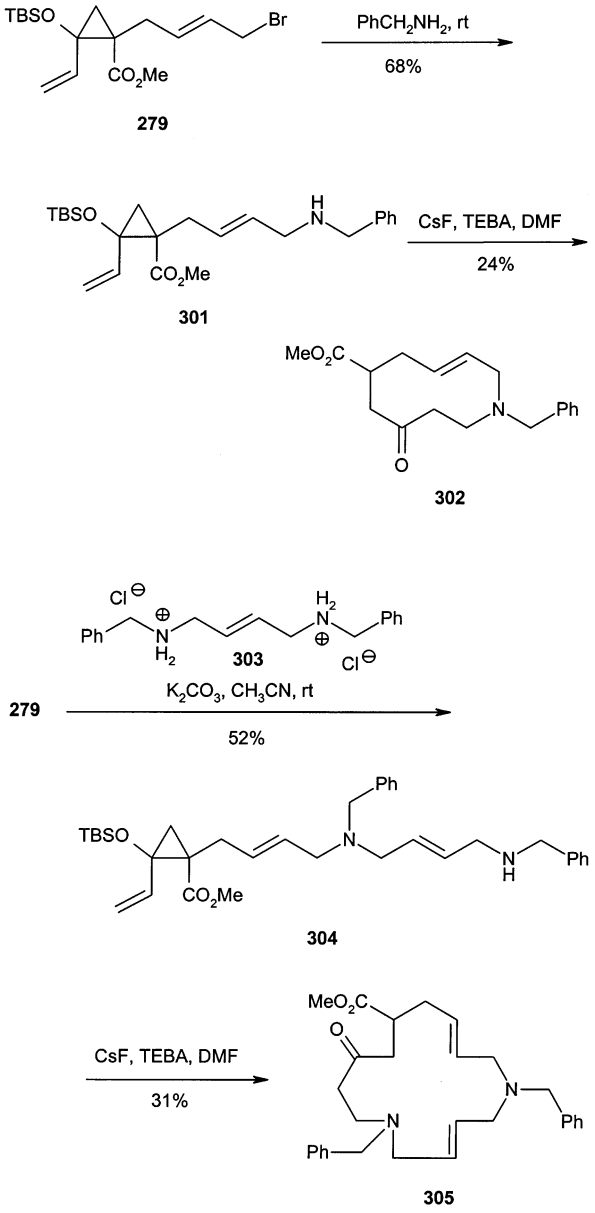


Interestingly, meta-substituted pyridine derivative **297** could again undergo the desired ring-cleavage/ ring-closure cascade reaction. It was easily available from parent vinylcyclopropane **121** by stepwise substitution with 2,6-bis(bromomethyl)pyridine (**296**) and dimethyl malonate (Scheme 83). Standard reaction conditions led to formation of [8](2,6)pyridinophane **298** in surprisingly high yield of 36%, together with the dimer **299**. The yield of dimer **299** could be slightly increased to 28%, if the reaction was performed without dilution. This modular approach toward macroheterocyclic compounds was also employed for construction of [13](2,6)pyridinophane **300**, which arose in excellent yield from a precursor closely related to **297**, but incorporating an additional C_5 spacer.[133]

Scheme 83



Scheme 84

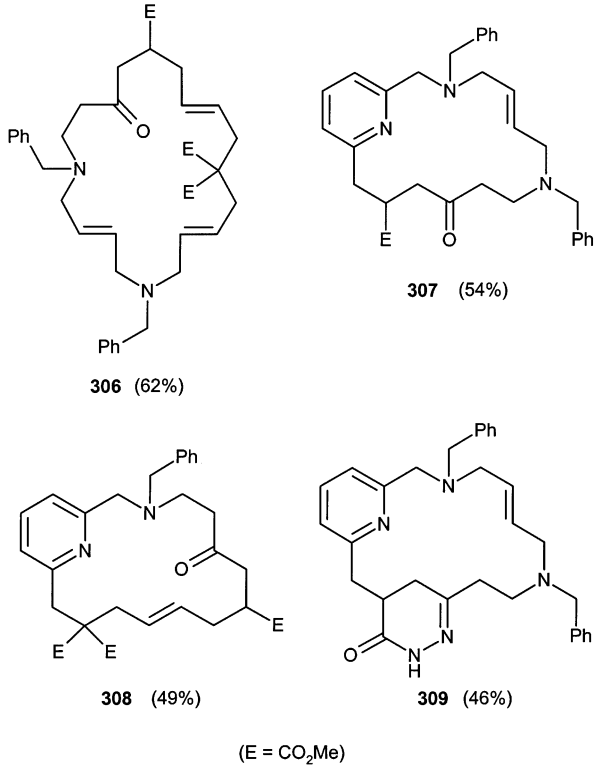


Whereas the extension of this concept was not successful for the construction of oxygen- and sulfur-containing macroheterocycles,[134,135] it could very nicely be applied to the preparation of a variety of large-ring compounds incorporating one or more nitrogen atoms. For this purpose, the dimethyl malonate unit of precursor compounds was substituted by a benzylamine moiety, which now served as a nucleophile in the ring-closure step. In Scheme 84, the principle synthetic route is illustrated. Bromide **279** (see Scheme 79) was treated with an excess of benzylamine, thus providing the required secondary amine **301**. Compound **301** was used for the ring-cleavage/ring-closure cascade, furnishing azecine derivative **302** in low yield together with the dimer. Alternatively, **301** may be chain-elongated and then leads to compounds better suitable for ring closure.[136,137] Reaction of bromide **279** with 1,4-(dibenzylamino)-2-butene dihydrochloride (**303**) furnished cyclopropane derivative **304** in reasonable yield, which was converted into the 15-membered ring **305** incorporating two nitrogen atoms, with moderate efficiency. Following this general modular approach for construction of the precursors, other macroheterocycles, e.g. **306**−**308**, were synthesized (Scheme 85). By treatment with hydrazine hydrate, pyridinophane **307** was transformed into macrocyclic pyridazinone **309** in moderate yield. These reaction sequences have obvious potential for preparation of large heterocycles that are difficult to obtain by alternative methods.[137]

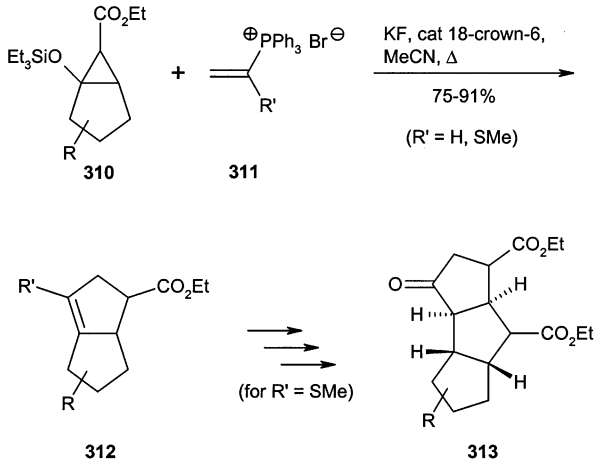
Fluoride-promoted ring opening of siloxycyclopropane **310** under aprotic conditions in the presence of vinylphosphonium salts **311** furnished cyclopentene derivatives **312** in good yields (Scheme 86). Here, the intermediate ester enolate generated by desilylation and ring cleavage underwent a Michael addition followed by an intramolecular Wittig reaction. For compound **312** with R′ = SMe, conversion into a ketone allowed repetition of the sequence, leading to tricyclic compounds such as **313**.[138]

A second approach to bicyclic derivatives involves easily accessible silyl enol ethers **314**. Their cyclopropanation smoothly furnished siloxycyclopropanes **315** formed without interference of the dienyl side chain (Scheme 87). Fluoride-assisted ring cleavage

Scheme 85



Scheme 86

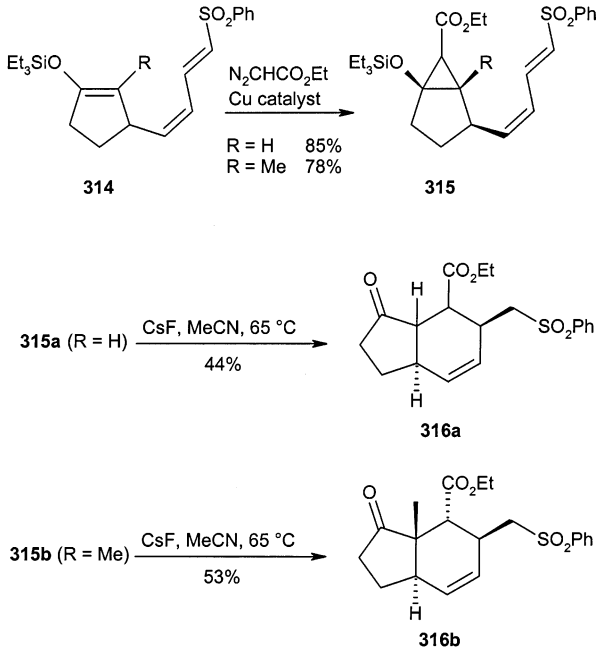


provided hydrindenone derivatives **316** in moderate yields. They were formed during this cascade process by intramolecular reaction of the ester enolate with the alkenyl sulfone moiety controlling the regioselectivity. The stereoselectivity of the process depends on substituent R.[139]

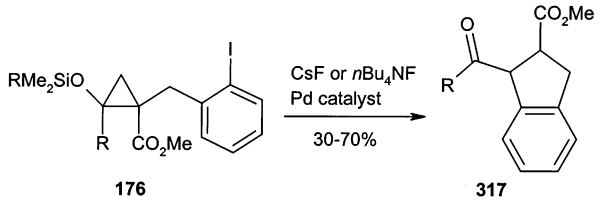
With iodo compounds **176** (see Scheme 50) a palladium-catalyzed ring-transformation process was detected. In situ ring opening by fluoride followed by an intramolecular enolate arylation gave 1,2-disubstituted indane derivatives **317** in moderate yield (Scheme 88).[140]

Preparation of *β*-formyl esters **162**, which are difficult to obtain by alternative methods, was already illustrated in Scheme 46. Since *trimethylsiloxy*cyclopropanes **318** undergo slow desilylation in protic solvents such as methanol, in situ generation and trapping of *β*-formyl esters was exploited in Ugi

Scheme 87

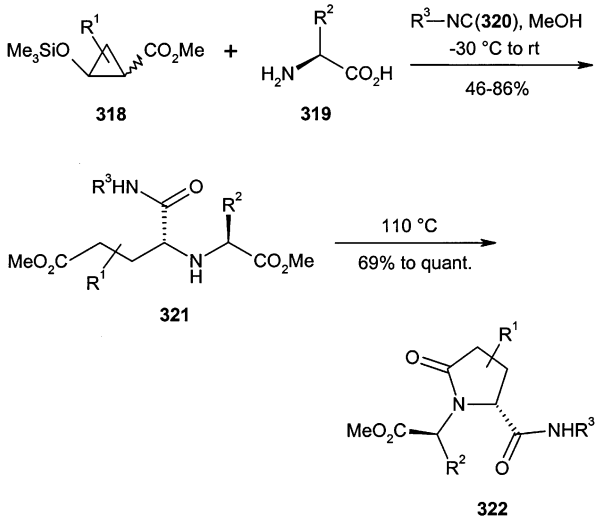


Scheme 88



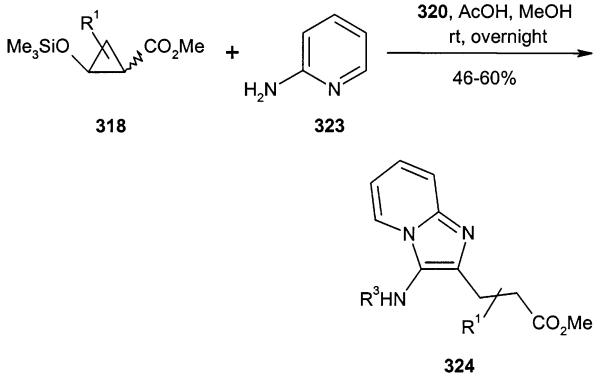
four-component reactions,[141] leading to new highly functionalized peptide-like compounds. Combination of α-amino acids **319** with suitable siloxycyclopropanecarboxylates **318** as aldehyde precursors and isonitriles **320** in methanol furnished amino acid derivatives **321** in moderate to good yields and as mixtures of diastereomers (the major isomer is presented in Scheme 89). These compounds could thermally be cyclized to provide the pyroglutamine derivatives **322**. The synthesis of **322** can also be executed as a one-pot transformation without isolation of **321**, which may be classified as a six-center–four-component reaction.[142]

Scheme 89



A similar Ugi multicomponent process uses siloxycyclopropanecarboxylates **318** together with 2-aminopyridine **323** and isonitriles **320** (Scheme 90). The

Scheme 90



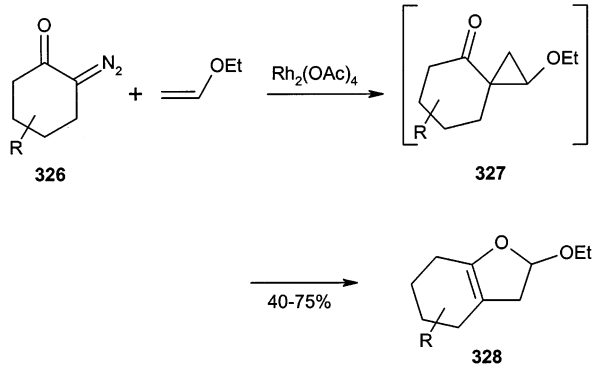
pyridinoimidazole derivatives **324** were obtained in moderate to good yields and may be regarded as dipeptide isosters.[143] Preliminary experiments also demonstrated that the equivalency of siloxycyclopropanecarboxylates **318** with functionalized aldehydes can be exploited for Gewald reactions.[144] Treatment of **318a** with fluoride followed by addition of methyl cyanoacetate, sulfur, and base gave the expected functionalized aminothiophene **325** in reasonable overall yield.[143] This conversion may be classified as a six-center−three-component reaction. Functionalized products of type **324** and **325** may serve as suitable starting materials for a variety of subsequent transformations. Therefore siloxycyclopropanes **318** and their one-pot conversions into heterocyclic compounds should have considerable potential for sequential reactions[145] and also lead to diversity-oriented organic synthesis.[146]

E. D–A Cyclopropanes as Transient Intermediates

1. (Formal) Pericyclic Reactions

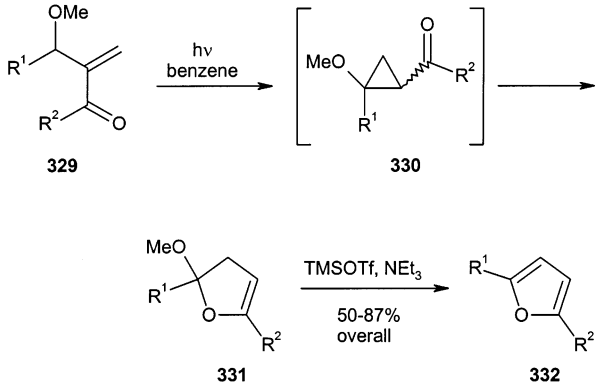
Donor-substituted cyclopropyl ketones are often not stable and undergo fast 1,3-rearrangements into the corresponding dihydrofuran derivatives, a sequence which was occasionally used for synthetic purposes. For instance, metal-catalyzed reactions of cyclic diazoketones **326** with ethyl vinyl ether afforded dihydrofurans **328** with fair efficiency (Scheme 91). In one case, the intermediate cyclopropyl ketone **327** was isolated and its smooth rearrangement to the dihydrofuran was demonstrated, suggesting that D−A cyclopropanes are generally intermediates in these formal [3 + 2] cycloadditions.[147] This may also be the case in a related synthesis of fluoroalkyl-substituted dihydrofuran derivatives.[148]

Scheme 91



An interesting route to 1,4-disubstituted furans employed Baylis−Hillman products **329** as starting materials, which were converted into dihydrofurans **331** via cyclopropyl ketones **330** (Scheme 92). The

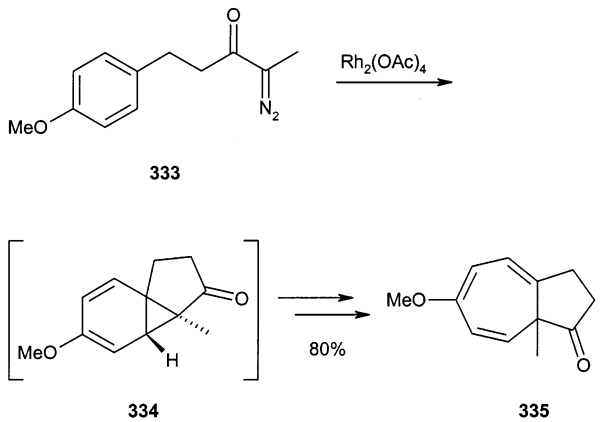
Scheme 92



crucial step is the photochemical conversion of **329** into **330**, which involves diradicals. Trimethylsilyltriflate treatment of **331** caused elimination of methanol and finally provided furans **332** in good overall yield.[149]

D−A cyclopropanes are also intermediates in intramolecular Buchner additions of diazo ketones to electron-rich aryl substituents. As a typical example, rhodium(II) acetate-catalyzed decomposition of diazo ketone **333** provided azulenone **335** in good yield (Scheme 93). Cyclopropane intermediate **334** suffers a ring cleavage of the norcaradiene−cycloheptatriene type, thus affording bicyclic product **335**. A detailed

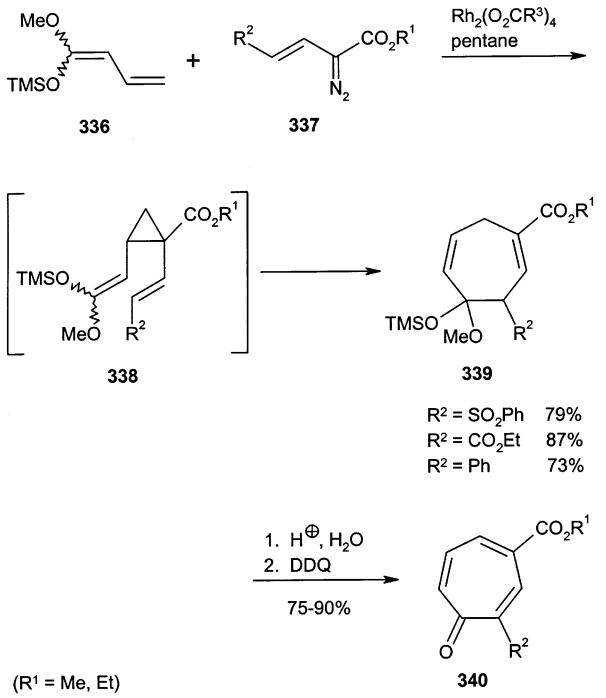
Scheme 93



study with substituted precursor compounds revealed interesting stereochemical aspects.[150]

Combining alkenyl-substituted diazo compounds with suitably substituted dienes, Davies et al. developed an elegant and very versatile tandem cyclopropanation−Cope sequence, which by 3,3-sigmatropic rearrangement directly leads to cycloheptadiene derivatives.[151] Among the many examples provided by this group, several sequences with involvement of D−A cyclopropanes were presented. Tropone derivatives such as **340** with rather differing substitution pattern were prepared by reaction of alkenyl-substituted diazoacetates **337** with 1,3-dienes such as **336** (Scheme 94). Rhodium(II) catalysis provided the

Scheme 94



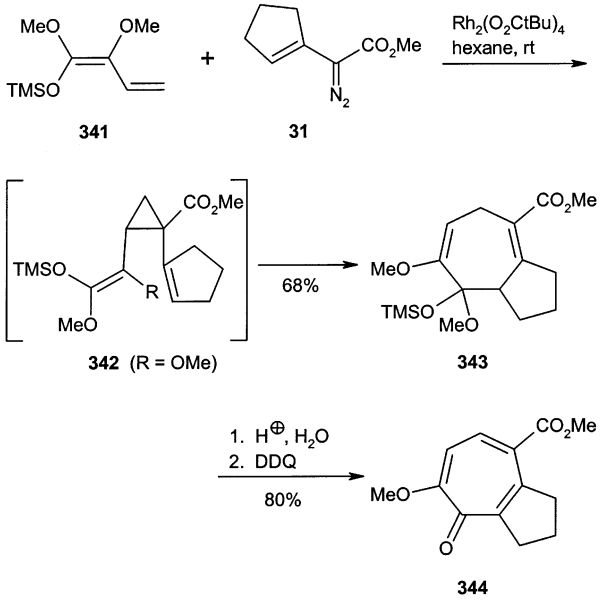
intermediate *cis*-dialkenylcyclopropane **338**, which immediately rearranges to product **339.** Its treatment with acid and oxidation with DDQ provided the desired tropolones **340** in good overall yield.[152]

Similarly, mono- and bicyclic tropolone derivatives are accessible when 1,3-dienes with additional alkoxy groups were employed as starting material. Rhodium(II)-catalyzed decomposition of cyclopentenyl-substituted diazoacetate **31** in the presence of 1,3-diene **341** furnished bicyclic product **343** via intermediate **342** (Scheme 95). Again, hydrolysis and oxidation afforded tropolone derivative **344** in reasonable overall efficiency.[153]

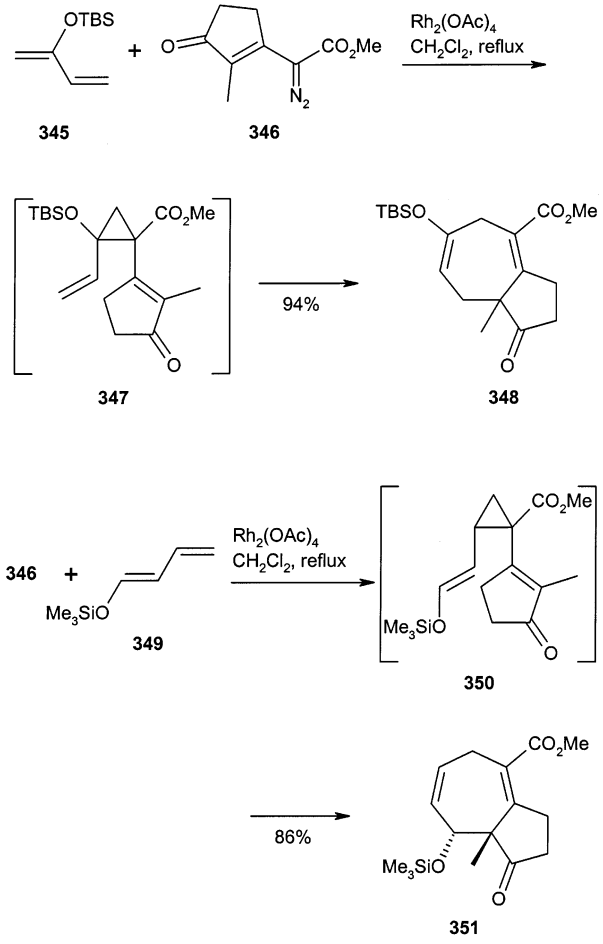
Hydroazulene derivatives are available when diazoacetates such as **346** reacted under rhodium(II) catalysis with 2-siloxy-1,3-butadiene (**345**) or 1-siloxy-1,3-butadiene (**349**) (Scheme 96). The ring-enlarged products **348** and **351** were obtained in excellent yields via the corresponding D−A cyclopropanes **347** and **350** as transient species.[154]

With furan as a special 1,3-diene and diazoacetate **35** bearing (*R*)-pantolactone as auxiliary, an asymmetric synthesis of the highly functionalized seven-membered ring compound **353** could be achieved,

Scheme 95



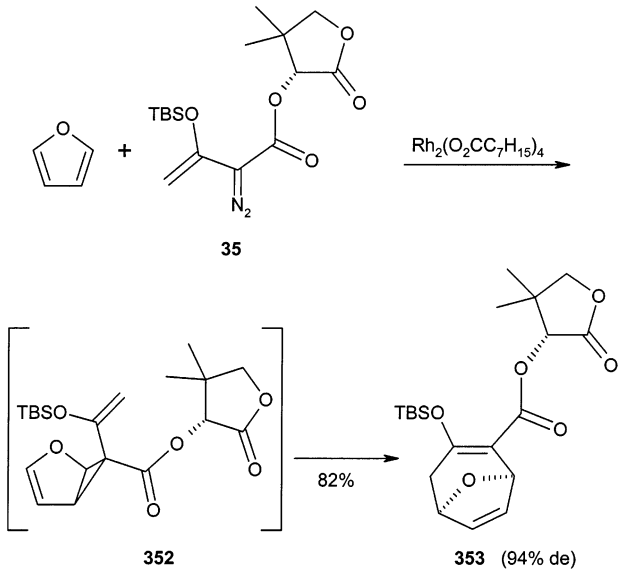
Scheme 96



cyclopropane **352** being the plausible intermediate (Scheme 97). The yield and the diastereomeric excess of 94% are very satisfying.[155]

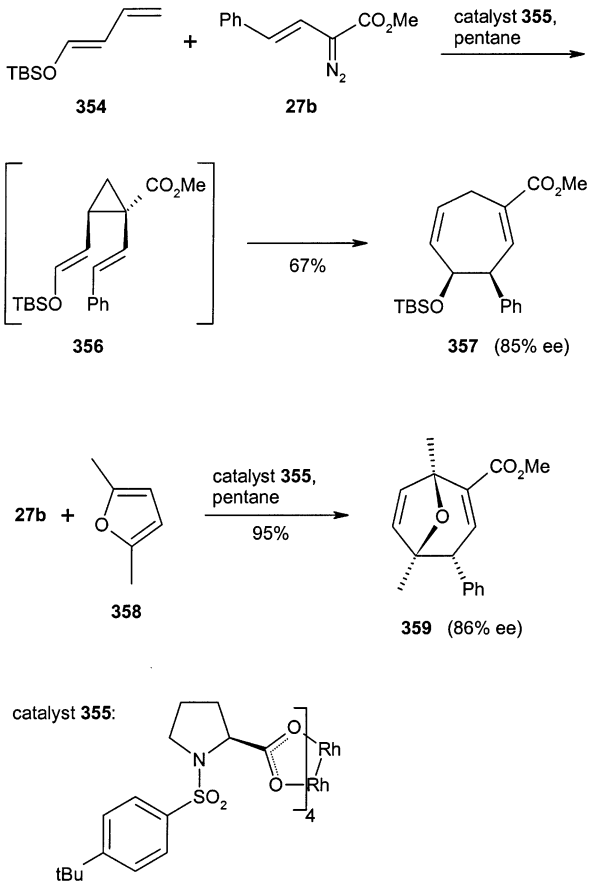
Not surprisingly, asymmetrically catalyzed reactions were also investigated employing the very successful rhodium prolinate complexes (see section II.A, Schemes 8 and 9). Decomposition of diazo compound **27b** in the presence of diene **354** and chiral

Scheme 97



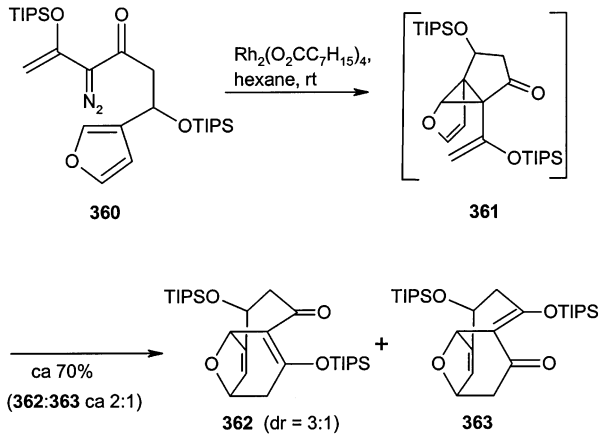
rhodium catalyst **355** provided—via cyclopropane **356**—cycloheptadiene **357** with 85% ee (Scheme 98). Reaction of **27b** with 2,5-dimethylfuran (**358**) in the presence of catalyst **355** gave bicyclic product **359** in excellent yield and with a similarly high enantiomeric excess.[156]

Scheme 98



A rhodium(II)-assisted *intramolecular* cyclopropanation started from **360**, which contains a furan ring and a diazo ketone moiety. This led to a mixture of two Cope products **362** and **363** in good yield

Scheme 99

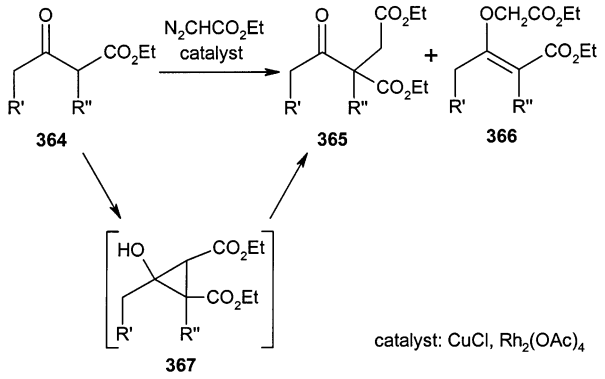


(Scheme 99). These two highly functionalized components differ in the location of the enol ether double bond and were both formed via the stereoselectively generated D−A cyclopropane **361** bearing two cis-located alkenyl groups.[157]

2. Polar Reactions Leading to γ-Keto Esters and Related Compounds

Several reactions are described in the literature where D−A cyclopropanes are very plausible transient intermediates. The catalyzed decomposition of ethyl diazoacetate in the presence of β-keto esters **364** provided mixtures of enol esters **366** and γ-keto esters **365**, which are formal products of a C−H insertion (Scheme 100). This result was interpreted

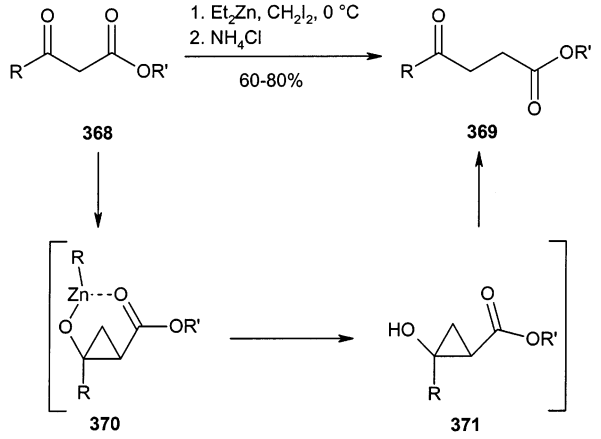
Scheme 100



as cyclopropanation of the enol form of **364** immediately followed by regioselective ring cleavage of the resulting unstable D−A cyclopropane **367**. The product distribution is strongly dependent on the catalyst employed and the structure (ring size) of the substrate **364**.[158]

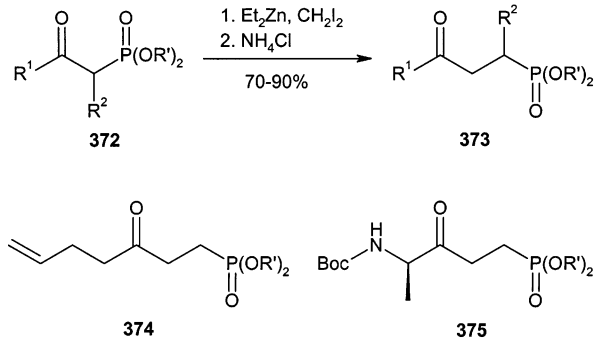
A similar homologation process is involved in reactions of β-keto esters **368** with Furukawa's reagent (diethylzinc/diiodomethane), which afforded γ-keto esters **369** in good yield (Scheme 101). It is plausible to assume that the zinc enolate derived from **368** is cyclopropanated to a species described as **370**, which by aqueous workup provides an unstable cyclopropanol **371**. Immediate ring opening finally furnishes the chain-extended keto ester **369**.[159] A similar process was reported for the related β-ketoamides.[160]

Scheme 101



In close analogy, β-keto phosphonates **372** were chain-elongated to γ-keto phosphonates **373** (Scheme 102). Again D−A cyclopropanes are rather plausible

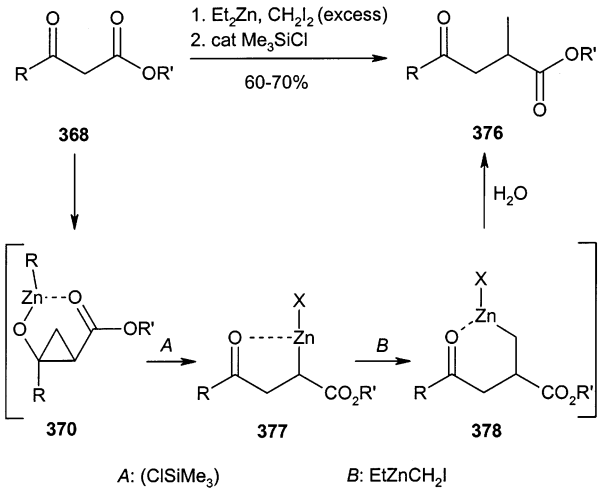
Scheme 102



transient species. Notably, compound **374** could be prepared under optimized conditions with only a low degree of the C,C-double bond cyclopropanation, and Boc-protected δ-amino-γ-keto phosphonate **375** was smoothly synthesized from the corresponding β-keto phosphonate.[161]

Even more exciting were experiments applying an excess of diethylzinc/diiodomethane to **368**, followed by addition of catalytic quantities of trimethylchlorosilane (Scheme 103). Products **376** incorporate two additional carbon atoms, and the

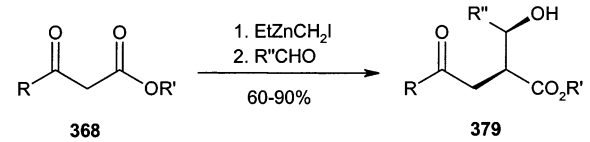
Scheme 103



overall process was therefore classified as a tandem chain extension/homoenolate reaction. The sequence is plausibly rationalized by formation of **370** (see Scheme 101), which undergoes ring opening to **377** (or an equivalent nucleophilic species) and can again react with the carbenoid to form new zinc species **378**. The exact effect of trimethylchlorosilane for these steps is not yet clear. Hydrolysis of **378** finally provides compound **376**.[162]

As a logical consequence of this mechanism, a tandem chain extension/aldol reaction was developed. Treatment of β-keto esters **368** with diethylzinc and diiodomethane followed by addition of aldehydes led to formation of the homologated aldol adducts **379** (Scheme 104). In this process the intermediate **377**

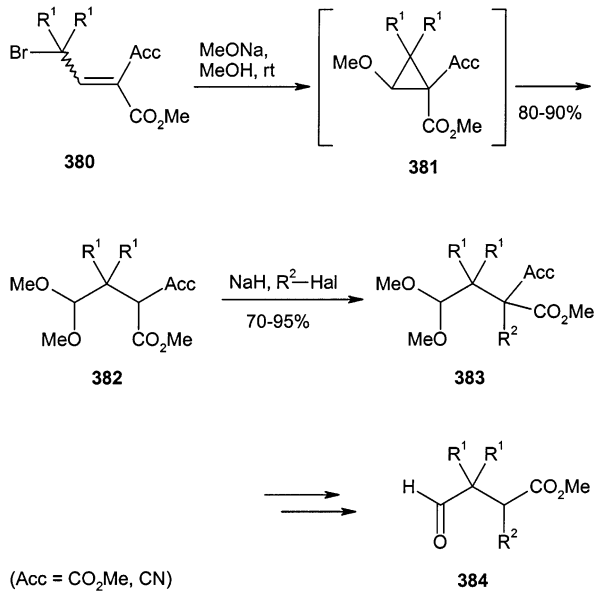
Scheme 104



(or its equivalent; see Scheme 103) was trapped by the aldehyde in a stereoselective fashion. Scheme 104 only shows the major *syn*-diastereomers of **379** formed in selectivities between 3:1 to > 20:1.[163]

By treatment with sodium methoxide unsaturated γ-bromo esters **381** were rearranged into acetals **382** (Scheme 105). Again, a D−A cyclopropane **381** is a

Scheme 105



highly plausible intermediate. The synthetically valuable building blocks **382** were further alkylated under standard conditions to furnish acetals **383**, which can be decarboxylated into monoesters and finally be converted into 3-formyl esters **384**.[164] This sequence to aldehydes of type **384** offers an interesting alternative to the route via siloxycyclopropanes **161** (see Scheme 46).

IV. Other D–A Cyclopropanes

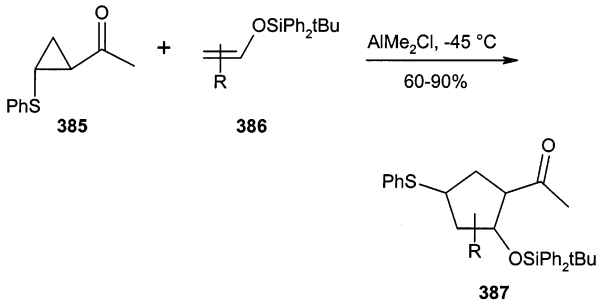
D−A cyclopropanes with donor groups other than oxygen or nitrogen substituents are synthetically not

very important. Only a limited number of examples will therefore be presented here. Acceptor groups other than those presented so far are sulfonyl groups and phosphorus substituents (for a few examples see section II.C).

A. Sulfur Substituents as Donor

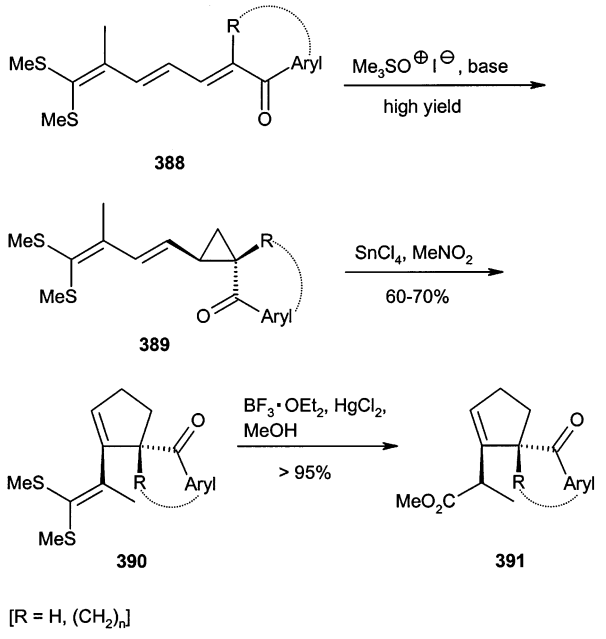
The Lewis acid-assisted formal [3 + 2] cycloaddition of D−A cyclopropanes with silyl enol ethers as described in Schemes 65−68 could also be performed with 2-phenylthiocyclopropyl ketone **385**. Reaction with **386** in the presence of dimethylaluminum chloride at low temperature afforded the expected cyclopentane derivatives **387** in good to excellent yields, but with varying diastereoselectivity (Scheme 106).[165]

Scheme 106



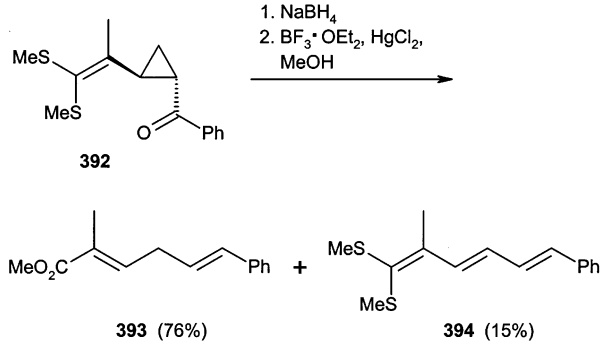
Donor−acceptor-substituted trienes **388** were regioselectively converted into cyclopropane derivatives **389** by treatment with oxodimethylsulfonium methylide (Scheme 107). The substitution pattern of

Scheme 107



cyclopropyl ketones **389** allowed Lewis acid-assisted ring enlargements, leading to the corresponding cyclopentene derivatives **390** in good yield. This rearrangement apparently requires the bis(methylthio)butadienyl group for sufficient stabilization of the carbenium ion site of an intermediate zwitterion, since the analogous cyclopropane derivative with a bis(methylthio)ethenyl group (see compound **392** in Scheme 108) did not undergo this transformation. Methanolysis of these intermediates provided δ-oxo esters **391** in excellent yields.[166]

Scheme 108

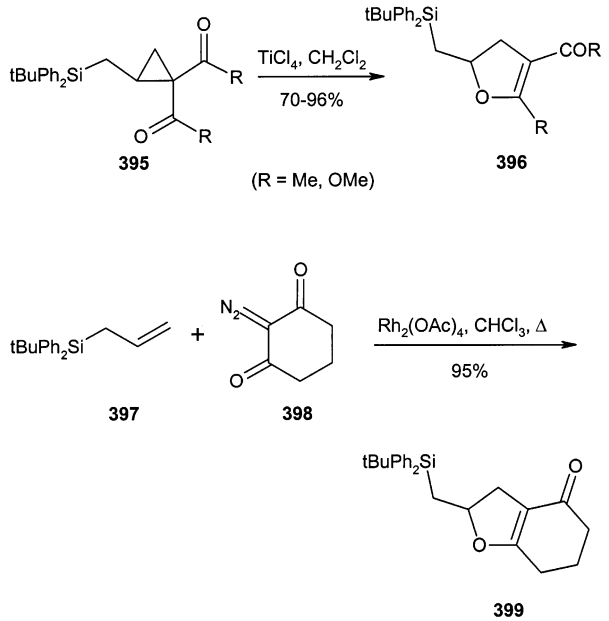


When D−A cyclopropanes such as **392** were treated with sodium borohydride or Grignard reagents, the resulting alcohols could be converted into unsaturated esters such as **393**. Ring cleavage by Lewis acid provided intermediate **394**, which was isolated as byproduct, and methanolysis finally gave compound **393**.[167]

B. Silylmethyl Substituents as Donor

Due to the β-effect of silicon a (trialkyl/aryl)-silylmethyl group can also be classified as donor substituent. Therefore, cyclopropyl diketones and diesters such as **395** show typical D−A cyclopropane behavior. Treatment of **395** with $TiCl_4$ induced ring enlargement and provided dihydrofuran derivatives **396** in good yield (Scheme 109). Rhodium(II)-promot-

Scheme 109

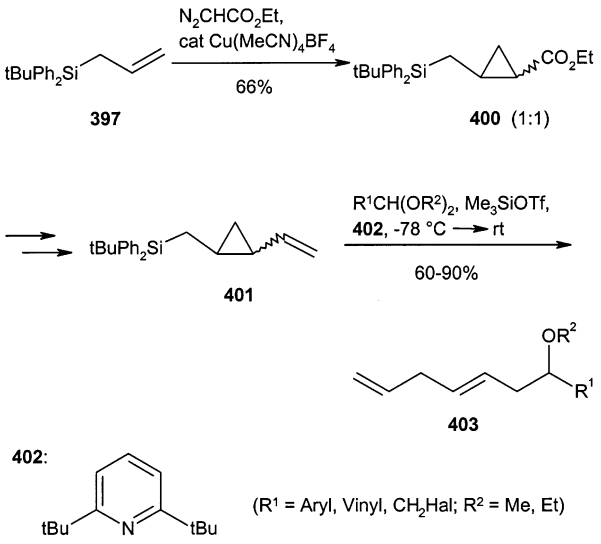


ed decomposition of 2-diazocyclohexane-1,3-dione **398** in the presence of allyl silane **397** did not furnish the corresponding cyclopropane derivative but directly led to bicyclic dihydrofuran **399**. The intermediate

D−A cyclopropane is probably too unstable and directly undergoes the ring enlargement (see section III.E.1).[168]

An interesting stereoselective synthesis of 1,4-dienes used silylmethyl-substituted vinylcyclopropane **401** as crucial precursor. This compound was easily prepared by cyclopropanation of allyl silane **397** and conversion of the resulting ethyl cyclopropanecarboxylate **400** into **401** by standard reactions (Scheme 110). Reaction of vinylcyclopropane **401** with

Scheme 110



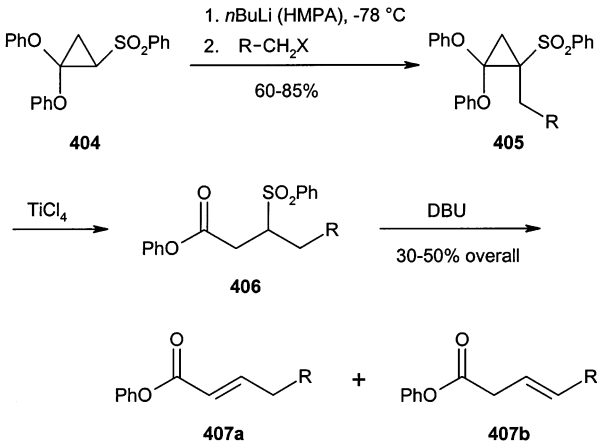
a variety of acetals in the presence of trimethylsilyltriflate and **402** occurred under ring opening and desilylation to provide dienes **403** in good yields and with excellent *E*-selectivity. The Lewis acid generates an oxocarbenium ion from the acetal, which attacks the vinyl group of **401**, thus inducing a ring cleavage of the cyclopropane (cf. Scheme 40).[169]

C. Other Groups as Acceptors

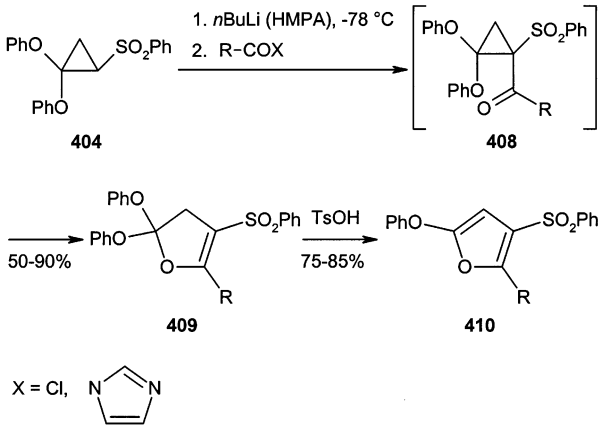
Although sulfonyl groups are strong electron-withdrawing substituents, only few examples are known exploiting this property in D−A cyclopropanes. Diphenoxy-substituted cyclopropylphenyl sulfone **404** could smoothly be deprotonated and subsequently treated with electrophiles. Reaction with alkylating agents provided new cyclopropane derivatives **405** in good yield (Scheme 111). Ring cleavage of these compounds proved to be difficult, but treatment with $TiCl_4$ allowed the expected conversion into ester **406**. This intermediate was further transformed by base-induced elimination to provide the final products **407a** (major) and **407b** (minor). In this sequence D−A cyclopropane **404** served as β-lithio acrylate equivalent after lithiation.[170]

Rather than giving the acylated cyclopropanes **408**, reaction of lithiated **404** with acyl halides or imidazolides directly led to their ring-enlarged products **409** in good to excellent yields (Scheme 112). Acid-promoted elimination of phenol allowed a straightforward preparation of interestingly functionalized furan derivatives **410**.[171]

Scheme 111

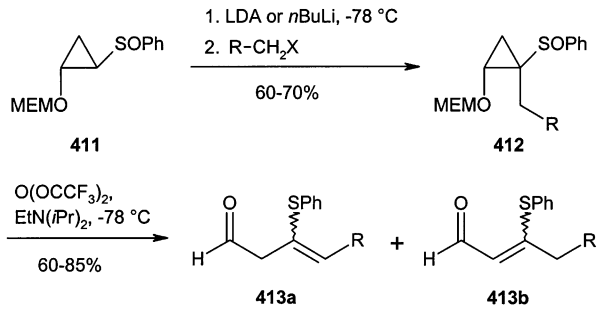


Scheme 112



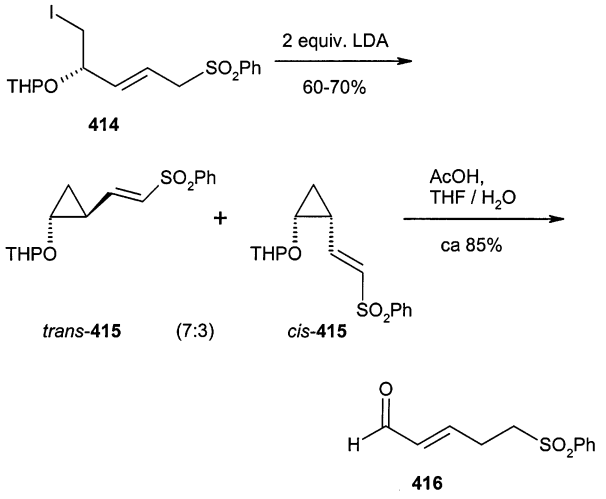
Related phenylsulfinyl cyclopropane **411** (1:1.5 mixture of diastereomers with respect to the SO unit) was similarly lithiated and treated with alkylating agents. By treatment with trifluoroacetic acid anhydride and Hünig base, the resulting products **412** suffered ring cleavage in a Pummerer-type reaction and furnished unsaturated aldehydes **413a** (major) and **413b** (minor) in good yield (Scheme 113).[172]

Scheme 113



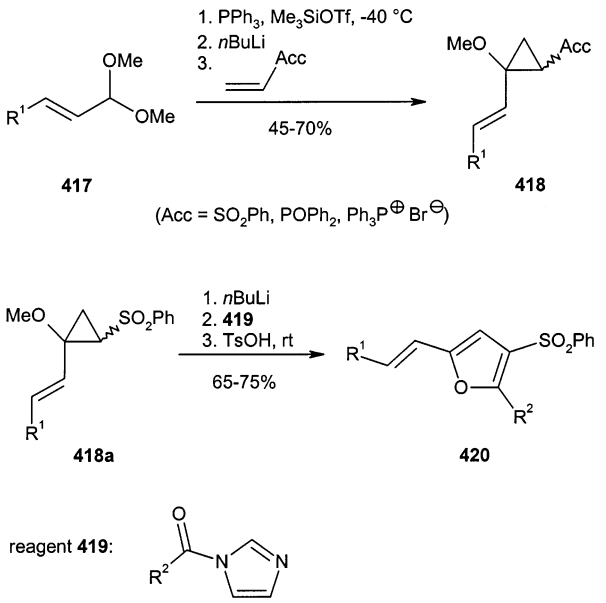
Treatment of the enantiomerically pure allylic sulfone **414** with LDA afforded diastereomeric cyclization products *trans*- and *cis*-**415**, which may be regarded as D−A cyclopropanes (Scheme 114). Accordingly, both diastereomers underwent a smooth acid-induced ring-opening reaction to furnish the α,β-unsaturated aldehyde **416**.[173]

Scheme 114



An interesting and flexible approach to alkenyl-substituted D−A cyclopropanes **418** involved treatment of unsaturated acetals **417** with triphenylphosphane and trimethylsilyltriflate (Scheme 115). The

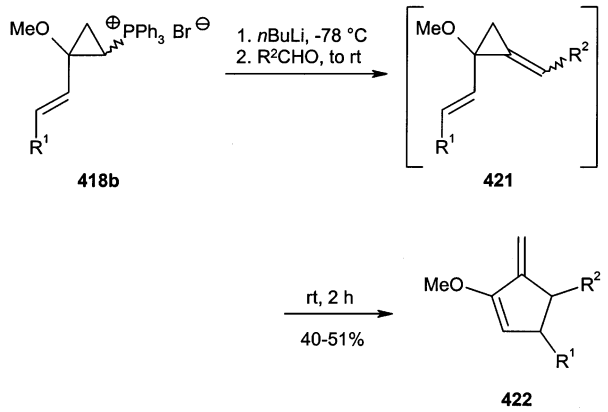
Scheme 115



resulting phosphonium salt was deprotonated and combined with Michael acceptors, which resulted in formation of the desired cyclopropanes **418** in moderate to good yields. These turned out to be very versatile intermediates. Deprotonation of sulfones **418a**, followed by reaction with acyl imidazolides **419** and elimination of methanol, delivered alkenyl-substituted furans **420** in good yield (cf. Scheme 112). Sulfones **418a** were also used as starting materials for vinylcyclopropane−cyclopentene rearrangements. Phosphonium salts **418b** underwent Wittig reactions, furnishing alkylidene cyclopropanes **421** as intermediates that suffered a surprisingly smooth ring enlargement at room temperature, providing methylene cyclopentene derivatives **422** as products (Scheme 116).[174]

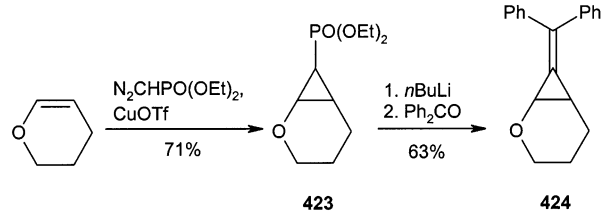
Donor-substituted alkylidene cyclopropane **424** was prepared via cyclopropylphosphonic ester **423**, which

Scheme 116



was obtained by copper(I) triflate-catalyzed cyclopropanation of dihydropyran with the corresponding diazo compound (Scheme 117). Wittig−Horner reaction of **423** with benzophenone furnished **424** in moderate yield. Compounds of this type can serve as starting material for palladium-catalyzed [3 + 2] cycloadditions.[175]

Scheme 117



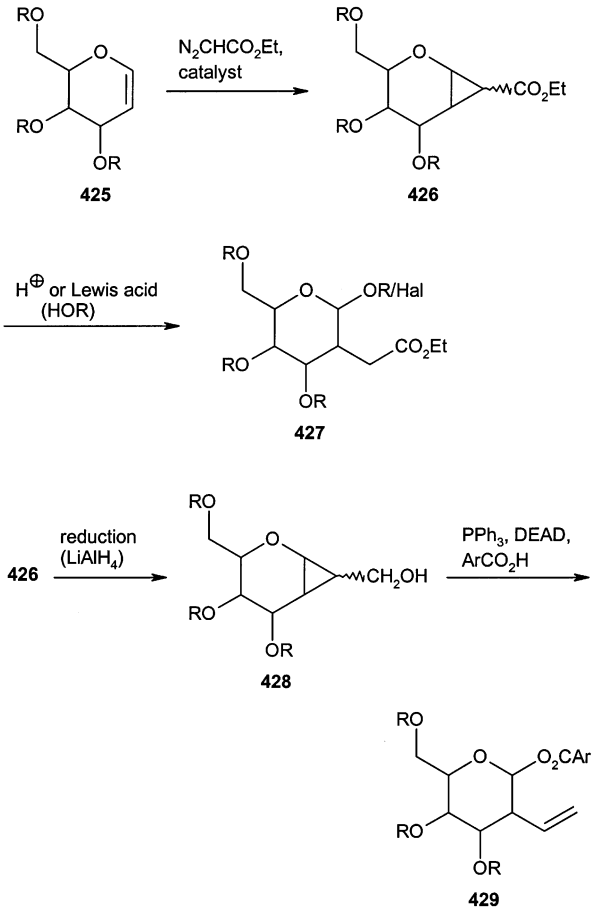
V. Synthesis of Natural Products or Analogues via D–A Cyclopropanes

A. Carbohydrate Derivatives

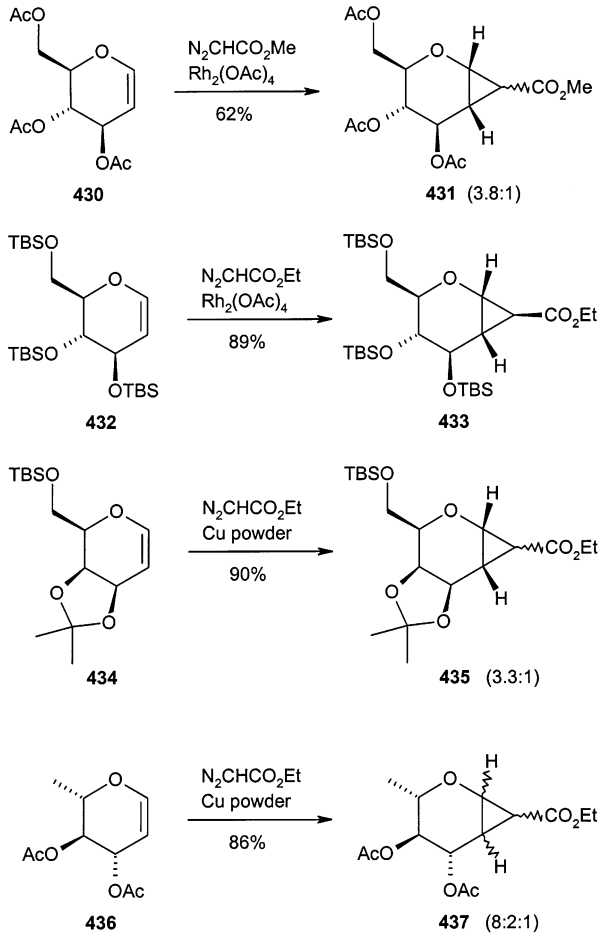
Cyclopropane derivatives of carbohydrates have frequently been studied during the past decade.[176] The general scheme of the preparation and application of carbohydrate-derived D−A cyclopropanes is illustrated in Scheme 118. Usually glycals **425** equipped with suitable protective groups were treated with diazo esters, affording the corresponding cyclopropanated sugars **426**. These underwent the typical ring opening of D−A cyclopropanes by treatment with acids or Lewis acids (see section III.C.1) and furnished the expected esters **427**, bearing either an acetal or haloether group (glycosyl halides). Use of a platinum catalyst for this transformation was also reported.[177] An alternative application involves transformation of **426** into vinyl-substituted carbohydrates **429**. This was achieved by reduction of the cyclopropanecarboxylate to alcohol **428**, which upon treatment under Mitsunobu conditions suffers a cyclopropylcarbinyl−homoallyl rearrangement to **429**.

As enol ether double bonds in glycols are less electron-rich and thus less reactive due to the negative inductive effect of the numerous oxygen functions, cyclopropanations of these compounds are generally more difficult. Frequently a larger excess of the diazo esters must be applied for obtaining a reasonable yield. Typical examples are collected in

Scheme 118



Scheme 119



Schemes 119−121. Rhodium(II) acetate-catalyzed reaction of triacetyl glucal **430** furnished the expected cyclopropanated product **431** in reasonable yield and with modest diastereoselectivity (Scheme 119).[178] Interestingly, exchange of the electron-withdrawing *O*-acetyl substituents against the weaker acceptor *O*-TBS considerably increased the reactivity, which led to a much more efficient transformation of **432** into **433**. The cyclopropanated sugar derivative was essentially formed as a diastereomerically pure compound.[179] Synthesis of **435** from galactal **434** was efficient when copper powder was the catalyst, but the diastereoselectivity was only moderate. The related transformation of rhamnal derivative **436** into **437** was even less selective, providing three diastereomers in a ratio of 8:2:1.[180]

Dihydrofuran derivative **438** gave bicyclic compound **439** in moderate yield (Scheme 120). Disaccharide derivatives were also cyclopropanated under similar conditions.[181] Glycal **440**, which is available from D-mannose in few steps, was cyclopropanated under standard conditions to provide **441** in moderate yield as a mixture of two diastereomers. Its ring cleavage with acid furnished acetal **442**, which was subsequently converted into **443**. This compound constitutes the side chain of marine natural products belonging to the norrisane family.[182]

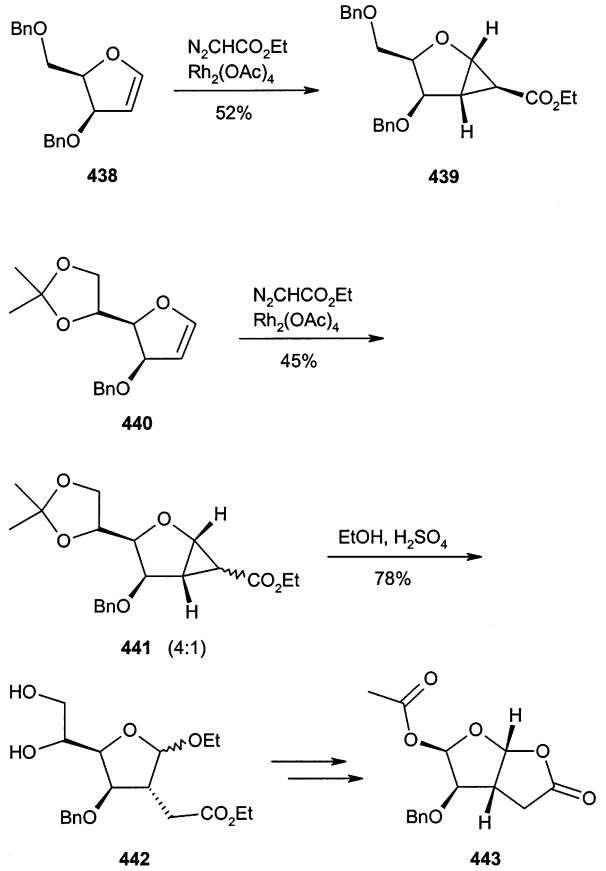
Two exo-methylene carbohydrate derivatives were cyclopropanated with ethyl diazoacetate under copper catalysis. The D-glucose-derived compound **444** as well as the D-mannose-configurated precursor **446** provided the expected spiro carbohydrate derivatives **445** and **447** in excellent yields, but with moderate diastereoselectivity (mixture of four diastereomers) (Scheme 121). Cyclopropane **445** was also synthesized by reacting the correponding carbohydrate diazirine **455** (see Scheme 125) with ethyl acrylate, which resulted in a slightly lower yield and differing diastereoselectivity.[183]

Cyclopentene derivative **448**, which was prepared from D-glucose, was converted into bicyclic ester **449** under standard conditions (Scheme 122). The two diastereomers were separated and, by Curtius-rearrangement, converted into cyclopropylammonium salts **450a** and **450b**. They are of interest as inhibitors of β-mannosidases.[184]

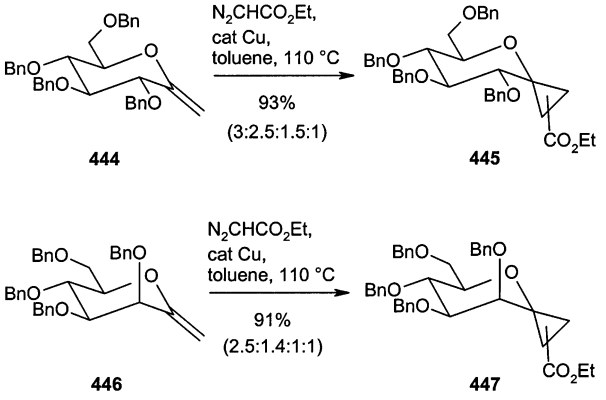
An intramolecular cyclopropanation of glucals **451** afforded tricyclic products **452** in excellent yields and with the configuration required for syntheses of bislactones such as xylobovide, canadensolide, or sporothriolide (Scheme 123).[185] The high efficiency and perfect stereocontrol of this intramolecular approach promise great potential for synthetic explorations of carbohydrate-derived D−A cyclopropanes. Compounds of type **452** have successfully been employed in Lewis acid-assisted ring-cleavage reactions incorporating nucleophiles such as thiophenol and allylsilane.[185]

Glycosidene carbenes have also been employed for the synthesis of carbohydrate-derived D−A cyclopropanes. For this purpose, the sodium salts of tosyl-

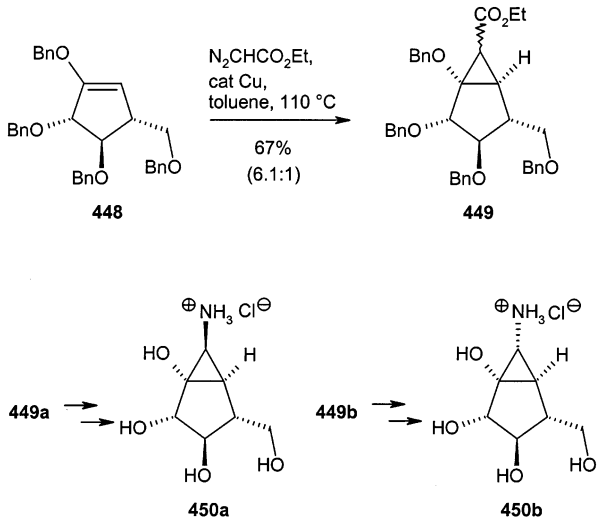
Scheme 120



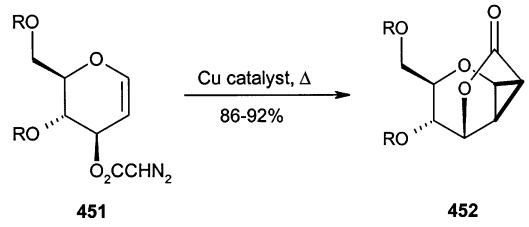
Scheme 121



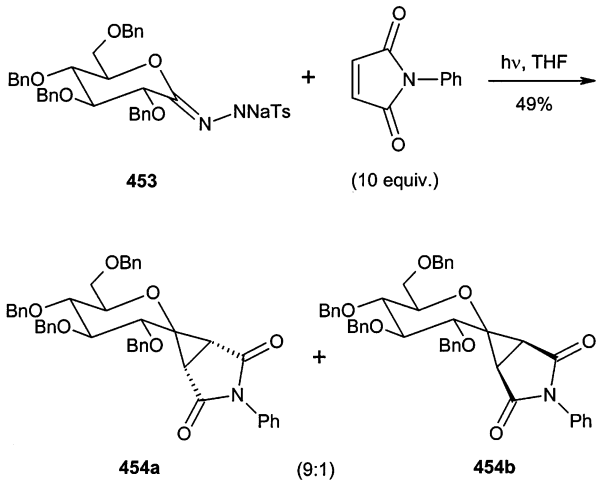
Scheme 122



Scheme 123



Scheme 124



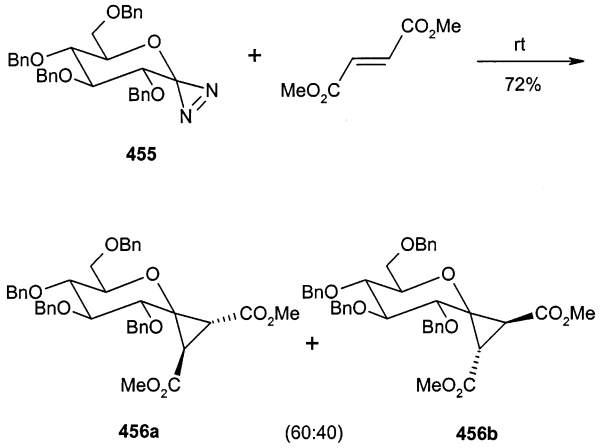
hydrazones such as **453** were photolyzed in the presence of an excess of electron-deficient olefins.[186,187] In Scheme 124, reaction of **453** with *N*-phenylmaleimide is presented as a typical example furnishing sugar derivative **454** in moderate yield but good diastereoselectivity. Photolytic generation and trapping of a glycosidene carbene with acrylonitrile were also accomplished with glucopyranosylidene diazides as precursor compounds.[188]

Alternatively, diazirines such as **455** may be employed as starting material (see section II.C). Reaction of **455** with dimethyl fumarate furnished two diastereomeric spirocyclopropanes, **456a,b**, in good yield (Scheme 125). The corresponding cycloaddition of **455** with dimethyl maleate provided a mixture of four isomers. These results demonstrate that the reaction is not stereospecific and probably involves zwitterions as intermediates. The combination of **455** with *N*-phenylmaleimide provided two diastereomeric spirocyclopropanes **454a,b** (see Scheme 124) with low diastereoselectivity. All these benzyloxy-substituted carbohydrate derivatives may smoothly be deprotected by hydrogenolysis.[189,190]

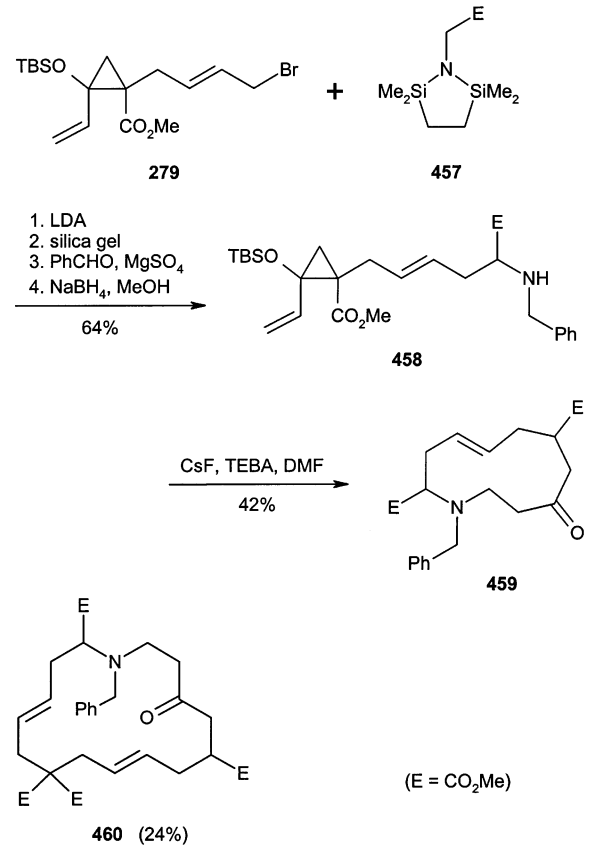
B. Amino Acids and Peptides

The route to macroheterocyclic compounds as described in section III (Schemes 84 and 85) was extended to the construction of peptide-mimicking compounds such as **459** and **460**, which may be regarded as ring-enlarged proline derivatives. For this purpose, bromide **279** was combined with the enolate of protected glycine ester **457**, and the resulting amino acid derivative was equipped with an

Scheme 125



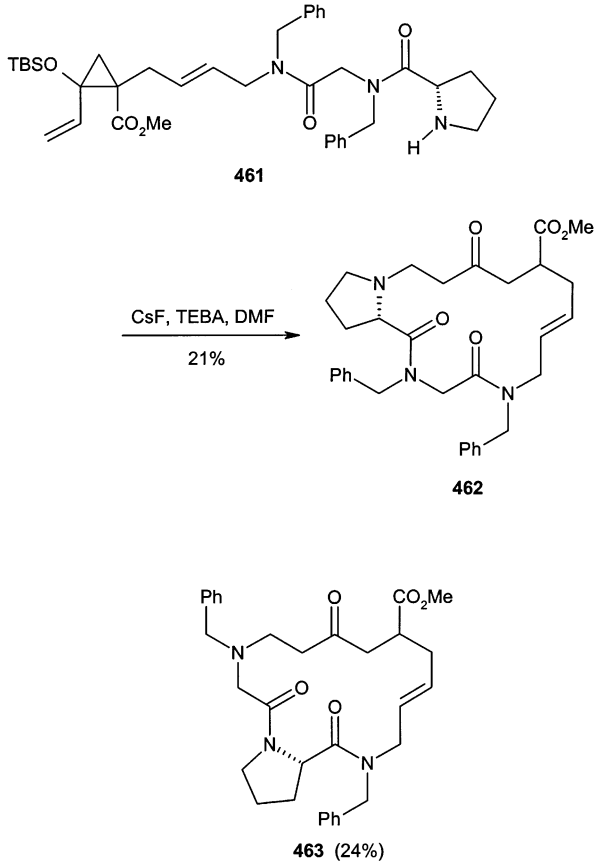
Scheme 126



N-benzyl group by standard methods (Scheme 126). The precursor obtained, **458**, was treated with fluoride to induce the anticipated ring-opening/ring-closure cascade, which actually provided cyclic functionalized amino acid derivative **459**. A similar synthesis employs dimethyl malonate **280** (Scheme 79) as starting material, and chain elongation under introduction of the amino acid moiety with **457** provided a precursor for the related extended macroheterocyclic compound **460**.[137]

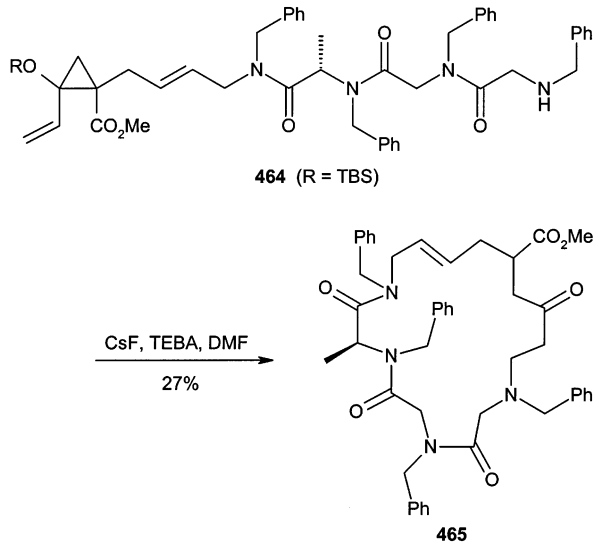
The methods described in Schemes 84 and 85 were also applied to syntheses of macrocycles containing peptide substructures. Thus, the glycine/proline derivative **461** was cyclized to compound **462** in moderate yield (Scheme 127). Its constitutional isomer **463**, which contained the α-amino acids in an inverted

Scheme 127



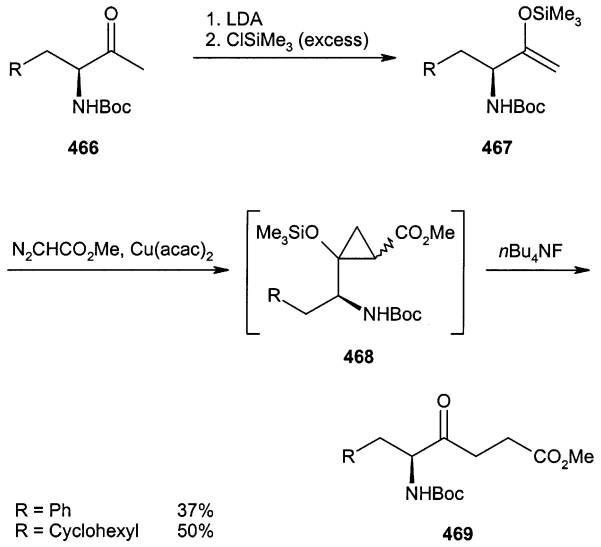
manner, was prepared with comparable efficiency. Similarly, precursor **464**, which incorporates a tripeptide, was transformed into 19-membered ring compound **465** (Scheme 128).[136] Conformationally restricted peptides may exhibit interesting biological activity.

Scheme 128



Preparation of enantiopure γ-keto-δ-amino esters **469**, which are important building blocks of enzyme inhibitors, was achieved by following the route illustrated in Scheme 129. Methyl ketones **466**, easily available from the corresponding α-amino acids, were

Scheme 129

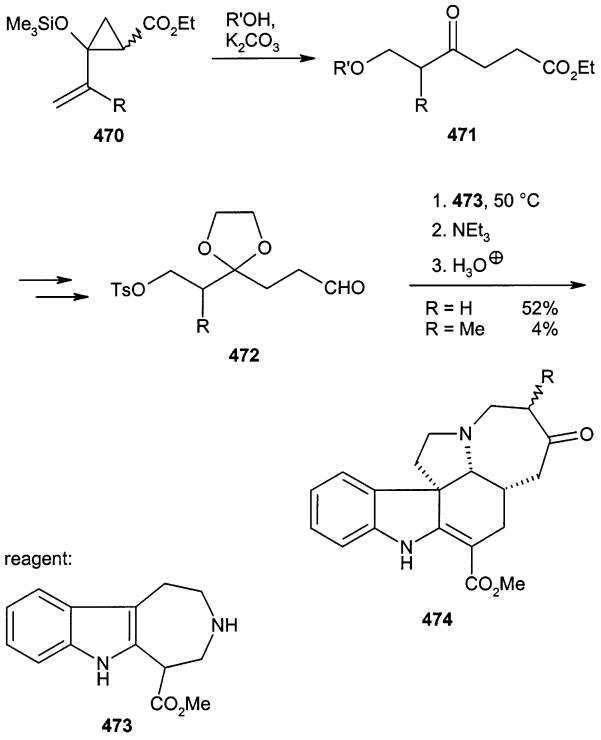


converted into silyl enol ethers **467**. As crude products they were transformed into the siloxycyclopropanecarboxylates **468** under standard conditions. Purification of **468** was not required, since direct treatment with fluoride converted it into the desired γ-keto esters **469** in reasonable overall yield.[191]

C. Alkaloids

Alkenyl-substituted siloxycyclopropanecarboxylates **470** turned out to be excellent starting materials for synthesis of building blocks **472** required for a biomimetic approach to alkaloids (Scheme 130).

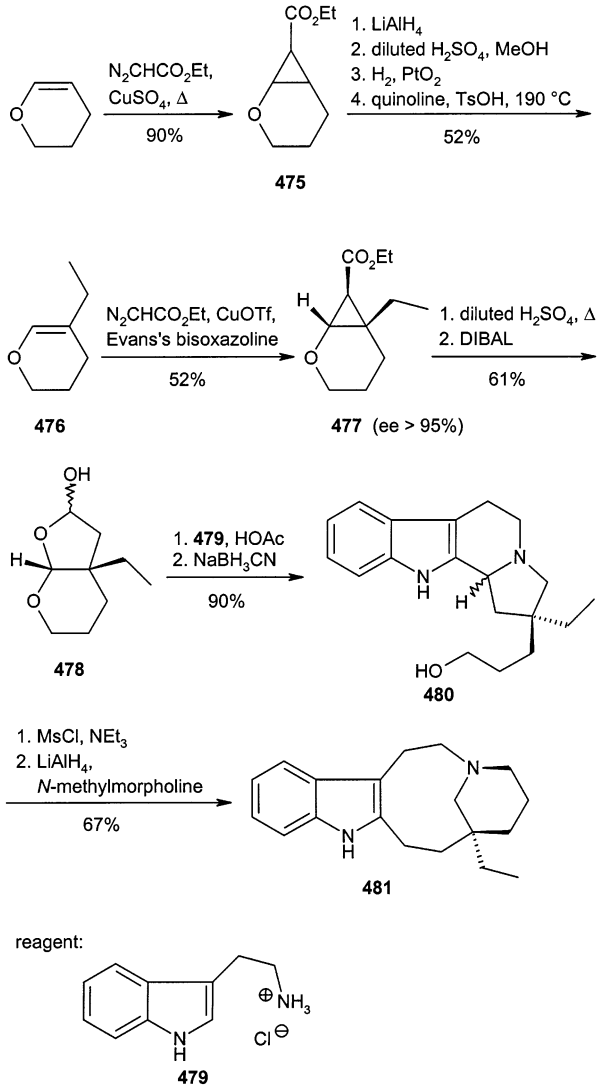
Scheme 130



Sequential ring cleavage and Michael addition of alcohols (see Scheme 73) efficiently transformed **470** into ϵ-alkoxy-γ-keto esters **471**, which were converted into aldehydes **472** in a straightforward manner. Reaction of these biselectrophiles with indoloazepine **473** furnished pentacyclic alkaloids **474** belonging to the ioboxyphylline family.[192]

A total synthesis of (+)-quebrachamine **480** employed D−A cyclopropanes in a repetitive manner. The required ethyl-substituted dihydropyran **476** was first prepared under standard conditions from dihydropyran via cyclopropane **475**, followed by its reduction and acid-assisted rearrangement (Scheme 131).

Scheme 131

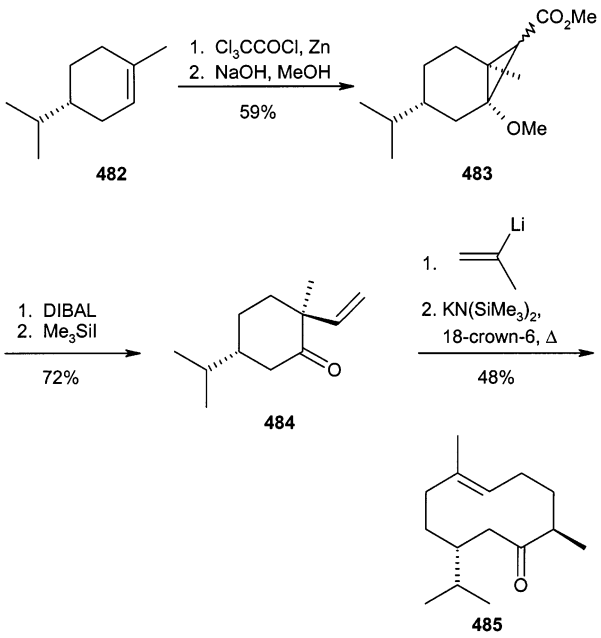


A second cyclopropanation was then performed with **476** in the presence of Evans' chiral ligand and copper(I) triflate, providing the crucial D−A cyclopropane **477** with an ee of >95%. Acid-induced rearrangement to a γ-lactone and reduction furnished lactol **478**, which was condensed with tryptamine **479** and reduced with sodium cyanoborohydride to furnish tetracyclic intermediate **480**. Two further steps smoothly converted this compound into (+)-quebrachamine **481**.[193]

D. Terpenoid Compounds and Steroids

Selective hydrogenation of (−)-limonene afforded chiral cyclohexene derivative **482**, which was stereoselectively converted into D−A cyclopropane **483** via

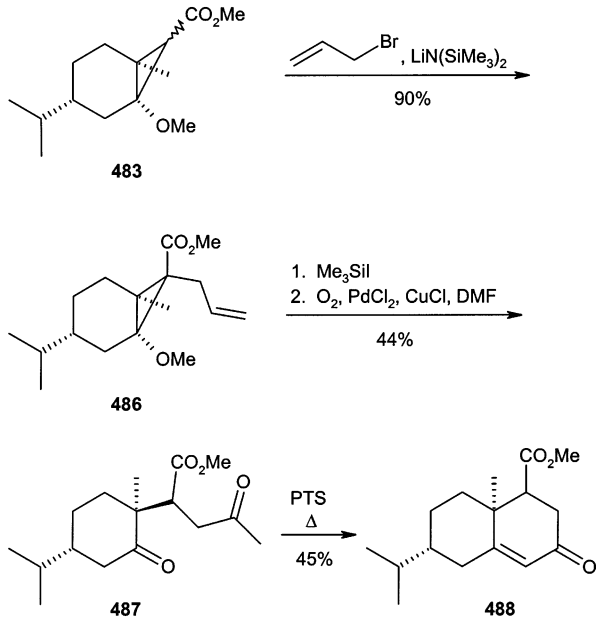
Scheme 132



the corresponding dichlorocyclobutanone (see Schemes 55 and 132). Reduction of the methoxycarbonyl function and treatment with trimethylsilyl iodide smoothly furnished the required α-vinylcyclohexanone **484** as crucial intermediate. Addition of 2-propenyllithium and a subsequent anionic oxy-Cope rearrangement produced compound **485** as single diastereomer in moderate yield. This approach allows stereocontrolled synthesis of germacrane-type terpenes.[194]

D−A cyclopropane **483** was also used as starting material for establishing the eudesmane-type structure **488** (Scheme 133). Deprotonation of **483** and

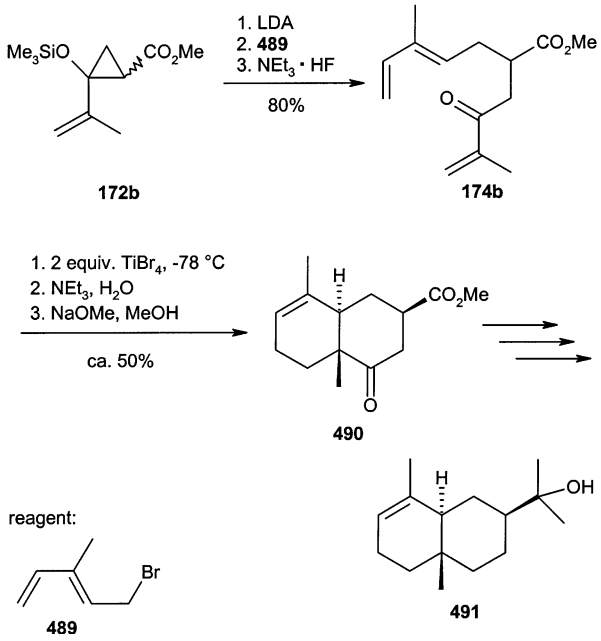
Scheme 133



stereoselective allylation furnished intermediate **486**, which was ring-opened with trimethylsilyl iodide and converted into diketone **487** by Wacker oxidation. This compound could be converted into bicyclic enone **488** by acid-catalyzed aldol condensation.[194]

A short synthesis of the sesquiterpene (±)-α-eudesmol **491** was achieved with siloxycyclopropane **172b** as starting material and the corresponding 1,7,9-decatrien-3-one **174b** as crucial intermediate (Scheme 134). Alkylation of deprotonated **172b** with

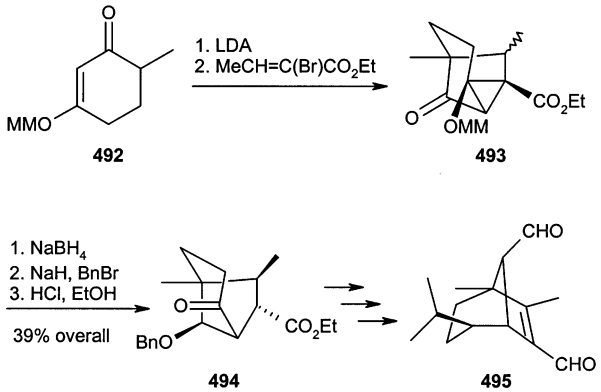
Scheme 134



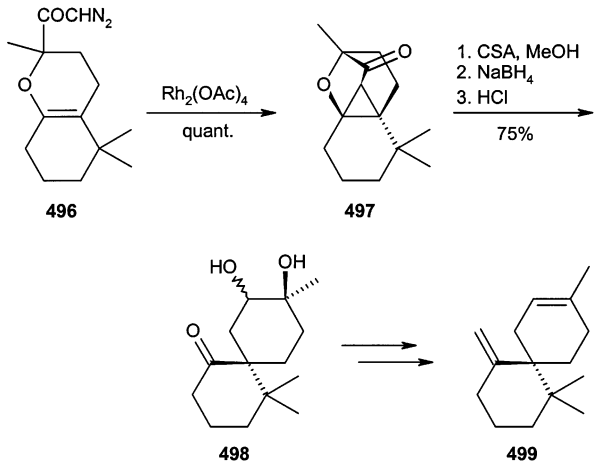
halide **489** and ring cleavage furnished **174b** in good yield, which provided the required bicyclo[4.4.0]-decene skeleton by chelate-controlled intramolecular Diels−Alder reaction (see Scheme 49). $TiCl_4$ and $TiBr_4$ proved to be the best Lewis acids for highly trans-selective cycloadditions (trans:cis up to 85:15), and combined with a subsequent base-catalyzed equilibration, the desired diastereomer **490** was isolated in good overall yield. Three simple steps converted this intermediate into racemic α-eudesmol **491**.[195]

The total synthesis of (±)-helminthosporal **495** started with enone **492**, which was converted into crucial tricyclic intermediate **493** via the dienolate and treatment with ethyl 2-bromocrotonate (see Schemes 52 and 135). After stereoselective reduction, the resulting D−A cyclopropane was cleaved with hydrochloric acid, furnishing bicyclic γ-keto ester **494** in good overall yield. Ten further steps were required to transform this compound into the racemic natural product **495**.[196]

Scheme 135



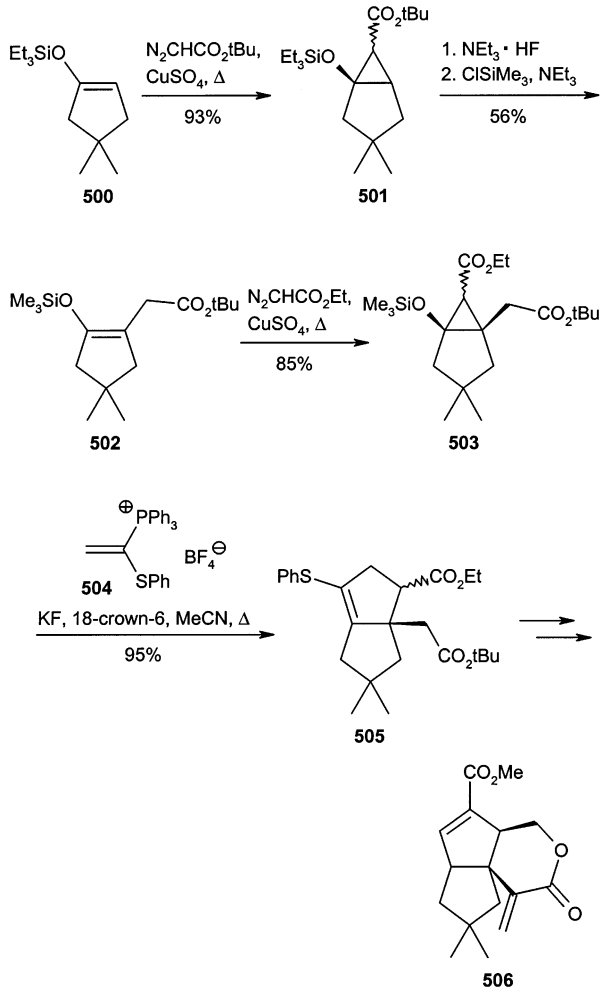
Scheme 136



Spirocyclic sesquiterpene (±)-*β*-chamigrene **499** was prepared with tetracyclic D−A cyclopropane **497** as crucial intermediate, which was accessible from diazo carbonyl compound **496** by intramolecular cyclopropanation (Scheme 136). Acid-promoted ring cleavage of **497** gave an acetal that was deprotected and reduced. The resulting spiro compound **498** was obtained in good overall yield, and a few further steps were required to transform this intermediate into racemic natural product **499**.[197]

A repetitive cyclopropanation was exploited for a synthesis of (±)-pentalenolactone E methyl ester **506**

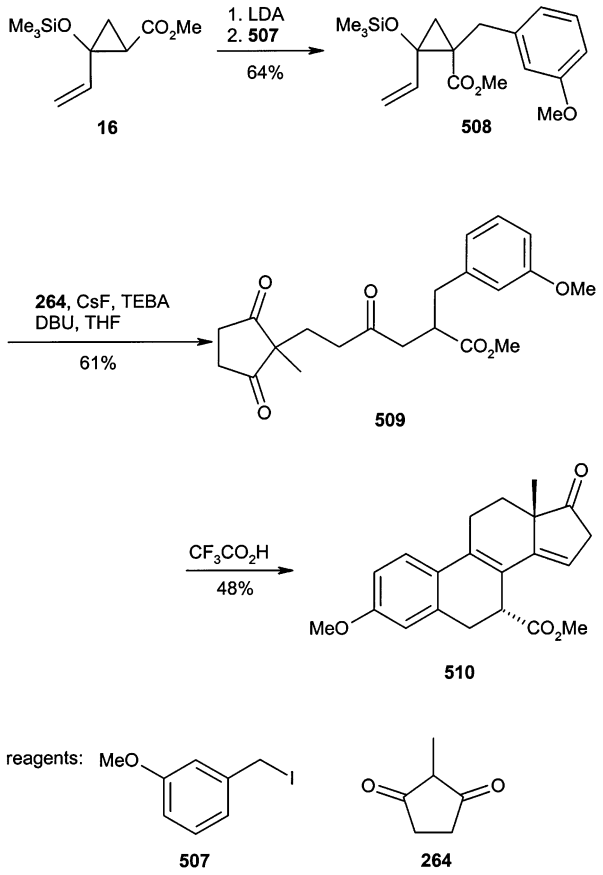
Scheme 137



(Scheme 137). Conversion of silyl enol ether **500** into the corresponding siloxycyclopropanecarboxylate **501** and fluoride-assisted ring opening to a *γ*-keto ester were performed under standard conditions. Generation of substituted silyl enol ether **502** could be achieved with good regioselectivity, and a second cyclopropanation afforded the crucial intermediate **503** in very good yield. Its ring cleavage with fluoride under aprotic conditions and trapping of the intermediate ester enolate with vinylphosphonium salt **504** resulted in a [3 + 2] annulation process, providing bicyclic diester **505** in excellent yield (see Scheme 86). Several subsequent steps converted this compound into racemic lactone **506**.[198]

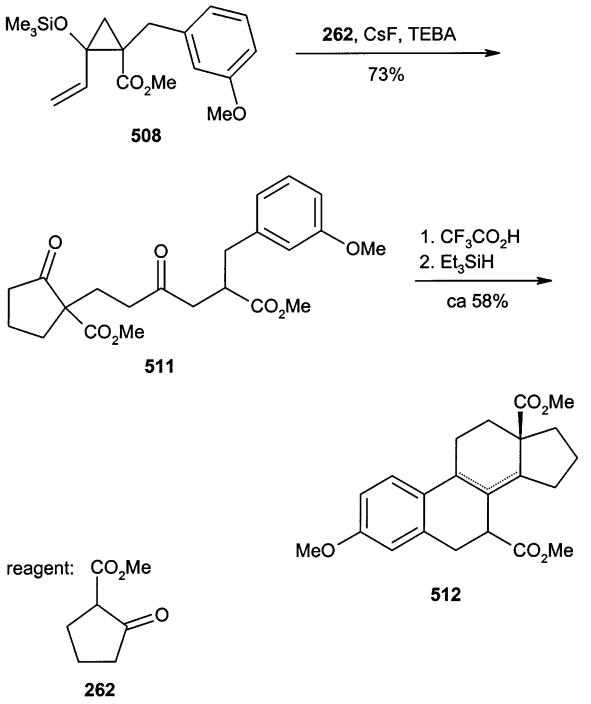
Alkenyl-substituted siloxycyclopropanecarboxylate **16** was used as functionalized enone equivalent (see Schemes 73−75) for preparation of estrone derivatives. Standard alkylation of **16** with halide **507** provided **508**, which by fluoride treatment underwent ring opening, followed by Michael additions of the intermediate enone with C-nucleophiles such as **264** and **262**. This sequential reaction led to polyfunctionalized compounds **509** (Scheme 138) and **511**

Scheme 138



(Scheme 139) in good yield. Acid-promoted cyclization of **509** afforded steroid derivative **510** in moderate yield. This could chemoselectively be reduced to 7-substituted estrone derivatives. Treatment of **511** with acid directly followed by ionic reduction with triethylsilane furnished a mixture of three tetracyclic compounds **512**, which differ in the location of the double bond and their configuration.[125]

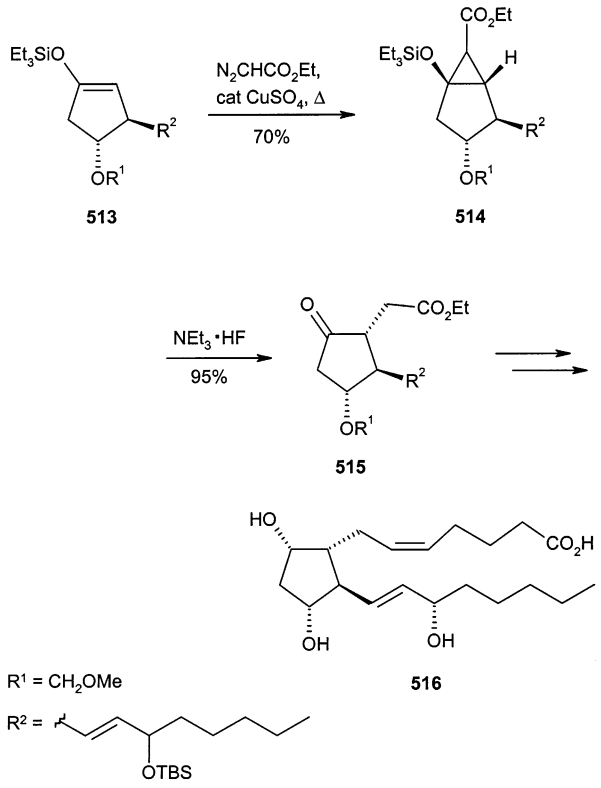
Scheme 139



E. Other Natural Products

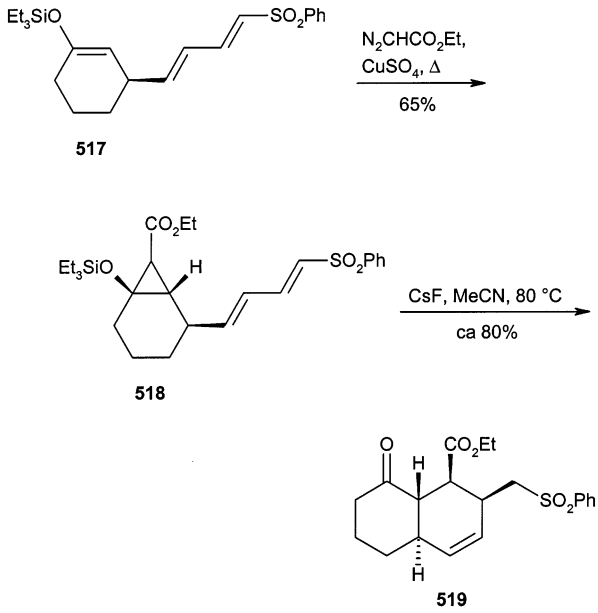
A synthesis of prostaglandin (±)-$PGF_{2\alpha}$ **516** started from silyl enol ether **513**, which was prepared from cyclopentadiene monoepoxide in few steps (Scheme 140). Diastereoselective cyclopropanation of **513** with ethyl diazoacetate furnished D−A cyclopropane **514**, and smooth ring cleavage under retention of the newly generated stereogenic center at the cyclopentene ring provided keto ester **515** in good overall yield. This intermediate was subsequently converted into prostaglandin **516** and its 15-epimer.[199]

Scheme 140



A highly convergent and stereoselective synthesis of an intermediate for dihydrocompactin employs silyl enol ether **517**, which was converted into the corresponding siloxycyclopropanecarboxylate **518** with high chemo- and diastereofacial selectivity (Scheme 141). Treatment with fluoride caused ring cleavage

Scheme 141

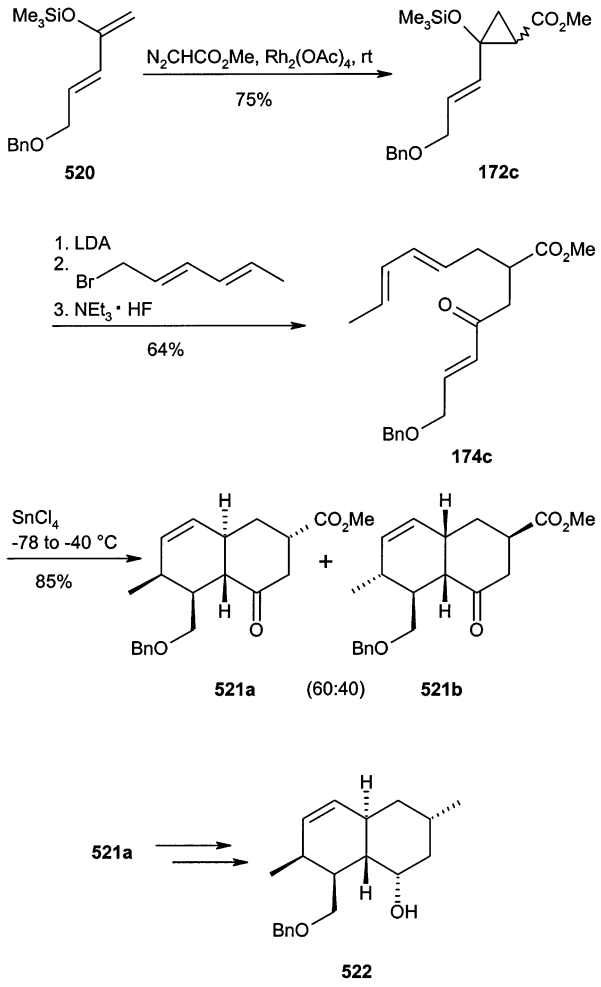


and the generated ester enolate was trapped by the attached vinyl sulfone. This elegant intramolecular Michael addition stereoselectively furnished compound **519**, which contains the octahydronaphthalene skeleton of dihydrocompactin.[200]

The closely related dihydromevinolin structure was approached by an intramolecular Diels–Alder reaction as key step, for which starting material **174c** was efficiently prepared via alkenyl-substituted siloxycyclopropanecarboxylate **172c**. Cyclopropanation of siloxydiene **520**, alkylation of **172c**, and ring opening with fluoride afforded the required trienone **174c** in a straightforward and fairly efficient manner (Scheme 142). Its chelate-controlled cycloaddition was best performed in the presence of $SnCl_4$, which delivered the highest ratio of **521a**:**521b** (60:40). Major isomer **521a** was converted into diol **522**, which was a precursor of (+)-dihydromevinolin in a literature-known synthesis.[201]

Siloxycyclopropane **16** and 1-nitropropane were combined to undergo the base-induced ring-opening Michael addition sequence (see Scheme 75), and the intermediate γ-keto ester was protected as acetal to finally give **523** (Scheme 143). An oxidative version of the Nef reaction smoothly converts the nitro group of **523** into the carbonyl function, furnishing **524** in excellent yield. This compound was reduced, and by treatment with acid a moderate yield of racemic chalcogran **525** was obtained, which is an aggregation pheromone of a beetle. In a very similar fashion, trifunctional or tetrafunctional compounds **526** and **527** were accessible from **16** and other nitro alkanes. They are suitable building blocks for synthesis of

Scheme 142



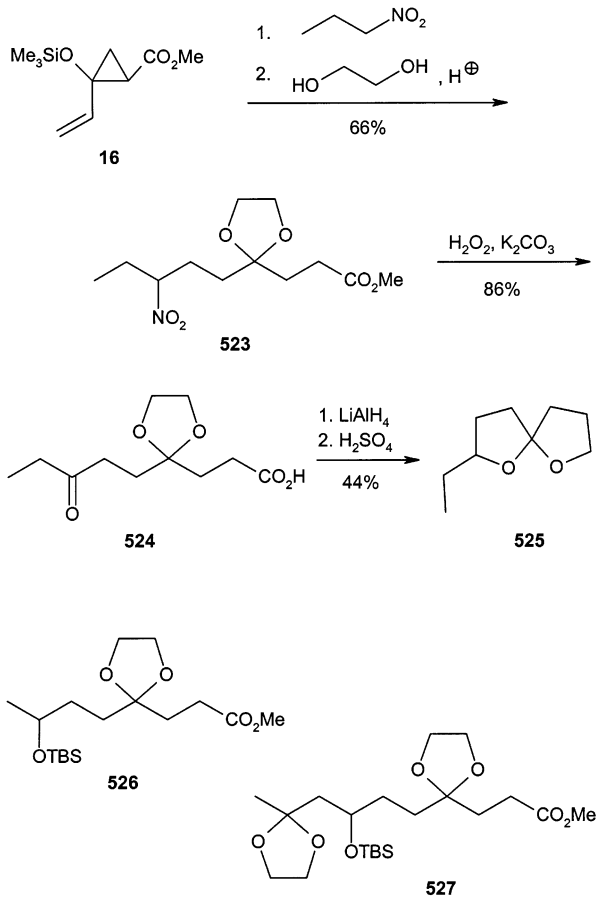
antibiotic macrolides such as pyrenophorin and vermiculin.[128]

Enantiopure γ-keto ester **530** was most efficiently synthesized by trimethylsilyl chloride-assisted conjugate addition of in situ generated lower order cuprate **529** to enone **528** (Scheme 144). This compound was available in reasonable scale from the ethyl ester analogue of **16** (see Scheme 5) by standard treatment with fluoride. Compound **530** served as a crucial building block in a stereocontrolled synthesis of the antibiotic macrocyclic lactam−lactone myxovirescin.[202]

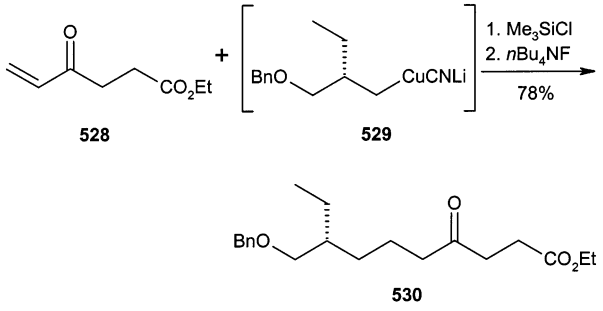
Cyclopropanation of ethyl propenyl ether with diazoalkane **531** furnished vinylcyclopropane **532** in very good yield (Scheme 145). Under optimized conditions this intermediate could be rearranged into γ-lactones **533a,b**. The major diastereomer **533a** was methylated to provide (±)-acetomycin **534**.[203]

Enantioselective cyclopropanation of furan-2-carboxylic methyl ester **21** in the presence of Evans' ligand (see Scheme 6) nicely afforded bicyclic D−A cyclopropane **22a** in good yield and with excellent enantiopurity after one recrystallization. As already described in section III, ozonolysis furnished new functionalized cyclopropanes such as **535**, which react with nucleophiles under very good stereocontrol (Scheme 146). Addition of trimethylallylsilane to **535** provided intermediate **536**, which underwent ring opening and subsequent protection by treatment with

Scheme 143



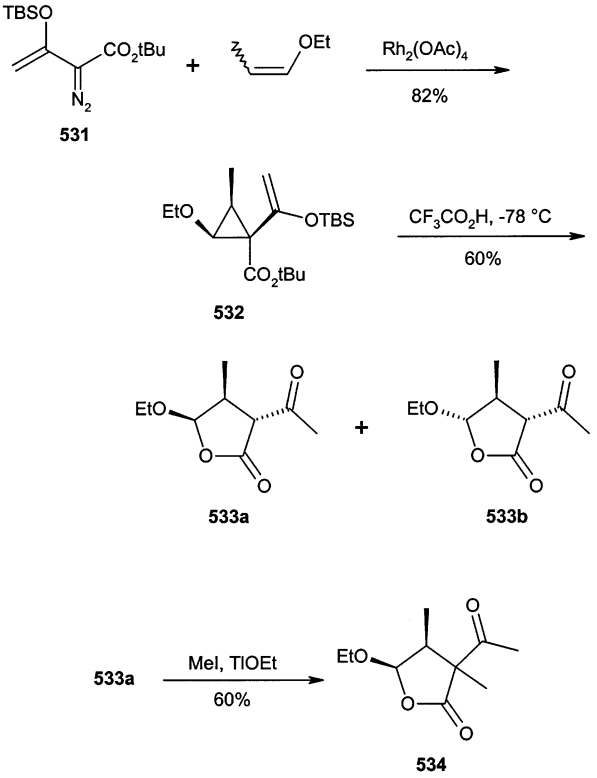
Scheme 144



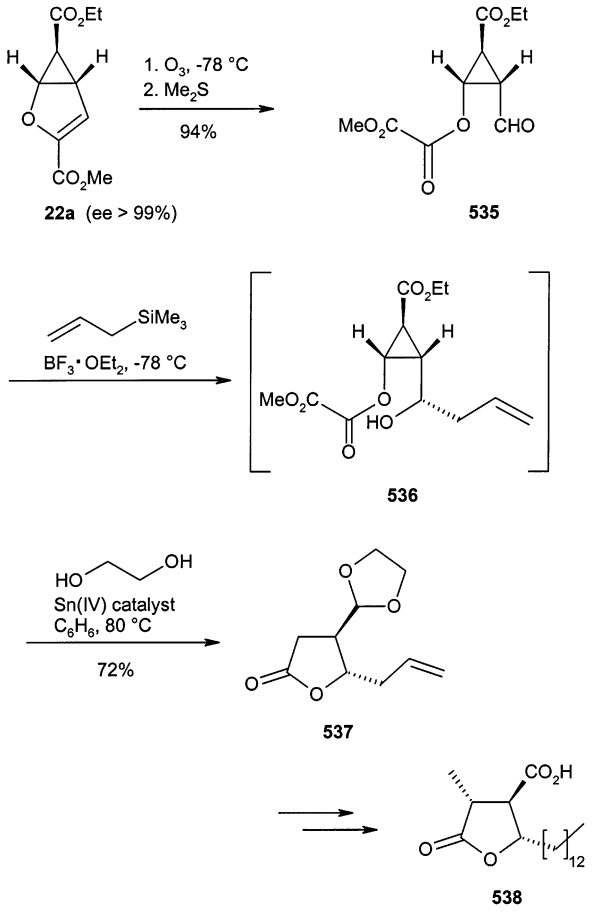
glycol in the presence of Otera's tin(IV) catalyst (see Scheme 47). A few straightforward subsequent reactions transform the resulting product **537** into (−)-roccellaric acid **538**.[21] This very elegant and general approach to enantiopure functionalized γ-lactones has been further exploited for synthesis of other paraconic acids such as (−)-nephrosteranic and (−)-protopraesorediosic acid, as well as related α-methylene γ-lactones.[21]

Cyclopropanation of 2-hexylfuran **539** with diazo ketone **540** produced D−A cyclopropane **541**, which was not stable but suffered ring cleavage to dienyl diketone **542** (Scheme 147). Since some *E,Z*-diene was also formed, the mixture was treated with catalytic amounts of iodine to selectively provide the required *E,E*-diene **542**. Its conversion into the free carboxylic acid, which is the plant cytotoxin ostopanic acid, was achieved by reduction with $LiAlH_4$ and reoxidation.[204]

Scheme 145

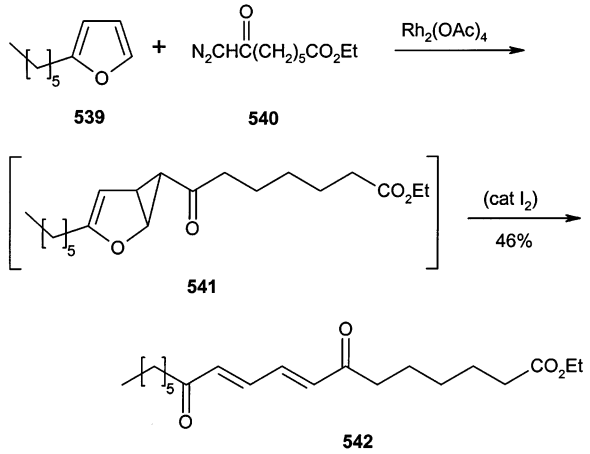


Scheme 146



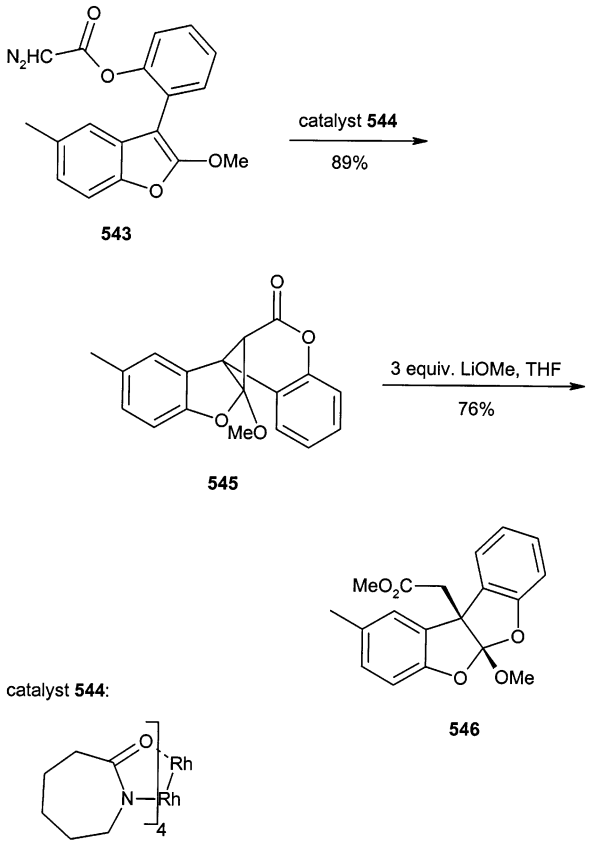
This approach was based on the important findings of Wenkert et al., who systematically investigated cyclopropanations of furan derivatives and applied this knowledge to syntheses of polyene-containing natural products such as retinol–carotene fragments, (±) 6(E)-LTB eukotrienes, and corticrocin.[205]

Scheme 147



The synthesis of benzofuran-derived bisaryl quaternary centers—a structural element of diazonamide A—was achieved by intramolecular cyclopropanation of benzofuran **543** in the presence of rhodium catalyst **544** (Scheme 148). D–A cyclopropane **545** was obtained in excellent yield and it could be transformed into the required tetracyclic ortho ester **546** by treatment with lithium methoxide. If a chiral rhodium catalyst was employed, an ee of 45% was recorded for **545**.[206]

Scheme 148



VI. Conclusions

The manifold synthetic methods and their applications presented in this review demonstrate consider-

able growth of the chemistry of D−A cyclopropanes during the last 15 years. Although most of the principles employed have long been known, quite a number of new modifications and variations were developed that characterize D−A cyclopropanes as extremely versatile and valuable tools for organic synthesis.

Their ring opening for the preparation of substituted and functionalized 1,4-dicarbonyl compounds and derivatives thereof is remarkably successful. Of particular value are methods involving β-formyl esters that will increasingly serve as intermediates in sequential transformations and multicomponent reactions. Alkenyl-substituted siloxycyclopropanes mask functionalized enones and are most successfully employed as intermediates for (intramolecular) Diels−Alder reactions and Michael reactions, leading to products of relatively high complexity within a few steps. Further applications of the repetitive methods developed can be expected.

D−A cyclopropanes are also involved in numerous syntheses of five-membered and seven-membered heterocycles, either by simple condensation reactions or by processes under deprotonation of the cyclopropane followed by reactions with apt electrophiles. Alternatively, heterocycles are accessible by Lewis acid-assisted ring opening and subsequent trapping with suitable reagents.

Concerning natural product syntheses, D−A cyclopropanes were most successfully used for preparation of modified carbohydrates. The precursor glucals are generally very easy to obtain. It can be anticipated that cyclopropanated carbohydrate derivatives will also serve as intermediates for enantioselective syntheses of other natural products or their analogues.

Although methods for synthesis of D−A cyclopropanes are very versatile and usually efficient, a general solution for enantioselective preparation of this class of small-ring compounds is still missing. It is surprising that only few reactions of D−A cyclopropanes were performed by radical promotion or under the influence of transition metals. Here should be space for future developments. Also, acceptor groups other than carbonyl substituents were so far rarely engaged for methods based on D−A cyclopropanes. Sulfonyl- and phosphonyl-substituted D−A cyclopropanes should offer a variety of new applications, as these functional groups allow rather different synthetic transformations. Finally, the cyclobutane analogues, i.e., D−A cyclobutanes, have only very rarely been employed for synthetic adventures.[207] They should be similarly versatile building blocks for organic synthesis as D−A cyclopropanes.

VII. Acknowledgment

The intellectual and experimental contributions of the many members of our research group to the topic of this review are most gratefully acknowledged. We also thank Alexandra Hölemann for her help during preparation of the manuscript. The authors thank the Deutsche Forschungsgemeinschaft, the Volkswagen-Stiftung, the Alexander von Humboldt Foundation, and the Fonds der Chemischen Industrie for continuous and generous support of our research. In addition, we gratefully appreciate support by Merck KGaA (Darmstadt), Arzneimittelwerk Dresden, and Schering AG (Berlin).

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