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Synthetic Methods

Dendralenes Branch Out: Cross-Conjugated Oligoenes Allow the Rapid Generation of Molecular Complexity**

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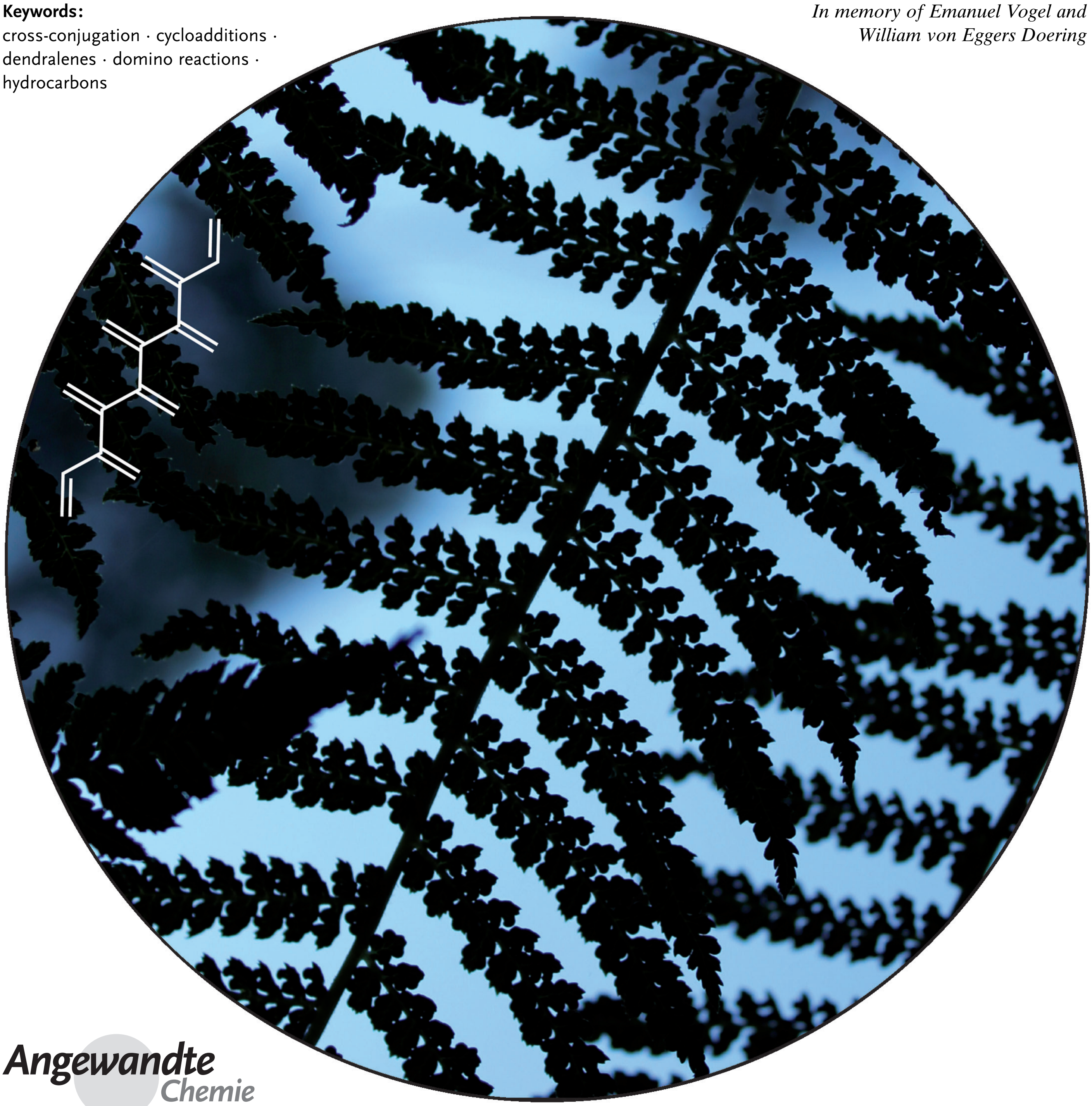
Keywords:
cross-conjugation · cycloadditions · dendralenes · domino reactions · hydrocarbons

In memory of Emanuel Vogel and William von Eggers Doering



Twenty-seven years ago, H. Hopf published the only previous comprehensive review on branched oligoenes that had the title "Dendralenes: A Neglected Family of Hydrocarbons". The dendralenes are no longer neglected. Research into the synthesis, properties, and applications of dendralenes is rapidly gaining momentum and this Review summarizes important recent findings. From significant fundamental properties (the first demonstration of alternating behavior since the annulenes) through to unparalleled complexity-generating synthetic transformations, this fundamental oligoene family is coming of age. Effective synthetic approaches to cyclic and acyclic dendralene systems are analyzed and classified. The most powerful synthetic transformations of the dendralenes, diene-transmissive Diels–Alder reactions, are surveyed in detail.

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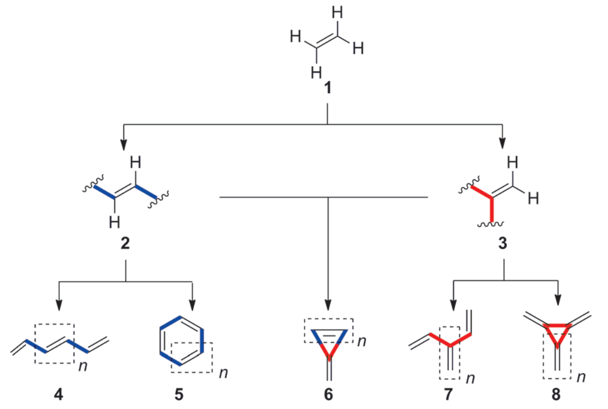
1. Introduction

Two alternatives exist for building complex unsaturated structures out of ethylene units (**1**; Scheme 1): the new bonds may be formed from both carbon atoms of **1** (blue vicinal connection, **2**) or from one (red geminal connection, **3**). If only building blocks of the former type are employed, two oligoene structures can result: the linear polyenes **4** or the cyclic annulenes **5**. With **4**, there are no restrictions as far as the configuration of the ene moiety is concerned, and *E* and *Z* diasteromers become possible for the parent systems (and are known) with at least three consecutive double bonds. In contrast, for the molecules **5**, strain restrictions allow the formation of *E* isomers only when the rings become ten-membered or larger.[1] When only the geminal connection mode is used, two structure types are again conceivable: acyclic ones **7**, called dendralenes, and cyclic ones, the radialenes **8**. Finally, "hybrid" molecules are possible, in which vicinal and geminal connectivity are used simultaneously: the fulvenes (**6**).

From the above five classes of oligoenes, the conjugated polyenes **4** and the (aromatic and antiaromatic) annulenes **5** have received the most attention. Indeed, the aromatic annulenes, in the form of benzene derivatives, are of huge commercial importance and value. Linear conjugated polyenes and their derivatives have not only been isolated from natural sources (for example, terpenoids such as the carotenoids and retinoids, fatty acids such as mycangimycin, and polyketides such as amphotericin B), but also form the parent structure of various "organic metals" (for example, doped polyacetylene). Compared to these two classes, the remaining three are, so far, of lesser value; one important reason is that they have only rarely been isolated from natural sources. However, a growing number of "dendralenic" natural products have been reported, as will be shown in Section 9.

Dendralenes—like dendrimers—derive their name from the Greek word for tree (δένδρον) and, by replacing the nonterminal hydrogen atoms of these branched structures by vinyl substituents, an ever-growing series of compounds can be obtained. Their trivial names involve placing the number of alkene units in brackets before the word dendralene.



Scheme 1. Conceptualized molecule building with ethylene.

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[**] The Frontispiece shows an image of a Rainbow Fern, *Calochlaena dubia* (Tidbinbilla Nature Reserve, Australian Capital Territory).

Whereas several reviews of the radialenes[2] and fulvenoid compounds[3] have been published, to our knowledge only one comprehensive summary dedicated exclusively to the dendralenes[4] has so far appeared, apart from several shorter ones[5,6] that concentrate on more recent developments. Furthermore, dendralenes form a section of a review on oligomeric and polymeric systems containing cross-conjugated π frameworks published in 2006 by Gholami and Tykwinski.[7]

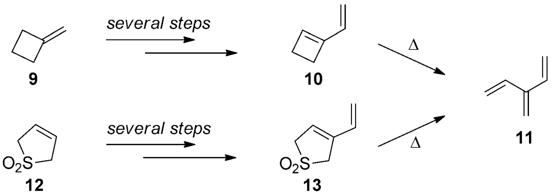
Oligoenes **7** and **8** are related in the sense that they are cross-conjugated hydrocarbons. In our view, the phenomenon of cross-conjugation deserves more thorough study. Although cross-conjugation is widespread, for example in countless dye-stuffs from indigo to the triphenylmethane and branched polymethine dyes,[8] as far as synthesis and theoretical investigations[9] are concerned, the volume of work in this area presently cannot compare with that on **4** and **5**.

The hydrocarbons **7** form the basic framework and bonding pattern for numerous other compounds, as becomes apparent if one or more of its methylene groups are replaced by heteroatoms such as oxygen or nitrogen. The resulting cross-conjugated carbonyl compounds,[10] imines,[11] etc. will not, however, be dealt with in this Review. We will also not survey many of the historical findings on the dendralenes in detail; for these the reader is referred to the older comprehensive review by one of the authors.[4] Furthermore, we will not include cross-conjugated hydrocarbons in which one of the terminal double bonds of a [3]dendralene has been replaced by an aromatic ring system or an alkyne, since these π systems have been discussed at length in the review by Gholami and Tykwinski.[7] We will also not discuss reactive intermediates having a cross-conjugated arrangement of π electrons (i.e. radicals,[12,13] carbocations,[14] carbanions,[15,16] and radical ions[17]).

Since the first comprehensive review was published 27 years ago, many interesting new developments have been reported. This Review will focus on the synthesis and properties of substituted and functionalized [*n*]dendralenes. The synthesis section of the Review is divided into three parts: the parent compounds, acyclic derivatives, and cyclic derivatives. We have tried to select those dendralene syntheses that are preparatively useful, and we have attempted to identify common themes in dendralene synthesis. Generally speaking, the scope and limitations of a dendralene synthesis were more important to us than just the production of a cross-conjugated compound as a singular product in an otherwise unrelated study. In the transformations section, we have also attempted to provide a comprehensive survey of the most important reactions of dendralenes: diene-transmissive cycloadditions. As will become clear, these processes allow the rapid construction of multicyclic ring systems. As far as the depth of our literature search is concerned, we have attempted to cover (within the restrictions mentioned above) the literature up to January 2011.

2. Parent Dendralene Systems

In the early synthetic studies on the [*n*]dendralenes—work that actually only dealt with the preparation of [3]- and [4]dendralenes—the classical methods of olefin synthesis were employed: β-elimination of appropriate halides (mostly bromides), acetate pyrolysis, Hofmann elimination, and pericyclic reactions. These methods often involved high temperatures and—although of certain merit for the preparation of the parent hydrocarbons—are of limited value for the preparation of substituted systems, which could undergo side reactions under the rather severe reaction conditions. Furthermore, none of these approaches involved a general concept that, in principle, might be extended to allow for the preparation of the whole series of [*n*]dendralenes.



Scheme 2. Early masked diene approaches to [3]dendralene.

The first broad concept that slowly began to evolve is summarized in Scheme 2, which shows that a general approach might be developed if suitable precursor molecules containing a future diene moiety in a masked or storage form became readily available. Consider, for example, methylenecyclobutane (**9**, Scheme 2); this can be converted by a number of steps into 1-vinylcyclobutene (**10**), which on heating to

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Michael Sherburn (born 1966) studied chemistry at the University of Nottingham, UK, and received his PhD in 1991 with John A. Murphy. He then moved to Australia and worked as a post-doctoral fellow in the Research School of Chemistry at the Australian National University (ANU) with Lewis N. Mander. He held academic positions at Massey University in New Zealand and the University of Sydney before being appointed at the Research School of Chemistry, ANU in 2002. His awards include the Le Févre Memorial Prize of the Australian Academy of Science (2006) and the A. J. Birch Medal of the RACI (2008).

335 °C undergoes 4π electrocyclic ring opening to give [3]dendralene (**11**) in quantitative yield, with the cyclobutene ring serving as the masked form of a 1,3-butadiene moiety.[18,19]

A related approach involves cyclobutanone as the starting material.[20,21] From a preparative viewpoint (availability of substrates, numbers of intermediates, and products prepared) both of these approaches leave something to be desired. It was, therefore, a real step forward when Cadogan et al. were able to convert the "stored 1,3-butadiene" 3-sulfolene (**12**) in several steps into its vinyl derivative **13**, which on heating to 550 °C provided [3]dendralene (**11**) in 87 % yield.[22] This synthesis not only made the hydrocarbon available in multigram amounts, but it also set the stage for a first truly general synthesis of [*n*]dendralenes, as will be discussed below.

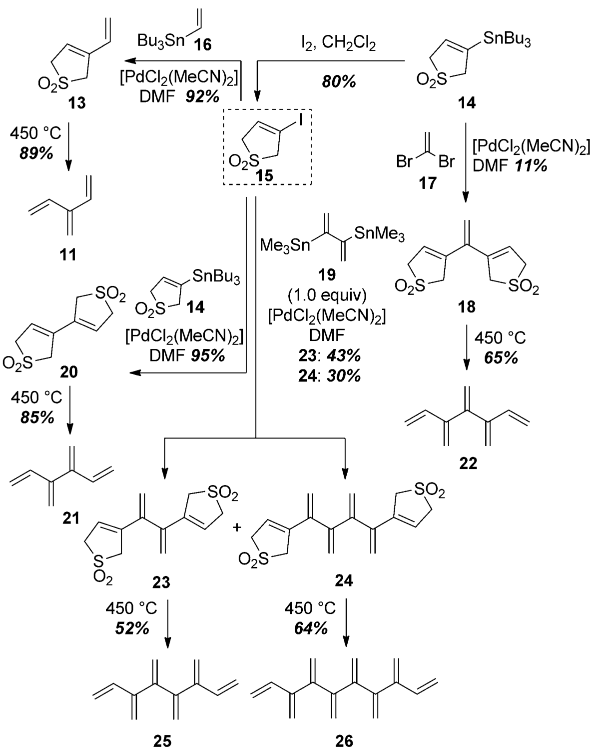
About half a dozen approaches to [4]dendralene (**21**) have been reported in the literature,[4] most of them modes of formation (i.e. using specialized equipment and methods, low yielding, many steps), rather than preparatively useful routes to this higher "vinylogue" of **11**. Furthermore, in many cases, the synthetic protocols are buried in the patent and academic literature (i.e. PhD theses).

The first general synthesis of dendralenes, published in 2000, was (in the opinion of the senior author) a real breakthrough in this area of unsaturated hydrocarbon chemistry.[23] In their approach, Sherburn and co-workers took the so far tacitly assumed (and sometimes documented) instability of the dendralenes into account from the very beginning, by employing the "storage concept" throughout their whole route. In other words, the terminal 1,3-butadiene moieties of the dendralene structure were masked as 3-sulfolene derivatives and were not revealed until the very end.

As summarized in Scheme 3, a series of Stille cross-coupling reactions gave the masked dendralene intermediates. The key building blocks were Sweeney's sulfolene (**14**),[24] 3-iodosulfolene (**15**), tributylvinylstannane (**16**), 1,1-dibromoethylene (**17**), and 2,3-bis(trimethylstannyl)-1,3-butadiene (**19**). Cadogan's [3]dendralene precursor **13** was prepared in high yield by cross-coupling **15** with **16**, whereas masked [4]dendralene **20** was obtained from the coupling of **14** with **15**. The masked [5]dendralene **18** was prepared in low yield by a twofold coupling of **14** with **17**. Masked [6]dendralene **23** was obtained from a twofold cross-coupling of **15** with **19**, a reaction which also gave the [8]dendralene precursor **24** as a by-product.

The masked dendralenes **13**, **18**, **20**, **23**, and **24** are colorless solids, which are stable at room temperature for weeks when stored under nitrogen. Pyrolysis of these sulfolenes at 450 °C gave the pure dendralenes **11**, **21**, **22**, **25**, and **26** in moderate to good yields on a scale of a few milligrams (Scheme 3). Their structural assignment rests largely on their spectroscopic properties, as discussed in Section 5.

It was shown later by the Sherburn research group that the approach summarized in Scheme 3 could still be further improved. In fact, practical syntheses of the dendralenes were developed which avoid both the use of a temporary protection and high temperatures. The successful approach exploits an important result from their previous studies, namely that the postulated extreme instability/reactivity of the dendralenes was a myth.[25–29] The successful approaches once again involve cross-coupling reactions, this time of the Kumada and Negishi types, and are based on the chloroprene Grignard reagent **29** as a readily available starting material (Scheme 4).[26]

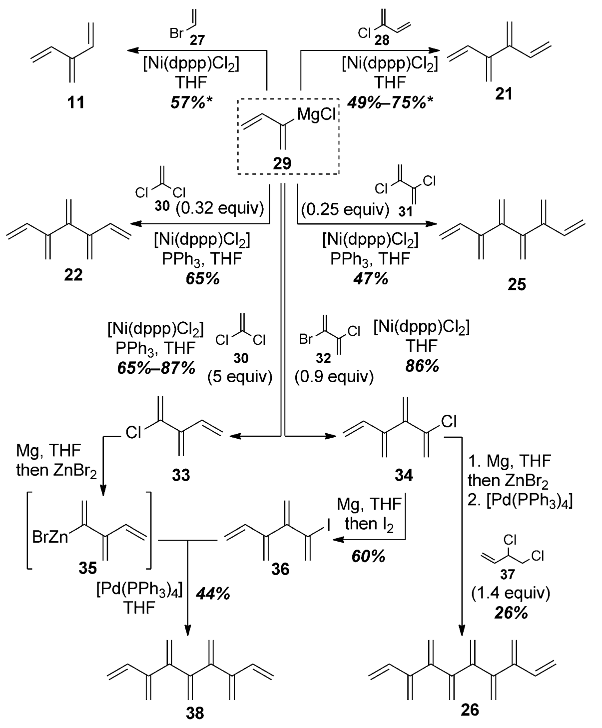


Scheme 3. First unified approach to the parent dendralenes.

The lower members of the dendralene family, namely [3]-, [4]-, [5]-, and [6]dendralenes, can be prepared in one step through nickel(0)-catalyzed Kumada coupling reactions of the chloroprene Grignard reagent **29**. In the first two cases, vinyl bromide (**27**) and chloroprene (**28**) were employed as electrophiles; in the latter two cases, twofold coupling reactions were carried out with the double electrophiles 1,1-dichloroethylene (**30**)[27] and 2,3-dichloro-1,3-butadiene (**31**), respectively.

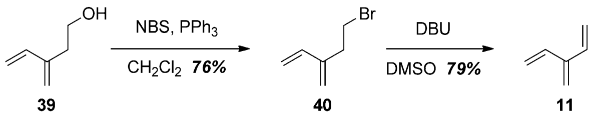
Currently, the higher dendralenes are a little more difficult to synthesize. [7]Dendralene (**38**) was accessed for the first time through Negishi coupling of iodotetraene **36** and trienylzinc **35**,[28] which were in turn prepared by monocoupling **29** with dihalides **30** and **32**, respectively. The first practical approach to [8]dendralene (**26**) involved a palladium(0)-catalyzed oxidative homocoupling of the organozinc species derived from chlorotetraene **34**. These routes allow rapid access to the hydrocarbons in synthetically useful amounts (200 mg–5 g), and have led to the first exploratory investigations into the properties of the dendralene family (see Sections 5–8).

Whereas the direct coupling approach allows the extremely rapid synthesis of the dendralenes, it currently only allows the preparation of the triene as a solution in THF, since the boiling points of the [3]dendralene and THF are very



Scheme 4. Preparative syntheses of [3]–[8]dendralenes. *Yields with asterisks refer to THF solutions. dppe = ethane-1,2-diylbis(diphenylphosphane), dppp = propane-1,2-diylbis(diphenylphosphane).

similar. The problem of obtaining practical amounts of [3]dendralene (**11**) in a solvent-free form was recently solved through the sequence depicted in Scheme 5.[25] The successful approach involved the mild elimination of HBr from bromide **40**, which is stable, less volatile than [3]dendralene, and can be prepared on a large scale from alcohol **39**. The triene-forming elimination step (**40**→**11**) is carried out by slow addition of DBU to a solution of the bromide **40** in DMSO at room temperature and under a modest vacuum; the triene distils as it is formed and is collected in a cold trap. Up to 5 g batches of the hydrocarbon of high (> 95 %) purity can be prepared in this manner using standard laboratory equipment.



Scheme 5. Preparative synthesis of [3]dendralene in solvent-free form. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NBS = *N*-bromosuccinimide.

In the case of the slightly less volatile [4]dendralene (**21**), careful removal of THF following the cross-coupling reaction (Scheme 4) allows the isolation of the solvent-free hydrocarbon, albeit with some loss of material. The Kumada cross-coupling approach to the tetraene (Scheme 4) is higher yielding and more convenient than the homocoupling approach reported earlier.[29]

These versatile approaches to the [*n*]dendralenes currently reach their limit with the synthesis of [8]dendralene (**26**). The main hindrance towards extension of this protocol is caused by the lack of access to difunctional dendralene building blocks, such as 2,4-dichloro[3]dendralene. Theoretical calculations on higher dendralenes have, however, been published.[30]

The parent dendralenes are readily handled under standard laboratory conditions. As will be discussed in Sections 5 and 6, members of the dendralene family with odd numbers of olefins behave differently to those with even numbers of alkene bonds. Specifically, the odd dendralenes are significantly less stable than the even dendralenes.

3. Acyclic Dendralene Derivatives

As a consequence of the up-surge in interest in dendralenes and, notably, their ever-increasing role in diene-transmissive Diels–Alder reactions (DTDA reactions, see Section 6), numerous new methods to prepare substituted dendralenes have recently been described. It is not very surprising that most of these concentrate on the preparation of the simplest systems, that is, substituted [3]dendralenes. We assume that this will change in the next few years.

Five of the carbon atoms of [3]dendralene are available for substitution and, when geometrical isomers are taken into account, four monosubstituted [3]dendralenes are possible: **41**–**44** (Figure 1). Herein, we will call **44** 3-substituted, since the quaternary carbon atom cannot carry a substituent. This numbering convention has been extended to the higher dendralenes, of which there are very few examples in the literature.

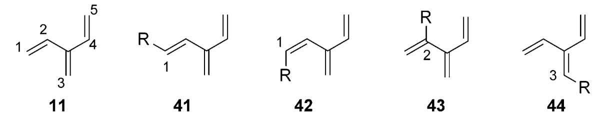
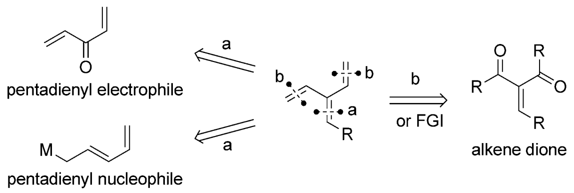


Figure 1. Numbering in [3]dendralene and monosubstituted analogues.

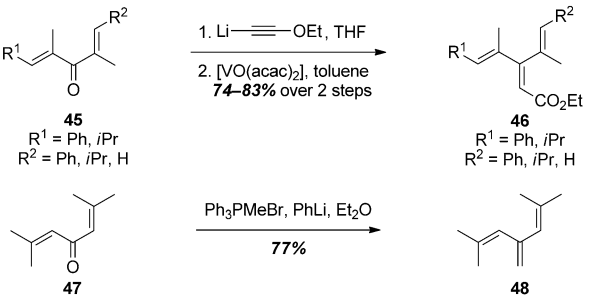
In general terms, synthetic approaches to acyclic [3]dendralenes can be divided into two general classes: 1) those that involve construction of an alkene bond (Scheme 6) and 2) those that involve construction of a C–C single bond (Schemes 13 and 16). An additional and smaller (but still important) group of synthetic approaches involve more specialized methods for the assembly of the branched triene skeleton. These distinct approaches to the construction of dendralenes will be discussed in turn.

An enduring approach to the synthesis of substituted [3]dendralenes involves formation of an alkene bond (Scheme 6). Three general themes for the synthesis of dendralenes by formation of an alkene have emerged: retrosynthetic disconnection of the internal alkene (pathway a) leads to either a pentadienyl nucleophile or electrophile. Alternatively, disconnection of both terminal alkenes leads to cross-conjugated alkene-1,1-diones (pathway b).



Scheme 6. Alkene disconnections in [3]dendralene synthesis. FGI = functional group interconversion.

As was the case for the parent triene hydrocarbon (see Section 2), approaches involving construction of an alkene unit were the most important classical methods for the preparation of substituted [3]dendralenes. The early literature contains several transformations of 1,4-dien-3-ones into substituted [3]dendralenes through Wittig reactions,[31] ketene additions (followed by decarboxylation),[32] and Grignard reactions (followed by dehydration).[33] More elegant versions of this general approach continue to appear in the literature, undoubtedly in part because of the readily available nature of dienones such as **45** and **47** (Scheme 7).

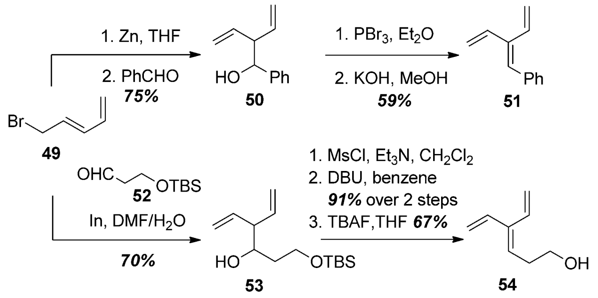


Scheme 7. Representative examples of pentadienyl electrophiles for the synthesis of [3]dendralenes. acac = acetylacetonato.

Recent examples include Peterson-type olefinations[34,35] and Reformatsky reactions.[36] Recent studies by West and co-workers have shown that olefination of dienones **45** can be achieved through the addition of lithiated ethoxyacetylene followed by a Meyer–Schuster rearrangement.[37,38] The highly substituted dienone **47** undergoes smooth Wittig olefination to form **48**.[40] Related olefination reactions of dienone **47** have also been reported.[39,41]

Currently, there are two significant limitations of the dienone olefination method for the synthesis of [3]dendralenes: firstly, until very recently, only dienones substituted at both the 1- and 5-positions were utilized as the olefination precursors. We suspect that there is a problem with competing conjugate addition. The most recent contribution from the West research group[37,38] is significant since it demonstrates, to our knowledge, the first successful olefination of a terminally unsubstituted dienone. The second limitation relates to the lack of control of the alkene configuration in the product when unsymmetrically substituted dienones are employed.[37,38]

The use of pentadienyl nucleophiles in the synthesis of substituted [3]dendralenes (Scheme 8) has been dominated by Barbier reactions involving 5-bromopenta-1,3-diene (**49**).

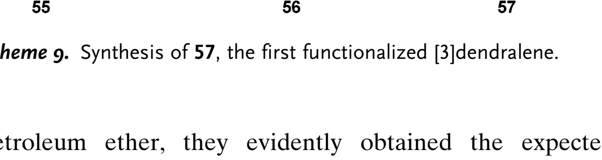


Scheme 8. Representative examples of pentadienyl nucleophiles for the synthesis of [3]dendralenes. Ms = methanesulfonyl, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

In 1964, the Miginiacs treated the organozinc compound derived from **49** with benzaldehyde. They then converted the resulting alcohol **50** into its bromide, which, upon base-induced elimination, furnished 3-phenyl[3]dendralene (**51**) in moderate yield.[42] A subsequent report by Spangler described similar findings with a related structure.[43]

Recently, the Miginiac–Barbier approach to functionalized [3]dendralenes was modernized and generalized by Fallis and co-workers (Scheme 8).[44,45] Pentadienylindium, generated in situ from **49** was treated with an aldehyde, such as **52**, to provide the alcohol **53**. Dehydration (through base-induced β-elimination of the corresponding mesylate;[45] or under Mitsunobu conditions[44]) afforded 3-substituted [3]dendralene **54** in good yield.[46] Clearly, the high degree of variability that can be tolerated in building block **52** means that this approach has great potential for the synthesis of 3-substituted [3]dendralenes. An appealing aspect of this reaction is that it does not require anhydrous solvents or an inert atmosphere. The Miginiac–Fallis method has since been used by other research groups to create libraries of 3-substituted [3]dendralenes,[47–49] and a variation on the theme to produce 2-bromo[3]dendralenes has been reported.[50]

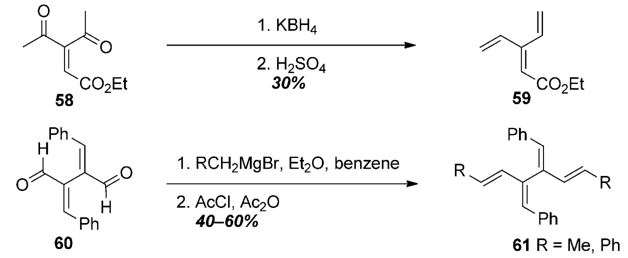
The first functionalized dendralene was made through an earlier transformation that is related to the pentadienylation of aldehydes (Scheme 9). When, in 1951, Paul and Tchelitcheff metalated trivinylmethane (**55**) with amyl sodium in petroleum ether, they evidently obtained the expected carbanion **56**, since the intermediate on quenching with carbon dioxide provided the carboxylic acid **57** in excellent yield.[51] It is notable that this synthesis predates the first



Scheme 9. Synthesis of **57**, the first functionalized [3]dendralene.

reported preparation of the parent [3]dendralene in 1955.[52–54] When **57** was heated with maleic anhydride it furnished—in the first ever reported diene-transmissive Diels–Alder addition (see Section 6)—the expected 2:1 cycloaddition product.

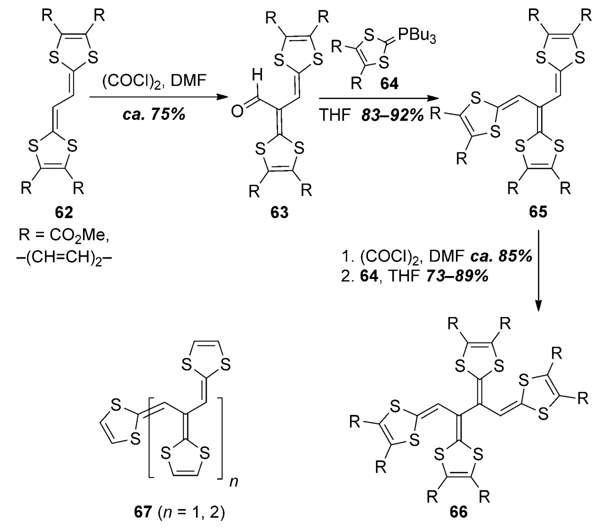
Returning to alkene disconnections in the synthesis of acyclic dendralenes (Scheme 6), the last theme involves an alkene-dione precursor (pathway b). Such compounds have been converted into substituted dendralenes by either the olefination of aldehydes or through functional group interconversions. In an example of the latter, 3-ethoxycarbonyl[3]-dendralene (**59**) was prepared by reducing the cross-conjugated diketone **58** to the diol then dehydrating it to the triene (Scheme 10).[55] Related [3]dendralene syntheses involve the conversion of acetyl groups into chloroalkenes[58] and silyl enol ethers.[59,60]



Scheme 10. Representative examples of double electrophile approaches to [3]dendralenes.

In an example of the aldehyde olefination approach, a double Grignard addition/double dehydration of dialdehyde **60** gave tetrasubstituted [4]dendralenes **61**.[57] Ferrocene derivatives of [3]dendralene have also been prepared in this manner.[56] An iterative variant of this much-used transformation has been devised to prepare more complex dendralene structures with redox-active substituents (Scheme 11).[61,62] Thus, Yoshida and co-workers synthesized [3]- and [4]dendralene derivatives **65**–**67** by a route beginning with electron-rich diene **62**, which underwent a selective, single electrophilic formylation to form cross-conjugated diene aldehyde **63** (Scheme 11).[61] A Wittig reaction with phosphorane **64** gave [3]dendralene derivative **65** in good yield. Repetition of the sequence led to [4]dendralene **66**. When R = CO_2Me, both **65** and **66** could be demethylated and decarboxylated to afford their parent systems **67** on treatment with lithium bromide in hexamethylphosphoramide. These compounds bear a structural relationship to tetrathiafulvalene, of which they are "stretched" versions.

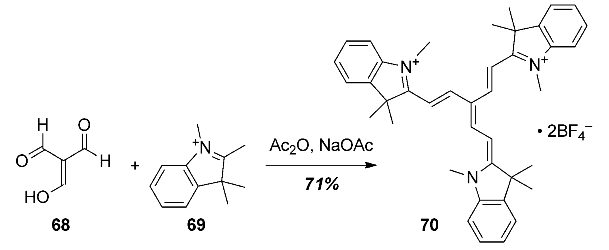
In a related approach, Bryce et al. carried out twofold Horner–Wadsworth–Emmons (HWE) olefinations to give [3]- and [4]dendralenes.[63] The electrochemistry of these compounds has been studied in detail.[63,64] Unfortunately, the elegant chemistry described by Yoshida and co-workers is unlikely to prove more generally applicable for the synthesis of dendralenes. The problem is that 1,3-butadien-2-ylcarbonyl compounds undergo rapid Diels–Alder dimerization.[65] In other words, the stability of dienals such as **63** (Scheme 11) is unusual. Presumably, only electron-rich butadienes that are



Scheme 11. Iterative synthesis of "stretched tetrathiafulvalenes" according to Yoshida and co-workers.

heavily substituted at the terminal positions are likely to be isolable and suited to this sequence.

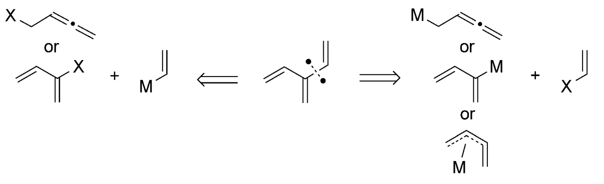
We complete this section on olefination routes to acyclic [3]dendralenes with a very efficient triple condensation approach (Scheme 12). This general approach has not only



Scheme 12. Threefold olefination routes to [3]dendralene dyes.

been employed for the preparation of acyclic [3]dendralenes with extended conjugation such as **70**,[66] it has also been used widely for the preparation of 1,1-cyclo- and 3,3-cyclo[3]-dendralenes, structures that have found application in many polymethine dyes.[66–68]

Moving away from olefination approaches, a significant number of recent methods for the synthesis of substituted acyclic [3]dendralenes involve the assembly of C–C single bonds. We have already seen that cross-coupling approaches were employed for the preparation of the parent dendralenes (Section 2). As depicted in a more general sense in Scheme 13, disconnection of one C–C bond of [3]dendralene leads to ethenyl- and 1,3-butadien-2-yl precursors suitable for metal-catalyzed cross-coupling reactions that allow access to a very wide range of derivatives. It is perhaps less apparent that [3]dendralenes can also be assembled in this manner from the structures resulting from allylic transposition of the 1,3-butadien-2-yl synthons, namely allenes. Indeed, in the case

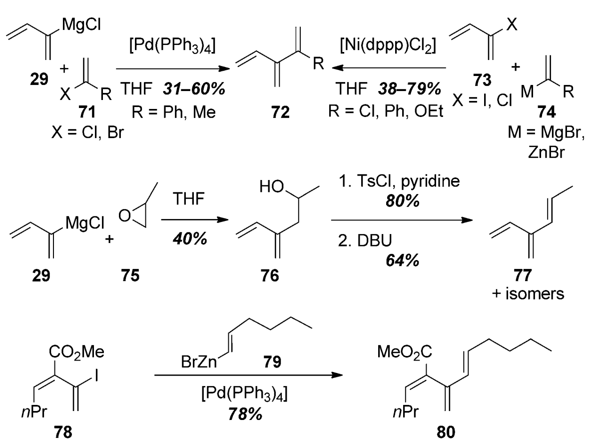


Scheme 13. Single C—C bond disconnections in the synthesis of [3]dendralenes.

of the nucleophilic coupling partner, π-allyl complexes may also play a role.

Despite the enormous number of papers detailing cross-coupling methods in synthesis, the overwhelming majority describe reactions involving arenes as at least one of the two partners. A relatively small percentage of papers describe cross-coupling reactions between two alkenic partners and, of these, only a few concern the synthesis of branched trienes and higher.

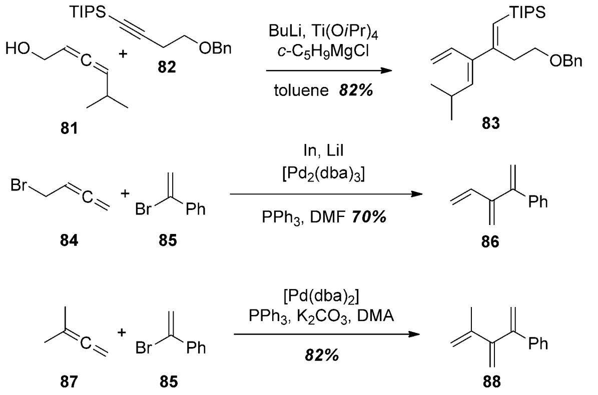
The first reports on the syntheses of [3]dendralenes by cross-coupling reactions of the types depicted in Scheme 13 were single examples in publications describing broader cross-coupling studies.[69,70] A general route to 2-substituted [3]dendralenes **72** by way of Kumada- or Negishi-type cross-coupling reactions was reported by Sherburn and co-workers in 2007 (Scheme 14).[28] This study extends some of the methods developed for the synthesis of the parent dendralene (see Section 2). The 1,3-butadien-2-yl coupling partner can be either the nucleophilic or the electrophilic component (Grignard reagent **29** or 2-halo-1,3-butadiene **73**, respectively) in these reactions. Thus, a range of 2-substituted [3]dendralenes **72** was obtained by coupling 2-halo-1,3-butadiene **73** (or its corresponding Grignard reagent **29**) with a suitably substituted alkenyl Grignard reagent or alkenyl zinc halide **74** (or alkenyl halide **71**). As shown in Scheme 4 (see Section 2), the Kumada-type coupling of Grignard reagent **29** and 2-bromo-3-chlorobutadiene (**32**) has also been used to synthesize 2-chloro[4]dendralene (**34**), en route to [8]dendralene.[26]



Scheme 14. Representative 1,3-butadien-2-yl building blocks in the synthesis of substituted [3]dendralenes. Ts = toluene-4-sulfonyl.

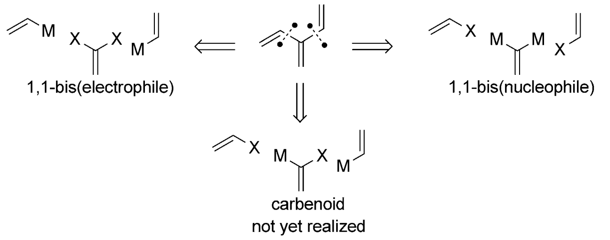
In terms of both step count and selectivity, cross-coupling methods compare rather favorably with more traditional approaches for the synthesis of dendralenes that also involve the formation of C—C bonds.[71,72] For example, the synthesis of a substituted dendralene by Tsuge and co-workers 1986[71] is reproduced in Scheme 14. This important early study involves nucleophilic epoxide ring opening (**29** + **75**→**76**), alcohol derivatization, as well as elimination and produces the desired product **77** as a mixture of its stereo- and regioisomers. Cross-coupling methods generally do not lead to the formation of isomeric mixtures and have the added benefit of permitting more highly substituted 1,3-butadien-2-yl coupling partners.[73,74,76] Iododiene **78**, for example, was shown by Ma and co-workers to be an effective coupling partner in a Negishi cross-coupling to afford trisubstituted [3]dendralene **80**.[75]

There are several successful syntheses of substituted [3]dendralenes that proceed through participation of 1,2-butadien-4-yl precursors—the allylic transposed form of the 1,3-butadien-2-yl unit (Scheme 15). A representative example includes a recently described titanium-mediated cross-coupling reaction of allenic alcohols with an internal alkyne. This process, which involves divergent reaction pathways to yield either stereocontrolled 1,4-dienes or substituted [3]dendralenes such as **83**, is illustrated by the addition of the allenyl alcohol **81** to the alkyne **82**. The substitution on the allene plays a critical role in the determination of the reaction pathways.[77,78] The palladium(0)-catalyzed coupling of bromomethyl allene **84** to alkenyl bromide **85** presumably involves the intermediacy of the 1,3-butadien-2-ylindium species.[79] Several other—albeit isolated—examples of cross-coupling reactions involving 1,2-butadien-4-yl electrophiles to form [3]dendralenes have been reported.[69,80] A particularly interesting variation involves the palladium(0)-catalyzed Mizoroki–Heck reaction of 2-bromostyrene (**85**) with dimethylallene (**87**) to form 2-methyl-4-phenyl[3]dendralene (**88**).[81]



Scheme 15. Cross-coupling reactions of 1,2-butadien-4-yl units in the synthesis of substituted [3]dendralenes. Bn = benzyl, dba = *trans,trans*-dibenzylideneacetone, DMA = *N,N*-dimethylacetamide.

Double cross-coupling reactions have also been used successfully for the synthesis of many dendralene derivatives. As depicted in Scheme 16, three general approaches can be



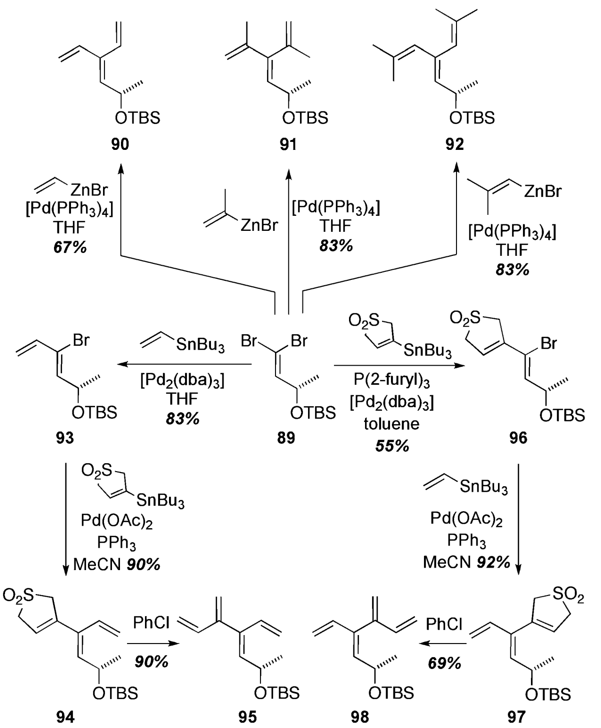
Scheme 16. Twofold C–C bond disconnections in the synthesis of [3]dendralenes.

envisioned. Thus far, only two of these have been used for the synthesis of dendralenes: namely, double coupling reactions of either 1,1-bis(electrophile)s or of 1,1-bis(nucleophile)s.

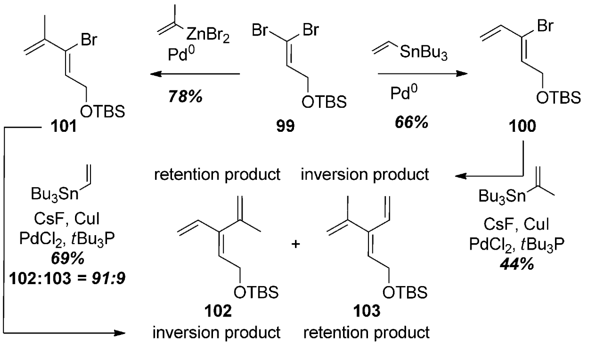
The 1,1-bis(electrophile) approach has been more thoroughly investigated for the synthesis of dendralenes because these precursors are readily available. 1,1-Dibromoalkenes are particularly easily synthesized through the Ramirez dibromo-olefination of aldehydes (with PPh_3 and CBr_4),[82] and many successful examples of single cross-coupling reactions of these (and other) 1,1-dihaloalkenes have been published.[83] In contrast, there are relatively few double cross-coupling reactions of 1,1-dihaloalkenes. The first example of a double coupling of a 1,1-dihaloalkene to form a [3]dendralene was an isolated example reported by Wang and Shen in 1998.[84] In 2000, the parent 1,1-dibromoethylene was coupled in low yield with Sweeney's sulfolene to afford a masked version of the parent [5]dendralene (see Section 2, Scheme 3).[23] In 2002, Oh and Lim demonstrated that a 1,1-dibromoalkene, obtained by a Ramirez dibromo-olefination of benzaldehyde, undergoes double Suzuki–Miyaura reactions with alkenyl boronic acids in respectable yields[85] and since then, several other isolated examples of this process have been reported.[86]

The first report of a more general route to substituted dendralenes through cross-coupling reactions of 1,1-dibromoalkenes was disclosed in 2007 by the Sherburn research group (Scheme 17).[48] Many compounds were prepared from the same 1,1-dibromoalkene **89**, including the first chiral [3]dendralenes, which demonstrates the versatility of the cross-coupling approach for the synthesis of dendralenes. Twofold Stille and Negishi coupling reactions furnished the substituted [3]dendralenes **90–92**; the [4]dendralenes **95** and **98** were prepared by stepwise Stille coupling reactions with two different alkenylstannanes, the second was a sulfolene, which gave rise to the chiral [4]dendralenes **95** and **98** on heating. The first coupling is invariably much faster than the second and furnishes the *Z* isomer of the 2-bromodiene with high selectivity.[83] It is noteworthy that the second cross-coupling reaction (**93**→**94**; **96**→**97**) proceeds in this series with clean inversion of the alkene geometry; such a process was first reported by Negishi and co-workers in 2003.[87]

Cross-coupling reactions of 2-bromo-1,3-butadienes with nucleophiles can be capricious, with a mixture of stereoisomers often obtained. An example of this problem was encountered en route to the natural product triptolide (Scheme 18).[88] The synthesis required 2,3-disubstituted [3]dendralene **103**, which would result from sequential cross-coupling reactions of dibromide **99** with vinyl- and 2-propenyl-containing coupling partners. Mixtures of stereoisomers—as a result of both retention and inversion pathways—were formed under all the investigated reaction conditions.

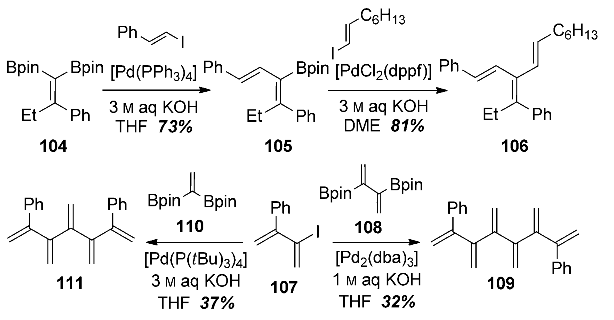


Scheme 17. Double cross-coupling reactions of 1,1-dibromoalkenes in the synthesis of substituted [3]- and [4]dendralenes.



Scheme 18. Stereochemical problems with the double coupling approach to [3]dendralenes.

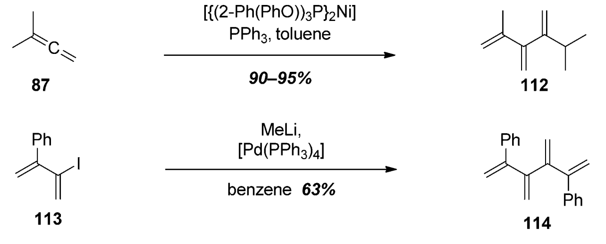
In comparison to the use of 1,1-bis(electrophile)s, double coupling reactions involving 1,1-bis(nucleophile)s are rare, mainly because of the lack of robust synthetic approaches to 1,1-dimetalloalkenes. Indeed, Shimizu et al. have reported the only successful examples of this type (Scheme 19).[89] They employed 1,1-bis(pinacolatoboryl)ethylene (**110**) and its higher ethenologue **108** as precursors to a number of substituted dendralenes. Both double and single coupling reactions have been achieved, although yields of single coupled products are modest and the only reported examples



Scheme 19. Double cross-coupling reactions of 1,1-diboronylalkenes in the synthesis of substituted [3]- to [6]dendralenes according to Shimizu et al. Bpin = pinacolatoboryl, DME = 1,2-dimethoxyethane, dppf = bis(diphenylphosphanyl)ferrocene.

involve iodide **107**. Nevertheless, the scope of this approach is, in principle, very wide indeed and, once these difficulties are overcome, this has the potential to be one of the most powerful approaches for the synthesis of dendralenes.

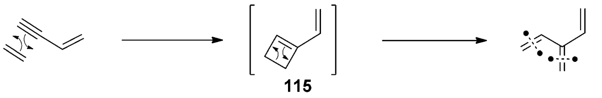
Aside from cross-coupling methods, oxidative homocoupling and related dimerizations have also been explored. These approaches are necessarily more limited in scope—in terms of product structure—than cross-coupling methods. Allenes are common precursors in homocoupling reactions to [3]- and [4]dendralenes, and we believe that there is potential in this area for significant development. The first example of allene dimerization was reported in 1972, and involved the conversion of 1,1-dimethylallene (**87**) into 2,4-disubstituted [3]dendralene **112**, by using a nickel(0) promoter (Scheme 20).[90] A palladium(0)-catalyzed version involving monosubstituted allenes has also been reported.[91]



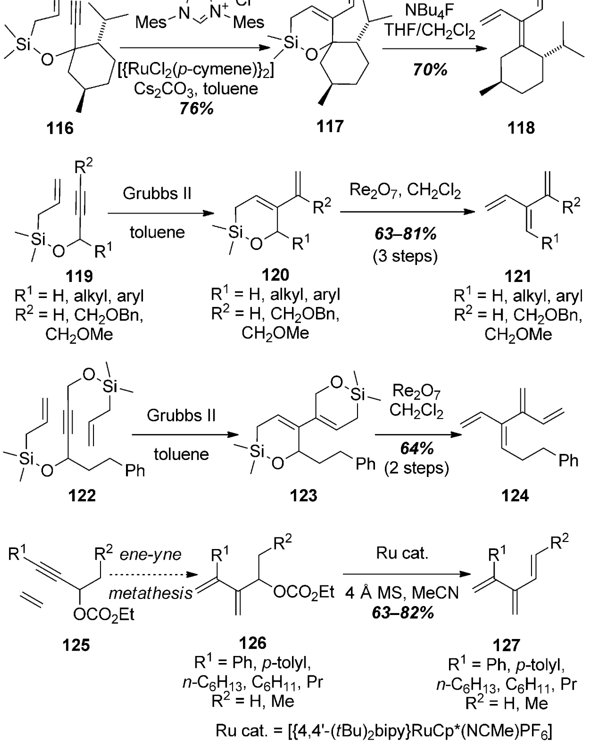
Scheme 20. Allene and diene dimerizations leading to [3]- and [4]dendralenes.

Symmetrically substituted [4]dendralenes have been prepared in synthetically useful yields as unexpected products.[92] It would appear that Suzuki–Miyaura and Murahashi[93] (e.g. **113**→**114**) coupling reactions occur between the precursors and the organoboron/organolithium species formed in situ. Further examples of catalyzed dimerizations leading to substituted dendralenes have been reported.[94] Finally in this section, we note that the first practical synthesis of the parent [4]dendralene (**21**) was based upon an oxidative homocoupling of the chloroprene Grignard reagent.[29] This approach is pre-dated by a patented procedure involving chloromethylallene as a precursor.[95]

In recent times, a new theme has begun to emerge for the synthesis of dendralenes, which is enjoying significant current activity. This approach involves ene-yne metathesis, a process that generates a new 1,3-butadiene unit in one step via intermediate **115** (Scheme 21). Two distinct types of processes have been employed in this approach: those requiring metathesis catalysts and those involving spontaneous (i.e. uncatalyzed) reactions. So far, examples of the former variety are limited to intramolecular processes that form semicyclic dienes that undergo ring-opening eliminations to form dendralenes (Scheme 22). The first examples were reported by Bruneau and co-workers in 2003.[96] The procedure begins with a catalytic ene-yne cross-metathesis of precursor **116** to form cyclic siloxanes **117**. The catalyst was generated in situ from [{RuCl$_2$(p-cymene}$_2$], 1,3-bis(mesityl)imidazolinium chloride, and cesium carbonate. Desilylation/deoxygenation with a fluoride salt subsequently provided the dendralene terpenoid **118**.



Scheme 21. Ene-yne cross-metathesis in the synthesis of [3]dendralenes.

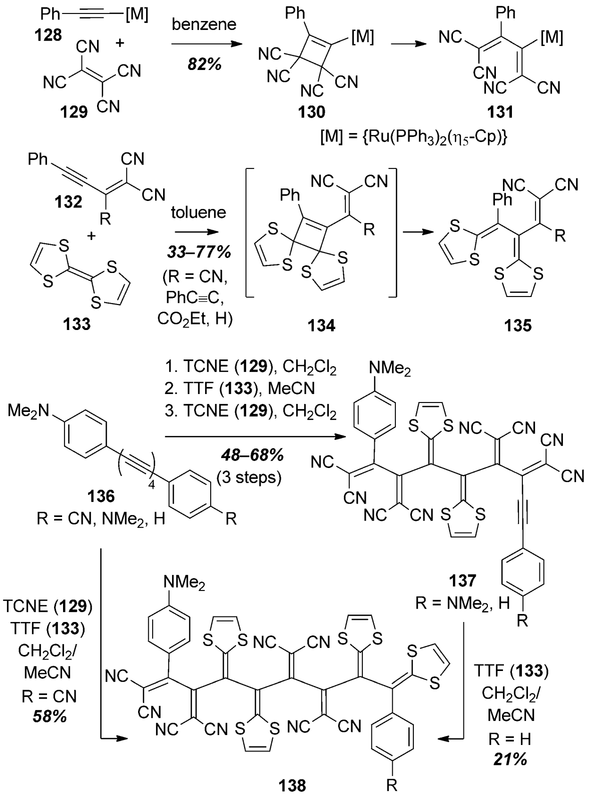


Scheme 22. Dendralene synthesis by way of catalyzed ene-yne metathesis. Cp* = pentamethylcyclopentadienyl, Mes = 2,4,6-trimethylphenyl, 4,4'-(tBu)$_2$bipy = 4,4'-di-*tert*-butylbipyridyl.

A range of mono- and disubstituted [3]dendralenes **121** were subsequently synthesized in good yields by Park and Lee through ring-closing ene-yne metathesis of **119** with the Grubbs II catalyst, followed by a rhenium oxide promoted elimination.[97] In a very nice double metathesis reaction, dienyne precursor **122** was transformed into monosubstituted [4]dendralene **124** upon treatment with the Grubbs II catalyst followed by Re_2O_7.[97] Considering what has been accomplished preparatively here, the yield of 64% is excellent. A related approach has been reported with the synthesis of a functionalized benzo[*b*]oxepine through ene-yne metathesis and its subsequent base-mediated ring opening to form a 1-substituted [3]dendralene.[98]

Bruneau and co-workers have recently described a different ene-yne metathesis/elimination sequence to substituted [3]dendralenes.[99] This new approach involves metathesis between propargylic carbonates and ethylene. The resulting 1,3-dienic allylic carbonates **126** undergo a ruthenium-catalyzed elimination reaction to furnish substituted [3]dendralenes **127**, generally in acceptable to good yields. From the various catalysts tested, the one shown in Scheme 22 provided the best results.

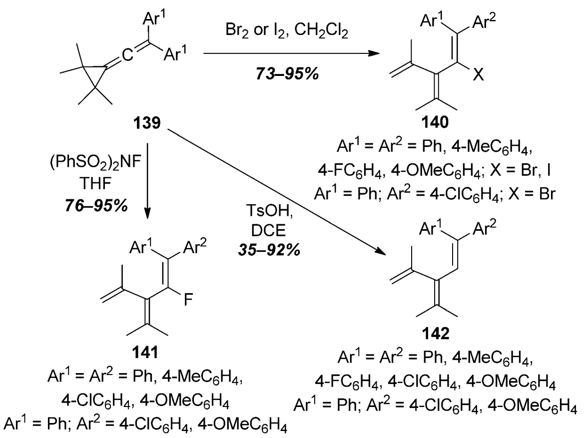
Almost 30 years ago, Bruce et al. found that electron-deficient metalated acetylene **128** "splits" the double bonds of reactive olefins, such as tetracyanoethylene (TCNE, **129**) to afford diene **131** in good yield (Scheme 23).[100,101] This uncatalyzed metathesis process presumably involves the generation of a cyclobutene intermediate **130** by [2+2] cycloaddition, which subsequently opens by an electrocyclic reaction to give the product **131**. An analogous process was discovered 10 years later by Hopf et al., who found that the electron-rich olefin tetrathiafulvalene (TTF, **133**) added to the electron-depleted triple bond of the enynes **132**.[102] Again, overall cleavage of the TTF C=C bond was observed, and the ring-opened products **135**—highly functionalized [3]dendralenes—were isolated, presumably again via a cyclobutene intermediate **134**. The triple bond in the substrate evidently required the presence of the strongly electron-withdrawing functional group, since dimethyl acetylenedicarboxylate did not react.[103]



Scheme 23. Dendralene synthesis by way of uncatalyzed ene-yne metathesis. Cp = cyclopentadienyl.

Diederich and coworkers have since used successive electronically controlled [2+2] cycloadditions/electrocyclic ring-opening sequences of TCNE (**129**) and TTF (**133**) with end-capped (activated) tetraynes **136** to synthesize a series of highly substituted [*n*]dendralenes in good yields.[104–106] For example, tetraynes **136** (R = NMe_2, H) gave the [6]dendralene adducts **137** in good yields over three steps.[104] Further reaction of **137** (R = H) with TTF (**133**) at an elevated temperature afforded [8]dendralene **138** (R = H), although in a low yield (21%). Furthermore, adding a mixture of TCNE (**129**) and TTF (**133**) to the CN-substituted tetrayne **136** resulted in a cascade of successive TCNE and TTF cycloadditions to provide [8]dendralene **138** (R = CN) in a remarkably high yield (58%) given the eight distinct processes occurring in this one-pot process.[105] To rationalize this amazing cascade of additions, the authors suggest that after the [2+2] cycloaddition of TCNE (**129**) to the substrate to provide the corresponding tetracyano-1,3-butadiene (TCBD) derivative, the triple bond next to this TCBD moiety is sufficiently electron deficient to participate in a subsequent [2+2] cycloaddition with **133**. The regioselectivity of the second TCNE addition is then determined by the generated 1,2-di(1,3-dithiol-2-ylidene)ethylene donor unit—and so on until all the triple bonds of the polyacetylene unit have been consumed, with the only restriction that the very last remaining triple bond must carry an electron-deficient substituent (for example a *p*-cyanophenyl group in the above case) for the ultimate cycloaddition to take place.[107] However, the old adage that all synthetic protocols have their limits has also been observed here: although hexaynes analogous to **136** could be prepared, their complete conversion into a [12]dendralene derivative failed.[105]

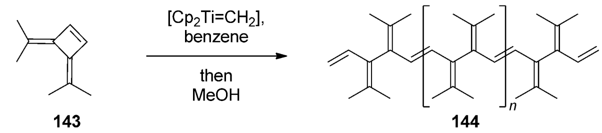
Several new routes to polysubstituted acyclic dendralenes involve unusual (and presumably very energy-rich) starting materials as described by Shi et al. Cyclopropylidene-allenes are the substrates in question. When the bis(aryl)cyclopropylidene-allenes **139** are halogenated with either elemental bromine or iodine, the halogenated [3]dendralenes **140** are produced in very good yields (73–95%) (Scheme 24).[108] *N*-Bromosuccinimide (NBS) has also been used in this transformation, thereby affording **140** ($R^1 = R^2 =$ H, X = Br) in high yield (95%).[109] The fluoro derivatives **141** were successfully synthesized from **139** using *N*-fluorodibenzenesulfonimide.[110] An analogous process occurs upon treatment of cyclopropylidene-allenes **139** with *p*-toluenesulfonic acid (*p*-TSA), which causes clean isomerization to the pentasubstituted [3]dendralenes **142**.[111] Related transformations of vinylidenecyclopropanes[112] and vinylcyclopropenes[113] have also been reported. It can be assumed that the strain energy of these compounds—coupled with the



Scheme 24. Cyclopropylidene allenes in the synthesis of a highly substituted [3]dendralene by Shi et al. DCE = 1,2-dichloroethane.

formation of highly stabilized carbocationic intermediates—provides a substantial part of the driving force for their transformations into dendralenes. Whilst having significant merit, we suspect that this type of approach will be limited to the synthesis of a relatively small range of structural subtypes.

Finally in this section on synthetic approaches to acyclic systems, an interesting cross-conjugated polymer, which formally contains dendralene subunits has been obtained by treating the bis(methylene)cyclobutene **143** with methylidenetitanocene (Scheme 25).[114] The average molecular weight of **144**, a colorless, fairly stable material, is 12000–51000. It has a low dispersity (polydispersity index (PDI) = 2.1) and oxidative doping with iodine, for example, generates a material with moderate conductivity and paramagnetism.



Scheme 25. Synthesis of a cross-conjugated polymer.

These interesting recent examples complete our survey of synthetic approaches to acyclic dendralenes. The reader will, no doubt, be struck by the relatively small number of distinct synthetic approaches that currently exist in the literature, and by the significant limitations inherent in many of them. We now move on to cyclic dendralenes, a group of structures that have recently become the topic of intense synthetic efforts.

4. Cyclic Dendralene Derivatives

Dendralenes can be incorporated into cyclic molecules in virtually countless ways. The purpose of connecting different carbon atoms of a dendralene with functionalized or unfunctionalized bridging elements is twofold. On the one hand, molecular bridges make the original dendralene parent system less flexible. This facilitates planarization and the study of the electronic properties of the now "fixed" cross-conjugated π systems, which should lead to better overlap of the p orbitals. Preparatively, on the other hand, (poly)cyclic dendralenes allow the construction of sometimes very complex carbon frameworks very quickly and economically. We predict this area will see many exciting future developments, especially if functionalized dendralenes become more readily available. We thought it useful to dedicate a separate section of this Review to cyclic dendralenes because of their interesting structural and chemical properties. Furthermore, as we shall see, powerful synthetic approaches to specific subclasses of cyclic dendralenes have emerged that are distinct from those devised for the acyclic systems.

There are eight possible monocyclic [3]dendralenes, which can be named according to their substitution about the triene framework. We have arranged these eight cyclo[3]dendralenes into three subtypes (Figure 2) on the basis of their chemical and physical properties. Three of these—the 1,2-, 1,3-, and 2,3-cyclo[3]dendralenes **145**, **146**, and **147**, respectively—are free to undergo rotation about at least one of their C–C bonds (marked in bold in Figure 2) and, therefore, interconvert between *s-cis-* and *s-trans-*1,3-butadiene conformers. Three more—the 1,4-, 1,5-, and 2,4-cyclo[3]dendralenes **148**, **149**, and **150**, respectively—are not able to undergo *s-cis/s-trans* interchange, at least in small-ring systems. 1,1- and 3,3-Cyclo[3]dendralenes **151** and **152** were discussed in Section 3, because their synthesis and properties are akin to those of acyclic dendralenes. We will now examine the known synthetic routes to each of these cyclic dendralene subtypes in turn, before completing this section with physical properties of the various cyclic dendralenes.

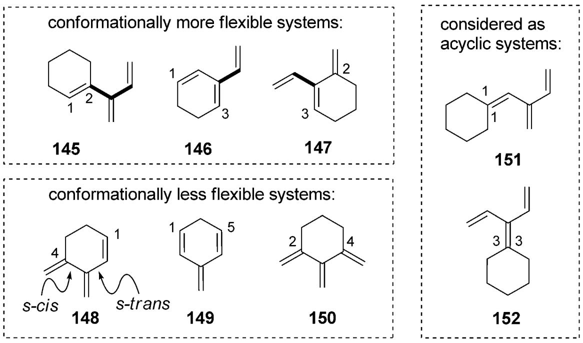
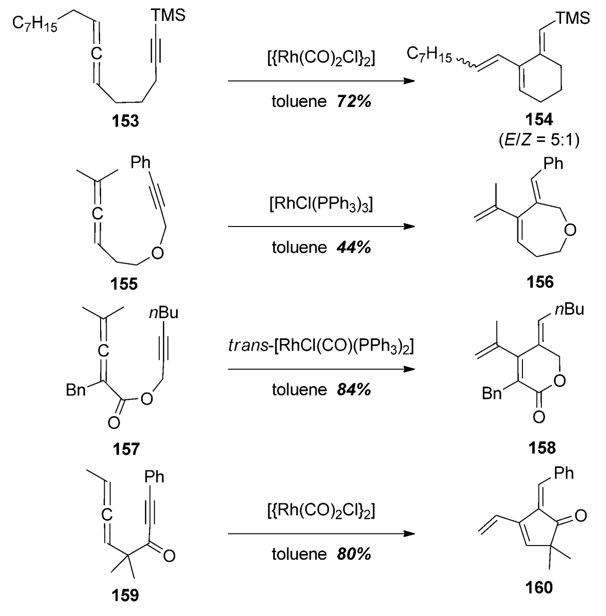


Figure 2. The eight possible monocyclic [3]dendralenes, with a six-membered ring as an example. Dashed boxes denote subtypes.

We will begin with one of the success stories of modern cyclo[3]dendralene synthesis: the cycloisomerization of substituted allenynes. Represented in Scheme 26, this approach is the method of choice for 2,3-cyclo[3]dendralenes **147** containing five, six, and seven-membered carbocyclic and heterocyclic rings, and has been the topic of some 30 publications over the past decade. This transformation—formally an intramolecular Alder-ene process between an alkyne and a substituted allene—is noteworthy for its atom economy and wide substrate scope. The transformation can be thought of as an extension of the well-known enyne cycloisomerization chemistry developed by Trost.[115]



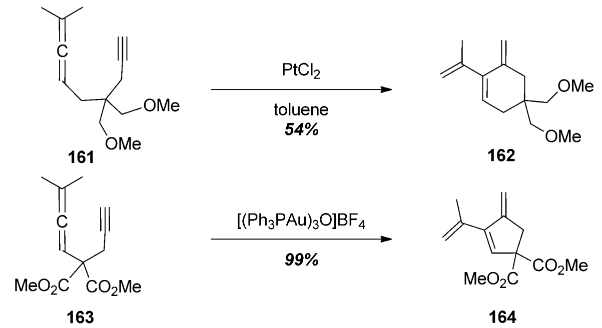
Scheme 26. The rhodium(I)-catalyzed cycloisomerization route to 2,3-cyclo[3]dendralenes. TMS = trimethylsilyl.

Several different transition-metal catalysts achieve the cycloisomerization of allenynes, but clear "winners" have emerged. Following important early observations by the research groups of Malacria[116] and Sato,[117] and building on single results of low-yielding processes reported by Oh et al.[118] and Livinghouse and co-workers,[119] the breakthrough came in 2002 with a publication by Brummond et al.,[120] who employed the rhodium(I)biscarbonyl chloride dimer as a catalyst for the cycloisomerization (e.g. **153**→**154**).

Brummond and co-workers demonstrated the power of the method for the synthesis of six-membered carbocycles and heterocycles with low (generally 0.02 equiv) catalyst loadings and a high functional group tolerance (alcohols, ethers, sulfonamides, esters, alkenyl- and alkynylsilanes are untouched). This important study, which was the first in a series of instructive contributions from the Brummond research group, was closely followed by a report by Shibata et al.[121] This study described the use of the Wilkinson catalyst for related transformations under essentially identical reaction conditions, with the first example of a seven-membered analogue (**155**→**156**). Mukai et al.[122] subsequently reported more examples of the synthesis of six and seven-membered rings, this time in the carbocycle series, starting from sulfone-substituted allenes. Later, Jiang and Ma[123] found that *trans*-$[Rh^ICl(CO)(PPh_3)_2]$ was needed for the cycloisomerization of propargyl esters of allenic acids **157** to six-membered triene esters **158**. In contrast, Brummond et al. demonstrated that $[\{Rh^I(CO)Cl\}_2]$ works well for the synthesis of triene lactams through the cyclization of substrates carrying allenes and alkynes tethered through an amide group.[124] Brummond and Yan also demonstrated the synthesis of five- and six-membered cyclic trienones (e.g. **159**→**160**), as well as five-, six-, and seven-membered cyclic trienamides using the same catalyst.[125]

One of the most challenging aspects of this reaction is the development of a way to obtain a selective hydride transfer from one of two different terminal allene substituents. Most studies have avoided this complication through the use of substrates that can only produce one product. The studies of Brummond and McCabe en route to ovalicin show that the regio- and stereochemical outcome is sensitive to temperature, solvent, catalyst, and the ability of the substrate to complex to the catalyst.[126]

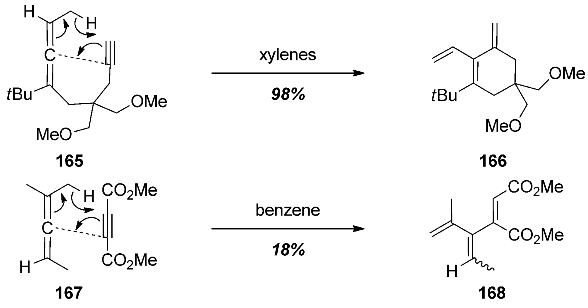
Concurrent with these developments, a different subset of cycloisomerizations to 2,3-cyclo[3]dendralenes began to emerge. In 2004, Malacria and co-workers reported a single example of a $PtCl_2$-catalyzed allenyne cycloisomerization reaction (**161**→**162**; Scheme 27).[127] The proposed mechanism was essentially identical to the rhodium(I)-catalyzed process. Subsequent studies demonstrated successful cycloisomerizations with other platinum(II) and certain gold(I) complexes and a more complex mechanistic picture.[127,128] Mixtures of products were generally formed in these reactions, which exhibited a strong dependence upon the nature of the catalyst employed. Most recently, Toste and co-workers have shown that the gold(I) complex $[(Ph_3PAu)_3O]BF_4$ catalyzes the cycloisomerization of allenynes in high yields (e.g. **163**→**164**).[129] Both five- and six-membered carbocyclic trienes are accessible, but the reaction appears limited to terminal alkynes.



Scheme 27. Platinum(II)- and gold(I)-catalyzed allenyne cycloisomerizations.

The uncatalyzed (i.e. thermal) intramolecular Alder-ene reaction of allenynes to 2,3-cyclo[3]dendralenes was demonstrated recently by Aubert and co-workers[128,130] as well as Mukai et al.[131] In certain circumstances, high yields of cyclic trienes can be obtained (Scheme 28, **165**→**166**), although the intramolecular [2+2] cycloaddition products are often formed as by-products.

The reader may wonder if the intermolecular allene-alkyne Alder-ene reaction is a viable approach to [3]dendralenes. The early work of Taylor and co-workers[132] indicates that uncatalyzed reactions between substituted allenes and reactive electron-poor alkynes such as dimethyl acetylenedicarboxylate (DMAD) or CF_3CCCF_3 lead to disappointingly low yields of trienes, with allene isomerization and subsequent Diels–Alder cycloaddition being a major competing reaction sequence (**167** + DMAD→**168**). Of course, most



Scheme 28. Thermal allenyne cycloisomerizations (i.e. ene reactions).

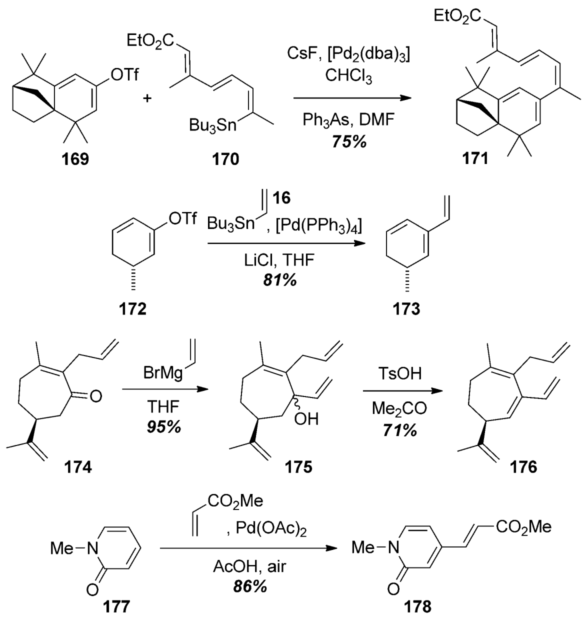
[3]dendralenes are excellent dienes in Diels–Alder reactions. Any improvement to the intermolecular allene-alkyne Alder-ene route to acyclic dendralenes must address this issue.

In contrast to the 2,3-cyclo[3]dendralenes, the literature of the two other "nonrigid" cyclic dendralenes, the 1,2-cyclo and 1,3-cyclo systems (**145** and **146**; Figure 2), is significantly more limited. The chemistry of the 1,3-cyclo[3]dendralenes **146** is dominated by six-membered ring systems. We do not consider styrene and its five-membered heteroaromatic analogues 3-vinylfuran, 3-vinylpyrrole, and 3-vinylthiophene to be true dendralenes, since these structures contain annulenes and related cyclic conjugated π systems. For the same reason we exclude azulenes, vinyltropolones, and vinylcyclobutadienes. We have also chosen to exclude 4-alkenyl-1,2-benzoquinones, whose chemistry is dominated by the quinone functionality and not the cross-conjugated triene.

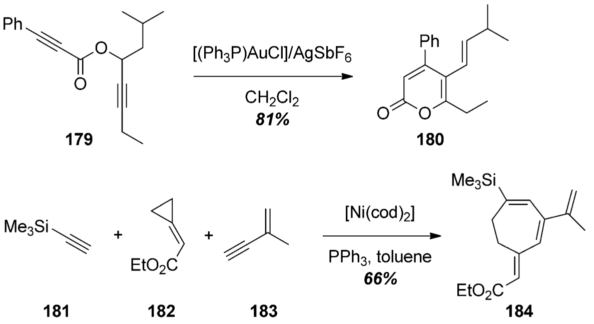
A relatively modest number of papers describing synthetic approaches to 1,3-cyclo[3]dendralenes (**146**; Figure 2) have appeared. The published approaches can be divided into two types: a) those involving the attachment of an alkene unit to a cyclic diene, and b) those involving ring formation (Scheme 29). Of the former variety, Stille and Negishi reactions of enol triflates have been employed in the formation of the C−C bond between cyclic-1,3-diene electrophiles and alkenyl nucleophiles (**169** + **170** → **171**; **172** + **16** → **173**).[133,134] A more classical approach, involving 1,2-nucleophilic addition of an alkenylmetal to a conjugated enone **174** followed by regioselective dehydration (**175** to **176**) has also been employed.[135]

Several reports of cross-coupling approaches to afford 4-(or 5-)alkenyl 2-pyrones (or 2-pyridones) have been published. The majority of examples employ a halogenated 2-pyrone (2-pyridone) and Mizoroki–Heck,[136] Suzuki–Miyaura,[137] Stille,[138] as well as Negishi reactions are known. As reported by Itahara and Ouseto in 1984 (Scheme 29),[139] *N*-methyl-2-pyridone (**177**) was converted into the corresponding 4-alkenyl analogue **178** in an example of C−H activation that pre-dates the current interest in this transformation by over 20 years.

Metal-catalyzed annulation approaches to afford 1,3-cyclo[3]dendralenes are also beginning to appear (Scheme 30). At the moment, these methods lack the generality of the cross-coupling route, but they offer the advantage of efficiency, by assembling the dendralene in short order from relatively simple precursors through the generation of several new bonds in one step. Thus, Luo and Schreiber recently reported an interesting gold-catalyzed cycloisomerization reaction of propargyl propiolate **179** to alkenyl-2-pyrone **180**.[140]



Scheme 29. Synthesis of 1,3-cyclo[3]dendralenes by alkenylation of cyclic dienes.

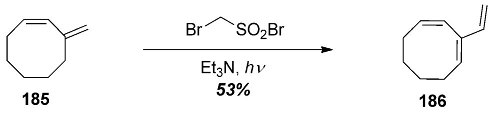


Scheme 30. Annulation approaches to 1,3-cyclo[3]dendralenes. cod = 1,5-cyclooctadienyl.

A [3,3] sigmatropic rearrangement generates an enyne-allene, which undergoes a 6-*endo*-dig cyclization and tautomerization to generate the alkenyl-2-pyrone. Saito and co-workers recently reported a nickel(0)-catalyzed annulation of methylene cyclopropanes with alkynes to form alkenyl-cycloheptadienes.[141] Three-component coupling reactions are possible (**181** + **182** + **183** → **184**). How general these processes are for the synthesis of other 1,3-cyclo[3]dendralenes remains to be seen. Nevertheless, such sequences lead the way in terms of atom efficiency.[142]

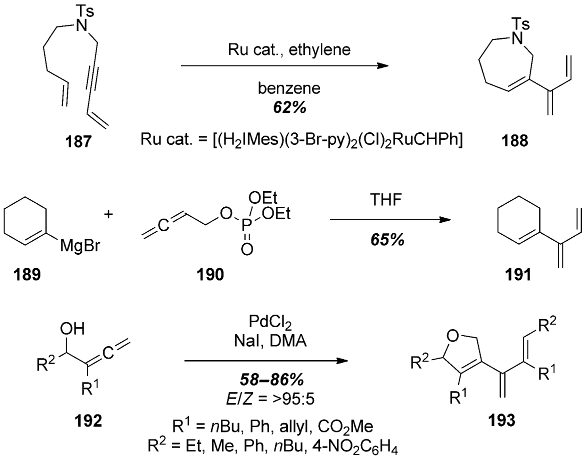
An interesting and general—at least in terms of ring size—approach to 1,3-cyclo[3]dendralenes was reported in 1986 by Block et al. as part of a more general conversion of exocyclic alkenes **185** into semicyclic dienes **186**

(Scheme 31).[143] The transformation involves the radical addition of bromomethanesulfonyl bromide to the exocyclic alkene of a conjugated methylenecycloalkene followed by a base-mediated "vinylogous" Ramberg–Bäcklund rearrangement. Yields are moderate and mixtures of positional isomers are obtained in some cases.



Scheme 31. Synthesis of 1,3-cyclo[3]dendralenes according to Block et al.

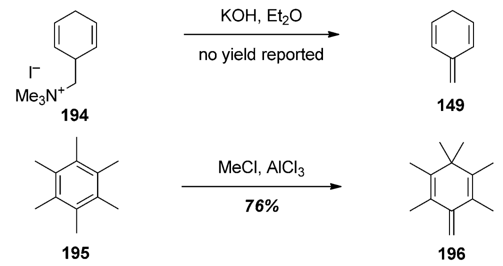
When 2-aryl-1,3-butadienes are discounted from the survey (on account of their chemistry being influenced by the annulenic π system), relatively few publications describe the preparation of 1,2-cyclo[3]dendralenes (**145**; Figure 2). Furthermore, all the reported methods describe variations of routes that we have already encountered in this Review in the section on acyclic systems. Thus, ene-yne metathesis, cross-coupling reactions, and allenol dimerizations have been pursued (Scheme 32). As an example of the metathesis approach, substrate **187** undergoes an intramolecular ene-yne metathesis reaction with the fast-initiating Grubbs catalyst [$(H_2IMes)(3\text{-Br-py})_2(Cl)_2RuCHPh$] to afford the 1,2-cyclo[3]dendralene **188** in good yield.[144] Other isolated examples of ene-yne metathesis-type transformations have also been reported.[135,145]



Scheme 32. Synthetic approaches to 1,2-cyclo[3]dendralenes. 3-Br-py = 3-bromopyridyl, H_2IMes = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene.

Reported cross-coupling approaches to 1,2-cyclo[3]dendralenes involve Mizoroki–Heck reactions[81] and a palladium(0)-catalyzed cross-coupling between an organoindium compound and an enol triflate.[79] These reactions are variants of routes to acyclic systems previously discussed in this Review (see Section 3, Scheme 15). Cross-coupling reactions have also been used to synthesize the masked versions of the parent [5]-, [6]-, and [8]dendralenes, which are themselves 1,2-cyclodendralene derivatives (**18**, **23**, and **24**; Scheme 3, Section 2).[23] Notably, with the correct choice of substrates, simple S_N2' processes can also be employed, as demonstrated in 1984 by the reaction of Grignard reagent **189** with phosphonate **190** (Scheme 32).[146] An interesting variation of the allene dimerization theme (Scheme 20, Section 3) has been employed by Ma and co-workers to produce 1,2-oxacyclo[3]dendralenes **193**.[147] The reaction is thought to involve an intramolecular oxycyclopalladation of allenols **192** followed by intermolecular carbopalladation and β-hydroxide elimination to form trienes **193**. Similar transformations have been reported by Alcaide et al.[148] Finally, acid-catalyzed rearrangements of spirocyclic cyclopropanes analogous to those described in Section 3 (Scheme 24) have been reported for the preparation of substituted 1,2-cyclo[3]dendralenes.[111]

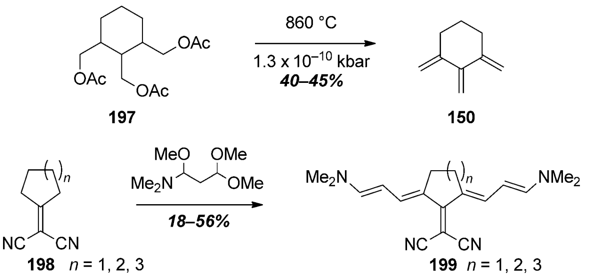
We now move on to the more conformationally restricted monocyclic [3]dendralenes (Figure 2). The 1,5-cyclo[3]dendralenes **149** carry two 1,3-butadiene groups locked in the *s-trans* conformation and require at least a six-membered ring, otherwise we are dealing with pentafulvene structures (Scheme 1). Perhaps not surprisingly, the literature concerning 1,5-cyclo[3]dendralenes is dominated by six-membered ring systems, with most synthetic routes commencing with a benzene derivative (Scheme 33). The synthesis of the parent 1,5-cyclo[3]dendralene **149**, by way of Hofmann elimination, was reported in 1965.[149] The precursor **194** was obtained after several steps, the most significant of which was a Birch reduction of benzoic acid.



Scheme 33. Synthetic approaches to 1,5-cyclo[3]dendralenes.

Several Wittig olefinations[15,150] and Horner–Wadsworth–Emmons olefinations[151,152] of 1,4-cyclohexadien-3-ones have been reported to yield 1,5-cyclo[3]dendralenes, an approach that has also been used in the synthesis of acyclic [3]dendralenes (Scheme 7). The direct conversion of benzene derivatives into 1,5-cyclo[3]dendralenes has been achieved with remarkable ease. Thus, hexamethylbenzene (**195**) has been converted into triene **196** under Friedel–Crafts alkylation conditions,[153] and benzyl chlorides undergo de-aromatization to afford 1,5-cyclo[3]dendralenes under Stille coupling conditions with allyltributylstannane[154] and allenyltributylstannane.[155]

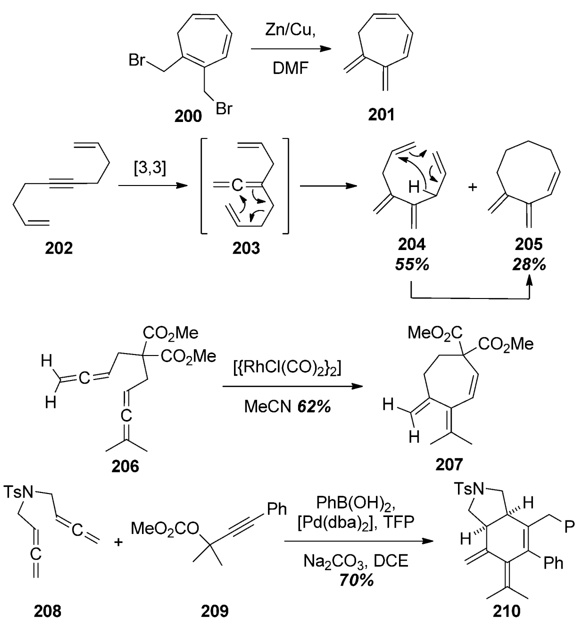
The 2,4-cyclo[3]dendralenes (**150**; Figure 2) have two 1,3-butadiene units that—at least for small-ring systems—are locked in *s-cis* conformations. Their structures are closely related to the radialenes (**8**; Scheme 1). Nevertheless, 2,4-cyclo[3]dendralenes (and higher oligoenes) are distinct from the radialenes in that the π systems of the former lack the unbroken cyclic connection of the latter. The majority of reported 2,4-cyclo[3]dendralenes are five- and six-membered ring systems, and reported syntheses follow one of two well-established classical methods (Scheme 34). The parent six-membered carbocyclic system **150** has been prepared by Trahanovsky and Koeplinger by flash vacuum pyrolysis of the trisacetate **197**.[156] The compound was found to be more prone to dimerization than [3]dendralene. The other common synthetic approach to 2,4-cyclo[3]dendralenes involves a well-established method for the synthesis of symmetrical dendralenes that we have seen several times already, namely, the olefination of suitably substituted cyclic 1,4-dien-3-ones.[34,157–159] In an alternative, double condensation approach, strongly polarized alkenes **198** have been shown to condense with 1-dimethylamino-1,3,3-trimethoxypropane to afford captodative triene systems **199**.[160] Once again, the only 2,4-cyclo[3]dendralenes thus far reported have been symmetrically substituted examples.



Scheme 34. Synthetic approaches to 2,4-cyclo[3]dendralenes.

The last monocyclic [3]dendralene subtype is the less-symmetrical 1,4-cyclo[3]dendralene system (**148**; Figure 2), a structure that contains one *s-cis-* and one *s-trans*-1,3-butadiene unit. Although perhaps the least well studied of all the cyclic dendralenes, several isolated synthetic studies on these systems have been reported (Scheme 35). A more traditional method involves the 1,4-debromination of the unsaturated dibromide **200** with a zinc/copper couple in DMF, which furnishes the tetraene **201** in near quantitative yield (Scheme 35).[161] For the preparation of the eight-membered ring system **205**, a sequence of three pericyclic steps was exploited: heating the dienyne **202** in the gas phase either under stationary or flow conditions initiated two consecutive Cope rearrangments and provided 2,3-bis(allyl)buta-1,3-diene (**204**) in 55% yield, along with 1,4-cyclo[3]dendralene **205** (28%), which arises from an intramolecular ene reaction.[162] Several photoisomerizations involving the formation of 1,4-cyclo[3]dendralenes have been reported.[163,164]

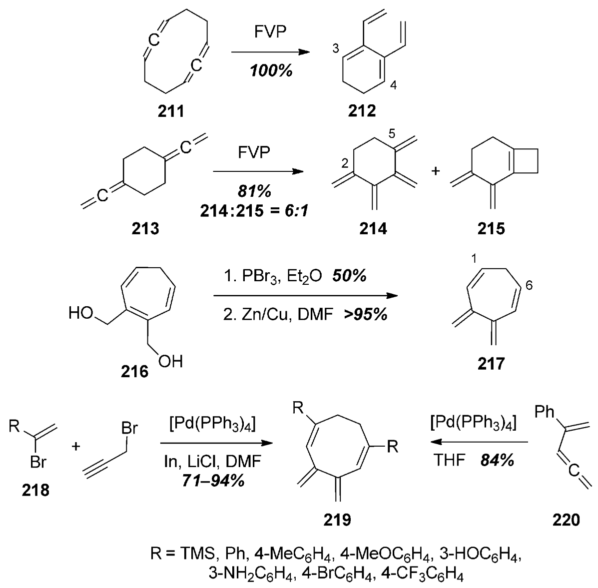
More convenient—and perhaps more general—synthetic approaches to 1,4-cyclo[3]dendralenes involving bis(allene) precursors have begun to appear. In a transformation closely related to allenyne cycloisomerizations (Scheme 26), Ma and co-workers have shown that bis(allenes) **206** cycloisomerize to afford 1,4-cyclo[3]dendralenes **207** when treated with a rhodium catalyst.[165] We end this section with another beautiful example from the Ma research group. In a recent report, a powerful three-component cascade reaction leading to 1,4-cyclo[3]dendralenes such as **210** has been disclosed.[166] Thus, treating the propargyl carbonate **209** and the bis(allene) **208** with phenylboronic acid in the presence of a palladium(0) catalyst provided the *cis*-fused bicyclo[4.3.0]nonene **210** with high regio- and stereoselectivity in good yield (70%). Other aryl boronic acids were also used in this reaction to introduce a range of aryl substituents. Several [3]dendralenes of this type containing seven- and eight-membered rings have been reported over the last decade.[165,167]



Scheme 35. Synthetic approaches to 1,4-cyclo[3]dendralenes. TFP = tris(2-furyl)phosphine.

To complete our survey of synthetic approaches to cyclic dendralenes, we will now examine the reported methods for the synthesis of cyclic structures containing cross-conjugated systems larger than the triene. Interestingly, relatively little is known about cyclic [4]- and higher dendralenes, and the examples in this section represent somewhat isolated studies in an as yet undeveloped research field. The only examples that we have been able to find in the literature are of the 3,4-cyclo-, 2,5-cyclo-, and 1,6-cyclo[4]dendralenes.

To our knowledge, the first synthesis of a cyclic [4]dendralene was reported by Skattebøl and Solomon in 1965, who, in a classic study, described the thermal Claisen rearrangement of bis(allene) **211** to 3,4-cyclo[4]dendralene **212** in quantitative yield (Scheme 36).[168,169] The dimethyl analogue of Skattebøl's compound has also been prepared, through flash vacuum pyrolysis of a strained precursor.[170] 2,5-Cyclo[4]dendralene **214**, the higher "dendrologue" of **150** (Figure 2) has been prepared by flash vacuum pyrolysis of the bis(allene) **213**.[171–173] Cyclic [4]dendralene **214** was always accompanied by small amounts of a side product which was shown, by spectroscopic methods, to be the 2,4-cyclo[3]-



Scheme 36. Synthetic approaches to cyclo[4]dendralenes. FVP = flash vacuum pyrolysis.

dendralenic hydrocarbon **215**. The only nonthermolytic routes to higher cyclic dendralenes involve the preparation of 1,6-cyclo[4]dendralenes. Thus, in a transformation related to that depicted in Scheme 35, diol **216**, after conversion into its dibromide, has been reduced to 3,4-dimethylene-1,5-cycloheptadiene (**217**),[174] a 1,6-cyclo[4]dendralene for which a {Fe(CO)$_3$} complex has also been described (see Section 7 for metal complexes of the dendralenes).[175] Finally, 1,6-cyclo[4]dendralenes **219** are obtained in very good yields when 1-bromoalkenes **218** and propargyl bromide are coupled by an indium-mediated, palladium(0)-catalyzed reaction. The in situ generated 2-substituted vinylallene (e.g. **220**) cyclodimerizes under the influence of the [Pd(PPh$_3$)$_4$] catalyst to give the eight-membered ring system.[176,177] It was shown that an authentic sample of 2-phenylvinylallene (**220**) furnishes **219** (R = Ph) in a similar yield when treated with [Pd(PPh$_3$)$_4$] in THF.[178]

In summary, we believe that existing synthetic approaches to cyclic dendralenes are limited in scope. Of the six possible monocyclic [3]dendralene systems, only one has a general, robust, and well-developed synthesis in place. Thus, whereas the cycloisomerization of substituted allenynes to afford 2,3-cyclo[3]dendralenes represents the gold standard for the synthesis of cyclic dendralenes, the other five structural subtypes (Figure 2)—and their multicyclic and higher dendralene analogues—remain neglected members of the dendralene family.

5. Spectroscopic and Structural Properties

The increasing conjugation witnessed in the parent all-*E* linear polyenes (**4**; Scheme 1) with increased chain length is verified by longer wavelengths (λ_{max} increases by ca. 25 nm for each additional −HC=CH− unit) and increasing molar extinction coefficients for their UV/Vis absorption maxima.[179] In contrast, in all but one case, the first six members of the parent dendralenes show a single UV/Vis absorption maximum at λ_{max} = 215–217 nm (hexane), similar to that of 1,3-butadiene (217 nm, hexane).[180] The exception is [3]dendralene, which exhibits two maxima (206 and 231 nm, hexane). When the observed molar extinction coefficients are plotted against the number of C=C bonds present in the structure, a clear pattern emerges (Figure 3). Evidently, dendralenes with an even number of C=C bonds contain multiples of 1,3-butadiene moieties and the incorporation of additional pairs of alkenes has the effect of increasing the molar extinction coefficient of the absorption maximum by about 10000 units. Dendralenes with odd numbers of double bonds behave differently, exhibiting significantly lower extinction coefficients than might be expected.

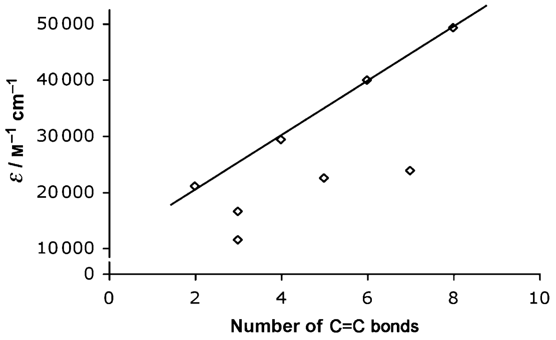


Figure 3. UV/Vis extinction coefficients (ε) of the parent dendralenes plotted as a function of the number of C=C bonds. λ_{max} = 215–217 nm in all cases except [3]dendralene, which exhibits two maxima at 206 and 231 nm.

These experimental findings were explained by Paddon-Row, who calculated the preferred conformations of the dendralenes by using DFT.[26] The two most stable conformations of [3]dendralene (**11**) and [4]dendralene (**21**) are depicted in Figure 4. Thus, the lowest energy conformations of the even dendralenes consist of *s-trans*-butadienes, with each diene unit nearly orthogonal to adjacent ones (Figure 4c). In contrast, the lowest energy conformations of the odd series have at least one quasi-*s-cis* unit (Figure 4a). These calculated geometries are in very good agreement with experimental values obtained through electron diffraction

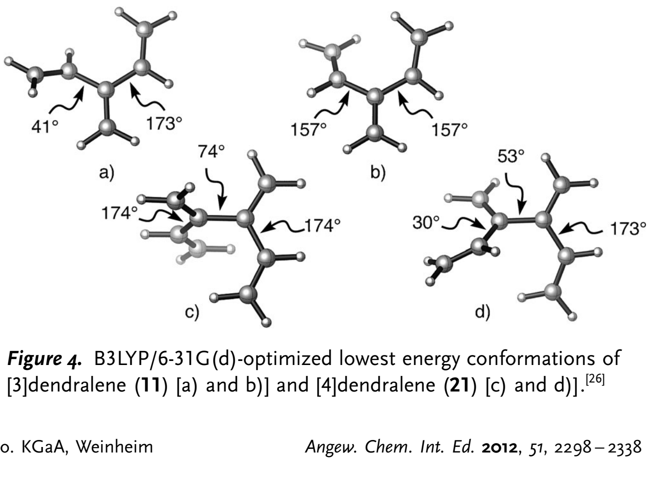


Figure 4. B3LYP/6-31G(d)-optimized lowest energy conformations of [3]dendralene (**11**) [a) and b)] and [4]dendralene (**21**) [c) and d)].[26]

investigations on [3]dendralene (**11**)[181,182] and [4]dendralene (**21**).[183,184]

In all other respects, the dendralenes exhibit IR and NMR spectroscopic and mass spectrometric data as expected, and the reader is referred to the original literature[23,26] for specific information. So far, X-ray crystallographic data on the parent dendralenes is lacking. Nevertheless, X-ray crystal structures of several substituted [4]dendralenes have been reported. Interestingly, despite significant differences in substitution patterns, the reported X-ray crystal structure conformations of substituted [4]dendralenes are in very close agreement. All exhibit an essentially orthogonal arrangement between two in-plane, *s-trans* dienes.[27,107,185] This matches both the calculated lowest energy conformation of the parent [4]dendralene (**21**; see Figure 4c) and the experimental, gas-phase electron diffraction conformation.

The planarization and fixation of [3]- and [4]dendralenes in rigid structures causes bathochromic shifts in their UV/Vis absorption maxima, as demonstrated by the data of selected [3]- and [4]dendralenes in Figure 5. Connecting the terminal carbon atoms of the parent [3]dendralene (**11**), as in 1,5-cyclo[3]dendralenes (isotoluene, **149**), causes a bathochromic shift of about 20 nm,[149,186] similar to that observed for the 2,3-cyclo[3]dendralene **221**.[20,187] Even more rotational freedom is removed in the dihydropentalene **222**, which causes a further shift to longer wavelengths.[188] Going from [4]dendralene (**21**) to the 3,4-cyclo[4]dendralene analogue **212** produces a modest shift in the UV bands,[168,189] but stiffening the whole system, as in the 2,5-cyclo system of 1,2,3,4-tetramethylenecyclohexane **214**,[172] results in a massive displacement. It comes as no surprise that the planar derivative of **11**, namely fixed pentaene **223**, displays a very strong bathochromic shift compared to the other cyclic dendralenes.[190]

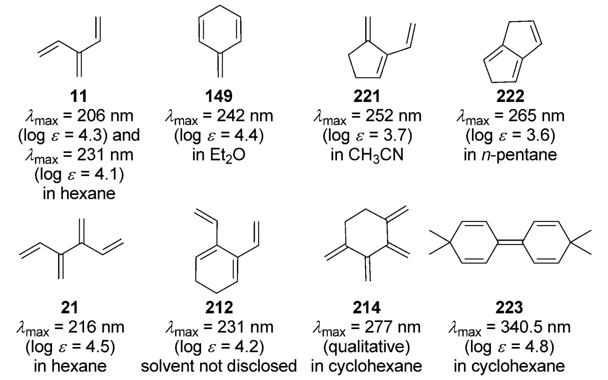
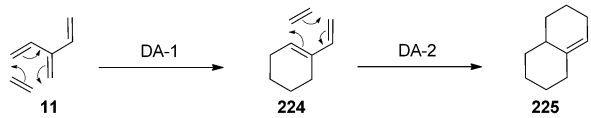


Figure 5. UV/Vis absorption maxima of cyclic dendralenes.

6. Diene-Transmissive Diels–Alder (DTDA) Sequences of Dendralenes

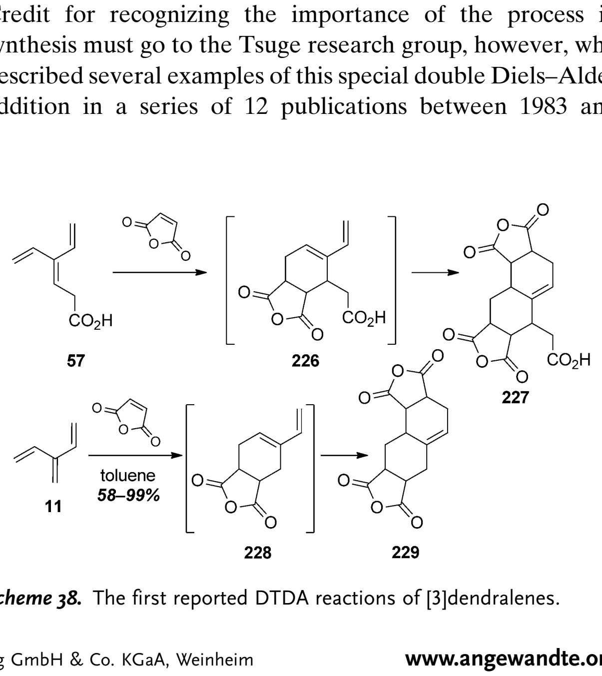
The Diels–Alder chemistry of dendralenes is rich and varied, and the reactivity of dendralenes as dienes is their most interesting and important synthetic attribute. Dendralenes have been shown to undergo single, double, and triple cycloadditions with dienophiles. Since each Diels–Alder reaction produces a new six-membered ring and two new bonds, sequences of two or three Diels–Alder reactions are extremely powerful methods for the rapid generation of multicyclic frameworks. Indeed, they are amongst the most efficient—in terms of atom economy[191] and step economy[192]—of all sequential transformations.[193] Within the realm of so-called "tandem Diels–Alder reactions",[194] dendralenes are of paramount importance, on account of their unique ability to engage in diene-transmissive Diels–Alder (DTDA) sequences.

In its simplest form, a diene-transmissive Diels–Alder sequence involves the addition of a dienophile to [3]dendralene (**11**), thereby forming a new semicyclic diene **224** that may participate in a subsequent Diels–Alder reaction with a second dienophile (Scheme 37). Thus, the first addition installs a new C=C bond (the cyclic alkene) at a site of conjugation with an existing (acyclic) alkene; in effect, the first cycloaddition "transmits" diene character to a new location, hence the name of the overall sequence. This strikingly efficient process forms four covalent bonds and as many as eight stereocenters, brings together three molecules, and forms a new decalin system, yet it involves only two bond-forming events.



Scheme 37. The prototypical diene-transmissive Diels–Alder sequence. DA = Diels–Alder reaction.

As already mentioned in Section 3, the first DTDA sequences were reported in the early 1950s[51–54] and involved reactions of 3-substituted carboxylic acid derivative **57** (see Scheme 9, Section 3)[51] and parent [3]dendralene (**11**)[52–54] with maleic anhydride and various quinones (Scheme 38). Credit for recognizing the importance of the process in synthesis must go to the Tsuge research group, however, who described several examples of this special double Diels–Alder addition in a series of 12 publications between 1983 and

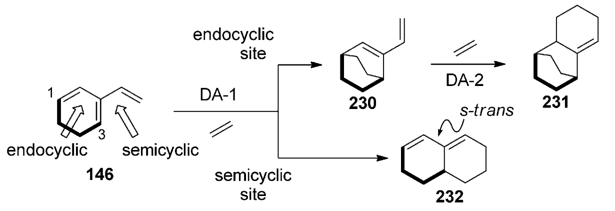


Scheme 38. The first reported DTDA reactions of [3]dendralenes.

1999.[59,60,71,195,196] Indeed, it was Tsuge et al. who first coined the term diene-transmissive to describe such processes.[60]

The power of DTDA sequences lies in their ability to rapidly generate a wide variety of multicyclic frameworks. When the many variations in both the [*n*]dendralene and dienophile structures are considered, an almost bewildering number of possibilities exist. It turns out that the vast majority of studies carried out so far involved the use of [3]dendralenes as double dienes, and activated alkenes as dienophiles. In fact, very few studies have been conducted with [4]dendralenes and higher. Heteroatoms can be incorporated in both diene and dienophile π systems. Indeed, several important and elegant studies by Spino and co-workers[197,198] and by Saito and co-workers[199] on "heterodendralenes" have been reported. With one exception (see Section 10), we have omitted such contributions from this Review, since we wish to focus attention on the oligoene systems. Although not yet reported in the literature, dendralenes engage in productive hetero-Diels–Alder reactions with common heterodienophiles.[200]

In the case of the parent [3]dendralene and symmetrically substituted analogues, only one DTDA sequence is feasible. Unsymmetrical substitution about a dendralene leads to two possible pathways. 1,3-Cyclo[3]dendralene **146** (Scheme 39), for example, might undergo a first cycloaddition with a dienophile at either of two discrete diene sites: the endocyclic one or the semicyclic one. An initial addition of a dienophile at the endocyclic diene site gives bridged bicyclic system **230** carrying a new "transmitted" semicyclic diene, which could undergo a second cycloaddition to give tricycle **231** in a DTDA sequence. Conversely, cycloaddition of precursor **146** at the semicyclic diene site produces a new diene **232** locked in the *s-trans* conformation, which is thus unable to participate as a diene in a second cycloaddition.



Scheme 39. Site-selectivity issues in Diels–Alder reactions of 1,3-cyclo[3]dendralene **146** (ethylene as dienophile).

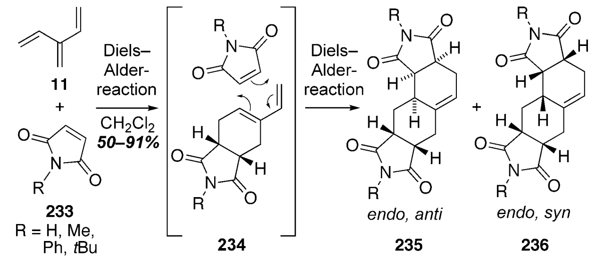
Within each DTDA sequence, there is also the issue of chemoselectivity. Taking the DTDA sequence **146**→**230**→**231** (Scheme 39) as an example, if the first cycloaddition is significantly faster than the second, the monoadduct **230** can be isolated and different dienophiles can be used in the two Diels–Alder events. Conversely, if the second addition is significantly faster than the first, then exposure of precursor **146** to the dienophile will prompt a domino reaction,[193] which leads to bisadduct **231** as the only isolable product. Of course, if the rates of the two cycloaddition reactions are similar, then mixtures of mono- and bisadducts **230** and **231** will be generated.

These issues of site selectivity and chemoselectivity add an additional layer of complexity to DTDA sequences, since the usual regio- and stereoselectivity concerns pertaining to Diels–Alder reactions must also be addressed. Thus, orientational regioselectivity (with unsymmetrical dienophiles) and the two facets of stereoselectivity (*endo*/*exo* stereoselectivity and π-facial stereoselectivity) must also be considered.

In this section, the Diels–Alder reactions of [3]dendralenes will be reviewed first, then those of [4]dendralenes, and finally those of the higher dendralenes.

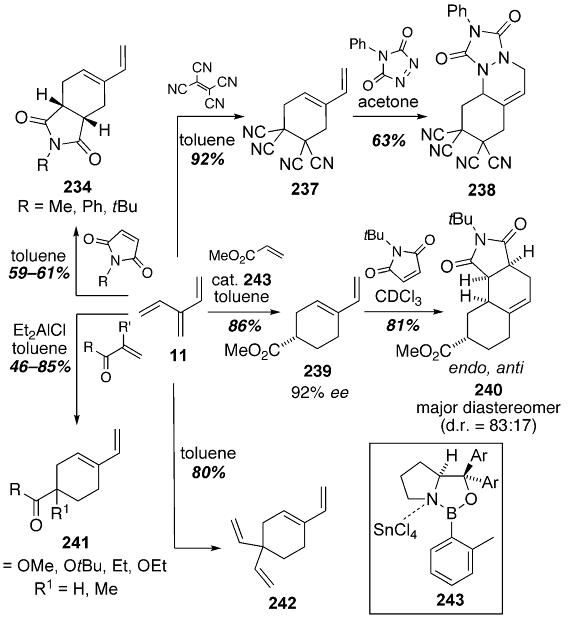
The earliest examples of DTDA sequences involving [3]dendralene (**11**) involved reactions with the reactive, electron-poor dienophiles maleic anhydride (Scheme 38),[52–54] quinones,[52,53] *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD),[22] dimethylacetylene dicarboxylate,[22] and maleimide.[22] In these important exploratory studies, the stereochemical outcome of the DTDA sequence was mentioned only in the case of maleimide, where a single diastereomer **235** (Scheme 40) was reported to be produced.[22]

The DTDA reaction of [3]dendralene with maleimide has recently been re-examined as part of a wider study with substituted maleimides (Scheme 40),[25] and it has been shown that two diastereomeric bisadducts **235** and **236** are produced in all cases. Nevertheless, the stereoselection is high (d.r. = 87:13–96:4) and improves as the size of the N substituent increases. Both products are the result of an *endo* addition of the second dienophile (it is not possible to ascertain the *endo*/*exo* selectivity of the first cycloaddition), and the major diastereomer **235** results from an approach of the second maleimide dienophile to the less sterically encumbered (i.e. *anti*) π diastereoface of the bicyclic monoadduct.



Scheme 40. DTDA sequences of [3]dendralene with maleimide dienophiles.

It was the Cadogan research group who first demonstrated that Diels–Alder monoadducts of [3]dendralene could be isolated.[22] Specifically, they showed that monoadducts such as **234** could be obtained upon exposure of the triene to one molar equivalent of common reactive dienophiles (quinone, dimethylacetylene dicarboxylate, and tetracyanoethylene). They went on to show that the tetracyanoethylene monoadduct **237** could be transformed into "mixed" bisadducts such as **238** (Scheme 41) in good yields. The demonstration that the second cycloaddition in the DTDA sequence of [3]dendralene is slower than the first is an important one, and one that led the way for synthetic developments by other research groups. Up until this point, some researchers had even developed dienes that could function as synthetic



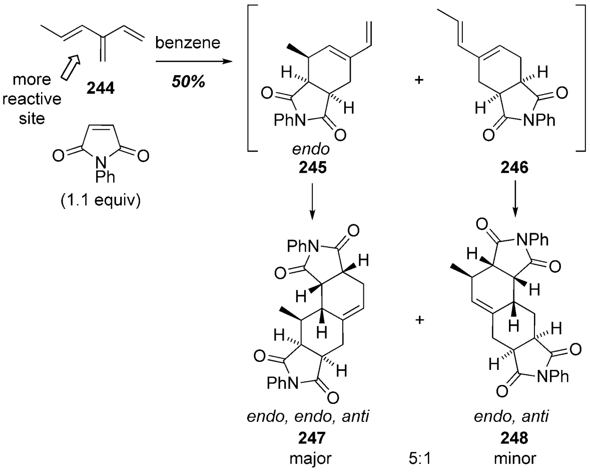
Scheme 41. Diels–Alder reactions of [3]dendralene: monoadducts, "mixed" bisadducts, orientational regioselectivity, and enantioselectivity.

equivalents of [3]dendralene so as to carry out the two cycloadditions in a stepwise manner.[196,201]

Recently, it was demonstrated that the chemoselectivity of [3]dendralene towards mono-cycloaddition is a general phenomenon (Scheme 41).[25] Thus, monoadducts **234** were obtained in good yields from the single Diels–Alder reaction of [3]dendralene with maleimide dienophiles. Importantly, monoadducts could also be obtained in good yields under Lewis acid activation with less reactive dienophiles, namely acrylates, methacrylates, and ethyl vinyl ketone, even in the presence of excess dienophile. These cycloadditions proceed with complete orientational selectivity, thereby affording only the "*para*" regiosiomer in all cases. It was also demonstrated for the first time that enantioselective Diels–Alder reactions with the parent [3]dendralene (**11**) are possible. Thus, through the application of a modified[28,202] version of Corey's oxazaborolidinium catalyst, **243**, the mono-cycloaddition of methyl acrylate to [3]dendralene (**11**) produced monoadduct **239** in a respectable 86 % yield and 92 % *ee*. It was demonstrated that the presence of a bicyclic framework is not necessary for good *anti*-π-diastereofacial stereoselectivity (cf. **11**→**235** and **236**; Scheme 40) by the conversion of methyl acrylate monoadduct **239** into *endo*,*anti* "mixed" bisadduct **240**, on exposure to *N*-*tert*-butylmaleimide.

To complete our segment on the Diels–Alder reactions of the parent [3]dendralene, we will now examine its decomposition pathway. The literature from the 1950s contains two reports that warn of the propensity of the triene to dimerize, but no structural information was offered.[53,54,156] It was not until 1992 that Trahanovsky and Koeplinger identified the structure of the major decomposition product of [3]dendralene as a Diels–Alder dimer.[156] Data on the rate of decomposition of [3]dendralene as a neat liquid at ambient temperature was not reported until 2010.[25] The hydrocarbon has a half-life of about 10 h at 25 °C and undergoes a relatively clean dimerization to form adduct **242** in 80 % yield after 4 weeks at room temperature (Scheme 41). The 1,1-disubstituted ethylene unit serves as the dienophile in the dimerization reaction, a result that was explained qualitatively through a Dewar mechanistic analysis by Paddon-Row and co-workers.[25] Certain substituted [3]dendralenes also appear to dimerize in a Diels–Alder fashion.[156,203,204]

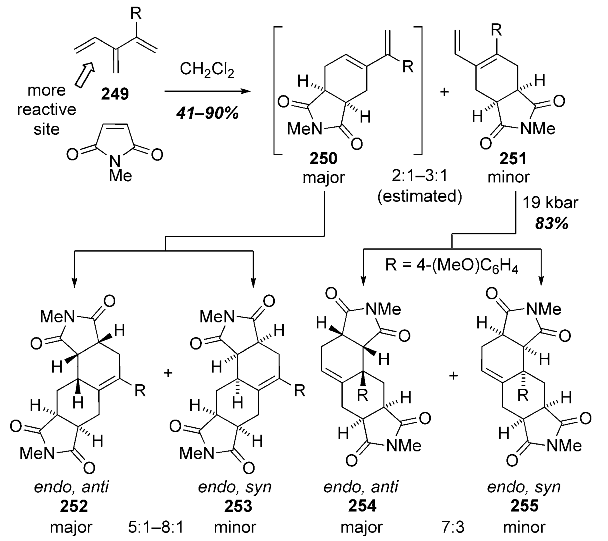
The two potential Diels–Alder diene sites of [3]dendralene are, of course, equivalent, and this is the case for all symmetrically substituted [3]dendralenes. The issue of site selectivity emerges with unsymmetrically substituted [3]dendralenes. Of the four possible monosubstituted [3]dendralenes (Figure 1), the 1-substituted system was one of the first to be examined by Tsuge and co-workers in 1986.[71] The Diels–Alder reaction of 1-*E*-methyl[3]dendralene (**244**), synthesized from the Grignard reagent derived from chloroprene and methyloxirane and subsequent dehydration (Scheme 14, Section 3), was selective for the more-substituted diene site.[71] Thus, reaction of **244** with *N*-phenylmaleimide resulted in the formation of a 5:1 ratio of the two double cycloadducts **247** and **248**, respectively (Scheme 42). In some cases it could be demonstrated that the Diels–Alder reactions proceed via *endo* transition states, and the second dienophile approaches the semicyclic diene monoadducts from the less-hindered convex face. In contrast to the outcome observed with the parent [3]dendralene, the second cycloadditions in this reaction manifold appear to exhibit complete π-diastereofacial selectivity. The implication that monoadducts **245** and **246** are more reactive than the precursor [3]dendralene **244** is not consistent with findings with the parent [3]dendralene (Scheme 40) and we suspect that this observation is an error: the precursor triene **244** was reportedly unstable and difficult to purify, and we are inclined to think that the abnormally low yield for this reaction—based upon the quantity of hydrocarbon used—reflects a mistake in the amount of precursor employed. Lower site selectivities were observed with



Scheme 42. A DTDA sequence with 1-*E*-methyl[3]dendralene **244** exemplifying good diene site selectivity.

dimethyl acetylenedicarboxylate and methyl vinyl ketone, but these two dienophiles gave good yields of monoadducts. Attempts to enhance the site selectivity of reactions of 1-substituted [3]dendralenes were thwarted by the instability of the 1-ethoxy- and 1-phenylthiyl analogues of **244**.

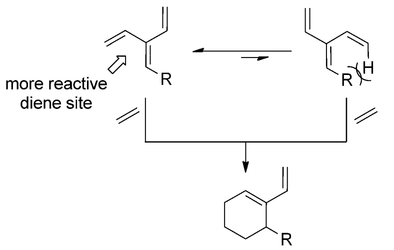
2-Substituted [3]dendralenes exhibit particularly interesting and complex, but also somewhat surprising, behavior in their Diels–Alder reactions. Building on a seminal DTDA study with 2-ethoxy[3]dendralene by Tsuge and co-workers,[196] the Sherburn research group investigated the Diels–Alder reactivity of a family of 2-substituted systems **249**, with a total of seven substituents with various steric and electronic demands (Scheme 43).[28] In all cases, the less-substituted diene site was the faster reacting one, albeit with modest (ca. 2:1–3:1) selectivity in all cases apart from Tsuge's 2-ethoxytriene, which was significantly more selective (ca. 9:1) for the less-substituted site. On face value this is a rather unexpected outcome for a "normal electron demand" Diels–Alder reaction, in which increased selectivity for addition of an electron-deficient dienophile to a site carrying an electron-donating group might be anticipated. The preference for the less-substituted diene site was traced by Paddon-Row and co-workers[28] to steric effects at play in the triene precursors **249** and the transition states of the first Diels–Alder reaction. Specifically, a steric clash between the substitutent at the 2-position and the unsubstituted vinyl group destabilizes the *s-cis* conformation of the more-substituted diene. The decreased population of this conformation—required for the Diels–Alder reaction—is sufficient to override the electronic impact of the substituent.



Scheme 43. DTDA sequences with 2-substituted [3]dendralenes, exemplifying modest to good diene site selectivity. R = Cl, Me, CO$_2$Me, OEt, Ph, *p*-(MeO)C$_6$H$_4$, *p*-(O$_2$N)C$_6$H$_4$.

Despite the modest site selectivity, the products from the two pathways are readily separated. Whereas the product of addition to the less-substituted diene **249** proceeds at ambient temperature and pressure to form DTDA products **252** and **253**, the minor monoadduct **251** does not, presumably because of the low population of the reactive *s-cis* conformation of this semicyclic diene, on account of the inside R substituent. Nevertheless, reaction can be induced under high-pressure conditions. The π-diastereofacial selectivity seen in the major bisadduct series is significantly higher than in the minor series.

The majority of DTDA sequences of substituted [3]dendralenes has been performed on 3-substituted systems. There are two reasons for this. Firstly, robust synthetic methods have been in place for their preparation for some time (see Section 3) and, secondly, diene site selectivity is not an issue with these systems. The *s-cis* conformation of one of the diene units of a 3-substituted [3]dendralene is disfavored due to steric interactions from the inside substituent (Scheme 44). Assuming that the activation barrier towards (single kinetic step) cycloaddition of a dienophile at each diene site is roughly equal, the initial Diels–Alder reaction would be expected to occur at the diene site with the more populated *s-cis* conformation. Nevertheless, unless further (unsymmetrical) substitution is present on the triene unit,[77] no difference in the outcome of the DTDA sequence will be detectable.

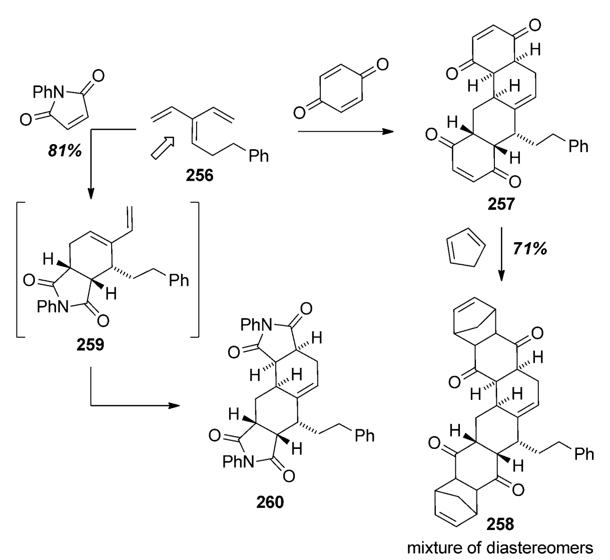


Scheme 44. Site selection in C3-substituted [3]dendralenes.

The first example of a DTDA sequence involving a 3-substituted [3]dendralene was the often overlooked 1951 study by Paul and Tchelitcheff.[51] When carboxylic acid **57** (see Scheme 38) was heated with maleic anhydride it furnished—in the first ever reported diene-transmissive Diels–Alder addition—the expected 2:1 cycloaddition product.

The Fallis research group was instrumental in the promotion of DTDA sequences in the modern era. They have made significant and elegant contributions, both in the synthesis of 3-substituted [3]dendralenes and in the development of DTDA sequences involving them.[44,45,205,206] A representative example from 1999 is shown in Scheme 45.[45]

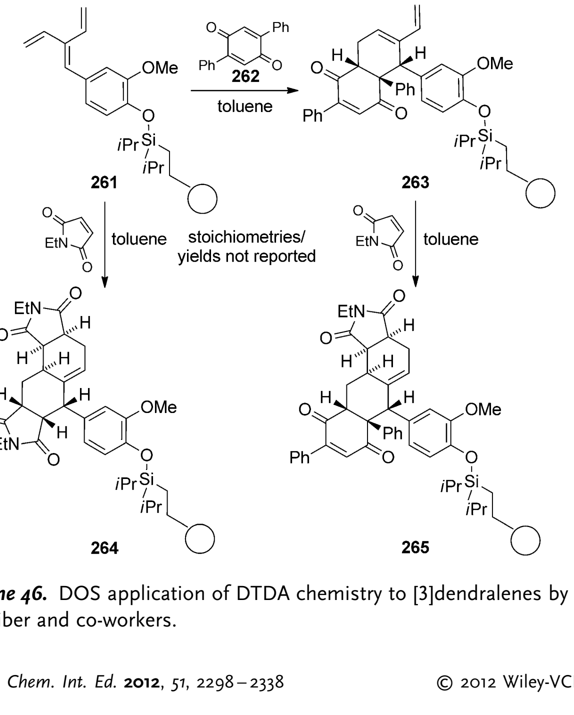
Addition of *p*-benzoquinone or *N*-phenylmaleimide (NPM) to internally substituted [3]dendralene **256** proceeds with high stereoselectivity to furnish bisadducts **257** and **260**, respectively. The influence of the substituent upon the site selectivity and π-diastereofacial selectivity can be ascertained from the product stereochemistry: bisadduct **260** must result from *endo* approach of the NPM dienophile to the convex face of the monoadduct **259**. Since only one diastereomer is seen, it would appear that the substituent (in this case the phenethyl group) enhances the inherent *anti* π-diastereofacial selectivity witnessed with the unsubstituted [3]dendralene (cf. Scheme 40). Monoadduct **259** most likely results from *endo*



Scheme 45. DTDA reactions on internally substituted [3]dendralene by Fallis and co-workers.

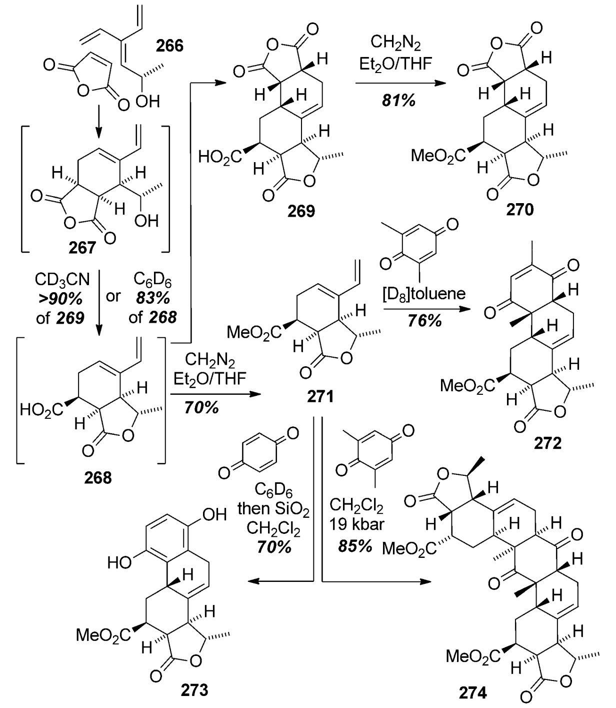
addition of NPM to the diene, which lacks the inside substituent. In a demonstration of how quickly dendralenes can be elaborated into complex multicyclic systems, bisadduct **257** reacts with cyclopentadiene to give octacyclic skeleton **258** as a mixture of diastereoisomers.

Schreiber and co-workers demonstrated the power of dendralenes in diversity oriented synthesis (DOS) in 2002, by employing the approach developed by Fallis and co-workers to synthesize 40 dendralenes from phenolic aldehyde-loaded macrobeads.[47,207] These solid-supported dendralenes were used in the synthesis of a library of 29400 discrete polycyclic compounds with 10 different ring skeletons by DTDA sequences with different dienophiles (Scheme 46). Of course, the double Diels–Alder reaction of a [3]dendralene with an alkenic dienophile always forms the same bicyclo[4.4.0]decene framework; the diversity in this synthesis originates from varying the structure of the two dienophiles used in the DTDA sequence. It was reported that disubstituted dienophiles, such as *N*-ethylmaleimide (NEM), underwent double cycloaddition to give the bisadducts, whereas tri- or tetrasubstituted dienophiles, such as **262**, underwent monoaddition. In 2006, a similar DTDA approach with internally substituted [3]dendralenes—this time in solution—was used to synthesize a library of 180 tetracycline analogues.[49]



Scheme 46. DOS application of DTDA chemistry to [3]dendralenes by Schreiber and co-workers.

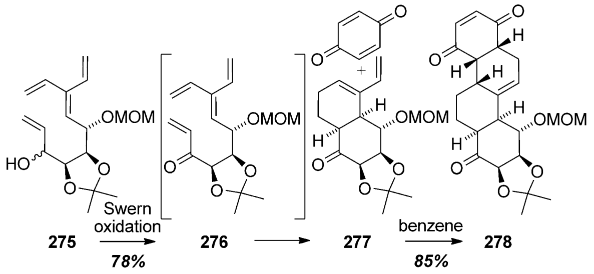
The publications surveyed so far describe the use of achiral dendralenes. In 2007, the Sherburn research group showed that chiral 3-substituted [3]dendralene **266** participates in DTDA sequences to give enantiomerically pure multicyclic compounds. Representative transformations from this study are depicted in Scheme 47.[48] Thus, a mixture of chiral [3]dendralene **266** and maleic anhydride (MA, 2 equiv) in acetonitrile at room temperature gave tetracyclic lactone acid **269** in high yield and as a single diastereomer, within the limits of detection (^{1}H NMR spectroscopy). The transformation presumably proceeds by the *endo* approach of MA to one π diastereoface of **266** to give short-lived **267**. This hydroxy anhydride cyclizes rapidly to bicyclic lactone acid **268**, which in turn reacts with MA through *endo* approach of the dienophile to the convex face of the bicyclic diene to form **269**. Thus, the conversion of dendralene **266** into tetracycle **269** involves the formation of five new covalent bonds and six new stereocenters, and proceeds in high yield with complete stereocontrol and atom economy.



Scheme 47. Use of a simple, chiral 3-substituted [3]dendralene for the generation of multicyclic frameworks.

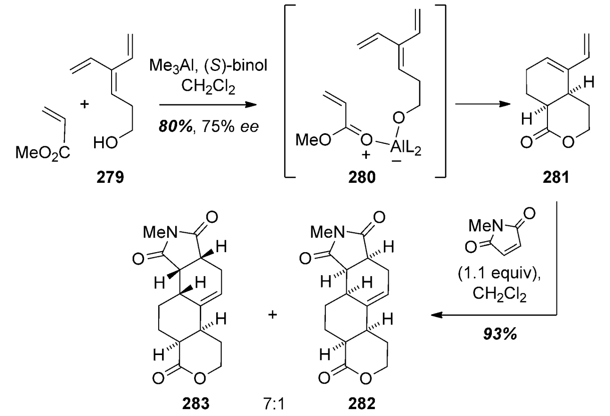
By carrying out the reaction between alcohol **266** and MA in benzene, rather than acetonitrile, the mono-cycloadduct, namely lactone acid **268**, could be isolated (Scheme 47). Esterification with diazomethane gave the corresponding methyl ester **271**, which was more soluble in nonpolar organic solvents. Reaction of this semicyclic diene with benzoquinone dienophiles proceeded with high regio- and stereoselectivity to form terpene-like frameworks **272** and **273**. A twofold cycloaddition of **271** with 2,6-dimethyl-*p*-benzoquinone gave heptacycle **274**, a result which exemplifies the striking level of structural complexity that can be rapidly generated from chiral dendralenes.

Fallis and co-workers reported the first example of an intramolecular/intermolecular DTDA sequence on a dendralene in 1999 (Scheme 48).[206] [3]Dendralene **275** was synthesized in eight steps from L-arabinose. Swern oxidation to afford ketone **276** with a concomitant intramolecular Diels–Alder (IMDA) reaction gave semicyclic diene **277** in 78% yield. The *cis*-ring fusion of product **277** is the result of an *endo* cycloaddition, with the π-diastereofacial selectivity of the process dictated by the tether substituents. An intermolecular Diels–Alder reaction with *p*-benzoquinone gave the terpene-like structure **278** as a single product.



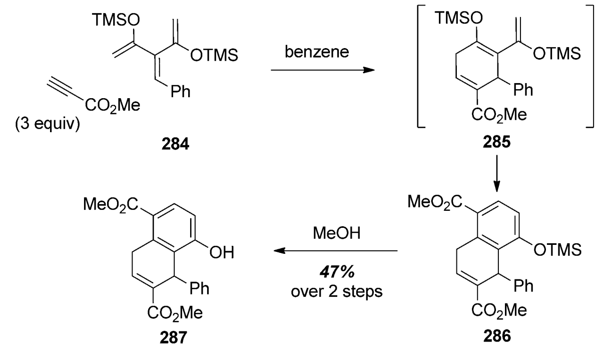
Scheme 48. An intramolecular/intermolecular Diels–Alder sequence involving a 3-substituted [3]dendralene. MOM = methoxymethyl.

In 2007, the Fallis research group used a temporary tether approach to bring about an enantioselective Diels–Alder reaction of internally substituted [3]dendralene **279** (Scheme 49).[44] Thus, reaction with a large excess of methyl acrylate in the presence of stoichiometric amounts of (*S*)-binol and Me_3Al according to a procedure originally reported by Ward et al.[208] gave, after work up and in situ lactonization, monoadduct **281** in 80% yield and 75% *ee*. The reaction presumably proceeds through intermediate **280**, with the configuration of the product being influenced by the binol ligand. Exposure of **281** to *N*-methylmaleimide (NMM) resulted in the formation of two tetracyclic products **282** and **283** in a 7:1 ratio, with the major diastereomer resulting from *endo* approach to the convex face of the bicyclic monoadduct.



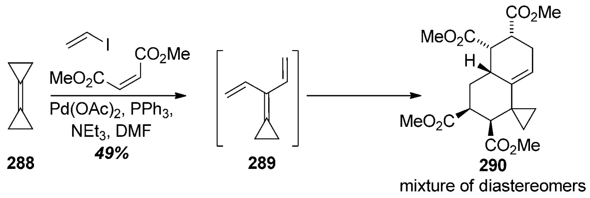
Scheme 49. Use of a temporary tether and chiral ligand to bring about a regio- and enantioselective DTDA sequence. (*S*)-binol = L = (*S*)-1,1′-binaphthalene-2,2′-diol.

This elegant contribution from the Fallis research group brings our survey of DTDA reactions of monosubstituted [3]dendralenes to a close. As mentioned on several occasions, the Tsuge research group made significant contributions to the early development of DTDA chemistry[59,60,71,195,196] and, in fact, was the pioneering group in this area. We have already seen some of the studies of the Tsuge research group with monosubstituted [3]dendralenes. Much of this work, however, involves 2,4-bis(trimethylsilyloxy)[3]dendralenes. Before we move on to DTDA sequences involving cyclo[3]dendralenes, we will examine one instructive example from these studies which demonstrates the significant potential of dendralenes for the one-step construction of dihydronaphthalenes.[60] Thus, the 1,4-dihydronaphthalene **287** was isolated in 47% yield upon reaction of 2,3,4-trisubstituted [3]dendralene **284** with excess methyl propiolate, followed by work up with methanol (Scheme 50). The orientational regioselectivity for each cycloaddition is expected from the substitution of each diene and dienophile.[209]



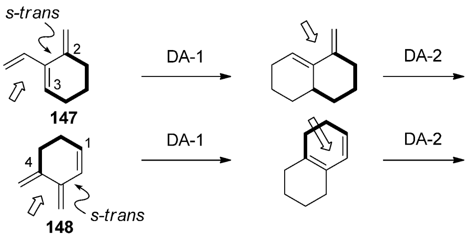
Scheme 50. One-pot DTDA/aromatization sequence according to Tsuge and co-workers.

As discussed in Section 4, there are eight structural classes of monocyclic [3]dendralenes, which can be divided into three subtypes, namely those that are more or less conformationally flexible and those that are more akin to acyclic systems in their behavior (Figure 2). The 1,1-cyclo- and 3,3-cyclo[3]-dendralenes are of the last type. Only one study exists of DTDA reactions of dendralenes of this type and it is a rather unique example that involves the double cycloaddition as part of a longer sequence. Thus, the de Meijere research group reported a novel sequence involving a Mizoroki–Heck reaction, cyclopropane ring opening, and β-hydride elimination to generate 3,3-cyclopropylidene[3]dendralene (**289**). This was followed by an in situ DTDA sequence to give a mixture of four diastereomeric bisadducts **290** (Scheme 51).[74,210] The spiro-cyclopropane ring in product **290** should be readily converted into the *gem*-dimethyl group. If the two cycloaddition processes can be controlled, this sequence might find application in the total syntheses of terpenoid natural products.



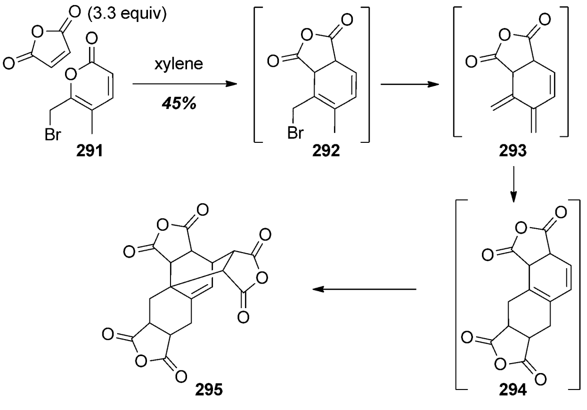
Scheme 51. One-pot Mizoroki–Heck/DTDA process by de Meijere and co-workers.

From a DTDA perspective, cyclo[3]dendralenes that contain one diene unit locked in an unreactive *s-trans* orientation, namely **147** and **148**, have the most appeal. As a consequence of the requirement for an *s-cis* diene in the Diels–Alder reaction, the site selectivity of Diels–Alder reactions involving these trienes must be complete (Scheme 52). DTDA sequences of structures of the general type **147** have been examined in detail. With the exception of the special case of *ortho*-quinone dimethides, which are not dendralenes and thus outside the scope of this Review, structures of type **148** are virtually unexplored. Once again, synthetic accessibility is responsible for the disparity in attention paid to structures **147** and **148**.



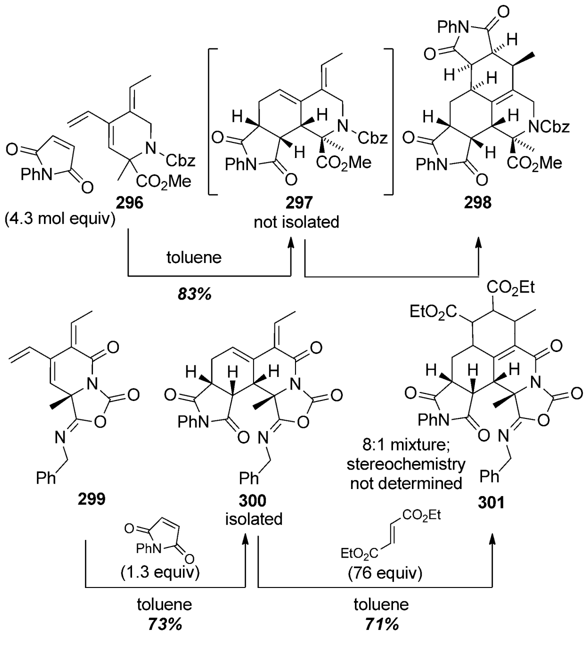
Scheme 52. Simplified DTDA sequences on cyclo[3]dendralenes that are constrained to proceed with complete site selectivity.

The only example of a DTDA reaction involving a 1,4-cyclo[3]dendralene **148** entails a quite remarkable cascade reported in 1965 (Scheme 53).[211] Thus, γ-pyrone **291** undergoes a Diels–Alder reaction with maleic anhydride followed by a retro-Diels–Alder reaction, with loss of CO_2, to give substituted cyclohexadiene **292**. 1,4-Elimination of HBr forms the 1,4-cyclo[3]dendralene **293**, which participates in a DTDA sequence to form hexacyclic system **295**, by way of cyclohexadiene **294**. This sequence involves the generation of no less than six C−C bonds and deserves further scrutiny.



Scheme 53. A sequence involving the generation and DTDA reaction of a 1,4-cyclo[3]dendralene.

The significant recent interest in cycloisomerizations of allenynes (see Section 4) has been the driving force for investigations into DTDA reactions of 2,3-cyclo[3]dendralenes **148**. The reaction of *N*-phenylmaleimide (NPM) with dendralenes **296** and **299** derived from α-amino acids[212] are representative of reports[212,213] involving a sequence of two intermolecular Diels–Alder reactions. The Brummond research group demonstrated that three (from a possible four) stereoisomeric bisadducts are formed in a 5:2:1 ratio on reaction of NPM with **296** (Scheme 54). The major product results from both Diels–Alder reactions proceeding with *endo* selectivity, with NPM dienophiles approaching from the less sterically hindered π diastereoface of the diene. Attempts to isolate the monoadduct **297** were not successful, presumably

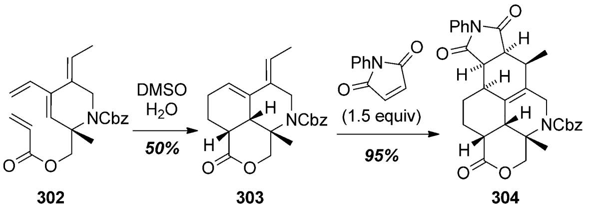


Scheme 54. Intermolecular DTDA sequences on 2,3-cyclo[3]dendralenes by Brummond and co-workers.

because of the higher reactivity of the diene **297** (locked in an *s-cis* conformation) relative to the starting triene **296**.

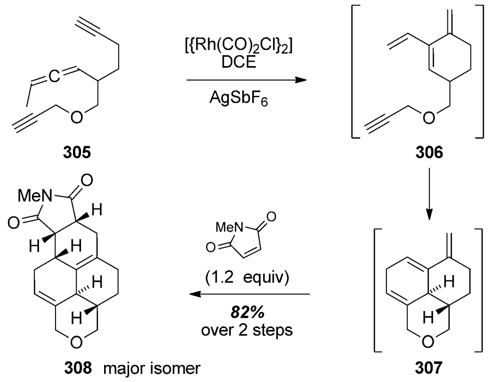
Structural modifications to the 2,3-cyclo[3]dendralene allowed both a significant improvement in the stereoselectivity of the DTDA sequence as well as the ability to interrupt the sequence after the first cycloaddition. Thus, the heterocyclic ring of bicyclic [3]dendralene **299** inhibits the approach of a dienophile from the bottom π diastereoface, and the amide carbonyl group retards the rate of the second Diels–Alder reaction (Scheme 54). The reaction of **299** with NPM gave the monoadduct **300** as the sole product, which was converted into the double adduct **301** with high (8:1) diastereoselection by using diethyl fumarate as the dienophile.

Higher levels of chemo- and stereoselectivity can be obtained through tethering the first dienophile to the dendralene, as is seen with **302** (Scheme 55).[212] An *endo* intramolecular Diels–Alder reaction of ester-tethered substrate **302** gave tricycle **303** as a single isomer. The complete π-diastereofacial selectivity of this reaction is the result of the dienophile being constrained to approach the bottom face of the piperidine ring. Intermolecular Diels–Alder reactions were carried out between **303** and a variety of dienophiles. The reaction with NPM proceeded at room temperature to give the pentacycle **304** with greater than 10:1 diastereoselectivity. In addition to improving the diastereoselection and facilitating the isolation of the monoadduct, conducting the first cycloaddition intramolecularly also leads to increased complexity, since the products of such sequences carry an additional ring.



Scheme 55. An intramolecular/intermolecular DTDA sequence on a 2,3-cyclo[3]dendralene by Brummond and co-workers. Cbz = benzyloxycarbonyl.

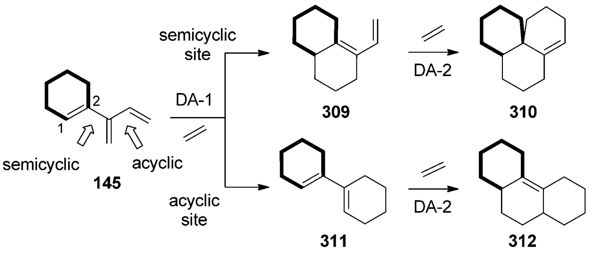
How far this sequential methodology has been developed will be illustrated in a final example, in which acyclic allene-diyne **305** is converted into pentacyclic products **308** (Scheme 56).[214] This impressive sequence, reported by Brummond and You, involves a rhodium-catalyzed ene-type cycloisomerization followed by a rhodium-catalyzed intramolecular [4+2] cycloaddition and then an intermolecular Diels–Alder reaction. The rhodium-catalyzed ene-type cycloisomerization led to the (not isolated) dendralene **306**, in which the terminal triple bond now participates in a second rhodium-catalyzed cycloisomerization: this time a cycloaddition-type process. A number of permutations were examined in the subsequent intermolecular Diels–Alder reaction, with the best outcome obtained through the use of NMM as the dienophile. This gave pentacycle **308** as the major product in a 5:1 ratio of diastereomers. The rhodium-catalyzed cycloaddition gives a single isomer, while the intermolecular Diels–Alder reaction gives the two *endo* products resulting from addition of the dienophile to either π diastereoface of **307**.



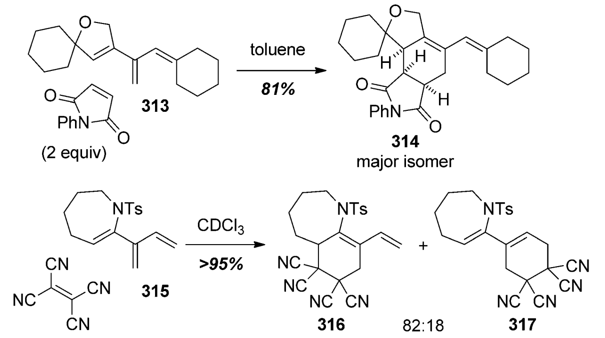
Scheme 56. A cycloisomerization/cycloisomerization Diels–Alder sequence involving a 2,3-cyclo[3]dendralene by Brummond and You.

This example from the Brummond research group completes our survey of DTDA reactions of cyclo[3]dendralenes that are constrained to react with complete site selectivity. The remaining cyclo[3]dendralene subtypes, namely **145** and **146**, offer the prospect of competition between less-substituted and more-substituted diene sites (Scheme 39 and Scheme 57).

1,2-Cyclo[3]dendralenes **145** can undergo cycloadditions at either the acyclic or semicyclic diene sites and, in principle, could go on to form the two a tricyclic frameworks **310** and **312** through alternative DTDA sequences (Scheme 57). The majority of reported examples involving 1,2-cyclo[3]dendralenes actually involve Diels–Alder reactions with the products of cycloadditions that afford [4]dendralenes, which will be discussed below. Two other examples have recently been reported (Scheme 58). Interestingly, both **313** and **315** exhibit a preference for addition to the semicyclic site and show chemoselectivity for monoaddition to give **314** and **316**, respectively. The selectivity for the semicyclic site can be enhanced by intramolecularity.[215] As an aside, we mention here that styrenes (which might be thought of as a special group of 1,2-cyclo[3]dendralenes) have also been used as double dienes in DTDA reactions.[216]

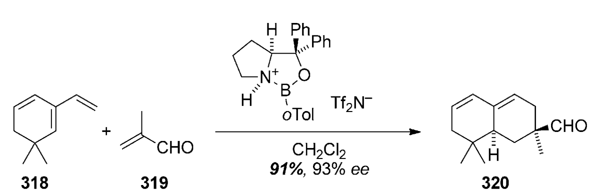


Scheme 57. Site-selectivity issues in DTDA sequences on 1,2-cyclo[3]-dendralenes.



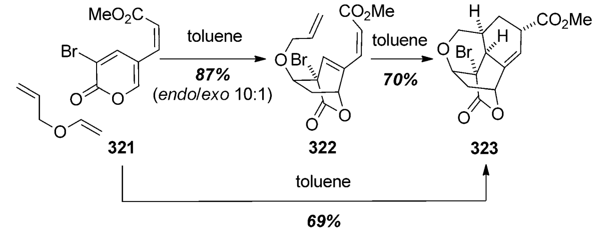
Scheme 58. Diels–Alder reactions of 1,2-cyclo[3]dendralenes.

1,3-Cyclo[3]dendralenes **146** (Scheme 39) carry both endocyclic and semicyclic dienes. An initial addition of a dienophile to the semicyclic diene produces a new diene **232**, locked in the *s-trans* conformation, and is thus unable to participate as the diene in a second cycloadddition (Scheme 39). Conversely, if addition occurs first at the endocyclic diene, then a DTDA sequence can ensue. As we shall see, both pathways are known. Does the site selectivity of the reaction depend upon the nature of the ring? The answer is yes. Cycloaddition at the endocyclic diene is favored in 2-alkenyl cyclopentadienes,[217,218] but in six-[134,219,220] and seven-membered[141] rings the semicyclic diene is usually preferred. Enantioselective Diels–Alder reactions of 1,3-cyclo[3]dendralenes (e.g. **318**+**319**→**320**; Scheme 59) were recently employed by Hong and Corey in the synthesis of structural analogues of the natural products georgyone and arborone.[134]



Scheme 59. Synthesis of natural product analogues from 1,3-cyclo[3]-dendralenes according to Hong and Corey. Tf = trifluoromethanesulfonyl, Tol = tolyl.

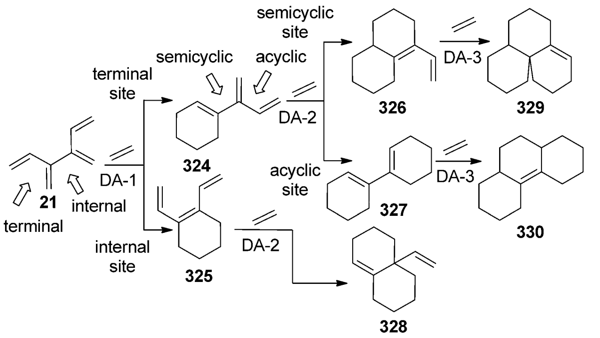
Substitution can reverse the preference, however. An intermolecular/intramolecular DTDA sequence involving γ-pyrone-based [3]dendralenes was reported by Cho and coworkers.[138] *Z*-Alkenyl pyrone **321** and its *E* isomer undergo highly regio- and stereoselective DTDA sequences with a variety of allyl vinyl ethers to give bridged tetracycles **323** (Scheme 60). The first Diels–Alder reaction occurs between the endocyclic diene and the vinyl group of the allyl vinyl ether. The second Diels–Alder reaction in the sequence is an intramolecular one between the newly formed semicyclic diene and the allyl ether. The sequence can be stopped after the first cycloaddition or can be carried out in one pot if more forcing conditions are used. Presumably, care must be taken to avoid retro-Diels–Alder decarboxylation of monoadducts **322**.



Scheme 60. DTDA sequence involving γ-pyrone-based 1,3-cyclo[3]dendralenes according to Cho et al.

In concluding our survey of cycloaddition reactions involving [3]dendralenes we note that DTDA reactions of dihydropentalene **222** (Figure 5)—which can also be considered as a bicyclic [3]dendralene analogue—have been reported.[221]

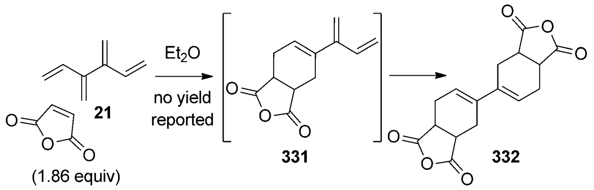
As mentioned already, relatively few studies into DTDA sequences with [4]dendralenes have been reported. We have already seen many intricate sequences involving [3]dendralene as a double diene. The situation becomes significantly more complex with higher dendralenes. [4]Dendralene (**21**), for example, can undergo three distinct sequences of Diels–Alder reactions, all involving diene-transmissive character (Scheme 61). The initial addition can occur at either the terminal or the internal site of the tetraene. The internal monoadduct **325** undergoes a second cycloaddition to give bicycle **328** as the final product, whereas the terminal monoadduct **324** is another point of divergence, with both paths leading to a distinct tricyclic triple adduct, namely **329** and **330**.



Scheme 61. Site-selectivity issues in Diels–Alder reactions of [4]dendralene (**21**; ethylene as dienophile).

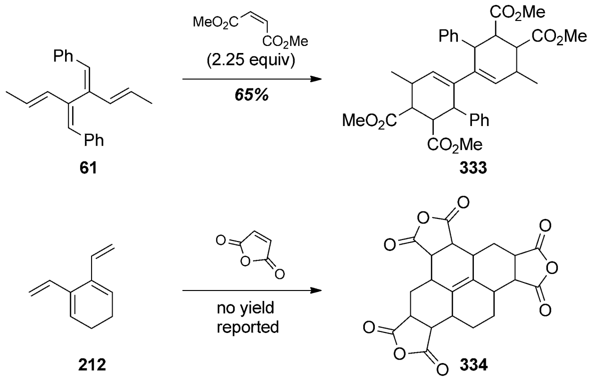
Inevitably, the key to unlocking the synthetic potential of the higher dendralenes is selectivity: the issues of chemoselectivity (i.e. single, double, or triple additions), site selectivity, orientational regioselectivity (with unsymmetrical dienophiles), and stereoselectivity (*endo*/*exo* and π-facial) must all be addressed. Suffice to say, these are significant challenges and many issues remain that have been inadequately addressed.

The first study of Diels–Alder reactions involving [4]dendralene (**21**) was reported in 1962 by Bailey and Nielsen, who were also the first to report the preparation of the hydrocarbon.[222] In this seminal study, when **21** was treated with either maleic anhydride or *p*-benzoquinone, bisadducts such as **332** were obtained (Scheme 62). This product arises from an initial addition at one of the two equivalent terminal sites, followed by a second addition to the acyclic site of the monoadduct. Attempts to isolate the trisadduct from the reaction of the bisadduct **332** with an excess of maleic anhydride, which would represent a DTDA sequence, were unsuccessful.



Scheme 62. The first reported Diels–Alder reaction of [4]dendralene (**21**) by Bailey and Nielsen.

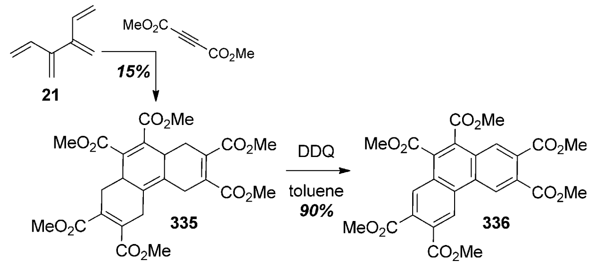
To our knowledge, apart from the parent hydrocarbons, the DTDA reactions of only two analogues of [4]dendralene have been reported. In 1988, Wehbe and Lepage reported that the reaction between substituted [4]dendralene **61** and dimethyl maleate led to the formation of bisadduct **333** (Scheme 63).[57] The site selectivity witnessed here is less surprising than that seen with the parent hydrocarbon, since the two inside phenyl groups of tetraene **61** will destabilize the *s-cis* conformation at the central C–C bond, thereby disfavoring addition to the internal site.



Scheme 63. The only reported Diels–Alder reactions of [4]dendralene analogues.

Some 20 years earlier, Skattebøl and Solomon reported the conversion of 3,4-cyclo[4]dendralene **212** into the triple maleic anhydride Diels–Alder adduct **334** (Scheme 63).[168] This spectacular transformation involves an initial addition at the terminal, semicyclic diene site of divinylcyclohexadiene **212**; after this first addition, the fate of this precursor is sealed in that the second dienophile is constrained to add at the other semicyclic site.

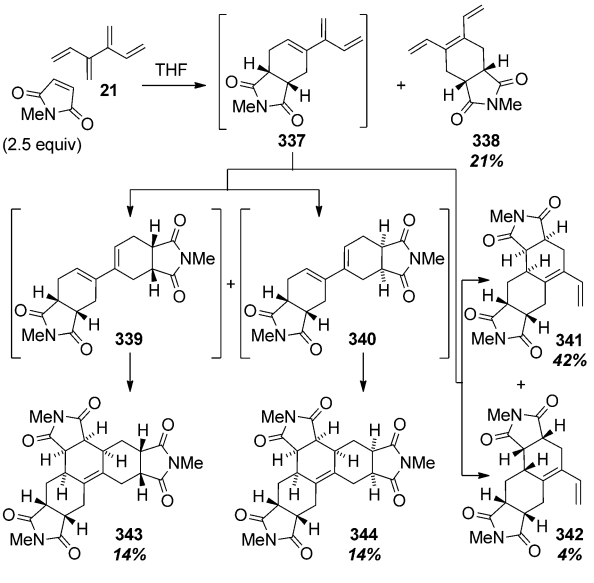
In 2003, Hopf first demonstrated that the parent [4]dendralene (**21**) was capable of participating in a diene-transmissive triple Diels–Alder sequence[6] (Scheme 64), and full details of this study were recently disclosed.[223] The hydrocarbon was treated with dimethyl acetylenedicarboxylate (used as the solvent) to give the trisadduct **335**, which was aromatized to give polysubstituted phenanthrene **336**.



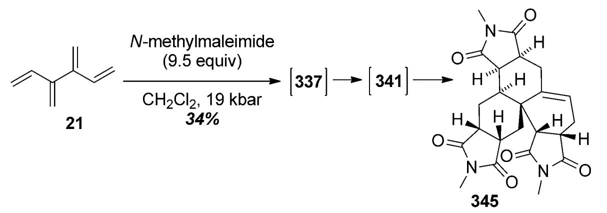
Scheme 64. The first diene-transmissive triple Diels–Alder sequence on [4]dendralene (**21**) according to Hopf. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In 2005, the Sherburn research group demonstrated that **21** is capable of participating in diene-transmissive Diels–Alder sequences to give a variety of multicyclic products (Schemes 65 and 66).[29] When [4]dendralene (**21**) was treated with an excess of *N*-methylmaleimide (NMM) at room temperature and ambient pressure, a mixture of five products (**338**, **341**–**344**) was obtained in excellent overall yield (Scheme 65).

The first of these products is the internal monoadduct **338**, which was isolated in 21 % yield. Under the reaction



Scheme 65. Reactions of [4]dendralene (**21**) with excess NMM at ambient temperature and pressure.



Scheme 66. A diene-transmissive triple Diels–Alder sequence involving [4]dendralene (**21**) at elevated temperature and pressure.

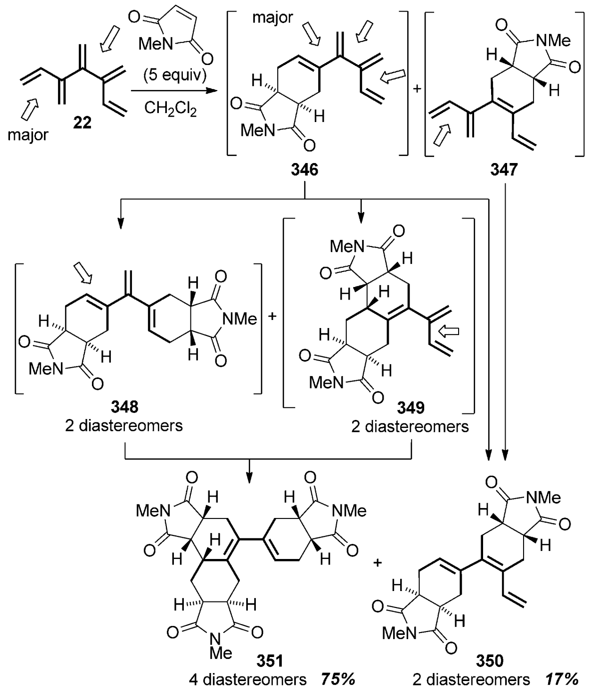
conditions, monoadduct **338** is inert towards further reaction with the potent dienophile NMM. The remaining four products stem from an initial Diels–Alder reaction at one of the two equivalent terminal diene sites of **21** to form monoadduct **337**, a 1,2-cyclo[3]dendralene. This compound reacts further, and different products are formed through reaction at both diene sites of **337**. Reaction at the semicyclic diene site of **337** gives diastereomeric bisadducts **341** and **342**. Both carry a new diene, but are unreactive towards a third addition under these conditions. The major product, **341**, is the result of an *endo* approach of NMM to the more accessible, convex face of the semicyclic diene of **337**. Monoadduct **337** also reacts through the acyclic site, thereby leading to the two diastereomeric bisadducts **339** and **340**, which undergo a third Diels–Alder reaction to give trisadducts **343** and **344** in a 1:1 ratio. Thus, the second cycloaddition (**337** to **339** + **340**) is nonstereoselective, but each of the bisadducts produces only one trisadduct.

Ignoring the stereochemistry, three products are formed from the reaction of [4]dendralene (**21**) with NMM (Scheme 65), namely monoadduct **338**, bisadducts **341**/**342**, and trisadducts **343**/**344**. Since bisadducts **341**/**342** are the major products, the favored pathway for an uncatalyzed Diels–Alder sequence between [4]dendralene (**21**) and NMM involves an initial addition at the terminal site of **21** followed by a second addition to the semicyclic diene site of the 1,2-cyclo[3]dendralene **338**. When a mixture of **21** and NMM are allowed to react under high pressure at elevated temperature, a new trisadduct **345** is formed as the major product in 34 % yield (Scheme 66). This is the product of *endo* cycloaddition to the less sterically hindered π diastereoface of diene **341**, and is the result of a DTDA sequence involving additions that occur progressively from one end of the π system to the other.

These pathways are interesting but, inevitably, higher site selection will be needed for applications in total synthesis. Ref. [29] describes the first tentative steps in this direction, with the disclosure that promotion by Lewis acids can lead to the generation of either the terminal or internal monoadducts.

It is evident that progressively increasing levels of structural complexity are achievable through Diels–Alder sequences with higher dendralenes. We have seen that [3]dendralenes undergo sequences of two cycloadditions, and [4]dendralenes participate in sequences of three cycloadditions. In fact, it is a general rule that an [*n*]dendralene can undergo a maximum of ($n-1$) Diels–Alder reactions. Nevertheless, the larger the dendralene, the greater the number of conceivable cycloaddition sequences.

The largest dendralene that has been subjected to a detailed DTDA study is [5]dendralene (**22**),[27] and the results of this study, involving excess NMM at ambient temperature and pressure, are summarized in Scheme 67. The pentaene **22** has two distinct diene sites available for reaction with a dienophile, and the inherent preference (ca. 80:20) is for addition of the dienophile to the terminal site of **22** to form monoadduct **346**. The less-favored internal monoadduct **347** undergoes a second—and final—addition to the terminal site, since this is the only one of the three available 1,3-butadienes that lacks an inside substituent. The resulting bisadduct **350** is unreactive towards NMM under these conditions.

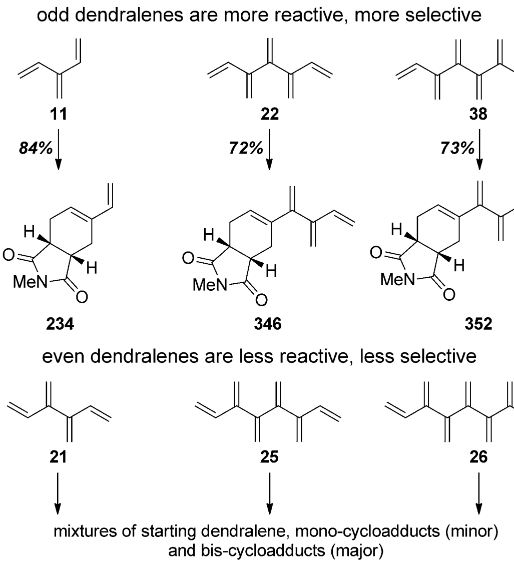


Scheme 67. Summarized outcome of the reaction of [5]dendralene (**22**) with excess NMM at ambient temperature and pressure.

The major monoadduct **346** can be recognised as a 1,2-cyclo[4]dendralene. Interestingly, from the three possible sites for addition by NMM, it undergoes addition to the more-substituted semicyclic one to form bisadduct **349**. Nevertheless, the selectivity is rather modest and the two other possible bisadducts **348** and **350** are also formed. Bisadducts **348** and **349** are substituted [3]dendralenes and both lead to trisadduct **351**. The 1,3-butadiene group of trisadduct **350** did not undergo a Diels–Alder reaction with a range of common, reactive dienophiles under a range of forcing reaction conditions. Evidently, this diene is significantly sterically shielded.

Reactivity patterns for the dendralenes are beginning to emerge from these studies. From an analysis of Schemes 65 and 67, it is evident that there is a preference for addition to an unsubstituted dendralene at a terminal site rather than an internal site. This produces a 1,2-cyclodendralene, which undergoes preferential addition at the semicyclic diene site, at least with the activated dienophile NMM.

The results described so far for [4]- and [5]dendralenes are the outcomes of exhaustive reactions with NMM. Reactions conducted on the family of dendralenes with stoichiometric amounts of the dienophile are particularly instructive: they highlight an alternation in behavior between "odd" and "even" members (Scheme 68). Thus, [3]-, [5]-, and [7]dendralenes undergo a rapid and clean conversion into (predominantly) the corresponding terminal monoadduct at ambient temperature, even in the presence of a small excess of the dienophile. In contrast, [4]-, [6]-, and [8]dendralenes exhibit significantly lower reactivity towards NMM, requiring longer reaction times and producing mixtures of starting dendralenes as well as mono- and bisadducts. Multiple cycloaddition to the even dendralenes could not be arrested, even with a substoichiometric amount of the dienophile.



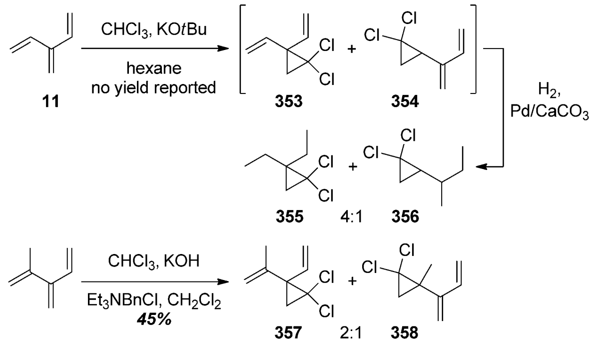
Scheme 68. Divergent reactivities of "odd" and "even" dendralenes on exposure to a stoichiometric amount of dienophile. All reactions involve treatment with NMM (1 equiv) in $CDCl_3$ (0.05 M) at RT.

Paddon-Row provided a convincing explanation of this marked difference in reactivity between odd and even dendralenes through an analysis of their conformational preferences (Section 5).[26] Why are even dendralenes less reactive than odd dendralenes? As discussed earlier, even dendralenes comprise *s-trans* 1,3-butadienes that are roughly orthogonal to one another. Odd dendralenes, on the other hand, possess a quasi *s-cis* diene component, which is predisposed to react as the diene component in a Diels–Alder reaction. Why do odd dendralenes undergo clean monoaddition whereas even dendralenes give mainly double addition products? Addition to the terminal site of an [*n*]dendralene gives a substituted [$n-1$]dendralene; odds go to evens and vice versa. A more-reactive odd dendralene forms a less-reactive even dendralene, hence resulting in a clean transformation. A less-reactive even dendralene is converted into a more-reactive odd dendralene, which reacts in preference to the starting material.

This concludes our survey of DTDA reactions of the dendralenes. In summary, important isolated contributions from several research groups in the 1950s and 1960s, followed by the groundbreaking series of publications on [3]dendralenes by Tsuge and co-workers in the 1980s, set the scene for the most recent burst of activity. The last decade has witnessed a rapid and sustained growth in this field. Nevertheless, work in this area has been mainly exploratory in nature. Current efforts continue this trend and highlight the promise of DTDA reactions of the dendralenes in synthesis. As we will see in the final section of this Review, the first applications are beginning to appear. However, it is fair to say that the potential of these transformations in total synthesis has not yet been realized.

7. Other Transformations of Dendralenes

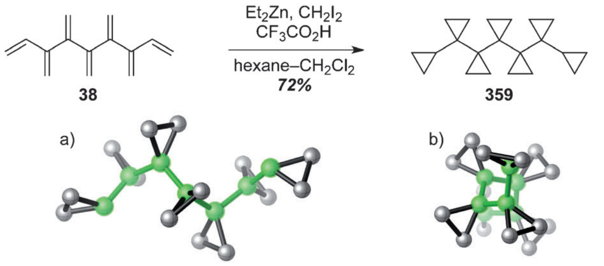
As we have seen, the reactivity of the dendralenes as 1,3-butadienes is well established. Interestingly, reports of reactions occurring at single alkene units of the dendralenes are comparatively rare. With such reactions, the issue of site selectivity exists even with the smallest member of the family, [3]dendralene (**11**). The first addition of a carbene to a dendralene appears to have been reported by Kostikov and Molchanov (Scheme 69).[224] By adding dichlorocarbene to [3]dendralene (**11**), the authors obtained a mixture of the two monoadducts **353** and **354**. Stability issues precluded the isolation of the two products, but hydrogenation gave separable products **355** and **356** in a 4:1 mixture. The major product was the result of the addition of dichlorocarbene to the central C=C bond of [3]dendralene (**11**). In a subsequent report, the 2-methyl derivative of **11** was treated with dichlorocarbene. This derivative carries three different alkenes. Products resulting from additions at each of the two 1,1-disubstituted alkenes were observed, with addition to the central C=C bond again dominating (ratio: 2:1).[225]



Scheme 69. Addition of dichlorocarbenes to [3]dendralenes, according to Kostikov and Molchanov.

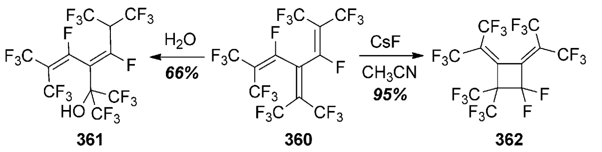
The preference for addition at the central C=C bond of [3]dendralene has also been noted during the Diels–Alder dimerization of the hydrocarbon (see Section 6, Scheme 41). Evidently, the central alkene of [3]dendralene (**11**) is significantly more reactive than the terminal one, particularly when the statistical bias towards the latter is taken into account. Whether this selectivity extends to higher members of the family remains to be seen.

An investigation into the exhaustive cyclopropanation of the [*n*]dendralenes was recently reported by Sherburn and co-workers. The resulting family of 1,1-oligocyclopropanes, termed ivyanes,[226] were prepared by a one-pot, multiple Simmons–Smith type cyclopropanation of the alkene units of [3]- to [8]dendralenes (Scheme 70). The ivyanes are quite different from their dendralene precursors in that they adopt chiral helical conformations in both the solid and solution phases. They also exhibit some of the highest experimental heats of combustion recorded for hydrocarbons. It was also demonstrated that ring-opening reactions of ivyanes furnish structures that are difficult to access by other means.



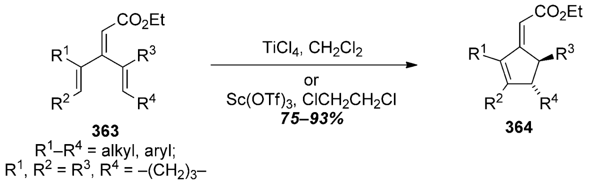
Scheme 70. Exhaustive cyclopropanation of dendralenes leads to the ivyanes. The cyclopropanation of [7]dendralene (**38**) is representative. The X-ray crystal structures show the helical nature of the hydrocarbon **359**: a) from the side, and b) down the longest chain.

The behavior of dendralenes in ionic additions has hardly been studied at all, and the few reported examples concern highly substituted [3]dendralenes (Scheme 71). The perfluoro compound **360**[227–230] is readily available by trimerizing perfluoroisobutylene under the influence of triphenylphosphine,[230] and has been studied carefully by Ter-Gabrielyan and co-workers. To mention just two of their ionic reactions: with water **360** forms the 1,4-addition product **361** in good yield,[229] and with CsF, the cyclobutene product **362** predominates.[227] The highly substituted [3]dendralenes prepared by Shi and co-workers (see Section 3, Scheme 24) also have potential in aromatic chemistry.[111]



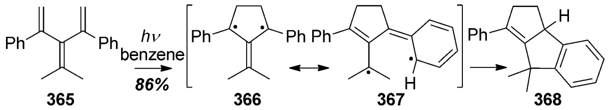
Scheme 71. Ionic reactions of substituted [3]dendralenes.

At first sight, a [3]dendralene in an all-*trans* conformation (Scheme 72) looks predestined to undergo a Nazarov cyclization, a long-known route for the preparation of cyclopentenone derivatives.[231] In fact, the possibility of such an acid-promoted 4π electrocyclization was hinted at in an early MO calculation in 1972.[232] Indeed, a "vinylogous" Nazarov cyclization of a [3]dendralene has recently been reported.[38] Treatment of [3]dendralenes **363** with titanium(IV) chloride or scandium(III) triflate furnished the Nazarov products **364** in good yields and stereoselectivity. Several other routes to Nazarov-type electrocyclizations from dendralenes can be envisioned, including sequential multiple bond-forming transformations. We anticipate interesting future developments in this area.



Scheme 72. "Vinylogous" Nazarov reactions of [3]dendralenes according to West and co-workers.

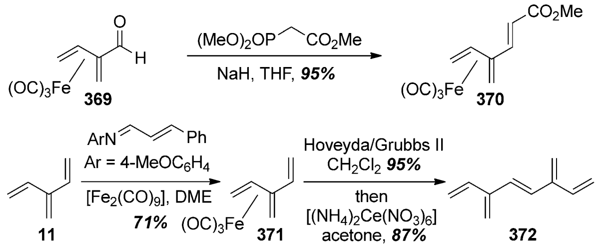
The photochemistry of dendralenes has so far received very little attention, one reason presumably being their non-availability until very recently. In fact, in our literature search, we could only find two references relating to the photochemical behavior of dendralenes. Triplet-sensitized irradiation of the tetrasubstituted [3]dendralene **365** with a high-pressure mercury lamp caused isomerization to the tricyclic hydrocarbon **368** (Scheme 73).[111] To rationalize the formation of **368**, the authors propose that, in the initial step, the substituted trimethylenemethane biradical intermediate **366** is generated, which undergoes biradical coupling through resonance form **367**, followed by 1,3-hydrogen transfer. A photochemical isomerization of a substituted [3]dendralene into a "skipped" triene has also been reported.[233]



Scheme 73. A photochemical transformation of a [3]dendralene.

Scattered reports exist on metal complexes of dendralenes, with the majority focusing on 1,3-butadiene–irontricarbonyl complexes. Of course, the complexation of unstable dienes with the {Fe(CO)$_3$} group to generate stable complexes is well established.[234] Nevertheless, the preparation and reactions of metal complexes of dendralenes have been poorly investigated until recently. Two general strategies can be envisioned for the formation of {Fe(CO)$_3$} complexes of dendralenes: a 1,3-butadiene–{Fe(CO)$_3$} complex might be decorated with a 2-alkenyl group, or a dendralene could be complexed with an {Fe(CO)$_3$} group. Both approaches are known, with the former being studied by Martina, Franck-Neumann, and co-workers.[235] In a representative example, the {Fe(CO)$_3$} complex of 2-formyl-1,3-butadiene (**369**) undergoes a Horner–Wadsworth–Emmons reaction to generate unsaturated ester **370** (Scheme 74).

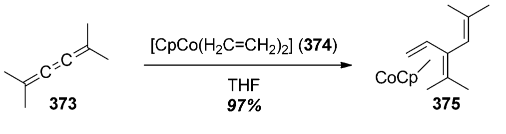
Building on an important early study on the $\{Fe(CO)_3\}$ complexes of [4]dendralene (**21**) by Greene et al.,[236] Sherburn and co-workers demonstrated that the tricarbonyliron complexes of [3]- and [4]dendralene can be readily prepared in good yield on a multigram scale through an azabutadiene-catalyzed reaction of $[Fe_2(CO)_9]$ with the parent hydrocarbon **11** (Scheme 74).[237] The structures, properties, and reactions of these complexes were studied through a joint computational/experimental approach with Paddon-Row and co-workers. This study demonstrated the utility of these complexes in the formation of products that cannot be accessed directly from the dendralenes, including unprecedented hybrid linear/branched conjugated hydrocarbon **372**.



Scheme 74. $\{Fe(CO)_3\}$ complexes of dendralenes.

In other studies, iridium–dendralene complexes of the type $[Ir(\eta^4\text{-}(RCH{=}C(CH{=}CH_2)_2)(PPh_3)_2(CO)]^+$ have been prepared by reaction of the alkynylbis(ethenyl) complexes $[Ir(CH{=}CH_2)_2(C{\equiv}CR)(PPh_3)_2(CO)]$ with HBF_4.[238] It has also been shown that when treated with iron dodecacarbonyl, acetylene forms two metal complexes, one of which has the structure of a [3]dendralene bound to two $\{Fe(CO)_3\}$ fragments.[239] Finally, another report exists in the literature involving complexation of $\{Fe(CO)_3\}$ to a cross-conjugated triene-one referred to as "pseudoionone".[240,241]

Moving on to other metals, the {CpCo}–1,3-butadiene complex **375** is isolated in almost quantitative yield when **373** is treated with complex **374** (Scheme 75).[242] The reaction involves the formal addition of a C–H bond of ethylene across the cumulenic C=C bond. This is an isolated example; a reaction of broader scope would represent a valuable method for the synthesis of dendralenes.



Scheme 75. Synthesis of a {CpCo}–[3]dendralene complex by Stehling and Wilke.

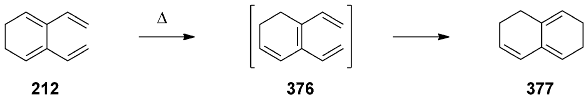
To conclude this section on metal complexes of dendralenes, we note that calculations into the binding energies of d^{10}, d^8, and d^6 complexes of Pt and Pd with several π-conjugated systems, including dendralenes, have been reported.[240]

To bring our survey of basic dendralene reactivity patterns to a close, we briefly discuss the application of these structures in polymerization reactions. Since [3]dendralene (**11**) is a double diene, its DTDA reaction with a double dienophile should, in principle, yield a polymer. Bailey et al. showed that this is indeed the case, through reaction of **11** with the double dienophiles *p*-benzoquinone, *N,N′-m*-phenylenebismaleimide, ethylene diacrylate, and other double dienophiles. In all cases, polymers were obtained, although these were not characterized thoroughly.[243]

Applications of dendralenes in perhaps more familiar ionic polymerizations can also be found. Thus, dendralenes have been mentioned in the patent literature several times, but it is difficult to locate structural information. For example, a patent has been granted to the du Pont company for the preparation of 2,4-dimethyl-3-methylene-1,4-pentadiene (2,4-dimethyl[3]dendralene)[244] for use as a monomer in polymerization studies.[245] In addition, cyano-substituted polyesters, urethanes, and epoxy resins have been derived from the [3]dendralene monomer 2,6-bis(4-hydroxybenzylidene)-1-dicyanomethylenecyclohexane.[246]

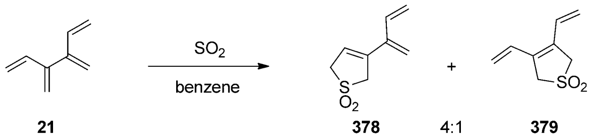
8. From Dendralenes to Dendralenes, Radialenes, and Related Compounds

An important subgroup of dendralene transformations involve interconversions of members of the five fundamental classes of oligoenes (Scheme 1). The majority are conversions of one dendralene into another, but examples of transformations into annulenes and radialenes are also known. The reactions are often either isomerizations or cycloadditions. A typical example of the former type is a dendralene-to-dendralene isomerization involving three different cross-conjugated hydrocarbons (Scheme 76).[169] Heating the monocyclic [4]dendralene **212** in the gas phase at 260 °C results in the formation of bicyclo[3]dendralene hydrocarbon **377**. Presumably, the process is initiated by a 1,5-hydrogen shift and the resulting linear/cross-conjugated tetraene **376** undergoes a 6π-electrocyclic ring closure.



Scheme 76. Dendralene isomerizations by Roth et al.

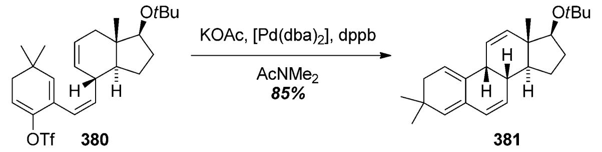
The addition reactions usually involve a higher dendralene, which is converted by a cheleotropic addition or a Diels–Alder addition into a lower dendralene. We have seen several examples of the latter type already (Section 6); the conversion of [4]dendralene (**21**) into the 1,2-cyclo[3]dendralene **378** and its isomer **379** by chelotropic addition of sulfur dioxide serves as an example of the former type (Scheme 77).[247] It



Scheme 77. Cheleotropic addition of SO$_2$ to [4]dendralene (**21**) by Roth et al.

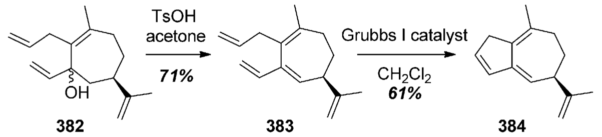
should be noted that the site selectivity for the terminal versus internal position matches that seen in Diels–Alder reactions of [4]dendralene (**21**; Section 6) very closely.

Three examples of transformations of 1,3-cyclo[3]dendralenes into other cross-conjugated trienes have been reported. An intramolecular Mizoroki–Heck reaction of 3-trifluoromethanesulfonyloxy-2-alkenyl-1,3-cyclohexadiene **380** to give a steroid **381** containing a [3]dendralene was reported by Tietze and Petersen (Scheme 78).[248] A similar precursor underwent Negishi cross-coupling reactions with arylzinc halides to give 3-aryl-2-alkenyl-1,3-cyclohexadienes.[4,12,249]



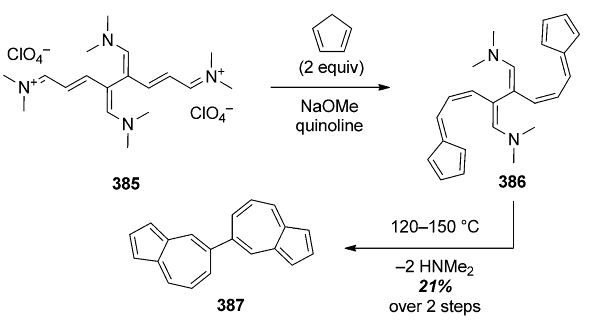
Scheme 78. Dendralene-to-dendralene conversion through intramolecular Mizoroki–Heck reaction by Tietze and Petersen. dppb = 1,1′-bis(diphenylphosphanyl)butane.

Finally, a ring-closing metathesis reaction of 2-vinyl-3-allylcycloheptadiene **383** led to bicyclo[3]dendralene **384**, an intermediate en route to guaiane sesquiterpenes (Scheme 79).[135] 1,3-Butadienes are usually inert to reactions with the Grubbs metathesis catalysts, and the success of this transformation must hinge upon an initial reaction at the isolated monosubstituted alkene unit of precursor **383**.



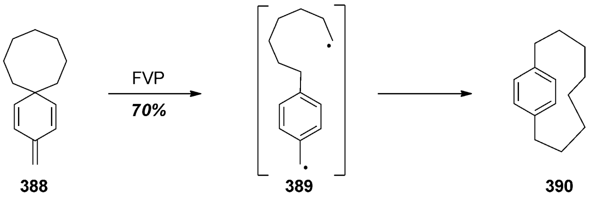
Scheme 79. RCM reaction involving a [3]dendralene by Brocksom et al.

A remarkable synthetic achievement employing a dendralene-to-dendralene/fulvene-to-annulene conversion has been achieved with the readily available [4]dendralene pentamethinium salt **385** (Scheme 80).[4,12,249,250] When **385** is treated with 2 mol equiv of cyclopentadiene in the presence of sodium methoxide in quinoline, a double condensation ensues and the "stretched" bisfulvene **386**, a substituted [4]dendralene, is formed. On heating this intermediate to 120–150 °C it undergoes the expected Ziegler–Hafner azulene ring closure and furnishes 5,5′-biazulenyl (**387**).



Scheme 80. Dendralene→dendralene/fulvene→annulene conversion by Jutz and Hanke.

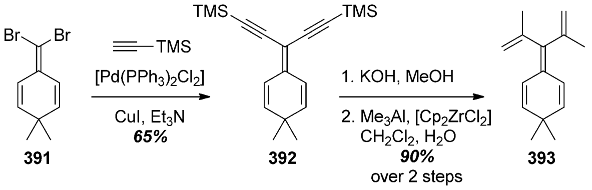
The next transformation (a dendralene-to-annulene conversion) shows the special power of flash vacuum pyrolysis (FVP) for the connection of vastly different structural classes of compounds through a rather simple chemical process. As shown by Bickelhaupt and co-workers, spiro-fused 1,5-cyclo[3]dendralene **388**, upon flash vacuum pyrolysis at 550 °C, isomerizes in surprisingly high yield (70%) to give [8]paracyclophane (**390**), presumably through diradical **389** as an intermediate (Scheme 81).[251]



Scheme 81. Rearrangement of a 1,5-cyclo[3]dendralene to a paracyclophane by Bickelhaupt and co-workers.

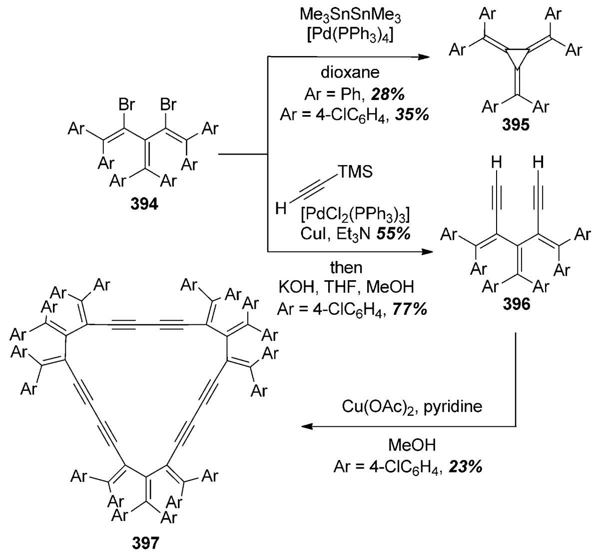
In a dendralene-to-dendralene interconversion, 1,5-cyclo[3]dendralene **391** was first transformed by a double Sonogashira coupling with trimethylsilylacetylene into the cross-conjugated bisacetylene derivative **392**, which, after deprotection with aqueous potassium hydroxide, was reductively alkylated to **393** (Scheme 82).[152] This interesting structure—a derivative of tetravinylethylene (also see **223**, Figure 5)—can be thought of as a pair of [3]dendralenes that have been conjoined at the central methylene group.

2,4-Dibromohexaaryl[3]dendralenes **394** have been used in the synthesis of radialenes, 2,4-alkynyl[3]dendralenes, and



Scheme 82. Transformation of a [3]dendralene into a tetravinylethylene analogue by Hopf et al.

expanded radialenes (Scheme 83).[252] Thus, dibromides **394** undergo an intermolecular/intramolecular Stille cross-coupling sequence to afford hexaaryl[3]radialenes **395** on treatment with hexamethylditin and [Pd(PPh$_3$)$_4$] in dioxane at 160 °C. Alternatively, Sonogashira coupling with trimethylsilylacetylene provides the diacetylenic derivative **396**, which undergoes a threefold Glaser coupling to form the cyclic trimer **397**, a 21-membered, completely unsaturated ring system, in the surprisingly high yield of 23 %. For related "expanded" dendralenes, in which ethynyl units are inserted between each 1,1-etheno group in the structure, the reader is referred to previous reviews.[7,253] In a related dendralene-to-radialene conversion, Yoshida's "stretched tetrathiafulvalenes", summarized in Scheme 11, were transformed into their cyclic congeners.[61]



Scheme 83. Application of 2,4-dibromohexaaryl[3]dendralenes in the synthesis of π-rich frameworks by Iyoda and .

9. Naturally Occurring Dendralenes

As far as dendralenes from natural sources are concerned we found references to a surprisingly high number of compounds (Figure 6). The simplest three structures reported to occur naturally are monoterpenes **398**, **399**, and **401**. The terpene alcohol 4-ethenyl-2,5-dimethyl-3,5-hexadien-2-ol (**398**), was isolated as a constituent of the essential oil from leaves of *Liquidambar styraciflua* L.[254] Interestingly, a dendralenic isomer of this compound, 2-methyl-6-methylen-4*E*,7-octadien-2-ol (**399**) was reported in another plant, *Ledum palustre*,[255] but this structure was later corrected to the nondendralenic isomer **400**.[256] The hydrocarbon **401** is one of the 76 identified compounds amongst the 97 separated substances from the essential oil of the Chinese plant Dong quai,[257] and has also been identified in the liquid obtained after tire pyrolysis in a bed reactor.[258] Furthermore, it has been synthesized by Stehling and Wilke in a one-step process.[242] This is, perhaps, one of the few examples of a total synthesis that has not been identified as such by the authors! It also represents the first total synthesis of a dendralene natural product.

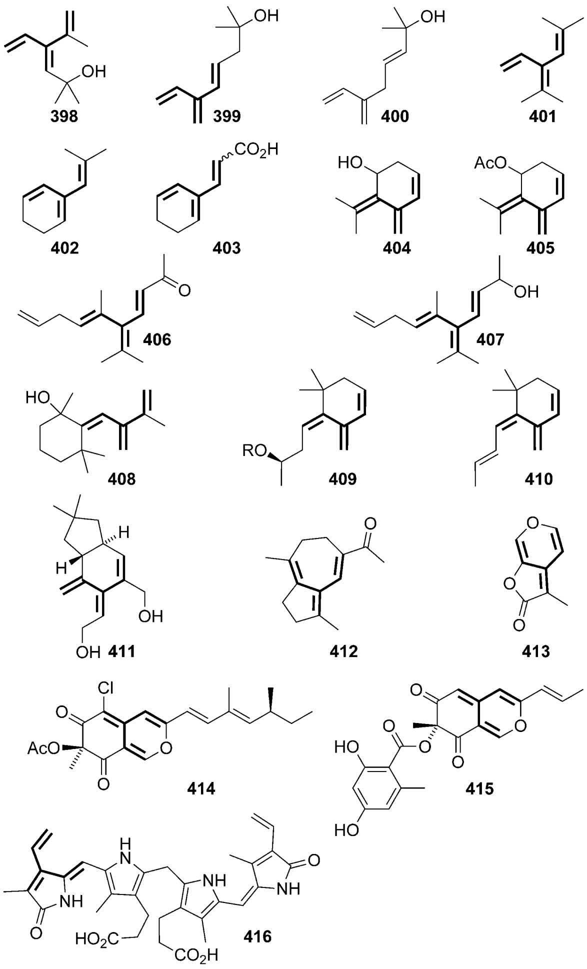


Figure 6. Naturally occurring dendralenes.

The monocyclic [3]dendralene **402** has been mentioned several times in the literature. It occurs in the essential oil in lamina and petiole of *Heracleum dissectum* leaves[259] and is evidently also produced during ripening in "Kensington Pride" mangoes.[260] The closely related acid **403** is a constituent of *Helichrysum* essential oil.[261] Dendralene alcohol **404** occurs in honey,[278] and its acetate **405** is a constituent of leaf and inflorescence oils of *Hyptis suaveolens (L.) Poit.*, a Bangladeshi aromatic plant.[279] The dendralenic methyl ketone **406** and the closely related secondary alcohol **407** have been identified as components of the essential oil extracted from different parts of *Carpesium macrocephalum*[280] and from Panax ginseng and its endophytic fungus, respectively.[281]

1,1-Cyclo[3]dendralene **408** and bicyclo[3]dendralene **412** have been identified in essential oils isolated from *Eucalyptus camaldulensis* growing in Bangladesh.[282] This species is an iconic tree in Australia that is known as the Red River Gum. 1,4-Cyclo[3]dendralene alcohol (**409**, R = H) is a secondary metabolite in grapes,[264] and the acetate (**409**, R = Ac) has been detected by GC/MS analysis in historical varnishes of ancient Italian lutes and a Stradivarius violin.[283] The closely related cross-conjugated tetraene **410** has been isolated from the starfruit (*Averrhoa carambola* L.)[262] and from stinging nettles (*Urtica dioca* L.).[263] It seems likely that during formation of these latter dendralenes, a photoisomerization of the type shown in Scheme 35 has taken place with the appropriate terpene precursors.

How structurally complex naturally occurring dendralenic terpenoids occasionally are is demonstrated by candicansol (**411**), a novel sesquiterpenoid isolated as a fungal metabolite from *Clitocybe candicans*.[284] The butenolide karrikin (**413**) has recently been isolated and characterized as a component of the smoke derived from the combustion of cellulose, and thus can be expected to be produced in all natural fires. Interestingly, the compound has been demonstrated to increase germination of a wide range of plant species from Australia, North America, and South Africa.[265] The original report was followed by several publications describing the total synthesis of the natural product and the preparation of analogues.[266] The first preparation of a structure of this type was reported by Katritzky and co-workers in 1976.[267]

Sclerotionin (**414**)[268] and mitorubrin (**415**)[269] are two examples of a larger family of bicyclo[3]dendralenes containing a "vinylogous" 4-pyrone group. These natural products are termed azaphilones, because of their reactivity with primary amines. Conjugate addition results in the formation of the corresponding "vinylogous" 4-pyridones, a process that is related to the biological activity of these compounds.

We complete this section on dendralene natural products with an alkaloid compound that is representative of several related structures in the class. Bilirubin (**416**)[270] is a 1,3-cyclo[3]dendralene pigment produced through the catabolic breakdown of heme. This endogenous compound is the origin of the yellow color of bruises and jaundice.

Our search did not uncover any natural products containing [4]dendralenes or higher. Only time will tell if such a natural product exists. In light of the enhanced stability of the parent tetraene **21** relative to the triene **11** (Section 6), we would not be surprised if an "even dendralene" natural product was discovered.

10. Summary—Perspectives—Applications

The last 25 years have seen a vast increase in knowledge about cross-conjugated π systems in general, and about [*n*]dendralenes in particular. Clearly, this class of unsaturated hydrocarbons is not "a neglected compound class" any more, as postulated in the heading of the first review.[4] The series of parent hydrocarbons has been prepared up to [8]dendralene on a practical scale, a progress unthinkable only a decade ago. Numerous routes to functionalized dendralenes have been developed, and it can be taken for granted that this area of synthesis will stand in the foreground for years to come. One important reason is the extraordinary preparative usefulness of the diene-transmissive Diels–Alder reactions that can be carried out with these cross-conjugated oligoenes, which have become the hallmark of this class of hydrocarbons.

The [*n*]dendralenes have also remained fascinating compounds from a structural point of view. It is hoped that for the higher dendralenes, detailed structural investigations of the same quality as those described for [3]dendralene (**11**) and [4]dendralene (**21**) will be carried out. With their nonplanar (or possibly even orthogonal) structures, these molecules are inherently chiral. The introduction of substituents into these axially chiral parent structures makes their stereochemical properties significantly more complex, but also offers many new opportunities and challenges in stereoselective synthesis.

Of the many possible reactions of the [*n*]dendralenes, very few have been examined so far. This is particularly true for photochemical processes, electrophilic and radical additions, and transition-metal-promoted additions, to name but a few of the many reactions that can be imagined. Furthermore, applications of dendralenes, for example as monomers in polymerizations and as ligands for metal complexes, are virtually untapped.

As far as applications in polymer chemistry are concerned, reactions of dendralenes with double dienophiles have been explored only tentatively.[243] The family of [*n*]dendralenes, with their multidiene potential, are now available for exploration. Molecules carrying several discrete dendralene groups could also be employed as monomers. Such structures would be expected to lead to novel types of cross-linked and dendritic polymer systems.

The development of new extended π systems involving dendralenes should lead to many applications in materials science. The dendralene motif, embedded in more complex structures, has already been demonstrated to play a central role in photochromic materials.[17,271] Applications in liquid-crystalline materials[272] and in sensitized photopolymerization[273] have also been reported.

In terms of energy research, the first patents on the use of dendralenes as components of dye-sensitized photoelectric converters and dye-sensitized solar cells have recently been published.[274] We are convinced that the studies reported so far are merely the tip of the iceberg.

It also seems likely that more dendralenic natural products will be discovered and that many new and interesting dendralenic "non-natural products" will be prepared. Interesting candidates for designed molecules include hybrid structures of dendralenes and the other four fundamental oligoenes (Figure 1) and allene-containing systems. As for natural products, it is more difficult to make predictions. Nevertheless, we feel that it is only a matter of time before a [4]dendralene-containing natural product is reported.

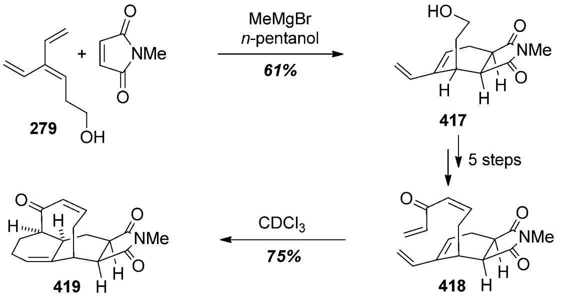
We predict that the next few years will witness a significant increase in publications concerning dendralenes. We make this prediction on the basis of two facts: a) the dendralenes (particularly [3]dendralenes) are no longer exotic species: their stability is well established and many good methods are available for their synthesis; b) the basic DTDA reactivity patterns (again, particularly for [3]dendralenes) are well documented. This Review brings together much information for the first time, and we hope that it will serve as inspiration for future applications.

We finish this Review with a perspective on one area that so far has seen only a modest number of contributions involving dendralenes, namely applications of dendralenes and related systems in the total synthesis of natural products. At a time when total synthesis is experiencing a significant push towards step economy, DTDA sequences can hardly be ignored. We are excited by the enormous potential of the dendralenes in the development of more efficient syntheses, and we anticipate many exciting contributions in this area in the near future.

Single Diels–Alder reactions of [3]dendralenes have been employed in total synthesis. In these reactions, the dendralene reacts as a diene and the third alkene is merely a spectator. Thus, an intramolecular Diels–Alder reaction of a 1,3-cyclo[3]dendralene was employed in the 1974 synthesis of andranginine by Scott and co-workers.[219] Gesson et al.[275] and others[276] have used 1,4-cyclo[3]dendralenes since 1980 for the construction of anthracyclines and anthracyclinones. As elegant as these approaches are, the true potential of a dendralene is only realized when it is used in a sequence of two (or more) cycloaddition reactions.

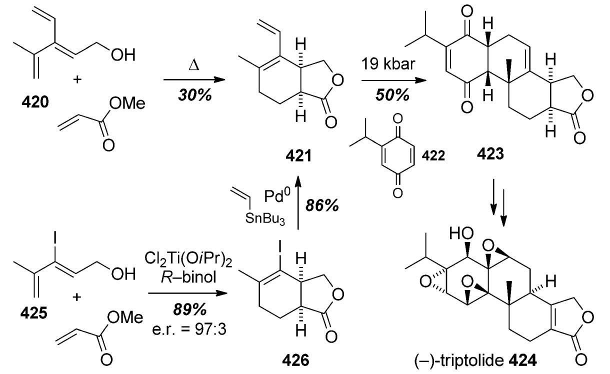
At the time of writing, only three publications describe synthetic approaches to natural products that employ two Diels–Alder reactions linked in a DTDA manner, and all have appeared in the last five years. None of these sequences work in a true domino sense. In fact, in some cases the two cycloadditions are separated by several synthetic steps, in which the requisite functionality for the second cycloaddition is built into the adduct from the first.

Two independent but related studies describe synthetic approaches to the natural product vinigrol. In 2007, Fallis and co-workers described a synthesis of the carbocyclic core of the natural product (Scheme 84).[205] Thus, the 3-(2-hydroxyethyl)[3]dendralene (**279**) underwent a mono-cycloaddition with NMM under conditions involving a temporary Lewis acid tether to yield *endo* adduct **417**. After elaboration into precursor **418**, which carries the bridging chain and appended dienophile, an intramolecular Diels–Alder reaction gave rise to tetracycle **419**, which contains the vinigrol carbocyclic core. The successful total synthesis of vinigrol by the Baran research group[277] also involved two separate Diels–Alder reactions and employed a strategy based upon a 1,3-cyclo[3]-dendralene.



Scheme 84. DTDA approach to the C_4-bridged tetrahydronaphthalene framework of vinigrol according to Fallis and co-workers.

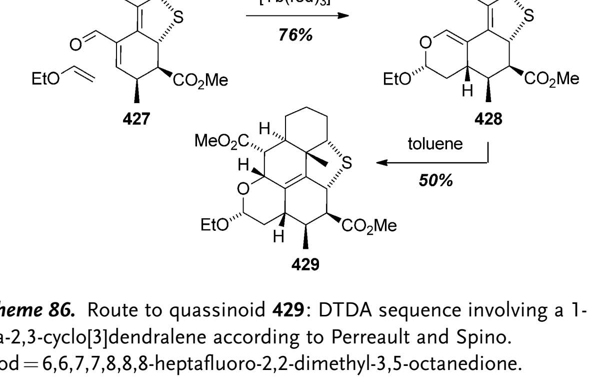
A recent approach to the natural product triptolide[88] involved a DTDA sequence on a disubstituted [3]dendralene **420** (Scheme 85). The sequence allows the very rapid assembly of the core framework of the natural product **424** through Diels–Alder reactions first with methyl acrylate to furnish bicycle **421**, then with quinone **422** to give tetracycle **423**. The modest yields for the first cycloaddition was addressed through the development of an alternative approach, in which the dendralene was replaced by 2-iodo-1,3-butadiene **425**. This gave a higher yielding (and enantioselective) initial cycloaddition to afford **426**. A subsequent cross-coupling with vinyltributylstannane then gave the semicyclic diene **421**.



Scheme 85. Key steps in the formal total synthesis of triptolide by Sherburn and co-workers.

The Spino research group has published several reports on a DTDA strategy involving an intermolecular hetero-Diels–Alder reaction followed by an intramolecular Diels–Alder reaction to synthesize the quassinoid skeleton.[197,198] They recently reported the synthesis of an advanced intermediate to the quassinoids **429** (Scheme 86).[197] Thus, a hetero-Diels–Alder reaction between 1-oxa-2,3-cyclo[3]dendralene **427** and ethyl vinyl ether gives adduct **428**, which undergoes an intramolecular Diels–Alder reaction to give pentacycle **429** as a single isomer.

We end our Review with this approach to quassinoids for three reasons. Firstly, it involves the same DTDA sequence that we have seen throughout this Review (in fact, it predates most of the other DTDA studies with 2,3-cyclo[3]dendra-



Scheme 86. Route to quassinoid **429**: DTDA sequence involving a 1-oxa-2,3-cyclo[3]dendralene according to Perreault and Spino. Hfod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione.

lenes). Secondly, it is a particularly beautiful application of the DTDA theme in total synthesis, with six new stereocenters and three of the four rings of the natural product framework generated. Finally, it demonstrates that cross-conjugated systems and their DTDA reactions are by no means limited to the all-carbon systems that have been the focus of the this Review.

We thank the co-workers from our research groups for their outstanding contributions to the development of the chemistry of dendralenes. We also thank Dr. Diane Robinson for her assistance in preparing this manuscript. M.S.S. warmly thanks Professor Mike Paddon-Row for his insightful and creative contributions to their research collaboration in the field of dendralenes, and gratefully acknowledges financial support from the Australian Research Council.

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