Allenes in Diels-Alder Cycloadditions

by

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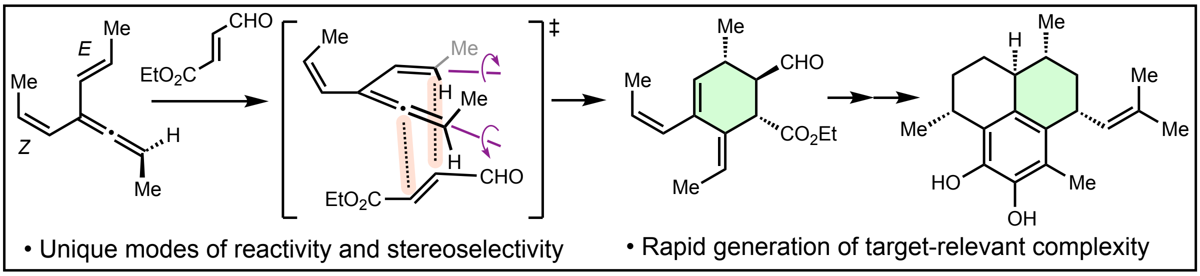
Abstract: For a long time, allenes – and cumulenic systems in general – played a relatively minor role in Diels-Alder cycloadditions. This situation has changed, since allenes are more readily available and as their unique stereochemical features in [4+2]cycloadditions are more widely recognized. This review presents a comprehensive overview of allenes in Diels-Alder processes using selected examples. Allenes as components in dienes and dienophiles are covered, inter- and intramolecular Diels-Alder cycloadditions are discussed, and stereochemical features of the addition process are described. Areas of emerging importance are also covered, including allenic components in dehydro-Diels-Alder

processes, and dendralenic allenes in Diels-Alder sequences for the rapid generation of target-relevant molecular complexity. Preparatively useful methods for allenic precursor synthesis are also discussed.

Graphical abstract:



• Unique modes of reactivity and stereoselectivity

• Rapid generation of target-relevant complexity

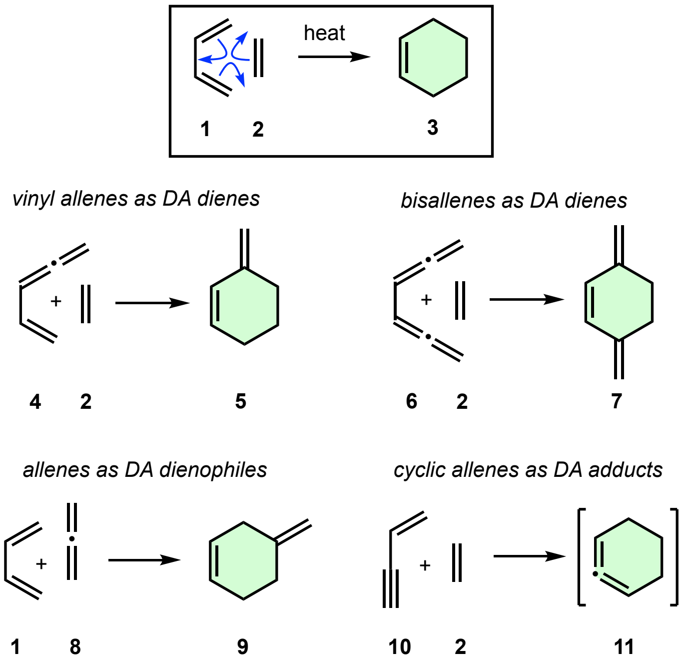
Contents

1. Introduction

The Diels-Alder addition between a conjugated diene (**1**) and a dienophile (**2**)[1] is one of the most important reactions in organic chemistry.[2] It allows the preparation of a cyclohexene (**3**) in a preparatively simple, one-step, stereoselective, and often high-yielding process; no wonder that its discovery and application has been rewarded by a Nobel Prize (to Diels and Alder in 1950[3]). In its standard form it requires the availability of a *cisoid*-conformation electron-rich diene, and an electron depleted dienophile (**Scheme 1**). An oppositely polarized arrangement with an electron poor diene and an electron-rich dienophile is, however, also well known (Diels-Alder additions with inverse electron demand). When the two starting components of a Diels-Alder addition are part of one and the same molecule, i.e. are connected by a tether (of any complexity), one speaks of an intramolecular Diels-Alder addition.[4]

Scheme 1 summarizes the four main ways in which allenes can be involved in [4+2]cycloaddition reactions. If one of the two C=C bonds of the prototypical Diels-Alder (DA) diene is replaced by an allene, vinylallene **4** is the new reactant. In this case, the cycloadduct **5** carries an exocyclic C=C bond in conjugation with the usual cyclohexene one. With bisallene **6** as the reactant DA diene, conjugated triene **7** is the cycloadduct. If allene **8** is the dienophile, then non-conjugated diene **9** is produced.

Allenes can also be generated in [4+2]cycloaddition reactions, in so-called dehydro-Diels-Alder processes.[5] Thus, the reaction between vinylacetylene **10** and ethylene **2** would generate cyclohexa-1,2-diene **11**, a reactive cyclic allene.



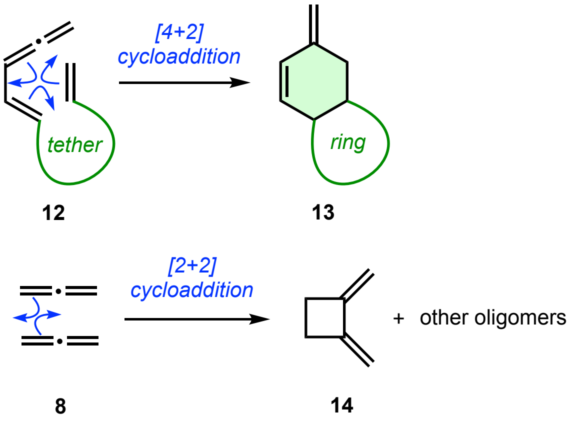
Scheme 1: The prototypical [4+2]cycloaddition (in the box) and the various ways that allenes can participate in Diels-Alder reactions.

This review is structured primarily around these four subtypes of allenic Diels-Alder processes. In the case of Diels-Alder reactions involving vinylallenes and bisallenes, pertinent information on the structure and preparation of the allene-containing precursors is also presented.

One profound consequence of allenic reactants in Diels-Alder processes relates to stereochemistry. Since 1,3-disubstituted allenes are chiral, their inclusion as dienes and dienophiles is accompanied by the transformation of axially chiral precursors into cycloadducts with stereocenters.[6] Cycloadditions of substituted allenes also feature unique aspects of diastereoselection in cycloadduct alkene formation. Since the usual stereochemical features of [4+2]cycloadditions–*endo/exo*-selectivity and π-facial selectivity–also operate with allenic reactants, their cycloadditions are uniquely complex.

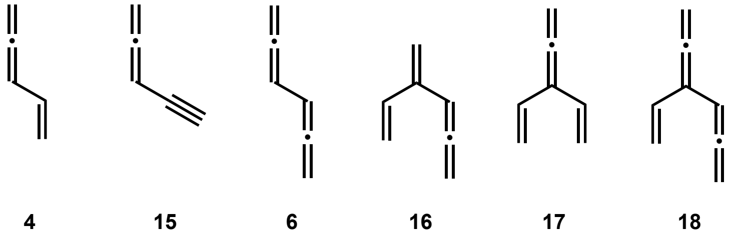
Intramolecularization of the allenic [4+2]cycloaddition, by the connection of the diene to the dienophile through a tether as in **12** (**Scheme 2**), generates a product with two new rings, e.g. **13**. Performing the Diels-Alder reaction intramolecularly *a priori* has no consequences: as long as the tether has the requisite conformational flexibility such that the reacting units may come together. If this factor holds then the intramolecular Diels-Alder (IMDA) process is entropically favored. Many IMDA processes involving allene-containing precursors have been reported and a representative selection is provided in **Section 5**.

An alternative [2+2]cycloaddition mode of cumulenic systems leads to the formation of four-membered rings. 1,2-Bismethylenecyclobutane (**14**) as the primary product from the parent allene **8**.[7] In a few situations, the [2+2]cycloaddition pathway is preferred over the [4+2]cycloaddition but this is not a common problem with allenic precursors.



Scheme 2: Allenic dienes becoming partners in Diels-Alder reactions.

Starting from vinylallene **4** and the hybrid character of its structure (i.e. both a cumulated and a conjugated diene) many other π-systems can be designed, prepared and studied. And many of these compounds are particularly interesting from the perspective of their reactivity as Diels-Alder dienes and in the generation of cyclic allenes in [4+2]cycloadditions. A small selection is collected in **Scheme 3**.



Scheme 3: Conjugated-allenic hybrid π-systems related to vinylallene.

The conjugated allenyne **15** is another (cf. **10**, **Scheme 1**) "dehydro-diene" which offers itself to the increasingly studied dehydro variants of the Diels-Alder process (see **Section 5**); the aforementioned bisallene **6** formally consists of an inner buta-1,3-diene, and two outer allene systems, whereas in 2-(buta-1,3-dienyl)allene **16**, two buta-1,3-diene and one allene subunits can be recognized. 1,1-Divinylallene (**17**) is an isomer of **16** and also contains two buta-1,3-diene moieties as well as an allenic part. As described in **Section 2.3**, this compound reacts as a triple Diels-Alder diene, undergoing a sequence of three [4+2]cycloadditions. Finally, structure **18** shows a hybrid of two buta-1,3-diene and also two allene building blocks. It is obvious that by incorporations of further unsaturated units – double and triple bonds, cumulenic systems, phenyl substituents and other aryl groups – countless structures can be generated, many of them unknown so far.[8]

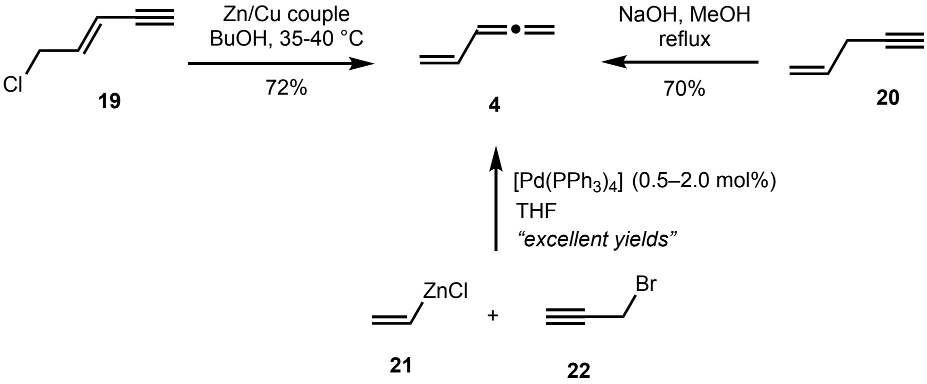
In closing this introductory section, it should be mentioned that the transformations discussed here are the binary prototypes (compounds containing only C and H) of countless cumulenic hetero-organic systems such as ketenes or ketenimines. As far as hetero-organic dienophiles are concerned, azo-compounds,[9,10] nitroso derivatives,[11] aldehydes[12,13] and imines[14] should be mentioned, which have been used to prepare numerous heterocyclic compounds by Diels-Alder routes involving conjugated allenic systems.

Entry into the allene cycloaddition field discussed here is comparatively easy, since a comprehensive review literature exists; it extends from classical monographs[15] to more recent summaries of the literature.[16,17] Our review differs from these earlier contributions in that we attempt to provide an overview of all aspects of allene cycloadditions in one (at the time of publication) up-to-date article.

2. Allenic Dienes

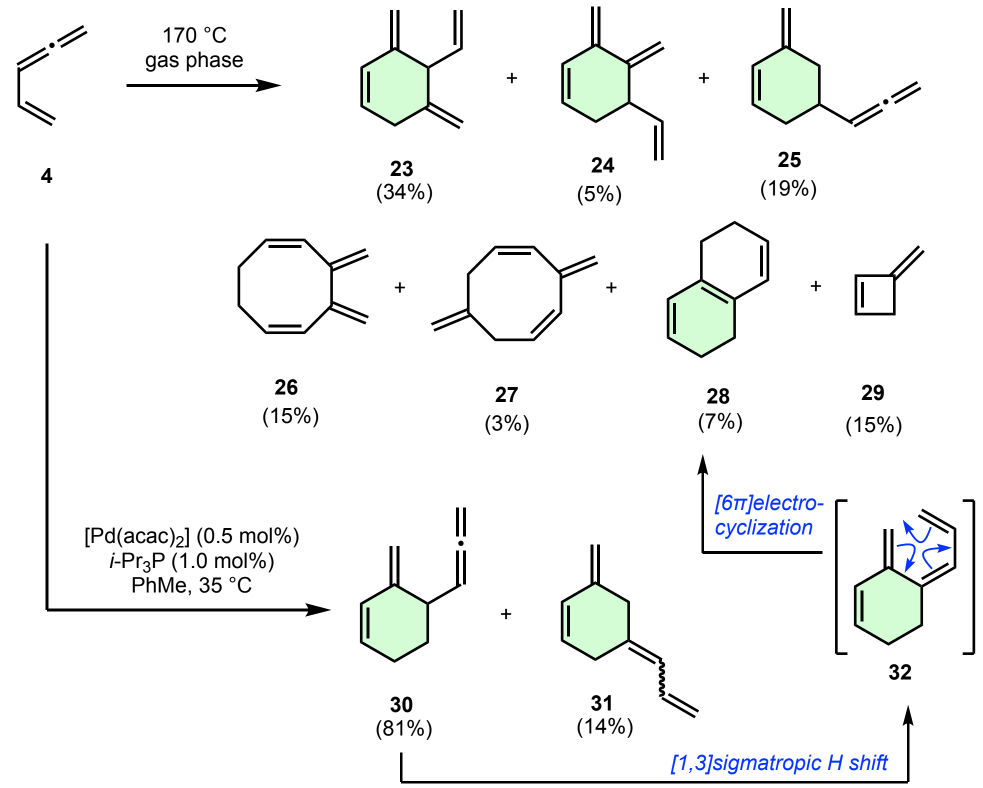
2.1 Vinylallenes

The simplest allenic hydrocarbon which can participate in an intermolecular Diels-Alder reaction as a 4*π* component is vinylallene (**4**). The compound was initially prepared by Jones and co-workers[18] by treatment of unsaturated chlorides such as *E*-5-chloro-pent-3-en-1-yne (**19**, **Scheme 4**) with Zn/Cu-couple in butanol. Later authors accessed this simple hydrocarbon by sodium hydroxide induced isomerization of pent-1-en-4-yne (**20**)[19] or Pd(0)-catalyzed Negishi cross-coupling of vinylzinc chloride (**21**) with propargyl bromide (**22**).[20] Vinylallene can be purified by distillation and is available in gram quantities.



Scheme 4: The synthesis of penta-1,2,4-triene (vinylallene).

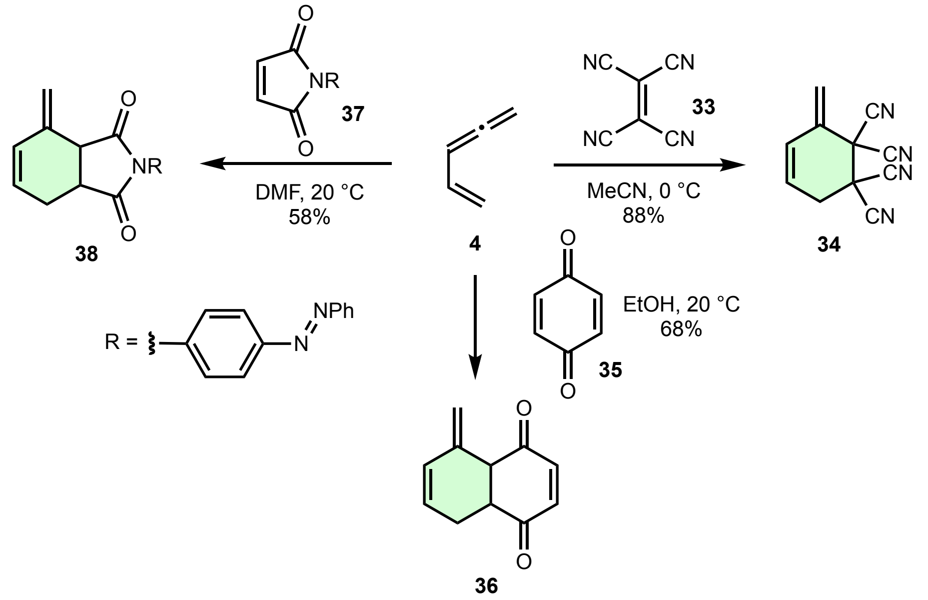
On heating the pure hydrocarbon **4** at 170 °C in the gas phase, a complex mixture of dimeric products **23**-**28** is produced besides small amounts of the 4*π*-electrocyclization product methylenecyclobutene (**29**) (**Scheme 5**). Formally, dimers **23**-**25** are [4+2]cycloaddition products, for whose formation one molecule of **4** serves as a diene component and the second one serves as the dienophile, participating either with its internal allenic C=C bond (orientational regioisomers, **23** and **24**) or olefinic part (one orientational isomer, **25**). Dimers **26** and **27** are formal [4+4]cycloadducts.[21]



Scheme 5: The divergent dimerization behavior of vinylallene under pyrolysis and Pd(0)-catalyzed conditions.

The Pd(0)-catalyzed dimerization of **4** occurs at much lower temperature, and leads to the formal Diels-Alder adduct **30** as the main product of the reaction (81%), which is the unseen orientational regioisomer involving the vinyl group as dienophile from the pyrolysis reaction. A mixture of geometrical isomers of adducts from reaction at the terminal allenic C=C bond dienophile **31** is also seen. Treatment of the major product **30** with base led to bicycle **28** by way of through- and cross-conjugated tetraene **32**.[22] Thus, we have a potential origin for **28** from the pyrolysis experiment.

Classical Diels-Alder cycloadditions of **4** with typical dienophiles have been reported by Jones and coworkers in pioneering studies that are summarized in **Scheme 6**.[18] Thus, the addition of tetracyanoethylene **33** to **4** provided the methylenecyclohexene adduct **34** in excellent yield at ambient temperature. With *para*-benzoquinone (**35**), adduct **36** was obtained (68%), which could be converted to 5-methyl-1,4-naphthoquinone by treatment with methanolic sodium hydroxide, then acetic acid and potassium dichromate. Diels-Alder addition of **4** and *p*-phenylazomaleimide (**37**) yielded the adduct **38** in 58% yield.

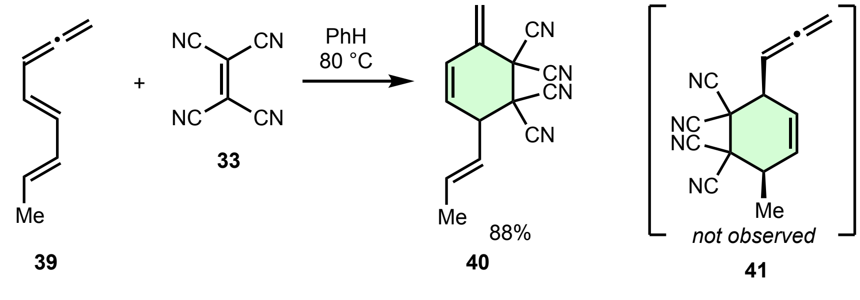


Scheme 6: Diels-Alder addition of vinylallene with typical dienophiles. The relative stereochemistry of products **34** and **36** was not given[18] but can be safely assumed to be a *cis*-ring junction geometry.

To investigate additional aspects of stereoselectivity of the Diels-Alder addition of conjugated vinylallenes with various carbon-centered dienophiles, substituted vinylallenes had to be prepared and studied.

Before discussing the corresponding [4+2]cycloadditions, we have to focus on the conformation of vinylallene (**4**). This simplest allene-containing buta-1,3-diene prefers the *s-trans* conformation, which possesses C_s molecular symmetry. This has been established by numerous physical methods from gas phase electron diffraction,[23] Raman and IR spectroscopy,[24] photoelectron spectroscopy[25] and NMR spectroscopy.[26] These experimental results are backed up by theoretical calculations, which confirm a 2.8 kcal/mol preference for the s-*trans* conformer over the s-*cis* conformer.[27]

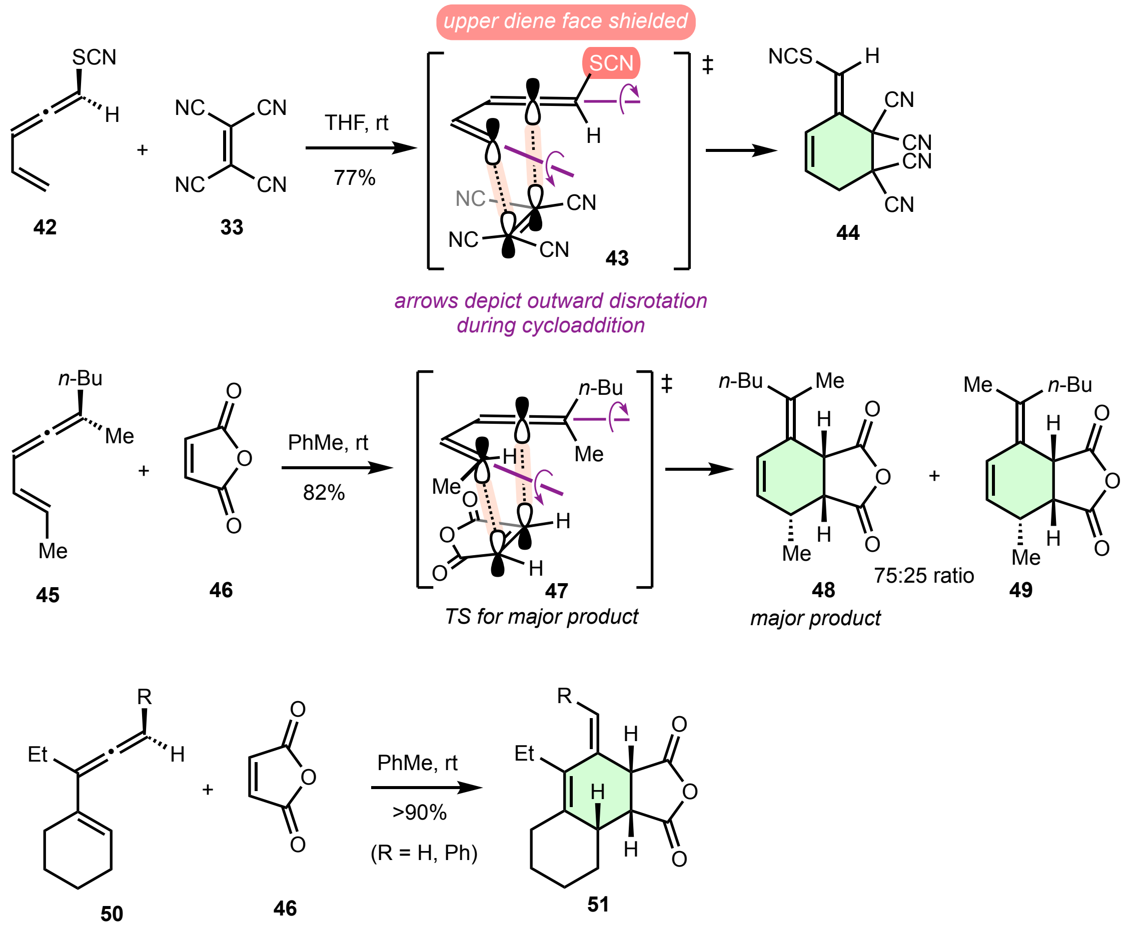
Does the presence of an allene in a buta-1,3-diene lead to a more or less reactive Diels-Alder diene? **Scheme 7** depicts the structure of (*E,E*)-octa-1,2,4,6-tetraene **39**, which contains both a buta-1,3-dienyl subunit and a vinylallenyl subunit and hence possesses the possibility to react in two different Diels-Alder modes. As it turns out, in the reaction with TCNE **33**, only its vinylallene part undergoes the [4+2]cycloaddition.[28] This outcome is consistent with calculations of the Diels-Alder reactions of ethylene (as dienophile) with the series of dienes buta-1,3-diene **1**, vinylallene **4** and bisallene **6**, which indicate that activation barriers are progressively lower and reaction exothermicities are higher as allene content increases.[29] Similar results are seen in computational studies on the [4π]electrocyclizations of **1**, **4** and **6**.[30] Evidently, a vinylallene is a more reactive Diels-Alder diene than a buta-1,3-diene.



Scheme 7: Addition of TCNE **33** to compound **39**, a structure containing both a buta-1,3-diene and a vinylallene.

Considering the steric and electronic influence of substituents on the s-*cis*/s-*trans* conformational equilibrium of vinylallene **4**, we would expect similar effects as observed for the classical 1,3-dienes used in the Diels-Alder process: bulky substituents, especially where more than one is present, would favor the *transoid*-conformation, slowing down the addition process or preventing it altogether. "Freezing" a conformation in a *trans*-arrangement such as in 3-methylenecyclohexene would cause the same result, whereas *cis*-fixed structures as in 1,2-bismethylenecyclopentane would ease the cycloaddition process, so long as the C1---C4 interatomic distance is favorable for orbital overlap with the dienophile.[31]

There is, however, one decisive difference between a simple buta-1,3-diene and a vinylallene: the 90° twist caused by the *sp*-hybridized carbon atom in the allenic diene. Because of this, with vinylallenes carrying a terminal allene substituent, the two possible reacting sides of the buta-1,3-diene are different, with one π-diastereoface being more and the other less sterically hindered. This is illustrated in **Scheme 8** by the vinylallene derivative **42** (shown in its *cisoid*-conformation), which carries a substituent (SCN) at its allene terminus. The dienophile **33** approaches the diene **42** from the sterically less shielded side, through transition state (TS) **43**, yielding the *E*-configured adduct **44** in good yield.[32]

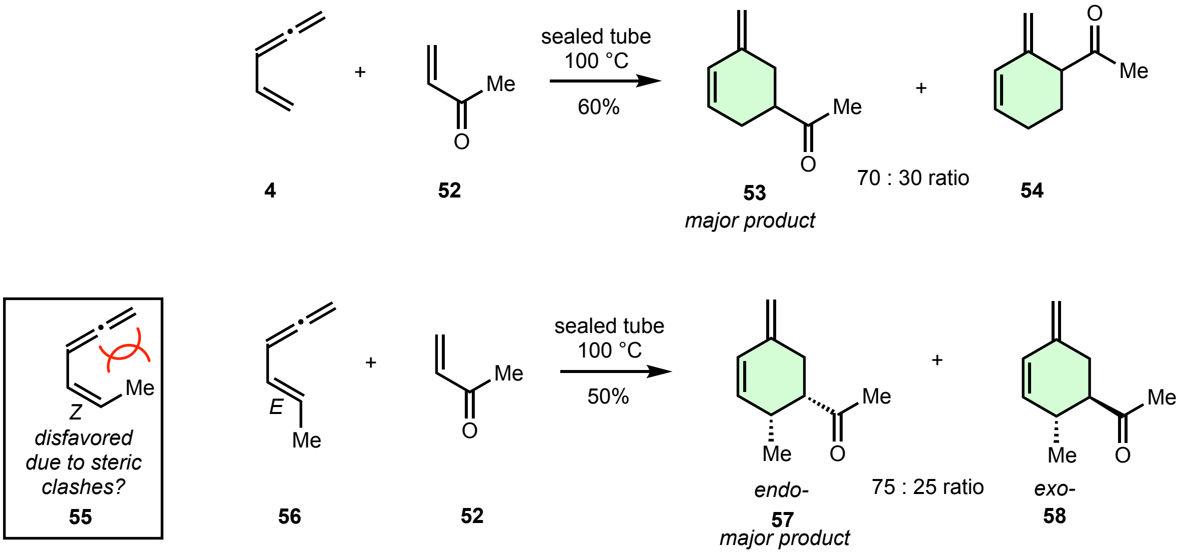


Scheme 8: Diels-Alder additions of dienophiles to vinylallenes with substituents at the allene terminus.

The other examples in **Scheme 8**, involving maleic anhydride (**46**), introduce the additional complexity of *endo/exo*-stereoselectivity. Further to dienophile approach to the less sterically shielded π-

diastereoface of the substituted vinylallene, a strong preference for *endo*-mode approach of the dienophile **46** is seen in each case. Thus, reaction of **45** with **46** yields predominantly *endo*-adduct **48** (through preferred TS **47**) over *exo*-adduct **49**,[33] and reaction of **50** (R = H or Ph) with **46** gives **51** for similar reasons.[13] The preference for *endo*-mode cycloadditions has been ascribed to stabilizing secondary orbital interactions (SOIs) in the transition state.[34]

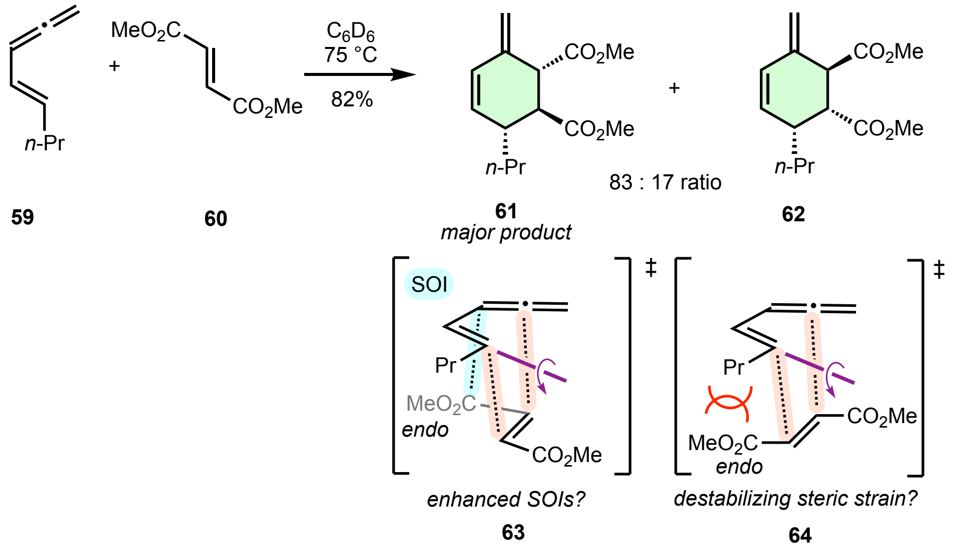
The regioselectivity of [4+2]cycloadditions to vinylallenes was reported in classical studies by Bertrand and co-workers.[35] As shown in **Scheme 9**, methyl vinyl ketone (**52**, MVK) cycloadds to vinylallene **4** to furnish the two regioisomers **53** and **54**, the former being the main product (70:30 ratio). The formation of major product **53** is consistent with advanced TS bond formation between the β-carbon of the enone and to the *sp* carbon of the vinylallene. The generation of the major product can be understood by preferential bond formation between the more electron-deficient carbon of the dienophile and the more electron-rich carbon of the diene. Lewis acid catalysis would, most likely, lead to significantly enhanced selectivity for regioisomer **53**.



Scheme 9: Regio- and stereochemical aspects of addition of MVK **52** to substituted vinylallenes.

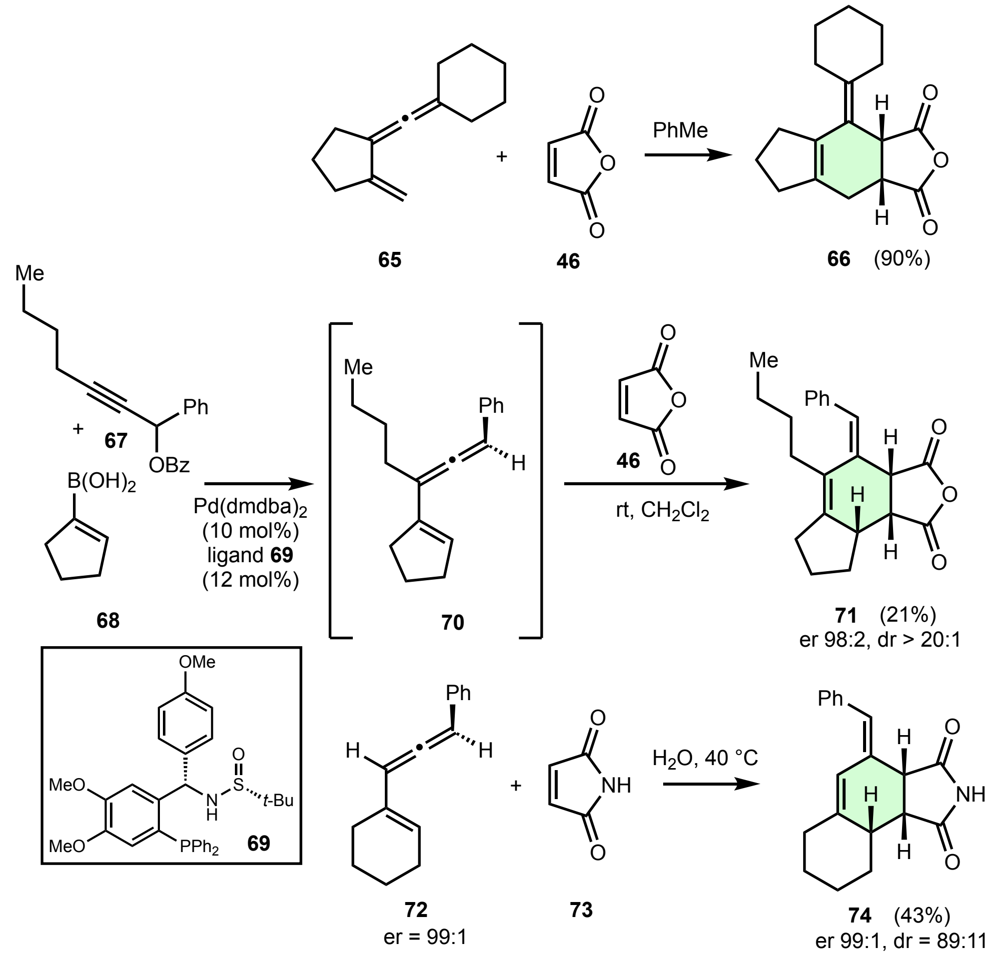
The presence of a methyl substituent at the vinyl terminus of vinyl allene enhances the orientational regioselectivity of the reaction (compare the regioselectivities of the two reactions in **Scheme 9**). The preferential formation of *endo*-adduct **57** over its *exo*-stereoisomer **58** from the disubstituted vinylallene **56** and MVK **52** is due to SOIs in the TS leading to the former. The *endo*-preference of the dienophile MVK **52** is generally not as strong as that for MA **46** (cf. **Scheme 8**). The *Z*-diastereomer **55** did not add under the reaction conditions, presumably because the *cisoid* conformation of this particular vinylallene is disfavored.[36]

That the reactions between vinylallenes and appropriate dienophiles display the typical characteristics of a Diels-Alder process (i.e. concerted, suprafacial addition with respect to both diene and dienophile) is also emphasized by preservation of dienophile geometry in the reaction between substituted vinylallene **59** and dimethyl fumarate (**60**), leading to a mixture of adducts **61** and **62** in good yield (**Scheme 10**).[37] The interesting preference for diastereomer **61** could be the result of a shorter developing bond at the *sp* carbon in TS **63**, which might give rise to stronger stabilizing SOI interactions with the *endo*-oriented –CO_2Me group. Alternatively, destabilizing steric clashes in TS **64** between the *endo*-oriented –CO_2Me group and the proximate *n*-Pr substituent on the vinylallene might disfavor the formation of adduct **62**.



Scheme 10: Maintenance of dienophile stereochemistry in the cycloaddition of a substituted vinylallene, and an interesting *endo/exo* preference with a fumarate dienophile.

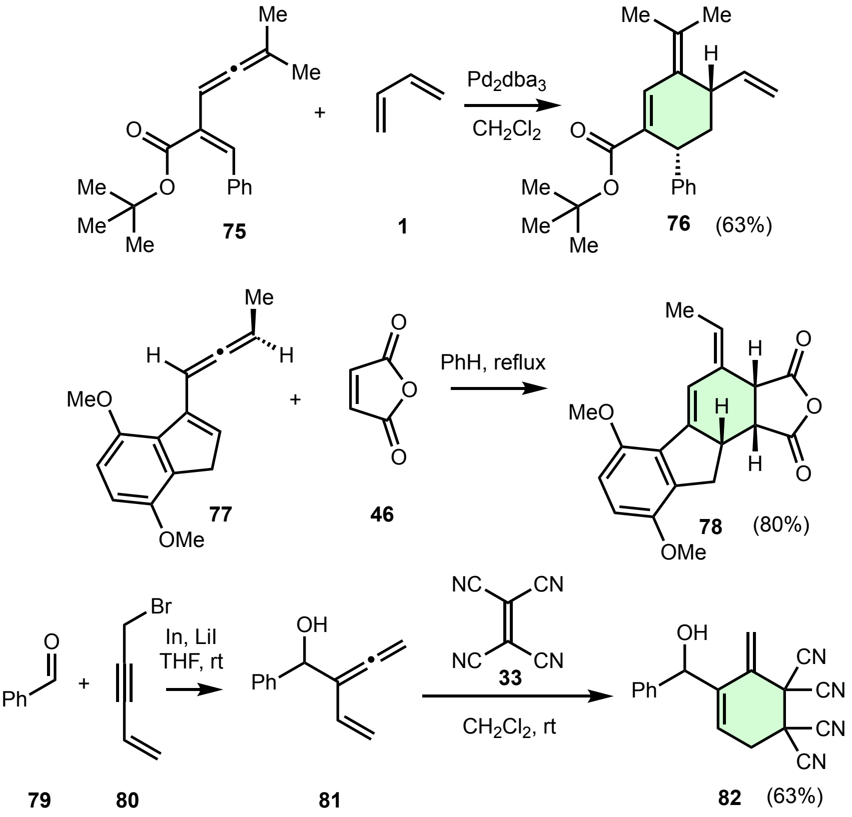
Vinylallenes are versatile Diels-Alder dienes, permitting polycycle construction in short order. **Schemes 11** and **12** summarize a small selection of the vast literature describing precursors with pre-existing rings.



Scheme 11: A selection of intermolecular cycloaddition reactions of vinylallenes: hydrocarbon systems (dmdba = 3,5,3′,5′-dimethoxydibenzylideneacetone).

Pure hydrocarbon systems including polyalkylated, alkenyl and arylated vinylallenes,[38] and vinylallenes in a fixed cisoid orientation (**65**), provide the expected Diels-Alder adducts (such as **66**) with common dienophiles such as MA **46**, in usually good to excellent yields.[39] The retention of enantiopurity during the conversion of axially chiral vinylallenes into cycloadducts with stereocenters is also shown in **Scheme 11**. Highly enantiomerically enriched precursors **70** and **72** were subjected to Diels-Alder addition with dienophiles **46** and **73**, respectively. In the former case, the adduct **71** was obtained with high stereoselectivity (er 98:2, dr > 20:1) from relatively simple precursors **67** and **68**.[40] An enantioselective Pd(0) catalyzed cross-coupling process, brought about by an in situ generated catalyst deploying chiral ligand **69**, generated the vinylallene **70**, which underwent cycloaddition with added dienophile **46** in a one flask operation. In the latter case, vinylallene **72** was isolated then subjected to an “on water” Diels-Alder reaction with maleimide **73** to give adduct **74** with no loss in enantiopurity.[41]

Turning to functionalized vinylallene components next, the selection summarized in **Scheme 12** is typical. The formal Diels-Alder transformation of substituted vinylallene **75** into adduct **76** demonstrates that even hydrocarbons like buta-1,3-diene (**1**) can be brought about to serve as a dienophile under Pd(0)-catalysis (c.f. **Scheme 5**).[42]

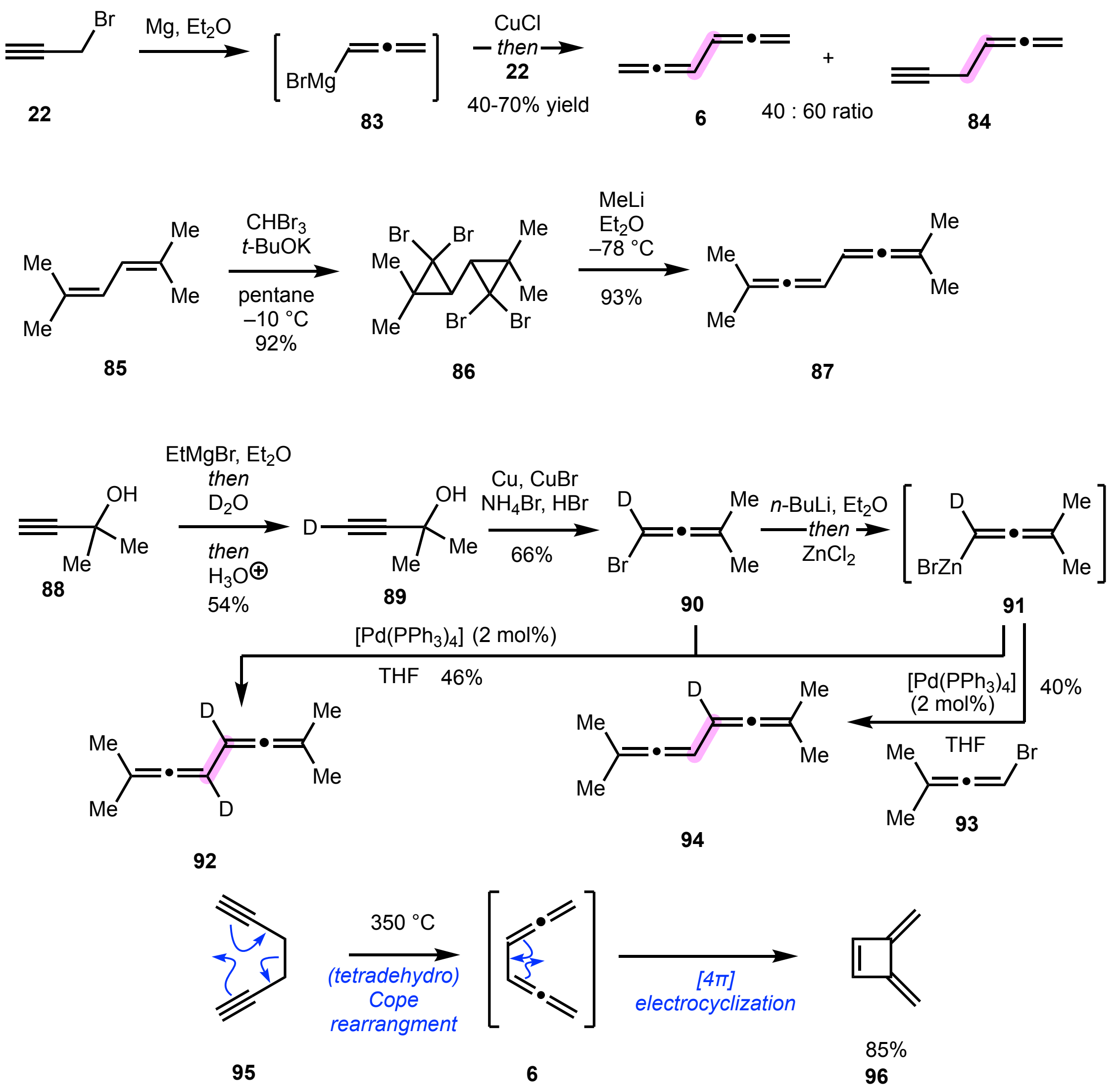


Scheme 12: A selection of intermolecular cycloaddition reactions of vinylallenes: functionalized systems.

The example **77** + **46** → **78**[43] demonstrates that polycyclic ring systems related to terpenoid natural products can be rapidly constructed. The last example in **Scheme 12** depicts firstly, an operationally simple preparation of vinylallene **81** from Barbier-type addition of an organoindium species derived from bromide **80** to benzaldehyde **79**. Next, addition of the dienophile TCNE **33** gives Diels-Alder adduct **82**.[44]

2.2 Bisallenes

For the preparation of the parent compound of the conjugated acyclic bisallenes, hexa-1,2,4,5-tetraene (**6**, biallenyl),[45] propargyl bromide (**22**) was first converted into its Grignard reagent **83**, which has an allenic structure (**Scheme 13**). Subsequently CuCl is added, which very likely generates an organocuprate intermediate, which is then coupled with a second equivalent of **22** to yield the desired **6** and its propargylic isomer, hexa-1,2-dien-5-yne (**84**, propargylallene).



Scheme 13: The preparation of hexa-1,2,4,5-tetraene **6** and some simple derivatives.

The two C_6H_6-isomers **6** and **84** are produced in *ca*. 40:60 ratio and the total yield varies between 40-70% depending largely on the work-up conditions.[46] Separation of the two hydrocarbons by distillation suffers from their instability and similar physical properties. Analytically pure isomers **6** and **84** have been obtained by preparative gas chromatography as well as selective removal of **6** by Diels-Alder additions with dienophiles (see below). Solutions of **6**/**84** in ether containing up to 50 g of the former can be readily prepared.[46]

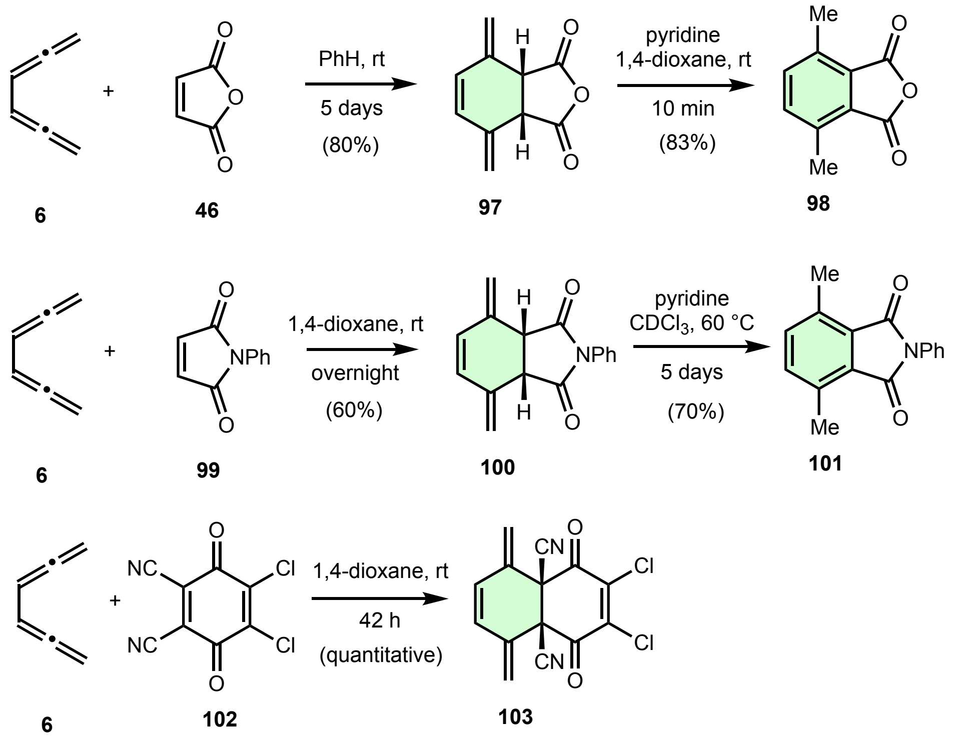
One of the most general routes to (alkylated) bisallenes consists of the formal insertion of carbon into the C=C double bonds of a conjugated diene. This is illustrated by the conversion of the tetramethyl derivative **85** into its bisallenic counterpart **87** (**Scheme 13**).[47] In the first step, the starting diene **85** is dibromocyclopropanated to the tetrabromobicyclopropyl derivative **86**. On treatment with an alkyllithium reagent, each dibromocyclopropane is dehalogenated to generate a carbene, which undergoes an electrocyclic ring opening to the allene (Doering-Moore-Skattebøl route[48]).

Another general protocol to conjugated bisallenes is reminiscent of the route to conjugated vinylallenes described above in **Scheme 4**; it will be illustrated here for the synthesis of deuterated derivatives of hydrocarbon **87** (**Scheme 13**).[49] In its first step, the bromoallene building block **90** was prepared from substituted propargyl alcohol **88** *via* the deuterio-derivative **89** by standard methods of acetylene/allene chemistry. The organozinc reagent **91** was subsequently prepared by first treating **90** with *n*-butyl lithium in ether to form the organolithium species then transmetallating with $ZnCl_2$. Negishi coupling in the presence of $[Pd(PPh_3)_4]$ with either **90** or **93** finally furnished the deuterio derivatives **92** and **94**.

Among the many other routes to conjugated bisallenes (which are often represented in the literature through only one or two examples), noteworthy methods include those in which all the required atoms of the target molecule are already present in the starting material. A case in point is the thermal [3,3]sigmatropic rearrangement of hexa-1,5-diyne **95** to the bisallene **6**. While some highly substituted examples have preparative value for bisallene synthesis,[50] less substituted molecules – such as the parent system **6** – undergo facile [4*π*]electrocyclic ring closure to 3,4-dimethylenecyclobutene **96**.[45,51] Since the preparation of numerous substituted and/or functionalized bisallenes was reviewed relatively recently (in 2012)[16] we stop our summary of preparative methods providing these compounds here.

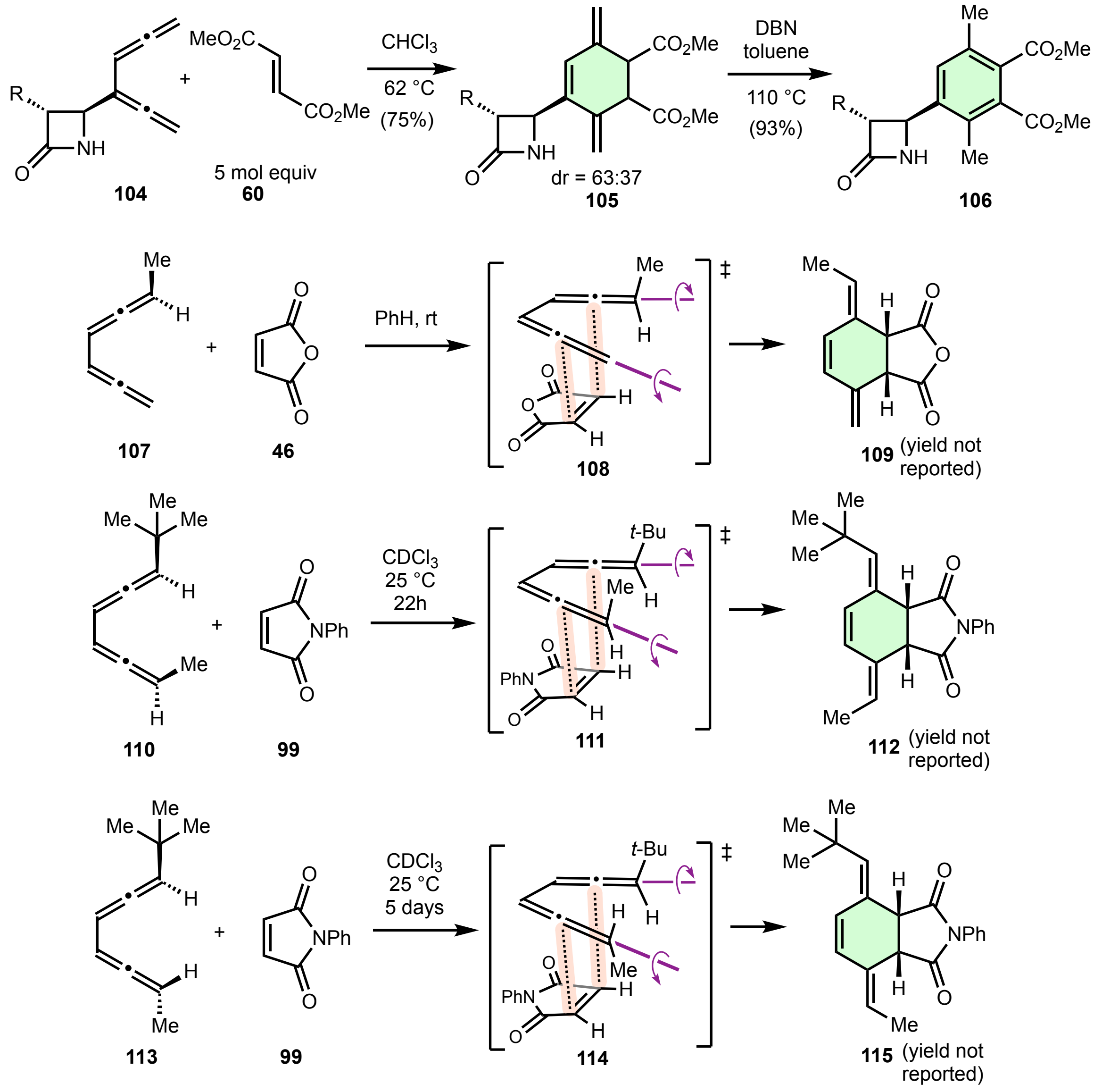
From a structural viewpoint, the most thoroughly investigated conjugated bisallene is the parent compound **6**. Not only has its vibrational spectrum been measured and interpreted,[52] but its most stable conformation in the gas phase has been determined by electron diffraction (GED).[53] Both of these methods support the C_{2h}-symmetry of **6**, i.e. a *transoid* conformation as the most stable conformation. This is supported by NMR measurements in a nematic solvent at room temperature[54] and its photoelectron spectrum (PES).[55] Although no X-ray analysis of **6** has been reported (the compound is a liquid at room temperature), X-ray structural analyses of about 4 dozen solid derivatives of **6** have been reported in the Cambridge Crystallographic Database.[16]

Turning to Diels-Alder cycloadditions now, while we have been unable to locate a publication describing the experimental or computed conformational dynamics of the molecule, it is clear that **6** has no difficulties acquiring the *cisoid* conformation required for the reaction to take place. As mentioned earlier, calculations point to a faster and more thermodynamically favorable Diels-Alder reaction with **6** as a diene than with vinylallene **4**.[29] Addition of MA **46** to **6** affords the expected Diels-Alder adduct **97** in good yield, which can be aromatized to the dimethylphthalic anhydride **98** in good yield (83 %) by treatment with a weak base such as pyridine in dioxane (**Scheme 14**).[9]



Scheme 14: Diels-Alder additions to hexa-1,2,4,5-tetraene **6**.

Likewise, the addition of *N*-phenylmaleimide (**99**, NPM) provides **100** (60%) which can be isomerized to **101**. When the dienophile lacks hydrogen atoms, as in **102** (DDQ), the addition process stops after the primary process (quantitative formation of **103**). Many additions of substituted bisallenes have been reported and **Scheme 15** shows a small but representative selection.



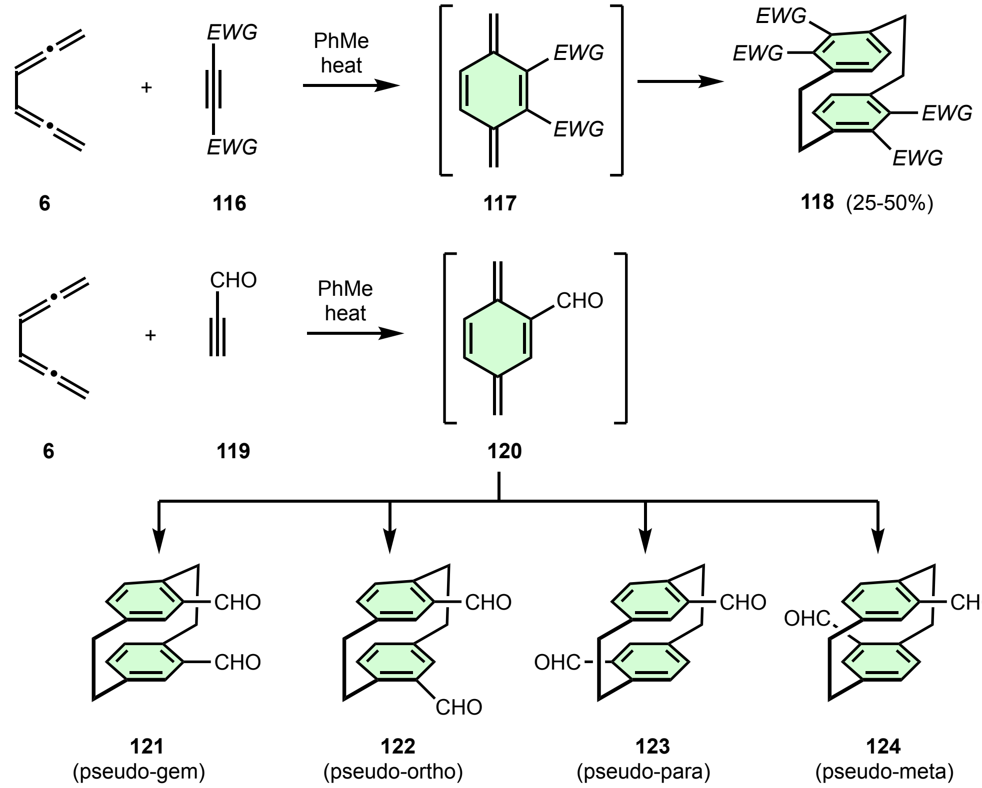
Scheme 15: Diels-Alder additions to substituted bisallenes.

Azetidinones (ß-lactams) **104** were reacted with different double bond dienophiles, of which dimethyl fumarate **60** is representative, to provide the [4+2]cycloadducts such as **105**, which subsequently were aromatized to **106** in a similar manner to the previous Scheme.[56]

To investigate aspects of the stereochemistry of the addition process, both hepta-1,2,4,5-tetraene (**107**)[9] and the two diastereomeric bisallenes **110** and **113** were trapped by MA (**46**) and NPM (**99**), respectively.[57] As shown in **Scheme 15** for all three dienes, the addition of the dienophiles takes place from the less hindered π-diastereoface (TSs **108**, **111** and **114**), furnishing adducts **109**, **112** and **115**, in which the more bulky substituent points away from the heterocycle. As expected, the addition to **110**, in which one of the π-diastereofaces of the diene component is "free", occurs faster than in the diastereomeric case **113**, in which both π-diastereofaces are hindered.

Turning to symmetrically disubstituted triple bond dienophiles **116** (**Scheme 16**, EWG = CHO, COMe, CO_2Me, CN, CF_3) next, **6** reacts readily to provide tetra-substituted, *anti*-configured [2.2]paracyclophanes **118** in 25-50% yields. Presumably, this surprisingly short preparative route to functionalized paracyclophanes involves the formation of a *p*-xylylene intermediate **117** in its first

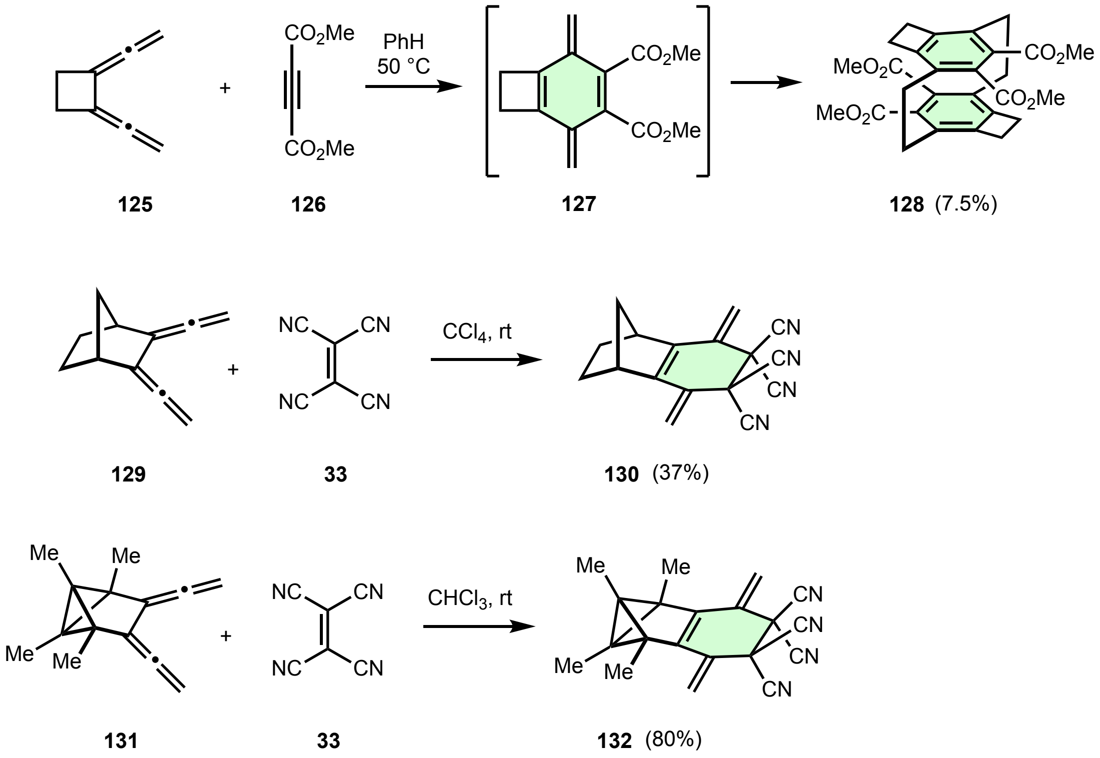
(Diels-Alder) step, followed by a dimerization of this highly reactive species.[46,58] Parenthetically, the dimerization proceeds most likely through a stepwise mechanism involving a biradical intermediate.[59] The substituted [2.2]paracyclophane synthesis is restricted to activated dienophiles **116**, with compounds such as tolane, but-2-yne and cyclooctyne showing no tendency to cycloadd.



Scheme 16: Addition of triple bond dienophiles to hexa-1,2,4,5-tetraene **6**.

Replacing **116** by an unsymmetrically-substituted dienophile such as propiolic aldehyde (**119**) leads to the generation of a monosubstituted *p*-xylylene intermediate **120**, which has four different options to dimerize, as shown in **Scheme 16**. Experimentally, a mixture of all four possible disubstituted dialdehydes **121**-**124** was generated, without a pronounced preference for either one, in up to 45% yield.[60] The different isomers **121**-**124**, which can be separated easily by column chromatography, are interesting starting materials in cyclophane chemistry.[61] Other monosubstituted triple bond dienophiles such as cyanoacetylene and methyl propiolate react correspondingly.

A few examples have been reported in which the *cisoid*-conformation of **6** is fixed by the introduction of bridging structural elements (**Scheme 17**). Thus, the cyclobutane carrying two semicyclic allene groups **125** furnishes the [2.2]paracyclophane derivative **128** in 7.5% yield when treated with dimethyl acetylenedicarboxylate (**126**, DMAD) in benzene at 50 °C; again, the most reasonable intermediate being the bridged *p*-xylylene **127**.[62]



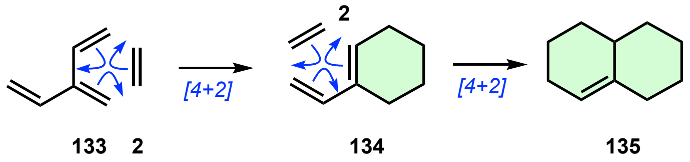
Scheme 17: Diels-Alder reactions of conformationally constrained bisallenes.

Analogously, the rigid bisallenes **129** and **131** react with TCNE **33** to furnish Diels-Alder adducts **130**[63] and **132**.[64]

Closing this section on Diels-Alder additions of conjugated bisallenes, it might be mentioned that other pericyclic reactions of this compound class have been studied also, including the addition of *N*-sulfinylaniline, various carbenes and their higher molecular weight analogues (silylenes, germylenes), sulfur dioxide etc.[16] In most of these cases the heterocyclic adducts produced are formed by routes in accordance of the Woodward-Hoffmann rules.

2.3 Cross-conjugated allenes

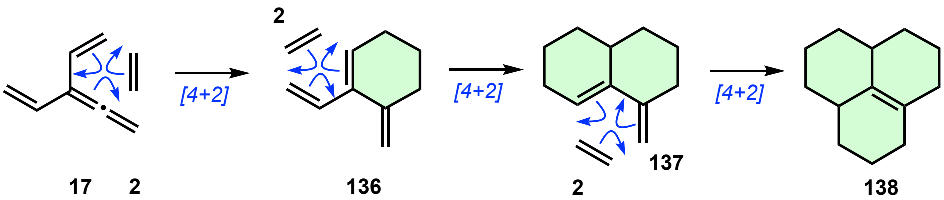
We elected to summarize the Diels-Alder chemistry of cross-conjugated allenic systems in a separate section since this chemistry is uniquely powerful for rapid structure complexity generation. The simplest cross-conjugated hydrocarbon molecule, [3]dendralene **133**, reacts as a double diene, undergoing a sequence of two Diels-Alder reactions with two separate dienophiles. Shown in **Scheme 18** is the simplest incarnation of this sequence, in which the two hypothetical dienophiles are ethylene (**2**) molecules.



Scheme 18. The prototypical diene-transmissive Diels-Alder sequence between [3]dendralene **133** and two molecules of ethylene **2**.

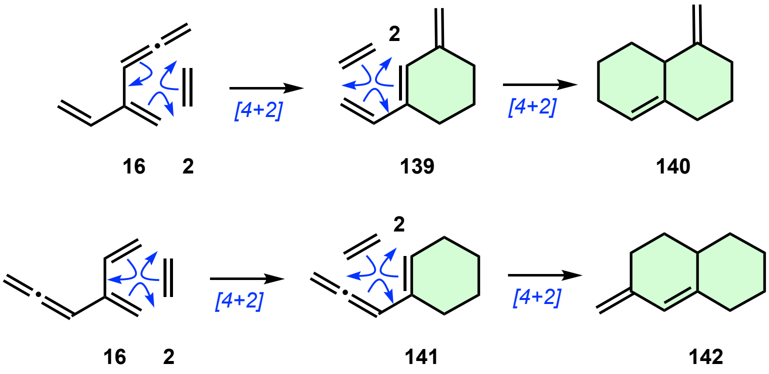
Cycloaddition of the first ethylene dienophile **2** to either one of the two equivalent dienes of the [3]dendralene **133** generates vinylcyclohexene **134**, which can next react with the second ethylene dienophile molecule **2** to form bicyclic octalin product **135**. This double cycloaddition process has been long known[65] as a diene-transmissive Diels-Alder sequence:[66] the first cycloaddition brings about transmission of C=C bond character to the C2–C3 site of the first reacting diene, bringing it into conjugation with the bystander vinyl group from the first cycloaddition event, thereby generating a second buta-1,3-diene moiety.

When the central C=C bond of [3]dendralene is "stretched" into an allene, a diene-transmissive sequence of *three* Diels-Alder reactions is permitted. **Scheme 19** depicts the imaginary, stripped back scenario with no substituents on 1,1-divinylallene **17** and ethylene **2** as the hypothetical dienophile for all three cycloadditions. The first dienophile can cycloadd to either of the two equivalent vinylallene ends of the molecule, through which it generates 2,3'-cyclo[3]dendralene **136**. The second cycloaddition of the C=C dienophile is constrained to occur at the semicyclic diene site of **136**, since this is the only one that can adopt the *cisoid* diene conformation. A third ethylene dienophile addition to bicycle **137** completes the trio of cycloadditions in sequence, resulting in the formation of a decahydro-phenalene tricyclic ring system **138**.



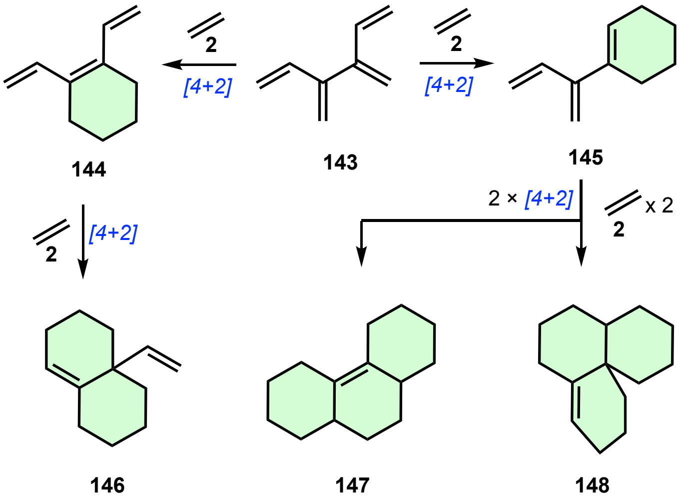
Scheme 19. The prototypical diene-transmissive triple Diels-Alder sequence on 1,1-divinylallene **17**.

A cross-conjugated hydrocarbon with *n* × C=C bonds can react, in a diene-transmissive manner, through an optimal sequence of (*n*-1) [4+2]cycloadditions. Not every cross-conjugated system can behave this way, however, since the correct arrangement of π-bonds is needed. Thus, the allene positional isomer of 1,1-divinyl allene **17**, namely (buta-1,3-dien-2-yl)allene **16** (**Scheme 20**) can undergo a maximum of only two cycloadditions, since the two double adducts **140** and **142** carry dienes that are not reactive in Diels-Alder additions. These two regioisomeric double adducts result from the two possible sites for the first ethylene dienophile to react, either at the vinylallene part of hydrocarbon **16** to give through-conjugated triene **139** (which has only one *cisoid* diene portion for a second addition) or the buta-1,3-diene part of **16** to give cyclohexenyl-allene **141**.



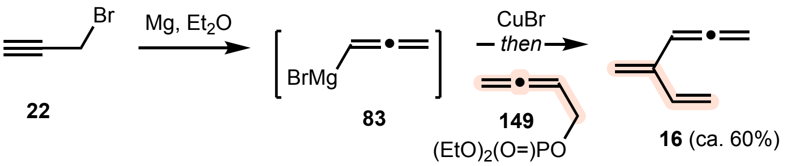
Scheme 20. Two possible diene-transmissive double Diels-Alder sequences on (buta-1,3-dien-2-yl)allene **16.**

It is worth noting that, even if a cross-conjugated hydrocarbon system can behave in a diene-transmissive way, diene site selection is often needed in order for the maximum number of cycloadditions to be realized. A case in point is [4]dendralene **143** (**Scheme 21**): An initial addition to one of the two equivalent terminal diene sites gives the 1,2-cyclo[3]dendralene mono-adduct **145**, which can react on through two separate diene-transmissive Diels-Alder pathways to form triple adducts **147** and **148**. In contrast, an initial addition to the central diene site of [4]dendralene **143** forms monoadduct **144**, which can only undergo one further cycloaddition to yield double adduct **146**.



Scheme 21. Site selectivity is needed for exhaustive diene-transmissive Diels-Alder sequences.

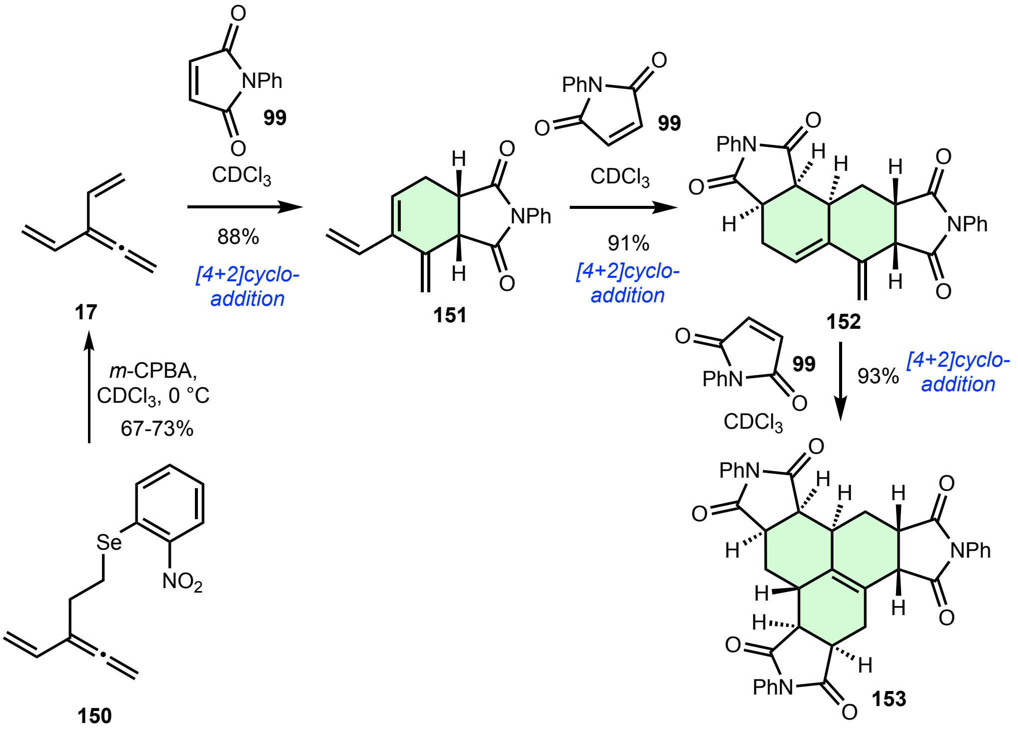
Returning to cross-conjugated allenes, the synthetic generation of both of the two simplest hydrocarbons, 1,1-divinyl allene **17** and (buta-1,3-dien-2-yl)allene **16**, have been reported. The successful route to (buta-1,3-dien-2-yl)allene **16** involves the S_N2'-like substitution of allenol-derived phosphate **149** with allenyl magnesium bromide **83** under CuBr catalysis (**Scheme 22**).[67] The compound is generated in this manner in ca. 60% yield, but the majority of the material decomposes upon attempted purification. The so-far unreported Diels-Alder reaction of this hydrocarbon with a dienophile would reveal its selectivity towards competing buta-1,3-diene and vinylallene sites, which would complement the previously described study in the through conjugated series (**Scheme 7**).



Scheme 22. Synthesis of (buta-1,3-dien-2-yl)allene **16**.

The synthesis of the parent 1,1-divinylallene **17** (**Scheme 23**) involves the Grieco-Sharpless elimination of the selenoxide derivative of precursor **150**.[68] The volatile hydrocarbon **17** is co-distilled from the reaction mixture with the $CDCl_3$ solvent, as a simple method of separation from the byproducts of the reaction and generation of an NMR-ready solution. 1,1-Divinylallene **17** polymerizes too rapidly to be handled in neat form at ambient temperature, so it is best generated and characterized in solution. The hydrocarbon undergoes a diene-transmissive, triple Diels-Alder sequence with NPM **99** to form hexacyclic product **153**. The sequence was discussed above for the case of a hypothetical dienophile ethylene **2** (**Scheme 19**). With the NPM dienophile, issues of *endo/exo*-diastereoselectivity and π-

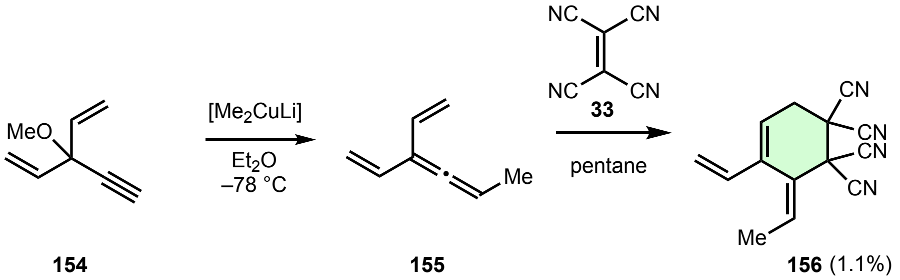
diastereofacial selectivity exist, hence the situation is considerably more complex. Nonetheless, the first two cycloadditions occur with (within the limits of detection) complete *endo*-diastereoselection, with the second dienophile molecule approaching the less sterically encumbered diene face of the mono-adduct **151** to form bis-adduct **152**. Uncommonly for this type of dienophile, the third cycloaddition is *exo*-selective, presumably on account of both of the possible *endo*-approaches of the dienophile to the diene **152** being sterically blocked.



major isomer : Σ (other isomers)
= 65:35

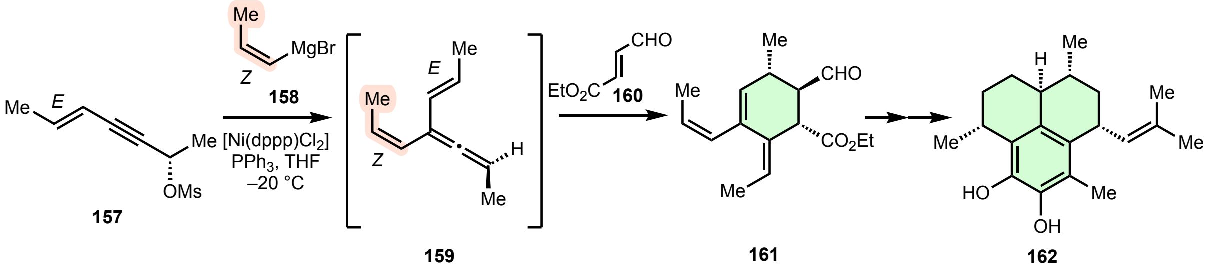
Scheme 23. Synthesis and triple Diels-Alder reaction of 1,1-divinylallene **17**.

The generation and Diels-Alder reaction of the methyl substituted 1,1-divinylallene **153** were reported more than two decades earlier than the preparation of the parent 1,1-divinyl allene **17**.[67] As shown in **Scheme 24**, the compound was prepared through regioselective substitution of methyl ether **154**, which has three potential sites for *S$_N$2'*-type reaction, specifically the termini of the two vinyl groups or the one ethynyl substituent. Reaction occurs selectively at the alkyne terminus to generate allene **155**, high quality spectra for which were unobtainable due to its instability. The TCNE Diels-Alder adduct **156** was isolated from a reaction in pentane at ambient temperature, albeit in low yield.



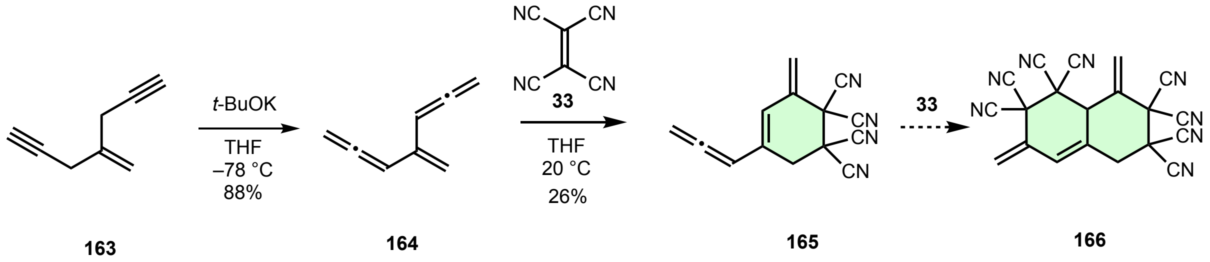
Scheme 24. Generation and Diels-Alder reaction of the first substituted 1,1-divinylallene **155**.

The first chiral 1,1-divinylallene reported in the literature was trimethyl analogue **159**,[69] which was prepared through a Kumada-type cross coupling between propargylic mesylate **157** and Grignard reagent **158**, during which the now familiar propargyl- to allenyl-transposition ensued (**Scheme 25**). This compound can be prepared on scales over several grams but, once again, is best generated in solution and used *in situ*, due to its propensity to polymerize when neat at ambient temperature. Uncatalyzed Diels-Alder reaction with dienophile **160** furnished mainly the 2,3'-cyclo-[3]dendralene **161**, in a ca. 5:1 ratio with other isomers. An essentially complete retention of enantiopurity was seen on switching from central (**157**) to axial (**159**) chirality, and back to central (**161**) chirality once again. Reaction of the mono-cycloadduct **161** in two further Diels-Alder reactions led ultimately to natural product **162**.



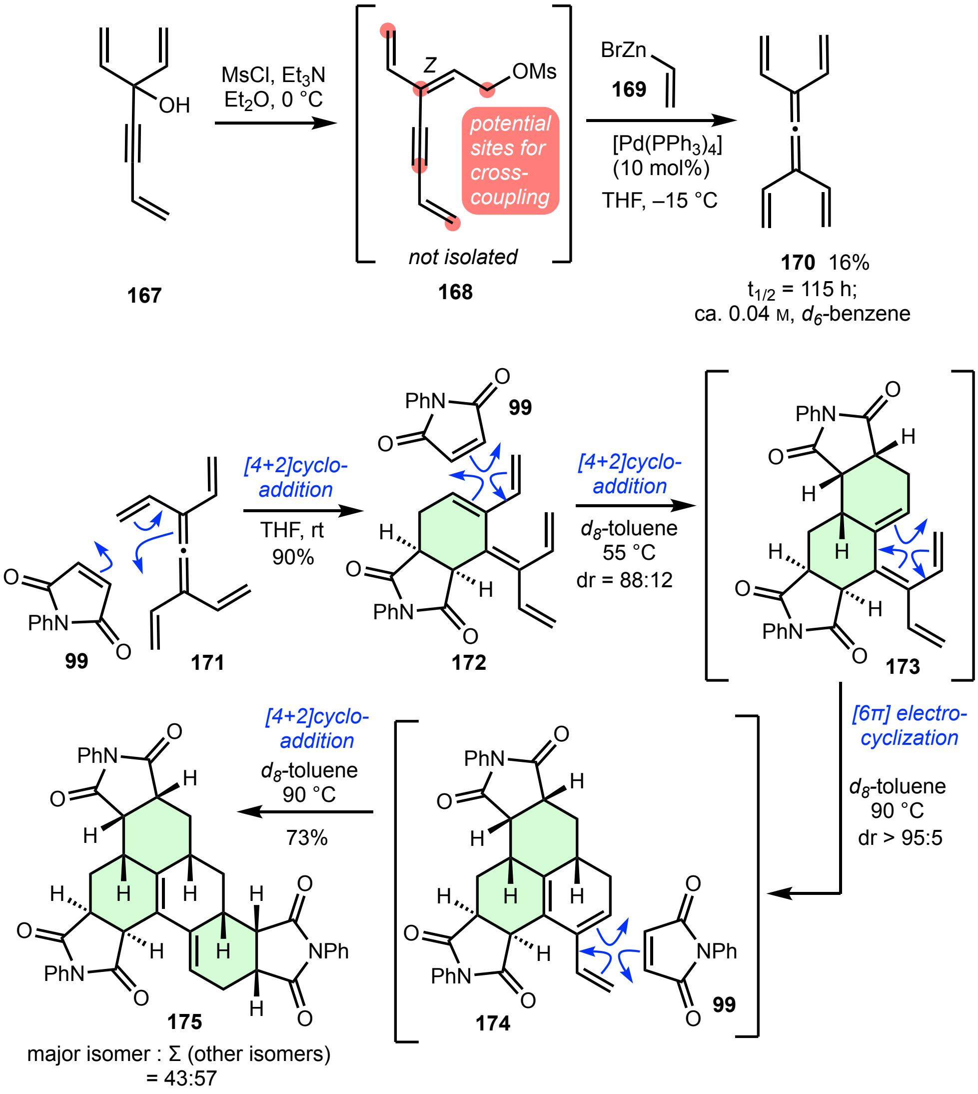
Scheme 25. Chiral 1,1-divinylallene **159** and the first of its three Diels-Alder reactions in the total synthesis of pseudopterosin natural product **162**.

The first synthesis of 1,1-diallenylethylene **164** involved the base-catalyzed twofold propargyl- to allenyl-isomerization from 1,1-dipropargylethylene **163** (**Scheme 26**).[67] The reaction is high yielding but, once again, the susceptibility of bis-allene **164** to polymerization thwarted attempts to purify and fully characterize the hydrocarbon. A Diels-Alder addition with TCNE **33** at ambient temperature gave mono-adduct **165** in modest yield. A second dienophile addition to the newly-created vinylallene portion of mono-adduct **165** would give putative double adduct **166**. This as yet unexplored sequence offers significant potential in synthesis.



Scheme 26. Generation and Diels-Alder reaction of 1,1-diallenylethylene **164** with TCNE **33**.

Finally in this section, tetravinylallene **170** was recently prepared, along with several substituted analogues (**Scheme 27**).[70] Hydrocarbon **170** was prepared reproducibly, albeit in low yield, through a challenging Negishi cross-coupling with transposition, between the sensitive methanesulfonate derivative **168** of trienol **167** with vinylzinc bromide **169**. Tetravinylallene **170** is a little more kinetically stable (and less volatile) than the previous unsubstituted molecules described in this section, being amenable to purification by flash column chromatography. The hydrocarbon **170** undergoes a spectacular sequence of three Diels-Alder reactions with NPM **99**, with a highly torquoselective 6π electrocyclization punctuating the second and third cycloadditions. The first dienophile molecule has four equivalent vinylallene sites to which it may react, generating mono-adduct **172**. The second addition occurs at the transmitted diene site, forming bisadduct **173**, which undergoes the electrocyclization to **174**. The final cycloaddition occurs to the semicyclic diene site of the 1,3'-cyclo[3]dendralene **174** to give heptacyclic product **175**, with seven C–C bonds and four rings formed about the tetravinylallene core.

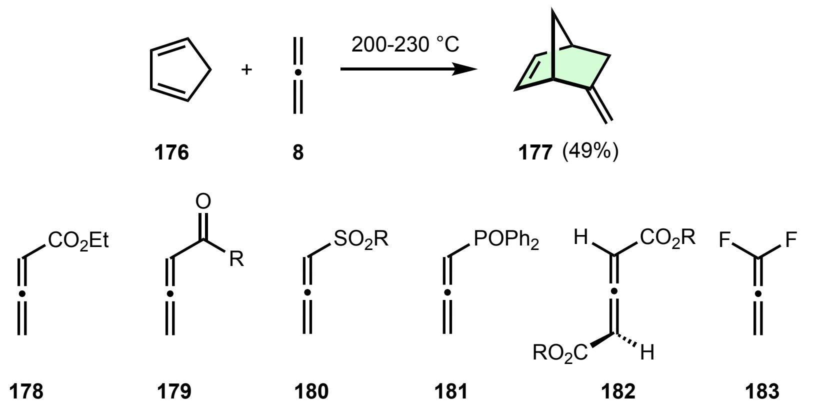


Scheme 27. Synthesis and Diels-Alder reaction sequence of tetravinylallene **170**.

Thus, cross-conjugated allenic systems serve as a central hub for the generation of polycyclic systems by way of diene-transmissive Diels-Alder sequences, which can also involve electrocyclization events. The allenes in these molecules, akin to all allenic systems covered thus far, react as a part of a Diels-Alder diene. In the next section, we move onto the dienophile reactivity of allenic molecules.

3. Allenic dienophiles

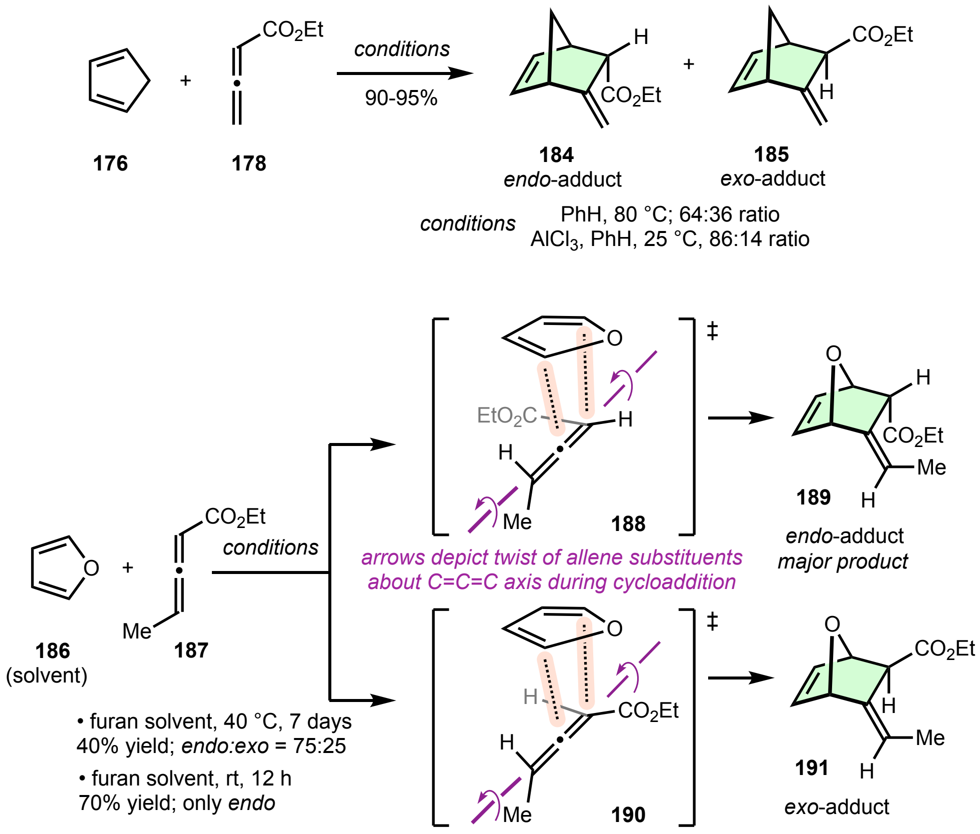
Compared to allenic dienes (**Section 2**), the number and particularly the structural variety of acyclic allenic dienophiles which have been studied or used in synthesis is comparatively small. The simplest dienophile of this type is allene (**8**) itself. As shown in **Scheme 28**, it reacts with cyclopentadiene (**176**) under drastic conditions to provide adduct **177** in moderate yield.[71]



Scheme 28: Allenes as dienophiles in Diels-Alder additions.

Other unactivated allenes such as 1,1-dimethylallene (3-methylbuta-1,2-diene) react similarly.[72] Much more often, though, electron-deficient allenes are employed. Introducing an electron-withdrawing (and generally conjugating) substituent lowers the LUMO energy of the allene. The C=C bond of the allene in conjugation with the electron-withdrawing substituent is the one that is activated for reaction in a normal electron-demand cycloaddition with an electron rich diene. This fact is borne out by numerous examples using allenic esters such as **178** and **182**, ketones (**179**), sulfonyl allenes (**180**), fluoroallenes (**183**), allenyl phosphine oxides (**181**) to name but a few.[73]

Insights into the stereochemical course of the addition of allenic dienophiles to various dienes can be gleaned through the reactions summarized in **Scheme 29**.

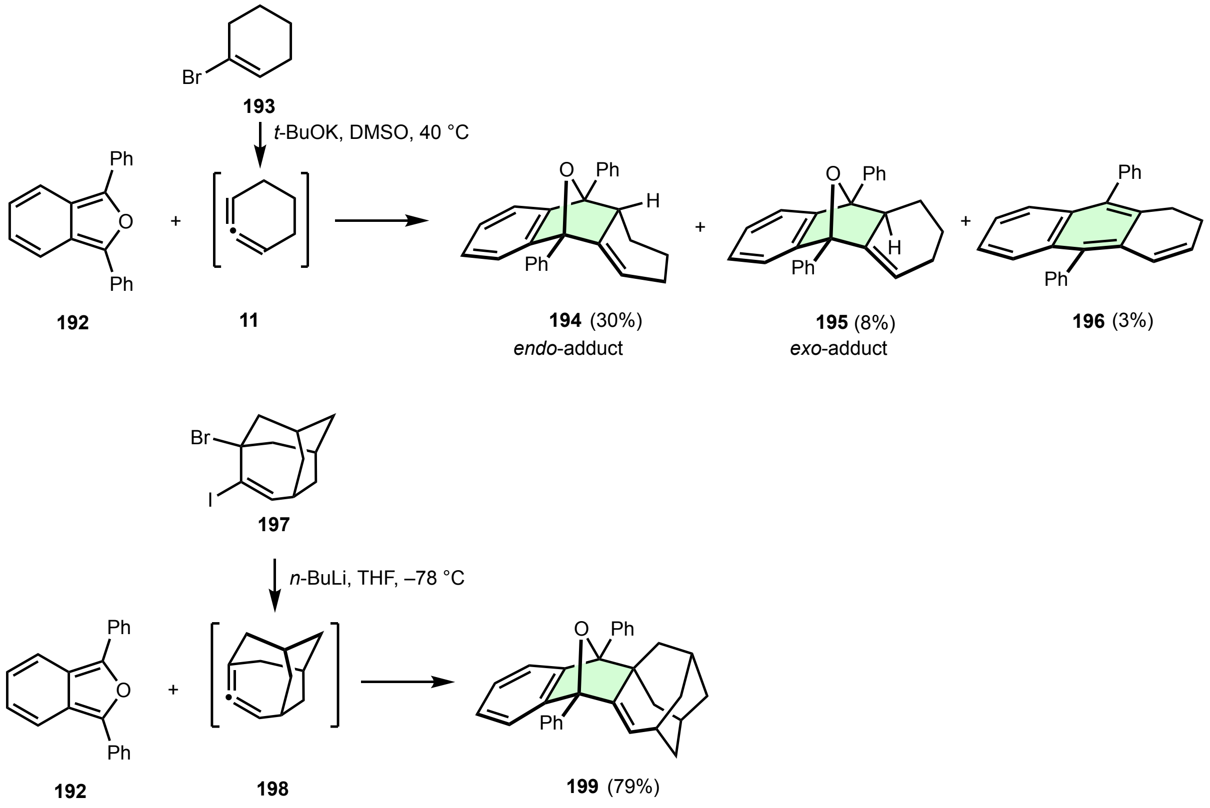


Scheme 29: Stereoselection in Diels-Alder additions of allenic dienophiles.

The reaction between allenic ester **178** and cyclopentadiene **176** leads to a mixture of *endo*- and *exo*-cycloadducts **184** and **185**, under conditions significantly milder than those required for the parent allene. When carried out thermally, the Diels-Alder addition is mildly *endo*-selective but a Lewis acid promoter gives a significant rate enhancement and improved *endo*-preference.[74]

The more complex case of the cycloaddition of the (chiral, racemic) allene ester **187** to furan **186** yielded *endo*-adduct **189** via transition state **188** and *exo*-adduct **191** via the competing transition state **190**. In both cases, approach from the less hindered face of allene **187** occurs (i.e. the π-diastereofacial selectivity of the reaction is due to the diene avoiding the allenic dienophile's methyl substituent). The geometry of the exocyclic alkene is determined by the twisting that occurs during the cycloaddition, resulting from the change in hybridization at four carbon atoms of the diene and dienophile. In an uncatalyzed cycloaddition with furan as solvent at reflux temperature (40 °C), the total yield amounts to 40% and the *endo:exo* ratio is 75:25. In the catalyzed (1 mol% Eu(fod)$_3$) reaction performed at ambient temperature, *endo*-adduct **189** is produced exclusively and in better total yield (70%).[75] Furan diene cycloadditions can be reversible on account of the molecule's aromaticity, with kinetic *endo*-adducts favored from shorter reactions at lower temperatures and thermodynamic *exo*-adducts from longer reactions. While the improvement in *endo*-selectivity with Eu(fod)$_3$ is most likely due to an enhancement in SOIs, a LUMO-lowering rate enhancement (hence lower reaction temperature and time) would also reduce the prospect of reversibility, hence channeling towards the *exo*-adduct.

The reactivity of the allene component in these cycloadditions may not only be increased by electron-withdrawing substituents, but also by incorporating the allene unit into ring systems. Two examples are shown in **Scheme 30**. When 1-bromo-cyclohex-1-ene (**193**) is treated with potassium *tert*-butoxide in DMSO, cyclohexa-1,2-diene (**11**) is generated as a reactive intermediate which can be trapped by diphenylisobenzofuran (**192**) as the diene component to furnish *endo*- and *exo*-adducts, **194** and **195** respectively, as the main products as well as the deoxygenated adduct **196** as a trace compound.[76]



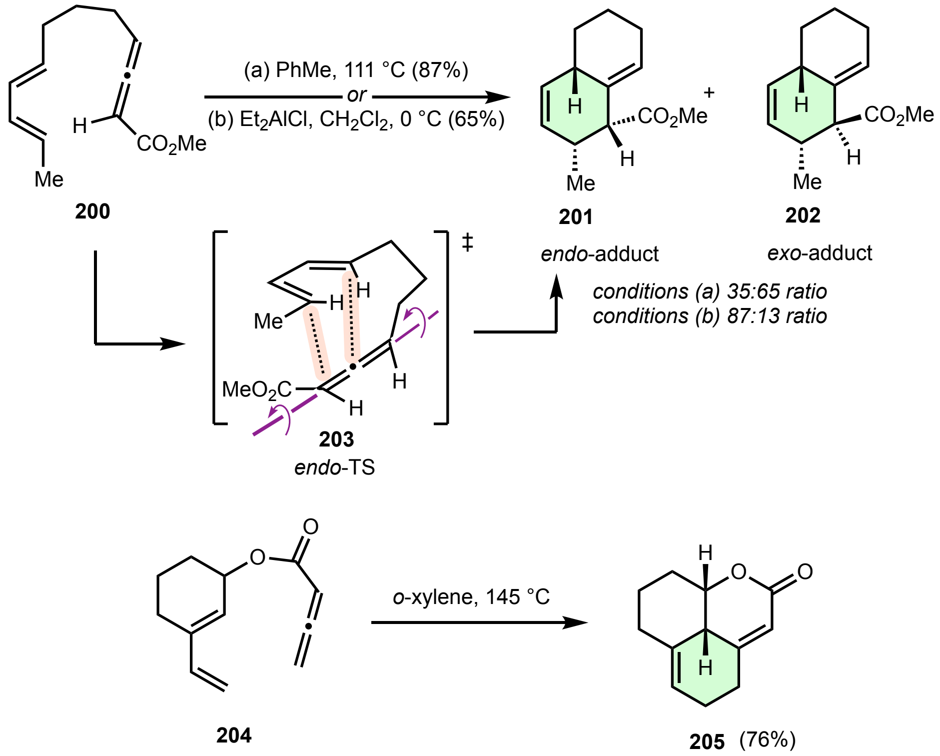
Scheme 30: Strained cyclic allenes as dienophiles.

Analogously, when the homoadamantane derivative **197** is di-dehalogenated by treatment with *n*-butyllithium in THF at –78 °C in the presence of diphenylisobenzofuran (**192**), the adduct **199** is produced in good yield: clearly by the Diels-Alder addition of the initially generated polycyclic allene intermediate **198**.[77] Notably, the more strained bridgehead C=C bond reacts in this case.

So far, the Diels-Alder reactions of allenes described in this review have been limited to those involving separate diene and dienophile molecules. In the next section we describe representative examples of intramolecular processes.

4. Intramolecular Diels-Alder additions involving allenes

Connecting a diene and dienophile by a molecular linker or spacer (of any complexity) as in **12** (**Scheme 2**) results in a reduction of pathways by which these two components of a Diels-Alder process can approach each other in three-dimensional space. It hence comes as no surprise that this pre-orientation has often been applied to influence or control the regio- and stereochemistry of a [4+2]cycloaddition. This is also the case for the reaction between allenic dienophiles and dienes. Typical examples are reproduced in **Scheme 31**.[78]

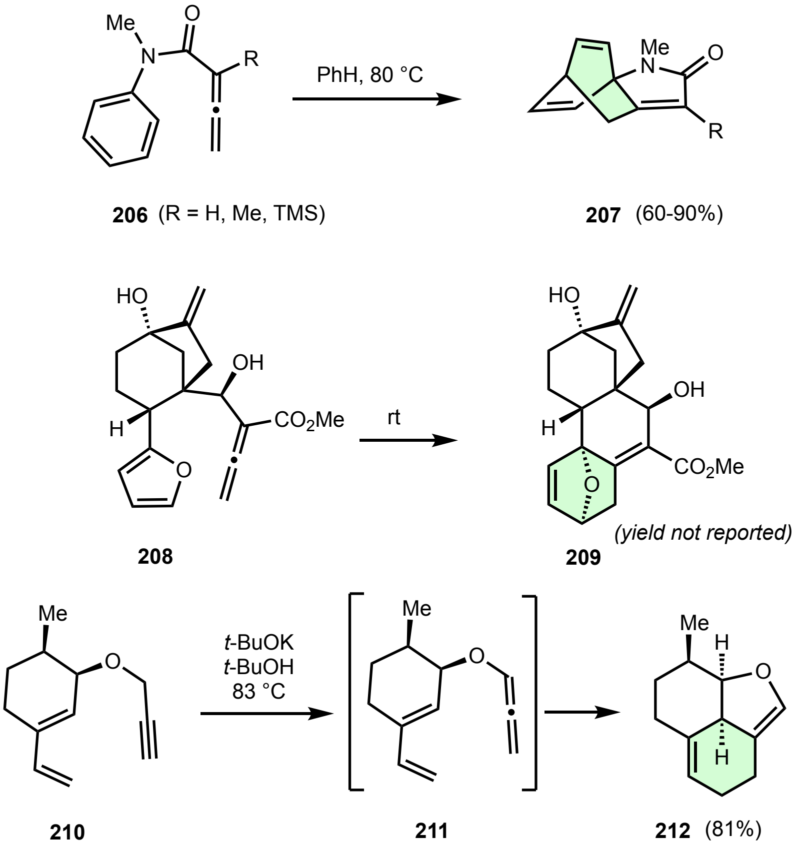


Scheme 31: Intramolecular reactions between an activated allene unit and a typical buta-1,3-diene moiety.

When the acyclic precursor **200**, in which the two moieties of a Diels-Alder addition are connected by a (flexible) trimethylene chain, is heated in toluene at reflux temperature, a mixture of the *endo*- and *exo*-adducts **201** and **202** is produced in 87% yield in a 35:65 ratio. These are the products to be expected for an allene-dienophile reacting at its more reactive double bond (see above), although in the acyclic pendant we would have expected the *endo*-adduct (formed through TS **203**) to predominate. If the reaction is carried out in the presence of a Lewis acid (Et_2AlCl), a slight reduction in total yield is noted (65%), the reaction temperature is drastically reduced and the *endo*-isomer **201** predominates (87:13 ratio). Evidently, complexation of the ester group to the Lewis acid has a LUMO-lowering effect, which also enhances SOIs in the *endo*-TS.

In the less flexible compound **204**, it is the terminal allene double bond that reacts preferentially, furnishing adduct **205** in 76 % yield.[79] Approach of the allene to the bottom face of the semicyclic diene is controlled by the configuration of the pre-existing stereocenter. The dienophile site selectivity was ascribed to the preference of the ester group in the tether to adopt a transoid conformation.

In certain cases, even a benzene ring can be induced to participate as a 4π-component in an intramolecular Diels-Alder addition, a case in point being provided by the cycloaddition of the allene amide **206** to the tricyclic adduct **207** (**Scheme 32**).[80] These so-called Himbert cycloadditions were originally performed only on amide-tethered precursors. More recently, they have been shown to proceed through concerted mechanisms and with a broader range of tethers.[81] The broadened scope of Himbert-type cycloadditions has resulted in renewed synthetic interest in this well-established process.[82,83]

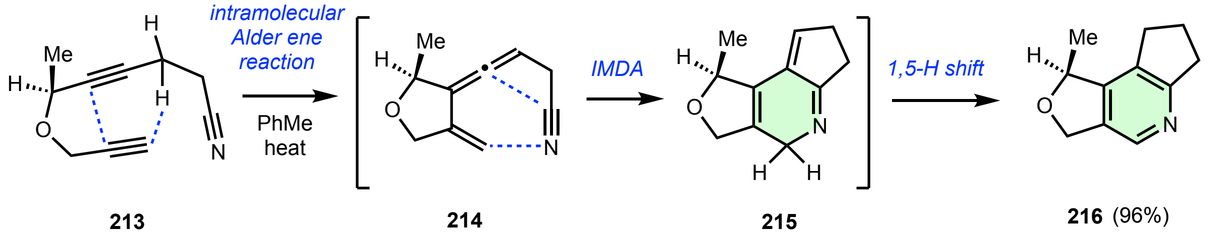


Scheme 32: Intramolecular cycloadditions involving aromatic and heteroaromatic diene units, and in situ-generated allenic dienophiles.

Occasionally the linker unit can be quite complex and provide additional stereochemical information, as in the conversion of **208** into **209**, which took place at room temperature on concentrating HPLC fractions.[84] The electronically less activated C=C bond is the one that reacts. The lack of reaction at the more activated site was explained in terms of developing steric repulsion between a terminal methylene H and the furan diene in this alternative IMDA TS.

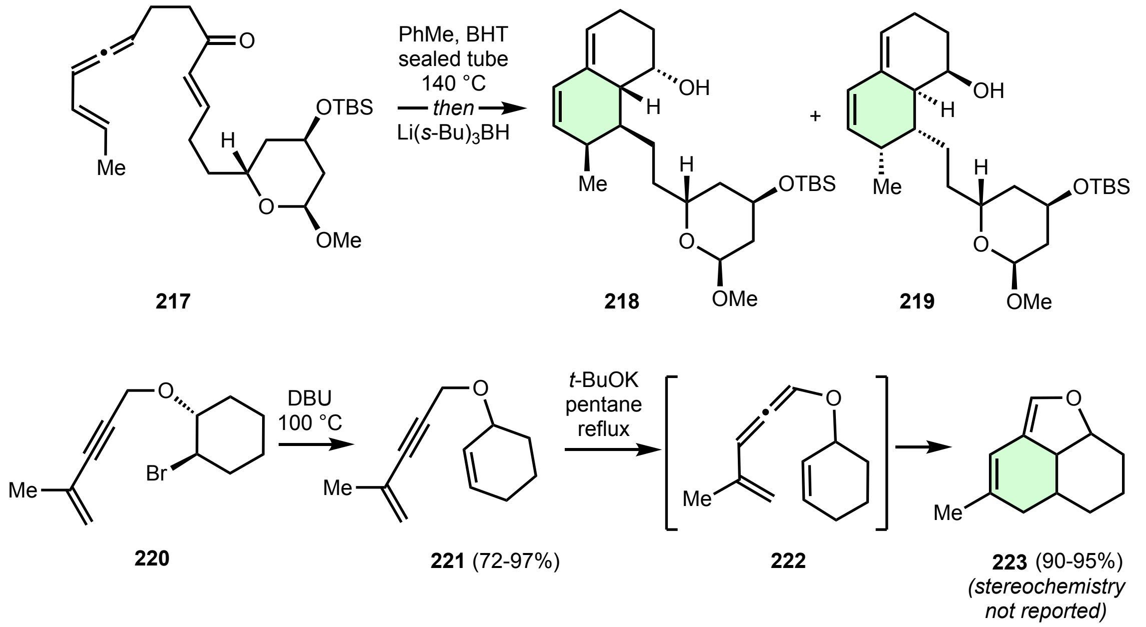
It is not necessary for the allenic dienophile to be present in the substrate: it can be generated as a reaction intermediate. This is demonstrated by the initial conversion of the propargyl ether **210** into its allenic isomer **211** by base treatment. Subsequently cycloaddition to the terminal C=C bond of allene **211** generates tricyclic enol ether **212**.[85]

Another pericyclic reaction cascade starts from the nitrile **213** and subjects its toluene solution to longer reaction times under reflux conditions (**Scheme 33**). In the first step of the transformation an intramolecular Alder ene (perhaps a tetradehydro-ene) reaction takes place to provide a cyclized vinylallene **214**. This is subsequently trapped by an intramolecular dehydro-Diels-Alder addition of a nitrile function to yield, after 1,5-H shift of initial adduct **215**, the pyridine derivative **216** in excellent yield.[86]



Scheme 33: A substituted tricyclic pyridine from acyclic cyano-diyne through an intramolecular hetero Diels-Alder reaction involving a vinylallene.

Not surprisingly, the butadiene section of vinylallenes has also been shown to participate in intramolecular allene Diels- Alder reactions.[87,88,89,90] Typical examples are summarized in **Scheme 34**.

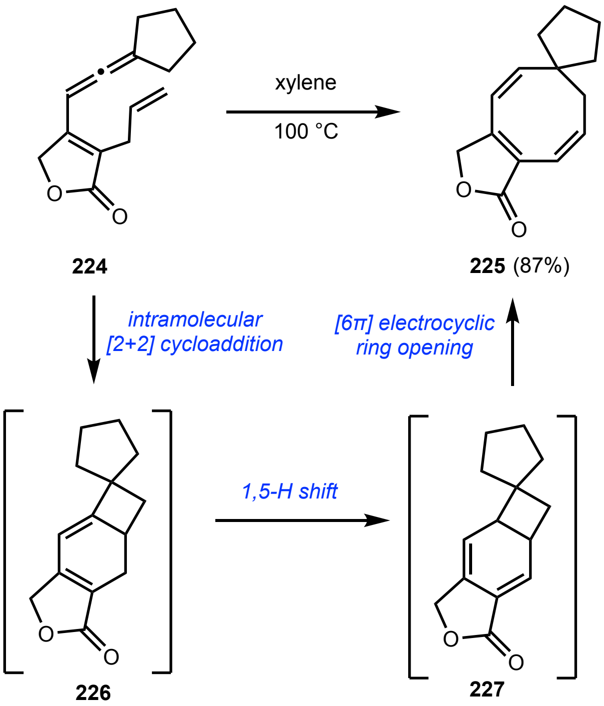


Scheme 34: Intramolecular cycloaddition of a vinylallene to α,β-unsaturated ketone.

The intramolecular Diels-Alder addition of **217** took place at 140 °C, and the resulting 1:1 mixture of diastereomeric ketone adducts were reduced to the alcohols **218** and **219**, valuable intermediates in the total synthesis of the natural product (+)-compactin and a diastereomer.[91,92] Precursor **217** was used as a 1:1 mixture of diastereomers about the allene moiety, and the two products **218** and **219** have opposite configurations at the four stereocenters generated in the IMDA-reduction sequence.

The diene partner in these processes can also be prepared en route, as shown by the dehydrobromination of **220** to the cyclohexene derivative **221**, which on base-catalyzed isomerization yielded the vinylallene intermediate **222** first, which subsequently underwent the cycloaddition to **223** under mild conditions in high yield.[93]

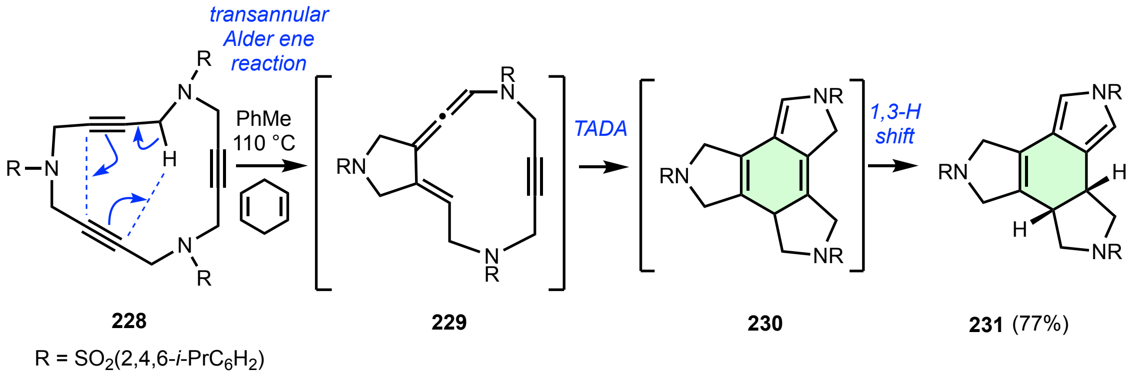
Other pericyclic processes may compete with a desired intramolecular Diels-Alder addition if the tether does not permit the diene and dienophile to dock in the required manner. An example involving lactone **224** is shown in **Scheme 35**.



Scheme 35: A short vinylallene-alkene tether favors a [2+2]cycloaddition pathway.

Rather than adding in a [4+2]mode to the vinylallenic part of **224**, an alternate pathway is followed, presumably due to the short vinylallene-alkene tether.[94] To explain the formation of the cyclooctatriene product **225**, a sequence of no less than three pericyclic steps have been proposed: [2+2]cycloaddition of **224** to **226**, which isomerizes to **227** by a thermal 1,5-hydrogen shift. Formally the latter is a 1,2-divinylcyclobutane derivative which, driven a release in ring-strain, undergoes electrocyclic ring opening to the isolated product **225**.

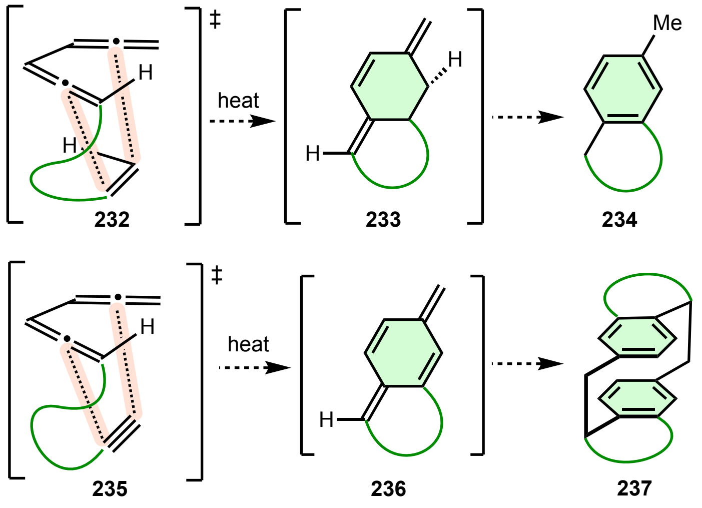
An interesting final example from the heterocyclic field (**Scheme 36**) involves the thermal isomerization/cyclization of the triazamacrocyclic compound **228** to the vinylallene intermediate **229** which is subsequently trapped by the opposing triple bond in a transannular cycloaddition. The initial tetracyclic product **230** tautomerizes to the heteroaromatic product **231** in very good overall yield, considering the molecular transformation that has taken place from starting material **228** to product **231**.[95]



Scheme 36: A cascade process connecting a macrocyclic substrate to a tetracyclic product.

It should be noted that all the intramolecular Diels-Alder additions presented here have been reported for suitable vinylallene systems, no bisallenic compounds containing a hexa-1,2,4,5-tetraene subunit having been described. Although e.g. cyclic, conjugated bisallenes have been postulated as reaction intermediates[96] none have been trapped–either by an added or tethered dienophile.

As illustrated in **Scheme 37**, intramolecular [4+2]cycloadditions of double and triple bond dienophilic moieties to bisallene units could lead to useful and interesting aromatic systems. For example, **232** could provide the Diels-Alder adduct **233** as in the case of the intermolecular addition of double bond dienophiles to hexa-1,2,4,5-tetraene (see **Scheme 16**) which, in turn might tautomerize to the fused aromatic system **234**. Likewise, **235** would yield the reactive *p*-xylylene intermediate **236** initially, which could dimerize to the [2.2]paracyclophane **237** (see **Scheme 17**). The preferred mode of dimerization to form compounds akin to **237** will depend on the activating groups present in the starting materials, the length and composition of the spacers and the relative orientations of the two intermediates **236** with respect to each other (*cf*. **Scheme 16**).

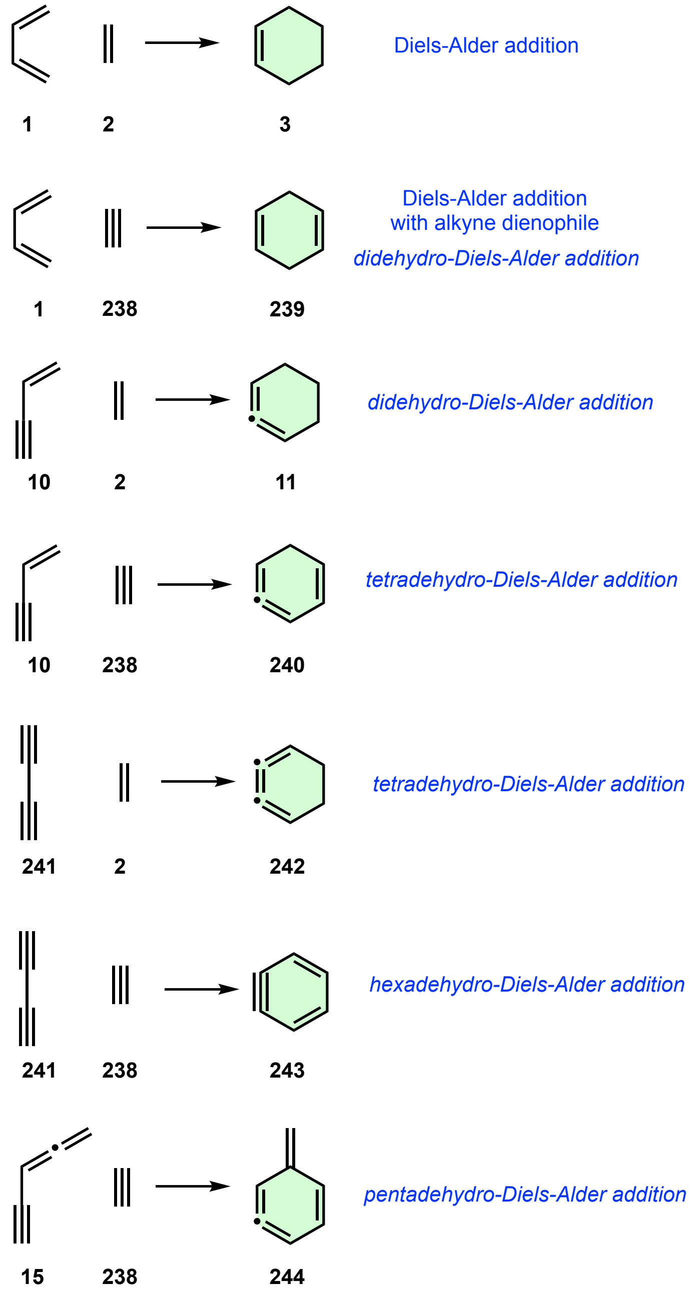


Scheme 37: Possible intramolecular cycloadditions involving bisallenes.

5. Allenic cycloadducts

Traditionally, strained cycloallenes have been generated either by elimination reaction as shown by the examples summarized in **Scheme 30** or by using the Doering-Moore-Skattebol procedure (see **Scheme 13**), starting from the next lower-membered cycloalkene.

Recently, however, strained cyclohexa-1,2-dienes (**11**) and related systems such as cyclohexa-1,2,3-triene (**242**), a cyclic [3]cumulene, have become available by routes that formally resemble Diels-Alder additions and have been termed dehydro-Diels-Alder additions; **Scheme 38** summarizes the presently known processes of this novel type of cycloaddition, which preparatively has resulted in an enormous extension of the classical [4+2]process.[97,98]



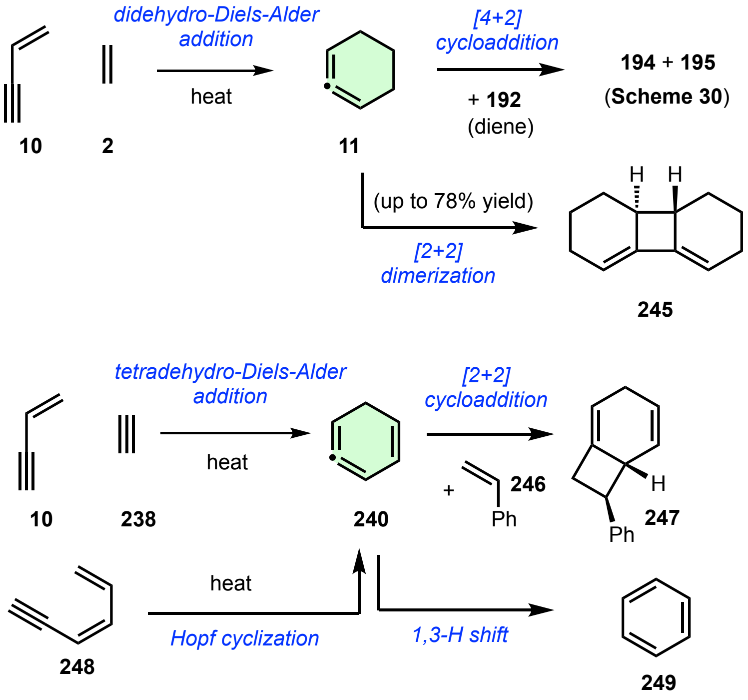
Scheme 38: From the classical Diels-Alder reaction to various types of dehydro-Diels-Alder processes.

Starting from the classical "diene reaction" in which buta-1,3-diene **1**, for example, reacts with a dienophile of general structure **2** to provide a cyclohexene derivative **3**, the replacement of **2** by a triple bond dienophile **238** is a didehydro-Diels-Alder process;[99] the product now being a cyclohexa-1,4-diene (**239**). Another variant of the didehydro-Diels-Alder reaction involves a triple bond as part of the diene, in its simplest form vinylacetylene (**10**). When this cycloadds to ethylene **2**, cyclohexa-1,2-diene (**11**) results, whose actual existence was already proven by the trapping experiment in **Scheme 30**.

Replacement of ethylene **2** by acetylene **238** and carrying out the cycloaddition with **10** leads to the next higher level of oxidation, i.e. a tetradehydro-Diels-Alder addition and furnishes a cycloadduct (**240**) which has been termed "isobenzene" (see below). Again, there exists a second alternative: employing diacetylene (**241**, 1,4-butadiyne) and **2** leads to the cyclocumulene **242**. Finally, when all hydrogen atoms of both components are removed, a hexadehydro-process results and generates 1,2-didehydrobenzene (**243**) as an intermediate.[100,101]

As shown in **Scheme 38**, these cycloadditions are not restricted to "diene components" involving four carbon atoms. With penta-1,2-dien-4-yne (**15**) and a triple bond dienophile (**238**), the [4+2]cycloaddition mode furnishes an α,3-dehydrotoluene **244** as a reactive intermediate in a pentadehydro-Diels-Alder cycloaddition.[102]

Before we discuss several examples of these dehydro-Diels-Alder additions in more detail, we want look at the reaction of **10** with either a double (**2**) or a triple bond dienophile (**238**) in greater detail (**Scheme 39**).We do not intend to present a comprehensive discussion of these "dehydro-processes" here, the main reason being that the cycloadditions summarized in the rest of this review display more or less complex allenic starting materials (as dienes and dienophiles), not intermediately generated allenic and/or cumulenic species whose existence is inferred from their subsequent chemical behavior.

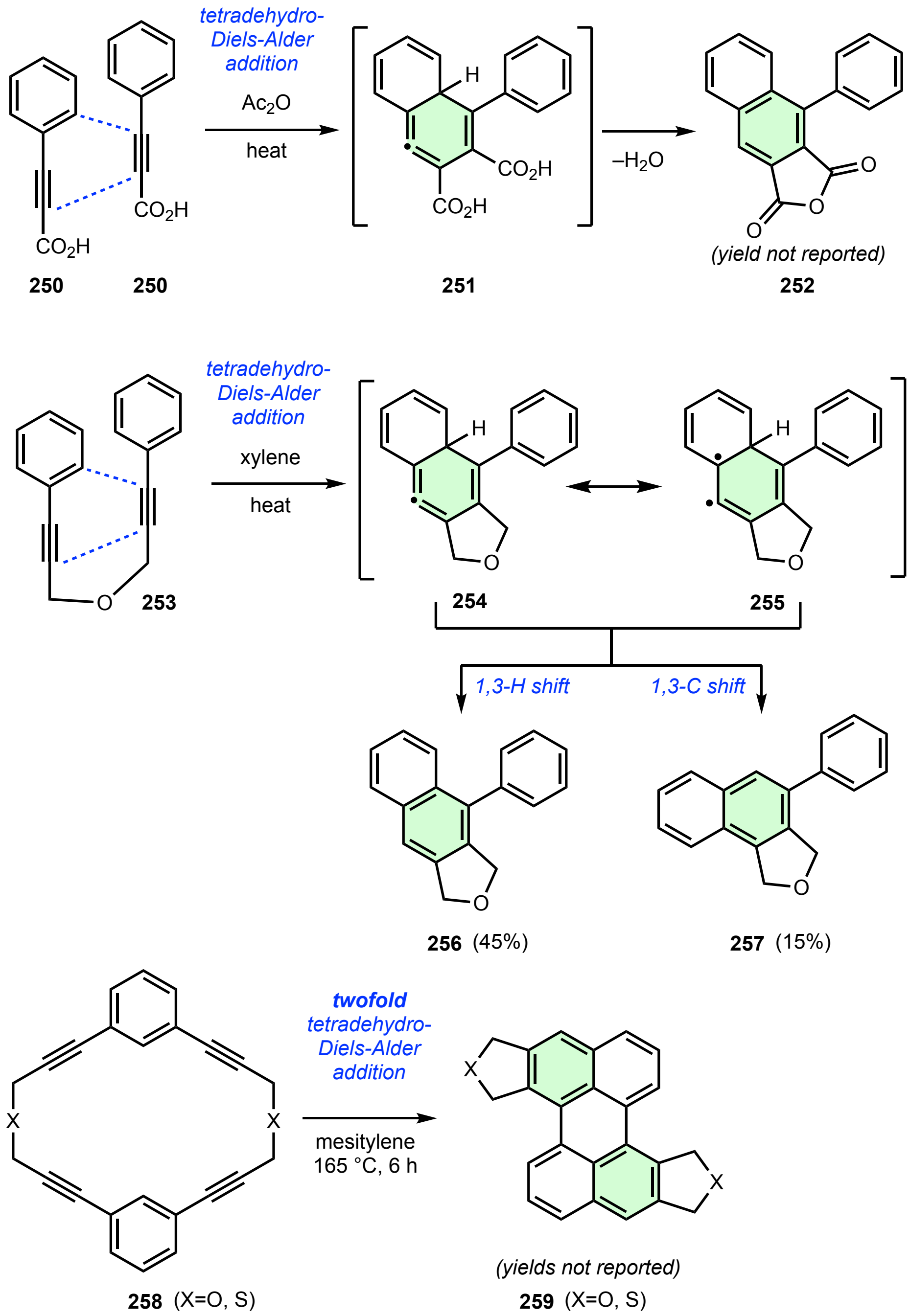


Scheme 39: Dehydro-Diels-Alder additions with vinylacetylene (**10**).

The highly reactive 1,2-cyclohexadiene **11** formed from **10** and **2** has two pathways to react further. In the presence of a trapping agent such as diphenylisobenzofuran (**192**) it can provide either the trapping products **194** and **195** (see **Scheme 30**), or self-trap (dimerize) to the tricyclic hydrocarbon **245**.[103]

When **2** is replaced by **238**, isobenzene **240** results, which by a 1,3-hydrogen shift isomerizes to the most stable C_6H_6 hydrocarbon, benzene **249**. That **240** is indeed generated as the first step of this aromatization reaction was shown by intercepting it with added styrene **246** in a [2+2]cycloaddition to give adduct **247**.[104] Heating the acyclic precursor **248** in the gas phase brings about cycloaromatization to benzene **249**, the so-called Hopf cyclization,[105] which also proceeds through cyclic vinylallene **240**.

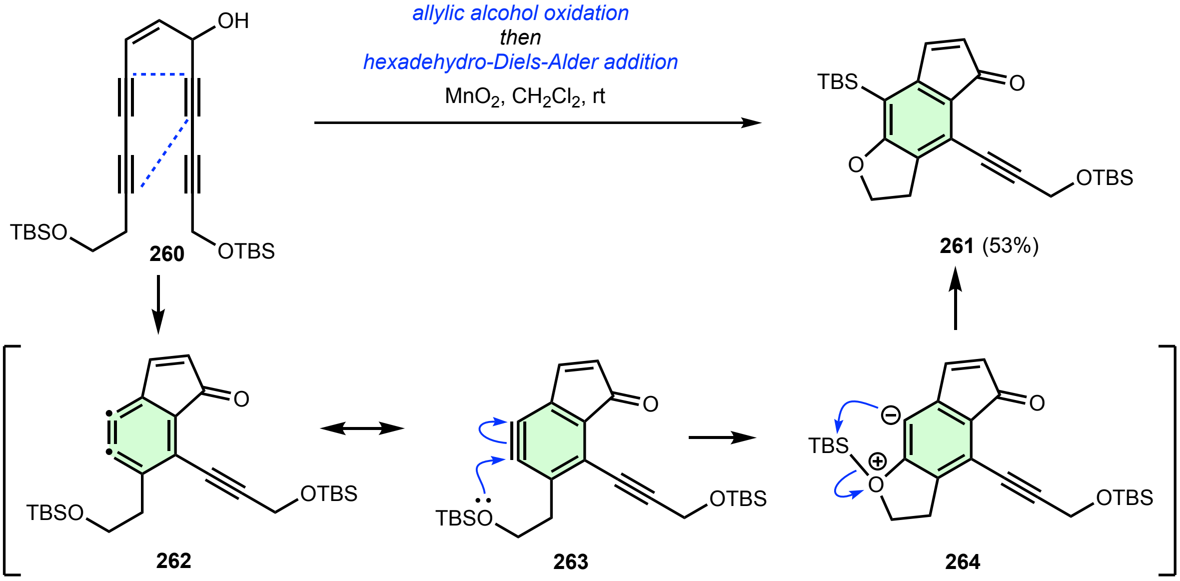
Many thermal dehydro-Diels-Alder reactions involve enyne components in which the double bond is part of an aromatic system. In one of the earliest reactions of this type – observed more than 100 years ago – phenylpropiolic acid (**250**) was heated in a sealed tube in the presence of acetic anhydride (**Scheme 40**). The cyclized anhydride **252** was presumably formed via the isobenzene intermediate **251**.[106]



Scheme 40: Inter- and intramolecular tetradehydro Diels-Alder cycloadditions.

Often in these cycloaromatizations, mixtures of isomers are produced. A case in point is the intramolecular tetradeydro Diels-Alder reaction of the ether **253**, which provides a mixture of **254** and **255** in a 75:25 ratio when heated in xylene.[107] The initial [4+2]cycloadduct is the isobenzene derivative **254**. It has been suggested[108] that this highly reactive intermediate displays diradical character, resulting from uncoupling of the allene unit to better accommodate the inherent strain of the intermediate. This is indicated by resonance structure **255** in **Scheme 40**. When this undergoes a 1,3-hydrogen shift reaction, the main isomer **256** is produced, whereas a 1,3-carbon shift leads to side product **257**. The macrocyclic substrate **258** allows for a twofold transannular dehydro-cyclization process and furnishes the fused perylene derivatives **259**.[109]

The still higher oxidized form of a dehydro Diels-Alder addition is provided by the hexadehydro process summarized in **Scheme 41**.[101]



Scheme 41: An intramolecular hexadehydro Diels-Alder reaction.

When the tetrayne alcohol **260** is oxidized with MnO_2 at room temperature in dichloromethane a deep-seated transformation takes place to provide dihydrobenzofuran **261** in acceptable yield. To rationalize this amazing transformation, the authors have proposed an initial oxidation to the ketone derived from **260**. In the subsequent step the hexadehydro addition takes place to furnish intermediate **262**, a cyclic cumulene which looks more familiar when displayed in its resonance form **263**, a 1,2-didehydrobenzene. Ring closure by the pending substituent then leads to the zwitterion **264**, which can undergo a retro-Brook rearrangement to the isolated product. There are direct hints that **262**/**263** is passed en route, since this intermediate can be trapped by benzene (used as a solvent), norbornene and other trapping reagents.

6. Conclusions and outlook

Allenic dienes and dienophiles played no significant role as components of the Diels-Alder reaction for a long time. This review demonstrates that allenes are becoming well established in Diels-Alder chemistry, and it is appropriate to speculate on reasons for this change.

The broader use of allenes in [4+2]cycloadditions has to do with several factors, the first one being availability. Traditionally, allenes were prepared by the classical routes of preparative chemistry for unsaturated molecules, namely elimination and isomerization. Base-catalyzed isomerizations of propargylic systems were commonly employed, since the high energy content of acetylenic bonds provides a thermodynamic driving force for allene formation: But-1-yne, for example, is thermodynamically less stable than its isomer buta-1,2-diene.

The second traditional approach for allene synthesis involved the formal insertion of a single carbon atom between the two carbon atoms of a C=C bond. In the laboratory this has been accomplished over two steps, the first of which is an addition of a dihalocarbene to an alkene. The resulting dihalocyclopropane is subsequently dehalogenated by treatment with an alkyllithium reagent at low temperature, leading to a “carbenacyclopropane”, which, because of its high strain energy, undergoes electrocyclic ring opening to the allene.

These two classical approaches for allene synthesis involve the deployment of either alkenes or alkynes as precursors. Strategically, they are functional group interconversions which require harsh reagents, and base-sensitive functionality in particular are not tolerated. In contrast, the present-day preferred methods of allene synthesis involve metal-catalyzed C–C bond-forming cross-coupling reactions. Not only do they generally take place under mild conditions, they can also be used *constructively*, to generate the C–C bond that connects the vinyl group with the allenyl group in a vinylallene, for example. Thus, the cross-coupling methods promote the invention of convergent synthetic pathways to precursors for Diels-Alder reactions. Moreover, they permit the generation of allenic precursors in enantiomerically-enriched form.

Another reason for the slow uptake of allenic precursors in Diels-Alder reactions relates to their undeserved reputation for being capricious. A consequence of concentrating a maximum number of π-electrons over a comparatively small number of carbon atoms is the generation of reactive species. Allenes, vinylallenes and the related through- and cross-conjugated molecules have, as this review has shown, an abundance of reactivity. Nonetheless, even the most reactive of the allenic substrates described in this review are, based upon our own experience, manageable compounds. The majority can be worked with in the same way as any other compound in synthesis. The challenging reputation concerning the handling of an allene, vinylallene and bisallene in the laboratory, in our opinion, erroneous.

Presently, the majority of reported Diels-Alder reactions involving allenes are focused on methodological contributions. Applications in total synthesis, materials and biology are comparatively rare. Looking forward, we feel that there are many valuable and thus far unexplored possibilities for allenic [4+2]cycloadditions in these and other fields. The high reactivity of allenes permits their participation in types of Diels-Alder additions that are either difficult to achieve – perhaps even unachievable, when using the corresponding alkenes and alkynes. The bourgeoning field of bioorthogonal reactions, of which uncatalyzed cycloadditions already play an important role, would benefit significantly from utilizing certain allenic precursors and their Diels-Alder processes.

Of the methodological contributions made so far, most of the reported examples are of the electron-deficient dienophile/electron-rich diene-type. Inverse electron demand allenic Diels-Alder reactions should be investigated more thoroughly.

In terms of mechanistic and physical organic studies, experimental investigations involving “hard” physical methods (e.g. gas phase electron diffraction for conformational information on dienes) are being gradually replaced by computational approaches. Nonetheless, a strong case can be made for more experimental studies into structure and reactivity (e.g. kinetics studies), since such data is both scarce and of great value.

We predict that the interest in allenic components in dehydro-Diels-Alder processes will continue to expand, as will the use of arenes as diene and dienophile components in allenic Diels-Alder reactions. The absence of target synthesis applications of these processes–arguably the ultimate test of any synthetic methodology–is an obvious opportunity for creative researchers in the field.

The authors believe that the concept of blending the chemical and structural properties of different π-systems, as shown with cross-conjugated systems, has a particularly bright preparative future. When both its constructive potential and scope are considered, the Diels-Alder reaction is the most powerful molecule-building reaction. In the era of synthetic efficiency and practicality, endeavors focusing on the invention of molecules that can rapidly build complex, target-relevant structures through domino sequences of this most powerful reaction are worthy of greater consideration.

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