Tetrahedron report number 552

Recent chemistry of benzocyclobutenes

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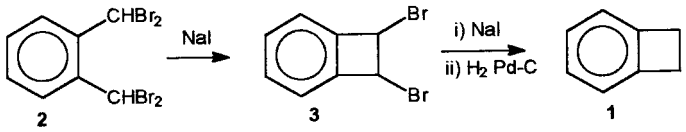
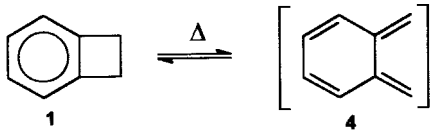


Scheme 1.

1. Introduction

The bicyclo[4.2.0]octa-1,3,5-triene **1**, often referred to (incorrectly) in the literature as benzocyclobutene (BCB), and its derivatives have a long and interesting history.[1] BCB **1** has also been named as benzocyclobutane, cardene, benzocyclobutene-1,2-dihydro, cyclobutabenzene and generically as cyclobutarene in the chemical literature. In 1909, Finkelstein reported the first authenticated preparation of BCB through 1,4-elimination in α,α,α′,α′-tetrabromo-*o*-xylene **2** with sodium iodide.[2] The work formed part of his doctoral thesis and was overlooked for decades as it was not published until 1959.[3] In 1956, however, Cava and Napier[4] prepared the parent BCB **1** from the dibromide **3** by catalytic hydrogenation and confirmed the earlier work of Finkelstein (Scheme 1).

BCB derivatives represent a unique class of reactive molecules because of the thermodynamic stability associated with the aromatic system and the kinetic reactivity of the strained cyclobutene ring. They are useful building blocks because of their ability to isomerize to *o*-xylylenes (e.g. **4**) upon thermal activation (Scheme 2). The ease with which *o*-xylylenes participate in inter- and intramolecular Diels–Alder reactions with various dienophiles makes BCBs useful as building blocks in the synthesis of complex polycyclic compounds. Jensen and Coleman were the first to carry out thermolysis of *trans*-1,2-diphenylbenzocyclobutene **5** in the presence of maleic anhydride to give the tetralin derivative **7** and suggested the intermediacy of *o*-xylylene (or *o*-quinodimethane) **6** (Scheme 3).[5] The driving force for these reactions is aromaticity recovery and Huisgen demonstrated that they generally proceeded in a stereoselective manner.[6] The thermolytic ring opening of BCBs occurs in a conrotatory manner in conformity with the predictions based on orbital symmetry rules.[7] Methods for the generation of *o*-xylylenes and their synthetic utility has been reviewed.[8]



Scheme 2.

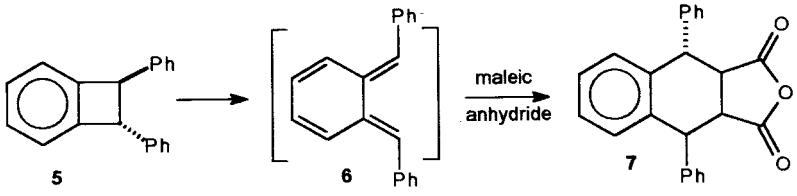
Over the years, BCBs have emerged as versatile chemical entities and their molecular structure, structural diversity, syntheses and chemical reactivity continue to engage the attention of organic chemists. More recently, BCBs have served as important building blocks for natural product syntheses and for new polymers and advanced materials. These developments and the future potential of BCBs have provided an impetus to present an overview of their chemistry and form the subject matter of this report.

1.1. Scope of the review

This review will cover aspects related to the synthesis, reactions and applications of BCBs and provide an overview of the existing literature with appropriate emphasis on recent examples. Various synthetic targets such as steroids, alkaloids, anthracyclines, organic derivatives of C_{60} and cyclophanes using BCBs as intermediates will be discussed. Although the recent examples are given more emphasis, earlier efforts are also included in order to provide a balanced overview of the topic. Several theoretically interesting molecules related to BCBs (e.g. extended biphenylene derivatives) are not included as these are discussed in a monograph[9] and a recent review.[10] For a comprehensive coverage of specific uses of BCBs in synthesis, the reader is referred to specialized review articles (e.g. *o*-xylylenes,[8] and BCBs in steroid[11] and polymer synthesis[12]).

1.2. Structure and reactivity aspects

The total energy of BCB **1** has been calculated employing different levels of theory and the values vary from 303.85332 to 308.57922 kcal/mol.[13] The structures of the ground states of **1** and **4** have been studied by ab initio SCF calculations and these confirmed that the open form **4** has pronounced single-bond/double-bond alteration in the hexagonal ring, whereas the bicyclic form **1** has a benzenoid structure.[14,15] The calculated energies indicate that BCB **1** is more stable than *o*-xylylene **4** by 55 KJ mol^{-1}. The microwave spectra of BCB and its deuterated species have been determined[16] and the ΔI values suggest that only four hydrogen atoms are located out of the molecular skeletal plane of **1**. A series of BCBs with increasing distortion have been computationally studied through Hartree–Fock calculations the 6-31G* level and the π electrons showing increasing stability relative to those in the corresponding



Scheme 3.

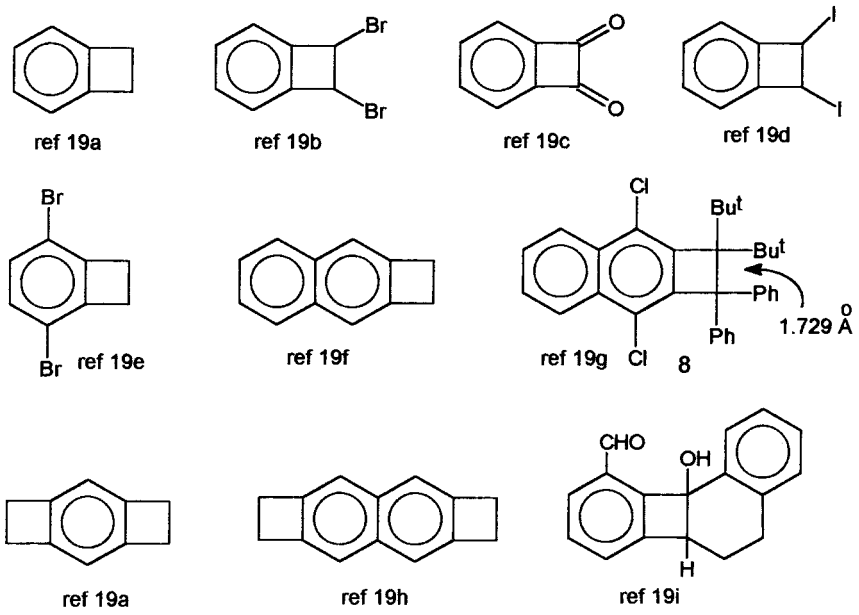


Figure 1. Some examples of BCB derivatives whose X-ray structures have been determined.

methyl-substituted benzene systems. This result is in accord with the photoelectron spectroscopic data and the notion that π electrons in benzene disfavor the symmetric structure.[17] EPR spectral evidence on 3,6-dimethyl-1,2,4,5-tetrahydrobenzobiscyclobutene and 3,4,5,6-tetramethyl-BCB shows that the Ψ_A MO lies above the Ψ_S MO and this observation is rationalized in terms of rehybridization of the arene carbon atoms imposed by ring strain.[18] X-Ray crystallographic analysis of BCB at −170°C shows an unusual structure and the bonds in the benzene ring adjacent to the annelated ring are shortened. Some other BCB derivatives the X-ray structures of which have been studied are tabulated in Fig. 1.[19] An extremely long C–C bond (1.729 Å) has been observed in (−)-1,1-di-*t*-butyl-2,2-diphenyl-3,8-dichlorocyclobuta[*b*]naphthalene **8**, and this is amongst the longest C–C bonds encountered to date.[19g]

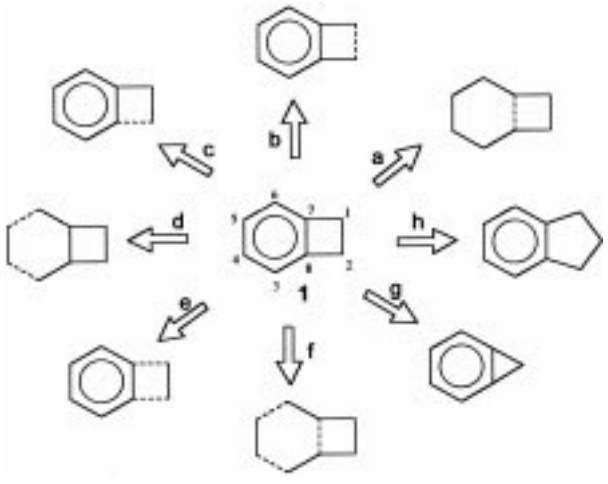


Figure 2. Various retrosynthetic approaches to BCB ring system.

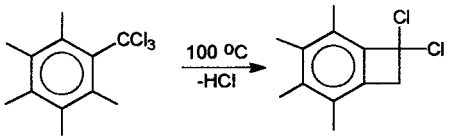
2. Preparation of benzocyclobutenes

Despite its reported preparation in 1909,[2] interest in BCB lay dormant for a long time. During the late 1950s, through the pioneering efforts of Cava and co-workers, several BCB derivatives became readily available for synthetic exploration. Subsequently, several groups became interested in BCBs and this resulted in diverse applications of these systems. Presently, several methods are available for the preparation of BCB derivatives and each of these have their own strength and limitation with regard to ease of preparation, availability of starting materials and adaptability to functionalization. Retrosynthetic approaches involving various C–C bond connectivity through which the BCB ring system can be constructed are shown in Fig. 2. These approaches are based on single-bond (a–c), two-bond (d, e), three-bond (f) disconnection and ring adjustment reactions (g, h) (Fig. 2). Most of these approaches (b, c, e, g, h) employ pre-formed benzene derivatives as starting materials. In the case of the two-bond disconnection approaches (d, e) either benzene or cyclobutane derivatives may be used. In the three-bond disconnection approach (f), however, both benzene and cyclobutane rings are formed simultaneously. Ring adjustment approaches involve either ring-contraction (h) or ring-expansion (g) tactics.

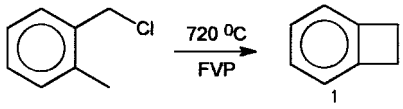
2.1. Elimination method

1,4-Elimination from suitably functionalized benzene derivatives offers the most convenient way to access BCBs and the original Finkelstein method,[1,3] as well as Cava and co-workers' preparation of the parent **1** from α,α,α′,α′-tetrabromo-*o*-xylene **2** followed this route.[4] A later modification has enabled large scale preparation of the parent BCB via two step 1,4-elimination and reductive dehalogenation.[20]

Polysubstituted trichloromethylbenzenes, when warmed

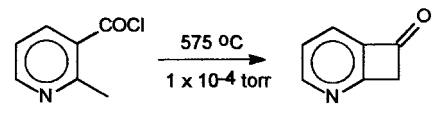


Scheme 4.

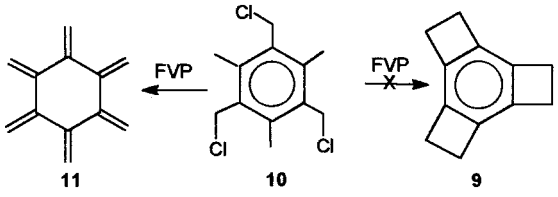


Scheme 5.

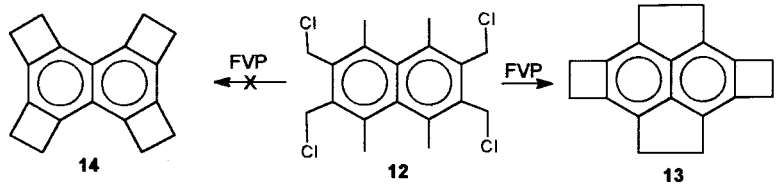
above their melting point, lose HCl to give 1,1-dichlorobenzocyclobutenes (Scheme 4).[21] This method has been extended and improved for the large scale preparation of BCB **1** under flash vacuum pyrolysis (FVP) (Scheme 5).[22–25] An interesting extension of this simple pyrolytic approach is the preparation of a pyridine analogue of BCB (Scheme 6).[26] The ready availability of starting materials, good yield and the stability of the four-membered ring under FVP conditions makes this pyrolytic route competitive with other synthetic methods for accessing a variety of highly functionalized BCBs. This procedure, however, could not deliver highly strained systems such as tricyclobutabenzene **9** from the commercially available 2,4,6-tris-(chloromethyl)-mesitylene **10** during FVP conditions and only hexaradialene **11** (60%) was formed (Scheme 7).[27a] The direction of the ring closure during 1,4-elimination is not always predictable and the tetrachloro-methylnaphthalene derivative **12** on FVP furnished cyclophane based BCB **13** instead of the expected **14** as shown in Scheme 8.[27b] Another interesting route to BCBs is through fluoride ion mediated 1,4-elimination in α,α′-dialkyl-*o*-[(trimethylsilyl)-methyl]benzyl-*p*-tolyl sulphones **15** to give α,α′-dialkylbenzocyclobutenes **16** (Scheme 9).[28]



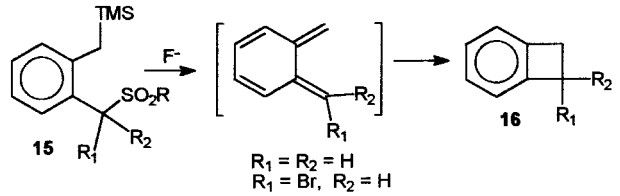
Scheme 6.



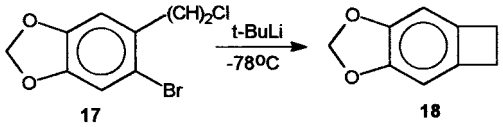
Scheme 7.



Scheme 8.



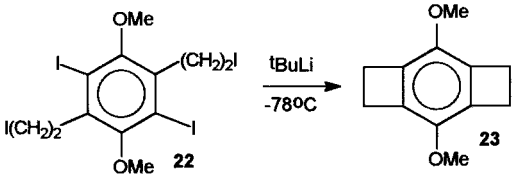
Scheme 9.



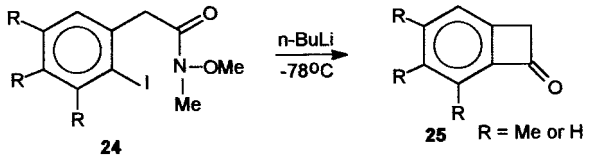
Scheme 10.

2.2. Parham cyclization

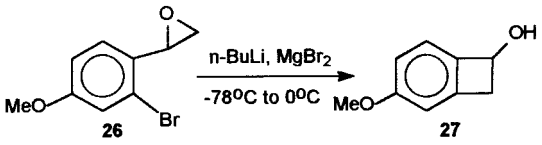
A simple method of general applicability for the preparation of BCBs involves intramolecular displacement via aryl anions (Parham cyclization). For example, the *o*-bromo-β-phenethyl chloride **17** on halogen-metal exchange gave the BCB derivative **18** in greater than 90% yield (Scheme 10).[29] The methodology can be conveniently applied to the preparation of substituted BCB derivatives (e.g. **19**, **20** and **21**).[30] The metalation-intramolecular displacement strategy has been adapted by Buchwald et al for the synthesis of **23** from **22** (Scheme 11).[31]



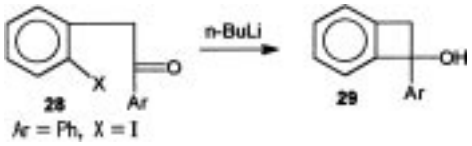
Scheme 11.



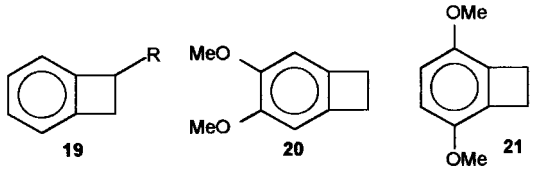
Scheme 12.



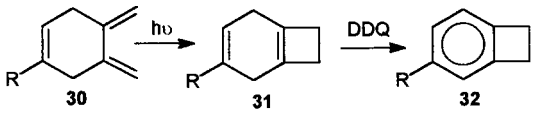
Scheme 13.



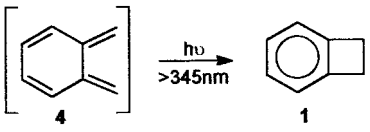
Scheme 14.



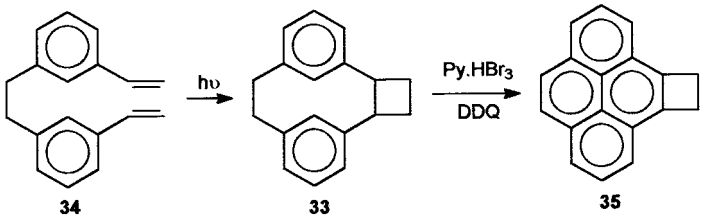
Lithium–iodine exchange-initiated cyclizations of *o*-iodo-*N*-methoxy-*N*-methyl phenylacetamides **24** provide a simple and efficient route to the benzocyclobutenones **25** (Scheme 12).[32] A slight variation of the above strategy involves treatment of the *o*-bromostyreneoxide **26** with *n*-BuLi to generate the BCB ring system **27** (Scheme 13).[33] Lithium–halogen exchange with *n*-BuLi has been achieved in **28** even in the presence of a carbonyl group to provide an entry into 1-arylbenzocyclobutenols **29** (Scheme 14).[34]



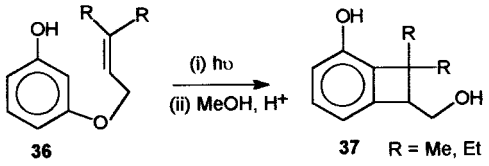
Scheme 15.



Scheme 16.



Scheme 17.



Scheme 18.

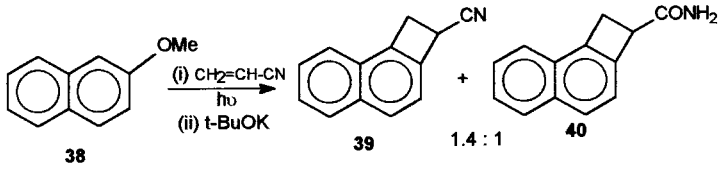
2.3. Photochemical approaches

Both inter- and intramolecular [2+2] photocycloaddition-based approaches have been employed for the synthesis of BCBs. For example, the diene **30**, readily undergoes an intramolecular [2+2] photocycloaddition reaction to generate the bicyclic system **31** which on further oxidation with DDQ gives the BCB derivative **32** (Scheme 15).[35] Irradiation of **4** ($\lambda > 345$ nm) at 77 K resulted in the formation of BCB **1** (Scheme 16).[36] Nishimura and co-workers prepared dihydrocyclobuta[e]pyrene **35** starting from the bis-styrene derivative **34**, via **33** employing an intramolecular [2+2] photocycloaddition as a key step (Scheme 17).[37] Another interesting approach to substituted BCBs is through intramolecular [2+2] photocycloaddition in 3-alkylphenols **36** followed by hydrolysis to yield functionalized benzocyclobutene derivatives **37** (Scheme 18).[38]

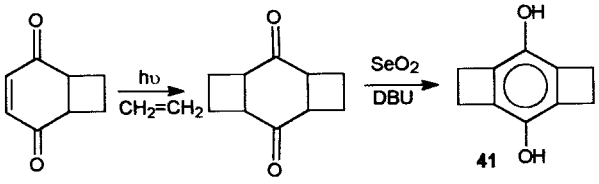
Intermolecular [2+2] photocycloaddition between β-methoxynaphthalene **38** and acrylonitrile furnished a tricyclic compound which upon base treatment gave the naphthocyclobutene derivatives **39** and **40** (Scheme 19).[39] Oda and co-workers have reported the synthesis of 3,6-dioxygenated BCB derivatives such as **41** using [2+2] photocycloaddition as a key step (Scheme 20).[40]

Intramolecular [2+2] photocycloaddition via a photo-enolization strategy has been employed for the preparation of various BCB derivatives. For example, the highly functionalized BCB derivatives **44** were obtained by the irradiation of *o*-alkyl substituted aromatic aldehydes or ketones **42**, which can undergo photo-enolization via a photochemical [1,5]-hydrogen shift to **43** followed by intramolecular cycloaddition (Scheme 21).[41] Irradiation of *o*-alkylphenyl 1,3-diketones **45** gave the benzocyclobutenols **46** via a Norrish-type photochemical reaction and these aldol intermediates underwent thermal retro-aldol cleavage to yield the benzocyclobutenones **47** (Scheme 22).[41]

The photochemically induced Wolff rearrangement has proved to be an excellent method for the preparation of BCB derivatives- by a ring contraction protocol- which are otherwise difficult to prepare. Thus, the α-diazo-indanones **48** undergo a ring contraction reaction under a



Scheme 19.



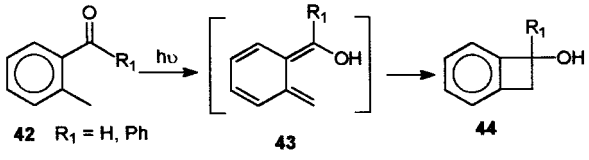
Scheme 20.

suitable irradiation regime to give the benzocyclobutenecarboxylic acids **49** (Scheme 23).[42] This photochemical ring contraction method allows a great variety of BCB carboxylic acids to be prepared. Interestingly, the diazoketone **50**, under photochemical conditions, gave only the undesired ring-opened products presumably via the benzocylobutene intermediate **51**. Wolff rearrangement under thermal conditions formed **51**, however, without any complications (Scheme 24).[43] It was claimed that this was the first example of the formation of a strained ring system via uncatalysed thermal Wolff rearrangement.

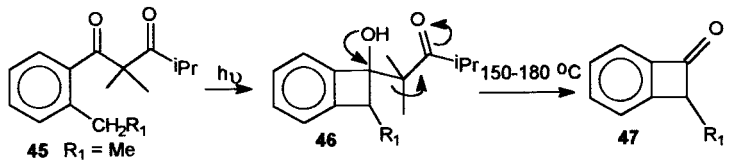
Photodecarbonylation of 2-indanone derivatives has proved to be a useful route to benzocyclobutene-1,2-dione **52** (Scheme 25).[44] The preparation of *trans*-1,2-diphenylbenzocyclobutene **5** is possible via a decarbonylation route (Scheme 26).[45]

2.4. Extrusion reactions

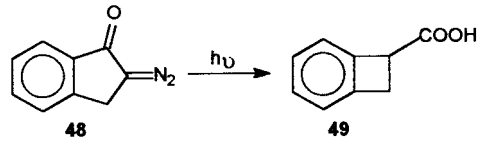
Several approaches towards BCB **1**, employing a thermally induced extrusion reaction as the key step, have been explored and these are summarized in Scheme 27.[46] Thus, the tellurophene **53** on FVP gave BCB 1 in 70% yield. Similarly, 3-isochromanone **54** and the sulfone **55** gave **1** by extrusion of CO_2 and SO_2, respectively. Thermal extrusion of sulfur dioxide from 2,5-dihydrobenzothiophene-2,2-dioxides finds many applications in BCB chemistry. This



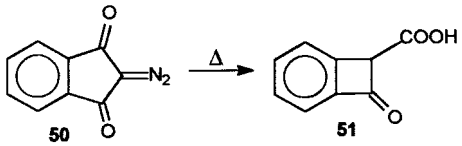
Scheme 21.



Scheme 22.



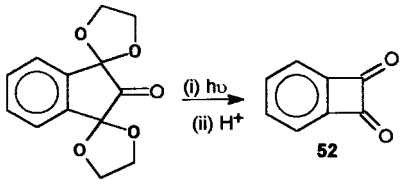
Scheme 23.



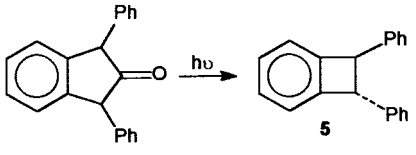
Scheme 24.

reaction presumably occurs via the ring closure of thermally generated *o*-quinodimethane intermediates. Since sulphones can be readily alkylated,[47] several polycyclic molecules may be prepared by adapting this technology and trapping the *o*-xylylene intermediates using an intramolecular Diels–Alder reaction.[48]

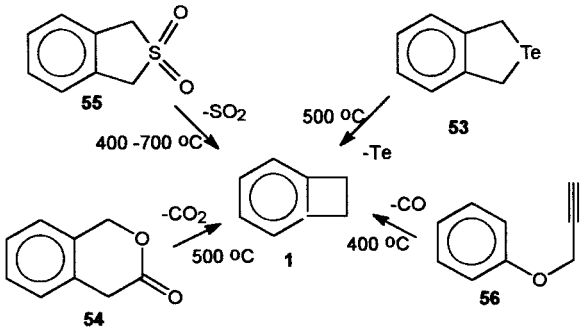
BCBs with oxygenated substituents on the aryl ring can also be efficiently prepared by an extension of this SO_2 extrusion methodology. When the trisulphone **57** was subjected to FVP conditions, however, hexaradialene **11** was obtained



Scheme 25.



Scheme 26.



Scheme 27.

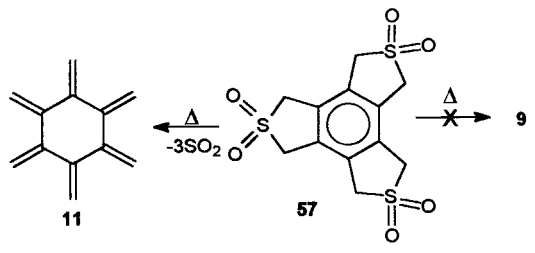
instead of the targeted tricyclobutabenzene **9** (Scheme 28).[49] An interesting thermal route to BCB 1 is via the pyrolysis of phenyl propargyl ether **56** involving the extrusion of CO (Scheme 27).

2.5. Diels–Alder reaction based approaches

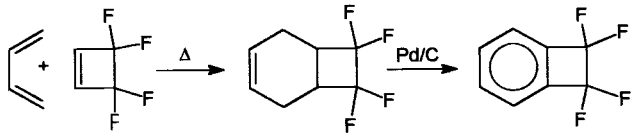
The synthesis of fluorinated BCB derivatives has been reported through the dehydrogenation of the bicyclo-[4.2.0]octane system, obtained by a Diels–Alder reaction between butadiene and cyclobutene (Scheme 29).[50] A similar procedure was adopted to prepare the more embellished 3,6-dimethyl-4,5-dicarbomethoxy-benzocyclobutene **58** (Scheme 30). This methodology which involves aromatization of compounds with fused cyclobutene rings seems to be well suited for condensed polycyclic aromatic compounds containing multiple fused cyclobutane rings. Milder reaction conditions used here allow the preparation of the highly strained tricyclobutabenzene **9**, which is not readily accessible by other methods (vide supra) (Scheme 31).[51] Diels–Alder reaction of 3-chloro-3-cyclobutene-1,2-dione **59** with 1,3-butadiene derivatives followed by oxidation gave benzocyclobutenediones **52** (Scheme 32).[52]

2.6. Benzyne intermediates

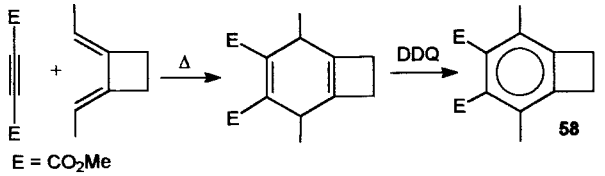
Conceptually, the synthesis of BCBs from aromatic precursors can be envisaged via [2+2] cycloadditions between a benzyne intermediate and an alkene and this approach has found much favor for the synthesis of these compounds.[53] In order to circumvent the use of diazonium salts as benzyne precursors, a metal–halogen exchange process has been employed in both the inter- and intramolecular modes to generate aryne intermediates. Suzuki and co-workers have reported a high yield synthesis of the benzocylobutenone **62** involving [2+2] cycloaddition of the ketene silyl acetals **61** and the aryne generated from *ortho*-haloaryl triflates **60** (Scheme 33).[54] An intramolecular version of this aryne



Scheme 28.



Scheme 29.

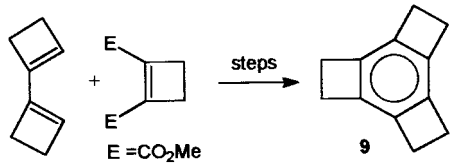


Scheme 30.

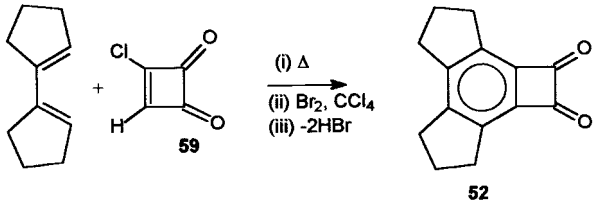
route has been used extensively by Kametani's group in preparing precursors for natural product syntheses. Treatment of the nitrile **63** with sodium amide gave the BCB derivative **64** (Scheme 34). The cyano group in the BCB **64** can be manipulated into a variety of functionalities for further appending the dienophile portion.[55]

2.7. [2+2+2] Cycloaddition approaches

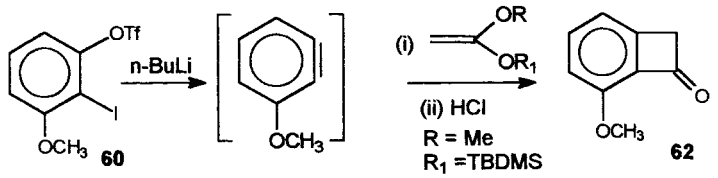
Vollhardt and his co-workers have pioneered a novel methodology for the synthesis of silyl substituted BCB derivatives which involves the cyclotrimerization of bis(trimethylsilyl)acetylene (BTMSA) with 1,5-hexadiyne in the presence of a catalytic amount of $C_pCo(CO)_2$ (Scheme 35).[56] In this method, the six-membered ring is constructed via a cobalt catalysed cyclization in which the four-membered ring arises through the appropriate choice of the diyne substrate. The presence of the bulky TMS group in BTMSA helps to prevent alkyne self-trimerization. The advantage of this method is that the silyl groups provide a good handle for the introduction of various substituents in the benzene ring through electrophilic aromatic substitutions. In the course of preparing novel polyurethanes bicapped with a BCB moiety, 4-(benzocyclobutenyl)methanol **66** was prepared by Farona et al from the suitably protected monoalkyne **65** and 1,5-hexadiyne (Scheme 36).[57] Recently, this methodology has been used for the



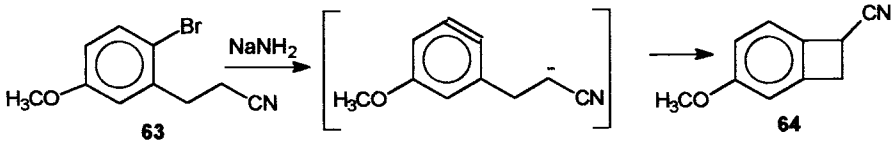
Scheme 31.



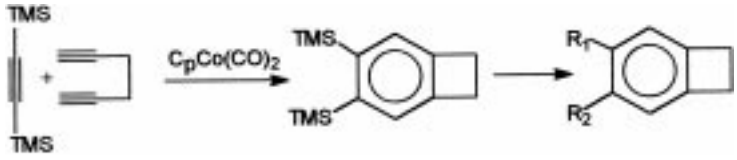
Scheme 32.



Scheme 33.



Scheme 34.

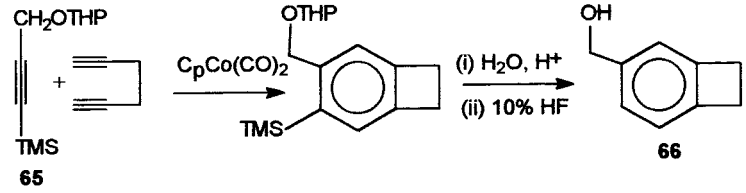


Scheme 35.

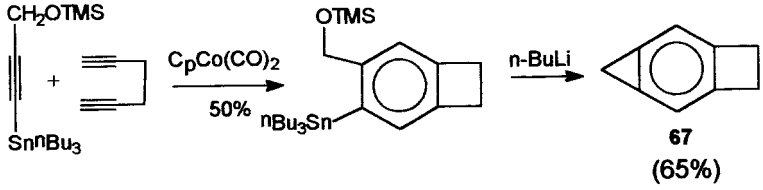
improved preparation of cyclopropa[4.5]benzocyclobutene **67** (rocketene) (Scheme 37).[58]

2.8. Ring expansion methods

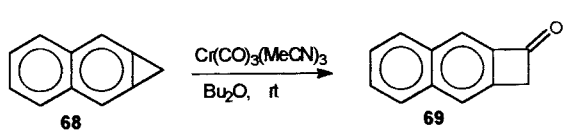
BCBs have been prepared from benzocyclopropene-related substrates through ring expansion. For example, the reaction of 1*H*-cyclopropa[*b*]naphthalene **68** with tris-(acetonitrile)-tricarbonylchromium affords cyclobutanaphthalenone **69** in 57% yield (Scheme 38).[59] This reaction proceeds through oxidative addition of the metal to the cyclopropene ring followed by CO insertion into the C–Ar–Cr bond and reductive elimination of the metal. Formation of a 1,1-dihalobenzocyclobutene **70** has been observed during the reaction between benzocyclopropene and the dihalocarbene (Scheme 39).[60] Since benzocyclopropene derivatives are difficult to prepare, this method may not be useful from a preparative point of view. Another sequence involving dihalocarbene intermediates and leading to BCB derivatives is shown in Scheme 40.[61] In a related sequence,



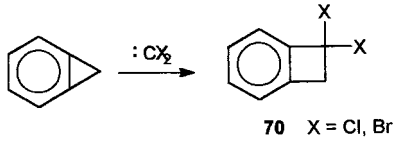
Scheme 36.



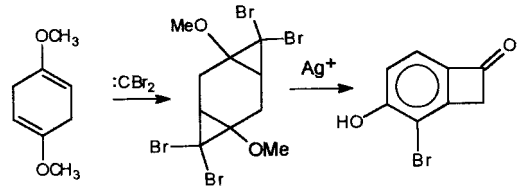
Scheme 37.



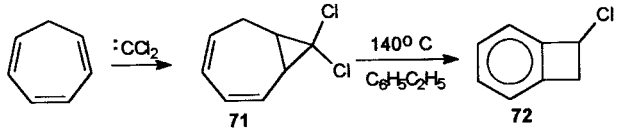
Scheme 38.



Scheme 39.



Scheme 40.



Scheme 41.

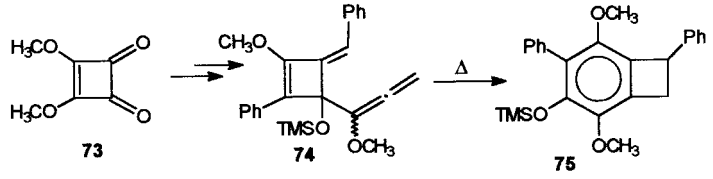
1-chlorobenzocyclobutene **72** was prepared from cycloheptatriene through its dihalocarbene adduct **71** and further rearrangement (Scheme 41).[62]

2.9. Allene intermediates

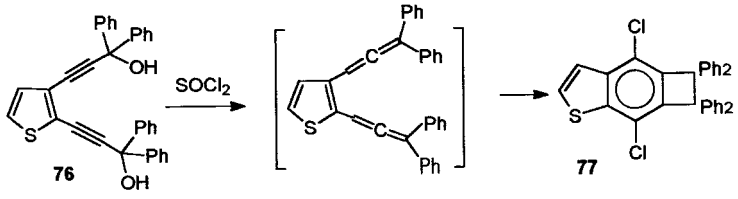
Recently, ring expansion of 3-alkylidene-4-allenylcyclobutenones **74** has been shown to provide a route to highly functionalized BCB derivatives **75**. The starting allenyl substituted alkylidenecyclobutenes originate from dimethylsquarate **73** (Scheme 42).[63] Another route via 6π-electron cyclization of *o*-diallenyl-arenes and -heteroarenes for the synthesis of the BCB derivatives **77** has been reported by Toda and co-workers involving the thermal cyclization of the enediynediol **76** (Scheme 43).[64] 1,2-Diphenylnaphtho[b]cyclobutene **79** has been prepared from *o*-bis(α-acetoxypropargyl)benzene derivatives **78** through SmI_2 mediated coupling in the presence of a Pd(0) catalyst and involving an *o*-diallenylarene intermediate (Scheme 44).[65]

2.10. Miscellaneous methods

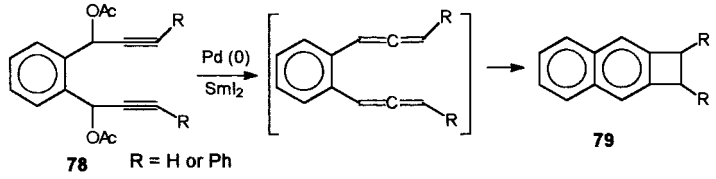
Cyclodimerization of polyhalogenated 2-phenyl- and 2-pentachlorophenyl-substituted butenynes **80** under thermal conditions furnishes the bicyclo[4.2.0]octane derivative which can be further hydrolysed/aromatized to the benzocyclobutenones **81** (Scheme 45).[66] An apparently general and regioselective synthesis of substituted benzocyclobutenediones **84** has been reported via palladium-catalysed coupling of a variety of 4-chlorocyclobutenones **82** with the tributylstannylcyclobutenone derivative **83** followed by hydrolysis (Scheme 46).[67] Some of the BCB derivatives prepared by this route are not accessible by other



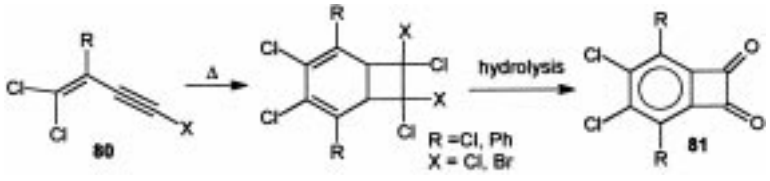
Scheme 42.



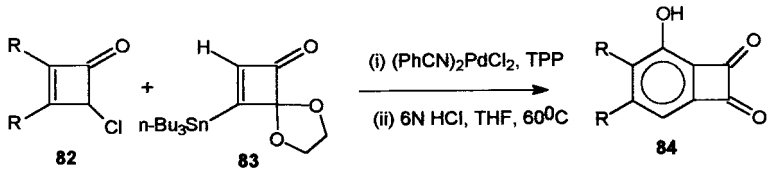
Scheme 43.



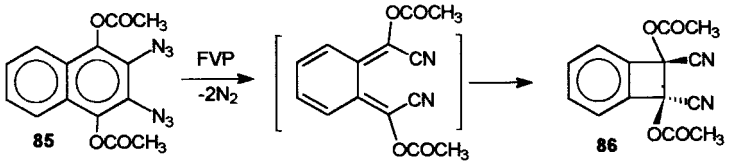
Scheme 44.



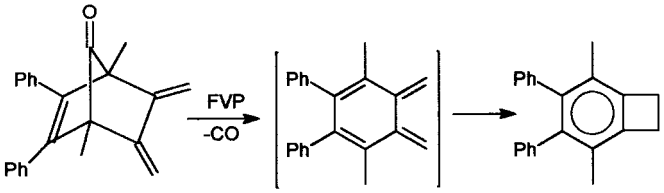
Scheme 45.



Scheme 46.



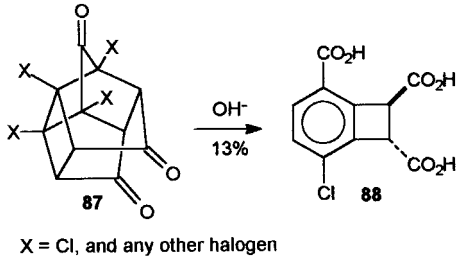
Scheme 47.



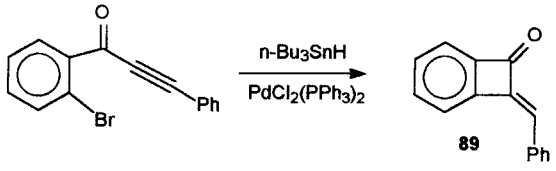
Scheme 48.

known routes. *trans*-1,2-Dicyanobenzocyclobutene **86** has been reported through FVP of 2,3-diazidonaphthalene **85** (Scheme 47).[68] Another FVP-based method leading to a BCB derivative, which involves decarbonylation of a norbornenone derivative, has been reported by Warrener and co-workers (Scheme 48).[69] An unusual uncaging of the caged trione **87** leading to the BCB derivative **88** has been observed during an attempted base-mediated Favorskii rearrangement (Scheme 49).[70]

The formation of a BCB derivative **89** involving radical cyclization as a key step is shown in Scheme 50.[71] Palladium-catalyzed reaction of 1,4-dibromobenzene with bicyclo[2.2.1]hept-2-ene led to the observation of products



Scheme 49.



Scheme 50.

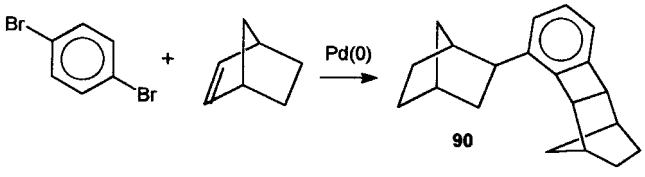
bearing a BCB moiety **90** derived from the insertion of norbornene into the aryl-palladium bond (Scheme 51).[72]

3. Reactions of benzocyclobutenes

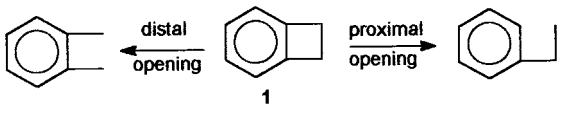
The chemical reactivity of a BCBs can be manifested through either of the two rings. While the six-membered ring, as expected, exhibits reactions characteristic of an aromatic compound, the strained cyclobutane ring is prone to ring cleavage reactions. Alternatively, the ring opening of BCB to *o*-quinodimethane or *o*-xylylene intermediates provides the opportunity to explore its rich cycloaddition chemistry.

3.1. Cyclobutane ring cleavage reactions

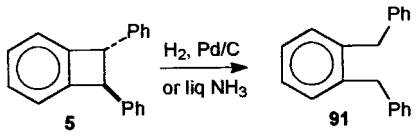
The cyclobutane ring in BCB can be opened by proximal ring opening or by distal ring opening (Scheme 52). Thus, distal C–C bond cleavage was observed during the Birch



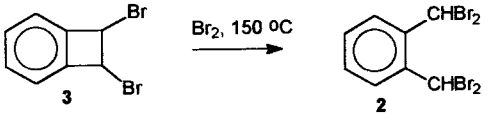
Scheme 51.



Scheme 52.



Scheme 53.

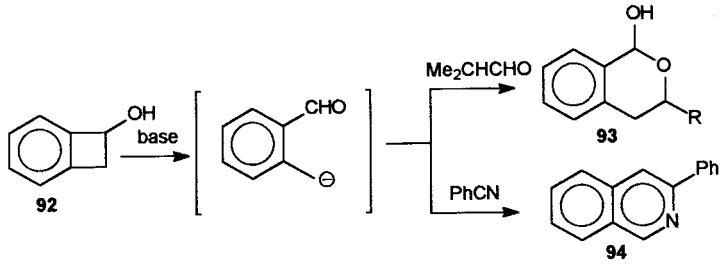


Scheme 54.

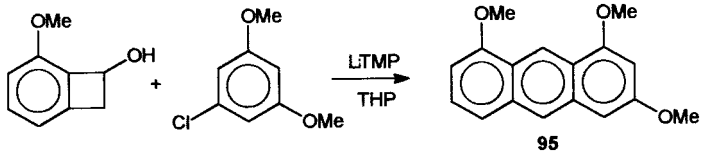
reduction of *trans*-1,2-diphenyl BCB **5** to give the *o*-dibenzyl derivative **91** as shown in Scheme 53.[5] Similarly, in the addition of bromine to the BCB dibromide **3**, distal cyclobutane bond cleavage led to the *o*-xylene tetrabromide **2** (Scheme 54).[2] One of the early examples of distal C–C bond cleavage in BCBs was the base-mediated opening of benzocyclobutenols. Deprotonation of the benzocyclobutenol **92** leads to *o*-tolualdehyde anions which can be trapped by electrophiles such as aldehydes and nitriles to furnish the benzopyranols **93** and isoquinolines **94**, respectively (Scheme 55). The benzopyranols **93** can be easily oxidized to 3-substituted isocoumarins[73] and this methodology has been applied to the synthesis of 3,4-dihydroisocoumarin natural products. *o*-Tolualdehyde anions in the presence of nitriles cyclize to 3-substituted isoquinoline derivatives **94** which are not readily accessible through standard Bischler–Napieralski isoquinoline synthesis.[74] Recently, Olofson and co-workers have reported the preparation of various unsymmetrical anthracenes such as **95** by simultaneously generating the *o*-tolualdehyde anion and the benzyne intermediate from benzocyclobutenols and halogenated aromatic compounds, respectively, in the presence of lithium 2,2,6,6-tetramethylpiperidine (Li-TMP) (Scheme 56).[75] Exposure of the BCB derivative **96** bearing a tertiary hydroxy group to base furnished a distal ring-opened product **97** (Scheme 57).[76] Interestingly, the regiochemistry of cyclobutane ring cleavage was reversed in the case of the tricarbonylchromium(0) complex **98** of **96** and the proximal bond cleavage product **99** was observed (Scheme 58).

Distal C–C bond cleavage is also encountered in the benzocyclobutenone **100** which on exposure to sodium hydride gave the dimer **101** as the major product (Scheme 59).[77] In the presence of Li-TMP and an aromatic aldehyde, however, the benzocyclobutenone undergoes proximal C–C bond cleavage and subsequent reaction with aldehyde gives the isochroman-3-one **102** in high yield.[78]

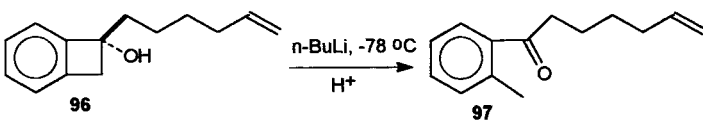
BCB **1**, on the other hand, is known to undergo a proximal ring-opening reaction on treatment with sodium-potassium



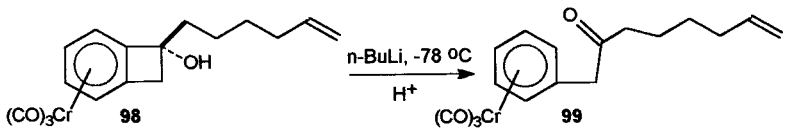
Scheme 55.



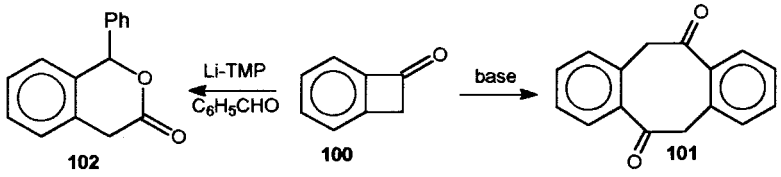
Scheme 56.



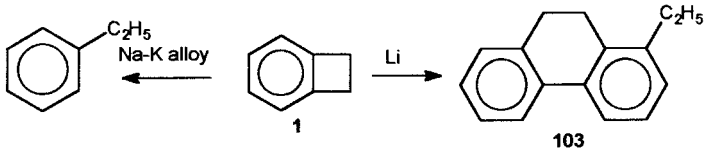
Scheme 57.



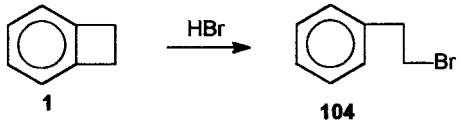
Scheme 58.



Scheme 59.

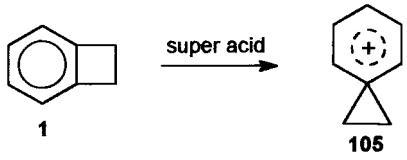


Scheme 60.



Scheme 61.

alloy in THF.[79] The reaction with lithium, however, takes a more complex course and gave 1-ethyl-9,10-dihydrophenanthrene **103** via a dimerization pathway (Scheme 60).[80] Interestingly, HBr readily opens the four-membered ring of **1** at the proximal C–C bond site to furnish phenylethyl bromide **104** (Scheme 61).[81]

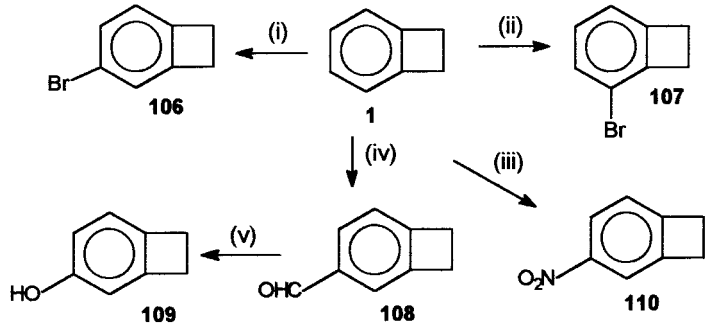


Scheme 62.

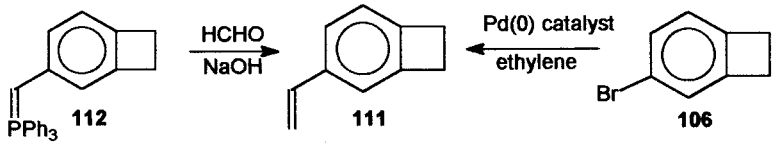
3.2. Electrophilic aromatic substitution reactions

BCBs exhibit varying stability and susceptibility towards protic acids. For example, BCB remains unchanged on exposure to concentrated HCl but readily forms a viscous polymer with concentrated H_2SO_4 or liquid HF. When electron withdrawing groups are present on the BCB ring, its stability towards strong protic acids is shown to be excellent.[19e] This aspect is important because some BCB derivatives could be used in the synthesis of high-performance polymers requiring strong acids and high temperatures. In a super acid medium ($HF–SbF_5/SO_2ClF$, −90°C), BCB rearranges to a stable phenonium ion **105** (Scheme 62).[82]

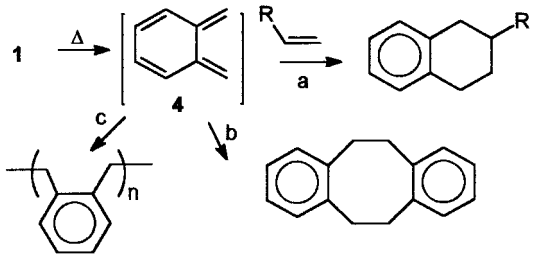
Classical electrophilic substitution reactions have been exploited to prepare aryl-substituted BCBs as shown in Scheme 63. For example, direct bromination of BCB **1**



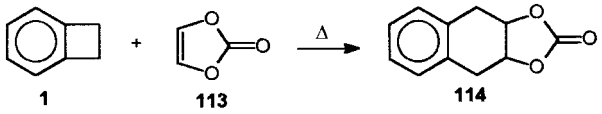
Scheme 63. (i) Br_2, I_2 (cat), AcOH; (ii) *n*-BuLi/TMEDA, TMSCl, Br_2; (iii) K-10 clay, Ac_2O, HNO_3; (iv) $TiCl_4$, $Cl_2CHCOCH_3$; (v) permonophosphoric acid.



Scheme 64.



Scheme 65.

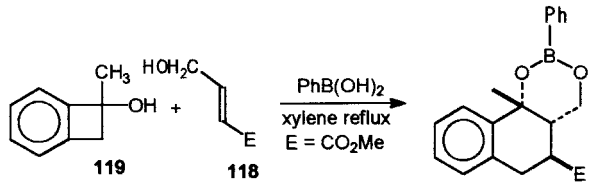


Scheme 66.

gives 4-bromobenzocyclobutene **106**, whilst 3-bromobenzocyclobutene **107** could be prepared in an indirect manner using metalation as the key step.[83] Although the metalation reaction does not give very high yields, this procedure is useful for the preparation of various 3-substituted BCBs. Formylation of BCB gave **108** which upon further BV oxidation was transformed to the corresponding phenol **109**.[84] Nitration of BCB **1** using acetyl nitrate (generated in situ by a continuous process) in the presence of a montmorillonite K-10 clay catalyst gave 4-nitro BCB **110** in 60% yield which is a two-fold increase over known methods.[85] Substituted BCBs obtained by electrophilic substitution are precursors of industrially important products. For example, the vinyl BCB derivative **111**, which is an important building block for high performance T_g-thermoset polymers, is accessed from either 4-bromo BCB **106** via Pd(0) mediated Heck coupling or through Wittig olefination of the ylide **112** (Scheme 64).[86]

3.3. Thermally induced reactions

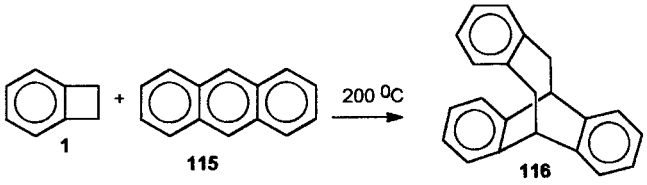
BCB undergoes three types of reactions under thermal activation. It is well established that BCBs readily isomerize to *o*-xylylene **4**, which can be trapped with various dienophiles in inter- and intramolecular fashion to generate various polycyclic systems (path a, Scheme 65). *o*-Xylylene intermediates in the absence of dienophiles dimerize or polymerize. The dimerization process has been employed



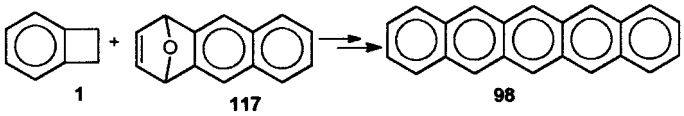
Scheme 69.

for the preparation of cyclophanes from suitably substituted benzocyclobutene precursors (path b). Alternatively, polymerization (path c) constitutes an important route for the synthesis of high performance polymers for applications in the electronics and aerospace industries. The fate of *o*-xylylene in the absence of other co-reactive species appears to depend to a large extent upon the conditions under which it is generated.

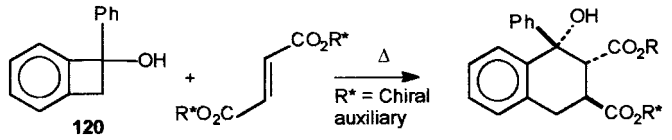
A range of dienophilic partners engage BCBs via their *o*-xylylene intermediates in [4+2] cycloadditions. A few representative examples will be discussed here. Addition of BCB to vinylene carbonate **113** and anthracene **115** leads to Diels–Alder adducts **114** (Scheme 66) and **116** (Scheme 67), respectively.[87–88] The cycloaddition of *o*-xylylene to an arene 1,4-oxide **117** was used to construct a linear arene array (Scheme 68).[89] Phenylboronic acid has been used as a template in the Diels–Alder reaction between methyl 4-hydroxy-2-butenoate **118** and the α-hydroxy-*o*-xylylene intermediate generated from the benzocyclobutenol **119** by thermolysis (Scheme 69).[90] Charlton et al have described a highly diastereoselective Diels–Alder addition between the α-hydroxy-*o*-xylylene derived from **120** and a fumaric acid diester bearing a chiral auxiliary (Scheme 70).[91] Keay and co-workers have reported that 1-methoxybenzocyclobutenes such as **121** are good substrates for the preparation of highly functionalized naphthalene derivatives **122** via [4+2] cycloaddition (Scheme 71).[92] Recently, a polymer-supported BCB derivative **123** bearing a traceless linker has been shown to undergo Diels–Alder reactions with homo- and heterodieneophiles. The adducts formed may be cleaved from the solid support in both reductive and C–C bond forming modes (Scheme 72).[93] Intramolecular [4+2] cycloadditions of BCBs via *o*-xylylene intermediates proceed in a very facile manner and, later in this review, several applications of this protocol to natural product synthesis will be described.



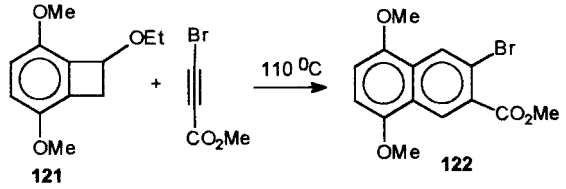
Scheme 67.



Scheme 68.

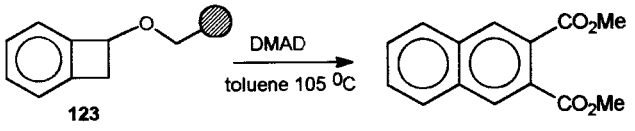


Scheme 70.



Scheme 71.

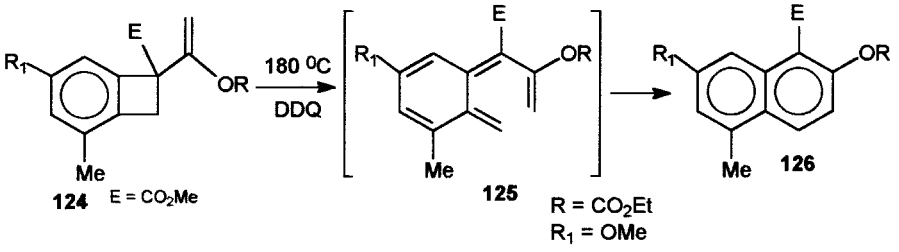
BCB-derived *o*-xylylene intermediates bearing an additional conjugating 2π component on thermal activation exhibit a propensity towards 6π electrocyclization to generate six-membered rings. Fukumoto and co-workers have reported[94] the construction of the naphthalenic portion **126** of the antitumor antibiotic neocarzinostatin employing an electrocylic reaction of the intermediate *o*-xylylene **125** derived from the BCB derivative **124** as the key step (Scheme 73). A similar strategy has been employed for the synthesis of naproxen (Scheme 74).[95] α-Tetralones such as **129** are prepared from the benzocyclobutenol **127** via a sequential thermal electrocyclic reaction of the intermediate **128** (Scheme 75).[96] Under thermal activation, the benzocyclobutenyl ketone oximes **130** gave 3,4-disubstituted isoquinolines **132** via *o*-xylylene intermediates **131** (Scheme 76).[97]



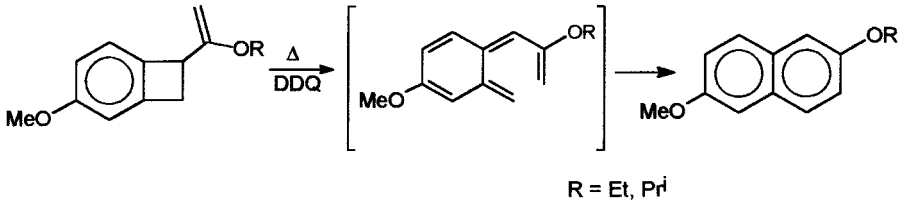
Scheme 72.

3.4. Photochemical reactions

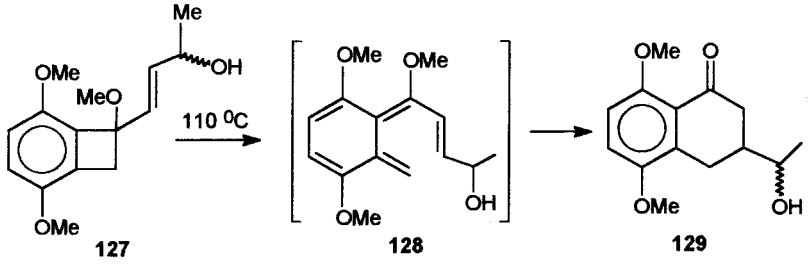
Irradiation of the parent BCB **1** in pentane solution at 254 nm yields two dihydropentalenes **133** and **134** (Scheme 77).[98] In the irradiation of substituted BCBs, however, electrocyclic ring opening to *o*-xylylene is the major pathway. Thus, the photo-induced cycloaddition of *cis*-1,2-diphenyl BCB **135** to tetracyanoethylene to furnish the [4+2] cycloaddition product **136** has been reported (Scheme 78).[99] *cis*-1,2-Diphenyl BCB **135** on irradiation in the presence of 9,10-dicyanoanthracene gave significant



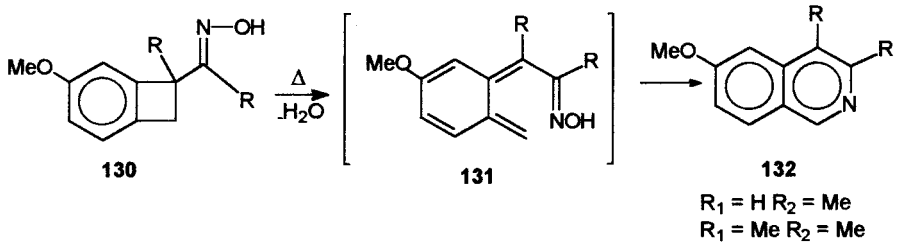
Scheme 73.



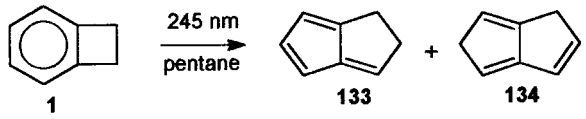
Scheme 74.



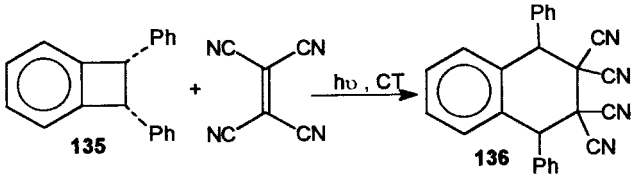
Scheme 75.



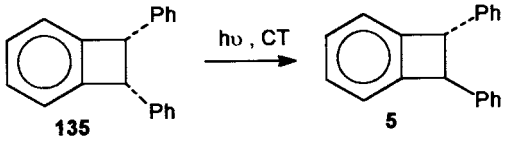
Scheme 76.



Scheme 77.



Scheme 78.

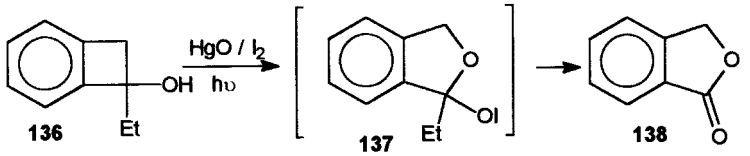


Scheme 79.

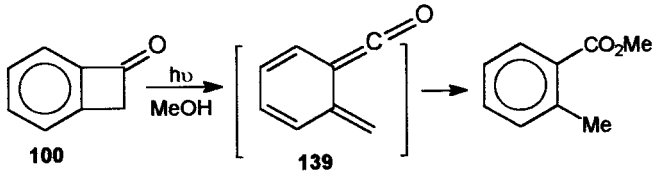
amounts of *trans*-diphenyl BCB **5** via the corresponding *o*-xylylene intermediate (Scheme 79). Kobayashi et al have reported a general method for the synthesis of the phthalides **138** from BCB derivatives. This methodology involves regioselective single or double β-scission of the alkoxy radicals generated by photolysis of the hypoiodite **137** of 1-ethyl-benzocyclobuten-1-ol **136** (Scheme 80).[100–101] Lastly, irradiation of the benzocylobutenone **100** in methanol gave the methyl benzoate as the major product, presumably involving the ketene intermediate **139** (Scheme 81).[26,102]

3.5. Oxidation and reduction reactions

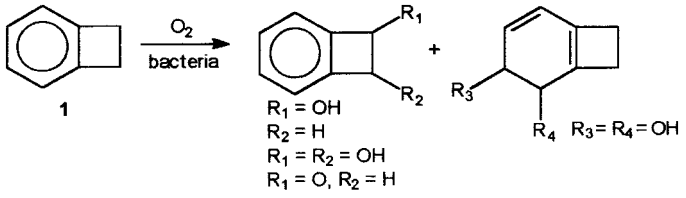
BCB 1 shows a unique reactivity towards the soil bacterium *Pseudomonas putida* when compared to other benzocycloalkenes. Biotransformation of BCB gave monooxygenation, dioxygenation and trioxygenation products involving a complex metabolic profile (Scheme 82).[103] Oxidation of BCB by intact cells of *Pseudomonas fluorescens* 127-68 XVII, containing naphthalene dioxygenase, yielded exclusively the benzylic oxidation products, benzocyclobutene-1-ol **92** and benzocyclobutene-1-one **100**.[104] No evidence for the incorporation of oxygen into



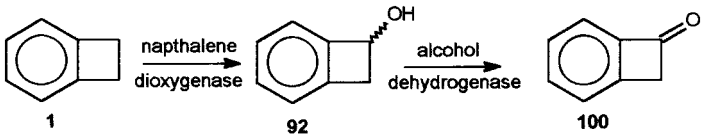
Scheme 80.



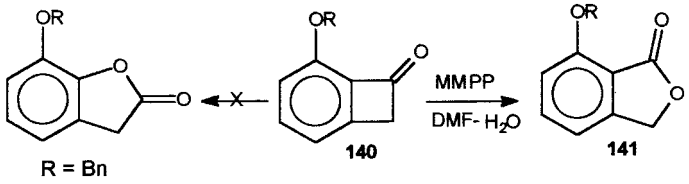
Scheme 81.



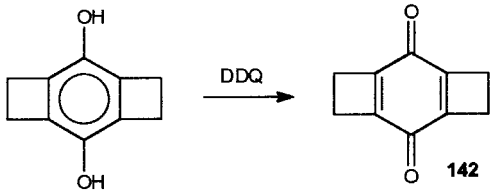
Scheme 82.



Scheme 83.

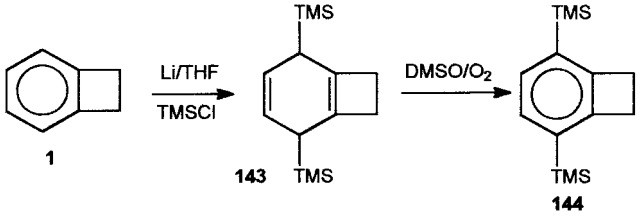


Scheme 84.



Scheme 85.

the aromatic ring was found (Scheme 83). Bayer–Villiger oxidation of benzocyclobutenones such as **140** proceeds with rigorous regioselectivity to give the phthalides **141** in high yield (Scheme 84).[105] DDQ was found to be a useful oxidizing reagent to generate the dicyclobuta-*p*-benzoquinone derivative **142** (Scheme 85).[40]

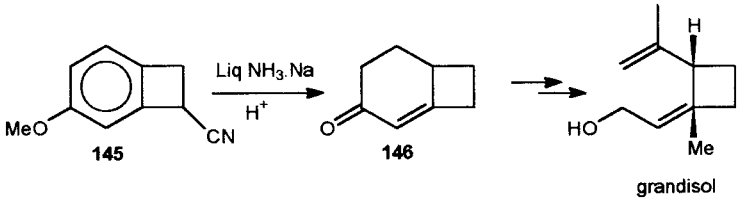


Scheme 86.

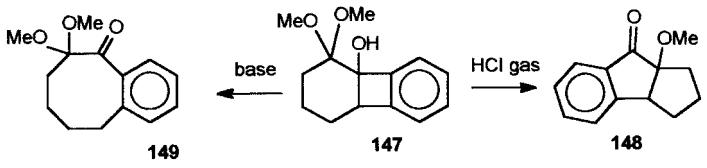
The arene ring of BCBs undergoes Birch reduction along the expected lines. Reductive silylation of BCB **1** under Birch reduction conditions or on electrochemical reduction gives the unsaturated derivative **143** which on rearomatization in air gave the 3,6-bis-(trimethylsilyl) BCB derivative **144** (Scheme 86).[23] Birch reduction of **145** was a key step in the synthesis of grandisol (Scheme 87). The aromatic ring in the BCB derivative **145** was reduced to the bicyclic enone **146** and further elaborated to grandisol via ring cleavage reactions.[106]

3.6. Ring adjustment reactions

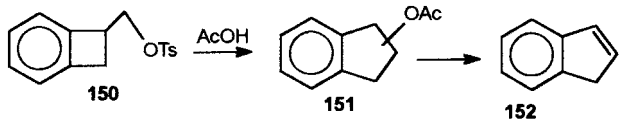
Appropriately substituted BCBs can be restructured through ring expansion and ring contraction protocols. Thus, the benzocyclobutenol **147** can be either converted to the indanone **148** on treatment with protic acids or to the benzocyclooctenone **149** by base (Scheme 88).[107] Solvolysis of benzocyclobuten-1-ylcarbinyl toluenesulfonate **150** results in ring expansion to indene **152** via the intermediate **151** (Scheme 89).[108] Similarly, the benzocyclobutenyl alcohol **153** rearranges to the indane derivative **154** when reacted with SO_2Cl (Scheme 90).[109] 8-Hydroxy-4a,5,8,8a-tetrahydrobiphenylene-5-carboxylic acid **155** undergoes an acid-catalyzed rearrangement to give the bridged benzocycloheptane derivative **156**. Interestingly, no products derived from the thermodynamically favored benzylic cation could be found (Scheme 91).[110]



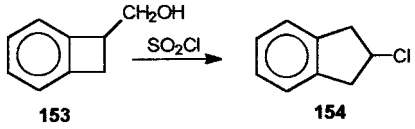
Scheme 87.



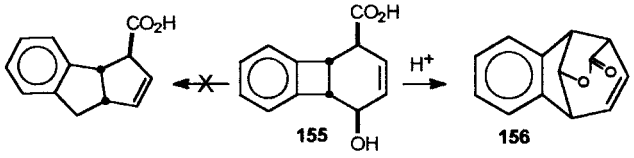
Scheme 88.



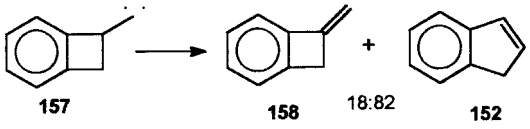
Scheme 89.



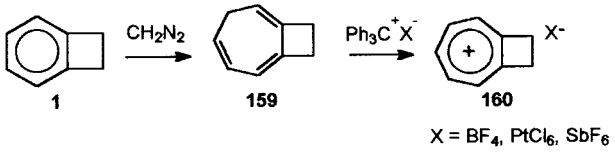
Scheme 90.



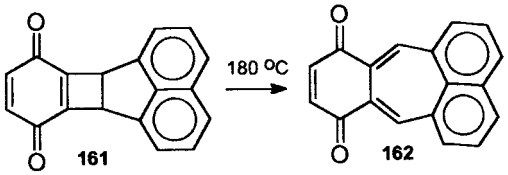
Scheme 91.



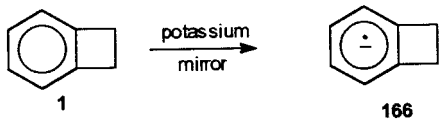
Scheme 92.



Scheme 93.



Scheme 94.



Scheme 96.

Benzocyclobuten-1-ylcarbene **157** generated under photolytic conditions gave 1-methylenebenzocyclobutene **158** and indene **152** in a ratio of 18:82 (Scheme 92).[111] Interestingly, the reactive methylene from diazomethane inserts into the aromatic ring of BCB to furnish a mixture of cyclobutane-fused cycloheptatrienes (e.g. **159**). Treatment of this mixture with a trityl salt affords the cyclobutane-fused tropylium salt **160** in an essentially pure form (Scheme 93).[112] A new pleiadenequinone **162** with considerable electron affinity was prepared via ring expansion of the BCB-based quinone **161** (Scheme 94).[113]

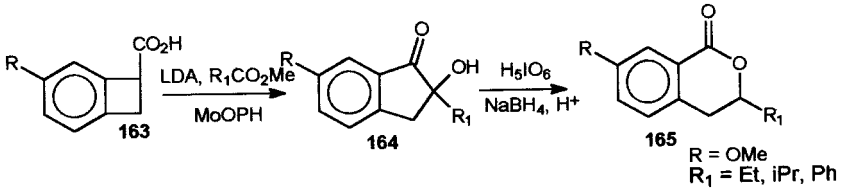
BCB carboxylic acid derivatives **163** undergo an alkoxide-mediated oxidative ring expansion to the hydroxyindanones **164** as shown in Scheme 95. These indanones can be further converted to dihydroisocoumarine derivatives such as **165**.[114]

3.7. Reactive intermediates involving BCBs

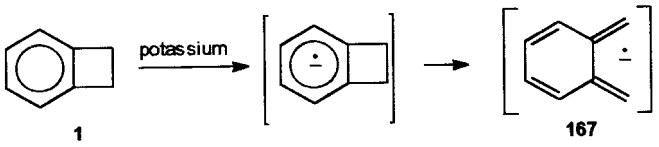
Reduction of BCB with a potassium mirror at −78°C generates the stable BCB radical anion **166**, having a characteristic 69-line ESR spectrum (Scheme 96).[115] When BCB is contacted with K or Na/K in THF at −80°C, however, the only radical which is observed, and which is formed virtually immediately, is the anion radical of *o*-xylylene **167** (Scheme 97).[116] Cyclobuta[1,2-*d*]benzyne **169** has been generated from 4,5-bromoiodobenzocyclobutene **168** and butyllithium (Scheme 98). The transient reactive species can be trapped with furan as the Diels–Alder adduct **170**. In the absence of trapping agents, dimerization of the intermediate benzyne is observed. [117]

3.8. Reactions via benzocyclobutadiene

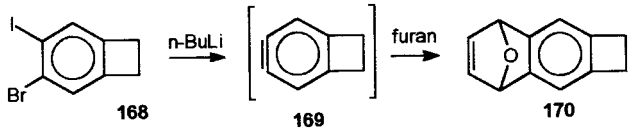
Transient benzocyclobutadiene intermediates are readily generated from BCBs and exhibit novel reaction products. For example, the *trans*-dibromide **3** is rapidly debrominated under a variety of reaction conditions to give the intermediate benzocyclobutadiene **171** which undergoes a range of dimerization and trimerization reactions (Schemes 99–102).[118]



Scheme 95.



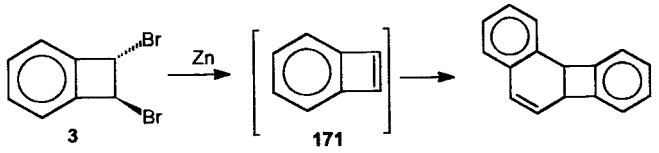
Scheme 97.



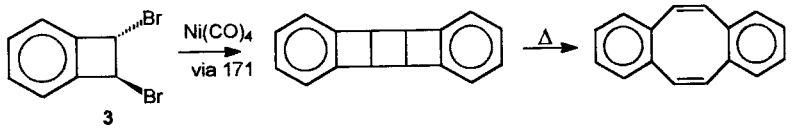
Scheme 98.

3.9. Miscellaneous reactions of BCBs

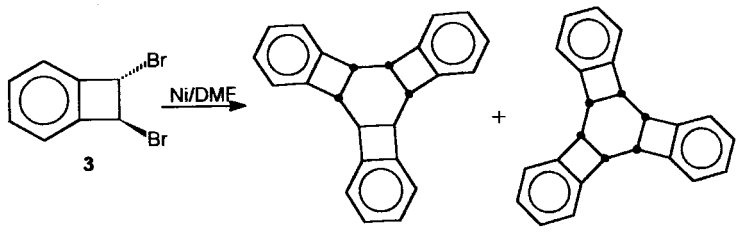
Many interesting but isolated reactions of BCBs reported in the recent literature are described in this section. An unexpected rearrangement of the spiro[benzocyclobutene-1,3′-piperidine] **172** in the presence of aluminium trichloride has been reported (Scheme 103).[119] Application of the Schmidt reaction to 1,2-dihydrobenzocyclobutenol derivatives **173** provides a new route to indole derivatives as shown in Scheme 104.[120] Reductive coupling of 1-chloro BCB **174** with a chromium(0) complex led to the corresponding dimer **175** (Scheme 105).[121] Nucleophilic substitution in perchlorobenzocyclobutenes such as **176** in methanolic sodium hydroxide leads to the methoxy-substituted derivative **177** (Scheme 106).[122]



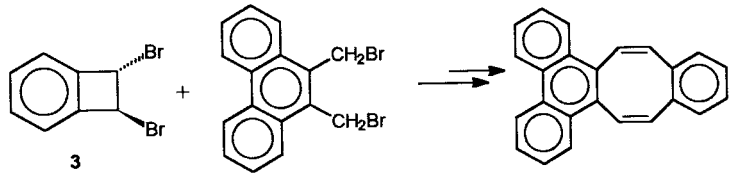
Scheme 99.



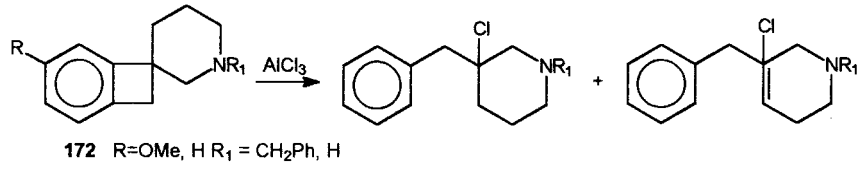
Scheme 100.



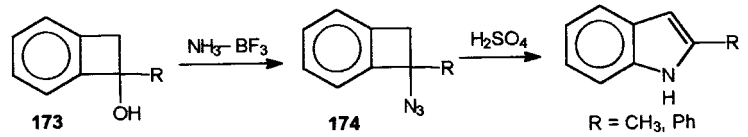
Scheme 101.



Scheme 102.

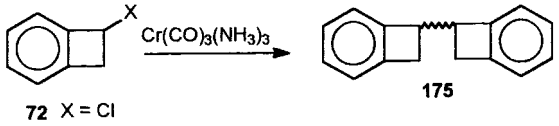


Scheme 103.



173 174

Scheme 104.



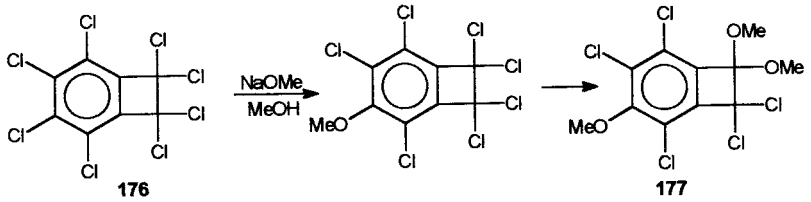
72 X = Cl 175

Scheme 105.

Tricarbonylchromium(0) BCB **178** can be readily deprotonated with *n*-BuLi/-TMEDA base and quenching of the anion with chlorotrimethylsilane leads to the formation of the 3- and 4-trimethylsilyl derivatives **179** and **180** (Scheme 107).[123]

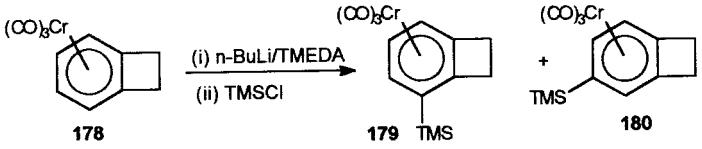
4. Reactions of benzocyclobutenedione (BCBD)

Benzocyclobutenediones (BCBDs) are important derivatives of BCBs and exhibit interesting chemical reactivity. The orthoquinonoid vinylketenes generated thermally or photochemically from a BCBD such as **181** undergo cycloaddition with a bicyclic benzoquinone derivative **182** to yield tetracyclic 10-deoxydaunomycinone derivative **183** (Scheme 108).[124] Staab and Ipaktschi have reported that the photolysis of benzocyclobutene-1,2-dione **52** in the absence of trapping reagents led to the formation of a number of dimers such as **185** and **186** and their formation is indicative of the intermediacy of the bis-ketene **184** (Scheme 109).[125] Reactions of arenetricarbonylchromium(0) complexes of the BCBD show an interesting reactivity pattern. The BCBD complex **187**, when reacted with excess vinyllithium, furnished the benzoannulated cyclooctane-1,4-dione **189** as a result of a double anionic oxy-Cope rearrangement in **188** (Scheme 110).[126] Iron metallocycles, such



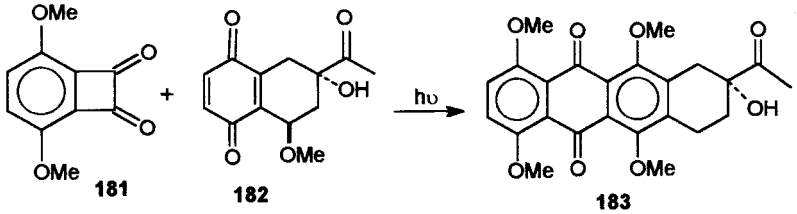
176 177

Scheme 106.



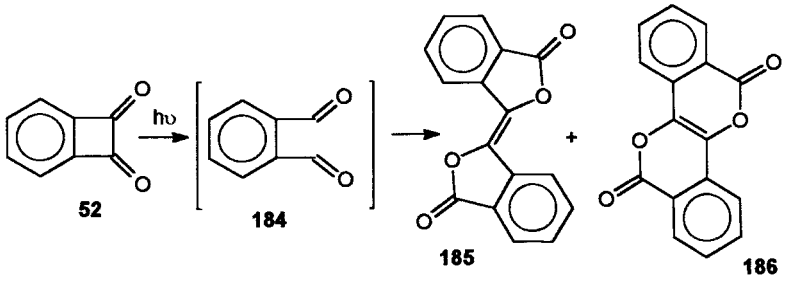
178 179 180

Scheme 107.



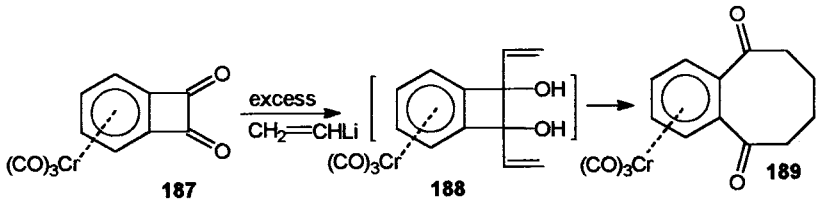
181 182 183

Scheme 108.

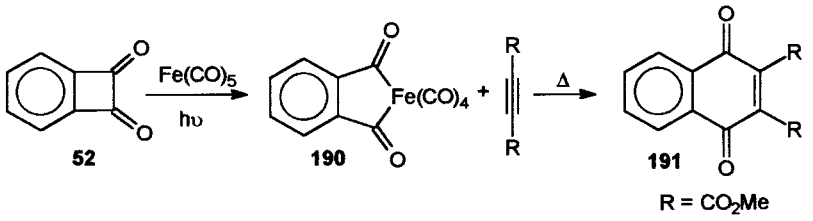


52 184 185 186

Scheme 109.



Scheme 110.



Scheme 111.

as **190**, derived from BCBD react with a wide variety of alkynes to give naphthoquinones **191** in good yields (Scheme 111).[127]

5. Applications of BCBs in synthesis

As mentioned earlier, the major applications of BCBs in syntheses emanate through their ready conversion to *o*-xylylene intermediates that exhibit a high propensity towards inter- and intramolecular cycloadditions. The use of pre-formed BCB derivatives in complex synthesis was introduced by Oppolzer in 1971 with his seminal synthesis of the isoquinoline alkaloid chelidonine.[128] Following on from this work, several other groups have used BCB-derivatives extensively as starting materials to generate various polycyclic frameworks of biological and theoretical importance. Representative targets of topical interest that have been pursued via the BCB route are shown in Fig. 3. In order to limit the size of this article, a small selection of examples to demonstrate the synthetic utility of BCBs are now presented.

5.1. Alkaloid synthesis

The inter- and intramolecular Diels–Alder reaction has been widely used as a key step in the stereocontrolled synthesis of various heterocyclic compounds via BCB intermediates. The three possible strategies through which heteroatom(s)

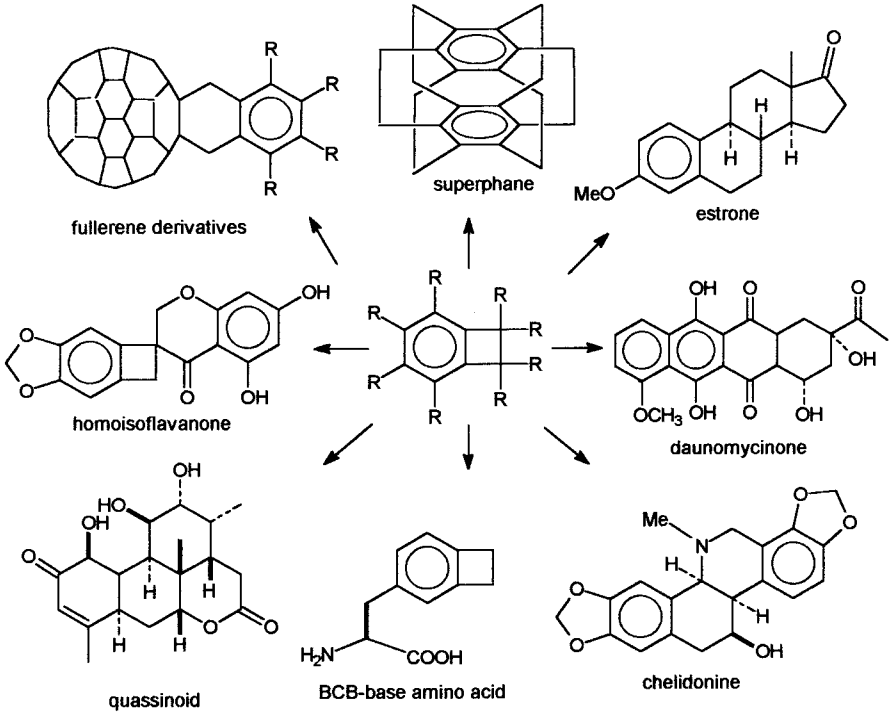
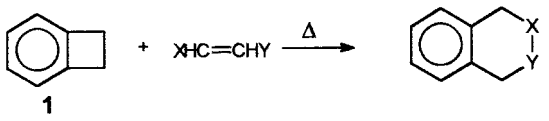
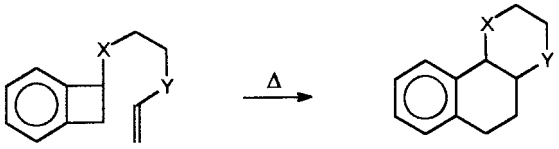


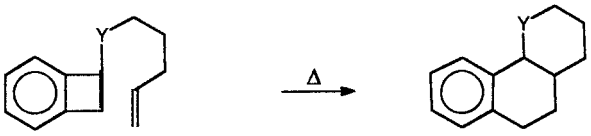
Figure 3. Application of BCB-based strategies for various molecular frameworks.



Scheme 112.



Scheme 113.



Scheme 114.

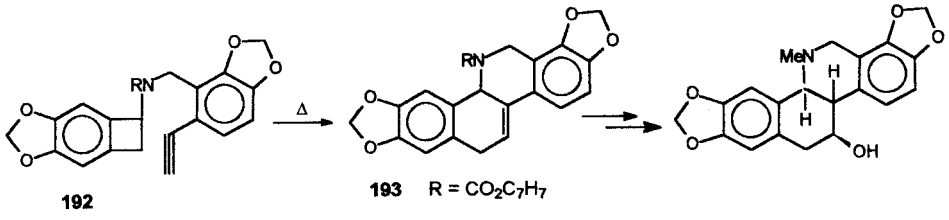
can be introduced into the target structures via the BCB route are shown in Schemes 112–114.

As mentioned above, the first application of *o*-xylylenes in the natural product area was the synthesis of chelidonine **194**, the main alkaloid of *Chelidonium majus*, from the BCB derivative **192**. Thermal activation of **192** gave **193** in 73% yield via the *o*-xylylene intermediate which was further elaborated to dl-chelidonine **194** (Scheme 115).[128]

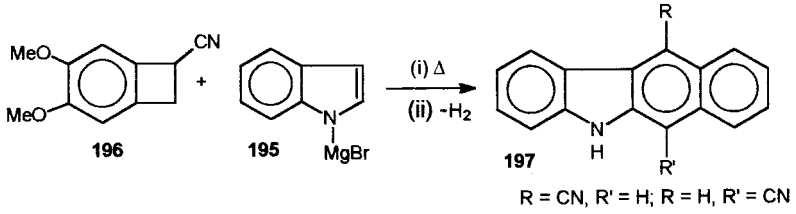
In studies aimed at the synthesis of antitumor carbazole alkaloids such as olivacine and ellipticine, indolylmagnesium bromide **195** was reacted with 1-cyano-4,5-dimethoxybenzocyclobutene **196** to produce a mixture of compounds which could be aromatized to the benzocarbazole derivatives **197** under dehydrogenating conditions (Scheme 116).[129] A regioselective intermolecular cycloaddition between the *o*-xylylene intermediate derived from the 1-cyanobenzocyclobutene **198** and 3,4-dihydro-β-carboline **199**, and reductive decyanation afforded the pentacyclic hexadehydroyohimbane **200** (Scheme 117).[130] A novel and general route to the morphinane alkaloid skeleton **201** was reported via an intramolecular [4+2] cycloaddition reaction of a BCB derivative (Scheme 118).[131]

The tetracyclic framework **203**, present in the complex aconite-garaya diterpene alkaloids, has been constructed via an electrocyclic reaction of the (*Z*)-*o*-quinodimethane BCB derivative derived from **202** under thermal conditions (Scheme 119).[132]

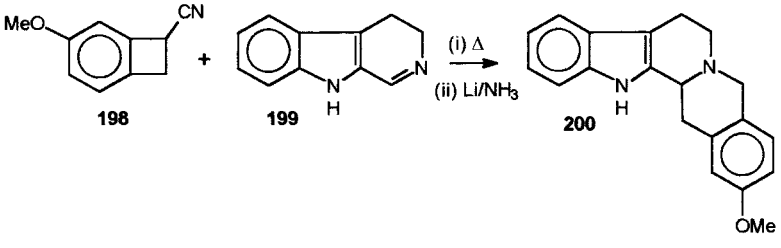
A one-pot procedure has been developed for the synthesis of 4,4-disubstituted isochroman-3-ones **206** using the tandem electrocyclic-[3,3] sigmatropic reaction of the (*Z*)-*o*-xylylene **205** starting from the BCB derivative **204** (Scheme 120).[133] The isochroman derivative **206** is a useful intermediate in the synthesis of various indole alkaloids. The tetrahydroprotoberberine alkaloid, (±)-tetrahydropalmatine **209**, was synthesized through cycloaddition in the 1-benzocyclobutenyl-3,4-dihydroisoquinoline **207**, followed by reduction of the enamine **208** with sodium borohydride



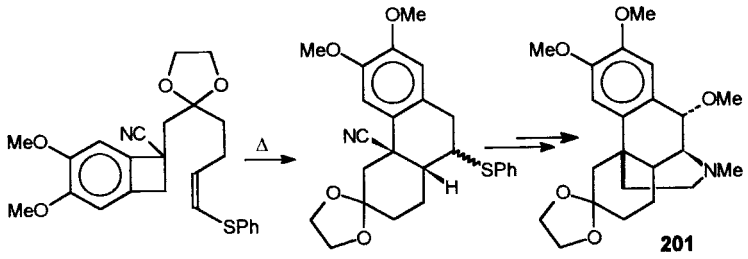
Scheme 115.



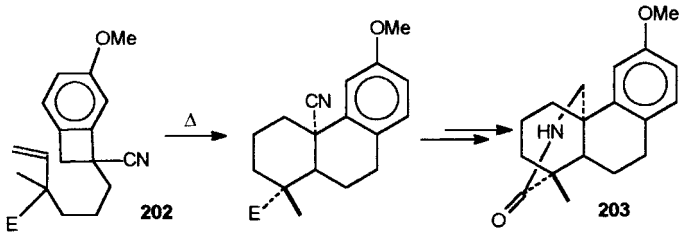
Scheme 116.



Scheme 117.



Scheme 118.

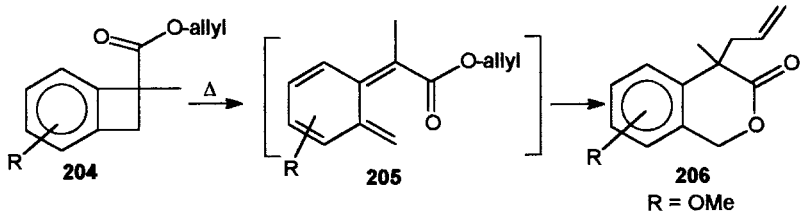


Scheme 119.

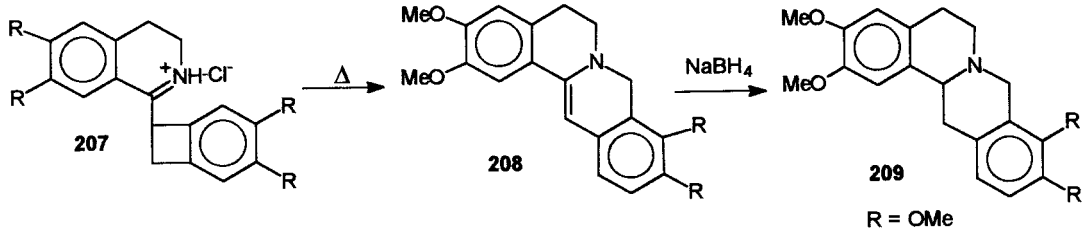
(Scheme 121).[134] The ochotensine type spirobenzylisoquinoline **211** was prepared via an electrocyclic reaction of the corresponding BCB derivative **210** (Scheme 122).[135]

5.2. Steroid synthesis

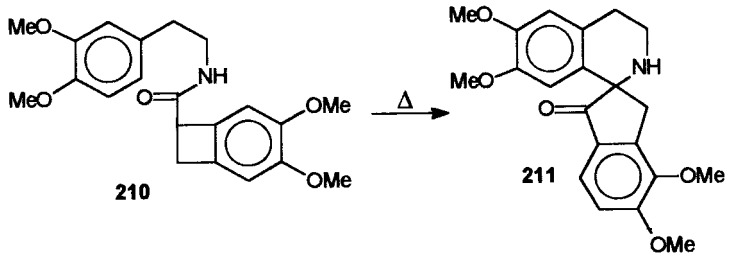
The strategy for the synthesis of the steroid framework via BCB derivatives comprises the two stages shown in Scheme 123. The first stage involves the construction of an appropriately substituted BCB derivative **212** containing a dienophilic moiety and in the second stage the (*E*)-*o*-xylylene intermediate **213** derived from BCB **212** participates in an intramolecular cycloaddition reaction in a regio- and stereoselective manner to form the tetracyclic derivative **214**.[136]



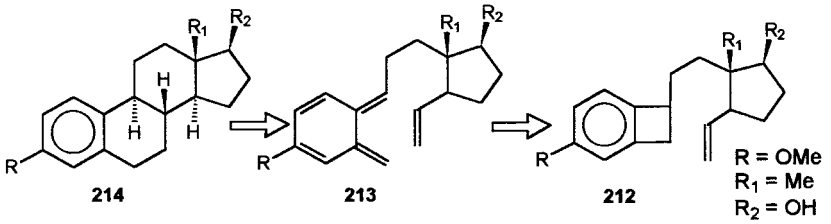
Scheme 120.



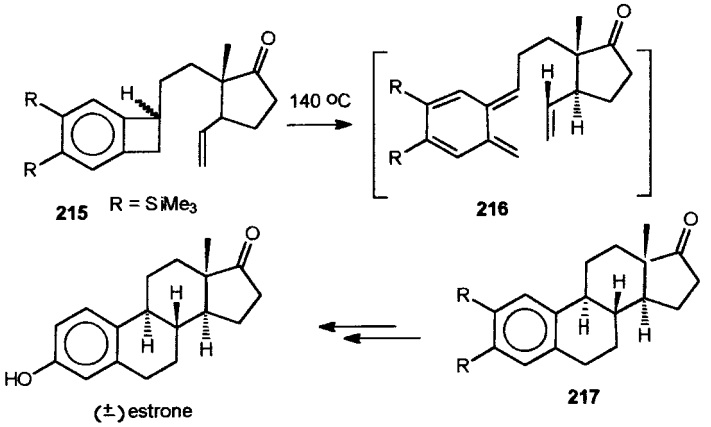
Scheme 121.



Scheme 122.

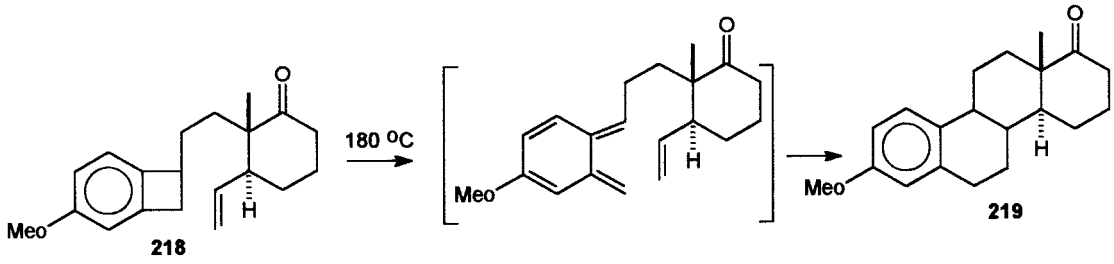


Scheme 123.

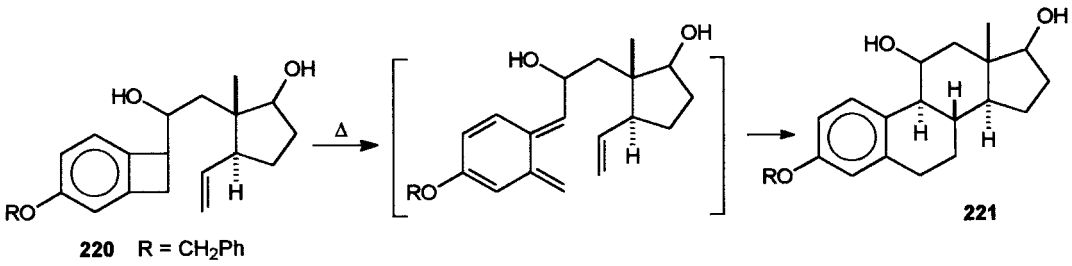


Scheme 124.

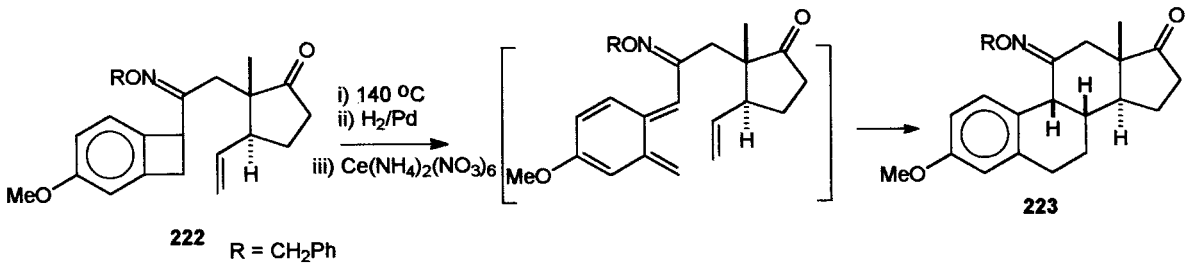
Vollhardt's novel approach to estrone utilizes [2+2+2] and [4+2] cycloaddition reactions as the most important steps. The key intermediate, the benzocyclobutene **215**, on thermal activation ring opens to the *o*-xylylene **216** which then undergoes a stereospecific intramolecular *exo*-Diels–Alder cycloaddition to produce the steroidal framework **217** in the correct *trans–anti–trans* configuration in a remarkably efficient sequence. Subsequent transformations on **217** afford (±)-estrone in an overall yield of 28% from commercially available 1,5-hexadiyne (Scheme 124).[137] Another approach to the steroid ring system was derived by Kametani and his co-workers for the synthesis of (±)-D-homoestrone **219** from the precursor derivative **218** (Scheme 125).[138] Oppolzer's approach to the steroidal framework **221** involving the BCB intermediate **220** is shown in Scheme 126.[139] In a subsequent synthesis, involving compound **222**, exclusive formation of the *cis–anti–trans* product **223** was observed via an *endo* transition state in contrast to the usual *trans–anti–trans* sterochemical outcome during IMDA strategy of steroidal molecules (Scheme 127).[140] This example clearly illustrates how the delicate stereochemical outcome of the IMDA reaction can be influenced by changing the nature of the substitution on the incipient ring C.



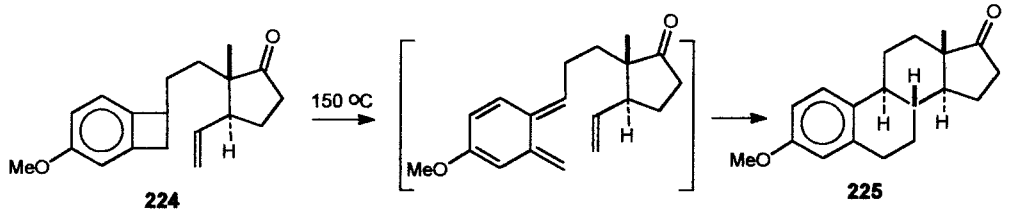
Scheme 125.



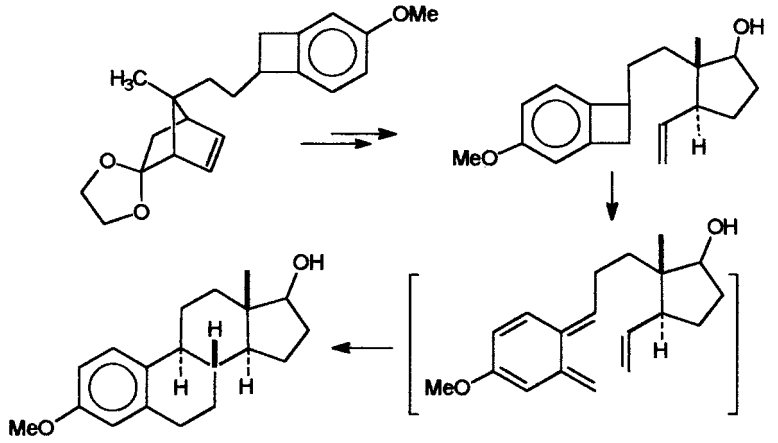
Scheme 126.



Scheme 127.

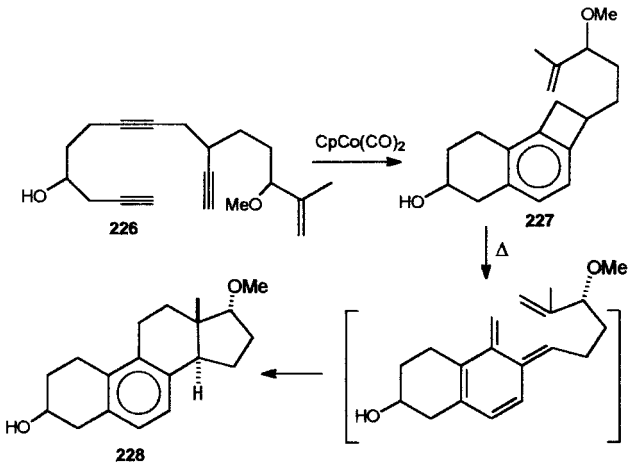


Scheme 128.



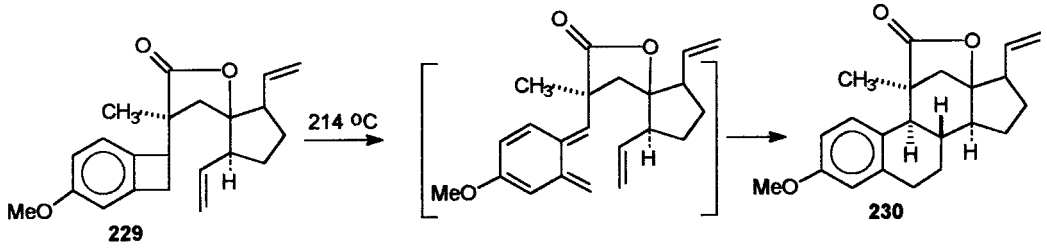
Scheme 129.

Asymmetric synthesis of the estrone derivative **225** involving the key BCB intermediate **224** is shown in Scheme 128.[141] This intermediate **224** differs from that used in the earlier strategy where the *o*-benzyloxy functionality (i.e. intermediate **220**) is replaced by a carbonyl group and this is sufficient to favor the *exo*-transition state leading to a *trans–anti–trans* product. The bicyclo[2.2.1]heptanone building block which has been exploited extensively in the synthesis of many natural products (e.g. prostaglandins) has also found its way into estrone synthesis through intervention with the BCB moiety as reported by Grieco and co-workers. The key transformations leading to the required stereochemistry are shown in Scheme 129.[142] Another interesting example involving the intramolecular ene-triyne cyclization of an acyclic precursor **226** to the BCB derivative **227** followed by intramolecular [4+2] cycloaddition to a ring-B aromatic steroid **228** has been reported (Scheme 130).[143] This approach is unique in the sense that the four rings are all assembled in one step with complete control of the crucial stereochemistry of the C–D ring junction.



Scheme 130.

An extremely simple and short route to the estrone derivative **230** from a 1,3-butadiene derivative has been reported. The key transformation involving the BCB intermediate **229** is shown in Scheme 131.[144] Recently, a French group has reported an abridged route to a key intermediate in Kametani's synthesis of the steroid derivative **232**. This



Scheme 131.

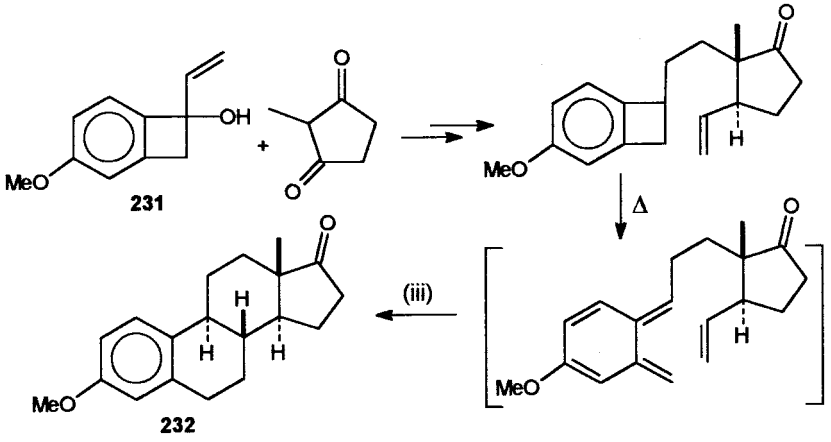
strategy involves a Torgov-like reaction of 2-methylcyclopentane-1,3-dione with the BCB intermediate **231** (Scheme 132).[145] In connection with des-A,B-aromatic steroids, Fukumoto's group has reported an asymmetric synthesis of the tricyclic intermediate **234** starting from the BCB derivative **233** (Scheme 133),[146] in which a chiral oxathiane system was used as the stereodirecting group. In a related study, the tricyclic intermediate **236** was prepared from the BCB derivative **235** (Scheme 134).[147]

5.3. Anthracycline and related quinone synthesis

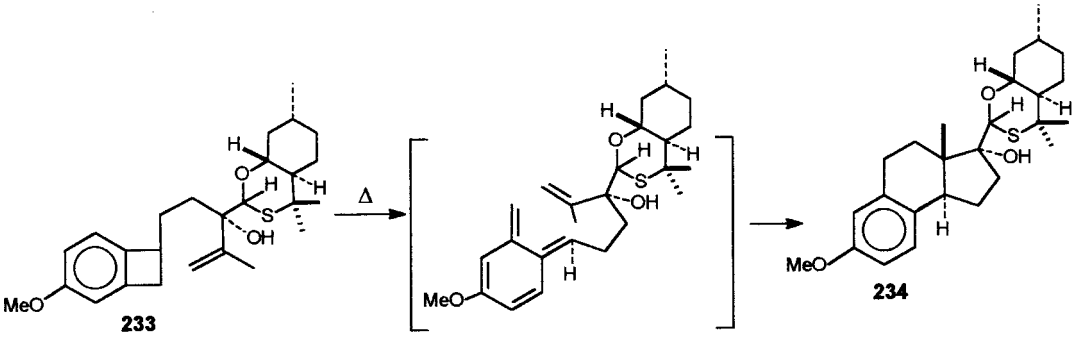
Several anthracycline antibiotics such as daunomycin, 4-demethoxydaunomycin and adriamycin have found clinical use in the treatment of various types of cancer and this has stimulated much research into the synthesis of their tetracyclic aglycons.[148] In this section some examples in which BCB derivatives are employed for the synthesis of anthracycline derivatives are described.

Kametani's group studied the Diels–Alder chemistry of the tetrahydronaphtho-quinone **238** and the 1-cyanobenzocyclobutane derivative **237** to furnish the tetracyclic compound **239** en route to the anthracyclines (Scheme 135).[149] The cyclobuta[*b*]anthracene derivative **240** undergoes a facile intermolecular Diels–Alder reaction with various dienophiles (methyl vinyl ketone) to generate the tetracyclic compound **241** related to anthracyclinones (Scheme 136).[150] The annelated cyclobutane strategy for the generation of *o*-xylylene intermediates gives better yields when compared with the other alternate starting material.

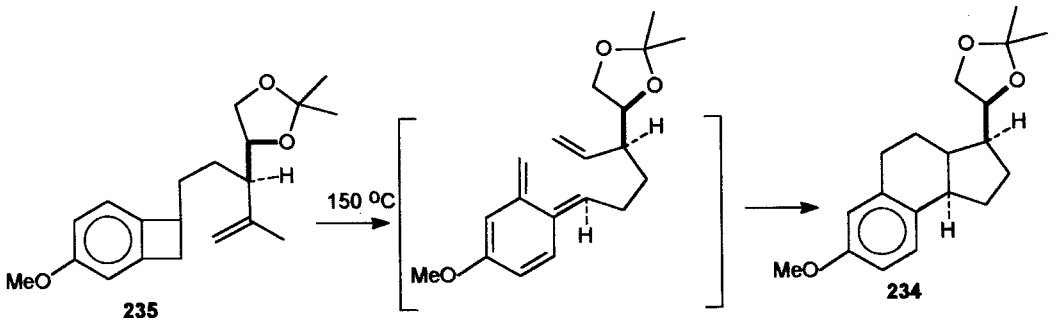
Swenton et al. used metallation strategy to couple the BCB derivative **242** and the sulphone **243** to obtain the tetracyclic



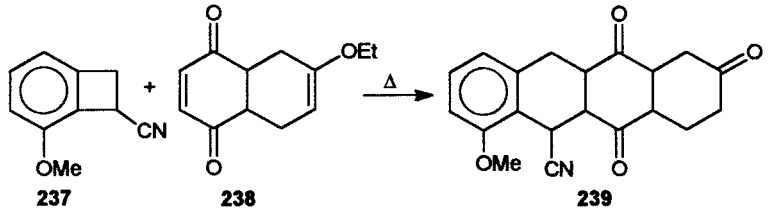
Scheme 132.



Scheme 133.



Scheme 134.

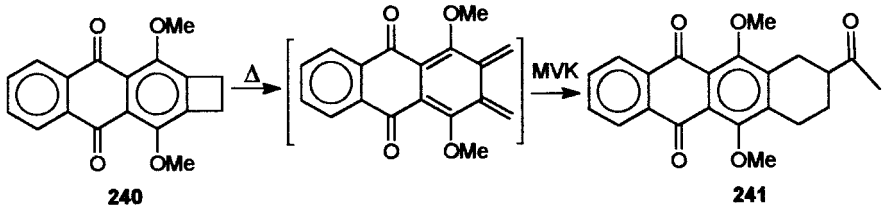


Scheme 135.

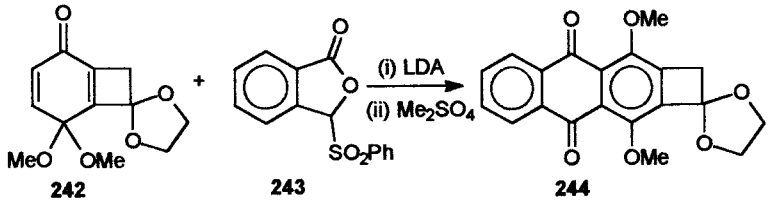
intermediate **244**, suitable for further elaboration (Scheme 137).[151] A potential anthracycline derivative **247** has been prepared from the benzocyclobutenone **245** and the quinone acetal **246** as starting materials (Scheme 138).[152] Several conjugated semiquinones such as **250** have been prepared via Diels–Alder strategy using the BCB intermediate **248** and the quinone **249** (Scheme 139).[153]

5.4. Derivatization of fullerenes

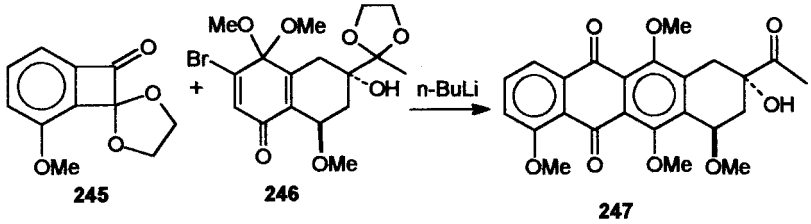
Functionalization of fullerenes and particularly of C_{60} for further processing as useful materials has received considerable attention in recent years. C_{60} has been known to exhibit dienophilic character through the participation of the 6-C double bond in [4+2] cycloadditions. A range of BCBs



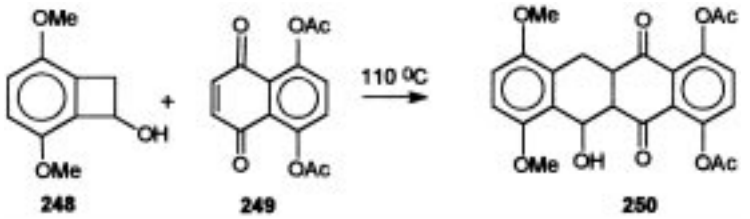
Scheme 136.



Scheme 137.



Scheme 138.



Scheme 139.

have been employed to engage C_{60} in [4+2] cycloadditions through the corresponding *o*-xylylene intermediates. In most instances *o*-xylylenes were generated by the thermal ring opening of BCB derivatives or by 1,4-elimination of Br_2 from 1,2-bis(bromomethyl)arenes. A number of BCBs and related derivatives that undergo cycloaddition reactions with C_{60} are shown in Fig. 4.[154]

5.5. Cyclophane synthesis

In cyclophanes the close proximity of two benzene rings provides strong interaction of the π-systems and therefore synthesis of 'phane' systems has attracted considerable attention. Superphane **251**, a multibridge [2_n]cyclophane, has been synthesized and BCB and its derivatives play a pivotal role (Scheme 140).[155] The key to the successful synthesis of this intricate molecule is the multiple deployment of BCB precursors which dimerize through *o*-xylylene intermediates to introduce more than one bridge at a time. Reaction of BCB 1 with the tetrasilylcycloocta-1,5-diyne derivative **252** gave the orthocyclonaphthophane **253** (Scheme 141).[156]

5.6. Miscellaneous applications of BCBs

Birch reduction of the BCB derivative **254** is the key step in

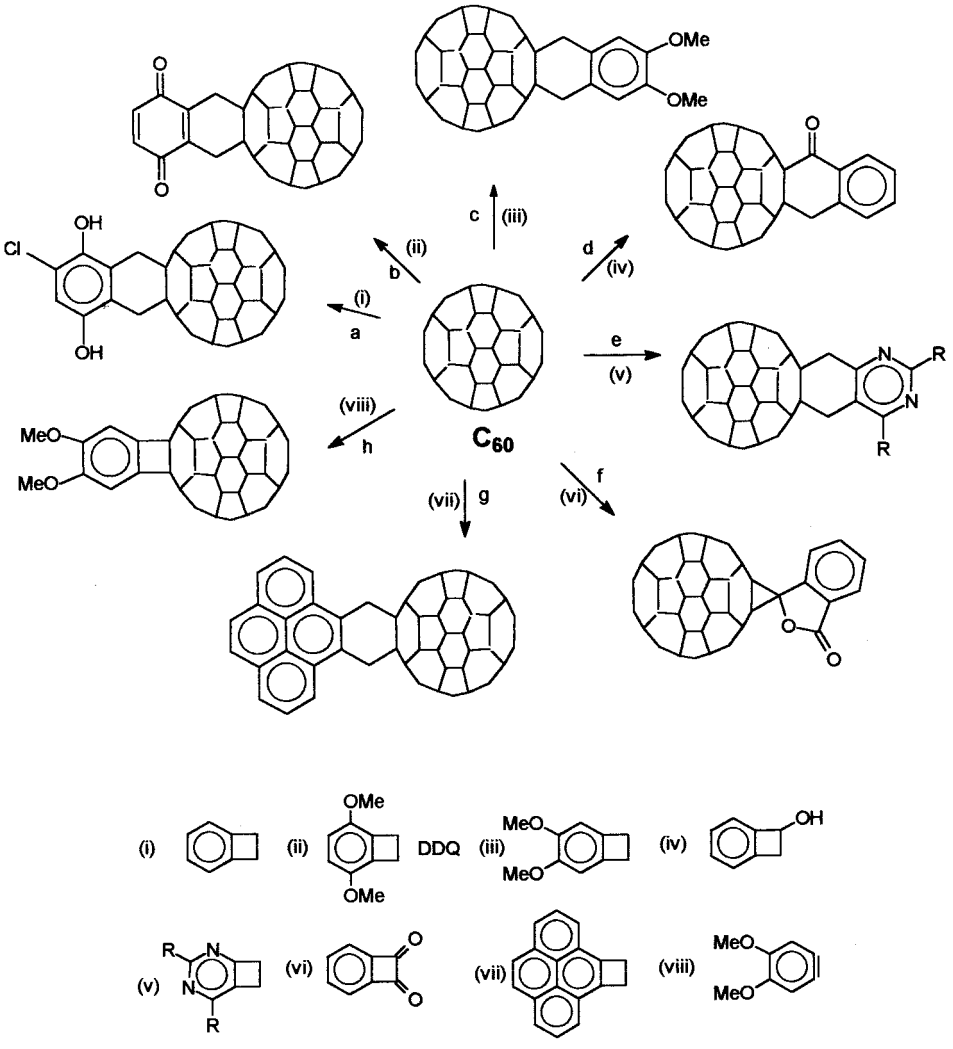
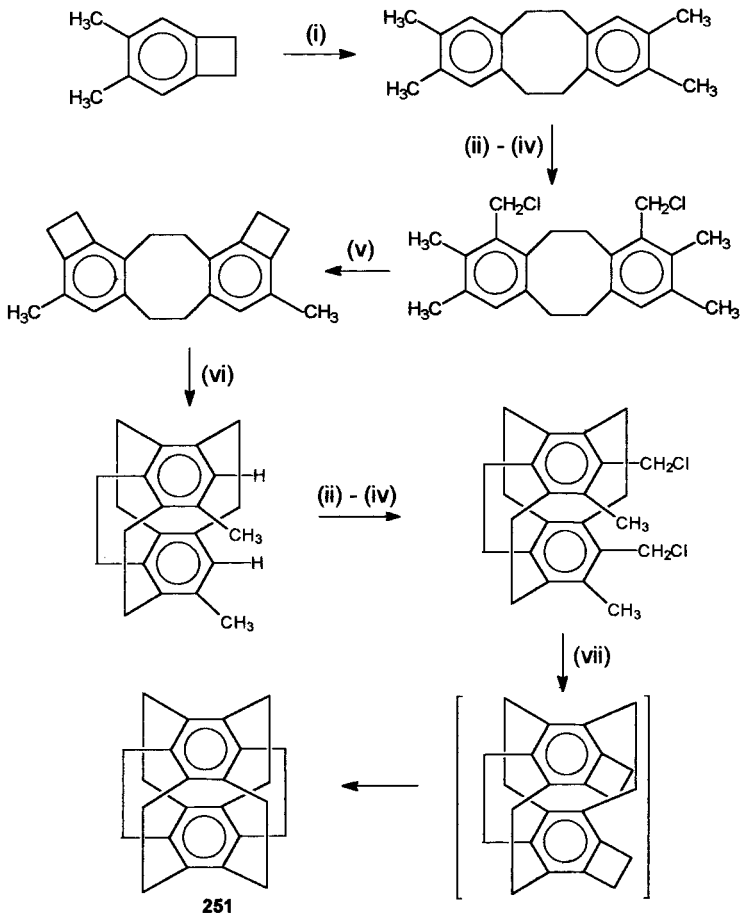
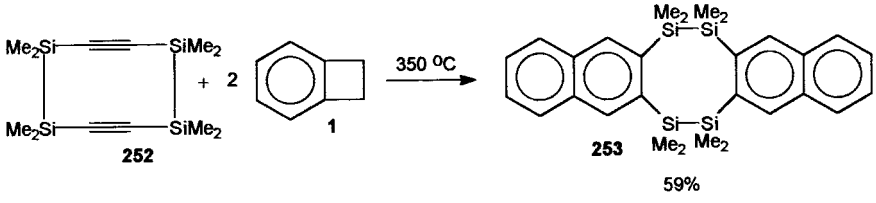


Figure 4. Various Diels–Alder reactions of C_{60} with BCB derivatives.

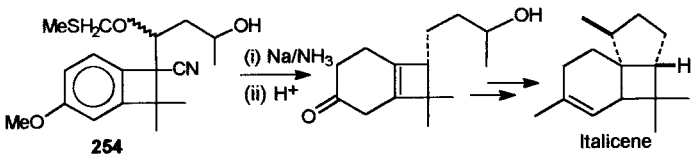


Scheme 140. (i) 400°C, N_2, 1 atm; (ii) Cl_2CHOCH_3, $SnCl_4$; (iii) $NaBH_4$; (iv) $SOCl_2$; (v) 700°C, 10^{-2} mm; (vi) 650°C, 10^{-2} mm.

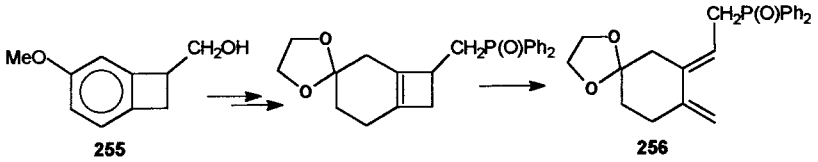
the synthesis of the cyclobutane sesquiterpene, italicene (Scheme 142).[157] Similarly, the vitamin D_3 precursor **256** has been prepared[158] from the BCB derivative **255** involving Birch reduction as a key step (Scheme 143). Malacria and co-workers have generated the basic skeleton of tetracyclic diterpenes (phyllocladane and kaurane) via a sequence of consecutive [3+2], [2+2+2] and [4+2] cycloaddition reactions. A carbonyl group at the C-12 position of compound **257** favored the kaurane stereochemistry (58:42), whereas an acetal function at that position led to a highly stereoselective formation of the phyllocladane streochemistry (e.g. **258**) (Scheme 144).[159] In their studies on stemodin synthesis, the same group prepared spiro-substituted BCB derivatives such as **259** and this was shown to undergo a [4+2] cycloaddition reaction via *o*-xylylene intermediates to generate the tetracyclic system **260** (Scheme 145).[160]



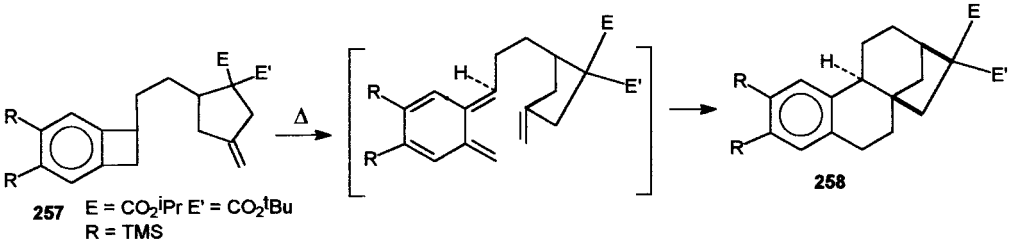
Scheme 141.



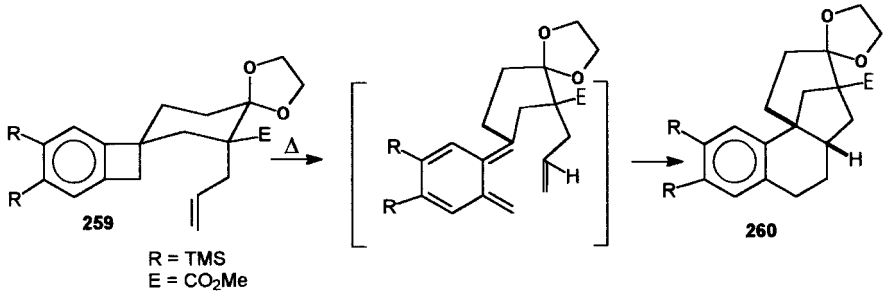
Scheme 142.



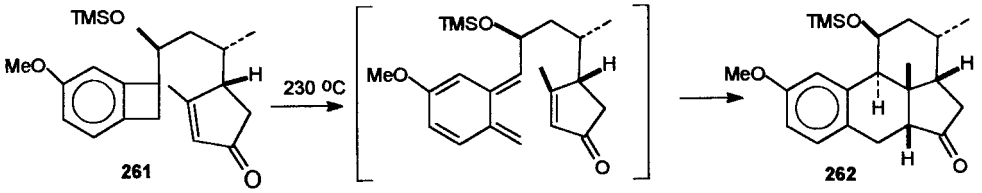
Scheme 143.



Scheme 144.



Scheme 145.



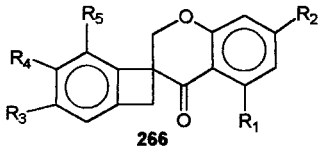
Scheme 146.

IMDA reaction of the BCB derivative **261** has also been used in the synthetic approach towards the quassinoid ring system **262** (Scheme 146).[161] Chrome B, a tricyclic terpenoid *p*-benzoquinone **263**, isolated from *Cordia millenii*, was synthesized in a three-step sequence starting from 3,6-dimethoxy BCB **21** and 3-methylcyclohexene-1-one **264** employing a Diels–Alder reaction as a key step (Scheme 147).[162]

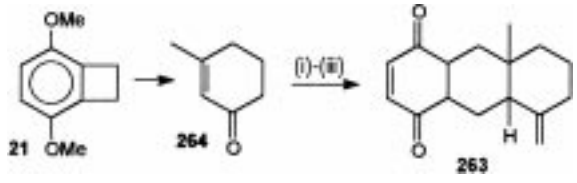
In a building block approach towards the synthesis of unusual α-amino acids, Kotha et al have recently reported the first synthesis of an optically active BCB-based amino acid derivative **265** in a highly diasteroselective manner via a six-step sequence using a Schöllkopf chiral auxiliary (Scheme 148).[163]

6. Synthesis of natural products containing a BCB unit

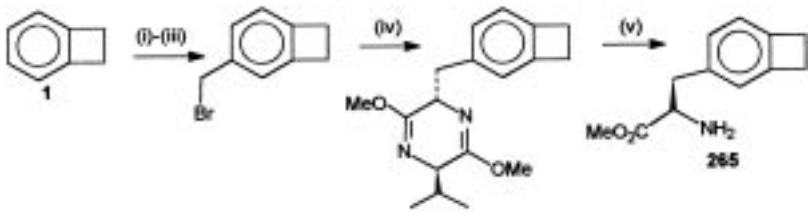
Several interesting natural products having the general structure **266** and incorporation of a BCB moiety have been isolated from Muscari species.[164]



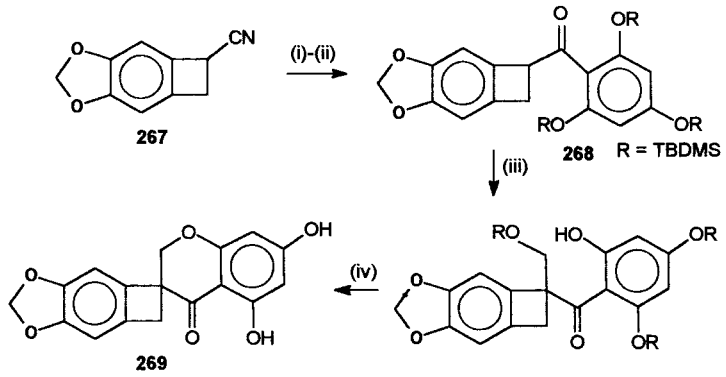
There are two reported syntheses of these natural products. The first synthesis starts with the known 1-cyano-4,5-methylenedioxybenzocyclobutene **267**. Condensation of



Scheme 147. (i) 220°C; (ii) Witting reaction; (iii) CAN.



Scheme 148. (i) $TiCl_4$, Cl_2CHOCH_3; (ii) $NaBH_4$, MeOH, NaBr, BF_3OEt_2, CH_3CN; (iv) *n*-BuLi, chiral auxiliary, THF; (v) 1N HCl.



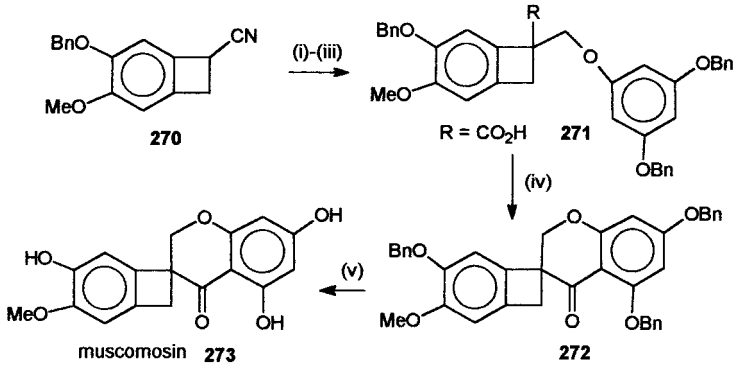
Scheme 149. (i) Phloroglucinol, HCl, ether, $ZnCl_2$; (ii) $^tBuMe_2SiCl$, DMF, imidazole; (iii) para formaldehyde, KO *t*-Bu; (iv) 40% HF/CH_3CN.

the cyano compound **267** with phloroglucinol under acidic conditions (HCl/ether/$ZnCl_2$) gave the hydroxy ketone **268**. Protection of the hydroxyl functionality as the *t*-butyldimethylsilyl derivative followed by treatment with a catalytic amount of *t*-BuOK and hydrolysis gave the required flavone derivative. Desilylation produced the target BCB derivative **269** (Scheme 149).[165]

The second synthesis of these natural products, namely of muscomosin **273**, is more straightforward and starts with the alkylation of **270** with dibromomethane to give the alkylated product, which was *o*-alkylated with phloroglucinol dibenzyl ether. Hydrolysis of the cyano compound gave **271** which on intramolecular Friedel–Crafts acylation afforded the spiro compound **272** and this was elaborated to muscomosin **273** (Scheme 150).[166]

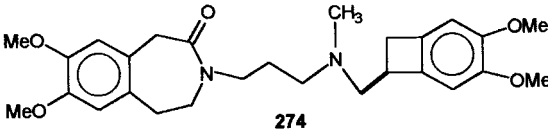
7. Concluding remarks

Certain molecular entities, because of their novel structural features and their interesting reactivity profile, have been the objects of sustained attention of organic chemists. BCB and its derivatives fall into this category and, for over four decades, their physicochemical characteristics, chemical reactivity and their utility in complex syntheses have been widely explored. In this review, the unusual reactivity pattern of BCBs has been described and their efficacy in complex syntheses by engaging in cycloaddition processes that result in the formation of several C–C bonds in single pot reactions has been highlighted. During the past few years, another dimension has been added to BCB chemistry since its derivatives are beginning to find applications in biology and materials science. For example, an interesting



Scheme 150. (i) $Br(CH_2)_2Br$, NaH/DMF, 0°C, 95%; (ii) phloroglucinol dibenzyl ether, K_2CO_3 DMF, 100°C (iii) K_2CO_3, EtOH, Δ; (iv) $(CF_3CO)_2O$, toluene 49%; (v) Pd–C, H_2, 95%.

BCB derivative **274** was recently listed as a bradycardic agent in a WHO drug information list.[167] A new family of antitumor agents based on tetrahydrobenzocyclobutacarbazoles such as **275** have been synthesized recently.[168] A synthesis of the 1-benzocyclobutenyl amino acid **276** has been described and this is disclosed as depressant in the patent literature.[169] Some of the benzocyclobutene-maleimide AB type monomers (e.g. **277**) polymerize to yield exceptionally tough high T_g resins. A lateral covalent bonding in polymers is achieved by incorporating into the molecular backbone a thermally activated cross-linking agent such as 1,2-dihydrocyclobutabenzene-3,6-dicarboxylic acid **278**.[170] With growing importance of the utility of BCBs in biology, polymer science and materials chemistry, it is hoped that this review may act as catalyst for further exploration of these interesting molecules.



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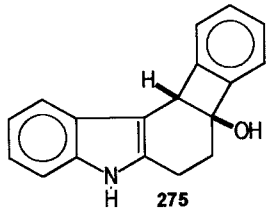

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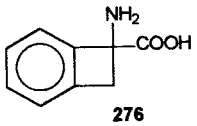

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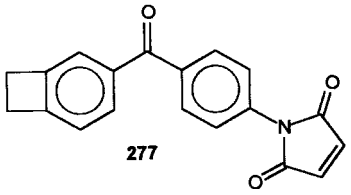

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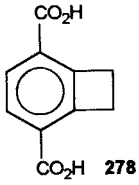

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