Cyclobutarenes and Related Compounds

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I. Introduction

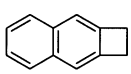
Due to the thermodynamic stability associated with the aromatic system and the kinetic reactivity of the strained cyclobutene ring, the cyclobutarenes represent a unique class of reactive molecules. In addition to having provided an interesting playground for the theoretician, the *o*-quinodimethanes that are formed upon thermolysis of cyclobutarenes have found important applications in the synthesis of a wide range of polycyclic products via inter- and intramolecular Diels−Alder reactions. The growing interest in the chemistry of these compounds has, in turn, stimulated the development of alternative approaches aimed at selectively introducing structural and chemical diversification.

The cyclobutarenes have been the subject of several previous reviews[1−6] and an account.[7] The related *o*-quinodimethanes[8−10] and their hetero analogues[11,12] have also been reviewed previously. This review intends to collect systematically the widespread knowledge regarding the synthetic methods, reactions, and physical characteristics of this class of compounds. The review covers literature from 1970 to early 2002. Cyclobutarenes in polymer synthesis[13] and theoretically interesting molecules (i.e., biphenylene derivatives) related to cyclobutarene are not included, as these have been discussed in recent reviews.[14]

Although the parent hydrocarbon **1** and its derivatives are referred to frequently as benzocyclobutenes, cyclobutabenzenes, and benzocyclobutadienes, in this review we will use contemporary nomenclature and refer to this class of compounds as cyclobutarenes. The IUPAC name for **1** is bicyclo[4.2.0]octa-1,3,5-triene, whereas the naphthalene derivatives **2** and **3** would be 1,2-dihydrocyclobuta[*b*]naphthalene and 1,2-dihydrocyclobuta[*a*]naphthalene, respectively.

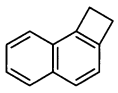
1

bicyclo[4.2.0]octa-1,3,5-triene



2

1,2-dihydrocyclobuta[*b*]naphthalene



3

1,2-dihydrocyclobuta[*a*]naphthalene

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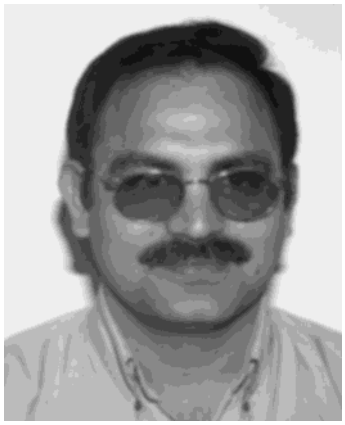
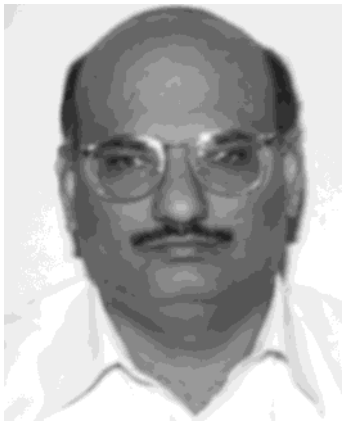
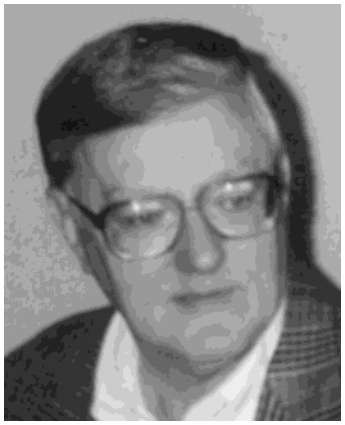


Anil K. Sadana was born in Panipat, India. He did his M.Sc (1990) and M. Phil (1992) from Kurukshetra University, India. He obtained his Ph.D. degree in 1999 under the guidance of Prof. Om Prakash. His Ph.D. work focused on the utility of hypervalentiodine reagents in the synthesis of heterocyclic compounds. He then joined Prof. W. E. Billups lab as postdoctoral research associate in 2000. He is presently working on small ring compounds and carbon nanotubes.



Rajesh Kumar Saini was born in 1966 in Ambala, India. He received his masters degree in 1989 and his Ph.D. in 1996 from Kurukshetra University, India. After his doctorate he moved to the United States for his postdoctoral studies. After a brief stay at Sam Houston State University he joined Rice University, where he is working as a Research Scientist in the laboratories of Prof. W. E. Billups and Prof. Richard E. Smalley. His research has concentrated on small ring compound and the development of carbon nanotube chemistry.



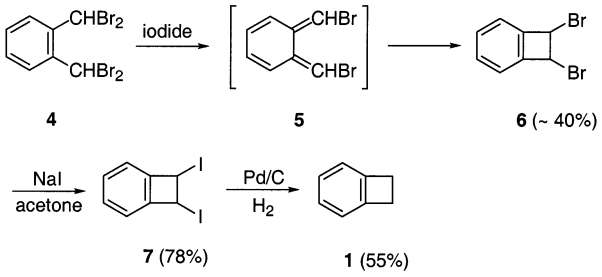
W. E. Billups was born in 1939 in Huntington, West Virginia. He received his B.S. in Chemistry Degree from Marshall University in 1961. This was followed by a period in industry after which he entered the graduate school of the Pennsylvania State University in 1968 and received the Ph.D. in 1970. He then joined the chemistry department at Rice University. He served as the Department Chair from July 1985 until December 1991. His research interests are divided among the areas of small-ring compounds, reactive intermediates, chemistry of free metal atoms and more recently fullerene and carbon nanotube chemistry.

II. Synthesis

A. From *o*-Quinodimethanes

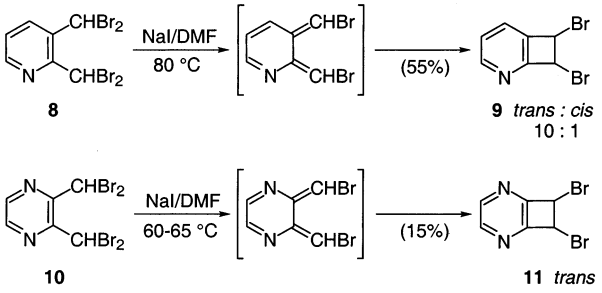
A general method for the synthesis of cyclobutarenes involves 1,4-elimination from adjacent benzylic positions, followed by ring closure of the resulting *o*-quinodimethane. The earliest report in which an *o*-quinodimethane was implicated was the reaction of α,α,α′,α′-tetrabromo-*o*-xylene (**4**) with iodide to give the 1,2-dibromocyclobutarene **6**, via *o*-quinodimethane **5**. Treatment of **6** with NaI in acetone gave diiodide **7**, which on catalytic reduction gave **1** (Scheme 1).[15−17] Cava and co-workers confirmed that **5** was an intermediate by trapping experiments using several dienophiles.[18] A similar procedure has been used to prepare 1,2-diphenylcyclobutarene.[19]

Scheme 1



Heterocyclic analogues may also be prepared by the 1,4-elimination of halogen from suitable precursors. Compounds **9** and **11** have been synthesized from **8** and **10**, respectively, as illustrated in Scheme 2.[20]

Scheme 2

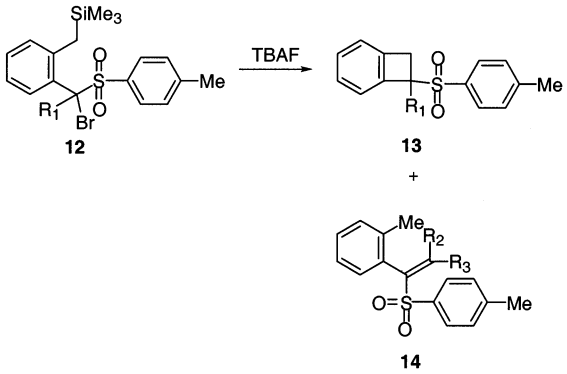


A variation of the method involves the conversion of α-alkyl-α-bromosulfones into cyclobutarenes using tetrabutylammonium fluoride (TBAF) in acetonitrile at 20−25 °C to effect the elimination.[21] The desired cyclobutarene is often accompanied by olefinic side products, as illustrated in the preparation of cyclobutarene **13**, which is accompanied by **14** (eq 1) (Table 1).

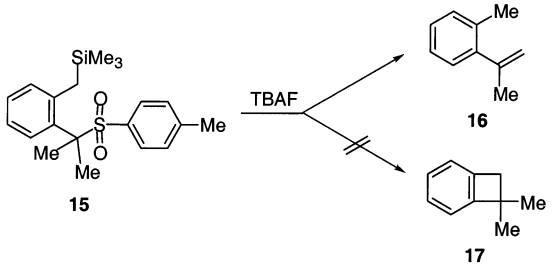
Table 1. Synthesis of Cyclobutarenes 13 and Vinyl Sulfones 14 from α-Alkyl-α-bromosulfones 12

α-bromosulfone **12**	cyclobutarene **13**		vinyl sulfone **14**		
R_1	R_1	yield (%)	R_2	R_3	yield (%)
Me	Me	11	H	H	61
Et	Et	54	H	Me	15
Bu	Bu	61	H	Pr	15
Bn	Bn	59	H	Ph	17
CH_2=$CH(CH_2)_3$	CH_2=$CH(CH_2)_3$	50	H	CH_2=$CH(CH_2)_2$	22
$(Me)_2CH$—	$(Me)_2CH$—	49	Me	Me	21

In some cases, the olefin is the sole product. Thus, the desired cyclobutarene **17** could not be isolated



when α,α-dimethyl sulfone **15** was treated with fluoride. In this case, only **16** could be isolated (eq 2).[22]

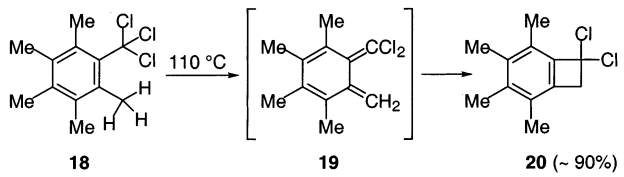


The sterically congested benzene derivative **18**[23] has been converted thermally into the cyclobutarene **20** in nearly quantitative yield. The facile elimination of HCl from **18** may be attributed to steric strain in **18**,[24] whereas stabilization of the four-membered ring in **20** probably results from the buttressing effect of the aromatic ring substituents (Scheme 3).

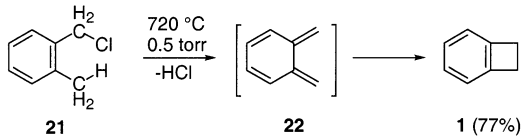
A thermolysis route has been developed for the large-scale preparation of **1** from **21** via *o*-quinodimethane **22** under flash vacuum pyrolysis (FVP) conditions (Scheme 4).[25] This reaction, which was first reported by Maccoll,[26] has also been used for the preparation of substituted cyclobutarenes.[27−30]

Boekelheide et al. have reported a convenient method for the synthesis of simple bicyclobutarenes

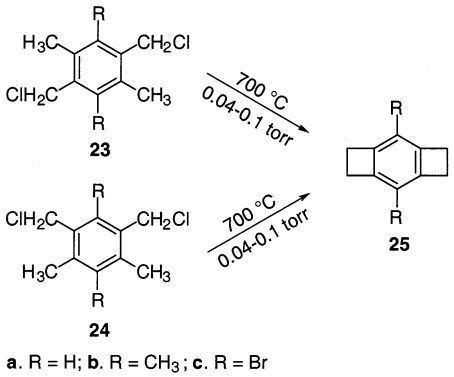
Scheme 3



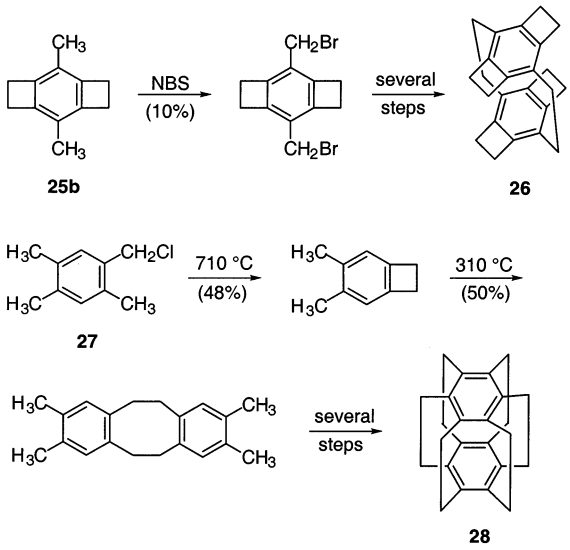
Scheme 4



Scheme 5

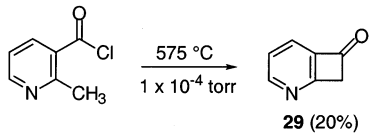


Scheme 6



25a−**c** from either **23** or **24**. The yield in each instance is about 30%; however, the pyrolysis of **24** yields cleaner products (Scheme 5). Bicyclobutarene **25b** has been used as an intermediate for the synthesis of the novel cyclophane **26** (Scheme 6). Following the same approach, superphane **28** was prepared in several steps using **27** as a point of departure (Scheme 6).[31]

Other novel compounds that have been prepared using the pyrolytic approach include the pyridine derivatives **29** (eq 3)[32] and **30** (eq 4).[33,34]



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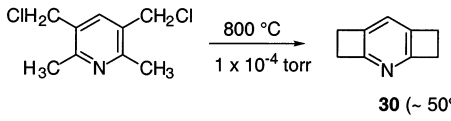
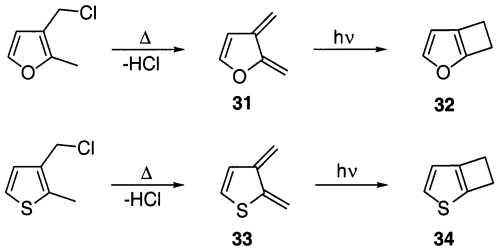


(4)

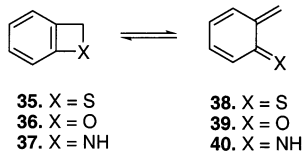
Münzel and Schweig used the FVP route to generate **31** and **33** in nearly quantitative yield. Photolysis of the dienes in an argon matrix afforded the heterocycles **32** and **34** (Scheme 7).[35]

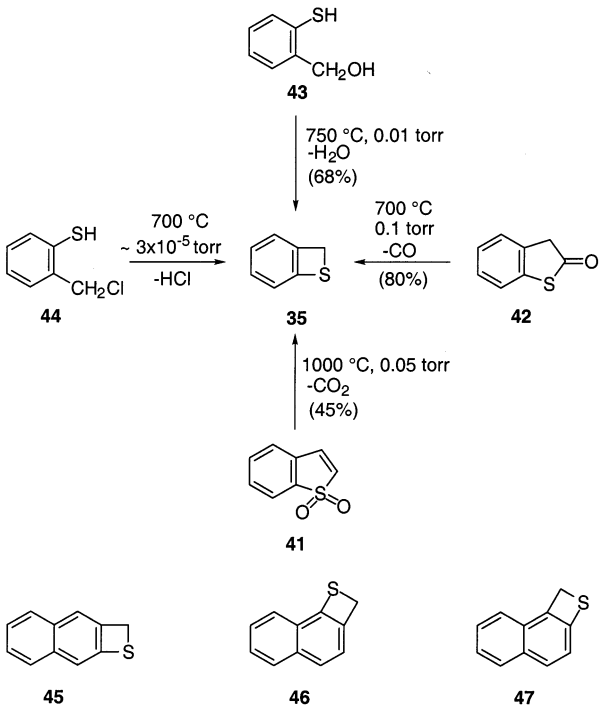
The FVP procedure has also been used to prepare the benzo-condensed four-membered heterocycles **35**−**37**. The benzothiete **35**, which was first prepared by Meier et al.,[36] is stable at room temperature.

Scheme 7

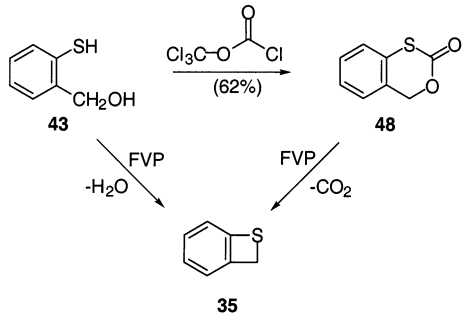


Scheme 8

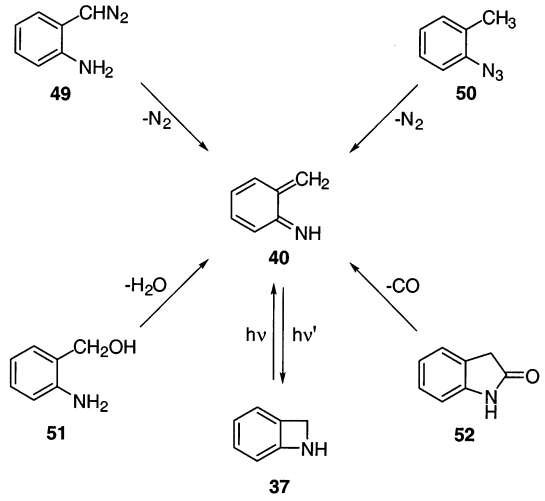




Scheme 9



Scheme 10



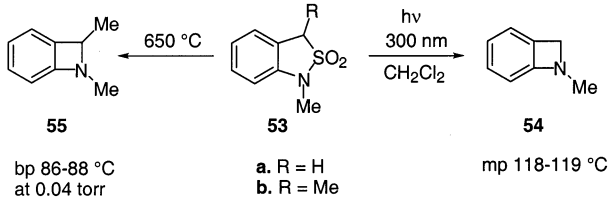
Subsequently, **35** was prepared by the extrusion of CO_2 from benzo[*b*]thiophene-1,1-dioxide **41**,[37] CO from thiolactone **42**,[38] H_2O from thiophenol **43**,[39] and HCl from thiophenol **44**[40] (Scheme 8). Isomeric naphthietes **45**−**47** have also been synthesized by the extrusion of H_2O from suitable thionaphthols.[41]

Thermal extrusion of CO_2 from **48** provides an alternative route to **35** (Scheme 9). Thus, oxathione **48** can be obtained readily by reaction of the thiophenol **43** with trichloromethyl chloroformate. Thermolysis of **48** was carried out by slow vaporization through a quartz tube at 550 °C and 0.75 Torr to afford **35** in 60% yield. Naphthietes **45**−**47** have also been synthesized by this procedure.

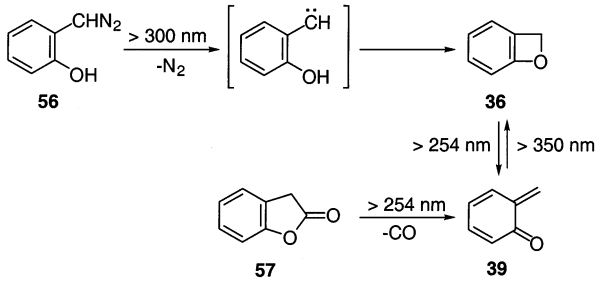
Several compounds, including **49**−**52**, have been investigated as precursors to benzazetidine **37**. FVP of **49**−**51** leads to high yields of *E*/*Z* mixtures of **40**. Benzazetidine **37** is formed by photolysis of **40**, but not thermally by FVP of any precursor (Scheme 10). A benzenoid structure with the four-membered ring only slightly twisted has been proposed. The bond angles in the four-membered ring are close to 90°, and the C(7)−N(8) distance is 213.8 pm.[42]

Photolysis of 1-methyl-2,1-benzisothiazoline-2,2-dioxide **53a** yields 1-methylbenzazetidine **54** as a white crystalline product in 62% yield. FVP of **53b** provided 1,2-dimethylbenzazetidine **55** in 61% yield. Curiously, the formation of stable benzazetidines **54** and **55** indicates that a single methyl group on the four-membered ring of benzazetidine will stabilize the molecule (Scheme 11).[43]

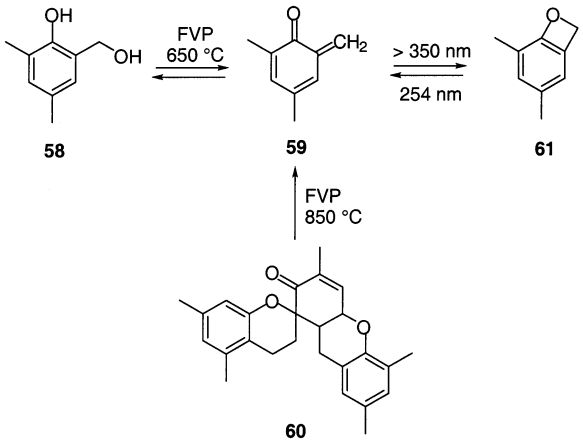
Scheme 11



Scheme 12



Scheme 13

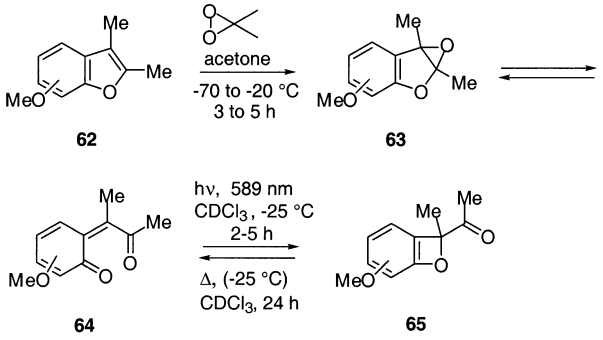


Irradiation of either *o*-hydroxyphenyldiazomethane **56** or benzofuran **57** in an argon matrix at 10 K leads to benzoxete (**36**) (Scheme 12).[44] Wentrup et al.[45] have also generated **36** by FVP of **56** and **57**, followed by photochemical cyclization of the *o*-quinone methide **39**. Their warm-up experiments demonstrated that **36** is stable up to 155 K.

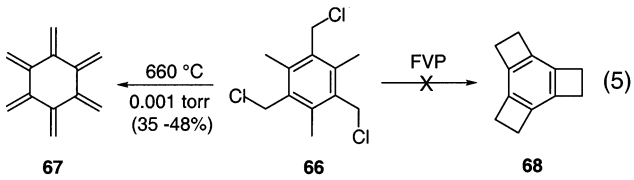
A stable benzoxete, compound **61**, was formed when **59** was photolyzed at 7.6 K using long-wavelength light (>350 nm). FVP of alcohol **58** or the trimer **60** gave *o*-quinone methide **59**, which was isolated in an Ar matrix at 7.6 K. The methyl groups on the benzene ring of **61** appear to provide stabilization, as the benzoxete could be detected spectroscopically at room temperature (Scheme 13).[45]

Oxidation of benzofuran **62** by dimethyldioxirane afforded an equilibrium mixture of the epoxide **63** and **64**. Irradiation afforded the novel benzoxete **65**. The strained and highly labile benzoxete was sufficiently stable for characterization at subambient temperatures. After 2−3 days at −20 to 10 °C, the benzoxete reverted to the quinone methide **64** and/or benzofuran epoxide **63** (Scheme 14).[46]

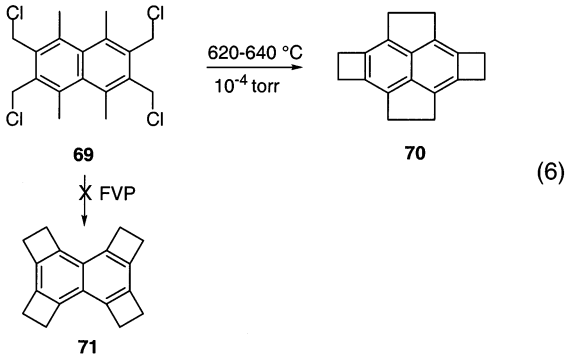
Scheme 14



The FVP procedure could not deliver highly strained systems such as tricyclobutarene **68** from **66**, as only hexaradialene **67** was formed (eq 5).[47]



Similarly, pyrolysis of **69** yields the cyclophane **70** in ∼15% yield instead of the desired hydrocarbon **71** (eq 6).[48]



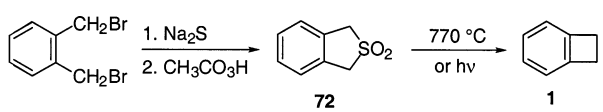
Cava and Deana showed that thermolysis of **72** over a Nichrome wire heated to 770 °C affords **1** in 67% yield (Scheme 15).[49] Photochemical desulfonation of **72** also affords **1**.[50] Optimization of this approach has provided an efficient synthesis of **1** in an overall yield of 56% for the three steps.[51]

The extrusion of SO_2 from **73** proceeds stereospecifically. Thus, thermolysis of **73** proceeds formally by disrotatory opening, followed by conrotatory ring closure to dideuterated **1** (Scheme 16).[52]

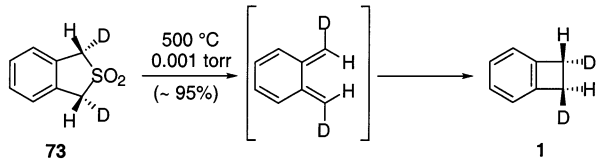
Similarly, refluxing *cis*-1-acetoxy-3-phenyl-1,3-dihydrobenzo[*c*]thiophene-2,2-dioxide (**74**) in benzene with ZnO gives **75** in 76% yield (Scheme 17).[53]

The quinoxaline **78** has been prepared via **77** in quantitative yield by thermal extrusion of SO_2 from quinoxalino-fused sultine **76** at 200 °C (Scheme 18).[54] This compound had earlier[55] been prepared by SO_2 extrusion from quinoxalino-3-sulfolene, albeit in only

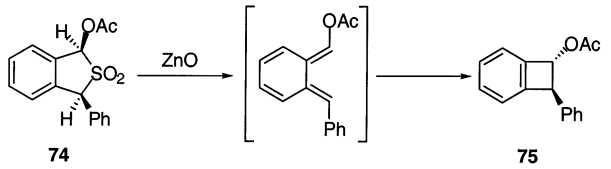
Scheme 15



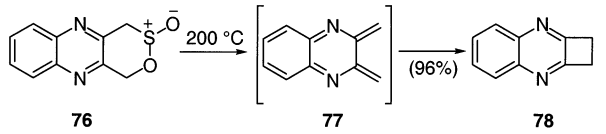
Scheme 16



Scheme 17

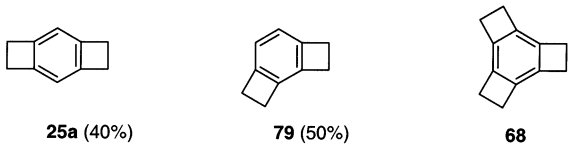


Scheme 18

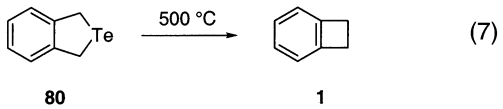


10% yield. A significant advantage in using sultines is that the thermolysis occurs at a much lower temperature than with the corresponding sulfolene.

A double-barreled version of this approach has been used to prepare **25a**[56] and **79**,[57] albeit in somewhat lower yields. It was not possible to secure tricyclobutabenzene **68** using this approach.[58]

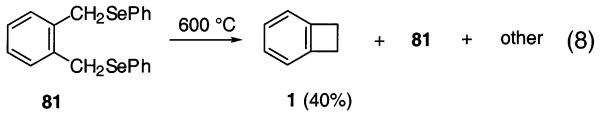


A similar extrusion reaction occurs when tellurophene **80** is pyrolyzed at 500 °C to give **1** in 74% yield.[59] The naphthalene derivative **2** has been prepared in a similar way by extrusion of SO_2 or Te (eq 7).[59,60]



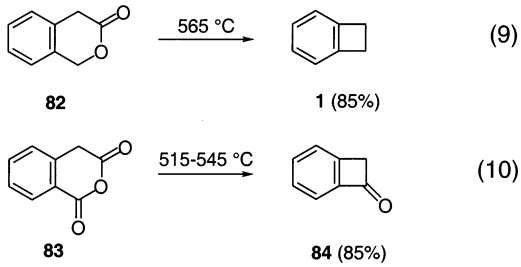
(7)

Flash pyrolysis of 1,2-bis(phenylselenomethyl)-benzene (**81**) also yields **1** along with unreacted starting material and several byproducts (eq 8).[61]



(8)

Spangler and co-workers have shown that CO_2 can be extruded from isochromone **82** at 565 °C to provide up to 85% of **1** (eq 9).[62] In strict analogy, **84** was obtained in high yield by pyrolysis of the commercially available anhydride **83** at 515−545 °C (eq 10).[63]

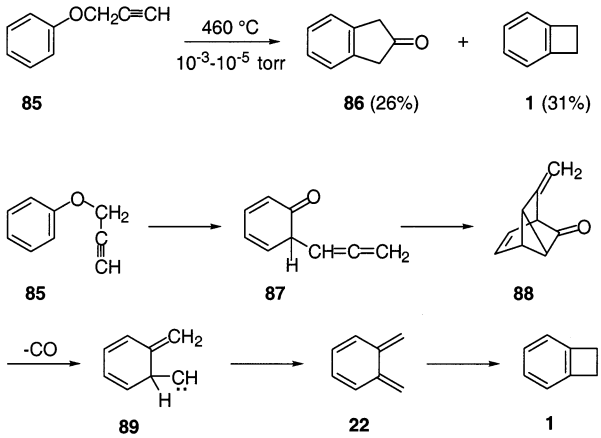


(9)

(10)

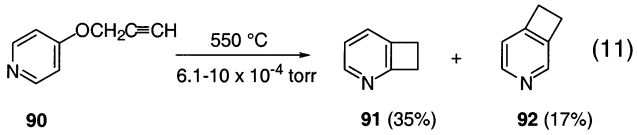
Trahanovsky and co-workers have reported that pyrolysis of phenyl propargyl ether **85** at 460 °C produces **1** and indan-2-one **86** (Scheme 19).[64] The

Scheme 19



fact that indan-2-one does not extrude CO under the reaction conditions led these workers to propose a mechanism involving an initial Claisen-type rearrangement to give the allene **87**, which then undergoes a thermally induced conversion into the tricyclic ketone **88**. Loss of CO would provide carbene **89**, which upon C−H insertion and ring closure would provide **1**.

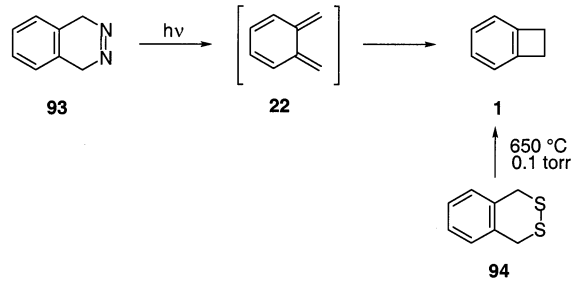
The analogous reaction for propargyl 4-pyridyl ether **90** provides an extremely efficient route to pyridines **91** and **92** (eq 11).[65]



(11)

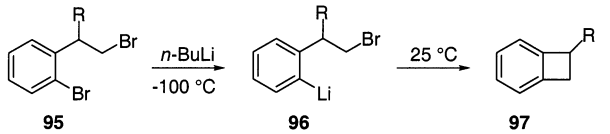
Extrusion of dinitrogen from **93** by irradiation using a high-pressure mercury lamp at −196 °C for 15−20 min gives the intermediate *o*-quinodimethane **22**, which on further irradiation gives **1**.[66] Cyclobutarene **1** was also formed by FVP of **94**, although in <10% yield (Scheme 20).[67] Photoextrusion of CO of various indan-2-ones has been reported to give cyclobutarenes.[68a−e] Plasmolysis of indan-2-one (**86**) also gives **1** as a major product.[68f] Ouchi and co-workers have studied the photochemical efficiency of *o*-quinodimethane ring closure to **1** in room-temperature solutions by using time-delayed and two-color photolysis techniques, and they reported that ring closure is not the major pathway in solution.[69]

Scheme 20



93 22 1 94

Scheme 21

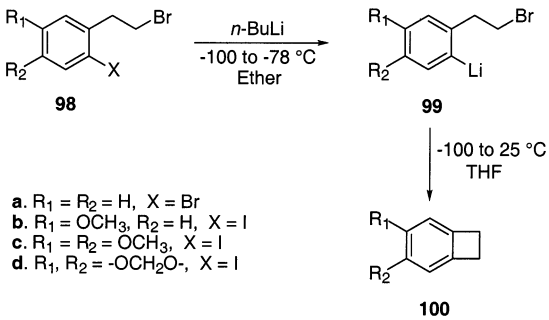


95 96 97

a. R = H
b. R = PhCH$_2$
c. R = Bu

1. R = H (68%)
97a. R = PhCH$_2$ (78%)
97b. R = Bu (86%)

Scheme 22



98 99 100

a. $R_1 = R_2 = H$, X = Br
b. $R_1 = OCH_3$, $R_2 = H$, X = I
c. $R_1 = R_2 = OCH_3$, X = I
d. $R_1, R_2 = -OCH_2O-$, X = I

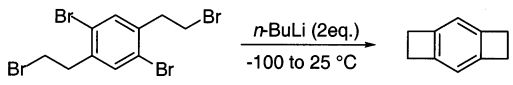
1. $R_1 = R_2 = H$ (87%)
100a. $R_1 = OCH_3$, $R_2 = H$ (93%)
100b. $R_1 = R_2 = OCH_3$ (91%)
100c. $R_1, R_2 = -OCH_2O-$ (96%)

B. Parham Cyclialkylation

Aryllithium reagents **96** substituted by a halogenated side chain ortho to the lithium atom undergo facile intramolecular cyclization reactions[70] (the Parham cyclialkylation). The simplest example of the Parham cyclialkylation is the butyllithium-promoted ring closure of **95a**−**c** to cyclobutarenes **1**, **97a**, and **97b**. The reaction is carried out by selective arylhalogen lithium exchange[71] at −100 °C, followed by intramolecular cyclization of the resulting aryllithium **96** (Scheme 21).[72,73]

Extension of the Parham cyclization methodology has led to the synthesis of 1-substituted and arylsubstituted[74,75] cyclobutarenes such as **1** and **100** in high yield (Scheme 22). The method has proved to be a convenient nonpyrolytic route to cyclobutarene and its derivatives.

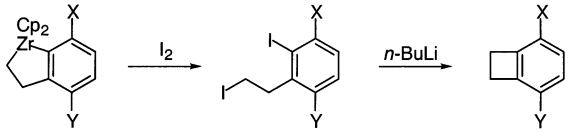
A two-fold cycloalkylation of **101** to afford benzo[1,2:4,5]dicyclobutene **25a** in 64% yield emphasizes the utility of this process (eq 12).[76]



101 25a (12)

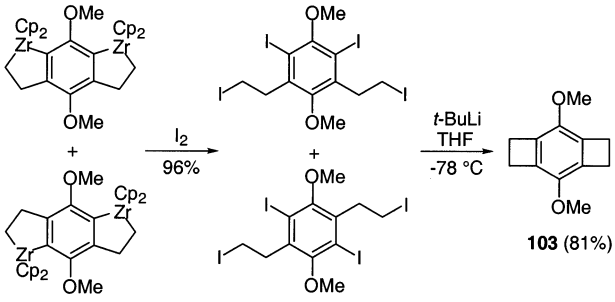
A recent development involves the use of zirconocenes as reagents for the preparation of precursors that can be converted into functionalized cyclobutarenes such as **102** and **103** (Scheme 23).[77a,b]

Scheme 23



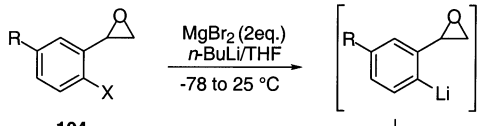
102

X	Y	Yield
OMe	H	(50%)
Me	OMe	(69%)
OMe	OMe	(70%)
Me	H	(65%)



103 (81%)

Scheme 24



104

a. R = H, X = Br
b. R = OMe, X = Br
c. R = OMe, X = I

105

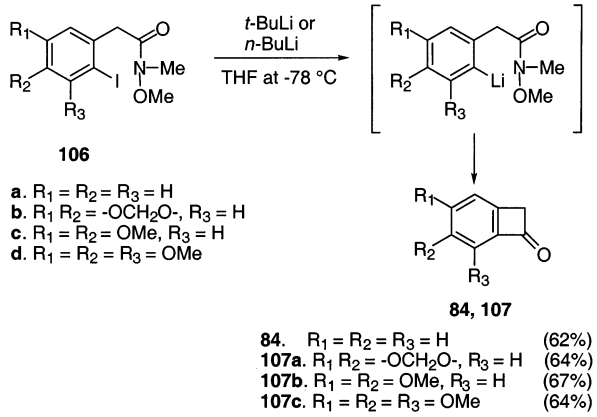
a. R = H (83%)
b. R = OMe (70%)
b. R = OMe (72%)

Intramolecular displacement of the methoxy group from *N*-(*o*-bromobenzyl)methoxyamine (**108**) by organolithium reagents affords *N*-acetylbenzoazetidine (**109**) in 21% yield (Scheme 26). Double lithiation of the aryl bromide **108** and subsequent intramolecular ring closure in exocyclic fashion explains the formation of **109**. X-ray structure determination of **109** is also reported.[81]

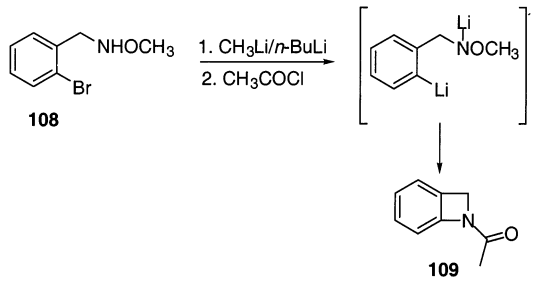
C. Cycloaddition Approaches

Photoinduced cycloaddition reactions have been used extensively to synthesize intermediates that may be converted to cyclobutarenes. For example, irradiation of a mixture of anisole and acrylonitrile in acetonitrile or ethyl acetate leads to stereoisomers

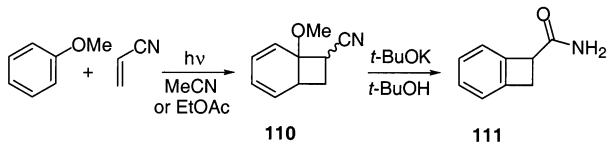
Scheme 25



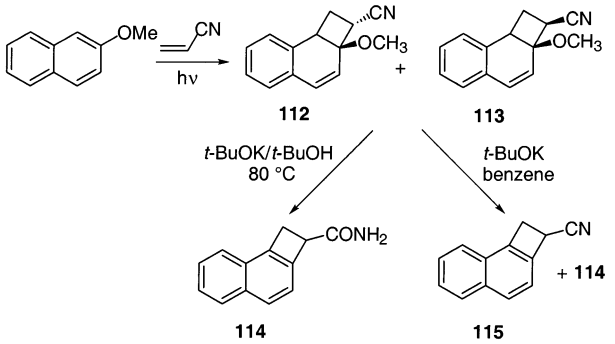
Scheme 26



Scheme 27



Scheme 28

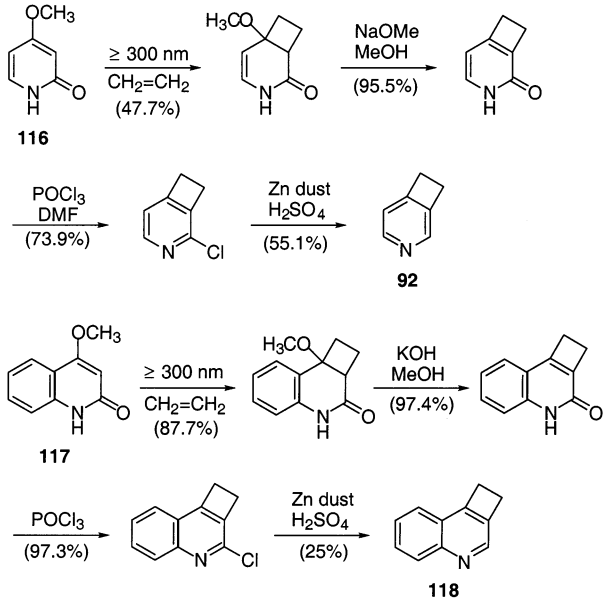


of **110** in 73% yield. Treatment of **110** with *t*-BuOK in *t*-BuOH furnishes **111** in 79% yield (Scheme 27).[72]

McCullough and co-workers have reported that photolysis of 2-methoxynaphthalene and acrylonitrile in ethanol affords a mixture of **112** and **113**. The endo isomer **113** is more stable, and upon base-catalyzed equilibration, it predominates (9:1). Treatment of either isomer with *t*-BuOK in *t*-BuOH at 80 °C affords the carboxamide **114** in 22% yield.[83a,b] When the adducts are refluxed with *t*-BuOK in dry benzene, the formation of **115** (48%) along with **114** (35%) is observed (Scheme 28).[84]

Kaneko et al. have used the same approach for the synthesis of **92** from **116** and **118** from **117** (Scheme 29).[85−87]

Scheme 29



Scheme 30

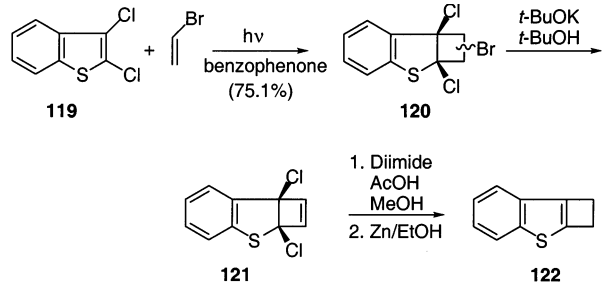
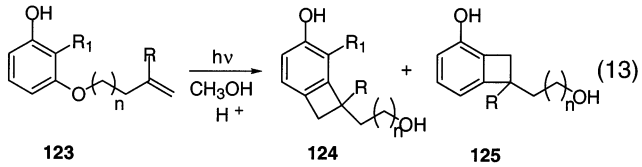


Table 2. Cyclobutarenes from the Photolysis of 3-Alkenyloxyphenols

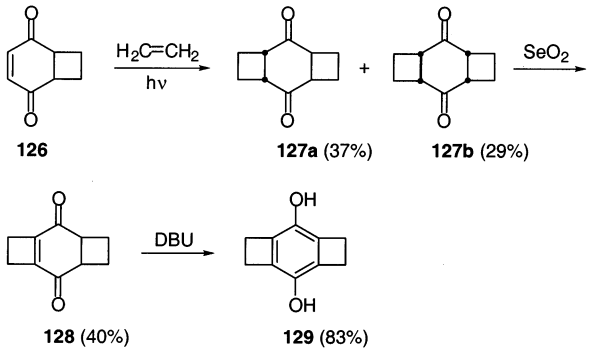
R	R_1	*n*	yield (%)	ratio **124**/**125**
H	H	1	50	9/1
H	H	2	59	2/1
CH_3	H	1	60	5/1
H	CH_3	1	49	1/0

2,3-Dichlorobenzo[*b*]thiophene (**119**) undergoes photocycloaddition with vinyl bromide in a benzophenone-sensitized reaction. Addition of 2,6-di-*tert*-butyl-*p*-cresol as a free radical inhibitor circumvents the photopolymerization of the olefin. Dehydrobromination of the cycloadduct **120** with *t*-BuOK/*t*-BuOH gives **121** in 77% yield. Reduction of **121** with diimide and then with Zn dust affords **122** as a clear oil in 45% yield (Scheme 30).[88]

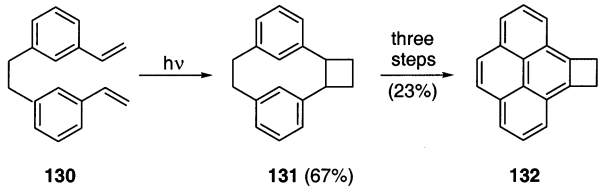
Photolysis of 3-alkenyloxyphenols **123** in acidic methanol affords **124** and **125**. The reaction is sensitive to the chain length of the 3-alkenyloxyphenols (eq 13) (Table 2). When the double bond in **123** is substituted by alkyl groups, complex mixtures are obtained.[89]



Scheme 31



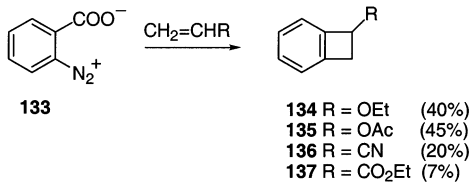
Scheme 32



Photochemical cycloaddition of **126** and ethylene gives a mixture of syn and anti adducts **127a** and **127b**. Upon treatment with SeO_2, both stereoisomers are converted into **128**, which on further oxidation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) affords **129** (Scheme 31).[90]

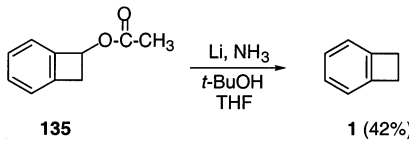
Synthesis of 1,2-dihydrocyclobuta[*e*]pyrene **132** has been accomplished by photolysis of **130** as a key step in a multistep synthesis (Scheme 32).[91]

The benzyne−alkene cycloaddition is thermally allowed due to the unusually low-lying lowest unoccupied molecular orbital (LUMO) of benzynes. Thus, 1-substituted cyclobutarenes may be prepared in fair yield by the reaction of benzyne, generated from benzenediazonium-2-carboxylate **133**, with olefins (eq 14).[92a−c] Benzyne, generated from **133**, is also reported to react with *cis*-, *trans*-1,2-dichloroethene[92d] and 1,1-dichloroethene[92e] to afford the corresponding substituted cyclobutarenes.



(14)

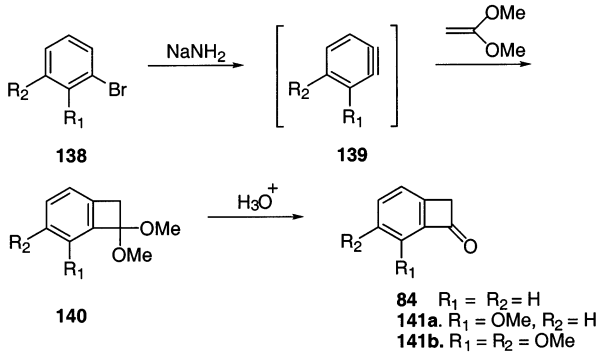
Markgraf et al. have reduced **135** to **1** using Li/NH_3 under conditions similar to those of the Henbest reaction (eq 15).[93]



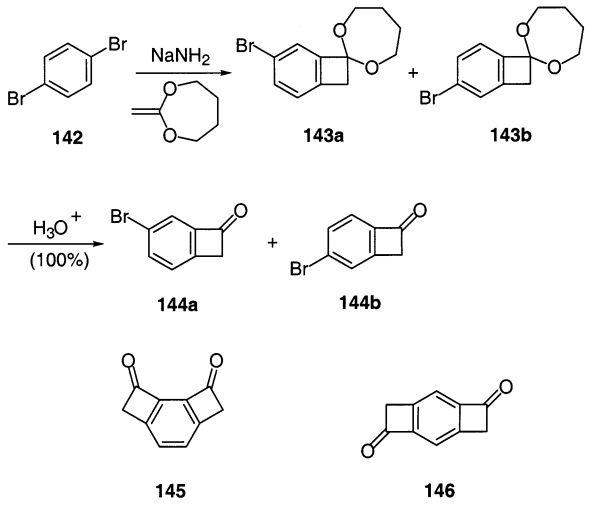
(15)

Upon hydrolysis, the cycloaddition adducts of functionalized benzynes **139** and 1,1-dimethoxyethylene afford cyclobutenones in 60−70% yield (**84**, **141a**,**b**) (Scheme 33).[94] The same approach has been modified by using 2-methylene-1,3-dioxepane to synthesize

Scheme 33



Scheme 34

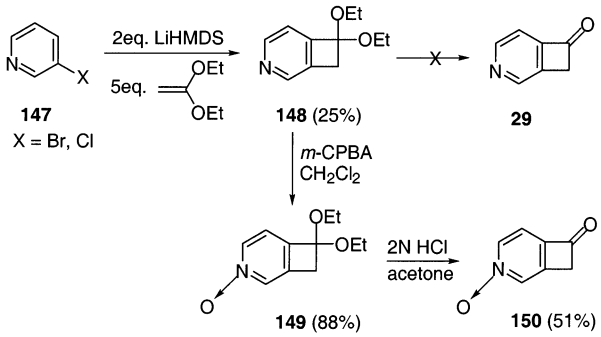


benzocyclobutenones **144a** and **144b**. Thus, treatment of 1,4-dibromobenzene **142** with 1 equiv of $NaNH_2$ in the presence of 2-methylene-1,3-dioxepane led to the formation of ketal regioisomers **143a** and **143b** in an 8:2 ratio in 21% yield. Ketals **143a** and **143b**, on acid hydrolysis, gave benzocyclobutenones **144a** and **144b** in 100% yield. When **142** was treated with 3 equiv of $NaNH_2$, the regioisomer **145** was formed instead of **146**,[95] as reported earlier (Scheme 34).[96]

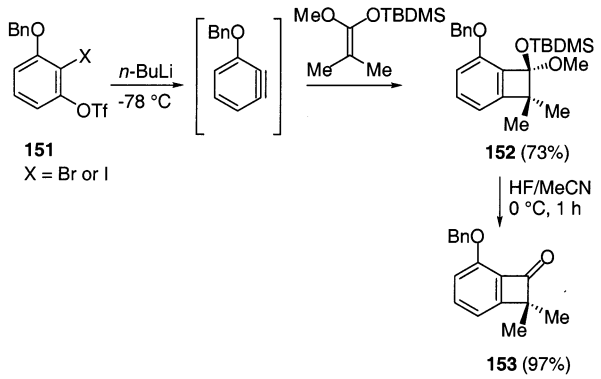
This approach has been used to synthesize an analogue of pyrido[*c*]cyclobuten-4-one **150**, by cycloaddition of 1,1-diethoxyethylene and 3,4-pyridyne generated from **147**. The reaction is totally regioselective, leading to the formation of regioisomer **148** in 25% yield. Surprisingly, the deprotection of **148** could not be effected to afford **29**. The fact that a similar carbocyclic compound undergoes hydrolysis smoothly indicates that this reaction is affected by the nitrogen atom of the pyridyl ring. However, oxidation of **148** with *m*-CPBA produced *N*-oxide **149**, which underwent acid hydrolysis to provide the pyridoketone **150** in 51% yield (Scheme 35).[97a] Benzothietes have also been prepared by [2 + 2] cycloaddition of stabilized thiones with benzynes.[97b]

When *o*-haloaryl triflates **151** are subjected to halogen−lithium exchange in the presence of ketene silyl acetals, the resulting arynes are trapped to give cycloadducts **152** in high yield.[98] Subsequent acid hydrolysis of **152** gives **153** in nearly quantitative yield (Scheme 36). The regiochemical outcome is explained by the inductive effect of the alkoxy group,

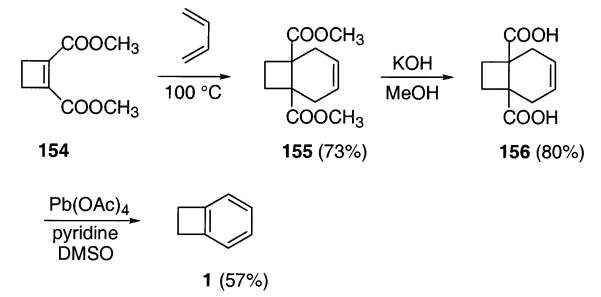
Scheme 35



Scheme 36



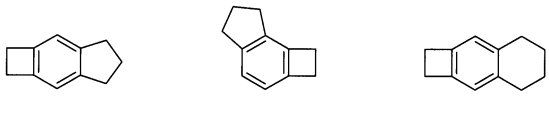
Scheme 37



which directs the nucleophilic attack of the β-carbon of the ketene silyl acetal at the site distal from the alkoxy group.

The Diels−Alder reaction provides a useful route to annelated derivatives of cyclobutene. The cycloaddition of butadiene to cyclobutene ester **154** occurs smoothly at 110 °C to give adduct **155** in 73% yield. Hydrolysis of **155**, followed by oxidative decarboxylation of **156**, gives **1** (Scheme 37).[99,100] The Diels−Alder approach has also been employed in the synthesis of fluorinated cyclobutarenes.[101]

Bisannelated benzenes such as **25a**, **79**, **157**, **158**, and **159** have also been prepared using the Diels−Alder approach.[100,102]



157 **158** **159**

The venerated hydrocarbon tricyclobutabenzene **68**[103] was finally prepared via the Diels−Alder approach (Scheme 38).

Scheme 38

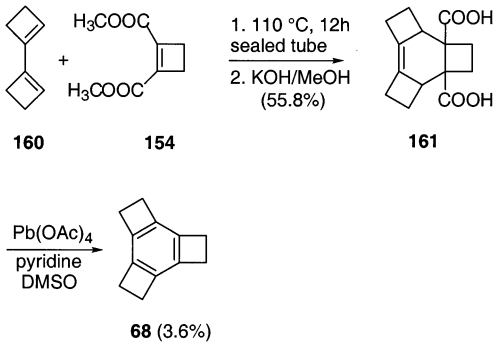
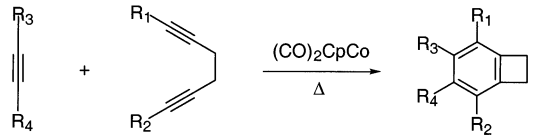


Table 3. Cyclobutarenes from the [2 + 2 + 2] Cycloaddition of Hexa-1,5-diynes with Acetylenes

R_1	R_2	R_3	R_4	yield (%)
H	H	CO_2Me	CO_2Me	14
H	H	H	Ph	17
H	H	Ph	Ph	48
H	H	C_6H_{13}	H	13
H	H	TMS	TMS	>60
H	H	CH_2OMe	CH_2OMe	33
H	H	CH_2OMe	TMS	55
H	H	CH_2OH	H	14
Me	Me	Ph	Ph	20
Me	Me	CO_2Me	CO_2Me	28
TMS	H	TMS	H	13
TMS	TMS	TMS	H	2
TMS	H	TMS	CH_2OMe	16

Cobalt-mediated [2 + 2 + 2] cyclization of hexa-1,5-diynes **163** with acetylenes **162** results in the formation of cyclobutarenes.[104,105] Commercially available dicarbonyl(η^5-cyclopentadienyl)cobalt(0) [$(CO)_2$-CpCo] is the catalyst of choice for these reactions. The lability of the carbonyl ligands under thermal or photochemical conditions makes possible the formation of a catalytically active, coordinatively unsaturated cobalt species. A range of functionalities can be tolerated, but particularly good yields are obtained when R_3 and R_4 are trimethylsilyl groups (eq 16) (Table 3).[106,107] These bulky trimethylsilyl substituents hinder self-trimerization of the monoacetylenic component. The trimethylsilyl group in **164** can be substituted by different electrophiles in a selective, stepwise fashion.[108]



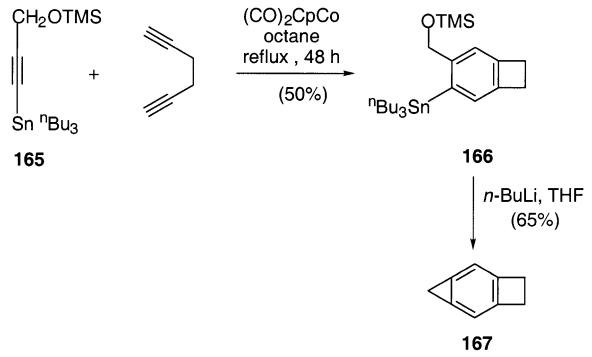
(16)

162 **163** **164**

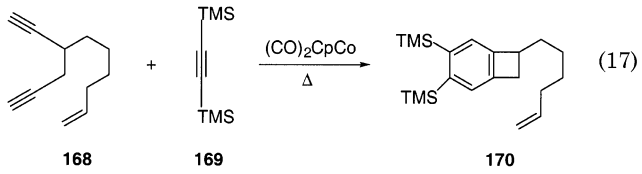
Appropriately substituted cyclobutarenes can serve as important intermediates in the preparation of numerous polycyclic systems[109] and polymers.[13] Stang et al. have developed a short and improved high-yield procedure for the preparation of cyclopropa[4,5]-benzocyclobutene (Rocketene, **167**) (Scheme 39).[110]

The cobalt-mediated cycloaddition strategy is also applicable to the synthesis of cyclobutarenes carrying a substituent on the cyclobutene moiety. For example, co-oligomerization of 4-ethynyl-9-decen-1-yne (**168**) with bis(trimethylsilyl)acetylene (**169**) is cata-

Scheme 39



lyzed by dicarbonyl(η^5-cyclopentadienyl)cobalt(0) to give 1-(hex-5-enyl)-4,5-bis(trimethylsilyl)benzocyclobutene (**170**) in 60% yield (eq 17).[111]

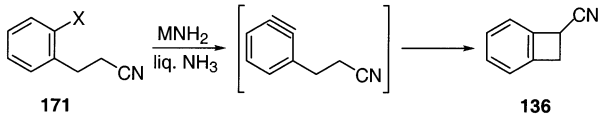


(17)

D. Intramolecular Addition of Carbanions to Benzynes

Intramolecular addition of carbanions generated on the side chain of the aryne constitutes an efficient pathway to substituted cyclobutarenes. Thus, treatment of **171** with $NaNH_2$ or KNH_2 in liquid NH_3 affords 1-substituted cyclobutarenes **136** (Scheme 40).[112−114] The synthesis of 1-cyanobenzocyclobutenes

Scheme 40

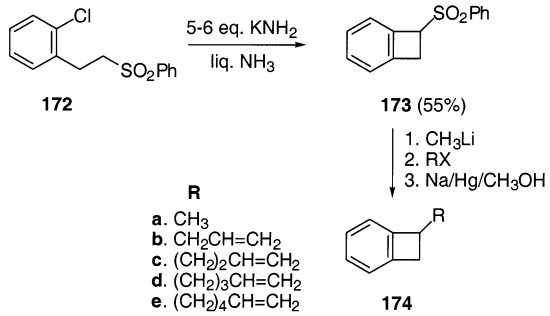


X = Cl, Br
M = Na, K

has been used extensively by Kametani and coworkers for the preparation of precursors for natural product syntheses.[115] Cyclobutarenes **136** substituted at the C-1 position[116] can be manipulated into a variety of functionalities for further appending the dienophile portion. Birch reduction of **136** is reported to afford **1** in 98% yield.[117]

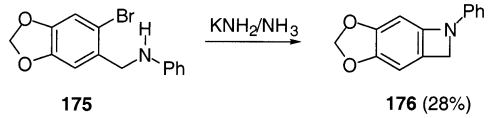
This route has been used by Gowland and Durst and also by Iwao to afford several 1-benzocyclobutyl

Scheme 41



phenyl sulfones in good yields (Scheme 41).[118] Sulfone **173** has been further converted into 1-substituted cyclobutarenes **174** via reaction of its α-sulfonyl carbanion with typical electrophiles, followed by desulfonation, in >80% yields (Scheme 41).[119]

The *N*-phenylbenzoazetidine derivative **175** was obtained by an intramolecular amination of the aryne formed from *N*-(2-bromobenzyl)aniline (**176**) (eq 18).[120]

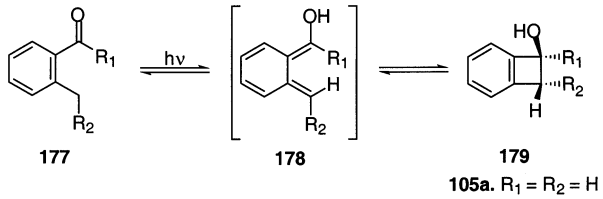


(18)

E. Rearrangements with Hydrogen Transfer

1-Acyl-2-alkylbenzene derivatives **177** undergo photoenolization via a [1,5] hydrogen shift, followed by cyclization of the intermediate **178**, to give benzocyclobutenols (**105a**, **179**) (Scheme 42, Table 4).[121−124]

Scheme 42

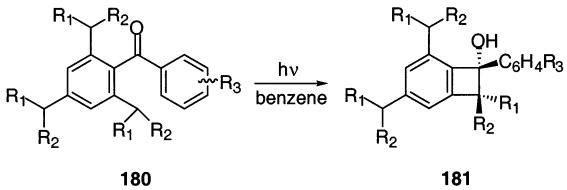


105a. $R_1 = R_2 = H$

Table 4. 1,2-Dihydrocyclobuten-1-ols from the Photolysis of 1-Acyl-2-alkylbenzene Derivatives

entry	R_1	R_2	product yield (%)
a	H	H	10
b	Me	Me	~100
c	Me	OMe	~100
d	Me	$CH_2OCH_2CH{=}CH_2$	~100
e	Me	$CH_2OCH_2CH_2CH{=}CH_2$	~100
f	CF_3	$CH_2CH_2CH{=}CH_2$	39
g	Ph	H	~100

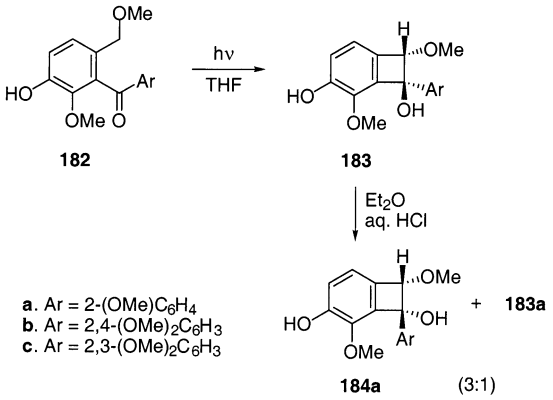
This is the method of choice for the stereoselective synthesis of benzocyclobutenols.[125,126] Highly substituted 2,4,6-trialkylaroylbenzenes **180** undergo efficient conversion to 1-aryl-4,6-dialkylbenzocyclobutenols **181** on irradiation in benzene (eq 19).[127−129]



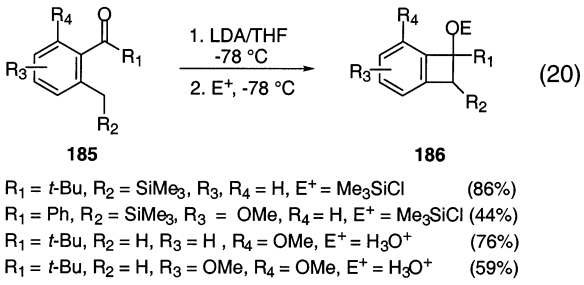
(19)

Irradiation of highly congested phenolic 2-(methoxymethyl)benzophenones **182** provides a rapid, efficient, and stereoselective entry into the corresponding 1-aryl-1-hydroxy-2-methoxybenzocyclobutenes **183** in >90% yield (Scheme 43).[130,131] Treatment of an ethereal solution of **183a** with 6 N HCl at room temperature for several hours yielded a 3:1 equilibrium mixture of **183a** and **184a**. Formation of **184a** is assumed to be a consequence of acid-promoted isomerization of tertiary alcohol **183a**, to give the more stable isomer **184a**.

Scheme 43



The formation of benzocyclobutenols **186** has been achieved by intramolecular cyclization of 2-acylbenzyllithium agents. These are prepared by the reaction of 1-acyl-2-alkylbenzenes **185** with lithium diisopropylamide. Cyclization of the 2-acylbenzyllithium intermediate in the presence of trimethylsilyl chloride gives trimethylsilyl ethers. Free alcohols are obtained if aqueous ammonium chloride is used instead of trimethylsilyl chloride (eq 20).[132]



(20)

Irradiation of *o*-alkylphenyl 1,3-diketones **187** in hexane gives benzocyclobutenols **188**. Pyrolysis of benzocyclobutenols **188a**,**b**,**d**−**f** ($R_1 = R_2 = H$) gave the corresponding benzocyclobutenones **84** and **189** in good yield. In contrast to **188a**,**b**,**d**−**f**, the pyrolysis of **188c**,**g** ($R_1 = CH_3$) gave starting ketones **187** as the major product, along with a small amount of benzocyclobutenone **189** and ketone **190** (Scheme 44, Table 5).[133−136]

Cycloocta-1,3-dien-5-yne **192**, generated by the thermolysis of **191** at 140−180 °C, isomerizes to **1**

Scheme 44

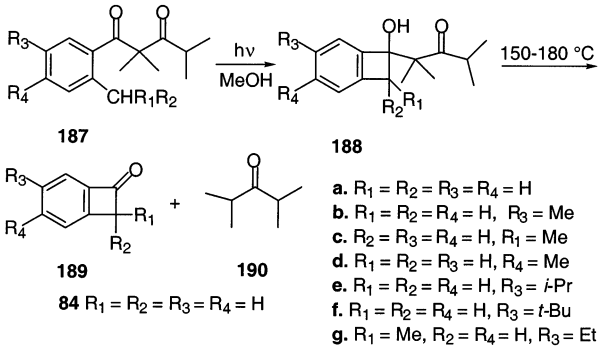
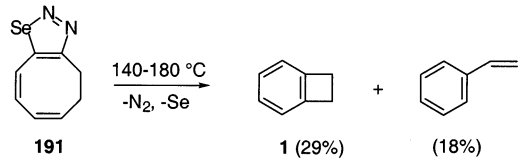


Table 5. Benzocyclobutenones 189 via Photochemical Cyclization of Diketones 187

entry	diketone **187**	yield **188** (%)[a]	conditions of pyrolysis of **188** temperature and pressure (°C/ Torr)	yield **189** (%)
1	**a**	72	180/0.5	72[b]
2	**b**	87	150/0.7	87[b]
3	**c**	60	180/0.5	∼10
4	**d**	42	150/760	75[b]
5	**e**	44	150/0.5	58[b]
6	**f**	58	150/0.5	67[b]
7	**g**	50	150/0.5	∼10

[a] Based on converted starting material. [b] Isolated yield

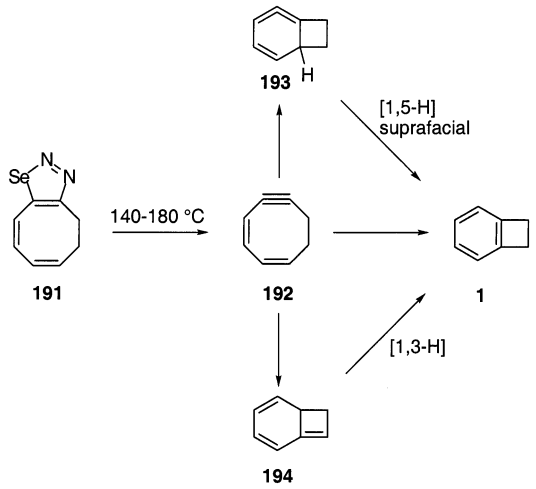
and styrene (eq 21).[137] Speculative pathways for the



(21)

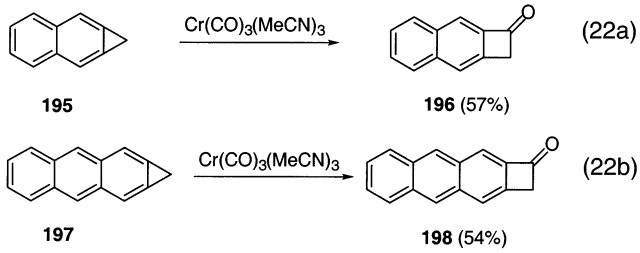
formation of **1** are described in Scheme 45.

Scheme 45



F. By Ring Expansion Reactions

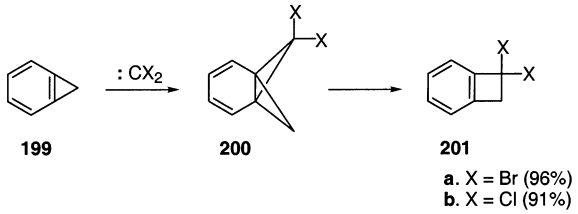
The reaction of 1*H*-cyclopropa[*b*]naphthalene (**195**) and 1*H*-cyclopropa[*b*]anthracene (**197**) with tris(acetonitrile)tricarbonylchromium affords cyclobutanaphthalenone **196** and cyclobutaanthracenone **198**, respectively (eqs 22a and 22b).[138] Formation of the ketones may be explained by the oxidative addition of the metal to the strained ring, followed by insertion of CO into the C_{Ar}−C bond. Reductive elimination of the metal would provide the ketones.



(22a)

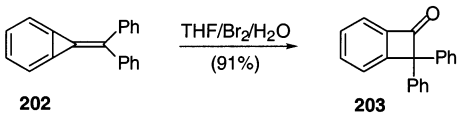
(22b)

Scheme 46



Cycloproparene **199** reacts smoothly with dibromo- and dichlorocarbene to give **200**, which rearranges to 1,1-dihalobenzocyclobutene **201** (Scheme 46).[139]

Bromination of alkylidene cycloproparene **202** leads to the ring expansion product **203**. The reaction is rapid, and the electrophile is first captured at the exocyclic carbon center. The ensuing cycloproparenyl cation is stabilized by a number of routes available to it. One such route leads to the ring-expanded product (eq 23).[140]



(23)

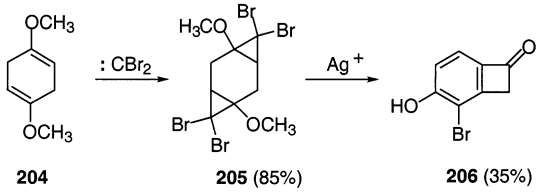
Addition of dibromocarbene to **204** affords **205**. The action of silver salts on **205** results in the formation of benzocyclobutenone **206**, although in low yield (Scheme 47).[141,142] Another example involves the rearrangement of **207** at 140 °C to 1-chlorobenzocyclobutene **208**, with the evolution of HCl (Scheme 48).[143]

G. From Diallenes

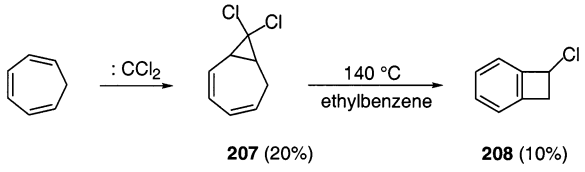
Conjugated acyclic diallenes and *o*-diallenylarenes undergo cyclization to afford cyclobutarenes. The two possible diastereomers of **210**, formed in a ratio of 3:2, were independently subjected to thermolysis in refluxing *p*-xylene. Electrocyclic ring opening of **210**, followed by ring closure, leads to the *o*-quinodimethane **212** and ultimately to cyclobutarene **213** in 49−82% yield (Scheme 49).[144]

Toda and co-workers have reported a very simple route to cyclobutarene **216** following the *o*-diallene approach. Enediynediol **214**, on treatment with $SOCl_2$, rearranges to diallene intermediate **215**, which after thermal cyclization leads to **216**. However, acetylenic

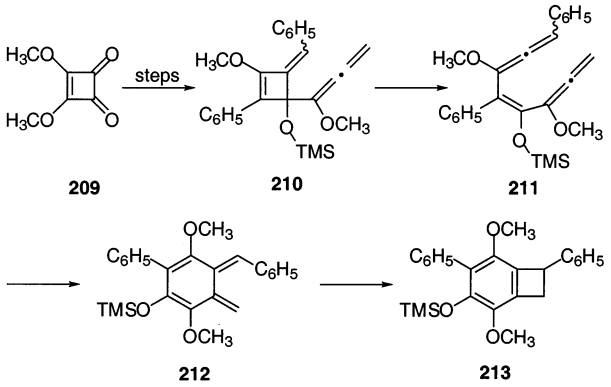
Scheme 47



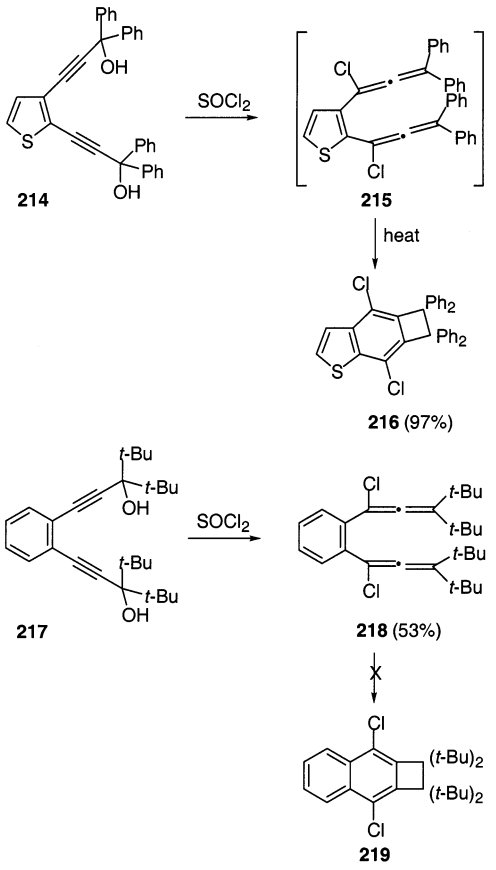
Scheme 48



Scheme 49



Scheme 50



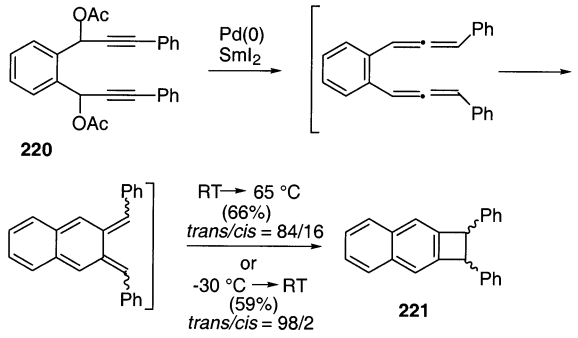
alcohol **217** substituted by bulky *tert*-butyl groups reacted only as far as the thermally stable diallene intermediate **218** (Scheme 50).[145]

Similarly, **220**, on reduction with Pd(0)−SmI_2, followed by ring closure, affords a mixture of *trans*- and *cis*-**221**. When the reduction was performed at −30 °C and the reaction was stirred at room temperature for several hours, a mixture of the diastereoisomers of **221** (trans:cis = 98:2) was obtained in 59% yield (Scheme 51).[146]

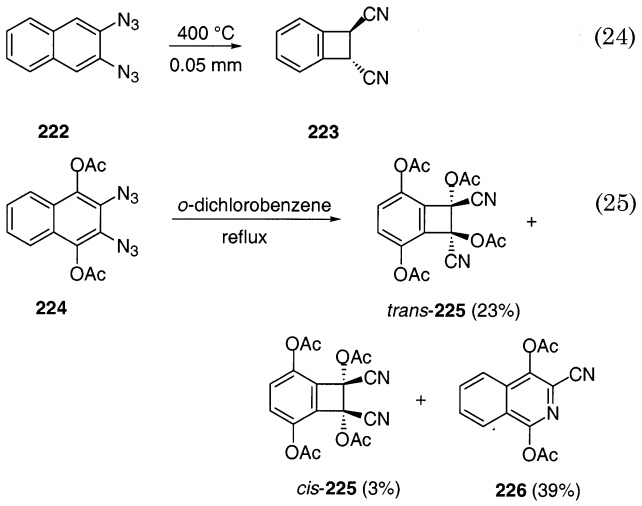
H. Miscellaneous Routes to Cyclobutarenes

FVP of 2,3-diazidonaphthalene (**222**) furnished *trans*-1,2-dicyanobenzocyclobutarene (**223**) in 55% yield (eq 24).[147] In contrast, thermolysis of **224** in refluxing *o*-dichlorobenzene gave a mixture of *cis*-

Scheme 51



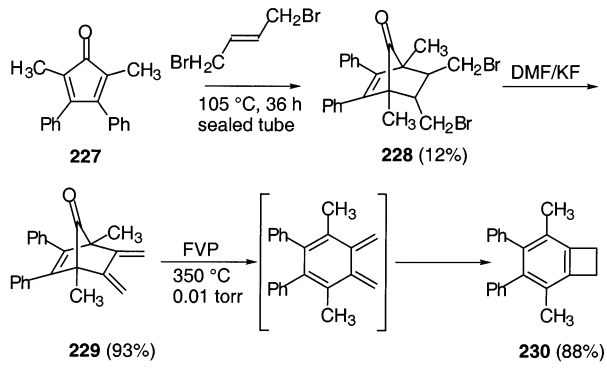
and *trans*-**225**, along with the unexpected isoquinoline **226** (eq 25).[148]

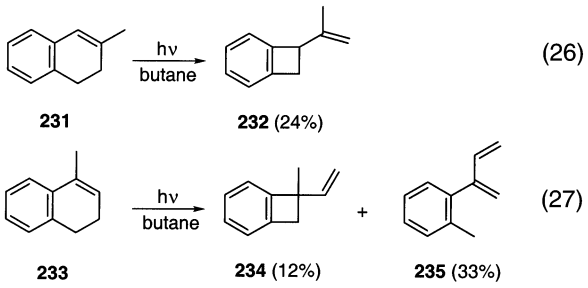


Reaction of hemicyclone **227** with (*E*)-1,4-dibromobut-2-ene in a sealed tube yielded adduct **228**. FVP of trienone **229**, obtained by dehydrobromination of **228** by fluoride ion, led to decarbonylation to afford cyclobutarene **230** (Scheme 52).[149] Theoretical studies conclude that the loss of carbon monoxide from **229** is a thermally allowed cheletropic process, that is further aided by relief of strain in the bicyclic ring system and the formation of a stable aromatic species.

Gas-phase irradiation of **231** in the presence of a large excess of butane gave **232** in 24% yield. Similarly, **233** gave a mixture of **234** and **235** (eqs 26 and 27).[150]

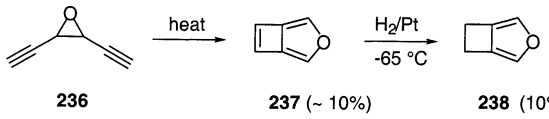
Scheme 52



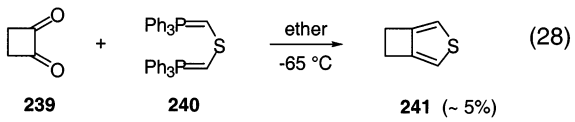


Bergman and Vollhardt have prepared **237** by the thermal rearrangement of **236**. Partial hydrogenation of **237** gives 3-oxabicyclo[3.2.0]hepta-1,4-diene (**238**) (Scheme 53).[151]

Scheme 53



3-Thiabicyclo[3.2.0]hepta-1,4-diene (**241**) has been synthesized by a Wittig reaction between cyclobutane-1,2-dione (**239**) and the bis(ylide) **240** (eq 28).[152,153]

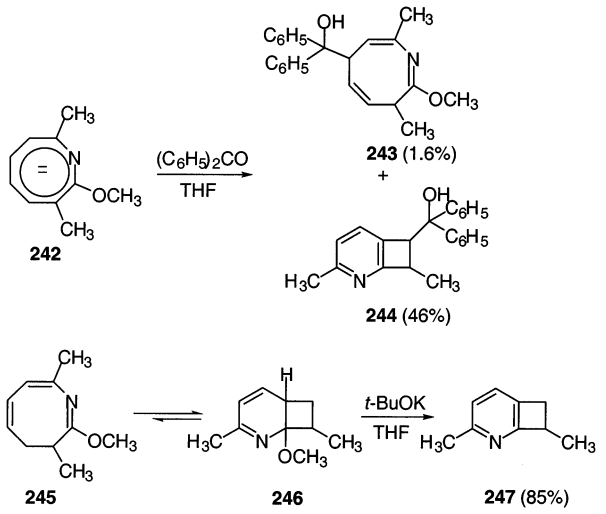


Reaction of 2-methoxyazocines with alkali metals in liquid ammonia, tetrahydrofuran, or dimethoxyethane generates azocinyl dianions. Several 2-methoxyazocinyl dianions, on treatment with benzophenone and benzaldehyde, give C_6-monoalkylation products together with 2,3-pyridocyclobutene derivatives. These strained heterocycles are formed by initial carbon−carbon bond formation at C_4, valence isomerization to 1-methoxy-2-azabicyclo[4.2.0]octadiene, and intramolecular 1,5-hydrogen transfer with concomitant loss of methoxide ion and aromatization. For example, reaction of dipotassium 3,8-dimethyl-2-methoxyazocinate (**242**) in THF with benzophenone gives triene **243** and 2,3-pyridocyclobutene **244**. The generation of the 2,3-pyridocyclobutene system is general. For example, 3,4-dihydro-3,8-dimethyl-2-methoxyazocine (**245**), on treatment with *t*-BuOK in refluxing anhydrous THF, affords dimethyl-2,3-pyridocyclobutene **247** in good yield (Scheme 54).[154]

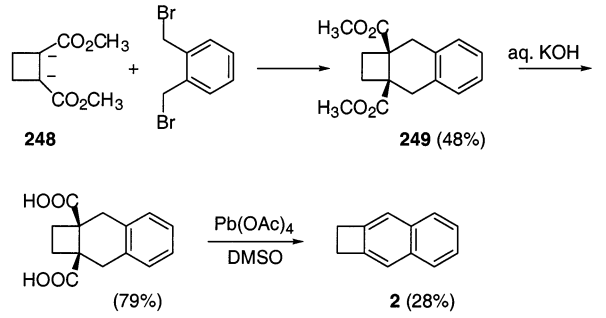
Dimethyl cyclobutane-1,2-dicarboxylate dianion (**248**) reacts with α,α′-dibromo-*o*-xylene to give the annelated product **249**. Base hydrolysis, followed by decarboxylation using $Pb(OAc)_4$ in DMSO, gives **2** (Scheme 55).[155]

Markgraf and co-workers have synthesized **251** and its derivatives by base-catalyzed condensation of cyclobutanone **250** with *o*-aminobenzaldehyde (eq

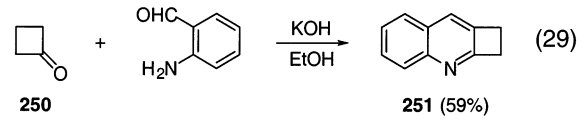
Scheme 54



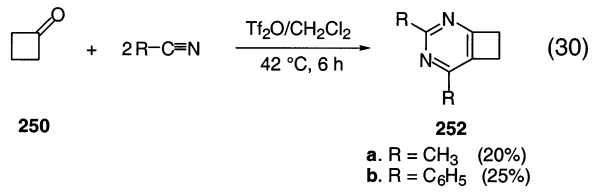
Scheme 55



29).[156,157] Wilk et al. also reported a synthesis of **251** but in only 6% yield.[158]



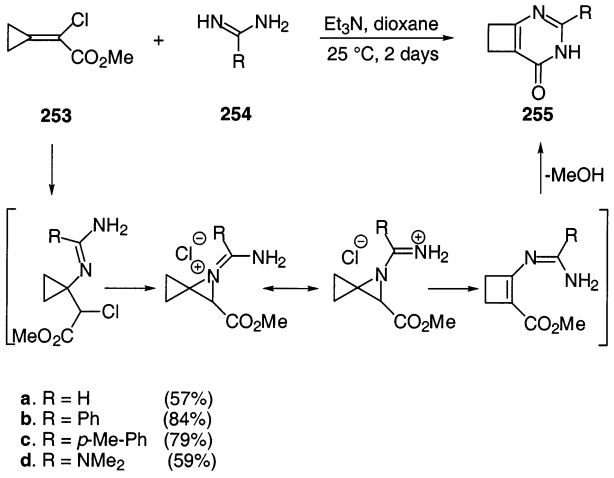
Cyclobutanone **250** reacts with aliphatic or aromatic nitriles in the presence of triflic anhydride (Tf_2O) to give 2,4-dialkyl/diarylcyclobutapyrimidines **252** (eq 30).[159]



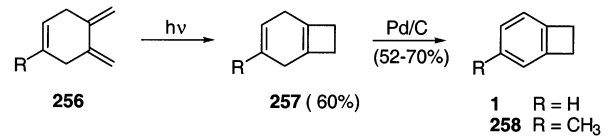
Recently, an efficient one-step synthesis of 2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-ones (**255**) from cyclopropylideneacetate **253** and amidines **254** as well as *N*,*N*-dimethylguanidine has been reported (Scheme 56).[160]

Inter- and intramolecular photocyclization reactions have been employed for the synthesis of cyclobutarenes. Garrett and Fonken reported the synthesis of **1** and the 3-methyl derivative **258** by photolysis of triene **256**, followed by catalytic dehydrogenation of the intermediate **257** (Scheme 57).[161]

Scheme 56



Scheme 57

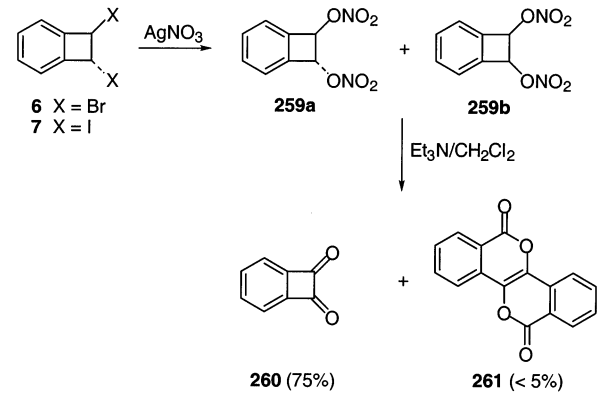


I. Benzocyclobutenedione Syntheses

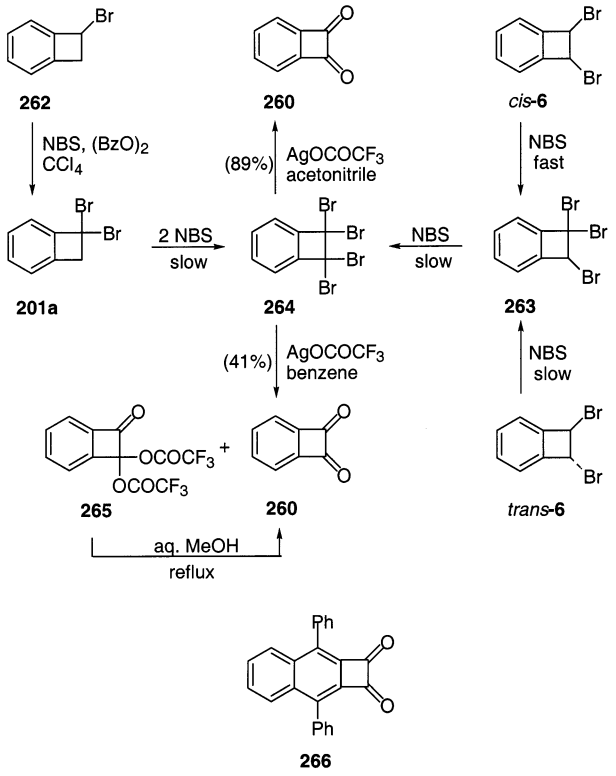
Benzocyclobutenedione **260** has been the subject of previous reviews.[162,163] The first synthesis was achieved in 1957 by Cava and Napier, as outlined in Scheme 58.[164] The dinitrates **259a** and **259b**, prepared by reacting **7** with silver nitrate, could be converted to the dione in 75% yield by treatment with triethylamine in refluxing methylene chloride. A small amount (<5%) of the dimer **261** was also isolated.[164,165] The dibromide **6** has also been used for the synthesis of **260**.[165] Benzocyclobutenedione is thermally stable and can be sublimed without decomposition at 100 °C at 0.2 Torr.

The tetrabromide **264** has also been used as a point of departure in the synthesis of **260**. The tetrabromide was prepared by bromination of either 1-bromobenzocyclobutene or 1,2-dibromobenzocyclobutene (cis or trans) by *N*-bromosuccinimide (NBS).[166−168] Conversion into the dione **260** was achieved in 89% yield by treatment with silver trifluoroacetate in acetonitrile (Scheme 59).[165] However, hydrolysis of **264** in silver trifluoroacetate in benzene gave **260** in 41% yield and a small amount of byproduct **265**.

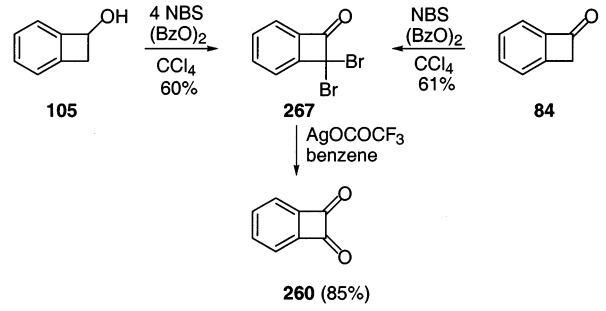
Scheme 58



Scheme 59



Scheme 60

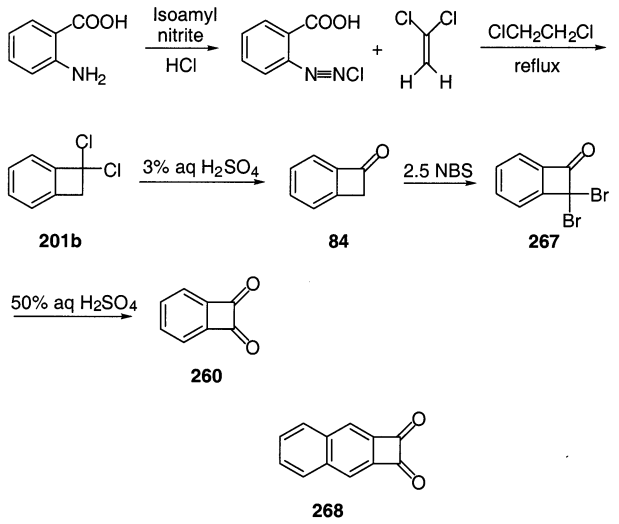


Byproduct **265** can be converted into benzocyclobutenedione in refluxing aqueous methanol.[165−168] 3,8-Diphenylnaphtho[*b*]cyclobutene-1,2-dione **(266)** has been synthesized in strict analogy to the route used for **260**.[169]

1,1-Dibromobenzocyclobutenone **267**, an alternative precursor, can be prepared by bromination of either benzocyclobutenol **105** or benzocyclobutenone **84** and converted into **260** in 85% yield by reaction with silver trifluoroacetate, followed by aqueous workup (Scheme 60).[170,171]

An alternative route to **267**,[170−172] developed by South and Liebeskind, uses the cycloadduct **201b** of benzyne and vinylidene chloride as a point of departure.[173] Hydrolysis of **201b** using aqueous sulfuric acid yielded benzocyclobutenone **84**, which was subsequently converted to the dione **260**. Bromination of **84** using 2.5 equiv of NBS gave **267**, which on hydrolysis by 50% H_2SO_4 gave **260** in 40% overall yield (Scheme 61).[173] The benzyne approach has been exploited by McOmie et al. for the synthesis of 3,6-dimethoxybenzocyclobutenedione[174] and its naphtho analogue **268**.[92e]

Scheme 61



Scheme 62

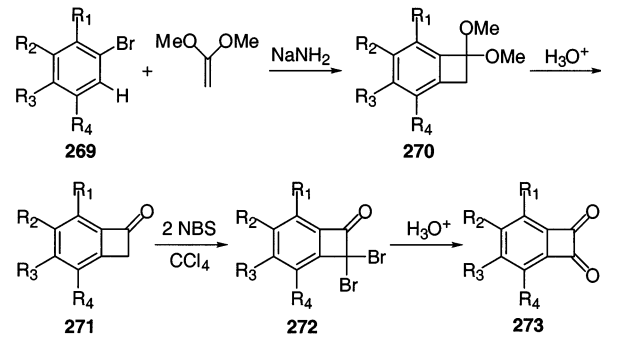


Table 6. Benzyne-Mediated Synthesis of 273

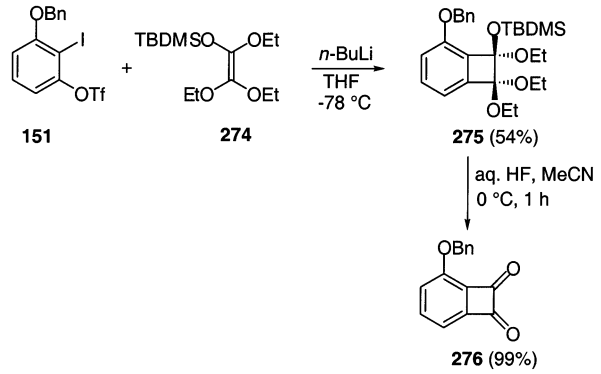
273	R_1	R_2	R_3	R_4	yield (%)
a	OCH_3	H	H	H	55
b	H	OCH_3	H	H	50
c	OCH_3	OCH_3	H	H	60
d	OCH_3	H	OCH_3	H	88
e	OCH_3	H	H	OCH_3	66
f	$-OCH_2O-$		H	H	53
g	F	H	H	H	66

A similar approach affords substituted benzocyclobutenediones. The cycloadduct **270**, prepared from the reaction of 1,1-dimethoxyethylene and the tetrasubstituted benzyne that is generated in situ by dehydrohalogenation of **269**, affords substituted benzocyclobutenones **271** in moderate to good yields (Scheme 62). The benzocyclobutenones are then subjected to bromination using NBS, followed by acid-catalyzed hydrolysis of the geminal dibromo group to give **273** (Scheme 62, Table 6).[95] In most cases, only one regioisomer of **270** was formed.

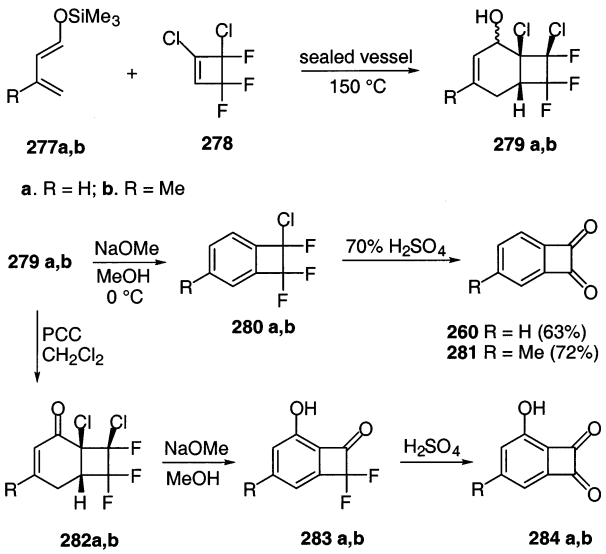
Another variation of the benzyne approach uses *o*-haloaryl triflate **151** as the source of the benzyne. Derivatives of **260**, substituted at the 3-position, have been prepared from this reagent. Thus, treatment of **151** with *n*-BuLi (THF, −78 °C) in the presence of the silyl acetal **274** affords **275**. Hydrolysis of **275** gives **276** (Scheme 63).[98]

The reaction of 1,4-dichloro-3,3,4-trifluorobutene **278** with 1-trimethylsiloxy dienes **277a** and **277b** occurred regiospecifically in the absence of solvent

Scheme 63



Scheme 64



in a pressure-sealed vessel at 150 °C to give cycloadducts **279a** and **279b** in high yield. These adducts exist as a mixture of two epimeric alcohols and can be aromatized readily by treatment with NaOMe/MeOH at 0 °C to give **280a** and **280b**. Subsequent hydrolysis of **280a** and **280b** with 70% H_2SO_4 at 100 °C provides benzocyclobutenediones **260** and **281** in an overall yield of 63% and 72%, respectively. Alternatively, the Diels–Alder adducts **279a**,**b** can be oxidized to enones **282a**,**b**, which can then be readily aromatized by NaOMe/MeOH, followed by dilute acid hydrolysis (1.2 N HCl/MeOH) to give benzocyclobutenones **283a**,**b**. More vigorous hydrolysis of **283a**,**b** by H_2SO_4 produced **284a** and **284b** in 36% and 63% overall yield, respectively (Scheme 64).[173]

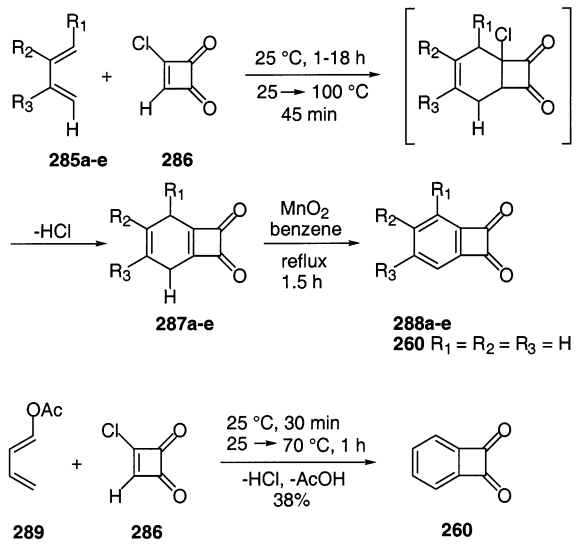
Schmidt et al. used 3-chlorocyclobut-3-ene-1,2-dione (**286**), a highly reactive dione, for the construction of dihydrobutenedione derivatives. The success of this route relies on the large number of dienes that can be used. For example, the tandem Diels–Alder/dehydrochlorination reaction of 3-chlorocyclobut-3-ene-1,2-dione (**286**) with dienes **285a**–**e**, on careful heating at 100 °C, affords **287a**–**e**, which is readily oxidized by activated MnO_2 to afford **288a**–**e** (Table 7). The parent dione **260** has been prepared in a one-pot Diels–Alder reaction by heating a mixture of **286** and 1-acetoxy-1,3-butadiene **289** (Scheme 65).[175]

Similarly, Schmidt and co-workers synthesized dicycloalkano-annulated dihydrobenzocyclobutenediones **291a**,**b** (n = 1, 2). Treatment of a carbon tetrachloride solution of **291a**,**b** with bromine at reflux temperature affords the corresponding benzocyclobutenediones **292a**,**b**. Surprisingly, the reaction of **286** with **290c**,**d** (n = 3, 4) gave benzocyclobutenedione **292c**,**d** (Scheme 66) directly.[176] Using a similar approach, higher analogues of benzocyclobutenedione, i.e., cyclobuta[*c*]- and cyclobuta[*a*]phenanthrene-1,2-dione and cyclobuta[*a*]triphenylene-11,12-dione, can be prepared.[177] Linearly fused dihydrobenzocyclobutenedine and benzocyclobutenediones are also prepared via annulation of 1,2-bis(methylene)carbocycles by **286**.[178]

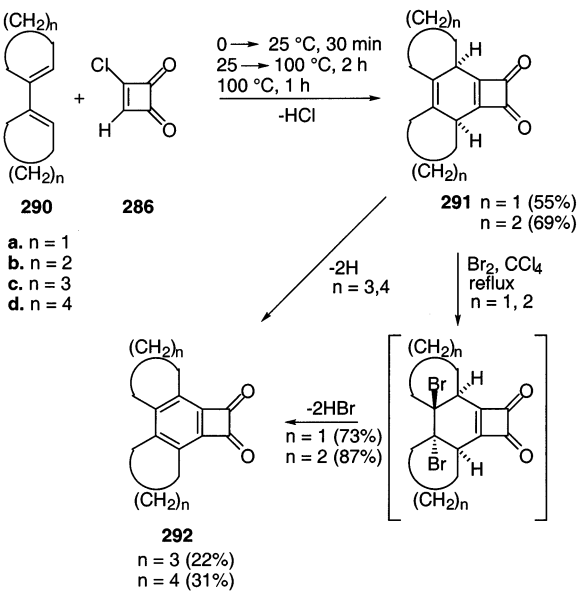
Table 7. Diels–Alder Synthesis of 288

288	R_1	R_2	R_3	yield (%)
a	H	H	H	62
b	Me	H	H	62
c	H	Me	H	82
d	Me	H	Me	81
e	H	Me	Me	75

Scheme 65



Scheme 66



Scheme 67

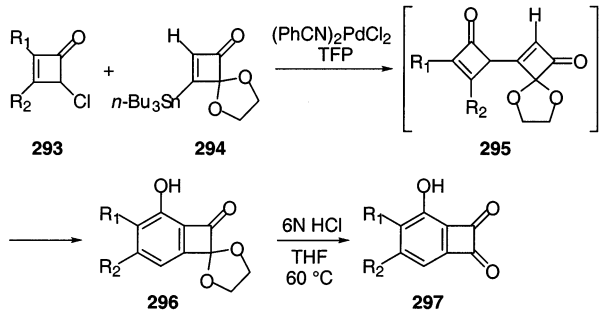


Table 8. Synthesis of Benzocyclobutenedione Monoacetal 296

296	R_1	R_2	yield (%)
a	Me	*i*-PrO	95
b	*n*-Bu	*i*-PrO	99
c	*s*-Bu	*i*-PrO	91
d	*t*-Bu	*i*-PrO	69
e	Ph	*i*-PrO	90
f	Et	Et	61
g	Me	Ph	56
h	Ph	Me	75
i	Me	*n*-Bu	72
j	*n*-Bu	Me	71

A general, regioselective synthesis of substituted benzocyclobutenedione monoacetals **296** by Pd-catalyzed coupling of 4-chlorocyclobutenones **293** with **294** at 70−100 °C has been reported. The proposed intermediate **295** is thought to yield **296** via a series of thermally induced electrocyclic reactions as the key steps. Benzocyclobutenedione monoacetals **296** are easily transformed into the parent diketone **297** by treatment with 6 N HCl in THF (Scheme 67, Table 8).[179]

Thermal dimerization of substituted butenynes **298a**−**f** at 80−100 °C furnishes the bicyclo[4.2.0]octa-1,5,7-trienes **299a**−**f** (α-dimers), whereas, at elevated temperatures (120−180 °C), formation of benzocyclobutenes **300a**−**f** (*β*-isomer) is observed. The α-dimers can also be converted to *β*-dimers at 120−180 °C. Benzocyclobutenes **300a**−**f** can be further hydrolyzed by sulfuric acid or silver trifluoroacetate to give substituted benzocyclobutenediones **301a**−**f** (Scheme 68, Table 9).[180−184]

Phthalazine-1,4-dione **304** can be generated readily in solution by oxidation of **302**. Although the hydrazide is a labile species that polymerizes on attempted isolation, it adds rapidly to dienes, forming stable Diels−Alder adducts. Oxidation by $Pb(OAc)_4$ in the presence of cyclopentadiene gave adduct **303**, which on pyrolysis at 500 °C/0.01 Torr gave pure benzocyclobutenedione in 88% yield. The process proceeds through a retro-Diels−Alder reaction, followed by nitrogen extrusion from **304** and intramolecular cycloaddition of the intermediate bisketene **305** (Scheme 69).[185] An analogous adduct of phthalazine-1,4-dione with indene gave **260** in 64% yield.[185] Similarly, the cyclopentadiene adduct of 6,7-dimethoxyphthalazine-1,4-dione gave 4,5-dimethoxybenzocyclobutenedione in 12% yield.[186]

Pyrolytic routes to benzocyclobutenediones are abundant. McOmie modified the Rees[185] procedure

Scheme 68

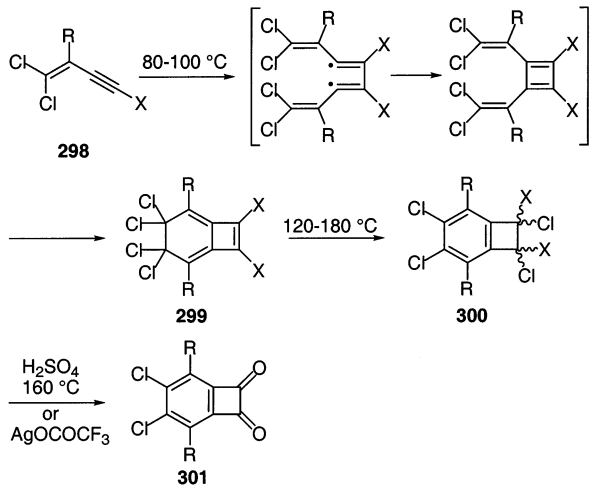
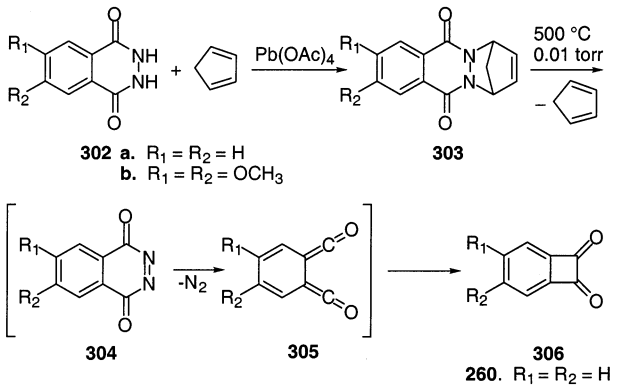


Table 9. Thermal Dimerization of Substituted Butenynes 298a−f To Afford 301

298, 299, 300, 301	R	X	conditions	yield 301 (%)
a	Cl	Cl	H_2SO_4, 160 °C	60
b	CH_3	Cl	H_2SO_4, 100 °C	56
c	Br	Cl	H_2SO_4, 100 °C	88
d	C_6H_5	Cl	$AgOCOCF_3$	57
e	C_6H_5	Br	$AgOCOCF_3$	57
f	C_6Cl_5	Cl	$AgOCOCF_3$	42

Scheme 69



for the synthesis of substituted benzocyclobutenediones by replacing cyclopentadiene with anthracene. Vapor-phase pyrolysis of anthracene adducts **307**, bearing substituents as shown in Table 10, gave benzocyclobutenediones under fairly mild conditions (Scheme 70).[186−188,173] Similarly, cyclobuta[*b*]naphthalene-1,2-dione and cyclobuta[*a*]naphthalene-1,2-dione (**268** and **310**), as well as cyclobuta[*b*]pyridine-1,2-dione and cyclobuta[*c*]pyridine-1,2-dione (**311** and **312**), have been prepared using this approach. The diones **310**−**312** are unstable.[188]

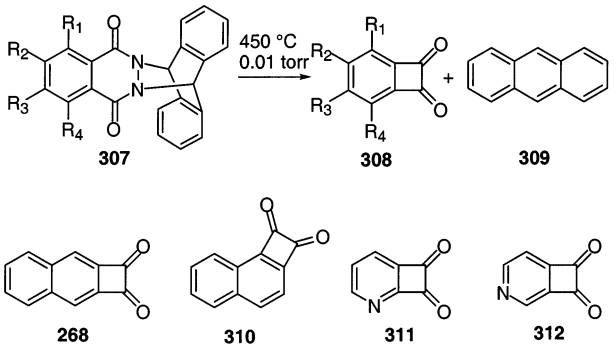
Oxidation of *N*-aminophthalimide **313** by lead tetraacetate in the presence of sulfoxides **314** leads to the formation of *N*-phthalimidosulfoxamide **315**. Extrusion of dinitrogen from **315** at 420−450 °C/0.01 Torr results in the formation of benzocyclobutenedione. Pyrolysis of diphenyl sulfoxamide **315a** gives **260** (70%) and diphenyl sulfoxide (80%). Dimethyl sulfoxamide **315b** gives **260** (35%) and phthalimide **316**

Table 10. Substituted Benzocyclobutenedione Prepared by Vapor-Phase Pyrolytic Method

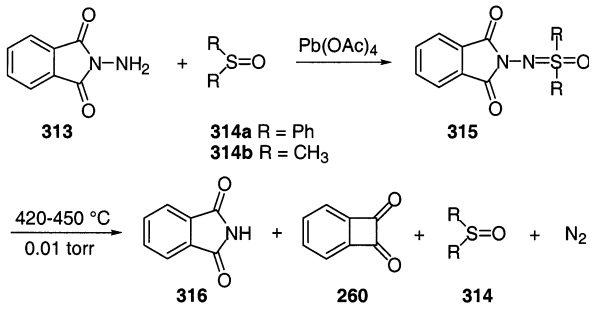
308	R_1	R_2	R_3	R_4	yield 308 (%)	ref
a[a]	H	H	H	H	88	185
b[b]	H	H	H	H	64	185
c[c]	H	OCH_3	OCH_3	H	12	173, 186
d	H	OCH_3	OCH_3	H	98	173, 186
e[d]	H	OH	OH	H	44	186
f	H	H	H	OCH_3	33	187
g	H	H	H	OCH_2OCH_3	61	187
h	H	H	Cl	H	94	186, 188
i	Cl	H	H	Cl	92	186, 188
j	H	Cl	Cl	H	92	186, 188
k	H	Br	Br	H	75	186, 188
l	H	CH_3	CH_3	H	80	186, 188
m	H	−CH=CH−CH=CH−		H	71	186, 188
n	−CH=CH−CH=CH−		H	H	5	188
o	H	H	OCH_3	H	83	173

[a] From cyclopentadiene adduct. [b] From indene adduct. [c] From cyclopentadiene adduct. [d] From hydrolysis of **d** with HBr.

Scheme 70



Scheme 71

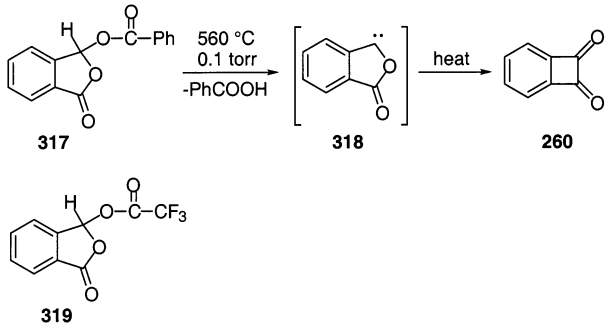


(48%). The formation of phthalimide probably involves the transfer of a hydrogen atom from the *S*-methyl group since it does not occur with the diphenyl sulfoxamide (Scheme 71).[189,190]

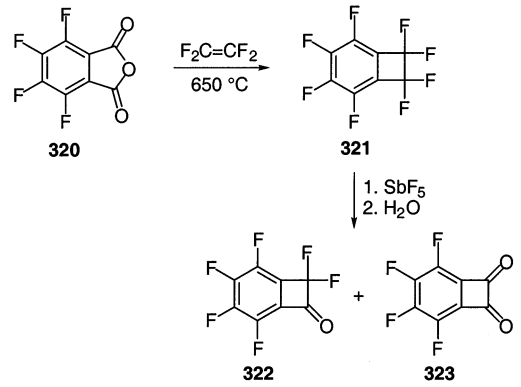
Benzocyclobutenedione **260** can also be obtained in 33% yield by pyrolysis of 3-benzoyloxyphthalide **317** through a silica column at 560 °C/0.1 Torr. The process is thought to involve the α-elimination of benzoic acid, followed by ring contraction of the carbene **318** (Scheme 72).[191] Similarly, 3-trifluoroacetoxyphthalide **319**, on pyrolysis at 540 °C/0.01 Torr, gave **260** in 46% yield based on consumed starting material.[26c]

Pyrolysis of tetrafluoroanhydride **320** at 650 °C in the presence of C_2F_4 affords **321**, which on treatment with SbF_5 (followed by water) gives a mixture of ketone **322** and dione **323** in 45% and 27% yield, respectively (Scheme 73).[192]

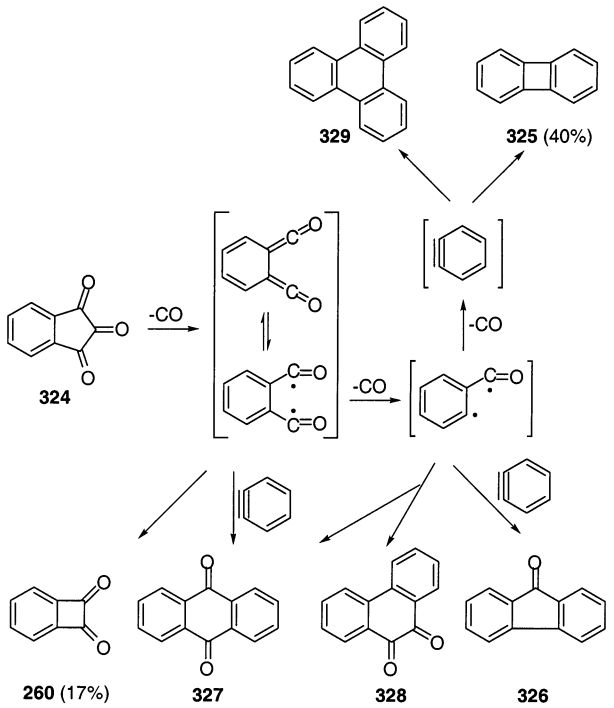
Scheme 72



Scheme 73



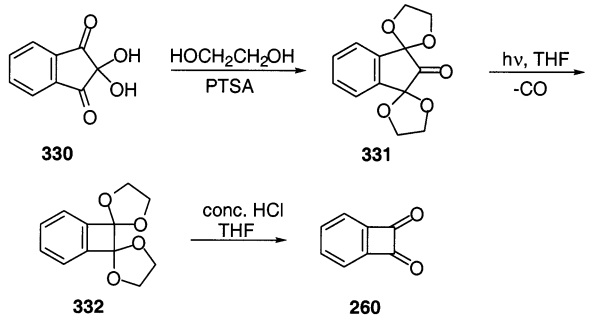
Scheme 74



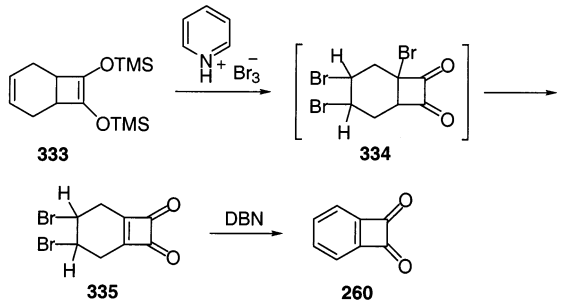
Pyrolysis of indanetrione **324**, sublimed in a pyrolysis tube packed with silica tubing at 600 °C/0.2 Torr, gave benzocyclobutenedione **260** (17%) and biphenylene **325** (40%), along with fluorenone **326**, anthraquinone **327**, phenanthrenequinone **328**, and triphenylene **329** in minute quantities. The probable pathway for the formation of different products is given (Scheme 74).[193,194]

Photoextrusion (Pyrex, 125 W, 5 h, 20 °C) of carbon monoxide from **331**, obtained by the selective protec-

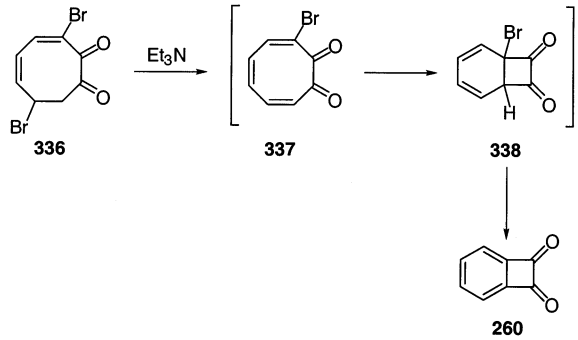
Scheme 75



Scheme 76



Scheme 77



tion of ninhydrin **330**, gave diacetal **332**. Deprotection of **332** by concentrated HCl in tetrahydrofuran afforded **260** in 41% overall yield (Scheme 75).[68e]

Oxidation of bis-silyl ether **333** by pyridinium hydrobromide perbromide yields dibromide **335**, presumably via **334**. Dehydrobromination of **335** using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) afforded **260** in 92% yield (Scheme 76).[195]

Finally, an attempt by Legoff to isolate a derivative of the elusive 1,2-cyclooctatrienedione family by dehydrobromination of **336** using triethylamine leads instead to **260**. The intermediacy of **337** and the bicyclic tautomer **338** is clearly implicated (Scheme 77).[196] Oda et al. were able to synthesize 1,2-cyclooctatrienedione at −50 °C, which upon warming to room temperature gave **260** in poor yield.[197]

III. Physical and Theoretical Aspects of the Cyclobutarenes

A. X-ray Crystal Structures

X-ray crystal structures have been determined for a number of cyclobutarenes, e.g., **1**,[198a,b] **2**,[198c] **6**,[198d] **7**,[198e] **25a**,[198a] **109**,[81] **260**,[198f] and **558a**.[198g] Exact bond

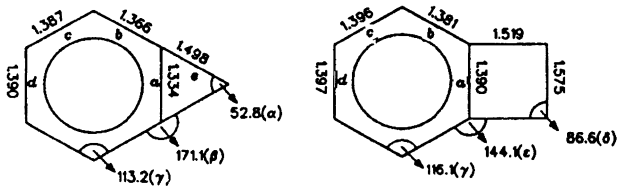


Figure 1. Distances in angstroms and angles in degrees.

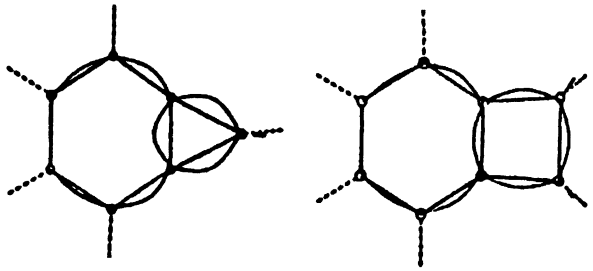


Figure 2. Bond paths of cycloproparene and cyclobutarene.

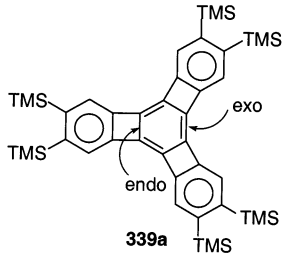
lengths and angles have been determined for a large number of compounds in which strained rings are annelated with benzene.[199,200] Bond lengths and angles for cycloproparene and cyclobutarene are shown in Figure 1. These studies have been spurred on by the expectation that these compounds might exhibit bond localization, as predicted by Mills and Nixon.[201] The structural work has been carried out for the most part in Essen by Boese and co-workers, and the reader is referred to his account of this work for a thorough discussion of these effects.[199]

The parent hydrocarbon **1** (Figure 1) was found to have a shortened bridging bond *a* compared to benzene. Curiously, the adjacent distance *b* is even shorter. Bonds *c* and *d* have equal distances and are longer than *b*. Thus, the fixation model, as predicted by the Mills−Nixon hypothesis, does not apply since *d* should also be shortened. This stands in contrast to the observations made when cyclopropene is fused to benzene, where the bridging bond is found to be shorter than the two adjacent bonds (Figure 1). The formation of "banana" bonds in both systems leads to misleading interatomic distances. This effect can be illustrated by observing "bond paths" for the cycloannelated benzene derivatives illustrated in Figure 2. The effects of geometric distortion on the aromaticity of various cycloproparenes and cyclobutarenes have been studied, and it has been observed that both cycloproparenes and cyclobutarenes retain aromatic character.[202,203]

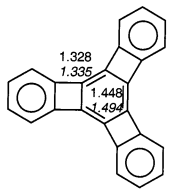
Strain-induced bond alteration in benzenoid molecules has led to conflicting theoretical papers.[204,205] The suggestion that the geometry of cycloannulated benzenes is dominated by the σ frame, but that the π frame might reveal bond fixation by considering the respective energies of the π orbitals, seems relevant.[198d,206] Indeed, it is argued that the Mills−Nixon effect is not real.[207−209] Nevertheless, arguments in favor of the Mills−Nixon hypothesis still prevail, and the topic has become one of considerable controversy.

Interestingly, the X-ray analysis of tricyclobuta[*a*,*c*,*e*]benzenes **339a** and **339b** has revealed the

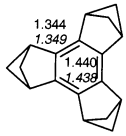
manifestation of pronounced bond alternation in the central benzene ring, although in this case the outer rings are biased by the central benzene ring.[210,211] Star-phenylene **339b** has been reported to undergo reactions characteristic of olefins, including hydrogenation,[212,213] epoxidation,[214] and cyclopropanation.[214] Seigel et al. have reported the synthesis of tris(bicyclo[2.1.1]hexeno)benzene **340**,[215] the first *mononuclear benzenoid hydrocarbon* with a cyclohexatriene-like geometry ($\Delta R = 0.089$ Å).[216] Bond lengths (Å) calculated at the RHF/6-31G** level are indicated for the benzene ring; values from (averaged) single-crystal X-ray measurements for **339b** and **340** are indicated in italics.



339a



339b

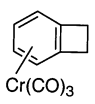


340

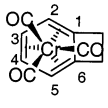
Although the degree of bond alternation in **340** is smaller than that in **339b**, both epoxidation and cyclopropanation of **340** take place readily.[218] However, **340** is inert to catalytic hydrogenation and reduction by diimide.

Very recently, the degree of aromaticity of highly strained annelated benzenes has been assessed according to magnetic criteria. The computed nucleus-independent chemical shifts (NICS) for the central benzene rings [**340**, −8.0 ppm (0.0 Å);[202] **339b**, −1.1 ppm (1.0 Å)[219]] and direct visualization of induced current density[220] predict that **340** is aromatic, whereas **339b** is not.[202]

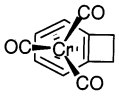
Theoretical studies have suggested that bond alternation will be observed in organometallic complexes of cyclobutarenes as well.[221] Stanger et al. later confirmed this on the basis of crystal structure analysis of **341**. The conformation of the CO ligands relative to the arene is indicative of bond localization. Thus, chromium adopts a pseudo-octahedral (carbonyl bisecting the single bonds) coordination sphere, which suggests Cr−arene bonding through the π bonds anti to the carbonyls. Indeed, $(CO)_3Cr$ complexes of systems that are bond-localized as free ligands (e.g., biphenylene,[222] angular [3]phenylene,[223,224] and star phenylene **339b**,[225] where a substantial rotational barrier around the Cr−arene axis was measured) show this endo bonding, even when steric considerations would suggest that the exo rotamer is more stable. In cyclobutarene complexes of $Cr(CO)_3$, the two rotamers are found in different systems, i.e., structures of type **342a** and **342b**.[226] Stanger and co-workers, however, found only the rotamer **342a** in the case of complex **341**. This implies that bonds C(1)−C(2), C(3)−C(4), and C(5)−C(6) have more pronounced double bond character than the remaining three double bonds.[227] These results are in full agreement with $^{13}C-^{13}C$ *J*-coupling experiments on a substituted $(CO)_3Cr$ cyclobutabenzene system.[228]



341



342a

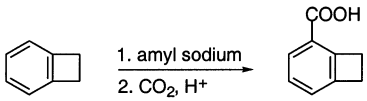


342b

B. Acidity of Cyclobutarenes

Streitweiser and co-workers determined that deprotonation of **1** at the α-position by cesium cyclohexylamide occurs 7 times more rapidly than that at the β-site.[229] The thermodynamic deprotonation/carboxylation of **1** with amylsodium/CO_2 affords only the α-carboxy isomer **343** and not the β-isomer (eq 31).[230]

This increased acidity of the α-proton relative to



(31)

343

the β-proton in cyclobutarene is proposed to originate from rehybridization of the bridging carbon atoms. Thus, the hybrid orbital extending toward the α-position possesses more σ-character as a result of the increased π-character in the bridged bond (Figure 3).[229−231]

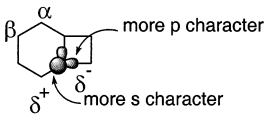


Figure 3.

Thummel and co-workers determined the basicities of annelated pyridines by standard titrimetric techniques. The lower basicity of cyclobuta[*b*]pyridine (**91**), compared to that of its isomeric cyclobuta[*c*]-pyridine **92**, has been explained on the basis of rehybridization theory. Thus, the lone pair of electrons on nitrogen in **91** is held more tightly than in **92**, where the ipso carbon uses an orbital of higher s character.[232−234] Earlier, Markgraf and co-workers determined the basicities of different cyclobutaquinolines.[235] The geometry of the heterocyclic ring is also reported to increase the s character of the nonbonding orbital on nitrogen.[237]

91

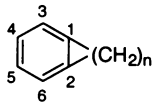
$pK_a = 4.85$

92

$pK_a = 6.75$

Similar observations have been made by Eaborn and co-workers in their studies on the base-induced desilylation of cyclobutarenes **344**−**346**.[238,239] The α-position was found to desilylate about 9 times

Table 11. ^{13}C Chemical Shifts[a] and Coupling Constants[b] in Annelated Benzenes[246]

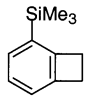


entry	n	$\delta(C_{1,2})$	$\delta(C_{3,6})$	$^1J(^{13}C_3-H)$	$\delta(C_{4,5})$	$^1J(^{13}C_4-H)$
1	5	142.7	128.7	155	125.7	161
2	4	136.4	128.8	155	125.2	159
3	3	143.3	124.0	155.5	125.8	157
4	2	145.2	122.1	162	126.8	157.5
5	1	125.4	114.7	168.5	128.8	159

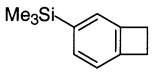
[a] In ppm downfield from internal TMS; concentration was 0.1 M in $CCl_4/CDCl_3$ (3:1); experimental error, ±0.1 ppm. [b] In hertz; maximum error, ±1.3 Hz.

faster than the dimethyl acyclic reference compound and 11 times more rapidly than the β-substituted silane. The β-isomer was found to exhibit little rate acceleration in comparison to the dimethyl derivative.

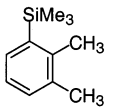
The gas-phase acidities of the two aromatic sites



344



345



346

of **1** have been determined by Fourier transform mass spectrometry.[240] This work showed that fusion of the four-membered ring to benzene results in a slight acidifying effect at the α-position, but little or no effect was observed for the β site. As expected, the benzylic ion is the most stable of the three anions. Ab initio calculations were carried out to obtain structural parameters as well as to provide insight into the electronic structures of the anions. Moreover, electrophilic reactions with cyclobutarene **1** are known to yield β-substituted products almost exclusively.[241−244]

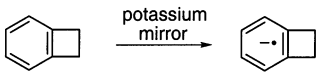
C. ^{1}H and ^{13}C Nuclear Magnetic Resonance Spectra

Extensive analyses of the nuclear magnetic resonance spectra of benzocycloalkenes, including cyclobutarenes, have been reported.[228,245−249] It is not surprising that early studies examined the proton−proton spin−spin couplings for any features that would indicate partial bond fixation that might be ascribable to ring strain. Subsequent workers have analyzed the ^{1}H and ^{13}C nuclear magnetic resonance spectra in considerable detail. The one-bond ^{13}C−^{1}H coupling ($^1J_{CH}$) is of particular significance for strained benzoalkenes, as it increases with increased σ-character of the ^{13}C−^{1}H bond and with angular distortion. A compilation of nuclear magnetic resonance data has been presented for different annelated benzenes (Table 11).[426] The one-bond ^{13}C−^{1}H coupling constant for the α-carbon in the strained annelated benzene ring shows a regular increase with decreasing ring size. The larger J_{CH} values for cycloproparene (entry 5, Table 11) and **1** (entry 4, Table 11) correlate with greater σ-character in the bonding orbital, which is in turn explained by rehybridization leading to attenuation of electron density at the α−position. J_{CH} data do not, however, indicate any bond fixation effects.

D. Radical Ions of Cyclobutarene

The radical cations of a series of cyclobutarenes have been generated by irradiation of the hydrocarbon in the presence of mercury(II) trifluoroacetate, and evidence for the Mills−Nixon effect has been claimed.[250−251]

Reike et al. have generated the radical anion of **1** by metallic and electrochemical reduction.[252−256] For example, reduction of **1** using a potassium mirror at −78 °C generates the stable radical anion **347** (eq 32). The cyclobutene ring remains intact after reduction. Similarly, reaction of **1** with K or Na/K in THF at −80 °C leads to the same radical anion.



(32)

1 **347**

IV. Chemistry of Cyclobutarenes

A. Cyclobutene Ring Cleavage

The chemistry of cyclobutarenes is dominated by ring opening of the four-membered ring. A conrotatory electrocyclic process is implied for the thermal opening of cyclobutarene into the corresponding *o*-quinodimethane according to Woodword−Hoffmann rules.[257] Roth and co-workers have determined the energy profile for the equilibrated opening of cyclobutarene **1** into *o*-quinodimethane **22** and for its cyclization. Consequently, **1** exhibits a greater stability by 11.0 kcal mol^{-1} (Figure 4).[258−260]

Although the reactivity of *o*-quinodimethane parallels that of a highly reactive diene, it may also be represented as resonance structure **22a**, a highly stabilized biradical.[66,261−263] This biradical has been isolated in a glassy matrix at −196 °C by irradiation of 1,4-dihydrophthalazine. It was found to be stable under these conditions and appears to be a ground-state singlet. It dimerizes readily upon warming above −40 °C to give the spiro dimer **348** as the major product. Irradiation converts it into **1**. The same

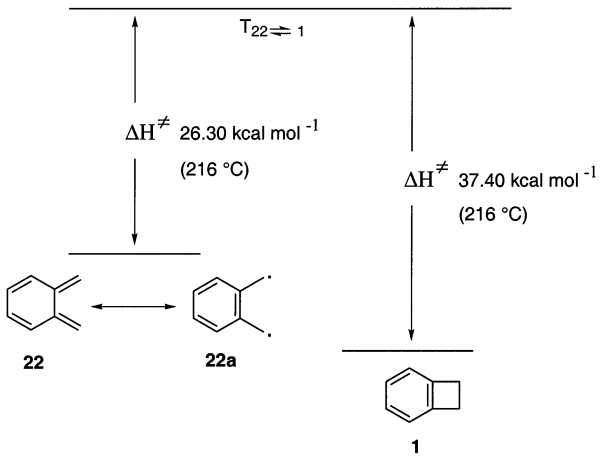
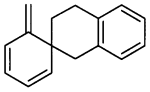


Figure 4. Energy profile of the equilibrium system **22** ⇌ **1**.

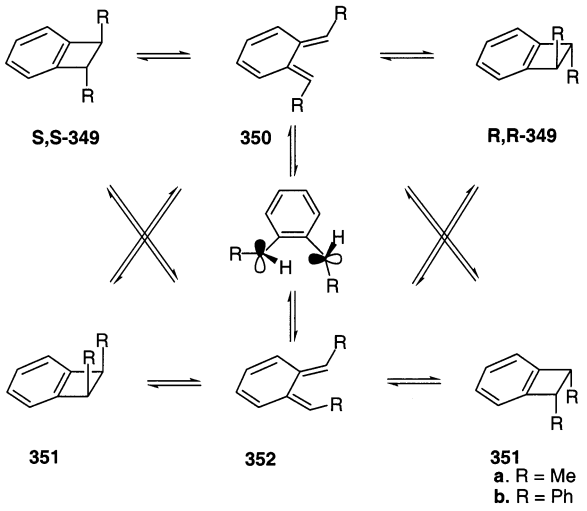
biradical was also isolated under identical conditions by photolysis of several additional compounds.



348

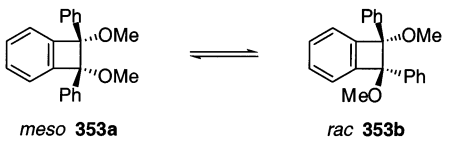
An impressive study of the energy profiles for the conrotatory and disrotatory opening of 7,8-disubstituted derivatives of **1** has been reported by Roth and co-workers, who used elegant NO and oxygen trapping experiments. For the dimethyl derivative, a difference of 4.90 kcal mol^{-1} between the activation barriers for the forbidden and the conrotatory isomerization was estimated. In the case of the diphenyl derivative, this difference dropped to 1.0 kcal mol^{-1} (Scheme 78). The smaller value for the diphenyl

Scheme 78



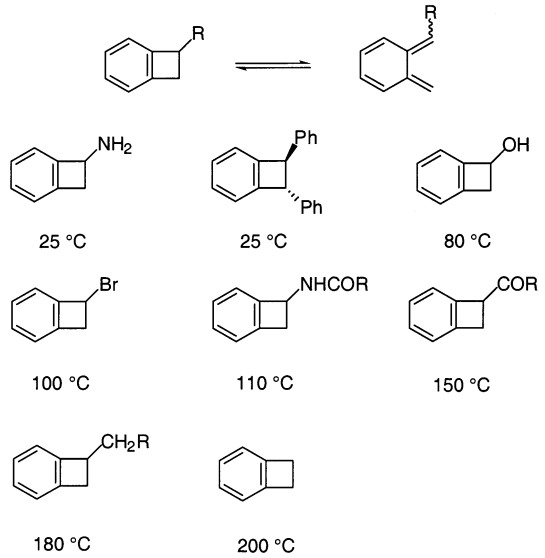
derivative may be attributed to the benzyl-type stabilization of the biradical intermediate. Using optically active starting materials, it was established that the enthalpy for the transition states for the forbidden pathway is identical with the heat of formation of the orthogonal biradical derived by geometrical isomerization of the transient *o*-quinodimethane (Scheme 78).[264]

In a subsequent elegant study, Korth, Sustmann, and their co-workers found that **353a** racemizes at room temperature in the absence of oxygen. In this case, the energy difference between the conrotatory and the forbidden process virtually vanishes. In fact, it is proposed that the energy difference probably favors the "forbidden" one due to the additional stabilizing effects of the methoxy groups (eq 33).[265] This paper includes a relevant discussion regarding the nature of the biradicals involved in these reactions, i.e., intermediate vs transition sate.



meso **353a** *rac* **353b** (33)

Scheme 79



Sakai has calculated the potential energy surfaces for the cyclization of *o*-quinodimethane **22** to cyclobutarene **1** by the ab initio CASSCF MO method.[266] The transition state for the conrotatory pathway was 8.0 kcal mol^{-1} lower than that for the disrotatory pathway, and about half of the energy difference for both transition states comes from the orbital phase effects.

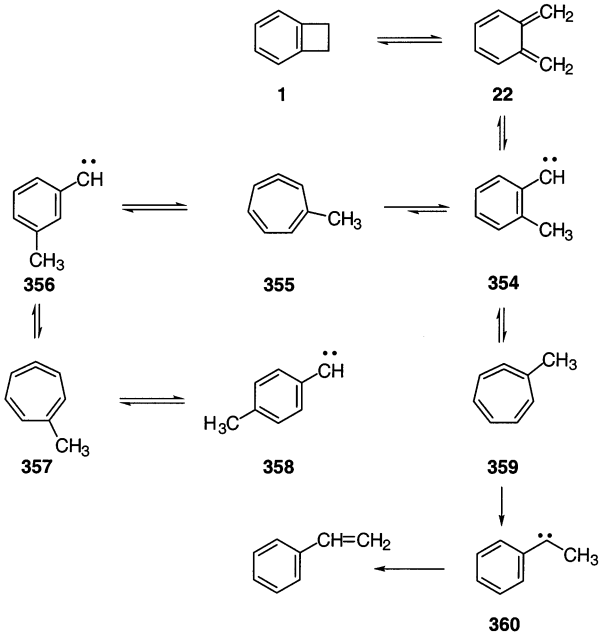
Derivatives bearing a substituent on the cyclobutene ring undergo thermally allowed conrotatory ring opening, preferentially outward, to give the sterically less hindered diene.[16,267] Earlier experiments and recent ab initio calculations indicate that the tendency for outward rotation leading to *E*-QDM increases with the donor character of the substituents.[268] The presence of electron-rich substituents on the cyclobutene ring makes the ring opening easier, and the ease of ring opening parallels the electron-donating capability of the substituent (Scheme 79).[16] Base-catalyzed, anion-driven ring opening of benzocyclobutenols takes place at temperatures below 0 °C.[269]

Pyrolysis of **1** at elevated temperatures (>770 °C)[49,270] has been investigated in detail from a mechanistic standpoint using ^{13}C-[271,272] and ^{2}H-labeled[273,274] compounds. It has been proposed that the initially formed *o*-quinodimethane **22** rearranges to *o*-tolylmethylene **354**.[275,276] Subsequent interconversion of *o*-tolylmethylene **354** with the meta isomer **356** and *p*-tolylmethylene **358** takes place via cycloheptatetraene intermediates **355** and **357**. Rearrangement of **359** yields styrene via α-methylphenylmethylene **360**. The conversion of *o*-quinodimethane into *o*-tolylmethylenes has the highest barrier between benzocyclobutene and styrene (Scheme 80).[275−278] Similar studies have also been reported.[279−282]

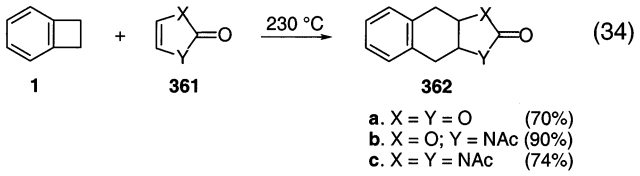
B. Diels–Alder Reactions

As cis-dienes, the *o*-quinodimethanes exhibit a strong predilection to undergo Diels−Alder reactions. *o*-Quinodimethanes are constituted by two diene units, one endocyclic and the other exocyclic; however, it is the exocyclic diene which participates in cycloaddition reactions.[283] *o*-Quinodimethane not only

Scheme 80



reacts with electron-poor and electron-neutral dienophiles, but it also reacts with electron-rich dienophiles. For example, *o*-quinodimethanes undergo efficient, stereoselective cycloaddition reactions with 1,2-heteroethylenes such as **361** to give 2,3-diheterotetrahydronaphthalenes **362** in good to excellent yields (eq 34).[284]

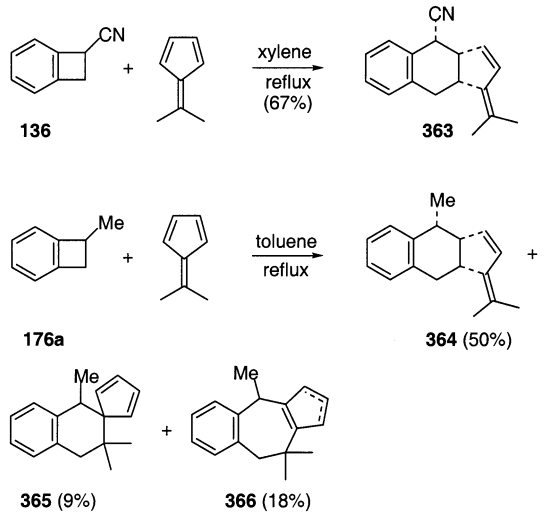


(34)

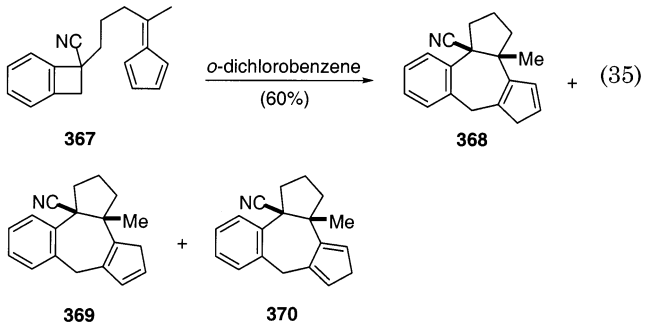
a. X = Y = O (70%)
b. X = O; Y = NAc (90%)
c. X = Y = NAc (74%)

The cycloaddition product of **136** and 6,6-dimethylfulvene results from an endocyclic transition state and involves an electron-rich double bond (Scheme 81). However, the reaction with 1-methylbenzocyclobutene **176a** gives a mixture of **364**, spiro adduct **365**, and the [6 + 4] adduct **366** (Scheme 81).[285]

Scheme 81



In contrast, the intramolecular reaction of *o*-quinodimethane with the fulvene moiety in **367** gives the [6 + 4] cycloadducts **368**−**370** in a ratio of 4.0:1.7:1.0 (eq 35).[286]

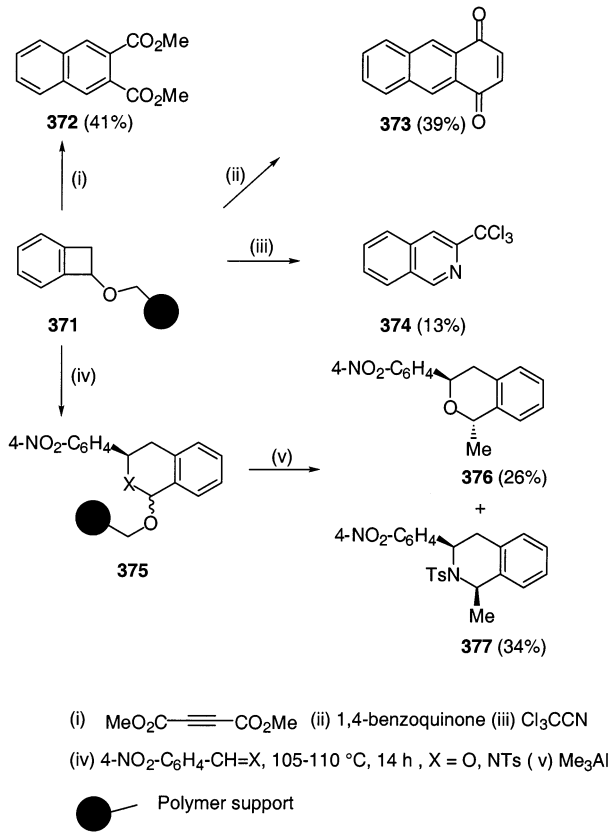


(35)

Polymer-supported cyclobutarene **371** reacts with homodienophiles such as dimethyl acetylenedicarboxylate, 1,4-benzoquinone, and trichloroacetonitrile to afford **372**, **373**, and **374**, respectively. Heterodienophiles such as aldehydes and imines gave polymer-supported benzohydropyrans and tetrahydroisoquinolines **375**, which on treatment with Lewis acids undergo cleavage to afford benzohydropyrans **376** and tetrahydroisoquinolines **377** (Scheme 82).[287]

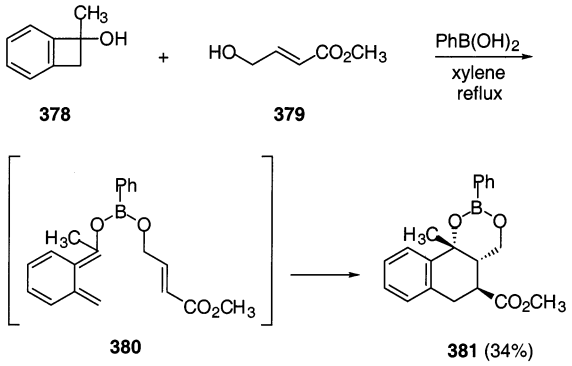
Boron compounds have proven to be efficient trapping agents for the *o*-quinodimethane generated from cyclobutarene **378**. Thus, **378** could be reacted with **379** and converted into the mixed boronate **380**. Adduct **380** undergoes an intramolecular Diels−Alder reaction regioselectively to yield **381** (Scheme 83).[288]

Scheme 82



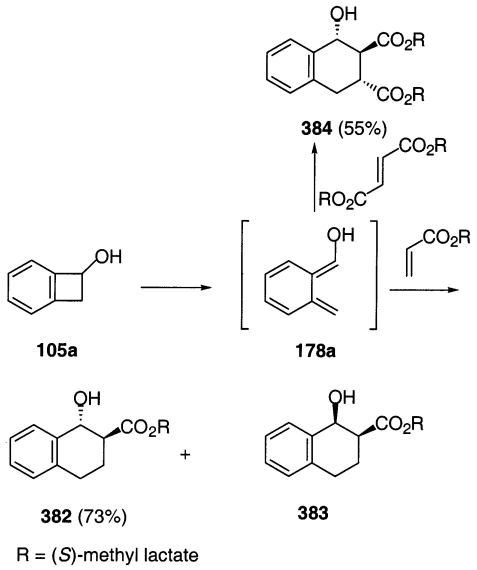
(i) $MeO_2C{-}{\equiv}{-}CO_2Me$ (ii) 1,4-benzoquinone (iii) Cl_3CCN
(iv) 4-NO_2-C_6H_4-CH=X, 105-110 °C, 14 h , X = O, NTs (v) Me_3Al
Polymer support

Scheme 83



378 **379** **380** **381** (34%)

Scheme 84

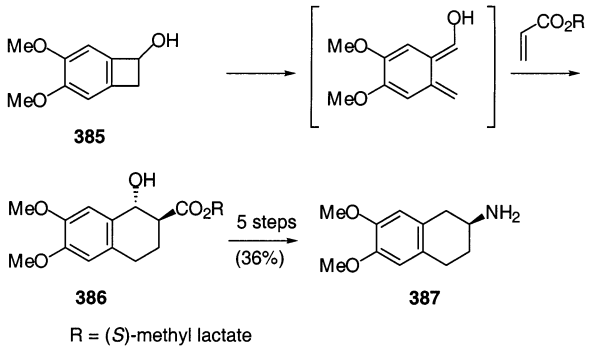


Charlton et al. have investigated the asymmetric Diels−Alder reactions of **178a** with fumarate, maleate, and acrylate, bearing the chiral auxiliary (*S*)-methyl lactate.[289−293] The reaction of **178a**, generated by thermolysis of **105a**, with acrylate affords a mixture of optically active cycloadducts **382** and 3**83** in a ratio of 19:1. A similar reaction of benzocyclobutenol **105a** with fumarate affords only the homochiral cycloadduct **384** in 55% yield (Scheme 84). The diastereoselective excess (de) is >95%, and the cycloadducts have a 1,2-trans configuration. It is noteworthy that this stereochemical outcome is inconsistent with the Alder endo rule, and with the reactions of other dienophiles with **178a**.[294,295]

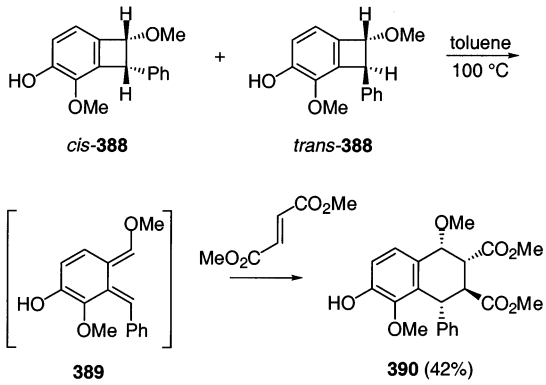
This strategy has been applied to the asymmetric synthesis of 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN).[296] Thus, the reaction of **385** with the chiral acrylate in refluxing toluene gave cycloadduct **386** as the major product in 80% yield, along with three minor cycloadducts. The adduct **386** was subsequently converted into (−)-(2*S*)-2-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene **387**, which was then converted into ADTN (Scheme 85). The potential of this approach, using cyclobutarenes for the preparation of highly substituted 1,2,3,4-tetrahydronaphthalene, has been demonstrated.[297−299]

The synthesis of highly substituted 1,2,3,4-tetrahydronaphthalenes is presented in Scheme 86, where

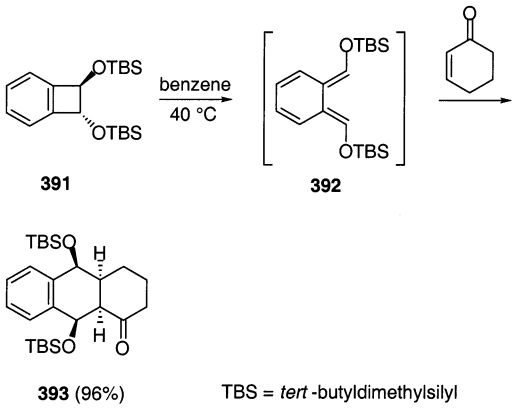
Scheme 85



Scheme 86



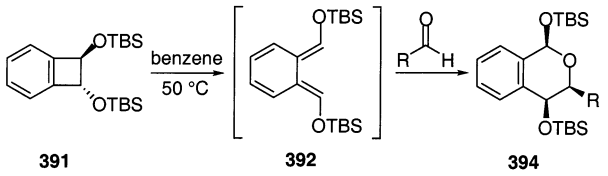
Scheme 87



a mixture of *cis*- and *trans*-**388** was reacted directly with dimethyl fumarate to yield 1,2,3,4-tetrahydronaphthalene **390**. An isomerization of the cis- to trans-isomer preceded the electrocyclic ring opening, leading to the intermediate **389**.[131]

Danishefsky and co-workers have made important applications of 1,2-*trans*-disiloxybenzocyclobutenes (**391**) in synthesis.[300,301] Thermal ring opening of cyclobutarene **391** generates **392** at ambient temperature.[300,301] Subsequent reactions of **392** with carbon dienophiles yield cycloadducts in nearly quantitative yield with complete stereospecificity. The formation of **393** from cycloaddition of **392** with 2-cyclohexen-1-one (a highly sluggish dienophile) at 40 °C, in an uncatalyzed reaction, illustrates the "*trans*-1,2-bissiloxy effect" (Scheme 87). Cyclobutarene **391** exhibits thermochromic behavior, a characteristic that simplifies the monitoring of these reactions. It exists as a colorless oil at temperatures below 0 °C and becomes yellow at room temperature. This color is discharged

Scheme 88



391 **392** **394**

TBS = *tert*-butyldimethylsilyl

Table 12. Cycloaddition of 392 with Aldehydes

entry	R	time (h)	yield **394** (%)
1	Ph	2	92
2	CH_3	2	90
3	$CH_3CH_2CH_2$	8	88
4	$(CH_3)_2CHCH_2$	8	90
5	$(CH_3)_2CH$	13	89

upon cooling or upon exposure to a dienophile. The yellow color has been attributed to the low equilibrium concentration of **392**.[302] The scope of this reaction has been expanded by carrying out similar cycloaddition reactions with various heterodienophiles in either benzene or toluene (Scheme 88). The uncatalyzed reactions occurred under remarkably mild conditions with complete stereospecificity. Facile reactions were also observed with aliphatic aldehydes sterically encumbered by α and *β* branching (Table 12, entries 5 and 4).

Benzothiete **35** has proved to be a versatile reagent for the synthesis of sulfur heterocycles. Facile thermal or photochemical ring opening of **35** leads to the highly reactive *o*-thiobenzoquinonemethide **38**, which has an extremely low lying LUMO and thus behaves as an electron-deficient diene. Cycloaddition reactions of **35** with a variety of dienophiles and heterodienophiles, e.g., C=C, C=N, C=O, N=N, and N=S, have been reported.[303,304] Recently, the reaction of **35** with cyclic trithiocarbonates and thioketones has been reported to give spiro compounds in quantitative yield. Thus, reaction of **35** with 1,3-dithilane-2-thione

Scheme 89

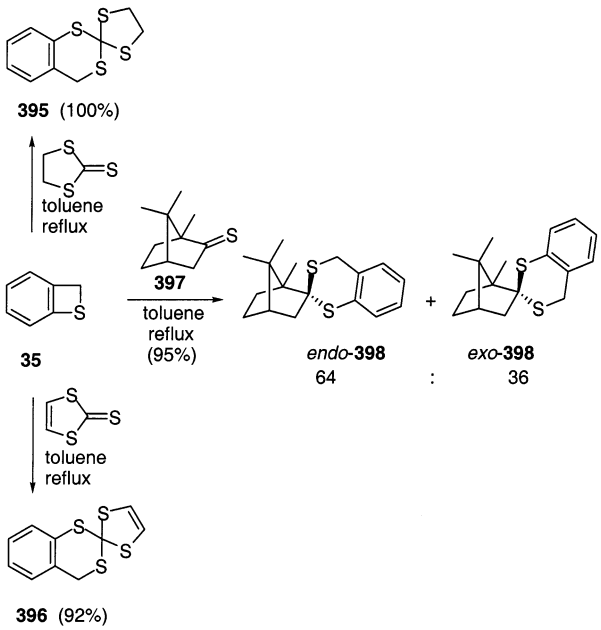


Table 13. Formation of Cycloadduct 400

			ratio of trans/cis isomers[a]	
entry	X	Y	in the product as formed	after equilibration[b]
1	COOMe	H	~2	3/4
2	COOMe	COOMe	~3	1/3

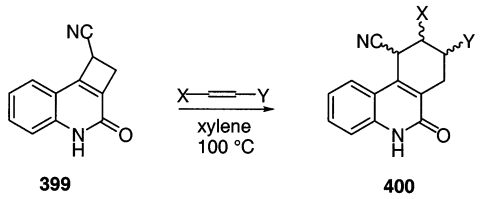
[a] Cis and trans isomers refer to the relation between CN and X functions. [b] The equlibrium was reached after 15−20 h of heating (100 °C) in pyridine-d_5. The ratios were determined from ^{1}H NMR spectra.

Table 14. Formation of Naphthalene Derivatives 403

R_1	R_2	R_3	R_4	yield **403** (%)
H	OMe	$CH_3CONMeOMe$	H	72
H	OMe	CO_2Me	CO_2Me	84
H	OMe	CO_2Et	Br	82
H	OMe	CO_2Et	H	93
OMe	H	CO_2Me	CO_2Me	95

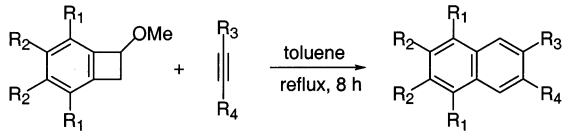
led to the formation of **395**. The related 1,3-dithiole-2-thiones reacted chemoselectively at the C=S bond, resulting in the spiro compound **396**, which showed no tendency for cycloaddition at the double bond. Addition of **35** to (1*R*)-(−)-thiocamphor **397** took place preferentially on the endo face (Scheme 89).[305]

Cycloaddition reactions of **399** with olefins affords cycloadducts **400** in 90−95% yield (eq 36) (Table 13). This cycloaddition proceeds under kinetic control, leading to the formation of the thermodynamically less stable trans isomer as the major product.[306]



399 **400** (36)

The reaction of cyclobutarene **401** with acetylenic dienophiles **402** yields substituted naphthalene derivatives **403** (eq 37) (Table 14).[307]

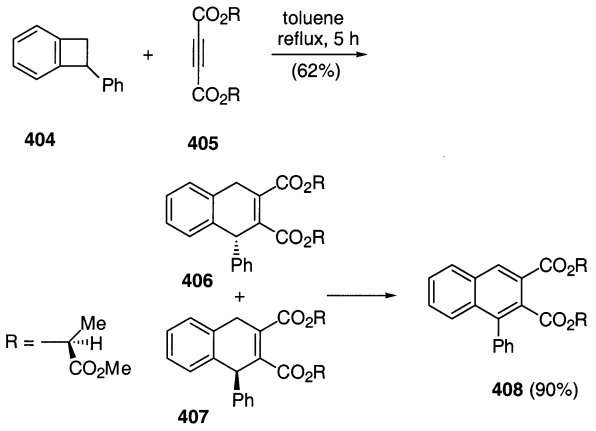


401 **402** **403** (37)

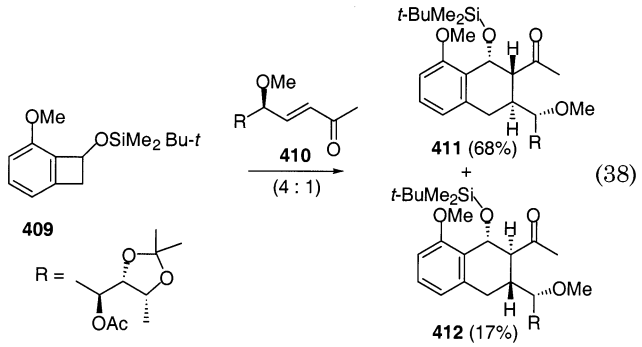
α-Phenyl-*o*-quinodimethane, prepared thermally from 1-phenylcyclobutarene **404** in refluxing toluene, reacted nonstereoselectively with chiral ester **405** to give a mixture of diastereoisomers **406** and **407** in a 1:1.4 ratio. The structures of the diastereoisomers **406** and **407** were confirmed by azomatization using Pd/C to afford phenylnaphthalene **408** (Scheme 90).[308]

Franck et al. investigated the reaction of cyclobutarene **409** with ketone **410** containing two different allylic substituents and observed that the cycloaddition is controlled by orbital effects and not by steric effects (eq 38).[309] The Houk theory also predicts that

Scheme 90

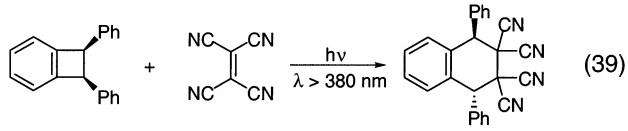


the LUMO−HOMO interaction of syn methoxy is more unfavorable than the syn alkyl interaction.[310]

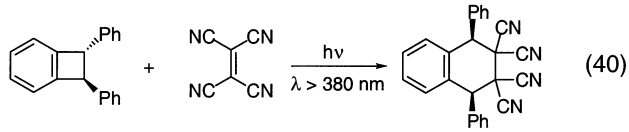


(38)

Photolysis (λ > 380 nm) of *cis*-1,2-diphenylbenzocyclobutene (**351b**) in the presence of tetracyanoethylene leads to the formation of *trans*-1,4-diphenyl-2,2,3,3-tetracyanotetralin (**413**) in 90% yield, while *trans*-**349b** provides the *cis*-diphenyltetralin derivative **414** in 70% yield (eqs 39 and 40).[311] Huisgen, Quinkert, and co-workers previously reported the formation of cycloadducts **413** and **414** by thermally induced Diels−Alder reactions and concluded that these cycloadducts arise by the stereospecific conrotatory opening of the cyclobutene ring.[312,313]

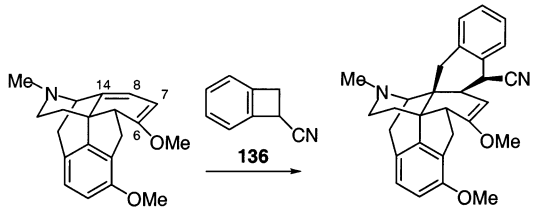


(39)

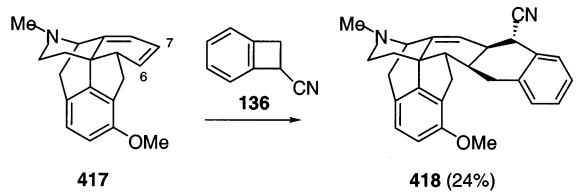


(40)

The Diels−Alder reaction of opiate dienophiles with *o*-quinodimethane generated from cyclobutarene **136** has led to the synthesis of tetrahydronaphthalene-fused opiates. Cycloaddition takes place from the sterically less hindered β-face of the thebaine **415**, and the regioselectivity of the cycloaddition has been established to involve the C-8 and C-14 double bond to give **416**. Interestingly, cycloaddition of thebaine **417** and cyclobutarene **136** takes place regioselectivity at the C-6 and C-7 double bond to afford **418** (eqs 41 and 42).[314]



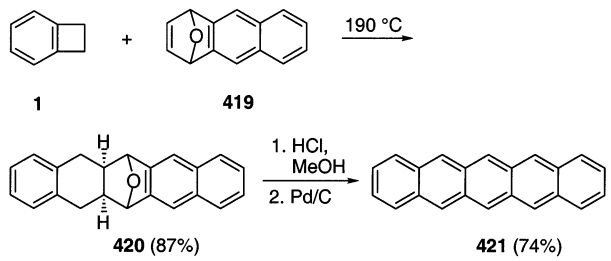
(41)



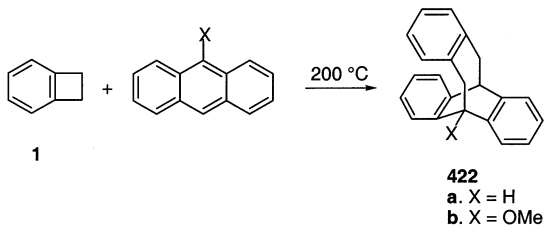
(42)

The cycloaddition of *o*-quinodimethane to arene 1,4-endoxides has been used to construct linear arene derivatives. For example, heating cyclobutarene **1** with anthracene 1,4-endoxide (**419**) gives **420**, which on dehydration and dehydrogenation gives pentacene **421** in 74% yield (Scheme 91).[315] Similarly, Diels−

Scheme 91



Alder reaction of anthracene with **1** gave the cycloadduct **422** (eq 43).[316] Other adducts of anthracenes and cyclobutarenes have also been reported.[317,318]

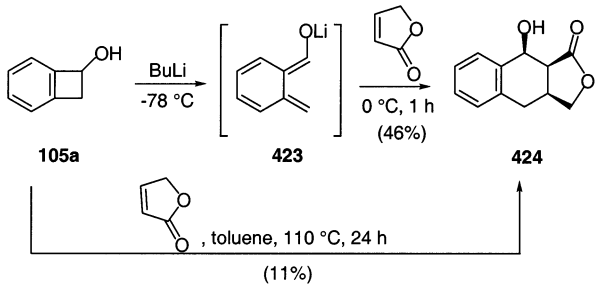


(43)

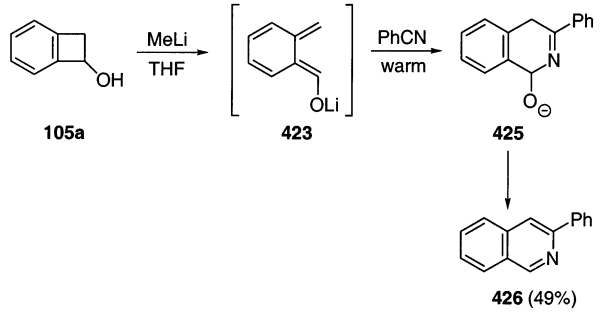
The anion-accelerated ring-opening reaction of **105a** at −78 °C generates *o*-quinodimethane **423**, which undergoes a Diels−Alder reaction with 2,5-dihydrofuran-2-one to afford the endo cycloadduct **424** (Scheme 92).[269,320] It is noteworthy that the reaction takes place smoothly and under milder conditions than the analogous thermal reaction.

Similarly, **423** reacts with benzonitrile to afford isoquinoline **426**, which is not readily accessible through standard Bischler−Napieralski isoquinoline synthesis (Scheme 93).[321] Synthesis of hypecumine, an alkaloid having a rare urethane moiety, was achieved in 50% yield using this approach

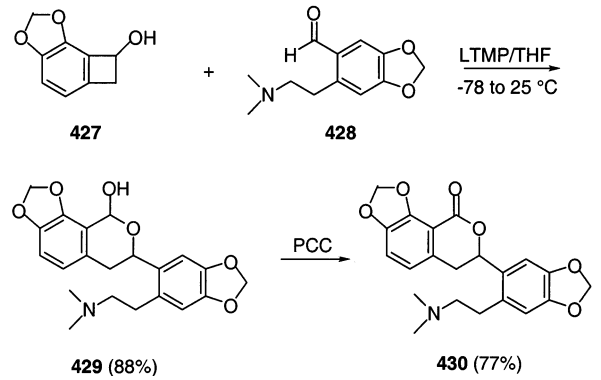
Scheme 92



Scheme 93



Scheme 94



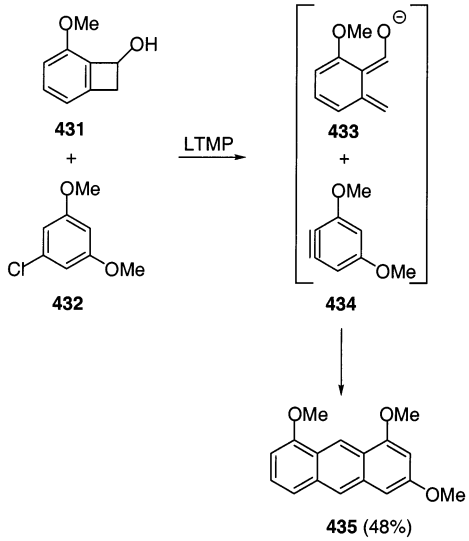
Olofson and co-workers have exploited the anion-accelerated ring opening of benzocyclobutenol **427** to afford an alkaloid, (±)-peshawarine (**430**), in 65% overall yield (Scheme 94).[322] Reaction of various cyclobutarenones with aromatic aldehydes affords isochroman-3-ones in high yield.[323]

Various unsymmetrical anthracenes, such as **435**, have been prepared by simultaneously generating the intermediate **433** and the benzyne **434** using lithium 2,2,6,6-tetramethylpiperidide (LTMP) (Scheme 95).[324]

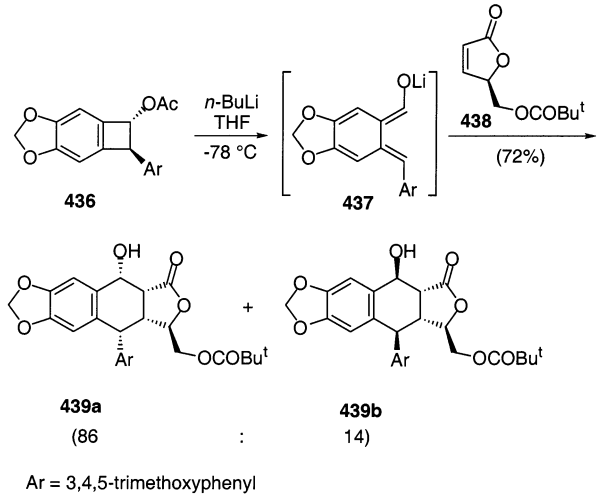
This methodology has been employed in an enantioselective total synthesis of the 7,8,8′-triepimer of podophyllotoxin **439**. The key step in this synthesis is an asymmetric Diels−Alder reaction between an optically active butenolide **438** and α-oxy-*o*-quinodimethane **437**, formed in situ from cyclobutarene **436**, with *n*-BuLi at −78 °C (Scheme 96).[320]

Among the plethora of methods reported for the functionalization of C_{60} fullerenes, cycloadditions and, in particular, Diels−Alder reactions play a very important role. Addition occurs at the 6−6 double bonds of C_{60}, which exhibit the characteristics of dienophiles.[158,325−341] Representative examples of C_{60} fullerene adducts with different cyclobutarenes are shown in Figure 5.

Scheme 95



Scheme 96



C. Other Pericyclic Reactions

On heating, alkene-tethered cyclobutarenes give *o*-quinodimethane intermediates that undergo facile cyclization to generate six-membered rings. This methodology is a useful feature of preparative cyclobutarene chemistry and provides a powerful tool for constructing naphthalene derivatives. For example, the vinylcyclobutarene **440**, on heating at 250−300 °C, rearranged cleanly to 1,2-dihydronaphthalene **442** via *o*-quinodimethane **441** (Scheme 97).[342]

Fukumoto and co-workers have reported an efficient route to the naphthalene moiety of the antitumor antibiotic neocarzinostatin by thermolysis of **443**. Thus, in refluxing *o*-dichlorobenzene, **443** gave dihydronaphthalene **445** via (*E*)-*o*-quinodimethane **444**. Dehydrogenation and alkaline hydrolysis of **445** gave **446** (Scheme 98).[343,344] A similar strategy has been employed for the synthesis of (±)-naproxen **449** (Scheme 99).[345]

1-Alkenylbenzocyclobutenols **451**, prepared from cyclobutarenones via the addition of alkenyl Grignard reagents, give substituted 3,4-dihydro-1-(2*H*)-naphthalenones (**452**) in refluxing toluene (Scheme

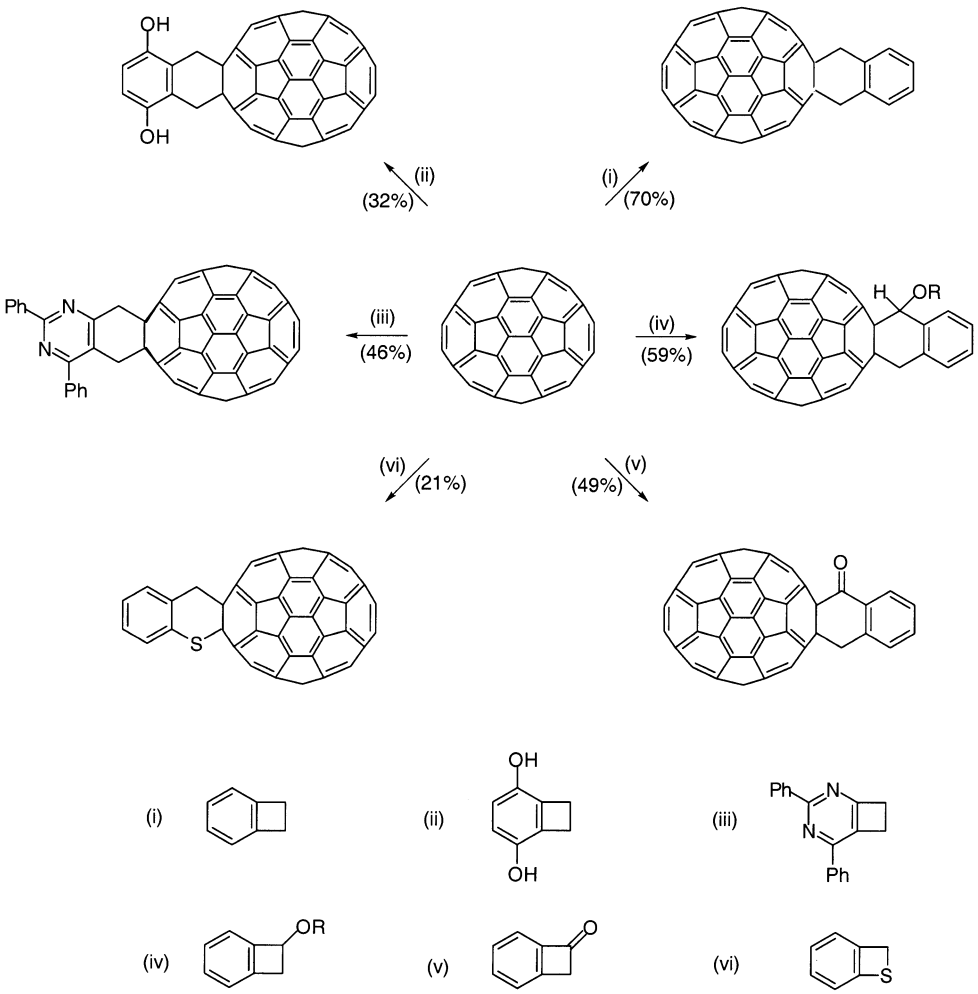
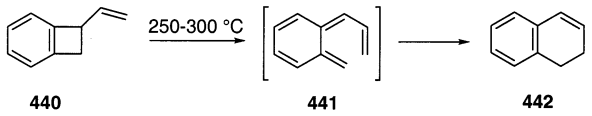
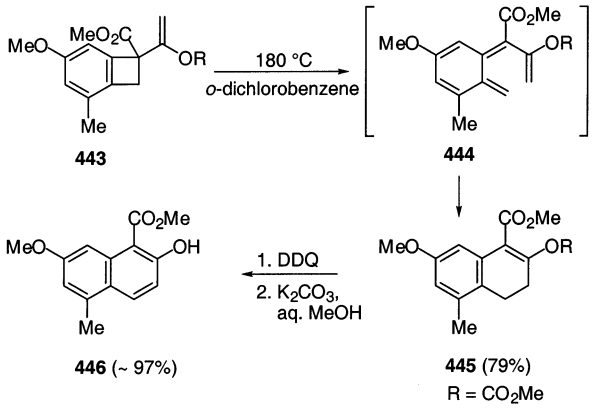


Figure 5. Diels−Alder adducts of cylobuatrenes with C_{60} fullerene.

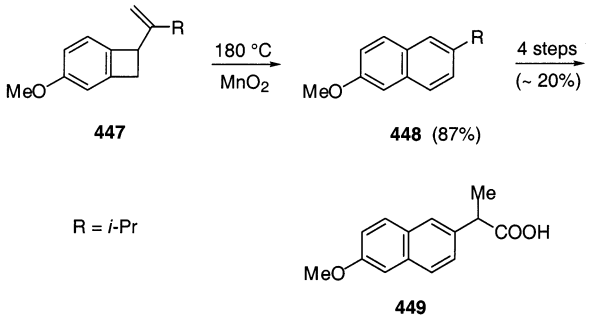
Scheme 97



Scheme 98



Scheme 99



100).[346,347] While benzocyclobutenols **451a**−**f** were isolated and were subsequently converted into tetralones **452** on refluxing in toluene, benzocyclobutenol **451g** could not be isolated and gave tetralone **452g** directly in 56% yield (Table 15). This destabilizing influence of β-substituents in carbinols **451g**,**h** can be rationalized in terms of their effects on electron density at the α-position, to which the four-membered ring is particularly sensitive.[348]

Ring expansion of vinylbenzocyclobutenone **453** provides a facile route to hindered 1-arylnaphthalene derivatives. Thus, treatment of vinylbenzocyclobutenone **453** with phenyllithium in THF afforded alcohol **455** in 81% yield. Alcohol **455** was dehydrated in quantitative yields by treatment with MsCl−Et_3N (Scheme 101).[349]

Suzuki et al. studied the stereochemistry of the thermal conversion of alkenylbenzocyclobutenol into dihydronaphthalene and observed that the product was composed mainly of the stereostructure opposite to that expected from orbital considerations. The *cis*-dioxybenzocyclobutene **457**, possessing an α,β-di-

Scheme 100

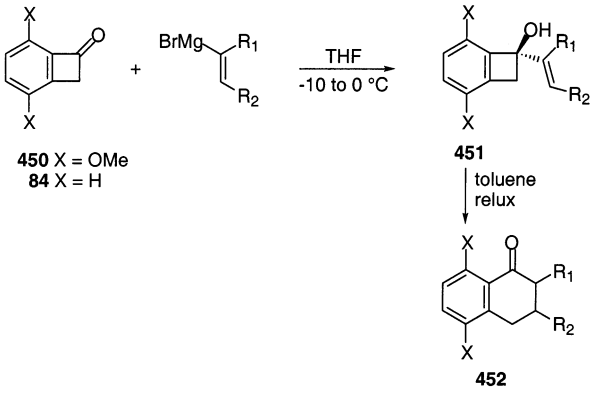
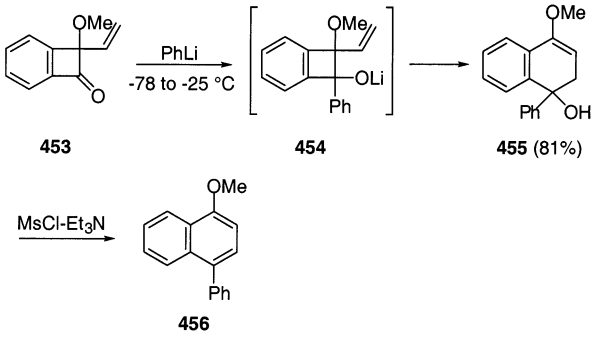


Table 15. Preparation of Alkenylbenzocyclobutenols 451 and Tetralones 452

				yield (%)	
entry	ketone	R_1	R_2	**451**	**452**
a	84	H	H	82	96
b	84	Ph	H	80	91
c	84	Me	H	87	94
d	450	H	H	87	90
e	450	Ph	H	75	71
f	450	Me	H	91	65
g	450	H	Ph	—[a]	56
h	450	H	Me	—[b]	—

[a] The benzocyclobutenol **451g** could not be isolated. [b] The reaction produced a complex mixture from which no product could be isolated.

Scheme 101

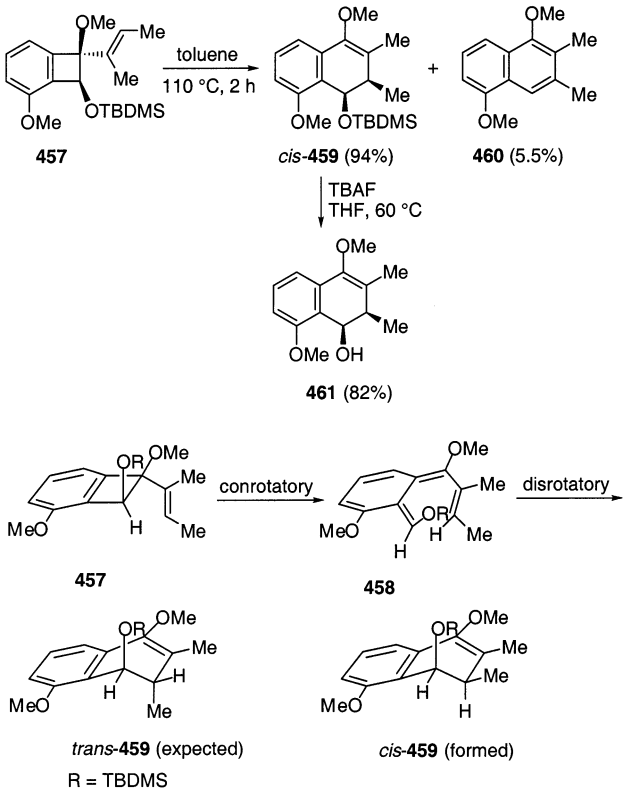


methylvinyl group with (*E*)-configuration, on refluxing in toluene for 2 h, afforded the cis ether **459** ($J_{1,2}$ = 3.3 Hz) as a single isomer, which was verified unambiguously by X-ray analysis of alcohol **461**. The expected sequence is the conrotatory opening of **457** to the quinodimethene **458** and its 6π-electrocyclization in a disrotatory fashion to give the *trans*-silyl ether **459**, whose stereochemistry would be opposite to that of the observed *cis*-**459** (Scheme 102).[350,351]

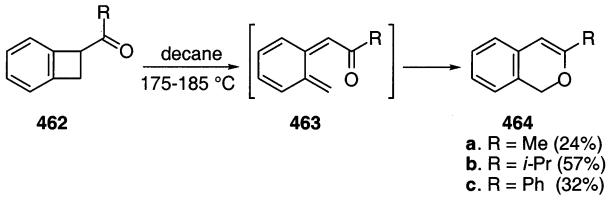
1-Acylcyclobutarenes **462**, on heating in decane at 175−185 °C, undergo ring opening to give *o*-quinodimethanes **463**, which cyclize spontaneously to give the isochromenes **464** (Scheme 103).[352,353] Fukumoto, Kametani, and co-workers extended the scope of this reaction to the syntheses of other substituted isochromanes.[354]

Upon thermal activation, the benzocyclobutenyl ketone oximes **465** gave 3,4-disubstituted isoquinolines **467** via *o*-quinodimethane intermediate **466**

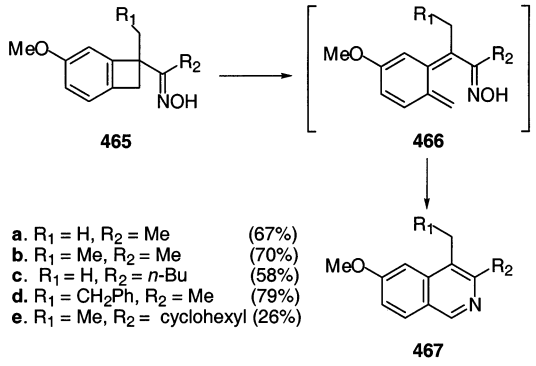
Scheme 102



Scheme 103



Scheme 104

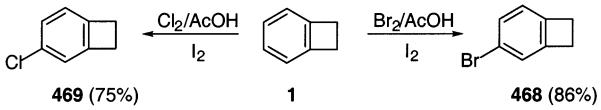


(Scheme 104).[355] Several additional examples of related pericyclic reactions have been reported.[347,356−358]

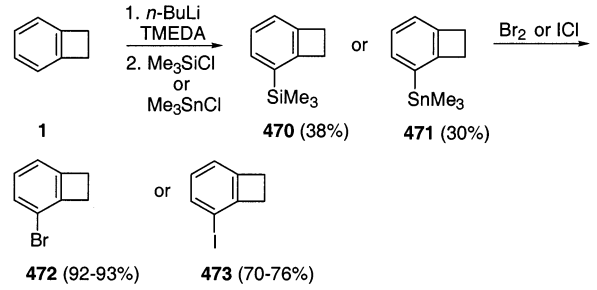
D. Electrophilic Substitution Reactions

Reactions of cyclobutarenes with electrophilic reagents generally follow two competing pathways. Substitution occurs mainly at the 4-position, although minor products resulting from substitution at the 3-position are sometimes observed. In other cases, electrophilic attack occurs at the bridgehead carbon to open the four-membered ring and give ortho-substituted 2-phenylethyl derivatives. Bromi-

Scheme 105



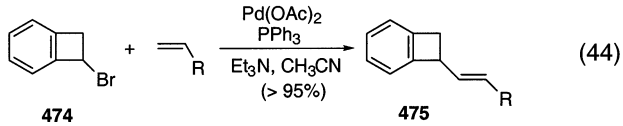
Scheme 106



nation and chlorination of **1** in the presence of iodine in 95% acetic acid gave **468** and **469** in 86% and 75% yield, respectively (Scheme 105).[243]

Lithiation of **1** occurs exclusively at the 3-position. The lithiated species can then be coupled with chlorotrimethylsilane or chlorotrimethylstannane to give **470** or **471**, respectively, which can be reacted with electrophilic reagents to yield 3-substituted halogen derivatives such as **472** and **473** (Scheme 106).[359]

Cyclobutarenes halogenated on the cyclobutene ring serve as intermediates for the synthesis of other functionalized cyclobutarenes. For example, palladium-catalyzed coupling of **474** with olefins (Heck reaction) provides a viable route to **475** (eq 44).[239,244] These compounds serve as monomers for the preparation of polymeric materials that have been commercialized for use as electronic, composite, and thermoplastic applications.[360−362] Nickel-catalyzed coupling has also been used to prepare **475** from the bromide **474**.[363]



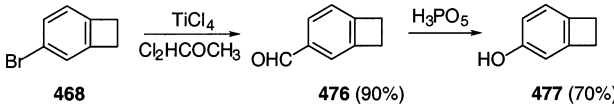
(44)

R = H, Ph, *p*-tolyl, trimethoxysilane, triethoxysilane, benzocyclobutenyl

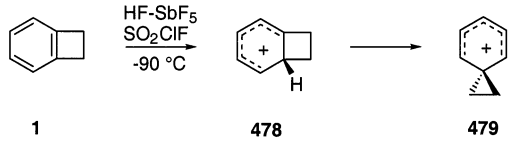
Formylation of **468** by dichloromethyl methyl ether in the presence of $TiCl_4$ gives aldehyde **476**, which undergoes a Baeyer−Villiger reaction using permonophosphoric acid (H_3PO_5) to give phenol **477** (Scheme 107).[364] Aldehyde **476** can also be prepared by treating the Grignard reagent derived from **468** with DMF, followed by quenching with NH_4Cl.

Cyclobutarene **1** is highly sensitive to Brønsted and Lewis acids, and it is also unstable at elevated temperatures under acidic conditions.[365,366] It under-

Scheme 107

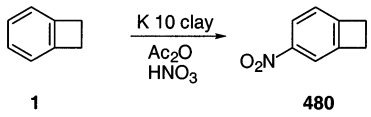


Scheme 108



goes ipso attack upon sulfonation.[367] In superacid medium (HF−SbF_5/SO_2ClF, −90 °C), **1** rearranges to the stable phenonium ion **479** via the protonated bridgehead intermediate **478** (Scheme 108).[368,369]

Since ring-opening reactions prevail under acidic conditions, classical nitration and Friedel−Craft reactions give low yields of substitution products. An improved nitration procedure using acetyl nitrate, generated in situ by a continuous process, in the presence of montmorillonite K 10 clay gives 4-nitrobenzocyclobutene **480** in 60% yield. This represents a 2-fold increase in yield over other methods (eq 45).[370]

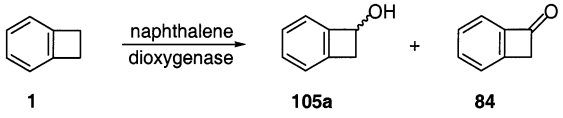


(45)

E. Oxidation and Reduction Reactions

Cyclobutarenes undergo bacterial oxidation, preferentially at the benzylic position, to give monooxygenated products. For example, naphthalene dioxygenase-catalyzed oxidation of **1** in intact cells of *Pseudomonas fluorescens* 127-68 XVII yielded exclusively the benzylic oxidation products, benzocyclobutenol (**105a**) and cyclobutarenone (**84**). Cyclobutarenone (**84**) is presumed to result from the action of alcohol dehydrogenase on **105a**. No evidence for the incorporation of oxygen into the aromatic ring was found (Scheme 109).[371]

Scheme 109

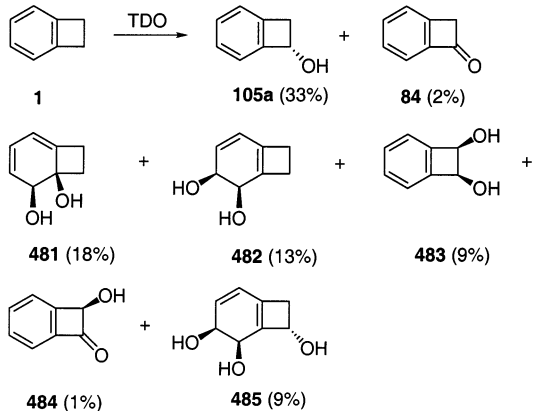


Similarly, **1** is regiospecifically hydroxylated to (±)-1-hydroxybenzocyclobutene by biocatalyst P450cam.[372] In contrast, biotransformation of **1** by toluenedioxygenase (TDO) in intact cultures of *Pseudomonas putida* UV4 gave monooxygenation (**105a**, **84**), dioxygenation (**481**−**484**), and trioxygenation (**485**) products (Scheme 110).[373,374]

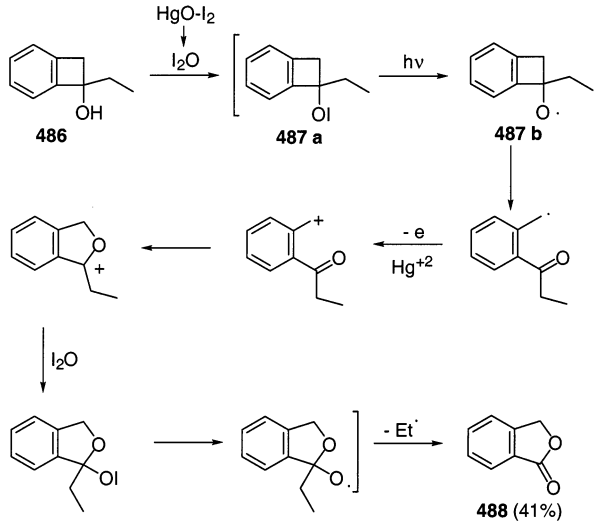
Kobayashi et al. have reported a useful method for the synthesis of the phthalides **488** from cyclobutarene derivative **486**. Their procedure involves regioselective *β*-scission of the alkoxy radical **487b** generated by photolysis of the hypoiodite **487a** (Scheme 111).[375,376]

The Baeyer−Villiger oxidation of cyclobutarenes such as **489** proceeds with rigorous regioselectivity to give **490** in high yield (Scheme 112).[377]

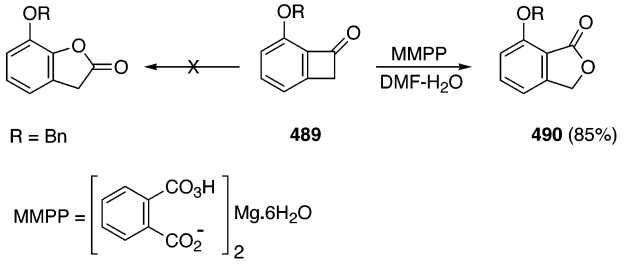
Scheme 110



Scheme 111



Scheme 112



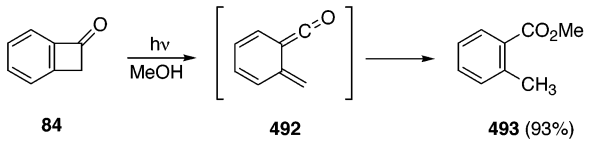
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was found to be a useful oxidizing agent for the preparation of **491** from **129** (eq 46).[90,378]

(46)

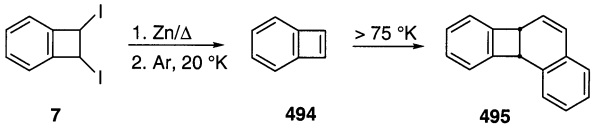
Irradiation of **84** in methanol gave **493** as the major product, presumably via the ketene intermediate **492** (Scheme 113).[32,379]

Reduction of **7** with Zn dust gives the highly reactive benzocyclobutadiene **494**.[380] The hydrocarbon has been isolated by Chapman and co-workers

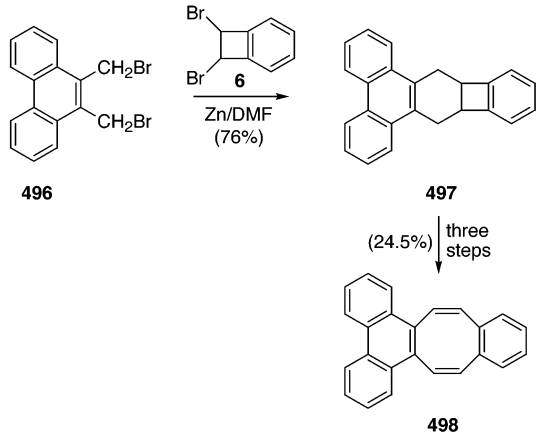
Scheme 113



Scheme 114



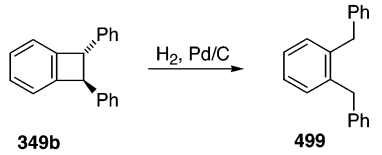
Scheme 115



in an Ar matrix at 20 K. A dimer identified as **495** was formed upon warming (Scheme 114).[381]

Zn dust reduction of 1,2-dibromobenzocyclobutene (**6**) has been exploited as a route to **498** (Scheme 115).[382]

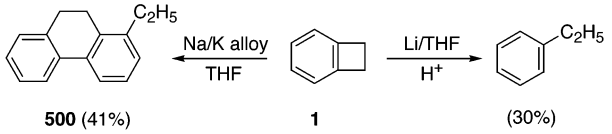
Catalytic reduction of **349b** leads to the distal C−C bond cleavage of the cyclobutene ring to give the *o*-dibenzyl derivative **499** (eq 47).[19] On the other hand, cyclobutarene is known to undergo a proximal ring-opening reaction to ethylbenzene upon treatment with lithium in THF.[383] In this reaction, THF acts as a source of hydrogen, which was confirmed by the use of THF-d_8. The reaction with Na/K alloy, however, gave 1-ethyl-9,10-dihydrophenanthrene **500** via a dimerization pathway (Scheme 116).[384] The



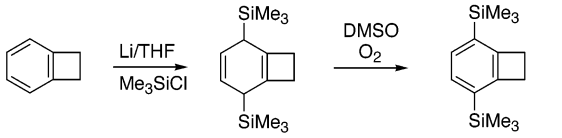
(47)

arene ring of **1** undergoes Birch reduction, as expected. Reductive silylation of **1** under Birch conditions or upon electrochemical reduction gives the unsaturated derivative **501**, which on rearomatization in air gives **502** (Scheme 117).[28]

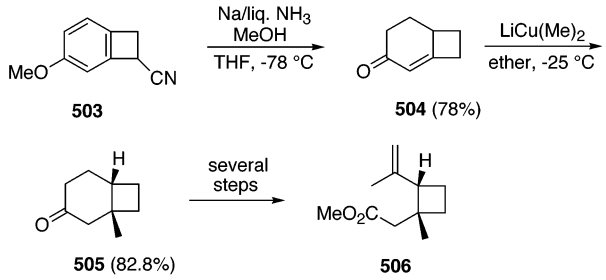
Scheme 116



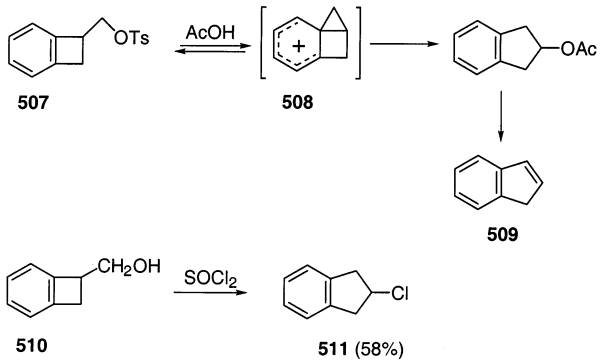
Scheme 117



Scheme 118



Scheme 119



Kametani and co-workers have synthesized the grandisol derivative **506** from cyclobutarene **503**. Birch reduction of **503** affords bicyclic enone **504**, which is further converted into **505** by treatment with lithium dimethylcuprate. Further elaboration of **505** via a series of ring-opening reactions gives **506** (Scheme 118).[385]

F. Rearrangement Reactions

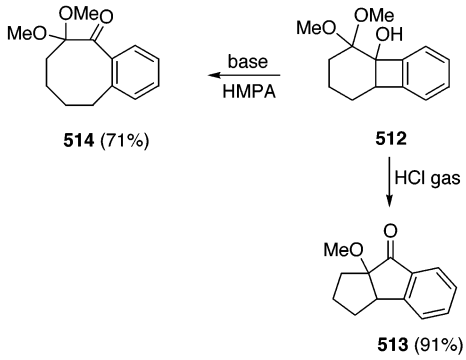
Suitably substituted cyclobutarenes undergo reconstruction via ring-enlargement and ring-contraction reactions. For example, solvolysis of **507** in acetic acid results in ring expansion to indene **509** via bicyclo[2.1.0]pentylphenonium ion **508** (Scheme 119).[386] Similarly, alcohol **510**, upon reaction with $SOCl_2$, gives the ring-expanded product **511** (Scheme 119).[348]

Treatment of **512** with hydrochloric acid led to the formation of alkoxy indanone **513**, while treatment with base led to the formation of monoprotected dione **514** (Scheme 120).[387]

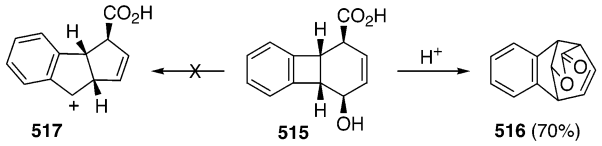
An acid-catalyzed rearrangement of **515** led to the novel bridged ester **516**. Surprisingly, no product derived from the thermodynamically favored benzylic cation **517** was formed (Scheme 121).[388]

Ring-expansion of quinone **518**, via electrocyclic ring opening of the cyclobutene ring, leads to the formation of the novel pleidenequinone **519** (eq 48).[389]

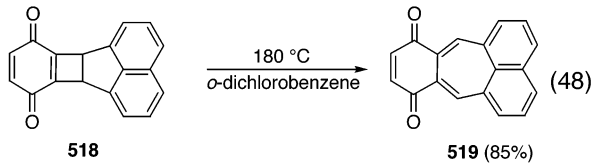
Scheme 120



Scheme 121



Quinone **519** exhibits electron affinity comparable to that of *p*-benzoquinone.



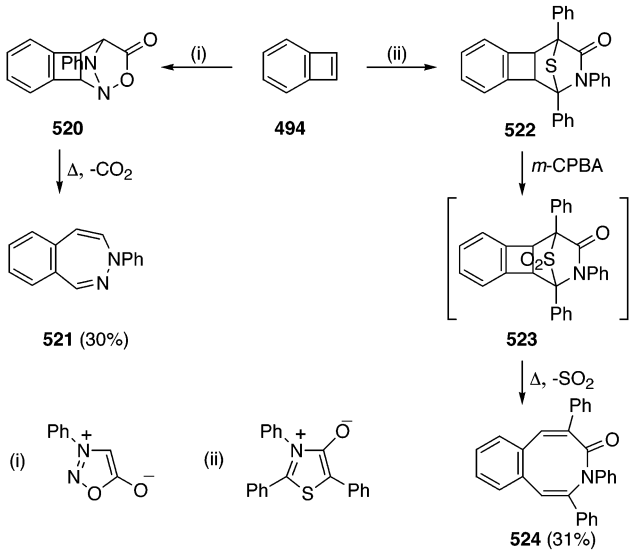
(48)

Rearrangements of cyclobutarenes **520** and **523**, which are formed by dipolar cycloadditions of **494**, gave benzo-fused heterocyclic compounds **521** and **524**, respectively, by electrocyclic ring opening of the cyclobutene ring and extrusion of either CO_2 or SO_2 (Scheme 122).[390]

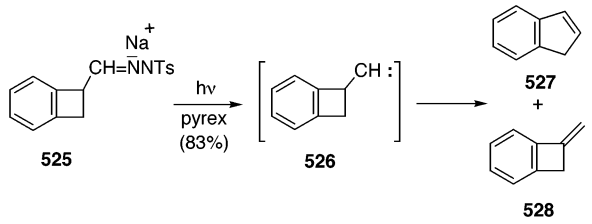
Irradiation of the sodium salt **525** in THF solution through Pyrex gave indene **527** and 1-methylidenebenzocyclobutene **528** via benzocyclobuten-1-ylcarbene **526** in a ratio of 82:18 (Scheme 123).[391]

Photolysis of cyclobutarene in pentane at 254 nm yields 1,2-dihydropentalene (**529**) and 1,5-dihydro-

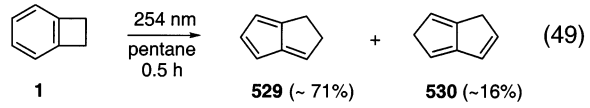
Scheme 122



Scheme 123



pentalene (**530**) as major products. Formation of **529** and **530** has been explained on the basis of a prebenzvalene−carbene rearrangement (eq 49).[392]



(49)

Acylation of carboxylic acid derivative **531** by methyl esters, followed by oxidative ring expansion, leads to the formation of 2-hydroxy-1-indanone **532** as the major product. The minor product **533** can also be converted into **532** by treatment with lithiumdiisopropylamide (LDA) and MoO_5·pyridine hexamethylphosphorictriamide (HMPA) (MoOPH). These indanones can be further converted into 3,4-dihydroisocoumarins such as **534** (Scheme 124, Table 16).[393]

The insertion of methylene from diazomethane into the aromatic ring of **1** leads to a mixture of cyclobutane-fused cycloheptatrienes **535**−**537**. Treatment of this mixture with a trityl salt affords the cyclobutane-fused tropylium salt **538** in essentially pure form.

Scheme 124

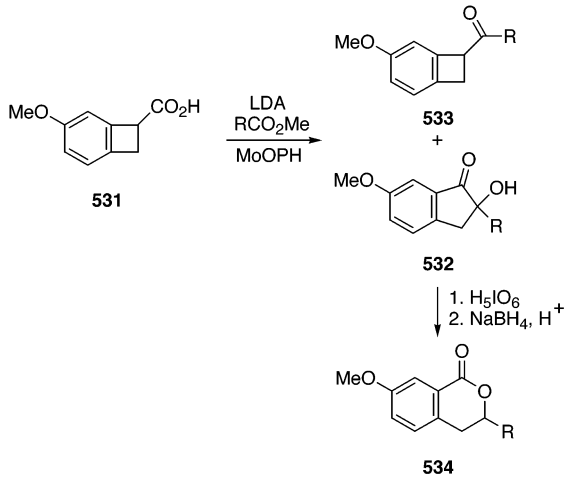
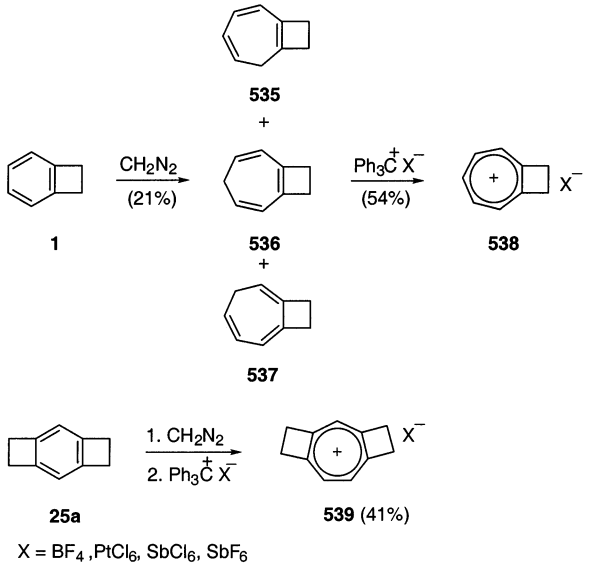


Table 16. Syntheses of 2-Hydroxy-1-indanones 532 and 3,4-Dihydroisocoumarines 534

entry	R	yield (%)[a] 532	yield (%)[a] 533	conversion (%)[a] of **533** into **532**	yield **534** (%)[a]
1	Et	26	13	48[b]	47
2	*t*-Bu	58	8	97	48
3	*i*-Pr	53	12	93	64
4	cyclohexyl	33	25	97[b]	63
5	Ph	75	0	91	74
6	*p*-$MeOC_6H_4(CH_2)_2$	11	12	93[b]	73

[a] Not optimized. [b] Based on consumed ketone **533**.

Scheme 125



Scheme 126

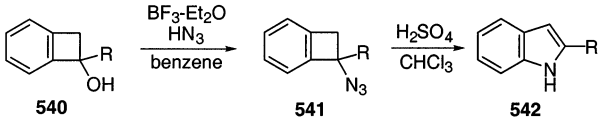


Table 17. Conversion of Benzocyclobutenol Derivatives 540 into 2-Substituted Indoles 542

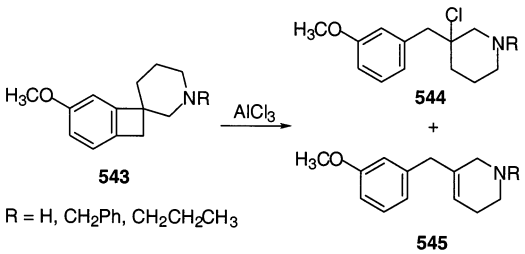
entry	R	yield (%) **541**	yield (%) **542**
1	CH_3	90	90
2	$CH_3CH{=}CH_2$	85	85
3	C_6H_5	75	98
4	$C_6H_5CH_2$	80	98

Similarly, dicyclobutabenzene **25a** gives tropylium salt **539** (Scheme 125).[394]

G. Miscellaneous Reactions

Application of the Schmidt reaction has been made in the conversion of benzocyclobutenol derivatives **540** into 2-substituted indoles. Treatment of benzocyclobutenols **540** with hydrazoic acid in BF_3−Et_2O gives azide **541**, which on subsequent treatment with concentrated H_2SO_4 at 0 °C affords 2-substituted indoles **542** (Scheme 126, Table 17).[395]

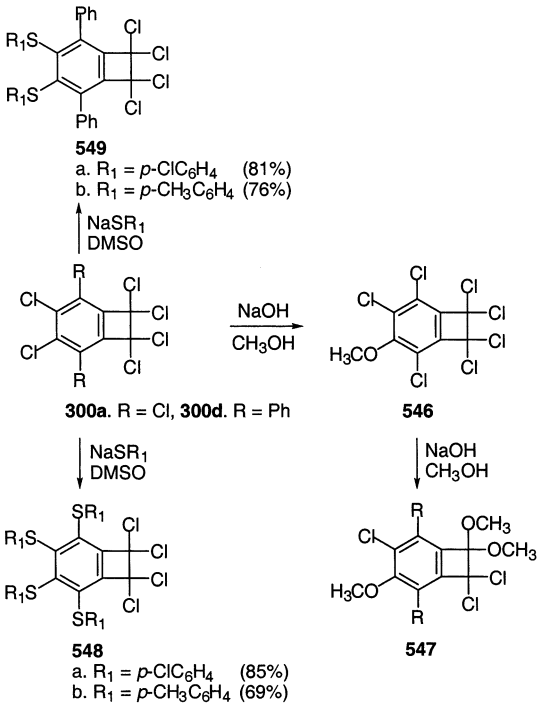
An unexpected rearrangement of **543** affords **544** and **545** in the presence of $AlCl_3$. The tertiary chloride **544** was obtained in >90% yield, along with a small amount of **545** (eq 50).[396]



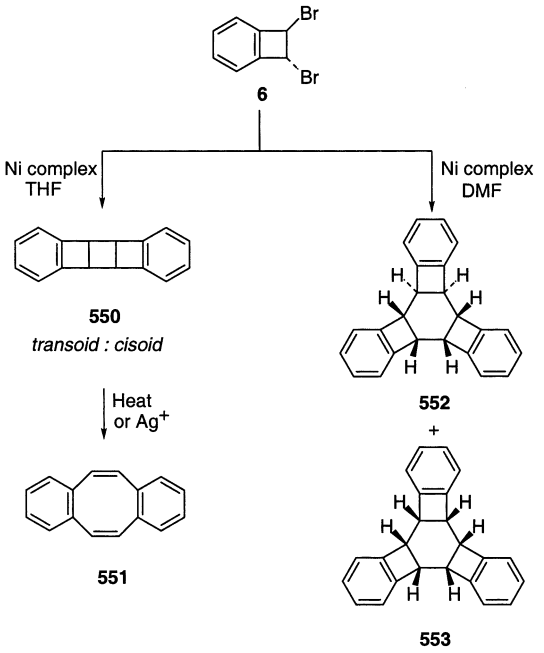
(50)

Nucleophilic substitution of perchlorobenzocyclobutene (**300a**, R = Cl; **300d**, R = Ph) by methanolic

Scheme 127



Scheme 128



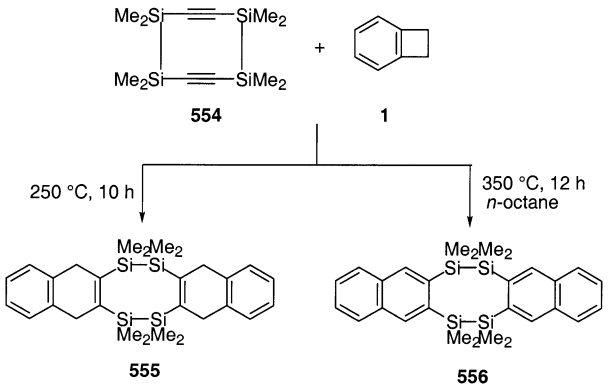
sodium hydroxide occurs first at the benzene nucleus, giving **546**, and then at the four-membered ring to afford **547**. However, reaction of **300a** and **300d** with thiolates in DMSO gave only **548** and **549** (Scheme 127).[397]

Nickel-catalyzed cyclooligomerization of **6** in THF yielded mainly the transoid and cisoid dimers **550**.[398−400] These compounds rearrange to **551** upon heating or by treatment with silver ion. In contrast, the reaction of **6** with Ni complex in DMF gave the trimers **552** and **553** as major products (Scheme 128, Table 18).[400] Low-valent nickel complexes were generated in situ by reduction of $NiBr_2L_2$ (L = PPh_3 or PBu_3) with Zn dust in the presence of ligand (PPh_3 or PBu_3) or an iodide (Et_4NI or NaI).

Reaction of **554** with **1** at 250 °C for 10 h gave **555** in 56% yield. When the reaction was carried out at 350 °C for 12 h, **556** was obtained in 59% yield (Scheme 129).[401]

3,6-Diarylcyclobutarenes can be prepared using the Suzuki−Miyaura coupling reaction as the key step. The 3,6-dihalocyclobutarene precursors **558a**,**b** were prepared by treating **557** with Br_2/MeOH or ICl/CCl_4. Coupling of **558** with arylboronic acids in the presence of Pd(0) gave the corresponding 3,6-diarylcyclobutarene **559**. The highest yields were obtained when 3,6-diiodocyclobutarenes were used in the coupling reactions (Scheme 130).[402]

Scheme 129



Scheme 130

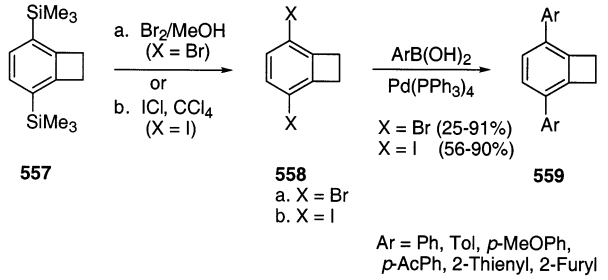
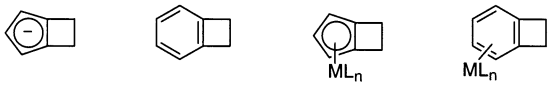


Table 18. Reaction of 1,2-Dibromocyclobutarene (6) with Low-Valent Nickel Complexes

				yield of products (%)				
entry	$NiBr_2L_2$	additive	solvent	*transoid*-**550**	*cisoid*-**550**	**551**	**552**	**553**
1	$NiBr_2(PPh_3)_2$	PPh_3	THF	18	trace	4	7	1
2	$NiBr_2(PPh_3)_2$	Et_4NI	THF	31	13	0	21	0
3	$NiBr_2(PBu_3)_2$	PBu_3	THF	7	2	8	5	0
4	$NiBr_2(PPh_3)_2$	PPh_3	DMF	6	trace	1	38	4
5	$NiBr_2(PBu_3)_2$	PBu_3	DMF	2	1	2	38	1
6	$NiBr_2(PPh_3)_2$	Et_4NI	DMF	6	trace	2	38	trace
7	$NiBr_2(PPh_3)_2$	NaI	DMF	5	trace	2	40	1

H. Transition Metal Complexes

Cyclobutarene and the homologue **560** form organo transition metal complexes readily. In neutral complexes of type **561**, there is considerable Coulombic interaction between the anion **560** and the metal. However, in the electroneutral complexes of type **562**, there is coordinate bonding between the neutral ligand and the metal. This leads to less ionic interaction, which makes these complexes thermally less stable than complexes of **560**.



560 **1** **561** **562**

As complexation can take place at both faces of the aromatic ring, diastereomeric mixtures are obtained from cyclobutarenes with substituents at C-1. Diastereomers with the ligand−metal fragment on the same face of the π-system are called endo or syn (**563A**), whereas complexes with the ligand−metal fragment on the opposite face are called exo or anti (**563B**). The exo diastereomer usually predominates.

563A **563B**

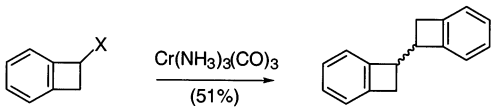
When the cyclobutarene plane provides the only element of symmetry (e.g., 3-methyl or 1-oxo), chirality is introduced by complexation to a metal, leading to the formation of enantiomers (**564** and **565**).

564 **565**

1. Synthesis

Complexes of group VI metals with cyclobutarenes have probably received the most attention. These electroneutral complexes are generally prepared by treating the cyclobutarene with complexation agents such as $Cr(CO)_6$, $(NH_3)_3Cr(CO)_3$, $(C_6H_6)Mo(CO)_3$, and $(EtCN)_3W(CO)_3$. Among the complexes reported, most are tricarbonylchromium complexes,[403−410] although a few reports describe tricarbonylmolybdenum[411] and tricarbonyltungsten complexes.[405a,411] Some representative examples are illustrated in Table 19.

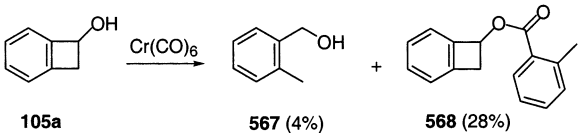
As expected, cyclobutarenes with functional groups capable of reacting with chromium reagents usually follow a different pathway. For example, the reaction of $Cr(CO)_3(NH_3)_3$ with 1-halocyclobutarenes **208** and **474** proceeds by reductive coupling to give **566** (eq 51).[412]



208 X = Cl
474 X = Br

566 (51)

Reaction of benzocyclobutenol (**105a**) with $Cr(CO)_6$ leads to the formation of **567** and **568** (eq 52).[405a,413] These compounds appear to have been formed by ring opening of the cyclobutene, followed by disproportionation and coupling.



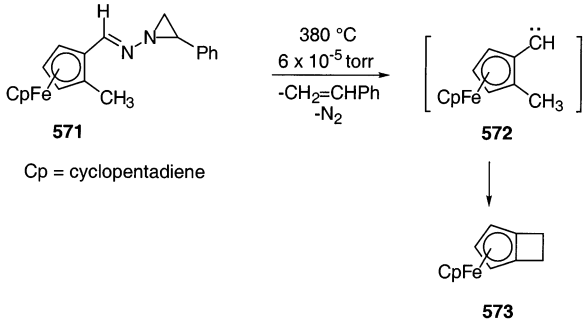
105a **567** (4%) **568** (28%) (52)

Bis(η^6-benzocyclobutene) complexes **569** and **570** have been prepared by co-condensation of metal vapor with the hydrocarbon. These air-sensitive compounds have been characterized by spectroscopic techniques.[405b,410]

569 M = Cr, Mo, W **570**

FVP of hydrazone **571** gives ferrocenocyclobutene **573**, presumably by formation of carbene **572**, which rearranges to **573** by C−H insertion. Complex **573** was obtained in high purity (>95%) in 30−35% yield (Scheme 131).[414]

Scheme 131

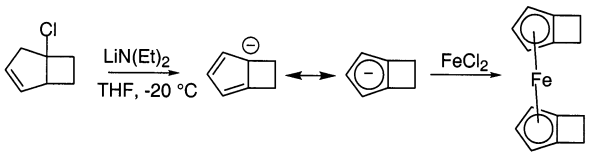


571 **572** **573**

Cp = cyclopentadiene

Oda and Breslow have prepared the ferrocene-like derivative **575** in 65% yield as yellow prisms by treating the anion **560**, prepared from **574**, with $FeCl_2$ (Scheme 132).[415]

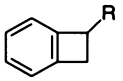
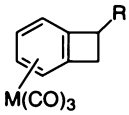
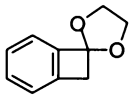
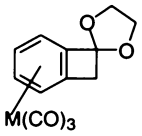
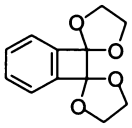
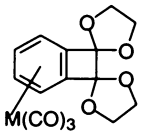
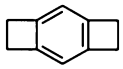
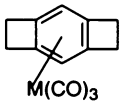
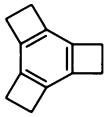
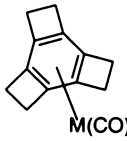
Scheme 132



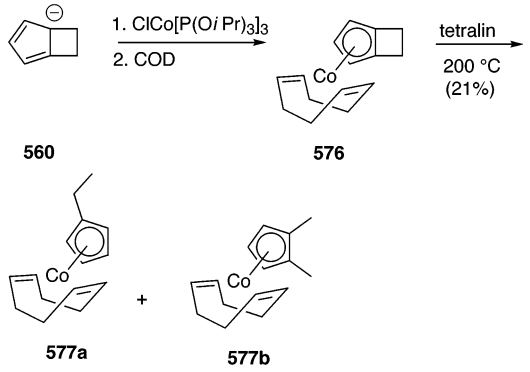
574 **560** **575**

Reaction of **560** with chlorotris(trisisopropyl phosphite)cobalt(I), and subsequent treatment with cycloocta-1,5-diene (COD), affords **576** in 49% yield

Table 19. Cyclobutarene Complexes Formed by Direct Complexation of the Ligand

cyclobutarene	complex	M	R	yield (%)	endo:exo	ref
		Cr	H	40	–	403-405
				51	–	
		Cr	OEt	70	4:6	406
		Cr	OH	35	9:1	407
		Cr	OAc	70	1:1	408
		Cr	OMe	54	55:45	407
		Cr	OMEM	58	81:19	407
		Cr	OTHP	61	97:3	407
		Cr	Me	62	4:6	403, 404
		Cr	Bu	27	1:1	403, 404
		Cr	$(CH_2)_2CH{=}CH_2$	49	12:88	403, 404
		Cr	$SiMe_3$	64	24:76	403, 404
		Cr	$SnMe_3$	89	–	403, 404
		Mo	Me	70	1:1	411
		Mo	Bu	33	1:9	411
		Mo	$SiMe_3$	50	15:85	411
		Mo	$SnMe_3$	68	–	411
		W	H	31	17:83	411
		Cr	–	83	–	403, 404
		Mo	–	34	–	411
		Cr	–	82	–	409
		Cr	–	78	–	405b, 410
		Cr	–	21	–	411a

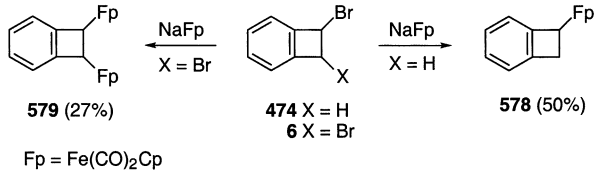
Scheme 133



(Scheme 133). Thermolysis of **576** in tetralin at 200 °C gives a 1:1 mixture of isomers **577a** and **577b** in 21% yield. Short heating of **576** at 260 °C, however, gives COD as the only characterized product, in addition to decomposed material.[416]

A few reports describe cyclobutarenyl σ-complexes where the metal atom is bound to the carbon atoms of the four-membered ring. The iron complexes **578** and **579**, the first compounds of this type, were obtained by the reductive metalation of 1-bromocyclobutarene **474** and 1,2-dibromocyclobutarene **6**, respectively, using NaFp in THF (Scheme 134).[417−419]

Scheme 134



2. Chemistry

In general, cyclobutarene complexes are activated for nucleophilic substitution reactions and deactivated toward electrophilic substitution. The arene protons become more acidic and can therefore be readily lithiated. The metal fragment blocks one face of the arene in cyclobutarene and thus directs the incoming reagents to the opposite uncomplexed face. Usually these complexes cannot be heated above 200 °C without decomposition. The following reactions illustrate the effects of complexation on the chemistry of the cyclobutarenes.

The reactions of electrophiles with deprotonated arene(tricarbonyl)chromium complexes provides a convenient route to substituted cyclobutarenes.[420] Thus, treatment of [η^6-(bicyclo[4.2.0]octa-1,3,5-triene)]tricarbonylchromium(0) (**341**) with *n*-BuLi or lithium 2,2,6,6-tetramethylpiperidide (LTMP) at −100 °C facilitates a regioselective deprotonation at C-3.

Scheme 135

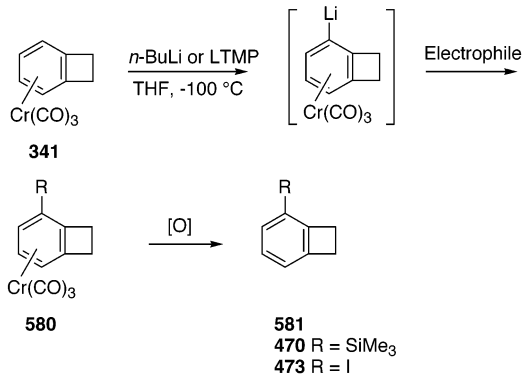
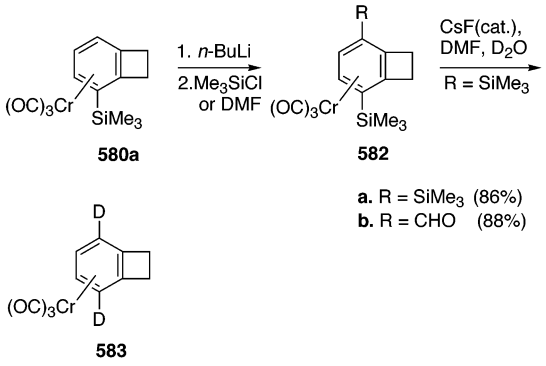


Table 20. Regioselective Deprotonation of Complexed Cyclobutarene 341 Followed by Treatment with Electrophiles

entry	electrophile	R	yield (%)
a	Me_3SiCl	Me_3Si	91
b	D_2O	D	92
c	MeI	Me	80
d	I_2	I	50
e	Ph(Me)NCHO	CHO	67
f	CO_2	CO_2Me	81

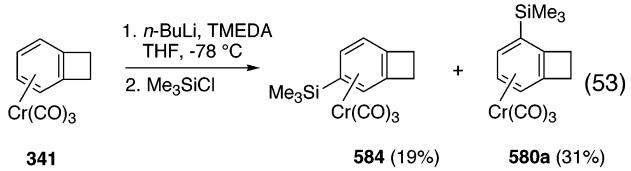
Scheme 136



Two examples are illustrated in Scheme 135. The $Cr(CO)_3$ group can be removed easily by oxidation using I_2 or Ce(IV), or by $O_2/h\nu$, to afford the 3-substituted decomplexed cyclobutarene derivatives **581** (Table 20).[421]

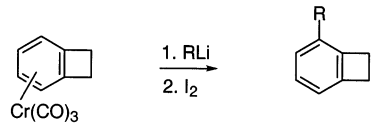
Regioselective deprotonation of **580a** by *n*-BuLi, followed by reaction with trimethylsilyl chloride or dimethyl formamide, gave disubstituted products **582a**,**b**. The bis(trimethylsilyl) derivative **582a** can be deuterated using a catalytic amount of cesium fluoride in DMF/D_2O to afford the dideuterio complex **583** in 85% yield (Scheme 136).[421]

Treatment of **341** by *n*-BuLi/TMEDA in THF at −78 °C gave, upon addition of chlorotrimethylsilane, a mixture of **584** and **580a** (eq 53).[404,405]



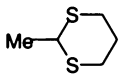
(53)

3-Substituted cyclobutarenes **585** are readily accessible from **341** via a two-step sequence that involves addition of the nucleophile, followed by oxidation using I_2 (eq 54) (Table 21).[422,423]

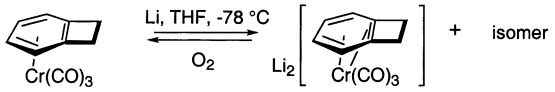


(54)

Table 21. Formation of 585 from 341

entry	R	solvent	yield **585** (%)
1	CH_2CN	THF/HMPA 10:1	65
2	CMe_2CN	THF	86
3	CMe_2CO_2Me	THF/HMPA 4:1	96
4		THF	69
5		THF/HMPA 10:1 or THF	64

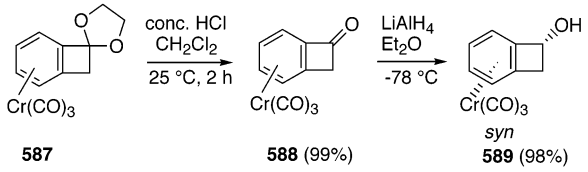
The reaction of tricarbonylchromium complex **341** with lithium at −78 °C gave the two-electron-reduced product **586**. Ring-slippage reaction occurs[424] as the arene ligand changes hapticity from η^6 to η^4. Apparently, the strained bridging bond in **586** remains coordinated. Exposing **586** to atmospheric oxygen results in reoxidation to **341** (eq 55).[425,426]



(55)

The electron-withdrawing effect of the tricarbonylchromium group results in significant enhancement of the carbonyl reactivity in cyclobutarenone. Tricarbonylchromium complex **588**, obtained by hydrolysis of **587**, was reduced readily by $LiAlH_4$.[427] The reaction temperature (−78 °C) is ∼100 °C lower than that for the corresponding reduction of the cyclobutarenone **84**.[428] The reduction gives syn-alcohol **589** with complete diastereoselectivity (Scheme 137).

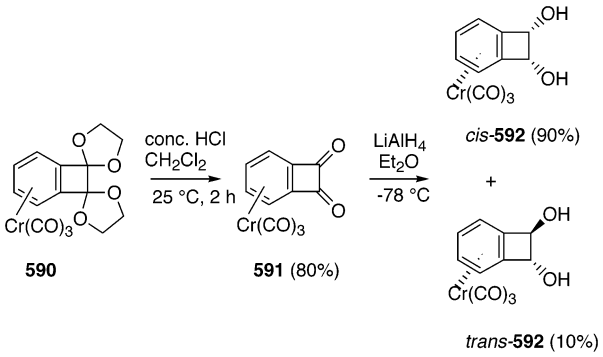
Scheme 137



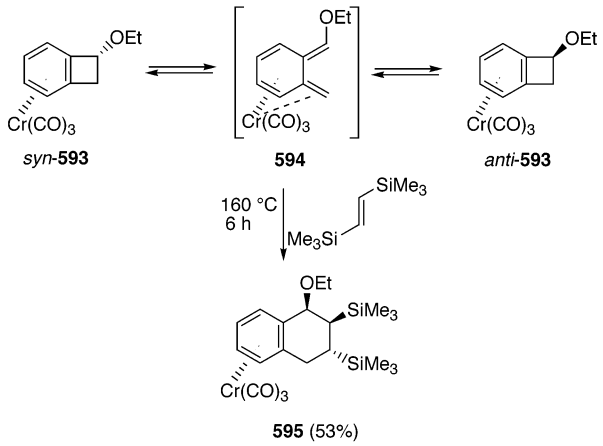
Similarly, reduction of diketone complex **591** with $LiAlH_4$ under identical conditions yields predominantly the syn-cis-diol complex **592** in 90% yield (Scheme 138).[429]

$Cr(CO)_3$ complexes of 1-substituted *o*-quinodimethanes generated in situ undergo cycloaddition reactions with dienophiles exclusively at the face opposite the metal center. Selectivity varies from preferentially endo to exclusively exo addition. For example, the reaction of the coordinated *o*-quinodimethane **594**, obtained from *syn*-tricarbonyl(η^6-1-ethoxybenzocyclobutene)chromium(0) **593** at 160 °C with (*E*)-1,2-bis(trimethylsilyl)ethene, gave tetralin

Scheme 138



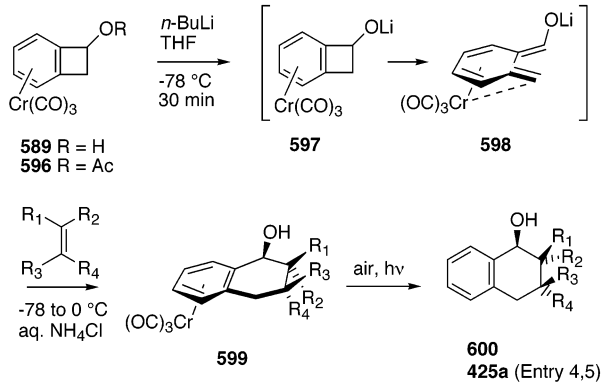
Scheme 139



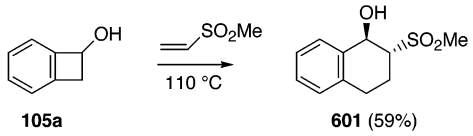
complex **595** in 53% yield, in addition to a minor isomer (3%) and a mixture (35%) of starting *syn*- and *anti*-**593**. The diastereomeric excess (de) for this reaction is >95%, and the cycloadducts have a 1,2-cis configuration. The interconversion of *syn*- and *anti*-**593** has also been reported (Scheme 139).[430] Differential scanning calorimetry (DSC) analyses indicate that the ring opening of the chromium complexes occurs at a slightly higher temperature than that of uncoordinated cyclobutarene.[413]

Complex **597** experiences facile anion-accelerated ring opening to give the reactive intermediate **598**. This intermediate can be trapped by dienophiles with face selectivity varying from preferentially endo to exclusively exo (Table 22).[407,408,427,431,432] Cycloaddition of **598**, generated in situ with olefins (entries 1−6), affords the 1,2-cis (endo addition) product (Scheme 140). The observed stereochemistry can be explained by assuming a torquoselective[122,268] ring-opening reaction, resulting in an *E* configuration of the enolate double bond.

Scheme 140



Cycloaddition of **598** with vinyl sulfones (entries 7−12) affords the 1,2-trans isomer as the major product (Scheme 140, Table 22). Heating of **105a** at 110 °C in the presence of vinyl sulfone also gave cycloadduct **601**, indicating that the reason for the stereoselectivity does not lie in coordination to the metal (eq 56). Thus, 1,2-trans configuration implies a rare exo transition state for the cycloaddition. A 1,2-trans cycloaddition product is also reported for the reaction of **105a** with some esters bearing a chiral auxiliary (Scheme 85).[289−293] A comparative study of cycloaddition reactions of complexed α-oxy-*o*-quinomethane **598** with dienophiles is given in Table 22.



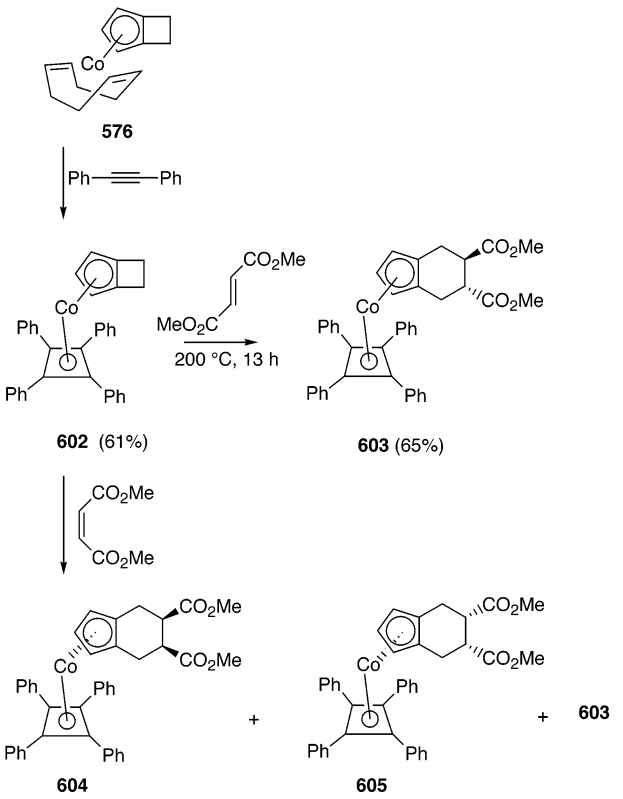
(56)

Complexes of type **561** also undergo ring opening, followed by cycloaddition, provided the activation

Table 22. Cycloaddition Reactions of Complexed α-Oxy-*o*-quinomethanes 598

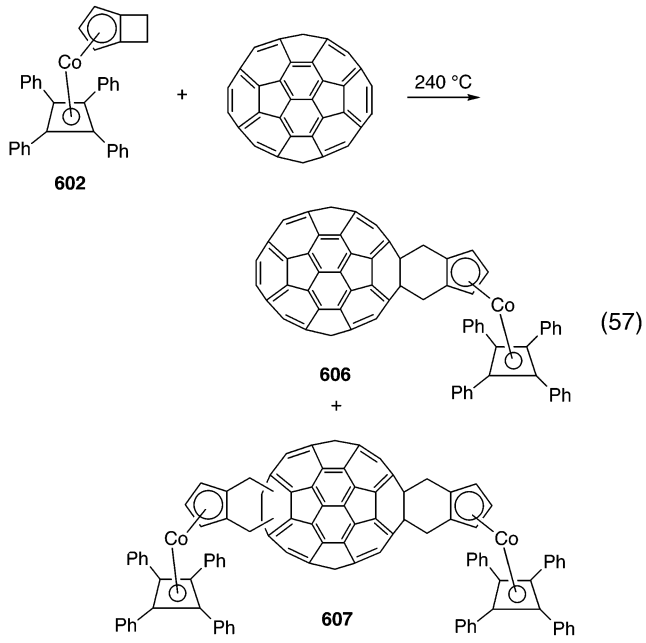
entry	substrate	R_1	R_2	R_3	R_4	product ratio 1,2-cis:1,2-trans	ref
1	*anti*-**502**	CO_2Me	H	H	H	75:25	408, 431
2	*syn*-**495**	CO_2Me	H	H	H	83:17	408, 432
3	*syn*-**502**	CO_2Me	H	H	CO_2Me	73:27	408, 431
4	*anti*-**502**	CO_2Me	H	H	CO_2Me	72:28	408, 431
5	*syn*/*anti*-**502**	CN	H	H	H	75:25	408, 431
6	*syn*-**495**	CN	H	H	H	74:26	408
7	*syn*/*anti*-**502**	SO_2Ph	H	H	H	10:90	408
8	*syn*-**502**	SO_2Ph	H	H	H	12:88	408
9	*syn*-**495**	SO_2Ph	H	H	H	0:100	408, 432
10	*syn*-**495**	SO_2Me	H	H	H	0:100	448
11	*syn*-**502**	SO_2Ph	H	H	Ph	0:100	408
12	*syn*-**495**	SO_2Ph	H	H	Ph	0:100	408, 432

Scheme 141

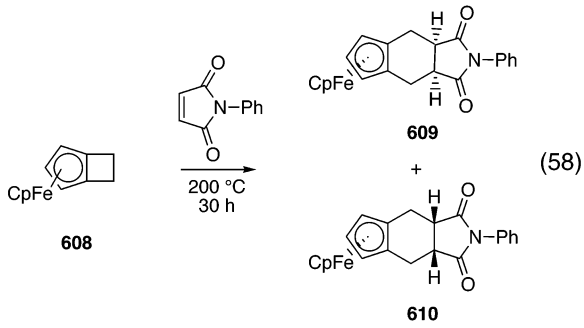


barrier for the ring opening is smaller than that of decomplexation of other ligands. For example, complex **576** is unsuitable for cycloaddition reactions since the activation energy exceeds that of decomplexation of the electroneutral COD ligand.[433] However, η^5-(bicyclo[3.2.0]hepta-1,3-dienyl)(η^4-tetraphenylcyclobutadiene)cobalt(I) complex (**602**), in which COD is replaced by less easily cleavable ligand, undergoes a cycloaddition reaction with dimethyl fumarate to afford the cycloadduct **603** in 65% yield (Scheme 141).[434,435] Formation of **603** from **602** is thought to occur by ring slippage, with the hapticity of the reacting ligand changing from η^5 to η^3. Interestingly, reaction of **602** with dimethyl maleate under similar conditions affords a mixture of **603**, **604**, and **605** (0.9:0.5:1.0) in 90% yield. Isomerization of dimethyl fumarate to dimethyl maleate may be responsible for the formation of **603**, but the formation of the syn-cis-cycloadduct **605** as the major product and not the anti-cis-isomer **604** is surprising. It is proposed that precomplexation of the dienophile takes place, followed by cycloaddition from the coordinated face of the diene.

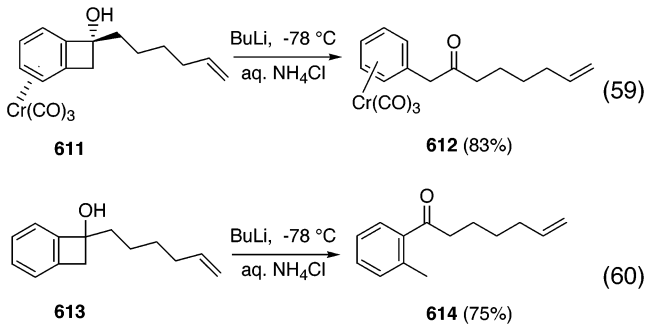
The thermally induced reaction of **602** and C_{60} fullerene afforded mono **606** (28%) and disubstituted **607** (12%) Diels−Alder adducts (eq 57).[326,329,436,437]



Ferrocenocyclobutene **608** undergoes cycloaddition reaction with *N*-phenylmaleimide to afford the stereoisomeric Diels−Alder adducts **609** and **610** in a 11:1 ratio. Only **609** could be separated in pure form in 13% yield (eq 58).[437]

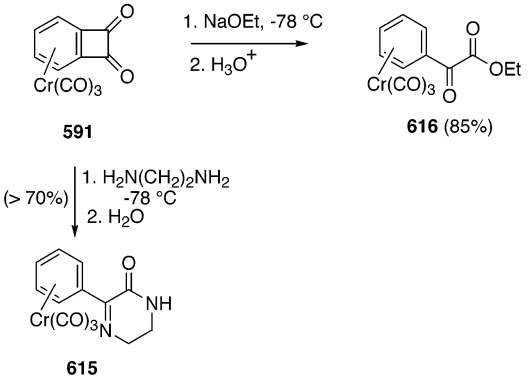


An unexpected proximal ring opening of the annellated cyclobutene ring of complex **611** took place upon treatment with BuLi at −78 °C. The expected intramolecular cycloaddition product was not formed. The uncomplexed benzocyclobutenol **613**, under identical reaction conditions, underwent distal ring opening to afford **614** (eqs 59 and 60).[438]



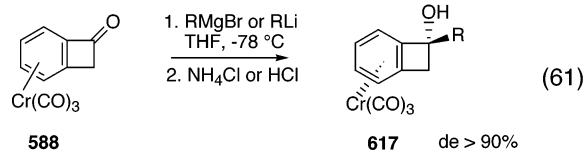
Reaction of benzocyclobutenedione complex **591** with basic O- and N-nucleophiles such as alkoxides or amines leads to proximal ring opening under mild conditions. Thus, benzocyclobutenedione complex **591**, on treatment with sodium ethoxide at −78 °C,

Scheme 142



gives **616** in 85% yield. 1,2-Diaminoethane leads to **615** by a nucleophilic addition with proximal ring opening, followed by intramolecular condensation (Scheme 142).[439]

Nucleophilic addition is facilitated by the electron withdrawal of the tricarbonylchromium group and by the rigidity of the annelated four-membered ring. Thus, treatment of **588** with Grignard or alkyllithium reagents at −78 °C affords *endo*-1-benzocyclobutenol chromium complexes **617** in high yield (eq 61) (Table 23).[439, 440]



(61)

Addition of acyl anion equivalents to **588** provides additional functionality. Thus, treatment of **588** with 1-lithio-1-methoxyallene at −78 °C, followed by quenching with saturated NH_4Cl solution, gave **618** in 100% yield. However, the alkoxy anion accelerated

Scheme 143

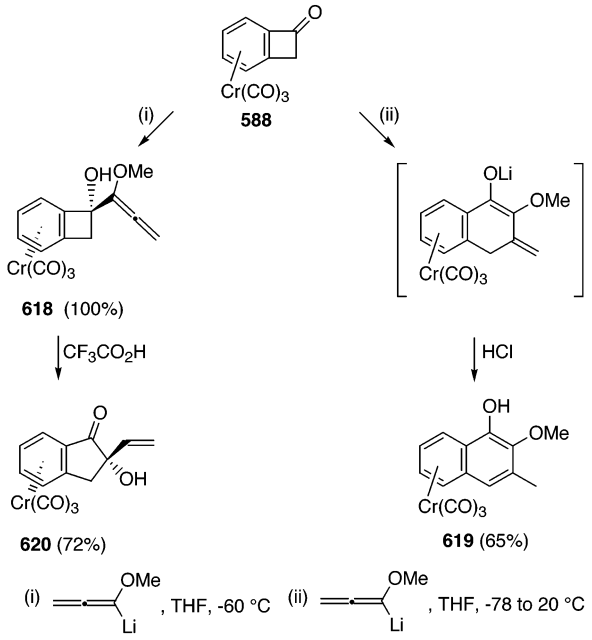
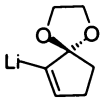
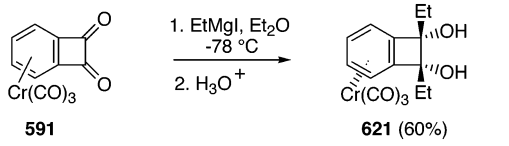


Table 23. Nucleophilic Addition of RMgBr or RLi on 588

entry	RMgBr or RLi	yield **617** (%)	ref
1	CH_3MgBr	98	439
2	$CH_2{=}CHMgBr$	96	439
3	$CH_2{=}CHCH_2MgBr$	88	440
4	$CH_2{=}CH(CH_2)_3MgBr$	61	440
5	$CH_2{=}CH(CH_2)_4MgBr$	93	439
6	t-$BuMe_2SiO(CH_2)_4MgBr$	46	439
7	PhLi	80	440
8		80	440

ring opening took place before aqueous workup when the reaction mixture was warmed to 20 °C, leading to the formation of naphthol complex **619** (Scheme 143). The driving force for this rearrangement seems to be aromatization in the final step. Deprotection of the carbonyl function of the adduct **618** affords ring-expanded product **620**.[440,441]

Addition of Grignard reagents to both carbonyl groups of **591** gives the cis-diadduct **621** (eq 62).[426] The analogous reaction with uncomplexed benzocyclobutenedione **260** usually results in decomposition.[442]



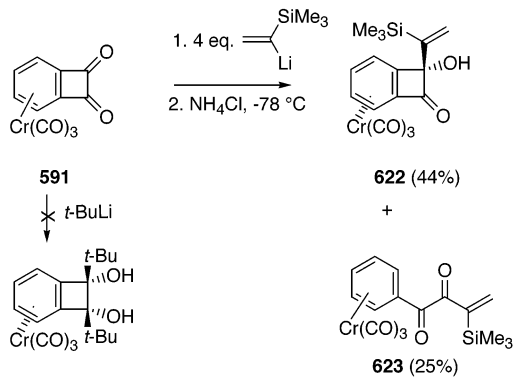
(62)

Addition to only one carbonyl is observed when sterically hindered nucleophiles are employed. Thus, reaction of **591** with 4 equiv of 1-lithio-1-(trimethylsilyl)ethene gives **622**, along with proximal ring-opened product **623** (Scheme 144).[443] Reaction of **591** with *t*-BuLi failed to give isolable products.

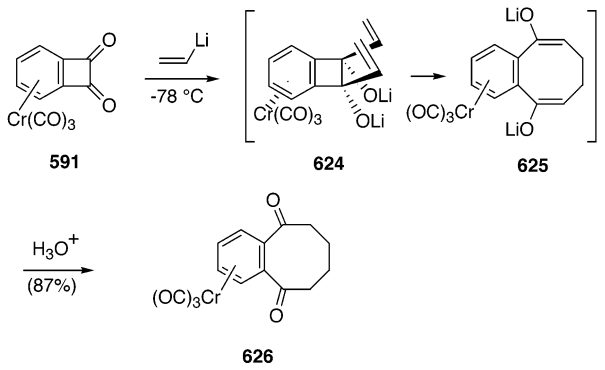
Treatment of complex **591** with 7 equiv of vinylmagnesium bromide or, better, vinyllithium in THF affords 1,2-*cis*-divinyldiolate **624**, which undergoes a dianionic oxy-Cope rearrangement to give **625**. Hydrolytic workup of **625** provides complex **626** (Scheme 145). The dienolate **625** can be trapped as a bis(trimethylsilylenol) ether.[429,444,445]

If **591** is treated with 2 equiv of vinylmagnesium bromide, the monovinyl adduct **627** is isolated in 90%

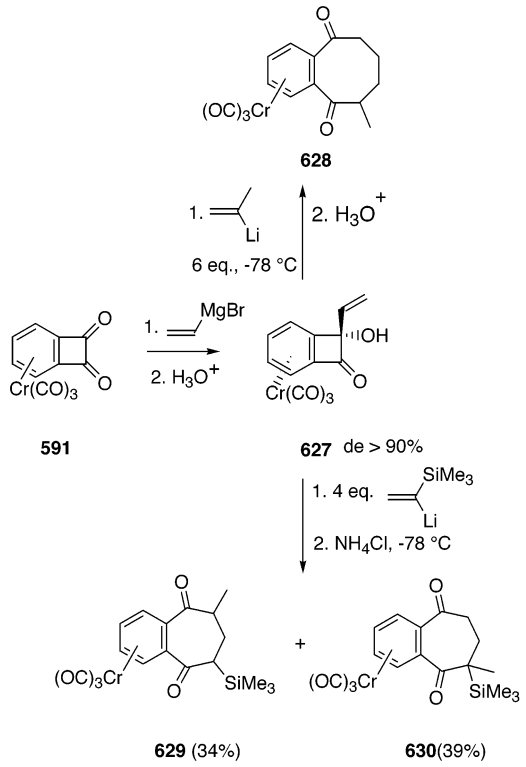
Scheme 144



Scheme 145



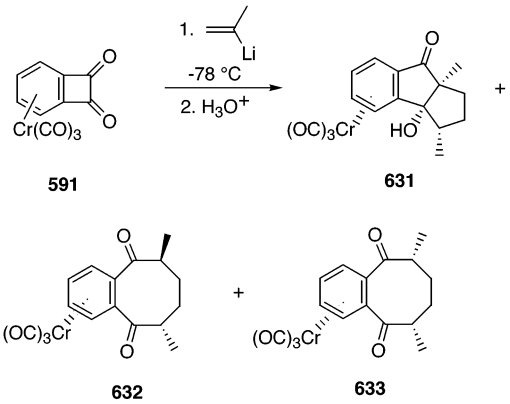
Scheme 146



yield. This adduct, on subsequent treatment with propen-2-yllithium, affords **628** (as a single diastereomer), resulting from anionic oxy-Cope rearrangements.[426] However, when adduct **627** was treated with 1-lithio-1-(trimethylsilyl)ethene, a 1:1 regioisomeric mixture of benzocycloheptenedione complexes[629,630] was obtained in 73% yield (Scheme 146).[443]

In some cases, dianionic oxy-Cope rearrangement is followed by intramolecular aldol condensation. For example, treatment of complex **591** with excess of propen-2-yllithium, followed by acid hydrolysis, affords **631**, **632**, and **633** in a 6:2:1 ratio. The aldol addition product **631** is formed stereoselectively, as the enolate intramolecularly attacks the keto group from the face opposite to the tricarbonyl group (eq 63).[445,446]

Addition of vinylmagnesium bromide to **634** results in the formation of isomeric mono addition products **635** and **636** in a 3:1 ratio in 80% yield. Formation



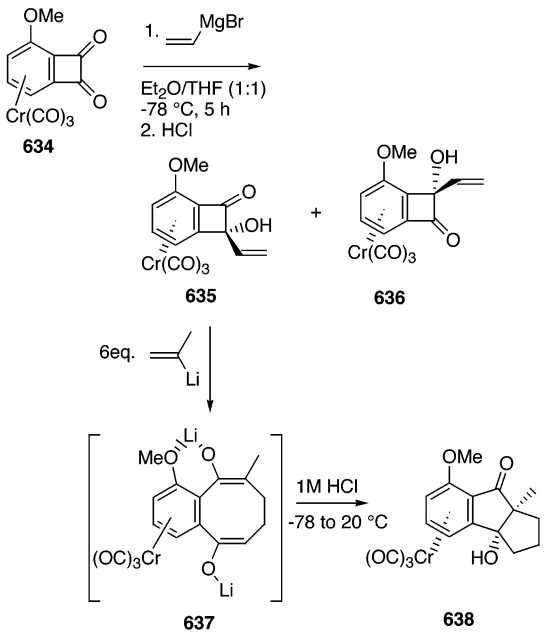
(63)

of isomer **635** as the major product indicates that the C-1 carbonyl is more electrophilic than that of C-2. Treatment of **635** with 6 equiv of propen-2-yllithium at −78 °C provides bis(enolate) **637**, which undergoes regioselective intramolecular aldol addition to afford **638** in 76% yield (Scheme 147). The regioselective formation of **638** indicates some stabilization of the enolate or enol moiety next to the methoxy group. This stabilization may be rationalized by assuming chelation of the enolate lithium cation or the enol proton by the lone pairs of the neighboring methoxy group, as shown in **637**.[447]

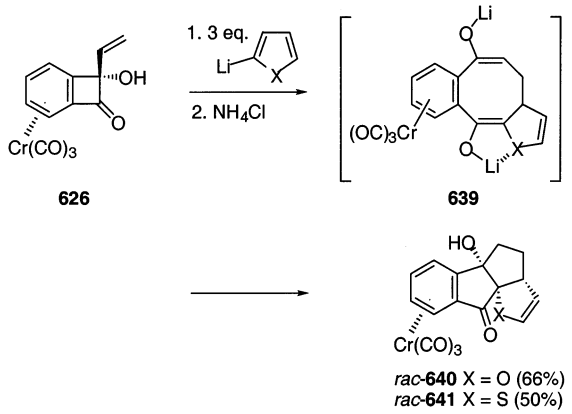
Recently, Butenschön and co-workers extended the scope of this reaction by treating monovinyl adduct **626** with 2-lithiothiophene and 2-lithiofuran to afford the dianionic oxy-Cope rearrangement intermediate **639**, which subsequently undergoes regioselective aldol addition to give *rac*-**640** and *rac*-**641**, respectively. It is significant that this reaction allows highly complicated polycycles to be constructed diastereoselectively in only a few steps. The enol ether functionality can be further exploited (Scheme 148).[448]

Tanaka et al. have reported the asymmetric Horner−Wadsworth−Emmons (HWE) olefination of dione complex **591** using the anion of (*S*)-**642** to afford

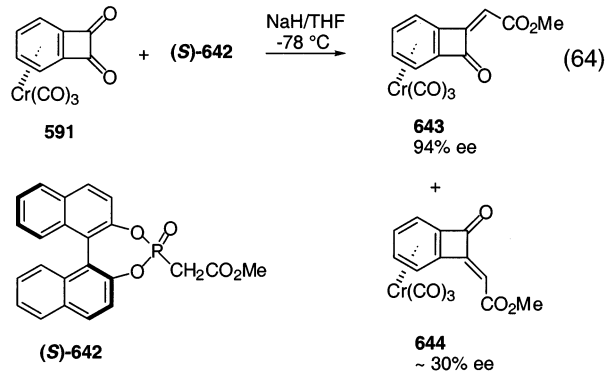
Scheme 147



Scheme 148



Z-olefin **643** in 61% yield, along with the minor *E*-isomer **644** in 29% yield (eq 64).[449]



The cation **645** has been prepared in 88% yield by treating **578** with trityl hexafluorophosphate and has been reacted with a large number of reagents. Exposure to the reagents illustrated in Scheme 149 affords the respective C-1-substituted compounds (**646**−**651**) in moderate to good yields. The hydroxy derivative **649**, prepared by treating **645** with a mixture of CH_2Cl_2 and aqueous $NaHCO_3$, was unstable and decomposed to give cyclobutarenone **84** (Scheme 149).[450,451] Other related examples can also be found in the literature.[452−457]

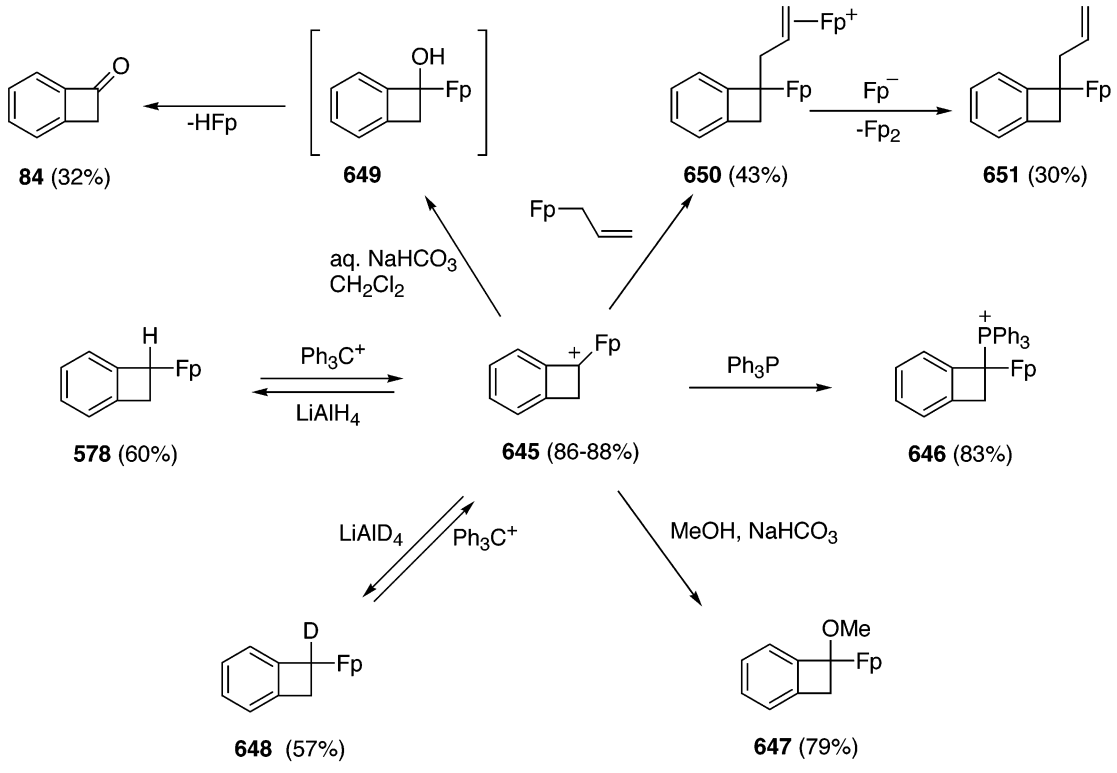
Simple high-yielding syntheses of the metalla-2-indane-1,3-diones (phthaloylmetal complexes) by insertion of low-valent transition metal complexes such as $(Ph_3P)_3RhCl$, $(Ph_3P)_3CoCl$, and $Fe(CO)_5$ into benzocyclobutenedione have been reported.[458−461] The metallacycles **652** and **653** react with a wide variety of alkynes to give 1,4-naphthoquinones **654** (Scheme 150, Table 24). Other metallacycles of benzocyclobutenedione have also been reported.[462−465]

I. Reactions of Benzocyclobutenedione

Although benzocyclobutenedione **260** behaves as an α-diketone and undergoes many of the usual reactions of the carbonyl group, it also participates in reactions that result from ring cleavage of the strained ring. For example, the condensation reaction of **655a**,**b** (and **260**) with *o*-phenylenediamine gives **656**. This tetracycle was the first heteroatom-containing biphenylene derivative to have been reported. However, the reaction of *o*-phenylenediamine with **655c**−**e** unexpectedly gave **657** (Scheme 151).[165,466,467]

The *E*-and *Z*-isomers of **658** were obtained by treating **260** with 1 equiv of arylhydrazine in 52−89% yield.[468] In constrast, the reaction with hydra-

Scheme 149



Fp = $Fe(CO)_2Cp$

Scheme 150

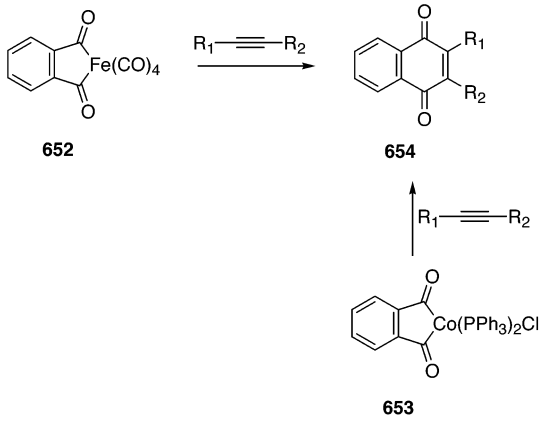
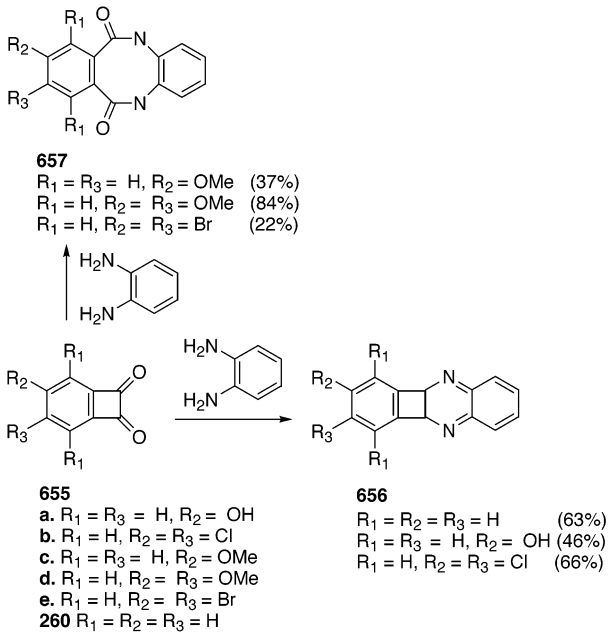


Table 24. 1,4-Naphthoquinones from Phthaloylmetal Complexes 652 and 653

			yield (%)	
entry	R_1	R_2	from Fe	from Co
1	Me	Me	99	73
2	Et	Et	95	90
3	Ph	Ph	88	68
4	Me	Ph	100	78
5	*n*-Bu	H	95	65
6	Ph	H	94	57
7	*t*-Bu	Me	37	72
8	Et	CH_2=CH−CH_2	75	80
9	*n*-Bu	TMS	22	68
10	$HOCH_2CH_2$	Ph	81	27
11	$COOC_2H_5$	Me	74	0
12	CH_3CO	Et	68	0

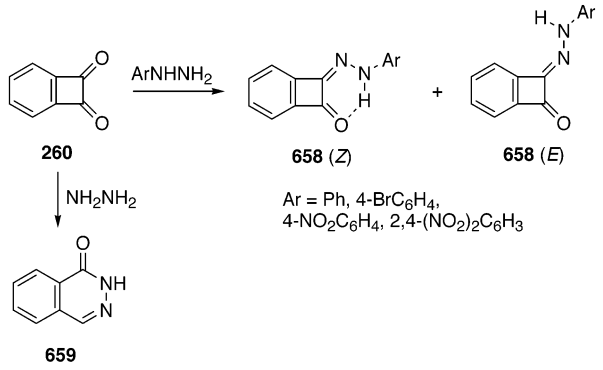
Scheme 151



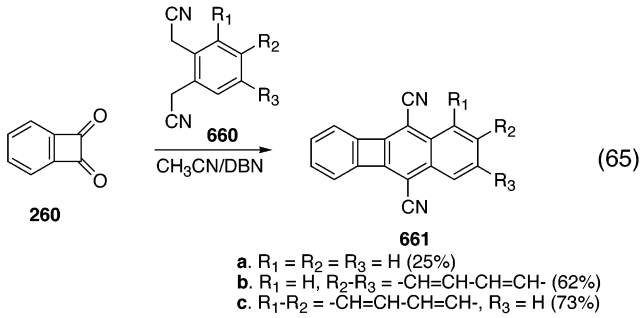
zine gave 1-(2*H*)-phthalazinone (**659**) and not the hydrazone (Scheme 152).[469]

The base-induced condensation of **260** with reagents bearing active hydrogen leads to condensation products, as illustrated in the reaction with **660** (eq 65). In the presence of 1,5-diazabicyclo[4.3.0]non-5-

Scheme 152

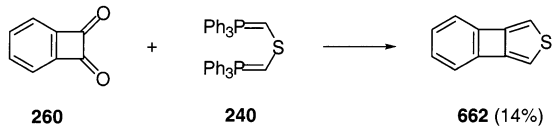


ene (DBN), the condensation product **661** is formed. Addition of calcium hydride as a desiccant led to a higher yield in most instances (eq 65). However, dimer **261** was formed in 73% yield when **260** was exposed to a catalytic amount of DBN.[470]



(65)

The bis(ylide) **240** participates in a Wittig reaction, leading to the formation of **662** in 14% yield (eq 66).[471] Similarly, **260** was found to react with other ylides to afford Wittig products.[472,473] It is interesting that the thiophene ring of **662** was found to exhibit olefinic character.

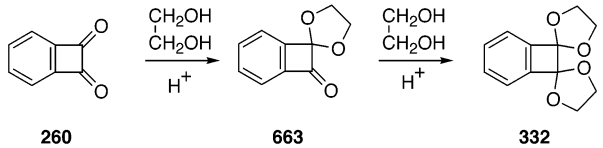


(66)

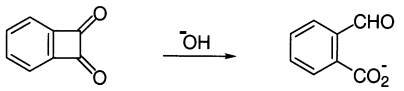
A mixture of **260** and ethylene glycol in refluxing benzene containing a trace of *p*-toluenesulfonic acid gave bisketal **332** in 77% yield via the monoketal **663** (Scheme 153).[474] Hydrolysis using concentrated HCl converts **332** back to the diketone in 99% yield.[195]

The base-catalyzed ring opening of **260** leads to **664** in quantitative yield. The reaction has been investigated from a mechanistic standpoint and found to be

Scheme 153



first order in both benzocyclobutenedione and hydroxide (eq 67).[161,475]



260 664 (67)

Addition of Grignard reagents to benzocyclobutenediones **260** and **665** gave adducts **666** and **667** in good yield. In the case of substituted benzocyclobutenediones **665**, the addition of Grignard reagents takes place preferentially at the more electron deficient carbonyl group. The increase in the selectivity (entry 5, Table 25) suggests that there is a strong steric

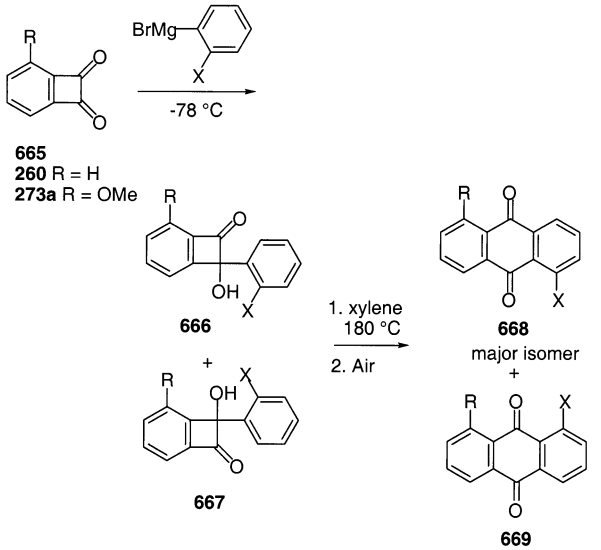
Table 25. Anthraquinones by Thermolysis of 2-Aryl-2-hydroxybenzocyclobutenones

entry	R	X	yield (%)	**666**:**667**	yield **668** (%)	**668**:**669**
1	H	H	61	–	83	–
2	OCH_3	CH_3	81	6.6:1	81[a]	–
3	OCH_3	OCH_3	70	3.5:1	96	3.5:1
4	OTBDMS	H	80	>20:1	76[a,b]	–
5	OTBDMS	OCH_3	67	>20:1	89[a,b]	–

[a] Yield of major isomer. [b] After treatment with F^-.

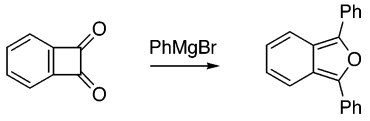
influence. Refluxing of cyclobutarenones **666** and **667** in xylene, and subsequent oxidation, provides a variety of quinones, such as **668**, in a highly regiospecific manner. This transformation is thought to occur by conrotatory ring opening of the cyclobutenone ring, leading to an outward rotation of the hydroxy group (Scheme 154).[476]

Scheme 154



Curiously, reaction of **260** with an excess of phenylmagnesium bromide did not give the expected addition product, but instead 1,3-diphenylisobenzofuran **670** was isolated in 60% yield (eq 68).[477]

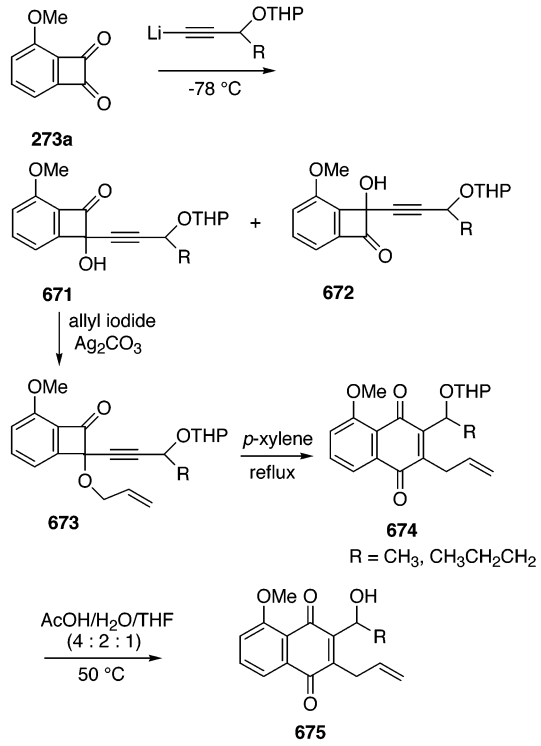
Addition of alkynylating agents to benzocyclobutenedione **273a** also leads to the formation of a mixture of the regioisomers **671** and **672**.[477–479] The regioselectivity of the alkynylation of **273a** was strongly influenced by the choice of alkynylating reagent and



260 670 (68)

reaction conditions. For example, alkynylation of **273a** with the lithium salt of 3-(tetrahydropyranyloxy)propyne (2:1 mixture of diastereoisomers) at −78 °C in THF gave **671** and its regioisomer **672** in a ratio of 3:1. Each regioisomer was formed as a 2:1 mixture of diastereomers (Scheme 155). However, when the

Scheme 155



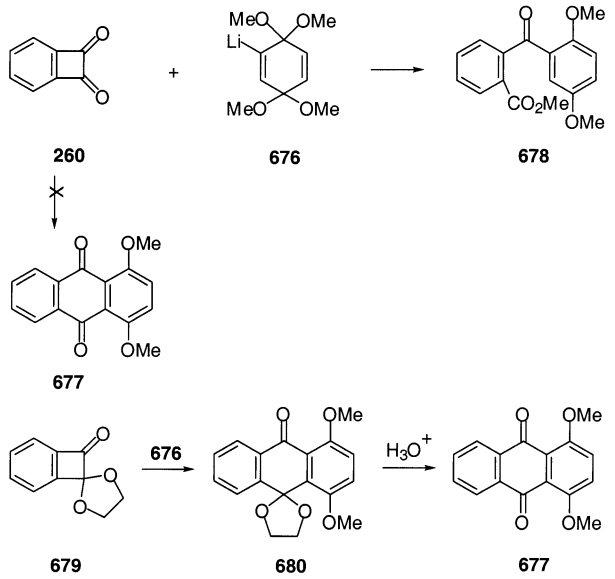
same experiment was done at −100 °C in THF/Et_2O (1:1), regioisomers **671** and **672** were obtained in a 97:3 ratio, although in lower yields (Table 26). Treatment of **671** with allyl iodide gave **673**, which on refluxing in *p*-xylene, followed by removal of the tetrahydropyranyl (THP) protecting, group gave naphthoquinones **675** in high yield (Scheme 155).[478]

The reaction of lithiated quinone bisketal **676** with **260** did not yield the desired product **677** but instead gave the ring-opened product **678**.[480] However, the reaction of the monoketal of benzocyclobutenediol **679**[469] with lithiated quinone bisketal **676** afforded **680** in 70% yield. Hydrolysis of **680** with 5% HCl gave **681** in quantitative yield (Scheme 156).[473,481] The

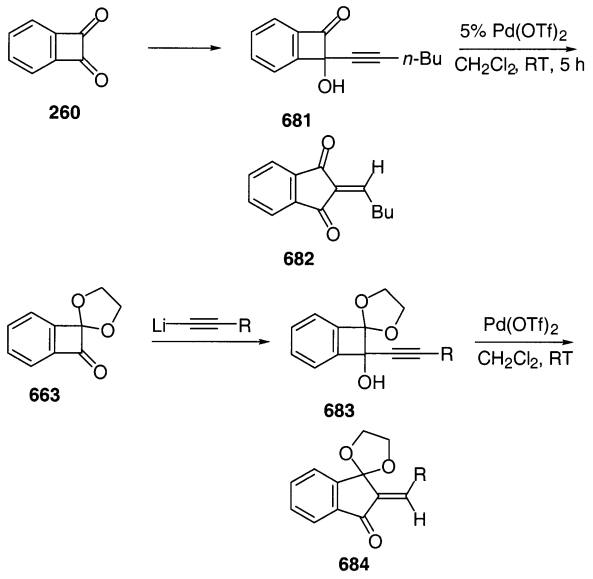
Table 26. Alkynylation of Benzocyclobutenedione 273a

entry	R	reaction conditions	yield (%)	ratio **671**:**672**
1	H	THF, −78 °C	83	2:1
2	CH_3	THF, −78 °C	85	3:1
3	$CH_3CH_2CH_2$	THF, −78 °C	85	4:1
4	H	1:1 THF/Et_2O, −100 °C	52	97:3
5	CH_3	1:1 THF/Et_2O, −100 °C	54	98:2
6	$CH_3CH_2CH_2$	1:1 THF/Et_2O, −100 °C	58	98:5

Scheme 156



Scheme 157

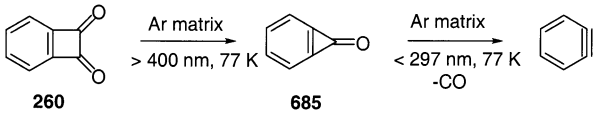


reaction is thought to take place by ring opening of the initially formed lithium salt of benzocyclobutenol, followed by ring closure.[482]

The dione reacts with 1-lithiohexyne to give **681** in 83% yield. A palladium-catalyzed ring expansion afforded **682**, as judged from IR and ^{1}H NMR spectra of the crude mixture (Scheme 157). Alkylidene indanedione **682** was neither stable to chromatography nor to distillation. Interestingly, the instability of **682** was circumvented by performing the same reaction with **663** instead of **260**, and thus a highly stereoselective synthesis of alkylidene indanediones **684** was achieved (Scheme 157, Table 27). [483−485]

The photochemistry of benzocyclobutenedione **260** has been investigated in solution and at cryogenic temperatures. Depending on the experimental conditions, a variety of intermediates have been proposed. On the basis of both spectral data and the observation of dimeric products, benzyne has been proposed as an intermediate in the photolysis of **260** in solid argon.[486−489] Photolysis (λ > 400 nm) of **260** at 77 K in an argon matrix leads to the highly strained benzocyclopropenone **686**. Simon et al. have recorded the ^{1}H and ^{13}C NMR spectra of **686**, along with its decomposition products in acetone-d_6. Upon further photolysis (λ < 297 nm) at 77 K, **686** is converted into benzyne by extrusion of CO (Scheme 158).[489−491]

Scheme 158



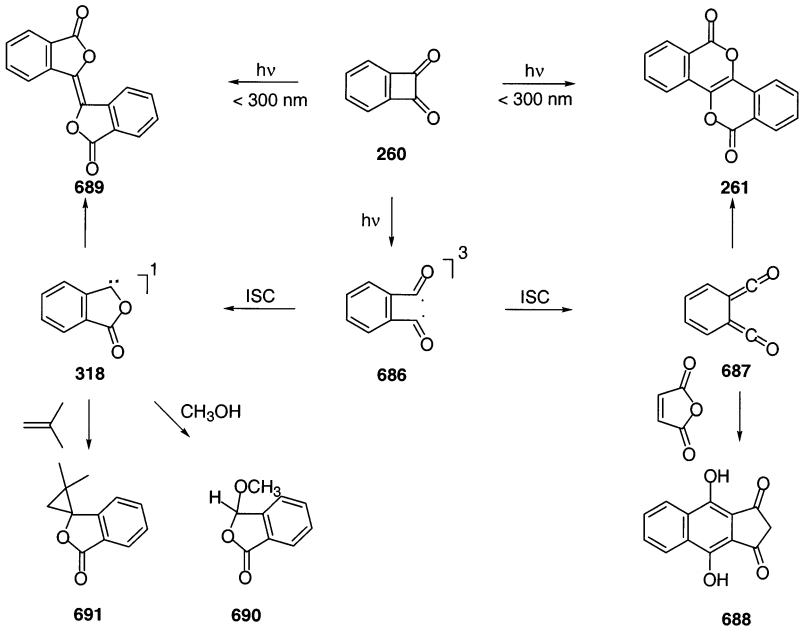
The behavior of **260** in solution has been examined by laser flash photolysis.[492−494] Two rapid processes appear to compete. One leads to the formation of the long-lived bisketene **687**, which can be readily observed (λ_{max} = 380 nm, toluene). The other leads to oxacarbene **318** (λ_{max} < 300 nm, toluene). Photoproducts from **260** are primarily derived from the trapping of oxacarbene **318**. For example, in methanol the major product is **690**,[486,495] while irradiation of **260** with isobutylene gives the spirolactone **691** in 65% yield.[496,497] However, oxacarbene dimers **689** and bisketene dimer **261** are formed upon irradiation of **260** in inert solvents and in the absence of trapping agents.[498] Ring closure of bisketene **687** to **260** is calculated to be strongly exothermic.[499] Trapping of bisketene by electron-deficient dienophiles such as maleic anhydride gives the cycloaddition product **688** (Scheme 159).[497]

Bisketenes, generated thermally or photochemically from benzocyclobutenediones, can be trapped by dienophiles.[500−502] For example, the cycloaddition of

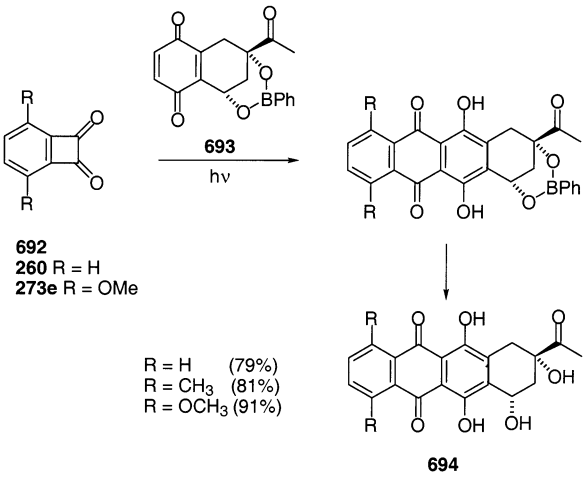
Table 27. Palladium-Catalyzed Formation of (*Z*)-2-Alkylideneindane-1,3-dione Monoketals 684

entry	R	yield **683** (%)	conditions (%, h)	yield **684** (%)	isomer ratio
1	n-C_4H_9	92	2.5 $Pd(OTf)_2$, 12	91	36:1
2	n-C_6H_{13}	81	2.5 $Pd(OTf)_2$, 24	51	26:1
3	c-C_6H_{11}	97	2.5 $Pd(OTf)_2$, 10	75	>25:1
4	$SiMe_3$	84	2.5 $Pd(OTf)_2$, 12	56	20:1
5	Ph	92	2.5 $Pd(OTf)_2$, 12	89	20:1
6	CH_2OCH_3	90	2.5 $Pd(OTf)_2$, 12	84	>25:1
7	$CH(OTBDMS)CH_3$	97	5.0 $Pd(OTf)_2$, 10	66	18:1
8	$(CH_2)_2OTBDMS$	74	5.0 $Pd(OTf)_2$, 12	75	22:1

Scheme 159

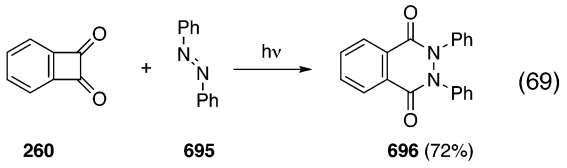


Scheme 160



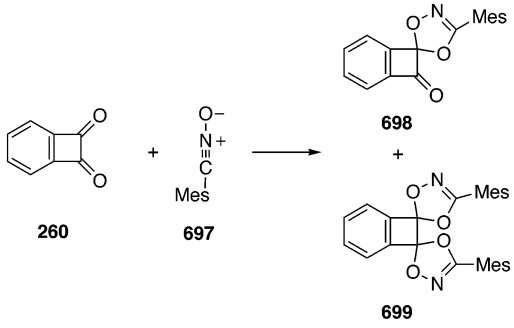
the bisketene obtained photochemically from **692** with enantiomerically pure **693** affords the symmetrically substituted daunomycinones **694** in only two steps (Scheme 160).[503]

Reaction of benzocyclobutenedione **260** with *trans*-azobenzene **695** under the influence of a high-pressure lamp in a quartz vessel afforded **696** in 72% yield (eq 69).[497]



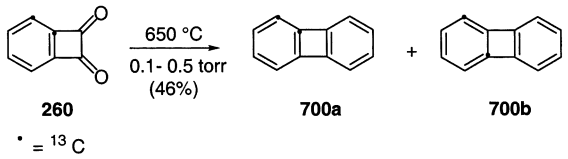
(69)

Benzocyclobutenedione reacts with mesitonitrile oxide **697**, affording a mixture of the mono and bis dipolar cycloaddition adducts **698** and **699** in 18% and 6% yield, respectively (eq 70).[503]



(70)

FVP of **260** labeled with ^{13}C gives benzyne, which dimerizes to yield biphenylenes **700a** and **700b** (eq 71).[504−506]



(71)

J. Applications in Syntheses

The synthetic utility of cyclobutarenes emanates mostly through the formation of *o*-quinodimethane and its derivatives. The *o*-quinodimethanes exhibit a high propensity to undergo intra- and intermolecular Diels−Alder reactions. This strategy was first investigated by Oppolzer in 1971, who pointed out that heating of a cyclobutarene carrying an unsaturated side chain gives a variety of polycyclic annelated

Scheme 161

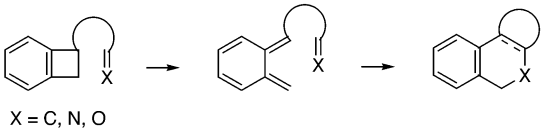


Table 28. Uses of Cyclobutarenes as Intermediates for Alkaloid Syntheses

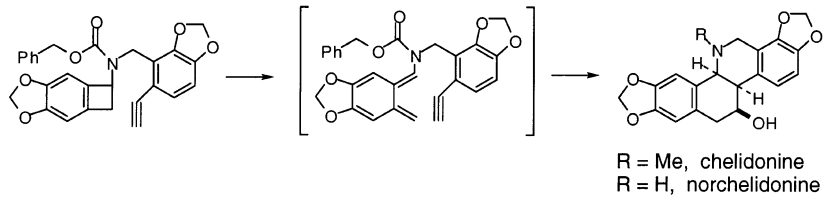
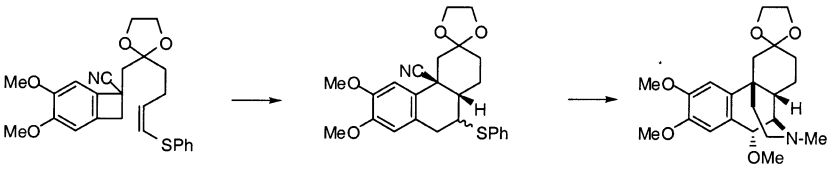
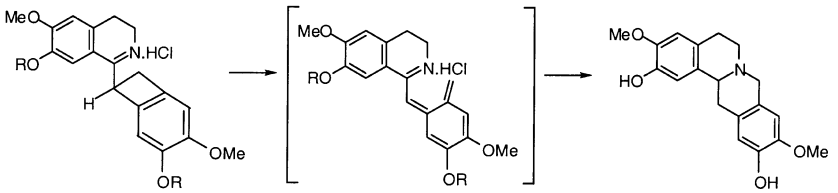
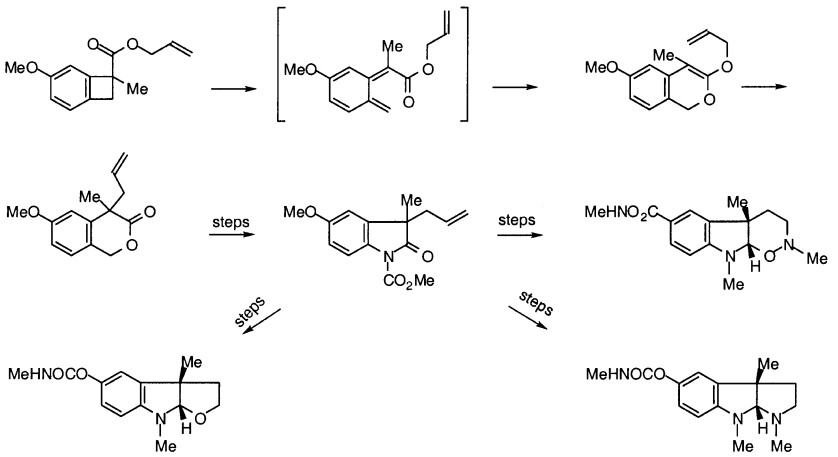
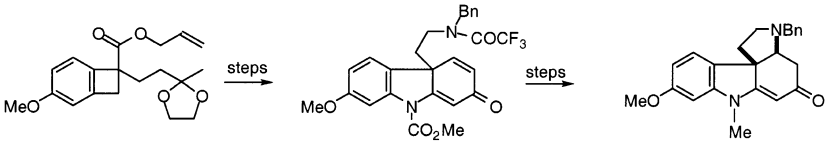
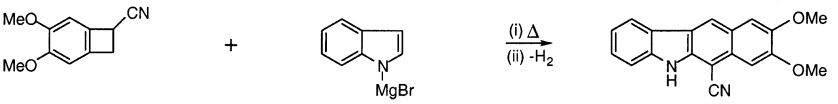
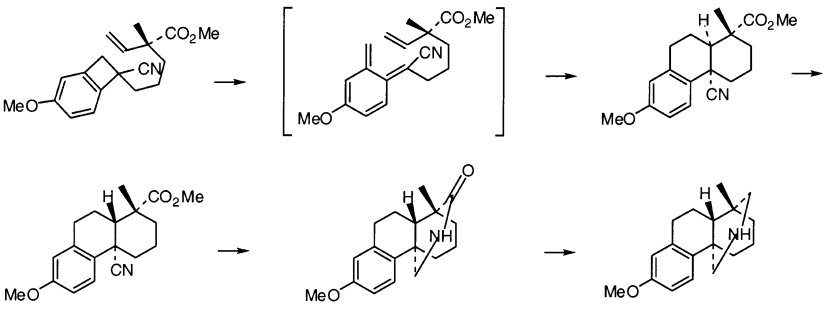
Entry No.		Refs.
1.	 R = Me, chelidonine R = H, norchelidonine	511,512
2.		513-515
3.	 R = CH_2Ph (±)-coreximine	516-521
4.		522,523
5.		524
6.		525
7.		526,527

Table 28. (Continued)

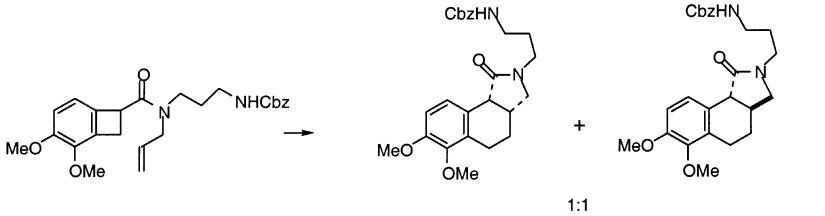
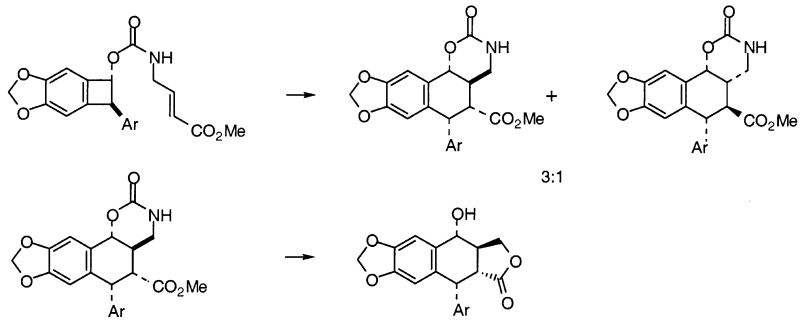
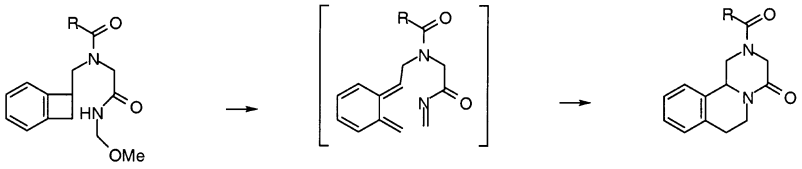
Entry No.		Refs.
8.		528,529
9.	 Ar = 3,4,5-trimethoxyphenyl precursor of etoposide	530,531
10.	 R = cyclohexyl praziquantel	532

Table 29. Uses of Cyclobutarenes as Intermediates for Steroid Syntheses

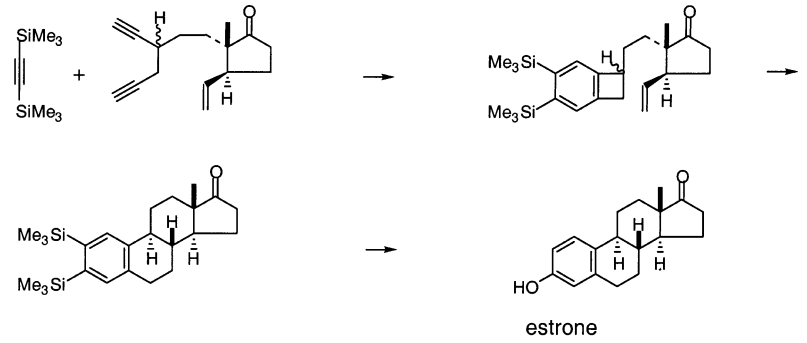
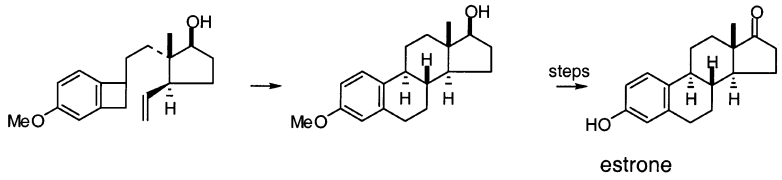
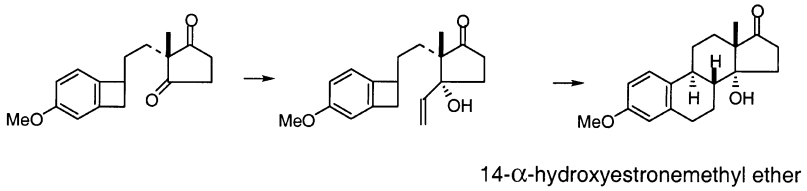
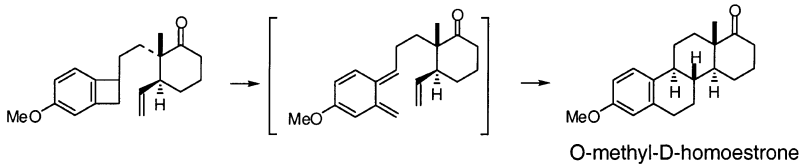
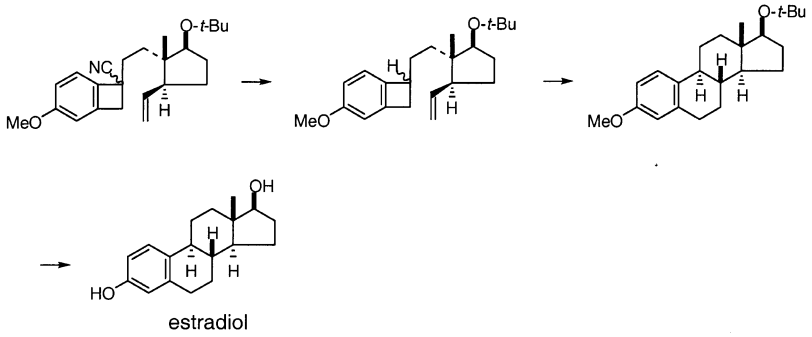
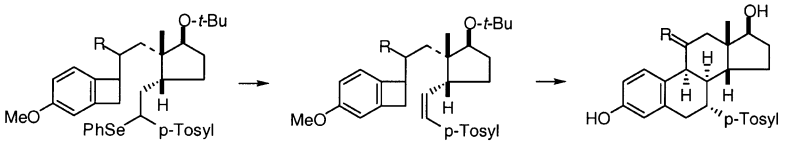
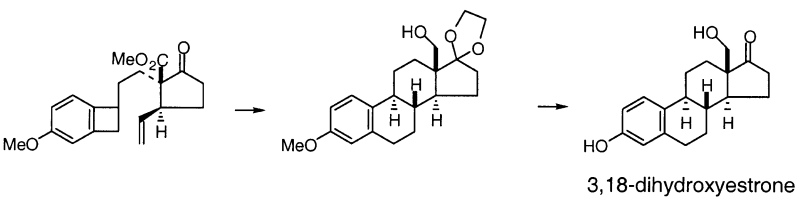
Entry No.		Refs.
1.	 estrone	533
2.	 estrone	534-537
3.	 14-α-hydroxyestronemethyl ether	538-540
4.	 O-methyl-D-homoestrone	541
5.	 estradiol	542
6.	 derivatives of estradiol R = H_2, O	298
7.	 3,18-dihydroxyestrone	543

Table 29. (Continued)

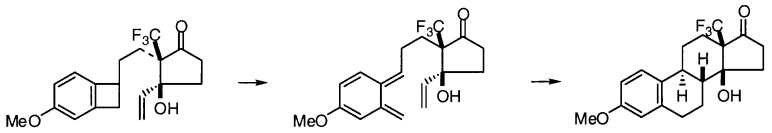
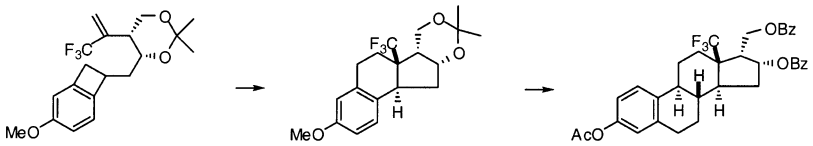
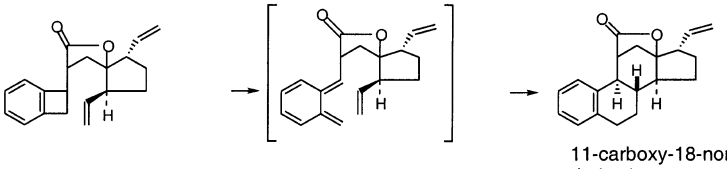
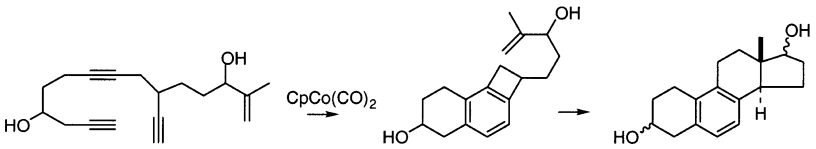
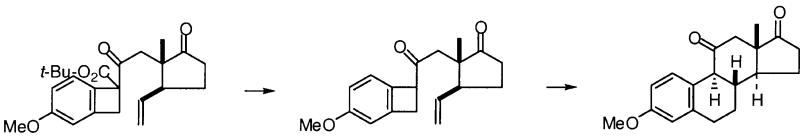
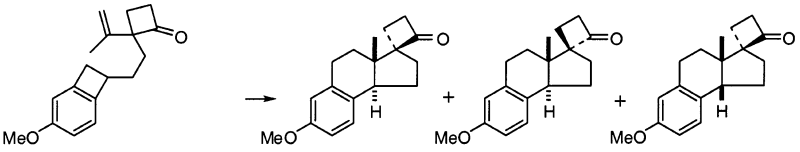
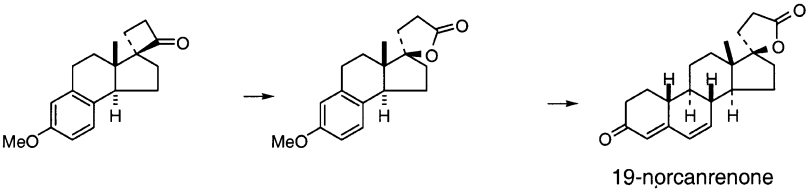
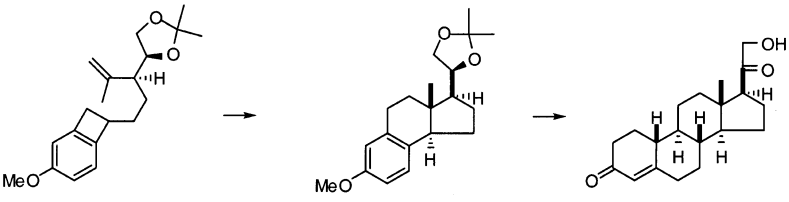
Entry No.		Refs.
8.	 3-*O*-methyl-14β-hydroxy-18,18,18-trifluoroestrone	544
9.	 18,18,18-trifluorosteroid	545
10.	 11-carboxy-18-norestrane derivative	546,547
11.	 equileine	548
12.	 11-oxoesterone	549
13.	 2.33 : 5 : 1  19-norcanrenone	550
14.	 (+)-19-nordeoxycorticosterone	551, 552

Table 29. (Continued)

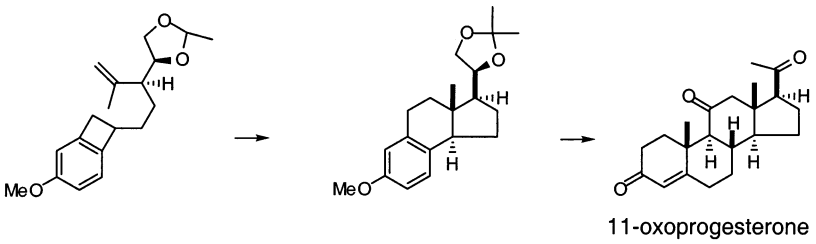
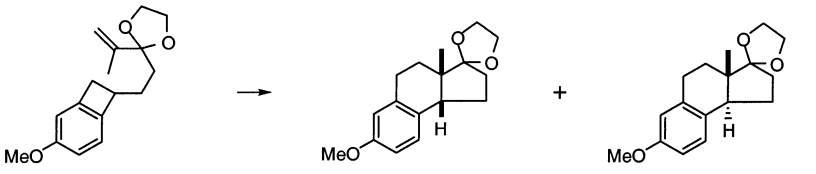
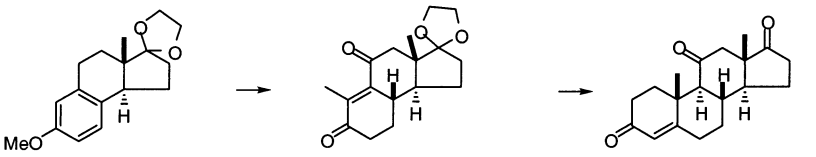
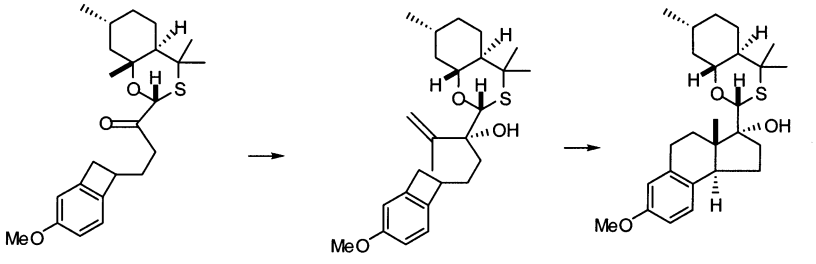
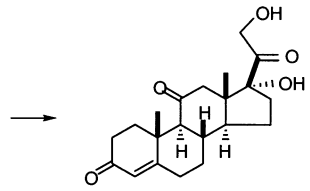
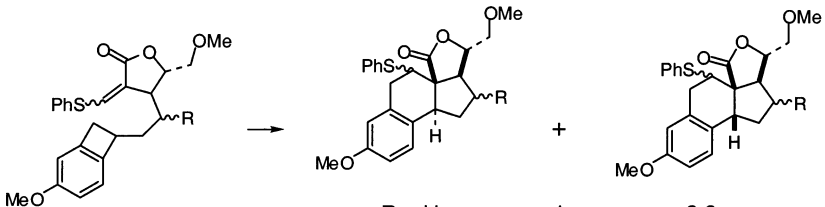
Entry No.		Refs.
15.	 11-oxoprogesterone	553,554
16.	 (5 : 95)	555,556
	 adrenosterone	
17.	  (+)-cortisone	557
18.	 R = H, 1 : 2.3 R = SO_2Tol, 2.65 : 1	558,559

Table 29. (Continued)

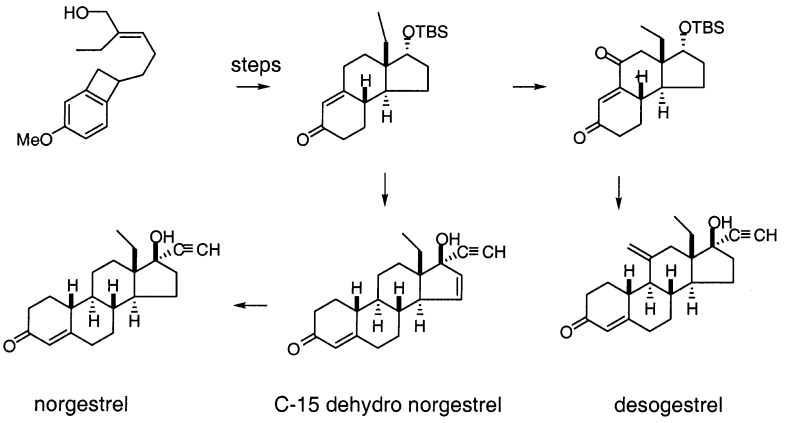
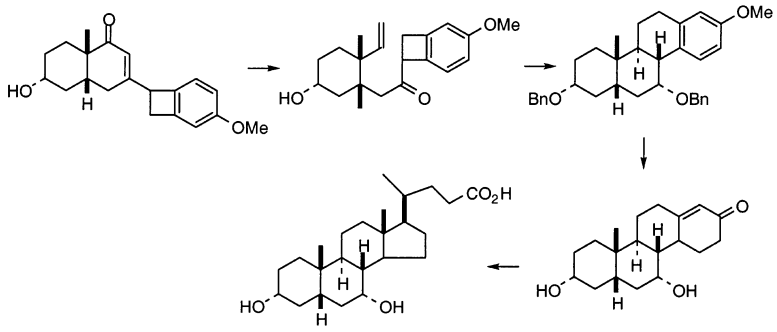
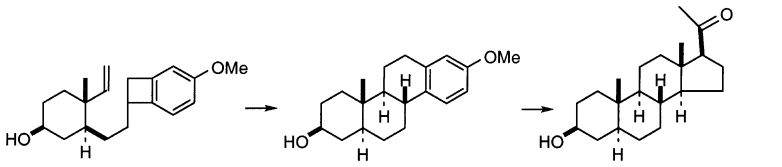
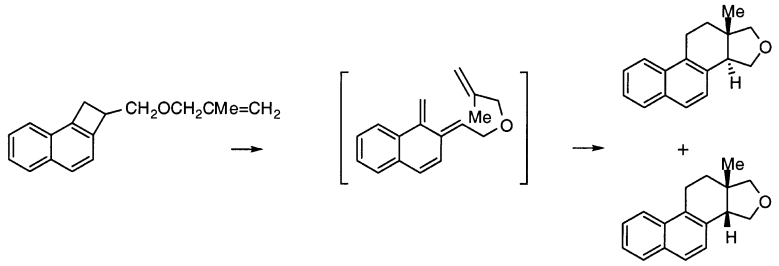
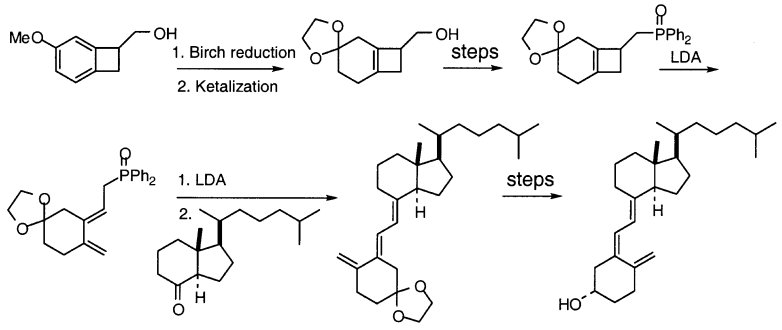
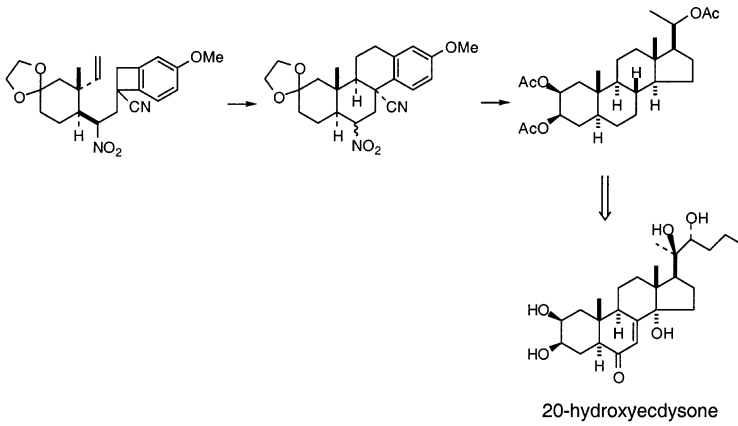
Entry No.		Refs.
19.	 norgestrel C-15 dehydro norgestrel desogestrel	560
20.	 (+)-chenodeoxycholic acid	561,562
21.	 (+)-5-α-dihydropregnenolone	563
22.		564
23.		565

Table 29. (Continued)

Entry No.		Refs.
24.	 20-hydroxyecdysone	566,567

systems (Scheme 161). This area has been covered in several review articles.[10,16,507−510] Tables 28−32 provide relevant examples.

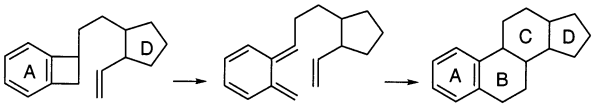
1. Alkaloid Syntheses

See Table 28 for a summary.

2. Steroid Syntheses

Convergent syntheses based on the approach A + D → AD → ABCD constitute an efficient synthetic route to steroids. This methodology has a remarkable advantage for the formation of the B/C cycle, starting from an *o*-quinodimethane precursor and a cyclopentane derivative bearing a vinyl group (Scheme 162). Specific examples regarding the synthesis of steroids are illustrated in Table 29.

Scheme 162



3. Synthesis of Polycyclic Natural Compounds

See Table 30 for a summary.

4. Synthesis of Anthracycline and Related Quinones

See Table 31 for a summary.

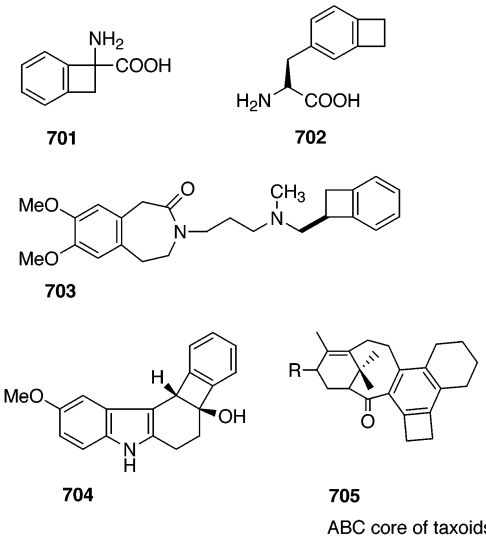
5. Synthesis of Naturally Occurring Cylobutarenes

Although cyclobutarenes have been utilized as powerful synthons for various types of natural products, the occurrence of cyclobutarene derivatives in nature is less common. In 1973, sciascillan was isolated from *Scila scilloides*.[588] Synthesis of sciascillan was reported by Cava in 1983.[589]

A number of homoisoflanone derivatives have been isolated from *Muscari* species.[590−592] Another naturally occurring cyclobutarene, muscomsin, has been synthesized by Honda and Toya using a modification of the Cava procedure (Table 30).[593] See Table 32 for a summary.

K. Miscellaneous Biological Applications

Cyclobutarenes are beginning to find applications in biology as well. For example, 1-benzocylobutenyl amino acid **701** is reported to be a central nervous system depressant.[594] Another synthetic α-amino acid **702** has been prepared by Kotha et al. in a highly diastereoselective manner.[595] Cyclobutarene derivative **703** has been listed as a bradycardic agent.[596] Tetrahydrobenzocyclobutacarbazoles **704** exhibit antitumoral properties.[597] Recently, Malacria et al. have reported an efficient synthesis of cyclobutarene **705**, which contains the ABC core of taxoids.[598]



701 **702**

703

704 **705**

ABC core of taxoids

V. Acknowledgment

We gratefully acknowledge financial support from the National Science Foundation (CHE-9710042) and the Robert A. Welch foundation. We also acknowledge the reviewers for their constructive suggestions during the preparation of the manuscript.

Table 30. Synthesis of Naturally Occurring Polycyclic Compounds from Cyclobutarenes

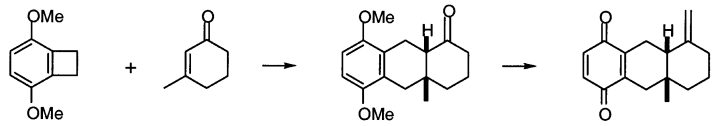
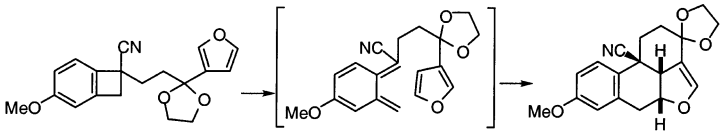
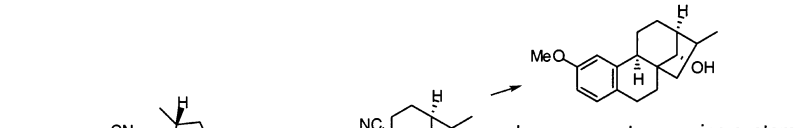
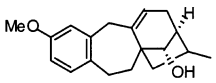
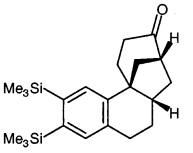
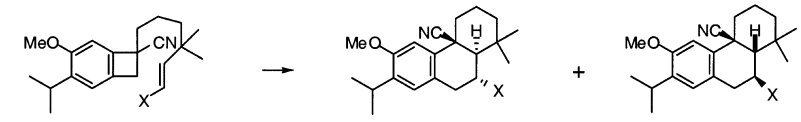
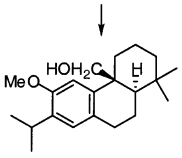
Entry No.		Refs.
1.	 cordiachrome B	568
2.	 potential intermediate for helenaquinol and helenaquinone	569
3.	 homogyranotoxane ring system  phyllocladene ring system	570,571
4.	 stemodan framework  aphidicoloan framework	572,573
5.	 X = H, SO_2Ph  pisiferol	574,575

Table 30. (Continued)

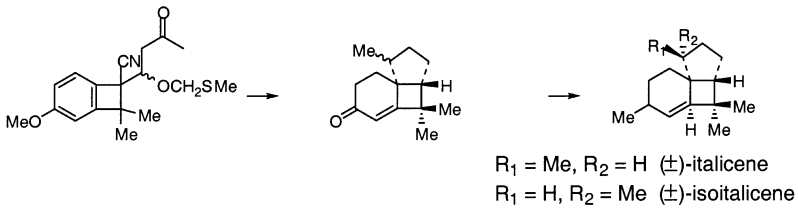
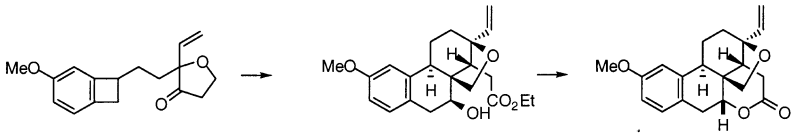
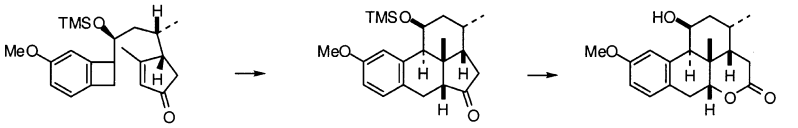
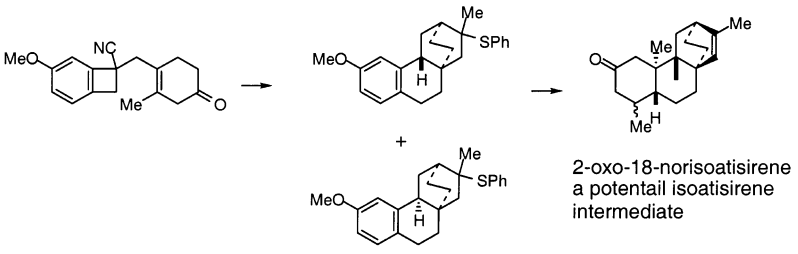
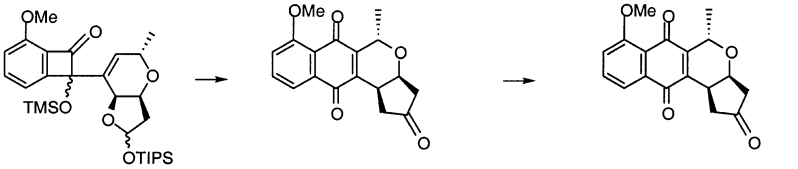
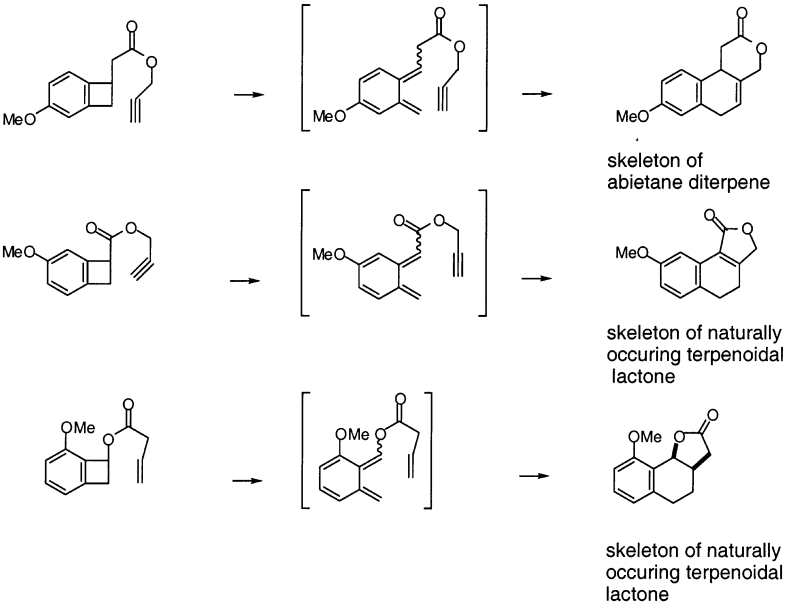
Entry No.		Refs.
6.	 R_1 = Me, R_2 = H (±)-italicene R_1 = H, R_2 = Me (±)-isoitalicene	576
7.	 bruceantin skeleton	577,578
8.	 klaineanone skeleton	579
9.	 2-oxo-18-norisoatisirene a potentail isoatisirene intermediate	580
10.	 (−)-nanaomycin D	581
11.	 skeleton of abietane diterpene skeleton of naturally occuring terpenoidal lactone skeleton of naturally occuring terpenoidal lactone	582,583

Table 31. Anthracycline and Related Quinone Syntheses from Cyclobutarene Derivatives

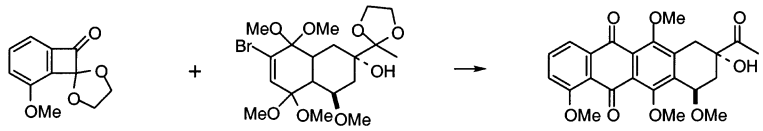
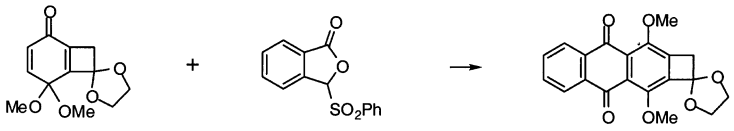
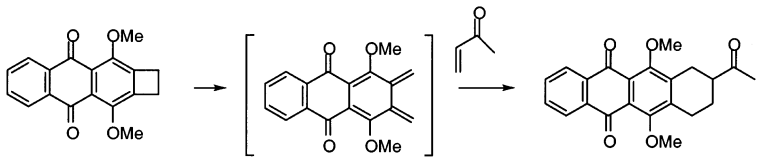
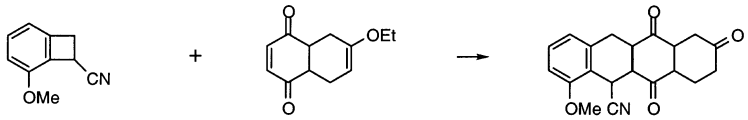
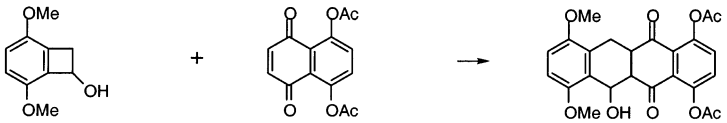
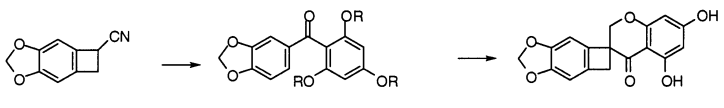
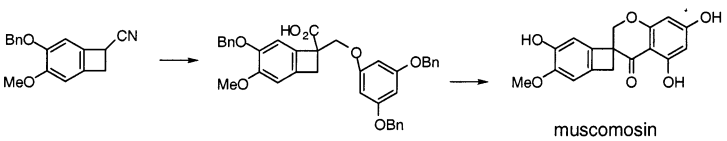
Entry No.		Refs.
1.		473
2.		584
3.		585
4.		586
5.		587

Table 32. Synthesis of Naturally Occurring Cyclobutarenes

Entry No.		Refs.
1.	 scillascillin R = *t*-BuMe$_2$Si-	588
2.	 muscomosin	593

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