# Diversity-Oriented Approaches to Polycyclics and Bioinspired Molecules via the Diels−Alder Strategy: Green Chemistry, Synthetic Economy, and Beyond

Sambasivarao Kotha,* Arjun S. Chavan,[†] and Deepti Goyal[‡]

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400 076 India

ABSTRACT: We describe diverse approaches to various dienes and their utilization in the Diels−Alder reaction to produce a variety of polycycles. The dienes covered here are prepared by simple alkylation reaction or via the Claisen rearrangement or by enyne metathesis of alkyne or enyne building blocks. Here, we have also included the Diels−Alder chemistry of dendralenes, a higher analog of cross-conjugated dienes. The present article is inclusive of o-xylylene derivatives that are generated in situ starting with benzosultine or benzosulfone derivatives. The Diels−Alder reaction of these dienes with various dienophiles gave diverse polycyclic systems and biologically important targets.

KEYWORDS: diversity-oriented synthesis, dienes, Diels−Alder reaction, green chemistry, polycyclics, amino acids
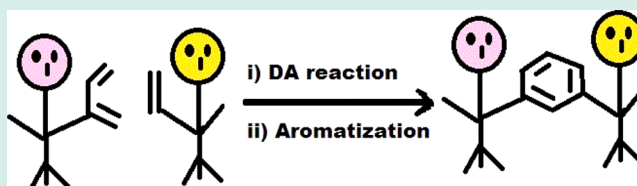
INTRODUCTION

The Diels−Alder (DA) reaction[1] is a powerful tool to construct C−C bonds and has been extensively used to prepare polycyclic compounds containing six-membered rings. The DA reaction provides 100% atom economy, and hence, its use has expanded enormously for the synthesis of natural and nonnatural products[2] since its discovery[3] in 1928 by the German chemists Otto Diels and Kurt Alder. In general, electron-donating groups in the diene and electron-withdrawing group in the dienophile are used to make the reaction very facile. DA reactions involving less reactive partners are facilitated by conditions, such as high pressure, ultrasound, ionic liquids, and use of polar solvents and Lewis acids.[4] The DA reaction catalyzed by biomolecules such as antibodies, enzymes, and RNA has also generated some interest in organic and bioorganic chemistry.[5] Many variations on the classical DA reaction are also popular, including (a) hetero-DA (in which one or more heteroatoms is included in the newly formed six-membered ring), (b) transannular DA (involving diene and dienophile present in a macrocycle giving a tricyclic product; although this is well suited to the generation of complex molecules,[6] it is not covered here), (c) dehydro-DA (reactions of conjugated enyne with alkene or alkyne, and diyne with alkene),[7] and (d) hexadehydro-DA (involving conjugated diyne and alkyne).[8] Stereochemistry is usually predictable: when the diene or dienophile is cyclic in nature, the product is often predominantly an endo isomer, but exo isomers are also reported under different reaction conditions, such as photochemical,[9] organocatalytic,[10] or catalyzed by metal complexes.[11] These advances further expand the scope of chemical space accessible by DA reaction.

We organize our classification of DA reactions by diene structure (Figure 1), classified as open-chain dienes (**1**−**4**), dendralenes (**5**−**6**), outer-ring dienes (**7**−**10**), o-xylylenes or

o-quinodimethanes (**11**−**13**), inner-outer-dienes (**14**−**17**), inner-ring dienes (**18**−**21**), and across-ring dienes (**22**−**24**). Inner-ring dienes are further divided into carbocyclic and aromatic hydrocarbons. Heteroannular (**25**−**26**) and semicyclic diene **27** are unreactive toward the DA reaction.[12]

The use of DA in combinatorial and high-throughput applications has been greatly enhanced by ring-closing enyne metathesis (RCEM) and ethylene-mediated cross-metathesis (CM), which provide easy access to various dienes containing polar functional groups. Such intricate dienes are difficult to generate by conventional methods. Figure 2 shows various metathesis catalysts used for the generation of diene derivatives by enyne metathesis.

By varying the diene and the dienophile components in the DA reaction, one can generate a great deal of molecular diversity in the end products. Although DA and related cycloaddition processes have been extensively reviewed in the context of diversity-oriented synthesis,[13] we focus here on the facile generation of useful dienes or diene precursors (usually by metathesis,[14] Claisen rearrangement,[15] or specialized reagents[16]) and their transformation into polycyclics via DA reaction involving different dienophiles **28**−**64** (Figure 3).

OPEN-CHAIN DIENES

1,3-Butadiene (**1**) and its derivatives can be generated by a number of methods; for example, cross-enyne metathesis (CEM) of alkyne and alkene; chelotropic elimination of SO_2 from sulfolene derivatives; Luche reduction of α,β-unsaturated carbonyl compounds, followed by triethylamine-catalyzed
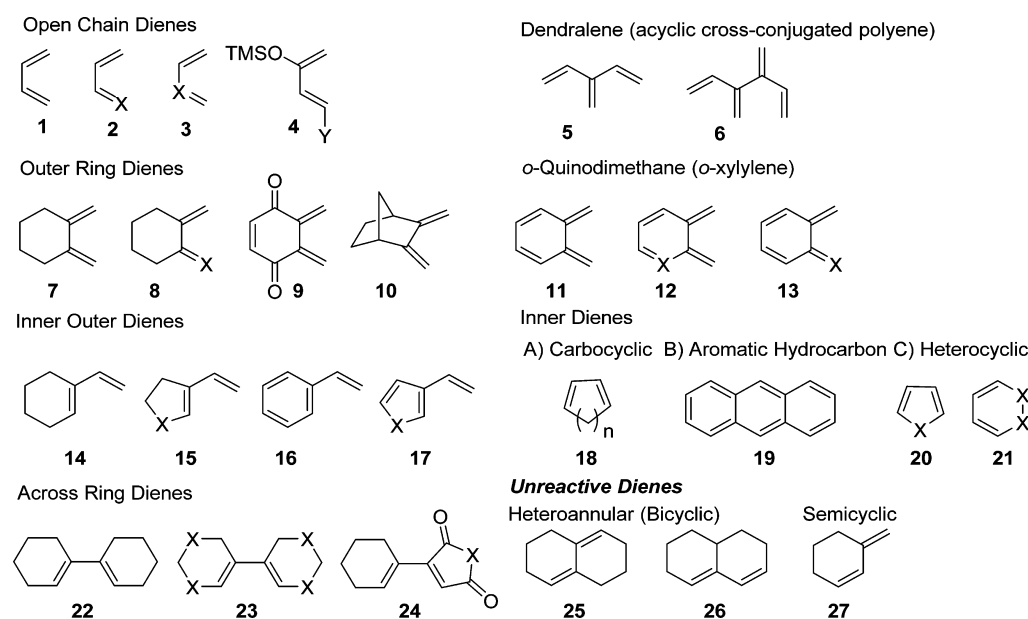
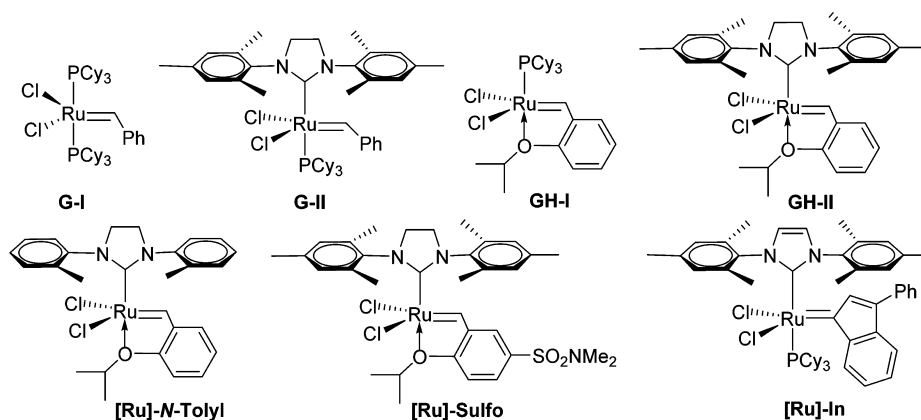**Figure 1.** Various types of dienes used in DA reaction (**1–24**).

Figure 2. Metathesis catalysts used for diene production.

tandem one-pot methanesulfonylation and elimination; and enolization of conjugated ketone followed by silyl protection (Figure 4).[12] An example of the utility of the parent 1,3-butadiene was provided by the 1995 report of Cativiela and co-workers, who reported the synthesis of cyclic γ-hydroxy-α-amino acid (homoserine) **67** by the DA reaction of **1** and methyl-2-acetamidoacrylate (**36**)[17a] in the presence of titanium tetrachloride. The iodo-oxazination of DA adduct **65**, followed by deiodination and subsequent acid hydrolysis, yielded the cyclic γ-hydroxy-α-amino acid, homoserine **67**, in good yield (Scheme 1).[17b]

We have found that a strategic utilization of cross-enyne metathesis (CEM) and DA reaction is useful to generate diverse polycyclics[18] and benzannulated products.[19] To this end, conformationally constrained quinone-based phenylalanine (Phe) derivatives were assembled by a combination of CEM and DA reaction (Scheme 2).[20] Ethyl isocyanoacetate (EICA) is a useful glycine equivalent, wherein the isonitrile group is easily hydrolyzed to the amino group.[21] However, it is difficult to stop at monoalkylation stage with EICA. Therefore, the alkyne building block **70** was prepared from the Schiff base of ethyl glycine ester **68** via propargylation under basic conditions using phase-transfer catalysts (PTC), followed by acid

hydrolysis and protection of the amino group. The G-I catalyst mediated EM of alkyne building block **70** with ethylene as a cross metathesis partner gave the expected diene **71**, then the diene **71** was subjected to the DA reaction with various dienophiles, and subsequent aromatization of the DA adducts gave the Phe-based α-amino acid (AAA) derivative **72** in good yield. If needed, this recemic protocol can be extended for the synthesis of optically active building blocks by employing suitable phase-transfer catalyst.[22]

Similarly, Hiemstra and co-workers have reported the synthesis of various amino acid and peptide-based dienes by employing allene chemistry (Scheme 3).[23] They reported naturally occurring diene containing amino acid synthesis and its glutamyl dipeptide from **73** and allenylmethylsilane via N-acyliminium ion formation. The compound **73** and allenylmethylsilane under Lewis acid catalysis conditions gave the diene-containing amino acid derivative **74**, which was hydrolyzed under basic conditions to deliver **75**. Later, the amino group present in **75** was deprotected under acidic conditions to generate the free amino acid **76**. The compound **74** was directly deprotected to give **77** and coupled with another amino acid derivative to generate the diene-containing dipeptide. Enzymatic resolution was used to obtain the enantiopure dienyl amino acid.
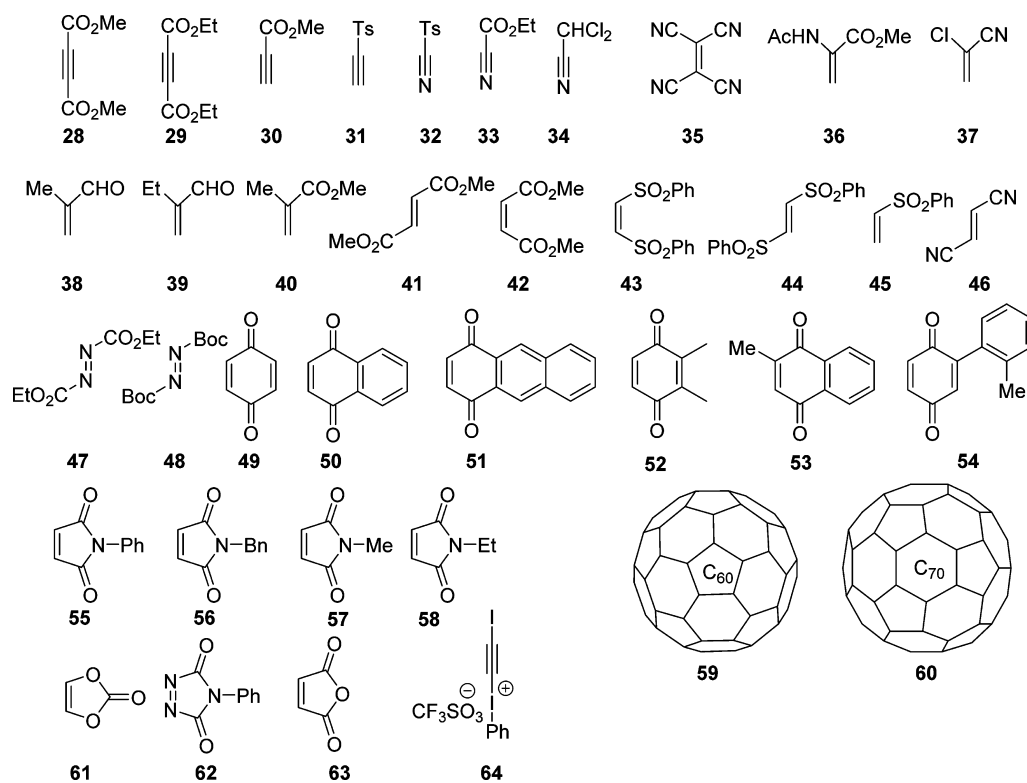
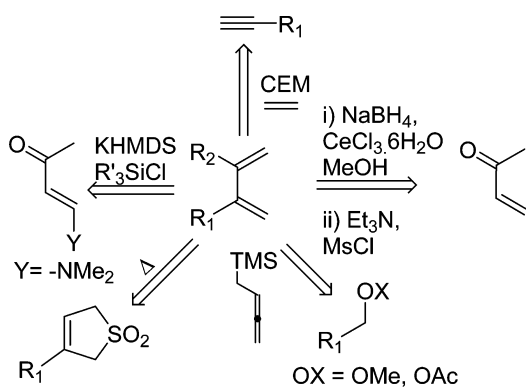**Figure 3.** Various dienophiles mentioned in this review.

**Figure 4.** Approaches toward the generation of open-chain dienes.

The preparation of diene **71** with different N-protecting groups was reported by Baldwin and co-workers, and this diene building block was used for the synthesis of various unusual AAA derivatives.[24] For example, commercially available diethyl acetamidomalonate (DEAM) **78** was alkylated with 2,3-dibromoprop-1-ene under basic conditions, then the selective monohydrolysis of diester **79**, followed by decarboxylation, gave the amino acid-based vinyl bromide **80**, which was converted to the diene derivative **81** as a key building block by the Pd-mediated coupling methodology of Denmark. DA reaction

of diene **81** with various dienophiles generated the unusual AAA derivatives **82** (Scheme 4).

Post-assembly peptide modifications are useful to design peptide drugs and peptidomimetics. In view of this, recently we disclosed the modification of peptides by CEM and DA reaction as key steps (Scheme 5).[25] In this regard, the dipeptide-based alkyne building block **83** has been assembled from commercially available DEAM **78** by adopting several steps. This alkyne precursor **83** on exposure to G-II catalyst undergoes EM in the presence of ethylene to generate the peptide-based diene **84**, which on treatment with DMAD (**28**) or 1,4-naphthoquinone (**50**) followed by aromatization gave the modified Phe-based peptides **85** and **86**, respectively. Here, we have generated the Phe residue from the propargylated glycine derivative by a combination of CEM and DA reaction without racemization, and the peptide integrity has been preserved. By employing similar synthetic sequence, tripeptide modification was also accomplished. Similarly, by altering the amino acid unit in the peptide backbone or varying the dienophile in DA sequence, one can prepare a library of peptides.

Earlier in 2000, highly functionalized Phe derivatives were reported by CEM of the alkyne building block **87** (Scheme 6).[26] The required alkyne precursors **87** have been prepared from the Schiff base of ethyl glycine ester via propargylation, followed by
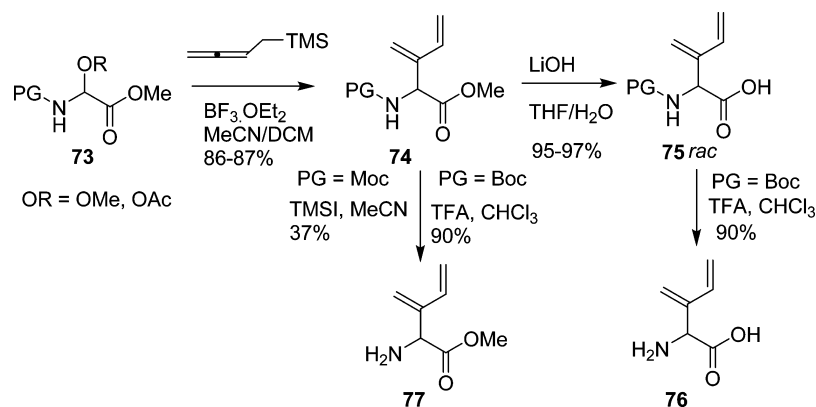
**Scheme 1. Synthesis of Cyclic γ-Hydroxy-α-amino Acid 67**
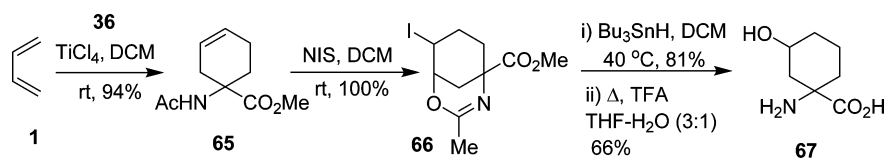
Scheme 2. DA Approach to Modified Phenylalanine-Based Amino Acid Derivatives

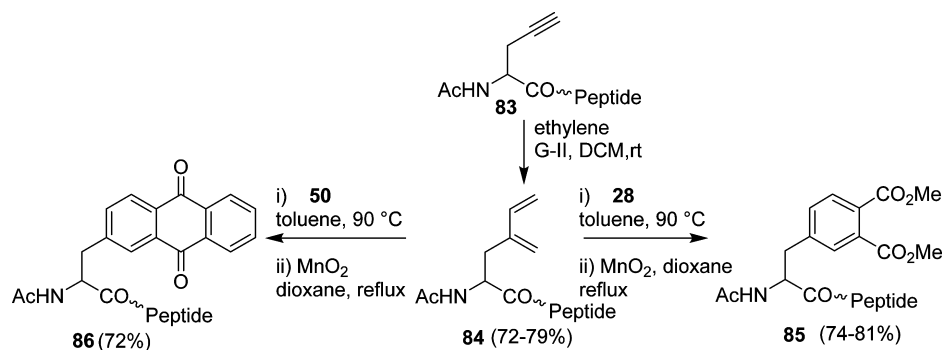| Dienophile	28	50	51	52
Yield (%)	67	77	93	81
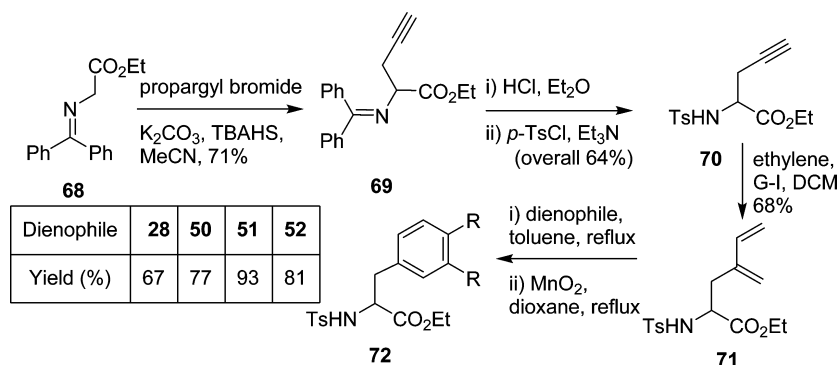
Scheme 3. Synthesis of Amino Acid-Containing Dienes by Employing Allene Chemistry

Scheme 4. Approach to Unusual Amino Acid Derivatives 82 via DA Chemistry

| Dienophile	28	35	49	55	62
Yield (%)	92	84	82	80	76
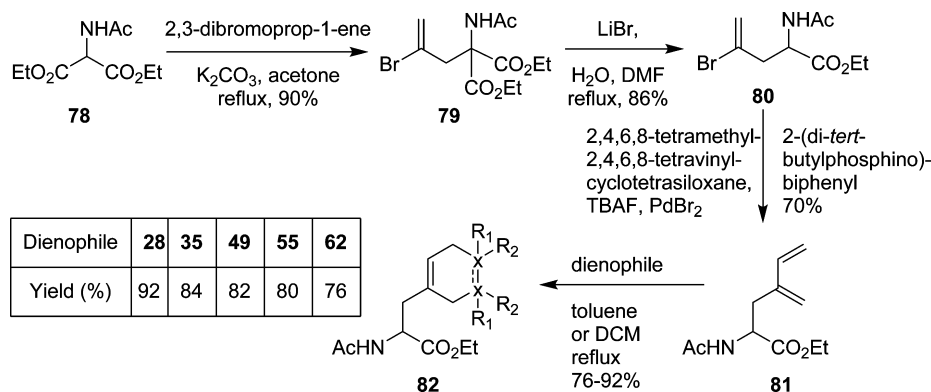
**Scheme 5. Peptide Modification by CEM and DA Reaction**

hydrolysis and protection of the amino group. The G-I catalyst-mediated CEM of the alkyne building blocks **87** with allyl acetate as a cross-metathesis partner gave the diene moieties **88**, which on DA reaction with DMAD (**28**) and the subsequent

Scheme 6. Synthesis of Highly Functionalized Phe Derivatives
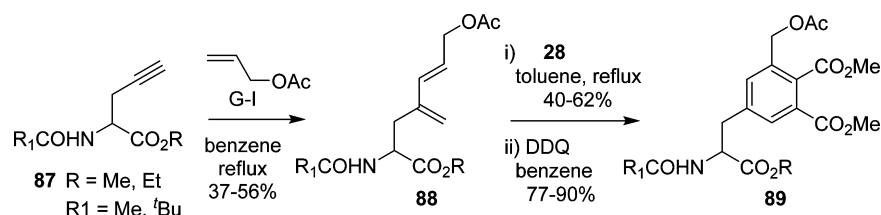
Scheme 7. Assembly of Phe-Based AAA Derivatives 96 via DA Reaction

[TMG = 1,1,3,3-Tetramethylguanidine]

| Dienophile	28	50	51
Yield (%)	56	57	61
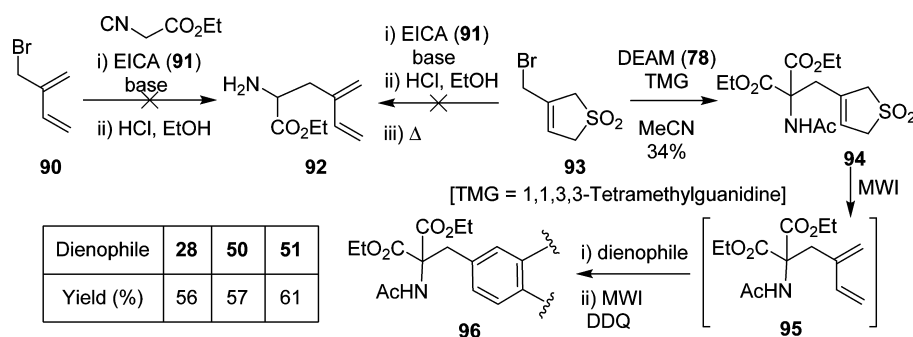
aromatization of the DA adduct gave highly functionalized Phe derivatives **89**. Since unusual AAAs are important in peptidomimetics and artificial protein synthesis, this strategy has potential applications in medicinal chemistry.

Masked dienes containing the AAA moiety are extremely useful for DA strategy; however, it is not easy to attach sulfone moiety to an amino acid component. To this end, the synthesis of amino acid-based diene **92** by alkylation of the EICA (**91**) using the 2-bromomethyl 1,3-butadiene (**90**) or the sulfolene methyl bromide (**93**) were unsuccessful. Then we coupled the sulfolene methyl bromide (**93**) with DEAM (**78**) to generate the amino acid-based diene precursor **94**, which undergoes DA reaction with various dienophiles to generate the Phe-based AAA derivatives **96** (Scheme 7).[27] 1,1,3,3-Tetramethylguanidine (TMG) usage is critical for success of this reaction; other bases gave elimination products.

Later, this building block approach was extended to generate the fullerene-based dicarba analogs of cystine via DA chemistry (Scheme 8).[20] To this end, the alkyne building block **97** has been prepared as a mixture of isomers by reacting the 1,4-dibromo-2-butyne with 2 equiv of the Schiff base derived from ethyl glycine ester **68** under basic conditions in the presence of PTC and subsequent acid hydrolysis, followed by protection of the amino functionality as a *N*-acetyl group. The GH-II catalyst-mediated CEM of the alkyne building block **97** with ethylene gave the diene **98** containing the bis-armed AAA derivative. Next, the DA reaction of the diene **98** with various dienophiles and subsequent aromatization of the DA adducts gave the Phe-based AAA derivatives **99** in good yields. Similarly, DA reaction of the diene **98** with fullerene (C$_{60}$) gave the AAA derivatives **100**.

The diphenylalkane skeleton is present in many natural products and biologically important molecules.[28] A novel approach with four points of diversity has been reported to highly functionalized diphenylalkane derivatives by strategic utilization of a [2 + 2 + 2] cotrimerization, CEM, and DA reaction as key steps (Scheme 9).[29] In this regard, the alkyne building blocks **103** were prepared starting with dialkyne **101** and DMAD (**28**) involving [2 + 2 + 2] cotrimerization using

**Scheme 8. Synthesis of Fullerene-Based Dicarba Analogs of Cystine**

Dienophile	28	50	51	52
Yield (%) meso	71	81	94	82
Yield (%) racemic	72	86	55	79
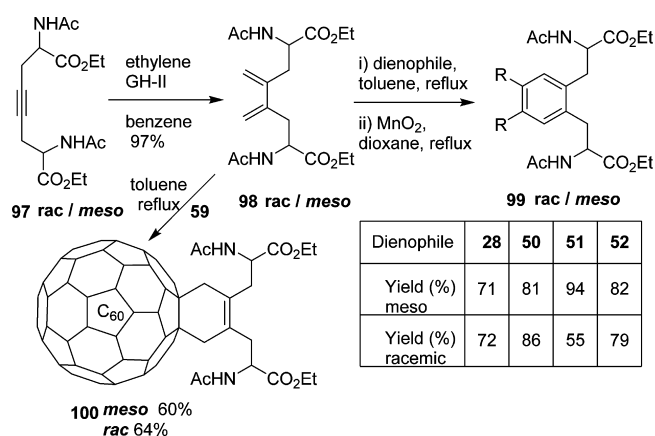
Wilkinson's catalyst [Rh(PPh$_3$)$_3$Cl] under ethanol reflux conditions. Later, the CEM of **103** with ethylene in the presence of G-II catalyst delivered the diene **104**. Finally, DA reaction of the dienes **104** with DMAD (**28**) and subsequent aromatization of the DA adducts under microwave irradiation (MWI) conditions delivered the diphenylalkane derivatives **105**.

A couple of dienes from the hydroxy-protected but-2-yne-1,4-diol derivatives **106** by CEM under ethylene atmosphere have been reported (Scheme 10).[30] These dienes **107** are useful in assembling the key building block **108** and useful for the synthesis of benzosultine-sulfone (see Schemes 62 and 65). The tosyl-protected diene **107a** was unreactive in the DA reaction with various dienophiles under a variety of conditions; however, the acetyl derivative **107b** on DA reaction with DMAD (**28**) in toluene at 80 °C resulted in the expected DA adduct, which on further oxidation with DDQ in benzene or MnO$_2$/dioxane under reflux conditions gave the benzoannulated product **108**.

Biphenyl derivatives are generally prepared by cross-coupling reactions. The DA approach to these important targets is highly

Scheme 9. Preparation of Diphenylalkane Derivatives by DA Chemistry
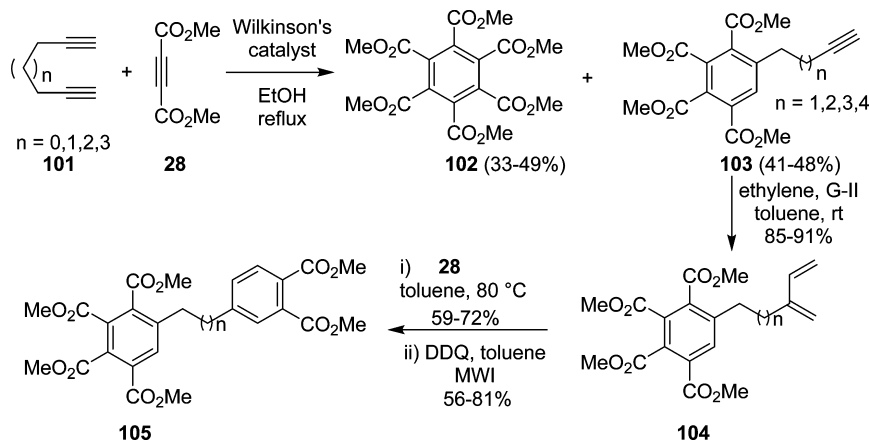
Scheme 10. Synthesis of Highly Functionalized Benzene Derivative via DA Chemistry
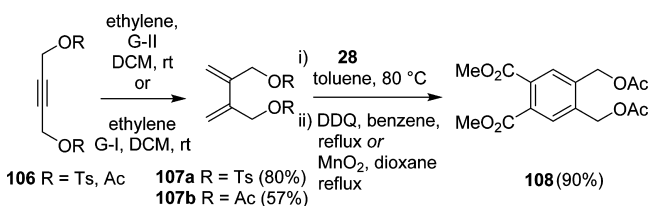
desirable. In continuation of our efforts in designing polycyclics by CEM and DA reaction, recently the synthesis of biphenyl derivatives from phenyl acetylenes 109 by employing a similar synthetic sequence (Scheme 11) has been reported.[31] The G-II catalyst-mediated CEM of phenyl acetylenes 109 has been carried out with ethylene as a cross-metathesis partner to generate 2-phenyl-substituted 1,3-butadienes 110. Later, its DA reaction with DMAD (28) and aromatization via DDQ oxidation produced highly functionalized biphenyls 111. These halogen substituted biaryl derivatives are important precursors for the synthesis of terphenyl derivatives by the application of Suzuki−Miyaura (SM) cross-coupling reaction.[32] A diversity-oriented approach has been used to assemble a library of biphenyl derivatives by varying the cross-metathesis partner; dienophile; and later, various boronic acids during the cross-coupling reaction.

Similarly, phenylacetylenes 109 on treatment with 1,5-hexadiene as a cross-metathesis partner gave the dienes 112. Two products were observed under toluene reflux conditions: the expected CEM product 112 and benzoannulated product such as biphenyl derivative 113. Then the DA reaction of these dienes 112 with DMAD (28) followed by aromatization with DDQ led to the biphenyl derivatives 114. The reactive

functionalities present in 114 can be further used as a handle for the generation of highly functionalized polycyclics (Scheme 12).[31]

The DA approach to the synthesis of spirocycles is rare. In 2007, we intented to prepare the spirocyclic compound 116 containing two inner-outer-ring type of diene moieties, which can be further elaborated by the DA chemistry.[33] The enyne precursor 115 failed to give the bis-spirocyclic diene 116 under G-I, G-II, and GH-II catalyst reaction conditions (Scheme 13).

When the enyne precursor 115 was treated with G-I catalyst under an ethylene atmosphere in DCM at room temperature, three products were isolated (Scheme 14). The first compound, 117, was formed as a result of EM of an alkyne moiety and RCM of two double bonds, the second product 118 has been derived from EM at both ends alkyne moieties and RCM of two double bonds, and the final product 119 was derived as a result of RCM of allyl groups. Surprisingly, when we treated the enyne precursor 115 with G-II catalyst in DCM at room temperature, only two products were isolated. Compound 120 has been derived by EM at one alkyne end in comparatively better yield than compound 121, which involves EM at both alkynes. In this case, the RCM product was not observed. Under ethylene free reaction conditions, no metathesis product was observed with G-II catalyst; however, in the case of G-I, in situ-generated ethylene was reacted with the alkyne moieties. Here, we have observed chemoselectivity with G-I and G-II catalysts under ethylene atmosphere.

Cross-enyne metathesis (CEM) is widely used tool for the synthesis of various natural and nonnatural bioactive molecules containing diene moieties. In 2002, Mori and co-workers reported the synthesis of anolignan A and anolignan B by CEM as a key step.[34] The 1,3-diene moiety present in these natural products was constructed by ethylene-mediated EM of alkyne derivative using Grubbs catalyst. Anolignan A and anolignan B
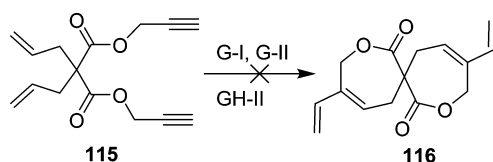
Scheme 11. Generation of Biphenyl Derivatives from Phenyl Acetylenes Involving DA Chemistry
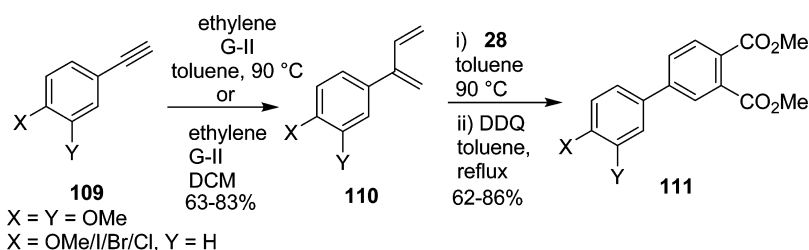
Scheme 12. Synthesis of Biphenyl Derivatives 114 via CM and DA Chemistry
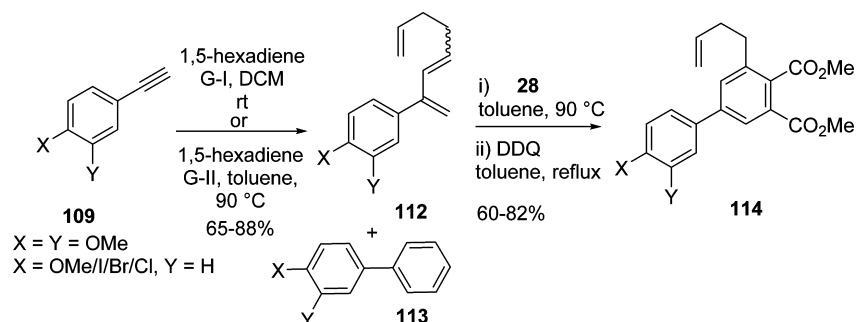
Scheme 13. Attempt for the Synthesis of Spirocyclic Diene 116

are new dibenzylbutadiene derivatives and are active HIV-1 reverse transcriptase inhibitors isolated from *Anogeissus acuminata*.[35] Toward the synthesis of anolignan A (125), the alkyne precursor 122 was subjected to the CEM with G-II catalyst under ethylene atmosphere to yield the diene moiety 123 in excellent yield. Later, the removal of two acetoxy groups was achieved by treatment with Pd$_2$(dba)$_3$·CHCl$_3$ and Bu$_3$P in the presence of formic acid and triethyl amine to obtain the 1,3-butadiene derivative 124. Then deprotection of the dimesyloxy groups in 124 using PhLi led to the phenolic compound anolignan A (125) in 30% overall yield (Scheme 15). Similarly, the synthesis of anolignan B was also reported by CEM starting with appropriate alkyne derivative.

The *C*-aryl glycosides are stable to both enzymatic and acid hydrolysis. Their unusual stability has been manifested in some interesting biological properties. Kaliappan and Subrahmanyam have developed a versatile strategy to generate *C*-aryl glycosides by utilization of CEM as a key step.[36] To this end, the glycoside-based dienes 127 were generated by CEM of the alkyne derivatives such as 126 under ethylene atmosphere with G-II catalyst. Further, these dienes 127 on DA reaction with different quinones 128 followed by aromatization of the DA adducts gave the *C*-aryl glycosides 129 having quinone moiety (Scheme 16). Alternatively, these glycoside-based dienes 127 were also subjected to the DA reaction with DMAD (28). This diversity-oriented approach can be useful for the synthesis of a

variety of *C*-aryl glycosides by utilizing different sugar-based alkynes and dienophiles. Later, they extended this approach to a variety of *C*-aryl and spiro-*C*-aryl glycosides.[37]

They have also synthesized various benzylic fluorides through the DA reaction of fluorinated 1,3-dienes with different dienophiles. Open-chain 1,3-dienes 131 having fluorine-containing side chain at the 2-position were prepared starting with propargylic fluoride 130 by CEM using G-II catalyst. Next, the DA reaction with diethyl acetylenedicarboxylate (29) followed by the oxidation of the DA adduct using MnO$_2$ gave the benzylic fluoride 132 and the DA reaction with 1,4-naphthoquinone (50), followed by aromatization with silica gel/triethyl amine produced the quinone based benzylic fluoride 133 (Scheme 17).[38] They have prepared an enantio-enriched monofluorinated diene starting with enantiopure propargylic fluoride. By utilizing this strategy, mono- and gem-difluorinated dienes and benzylic fluorides were prepared. Likewise, Fustero and co-workers have reported the CEM of amide-based difluorinated alkyne derivatives and the DA reaction of the resulting dienes with a variety of dienophiles in one pot.[39]

Fustero and co-workers have reported a multicomponent tandem CEM and DA reaction approach with 1,7-octadiene as a source of ethylene, which is generated in situ by RCM of 1,7-octadiene. In this regard, various aliphatic, aromatic alkynes, fluorinated alkynes, and amidoalkynes with several dienophiles, such as DEAD (29), 1,4-naphthoquinone (50), and *N*-phenyl-maleimide (55) under tandem CEM/DA conditions gave the carbo- and heterocyclic derivatives 135 and 137 in good yields (Scheme 18).[40] This methodology is a good alternative to the ethylene-mediated CEM reaction, and it is compatible with a wide variety of functional groups. By varying alkyne and dienophile moieties, one can generate a library of annulated aromatics in a predetermined fashion under mild reaction conditions. This type of building block approach provides better
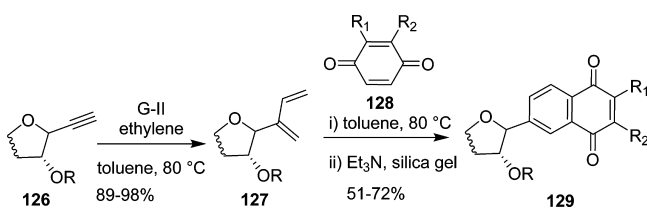
Scheme 14. Reactivity of 115 with G-I and G-II Catalysts under Ethylene Atmosphere
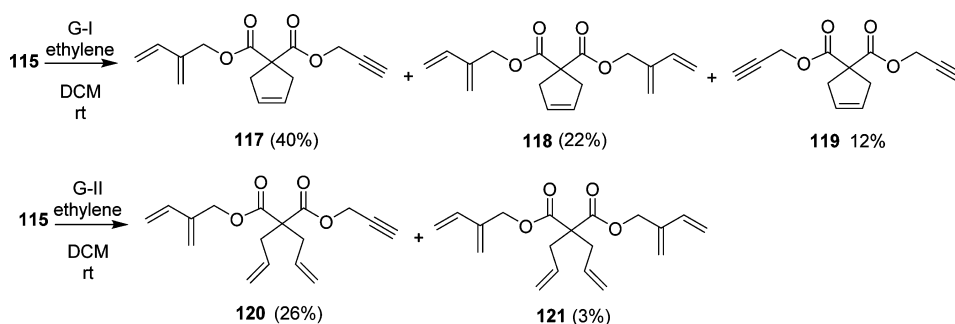
Scheme 15. Synthesis of Anolignan A
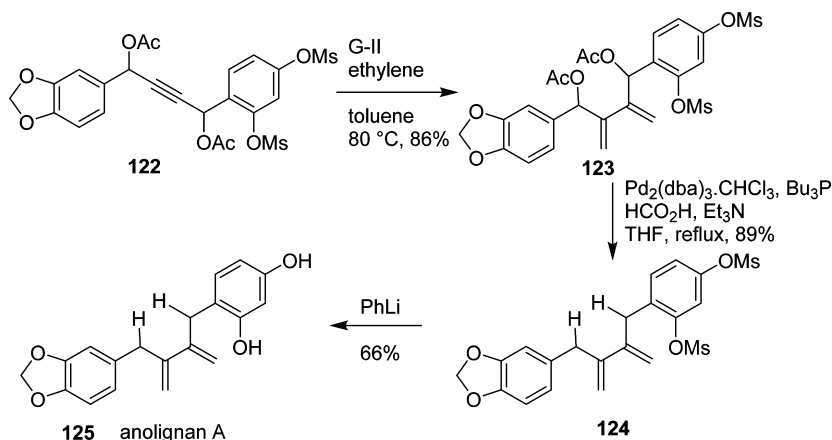
Scheme 16. Preparation of *C*-Aryl Glycosides 129 via DA Chemistry


control in installing substituents in the aromatic rings, whereas traditional aromatic electrophilic substitution protocol suffers regiocontrol problem.

Recently, Karabulut et al. reported [RuCl$_2$(*p*-cymene)]$_2$/IPr (IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) catalyzed in situ CEM and DA reaction protocol.[41] The phenyl-substituted 1,3-dienes formed during the enyne metathesis of phenyl acetylenes **138** were reacted in situ with DMAD (**28**) to form the DA adducts **139** and with *N*-phenylmaleimide (**55**) and maleic anhydride (**63**) gave the product **140** (Scheme 19). Here, they have shown [RuCl$_2$(*p*-cymene)]$_2$ in combination with a sterically hindered *N*-heterocyclic carbene/(IPr) catalytic system switch the reaction of phenylacetylene from cyclotrimerization to cross-enyne metathesis. This is an efficient protocol to construct cyclic compounds in one pot.

Daunomycin and Adriamycin are used clinically as anticancer agents.[42] In 2002, Kotha and Stoodley reported an entantioselective synthesis of (+)-4-demethoxy-1,4-dimethyldaunomycinone,[43] an analog of anthracycline antibiotics. The synthesis

Scheme 18. Synthesis of Carbo- and Heterocyclics by Tandem CEM–DA Reaction
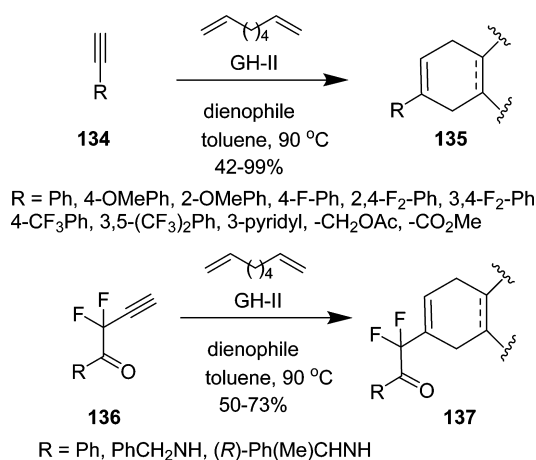
of (+)-4-demethoxy-1,4-dimethyldaunomycinone **145** was achieved by the DA reaction of the oxirane-based dienophile **142** and the sugar-based diene **143**. The oxirane-based dienophile **142** was prepared from the DA cycloadduct **141** of 2,5-dimethylfuran and maleic anhydride by a four-step sequence, then the reaction of **142** with the sugar-based diene **143** and treatment of the DA adduct with dilute hydrochloric acid gave the epoxy-ketone **144**, which was then converted to (+)-4-demethoxy-1,4-dimethyldaunomycinone **145** in five steps (Scheme 20).

Scheme 17. CEM–DA Approach to Quinone-Based Benzylic Fluoride
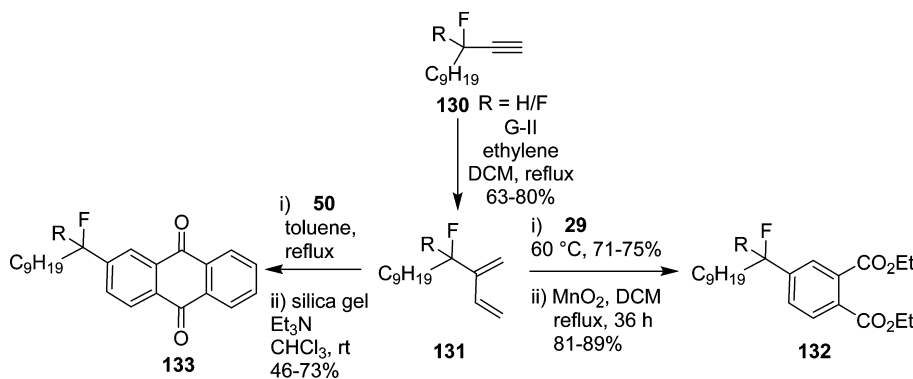
Scheme 19. Role of Catalyst in Controlling the Cyclotrimerization/Cross-Enyne Metathesis

R =	H	H
Dienophile	55	63
Yield (%)	66	79

R =	H	4-Me	2-Me	4-OMe	2-OMe
Yield (%)	75	80	72	78	62
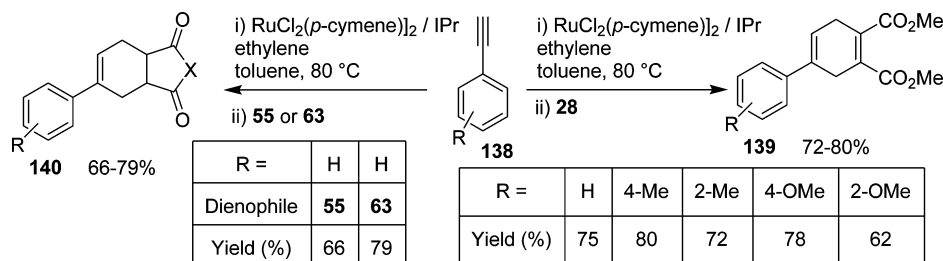
Scheme 20. Synthesis of (+)-4-Demethoxy-1,4-dimethyldaunomycinone 145 via DA Chemistry
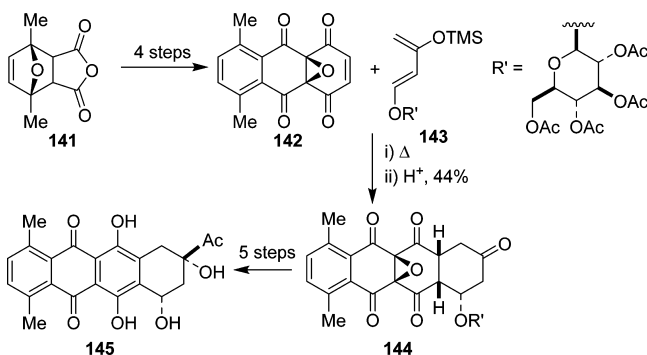
Olefin metathesis is a very useful tool to design unusual ring systems, for example, propellanes, catenane, etc. In 2011, Kotha and co-workers reported the synthesis of *cis*- and *trans*-decalins by DA reaction and RCM as key steps, and further, *cis*-decalin was used as a precursor for 3,8-dioxa[8.4.4]propellane derivative **151**.[44] In this regard, sulfone **146** was used as a source of 1,3-butadiene (**1**) and reacted with maleic anhydride (**63**). Next, ethanolysis of the cycloadduct **147** under acid catalysis conditions gave the cyclohexenediester **148**. Allylation of the diester **148** gave the stereoisomeric mixture of diallyl cyclohexenediester **149** in a 3:2 ratio (cis/trans), which on RCM with G-II catalyst and hydrogenation under Pd/C catalysis conditions produced the pure *cis*- and *trans*-decalin diesters **150**. Later, the *cis*-decalin diester was used for the synthesis of 3,8-dioxa[8.4.4]propellane derivative **151** in four steps (Scheme 21).

Scheme 21. Synthesis of 3,8-Dioxa[8.4.4]propellane Derivative 151 Involving DA Chemistry
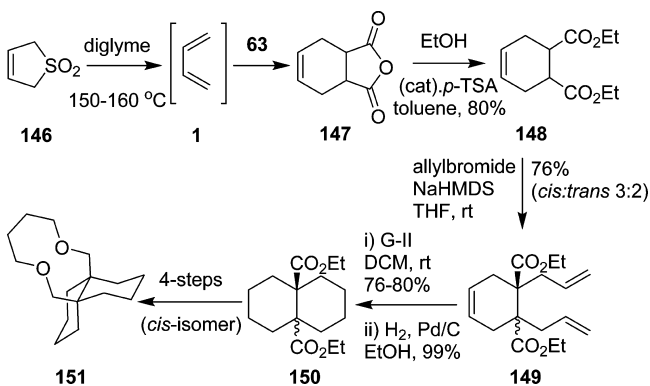
In 2009, Piettre and co-workers explored substituted benzofurans as an efficient dienophiles. The reaction of 3-substituted

benzofurans **152** with 2,3-dimethylbutadiene (**153**) led to the generation of tricyclic compound **154** in quantitative yield. In all cases, the formation of the expected tricyclic compounds confirmed the reactivity of an aromatic C-2/C-3 double bond of the substituted benzofuran ring as an electron-poor dienophile. The use of sensitive dienes such as 2-trimethylsilyloxybutadiene **155** in the DA reaction with 3-substituted benzofuran **152** under high pressure conditions followed by hydrolysis gave **156**. (Scheme 22).[45] The Danishefsky's diene induces a competition for the reactivity site. The preferred site for the DA reaction is clearly the aromatic 2,3-carbon−carbon double bond, delivering the expected tricyclic adducts **156**. However, the carbonylated unit in position-3 seems to be a competitive dienophile under the influence of Lewis acid to deliver the hetero-DA products.
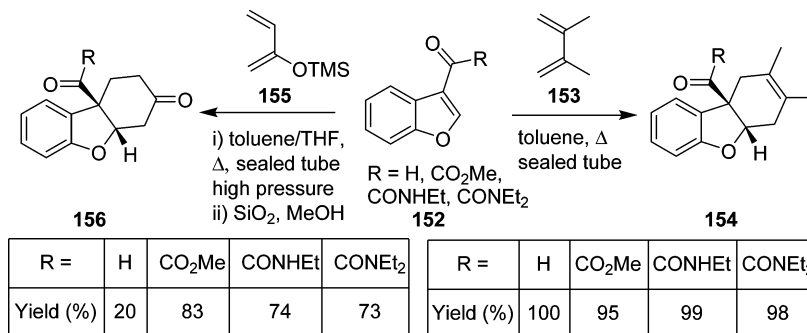
Usuki and co-workers have described the synthesis of a novel fluorinated Kitahara−Danishefsky's diene analog **157** by a Pd-catalyzed process.[46] (*E*)-1-Benzyloxy-3-fluoro-1,3-butadiene **157** was reacted with various dienophiles to deliver useful 1-fluorocyclohexene derivatives **158−159** in good yields (Scheme 23). By utilizing this diene derivative and varying the dienophile moiety in DA reaction, one can generate a diverse fluorinated molecules in an efficient manner.

In 2013, Moody's group reported the synthesis of quinone building blocks that are useful for assembling aminonaphthoquinone antibiotics.[47] The key reaction involved here is the DA reaction of a new series of esters containing Danishefsky-type dienes **161−164** with *N*-protected aminobenzoquinones **160**. Various dienes containing silyl protecting groups (**161−164**) were reacted with aminobenzoquinone (**160**) to generate amino-substituted naphthoquinone derivatives **165−168** (Scheme 24).

In 1997, Kozmin and Rawal for the first time reported the 1-amino-3-siloxy-1,3-butadiene (**173**), an analog of Danishefsky's diene and now recognized as Rawal's diene, prepared from vinylogous amide **170** and its DA reaction with a variety of dienophiles to give endo products stereoselectively (Scheme 25). In the case of reaction with diethyl acetylenedicarboxylate (**29**), the aromatized product **174** was obtained. The DA reactions of Rawal's diene (**173**) were carried out under relatively mild reaction conditions. As compared Danishefsky's diene, Rawal's diene shows a significantly higher reactivity in the DA reaction. They have also explored the scope of this diene by carrying out the DA reactions with a variety of dienophiles, such as methacrolein (**38**), methyl 2-methyl acrylate (**40**), and *N*-phenylmaleimide (**55**). Later, some of the cycloadducts were transformed into valuable intermediates by simple synthetic transformations.[48]

Kozmin and Rawal also reported the chiral version of amino siloxy diene from vinylogous amide and *trans*-diphenylpyrrolidine. This chiral diene **178** on DA reaction with various

Scheme 22. Synthesis of 154 and 156 via DA Reaction

R =	H	CO$_2$Me	CONHEt	CONEt$_2$
Yield (%)	20	83	74	73

R =	H	CO$_2$Me	CONHEt	CONEt$_2$
Yield (%)	100	95	99	98

Scheme 23. Synthesis of 1-Fluorocyclohexene Derivatives 158-159 via DA Chemistry

| Dienophile	28	41	42	43	45	47	63
Yield (%)	93	85	16	70	66	90	80
dr	---	52:48	33:67	0:100	7:93	---	81:19
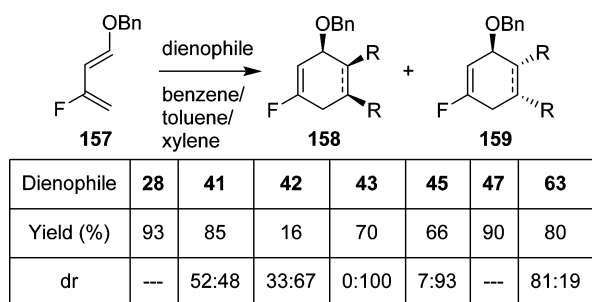
dienophiles gave the endo cycloadducts with high disterose-lectivity under mild reaction conditions. These cycloadducts were further converted to enantiopure cyclohexenone derivatives.

Later, the DA cycloadduct of chiral diene **178** and methacrolein (**38**) were utilized for enantioselective synthesis of (−)-α-elemene **180** (Scheme 26).[49] Moreover, Maier's group has used the Rawal's diene **173** for the formal total synthesis of naturally occurring antitumor compound, a dysidiolide.[50]

Later, Rawal's group extended the use of 1-amino 3-siloxy diene for the synthesis of alkaloids. To this end, they have reported the synthesis of the aspidosperma family of indole alkaloids, such as (±)-tabersonine, (+)-aspidospermidine, (−)-quebrachamine, (−)-dehydroquebrachamine, (+)-tabersonine, and (+)-16-methoxytabersonine. In this regard, the N-allylated diene derivative **181** on reaction with ethylacrolein (**39**) produced the endoselective cycloadduct **182**, which was then transformed to (±)-tabersonine **183** in nine steps (Scheme 27). They utilized an enantioselective DA reaction

Scheme 24. Synthesis of Amino-Substituted Naphthoquinones 165−168 via DA Chemistry
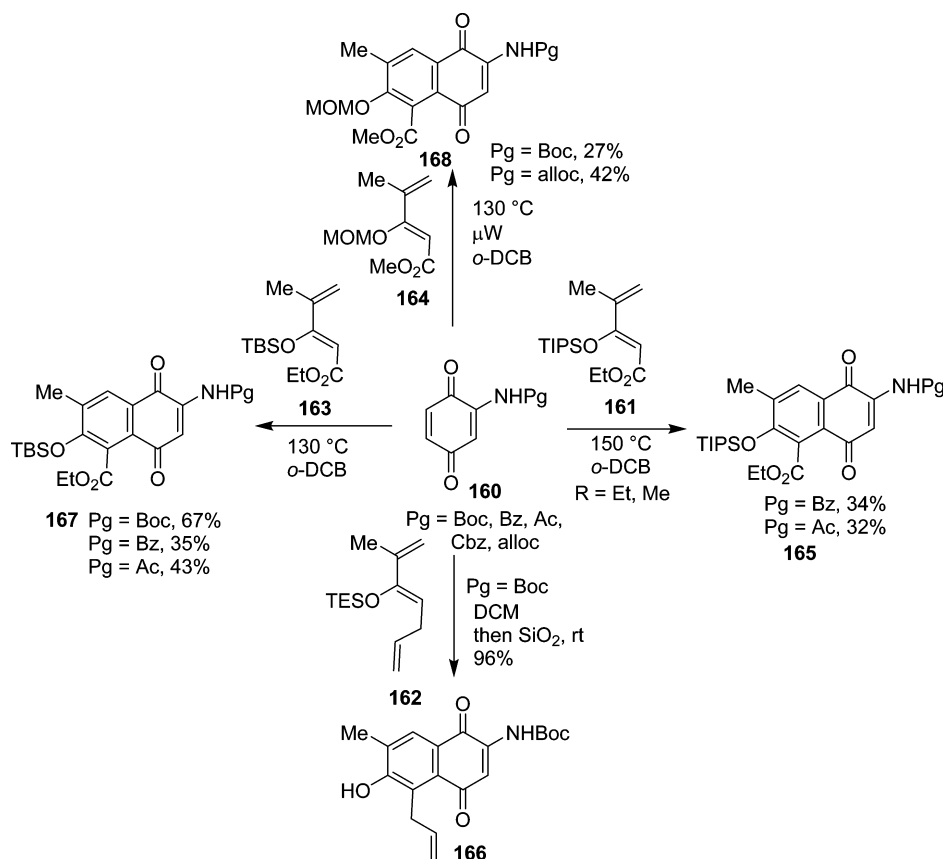
Scheme 25. DA Chemistry with Rawal's Diene 173
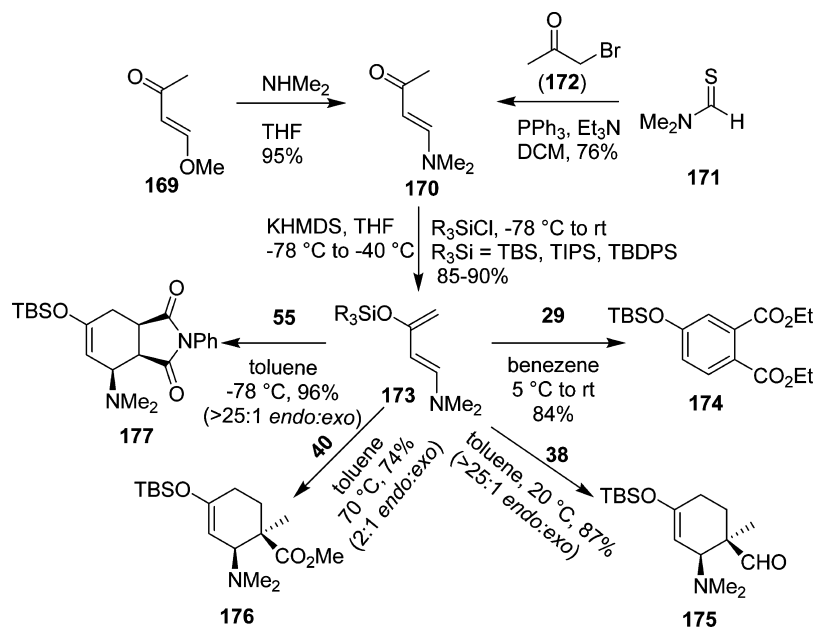
Scheme 26. Synthesis of (−)-α-Elemene 180 via DA Chemistry
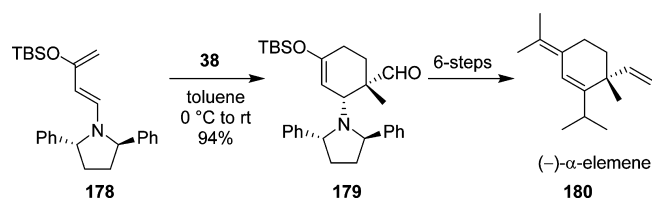
under fluoroborate catalyst conditions for the stereoselective synthesis of aspidosperma family of indole alkaloids.[51]

Similarly, Gravel's group has reported the 1-alkylthio-3-silyloxybutadienes **184**, another analog of Danishefsky's diene. It was prepared from 4-methoxy-3-buten-2-one (**169**) through the formation of vinylogous thioester. The DA reaction of diene **184** with various dienophiles gave highly functionalized cycloadducts **185−188** with endoselectivity. Then cleavage of silyl enol ether using a HF·pyridine complex gave sulfide-containing ketones **189** and **190**, which are useful for further synthetic manipulation (Scheme 28).[52] Interestingly, the 1-alkylthio-3-silyloxybutadienes are relatively less reactive than Danishefsky's diene and Rawal's diene.

Generally, low stability of boron-functionalized 1,3-dienes and low reactivity of alkynylboronic esters limits their use in the DA reaction. In 2003, Hilt and Smolko reported the cobalt-catalyzed DA reaction of 1,3-butadiene derivatives **192** with low reactive alkynylboronic esters **191** to obtain the DA cycloadduct **193** in a regioselective manner. Then the Suzuki

coupling of cycloadducts, dihydroaromatic derivatives **193** with aryl, alkenyl, or alkynyl halides gave the coupling product, which on DDQ oxidation gave the polyfunctional benzannu-lated derivatives **194** (Scheme 29).[53] Further, the isopropenyl-substituted building block has been used for the generation of the cannabinoid family of natural products. Generally, dienes with electron-donating groups and dienophiles with electron-withdrawing groups are suitable for normal DA reaction, but the transition metal (such as cobalt, palladium)-catalyzed DA reaction can occur with a variety of dienes and dienophiles independent of the substituents present. Therefore, the metal-catalyzed regioselective DA reaction can be utilized to generate diverse polycyclic compounds containing useful functionalities that were previously not possible by conventional DA reaction conditions.

Further, Hilt and co-workers have extended the use of isopropenyl-substituted cycloadduct **195** for the synthesis of phenanthrenes **197** and phenanthridines **200**. In this regard, the cycloadduct **195** on treatment with o-diiodobenzene **196** under palladium catalysis conditions followed by DDQ oxidation gave the phenanthrene derivative **197** by domino Suzuki coupling/Heck reaction. Similarly, the authors have utilized the o-iodoaniline **198** for the generation of phenan-thridine derivatives **200**. The Suzuki coupling of **195** with o-iodoaniline **198** and subsequent DDQ oxidation gave the biarylamine derivatives **199**, then the acid-catalyzed intra-molecular hydroamination of **199** gave a highly substituted phenanthridine derivative, **200**. Compound **199** was converted

Scheme 27. Synthesis of (±)-Tabersonine by the Endo-Selective DA Reaction
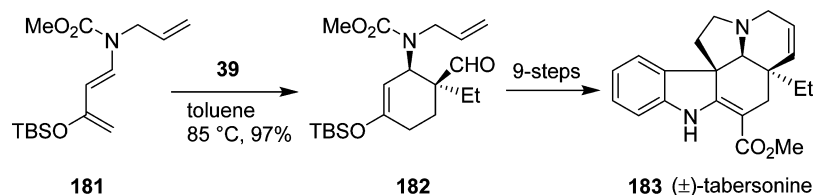
Scheme 28. Synthesis of Highly Functionalized Cycloadducts 185−188 with Endoselectivity
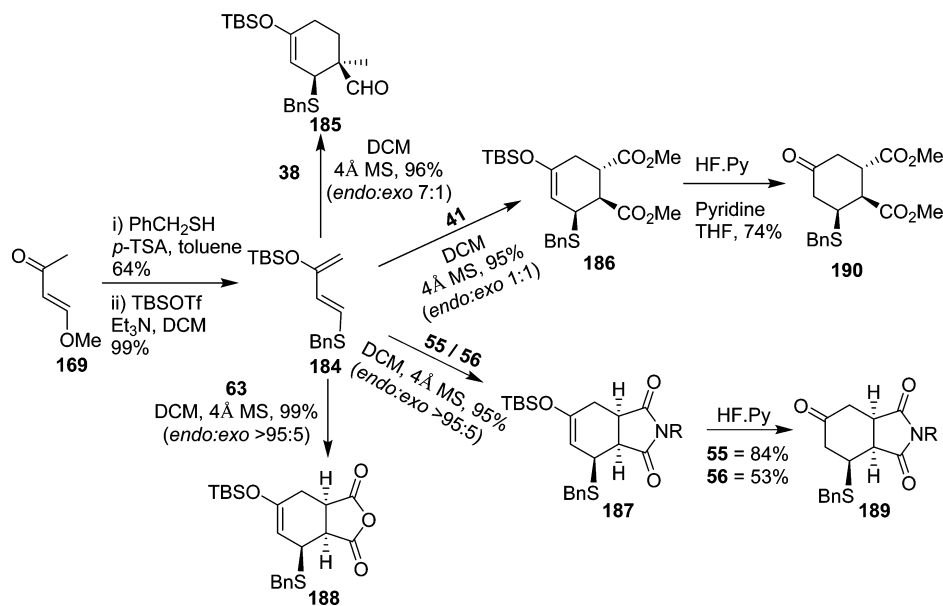
Scheme 29. Preparation of Polyfunctional Benzannulated Derivatives
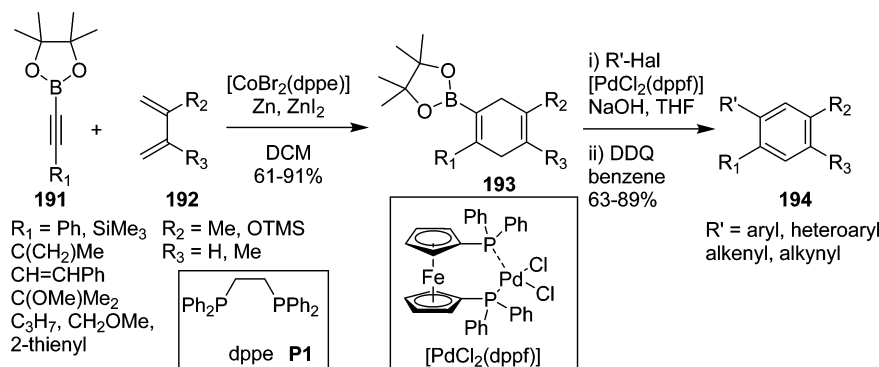
Scheme 30. Synthesis of Phenanthrenes 197 and Phenanthridines 200
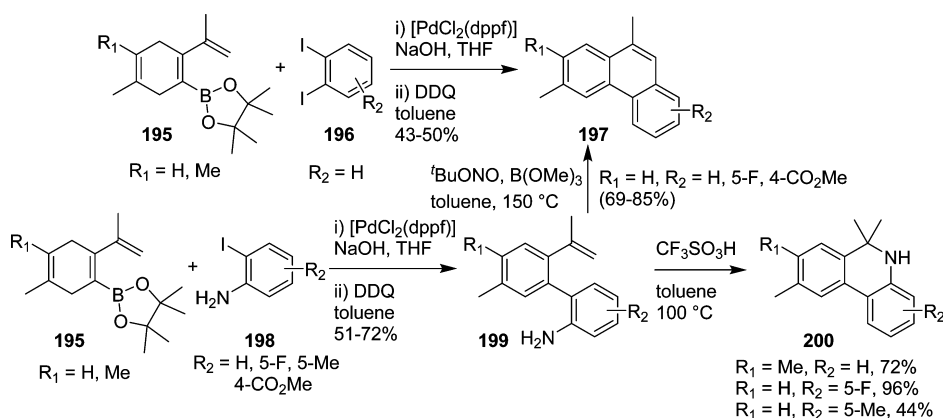
to phenanthrene derivative **197** by treatment of nitrite ester and borate ester (Scheme 30).[54]

In continuation of cobalt-catalyzed DA chemistry,[55] Hilt and Janikowski have reported a regiocontrolled DA reaction of 2-methyl 1,3-butadiene (**201**) with terminal or internal alkynyl silanes **202**. Then, the DA reaction of **201** with alkynyl silanes **202** under different cobalt-catalyst conditions gave the cycloadducts in a regioselective manner, which subsequently

undergo aromatization with DDQ to deliver silicon-containing benzannulated compounds **203a−b** (Scheme 31).[56] The silicon functionality is a useful handle for further synthetic manipulation. Here, the regiochemistry of the DA products has been controlled by the application of two different cobalt catalyst systems bearing either **P1** or **P2** ligands. A catalyst system containing **P1** generates predominantly products **203a** with a 1,4-substitution pattern, whereas the catalyst system with ligand **P2**

Scheme 31. DA Reaction Involving Dienophiles without Electron-Withdrawing Groups
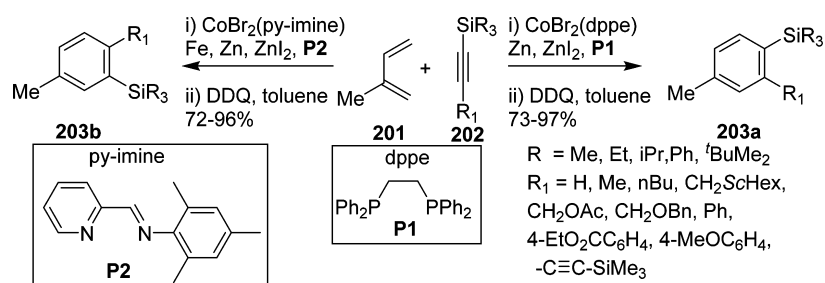
Scheme 32. Synthesis of Nonconjugated Cyclohex-3-enones Involving a Co-catalyzed DA Reaction
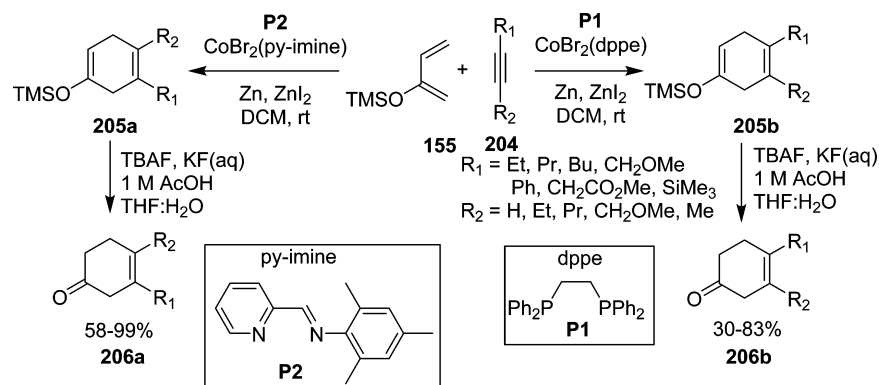
Scheme 33. Synthesis of Fluorenone and Anthraquinone Derivatives via DA Reaction
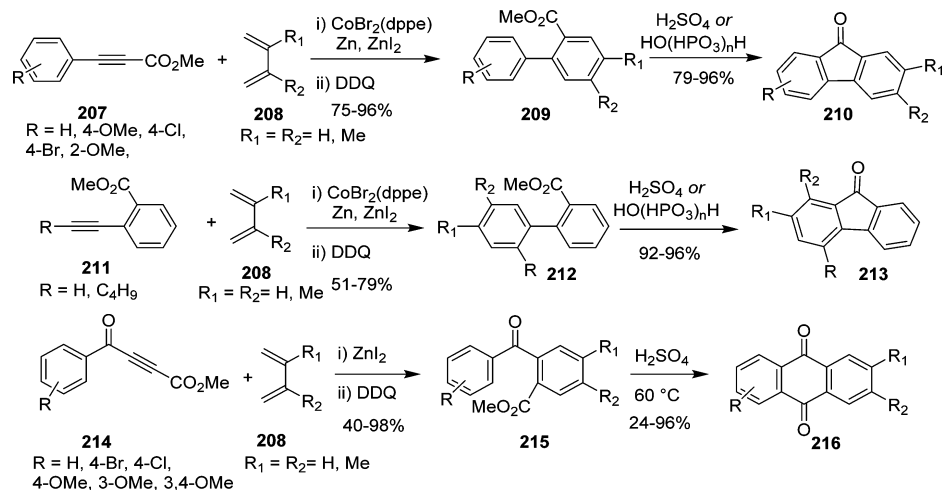
prefers to form the 1,3-substituted regioisomer **203b** with mono- or disubstituted alkyne derivatives. Furthermore, the authors have used this cobalt-catalytic condition with a variety of dienes and dienophiles to generate polyfunctional arenes.[57] The unique capability of this approach is that both regioisomers **203a** and **203b** are assembled from a common precursor using two different ligands, **P1** and **P2**, under the cobalt catalyst conditions.

In 2012, Hilt and co-workers reported the synthesis of nonconjugated cyclohex-3-enones **206a–b** by a regiodivergent cobalt-catalyzed DA reaction of 2-(trimethylsilyloxy)buta-1,3-diene **155** with a variety of electron-rich or electron-deficient alkynes, **204**. The DA reaction of **155** with alkynes **204** and subsequent desiloxylation gave the cyclohex-3-enone derivative **206a** and the regioisomeric cyclohex-3-enone derivative **206b** under different catalytic conditions (Scheme 32).[58] Further,

they extended this DA approach with the cobalt catalytic system for the construction of cyclopropylarenes.[59]

In addition, Hilt and co-workers have demonstrated the synthesis of fluorenone derivatives **210** and **213** from aryl-substituted propiolates **207** and **211** via cobalt-catalyzed DA reaction/DDQ oxidation and Friedel−Crafts type cyclization. Further, various anthraquinone derivatives **216** were assembled from aroyl-substituted propiolates **214** using a zinc iodide-catalyzed DA reaction with 1,3-dienes **208** (Scheme 33).[60]

Tripathi and co-workers have developed an efficient strategy for the synthesis of a diverse anthraquinone-based aryl-C-glycosides by a DA approach. The required butadienyl glycoside building blocks **218** were prepared from the butenoyl glycosides **217** by Luche reduction, followed by triethylamine-catalyzed tandem one-pot methanesulfonylation and elimination sequence. Then a sequential DA reaction of glycosyl dienes

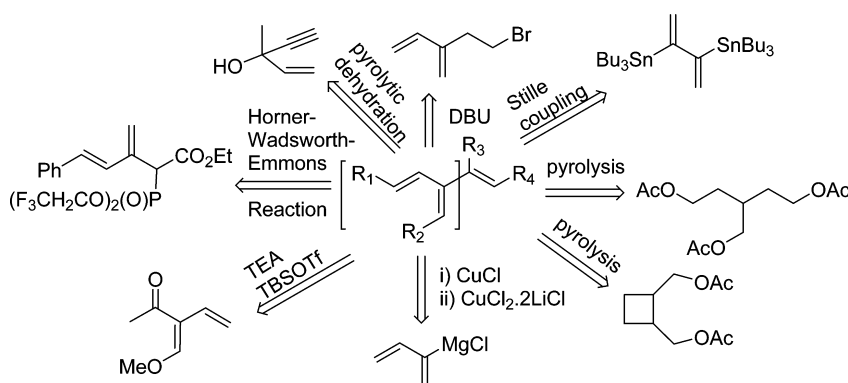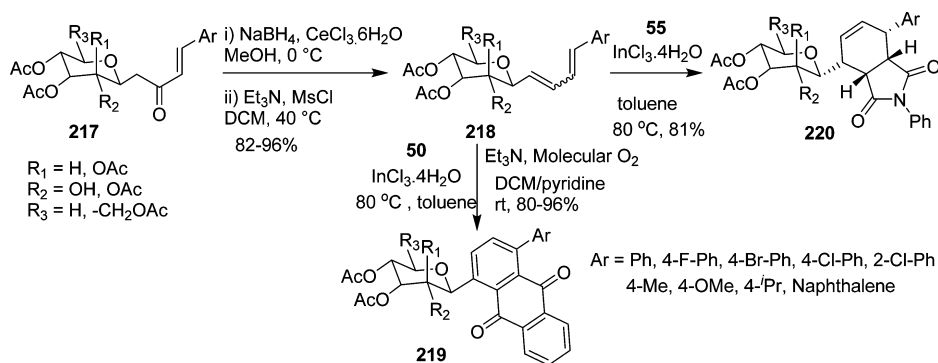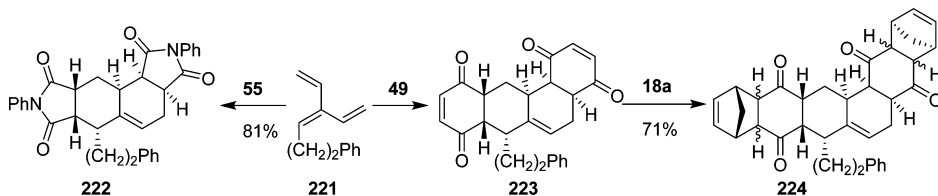**Scheme 34. Approach to Anthraquinone-Based Aryl-C-glycosides via DA Strategy**

Figure 5. Synthetic approaches to dendralene derivatives.

Scheme 35. Tandem Intermolecular DA Reactions Involving Dendralene 221

218 with 1,4-naphthoquinone (**50**) and subsequent aromatization gave a range of aryl-C-glycosides **219**. Later, they extended this cycloaddition-aromatization approach to other dienyl glycosides **218** derived from D-glucose, D-xylose, and D-mannose with 1,4-naphthoquinone (**50**) to obtain structurally diverse aryl-C-β-D-glycosides. The DA reaction of dienyl glycoside **218** with N-phenylmaleimide (**55**) gave the cycloaddition product **220** with endo selectivity (Scheme 34).[61] In a similar way, one can generate diverse aryl-C-glycosides by varying the carbohydrate moiety, the aromatic system, and dienophile components.

DENDRALENE

Dendralenes belong to a class of discrete acyclic cross-conjugated dienes.[62] The word dendralene has been derived from three words dendrimers, linear, and alkene. These are interesting building blocks because of their widespread applications in the synthesis of diverse polycycles through DA chemistry. Dendralenes are prepared by various methods involving pyrolytic elimination sequence, Stille coupling, Horner−Wadsworth−Emmons reaction of 1,3-butadien-2-ylphosphonoacetate with various aldehydes, or metal-catalyzed dimerization (Figure 5).[63]

In 1999, Fallis and co-workers reported a method for the generation of cross-conjugated trienes, which on intermolecular tandem DA reaction with various dienophiles produced various polycycles. The reaction of [3]-dendralene (triene) derivative **221** with N-phenylmaleimide (**55**) gave the double DA adduct **222**. Similarly, the triene **221** was added to 1,4-benzoquinone (**49**) to deliver the tetracyclic compound **223**. Further reaction of the bis-quinone adduct **223** with an excess amount of cyclopentadiene **18a** afforded the octacyclic compound **224** as a mixture of diastereomers (Scheme 35).[64]

In 2002, Schreiber and co-workers reported a diversity-oriented approach that yielded 29 400 discrete compounds having 10 distinct polycyclic skeletons. A library of compounds were assembled by using an inexpensive "one bead-one stock solution" technology platform. The triene system **225** was generated by using a method reported by Fallis and co-workers.[64] The triene system **225** with tri- and tetrasubstituted dienophile delivered a monocycloaddition product **226** exclusively. Later, the DA reaction of **226** with another dienophile gave the cycloaddition product **227**. The triene system **225** with a disubstituted dienophile delivered a tandem DA product **228**. Finally, the removal of the microbead support using a

Scheme 36. Synthesis of Polycyclic Compounds via DA Reaction of Dendralene
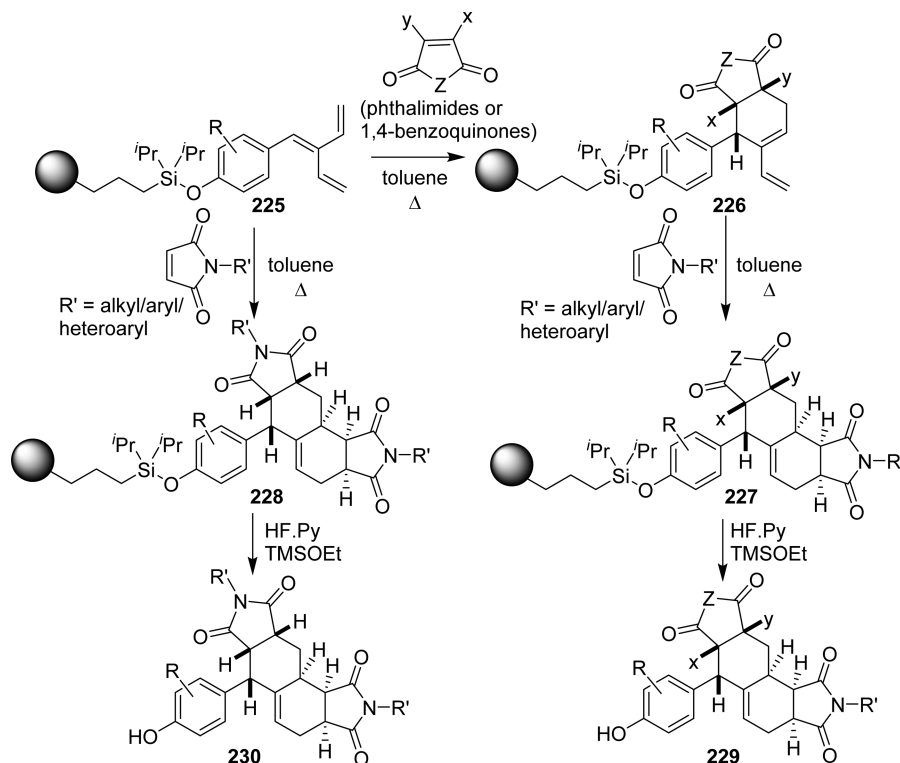
Scheme 37. Synthesis of TetR-Directed Carbocyclic Scaffolds

R =	*p*-BrPh	3-pyridyl	*m*-BrPh	*p*-MeOPh	*p*-ClPh	*m*-ClPh	*p*-FPh	Ph
Yield (%)	72	73	76	63	78	67	75	78
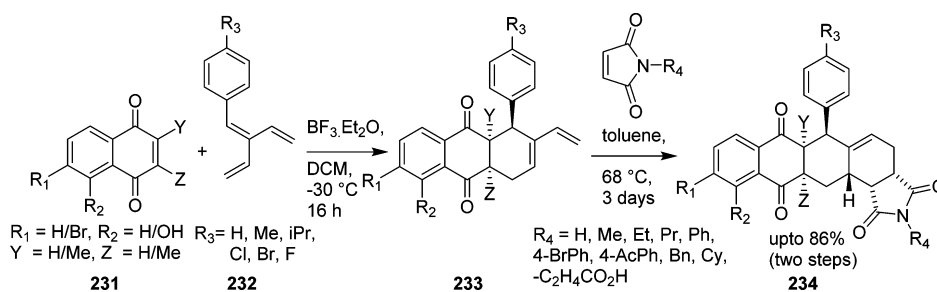
Scheme 38. DA Homodimerization of [3]Dendralene to Substituted Cyclohexenes 237
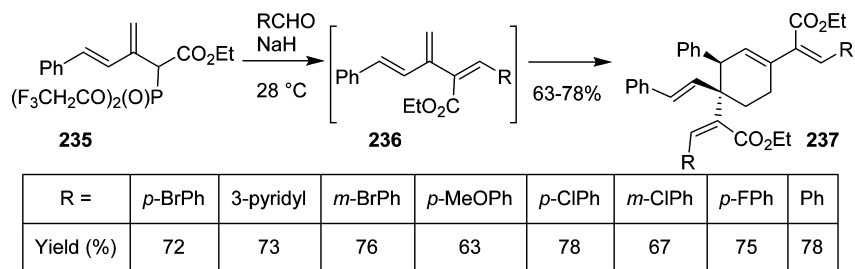
HF·pyridine complex gave diverse polyannulated compounds **229** and **230** (Scheme 36).[65]

Gmeiner and co-workers have reported a combinatorial library of analogs of tetracycline-inducible repressor protein (TetR) by a solution phase parallel synthesis utilizing a stepwise DA approach.[66] In this regard, DA reaction of the triene **232** with various quinones **231** under Lewis acid-catalysis conditions gave the expected DA monoadduct **233** with endo selectivity, where the phenyl and vicinally bridged substituent (Y) are in trans disposition. Later, thermal DA reaction of this

quinone-based inner-outer diene **233** with several maleimides gave diverse tetracyclic products **234** with endo selectivity (Scheme 37). This three-dimensional solution phase parallel synthesis by highly regio- and stereoselective stepwise DA reaction is useful to generate a TetR-directed library of carbocyclic scaffolds.

In 2011, Ghosh and co-workers demonstrated the synthesis of substituted [3]-dendralenes **236**, which underwent an in situ double DA sequence.[67] In this regard, 1,3-butadien-2-ylphosphonoacetate **235** was reacted with various aldehydes in the presence of NaH to yield the [3]dendralene **236** but under

Scheme 39. Synthesis of Tetraester 244 via DA and Aromatization Sequence
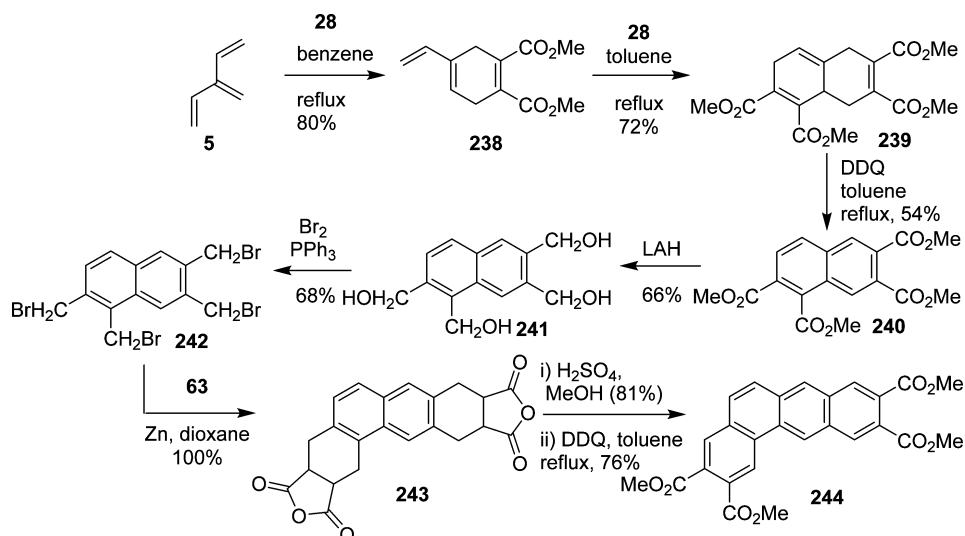
Scheme 40. Synthesis of Phenanthrene Hexaester 247 via DA and Aromatization Sequence
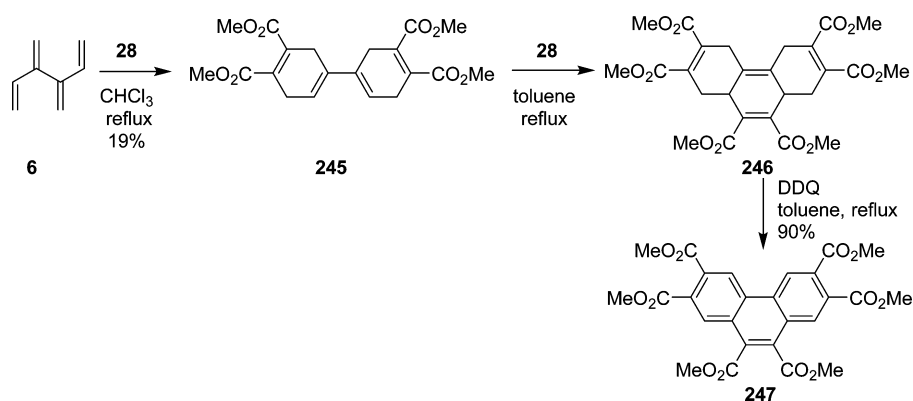
Scheme 41. Synthesis of Amphilectene 253

(±)-7-Isocyano-11(20),14-epiamphilectadiene
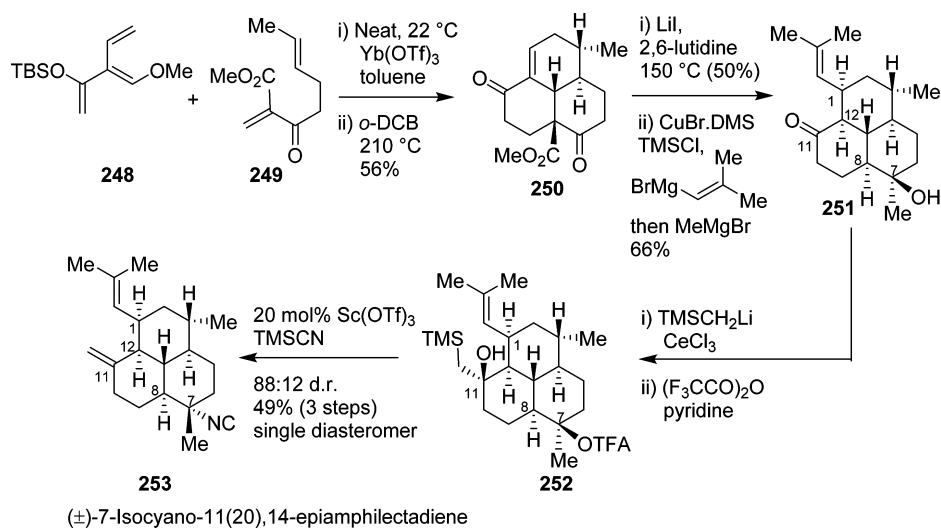
these reaction conditions, a highly reactive [3]dendralene undergoes the DA homodimerization to highly substituted cyclohexenes **237** with very high regio- and stereoselectivity (Scheme 38).

In 2011, Hopf and co-workers have reported highly functionalized angularly anellated aromatic compounds **244** and **247** starting with dendralenes.[68] The synthesis of benz[*a*]-anthracene tetraester **244**, begins with the two sequential DA cycloadditions of DMAD (**28**) to [3]dendralene **5**. Under harsh conditions, double DA reaction generates the cycloadduct **239**, and the subsequent aromatization delivered tetramethyl naphthalene-1,2,6,7-tetracarboxylate **240**. Later, reduction of

Scheme 42. Synthesis of (+)Diamino-tetrol 258
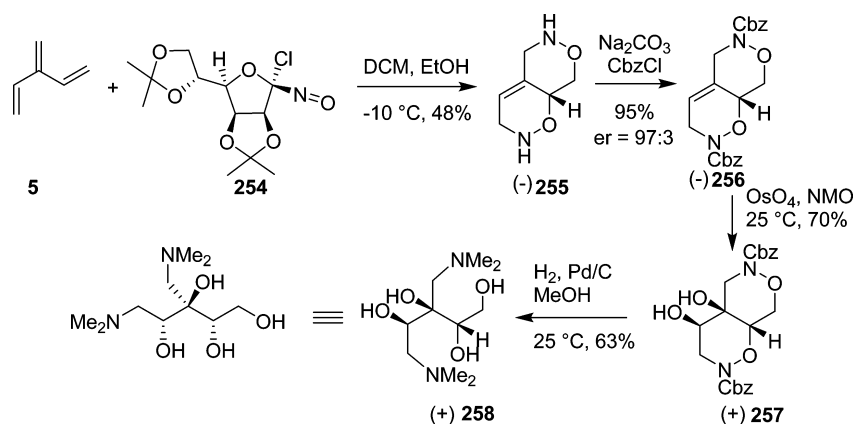
Scheme 43. Tandem DA Reaction of Dendralenes 260 with Activated Dienophiles

R	C_7H_{15}	3,4,5-$(OMe)_3$-$Ph(C_2H_4)$-	2-cyclo-hexenyl
Dienophile	49	49	49
Yield(%)	76	75	78
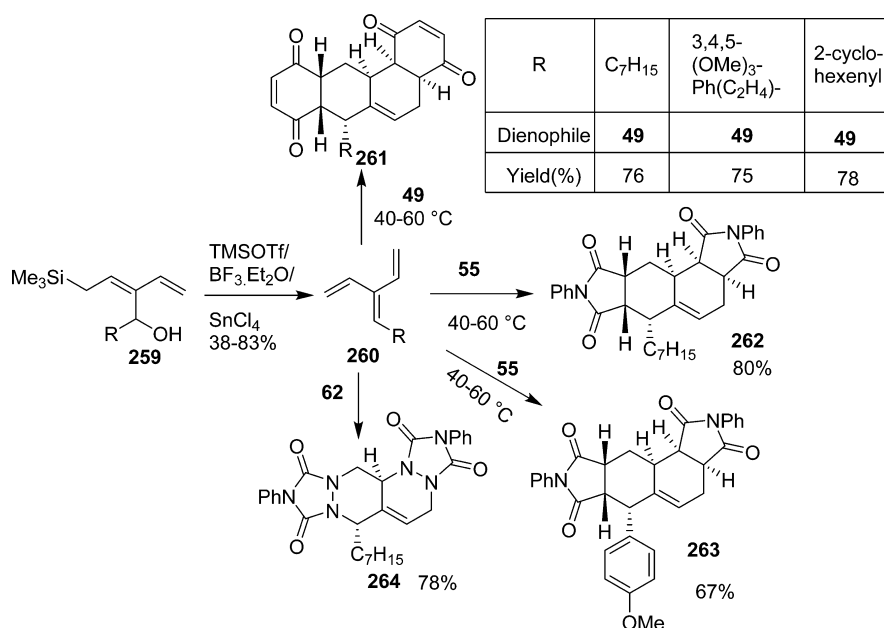
240, followed by bromination, gave the tetrabromide **242**. The DA reaction of in situ generated *o*-QDM from **242** with maleic anhydride (**63**) furnished the adduct **243**, which upon acid-catalyzed methanolysis yielded the corresponding tetraester **244** (Scheme 39). Similarly, the next higher vinylog [4]-dendralene **6** on DA reaction with DMAD (**28**) followed by aromatization using DDQ gave the phenanthrene hexaester **247** (Scheme 40).

Dendralenes also found their application in total synthesis. Shenvi and co-workers have described the synthesis of a potent antimalarial amphilectene **253** in seven steps starting with readily available starting materials.[69] In this regard, the dendralene **248** was reacted with methyl ester **249** (dienophile) in the presence of Yb(OTf)$_3$ to yield the cross-conjugated enone, which underwent the second DA reaction to give the tricyclic product **250**. The compound **250** was then subjected to the modified Krapcho decarboxylation to remove the methyl ester, then conjugate addition, followed by the Grignard reaction gave **251**. Later, trimethylsilylmethyl cerium chloride addition to ketone **251** and selective trifluoroacetylation of tertiary alcohol gave **252**, which on treatment with a Lewis acid

such as Sc(OTf)$_3$ and TMSCN gave the target molecule **253** (Scheme 41).

Another interesting application of dendralene involving cycloaddition reaction has been reported. To this end, Sherburn et al. disclosed the first heteroatom-based cyclo-addition to [3]dendralene.[70] Vasella's nitroso-sugar **254** on reaction with the [3]dendralene **5** gave bicyclicoxaxine **255**, then the protection, diastereoselective dihydroxylation, and deprotection/ring-opening/*N*-methylation furnished an enan-tiomerically pure (+)-diaminotetrol **258** (Scheme 42).

A new approach to the synthesis of [3]dendralene derivative **260** was reported from the (*Z*) 3-bromopentadienyltrimethyl-silane via the formation of alcohol **259**. Later, the dendralenes **260** with different activated dienophiles on tandem DA reaction delivered the tetracyclic structures **261**−**264** as a single dia-steromer (Scheme 43).[71] Similarly, the double DA reaction of the dendralene **265** gave a single diasteromer, **268**, in moderate yield (Scheme 44).

Organo-catalyzed cascade involving two DA reactions was reported by Sherburn and co-workers.[72] The [4]dendralene **6** was reacted with acrolein **269**, and further reduction of the DA adduct with sodium borohydride furnished a bicyclic building

Scheme 44. Double DA Reaction on the Dendralene 265
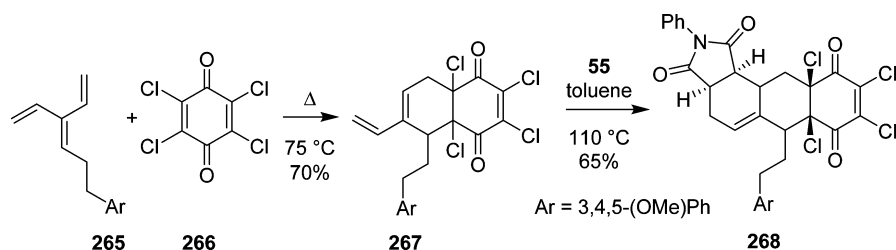
Scheme 45. DA Reactions of Dendralene 6
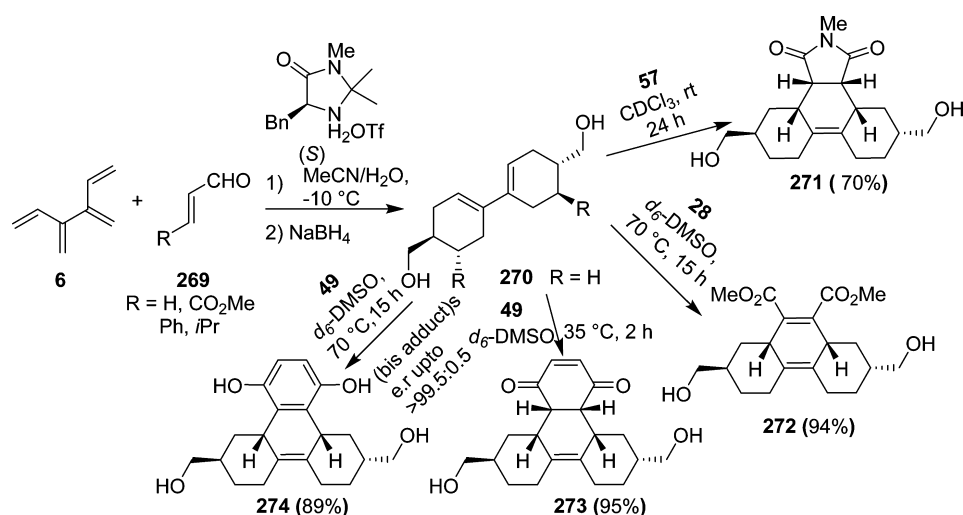
Scheme 46. Tandem DA Reaction of Furan-Containing Dendralene with Maleimide
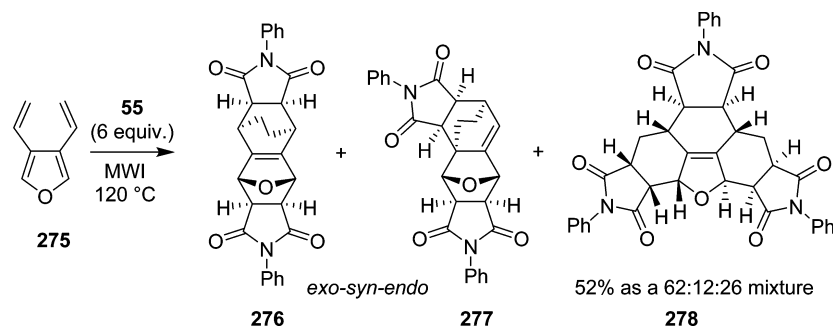
block, **270**, with four new C—C bonds. A similar reaction was observed with [6]- and [8]-dendralene, and the products were obtained in very high enantioselectivity, in accordance with the Horeau principle.[73] The bicyclic compound **270** reacted readily with various dienophiles, such as N-methylmaleimide (**57**), DMAD (**28**), and 1,4-benzoquinone (**49**), to generate enantiomerically enriched triple cycloadducts **271**−**274**, multicyclic systems containing aliphatic and aromatic rings, in high yield (Scheme 45).

Paddon-Row and co-workers have reported a tandem DA reactions of furan-based dendralenes with the maleimide under microwave irradiation conditions.[74] To this end, the furanodendralenes, 3,4-divinylfuran **275** was synthesized from 3,4-dibromofuran and vinyl magnesium bromide by the nickel-catalyzed Kumada−Tamao−Corriu cross-coupling reaction. Thus, the microwave-assisted DA reaction of furanodendralene **275** with N-phenylmaleimide (**55**) gave three different DA products, such as **276**−**278**. Products **276** and **277** were formed

through the DA reaction, followed by 6π-electrocyclization and subsequent DA reaction. The product **278** was formed as a single stereoisomer through a triple DA sequence (Scheme 46).

■ OUTER-RING DIENES

Outer-ring dienes are useful to generate linearly fused aromatics. The general approaches for their preparation are shown in Figure 6. General methods toward the preparation of outer-ring dienes include the coupling of diiodo derivatives with active methylene compounds,[75] CEM of cyclic alkynes with alkene,[18] iridium-catalyzed cycloisomerization of enyne substrate,[79] and elimination reactions (Figure 6).

Indane is an important structural unit present in several bioactive targets. Indane-based AAA is considered a constrained analog of phenylalanine. Various approaches to the indane-based AAA derivatives have been demonstrated by strategic utilization of metathesis, [2 + 2 + 2] cyclotrimerization, and the DA reaction as key steps. On the basis of this, it was shown that
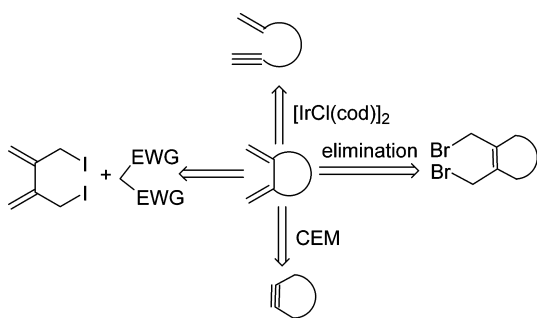
Figure 6. General approaches to outer-ring dienes.

the DA approach involving the 5-membered outer-ring diene is useful to generate linearly annulated and highly functionalized indane-based AAA derivatives, and it is applicable to generate molecular diversity.[75] In this regard, a five-membered outer-ring diene containing AAA building block 282 was prepared by simple synthetic transformations from 2,3-dimethyl-1,3-butadiene. The tetrabromide 279 was prepared by 1,4-addition of bromine to 2,3-dimethyl-1,3-butadiene, followed by allylic bromination of 1,4-addition product, and then it was converted to the diiodo compound 280 by reductive debromination. Later, alkylation of EICA (91) with the diiodo compound 280 gave the diene 281, which was hydrolyzed, and the amino functionality was protected with an acetyl group. Then the DA reaction of this diene 282 with various dienophiles delivered the expected DA adducts, which on oxidation with DDQ gave conformationally constrained indane-based AAA derivatives 283 (Scheme 47).

To expand new synthetic strategies to spirocyclics,[76] a key diene building block, 285, was prepared by direct alkylation of the 1,3-indanedione (284) with 2,3-bis(iodomethyl)buta-1,3-diene (280) under PTC conditions. Treatment of the diene 285 with various dienophiles under toluene reflux conditions gave the aromatized products 286 without involvement of any oxidizing agent (Scheme 48).[77] This strategy may be extended for the synthesis of various indane-based biologically active molecules.

The seven-membered outer-ring diene was also prepared via double ortho ester Claisen rearrangement of 2-butyne-1,4-diol (287) with triethyl orthoacetate (Scheme 49).[75] The reduction of the ester 288 with LAH, followed by tosylation, gave the ditosylate 289, then the ditosylate 289 was treated with sodium iodide in acetone to generate the diiodo compound 290. Later, alkylation of EICA (91) with the diiodo compound 290 under PTC conditions gave the required coupling product 291, which

was hydrolyzed, and the amino functionality was protected with an acetyl group. Further, the DA reaction of the diene 292 with three dienophiles delivered the expected DA adducts, which on dehydrogenation with DDQ gave conformationally constrained benzocycloheptane-based AAA derivatives 293. The synthesis of these AAA derivatives is not easy by conventional methods, such as the Bucherer−Burgs method, because preparation of the required keto precursor is not a trivial exercise. By utilizing a similar strategy, one can generate a library of linearly fused unnatural AAA derivatives or polycycles in an efficient manner.

Recently, we reported a crownophane-based diene, such as 295, by CEM starting from the commercially available dihydroxybenzenes in two steps (Scheme 50 and 51).[78] The diene 295 was generated by CEM of the corresponding diacetylenic derivative 294, and the DA reaction of the diene 295 with DMAD (28) under toluene reflux conditions gave the cycloadduct. Subsequent aromatization of the cycloadduct with DDQ gave the crownophane 296. Along similar lines, ortho- and meta-crownophanes were assembled.

Several crownophanes are reported by the application of the same protocol, and in this regard, the required diene 298 has been generated by CEM of acetylene derivative 297 using G-II catalyst under ethylene atmosphere. Later, the DA reaction of the diene 298 with DMAD (28) under toluene reflux conditions, followed by aromatization with DDQ, gave the functionalized crownophane 299 (Scheme 51). Along similar lines, ortho- and meta-crownophanes were also assembled.

Yamamoto et al. have reported the synthesis of various polycyclic pyrrole-2-carboxylates, such as 306, by a domino coupling relay approach. The key enyne building blocks 303 were prepared from the N-benzylallylamine (300), ethyl glyoxalate (301), and the alkyne 302 through Cu-catalyzed Mannich condensation, then the glycine-based enyne substrates on iridium-catalyzed cycloisomerization gave the exocyclic dienes, which were trapped in situ with N-phenylmaleimide (55) to produce a library of pyrrole-2-carboxylates 306 via the DA strategy (Scheme 52). Here, they have demonstrated a diversity in this sequence with several types of alkynes and other dienophiles, such as maleic anhydride 63 (52%) and 1,4-naphthoquinone 50 (35%), to generate various polycyclic pyrrole-2-carboxylates.[79]

In Situ Generated Outer-Ring Dienes (o-Xylylene or o-QDM). o-Xylylene or o-quinodimethane (o-QDM) has attracted a considerable amount of interest in aromatic chemistry because of its high reactivity in the DA reaction. Various approaches to this transient intermediate include dehalogenation of α,α′-dihalo-o-xylenes and thermal or photochemical extrusion of stable molecules, such as N2, CO, CO2, SO2, from the corresponding aromatic precursor or ring opening of

Scheme 47. Synthesis of Conformationally Constrained Indane-Based AAA Derivatives 283

Dienophile	28	31	50
Yield (%)	97	96	89
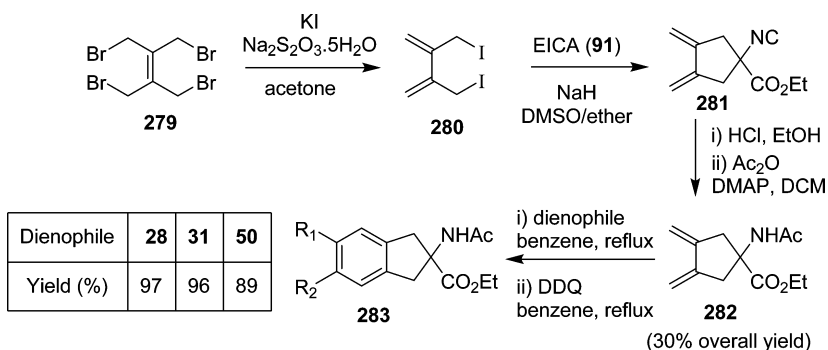
Scheme 48. Synthetic Strategy to Spirocyclic Compounds

Dienophile	28	30	31	49	50	55
Yield (%)	87	53	54	45	75	65
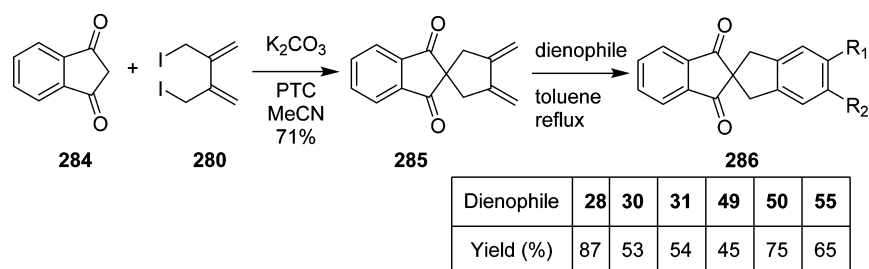
Scheme 49. Synthesis of Conformationally Constrained AAA Derivatives 293

Dienophile	28	31	50
Yield (%)	99	92	74
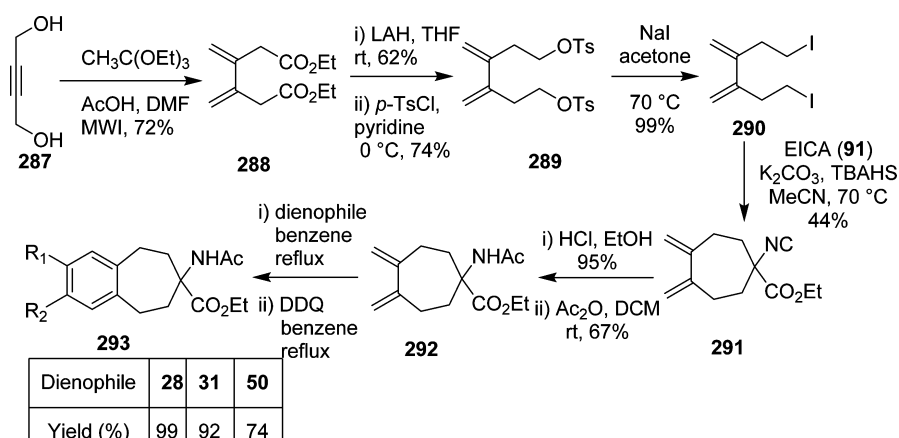
Scheme 50. Synthesis of Crownophane 296 by CEM and DA Approach
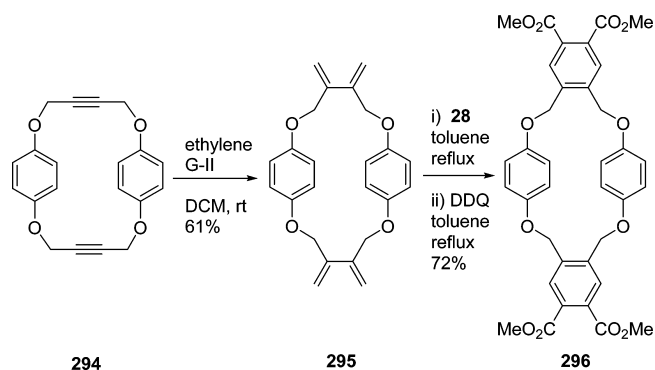
benzocyclobutenes (Figure 7).[80] In 1991, Hoey and Dittmer reported the synthesis of sultine derivative using rongalite (HOCH$_2$SO$_2$Na) under phase-transfer catalysis (PTC) conditions, and they have shown the generation of o-QDM at the

relatively low temperature of ~80 °C.[81] Interestingly, the benzosultines and benzosulfones open up under mild reaction conditions, as compared with other o-xylylene precursors, such a benzocyclobutenes. In our studies, we have used some of these precursors extensively for the generation of o-QDM derivatives, and then they were trapped with different dienophiles in a DA fashion to generate the diverse polycycles.

To design various polycyclics and unusual AAA derivatives via rongalite,[16] a tetralin-based AAA derivative (which is a constrained analog of Phe) has been prepared by the DA reaction between o-QDM precursor and methyl 2-acetamidoacrylate (36) (Scheme 53).[82] The dienophile, methyl 2-acetamidoacrylate (36) is heat-sensitive, so the DA reaction should be carried out at a relatively low temperature. To this end, various dibromo compounds 307 were converted to the sultine derivatives 308 by treatment with sodium hydroxymethanesulfinate (rongalite), then thermal activation of sultine delivered the o-QDM's 309, which on reaction with methyl 2-acetamidoacrylate (36) gave the desired tetralin-based AAA derivatives 310. To produce a library of tetralin-based AAA derivatives, several sultine derivatives were

Scheme 51. Synthesis of Crownophane 299 by CEM and DA Approach
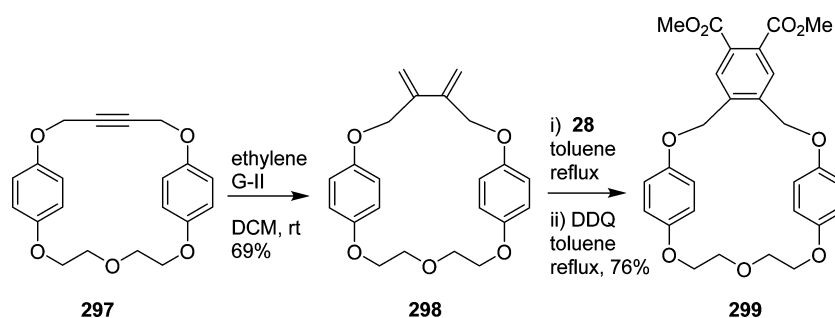
Scheme 52. Approach to Polycyclic Pyrrole-2-carboxylates 306 via DA Reaction

R =	Ph	^{n}Bu	-CH$_2$OMe	-(CH$_2$)$_3$OMe	-(CH$_2$)$_3$Cl	-(CH$_2$)$_3$CO$_2$Me	ferrocene	^{n}Bu
X=	NPh	NPh	NPh	NPh	NPh	NPh	NPh	O
Yield (%)	54	62	41	51	62	74	54	52
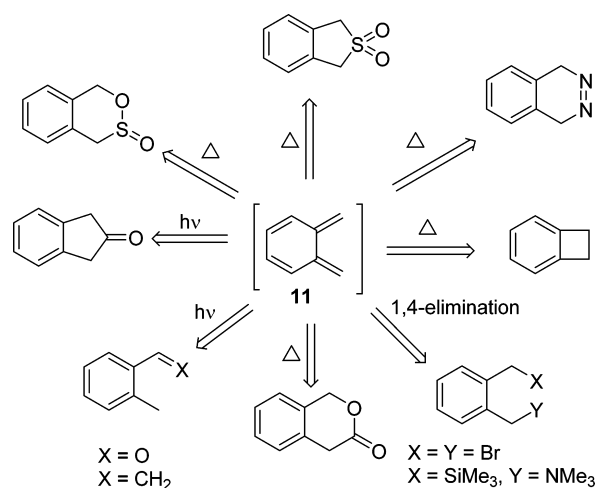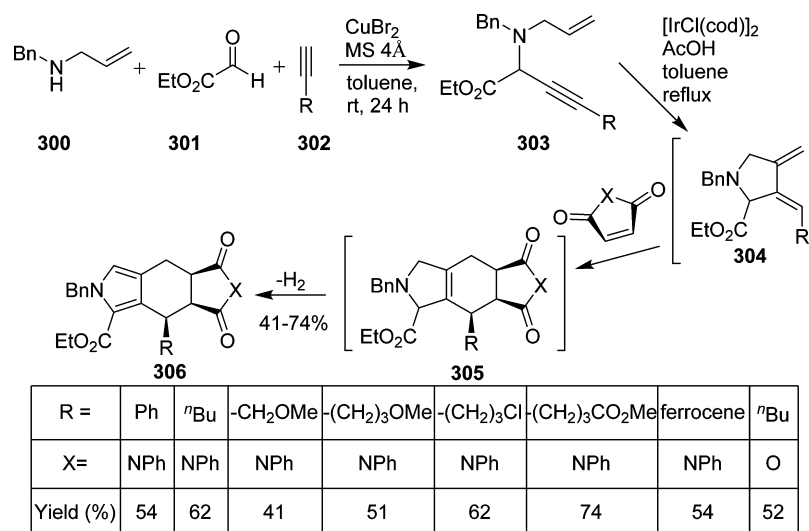
Figure 7. Diverse approaches to *o*-quinodimethane (*o*-QDM) intermediate.

assembled to generate the corresponding *o*-xylylene derivative, and later, they were trapped with methyl 2-acetamidoacrylate (**36**) to generate a variety of tetralin-based AAA derivatives. Our recent review has covered various other type of reactions using this building block, **36**.[17a]

The AAA derivative containing halogen atoms in a benzene ring has been further modified by the SM cross-coupling reaction.[32] The diiodo-substituted tetralin-based AAA derivative **310d** was treated with various aryl and heteroaryl boronic acids to assemble highly functionalized unusual AAA derivatives **311** by a short synthetic sequence in good yields (Scheme 54).[82]

Because the polyhalogenated compounds play a critical role in bioorganic chemistry, this DA strategy has been extended to these molecules. To this end, the polyhalogenated sultine derivatives **313** were prepared from bromomethyl derivatives **312**, and their DA reaction with different dienophiles gave diverse polyhalogenated compounds **315−317**. By utilizing this strategy, various polyhalogenated AAA derivatives **316** were prepared by

Scheme 53. Synthesis of Library of Tetralin-Based AAA Derivatives

a R$_1$= R$_4$ = H   R$_2$ = R$_3$ = H

b R$_1$= R$_4$ = OMe R$_2$ = R$_3$ = H

c R$_1$= R$_4$ = H   R$_2$ = R$_3$ = Br

d R$_1$= R$_4$ = H   R$_2$ = R$_3$ = I

e R$_1$= R$_4$ = H   R$_2$ = R$_3$ = Me

f R$_1$= R$_4$ = H, R$_2$ = R$_3$ =

g R$_1$= R$_4$ = H R$_2$ = R$_3$ =

h R$_1$= R$_4$ = H R$_2$ = R$_3$ =

i R$_1$= R$_4$ = H R$_2$ = R$_3$ =

j R$_1$= R$_4$ = H R$_2$ = R$_3$ =
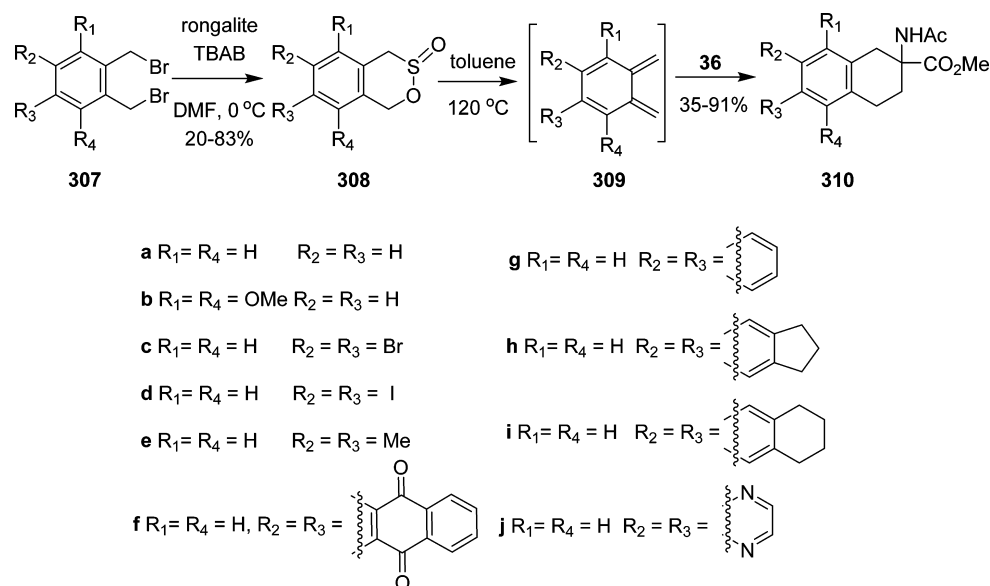
Scheme 54. Modification of Tetralin-Based AAA Derivative 310d by SM Cross-Coupling
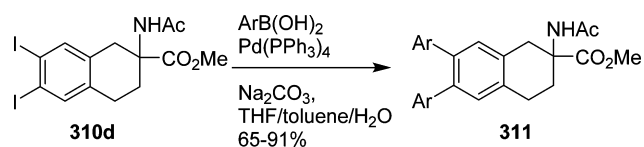
trapping the *o*-xylylene intermediate **314** with methyl 2-acet-amidoacrylate (**36**) (Scheme 55).[83]

To devise various synthetic routes to polycycles via the DA strategy and the SM cross-coupling, we started with diiodo-benzosultine **308d**, and it was prepared from the corresponding bis(bromomethyl) derivative **307d** involving rongalite. A SM cross-coupling reaction of **308d** with various aryl boronic acids gave different sultine derivatives **318**. Further, the DA reaction of these sultine derivatives **318** with two different dienophiles followed by aromatization gave the functionalized polycycles **320** (Scheme 56).[84]

The DA reaction in combination with a [2 + 2 + 2] cyclo-addition reaction has been used to synthesize various indane-based AAA derivatives.[85] The key precursor, indane-based sultine **324**, has been prepared from the dibromo compound **323**, which was assembled by [2 + 2 + 2] cotrimerization of the dialkyne building block **321** and the 2-butyne-1,4-diol (**287**). Here, use of the 2-butyne-1,4-diol (**287**) as a cotrimerization partner is critical to prepare the sultine derivative, whereas the DMAD usage generates a precursor that contains incompatible functional groups for the generation of the sultine precursor. Then, the DA reaction of the sultine **324** with different dienophiles gave various AAA derivatives, which on aromatiza-tion gave benzannulated AAA derivatives **326**. The indane-based sultine derivative **324** was also reacted with an amino acid-containing dienophile, such as methyl 2-acetamidoacrylate (**36**), to produce the diamino acid derivative **327** and also with fullerene (C$_{60}$) to generate the fullerene-based AAA derivative **328** (Scheme 57). Later, indane-based AAA derivative **324** containing the sultine moiety was converted to the sulfone derivative **329** by thermal rearrangement (Scheme 58). This methodology has been further utilized to prepare a library of highly functionalized indane-based targets. In another occasion, Roglans and co-workers used the same strategy for the syn-thesis of nonproteinogenic AAA derivatives.[86] Similarly, Dieters and co-workers used a [2 + 2 + 2] cotrimerization strategy for assembling various unnatural indanone derivatives.[87] Further, a

C$_{70}$ fused-indane derivative has been prepared by a similar approach because with its hydrophobic nature, one would anticipate several biological applications, and moreover, full-erene can also act as an electron sink.[88]

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) is an important, unusual AAA used in opioid receptor studies. In this regard, a sequential usage of [2 + 2 + 2] cotrimerization and a [4 + 2] cycloaddition strategy have been extended to generate various Tic-based AAA derivatives (Scheme 59).[89] To this end, the Tic-based diol **331** was assembled from the 2-butyne-1,4-diol (**287**) and the dialkyne building block **330** by utilizing rhodium-catalyzed [2 + 2 + 2] cotrimerization. Then, the diol **331** was converted to the dibromide **332**, which on treatment with rongalite gave the sultine derivative **333**. Heating the sultine **333** produced the *o*-xylylene intermediate **334**, which on reaction with various dienophiles gave the corresponding DA adduct, which on aromatization gave a highly functionalized Tic-based AAA derivative, such as **335**. Recently, Dixneuf and co-workers reported various fluorinated Tic derivatives by utilizing a [2 + 2 + 2] cotrimerization approach.[90]

Variation of the aromatic portion of the benzo crown ether moiety is not a trivial exercise. For this challenge, two crown ether derivatives were modified by the DA reaction using rongalite chemistry. To this end, the bis(bromomethyl)benzo-crown ether **336** has been prepared by bromomethylation of benzo-15-crown-5 ether, and then it was converted to the sulfone derivative **337** by using rongalite under PTC condi-tions. Heating the sulfone derivative **337** with various dienophiles delivered the annulated benzo-15-crown-5 ethers **339** in good yield without any oxidizing agent for an aromatization sequence (Scheme 60).[91]

Along similar lines, we have also annulated the benzo-18-crown-6 ether via the DA reaction using rongalite (Scheme 61).

Design of hybrid molecules that are capable of generating *o*-QDM precursors in a sequential manner is of great interest for generating unsymmetrical quinone derivatives useful for material science applications. These hybrid molecules contain-ing benzosultine, benzosulfone, and BCB moieties are em-bedded in the same molecule and, hence, are capable of producing *o*-QDM precursor selectively because benzosultine, benzosulfone, and benzocyclobutene open at different temper-ature. Therefore, three possible combinations were identified: BCB-sultine **344**, BCB-sulfone **346**, and sultine−sulfone system **347** (Scheme 62). By employing a temperature-controlled regioselective opening of one end of these hybrid molecules

Scheme 55. Synthesis of Various Polyhalogenated AAA Derivatives 316

X =	Br	Cl	F
Dienophile		Yield	(%)
28	65	67	66
35	42	53	48
36	51	50	63
50	50	--	--
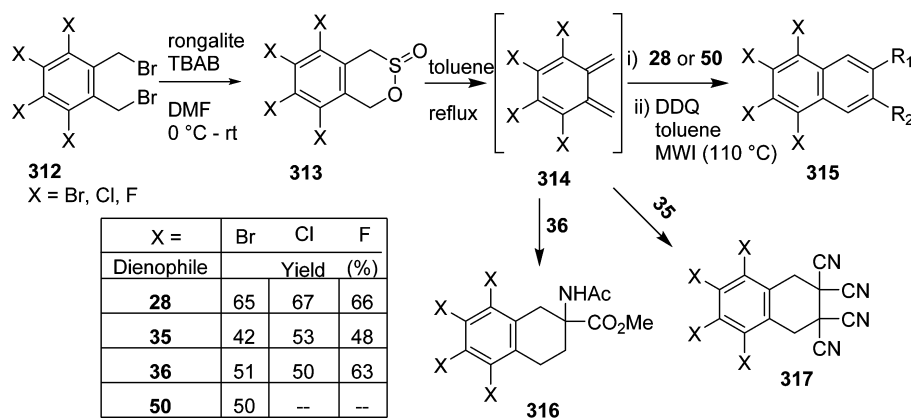
Scheme 56. Synthesis of Highly Functionalized Polycyclic Compounds 320 Using DA and SM Strategy

Ar = Ph, 26%
Ar = 3-CF$_3$-Ph, 31%

Dienophile	28	50
Yield (%)	78	41
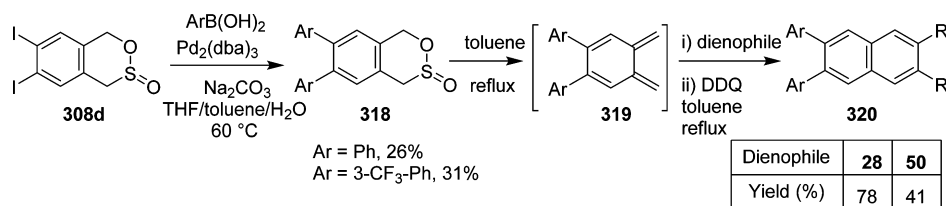
Scheme 57. DA Chemistry Involving *o*-Xylylene Intermediate 325

Dienophile	28	30	49	50	51	55
Yield (%)	78	43	90	89	92	96
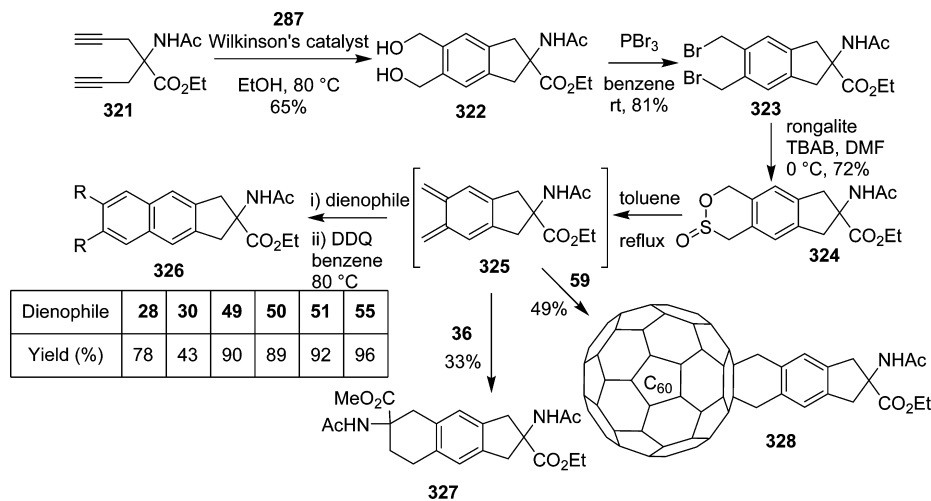
Scheme 58. Thermal Rearrangement of Sultine Derivative 324 to Sulfone Derivative 329

Scheme 60. Synthesis of Annulated Benzo-15-crown-5 Ethers 339 via 338

Dienophile	28	50
Yield (%)	58	64
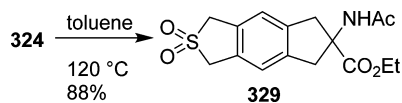
(344−347) and trapping the resulting *o*-xylylene intermediate with appropriate dienophiles, one can generate the BCB or sulfone-based benzannulated products. Moreover, these building blocks are also useful for the preparation of a library of BCB and benzosulfone derivatives. These are useful precursors for realizing a temperature-controlled DA reaction in a stepwise manner containing two different latent diene moieties. However, in the case of bis(*o*-QDM) precursors containing the same latent diene derivatives,[92] a regioselective opening was not observed.

Scheme 59. Synthesis of Functionalized Tic-Based AAA Derivatives via 334

Dienphile	28	49	50	51	52
Yield (%)	70	71	77	82	72
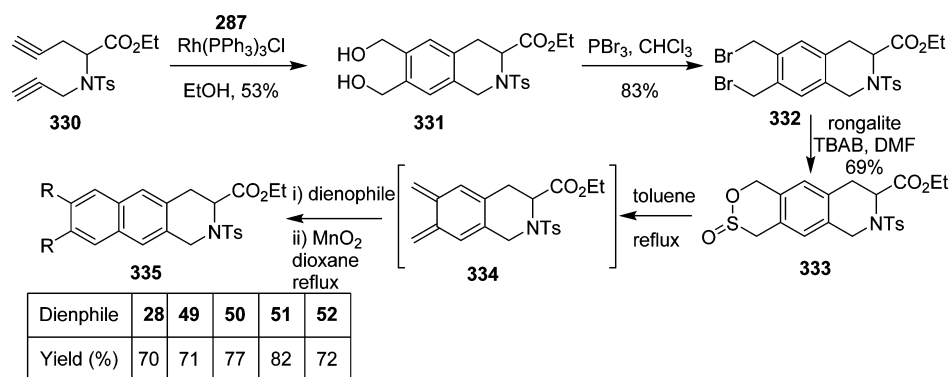
Scheme 61. Annulation of Benzo-18-crown-6 Ether via the DA Approach

Dienophile	28	50	51
Yield (%)	63	67	62
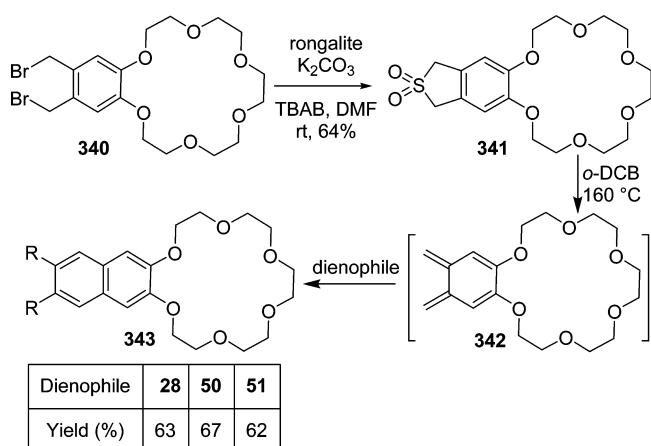
Scheme 62. Regioselective Opening of Hybrid Molecules 344, 346, and 347
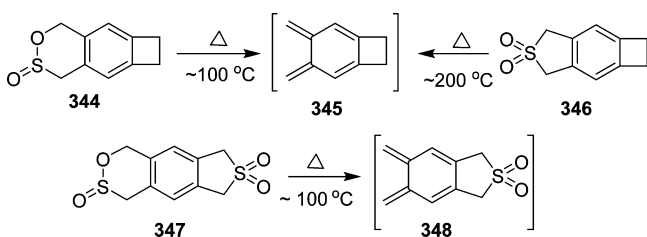
Synthesis of BCB[93]-based sultine **344** and sulfone **346** were assembled by a transition metal-catalyzed [2 + 2+2] cotrimerization as a key step.[94] To this end, the diester **349** was prepared from the respective dialkyne and DMAD (**28**), involving [2 + 2 + 2] cotrimerization under high dilution conditions. Subsequently, the diester **349** was reduced to the corresponding diol, which was converted to the dibromide **350**, as a key precursor for the generation of BCB-based sultine **344**. The dibromide **350** was then converted to the BCB-based sultine **344** by treatment with rongalite, and its regioselective DA reaction on the sultine side with DMAD (**28**) yielded the
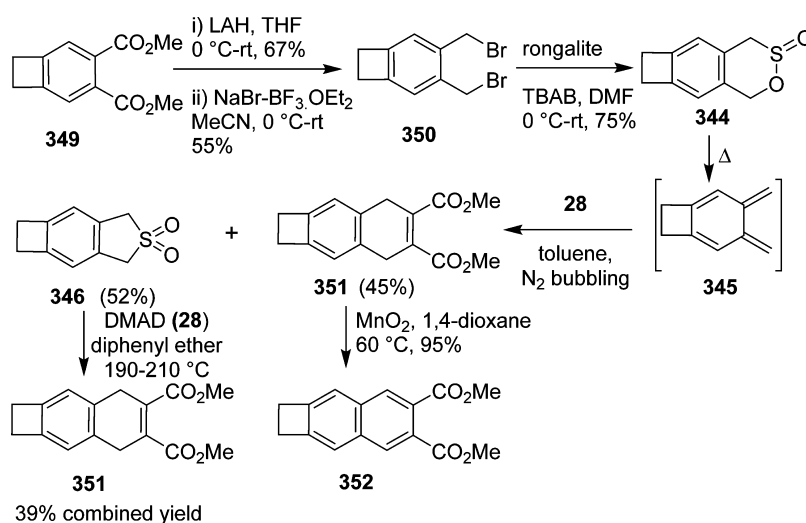
expected DA adduct **351** along with the rearranged BCB-based sulfone **346**. Next, the BCB-based sulfone **346** was also treated with DAMD (**28**) at high temperature to obtain the same BCB-based DA adducts **351**, which on aromatization with MnO$_2$ gave the benzannulated product **352** (Scheme 63).

The above strategy has been further extended to the synthesis of various annulated benzocycloalkane-based AAA derivatives by utilizing the corresponding dialkyne derivative using a [2 + 2 + 2] cotrimerization step and the DA reaction of sultine derivative **353** with methyl 2-acetamidoacrylate (**36**) to generate the unusual AAA derivatives **355** (Scheme 64).[95]

Scheme 64. Synthesis of Benzocycloalkane-Based AAA Derivatives
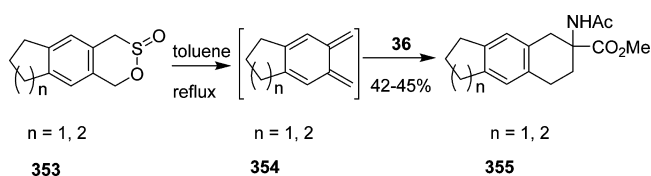
To design bis(o-QDM) precursors, another key building block was assembled from the bis(bromomethyl) compound **356**, which can be prepared either from **108** or from the DA reaction of 2,3-dimethyl-1,3-butadiene and DMAD (**28**), followed by the benzylic bromination of the aromatized DA product. Later, the dibromide **356** was treated with rongalite to generate the sultine derivative **357**. Subsequently, it was rearranged to sulfone **358** by heating in toluene in the absence of a dienophile. A selective reduction of ester groups present in **358** in the presence of sulfone moiety was achieved by using KBH$_4$/LiCl in refluxing THF to produce the diol **359**. The diol containing sulfone **359** was treated with phosphorus tribromide to deliver the dibromosulfone **360**. Finally, the dibromide **360** was converted to the target benzosultine−sulfone building block **347** by treatment with rongalite (Scheme 65).[30]

Next, a regioselective opening of the sultine portion of the hybrid molecule **347** and trapping of the resulting o-xylylene intermediate **348** in a DA fashion with DMAD (**28**) or methyl-2-acetamidoacrylate (**36**) produced the corresponding sulfone-based building blocks (**361−362**). These sulfone derivatives **361** and **362** can be further utilized to design various

Scheme 63. DA Chemistry of 344

Scheme 65. Synthesis of Benzosultine-sulfone Building Block 347
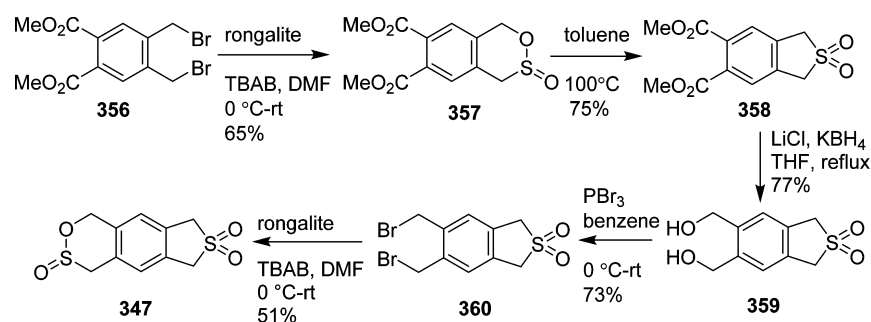
Scheme 66. Regioselective DA Reaction of the Building Block 347
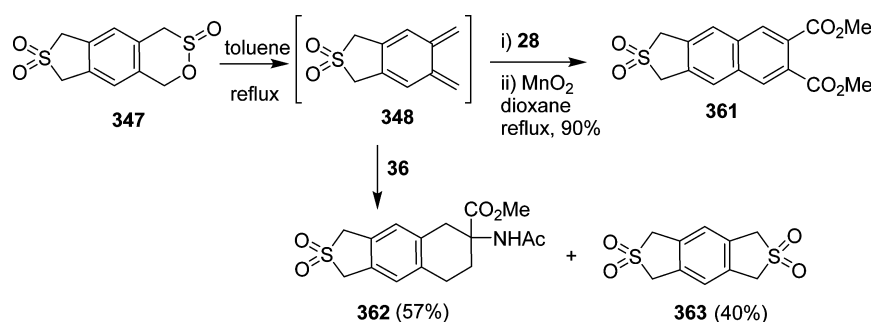
Scheme 67. DA Chemistry of 365
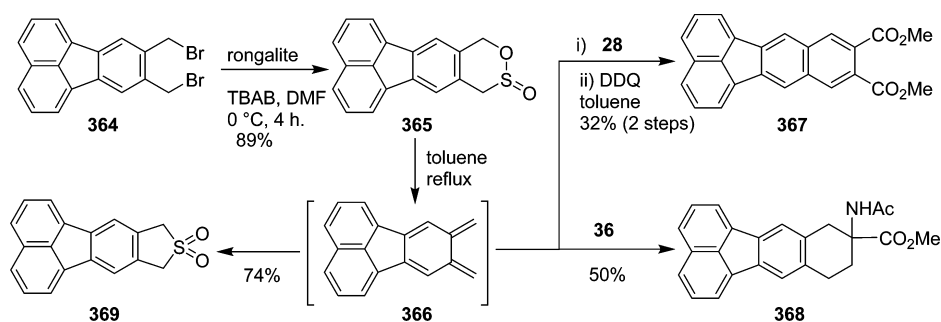
Scheme 68. DA Reactions of the *o*-Xylylene Intermediate 374

Dienophile	28	50	55
Yield (%)	63	61	68
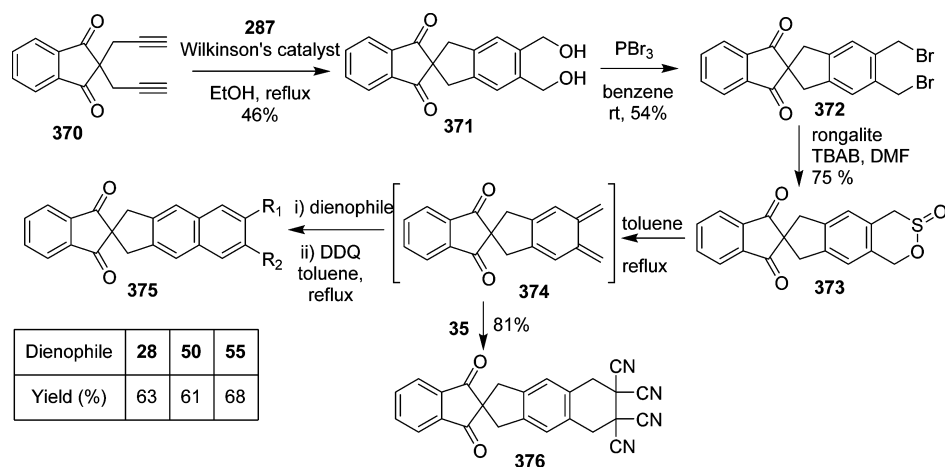
polycyclics (Scheme 66). The DA reaction with methyl-2-acetamidoacrylate (36) gave the disulfone 363 as a side product due to the low reactivity of the dienophile.

Fluoranthene-fused polycycles exhibit interesting photochemical and electrochemical properties. Recently, we assembled

flouranthene-fused sultine 365 from the corresponding bis-(bromomethyl) derivative 364 using rongalite under PTC conditions. Then, the DA reaction of 365 with DMAD (28), followed by dehydrogenation, gave the flouranthene-fused diester 367 and with methyl-2-acetamidoacrylate (36) delivered the

Scheme 69. DA Reactions of the *o*-Xylylene Intermediate 382

Dienophile	28	49	55
Yield (%)	73	70	86
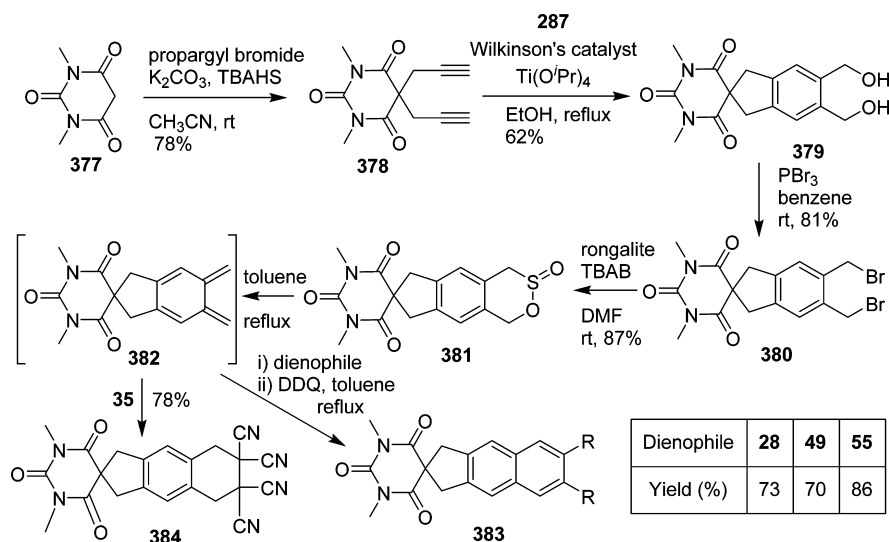
Scheme 70. Trapping of *o*-Xylylene Derivatives 389 with Various Dienophiles

R =	C₆H₄	C₆H₄	C₆H₄	C₃H₆	CH₂C(Me)₂CH₂	CH₂C(Me)₂CH₂
Dienophile	28	35	50	35	28	35
Yield (%)	89	68	84	89	72	95
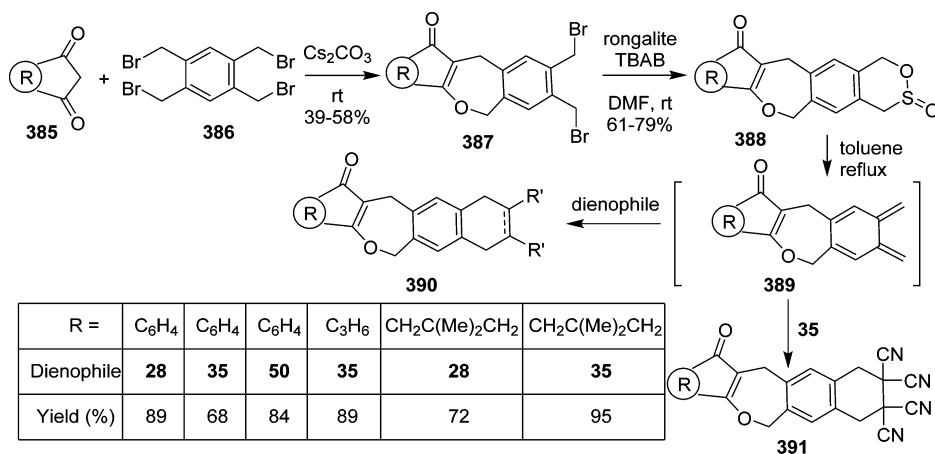
AAA derivative **368**. Later, the flouranthene-fused sultine **365** was converted to the corresponding sulfone derivative **369** by thermal rearrangement (Scheme 67).[96]

We have also prepared the spiro diene intermediate **374** via sultine derivative **373**. To this end, the diol **371** was assembled by a [2 + 2 + 2] cotrimerization of 1,3-indanedione-based dialkyne **370** and 2-butyne-1,4-diol (**287**) using the Wilkinson catalyst. Later, the diol **371** was converted to the corresponding dibromide **372** using phosphorus tribromide, then the dibromide **372** on treatment with rongalite gave the sultine derivative **373**, which is a key precursor to the *o*-xylylene intermediate **374**. Capturing in situ generated diene **374** with various dienophiles or subsequent aromatization of the DA adducts using DDQ gave the polycycles **375−376** containing the spiro linkage in good yields (Scheme 68).[97] Along similar lines, spirobarbituric acid-based *o*-xylylene precursor **381** has been prepared, and its DA reaction with various dienophiles was also reported (Scheme 69).[98]

To expand the spiro strategy with the tetrabromide **386**, we attempted to dialkylate the 1,3-diketo compounds, such as **385**, using the tetrabromide **386** under basic conditions. However, in the case of 1,3-indanedione, 1,3-cyclohexadione, and 5,5-dimethyl 1,3-cyclohexadione, we isolated the *C* and *O*-alkylated products **387**, then the dibromides **387** were converted to the

corresponding sultine derivatives **388** by rongalite under PTC conditions, and later heating of the these sultine derivatives gave the diene intermediates **389**. Subsequent trapping of *o*-xylylene derivatives **389** with different dienophiles, such as DMAD (**28**), 1,4-naphthoquinone (**50**) and TCE (**35**), gave the expected DA adducts **390** and **391** (Scheme 70).[99]

In 2000, Chung and co-workers demonstrated the DA reaction of heterocyclic *o*-QDM with electron-poor olefins and fullerene (C₆₀).[100] In this regard, the sultines **392** were heated in a sealed tube with various dienophiles to deliver the DA adducts (**393−396**) in good to excellent yields (Scheme 71).

Fullerene (C₆₀) and its derivatives have a wide range of applications in the material science, electronics, and nanotechnology areas. In 1995, Martin and co-workers reported methods for functionalization of the fullerenes by a microwave-assisted DA reaction involving a sultine intermediate under mild reaction conditions that involved generation of *o*-QDM at low temperature. Thus, the *p*-dialkoxy-substituted sultine **397** was prepared by using rongalite, and at a later stage, the sultine derivative was subjected to DA reaction with the fullerene in a microwave oven under toluene reflux conditions to obtain an electroactive fullerene derivative **399** (Scheme 72).[101]

Similarly, they reported the synthesis of several novel electron acceptor organofullerene derivatives by the DA reaction of

Scheme 71. DA Reaction of Heterocyclic *o*-QDM
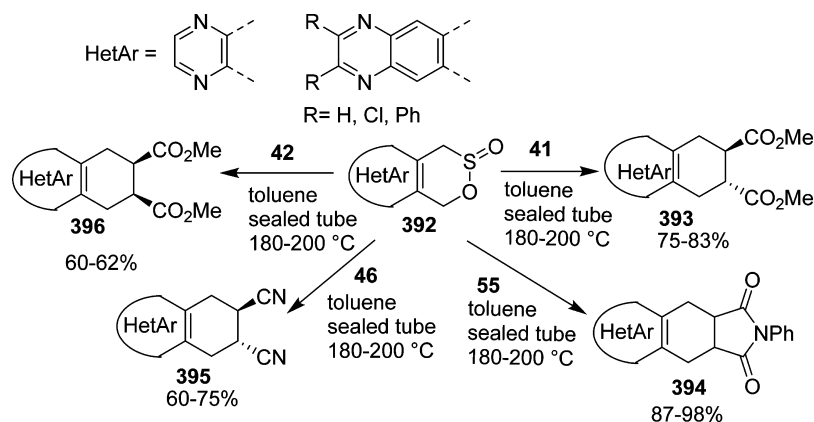
Scheme 72. Synthesis of Electroactive Fullerene Derivative 399
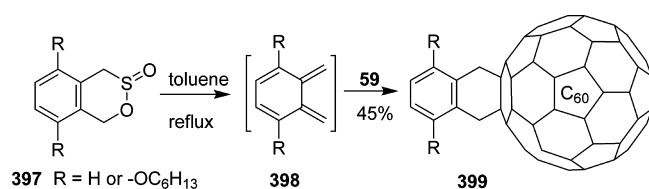
fullerene with various hydroquinone sultine derivatives. The sultine derivatives **400** were subjected to the DA reaction under toluene reflux conditions to obtain the DA adducts **402**; the methoxy groups were deprotected with BBr$_3$ to produce the hydroquinone derivatives **403** and further oxidized with DDQ to deliver benzoquinone-C$_{60}$ adduct **404** (Scheme 73).[102] This type of *p*-benzoquinone−C$_{60}$ adducts is the valuable precursors for the organofullerene acceptors derived from tetracyano-*p*-quinodimethane (TCNQ) and dicyano-*p*-quinonediimine (DCNQI).[103]

Fillion and co-workers have reported one-pot synthesis of tetrahydrofluorenones **406** by a sequential usage of DA reaction and Friedel−Crafts acylation. The DA reaction of benzosultine **308a** with various alkylidene Meldrum's acids **405**, followed by the Friedel−Crafts acylation, gave a variety of tetrahydro-fluorenones **406** (Scheme 74).[104] By utilizing this strategy, they have prepared a library of tetrahydrofluorenone derivatives. Some of these tricyclic systems are basic structural units found in norditerpenoid natural products.

Yoshida and co-workers have used borylalkenes as efficient dienophiles in a cycloaddition reaction with *o*-QDM to generate diverse boryltetralins.[105] 2-[(Trimethylsilyl)methyl]-benzyl phenyl carbonate **407** was used as a precursor to generate *o*-QDM in situ, which when reacted with (*E*)-borylalkenes **408** gave the cycloaddition product, 3-substituted-2-boryltetralin **409**. The configuration between the alkyl or aryl and boryl substituent in the product **409** was found to be anti, which suggests that the (*E*)-stereochemistry of the dienophile was retained during the reaction sequence. The DA adducts **409** were aromatized using NBS or DDQ to 3-substituted-2-boryl naphthalenes **410** (Scheme 75), and further functionalization can be achieved by the SM cross-coupling reaction.

Further progress in the DA reaction of the *o*-QDM intermediate was expanded to an asymmetric DA reaction under chiral catalysis conditions by various groups in the past decade.[106] This aspect is well suited for the synthesis of enantiopure bioactive compounds under mild reaction conditions.

■ INNER-OUTER-RING DIENES

Inner-outer-ring dienes are critical in generating the angularly appended frameworks. The general methods for their preparation are shown in Figure 8. They have been assembled by various methods, which include RCEM of enyne substrate; methylation of ester-containing molecules with Tebbe reagent; Wittig reaction on conjugated aldehyde; and finally, the Grignard reaction, followed by dehydration of cyclic ketones.[12]

Because various indane-based AAA derivatives are useful building blocks in bioorganic and medicinal chemistry, we have designed diverse angularly substituted indane derivatives by EM and DA reaction as key steps. These derivatives were prepared by DA reaction of the key inner-outer-ring diene building block with different dienophiles. To this end, the enyne building block **412** containing an AAA moiety was assembled by propargylation and allylation of the Schiff base **68** under PTC conditions, followed by acid hydrolysis and amino group protection by an acetyl group; however, a stepwise allylation and propargylation of the EICA (**91**) under PTC conditions gave a low yield of the final product. The alkylated product **413** was then hydrolyzed, and the amino group was protected as an acetyl derivative to generate the key enyne building block **412** (Scheme 76). RCEM of the enyne building block **412** using the G-I catalyst gave the five-membered inner-outer-ring diene building block **414** in good yield. The diene **414** on DA reaction with a variety of dienophiles followed by aromatization using DDQ delivered an angularly substituted indane-based AAA derivative, **415** (Scheme 77).[107] The Undheim group has reported various enyne-containing AAA moieties by enyne metathesis.[108] By varying the dienophile moiety during the DA reaction, one can generate angularly fused, diverse, unnatural amino acid derivatives and polycyclic compounds.

Along similar lines, angularly substituted 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives[109a,b] were also synthesized by EM and DA reaction conditions (Schemes 78 and 79).[109c,d] The enyne building blocks **417** and **420** were prepared from a Schiff base by a stepwise alkylation under mild reaction conditions. The RCEM of enyne building blocks **417** and **420** using G-I catalyst generates inner-outer-ring dienes **418** and **421**. Then, the DA reaction of these diene building blocks **418** and **421** with DMAD (**28**) and 1,4-naphthoquinone (**50**), followed by aromatization with DDQ, gave angularly substituted Tic derivatives **419** and **422** (Scheme 79). By this strategy, diverse Tic derivatives **419** and **422** were synthesized, which are not accessible by traditional methods, such as Pictet−Spengler or Bischler−Napieralski reactions.

Scheme 73. Synthesis of Organofullerene Derivatives by the DA Reaction
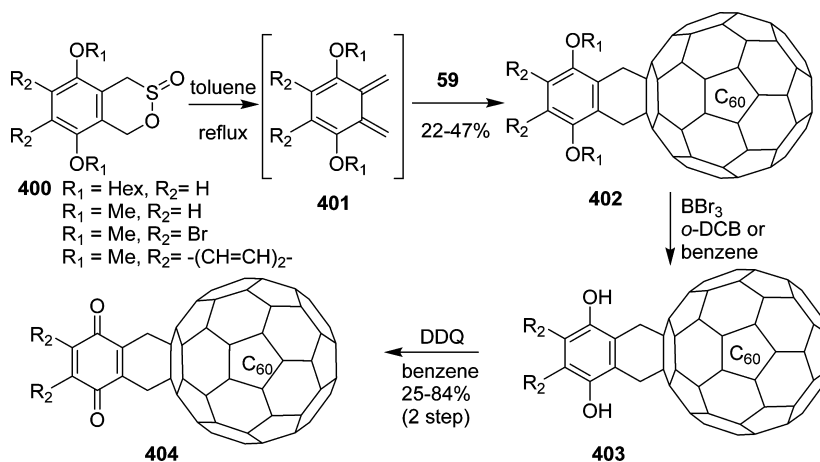
Scheme 74. One-Pot Synthesis of Tetrahydrofluorenones 406
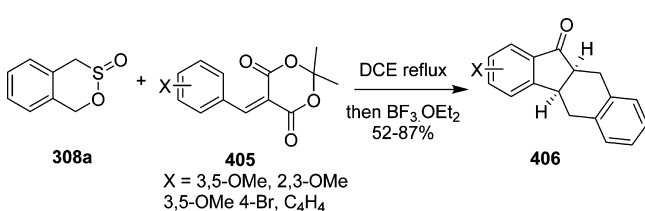
Scheme 75. Synthesis of Diverse 3-Substituted 2-Boryl Naphthalenes 410

Figure 8. General approaches to inner-outer-ring dienes.
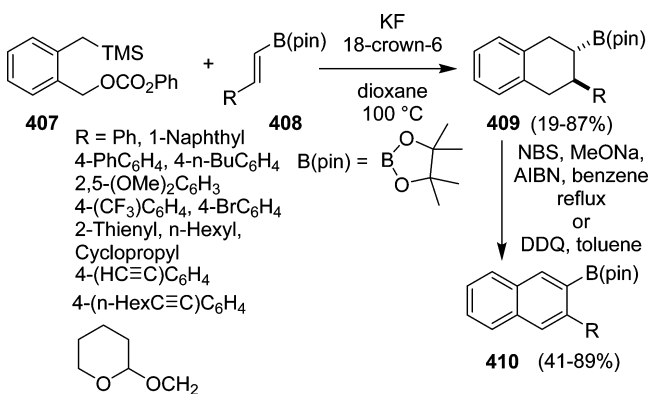
Scheme 76. Synthesis of Enyne Building Block 412
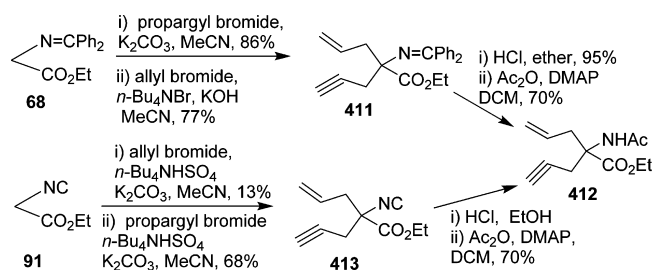
Later, a similar strategy was demonstrated to synthesize a higher analog of the Tic derivative by increasing the length of the alkenyl chain during the alkylation sequence (Scheme 80).[110] To this end, the propargylated glycine ester **70** was *N*-alkylated with 4-bromo-1-butene under mild reaction conditions, and G-II catalyst mediated RCEM of the resulting enyne building block **423** gave the key inner-outer-ring diene **424**. Later, the DA reaction of the diene **424** with DMAD (**28**) and subsequent oxidation of the DA adduct with DDQ gave a highly functionalized and conformationally constrained AAA derivative, **425**.

Claisen rearrangement in combination with metathesis protocol is also an important strategy to assemble various polycycles.[111] To realize the diversity oriented approach to biologically relevant molecular frameworks starting from commercially available β-naphthol was reported (Scheme 81).[112] The enyne building blocks **427** were prepared in a three-step sequence involving the *O*-allylation of β-naphthol and the Claisen rearrangement of the *O*-allylated product, followed by *O*-propargylation. Then RCEM of enyne building blocks **427** gave the expected inner outer-ring diene **428** in good yields. The DA reaction of these dienes **428** with different dienophiles gave annulated oxepine derivative **429**. This diversity oriented approach may find useful applications in design of druglike molecules.

Recently, we employed a RCEM for the generation of indane-based spirocycles.[97] In this regard, the enyne precursor **430** was prepared from 1,3-indanedione (**284**) by a stepwise propargylation and allylation sequence, then the G-II catalyst-mediated RCEM of **430** in the presence of Ti(ⁱOPr)₄ gave the expected inner-outer diene **431** in a moderate yield. The DA reaction of the diene **431** with various dienophiles followed by aromatization of the cycloadduct gave the indane-based spiro-cyclic compounds **432** in moderate to good yields. Similarly,
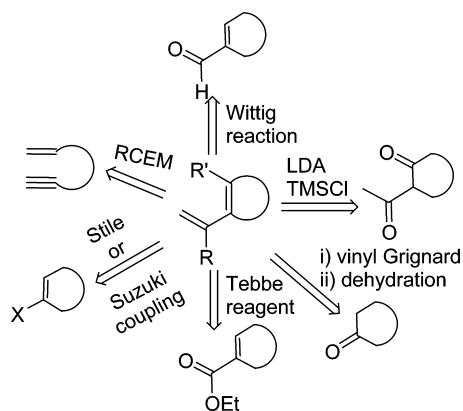
Scheme 77. Synthesis of Angularly Substituted Indane-Based AAA Derivatives 415

Dienophile	28	30	31	49	50
Yield (%)	88	67	82	67	87
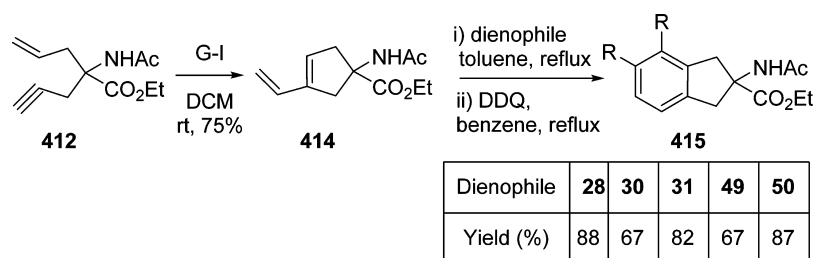
Scheme 78. Synthesis of Angularly Substituted Tic Derivatives 419 by EM and DA Reaction

Dienophile	28	50
Yield (%)	93	52
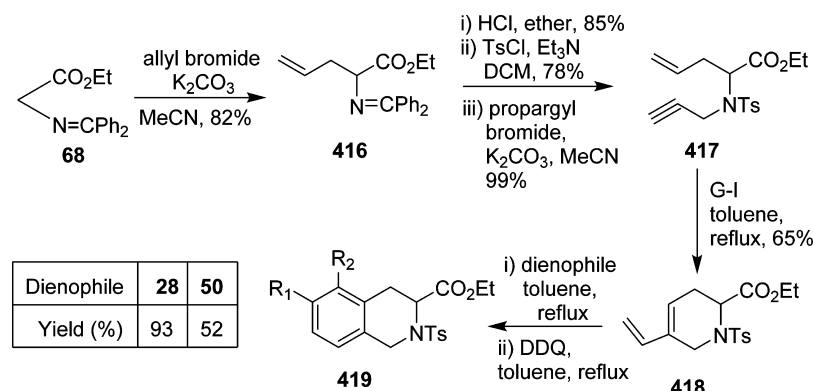
Scheme 79. Diversity-Oriented Approach to Tic Derivatives 422 by EM and DA Reaction

Dienophile	28	50
Yield (%)	85	45
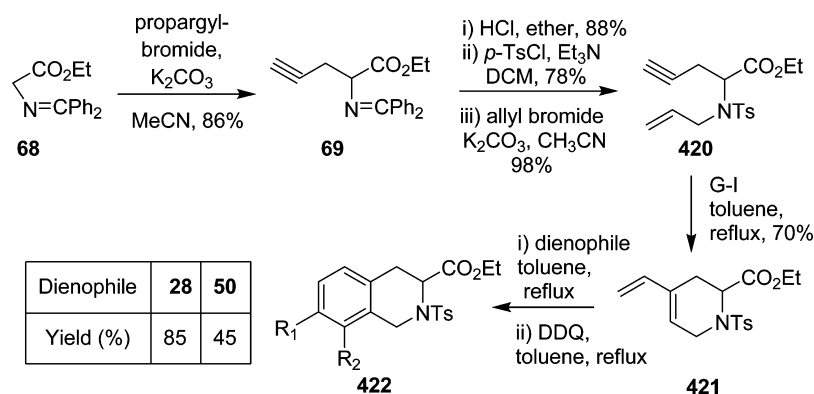
Scheme 80. Preparation of Higher Analog of Tic Derivative
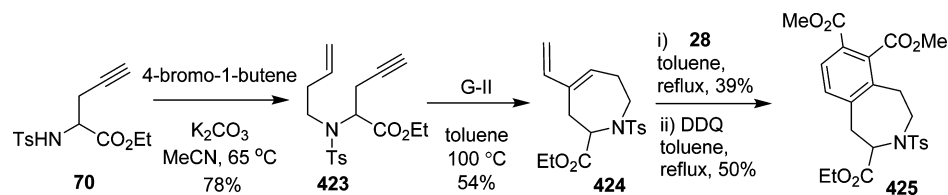
compounds **433** and **434** were assembeled via the DA reaction of **431** with **35** and **62**, respectively (Scheme 82).

Along similar lines, 1-indanone-based spirocycles were assembled by utilizing RCEM. Thus, the enyene precursor **435** was prepared starting with 1-indanone by a stepwise allylation and propargylation sequence, then the G-II catalyst-mediated RCEM of **435** in the presence of 1,5-hexadiene gave the inner outer-ring diene **436** in 52% yield along with another spiro diene **437** in low yield (Scheme 83).[113]

To expand these strategies to spirocyclics, RCEM and DA reactions were conceived as key steps, and in this regard,

various spiro dienes **439** were prepared using a variety of active methylene compounds (AMC's) such as diethyl maleate, 1-indanone, and α-tetralone. These enyne building blocks **438** were prepared by a stepwise allylation, and propargylation followed by RCEM using G-II catalyst in the presence of titanium(IV) isopropoxide gave spiro dienes **439**. These spirodienes on DA reaction with DMAD (**28**), followed by aromatization of DA adduct, generated angularly annulated spirocycles **440**. Similarly, these dienes on DA reaction with tetracyano ethylene (**35**) gave the expected spirocycles **441** (Scheme 84).[114]

Scheme 81. Synthesis of Functionalized Oxepine Derivative

R =	H	H	H	H	Br	OMe
Dienophile	28	31	55	44	44	44
Yield (%)	49	61	38	42	74	55
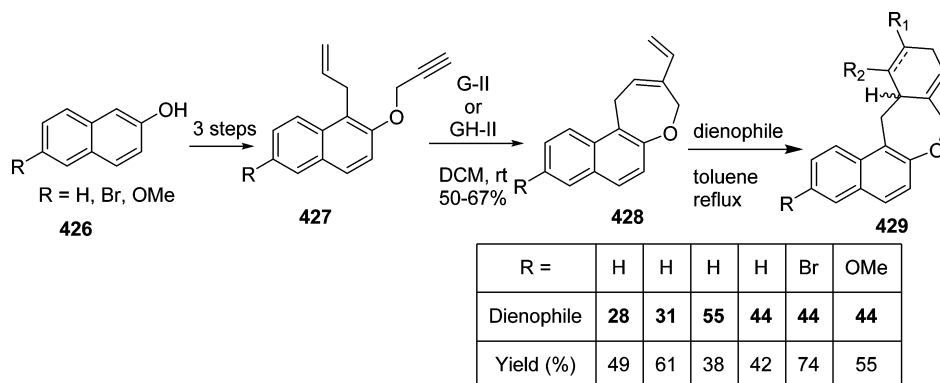
Scheme 82. Generation of Indane-Based Spirocycles by RCEM

Dienophile	28	49	50	51	55
Yield (%)	76	57	49	55	65
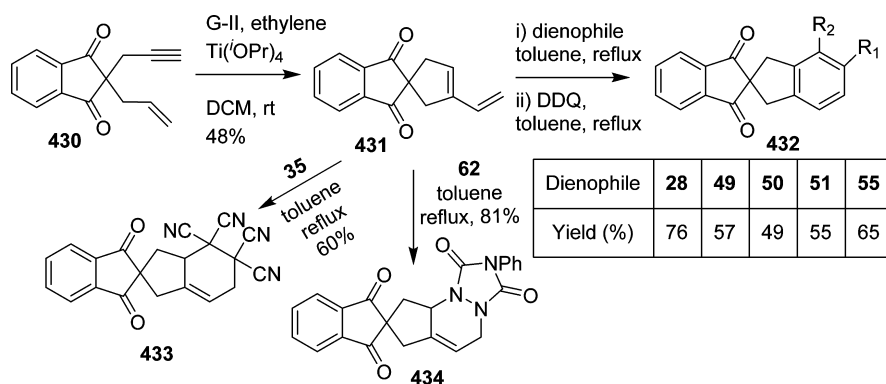
Scheme 83. Synthesis of Spirocyclic Inner Outer Dienes 436 and 437
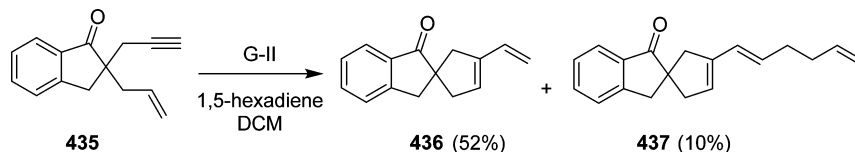
Scheme 84. Synthesis of Angularly Annulated Spirocycles 440 and 441

AMC	I	I	II	II	III	III	IV	IV
Dienophile	28	35	28	35	28	35	28	35
Yield (%)	73	85	59	72	69	91	75	79
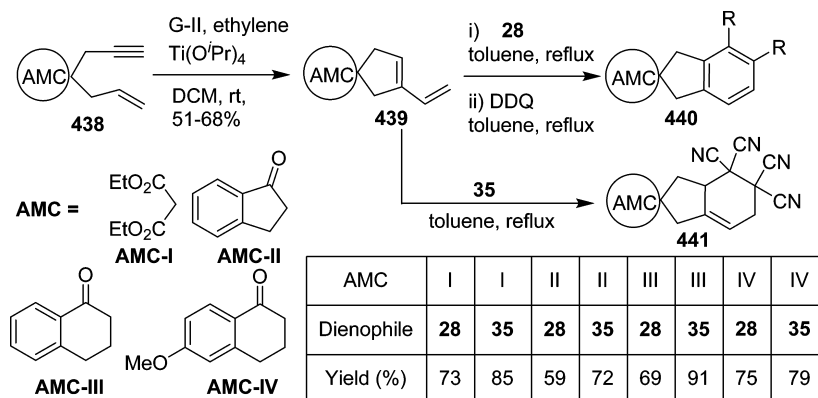
Ring-rearrangement metathesis can produce complicated polycycles in an imaginative manner. Recently, enyne ring-rearrangement metathesis (ERRM) has been reported to deliver the diene derivative **444** and its DA reaction with various dienophiles. In this regard, tricyclic propargylic ether **443** was prepared from tricyclic alcohol **442** and subjected to ERRM under ethylene atmosphere in the presence of G-I to obtain the ring-rearranged tricyclic diene **444**. Later, the DA reaction of the tricyclic diene **444** with *N*-phenyl maleimide (**55**) and maleic anhydride (**63**) under toluene reflux conditions generated the corresponding DA adduct **445** in good yield. Similarly, we have prepared different dienes, **446** and **447**, by ERRM sequence, and **447** gave the corresponding DA adducts with *N*-phenyl maleimide (**55**) (Scheme 85).[115]

Chattopadhyay and co-workers have developed a new route to various carbazole derivatives via Claisen rearrangement,

Scheme 85. Synthesis and DA Reactions of 444 and Related Compounds

X =	NPh	O
Dienophile	**55**	**63**
Yield (%)	77	79
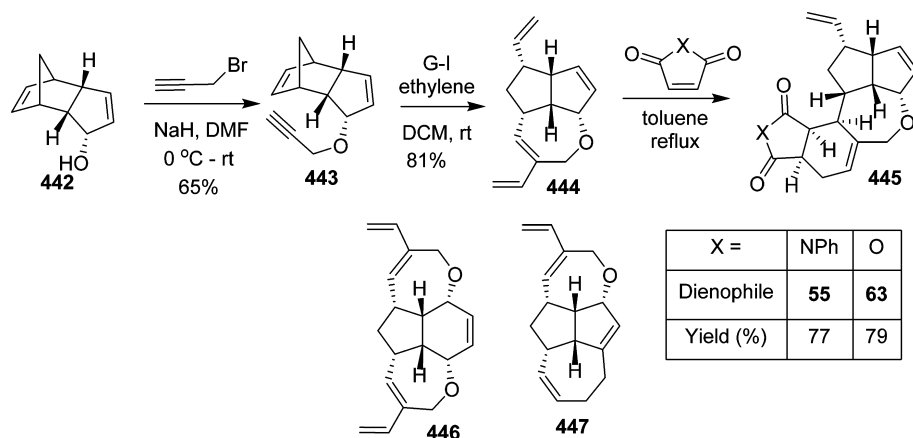
Scheme 86. Synthesis of an Oxacyclic-Annulated Carbazole Derivatives

452 (42%) +
(stereoisomer 24%)

451 (44%) +
(stereoisomer 27%)
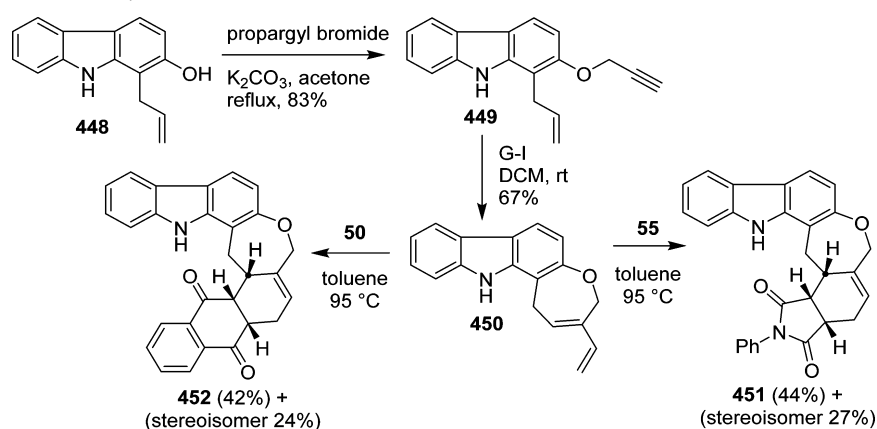
Scheme 87. Diversity Oriented Approach to Various Phenanthridine Derivatives

R = H, Me, OMe,
Cl, Br, F,
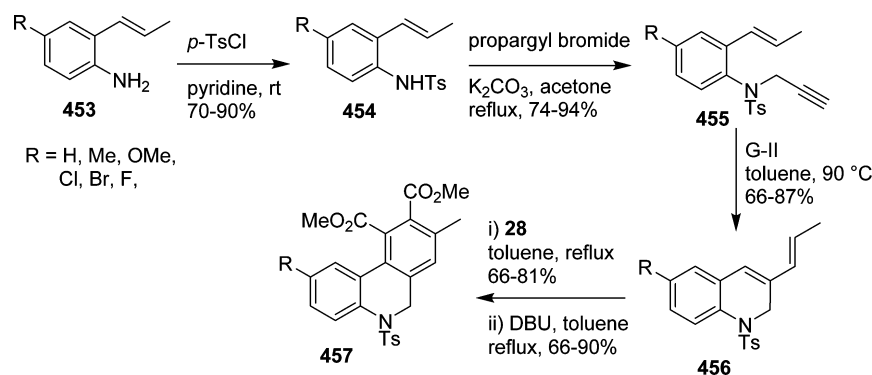
olefin metathesis, and DA reaction as key steps. To this end, the enyne building block **449** has been prepared from the corresponding hydroxyl derivative by a sequential allylation, Claisen rearrangement, followed by O-propargylation. Later, RCEM of the enyne building block **449** with G-I catalyst gave the expected diene **450**, which on DA reaction with N-phenylmaleimide (**55**) and 1,4-naphthoquinone (**50**) gave the corresponding DA adducts **451** and **452** as oxacyclic-annulated carbazole derivatives (Scheme 86).[116]

Chattopadhyay and co-workers have realized a diversity-oriented approach to various phenanthridine derivatives[117] that is based on a sequential application of three atom-economic processes, such as aza-Claisen rearrangement,[118] olefin metathesis,

and DA reactions. Here, they have observed an unexpected isomerization of the double bond during the aza-Claisen rearrangement. They employed a tosyl group for N-protection of **453**. Later, N-propargylation gave the enyne building block **455**, which was further subjected to RCEM to generate the required diene **456**. Later, the DA reaction of this diene **456** with DMAD (**28**), followed by aromatization of the resulting DA adduct, gave the phenanthridine derivative **457** in good yield (Scheme 87).

Srinivasa Reddy and co-workers have reported the synthesis of tetrahydronaphthalenic diterpenic diol, isofregenedadiol (**461**) from D-(−)-pantolactone utilizing a tandem ring-closing enyne metathesis/cross-metathesis/DA reaction/aromatization

Scheme 88. Synthesis of 464a and 464b by Ultrasound-Promoted DA Reaction
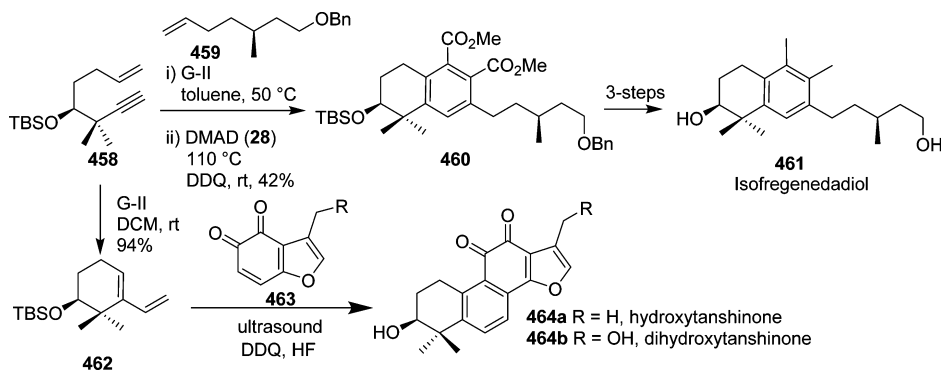
Scheme 89. Synthesis of Angularly Fused Tetracyclic Quinone 468
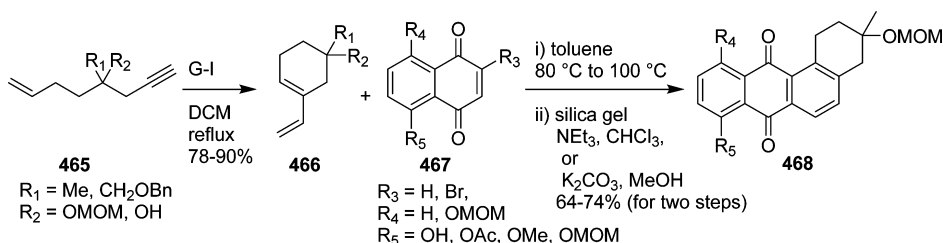
Scheme 90. DA Reactions of the Diene 472 with Various Dienophiles

n =	1	1	1	1	1	1	0	0	0	0
Dienophile	30	42	50	35	55	62	30	50	55	62
Yield (%)	48	39	61	66	72	75	45	47	62	46
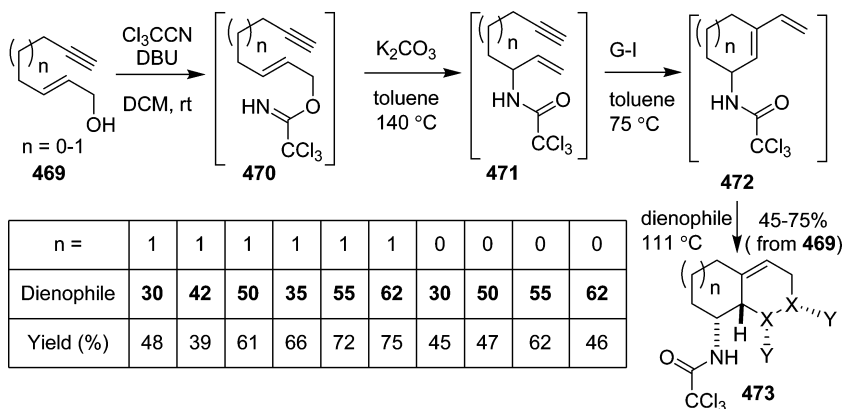
sequence.[119] The required enyne building block **458** has been prepared from (−)-pantolactone and subjected to a tandem ring-closing enyne metathesis/cross-metathesis protocol with a long chain alkenyl ether **459**, followed by a DA reaction/aromatization sequence to give **460**, a precursor to isofregenedadiol synthesis. Subsequent synthetic transformations gave the naturally occurring isofregenedadiol (**461**). Further, they utilized this enyne building block **458** for the formal synthesis of hydroxytanshinone **464a** and dihydroxytanshinone **464b** by ultrasound-promoted DA reaction involving *o*-quinone derivative **463** (Scheme 88).

Recently, Vanga and Kaliappan reported the synthesis of angucyclinone antibiotics by utilizing a similar reaction sequence involving RCEM and DA reaction.[120] Here, they prepared various inner-outer-ring diene derivatives **466** by RCEM of the corresponding alcohol or the ether-based enyne derivative **465**, and then the DA reaction with functionalized 1,4-naphthoquinones **467**, followed by aromatization, gave the angularly fused tetracyclic skeleton **468** (Scheme 89), which on further synthetic transformation gave the angucyclinone antibiotics. These angucyclines have a benz[*a*]anthraquinone

ring system as a common structural scaffold. The diversity involved in this synthetic sequence was introduced by carrying out the DA reaction of different enynes with various substituted quinones. Further, they extended the RCEM and DA reaction sequence to the synthesis of (−)zenkequinone B.[121]

Recently, Sutherland and co-workers have disclosed a tandem process involving an Overman rearrangement, RCEM, and hydrogen-bonding-directed DA reaction for diastereoselective synthesis of functionalized amino-substituted tetralin and indane ring systems. To this end, the allyl alcohol **469** was treated with trichloroacetonitrile to obtain the trichloroacetimidate **470**, which on Overman rearrangement under thermal conditions gave the rearranged product **471** as a key enyne building block. Later, treatment of **471** with G-I catalyst gave the RCEM product **472**. Subsequent DA reaction of the resulting diene **472** with various dienophiles gave the final bicyclic product **473** as a single diastereomer in four steps (Scheme 90).[122] These types of ring systems are present in many natural products, such as antitumor antibiotic, (−)-ptilocaulin, and the antibacterial family of hapalindole A.[123]

Scheme 91. Synthesis of Amino-Substituted Indane, Tetralin, Pyridine and Pyridazine Derivatives (475−478)
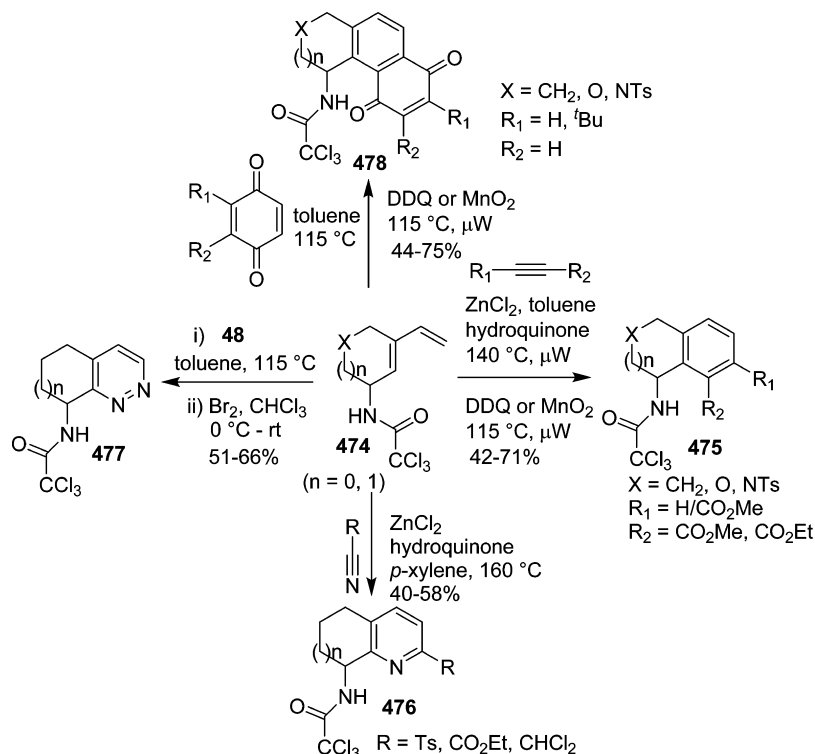
Scheme 92. Synthesis of Benzopyrans
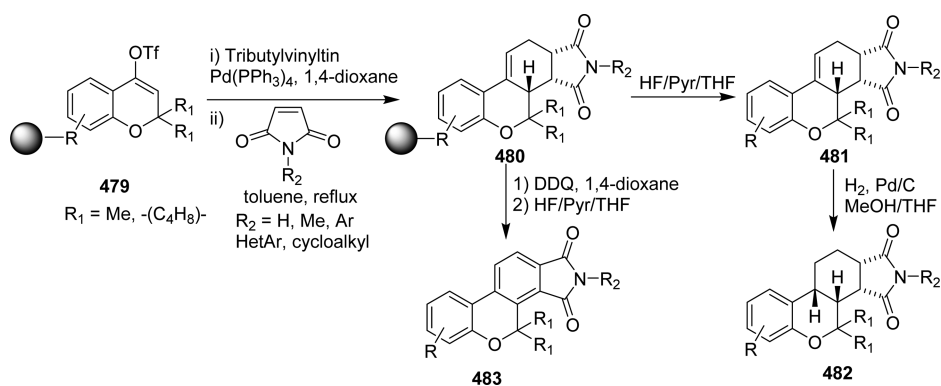
Along similar lines, this strategy has been applied to various indane, tetralin, pyridine, and pyridazine derivatives.[124] Further, the dihydropyran and tetrahydropyridine dienes **474** were utilized for the synthesis of heterocyclic compounds. Various diene derivatives containing an oxygen atom or *N*-tosyl group were synthesized by the same synthetic sequence, starting with a suitable precursor, then a regioselective DA reaction of **474** with activated alkynes (**28−30**), nitriles (**32−34**), azodicarboxylates (**48**), or quinones followed by oxidation gave a library of amino-substituted indane, tetralin, pyridine, and pyridazine derivatives (**475−478**) (Scheme 91).

Park and co-workers have investigated a diversity-oriented approach to polyheterocyclic benzopyrans via one-pot Stille coupling and DA reaction on a solid support. Thus, benzopyran-based vinyl triflate **479** has been coupled with tributylvinyltin, and the resulting diene was reacted with various maleimides to give an endo-selective DA adduct containing benzopyran derivative **480** with high diastereoselectivity. Later, they expanded the molecular diversity by transforming the

polyheterocyclic skeleton in two directions: Pd/C-catalyzed hydrogenation to **482** and DDQ-mediated oxidation to **483**. By utilizing this diversity-oriented approach, they have prepared a library of polyheterocyclic benzopyrans (Scheme 92).[125] Similarly, Bräse and Park's group independently prepared several polyheterocyclic benzopyran (chromene) scaffolds by a DA approach. Instead of using Stille coupling, the diene building block was prepared by the Wittig reaction with keto-substituted benzopyrans, and then the DA reaction with various dienophiles generated various polycyclic benzopyran derivatives.[126] The Park group has utilized Suzuki coupling by reacting vinyl boronate with bromo-substituted benzopyrans, and subsequent DA reaction with triazolinedione and maleimides gave a library of functionalized benzopyran derivatives.[127]

In 2011, Kwon and co-workers demonstrated a diversity-oriented approach to a library of heterocyclic compounds.[128] In this regard, the pyrrolines **484** and tetrahydropyridines **487** were assembled through phosphine-catalyzed ring-forming reactions between the allenoates and the imines. Later, Tebbe

Scheme 93. Synthesis of Heterocyclic Scaffolds 486 and 489 via DA Chemistry

P = Bs, Ts
Ar = Ph, 4-MePh, 4-EtPh, 4-ClPh,
3-ClPh, 2-thiophenyl, 2-naphthyl
R = H, ^{i}Pr, nPent, ^{t}Bu, Ph

Dienophile	35	49	55	62
Yields (%)	37-61	56	56-76	35-83

P = Bs, Ts
Ar = Ph, 4-MePh, 4-EtPh, 4-ClPh,
3-ClPh, 2-thiophenyl, 2-naphthyl
R = H, ^{i}Pr, nPent, ^{t}Bu, Ph

Dienophile	35	55	62
Yields (%)	56-85	67-84	55-85
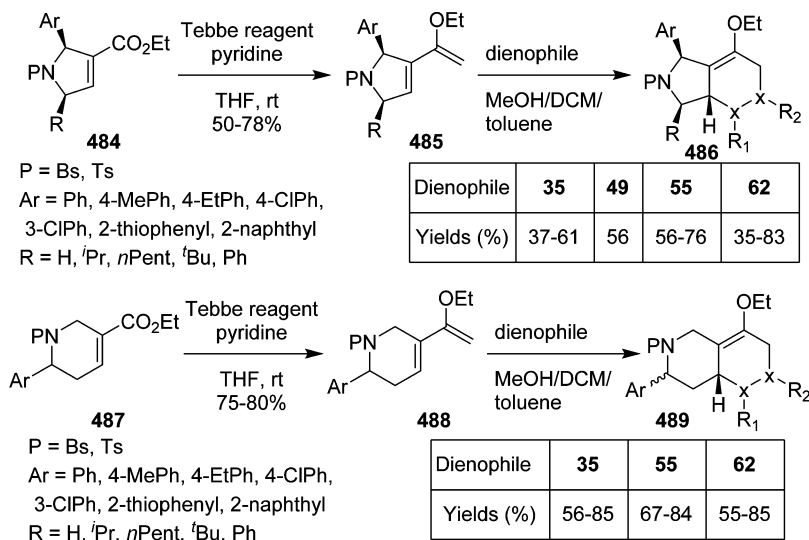
Scheme 94. Synthesis of Macrocyclic Scaffolds by Utilizing Two-Directional DA Reaction

X =	-(CH$_2$)$_2$-	-C$_6$H$_4$-	-C$_6$H$_4$-	-C$_6$H$_4$-C$_6$H$_4$-	-(CH$_2$)$_2$-	-(CH$_2$)$_2$-
Y =	-CH$_2$-C$_6$H$_4$-CH$_2$-	-CH$_2$-C$_6$H$_4$-CH$_2$-	-(CH$_2$)$_5$-	-(CH$_2$OCH$_2$)$_2$-	-(CH$_2$)$_5$-	-(CH$_2$OCH$_2$)$_2$-
Yield (%)	16	32	26	30	16 +11[b]	26 +18[b]

[b]other regioisomeric product
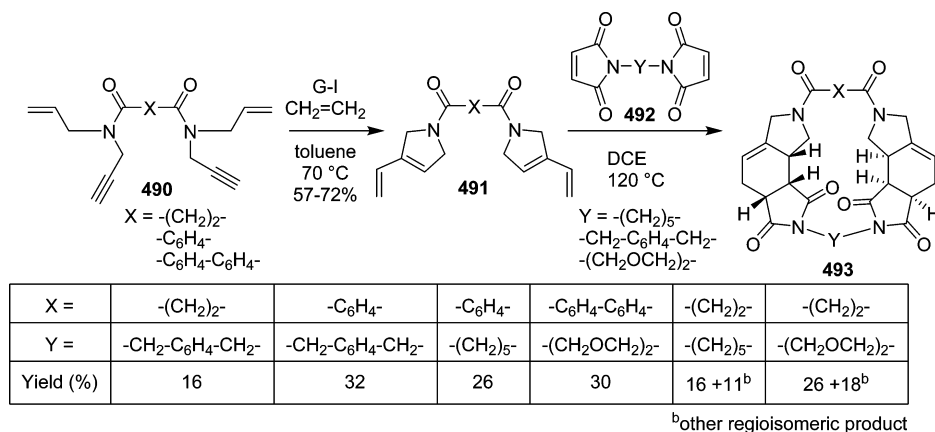
olefination of **484** and **487** delivered the ethoxy dienes **485** and **488**. The DA reaction of these dienes **485** and **488** with various dienophiles gave the heterocyclic scaffolds **486** and **489** (Scheme 93). The DA reaction is highly stereoselective, yielding a single diastereoisomer. They also reported the synthesis of octahydro-1,6-naphthyridine derivatives by hetero-DA reaction with various imine dienophiles. The selective cycloaddition products were then converted to the keto derivatives by mineral acid treatment. In another event, the same group synthesized and screened a library of chemical probes that enhance innate immunity through endothelial cell activation.[129]

Recently, Spring and co-workers reported an efficient strategy to a diversity-oriented synthesis of macrocyclic scaffolds by utilizing the DA reaction as a key step in a two-directional manner.[130] In this regard, amide-based dienynes **490** were prepared by coupling the appropriate dicarboxylic acids with *N*-prop-2-ynyl allylamine. Later, RCEM of dienynes **490** with G-I catalyst gave the required diene derivative **491**, then a double DA reaction of the diene **491** with various bis-maleimides **492** generated the macrocycles **493** (Scheme 94). Generally, a single diastereomeric macrocyclic product was isolated by endo-selective tandem DA reaction. However, in a few cases, endo as well as exo transition states were involved to generate the end products.

Tilve and co-workers have demonstrated a new approach to carbazolones by domino Wittig–DA reaction sequence.[131] Indole-3-carboxaldehyde (**494**) was treated with phosphorane **495** to deliver a mixture of two diastereomers, **496**, in a 1:1 ratio. During a one-pot reaction, first the Wittig reaction takes place to form *E*-unsaturated ester **496**, which undergoes an intramolecular DA reaction to form **497**. Later, the intermediate **497** rapidly isomerizes to **498**, which on DDQ oxidation gave the final carbazole derivative **499** (Scheme 95).

In 2013, Prajapati and co-workers realized a facile synthesis of iminoquinazoline-2,4-dione derivatives **503** (Scheme 96).[132] In this regard, a solvent and catalyst-free DA reaction was performed with 6-(2-morpholinovinyl)-1,3-dimethyluracil **500**; cinnamaldehyde **501**; and an amine, **502**. The strategy has been extended for the synthesis of various iminoquinazolinediones.

■ INNER-RING DIENES

The cyclic dienes with conjugated double bonds within a ring belong to this class of dienes, and they are further subdivided into carbocyclic dienes and dienes based on aromatic systems.

A. Carbocyclics. In this class of dienes, systems contain conjugated double bonds involving a nonaromatic ring system. Typical examples include cyclopentadiene (**18a**) and 1,3-cyclohexadiene (**18b**). Pyne and co-workers realized the synthesis of (+)-(2S)-2-aminobicyclo[2,2,2]-octane-2-carboxylic acid salt

Scheme 95. Synthesis of 499 via Domino Wittig–DA Reaction Sequence
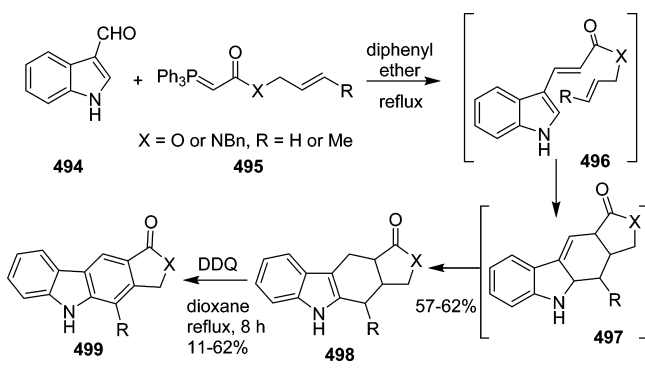
Scheme 96. Synthesis of Iminoquinazoline Derivatives 503 via DA Reaction
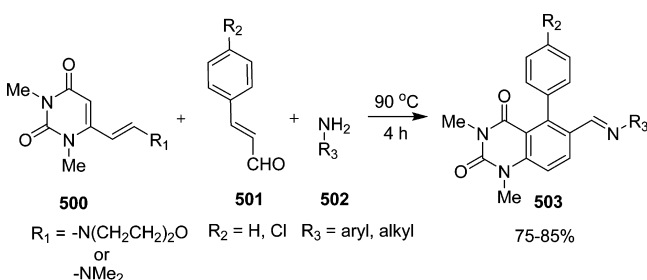
508 involving the DA reaction of a cyclohexadiene (**18b**) and oxazolidinone **504**. The DA reaction of chiral oxazolidinone **504** and cyclohexadiene (**18b**) afforded a diasteromeric mixture **505**, which on esterification with methanol gave the ester **506** as a single diastereomer. The diastereomeric mixture has been derived from a thermally induced C-2 epimerization during the DA reaction. Later, hydrogenation followed by acid hydrolysis afforded the amino acid hydrochloride salt **508** (Scheme 97).[133]

Scheme 97. Synthesis of (+)-(2S)-2-Aminobicyclo[2,2,2]-octane-2-carboxylic Acid Salt 508
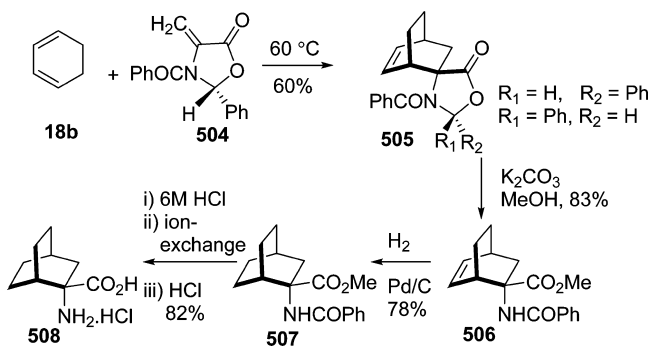
Park and Kurth demonstrated the synthesis of a bicyclic AAA derivative, 2-aminobicyclo[2,2,1]heptane-2-carboxylic acid from the cyclopentadiene (**18a**) and 2-phenyl-4-benzyliden-5(4H)-oxazolone (**509**). The DA reaction of cyclopentadiene (**18a**) and oxazolone derivative **509** resulted in spiroxazolones **510** and **511**, in which the endo/exo ratio is independent of the nature of the substituent. The spiroxazolones mixture separation was achieved by iodolactonization. Later, esterification with diazomethane and subsequent hydrogenation using 10%

Pd/C gave the saturated bicyclic AAA derivatives **512** and **513**. Finally, the free amino acids **514** and **515** were obtained by treatment with HCl and propylene oxide (Scheme 98).[134]

In 2000, Nájera and co-workers synthesized new chiral amino acid derivatives **520** and **521** by the DA approach.[135] The didehydroamino acid derivative **516** was used as a dienophile in the DA reaction with various dienes to deliver the cycloaddition products **517**−**519**. Acid hydrolysis of the imine moiety of cycloadducts **518** and **519**, followed by catalytic hydrogenation of the double bond and subsequent hydrolysis of the ester functionality yielded the corresponding amino acid hydrochlorides **520** and **521**, respectively (Scheme 99).

Recently, Kotha and co-workers realized the synthesis of bis-spirolactone by DA reaction as a key step. The cyclopentadiene (**18a**) on reaction with dimethyl maleate (**42**) gave the cyclo-adduct **522** as a bicyclic diester, then the diallylation of **522** using allyl bromide under basic conditions gave the diallyl diester **523**, which on treatment with mineral acid gave the bis-spirolactone **524** in a short synthetic sequence (Scheme 100). Similarly, they prepared the simple bis-spirolactone of diethyl diallylmalonate by mineral acid treatment.[136]

Compounds related to Cookson's diketone are useful in the synthesis of natural products and nonnatural products and also as a high energy fuels and explosive materials for military applications.[137] These derivatives are assembled by a DA reaction of cyclopentadiene derivatives and 1,4-benzoquinones. The spiro-cyclopentadiene derivative **525** was prepared by direct alkylation of cyclopentadiene (**18a**) with 1,2-dichloro-ethane under basic conditions, then the DA reaction of spirocyclic diene **525** with 1,4-benzoquinone (**49**) in micellar media gave the expected DA adduct **526**, which upon photo-chemical irradiation gave the hexacyclic dione **527**. Further, it was converted to the dibromo compound **529**, and later radical allylation of the dibromo compound **529** with allyltributyltin in toluene gave the diallylated compound **530** (Scheme 101).[138] However, direct allylation of the compound **528** was not successful under basic conditions because of a facile and un-wanted transannular cyclization and aldol-type reactions.

Retro-DA (rDA) reaction has also gained a significant value in design and synthesis of diverse polycycles.[139] Spiro-cyclopentadiene **525** has played a critical role in the outcome of rDA (Scheme 102).[140] In this regard, we prepared the various DA adducts **531** involving 1,4-benzoquinone deriva-tives. Our experimental study clearly indicates that the spiro-cyclopropane-based systems undergo facile rDA reaction, as compared with the parent cyclopentadiene-based DA adduct. The effective orbital interactions involving cyclopropane bond orbitals stabilize the transition state, consequently lowering the kinetic barrier for the rDA reaction. We found that these DA adducts **531** undergo rDA reaction at much lower temperature (at MeCN reflux conditions) as compared with the harsh reaction conditions generally used (∼300 to 500 °C) for this purpose. The longer carbon−carbon bond length in the DA adduct is responsible for easy rDA reaction. Recently, the correlation between the elongated carbon−carbon distance and the ease of the rDA reaction was explained on the basis of X-ray crystallographic data.[141]

Recently, this aspect was successfully used by Srinivasa Reddy's group to synthesize an antimalarial and antibacterial agent, CJ-15,801, by a green synthetic route.[142] In this regard, they prepared the cyclopropyl-containing bicyclic amino acid ester from the spirocyclopentadiene derivative **525** and (E)-allyl 3-nitroacrylate **532** by the DA reaction, followed by

Scheme 98. Synthesis of Saturated Bicyclic AAA 514 and 515
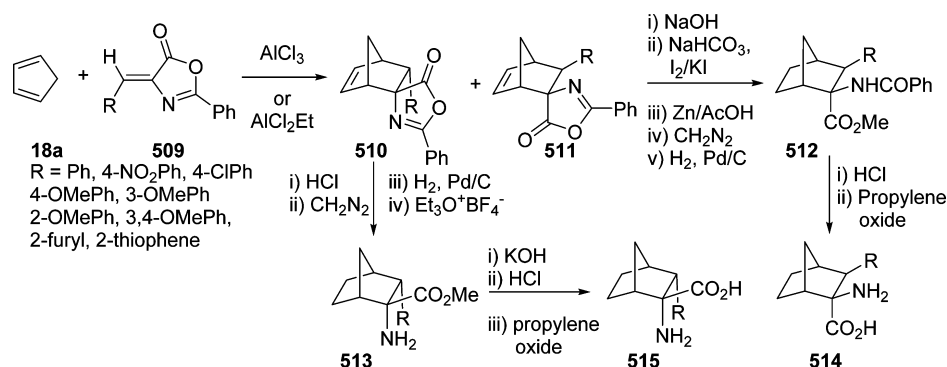
Scheme 99. Synthesis of New Chiral Amino Acid Derivatives 520 and 521 by the DA Approach
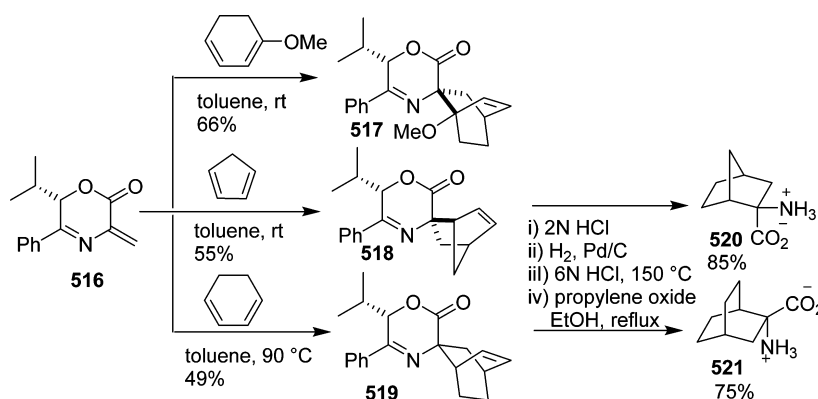
Scheme 100. Synthesis of bis-Spirolactone by DA Reaction As a Key Step
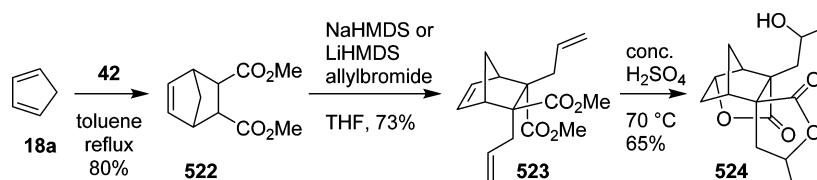
Scheme 101. Synthesis of Diallylated Hexacyclic Compound 530 via DA Reaction
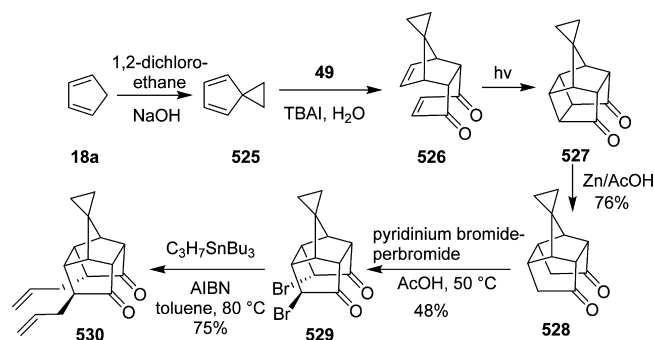
Scheme 102. DA and rDA Chemistry of Compound 531

Quinone	49	50	51	52
Yield (%)	62	75	81	35

Quinone	49	50	51	52
Yield (%)	67	62	91	73

$Pd(PPh_3)_4$ catalysis condition to obtain the final target, CJ-15,801[143] (Scheme 103).

To expand the metathesis strategies to spirocycles, we reported another spirodiene **536** via alkylation of cyclopentadiene (**18a**) with α,α'-dibromo-*o*-xylene with an improved yield under PTC conditions.[144] The DA reaction of the diene **536** with an acyclic dienophile, such as DMAD (**28**), failed to give the DA adduct; however, when diene **536** was subjected to the DA reaction with various quinones, the expected DA adducts **537** were generated in good yield under aqueous MeOH conditions at room temperature. Later, two of these DA

reduction of the DA adduct. The bicyclic amino acid ester was isolated as a diastereomeric mixture of compounds **533a** and **533b**. Treatment of the bicyclic amino acid ester with D-(−)-pantolactone and subsequent rDA reaction gave the N-acyl vinylogs carbamic acid ester **534** in good yield at low temperature. The bicyclic amino acid ester without cyclopropyl substitution gave a low yield of rDA product, even at high temperature. Later, the allyl group was deprotected under

Scheme 103. Synthesis of Antimalarial and Antibacterial Agent CJ-15,801
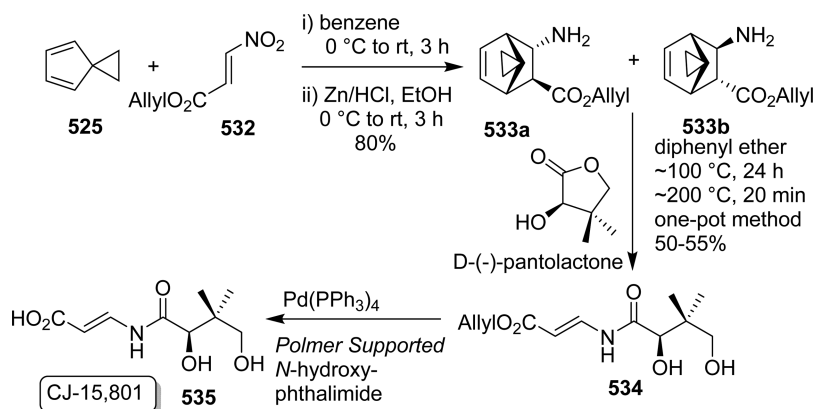
Scheme 104. Synthesis of Spiroindane Derivatives 538 via DA Reaction

Quinone	49	50	51	52	53	54
Yield (%)	55	62	65	61	52	56
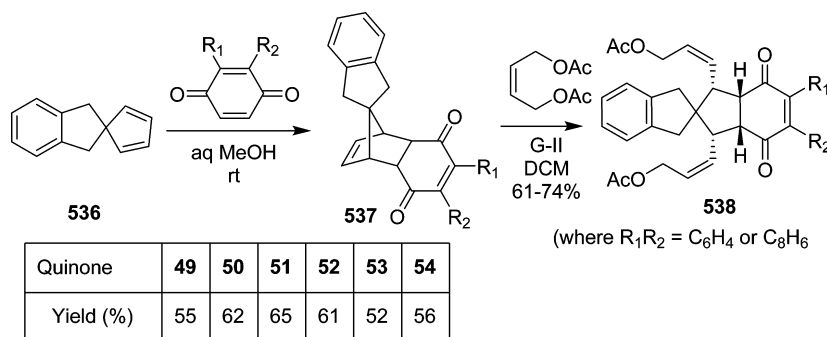
Scheme 105. Synthesis of Dibenzylated Indanedione 541
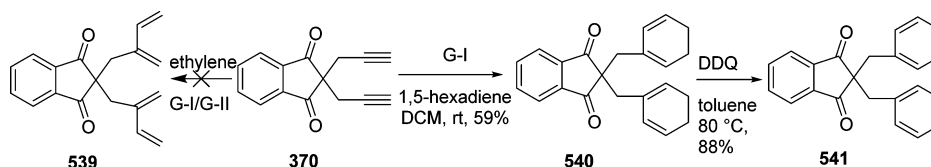
adducts were utilized to generate spiroindane derivatives **538** by ring-opening cross-metathesis (ROCM) sequence (Scheme 104).

The other carbocyclic diene reported from our group involves CEM of the dialkyne building block **370** and 1,5-hexadiene as a cross-metathesis partner (Scheme 105).[113] In this regard, we anticipated the open chain tetraene by CEM of alkyne **370** and ethylene as a metathesis partner, but this failed to deliver the expected tetraene **539** under different reaction conditions. Later, the 1,5-hexadiene was used as a cross-metathesis partner, and the diene **540** was isolated in good yield. It was oxidized with DDQ to obtain the dibenzylated indanedione **541**. The structure of the dione **541** was compared with the product obtained by direct benzylation of the indanedione under basic reaction conditions, and ^{1}H NMR spectral data obtained in both cases were identical.

Kotha and Dipak have used the RCM approach to synthesize caged propellane derivatives. In this regard, the *O*-allylhydroquinone **542**, upon Claisen rearrangement, gave 2,3- and 2,5-diallyl hydroquinones **543a−b**. The 2,3-diallyl hydroquinone **543b** was then oxidized to diallyl quinone **544** by MnO₂, and the DA reaction of the diallyl quinone **544** with 1,3-cyclopetadiene (**18a**) gave the cycloadduct **545**, which on [2 + 2] photoaddition gave the caged dione **546**. Finally, the

diallyl dione **546** on RCM with G-I catalyst gave the propellane derivative **547**, which was hydrogenated to the saturated propellane derivative **548** (Scheme 106).[145]

Similarly, the 2,5-diallyl hydroquinone **543a** was converted to diallyl quinone **549** and its DA reaction with 1,3-cyclopentadiene (**18a**) gave the cycloadduct **550**, which on [2 + 2] photocycloaddition generated the caged diallyl dione **551**. The dione **551**, on Grignard reactions with allyl or vinyl magnesium bromide, gave the tetraalkenyl diols **552** and **554**, respectively. Finally, the RCM of these olefinic derivatives **552** and **554** under G-II catalysis conditions generated polycyclic compounds **553** and **555**, respectively (Scheme 107).[146]

Camps and Gómez have demonstrated DA reactions of methyl 1-benzylcyclopenta-2,4-diene-1-carboxylate (**557**), which was prepared from the cyclopentenone derivative **556** in two steps. The stable diene **557** on dimerization at room temperature gave a stereoisomeric dimer, **558**. Reaction of the diene **557** with maleic anhydride (**63**) and *cis*-1,2-bis(phenylsulfonyl)ethylene (**43**) gave the corresponding endo adducts **559** and **560**, respectively. Endo adduct is derived from the addition of dienophile to the diene from the side of the less bulky methoxycarbonyl group. The diene **557** on treatment with (2-iodoethynyl)(phenyl)-iodonium triflate (**64**) in MeCN at room temperature gave the DA adduct **561** (Scheme 108).[147]

Scheme 106. Synthesis of Propellane Derivatives via DA Reaction and RCM as Key Steps
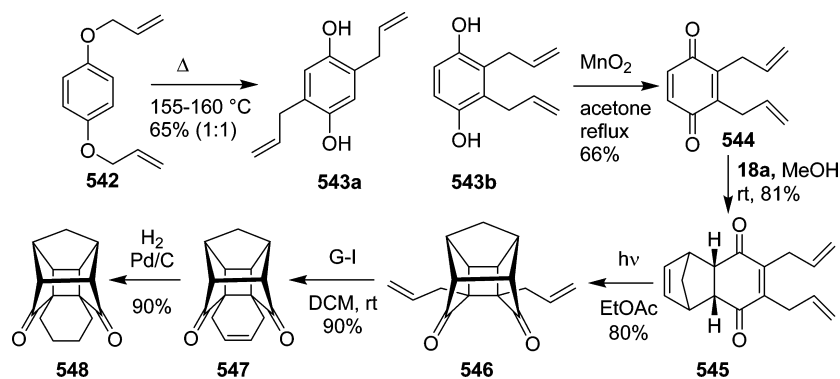
Scheme 107. Synthesis of Polycyclic Compounds 553 and 555 Involving DA Reaction
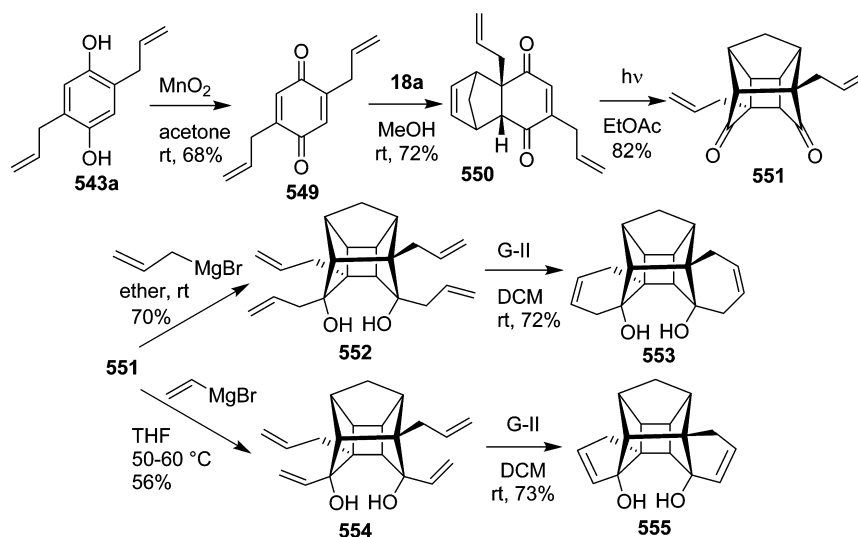
Nencka and co-workers synthesized a series of 5,6-substituted norbornenes by using microwave-assisted DA reaction. Dicyclopentadiene dimer **562** under MWI with a series of dienophiles generated the substituted norbornenes **563−566** (Scheme 109).[148] Microwave exposure facilitated accelerating the reaction and thus avoided the cumbersome cracking and handling of unstable cyclopentadiene and still provided very good to excellent yields. They further extended this approach to assemble 5,6-substituted polychlorinated norbornenes by using a suitable precursor (polychlorinated cyclopentadiene).

In 2005, Schreiber and co-workers designed a strategy for the synthesis of 14-membered paracyclophanes **569**. The Lewis acid-catalyzed DA reactions of microbead-supported steroid-derived diene **567** with various alkynes afforded the adduct **568**, and subsequent rDA reaction delivered the target cyclophane **569** (Scheme 110). A library of more than 4000 skeletally diverse molecules was assembled.[149]

B. Aromatic Dienes. Use of anthracene as a diene in the DA reaction has gained the increasing attention of organic chemists. The first DA reaction of anthracene (**19**) with maleic anhydride (**63**) was reported by Diels and Alder in 1931 via a fusion reaction at 260 °C (Scheme 111).[150] Later, Clar reported the same product by heating a solution of these two reactants in xylene (90%).[151]

Later, several groups reported the DA reaction of the anthracene with various dienophiles under different reaction conditions, including photochemical, microwave, use of Lewis acids, and high pressure, to generate various polycycles, and in 2003, these aspects were reviewed by Atherton and Jones.[152] To design unusual AAA derivatives, we recently reported the synthesis of a conformationally constrained AAA derivative by DA reaction of the anthracene (**19**) and methyl 2-acetamidoacrylate (**36**).[153] To this end, anthracene (**19**) was heated with methyl 2-acetamidoacrylate (**36**) in toluene under sealed tube conditions or BF₃·OEt₂ in chloroform reflux conditions, and the DA product **571** was obtained in excellent yield (Scheme 112). This approach involves a single step and 100% atom economy to conformationally constrained AAA derivatives. By utilizing this strategy, various biologically active compounds are prepared and covered in international patents.[154]

To test the applicability of this strategy to heteroaromatic systems, we tried the DA reaction of furan (**20**) with methyl 2-acetamidoacrylate (**36**) under similar reaction conditions. The Friedel−Craft alkylation product **572** was obtained predominantly, and the DA product was not formed (Scheme 113).

As an extension of our work, Yang and Doweyko utilized this strategy to synthesize various other conformationally constrained bicyclic bis-aryl AAA derivatives starting with 9-substituted anthracene **573** and methyl 2-acetamidoacrylate (**36**) by the DA reaction. Here, they have observed that the meta product, **574a**, was predominant over the ortho product, **574b**, under different reaction conditions (Scheme 114).[155]

Scheme 108. DA Reactions of 557 with Various Dienophiles
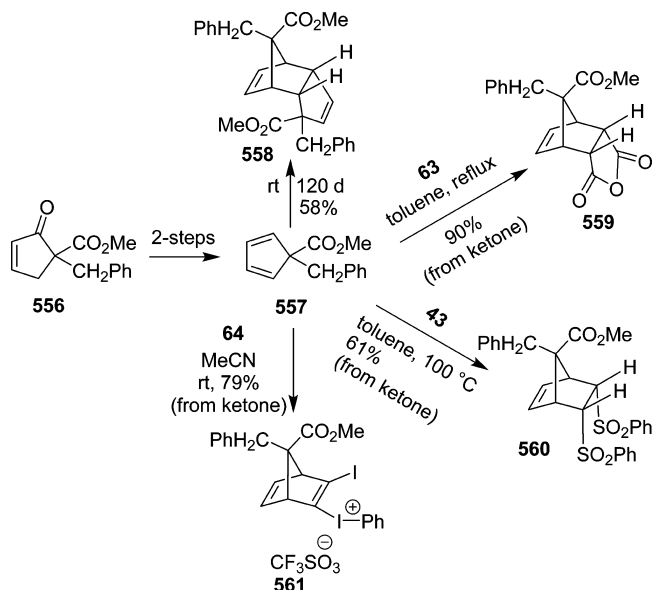
Scheme 109. Synthesis of Substituted Norbornenes 563−566 via the DA Strategy

R_1 = CO_2Et, OAc, OEt, Ph, Ac, OBz
R_2 = H, CO_2Et
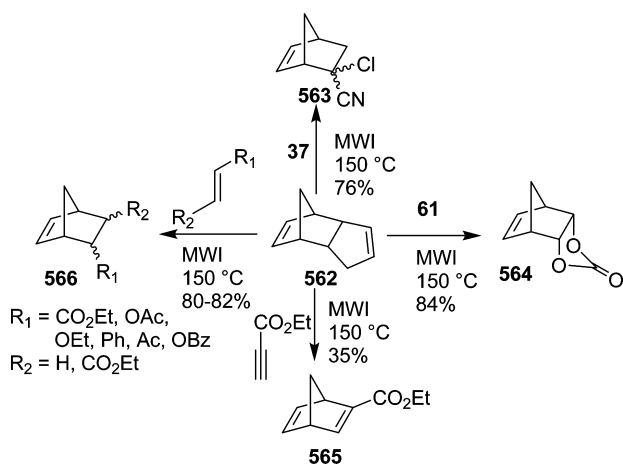
To expand the utility of anthracene in designing unusual AAA derivatives, DA reactions of dibromosubstituted anthracene was studied.[156] In this regard, the dibromoanthracene derivatives 575 and 578 were treated with the methyl-2-acetamidoacrylate (36) in a sealed tube at 150 °C to obtain the expected DA product 576 and 579. These dibromo derivatives 576 and 579 were further functionalized by the SM cross-coupling reaction with various boronic acids to assemble a library of constrained AAA derivatives (Scheme 115).[157]

To study the role of the substituent on anthracene in designing unusual amino acid derivatives, we prepared various

Scheme 111. DA Reaction of Anthracene (19) with Maleic Anhydride (63)
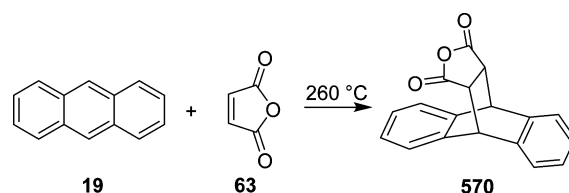
Scheme 112. DA Reaction of Anthracene (19) And Methyl-2-acetamidoacrylate (36)
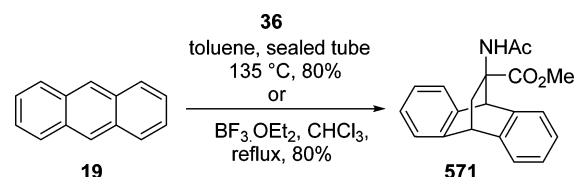
Scheme 113. Unexpected Friedel−Craft Alkylation of Furan
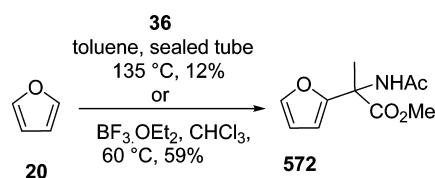
constrained AAA derivatives by DA reaction of the anthracene derivative 581 and coupling of the DA adduct 582 with EICA (91) and DEAM (78). The dibromide 581 upon DA reaction with DMAD (28) gave the DA adduct 582. The coupling of 582 with EICA (91) followed by hydrolysis and protection of the amino group as the acetyl derivative generated a constrained AAA derivative 583. Similarly, the dibromide 582 was coupled under basic conditions with DEAM (78) to prepare the Tic derivative 584. Further, the dibromide 582 on treatment with rongalite gave the expected sultine derivative 585 as a regioisomeric mixture, and its DA reaction with methyl 2-acetamidoacrylate (36) gave the tetralin-based AAA derivative 587 along with rearranged sulfone derivative 588. The sultine 585 was independently rearranged to sulfone 588 under toluene reflux conditions. These functionalized bicyclo[2.2.2]-octane derivatives can be further utilized to prepare various other constrained AAA derivatives (Scheme 116).[158]

To design anthracene-based cyclophanes, Kotha and Meshram realized the synthesis of 9,10-bridged anthracene derivative 593 via the DA reaction and RCM as key steps. In this regard, the anthracene (19) was reacted with vinylene carbonate (61), and the cycloadduct 589 was converted to the diketone 590 through hydrolysis under basic conditions, followed by oxidation of the resulting diol. The diketone 590

Scheme 110. Synthesis of 14-Membered Paracyclophanes 569 via DA and rDA Strategy
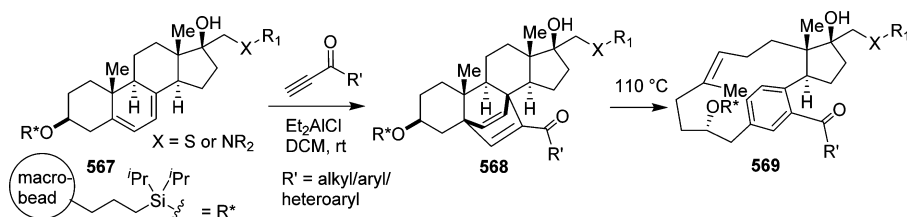
Scheme 114. Synthesis of Conformationally Constrained Bicyclic bis-Aryl AAA Derivatives

573
R = Me, Cl, NO₂, Br, CH₂OCH₃

meta-major **574a** + ortho-minor **574b**

up to >99:1 meta/ortho ratio
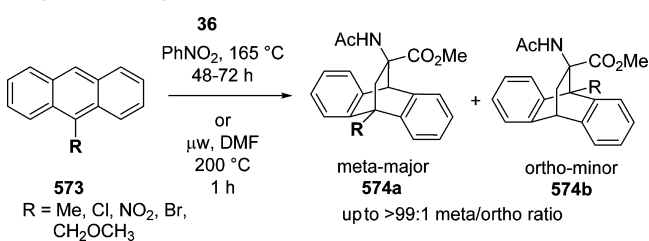
was then converted to the diallyl diol **591** through a stepwise allylation involving indium and magnesium reagents. Later, the G-I catalyzed RCM of the diallyl diol **591** and subsequent hydrogenation under Pd/C catalysis conditions gave the diol **592**, which was transformed to the 9,10-bridged anthracene derivative **593** via the cleavage of diol **592** (Scheme 117).[159] An aromatization step was not realized to generate anthracene-based cyclophane.

Recently, McGlinchey and co-workers have observed the steric control between 9,10- versus 1,4-cycloaddition of 9-ferrocenylanthracene (**594**) and 9,10-diferrocenylanthracene (**597**) with DMAD (**28**) and N-methylmaleimide (**57**).[160] The DA reaction of 9-ferrocenylanthracene **594** with N-methylmaleimide (**57**) gave 9-ferrocenylbarrelenes **595** and with DMAD (**28**) gave 11,12-dicarbomethoxy-9-ferrocenylbarrelene (**596**), whereas the DA reaction of 9,10-diferrocenylanthracene **597** with N-methylmaleimide (**57**) occurs not only across C9 and C10 but also across C1 and C4 to yield ethenoanthracenes **598** as both endo and exo adducts, and the DA reaction of 9,10-diferrocenylanthracene **597** with DMAD (**28**) gave the C1 and C4 addition product **600** (Scheme 118).

Recently, Branda and co-workers developed a synthetic route to molecular photoswitches by the DA reaction of 3,4-dithienylfuran derivatives **601** with various dienophiles.[161] The DA reaction of chloro- or carboxyethyl thienyl-substituted furan derivatives **601** with N-ethylmaleimide (**58**) at 70 °C gave the bicyclic products **602**, which can be utilized for molecular switches. On irradiation with UV and visible light, these products undergo bidirectional ring-closing and -opening isomerization reactions. The ring-closure would turn off the reversibility of the DA reaction, and again, irradiation regenerates the ring-opened isomer, which can undergo the rDA

reaction (Scheme 119). This type of 3,4-dithienylfuran-based molecular switches has found applications in material science.

Stuparu and co-workers have designed a new synthetic strategy to corannulene-based ribbon-shaped molecules through a repetitive DA reaction.[162] In this regard, the DA reaction between **604** and furan (**20**) through in situ generation of corannulyne gave the cycyloadduct **605**, which on further DA reaction with tetracyclone generated the compound **606** as an exo–endo addition product. Further, heating of the compound **606** involves the cheleotropic elimination of CO, and subsequent rDA reaction forms isocorannulenofuran **607**, which was trapped with **605** to afford corannulene dimer **608** as a single isomer (Scheme 120). By utilizing these synthetic sequences, the authors has reported synthesis of the corannulene trimer from the tetrabromocorannulene.

Diversity-oriented synthesis can generate a library of complex molecules with a high degree of structural diversity. Because of high stereo-, regio-, and chemoselectivity in a single step, the DA reaction has been extensively used for diversity-oriented synthesis of various complex molecular frameworks. The diversity-oriented cycloaddition reactions are also employed in carbohydrate chemistry. Along with the DA reaction, other cycloaddition reactions, such as 1,3-dipolar cycloaddition, [2 + 2 + 2]-cycloaddition, Pauson-Khand reaction, and other cycloaddition reactions, have been adopted for the diversity-oriented synthesis to generate a library of useful targets. Diversity-oriented synthesis has also been employed in generation of peptidomimetics and amino acid derivatives because of its ease of adoptability to create a molecular diversity. This diversity-oriented approach has been extended to generate macrocyclic peptides suitable for drug discovery.[13]

Additional Advances in DA Reaction. The DA reaction has enhanced its utility in polycyclic chemistry with some recent notable advancements. In 2009, Xu and co-workers reported the asymmetric DA reaction in aqueous salt solution, such as seawater or brine under organocatalytic conditions, to generate cycloadducts with excellent chemo-, regio-, and stereoselectivity.[163] Recently, Scott's group reacted acetylene gas with polycyclic aromatic hydrocarbons, such as phenanthrene, perylene, and bisanthene, in a [4 + 2] cycloaddition manner to generate a higher polycyclic aromatic hydrocarbon.[164] Mukherjee and co-workers have utilized an electron-rich porous metal–organic framework (MOF), a heterogeneous catalyst for

Scheme 115. Synthesis of Highly Functionalized Constrained AAA Derivatives via DA Reaction

Ar	4-(CHO)Ph	4-(Ac)Ph	4-(OMe)Ph
Yield (%)	69ᵃ	34	24

ᵃYield without ligand

Ar	4-(CHO)Ph	4-(Ac)Ph	4-(OMe)Ph
Yield (%)	33	29	75
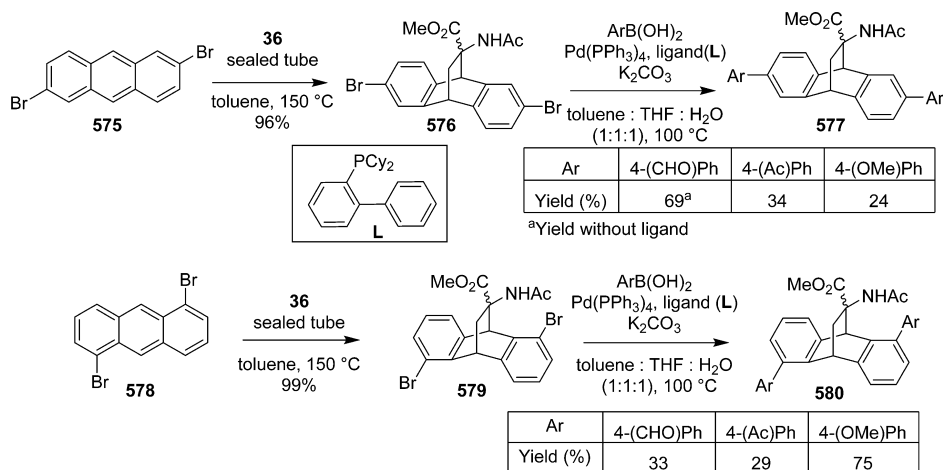
Scheme 116. Synthesis of Functionalized Bicyclo[2.2.2]octane Derivatives via DA Reaction
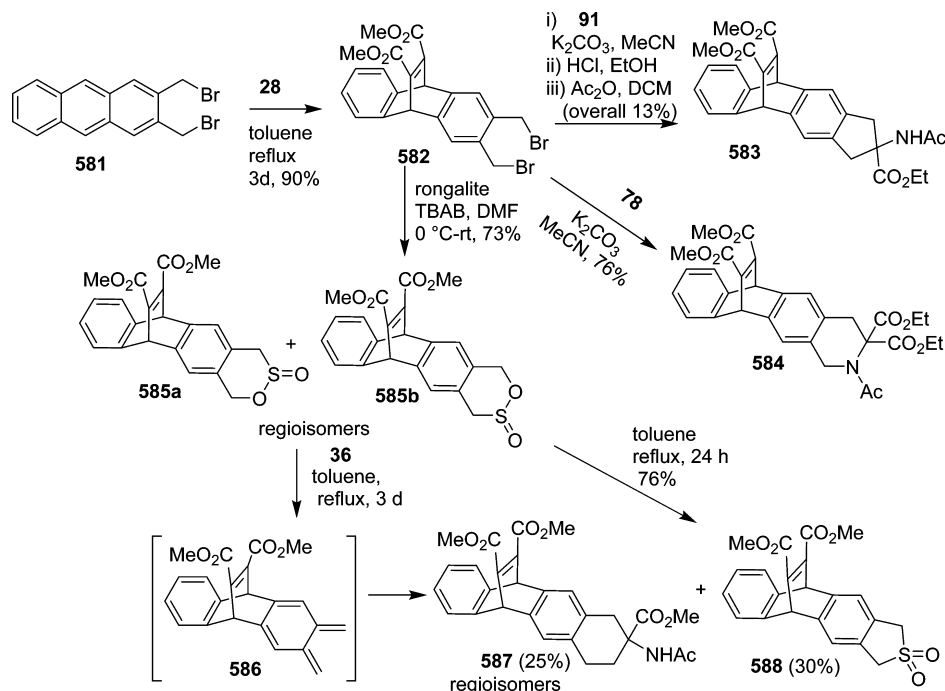
Scheme 117. Synthesis of 9,10-Bridged Anthracene Derivative 593 Involving DA Reaction and RCM As Key Steps
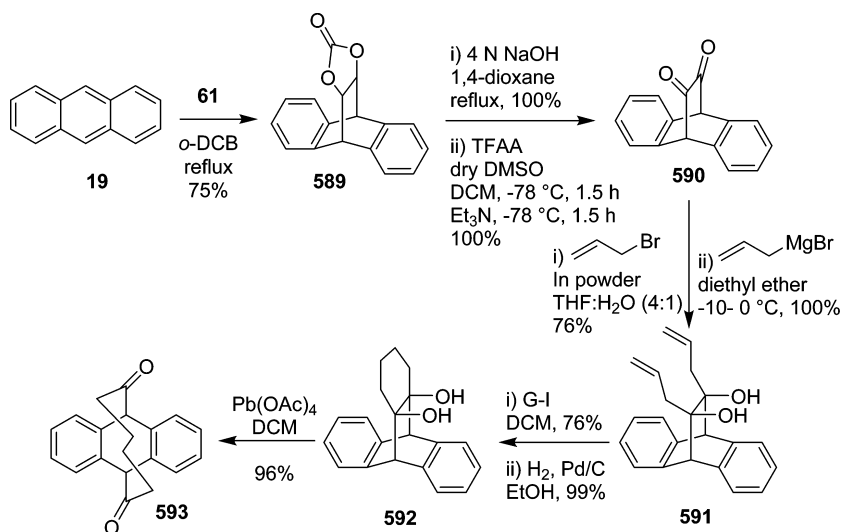
DA reaction in an efficient manner due to its high surface area, high thermal stability, and large pore volume.[165] The sequential DA reaction in combination with various other reactions, such as aldol condensation, Michael addition, Knoevenagel reaction, Pauson–Khand reaction, Ugi reaction, and enyne isomerization, have also been used. These synergistic approaches are widely and very efficiently utilized for the generation of polycyclic systems.[166] Recently, the groups of Glorius and Fu have independently disclosed the generation of cross-conjugated diene (dendralene) derivatives by Rh(III)-catalyzed C–H activation with allenes and their DA reactions with different dienophiles.[167]

■ CONCLUSIONS AND FUTURE PROSPECTS

The scope and power of the DA approach in generating diverse polycycles and unusual AAA derivatives are summarized here. Various dienes are generated easily from the alkyne building blocks by a variety of metathesis reactions, and their DA reactions with various dienophiles gave the polycycles and unusual AAA derivatives. Similarly, several o-xylylene intermediates shown here demonstrate their importance in DA chemistry for the generation of polycycles and unusual AAA derivatives. Rongalite plays a critical role in widening the scope for generating dienes. For example, methyl 2-acetamidoacrylate usage as a dienophile for tetralin-based amino acid synthesis came into use because of rongalite application. It is our opinion that if a realizable retrosynthetic path for a given target could be identified by DA strategy, it would be difficult to come up with a better strategy by other means.

By judicious choice of the diene and the dienophile, one can incorporate diversity and complexity in DA adducts. Enyne metathesis provides easy access to highly functionalized inner-outer-ring dienes. These dienes on DA reaction generate

Scheme 118. Steric Control in the DA Reaction of Substituted Anthracenes
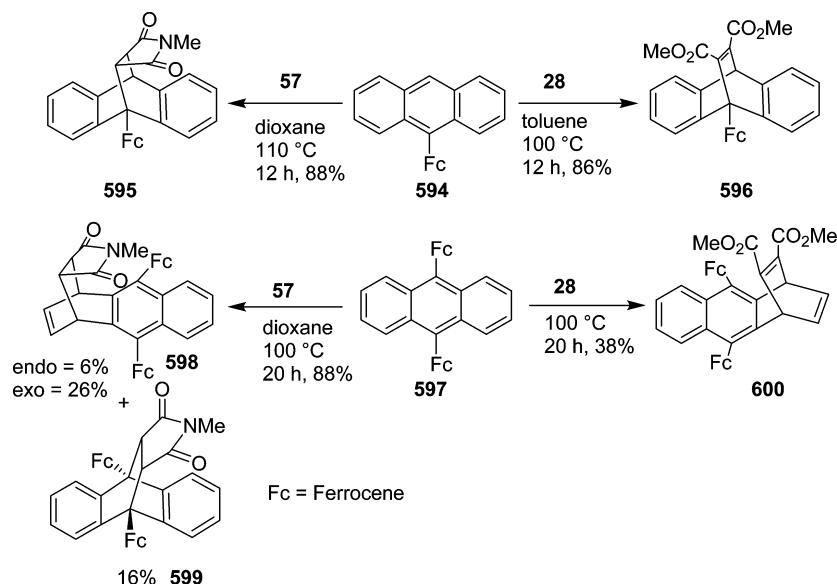
Scheme 119. Synthetic Route to Molecular Photoswitches by the DA Reaction
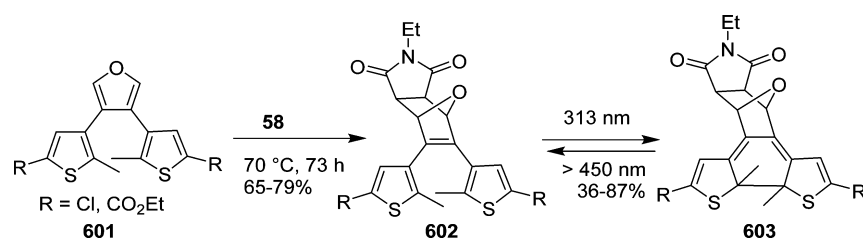
Scheme 120. Synthesis of Corannulene-Based Molecule through a Repetitive DA Reaction
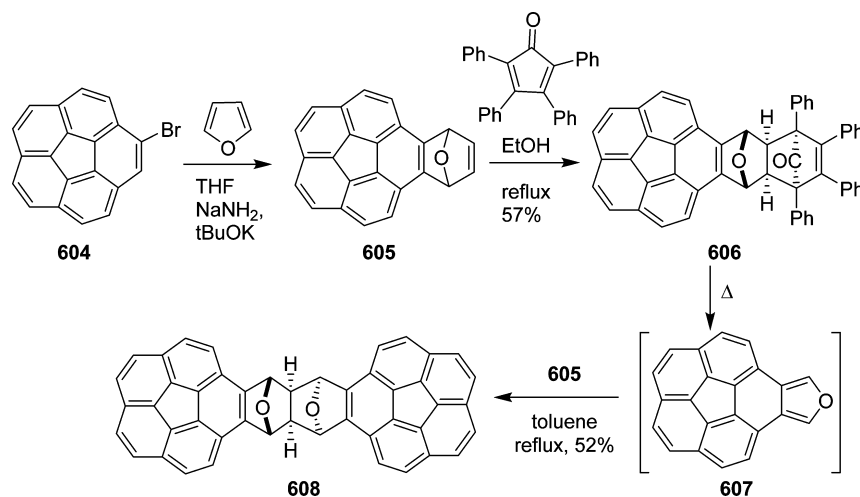
angularly annulated DA adducts. By using Hilt's condition, one could utilize nonpolar dienophiles in the DA reaction and, thus, provide access to different end products. In a complementary fashion, exo-DA reaction opens the door for the construction of other stereochemically disposed scaffolds for diversity-oriented applications. Even simple advances, such as utilization of acetylene gas as a dienophile in the DA reaction, proved to be a useful tool in the preparation of large aromatic hydrocarbons, carbon nanotubes.

By employing the DA strategy, one can build structural complexity with astonishing speed from small hydrocarbons.

By employing a cobalt catalyst system, formation of meta-substituted products is feasible, whereas normal thermal DA reaction provides ortho products predominantly. The DA reaction provides some unique advantages for diversity-oriented synthesis because a large number of dienophiles are commercially available.

Advances in diene synthesis directly translate into progress in polycyclic chemistry by DA reaction. The DA reaction is an indispensable tool in organic synthesis. The strategies reported here have enormous potential in bioorganic and medicinal chemistry and in material science. Both the power and the

scope of the DA reaction have been amply demonstrated by the examples covered here. The use of the DA reaction for the preparation of polycycles continue to grow, and the efforts to design new dienes and their utility in the DA reaction will provide efficient routes to tailor-made, complicated organic molecules.

■ AUTHOR INFORMATION

Corresponding Author
*Phone: +91 22 25767160. Fax: +91 22 25767152. E-mail: srk@chem.iitb.ac.in.

Present Addresses
†(A.S.C.) Department of Chemistry, Thakur College of Science and Commerce, Kandivali (E), Mumbai 400 101, India.
‡(D.G.) Department of Chemistry, Sri Guru Granth Sahib World University, Fatehgarh Sahib 140406, Punjab, India.

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ ABBREVIATIONS

AAA	α-amino acid
Ac	acetyl
AIBN	azobis(isobutyronitrile)
AMC	active methylene compound
aq	aqueous
BCB	benzocyclobutene
BTF	benzotrifluoride
Bz	benzoyl
CEM	cross-enyne metathesis
CM	cross-metathesis
DA	Diels−Alder
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DCNQI	dicyano-p-quinonediimine
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAM	diethyl acetamidomalonate
DEAD	diethyl acetylenedicarboxylate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
EICA	ethyl isocyanoacetate
EM	enyne-metathesis
G-I	Grubbs first-generation catalyst
G-II	Grubbs second-generation catalyst
GH-I	Grubbs−Hoveyda first-generation catalyst
GH-II	Grubbs−Hoveyda second-generation catalyst
HOMO	highest occupied molecular orbital
IPr	2,6-(diisopropyl)benzene
LAH	lithium aluminum hydride
LUMO	lowest unoccupied molecular orbital
MOM	methoxy methyl
MWI	microwave irradiation
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
o-DCB	ortho-dichlorobenzene
o-QDM	ortho-quinodimethane
p-TsCl	para-toluenesulfonyl chloride
p-TsOH/p-TSA	para-toluenesulfonic acid
Phe	phenylalanine
PTC	phase-transfer catalyst
RCEM	ring-closing enyne metathesis
RCM	ring-closing metathesis
rDA	retro Diels−Alder
ROCM	ring-opening cross-metathesis
SM	Suzuki−Miyaura
TBAB	tetrabutylammonium bromide
TBAHS	tetrabutylammonium hydrogen sulfate
TBAI	tetrabutylammonium iodide
TBS	tert-butyldimethylsilyl
TCE	tetracyanoethylene
TCNQ	tetracyano-p-quinodimethane
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
TIPS	triisopropylsilyl
TMG	1,1,3,3-tetramethylguanidine

■ REFERENCES

(1) (a) Carruthers, W. Cycloaddition Reactions in Organic Synthesis. In *Tetrahedron Organic Chemistry Series*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon: Oxford, UK, 1990; Vol. 8; pp 1−373. (b) Paquette, L. A. *Comprehensive Organic Synthesis*; Pergamon: Oxford, UK, 1991; Vol. 5. (c) Alexandrovna, M. I.; Ionin, B. I. *Alkynes in Cycloadditions*; Tebby, J. C., Ed.; John Wiley & Sons Ltd.: Chichester, UK, 2014.

(2) (a) Nawrat, C. C.; Moody, C. J. Quinones as Dienophiles in the Diels−Alder Reaction: History and Applications in Total Synthesis. *Angew. Chem., Int. Ed.* **2014**, *53*, 2056−2077. (b) Funel, J.-A.; Abele, S. Industrial Applications of the Diels−Alder Reaction. *Angew. Chem., Int. Ed.* **2013**, *52*, 3822−3863. (c) Brocksom, T. J.; Corrêa, A. G.; Naves, R. M.; Silva, F., Jr.; Catani, V.; Ceschi, M. A.; Zukerman-Schpector, J.; Toloi, A. P.; Ferreira, M. L.; Brocksom, U. Diels−Alder Reactions in the Synthesis of Higher Terpenes. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; Elsevier Science Ltd.: Oxford, UK, 2001; Vol. 5, pp 39−87. (d) Takao, K.-i.; Munakata, R.; Tadano, K.-i. Recent Advances in Natural Product Synthesis by Using Intramolecular Diels−Alder Reactions. *Chem. Rev.* **2005**, *105*, 4779−4806. (e) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels−Alder Reaction in Total Synthesis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (f) Quinkert, G.; del Grosso, M. Progress in the Diels−Alder Reaction Means Progress in Steroid Synthesis. In *Stereoselective Synthesis*; Ottow, E., Schollkopf, K., Schulz, B. G., Eds.; Springer-Verlag: Berlin, 1994. (g) Juhl, M.; Tanner, D. Recent Applications of Intramolecular Diels−Alder Reactions to Natural Product Synthesis. *Chem. Soc. Rev.* **2009**, *38*, 2983−2992. (h) *[4 + 2]-Cycloadditions in Natural Products Synthesis Through Pericyclic Reactions*; Desimoni, G., Tacconi, G., Barco, A., Pollini, G. P. ACS Monograph 180; American Chemical Society: Washington, DC, 1983.

(3) Diels, O.; Alder, K. Synthesen in Der Hydroaromatischen Reihe. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98−122.

(4) (a) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: New York, USA, 2002. (b) Pindur, U.; Lutz, G.; Otto, C. Acceleration and Selectivity Enhancement of Diels−Alder Reactions by Special and Catalytic Methods. *Chem. Rev.* **1993**, *93*, 741−761. (c) Jiang, X.; Wang, R. Recent Developments in Catalytic Asymmetric Inverse-Electron-Demand Diels−Alder Reaction. *Chem. Rev.* **2013**, *113*, 5515−5546.

(5) (a) Tarasow, T. M.; Tarasow, S. L.; Eaton, B. E. RNA-Catalysed Carbon-Carbon Bond Formation. *Nature* **1997**, *389*, 54−57. (b) Pohnert, G. Diels−Alderases. *ChemBioChem* **2001**, *2*, 873−875. (c) Tarasow, T. M.; Eaton, B. E. The Diels−Alder Reaction and Biopolymer Catalysis. *Cell. Mol. Life Sci.* **1999**, *55*, 1463−1472. (d) Seelig, B.; Jäschke, A. A Small Catalytic RNA Motif with Diels− Alderase Activity. *Chem. Biol.* **1999**, *6*, 167−176. (e) Tarasow, T. M.; Tarasow, S. L.; Tu, C.; Kellogg, E.; Eaton, B. E. Characteristics of an RNA Diels−Alderase Active Site. *J. Am. Chem. Soc.* **1999**, *121*, 3614− 3617. (f) Seelig, B.; Keiper, S.; Stuhlmann, F.; Jäschke, A. Enantioselective Ribozyme Catalysis of a Bimolecular Cycloaddition Reaction. *Angew. Chem., Int. Ed.* **2000**, *39*, 4576−4579. (g) Helm, M.; Petermeier, M.; Ge, B.; Fiammengo, R.; Jäschke, A. Allosterically Activated Diels−Alder Catalysis by a Ribozyme. *J. Am. Chem. Soc.* **2005**, *127*, 10492−10493. (h) Chandra, M.; Silverman, S. K. DNA and RNA can be Equally Efficient Catalysts for Carbon−Carbon Bond Formation. *J. Am. Chem. Soc.* **2008**, *130*, 2936−2937. (i) Keiper, S.; Bebenroth, D.; Stuhlmann, F.; Jäschke, A. RNA as a Catalyst: The Diels−Alderase Ribozyme. In *Highlights in Bioorganic Chemistry: Methods and Applications*; Schmuck, C., Wennemers, H., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005. (j) Jäschke, A. RNA as a Catalyst: The Diels−Alderase Ribozyme. In *The Chemical Biology of Nucleic Acids*; Mayer, G., Ed.; John Wiley & Sons, Ltd.: Chichester, UK, 2010.

(6) (a) Deslongchamps, P. Transannular Diels−Alder Reaction on Macrocycles. A General Strategy for the Synthesis of Polycyclic Compounds. *Pure Appl. Chem.* **1992**, *64*, 1831−1847. (b) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. The Transannular Diels− Alder Strategy: Applications to Total Synthesis. *Tetrahedron* **2001**, *57*, 4243−4260. (c) Balskus, E. P.; Jacobsen, E. N. Asymmetric Catalysis of the Transannular Diels−Alder Reaction. *Science* **2007**, *317*, 1736− 1740. (d) Jung, M. E.; Zhang, T.-H.; Lui, R. M.; Gutierrez, O.; Houk, K. N. Synthesis of a trans, syn, trans-Dodecahydrophenanthrene via a Bicyclic Transannular Diels−Alder Reaction: Intermediate for the Synthesis of Fusidic Acid. *J. Org. Chem.* **2010**, *75*, 6933−6940. (e) Prathyusha, V.; Ramakrishna, S.; Deva Priyakumar, U. Trans-annular Diels−Alder Reactivities of 14-Membered Macrocyclic Trienes and Their Relationship with the Conformational Preferences of the Reactants: A Combined Quantum Chemical and Molecular Dynamics Study. *J. Org. Chem.* **2012**, *77*, 5371−5380. (f) Iafe, R. G.; Kuo, J. L.; Hochstatter, D. G.; Saga, T.; Turner, J. W.; Merlic, C. A. Increasing the Efficiency of the Transannular Diels−Alder Strategy via Palladium(II)-Catalyzed Macrocyclizations. *Org. Lett.* **2013**, *15*, 582−585. (g) Campbell, E. L.; Skepper, C. K.; Sankar, K.; Duncan, K. K.; Boger, D. L. Transannular Diels−Alder/1,3-Dipolar Cycloaddition Cascade of 1,3,4-Oxadiazoles: Total Synthesis of a Unique Set of Vinblastine Analogues. *Org. Lett.* **2013**, *15*, 5306−5309.

(7) (a) Wessig, P.; Müller, G. The Dehydro-Diels−Alder Reaction. *Chem. Rev.* **2008**, *108*, 2051−2063. (b) Wessig, P.; Matthes, A.; Pick, C. The Photo-Dehydro-Diels−Alder (PDDA) Reaction. *Org. Biomol. Chem.* **2011**, *9*, 7599−7605. (c) Zhang, M.; Zhang, J. Base-Catalyzed Tandem Michael/Dehydro-Diels−Alder Reaction of α,α-Dicyanoolefins with Electron-Deficient 1,3-Conjugated Enynes: A Facile Entry to Angularly Fused Polycycles. *Chem.—Eur. J.* **2014**, *20*, 399−404. (d) Kocsis, L. S.; Benedetti, E.; Brummond, K. M. A Thermal Dehydrogenative Diels−Alder Reaction of Styrenes for the Concise Synthesis of Functionalized Naphthalenes. *Org. Lett.* **2012**, *14*, 4430− 4433.

(8) (a) Bradley, A. Z.; Johnson, R. P. Thermolysis of 1,3,8-Nonatriyne: Evidence for Intramolecular [2 + 4] Cycloaromatization to a Benzyne Intermediate. *J. Am. Chem. Soc.* **1997**, *119*, 9917−9918. (b) Tsui, J. A.; Sterenberg, B. T. A Metal-Templated 4 + 2 Cycloaddition Reaction of an Alkyne and a Diyne To Form a 1,2-Aryne. *Organometallics* **2009**, *28*, 4906−4908. (c) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. The Hexadehydro-Diels−Alder Reaction. *Nature* **2012**, *490*, 208−212. (d) Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P.; Hoye, T. R. Synthesis of Complex Benzenoids via the Intermediate Generation of *o*-Benzynes Through the Hexadehydro-Diels−Alder Reaction. *Nat. Protoc.* **2013**, *8*, 501−

508. (e) Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. Alder-Ene Reactions of Arynes. *Org. Lett.* **2013**, *15*, 1938−1941. (f) Karmakar, R.; Yun, S. Y.; Wang, K.-P.; Lee, D. Regioselectivity in the Nucleophile Trapping of Arynes: The Electronic and Steric Effects of Nucleophiles and Substituents. *Org. Lett.* **2014**, *16*, 6−9. (g) Niu, D.; Wang, T.; Woods, B. P.; Hoye, T. R. Dichlorination of (Hexadehydro-Diels−Alder Generated) Benzynes and a Protocol for Interrogating the Kinetic Order of Bimolecular Aryne Trapping Reactions. *Org. Lett.* **2014**, *16*, 254−257. (h) Holden (née Hall), C.; Greaney, M. F. The Hexadehydro-Diels−Alder Reaction: A New Chapter in Aryne Chemistry. *Angew. Chem., Int. Ed.* **2014**, *53*, 5746−5749.

(9) Pandey, B.; Dalvi, P. V. Photo-induced exo-Selective Diels−Alder Reactions. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1612−1613.

(10) (a) Sibi, M. P.; Nie, X.; Shackleford, J. P.; Stanley, L. M.; Bouret, F. Exo- and Enantioselective Diels−Alder Reactions: Pyrazolidinone Auxiliaries as a Means to Enhanced Exo Selectivity. *Synlett* **2008**, 2655−2658. (b) Kano, T.; Tanaka, Y.; Maruoka, K. Exo-Selective Asymmetric Diels−Alder Reaction Catalyzed by Diamine Salts as Organocatalysts. *Chem.—Asian J.* **2007**, *2*, 1161−1165. (c) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. Exo-Selective Asymmetric Diels−Alder Reaction of 2,4-Dienals and Nitroalkenes by Trienamine Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638−8641. (d) Gotoh, H.; Hayashi, Y. Diarylprolinol Silyl Ether as Catalyst of an exo-Selective, Enantioselective Diels−Alder Reaction. *Org. Lett.* **2007**, *9*, 2859−2862. (e) Kano, T.; Tanaka, Y.; Maruoka, K. Exo-Selective Asymmetric Diels−Alder Reaction Catalyzed by Diamine Salts as Organocatalysts. *Org. Lett.* **2006**, *8*, 2687−2689.

(11) (a) Maruoka, K.; Imoto, H.; Yamamoto, H. Exo-Selective Diels−Alder Reaction Based on a Molecular Recognition Approach. *J. Am. Chem. Soc.* **1994**, *116*, 12115−12116. (b) Node, M.; Nishide, K.; Imazato, H.; Kuroasaki, R.; Inoue, T.; Ikariya, T. Exo-Selective Diels−Alder Reaction of Nitroolefins with Danishefsky's Diene. *Chem. Commun.* **1996**, 2559−2560. (c) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D.; Waltermire, B. E.; Rheingold, A. L. Asymmetric Exo-Selective Diels−Alder Reactions by Steric Attenuation of Secondary Orbital Interactions. *J. Am. Chem. Soc.* **1997**, *119*, 6438−6439. (d) Lam, Y.-H.; Cheong, P. H.-Y.; Blasco Mata, J. M.; Stanway, S. J.; Gouverneur, V.; Houk, K. N. Diels−Alder Exo Selectivity in Terminal-Substituted Dienes and Dienophiles: Experimental Discoveries and Computational Explanations. *J. Am. Chem. Soc.* **2009**, *131*, 1947−1957.

(12) (a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; Wiley-VCH: New York, USA, 1990. (b) Fringuelli, F.; Taticchi, A. *The Diels−Alder Reaction: Selected Practical Methods*; Wiley-VCH: New York, USA, 2002.

(13) (a) Schreiber, S. L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science* **2000**, *287*, 1964−1969. (b) Spring, D. R. Diversity-Oriented Synthesis; A Challenge for Synthetic Chemists. *Org. Biomol. Chem.* **2003**, *1*, 3867−3870. (c) Burke, M. D.; Schreiber, S. L. A Planning Strategy for Diversity-Oriented Synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58. (d) Tan, D. S. Diversity-Oriented Synthesis: Exploring the Intersections between Chemistry and Biology. *Nature Chem. Biol.* **2005**, *1*, 74−84. (e) Radha Krishna, P.; Srinivas Reddy, P. Diversity Oriented Synthesis of Functionalized Chiral Tetrahydropyridines: Potential GABA Receptor Agonists and Azasugars from Natural Amino Acids via a Sequential Baylis−Hillman Reaction and RCM Protocol. *J. Comb. Chem.* **2008**, *10*, 426−435. (f) O'Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. Diversity-Oriented Synthesis: Producing Chemical Tools for Dissecting Biology. *Chem. Soc. Rev.* **2012**, *41*, 4444−4456. (g) *Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery and Chemical Biology*; Trabocchi, A., Ed.; John-Wiley & Sons, Inc., Hoboken, New Jersey, USA, 2013. (h) *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; ACS Symposium Series 494, American Chemical Society: Washington, DC, 1992.

(14) (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2003; Vol. *1−3*. (b) Grubbs, R. H.; Schrock, R. R.; Fürstner, A. *Advanced Synthesis & Catalysis, Olefin Metathesis*; Wiley-VCH Verlag GmbH & Co.

KGaA: Weinheim, Germany, 2007, Vol. 349, pp 1−265. (c) Kotha, S.; Lahiri, K. Synthesis of Diverse Polycyclic Compounds via Catalytic Metathesis. *Synlett* **2007**, 2767−2784. (d) Grubbs, R. H. Olefin Metathesis. *Tetrahedron* **2004**, 60, 7117−7140. (e) Fürstner, A. Olefin Metathesis and Beyond. *Angew. Chem., Int. Ed.* **2000**, 39, 3012−3043. (f) Hoveyda, A. H.; Zhugralin, A. R. The Remarkable Metal-Catalysed Olefin Metathesis Reaction. *Nature* **2007**, 450, 243−251. (g) Kotha, S.; Sreenivasachary, N. Catalytic Metathesis Reaction in Organic Synthesis. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2001**, 40B, 763−780. (h) Kotha, S.; Dipak, M. K. Strategies and Tactics in Olefin Metathesis. *Tetrahedron* **2012**, 68, 397−421. (i) Wojtkielewicz, A. Application of Cross Metathesis in Diene and Polyene Synthesis. *Curr. Org. Synth.* **2013**, 10, 43−66.

(15) *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007.

(16) Kotha, S.; Khedkar, P. Rongalite: A Useful Green Reagent in Organic Synthesis. *Chem. Rev.* **2012**, 112, 1650−1680.

(17) (a) Kotha, S.; Bandarugattu, V. B.; Krishna, N. G. Diversity-Oriented Approach to Unusual Amino Acid Derivatives and Heterocycles via Methyl 2-Acetamidoacrylate and its Congeners. *Tetrahedron* **2014**, 70, 5361−5384. (b) Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. Synthesis of a New Constrained Homoserine. *Synlett* **1995**, 891−892.

(18) Kotha, S.; Meshram, M.; Tiwari, A. Advanced Approach to Polycyclics by a Synergistic Combination of Enyne Metathesis and Diels−Alder Reaction. *Chem. Soc. Rev.* **2009**, 38, 2065−2092.

(19) Kotha, S.; Misra, S.; Halder, S. Benzannulation. *Tetrahedron* **2008**, 64, 10775−10790.

(20) Kotha, S.; Mandal, K.; Banerjee, S.; Mobin, S. M. Synthesis of Novel Quinone−Amino Acid Hybrids via Cross-Enyne Metathesis and Diels−Alder Reaction as Key Steps. *Eur. J. Org. Chem.* **2007**, 1244−1255.

(21) (a) Kotha, S.; Halder, S. Ethyl Isocyanoacetate as a Useful Glycine Equivalent. *Synlett* **2010**, 337−354. (b) Kotha, S.; Brahmachary, E. Synthesis of Conformationally Constrained α-Amino Acid Derivatives Using Ethyl Isocyanoacetate as Glycine Equivalent. *Bioorg. Med. Chem. Lett.* **1997**, 7, 2719−2722.

(22) (a) Maruoka, K.; Ooi, T. Enantioselective Amino Acid Synthesis by Chiral Phase-Transfer Catalysis. *Chem. Rev.* **2003**, 103, 3013−3028. (b) O'Donnell, M. J. The Enantioselective Synthesis of α-Amino Acids by Phase-Transfer Catalysis with Achiral Schiff Base Esters. *Acc. Chem. Res.* **2004**, 37, 506−517. (c) Ooi, T.; Maruoka, K. Recent Advances in Asymmetric Phase-Transfer Catalysis. *Angew. Chem., Int. Ed.* **2007**, 46, 4222−4266. (d) Shirakawa, S.; Maruoka, K. Recent Developments in Asymmetric Phase-Transfer Reactions. *Angew. Chem., Int. Ed.* **2013**, 52, 4312−4348. (e) Ooi, T. Cinchona-Derived Chiral Phase-Transfer Catalysts for Amino Acid Synthesis. In *Asymmetric Phase-Transfer Catalysis*; Maruoka, K., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008.

(23) Berkheij, M.; Dijkink, J.; David, O. R. P.; Sonke, T.; IJzendoorn, D. R.; Blaauw, R. H.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H. Synthesis of a Naturally Occurring Diene-Containing Amino Acid and Its Glutamyl Dipeptide via N-Acyliminium Ion Chemistry. *Eur. J. Org. Chem.* **2008**, 914−924.

(24) Chen, R.; Lee, V.; Adlington, R. M.; Baldwin, J. E. A Facile Synthesis of Ethyl 2-Acetamido-4-methylenehex-5-enoate, a Versatile Diels−Alder Synthon for the Parallel Synthesis of Novel α-Amino Acid Derivatives. *Synthesis* **2007**, 113−117.

(25) Kotha, S.; Goyal, D.; Thota, N.; Srinivas, V. Synthesis of Modified Phenylalanine Peptides by Cross Enyne Metathesis and a Diels−Alder Reaction as Key Steps. *Eur. J. Org. Chem.* **2012**, 1843−1850.

(26) (a) Kotha, S.; Halder, S.; Brahmachary, E.; Ganesh, T. Synthesis of Unusual α-Amino Acid Derivatives via Cross-Enyne Metathesis Reaction. *Synlett* **2000**, 853−855. (b) Kotha, S.; Halder, S.; Brahmachary, E. Synthesis of Highly Functionalized Phenylalanine Derivatives via Cross-Enyne Metathesis Reactions. *Tetrahedron* **2002**, 58, 9203−9208.

(27) Kotha, S.; Vijayalaxmi, B. Diversity Oriented Approach to Phenylalanine Derivatives via the Diels−Alder Reaction Involving Sulfolene Intermediates. *Heterocycles* **2015**, 90, 226−237.

(28) (a) Su, C.-R.; Shen, Y.-C.; Kuo, P.-C.; Leu, Y.-L.; Damu, A. G.; Wang, Y.-H.; Wu, T.-S. Total Synthesis and Biological Evaluation of Viscolin, A 1,3-Diphenylpropane as a Novel Potent Anti-Inflammatory Agent. *Bioorg. Med. Chem. Lett.* **2006**, 16, 6155−6160. (b) Hwang, T.-L.; Leu, Y.-L.; Kao, S.-H.; Tang, M.-C.; Chang, H.-L. Viscolin, a New Chalcone from Viscum Coloratum, Inhibits Human Neutrophil Superoxide Anion and Elastase Release via a Camp-Dependent Pathway. *Free Radical Biol. Med.* **2006**, 41, 1433−1441. (c) Greer, V. P.; Mason, P.; Kirby, A. J.; Smith, H. J.; Nicholls, P. J.; Simons, C. Some 1,2-Diphenylethane Derivatives as Inhibitors of Retinoic Acid-Metabolising Enzymes. *J. Enzyme Inhib. Med. Chem.* **2003**, 18, 431−443.

(29) Kotha, S.; Khedkar, P. A Diversity-Oriented Approach to Diphenylalkanes by Strategic Utilization of [2 + 2 + 2] Cyclotrimerization, Cross-Enyne Metathesis and Diels−Alder Reaction. *Eur. J. Org. Chem.* **2009**, 730−738.

(30) Kotha, S.; Chavan, A. S. Design and Synthesis of Benzosultine-sulfone as an o-Xylylene Precursor via Cross-Enyne Metathesis and Rongalite: Further Expansion to Polycyclics via Regioselective Diels−Alder Reaction. *J. Org. Chem.* **2010**, 75, 4319−4322.

(31) (a) Kotha, S.; Vittal, S. Diversity-Oriented Synthesis of Biaryl Derivatives Using Cross-Enyne Metathesis, Diels−Alder Reaction, and Suzuki−Miyaura Cross-Coupling as Key Steps. *Synlett* **2011**, 2329−2334. (b) Kotha, S.; Vittal, S.; Banerjee, S.; Dipak, M. K. Diversity-Oriented Approach to Polycyclics via Cross-Enyne Metathesis and Diels−Alder Reaction as Key Steps. *J. Chem. Sci.* **2015**, 127, 155−162.

(32) (a) Kotha, S.; Lahiri, K.; Kashinath, D. Recent Applications of the Suzuki−Miyaura Cross-Coupling Reaction in Organic Synthesis. *Tetrahedron* **2002**, 58, 9633−9695. (b) Kotha, S.; Lahiri, K. Expanding the Diversity of Polycyclic Aromatics through a Suzuki−Miyaura Cross-Coupling Strategy. *Eur. J. Org. Chem.* **2007**, 1221−1236. (c) Kotha, S.; Mandal, K. A Retrospective on the Design and Synthesis of Novel Molecules Through a Strategic Consideration of Metathesis and Suzuki−Miyaura Cross-Coupling. *Chem.—Asian J.* **2009**, 4, 354−362.

(33) Kotha, S.; Mandal, K. Metathesis of a Novel Dienediyne System: A Unique Example Involving the Usage of In Situ Generated Ethylene as Cross-Enyne Metathesis Partner. *J. Organomet. Chem.* **2007**, 692, 4921−4927.

(34) Mori, M.; Tonogaki, K.; Nishiguchi, N. Syntheses of Anolignans A and B Using Ruthenium-Catalyzed Cross-Enyne Metathesis. *J. Org. Chem.* **2002**, 67, 224−226.

(35) Rimando, A. M.; Pezzuto, J. M.; Farnsworth, N. R. New Lignans from Anogeissus Acuminata with HIV-1 Reverse Transcriptase Inhibitory Activity. *J. Nat. Prod.* **1994**, 57, 896−904.

(36) Kaliappan, K. P.; Subrahmanyam, A. V. A New Versatile Strategy for C-Aryl Glycosides. *Org. Lett.* **2007**, 9, 1121−1124.

(37) Subrahmanyam, A. V.; Palanichamy, K.; Kaliappan, K. P. Application of an Enyne Metathesis/Diels−Alder Cycloaddition Sequence: A New Versatile Approach to the Syntheses of C-Aryl Glycosides and Spiro-C-Aryl Glycosides. *Chem.—Eur. J.* **2010**, 16, 8545−8556.

(38) Pujari, S. A.; Kaliappan, K. P.; Valleix, A.; Grée, D.; Grée, R. A Rapid Access to New Fluorinated 1,3-Dienes and Benzylic Fluorides via Metathesis on Propargylic Fluorides. *Synlett* **2008**, 2503−2507.

(39) Fustero, S.; Bello, P.; Miró, J.; Sánchez-Roselló, M.; Haufe, G.; del Pozo, C. One-Pot Cross-Enyne Metathesis (CEYM)/Diels−Alder Reaction of Gem-Difluoropropargylic Alkynes. *Beilstein J. Org. Chem.* **2013**, 9, 2688−2695.

(40) Fustero, S.; Bello, P.; Miró, J.; Simón, A.; del Pozo, C. 1,7-Octadiene-Assisted Tandem Multicomponent Cross-Enyne Metathesis (CEYM)/Diels−Alder Reactions: A Useful Alternative to Mori's Conditions. *Chem.—Eur. J.* **2012**, 18, 10991−10997.

(41) Karabulut, S.; Sariaslan, B.; Öztürk, B. Ö. A Ruthenium-Based Catalytic System with Switchable Selectivity Between Cyclotrimeriza-

tion and Enyne Metathesis/Diels—Alder Reactions of Terminal Alkynes. *Catal. Commun.* **2013**, *41*, 12—16.

(42) (a) Krohn, K. Total Synthesis of Anthracyclinone. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790—807. (b) Lown, J. W. Discovery and Development of Anthracycline Antitumour Antibiotics. *Chem. Soc. Rev.* **1993**, *22*, 165—176.

(43) Kotha, S.; Stoodely, R. J. Enantioselective Synthesis of (+)-4-Demethoxy-1,4-dimethyldaunomycinone. *Bioorg. Med. Chem.* **2002**, *10*, 621—624.

(44) Kotha, S.; Chavan, A. S.; Dipak, M. K. Synthetic Approach to *cis*- and *trans*-Decalins via Diels—Alder Reaction and Ring-Closing Metathesis as Key Steps: Further Extension to Dioxapropellane Derivative by Ring-Closing Metathesis. *Tetrahedron* **2011**, *67*, 501—504.

(45) Chopin, N.; Gérard, H.; Chataigner, I.; Piettre, S. R. Benzofurans as Efficient Dienophiles in Normal Electron Demand [4 + 2] Cycloadditions. *J. Org. Chem.* **2009**, *74*, 1237—1246.

(46) Hayashi, T.; Usuki, Y.; Wakamatsu, Y.; Iio, H. Synthesis of (*E*)-1-Benzyloxy-3-fluoro-1,3-butadiene: A Novel Fluorinated Diene for Diels—Alder Reactions. *Synlett* **2010**, 2843—2846.

(47) Nawrat, C. C.; Palmer, L. I.; Blake, A. J.; Moody, C. J. Two Approaches to the Aromatic Core of the Aminonaphthoquinone Antibiotics. *J. Org. Chem.* **2013**, *78*, 5587—5603.

(48) Kozmin, S. A.; Rawal, V. H. Preparation and Diels—Alder Reactivity of 1-Amino-3-siloxy-1,3-butadienes. *J. Org. Chem.* **1997**, *62*, 5252—5253.

(49) Kozmin, S. A.; Rawal, V. H. Asymmetric Diels—Alder Reactions of Chiral 1-Amino-3-siloxy-1,3-butadiene: Application to the Enantioselective Synthesis of (−)-α-Elemene. *J. Am. Chem. Soc.* **1997**, *119*, 7165—7166.

(50) Paczkowski, R.; Maichle-Mössmer, C.; Maier, M. E. A Formal Total Synthesis of Dysidiolide. *Org. Lett.* **2000**, *2*, 3967—3969.

(51) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. An Efficient Approach to Aspidosperma Alkaloids via [4 + 2] Cycloadditions of Aminosiloxydienes: Stereocontrolled Total Synthesis of (±)-Tabersonine. Gram-Scale Catalytic Asymmetric Syntheses of (+)-Tabersonine and (+)-16-Methoxytabersonine. Asymmetric Syntheses of (+)-Aspidospermidine and (−)-Quebrachamine. *J. Am. Chem. Soc.* **2002**, *124*, 4628—4641.

(52) Holmes, J. M.; Albert, A. L.; Gravel, M. Practical Synthesis and Highly Diastereoselective Diels—Alder Reactions of 1-Alkylthio-3-silyloxybutadienes. *J. Org. Chem.* **2009**, *74*, 6406—6409.

(53) Hilt, G.; Smolko, K. I. Alkynylboronic Esters as Efficient Dienophiles in Cobalt-Catalyzed Diels—Alder Reactions. *Angew. Chem., Int. Ed.* **2003**, *42*, 2795—2797.

(54) Hilt, G.; Hess, W.; Schmidt, F. Dihydroaromatic Boronic Esters as Building Blocks for the Synthesis of Phenanthrenes and Phenanthridines. *Eur. J. Org. Chem.* **2005**, 2526—2533.

(55) Hilt, G.; Pünner, F. Diels—Alder Reactions. In *Transition Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; John-Wiley & Sons, Inc.: Hoboken, New Jersey, USA, 2013.

(56) Hilt, G.; Janikowski, J. Regiocontrolled Cobalt-Catalyzed Diels—Alder Reactions of Silicon-Functionalized, Terminal, and Internal Alkynes. *Org. Lett.* **2009**, *11*, 773—776.

(57) Danz, M.; Hilt, G. Regiodiverse Three-Component Synthesis of Arenes. *Adv. Synth. Catal.* **2011**, *353*, 303—308.

(58) Kuttner, J.-R.; Warratz, S.; Hilt, G. Straightforward Synthesis of Nonconjugated Cyclohex-3-enone and Conjugated 4-Methylenecyclohex-2-enone Derivatives. *Synthesis* **2012**, 1293—1303.

(59) Arndt, M.; Hilt, G.; Khlebnikov, A. F.; Kozhushkov, S. I.; de Meijere, A. Diels—Alder Reactions for the Construction of Cyclopropylarenes. *Eur. J. Org. Chem.* **2012**, 3112—3121.

(60) Pünner, F.; Schieven, J.; Hilt, G. Synthesis of Fluorenone and Anthraquinone Derivatives from Aryl- and Aroyl-Substituted Propiolates. *Org. Lett.* **2013**, *15*, 4888—4891.

(61) Anand, N.; Upadhyaya, K.; Ajay, A.; Mahar, R.; Shukla, S. K.; Kumar, B.; Tripathi, R. P. A Strategy for the Synthesis of Anthraquinone-Based Aryl-*C*-glycosides. *J. Org. Chem.* **2013**, *78*, 4685—4696.

(62) (a) Hopf, H. Dendralenes: The Breakthrough. *Angew. Chem., Int. Ed.* **2001**, *40*, 705—707. (b) Hopf, H. Forgotten Hydrocarbons Prepared. *Nature* **2009**, *460*, 183—184. (c) Hopf, H.; Sherburn, M. S. Dendralenes Branch Out: Cross-Conjugated Oligoenes Allow the Rapid Generation of Molecular Complexity. *Angew. Chem., Int. Ed.* **2012**, *51*, 2298—2338.

(63) Bradford, T. A.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. Practical Synthesis and Reactivity of [3]Dendralene. *J. Org. Chem.* **2010**, *75*, 491—494 and references cited therein..

(64) Woo, S.; Squires, N.; Fallis, A. G. Indium-Mediated γ-Pentadienylation of Aldehydes and Ketones: Cross-Conjugated Trienes for Diene-Transmissive Cycloadditions. *Org. Lett.* **1999**, *1*, 573—576.

(65) Kwon, O.; Park, S. B.; Schreiber, S. L. Skeletal Diversity via a Branched Pathway: Efficient Synthesis of 29400 Discrete, Polycyclic Compounds and Their Arraying into Stock Solutions. *J. Am. Chem. Soc.* **2002**, *124*, 13402—13404.

(66) Kormann, C.; Heinemann, F. W.; Gmeiner, P. A Consecutive Diels—Alder Approach Toward a Tet Repressor Directed Combinatorial Library. *Tetrahedron* **2006**, *62*, 6899—6908.

(67) Singh, R.; Ghosh, S. K. Synthesis of Substituted [3]Dendralenes and Their Unique Cycloaddition Reactions. *Chem. Commun.* **2011**, *47*, 10809—10811.

(68) Hopf, H.; Yildizhan, S. Highly Functionalized, Angularly Anellated Aromatic Compounds from Dendralenes. *Eur. J. Org. Chem.* **2011**, 2029—2034.

(69) Pronin, S. V.; Shenvi, R. A. Synthesis of a Potent Antimalarial Amphilectene. *J. Am. Chem. Soc.* **2012**, *134*, 19604—19606.

(70) Wang, R.; Bojase, G.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. Nitroso-Dienophile Additions to Dendralenes: A Short Synthesis of Branched Aminosugars. *Org. Lett.* **2012**, *14*, 5652—5655.

(71) Rahif, M.; Roux, M.; Thibonnet, J.; Parrain, J.-L. 3-Bromopenta-2,4-dienylsilane: A Useful Reagent for the Preparation of [3]-Dendralenes and Polycyclic Compounds. *Mol. Divers.* **2013**, *17*, 49—53.

(72) Green, N. J.; Lawrence, A. L.; Bojase, G.; Paddon-Row, M. N.; Sherburn, M. S. Domino Cycloaddition Organocascades of Dendralenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 8333—8336.

(73) Vigneron, J. P.; Dhaenens, M.; Horeau, A. Nouvelle Methode Pour Porter au Maximum la Purete Optique D'un Produit Partiellement Dedouble Sans L'aide D'aucune Substance Chirale. *Tetrahedron* **1973**, *29*, 1055—1059.

(74) Fallon, T.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. Furanodendralenes. *J. Org. Chem.* **2014**, *79*, 3185—3193.

(75) (a) Kotha, S.; Brahmachary, E.; Sreenivasachary, N. Synthesis of Constrained α-Amino Acid Derivatives via Diels—Alder Approach. *Tetrahedron Lett.* **1998**, *39*, 4095—4098. (b) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. Synthesis of Benzocycloheptene-Based Amino Acid Derivatives via a [4 + 2] Cycloaddition Reaction as a Key Step. *Tetrahedron* **2001**, *57*, 6261—6265.

(76) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. Selected Synthetic Strategies to Spirocyclics. *Synthesis* **2009**, 165—193.

(77) Kotha, S.; Manivanann, E. Synthesis of Spiro-Indanes by Cycloaddition Strategy. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2543—2547.

(78) Kotha, S.; Waghule, G. T. Diversity Oriented Approach to Crownophanes by Enyne Metathesis and Diels—Alder Reaction as Key Steps. *J. Org. Chem.* **2012**, *77*, 6314—6318.

(79) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. Domino Coupling Relay Approach to Polycyclic Pyrrole-2-carboxylates. *J. Am. Chem. Soc.* **2005**, *127*, 10804—10805.

(80) (a) Segura, J. L.; Martin, N. *o*-Quinodimethanes: Efficient Intermediates in Organic Synthesis. *Chem. Rev.* **1999**, *99*, 3199—3246. (b) Martin, N.; Seoane, C.; Hanack, M. Recent Advances in *o*-Quinodimethane Chemistry. *Org. Prep. Proced. Int.* **1991**, *23*, 237—272. (c) Charlton, J. L.; Alauddin, M. M. Orthoquinodimethanes. *Tetrahedron* **1987**, *43*, 2873—2889. (d) Oppolzer, W. Intramolecular Cycloaddition Reactions of ortho-Quinodimethanes in Organic

Synthesis. *Synthesis* **1978**, 793−802. (e) Bieber, L. W.; Da Silva, M. F. Generation and Cycloaddition of *o*-Quinodimethane in Aqueous Medium. *Molecules* **2001**, *6*, 472−476.

(81) Hoey, M. D.; Dittmer, D. C. A Convenient Synthesis of 1,4-Dihydro-2,3-Benzoxathiin 3-Oxide, A Useful Precursor of *o*-Quinodimethane. *J. Org. Chem.* **1991**, *56*, 1947−1948.

(82) (a) Kotha, S.; Ganesh, T.; Ghosh, A. K. Diels−Alder Approach to Tetralin-Based Constrained *α*-Amino Acid Derivatives. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1755−1757. (b) Kotha, S.; Ghosh, A. K. The Diels−Alder Approach for the Synthesis of Tetralin-Based *α*-Amino Acid Derivatives and their Modification by the Suzuki−Miyaura Cross-Coupling Reaction. *Synthesis* **2004**, 558−567.

(83) Kotha, S.; Misra, S.; Srinivas, V. Diversity Oriented Approach to Polycyclic Compounds through the Diels−Alder Reaction and the Suzuki Coupling. *Eur. J. Org. Chem.* **2012**, 4052−4062.

(84) Kotha, S.; Meshram, M. Synthesis of Polycyclic Aromatics from a Diiodosultine by Suzuki−Miyaura Cross-Coupling and Diels−Alder Reaction. *Heterocycles* **2011**, *82*, 1663−1668.

(85) (a) Kotha, S.; Ghosh, A. K. A Diels−Alder Approach for the Synthesis of Highly Functionalized Benzo-Annulated Indane-Based *α*-Amino Acid Derivatives via a Sultine Intermediate. *Tetrahedron Lett.* **2004**, *45*, 2931−2934. (b) Kotha, S.; Ghosh, A. K. Cycloaddition Approach to Benzo-Annulated Indane-Based *α*-Amino Acid Derivatives. *Tetrahedron* **2004**, *60*, 10833−10841.

(86) Garcia, L.; Pla-Quintana, A.; Roglans, A. Synthesis of Non-Proteinogenic Phenylalanine Derivatives by Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition Reactions. *Org. Biomol. Chem.* **2009**, *7*, 5020−5027.

(87) Senaiar, R. S.; Teske, J. A; Young, D. D.; Deiters, A. Synthesis of Indanones via Solid-Supported [2 + 2 + 2] Cyclotrimerization. *J. Org. Chem.* **2007**, *72*, 7801−7804.

(88) (a) Bianco, A.; Da Ros, T.; Prato, M.; Toniolo, C. Fullerene-Based Amino Acids and Peptides. *J. Pept. Sci.* **2001**, *7*, 208−219. (b) Da Ros, T.; Prato, M. Medicinal Chemistry with Fullerenes and Fullerene Derivatives. *Chem. Commun.* **1999**, 663−669. (c) Burley, G. A.; Keller, P. A.; Pyne, S. G.; Ball, G. E. Synthesis and Characterization of Mono- and Bis-methano[60]fullerenyl Amino Acid Derivatives and Their Reductive Ring-Opening Retro-Bingel Reactions. *J. Org. Chem.* **2002**, *67*, 8316−8330.

(89) (a) Kotha, S.; Banerjee, S. Synthesis of Novel 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid Derivatives Through the Application of Rongalite: A Synergistic Combination of [2 + 2 + 2]- and [4 + 2] Cycloaddition Reactions. *Synthesis* **2007**, 1015−1020. (b) Kotha, S.; Sreenivasachary, N. A New Synthetic Approach to 1,2,3,4-Tetrahydroisoquinoline-3-Carboxylic Acid (Tic) Derivatives via a [2 + 2 + 2] Cycloaddition Reaction. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1413−1415.

(90) Shchetnikov, G. T.; Osipov, S. N.; Bruneau, C.; Dixneuf, P. H. Ruthenium-Catalyzed Cyclotrimerization of 1,6- and 1,7-Azadiynes: New Access to Fluorinated Bicyclic Amino Acids. *Synlett* **2008**, 578−582.

(91) Kotha, S.; Kashinath, D.; Khedkar, P. Synthesis of Crown-Based Sulfones via Rongalite: Diversity-Oriented Approach to Annulated Benzocrowns by Diels−Alder Reactions. *Synthesis* **2007**, 3357−3360.

(92) (a) Wu, A.-T.; Liu, W.-D.; Chung, W.-S. The Synthesis of Naphthosultine and Benzodisultines and Their Pyrolysis with Dienophiles: Studies on *o*-Naphthoquinodimethane and Bis-*o*-Quinodimethane. *J. Chin. Chem. Soc.* **2002**, *49*, 77−82. (b) Cava, M. P.; Deana, A. A.; Muth, K. Condensed Cyclobutane Aromatic Compounds. XI. Benzo[1,2:4,5]dicyclobutene. *J. Am. Chem. Soc.* **1960**, *82*, 2524−2525. (c) Gügel, A.; Belik, P.; Walter, M.; Kraus, A.; Harth, E.; Wagner, M.; Spickermann, J.; Müllen, K. The Repetitive Diels−Alder Reaction: A New Approach to [60]Fullerene Main-dashchain Polymers. *Tetrahedron* **1996**, *52*, 5007−5014.

(93) Mehta, G.; Kotha, S. Recent Chemistry of Benzocyclobutenes. *Tetrahedron* **2001**, *57*, 625−659.

(94) Kotha, S.; Khedkar, P. Differential Reactivity Pattern of Hybrid *o*-Quinodimethane Precursors: Strategic Expansion to Annulated Benzocycloalkanes via Rongalite. *J. Org. Chem.* **2009**, *74*, 5667−5670.

(95) Kotha, S.; Krishna, N. G. Synthetic Approach to Linearly Annulated Tetralin-Based Constrained *α*-Amino Acid Derivatives via Rongalite. *Curr. Sci.* **2011**, *101*, 923−926.

(96) Kotha, S.; Meshram, M. Synthesis of Novel Fluoranthene-Based Conformationally Constrained *α*-Amino Acid Derivatives and Polycyclic Aromatics via the Diels−Alder Reaction. *Synthesis* **2014**, 1525−1531.

(97) (a) Kotha, S.; Ali, R.; Tiwari, A. Diversity-Oriented Approach to Novel Spirocyclics via Enyne Metathesis, Diels−Alder Reaction, and a [2 + 2 + 2] Cycloaddition as Key Steps. *Synlett* **2013**, 1921−1926. (b) Kotha, S.; Ali, R. Diversity-Oriented Approach to Linearly Fused Spirocycles via Strategic Utilization of a [2 + 2 + 2] Cycloaddition and the Diels−Alder Reaction. *Tetrahedron* **2015**, *71*, 1597−1603.

(98) Kotha, S.; Ali, R. Diversity Oriented Approach to Spirobarbituric Acid Derivatives via a [2 + 2 + 2] Cycloaddition and Diels−Alder Reaction as Key Steps. *Heterocycles* **2014**, *88*, 789−797.

(99) Kotha, S.; Ali, R. Diversity-Oriented Approach to Oxepine Derivatives: Further Expansion via Diels−Alder Reaction. *Heterocycles* **2015**, *90*, 645−658.

(100) Liu, J.-H.; Wu, A.-T.; Huang, M.-H.; Wu, C.-W.; Chung, W.-S. The Syntheses of Pyrazino-Containing Sultines and Their Application in Diels−Alder Reactions with Electron-Poor Olefins and [60]-Fullerene. *J. Org. Chem.* **2000**, *65*, 3395−3403.

(101) Illescas, B.; Martín, N.; Seoane, C.; de la Cruz, P.; Langa, F.; Wudl, F. A Facile Formation of Electroactive Fullerene Adducts from Sultines via a Diels−Alder Reaction. *Tetrahedron Lett.* **1995**, *36*, 8307−8310.

(102) Illescas, B. M.; Martín, N.; Seoane, C.; Orti, E.; Viruela, P. M.; Viruela, R.; de la Hoz, A. Reaction of C60 with Sultines: Synthesis, Electrochemistry, and Theoretical Calculations of Organofullerene Acceptors. *J. Org. Chem.* **1997**, *62*, 7585−7591.

(103) (a) Martín, N.; Behnisch, R.; Hanack, M. Syntheses and Electrochemical Properties of Tetracyano-*p*-Quinodimethane Derivatives Containing Fused Aromatic Rings. *J. Org. Chem.* **1989**, *54*, 2563−2568. (b) Hünig, S. *N,N′*-Dicyanoquinone Diimines (DCNQIs): Unique Acceptors for Conducting Materials. *J. Mater. Chem.* **1995**, *5*, 1469−1479. (c) Martín, N.; Seoane, C. *Handbook of Conductive Molecules and Polymers*; Nalwa, H. S., Ed.; John-Wiley & Sons Ltd: New York, USA, 1997, Vol. 1.

(104) Fillion, E.; Dumas, A. M.; Hogg, S. A. Modular Synthesis of Tetrahydrofluorenones from 5-Alkylidene Meldrum's Acids. *J. Org. Chem.* **2006**, *71*, 9899−9902.

(105) Yoshida, H.; Mukae, M.; Ohshita, J. Facile Access to Boryltetralins and Borylnaphthalenes via a Cycloaddition Using *o*-Quinodimethanes. *Chem. Commun.* **2010**, *46*, 5253−5255.

(106) (a) Grosch, B.; Orlebar, C. N.; Herdtweck, E.; Massa, W.; Bach, T. Highly Enantioselective Diels−Alder Reaction of a Photochemically Generated *o*-Quinodimethane with Olefins. *Angew. Chem., Int. Ed.* **2003**, *42*, 3693−3696. (b) Takinami, M.; Ukaji, Y.; Inomata, K. Enantioselective Diels−Alder Reaction of *o*-Quinodimethanes by Utilizing Tartaric Acid Ester as a Chiral Auxiliary. *Tetrahedron: Asymmetry* **2006**, *17*, 1554−1560. (c) Kise, N.; Mimura, R. Diastereoselective Cycloaddition of Chiral 1-Acryloyl-2-Imidazolidinone and *o*-Quinodimethane Generated by Reduction of 1,2-Bis(bromomethyl)benzene with Zinc. *Tetrahedron: Asymmetry* **2007**, *18*, 988−993. (d) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. Asymmetric Catalysis of Diels−Alder Reactions with in Situ Generated Heterocyclic ortho-Quinodimethanes. *J. Am. Chem. Soc.* **2011**, *133*, 15212−15218. (e) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. Multicatalytic Asymmetric Synthesis of Complex Tetrahydrocarbazoles via a Diels−Alder/Benzoin Reaction Sequence. *Org. Lett.* **2012**, *14*, 1310−1313. (f) Xiao, Y.-C.; Zhou, Q.-Q.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. Asymmetric Diels−Alder Reaction of 2-Methyl-3-indolylmethanols via in Situ Generation of *o*-Quinodimethanes. *Org. Lett.* **2012**, *14*, 5940−5943.

(107) (a) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. Synthesis of Constrained *α*-Amino Acid Derivatives via Enyne Metathesis Reaction. *Tetrahedron Lett.* **1998**, *39*, 2805−2808. (b) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. Constrained Phenylalanine

Derivatives by Enyne Metathesis and Diels–Alder Reaction. *Eur. J. Org. Chem.* **2001**, 787–792.

(108) Undheim, K. The Schöllkopf Chiron and Transition Metal Mediated Reactions, A Powerful Combination for Stereoselective Construction of Cyclic α-Quaternary-α-Amino Acid Derivatives. *Amino Acids* **2008**, *34*, 357–402 and references cited therein.

(109) (a) Kotha, S.; Deodhar, D.; Khedkar, P. Diversity-oriented Synthesis of Medicinally Important 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) Derivatives and Higher Analogs. *Org. Biomol. Chem.* **2014**, *12*, 9054–9091. (b) Kotha, S.; Sreenivasachary, N. Synthetic Approaches to Tetrahydroisoquinoline-3-carboxylic Acid Derivatives. *J. Indian Inst. Sci.* **2001**, *81*, 277–286. (c) Kotha, S.; Sreenivasachary, N. A New Synthetic Approach to 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (Tic) Derivatives via Enyne Metathesis and the Diels–Alder Reaction. *Chem. Commun.* **2000**, 503–504. (d) Kotha, S.; Sreenivasachary, N. Synthesis of 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (Tic) Derivatives by Cycloaddition Approaches. *Eur. J. Org. Chem.* **2001**, 3375–3383.

(110) Kotha, S.; Khedkar, P. Synthesis of a Conformationally Constrained Phenylalanine Derivative by a Strategic Combination of Ring-Closing Enyne Metathesis and Diels–Alder Reaction. *Synthesis* **2008**, 2925–2928.

(111) Kotha, S.; Krishna, N. G.; Halder, S.; Misra, S. A Synergistic Approach to Polycyclics via a Strategic Utilization of Claisen Rearrangement and Olefin Metathesis. *Org. Biomol. Chem.* **2011**, *9*, 5597–5624.

(112) Kotha, S.; Mandal, K.; Tiwari, A.; Mobin, S. M. Diversity-Oriented Approach to Biologically Relevant Molecular Frameworks Starting with β-Naphthol and Using the Claisen Rearrangement and Olefin Metathesis as Key Steps. *Chem.—Eur. J.* **2006**, *12*, 8024–8038.

(113) Tiwari, A. Design and Synthesis of Spirocyclics, Propellanes and Cyclophanes via Olefin Metathesis. Ph.D. Thesis, IIT-Bombay, 2012.

(114) Kotha, S.; Ali, R.; Tiwari, A. Design and Synthesis of Angularly Annulated Spirocyclics via Enyne Metathesis and the Diels–Alder Reaction as Key Steps. *Synthesis* **2014**, 2471–2480.

(115) (a) Kotha, S.; Ravikumar, O. Diversity-Oriented Approach to Carbocycles and Heterocycles through Ring Rearrangement Metathesis, Fischer Indole Cyclization, and Diels–Alder Reaction as Key Steps. *Eur. J. Org. Chem.* **2014**, 5582–5590. (b) Kotha, S.; Ravikumar, O. Design and Synthesis of Oxa-bowls via Diels–Alder Reaction and Ring-Rearrangement Metathesis as Key Steps. *Tetrahedron Lett.* **2014**, *55*, 5781–5784.

(116) Chattopadhyay, S. K.; Roy, S. P.; Ghosh, D.; Biswas, G. Synthesis of Oxepine-, Oxocine- and Azepine-Annulated Carbazole Derivatives by Combined Claisen Rearrangement and Diene/Enyne Metathesis. *Tetrahedron Lett.* **2006**, *47*, 6895–6898.

(117) Mondal, P.; Thander, L.; Chattopadhyay, S. K. A New Entry to the Phenanthridine Ring System. *Tetrahedron Lett.* **2012**, *53*, 1328–1331.

(118) (a) Kotha, S.; Shah, V. R. Design and Synthesis of 1-Benzazepine Derivatives by Strategic Utilization of Suzuki–Miyaura Cross-Coupling, Aza-Claisen Rearrangement and Ring-Closing Metathesis. *Eur. J. Org. Chem.* **2008**, 1054–1064. (b) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. Recent Advances in the Aza-Claisen Rearrangement. *Synthesis* **2009**, 2117–2142. (c) Nubbemeyer, U. Aza-Claisen Rearrangement. In *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007; pp 461–523.

(119) Kurhade, S. E.; Sanchawala, A. I.; Ravikumar, V.; Bhuniya, D.; Srinivasa Reddy, D. Total Synthesis of Isofregenedadiol. *Org. Lett.* **2011**, *13*, 3690–3693.

(120) Vanga, D. G.; Kaliappan, K. P. A Unified Strategy for the Syntheses of Angucyclinone Antibiotics: Total Syntheses of Tetrangulol, Kanglemycin M, X-14881-E, and Anhydrolandomycinone. *Eur. J. Org. Chem.* **2012**, 2250–2259.

(121) Vanga, D. G.; Kaliappan, K. P. Total Synthesis and Stereochemical Assignment of (−)-Zenkequinone B. *Synlett* **2012**, 2931–2934.

(122) Grafton, M. W.; Farrugia, L. J.; Senn, H. M.; Sutherland, A. Discovery of a Multi-Bond Forming, Four-Step Tandem Process: Construction of Drug-Like Polycyclic Scaffolds. *Chem. Commun.* **2012**, *48*, 7994–7996.

(123) (a) Walts, A. E.; Roush, W. R. A Stereorational Total Synthesis of (−)-Ptilocaulin. *Tetrahedron* **1985**, *41*, 3463–3478. (b) Bonjouklian, R.; Moore, R. E.; Patterson, G. M. L. Acid-Catalyzed Reactions of Hapalindoles. *J. Org. Chem.* **1988**, *53*, 5866–5870.

(124) Grafton, M. W.; Farrugia, L. J.; Sutherland, A. Synthesis of Amino-Substituted Indanes and Tetralins via Consecutive Multibond-Forming Tandem Processes. *J. Org. Chem.* **2013**, *78*, 7199–7207.

(125) Oh, S.; Jang, H. J.; Ko, S. K.; Ko, Y.; Park, S. B. Construction of a Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway. *J. Comb. Chem.* **2010**, *12*, 548–558.

(126) Kapeller, D. C.; Bräse, S. Versatile Solid-Phase Synthesis of Chromenes Resembling Classical Cannabinoids. *ACS Comb. Sci.* **2011**, *13*, 554–561.

(127) Zhu, M.; Lim, B. J.; Koh, M.; Park, S. B. Construction of Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway: Part II. *ACS Comb. Sci.* **2012**, *14*, 124–134.

(128) Wang, Z.; Castellano, S.; Kinderman, S. S.; Argueta, C. E.; Beshir, A. B.; Fenteany, G.; Kwon, O. Diversity Through a Branched Reaction Pathway: Generation of Multicyclic Scaffolds and Identification of Antimigratory Agents. *Chem.—Eur. J.* **2011**, *17*, 649–654.

(129) Cruz, D.; Wang, Z.; Kibbie, J.; Modlin, R.; Kwon, O. Diversity Through Phosphine Catalysis Identifies Octahydro-1,6-naphthyridin-4-ones as Activators of Endothelium-Driven Immunity. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6769–6774.

(130) O'Connell, K. M. G.; Beckmann, H. S. G.; Laraia, L.; Horsley, H. T.; Bender, A.; Venkitaraman, A. R.; Spring, D. R. A Two-Directional Strategy for the Diversity-Oriented Synthesis of Macrocyclic Scaffolds. *Org. Biomol. Chem.* **2012**, *10*, 7545–7551.

(131) Torney, P.; Patre, R.; Tilve, S. A Rapid Assembly of Furo[3,4-b]- and Pyrrolo[3,4-b]carbazolones by Domino Wittig/Diels–Alder Reaction. *Synlett* **2011**, 639–642.

(132) Sarmah, M. M.; Bhuyan, D.; Prajapati, D. An Efficient and Facile Synthesis of Iminoquinazolinedione Derivatives by Solid-State Diels–Alder Reaction under Catalyst-Free Conditions. *Synlett* **2013**, 1667–1670.

(133) (a) Pyne, S. G.; Safaei-G, J.; Hockless, D. C. R.; Skelton, B. W.; Sobolev, A. N.; White, A. H. Exo Diastereoselective Diels–Alder Reactions of (R)-2-Phenyl-4-methylene-oxazolidin-5-one. *Tetrahedron* **1994**, *50*, 941–956. (b) Pyne, S. G.; Safaei-G, J. Synthesis of (+)-(2S)-2-Aminobicyclo[2.2.2]octane-2-carboxylic Acid. *J. Chem. Res. (Part S)* **1996**, 160–161.

(134) Avenoza, A.; Busto, J. H.; Paris, M.; Peregrina, J. M.; Cativiela, C. The Use of 4-Hetaryliden- and 4-Arylidden-5(4H)-oxazolones as Dienophiles. Appropriate Reagents for the Synthesis of Cyclic Analogues of Natural Amino Acids. *J. Heterocycl. Chem.* **1997**, *34*, 1099–1110.

(135) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. New Chiral Didehydroamino Acid Derivatives from a Cyclic Glycine Template with 3,6-Dihydro-2H-1,4-oxazin-2-one Structure: Applications to the Asymmetric Synthesis of Nonproteinogenic α-Amino Acids. *J. Org. Chem.* **2000**, *65*, 3034–3041.

(136) Kotha, S.; Dipak, M. K.; Mobin, S. M. Serendipitous and Acid Catalyzed Synthesis of Spirolactones. *Tetrahedron* **2011**, *67*, 4616–4619.

(137) (a) Mehta, G.; Srikrishna, A. Synthesis of Polyquinane Natural Products: An Update. *Chem. Rev.* **1997**, *97*, 671–720. (b) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: London, U.K., 1987. (c) Marchand, A. P. Polycyclic Cage Compounds: Reagents, Substrates, and Materials for the 21st Century. *Aldrichim. Acta* **1995**, *28*, 95–104.

(138) Kotha, S.; Manivannan, E.; Sreenivasachary, N. Allylation of Caged Diketones via Fragmentation Methodology. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2845–2848.

(139) Kotha, S.; Banerjee, S. Recent Developments in the Retro-Diels–Alder Reaction. *RSC Adv.* **2013**, *3*, 7642–7666.

(140) Kotha, S.; Banerjee, S.; Patil, M. P.; Sunoj, R. B. Retro Diels–Alder Reaction under Mild Conditions: Experimental and Theoretical Studies. *Org. Biomol. Chem.* **2006**, *4*, 1854–1856.

(141) Kotha, S.; Banerjee, S.; Shaikh, M. Correlation between Carbon-Carbon Bond Length and the Ease of *retro* Diels–Alder Reaction. *J. Chem. Sci.* **2014**, *126*, 1369–1371.

(142) Kashinath, K.; Swaroop, P. S.; Srinivasa Reddy, D. A Green Synthetic Route to Antimalarial and Antibacterial Agent CJ-15,801 and its Isomer Cis-CJ-15,801. *RSC Adv.* **2012**, *2*, 3596–3598.

(143) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. Copper-Mediated Synthesis of *N*-Acyl Vinylogous Carbamic Acids and Derivatives: Synthesis of the Antibiotic CJ-15,801. *Org. Lett.* **2004**, *6*, 27–30.

(144) Kotha, S.; Deb, A. C.; Chattopadhyay, S. Design and Synthesis of Spirocyclics via the Diels–Alder Reaction and Ring-Opening Cross-Metathesis as Key Steps. *Lett. Org. Chem.* **2006**, *3*, 128–134.

(145) Kotha, S.; Dipak, M. K. Design and Synthesis of Novel Propellanes by Using Claisen Rearrangement and Ring-Closing Metathesis as the Key Steps. *Chem.—Eur. J.* **2006**, *12*, 4446–4450.

(146) (a) Dipak, M. K. Design and Synthesis of Novel Polycyclics via Catalytic Metathesis. Ph.D. Thesis, IIT-Bombay, 2009. (b) Kotha, S.; Dipak, M. K. Design and Synthesis of Novel Bis-Annulated Caged Polycycles via Ring-Closing Metathesis: Pushpakenediol. *Beilstein J. Org. Chem.* **2014**, *10*, 2664–2670.

(147) Camps, P.; Gómez, T. Synthesis and Reactions of a New 1,1-Disubstituted Cyclopentadiene. *ARKIVOC* **2011**, No. iii, 128–139.

(148) Dejmek, M.; Hřebabecký, H.; Šála, M.; Dračínský, M.; Nencka, R. Microwave-Assisted Solvent-Free Diels–Alder Reaction—A Fast and Simple Route to Various 5,6-Substituted Norbornenes and Polychlorinated Norbornenes. *Synthesis* **2011**, 4077–4083.

(149) Kumar, N.; Kiuchi, M.; Tallarico, J. A.; Schreiber, S. L. Small-Molecule Diversity Using a Skeletal Transformation Strategy. *Org. Lett.* **2005**, *7*, 2535–2538.

(150) Diels, O.; Alder, K. Synthesen in der Hydroaromatischen Reihe. VIII. Mitteilung: Dien-Synthesen des Anthracens. Anthracen-Formel. *Justus Liebigs Ann.Chem.* **1931**, *486*, 191–202.

(151) Clar, E. Zur Kenntnis Mehrkerniger Aromatischer Kohlen-wasserstoffe und ihrer Abkömmlinge, XI. Mitteil.: Über die Konstitution des Anthracens, II.: Bemerkungen zu einer Arbeit von Otto Diels und Kurt Alder. *Ber. Dtsch. Chem. Ges. A/B* **1931**, *64*, 2194–2200.

(152) Atherton, J. C. C.; Jones, S. Diels–Alder Reactions of Anthracene, 9-Substituted Anthracenes and 9,10-Disubstituted Anthracenes. *Tetrahedron* **2003**, *59*, 9039–9057.

(153) Kotha, S.; Ghosh, A. K.; Behera, M. Synthesis of Highly Constrained Unusual α-Amino Acid Derivative by the Diels–Alder Approach. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2002**, *41B*, 2330–2332.

(154) (a) Duan, J.; Sheppeck, J.; Jiang, B.; Gilmore, J. L. (2,3–5,6 Aryl-heteroaryl)-bicyclo(2,2,2)octane-amide Derivatives; Antiinflammatory, Obesity, Antidiabetic Agent, Autoimmune Disease, Asthma, Arthritis; Non-Steroidal; Side Effect Reduction; Pharmacokinetics. U.S. Patent US 2005176716(A1) 2005-08-11, 2005. (b) Weinstein, D. S.; Sheppeck, J.; Gilmore, J. L. Heterocyclic Modulators of the Glucocorticoid Receptor, AP-1, and/or NF-kB Activity and Use Thereof. U.S. Patent US 2005182083(A1) 2005-08-18, 2005. (c) Sheppeck, J.; Dhar, T. G. M.; Doweyko, L.; Gilmore, J.; Weinstein, D.; Xiao, H.-Y.; Yang, B. V.; Doweyko, A. M. Preparation of Bicyclooctanecarboxamides as Modulators of Glucocorticoid Receptor, AP-1 and NF-κB Activity and Use Thereof. U.S. Patent Appl. Publ. US 2006154973(A1) 2006-07-13, 2006. (d) Yang, B. V. Preparation of Dibenzobicyclo[2.2.2] octadienylcarboxamides as Modulators of the Glucocorticoid Receptor, ap-1, and/or NF-kb Activity and Use Thereof. U.S. Patent Appl. Publ. US 2006154962(A1) 2006-07-13, 2006. (e) Duan, J.; Sheppeck, J.;

Jiang, B.; Gilmore, J. L. Preparation of Azolylamino Benzopyridobi-cyclooctanecarboxamides and Dipyridobicyclooctanecarboxamides as Modulators of Activator Protein 1 (AP-1) and/or NF-κB Activity. U.S. Patent US 7625921(B2) 2009-12-01, 2009. (f) Weinstein, D. S.; Sheppeck, J.; Gilmore, J. L. Preparation of Heterocyclic Bicyclooctyl-carboxamide Derivatives as Modulators of Glucocorticoid Receptor, AP-1, and/or NF-κB. U.S. Patent US 7605264(B2) 2009-10-20, 2009. (g) Duan, J.; Jiang, B.; Sheppeck, J.; Gilmore, J. L. Fused Aryl and Heteroaryl Bicyclo[2.2.2]octane Derivative Modulators of the Glucocorticoid Receptor, AP-1, and/or NF-κB Activity, and Therapeutic Use Thereof. U.S. Patent US 7569689(B2) 2009-08-04, 2009.

(155) Yang, B. V.; Doweyko, L. M. Highly Regioselective Diels–Alder Reactions of 9-Substituted Anthracenes and 2-Acetamidoacrylate: Synthesis of Conformationally Constrained α-Amino Acids. *Tetrahedron Lett.* **2005**, *46*, 2857–2860.

(156) Meshram, M. Design and Synthesis of Conformationally Constrained α-Amino Acid Derivatives and Polycyclic Aromatics via the Diels—Alder Reaction as a Key Step. Ph.D. Thesis, IIT-Bombay, 2013.

(157) Kotha, S.; Meshram, M.; Muthusamy, G. Synthesis of Conformationally Constrained α-Amino Acid Derivatives Containing Bicyclo[2.2.2]octane Unit via the Diels–Alder Reaction and the Suzuki–Miyaura Cross-Coupling as Key Steps. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2015**, *54B*, 505–513.

(158) Kotha, S.; Meshram, M. Design and Synthesis of Conformationally Constrained Bicyclo[2.2.2]octane-Based Unusual α-Amino Acid Derivatives via the Diels–Alder Reaction. *Heterocycles* **2015**, *90*, 357–371.

(159) Kotha, S.; Meshram, M. Functionalization of Anthracene by Strategic Utilization of the Diels–Alder Reaction and the Ring-Closing Metathesis. *J. Indian Chem. Soc.* **2013**, *90*, 1789–1794.

(160) Nikitin, K.; Müller-Bunz, H.; McGlinchey, M. J. Diels–Alder Reactions of 9-Ferrocenyl- and 9,10-Diferrocenylanthracene: Steric Control of 9,10-versus 1,4-Cycloaddition. *Organometallics* **2013**, *32*, 6118–6129.

(161) Erno, Z.; Asadirad, A. M.; Lemieux, V.; Branda, N. R. Using Light and a Molecular Switch to 'Lock' and 'Unlock' the Diels–Alder Reaction. *Org. Biomol. Chem.* **2012**, *10*, 2787–2792.

(162) Furrer, F.; Linden, A.; Stuparu, M. C. Towards Molecular Ribbons of Corannulene. *Chem.—Eur. J.* **2013**, *19*, 13199–13206.

(163) Xu, D.-Q.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. In Situ Enamine Activation in Aqueous Salt Solutions: Highly Efficient Asymmetric Organocatalytic Diels–Alder Reaction of Cyclohexenones with Nitroolefins. *Angew. Chem., Int. Ed.* **2009**, *48*, 3821–3824.

(164) Fort, E. H.; Jeffreys, M. S.; Scott, L. T. Diels–Alder Cycloaddition of Acetylene Gas to a Polycyclic Aromatic Hydrocarbon Bay Region. *Chem. Commun.* **2012**, *48*, 8102–8104.

(165) Gole, B.; Bar, A. K.; Mallick, A.; Banerjee, R.; Mukherjee, P. S. An Electron Rich Porous Extended Framework as a Heterogeneous Catalyst for Diels–Alder Reactions. *Chem. Commun.* **2013**, *49*, 7439–7441.

(166) (a) Chang, M.-Y.; Wu, M.-H. Synthesis of Tetrahydroan-thracen-9-ones by the Domino Aldol Condensation/Diels–Alder Cycloaddition. *Tetrahedron Lett.* **2012**, *53*, 3173–3177. (b) Enders, D.; Joie, C.; Deckers, K. Organocatalytic Asymmetric Synthesis of Tetracyclic Pyridocarbazole Derivatives by Using a Diels–Alder/aza-Michael/Aldol Condensation Domino Reaction. *Chem.—Eur. J.* **2013**, *19*, 10818–10821. (c) Pandit, R. P.; Lee, Y. R. Efficient One-Pot Synthesis of Novel and Diverse Tetrahydroquinolines Bearing Pyranopyrazoles Using Organocatalyzed Domino Knoevenagel/Hetero Diels–Alder Reactions. *Mol. Divers.* **2014**, *18*, 39–50. (d) Majumdar, K. C.; Taher, A.; Nandi, R. K. Synthesis of Heterocycles by Domino-Knoevenagel/Hetero-Diels–Alder Reactions. *Tetrahedron* **2012**, *68*, 5693–5718. (e) Bryhas, A. O.; Matiychuk, V. S.; Lis, T.; Kinzhybalo, V.; Smalius, V. V.; Obushaka, M. D. A Four-Step Domino Knoevenagel/Hetero-Diels–Alder Reaction. *Tetrahedron Lett.* **2013**, *54*, 5667–5670. (f) Choi, S. Y.;

Lee, S. I.; Park, K. H.; Chung, Y. K. Sequential Diels−Alder and Cobalt Octacarbonyl Catalyzed Pauson-Khand Reactions in the Formation of Polycyclic Enones. *Synlett* **2007**, 1857−1862. (g) Akritopoulou-Zanze, I.; Wang, Y.; Zhao, H.; Djuric, S. W. Synthesis of Substituted Fused Pyridines, Pyrazines and Pyrimidines by Sequential Ugi/Inverse Electron Demand Diels−Alder Transformations. *Tetrahedron Lett.* **2009**, *50*, 5773−5776. (h) Schelwies, M.; Farwick, A.; Rominger, F.; Helmchen, G. Platinum(II) Chloride-Catalyzed Stereoselective Domino Enyne Isomerization/Diels−Alder Reaction. *J. Org. Chem.* **2010**, *75*, 7917−7919. (i) Parvatkar, P. T.; Kadamb, H. K.; Tilve, S. G. Intramolecular Diels−Alder Reaction as a Key Step in Tandem or Sequential Processes: A Versatile Tool for the Synthesis of Fused and Bridged Bicyclic or Polycyclic Compounds. *Tetrahedron* **2014**, *70*, 2857−2888.

(167) (a) Wang, H.; Beiring, B.; Yu, D.-G.; Collins, K. D.; Glorius, F. [3]Dendralene Synthesis: Rhodium(III)-Catalyzed Alkenyl C−H Activation and Coupling Reaction with Allenyl Carbinol Carbonate. *Angew. Chem., Int. Ed.* **2013**, *52*, 12430−12434. (b) Gong, T.-J.; Su, W.; Liu, Z.-J.; Cheng, W.-M.; Xiao, B.; Fu, Y. Rh(III)-Catalyzed C−H Activation with Allenes to Synthesize Conjugated Olefins. *Org. Lett.* **2014**, *16*, 330−333.