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Benzannulation

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1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) play an important role in different areas of organic chemistry (e.g., organic electro-active materials, chiral helicenes), and biochemistry (carcinogenic PAHs, DNA intercalation).[1] They are also useful for the preparation of novel materials such as molecular devices (ferromagnets, liquid crystalline materials) and other electronic devices. In addition, functionalized aromatics are useful building blocks in organic synthesis and medicinal chemistry. Generally, they are accessible by functional group manipulation of preformed aromatic derivatives. These strategies provide aromatics with a limited substitution pattern and there is therefore a need for the development of new strategies for aromatic annulation. To this end, benzannulation reactions, which append an aromatic ring to the pre-existing polycyclic moiety have been pursued vigorously. The annulation approach has several advantages over the classical methods for the synthesis of highly functionalized molecules. For example, these approaches are likely to reduce the number of steps and intrinsically exhibit better regiochemical control.

Since the discovery of the remarkable properties of the fullerenes C_{60} and C_{70}, PAH chemistry has expanded.[2] Various synthetic approaches have been reported for the preparation of the smallest curved structure called Buckybowl (corannulene). The discovery of fullerene derivatives paved the way to carbon nanotubes. They form a cylindrical shape, which makes them potentially useful materials in nanotechnology, electronics, optics and material science.[3]

In connection with the synthesis of several biologically active antitumour anthracycline antibiotics[4] such as idarubicin (**1**), doxorubicin (adriamycin) (**2**) and daunorubicin (**3**), the benzannulation strategy has been extensively used. Other natural antibiotics such as rifamycin (**4**) that inhibits viral replication and (*S*,*S*)-isodityrosine (**5**), a biologically active macromolecule, have been produced by a benzannulation strategy (Fig. 1).[5]

2. Scope of the review

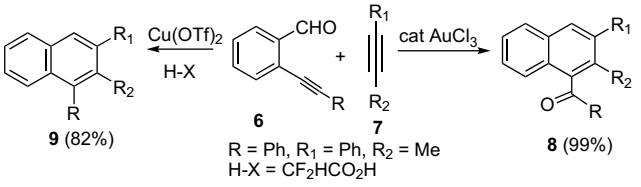
This review comprises an overview of the various modern synthetic methods for the construction of new benzene ring(s). The traditional methods for the synthesis of benzene analogues or PAHs are not discussed in detail. Due to space limitations, only some selected examples are included in this article.

A variety of synthetic methodologies for the creation of new benzene rings called benzannulation have been developed, starting from acyclic or cyclic precursors. Some of these synthetic strategies are discussed in the following sections.

3. Benzannulation via Diels–Alder reaction

The Diels–Alder (DA) cycloaddition has been utilized for the synthesis of functionalized polycyclic aromatic compounds, starting with a suitably substituted diene and dienophile. It should be pointed out that controlling the regiochemistry in DA strategy is not a trivial exercise.

Yamamoto and co-workers have reported functionalized aromatics by treating an enynal [*o*-(alkynyl)benzaldehyde] **6** with an alkyne **7** in the presence of catalytic amounts of $AuCl_3$ or $Cu(OTf)_2$. They found that, in the presence of $AuCl_3$, the naphthyl ketone derivative **8** appeared to be the major product. When $Cu(OTf)_2$ was used in the presence of stoichiometric amounts of Brønsted acids, the decarbonylated naphthalene derivative **9** was obtained selectively (Scheme 1).[6] The reaction rate and yield were dramatically enhanced at high temperatures when $AuBr_3$ was used instead of $AuCl_3$.



Scheme 1.

Similar results were obtained by Asao and Aikawa when they used a carbonyl compound **10** instead of the alkyne **7** (Scheme 2).[7]

Since I^+ is a useful alternative to metal catalysts, Barluenga and co-workers have reported the synthesis of iodonaphthalene derivatives by using the I^+ ion instead of a metal catalyst. When the aldehyde derivative **6** was treated with a suitable alkyne **7** in the presence of (IPy_2BF_4) [bis(pyridine)iodonium tetrafluoroborate], the iodonaphthalene derivative **10** was obtained as the major product with complete regioselectivity and the naphthyl ketone derivative **8** was a minor product (Scheme 3).[8]

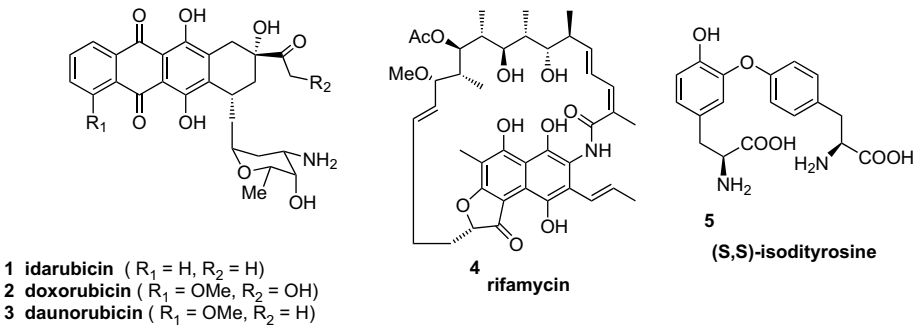
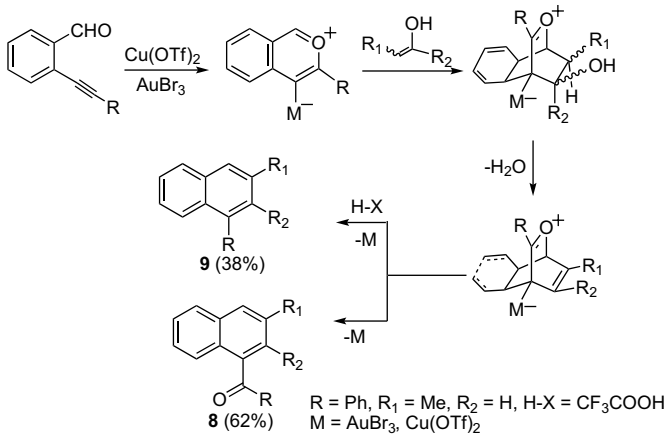
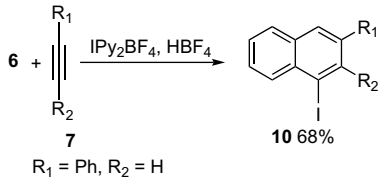


Figure 1. Biologically active benzannulated molecules.

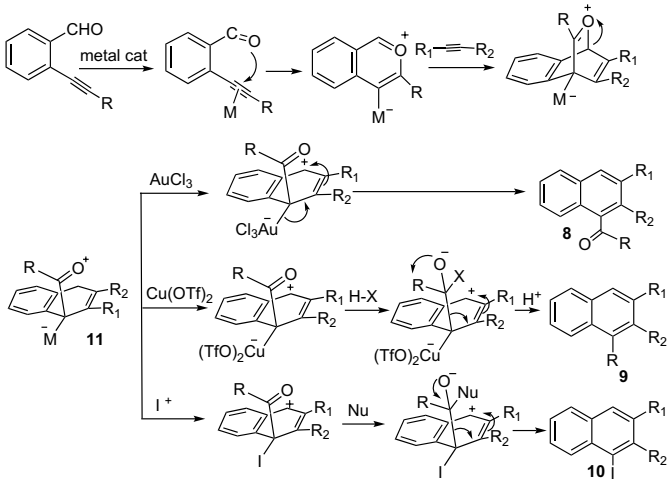


Scheme 2.



Scheme 3.

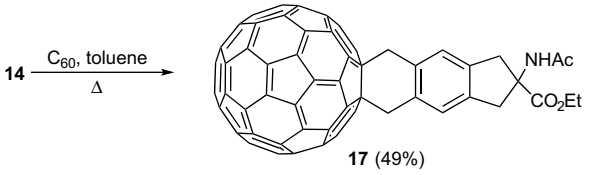
The formation of three products (**8**–**10**) by using different reaction conditions can be explained on the basis of the mechanistic study shown in Scheme 4. The regioselectivity in the naphthalene ring can be achieved by differential activation of the intermediate **11**.



Scheme 4.

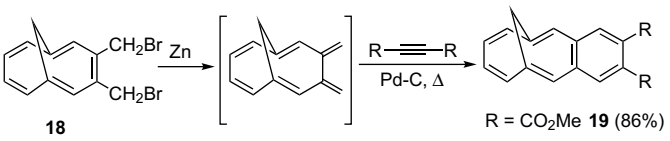
Kotha and co-workers have described[9] the synthesis of various benzannulated indane-based α-amino acid (AAA) derivatives via a [4+2] cycloaddition reaction as a key step. Indane-based cyclic amino acids are potent ligands of the angiotensin-II receptor with agonistic or antagonistic activity and have been extensively used in the synthesis of various biologically active peptides. In this regard, Kotha and co-workers have generated an *o*-xylylene (or *o*-quinodimethane) intermediate **13** containing an amino acid moiety via a sultine derivative such as **14**. The sultine derivative **14** has been synthesized by a six-step sequence, starting from ethyl isocyanoacetate (**12**) as a glycine equivalent and Rongalite (sodium hydroxymethanesulfinate) as a source of sulfoxylate dianion.[9a] When the sultine building block **14** was treated with various dienophiles, e.g., dimethyl acetylenedicarboxylate (DMAD) in the presence of toluene at 120 °C, subsequent oxidation of the DA adduct **15** with DDQ gave the benzannulated indane-based AAA derivative **16** in good yield (Scheme 5). Some of the AAA derivatives that were synthesized contain keto functional groups, which are not accessible by conventional methods such as the Bucherer–Berg method.

Later, this methodology was successfully extended to the synthesis of a fullerene-based AAA derivative **17**, which may be a useful precursor for biological applications (Scheme 6).



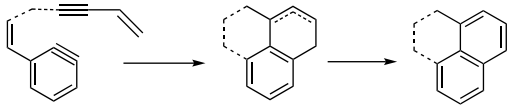
Scheme 6.

Kuroda and co-workers have utilized a [4+2] cycloaddition approach towards the synthesis of a benzene ring-fused [10] annulene (**19**) from **18** as outlined in Scheme 7.[10]

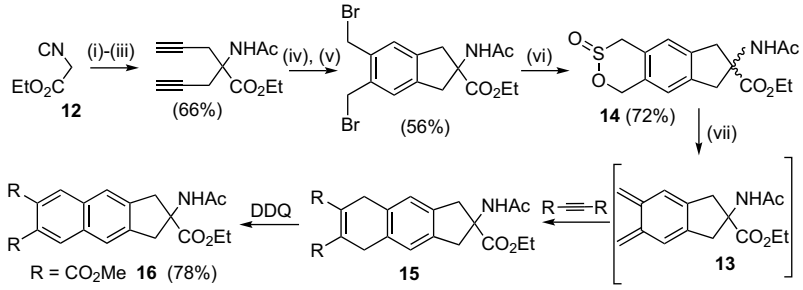


Scheme 7.

Danheiser and co-workers claimed the first intramolecular [4+2] cycloaddition of in situ-generated benzynes with conjugated enynes (and arenynes) to form condensed polycyclic aromatic compounds. A general theme is shown in Scheme 8. The mechanism of this reaction can be explained either by a concerted cycloaddition or by the stepwise involvement of an intermediate biradical.



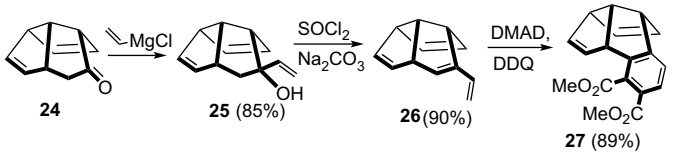
Scheme 8.



Scheme 5. (i) Propargyl bromide, K_2CO_3, *n*-Bu_4NHSO_4, (ii) HCl, EtOH, (iii) Ac_2O, (iv) $Rh(PPh_3)_3Cl$, 2-butyne-1,4-diol, 80 °C, (v) PBr_3, rt, (vi) Rongalite, TBAB, DMF, (vii) DMAD, toluene, 120 °C.

The enyne building block **20** (prepared from **21**) was converted into benzyne intermediate **22** by using TBAT (tetrabutylammonium triphenyldifluorosilicate) in the presence of a stoichiometric amount of BHT (butylated hydroxytoluene). Surprisingly, the benzyne intermediate **22** undergoes an intramolecular [4+2] cycloaddition reaction at room temperature to deliver the polycyclic aromatic derivative **23** in good yields. Generally, the enyne and arenyne cycloaddition strategy requires an elevated temperature (Scheme 9).[11]

A benzannulated triquinacene derivative **27** has been realized by Paquette and co-workers. Triquinacene derivative **24**, on reaction with vinylmagnesium chloride, gave the vinyl alcohol **25**, which, on dehydration, afforded vinyltriquinacene **26**. DA reaction of **26** with DMAD, followed by aromatization with DDQ, gave the benzannulated triquinacene derivative **27** in 89% yield (Scheme 10).[12]

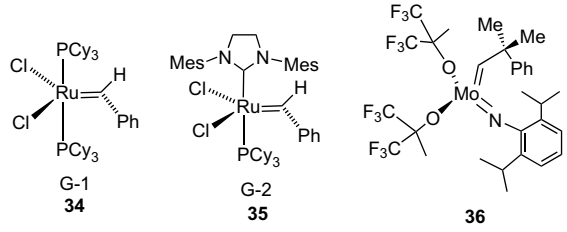


Scheme 10.

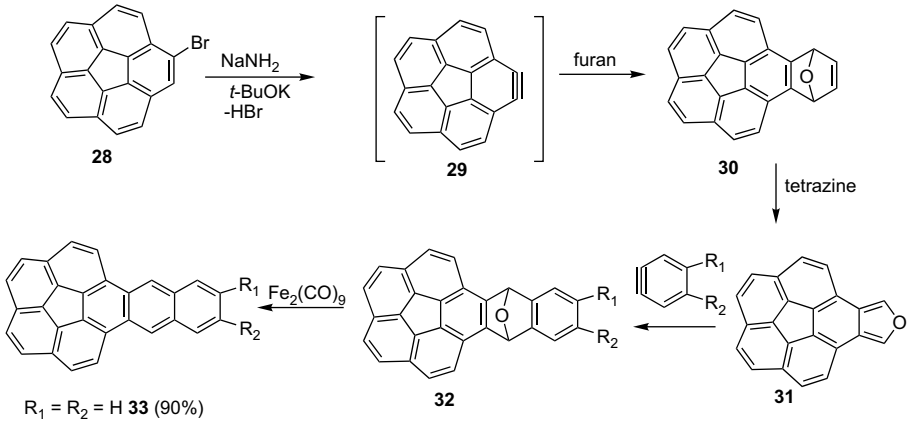
Recently, Sygula and co-workers have synthesized large-sized PAHs with corannulene subunits by utilizing a [4+2] cycloaddition reaction (Scheme 11).[13] Thus, HBr elimination of bromo-corannulene **28** in the presence of a strong base such as *t*-BuOK/$NaNH_2$, followed by trapping the benzyne intermediate **29** with furan, gave the DA adduct **30**. Elimination of acetylene from **30** by tetrazine gave the isobenzofuran derivative **31**. DA reaction of **31** with a reactive dienophile such as benzyne, followed by deoxygenation of **32** with diiron nonacarbonyl, gave the annulated PAHs with a corannulene subunit **33**. This methodology represents a unique application of the benzannulation strategy for the synthesis of bowl-shaped or planar PAH networks structurally related to fullerene chemistry.

4. Benzannulation via ring-closing metathesis (RCM)

Transition-metal-catalyzed C–C bond-formation protocols are attractive processes, because of the mild reaction conditions employed. To this end, ring-closing metathesis (RCM) appears to be a powerful tool for the preparation of cyclic compounds. The RCM methodology leads to cyclic products from acyclic dienes, is a powerful strategy and has found a wide range of applications in organic synthesis. By this strategy, several complex molecules with multiple functional groups have been synthesized. The strategy has been successfully employed for the synthesis of a wide variety of carbo- and heterocyclic compounds and has also been extended to the preparation of aromatic compounds. Although RCM was reported as early as 1980, it did not find utility in organic synthesis, because of a lack of efficient catalyst systems and also because the early catalysts had limited functional group tolerance. The renewed interest in the metathesis protocol can be attributed to the availability of well-defined catalysts such as **34**–**36** that tolerate a variety of functional groups, as reported by Schork and Grubbs.[14]

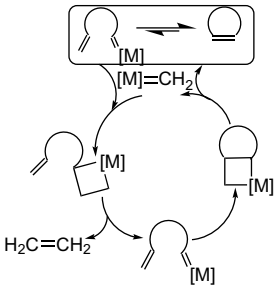


The overall mechanism of the RCM reaction is generally believed to proceed via a [2+2] cycloaddition/cycloreversion step, as outlined in Scheme 12. The reaction is under thermodynamic control and the equilibrium is constantly shifted towards the cycloalkene,



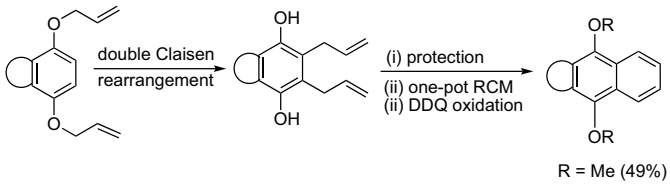
Scheme 11.

due to the release of highly volatile ethylene gas. Recent advances in RCM include supercritical CO_2 conditions[15] and also the use of solid supports.[16]



Scheme 12. Mechanism of RCM reaction.

Kotha and Mandal have described a simple methodology for benzannulation using a double Claisen rearrangement followed by a one-pot RCM and DDQ oxidation sequence, as depicted in Scheme 13.[17] Several interesting molecular frameworks, which are not accessible by conventional methods have been synthesized by this route.

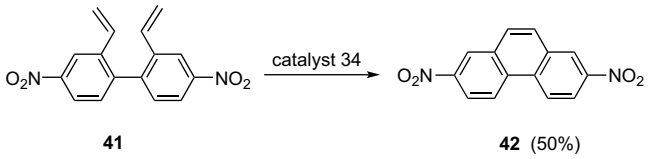


Scheme 13.

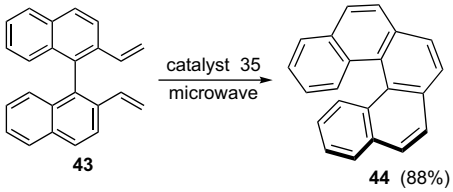
The required precursors for the double Claisen rearrangement have been prepared by O-allylation of the corresponding 1,4-dihydroxybenzene derivative **37**. The bis-alkoxy derivative **38**, on treatment with sodium dithionate and NaOH under thermal conditions, gave the desired double rearranged product. Next, the phenolic OH groups were protected as alkyl or acetyl groups to prevent complexation with Grubbs' catalyst. The protected anthraquinone derivative such as **39** underwent an RCM reaction to deliver the tetracyclic compound. Subsequent oxidation of the RCM product with DDQ gave the benzoannulated derivative **40** in good yield (Scheme 14).

Iuliano and co-workers have reported the synthesis of several substituted phenanthrene derivatives **42** by RCM of 2,2′-divinylbiphenyls **41** using a First-generation Grubbs' catalyst **34** (Scheme 15).[18] It is worth mentioning that the phenanthrene core represents a key structural element for various biologically important molecules, which exhibit antimalarial, anticancer and emetic activities.

Collins and co-workers have described the preparation of chiral helicene **44** using RCM for the introduction of a newly formed benzene ring. The divinyl precursor **43**, prepared from 2,2′-binaphthol, underwent an RCM reaction in the presence of a second-generation Grubbs' catalyst **35** under microwave conditions to generate the [5]helicene **44** in 88% yield (Scheme 16).[19] Similarly, the [6]helicene and [7]helicene derivatives were synthesized using



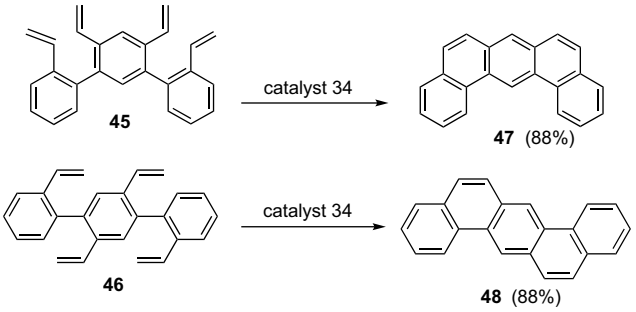
Scheme 15.



Scheme 16.

the RCM strategy. These types of chiral helicene molecules exhibit interesting optical and electronic properties, and are also useful building blocks in medicinal chemistry.

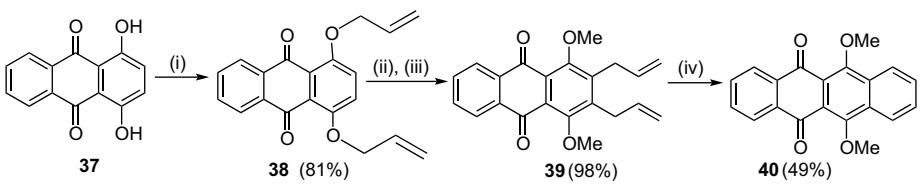
King and co-workers have described a general methodology for the regioselective synthesis of PAHs by adopting a double RCM strategy. Thus, vinyl-substituted terphenyl derivatives such as **45** and **46** when subjected to RCM in the presence of a first-generation Grubbs' catalyst **34** gave the dibenzanthracene derivatives **47** and **48** in 88% yields each (Scheme 17).[20]



Scheme 17.

Rebeccamycin (**49**) and furostifoline (**50**) (Fig. 2) belong to the carbazole-based products with interesting biological properties. For example, rebeccamycin binds to DNA and exhibit antitumour properties. de Koning's group succeeded in preparing the core moiety of rebeccamycin (**49**) and furostifoline (**50**), respectively, by RCM as a key step.[21]

Recently, Kotha and co-workers have discovered a simple and novel methodology for benzannulation. In this regard, they have demonstrated that the Suzuki–Miyaura coupling reaction and RCM are useful steps (Scheme 18).[17b] Thus, the amino derivative **51** has been converted to diiodo compound **52** by diazotization sequence. Allylation followed by RCM of **53** and dehydrogenation gave naphthalene derivative **54**. In another event, compound **55** has been converted to the indole derivative **56**.



Scheme 14. (i) Allyl bromide, K_2CO_3, (ii) $Na_2S_2O_4$, NaOH, Δ, (iii) MeI, (iv) RCM, DDQ.

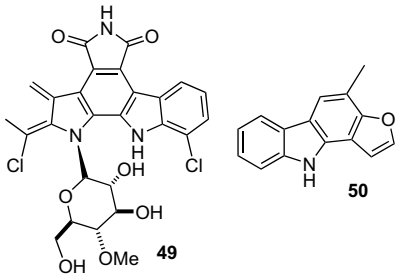
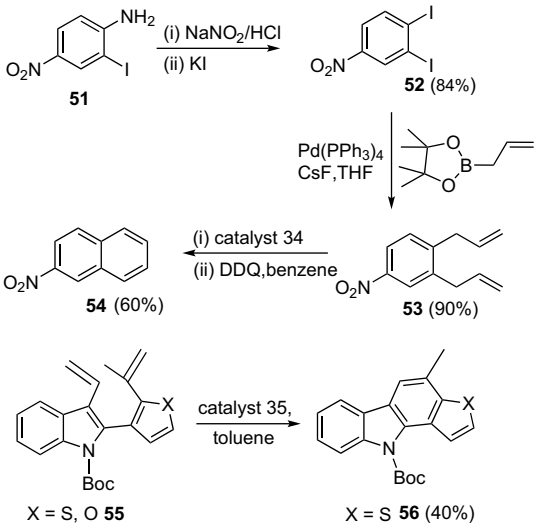


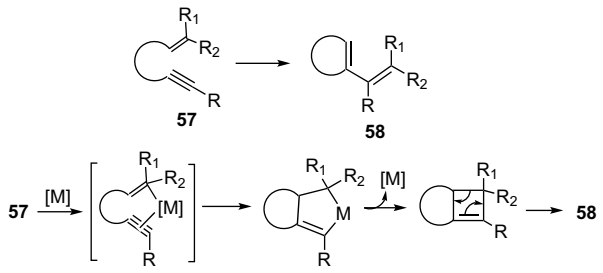
Figure 2. Structures of rebeccamycin **49** and furostifoline **50**.



Scheme 18.

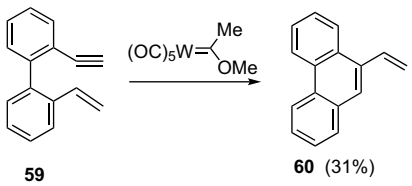
4.1. Enyne metathesis

The enyne metathesis strategy has found many applications for the synthesis of densely functionalized and, in some cases, highly sensitive dienes. This reaction occurs between an alkene and alkyne in the presence of transition-metal catalysts in which the double bond of the alkene is cleaved and each alkylidene fragment migrates from the alkene part to the alkyne carbon and delivers the diene moiety. Enyne metathesis is known to proceed via carbene complexes involving a [2+2] cycloaddition reaction. The mechanism of the reaction is outlined in Scheme 19.[14]



Scheme 19.

In 1985, Katz and Sivavec first described the intramolecular enyne metathesis reaction for the synthesis of 9-vinylphenanthrenene (**60**) from **59** by using a Fischer tungsten–carbene complex (Scheme 20).[22]



Scheme 20.

Recently, Kotha and co-workers have synthesized diene building blocks containing α-amino acid (AAA) moieties by a cross-enyne metathesis reaction.[23a] These functionalized dienes are useful synthons for the preparation of constrained AAA derivatives. In order to prepare angularly substituted indane-based AAA derivatives, it was considered that both the alkene and alkyne moieties are present in the same molecule, for example **61** is a suitable substrate to generate the diene **62**. This substituted diene reacts with a suitable dienophile such as naphthaquinone in a DA fashion, followed by a dehydrogenation sequence, to give the aromatic derivative **63** (Scheme 21).[23b] This methodology has found many applications for the generation of complex molecular frameworks.

Similarly, tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives were synthesized by enyne metathesis as a key step. Tic is an important structural element present in various important alkaloids and other medicinally useful compounds. The diene moieties **65** or **68** were synthesized by enyne metathesis of **64** or **67** using Grubbs' Ru catalyst **34**. The DA reaction of **65** or **68** with various dienophiles and subsequent oxidation of the DA adducts with DDQ gave angularly substituted Tic derivatives (**66** or **69**) in good yields (Scheme 22).[24]

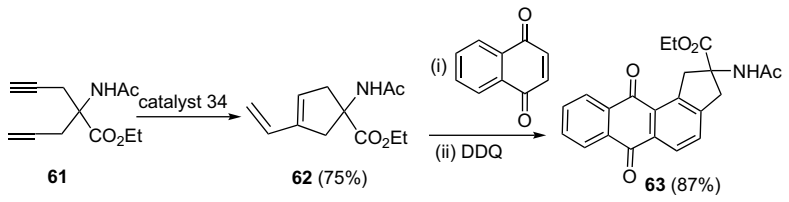
The hybrid natural products are useful for biological evaluation. For example, the sugar-oxasteroid-quinone (**73**), a hybrid molecule with a steroid backbone, was prepared by Kaliappan and Ravikumar. They have utilized Kotha's strategy, where enyne metathesis, DA reaction and DDQ oxidation are used as key steps. Intramolecular enyne metathesis of **71** with Grubbs' first-generation catalyst **34** gave the diene **72**. Later, an intermolecular DA reaction of diene **72** with 1,4 benzoquinone **70**, followed by aromatization, gave an interesting sugar-steroid hybrid molecule **73**, as depicted in Scheme 23.[25]

5. Benzannulation via Danheiser protocol

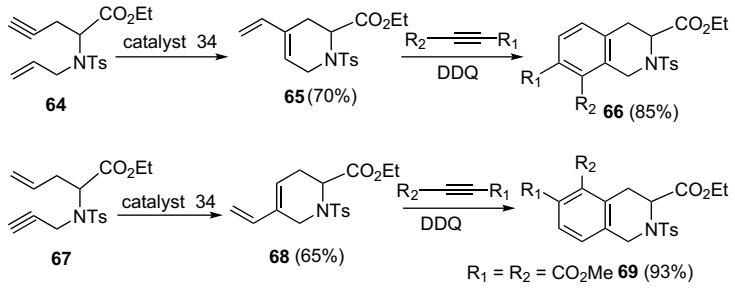
The regiocontrolled syntheses of highly functionalized aromatic systems have been achieved through annulation strategies. The requisite aromatic unit can be appended in a single step using activated (hetero-substituted) or inactivated acetylenes and vinylketenes, followed by a series of pericyclic reactions.

Danheiser and co-workers have used a simple annulation strategy starting with cyclobutane derivative **75** to construct (−)-ascochlorin (**77**), via **76**, which exhibits antiviral, antibiotic and antitumour activities. Their protocol involves a series of pericyclic reactions through intermediates **78**–**80** (Scheme 24).[26a] Their regioselectivity of this process is governed by the regiospecific [2+2] cycloaddition between a ketene **78** and an acetylene derivative **74**. This methodology delivers polysubstituted resorcinols using (trialkylsilyl)vinylketenes and lithium ynolates.[26b]

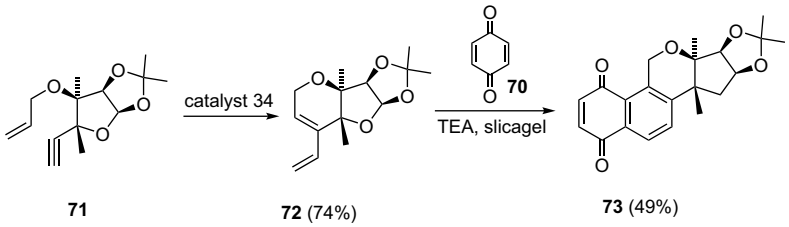
The scope of this methodology has been expanded to a higher level, when the vinylketene **83** was generated by a photochemical Wolff rearrangement of an unsaturated α-diazo ketone **82**, which is easily available from simple ketones or acid chlorides in one step. This second-generation Danheiser annulation protocol delivers a wide variety of functionalized polyaromatic and heteroaromatic systems involving acetylene building blocks such as **81** (Scheme 25).[27a]



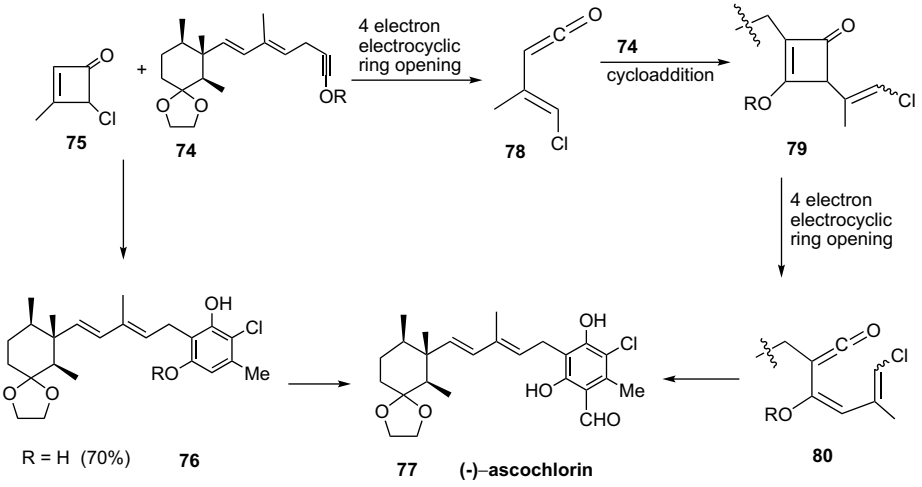
Scheme 21.



Scheme 22.

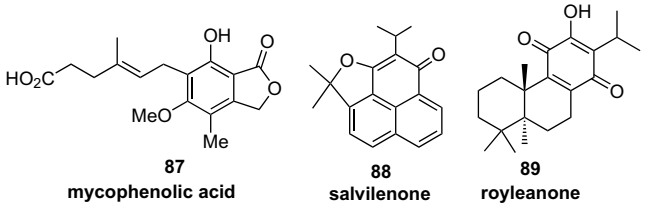


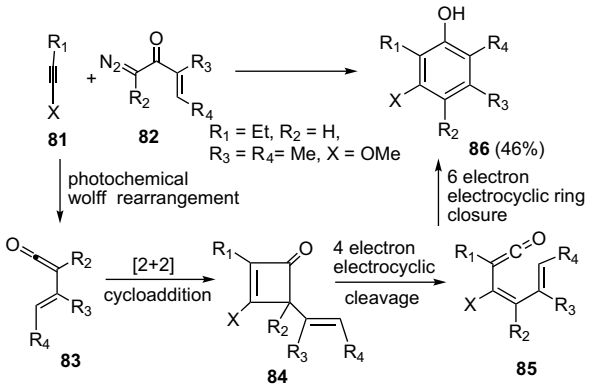
Scheme 23.



Scheme 24.

A range of substituted phenols, naphthalenes, benzofurans, benzothiophenes and indoles can be prepared by this method. This strategy proceeds with a series of ring-opening and ring-closing reactions (**84**–**86**). Several natural products such as mycophenolic acid **87**, salvilenone **88** and royleanone **89** have been realized by using this methodology.[27b–d]





Scheme 25.

Cylindrocyclophanes are 22-membered carbocyclic [7,7]-paracyclophane derivatives, which have been isolated from blue-green algae. They exhibit in vitro cytotoxicity against tumour cell lines. Smith and co-workers have used Danheiser annulations and RCM to construct highly functionalized benzene derivatives for the total synthesis of cylindrocyclophane-F (**93**), starting with **90** and **91**. The diolefinic derivative **92** has been converted into cyclophane derivative **93** via metathesis sequence as a key step (Scheme 26).[28]

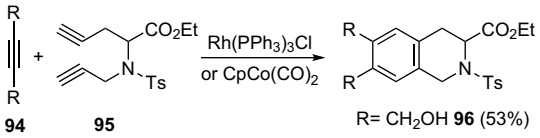
6. Benzannulation via cycloaddition tactics

6.1. [2+2+2] Cycloaddition reaction

The transition-metal-mediated [2+2+2] cycloaddition reaction of alkynes is an elegant method for the construction of annulated polycyclic aromatic hydrocarbon derivatives. This strategy is useful for the synthesis of various biologically active molecules, unusual amino acids, heterocycles and theoretically interesting molecules. The approach is atom economical and a wide variety of catalysts are available for the synthesis of various target molecules. The problem associated with this strategy is the synthesis of key building blocks, which requires a lengthy synthetic sequence. Recent developments dealing with [2+2+2] cycloaddition reactions have been reviewed.[29]

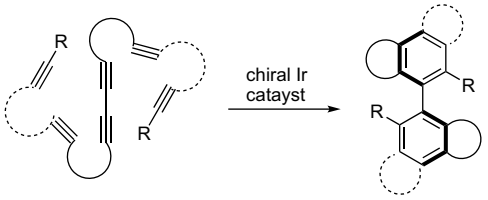
Kotha and Sreenivasachary have prepared a series of Tic derivatives via an alkyne co-trimerization reaction. To this end, treatment of the diyne **95** with various mono-alkynes **94** involving a [2+2+2] cycloaddition reaction in the presence of Wilkinson's catalyst or $CpCo(CO)_2$ proceeded smoothly to afford various Tic derivatives such as **96** in good-to-moderate yield (Scheme 27).[30]

Shibata[31a] and co-workers found that a chiral iridium complex catalyzed a consecutive and enantioselective [2+2+2] cycloaddition of polyynes to give axially chiral compounds. It was suggested that axial chirality has been introduced between aryl substitution on the alkyne termini of the substrates and the formed benzene ring(s) via enantioselective inter- and intramolecular [2+2+2]



Scheme 27.

cycloaddition of tetraynes and hexaynes, possessing a 1,3-diyne moiety, as shown in Scheme 28.[31b–e]



Scheme 28.

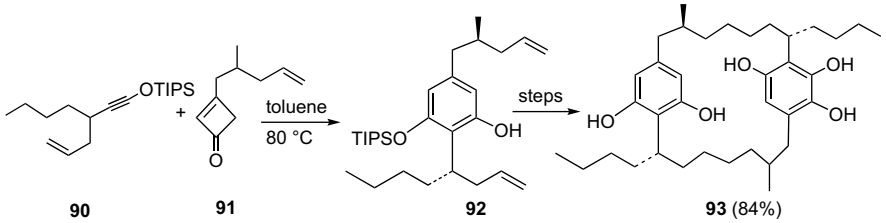
In this connection, a carbon-tethered tetrayne **97** was treated with 1,4-dimethoxybut-2-yne **98** using a chiral iridium catalyst, which was prepared in situ from $[IrCl(cod)]_2$ and Me-DUPHOS, to give the desired quateraryl product **99** in 33% yield along with mono-cyclized product **100** (Scheme 29).

6.2. [3+3] Cycloaddition reaction

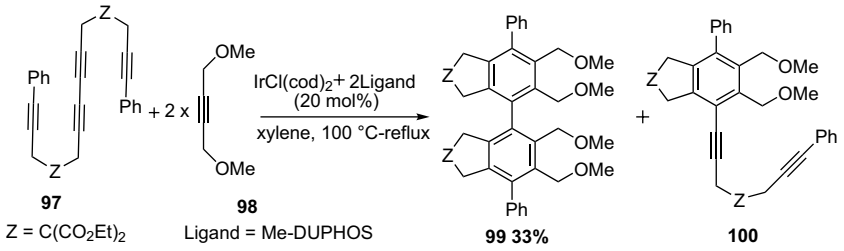
The [3+3] cycloaddition strategy plays an important role in designing polycyclic aromatic compounds, due to the ready availability of suitable precursors and the well-controlled regiochemistry. The strategies based on [3+3] cycloaddition for benzannulation involve three steps: (i) nucleophilic attack; (ii) cyclization which proceeds via a cationic, anionic or radical mechanism and (iii) aromatization through elimination or oxidation (Scheme 30).[32]

Junjappa and co-workers have synthesized several derivatives of fluoranthene, namely benzofluoranthene, which has a resemblance to partial structures of C_{60} fullerene, and novel acenaphtho-based five- and six-membered heterocycles, via a [3+3] cycloaddition reaction. Thus, compound **102** (α-oxoketene dithioacetal), prepared by treatment of acenaphthenone (**101**) with NaH and CS_2 in DMF, reacted with allylmagnesium chloride resulting in the formation of the carbinol acetal (**103**). This intermediate undergoes cycloaromatization in the presence of $BF_3 \cdot Et_2O$ in refluxing benzene to afford a polycyclic compound such as **104**. The parent fluoranthene has been prepared by reductive dethiomethylation of **104** with Raney-Ni in 70% yield.[32]

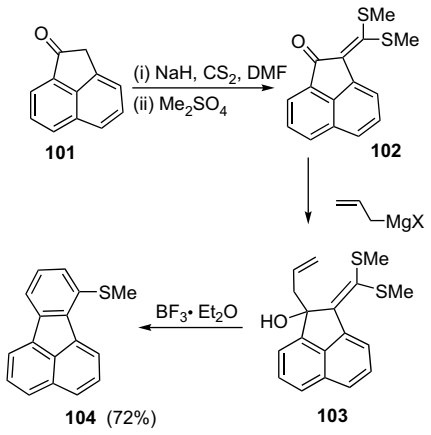
Several acenaphthane-based heterocycles such as **105** and **107** (via **106**) were synthesized starting with the key building block **102**, as depicted in Scheme 31.[32]



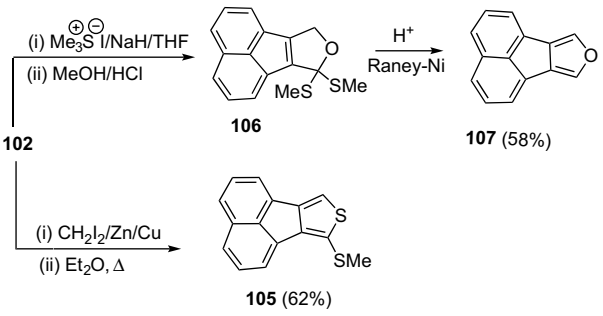
Scheme 26.



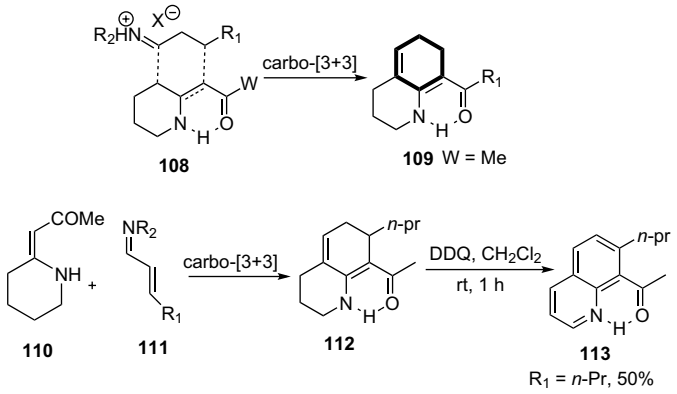
Scheme 29.



Scheme 30.



Scheme 31.



Scheme 32.

Hsung and co-workers elaborated the aza and carbo-[3+3] annulations of *exo*-cyclic vinylogous amides **110** and urethanes **111** through the synthesis of tetrahydroindolizidines and hexahydroquinolines **113** through the intermediate **112**. They observed that pyrrolidine- and azepane-based vinylogous amides or urethanes undergo aza-[3+3] annulations and piperidine-based vinylogous amides follow a carbo-[3+3] annulation. The carbo-[3+3] annulations (**108**→**109**) provide a powerful synthetic strategy to construct nitrogen heterocycles that can give rise to a wide variety of prevalent structural motifs among alkaloids (Scheme 32).[33]

6.3. [6+4] Cycloaddition reaction

The chromium(0)-promoted higher-order cycloaddition reaction has found to be a powerful tool for the construction of bicyclic systems. This benzannulation strategy involves a cycloaddition reaction by irradiation of (η^6-thiepine 1,1-dioxide)-tricarbonylchromium(0) (**114**) in the presence of a diene (**115**), followed by a Ramberg–Backlund rearrangement. This tricyclic adduct **116**, on treatment with *t*-BuOK in THF, followed by trapping of the intermediate carbanion with *N*-chlorosuccinimide (NCS) and exposure to a further equivalent of *t*-BuOK, produced hexahydroanthracene (**117**), as shown in Scheme 33.[34]

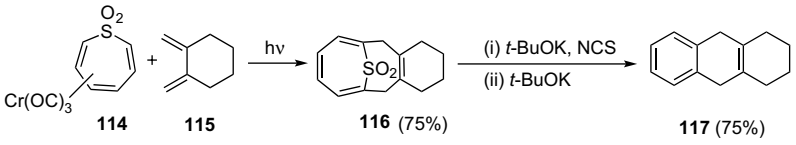
This type of benzannulation strategy always gives completely diastereo selective products when the starting precursors contain a stereogenic centre [e.g., **118**], as illustrated in Scheme 34. Here, the Ramberg–Backlund reaction of sulfone derivative **119** gave the final target **120**.

7. Benzannulation via base-induced rearrangement

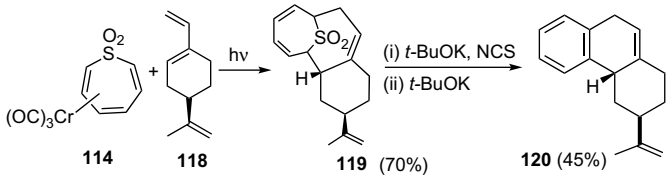
This strategy is useful to construct aromatic moieties present in various biologically active molecules. It involves the mild base-promoted cyclization of substituted 3-alkoxycarbonyl-3,5-hexadienone acids such as **121** to a substituted 3-hydroxybenzoic acid derivative **122** (Scheme 35).[35] Various highly functionalized aromatic compounds, which are not accessible by traditional methods can be easily prepared by this route.

Recently, Serra and Fuganti extended this methodology to the synthesis of *C*-aryl glycosides, which are an important subclass of glycosides found in many natural products. Towards the synthesis of sugar derivative such as the 3-hydroxy-4-(β-glucopyranosyl)benzoate (**127**), a readily available 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**123**) was converted into the target compound by a benzannulation reaction (via **124**–**126**), as shown in Scheme 36.[36]

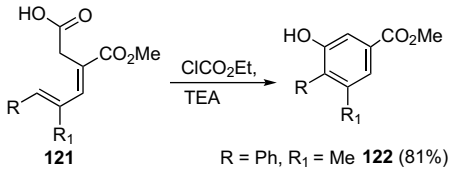
Along similar lines, Serra has synthesized 2,2,6,6-tetrasubstituted pyran-based natural products such as (*R*)-(+)-sydowic acid (**132**) and (*R*)-(+)-curcumene using a benzannulation reaction of a 3-alkoxycarbonyl-3,5-hexadienone acid (**131**) without any racemization. This is a useful tool for the stereoselective synthesis of sesquiterpenes bearing sterically crowding quaternary stereocenters (Scheme 37).[37] The key starting material **131** has been assembled by a series of C–C bond forming reactions (**128**–**130**).



Scheme 33.



Scheme 34.



Scheme 35.

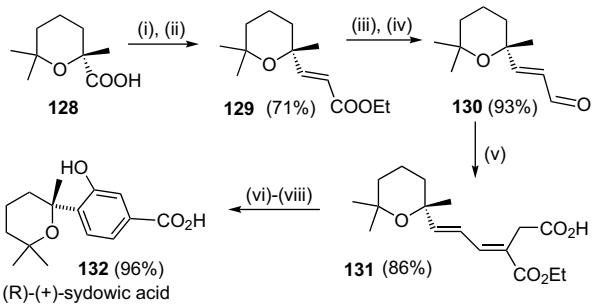
7.1. From aromatic ketones

The most common substrates for benzannulation are alkynes and ketones and thus the reaction of a keto-enolate **134** with the phosphonium salt **133** produced a bicyclic alcohol **135**, which, on dehydration with PTSA, provides 2-phenylnaphthalene **136**, as depicted in Scheme 38.[38] This protocol seems to be a useful procedure to prepare a wide variety of naphthalene derivatives.

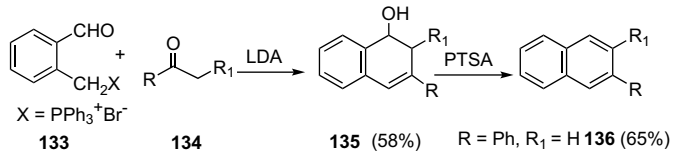
7.2. Base-induced rearrangement

Recently, Wurthwein and co-workers developed a new rearrangement reaction, initiated by the deprotonation of imines, leading to polysubstituted aminobenzoannulated heterocycles. In this regard, the imine **137** undergoes deprotonation with LDA at −78 °C, with subsequent warming to room temperature for 16 h, followed by quenching with ammonium chloride solution, leading to the aniline derivative **138** in good or excellent yields (Scheme 39).[39]

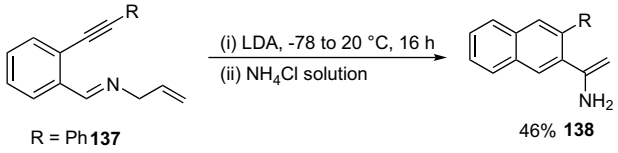
A multistep mechanism (**139**–**144**) has been proposed for the formation of polysubstituted aminobenzoannulated heterocycles via a 2-azaallyl anion, an azepine anion and an anionic nitrile intermediate (Scheme 40).[39]



Scheme 37. (i) CH_2N_2/Et_2O, $LiAlH_4/Et_2O$, ClCO–COCl/DMSO, (ii) $Ph_3PCHCO_2Et/CHCl_3$, (iii) DIBALH, (iv) $MnO_2/CHCl_3$, (v) triphenyl-(carbethoxy-β-carboxyethyl)phosphonium betaine, $CHCl_3$, (vi) $(CF_3CO)_2O$, (vii) $NaBH_4$/EtOH/HCl, (viii)KOH/MeOH.



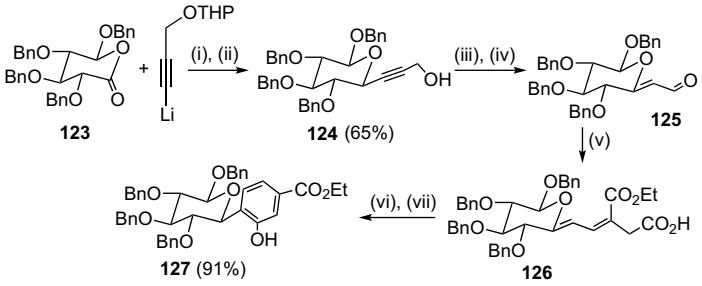
Scheme 38.



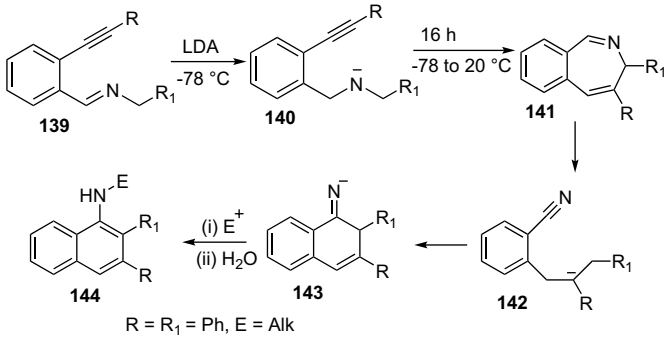
Scheme 39.

8. Benzannulation via photo-induced cyclization

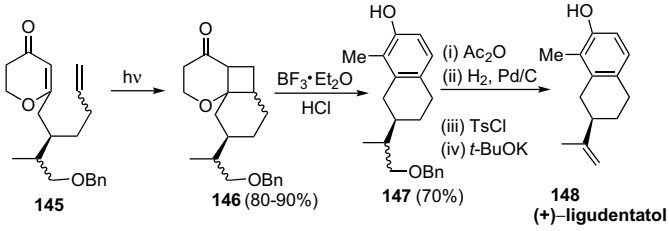
Substituted phenols have found useful applications as insecticides and anti-allergic and anti-inflammatory agents. A number of natural products containing this core skeleton such as (+)-ligudentatol (**148**) were synthesized by a [2+2] photocycloaddition followed by fragmentation of **146** in the presence of boron trifluoridetherate to produce the benzannulated product **147**, which was further converted into the ligudentatol, as described in Scheme 41.[40]



Scheme 36. (i) THF, −78 °C, (ii) $Et_3SiH/BF_3{\cdot}Et_2O$, (iii) RED-Al, Et_2O, 0 °C, (iv) MnO_2, (v) triphenyl-(carbethoxy-β-carboxyethyl)phosphonium betaine, (vi) $ClCO_2Et$, Et_3N, (vii) NaOH/EtOH, HCl.

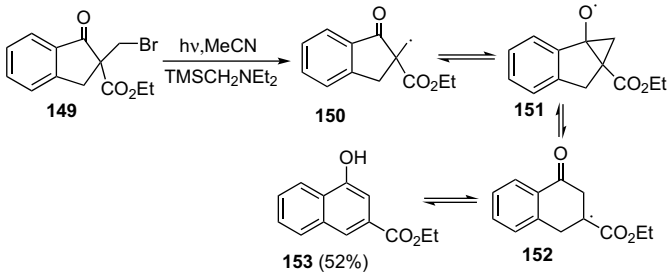


Scheme 40.



Scheme 41.

Hasegawa and co-workers have prepared naphthalene derivatives such as **153** through a ring-expansion strategy via the intermediates **150**–**152**. This involves a one-electron transfer photo-reaction of the halomethyl-substituted keto derivative **149**, followed by an aromatization sequence (Scheme 42).[41]

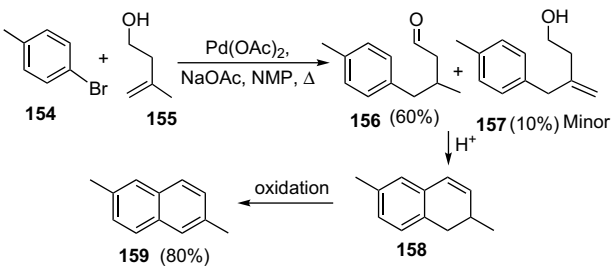


Scheme 42.

9. Benzannulation via transition-metal-promoted processes

9.1. Palladium-catalyzed reactions

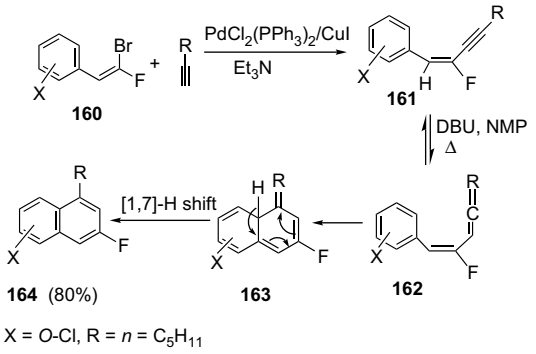
High-performance polyesters, e.g., polyethylene naphthalene (PEN), have many useful applications in films and fibres and in the packaging industry, due to their thermal and electrical properties. 2,6-Dimethylnaphthalene [2,6-DMN] (**159**), a useful starting material for the synthesis of PEN, is constructed by a ligand-free Heck coupling reaction of 4-bromotoluene (**154**) and 3-methyl-3-butene-1-ol (**155**), followed by aromatic electrophilic cyclodehydration reactions, as depicted in Scheme 43.[42] The ratio (e.g., **156**–**157**) of the Heck coupling product varied along with change in the base. It was found that the cyclodehydration reaction of **156** occurs in the presence of 10-camphorsulfonic acid (CSA) in the presence of solid acids like amberlyst via the dehydrogenative product **158** followed by oxidation, which resulted in the maximum yield of 2,6-DMN.



Scheme 43.

9.1.1. Synthesis of fluorinated naphthalene and phenanthrene derivatives

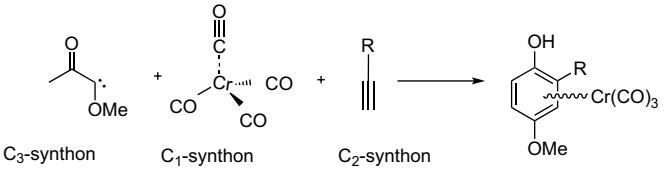
Fluoro compounds are useful building blocks in polymer science, medicinal chemistry and in the pharmaceutical industry. The Sonogashira reaction of a bromofluoro-substituted alkene (**160**) with a terminal alkyne in the presence of a $PdCl_2(PPh_3)_2$/CuI catalyst, followed by base-catalyzed cyclization, affords site-specific fluorinated naphthalene and phenanthrene derivatives. The mechanism for the formation of naphthalene derivatives involving intermediates **161**–**164** is included in Scheme 44.[43]



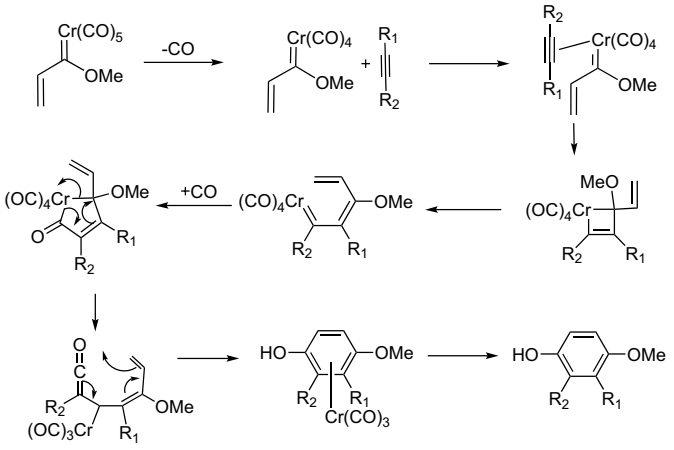
Scheme 44.

9.2. Chromium-assisted methods—Dötz benzannulation

The most widely used transition-metal-promoted method for the construction of densely functionalized benzene ring compounds is Dötz benzannulation, which proceeds through a [3+2+1] cycloaddition reaction. This involves an α,β-unsaturated carbene ligand (C_3-synthon), an alkyne (C_2-synthon) and a carbonyl ligand (C_1-synthon) within the coordination sphere of a chromium(0) metal centre, which acts as a template, as shown in Scheme 45. This unique type of metal–carbene complex reaction provides a simple route to highly substituted aromatic compounds.

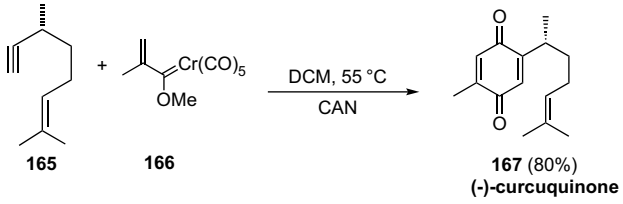


Dötz and co-worker have synthesized a marine natural product, (−)-curcuquinone (**167**), involving a chromium-mediated [3+2+1] benzannulation reaction as a key step. This overall protocol can be viewed as a convergent synthetic approach to generate a quinonoid core. To this end, a suitably functionalized alkyne moiety **165** was prepared from the commercially available geraneol. A benzannulation reaction of **165** with a



Scheme 45.

chromium-carbene complex (**166**), followed by ceric ammonium nitrate (CAN) oxidation, gave (−)-curcuquinone **167** in 80% yield (Scheme 46).[44] (−)-Curcuquinone displays antibacterial activity and is also a useful chiral building block for the synthesis of several natural products.



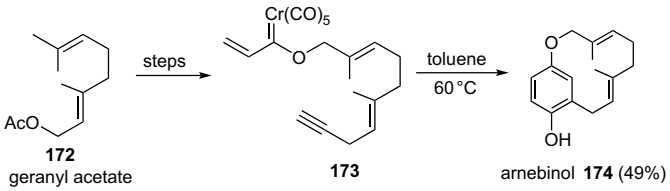
Scheme 46.

Danishefsky and Gordon have used the Dötz benzannulation strategy to assemble angucycline antibiotics. Angucyclines contain benz[α]anthracene as a core structural unit and exhibit antiviral and antibacterial activities. With reference to angucycline antibiotic synthesis, the *o*-substituted benzylchromium complex **169** was treated with alkyne **168** in the presence of THF under argon, followed by oxidation with CAN and transannular aldolization of **170** gave the highly functionalized benzannulated quinone derivative **171** in 65% yield (Scheme 47).[45]

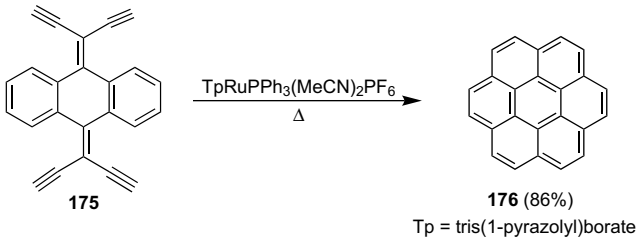
Nakata and co-workers have reported a novel intramolecular version of the Dötz reaction for the regioselective synthesis of arnebinol, an inhibitor of prostaglandin biosynthesis. They prepared the chromium–carbene complex **173** from geranyl acetate **172** and this undergoes a benzannulation reaction in toluene at 60 °C to deliver arnebinol **174** in 49% yield (Scheme 48).[46]

9.3. Ruthenium-mediated cyclizations

Large polycyclic aromatic compounds such as coronene (**176**) and its derivatives exhibit interesting applications as organic transistors and in photovoltaic devices and may be prepared by Ru-catalyzed benzannulation of enyne **175**, as shown in Scheme 49.[47]



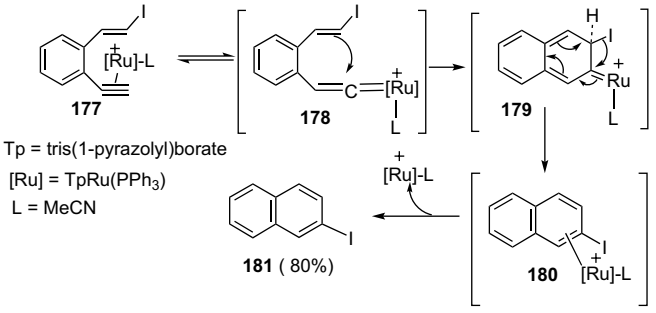
Scheme 48.



Scheme 49.

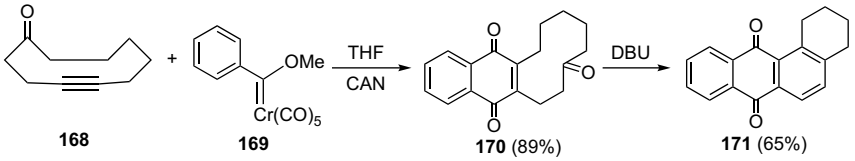
The [Ru]-catalyst used here is very efficient to give various PAHs by multiple benzannulation reactions.

Aromatic enynes containing a halogen group undergo [Ru]-catalyst electrocyclization via 1,2-migration of halogen to provide benzannulated derivatives. Thus, the [Ru]-catalyst reacts with the terminal alkyne to form a cationic ruthenium π-alkyne complex **177** that equilibrates with a ruthenium-vinylidene species **178**. Electrocyclization of **178** via 1,2-migration of halogen produces the naphthalene derivative **181** via the intermediates **179** and **180** (Scheme 50).[48]

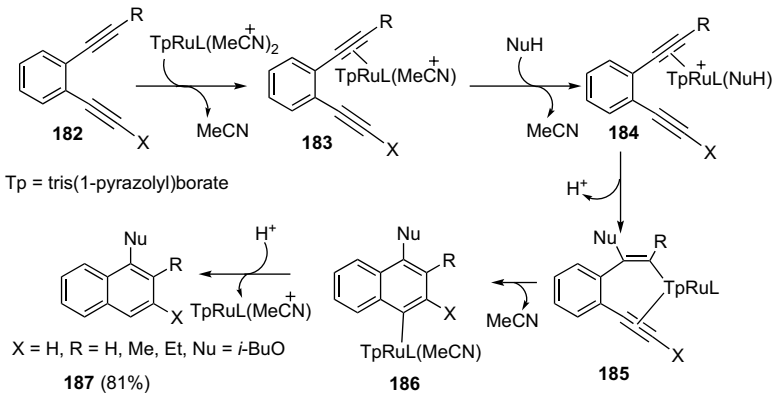


Scheme 50.

Additionally, a novel and advanced [Ru]-catalyzed aromatization of enediynes with mild nucleophiles generates functionalized aromatics, such as **187**, from the readily available unfunctionalized enediynes **182**, as shown in Scheme 51.[49] The significance of this cyclization is the regioselectivity of the nucleophilic addition, which occurs at the more electron-rich alkyne carbon and delivers the substituted PAHs from the readily available unsubstituted enediynes. The possible mechanism involving intermediates **183**–**186** is shown in Scheme 51.



Scheme 47.

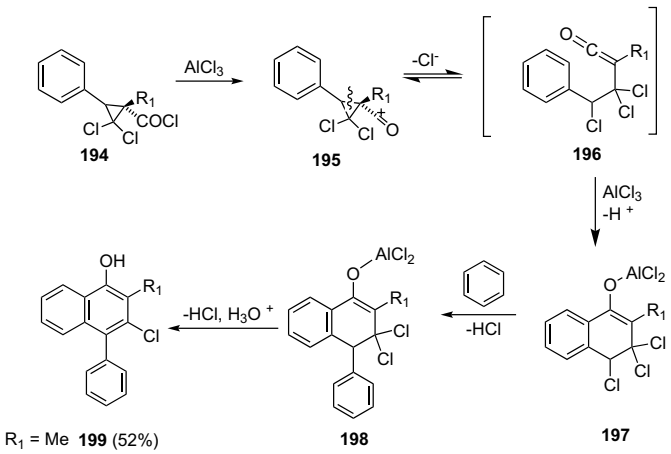


Scheme 51.

10. Benzannulation via Lewis acid-catalyzed cyclization of aromatic moiety

Nishii and co-workers have demonstrated an efficient method for the synthesis of highly substituted α-arylnaphthalenes (**191** or **193**) by utilizing the Lewis acid-promoted benzannulation of aryl-(2,2-dichlorocyclopropyl)methanols **188** in a moderate-to-excellent yield. This methodology proceeds by ring expansion of cyclopropane involving the intermediate **189**, followed by an intramolecular Friedel–Crafts reaction. The regioselectivity of the products depends on the type of Lewis acids used, which, in turn, determines the stability of the intermediate carbocation formed (**190** or **192**) by cleavage of the *gem*-dihalogenocyclopropane ring (bond a or b), as described in Scheme 52.[50]

In a related study, the synthesis of 4-aryl-1-naphthols such as **199**, a basic skeleton of lignin-type natural products, has been realized by sequential Friedel–Craft reactions of 3-aryl-2,2′-dihalocyclopropanecarbonyl chlorides **194**, followed by intermolecular coupling with substituted benzenes. The reaction proceeds via ketene **196** formation. A possible mechanism (**195**→**199**) is shown in Scheme 53.[51]

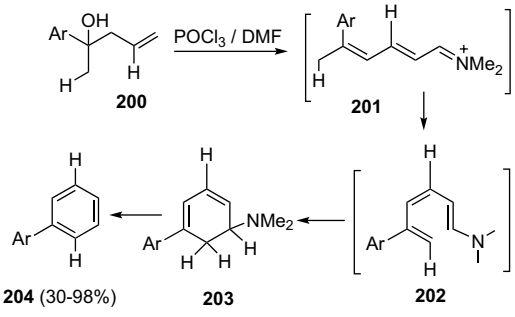


Scheme 53.

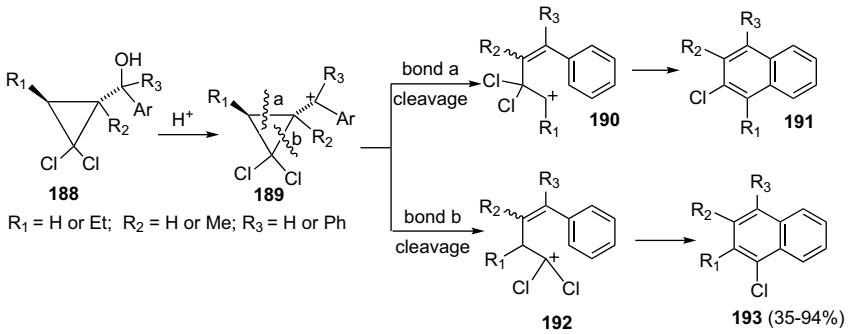
11. Benzannulation through miscellaneous methods

11.1. Vilsmeier reaction

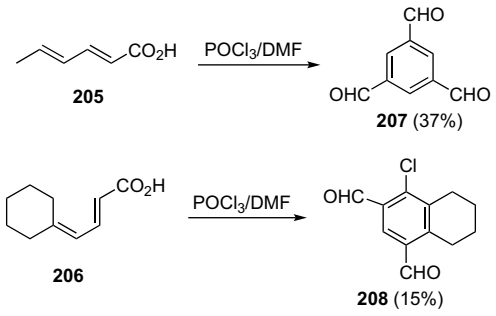
Rao and co-workers have reported a one-pot synthesis of biphenyl and 9,10-dihydrophenanthrene derivatives by utilizing the Vilsmeier reaction as a key step. Thus, homoallylic alcohols **200** in the presence of $POCl_3$/DMF form the 2,4-alkadienal equivalents **201**, which undergo ring closure via **202** and **203** to give the biphenyl derivatives **204** (Scheme 54).[52] Several useful



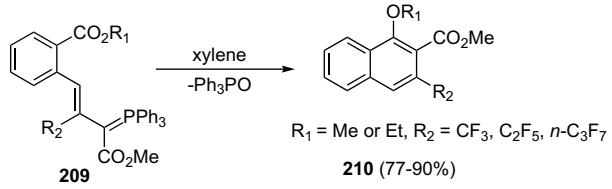
Scheme 54.



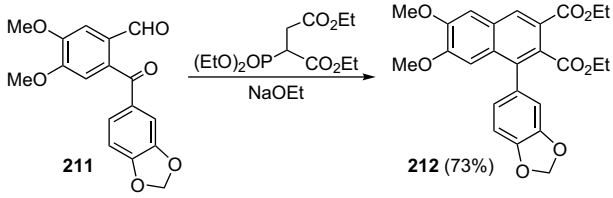
Scheme 52.



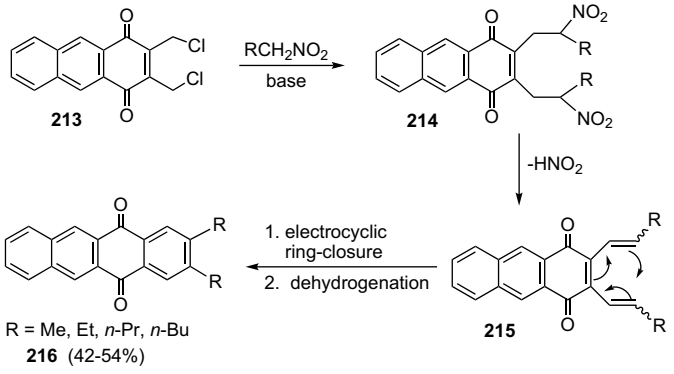
Scheme 55.



Scheme 56.



Scheme 57.



Scheme 58.

biphenyl derivatives were prepared by this benzannulation strategy.

Along similar lines, Rao and co-workers have reported a useful benzannulation sequence under Vilsmeier conditions with 2,4-hexadienoic acid **205** (or **206**) to give carboxaldehyde-substituted aromatic products **207** and **208**, respectively (Scheme 55).[53]

11.2. Phosphorous ylides

Ding and co-workers have utilized an intramolecular Wittig reaction suitable for the synthesis of substituted naphthalenes. To this end, thermolysis of the ylides (**209**) with loss of triphenylphosphine oxide afforded the fluoroalkylnaphthalene derivatives (**210**) (Scheme 56).[54]

Harrowven and co-workers have used a base-induced Horner–Emmons reaction between the ketoaldehde **211** and phosphonate, followed by a Claisen condensation, to prepare various natural product frameworks such as justicidin-B and retrojusticidin-B. These natural products (e.g., **212**) are potentially useful as inhibitors of HIV-1 reverse transcriptase (Scheme 57).[55]

11.3. Electrocyclic ring closure

Vanelle and co-workers have developed a new method for benzannulation by using a one-pot nitrous acid elimination, electrocyclic ring closure and dehydrogenation sequence (**213**–**216**) as shown in Scheme 58.[56] This type of reaction proceeds via $S_{RN}1$ reaction conditions (inert atmosphere, photostimulation) in a phase-transfer system. The advantage of this reaction is the easy accessibility of the starting material, as compared to the classical Diels–Alder reaction.

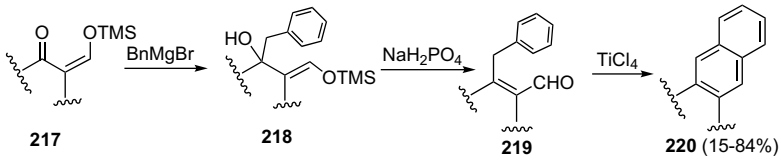
11.4. Carbonyl condensation

Tius and Galen have synthesized substituted naphthalene and anthracene derivatives by cationic cyclization, starting from the non-aromatic ketone precursors. In this process, a cyclic or acyclic ketone **217** was converted into an aldehyde **219** by a Grignard addition product **218**, followed by NaH_2PO_4 treatment. Cyclization of **219** using $TiCl_4$ at −30 °C gave the annulated products **220** (Scheme 59). The mechanism of this reaction involves a cationic cyclization.[57]

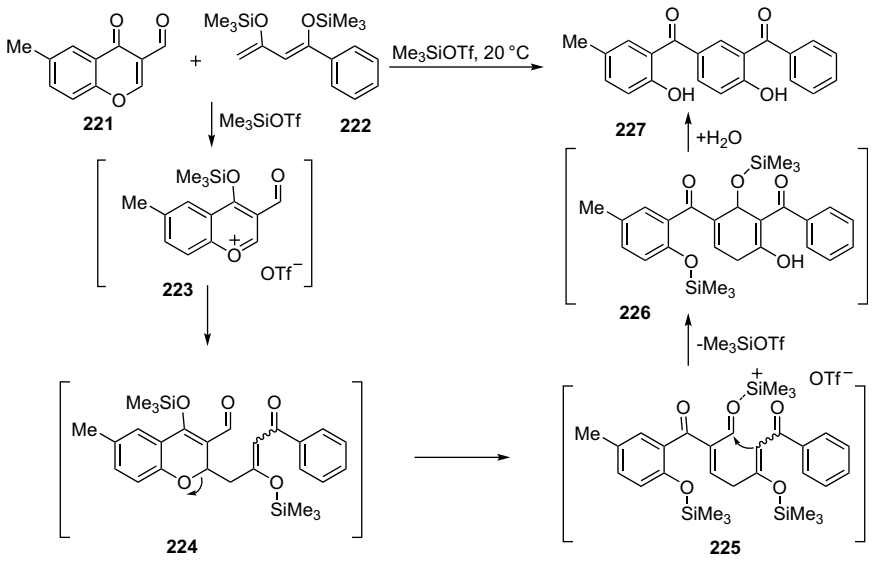
Langer and co-workers have synthesized a hydroxylated bis(benzophenone) **227** via an Me_3SiOTf-catalyzed reaction of 6-methyl-3-formyl-chromone (**221**) with 1-phenyl-1,3-bis-(trimethylsilyloxy)-1,3-butadiene (**222**). The synthetic approach can be explained by a 'Michael–retro-Michael–Mukaiyama–aldol' reaction (**223**–**227**) and the details are shown in Scheme 60.[58]

12. Conclusions

Various strategies for benzannulation have been included in this report. Most of these methods involve transition-metal-based



Scheme 59.



Scheme 60.

transformations and such transformations are likely to have extended utility in organic synthesis. We anticipate that several new advances involving tandem processes and catalytic processes under green conditions will continue to appear at a rapid rate.

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Somnath Halder was born in Bankura, West Bengal. He obtained his B.Sc. degree in Chemistry from Burdwan University, West Bengal in 1993 and his M.Sc. degree in Organic Chemistry from Burdwan University in December 1995. In 2002, he obtained his Ph.D. degree under the guidance of Professor S. Kotha from the Department of Chemistry, Indian Institute of Technology-Bombay. He then joined Ciba India Pvt. Ltd, Mumbai (2002–2003) as a Research Associate. During 2003–2004, he worked with Professor Jean-Luc Decout as a Postdoctoral fellow in the Département de Pharmacochimie Moléculaire (DPM) at Universitè Joseph Fourier-Grenoble, France. Subsequently, he joined the Nicholas Piramal Research Centre, Mumbai, and is currently working as a Senior Research Scientist. His research interests are in new synthetic methods, unnatural amino acids and medicinal chemistry.