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(Hetero)aromatics from dienynes, enediynes and enyne–allenes

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The construction of aromatic rings has become a key objective for organic chemists. While several strategies have been developed for the functionalization of pre-formed aromatic rings, the direct construction of an aromatic core starting from polyunsaturated systems is yet a less explored field. The potential of such reactions in the formation of aromatics increased at a regular pace in the last few years. Nowadays, there are reliable and well-established procedures to prepare polyenic derivatives, such as dienynes, enediynes, enyne–allenes and hetero-analogues. This has stimulated their use in the development of innovative cycloaromatizations. Different examples have recently emerged, suggesting large potential of this strategy in the preparation of (hetero)aromatics. Accordingly, this review highlights the recent advancements in this field and describes the different conditions exploited to trigger the process, including thermal and photochemical activation, as well as the use of transition metal catalysis and the addition of electrophiles/nucleophiles or radical species.

1 Introduction

Benzenes, polycyclic aromatic hydrocarbons (PAHs) and hetero-aromatics are key classes of compounds with diverse roles in many branches of chemistry, due to their use in the preparation of electroactive organic materials and molecular devices, as well as building blocks in organic synthesis and medicinal chemistry.[1–4] Accordingly, the construction and functionalization of aromatic rings have become key objectives for organic chemists. However, whereas a plethora of strategies has been developed for the functionalization of pre-formed rings, the available strategies to build an aromatic core starting from (poly)unsaturated systems is yet a quite unexplored field.[5–7] The most used strategies include: (1) the ring-closing metathesis (RCM) of non-conjugated trienes (Scheme 1, path a)[8] and enynes;[9–12] (2) intra- or intermolecular

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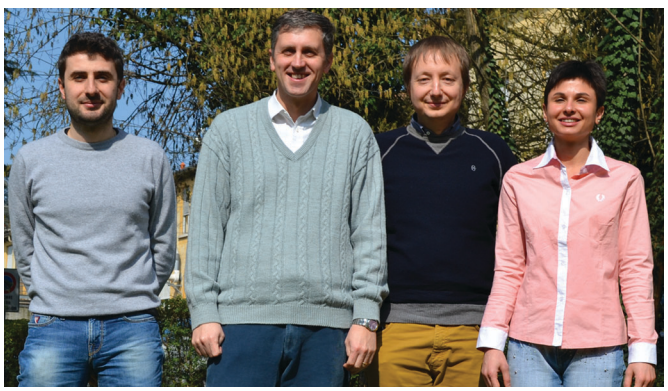

Left to right: Davide Ravelli, Maurizio Fagnoni, Stefano Protti and Carlotta Raviola

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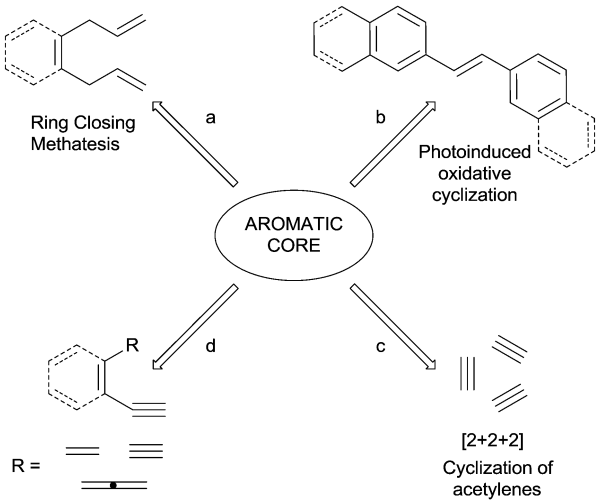


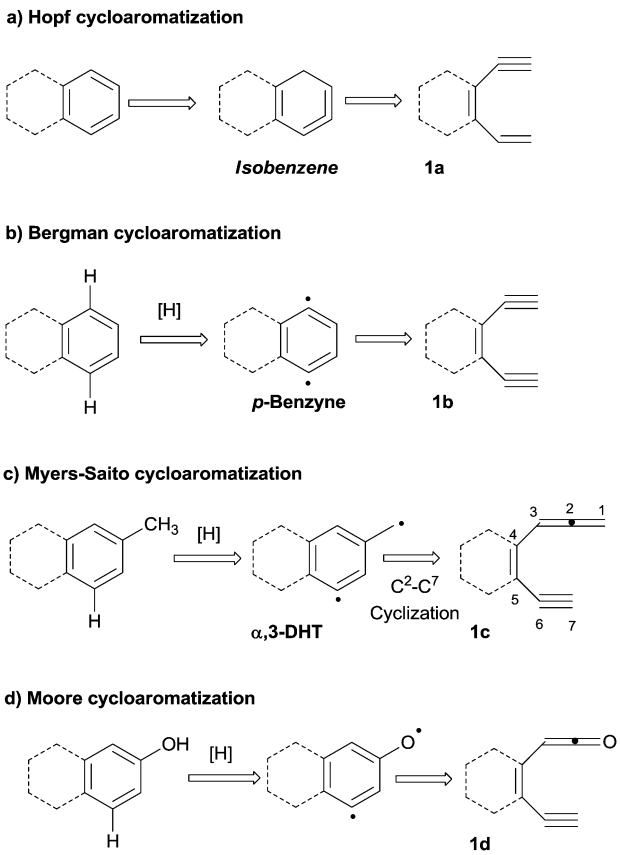
Scheme 1 Selected strategies for the construction of aromatic rings.

[3+3] benzannulation reactions;[13] and (3) cycloaddition processes involving *o*-quinodimethanes.[14,15] In such cases, a multi-step process is involved and the aromatization occurs after the construction of one or more σ bonds. One-pot strategies for the preparation of benzocondensed derivatives have been likewise reported, such as the photoinduced oxidative cyclization of stilbenes[16] introduced by Mallory in 1964 (path b) and the electrophilic cyclization of suitable arene-containing propargyl alcohols and 1-aryl-3-alkyn-2-ones.[17–19]

However, only a few strategies where both the cyclization and the aromatization processes take place in a single step have been reported. This is the case of transition-metal mediated [2+2+2] cycloaddition reactions of triple bonds (Scheme 1, path c).[20–25] These are atom-efficient processes and the high tolerance to several functional groups (such as alcohols, amines and unsaturated moieties), as well as the high regio- and chemoselectivities,[5] makes them an almost "*universal synthetic tool for the synthesis of benzene, pyridine, and other cyclic derivatives*".[20]

An appealing alternative is the construction of (hetero)aromatic rings from polyenes (dienynes, enediynes, enyne–allenes or their hetero-analogues; path d). The main advantage of this one-pot approach is that several conditions (involving different intermediates, mostly biradicals) can be adopted to trigger the cyclization event, as summarized in Scheme 2.[26]

In the so-called Hopf cyclization, the electrocyclization of hexa-1,3-dien-5-ynes (*e.g.* **1a**) gives arenes *via* a hydrogen shift in cyclohexa-1,2,4-trienes (also known as isobenzenes, Scheme 2a).[27] However, the first systematic investigation on polyenes as aromatic precursors was authored by Bergman, who described the thermal (200 °C) cyclization of (*Z*)-3-hexene-1,5-diynes (*e.g.* **1b**) to give 1,4-didehydrobenzene biradicals (*p*-benzynes, Scheme 2b). In the latter case, two radical centers and a new σ bond are formed at the expense of two π-orbitals in a process driven by the aromatic stabilization acquired in the intermediate.[28] A related cycloaromatization was later reported by the groups of Myers and Saito, who described the cycloaromatization of enyne–allenes (*e.g.* **1c**) *via* a C^2–C^7 mode to generate the corresponding



Scheme 2 Main approaches for the cycloaromatization of polyenes.

α,3-didehydrotoluenes (α,3-DHTs, Scheme 2c).[29–31] Heteroatom-substituted enyne–allene analogues undergo similar cyclizations, as in the case of the aza-Myers reaction[32] or in the Moore cyclization of enyne–ketenes (**1d**, Scheme 2d).[33] Similar processes take place in enyne–isocyanates,[34] enyne–ketenimines[35] and enyne–carbodiimides.[36] The Schmittel reaction (occurring in enyne–allenes *via* a C^2–C^6 mode) gives a non-aromatic biradical,[37–40] but several examples describe a subsequent intramolecular reaction involving a phenyl-substituent, likewise leading to benzocondensed aromatics.

20 years ago Wang excellently resumed the synthetic potentialities of cascade radical cyclizations *via* biradicals (Bergman, Moore and Myers–Saito reactions) for the preparation of complex structures.[41] Some synthetic applications have also been reported by Grissom *et al.* in their review focused on the reactivity of enediynes and analogues, published in the same year.[26]

While several reviews devoted to alkyne trimerization have been published over the last few decades,[20–25] the number of reports focused on the cyclization of conjugated polyenes is still limited. In fact, apart from the synthetic significance of these processes, the biradicals formed in these reactions have been claimed as the key intermediates to explain the chemotherapeutic activity of natural antibiotics containing polyenic moieties (*e.g.* enediynes).[42,43] Accordingly, much attention has been paid to elucidate the cyclization mechanism,[44–46] to predict the reactivity of the intermediates,[47–54] and to the synthesis of artificial polyene

precursors with potential biological activity.[42,43] The synthesis of polynuclear aromatics from dienynes has been sparsely reviewed,[55,56] but the main focus has been on mechanistic aspects of such cycloaromatizations and on the different approaches to accelerate the reactions.

On the basis of the above, the aim of the present review is to provide an overview of the most recent advances in the construction of aromatic and heteroaromatic rings starting from (*in situ* generated) conjugated polyenes, such as dienynes, enediynes and enyne–allenes. This review collects representative results (mainly) published since 1996 and has been organized according to the nature and the size of the (hetero)aromatics formed, preceded by a summary of the typical modes used to induce the cycloaromatization event.

2 Mode of activation of cycloaromatization

The great advantage of exploiting the cyclization of polyenes for synthetic purposes is that the cycloaromatization can be induced by heating, light irradiation, transition-metal catalysis or *via* the addition of electrophiles, nucleophiles or radicals, as summarized below.

2.1 Thermal activation

High temperatures (typically above 200 °C) are commonly required for the Hopf cyclization of acyclic hexa-1,3-dien-5-ynes.[27] Cycloaromatization of 11- and 10-membered carbocycles bearing a hexa-1,3-dien-5-yne moiety, however, took place at 100 °C and room temperature, respectively.[57] By contrast, for larger rings (up to 14-membered rings), the cyclization was inefficient or completely inhibited.[57]

The Bergman cycloaromatization is traditionally performed by heating the polyene moiety in the presence of an excess of either a hydrogen (1,4-cyclohexadiene – CHD – or methanol) or halogen (CCl_4) atom donor, depending on the desired product. The reactivity of (*Z*)-enediynes is influenced by different factors including, among others: (1) the distance between the two terminal acetylenic carbon atoms (generally speaking, the smaller the distance, the faster the cyclization; a value of 3.2–3.3 Å has been suggested as the limit to allow a cyclization at room temperature);[58] (2) the difference in strain energy between the enediyne and the transition state (the higher the strain relief in the transition state, the more reactive the enediyne);[59] and (3) substituent effects (the presence of substituents on the C=C double bond heavily affects the cyclization efficiency).[60] Accordingly, acyclic enediynes usually undergo cycloaromatization at a high temperature (150–200 °C), whereas milder conditions are required for cyclic analogues.[61] The most significant drawback of the thermal cycloaromatization of enediynes (mainly acyclic) and related derivatives is thus the high temperature required that is often incompatible with organic substrates.

Indeed, a shortening in the distance between the alkyne units in acyclic enediynes bearing chelating moieties (*e.g.* bisphosphane groups) can be induced by complexation with a metal ion, thus increasing the cycloaromatization rate.[62,63]

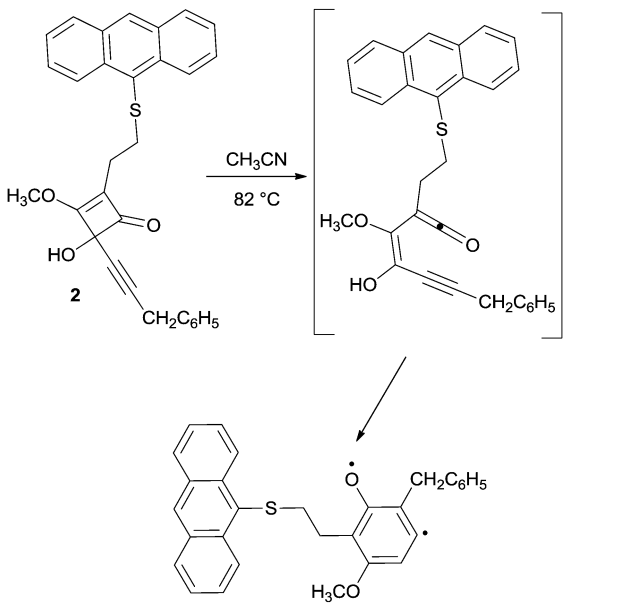
Interestingly, while the cyclization of (*Z*)-3-hexene-1,5-diyne was found to be endothermic (+13 kcal mol^{-1}),[64] the Myers–Saito cycloaromatization of the parent acyclic enyne–allene was found to be exothermic (−15 kcal mol^{-1}),[65] thus taking place at ambient or even sub-ambient temperature. In many cases, since enyne–allenes can be troublesome to handle due to their instability, they were generated *in situ via* the rearrangement of the corresponding enediynes.

The Myers–Saito reaction is generally the most energetically favorable process occurring in enyne–allenes. In substrates where the alkyne terminal hydrogen is replaced by a bulky moiety (such as the *tert*-butyl or trimethylsilyl groups), however, steric hindrance makes the enyne–allene more stable, thus favoring the Schmittel closure rather than the cycloaromatization.[39]

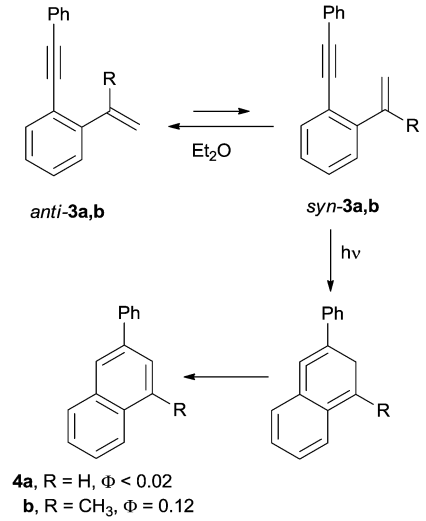
As for the Moore reaction, the intrinsic rate of cyclization could not be determined due to the high reactivity of enyne–ketenes, and the substrates are usually generated *in situ* by heating the corresponding 4-alkynylcyclobutenones (see for instance compound **2** in Scheme 3).[66]

2.2 Photochemical activation

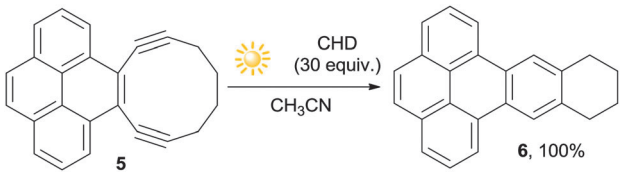
The quantitative conversion of *cis*-1,3-hexadiene-5-yne vapors in a 2 : 1 mixture of benzene and fulvene is the first example of photoinduced Hopf cycloaromatization. The process, however, occurred with a low quantum yield ($\Phi \sim 0.01$).[67] By contrast, the photocyclization took place efficiently when dienynes were irradiated in aprotic solvents in the presence of air.[56] The substitution pattern of the terminal alkene (*e.g.* the presence of a methyl group in position 2) was found to play a key role in allowing dienynes **3a,b** to exist in the less stable *syn* conformation, the actual photoreactive conformer precursor of naphthalenes **4a,b** (Scheme 4).[68]



Scheme 3 Moore cyclization *via* a thermally generated enyne–ketene.



Scheme 4 Photoinduced Hopf cycloaromatization.



Scheme 5 Sunlight-induced Bergman cyclization of strained *ortho*-dialkynylarenes.

In a related example, a photo-Hopf cyclization was used for the construction of the naphthalene core upon photocyclization/aromatizing fragmentation of benzannelated dienynes.[69]

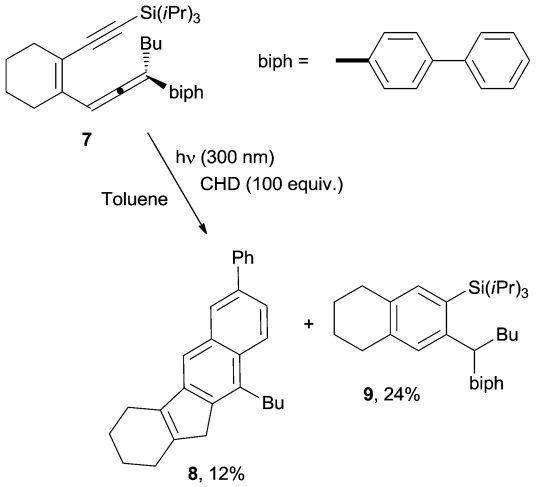
The chance of performing Bergman cyclizations by having recourse to a photochemical approach has been sparsely investigated,[70–73] with particular attention to the biological application of photoactivatable enediynes.[49,74] The approach was particularly efficient with strained *ortho*-dialkynylarenes (*e.g.* **5**, Scheme 5) that underwent cycloaromatization to **6** in quantitative yield upon 3 h exposure to sunlight.[71]

Recently, photochemical variants of the Myers–Saito and the Schmittel cyclizations have also been developed.[75,76] As an example, photolysis at 300 nm in toluene of enyne–allene **7** in the presence of CHD (100 equiv.) led to a mixture of **8** (12% yield) and **9** (24% yield) arising from the Schmittel and the Myers–Saito cyclizations, respectively (Scheme 6).[75]

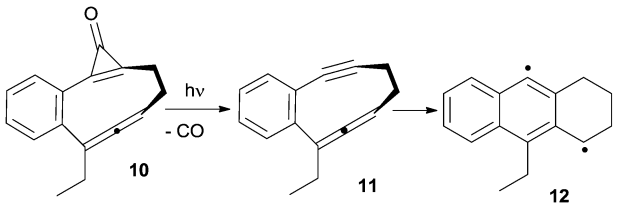
Photoinduced cyclizations, however, are often characterized by a low quantum yield. Thus, in most cases light was instead used to trigger the release of highly reactive enediynes or enyne–allenes from photoactive compounds. As an example, this strategy has been adopted for substrates such as **10**, which, upon photoinduced decarbonylation of the cyclopropenone moiety, afforded the corresponding enyne–allene **11** and the α,3-DHT **12** from it (Scheme 7).[77]

2.3 Activation by metal catalysis or *via* metal complexes

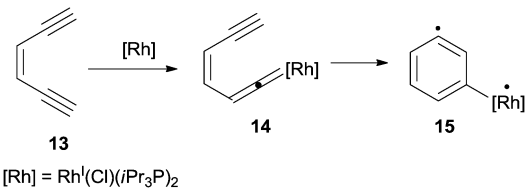
The coordinating properties of double and triple bonds of dienynes and enediynes towards metal ions and complexes



Scheme 6 Competitive Schmittel and Myers–Saito cyclizations in the photochemical reaction of enyne–allene **7**.



Scheme 7 Myers–Saito reaction *via* photogenerated enyne–allenes.



Scheme 8 Rhodium-catalyzed cyclization of enediyne **13**.

have been widely exploited to promote cycloaromatization processes under mild conditions.[78] As an example, Ruthenium and Rhodium species (*e.g.* the $Rh^{I}(Cl)(iPr_3P)_2$ complex) promoted the cyclization of enediynes bearing at least a terminal triple C–C bond (**13** in Scheme 8) *via* vinylidene intermediate **14** that evolved, through a Myers–Saito cyclization, into the corresponding biradical **15**.[79,80]

Au^{I},[81] Pd^{II}[82,83] and Fe^{II}[84] complexes have been likewise exploited to promote Bergman reactions. As in the case of thermal activation, the effect of metal catalysis can depend as well on the structure of the starting enediyne. Thus, cycloaromatization of strained-ring benzoenediynes was efficiently promoted by $Ru^{II}(\mu^5\text{-}C_5Me_5)(CH_3CN)_3^+$, whereas the process did not occur in the case of strain-free acyclic derivatives.[78]

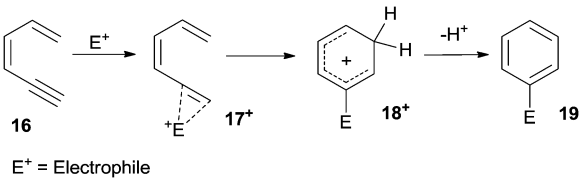
Less efforts have been devoted to the development of metal-catalyzed enyne–allene cyclizations. As an example, the Myers–Saito cycloaromatization took place in the presence of catalytic amounts of $Ag^{I}SbF_6$ and $Au^{I}(Cl)(Ph_3P)$.[85] In another instance,

the Pauson–Khand cyclocarbonylation and the Schmittel cyclization were induced, respectively, by the presence of a stoichiometric amount of $Mo^0(CO)_3(CH_3CN)_3$[86] and $Sm^{II}I_2$.[87]

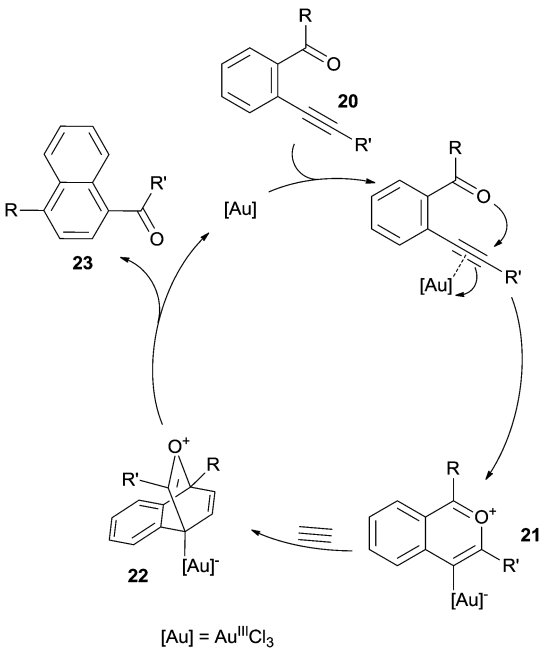
2.4 Activation by electrophilic, nucleophilic or radical species

The π-system of the alkyne in dienynes is an appealing target for metal and non-metal Lewis and Brønsted acids (E^+) that act as electrophiles and promote the formation of alkyne complexes, such as $\mathbf{17}^+$ from **16** (Scheme 9). Intramolecular 6-*endo*-dig attack of the terminal alkene followed by aromatization of the resulting carbocation $\mathbf{18}^+$ affords the desired aromatic ring (**19**). Protons arising from strong acids, as well as iodine, are commonly used as electrophiles. When metal derivatives (E^+ = Pd, Pt, Au, In-based species) are employed, a protodemetallation is commonly involved as the final step, leading to the desired product.[56]

A peculiar case is the Lewis acid catalyzed [4+2] benzannulation of enynals.[88–90] As an example, the electrophilic character of the alkyne moiety in compound **20** (Scheme 10) was enhanced by coordination with $Au^{III}Cl_3$, thus inducing a nucleophilic attack of the carbonyl oxygen to form the highly reactive ate complex **21**. This complex underwent a hetero Diels–Alder reaction with a dienophile (either an alkyne[88] or a benzyne[89,90]) and rearrangement of the so-formed adduct **22** led to the desired product **23**.



Scheme 9 Electrophile-induced cycloaromatization of dienynes.



Scheme 10 Au^{III}-catalyzed [4+2] benzannulation of enynals.

Typical electrophiles, such as iodine[91] and metal Lewis acids ($Au^I(Cl)(Ph_3P)$),[92] can also promote the cyclization of enediynes. Electrophilic activation, however, often led to a diverted chemistry with respect to the thermal approach and pentafulvenes could be obtained in place of the expected aromatics.[93,94]

When sufficiently activated, the terminal alkene in dienynes[56] or one of the triple bonds in enediynes[95] can likewise act as an electrophile and undergo nucleophilic attack (by a methoxide ion). Indeed, the use of nucleophiles to activate enediynes for the synthesis of heterocycles has been recently reviewed.[96]

Finally, the generation of a heteroatom-based radical (*e.g.* $Bu_3Sn^\bullet$) in the presence of dienynes[97] and enediynes can be exploited to induce a radical cascade useful for the construction of complex (poly)aromatic structures.[98]

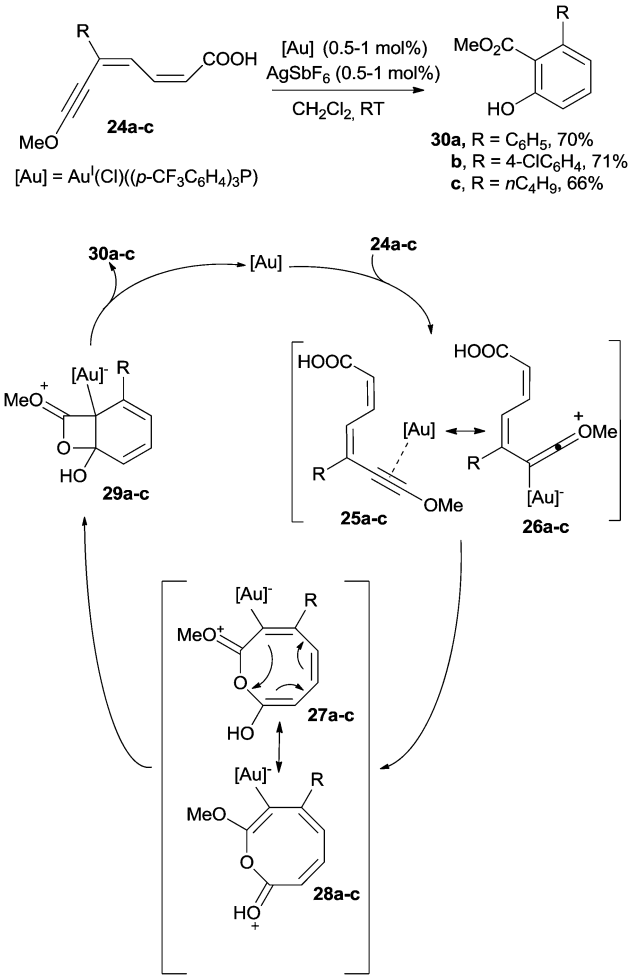
3 Synthesis of benzenes

Only a few cases in the literature deal with the cyclization of dienynes for the preparation of benzenes.[99–103] The ruthenium-catalyzed (by $(Cp)Ru^{II}(Ph_3P)_2(Cl)$, 5 mol%; Cp = $C_5H_5^-$) coupling of 2-(phenylethynyl)cyclohex-1-enecarbaldehyde with cyclopentanone under basic conditions gave a dienyne that smoothly cyclized to give an indanone derivative.[99,100] The cycloaromatization of dienynes was likewise accomplished under gold catalysis (by $Au^I(Ph_3P)NTf_2$, 5 mol%) and allowed the preparation of tetrahydronaphthalenes. The reaction was initiated by the coordination of the gold complex to the triple bond.[101]

In the field of gold catalysis, the preparation of phenols starting from captodative dienyne carboxylic acids is another interesting case (Scheme 11).[102] Thus, a Au^I complex coordinated the triple bond of **24a–c** leading to **25a–c**, which are stabilized by the presence of the alkoxy substituent through resonance structures **26a–c**. Thus, *cis–trans* isomerization followed by intramolecular cyclization promoted by the nucleophilic attack of the COOH group afforded an eight-membered intermediate represented by resonance structures **27a–c** and **28a–c**, which further evolved into bicyclic structures **29a–c**. Aromatization of **29a–c** promoted the four-membered ring opening, in turn allowing the formation of the corresponding phenols **30a–c** (*ca.* 70% yield). The reaction was particularly efficient when R in **24** was an aromatic ring.[102] When the MeO group in the starting substrate was substituted with an aromatic ring, however, the reaction course completely changed and a 1,6-cyclization/decarboxylation sequence led to biphenyl or *m*-terphenyl derivatives.[102]

Another interesting example is the synthesis of iodoarenes from dienynes through a cycloaromatization step promoted by an electrophile.[103] Thus, enyne–dioxinones **31a–d** underwent the addition of ICl and were converted into iodotrienyl cations $\mathbf{32}^+\mathbf{a–d}$ that, upon cyclization to $\mathbf{33}^+\mathbf{a–d}$ and subsequent aromatization, gave the desired iodobenzenes **34a–d** (Scheme 12). The yields of this reaction were satisfactory (50–95% yield) for a wide range of substituted aromatic rings. Derivatives bearing cyclopropyl and thienyl substituents have also been efficiently synthesized.[103]

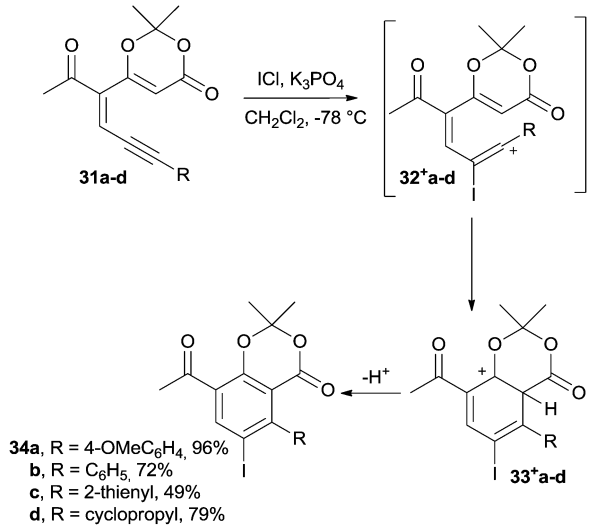
The Bergman cyclization is widely used for the preparation of substituted benzenes. The reaction can be induced either



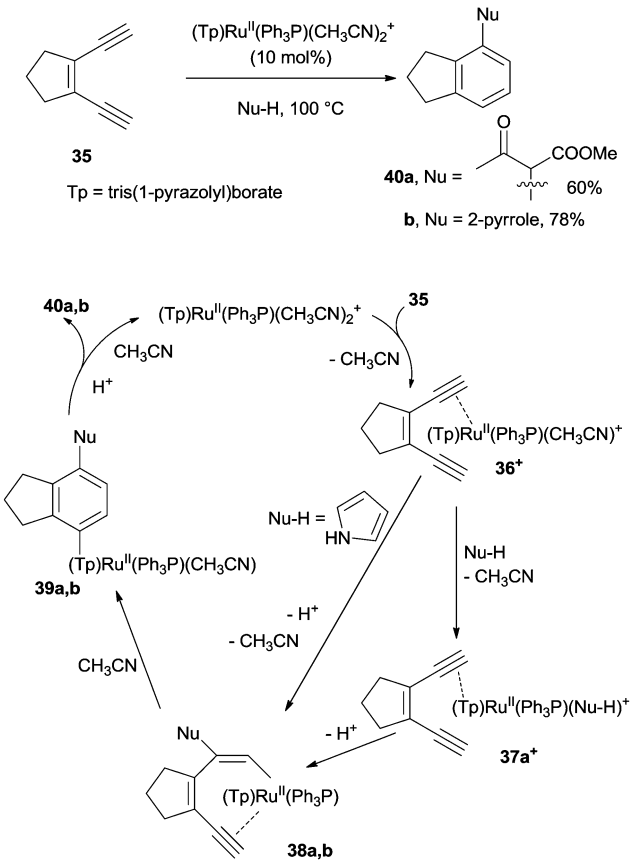
Scheme 11 Preparation of phenols by the metal-catalyzed reaction of captodative dienyne carboxylic acids.

thermally, as reported in the synthesis of cyclophane derivatives,[104] or photochemically, where the enediyne was photogenerated *in situ* and used to prepare tetrahydroanthracene-1,4-diones.[105]

The metal-catalyzed cycloaromatization of enediynes (*via* the intermediacy of a metal-alkyne species) has recently found widespread use in the synthesis of arenes. Under refluxing conditions, the ruthenium catalyst $(Tp)Ru^{II}(Ph_3P)(CH_3CN)_2PF_6$ (Tp = tris(1-pyrazolyl)borate)[80] was able to bind selectively to the more electron-rich triple bond of enediyne **35** leading to ruthenium π-alkyne complex **36**$^+$ (Scheme 13). In the presence of a nucleophile (methyl acetoacetate), a ligand exchange with CH_3CN took place to give **37a**$^+$ and then vinyl ruthenium complex **38a**. After 6-*endo*-dig cyclization to **39a** and aromatization, compound **40a** was obtained in 60% yield. In the case of pyrrole nucleophiles, a direct attack on **36**$^+$ to give **38b** and then **40b** (78% yield) was invoked, due to the poor ligand properties of pyrrole. The process was compatible with a wide range of nucleophiles (water, alcohols, acetylacetone, dimethyl malonate, anilines, and pyrroles) and a plethora of aromatics, including phenols, alkoxybenzenes and diphenylamines, could be prepared, accordingly.[80]

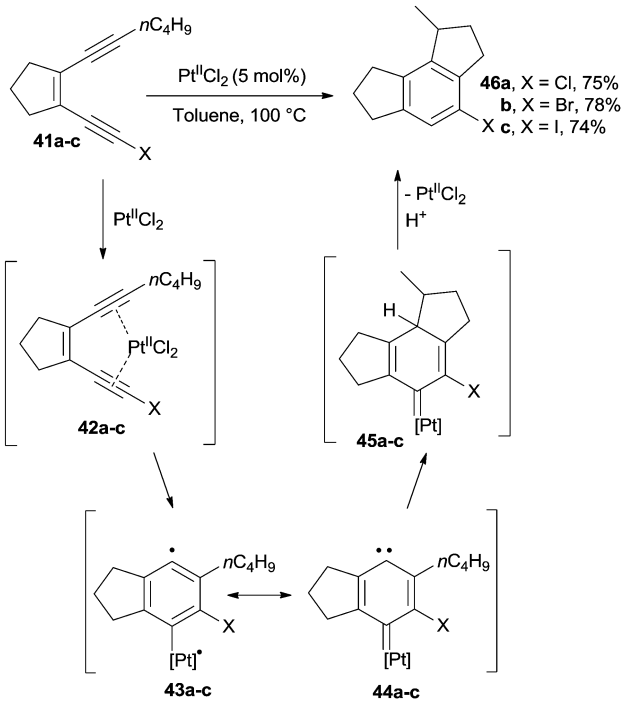


Scheme 12 Synthesis of iodoarenes from enyne–dioxinones.



Scheme 13 Ruthenium-catalyzed cycloaromatization of enediynes.

In a different application, the Bergman cyclization was catalyzed by $Pt^{II}Cl_2$. For instance, the benzene core of **46a–c** was obtained through the cycloaromatization of enediynes **41a–c** under platinum-catalyzed conditions.[83] Thus, Pt^{II} and **41a–c** gave π-alkyne complexes **42a–c** which cyclized to biradicals **43a–c** (also existing as the carbenoid forms **44a–c**). These carbenoid intermediates underwent insertion onto the side alkyl chain to give



Scheme 14 $Pt^{II}Cl_2$ as a catalyst for the preparation of indanes.

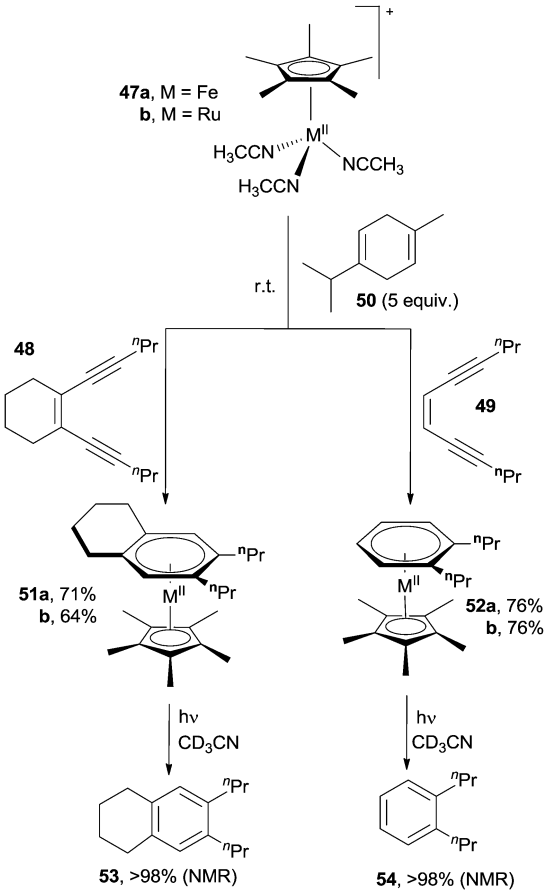
derivatives **45a–c** that, after release of the catalyst, led to the desired benzenes **46a–c** in *ca.* 75% yield (Scheme 14). This approach could be likewise extended to the preparation of polycyclic derivatives.[83]

In another instance, a bis(pyridine)enediyne was activated in the presence of $Mg^{II}Cl_2$.[106] In fact, the substituents of the alkyne moieties were able to chelate Mg^{II} and this non-covalent interaction induced a change of conformation that favored the aromatization process.[106]

A smooth synthesis of arenes was achieved *via* the use of cyclopentadienyl metal complexes, such as $(\eta^5\text{-}C_5Me_5)M^{II}(CH_3CN)_3^+$ (M = Fe^{II}, **47a**; Ru^{II}, **47b**). Indeed, alicyclic (**48**) and acyclic (**49**) enediynes cyclized at room temperature in the presence of **47a,b** and γ-terpinene **50** as radical trap to give the corresponding complexes **51a,b** and **52a,b**, respectively.[78,84] The so-formed arene ligands were then photochemically released leading to aromatic compounds **53** and **54** in excellent yields (Scheme 15). The well known photochemical interconversion of (*E*)- and (*Z*)-enediynes allowed an extension of this reaction also to (*E*)-enediynes.[78,84]

The Bergman cyclization was also applied to the synthesis of compounds with pharmaceutical interest under metal-free conditions, where the presence of a base (nucleophile) was in most cases required. A typical case is the base-induced ring opening of the lactam ring in *N*-fused lactendiynes to prepare aromatic β-amino acids.[107]

A nucleophilic attack onto the polyenic system was also adopted. For instance, phenanthridones or benzo[*c*]phenanthridones **56a,b** were obtained by treating benzonitriles containing an enediyne moiety **55a,b** with sodium methoxide (Scheme 16). The reaction was efficient in methanol mixed with 10% of a polar aprotic solvent (*e.g.* DMSO, HMPA, and THF). The methoxide anion



Scheme 15 Aromatics from cyclopentadienyl metal complexes.

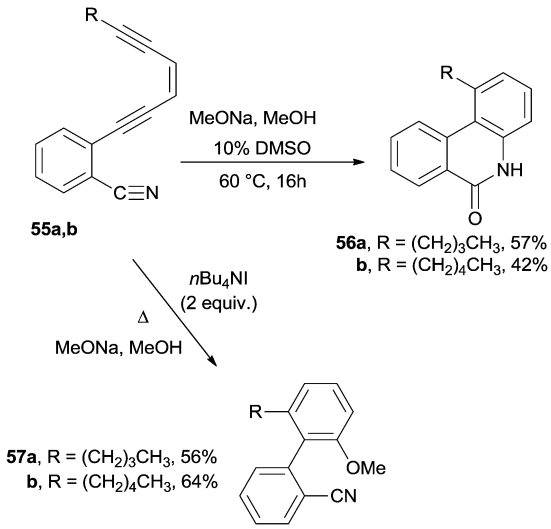
was added to the cyano group triggering the anionic cascade cycloaromatization.[108] In contrast, the course of the reaction changed in the presence of tetrabutylammonium iodide since methoxide attacked the C2 of the acetylenic moiety and induced a cyclization to the corresponding biphenyls **57a,b** (Scheme 16).

An alternative route made use of basic conditions (*t*BuOK) to generate a bicyclic trienediyne system prone to aromatization, giving a key intermediate for the preparation of cyanosporasides.[109,110]

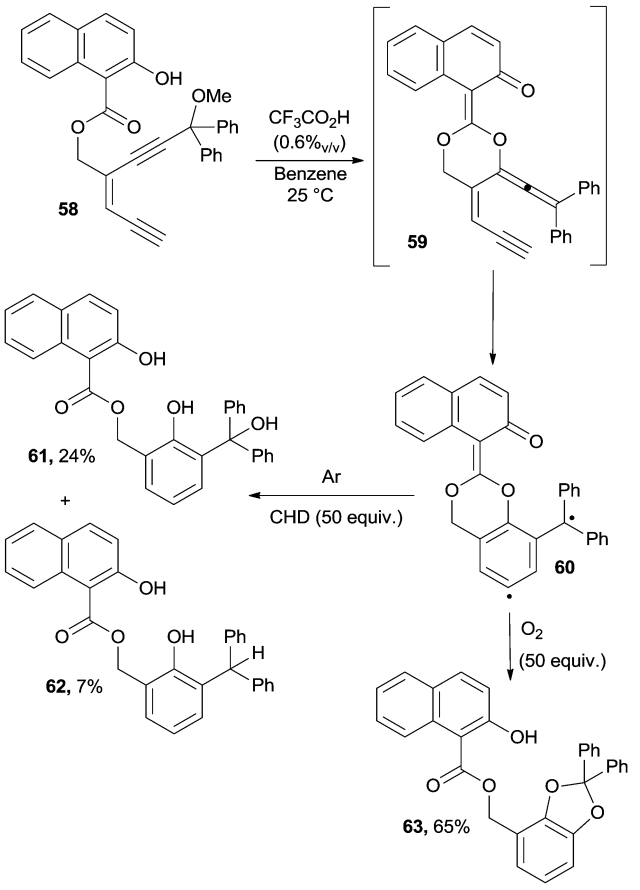
In some instances, enyne–allenes were the reactive unsaturated system(s). As an example, various enyne–allenes gave access in refluxing benzene to compounds having the tetracyclic steroidal skeleton.[111,112]

Enediynes could be converted into the corresponding enyne–allenes by acid catalysis. Indeed, when treated with TFA, compound **58** gave enyne–allene acetal **59** that underwent a Myers–Saito cyclization to biradical **60**. Different aromatic products **61–63**, depending on the reaction conditions (presence of hydrogen atom donors, oxygen, *etc.*), have been obtained, as illustrated in Scheme 17.[113]

Enyne–allenes can be considered as good precursors of substituted benzenes, including phenols. It was found that treating acetoxy-substituted enyne–allene **64** with MeLi gave the corresponding oxyanion (upon deprotection of the acetate group). This in turn cyclized (at −10 °C) to the corresponding phenol **65** in 30 minutes (Scheme 18).[114] The fate of the

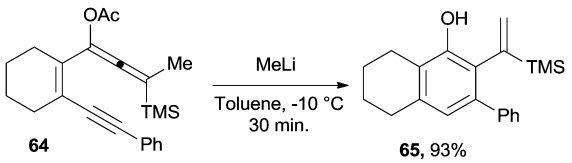


Scheme 16 Different pathways in the nucleophile-induced Bergman cyclization.



Scheme 17 Enedyines as a source of enyne–allenes for Myers–Saito cyclizations.

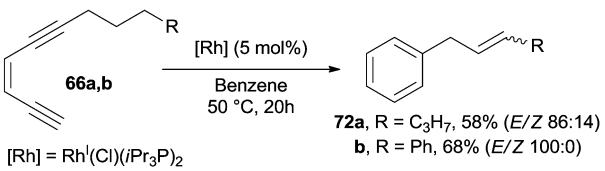
reaction, however, depended on the ring size and on the nature of the terminal substituents, the Schmittel cyclization being an important competitive pathway.

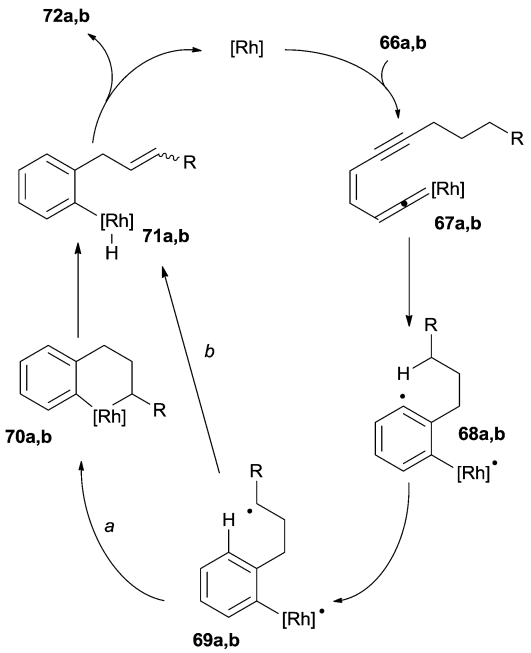


Scheme 18 Methyl lithium-induced cycloaromatization of enyne–allenes.

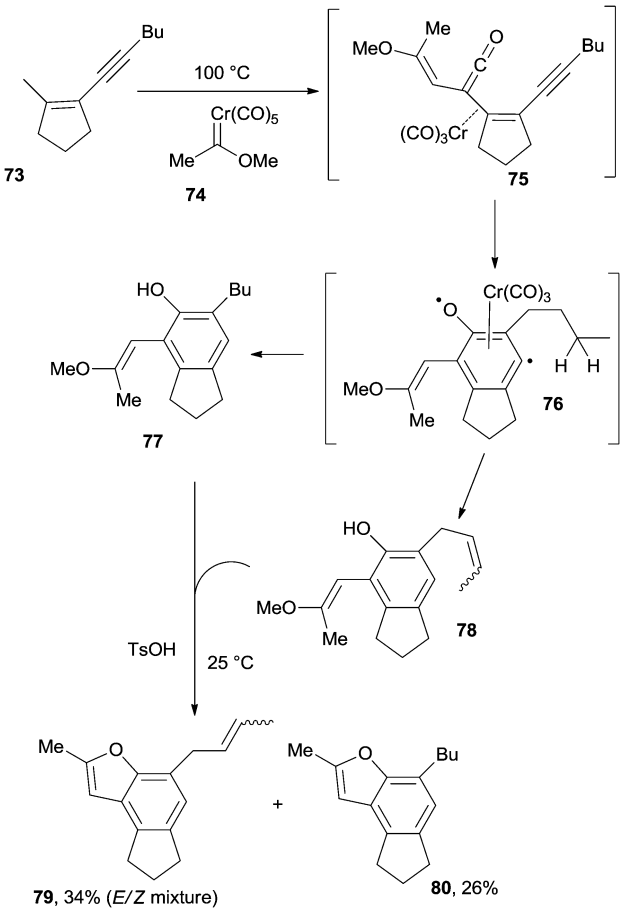
The intervention of a metal-catalyst can induce the formation of a vinylidene complex. For example, a modest variety of substituted benzenes were prepared by heating enediynes **66a,b** at 50 °C in the presence of a catalytic amount of $Rh^{I}(Cl)(iPr_3P)_2$.[79] The thus formed vinylidene-rhodium complexes **67a,b** underwent a Myers–Saito cyclization to the corresponding benzenoid radicals **68a,b**. A 1,5-hydrogen shift gave biradicals **69a,b** and intermediates **70a,b** (path a) after radical coupling. Compounds **72a,b** were then formed in good yields (50–70%) by a *syn* elimination of the β-hydride followed by reductive elimination (Scheme 19). An alternative mechanism was also postulated, where intermediates **71a,b** were formed by a second 1,5-hydrogen shift in **69a,b** (from the alkyl chain to the rhodium-centered radical, path b).

Another interesting example deals with the use of enyne–ketenes. The reaction of **73** with the chromium-carbene complex **74** led to enyne–ketene **75** that underwent a Moore cyclization to heterobiradical **76,** and a complex mixture containing **77** and **78** was then obtained. Treatment of the final mixture with a





Scheme 19 Rhodium-catalyzed synthesis of allyl aromatics.



Scheme 20 Synthesis of aromatics *via* enyne–ketenes.

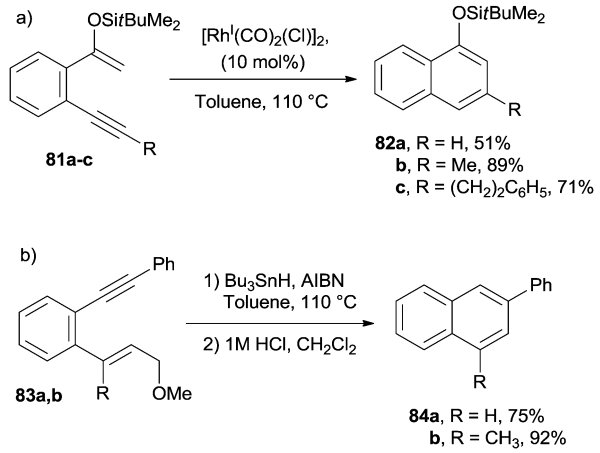
strong acid (TsOH), allowed the formation of benzofurans **79** and **80** (Scheme 20).[115] Moore cyclization of enyne–ketene intermediates (in turn prepared *via* the thermally induced ring opening of the corresponding 4-alkynylcyclobutenones) was also exploited as a key step in the synthesis of naturally occurring alkaloids pyrrolophenanthridine and assoanine.[116]

4 Synthesis of naphthalenes

Benzofused dienynes and enediynes are widely used to prepare naphthalene derivatives. The substrates can cycloaromatize directly or, in the case of enediynes, undergo rearrangement to the corresponding (and more reactive) enyne–allenes.

Despite the fact that fluorinated naphthalenes can be obtained *via* direct fluorination of the aromatic ring, the reaction often lacks selectivity and fluoronaphthalene isomers are difficult to separate. Accordingly, these derivatives were obtained from the base-catalyzed (DBU was used) cyclization of aromatic fluorodienynes in refluxing *N*-methyl-2-pyrrolidone (NMP).[117]

The electrocyclization of aromatic dienynes has also been achieved by having recourse to the (Tp)$Ru^{II}(Ph_3P)(CH_3CN)_2(PF_6)$ complex, in turn causing the formation of a metal–vinylidene intermediate.[118,119] Analogous results were obtained when using the $W^0(CO)_5$(THF) complex as the catalyst.[119] Cyclization of silyl

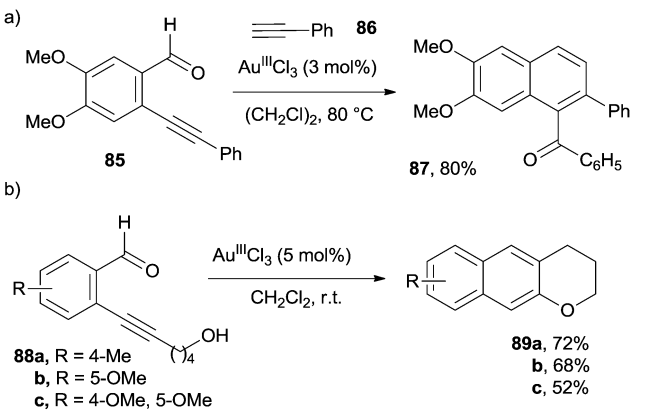


Scheme 21 Strategies for the synthesis of the naphthalene core from dienynes.

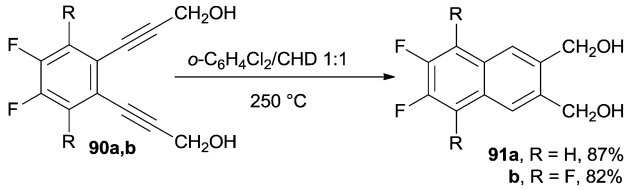
enol ethers **81a–c** was found to take place efficiently in the presence of Rh, Pd and Pt-based catalysts. The desired naphthalenes **82a–c** were obtained in good yields, independent of the aromatic substituent (Scheme 21a).[120] Substituted naphthalenes **84a,b** were also obtained *via* a tin-mediated radical cyclization/fragmentation reaction occurring on dienynes **83a,b** (Scheme 21b).[121,122]

Benzofused enynals and enynones are valuable substrates in benzannulation processes under Lewis acid catalysis. Thus, naphthyl ketone **87** was prepared by the reaction of *ortho*-alkynyl benzaldehyde **85** with phenyl acetylene **86** in the presence of a catalytic amount of $Au^{III}Cl_3$ (Scheme 22a).[123] The same process could be likewise carried out by replacing $Au^{III}Cl_3$ with $Cu^{II}(OTf)_2$ in the presence of an equivalent of a strong acid (*e.g.* CF_2HCO_2H).[88] More recently, [4+2] benzannulations between enynals and alkynes were carried out under heterogeneous catalysis (by using nanoporous gold materials), despite the fact that a high temperature (150 °C) was required.[124]

Indeed, an intramolecular variant of the process opened the way to substituted 2,3-dihydrophenanthrenones.[125] In a similar manner, 1-acyl-4-alkoxy and 1-acyl-4-alkylsulfanyl naphthalenes were prepared by treating *ortho*-ethynyl benzoates and benzothioates,



Scheme 22 Gold-catalyzed preparation of naphthalenes from *ortho*-alkynyl benzaldehydes.



Scheme 23 Polyfluorinated naphthalenes **91a,b** *via* thermal cyclization.

respectively, with vinyl ethers in the presence of a catalytic amount of $Pt^{II}Cl_2$.[126] Substituted benzochromanes **89a–c** have been synthesized in high yield *via* the $Au^{III}Cl_3$-catalyzed rearrangement of the corresponding 2-(ynol)aryl aldehydes **88a–c** (Scheme 22b).[127]

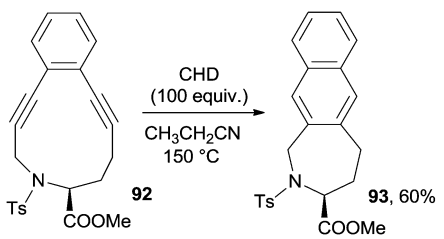
Polyfluorinated naphthalenes, such as **91a,b**, were synthesized in high yields *via* the Bergman cyclization of benzocondensed enediyne precursors **90a,b** (in turn obtained *via* an efficient Sonogashira cross-coupling) in the presence of a large excess of CHD as a hydrogen atom donor (Scheme 23).[128] Both 1- and 2-nitronaphthalene were obtained in 70% yield from the corresponding benzannelated enediynes.[129]

2-(Phenylethynyl)naphthalene and 2-naphthyl butyl sulfide were thermally obtained in discrete yield from the corresponding enetriyne[130] and butyl *ortho*-diethynylbenzene sulfide, respectively.[131]

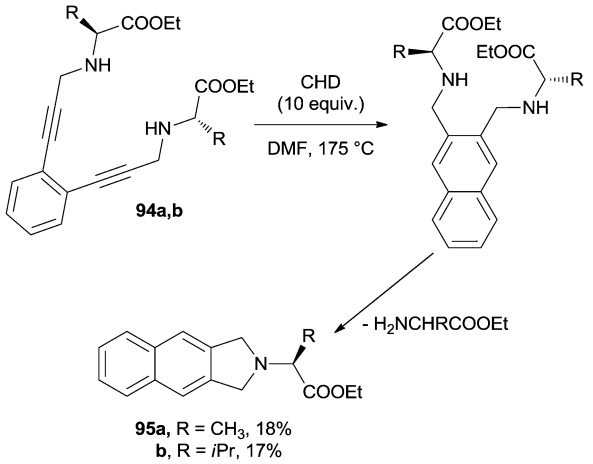
Recently, the thermal cyclization (at 250 °C) of porphyrin–enediyne hybrids to give the corresponding naphthyl-porphyrins in modest yields has been described.[132] Notably, traces of the cyclized product were also observed at a lower temperature (140 °C) under concomitant visible light irradiation (419 nm) of the starting solution.[132]

Enediyne-aminoacid conjugates are important substrates for biological applications. As an example, photoactivated lysine–enediyne conjugates caused double-stranded DNA damage and the amino acid residue played a key role in directing the selectivity of DNA cleavage.[133] Some of these derivatives, however, also have interesting synthetic applications. The Bergman cycloaromatization taking place in 11-membered cyclic enediyne-containing aminoacid moieties (such as **92**, prepared from homopropargylglycine) afforded the corresponding naphthalenes (**93**), though a high temperature (100–150 °C) and long reaction times (up to 9 days) were required (Scheme 24).[134] Microwave irradiation was otherwise exploited to promote the cyclization of this class of substrates.[135]

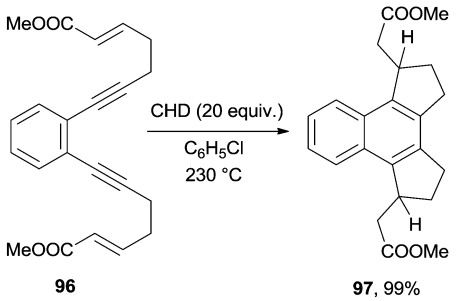
On the other hand, when using acyclic aminoacid-derived enediynes **94a,b**, the formation of the naphthalene core was followed by an intramolecular S_N2 substitution to give the



Scheme 24 Bergman cycloaromatization of 11-membered cyclic aminoacid-derived enediyne **92**.



Scheme 25 Synthesis of 2,3-dihydrobenzo[*f*]isoindoles **95a,b**.

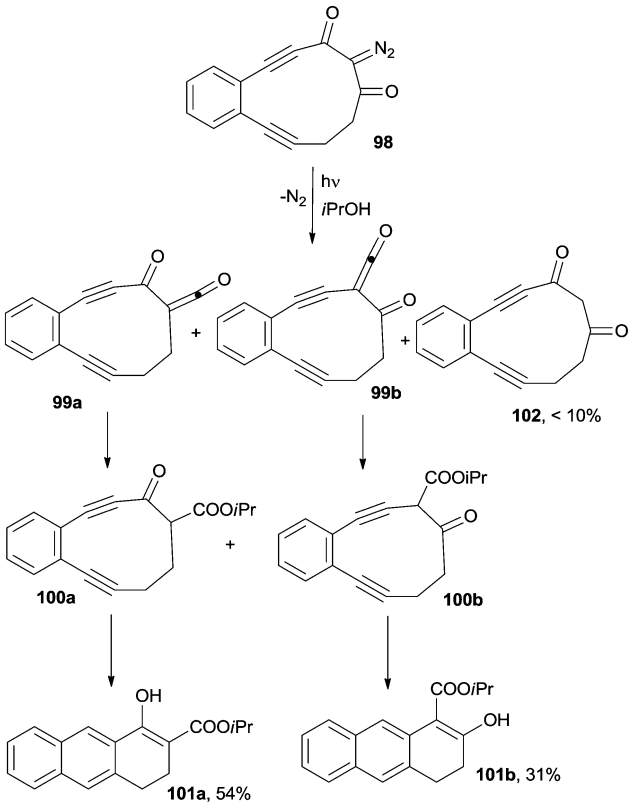


Scheme 26 Cascade radical cyclizations triggered by a Bergman cycloaromatization.

corresponding 2,3-dihydrobenzo[*f*]isoindoles **95a,b**, although in low yields (Scheme 25).[136]

Biradicals arising from cycloaromatization reactions have been exploited as key intermediates in cascade radical cyclizations. Tandem enediyne radical cyclizations were developed in the early 90s and applied, when selective, to the synthesis of different benzocondensed derivatives.[137] As an example, the thermal activation of enediyne **96** in the presence of CHD as a hydrogen atom donor resulted in the quantitative formation of **97**, obtained as a mixture of two diastereoisomers (Scheme 26).[137,138]

As hinted above, the synthetic significance of cycloaromatization reactions applied to acyclic enediynes is often limited by the high temperatures (typically >180 °C) required for the reaction and by the use of high amounts of (expensive) hydrogen atom donors (CHD). In some instances, however, photochemical activation can be a convenient alternative. An example deals with a photoinduced ring contraction, in turn triggering a thermal Bergman cyclization. Thus, irradiation (350 nm) in isopropanol of 11-membered enediyne **98**, incorporating a 2-diazo-1,3-diketone moiety, resulted in a Wolff rearrangement *via* the corresponding ketenes **99a,b** to produce strained, highly reactive, 10-membered enediynes **100a,b**, which afforded a mixture of dihydroanthracene derivatives **101a** (54%) and **101b** (31%), along with small amounts of diketone **102** (<10%; Scheme 27).[139,140] Analogously, the photochemical activation

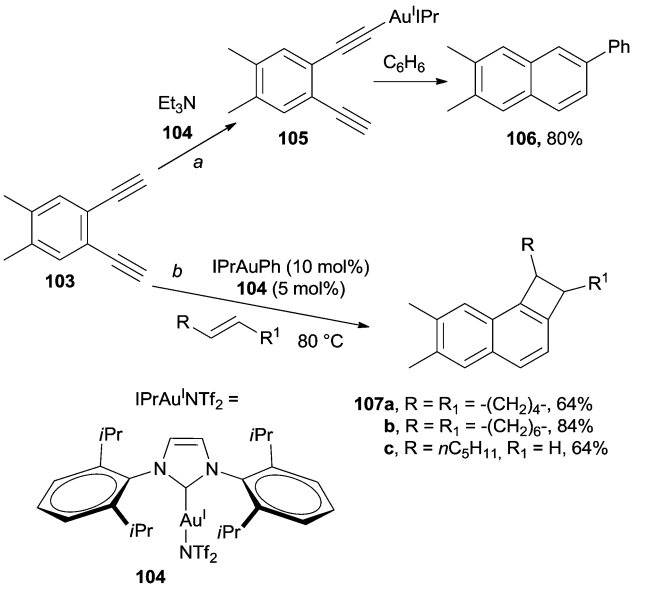


Scheme 27 Synthesis of naphthalenes *via* a photoinduced Wolff rearrangement.

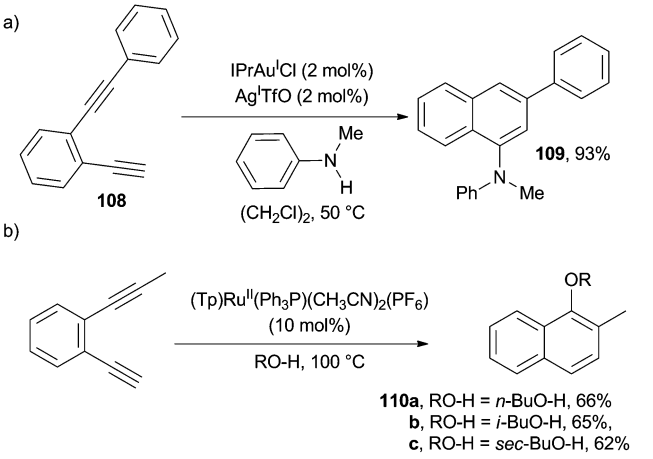
of a 9-membered ring enediyne precursor, with one of the triple bonds masked as cyclopropenone, resulted in the CO loss and in the final formation of the corresponding 1,4-didehydronaphthalene biradical, which yielded, after hydrogen atom abstraction from the reaction medium (2-propanol), the corresponding benzo[*f*]indanol as the only product (cycloaromatization yield not reported).[141]

The intervention of an organometallic or metallic species often allows for milder conditions to be adopted to promote the desired process. For example, gold complexes have found large application in this field. Coordination of arene-1,2-diyne **103** by Au^{I} complex **104** (used in catalytic amount) resulted in the formation of intermediate **105**.[142–145] When benzene was used as the solvent, trapping of **105** by the medium[143] to afford the corresponding β-phenyl naphthalene **106** took place as the preferred path (Scheme 28, path a; the α-isomer was also formed in 2% yield).[146] Cyclization of substituted 1,2-bis-(iodoethynyl)-benzenes in the presence of $IPrAu^{I}NTf_2$ (**104**, 5 mol%) in benzene afforded the desired 1-phenyl-2,4-diiodonaphthalene.[147] The scope of this reaction has been widely explored and the gold-catalyzed synthesis of cyclobutenes **107a–c** from **103** in the presence of several alkenes (that acted both as reactants and solvents, Scheme 28, path b) has been reported.[148]

Au^{I}-catalyzed cycloaromatization of benzofused enediyne **108** in the presence of various neutral *N*- and *O*-based nucleophiles (*e.g. N*-methyl aniline) afforded a wide range of naphthalene cores (*e.g.* **109**) functionalized at the 1-position (Scheme 29a).[149] Interestingly, in the presence of a Ru^{II}-complex, a different



Scheme 28 Gold-catalyzed synthesis of substituted naphthalenes.



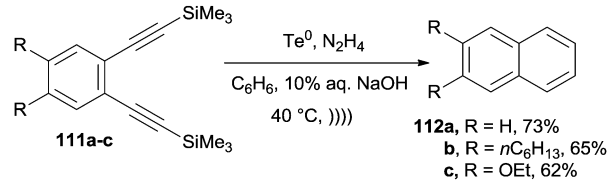
Scheme 29 Synthesis of 1-substituted naphthalenes.

substitution pattern of the final naphthalene ring (see products **110a–c** in Scheme 29b) was observed.[80]

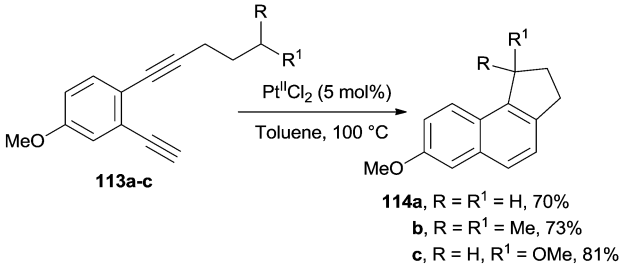
Desilylation/cycloaromatization of arenediynes **111a–c** to give **112a–c** took place in good yields at 40 °C in the presence of stoichiometric amounts of Te^0 and ultrasound irradiation. Notably, the reaction was repeated for substrate **111a** on a 5 g scale, with a similar yield (68%), and on differently substituted substrates. Comparable results were consistently obtained when the mixture was irradiated with visible light (Scheme 30).[150]

The highly coordinating $Pt^{II}Cl_2$ species is an efficient catalyst for promoting the cyclization of enediyne moieties having a tethered alkyl chain (*e.g.* **113a–c**). Under these conditions, the cycloaromatization process was followed by a C–H bond insertion to afford the corresponding naphthalenes **114a–c** (Scheme 31).[83]

Similarly, the $Pt^{II}Cl_2$-catalyzed cyclization cascade of enediyne–enone systems has been recently described.[151] By following this approach, tetracyclic chromenones were obtained in excellent



Scheme 30 Te-catalyzed cyclization of silylated arenediynes.

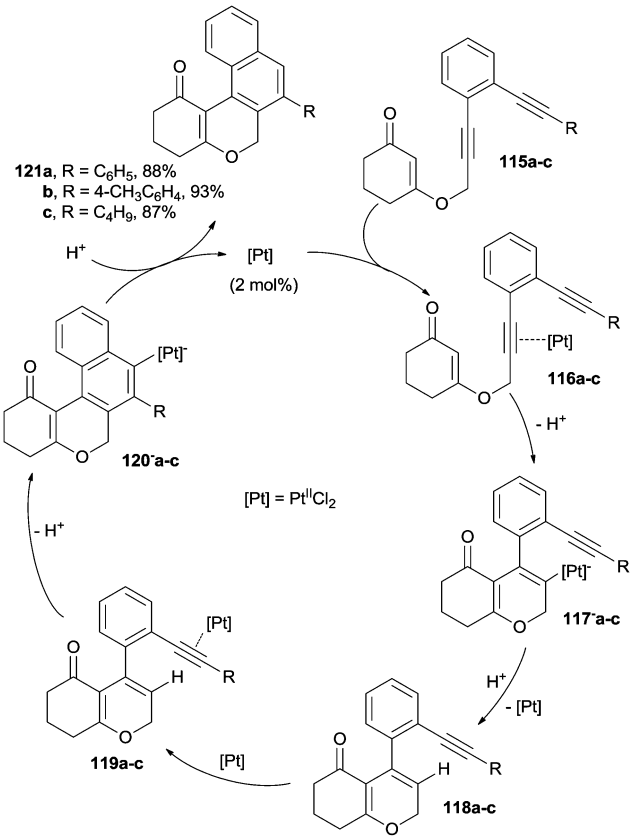


Scheme 31 Pt-catalyzed synthesis of methoxynaphthalenes.

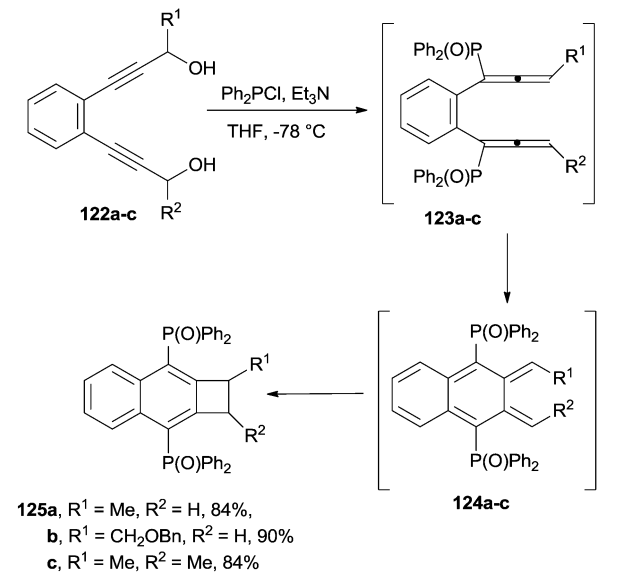
yields through two consecutive, highly regioselective, 6-*endo*-dig cyclizations, where two new C–C bonds and two new rings were formed. The proposed mechanism involved the initial coordination of the catalyst by one of the triple bonds of **115a–c** to afford complexes **116a–c**. Then, 6-*endo*-dig cyclization of the enone moiety occurred followed by deprotonation leading to intermediates **117⁻a–c**. Protodemetallation of **117⁻a–c** to **118a–c** and ensuing coordination of the remaining triple bond by the catalyst afforded **119a–c**. A second 6-*endo*-dig cyclization of the electron rich C5 pyran carbon onto the activated alkyne gave intermediates **120⁻a–c**, which further underwent protodemetallation to give the final products **121a–c** (Scheme 32).[151] The same catalyst has been employed in the synthesis of benzo- and naphthopyranones from the corresponding enediynes.[152] Treatment of 1,2-bis(ethynyl)arenes with hydrohalic acids in the presence of 5–10 mol% of $Pt^{II}Cl_2$ led to the formation of the corresponding 1-halonaphthalenes.[153] As for metal-free activation procedures, 1,2-bis(alkynyl)arenes reacted with highly electrophilic boranes, yielding boryl-functionalized naphthalenes.[154] Benzofused dihydroisoquinolones were obtained *via* TsOH-promoted cascade cyclization of diyne-tethered ynamides in the presence of $Au^{I}(CH_3CN)[(2\text{-biphenyl})(t\text{Bu})_2P]SbF_6$ as the catalyst.[155] The nucleophilic cycloaromatization of 1-aryl-3-hexen-1,5-diynes promoted by the methoxide anion was proposed as an efficient route to phenanthridinone and benzo[*c*]phenanthridinone derivatives.[108]

Naphthocyclobutenes **125a–c** were obtained by the treatment of the corresponding benzene-bridged bis(propargyl alcohols) **122a–c** with Ph_2PCl, in the presence of a base, *via* formation of 1,2-bis(phosphinyl)allenes **123a–c**, which were in turn converted to the corresponding *ortho*-quinodimethane intermediates **124a–c** (Scheme 33).[156]

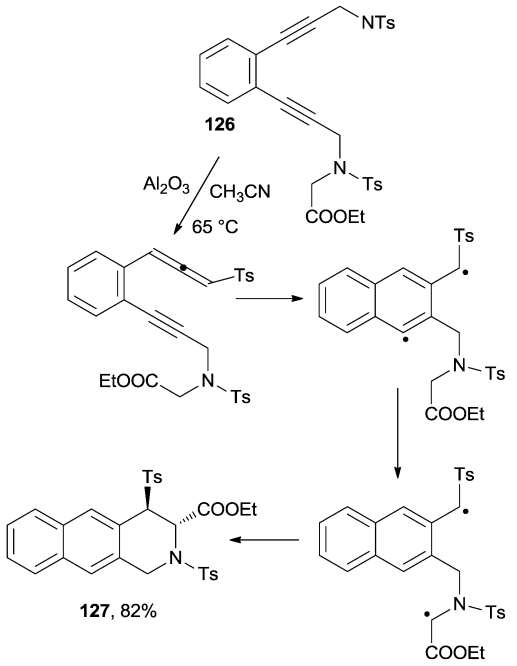
The cascade rearrangement of glycine derivatives containing an enediyne moiety took place *via* a base-catalyzed 1,3-proton shift, followed by the Myers–Saito cyclization of the obtained enyne–allene. 1,5-Hydrogen atom transfer and intramolecular coupling of the resulting biradical led to the formation of tri- and tetracyclic heterocycles with a quaternary stereogenic center with a very high level of stereoselectivity. Scheme 34 shows the case of **126** that was converted in 5 h at 65 °C (99% conversion according to ^{1}H NMR) to **127** as a single stereoisomer (82% yield).[157]



Scheme 32 Pt-catalyzed synthesis of tetracyclic chromenones.



Scheme 33 1,2-Bis(phosphinyl)allenes as intermediates in the synthesis of naphthalenes.



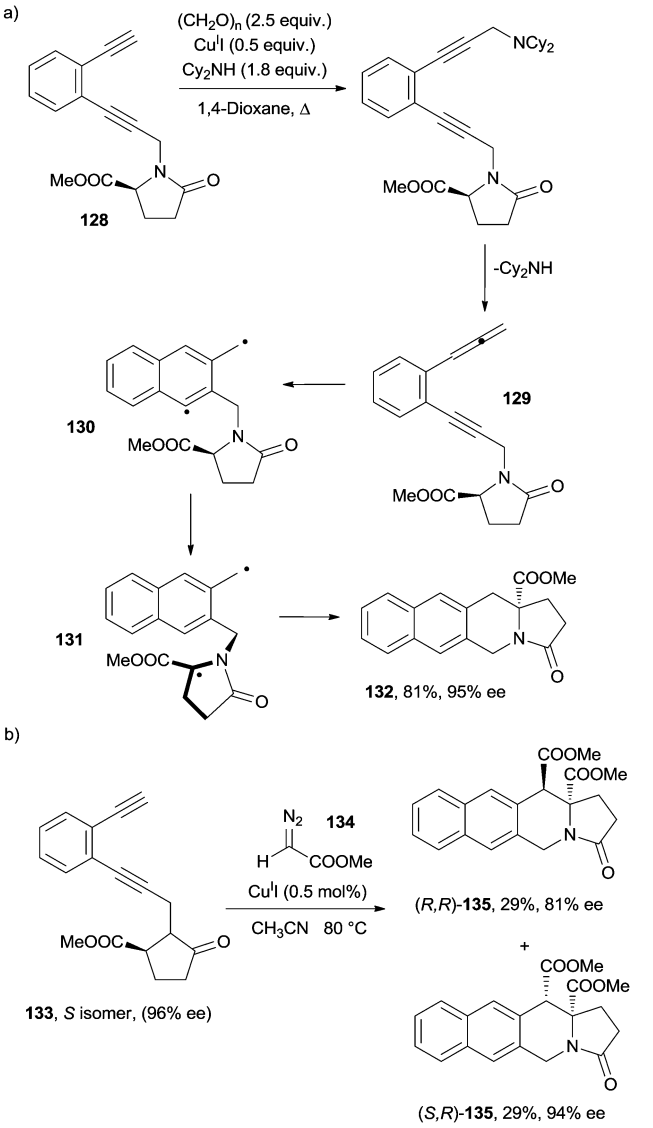
Scheme 34 Formation of tricyclic heterocycle **127**.

Recently, the chance to apply a memory of chirality (MOC) approach to the Myers–Saito cycloaromatization has been debated. Six- and seven-membered ring α-aminoesters were obtained in a stereoselective fashion through a tandem Crabbé homologation-radical rearrangement of terminal enediyne precursors.[158,159] Thus, upon reflux in dioxane in the presence of a secondary amine (Cy_2NH), $Cu^{I}I$ and paraformaldehyde, enediyne **128** was converted into the corresponding enyne–allene **129** that underwent a spontaneous Myers–Saito cycloaromatization to α,3-didehydrotoluene **130**. The latter evolved through a 1,5-hydrogen atom shift from the captodative position, leading to the formation of biradical **131** in a stereoselective fashion. Recombination of the two radical sites afforded cyclized product **132** (Scheme 35a).[158,159]

Two contiguous tetrasubstituted stereocenters were formed in compounds **135** *via* the Cu^{I}-catalyzed coupling of enediyne **133** with diazo ester **134** (Scheme 35b).[160] Recently, a mesoporous silica grafted with a tertiary amine was used as a basic nanocatalyst in the synthesis of **127** and **135** analogues from the corresponding enediynes.[161]

Cycloadditions ([2+2], [3+2] and [4+2]) taking place on alkynylchromium Fischer carbene complexes can trigger cascade reactions, in turn leading to the formation of functionalized polyaromatics. As an example, treating **136** with either 2,3-dihydrofuran (Scheme 36, path a) or nitrone **137** (path b) afforded adducts **138** and **139** that were in turn converted in discrete yields to the silylketene-containing naphthalene **140** and naphthoisooxazole **141**, respectively (Scheme 36).[162]

With respect to the Bergman cycloaromatization, the adoption of transition-metal catalyzed methods in the related Myers–Saito cyclization has received considerably less attention. The synthesis of aromatic ketones **144a–c** through the *in situ* generation of enyne–allene precursors is a representative example (Scheme 37).[85]

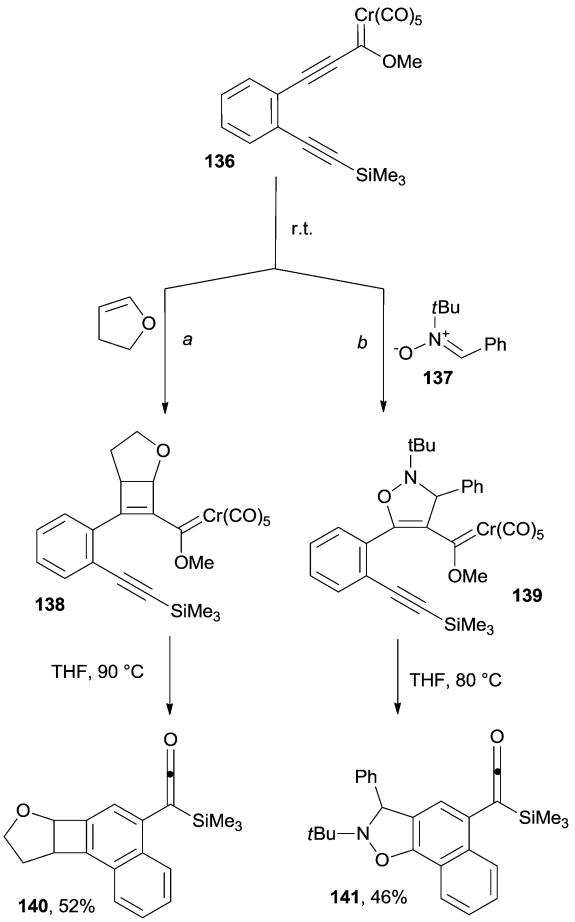


Scheme 35 Enantioselective cycloaromatizations exploiting the memory of chirality approach.

Enyne–allenes were obtained *via* an Ag^{I}-catalyzed sigmatropic rearrangement of an alkyne group. Thus, coordination of the Ag^{I} species to the triple bond of propargyl esters **142a–c** resulted in the formation of enyne–allenes **143a–c** through a [3,3]-sigmatropic rearrangement (Scheme 37, cycle A). The involvement of **143a–c** has been confirmed by isolation and characterization of these intermediates. Ensuing coordination of the residual alkyne moiety by the Ag^{I} species promoted a 6-*endo*-dig addition of the allenyl acetate to afford, after protodemetallation, **144a–c** in good yields (cycle B).

The base-promoted [2,3]-sigmatropic shift taking place on the enediyne moiety in derivatives **145a–c** led to the formation of enyne–allenes **146a–c** and substituted benzo[*e*]indanes **147a–c** from them *via* α,3-didehydrotoluene biradicals (Scheme 38).[138]

The Schmittel cyclization, a competing pathway for Myers–Saito cycloaromatization, has been exploited as well in the synthesis of polycondensed aromatic rings. Thus, naphthyl

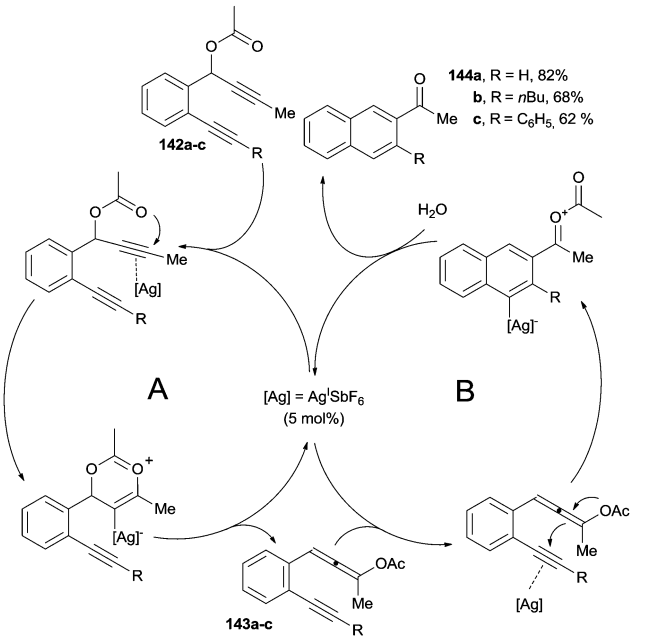


Scheme 36 Fischer carbene complexes as reactants for the synthesis of substituted naphthalenes.

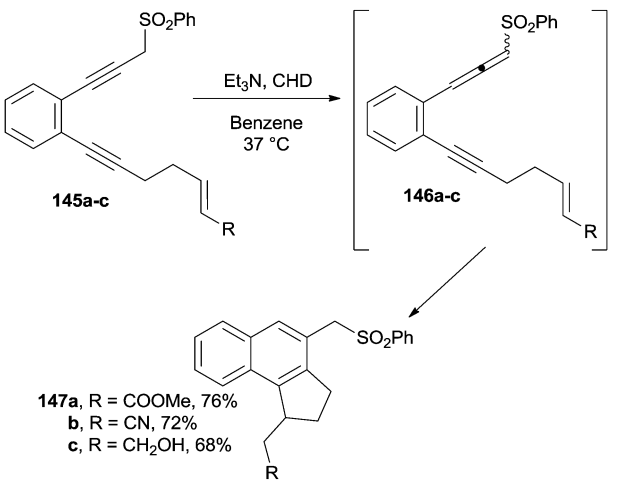
(see compound **152** in Scheme 39) and binaphthyl derivatives were obtained by treatment of the corresponding enediynes (*e.g.* **148**) with potassium *tert*-butoxide in refluxing toluene.[163] A 1,3-prototropic rearrangement was responsible for the *in situ* formation of enyne–allene **149** which in turn underwent a Schmittel cyclization to generate biradical **150.** An intramolecular radical–radical coupling finally afforded the corresponding benzo[*b*]fluorene derivative **152** upon hydrogen shift occurring in **151.** A small amount of compound **153** was likewise found as a by-product (Scheme 39). This approach has been also exploited in the two-step synthesis of bowl-shaped polycyclic aromatic hydrocarbons (see Section 5).[164]

The triazole–Au^{I} (TA–Au^{I}) catalyzed propargyl vinyl ether rearrangement taking place at room temperature in compounds **154a–c** (Scheme 40) triggered a Schmittel cyclization and the subsequent formation of the substituted naphthalene core in **155a–c.** Notably, the mild conditions employed avoided the need for sterically hindered groups (such as a *t*Bu) on the allene moiety to maintain a satisfactory selectivity.[165]

1,2-Ethynylbenzenes bearing one unsubstituted and one triarylmethyl-substituted alkyne (**156a–c**) were efficiently converted into substituted benzofluorenones **158a–c** through a one-pot reaction involving a gold-catalyzed cyclization to indenones **157a–c** followed by a photochemical cyclization/oxidation sequence (Scheme 41).[166]



Scheme 37 Acyl naphthalenes from the silver-catalyzed reaction of enyne–allenes.

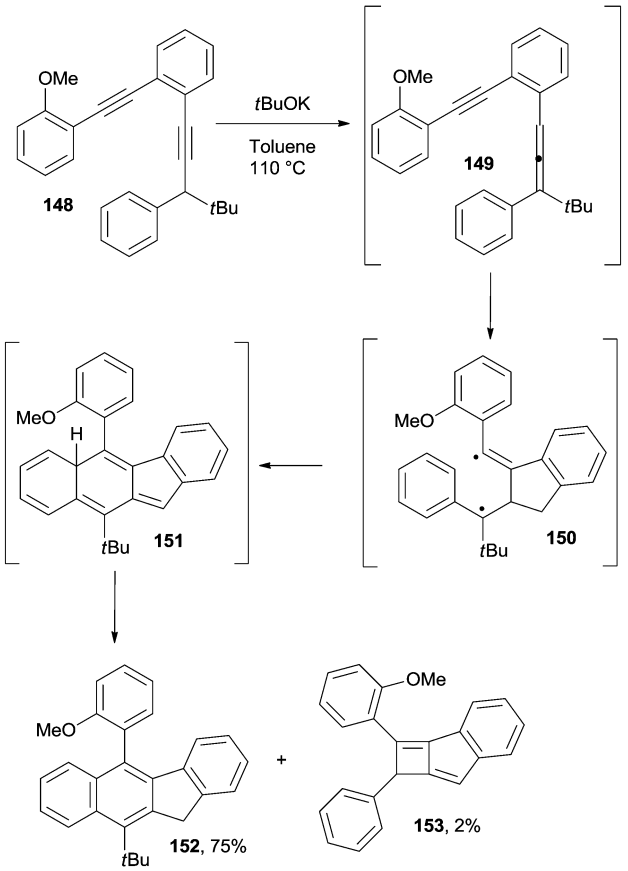


Scheme 38 Smooth preparation of benzo[*e*]indanes.

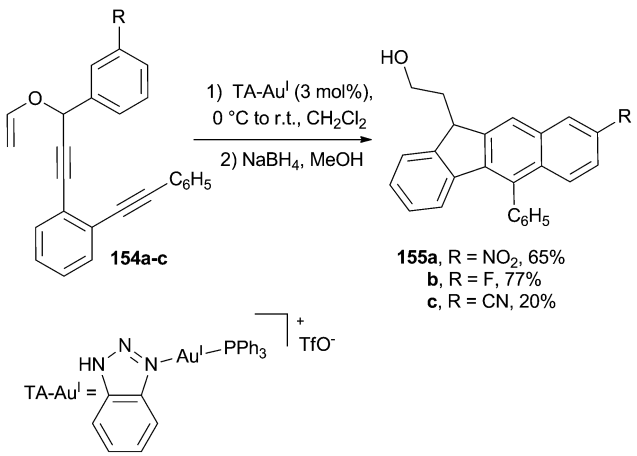
5 Synthesis of benzocondensed derivatives

Highly extended aromatic cores have recently gained increasing attention, particularly due to their application in the chemistry of materials. This section deals with the synthesis of aromatic nuclei larger than naphthalene (see Section 4) and the selected examples have been classified according to the size of the final aromatic nucleus.

Anthracene and its derivatives are linear polycyclic aromatic compounds showing high potential for use in materials science, particularly due to their photophysical properties (*e.g.* fluorescence probing, photochromic systems, and electroluminescence).[167]



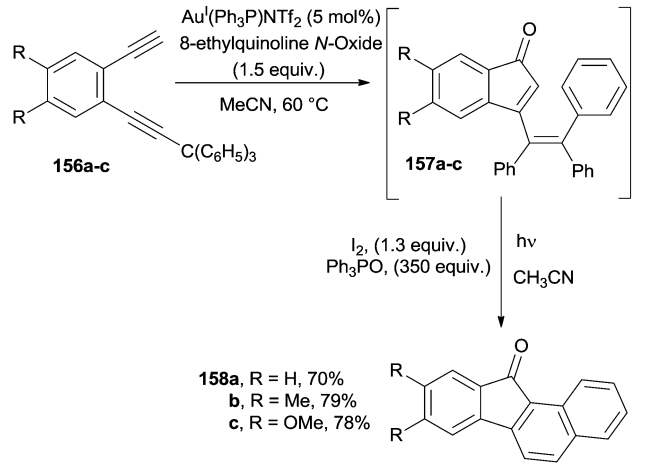
Scheme 39 Base-induced reactions on enediynes to give benzo[*b*]-fluorene derivatives.



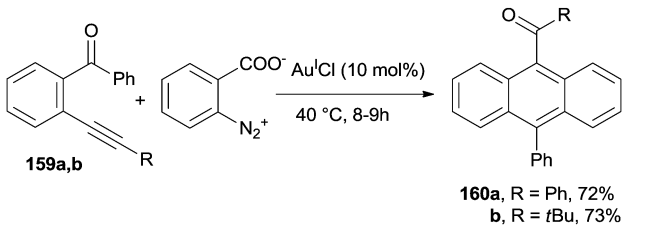
Scheme 40 Schmittel cyclization as the key step for the formation of a substituted naphthalene core.

Indeed, the substitution pattern plays a fundamental role in determining the actual properties.

The preparation of anthracene derivatives bearing a ketone group at the 9-position (**160a,b**) has been carried out under Au^{I}Cl-catalyzed conditions, starting from *o*-alkynyl(oxo)benzenes **159a,b** in the presence of benzenediazonium 2-carboxylate. The process occurred under mild conditions and good yields



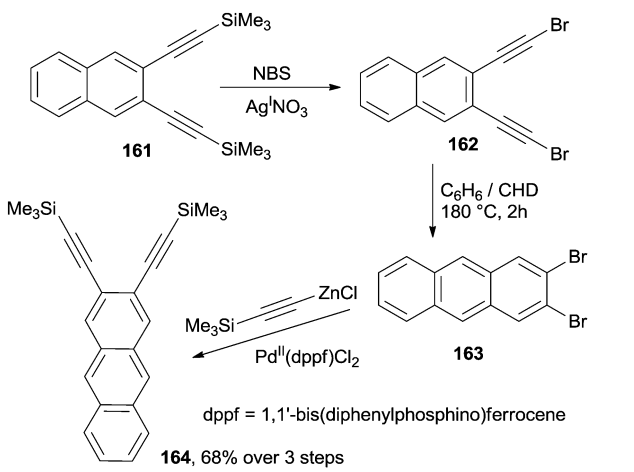
Scheme 41 Benzofluorenones by a two step process from 1,2-ethynyl-benzenes.



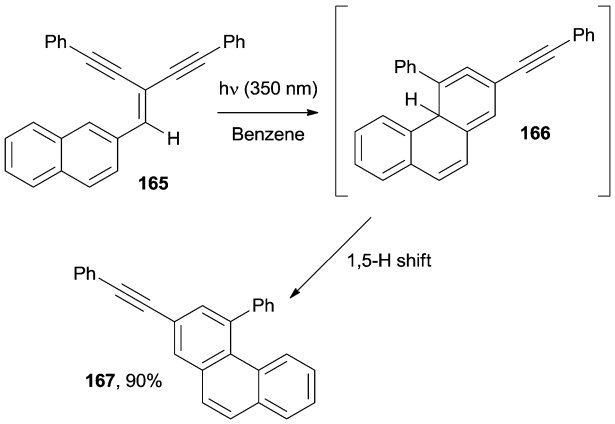
Scheme 42 Au^{I}-catalyzed conversion of *o*-alkynyl(oxo)benzenes into anthracene derivatives.

of the desired compounds were obtained (Scheme 42; for the mechanism, see Scheme 10).[89]

In a different example, anthracenes bearing substituents on the outer rings (a non-trivial synthetic target) have been prepared by a cycloaromatization process involving 2,3-bis(bromoethynyl)-naphthalene **162** (Scheme 43). This substrate has been in turn easily prepared *via* the desilylative halogenation of the corresponding trimethylsilyl derivative **161**. Heating a solution of the



Scheme 43 Multistep synthesis of 2,3-disubstituted anthracenes *via* Bergman cyclization.



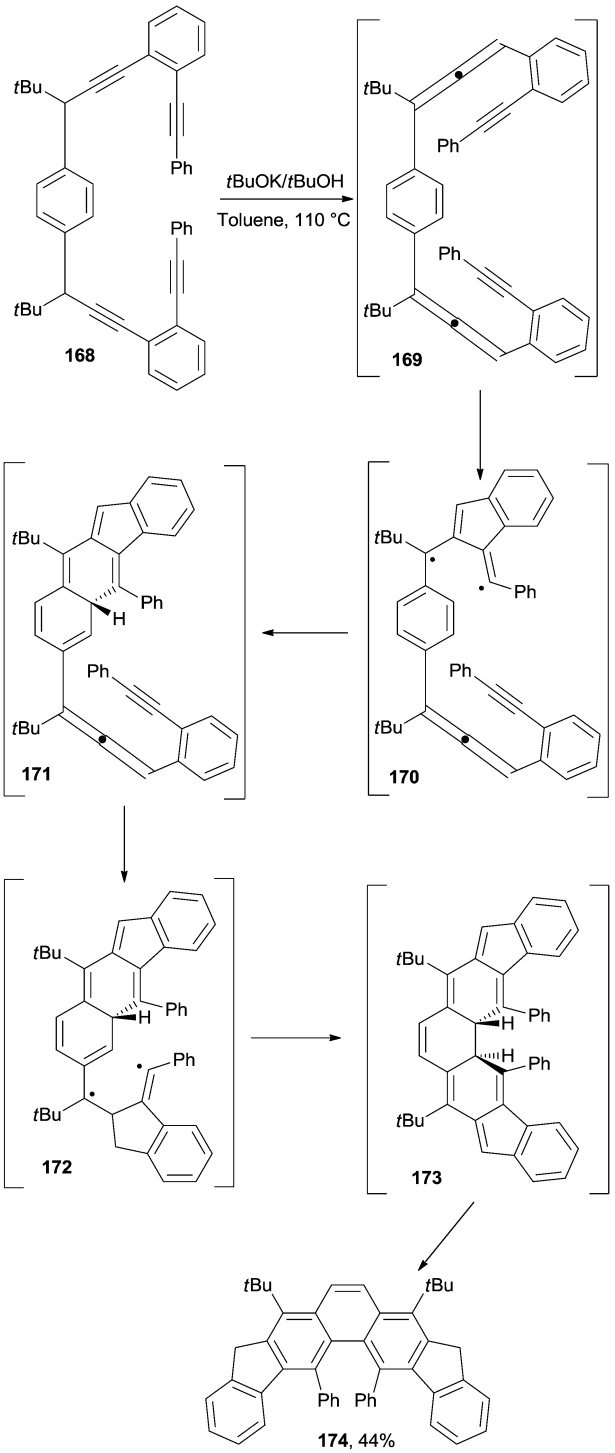
Scheme 44 Photoinduced preparation of substituted phenanthrenes.

so prepared enediyne in a $10:1_{v/v}$ benzene/CHD mixture at 180 °C in a steel bomb for 2 h led to 2,3-dibromoanthracene **163** in a good yield.[168] Further alkynylation of the resulting haloaromatic compound to afford the corresponding 2,3-diethynyl anthracene **164** generated a new enediyne system, homologated by one aromatic ring. This iterative methodology was also applied to the synthesis of unsubstituted naphthacenes.[168]

Similar conditions were applied to the synthesis of 2,3,6,7-tetrabromoanthracene from the corresponding 1,2,4,5-tetrakis-(bromoethynyl)benzene.[169]

Apart from acenes, polyenes have been likewise used for the synthesis of angularly fused derivatives. Phenanthrenes have been prepared adopting a photochemical approach starting from the so-called Y-enynes, *viz.* cross-conjugated enediynes, such as **165** (Scheme 44). Thus, irradiation of **165** at 350 nm promoted the photocyclization to **167** through the allene intermediate **166**. Interestingly, the mechanism was demonstrated to depend on the solvent polarity, with a 1,5-*H* shift or protonation at the central allene carbon occurring in non-polar (benzene and cyclohexane) and polar (methanol) solvents, respectively.[170,171]

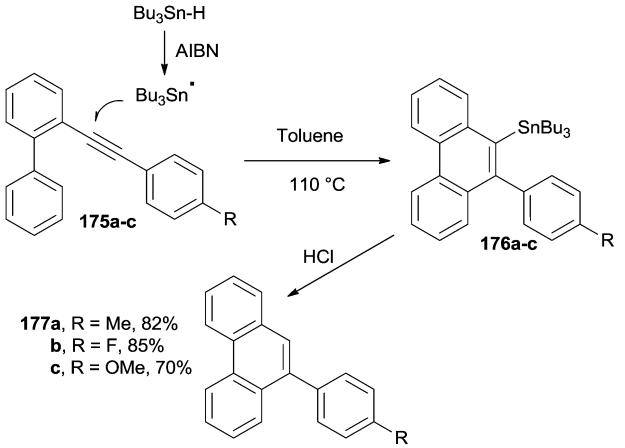
In a different approach, phenanthrenes have been synthesized *via* a C^2–C^6 cyclization occurring in enyne–allenes. In particular, this strategy gave access to 4,5-diarylphenanthrenes (**174** in Scheme 45) having a helical twist. The reaction involved treatment of the precursor (**168**) with *t*BuOK in refluxing toluene for up to 10 h, depending on the substitution pattern. The transformation proceeded through benzannulated enyne–allene **169**, in turn formed *via* a prototropic isomerization. A Schmittel cyclization ensued, giving non-aromatic biradical **170** and then intermediate **171** upon reaction with the central benzene ring. The same sequence was repeated through intermediates **172** and **173**, finally leading to product **174** upon tautomerization (Scheme 45).[172] The structure of **174** was demonstrated *via* X-ray analysis to bear the two phenyl substituents markedly bent away from each other, with the central aromatic system severely distorted.[172] Interestingly, highly congested diindenophenanthrenes containing four phenyl groups could be likewise synthesized by having recourse to this approach.[173] Similar strategies have been adopted to synthesize diindeno-fused 4*H*-cyclopenta[*def*]phenanthren-4-ones[174] and a set of



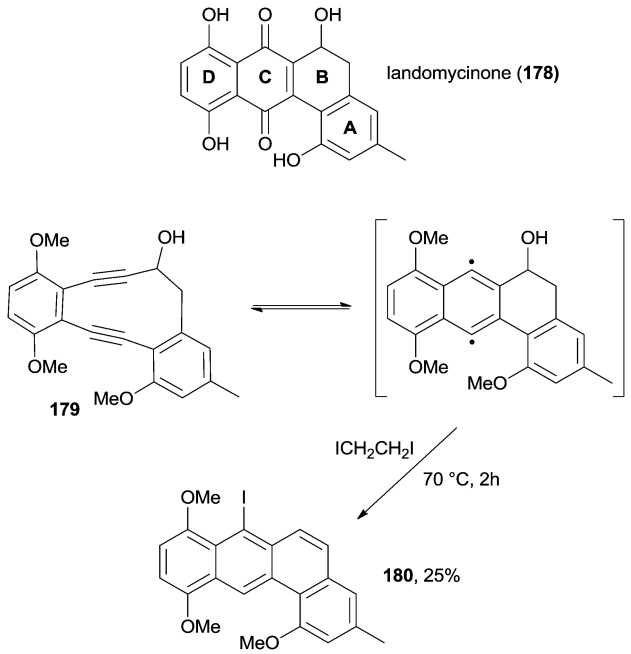
Scheme 45 Pathway for the base-induced synthesis of diindeno-phenanthrenes.

angularly fused polycyclic aromatic hydrocarbons containing the phenanthrene core.[175–177]

Phenanthrenes can be likewise synthesized from biphenyl aryl acetylenes (**175a–c**) under radical conditions, in the presence of a tin hydride derivative (Bu_3Sn-H) and an initiator (azobisisobutyrronitrile, AIBN). Thus, **175a–c** were treated in refluxing toluene to give the corresponding stannylated phenanthrenes **176a–c** (Scheme 46).



Scheme 46 Radical initiated cycloaromatization.

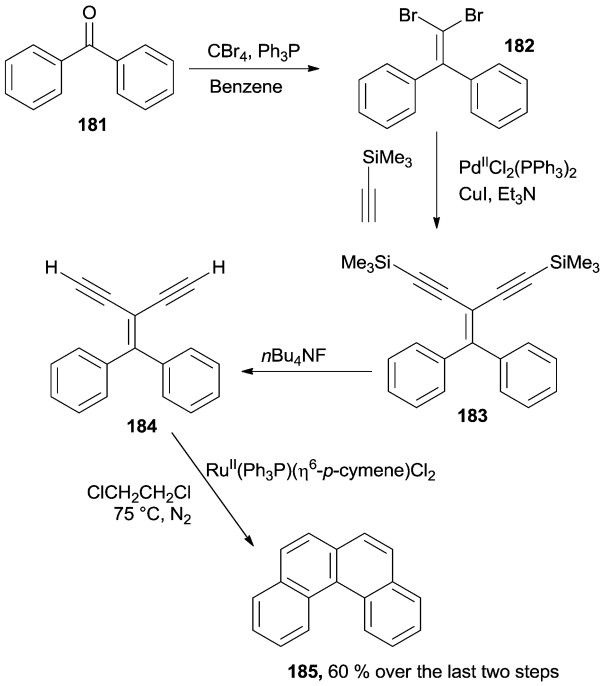


Scheme 47 Synthesis of the tetraphene core of landomycins.

Interestingly, the Sn-substituent could be removed *via* acid hydrolysis to give **177a–c** in good yields.[178]

Turning to aromatic hydrocarbons bearing 4 nuclei, a large number of isomeric structures are possible. Tetraphene derivatives are important due to the presence of this structural motif in landomycins, a class of antibiotics with potent antitumor and antibacterial activity. During a synthetic study intended to the synthesis of the structural motif contained in landomycinone **178** (Scheme 47), tetraphene **180** was synthesized in 25% yield starting from enediyne **179** through a Masamune–Bergman cyclization followed by the undesired elimination of the OH group (Scheme 47).[179]

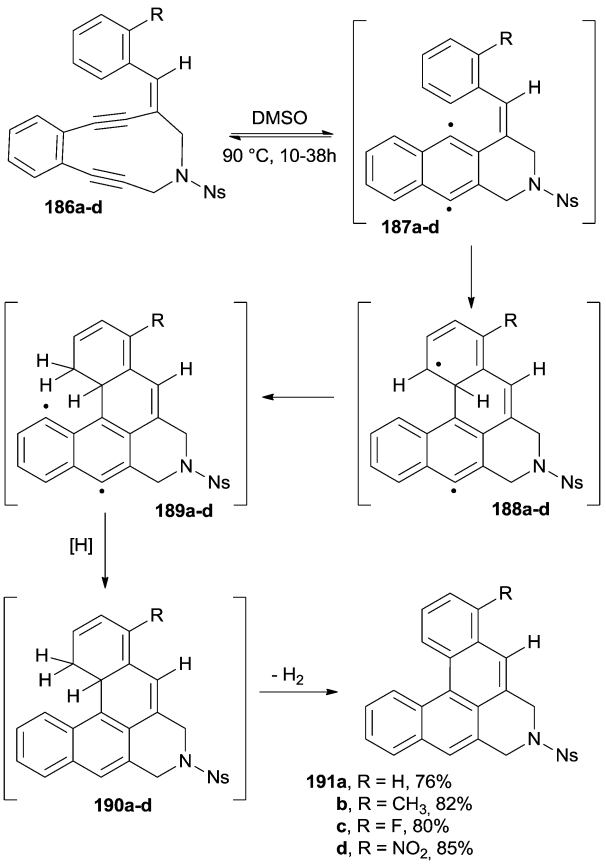
[4]Helicenes differ for the arrangement of the fused aromatic rings and can exist in two enantiomeric forms, due to steric hindrance that forces the molecule to adopt a helical-like structure.



Scheme 48 Ru^{II}-catalyzed synthesis of [4]helicenes.

Acyclic diaryl ketones can be exploited for the synthesis of [4]helicenes through a four-step reaction sequence, involving a Corey–Fuchs olefination, a Sonogashira coupling, a desilylation step and a Ru^{II}-catalyzed annulation process. Thus, benzophenone **181** was treated with CBr_4 and Ph_3P to yield dibromide **182** that was in turn converted to enyne **183** in the presence of $Pd^{II}(Ph_3P)_2Cl_2$. After the removal of the two Me_3Si-groups promoted by the fluoride ion, **184** was treated with a catalytic amount (*ca.* 30 mol%) of $Ru^{II}(Ph_3P)(\eta^6$-*p*-cymene)Cl_2 to afford [4]helicene **185** in a good yield (60% over the last two steps; Scheme 48). The mechanism proposed for the **184** to **185** conversion was postulated to involve the initial formation of a vinylidene–Ru intermediate (see Scheme 8).[180] Interestingly, $(Tp)Ru^{II}(Ph_3P)(CH_3CN)_2PF_6$ was likewise found to be very active in a plethora of catalytic benzannulation reactions involving the same strategy. Indeed, different polycyclic aromatic hydrocarbons, such as phenanthrene and various substituted coronene derivatives, could be synthesized.[181]

A general method for the synthesis of [4]helicenes is based on a Bergman cyclization applied to alkenyl enediynes (Scheme 49). Thus, compounds **186a–d** were heated at 90 °C in DMSO for 10–38 h to afford the corresponding (substituted) [4]helicenes in good yields. The proposed mechanism, also supported by deuterium labeling experiments by using d_6-DMSO as the solvent, claimed the involvement of three different biradical species. Biradicals **187a–d** arose from the initial Bergman cyclization and then underwent an intramolecular addition onto the lateral aromatic ring to give **188a–d** and then **189a–d** upon intramolecular hydrogen atom abstraction. Finally, radical quenching by the solvent ensued to give **190a–d**. Aromatization *via* elimination of a hydrogen molecule led to [4]helicenes **191a–d** (Scheme 49).[182]



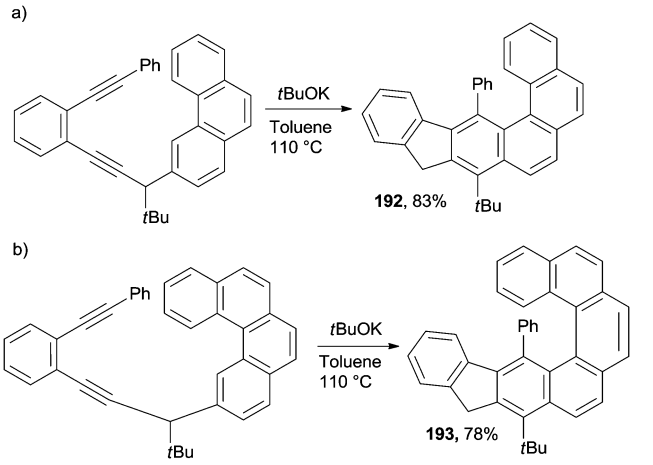
Scheme 49 Radical cascade in the synthesis of [4]helicenes **191a–d** (Ns = 4-$NO_2C_6H_4$).

Interestingly, chiral amino acids could be introduced into the skeleton of the starting material, imparting some diastereoselectivity to the process (the best results were obtained with L-leucine appended enediynes).[183] The same synthetic strategy could be extended also to the synthesis of [5]helicenes and was based on the use of naphthyl-substituted alkenyl enediynes.[183]

The same base-promoted approach reported above for the synthesis of phenanthrenes (Scheme 45) has been successfully extended to [4]helicenes (**192**, Scheme 50a)[175] and [5]helicenes (**193**, Scheme 50b).[175]

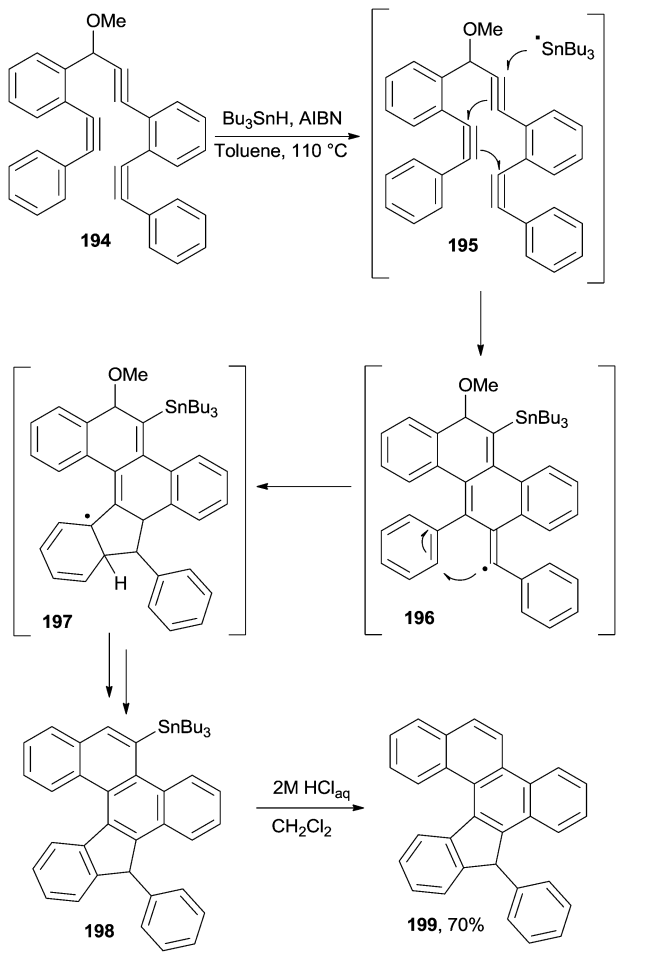
Recently, a general procedure for the synthesis of polyaromatic systems based on the use of oligoalkynes was proposed, making use of a highly selective radical cascade.[98,184] In one instance, the process occurred with the aid of a traceless directing group, lost at the end of the reaction. As an example, stannylated chrysene **198** was synthesized from tris-alkyne **194** using a radical chain process initiated by Bu_3Sn-H/AIBN in toluene at 110 °C through intermediates **195–197** (Scheme 51). The resulting Sn-containing product **198** could then be functionalized by treatment with a variety of electrophiles. In the simplest case, the Bu_3Sn group was eliminated *via* protodestannylation of compound **198** to give **199**.[184] [5]Helicenes could be obtained as well, when starting from the corresponding tetra-alkynes.[184]

The cycloaromatization of polyenynes was widely applied for the synthesis of polynaphthalene networks.[185–188] Perylene **201**

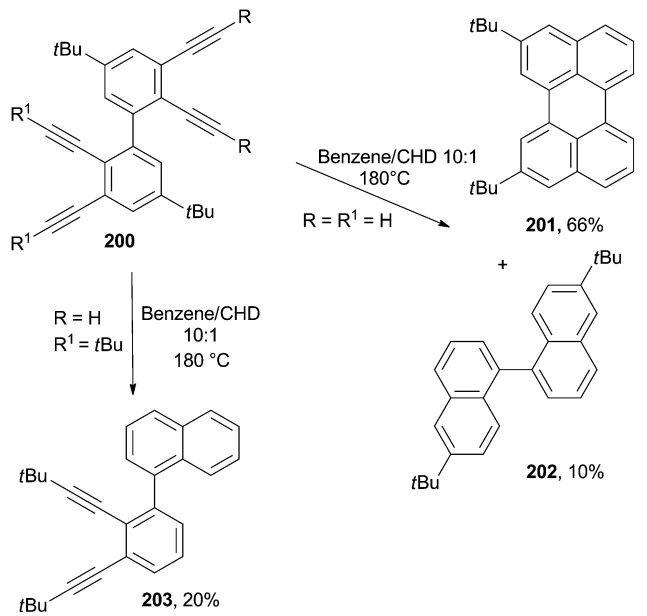


Scheme 50 Enediynes as precursors for the preparation of [4]helicenes and [5]helicenes.

was formed in 66% yield from a solution of the corresponding tetraethynylbiphenyl **200** in a $10:1_{V/V}$ benzene/CHD mixture heated to 180 °C in a sealed steel bomb. Binaphthyl **202** was likewise obtained as a minor product in 10% yield (Scheme 52).[189] Interestingly, when the same process was carried out on bulky



Scheme 51 Radical cascade in the synthesis of stannylated chrysene **198**.



Scheme 52 Different pathways in the cycloaromatization of tetraethynylbiphenyls.

derivatives (R^1 = *t*Bu), the cycloaromatization took place exclusively on the unsubstituted enediyne core, and naphthalene **203** was obtained in 20% yield along with a large amount of by-products (Scheme 52).[189]

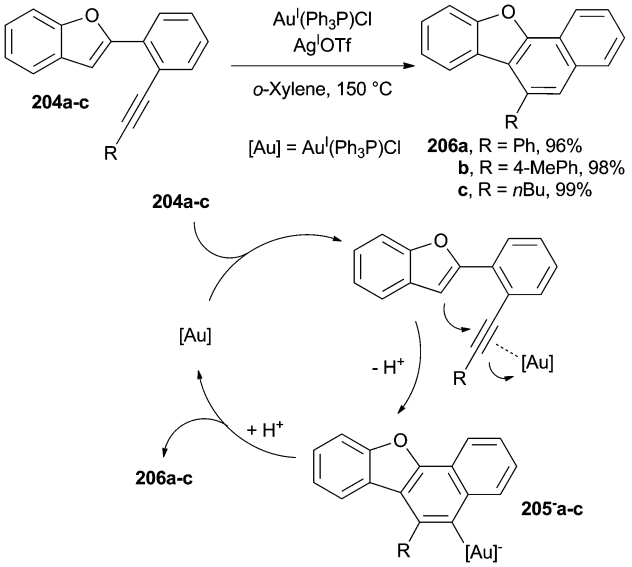
6 Synthesis of heteroaromatics

Heteroaromatic derivatives can be obtained by a cyclization step starting from azadienynes, *via* a (photochemical) Bergman reaction involving enediynes or starting from *ortho*-alkynylaryl isocyanides and eneallene-isonitriles. The ring formed, however, may either contain a heteroatom or be fused with a pre-existing heteroaromatic system.

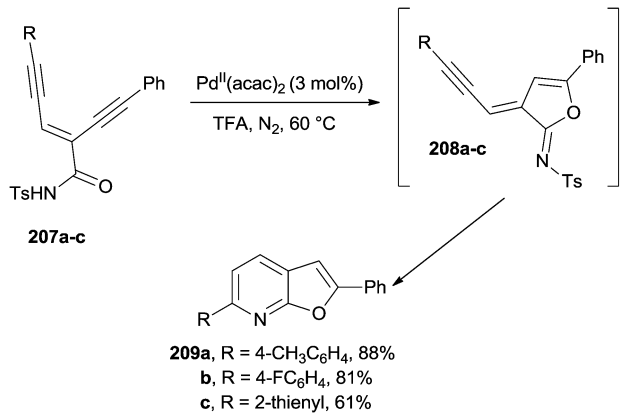
A nice example is the synthesis of naphtho[1,2-*b*]benzofurans **206a–c** by Au^I-assisted 6-*endo*-dig cyclization of benzofurans **204a–c** carried out at 150 °C in *o*-xylene (Scheme 53). The cyclization was initiated by the activation of the alkyne moiety by the Au^I species that allowed the addition of the triple bond onto the benzofuran (acting as the nucleophile). Compounds **206a–c** were then formed in a very good yield (mostly >90%) by proto-deauration of the cyclized intermediates **205⁻a–c**, also allowing the regeneration of the Au^I species.[92] Milder conditions were later applied (60 °C) to the synthesis of substituted carbazoles starting from (*Z*)-2-(enynyl)indoles by using Ag^ISbF_6 (5 mol%) and $Au^I(Ph_3P)Cl$ (5 mol%) as the catalytic system.[190]

Dienylalkynes cyclized even by using $Ru^{II}(\eta^6\text{-}p\text{-cymene})(Ph_3P)Cl_2$ (*ca.* 5 mol%) as the catalyst in the presence of NH_4PF_6 *via* vinylidene intermediates. As an example, 2-ethynyl-1-(2-furyl)cyclohexene was easily converted into 6,7,8,9-tetrahydronaphtho[1,2-*b*]furan in 89% yield in refluxing dichloromethane under stirring for 10 h.[191]

Pd^{II} catalysts are able to promote the flexible synthesis of furo[2,3-*b*]pyridines **209a–c** starting from substituted enediyne-imides **207a–c** (Scheme 54). The reaction was promoted by the coordination



Scheme 53 Gold-catalyzed preparation of naphtho[1,2-*b*]benzofurans.



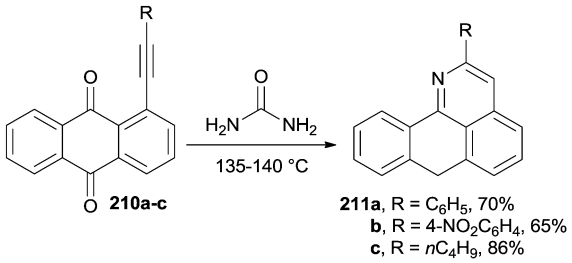
Scheme 54 Pd^{II}-catalyzed conversion of enediyne-imides into furo[2,3-*b*]pyridines.

of the alkyne moieties in **207a–c** by the Pd^{II} catalyst, in turn inducing a *trans*-oxypalladation to give imidates **208a–c**. A cycloisomerization ensued to afford substituted furopyridines **209a–c** in a very good yield upon tosyl group loss.[192]

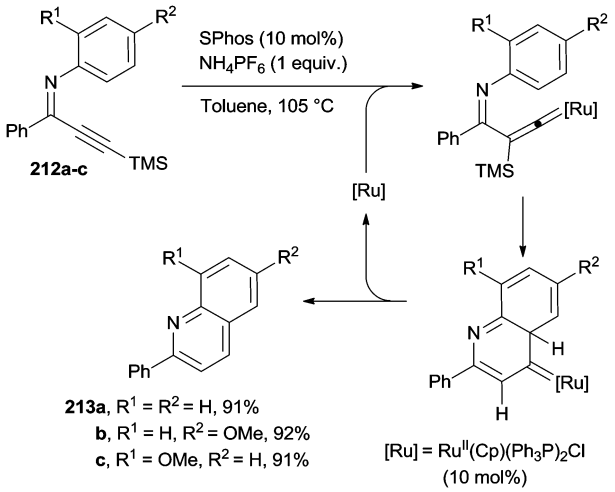
Peri-alkynyl-9,10-anthraquinones **210a–c** (Scheme 55) were efficiently employed as building blocks for the synthesis of aporphinoid alkaloid analogues 7*H*-dibenzo[*de*,*h*]quinolin-7-ones **211a–c**, upon heating in molten urea.[193]

Interestingly, the intermolecular version of the reaction involving the reductive dimerization of acetylenic anthraquinones in the presence of guanidine gave access both to 2*H*-dibenzo[*de*,*h*]-isoquinoline-3,7-diones (main product) along with tetrabenzo-[*a*,*de*,*j*,*mn*]tetracene-4,13-diones.[194]

The construction of the pyridine ring was likewise accomplished *via* the Ru^{II}-catalyzed protodesilylation and cycloisomerization of C_6-trimethylsilyl 3-azadienynes **212a–c** to give the corresponding aza-heterocycles **213a–c** (Scheme 56). The catalytic system made use of the $Ru^{II}(Cp)(Ph_3P)_2Cl$ complex, along with



Scheme 55 Synthesis of 7*H*-dibenzo[*de*,*h*]quinolin-7-ones *via* cycloaromatization.



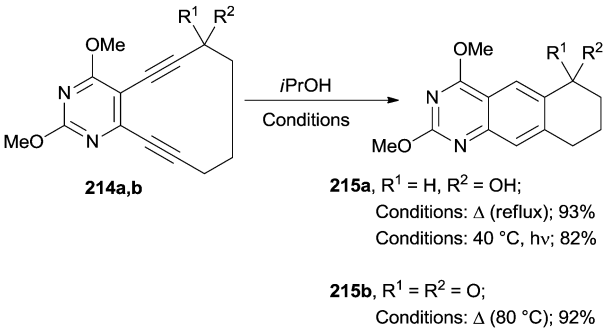
Scheme 56 Smooth entry to phenylquinolines *via* cycloaromatization of azadienynes.

the 2-dicyclohexyl-phosphino-2′,6′-dimethoxy-1,1′-biphenyl (SPhos) ligand in the presence of NH_4PF_6 as an additive.[195] Substituted phenylquinolines **213a–c** were then isolated in very good yields (Scheme 56).

The best approach for the synthesis of heterocycles is, however, by having recourse to a Bergman cyclization starting from cyclic enediynes. Scheme 57 illustrates a representative example where quinazolines **215a,b** were prepared either under thermal or photochemical conditions from 10-membered pyrimidine enediynes **214a,b**.[196] Interestingly, alcohol **214a** cyclized in iPrOH both by heating under reflux or under irradiation at 40 °C (overall yield >80%). The presence of a ketone moiety in compound **214b**, however, inhibited the formation of quinazoline **215b** upon irradiation (Scheme 57). This was probably due to the involvement of a triplet state.†

Analogously, irradiation of 11-membered 4,5-bis-(alkyn-1-yl)imidazoles gave the corresponding cycloaromatized products. The overall yields were satisfactory only when the reaction was applied to conformationally rigid derivatives and strongly depended on the solvent used.[197] A smooth procedure for the synthesis of 10-membered cinnoline-fused cyclic enediynes was

† A referee pointed out that a low energy triplet state could be involved thus interfering with the usual triplet Bergman cyclization (*per se* not an unfavorable process), see I. V. Alabugin and M. Manoharan, *J. Am. Chem. Soc.*, 2003, **125**, 4495–4509.

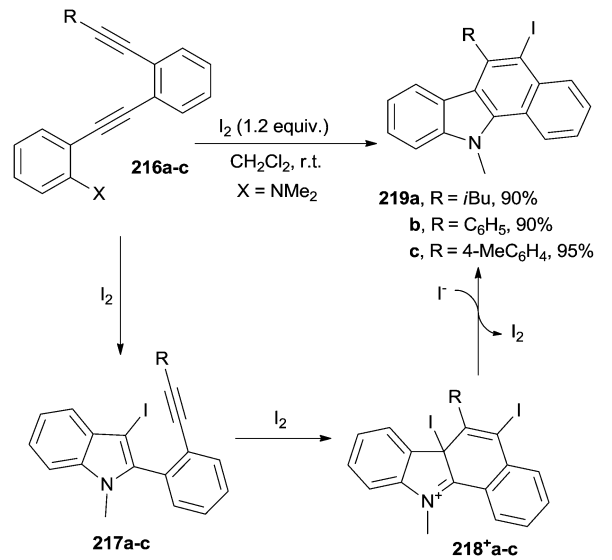


Scheme 57 Thermal and photoinduced Bergman cyclizations.

recently reported.[198] These compounds were prone to cyclization under mild conditions (75 °C, 24 h) in iPrOH to afford tetrahydrodibenzo[*c*,*g*]cinnolines *via* a Bergman cyclization. In particular, cinnolino[5,4-*c*]cyclodeca-4-ene-2,6-diyn-1-ol was shown to be four times more reactive than the benzo-fused analogue.[198]

Acyclic enediynes require harsh conditions to cyclize. A typical case is that of imidazole-fused (*Z*)-3-ene-1,5-diynes which required 145 °C to be converted into the corresponding benzimidazoles.[199] The cyclization rate, however, changed according to the substitution pattern of the nitrogen atom in the imidazole ring. Thus, *N*-aryl substitution was able to enhance the rate by up to seven-times with respect to the corresponding *N*-alkyl derivatives, although the reasons were not fully proven.[199]

A smooth way to induce the cycloaromatization in acyclic enediynes is by adding an electrophile (*e.g.* iodine), as summarized in Scheme 58. The process took place at room temperature within 2 h. Thus, treatment of *N*,*N*-dimethyl 2-[2-(2-ethynylphenyl)ethynyl]anilines **216a–c** with a slight excess of I_2 caused an initial cyclization to form iodinated indoles **217a–c**. Further addition of iodine followed by iodide attack onto cations **218$^+$a–c** formed the desired benzo[*a*]carbazoles **219a–c** in high yield, provided no bulky substitutents on the terminal alkyne (*e.g.* a *t*Bu group)



Scheme 58 Preparation of benzo[*a*]carbazoles.

or electron-withdrawing groups on the aniline ring were present.[91] A related process was used for the preparation of benzo[*b*]naphtha[2,1-*d*]thiophenes (X = SMe in compounds **216a–c**) under uncatalyzed[200] or catalyzed conditions ($Au^{I}(Ph_3P)Cl$ in combination with $Ag^{I}SbF_6$ as the catalyst).[201] Iodine, as well as *N*-iodosuccinimide, was used here as the electrophile.[200–202] Iodine-free carbazole derivatives were similarly prepared from substituted ethynylanilines (X = NH_2 in **216a–c**), again making use of Au/Ag catalysts in a process initiated by an intramolecular 5-*endo*-dig hydroamination cascade.[202]

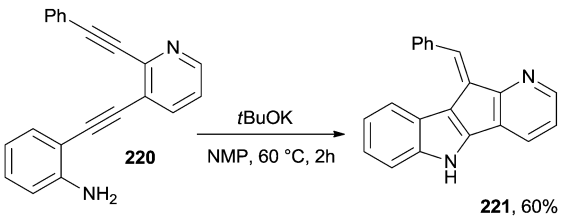
Carbazoles featuring a silylketene moiety have been obtained from the corresponding indole-based Fischer carbene complexes by following the same approach described in Scheme 36.[162]

The preparation of chlorinated analogues of **219a–c** has been accomplished by the treatment of compounds **216a–c** with $Pd^{II}Cl_2$ (10 mol%) in refluxing THF in the presence of an excess (2 equiv.) of $Cu^{II}Cl_2$.[82] In alternative, a stronger electrophile, such as $(C_6F_5)_3B$, was used to initiate the cyclization of N-heterocyclic 1,2-bis-(trimethylsilylethynyl)arenes *via* 1,1-carboboration. The method is versatile since highly substituted quinolines, benzothiophenes and carbazoles were accessed.[203]

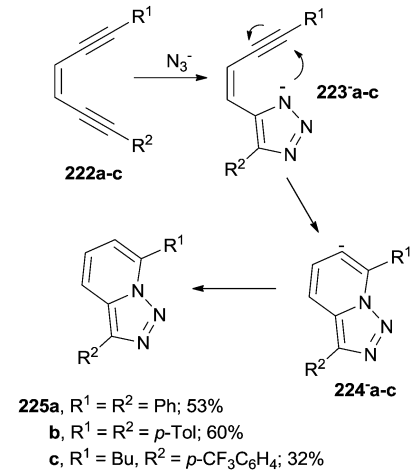
A particular case is the cyclization of compound **220** that, under basic conditions, cyclized to a halogen-free indole fused with a cyclopenta[*b*]pyridine unit (**221**, Scheme 59). It is noteworthy that the latter compound exhibited a significant antifungal activity against *T. mentagrophytes* and *T. rubrum*.[202] Bergman cyclization was likewise promoted under basic conditions by the treatment of a methanolic solution of various enediynylphenyl *tert*-butyldimethylsilyl ethers with sodium methoxide under reflux for 16 h to give a series of 5-substituted dibenzofurans.[204]

Addition of nucleophiles (*e.g.* the azide anion) onto enediynes is another viable approach for the construction of heterocyclic systems, as in the tandem cyclization of (*Z*)-1-aryl-3-hexen-1,5-diynes **222a–c** (Scheme 60). The heterocyclization was initiated by the formation of triazole anions **223**$^{-}$**a–c** followed by the attack of the charged nitrogen atom onto the neighboring triple bond to generate anions **224**$^{-}$**a–c** and [1,2,3]triazolo[1,5-*a*]pyridines **225a–c** from them.[205] The approach has been extended to the synthesis of [1,2,3]triazolo[1′,5′;1,2]pyrido[3,4-*b*]pyrazines.[206]

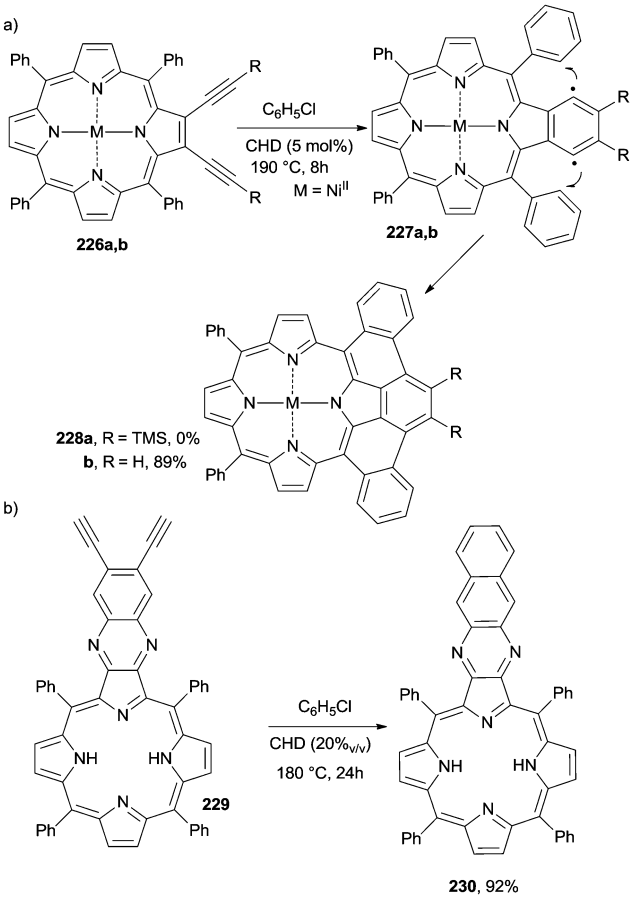
The wide application of porphyrin derivatives led to the development of procedures intended to extend the π-system in order to tune the electronic properties of the resulting derivatives. A first report dealt with the thermal annulation of Ni^{II} 2,3-dialkynyl-5,10,15,20-tetraphenylporphyrins **226a,b** to form picenoporphyrins **228a,b** (Scheme 61a).[207] The conditions were quite prohibitive, however, since the Bergman cyclization was carried



Scheme 59 Base-induced preparation of heteroaromatics.

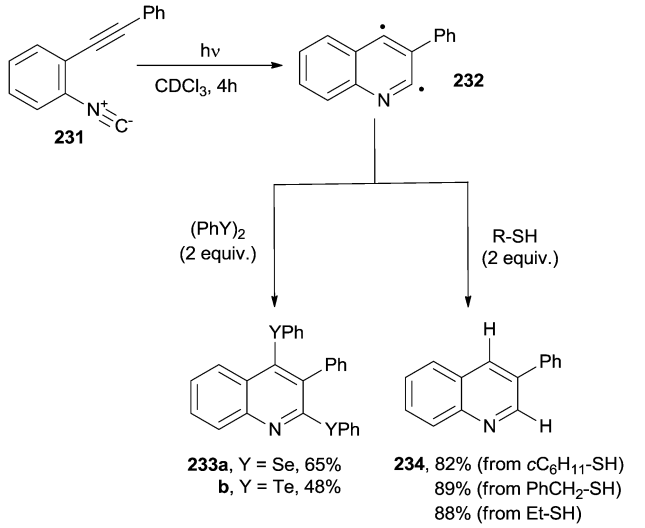


Scheme 60 Azide addition onto enediynes to give [1,2,3]triazolo[1,5-*a*]pyridines.



Scheme 61 Synthesis of arenoporphyrins.

out in a sealed Schlenk tube in chlorobenzene at 190 °C in the presence of CHD as a hydrogen atom donor. The reaction was very sensitive to the presence of substituents on the triple bonds and was particularly efficient only when using unsubstituted derivatives.[207] Arenoporphyrin 1,4-biradicals **227a,b** were postulated as the key intermediates (Scheme 61a). In the case of **226b**,

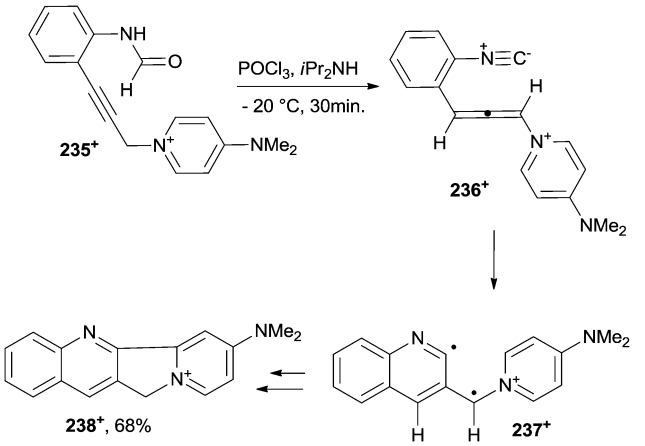


Scheme 62 Photocyclization of *ortho*-alkynylaryl isocyanides.

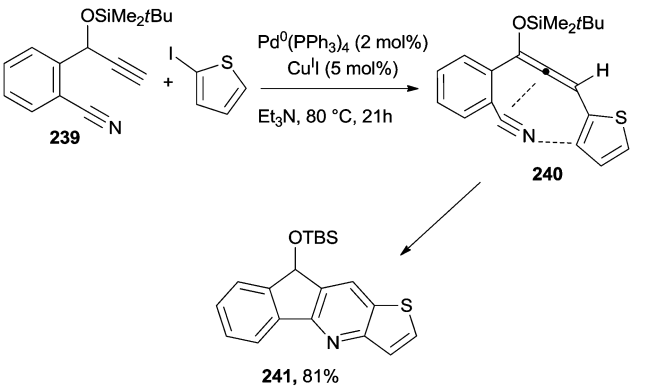
the addition of 2 equiv. of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), which plays the role of a hydrogen atom acceptor, markedly accelerated the process and allowed for milder reaction conditions (25 °C), despite the fact that a lower yield (30–40%) of picenoporphyrin **228b** was obtained.[208] Bergman cyclization took place even when starting from Zn^{II} tetraphenylporphyrin **226b** (M = Zn^{II}), again in the presence of CHD under thermal (120 °C, 70%) or photochemical ($\lambda \geq 395$ nm) conditions. In the latter case, however, only partial conversion of the starting enediyne resulted.[209] The presence of CHD was again required in the conversion of metal-free tetraphenyl diethynylquinoxalino[2,3-*b*]-porphyrin **229** into tetraphenylbenzoquinoxalino[2,3-*b*]porphyrin **230** (92%) under heating (Scheme 61b).[210]

Unsaturated aromatic isonitriles have been sparsely used for the synthesis of nitrogen-containing heterocycles. A typical case is the photocyclization of *ortho*-alkynylaryl isocyanides (**231**, Scheme 62). Thus, the photochemical ($\lambda \geq 300$ nm) addition of **231** onto organic dichalcogenides (diselenides or ditellurides) induced the formation of 2,4-bischalcogenated quinolines **233a,b** *via* the intermediacy of biradical **232**. The reaction did not take place, however, when using diphenyl disulfide as dichalcogenide.[211] As an alternative, 3-phenylquinoline **234** was smoothly prepared when the reaction was carried out in the presence of a hydrogen atom transfer reagent, such as a thiol (Scheme 62).[211] Substituted quinolines also arose from a radical cascade reaction involving *o*-alkenyl arylisocyanides and boronic acids in the presence of 3 equiv. of $Mn^{III}(acac)_3$.[212]

A nitrogen-containing six-membered ring was likewise obtained by the cycloaromatization of eneallene-isonitrile $\mathbf{236}^+$, in turn easily obtained *in situ* from pyridinium $\mathbf{235}^+$, as the mesylate salt. In such a way, a quinoline biradical $\mathbf{237}^+$ was generated that, upon intramolecular cyclization (*via* a formal [4+1] cycloaddition), afforded the end 11*H*-indolizino[1,2-*b*]quinolin-10-ium $\mathbf{238}^+$ in a good yield (Scheme 63).[213] A different path was observed instead when substituting a MeO group for the NMe_2 group in $\mathbf{235}^+$, where a 2-substituted indole was formed in place of the quinoline. This behaviour was attributed



Scheme 63 Easy route to 11*H*-indolizino[1,2-*b*]quinolin-10-ium.



Scheme 64 Cyano-Schmittel cyclization for the synthesis of **241**.

to the lower donation capability of the alkoxy group in intermediate $\mathbf{236}^+$. At any rate, in favourable cases this approach allowed for the construction of the heteroaromatic ring core of the antitumor agent camptothecin (as in the case of $\mathbf{238}^+$). Substituted 6*H*-indolo[2,3-*b*]quinolines and tetrahydropyrimido-[4,5-*b*]quinolines were obtained from the corresponding enyne–carbodiimides *via* thermal C^2–C^6 Schmittel[214] and C^2–C^7 Myers–Saito[215] reactions, respectively.

Pyridine-fused compounds (*e.g.* **241**) were easily prepared by making use of a cyano-Schmittel cyclization (Scheme 64). Thus, a Sonogashira coupling between benzonitrile **239** and 2-iodothiophene, followed by a base-induced propargyl–allenyl isomerization, afforded cyano-allene **240** that easily cyclized to **241**.[216]

7 Conclusions

The purpose of this Review was to demonstrate that the cyclization of dienynes, enediynes and enyne–allenes is a versatile method for the preparation of (hetero)aromatics. The main advantage of this approach, in comparison with other established benzannulation reactions, is that the cyclization event can be induced in different ways. The thermal cyclization of dienynes and enediynes (resulting in Hopf and Bergman

cycloaromatizations, respectively) takes place under harsh conditions (T mainly >150 °C), unless the unsaturated system has the right geometry (often encountered in cyclic polyenic derivatives). In contrast, enyne–allenes are very reactive and difficult to handle and they easily undergo the cycloaromatization process (Myers–Saito reaction). For this reason such polyenes are conveniently generated *in situ* from enediynes *via* rearrangement under basic conditions.

The photochemical approach allows the use of mild conditions for the activation of the polyenic substrate, but it has been applied so far only in rare instances to promote an efficient cycloaromatization. Addition of electrophiles or radicals onto the polyenic system is a valuable alternative since the incorporation of the promoting agent into the structure of the end product(s) is an added bonus of the reaction.[97,184] Metal-catalysis, however, is at present a widely applied strategy of activation and it is the main reason for the recent growth of these cycloaromatizations in modern organic synthesis. However, the strategies summarized in this review often lack generality, since different substrates usually require different modes of activation to achieve the desired target. Nonetheless, the use of dienynes, enediynes, enyne–allenes and hetero-analogues may open the way for innovative synthetic strategies for the preparation of (hetero)aromatic building blocks and polycyclic aromatic hydrocarbons (PAHs) useful in medicinal chemistry and in the preparation of electroactive organic materials and molecular devices.

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