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Modern methods for the synthesis of substituted naphthalenes

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1. Introduction

There are numerous examples of biologically active natural products that possess a naphthalene or naphthoquinone core.[1] Nanaomycin A **1**, for example, a member of the family of pyranonaphthoquinone antibiotics,[2] possesses a simple naphthoquinone backbone (Fig. 1). By contrast, the rifamycin series of macrocyclic antibiotics is more complex in structure, and members of the series are characterised by a polyketide-derived aliphatic (or *ansa*) chain linked to nonadjacent positions on a naphthoquinone or naphthalene nucleus. Rifampicin **2** (Fig. 1), a semi-synthetic derivative of the naturally occurring rifamycin B, is both an antibacterial and an antiviral agent.[3,4] It inhibits viral replication and bacterial RNA polymerase and is used extensively in the treatment of tuberculosis in Southern Africa and other areas of the world.

In 1886 racemic gossypol (see Fig. 2 for (*S*)-gossypol **3**), a

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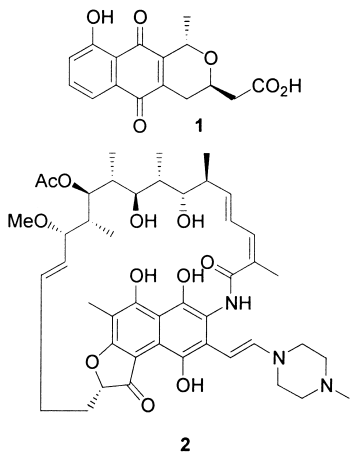


Figure 1.

natural toxin was isolated from cotton seeds, and its structure was elucidated some 50 years later.[5] This polyphenolic compound comprises two identical naphthalene units linked by a biaryl axis. Restricted rotation about this axis imparts chirality to the molecule. Pharmacologically it is known to be an oral antifertility agent in men and male animals, and it shows potential for the treatment of HIV infections, diabetic complications and cancer. Of interest, though, are the observations that (*R*)-gossypol is more effective than its atropisomer (*S*)-gossypol **3** against tumour cells and HIV-1, while the opposite is true for activity against herpes simplex virus, influenza and parainfluenza virus.

The biaryl linkage appears to be an important feature governing the biological activity of many naturally occurring naphthalenes or naphthoquinones. Conocurvone **4** (Fig. 2), isolated from a shrub indigenous to Western Australia, is composed of three naphthoquinone units linked by biaryl axes.[6,7] In contrast to gossypol, there is a low barrier to rotation about the biaryl bonds for this compound, and as a result a mixture of atropisomers exists in equilibrium. The interest in conocurvone is due to the exceptionally high anti-HIV activity exhibited by the

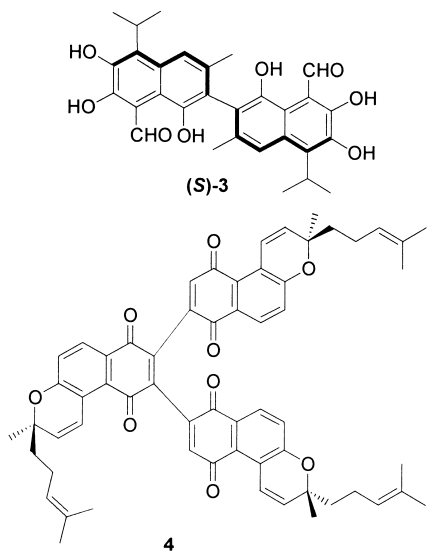


Figure 2.

atropisomeric mixture in a variety of in vitro tests conducted by the US National Cancer Institute. This physiological property is dependent on the trimeric nature of the compound, as the anti-HIV activity exhibited by the trimer is completely absent for the naturally occurring monomer.

Other compounds possessing prominent naphthalene motifs are the biaryl naphthylisoquinoline alkaloids, depicted in Figure 3, which include the korupensamines[8] (e.g. korupensamine A **5**), and their dimers, the michellamines[9–13] (e.g. michellamine B **6**). The former have anti-malarial properties, and the latter exhibit potent anti-HIV activity.

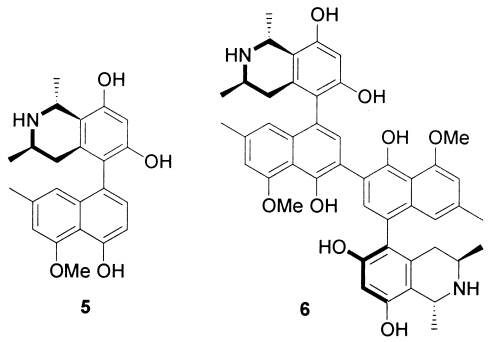


Figure 3.

Apart from their interesting biological activity, biaryl naphthalene compounds also find application as chiral reagents.[14] The first and most frequently used chiral phosphine ligand is BINAP **7**. This is illustrated by the work of Noyori who has shown that ruthenium complexes of **7** are capable of effecting asymmetric hydrogenations[15,16] and have even found industrial applications.[17]

The atropisomers of (1,1′-binaphthyl)-2,2′-diol **8** and its derivatives (Fig. 4) are widely used in asymmetric synthesis, either as ligands or as chiral auxiliaries.[18–21] These binaphthols have demonstrated excellent chiral induction, both catalytically and stoichiometrically, in a remarkable number of organic transformations ranging from Diels–Alder cycloadditions to polymerisation reactions. For example, the binaphthol derivative **9** has been used as a chiral ligand in the copper-catalysed Michael addition of dialkylzinc reagents to cyclic α,β-unsaturated ketones.[22]

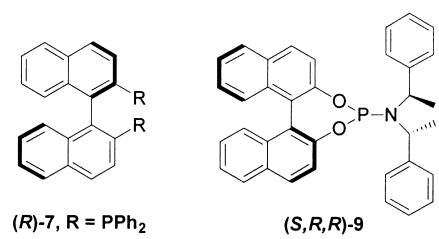


Figure 4.

One of the more important contributions using binaphthols in organic synthesis has come from the group of Shibasaki.[23–25] It has been shown that a number of characterised heterobimetallic asymmetric binaphthols such as **10** shown in Figure 5 are capable of catalysing a variety of reactions. For example, these types of catalysts

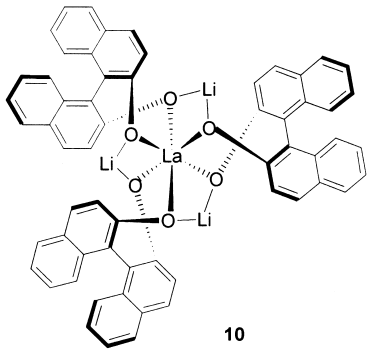


Figure 5.

have been used in asymmetric aldol reactions, epoxidation of enones and hydrophosphonylation of imines. Three reviews of this interesting area of research have been published recently.[23–25]

Cram has shown the use of chiral binaphthyls as molecular hosts for the complexation of a number of organic and inorganic guest molecules.[26] Chiral recognition in complexation has also been achieved, as demonstrated by the use of enantiomerically pure host **11**, depicted in Figure 6, in the separation of a racemic mixture of amino acids by liquid–liquid extraction. Separation of the D and L-amino acids was achieved by selective complexation, brought about by complementarity between host and guest of the (*R*,*R*)-D-configurations, with lack of complementarity in those of the (*R*,*R*)-L-configuration. In addition to its use in liquid–liquid extractions, (*R*,*R*)-**11** has also been covalently bound to polymer resins for the preparation of chiral stationary phases for chromatography.[19]

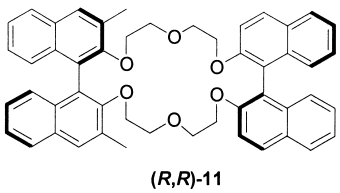


Figure 6.

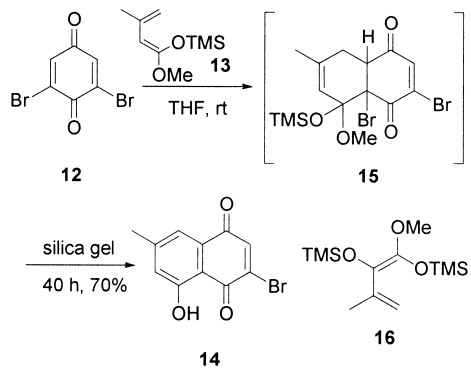
The preceding discussion has indicated the importance of naphthalenes and naphthoquinones as bioactive agents and in structural and synthetic chemistry. How the synthetic chemist gains access to such compounds forms the subject of this review. The synthesis of polysubstituted naphthalenes is often not simple by conventional electrophilic aromatic substitution owing to the important problem of regiochemical control. The current general de novo approaches to naphthalenes attempt to circumvent this problem, and include rearrangements and condensations in which the substitution pattern of the aromatic product is determined by the structure of the starting materials. This review, without attempting to be totally comprehensive, serves to illustrate the applications of these general methods and the variations thereof. We have also chosen to illustrate with representative examples mainly those methods that show the conversion of single ring benzene precursors into naphthalenes. Routes in which a pre-existing naphthalene core is modified are specifically excluded. Most of the material in this review covers the period from 1999 to the end of 2001, although common traditional methods for the synthesis of substituted naphthalenes will also be mentioned. Where deemed appropriate, some extensions to polycyclic aromatic compounds will also be included. While there is no general review on the synthesis of naphthalenes and naphthols, there are reviews on some aspects of the material covered in this review, which will be mentioned in the appropriate sections. Some partially related reviews covering benzannulation reactions have also recently been published.[27,28]

2. Diels–Alder reactions

The Diels–Alder cycloaddition reaction has been utilized extensively in the synthesis of substituted naphthalenes and naphthoquinones. Usually, the formation of more than one cycloadduct is possible for unsymmetrical dienes and dienophiles,[29] but in some cases there is a good degree of regiochemical control. The synthesis of complex precursors may be necessary to facilitate regioselectivity.

2.1. Diels–Alder addition of quinones to dienes

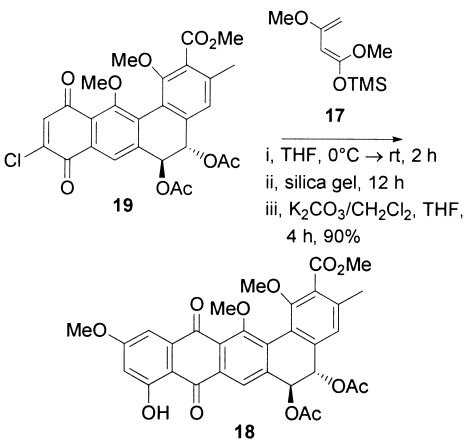
Almost 30 years ago, Brassard[30] and Danishefsky[31] reported the use of various vinyl ketene acetals as useful dienes in Diels–Alder cycloaddition reactions, and this methodology still finds application today. Recently, Bringmann and co-workers have applied this methodology in their synthesis of the naphthalene portion of the michellamines (see Fig. 3), a naturally occurring class of anti-HIV compounds isolated from *Ancistrocladus korupensis*.[32] As outlined in Scheme 1, treatment of benzoquinone **12** with diene **13** regioselectively afforded naphthoquinone **14** in 70% yield, after elimination of HBr and trimethlysilanol from the intermediate **15** in the presence of silica gel. Other dienes such as **16** have also been used in Diels–Alder reactions.[33]



Scheme 1.

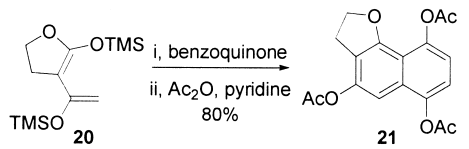
Suzuki and co-workers have utilized the Diels–Alder reaction and subsequent elimination steps in their synthesis of pradimicinone, an anthraquinone as outlined in Scheme 2.[34] This group made use of Brassard's diene **17** to achieve the desired substitution pattern of the product **18**. In both these examples, the regiochemistry is governed by the position of the halogen on the quinonoid starting materials **12** and **19**.

More recently so-called 'inner–outer-ring' dienes have



Scheme 2.

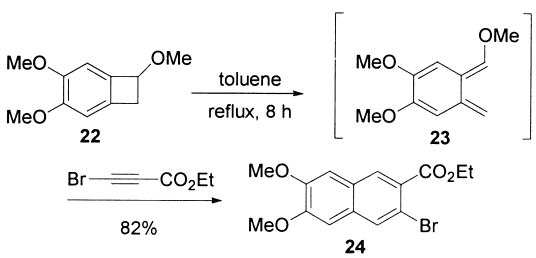
been used to make naphthalenes as shown in Scheme 3.[35,36] Reaction of the readily prepared diene **20** with benzoquinone afforded the substituted naphthalene **21** in good yield, after protection as the triacetate.



Scheme 3.

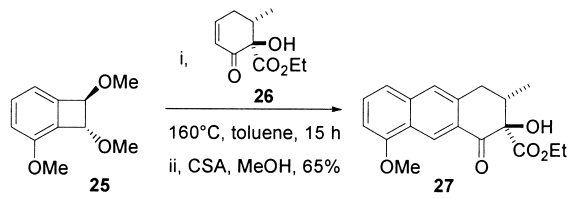
2.2. Diels–Alder addition of *o*-quinodimethanes

Several reviews covering the use of *o*-quinodimethanes for the synthesis of aromatic compounds have been published.[37–39] Variations of the Diels–Alder reaction include the addition of *o*-quinodimethanes to acetylenic dienophiles.[37] Benzocyclobutenes may also be used as precursors for *o*-quinodimethanes as shown in Scheme 4.[40] Benzocyclobutene **22** rearranged upon heating to give *o*-quinodimethane **23**. Reaction with the dienophile and subsequent elimination of methanol afforded the naphthalene product **24** in 82% yield. Frontier molecular orbital calculations may be used to predict the formation of the preferred regioisomer, although experimentally, mixtures of regioisomers may still be formed.[41,42]



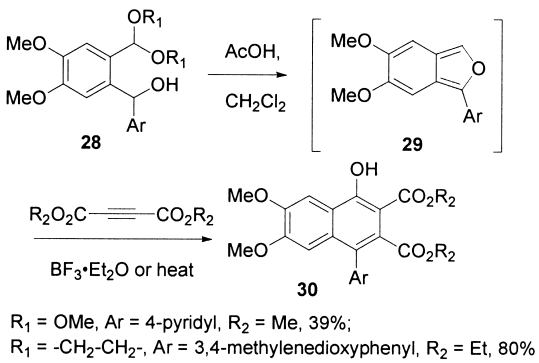
Scheme 4.

A recent application of *o*-quinodimethane methodology may be found in the synthesis of rishirilide B.[43] Model studies showed that the *o*-quinodimethane generated from **25**, on reaction with **26**, afforded the substituted naphthalene **27** after treatment with camphor-sulfonic acid (CSA) (Scheme 5). A methodological paper on the use of *o*-quinodimethanes for the synthesis of polycyclic compounds was published recently.[44]



Scheme 5.

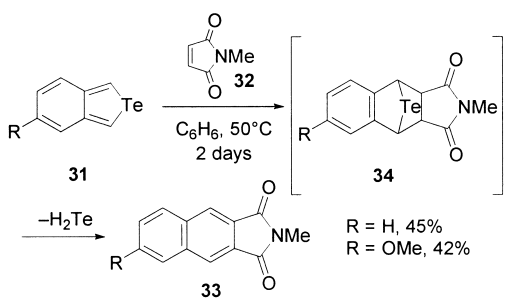
Hydroxy acetals such as **28**, precursors to transient isobenzofurans **29**, have been used to prepare naphthalenes **30** by trapping the isobenzofuran with acetylenes as shown in Scheme 6.[45–47]



R_1 = OMe, Ar = 4-pyridyl, R_2 = Me, 39%;
R_1 = -CH_2-CH_2-, Ar = 3,4-methylenedioxyphenyl, R_2 = Et, 80%

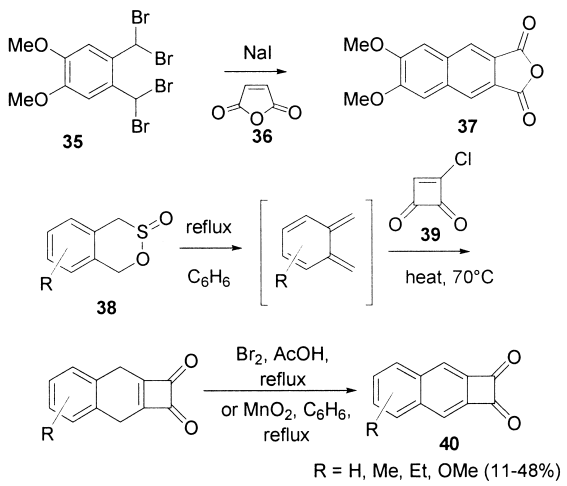
Scheme 6.

During an investigation of the unstable benzo[*c*]tellurophene compounds **31** by Cava and co-workers, it was discovered that **31** reacted readily with *N*-methylmaleimide **32** to afford *N*-methylnapthalimides **33** in moderate yields.[48] The products **33** were probably formed by facile expulsion of hydrogen telluride from the Diels–Alder adduct **34** as illustrated in Scheme 7.



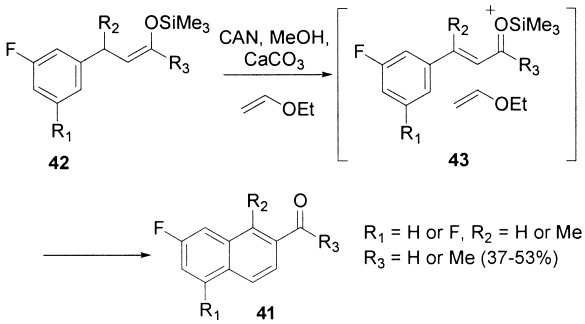
Scheme 7.

o-Quinodimethanes generated from brominated precursors **35** (also used by Silva and co-workers),[49] reacted with dienophiles such as **36** to afford naphthalenes **37**.[50] The transient *o*-quinodimethane formed by expulsion of sulfur dioxide from benzoxanthiin-3-oxides **38** upon heating reacted with semisquaric chloride **39** to give substituted naphthalenes **40**, in poor to acceptable yields, after aromatization (Scheme 8).[51]



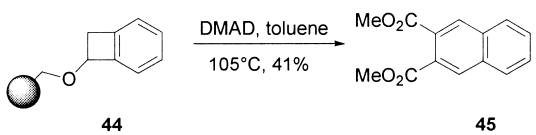
Scheme 8.

An interesting example in this section describes the work of Ruzziconi and co-workers, who have used a novel electrophilic aromatic cyclization strategy to synthesize fluorinated naphthalenes **41**.[52] Oxidation of the readily prepared *O*-silylalkenes **42** with ceric(IV) ammonium nitrate in the presence of ethyl vinyl ether afforded the substituted naphthalenes in moderate to good yields presumably by way of intermediate **43** (Scheme 9).



Scheme 9.

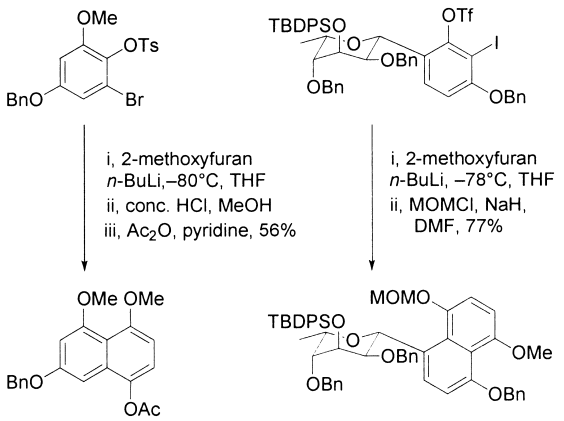
Finally in this section, a reaction which may involve *o*-quinodimethanes as intermediates has been reported to take place on solid supports. Treatment of the resin-supported *o*-quinodimethane precursor **44** with dimethyl acetylenedicarboxylate (DMAD) gave naphthalene **45** in an acceptable yield of 41% (Scheme 10), and unreacted starting material which was easily separated from the product.[53]



Scheme 10.

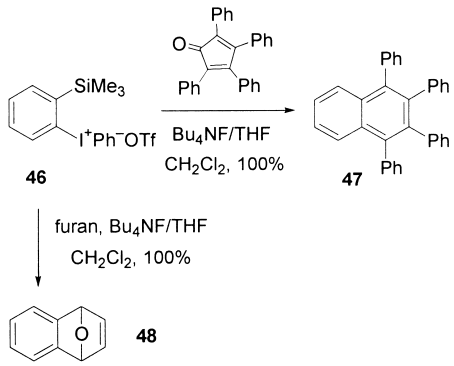
2.3. Diels–Alder addition of benzynes

The addition of benzynes to furans has been reported quite extensively[54,55] and only a few examples of this approach will be described. Some regiochemical control is possible with this method, as shown in Scheme 11.[56,57] In these cases, only one Diels–Alder adduct is formed, but unfortunately this is not always easy to predict.



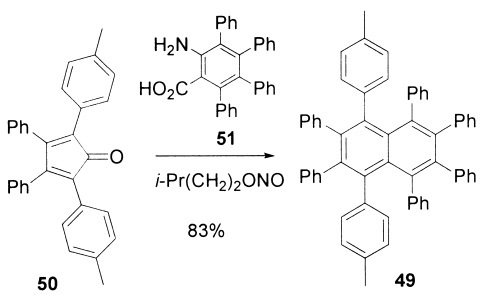
Scheme 11.

In the cases shown in Scheme 11, the benzyne is generated from the corresponding *ortho*-substituted halogenated tosylate or triflate. However, the benzyne can also be generated from the corresponding dihalide,[58] monohalide, anthranilic acid, or even a trimethylsilyl iodonium triflate such as **46** by treatment with a fluoride source (Scheme 12).[59] The use of this method afforded compounds **47** and **48** in excellent yields.



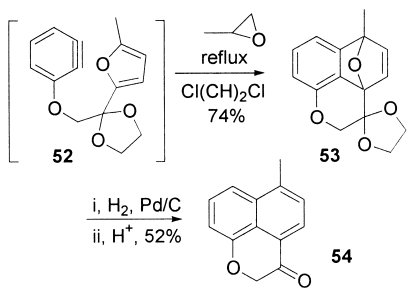
Scheme 12.

Another example leading to the synthesis of a sterically hindered naphthalene **49** is described in Scheme 13. Treatment of cyclopentadienone **50** with the benzyne generated from tetraphenylanthranilic acid **51** gave **49** in 83% yield.[60] The synthesis of a related naphthalene has been reported by the same workers.[61]



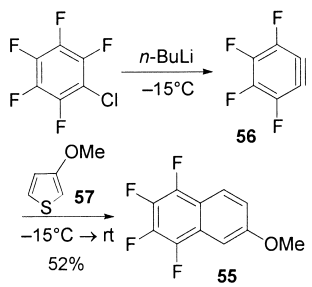
Scheme 13.

The problems associated with predicting the regiochemical outcome of these reactions can be overcome by employing intramolecular Diels–Alder cycloaddition reactions, where the use of a more complex substrate ensures formation of the desired regioisomer. One of the first examples reported is shown in Scheme 14 in which the benzyne component of **52** was tethered to a substituted furan.[62] The Diels–Alder adduct from this reaction, **53**, was obtained in 74% yield. Catalytic reduction and subsequent elimination of water gave the final aromatic product **54**. This principle was also recently applied in an interesting synthesis of azapolycyclic compounds.[63]

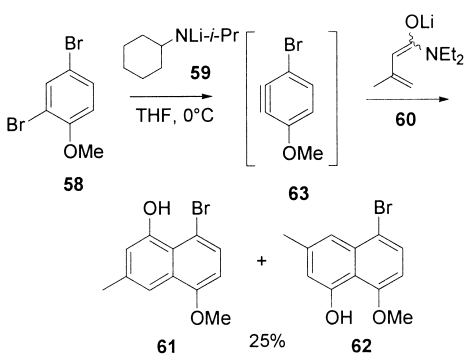


Scheme 14.

The synthesis of fluorinated derivatives of BINOL **7** and related compounds for catalysis is an intensive area of research. The synthesis of the precursor naphthalenes **55** (Scheme 15) has been carried out from the benzyne **56** and 3-methoxythiophene **57** as the dienophile. Interestingly, extrusion of sulfur takes place in situ under very mild conditions, to give compound **55**.[64] Related work has also been reported in the literature.[65]



Scheme 15.

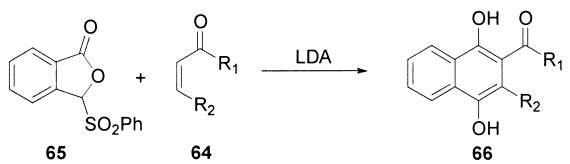


Scheme 16.

Finally, exposure of 2,4-dibromoanisole **58** to lithium isopropyl cyclohexylamide (LICA) **59** and subsequent reaction with lithium enolate **60** gave a mixture of regioisomers **61** and **62**, indicating that only benzyne **63** was formed during the reaction (Scheme 16).[66]

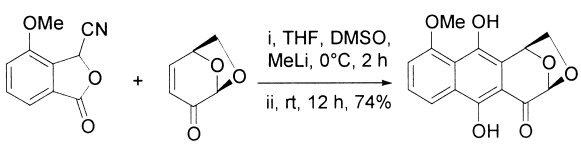
3. Phthalide annulations

In 1978, Hauser first described the annulation of Michael acceptors **64** with stabilised phthalide anions such as 3-phenylsulfonylphthalide **65** to afford naphthalene products **66** (Scheme 17).[67] The function of the phenylsulfonyl group is to stabilise the α-carbanion generated, and subsequently to act as a leaving group to allow aromatization following annulation. A similar reaction using the anion of 3-cyanophthalide was developed simultaneously by Kraus.[68]



Scheme 17.

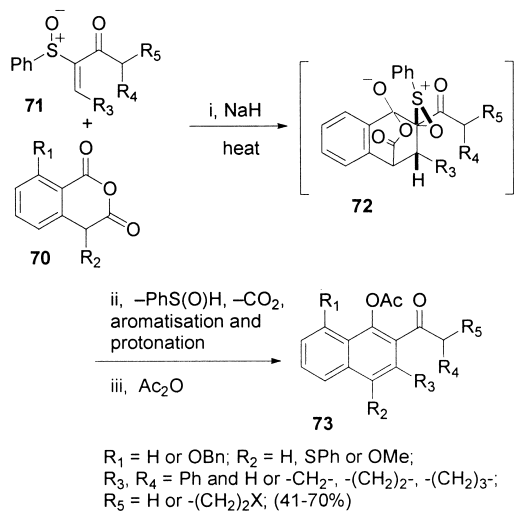
Since its discovery, this reaction has been applied to the synthesis of many natural products, as it provides a convergent route to naphthalenes and naphthoquinones that is under strict regiocontrol.[69] The regiochemistry of the sole product is determined by choosing the appropriately substituted phthalide and Michael acceptor. An example of this is evident in the synthesis of (−)-hongconin by Swenton et al.,[70] who employed the phthalide annulation of cyanophthalide **67** with levoglucosenone **68**, a compound available in chiral form by pyrolysis of cellulose, to give the naphthyl product **69** in 74% yield (Scheme 18). Further elaboration of this product afforded (−)-hongconin. Several other examples employing pthalide annulations and modifications thereof, have been reported recently.[71–74]



Scheme 18.

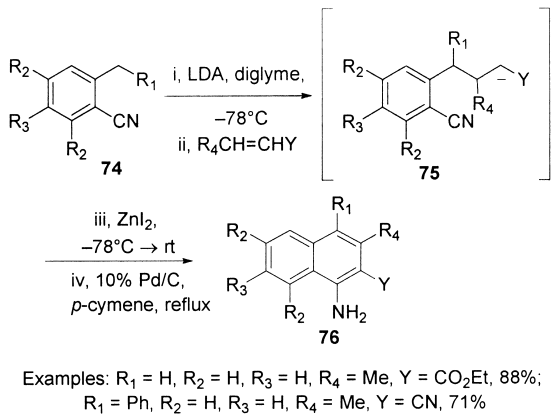
Recent work by Kita has extended this approach to other functionalised naphthalenes by employing the reaction of homophthalic anhydrides **70** with enolizable enones.[75–79] This general strategy is described in Scheme 19. The initial reaction is thought to involve a [4+2] cycloaddition or Michael-type addition between homophthalic anhydride **70** and sulfinyl-substituted dienophiles **71**. Intermediate **72** underwent aromatization to afford the naphthalenes **73** in moderate to good yields.

A variation on the phthalide annulation involves taking advantage of the acidity of the benzylic protons on

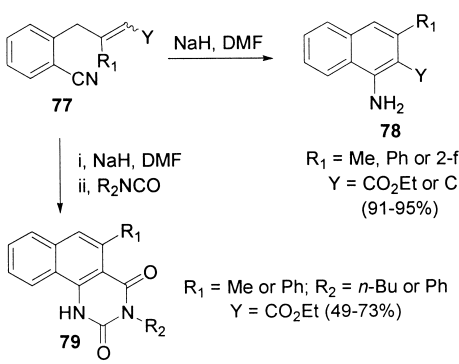


Scheme 19.

substrates such as **74** (Scheme 20). Abstraction of one of these protons and addition of the anion to a Michael acceptor, followed by reaction of the resulting nucleophile **75** with the nitrile *ortho* to this substituent afforded a number of dihydroaminonaphthalenes which could be aromatized to the corresponding substituted aminonaphthalenes **76**.[80] Related work utilizing α,β-unsaturated nitriles has also been reported by Barsy[81] and Sepiol,[82] and both these methods could be very useful for the synthesis of aminonaphthalenes.



Scheme 20.



Scheme 21.

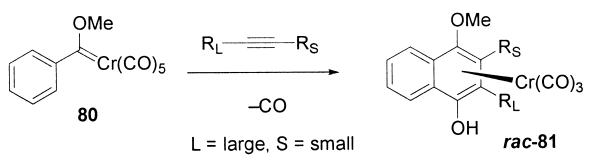
This work has recently been extended to include the cyclization of 4-(2-cyanophenyl)but-2-enoates and the corresponding nitrile **77** (Scheme 21) to afford aminonaphthalenes **78** in excellent yields. The amide anion intermediates could also be trapped with an isocyanate to afford the corresponding benzo[*h*]quinazolinedione derivatives **79** in good yields.[83,84]

4. Transition metal-mediated cyclizations

A widely used and rapidly growing method for the synthesis of naphthalenes and naphthols involves the use of transition metals in cyclization reactions.[85]

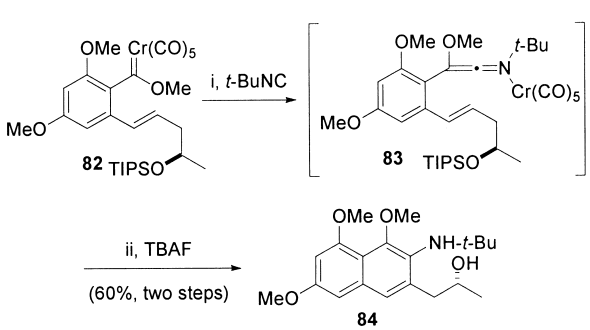
4.1. Chromium-assisted methods

At present, the most widely used transition metal-mediated method for the synthesis of naphthalenes is the Dötz benzannulation. The reaction of an alkoxy-aryl carbene complex such as **80** with an alkyne to afford a naphthol product **81** (Scheme 22) was first reported by Dötz 27 years ago.[86] Since its discovery, this chromium-mediated benzannulation, which allows access to densely functionalised arenes, has found application in the synthesis of many natural products with a naphthalene or naphthoquinone nucleus. Although few steps are involved in this method it is probably not viable for industrial purposes. This work has been the subject of several recent reviews[87–91] and therefore will not be covered in detail here. However, a few new developments will be discussed.



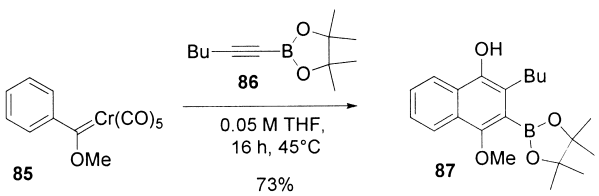
Scheme 22.

Merlic and co-workers have synthesized functionalised aminonaphthalenes using chromium carbene chemistry (Scheme 23).[92–96] Examples of their work include the reaction of carbene complex **82** with *tert*-butylisonitrile to afford an intermediate ketenimine **83**. This intermediate then underwent thermal electrocyclization to the *o*-alkoxynaphthylamine **84**, an important intermediate in the synthesis of the calphostins.



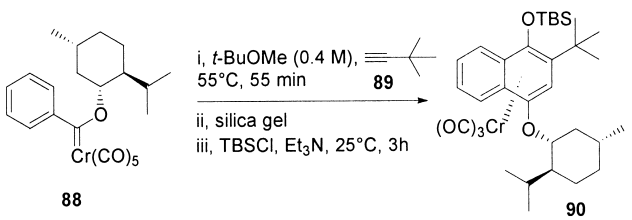
Scheme 23.

The reaction of alkynylboronates with Fischer carbene complexes has also recently been achieved (Scheme 24).[97,98] For example, reaction of chromium carbene **85** with boronate **86** gave the naphthaleneboronic ester **87** as a single regioisomer in 73% yield, with a minor amount of the deboronated side-product. It is likely that these products could be formed from aryl halides by lithium–halogen exchange followed by quenching with a suitable boronic ester, but not in the presence of a naphthol. This type of product could be used as a synthetic intermediate in Suzuki coupling reactions.

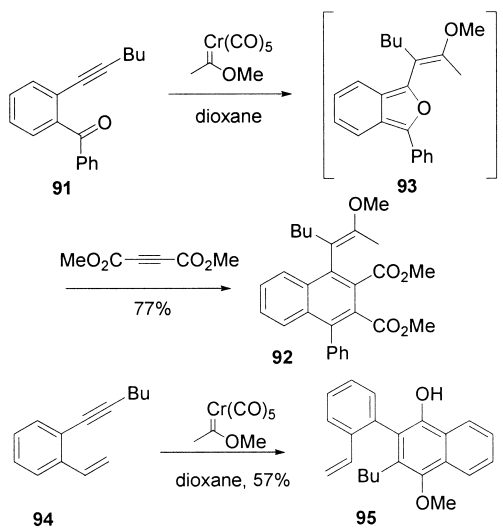


Scheme 24.

More recently, attempts have been made to use the Dötz reaction to make chiral planar arene–chromium tricarbonyl complexes using chiral auxiliaries. Dötz[99] has reported that reaction of (−)-menthol complex **88** with 3,3-dimethylbut-1-yne **89** gives naphthalene **90** in a diasteromeric ratio of 10:1 (Scheme 25). However, Wulff showed that very low asymmetric induction levels (0–20%) were obtained when trying to generalise this type of reaction.[100] Other approaches using chromium carbenes to synthesize multi-substituted naphthalenes have also been published by Dötz.[101]



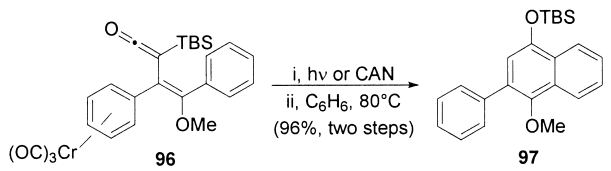
Scheme 25.



Scheme 26.

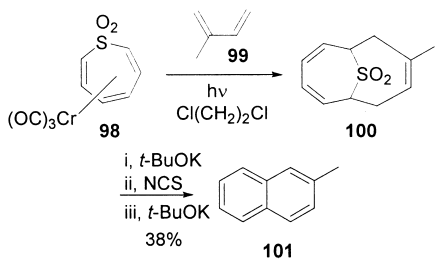
Chromium-containing Fischer carbenes react with enyne–aldehydes or ketones such as **91** in the presence of dimethyl acetylenedicarboxylate (DMAD) to afford naphthalenes such as **92** (Scheme 26).[102] It has been shown that the reaction proceeds by way of the intermediate isobenzofuran **93** which would undergo a Diels–Alder with DMAD. Herndon used *o*-alkynylstyrene derivatives such as **94** to give substituted naphthalenes **95**, in moderate yields, as illustrated in Scheme 26.[103]

Other recent examples utilizing the Dötz reaction include the synthesis of a highly oxygenated precursor of the antibiotic γ-rubromycin[104] and an application of the methodology to the synthesis of fredericamycin A.[105] Moser[106] has published a range of examples displaying the conversion of intermediates like **96** to substituted naphthalenes such as compound **97** (Scheme 27).



Scheme 27.

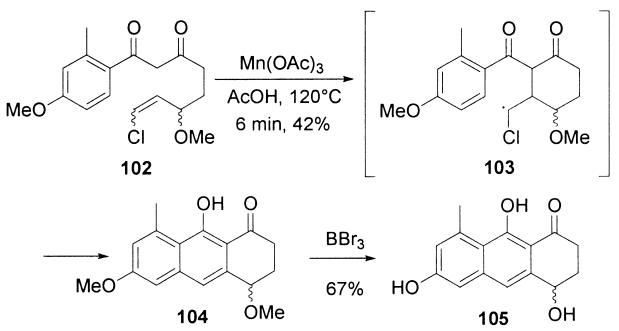
The chromium-promoted cycloaddition/-Ramberg–Backlund rearrangement has also been used for the synthesis of naphthalenes. Exposure of the tricarbonylchromium(0) complex **98** to diene **99** in the presence of light afforded intermediate **100**. Treating **100** with base and *N*-chlorosuccinimide (NCS), followed by a second equivalent of base afforded naphthalene **101** as shown in Scheme 28.[107] This method afforded low yields of naphthalene products and may not be very versatile as the production of a range of chromium complexes could be difficult.



Scheme 28.

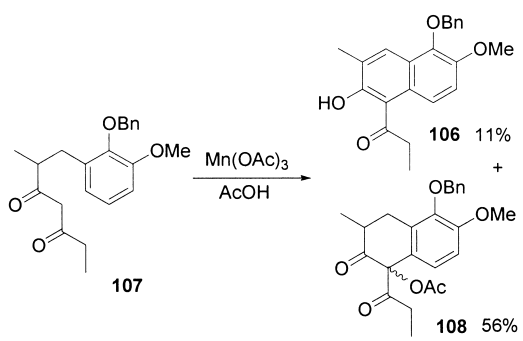
4.2. Manganese-mediated radical cyclization

A manganese-mediated radical cyclization involving two single-electron oxidations has been described by Snider and Zhang for the synthesis of the antitumour antibiotic okicenone.[108] The initial one-electron oxidation of **102** afforded the α-chloro radical intermediate **103**, which gave **104** in 42% yield after a second one-electron oxidation and loss of HCl (Scheme 29). Deprotection of both methyl ethers of **104** with boron tribromide gave okicenone **105**. Steric effects of the chlorine substituent appear to slow down the 7-*endo* cyclization, thereby favouring formation of the 6-*exo* product.



Scheme 29.

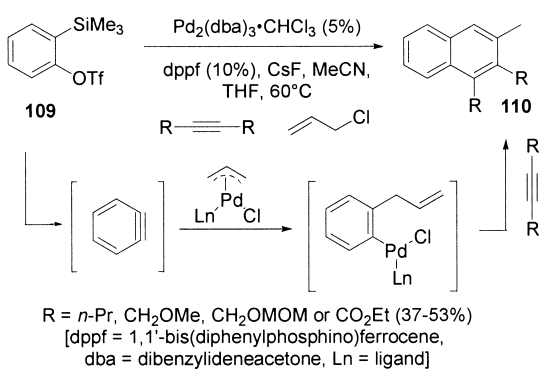
Rickards has reported another promising manganese-mediated method for the synthesis of naphthols **106** from diketones such as **107**.[109] However, it should be noted that often the major product is the tetralone such as **108** (Scheme 30), which could probably be converted into the corresponding naphthalene. This manganese-mediated radical cyclization has since been used for the synthesis of other polycylic systems.[110]



Scheme 30.

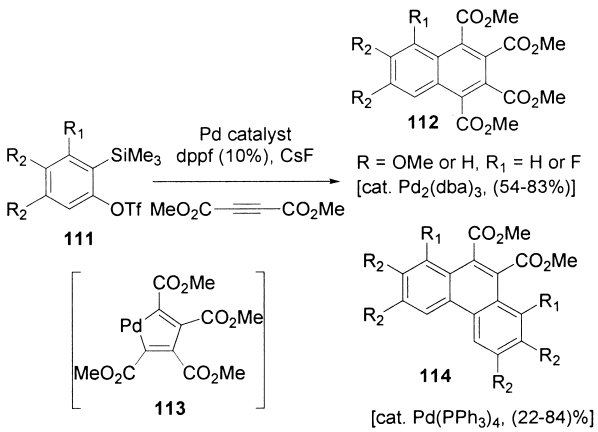
4.3. Palladium-catalysed cyclizations

4.3.1. From arynes. The synthesis of functionalised naphthalenes by the palladium-catalysed reaction of arynes with alkynes has been reported mainly by two groups. Yamamoto and co-workers generated benzynes from compound **109** by reaction with cesium fluoride, followed by a controlled carbopalladation with allyl chloride and functionalised alkynes to afford naphthalenes **110** in moderate yields.[111,112] A mechanism is proposed in Scheme 31.



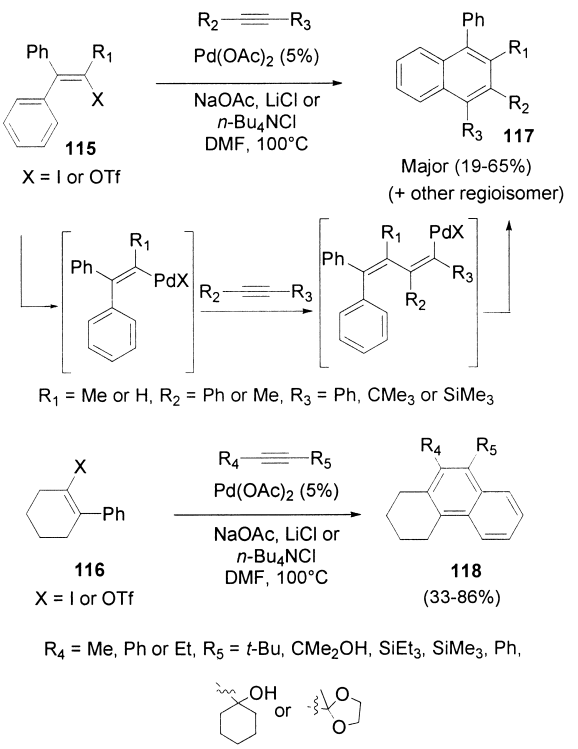
Scheme 31.

Pérez and co-workers generated benzynes in a similar fashion from **111**, and subsequent palladium-catalysed cocyclization of the benzynes with alkynes gave naphthalenes **112** in good yields (54–83%), probably via the formation of intermediate **113** (Scheme 32).[113,114] Of particular interest was their observation that the use of $Pd_2(dba)_3$ (dba=dibenzylideneacetone) gave naphthalenes **112** as the major products, while using $Pd(PPh_3)_4$ as catalyst afforded mainly phenanthrenes **114**.



Scheme 32.

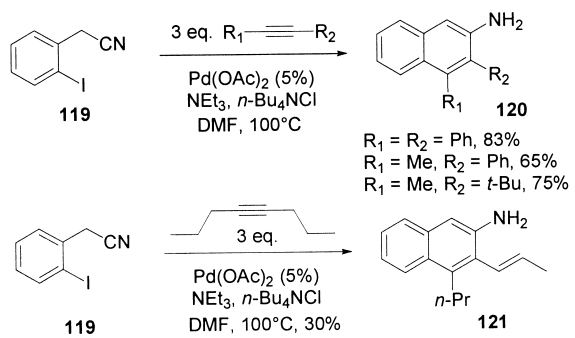
4.3.2. From vinylic iodides and triflates. Larock and co-workers have used the palladium-catalysed annulation of alkynes with vinylic iodides and triflates in their strategy towards functionalised naphthalenes as shown in Scheme 33.[115–118] The vinylic iodides and triflates used



Scheme 33.

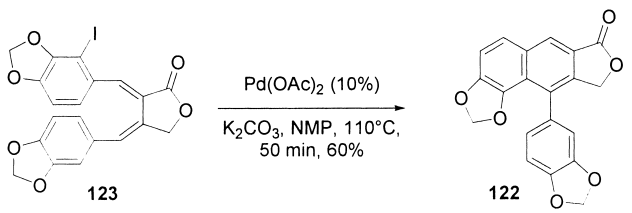
were of types **115** and **116** and all contained phenyl substituents. The resulting substituted naphthalenes **117** and **118** were isolated in low to good yields, and displayed a wide range of functional diversity. Possible intermediates involved in the synthesis of naphthalene **117** are included in Scheme 33.

An interesting route to functionalised 2-aminonaphthalenes was discovered by the Larock group when phenylacetonitriles **119** were treated with internal alkynes and a palladium catalyst (Scheme 34).[119] The 2-naphthylamines **120** were isolated in good yields, and only the reaction with 4-octyne resulted in a surprising product, 2-amino-3-(1-propenyl)-4-*n*-propylnaphthalene **121**, albeit in a rather disappointing yield. Larock and co-workers have also published other related approaches to naphthalenes.[120]



Scheme 34.

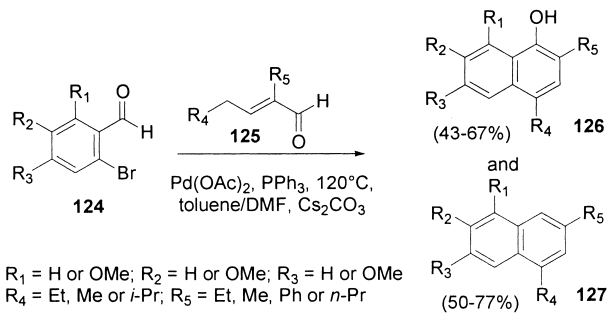
4.3.3. Miscellaneous annulations. The arylnaphthalene lignan lactone helioxanthin **122** was synthesized by Mizufune and co-workers by a novel regioselective benzannulation reaction from lactone **123** utilizing palladium acetate as catalyst (Scheme 35).[121] The proposed mechanism involves an initial oxidative addition of the catalyst into the aryl–halide bond followed by *syn* insertion into the intramolecular alkene. Although it is a single example, conceivably this reaction could be generalised for the synthesis of a variety of substituted naphthalenes.



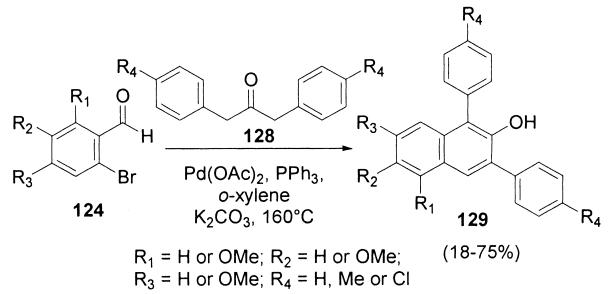
Scheme 35.

The synthesis of functionalised naphthols and naphthalenes by palladium-catalysed annulation of *o*-bromobenzaldehydes with carbonyl compounds has been elegantly exploited by the group of Miura.[122] When *o*-bromobenzaldehydes **124** reacted with α,β-unsaturated aldehydes **125** in the presence of palladium acetate, a mixture of naphthols **126** and naphthalenes **127** was isolated in reasonable yields (Scheme 36).

An extension of this work is shown in Scheme 37. Similar *o*-bromobenzaldehydes **124** were treated with diaryl-2-propanones **128**, and the products **129** were produced.

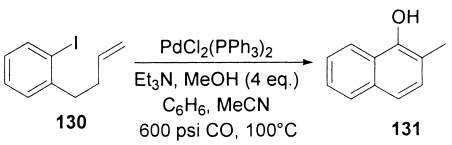


Scheme 36.



Scheme 37.

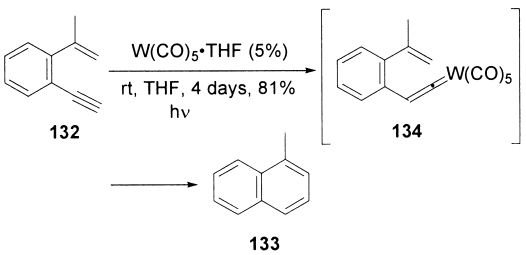
Another way to make substituted naphthols that has not been used extensively is to introduce the oxygen-bearing carbon atom as carbon monoxide. This has been done using a palladium-catalysed carbonylative cyclization reaction that converts substrate **130** into naphthol **131** as shown in Scheme 38.[123] Although this is the sole example presented, the method has potential for the synthesis of a variety of naphthols. Work utilizing palladium-mediated enyne-allene cycloaromatization resulting in the formation of substituted naphthalenes has also been published by Saalfrank and co-workers[124]



Scheme 38.

4.4. Transition metal-mediated electrocyclization

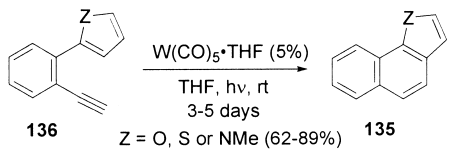
Work done by Iwasawa and co-workers involving treatment of aromatic enynes with a catalytic amount of $W(CO)_5$·THF, has been shown to afford naphthalene products.[125–127] For example, treatment of **132** with $W(CO)_5$·THF gave methylnaphthalene **133** by way of proposed vinylidene intermediate **134** (Scheme 39). This



Scheme 39.

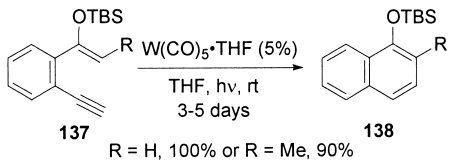
intermediate underwent a $_{\pi}6$ electrocyclic process followed by 1,2-hydrogen migration and regeneration of the catalyst to afford **133** in 81% yield.

This relatively new application of tungsten vinylidene intermediates gave 1-substituted and 1,2-disubstituted naphthalenes in moderate to excellent yields ranging from 31 to 100%. However, long reaction times of 3–5 days were required if catalytic amounts of tungsten were used. 2-Monosubstituted naphthalenes were not formed, and the nature of the starting material and proposed intermediates of the reaction prevent substitution at positions 3 and 4 of the newly formed ring. Naphtho-fused heterocycles (such as **135**) were also synthesized from substrates **136** in high yield (Scheme 40).[127]



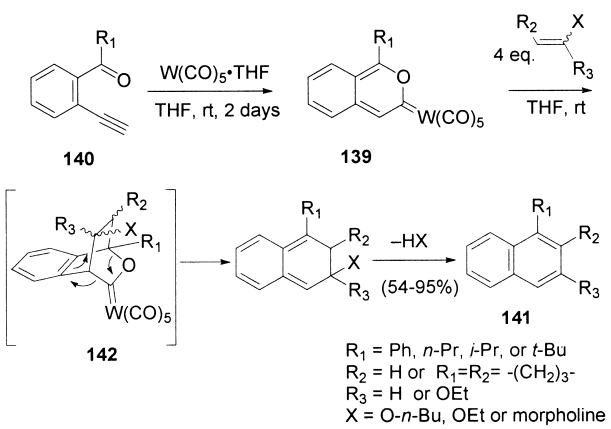
Scheme 40.

Another innovation developed by this group showed that silyl enol ethers such as **137** gave functionalised naphthalenes **138** in excellent yields (Scheme 41).



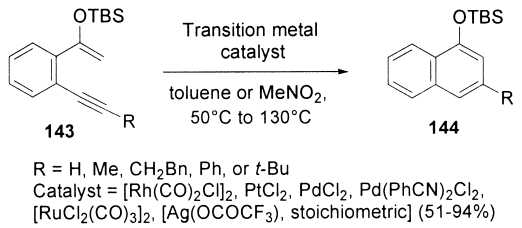
Scheme 41.

The Iwasawa research group succeeded in isolating the tungsten intermediates **139**, prepared from precursors **140**.[125] These compounds were then submitted to a Diels–Alder reaction with electron-rich alkenes. The resultant functionally diverse naphthalene derivatives **141**, presumably obtained by way of intermediate **142**, were isolated in good yields as shown in Scheme 42.



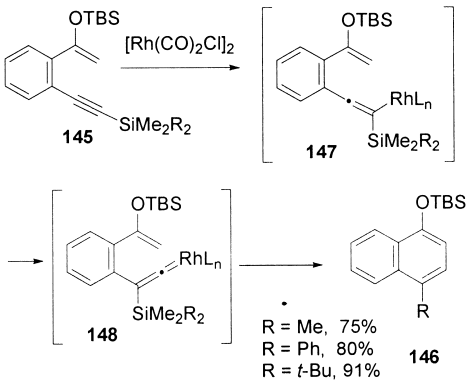
Scheme 42.

The cyclization of alkynyl silyl enol ethers such as **143** (Scheme 43) by a variety of different transition metal complexes has been pursued by Dankwardt.[128] The catalysts, based on rhodium, platinum, palladium and ruthenium, all gave the desired naphthalenes **144** in excellent yields. A noteworthy point is that even a silver complex was able to perform the transformation, although only if present in stoichiometric amounts.



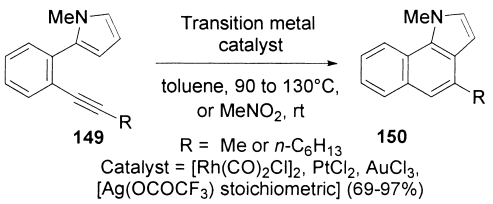
Scheme 43.

Of additional interest was the observation that naphthalenes formed from precursors that contained a silyl-substituted acetylene such as **145**, were functionalised at the 4- rather than at the 3-position in product **146**.[128] The proposed mechanism for the reaction is shown in Scheme 44 and involves rhodium complexes **147** and **148**.



Scheme 44.

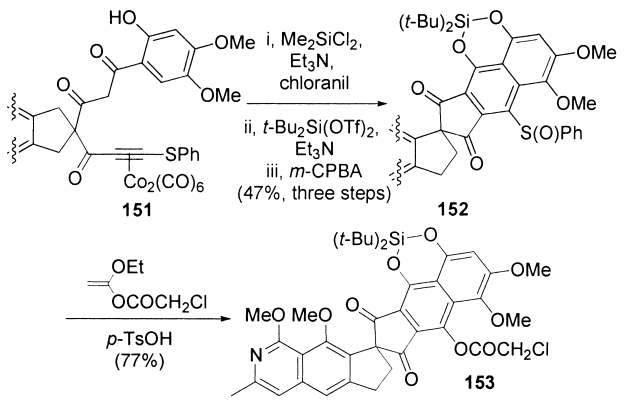
Dankwardt has applied the same reaction to the substituted pyrrole system **149**, and found that the transition metal catalysts were highly proficient in performing the required cyclization reaction to afford pyrrolo-fused naphthalenes **150** in good yields (Scheme 45).[128]



Scheme 45.

4.5. Cobalt-mediated reactions

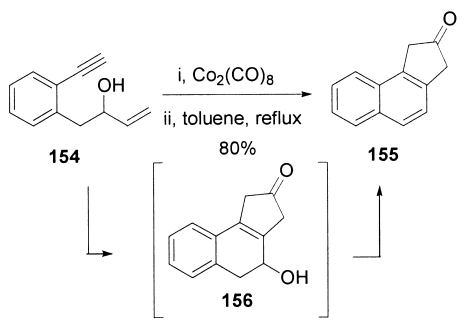
Kita and co-workers have published an interesting oxidative intramolecular [4+2] cycloaddition reaction of (phenylthio)acetylene-cobalt complex **151** which afforded compound **152** containing a multi-substituted naphthalene motif (Scheme 46).[129] This was followed by an aromatic



Scheme 46.

Pummerer-type reaction to replace the sulfinyl group with an oxygen functionality to give **153**, an advanced precursor to fredericamycin A. This may not be a general method for the synthesis of naphthalenes, but shows promise as an alternative approach to complex naphthalene skeletons.

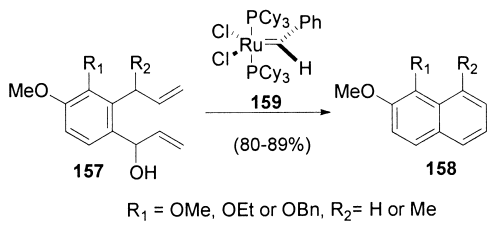
The Pauson–Khand reaction has also been used to synthesize a substituted naphthalene. As shown in Scheme 47, exposure of substrate **154** to $Co_2(CO)_8$ in refluxing toluene gave naphthalene **155**, presumably through intermediate **156**. The scope of this reaction needs to be explored further, and provided that a variety of substrates similar to **154** can be formed easily, this could be a versatile method for the formation of cyclopentanone-fused naphthalenes.[130]



Scheme 47.

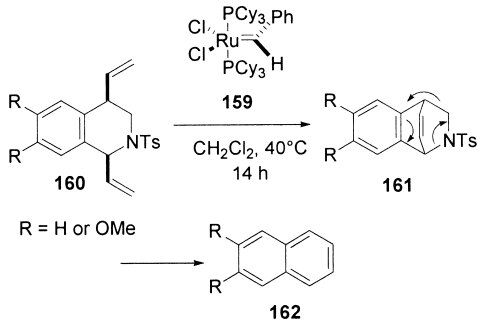
4.6. Ruthenium-catalysed ring-closing metathesis

Ring-closing metathesis (RCM) has recently emerged as a versatile method for constructing small to medium cyclic systems, and several examples of naphthalene syntheses have been published. Huang and Wang have synthesized suitable RCM precursors **157** and then formed the functionalised naphthalenes **158** in high yield using the Grubbs catalyst **159** (Scheme 48).[131]



Scheme 48.

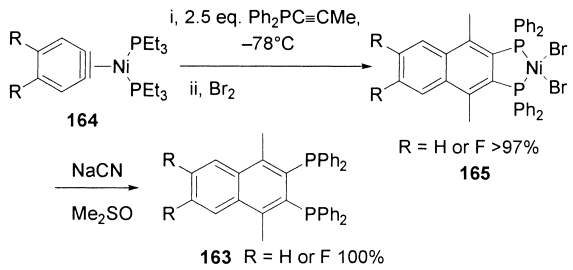
Grigg and co-workers have communicated the use of RCM in the synthesis of two naphthalenes from *N*-tosyl protected tetrahydroisoquinolines **160** (Scheme 49).[132] Metathesis and subsequent expulsion of the tosylimine fragment from intermediate **161** gave the naphthalenes **162** in unspecified yields, amongst other products.



Scheme 49.

4.7. Nickel-mediated cyclization

Elegant work by Bennett and co-workers has led to the regioselective synthesis of 2,3-naphthylenebis(diphenylphosphines) **163** starting from nickel(0)-benzyne complexes **164** (Scheme 50).[133] The reaction of benzyne **164** with diphenylprop-1-ynylphosphine at low temperatures with subsequent addition of bromine resulted in high yields of nickel complex **165**. Reaction of this complex with sodium cyanide afforded the bis(diphenylphosphines) **163**, which could be oxidized to their mono or bis(phosphine oxides). A topical microreview has recently been published on this work.[134]



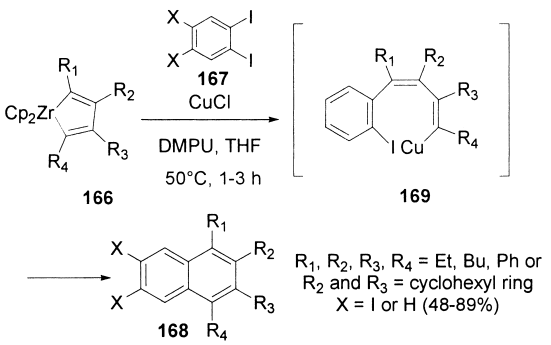
Scheme 50.

4.8. Copper, zinc and tin mediated cyclization of zirconocene complexes

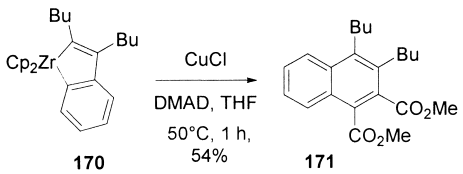
The copper-mediated coupling of zirconacyclopentadienes **166** with di- and tetra-halobenzenes **167** has been used by Takahashi and co-workers to synthesize a range of polyfunctional naphthalenes **168** (Scheme 51).[135] The reaction is thought to proceed via intermediate **169** and yields for a variety of highly functionalised naphthalenes were moderate to good.

Further extensions to this work have led to the reaction of zirconaindene **170** with dimethylacetylene dicarboxylate (DMAD) to afford naphthalene **171** in 54% isolated yield (Scheme 52).[136]

More recently, Duan has demonstrated that zirconaindenes **172** undergo reactions with allyl bromide and zinc bromide,

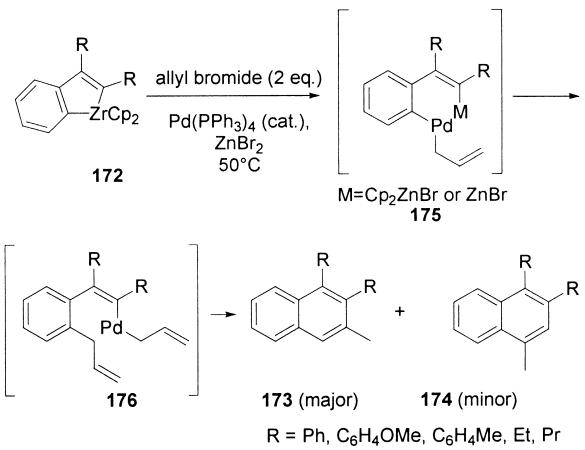


Scheme 51.



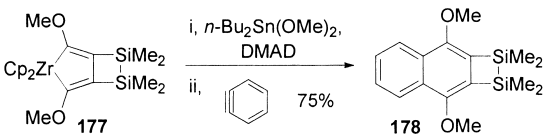
Scheme 52.

in the presence of a catalytic quantity of $Pd(PPh_3)_4$, to afford naphthalenes as a mixture of regioisomers **173** and **174** by way of proposed intermediates **175** and **176** (Scheme 53).[137] When R was a phenyl or substituted phenyl group, only the major regioisomer **173** was isolated in yields of 40–59%.



Scheme 53.

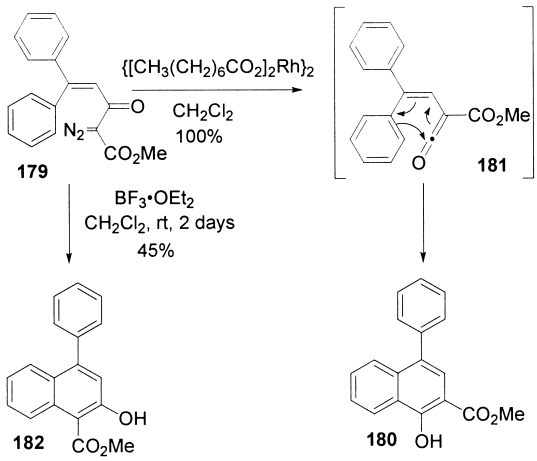
Finally, in this section, when the substituted zirconacyclopentadiene **177** was treated with a mole equivalent of dibutyltin dimethoxide, DMAD and benzyne, the disilylnaphthalene **178** was formed in good yield (Scheme 54).[138]



Scheme 54.

4.9. Rhodium-mediated cyclization

The group of Karady and Reamer found during a revision of their earlier published work that the rhodium-catalysed decomposition of diazoketone **179** afforded near quantitative yields of naphthol **180** (Scheme 55).[139] This result was rationalized as having occurred by a Wolff rearrangement, followed by cyclization of the ketene intermediate **181**. The same group also found that a Lewis-acid promoted ring closure of diazoketone **179** gave regioisomeric naphthol **182** in moderate yields.

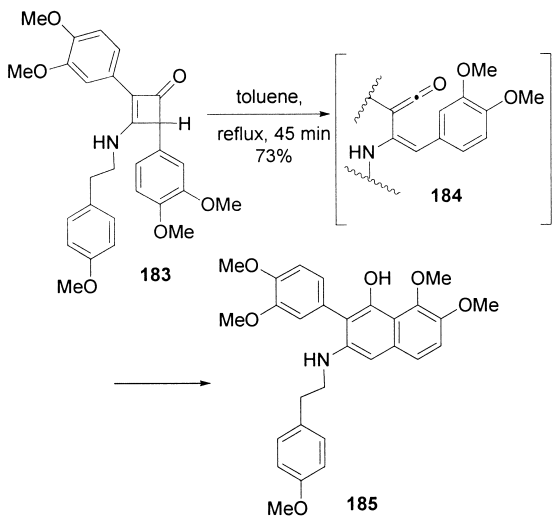


Scheme 55.

5. Rearrangement of strained rings

5.1. Rearrangement of cyclobutenones

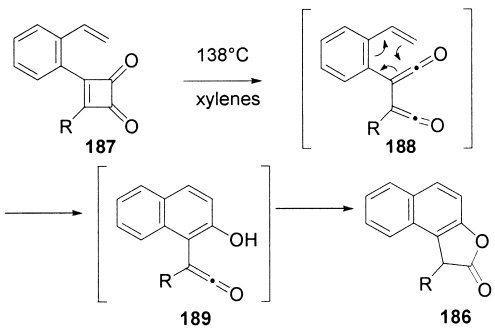
The thermally induced ring expansion of cyclobutenones affords aromatic products in relatively good yields.[140–145] The reaction appears to be tolerant of a wide variety of functional groups, including halides, esters and amines. Like the Fischer carbene benzannulation (Section 4.1) and the rhodium-catalysed reaction shown above, this reaction also proceeds through a dienylketene intermediate (Scheme 56). For example, thermolysis of **183** gave the ketene intermediate **184**, which, upon electrocyclic ring closure, formed the naphthol **185** in 73% yield.[146,147]



Scheme 56.

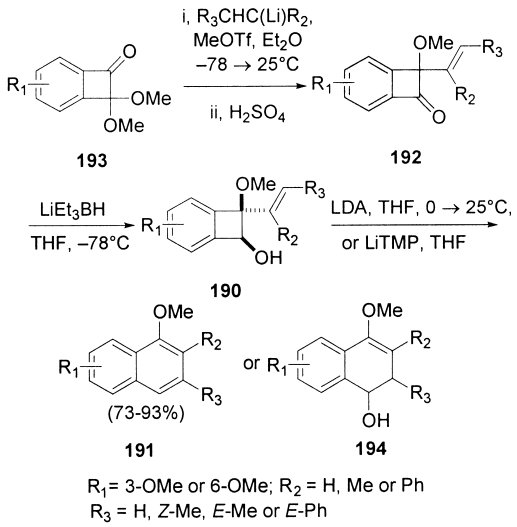
Moore has extended this work to the synthesis of naphtho[2,1-*b*]furan-2(3*H*)-ones **186**[148] and annulated furans.[149] The naphthofuranones were produced in

moderate to good yields by heating the corresponding cyclobutenediones **187** in xylene (Scheme 57). The mechanism of this reaction probably involves electrocyclic ring opening to dienyl ketene **188** followed by a $_{\pi}6$ electrocyclization and addition of the phenol to the ketene as depicted in intermediate **189**.[146]



Scheme 57.

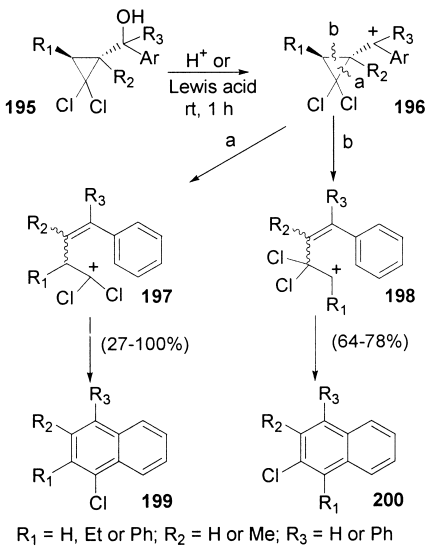
Another interesting rearrangement of the cyclobutenone skeleton has been demonstrated by Suzuki and co-workers in their base-promoted ring expansion of 2-alkoxy-2-vinylbenzocyclobutenols **190** to naphthalene derivatives **191** (Scheme 58).[150] The precursors **192** were prepared in high yield by the addition of an ethenyllithium reagent to **193**. Reduction of the ketone functionality produced the intermediate alcohol **190**. Lithium dialkylamides were then effective in facilitating the conversion of **190** into the naphthalenes **191**. When R_2 was H or Me, alcohol **194** was stable to dehydration during silica gel chromatography and was isolated in good to excellent yields. This method results in the formation of naphthalenes substituted at positions 1-, 2- and 3- of the newly formed ring.



Scheme 58.

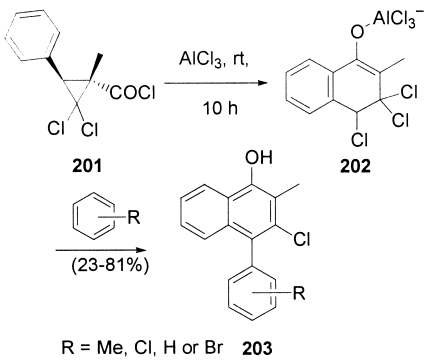
5.2. Rearrangement of cyclopropanes

Tanabe et al. have described the synthesis of halogenated naphthalenes and naphthols from suitably substituted cyclopropanes. Their synthesis of halogenated naphthalenes was brought about by the acid-catalysed ring opening of aryl(2,2-dihalocyclopropyl)methanols **195**, as outlined in Scheme 59.[151–153] One of two possible bond cleavages of **196** occurs, depending on the stability of the resulting carbocation intermediate **197** or **198**. The cation then undergoes an intramolecular Friedel–Crafts reaction to afford the corresponding naphthalene product **199** or **200**. Yields for a wide variety of functionalised naphthalenes were moderate to excellent.



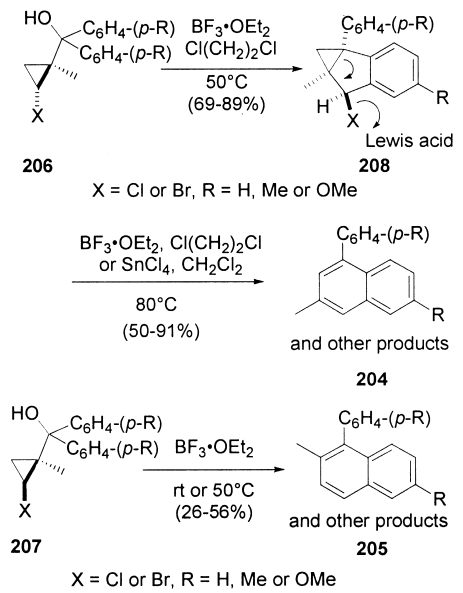
Scheme 59.

In a related transformation, the synthesis of naphthols has been achieved by two sequential Friedel–Crafts reactions of 3-aryl-2,2-dihalocyclopropanecarbonyl chlorides such as **201**.[154] An intramolecular cyclization similar to that shown in the previous scheme afforded intermediate **202**. This was followed by a second, intermolecular Friedel–Crafts coupling reaction to yield the naphthols **203** in moderate yields (Scheme 60).



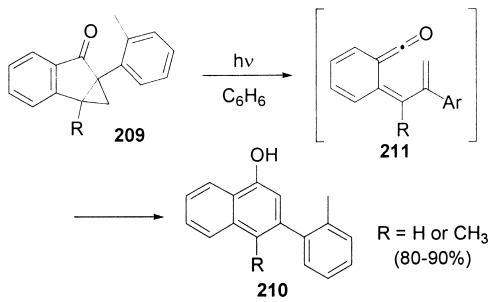
Scheme 60.

In other recently published work, Tanabe's group has synthesized regioisomeric naphthalenes **204** and **205** starting from the two cyclopropyl diastereoisomers **206** and **207**, respectively (Scheme 61).[155] This rearrangement is thought to go through an intermediate such as **208**, the stereochemistry of which determines the direction of ring expansion to give the two possible products. These last three methods provide a useful route to halogenated naphthalenes that could find application in metal-mediated coupling reactions.



Scheme 61.

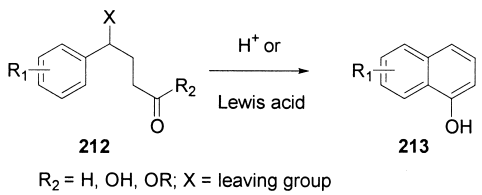
Chang and Park have reported a photoinduced rearrangement of benzobicyclo[3.1.0]hexanones **209** to give 1-naphthols **210**, probably via the dienyl ketene intermediate **211** (Scheme 62).[156] Yields of the biaryl products are good to excellent. It should be noted, however, that only two examples of this reaction have been published.



Scheme 62.

6. Acid- and Lewis acid-catalysed intramolecular cyclizations

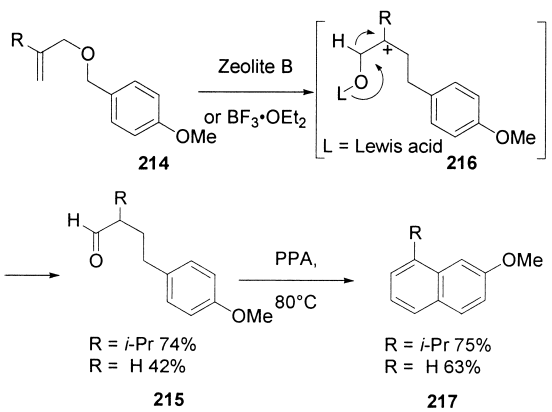
The naphthalene backbone can be synthesized by an intramolecular Friedel–Crafts acylation reaction. There are a number of variations of this method; however, each requires the formation of a suitably substituted aromatic precursor such as **212**. A limitation to this method is that the aromatic ring often has to be electron rich. However, in general, treatment of **212** with acid or a Lewis acid affords naphthol product **213** (Scheme 63). If the precursor is the carboxylic acid (i.e. R_2=OH), reaction with a chloroformate



Scheme 63.

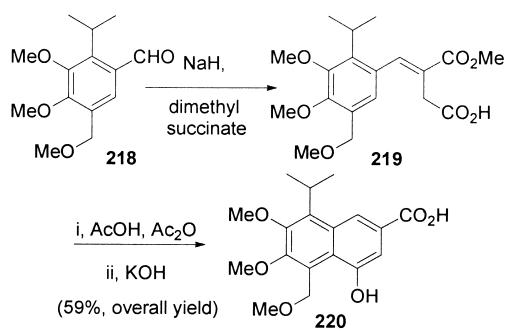
or trifluoroacetic anhydride affords naphthols of type **213**. A number of variations on this theme have been reported.[157]

Traditional methods for synthesising precursors such as compound **212** include, for example, the reaction of benzene with succinic anhydride in the presence of aluminum trichloride.[158] However some more recent methods do exist. For example, in the presence of zeolite β or $BF_3{\cdot}OEt_2$, certain benzyl allyl ethers **214** rearrange to the desired precursors **215**.[159] The reaction presumably proceeds by a 1,4 rearrangement followed by a 1,2-hydride shift as depicted in intermediate **216** (Scheme 64). When **215** was treated with polyphosphoric acid at elevated temperatures, naphthalene products **217** were isolated in moderate yields.



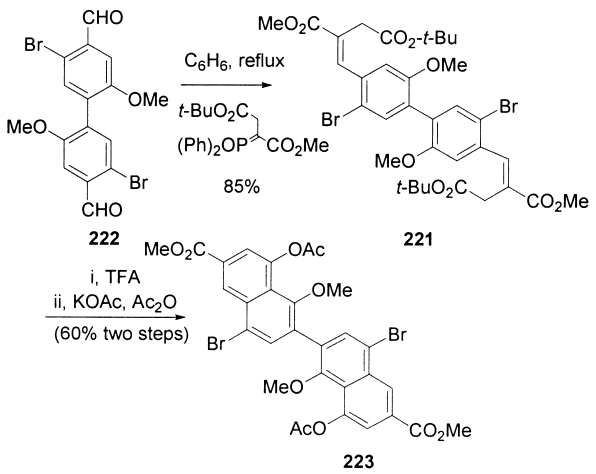
Scheme 64.

The Stobbe condensation has also been widely used in the synthesis of precursors such as **212**.[160] This condensation involves the reaction of an aromatic aldehyde with dimethyl or diethyl succinate. Recently, the Stobbe condensation has been utilized in the synthesis of (*S*)-(+)-gossypol **3**, the initial steps of which are shown in Scheme 65.[5,161] The aldehyde **218** was treated with dimethyl succinate and sodium hydride to afford the naphthalene precursor **219**. Treatment of compound **219** with a mixture of acetic acid and acetic anhydride effected cyclization to naphthalene **220**, which was isolated in 59% yield over three steps from aldehyde **218**. Other recent examples using similar methodology have also been published.[162]



Scheme 65.

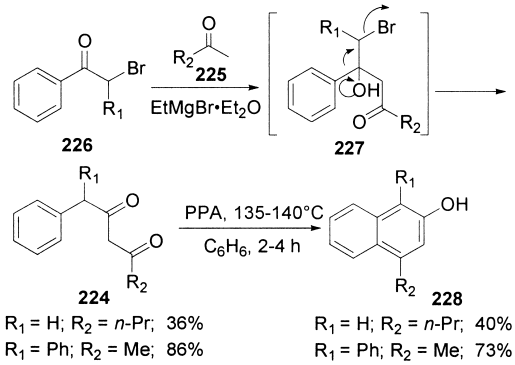
Sargent et al. employed a Wittig alternative to the Stobbe condensation in their synthesis of the toxin stypandrol.[163,164] As shown in Scheme 66, the naphthalene precursor **221** was synthesized in 85% yield by treatment of the dialdehyde



Scheme 66.

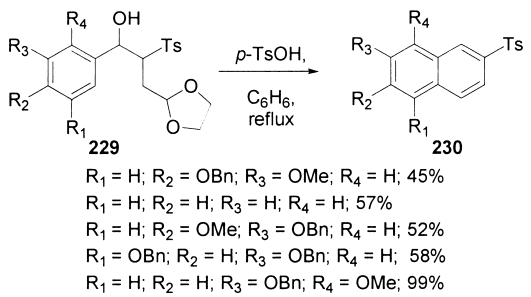
222 with a suitably substituted phosphorus ylide. Cyclization to the desired binaphthyl **223** was achieved by treatment of **221** with trifluoroacetic acid, followed by heating to reflux with potassium acetate and acetic anhydride. The binaphthyl product was isolated in reasonable yield from compound **221**. This approach has also been used by other researchers in the synthesis of natural products and analogues.[165,166]

Diones **224** have been used in intramolecular Friedel–Crafts reactions to afford substituted naphthalenes (Scheme 67). These precursors **224** were synthesized from methyl ketones such as **225** and aromatic α-bromo ketones **226**.[167] Treatment of the methyl ketone **225** with a magnesium base and reaction with **226** resulted in the formation of the desired 1-aryl-2,4-dione **224** by means of a 1,2-aromatic shift (as shown in **227**). Subsequent acid-mediated cyclization afforded the 1,4-disubstituted-2-naphthols **228** in moderate yields as shown in Scheme 67.



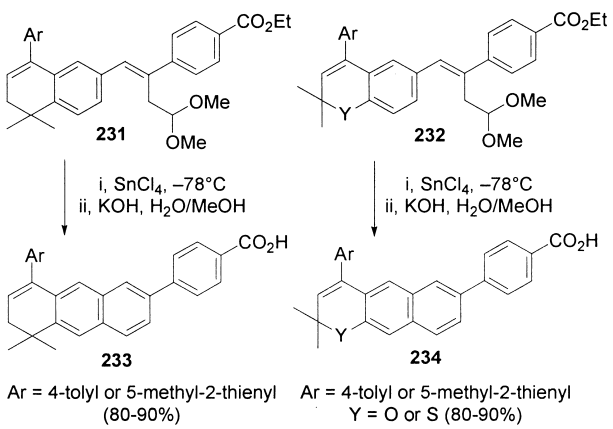
Scheme 67.

Another variation in the acid-catalysed synthesis of naphthalenes is by way of the acetal-protected benzene derivative **229**, as described by Chern and co-workers[168] (Scheme 68) and others.[169,170] The naphthalenes **230** synthesized by this method were isolated in moderate to good yields and were substituted at the 2-position on the newly formed ring.



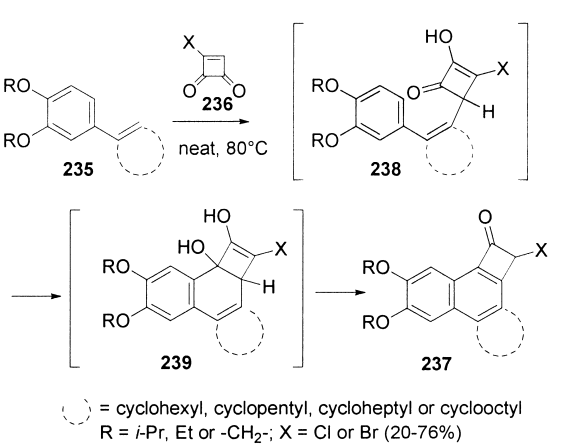
Scheme 68.

A related synthesis of polyfunctionalised naphthalenes has been reported by Vuligonda, Chandraratna and co-workers, who cyclized the *E*-geometrical isomers **231** and **232** with tin tetrachloride, followed by base mediated hydrolysis to give naphthalenes **233** and **234**, respectively, in excellent yields (Scheme 69).[171]



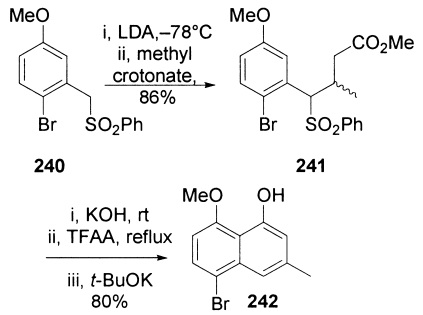
Scheme 69.

Schmidt and co-workers have reported the related annulation of aromatic dienes such as **235** with α-halobenzocyclobutenones **236** to produce fused naphthalenes **237** in poor to moderate yields (Scheme 70).[172] The proposed mechanism includes the two intermediates **238** and **239**. Of particular interest is that in this example a Lewis acid was unnecessary for the reaction to proceed.



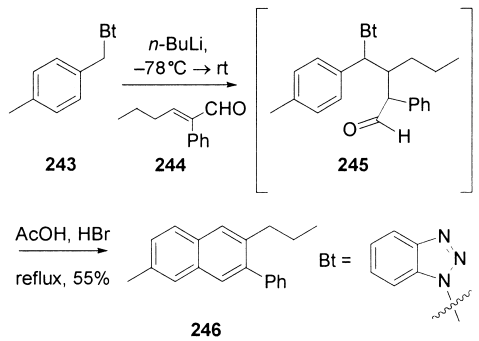
Scheme 70.

Hoye and co-workers utilized an acid-mediated transformation in their synthesis of the naphthalene portion of the michellamines (Scheme 71).[66,173] However, in this method the aromatic portion acts as the nucleophile. The 1,4-addition of the anion derived from sulfone **240** to methyl crotonate afforded **241** in 86% yield in a similar manner to the first step of the phthalide annulation. Hydrolysis of the ester, cyclization and aromatization gave the naphthalene **242** in 80% overall yield from **241**.



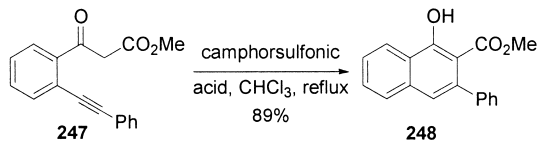
Scheme 71.

In a similar fashion, Katritzky et al. have employed the electron-withdrawing ability of the benzotriazole group to facilitate lithiation of aromatic precursors such as **243**.[174] These lithio derivatives readily undergo 1,4-addition with a variety of α,β-unsaturated ketones and aldehydes, for example **244**, as shown in Scheme 72. The intermediate addition product **245** then cyclized in situ in the presence of a mixture of acetic acid and hydrobromic acid, or polyphosphoric acid to afford the naphthalene **246** in a moderate yield. A representative example of the eight naphthalenes synthesized is described in Scheme 72.



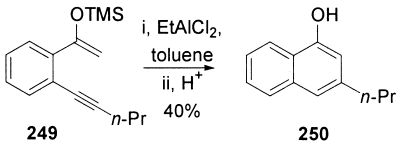
Scheme 72.

Another interesting synthesis of naphthalenes which is acid catalysed involves the treatment of substituted phenylacetylenes such as **247** with camphorsulfonic acid in hot chloroform to afford naphthol **248** (Scheme 73).[175] This work has been applied to a number of substrates to afford 2,3-disubstituted-1-naphthols.



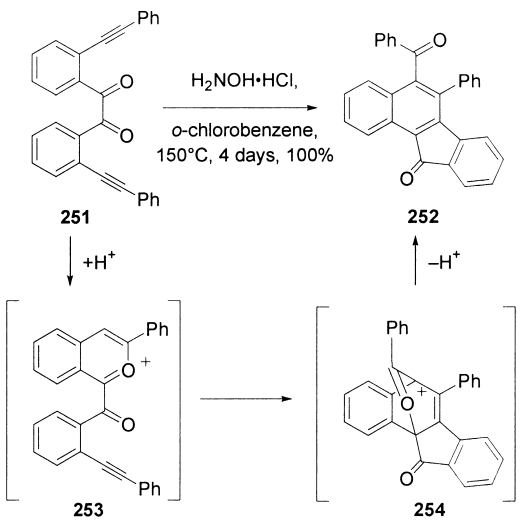
Scheme 73.

A related benzannnulation example has been reported by Yamamoto and co-workers (Scheme 74).[176] Treatment of the silyl enol ether **249** with a Lewis acid such as ethylaluminium dichloride resulted in the formation of naphthol **250** in moderate yield.



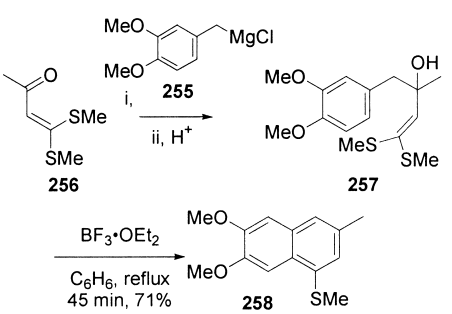
Scheme 74.

An interesting but isolated example of the rearrangement of bisalkynylbenzil **251** to afford the substituted naphthalene **252** has been reported (Scheme 75).[177] The authors postulate that the fused naphthalene **252** is formed by way of cationic intermediates **253** and **254**.



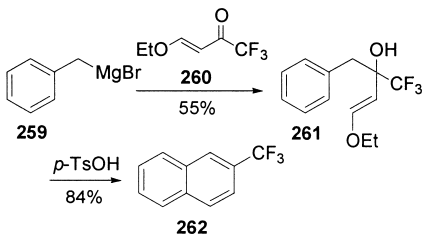
Scheme 75.

The condensation of α-oxoketene dithioacetals with aryl Grignard reagents has been employed by Junjappa and co-workers in their synthesis of substituted naphthalenes.[178–180] For example, the 1,2-addition of Grignard reagent **255** to α-oxoketene dithioacetal **256** gave the carbinol intermediate **257**. Lewis acid-catalysed cyclization of **257** afforded the naphthalene **258** in good yield (Scheme 76).



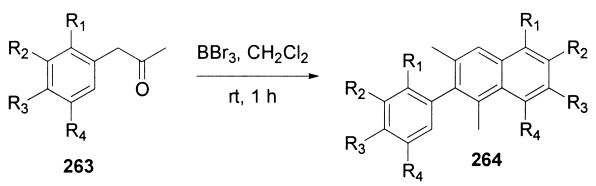
Scheme 76.

Another example of the use of Grignard reagents in the preparation of Friedel–Crafts precursors has been published by Mellor et al.[181] Reaction of benzylmagnesium bromide **259** with compound **260** afforded intermediate **261**, which, on treatment with *p*-toluenesulfonic acid afforded the trifluoromethylnaphthalene **262** (Scheme 77). With this methodology a number of substituted naphthalenes could be produced in good yields.



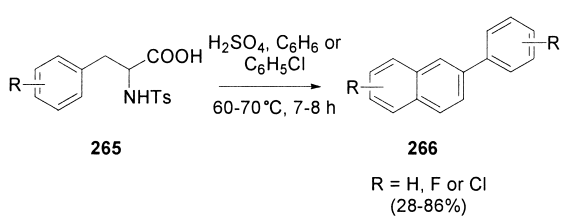
Scheme 77.

Cotelle and co-workers have reported the dimerisation of arylacetones **263** with boron tribromide to afford arylnaphthalenes **264** in moderate to good yields.[182–185] Some examples are illustrated in Scheme 78.



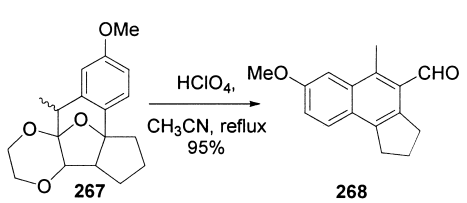
Scheme 78.

2-Arylnaphthalenes have been prepared by Kim et al. by treating *N*-tosylated phenylalanine derivatives **265** with sulfuric acid.[186] A number of naphthalene products **266** were isolated in yields of 26–86% using this method (Scheme 79).



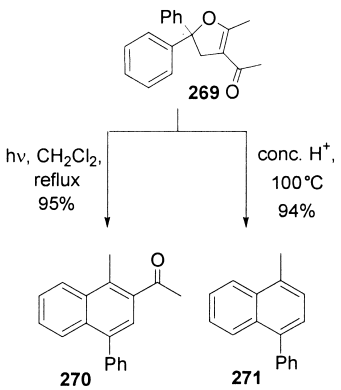
Scheme 79.

The acid catalysed rearrangement of some complex substrates has led to the formation of substituted naphthalenes. For example, exposure of **267** to $HClO_4$ afforded naphthalene **268** in high yield (Scheme 80).[187] This remarkable rearrangement is probably driven by the stability of the aromatic system, with the benzylic methyl group of **267** becoming the α-methyl substituent in the product **268**.



Scheme 80.

Finally, in this section, exposure of precursor **269** to light afforded acetylnaphthalene **270** (Scheme 81).[188] Interestingly, in the presence of protic acid but in the absence of light, deacetylated naphthalene **271** was produced from the same starting material **269** in high yield.

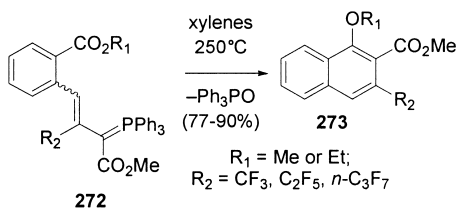


Scheme 81.

7. Phosphorus ylides in the synthesis of naphthalenes

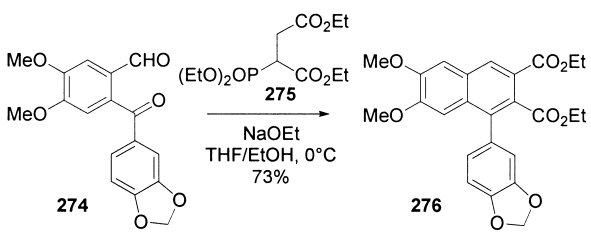
Only a few examples of phosphorus-assisted naphthalene syntheses have been recently reported as outlined below.

The first includes the synthesis of the naphthalene nucleus by an intramolecular Wittig reaction as shown in Scheme 82.[189] Thermolysis of the ylides **272** with loss of triphenylphosphine oxide afforded the desired fluoroalkylnaphthalenes **273** in excellent yields.



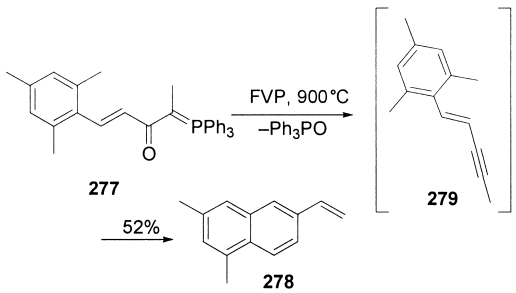
Scheme 82.

A Horner–Emmons reaction between ketoaldehyde **274** and phosphonate **275**, followed by a Claisen condensation was used by Harrowven and co-workers to assemble the lignan framework **276** of justicidin B and retrojusticidin B (Scheme 83).[190]



Scheme 83.

Apart from the Wittig-type reactions, stabilised phosphorus ylides **277** have found application in the synthesis of naphthalenes **278** by the thermal extrusion of triphenylphosphine oxide using flash vacuum pyrolysis (Scheme 84).[191] The reaction presumably occurs by way of intermediate **279**. The naphthalene products such as **278** were isolated in moderate yields.

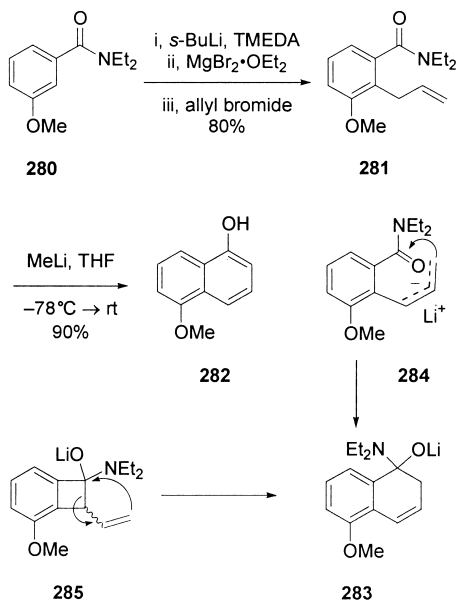


Scheme 84.

8. Anionic ring annulations

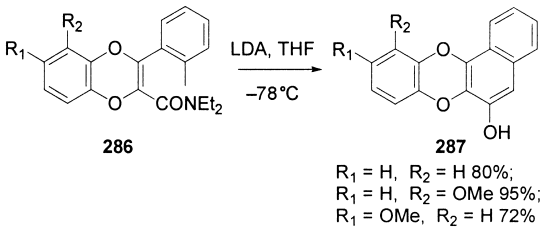
Over the last few years several examples of substituted naphthalene syntheses by way of base-induced methods have been disclosed. In this section of the review we will highlight some examples.

Snieckus and co-workers have used a novel anionic cyclization reaction in the synthesis of substituted naphthols[192] and 9-phenanthrols.[193,194] The precursors for this reaction were synthesized using the extensively reported directed *ortho* metallation methodology developed by this group.[195,196] As shown in Scheme 85, lithiation of aromatic benzamide **280** is directed *ortho* to the amide group, with subsequent transmetallation and substitution with allyl bromide affording the desired *o*-allylbenzamide **281**. Treatment of this precursor with a base such as lithium diisopropylamide or methyllithium resulted in the formation of naphthol **282** in good yield. An investigation of the mechanism of the reaction has revealed that the naphthol product could be formed from intermediate **283** by two pathways. The first involves direct cyclization from anion **284**, while the second involves formation of benzocyclobutane **285** followed by a [1,3]-sigmatropic rearrangement.



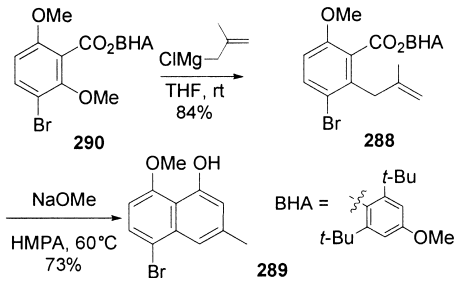
Scheme 85.

A number of years after Snieckus, Coudert and co-workers applied the same anionic cyclization procedure to substrates **286** to synthesize substituted naphthols **287** as described in Scheme 86.[197] Clive et al. have also used the Snieckus methodology to synthesize a naphthalene precursor used in their synthesis of fredericamycin A.[198]



Scheme 86.

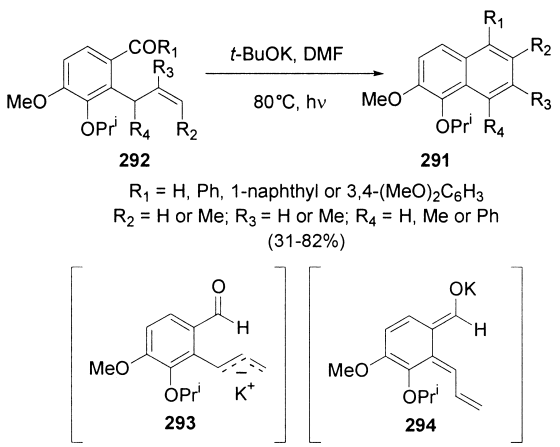
Hattori, Miyano and co-workers have used a base-promoted cyclization strategy to synthesize functionalised naphthols as described in Scheme 87.[199] It was found that reaction of **288** with sodium methoxide in HMPA gave a good yield of naphthol **289**. This naphthol is a key component of the michellamines (such as compound **6**). The synthesis of the precursor **288** was done by way of a nucleophilic aromatic substitution reaction on compound **290**.



Scheme 87.

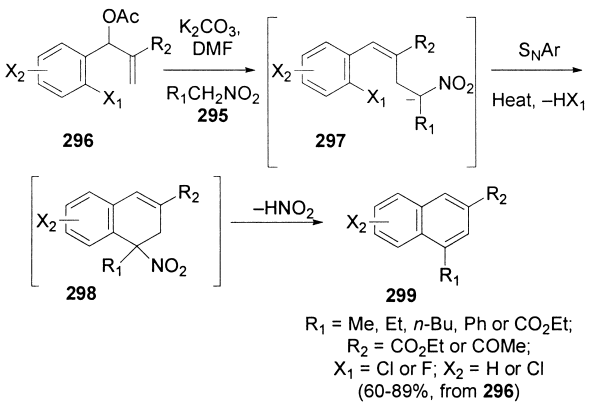
de Koning et al. have described a related base-mediated method which results in the synthesis of naphthalenes **291** rather than naphthols.[200,201] The main difference between this method and those described above is that the carbonyl containing substituent on the aromatic ring is an aldehyde or ketone, as in **292**, rather than an ester. In addition, it has been shown that light from a high pressure mercury lamp promotes this reaction and that much lower yields of naphthalenes are obtained when the reaction is carried out in the absence of light. Therefore, as shown in Scheme 88, the reaction may proceed by either an anionic mechanism, via intermediate **293** or by photoenolisation of **292** affording the possible intermediate **294**.

Kim and co-workers have used the well-known Baylis-Hillman reaction in the regioselective synthesis of substituted naphthalene derivatives (Scheme 89).[202] The nitronate anion generated from nitroalkane **295** was reacted with **296** to afford the Baylis–Hillman adduct **297**



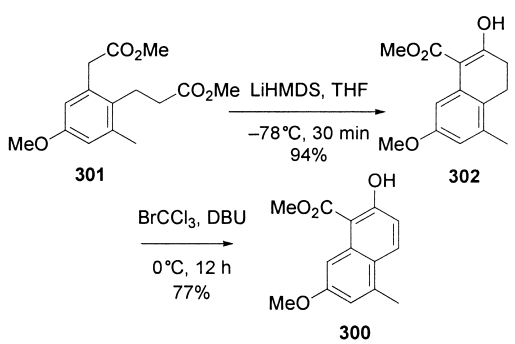
Scheme 88.

predominantly as the *E* isomer. A subsequent nucleophilic substitution on the electron-deficient aromatic ring to give intermediate **298** and elimination of nitrous acid then afforded the functionalised naphthalenes **299** in good to excellent yields.



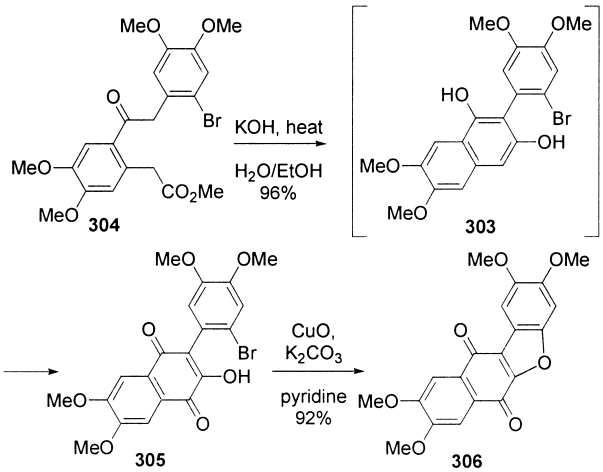
Scheme 89.

Naphthalene **300**, a precursor to neocarzinostatin carboxylic acid, was synthesized by a modified Dieckmann cyclization by Rucker and Brückner.[203] Although sodium methoxide was ineffective in achieving the condensation, lithium hexamethyldisilazide proved efficient in converting diester **301** into enol **302**, which was dehydrogenated to afford the naphthalene core in good yield (Scheme 90).



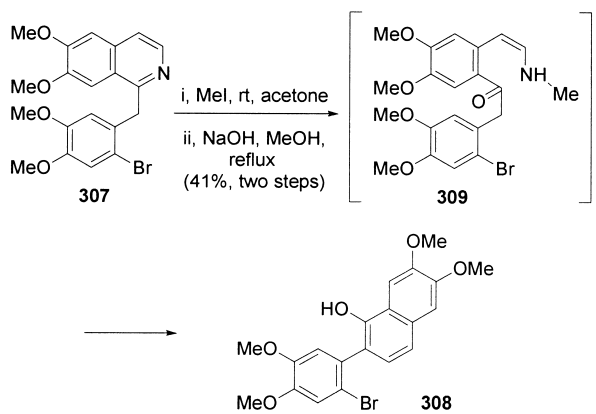
Scheme 90.

This route was also used by the group of Estévez, who formed naphthol **303** from ketone **304** by an intramolecular condensation.[204] The naphthalene product, surprisingly, was oxidized in situ to afford naphthoquinone **305** en route to benzofuronaphthoquinone **306**. This methodology was applied to the synthesis of a number of naphthoquinones, one example of which is illustrated in Scheme 91.



Scheme 91.

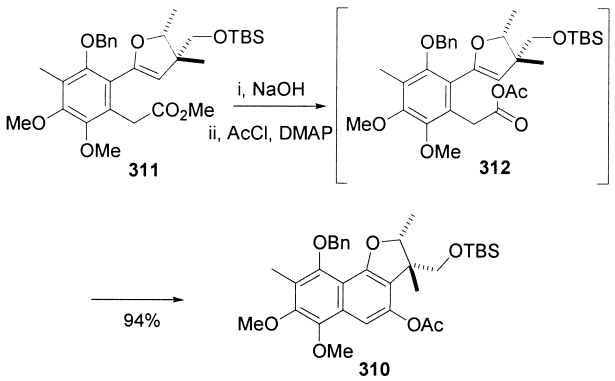
The same family of compounds was synthesized from a papaverine skeleton **307** by this group.[204] A representative example of this approach to afford functionalised naphthalene **308**, by way of intermediate **309**, is described in Scheme 92.



Scheme 92.

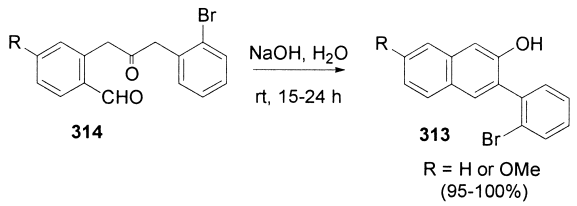
In their total synthesis of the furaquinocins, Suzuki and co-workers utilized an interesting route to naphthalene intermediate **310** (Scheme 93).[205] Saponification of dihydrofuran **311** with base and treatment with acetyl chloride generated mixed anhydride **312**. Heating under basic conditions then afforded naphthalene **310** in excellent yield. The authors postulated that this reaction could proceed by three possible mechanisms: attack by the internal enol ether on the mixed anhydride, formation of a ketene, or enol acetylation followed by electrocyclization.

In their synthetic approach towards benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones, Estévez and co-workers have also synthesized naphthols **313** from benzaldehydes **314** in excellent yields under basic conditions (Scheme 94).[206]



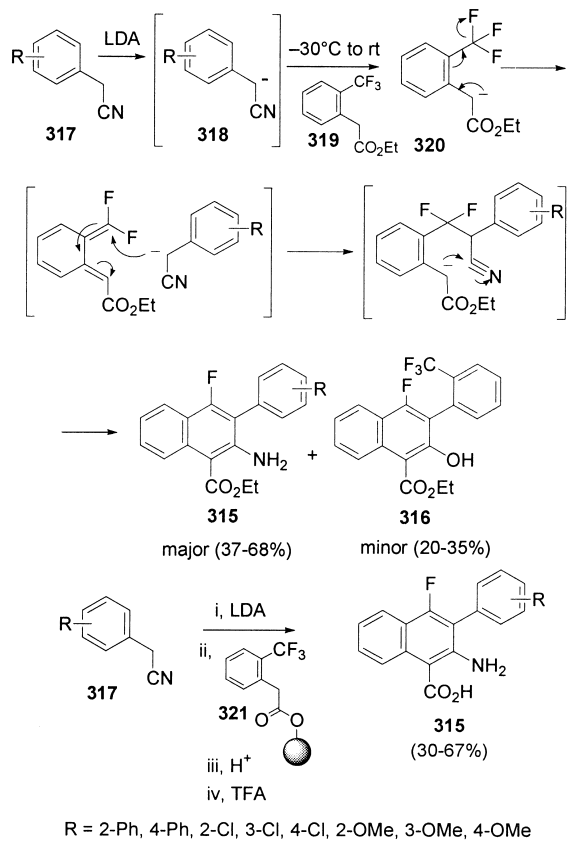
Scheme 93.

Sodium hydroxide facilitated an intramolecular aldol condensation followed by dehydration to give the targets **313** in excellent yields.



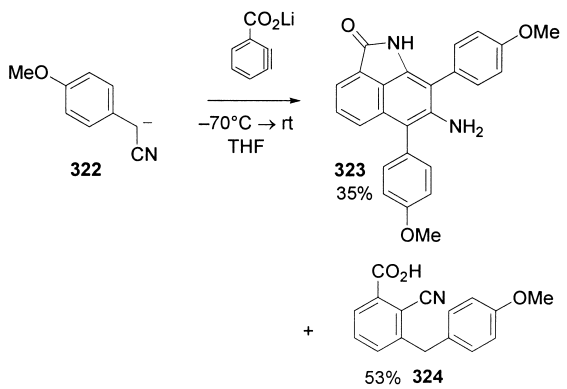
Scheme 94.

Kiselyov recently reported an approach to polysubstituted naphthalenes **315** and **316** from phenylacetonitrile derivatives **317**, which were treated with LDA at low temperature to generate anion **318**.[207,208] The reaction was quenched with ester **319**, and the new anion formed, **320**, then underwent reaction by the pathway proposed in Scheme 95. The major products, isolated in yields of 37–68%, were identified as naphthalene **315** as well as the self-condensation product **316** (20–35%). The product **316** could also be isolated in yields of up to 62% when only **319** was used as the starting material. To avoid the problems of self-condensation, the ester component **319** could be immobilized on a solid support to give **321**; reaction with the anion of **317** then only gave compounds **315** in 30–67% yields.



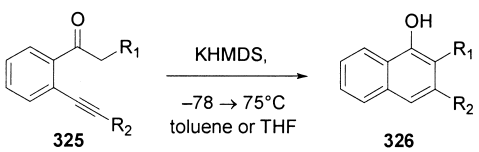
Scheme 95.

The reaction of an aryne with the lithium anion of a phenylacetonitrile such as **322** also constitutes the strategy developed by Biehl and co-workers to synthesize complex naphthylamines of which **323** is a representative example.[209] The yield of this product was 35% and 53% of the rearranged product **324** was also isolated as depicted in Scheme 96.



Scheme 96.

Makra and co-workers have reported that treatment of substrates **325** with base successfully generated functionalised naphthols **326** in good yields (Scheme 97).[210] A point of interest is that their experimental procedure requires the use of bases with potassium as counterion (e.g. potassium *t*-butoxide, potassium hexamethyldisilazide or potassium hydride). This procedure is very similar to the analogous acid-mediated cyclization reported earlier in Scheme 73, Section 6.

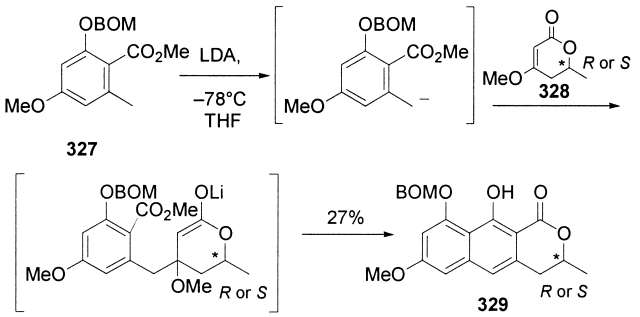


R_1 = H or Me; R_2 = Me, *n*-hexyl, cyclohexyl, *t*-butyl, benzyl or *i*-butyl
(70-95%)

Scheme 97.

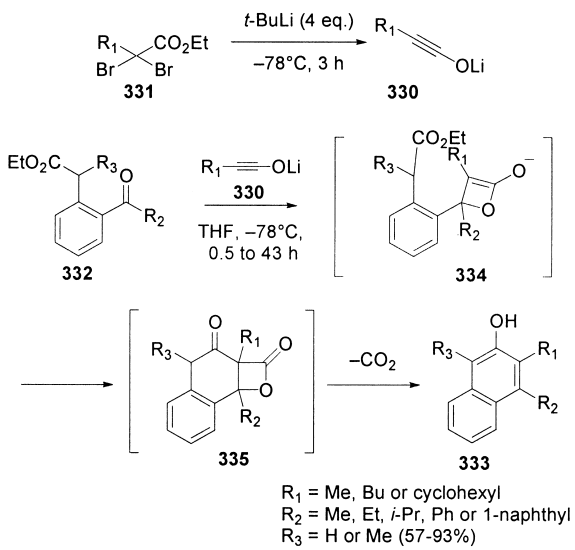
Drochner and Müller have used a tandem Michael reaction between an orsellinate **327** and a cyclic chiral Michael acceptor **328** to synthesize **329**, a precursor to the epimers of semi-vioxanthin (Scheme 98).[211]

Another anionic approach to the synthesis of naphthalenes has been reported by Shindo et al. as depicted in



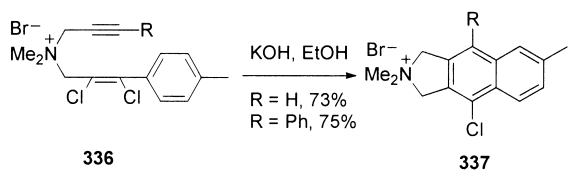
Scheme 98.

Scheme 99.[212] These researchers have generated ynolate anions **330** from α,α-dibromoesters **331**, and then used them in a tandem [2+2] cycloaddition-Dieckmann condensation reaction with ketones **332** to produce highly substituted naphthols **333**. It was postulated that the reaction proceeds via intermediates **334** and **335**.



Scheme 99.

In the final example described in this section, the ammonium salts **336** were transformed to their corresponding naphtho[2,3-*c*]pyrrolinium salts **337** by way of a base-catalysed intramolecular cyclization, as depicted in Scheme 100.[213]

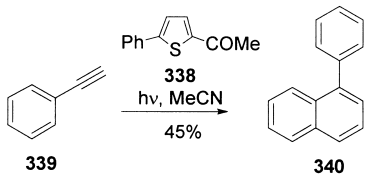


Scheme 100.

9. Photochemically-mediated reactions

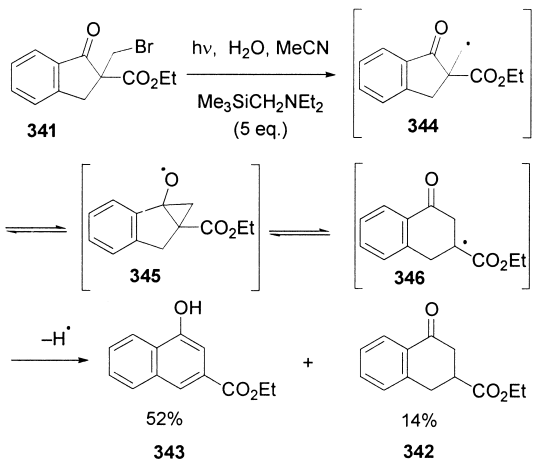
Reactions promoted by light have been a popular topic in modern organic synthesis.[214] Listed below are a number of recent photochemically-mediated reactions that have resulted in the formation of substituted naphthalenes.

D'Auria and co-workers found that irradiation of a solution containing 2-acetyl-5-phenylthiophene **338** and phenylacetylene **339** with a Nd:YAG laser (355 nm) gave 1-phenylnaphthalene **340** as the only detectable product (Scheme 101).[215] This was the only relevant example reported and it was postulated that the substituted thiophene is a sensitizer for this reaction, encouraging generation of the triplet state of phenylacetylene.



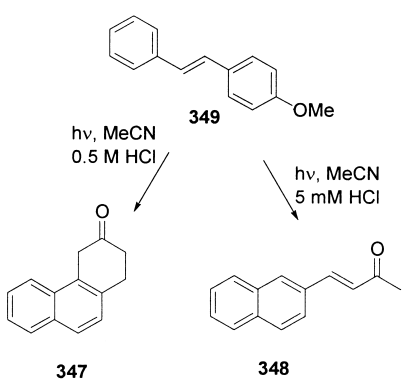
Scheme 101.

During an investigation by Hasegawa concerning the electron transfer photoreaction of halomethyl-substituted benzocyclic ketones such as **341** to give ring-expanded products, it was noted that instead of forming the expected product **342**, which was isolated in only 14% yield, the reaction afforded naphthalene **343** in 52% yield (Scheme 102).[216] The authors postulate that the mechanism includes the one-electron cascade depicted in intermediates **344**–**346**, followed by aromatization.



Scheme 102.

A study of the reaction pathways of stilbene analogues (traditionally used for the synthesis of phenanthrenes[217]) when irradiated in acidic media has resulted in the synthesis



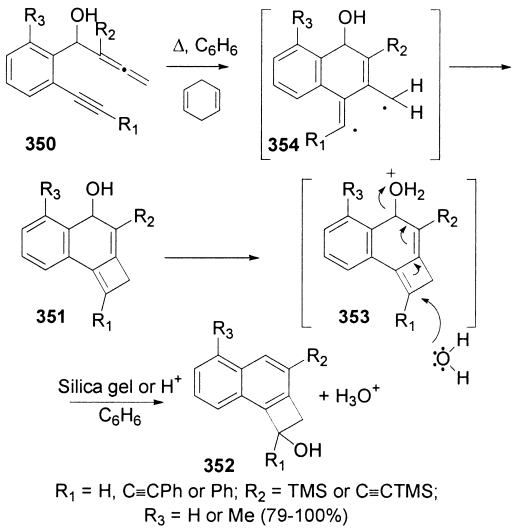
Scheme 103.

of a pair of substituted naphthalenes **347** and **348** as described in Scheme 103. This work by Ho and co-workers demonstrated that under dilute acidic conditions, the major product produced by the irradiation of *p*-methoxy-*trans*-stilbene **349** was the naphthylbuten-2-one **348** in 96% yield (53% conversion).[218] On the other hand, irradiation of **349** in a higher concentration of protic acid resulted in the formation of **347** (96% yield, 52% conversion).

10. Thermal cyclization reactions

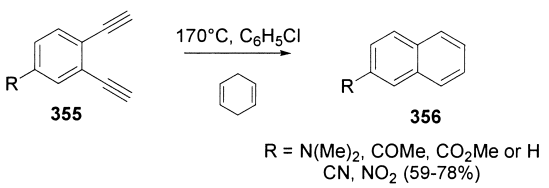
Thermal biradical cyclization methodology has been investigated extensively in the synthesis of natural products (e.g. enediyne antitumor antibiotics) and for the construction of novel complex molecules. Pioneers in this field are Bergman (enediynes), Myers–Saito (enyne-allenes) and Moore (enyne-ketenes) and their work is discussed in two topical reviews by Wang[219] and Grissom.[220] The reviews also include a number of examples with general synthetic applicability for the synthesis of functionalised naphthalenes. This section of our review will briefly highlight some recent applications of this strategy in the synthesis of functionalised naphthalenes.

Ueda and co-workers have used the thermal biradical cyclization of non-conjugated aromatic enyne-allenes such as **350** to synthesize alcohols **351**, which were readily converted into cyclobuta[α]naphthalene derivatives **352** by way of **353** in excellent yields during silica gel column chromatography.[221] The proposed mechanism includes the formation of a biradical species **354** (Scheme 104).



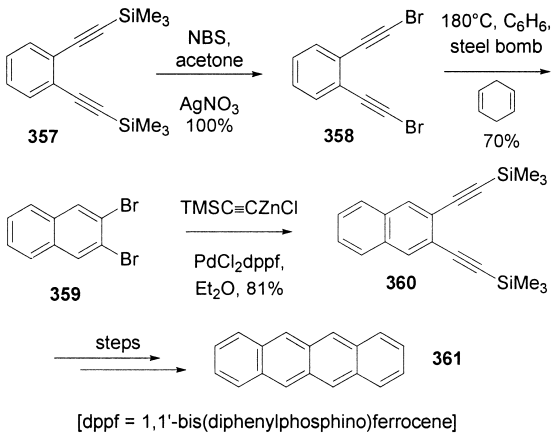
Scheme 104.

Russell and co-workers studied the Bergman cyclization of a number of 4-substituted-1,2-diethynylbenzenes **355** to determine the linear free energy relationships of these reactions.[222] The cyclizations resulted in the formation of 2-substituted naphthalenes **356** in moderate to good yields (Scheme 105). Other examples describing the use of this type of cyclization methodology have been published by Iyoda,[223] and König and Schreiner.[224]



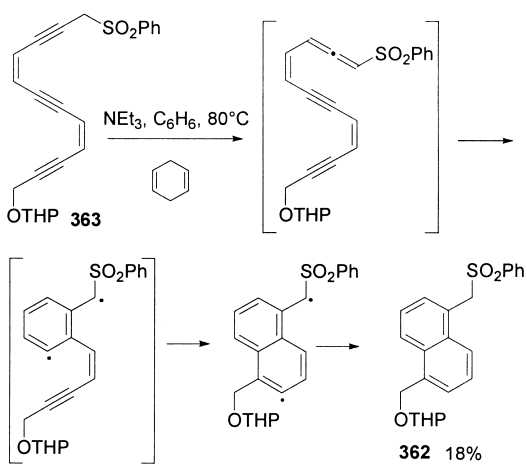
Scheme 105.

Recent work communicated by Bowles and Anthony utilizes the Bergman cycloaromatization reaction as a versatile tool in the synthesis of 2,3-disubstituted naphthalenes and their aromatic ring homologues as shown in Scheme 106.[225] Compound **357** was converted into the dibromide **358**, which was subjected to a thermal reaction that produced 2,3-dibromonaphthalene **359** in good yield. This naphthalene, in turn, could be converted into the diyne **360** by a palladium-catalysed coupling reaction, and **360** could then be converted into the next aromatic homologue by repeating the procedure. The authors demonstrated the formation of naphthacene **361** by this iterative approach. An extension of this work was recently published.[226]



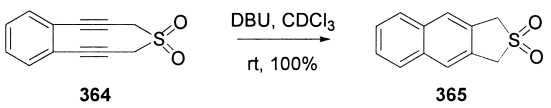
Scheme 106.

Lin and Wu have described the synthesis of a disubstituted naphthalene system **362** from an acyclic diene-triyne system **363** (Scheme 107).[227] Unfortunately, the product was obtained in a yield of only 18%. Its formation was thought to proceed via the diradical process illustrated in the scheme.



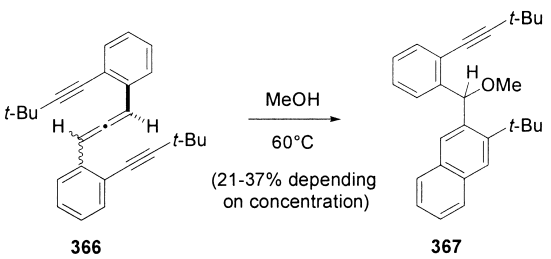
Scheme 107.

In probing the proposed mechanism of action of the naturally occurring enediynes, Braverman and colleagues have demonstrated that the sulfone **364** cyclizes quantitatively to form naphthalene **365** under mild conditions (Scheme 108).[228] The corresponding sulfoxide and sulfide starting materials also cyclized in a similar fashion, albeit at a slower rate.



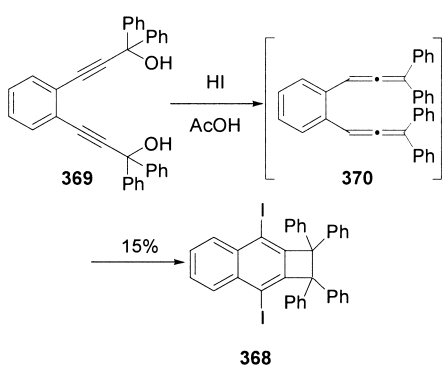
Scheme 108.

Dopico and Finn have demonstrated that the cycloaromatization of aromatic allene enynes such as **366** produced functionalised naphthalene **367** (Scheme 109).[229] The mediocre yield of **367** depended on the concentration of the reactant.



Scheme 109.

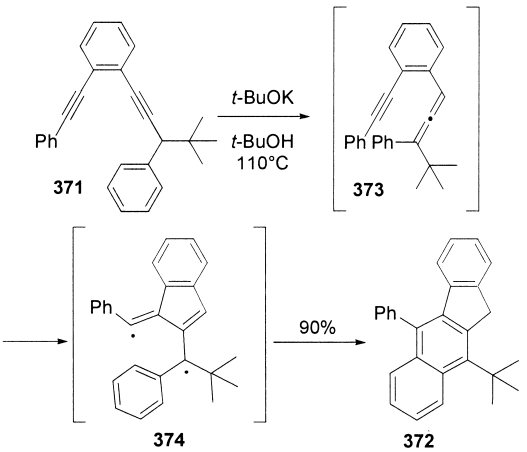
Toda and co-workers have successfully synthesized the sterically congested naphthalene **368** from diol **369** as demonstrated in Scheme 110.[230] The diol **369** was converted into the diallene **370** with hydriodic acid in acetic acid, and subsequent heating afforded naphthalene **368** in low yield. This reaction may be suitable for synthesising other sterically congested naphthalenes.



Scheme 110.

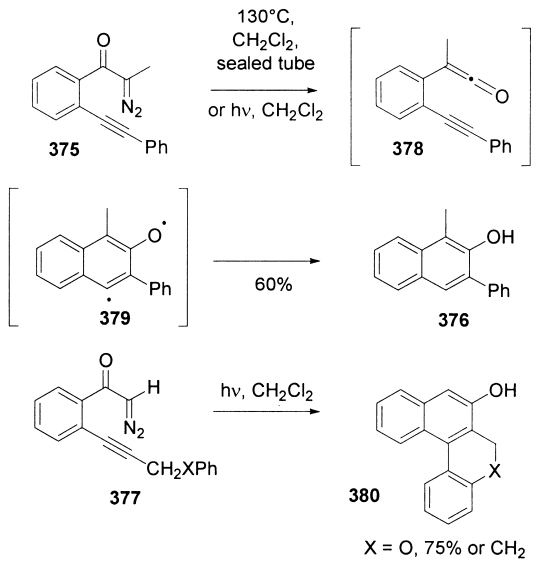
Wang and co-workers have used diacetylenes such as **371** to form highly substituted naphthalene cores in a similar approach to that demonstrated in the previous scheme.[231] An example of this is illustrated in Scheme 111, in which diyne **371** forms compound **372** in excellent yield via a proposed allene **373** and diradical intermediate **374**.

Padwa and co-workers showed that heating α-diazo carbonyl compounds such as **375** resulted in the formation



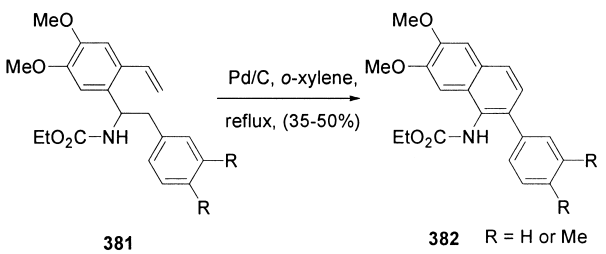
Scheme 111.

of naphthols **376** in reasonable yields (Scheme 112).[232] A similar transformation could also be achieved by photolysis of **377** in methylene chloride. The mechanism of these photochemical transformations was postulated to occur via a Wolff rearrangement to *o*-alkynyl substituted arylketene **378**, which cyclizes to the diradical species **379**. The diradical could be quenched by solvent to afford **376** or by a tethered aromatic ring to give **380**.



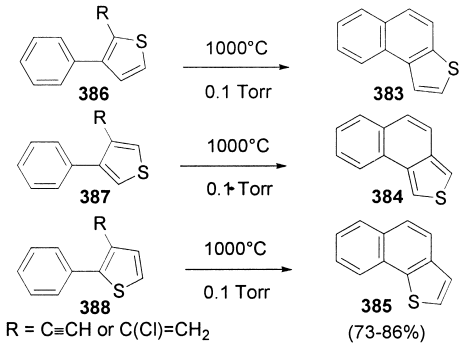
Scheme 112.

Estévez and co-workers demonstrated that styrene **381** could be converted into 2-phenylnaphthalene derivative **382** in moderate yields by thermal electrocyclization and aromatization reactions (Scheme 113).[233] This reaction presumably occurs by way of a bis-styrene intermediate.



Scheme 113.

Finally, Otsubo and co-workers have used the process of flash vacuum pyrolysis in their synthesis of a diverse selection of naphthothiophenes (Scheme 114).[234] This methodology resulted in good yields of the tricyclic thiophene-fused naphthalene systems **383–385** from precursors **386–388** respectively.



Scheme 114.

11. Conclusion

As shown in this review a large number of methods based on a wide variety of reactions are available for the synthesis of substituted naphthalenes. Clearly this is an active area of research and we look forward to novel innovative approaches to the synthesis of these compounds.

Acknowledgements

This review is based on the introductory chapter of the PhD thesis of A. L. R. This work was supported by the National Research Foundation (NRF), Pretoria, and the University of the Witwatersrand (University Research Council). Professor J. P. Michael (University of the Witwatersrand, Johannesburg, South Africa), Professor I. R. Green (University of the Western Cape, Cape Town, South Africa), Professor D. Ferreira (University of Mississippi, University, United States of America) and Professor R. G. F. Giles (Murdoch University, Perth, Australia) are thanked for reading the manuscript and making many valuable recommendations.

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