Modern methods for the synthesis of substituted naphthalenes

Charles B. de Koning, a, * Amanda L. Rousseau b and Willem A. L. van Otterlo a, *

a Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits, 2050 Johannesburg, South Africa
b CSIR, Bio/Chemtek, Speciality and Fine Chemicals Programme, Modderfontein, South Africa

Received 20 October 2002

Contents

1. Introduction 7
2. Diels–Alder reactions 9
2.1. Diels–Alder addition of quinones to dienes 9
2.2. Diels–Alder addition of o-quinodimethanes 10
2.3. Diels–Alder addition of benzynes 11
3. Phthalide annulations 12
4. Transition metal-mediated cyclizations 13
4.1. Chromium-assisted methods 13
4.2. Manganese-mediated radical cyclization 14
4.3. Palladium-catalysed cyclizations 15
4.3.1. From arynes 15
4.3.2. From vinylic iodides and triflates 15
4.3.3. Miscellaneous annulations 16
4.4. Transition metal-mediated electrocyclization 16
4.5. Cobalt-mediated reactions 17
4.6. Ruthenium-catalysed ring-closing metathesis 18
4.7. Nickel-mediated cyclization 18
4.8. Copper, zinc and tin mediated cyclization of zirconocene complexes 18
4.9. Rhodium-mediated cyclization 19
5. Rearrangement of strained rings 19
5.1. Rearrangement of cyclobutenones 19
5.2. Rearrangement of cyclopropanes 20
6. Acid- and Lewis acid-catalysed intramolecular cyclizations 21
7. Phosphorus ylides in the synthesis of naphthalenes 24
8. Anionic ring annulations 25
9. Photochemically-mediated reactions 28
10. Thermal cyclization reactions 28
11. Conclusion 31

1. Introduction

There are numerous examples of biologically active natural products that possess a naphthalene or naphthoquinone core. Nanaomycin A 1, for example, a member of the family of pyranonaphthoquinone antibiotics, possesses a simple naphthoquinone backbone (Fig. 1). By contrast, the rifamycin series of macrolide 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. 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
natural toxin was isolated from cotton seeds, and its structure was elucidated some 50 years later. 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 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 (Fig. 2), isolated from a shrub indigenous to Western Australia, is composed of three naphthoquinone units linked by biaryl axes. 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 concurvone is due to the exceptionally high anti-HIV activity exhibited by the 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 (e.g. korupensamine A 5), and their dimers, the michellamines (e.g. michellamine B 6). The former have anti-malarial properties, and the latter exhibit potent anti-HIV activity.

Apart from their interesting biological activity, biaryl naphthalene compounds also find application as chiral reagents. The first and most frequently used chiral phosphine ligand is BINAP. This is illustrated by the work of Noyori who has shown that ruthenium complexes of BINAP are capable of effecting asymmetric hydrogenations and have even found industrial applications. The atropisomers of (1,1'-binaphthyl)-2,2'-diol and its derivatives (Fig. 4) are widely used in asymmetric synthesis, either as ligands or as chiral auxiliaries. These binaphths 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 has been used as a chiral ligand in the copper-catalysed Michael addition of dialkylzinc reagents to cyclic \( \alpha,\beta \)-unsaturated ketones.

One of the more important contributions using binaphthols in organic synthesis has come from the group of Shibasaki. 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...
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

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, Brassard30 and Danishefsky31 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 trimethylsilanol from the intermediate 15 in the presence of silica gel. Other dienes such as 16 have also been used in Diels–Alder reactions.33

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
been used to make naphthalenes as shown in Scheme 3.\textsuperscript{35,36} Reaction of the readily prepared diene 20 with benzoxodimethane afforded the substituted naphthalene 21 in good yield, after protection as the triacetate.

\textbf{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.\textsuperscript{37–39} Variations of the Diels–Alder reaction include the addition of o-quinodimethanes to acetylenic dienophiles.\textsuperscript{37} Benzocyclobutenes may also be used as precursors for o-quinodimethanes as shown in Scheme 4.\textsuperscript{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.\textsuperscript{41,42}

A recent application of o-quinodimethane methodology may be found in the synthesis of rishirilide B.\textsuperscript{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.\textsuperscript{44}

\textbf{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.\textsuperscript{45–47}

\textbf{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.\textsuperscript{48} The products 33 were probably formed by facile expulsion of hydrogen telluride from the Diels–Alder adduct 34 as illustrated in Scheme 7.

\textbf{Scheme 7.}

A recent application of o-quinodimethane methodology may be found in the synthesis of rishirilide B.\textsuperscript{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.\textsuperscript{44}

\textbf{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.\textsuperscript{45–47}

\textbf{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.\textsuperscript{48} The products 33 were probably formed by facile expulsion of hydrogen telluride from the Diels–Alder adduct 34 as illustrated in Scheme 7.

\textbf{Scheme 7.}
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.\(^4\)\(^{1}\)\(^{5}\)\(^2\) Oxidation of the readily prepared O-silylalkenes 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 (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 with dimethyl acetylenedicarboxylate (DMAD) gave naphthalene in an acceptable yield of 41% (Scheme 10), and unreacted starting material which was easily separated from the product.

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

**2.3. Diels–Alder addition of benzynes**

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

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 benzene 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](image)

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 benzene 63 was formed during the reaction (Scheme 16).\(^56\)

### 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 \(\alpha\)-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](image)

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 phthalide annulations and modifications thereof, have been reported recently.\(^71\)–\(^74\)

![Scheme 18](image)

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
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 Barsy81 and Sepiol,82 and both these methods could be very useful for the synthesis of aminonaphthalenes.

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 benz[\(h\)]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 alkynyl 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 reviews87–91 and therefore will not be covered in detail here. However, a few new developments will be discussed.

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 electrocyclicization to the \(\alpha\)-alkoxy-naphthylamine 84, an important intermediate in the synthesis of the calphostins.
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 regiosomer 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.

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 α-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-rubromycin104 and an application of the methodology to the synthesis of fredericamycin A.105 Moser106 has published a range of examples displaying the conversion of intermediates like 96 to substituted naphthalenes such as compound 97 (Scheme 27).

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.
Rickards has reported another promising manganese-mediated method for the synthesis of naphthols from diketones such as 107. 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 polycyclic systems.

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 benzyne 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. A mechanism is proposed in Scheme 31.

Pérez and co-workers generated benzyne in a similar fashion from 111, and subsequent palladium-catalysed cocyclization of the benzyne with alkynes gave naphthalenes 112 in good yields (54–83%), probably via the formation of intermediate 113 (Scheme 32). 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.

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. The vinylic iodides and triflates used...
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). 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.

4.3.3. Miscellaneous annulations. The aryl naphthalene 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). 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.

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. 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.

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 carbynylative cyclization reaction that converts substrate 130 into naphthol 131 as shown in Scheme 38. Although this is the sole example presented, the method has potential for the synthesis of a variety of naphthalenes. Work utilizing palladium-mediated enyne-allene cycloaromatization resulting in the formation of substituted naphthalenes has also been published by Saalfrank and co-workers.

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. For example, treatment of 132 with W(CO)$_5$THF gave methyl naphthalene 133 by way of proposed vinylidene intermediate 134 (Scheme 39). This
intermediate underwent a ≈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

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

The cyclization of alkylnyl 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.

The 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 alkylnyl 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
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

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

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.

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 benzylene 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

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 zirconaindene 172 undergo reactions with allyl bromide and zinc bromide,
in the presence of a catalytic quantity of Pd(PPh₃)₄, to afford naphthalenes as a mixture of regioisomers 173 and 174 by way of proposed intermediates 175 and 176 (Scheme 53). When R was a phenyl or substituted phenyl group, only the major regioisomer 173 was isolated in yields of 40–59%.

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).

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). 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.

5. Rearrangement of strained rings

5.1. Rearrangement of cyclobutenones

The thermally induced ring expansion of cyclobutenones affords aromatic products in relatively good yields. 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.

Moore has extended this work to the synthesis of naphtho[2,1-b]furan-2(3H)-ones 186 and annulated furans. 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 \( \sigma_6 \) electrocyclization and addition of the phenol to the ketene as depicted in intermediate 189.146

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.

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.

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).

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.
Chang and Park have reported a photoinduced rearrangement of benzobicyclo[3.1.0]hexanones \( \text{209} \) to give 1-naphthols \( \text{210} \), probably via the dienyl ketene intermediate \( \text{211} \) (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.

### 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 \( \text{212} \). A limitation to this method is that the aromatic ring often has to be electron rich. However, in general, treatment of \( \text{212} \) with acid or a Lewis acid affords naphthol product \( \text{213} \) (Scheme 63). If the precursor is the carboxylic acid (i.e. \( R_2 = \text{OH} \)), reaction with a chloroformate or trifluoroacetic anhydride affords naphthols of type \( \text{213} \). A number of variations on this theme have been reported.\(^{157} \)

Traditional methods for synthesising precursors such as compound \( \text{212} \) 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 \( \beta \) or BF\(_3\)·OEt\(_2\), certain benzyl allyl ethers \( \text{214} \) rearrange to the desired precursors \( \text{215} \).\(^{159} \) The reaction presumably proceeds by a 1,4 rearrangement followed by a 1,2-hydride shift as depicted in intermediate \( \text{216} \) (Scheme 64). When \( \text{215} \) was treated with polyphosphoric acid at elevated temperatures, naphthalene products \( \text{217} \) were isolated in moderate yields.

The Stobbe condensation has also been widely used in the synthesis of precursors such as \( \text{212} \).\(^{160} \) 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 \( \Delta^3 \)-\((-)\)-gossypol \( \text{3} \), the initial steps of which are shown in Scheme 65.\(^{5,161} \) The aldehyde \( \text{218} \) was treated with dimethyl succinate and sodium hydride to afford the naphthalene precursor \( \text{219} \). Treatment of compound \( \text{219} \) with a mixture of acetic acid and acetic anhydride effected cyclization to naphthalene \( \text{220} \), which was isolated in 59% yield over three steps from aldehyde \( \text{218} \). Other recent examples using similar methodology have also been published.\(^{162} \)

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 \( \text{221} \) was synthesized in 85% yield by treatment of the dialdehyde...
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-workers168 (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 Vulligonda, 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-halo-benzocyclobutenones 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). 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.

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

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. 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.

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). This work has been applied to a number of substrates to afford 2,3-disubstituted-1-naphthols.

The condensation of α-oxoketene dithioacetals with aryl Grignard reagents has been employed by Junjappa and co-workers in their synthesis of substituted napththalenes. 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).
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 trifluoromethyl naphthalene 262 (Scheme 77). With this methodology a number of substituted naphthalenes could be produced in good yields.

![Scheme 77](image)

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

![Scheme 78](image)

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](image)

The acid catalysed rearrangement of some complex substrates has led to the formation of substituted naphthalenes. For example, exposure of 267 to HClO₄ 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.

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](image)

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 fluoroalkynaphthalenes 273 in excellent yields.

![Scheme 82](image)

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
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). The reaction presumably occurs by way of intermediate 279. The naphthalene products such as 278 were isolated in moderate yields.

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 and 9-phenanthrols. The precursors for this reaction were synthesized using the extensively reported directed ortho metallation methodology developed by this group. 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.

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. Clive et al. have also used the Snieckus methodology to synthesize a naphthalene precursor used in their synthesis of fredericamycin A.

Hattori, Miyano and co-workers have used a base-promoted cyclization strategy to synthesize functionalised naphthols as described in Scheme 87. 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.

de Koning et al. have described a related base-mediated method which results in the synthesis of naphthalenes 291 rather than naphthols. 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). The nitronate anion generated from nitroalkane 295 was reacted with 296 to afford the Baylis–Hillman adduct 297.
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.

Naphthalene 300, a precursor to neocarzinostatin carboxylic acid, was synthesized by a modified Dieckmann cyclization by Rucker and Brückner. 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).

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

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

In their total synthesis of the furaquinocins, Suzuki and co-workers utilized an interesting route to naphthalene intermediate 310 (Scheme 93). 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).
Sodium hydroxide facilitated an intramolecular aldol condensation followed by dehydration to give the targets 313 in excellent yields.

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. 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.

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. The yield of this product was 35% and 53% of the rearranged product 324 was also isolated as depicted in 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). 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.

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).

Another anionic approach to the synthesis of naphthalenes has been reported by Shindo et al. as depicted in
These researchers have generated ynlolate anions from α,α-dibromoesters and then used them in a tandem [2+2] cycloaddition-Dieckmann condensation reaction with ketones to produce highly substituted naphthols. It was postulated that the reaction proceeds via intermediates.

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

D'Auria and co-workers found that irradiation of a solution containing 2-acetyl-5-phenylthiophene and phenylacetylene with a Nd:YAG laser (355 nm) gave 1-phenylnaphthalene as the only detectable product (Scheme 101). 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.

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

A study of the reaction pathways of stilbene analogues (traditionally used for the synthesis of phenanthrenes) when irradiated in acidic media has resulted in the synthesis.
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). 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 and Grissom. 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[a]naphthalene derivatives 352 by way of 353 in excellent yields during silica gel column chromatography. The proposed mechanism includes the formation of a biradical species 354 (Scheme 104).

R3 OH2 \[ \Delta_C_6H_5 \] R1

R3 OH2 \[ + H_2O^+ \]

R1 = H, C6H5 or Ph; R2 = TMS or C=CTMS; R3 = C6H5 or Ph (79-100%)

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. 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 and König and Schreiner.

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. 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.

Lin and Wu have described the synthesis of a disubstituted naphthalene system 362 from an acyclic diene-triyne system 363 (Scheme 107). 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.
In probing the proposed mechanism of action of the naturally occurring enediyynes, Braverman and colleagues have demonstrated that the sulfone 364 cyclizes quantitatively to form naphthalene 365 under mild conditions (Scheme 108). The corresponding sulfoxide and sulfide starting materials also cyclized in a similar fashion, albeit at a slower rate.

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

Toda and co-workers have successfully synthesized the sterically congested naphthalene 368 from diol 369 as demonstrated in Scheme 110. 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.

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. 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 of naphthols 376 in reasonable yields (Scheme 112). 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 α-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.

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). This reaction presumably occurs by way of a bis-styrene intermediate.

Scheme 108.

Scheme 109.

Scheme 110.

Scheme 111.

Scheme 112.

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). 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.

References


Biographical sketch

Charles de Koning obtained his PhD from the University of Cape Town in 1988 under the supervision of Professor RGF Giles. After completing two post-doctorates (MIT, GH Büchi and University of Hawaii, RE Moore) he joined the University of Witwatersrand in 1992. He currently holds the position of associate professor.

Amanda Rousseau completed her PhD in Organic Chemistry in 2000 at the University of the Witwatersrand under the supervision of Professors Charles de Koning and Joseph Michael. Currently she is working at the Council for Scientific and Industrial Research in South Africa.

Willem van Otterlo completed his PhD in Organic Chemistry in 1999 at the University of the Witwatersrand under the supervision of Professors Charles de Koning and Joseph Michael. He then spent two years in the research group of Professor Stephen Hanessian (University of Montreal, Quebec, Canada) as a post-doctoral research fellow before returning to his alma mater as a lecturer in chemistry in 2001.