Selected synthetic strategies to cyclophanes

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Abstract
In this review we cover various approaches to meta- and paracyclophanes involving popular reactions. Generally, we have included a strategy where the reaction was used for assembling the cyclophane skeleton for further functionalization. In several instances, after the cyclophane is made several popular reactions are used and these are not covered here. We included various natural products related to cyclophanes. To keep the length of the review at a manageable level the literature related to orthocyclophanes was not included.

Introduction
Cyclophanes [1-38] are strained organic molecules which contain aromatic ring(s) as well as aliphatic unit(s). The aromatic rings provide rigidity to their structure, whereas the aliphatic unit(s) form bridge(s) between the aromatic rings and also provide flexibility to the overall structure. Cyclophanes play an important role in “host–guest” chemistry [39-43] and supramolecular assembly [44-47]. “Phane”-containing molecules show interactions with π-systems, and they can also bind to a large number of cations, anions, and neutral molecules. Cyclophanes are widely used in materials science and molecular recognition processes [48-52]. A general classification of cyclophanes is as follows: [n]orthocyclophane, [n]metacyclophane, and [n]paracyclophane (1–3) (Figure 1). The prefixes represent the position of the attachment to an aromatic system while [n] represents the number of methylene groups present in the aliphatic bridge. The orthocyclophanes are also known as benzocycloalkanes. Several cyclophanes consisting of two or more aromatic systems and aliphatic bridges have been reported in the literature [53]. The representative [2,2]ortho-, meta-, and paracyclophanes (4–6) are shown in Figure 1. In general, cyclophanes with one aromatic ring and two alkyl bridges are called [n,m]metapara or [n,n]paraparacyclophanes (7, 8) based on the position of the attachment of the alkyl chain to the aromatic system. In this review we are not discussing orthocyclophanes but rather focus on meta- and paracyclophanes only.

The aromatic ring present in the cyclophane system can be either heterocyclic or carboxyclic in nature. If there is a heteroatom present in the aromatic ring system then the system is called a heterophane (9) [54-56], whereas if the heteroatom is
Figure 1: General representation of cyclophanes.

Figure 2: Cyclophanes one or more with heteroatom.

A number of cyclophane derivatives have been employed as hosts, and their guest-binding properties have been widely investigated. A variety of reviews related to the cyclophane chemistry has been published. Although monomeric cyclophanes show moderate guest-binding abilities, an improved affinity can be achieved by polytopic hosts [61-63] through multivalency effects in macrocycles. Olefin metathesis has played a key role in the development of cyclophane chemistry. Some of the catalysts used for this purpose are listed in Figure 3. The development of new synthetic methods in this area is considered a useful exercise. To this end, name reactions or popular reactions, and rearrangement reactions are widely used. In connection with the synthesis of cyclophanes, we describe the employment of these reactions for C–C or C–heteroatom-bond formation. The first part of this review focuses on the syntheses of various cyclophanes related to natural products and the subsequent sections describe the use of various popular reactions in cyclophane synthesis.

Natural products containing a cyclophane skeleton

The cyclophane skeleton is a core structural unit in many biologically active natural products such as macrocidin A (19) and B (20) [64], nostocyclene A (21) [65], and in the turriane family of natural products [22–24] [66]. Cyclophanes are also applied in research areas such as pharmaceuticals [67,68], catalysis [69,70] and supramolecular chemistry [71].
Macrocidin A (19) and macrocidin B (20) [64] belong to a family of plant pathogens produced by Phoma macrostoma, a microorganism parasitic to Canadian thistle. Macrocidins contain a tetramic acid group in their skeleton and show selective herbicidal activity on broadleaf weeds but do not affect grasses. Nostocyctyne A (21) is an acetylenic cyclophane derivative isolated from a terrestrial Nostoc species, with antimicrobial activity (Figure 4). The turriane family of natural products 22–24 were isolated from the stem wood of the Australian tree Grevillea striata. Turrianes 22–24 are effective DNA-cleaving agents in the presence of Cu(II). Fürstner and co-workers [72] have reported the total synthesis of natural products 22–24 by using a metathesis reaction [73-82] as the key step. The ring-closing metathesis (RCM) has been utilized for the synthesis of the turriane with a saturated alkyl chain (22), whereas the unsaturated turrianes 23, 24 containing a (Z)-alkene moiety have been prepared by alkyne metathesis followed by reduction using Lindlar’s catalyst (Figure 5).

Muscopyridine and its analogues
Musk is a widely used component in Chinese pharmaceuticals and it has also been used in perfume industry. Muscopyridine was first isolated by a Swiss group [83] from the musk deer (Moschus moschiferus). Muscopyridine and its synthetical analogue normuscopyridine are heterophanes, more precisely metapyridinophanes. There are various routes to these compounds and related compounds which are discussed in detail in this review.
Review
Synthetic routes to cyclophanes

Addition reactions

Mannich reaction: In 2001, Erker and co-workers [84] have reported the synthesis of amino-substituted [3]ferrocenophane through an intramolecular Mannich reaction starting with the ferrocene framework. In the first step, the unsaturated amino-functionalized [3]ferrocenophane 28 was synthesized from 1,1'-diacetylferrocene (25) in the presence of an excess amount of dimethylamine and a stoichiometric amount of a Lewis acid such as TiCl₄. These conditions lead to the generation of the bisenamine 26, which was subsequently converted to the cyclophane 28 by a Mannich-type condensation reaction (40%) (Scheme 1).

Michael addition: In 1999, Reißig and co-workers [85] have synthesized a functionalized cyclophane by a cascade reaction, which proceeds with desilylation, ring opening, proton transfer, and finally, an intramolecular Michael addition to provide benzannulated large ring compounds 31 and 33. In this regard, substituted methyl 2-alkenyl-2-siloxycyclopropanecarboxylate 29 was converted into the alkylation product and further react with the ester enolate dibromide to yield vinyl cyclopropane derivatives 30 (62%) and 32 (44%). Later, Michael addition in the presence of caesium fluoride and benzyltriethylammonium chloride in DMF gave the benzannulated cyclodecanone derivatives 31 (11%) and 33 (10%) (Scheme 2).

Oxymercuration – Hantzsch pyridine synthesis: Kondo and Miyake [86] have reported the synthesis of [11](2,6)-pyridinophane (37), a normuscopidine analogue, by an oxymercuration–oxidation strategy. The ketoolefin 34 was converted to the hydroxyketone 35 by treatment with Hg(OAc)₂ and NaSH. Oxidation of the keto alcohol 35 gave diketone 36, which reacted with hydroxylamine hydrochloride and afforded [11](2,6)-pyridinophane (37) (Scheme 3).

Coupling reactions

Castro–Stephens coupling: Youngs and co-workers [87] have synthesized p-methoxy-substituted tribenzocyclotriyne 39 using the Castro–Stephens coupling reaction (Scheme 4). Compound 39 is a planar antiaromatic dehydroannulene that forms complexes with Ni(0), Cu(I), Co(0) and also with Ag⁺ cations.

Glaser–Eglinton coupling: Whitlock and Cloninger [88] have reported the synthesis of cyclophane 43 using the Glaser–Eglinton coupling reaction. In this regard, compound 40 was treated with 9,10-bis(chloromethyl)anthracene (41) under basic conditions to generate compound 42 which was further

Scheme 1: Synthesis of [3]ferrocenophanes through Mannich reaction. Reagents and conditions: (i) excess HNMe₂; (ii) TiCl₄, C₅H₁₂, −78 °C, 20 min, 40%.
subjected to a Glaser–Eglinton coupling to deliver cyclophane 43 (Scheme 5). A derivative of compound 43 was used as a host for compounds such as 6-nitro-2-naphthol, stilbene derivatives and serotonin mimics. This paper depicts the edge–face interaction between the face of the anthracene bridge present in the cyclophane molecule and the edge of the host molecule.
Bukownik and Wilcox [89] have synthesized macrocyclic C-glycosyl compounds, and obtained the chiral and water-soluble cyclophane 46. They reported on the use of its sulfonamide derivative in preparing glycophane molecule (Scheme 6).

Haley and Langsdorf [90] have reported the synthesis of a cyclophane-containing octacobalt complex 49 using the Glaser–Eglinton coupling reaction [91] as a key step (Scheme 7). In this regard, palladium-catalyzed alkynylation of
1,4-diiodobenzene with an excess amount of triisopropylsilylbutadiyne (47) followed by complexation with Co₂(CO)₈ furnished a pale yellow diyne 48. Exchange of the ligand with bis(diphenylphosphino)methane (dppm) afforded a bridged complex which is stable to fluoride ions. Subsequent desilylation, followed by Glaser–Eglinton coupling of the terminal acetylene groups provided complex 49 in 47% yield as fine, deep maroon crystals.

In connection with the cyclophane synthesis, Kotha and Waghule [92] demonstrated the use of the Glaser–Eglinton coupling as a key step. The dipropargylated compound 51 was subjected to a Glaser–Eglinton coupling to generate the macrocyclic bisacetylene derivative 52 in 94% yield. Finally, diyne 52 was subjected to a hydrogenation sequence with 10% Pd/C under 1 atm pressure of H₂ to generate cyclophane derivative 53 (92%). Alternatively, cyclophane 53 was also obtained by treatment of the bisphenol derivative 50 with 1,6-dibromohexane in the presence of K₂CO₃ in acetonitrile under reflux conditions (56%, Scheme 8).

Another interesting example of a Glaser–Eglinton coupling reaction reported by Rajakumar and Visalakshi [93] is the synthesis of cyclophane 54. Whitlock and co-workers have synthesized donut-shaped cyclophanes 55 and 56 by using the Glaser–Eglinton coupling as a key step (Figure 6) [94].

**Scheme 8**: Synthesis of cyclophane 53 through Glaser–Eglinton coupling. Reagents and conditions: (i) K₂CO₃, acetone, reflux, 12 h, 86%; (ii) Cu(OAc)₂·H₂O, pyridine, CH₃CN, 60 °C, 2 h, 94%; (iii) H₂, Pd/C, EtOH, 12 h, rt, 92%; (iv) 1,6-dibromohexane, K₂CO₃, reflux, CH₃CN, 56%.

**Figure 6**: Cyclophanes 54–56 that have been synthesized through Glaser–Eglinton coupling.
Morisaki and co-workers [95] have synthesized 4,7,12,15-tetrasubstituted [2.2]paracyclophane 57 and further studies were carried out to find out the properties of these macrocycles. These molecules show excellent chiroptical properties such as high fluorescence quantum efficiency and a large circularly polarized luminescence dissymmetry factor. Cyclophanes are carbon-rich materials containing extensive alkyne moieties with a persistent molecular architecture. Orita and co-workers have reported the synthesis of chiral cyclophyne 58 through the Eglinton coupling reaction [95]. A tandem inter- and intramolecular Eglinton coupling reaction affords the enantiopure threedimensional cyclophyne 58 with a large cavity size (Figure 7).

**Glaser–Hay coupling:** In 2010, Collins and co-workers [96] demonstrated a macrocyclization, with an inbuilt conformation control element to form rigid cyclophanes through the Glaser–Hay coupling. In this regard, diynes 59a–c were treated with CuCl₂ and TMEDA in the presence of oxygen to afford the cyclized products 61a–c (Scheme 9).

**Intramolecular Heck coupling:** In 2003, Snieckus and co-workers [97] have synthesized the seco-C/D ring analogues of ergot alkaloids through the intramolecular Heck reaction as a key step. The coupling precursors 63 and 68 were prepared from 4-bromoindoles by a sequential Vilsmeier–Haack, Henry

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**Figure 7:** Synthesis of tetrasubstituted [2.2]paracyclophane 57 and chiral cyclophyne 58 through Eglinton coupling.

**Scheme 9:** Synthesis of cyclophane through Glaser–Hay coupling reaction. Reagents and conditions: (i) CuCl₂ (12 equiv), TMEDA (12 equiv), O₂, PhMe, 18 h, 80 °C.
nitroaldol condensation, reduction with LiAlH₄, reductive amination and alkylation that afforded the indole derivatives 63 (18%) and N-Boc protected compound 68 (23%). The reaction of 63 with Pd(OAc)₂ (25 mol %) and tri(o-tolyl)phosphine (55 mol %) at reflux gave 9-endo-64a (24%) and 8-exo-65b (21%). However, the compound 68 under similar reaction conditions gave the cyclized product 8-exo-69 (30%) as the only isolable compound (Scheme 10).

**Kumada coupling:** Weber and co-workers [98] have synthesized muscopyridine 73 starting from 2,6-disubstituted pyridine. The Kumada cross-coupling reaction of 2,6-dichloropyridine (70) with the Grignard reagent 71 in the presence of a nickel phosphine complex 72 gave muscopyridine 73 in a single step (Scheme 11). This strategy has been applied to generate a variety of pyridinophanes by varying the chain length of the Grignard reagent.

**McMurry coupling:** Kuroda and co-workers [99] have reported the synthesis of polyunsaturated [10]paracyclophane annulated by two azulene rings by using the McMurry reaction [100,101]. The bis(trimethylsilyl)enol ether 74 was reacted with 3-methoxy carbonyl-2H-cyclohepta[b]furan-2-one (75) in refluxing decaline to generate the 1,4-diazulenobenzene derivative 76. Double chain elongation of the bis-azulene derivative 76 with a four-carbon unit has been accomplished by electrophilic substitution with 4,4’-dimethoxybutan-2-one (77) under acidic conditions and subsequent elimination of methanol under basic conditions gave the advanced precursor 78 (28%). The stereochemistry of the newly generated C–C double bonds in 78 was confirmed as trans with the aid of the NMR vicinal coupling constant. Finally, intramolecular McMurry coupling of 78 using titanium trichloride and lithium aluminum hydride (LAH) heated under reflux in THF provided the cyclophane derivative 79 (20%, Scheme 12).

In another occasion, Rajakumar and co-workers [102] have synthesized a series of stilbenophanes (e.g., 81) involving N-arylated carbazole moieties possessing small and large cavities. The precursor 80 required for the McMurry reaction was

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**Scheme 10:** Synthesis of seco-C/D ring analogs of ergot alkaloids through intramolecular Heck reaction. Reagents and conditions: (i) (a) POCl₃, DMF, 0–40 °C, 1 h, 78%; (b) MeNO₂, cat. NH₄OAc, reflux, 3 h, 80%; (c) LiAlH₄, THF, reflux, 4 h, 88%; (d) PhCHO, NaBH(OAc)_3, CH₂Cl₂/THF, rt, 46%; (e) allyl bromide, MeCN, rt, 24 h, 69–72%; (ii) 25 mol % Pd(OAc)₂, 55 mol % P(o-Tol)_3, NEt₃, MeCN, reflux, 12 h; (iii) DIBAL-H, 0 °C, 15 min, rt, 2 h, CH₂Cl₂, then allylNHMe, NaBH(OAc)_3, CH₂Cl₂, rt, 12 h, 38%.

**Scheme 11:** Synthesis of muscopyridine 73 via Kumada coupling. Reagents and conditions: (i) 72, THF, ether, 20 h, rt, 5–10%.
synthesized by the N-arylation of carbazole with the corresponding dibromide followed by formylation (Scheme 13).

In 2006, Rajkumar and co-workers [103] have published the synthesis of stilbenophane 85 via McMurry coupling as a key step (Scheme 14). Terphenyl derivative 82 was subjected to benzylic bromination in the presence of NBS to generate compound 83. Later, dibromide 83 was converted to bis-aldehyde 84. Finally, McMurry coupling of dialdehyde 84 provided the cyclophane derivative 85 (28%).

Yamoto and co-workers have reported the synthesis of mediumsized cyclophanes, [2.2]metacyclophane-1,2-diols 86 and 87 by using the McMurry coupling as a key step (Figure 8) [104-106]. Among the π-conjugated systems stilbene derivatives found a unique place in materials science due to their optical and charge conducting properties. Tsuge and co-workers [107] reported the synthesis of stilbene 88 by using the McMurry coupling and studies on the transmission of the electronic effect through transannular interactions. Rajakumar and Selvam [108] also synthesized chiral stilbenophane 89 with small to large cavity sizes. These chiral stilbenophanes forms a complex with tetracyanoethylene (TCNE) and tetracyanoquinodimethane (TCNQ). The same group also reported on the synthesis of indolophanes 90a–c by using the McMurry coupling [109]. Furthermore, they synthesized dioxastilbenophanes 91 and carried out charge transfer complexation studies which showed that these molecules form a complex with TCNE and TCNQ [110]. Due to the presence of nitrogen and sulfur atoms benzene rings in phenothiazinophanes exhibit a butterfly conformation and thus have shown an enhanced bending character. When the benzene rings are bent, the reactivity of these cyclophanes is altered. Considering this aspect, Müller and co-workers [111] have devised different routes to these molecules. They have reported the synthesis of ethylene-bridged phenothiazinophane 92 using the McMurry coupling reaction. Also cyclic voltammetry experi-

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**Scheme 12**: Synthesis of the cyclophane 79 via McMurry coupling. Reagents and conditions: (i) 75, decaline, reflux, 4 h, 10%; (ii) 77, NaHCO₃/HBF₄, 28%; (iii) TiCl₃/LiAIH₄, THF, reflux, 20%.

**Scheme 13**: Synthesis of stilbenophane 81 via McMurry coupling. Reagents and conditions: (i) TiCl₄, Zn, pyridine, THF, reflux, 12 h, 12%.
ments indicated the intramolecular electronic communication between the phenothiazinyl subunits. Calixarene-based macrocycles bind with various metal ions. Lee and Park [112] have synthesized various orthocyclophanes 93 which were further converted into spirobicyclic polyketals with a 2n-crown-2 moiety. Lee and co-workers [113] also reported the synthesis of bicyclic bis-cyclophane 94 by using the McMurry reaction as a key step. Oda and co-workers [114] have reported the first time synthesis of a fully conjugated ionic cyclophane by using the McMurry reaction. The McMurry coupling was carried out with tris(5-formyl-2-thienyl)methane to give an unsubstituted, etheno-bridged trithienylmethanophane 95. Later, it was converted into the novel cage-molecular monocation, dication, and dianion of substantial stability. Riccardin C (96) is a macrocyclic bis-bibenzyl entity with pharmacological properties, including antitumor and antibacterial effects, and cytotoxicity against P-388 mouse leukemia and KB cell lines from nasopharyngeal carcinoma. In view of these useful medicinal properties Harrowven and co-workers [115] have reported the synthesis of this molecule by using the McMurry reaction. Kawase and co-workers [116] have reported double-helically twisted macrocycles 97 exhibiting chiral sensor properties. Kasahara and co-workers [117] have reported the synthesis of ferrocenophane derivative 98 by McMurry reaction as a key step. Oda and co-workers [118] have reported the synthesis of cyclic paraphenylacetylene in which their spectral properties vary mainly with decrease of ring size of the molecule. They have synthesized intermediate 99 using the McMurry coupling which is required for the synthesis of the paraphenylacetylene compound. Tolanophanes are a new class of cyclophanes possessing a diphenylacetylene moiety which possess interesting structural, electronic, nonlinear optical and luminescent properties. Darabi and co-workers [119] have reported the syntheses of 100 molecules by using the McMurry reaction followed by hydrogenation. Pei and co-workers [120] have synthesized anthracene-based π-conjugated strained cyclophane 101 by using an intramolecular McMurry reaction. The combination of unsaturated linkages in these molecules might create a twisted conformation that imparts helical chirality. Double helically twisted chiral cyclophanes are important macrocycles due to their potential applications in optics and electronics. Kawase and co-workers [121] have reported the synthesis of 8,14,30,36-tetramethoxy[2.0.2.0](1,6)naphthalenophane-1,19-diyn (102) using the McMurry coupling (Figure 8).

**Scheme 14:** Synthesis of stilbenophane 85 via McMurry coupling. Reagents and conditions: (i) NBS (2 equiv), benzoyl peroxide, CCl₄, reflux, 40 h, 80%; (ii) tetrabutylammonium dichromate (TBADC), CHCl₃, reflux, 6 h, 69%; (iii) TiCl₄ (20 equiv), Zn (40 equiv), pyridine, THF, reflux, 6 h, 28%.

Pd(0)-catalyzed cross-coupling reaction: In 1997, Yamamoto and co-workers [122] have synthesized the exomethylene paracyclophane 108 via intramolecular benzannulation of conjugated enynes in the presence of palladium(0). In this regard, dibromoalkane 103 was treated with dilithiated 2-methyl-1-butene-3-yne (104) to generate the corresponding bis-enyne 105. Treatment with Pd(PPh₃)₄ in dry toluene under high dilution conditions at 100 °C afforded the exomethylene paracyclophane 106. The paracyclophane 106 was converted to oxocyclophane 107 by ozonolysis followed by deoxygenation which finally gave the paracyclophane 108 (85%, Scheme 15).

Pinacol coupling: Kanomata and co-workers [123] have reported the synthesis of the cyclophane 112 by using pinacol coupling [124] mediated by SmI₂. A double Sonogashira reaction of 1,4-diiodobenzene (109) with 4-pentyn-1-ol (110) generates the diyne product in quantitative yield. Next, the in situ prepared diyne was subjected to hydrogenation followed by oxi-
Figure 8: List of cyclophanes prepared via McMurry coupling reaction as a key step.
Scheme 15: Synthesis of paracyclophane by cross coupling involving Pd(0) catalyst. Reagents and conditions: (i) THF, rt, 72%; (ii) Pd(PPh$_3$)$_4$, PhMe, high dilution, ∆, 15 min, 32%; (iii) O$_3$, −78 °C, Pd/C (10 mol %), H$_2$, rt, 55%; (iv) Pd/C (10 mol %), H$_2$, 50 °C, rt, 85%.

Sonogashira coupling: Wegner and co-workers [125] have reported the synthesis of cyclophanes 122a–c via Sonogashira coupling [126] (Scheme 17). To this end, the 1,4-diodobenzene (109) was reacted with the cyclohexane-1,4-dione (114) in the presence of CeCl$_3$/LiCl/n-BuLi to generate the diol 115. Then, the hydroxy groups were protected as MOM groups to generate the key synthone 116. The other building blocks 119a–c were obtained by protection of dialkynes 117a–c with (3-cyanopropyl)dimethylsilyl chloride (CPDMSCI) (118). This protecting group was chosen to facilitate the separation of the mono- and diprotected products generated in this reaction. The two building blocks 116 and 119a–c were subsequently assembled via the Sonogashira reaction producing differently substituted diynes 120a–c. Deprotection of silyl groups in 120a–c using TBAF furnished the key intermediates 121a–c in moderate to good yields. Treatment of 121a–c with Pd(PPh$_3$)$_4$ and copper iodide in THF in the presence of diisopropylamine gave the desired macrocycles 122a–c (Scheme 17).

Suzuki-Miyaura coupling: Bodwell and Li [127] have reported the synthesis of the cyclophane 130 involving hydro-
Scheme 17: Synthesis of cyclophane derivatives 122a–c via Sonogashira coupling. Reagents and conditions: (i) CeCl₃, LiCl, n-BuLi, THF, −78 °C to rt, 2 h, 48%; (ii) MOMCl, iPrNEt₃, 19 h, rt, 98%; (iii) 118, EtMgBr, Et₂O, 30 min, 0 °C then 1 h, rt, further 24 h stirring; (iv) CuI, Pd(PPh₃)₄, diisopropylamine, THF, rt; (v) TBAF, THF, 30 min, rt; (vi) CuI (20 mol %), Pd(PPh₃)₄ (10 mol %), diisopropylamine, THF, 12 h, rt.

In 2012, Hutton and co-workers [136] have synthesized a highly strained bicyclic framework of mycocyclosin (135) by utilizing the intramolecular Suzuki–Miyaura [137] cross-coupling reaction as a key step. The L,L-cyclo(diiodotyrosin) (131) was subjected to a benzylation reaction to give the protected compound 132 (76%). A one-pot Pd-catalyzed borylation and Suzuki–Miyaura coupling was employed to generate the cross-coupling product 134 (42%). Finally, deprotection of 134 was carried out with trifluoroacetic acid (TFA) in the presence of pentamethylbenzene to generate mycocyclosin (135, 74%) (Scheme 19).

Wurtz coupling: The Wurtz reaction is one of the oldest methods to form a C–C bond in organic synthesis. Baker and co-workers [138] have reported the synthesis of cyclophanes...
Scheme 18: Synthesis of cyclophane 130 via Suzuki–Miyaura reaction as a key step. Reagents and conditions: (i) MeMgBr, allyl bromide, ether, 20 °C, overnight, 66%; (ii) KOH, allyl bromide, TBAB, rt, 6 h, 69%; (iii) KOH, I₂, DMF, 20 °C, 0.45 h, 100%; (iv) KOH, allyl bromide, rt, 6 h, 98%; (v) n-BuLi, allyl bromide, 77%; (vi) 9-BBN, THF; (vii) Pd(PPh₃)₂Cl₂, PPh₃, Cs₂CO₃, dioxane, 65 °C, 5 h, 30%.

Scheme 19: Synthesis of the mycocyclosin via Suzuki–Miyaura cross coupling. Reagents and conditions: (i) benzyl bromide (1.7 mmol), K₂CO₃ (1.7 mmol), DMF, 16 h, 76%; (ii) Pd(dppf)Cl₂, 133 (1 equiv), DMSO, K₂CO₃, 90 °C for 16 h, 42%; (iii) pentamethylbenzene (1.1 mmol), TFA, 1 h, 74%.

137 and 139 by using the Wurtz coupling as a key step (Scheme 20).

Metathesis

Alkyne metathesis reaction: In 2010, Murphy and Jarikote [139] have developed a useful protocol for assembling non-natural macrocyclic compounds containing carbohydrates. Compound 140 was prepared in several steps and was further subjected to the RCM with G-I (12) as a catalyst in CH₂Cl₂. Later, catalytic hydrogenation followed by deacetylation gave compound 141 (48%). Similarly, alkyne metathesis of compound 142 was carried out in the presence of Mo(CO)₆ and 2-fluorophenol in chlorobenzene and heated under reflux to yield the cyclized product. The cleavage of the acetate groups with sodium methoxide in methanol gave the glycophane (a glycophane is a hybrid of carbohydrate and cyclophane) 143 (27%, Scheme 21).

The synthesis of fullerene-related molecules with high binding affinity and/or high selectivity is an active research area due to the cost and energy demanding purification process and the poor processibility of the fullerenes. To this end, Zhang and
Scheme 20: Synthesis of cyclophanes via Wurtz coupling reaction. Reagents and conditions: (i) PhLi, Et₂O, C₆H₆, reflux, 39%; (ii) Na, NaI (cat), PhBr (cat), Et₂O, 12%; (iii) PhLi, Et₂O, C₆H₆, 60 °C, 30 min, 20%.

Scheme 21: Synthesis of non-natural glycophanes using alkyne metathesis. Reagents and conditions: (i) G-I, CH₂Cl₂, 8 h; (ii) Pd/C (5 mol %), NaOMe/MeOH, 48%; (iii) Mo(CO)₆, 2-fluorophenol, chlorobenzene, ∆; (iv) NaOMe/MeOH, 27%.

Co-workers [140] reported the synthesis of the bisporphyrin macrocycle 144 with an adaptable cavity by using alkyne metathesis with high efficiency. Tamm and co-workers [141] reported the synthesis of meta-cyclophane 145 at room temperature by ring-closing alkyne metathesis of 1,3-bis(3-pentynyl-oxymethyl)benzenes (Figure 9). This strategy has also been extended to ortho and para-derivatives.

Cross-enyne metathesis: Recently, Kotha and Waghule [142] have synthesized diverse crownophanes by using a cross-enyne metathesis and Diels–Alder (DA) reaction as key steps. Here, the macrocycles 146 and 149 were subjected to a cross-enyne metathesis protocol with ethylene to generate the dienes 147 and 150, respectively. These dienes were subjected to a DA reaction with different dienophiles followed by aromatization which gave the crownophanes (e.g., 148 and 151) (Scheme 22).

Cross metathesis: In 1992, (−)-cylindrocyclophane A (156) and (−)-cylindrocyclophane F (155) were isolated by Moore and co-workers [143] from a blue-green algae belonging to *Cylindrospermum licheniforme*. These paracyclophane derivatives exhibit potent cytotoxicity against the KB and LoVo tumor cell lines (IC₅₀ = 2–10 μg/mL). On another occasion, Smith and co-workers have reported the synthesis of (−)-cylindrocyclophane A (156) and (−)-cylindrocyclophane F (155) [144]. The dialkenyl derivative 152 was subjected to dimerization involving cross-metathesis with G-U/G-II/Schrock catalysts which generated the cyclized product 154. Subsequently, hydrogenation of the cyclophane 154 followed by minor functional group modification gave the natural products 155 and 156 (Scheme 23). Furthermore, the same group has reported the syntheses of (−)-cylindrocyclophanes A and F (156, 155) by a RCM approach using different strategies.
Figure 9: Synthesis of cyclophanes via ring-closing alkyne metathesis.

Scheme 22: Synthesis of crownophanes by cross-enyne metathesis. Reagents and conditions: (i) G-II (13), 5 mol %, CH₂Cl₂, 24 h, rt, (147, 78%), (150, 82%); (ii) DMAD, PhMe, reflux, 24 h, DDQ, reflux, 30 h, (148, 78%), (151, 83%).
Kotha and co-workers [145] have synthesized cyclophanes by using 1,3-indanedione using freshly prepared KF-Celite followed by SM cross-coupling reaction with an excess amount of allylboronic acid pinacol ester and afforded the required diallyl derivative 157 in good yield. Surprisingly, when the dialkyl compound 157 was subjected to RCM, instead of the monomer, the dimeric cyclophane 158 was obtained which was further subjected to hydrogenation to deliver the saturated cyclophane derivative 159 (Scheme 24).

To prepare \(\pi\)-conjugated three-dimensional molecules with potential isoelectronic properties and facile processibility, Kurata and co-workers [146] reported sexithiophene 163, a bridged cage shaped compound (Scheme 25). Its synthesis involves a Suzuki–Miyaura coupling reaction followed by cross metathesis. The molecule shows a hypsochromic shift which indicates rigidity in the molecule compared with the other linear molecules.

**Enyne metathesis:** In 1998, Fürstner and co-workers [147] have employed platinum(II)-catalyzed enyne metathesis as a key step to form cyclophane ring systems which are found in streptorubin B and metacycloprodigiosin [148-150]. In this context, the cyclooctene 164 was reacted with the intermediate formed in situ from chloramine-T and elemental selenium [151] and yielded the allylic amine derivative 165 (75%). An N-alkylation with propargyl bromide gave the enyne product 166 (92%), which on further acylation of terminal alkyne with butanoyl chloride delivered compound 167 (82%). Then, it was subjected to an enyne metathesis with simple platinum salts such as PtCl\(_2\) and PtCl\(_4\) to give product 168 (79%). A subsequent reduction of the \(\alpha,\beta\)-unsaturated ketone delivered the

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**Scheme 23:** Synthesis of \((-\text{-})\)-cylindrocyclophanes A (156) and \((-\text{-})\)-cylindrocyclophanes F (155). Reagents and conditions: (i) G-I/G-II/Schrock catalyst, 50–80%; (ii) (a) H\(_2\), Pd/C; (b) BBr\(_3\) (84% over 2 steps); (iii) (a) TBAF, THF; (b) H\(_2\), PtO\(_2\); (c) PhSH, K\(_2\)CO\(_3\), NMP (60% over 3 steps).

**Scheme 24:** Synthesis of cyclophane 159 derivatives via SM cross-coupling and RCM. Reagents and conditions: (i) G-II (13), CH\(_2\)Cl\(_2\) (0.002 M), 50 °C; (ii) H\(_2\), 10% Pd/C, CH\(_2\)Cl\(_2\)/MeOH, rt.
compound 169 (64%). Finally, aromatization of compound 169 by using potassium 3-aminopropylamide (KAPA) gave compound 170 (75%) (Scheme 26).

**Ring-closing metathesis (RCM):** In 2003, Tae and Yang [152] have reported an efficient macrocyclization of various alkenyl derivatives 171 via RCM/CM using G-I (12) or G-II (13) under high dilution conditions to obtain the \([n], [n,n]\) and \([n,n,n]\)para-cyclophanes 172–174. Compounds with a short alkenyl chain gave mainly \([n,n]\) and \([n,n,n]\)para-cyclophanes (173 and 174) by a dimerization or trimerization sequence. When the compound has a alkenyl chain of sufficient length the \([n]\)para-cyclophane 172 was obtained by an intramolecular cyclization (Scheme 27).

Alcaide and co-workers [153] have reported the synthesis of different bis(dihydrofuryl)cyclophane scaffolds 179 from carbonyl compounds. 1,4-Bis(3-bromoprop-1-ynyl)benzene (175) was reacted with azetidine-2,3-diones 176 under eco-friendly reaction conditions to generate bis(allene) 177. Compound 177 was then converted into bis(dihydrofuran) 178 by using AuCl₃.
Macrocyclization of 178 was carried out by using a Ru(II) or Ru(III) catalyst to generate 179 as a mixture of E/Z isomers (Scheme 28).

In the literature, there are limited reports on the preparation of cyclophane derivatives by a combination of the Suzuki–Miyaura (SM) coupling and an RCM as key steps. Kotha and Mandal [135] reported a new approach to assemble [1.1.6]metaparacyclophane derivative 183 via the SM cross coupling and an RCM as key steps. In this regard, the α,α'-dibromo-m-xylene (136) was treated with arylboronic acid 180, to give the dialdehyde 181 which on reaction with indium-mediated Grignard addition reaction gave diolefin 182. Later RCM of diolefin 182 delivered cyclophane 183. Subsequent oxidation of diol 183 gave [1.1.6]metaparacyclophane derivative 184 (Scheme 29).

Using the same approach, a butenyl Grignard reagent was added to compound 181 to generate diol 185. Surprisingly, after the addition of G-II catalyst 13, the two RCM products 186 and 189 were obtained [135]. The outcome of product 189 was explained on the basis of a tandem isomerization of a terminal double bond followed by the macrocyclization with G-II (13). Finally, the oxidation of diols 186 and 189 generated cyclophanes 187 and 190, respectively (Scheme 30).

Guan and coworkers [154] have reported a novel synthetic approach to cyclophanes by using a template-promoted cyclization involving the RCM as a key step. This approach proceeded via the condensation of compound 191 with acenaphthenequinone in the presence of p-TSA to deliver the RCM precursor 192, which facilitate the cyclization protocol with G-II (13) as a catalyst to generate cyclophane derivative 193.
containing an α-dimine functionality. Subsequently, the hydrogenation of 193 gave cyclophane 195. The removal of the template under hydrogenolytic conditions gave the macrocyclic compound 194 (Scheme 31).

In continuation of earlier work [145], Kotha and co-workers have demonstrated an interesting strategy to assemble [3.4]cyclophane derivative 197 by using the SM cross coupling and an RCM as key steps. The commercially available active methylene compound diethyl malonate was alkylated with a benzyl bromide derivative followed by the SM cross coupling to give dialkyl 196. Subsequently, an olefin metathesis with G-II (13) as a catalyst delivered dimeric 197 and monomeric 198 cyclophane derivatives. Later, the hydrogenation of 197 and 198 gave the corresponding saturated [3.4]cyclophane derivatives 199 and 200, respectively (Scheme 32).

Müllen and co-workers [155] have synthesized hexa-peri-hexa-benzocoronene cyclophane 201a–c. They studied their properties by carrying out differential scanning calorimetry (DSC), optical microscopy, wide-angle X-ray scattering (WAXD), and scanning tunneling microscopy (STM). Tunneling spectroscopy reveals a diode-like behavior which introduces a high caliber of these molecular complexes. The RCM protocol has been successfully employed to generate a series of dicyanobiphenylcyclophanes 202 which are useful as n-type semiconductors [156]. Winkelmann and co-workers [157] have synthesized chiral concave imidazolinium salts 203 as precursors to chiral concave N-heterocyclic carbenes. Molecular encapsulation was achieved by using double RCM to generate insulated oligoynes 204. Here, the masked hexayne plays an important role to lock the flanking chains [158]. The synthesis of planer chiral cyclophanes is a difficult task owing to the flipping of the ansa-chain.
Scheme 31: Template-promoted synthesis of cyclophanes involving RCM. Reagents and conditions: (i) acenaphthenequinone, p-TSA, C6H6; (ii) G-II (13), CH2Cl2 (0.002 M), 50 °C; (iii) Pd/C (10 mol%), H2, CH2Cl2/MeOH, rt.

Scheme 32: Synthesis of [3.4]cyclophane derivatives 200 via SM cross coupling and RCM. Reagents and conditions: (i) G-II (13), CH2Cl2 (0.002 M), 50 °C; (ii) H2, 10% Pd/C, CH2Cl2/MeOH, rt.

present in these molecules. Suzuki and co-workers [159] have reported the synthesis of enantiomerically pure planar-chiral [10]- and [12]paracyclophanes 205, which will serve as useful intermediates for the synthesis of various other cyclophane derivatives. Literature reports demonstrate the extensive use of RCM in the synthesis of different metallophanes involving ferrocenophane (e.g., 206) [160] and other metallophanes [161-164]. The synthesis of mechanically interlocked molecules such as catenanes and rotaxanes which are used to assemble molecular machines, sensors and nanomaterials is a challenging task.
Huang and co-workers [165] have reported a taco complex template method to synthesize a cryptand/paraquat [2]rotaxane and [2]catenane (e.g., 207) by using RCM as a key step. Structural features and interesting bioactivity of the hirsutellones have grabbed the attention of synthetic chemists. Liu and co-workers [166] have constructed the [10]paracyclophe 208 (skeleton of hirsutellones) via RCM. The 2,2’-bipyridine unit is an interesting building block due to its use in chelating ligands, as a binding agent and also a useful template in supramolecular chemistry. Rykowski and co-workers [167] have synthesized azathiamacrocycle 209 using RCM (Figure 10).

Collins and co-workers [168] have reported the application of auxiliaries that engage in quadrupolar interactions in a total synthesis of a macrocyclic portion of longithorone C. To investigate the macrocyclization with the pentafluorobenzyl ester auxiliary, ester 210 was synthesized in a multistep process and then subjected to olefin metathesis to deliver the macrocycle.
using the Blechert catalyst 17. The treatment of the pentafluorophenyl benzyl ester 210 with catalyst 17 in toluene afforded the rigid macrocycle 211 (39%, Scheme 33).

Kotha and Shirbhate [169] have reported the longithorone framework by using RCM as a key step. Dibromo compound 212 was reacted with monoalkylated ethyl acetoacetate 213 in the presence of NaH to deliver bis-alkylated product 214, followed by an oxidation the quinone derivative 215 (67%) was obtained. Next, the quinone 215 was subjected to RCM to generate the cyclized product 216 (71%, Scheme 34).

Nicolaou and Xu [170] assembled the floresolide B 219 via RCM as a key step. Compound 217 underwent cyclization in the presence of G-II (13) in DCM heated under reflux to generate the two isomers of 218 (89%). Subsequently, the cleavage of the nitrobenzoate group with K₂CO₃ in MeOH gave the floresolide B 219 (Scheme 35).

Fürstner and Leitner [171] have reported the synthesis of the normuscyporydine (223) by a cross-coupling reaction and an RCM as key steps. The treatment of the pyridine derivative 220 with an excess amount of the 5-hexenylmagnesium bromide in the presence of a catalytic amount of iron complex 18 as the precatalyst provides the dialkylation product 221 (75%). The treatment of the hydrochloride solution of 221 with Ru catalyst 17 in a dilute CH₂Cl₂ solution gave the cycloalkene 222 which on subsequent hydrogenation yielded the targeted normuscyporydine (223, 68%, Scheme 36).
Donohoe and coworkers [172] have reported the synthesis of muscopyridine (73) by RCM as a key step. The Wadsworth–Emmons olefination of the commercially available undecenal 224 provided acrylate 226, which was subjected to enantioselective copper-catalyzed conjugate addition with a methyl Grignard reagent involving (R)-tol-BINAP ligand to generate ester 227 in good yield and high enantiopurity. This intermediate was then converted to the key metathesis precursor involving a three step sequence of a Weinreb amide formation 228, epoxidation, and double addition of the vinyl Grignard to generate the advanced intermediate 230. Finally, RCM of diolefin 230 under high dilution conditions afforded muscopyridine (73) (Scheme 37).

Hagiwara and co-workers [173] have synthesized muscopyridine starting with methyl acetoacetate (231). They treated 231 with 5-bromo-1-pentene to generate keto ester 232 (60%). The coupling of keto ester 232 with vinyl ketone 233 under phase-transfer catalysis conditions generated the new keto ester 234 (93%), which on treatment with lithium chloride at 120 °C in dimethyl propylene urea (DMPU) gave dione 235 (72%). An RCM sequence of compound 235 in the presence of G-I (12) catalyst gave the RCM product 236. A subsequent catalytic hydrogenation generated the saturated dione 237. Finally, the pyridine ring has been introduced by reacting dione 237 with hydroxylamine hydrochloride in a sealed tube to furnish muscopyridine (73, 61%, Scheme 38).

Normuscopyridine has been also obtained by an RCM approach. To this end, commercially available 2,6-lutidine dibromide 238 was reacted with sodium benzenesulfinate to deliver 2,6-bis(benzenesulfonylmethyl)pyridine (239) in quantitative yield. Next, bis-sulfone 239 was reacted with 5-bromo-1-pentene (240) in the presence of NaN to give an inseparable mixture of cis and trans-sulfones 241a and 241b, respectively. An RCM sequence of these sulfones in the presence of the G-I (12) catalyst gave cyclophane 243 (51%) and dimeric cyclophane 242 (20%, Scheme 39) [174]. The reduction of the sulfonyl group with Mg/ethanol in the presence of 1,2-dibromoethane aided by TMSCI afforded cyclophane derivative 244.
Scheme 38: Synthesis of muscopyridine (73) via RCM strategy. Reagents and conditions: (i) NaH, n-BuLi, 5-bromo-1-pentene, rt, 2.5 h, 60%; (ii) 233, K₂CO₃, (n-Bu)₄NI, rt, 1 h, 93%; (iii) LiCl, DMPU, 120 °C, 7 h, 72%; (iv) G-I (12), CH₂Cl₂, 40 °C, 16.5 h, 90%; (v) Pd/C, H₂, EtOH, rt, 5 h, 98%; (vi) NH₂OH·HCl, 150–160 °C, 16 h, 61%.

Scheme 39: Synthesis of pyridinophane derivatives 223 and 245. Reagents and conditions: (i) PhSO₂Na, TBAB, CH₃CN, reflux, 12 h, 87%; (ii) 240, NaH, THF, rt, 24 h, 65%; (iii) G-I (12) (5 mol %), CH₂Cl₂, rt, 48 h, 243 (51%), 242 (20%); (iv) Mg/TMSCl, 1,2-dibromoethane, EIOH, 12 h, 80%; (v) H₂, EIOAc, Pd/C, rt, 12 h, 84%; (vi) Mg/TMSCl, 1,2-dibromoethane, EIOH, 12 h; (vii) H₂, EIOAc, Pd/C, rt, 12 h, (two steps 64%).

(80%). Subsequently, the hydrogenation of the double bond with Pd/C under a H₂ atmosphere gave normuscopyridine (223, 84%). Similar reaction conditions were employed with the dimeric product 242, to generate the macrocyclic pyridinophane 245 (64%).

It is interesting to note that when the same strategy was applied with a benzene analogue, dipentenylation of bis-sulfone 246 gave compounds 247 and 248, which were easily separable by column chromatography [174]. Moreover, it was observed that cis-sulfone generates the monomeric cyclophane 249 during the metathesis as confirmed by single crystal X-ray diffraction data while the trans-sulfone gave the dimer 252. Finally, the desulfonylation followed by the hydrogenation sequence of 249 and 252 generate the cyclophanes 251 and 253, respectively (Scheme 40).

With regard to the synthesis of cyclophane, Kotha and co-workers [174] have demonstrated another synthetic route to normuscopyridine (223) involving a short synthetic sequence. This route involves the reaction of dicyanopyridine 254 with alkenylmagnesium bromide to generate 255 and 256. Further, these compounds were cyclized with the aid of the G-II catalyst 13 to generate the corresponding RCM products 257 and 258, respectively. The removal of the two carbonyl groups and the hydrogenation of the double bond was accomplished in a one-pot reaction under Wolf–Kishner reaction conditions to generate 223 and 259, respectively (Scheme 41).
Scheme 40: Synthesis of metacyclophane derivatives 251 and 253. Reagents and conditions: (i) 240, NaH, THF, rt, 24 h; (ii) G-I (12, 5 mol %), CH₂Cl₂, rt, 48 h, 247 (29%), 248 (30%); (iii) Mg/TMSCl, 1,2-dibromoethane, EtOH, 12 h; (iv) H₂, EtOAc, Pd/C, rt, 12 h.

Scheme 41: Synthesis of normuscopyridine and its higher analogues. Reagents and conditions: (i) alkenyl bromide, Mg, ether, H₂O/H⁺; (ii) G-II (13, 5 mol %), PhMe, reflux; (iii) N₂H₄, K₂CO₃, ethylene glycol, 180 °C.

Cycloaddition reactions

[2 + 2] Cycloaddition: Roemer and Lentz [175] have reported the synthesis of fluorinated ferrocenophanes from 1,10-bis(trifluorovinyl)ferrocene and 1,4-(1,10-ferrocenediyl)-1,1,2,2,3,3,4-heptafluorobutane. The authors have reported a [2 + 2] cycloaddition reaction under thermal conditions. 1,10-Bis(trifluorovinyl)ferrocene (261) was synthesized starting with diiodoferrocene 260 by Negishi-type coupling. Compound 261 was subjected to a [2 + 2] cycloaddition sequence to generate cyclobutane derivative 262. Finally, the ring opening occurs with catalytic amounts of potassium hexacyanoferrate(III) in the presence of KF to deliver the fluorinated ferrocenophane 263 (Scheme 42).

Okada and Nishimura [6] have reported the synthesis of syn-[2,n]metacyclophane 270 as a key building block for the synthesis of calix[4]arene. Here, α,ω-bis(p-methoxyphenyl)alkanes 264 were used as starting materials. Compound 264 was treated with acetic anhydride and AlCl₃ in nitrobenzene and 1,1,2,2-tetrachloroethane to generate diketone 265 in 58–93% yield. Diketone 265 was then treated with LAH to generate diol 266 (72–92%). The dehydration of diol 266 with pyridinium p-toluenesulphonate in benzene gave diolefin 267. [2 + 2] Photocycloaddition of diolefin 267 was carried out by irradiation with a 400 W high-pressure Hg lamp (Pyrex filter) in benzene for 26–92 h. After evaporation, 268 and [2,n]metacyclophane 269 were isolated (61–87%). Finally, demethylation of compound 269 with BBr₃ in CH₂Cl₂ gave cyclophane 270 (Scheme 43).

[2 + 2 + 2] Co-trimerization: In 2003, Tanaka and Shirasaka [176] have reported a one-step synthesis of [6]metacyclophane 273 by a [2 + 2 + 2] co-trimerization of two different alkynes with a high chemo- and regioselectivity. The Rh(I)/H₈-BINAP complex catalyzed the partially intermolecular cycloisomerization of 1,9-decadiyne (271) and diethyl acetylenedicarboxylate...
Scheme 42: Synthesis of fluorinated ferrocenophane 263 via a [2 + 2] cycloaddition. Reagents and conditions: (i) Pd(OAc)$_2$, PPh$_3$, CF$_2$CFZnCl, THF, 5 h, reflux, 95%; (ii) PhMe, 110 °C, 2 h, 5%; (iii) K$_3$Fe(CN)$_6$, KF, H$_2$O, rt, 1 h, 67%.

Scheme 43: Synthesis of [2.ₙ]metacyclophanes 270 via a [2 + 2] cycloaddition. Reagents and conditions: (i) Ac$_2$O, AlCl$_3$, PhNO$_2$, Cl$_2$CHCHCl$_2$, rt, 12 h, 58–93%; (ii) LiAlH$_4$, THF, rt, 1 h, ~100%; (iii) PyHOTs, C$_6$H$_6$, reflux, 5 d, 72–92%; (iv) hv, C$_6$H$_6$, rt, 26–92 h, 61–87%; (v) BBr$_3$, CH$_2$Cl$_2$, rt, 12 h, 70–80%.

Scheme 44: Synthesis of metacyclophane 273 by a [2 + 2 + 2] co-trimerization. Reagents and conditions: (i) [Rh(cod)$_2$]BF$_4$/H$_8$-BINAP, CH$_2$Cl$_2$, 1 h, rt, 50%.

Tanaka and co-workers [178] demonstrated a useful approach to strained dioxo[7]paracyclophane 276 by the application of a [2 + 2 + 2] cycloaddition sequence (Scheme 45). To this end, [2 + 2 + 2] cycloaddition of 1,10-diyne 274 was carried out with methyl propiolate (275) in the presence of a cationic rhodium(I)-(S)-BINAP complex (10 mol %) as a catalyst. The desired [2 + 2 + 2] cycloaddition was carried out at room temperature to generate dioxo[7]paracyclophane 276 with a moderate ee value. The effect of biaryl bis(phosphine) ligands was examined, and it revealed the use of (S)-H8-BINAP afforded the cyclophane 276 with a good yield and optimum ee value.

Similarly, they also reported the synthesis of the planar-chiral carba-paracyclophane 278 by using the cationic rhodium(I)-(S,S)-bdpp-catalyzed [2 + 2 + 2] cycloaddition of
cyclic diyne 277 with terminal methyl propiolate (275) under high substrate concentration conditions (Scheme 46) [179].

Shibata and co-workers [180] have synthesized chiral tripodal cage compounds (e.g., 280) by using a [2 + 2 + 2] cycloaddition reaction of branched triynes (Scheme 47). The best results for a cycloaddition were observed when triyne 279 was added dropwise over a period of 10 min to a solution of a chiral catalyst at elevated temperature (120 °C). Also, highly enantioselective intramolecular reactions of different nitrogen-branched triynes were carried out to obtain diverse cyclophanes (Scheme 47).

Malacria and co-workers [181] have demonstrated an efficient use of a [2 + 2 + 2] cycloaddition reaction to generate the tetracyclic structure 282 related to taxane skeleton (Scheme 48).

Malacria and co-workers [181] have demonstrated an efficient use of a [2 + 2 + 2] cycloaddition reaction to generate the tetracyclic structure 282 related to taxane skeleton (Scheme 48).

Ohsima and co-workers [182] have reported a rhodium-catalyzed [2 + 2 + 2] cyclotrimerization of triynes 283 in a water-organic biphasic system. The biphasic system provides dilute reaction conditions suitable for macrocyclization. Selective cross-annulation between hydrophobic diynes and hydrophilic alkynes was achieved to generate ortho- and meta-cyclophane 284 and 285 (Scheme 49).

Maryanoff and co-workers [183] have synthesized the bis(indolyl)maleimido pyridinophanes via a [2 + 2 + 2] cycloaddition reaction as a key step. In this regard, indole-3-acetamide (286) was treated with 5-chloro-1-pentyne and NaH in DMF to deliver compound 287. Then, indole-3-glyoxylate 288 was

Scheme 45: Synthesis of paracyclophane 276 via a [2 + 2 + 2] cycloaddition reaction. Reagents and conditions: (i) [Rh(cod)_2]OTf (10 mol %), DCE, 120 °C, (77% yield, 98 ee).

Scheme 46: Synthesis of cyclophane 278 via a [2 + 2 + 2] cycloaddition reaction. Reagents and conditions: (i) 5–20 mol % [Rh(cod)_2]BF_4/H-BINAP, CH_2Cl_2, rt, 16 h, (91% ee).

Scheme 47: Synthesis of cyclophane 280 via a [2 + 2 + 2] cycloaddition. Reagents and conditions: (i) [(Rh(cod)(S,S)-Me-duphos)]OTf (10 mol %), DCE, 120 °C, (77% yield, 98 ee).

Scheme 48: Synthesis of taxane framework by a [2 + 2 + 2] cycloaddition. Reagents and conditions: (i) Cp(CO)_2 (5 mol %), xylene, hv, reflux.

Scheme 49: Synthesis of cyclophane 284 and 285 via a [2 + 2 + 2] cycloaddition reaction. Reagents and conditions: (i) RhCl(cod)_2tppts (2.5 mol %), H_2O/Et_2O, 20 h.
converted to N-alkylated derivative 289 by the treatment with 5-chloro-1-pentyne in the presence of cesium carbonate. The maleimide condensation of 287 and 289 was carried out in the presence of KOt-Bu at 0–23 °C to give the α,α'-diyne substrate 290 (63%, Scheme 50). Next, the diyne 290 was reacted with N,N'-dimethylcyanamide (291) or 292 and CpCo(CO)2 under argon to afford 17-membered m-pyridinophanes 293a,b and 18-membered parapyridinophanes 294a,b in 10–15% isolated yield (Scheme 50).

Maryanoff and co-workers [184] have reported the synthesis of various pyridinophanes by a [2 + 2 + 2] cycloaddition reaction mediated by a cobalt catalyst (Scheme 51). To this end, different bisalkynes 271 were reacted with p-toluenenitrile (295, 1 mol equiv) in 1:1 ratio to obtain [2,4]pyridinophane 296 and [2,5]pyridinophane 297 (Scheme 51).

[3 + 2] Cycloaddition (1,3-dipolar cycloaddition/click reaction): In 2010, Raghunathan and co-workers [185] have synthesized a C2-symmetric triazolophane by a copper(I)-catalyzed azide-alkyne cycloaddition, involving a click reaction. The dipropargyl fluorenyl derivative 299 was prepared from 9H-fluorene (298) and propargyl bromide, which on further treatment with 1,4-diazidobutane (300) and xylazides 302a–c in the presence of CuSO4·5H2O and sodium ascorbate in THF/water (1:1) gave the corresponding macrocycles (301, 42%) and (303a–c, 60–70% yield, Scheme 52).

Murphy and Leyden [186] have reported the synthesis of a glycotriazolophane 309 (carbohydrate–triazole–cyclophane hybrid) from a sugar amino acid via a copper-catalyzed azide-alkyne cycloaddition sequence. An aminosugar acid was identified as a useful building block to generate cyclophanes. Thus,

\[
\begin{align*}
286 & \xrightarrow{(i)} 287 \\
287 + 289 & \xrightarrow{(iii)} 290 \\
\xrightarrow{(iv)} & RRR'\text{N-CN}
\end{align*}
\]

\[
\begin{align*}
291 & R = R' = \text{Me} \\
292 & R = R' = (\text{CH}_2)_4 \\
293a & R = R' = \text{Me} 9\% \\
293b & R = R' = (\text{CH}_2)_4 12\% \\
294a & R = R' = \text{Me} 10\% \\
294b & R = R' = (\text{CH}_2)_4 15\%
\end{align*}
\]

Scheme 50: Synthesis of pyridinophanes 293a,b and 294a,b via a [2 + 2 + 2] cycloaddition. Reagents and conditions: (i) 5-chloro-1-pentyne, NaH, DMF, 0–55 °C, 12 h, 90%; (ii) 5-chloro-1-pentyne, Cs2CO3, DMF, 10 h, 59%; (iii) KOt-Bu, THF, 0–23 °C, 6 h, 63%; (iv) CpCo(CO)2, 1,4-dioxane, 105–110 °C, 24 h.

\[
\begin{align*}
\text{CN} + \text{Me} & \xrightarrow{(i)} 296 \\
271 + 295 & \xrightarrow{(i)} 296 + 297 \\
\end{align*}
\]

Scheme 51: Synthesis of pyridinophanes 296 and 297 via a [2 + 2 + 2] cycloaddition. Reagents and conditions: (i) 15 mol % CpCo(CO)2, o-xylene (0.001 M), 140 °C, 100 h, 50–61%.
the treatment of 304 with oxalyl chloride in the presence of DMF generated the acid chloride, which on further reaction with p-xylylenediamine (306) in the presence of N,N'-diisopropylethylamine (DIPEA) in dichloromethane followed by de-O-acetylation gave the bisazide 307 (37%). The latter compound was reacted with the dialkyne 308 in the presence of CuSO₄ and sodium ascorbate in acetonitrile/water to deliver the desired cyclophane derivative 309 (56%, Scheme 53).

Similarly, a novel BINOL-based cyclophane 310 has been synthesized via click chemistry by incorporating two triazole moieties in the macrocycle [187]. Li and co-workers [188] have...
reported the synthesis of the naphthalene-diimide-based cyclophane 311 for understanding supramolecular interactions by metal ions (Figure 11).

[3 + 2 + 1] Cycloaddition (Dötz benzannulation): In 2003, Wulff and co-workers [189] synthesized cyclophane derivatives using the Dötz benzannulation as a key step. They found that the Fischer carbene complex 314 in a coordinating solvent such as THF lead to the products 312 (15%) and 313 (42%) whereas a non-coordinating solvent like benzene delivered products 315 (40%) and 316 (21%, Scheme 54).

Wulff and Wang [190] have synthesized [6,6]metacyclophane via an intermolecular benzannulation reaction of Fischer carbene complexes with a residual alkyne to generate the 18-membered ring. Two molecules of the Fischer carbene complex 317 reacted by an intermolecular fashion to generate the [6,6]metacyclophane 318 (39%). Alternatively, a double benzannulation of a biscarbene complex 319 with 1,9-decadiyne (271) delivered [6,6]metacyclophane 318 (31%) (Scheme 55).

Dötz and Gerhardt [191] have synthesized the [2,2]metacyclophane via chromium-mediated intermolecular benzannulation. In this connection, methoxy(alkynyl)carbene complex undergo
an intramolecular benzannulation reaction in the presence of a polar solvent such as THF to deliver [6,6]metacyclophane (321a, 25%, 321b, 20% and 321c, 38%). Similarly metabenzoquinonophane 322 has been synthesized starting with 320 by an in situ oxidation of the benzannulated product by using cerium(IV) ammonium nitrate (40%, Scheme 56).

**Intramolecular Diels–Alder (DA) reaction:** Suwa and co-workers [192] have synthesized the muscopyridine by a [4 + 2] cycloaddition of the bisketene 325. The condensation of acid dichloride derived from 323 with two molecules of Meldrum’s acid gave 324 which on thermal activation in chlorobenzene yielded bisketenes 325a and 325b. These two ketene derivatives underwent an intramolecular cycloaddition to afford a 1:1 mixture of 326 and 327 (96%, Scheme 57). On heating with concentrated HCl, 326 and 327 were transformed to pyrone derivative 328 (89%). A solution of the compound 328 in ethanol saturated with ammonia was heated in a stainless steel tube for 3 days to deliver the pyridinone derivative 329 (87%). Further, chlorination of the pyridinone 329 afforded the chloropyridine 330 (93%). Subsequently, hydrogenolysis of the pyridine derivative 330 gave the target muscopyridine (73, 89%).

**[4 + 2] Cycloaddition (Diels–Alder reaction):** In 2003, Tochtermann and co-workers [193] have synthesized a bis[10]paracyclophane with two chiral planes and one chiral axis via the DA reaction as a key step. The bifuran derivative 331 was subjected to a DA sequence with dimethyl acetylenedicarboxylate (DMAD) to deliver compounds 332a,b (77%). These DA adducts were irradiated in diethyl ether/dichloromethane (5:1) to offer the corresponding bioxaquadricyclane 333, subsequent thermolysis gave the bioxepine 334 (81%). Finally, aromatization of bioxepine 334 with trifluoroacetic acid (TFA) delivered ketophenol 335 (37%), which on further treatment with potassium tert-butoxide/methyltriflate...
mixture, gave the dimethyl ether bis[10]paracyclophane 336 (63%, Scheme 58).

In 1980, Gassman and co-workers [194] have synthesized [8]paracyclophane via the DA reaction as a key step. In this connection, 1,3-cyclododecadiene (337) was reacted with maleic anhydride to give the DA product 338 (21%). Later, the DA adduct 338 was heated under reflux in 10%aq tetrahydrofuran to afford the diacid, which on decarboxylation in the presence of lead tetraacetate in a toluene/pyridine mixture delivered compound 339 (22%). Treatment of 339 with 1 equiv of m-chloroperbenzoic acid gave the epoxide 340 (80%), followed by HCl treatment gave [8]paracyclophane 341 (93%) (Scheme 59).

**Synthesis of the macrocyclic portion of longithorone C (DA reaction):** In 1994 longithorone A was first described by Schmitz and co-workers [195]. This unusual heptacyclic marine natural product is a cytotoxic agent. Its synthesis is considered difficult due to the stereocenters present in the ring system of longithorone A and E. Moreover, hindered rotation around the quinone moiety adds even more complexity to its synthesis.

Recently, Shair and co-workers [196] have reported the enantioselective synthesis of (−)-longithorone A by using a conventional synthesis to realize the proposed biosynthesis, which was put forward by Schmitz involving an intermolecular and an intramolecular DA reaction of two [12]paracyclophanequinone [197]. Based on this proposal Shair and co-workers attempted the synthesis of the natural product (−)-longithorone A. Diene 343 and the dienophile 342 were synthesized by several steps and subsequently subjected to the DA sequence to afford the rigid (−)-longithorone A (346, 90%, Scheme 60).

Nicolaou and co-workers [198] have reported the synthesis of sporolide B (349). The synthesis involves a DA reaction.
between \(o\)-quinone as the diene component and indene derivatives as dienophiles. This total synthesis also involves a Ru-catalyzed \([4 + 2]\) cycloaddition reaction to generate a highly substituted indene system containing a chlorine substituent on the aromatic ring (Scheme 61).

Cavicularin, a natural product containing a cyclopane system was isolated from the liverwort *Cavicularia densa*. Among several approaches to prepare this natural product, Beaudry and Zhao [199] have reported the synthesis of the basic architecture of (\(+\))-cavicularin (352) by using the DA reaction of pyrone and vinyl sulfone (Scheme 62). They have reported the first intramolecular enantioselective DA reaction of the \(\alpha\)-pyrone, also regioselective one-pot three-component Suzuki reaction of a dibromoarene to form a highly substituted terphenyl system (Scheme 62).
Scheme 62: Synthesis of the framework of (+)-cavicularin (352) via a [4 + 2] cycloaddition. Reagents and conditions: (i) cinchona alkaloid derivative, EtOAc, 3 Å MS, 45 °C; (ii) (a) Tf₂O, CH₂Cl₂, 0 °C, 45% (2 steps); (b) NH₄CO₂H, Pd/C, MeOH, 70 °C, quant.; (c) BBr₃, CH₂Cl₂, 80%.

Scheme 63: Synthesis of oxazole-containing cyclophane 354 via Beckmann rearrangement. Reagents and conditions: (i) polyphosphoric acid, toluene, reflux, overnight, 46%.

Rearrangement reactions
Beckmann rearrangement: Uemura and coworkers [200] have synthesized the cyclophane-containing oxazole moiety via a Beckmann rearrangement as a key step. α-Formylketoxime dimethyl acetal 353 was synthesized in several steps and subjected to a Beckmann rearrangement by using polyphosphoric acid in toluene heated under reflux conditions to give oxazole-based cyclophane 354 in 46% (Scheme 63).

Benzidine rearrangement: Benniston and co-workers [201] have reported the synthesis of cyclophanes 360a–c involving a benzidine rearrangement [202-208]. The m-nitrophenol (355) was reacted with ditosylate 356 to generate m-nitrophenol ether derivative 357, which on a reduction with Zn in MeOH gave azo-derivative 358. It was further converted into the hydrazo compound 359 which underwent a benzidine rearrangement under acidic conditions to deliver cyclophanes 360a–c. The cyclophanes obtained here involve the migration of nitrogen on the aromatic ring (Scheme 64).

Cho and co-workers [209] have reported the synthesis of 4,4-diaminobiphenyls (benzidine) connected with a polyether unit at the 2,2′-positions using the benzidine rearrangement. The cyclophane synthesis of 365 starts with the preparation of 361a–c starting with m-bromophenol and polyether ditosylates. The Cu(I)-catalyzed coupling reactions of the bis(m-bromophenyl) ethers 361a–c provided the monohydrazides 362a–c (53–57%). Cyclization reactions were carried out by using a Pd catalyst delivering diarylhydrazides 363a–c (46–50%). Later, the hydrazides 363a–c were heated in EtOH with a catalytic amount of aq HCl to generate the corresponding benzidines 364a–c, as indicated by their crude ¹H NMR spectra. These products were subjected to an acetylation sequence to generate the cyclophane-based acetamides 365a–c (Scheme 65).

Claisen–Dennstedt rearrangement: Reese and Dhanak [210] have synthesized a strained cyclophane such as [6](2,4)pyridinophane derivatives 367 by using a ring expansion strategy. Here, pyrrole derivative 366 was treated with dihalocarbene giving the cyclopropane intermediate 366a which was further converted into pyridinophane 367 by a ring expansion (Scheme 66).

Claisen rearrangement: To develop new strategies to diverse cyclophanes, Kotha and Waghule [211] have reported the synthesis of cyclophane 373 by using the double Claisen rearrangement and an RCM as key steps. Bisphenol 368 was converted to o-allyl derivative 369, which on a Claisen rearrangement followed by protection of the phenolic hydroxy groups gave 371. An RCM of 371 followed by the hydrogenation of the RCM product 372 gave cyclophane 373 (Scheme 67). By using a similar approach various cyclophanes were synthesized starting with resorcinol as well as hydroquinone and attaching an ethyleneoxy chain of different length (Scheme 67) [212].
Scheme 64: Synthesis of cyclophanes 360a–c via benzidine rearrangement. Reagents and conditions: (i) 356a–d, K₂CO₃, DMF; (ii) Zn, NaOH; (iii) HCl.

Scheme 65: Synthesis of cyclophanes 365a–c via benzidine rearrangement. Reagents and conditions: (i) BocNHNH₂, CuI, Cs₂CO₃, 1,10-phen, DMF, 80 °C, 24 h; (ii) Pd(OAc)₂, P(t-Bu)₃, PhMe, 110 °C, 12 h; (iii) aq HCl, EtOH, 80 °C, reflux, 2 h; (iv) AcCl, NaOAc, MeCN, rt, 12 h.

Scheme 66: Synthesis of metacyclophane 367 via Ciamician–Dennstedt rearrangement. Reagents and conditions: (i) Cl₂CO₂Na (5 equiv), 1,2-dimethoxyethane, reflux, 4 h; (ii) Hg(Ph)(CBr₃)₂ (2 equiv), benzene, reflux, 24 h.
Kotha and Shirbhate [213] have synthesized the cyclophane derivative 380. Commercially available 4-bromophenol (374) and allyl bromide were reacted in the presence of a mild base such as K₂CO₃ to generate O-allyl derivative 375 (98%). Later, commercially available 2,6-pyridinedicarbonitrile (254) was reacted with the Grignard reagent prepared from O-allyl bromophenol (375), activated magnesium turnings, and iodine (for activation) in THF. The desired bis-O-allyl derivative 377 was then directly subjected to a Claisen rearrangement at 180 °C in o-dichlorobenzene (o-DCB) for 8 h (Scheme 68). The diallylated compound 378 was subjected to RCM by using G-II (13) as a catalyst to generate the desired cyclophane 379 (62%) as a 1:1 mixture of cis and trans-isomers. However, the trans-isomer of RCM product 379 was crystallized in methanol and acetonitrile (1:1) after several attempts (Scheme 68).

**Cope rearrangement:** In 1986, Vögtle and Eisen [214] have succeeded in assembling a tetraarylbiallyl skeleton by doubly bridged metacyclopheane derivatives, which underwent a spontaneous Cope rearrangement under mild reaction conditions. Tetraaryl dialdehyde 381 was prepared in several steps and further reduction of the aldehyde functionality with NaBH₄ in methanol gave the diol. Bromination of the diol with PBr₃ gave the dibromotetraaryl derivative 382 (75%). Subsequently,
Favorskii rearrangement: In 2005, Gleiter and co-workers [215] have synthesized sterically stabilized cyclopropanophanes, containing non-benzenoid three-membered aromatic rings. Diketone 385 was subjected to bromination in the presence of bromine which afforded tetrabromide 386 with anti-orientation to the keto group with four equatorial bromine atoms (46%). Subsequently, tetrabromo derivative 386 was converted to cyclopropanophane 387 (27%) by Favorskii rearrangement and thus generated the three-membered ring systems (Scheme 70).

Photo-Fries rearrangement: It was shown that Diazonamide has potent in vitro activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cells and several attempts have been reported to synthesize this alkaloid. Magnus and Lescop have reported [216] the synthesis of the diazonamide core 388 by using a photo-Fries rearrangement with the substrate 389 (Scheme 71).

Schmidt rearrangement: The first approach described here involves the Stobbe condensation of cyclododecanone (390) with ethyl succinate to deliver carboxylic acid 391, which on cyclization with zinc chloride in polyphosphoric acid gave cyclopentanone derivative 392. Acidic hydrolysis of ester 392 and simultaneous decarboxylation gave the unsaturated ketone 393. Wolff–Kishner reduction of the cyclopentanone derivative 393 gave the two isomeric olefins 394 and 395. An application of the Schmidt reaction with a mixture of compounds 394 and 395 followed by dehydrogenation with Pd/C afforded [10](2,6)pyridinophane 223 and its 2,3-isomer 397 (Scheme 72) [217].

Tandem Claisen rearrangement: In 2008, Hiratani and co-workers [218] have reported the synthesis of the sulfur-containing crownophane 401 by using the tandem Claisen...
rearrangement as a key step. Diacetyl chloride 398 was coupled with various sulfur-containing diamines followed by tandem Claisen rearrangement of the resulting exemplar amide derivative 399 in N-methyl-2-pyrrolidone (NMP) which yielded the desired sulfur-containing crownophane 400. Later, the reaction of this crownophane 400 with Hg(OAc)$_2$ gave the organomercurated dihydrobenzofuran containing macrocycle 401 (Scheme 73).

Kotha and co-workers [212] have also attempted the synthesis of cyclophane derivatives involving the tandem Claisen rearrangement and an RCM as key steps. To this end, $p$-cresol (402) was reacted with allyl bromide to give allyl ether 403, which undergoes a Claisen rearrangement to deliver $O$-allylphenol derivative 404. Phenol derivative 404 was reacted with 3-chloro-2-(chloromethyl)-1-propane (405) to generate the key precursor 406. Tandem Claisen rearrangement of 406 in the presence of BCl$_3$ yielded the rearranged product 407 (27%). Various attempts to generate the RCM product 408 from 407 or its derivatives were not successful (Scheme 74).

**Alkylation**

Bates and Ogle [219] have reported the synthesis of the normuscopyridine and its analogues by reacting the dipotassium salt of lutidine with dibromoalkanes. To this end, 2,6-dimethylpyridine (409) was treated with $n$-BuLi and KO$_2$-Bu to generate dianion 410, which on reaction with dibromoalkanes gave the symmetrical pyridinophanes 411 in 5–10% overall yield (Scheme 75).

**Friedel–Crafts alkylation**

In 1954, Schubert and co-workers [220] have synthesized dimeric and trimeric benzocyclanone via Friedel–Crafts reaction as a key step. In this regard, compound 7-phenylheptanoyl chloride (412), was subjected to cyclization under high-dilution conditions to deliver dimer 413 (5%) and trimer 414 (0.4%, Scheme 76).

**Friedel–Craft acylation**

Georgi and Retey [221] have synthesized the isomer of muscopyridine 418 involving the pyrylium salt 417. The
Scheme 73: Synthesis of crownophanes by tandem Claisen rearrangement. Reagents and conditions: (i) diamine, Et$_3$N, THF; (ii) NMP, reflux; (ii) Hg(OAc)$_2$, DMF/ether.

Scheme 74: Attempted synthesis of cyclophanes via tandem Claisen rearrangement and RCM. Reagents and conditions: (i) allyl bromide, K$_2$CO$_3$, acetone, reflux, 16 h, 92%; (ii) 160–180 °C, 6 h, 77%; (iii) 405, K$_2$CO$_3$, acetone, reflux, 6 h, 84%; (iv) BCl$_3$, CH$_2$Cl$_2$, –60 °C to rt, 3 h, 27%.

Scheme 75: Synthesis of muscopyridine via alkylation with 2,6-dimethylpyridine anion. Reagents and conditions: (i) Kt-OBu, n-BuLi, C$_6$H$_{12}$, reflux, 1 h, 100%; (ii) dibromoalkanes, THF, –78 °C to rt.
overall yield of the reaction was low. Diacylation of isobutylene (416) with dichloride 415 in the presence of aluminum chloride gave pyrylium salt 417 which on further treatment with ammonia gave pyridinophane 418 in low yield (Scheme 77).

Kotha–Schölkopf reagent [222]

Kotha and co-workers [223] have reported the first and unexpected synthesis of macrocyclic cyclophane containing the unusual amino acid derivative 423 by using phosphazene as a base without high-dilution conditions (Scheme 78). Coupling of
the two bromo-substituted rings was carried out with ethyl isocyanooacetate (Kotha–Schölkopf reagent).

They also reported the synthesis of macrocyclic cyclophane-based unusual α-amino acid (AAA) derivatives 426 involving ethyl isocyanooacetate (421) and 1,2-bis(4-(bromomethyl)phenyl)ethane under phase-transfer catalysis (PTC) conditions using a phosphazene base (BEMP). Out of two isomers formed, trans-isomer 426a was crystallized from petroleum ether (Scheme 79) [224,225].

(p-Tolylsulfonyl)methyl isocyanide (TosMIC)
Shinmyozu and co-workers [226] have reported the synthesis of [34](1,2,4,5)cyclophane 430 by using the TosMIC reagent. This reagent is useful to prepare barrelenophane which can be further converted into semibullvalenophane (Scheme 80).

Synthesis of azacyclophane via nitrobenzenesulfonyl (Ns)-amide method
In 2008, Okamoto and co-workers [227] have synthesized diaza[32]cyclophanes and triaza[33]cyclophanes. To this end, bis-Ns-amide 431 was prepared by several steps and it was further treated with NaH in DMF to generate the bis-amidate anion, which was coupled under high-dilution conditions with 1,4-bis(chloromethyl)benzene (432) at 70 °C to give the dimer 433 as well as the trimer 434. Subsequently, deprotection of cyclophanes 433 and 434 was carried out with sodium ethanethiolate at 50 °C and the amino derivatives were acetylated with trifluoroacetic anhydride to generate cyclophanes 435 (26%) and 436 (5%), respectively (Scheme 81).

Acyloin condensation
Rubin and coworkers [228] have synthesized cyclophane 439 by acyloin condensation. Furthermore, studies were carried out to find out the behavior of intramolecular energy transfer reaction (Scheme 82).

Aldol condensation
Shinmyozu and co-workers [229] have reported the synthesis of multibridged [3n]cyclophanes 442 by aldol condensation. Due to an enhanced transannular π–π interaction between two benzene rings and the hyperconjugation of the benzyl hydro-
gens with the benzene rings multibridged cyclophane 442 shows a high π-donating ability. Aldol condensation of ketoaldehyde 440 gave keto derivative 441 which was further extended to multibridged cyclophane 442 (Scheme 83).

Intramolecular esterification reaction
In 2014, Preobrazhenskaya and co-workers [230] have synthesized [15]-, [16]-, and [17]-membered lactones containing bis-3,4(indol-1-yl)maleimide framework via an intramolecular esterification reaction as a key step. 2,3-Dibromomaleimide (443) was coupled with various (2,3-dihydridindol-3-yl)alkanals (444a–c) in the presence of Et3N to give the corresponding ω-hydroxyalkyl derivatives 445a–c. Next, the protection of the hydroxy groups with TBDMSCl led to the protected derivatives 446 (72–80%). The bromo derivatives 446 were subjected to dehydrogenation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to obtain 3-bromo-4-[3-(ω-hydroxyalkyl)indol-1-yl]maleimides 447 (72–75%), which were further coupled with various (3,4-dihydridindol-3-yl)alkanoic acids 448 to deliver the bisindole derivatives 449. The bisindoles 449 were then treated with a catalytic amount of p-toluenesulfonic
acid in benzene and heated under reflux to afford the macrolactones 450. Dehydrogenation by using DDQ oxidation gave various macrolactones 451 (68–75%, Scheme 84).

Yamaguchi esterification
Rohanna and Rainier [231] have reported the synthesis of muscopyridine (73) by using an olefin lactone cyclization strategy. The Yamaguchi esterification of acid derivative 452 gave lactone 454. Cyclization of lactone 454 yielded macrocyclic dihydropyran 455. Silica gel mediated hydrolysis of the enol ether gave hydroxy ketone 456, which served as a useful precursor to both muscone (458) and muscopyridine (73). Muscopyridine (73) has been generated via oxidation of the secondary alcohol 456, followed by treatment of the 1,5-diketone with NH$_4$OH. Alternatively, (R)-(−)-muscone (458) has been obtained from hydroxy ketone 456 by using the Barton–McCombie deoxygenation conditions (Scheme 85).

Elimination reactions
**Double elimination reaction:** In 2001, Bickelhaupt and co-workers [232] have synthesized a [5]metacyclophane derivative with an sp$^2$-center embedded at the central position of the bridge. Ditosylate 459 was converted to dibromide 460 by treatment with LiBr followed by the addition of dichlorocarbene to give the cyclopropane derivative 461 according to the Skattebøl method [233]. Next, it was rearranged to cyclopentane derivative 462 by using flash vacuum pyrolysis (FVP) [234]. The addition of dichlorocarbene to compound 462 by the method of Makosza [235] gave compound 463 which was cyclized with TosMIC [236,237] to generate propellane derivative 464. Finally, the cyclophane 465 was obtained (70%) from 464 by a double elimination reaction by using AgClO$_4$ and lutidine in THF (Scheme 86).

**Hofmann elimination reaction:** The Hofmann elimination [238-241] is also named the Hofmann degradation. This reaction involves the elimination of alkyltrimethylamines and the product formation proceeds with an anti-stereochemistry. This reaction is generally suitable for assembling alkenes with one or two substituents. A general procedure involves the conversion of an amine into a tertiary amine followed by the treatment with silver oxide, water and heating finally generates the alkene. The least substituted alkene is formed as a major product which is also known as the Hofmann rule [242,243]. The Hofmann elimination reaction is a classical and useful method to generate cyclophanes by cyclization of the obtained alkenes compounds. Using this method a variety of cyclophanes have been prepared, including 1,6(2,5)-difuranacyclodecaphane (466) [244], paracyclo[2](2,5)-furanophane (467) [244], and quadrapole-layered...
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Scheme 85: Synthesis of muscone and muscopyridine via Yamaguchi esterification. Reagents and conditions: (i) 453, THF, PhMe, NEt₃, DMAP, 45 °C, 6 h, 90%; (ii) TiCl₄, Zn, TMEDA, PbCl₂, CH₂CHBr₂, THF, 0 °C to rt, 2 h, 69%; (iii) SiO₂, CH₂Cl₂, 0 °C to rt, 10 h, 49%; (b) Bu₃SnH, AIBN, PhH, reflux, 4 h, 97%; (v) 454, NH₄OH, EtOH, 160 °C, 18.5 h, 54%.

Scheme 86: Synthesis of [5]metacyclophane via a double elimination reaction. Reagents and conditions: (i) LiBr, acetone, 12 h, reflux, 81%; (ii) CHCl₃, t-BuOK, C₆H₆, rt, 80%; (ii) FVP, 480 °C, 5 × 10⁻⁵ mbar, 90%; (iv) CHCl₃, PTC, NaOH (50%), 83%; (v) NaH, TosMIC, DMSO/Et₂O, 15%; (vi) AgClO₄/lutidine, THF, 90%.

paracyclophane 468 having charge-transfer properties [245]. Other examples of cyclophanes such as octamethyl[2.2]paracyclophane (469) [246,247], (2E,6E,9E,13E)-1,8(1,4)-dibenzenacyclotetradecaphane-2,6,9,13-tetraene (470) [248], difluoro[2,2]paracyclophane (471) [249], and 2,6-azulylene (472) [250] are shown in Figure 12.

Baylis–Hillman reaction
In 1994, Foucaud and co-workers [251] have synthesized a macrocyclic cryptophane based on the Baylis–Hillman reaction. Dialdehyde 473 was reacted with methyl acrylate in the presence of diazabicyclonooctane (DABCO) for 14 days at room temperature which resulted in the formation of diol 474. Diol 474 was then subjected to an acetylation in the presence of AcOH to obtain allylic acetate 475 (97%). Finally, dicacetate 475 was subjected to a nucleophilic substitution reaction by using ammonia in methanol to generate cryptophane 476 (28%, Scheme 87).

Double Chichibabin reaction
The Chichibabin reaction is one of the most elegant reactions to synthesize 2-substituted aminopyridines. Caulton and co-workers [252] have reported the synthesis of [2.n.1](2,6)pyridinophane 479 by double Chichibabin reaction starting with 477 (Scheme 88). Also, using ab initio and DFT calculations, they reported new macrocyclic ligands to achieve an “intermediate” degree of stability and reactivity of d6 metal alkyl hydrido complexes.
Zabel and co-workers [253] have reported the synthesis of 3,3-biindolizine-based cyclophane 483 via Chichibabin reaction as a key step. Compound 480 was reacted with α-bromoacetophenone (481) by adopting standard Chichibabin reaction conditions to deliver the crown ether derivative 482 (28%). Subsequently, compound 482 was treated with potassium hexacyanoferrate to get the desired cyclophane 483 via an intramolecular oxidative coupling (Scheme 89).

**Intramolecular S_N_Ar reaction**

In 2002, Zhu and co-workers [254] have synthesized cyclopeptide alkaloids containing paracyclophane with a peptidic tether
via an intramolecular S_N Ar reaction. Compound 484 was subjected to a ring closure in THF with TBAF as a base to give a mixture of two isomers 485 and 486 (65%). Subsequent acetylation gave cyclophane derivatives 487 and 488 (Scheme 90).

Muscopyridine via C-zip ring enlargement
Hadjabo and Hesse [255] have synthesized muscopyridine (73) via the C-zip ring enlargement reaction as a key step (Scheme 91). Aldehyde 489 was protected with ethylene glycol to generate the mono-acetal 490. Then, enone 491 was afforded with lithium disopropylamidom (LDA) and PhSeBr/H_2O_2. The intramolecular conjugated addition of the enone system 491 in the presence of Me_2CuLi gave a mixture of two diastereomers 492. The deprotection of the ketal with TsOH furnished aldehyde 493. A ring expansion involving an enamine reaction gave compound 494 (Figure 13), which was then hydrolyzed in 10% HCl to deliver 495. Nitroderivative 495 was subjected to a modified Nef reaction with TiCl_3 to deliver diketone 496. Finally, diketone 496 was converted to a pyridine derivative with hydroxylamine hydrochloride to generate muscopyridine (73, Scheme 91).

Nicholas reaction
Green and co-workers [256] have reported the synthesis of an indolophanetetrayne–cobalt complex by using the Nicholas reaction as a key step (Scheme 92). Sonogashira coupling of N-propargylindoles 497a–c with iodoarylpropargyl acetate 498 gave N-functionalized indole precursors 499a–c [257,258]. Both alkyne units of diynes 499a–c can be converted to the corresponding cobalt complexes 500a–c in the presence of an excess amount of Co_2(CO)_8. The protected complex 500a was
Scheme 91: Synthesis of muscopyridine (73) via C-zip ring enlargement reaction. Reagents and conditions: (i) HO(CH$_2$)$_2$OH, TsOH, benzene, $\Delta$; (ii) (a) LDA, PhSeBr, THF, $-78^\circ$C; (b) H$_2$O$_2$, AcOH; (iii) Me$_2$CuLi, PhMe, $-50^\circ$C; (iv) TsOH, acetone, H$_2$O; (v) C$_5$H$_{11}$NH$_2$, EtOH, 23 °C; (vi) 10% HCl, EtOH; (vii) (a) MeOH, MeONa, TiCl$_3$, NaOAc, (b) HCl, H$_2$O; (viii) NH$_2$OH·HCl, EtOH, 165 °C, 64%.

Figure 13: Mechanism of the formation of compound 494.

subjected to a cyclization reaction using BF$_3$·OEt$_2$ at room temperature to generate C-2-linked indolophanetetrayne 501a (55%, Scheme 92).

Radical cyclization
In 1990, Turro and co-workers [259] have demonstrated a new methodology involving the photolysis of large α-phenylcycloalkanes by an intramolecular para coupling of the acyl-benzyl biradical intermediate. Cyclododecanone 502 was subjected to photolysis to generate both α-cleavage and γ-hydrogen abstraction reaction to give compound 503. The photochemical irradiation of the large-ring containing 2-phenylalkenones 504 produce cyclophane 505 as the major product (Scheme 93).

Ramberg–Bäcklund olefination reaction
In 2010 Nicolaou and co-workers [260] have reported the asymmetric synthesis of (−)-cylindrocyclophanes A and F (156, 155) by employing the head-to-tail dimerization approach to this class of compounds, based on the Ramberg–Bäcklund olefination reaction. The monomeric bifunctional precursor 506 was dimerized to [7.7]paracyclophane by using NaOMe in MeOH at ambient temperature to generate macrocyclic bis(thioether). Macrocyclic bis(sulfone) 507 (51%) has been obtained by oxidation of bis(thioether) with H$_2$O$_2$ in the presence of (NH$_4$)$_6$Mo$_7$O$_{24}$·4H$_2$O). Then, sulfone 507 on treatment with alumina-impregnated KOH (KOH/Al$_2$O$_3$) in the presence of CF$_3$Br$_2$ in CH$_2$Cl$_2$/r-BuOH 1:1 gave the bis(olefin) 508 (70%). The dihydroxylation of compound 508 with AD-mix-β
Scheme 92: Synthesis of indolophanetetraysnes 501a,b using the Nicholas reaction as a key step. Reagents and conditions: (i) Pd(PPh₃)₄, CuI, iPr₂NH, rt, 12 h; (ii) Co₂(CO)₈, Et₂O, 0 °C, 3.5 h.; (iii) BF₃·OEt₂, 0 °C, 5 h.

Scheme 93: Synthesis of cyclophane via radical cyclization. Reagents and conditions: (i) cyclododecanone, phenyllithium 2 M, THF, –78 °C, hv, 2 h, 78%; (ii) 450 W mercury lamp, K₂CrO₃, 20–40 min.

Over 40 different alkaloids were isolated from the Lythraceae family ranging from type A–E. Type C–E were reported previously, but Fujita and co-workers [263] reported the synthesis of type A alkaloid lythranidine for the first time. The key intermediate 515 was synthesized by using the McMurry reaction as a key step. For decades, caged compounds have been found to be useful targets to accommodate different ions. By a simple modification and the utilization of the flexibility of the crown ethers they can be used for the trapping of a variety of metal ions. Wennerström and co-workers [264] reported the synthesis of bicyclophane 516 by using a six-fold Wittig reaction. The use of conjugated polymers in chemical and biological sensors is well-known. However, water solubility poses limitations on the extensive use of these molecules. Bazan and co-workers [265] have reported the synthesis of the water-soluble oligomer dimers 517 based on paracyclophane with two chromophores in close proximity which results in a strong interchromophore delocalization and a decreased tendency toward aggregation as shown by light-scattering experiments (Figure 14).
Scheme 94: Synthesis of (−)-cylindrocyclophanes A (156) and (−)-cylindrocyclophanes F (155). Reagents and conditions: (i) NaOMe, MeOH, 23 °C, 36 h; (ii) (NH₄)₆Mo₇O₂₄·4H₂O, H₂O₂, EtOH, 23 °C, 12 h, 51% over two steps; (iii) CF₂Br₂, KOH/Al₂O₃, CH₂Cl₂/t-BuOH 1:1, 0–23 °C, 2 h; then [Pd(CH₃CN)₂Cl₂], 40 °C, 4 h, 70%; (iv) AD-mix-β, MeSO₂N₃H₂, t-BuOH/H₂O 2:1, 23 °C, 12 h; (v) 509, PhMe, 125 °C, 5 h; (vi) AIBN, n-Bu₃SnH, PhMe, 100 °C, 1.5 h, 50% over three steps; (vii) MsCl, Et₃N, CH₂Cl₂, 0 °C, 0.5 h; then AIBN, 0 °C, 10 min; then BBr₃, 23 °C, 5 h, 71% one pot; (viii) DMP, NaHCO₃, CH₂Cl₂, 23 °C, 1 h; (ix) KHMDS, Comins reagent, THF, −78 °C, 1 h; (x) Fe(acac)₃, MeMgBr, THF/NMP 20:1, 0 °C, 1 h, 74% over three steps.

Scheme 95: Cyclophane synthesis via Wittig reaction. Reagents and conditions: (i) LiOEt (2.1 equiv), THF, −78 °C to 0 °C, 0.5 h; (ii) 513 (1.1 equiv), THF, −78 °C to 0 °C, rt, 4 h.
Figure 14: Representative examples of cyclophanes synthesized via Wittig reaction.

Thermal isomerization of Dewar benzene
In 1987, Tobe and co-workers [266] have explored different routes to assemble the [6]paracyclophane structure by utilizing thermal valence isomerization of Dewar benzene. The photocycloaddition of bicyclic enone 518 with methyl acrylate gave the head-to-tail endo product 519 (49%), which was subjected to ring contraction via (i) α-formylation (ii) diazo-transfer and (iii) Wolff photo rearrangement to generate propellane derivative 520 (35%). Phenylselenylation of 520 with an excess amount of LDA and diphenyl diselenide gave bis-selenide 521 (32%). Oxidation of 521 with hydrogen peroxide generated the Dewar benzene derivative 522 (73%). Finally, valence isomerization of propellane derivative 522 afforded [6]paracyclophane 523 (90%, Scheme 96).

Conclusion
We have summarized the utility of various popular reactions related to cyclophane synthesis. In some instances, cyclophanes are formed in low yield and also with side products. We feel that this compilation will be beneficial to design better routes and to improve the existing routes to cyclophanes. We have included popular reactions which in our view have potential for further expansion. We have also included structures of interesting cyclophane derivatives without going into detailed schemes to keep the volume of information at a manageable level.

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Scheme 96: Synthesis of the [6]paracyclophane via isomerization of Dewar benzene. Reagents and conditions: (i) methyl acrylate, ether, 500 W, 3–5 h, 49%; (ii) HCO₂Me, MeONa, TsN₂, hv, MeOH, 2 h, 35%; (iii) LDA, THF, −78 °C, Ph₂Se₂, HMPA, 1 h, 32%; (iv) pyridine, CH₂Cl₂, H₂O₂, 1.5 h, 40 °C, 73%; (v) C₆H₆, 50 °C, 95 h, 90%.
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References

1. Faust, R. Angew. Chem., Int. Ed. Engl. 1995, 34, 1429–1432. doi:10.1002/anie.199514291
2. Li, C. Chem. Commun. 2014, 50, 12420–12433. doi:10.1039/C4CC03170A
3. Kim, J. N.; Lee, K. Y. Curr. Org. Chem. 2002, 6, 627–645. doi:10.2174/1385272023374094
4. Sława, W.; Zujewksa, T. Heterocycles 2005, 65, 1713–1739. doi:10.3987/REV-05-596
5. Bodwell, G. J.; Nandaluru, P. R. Isr. J. Chem. 2012, 52, 105–138. doi:10.1002/ijch.201200003
6. Okada, Y.; Nishimura, J. J. Inclusion Phenom. Mol. Recognt. Chem. 1994, 19, 41–53. doi:10.1002/BF00708973
7. Schwartz, M. H. J. Inclusion Phenom. Mol. Recognt. Chem. 1990, 9, 1–35. doi:10.1002/1521-3765(19900500)9:3<1::AID-JIC3>3.0.CO;2-E
8. Štefan, M.; Grim, M.; Hruby, V.; Chmelík, M.; Strutt, N. L.; Barnes, J. C.; Butterfield, A. M.; Dale, E. J.; Naini, S. R.; Ranganathan, S.; Yadav, J. S.; Ramakrishna, K. V. S.; Tang, R.-Y.; Li, G.; Yu, J.-Q. Tetrahedron 2012, 68, 15812–15822. doi:10.1016/j.tet.2011.12.031
9. Ramaiah, D.; Neelakandan, P. P.; Nair, A. K.; Avirah, R. R. J. Inclusion Phenom. Macrocyclic Chem. 2014, 12, 653–663. doi:10.1002/ijch.201100080
10. Chen, F.; Weng, J.; Liu, Y.; Li, Y. J. Org. Chem. 2015, 11, 1274–1331. doi:10.1021/acs.joc.5b00384

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References

1. Faust, R. Angew. Chem., Int. Ed. Engl. 1995, 34, 1429–1432. doi:10.1002/anie.199514291
2. Li, C. Chem. Commun. 2014, 50, 12420–12433. doi:10.1039/C4CC03170A
3. Kim, J. N.; Lee, K. Y. Curr. Org. Chem. 2002, 6, 627–645. doi:10.2174/1385272023374094
4. Sława, W.; Zujewksa, T. Heterocycles 2005, 65, 1713–1739. doi:10.3987/REV-05-596
5. Bodwell, G. J.; Nandaluru, P. R. Isr. J. Chem. 2012, 52, 105–138. doi:10.1002/ijch.201200003
6. Okada, Y.; Nishimura, J. J. Inclusion Phenom. Mol. Recognt. Chem. 1994, 19, 41–53. doi:10.1002/BF00708973
7. Schwartz, M. H. J. Inclusion Phenom. Mol. Recognt. Chem. 1990, 9, 1–35. doi:10.1002/1521-3765(19900500)9:3<1::AID-JIC3>3.0.CO;2-E
8. Štefan, M.; Grim, M.; Hruby, V.; Chmelík, M.; Strutt, N. L.; Barnes, J. C.; Butterfield, A. M.; Dale, E. J.; Naini, S. R.; Ranganathan, S.; Yadav, J. S.; Ramakrishna, K. V. S.; Tang, R.-Y.; Li, G.; Yu, J.-Q. Tetrahedron 2012, 68, 15812–15822. doi:10.1016/j.tet.2011.12.031
9. Ramaiah, D.; Neelakandan, P. P.; Nair, A. K.; Avirah, R. R. J. Inclusion Phenom. Macrocyclic Chem. 2014, 12, 653–663. doi:10.1002/ijch.201100080
10. Chen, F.; Weng, J.; Liu, Y.; Li, Y. J. Org. Chem. 2015, 11, 1274–1331. doi:10.1021/acs.joc.5b00384

262. Orita, A.; Jiang, L.; Tsuruta, M.; Otera, J. Chem. Lett. 2002, 31, 136–137. doi:10.1246/cl.2002.136
263. Fuji, K.; Ichikawa, K.; Fujita, E. Tetrahedron Lett. 1979, 20, 361–364. doi:10.1016/S0040-4039(01)85971-2
264. Högborg, H.-E.; Thulin, B.; Wennerström, O. Tetrahedron Lett. 1977, 18, 931–934. doi:10.1016/S0040-4039(01)92795-9
265. Hong, J. W.; Gaylord, B. S.; Bazan, G. C. J. Am. Chem. Soc. 2002, 124, 11868–11869. doi:10.1021/ja027170r
266. Tobe, Y.; Nakayama, A.; Kakuuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. J. Org. Chem. 1987, 52, 2639–2644. doi:10.1021/jo00389a002

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