Unconventional Macrocyclizations in Natural Product Synthesis

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1. INTRODUCTION

Macrocycles are defined as molecules bearing a cyclic framework consisting of usually 12 or more atoms. Macroyclic compounds comprise a broad spectrum of different ring sizes and varying degrees of molecular complexity. From porphyrin derivatives (e.g., heme or vitamin B12) to cyclic oligopeptides (e.g., cyclosporin A), Nature expresses an enormous variety of powerful candidates for therapy against otherwise "drug-resistant" targets, as a result of their constrained threedimensional architecture which allows preorganization (enthalpic benefit) and high-affinity substrate—protein binding. From a synthetic point of view, the efficiency of macrocyclization events commonly suffers from entropic penalties as well as undesired intermolecular couplings (oligomerization). Although over the past several decades ring-closing metathesis, macrolactonization, or macrolactamization have become strategies of choice, the toolbox of organic synthesis provides a great number of versatile transformations beyond the aforementioned. This Outlook focuses on a selection of examples employing what we term unconventional macrocyclizations toward the synthesis of natural products or analogues.
drofuran with significant diastereoselectivity. Moreover, in the second total synthesis of I, Nicolaou established the B ring through an unconventional heteropinacol coupling. More recently, MacMillan published his approach toward I, based on a macroaldolization for the closure of ring A (setting the stage for one of the two oxazole syntheses) and a Suzuki–Miyaura aryl–aryl coupling for the second ring. The interest of several additional groups was sparked by the challenging structure of diazonamide A, and various formal syntheses have been reported.

In 2007, Magnus developed a powerful O-aryl to C-aryl migration technique, furnishing the C10 quaternary center with high diastereoselectivity. An elegant coupling was reported by Sammakia for the construction of the ring A of the natural product via a diastereoselective oxindole arylation, and in 2016, the formal synthesis of diazonamide A was disclosed by Moody, featuring a macro lactamization for the closure of ring A.

The pool of synthetic approaches toward I showcases the power of organic synthesis in overcoming complex challenges as well as the large variety of tools for the construction of macrocyclic compounds. This Outlook summarizes selected examples of synthetic endeavors that utilize unconventional macrocyclizations en route to natural products bearing large rings and aims at providing readers with a different perspective of these synthetic challenges.

2. Palladium-Mediated Cross-Couplings

Palladium-catalyzed cross-coupling reactions are a predominant tool for the construction of carbon–carbon bonds. Since the initial reports in the late 1960s by Tsuji and Heck, followed by the pioneering works of Negishi and Suzuki and Miyaura, Pd-mediated transformations have been extensively employed in the synthesis of natural products and derivatives, as well as valuable materials. Apart from these early examples, other protocols such as the Tsuji–Trost, Sonogashira, and Stille reactions have enriched the family of palladium-catalyzed cross-couplings. Unsurprisingly, a number of macrocyclization approaches rely on Pd-catalyzed cross-coupling reactions.

2.1. Stille Coupling

The term Stille coupling is used to describe the C–C bond-forming reaction between organostannanes and halides or pseudohalides under Pd(0)-catalysis. The coupling was developed by and named after J. K. Stille, even though the first reports were disclosed by the research group of M. Kosugi in 1977. Despite the toxicity of tin reagents, the Stille coupling remains one of the most common tools utilized in the total synthesis of natural products.
recent report by Liu described the total synthesis of the natural depsipeptide nannocystin A55 two years after the reported isolation.

One of the most fascinating applications of the Stille coupling is found in Nicolaou’s 1993 total synthesis of rapamycin (4), employing a “stitching” technique to construct the (E,E,E)-trienic moiety (Scheme 2).56 More precisely, the linear precursor 2 was treated with trans-vinylidestannane 3 in the presence of Hünig’s base and Pd(CH3CN)2Cl2, presumably forming intermediate 4-int via an intermolecular Stille coupling. Subsequently, a second Stille coupling takes place intramolecularly, forming a 29-membered ring and delivering the enantiomerically pure immunosuppressive natural product in 28% yield.

Five years later, Smith reported the first enantioselective total synthesis of macrolactin A (7), a potent antiviral polyene macrolide (Scheme 3a).57 Herein, treatment of a highly diluted solution of vinyl stannane 5 (0.7 mM) with Pd2dba3 and DIPEA in NMP formed the macrocycle 6, which was converted to the natural product after deprotection of the alcohols in 29% yield over two steps.

In 2006, Overman published the first total synthesis of the bis-macrocyclic alkaloid sarain A (10) (Scheme 3b).58 The key macrocyclization event proceeded via an intramolecular Stille coupling of 8—the first macrocycle having been formed using ring-closing metathesis—in the presence of catalytic Pd(PPh3)4 and an excess of lithium chloride, affording 9. Eventually, the enantiomerically pure alkaloid 10 was obtained after three additional steps.

2.2. Heck Coupling. The Heck reaction has undeniably won a place as a textbook methodology enabling carbon–carbon bond formation between an olefin and a (pseudo)-halide.59 In addition to the enhanced atom-economy of Heck couplings when compared to the rest of the family of Pd-catalyzed transformations, a notable advantage is the regioselectivity during the ring-closing process.

In 2009, Maier published the formal synthesis of palmerolide A,60 by constructing an advanced intermediate synthesized two years earlier by Nicolaou and Chen en route to the natural product.61 In this article, Maier highlighted the fact that an intramolecular Heck coupling for the regioselective construction of palmerolide A’s 20-membered ring was superior to a Stille approach, which delivered a mixture of olefin isomers. More recently, Reddy reported the total syntheses of solomonamides A and B from a common macrocyclic precursor constructed by a crucial Heck coupling.62,63

The same year, Menche disclosed the total synthesis of the potent antibiotic macrolide etnangien (13) (Scheme 4).64 The key Heck macrocyclization took place after treating cis-vinyl iodide 11 with Pd(OAc)2, tetrabutylammonium chloride, and potassium carbonate. The coupling proceeded successfully with high stereoselectivity (E/Z > 20:1), and the precursor 12 was isolated in 70% yield. Notably, when similar conditions were applied by the authors in an intermolecular context during the synthesis of archazolid A (not shown),65 a 6:1 mixture of E/Z isomers was obtained, underlining the significance of conformational restrictions for the stereoselectivity of Heck coupling reactions. Finally, etnangien (13) was obtained after seven further steps.

A more recent example of a Heck macrocyclization is the first total synthesis of biselyngbyolide B (16) by Goswami (Scheme 5a).66 The 18-membered polylene macrocycle was constructed from the linear precursor 14, which underwent cyclization under Pd(OAc)2-catalysis affording 15. Despite the presence of potentially competitive olefins in proximity, the Heck cyclization proceeded regio- and stereoselectively in 58% yield. Deprotection of the allylic alcohol quantitatively delivered the natural product 16.
In 2018, Choppin and Speicher established the first enantioselective total synthesis of the cyclophane isoplagiochin D (19) (Scheme 5b).\(^{57}\) Unquestionably, the high rigidity of such compounds provides a great synthetic challenge. The intriguing synthesis of 19 was carried out utilizing a Heck macrocyclization.

Treatment of enantiopure 17 with Pd\(_2\text{dba}_3\) delivered the strained macrocycle 18 in 80% yield with excellent atropo- and diastereoselectivity, selectivities that had not been achieved in a previously reported attempt by the same group.\(^{68}\) The key element of this impressive transformation is the chiral sulfinyl auxiliary which enables a configurational lock, presumably via intermediate 18-int, and dictates the atroposelectivity during the event. The traceless nature of the sulfinyl moiety is implemented with its replacement by a hydroxyl group en route to enantiopure 19.

**2.3. Suzuki–Miyaura Coupling.** Organoboron species can be coupled with electrophilic (pseudo)halides under palladium catalysis in the presence of an activating base. This reaction, known as the Suzuki–Miyaura coupling, is one of the most widely employed methods for the synthesis of C(sp\(^2\))–C(sp\(^2\)) and, more recently, C(sp\(^3\))–C(sp\(^3\)) bonds. It has also found broad application in the total syntheses of macrocyclic natural products.\(^{69}–73\)

Halcomb’s synthetic strategy toward phomactin A (22) involved an alkyl borane Suzuki–Miyaura coupling to achieve the crucial macrocyclization step (Scheme 6a).\(^{74}\) In particular, stereo- and regioselective hydroboration of the terminal olefin of 20 afforded the corresponding alkyl borane species which was treated with palladium(II) under Johnson’s conditions. The strained 12-membered macrocycle 21 was isolated in 37% yield (retaining the sensitive dihydrofuran), and further deprotection afforded the enantiomerically pure natural product 22.

In 2005, Snapper and Hoveyda reported the total synthesis and structural revision of isocomplestatin (24) (Scheme 6b),\(^{76}\) an atropisomer of the natural product complestatin, originally reported as isocomplestatin after its isolation in 2001. In this regard, advanced precursor 23 (the macrocycle of which was accessed via a Chan–Evans–Lam coupling similar to the chloropeptin I synthesis by the same research group—see Section 9.2)\(^{77}\) was treated with PdCl\(_2\)(dppf) and an excess of potassium carbonate, delivering the product of aryl–aryl coupling for the construction of the second macrocycle of isocomplestatin 24, which was eventually obtained after hydrolysis of the carboxylic acid.

More recently, Maulide accomplished the total synthesis of the potent immunosuppressive natural products FR252921 (27), FR252922 (28), and FR256523 (29), embedding a Suzuki–Miyaura coupling protocol in a carefully designed domino sequence (Scheme 7).\(^{78}\) Specifically, initial macrocyclization was achieved via a Suzuki–Miyaura coupling of 25, containing a vinylboronic ester and a remotely attached 1,2-disubstituted cis-chlorocyclobutene carboxylic ester. The 17-membered, fused macrobicycle immediately underwent in situ, thermal 4π-electrocyclic ring opening of intermediate 26-int, providing the enlarged 19-membered trienic macrocycle 26 in high yields. Conrotatory electrocyclic ring-opening ensured the (E,E,E)-triene configuration, which had been shown by computation and prior reports not to be thermodynamically preferred.\(^{79,80}\) Final TBAF-deprotection allowed the isolation of the enantiomerically pure natural products.
The coupling reaction of allylic electrophiles and nucleophiles under palladium(0)-catalysis is well-known as the Tsuji−Trost reaction. The scope of electrophiles ranges from allylic halides to allylic epoxides and even allylic cyclopropanes, but it is dominated by allylic acetates and carbonates. That, in combination with the large variety of potential nucleophilic partners, renders the Tsuji−Trost reaction a highly versatile tool. It is well established that the reaction proceeds via a π-allylpalladium(II) complex which provides the potential construction of two regioisomeric species, depending on the site of the attack of the approaching nucleophile. The enantioselective Tsuji−Trost coupling usually delivers the adducts with high regio- and stereoselectivity. This selectivity tool has been exploited in various macrocyclization strategies in total synthesis.

In 1997, Yamamoto reported the stereoselective total synthesis of humulene (32) (Scheme 8a). Therein, the sodium salt of β-ketoester 30 was treated with Pd(PPh3)4, affording the 11-membered ketone 31 in 45% yield and with excellent stereo- and regioselectivity. The first total synthesis of the antibiotic roseophilin (35) was disclosed by Fürstner, six years after its structural elucidation (Scheme 8b). Macrocyclization of the allylic epoxide 33 under Pd(0)-catalysis proceeded smoothly, and the 13-membered allylic alcohol 34 was obtained in high yield. The natural product 35 was obtained in 11 further steps. The first total synthesis and structural revision of macquarimicin A (38) were disclosed by Tadano in 2003 (Scheme 8c). In this report, carbonate 36 was successfully cyclized to the 17-membered ketone 37 after being slowly added to a dilute mixture of a catalytic amount of Pd(PPh3)4 and DPPE in THF. Subsequent elaboration of this ketone through nine more steps afforded the target molecule 38 as a single enantiomer.

2.5. Sonogashira Coupling. The Sonogashira reaction enables the coupling between terminal alkynes and vinyl or aryl halides in the presence of palladium(0) and copper(I) cocatalysts and an amine base. It is considered one of the most efficient methods for the construction of substituted alkynes and has found application in numerous natural product and drug
the 1,2-dihydroquinoline. Instead, the formation of a transannular Diels–Alder in the Synthesis of the Dynemicin A Core by Schreiber and (b) Hirama’s Development of a Kedarcidin Chromophore Fragment

Scheme 9. (a) Cascade Sonogashira Macrocyclization and Transannular Diels–Alder in the Synthesis of the Dynemicin A Core by Schreiber and (b) Hirama’s Development of a Kedarcidin Chromophore Fragment

reported the treatment of 39 with Pd(PPh3)4 and Cul, aiming at the formation of the 15-membered ring (cf. 40-int) fused to the 1,2-dihydroquinoline. Instead, the formation of a transannulation product 40, likely the product of domino Sonogashira cross-coupling/intramolecular Diels–Alder (IMDA) cycloaddition, was reported. Although surprising, as depicted in Scheme 9a, the 1,3-diene moiety of 40-int adopts the required s-cis conformation and is locked (by the enediyne moiety) in proximity to the electron-poor dienophile. IMDA cycloadditions, including further attempts toward advanced intermediate 40 will be discussed later (Section 5).

Highlighting the need for a suitable approach to enediyne natural products, Lear and Hirama successfully constructed diyne 44, a framework of the unstable and structurally strained kedarcidin chromophore (45) (Scheme 9b). The crucial macrocyclization succeeded via an intramolecular Sonogashira coupling of iodide 42, when treated with Pd2dba3·CHCl3 and copper(I) iodide in the presence of Hünig’s base. This efficient and reproducible coupling delivered the cyclic product 43 in 88–90% yield. Eventually, the target molecule 44 was accessed with just three subsequent operations.

2.6. Other Palladium-Mediated Couplings. The great utility of Pd-catalyzed cross-coupling reactions for the construction of unique macrocyclic scaffolds has been highlighted thus far. The reign of palladium-mediated macrocyclizations, however, expands beyond that.

In 2008, Trost developed an efficient route for the atom-economic total synthesis of bryostatin 16 (48) (Scheme 10a), a natural product commonly considered a synthetic precursor to the bryostatin family. The crucial macrocyclization was accomplished when diyne 46 was treated with palladium(II) acetate and tris(2,6-dimethoxyphenyl)phosphine (TDMPP) in toluene. Impressively, the 22-membered macrocycle 47 was obtained in 56% yield, while other attempts employing several solvent systems or metal/ligand ratios proved unsuccessful. From a mechanistic point of view, insertion of palladium into the carbon–hydrogen bond of the terminal alkyne allows the following regioselective carbometalation of the internal alkyne which, eventually, delivers the new enyne moiety and the macrocycle 47. Finally, the target molecule 48 is accessed in three subsequent operations.

The first total synthesis of streptide (51) was reported by Boger in 2019, brilliantly utilizing a Larock-indole-synthesis strategy for the ring-closing event (Scheme 10b). Here, linear peptide 49 underwent a palladium(0)-mediated indole annulation, delivering the 20-membered macrocycle 50 in 60% yield en route to the natural product 51. While this type of indole synthesis usually takes place in the presence of catalytic amounts of palladium, it is postulated that either the linear precursor or the cyclized product traps the catalyst thereby necessitating the use of stoichiometric amounts of palladium.

3. OLEFINATIONS

Since the 1953 discovery that the reaction of phosphonium ylides and carbonyl compounds results in olefnation by G. Wittig, the eponymous reaction has emerged as one of the most powerful tools for the construction of carbon–carbon double bonds. In addition, a series of newer protocols and modifications has been developed, allowing versatile approaches for the synthesis of double bonds with high chemo- and E/Z-stereoselectivity. Olefnations have thus found application in various total syntheses of natural products. It should also be stressed that, although olefin metathesis appears to dominate in the synthesis of macrocyclic olefins, most of the alkenes engaging in these metatheses are, ironically, constructed by an olefnation. This section briefly summarizes a selection of macrocyclization events via Wittig and Horner–
Wadsworth–Emmons reactions in the total synthesis of natural products.

3.1. Wittig Olefination. The Wittig reaction remains a staple reaction for alkene synthesis whereby the stereochemistry of the alkene product depends on the nature of the phosphonium ylide. While Wittig olefination is present in many synthetic protocols, the employment in macrocyclizations is rather rare, and two selected examples are discussed herein.

In 1993, Nógrádi reported the total synthesis and structural revision of garuganin III (54) (Scheme 11a).94 In the pursuit of an efficient synthetic strategy, macrocyclization proved quite challenging. Ring-closing approaches such as an Ullmann-type diaryl ether synthesis, aldol condensation, or intramolecular Wurtz-type coupling proved ineffective. Ultimately, Wittig olefination provided an alternative approach for the macrocyclization of 52, and the isoxazole served as a masked 1,3-dicarbonyl dedicated to the vinylogous ester of garuganin III. In the event, the strained macrocycle 53 was formed in good yield upon treatment of 52 with potassium tert-butoxide and was elaborated to the target natural product 54 in three further steps. A similar isoxazole-based strategy was published by Nógrádi the same year in the synthesis of garugamblin-1 utilizing a Wurtz-type macrocyclization, as will be discussed later (Section 7.3).

A remarkable strategy for the first enantioselective syntheses of trienomycins A (58) and F (59) was established by Smith in 1996 (Scheme 11b).95,96 The compelling ring-closing event hinged on a novel double Wittig olefination of dialdehyde 55. To this effect, excess NaHMDS was slowly added to a dilute solution of bis phosphonium chloride salt 56 and 55, initiating the domino inter- and intramolecular olefinations and successfully delivering the (E,E,E)-trienic ring in 21% yield. Gratifyingly, the resulting macrocycle 57 was a common precursor of both 58 and 59, the syntheses of which were realized in seven further steps.

3.2. Horner–Wadsworth–Emmons Olefination. Olefin synthesis through the coupling of phosphonate-stabilized carbanions with carbonyl compounds is known as the Horner–Wadsworth–Emmons (HWE) olefination.97–99 Advantages of the HWE reaction reside on the increased reactivity of phosphonate anions compared to phosphonium ylides and on the easy removal of the water-soluble, phosphonate salt byproducts. Additionally, HWE olefination is often the reaction of choice when high E-selectivity is required. This selectivity can be reversed under certain modification protocols (e.g., Still–Gennari, Corey–Kwiatkowski, or Ando modifications).100–103 It is no surprise, therefore, that HWE reactions occupy a privileged position in the synthesis of natural products, being employed in various transformations, including macrocyclizations.
In 2003, Kang reported the enantioselective total synthesis of lasonolide A (62) (Scheme 12). An intramolecular HWE olefination proved to be the method of choice for the construction of this highly strained 20-membered polyene from phosphonate 60. The macrocyclization delivered the (E,E)-dienoate macrolactone 61 in 71% yield and provided access to the product of interest (62) after three subsequent operations.

The enantioselective total synthesis of dactylolide (65) was accomplished by Keck in 2005 (Scheme 13a), four years after the macrolide’s isolation. Therein, the crucial ring closure was achieved in 60% yield, when phosphonate 63 was treated with NaHMDS. The resulting 18-membered, enantioenriched macrolactone 64 was subjected to two further operations en route to the natural product (65). Another example of an HWE reaction employed in macrocyclization can be found in the 2007 synthesis of archazolid A (67) by Menche (Scheme 13b). Therein, the α-methyl phosphonate 66 was treated with sodium hydride, furnishing the E-olefin with excellent stereoselectivity. Subsequently, diastereoselective reduction of the unsaturated ketone under Corey–Itano conditions followed by deprotection afforded the target natural product in 26% yield over three steps.

4. OXIDATIVE ARYL–ARYL COUPLINGS

Biaryl systems are common moieties, abundant in various natural products. In previous sections, we have already met a small series of such macrocyclic natural products, including diazonamide A (1), isocomplestatin (24), and roseophilin (35). Therefore, it is no surprise that many strategies for the total syntheses of natural products rely on aryl–aryl coupling events. This section covers selected examples of such couplings that led to the total syntheses of natural products.

As will be discussed in Section 6, C−H activation has emerged as a powerful logic in synthesis. Among the many elegant applications of the C−H activation strategy in total synthesis, aryl–aryl macrocyclization events are of present interest.

In 1998, Evans reported a remarkable synthesis of the aglycon of vancomycin (70), an antibiotic with a synthetically challenging core, given its triple atropisomeric architecture (Scheme 14a). The first macrocyclization for the synthesis of this complex molecule took place when 68 was treated with VOFs, BF3·Et2O (crucial for prevention of undesired attack by nucleophilic oxygens on the ring), and AgBF4 in a mixture of TFA and dichloromethane at 0 °C, followed by a reductive quench (NaHB(OAc)3 replacing the zinc powder commonly employed in this transformation). Interestingly, macrocycle 69 was delivered in 65% yield, possessing the unnatural R-atropisomeric configuration of the biaryl (d.r. > 19:1), which was, nevertheless, isomerized at a later stage to the desired S-configuration. The complex target 70 was achieved through a series of subsequent operations including two SAr couplings for the construction of the remaining two macrocycles.

Recently, Romesberg and Baran published a route for the facile and scalable synthesis of arylomycins (e.g., arylomycin A2 (73)), based on a copper-mediated coupling of arynes (Scheme 14b). Other strategies, such as macrolactamization or palladium-catalyzed cross-coupling, proved unfruitful in initial efforts. Their interest was then turned to oxidative coupling, and the arylomycin core 72 was successfully obtained upon treatment of 71 with 2 equiv of [Cu(MeCN)4][PF6] and TMEDA.

5. CYCLOADDITION

Cycloadditions represent an additional method of forming macrocyclic structures through formation of carbon–carbon or carbon–heteroatom bonds. One of the key features of this approach is the fact that, in addition to the macrocyclic structure, another is invariably formed, and further functionalization, rearrangement, or degradation of this fragment is often a mandatory feature.

5.1. Diels–Alder Reaction. The Diels–Alder reaction, arguably the most prominent of the cycloaddition reactions, has been implemented in key macrocyclizations for natural product synthesis. In particular, the intramolecular Diels–Alder reaction (IMDA) has proven a powerful synthetic tool.
for the formation of macrocyclic structures with annulated cyclohexenes and cyclohexadienes. Early examples of the application of IMDA reactions in total synthesis were laid forth by Stork in the syntheses of cytochalasins,120 Yamaguchi in the synthesis of 24-O-methylchlorothricolide,121 and Kishi in the synthesis of pinnatoxin A.122 While elegantly leading to the desired connectivity, these examples all suffered from only moderate levels of diastereoselectivity.

In 2005, Sorensen published a highly diastereoselective intramolecular Diels−Alder approach to macrocyclization, elegantly implemented in the synthesis of abyssomicin C (Scheme 15a).123 Therein, treatment of β-silyloxy ketone 74 with lanthanum-(III) triflate in boiling toluene smoothly led to β-elimination and subsequent IMDA of 75-int. This one-pot sequence afforded a 50% yield of the desired 11-membered tricyclic product 75, which was converted to the target molecule abyssomicin C (76) in three further steps. The same year, Corey reported the use of a chiral catalyst 78 in an enantioselective IMDA reaction for the syntheses of palominol (80) and dolabellatrienone (81) (Scheme 15b).124 The success of this approach hinged on three key interactions between the catalyst and the substrate (77), as can be seen in the endo-transition state 79-TS: while a Lewis acid−Lewis base interaction between the boron and the aldehyde promoted the cycloaddition by increasing the dienophility of the enal, a formyl hydrogen bond to the oxazaborolidine and π−π stacking between a phenyl group and the dienophile ensured facial selectivity. The substituted bicyclo[9.4.0]pentadecatriene framework 79 (formed with an enantiomeric excess of 90%) was further elaborated to 80 and 81 in six and seven steps, respectively. The relative ease with which this transformation proceeds is also highlighted by the comparatively high concentrations used for the reaction.

A delicate Diels−Alder macrocyclization/retro-hetero-Diels−Alder strategy was elegantly applied in Baran’s 2006 synthesis of the alkaloid haouamine A (83) (Scheme 16a),125 a sequence similarly applied in Beaudry’s 2013 synthesis of cavicularin.126 The crucial [4 + 2] cycloaddition between a pyrone and a distal alkyne present in 82 led to the formation of ester-bridged cyclohexadiene 83-int, which underwent cycloreversion in situ, extruding carbon dioxide and delivering the natural product 83. Notably, the formation of the desired bent aromatic ring was facilitated by this type of approach, involving a nonaromatic intermediate to introduce the desired conformation. Employing a hetero-Diels−Alder reaction, Nicolaou was able to construct a macrocyclic precursor for the synthesis of sporolide B (86) (Scheme 16b).127 Proceeding via the transition state 85-TS, the α-quinone 84 was transformed to 85 with remarkable regio- as well as facial selectivity.

A further example of a Diels−Alder reaction in the synthesis of the macrocyclic framework of a natural product was described in Schreiber’s 1993 synthesis of tri-O-methyl dynemicin A methyl ester (88) (Scheme 17).128,129 Therein,
the seco acid 87 was initially treated with trichlorobenzoyl chloride (Yamaguchi reagent) and PyBOP to effect macro-
lactonization and the formation of 40-int (see also Scheme 9a). This intermediate was ideally poised for direct intra-
molecular Diels−Alder reaction, contracting the original 15-
membered ring to the desired 10-membered enediyne motif (40).

5.2. 1,3-Dipolar Cycloaddition. Another mode of
cycloaddition that has been employed in the synthesis of
natural products is the 1,3-dipolar cycloaddition. In Evans’
1999 report on different synthetic approaches toward
(+)-miyakolide (91), macrocyclization is effected by two
alternative pathways.130 While the classical approach involves a macro lactonization reaction (not shown), the authors also
investigated the (3 + 2) cycloaddition between an alkyne and a
nitrile oxide which is generated in situ (90-int) from the
corresponding N-oxide 89 (Scheme 18). This reaction leads to

the formation of an isoxazole (90) that is readily cleaved to the
corresponding β-dicarbonyl. A similar strategy was employed
in the syntheses of 11-hydroxycurvularins by Lee,131 wherein
an alkene-nitrile oxide cycloaddition ultimately affords a
diastereomeric mixture of β-hydroxy ketones.

5.3. ox[a]-[3 + 3] Cycloaddition. An unusual ox[a]-[3 + 3]
cycloaddition was envisioned by Hsung to form the macro-
cyclic phomactin A core (93) (Scheme 19).132 Therein, the

silyl enol ether 92 was engaged in a formal cycloaddition with
an iminium ion formed in situ from the appended enal. While
the original approach, starting from the diketone,133 provided
the desired regioisomer 93 as the minor product, switching to
the silyl enol ether was able to improve regioselectivity.
Interestingly, the undesired regioisomer was isolated as an

Scheme 16. (a) Baran’s Diels−Alder/Retro-Diels−Alder
Approach for the Synthesis of Haouamine A’s Bent
Aromatic Ring and (b) Hetero-Diels−Alder Reaction
Enabling Nicolaou’s Synthesis of Sporolide B

Scheme 17. Macrolactonization/Diels−Alder Cyclization
Sequence to Form the Core of a Dynemicin A Derivative

Scheme 18. Evans’ Synthesis of Miyakolide via 1,3-Dipolar
Cycloaddition

Scheme 19. Hsung’s ox[a]-[3 + 3] Cycloaddition to Build the
Phomactin A Core
inseparable mixture of atropisomers (94 and 95), while no such atropisomerism was observed for 93.

6. C−H ACTIVATION

The activation of C−H bonds by transition metal catalysis has found widespread application in organic synthesis.110,111 The potential for this type of carbon−carbon and carbon−heteroatom bond formation has also been exploited in the synthesis of macrocyclic natural products. An elegant and highly enantioselective example of rhodium-catalyzed C−H activation for the synthesis of the core macrocyclic structure of cylindrocyclophanes (97) was reported by Davies in 2018 (Scheme 20).134 Remarkably, the choice of catalyst enables the highly selective functionalization of the most accessible unactivated methylene group, which is favored even over benzylic CH₂ moieties present in the substrate.

7. RADICAL PROCESSES

The generation of radical species allows swift carbon−carbon bond formation in contexts that are often orthogonal to, and not as susceptible to the negative effects of steric hindrance as, classical polar reactivity. It is therefore only logical that radical processes have been heavily employed in the formation of large rings.135 Examples of the wide range of radical-based named reactions utilized for macrocyclization in natural product synthesis shall be presented in this section.

7.1. Pinacol Coupling. The treatment of carbonyls with single-electron reductants to form ketyl radical anions, followed by the radical coupling of two of these intermediates, is referred to as pinacol coupling.136 In 1989, McMurry reported the synthesis of crassin (100), which relied on the treatment of keto aldehyde 98 with titanium(III) chloride and zinc−copper couple to form diol 99 (Scheme 21a).137 While this major product was shown to possess the undesired stereochemical configurations at both alcohols, 2-fold hydroxyl inversion of this intermediate of the classical McMurry reaction enabled the formation of 100 in just four additional steps. Employing samarium(II) iodide as the single-electron reductant in the synthesis of isoedunol (103) and β-araneosene (104), Corey was able to synthesize 102 as a single diastereomer, starting from diketone 101 (Scheme 21b).124 While the diastereoselectivity itself is remarkable, two-step inversion of the secondary alcohol was necessary to effect the desired ring expansion through pinacol rearrangement (upon treatment with methanesulfonyl chloride, not shown). One and three further steps, respectively, were required to furnish 103 and 104.

Samarium(II) iodide was also employed in Nicolau’s 2003 synthesis of diazonamide A (1) (Scheme 21c), in which a heteropinacol coupling between an aldehyde and an oxime (105) led to the desired macrocyclization.23,27 Proceeding alongside N−O bond cleavage and followed immediately by a peptide coupling with Fmoc-protected L-valine to afford 106, this reaction directly set the stage for the formation of the target molecule’s second oxazole. As exemplified by Waldmann’s use of [V₂Cl₃·(THF)]₆[Zn₂Cl₆] in the synthesis of (9S, 18R)-cyclamenol A, other single-electron reductants can also be employed to effect pinacol-macrocyclization (not shown).139

7.2. Witkop-Type Cyclization. As mentioned in the Introduction, many strategies have been followed for the synthesis of diazonamide A (1). An approach chosen both by Harran and by Nicolau involves variants of the Witkop cyclization, classically proceeding via a photoinduced electron transfer from the excited state of an indole chromophore.140 Apart from the Witkop reaction, Harran’s second attempt toward diazonamide A, the first having been thwarted by original misassignment of the structure,20,21 featured a further unusual macrocyclization (Scheme 22a).26 Oxidation of phenol 107 led to intermediate formation of a phenoxonium...
ion which engaged in an oxidative cycloaddition with the remote indole, forming indoline 108. The Witkop cyclization itself was initiated by treatment of the advanced intermediate 109 with lithium hydroxide and photoinduced electron transfer between the electron-rich indole and the comparatively electron-deficient bromoarene, as depicted in a simplified form (truncated structures 110-int1 and 110-int2, Scheme 22a). After mesolytic elimination of the bromide, radical−radical coupling afforded 110, which was elaborated to diazonamide A (1) in seven further steps. Notably, the presence of the phenolate—albeit ultimately superfluous—promoted the electron transfer to a large extent. This becomes particularly apparent when comparing this transformation to Nicolaou’s process (Scheme 22b). Having constructed the Western macrocycle of 111 through a macrolactamization, a very similar Witkop cyclization, in the absence of an additional electron donor, proceeded to afford 112 in only 30% yield (compared to Harran’s 72%). Despite this comparably low yield, the Witkop approach proved far superior to classical, stannane-based radical-cyclization conditions.

7.3. Wurtz-Type Cyclization. In 1993, Nógrádi disclosed the synthesis of garugamblin-1 (115) using a Wurtz-type macrocyclization. Herein, treatment of dibromide 113 with the radical anion generated from elemental sodium and tetraphenylethene led to sequential single-electron reduction of one of the benzylic halides, followed by substitution of the formed sodium organyl on the remaining bromoalkene (Scheme 23). Simultaneous reductive cleavage of the isoxazole moiety afforded the vinylogous amide 114, which was hydrolyzed and methylated to obtain a mixture of the target compound 115 and its methylation and double bond regioisomers.

7.4. Giese Addition. Reversible addition of a thiyl radical to a vinyl cyclopropane moiety (116) initiated Feldman’s 1993

 synthesis of the brendalin A and C core (Scheme 24). After formation of intermediate 121, radical opening of the cyclopropane, followed by Giese addition of the resultant radical to the enone, led to the formation of the α-keto radical
122. Subsequent transannular addition of this radical to the allyl sulfide moiety effected intramolecular allylic homolytic elimination to afford a mixture of four diastereomeric products, the main components of which were 117 (displaying the brefeldin stereochemistry) and 118.

8. ADDITION TO CARBONYLS

Carbonyls are arguably the prototypical reactive functional group in organic synthesis. Carbonyl addition as a tool for the formation of macrocyclic structures will be summarized in this section, highlighting well-known examples in the formation of large rings during natural product synthesis.

8.1. Aldol Addition. The aldol reaction, probably the most well-known reaction not named after its discoverers, Alexander Borodin and Charles-Adolphe Wurtz, is one of the best-developed transformations in organic chemistry. As such, it is not surprising that it has found application in the formation of macroyclic natural products. As aldol reactions can be run under both basic and acidic conditions, a large variety of protocols has been developed.

An example of a classical base-promoted aldol reaction was presented in Danishefsky’s 1996 synthesis of epothilone A (125) (Scheme 25a).143

Scheme 25. (a) Base- and (b) Lewis-Acid-Promoted Macroadolization Reaction for the Syntheses of Epothilone A and Diazonamide A

Formation of the potassium enolate of acetate 123 at low temperatures led to the formation of 124 after addition to the nonenolizable aldehyde. The authors noted that protonation of the intermediate potassium aldolate at low temperatures favored formation of the undesired diastereomer, while protonation at 0 °C allowed for the exclusive formation of the desired isomer (on analytical scale; preparative scale was less selective, yet still showed a preference of 6:1 for 124 over its isomer). For the synthesis of epothilone B, differing from A only by one methyl group at C-12 (see 123), the authors reported a considerably lower diastereoselectivity of 2.1:1 (not shown).144

Lewis-acid activation is also often employed to promote enolization and thereby aldol addition. Examples of such an approach to macrocycle formation in natural product synthesis include the Danishefsky synthesis of rapamycin (not shown)145 and MacMillan’s contribution to the variety of diazonamide A syntheses, published in 2011 (Scheme 25b).29 Herein, the macroadolization was triggered by the addition of magnesium bromide and triethylamine to α-amino thioester 126. Trimethylsilyl chloride proved a necessary additive for this reaction, trapping the magnesium alkoxide, and thereby preventing retro-aldol addition. The product 127 was formed in high yield and as a single, ultimately inconsequential, diastereomer.

Magnus’ 1997 synthesis of a protected derivative of calicheamicinone (131) was also achieved with the help of a macroadolization (Scheme 26).146 The conjugate addition of an aluminium thiophenolate to cyclohexenone 128 generated an enolate, which added to the cobalt-protected pyridine moiety to provide the aldol product 129 under highly concentrated conditions. Further transformations led to 130, which proved resistant to deprotection and further elaboration to the target compound 131.

8.2. Reformatsky Reaction. The classical Reformatsky reaction describes the condensation of aldehydes or ketones with α-halo esters or amides using metallic zinc.147 While therein oxidative addition of zinc into the carbon–halogen bond, and subsequent metathalotropic equilibration to the zinc enolate, represent the first steps, the use of other reducing agents can initiate the same reaction by different mechanisms. As shown by the 2014 synthesis of cebulactam A1 (134) by Yang (Scheme 27),148 reduction of an α-bromo amide (132) by samarium(II) iodide forms a samarium enolate that can add to a tethered α-chiral aldehyde. While product 133 was obtained as a pair of diastereomers on the newly formed chiral centers, subsequent oxidation to a 1,3-dicarbonyl moiety allowed access to a single, desired isomer due to in situ epimerization.

8.3. Hosomi–Sakurai Reaction. The nucleophilic addition of an allylsilane to an activated carbonyl moiety under (Lewis) acid catalysis is referred to as the Hosomi–Sakurai reaction.149 Mechanistically, the nucleophilic addition of an allylsilane can be considered a silyl-variation of the Prins reaction in which a simple alkene adds to an activated carbonyl.150 The Hosomi–Sakurai reaction, however, relies on the β-stabilization of positive charge by silicon, thereby

Scheme 26. Synthesis of an Advanced Intermediate of Calicheamicinone by Means of a Thiophenolate-Promoted Macroadolization

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ensuring increased reactivity and providing greater control over product distribution than its conceptual relative. As such, the Hosomi−Sakurai reaction is most often used as a method for allylation, especially in cases where the allyl moiety exhibits increased steric hindrance (cf. reverse prenylation).149

Owing to the increased reactivity of allylsilanes and the facile control of product formation, the Hosomi−Sakurai reaction has also been employed in total synthesis (Scheme 28). The synthesis of bryostatin 1 (137), published by Wender in its entirety in 2017,151−153 showcases the macrocyclization of an allylsilane onto an enal (135) (Scheme 28a). Herein, the aldehyde is activated by pyridinium p-toluenesulfonate in combination with trimethyl orthoformate and the in situ TES-deprotected alcohol, forming an oxocarbenium ion which is readily attacked by the nucleophilic alkene, now in close proximity. Thus, in one step, tetrahydropyran 136 is formed in excellent yield, allowing access to bryostatin 1 in just four additional steps. A Sakurai-dimerization/macrocyclization strategy was followed in Rychnovsky’s 2011 synthesis of the cyanolide A aglycon (140) (Scheme 28b).154 The activation of acetal 138 initially led to dimerization via the intermolecular Hosomi−Sakurai reaction, once again employing an adjacent alcohol to form a tetrahydropyran. Subsequent macrocyclization, also initiated by acetal-activation in the same step, afforded 139, which was elaborated to the target molecule in just two further operations.

8.4. Barbier Reaction. While Grignard reagents are generally prepared in a separate flask before addition to an electrophile, the in situ generation of an organometallic reagent from an alkyl halide in the presence of a carbonyl derivative is termed the Barbier reaction. Therefore, by definition, macrocyclizations cannot be performed using Grignard reagents. Barbier-type reactions, however, have been employed in macrocyclic natural product synthesis. In 2011, Romo disclosed the synthesis of gymnodimine (143) and its C-4 epimer, relying on macrocyclic ring closure of iodoalkane 141 (Scheme 29a).155 Treatment of 141 with an excess of tert-butyllithium at ambient temperature—this comparatively high temperature being critical to achieve conformational equilibria favoring macrocyclization, thereby preventing unselective additions and quenching pathways—led to halogen-metal exchange and subsequent addition to the tosyl-protected lactam, providing 142 in varying, but good, yields. A further Barbier-type protocol, involving the in situ generation of a

Scheme 27. Use of a Samarium-Mediated Reformatsky Reaction in the Synthesis of Cebulactam A1

Scheme 28. Hosomi−Sakurai Reactions Led to the Desired Macrocyclizations in the Syntheses of (a) Bryostatin 1 by Wender and (b) the Cyanolide A Aglycon by Rychnovsky

Scheme 29. (a) Romo’s Room-Temperature Barbier Reaction en Route to Gymnodimine and (b) Danishefsky’s Acetylide Addition for the Synthesis of Calicheamicinone
carbanionic species and subsequent addition onto a carbonyl, was presented in Danishefsky’s synthesis of calicheamicinone (131) (Scheme 29b). Herein, as in several other syntheses of enediyne natural products,158,159 deprotonation of a terminal alkyne (144) triggered cyclization onto an aldehyde, forming propargylic alcohol 145 with high diastereoselectivity.

8.5. Nozaki–Hiyama–Kishi Reaction. The coupling of halide-substituted sp²- or sp-carbon atoms with aldehydes using chromium salts and catalytic amounts of nickel is named the Nozaki–Hiyama–Kishi (NHK) reaction.160 This transformation has found widespread application in organic synthesis due to its remarkable selectivity for aldehydes over a range of other reactive functional groups, including ketones. In the context of macrocyclic natural product synthesis, the NHK reaction has particularly found application in approaches toward phomactin A (22) (Scheme 30).

8.6. Loh-Type α-Allylation. The Loh allylation allows regioselective α- or γ-allylation of aldehydes with allylindium reagents, enabling a switch in selectivity by choice of the solvent system and reaction conditions.163 In 2016, Banwell exploited this protocol’s selectivity in a macrocyclization en route to the resorcylic acid lactones paecilomycin F (152) and cochliomycin C (153) (Scheme 31).164 The treatment of allylic chloride 150 with indium powder in methylene chloride and water led to α-allylation of the remote aldehyde, resulting in macrocyclization and the formation of 151. Notably, initial attempts involving Nozaki–Hiyama–Kishi conditions provided exclusively the regiosomeric γ-allylation product. Subsequent global deprotection afforded paecilomycin F (152), and aromatic chlorination of this material provided cochliomycin C (153).

9. MISCELLANEOUS MACROCYCLIZATIONS

9.1. Nickel-Catalyzed Alkyne-Aldehyde Reductive Coupling. Jamison employed an alkyne-aldehyde reductive coupling on 154 in the syntheses of amphidinolides T1 (156) and T4 (Scheme 32),165 and terpestacin,166 using a nickel catalyst, tributylphosphine and triethylborane.167 Crucially, elevated temperatures had to be employed in order to observe the formation of the desired product 155, and optimal conditions included a comparatively high catalyst loading of 20%.

9.2. Chan–Evans–Lam Coupling. The coupling of an arylboronic ester and a phenol to form a macrocyclic biaryl ether was achieved by Hoveyda in 2003 (Scheme 33).77 Under modified Chan–Evans–Lam conditions,168–170 precursor 157 was first treated with sodium periodate, cleaving the pinacol ester and liberating the free boronic acid, after which coupling was performed using cupric acetate, triethylamine (instead of pyridine), and methanol as an additive. Methanol proved critical for the success of this transformation leading to 158, as yields lower than 20% were generally observed in its absence. The authors suspected methanol to play either of two roles: (i) enabling the in situ formation of the boronic acid dimethyl ester or (ii) increasing the solubility of the copper salt. The total synthesis of chloropeptin I (159) was...
achieved in 13 further steps, including a Stille coupling to form the second macrocycle.

9.3. Ullmann-Type Coupling. The copper-mediated oxidative coupling of aryl halides for the synthesis of symmetrical biaryls is known as Ullmann coupling and usually proceeds under extreme conditions with elemental copper. However, incorporation of a nucleophile results in a Cu-nucleophile intermediate which adds oxidatively to the aryl-halide bond and eventually delivers a new substituted arene after reductive elimination. This nucleophilic aromatic substitution is also referred to as an Ullmann-type reaction and serves as one of the exceptional strategies for the construction of macrocyclic natural products. A first example was disclosed by Boger, who utilized this reactivity in the enantioselective synthesis of piperazinomycin in 1993.171 More recently, Uchiro reported the synthesis of hirsutellone B (162) (Scheme 34),172 aiming at a more robust synthesis compared to Nicolaou’s173 who succeeded by a Ramberg–Bäcklund ring contraction (not shown). Uchiro approached the synthetic challenge of the highly strained 13-membered macrocycle by subjecting 160 to copper(I)-catalysis at 160 °C. The macrocyclization successfully afforded aryl ether 161, which was transformed into the natural product 162 in four subsequent operations.

9.4. Glaser–Hay Coupling. In order to overcome the inherent need for high dilution in macrocyclization reactions, Collins employed a biphasic solvent system in the formal synthesis of ivorenolide A (165) (Scheme 35).174 The crucial Glaser–Hay coupling of bis-alkyne 163 to afford 164 was performed in a mixture of PEG400 and methanol, ensuring solubilization of the substrate and the catalysts in different media. By limiting substrate–catalyst interaction to the liquid/liquid interface, the effective concentration of the substrate was considerably lowered, allowing the reaction to be performed in continuous flow at roughly 120 times the concentration of similarly successful batch reactions (24 mM compared to 0.2 mM).

9.5. Corey–Seebach Reaction. While classical nucleophilic substitution reactions have not heavily featured in this article,175 the synthesis of macrocyclic structures through the Corey–Seebach reaction shall be mentioned. In Harrowven’s 2016 synthesis of riccardin C (168), dithiane 166 was deprotonated with n-butyllithium, leading to umpolung of the former aldehyde carbon, and immediately engaged in substitution of the benzylic chloride to form 167 (Scheme 36).176 While only moderately successful in terms of yield, this reaction provided rapid access to the core structure of the target molecule which was synthesized in three additional steps.

■ SUMMARY AND OUTLOOK

Macrocyclic natural products and their nature-inspired analogues have sparked the interest of the synthetic and medicinal community as a result of their high potential as pharmaceuticals. This appears to derive from their specific three-dimensional architecture which allows a preorganization profile ensuring high-affinity binding interactions with protein targets. Nature possesses countless macrocyclic scaffolds with high bioactive potency that could serve as candidates in drug discovery. Therefore, the development of robust methodologies and approaches for the synthesis of these macrocyclic natural products and their non-natural analogues is a necessity.

This Outlook aimed to gaze beyond the common go-to-transformations when it comes to macrocyclization—namely,
olefin metathesis, macro lactonization, or lactamization—and provide examples of what we termed unconventional approaches (e.g., Pd-mediated couplings, olefinations, aryl–aryl couplings, cycloadditions, C−H activation, radical couplings, addition to carbonyls, and others) for the synthesis of macrocyclic cores en route to natural products or analogues. In this regard, we also highlighted the multidirectional approaches of various research groups toward the total synthesis of diazonamide A (1), a potent antimitotic agent bearing two synthetically challenging macrocycles. While a large variety of approaches enabling highly flexible strategies for the formation of almost any kind of macrocycle has been established, several challenges remain. We hope that this overview of unconventional macrocyclizations can serve as a useful resource that enhances the future development of novel strategies toward the synthesis of macrocyclic, bioactive substances.

While a large variety of approaches enabling highly flexible strategies for the formation of almost any kind of macrocycle has been established, several challenges remain.

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