CHEMICAL REVIEWS

Review

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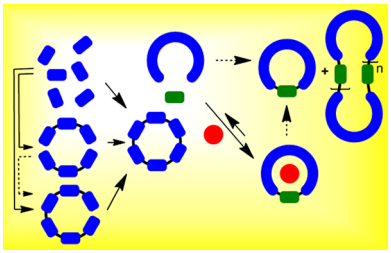
Macrocyclization Reactions: The Importance of Conformational, Configurational, and Template-Induced Preorganization

Vicente Martí-Centelles, Mrituanjay D. Pandey,† M. Isabel Burguete, and Santiago V. Luis*

Departament de Química Inorgànica i Orgànica, Universitat Jaume I, 12071 Castelló, Spain



CONTENTS

1. INTRODUCTION

Macrocyclic structures are common synthetic targets in drug discovery,[1,2] and therefore, interest in their study is continuously increasing in this field.[3,4] A classic example is provided by peptidic macrocycles, developed to restrict conformational flexibility (preorganization) and to increase stability.[3] Initial discoveries in this area can be dated back to 1926, when Ruzicka elucidated the structures of muscone **1** and civetone **2** (Figure 1). At that time, their cyclic character was considered surprising. This result, however, evidenced very early the importance of cyclic and macrocyclic organic compounds.[5] Macrocycles are common and broadly distributed in nature, and ~20% of all

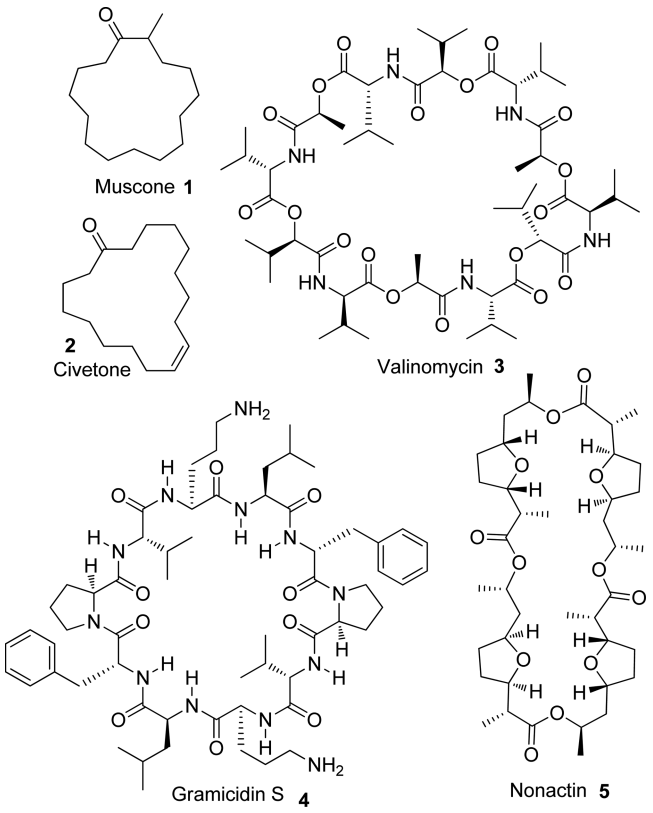


Figure 1. Structures of muscone and civetone elucidated by Ruzicka in 1926, and structures of nonactin, valinomycin, and gramicidin S.

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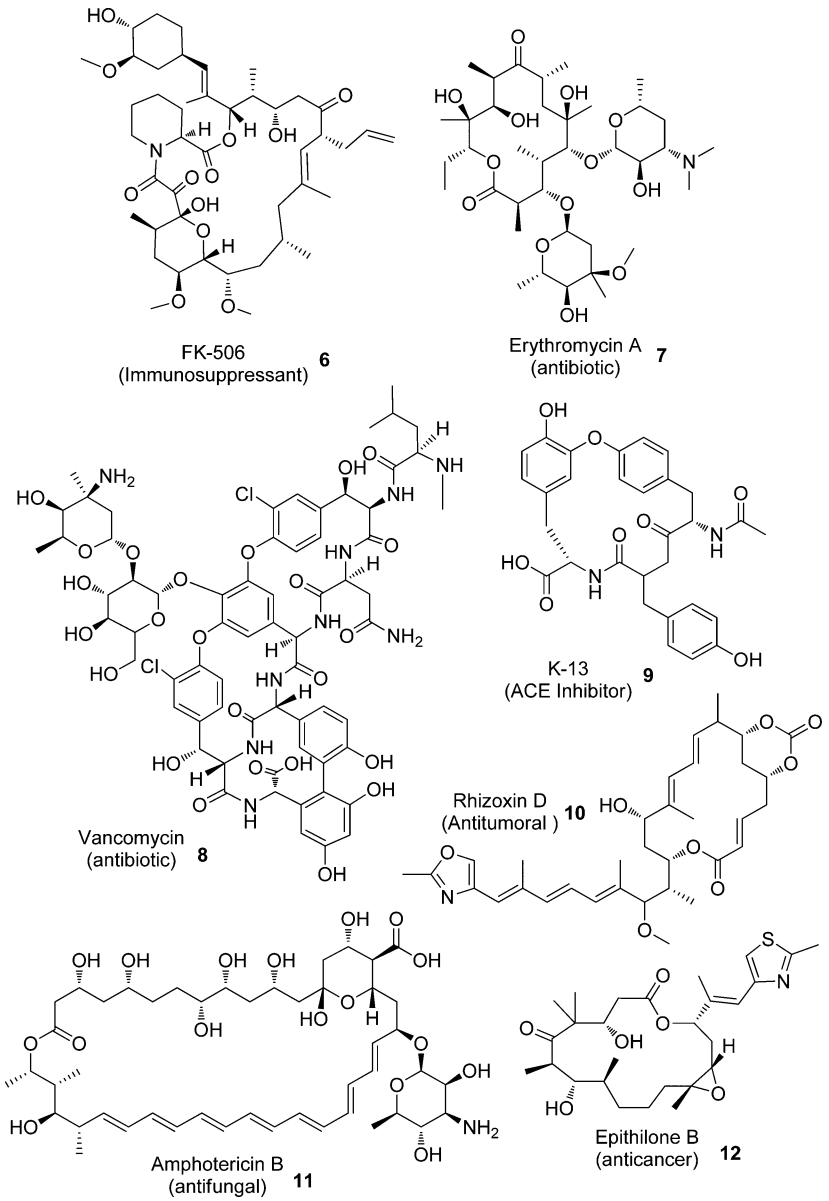

Figure 2. Natural macrocycles with important biomedical activity.

known natural products from terrestrial and marine sources possess cyclic structures.[6] Some relevant examples (Figure 1) include the antibiotics valinomycin **3**[7] and gramicidin S **4**, the macrolide nonactin **5**, cyclic DNA, and plasmids.[5]

Thus, the synthesis of macrocyclic structures is an important target nowadays. In this review, we have analyzed the most important approaches leading to the efficient synthesis of macrocyclic structures, as well as the most recent advances and examples in this field. Special emphasis has been given to the role of the structural or induced preorganization of the precursor. In considering macrocyclization processes, we have essentially concentrated on those systems of broader applicability. In this work, the term "macrocyclic structure" applies to compounds displaying a ring arrangement of atoms attached through covalent bonds. In this way, the formation of macrocyclic structures and cages involving the noncovalent assembly of components,[8−13] or the formation of organometallic and coordination bonds,[14−16] has not been taken into consideration in a systematic way. Some very specific classes of structures such as phthalocyanines and related compounds,[17−19] calixarenes,[20−22] cyclodextrins,[23−25] cucurbiturils,[26−28] etc. that have been analyzed in detail in dedicated reviews will also not be, in general, analyzed. Additional reviews devoted to the formation of cyclic supramolecular polymers[29−31] and other macrocyclic structures not included in this review can be found in the literature.[59,32] No attempt has been made for the exhaustive inclusion of all literature reports dealing with the preparation of macrocyclic structures. Even considering the structural limitations indicated above and the potential restriction of a literature search to a reduced period of time, the huge amount of reports involving the synthesis and study of macrocyclic structures makes this an impossible task. In contrast, we have made the utmost effort to include most of the recent references, in particular those from this century, involving new conceptual approaches and mechanistic insights, and highlighting the different methodologies currently implemented for the efficient preparation of macrocycles. On the other hand, in this work the literature search has been maintained up to the end of 2014. Further contributions

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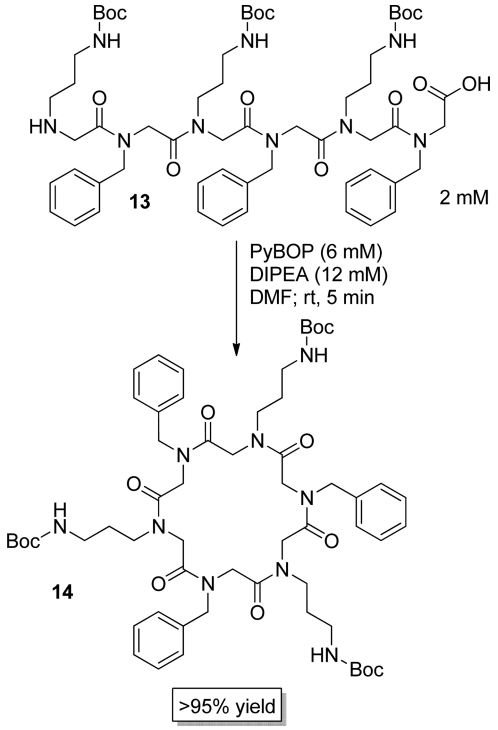

Figure 3. Boc protected linear and macrocyclic peptoids with antimicrobial activity.[42]

have not been included here. In order to get a more clear vision of the significance of the examples selected, the essential information regarding the macrocyclization conditions (concentration, temperature, yields) has been included, whenever possible, in the figures or in the corresponding figure captions.

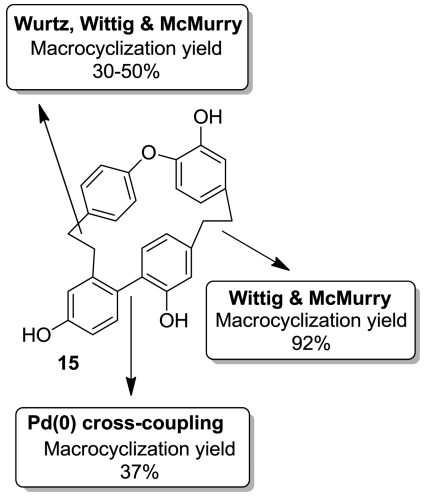

Figure 4. Different macrocyclization strategies for preparing Riccardin C **15**.[61]

2. MACROCYCLIC COMPOUNDS AND MACROCYCLIZATION STRATEGIES

Many natural macrocycles are very active biologically and can display important medicinal activities as shown in Figure 2 (**6**–**12**),[33] or have cytotoxic properties like the cylindrocyclophanes

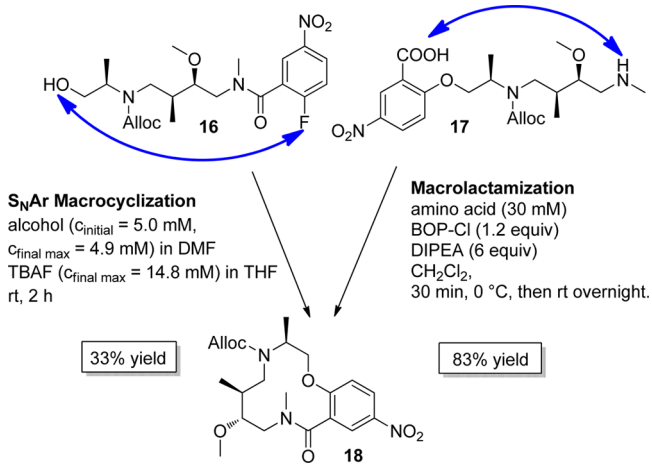

Figure 5. S_NAr reaction vs macrolactamization for the synthesis of 12-membered macrolactams.[62]

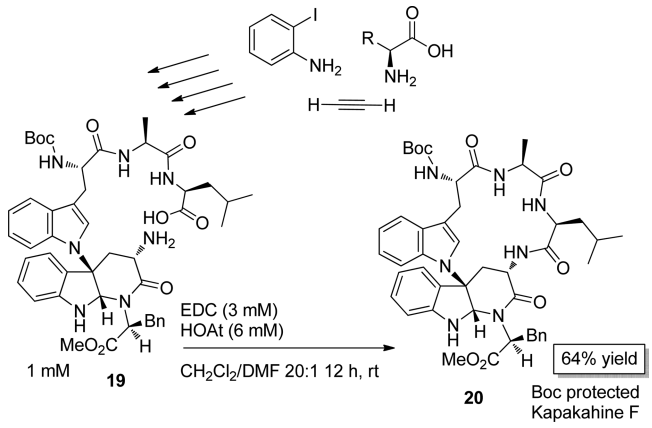

Figure 6. Preparation of kapakahine F **20** from different starting amino acids.[65,66]

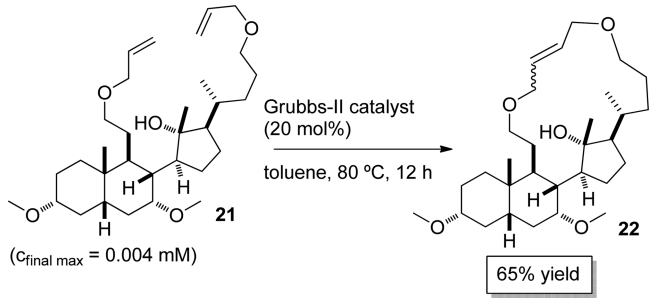

Figure 7. Synthesis of secosteroidal macrocycles by RCM.[76]

from photosynthetic cyanobacteria.[34] Nonribosomal peptides and polyketides also have important applications as therapeutic agents, and the biological activity of many of these complex products is associated with their cyclic structures.[35]

Thus, it is not surprising that natural and synthetic macrocycles have been successfully employed for drug discovery approaches.[36−39] Macrocyclic constraints may enhance the binding affinity, improve selectivity, and provide a higher metabolic stability.[40,41] As an example, Kirshenbaum and co-workers have reported the synthesis and application of peptoid macrocycles as potent and selective antimicrobials. An increase in the antimicrobial activity of the macrocyclic compound **14** was observed with regard to the corresponding open-chain system **13**

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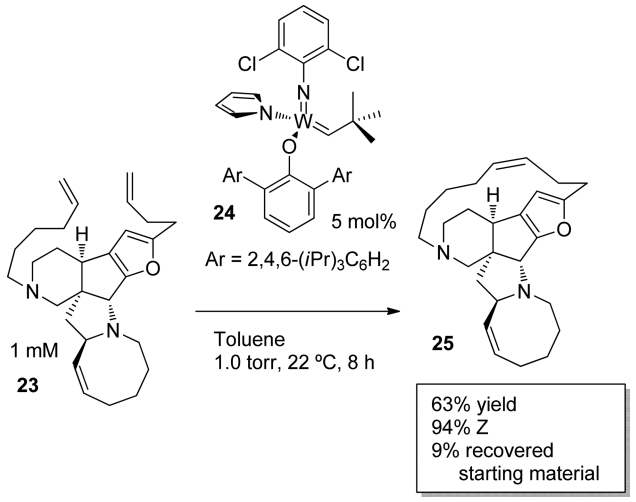

Figure 8. Synthesis of Nakadomarin A **25** through RCM using a W catalyst **24**.[77]

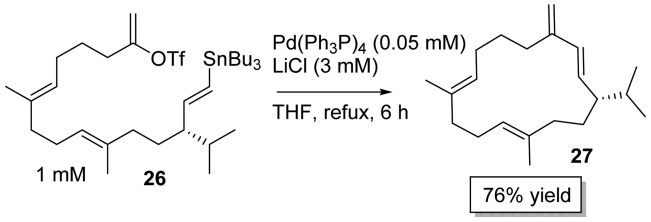

Figure 9. Macrocycle synthesis through a Stille reaction.[82]

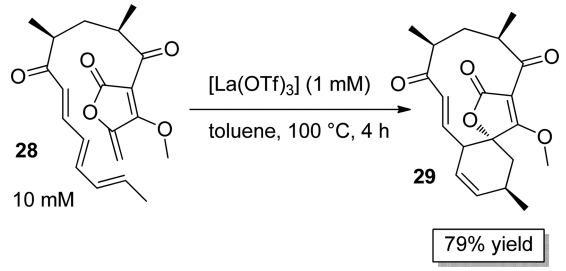

Figure 10. Intramolecular Diels–Alder reaction to provide the macrocyclic structure of Abyssomicin C **29**.[85]

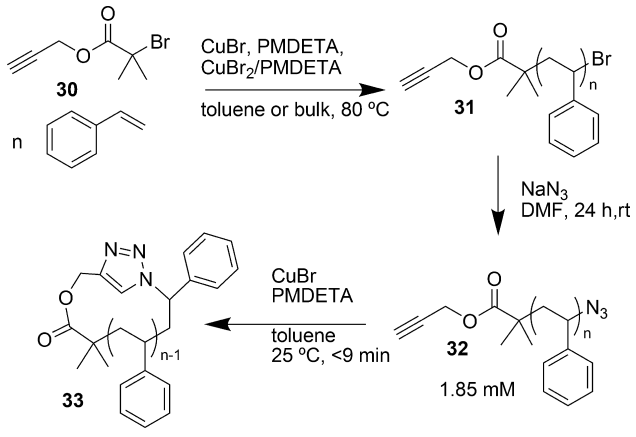

Figure 11. Procedure for the preparation of high-purity monocyclic polymers by CuAAC "click" reactions.[88] The letter *n* denotes the number of monomers in the monocyclic polymer.

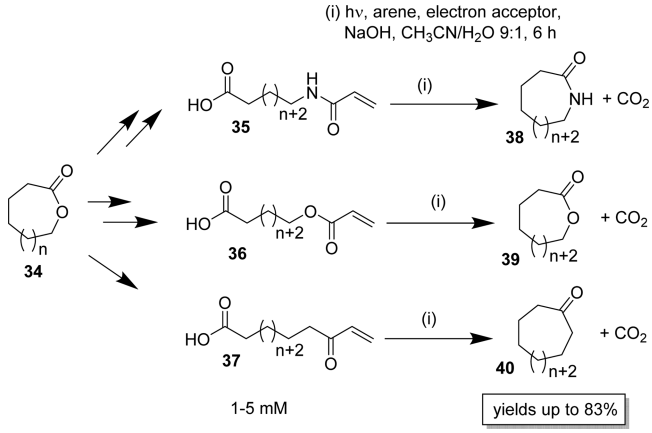

Figure 12. Photoinduced intramolecular radical macrocyclization.[89]

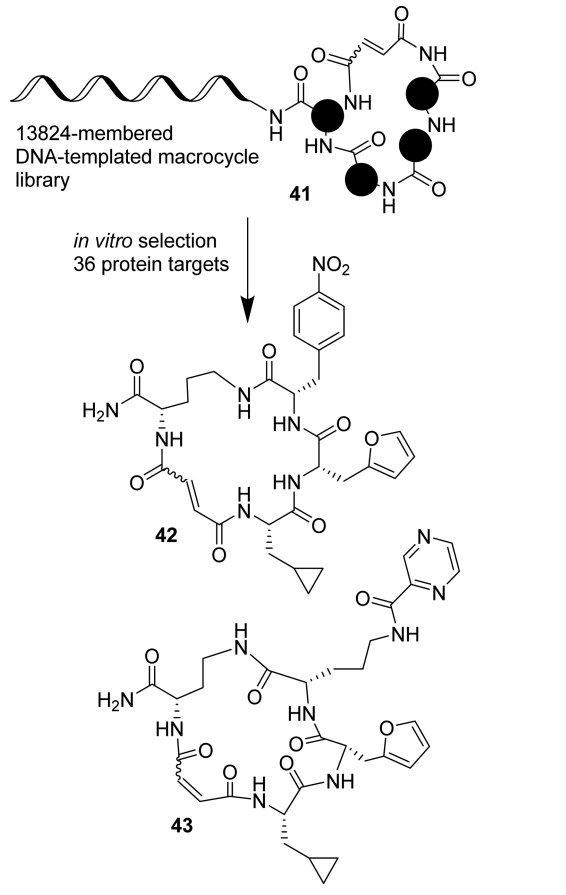

Figure 13. Development of macrocyclic kinase inhibitors **42** and **43** via in vitro selection of a DNA template library **41**.[92]

(Figure 3), revealing how the increase in the conformational order is beneficial for the antimicrobial activity.[42] Many other examples of the effect of macrocyclic constraints on binding affinities and selectivities and on properties such as antimicrobial activity are reported in the literature.[43−45]

As more than 100 macrocyclic compounds derived from natural products are used as commercial drugs, there is a continuing interest in exploring macrocyclic structures and macrocyclization reactions for the invention of new therapeutic agents,[46] and some recent examples represent important advances in medicinal chemistry.[47] These include the biomimetic synthesis and optimization of cyclic peptide analogues,[48] cyclic

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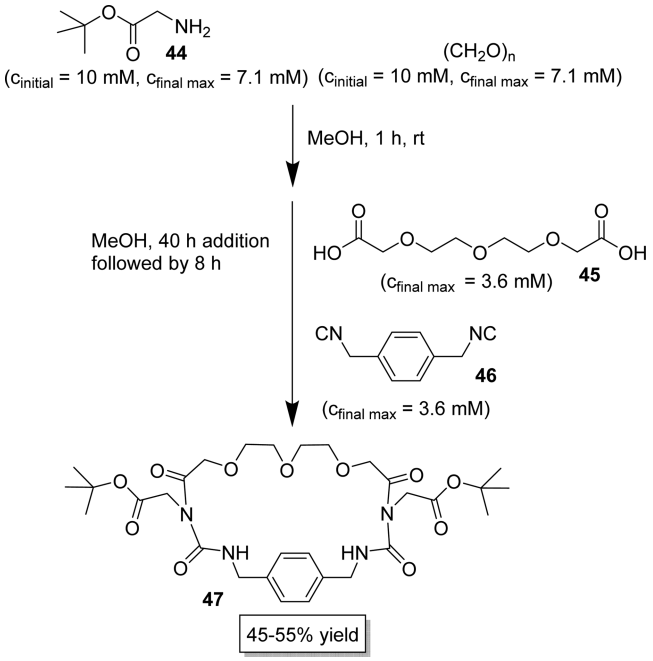

Figure 14. Multicomponent synthesis of a macrocyclic receptor containing polyether and urea groups.[95]

RGD β-lactam peptidomimetics that induce differential gene expression in human endothelial cells,[49] G-quadruplex ligands for anticancer therapeutics,[50] the excellent tumor uptake and pharmacokinetics of ^{64}Cu-labeled cyclic RGD peptide dimers with Gly and PEG linkers,[51] macrocyclic lactams as potent Hsp90 inhibitors with excellent tumor exposure and extended biomarker activity,[52,53] proteasome inhibitors,[54] inhibitors of HIV-1 capsid-human lysyl-tRNA synthetase,[55] macrocyclic lactams inspired on the skeleton of natural products with anticancer properties,[56] etc. Besides the considered biomedical applications, macrocyclic structures have found important applications in other fields such as chemical analysis[57,58] or nanotechnology.[59]

Macrocyclic compounds can be obtained using a large variety of chemical reactions for the key ring-closing step. Literature data show, however, that some specific reactions have been frequently used for this purpose. In some cases, this is associated with the presence of specific functionalities in the target macrocyclic structures but, in other situations, this reflects the existence of intrinsic features favoring the efficiency of the cyclization. Selecting the appropriate ring-closing reaction is a crucial step for any synthetic macrocyclization strategy. A good example is the preparation of the antitumor macrolide Rhizoxin D **10** (Figure 2), for which several macrocyclization approaches were considered to achieve, finally, the desired product via a Horner−Emmons olefination (reaction at 0.5 mM concentration) in 49% yield.[60] A second illustrative example of the multiple synthetic strategies available for the macrocyclization step in the synthesis of a cyclic compound is provided by the synthesis of Riccardin C **15** (Figure 4).[61]

Another example of the importance of selecting the appropriate ring-closing reaction has been highlighted by Fitzgerald and co-workers in the synthesis of a library of 7936 stereochemically diverse 12-membered macrolactams. For the optimization of the model cyclization conditions, they described two different synthetic approaches (Figure 5). When the final step was an intramolecular S_NAr reaction in **16**, the yield was in the range 25−45%. On the contrary, when the macrolactamization of **17** was employed, the desired product **18** was obtained in 83% yield.[62]

Probably, lactonization and lactamization reactions,[63,64] as illustrated in the synthesis of the complex structure of kapakahines (i.e., macrocyclization of **19** to **20** in Figure 6) containing a twisted 16-membered ring,[65,66] are some of the more usual processes found in macrocyclization. This is associated with the prevalence of lactone and lactam groups in many macrocyclic structures, either natural or synthetic. Thus, cyclic peptides are known to have important properties as they are more resistant to proteolytic degradation,[67,68] and the discovery of gramicidin S (**4**) in 1944 was very relevant as it was employed for treatment of gunshot wounds.[69] Since then, many efforts have focused on the development of efficient methodologies for peptide macrocyclization.[70]

Many other reactions have been reported for macrocyclizations. *Nucleophilic substitution* reactions, including aromatic substitution, represent one of the simplest conceptual approaches for cyclization. These reactions are critical for the formation of polyoxa, polythia, or polyaza macrocycles (crown ethers, thiocrown, and azacrown derivatives).[71] Wittig and related reactions have proved effective over a wide range of conditions and structures and often give excellent yields.[61]

On the other hand, many syntheses developed to obtain complex natural products containing macrocyclic rings involve C−C forming reactions with the use of transition-metal catalysis.[72] From the different reactions of this class,[73] the ring-closing metathesis (RCM) and related processes are between the most common and efficient. RCM reactions have been applied to the preparation of a variety of cyclic natural products,[74,75] and usually are carried out under diluted conditions to avoid the competence of intermolecular processes.[73]

One of the main drawbacks of this approach is the lack of control of alkene stereochemistry, with the formation of *E* and *Z* isomers. This is problematic as the open-chain precursor is usually obtained after a long sequence of chemical reactions. This is illustrated by the synthesis of secosteroidal macrocycles displayed in Figure 7. The cyclization reaction from **21** is very efficient, affording the corresponding macrocycle **22** in 65% yield with the use of the Grubbs II catalyst (20 mol %) and high dilution conditions, but a 8:2 *E*:*Z* mixture was obtained.[76]

Different approaches have been developed to overcome this drawback. In general, the *E*-isomer is thermodynamically more stable than the *Z*-isomer, but Yu, Wang, and co-workers developed a tungsten-based catalytic system that allowed the selective preparation of the corresponding *Z*-isomer in a variety of structures, including some macrocyclic compounds relevant for the synthesis of important natural products. This is the case of Nakadomarin A (**25**), for which the macrocyclization could be carried out efficiently, at concentrations around 1 mM of **23** using catalyst **24**, in 63% yield with 94% *Z*-selectivity (Figure 8).[77] Previous attempts with the use of a Ru catalysis have afforded the desired macrocyclic compounds in 62% yield but using a much higher catalyst loading (20%) and with a significantly reduced *Z*-selectivity (63% *Z*).[78] On the other hand, Grubbs and co-workers, and also other research groups, have developed recently a new family of efficient ruthenium catalysts that yield *Z*-selective macrocyclizations (up to 95% *Z*-selectivity) providing simultaneously high TON values.[79,80] The same kinds of catalysts have also been used to obtain the almost pure *E*-macrocycles (up to 95% *E*) by *Z*-selective ethenolysis of the *E*/*Z* mixtures.[79] Analogous advances in the catalyst design

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allowed obtaining catalyst-controlled stereoselective macrocyclic ring-closing metathesis.[81,133]

Pd catalyzed reactions have also been extensively used in macrocyclizations as is exemplified by the Stille coupling shown in Figure 9.[82,83] Cyclization was accomplished with tetrakis-(triphenylphosphine)palladium (5 mol %) in the presence of lithium chloride (3 equiv) under high dilution (1 mM **26**) in refluxing THF to obtain the macrocyclic product **27** in 76% yield. Boger and co-workers have reported a Pd(0)-mediated Larock indole annulation for macrocyclization reactions that allows obtaining the desired product in yields up to 82%.[84]

Diels–Alder reactions are well-known as key processes for the formation of small-to-medium size cycles. An appropriate design of the process also allows their use for macrocyclization. This is illustrated in the synthesis of the natural product Abyssomicin C (**29**) from the macrocyclic precursor **28**, which also requires a catalytic metal (La) for obtaining good results (Figure 10).[85] The potential of this approach was reviewed a few years ago.[86]

Different strategies for rapid and high-purity preparation of monocyclic polymers have been developed using the copper-catalyzed azide–alkyne cycloaddition (CuAAC).[87] In consequence, click chemistry is a valuable tool for the preparation of macrocyclic structures from oligomeric or polymeric open-chain precursors **32.** Figure 11 provides an illustrative example. In this case, the alkyne initiator **30** is used in conjunction with styrene to obtain the linear polymer **31** that can be easily transformed into the azide–alkyne **32**. Thus, the CuAAC methodology with these oligomers containing azide and acetylene as terminal groups allows obtaining the corresponding monocyclic polystyrene polymers **33** in high purity (>95%).[88]

Efficient photochemical approaches have also been described. Recently, Yoshimi and co-workers described a new method for the synthesis of macrocyclic lactams (**38**), lactones (**39**), and ketones (**40**), which utilizes the cyclization of the radical intermediates derived from the PET (photoinduced electron transfer) promoted decarboxylation of carboxylic acid tethered α,β-unsaturated carbonyl compounds, with yields up to 84%. The macrocyclization yields depend on the concentration of the open-chain acid (**35**–**37**) and are drastically reduced when increasing its concentration. In the case of the synthesis of lactones **39**, increasing the concentration from 1 to 5 mM involves a reduction in the cyclization yield from 84 to 29%. The reaction occurs in the presence of an arene and an electron acceptor, and for lactones and lactams, in most cases, best results were obtained using phenanthroline and 1,4-dicyanonaphthalene. As the open-chain precursors **35**–**37** were prepared from lactones, this methodology allows increasing the size of a given macrocyclic lactone (i.e., **34**) by a demacrocyclization/remacrocyclization sequence (Figure 12).[89]

Recent approaches also implicate the use of *combinatorial chemistry*, based on the analysis of structural motifs in natural bioactive compounds, allowing the preparation of libraries of related compounds and, eventually, the discovery of novel molecules with important biological activity. This approach has been used in particular for macrocyclic peptidomimetic[90] and macrolide[91] compounds. The preparation of a DNA-templated small molecule library (**41**), followed by their in vitro selection using 36 protein targets, has been described in order to obtain a new class of macrocyclic kinase inhibitors **42** and **43** (Figure 13).[92]

Although the head-to-tail cyclization of the corresponding open-chain precursor is a very common approach, macrocyclizations can also be achieved by means of multiple multicomponent processes. This methodology allows preparing macrocyclic structures of different complexities from several relatively simple building blocks in a one-pot reaction. Therefore, this avoids the protection/deprotection steps necessary in other macrocyclization approaches to prepare the open-chain macrocycle precursors.[93,94] Wessjohann and co-workers have used this Ugi-four-component (**44**, paraformaldehyde, **45**, and **46**) macrocyclization methodology for the preparation of different macrocyclic structures (**47**, Figure 14),[95] as well as macrobicyclic compounds.[96] Kurth and co-workers, who reported a multicomponent macrocyclization with highly reactive acyl ketene and nitrile oxide intermediates (using five components at 12 mM concentration), also used this methodology, which allowed short reaction times using low concentrations.[97]

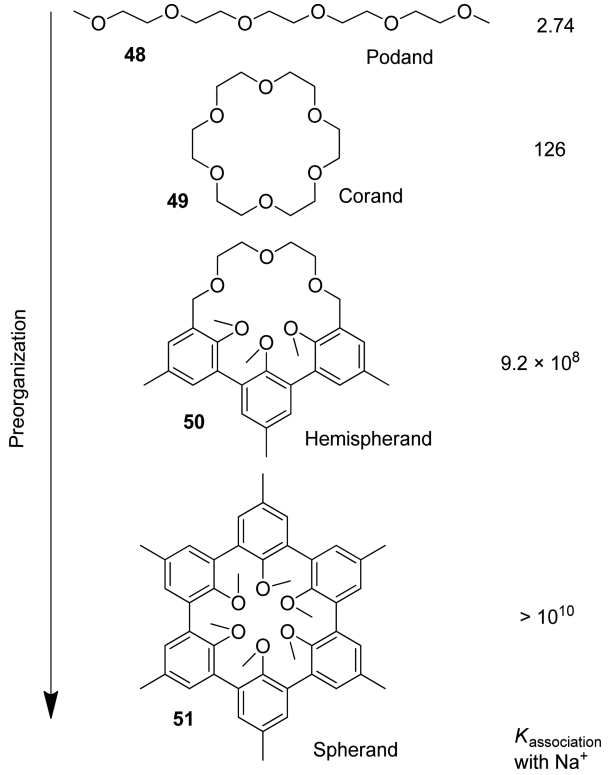

Figure 15. Na^+ association constants for receptors containing six oxygen donor atoms and having different levels of structural preorganization.[99−102]

3. ROLE OF PREORGANIZATION IN MACROCYCLIC CHEMISTRY

As mentioned above, macrocycles represent a well-understood example of the concept and potential of preorganization. Their specific properties, often associated with their preorganization, make them appropriate for important applications in many different fields. Their use, however, can be sometimes limited as their synthesis, involving a macrocyclization step, can become rather difficult.[98] Complex and long synthetic strategies can be needed to obtain macrocyclic structures with good yields. These synthetic limitations are the price to be paid in order to achieve a higher level of preorganization in the final structure.

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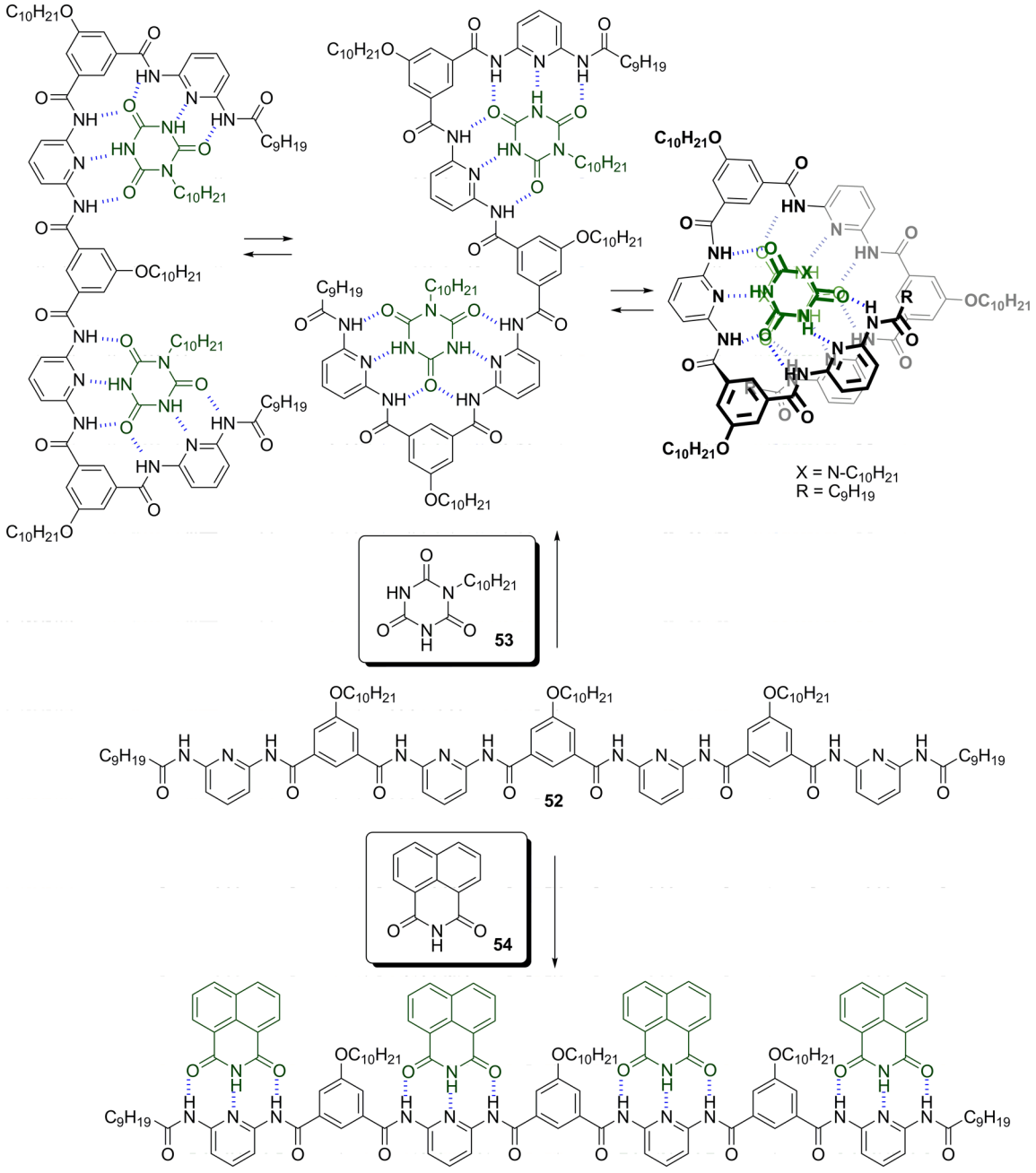

Figure 16. Hydrogen-bonded template expression of the information stored in the oligomeric compound **52** through a recognition process of **53** and **54**.[108]

The proper preorganization of functional elements at the active sites of biomolecules is at the origin of the unsurpassed efficiencies found for biological systems in the accomplishment of their specific functions. At the initial steps of the development of supramolecular chemistry, Cram was able to realize and highlight the key role of preorganization for understanding supramolecular interactions.[99] This seminal work was able to demonstrate how, for related systems, the higher the organization/rigidity of the hosts (**48**−**51**) the bigger the binding constants with the appropriate guest and therefore the importance of macrocyclic structures in this regard. This is exemplarized in Figure 15, showing the increase in the association constant values (K_a) with Na^+ for receptors containing six oxygen donor atoms, when going from the more flexible compound (**48**, podand) to the more rigid one (**51**, spherand).[99−104]

As can be seen, macrocyclic molecules are, intrinsically, preorganized systems. In general, host−guest supramolecular interactions[105] involve conformational changes in the receptor, and sometimes in the substrate, to achieve an optimal fitting between complementary groups or regions. This conformational rearrangement has an energy cost that reduces the final ΔG value for the formation of the supramolecular species (see eqs 1−3).

$$\Delta G_{\text{complexation}} = \Delta G_{\text{interaction}} - \Delta G_{\text{rearrangement}} \quad (1)$$

$$\Delta G_{\text{complexation(preorganized receptor)}} = \Delta G_{\text{interaction}} \quad (2)$$

$$\Delta G = -RT \ln K_{\text{association}} \quad (3)$$

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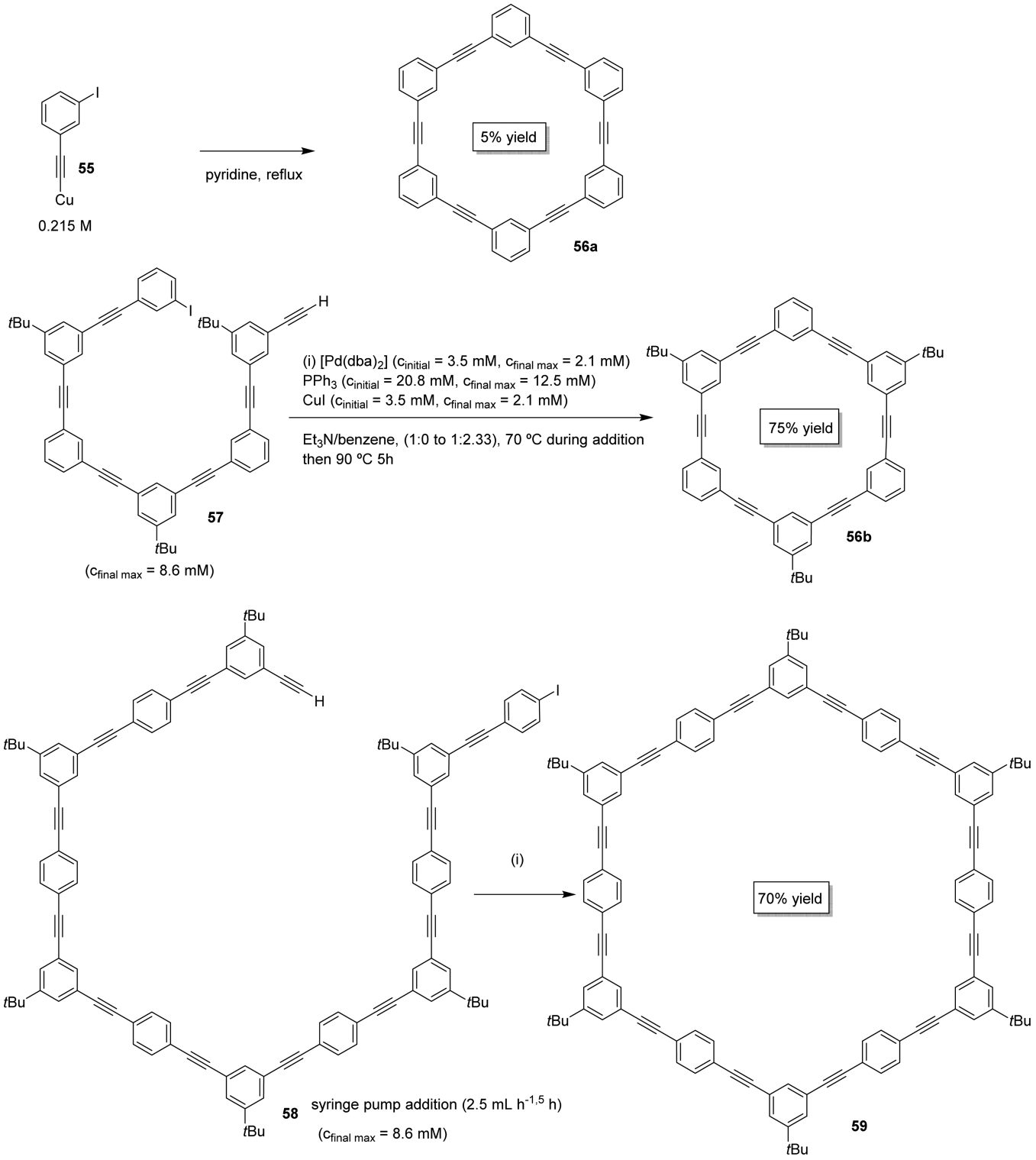

Figure 17. Synthesis of large phenylene acetylene macrocycles.[110−112]

For preorganized receptors (and substrates), this energy cost has been paid for in the synthetic procedure, which permits achieving more negative ΔG values and, accordingly, higher association constants in the recognition process. In some cases, the prevalence of appropriate conformations of the immediate precursor that provide a favorable preorganization for the macrocyclization step can be an essential factor for this reaction. In some instances, the proper conformation can be induced by a second species. Lehn has described this process by considering that molecules have molecular information that can be expressed through supramolecular interactions. A supramolecular preorganization event incorporates molecular information from the guest into the new supramolecular species.[106,107] Figure 16 illustrates how different guest molecules **53** and **54** allow obtaining different conformations of a single open-chain molecule **52**, including the generation of folded and pseudocyclic geometries.[108]

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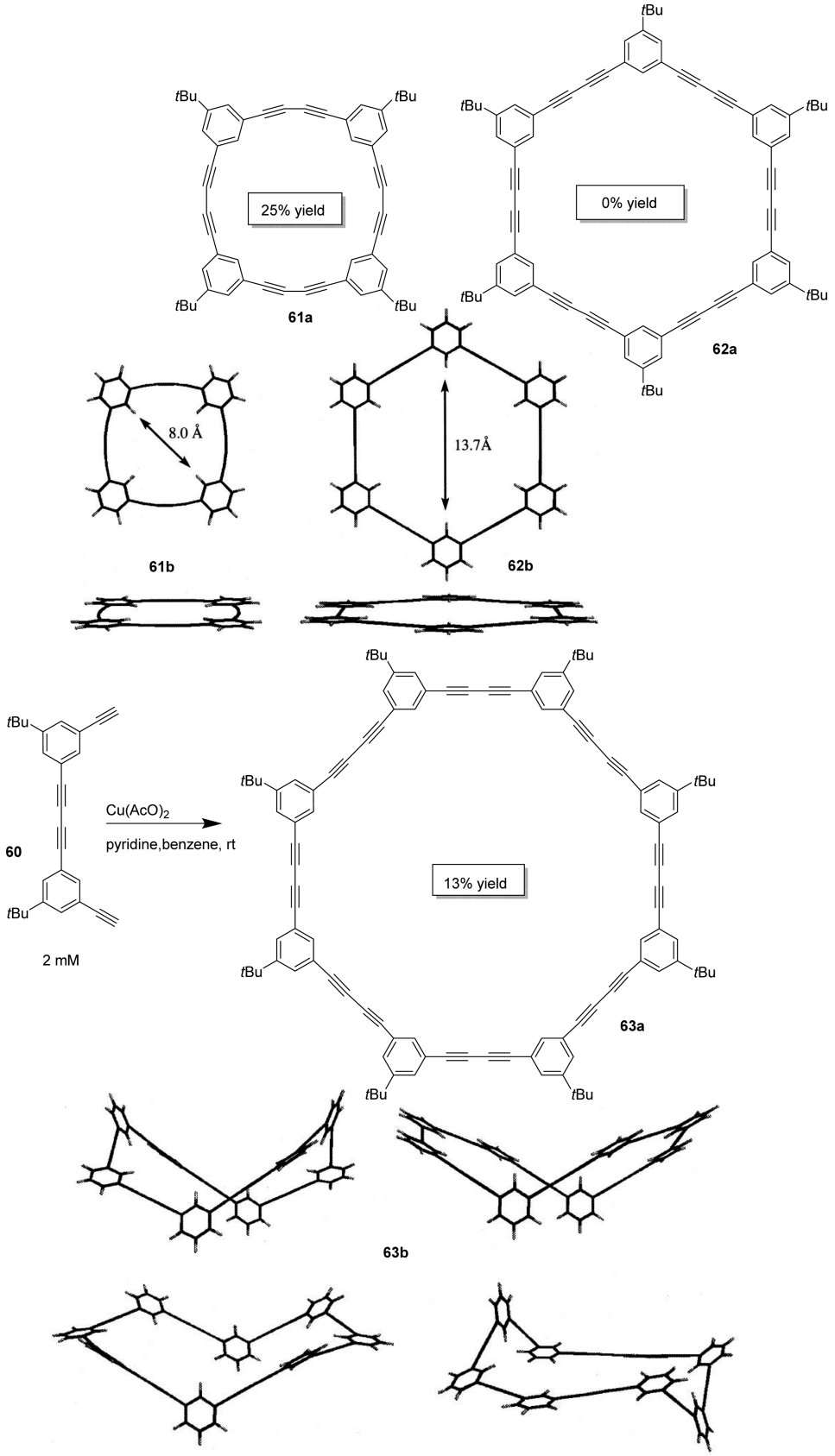

Figure 18. Synthesis of shape-persistent macrocycles.[114] AM1 optimized geometries of the related model macrocycles **61b**, **62b**, and **63b** (for the octameric structure **63b** four conformers are represented). Reprinted with permission from ref 114. Copyright 2001 Elsevier.

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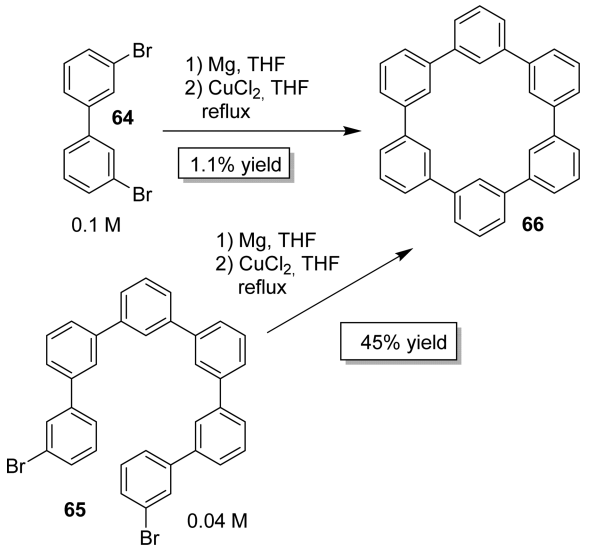

Figure 19. Macrocyclization using 3,3′-dibromobiphenyl **64** and open-chain precursor **65**.[117]

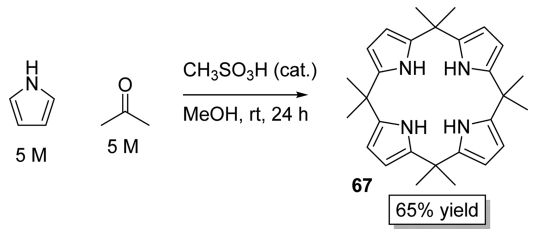

Figure 20. Synthesis of calix[4]pyrrole.[120]

4. EXPERIMENTAL ASPECTS IN THE SYNTHESIS OF MACROCYCLES

As mentioned, many classic approaches to the synthesis of macrocycles require complex synthetic sequences involving protection and deprotection steps, high dilution conditions, etc. The combination of the different structural and reaction parameters is responsible for the final results. In this regard, Collins and James developed the Emac index, defined as Emac = log(yield^3 × concentration), in an attempt to compare the efficiency of a given macrocyclization taking into account both the reaction yield and the concentration at which the experiment has been carried out.[109]

Even in systems and approaches where the structural or induced conformations of the open-chain precursors favor the macrocyclization reaction, the effect of reaction conditions can be critical. An illustrative example of this situation is given by the synthesis of phenylene acetylene macrocycles **56**, **58**, and **60** shown in Figure 17. Thus, the 6-mer macrocycle **56a** could be isolated from the one-pot reaction of the monomeric precursor **55** through six consecutive Stephens−Castro coupling reactions of the copper salt **55** (4.6% yield) as reported by Staab and co-workers.[110] The same macrocyclic structural motif incorporating *tert*-butyl groups **56b** can be, however, obtained in much higher yields (75% yield) by the cyclization of the 6-mer open-chain precursor **57** or **58** under pseudo-high-dilution conditions (*tert*-butyl groups were necessary to achieve the necessary solubility of the products).[111,112] An important drawback of the second approach was the need for several synthetic steps for preparing the open-chain precursors, each one involving protection and deprotection stages. However, one important advantage of the sequential synthesis is the possibility of synthesizing the much larger macrocycles **56b** or **59** through the proper selection of the structural components (Figure 17) as reported by Moore and co-workers.[112,113] The high yield for the macrocyclization from the 6-mer open-chain precursors **57** or **58** has been ascribed to the favorable preorganization provided by the presence of rigid phenylene and acetylene subunits. However, as the key step is catalyzed by transition metals, the role of the catalytic metal species as a templating element should also be considered as well as the use of high dilution conditions.

Tobe and co-workers have prepared related systems with one extra ethyne group in the building blocks (**60**). The Eglinton coupling yields the macrocyclic tetramer **61a** and the octamer **63a** but not the hexamer **62a** (Figure 18). The AM1 optimized geometries of the model macrocycles, lacking the *tert*-butyl group, **61b**, **62b**, and **63b** have been included in Figure 18 to illustrate the macrocyclic constraints of these systems.[114] Scott and co-workers have prepared related systems using 3,3-dimethylpenta-1,4-diyne and 1,1-diethynylcyclopropane with macrocyclization yields up to 70%.[114,115] Bäuerle and co-workers have used the formation of cyclic palladium complexes from terthiophene-diyne and *cis*-Pt(dppp)Cl$_2$ to obtain selectively, in 91% macrocyclization yield, the corresponding metallamacrocycle that was quantitatively transformed to the desired macrocycle by 1,1-reductive elimination of the Pt from the metallamacrocycle. This method improves the initial method (that does not use Pt) that afforded a non-size-selective macrocyclization in 9−14% yield only under pseudo-high-dilution conditions.[116]

Staab and co-workers also reported a similar trend in the preparation of shape persistent macrocycles **66** increasing the yield from 1.1 to 45% by changing from the small building blocks **64** to the well-preorganized open-chain precursor **65** (Figure 19).[117]

In contrast, the synthesis of the conformationally flexible calix[4]pyrrole macrocyclic structure **67**, first discovered by Baeyer in 1886,[118] and relevant to the formation of porphyrins,[119] could be performed at 5 M concentration in 65% isolated yield, reflecting the outstanding efficiency of this macrocyclization reaction even at high concentrations of starting materials (Figure 20).[120] Both the efficiency of the macrocyclization reaction and the remarkable anion binding properties of the calix[4]pyrrole macrocyclic motif are key elements to understand the big research efforts devoted to the preparation of a variety of synthetic receptors based on this versatile synthon.[121,122]

As mentioned in the former examples, high-dilution conditions or pseudo-high-dilution conditions have been frequently associated with successful macrocyclizations. The use of very diluted concentrations of the final open-chain precursor will always favor intramolecular processes leading to the macrocycle instead of intermolecular reactions producing oligomeric/polymeric species, some of which could eventually form higher order macrocycles. High dilution approaches usually involve slow addition of the components in a large volume of solvent.[106,123,124] A common and simple experimental assembly used for this purpose is a three-necked round-bottom flask equipped with two addition funnels. For more precision, the addition funnels can be substituted by electronically controlled syringe pumps or by more sophisticated glasswork.

Finn and co-workers have performed a highly efficient ring closure of aromatic dialdehydes (**68**−**70**) to form macrocyclic allenes (**71**−**73**). The highly efficient cyclization is attributed to

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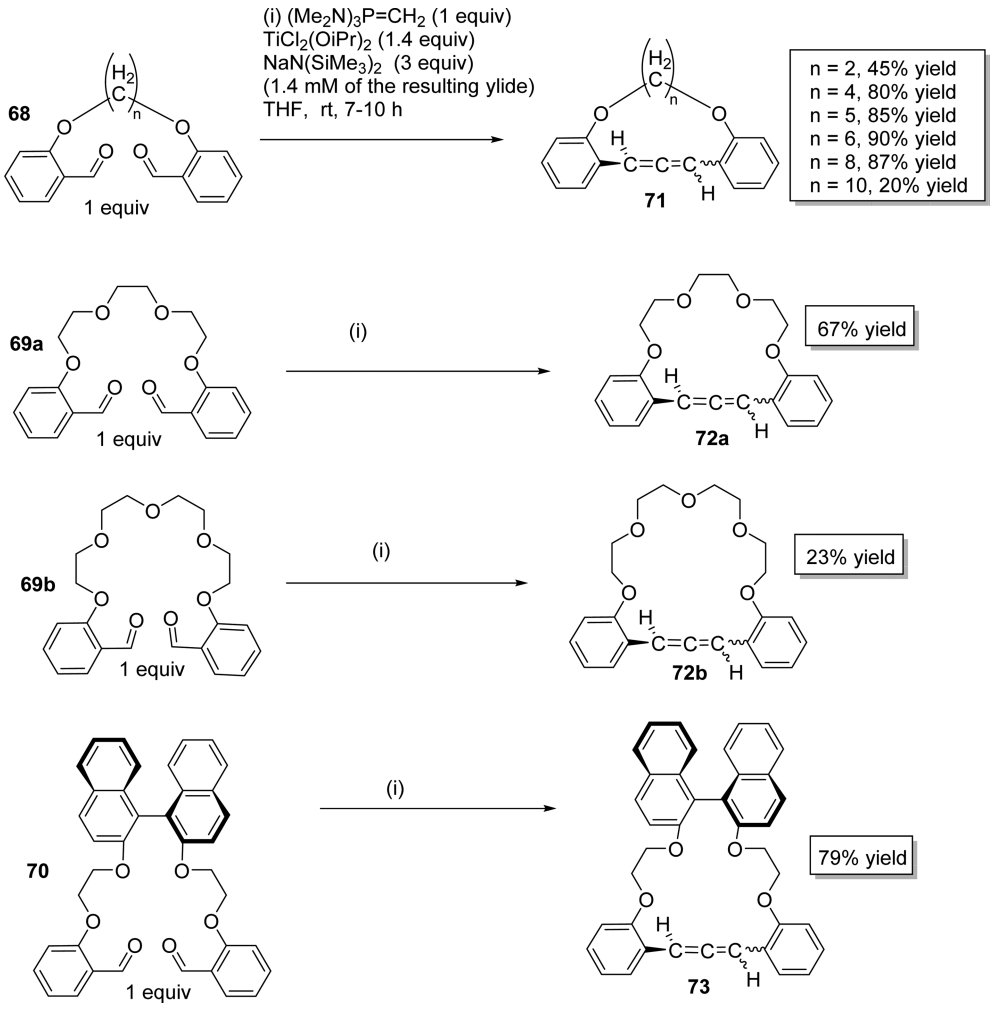

Figure 21. Synthesis of macrocyclic allenes.[125]

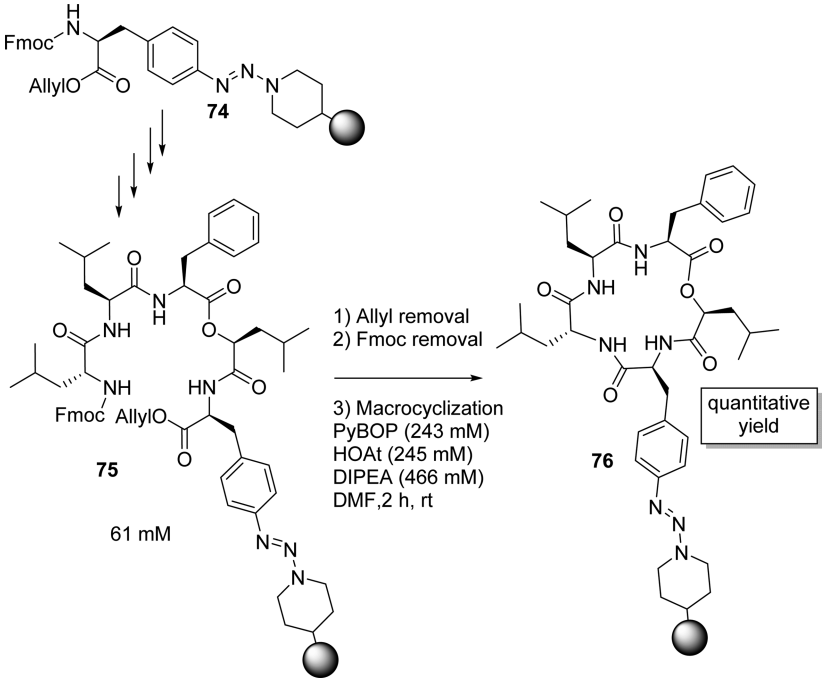

Figure 22. Resin peptide macrocyclization reaction.[140]

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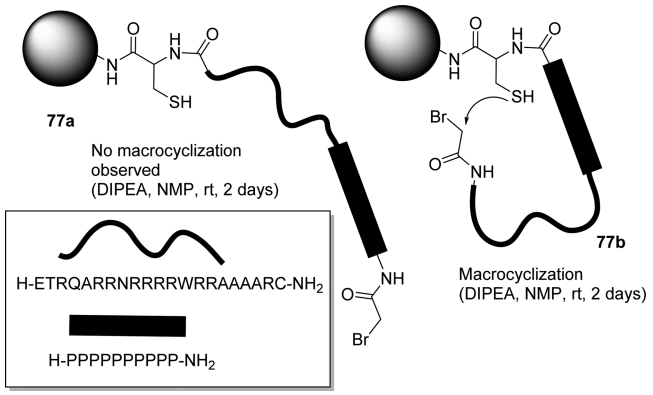

Figure 23. Resin macrocyclization reaction.[152]

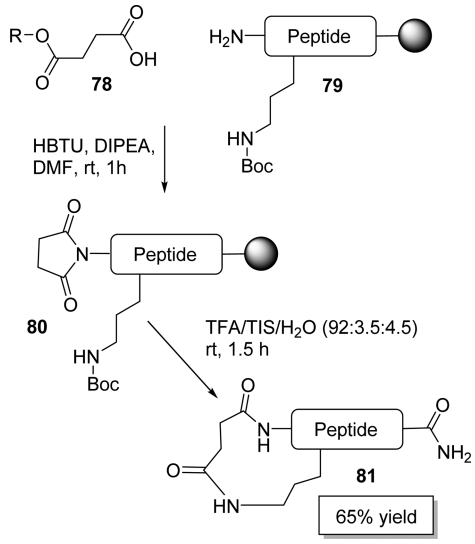

Figure 24. Tandem in situ peptide cyclization through trifluoroacetic acid cleavage.[153] TFA = trifluoroacetic acid; TIS = triisopropylsilane.

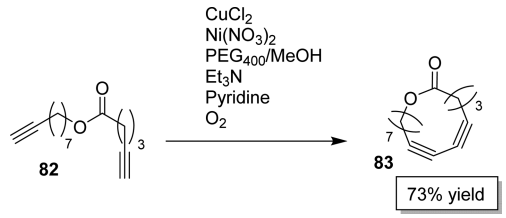

Figure 25. Macrocyclization using the Glaser–Hay coupling in two phases.[157]

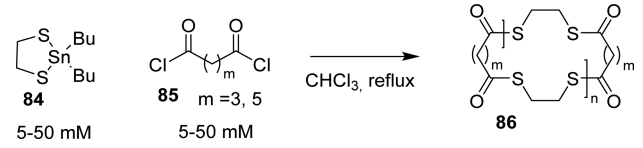

Figure 26. Synthesis of macrocyclic poly(thiolactones) **86** under kinetic control (see results in Tables 1 and 2).[174]

the specific combination of slow kinetic constants for the processes leading to the open-chain precursor. In this way, only very low concentrations of this precursor are present and the critical step takes place under actual high dilution conditions. However, the possible preorganization around the cation in the base of one of the intermediates has also been suggested, as the

Table 1. Results Obtained for the Reaction Described in Figure 26 for m = 3[174]

	% macrocyclic compound **86**							
	n							
C_0 (mM) **84** and **85**	0	1	2	3	4	5	6	∑cyclic structures (%)
5	20	44	20	7	2	–	–	93
10	10	46	23	10	6	2	–	97
50	4	35	19	12	9	5	2	86

Table 2. Results Obtained for the Reaction Described in Figure 26 for m = 5[174]

	% macrocyclic compound **86**							
	n							
C_0 (mM) **84** and **85**	0	1	2	3	4	5	6	∑cyclic structures (%)
1	91	8	–	–	–	–	–	99
5	65	28	6	2	–	–	–	101
10	42	34	13	6	3	1	–	99
50	14	26	12	6	5	3	2	68

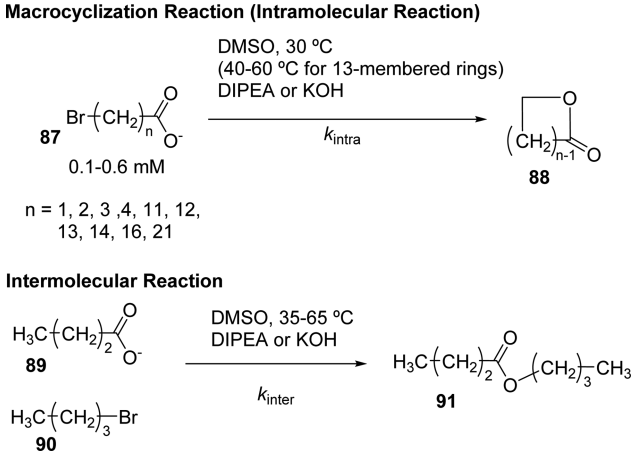

Figure 27. Macrolactonization of ω-bromoalkylcarboxylates and its intermolecular equivalent process.[175]

nature of the corresponding cation (Na^+ or K^+) has an effect on the macrocyclization yield.[125] Besides, the effect of the spacer between the two aldehyde fragments of the precursor (**68**–**70**) was analyzed, and it was observed that the final yield was directly related to this parameter (Figure 21).

The immobilization of precursors on functional resins (solid phase synthesis) has also been considered to introduce pseudodilution effects, in particular when low levels of functionalization and highly rigid polymeric supports are used.[70,126,127] This methodology can be used to perform on resin macrocyclizations based on palladium catalyzed reactions,[128] S_N2 reactions,[129] CuAAC click chemistry reactions,[130] Heck reactions,[131] thiol–ene photochemical reactions,[132] or *Z*-selective olefin metathesis.[133] Many different examples in which the preparation of cyclic structures without the interference of the competing intermolecular reactions is observed have been reported.[134−139] Thus, this methodology allowed a quantitative N to C on-resin macrocyclization reaction of the open-chain precursor **75** to obtain the macrocycle **76** using the side chain of a modified phenylalanine for the binding to the solid support via a

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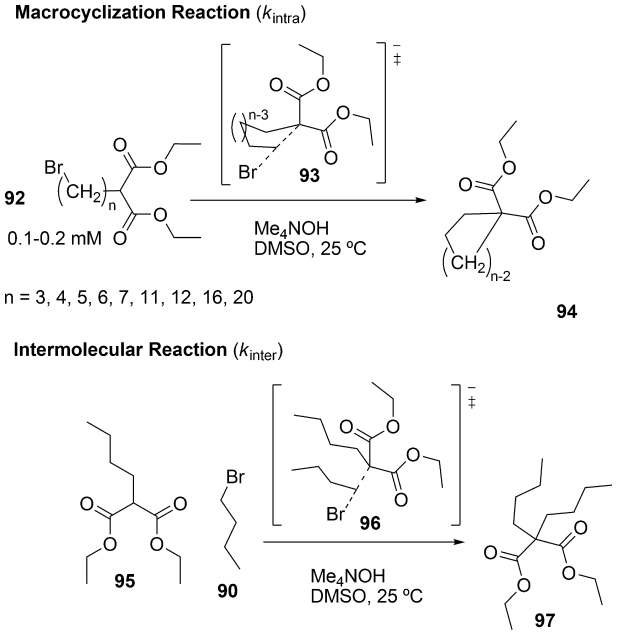

Figure 28. Cyclization of diethyl 2-(ω-bromoalkyl)malonates **92**. The model intermolecular reaction and the proposed transition state structure have also been included.[176]

Table 3. Yields and Kinetic Constants for the Cyclization of Diethyl 2-(ω-Bromoalkyl)malonates 92 (Figure 28)[176]

n	k_{intra} (s^{-1})	yield **94** (%)	EM (M)
3	0.42	quantitative	1.5
4	6×10^{2}	quantitative	2.1×10^{3}
5	0.72	100	2.6
6	6.3×10^{-3}	99	2.3×10^{-2}
7	1.1×10^{-4}	13	3.9×10^{-4}
11	2.9×10^{-4}	29	1.0×10^{-6}
12	5.3×10^{-4}	46	1.9×10^{-3}
16	2.1×10^{-3}	73	7.5×10^{-3}
20	3.1×10^{-3}	77	1.1×10^{-2}
I[a]	0.28 M^{-1} s^{-1}	78 (**97**)	

[a]Values for the related intermolecular reaction.

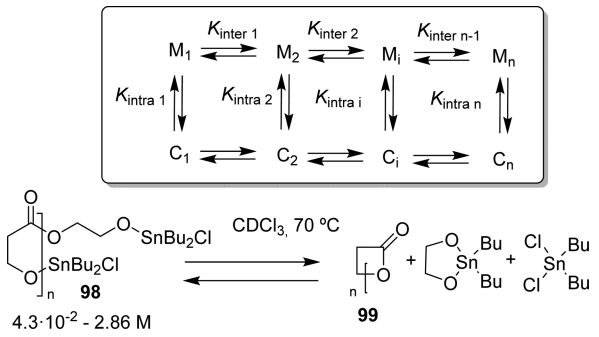

Figure 29. General equilibria associated with a system in which cyclization and oligomerization coexist under thermodynamic control (top). Example of cyclooligomerization of **98** under thermodynamic control (bottom).[180]

triazene linkage in the first amino acid of the peptidic sequence (**74**) (Figure 22).[140]

However, in some cases, the use of high dilution techniques seems more favorable than this approach, as the removal of the mutual interference of the reactive sites on polymeric matrixes can be incomplete.[141−149] Thus, Malesevic and co-workers compared the preparation of cyclic peptides employing high dilution techniques, using a slow simultaneous addition of the open-chain precursor and the coupling agent, and through an on-resin cyclization.[150,151] According to their results, the synthesis of *c*-(-Ile-Asp-Ser-β-HSer-Pro-Leu-Asn-) on-resin produced 1% yield of the desired cyclic product, while a 36% of macrocyclization was obtained under high dilution conditions using a dual syringe pump.[151] Structural effects can also play a key role; in this regard, Lim and co-workers have reported an on-resin macrocyclization dependent on the peptidic sequence of the open-chain precursor **77a** and **77b** highlighting the importance of the conformation of this precursor that must locate the reactive groups in close proximity (Figure 23).[152]

Friedler and co-workers have developed a new tandem strategy for side chain to N-terminus peptide macrocyclization (see Figure 90 for the definitions of peptide cyclization strategies). The main advantage of this approach (starting from the acid **78** and the resin-bound peptide **79**) is the simultaneous in situ deprotection, macrocyclization, and trifluoroacetic acid cleavage of the precursor peptide **80** (Figure 24). This method allows obtaining the macrocyclic product **81** by the formation of an amide bond between a lysine side chain and a succinic acid linker at the peptide N-terminus in 65% yield.[153]

On the other hand, different examples for the syntheses of cyclic peptides where the open-chain precursor is previously released from the resin to perform the macrocyclization in solution can also be found in the literature.[154] In nature, the biosynthetic macrocyclization reaction for the formation of macrocyclic peptides is catalyzed by a thioesterase domain at the C-terminal end of the assembly line.[155] However, release of the open-chain peptide for macrocyclization is also found in nature and it has been described, for example, for the imine macrocyclization of polypeptides at the C-terminal reductase domain of the respective nostocyclopeptide nonribosomal peptides that catalyzes the reductive release of the mature peptide chain.[156]

Biphasic conditions have also been used to control the pseudodilution of the precursors, allowing the use of relatively high concentrations of substrates (i.e., **82**) in the organic phase. In this regard, Collins and co-workers developed a Glaser−Hay coupling method, under biphasic conditions, to obtain a wide range of industrially important macrocycles (i.e., **83**), with different ring sizes and functional groups (Figure 25). The metal catalyst is located in the polar phase and, therefore, the reaction only takes place at the interphase.[157−160] It must also be taken into account that the mechanism for the Glaser−Hay coupling of acetylenes seems to involve the coordination of the acetylenic subunits to the same copper center.[161] Detailed investigations demonstrated that efficient macrocyclizations are due to aggregates of PEG_{400} that mimic phase separation. The use of PEG_{400}/MeOH solvent mixtures allows obtaining high macrocyclization yields at concentrations up to 0.1 M. The use of flow chemistry allows using concentrations up to 30 mM improving the yield with regard to the batch conditions. Thus, for instance, for a 21-membered macrolactone it was possible to increase the yield from 81 to 97%.[162] They have also used this phase-separation strategy for the macrocyclization of dienes by RCM using a Grubbs−Hoveyda second generation catalyst in a PEG_{500} dimethyl ether/MTBE solvent system at 100 °C using microwave radiation. This method allowed obtaining the target macrocyclic products in yields up to 82% using concentrations up to 60 mM.[163]

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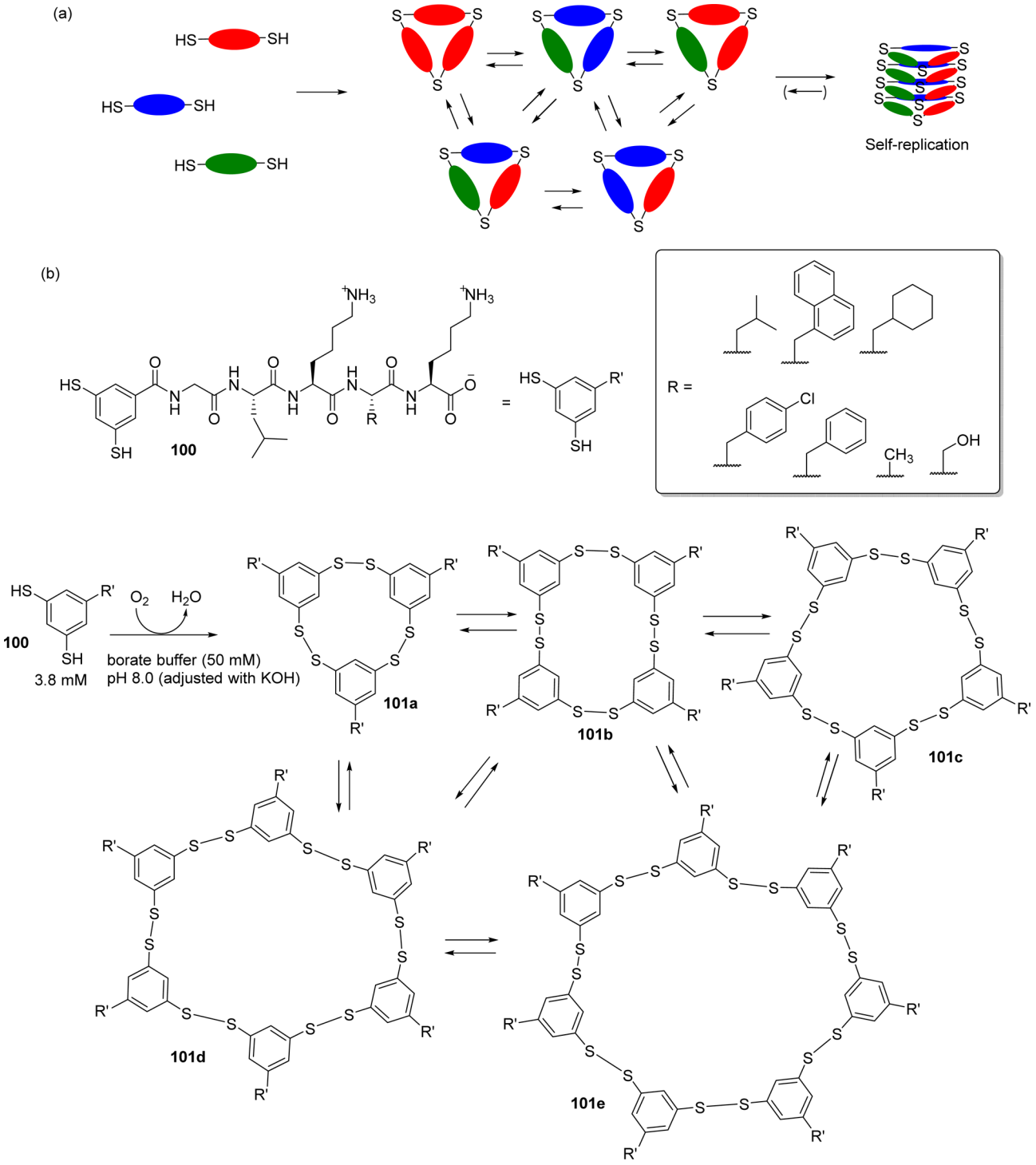

Figure 30. Self-replicating macrocycle synthesis. (a) Macrocycle that promotes its own formation by shifting the equilibrium by self-assembly in a dynamic molecular network. (b) Example of the macrocyclic products obtained in the dynamic library using the building block **101**.[185]

Other experimental factors can also have an important influence. Menche and co-workers reported how optimizing the conditions for the Heck macrocyclization step enabled the formation of the macrocyclic core of rhizopodin in 77%, whereas isolation of the macrocycle was not possible using the original standard conditions.[164] Walsh and co-workers demonstrated that the macrocyclization activity of the thioesterase from tyrocidine synthetase increases significantly in the presence of a nonionic detergent. The interaction of the enzyme with the detergent micelles seems to assist for the proper folding of the open-chain precursors so that both reactive ends are in the active site at the hydrophobic cavity.[165]

4.1. Kinetic Aspects

The success of a given macrocyclization involves a delicate balance of kinetic and thermodynamic factors. Actually, the use of high-dilution conditions, which has been, for years, the most usual approach to the preparation of macrocyclic structures, is based on kinetically favoring intramolecular versus intermolecular reactions. According to their different kinetic laws, this can

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be achieved by modifying the relative concentrations of the active species.

The first synthesis of macrocycles using high-dilution techniques can be dated to the work of Ruggli in 1912.[166] Since then, many studies have appeared on related subjects, analyzing the competing oligo/polymerization and ring formation reactions. In most cases, however, macrocyclizations have not been considered, just studying the formation of five- and six-membered rings.[167−170]

Ring formation from a bifunctional open-chain precursor is unimolecular in the reactant, whereas the formation of higher condensates and polymers proceeds bimolecularly. Different parameters such as the cyclization constant C[171,172] and, particularly, the effective molarity (EM), defined as k_{intra}/k_{inter},[173] have been used to define the influence of the concentration on the efficiency of the cyclization.

Dalla Cort et al. studied thoroughly the synthesis of macrocyclic poly(thiolactones) **86** from **84** and **85** under kinetic control in refluxing $CHCl_3$ (Figure 26). The formation of different cyclic oligomers of variable sizes (Tables 1 and 2) was detected in the reaction mixture by HPLC.[174]

Results in Tables 1 and 2 show that low concentrations of reactants **84** and **85** always favor the cyclization, leading to a prevalence of small cycles corresponding to [1 + 1] (n = 0) and [2 + 2] (n = 1) cyclizations. The formation of the [1 + 1] cycle **86** is favored, besides, by the presence of a more flexible structure (i.e., m = 5, instead of m = 3) in the diacid dichloride component **85**, which probably reduces strain at the transition state. Higher concentrations led to an increase in oligomerization reactions as shown by a decrease in the overall yield for macrocyclic compounds and by an increase in the formation of higher cyclic structures **86** (n > 1).

Lactonization is another important macrocyclization process. Illuminati and co-workers studied the kinetics and activation parameters for the formation of macrocyclic lactones of different sizes (**88**) from ω-bromoalkylcarboxylates **87**. As a reference, they also studied the related intermolecular process affording the ester **91** from **89** and **90** (Figure 27). The more favorable kinetic constant is the one leading to the five-membered ring (**88**, n = 3), followed by those producing rings of four and six members (**88**, n = 2 and 4). The smaller kinetic constants were found to correspond to the formation of rings of 8−12 members, being the lowest one associated with the formation of the eight-membered ring. It was observed that $k_{intra}(\Delta G^{\ddagger})$ remains relatively constant above 12-membered rings. These results are the combination of entropic and enthalpic factors as observed from the analysis of the calculated activation parameters. The highest strains (highest $\Delta H^{\ddagger}$ values) are observed for n = 1 and 6, while the probability term ($\Delta S^{\ddagger}$) decreases with the size (from −2.6 eu for n = 1 to −23.8 eu for n = 21), as could be expected.[175]

In the same way, Casadei et al. determined the kinetic parameters for the cyclization of 2-(ω-bromoalkyl)malonates **92** (Figure 28).[176] For comparison, they used the intermolecular process between **90** and **95** leading to **97** through the transition state **96**. The rate limiting step, as expected, is the final S_N2 reaction leading to the formation of the cycle, while carbanion formation is very fast (2×10^6 M^{-1} s^{-1} for Me_4NOH and $Cl(CH_2)_5CH(CO_2Et)_2$). The EM (k_{intra}/k_{inter}) represents the reactant concentration at which the rate of cyclization equals the rate of oligomerization. Accordingly, the more favorable the cyclization reaction, the higher the EM value. The results gathered in Table 3 can be interpreted by considering two different factors: the steric strain at the transition state **93** provided by transannular and torsional interactions and the entropic contribution disfavoring the formation of large rings by an intramolecular process, both of them decreasing the corresponding kinetic constant. Again, the formation of the five-membered ring (**94**, n = 4) is the most favored. The formation of four- and six-membered rings is associated with a higher level of strain at the transition state **93**. Ring formation for n > 5 is disfavored by the two factors, and this is reflected in the yields and kinetic parameters. The steric strain (transannular and torsional unfavorable interactions) is, however, released for very large macrocycle sizes (**94**, $n \geq 11$), and macrocyclization yields start to recover although they never reach the values observed for n = 4.[176]

4.2. Thermodynamic Aspects

In a thermodynamically controlled process, the relative Gibbs energies of all the species involved are directly related to their relative distribution at the equilibrium.[177] Therefore, the use of reversible reactions allows the preparation of macrocyclic structures under thermodynamic control when the corresponding cyclic compounds are more stable than the oligomeric ones. A simple example is that of shape-persistent macrocycles,[178] where the formation of small rings under thermodynamic control is unfavorable due to angle strain, while the formation of larger rings with no angle strain is possible.[177]

Theoretical analyses of macrocyclization equilibria in competing oligomerization/cyclization systems under thermodynamic control have been carried out in detail in the case of dynamic libraries based on transacetalation reactions.[179] A complete analysis of a thermodynamic macrocyclization was also carried out by Ercolani et al. in the case of the cyclooligomerization of **98** to afford lactones **99**.[180] These analyses involve the definition of the so-called critical monomer concentration. When the extent of the reaction is equal to 1, there is a concentration of the critical monomer below which the system is only formed by cyclic species.[180,181] On the contrary, above this critical monomer concentration, the concentration of each species remains constant and the excess of monomer **98** is only consumed for the formation of acyclic species (Figure 29).[180] Figure 29 shows the general equilibria involved, with M_n being the different open-chain oligomeric products formed by intermolecular reactions and C_n being the macrocyclic structures formed from M_n in an intramolecular process.[180]

Moore and co-workers have prepared high-molecular-weight macrocyclic poly(phthalaldehyde) with high purity by a thermodynamically controlled process. This cyclic polymer, formed exclusively by phthalaldehyde repeat units, can undergo re/depolymerization depending on the conditions.[182,183] Interestingly, they have studied the effect of the flexibility/rigidity of the monomers on the molecular weight distribution of the obtained macrocyclic structures, obtaining narrower distributions for the more rigid ones.[184]

Otto and co-workers have reported the synthesis of self-replicating macrocycles **101a−101e** by means of a dynamic combinatorial methodology from the corresponding monomer **100** (Figure 30). The amplification is achieved by the self-assembly of the replicators into fibrils. The selection criteria are based, in the first instance, on the size of the macrocycle that must have sufficient multivalency to enable their self-assembly into fibrils. In the second instance, the efficient replication occurs only for library components that are not favored in the absence of a replication mechanism (structures that are unlikely to be produced spontaneously).[185]

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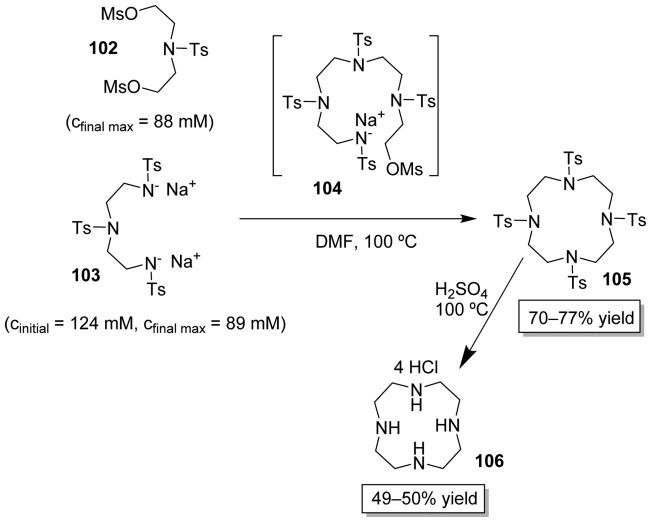

Figure 31. Richman–Atkins synthesis of cyclen **106**.[191]

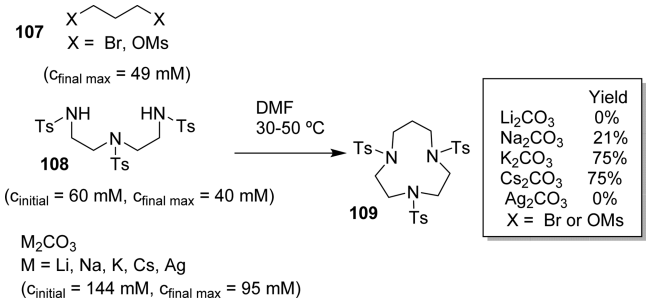

Figure 32. Synthesis of pertosylated polyazamacrocycles by in situ deprotonation of the pertosylated polyamine **108**.[193]

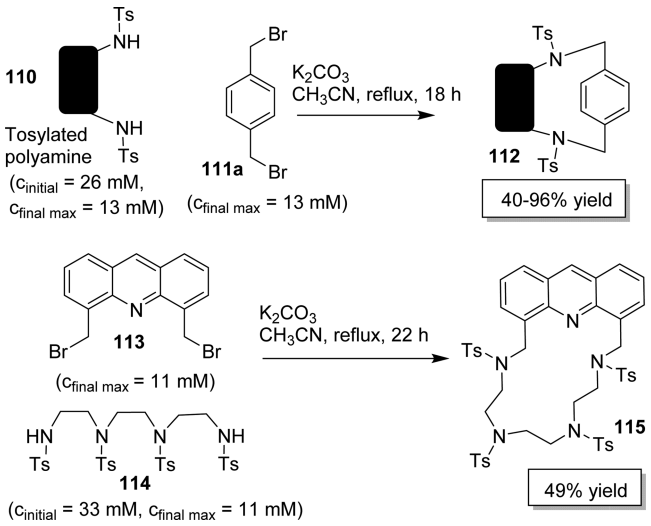

Figure 33. Synthesis of pertosylated polyaza[*n*]cyclophanes.[195,196]

5. SYNTHESIS OF MACROCYCLIC STRUCTURES ASSISTED BY THE INTRINSIC FAVORABLE PREORGANIZATION OF OPEN-CHAIN PRECURSORS

A favorable preorganization (i.e., appropriate conformation) of open-chain precursors is a key factor determining their propensity to cyclize.[186] As long as cyclization reactions are usually the final step of the synthetic procedure, a proper design of the precursors to obtain the best precyclization molecule

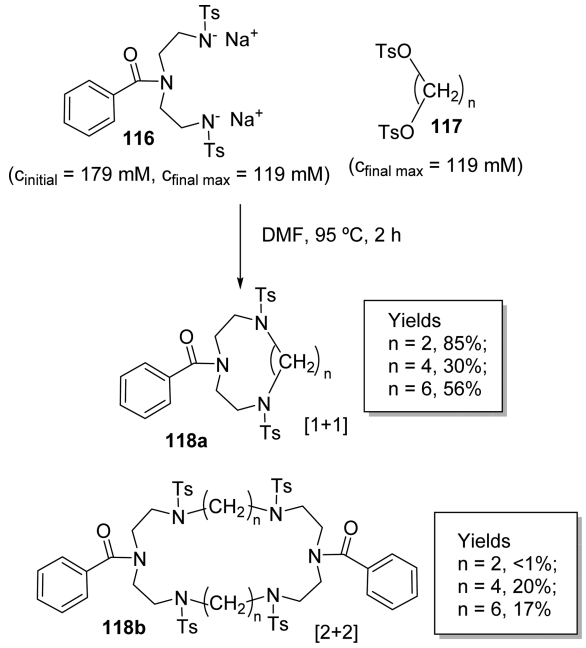

Figure 34. Synthesis of selectively protected polyaza macrocycles.[201]

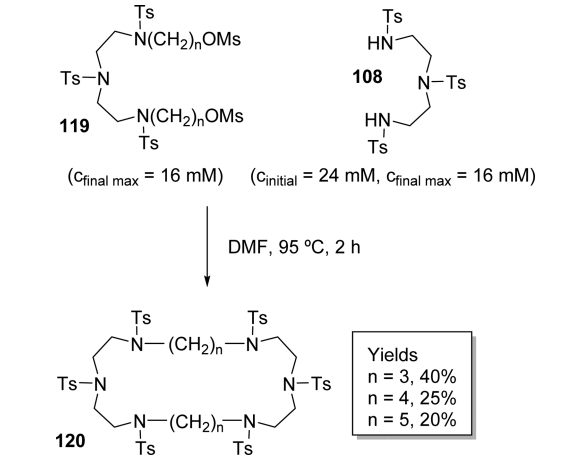

Figure 35. Synthesis of pertosylated hexamine macrocycles.[202]

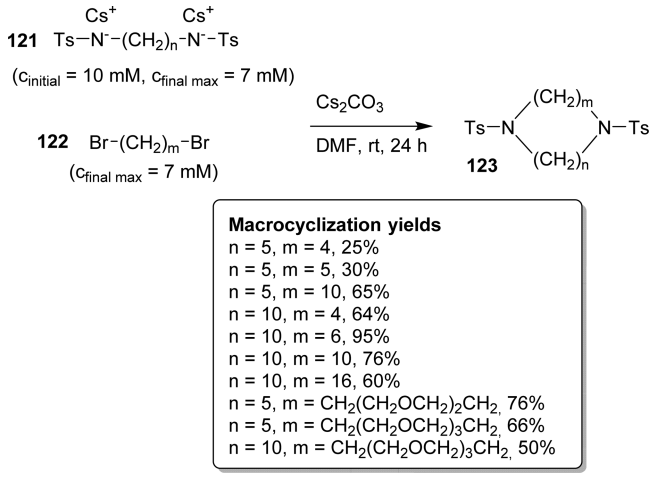

Figure 36. Synthesis of pertosylated diazamacrocycles.[203]

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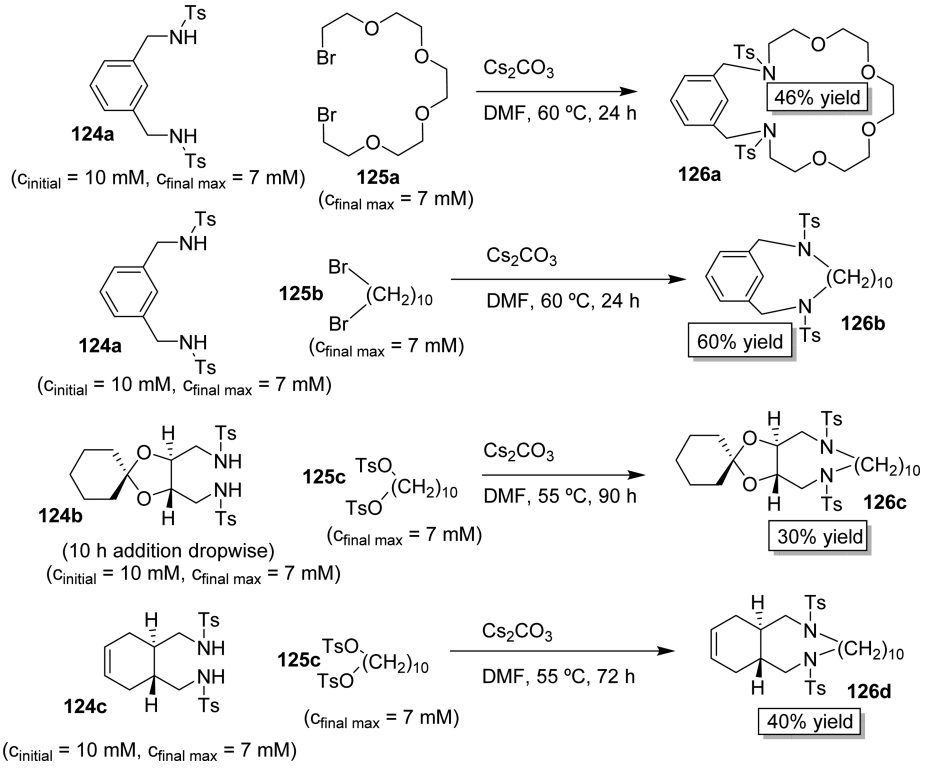

Figure 37. Synthesis of diazamacrocycles containing additional functionalities.[203]

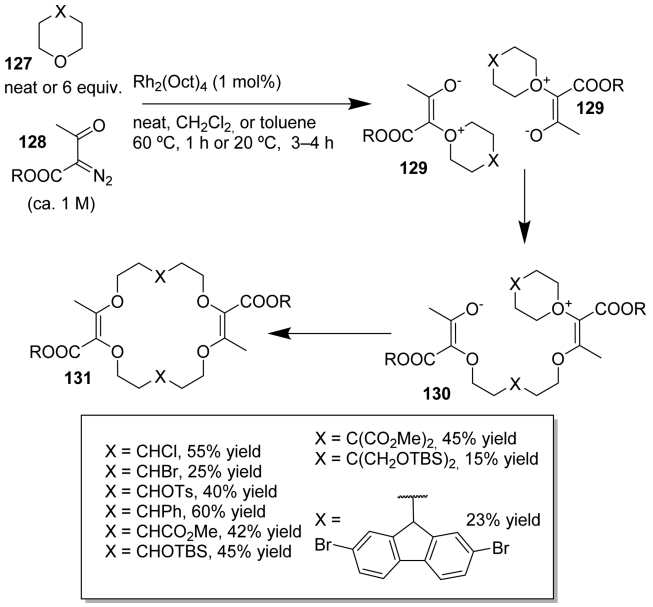

Figure 38. Synthesis of macrocyclic polyethers.[210]

(open-chain intermediate precursor) is essential, being the entropy and enthalpy changes at the macrocyclization step a key factor for the formation of the macrocyclic product or the unwanted oligomeric byproducts.[186]

This intrinsic favorable preorganization can be considered as conformational or configurational. Conformational preferences in open-chain molecules and intermediates can favor the presence of folded conformations in which the end-to-end distance is short, facilitating the cyclization and disfavoring the formation of longer oligomers. Configurational preorganization can be considered as a particular case of conformational preorganization in which the conformational preferences are associated with the stereochemical configurations of the chiral centers.

5.1. Conformational Preorganization

The most general synthetic strategy for the preparation of either crown ethers or azacrown ethers has been the use of nucleophilic substitution reactions for which one heteroatom (oxygen, sulfur, or nitrogen) acts as the nucleophile for the ring-closing step. This was the original approach of Pedersen for the discovery of crown ethers and that of Lehn and other authors for the synthesis of polyaza macrocycles and cryptands.[187−190]

5.1.1. Polyoxamacrocycles, Polyazamacrocycles, and Macrolactones. In the case of polyoxamacrocycles (crown ethers), the participation of cation-template effects is a key factor, as will be discussed below, but such effects seem to be absent in the Richman−Atkins methodology, one of the most efficient approaches for the synthesis of polyaza macrocycles (Figure 31).[191] In the original procedure, the cyclization was carried out by the reaction of the disodium salt of an N-tosylated polyamine **103** with a compound containing two tosyl or mesyl leaving groups **102**.[191] This affords the corresponding N-tosylated polyaza macrocycles **105** (through the macrocycle precursor **104**) from which the expected deprotected compounds can be obtained as the free bases or, more commonly, as their hydrochloride salts **106**.

With this method, it is possible to obtain a broad series of macrocyclic structures with 40−90% macrocyclization yields without the need for using high dilution techniques. It must be pointed out that the presence of long hydrocarbon spacers (longer than three methylene units) between the nitrogen atoms decreases the yield of the [1 + 1] cyclization products, and [2 + 2] compounds are obtained as side products.[192] Chavez and Sherry compared the effect of the leaving group and other reaction parameters using this methodology. They found that the leaving

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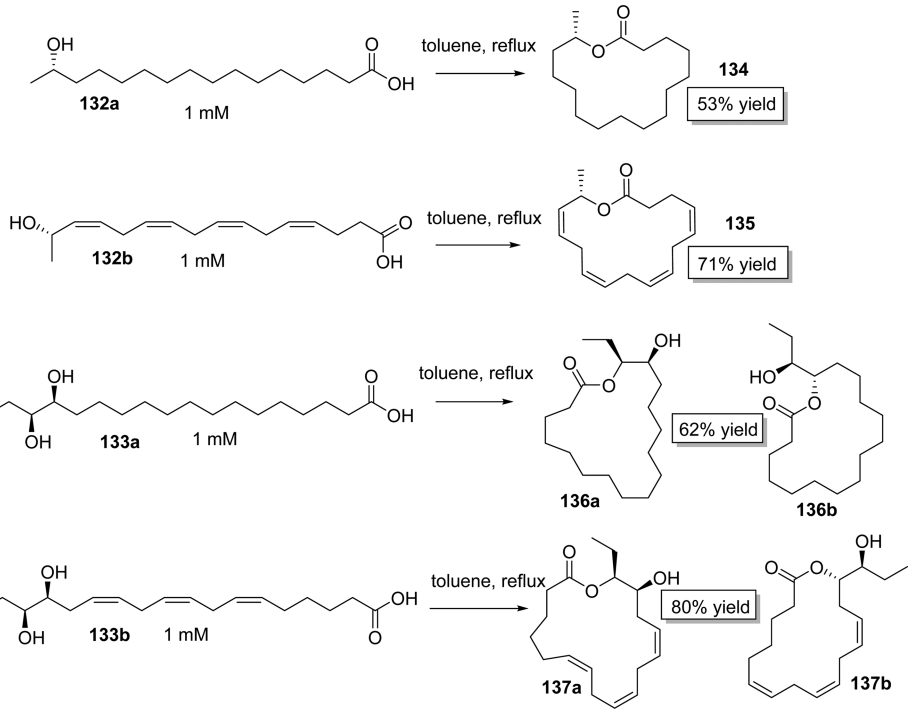

Figure 39. Macrolactonization of hydroxyfatty acids.[212]

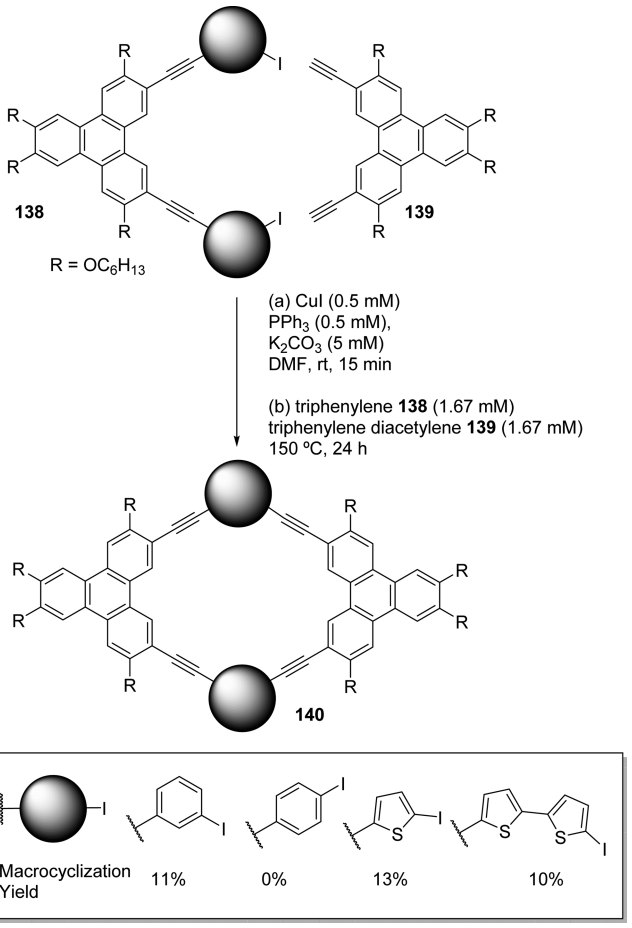

Figure 40. Synthesis of twinned triphenylenes.[218]

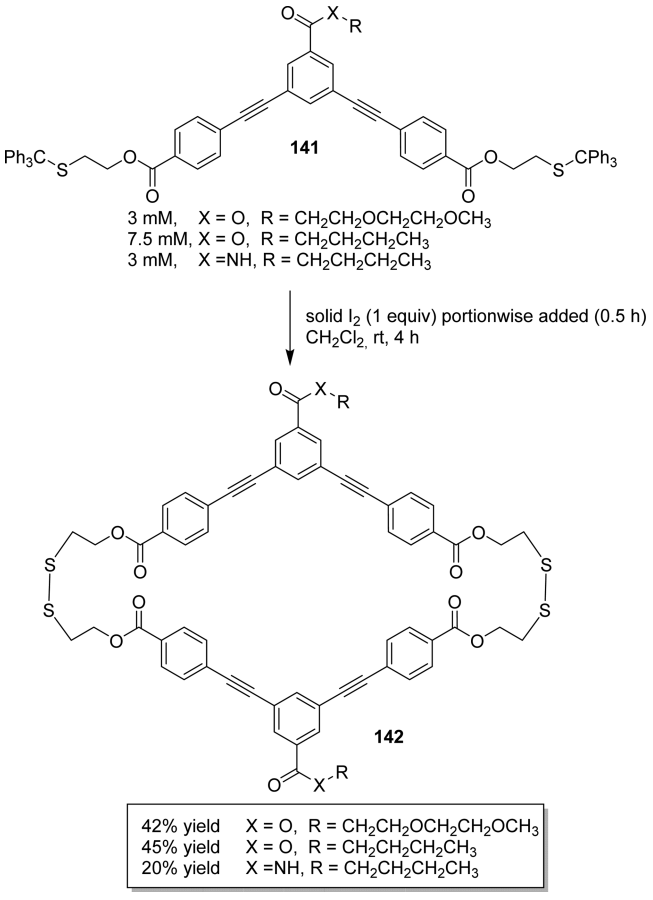

Figure 41. Synthesis of rigid macrocycles with a folded conformation.[221]

group in **107** has a marked effect on the macrocyclization rates. Bromides and mesylates (**107**) were the ones providing the fastest rates, with the reactions being completed in 24 h at 30 °C. Related chlorides and tosylates reacted slower under the same conditions, giving products in comparable yields after 24 h at 50

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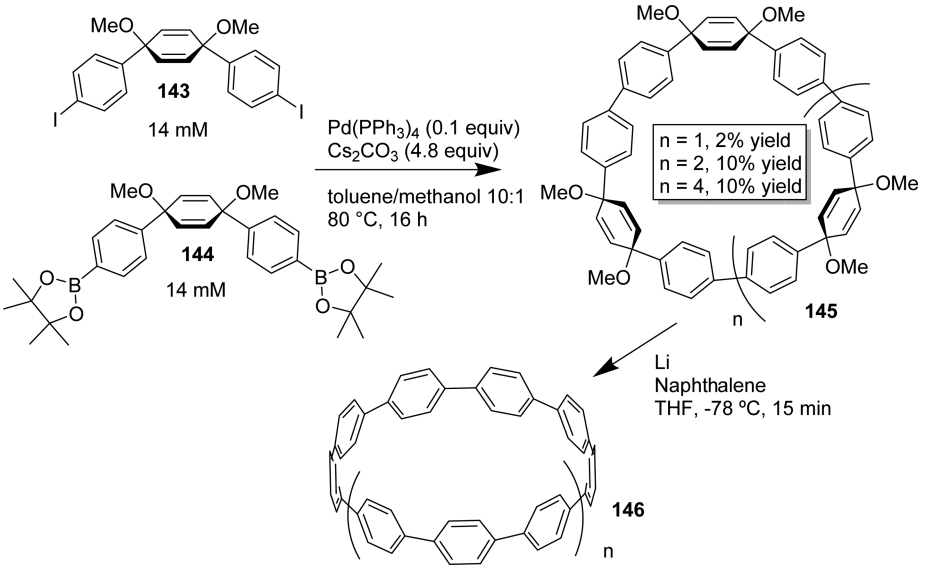

Figure 42. Synthesis of [12]-, [15]-, and [21]CPP.[222]

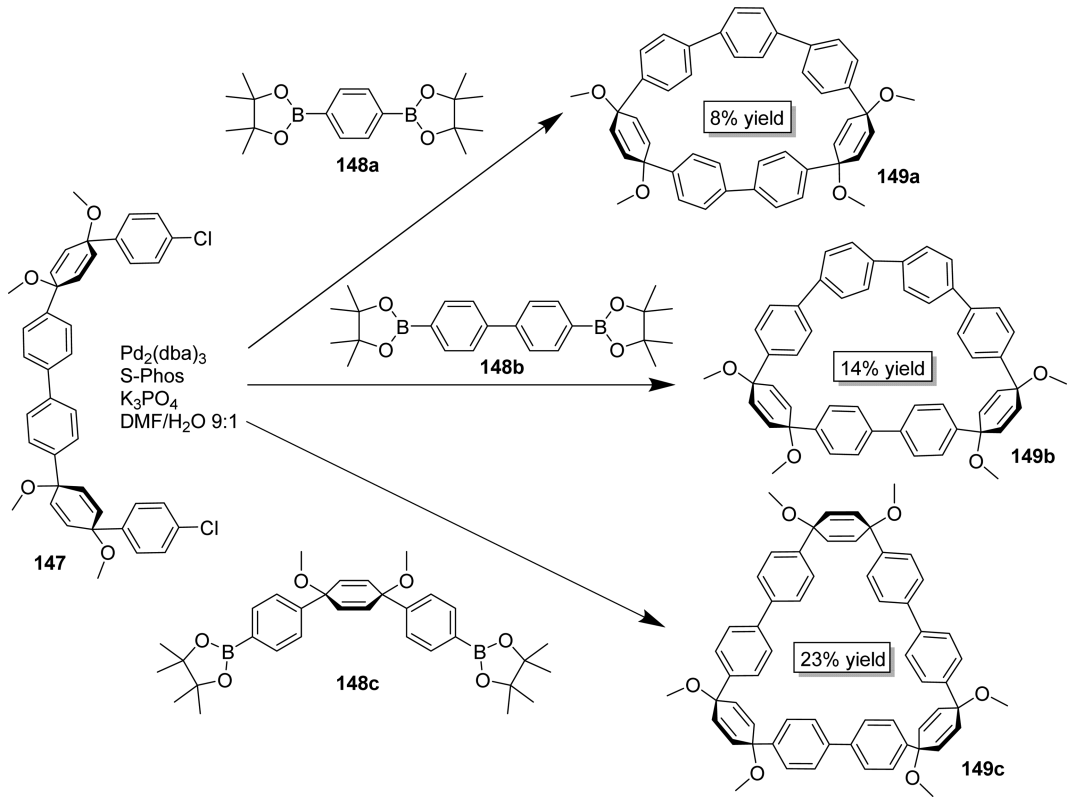

Figure 43. Synthesis of cycloparaphenylene precursors by successive orthogonal Suzuki−Miyaura coupling reactions. Representative reaction conditions for the synthesis of [7]CPP precursor **149a**: open-chain precursor **147** (5 mM), 1,4-benzenediboronic acid bis(pinacol) ester **148a** (6.5 mM), $Pd_2(dba)_3$ (0.4 mM), S-Phos (1.6 mM), and K_3PO_4 (10 mM) in DMF/water 9:1, 156 °C, 16 h, 8% macrocyclization yield.[223,225,226]

°C. In contrast, the iodides were too reactive and afforded complex reaction mixtures with large quantities of byproducts. They also demonstrated that the reaction also proceeds well when the tosylamide salts are generated in situ by reaction of the pertosylated polyamine with a metal carbonate. The cation used was shown to affect the macrocyclization. Thus, for the reaction of the pertosylated polyamine **108** with the bromide or mesylate **107**, the yields of macrocycle **109** using Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, or Ag_2CO_3 were 0, 21, 75, 75, and 0%, respectively. This effect seems to be associated with the capacity of the corresponding carbonate to efficiently form the tosylamide salt in the reaction media and not with their capacity to act as templates (Figure 32).[193,194]

The same methodology was implemented for the high yield preparation of polyaza[*n*]cyclophanes like **112** and **115** (Figure 33). In this case, the presence of the aromatic ring is a favorable structural factor and the corresponding pertosylated macrocycles **112** and **115** could be obtained in excellent yields from

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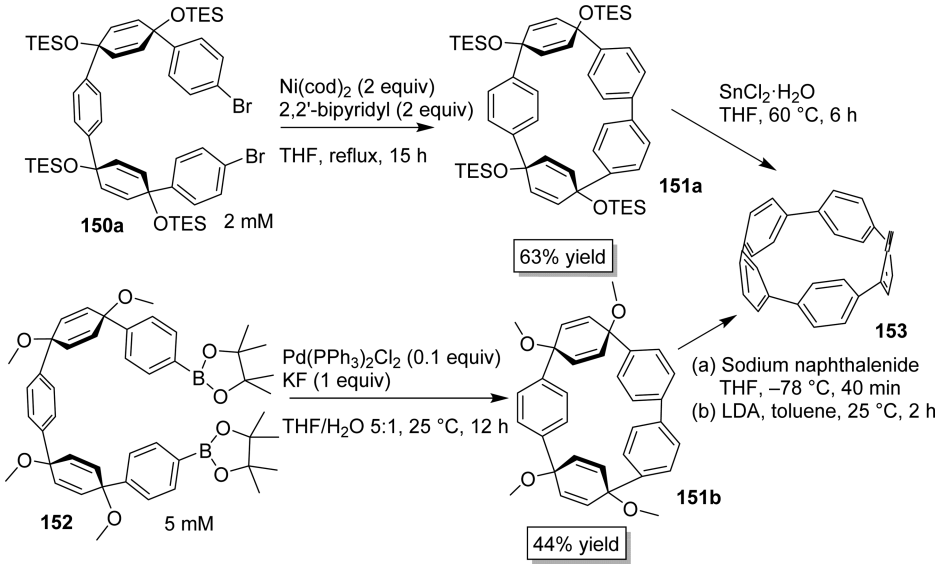

Figure 44. Synthesis of [5]cycloparaphenylene.[227,228]

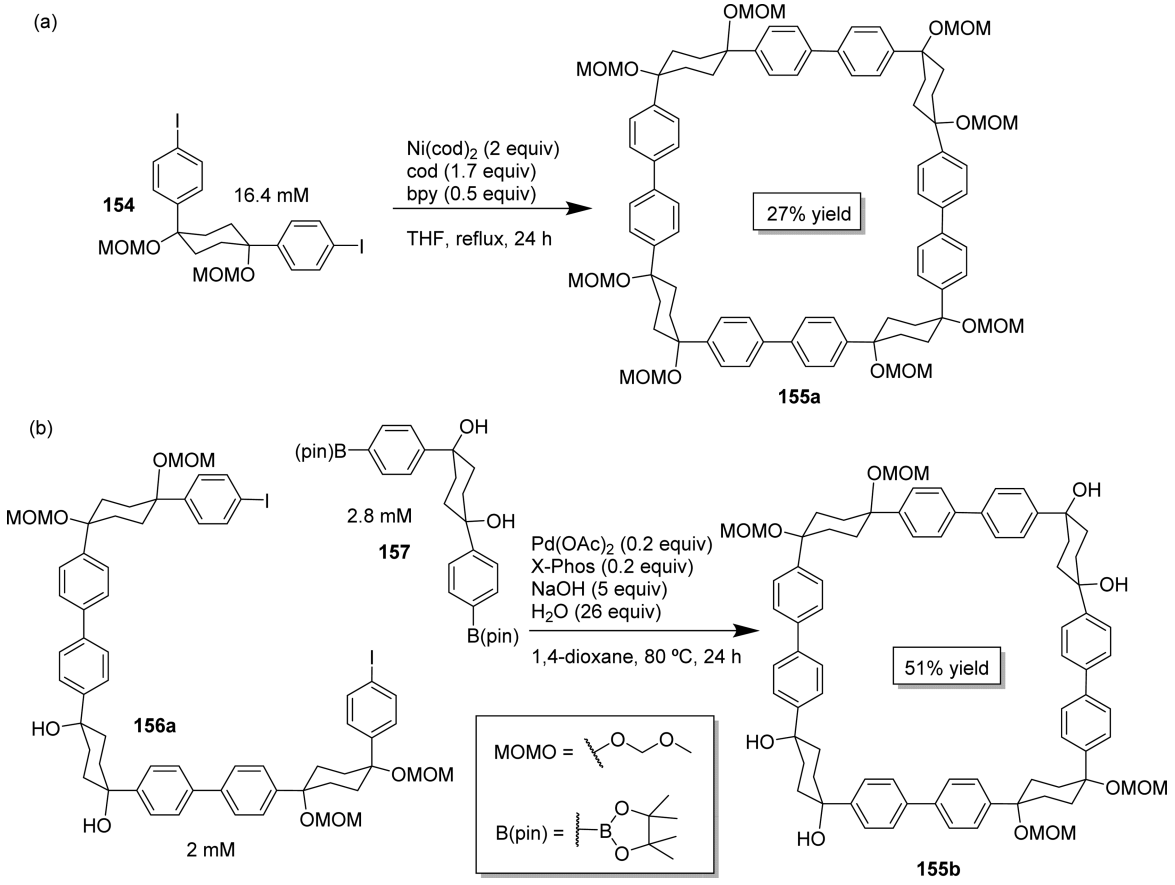

Figure 45. Alternative syntheses for the macrocyclic structure precursors of [12]CPP **155**. (a) From monomer **154**. (b) From building blocks **156a** and **157**.[229,230]

dibromides **111a** and **113** and tosylated polyamines **110** and **114**. This methodology could be applied with good results to a variety of aromatic systems, with different substitution patterns, and pertosylated polyamines.[191,192,195−197]

As the Richman−Atkins and related methodologies do not show any significant template effect by the cations or other species present in the media, all data indicate that the bulky *p*-toluenesulfonyl groups are the key structural elements restricting the rotational freedom on the polyaza chain of the open-chain intermediate. This will produce a decrease in the initial entropy and will therefore favor the macrocyclization as long as the loss in internal entropy on cyclization becomes smaller.[200] At the same time, those bulky hydrophobic groups can also shield the open-chain intermediate reducing additional intermolecular processes

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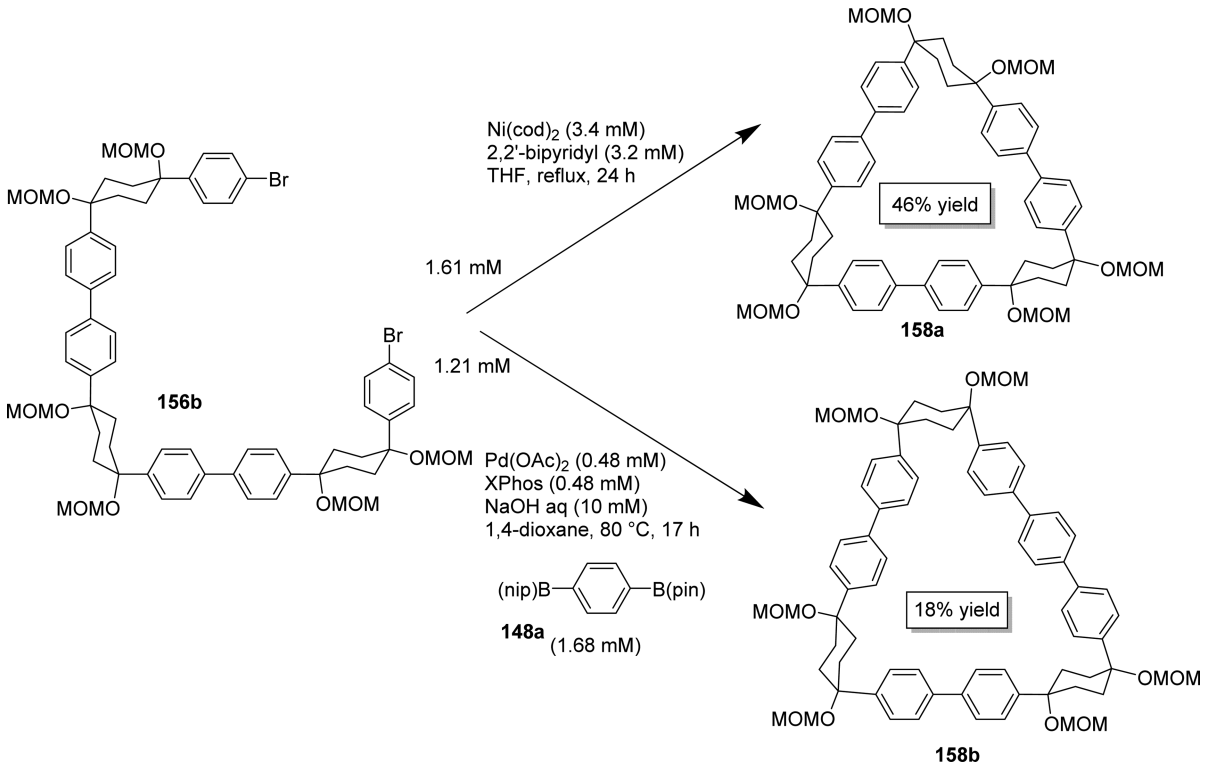

Figure 46. Synthesis of [9]CPP and [10]CPP macrocyclic precursors (**158a** and **158b**).[231]

and favoring the intramolecular reaction. Similar results have been reported for the use of related bulky N-protecting groups like the nosyl group.[198,199] For the preparation of the larger fully aliphatic macrocycles, the use of high dilution conditions was necessary to avoid the formation of open-chain oligomeric byproducts. This is associated with the large loss of entropy associated with the macrocyclization because of the need for properly approaching the two reactive ends in the open-chain intermediate.[200]

Other modifications of this synthetic procedure have been reported by Bulkowski and co-workers. They studied the preparation of tri- and hexaamine macrocycles **118a** and **118b**. The use of selectively protected diethylenetriamine units (**116**) and electrophile fragments having sulfonate ester leaving groups (**117**) led to good yields of the macrocyclization reaction (Figure 34).[201] On the other hand, a decrease of the yield of **118a** with the length of the spacer was observed. The same trend was reported for related pertosylated systems **120** from **108** and **119** (Figure 35).[202] The good final isolated yields were partially associated with the easy separation of the [1 + 1] macrocyclic compounds **120** from, presumably, polymeric materials.

The excellent behavior of organic cesium salts as nucleophiles in organic media led to the study of the corresponding cesium bistosylamides **121** for the synthesis of azamacrocycles by nucleophilic ring closure with aliphatic α,ω-halogenides **122** (Figure 36). Excellent results were observed for the formation of the resulting diazamacrocycles **123** even for high values of m and n, again without the need of high-dilution conditions.[203]

The main drawback associated with the use of the classical Richman–Atkins methodology is the rather drastic conditions usually required for the removal of the *N*-tosyl groups. To overcome this, a variety of alternative *N*-sulfonamides that can be removed under milder conditions have been developed. This is the case of the 2- or 4-nitrophenylsulfonyl group (nosyl group) that has been successfully assayed for the one-pot synthesis (including cyclization and deprotection) of different polyazamacrocycles, in some cases achieving isolated yields higher than 90%.[199,204] This approach is particularly important when the polyaza macrocycle contains relatively labile C–N bonds like those present in naphthalenic or anthracenic derivatives.[205] In this regard, Hoye and co-workers have reported the Richman–Atkins synthesis of polyazamacrocycles employing β-trimethylsilylethanesulfonamides (SES sulfonamides) that can be easily removed (using pseudo-high-dilution conditions with CsF in DMF at 90 °C for the cyclization step).[206] Other N-protecting groups, alternative to sulfonamides, such as the diethoxyphosphoryl group (DEP) have also been studied in this regard.[207−209]

More complex molecular geometries are also accessible with this methodology using, for example, precursors **124** and **125**. These include polyaza polyoxa macrocycles, cyclophanes, diazacyclophanes, or even more elaborate polyfunctional structures such as those depicted in Figure 37 (**126**). In the case of the compound containing a spiro ring, **124b**, considerable amounts of dimer were formed when using the general conditions, but the yields were improved by extending from 3 to 10 h the dropwise addition of the second component (Figure 37).[203]

Lacour and co-workers have reported the multicomponent synthesis of different polyether macrocycles **131** in one pot from ether **127** and α-diazo-β-ketoester **128** using rhodium(II) as the catalyst. This methodology does not require the use of high dilution conditions (Figure 38), and no kinetic or thermodynamic template effects were observed. A high concentration of the starting materials **127** and **128** is favorable here as this allows achievement of a significant concentration of the high-energy reactive intermediate **129** that must dimerize to form the precyclization intermediate **130**.[210,211]

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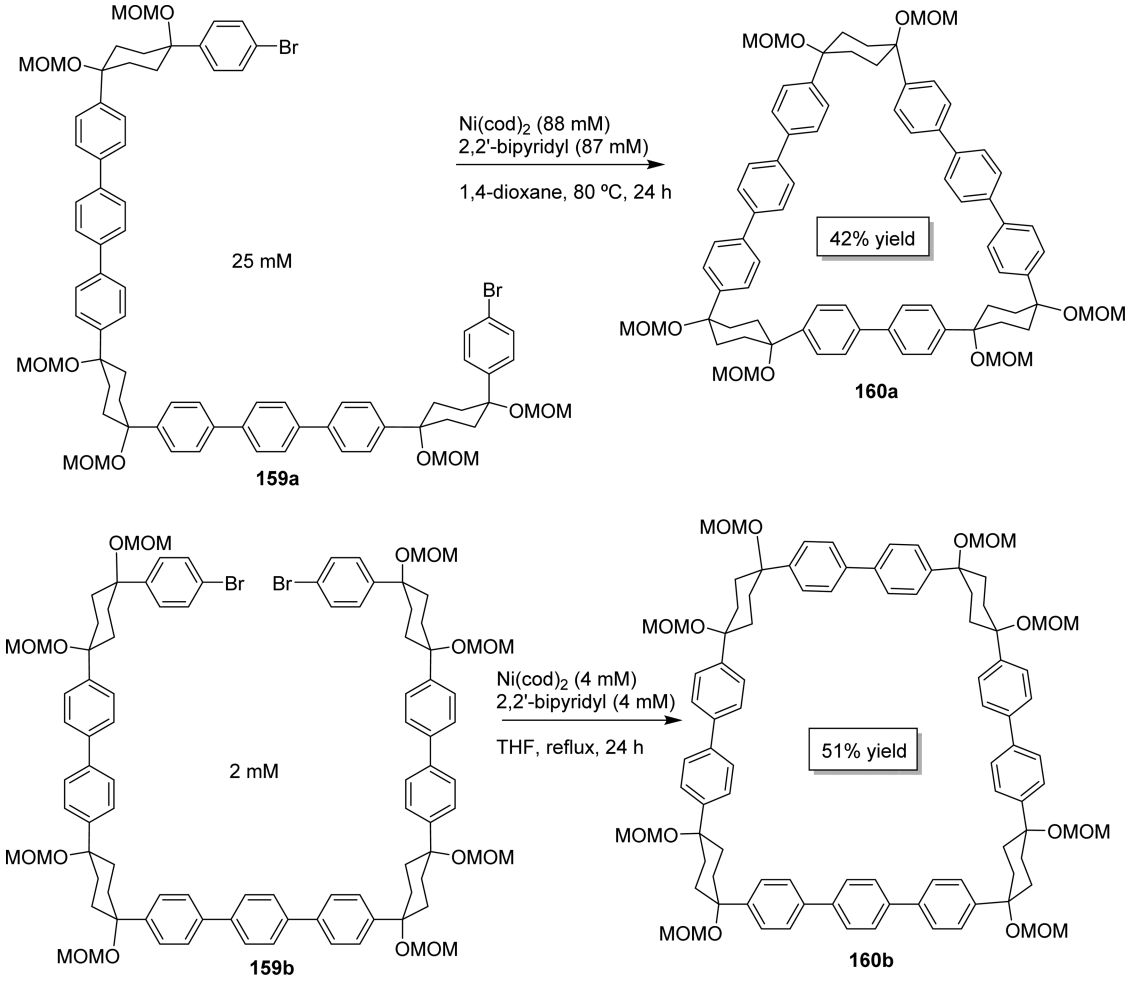

Figure 47. Synthesis of [11]CPP and [13]CPP macrocyclic precursors (**160a** and **160b**).[231]

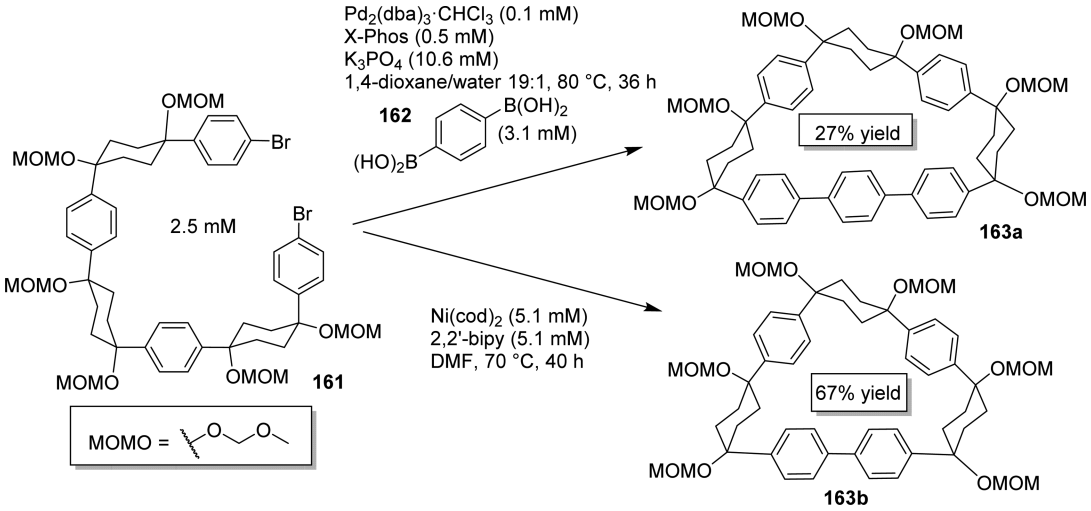

Figure 48. Synthesis of [7]CPP and [8]CPP macrocyclic precursors.[233]

The different molecular flexibility of unsaturated carbon chains in comparison with the saturated ones has a significant effect in the geometry of the molecule, and therefore in its tendency to macrocyclize. Spinella, Monaco, and co-workers have investigated the influence of the unsaturation on the macrolactonization of different hydroxyfatty acids **132** and **133** (Figure 39).[212] They found a clear influence of the unsaturation on the macrocyclization yield (**134**–**137**), with the yield being higher for the unsaturated compounds **132b** and **133b**. These results can be interpreted in terms of the torsional potential of the C−C bonds next to C═C bonds in **132b** and **133b** that present a degenerate minima leading to a larger number of folded conformers (Figure 39).[212]

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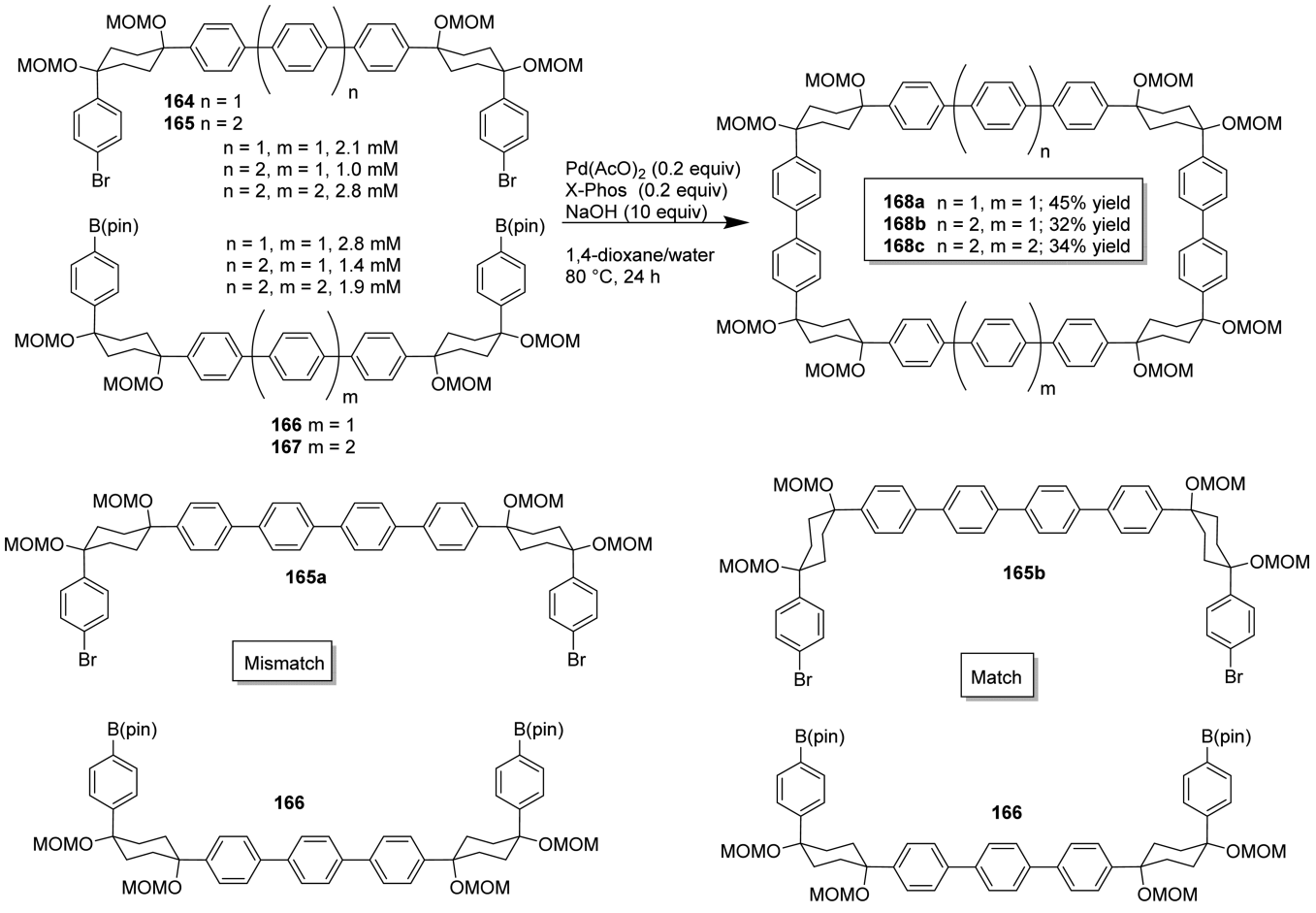

Figure 49. Synthesis of [14]-, [15]-, and [16]CPP macrocyclic precursors.[234]

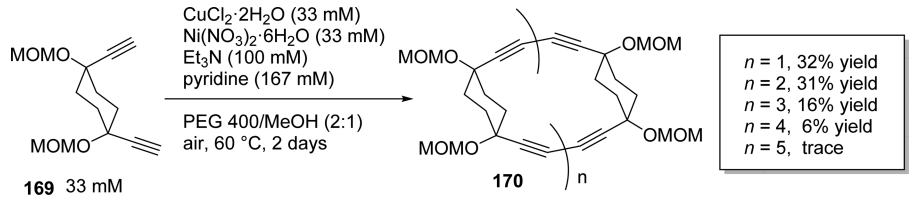

Figure 50. Macrocyclization using Glaser–Hay coupling conditions.[239]

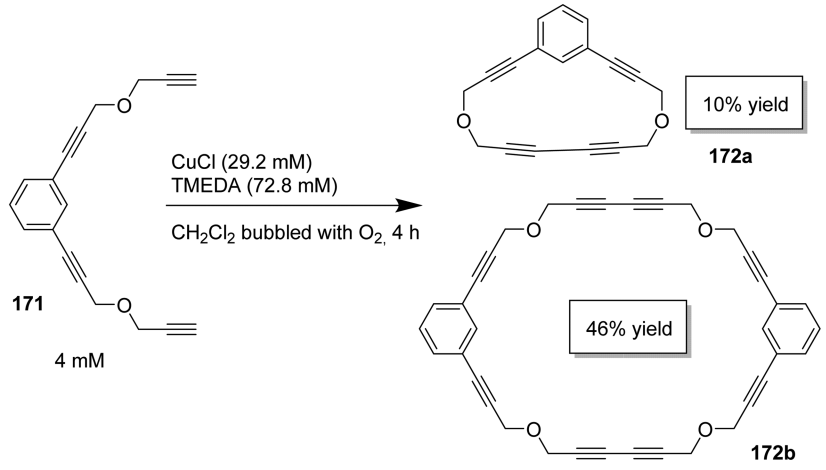

Figure 51. Macrocyclization using the Hay coupling.[240]

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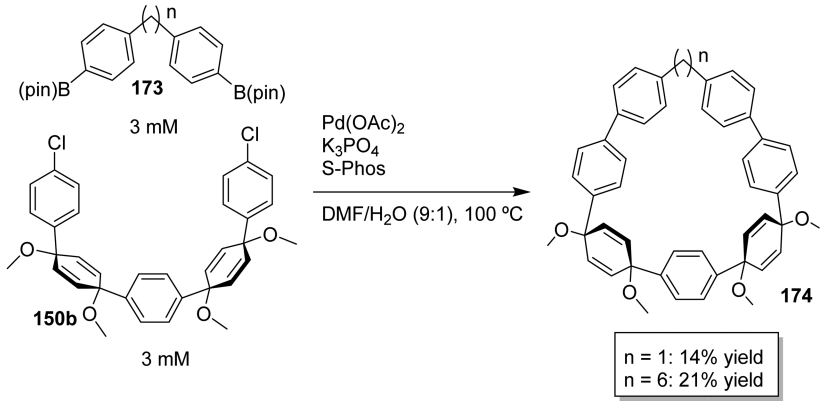

Figure 52. Synthesis of cycloparaphenylene macrocyclic precursors containing flexible aliphatic chains.[241]

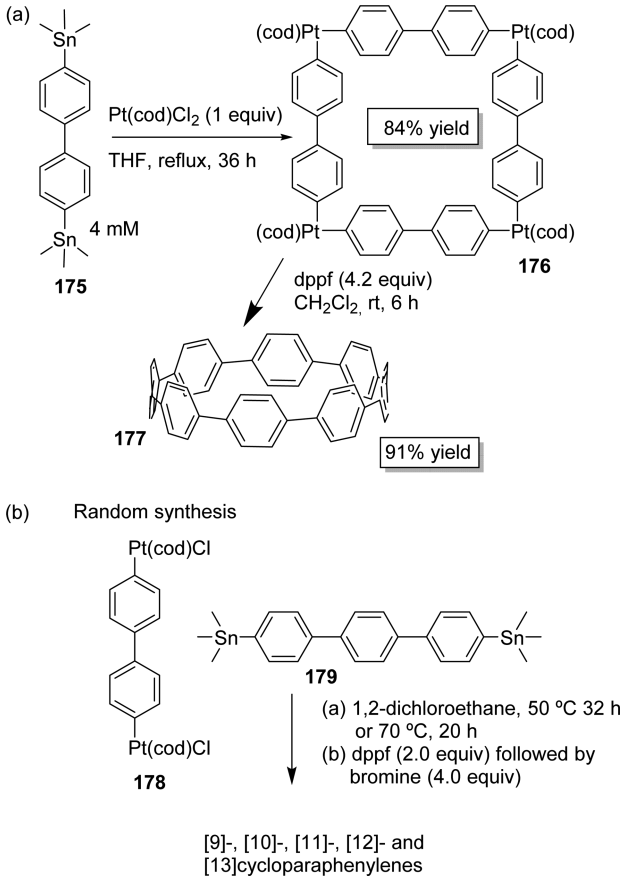

Figure 53. Synthesis of [8]cycloparaphenylene. (a) Through a macrocyclic metallocycle intermediate. (b) Random synthesis using building blocks **178** and **179**.[242]

5.1.2. Shape Persistent Macrocycles. In the case of macrocyclizations involving rigid building blocks, the geometry of these blocks is essential in determining the feasibility of the macrocyclization reaction.[213] In this regard, many examples in this area involve the use of components containing properly substituted aromatic rings, acetylenic units, and allenic subunits, in particular in connection with the very active area of shape persistent macrocycles (SPMs).[177,214−217] Cammidge and co-workers designed different twinned triphenylenes with a variety of bridging units (**140**). The different geometry of the bridging units has a direct influence in the overall strain of the macrocyclic product **140** obtained by the reaction of **138** with **139**, and accordingly on the strain at the transition state, leading to a successful macrocyclization if the geometry is suitable (Figure 40).[218] A similar strategy has been described by Hartley and co-workers with macrocyclization yields in the range 21−30%,[219] and by Nakamura and co-workers with 6−7% yields.[220]

Gong, He, and co-workers have reported the synthesis of rigid macrocycles **142** that present a folded conformation.[221] In the reaction mixture, the dominant species are the macrocyclic products, and the authors point out that this strategy based on directed structural ordering from precursor **141** can be used for the building of structures with well-defined conformations and shapes (Figure 41).

The efficient preparation of cycloparaphenylenes (CPPs) of different sizes, whose first synthesis was reported in 2008 by Bertozzi and co-workers (Figure 42),[222] has been studied in detail in recent years. The synthesis of this family of compounds has been achieved through different methodologies that use building blocks specifically designed to provide the conformation(s) required to favor the macrocyclization reaction. The first described synthesis allowed preparing milligrams of cyclic compounds **145** using a nonselective macrocyclization reaction affording the [1 + 1], [2 + 2], and [3 + 3] macrocycles as the major components. The easy aromatization of the benzoquinone-derived subunits present in **145** allowed the preparation of the desired cycloparaphenylenes **146**. The folded conformation of the building blocks **143** and **144** provided by the *syn* dimethoxy fragment derived from benzoquinone is a key element to favor the macrocyclization reaction.

New improved methods have allowed obtaining the corresponding products in gram scale using selective macrocyclization reactions. Jasti and co-workers have optimized the synthesis of cycloparaphenylenes of different sizes using successive orthogonal Suzuki−Miyaura coupling reactions (using building blocks **147** and **148**) for the building of the precursors and for the key macrocyclization step leading to the immediate precursors of the cycloparaphenylenes **149** (Figure 43).[223] They have reported the preparation of the cyclic intermediates [7]CPP in 12%,[224] [7]CPP (**149a**) in 8%, [8]CPP (**149b**) in 14%, [9]CPP (**149c**) in 23%, [10]CPP in 20%, [11]CPP in 12%, and [12]CPP in 30% macrocyclization yield (Figure 43). As could be expected, the lower yields correspond to the smaller cycloparaphenylenes according to the corresponding increase in strain energy.[225] They have also reported the synthesis of [8]CPP and [10]CPP precursors using different building blocks in 51 and 44% macrocyclization yields, respectively. The authors point out that the improved efficiency

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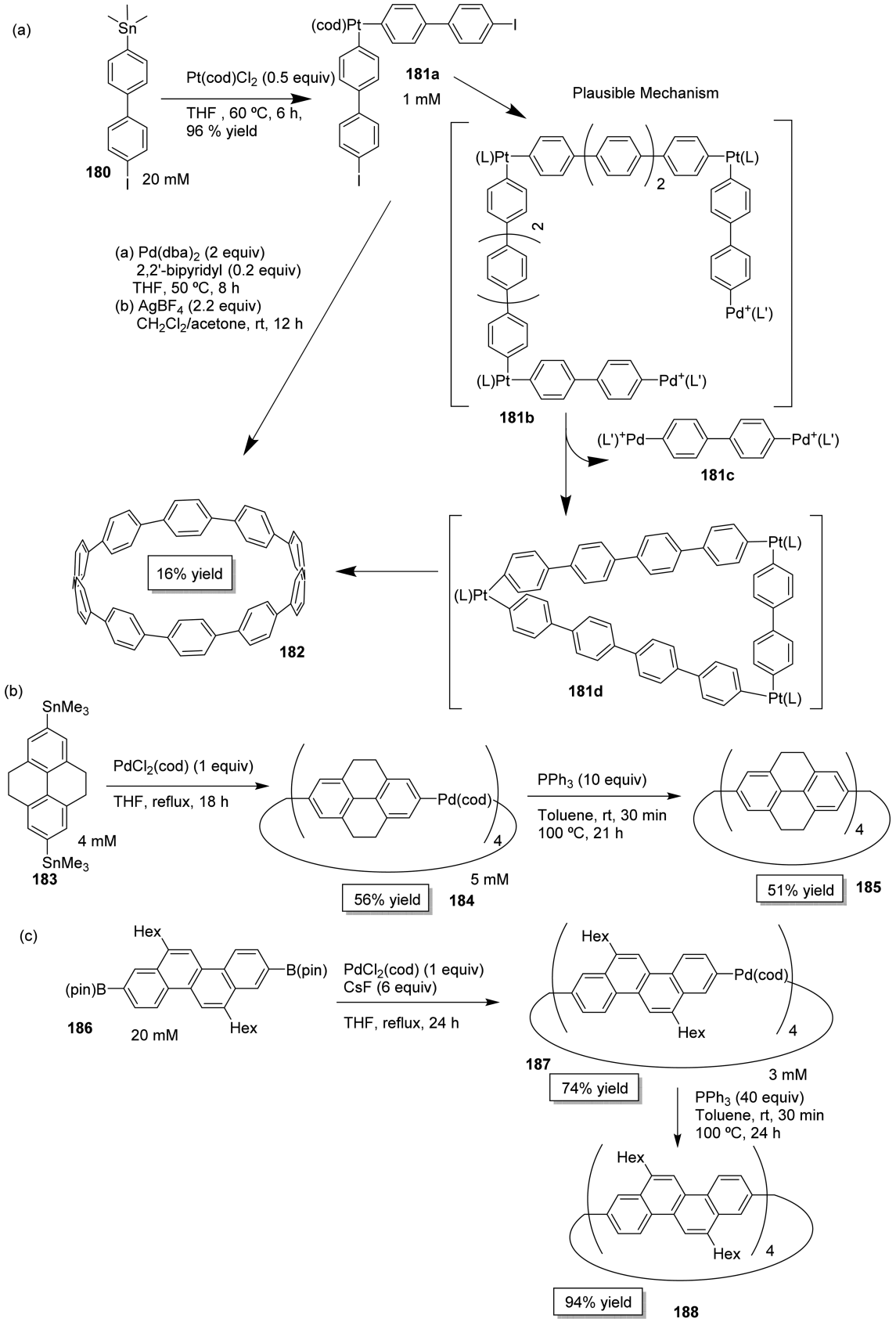

Figure 54. Synthesis of different cycloparaphenylenes. (a) [10]Cycloparaphenylene. (b) [4]Cyclo-2,7-pyrenylene. (c) [4]Cyclo-2,8-chrysenylene.[244]

allows the cost-effective preparation of the final cycloparaphenylene in gram scale in contrast to the other existing methodologies.[226] The aromatization of the different precursors can be achieved in 50−60% yields utilizing sodium naphthalide.

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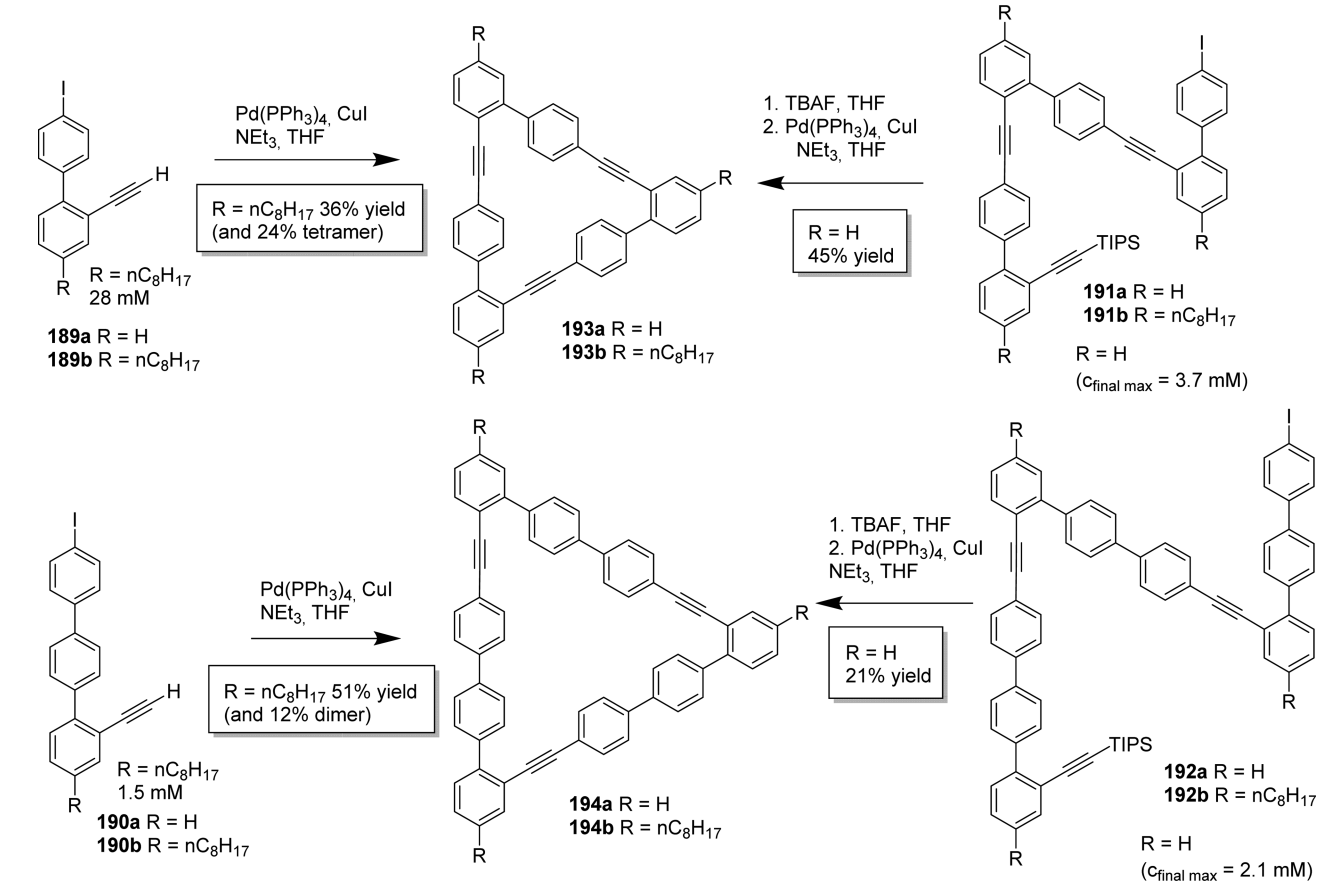

Figure 55. Synthesis of biphenyl and terphenyl arylene-ethyne macrocycles.[247]

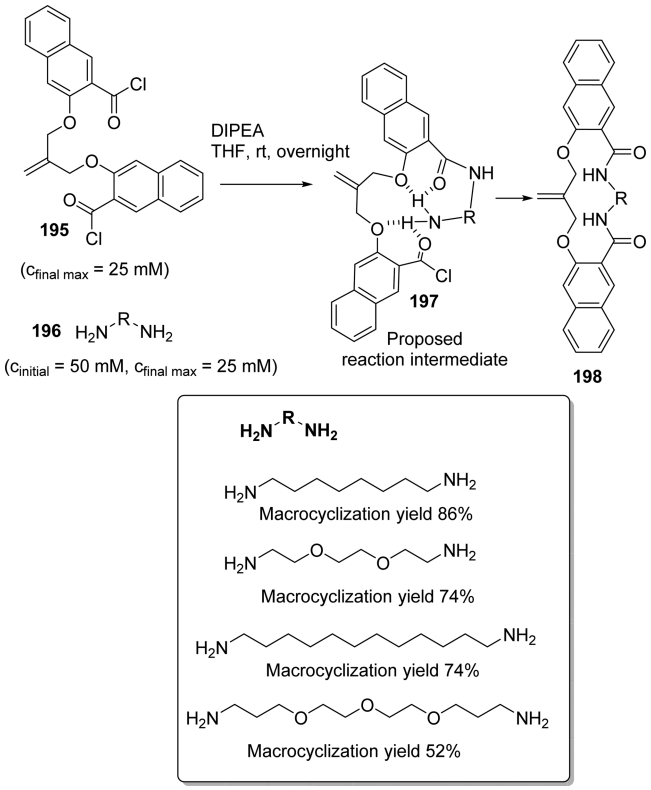

Figure 56. Hydrogen bond assisted [1 + 1] macrocyclization.[248]

The preparation of the smallest possible sidewall of a (5,5) carbon nanotube has been reported by Yamago and co-workers. They have described the synthesis of the highly strained [5]cycloparaphenylene **153** from macrocycle **151a** that was obtained in 63% yield using a head-to-tail macrocyclization starting from a similar open-chain precursor **150a** displaying a very favorable conformation (Figure 44). In this case, the 3,6-disubstituted *cis*-3,6-bis(triethylsilyl)cyclohexa-1,4-diene fragment **150a** provides the required folding for the easy preparation of the macrocycle **151a**.[227] Interestingly, the [5]CPP precursor **151b** was prepared by Jasti and co-workers by intramolecular boronate homocoupling from **152** in 44% yield (Figure 44).[228] It is also important to consider here that the final ring closing reaction is a metal mediated process that involves the initial formation of a metallocycle.

Itami and co-workers have also described the preparation of a variety of cycloparaphenylenes. In this case the synthetic approaches developed were based on the use of *cis*-1,4-bis(4-halophenyl)cyclohexane fragments **154** as a rigid L-shaped scaffold to provide the appropriate folding of the reaction intermediate precursors. Taking into account the almost perfect L-shape of this monomer, they postulated that its tetramerization in a nickel-promoted one-pot macrocyclization might proceed to give directly the macrocyclic precursor of the [12]CPP **155a** in a "shotgun" approach (Figure 45a). In agreement with their expectations, they could obtain the macrocycle **155a** in 27% yield using THF at reflux and a 16 mM concentration of **154**. A slightly lower yield (22%) was obtained when the corresponding dibromide was used instead of the diiodide **154**.[229] On the other hand, the initial *cis*-1,4-bis(4-halophenyl)cyclohexane **154**

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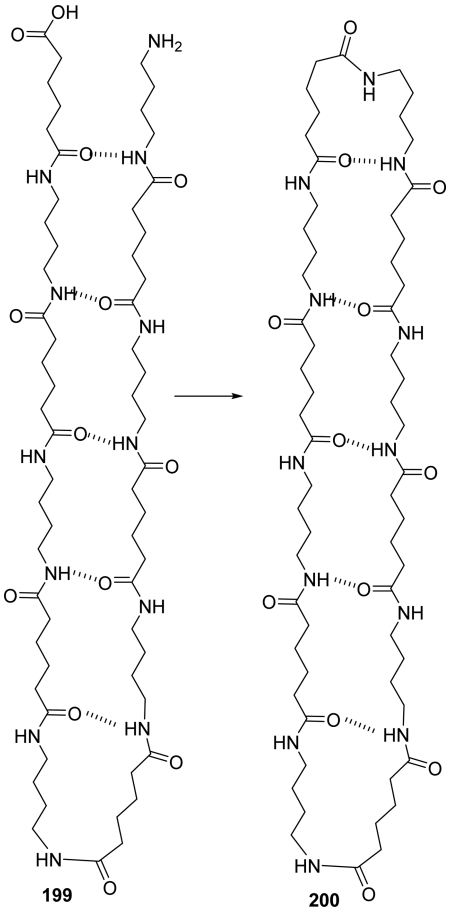

Figure 57. Possible pathway for the formation of a macrocyclic oligoamide.[249]

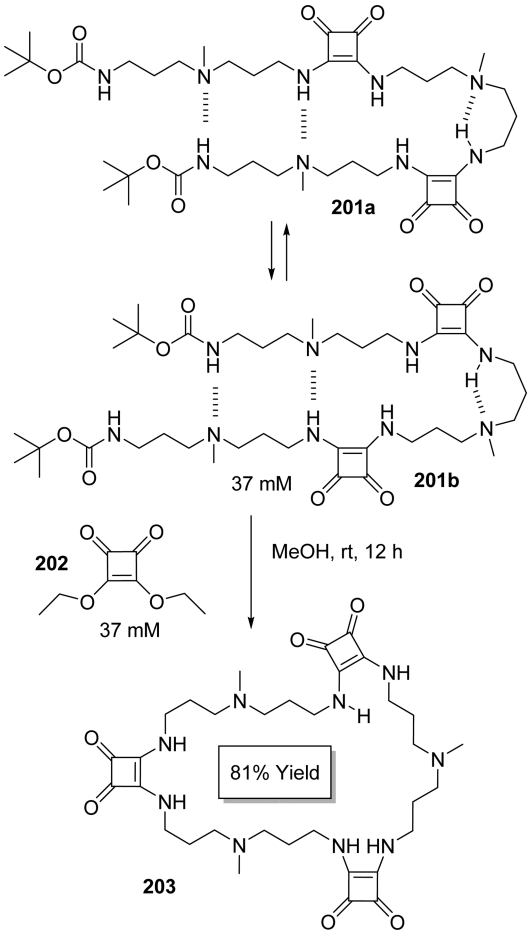

Figure 58. Folded conformations stabilized by intramolecular hydrogen bonds followed by the formation of the macrocyclic product **203**. For related compounds: 80% yield for the tetramer, 82% for the pentamer, and 80% for the hexamer.[251]

fragment can be easily transformed to elaborate more complex open-chain structures like **156a** via C−C coupling processes (i.e., Suzuki−Miyaura reactions), allowing for the formation of U-shaped and C-shaped compounds. This stepwise approach was used by the same authors for the selective synthesis of the [12]CPP precursor **155b** in a [1 + 1] process in 51% macrocyclization yield using a 2 mM concentration of the open-chain precursor **156a** and 2.8 mM **157** (Figure 45b).[230]

These oligomeric open-chain precursors (for example **156b**, **159a**, and **159b**) with different shapes provide a flexible set of building blocks to access a large variety of macrocycles by a combination of nickel-mediated head-to-tail macrocyclizations and Suzuki−Miyaura [1 + 1] couplings involving an additional aromatic borane component like **148a** (Figure 46). This methodology provided access to the size-selective synthesis of [9]-, [10]-, [11], and [13]CPP precursors **158a**, **158b**, **160a**, and **160b** in 46, 18, 42, and 51% macrocyclization yields, respectively, (Figures 46 and 47).[231,232]

Itami and co-workers have reported the synthesis of [7]- and [8]CPP precursors **163b** and **163a**, from a common C-shaped precursor **161**. Macrocycle **163a** was obtained in 27% macrocyclization yield from **161** and **162**, and macrocycle **163b** was obtained in 67% macrocyclization yield from **161** (Figure 48).[233] This method improves the efficiency of the previous reported 8% macrocyclization yield using a different method for the preparation of the immediate precursor **163b** of [7]CPP (Figure 43).[225]

The same group has also reported the modular and size-selective synthesis of [14]-, [15]-, and [16]CPP precursors **168** in 45, 32, and 34% macrocyclization yields, respectively. They used a methodology based on the assembly of bent and linear building blocks **164**−**167** in a controlled manner. The successful size-selective synthesis of the [15]CPP precursor **168b** is particularly important as it highlights the potential match/mismatch of the two components **165a** and **166**. This is associated with the different conformations present at the cyclohexane rings in the tetraphenylenic component that in the most favorable case (**165b**) allows compensating the different lengths of the tetra- and triphenylene spacers of the two reacting components (Figure 49).[234]

Using similar building blocks, they have also prepared the corresponding cycloparaphenylenes containing pyrene fragments (3 mM concentration of open-chain precursor with 17% macrocyclization yield),[235] 2,2′-bipyridine fragments (dibromide based compound (1.1 mM), diB(pin) precursor (1.4 mM) with 48% macrocyclization yield),[236] and 2,6-naphthylene fragments (dibromide based compound (2.0 mM), diB(pin) based compound (2.4 mM) with 35% macrocyclization yield),[237] as well as the synthesis of [9]cyclo-1,4-naphthylene in 2% macrocyclization yield using a 8.3 mM concentration of the open-chain precursor.[238] The preparation of thiophene-based analogues has also been reported through the initial formation of the polyacetylenic macrocycles **170** displayed in Figure 50. The

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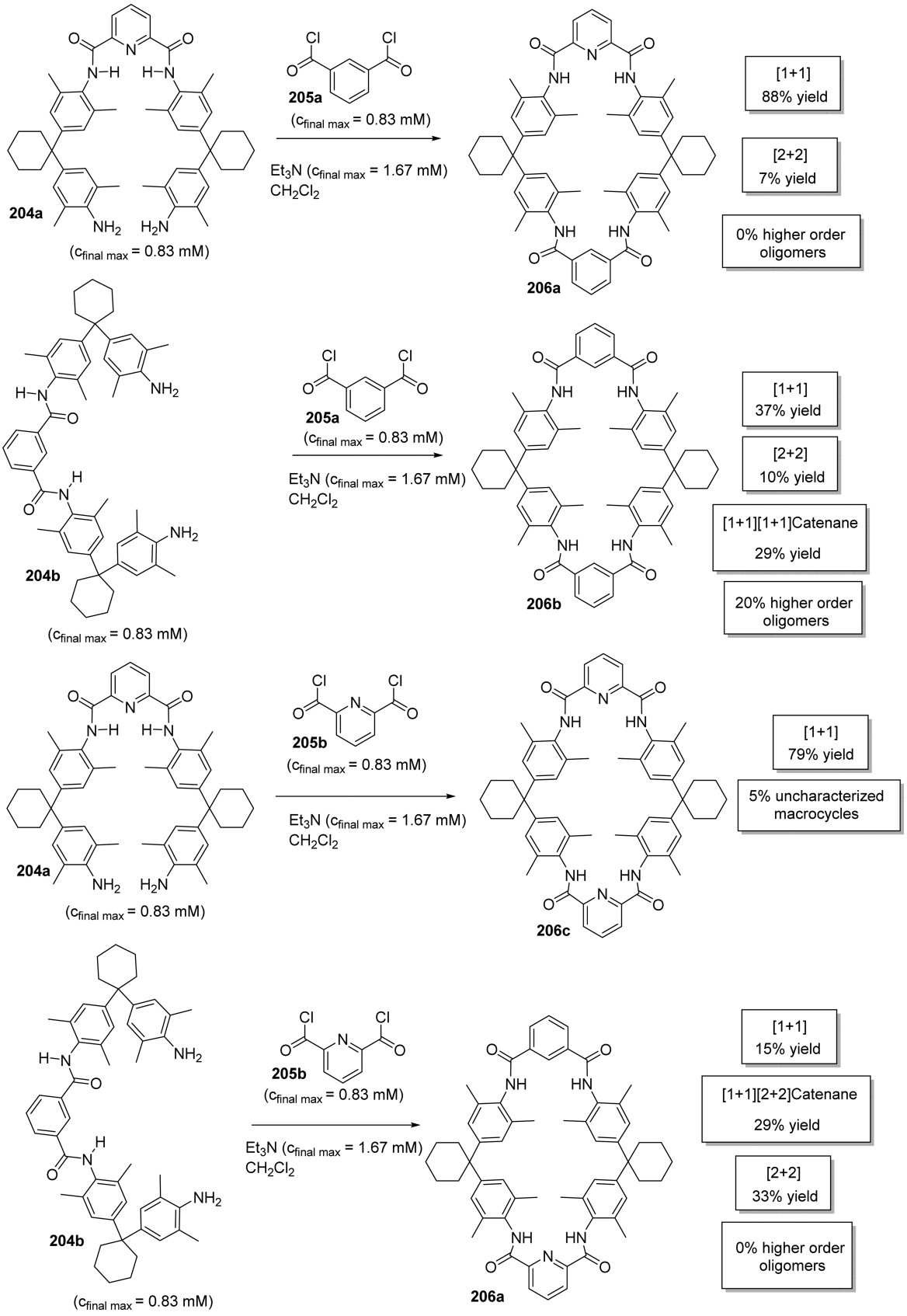

Figure 59. Hydrogen bonding directed synthesis of macrocycles.[252]

triple bonds could then be transformed into the thiophene subunits by reaction with $Na_2S·9H_2O$ at 160 °C using microwave heating. The macrocyclization process of **169** was achieved in 6–32% yields using Glaser–Hay coupling conditions. Interestingly, the macrocyclic product **170** with $n = 5$ could be isolated in 3% yield using a 133 mM concentration of the open-chain precursor,

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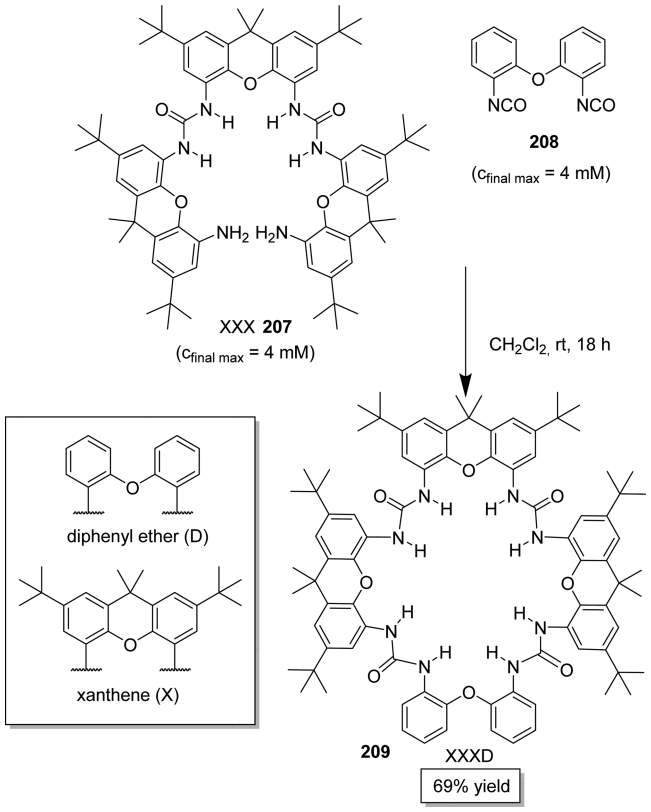

Figure 60. Synthesis of macrocyclic tetraureas.[253]

but only at the expense of a decrease in the total macrocyclization yield.[239]

In the case reported by Lauher and co-workers, the acetylenic precursor **171** seems have a suitable geometry to favor the efficient [1 + 1] macrocyclization, using a copper-catalyzed oxidative Hay coupling reaction. The reaction afforded the 2-mer macrocycle **172b** in 46% yield, the 1-mer macrocycle **172a** in 10% yield, and a small amount of the 3-mer macrocycle, and the rest of the starting compound was converted into polymeric material (Figure 51).[240]

Jasti and co-workers have described the synthesis of cycloparaphenylene precursors **174** containing flexible aliphatic chains in 14−21% macrocyclization yields from precursors **173** and **150b**. Lower yields were obtained in comparison to the more rigid related compounds described above. Here, the higher flexibility associated with the $-(CH_2)_n-$ chains present in **173**, and in the initial open chain intermediate obtained by the initial reaction of **173** and **150b**, seems to provide access to conformations much less favorable for the macrocyclization process (Figure 52).[241]

Yamago and co-workers have employed a methodology that uses Pt to initially form a macrocyclic metallocycle from which the cycloparaphenylene is obtained by a reductive elimination reaction from this cyclic intermediate **176**.[242,243] With this methodology, the [8]CPP **177** was obtained selectively from the monomeric precursor **175** (Figure 53a) as well as the [12]CPP. They have also described a random synthesis using **178** and **179** as the starting materials, for which the product distribution depends on the reaction conditions (Figure 53b). For 20 h of reaction at 70 °C the product distribution was 5.4, 9.6, 7.7, 3.8, and 0.8% yield for [9]-, [10]-, [11]-, [12]-, and [13]-cycloparaphenylenes, respectively. However, for 32 h at 50 °C, the product distribution was 2.4, 3.2, 5.3, 4.7, and 2.3% yield for [8]-, [9]-, [10]-, [11]-, and [12]cycloparaphenylenes, respectively.[242]

A modification of this methodology has been developed to prepare selectively [10]cycloparaphenylene **182** through the initial preparation of the intermediates **181** (Figure 54). The formation of **181d** from **181b** is suggested to take place with the liberation of the fragment **181c**. The use of $Pd(dba)_2$ is a key factor, as long as the use of $Ni(cod)_2$ yielded a mixture of cycloparaphenylenes of different sizes.[244] This methodology also allowed preparing [4]cyclo-2,7-pyrenylene **185** from monomer **183** using $Pt(cod)Cl_2$ to obtain the tetrameric metallo-macrocycle precursor **184** (Figure 54b).[245] In a related approach, Isobe and co-workers have reported the preparation of chiral (*n*,*m*) macrocyclic chiral carbon nanorings by tetramerization of chrysenylene derivatives (20 mM). The overall process is again a two-stage process in which a cyclic tetrameric Pt complex **187** is initially formed in 74% yield from monomer **186** and is then transformed into the desired product by a ligand exchange reaction, followed by a reductive elimination that provides the [4]cyclo-2,8-chrysenylene **188** in 94% yield (Figure 54c).[246]

Hughes and co-workers have described the preparation of related macrocyclic compounds (**193** and **194**) using a combination of benzene rings and triple bonds (precursors **189**−**192**). In the case of the biphenyl derivative with R = H (**189a**), the direct synthesis of the macrocycle by trimerization of the initial building block **189a** yielded a mixture of linear oligomers and macrocyclic species with poor solubility and which was very difficult to purify (18 mM, 20% yield of **193a**). In contrast, the macrocyclization from the preformed open-chain precursor **191a** displaying the appropriate folded conformation allowed preparing the macrocyclic compound **193a** in 45% yield. A similar observation was obtained for the related terphenyl-derived system **194a**. Additionally, the incorporation of octyl groups (R = *n*-C_8H_{17}) improved the efficiency of the processes and facilitated the purification steps (Figure 55).[247]

5.1.3. Macrocyclizations Favored by Hydrogen Bonding. In order to provide the appropriate conformation of the open-chain intermediate being the direct precursor of the macrocycle, the presence of specific intramolecular interactions such as hydrogen bonds can be a key element. This has been reported, for instance, by Hiratani and co-workers, who prepared a new family of macrocycles **198** through the amidation of a di(acid chloride) **195** with different diamine derivatives (**196**). They pointed to the formation of intramolecular hydrogen bonds in the reaction intermediate **197** as a key factor that provides an appropriate folded conformation of this species and favors good macrocyclization yields. In this example, the yield of the macrocyclization reaction was influenced by the length of the diamine **196**, being the yields lower for the longer diamines (Figure 56).[248]

The formation of such folded reaction intermediates is not only observed in the preparation of small and medium size molecular species, but it has also been observed in the preparation of polymers. In this case, the folded geometry of the open-chain precursors can yield cyclic oligomers. In this regard, Rulkens and Peters have reported the unusual formation of cyclic oligomers **200** containing 10 or 12 amide groups in the preparation of polyamide-4,6.[249] The lamellar packing observed in the solid state displays a well-structured hairpin folding for each five or six repeat units in **199**, based on the hydrogen bonding between complementary subunits, which, therefore, suggests that this geometry of the open-chain oligomers **199** can

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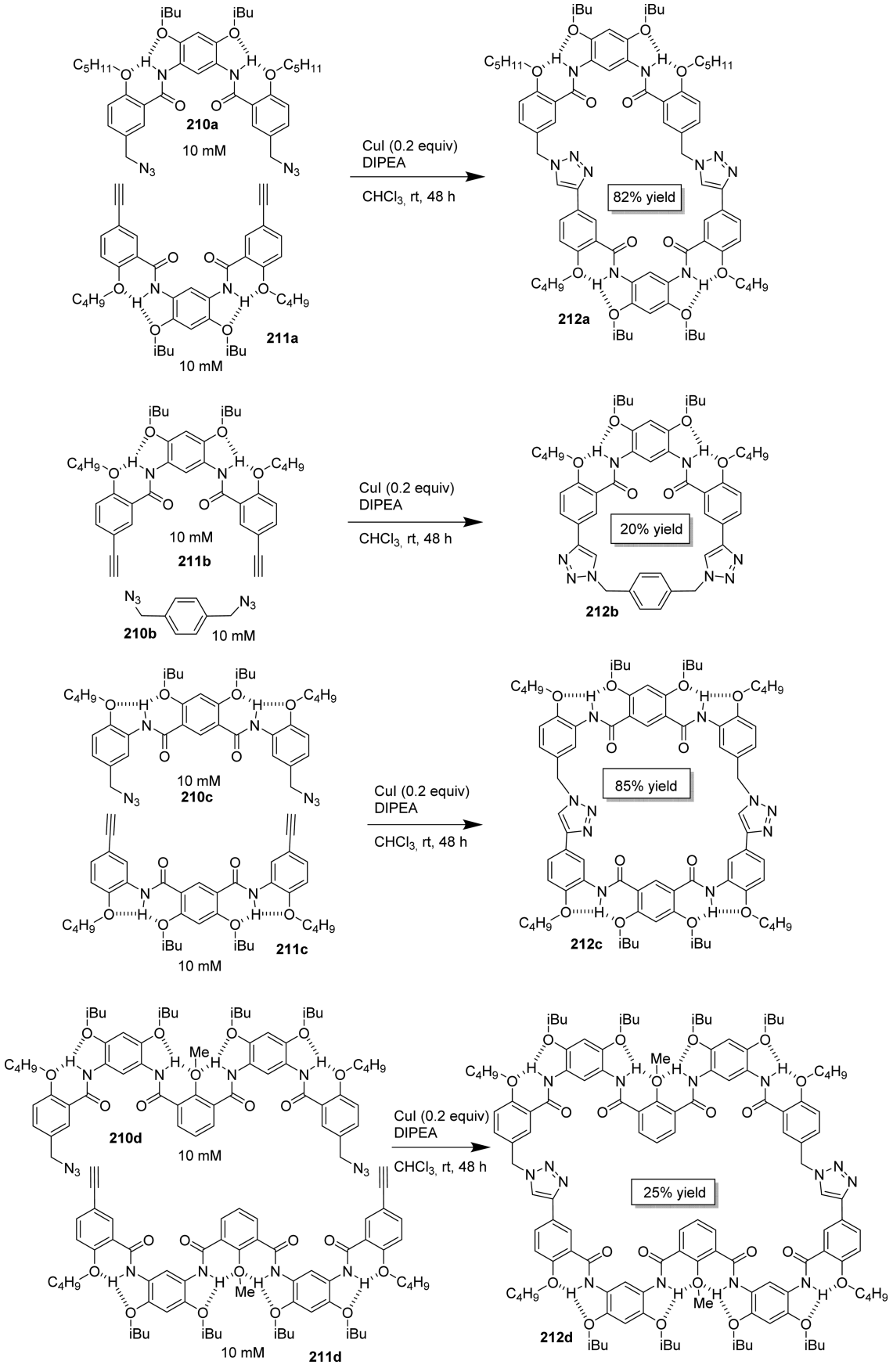

Figure 61. Macrocycle synthesis by CuAAC click reaction.[254]

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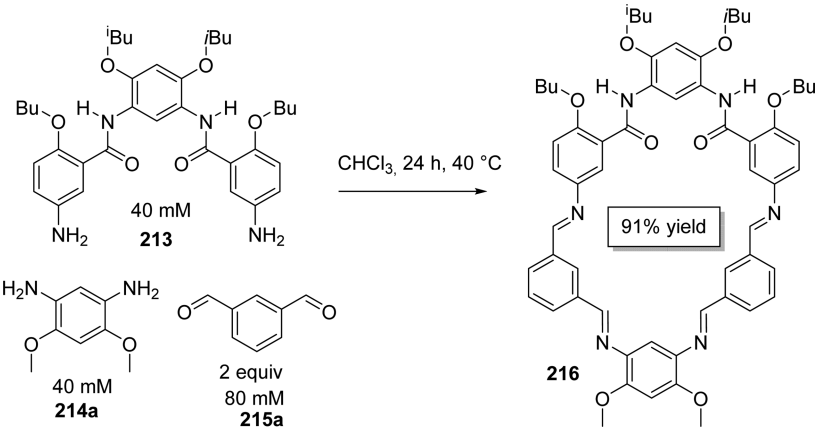

Figure 62. Three-component macrocyclization reaction.[255]

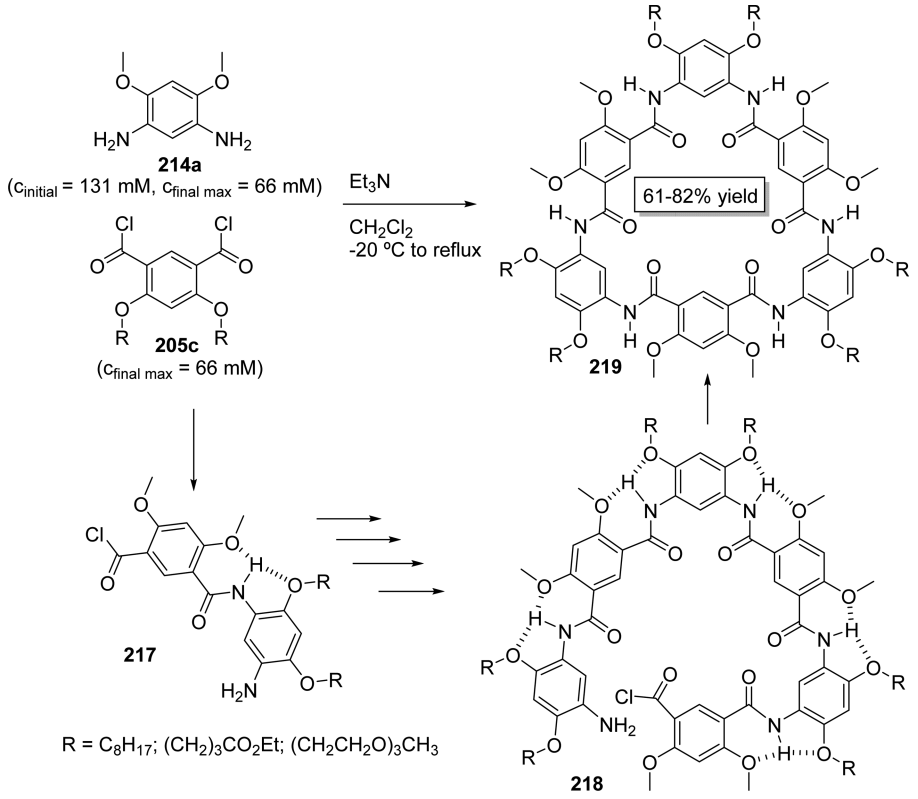

Figure 63. Synthesis of a macrocyclic structure by a [3 + 3] process.[257,259]

bring the reactive ends together, favoring the macrocyclization reaction (Figure 57).[250]

A similar intramolecular hydrogen bonding pattern involving the folding of the open-chain precursor was described by Costa, Rotger, and co-workers. They reported an efficient macrocyclization reaction to obtain **203** by reaction of palindromic oligosquaramides containing two very favorable folded conformations (**201a** and **201b**) and **202**. Hydrogen bonding was the main force contributing to the folding process (the folded structures were stable in polar solvents), which allows for the efficient one-step macrocyclization of the open-chain compounds of different lengths without the need for high dilution conditions (Figure 58).[251]

Even in the case of rigid building blocks, the formation of intramolecular hydrogen bonds can also contribute significantly to the appropriate folding and to the adoption of the required geometry of the open-chain macrocycle precursors. In this regard, many examples of efficient macrocyclizations involve the use of aromatic amides and related functionalities in combination with other functional groups (i.e., ether) that could act as hydrogen bond acceptors. Hunter and co-workers have described the preparation of macrocyclic structures in 80−90% yields by using intramolecular hydrogen-bonding interactions to favor the required folded conformations that bring together the reactive ends, facilitating the intramolecular cyclization and the formation of the corresponding cyclic structures (**206**). They demonstrated that in the absence of the intramolecular hydrogen bonding (by changing one pyridine ring to a benzene ring; **204a** vs **204b** and **205a** vs **205b**) these favorable conformations are lost and significantly lower yields are obtained for the [1 + 1] macrocyclization (Figure 59).[252]

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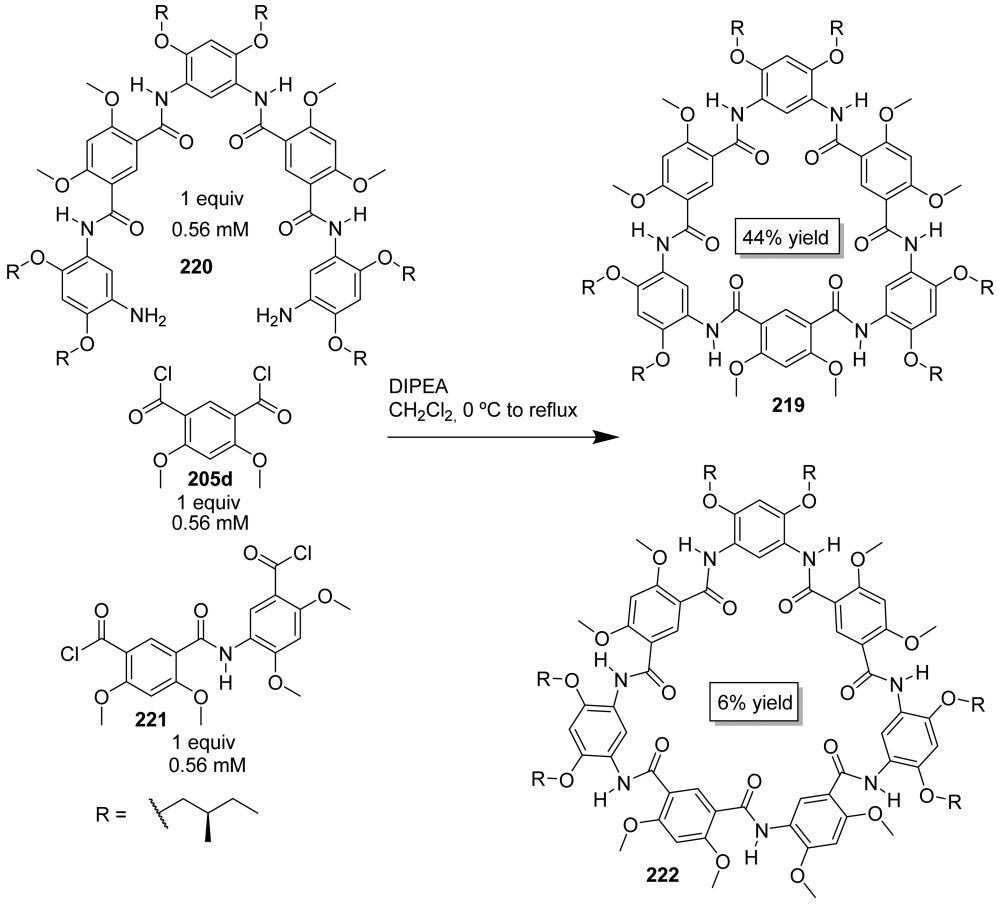

Figure 64. Competitive experiments for [1 + 1] macrocyclizations using a preorganized precursor.[261]

The combination of rigid and flexible building blocks facilitates the preparation of intermediates with different accessible conformations that can appreciably differ on the level of their preorganization for the macrocyclization, allowing for a deep analysis of these differences and their effects on the corresponding macrocyclization processes, as described by Böhmer and co-workers. They prepared a series of cyclic tetraureas having different flexibilities and therefore different binding affinities to anions, by combining rigid xanthene (X) and more flexible diphenyl ether (D) subunits (Figure 60).[253] The direct reaction of the xanthene or diphenyl ether diamines with nitrophenyl chloroformate as a bifunctional reagent afforded the corresponding homotetramers XXXX and DDDD in 15 and 58% yields. This indicates that the corresponding tetrameric open-chain intermediates are particularly well suited for cyclization, but it also reveals that the structural arrangement of the more rigid tetramer leading to XXXX does not provide the optimal disposition of the two reactive ends and here the presence of some flexibility is more favorable. The same trend was observed when the authors explored the cyclization process from a trimeric diamine and a diisocyanate to obtain the different possible heterotetrameric macrocycles (Figure 60). The reaction of a rigid trimeric diamine **207** with a flexible diisocianate **208** afforded excellent macrocyclization yields (XXXD: **209**, 69%), but the introduction of a second more flexible subunit in DXDX or XXDD reduced the macrocyclization yield (55 and 41%, respectively). Finally, the compound DDDX could not be obtained under the same conditions and needed to be prepared by use of an anion template (Cl^-) approach (see section 6.2). These results highlight the delicate balance between rigidity and flexibility that is always involved when considering the proper preorganization of the open-chain precursors.

A strong dependence of the macrocyclization yields with the size of the macrocycle in precursors containing an extended network of hydrogen bonds has been reported by Li and co-workers. They used a click chemistry approach for the synthesis of macrocycles **212** from aryl amide based precursors **210** and **211** (Figure 61). This approach was based on the strong conformational preferences based on hydrogen bonding and allowed the preparation of different macrocyclic structures. In this case, the yields for the smaller **212b** and larger **212d** macrocycles were lower (20 and 25%) than those for the related medium size compounds **212a** and **212c** (82 and 85%). This clearly illustrates that both the geometry of the individual components and their hydrogen bonding induced preorganization have a direct effect on the macrocyclization yields.[254]

The preparation of macrocycles from more than two building blocks, based on rigid aromatic components, has also been described in the literature. Li and co-workers have developed the synthesis of the rigid macrocyclic compound **216** from an open-chain precursor **213** and two small additional building blocks **214a** and **215a** under thermodynamic control. This synthesis involves the multicomponent assembly of three different starting materials directed by intramolecular hydrogen bonding. They studied the formation of different macrocycles from different building blocks, and it was found that the macrocycle with the less strained geometry is preferentially formed, which is in good agreement with a thermodynamically controlled process based on the presence of a reversible reaction for the macrocyclization step. An illustrative example is depicted in Figure 62.[255]

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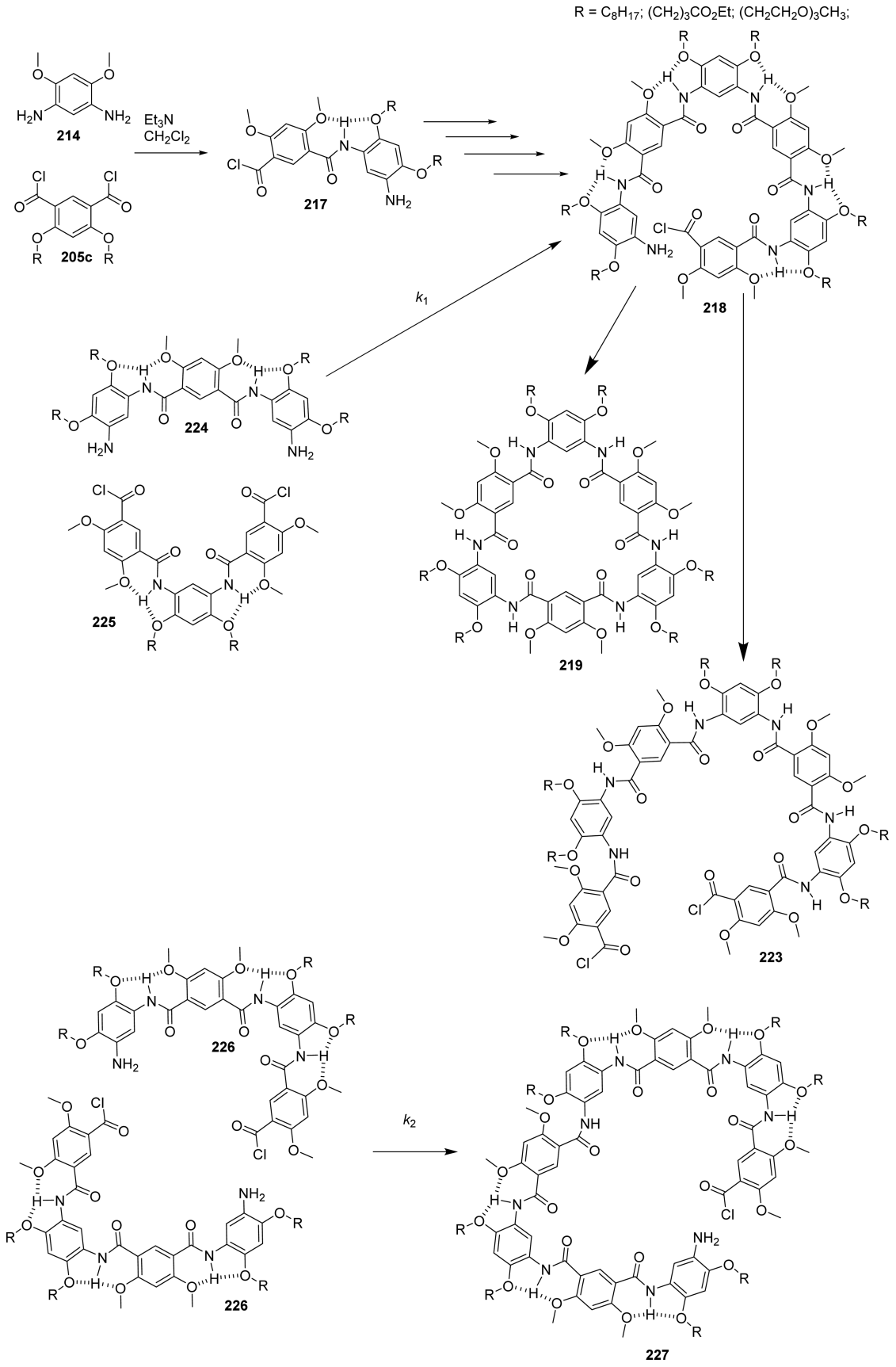

Figure 65. Different reaction pathways that could be involved in the formation of the hexameric macrocycle **219**.[262]

A different approach is the coupling of small size building blocks in a one pot $[n + n]$ macrocyclization, using irreversible reactions and avoiding the protection/deprotection steps required to synthesize the open-chain precursors. Gong and

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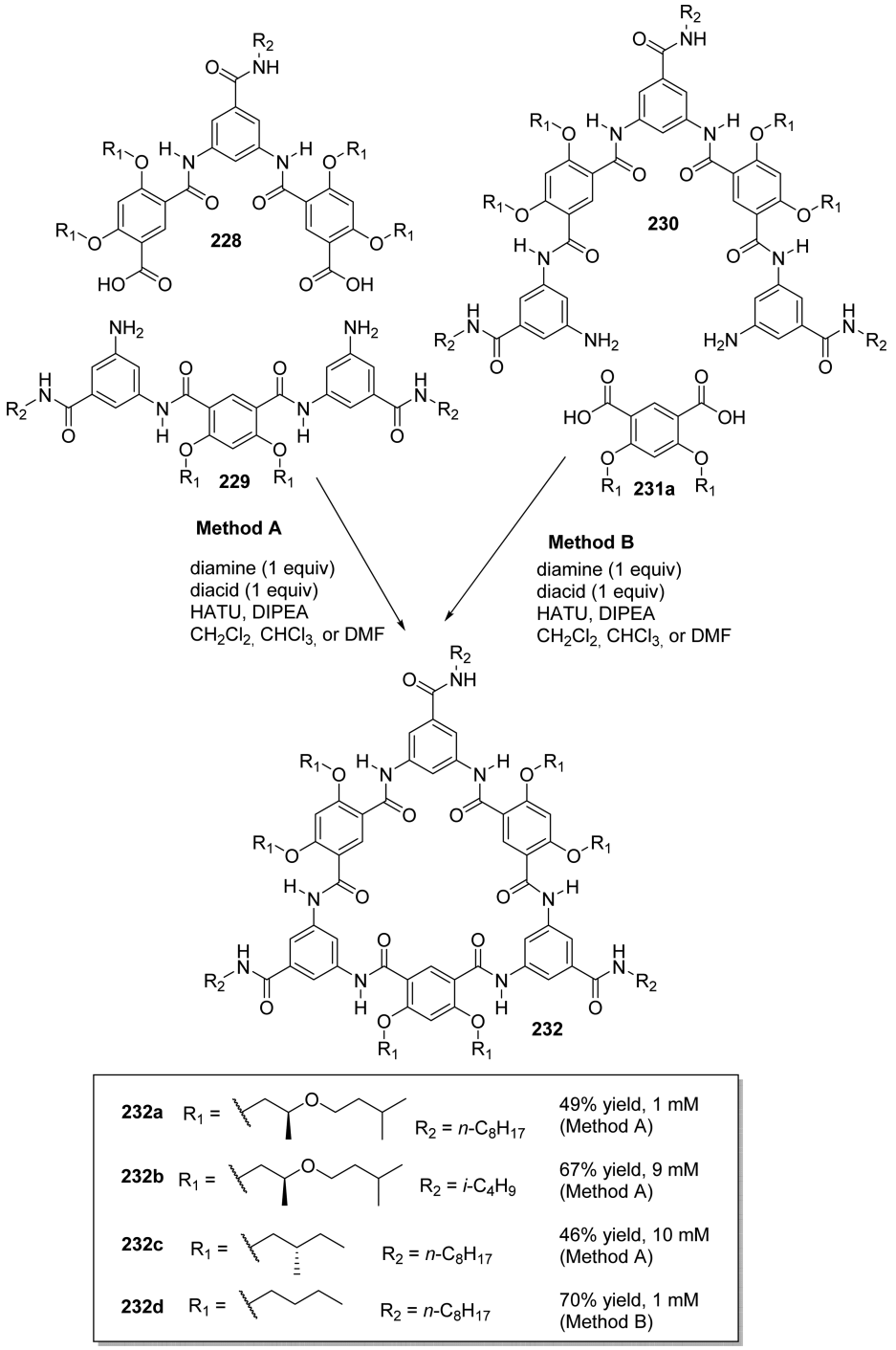

Figure 66. Synthesis of hexameric macrocycles with a partially constrained backbone.[263]

co-workers have studied extensively the preparation of rigid cyclic oligoamides of different sizes and structural features.[256,257] In one of the examples reported, they described a simple and highly efficient one pot multicomponent macrocyclization method to prepare large macrocyclic structures like **219** by the reaction of several units of an aromatic diamine (**214a**) and a substituted aromatic di(acid chloride) (**205c**).[258] This methodology is based in the crescent geometry of the in situ formed precursors (i.e., **217** and related oligomers) facilitating to overcome the entropy barrier of the macrocyclization process. The stepwise coupling of the monomers yields a folded conformation (**218**) that brings together the reactive ends for the formation of the [3 + 3] macrocyclic compound **219**. As a result, a highly efficient macrocyclization is achieved.[259] Studies at different temperatures showed that the 6-mer macrocycle **219** predominated when the macrocyclization reaction was carried out at low temperatures, and the formation of the 8-mer macrocycle increases at higher temperatures, which was assigned to the augmented flexibility of the folded oligomeric species (Figure 63).[260]

The same group also studied the role of the geometry of the precursors by performing competing kinetic experiments. They demonstrated that the folded conformation of the pentameric precursor **220** defines the most suitable counterpart structure for

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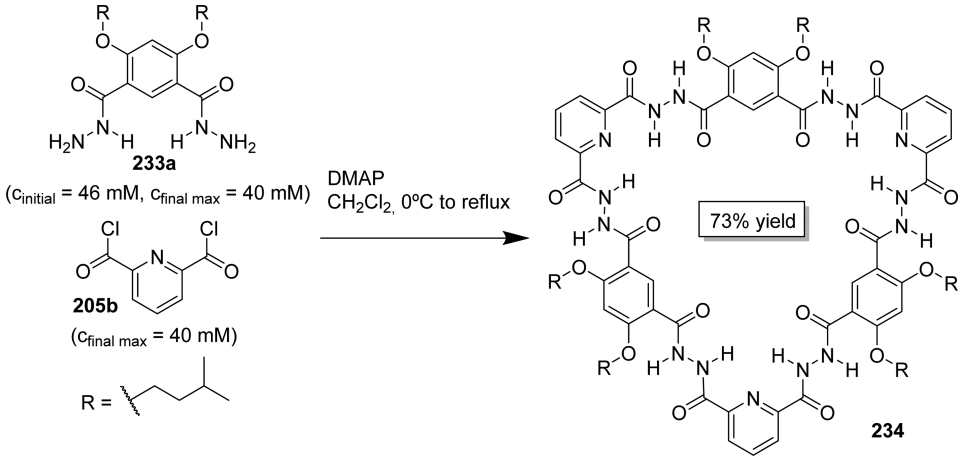

Figure 67. Single pot [3 + 3] macrocyclization for the synthesis of oligohydrazides.[265]

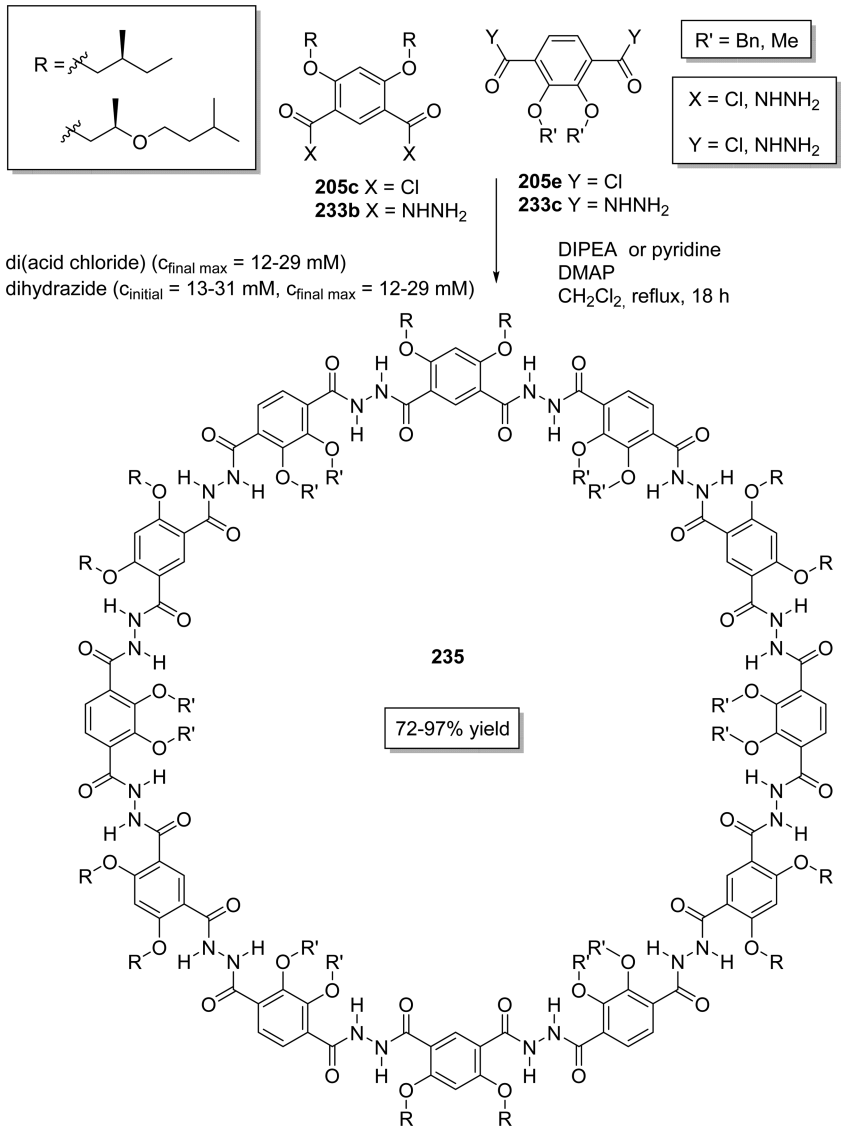

Figure 68. Single pot formal [6 + 6] macrocyclization for the synthesis of oligohydrazides.[265]

a [1 + 1] macrocyclization (Figure 64). When **220** was allowed to react with a mixture of **205d** and **221**, the acid chloride (**205d**) that allows the formation of the less strained macrocycle reacts faster, as this corresponds to a less strained transition state, and the corresponding macrocycle (**219**) is obtained in higher yields.[261]

A detailed mechanistic analysis has been carried out for this efficient kinetically controlled macrocyclization (Figure 65).[262]

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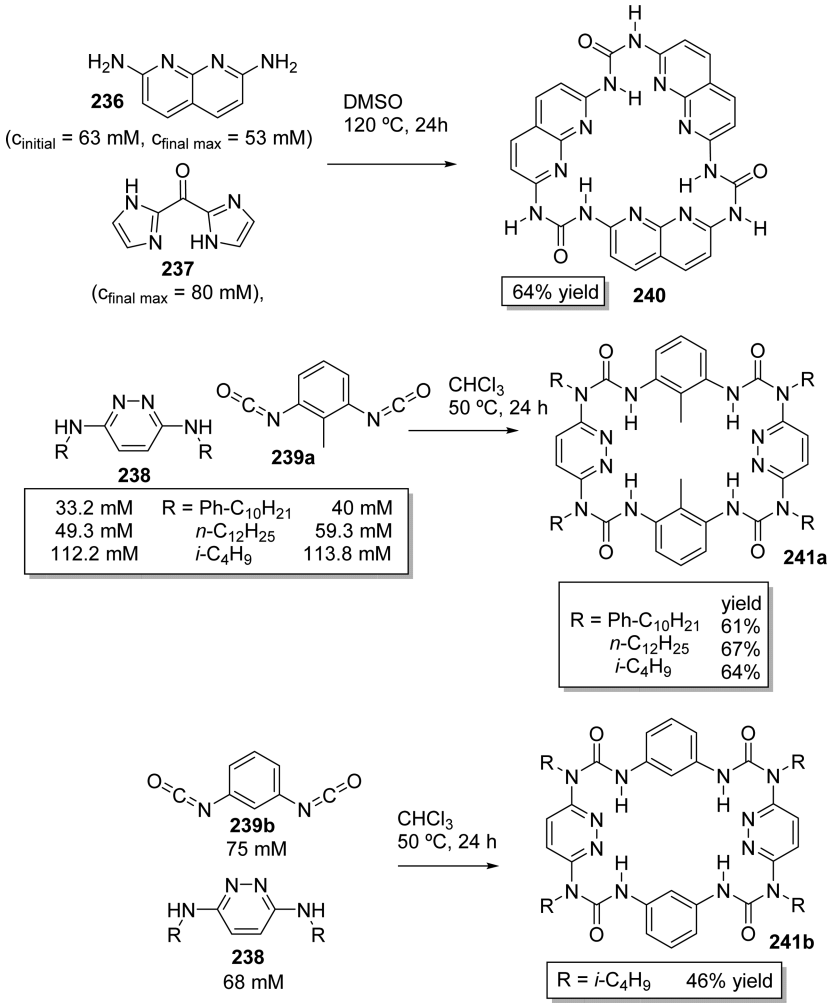

Figure 69. [2 + 2] macrocyclizations from diamines and diisocyanates or related compounds.[266]

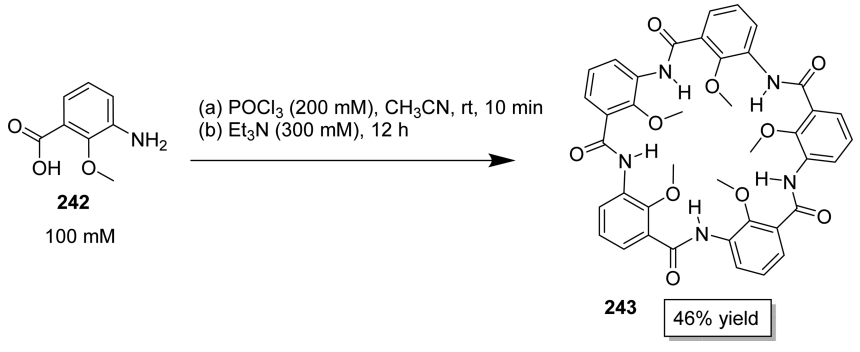

Figure 70. Formation of a cyclic pentamer from a single difunctional component.[268,270]

The adoption by the formed precursors of folded structures with a well-defined crescent conformation seems to play a critical role. This not only favors the cyclization of the hexameric immediate precursor **218**, but also provides remote steric effects that preclude or disfavor the formation of higher oligomers **223**. Thus, the immediate hexameric open-chain precursor **218** can be formed preferentially by stepwise addition of one additional monomer to the growing oligomer (pentamer in this case) or by reaction of very short oligomers, but the reactions of trimers or longer oligomers is disfavored. For example, the trimeric diamine **224** reacted faster with the monomeric di(acid chloride) **205c** than with a trimeric one (**225**), and the corresponding reaction rate is much higher than that for the reaction between two tetramers (**226**, $k_1 \gg k_2$) with all reactants being 0.5 mM to yield the oligomer **227**. Therefore, this explains the formation of the hexameric macrocycle **219** in high yields (>80%), and the absence of higher order oligomers (Figure 65). According to this hypothesis, the substitution of one of the *meta*-derivatives by a *para*-substituted derivative allowed the access to the preparation of much larger rings, again with high efficiencies.[262]

The former macrocyclization reactions and the strongly rigidified macrocycles resulting from them are associated with the formation of strong three-center hydrogen bonds involving the amide N−H and one OR group at each of the vicinal

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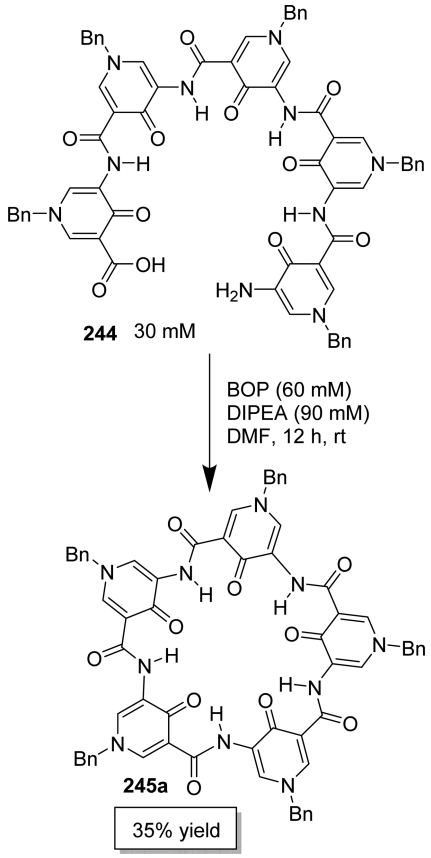

Figure 71. Formation of a cyclic pentamer containing pyridone subunits in a [1 + 1] process.[271]

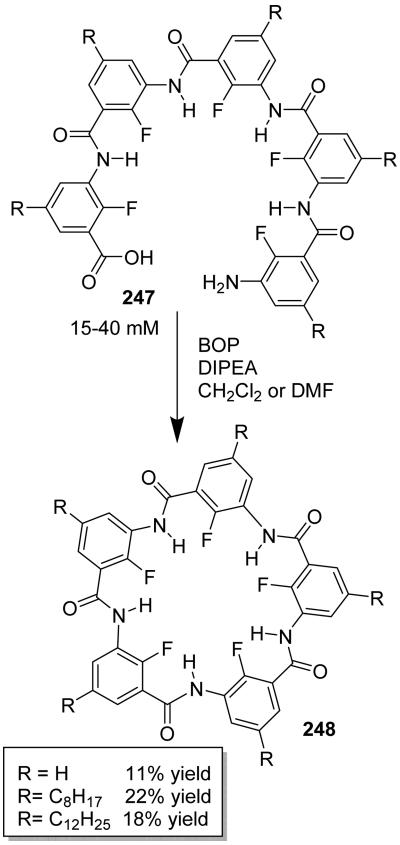

Figure 73. Synthesis of a cyclic pentameric oligoamide by cyclization of a difunctional precursor properly preorganized by C−F···H−N hydrogen bonds.[273,274]

subunits. The removal of these OR groups in one of the subunits produced important differences not only in the properties of the corresponding hexameric cyclic structures related to **219**, but also in the synthetic approach used for their preparation.[263] In this case, the approach using the corresponding monomeric acid chlorides **205c** and monomeric diamines **214** (formal [3 + 3] macrocyclization) did not yield the expected macrocyclic products and their synthesis was carried out by the coupling of the corresponding trimeric diamines **229** and diacids **228** (method A in Figure 66). This kind of [1 + 1] macrocyclization approach has been shown to be also effective for the preparation of some macrocycles with highly constrained backbones.[260,261,264] In some instances (synthesis of **232a**), the poor solubility of the intermediates precluded use of this general methodology, and it was necessary to perform the coupling of the pentameric diamines **230** and the monomeric diacid **231a** (method B in Figure 66). The corresponding hexameric macrocycles **232** were obtained in 46−70% yields (Figure 66).

Similar macrocyclic structures (**234**) in which the amide subunits have been substituted by hydrazide subunits were also obtained by He, Zeng, Gong, and co-workers in one-pot multicomponent [*n* + *n*] processes.[265] The use of monomeric subunits (**205b** and **233a**) with a *meta* arrangement of the reactive groups led to the nearly exclusive formation of the macrocyclic hexamer **234** depicted in Figure 67 (73% isolated yield), in a way similar to that found in the case of the oligoamides. As for the cyclic oligoamides, a change in the chemical structure of the building blocks, introducing a *para*

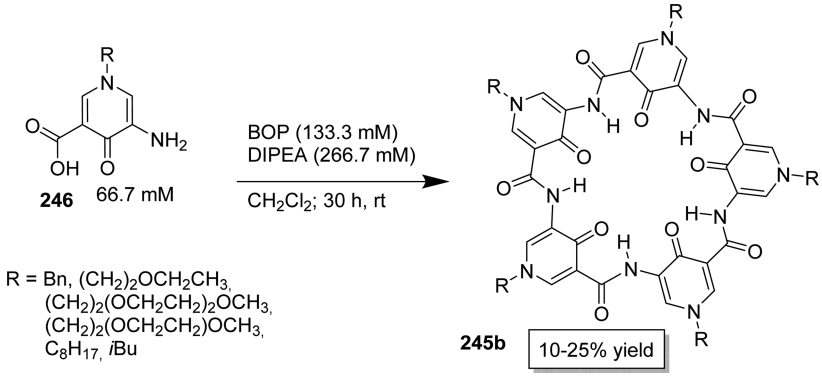

Figure 72. Formation of a cyclic pyridone pentamer from the one pot chain-growth approach from a single monomer.[272]

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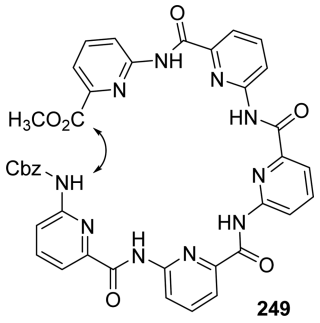

Figure 74. Pentameric open-chain oligoamide revealing the folded conformation. The short distance between the two potentially reactive ends is marked with an arrow.[275]

arrangement of the reactive groups in one of the components **205a**, **205e**, **233b**, or **233c**, allowed obtaining larger macrocyclic structures **235** (formed by 10 monomeric units in a [5 + 5] process). MALDI mass spectrometry and ^{1}H NMR experiments demonstrated that the macrocycle **235** was the predominant one in the crude of the reaction and the pure products could be isolated in 72−97% yields (Figure 68).

Cuccia and co-workers have reported an intramolecular hydrogen bond directed synthesis of pyridazine and naphthyridine containing macrocycles **240** and **241** in $[n + n]$ processes using monomeric components **236**−**239**.[266] The reported macrocyclic products **240** and **241** were obtained in 46−67% yields. These good yields were attributed to the favorable folded conformation of the open-chain precursors stabilized by intramolecular hydrogen bonds between the N−H urea protons and the heterocyclic nitrogen atoms (Figure 69).

Zeng and co-workers have developed a methodology for preparing macrocycles using multiple-center intramolecular H-bonds for the efficient generation of a crescent conformation of the intermediates in the assembly of small building blocks **242**.[267] They reported an elegant hydrogen bond directed one-pot macrocyclization of a difunctional monomer that predominantly yields the cyclic oligoamide pentamer **243** (Figure 70). The selective formation of the five-residue macrocycle **243** proceeds by a chain-growth mechanism through the successive addition of bifunctional monomer units.[268] The formation of the cyclic pentamer **243** seems to be favored as the open-chain pentameric precursor has the most suitable conformation to cyclize. They have also determined in detail the kinetics of the cyclization process, and the results confirmed the chain-growth mechanism, showing that the addition of one monomer **242** to the growing oligomer is faster than the condensation between two oligomers.[269,270]

Similar cyclic pentameric oligoamides like **245a**, containing pyridone subunits instead of alkoxy aromatic components, have also been investigated as good hosts for different cations such as Li^+, Na^+, K^+, Rb^+, and Cs^+ with binding constants in the range $(0.2-2) \times 10^8$ M^{-1} being selective for the smaller cations. The macrocyclic structure **245a** has been prepared from the open-chain precursor **244** in 35% yield (Figure 71). The one-pot reaction following the chain-growth mechanism of the difunctional monomers **246** allowed the preparation of the macrocyclic products **245b** in 10−25% yield (Figure 72).[271,272]

Despite that usually fluorine acts as a poor hydrogen bond acceptor, Zeng and co-workers have described the preparation of some cyclic oligoamides **248** using C−F···H−N hydrogen bonds, much weaker than the C═O···H−N hydrogen bonds, to appropriately preorganize the open-chain immediate precursor **247**. Macrocyclization yields obtained were in the 11−22% range (Figure 73).[273,274] The macrocyclization takes place by direct coupling of the two functional ends of the pentameric difunctional open-chain precursor **247**.

Zeng and co-workers have also investigated the influence of the folded conformation of the different oligomers **249** involved in the preparation of cyclic oligoamides containing pyridine subunits, demonstrating again that the proximity of the two reactive ends is an important factor determining the affinity of the compound they cyclize (Figure 74).[275] An in-depth analysis of the folding assisted by three-center H-bonds for the aromatic oligoamides formerly discussed has been reported by Gong and co-workers.[276]

MacLachlan and co-workers have described the synthesis of campestarenes **251** in quasi-quantitative yields (99%), through a dynamic covalent chemistry approach, from building blocks **250a**

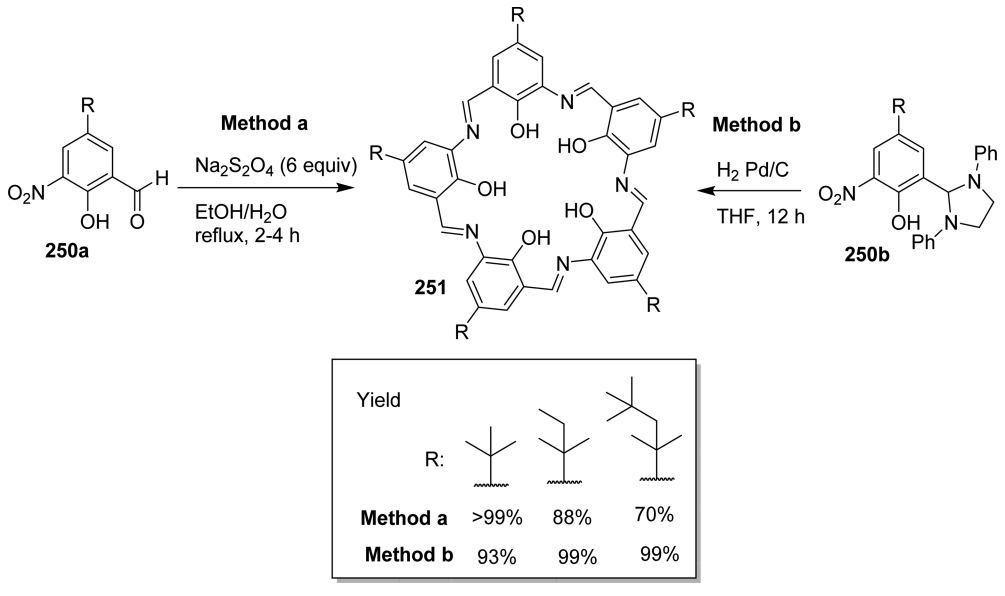

Figure 75. Thermodynamically controlled synthesis of campestarenes from a single monomeric structure.[277]

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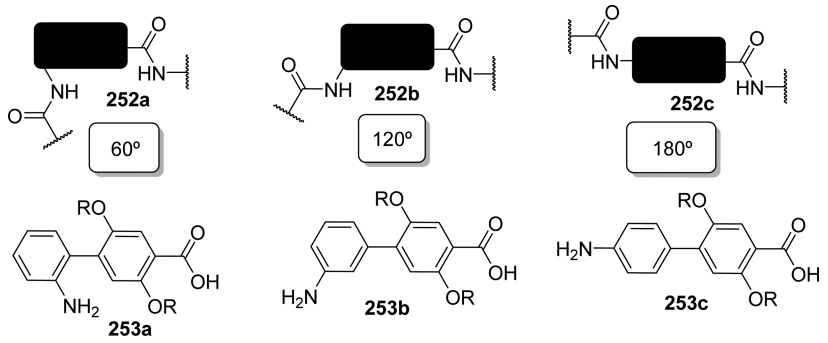

Figure 76. Building blocks for the preparation of the macrocycles designed by Nowick and co-workers.[278]

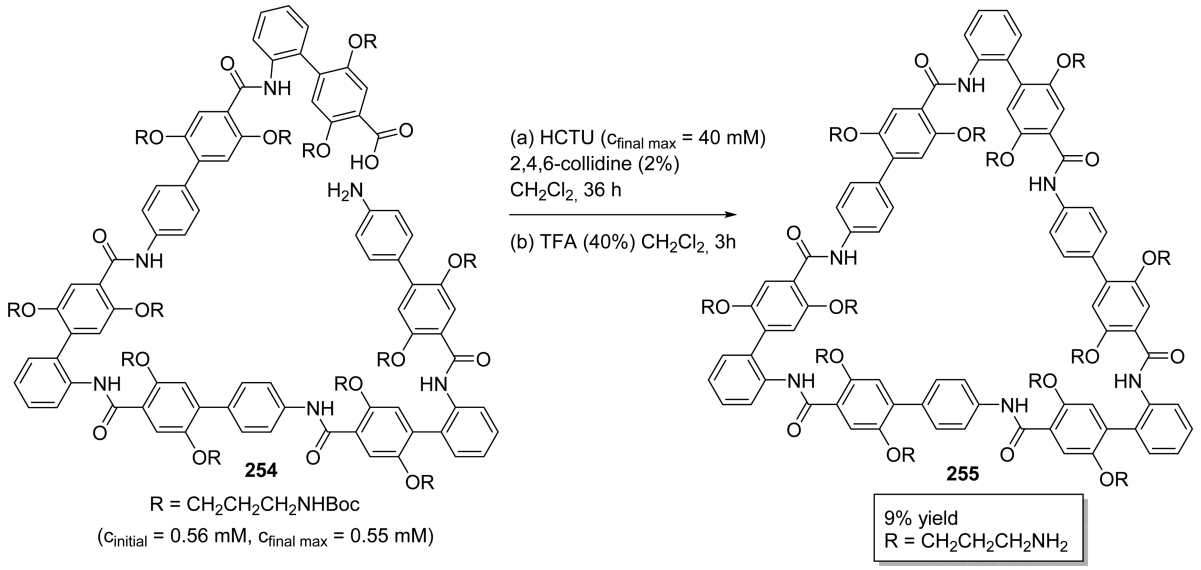

Figure 77. Synthesis of a cyclohexamer triangle from its open-chain precursor.[278]

and **250b**. The excellent yield was attributed to the formation of intramolecular three-center hydrogen bonds that direct the conformation of the open-chain oligomers favoring the formation of this particular 5-mer macrocyclic product **251** as the thermodynamically controlled product. The macrocyclization was assayed using a large excess of LiCl, NaCl, KBr, or CsCl, and in all cases only the 5-mer macrocycle was observed, which seems to disregard the participation of a metal template effect (Figure 75).[277]

Nowick and co-workers have prepared a series of different rigid water-soluble macrocycles of variable size and geometry (**255**–**263**) using three different non-natural amino acids (**253**) as difunctional building blocks providing diverse end-to-end angles between the functional groups present (**252**, Figure 76). The corresponding open-chain oligomers such as **254** were prepared by solid phase synthesis following a standard peptide synthesis protocol, and the macrocyclizations were assayed at 10 mM concentrations using collidine as the base after detachment from the resin (Figure 77). The HPLC analysis of the reaction mixtures revealed that they contained the desired macrocycles in good purity, which could be easily purified, in general, by RP-HPLC. The macrocycles **255**–**263**, of a nanometric scale, adopt geometries that can be termed as "triangles", "parallelograms", or "rings", ranging from a trimer **256** to a dodecamer **263**, with the ring sizes varying from 24 to 114 atoms (Figure 78, yields in the figure refer to the fraction isolated with a purity >98%).[278] The water solubility of the macrocycles was associated with the presence of ammonium groups in the side chains (R = $CH_2CH_2CH_2NH_3^+CF_3CO_2^-$).

5.1.4. Additional Factors for the Favorable Preorganization of Macrocyclic Precursors. Other intramolecular interactions able to provide or favor the adequate folding of the open-chain precursor(s) can also be important. Azumaya and co-workers provided examples proving the importance of aromatic–aromatic interactions in the synthesis of **266**. Thus, in Figure 79, the presence of $\pi-\pi$ interactions favors a folded conformation of the open-chain precursor **265a** (obtained from precursors **264** and **231b**) and the corresponding macrocycle **266a** was obtained in high yield. In contrast, these interactions are not possible using precursors **264** and **231c**, due to conformational constraints in the open-chain macrocyclic precursor **265b**, which results in a low macrocyclization yield for **266b** (Figure 79).[279]

Paleo, Sardina, and co-workers have reported a highly efficient method for the preparation in one step of bridged [*n*.2.2] bicyclic structures **270** by macrocyclization of the bis-enolate **269a** generated from the dimethyl anthracene-9,10-dicarboxylate **267** and a series of bis-electrophiles (**268**), thus combining a rigid component with a second more flexible subunit. The excellent macrocyclization yields observed can be attributed to the puckered conformation of the reaction intermediate **269b** formed after the first alkylation step that provides an appropriate geometry for the macrocyclization step (Figure 80).[280] Interestingly, in the case of using flexible subunits in the electrophile, yields were higher for the generation of smaller and

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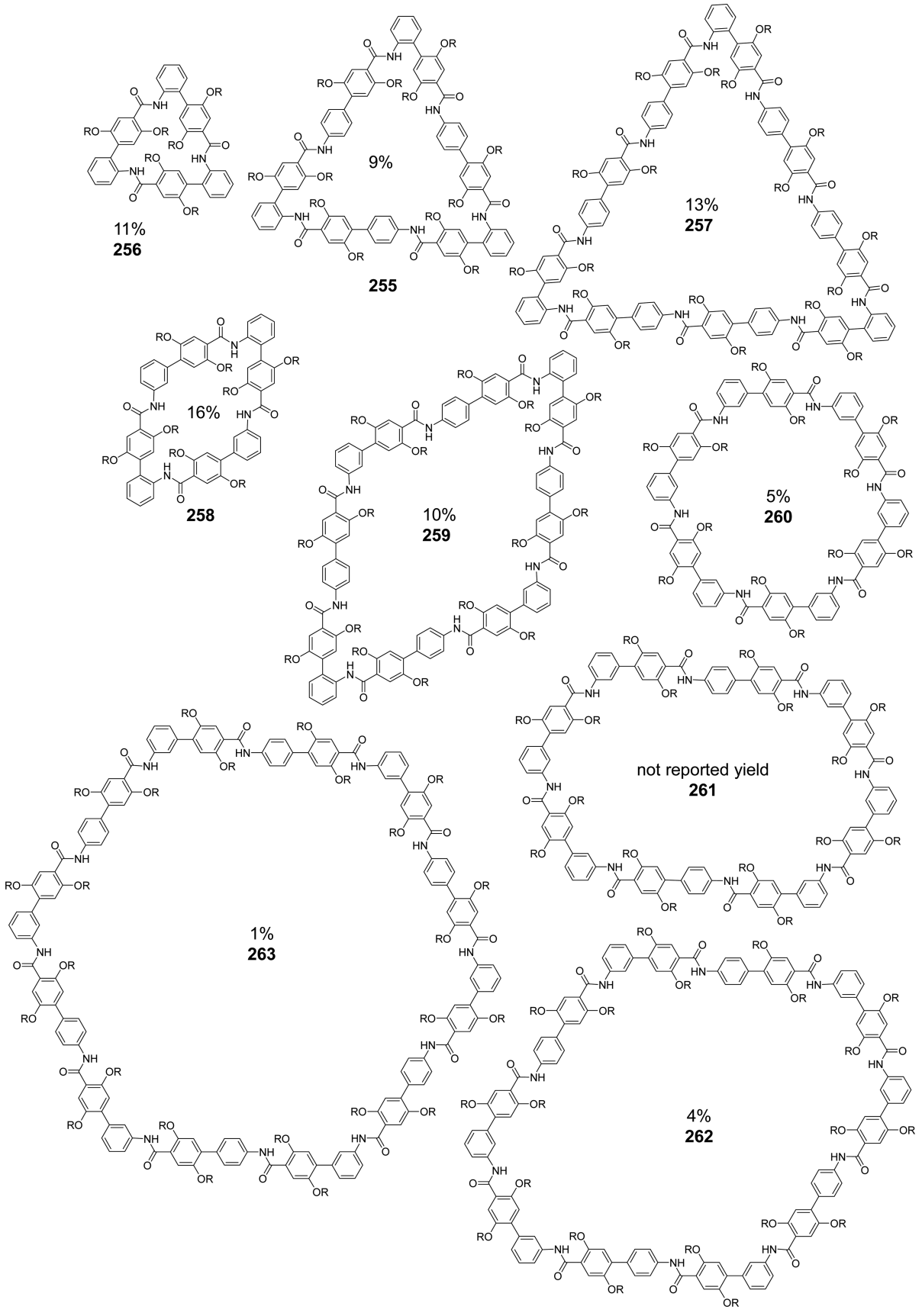

Figure 78. Different macrocyclic structures **255**−**263** obtained by Nowick and co-workers. Yields for the purified product (>98% purity) are given in each case.[278] R = $CH_2CH_2CH_2NH_2$.

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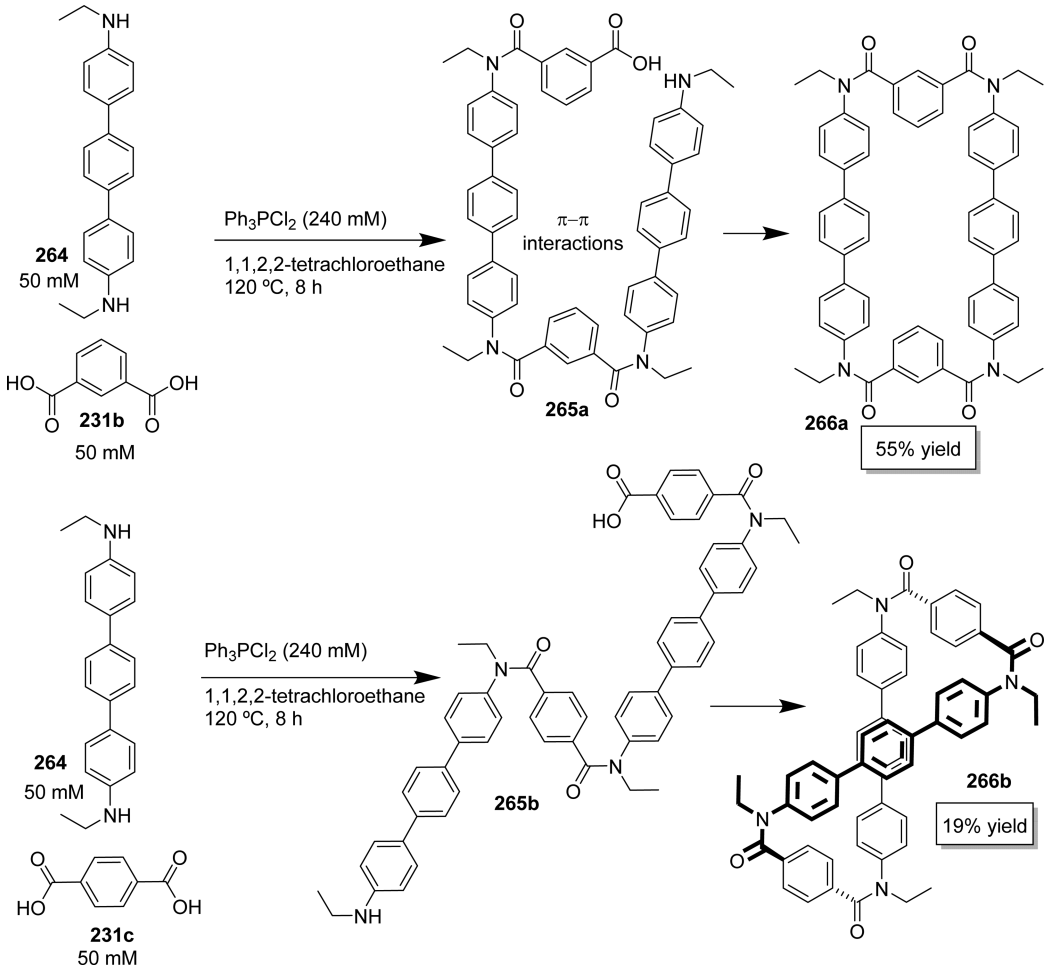

Figure 79. Importance of aromatic–aromatic interactions in the favorable preorganization of the reaction intermediate in the preparation of polylactane cyclophanes.[279]

larger rings, being smaller for medium-sized rings (0% for **268f** with n = 5, i.e., $Br(CH_2)_5Br$).

Davis and co-workers have described the synthesis of the [2 + 2] macrocyclic tetraamides **273a** and **276** and also the [3 + 3] macrocycle **273b**, under pseudo-high-dilution conditions using diamines **272** and **275** and activated diacids **271** and **274** as the building blocks (Figure 81).[281] The water-soluble compound derived from **273a** by hydrolysis of the *tert*-butyl ester groups was shown to be a simple and accessible synthetic lectin for glucose recognition and sensing. The overall yield for this receptor, considering also the deprotection step, was 23%, which can be compared with the 0.1% overall yield obtained, after 20 synthetic steps, for the preparation of a related octalactam cage developed by the same group for this purpose.[282] Smith and co-workers also prepared in 30% yield related tetraamides containing a different substitution pattern at the trisubstituted benzene subunit and being soluble in organic solvents.[283] The structure of the macrocycles and the expected intermediates suggest that aromatic interactions can be important in these examples.

Tetrametallic tetraaza macrocyclic compounds have been prepared, in some cases very efficiently, by Michael addition of different amines to α,β-unsaturated Fischer carbene complexes, taking advantage of the exceptional behavior as Michael acceptors of these α,β-unsaturated complexes.[284] In general, best cyclization yields, for [1 + 1] or [2 + 2] processes, were obtained when rigid building blocks based on aromatic spacers were used (Figure 82). Thus, the treatment of a rigid biscarbene **277** with the corresponding diamine **214b** in a 1:2 ratio at −78 °C followed, after the reaction was complete, by the addition of a second molecule of biscarbene **277** to **278** at low temperature afforded the [2 + 2] macrocycle **279** in 87% yield.[285]

The use, in open-chain macrocycle precursors, of rigid scaffolds of natural origin like steroids, in particular in combination with aromatic and/or acetylenic subunits, can provide systems affording macrocyclic structures in excellent yields.[286−289] Thus, the Glaser–Eglington coupling of dimeric concave estrone subunits **280** allowed the preparation of the corresponding tetrameric estrone-based macrocycles **281** in 60–77% yield in [1 + 1] macrocyclization processes (Figure 83).[290,291]

Appropriately disubstituted ferrocenes represent an excellent scaffold for the building of parallel chains preorganized in a folded conformation that favors macrocyclizations through reaction between their functional ends. The preparation of redox active ferrocene–peptide macrocycles **284** was reported by Kraatz and co-workers by reacting activated ferrocenedicarboxylic acid **282** with cystamine **283a** or with the appropriate amino acid–cystamine conjugate **283b**. The use of concentrations ≤2 mM was essential for obtaining reasonable yields (Figure 84).[292] In this case, the macrocyclization is based both in the use of high dilution conditions and in the presence of the

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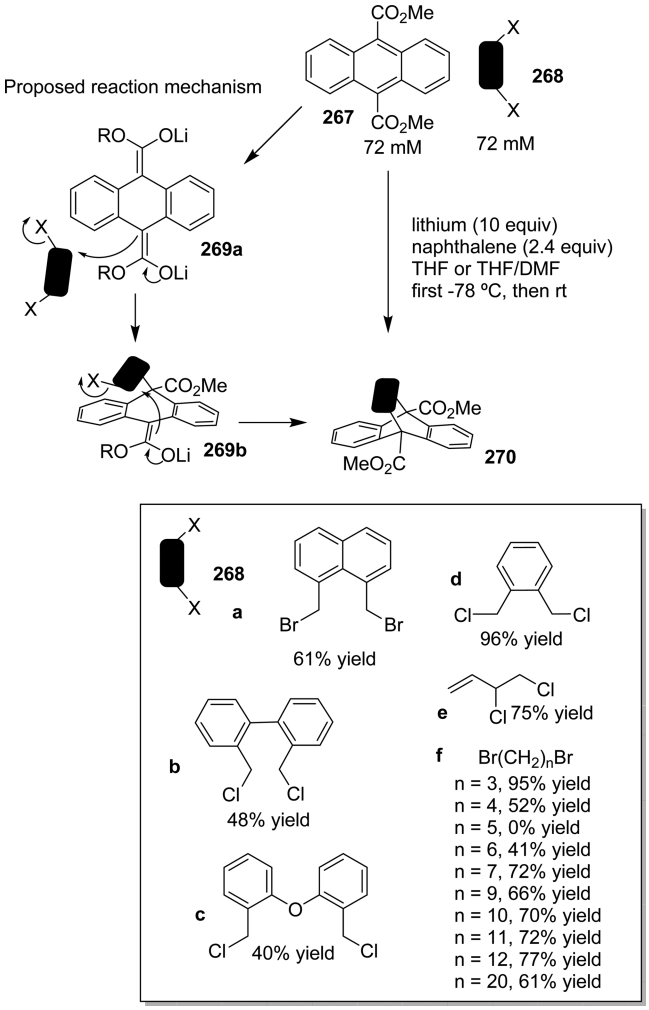

Figure 80. Synthesis of bridged macrocyclic structures.[280]

ferrocene subunit forcing the location of the two carboxylic subunits pointing to the same direction.

A similar approach was used by Beer and co-workers for the synthesis of amide ferrocene containing macrocycles capable of the electrochemical sensing of anions. By using high dilution conditions, reaction of activated diacid **285** with diamine **286** afforded the [1 + 1] macrocycle **287a** as the major product in 41% yield after chromatographic purification, while the [2 + 2] compound **287b** was isolated in 15% yield (Figure 85). This approach can also be connected with the preparation of related urea ferrocene macrocycles **290a** and **290b** containing lower-rim-substituted calix[4]arene subunits (Figure 86).[293] In this case, the calixarene scaffold can be considered a structural element also favoring the convergent orientation of the amine groups in **289** for the macrocyclization reaction with **288**.

Beer and co-workers have described the preparation of different ferrocene macrocyclic structures by the Eglinton coupling of the acyclic bis(alkyne) **291**. Under the reported reaction conditions, it is possible to obtain the monomeric macrocyclic product **293a** in 54% yield along with the [1 + 1] dimeric product **293b** in 12% yield. While methylation of the macrocyclic structure afforded the corresponding bis(triazolium) structures **294** as efficient receptors for benzoate and chloride in acetonitrile, all attempts to cyclize the open-chain bis(triazolium) **292** system failed (Figure 87).[294] In the last case, the electrostatic repulsion between the triazolium subunits seems to provide a divergent orientation of the chains, and accordingly of the alkyne fragments, that precludes cyclization.

Echavarren and co-workers have described how the correct conformation of precursors was key to determining the success of the gold(I) catalyst **296** for the intramolecular macrocyclization of 1,*n*-enynes (**295**). When a flexible spacer linking the alkene and the alkyne was present in the precursor **295a**, the macrocycle **297a** could not be obtained. On the contrary, precursors derived from *ortho* substituted aromatic rings (for example **295b**) afforded the corresponding macrocyclic structures (for example **297b**) in good yields (Figure 88).[295] The presence of the *ortho* substituted aromatic ring can reduce the degrees of rotational of freedom and orient the two reactive chains in the same direction, favoring again the cyclization.

Polymeric oligoesters represent an important family of polymeric materials, and different efforts have been carried out to understand the corresponding synthetic processes, including the formation of cyclic oligomers. Of particular relevance, in this context, are the processes involving salicylic acid derivatives, as the *ortho*-substitution pattern in the aromatic monomer again seems to provide a conformation of the growing open-chain intermediates with an appropriate geometry to favor the formation of cyclic oligomers. Thus, the vacuum thermolysis at 300−350 °C of acetylsalicylic acid afforded disalicylide and trisalicylide (**302**) in 9−30% yields,[296] while the thermal decomposition at 170 °C of 2-carboxyphenyl *p*-toluenesulfonate **301** or its salts has been shown to produce mixtures of oligosalicylides in which the trisalicylide (**302**) was the major component.[297] The polymerization of salicylic acid *O*-carboxyanhydride (SACA) **298**, on the other hand, has been also observed to produce cyclic poly(salicylide)s **300a** (with the linear polymer **300b** being also formed) under a variety of conditions. These include the thermal polymerization at 170 °C, the use of a highly nucleophilic carbene in dioxane at 20, 50, or 80 °C, or the imidazole-initiated polymerization at 140 °C involving intermediates **299a** and **299b** (Figure 89).[298−301]

5.1.5. Peptidic and Pseudopeptidic Macrocycles. Cyclic peptides have important applications in the pharmaceutical industry, but the cost for their efficient synthesis is often prohibitive and, therefore, the development of efficient methodologies for the cyclization of peptides is a critical target.[302] These macrocyclic structures have shown properties of interest in different areas such as transport across membranes, catalysis, gelators, organic nanotubes, recognition of important molecules, etc.[303,304] In particular, these amide-based ligands are excellently suited to act as receptors of anions, through the establishing of the corresponding supramolecular interactions with amide groups and the appropriate functional side chains.[305−307] Four possible synthetic approaches can be considered for the macrocyclization of an open-chain peptide (see **303** in Figure 90): (a) side chain to side chain,[308] (b) head to side chain,[309,310] (c) tail to side chain, and (d) head to tail.[70] In many instances, the formation of an amide bond takes place in the macrocyclization step, but other reactions can also be involved.[311] Excellent macrocyclization yields have been reported in many instances for the synthesis of cyclic peptides, which have been often attributed to the presence of appropriate folded conformations of the corresponding precursors approaching the reactive ends and therefore favoring entropically the macrocyclization reaction. Different factors can be involved in promoting this favorable folding, including, as exemplified above, the formation of intramolecular hydrogen bonds. However, the presence of specific structural elements favoring the formation of adequate

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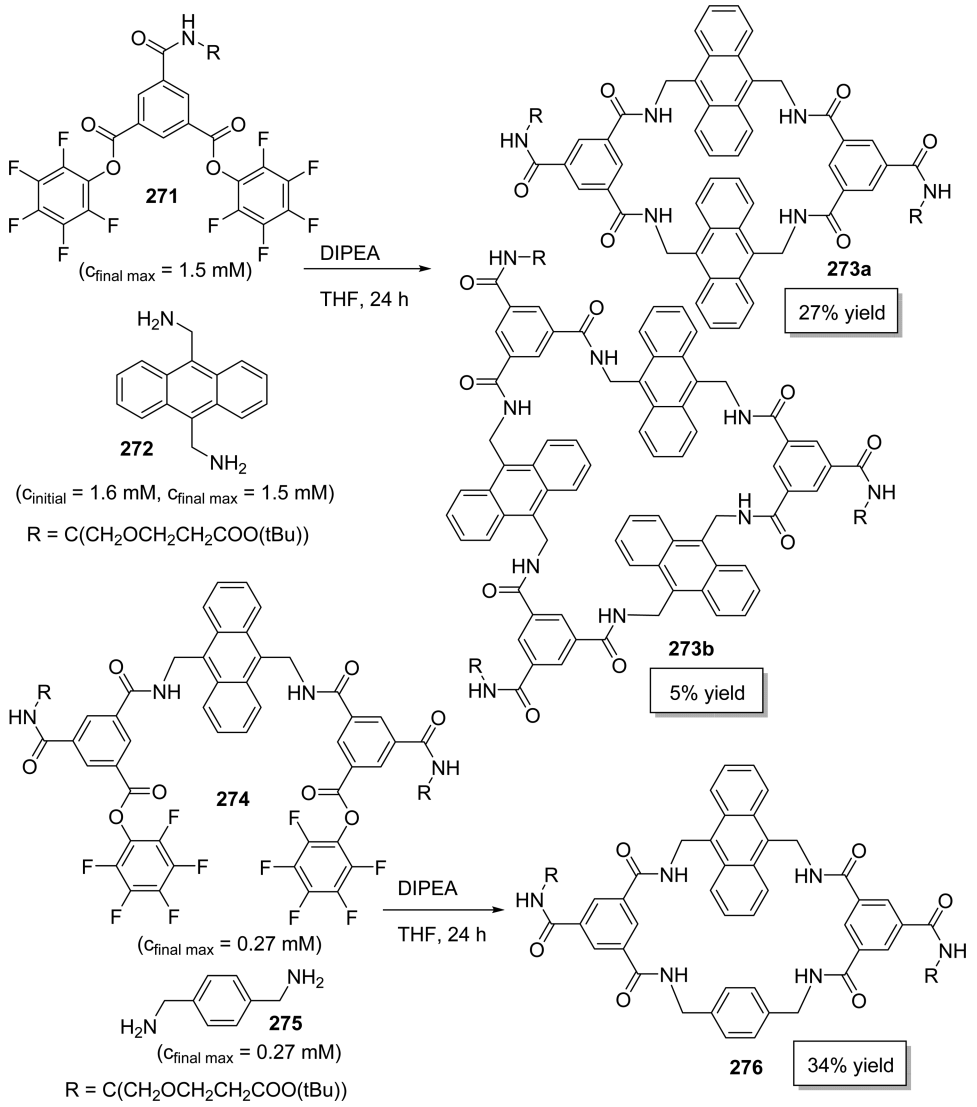

Figure 81. Synthesis of fluorescent macrocyclic tetraamides.[281]

foldamers can be of key importance.[312,313] The presence of chiral centers can also be prominent, but this has only been analyzed in detail in a few cases as will be discussed in section 5.2.

The head to tail cyclization represents the most frequent approach in this field, and different emerging strategies have been developed to access peptide macrocycles, incorporating in some cases nonproteinogenic fragments. The efficient preparation of seven- and eight-membered cyclic dipeptides and 10-membered cyclic tripeptides containing α-, β-, or γ-amino acid residues has been effected by a Staudinger-mediated ring closure involving the generation of the appropriate starting azido dipeptide thioesters. This allowed obtaining difficult medium-sized cyclic peptides in 51−73% yields.[314] Smythe and co-workers have reported the synthesis of highly strained cyclic tetrapeptides through the introduction of the 2-hydroxy-6-nitrobenzyl (HnB) auxiliary group at the N-terminus and in the "middle" of the peptidic sequence. The first auxiliary attached to the N-terminus performs a ring closure/ring contraction role (Figure 91). The cyclization of the HnB N-terminally substituted tetrapeptide **304** initially generates a less strained (more accessible) but reactive cyclic nitrophenylester intermediate **305**, which then experiences a ring contraction via an O-to-N acyl transfer to generate the desired, substituted, cyclic tetrapeptide structure **306**. In this way, the N-terminus HnB auxiliary increases the effective concentration of the reactive ends entropically favoring the macrocyclization reaction and reducing the competitive dimerization. On the other hand, the second HnB group attached to the middle backbone nitrogen atom acts as a *cis*-amide bond promotor facilitating the otherwise difficult ring contraction.[315] Finally, the HnB groups could be removed from the amide backbone by photolysis to obtain the final macrocycle **307**. A similar approach was also originally applied to the synthesis of less strained cyclic pentapeptides.[316,317]

Pentelute and co-workers have reported a side chain to side chain peptide macrocyclization via S_NAr cysteine perfluoroarylation. From the 98 macrocycles prepared, more than half could be prepared in macrocyclization yields greater than 90%, using a 0.1−2 mM concentration of the open-chain peptides.[318] A similar approach has been described by Tam and co-workers, who described the amide-to-amide transpeptidation of cysteine containing peptides.[319] The presence of reactive side chains often provides a further element of complexity for designing successful macrocyclization protocols for peptides. However, Li and co-workers have described the macrocyclization reaction of a peptide **308** with unprotected side chains that did not interfere with the serine ligation-mediated macrocyclization used,

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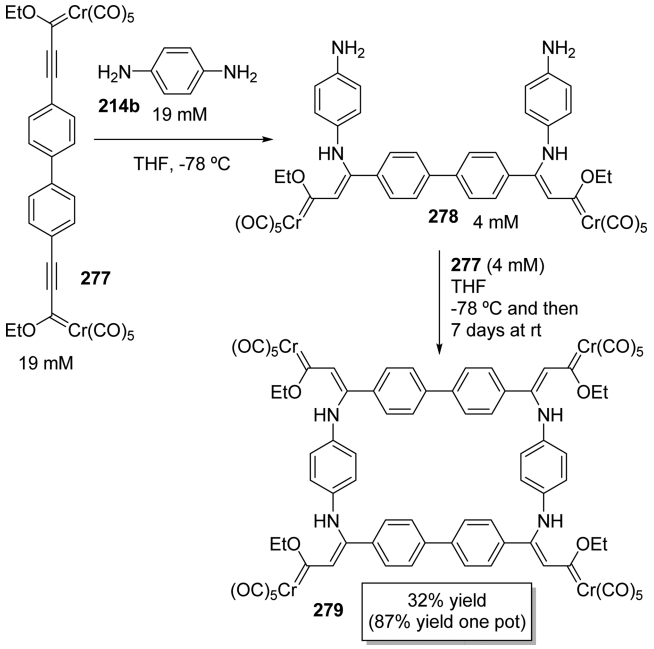

Figure 82. Synthesis of tetrametallic tetraaza macrocycles.[285]

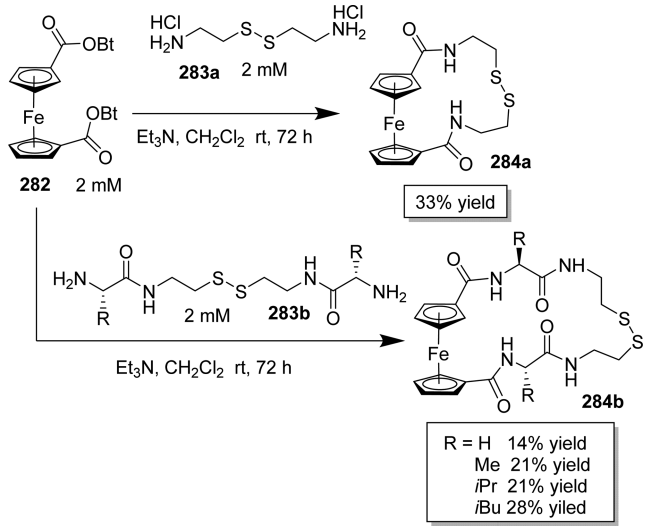

Figure 84. Synthesis of redox-active ferrocene−peptide macrocycles.[292]

allowing obtaining a 67% yield of the desired macrocycle **309** (Figure 92). The reaction was performed at a range of concentrations from 5 to 50 mM, being the monomeric cyclic peptide the only observed product.[154]

Most of the studies on the cyclization of peptides clearly reveal the importance of the exact peptidic sequence for the success of the macrocyclization. In the example reported in Figure 91, the change on one single amino acid (from Gly to Ala) made the cyclization unsuccessful.[315] Pei and co-workers, using combinatorial peptide libraries, have analyzed the on-resin macrocyclization efficiency of more than 2 million peptide sequences.[320] They have determined the effects of the ring size, the amino acid sequence in the open-chain precursor, and the solvent on the macrocyclization reaction.[321−323] The formation of medium and large macrocycles (cyclohexapeptides and larger) with PyBOP is very efficient for ≥99.96% of the sequences. In contrast, the formation of small-sized (cyclotetrapeptides and cyclopentapeptides) is significantly less efficient and, in this case, the formation of cyclic dimers was observed.[320]

In the case of cyclic peptoids the size of the macrocycle is also critical. An example of the efficient macrocyclization of a family of open-chain peptoids incorporating alternating *N*-methoxyethyl and *N*-phenylmethyl side chains in glycyl oligomers has been reported by Kirshenbaum and co-workers (Figure 93).[324] They studied the effect of the length of the open-chain oligomeric peptoids related to **310** on the cyclization yields and found that this process was quite efficient (89−97% yields, 97% for **311**) for a broad range of sizes ranging from the pentamer to the 20-mer. Only for the tetramer the yields were significantly lower (12%). The cyclization is not only more efficient than those assayed with related peptides, but also very fast, the reaction being complete

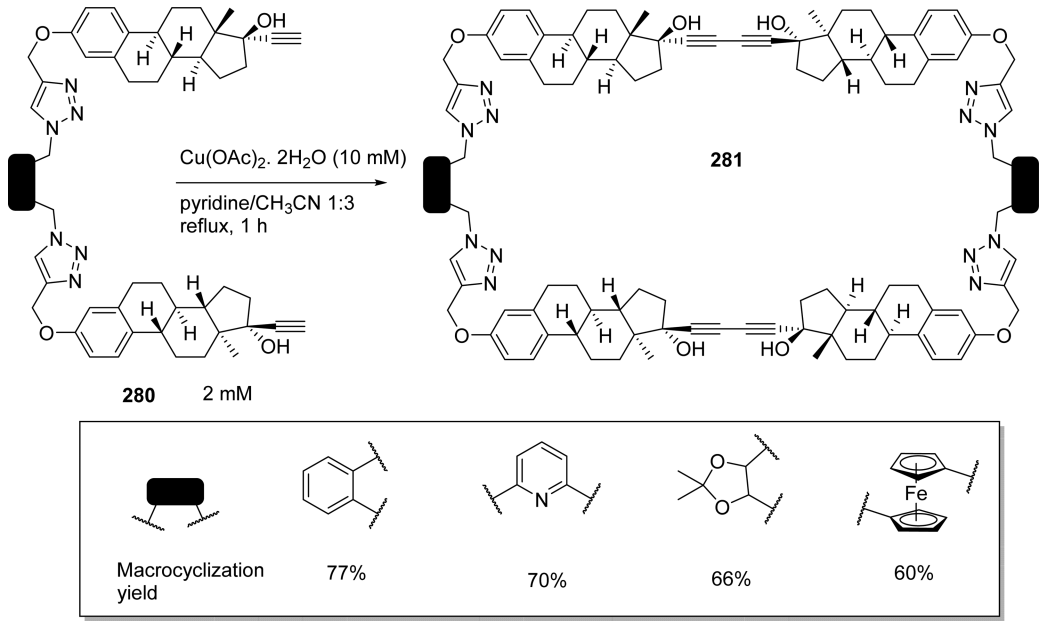

Figure 83. Synthesis of tetrameric estrone-based macrocycles.[290]

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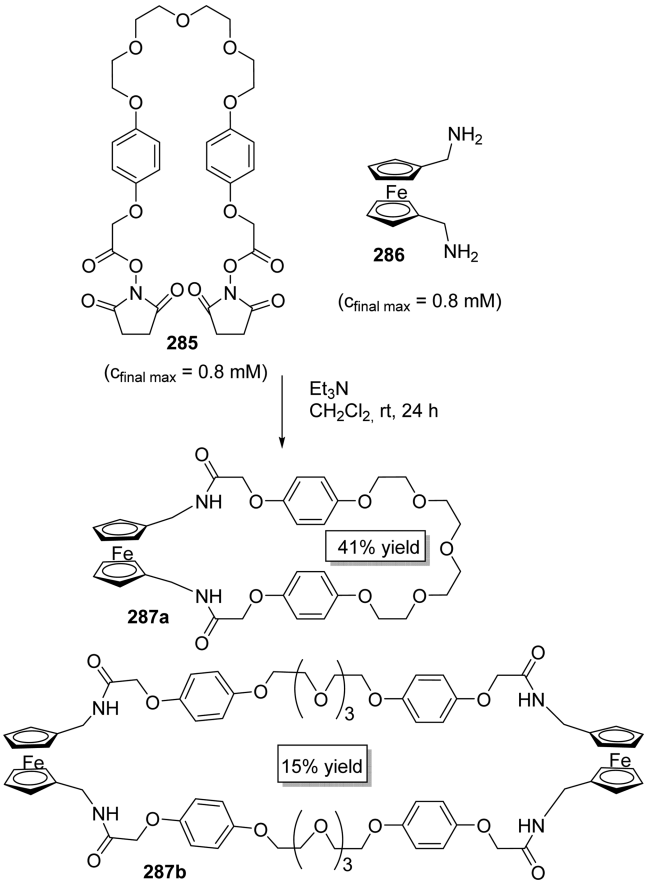

Figure 85. Preparation of amide ferrocene containing macrocycles.[293]

after 5 min at room temperature. This has been attributed to the reduction of the energy barrier for the interconversion between *cisoid* and *transoid* amide forms, facilitating the adoption of the U-turn folded structures required for cyclization. A similar behavior has been reported for peptides incorporating N-alkylated amino acid residues.[186,302,325,326] The nature of the N-substituents can also play a role in the proper organization of the folded intermediate. As observed in the crystal structure of the macrocycles, very preorganized systems can be attained with the two different (polar and apolar) residues situated on opposing sites and the phenyl rings providing intramolecular aromatic−aromatic interactions.[324,327] Interestingly, Zhang and co-workers demonstrated that cyclic poly(α-peptoid)s with controlled polymer molecular weights (MWs), narrow MW distributions, and in high purity can be synthesized by a ring opening polymerization of a N-substituted *N*-carboxylanhydride.[328]

The synthesis of conformationally constrained macrocyclic pseudopeptides from ribosomally derived polypeptides has been reported.[329] In many of the examples provided, the cyclization takes place after the release of the peptidic sequence from the ribosome and often involves the incorporation of the non-proteinogenic fragment. Fasan and co-workers have studied the macrocyclization reaction, making emphasis in the structure−reactivity relationships, of different organo-peptide hybrids using a dual bio-orthogonal ligation. The effect of the designed mutations within the genetically encoded precursor peptide sequence on the macrocyclization efficiency was fully investigated. Macrocyclization experiments were carried out using open-chain precursors **312**, with sequences of 4, 5, 6, 8, 10, 12, and 15 amino acids, and different oxyamine/amino-thiol synthetic precursors **313**. Results indicate that, for all of the variants, the desired macrocycles **315** were obtained, through intermediates **314a** and **314b** and the released of **314c**, as the only cyclic product. The macrocyclization yields ranged from 10 to 100% (Figure 94). The effect of the $i-1$ amino acid of the macrocycle precursor **313** on the macrocyclization process is critical. This position must provide low susceptibility to hydrolysis and high reactivity toward macrocyclization. Most of the 20 amino acids tested were compatible with the generation of the expected macrocyclic organo-peptide hybrids, but significant differences in the overall yields could be observed in some cases, as shown by the following average cyclization yields: Phe and Tyr (90%); Ala and Thr (70−75%); Trp, Asn, Arg, and Gln (50−60%); Met, Ser, Cys, and Glu (40%).[330] It must be noted that, in this case, the cyclization involves a formal tail to side chain process.

Open-chain peptidic precursors with folded conformations based on the presence of structural turn elements (e.g., Pro) approximate both N and C ends and usually show elevated cyclization efficiencies.[331,332] On the contrary, sequences with basic and polar residues next to the N-terminal residue (N-terminal Thr and an Arg-His-Ser motif) have been shown to be difficult to cyclize.[333] The combinatorial analysis carried out by Pei and co-workers revealed that peptides that are difficult to cyclize are generally rich in Lys(Boc) and Arg(Pbf) residues. Besides, the presence of sterically hindered residues at the N-terminus [e.g., Thr(*t*Bu)] also makes the macrocyclization difficult.[320] Therefore, the preparation of the appropriate open-chain peptidic precursor having a reduced steric hindrance at both ends can be a key issue, as has been observed in the synthesis of viequeamide A, a natural cyclic depsipeptide.[334] Substitution of the *N*-amide, and in particular N-methylation, also has a direct influence on the macrocyclization process as well as on the macrocycle conformation.[335,336] Open-chain precursors containing alternating D- and L-amino acids also show an increased macrocyclization efficiently, presumably because of less steric clashes among the side chains.[320,337−339] The cyclization efficiency can be improved by using aqueous additives that can break the hydrogen bonds of functional side chains with the C-terminal carboxylic group that could reduce its reactivity.[320] The presence of Gly residues can also complicate the adoption of the proper folded conformation. Ichikawa and co-workers have reported the synthesis of Quinaldopeptin-related macrocycles by the macrocyclization of the open-chain peptide containing the less sterically hindered Gly residue as the N-terminus and L-Pip as the C-terminus, using diphenylphosphoryl azide (DPPA) and $NaHCO_3$ in DMF (5 mM) for 6 days, although this procedure provided the desired cyclic peptide in low yields (18%) along with its epimer (27%).[340]

As could be expected, the macrocyclization is facilitated when the transition state geometry has a nonstrained geometry leading to the formation of the macrocycle.[341] Therefore, a computational analysis can allow planning the synthetic route that has a less strained transition state to obtain the desired macrocycle with the optimum yields.[70] As has been mentioned, the presence of structural elements providing a reverse turn in the protein secondary structure is a key element in this regard, as this strongly affects the distance between the two reactive ends in the linear precursor.[342] This is clearly illustrated by the important differences observed in macrocyclization yields obtained, using the same cyclization approach, when the different possible ring disconnections are considered for the same cyclopeptide **316**

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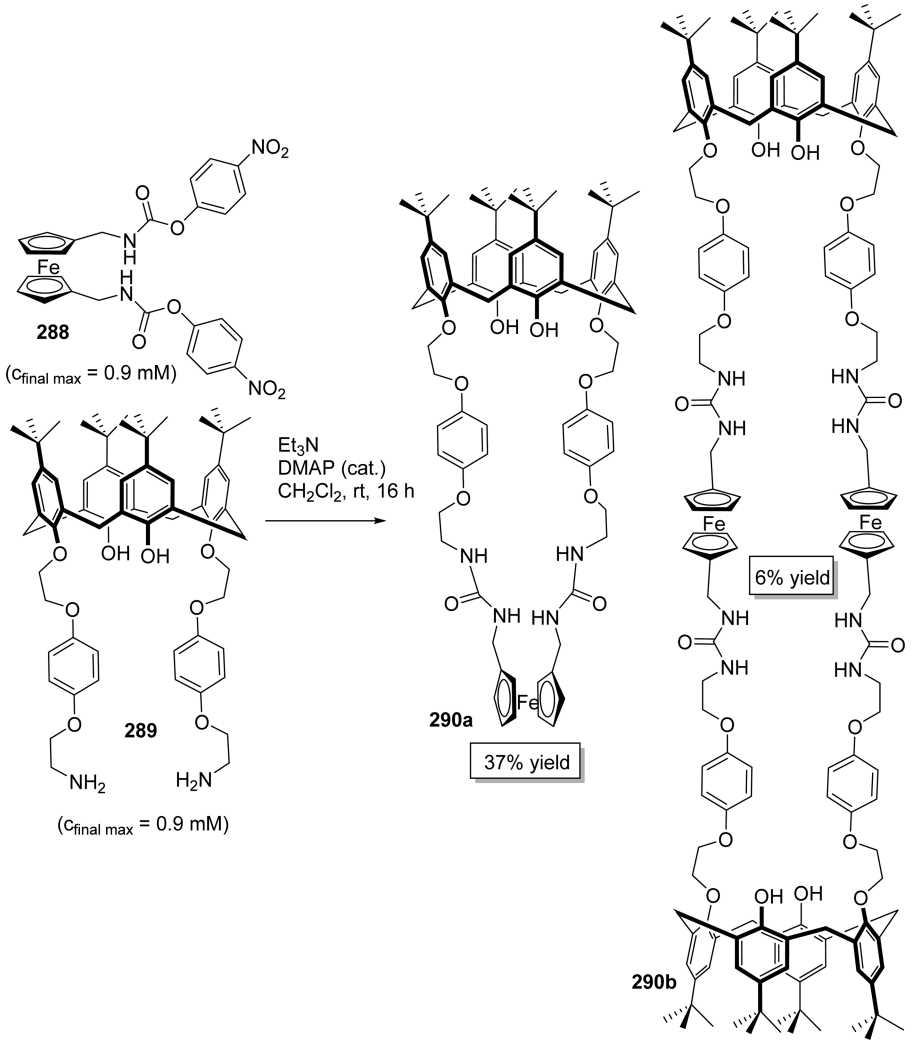

Figure 86. Preparation of urea ferrocene containing macrocycles derived from a lower-rim-substituted calix[4]arene.[293]

(*cyclo*-[Pro-Ala-Ala-Phe-Leu]) (Figure 95).[70,343] The *cis*-amide conformation associated with the Pro residue and the formation of a strong intramolecular hydrogen bond is the required feature defining the proper folding of the precursor.

The efficient macrocyclization of C_2-symmetric pseudopeptides has also been reported by the [1 + 1] reaction of the corresponding open-chain diamines **317** with bishalomethyl arenes **111** in the absence of high dilution conditions (Figure 96).[344−346] The expected cyclic products **319** are obtained essentially as the only major product in 49−69% yields after a thorough purification protocol. The folded conformation of the key intermediate **318** seems to be based on both the formation of intramolecular H-bonds and the presence of solvophobic effects. As a result, the two reactive ends of the open-chain reaction intermediate **318** are in close proximity favoring the macrocyclization reaction versus the competing oligomerization reactions. In addition, in this case, the exact nature of the amino acid side chain plays an important role in defining the conformation of the reaction intermediates **318** and, therefore, in the macrocyclization process.[347] The reaction is applicable to the preparation of macrocyclic pseudopeptides displaying a variety of central spacers and aromatic rings.[348−357]

A similar approach can be used for the highly efficient preparation of small pseudopeptidic three-dimensional cages **322** from simple precursors through the triple S_N2 reaction between tripodal tris(amido amines) **320** and several 1,3,5-tris(bromomethyl)benzene electrophiles **321** (Figure 96). The success of the macrobicyclization strongly depends on the central triamine scaffold in the open-chain tripodal precursor **320**. The nature of this motif dictates the correct preorganization of the intermediates in such a way that in the case of tren derivatives **320a** the corresponding cages **322a** can be obtained in 20−50% yields after chromatographic purification. However, when pseudopeptides **320b** derived from trisubstituted aromatic compounds were used, the expected cages **322b** could not be isolated from the reaction mixture. These cages **322a** are able to selectively encapsulate the chloride anion and participate in its transport through biomimetic lipidic membranes (Figure 97).[358,359]

Gellman, Freire, and co-workers have reported a similar trend in the preparation of macrocyclic parallel β-sheet peptidic macrocycles, for which the peptidic sequence of the open-chain precursors favors a folded conformation.[312,360] The synthesis of these compounds was carried out on resin, using standard coupling reagents in the final macrocyclization reaction (PyBOP, HOBt, DIPEA in DMF).[361] Very nicely, for the structures shown in Figure 98, the open-chain system **323** showed NOE contacts similar to those of the macrocyclic structure **324**, providing strong evidence for the occurrence of the appropriate folded conformation of the precursor. This was directly related to the

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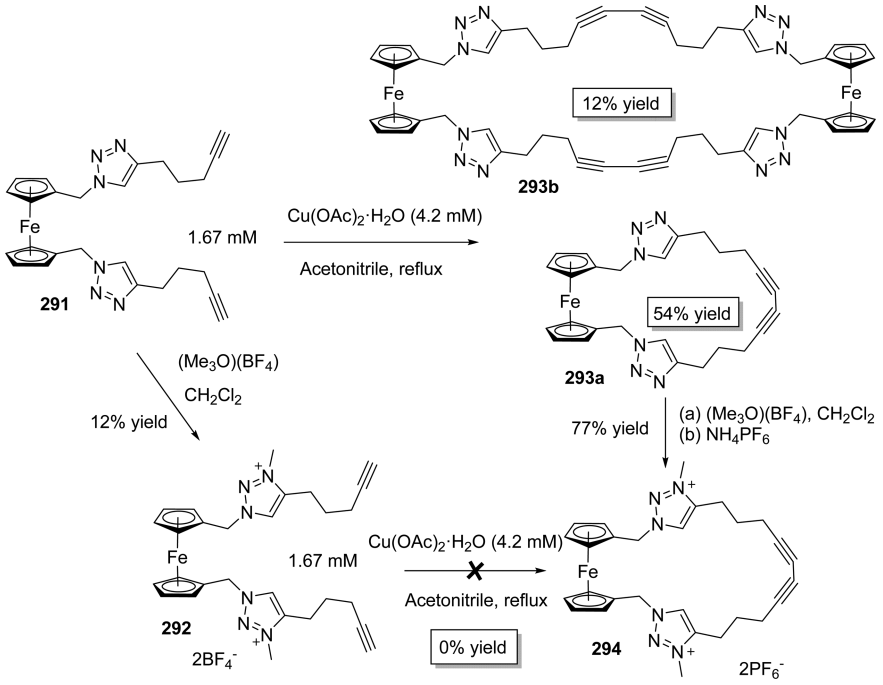

Figure 87. Synthesis of ferrocene macrocycles by Eglinton coupling.[294]

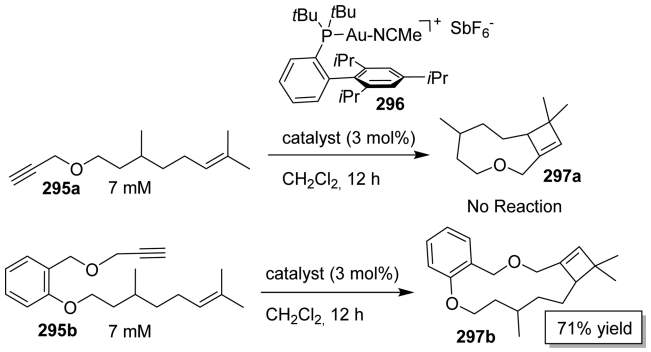

Figure 88. Gold(I) catalyzed macrocyclization of 1,*n*-enynes.[295]

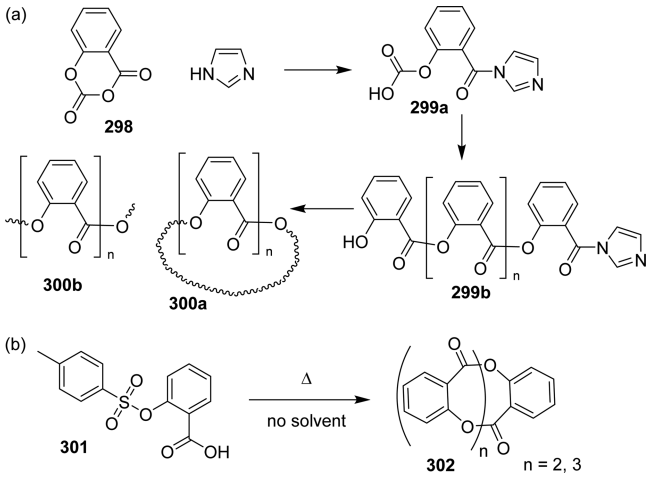

Figure 89. Synthesis of polyester macrocycles. (a) Simplified mechanism of the imidazole-initiated formation of the macrocyclic polyester compounds **300a**.[298−301] (b) Thermal decomposition of 2-carboxyphenyl *p*-toluenesulfonate **301**.[297]

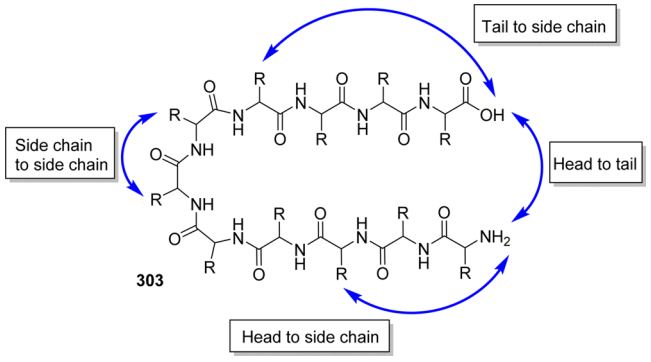

Figure 90. Different strategies for the preparation of cyclic peptides.[70]

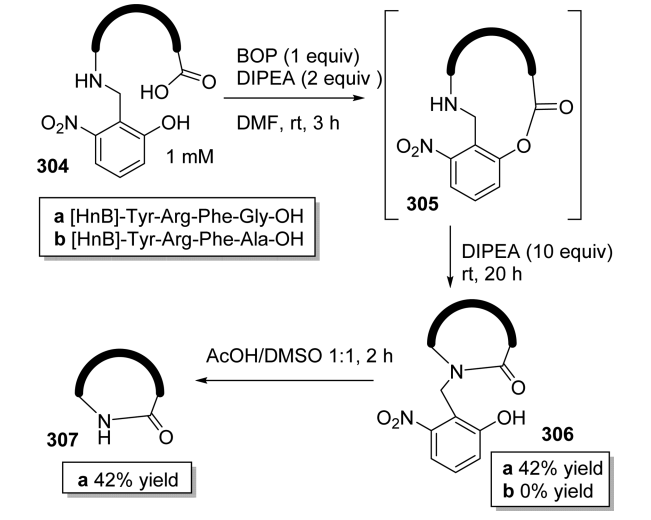

Figure 91. Preparation of cyclic peptides using the 2-hydroxy-6-nitrobenzyl (HnB) auxiliary group.[315]

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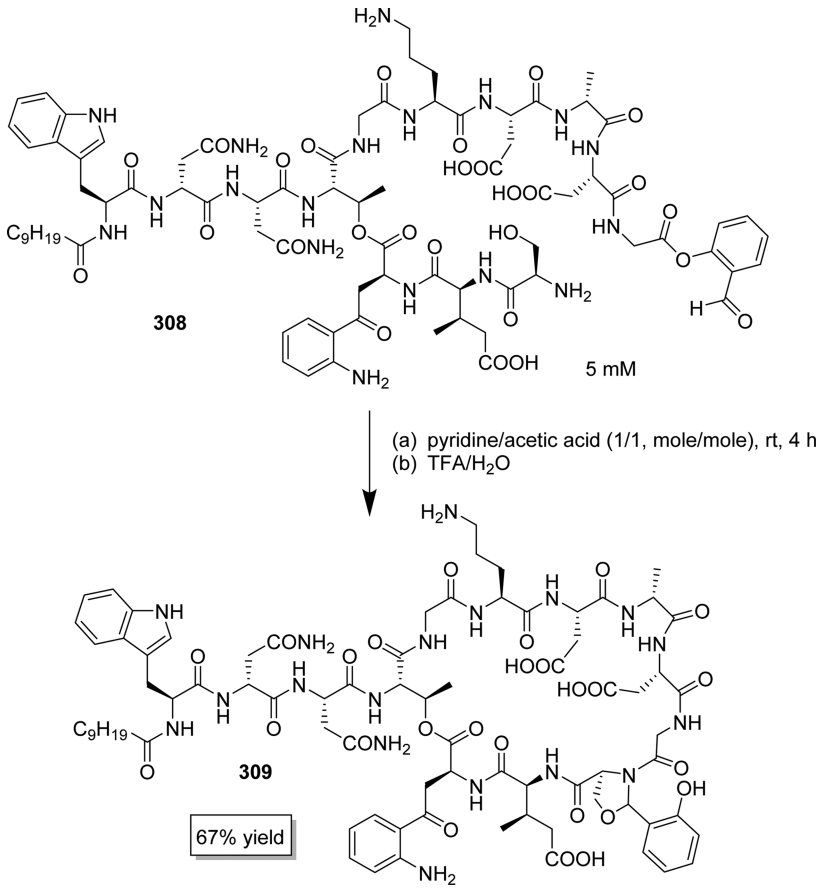

Figure 92. Macrocyclization reaction of a peptide with unprotected side chains.[154]

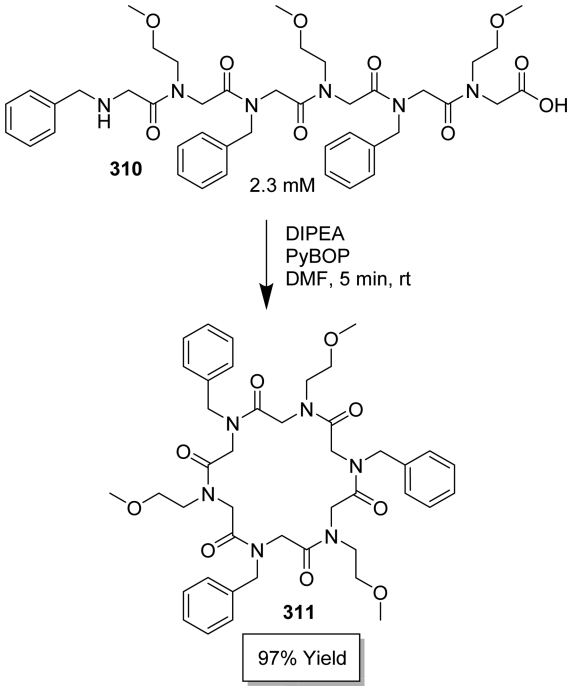

Figure 93. Macrocyclization of a tetrameric glycyl peptoid **310** with alternating *N*-methoxyethyl and *N*-phenylmethyl side chains.[324]

presence of specific nonpeptidic fragments that can produce a fold in the geometry of the linear peptide and promote the formation of parallel β-sheet folded fragments in the peptide strands. Albericio and co-workers have reported other turn inducers such as Cys pseudoprolines. They found that this Cys-protection approach can be conveniently used in SPPS, but simultaneously, they could observe that this structural motif clearly favors the on-resin macrocyclization of linear peptides related to two α-conotoxins (CnIB and A1.4). Complete macrocyclization was observed in the peptides containing Cys pseudoproline, whereas the related peptides with standard Cys amino acid protection only showed 52−70% macrocyclization yields.[362] The results suggest that the secondary amide introduced by the thiazolidine fragment leads to a more thermodynamically favorable *cis* rotamer, which may achieve a less strained transition state, increasing the reaction rate for the macrocyclization reaction.

Chiba and co-workers have described an efficient soluble tag-assisted liquid-phase approach toward peptide head-to-tail cyclization. This strategy uses an amide nitrogen atom for the introduction of the tag (**326**), instead of using the most common C-terminus tagging; this allows retaining the tag during the cyclization. This favors the solubility of the tag-functionalized open-chain precursor **325** in less polar solvents, which facilitates the adoption of the appropriate folded conformation. This results not only in a fast macrocyclization, but also in a simplified isolation of the macrocyclic compound. In the example described in Figure 99, using the C-terminus tag conventional approach, the presence of a high number of hydrophobic residues in the peptide backbone favors aggregation in polar solvents. However, when this C-terminus tag is removed, the required folding of the open-chain precursor is not attained. With the new N-amide tagging methodology, it was possible to prepare the correspond-

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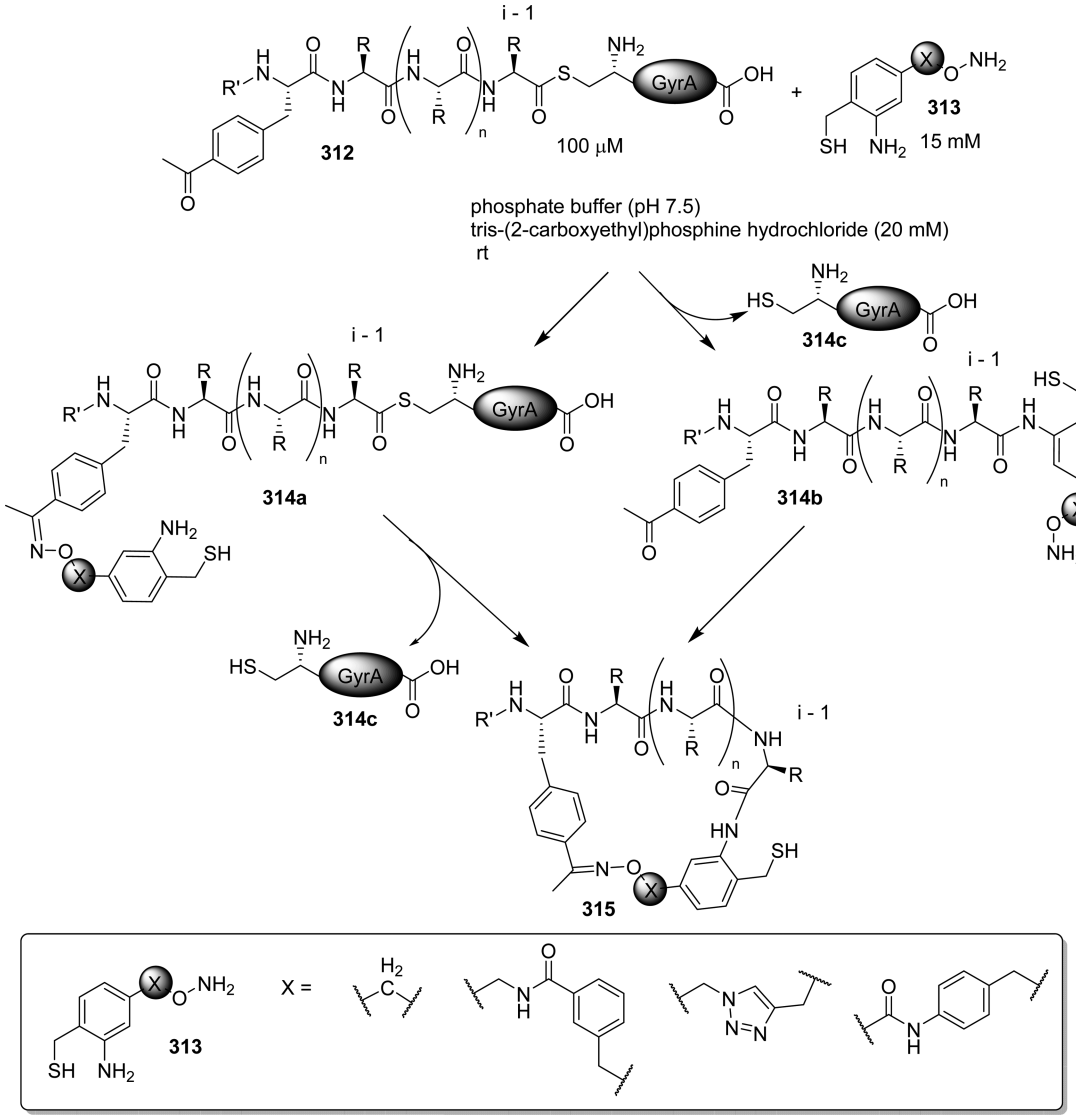

Figure 94. Mechanistic pathways for the generation of macrocyclic organo-peptide hybrids. GyrA = mini-intein from *Mycobacterium xenopi* (N198A variant); R′ = chitin binding domain; R = different amino acid sequences randomly chosen (4-, 5-, 6-, 8-, 10-, 12-, 15-mer) that include a representative subset of the 20 natural amino acids.[330]

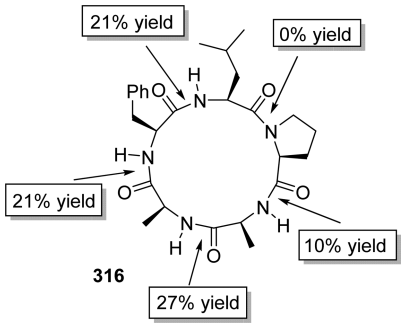

Figure 95. Yields obtained in the synthesis of *cyclo*-[Pro-Ala-Ala-Phe-Leu] structure (**316**) using pentafluorophenyl ester activation methods when different ring disconnections are considered. Reaction conditions: 0.9 mM pentapeptide activated ester in $CHCl_3$/1 N aqueous $NaHCO_3$ (2:1 solvent mixture).[70,343]

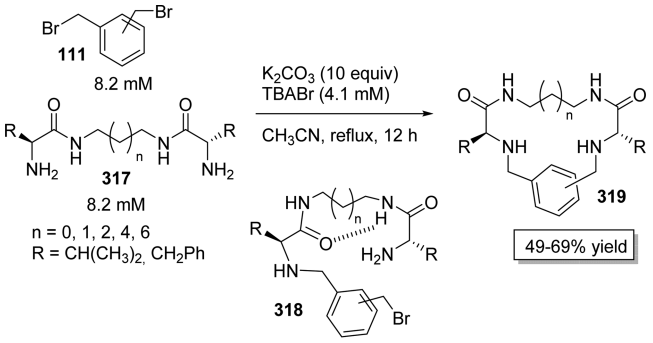

Figure 96. Efficient macrocyclization of C_2-symmetric pseudopeptides in a [1 + 1] process.[344]

ing macrocyclic compound **327** in 74% yield.[363] Removal of the N-tag could be carried out very efficiently with TFA in the example provided (76%) affording the antimalarial cyclic heptapeptide, mahafacyclin B.

It has been reported that short linear peptides can adopt a circular conformation based on the ion pairing between the N-

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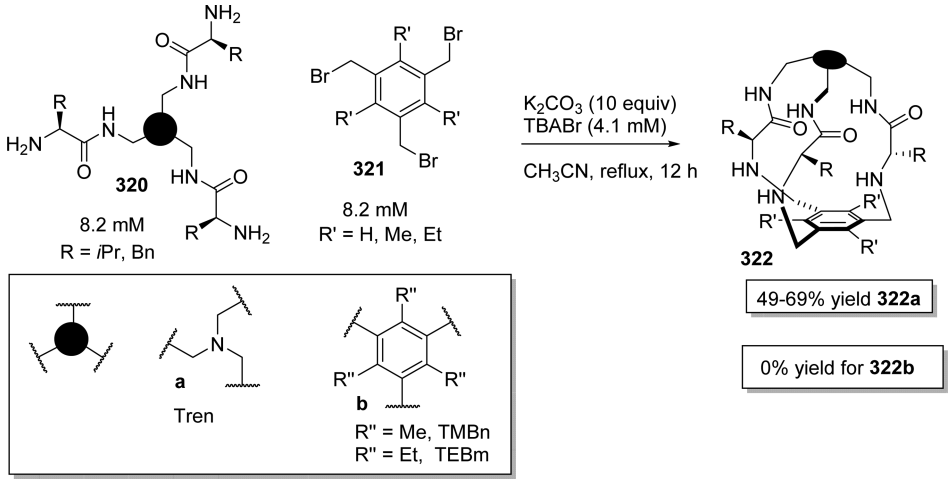

Figure 97. Efficient macrocyclization of C_3-symmetric pseudopeptides in a [1 + 1] process.[358,359]

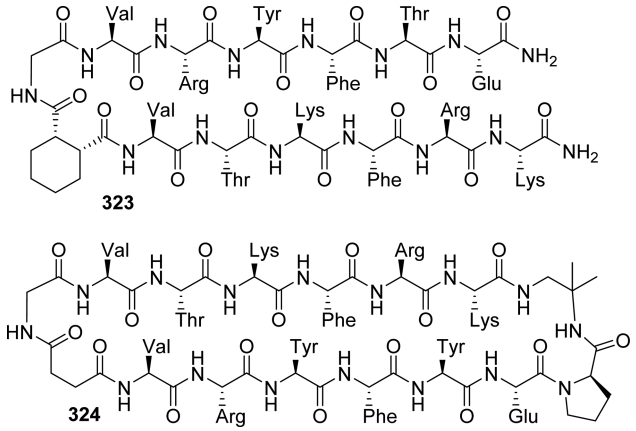

Figure 98. Comparison of folded structures in an oligomeric open-chain pseudopeptide and the related macrocycle.[360,312,361]

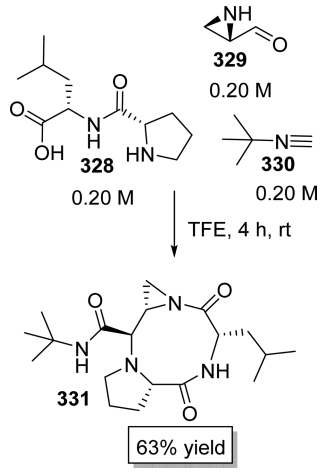

Figure 100. Synthesis of macrocyclic peptides from linear peptide precursors **328**, isocyanides **330**, and aziridine aldehydes **329**.[366]

and C-termini.[364] Thus, the unfavorable entropy factor involved in the adoption of the corresponding circular conformations required for the macrocyclization reaction can be overcome by the favorable enthalpy associated with the presence of intramolecular electrostatic and other polar interactions.[365] Yudin and co-workers have reported the synthesis of macrocyclic peptides **331** from linear peptide precursors **328**, isocyanides **330**, and amphoteric aldehydes (aziridine aldehydes) **329**, as is illustrated in Figure 100. It has been observed that the presence of the nucleophilic center at the α-position of the amino aldehyde **329** is essential for the high yields and stereoselectivities obtained. The synthesis and isolation of the macrocyclic product **331** is straightforward as it involves a three-component−one-pot procedure in which the analytically pure cyclic derivative **331** can be isolated directly by precipitation from the reaction mixture. Besides, the presence of the activated aziridine ring in the cyclic

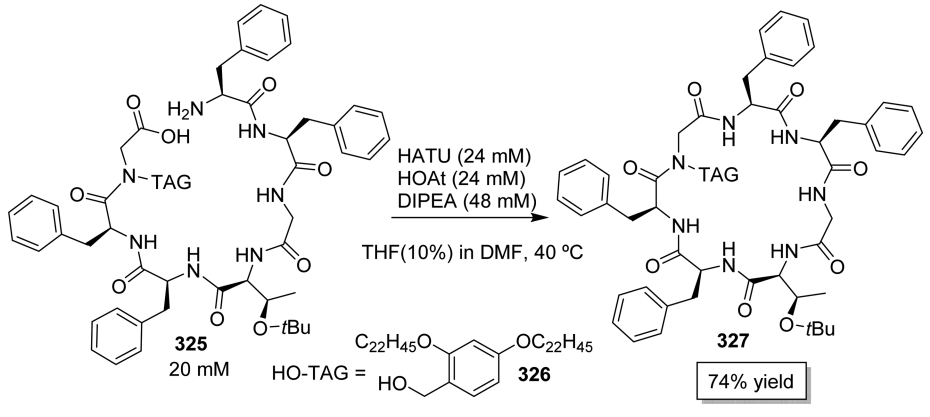

Figure 99. Macrocyclization reaction using hydrophobic N-tags to favor the cyclization.[363]

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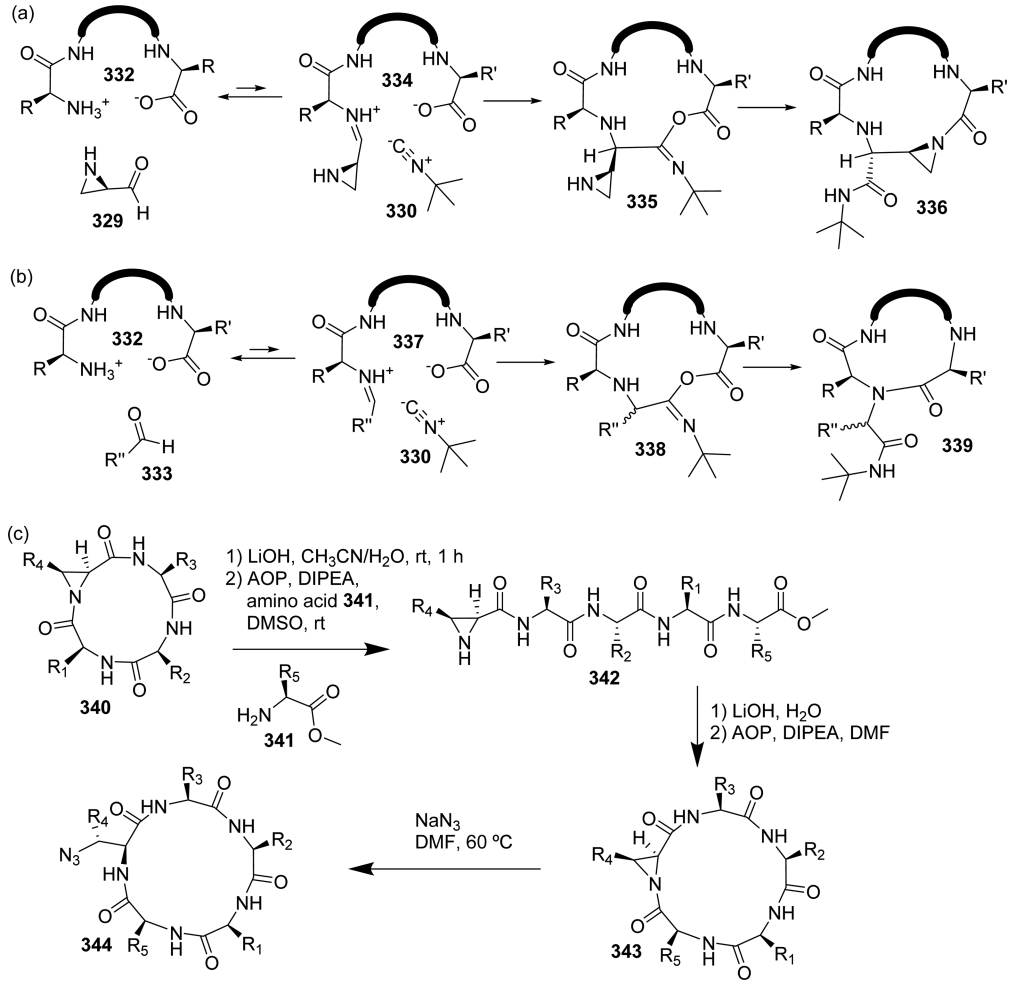

Figure 101. Comparison of macrocyclization processes based on the Ugi three-component reaction. (a) Amphoteric amino aldehyde **329**, high yields and only one diastereoisomer.[365] (b) Monofunctional aldehyde **333**, low yields and mixture of diastereoisomers. (c) Ring expansion of cyclopeptides **340** containing the aziridine subunit.[367] AOP: 7-(azabenzotriazol-1-yl)oxy tris(dimethylamino) phosphonium hexafluorophosphate.

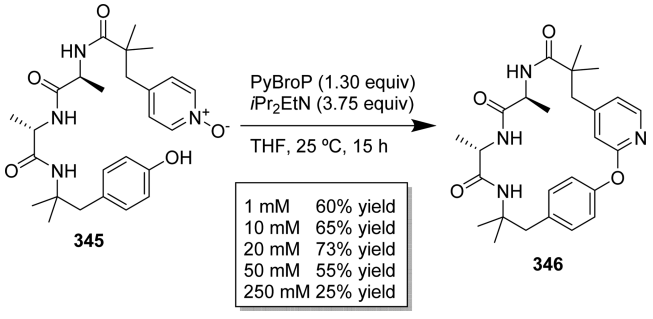

Figure 102. Head to side chain macrocyclization using the phenol group of a tyrosine residue. PyBroP: bromo-tris-pyrrolidinophosphonium hexafluorophosphate.[368]

peptide provides a useful functionality for the introduction of additional side chains via its nucleophilic ring opening. Taking into account the modular character of this approach, the preparation of a large variety of macrocyclic structures can be considered by modification of one or several starting materials (peptides, isocyanides, aziridine aldehydes, and/or the nucleophiles used for the aziridine ring opening).[366]

Thus, following this protocol, the macrocyclization of a variety of linear peptides **332** using isocyanides **330** and aziridine aldehydes **329** has been reported. The process involves

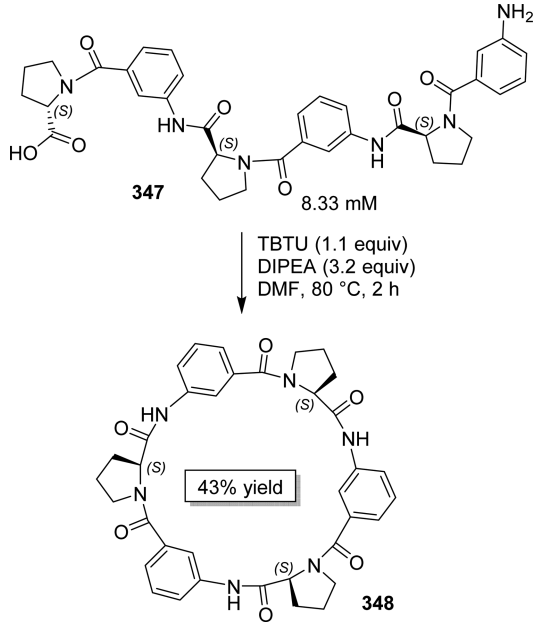

Figure 103. Synthesis of *cyclo*[(L)Pro-AB]$_3$.[371]

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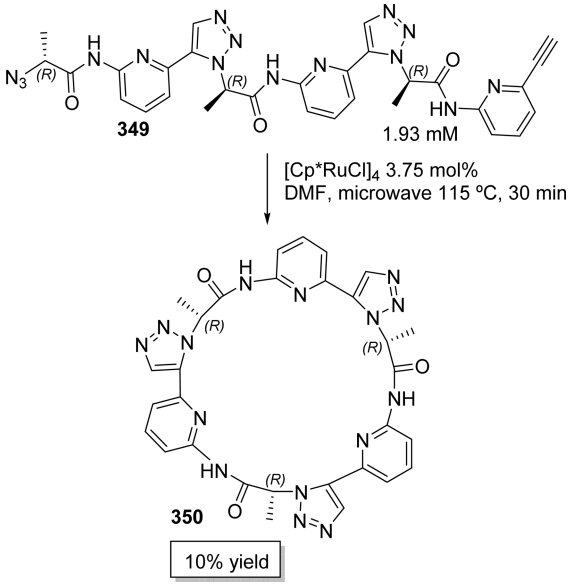

Figure 104. Cyclization of a pseudohexapeptide by click chemistry.[374]

intermediates **334** and **335** that afford cyclic structures **336** (Figure 101a).[365] This synthetic method does not require high dilution conditions and yields ranging from 73 to 88% can be attained, using 0.2 M initial concentrations of reactants, with reaction times from 2 to 9 h. In general, no byproducts are detected in the isolated product after the simple isolation workup and the procedure is significantly more efficient than the related process using simple monofunctional aldehydes **333** for the Ugi macrocyclization that results in low yields and a mixture of diastereoisomers for macrocycles **339** formed through intermediates **337** and **338** (Figure 101b). Very interestingly, a natural or non-natural amino acid (**341**) can be used as the nucleophile for the site-specific integration of fragments into macrocyclic peptides, using the reduced amidicity of aziridine amide bonds, and leading to the ring expansion of the cyclopeptides **340** and making possible the introduction of some nonpeptidic elements in the macrocycle. The reaction mechanism involves an open-chain intermediate **342** that upon cyclization forms macrocycle **343** that when treated with NaN_3 yields the final macrocyclic compound **344** (Figure 101c).[367]

Londregan and co-workers have reported a novel procedure for the macrocyclization of linear peptides to obtain a variety of pseudopeptidic cyclic structures as illustrated for **346** in Figure 102. In this approach, the functional side chains of the natural amino acids tyrosine (phenol), lysine (alkylamine), and histidine (imidazole) react intramolecularly with the pyridine-*N*-oxide group of a carboxamide attached to the N-terminus of the peptidic sequence, in a process that can be considered as a head to side chain cyclization. This methodology employs the PyBroP activator, and both the concentration of the open-chain precursor and the solvent affect the macrocyclization yields. For the case displayed in Figure 102, the best results in THF (73% yield) were obtained for a 20 mM concentration of the open-chain precursor **345**, whereas more diluted or more concentrated reaction conditions resulted in lower yields (1 mM, 60% yield; 10 mM, 65% yield; 20 mM, 73% yield; 50 mM, 55% yield; and 250 mM, 25% yield).[368]

Kubik and co-workers have studied in detail a variety of C_3 symmetric macrocyclic pseudohexapeptides for cation and anion recognition. The structural design is based on the presence of 3-aminobenzoic (AB) or 2-aminopicolinic (AP) acids as rigidifying elements. The corresponding head to tail macrocyclizations were always carried out under high dilution conditions.[369,370] In this context, the structure **347** based on an alternate sequence of 3-

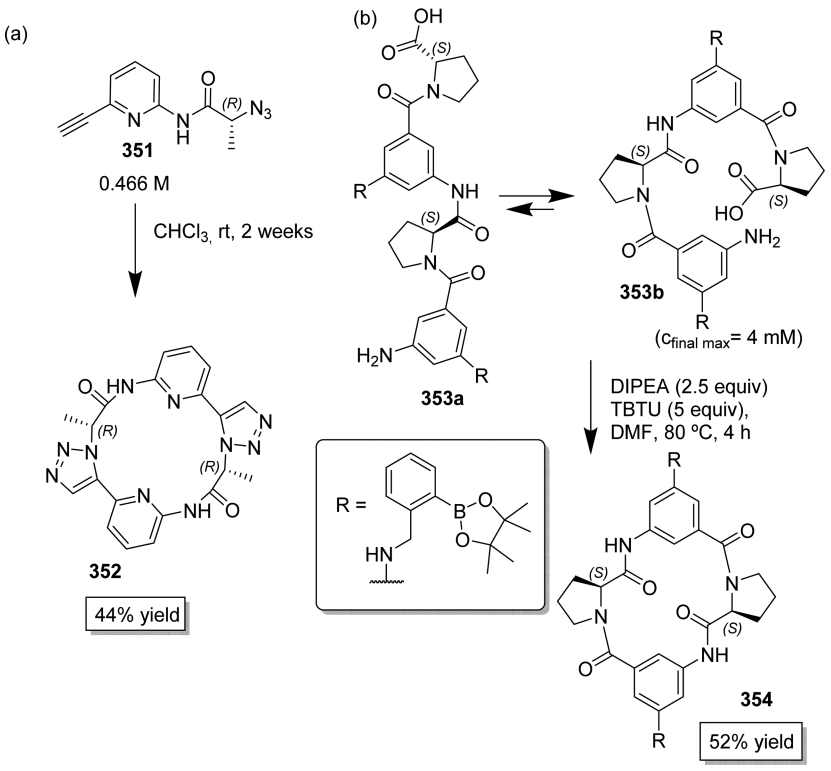

Figure 105. Preparation of cyclic pseudotetrapeptides by (a) azide−alkyne cycloaddition[375] and (b) amide bond formation.[376]

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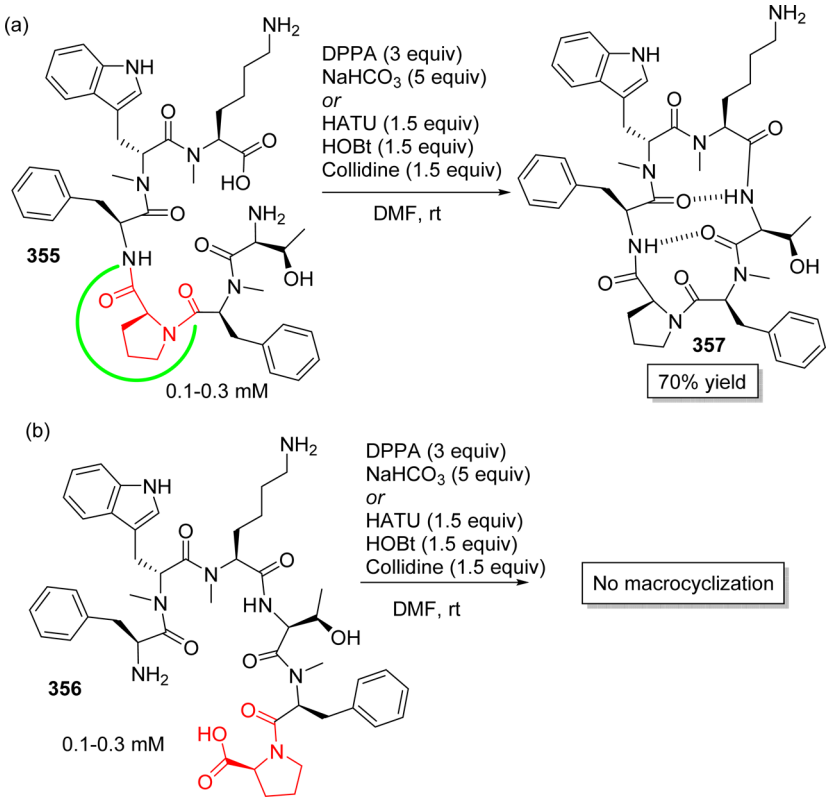
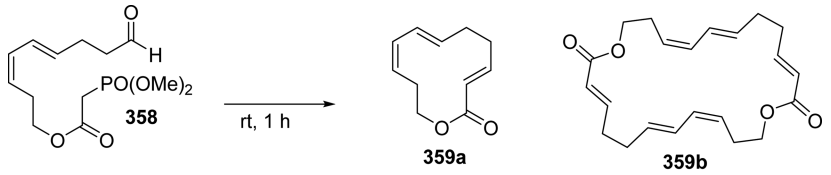


Figure 106. Influence of the ring disconnection in the efficiency of the synthesis of the cyclohexapeptide *cyclo*(−PFMewMeKTMeF−) **357**. (a) Favored macrocyclization reaction. (b) Disfavored macrocyclization reaction.[378−380]



		Macrocyclization Yield	
1.3 mM	K_2CO_3, 18-C-6, toluene	0%	65%
1.3 mM	LiHMDS, THF	0%	36%
1.3 mM	LiCl, DBU, THF	13%	60%
1.7 mM	$Zn(OTf)_2$, TMEDA, Et_3N, THF	78%	9%

Figure 107. *E*-selective Wadsworth−Emmons macrocyclization.[381] 18-C-6 = 18-crown-6.

aminobenzoic (AB) acid and (L)-proline ((L)Pro) fragments was designed to display a well-defined convergence of the NH amide groups, which is a well-suited feature for the efficient recognition of anions. At the same time, the presence of the proline moieties can also provide a favorable preorganization element to facilitate the cyclization. Thus, by using similar conditions, the corresponding *cyclo*[(L)Pro-AB]$_3$ **348** was isolated in 43% yield (Figure 103).[371] Similar results were obtained for related systems containing substituted AB fragments,[372,471] as well as when the 2-aminopicolinic acid was used instead of the AB moiety.[373]

Interestingly, the substitution of the proline subunits by 1,5-disubstituted 1,2,3-triazole rings also provides the appropriate convergent arrangement of the amide groups to improve the binding affinity of the macrocycles to anions (Figure 104). The corresponding macrocycles like **350** could be obtained with the use of several Ru-catalyzed azide−alkyne cycloaddition reactions, including the key cyclization process that was carried out under microwave irradiation. The obtained macrocycle **350** displays a stronger interaction with anions than the parent peptidic macrocycles (for example **348**).[374] However, the substitution of the proline by triazole subunits seems not to provide appropriate conformations of the open-chain precursor **349** for the macrocyclization reaction, as this resulted in the isolation of the product in lower yields (10%) (Figure 104).[374]

The same group, however, was able to efficiently prepare smaller pseudotetrapeptidic macrocycles by the cyclodimerization process of **351** involving a double thermal azide−alkyne cycloaddition that provided the cyclic structure **352** in 44% yield after crystallization (Figure 105).[375] The observed conformation in the crystallographic structure for this macrocycle (**352**) is fully comparable with that of the related *cyclo*[(L)Pro-AB]$_2$ **354**, a compound belonging to a series of cyclopeptides previously

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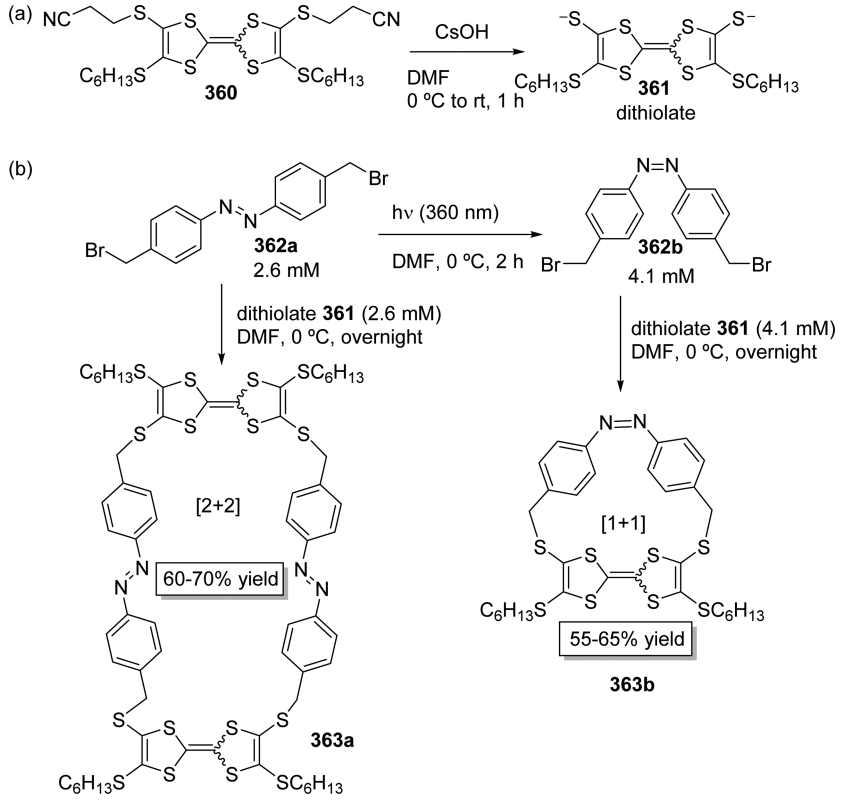

Figure 108. Light-controllable macrocyclization reaction. (a) In situ synthesis of dithiolate. (b) Macrocyclization reaction.[382]

discussed, which preparation, in yields up to 52%, required pseudo-high-dilution conditions (Figure 105). This reveals the importance of structural elements that facilitate the appropriate turn to the pseudopeptidic sequence (compare conformations **353a** and **353b**) resulting in good macrocyclization yields.[376,377]

Kessler and co-workers have described a protocol to prepare N-methylated cyclic peptides that consists of the preparation of the open-chain precursor by solid phase synthesis, including the N-methylation step, and then performing the macrocyclization in solution after detachment from the resin in a head to tail process. Again, they found that it is crucial to select the appropriate cyclization site to favor the correct folding of the linear peptide. The selection of an inappropriate ring disconnection may lead to low macrocyclization yields or to no cyclization at all. In this regard, amino acids that induce turns can be used to favor these folded conformations of the linear peptide reducing the end-to-end distance in solution.[378] Thus, for example, for the preparation of biologically active mono and multiply N-methylated somatostatin analogues,[379] it was observed, as displayed in Figure 106, how the linear peptidic sequence **355** containing a proline residue at the central part of the sequence afforded good yields (70% of macrocycle **357**) in the cyclization process under high dilution conditions. This was associated with the ability of the proline to strongly induce a βVI turn (Figure 106a). This turn is not present, however, when the proline is located at the C-terminus and, in this case, the linear peptide **356** fails to cyclize (Figure 106b). The N-methylation is an important element for the biological activity of these derivatives, but an increase in the number of N-methylations was found to decrease the final yields for the synthesis of the cyclic peptides. The presence of N-methylated amide groups can clearly decrease the number of intramolecular H-bonds, making difficult the appropriate folding of the linear precursor.[378−380]

5.2. Configurational Preorganization

Configurational preorganization can be considered as the one associated with the stereochemical configuration of the different structural elements in the open-chain precursor. In most cases, the configuration of stereogenic centers is the key element, but other stereochemical elements can also be of importance. A simple example is provided by the different preorganization provided by *E*-/*Z*-stereoisomers. Thus, Nagorny and co-workers have described the synthesis of a strained macrocycle by a Horner−Wadsworth−Emmons macrocyclization (Figure 107). The adequate stereochemistry of the diene fragment at the starting material **358** is needed for the appropriate cyclization. The reaction is *E*-selective regarding the formation of the new double bond, and the different reaction conditions allow the preparation of the monomeric (**359a**) and the dimeric (**359b**) macrocyclic products as the major components of the final mixture. The monomeric macrocyclic product **359a** was found to be unstable, easily polymerizing when stored in neat state, most likely because of the high strain present in this structure.[381]

Böckmann, Azov, and co-workers have reported the first example of a light-controllable macrocyclization reaction. This method is based in the isomerization of *E*- and *Z*-azobenzene producing a significant change in the distances between the terminal $-CH_2-$ groups. This directs the macrocyclization reaction with dithiolate **361** (obtained in situ from precursor **360** by removal of the bis-cyanoethyl groups with CsOH) toward the [2 + 2] macrocyclic product **363a** for the *E*-azobenzene **362a** and toward the [1 + 1] macrocyclic product **363b** for the *Z*-azobenzene **362b** (Figure 108).[382]

On the other hand, the univocal identification of a favorable preorganization based on the configurational elements, in particular when chiral elements are involved, is not always simple. Preferentially, we will consider under this section

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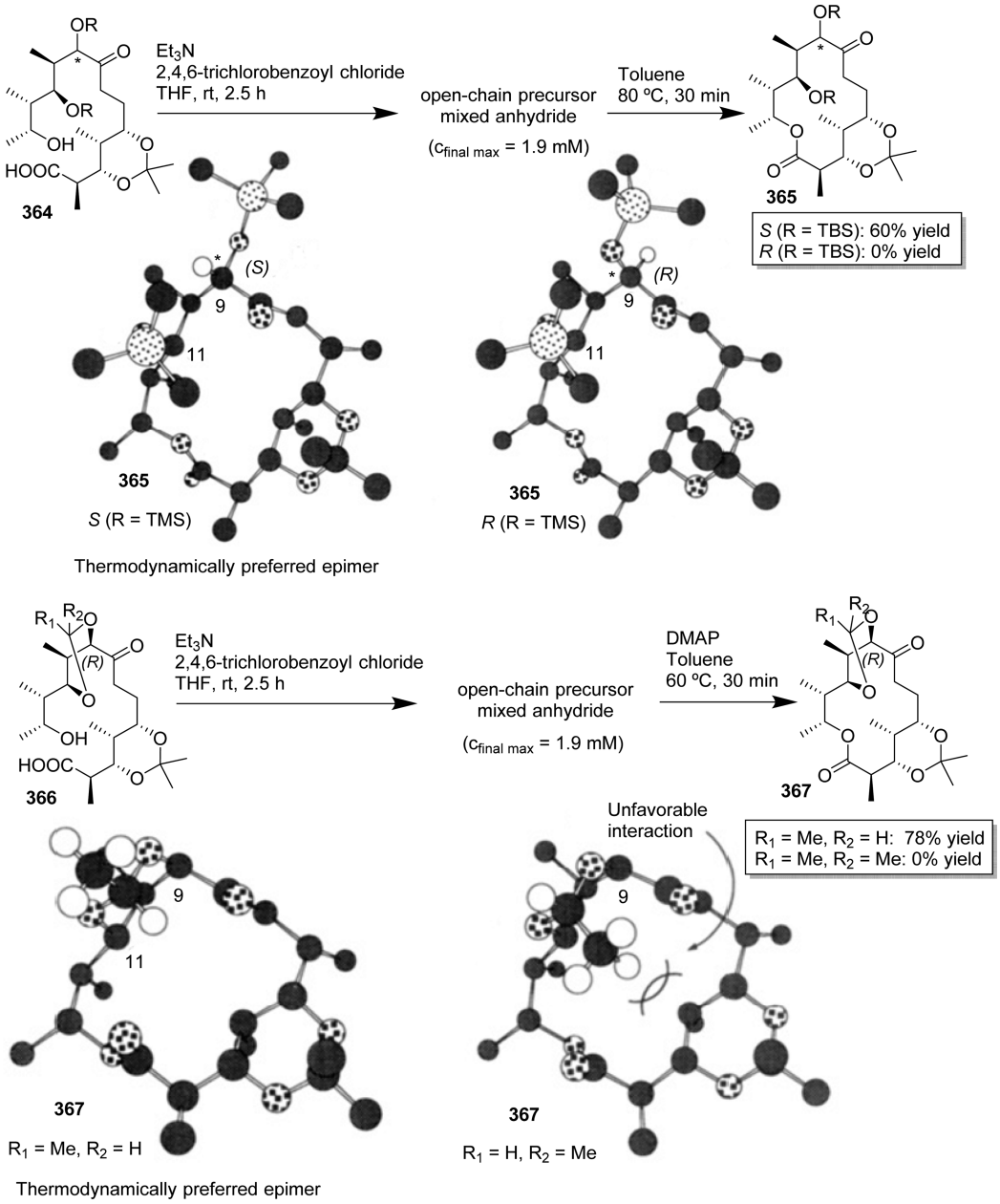

Figure 109. Synthesis of the erythromycin core.[383] Optimized structures for the resulting macrocycles. Reprinted from ref 383. Copyright 1994 American Chemical Society.

macrocyclization examples for which different outcomes are obtained when changing the configuration of one or several stereogenic centers. The synthesis of compounds having the erythromycin core (**365** and **367**) illustrates well both aspects. Thus, Paterson and co-workers described the requirements for a successful macrolactonization of open-chain precursors **364** and **366** using the Yamaguchi reaction conditions in a high dilution approach (Figure 109). They found that the configuration of the C9 in **364**, marked with an asterisk in Figure 109, has an impressive effect on the macrocyclization process, being the process only favored for the *S* stereoisomer. The change of the two TBS protecting groups at C9 and C11 by an ethylidene protecting group (**366**) also required the presence of the correct stereochemistry, including the acetal fragment. The importance of the associated steric factors was highlighted by the observed failure in the cyclization of the compound with acetonide protection at C9−C11 (**367** with $R_1 = R_2 = Me$).[383]

For many years, the presence of conformational restraining elements was considered essential for attaining an efficient lactonization of the erythromycin core structure **369**.[384] Such restraining conformational elements included one or several cyclic protecting groups (as seen in the former example) or the inclusion of heterocycles, olefins, or bulky groups as substituents in the hydroxy acid skeleton.[385−389] However, it has been demonstrated that the conformational preorganization provided by these biasing elements (**368a**) is not required for the efficient cyclization of the erythromycin core. This suggests that the proper arrangement of the chiral centers in the open-chain precursor **368b** (without biasing elements) provides an inherent conformation of the linear polypropionate structure facilitating the macrolactonization (Figure 110).[390]

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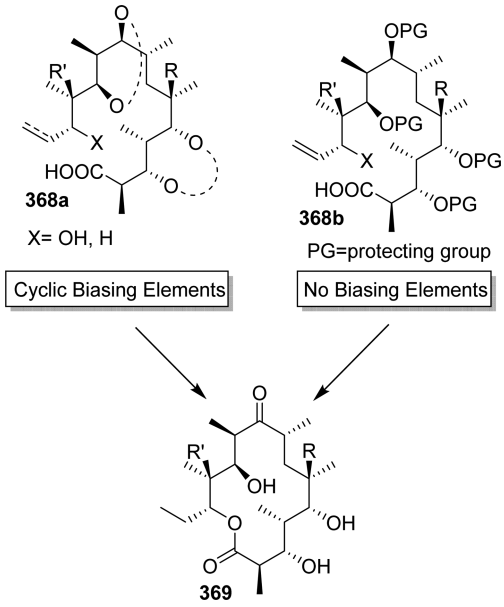

Figure 110. Synthesis of erythromycin with or without cyclic biasing elements.[384,390]

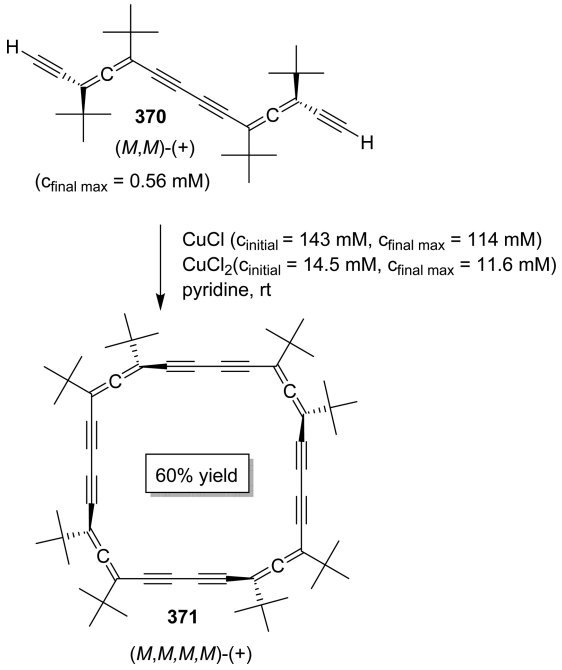

Figure 111. Synthesis of enantiomerically pure alleno-acetylenic macrocycles.[392]

It is worth mentioning that although the presence of chiral centers can significantly contribute to properly achieving the appropriate conformation of the precursor for the macrocyclization, the exact configuration of the chiral centers is not always a factor determining the success or the failure of the macrocyclization. Diederich and co-workers have prepared different alleno−acetylenic macrocycles (a representative example is depicted in Figure 111, **371**) by oxidative homocoupling of optically active and racemic 1,3-diethynylallenes under high dilution conditions.[391,392] The use of enantiomerically pure starting materials provided the corresponding enantiopure macrocycles. A similar process was used for the preparation in high yields (57%) of related shape persistent macrocycles incorporating pyridine rings in the cyclic structure.[393] However, when the racemic derivative was used, the macrocyclization yielded the six possible stereoisomeric macrocycles (two racemates and two achiral diastereoisomers) following a statistical distribution according to the purity of the starting materials (Figure 111).[391,392,394] Thus, the appropriate match of the absolute configuration at the chiral centers of **370** is not a requisite for macrocyclization in this case. A related observation was reported for the synthesis of ferrocene tethered macrocyclic bis-β-lactams through an intramolecular ring closing metathesis procedure or via an intramolecular Cu-catalyzed oxidative alkyne coupling, under high dilution conditions. Starting from a 1:1 *syn*:*anti* mixture of the open-chain precursors, a 1:1 *syn*:*anti* mixture of the corresponding macrocycles was always obtained. Similar results were also obtained for the synthesis of chiral macrocyclic bis-β-lactams by double Staudinger−Cu-catalyzed azide−alkyne cycloadditions.[395,396]

In the case of peptidic, pseudopeptidic, and related compounds, several factors can contribute in parallel to achieve a preorganization favorable for macrocyclization and very often it is difficult to differentiate the individual contributions. The presence of chiral centers is frequently a critical aspect in this regard. Following previous studies, discussed formerly, on the cyclization of peptoids, Kirshenbaum and co-workers explored the synthesis of macrocyclic structures **373**. The method used is based on a click reaction between azide and alkyne groups located on N-substituents at the i and $i + n$ positions of peptoid structures attached to a resin (Figure 112). Although the pseudodilution effect associated with the polymeric matrix can facilitate the macrocyclization, the distance between the two reactive N-substituents and the spatial preorganization of the chain are the key factors to explain the results obtained. Thus, for the resin-bound peptoid **372a** (Figure 112), for which the two reactive functionalities are located at positions 2 and 5 (i and $i + 3$) and the N-substituents are benzyl groups, the cyclization was obtained in 50% yield, with a 2:1 intramolecular/intermolecular cyclization ratio (monomer **373a** vs dimer structure **373b**). However, when the N-substituents were (*S*)-1-phenylethyl residues the cyclization yield was 80%, with a monomer/dimer ratio of 4:1 (**373a**/**373b**). This was explained through the formation of a helical structure **372b**, associated with the presence of the bulky α-chiral side chains, which will position the reactive groups in close proximity. The folded system is expected to contain roughly three residues per turn. In good agreement with this, excellent cyclization yields and monomer/dimer ratios were observed for a similar peptoid with the reactive functionalities located at positions 3 and 6 (i and $i + 3$), but lower yields and monomer/dimer ratios were observed when the reactive side chains were located at positions other than i and $i + 3$ along the helical scaffold.[397]

The presence of at least one N−Cα branched side chain seems to be essential to induce the appropriate folded conformation required for the efficient cyclization of other peptoids as has been shown, for instance, by Faure and co-workers in the macrocyclization of α,β-tetrapeptoids.[398] Their results also suggest that the easy interconversion between amide *cisoid* and *transoid* forms is key for achieving the correct cyclic structure.

Nicolaou and co-workers have reported a highly atropselective macrocyclization to prepare vancomycin model systems **376**, **377a**, and **377b**. The high selectivity obtained in the macrocyclization is due to the steric interactions between the TBSO auxiliary group and the TIPS protecting group favoring the formation of the corresponding atropisomer by minimization of

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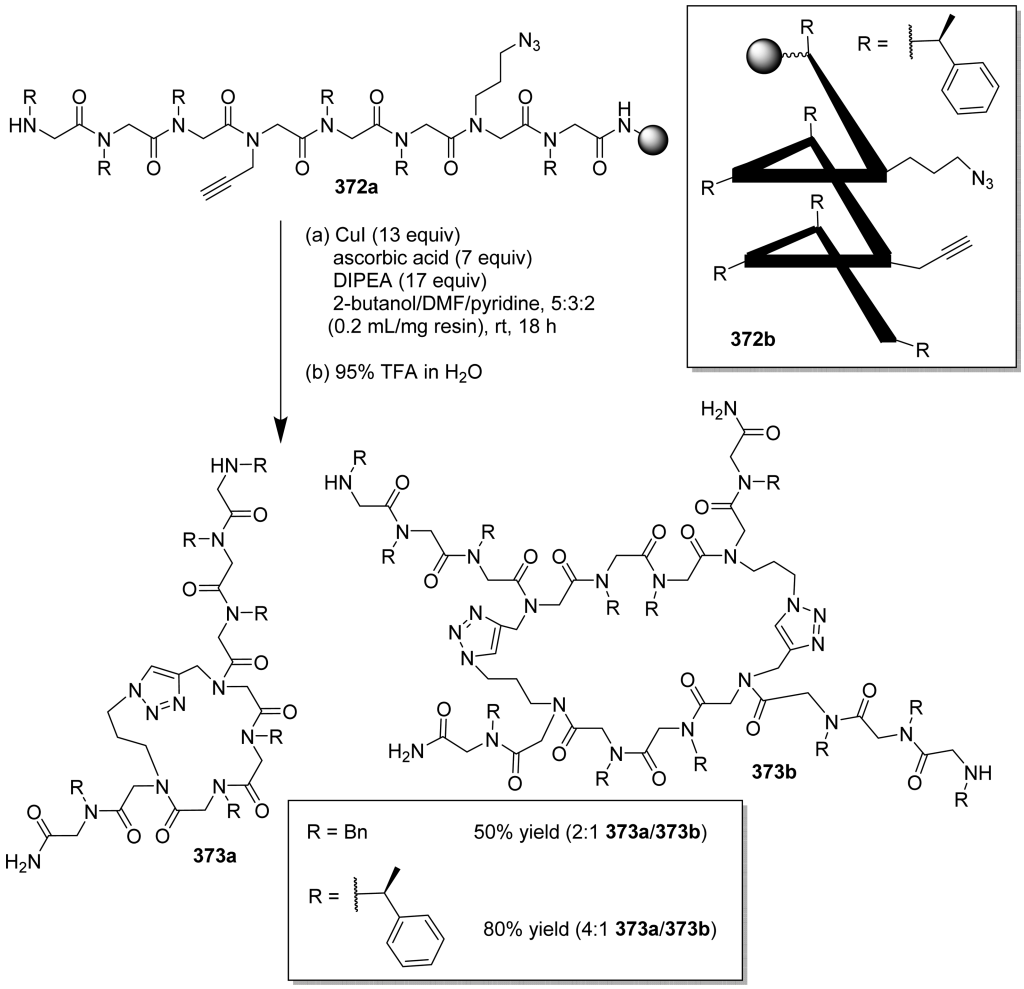

Figure 112. On-resin click macrocyclization of peptoids.[397] A schematic helical representation (**372b**) of the open-chain peptoid displaying the location of the azido and alkyne groups at positions *i* and *i* + 3 is presented in the inset.

the unfavorable steric interactions in the corresponding reaction intermediate **375b** with regard to **375a** (Figure 113). For the precursor **374a** with an *R* configuration in the non-natural amino acid related to tyrosine, 94% of the macrocyclic product **376** was obtained, whereas in the case of the precursor **374b** with the *S* configuration a mixture of atropisomeric macrocyclic compounds **377a** and **377b** was obtained, highlighting the importance of the stereochemical configuration in the macrocyclization process.[399]

The macrocyclization of linear peptides enabled by amphoteric aziridine aldehydes described by Yudin was discussed above in terms of the conformational preorganization of the open-chain precursor (Figures 100 and 101). This reaction can also be controlled by the configuration of the chiral centers of the linear peptide.[365] Thus, aziridine aldehydes having *S* stereocenters next to the carbonyl group undergo an efficient macrocyclization with the peptides that contain an L-amino acid residue at the N-terminus. However, the "mismatched" reaction involving the D-amino acid terminated peptide and the same aziridine is unproductive.

Peczuh and Ma have reported a ring closing metathesis (RCM) route for the synthesis of different [13]-macrodiolides **379** from dienes **378**. In good agreement with the importance of the positioning and configuration of some key atoms on the topology of these macrocycles, significant differences in macrocyclization yields were obtained according to the substitution pattern of the system (Figure 114). It is worth mentioning that the yield of the RCM reaction experienced a 2-fold increase just by changing the configuration of one of the stereocenters (see compounds **379a** and **379b** in Figure 114), highlighting the importance of the appropriate configurational preorganization both on the structure of the final product but also on the kinetics of the process.[400]

The reductive amination of rigid aromatic dialdehydes with C_2 symmetric pseudopeptides can afford efficiently [2 + 2] macrocyclic structures, but this is dramatically affected by the configurational preorganization of the open-chain precursors (**380a**, **380b**, and **381**). Thus, as shown in Figure 115, all attempts to obtain the macrocyclic compound **385** using the pseudopeptide containing a flexible ethylenic central spacer **381** and the dialdehyde **215b** failed (i.e., no macrocycle **383** or **385** was detected). However, very good yields for this [2 + 2] process were observed when a more rigid chiral spacer derived from cyclohexane-diamine **380a** was used (55% isolated yield of **384a** obtained by reduction from **382a**). Both the conformational restrictions provided by the chiral cyclohexane-1,2-diamine and the configuration of the stereogenic carbon atoms in this subunit are key factors for the efficient formation of the [2 + 2] macrocyclic product. Very interestingly, a *match/mismatch* effect was observed for the stereochemical configuration of the diamine and that of the constituent amino acid regarding their effects on the preorganization of the bis(amino amide).[401] When the

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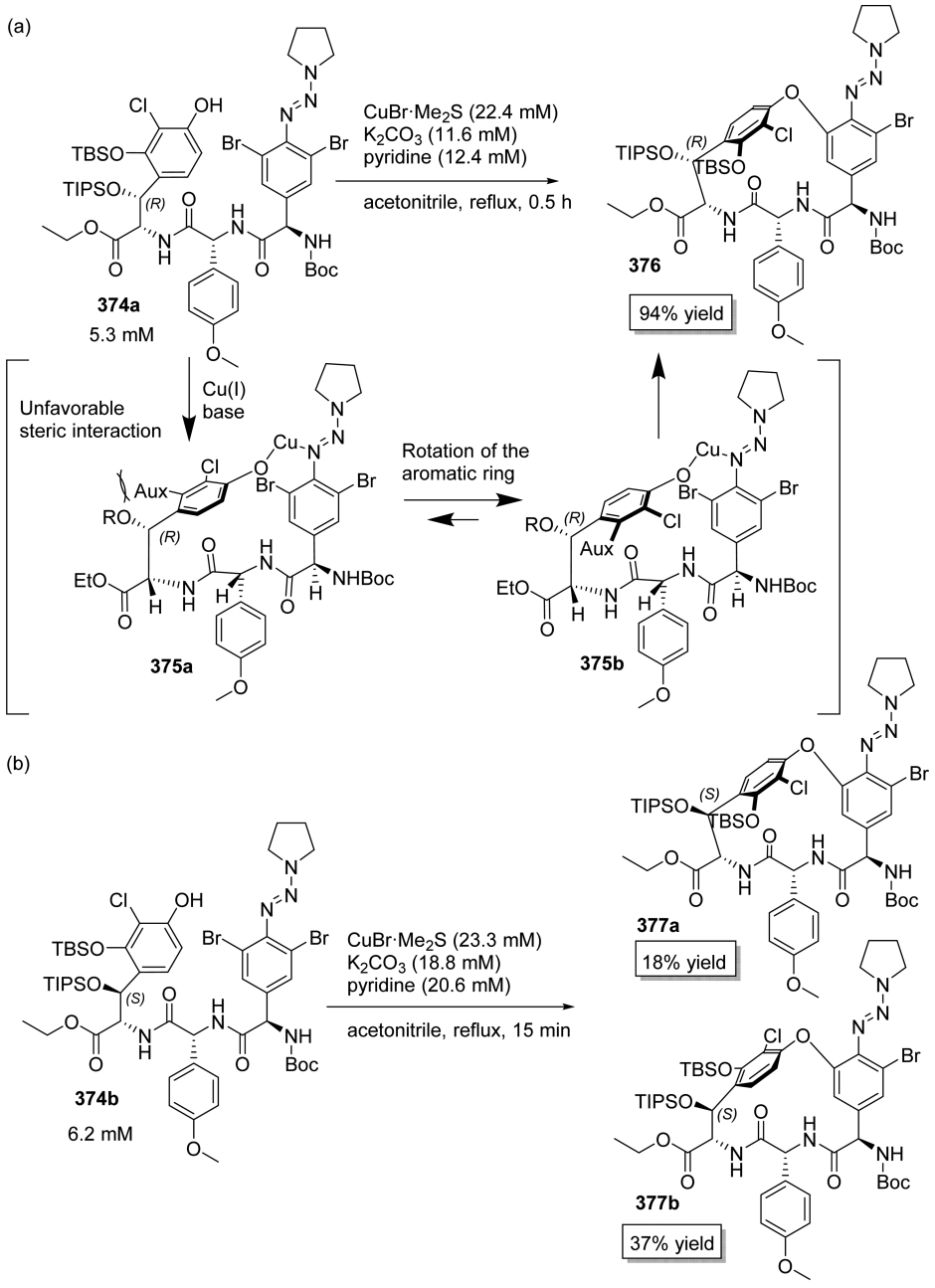

Figure 113. Atropselective macrocyclization of diaryl ether ring systems for the synthesis of vancomycin model structures. (a) Using precursor **374a**. (b) Using precursor **374b**.[399]

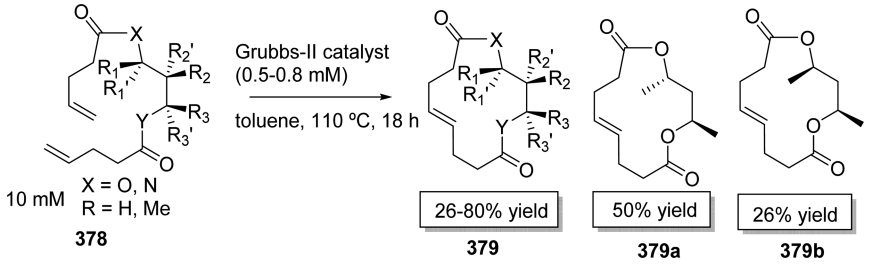

Figure 114. Synthesis of [13]-macrodiolides by RCM.[400]

pseudopeptidic fragment contained the (*R*,*R*)-cyclohexane-1,2-diamine subunit and two (*S*) amino acids (**380a**), the macrocyclization took place in excellent yields, while no macrocyclization was detected (**382b** and **384b**) when the pseudopeptidic component contained the same cyclohexanediamine but two (*R*) amino acids (**380b**).[402]

For highly preorganized open-chain hybrid precursors containing rigid fragments derived from natural products like

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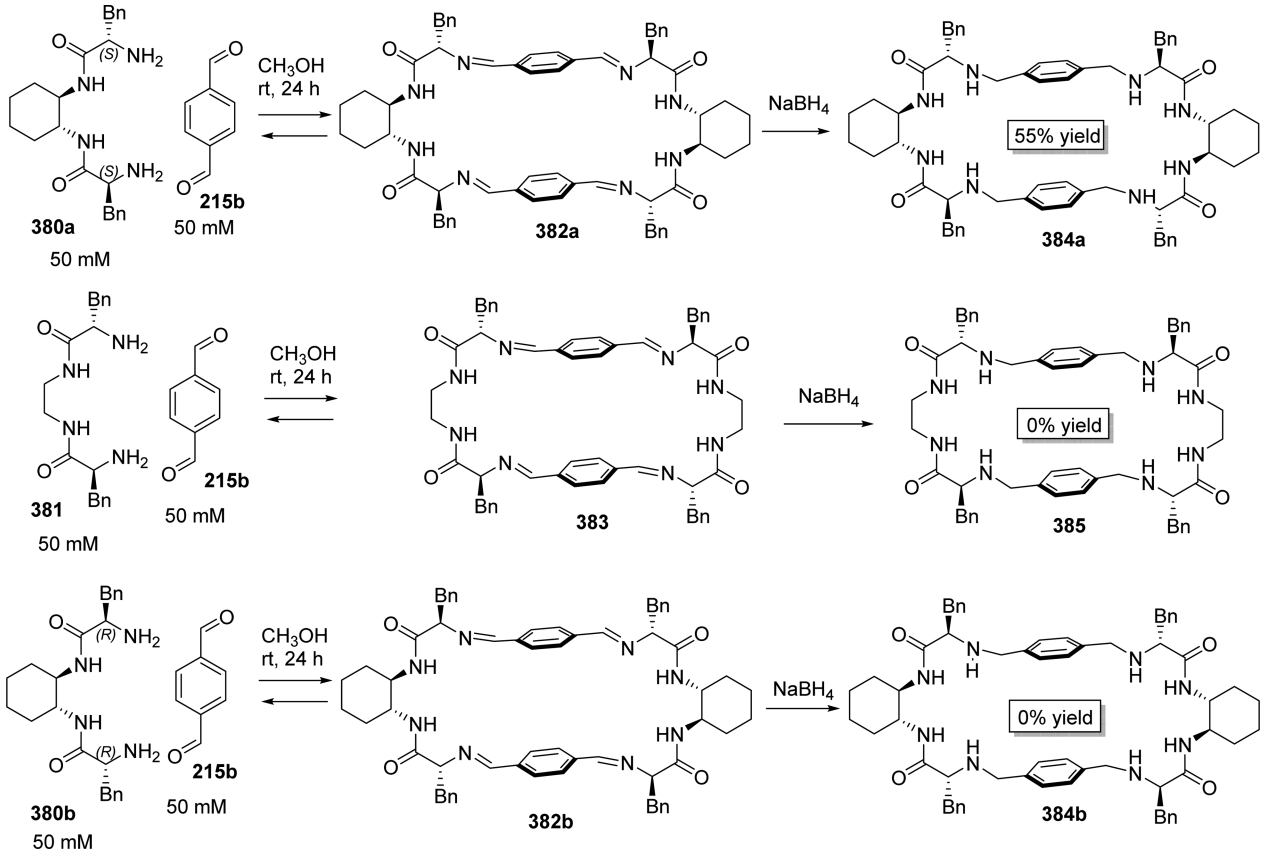

Figure 115. Configurational effects in the [2 + 2] macrocyclization of pseudopeptides and dialdehydes, involving a *match/mismatch* effect of the configuration of the components at the pseudopeptide.[401]

terpenes or steroids, the presence of these moieties provides a well-defined stereochemistry to the precursors and highly stereoselective macrocyclizations can be obtained. In the case of the terpene-derived system **386** displayed in Figure 116, the one step [2 + 2] macrocyclization, involving a Nicholas reaction of the hydroxy groups of **389** (obtained from **387** by reaction with an excess of diol **388**) with the Co-stabilized carbocations of **387**, afforded a single stereoisomer **390** in quantitative yield.[403]

6. SYNTHESIS OF MACROCYCLIC STRUCTURES BY A TEMPLATE-ASSISTED FAVORABLE PREORGANIZATION OF OPEN-CHAIN PRECURSORS

An important alternative to the intrinsic preorganization of the precursors is the possibility of using a template element to induce a favorable preorganization even in cases where conformational and configurational elements are not suitable. This section has been organized according to the main classes of templates described in the literature. Cations (section 6.1), anions (section 6.2), and different aromatic structures (section 6.3) are the most common templates reported. Other families of templates have been gathered in section 6.4. Finally, we have included section 6.5, which describes the biological and pseudobiological synthesis of macrocycles.

6.1. Metal Templated Macrocyclizations

There are many examples of metal templated macrocyclization reactions in the literature, and we have just selected some representative examples to illustrate the different roles of the metals in the synthesis of macrocycles. Two different subsections have been considered. The first one (section 6.1.1) includes examples for the synthesis of crown ethers and polyaza macrocycles, probably the most classical examples of the application of templates in macrocyclic synthesis. The second one (section 6.1.2) contains examples related to other families of macrocycles highlighting the synthetic polyvalence of the metal templates.

6.1.1. Crown Ethers and Polyaza Macrocycles. Crown ethers and their aza and polyaza equivalents represent an important family of cyclic compounds, with a large variety of ring sizes and additional structural features having being reported.[404−406] They are associated with the conceptual origin of supramolecular chemistry,[187,188,407,408] and the need of obtaining those compounds in pure form in relatively large quantities for further studies led to the development of important strategies and concepts in macrocyclization, in many cases involving the use of templates. As a matter of fact, the original synthesis of crown ethers (for example **394**) developed by Pedersen represents one of the most classical examples of a macrocyclization assisted by metal cations. Although the original research involved mainly the use of alkaline cations as templates, a whole set of analyses on the effects of different cations has been carried out.[189] The synthesis of crown ether **394** involves diol **391a** and dichloride **392**, and the ability of the polyether chain to coordinate alkaline cations, wrapping around them and thus approaching both reactive ends (**393**), is at the origin of the observed effects in most cases (Figure 117).

In parallel to the development of the chemistry of crown ethers, the nickel(II) templated synthesis of cyclam was carried out. In the mechanism for the reaction of tetraamine **395** and glyoxal (**396**), the corresponding metal complex **397a** and the diimine macrocycle **379b** are the key intermediates allowing

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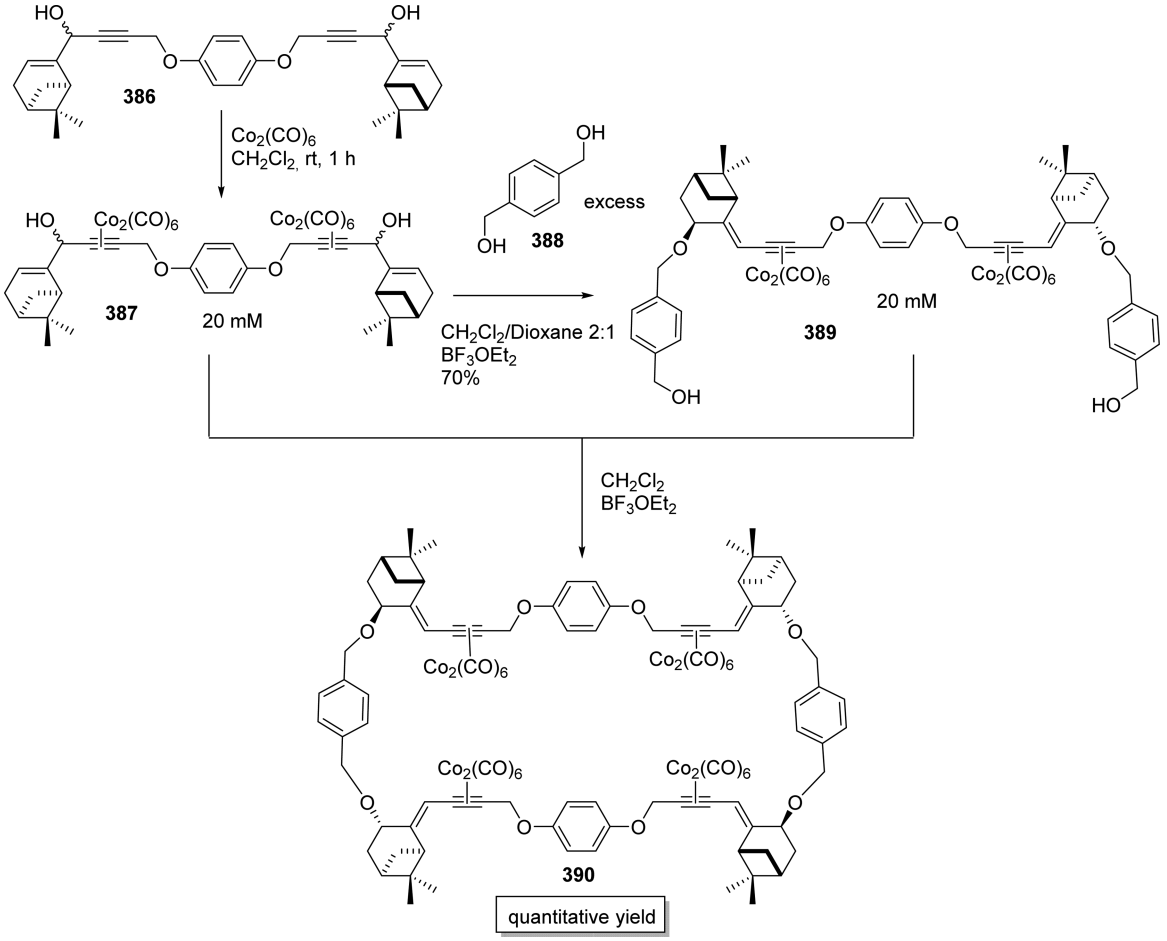

Figure 116. Synthesis of a polymetallic terpene-derived macrocycle through a Nicholas reaction.[403]

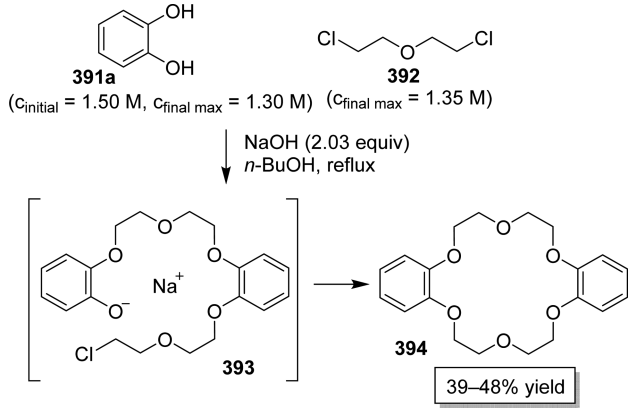

Figure 117. Pedersen's crown ether synthesis.[189]

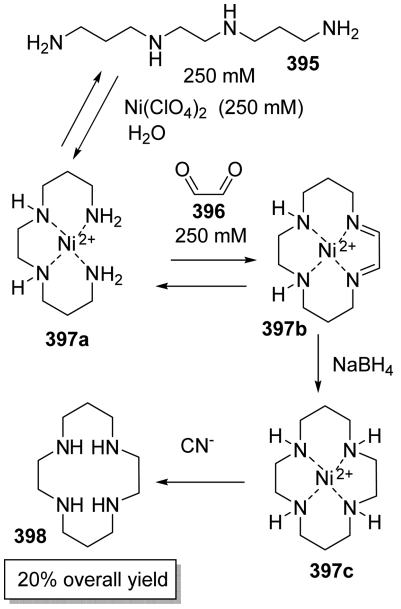

Figure 118. Ni(II) templated synthesis of cyclam.[409]

obtaining free cyclam **398** in ca. 20% overall yield (Ni(II) is removed from **397c** using cyanide). This synthesis represented a landmark in this field (Figure 118),[409,410] although some reports on the Ni(II) templated synthesis of other azamacrocycles had been published previously.[411−413]

These general strategies for the synthesis of crown ethers and aza derivatives have been widely used, and they are at the origin of a number of different specific approaches described in the literature. Thus, for instance, several research groups have reported the synthesis of a variety of N-substituted azacyclam compounds using Ni(II) and other metal cations as templates. For example, precursor **401** was obtained from the metal complex **399** that upon reaction with the amine **400** gave the macrocycle **402** (Figure 119).[414] In the same way, a variety of related cagelike compounds such as **405** have been prepared following the pioneering work by Sargeson and co-workers, who used cobalt(II) as the corresponding template to obtain

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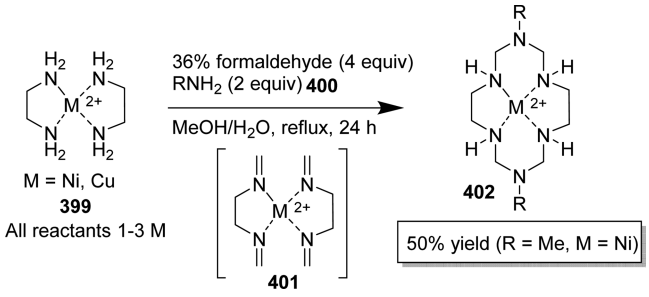

Figure 119. General metal-templated synthesis of aza-cyclams.[416]

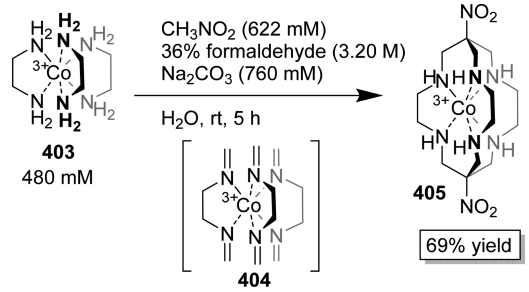

Figure 120. General metal-templated synthesis of a cage macrocyclic structure.[415]

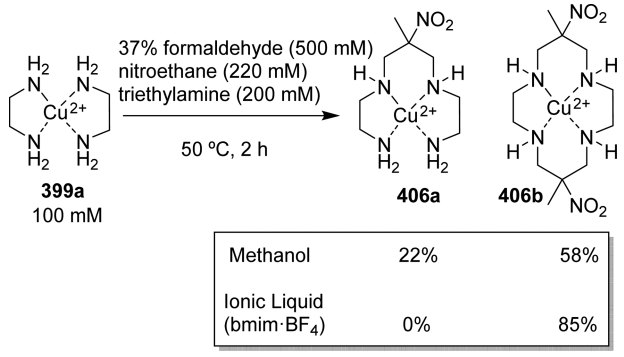

Figure 121. Metal-templated synthesis of polyazamacrocycles in ionic liquids.[417]

precursor **403** that reacted with formaldehyde to yield intermediate **404** that further reacted with CH_3NO_2 to give the final cage **405** (Figure 120).[415]

Recently, Lawrance and co-workers have described the advantages of the use of an ionic liquid as the solvent for the metal-directed macrocyclization reactions of **399a** instead of using classical organic solvents like methanol. They reported an increase in the yield and less formation of acyclic byproducts. Besides, the formation of larger rings was found to be easier in ionic liquids. Thus, a mixture of the acyclic product **406a** (22% yield) and the macrocycle **406b** (58% yield) was observed when the reaction was performed in methanol, whereas when the reaction was performed in the ionic liquid 1-butyl-3-methyl-imidazolium tetrafluoroborate (bmin·BF_4), the macrocyclic product **406b** was obtained in 85% yield, avoiding the formation of byproducts. The authors pointed out that the ionic liquid may have an effect in stabilizing the reaction intermediates in the macrocyclization process and therefore favoring the Mannich-type reaction (Figure 121).[417]

In spite of the many classical and detailed studies regarding the role of metal cations as templates in the synthesis of crown ethers,[59,187−190,405,406,418,419] additional reports in this field still continue to appear. Thus, Schalley and co-workers analyzed the templated versus nontemplated synthesis of benzo-21-crown-7 **408a** from the open-chain precursor **407** (Figure 122).[420] Their results seem to indicate that K^+ acts as a much more efficient template than Na^+ for the synthesis of this specific crown ether (almost a 3-fold increase in the yield). It is important to note, however, that this study involves two different synthetic sequences. In the case of the reaction studied in the presence of Na^+, the direct cyclization of precursor **407** was used affording the expected macrocyclic structure **408a** in 24% yield along with the [1 + 1] cyclodimer **408b** as the major product in 31% yield (Figure 122a). On the contrary, the synthetic approach using catechol (**391a**) and the ditosylate **409a** in the presence of K^+ involves an efficient (69−70% yield) [1 + 1] macrocyclization carried out under pseudo-high-dilution conditions. Different studies have revealed that the exact synthetic strategy and the ring-disconnection approach can have a significant effect on the efficiency of the cyclization reaction to obtain benzo-crown ethers under similar conditions.[421]

Lukyanenko and co-workers have studied the influence of the different synthetic parameters for the synthesis of several benzo-crown-ethers under phase transfer conditions.[422] Very different results were obtained for the diverse conditions and strategies assayed, including the nature of the leaving groups, the concentration of the reactants, or the ring-disconnection considered. The [1 + 1] synthesis of benzo-15-crown-5 (**411**) was used for the optimization of the reaction conditions, employing catechol (**391a**) and triethylene glycol ditosylate or dihalide **410**. The results revealed an important influence of the leaving group that seems to produce a change in the reaction kinetics of the macrocyclization process (Figure 123). They also explored other [1 + 1] macrocyclization processes involving different ring disconnections for the preparation of benzo-crown-ethers of diverse sizes (**415**). Strong differences in the macrocyclization yields were obtained using starting materials with different flexibilities (**391a**, **409**, **412**−**414**). However, this last effect was lower than expected from single-phase experiments, at least for some of the synthetic procedures considered, which was assigned to a decrease in the importance of the Na^+ template effect under phase transfer conditions (toluene/water). This is reasonable taking into consideration the presence of a strongly coordinating solvent (water) for the metal cation (Figure 124).

In the metal-templated synthesis of crown ethers, it is clear that the best approach for the synthesis of a specific molecule is to use the cation that best fits into the cavity of the crown ether. Thus, larger crown ethers require the use of larger cations like Cs^+.[423] The advantages of this approach are fully realized for the synthesis of very large crown ethers, often required for the preparation of catenanes or rotaxanes, but require a careful design of the synthetic strategy. This is illustrated, for instance in the work of Stoddart and co-workers.[424] Thus, in the reaction of resorcinol (**391b**) with tetraethylene glycol bistosylate (**409b**) in the presence of cesium salts and under pseudo-high-dilution conditions, the major product (54% yield) is the [1 + 1] macrocycle **416a** with the cavity in which cesium fits better. At the same time, the [2 + 2] and [3 + 3] macrocycles **416b** and **416c**, having larger cavities, were isolated in much lower yields (8.4 and 1.7% yields respectively, Figure 125). However, the macrocycle **418a** with a cavity size comparable to **416b** could be synthesized with high efficiency (51% yield) just by using a different ring-disconnection strategy in a [1 + 1] macro-

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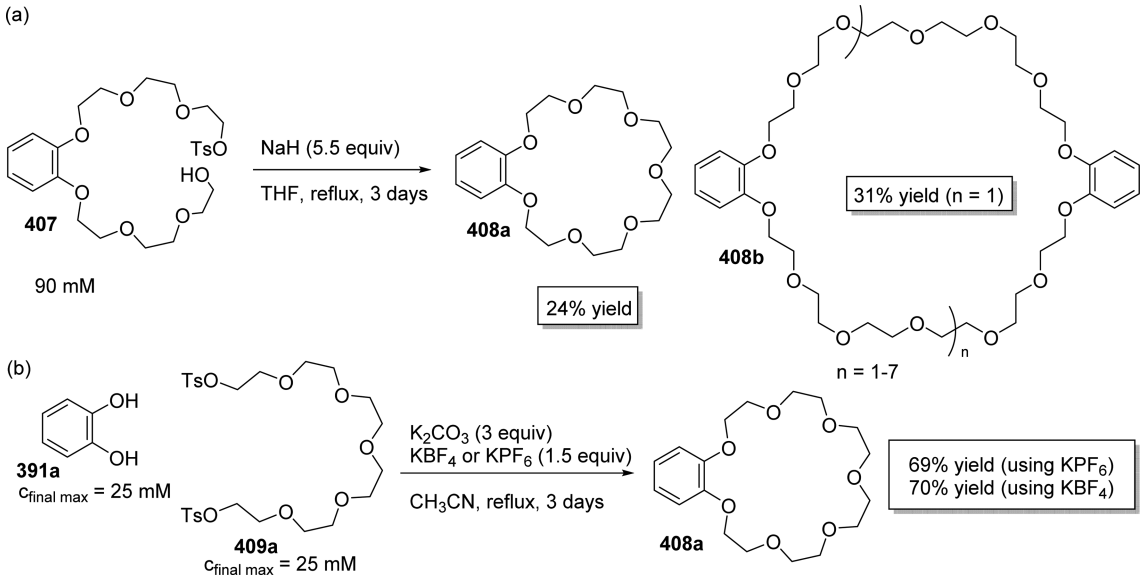

Figure 122. Synthetic strategies for the preparation of benzo-21-crown-7 **408a**. (a) Using difunctional precursor **407**. (b) Using precursors **391a** and **409a**.[420]

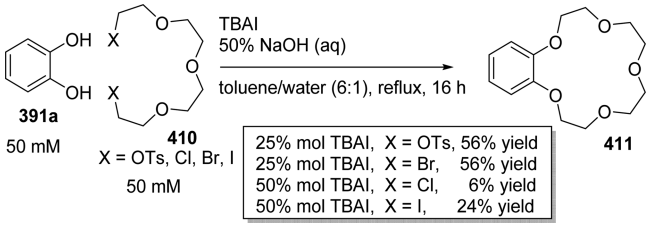

Figure 123. Synthesis of benzo-15-crown-5 under phase transfer conditions.[422]

cyclization process (using precursors **391b** and **417**), although the corresponding [2 + 2] macrocycle **418b** was also obtained in 11% yield (Figure 126).

The Na^+ cation has been shown to also act as a very efficient template in the synthesis of diaza trioxa macrocycles **421** from precursors **215a** and **419** (Figure 127).[425] In this case, Chiu and co-workers used sodium tetrakis(3,5-trifluoromethylphenyl)-borate (NaTFPB) as the source of the template cation to minimize the interaction between the cation and the anion. Using 1 equiv of Na^+ the corresponding macrocycle **421** was obtained in 65% overall yield, including the cyclization step, the

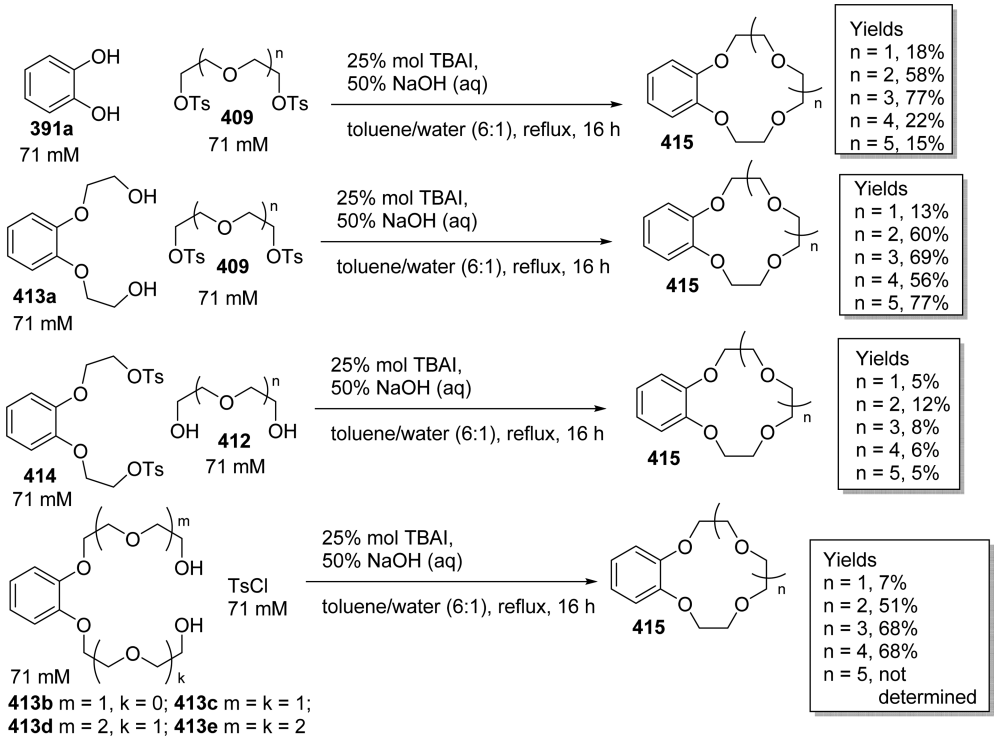

Figure 124. Synthetic strategies for the preparation of benzo-crown-ethers under phase transfer conditions.[422]

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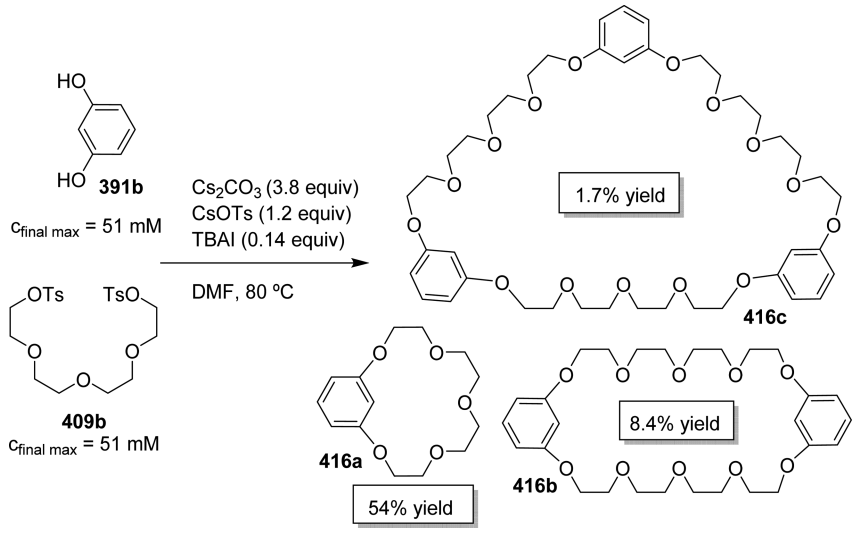

Figure 125. Synthesis of crown ethers by reaction of resorcinol with tetraethylene glycol bistosylate in the presence of cesium salts.[424]

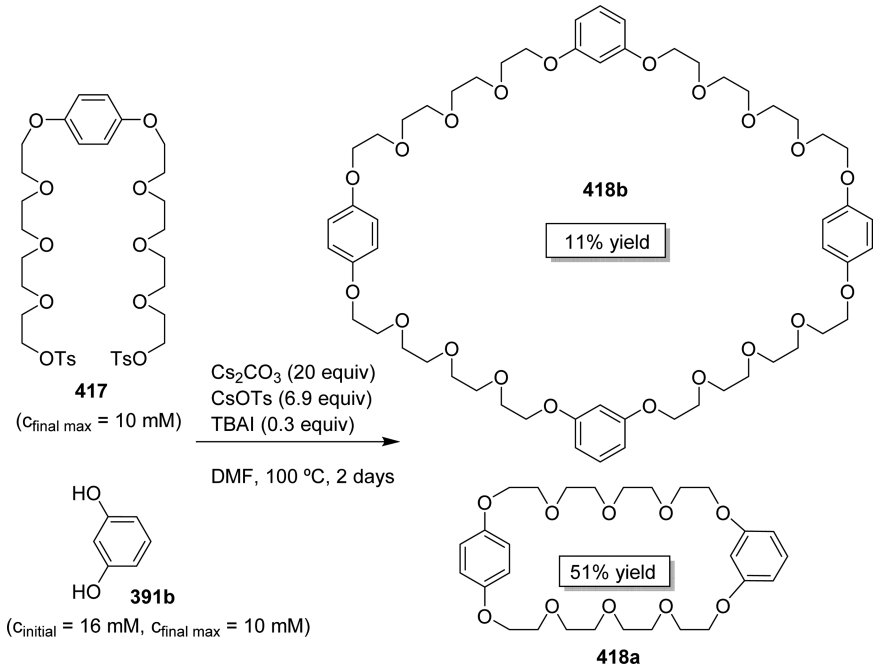

Figure 126. Efficient synthesis of macrocycle **418a** through a [1 + 1] process.[424]

imine reduction step for **420**, and the chromatographic purification of the final product. Interestingly, when 0.5 equiv of the sodium template was used, the diethylene glycol **419** self-assembled orthogonally (forming the interlocked imine **422**) allowing the preparation of the corresponding [2]catenane **423** in 17% overall yield. This is a remarkable result, as most of the reported template assisted syntheses of catenanes involve the use of anions[426,427] or transition metal cations as templates.[428,429]

Voyer and co-workers have reported the synthesis of the anion-binding diaza dioxa macrocyclic structure **426** containing a non-natural amino acid fragment (Figure 128).[430] The macrocyclization reaction of **424** with **425** was carried out under high dilution conditions using CsBr for halide conversion in **424** (chloride to bromide) in order to reduce the reaction time. It seems reasonable to assume that Cs^+ could also act as a template in this reaction, although no further studies were carried out in this regard.

Shockravi and Bavili have described the preparation of dibenzosulfide-derived macrocyclic dioxa diamides using a classical synthesis from a di(acid chloride) or dimethyl ester and the corresponding diamine. Although the yields in the absence of metal cation range from 40 to 85% for the different approaches considered, the authors mention that the use of a metal template such as Na_2CO_3, K_2CO_3, and specially Cs_2CO_3 increased the macrocyclization yield and reduced the formation of byproducts.[431]

The Nicholas reaction involving a nucleophilic attack of a heteroatom on a stabilized carbocation is a useful approach to the preparation of cyclic ethers. Thus, when the dicobalt hexacarbonyl complex **427** shown in Figure 129 was treated with a Lewis acid, a mixture of the [1 + 1] and [1 + 1 + 1] macrocycles was obtained (**428a** and **428b** respectively).[432] Taking into account that this is a reversible reaction, the authors were able to observe the rearrangement of the dimeric species

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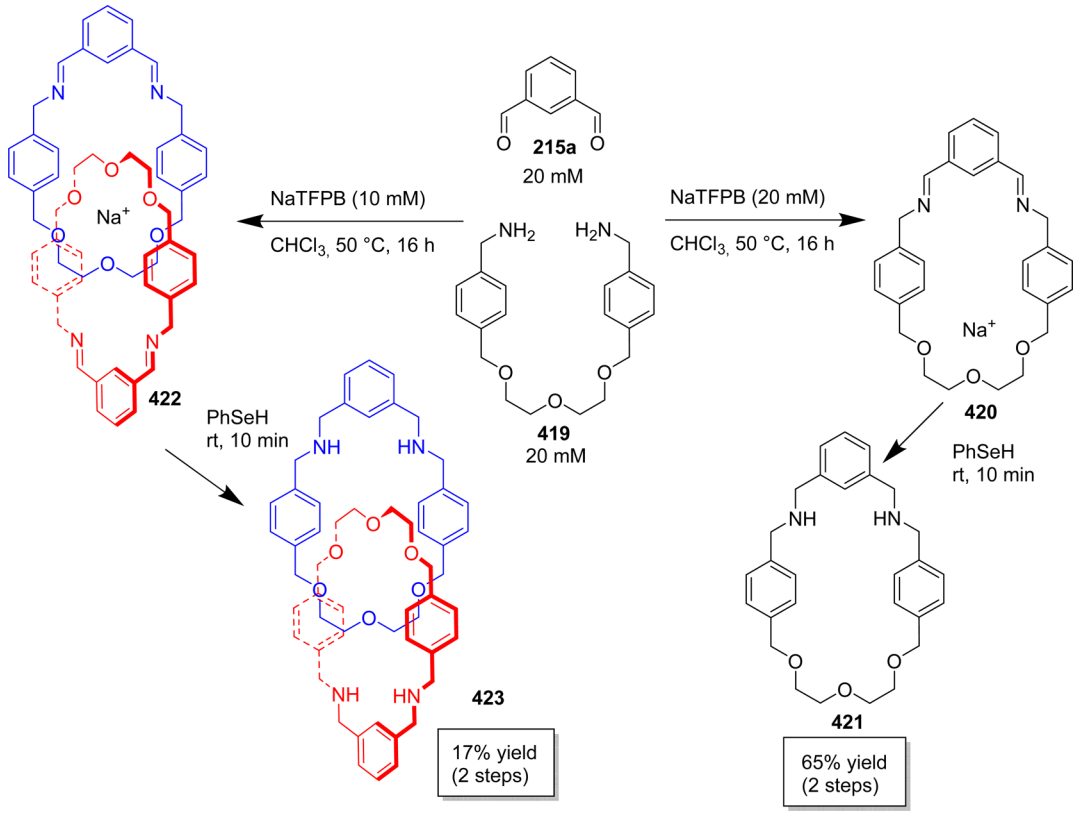

Figure 127. Na^+-templated synthesis of a diaza trioxa macrocycle.[425]

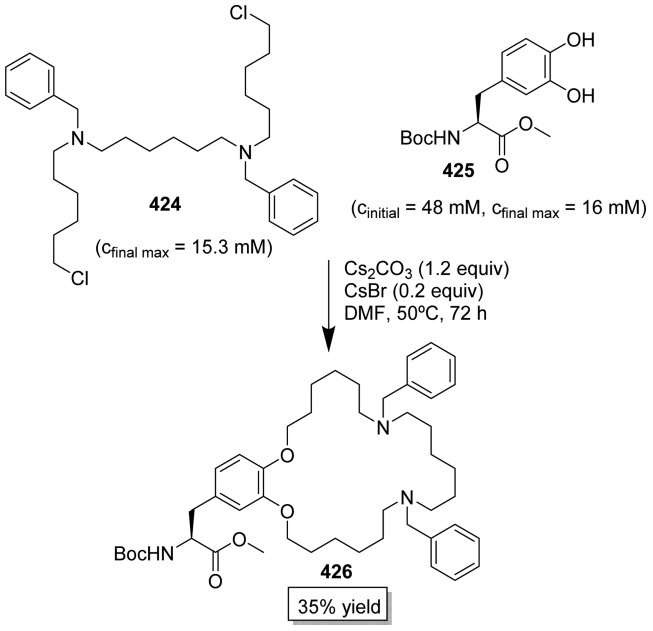

Figure 128. Synthesis of an anion-binding macrocyclic amino acid.[430]

(**428a**) into the trimeric ones (**428b**) by the use of the corresponding acidic conditions in the presence of an appropriate cationic template, in particular Na^+. After deprotection, the 21-membered triacetylenic macrocycle **428b** could be transformed into a hexasubstituted tetracyclic benzene derivative containing three oxepane rings. The analogous aza version of this process was also developed, although the potential effect of cationic templates was not analyzed.

6.1.2. Nonclassical Metal Template Effects. Many macrocyclizations based on the conformational or configurational preorganization of the corresponding open-chain precursors involve the use of metal salts or metal-based catalytic species, so the participation of the corresponding metal cations as templates can also play a significant role in the process, even if, in many cases, this has not been studied in detail. One such example is the *E*-selective Horner–Wadsworth–Emmons macrocyclization discussed to illustrate the importance of the stereochemistry at the double bonds in the open-chain precursors (see Figure 107).[381] The excellent results obtained for the intramolecular cyclization when using $Zn(OTf)_2$ were interpreted by the authors in terms of the strong template effect exhibited by Zn^{2+}, larger in size and more polarizable, relative to the cations present in the other salts used, although this issue was not further explored.

Very often, the key step for organometallic catalytic processes is the attachment of the two individual components or the two reactive ends of the open-chain precursor to the metal center. It is clear that this is not a "classical" template effect involving the wrapping of the macrocyclic precursor around the template as occurs in the case of the crown ethers. However, this can also be considered in terms of the metal cation acting as a template to bring together the two reactive ends and to decrease the distance between them, exactly the same outcome of the classical template effect. A simple illustration of this is the atropselective macrocyclization of diaryl ether ring systems used for the synthesis of vancomycin model compounds that was discussed previously in terms of the relevance of the configurational effects observed (see Figure 113).[399] In this case, the key intermediate **375b** considered for the cyclization involves the coordination of the triazine and the phenoxy groups located at both ends of the precursor to a single copper cation, thus approaching the reactive

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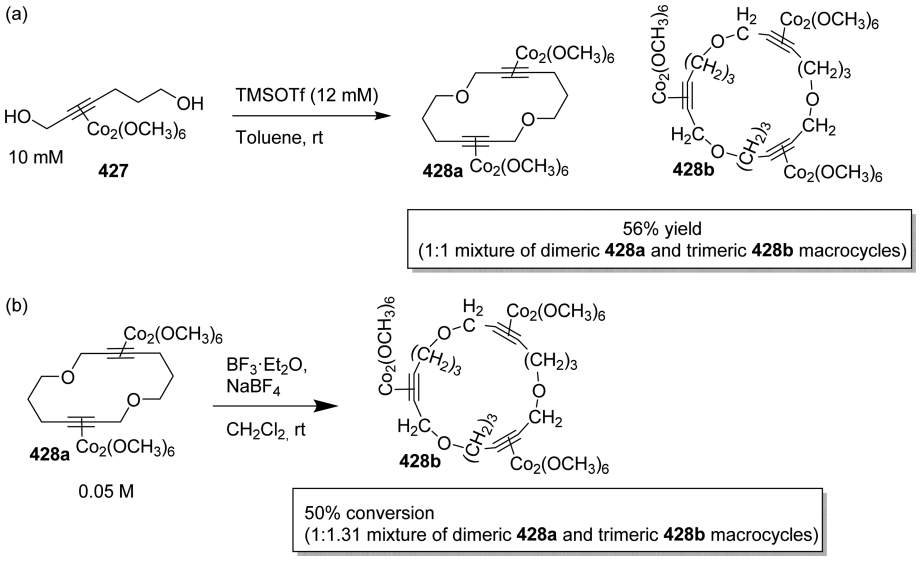

Figure 129. Macrocycle formation through the Nicholas reaction. (a) Macrocyclization reaction. (b) Transformation of the dimeric macrocycle **428a** in the trimeric macrocycle **428b**.[432]

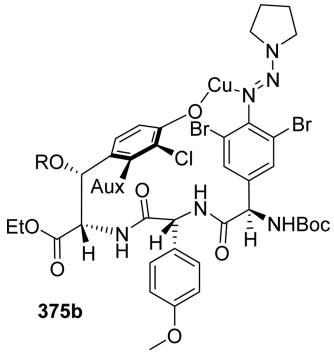

Figure 130. Proposed intermediate for the cyclization of diaryl ether ring systems in the synthesis of vancomycin analogues.[399]

ends and facilitating the appropriate macrocyclization (Figure 130).

In principle, however, the two functions attached to the metal center could belong to two different substrates, i.e., providing a [1 + 1] cyclodimerization reaction. Thus, for instance, Bruneau and co-workers had reported the macrocyclization of substituted *β*-

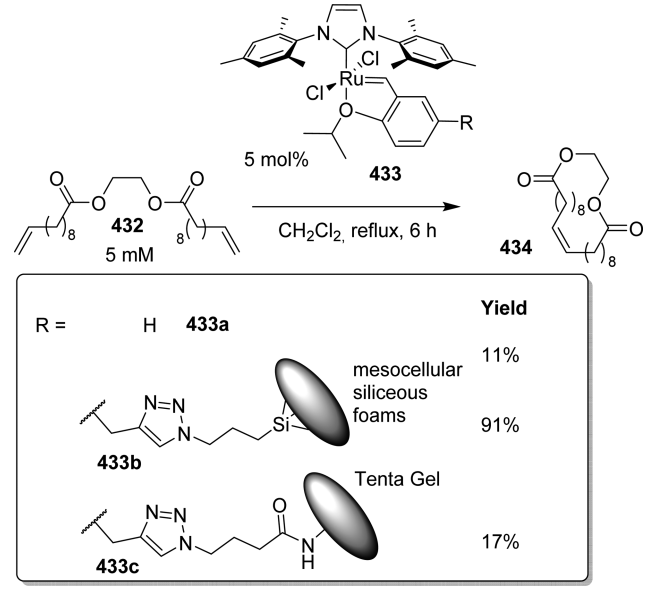

Figure 132. Use of supported Ru catalysts for RCM.[435]

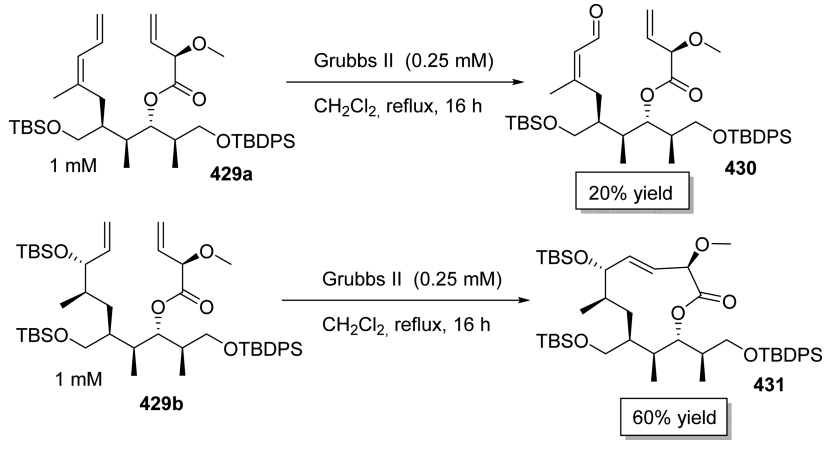

Figure 131. Synthesis of the A ring of halichomycin by RCM.[434]

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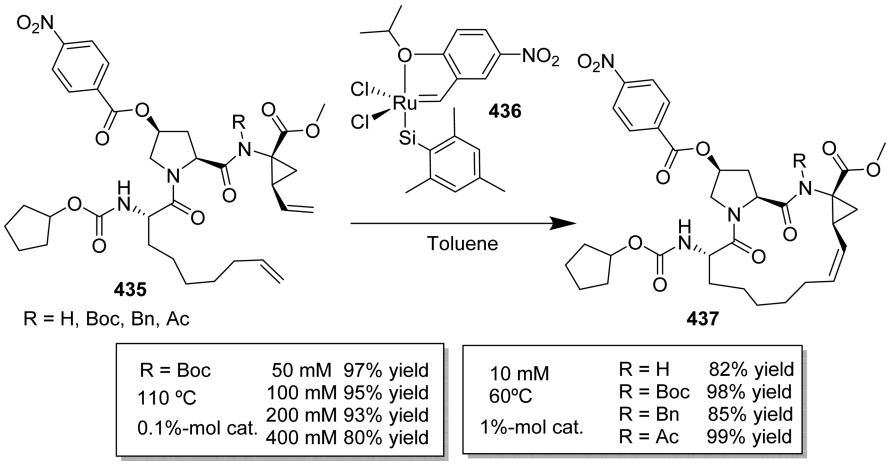

Figure 133. Effect of N-substitution on the RCM of an open-chain precursor **435** for the synthesis of the HCV protease inhibitor BILN 2061 **437**.[436]

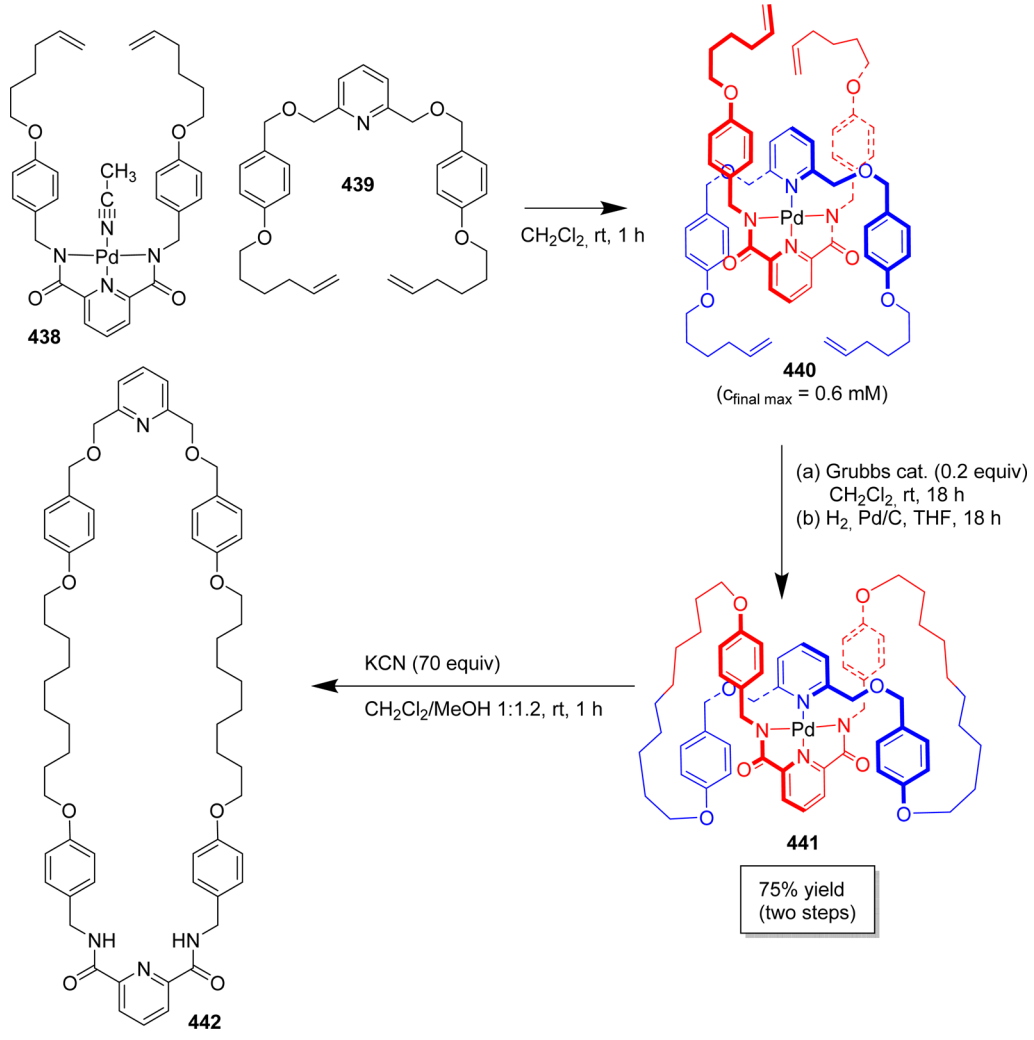

Figure 134. Pd-templated RCM synthesis of a large macrocycle.[437]

dipeptides by RCM using a Grubbs II catalyst at 4 mM concentrations of the starting materials with yields up to 84% for monomeric macrocycles and yields up to 76% for dimeric macrocycles.[433] The reaction can proceed through an intramolecular RCM macrocyclization or by a [1 + 1] cyclodimerization process depending on the open-chain precursor geometry. The exact position of the allyl groups involved in the cyclization is the main factor defining the outcome and yield of the process, associated with the steric bulk at the β position of the amino acid and the presence of H-bonding interactions.

Jia and Mao have reported the synthesis of the A ring of halichomycin showing the importance of the conformation of the backbone of the open-chain precursor (**429a** and **429b**) on the RCM macrocyclization reaction. As shown in Figure 131, the first

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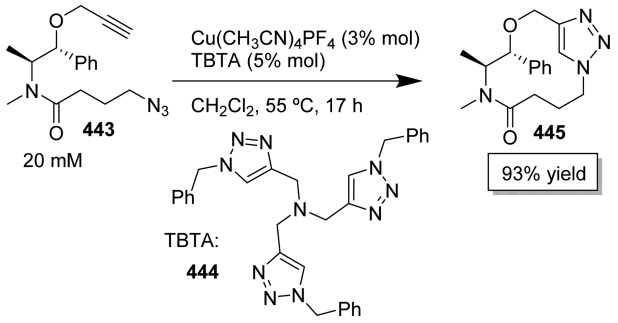

Figure 135. Macrocyclization reaction by click copper chemistry.[438]

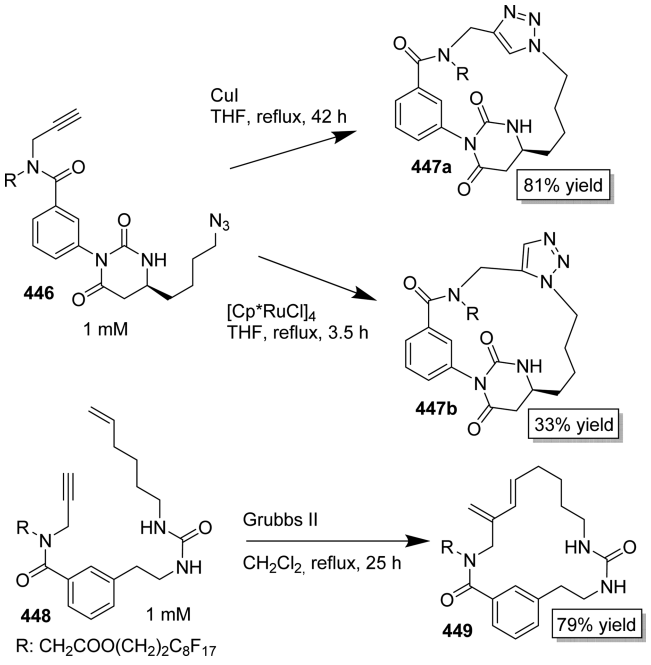

Figure 136. Synthesis of macrocyclic scaffolds using multidimensional coupling.[443]

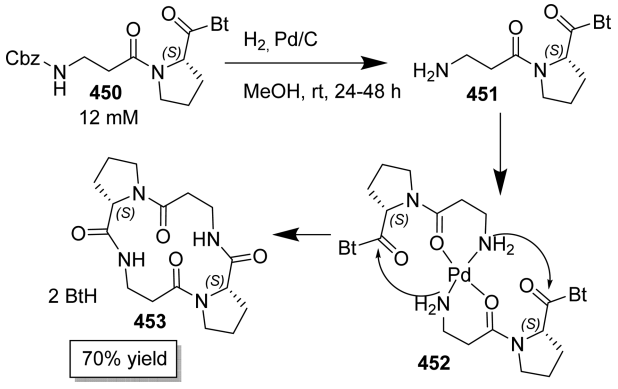

Figure 137. Palladium-promoted tandem deprotection/cyclodimerization.[444]

approach considered did not provide the expected macrocyclization product under a variety of RCM reaction conditions (catalysts, solvents, and additives). Instead, a 20% yield of aldehyde **430** was obtained along with 20% of the starting material **429a**. The second approach with the (*Z*)-olefin masked as a hydroxyl group (**429b**) allowed obtaining the desired product **431** in 60% yield using a high catalyst loading. The

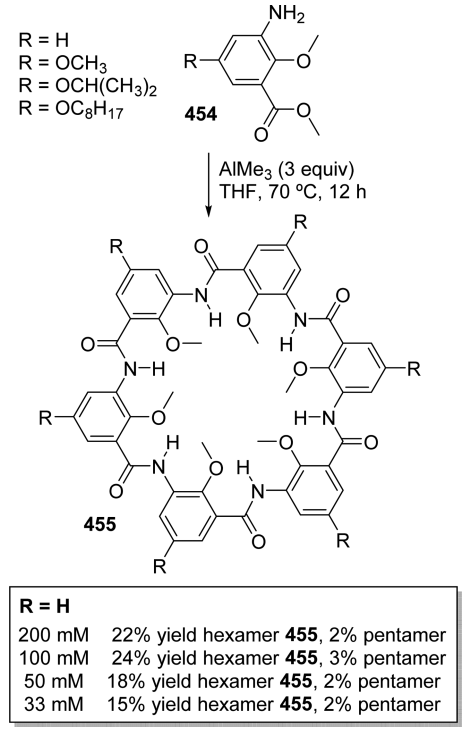

Figure 138. $AlMe_3$ mediated synthesis of a macrocyclic hexamer.[445]

reaction took place with excellent selectivity to the *E*-macrocycle **431**, with no *Z* or dimeric products being detected.[434]

As for other cases discussed, the immobilization of Grubbs catalysts has a direct influence on macrocyclizations taking place through RCM. Although the activity of the catalyst **433a** can be reduced, the macrocyclization process of **432** can be significantly more selective toward the formation of the corresponding macrocyclic structure **434** via intramolecular processes.[435] As observed for many other supported systems, the results are greatly affected by the chemical and morphological nature of the support (**433b** and **433c**) (Figure 132) and, as could be expected, the yields for the macrocyclization increase with the reduction in the loading of the polymer chains in the solid support.[127,144]

The work of Shu et al. is illustrative of the involvement of different factors, including the role of the metal center, for the success of a cyclization by RCM. In order to develop a truly practical RCM macrocyclization for production-scale manufacturing (with concentrations ≥0.2 M and loadings of catalyst **436** ≤0.1 mol %) of the HCV protease inhibitor BILN 2061 **437**, they studied in detail the macrocyclization process of the key precursor and the effect of different structural variables. Thus, they found that the nature of the substituent at the C4 position of the hydroxyproline fragment in **435** had detectable effects on the rate of the cyclization, which was assigned to the modification of conformational preferences. However, the most relevant effects were observed for the N-substitution pattern of the amide group linking the proline and the cyclopropane moieties (Figure 133). The reaction is favored by N-substitution of precursor **435** with electron-withdrawing groups (Boc and Ac) as this inhibits the carbene transfer at the vinylcyclopropane fragment and its stabilization by chelation, which was observed to reduce the rate of the corresponding RCM. The presence of the acetyl or Boc groups also contributes to increase the thermodynamic effective molarity, reducing the ring strain by removal of the enforced

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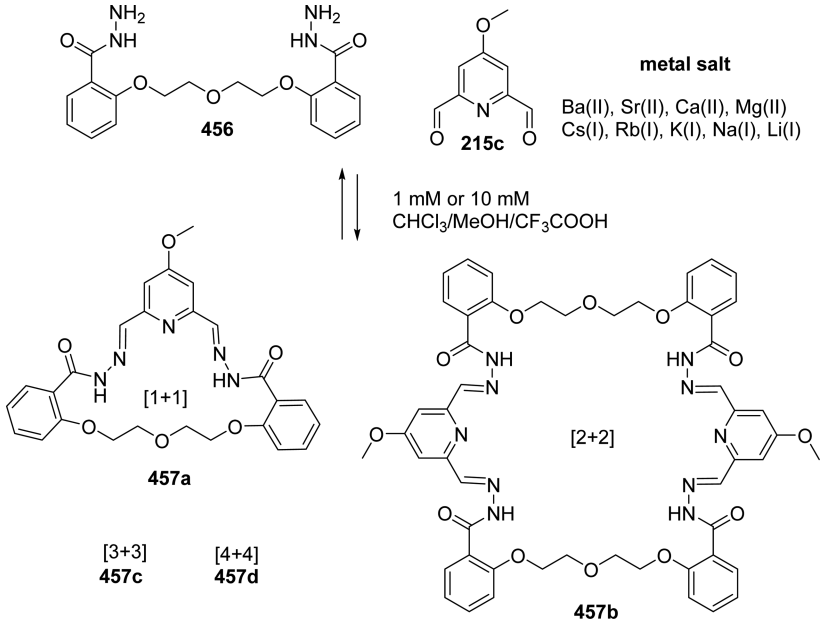

Figure 139. Macrocyclic structures obtained in the DCLs developed by Sanders.[455]

Table 4. Yields for Macrocycles Described in Figure 139 Obtained from DCLs Using Different Metal Cations[455]

	macrocycle [1 + 1] **457a**	macrocycle [2 + 2] **457b**	macrocycle [3 + 3] **457c**	macrocycle [4 + 4] **457d**
Ba(II)	13	61	17	9
Sr(II)	19	73	4	4
Ca(II)	51	49	–	–
Mg(II)	82	18	–	–
Cs(I)	85	15	–	–
Rb(I)	86	14	–	–
K(I)	86	14	–	–
Na(I)	87	13	–	–
Li(I)	88	12	–	–
no template	93	7	–	–

planarity at this region, as well as the use of bulky substituents at the metal center.[436] An excellent stereoselectivity was observed under the optimized conditions, achieving essentially quantitative yields for the desired macrocyclic product **437**, without formation of macrocyclic dimers.

Very interestingly, Leigh and co-workers have employed the RCM strategy in combination with the use of palladium(II) as a square planar template for the preparation of a very large macrocycle (**576**). Precursors **438** and **439** were assembled together by coordination to palladium(II) forming the metal complex **440**. The RCM reaction of **440** allows obtaining product **441** with a "figure of eight" conformation able to encapsulate a Pd atom in a square planar tetradentate arrangement. Removal of Pd from the complex **441**, using cyanide, afforded the free macrocycle **442** (Figure 134).[437] It must be noted that only a single macrocyclic structure (**442**) was obtained.

James and co-workers have studied the factors that favor a CuAAC-mediated macrocyclization. The macrocyclization reaction in the absence of any ligands able to coordinate copper yielded essentially oligomeric byproducts. The use of ligands that coordinate strongly to copper have a positive effect on the yields

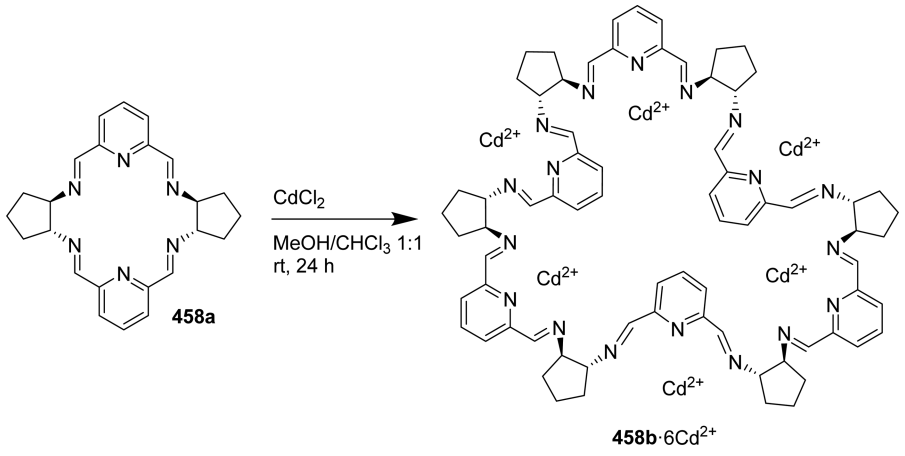

Figure 140. Templated synthesis of a [6 + 6] macrocycle under thermodynamic control. Reaction conditions: $CdCl_2$ (6.72 mmol) was added to the suspension of the [2 + 2] macrocycle **597** (1.07 mmol) in methanol/chloroform 1:1 (600 mL), room temperature, 24 h. Imine groups of the product were reduced using $NaBH_4$, and Cd(II) removed using Na_2S, 30% yield.[457]

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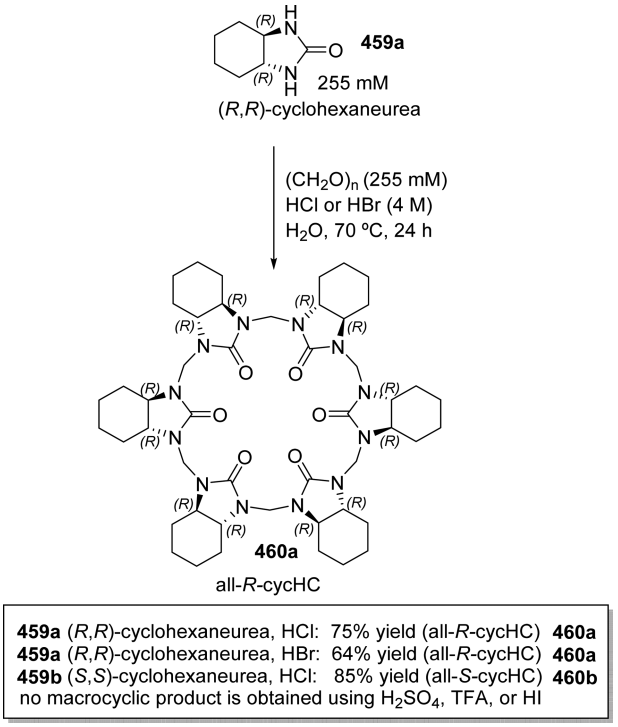

Figure 141. One-step synthesis of enantiomerically pure cyclohexylhemicucurbit[6]urils (cycHC).[464]

obtained for the monomeric macrocycle **445**, reducing also the formation of dimeric macrocyclic species and the formation of oligomers. Therefore, the selection of the appropriate ligand (best results were obtained for TBTA **444**) along with the appropriate halide counterions in the copper salt (best results were obtained using $Cu(CH_3CN)_4BF_4$) allowed them to optimize the macrocyclization conditions obtaining a 93% macrocyclization yield at 20 mM concentration of the open-chain precursor **443** (Figure 135).[438] Very interestingly, this process could be further optimized under environmentally friendly conditions when the reaction was carried out in flow. The copper tubing used provides a copper-surface-catalyzed AAC macrocyclization, clearly favoring the intramolecular reaction over intermolecular processes. This allowed the preparation of the corresponding 12- to 22-membered macrocycles in high yields using ca. 0.015 M concentrations of the precursors.[439,440] Following this general strategy of catalyst design and reaction condition optimization to reduce the unwanted intermolecular processes, they have also reported the synthesis of druglike macrocycles. It was possible to employ relatively high concentrations of reactants (from 20 to 100 mM) using the Ullmann coupling methodology with macrocyclic yields up to 97%.[441] The nature of the additives present, in particular those able to coordinate to the catalytic metal, were also shown to be critical for an efficient palladium-catalyzed C–H arylation macrocyclization reaction allowing obtaining the expected macrocycles in 40–75% yields at 30 mM concentration.[442]

Thus, the exact nature of the metal center and its overall coordination sphere is essential to define the ability of a transition metal catalyst to properly act favoring the head to tail macrocyclization of a given open-chain macrocycle precursor, simultaneously precluding intermolecular processes leading to the $[n + n]$ macrocycles and to open-chain oligomers. Spring and co-workers have used a synthetic strategy using a multidimensional coupling for the preparation of a library of 73 macrocyclic compounds with molecular shape diversity comparable to that of natural products. They assayed different cyclization methodologies and conditions, and they could observe that for a given open-chain substrate the cyclization yields could vary strongly

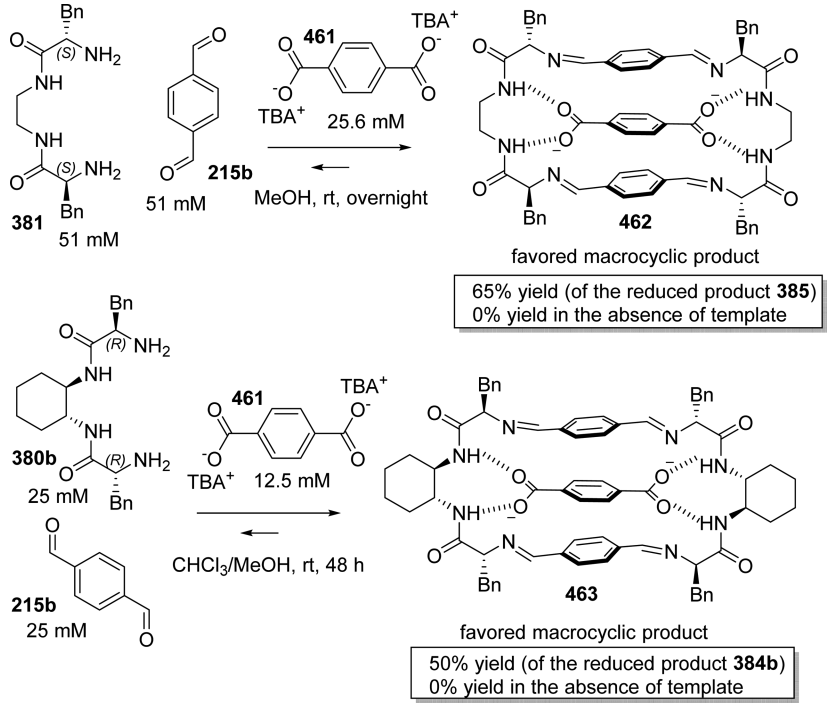

Figure 142. Anion templated synthesis of macrocyclic pseudopeptidic compounds. Only oligomeric products obtained in the absence of the anionic template.[466,467]

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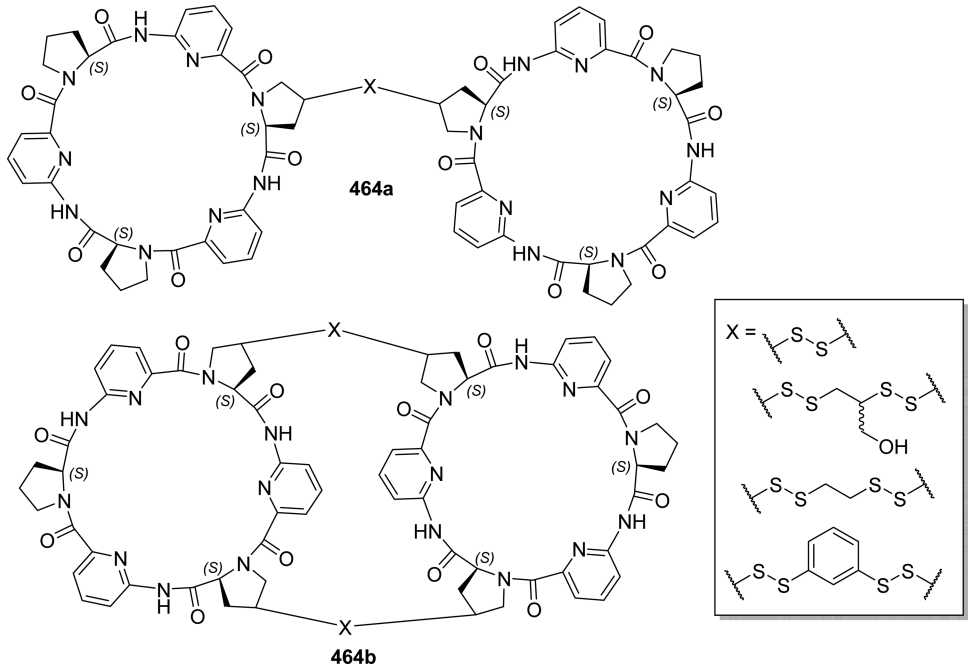

Figure 143. DCL based on the cyclopeptidic structures developed by Kubik and co-workers.[473]

depending on the catalyst and the conditions, although, as formerly considered, the disconnection selected can also be critical. They have reported macrocyclization average yields (using 1 mM concentrations for open-chain precursors **446** and **448**) of 81% for CuAAC macrocyclization (**447a**), 33% for RuAAC macrocyclization (**447b**), and 79% for enyne metathesis macrocyclization (**449**) (Figure 136).[443]

Katritzky and co-workers have developed a novel methodology for the synthesis of cyclotetrapeptides by palladium-promoted tandem deprotection/cyclodimerization from readily available Cbz-dipeptidoyl benzotriazolide precursors (for instance **450**) in yields up to 86%. The more favorable formation of the dimeric [1 + 1] macrocycle **453** may be attributed to the coordination of two molecules of N-unprotected dipeptide **451** to one Pd center, therefore stabilizing the corresponding transition state **452** through a classical template effect (Figure 137).[444]

Qin, Zhang, Zeng, and co-workers have reported the synthesis of energetically not favored strained macrocyclic hexamers **455** from monomer **454** using trimethyl aluminum as the coupling reagent (Figure 138). The use of this coupling reagent is essential to prepare the macrocyclic compounds **455** as other coupling reagents were not successful. Taking into account the nature of the resulting cavity, the participation of a template effect involving the participation of Al species could explain these results. They also reported the effect of the temperature in the macrocyclization reaction; decreasing the temperature the formation of the 2−5-mers increases and the macrocyclization yield decreases.[445]

The use of reversible reactions allows the generation of dynamic combinatorial libraries (DCLs). Intrinsically, the distribution of the different species at the equilibrium in these dynamic systems can be shifted by the addition of external factors, providing the molecular evolution of the systems by adapting the dynamic library to the new conditions.[446] Different approaches are used to prepare these dynamic systems.[447] Nevertheless, the imine bond formation, involving its reversible formation in equilibrium with the amine and aldehyde reactants, has been widely used by chemists in dynamic covalent chemistry (DCC). In the case of DCLs based on imines, the equilibrium can be shifted to the formation of the products by removing H_2O from the reaction mixture using a Dean−Stark apparatus or by adding a drying agent.[448] This methodology has been employed for the preparation of different macrocyclic structures that selectively recognize a particular chemical target that, accordingly, can act as a template for the improved synthesis of the corresponding receptor.[449] Thus, the addition of a template can shift the dynamic equilibrium to the formation of a particular product, and therefore the library is amplified to the formation of this one.[450] The selective formation of several alternative products (cyclic or noncyclic) can be obtained in this way.[451] In this regard, the use of Cd(II) allowed a highly diastereoselective amplification of a dynamic combinatorial library of macrocyclic oligoimines to provide a single cycle and a single diastereomer from the mixture.[452] In the same way, the presence or absence in the reaction medium of the sodium cation can be used to shift the prevalence of the [1 + 1] or the [2 + 2] macrocycles for a series of polyazamacrocycles, containing a furan moiety.[453]

Sanders and co-workers have used dynamic combinatorial libraries for the recognition of heavy metal ions, and they studied the amplification of the different macrocyclic species obtained from monomeric units **456** and **215c** (Figure 139) by the corresponding metal cation. When no metal is present, the formation of the [1 + 1] macrocycle (**457a**) is favored. In contrast, in the presence of a metal cation the formation of the [2 + 2] macrocycle (**457b**) increases, being the predominant product for Ba^{2+} and Sr^{2+} (along with the formation of smaller amounts of the [3 + 3] (**457c**) and the [4 + 4] (**457d**) macrocyclic compounds) (Table 4). On the other hand, an alternative shift of the equilibrium is also possible in this case. In the absence of any template the [2 + 2] macrocyclic product **457b** starts to precipitate if the concentration of the starting materials is 10 mM, and at 30 mM concentration the [2 + 2] macrocyclic product **457b** precipitates completely. Thus, for this DCL a double mechanism of amplification is possible. At 1−5

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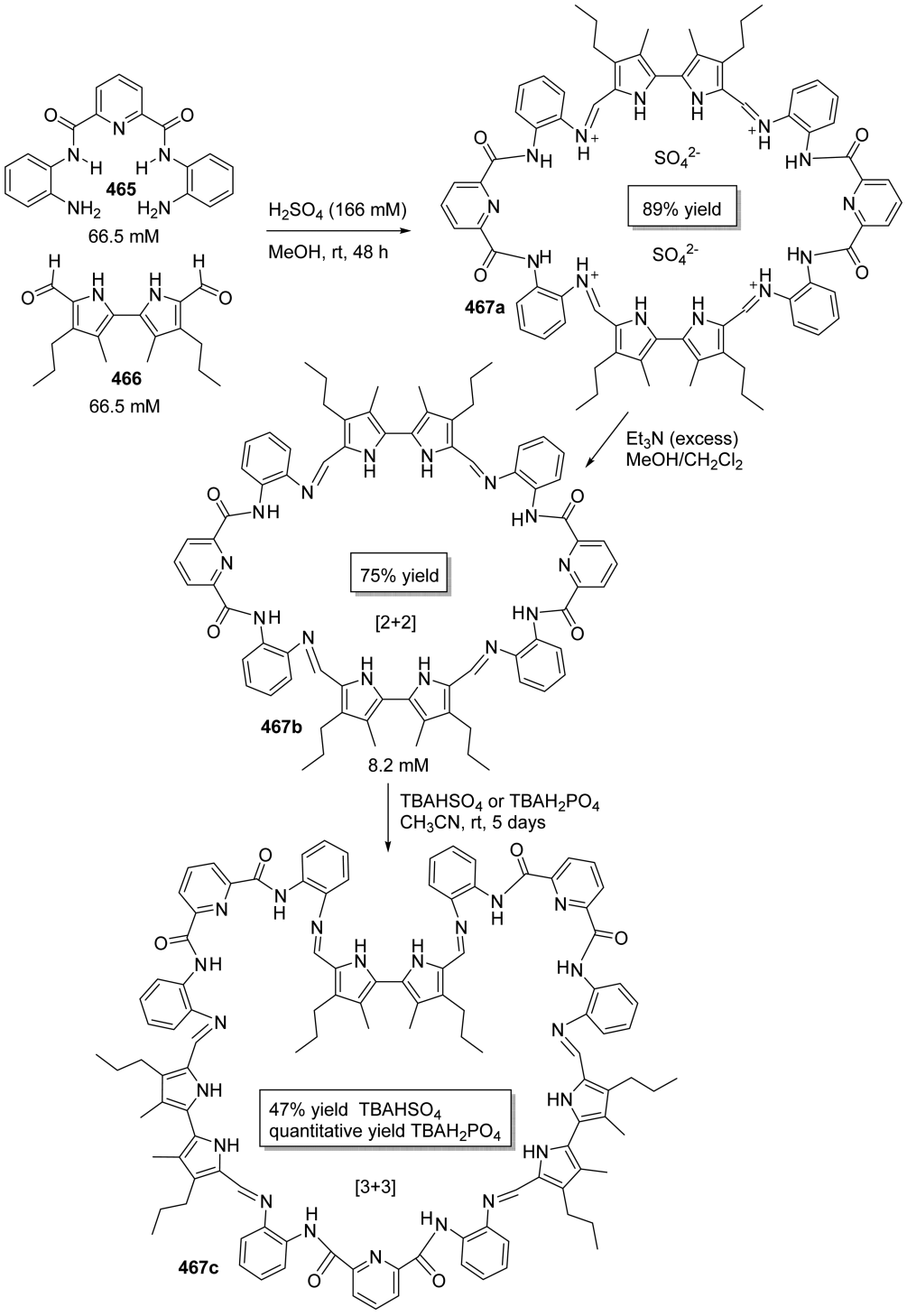

Figure 144. Anion templated macrocyclization reaction under thermodynamic control.[474]

mM concentration of the starting materials a 100% yield of the [1 + 1] macrocyclic product **457a** can be obtained, whereas if the concentration is 30 mM a 97% yield of the [2 + 2] macrocyclic product **457b** is formed.[454,455] Some of these macrocycles have been found to form complexes with lanthanides.[456]

In a similar way, Lisowski, Gregoliński, and co-workers have described the synthesis of a [6 + 6] macrocycle **458a** from the [2 + 2] macrocycle analogue **458b** using Cd(II) as the template (Figure 140). The binding of six Cd(II) to the [6 + 6] macrocycle **458b**, favoring its formation, has been suggested.[457]

6.2. Anion Templated Macrocyclizations

The supramolecular chemistry of anions has been deeply investigated, and many anion receptors have been developed.[463,458−460] The use of anions as templates for macrocyclization reactions is also a subject of increasing interest as long as they can be really efficient for such processes. Anions can induce important conformational changes on the receptors and, therefore, they can play an important role in the related conformational changes of the precursors, reaction intermediates, and transition structures leading to such hosts (i.e., having

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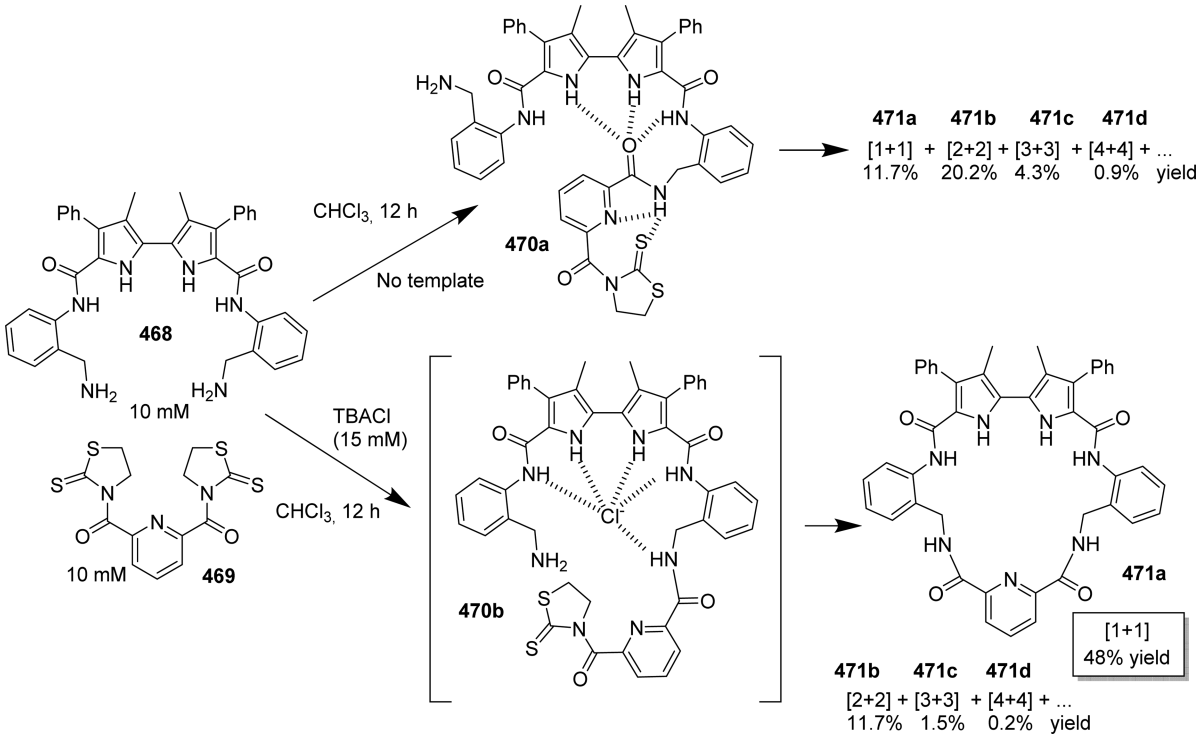

Figure 145. Anion templated synthesis of macrocyclic tetraamides.[475]

Table 5. Anion Template Effects in the Synthesis of Macrocyclic Tetraamides (Figure 145)[475 a]

	no template	$H_2PO_4^-$	HSO_4^-	OAc^-	Cl^-	Br^-	I^-	NO_3^-
[1 + 1] **471a**	11.7	55.0	34.0	63.8	47.8	7.5	0.6	2.9
[2 + 2] **471b**	20.2	5.4	0.6	11.9	11.7	20.0	21.3	20.0
[3 + 3] **471c**	4.3	0.7	0.1	1.6	1.5	3.0	4.0	4.4
[4 + 4] **471d**	0.9	0.1	0	0.4	0.2	0.4	0.9	0.9

[a]Yields obtained in the presence or absence of anions.

an effect on the thermodynamic and/or kinetics of the macrocyclization reaction).[461] Anions have also been used for the construction of sophisticated interweaved motifs and for the amplification of DCLs.[462,463]

As has been mentioned in the case of metal templates, many cyclization reactions also take place in the presence of different anions and the relative importance of conformational, configurational, and template effects, including those of the corresponding countercations, is again difficult to analyze. Thus, for instance, Aav and co-workers developed a method to prepare enantiomerically pure cyclohexylhemicucurbit[6]urils (all-*R* or all-*S*) from a single enantiopure building block ((*R*,*R*)-cyclohexaneurea **459a** or (*S*,*S*)-cyclohexaneurea **459b**) in a one-step process. The reaction is performed under thermodynamically controlled conditions and the all-*R*-macrocyclic compound **460a** precipitates from the reaction mixture as its HCl or HBr complex in good yields, 75 and 64% respectively, using (*R*,*R*)-cyclohexaneurea **459a** as the starting material (Figure 141).[464] The enantiomeric purity of the starting cyclohexaneurea is maintained in the process, and the use of (*S*,*S*)-cyclohexaneurea (**459b**) afforded the corresponding all-*S*-cycHC **460b** in 85% yield. However, the fact that no macrocyclic product is obtained when using other acids such as sulfuric, trifluoroacetic, or hydroiodic acid also suggests that the corresponding anions could play a key role as templates in this process.

The synthesis of [2 + 2] macrocyclic structures by the reductive amination of rigid aromatic dialdehydes with C_2 symmetric pseudopeptides can be favored by the use of an anionic dicarboxylate template **461**. In those cases where the open-chain precursor lacks the appropriate conformational/configurational preorganization (i.e., **381** and **380b**), it was not possible to obtain the macrocyclic compounds in the absence of the template (see Figure 115).[465,466] Remarkably, the effect of the anionic template is so important as to favor the formation of geometrically disfavored macrocycles from a dynamic covalent mixture of open-chain oligoimines by the formation of energetically stable supramolecular complexes **462** and **463**. This allows counterbalancing the "mismatch" effect of the configurations of the stereogenic centers at the spacer and at the amino acid derived fragments (Figure 142).[467] The extension of this approach has allowed the preparation of related [3 + 2] pseudopeptidic cages involving the reductive amination of two aromatic trialdehydes (1,3,5-substituted) with three C_2 symmetric pseudopeptides. The presence of the 1,3,5-benzene tricarboxylate anion allows the self-correction of the initially formed dynamic covalent system. After 3 h of the anion template addition, more than 80% of the dynamic library corresponds to the desired imine derivative macrobicyclic cage as observed by ^{1}H NMR.[468,469]

Kubik and co-workers also developed a family of pseudopeptidic compounds that recognize anions in water. These

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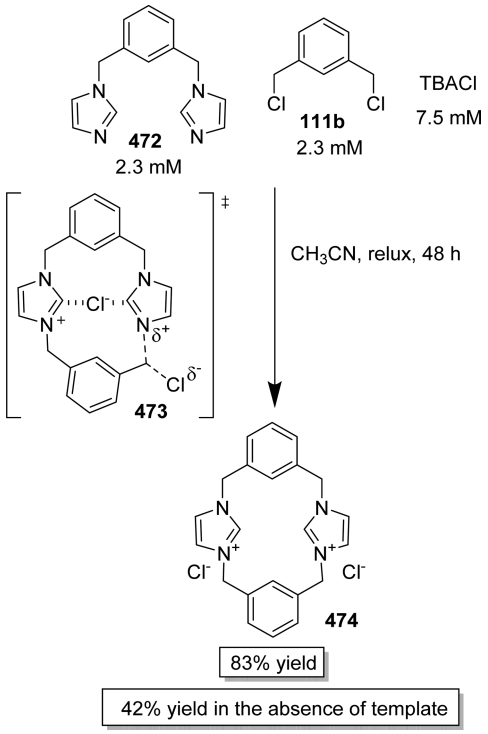

Figure 146. Chloride templated macrocyclization to form a bisimidazolium compound.[476,477]

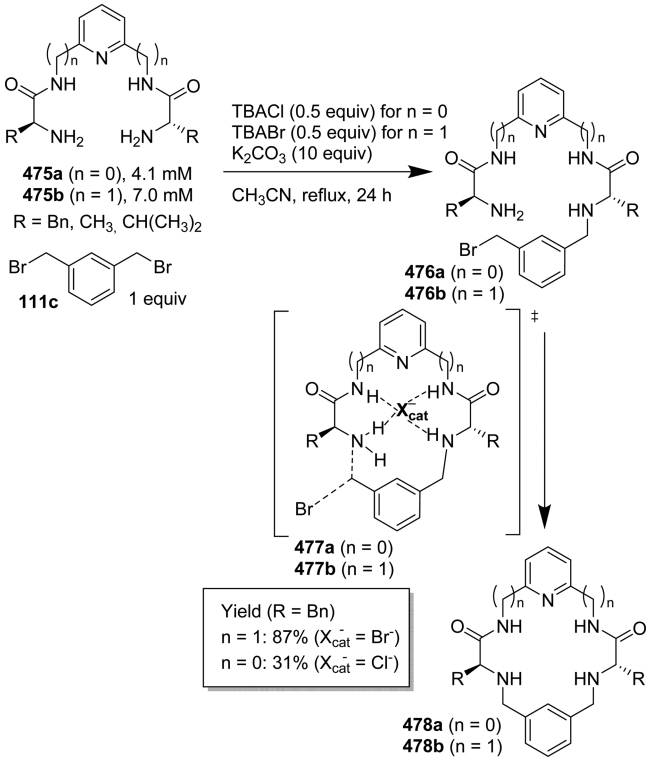

Figure 147. S_N2 anion templated synthesis of macrocyclic pseudopeptides with the proposed transition structure.[478]

macrocyclic host molecules have a strong tendency to form sandwich complexes, and interestingly this was found to be a highly cooperative process.[470,471] The anion-promoted self-assembly of two cyclopeptide rings to form 2:1 sandwich-type complexes has been used to prepare cyclopeptidic cages by

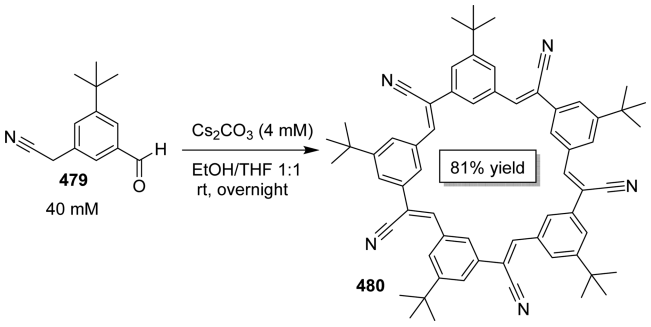

Figure 148. Macrocyclic synthesis by Knoevenagel self-condensation.[481]

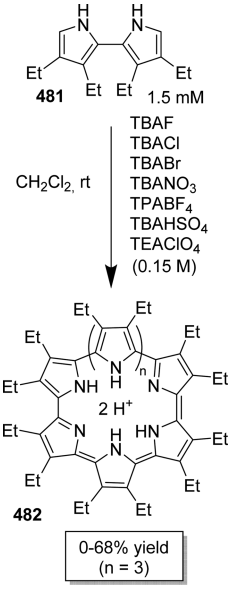

Figure 149. Electrochemical macrocyclization reaction to obtain cyclo[*n*]pyrrole.[483]

Table 6. Yields for the Preparation of the Macrocyclic Cyclo[8]pyrrole 482 (*n* = 3) for the Electrochemical Macrocyclization Reaction Described in Figure 149[483a]

electrolyte	yield **482** (%)
TBAF	0
TBACl	17
TBABr	33
$TBANO_3$	54
$TPABF_4$	55
$TBAHSO_4$	68
$TEAClO_4$	11

[a]TEA = tetraethylammonium; TPA = tetrapropylammonium; TBA = tetrabutylammonium.

linking the two substituted macrocycles by click chemistry.[472] In this regard, the same group has developed an anion-induced amplification of a macrobicyclic combinatorial library based on the presence of disulfide bonds. The corresponding DCLs were prepared by mixing the original bis(cyclopeptide) (**464a** and **464b** with X = −S−S−) with various dithiol spacers in acetonitrile−water solvent mixtures, in the presence of different anions as templates. After equilibration for 6 days the composition of the resulting DCLs showed a significant amplification of some of the components, in comparison with

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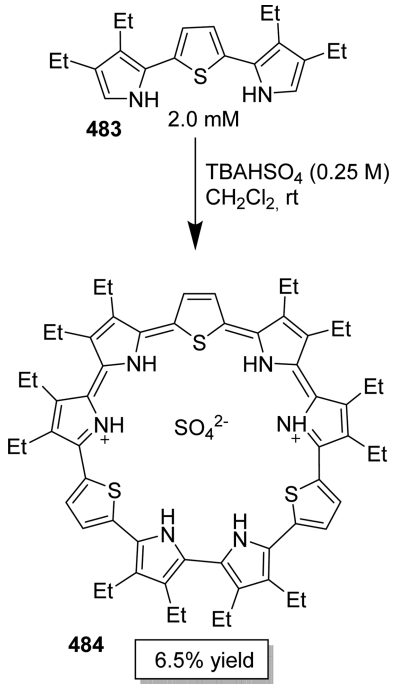

Figure 150. Electrochemical macrocyclization reaction templated by sulfate anions.[484]

the results obtained in the absence of the templating anion, in particular in the case of sulfate. These structures correspond to receptors with an exceptional affinity to sulfate anions in aqueous solution (log $K_{association}$ = 8.64), and the fine balance between affinity and rigidity of the receptor is a key factor (Figure 143).[473]

Sessler and co-workers have reported the anion-templated synthesis of polypyrrolic macrocycles under reversible thermodynamic conditions. They have found that the acid used (HCl, HBr, CH_3COOH, CF_3COOH, H_3PO_4, H_2SO_4, or HNO_3) for the condensation process of monomers **465** and **466** leading to imine formation plays a critical role in the distribution of the different products, favoring the formation of the desired macrocycle **467a** or the formation of unwanted oligomeric materials. Interestingly, treatment of the [2 + 2] macrocycle **467b** with $TBAHSO_4$ or $TBAH_2PO_4$ induces its conversion into the more stable [3 + 3] macrocyclic structure **467c** highlighting the crucial role of the anions in the thermodynamic stability of the resulting macrocyclic structures (Figure 144).[474]

Kataev and co-workers have demonstrated that anions can also template the generation of macrocyclic compounds when the formation of amide bonds is involved (Figure 145). They evaluated different anions (Cl^-, Br^-, I^-, CH_3COO^-, HSO_4^-, $H_2PO_4^-$, and NO_3^-) as anionic templates, finding that the best templates were Cl^-, CH_3COO^-, HSO_4^-, and $H_2PO_4^-$. For these reactions the structure of the reaction intermediate (**470a** or **470b**) determines the product distribution, with the obtained yields for the macrocyclic products in the ranges 1−64% for the [1 + 1] macrocyclic product **471a**, 1−21% for the [2 + 2] macrocyclic product **471b**, 0−4% for the [3 + 3] macrocyclic product **471c**, and 0−1% for the [4 + 4] macrocyclic product **471d** (Table 5). They proved by fluorescence experiments the presence of the expected reaction intermediate **470b** using TBACl as the catalyst. After optimizing the reaction conditions, they could obtain the [1 + 1] macrocyclic product **471a** in 95% yield using 10 equiv of TBACl. They rationalized these results by the calculation of the corresponding kinetic constants, showing

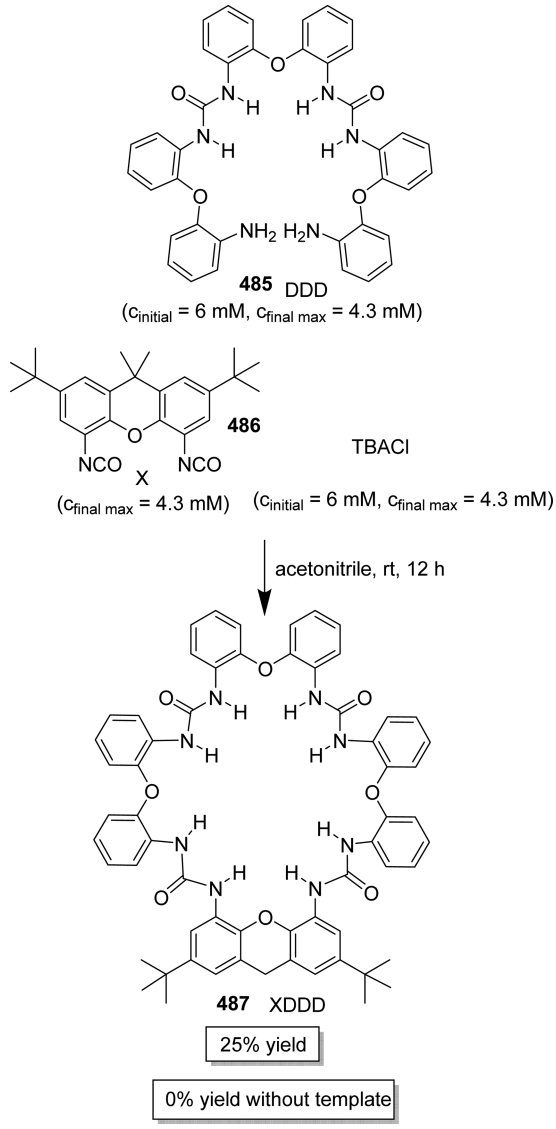

Figure 151. Chloride templated macrocyclization.[253]

that the addition of TBACl increased the macrocyclization kinetic rate constant.[475]

Alcalde and co-workers have reported the chloride and bromide templated macrocyclization reactions of **472** and **111b** with 83 and 75% macrocyclization yields, respectively. The effect of the anionic template is important as long as in the absence of the template the desired macrocyclic product **474** could only be obtained in 42% yield. They suggested a stabilizing interaction of the templating anion with the open-chain intermediate at the transition state **473** that yields the macrocyclic product. They have determined the kinetic constants for the macrocyclization reaction step in the presence of chloride, demonstrating its catalytic effect. The interaction of the chloride anion with the transition state **473** is stronger than the interaction with the open-chain precursor due to the macrocyclic nature of the transition state and the development of a positive charge on the initially neutral nitrogen atom, decreasing the energy barrier of the macrocyclization reaction step (Figure 146).[476,477]

Luis and co-workers have also demonstrated that appropriate anions can act as specific kinetic templates, involving supramolecular stabilizing interactions at the transition state, for the

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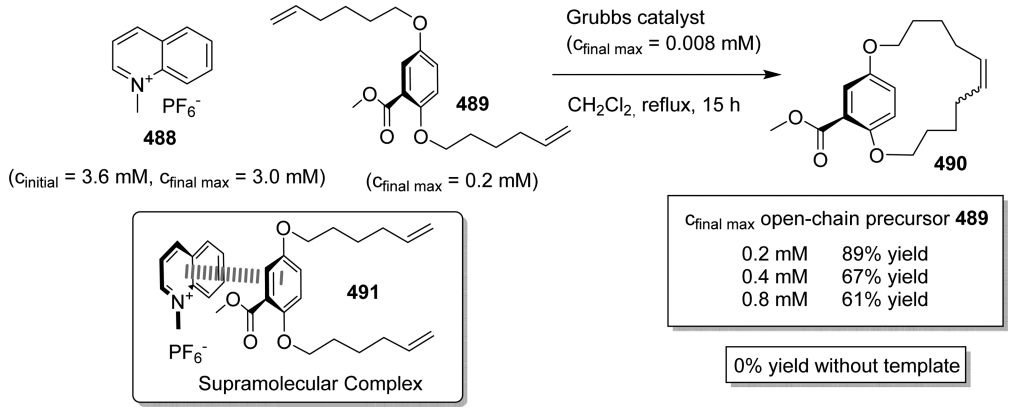

Figure 152. Arene templated macrocyclization reaction.[489]

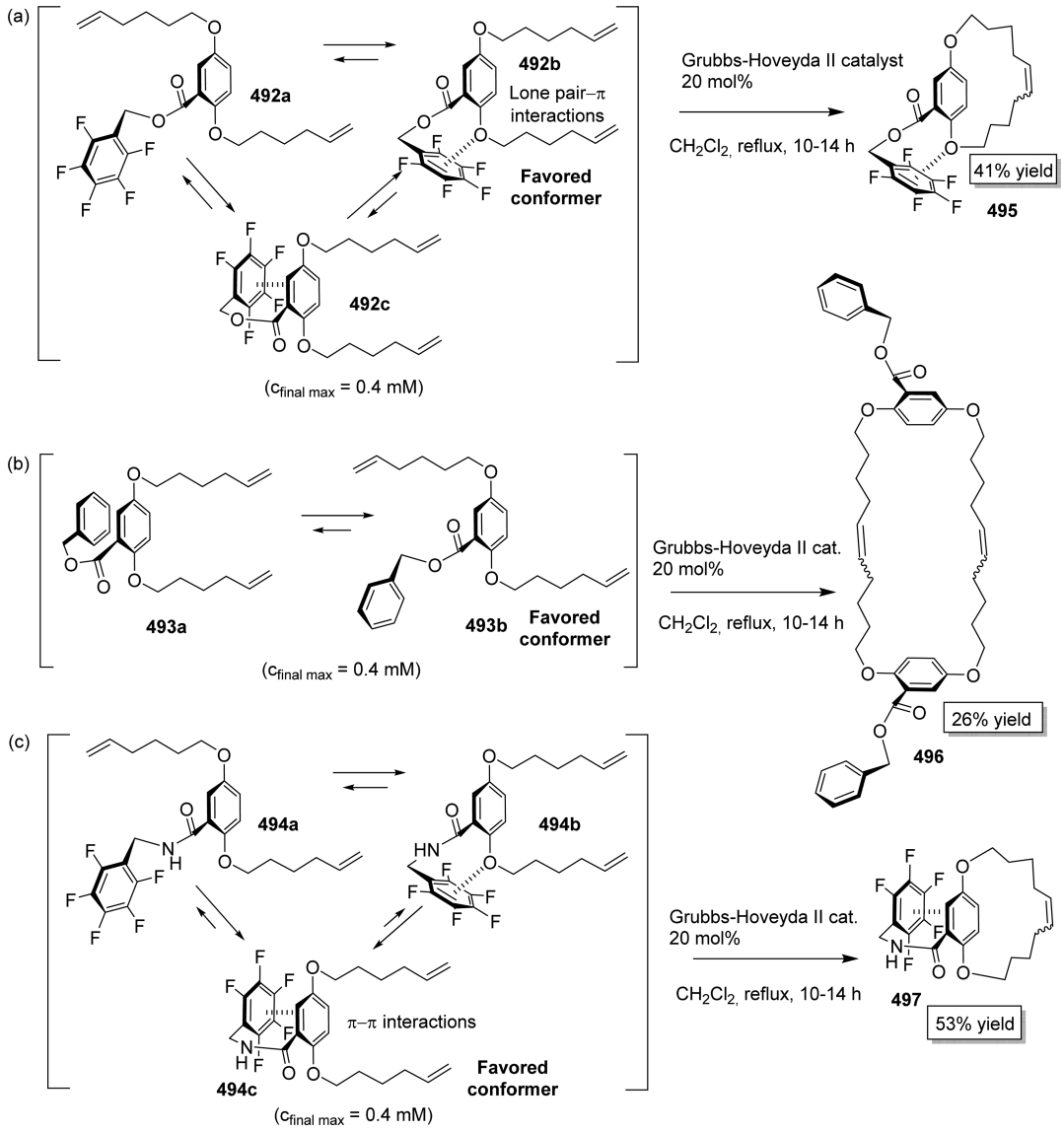

Figure 153. Effect of an arene auxiliary on the conformation of the starting material. (a) Ester bonded pentafluorophenyl auxiliary. (b) Ester bonded phenyl auxiliary. (c) Amide bonded pentafluorophenyl auxiliary.[490−492]

S_N2 ring-closing step in the macrocyclization reactions of C_2-symmetric pseudopeptides **475a** and **475b** with dibromide **111c** (Figure 147).[478−480] These macrocyclizations are affected by the presence of different anions, and the selection of the proper anion gives excellent results for the preparation of the corresponding macrocyclic structure (**478a** and **478b**). Thus, the optimum anion is Br^- when the central spacer is derived from 2,6-bis(aminomethyl)pyridine (**475b**), and Cl^- when the central

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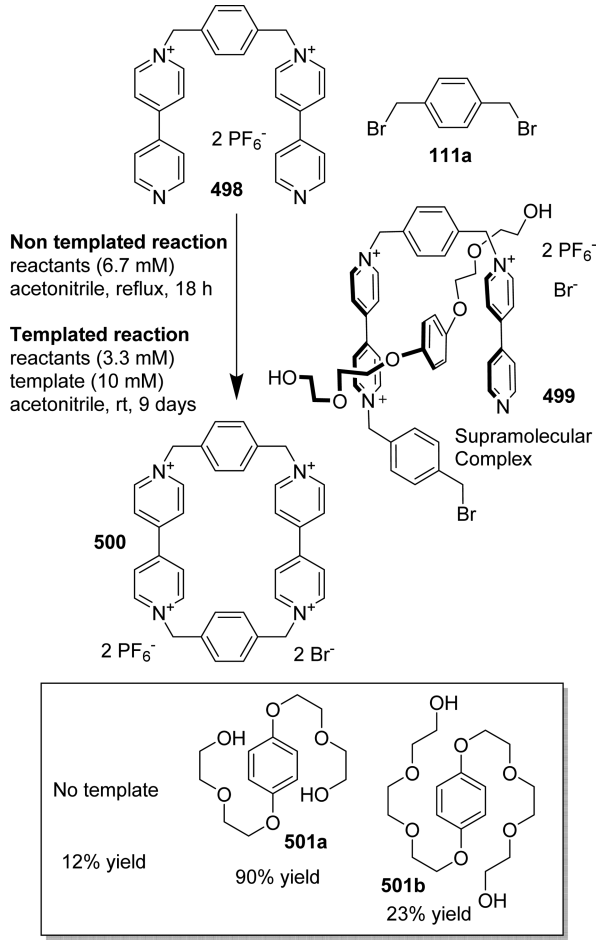

Figure 154. Electron rich templates for the synthesis of CBPQT^{4+}.[486]

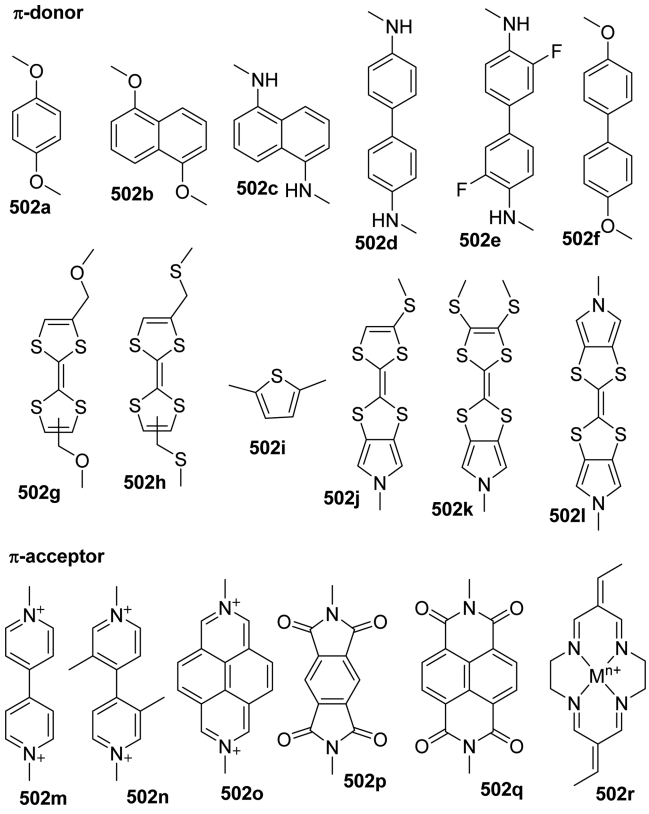

Figure 155. Arene and π-containing motifs used in the templated formation of mechanically interlocked molecules.[494]

spacer is derived from 2,6-diaminopyridine (**475a**). The kinetic studies show that the presence of those anions enhances both the yield and the rate of the macrocyclization reaction of the reaction intermediate **476b**. The anion stabilizes the transition state involved in the formation of the macrocyclic structure (**478a** and **478b**) more than the transition states involved in the oligomerization reactions or in the first reaction step. Therefore, the anion is able to act as a template forcing the two ends of the open-chain intermediate (**476a** and **476b**) to approach each other by forming hydrogen bonds with the two amino acid subunits (Figure 147).[478]

Flood and co-workers have described a multigram scale one-pot macrocyclization reaction in a 81% yield. This reaction providing a C_5 symmetric star-shaped molecule **480** is obtained in a process involving successive chain extension from **479** followed by the macrocyclization of the corresponding pentameric open-chain precursor. Although this precursor can have a high level of favorable preorganization associated with the stereochemistry of the double bonds formed, the authors suggest the participation of the carbonate base as a template (Figure 148). This suggestion was based on the fact that the use of charge-neutral bases such as piperidine, pyridine, triethylamine, and 1,8-diazabicycloundec-7-ene only yields low quantities of dimers and unconsumed starting monomer, in the presence and absence of $TBAPF_6$.[481,482]

Sessler and co-workers have described the electrochemical syntheses of cyclo[*n*]pyrrole assisted by the anions present in the salts employed as electrolytes. They demonstrated that the use of the appropriate anions, acting as templates, favors the electrochemical oxidative conversion of 3,3′,4,4′-tetraethyl-2,2′-bipyrrole **481** into the corresponding cyclo[8]pyrrole **482** in yields from 0 (using TBAF) to 68% (using $TBAHSO_4$) (Figure 149 and Table 6).[483] Similar results were found for the related precursor (**483**) of the macrocycle **484** using $TBAHSO_4$ as the electrolyte (Figure 150).[484]

In the case of the preparation of tetrameric macrocycles obtained from xanthene (X) and biphenyl oxide (D) subunits discussed in section 5.1.3 (see Figure 60), the preparation of the XDDD macrocycle **487** from diamine **485** and diisocyanate **486** was only possible using TBACl in acetonitrile as the solvent. Under these reaction conditions, the Cl^- anion templates the macrocyclization reaction allowing obtaining the macrocyclic compound **487** in 25% yield, while it was not possible to obtain the macrocycle **487** in the absence of the template (Figure 151).[253]

6.3. Arene Templated Macrocyclizations

Arene moieties have also been used to facilitate macrocyclization reactions. Molecules containing arene subunits can act as preorganizing elements favoring the adoption of the conformations most appropriate for the cyclization by participating in different types of aromatic interactions with the corresponding structural fragments of the precursor. In general, the use of organic molecules as templates can be extremely challenging when compared with spherical cations or anions. This difficulty arises from the generally weaker and more directional noncovalent interactions in which they participate.[485−487] In some instances, the effect can be described in terms of the classical template effect in which the precursor wraps around the template to facilitate the cyclization, but in many other instances the

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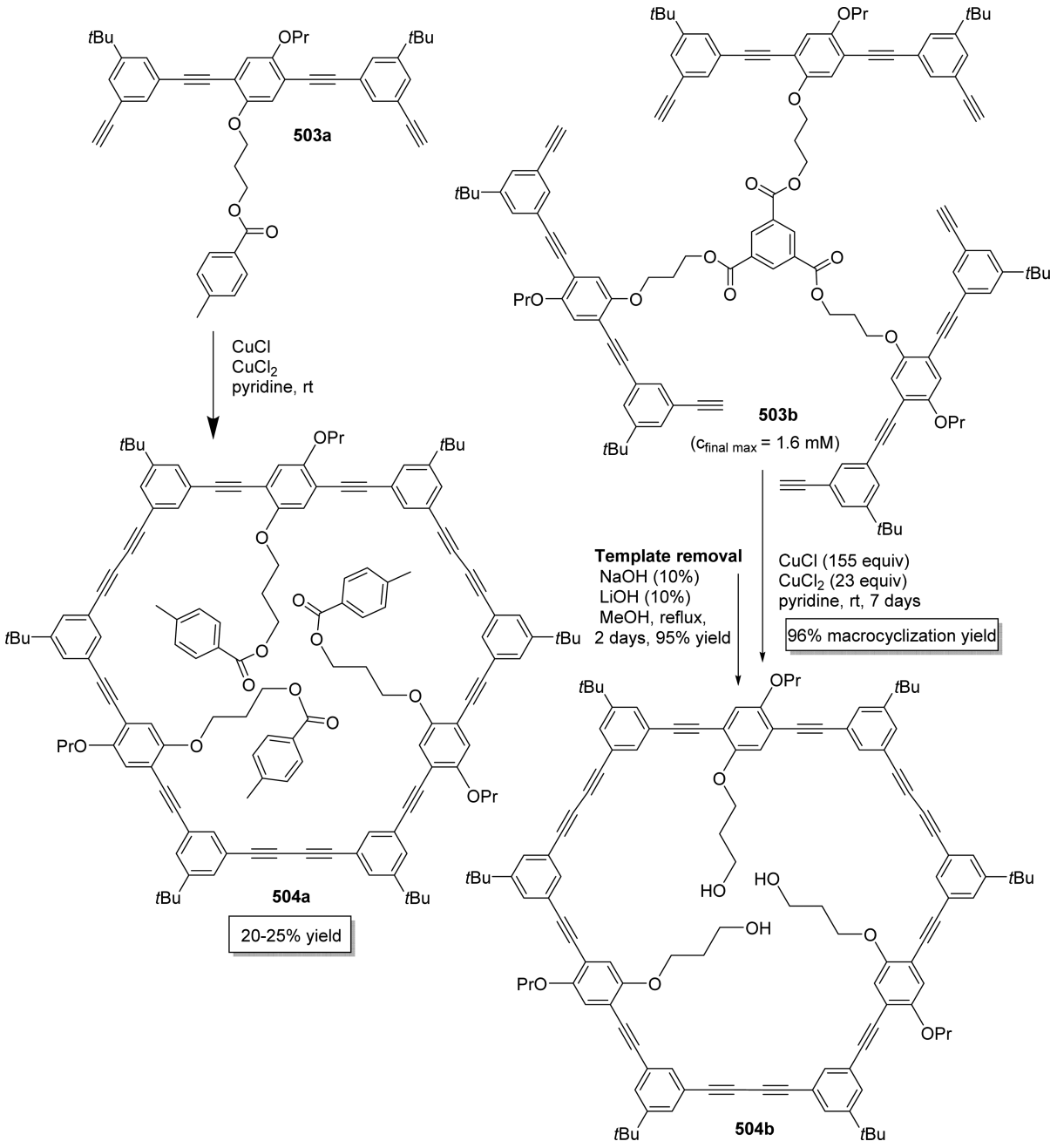

Figure 156. Nontemplated and covalent-templated synthesis of cyclophanes under high dilution conditions.[178,498]

preorganization of the precursor follows a different mechanism. Interestingly, Santoyo-Gonzalez and co-workers have described the preparation of a cage compound templated by toluene used as the solvent. For this reaction, the toluene acts as an arene template by establishing aromatic interactions with the open-chain precursor and allowing obtaining the expected cage in 78% yield.[488] Collins and co-workers have described an efficient macrocyclization using intermolecular noncovalent aromatic interactions to properly preorganize the open-chain precursor **489** (Figure 152).[489] The use of the external conformational driving element plays a crucial role favoring the formation of the supramolecular complex **491.** The macrocyclic product **490** was not obtained in the absence of **488**. Additionally, **488** can be recovered from the reaction mixture by filtration and it can be reused without any drop in the macrocyclization yield. This methodology avoids the need for additional reaction steps used in traditional strategies that introduce the template covalently attached to the molecule and remove it after performing the macrocyclization reaction (Figure 153).

Though we will not describe in detail the use of covalent templates, the use of aromatic auxiliaries can be used to highlight this approach as they have been used in several cases for the conformational control of the precyclization product to obtain different macrocyclic compounds by ring closing metathesis (Figure 153).[490−492] The most stable conformations, formed through the involvement of lone pair−π and/or $\pi-\pi$ interactions, orient the alkyl side chains to the same face reducing the entropic barrier for the macrocyclization reaction and increasing the yield of the macrocyclic product. The corresponding macrocycles (**495**−**497**) are obtained with yields in the range 10−63%. It must be noted that the proper selection of the aromatic auxiliary, which will determine the conformation

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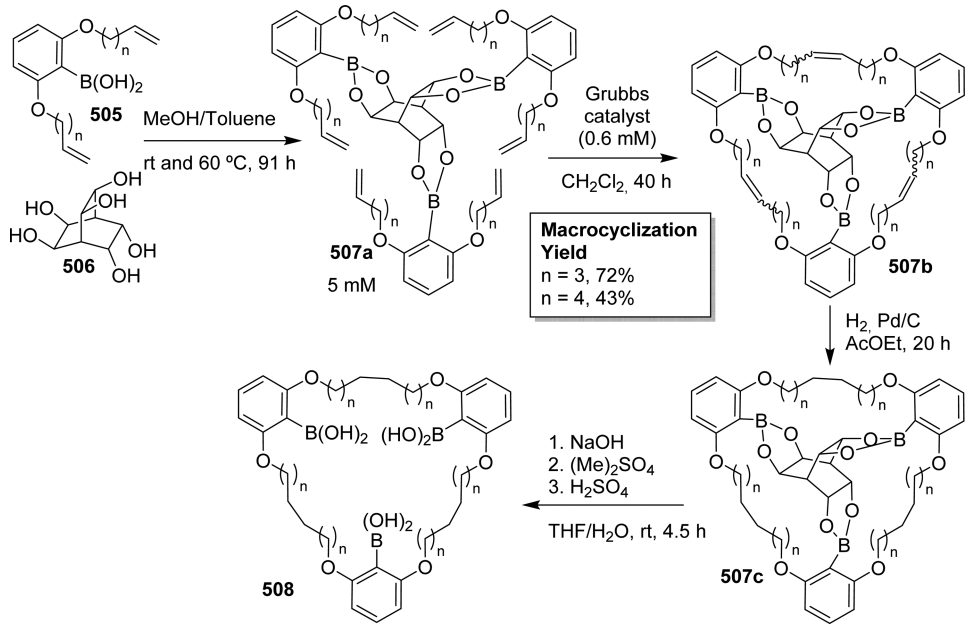

Figure 157. Synthesis of macrocycles using a covalent template based on boronic acid chemistry.[500]

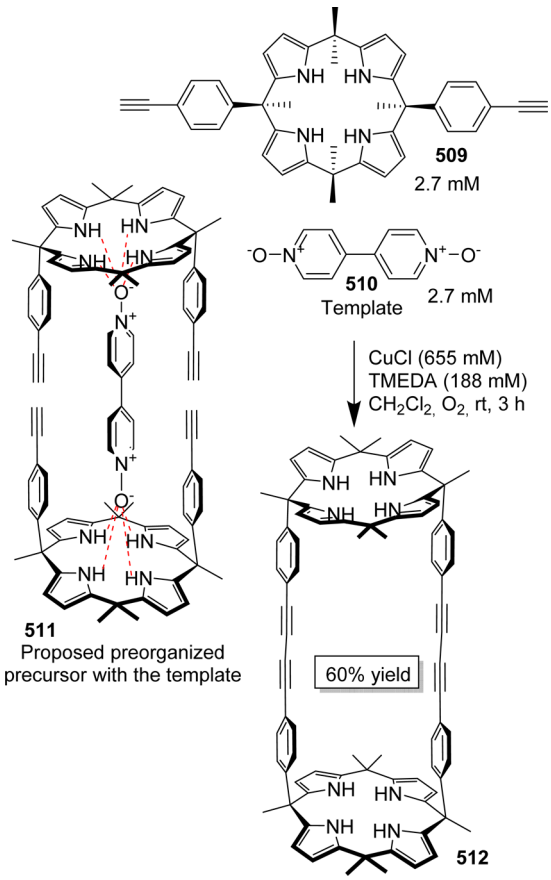

Figure 158. Templated synthesis of a calix[4]pyrrole based macrocyclic cage.[504]

of the open-chain precursor, can determine the formation of intramolecular/intermolecular cyclization products or the formation of byproducts obtained by intermolecular reactions (Figure 153). Important differences were associated with the attachment of the auxiliary by an ester (Figure 153a) or an amide bond (Figure 153c). It was found that the amide linkage increased the macrocyclization yields by 7−27% with regard to the yields obtained in the case of the ester linkage.[490−492] These results were rationalized by means of computational calculations (optimized conformers are schematized in Figure 153 as structures **492**−**494**). The optimized structures with the auxiliary attached by an amide bond display auxiliary−arene $\pi-\pi$ interactions in the most stable conformer **494b** (Figure 153c). In contrast, for the auxiliary attached by an ester bond (Figure 153a) only lone pair−π interactions are present in the most stable conformer **492b**. Therefore, the $\pi-\pi$ interactions present in **494b** favor efficiently the intramolecular macrocyclization reaction in contrast to the lone pair−π interactions existing in **492b**. Additionally, when the auxiliary−arene interactions are not favored, the most stable conformer was **493b**. In this case, the intermolecular macrocyclization yielding the dimeric macrocycle **496** is favored with regard to the intramolecular macrocyclization. These examples highlight the important role of the geometry of the most stable conformer in the macrocyclization process.

Of high relevance in this field have been the contributions made by Stoddart and other groups in the synthesis of interlocked structures, although, as mentioned in the Introduction, we will not consider in detail this area. Stoddart and co-workers studied the use of different neutral templates in the macrocyclization reactions to obtain tetracationic cyclophanes, in particular cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$, **500**) from precursors **498** and **111a**.[487] Besides the $\pi-\pi$ staking in which the electron-rich hydroquinone moiety of the template (**501a** and **501b**) can participate in the reaction intermediate **499**, its polyglycol chain has a definite effect on the efficiency of the reaction. The most efficient one is the template with a shorter chain (**501a**) providing the $CBPQT^{4+}$ in 90% yield (Figure 154).[486] They have also described a method using pyrene as the template to obtain a series of extended bipyridinium cyclophanes (Ex^nBox^{4+}) with yields up to 66%, performing the reaction with a 2 mM concentration of the open-chain precursors and a 12.5 mM concentration of the template.[493]

In this context, Stoddart and co-workers have developed a large variety of building blocks **502** with π-donor or π-acceptor

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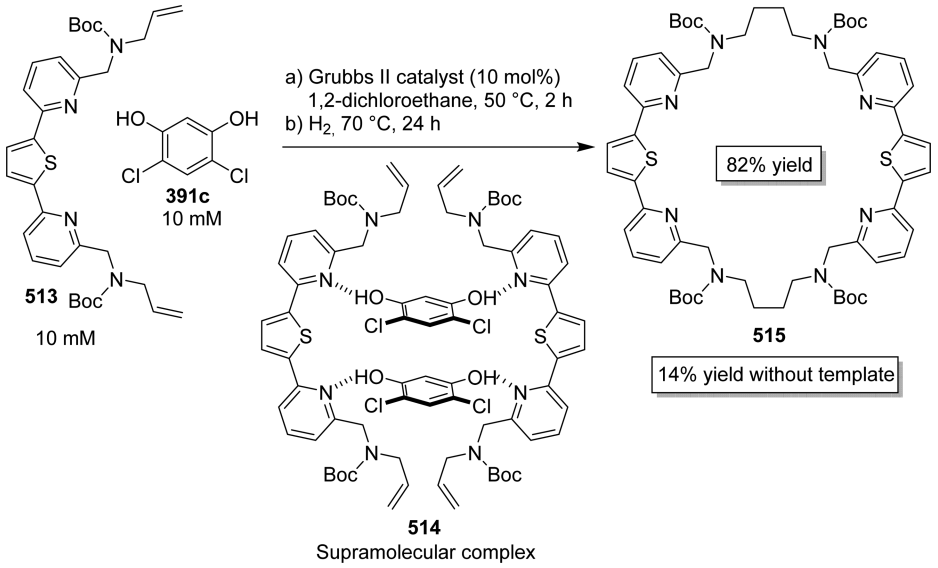

Figure 159. Hydrogen bonded templated macrocyclization reaction with the simultaneous use of two template molecules.[505]

properties that can be employed efficiently in the templated synthesis of mechanically interlocked molecules involving donor−acceptor interactions (Figure 155).[494−497]

6.4. Other Templates in Macrocyclizations

In order to improve the efficiency of the macrocyclization process, the use of a large variety of templates has been investigated. As in other related systems, the target is not only to enhance the macrocyclization yields, but also to allow obtaining more sophisticated macrocyclic structures that are not possible to prepare under nontemplate conditions. The widespread variety of shapes of possible templates based on organic molecules can facilitate the preparation of a diversity of complex cyclic or interpenetrated geometries. Many of the templates considered in this section can partially share structural features with some of the templates previously described (i.e., aromatic fragments or charged organic moieties), but, in general, they operate through a more complex set of hydrogen bonding, $\pi-\pi$, or ion pairing interactions.

A few additional examples in which the template and the open-chain precursor(s) are temporarily linked by covalent bonds will also be described to illustrate the very different alternative approaches that can be used in this area. Covalent templates can favor the macrocyclization with regard to the free monomers by the increase of the effective molarity of the reactive groups. Thus, for instance, Höger and co-workers utilized ester linkages to attach covalently three monomeric fragments, and therefore to bring in close proximity their reactive ends (**503b**) allowing the preparation of the corresponding trimeric macrocyclic compound **504b** in 96% yield. Under nontemplated conditions, the macrocycle **504a** could only be prepared in 20−25% yield from monomer **503a**, not being possible its isolation from the reaction mixture by recrystallization or column chromatography (Figure 156).[178,498] They have used this methodology to prepare related systems based on the use of a covalent template linking of two building blocks. This allows preparing the corresponding dimeric macrocycles in 88−92% yield using a concentration of the precursors around 1.5 mM, highlighting the extraordinary efficiency that can be achieved for the macrocyclization step assisted by a covalent template.[499]

Using this approach, Lüning and co-workers have synthesized the macrocyclic products **508**, by ring-closing metathesis, using a Grubbs' catalyst for the trimerization of boronic acids containing two alkene fragments (**505**) and employing the hexaol tridentate template **506** (Figure 157). They first studied the effect of the length of the chains (n = 3−6) for the macrocyclization reaction (to afford **507b**) by ^{1}H NMR and MS experiments. Best results were obtained for the open-chain precursors **507a** with n = 3, 4, and 6. For n = 5, a less efficient macrocyclization was observed. Using the conditions optimized from these experiments, they could prepare and isolate the trimeric macrocyclic products **508** with n = 3 and n = 4 (obtained by hydrogenation of the double bonds of **507b** and template removal from **507c**) with macrocyclization yields of 72 and 43%, respectively.[500] They have also prepared related dimeric macrocyclic systems using a bidentate template, obtaining similar yields in the macrocyclization step.[501−503]

Many other examples of the use of covalent templates can be found in the literature. However, the main drawbacks of this approach are the need for two extra reaction steps: one to attach the template to the building blocks and a second one for its removal from the macrocyclic product. The use of templates that operate by supramolecular interactions such as hydrogen bonds eliminates these drawbacks. Thus, Ballester and co-workers have prepared the cage structure **512** derived from a calix[4]pyrrole by a templated Hay coupling of two monomers (**509**). They used 1 equiv of 4,4′-dipyridyl *N*,*N*-dioxide (**510**) as the template to obtain the macrocyclic product **512** in 60% yield (Figure 158). The template assembles the two building blocks by the formation of hydrogen bonds facilitating the Hay coupling reaction between the reactive ends of **511**.[504]

Chevallier and co-workers have described a ditopic template that approximates two building blocks by hydrogen bonding (Figure 159). The use of 4,6-dichlorobenzene-1,3-diol (**391c**) as the template facilitates the hydrogen bonded templated macrocyclization through olefin metathesis. In this case, it has been reported that two molecules of the template act simultaneously to form a supramolecular complex (**514**), orthogonally assembled, between two template molecules (**391c**) and two monomeric units (**513**). This arrangement of the monomers facilitates the formation of the dimeric macro-

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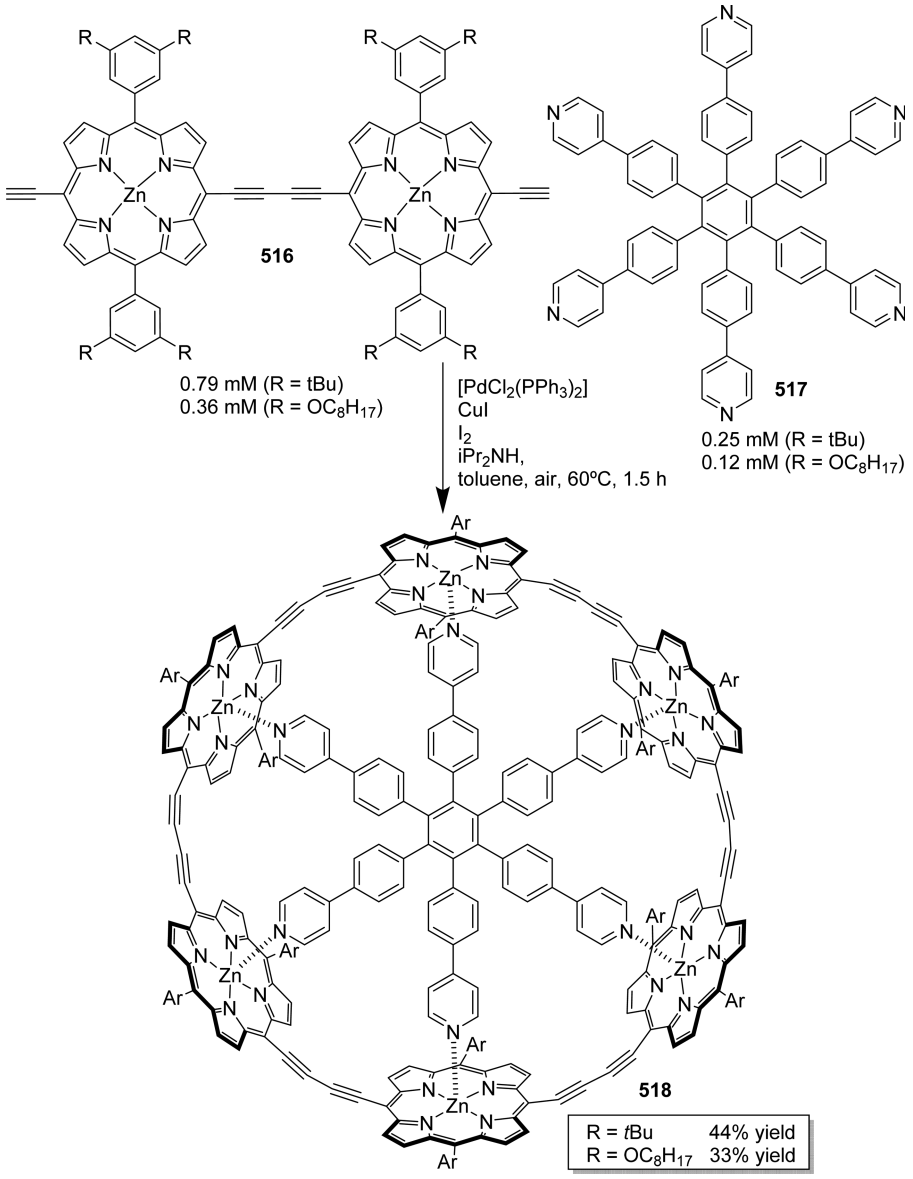

Figure 160. Templated porphyrin[6] nanoring synthesis.[506,507]

cyclic structure by approaching the reactive ends of the monomeric units. The in situ hydrogenation of the resulting double bonds allowed obtaining the target macrocyclic product **515** in 82% yield. In the absence of template, the macrocyclic product **515** was obtained in 14% yield at a 10 mM concentration of **513** (17% yield at 0.1 mM concentration) highlighting the critical role of the template in the reaction.[505]

The assembly of more than two building blocks is also possible by using the appropriate template with the necessary number of coordinating points in the correct geometrical disposition. Using this approach, Anderson and co-workers have described an efficient templated synthesis of the strained π conjugated D_{6h} porphyrin[6] nanoring **518** where the template **517** is bonded to the building blocks **516** by the formation of Zn−N(pyridine) bonds.[506] The stepwise effective molarities justify the good macrocyclization yields (33−44%) (Figure 160).[507] It was found that the effective molarity in the presence of the hexameric template **517** is in the range 100−1000 M and they have demonstrated that this is a cooperative process; i.e., each step is more favored than the previous one. The use of more flexible templates based on α- and β-cyclodextrins has also allowed obtaining the hexameric and heptameric porphyrin nanorings, respectively. It is worth mentioning that the flexible cyclodextrin templates act as effectively as the previously described rigid ones for templating the synthesis of porphyrin nanorings. The porphyrin[6] nanoring was obtained in 22% yield from the diethynyl-porphyrin monomer (0.80 mM) using α-cyclodextrin as the template (0.10 mM) and in 59% yield from the diethynyl-porphyrin dimer (0.40 mM) using α-cyclodextrin (0.10 mM) as the template. The porphyrin[7] nanoring was obtained in 4.7% yield from the diethynyl-porphyrin monomer (0.80 mM) using β-cyclodextrin (0.10 mM) as the template.[508]

Another elaborated strategy to template the approaching of both reactive ends of the open-chain precursor has been reported by Beer and co-workers. This strategy combines the use of anions and positively charged organic fragments that can participate in hydrogen bonding and aromatic interactions.[509] Some illustrative examples are gathered in Figure 161. They performed the macrocyclization reaction of the di(acid chloride) **205f** and the diamine **519** in the absence of the template obtaining the

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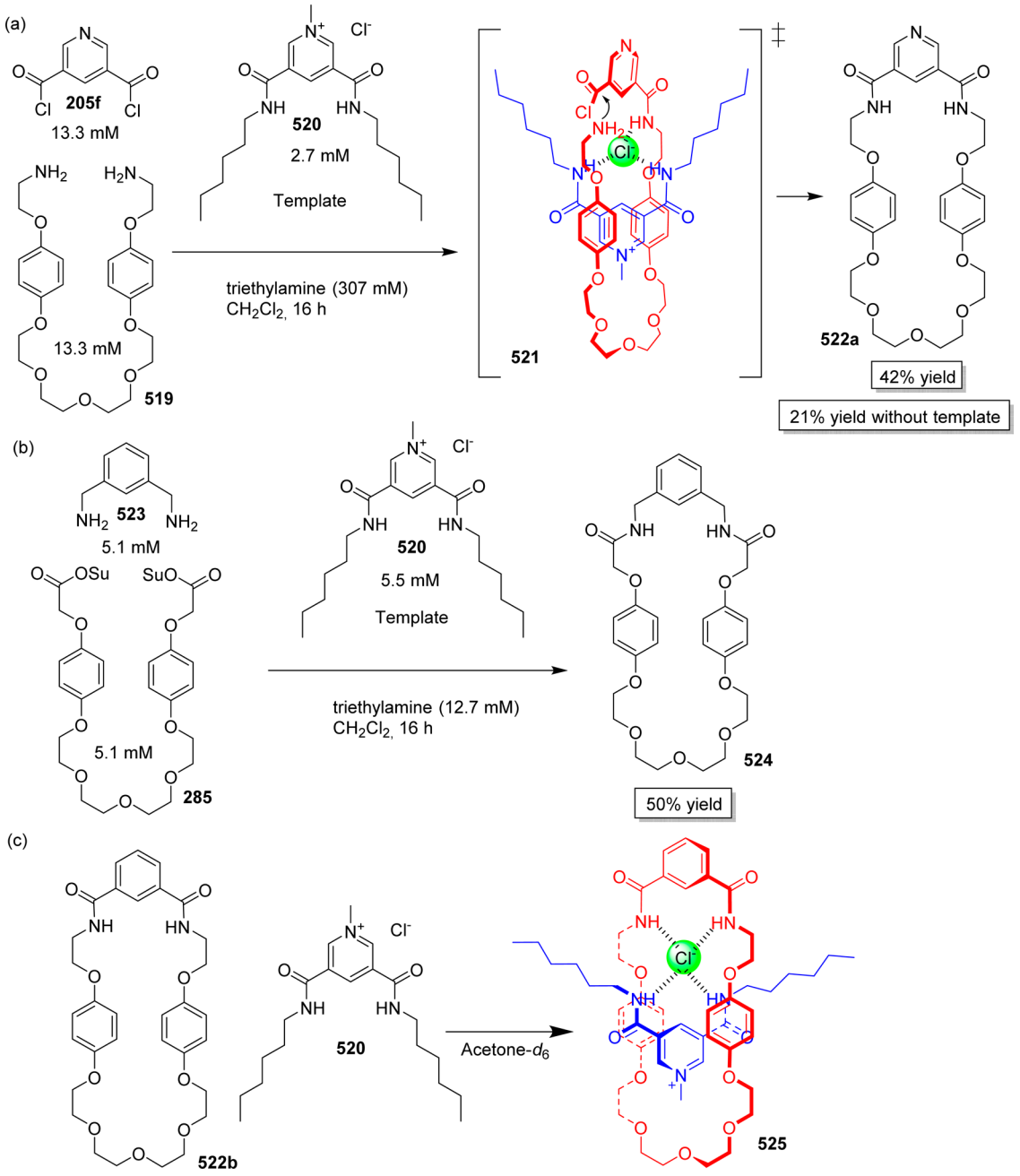

Figure 161. Macrocycle templated synthesis by ion-pair association, $\pi-\pi$ stacking, and hydrogen bonding. (a) Synthesis of macrocycle **522b**.[511] (b) Synthesis of macrocycle **524**.[510] (c) Chloride templated pseudorotaxane assembly.

macrocycle **522a** in 21% yield. The same macrocyclization reaction in the presence of the template **520** afforded the macrocycle **522a** in 42% yield. This increase in the macrocyclization yield is rationalized by the formation of a supramolecular complex that stabilizes the corresponding transition state **521** (Figure 161a). The use of the same template allowed the preparation of the macrocycle **524** in 50% yield from the activated diacid **285** and the diamine **523** (Figure 161b). Different experiments show that the threading of the template **520** in the macrocyclic cavity **522b** only takes place when the chloride anion is used, and no threading is observed when the corresponding hexafluorophosphate is used. This highlights the important role of the counteranion for the formation of the pseudorotaxane assembly. The hydrogen bonds between the anion and both macrocyclic **522b** and thread **520** components stabilize the pseudorotaxane **525** (Figure 161c).[510,511] This methodology was employed to prepare different interpenetrated and interlocked structures.[512−516] Overall, the nature of the anion and the anion recognition site of the open-chain receptor are important factors for an efficient templation. Additionally, the strength of the ion-pair association, $\pi-\pi$ stacking, and hydrogen bonding interactions in which the anion is involved with the macrocycle and the thread are essential factors.[510,514,517]

As has been mentioned previously, the use of templates in dynamic combinatorial synthesis can produce an amplification of the species that form the most stable complex. Using this approach, Stoddart and co-workers have described the use of a cationic template (in this case dibenzylammonium **527**) that operates under thermodynamic control and shifts the corresponding equilibria toward the assembling of the pseudorotaxane

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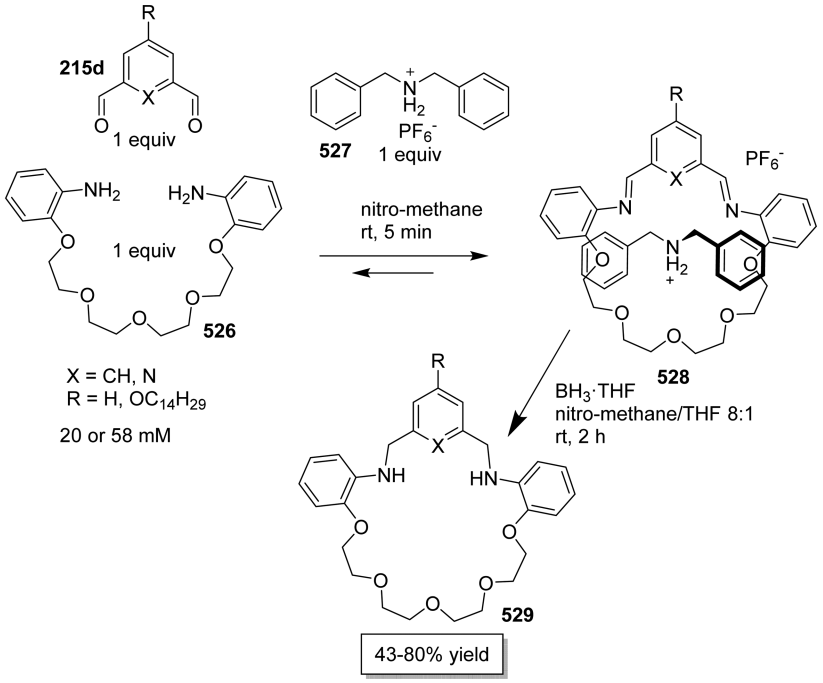

Figure 162. Macrocycle templated synthesis under thermodynamic control using dibenzylammonium as the template.[518,519]

528 from dialdehyde **215d** and diamine **526**. The free macrocycle **529** is obtained after reduction of the imine bonds in 43−80% yield (Figure 162). The template avoids the formation of other macrocyclic or oligomeric products,[518,519] and this methodology has also been used for rotaxane[520,521] or catenane[522] preparation. It is important to note that, in many instances, the use of ammonium cations as templates involves a complex series of supramolecular interactions, well beyond the mere electrostatic attraction with electron rich fragments.

The influence of the molecular structure of different organic ammonium cations as templates in the amplification of dynamic libraries has been studied in detail by Sanders and co-workers. The dynamic library was set up by the in situ deprotection of **530a** to obtain the difunctional aldehyde−hydrazide monomer **530b**. They have demonstrated that under kinetic control the process yielded more than 14 cyclic species for the nontemplated reaction. Under thermodynamic control, the cyclic dimer **531a** was obtained as the major cyclic compound (88% yield) with the corresponding trimer **531b** being obtained in 11% yield. However, with the use of acetylcholine (**532**) as the appropriate cationic template, the cyclic trimer **531b** was obtained in 86% yield, while the dimer **531a** was formed in 13% yield along with minor quantities of higher oligomers. The use of 1-methylquinuclidin-1-ium cation (**533**) as the template also shifts the distribution of products, providing a 41% yield of the dimer **531a**, a 56% yield for the trimer **531b**, and traces of higher oligomers (Figure 163). Moreover, it was found that an increase of the concentration of the template amplifies the formation of the specific product.[523] The analysis of the corresponding supramolecular complexes between the macrocyclic compounds and the templates suggest that the driving force for this template effect and the accompanying molecular amplification is the formation of C−H···O hydrogen bonds between the amide oxygen atoms of the carbonyl groups of the macrocycle and the ammonium hydrogen atoms of the cationic template. Using a similar approach, the amplification of two sets of diastereomeric receptors induced by a large variety of neutral and complex ammonium guests, including biologically relevant compounds such as acetylcholine and morphine, has been fully investigated.[524] In general, the results obtained showed that the relative amplification provided for a given host by a series of guests correlates well their relative affinities for that host. Besides, this amplification can be selective for the best receptor if relatively small amounts of the template guest are used.

Among the different organic molecules that can be used as templates, one family of particular interest is that of polyamines. Thus, the spermine binding ability to the array of negative charges of the DNA backbone inspired Sanders and co-workers for its use in the templated dynamic synthesis of a [3]catenane from monomers **534** and **535**. The use of spermine (**536**) as a template was found to be key to favor the formation of the [3]catenane compound **537** as long as in the absence of template only [1 + 1] macrocyclic compounds and the [2]catenane are obtained (Figure 164). This appreciable effect of the template is attributed to the strong interaction between spermine **536** and the [3]catenane **537**, the formation of which is also stabilized by $\pi-\pi$ donor−acceptor interactions. The authors propose that the spermine template can interact with the catenane carboxylate ions in a similar fashion that spermine interacts with the phosphate groups of the double helix of DNA.[525]

6.5. Biological and Pseudobiological Macrocyclizations

Many biological syntheses involve the use of the appropriate template biomolecules encoding the information required to develop the correct structure. These also include the synthesis of macrocyclic compounds. Different efforts have been reported for the use of biocatalytic approaches for the preparation of macrocycles in the laboratory, and a few examples have been discussed in other sections. Additional examples include the biosynthesis of cyclic structures via extensive post-translational modification of ribosomally encoded peptides. Prepeptide gene replacement and in vivo processing have allowed modifying the ring size in the case of thiocillins.[526] Boddy and co-workers characterized in vitro the thioesterase from PKS13 involved in zearalenone (a fungal macrocyclic polyketide) biosynthesis (Zea-

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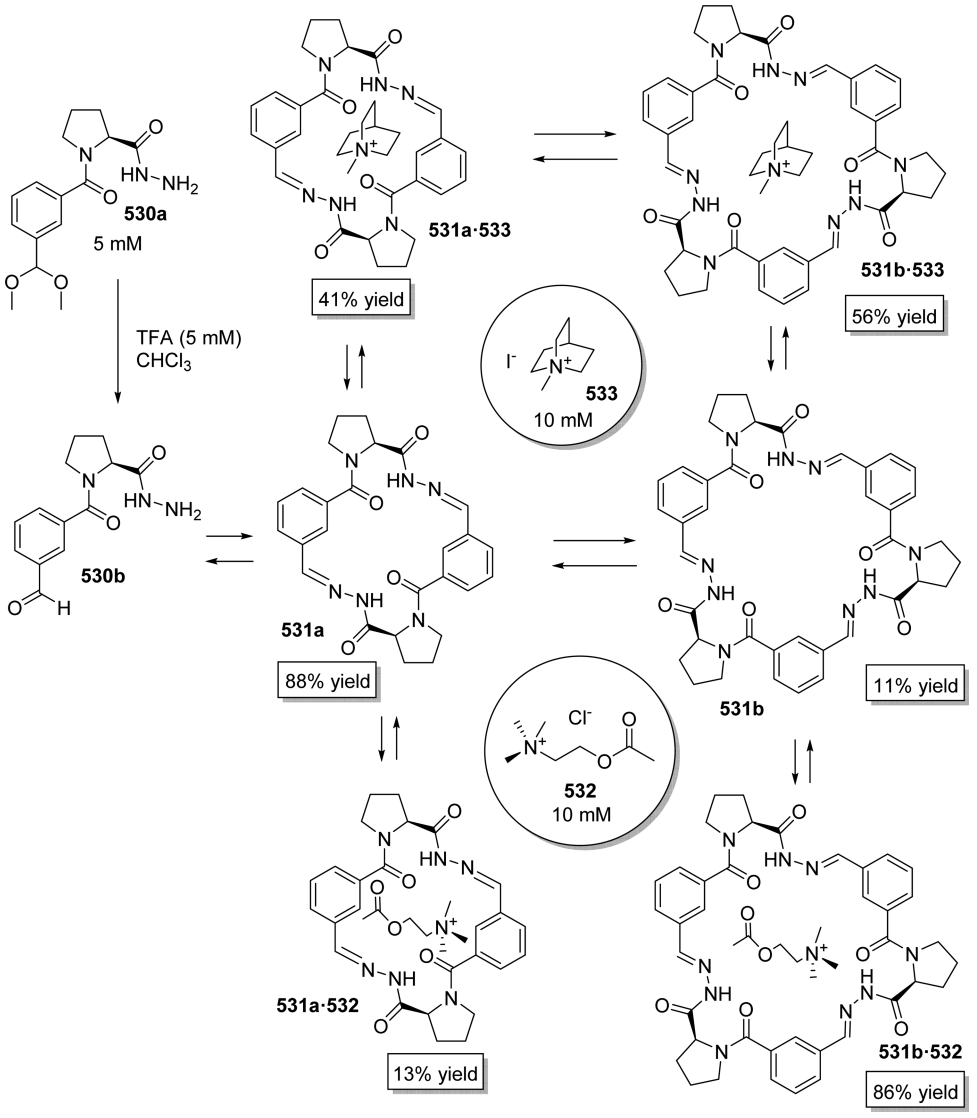

Figure 163. Evolution of dynamic combinatorial macrocyclic libraries under thermodynamic control in the absence and presence of ammonium templates.[523]

TE) and were able to show that it efficiently catalyzed the macrocyclization of a linear thioester-activated model of zearalenone. Additionally, this Zea-TE also catalyzed the cross coupling of a benzoyl thioester with an alcohol and an amine.[527] The thioesterase (TE) domain from iterative polyketide synthases (iPKSs) has been shown to play a key role in the nature of the fungal polyketide release from the final iPKS-bound intermediate, in order to provide lineal, cyclic, or macrocyclic polyketides.[528] Catalyzed macrocyclizations by the erythromycin polyketide synthase TE (DEBS TE) have been reported to be highly stereospecific and regiospecific, with the exclusive formation of a 14-member ring from a diol that could also form an alternative 12-member lactone.[529] Schmidt and co-workers characterized the first natural peptide-cyclizing enzyme as a pure protein, and used this PatG protease for the macrocyclization of different open-chain peptidic substrates (i.e., **538** to afford **539**, Figure 165),[530] including nonribosomal peptides and hybrid polyketide−peptides. The efficiency of the macrocyclization depends on the peptidic sequence yielding a mixture of linear and macrocyclic products in some instances.[531] The overall mechanism seems to be quite similar to those observed in thioesterases but involving a transamidation reaction (Figure 165).

It is clear that, in the case of enzyme-catalyzed macrocyclizations, the active site of the enzyme templates the required folding of the open-chain precursor and the approaching, with the proper orientation, of its two reactive ends. This template effect, however, is quite different from the classical template effect we have described in most cases. In the classical example, the template occupies the center of the developing macrocyclic structure and the fragments or functional groups defining its template activity are oriented in a convex arrangement. Here, the macrocycle precursor is accommodated in the cavity of the catalytic site and the fragments and functional group of the enzyme defining the template and the catalytic activity need to be organized in a concave arrangement relative to the developing macrocycle (**540**). Such a strategy involving the presence of concave templates has not been fully exploited yet in the case of abiotic systems, but recent advances in the field of supramolecular capsules reported by Rebek and co-workers (see complex **540**) represent a clear step forward toward this target (Figure 166).[532,533]

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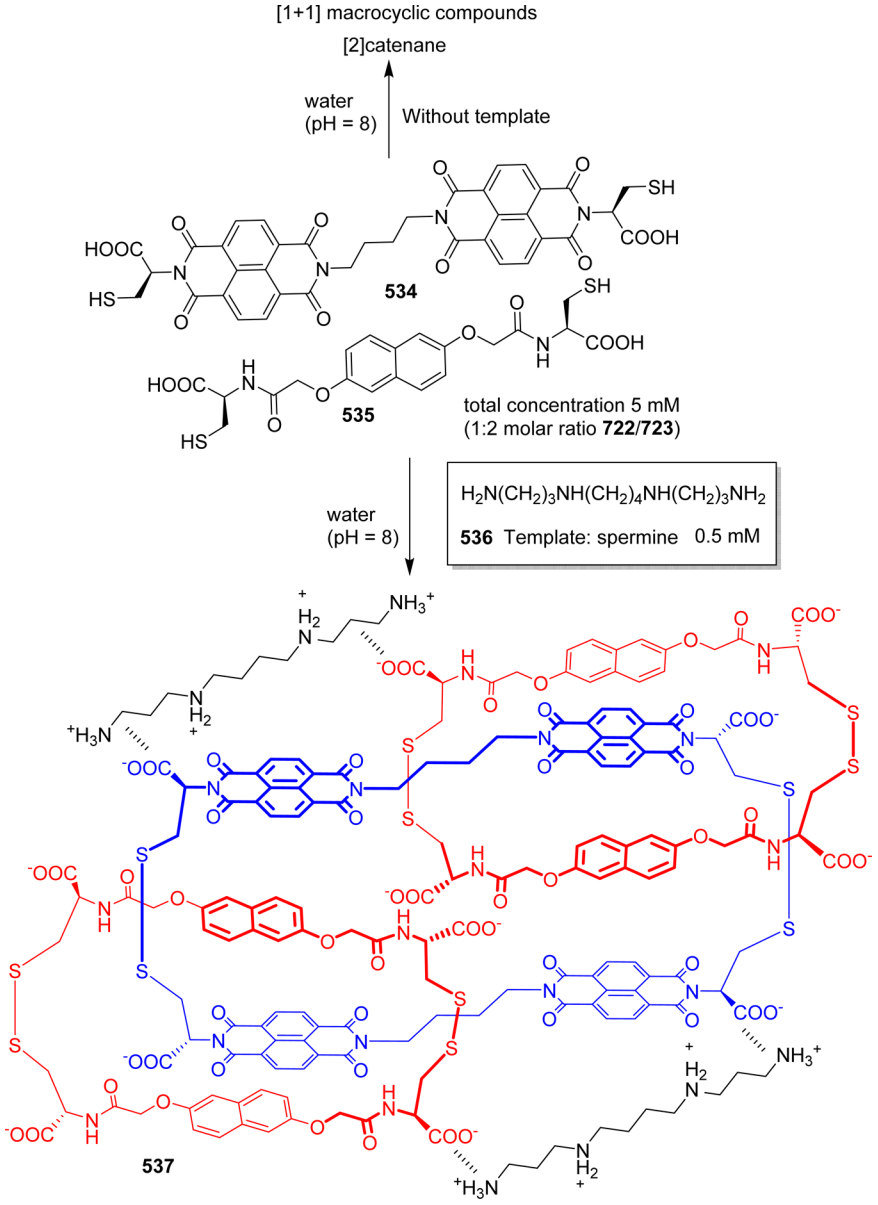

Figure 164. Synthesis of a [3]catenane templated by spermine.[525]

7. OUTLOOK AND CONCLUSIONS

The contributions in the field of macrocyclic synthesis presented here reveal that this is still a very active field of research. This interest arises from the addition of different elements: (i) the relevant biological activities of many natural and non-natural macrocyclic structures; (ii) the current interest in developing new challenging macrocyclic structures, in particular those associated with polyconjugated systems or shape-persistent macrocycles; (iii) the ability of synthetic chemists (and biochemists) to develop new synthetic tools and new synthetic strategies for which their application to macrocyclization reactions represents a challenging benchmarking step.

The success of a given macrocyclization reaction involves a very delicate balance of many different factors. First, a proper understanding of the basic thermodynamic and kinetic concepts underlying these processes is essential in defining the strategies to obtain the targeted cyclic structures and the experimental elements to be optimized. From this point of view, the use of high dilution or pseudo high dilution conditions still represents an important experimental approach to favor macrocyclizations and they are commonly used on a routine basis. For most of the examples gathered in this review, the actual maximum concentration of the reactants is in the range 0.1−10 mM with only a few examples reporting efficient macrocyclization reactions with larger concentrations.

A second essential element for achieving high yields in a macrocyclization process is the appropriate selection of the disconnection site. This defines the reaction used for the key step, which will clearly affect the overall process, but also delineates the nature and structure of the immediate linear precursor. The presence of structural elements, including configurational elements, able to induce a favorable folding of this linear precursor in such a way that both reactive ends approach with the proper orientation provides significant enhancements in macrocyclizations.

Finally, the use of templates of very different natures is a versatile strategy to overcome the limitations of the other macrocyclization strategies. The interaction of the template with

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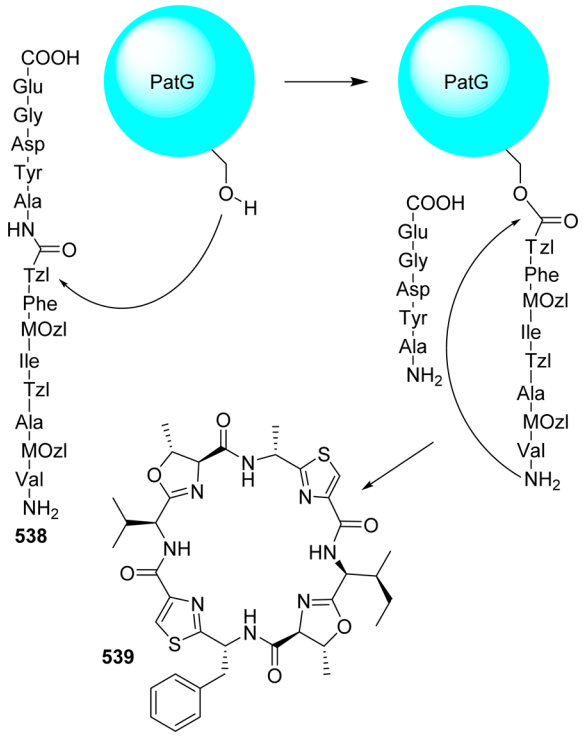

Figure 165. Macrocyclization of a peptide using the PatG protease. Tzl, thiazol(ine); MOzl, methyloxazoline.[530]

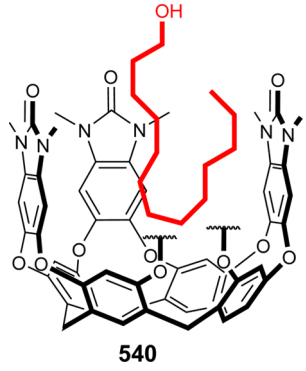

Figure 166. Cartoon representation of the complex of an *n*-alcohol in a cavitand highlighting folded conformation.[532]

the lineal substrate forces this precursor to adopt a preorganized conformation well-suited to carry out the corresponding macrocyclization even in cases where, in the absence of the template, this cyclization does not take place efficiently. The use of templates has allowed the preparation of a variety of macrocyclic structures in better yields and usually in shorter reaction times, and often allows easier purification protocols. It is important to note that templates can act kinetically or thermodynamically or through a combination of both.

Many challenges still remain in this field, and according to the efforts devoted to this area in recent years, important advances can be expected for the near future. Some of these advances will be associated with the development of new experimental methodologies to favor the macrocyclization processes, in particular reducing the need of using high-dilution conditions. This could allow working at concentrations (above the millimolar range) and scales applicable to industrial and environmentally sustainable processes, reducing dramatically the quantity of the solvent needed. This will include the use of new cyclization reactions but also an intensive use of new techniques such as new supported systems providing efficient pseudodilution effects and the exploitation of flow chemistry and microfluidic devices. The use of enzymes and other biomolecules to facilitate or catalyze the formation of macrocyclic structures represents an alternative methodology to be exploited. There is no doubt that the use of templates to favor macrocyclization reactions will continue to expand. In this regard, the use of organic molecules (neutral, cationic, or anionic) provides an infinite variety of shapes, topologies, and functionalities that can be used advantageously to preorganize adequately a given linear precursor. This can be expected to include, in the future, the exploitation of synthetic concave templates. The progress obtained in the application of DCC (dynamic combinatorial chemistry) for the generation of new macrocyclic structures is closely connected with the use of template species, and significant advances can be expected in this area. Finally, developing the ability to use computational tools to predict the outcome of an expected macrocyclization reaction represents also an essential target. This can represent a key approach for the design of template species to be used efficiently in a given process.

AUTHOR INFORMATION

Corresponding Author

*E-mail: luiss@uji.es. Tel.: (+34) 964 728 239. Fax: (+34) 964-728-214.

Present Address

†M.D.P.: Department of Chemistry, Dr. H. S. Gour Central University Sagar, MP 470003, India.

Notes

The authors declare no competing financial interest.

Biographies

Dr. Vicente Martí-Centelles was born in 1984 in La Pobla Tornesa (Castellón, Spain). He graduated in Chemistry with honors in 2007 at the Universitat Jaume I in Castellón (Spain). Then he received a grant from the Spain Ministry of Education to develop his Ph.D. under the supervision of Prof. Santiago V. Luis and Prof. M. Isabel Burguete at the Universitat Jaume I, and he received his Ph.D. with honors in 2012. During this period he was a postgraduate visiting student at Carlos Cativiela's research group at Universidad de Zaragoza in 2009 and at Ramón Vilar's research group at Imperial College London in 2010. His Ph.D. work was focused on developing new pseudopeptidic macrocyclic hosts with applications in molecular recognition. After completing his Ph.D., in 2013 he received a postdoctoral grant from the Generalitat

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Valenciana to develop a project at Universitat Jaume I under the supervision of Prof. Santiago V. Luis and at Oxford University under the supervision of Prof. Paul D. Beer. His current research interests are focused on the synthesis of macrocyclic host systems designed to recognize anions of biological and environmental importance.

Dr. Mrituanjay D. Pandey was born in 1978 in Pratapgarh, UP, India. He graduated in Chemistry in 2001 at University of Allahabad and received a grant (JRF-NET) from the CSIR India to pursue his Ph.D., which he received under the supervision of Prof. R. K. Dubey in 2007. He did his SRF and SRF-Ext (CSIR) at IIT Delhi under the supervision of Prof. Siddharth Pandey in 2006−2007. He worked as project scientist during 2007−2010 at IIT Kanpur under the supervision of Prof. V. Chandrasekhar and Prof. Sandeep Verma. He also completed his DST-FAST Young Scientist project at same institute with Prof. V. Chandrasekhar during 2010−2011. He completed his postdoctoral work at Universitat Jaume I with Santiago V. Luis from a grant of Mobility Stays of Foreign Researchers in Spanish Centers, Ministerio de Education, Spain during 2011−2013. Prior to joining as an assistant professor of chemistry at Dr. H. S. Gour Central University, Sagar, he was assistant professor (ad hoc) of chemistry at University of Delhi. His current research interests are focused on metallomics, bioinorganic chemistry, and bioorganometallic chemistry.

Dr. M. Isabel Burguete Azcárate was born in 1955 in Aibar (Navarra, Spain), studied chemistry at the University of Zaragoza (Spain), and completed her Ph.D. at the University of Valencia (Spain) in 1989 under the direction of Prof. F. Gaviña, after a predoctoral stay at the University of Pittsburgh (USA) under the supervision of Prof. J. Rebek. She got a permanent position at the Universitat Jaume I in 1993 and then a full professorship at the same university in 2009, where she continues working as a researcher in the Supramolecular and Sustainable group at Universitat Jaume I. Her current research interest focuses on the areas of green and sustainable chemistry involving supported catalysts, in particular supported ionic liquids and the supramolecular chemistry of pseudopeptides.

Dr. Santiago V. Luis was born in 1955 in Cariñena (Zaragoza), studied chemistry at the University of Zaragoza (Spain), and completed his Ph.D. at the University of Valencia (Spain) in 1983 under the direction of Prof. F. Gaviña. After a postdoctoral stay in 1985 at the University of Pittsburgh (USA) under the supervision of Prof. J. Rebek, he got a permanent position at the University of Valencia (1987) and then a full professorship at the Universitat Jaume I (1995). He is currently the leader of the Supramolecular and Sustainable Chemistry group at Universitat Jaume I. His current research interest focuses on the areas of supramolecular chemistry, pseudopeptides, catalysis, and sustainable chemistry.

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