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Perspective

Macrocyclization Reactions at High Concentration (≥0.2M): The Role of Catalysis

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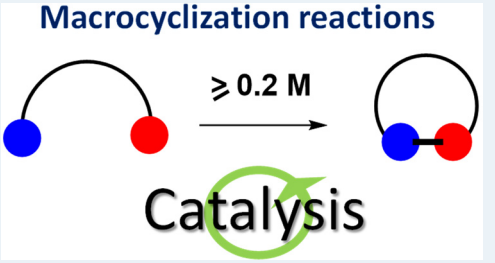
ABSTRACT: The synthesis of macrocycles is fundamental to obtain useful quantities of this unique family of organic compounds. However, most current syntheses still require highly diluted conditions (generally < 0.1M), which makes the synthesis extremely inefficient in the reactor volume. Here we review, quantify, and analyze the few synthetic methods for macrocycles reported so far where the reaction solution is at ≥ 0.2 M concentration. Parametrization of the results with the Emac (efficiency macrocyclization) index unveils that catalytic methods are much more efficient than non-catalyzed methods. Beyond this conclusion, the present study also shows clear evidence that high-concentration macrocyclization reactions are not only possible but necessary, and suggests the use of catalytic reactions, including solid catalysts and in-flow reactions, to develop macrocyclization reactions under high concentration conditions.



KEYWORDS: *macrocyclization reaction, high concentration, catalysis, in-flow chemistry, solid catalysts, macrocycles, organic synthesis, sustainable chemistry*

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INTRODUCTION

Macrocyclic molecules (macrocycles, by definition cyclic organic molecules containing 12 or more atoms) are abundantly distributed in nature, and have an enormous impact in the fields of chemistry, biology, and medicine.[1] Historically, the first macrocycles originated from natural sources, such as the drugs rapamycin, erythromycin, epothilone, vancomycin, and cyclosporine.[2] However, the number of commercial macrocycles available as starting materials to prepare other macrocycles is limited and merely involves some natural products and the C_{12} precursors for the nylon industry cyclododecatriene and cyclododecanone. The synthetic planning for a macrocyclic compound requires the selection of an adequate macrocyclization reaction at some point, which often is the bottleneck and determines the general efficiency of the planned route.[3]

The synthetic community has invested much effort in the total synthesis of macrocyclic products and in exploring the scope of different macrocyclization reactions.[4] Earlier synthetic strategies were not based on catalysis and mainly involved reactions such as macrolactamization,[5] macrolactonization,[6a−c] the acyloin reaction,[6d,e] McMurry's reaction,[6f] and template-based macrocyclization reactions,[7] to name a few. These reactions can now be considered classical and are studied in most organic textbooks. However, they operate under very diluted conditions to avoid intermolecular reactions,[8] which severely hampers the productivity of the reaction. Indeed, macrocyclization reactions are still routinely performed at either <1 mM concentration ("very high dilution conditions"),[9a] 1 mM ("high dilution conditions") or ∼10 mM ("moderate dilution conditions").[9b] For the latter, a simple calculation gives that, even for the smallest of the macrocycles that could be considered (molecular weight ∼ 200 Da.), a 500:1 solvent-to-substrate ratio (500 Kg or L of solvent per Kg of macrocycle) is required, which is obviously unacceptable from a sustainable and economic point of view.[10]

Catalytic methods have been applied during decades to macrocycle synthesis, particularly ring-closing metathesis[11] and cross-coupling reactions.[12] Despite their success in many cases, the reaction concentration was still kept at < 0.01 M in most cases.[13] However, in the last years, some advances in what is called here "high concentrated conditions" (>0.2M) have been achieved, mainly with the proper use of catalytic conditions. For instance, the groups of Collins,[14a,b] Grela[15] and Fairlamb,[16] to name some, are very active in this field. It is worthy to notice here that catalysis also may lead to oligomers plus the desired macrocycles; thus, the use of catalysis is not necessarily a way to avoid oligomers.

The aim of this Perspective is to summarize the macrocyclization reactions reported so far at reaction concentrations of ≥0.2M, with special emphasis on catalytic methods (Figure

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1). To our knowledge, the most recent and authoritative reviews on macrocyclization reactions cover synthetic strategies, such as in-flow synthesis[14] and metal-catalyzed reactions,[16] but do not specifically cover high reaction concentrations, despite the same reports acknowledge the transcendence of the reaction concentration by, i.e., putting in bold the concentration value in each reaction scheme (we will also put in bold here the concentration values).[16] Thus, we think that a review on high concentrated (≥0.2M) macrocyclization reactions, highlighting the most recent advances and pointing to synthetic methodologies, is timely to perhaps settle in the near future high concentrated macrocyclization reactions as the norm rather than the exception.

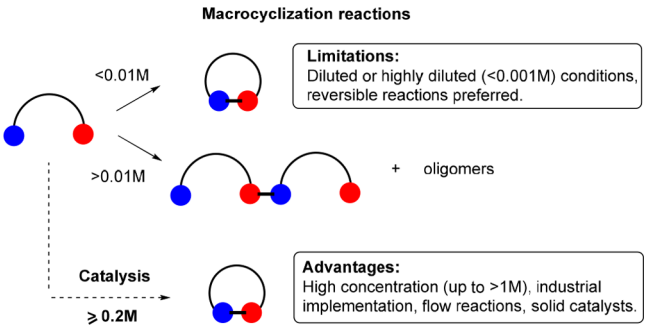

Figure 1. Schematic representation of the limitations and advantages of macrocyclization reactions under highly concentrated (≥0.2M) and catalytic conditions.

The only previous review on highly concentrated macrocyclization reactions (as far as we know) was reported in 2012[17a] and an index to quantify the efficiency of a macrocyclization reaction was defined, called Emac and calculated as:

$$\text{Emac index} = \log_{10}[\text{yield}(\%)^3 \cdot \text{concentration}(\text{mM})] \quad (1)$$

We will also use the Emac index here to list the macrocyclization reactions commented along the text (see each Figure), since this index may help practitioners to ponder the productivity of any macrocyclization reaction in terms of solvent expenses. The examples will include catalytic and noncatalytic strategies, and we will see that the employment of catalytic techniques is the most successful approach to achieve macrocyclization reactions with high Emac indexes. Each Figure also highlights in bold the new bond formed during the macrocyclization reaction.

The concept of "pseudo-dilution" will pervade some of the macrocyclization systems reported here. This concept (Figure 2) shows that a difficult to reach reactant or catalytic site, i.e., by residing in a different phase (solid or biphasic liquid mixture, or even distillation) than the other reactant, will hamper the intermolecular vs the intramolecular reaction, thus favoring the macrocyclization reaction. The pseudo-dilution concept dates to the 1970s and is the basis of the seminal work by Trost and Warner on the use of a polymer-supported metal catalyst (see section 1.4.2 ahead).[17b] Another seminal work, that of Carothers and Spanagel (entitled simply "Macrocyclic Esters"),[17c] clearly exemplifies another concept that permeates through the different macrocyclization reaction studies, which is the influence of the substituent functional groups in the molecule on the macrocyclization outcome.[17d] In this way, simple cyclic esters started to be formed in 7−8 atom rings;

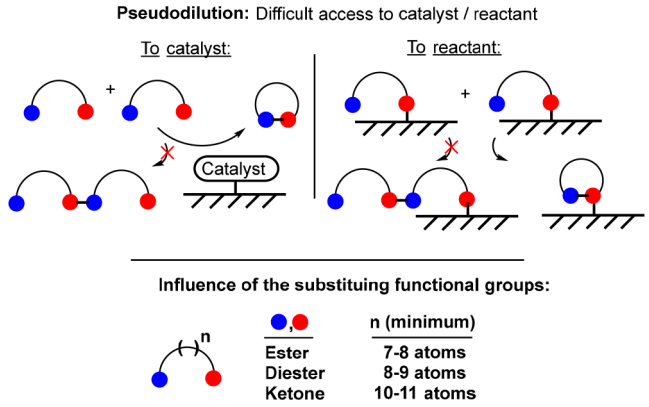

Figure 2. Pseudo-dilution effect, which favors macrocyclization reactions by impeding easy access of two molecules (intermolecular) to the active reactant or catalytic site, and the influence of functional groups in the macrocyclization outcome.

however, if a diester is the functional group present in the linear precursor, the new cycle required at minimum 8−9 atoms, and 10−11 atoms for cyclic ketones (Figure 2). In other words, the existence in the linear starting material of one or another functional group determines the macrocyclization outcome. These two issues (pseudo-dilution and functional group influence) must be kept in mind when designing a macrocyclization reaction and analyzing the results.

HIGH CONCENTRATED MACROCYCLIZATION REACTIONS

1. Catalytic Strategies. *1.1. Acid-Catalyzed Reactions.* High concentrated macrocyclization reactions catalyzed by simple acids are rare; however, as early as in 1886, Baeyer coupled indole **1** with acetone **2** at 5 M concentration to prepare for the first time the calix[4]pyrrol **3** with methanesulfonic acid (MSA) as a catalyst (Figure 3).[18] The

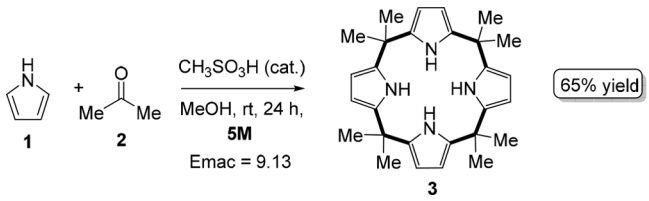

Figure 3. Macrocyclization reaction of indole **1** and acetone **2** to give calix[4]pirrol **3** at a 5 M concentration.

macrocyclic compound could be synthesized with an impressive isolated yield of 65% and an Emac= 9.13, which reflects the high efficiency of the reaction.[19] Due to this reaction efficiency, and the great ability of calix[4]pyrroles to bind anions into its structure[4], great research efforts have been devoted to the synthesis of a collection of these receptors, which are a rare example of macrocycles prepared under high concentrated conditions.[20a] Indeed, related porphyrin macrocycles could be prepared under nearly solvent-free mechanochemical conditions,[20b] and this mechanochemical approach somehow relates to the pseudo-dilution concept where a hampered diffusion of the reactant favors intra- vs intermolecular reactions. The seminal Carother's macrolactone production, commented above,[17c] is also an example of acid-

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catalyzed macrocyclization reaction, with a variety of metal salts tested.

In a much more recent example, Tripathi et al. have shown a novel approach to synthesize macrocyclic glycoconjugates with tetrabutylammonium hydrogen sulfate (TBAHS) as catalyst in 20 mol% (Figure 4).[21] The intramolecular cycloaddition

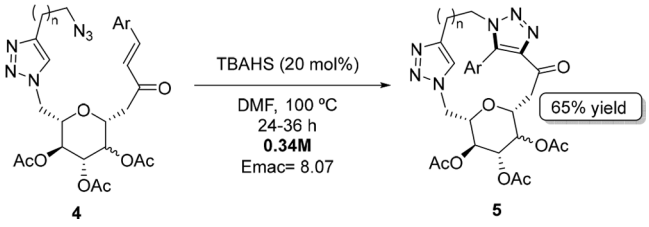

Figure 4. Macrocyclization reaction of azide butenone **4** catalyzed by TBAHS at a 0.34 M concentration to give the macrocyclic glycoconjugate **5**.

between the azide and the propenone functional groups in the *C*-glycopyranosyl-*C*-butenone **4**, engineered from a *D*-glucose and *D*-mannose, allows to obtain the druglike macrocycle **5** in good yields (61−76%) at 0.34 M concentration, and even a 0.6 M concentration is still operative.

1.2. Base-Catalyzed Reactions. Bases are commonly used in stoichiometric amounts during macrocyclization reactions (see i.e. section 1 ahead), and the acyloin reaction is one classical example;[6d,e] however, we found an example where the base is used in catalytic amounts and at a high concentrated reaction. The ring expansion of a *N*-(3-halogenoacyl)-*ε*-caprolactam **6** has been reported by Robertz et al. in water alkaline medium at 0.25 M concentration.[22] Under these conditions, the intramolecular substitution of the halogen atom takes place to yield the corresponding cyclic ester amides **7** in up to 60% yield. Monomers polymerized anionically, and an alternative pathway through proton transfer enables the formation of intermediate cyclic tetraesteramide anions **8** from a starting material **9** at 0.7 M concentration, to give alternating macrocyclic polyesteramides **10**.[22b] These methodologies have been employed during the total synthesis of the fourteen-membered cycle natural substance serratamolide **11**, with antibiotic activity, using triethylamine in catalytic amounts.[22a] Yields are low if HX is generated since the latter induces the formation of *N*-crotonyl or *N*-acryloyl groups. Since this macrocyclization reaction is not a canonical cyclization as shown in Figure 1 above, a dedicated Figure is not included here (please see the different compounds **6**−**10** in the corresponding references); however, the following paragraph must depict in detail a ring-expansion reaction since it is a representative example of industrial macrocycle production.

Another related example of ring-expansion reaction for the synthesis of a macrocycle is the commercial synthesis from precursor **12** of Exaltolide™ **13**, which uses a catalytic amount of trifluoroacetic acid, then aqueous NaOH and, in a third separate step, copper(II) acetate as a catalyst in water/polyethylene glycol (PEG) solutions to give the final product in 43% yield.[23a,b] Figure 5 shows the reaction conditions. Since it is a sequential process with different steps, we have not included here exact concentration and Emac values. Ring expansion macrocyclization reactions are the most typical and the industrial level, since it is easier to minimize solvent

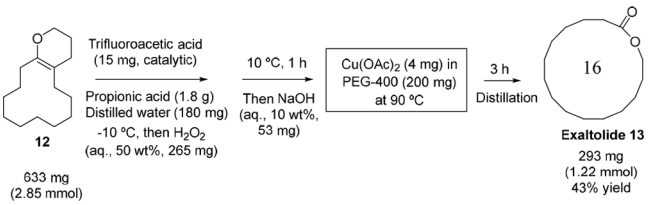

Figure 5. Reaction conditions for an industrial example of macrocycle production, from precursor **12** to musk ingredient Exaltolide™ **13**. Exact concentration and Emac values are not included since it is a sequential process with different reaction conditions.

amounts; however, as said above, they do not fit exactly in the macrocyclization reaction concept shown in Figure 1.

Although the reaction concentration is not totally specified, it seems that a 1−2 M concentration is used (Emac = 8.08).[23b] Another fragrance compound such as cyclopentadecanone (Exaltone™) can be prepared by the classical Ružička and Dieckman cyclization reactions under moderate dilution conditions.[23c]

1.3. Ruthenium-Catalyzed Alkene Metathesis Reactions. This synthetic methodology, also called ring-closing metathesis, has been arguably the most employed during the last years to effect macrocyclization reaction in complex organic synthesis.[24a] However, as for the rest of the synthetic methods described here, the vast majority of reported examples are carried out under diluted conditions. Nevertheless, recent findings contradict this assumption.

Grela et al., in a seminal work, have shown that new structural variations in the Ru metathesis catalysts, beyond the classical Grubbs and Hoveyda catalysts, enable to run the ring-closing metathesis reaction of linear alkyl chain alkenes **14** at concentrations up to 1.2M, for the synthesis of apparently simple but significant macrocycle structures **15**, i.e., for fragrance compounds (Figure 6).[15] An unsaturated analogue

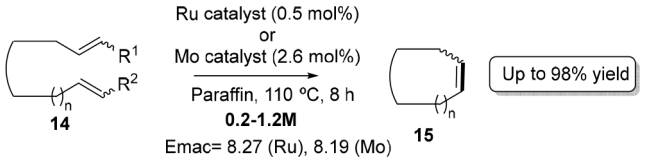

Figure 6. Ring-closing metathesis of **14** to **15** up to 1.2 M concentration.

of Exaltolide could be isolated at 3-gram scale. The lack of macrocyclization procedures in multigram amounts is inherent to the lack of methodologies where minimal amounts of solvent can be employed. The use of the reactive distillation technique allows to displace the metathesis equilibrium toward the desired compounds, and a MOF support for the Ru catalyst can also be used.[24b] The reactive distillation has also been accomplished recently with Schrock's type catalysts.[24c] These studies also show that Lewis basic sites in the substrate are not necessary to achieve RCM macrocyclization reactions at high concentrations.

We have recently found that the related ring-closing metathesis reaction of **16** can be exerted with the nitro-Grela™ catalyst under standard batch conditions, without reactive distillation, to give **17**, a precursor of the fragrance compound dehydromuscone **18** (Figure 7).[25a] Although the yield to **17** is moderate (42%), the reaction can be run in 0.2 M toluene and with just 0.1 mol% Ru catalyst. It is noteworthy

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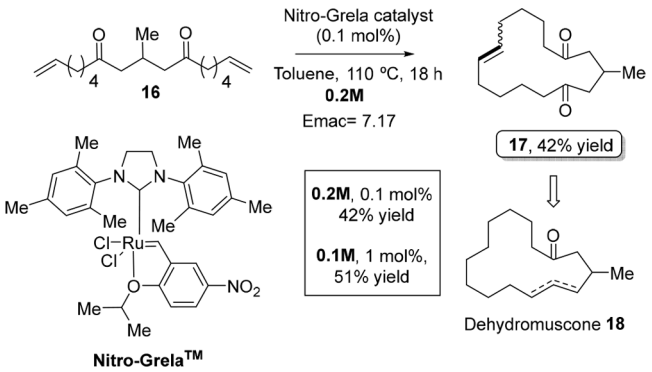

Figure 7. Ring-closing metathesis of **16** to **17**, precursor of the fragrance compound dehydromuscone **18**, at a 0.2 M concentration.

that an increase in the reaction concentration, from 0.1 M to 0.2M, allows the decrease of 1 order of magnitude of the amount of Ru catalyst employed, from 1 to 0.1 mol%, without severely decreasing the final yield of **17** after total conversion of the starting material. These results further showcase the advantages of using higher reaction concentrations.

The results above for the synthesis of musklike fragrances[25b,c] by RCM are in line with those obtained at diluted conditions (0.05M) in batch and in flow, where a 57% yield of the desired macrocycle is obtained at long reaction times (5 d). A continuous flow strategy provided a lower yield of 32%.[26]

High concentrated Ru-catalyzed alkene metathesis reactions have also been used in complex pharmaceutical intermediates. Shu et al., using very similar reaction conditions to those above, have developed a practical ring-closing metathesis reaction of compounds **19** to **20** for the production-scale manufacturing of the hepatitis C virus (HCV) protease inhibitor BILN 2061 (Figure 8).[27a] The reaction concentration

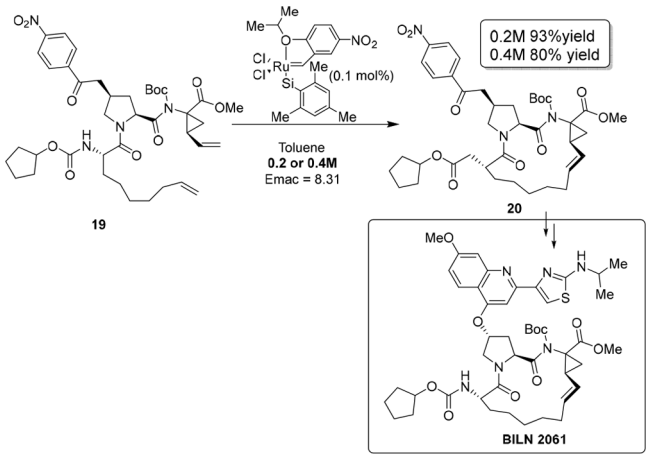

Figure 8. Ring-closing metathesis of compounds **19** to the precursor of the HCV protease inhibitors BILN 2061 **20**, up to 0.4 M concentration.

can be increased up to ≥ 0.2 M without severely diminishing the final product yield (80−97%), and using a catalyst loading of just 0.1 mol%. They also studied in detail the macrocyclation process of the key precursor and the effect of different structural variables and found that both the nature of the substituent at position C4 of the hydroxyproline fragment and the *N*-substitution pattern of the amide group that binds the proline and cyclopropane units of **19** had detectable effects on the cycling rate, which was assigned to conformational modifications. This is a clear example of how the functional groups of the starting material influence the macrocyclization reaction (see Figure 2 above).

In a similar way, Wei et al. achieved a large-scale, highly convergent synthesis of another HCV protease inhibitor, i.e. the 15-member BI 201302 macrocyclic compounds **22**, after ring-closing metathesis of **21** in high yield (93%, Figure 9).[27b]

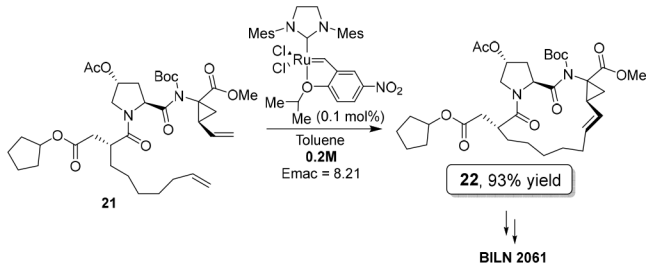

Figure 9. Ring-closing metathesis of compound **21** to the precursor **22** for the HCV protease inhibitors BILN 2061, at a 0.2 M concentration.

RCM reactions at 0.1 M concentration have also been reported. Muranaka et al. showed the synthesis of an Hsp90 inhibitor through a RCM reaction catalyzed by the Grubbs type 1 catalyst in 98% yield (Emac = 7.97), which demonstrates that classical alkene metathesis catalysts can also be employed in relatively high concentrated macrocyclization reactions.[28]

1.4. Metal-Catalyzed Cross-Coupling Reactions. 1.4.1. Carbon−Carbon Couplings: Palladium and Copper Catalysts. Macrocyclization reactions based on the formation of new C−C bonds with palladium catalysts are perhaps the second more reported synthetic strategy after RCM reactions. The presented examples are just a few of some others. As mentioned above and as early as in 1982, Trost and coworkers employed what was later named as a Tsuji−Trost coupling-type reaction, to form medium and large rings at 0.1−0.5 M concentrations (Figure 10).[17b] A polymer-supported palladium phosphine catalyst mediated the macrocyclization reaction of **23** to **24** in 66% yield and with a *E*/*Z* isomeric ratio of 4 to 1.

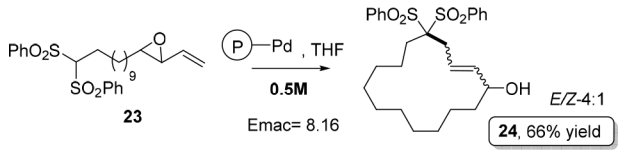

Figure 10. Tsuji−Trost macrocyclization coupling-type reaction of alkene **23** to macrocycle **24**, at a 0.5 M concentration.

However, the use of high concentrated conditions during palladium-catalyzed cross-coupling reactions is still scarce, as showcased in a recent review where only 1 out of 48 described transformations employed a >0.2 M concentration during the coupling reaction, and another one a 0.15 M concentration.[29,30] The >0.2 M transformation consisted in a Sonogashira macrocyclation coupling, reported by Mohapatra and his co-workers,[29] during their first total synthesis of penarolide sulfate A_1, a α-glucosidase inhibitor. A high amount of palladium (and also copper) catalysts was employed [9 mol

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% of $Pd(PPh_3)_4$ and 18 mol% of CuI, respectively], and the cyclization of the 30-member macrocycle **25** was achieved at 0.22 M concentration in only 30 min at room temperature, to give macrocycle **26** in 35% yield (Figure 11).

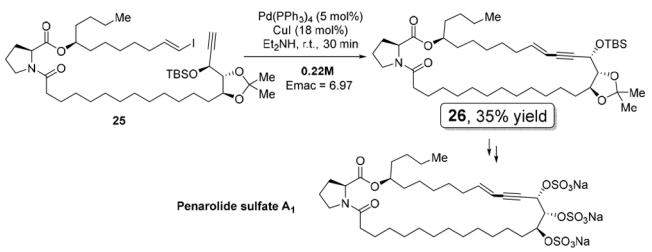

Figure 11. Sonogashira coupling of alkyne **25** to give macrocycle **26**, at 0.22 M concentration, toward the synthesis of penarolide sulfate A_1.

The 0.15 M transformation consisted in a Stille reaction catalyzed by the unusual palladium complex $PdCl_2(Cl_3CCN)_2$, employed during the formal total synthesis of the cytotoxic macrolide palmerolide A.[30]

We have recently reported an intramolecular Mizoroki–Heck reaction of ω-iodide cinnamates **27** at 1 M concentration catalyzed by ligand-free Pd_{3-4} clusters, either supported or in solution (Figure 12).[31] Macrocycles **28** are obtained in

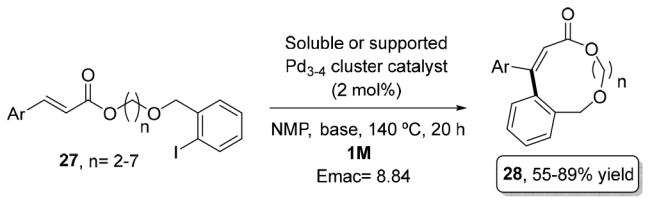

Figure 12. Mizoroki–Heck reaction of ω-iodide cinnamates **27** at 1 M concentration to give macrocycles **28**. The reaction can be run in a bath or in flow with the supported solid catalyst.

reasonable yields (55–89%) after using a 2 mol% of palladium catalyst. An Emac = 8.84 is calculated, which is, to our knowledge, the second highest observed to date after that of calix[4]pyrrol **3** (Figure 3 above) and the highest obtained for a metal-catalyzed macrocyclization reaction. The high concentration of the reaction enabled the use of a metal-supported solid catalyst for the Mizoroki–Heck reaction in flow, which constitutes one of the first examples of metal-catalyzed macrocyclization reactions under continuous reaction conditions.

The use of copper catalysts for the formation of new C–C bonds during highly concentrated macrocyclization reactions is relatively common compared to palladium catalysts, despite the fact that the latter historically dominate the C–C cross couplings arena.

The fact that copper catalysts can operate at >0.2 M during intramolecular C–C bond-forming reactions is perhaps illustrated by the Castro–Stephens coupling reaction of the phenylacetylide copper salt **29**, as reported by Staab et al. (Figure 13).[32] The 6-group macrocycle **30** could be isolated in 4.6% yield at a 0.215 M concentration. This example is one among others.

In a series of work, Collins and collaborators developed a phase separation/continuous flow strategy employing an oxidative Glaser–Hay coupling of alkynes, including the use of microwave conditions.[33] Biphasic conditions were employed

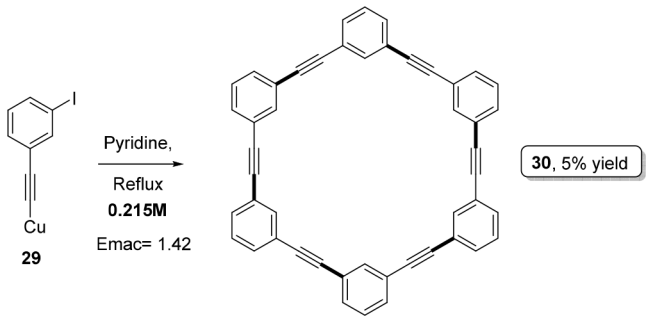

Figure 13. Castro–Stephens coupling reaction of the copper salt **29** to give macrocycle **30**, at 0.215 M concentration.

to locate the metal catalyst in the polar phase and the reaction at the interface. Dendritic PEG cosolvents were employed in the phase separation strategy at concentrations up to 0.1 M, to obtain similar yields than in the common slow addition/high dilution techniques (~70% yield, Emac = 7.53). Mechanistic investigations revealed the key role of the PEG units during the Glaser–Hay coupling.[34] The methodology has been applied toward the synthesis of the macrocyclic core of the complex pharmaceutical vaniprevir, although the reaction concentration here was <0.2 M.[33e]

1.4.2. Carbon–Heteroatom Couplings. It is difficult to find catalytic carbon–heteroatom coupling reactions at >0.2 M concentration. The only example we found, apart from the Zr(IV)-catalyzed dimerization of amino esters already commented in a previous review (Emac = 8.49),[17,35a] is the carbene-type multicomponent coupling of ethers **31** and diazocarbonyl compounds **32** reported by Lacour et al., to synthesize the different polyether macrocycles **33** in the presence of a rhodium(II) catalyst (Figure 14).[35b,c] A ca. 1 M

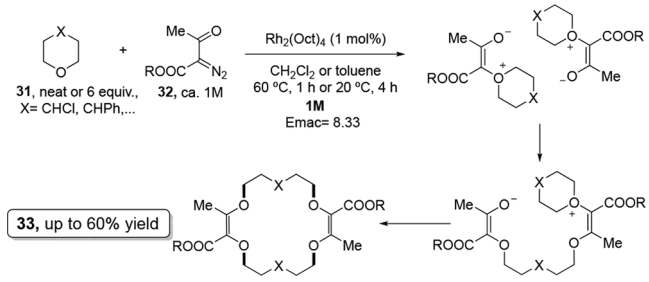

Figure 14. Rhodium-catalyzed multicomponent coupling of ethers **31** and diazocarbonyl compounds **32** at ca. 1 M concentration to give macrocycles **33**.

solution based on **24** is employed, since the high concentration of starting materials favors that the unstable charged reactive intermediates dimerize to form the final macrocycle compound in up to 60% yield.

The intramolecular copper-catalyzed Ullmann coupling of either phenols or imidazoles with aryl iodides has been reported for the synthesis of macrocycles with pharmaceutical properties, however, in up to 0.1 M concentration and with high copper catalyst loadings (5–10 mol%), at 150 °C under microwave conditions.[36]

2. Noncatalytic Strategies. *2.1. Macrolactamization Reactions.* The formation of new amide bonds is one of the main tools to generate new macrocycles in an easy way, since the strength of the amide bond is higher than the ester bond and somehow assures the non-reversibility of the newly formed

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compound. Thus, it is not surprising that peptide cyclization is one of the most studied macrocyclization reactions at high concentration and, indeed, a new chemoselective method termed "CyClick", which operates exclusively in intramolecular fashion and prevents the formation of commonly occurring side products such as dimers and oligomers at relatively high concentrations, has been developed.[37] CyClick chemistry (Figure 15) makes use of the intermediate formation of a

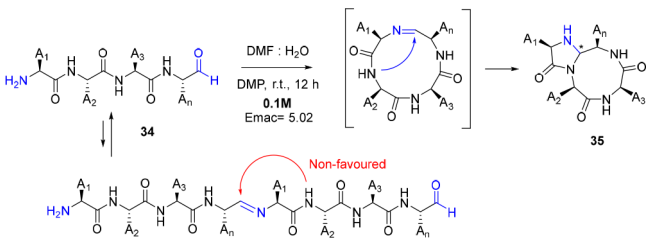

Figure 15. Scheme (Click) for the CyClick chemistry concept. DMAP: (Dimethylamino)pyridine. * Denotes chiral center.

cyclic imine, after condensation of the terminal amine and aldehyde groups in the starting material **34**, to catch this intermediate with another amine present in the cyclic compound and generate the stable 4-imidazolidinone cyclic peptide **35**. This 4-imidazolidinone moiety is not formed in the case of the corresponding linear dimer, due to unfavorable entropic effects; thus, the reversible condensation reaction gets back to the starting material. This smart technique is highlighted here despite that a ≤0.1 M concentration is typically used and Emac values are still moderate.

Nevertheless, classical macrolactamization reactions have found application at >0.2 M concentration. The following examples are just a few of others. Yudin et al. reported the synthesis of macrocyclic peptides **37** at 0.2 M concentration and in 63% yield, from linear peptide precursors **36**, amphoteric aldehydes (aziridine aldehydes) and isocyanides (Figure 16).[38] Short linear peptides can adopt a circular

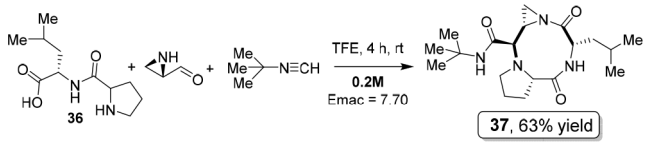

Figure 16. Modular synthesis of macrocyclic peptides **37** at 0.2 M concentration.

conformation based on the pairing of ions between the *N*-atom and *C*-atom ends. Therefore, the unfavorable entropy factor involved in adopting the corresponding circular conformations required for the macrocyclization reaction can be overcome by the favorable enthalpy associated with the presence of intramolecular electrostatics and other polar interactions. Here, the presence of the nucleophilic site in position α of the amino aldehyde is essential for the high yields and stereoselectivities obtained. The macrocyclic product **37** is straightforwardly isolated by precipitation from the reaction mixture. This constitutes another example of functional group directed (or enabled) macrocyclization reaction.

Two more examples of macrolactamization reactions at relatively high concentration (>0.1M) can be found. In one hand, Zeng et al. relied on a multi-macrolactamization reaction of building block **38** for the synthesis of oligoamide pentamer **39** in 46% yield, achieving the appropriate configuration with the help of hydrogen atom interactions at reactant concentrations 0.1−0.3 M (Figure 17A).[39] $POCl_3$ is employed here as

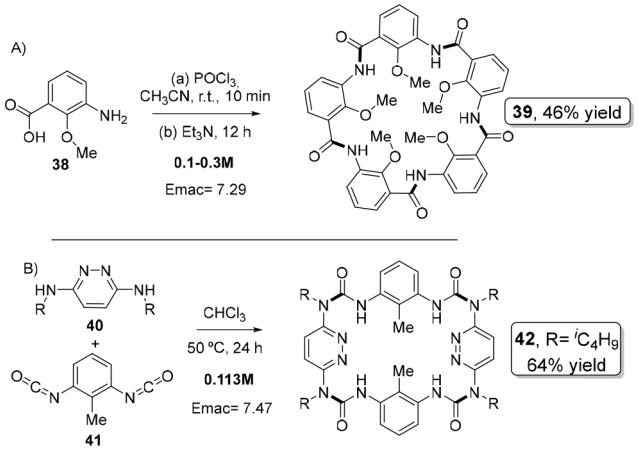

Figure 17. Examples of macrolactamization reactions at >0.1 M concentration with bifunctional monomer **38** to give pentamer **39** (A), and diamides **40** and diisocyanates **41** to give macrocycle **42** (B).

a classical activator for the carboxylic group. On the other hand, Cuccia et al. reported a macrocyclization between diamides **40** and diisocyanates **41**, to give macrocycle **42** in 64% yield at 0.113 M concentration (Figure 17B).[40] This good yield for product **42** reportedly comes from the correct and favorable folded conformation of the open chain precursors, stabilized by intramolecular hydrogen bonds between the nitrogen atoms of the heterocycles and the N−H urea protons.

2.2. Macrolactonization and Etherification Reactions. Macrolactonization reactions arguably constitute the most classical methodology to prepare new macrocycles, i.e., exemplified by the Yamaguchi esterification.[41] The following examples are just perhaps a few of the others. However, it is difficult to find examples that operate at >0.2 M concentration. In a rare example, already reported in 1951 and later studied by Kricheldorf et al., the thermal decomposition of neat acetylsalicylic acid derivatives such as **43** produced disalicilide and trisalicilide **44** in 9−30% yields (Figure 18).[42]

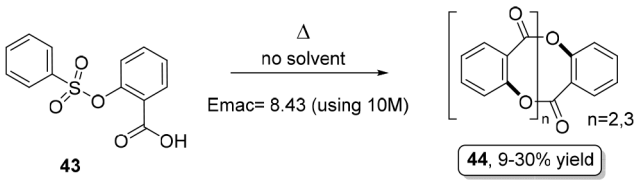

Figure 18. Thermal decomposition of neat sulfonated salicylic acid **43** gave disalicilide and trisalicilide **44**.

The etherification reaction is also commonly employed for macrocyclization reactions, particularly for the synthesis of crown ethers by template methods (section 3 ahead). However, an etherification reaction without any template and up to at 0.25 M concentration was reported by Londregan et al.[43] In that work, linear peptides **45** were converted to a variety of pseudopeptide cyclic structures **36** after intramolecular coupling of the functional side chains of the natural amino acids tyrosine (phenol), lysine (alkylamine), and histidine (imidazole) with the pyridine-*N*-oxide group of a

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carboxamide attached to the *N*-terminal end of the peptide sequence, in a process that can be thought of as a side-by-side chain cyclization (Figure 19). This methodology employs

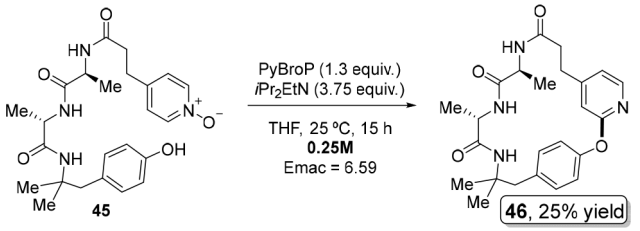

Figure 19. Intramolecular etherification reaction of phenol **45** up to 0.25 M concentration for the synthesis of macrocycle pseudopeptide **46**.

PyBroP as an activator, and both the concentration of the open-chain precursor and the solvent affect the macrocyclization yields. Although the best results in THF were obtained for a 20 mM concentration of **45** (73% yield), a reasonable 25% yield of **46** was obtained at 0.25M.

2.3. Macrocyclization Reactions with Templates. The use of templates is essential in the synthesis of (aza)crown ethers and cryptands, which necessarily occurs by macrocyclization reactions, and high concentration conditions have been claimed during the syntheses.[44] However, the number of examples found at high concentration (>0.2M) is extremely limited; the nature of the template can vary, and very few macrocycles rather than crown ethers can be prepared through template-mediated technologies. It is worthwhile to mention here that the effect of metal templates during reaction could include or be considered as catalytic effects, and more work may be necessary to study this issue.

2.3.1. Anion Templates. The use of anions as templates for macrocyclization reactions is of interest since anions can induce important conformational changes in the receptors (substrates and macrocycles here) and can therefore play an important role in the conformational changes of reaction intermediates and transition structures that lead to such host−guest entities (i.e., they have an effect on the thermodynamics and/or kinetics of the macrocyclization reaction). However, as mentioned above, the use of >0.2 M concentrations is extremely rare.

Aav and collaborators developed a method to prepare enantiomerically pure all-*R* or all-*S* cyclohexylhemicucurbit-[*6*]urinals **48** from a single enantiopure building block [(*R*,*R*)-cyclohexaneurea (*R*)-**47** or (*S*,*S*)-cyclohexaneurea (*S*)-**47**)] in a one-step process at 0.255 M concentration.[45] The reaction is performed under thermodynamically controlled conditions, and the macrocyclic compound all-*R*-**48** precipitates from the reaction mixture as its HCl or HBr complex in good yields, 75% and 64% respectively (Figure 20). The enantiomeric purity of the starting cyclohexanourea is maintained in the process, and the use of (*S*)-**47** provided the corresponding all-*S*-**48** in 85% yield. The fact that the macrocyclic products are not obtained when other acids such as sulfuric, trifluoroacetic, or hydroiodic acids are used instead of HCl or HBr, strongly suggests that the nature of the anion is crucial as a template in this process.

Bromide anions as a template have also been very recently used for the preparation of pseudopeptidic macrocycles containing the hexahydropyrrolo-[*3,4-f*]-isoindolocyclophane

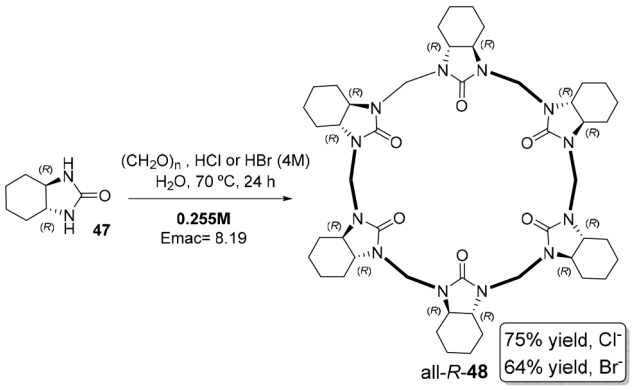

Figure 20. Anion-templated (Cl^- or Br^-) macrocyclization reaction of (*R*)-**47** to give macrocycle all-*R*-**48**, at a 0.255 M concentration.

scaffold, in a continuous flow methodology.[46] The macrocyclization reaction involves four coupled substitution reactions, and the implementation of flow protocols allowed a ca. 20-fold increase in productivity as well as reducing the environmental impact almost 2 orders of magnitude in comparison with the related batch macrocyclization process.

2.3.2. Metal Templates. Crown ethers and polyazamacrocycles constitute an important family of cyclic compounds with a wide variety of ring sizes and additional structural features,[47] associated with the conceptual origin of supramolecular chemistry.[48] The need to obtain these compounds in pure form in relatively large quantities for further studies led to the development of important strategies and concepts in macrocyclization chemistry, in many cases involving the use of templates. Nowadays, metal-template macrocyclization reactions are the synthetic method of choice for these compounds, and some of these protocols include the use of high concentration conditions, indeed, seminal studies operated at >0.2 M concentration. For instance, the original synthesis of corona ethers developed by Pedersen in 1972, now a classic example of a metal cation (Na^+)-assisted macrocyclization reaction, proceeds at >1 M concentration (Figure 21).[49] The

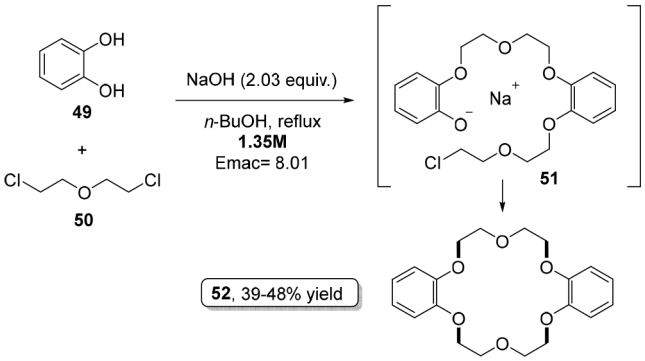

Figure 21. Classic Petersen's synthesis of crown ether **52** by metal-template assisted macrocyclization reaction of precursors **49** and **50** at >1 M concentration.

synthesis of crown ether **52** in ∼40% yield involves the etherification reaction between diol **49** and dichloride **50**, and the ability of the polyether chain to coordinate alkaline cations, enveloping them and approaching both reactive ends (intermediate **51**), is the origin of the effective macrocyclization reaction observed.

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The use of nickel (II) as a template for azamacrocycles was developed[50] in parallel to the chemistry of crown ethers with alkaline cations. In particular, the synthesis of cyclam macrocycles by Barefield and co-workers can be considered a milestone in the field,[51] carried out at 0.25 M concentration (Figure 22). In this macrocyclization reaction, tetraamine **53**

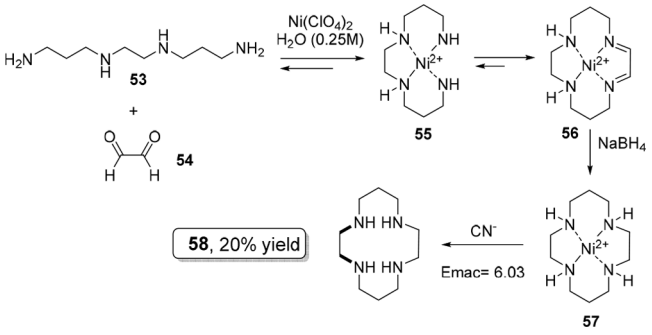

Figure 22. Classic Barefield's synthesis of cyclam **58** from tetraamine **53** and glyoxal **54** at a 0.25 M concentration.

and glyoxal **54** react in the presence of a nickel(II) salt to give the corresponding metal complex **55** and the macrocycle diimine **56**, which after reduction give free cyclam **58** in 20% yield [the nickel(II) template is removed from **57** using cyanide].

These early studies marked a general strategy for the synthesis of crown ethers and azaderivatives at high concentrations, at the origin of several specific approaches described in the literature. For example, several research groups have reported the synthesis of a variety of *N*-substituted azacyclam compounds using Ni(II) and other metal cations as templates. Intermediate **61** was obtained from the reaction of metal complex **59** and amine **60** at 1−3 M concentration, to give macrocycle **62** in 50% yield (Figure 23).[52] Recently,

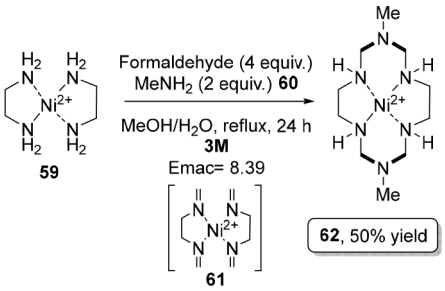

Figure 23. Use of Ni(II) as a template for the synthesis of macrocycle **62**, at 1−3 M concentration of complex **59**.

Lawrance and collaborators have described the advantages of using an ionic liquid as a solvent for **59** (M = Cu) instead of methanol at 0.1 M concentration, since a yield increase from 58% to 85% (Emac = 7.79), associated to a lower formation of acyclic byproducts (22% in methanol), is observed.[53]

In another example, a variety of cage-like compounds such as **65** have been prepared following the pioneering work of Sargeson and co-workers.[54] Cobalt(II) is used as the corresponding template to obtain the substrate **63** at 0.48 M concentration, which, after reacting with formaldehyde, produces the intermediate **64** that further reacts with nitromethane to give the final cage **65** in 69% yield (Figure 24).

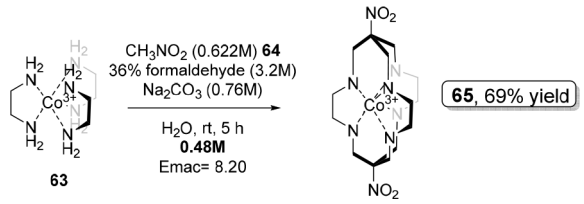

Figure 24. Use of Co(II) as a template for the synthesis of macrocycle **65**, at a 0.48 M concentration of complex **63**.

Qin, Zhang, Zeng and their collaborators have reported the synthesis of macrocyclic hexamers **67** in 22% yield, from monomer **66** at 0.2 M concentration and using trimethylaluminum as the coupling reagent and template (Figure 25).[55] A

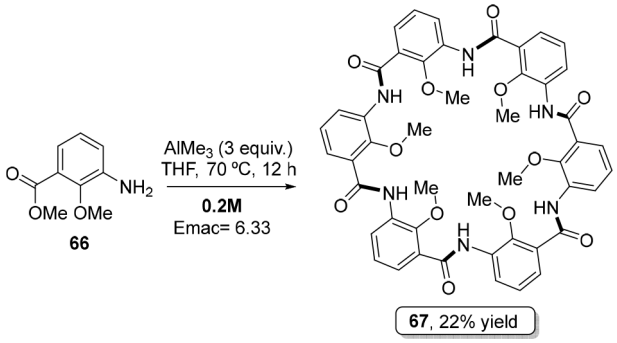

Figure 25. Synthesis of macrocyclic hexamers **67** from precursor **66** at 0.2 M concentration after reaction with $AlMe_3$.

22% of the corresponding pentamer product was observed under these reaction conditions, and other coupling reagents were unsuccessful, which supports the involvement of the aluminum atom in the template effect.

3. Analysis of the Results: Perspectives and Challenges. Figure 26 summarizes the Emac values observed for the highly concentrated macrocyclication reactions commented on above, in order of appearance in the text (i.e., divided by the reaction strategy employed). The results show that catalytic reactions are, by far, the most efficient transformations, since they have > 0.5 average Emac values than non-catalytic strategies. It is worthy to commenting here that the Emac difference is logarithmic, thus the efficiency values are at least five times higher for the catalytic processes. If we remove the atypically high Emac value for the synthesis of Calix[4]pyrrole (Emac = 9.13), the average Emac values for non-metal and metal-catalyzed reactions are very close (8.04 and 8.03, respectively). Ruthenium and palladium catalysts are the most used catalysts.

The industrial implementation of an organic synthesis process in batch requires Emac values ∼9, since it corresponds to less than 1 or 2 volume equivalents of solvent respect to reactants (∼25% reactor occupancy). Even considering very high (>90%) macrocyclization yields, a 1−2 M solution of an average macrocycle (i.e., 400 u.m.a.) is necessary to achieve those Emac values. The total number of reports on macrocyclization reactions at high concentration (0.2 M or higher) is still very low (<30 examples found), and Emac values approaching 9.0 are very rare.

Regarding the type of solvent employed, we can find a wide variety. We find examples from paraffin to water as a solvent, and other organic solvents in this perspective use a range of

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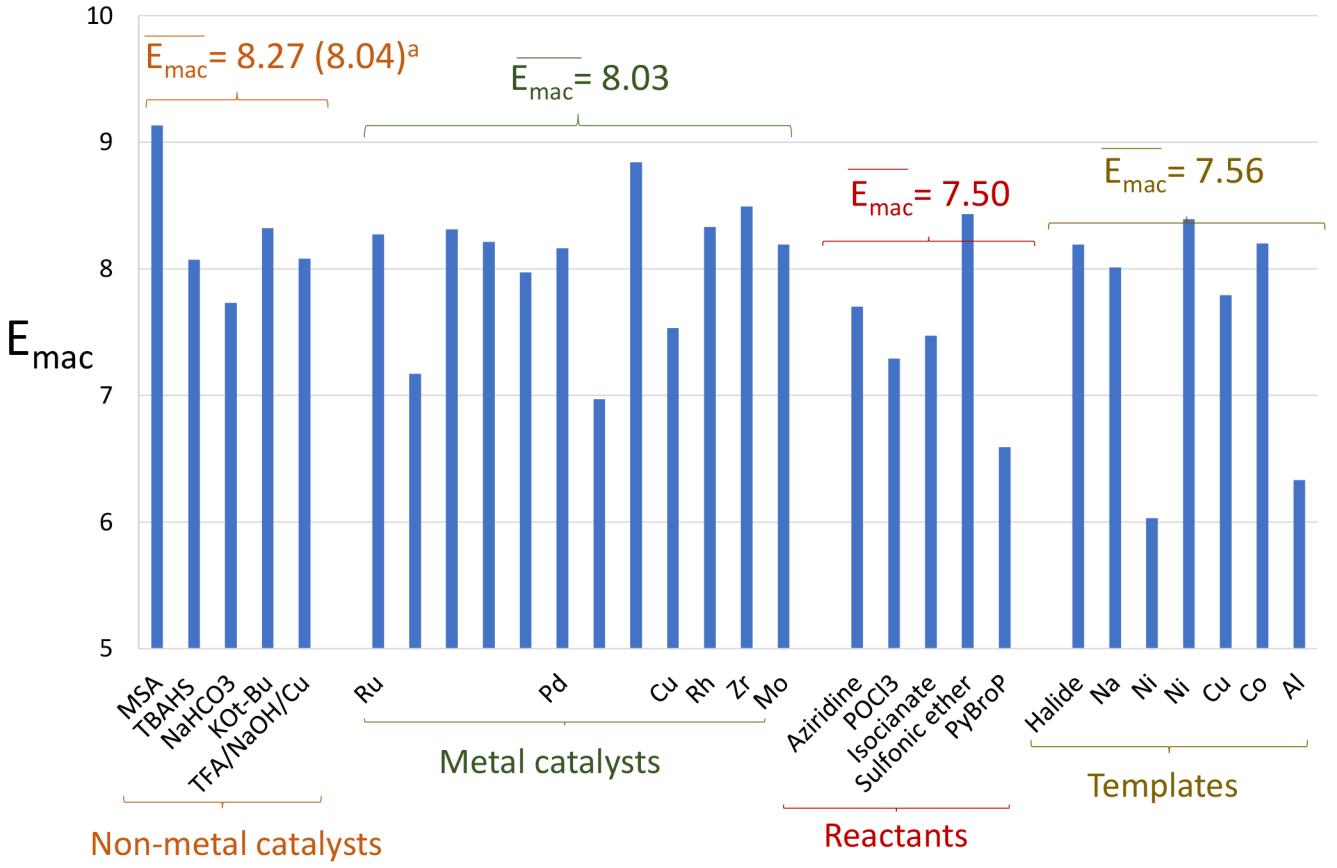

Figure 26. Analysis of the Emac values for the different macrocyclization strategies shown in this study, also showing the average values for type of reaction. [a]Not considering MSA.

polarities, such as toluene, DCM, THF, DMF, pyridine, ACN, MeOH, and a combination of them. The conclusion here is that there is not a preferential solvent for highly concentrated macrocyclization reactions, which is inherently good, since many types of reactions can be tested. The increase in solvent concentration enables a decrease in the catalytic amount required to drive the macrocyclization reaction since the catalyst concentration also increases. Besides, the difficulties in finding macrocyclization procedures in multigram amounts may come from the inherent lack of methodologies with reasonable amounts of solvent. Thus, the benefits of high reaction concentration conditions are multiple.

The results in Figure 26 also show that different acids, bases, and metal catalysts enable the synthesis of macrocycles under different reaction conditions and mechanisms. Catalytic bases are perhaps the less used methodology, and further studies should be stimulated. More studies on macrolactonization and macrolactamization reactions are also encouraged. We expect that the coming years will see a significant increase in the number of examples where the macrocyclization reaction is performed with reasonable amounts of solvent, as any other type of reaction is carried out, to boost scaling up and implementation at the industrial level. This is not only a scientific challenge but also a necessity to bring biologically and industrially relevant macrocycles to its deserved quote of accessibility among the rest of chemicals.

The challenge of achieving Emac values ∼9 or higher does not necessarily pass through catalysis, and classical methodologies, such as template synthesis, will play a role. However, the diversity of reactions that catalysis, in particular metal catalyst, can play suggests that metal-catalyzed processes are the first strategy to indagate when designing a highly concentrated macrocyclization process. Of course, the use of ruthenium-catalyzed RCM reactions and palladium-catalyzed cross-coupling reactions will still be fundamental in this regard; however, it is desirable that many other coupling synthetic methodologies are attempted. The portfolio of metal-catalyzed carbon−carbon and carbon−heteroatom bond forging reactions in organic synthesis is huge, and more and more reactions are discovered every year. The potential catalytic effect of metal templates during reaction may be studied, which will bring a bifunctional role for metals during some macrocyclization reactions. Thus, not only researchers devoted to macrocyclization reactions but also researchers working in catalysis for synthetic reactions, particularly those that could be suitable for macrocycle synthesis, should be interested in testing new reaction strategies at high concentration conditions.

Of course, the functional groups present in the starting linear molecule play a key role for the macrocyclization reaction outcome, not only by providing a particular electronic and steric environment to the reaction but also by determining the stability of the final macrocycle. Besides, when catalysts are involved, the interaction of these functional groups with the catalytic site can change the macrocyclization pathway. With the low number of examples in hand so far for highly concentrated macrocyclization reactions, it is difficult to establish a pattern; however, it would be desirable in the near future to correlate the precursor structure with the final

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macrocycle product, at least for a given type of reaction, for prediction purposes.

Solid catalysts can also play a differential role in macrocyclization reactions (different from solid-phase reaction conditions). As can be seen above, the use of solid catalysts in macrocyclization reactions, concentrated or not, is still scarce; thus, much effort must be put in this direction. It is true that solid catalysts require high concentration conditions; otherwise, the inherent diffusion limitations associated with solid surfaces will irremediably decrease the macrocyclization rate to a useless point. Thus, high concentration conditions and the use of solid catalysts should go hand in hand. And then, the use of flow reaction conditions with solid catalysts will become another valid strategy to improve the throughput of the macrocyclization reaction and save solvent amounts. A convenient flow rate and residence time on solid catalysts will enable one to adjust the solvent amount to the minimum and, moreover, recycle, after subsequent passes of the reaction mixture over the solid catalyst bed in a tubular reactor.

CONCLUSIONS

Macrocyclization reactions at 0.2 M (or more) concentration are still the exception rather than the norm, even in the laboratory, despite that a high concentration of reactant is often crucial for high scale and, ultimately, industrial implementation. Analysis of the few systems reported so far (<30 examples shown here) concludes that catalytic strategies are at the forefront of the most successful macrocyclization reactions, with Emac values ∼9 in some cases, thus with solvent amounts manageable in industrial environments. We hope that the necessity of high concentration during macrocyclization reactions will be considered in coming studies.

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Author Contributions

F.G.-P. searched the literature and extracted conclusions about the data. A.L.-P. conceived the idea, searched and compared the literature, and supervised the whole work. Both authors have participated in the writing of the manuscript.

Notes

The authors declare no competing financial interest.

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