International Journal of Chemistry and Materials Science

Review

Chemical Control Methods for Intramolecular Ring-Closing Selectivity in Peptide Macrocyclization

Yifang Yang[1,*]

[1] Yuncheng University, Yuncheng, China
* Correspondence: Yifang Yang, Yuncheng University, Yuncheng, China

Abstract: Peptide macrocyclization is a pivotal strategy in the development of bioactive cyclic peptides, yet achieving precise intramolecular ring-closing selectivity remains a formidable synthetic challenge. Multiple competing reaction pathways, including undesired intermolecular oligomerization, self-cyclization at alternative nucleophilic sites, and epimerization, frequently compromise the yield and fidelity of the desired macrocyclic product. To elucidate the primary factors governing intramolecular ring-closing selectivity during peptide macrocyclization and the underlying mechanistic principles, this review systematically examines the effects of precursor conformation, the presence of multiple reactive sites, and competitive side reactions on ring-closing behavior. Drawing upon a comprehensive analysis of recent literature, we outline three principal regulatory strategies: conformational pre-organization through template-assisted or solvent-mediated folding, reaction site orientation via protecting group adjustment and steric shielding, and reaction system control encompassing reagent selection, temperature optimization, and solvent engineering. The analysis reveals that these distinct regulatory approaches operate by modulating spatial accessibility, site-specific reactivity, and kinetic competition, respectively, and that their overall effectiveness is jointly constrained by ring size and sequence characteristics. Appropriately matching regulatory methods to the structural features of the target peptide significantly enhances the selectivity and controllability of the desired ring closure. This review provides a practical framework for the rational design of selective peptide macrocyclization protocols and highlights emerging opportunities in the field.

Keywords: peptide macrocyclization; intramolecular cyclization; cyclization selectivity; conformational preorganization; site-directed control

1. Introduction

Peptide macrocyclization represents a pivotal strategy in modern peptide chemistry, enabling conformational restriction that enhances proteolytic stability membrane permeability, and target-binding affinity. By covalently linking distal functional groups—such as N-terminus to C-terminus, side chain to terminus, or side chain to side chain—the resulting cyclic architecture significantly reduces backbone flexibility, thereby stabilizing bioactive conformations often inaccessible to linear analogues. Nevertheless, the synthetic execution of intramolecular ring closure remains inherently challenging due to the entropic penalty associated with bringing reactive termini into proximity, coupled with the high degree of conformational freedom in flexible peptide chains [1, 2]. This dynamic behavior frequently leads to competing intermolecular oligomerization or polymerization, undesired regioisomeric cyclization, epimerization at chiral centers under harsh conditions, and hydrolytic degradation of activated intermediates. Moreover, sequence-dependent effects—including steric bulk, hydrogen-bonding networks, and local secondary structure propensities—introduce additional layers of complexity that influence both cyclization efficiency and product distribution. Consequently, achieving high-yielding, chemoselective, and stereospecific macrocyclization demands careful orchestration across multiple interdependent dimensions: pre-organizational control of

Received: 08 July 2026
Revised: 26 August 2026
Accepted: 09 September 2026
Published: 15 September 2026

peptide conformation prior to bond formation; precise spatial alignment of reacting functional groups through templating, directing groups, or engineered turn motifs; and fine-tuned modulation of the reaction environment—including solvent polarity, content, temperature, catalyst identity, and additive composition—to suppress off-pathway processes. This work systematically examines these interconnected determinants, establishing a unified conceptual framework for rational macrocycle design grounded in mechanistic insight rather than empirical optimization alone.

2. Issues of Ring-Forming Selectivity in Peptide Macrocyclization

Ring-forming selectivity in peptide macrocyclization is a multifaceted challenge that governs not only the overall efficiency of the cyclization process but also the structural fidelity, functional integrity, and reproducibility of the resulting macrocyclic peptides. This selectivity operates across three interdependent yet mechanistically distinct dimensions. First, at the kinetic and thermodynamic level, linear precursors must favor intramolecular ring-closing over competing intermolecular side reactions—such as dimerization, oligomerization, or polymerization—which are often entropically disfavored but can dominate under high-level conditions or with insufficient conformational preorganization [1, 3]. Second, when multiple nucleophilic or electrophilic functional groups are present—for instance, lysine ε-amines, cysteine thiols, aspartic acid carboxyls, or N-terminal α-amines—the reaction must exhibit chemoselectivity to ensure that only the designated residues engage in bond formation, necessitating careful design of protecting group strategies, orthogonal coupling reagents, or templated activation. Third, for peptides containing more than two potential cyclization points, regioselectivity and topological control become critical: the same amino acid sequence may yield head-to-tail, side-chain-to-tail, or side-chain-to-side-chain macrocycles with markedly different ring sizes, backbone conformations, and biological activities. Consequently, achieving high ring-forming selectivity demands integrated optimization of precursor conformation, reactant level, solvent polarity, temperature, catalyst identity, and temporal control—each parameter influencing one or more selectivity tiers without universally improving all simultaneously.

2.1. Excessive Conformational Freedom of the Precursor

Linear peptide precursors possess a high degree of conformational flexibility due to the presence of numerous rotatable bonds along the main chain. As a result, their structural ensemble spans a broad spectrum of spatial arrangements—including fully extended conformations, partially folded intermediates, and locally distorted or twisted geometries. For successful intramolecular cyclization to occur, the reactive termini must simultaneously satisfy stringent spatial prerequisites: the interatomic distance must fall within an optimal range for bond formation, their relative orientation must align with orbital overlap requirements, and the local backbone geometry must support proper transition-state geometry. Excessive conformational freedom diminishes the population fraction of those rare conformers that meet all these criteria concurrently, thereby lowering the effective probability of productive ring closure [3, 4]. This entropic penalty arises because the system must overcome substantial disorder to adopt the highly ordered transition state required for cyclization. Structural features such as proline residues, D-configured amino acids, N-methylated amide bonds, and bulky side chains further modulate local dihedral angle distributions, altering the statistical likelihood of terminal group proximity. Prolonged residence in nonproductive conformations leads to kinetic limitations.: activated intermediates become increasingly susceptible to competitive hydrolysis, while intermolecular side reactions or off-target intramolecular couplings gain relative advantage. Consequently, precursor conformational dynamics exert fundamental control not only over cyclization yield but also over the intrinsic selectivity landscape—governing which reaction pathway dominates under given physicochemical conditions.

2.2. Competition among Multiple Reaction Sites

Functional groups such as the N-terminal amino group, the epsilon-amino group of lysine side chains, the thiol group of cysteine residues, the carboxyl groups of aspartic and glutamic acid side chains, and the hydroxyl groups of serine and threonine residues commonly coexist within a single polypeptide chain [5]. Due to overlapping pKa ranges, comparable nucleophilic strengths under physiological or mildly controlled reaction conditions, and similar susceptibility to common activating reagents, these groups frequently engage in competitive reactions during chemoselective modifications—particularly in intramolecular ring-closure processes. Moreover, the local microenvironment—including hydrogen-bonding networks, electrostatic interactions with nearby charged residues, solvent accessibility, conformational effects imposed by secondary or tertiary structure elements, and proximity to catalytic metal ions—can significantly modulate the protonation state, effective nucleophilicity, and steric availability of each functional group. As a result, observed reactivity often deviates markedly from predictions based solely on intrinsic chemical properties derived from small-molecule analogues. When coupling reagents or activation strategies lack sufficient selectivity, undesired acylation, alkylation, oxidation, or cross-linking events may occur at non-target sites, generating complex mixtures containing regioisomeric cyclic products, oligomeric side products, and scrambled linkage architectures. Therefore, multisite competition must be understood not merely as a combinatorial challenge arising from functional group multiplicity, but as a dynamic interplay among intrinsic chemical reactivity, residue-specific microenvironmental perturbations, and three-dimensional spatial positioning. Strategic design of reaction conditions—including pH optimization, temperature control, chelating agents, protecting-group logic, and tailored bifunctional linkers—is essential to amplify reactivity differentials and enforce selective bond formation at the intended locus within architecturally intricate peptide sequences.

2.3. Competitive Reactions Interfere with Ring-Closing

Ring-closing reactions in macrocycle synthesis are inherently challenged by the presence of multiple concurrent reaction pathways that compete with the desired intramolecular cyclization. Activated peptide precursors—such as those bearing activated esters, thioesters, or other electrophilic C-terminal derivatives—are susceptible to a range of side transformations, including intermolecular coupling, hydrolytic degradation, oligomerization, and epimerization at stereolabile centers. Elevated precursor loading or suboptimal ring-closing kinetics significantly elevate the probability of intermolecular encounters, thereby favoring dimeric and higher-order oligomeric adducts over the target cyclic structure. Prolonged residence time of reactive intermediates in solution further exacerbates hydrolysis, progressively diminishing the pool of viable cyclization-competent species. Moreover, certain condensation conditions—particularly those involving elevated temperature, non-optimal pH, or strongly nucleophilic additives—may induce partial racemization or epimerization at the C-terminal amino acid residue, compromising stereochemical fidelity. Solvent polarity, ionic strength and the intrinsic electrophilicity of the activating reagent modulate the relative activation barriers for each competing process. Consequently, accelerating overall substrate consumption does not guarantee enhanced macrocyclization efficiency; if side reactions accelerate disproportionately, the absolute and relative yield of the target macrocycle may decline despite rapid starting material depletion [6, 7]. Strategic optimization therefore focuses on maximizing the kinetic preference for intramolecular ring closure—through judicious control of dilution, conformational preorganization, protecting group strategy, and catalyst design—to ensure that the majority of reactive intermediates undergo productive cyclization rather than unproductive side-channel transformations.

3. Chemical Methods for Regulating Intramolecular Ring-Closing Selectivity

3.1. Conformational Pre-Organization Regulation

The key to conformational pre-organization lies in strategically guiding the conformational equilibrium of the linear peptide precursor toward a spatial arrangement that aligns with the geometric and topological requirements of the desired intramolecular ring-closing reaction [8]. This approach goes beyond merely reducing backbone flexibility; it emphasizes the selective stabilization of productive conformers in which reactive termini are positioned at optimal distances and orientations for bond formation. As illustrated in Figure 1, incorporation of structural motifs such as proline residues, D-configured amino acids, or N-methylated amide bonds systematically modulates local dihedral angles (e.g., φ, ψ, and ω) and restricts rotational freedom around peptide bonds, thereby promoting favorable proximity between distal functional groups. Complementary strategies—including transient templating agents, directional hydrogen-bond networks, and reversible covalent linkages—further refine inter-terminal spatial relationships by fixing relative positions and controlling trajectory alignment during cyclization. Crucially, successful pre-organization must account for both macrocycle size and the stereoelectronic demands of the bond-forming step; over-rigidification or misfolded conformations can introduce unfavorable steric or angular strain into the transition state, counteracting the kinetic benefits intended by conformational control. Thus, the objective is not maximal constraint but precise conformational matching—engineering a precursor structure whose three-dimensional architecture inherently mirrors the topology and bond geometry of the target cyclic product, ensuring high selectivity and efficiency in macrocyclization.

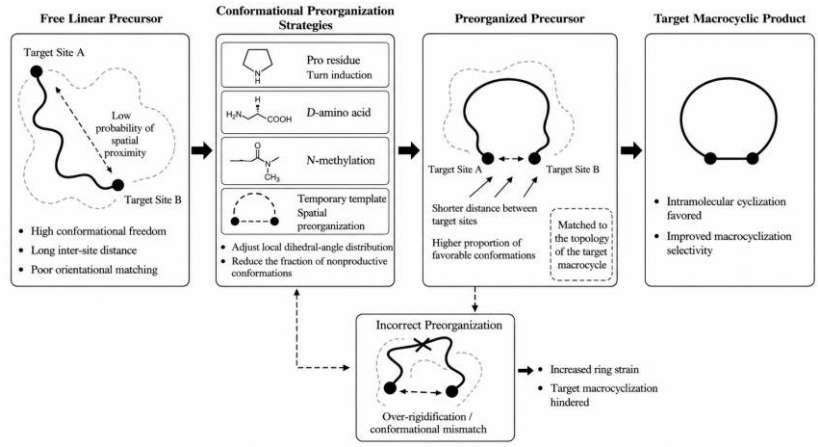

Figure 1. Schematic Illustration of the Mechanism by Which Conformational Preorganization Regulates Intramolecular Ring-Forming Selectivity in Peptides

3.2. Site-Specific Regulation of Reaction Sites

The core objective of site-specific control in macrocyclization is to enhance the differential reactivity between the designated functional group and other chemically similar sites present in the precursor molecule, thereby steering the cyclization process toward selective bond formation at the intended location [9, 10]. This strategic redirection transforms an inherently promiscuous reaction landscape—where multiple nucleophilic or electrophilic residues such as lysine ε-amines, cysteine thiols, aspartic acid carboxylates, or glutamic acid side chains could compete for coupling—into a highly discriminating transformation dominated by a single, preselected site. Implementation proceeds across three complementary tiers: temporary masking of non-target functionalities, orthogonal chemical transformations, and context-dependent modulation of intrinsic reactivity. Protective group strategies, including acid-labile Boc, base-labile Fmoc, or thiol-specific trityl derivatives, provide reversible steric and electronic shielding of reactive side chains, significantly curtailing undesired acylation, alkylation, or intermolecular cross-linking

during cyclization. Orthogonal reaction systems—such as copper-catalyzed or strain-promoted azide–alkyne cycloadditions, inverse-demand Diels–Alder reactions, or chemoselective native chemical ligation—introduce reaction handles with mutually exclusive kinetic and thermodynamic profiles, enabling sequential, non-interfering bond formation even within densely functionalized peptide scaffolds. In cases where extensive synthetic modification is impractical—for instance, in late-stage functionalization of biologically derived precursors—reactivity can instead be tuned through microenvironmental engineering: proximity-driven effective molarity enhancement, localized protonation state control via neighboring acidic or basic residues, differential solvent accessibility governed by secondary or tertiary structural effects, and selective activation using wavelength-specific photolysis or enzyme-triggered cleavage. Critically, these approaches are not isolated solutions but synergistic components of a unified reactivity management framework; their combined application often yields superior selectivity compared to any single method alone. Such site-selective methodologies are especially valuable for complex linear precursors bearing multiple ionizable or nucleophilic side chains, though they entail trade-offs including extended synthetic routes, potential epimerization risks during protection/deprotection cycles, and the necessity of installing exogenous functional groups prior to cyclization.

3.3. Selective Regulation of the Reaction System

Selective modulation of the reaction system centers on achieving preferential kinetic favorability for the desired intramolecular ring-closing transformation relative to alternative reaction channels, including intermolecular coupling, hydrolysis, and rearrangement pathways. A reduction in precursor loading diminishes the frequency of bimolecular encounters, thereby suppressing dimerization and oligomerization events; meanwhile, covalent connectivity within a single precursor molecule ensures persistent spatial proximity between reactive termini, sustaining efficient cyclization efficiency. Solvent polarity, thermal energy input, and acid–base conditions collectively influence peptide backbone flexibility, protonation equilibria of nucleophilic or electrophilic side chains (e.g., lysine ε-amino, aspartic acid carboxyl), and the stability of transient high-energy intermediates such as O-acylisourea or N-acylbenzotriazole species—each factor contributing to a dynamic rebalancing of competing rate constants. Chemical activators and catalytic platforms—including phosphonium- and uronium-based coupling reagents, transition-metal complexes, or enzyme mimics—differentially lower activation barriers at distinct functional sites; however, overactivation risks accelerating undesired side reactions (e.g., racemization, aspartimide formation), whereas underactivation extends the residence time of labile intermediates, increasing susceptibility to decomposition or water-mediated cleavage. Consequently, systematic optimization targets not absolute reaction speed but precise kinetic partitioning among parallel pathways. This approach proves especially valuable when evaluating sequence-dependent behavior: smaller macrocycles (e.g., ≤7-membered rings) often suffer from transannular strain and entropic penalty, while larger rings (>12 atoms) face competing conformational ensembles that hinder productive alignment. Moreover, residues bearing similar intrinsic reactivity—such as two solvent-exposed serine hydroxyls or adjacent lysine amines—pose inherent challenges for differentiation solely through bulk-phase parameter adjustments. Hence, environmental tuning functions most effectively as an enabling complement to structural preorganization (e.g., via turn-inducing motifs or metal-chelating tags) or site-selective protection/deprotection strategies [11]. In highly flexible linear precursors containing multiple chemically analogous nucleophiles or electrophiles, integrated control—combining conformational restriction, molecular recognition elements, and temporally resolved kinetic regulation—offers superior management of multifaceted side-reaction networks and enhances overall cyclization fidelity and yield.

4. Analysis of the Applicability of Chemical Control Methods

4.1. Characteristics of Ring Size Applicability

Ring size plays a decisive role in governing the interplay between geometric restrictions and conformational flexibility during peptide macrocyclization; however, the literature lacks consensus on precise numerical boundaries—whether defined by residue count or total ring atoms—for categorizing macrocycles as small, medium, or large. Consequently, ring size functions more effectively as a comparative parameter for discerning which physical or energetic factor dominates the cyclization pathway. In smaller macrocycles, spatial proximity requirements for bond formation are particularly stringent, necessitating precise alignment of reactive termini; insufficient backbone curvature may elevate internal strain energy, whereas excessive pre-organization can kinetically trap the linear precursor in nonproductive conformations that hinder productive cyclization. Under these conditions, strategic incorporation of residues with favorable rotational profiles—and careful modulation of local dihedral angles—becomes essential to guide folding toward the desired macrocyclic topology. Medium-sized systems generally exhibit an optimal compromise: sufficient conformational restriction to favor intramolecular reaction over intermolecular side reactions, yet enough flexibility to accommodate diverse transition-state geometries; thus, outcomes are increasingly governed by differential reactivity of functional groups, activation kinetics, and the efficiency of coupling reagents. As ring dimensions expand further, the influence of ring strain diminishes progressively, but the entropic penalty associated with bringing reactive ends into proximity grows substantially due to the exponential rise in accessible conformational states [4]. This leads to a marked reduction in the effective local molarity between reacting sites, thereby elevating the probability of intermolecular dimerization, oligomerization, or polymerization. To counteract this, experimental strategies such as high-dilution protocols, transient templating agents, and rapid, chemoselective ligation methods assume heightened importance. Ultimately, variation in ring size does not prescribe a singular optimal control strategy; rather, it systematically reshapes the hierarchy of selectivity-determining factors—from strain-dominated conditions in small rings to entropy- and kinetics-dominated conditions in larger architectures.

4.2. Peptide Sequence Adaptability

The peptide sequence fundamentally governs the conformational behavior of the macrocyclization precursor, directly influencing both the spatial arrangement of reactive functional groups and the thermodynamic and kinetic feasibility of intramolecular ring closure. Consequently, identical nominal ring sizes may exhibit markedly divergent cyclization efficiencies due to sequence-dependent structural pre-organization. Sequences incorporating proline residues, D-configured amino acids, or N-methylated backbones tend to adopt well-defined turn motifs or sterically restricted conformations, thereby enhancing the probability of productive proximity between designated reaction termini. In contrast, sequences enriched in glycine or composed of multiple consecutive flexible residues—such as alanine, serine, or threonine—sample a significantly broader ensemble of conformers, resulting in lower effective molarity and greater dependence on external factors—such as solvent composition, temperature, or templating agents—to achieve productive alignment. Furthermore, an elevated density of nucleophilic or acidic side chains—including lysine, cysteine, aspartic acid, and glutamic acid—introduces competing intermolecular and intramolecular reaction pathways, thereby diminishing selectivity for the desired macrocyclic product. Additional modulating influences include hydrophobic interactions, intra-chain hydrogen-bond networks, and steric occlusion effects, all of which determine the solvent accessibility and reactivity of target functional groups. Therefore, comprehensive evaluation of sequence adaptability must integrate three interdependent dimensions: intrinsic conformational propensity, reactive site density and distribution, and local microenvironmental modulation. As the interplay among these dimensions intensifies, the precursor bears a correspondingly higher selectivity burden, rendering single-variable optimization insufficient; instead, robust

macrocyclization outcomes increasingly rely on synergistic, multi-parameter chemical control strategies.

4.3. Criteria for Selecting Regulatory Methods

Different intramolecular ring-closing strategies operate through distinct mechanistic principles to achieve selective macrocyclization. Conformational preorganization functions by biasing the precursor's three-dimensional structure toward geometries that favor proximity and proper orbital alignment between reacting termini, thereby enhancing effective molarity and reducing entropic penalties associated with cyclization. Site-directed approaches rely on differential chemical behavior—such as nucleophilicity, acidity, or redox potential—among functional groups within the same molecule; this selectivity is amplified through strategic chemical modifications that render only the desired site reactive under given conditions. Reaction system modulation involves fine-tuning bulk-phase parameters—including solvent polarity, temperature, catalyst loading, and stoichiometric balance—to differentially influence competing kinetic pathways. Protective group shielding temporarily masks non-target functionalities, orthogonal reaction handles enable sequential, chemoselective transformations without cross-reactivity, and selective activation leverages subtle differences in electronic environment or steric accessibility to trigger bond formation at a single locus. Combined strategy deployment is not an independent selectivity mechanism but rather a synergistic integration of two or more complementary approaches, particularly valuable when precursors contain multiple reactive centers, conformational heterogeneity, or structural motifs prone to aggregation or decomposition. The optimal selection among these strategies must be guided by systematic evaluation of structural features—including target ring size (e.g., 5–7-membered rings versus medium or large macrocycles), backbone rigidity or flexibility, density and spatial distribution of nucleophilic/electrophilic sites, and the dominant side reaction profiles such as hydrolysis, polymerization, epimerization, or intermolecular coupling.

As shown in Table 1, the suitability of each strategy correlates strongly with the rate-determining factor governing successful ring closure. For highly flexible linear precursors—especially those lacking internal hydrogen-bonding motifs or rigidifying elements—the probability of productive end-to-end encounter remains low; in such cases, conformational preorganization via templating agents, metal coordination, or covalent tethers significantly improves cyclization efficiency and fidelity [5]. When multiple chemically similar residues—such as lysine ε-amines and cysteine thiols—are present, intrinsic reactivity differences are often insufficient for selective differentiation; therefore, selective protection, differential deprotection kinetics, or orthogonal coupling chemistries become essential to ensure regioselective ring formation. In systems where dimeric or oligomeric species dominate—or where labile intermediates undergo rapid solvolysis—adjustments to solvent composition, dilution protocols, and activation methodology serve to suppress intermolecular events and stabilize transient cyclization-competent species. Complex peptide or hybrid scaffolds frequently necessitate combined strategies, though this introduces additional synthetic complexity, including extended synthetic sequences, increased purification burden, and broader parameter space for optimization. Consequently, method selection must be evaluated holistically—not only by yield of the target macrocycle—but also by the ratio of regioisomeric byproducts, extent of undesired sequence modification (e.g., racemization, oxidation), and scalability of the overall process under reproducible laboratory conditions.

Table 1. Comparison of the Applicability of Different Regulatory Methods for Intramolecular Cyclization

Regulation Method	Primary Source of Selectivity	Characteristics of Suitable Precursors	Suitability for Ring Size	Multisite Adaptability	Key Advantages	Key Limitations
Conformational Pre-organization Regulation	Restricts conformational space and increases the probability of approaching the target site	Precursors with high flexibility and well-defined target sites	Small and medium rings are more prominent; large rings can be used in conjunction with templates	Moderate	Can directly improve ring-forming geometric conditions	Conformational mismatch may increase ring tension
Directional control via protecting groups	Shields off-target functional groups and increases site-specific reactivity differences	Sequences with a high density of similar active sites, such as Lys and Cys	Broad applicability	High	Well-defined site-specific control; established methodology	Additional protection and deprotection steps
Orthogonal site regulation	Establishment of specific reaction pairs	Sequences with complex natural functional groups and numerous competing sites	Broad applicability	Very high	Strong chemical selectivity, few side reactions	Often requires the incorporation of non-natural reaction handles
Control of the reaction system	Adjusting the rate difference between intramolecular and intermolecular reactions	Precursors with pronounced tendencies toward dimerization, oligomerization, or hydrolysis	Mid-ring and macrocyclic structures offer greater potential for regulation	Low to moderate	Conditions are easy to adjust; no sequence modification is required	Difficult to resolve multisite competition when intrinsic activities are similar
Combined regulation	Synergy between conformational constraints	Complex sequences with high flexibility and	Ring sizes of all types can be custom-designed	Very high	Multiple competing paths can be simulated simultaneously	Method design and condition screening are relatively complex

and site reactivity	multiple active sites

5. Conclusions

The selectivity observed in peptide macrocyclization arises not from any single experimental parameter, but from the integrated interplay among three interdependent factors: the conformational accessibility of reactive termini or side chains, the intrinsic chemical reactivity of specific functional groups under given reaction conditions, and the presence of alternative reaction pathways—including oligomerization, hydrolysis, or intramolecular side reactions—that compete with productive cyclization. Conformational preorganization governs the spatial proximity and orientation of reacting moieties, effectively reducing entropic barriers; site-directed modulation enables selective activation or deactivation of particular residues through protecting-group strategies, temporary derivatization, or orthogonal coupling chemistries; and reaction-system control orchestrates kinetic and thermodynamic parameters—such as reaction level, temperature, and additive composition—to drive the equilibrium toward the desired product, temperature, catalyst loading, and solvent polarity—to favor cyclization over linear propagation. Each of these approaches is further modulated by structural determinants, including the target ring size (e.g., 8- to 20-membered rings exhibit distinct strain and flexibility profiles) and sequence-dependent features such as backbone stereochemistry, side-chain bulk, hydrogen-bonding propensity, and local secondary structure propensity. To advance the field toward rational design, future efforts must prioritize high-fidelity computational modeling of cyclic transition states, quantitative frameworks for predicting residue-specific reactivity in constrained environments, and integrative experimental platforms that simultaneously tune conformational, chemical, and kinetic variables—thereby enabling predictive, sequence-to-selectivity mapping and transitioning macrocyclization from iterative optimization to first-principles engineering.

References

1. R. C. Larock and S. Babu, "Synthesis of nitrogen heterocycles via palladium-catalyzed intramolecular cyclization," *Tetrahedron Letters*, vol. 28, no. 44, pp. 5291–5294, 1987.
2. K. C. Majumdar, "Regioselective formation of medium-ring heterocycles of biological relevance by intramolecular cyclization," *RSC Advances*, vol. 1, no. 7, pp. 1152–1170, 2011.
3. N. Kumagai, S. Matsunaga, and M. Shibasaki, "An efficient synthesis of bicyclic amidines by intramolecular cyclization," *Angewandte Chemie*, vol. 116, no. 4, pp. 484–488, 2004.
4. A. Speranca, B. Godoi, and G. Zeni, "Iron(III) chloride/diorganyl diselenides: A tool for intramolecular cyclization of alkynone O-methyloximes," *The Journal of Organic Chemistry*, vol. 78, no. 4, pp. 1630–1637, 2013.
5. A. Takeda, S. Kamijo, and Y. Yamamoto, "Indole synthesis via palladium-catalyzed intramolecular cyclization of alkynes and imines," *Journal of the American Chemical Society*, vol. 122, no. 23, pp. 5662–5663, 2000.
6. Y. Wang, P. Zhang, X. Di, Q. Dai, Z. M. Zhang, and J. Zhang, "Gold-catalyzed asymmetric intramolecular cyclization of N-allenamides for the synthesis of chiral tetrahydrocarbolines," *Angewandte Chemie*, vol. 129, no. 50, pp. 16121–16125, 2017.
7. H. A. Bates and H. Rapoport, "Synthesis of anatoxin a via intramolecular cyclization of iminium salts," *Journal of the American Chemical Society*, vol. 101, no. 5, pp. 1259–1265, 1979.
8. D. L. Boger and R. J. Mathvink, "Acyl radicals: functionalized free radicals for intramolecular cyclization reactions," *The Journal of Organic Chemistry*, vol. 53, no. 14, pp. 3377–3379, 1988.
9. H. Iida, Y. Yuasa, and C. Kibayashi, "Intramolecular cyclization of enaminones involving arylpalladium complexes. Synthesis of carbazoles," *The Journal of Organic Chemistry*, vol. 45, no. 15, pp. 2938–2942, 1980.
10. G. Stork and J. Ficini, "Intramolecular cyclization of unsaturated diazoketones," *Journal of the American Chemical Society*, vol. 83, no. 22, p. 4678, 1961.
11. J. G. Garcia, B. Ramos, L. M. Pratt, and A. Rodríguez, "Intramolecular cyclization of enyne [3] cumulenals," *Tetrahedron Letters*, vol. 36, no. 41, pp. 7391–7394, 1995.