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Total Synthesis **Hot Paper**

Rapid Construction of a Tyr C6–Trp C5′ Linkage: Application in the Total Synthesis of Micitide 982, a Noncanonical Cyclic Peptide

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Abstract: In this study, a facile synthesis method for a highly strained Tyr C6-to-Trp C5′ linkage was developed. This method enables the convergent introduction of arbitrary biaryls to peptide linkers through electrochemically assisted Ni-catalyzed cross-electrophile coupling, followed by regioselective Larock macrocyclization. Additionally, using this approach, the total synthesis of the ribosomally synthesized and post-translationally modified peptide (RiPP) molecule micitide 982 was accomplished. Furthermore, this synthetic strategy allows for the incorporation of various biaryls.

Introduction

A variety of RiPPs have been isolated in recent years due to their ability to quickly and accurately predict chemical structures from genomic sequences, making them more accessible for prediction than natural compounds such as terpenoids and alkaloids.[1–6] These RiPPs, synthesized by ribosomes and subsequently generated by diverse tailoring enzymes, exhibit intriguing structures and biological activities. Among the natural products of these RiPPs, highly strained structures and those containing peculiar biaryl linkages are frequently observed.[5]

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To date, numerous noncanonical cyclic peptides containing biaryl moieties have been isolated (Figure 1a). Among these, some are known to possess atropoisomerism at the linkage site connecting the two aromatic rings. Representative frameworks exhibiting atropisomerism within biaryl regions include cross-linkages formed by tryptophan–tryptophan, tryptophan–tyrosine, and tryptophan–histidine linkages; for several of these cross-linkages, established synthetic methods are available. However, a synthesis strategy has yet to be developed for certain linkages (Figure 1a). In this study, we report the development of a simple method for constructing the highly strained Tyr C6-to-Trp C5′ linkage present in micitide 982 (**1**).

Micitide 982 (**1**), isolated in 2023, is a novel cyclic peptide belonging to the RiPPs class (Figure 1a).[7] Structurally, it consists of three amino acid residues, namely L-tyrosine, L-proline, and L-tryptophan, forming a highly strained Tyr-Trp linkage with a cyclic peptide structure. Micitide 982 (**1**) was isolated from a 10 L of fermentation of a bacterial strain expressing the precursor peptide and P450 for its biosynthesis, yielding 5 mg of the compound. However, due to its limited quantity, the biological activity of micitide 982 (**1**) remains unknown. Furthermore, the highly strained Tyr-Trp linkage, composed of the three amino acid residues in micitide 982 (**1**), is also found in pseudosporamide (**2**), which was isolated in 2020.[8] In this study, a new and convenient synthetic route for the highly strained Tyr C6-to-Trp C5′ linkage was developed, utilizing Ni-catalyzed electrochemical cross-electrophile coupling followed by regioselective Larock macrocyclization. This modular approach enabled the concise construction of the Tyr C6-to-Trp C5′ linkage, marking the total synthesis of micitide 982 (**1**), and facilitated the straightforward synthesis of its analogs.

The biosynthetic pathway for biaryl-containing RiPPs has been proposed as follows (Figure 1b).[9–18] Ribosomally synthesized linear peptides containing leader sequences are cyclized through oxidation by cytochrome P450 (CYP450) enzymes that harbor heme at their active sites, resulting in the formation of cross-linkages with biaryl moieties. Subsequently, the leader peptides, which serve as recognition elements for the enzymes, are enzymatically cleaved, ultimately yielding noncanonical cyclic peptides that feature biaryl cross-linkages.

Recently, considerable progress has been made in the artificial biosynthesis of biaryl cross-linkages (Figure 1c).[6,7,19–26] Typically, this involves harnessing enzymes identified through genomics that catalyze the formation of biaryl bonds. For example, P450 enzymes, implicated in cross-linkage

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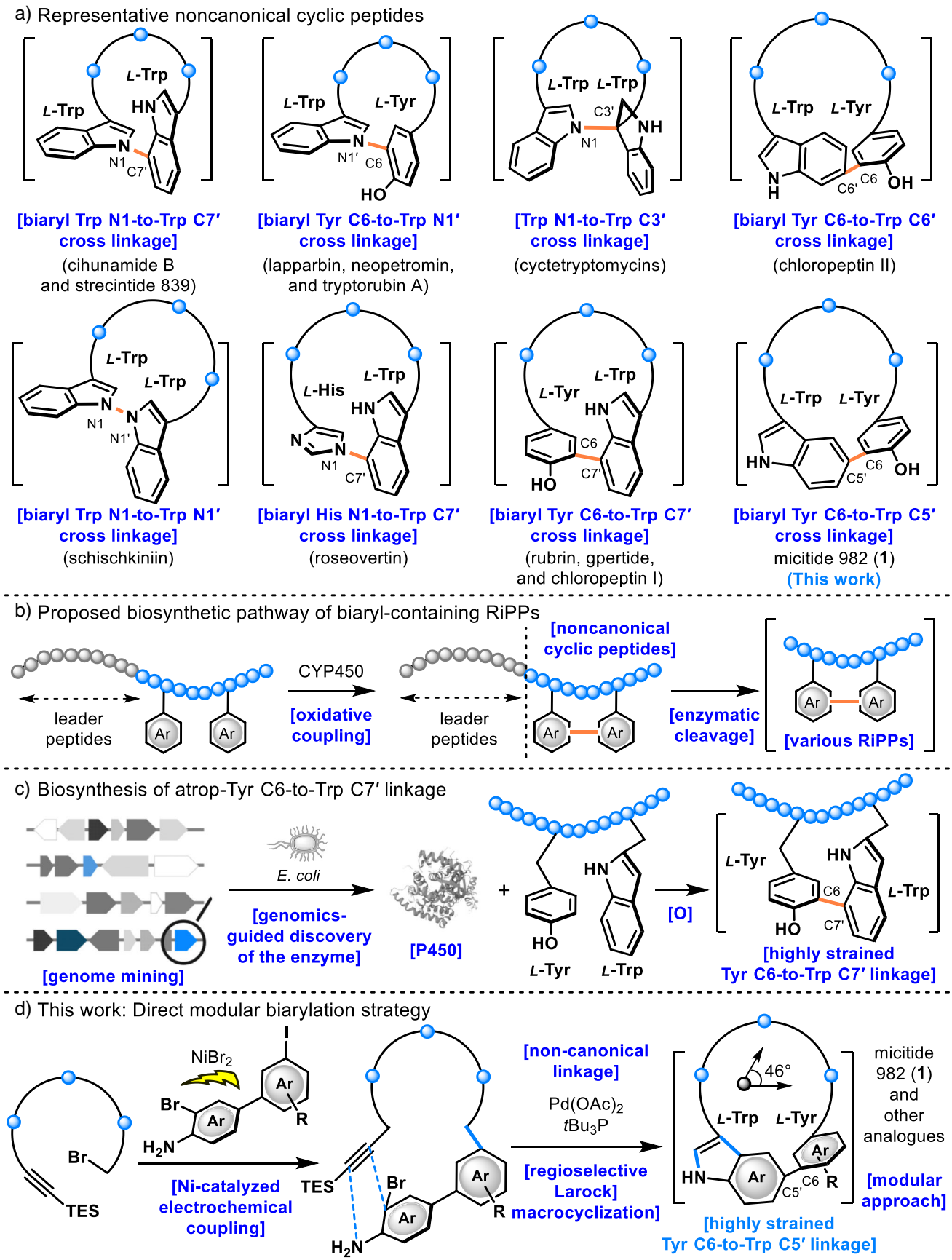


Figure 1. a) Representative noncanonical cyclic peptides. b) Proposed biosynthetic pathway. Cc) Biosynthesis. d) This work.

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biosynthesis according to genomic data, are expressed in *Escherichia coli*. Then, chemical synthesis can produce linear peptides, which are subsequently incubated with the cultured P450 enzymes to enable atroposelective and artificial biosynthesis of biaryl moieties.[19,20] However, due to the enzyme-specific nature of these reactions, their applicability is often limited to specific substrates, making the creation of diverse biaryl cross-linkages a persistent challenge.[7,21]

This study reports the development of a modular and straightforward chemical synthesis method for biaryl-containing cross-linkages—specifically, the Tyr C6-to-Trp C5′ linkage that does not rely on enzymatic catalysis (Figure 1d). By employing peptide linkers bearing terminal halogens and alkynes, this approach allows for the modular introduction of various biaryl units. Notably, the combination of Ni-catalyzed electrochemical cross-electrophile coupling and subsequent regioselective Larock macrocyclization proved to be highly effective. The electrochemical cross-electrophile coupling facilitated by Ni catalysts occurs under mild conditions at room temperature, enabling the facile incorporation of biaryl motifs into peptide linkers with only three amino acid residues. Furthermore, the subsequent Larock macrocyclization enabled the construction of the Tyr C6-to-Trp C5′ linkage from simple starting materials in just two steps. This modular strategy also enables the synthesis of analogs that are difficult to produce via enzymatic methods, thereby expanding the diversity of biaryl cross-linkages that can be generated.

Results and Discussion

One of the most common methods for the synthesis of cyclic peptides is macrocyclization through amide coupling.[27–41] Therefore, an attempt was made to construct the highly strained Tyr C6-to-Trp C5′ linkage in **4** through macrocyclization via amide coupling (Figure 2a). Compounds **2** and **3** were synthesized as precursors for cyclization, and various representative amide coupling reagents were screened. As a result, compound **4** derived from **2** was not observed under the conditions employing EDCI, DCC, DMTMM, PyBOP, HATU, or COMU. Even when using compound **3**, compound **4** was not observed under the conditions employing EDCI, DCC, DMTMM, or PyBOP. Further screening revealed that while trace amounts of **4** were detected using compound **3** under the conditions employing HATU or COMU, the yield was significantly low (<5%). From these results, it was revealed that the synthesis of the Tyr C6-to-Trp C5′ linkage **4** via macrocyclization using amide coupling is challenging due to the significant strain caused by the rigidity and linearity of the biaryl moiety.

Based on the above background, the design for the straightforward construction of the Tyr C6-to-Trp C5′ linkage and the synthesis plan for micitide 982 (**1**) are depicted in Figure 2b. The most challenging aspect of synthesizing micitide 982 (**1**) lies in forming the highly strained Tyr C6-to-Trp C5′ linkage. Conversely, our group recently reported the synthesis of several RiPPs containing biaryl motifs, such as cihunamide B,[42] strecintide 839,[43] lapparbin,[44] and neopetromin.[45] In these syntheses, Larock macrocyclization was demonstrated to be effective for constructing strained cyclic peptides. Specifically, for the total syntheses of cihunamide B[42] and strecintide 839,[28] atroposelective construction of the Trp N1-to-Trp C7′ linkage was achieved through Larock macrocyclization. Additionally, in the syntheses of lapparbin[44] and neopetromin,[45] a modular approach utilizing C–H arylation of alanine derivatives followed by Larock macrocyclization enabled the formation of the Tyr C6-to-Trp N1′ linkage. However, in all these methods, the direct incorporation of arbitrary biaryl moieties into peptide linkers containing multiple amino acid residues remained challenging. For example, in the syntheses of lapparbin[44] and neopetromin,[45] C–H arylation was performed using an alanine derivative bearing an aminoquinoline as a directing group. In 2024, the construction of the micitide core via carboxylate-assisted C–H activation using *N*-phthaloylalanine was reported by our group.[46] In both cases, the direct incorporation of diverse biaryl units into polypeptides was not feasible. Consequently, assembling the macrocyclic core required multiple amide couplings after C–H arylation, rendering the approach less convergent and of limited scope. To address this, we devised a synthetic strategy enabling the efficient and convergent construction of the highly strained Tyr C6-to-Trp C5′ linkage and micitide 982 (**1**) with higher modularity. This involved installing the biaryl unit into peptide linkers with multiple amino acid residues in just two steps. This approach allows for the late-stage introduction of any desired biaryl motif, making the synthesis more convergent and suitable for analog development.

The core structure of micitide 982 (**1**), the Tyr C6-to-Trp C5′ linkage, was planned to be constructed via a combination of Ni-catalyzed electrochemical cross-electrophile coupling and subsequent Larock macrocyclization, applied to a three-residue peptide linker bearing terminal halogen and alkyne functionalities (Figure 2b). The corresponding biaryl fragments were prepared through Suzuki coupling of the specified 3-substituted aromatic precursor **9** or **10**. Meanwhile, the peptide linkers were synthesized via amide coupling of amino acid fragments **11**–**16**. This synthetic strategy is advantageous because it employs inexpensive, readily accessible building blocks to synthesize rigid biaryl linkages in a straightforward manner, exhibiting high convergence.

The synthesis of the Tyr C6-to-Trp C5′ linkage and synthesis of micitide 982 (**1**) commenced from peptide linker construction (Scheme 1). N-Boc-L-proline (**16**) was coupled with alkyne fragment **11** using HATU-mediated amide formation to afford compound **17**. Subsequently, compound **17** underwent Boc deprotection with TFA, followed by condensation with N-Boc-L-serine (**18**) using DMTMM to yield the three-residue peptide linker. This intermediate was then selectively brominated at the primary alcohol using triphenylphosphine (PPh_3) and N-bromosuccinimide (NBS), resulting in peptide linker **19**. The synthesis of the biaryl fragment **22** was initiated from 2-bromo-4-iodoaniline (**9**). Following protection of the amino group with an acetyl group, boronic acid **20** was obtained on a decagram scale via Miyaura borylation, followed by pinacol deprotection. Boronic acid **20** was then subjected to Suzuki coupling with aryl iodide

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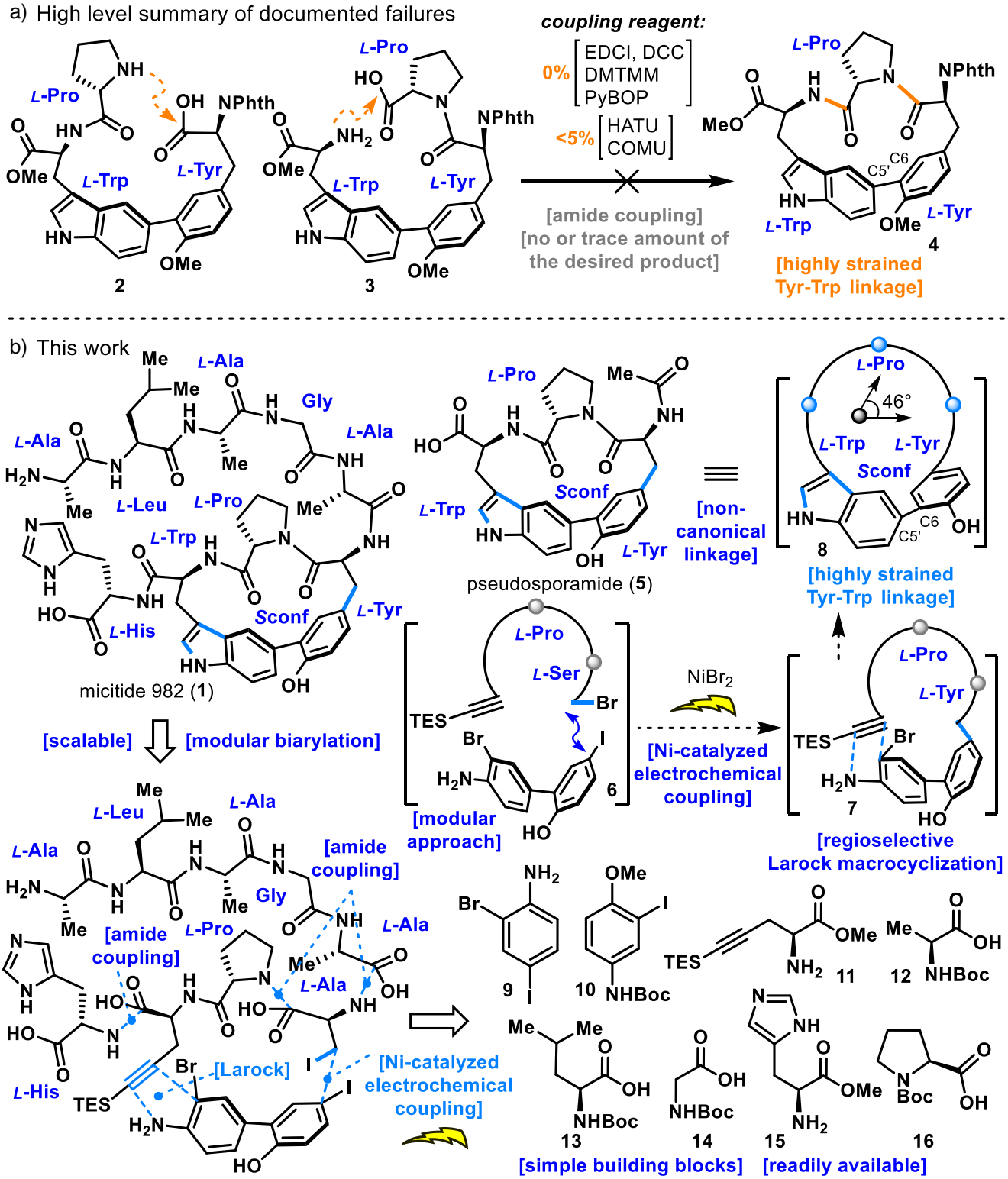


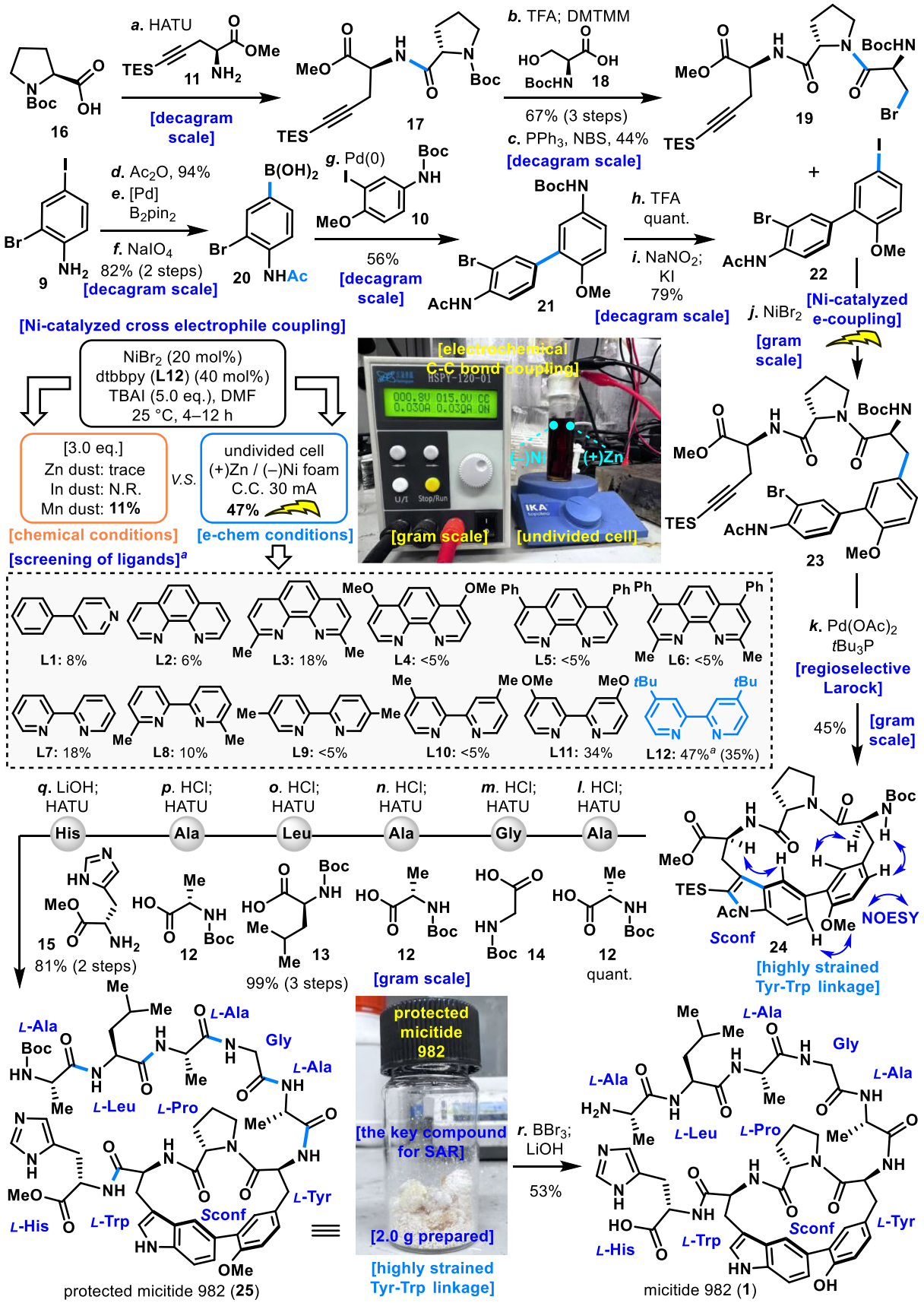
Figure 2. a) High level summary of documented failures. b) A synthetic approach to micitide 982 (**1**).

10 to afford biaryl compound **21**. To prepare for subsequent Ni-catalyzed electrochemical cross-electrophile coupling, biaryl **21** was scaled up to a decagram quantity and converted to aryl iodide **22** through Boc deprotection and a Sandmeyer reaction.

Subsequently, the Ni-catalyzed cross-electrophile coupling of peptide linker **19** with aryl iodide **22** was attempted. As previously mentioned, the direct introduction of the biaryl derivative **22** into the three-residue peptide linker **19** is a critical challenge for increasing the overall convergence

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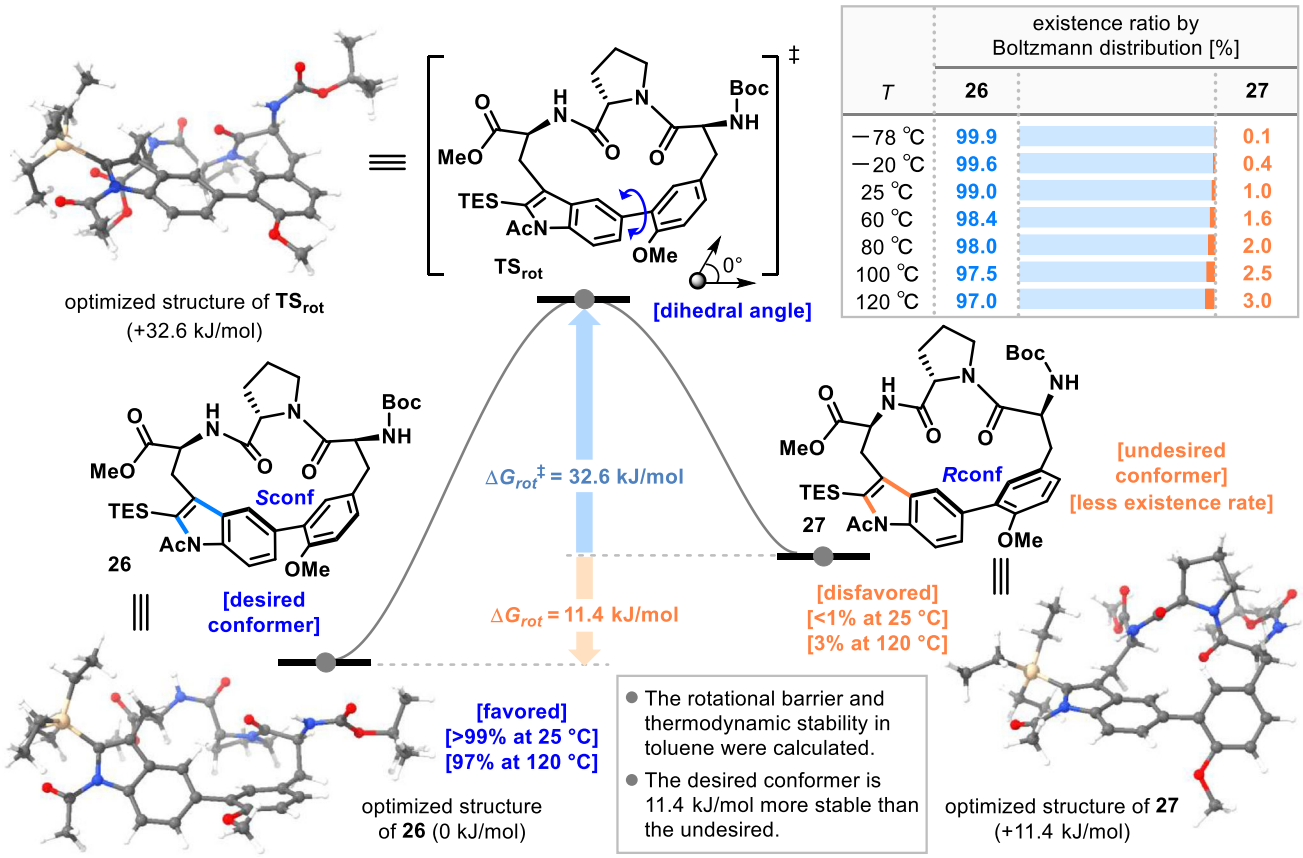
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Scheme 1. Concise construction of the Tyr C6-to-Trp C5′ linkage and the total synthesis of micitide 982 (1)[a]. [a]For detailed reagents and conditions, see the Supporting Information.

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Scheme 2. Thermodynamic stability of conformers **26** and **27**.

of the synthetic route. In recent years, numerous useful reactions for Ni-catalyzed cross-electrophile coupling have been reported.[47–50] Many of these reactions proceed under mild conditions at room temperature, making them effective for substrates with complex and sensitive functional groups, such as peptides.[51–67] Initially, the coupling was performed using the most common reaction conditions reported for Ni-catalyzed cross-electrophile coupling, with DMF (*N*,*N*-dimethylformamide) as the solvent, $NiBr_2$ (20 mol%) as the Ni source, 4,4′-Di-*tert*-butyl-2,2′-bipyridyl (dtbbpy (**L12**), 40 mol%) as the ligand, and zinc dust (3.0 equivalents) as the reducing agent.[51–67] The mixture of linker **19** and aryl iodide **22** was stirred under a nitrogen atmosphere at 25 °C for 12 hours. However, the desired coupling product **23** was not obtained; only complex mixtures were observed. Substituting zinc dust with manganese (Mn) or indium (In) dust was also attempted. While no product was formed using indium, the use of Mn dust yielded the desired coupling product **23** in an 11% isolated yield. Further efforts to improve the reaction conditions, including the optimization of the Ni source, ligands, and additives, were conducted; however, the yield of product **23** remained consistently low, making efficient synthesis challenging under these conditions. Additionally, cross-electrophile coupling using iodine instead of bromine in the alkyl bromide **19** was tested, but the yields of the desired product remained low and showed no significant improvement (for further details, see Supporting Information).

Meanwhile, recent advances have reported electrochemical Ni-catalyzed cross-electrophile coupling for sp^2–sp^3 carbon–carbon bond formation.[68–75] These reactions are highly advantageous due to their ability to form C─C bonds under mild conditions. Consequently, an attempt was made to synthesize coupling product **23** by applying Ni-catalyzed electrochemical cross-electrophile coupling between linker **19** and aryl iodide **22**. After screening a broad range of reaction conditions, it was determined that using $NiBr_2$ (20 mol%) as the Ni source, with a constant current of 4 mA in an undivided cell equipped with zinc and nickel foam electrodes under a nitrogen atmosphere, produced the best results. Further ligand screening was undertaken to optimize the conditions: initial trials with pyridine derivatives (**L1**) and 1,10-phenanthroline (**L2**) resulted in low yields of 8% and 6%, respectively. Substituted 1,10-phenanthroline derivatives (**L3**–**L6**) were also tested; however, the highest yield achieved was only 18% (**L3**). Among bipyridine-type ligands (**L7**–**L12**), the use of more electron-rich ligands such as 4,4′-dimethoxy-2,2′-bipyridine (**L11**) and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbbpy, **L12**) enhanced yields, reaching 34% and 47%, respectively (for further details, see Supporting Information). Based on these results, direct installation of biaryl **22** onto the three-residue peptide linker **19** under mild room temperature conditions was successfully achieved.

Next, the construction of the highly strained Tyr C6-to-Trp C5′ linkage **24** from coupling product **23** was attempted.

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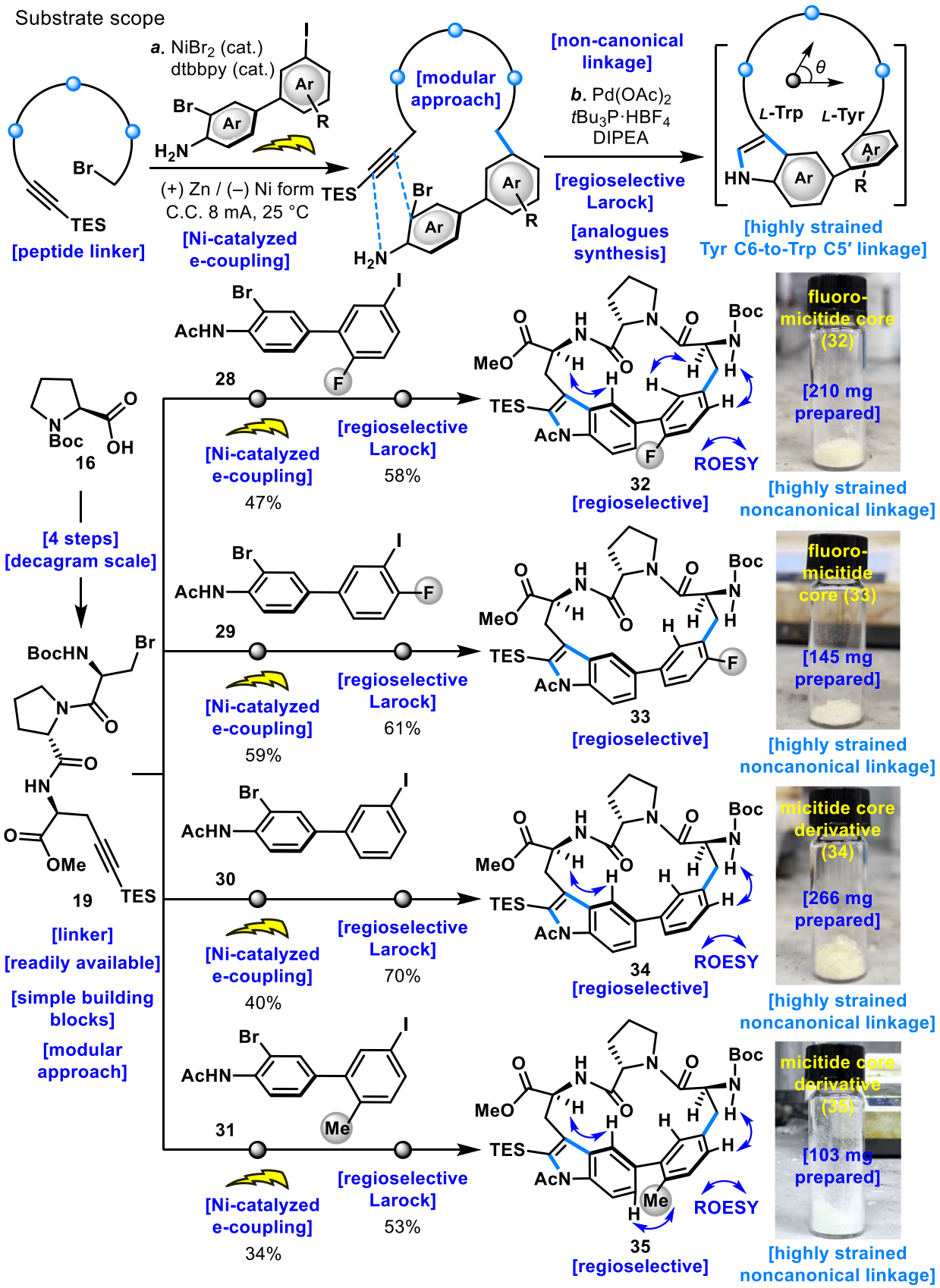


Figure 3. Substrate scope for the modular biarylation[a]. [a]For detailed reagents and conditions, see the Supporting Information.

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The most challenging aspect of the synthesis of micitide 982 (**1**) is the formation of this highly strained linkage. As previously described, using intramolecular amide bond formation conditions with precursors **2** and **3** led to excessive strain caused by the rigidity (linearity) of the biaryl moiety, preventing formation of the desired highly strained Tyr–Trp linkage **4** (Figure 2a). In contrast, Larock macrocyclization is a chemo-selective organic chemistry reaction that proceeds under mild conditions with Pd catalysts in the presence of alkynes.[76–88] It has been proven to be highly effective in synthesizing macrocyclic peptides with substantial strain. Utilizing Larock macrocyclization conditions inspired by the prior studies reported by Riesman,[88] Baran,[82] and Sarlah[83] et al., precursor **23** was successfully converted to the target macrocyclic compound **24** in 45% yield. The conformational state of the obtained cyclized product was confirmed by NOESY spectroscopy to be identical to that of micitide 982 (**1**). The optimal conditions for this macrocyclization involved $Pd(OAc)_2$ as the catalyst and tri-*tert*-butylphosphine (tBu$_3$P) as the ligand.

The remaining challenges for the synthesis of micitide 982 (**1**) involve the introduction of side-chain amino acids to macrocyclic compound **24** and the removal of protecting groups. The macrocyclic intermediate **24** obtained via Larock cyclization was subjected to deprotection with HCl to remove Boc and TES groups, followed by coupling with Boc- L -alanine (**12**) using HATU, thereby introducing the amino acid side chain. In a similar manner, additional amino acids (Boc-glycine (**14**), Boc-L-alanine (**12**), Boc- L-leucine (**13**), Boc-L-alanine (**12**)) were sequentially incorporated. Subsequently, hydrolysis of the methyl ester and the introduction of L-histidine methyl ester (**15**) afforded the protected micitide 982 (**25**) on a 2.0 g scale. Finally, the Boc and methyl-ether protecting groups of compound **25** were removed with BBr_3, and the methyl ester was hydrolyzed with LiOH. These steps culminated in the synthesis of micitide 982 (**1**).

The mechanistic elucidation of the Larock cyclization is illustrated in Scheme 2. To determine whether conformational state **26** can rotate and isomerize into **27**, the thermodynamic stability and rotational barrier between conformational states **26** and **27** were evaluated by DFT calculations. The computed activation free energy for interconversion ($\Delta G^{\ddagger}$) was +32.6 kJ/mol, and the thermodynamic energy difference between the two conformers was determined to be 11.4 kJ/mol. These results suggest that, although the conformational conversion from **26** to **27** is kinetically accessible at room temperature, the pronounced thermodynamic bias leads to an existence ratio of approximately 99:1 at 25 °C. Even at elevated temperatures (e.g., 120 °C), conformer **26** remains the predominant species, with a calculated ratio of 97:3. Accordingly, the isomerization is effectively negligible under ambient conditions, consistent with the experimental observation that conformer **26** was obtained as a single, isolable conformer. Furthermore, to address the conformational selectivity of the Larock cyclization from a kinetic standpoint, transition state calculations were conducted. These calculations demonstrated that conformer **26** is formed through a more stable transition state, thereby confirming its kinetic preference as the major product. (see Figure S4) Together, these findings confirm that conformer **26** is both kinetically and thermodynamically favored.

To demonstrate the utility of this synthetic strategy, an application was explored in which an arbitrary biaryl unit was directly introduced into a three-residue peptide linker **19**. As shown in Figure 3, cyclic peptides are generally more resistant to proteolytic degradation compared to linear peptides due to their cyclic structure, conferring enhanced stability within biological systems.[89–92] Furthermore, their cyclic conformation increases lipophilicity and membrane permeability, making cyclic peptides attractive as next-generation medium molecule drugs for therapeutic applications.[93,94] Four biaryl derivatives (compounds **28**–**31**) were prepared as model compounds. Subsequently, the incorporation of these biaryl derivatives into peptide linker **19** was attempted via Ni-catalyzed electrochemical cross-electrophile coupling. The desired C─C bond formation products were obtained in yields ranging from 34% to 59%. Notably, the reaction proceeded under mild, room-temperature conditions. After this, each macrocyclization precursor was subjected to Larock macrocyclization using Pd catalysis, which proceeded smoothly to afford the target macrocyclic compounds **32**–**35** in isolated yields of 53%–70%. This synthetic approach offers a concise and convergent methodology, enabling the introduction of biaryl units into peptides in just two steps starting from peptide linker **19**.

Conclusion

In summary, this study demonstrated that the highly strained Tyr C6-to-Trp C5′ linkage could be introduced into peptide linkers in just two steps by combining Ni-catalyzed electrochemical cross-electrophile coupling with subsequent regioselective Larock macrocyclization. Furthermore, this scalable and modular strategy facilitated the total synthesis of micitide 982 (**1**). Notably, protected micitide 982 (**25**) was prepared on a 2.0 g scale. In addition, this modular strategy facilitated the incorporation of various biaryl derivatives into peptide linkers. It is anticipated that this methodology will find broad applications in the field of medicinal chemistry, particularly in the synthesis of macrocyclic peptides and related bioactive molecules. Moreover, the two-step biarylation approach developed in this study has the potential for extensive application in the synthesis of a wide range of bioactive RiPPs beyond micitide 982 (**1**).

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University of Hong Kong (7020157). The computation was partly performed using Research Center for Computational Science, Okazaki, Japan (Project: 23-IMS-C119, Y.N.).

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Biaryl Peptides · Electrochemistry · Noncanonical Cyclic Peptide · RiPPs · Total Synthesis

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