Modular, Atroposelective Total Synthesis of Micitide 982

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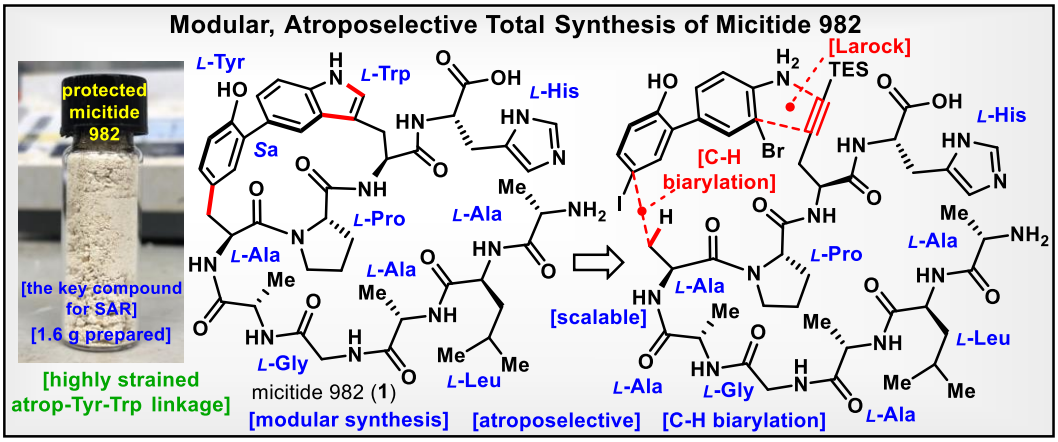
Supporting Information Placeholder



ABSTRACT: A modular, atroposelective total synthesis of micitide 982 (**1**) is reported. The feature of this report is the gram-scale C-H biarylation of *N*-phthaloyl-L-alanine followed by atroposelective Larock macrocyclization. This modular approach allowed the construction of a highly strained atrop-Tyr-Trp cross-linkage with unprecedented atropisomerism, as well as the first total synthesis of micitide 982 (**1**).

INTRODUCTION

A variety of RiPPs (ribosomally synthesized and post-translationally modified peptides) 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 terpenes and alkaloids.[1] 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.[1e]

Micitide 982 (**1**), isolated in 2023, is a novel cyclic peptide belonging to the RiPPs class (Figure 1A).[2] Structurally, it consists of three amino acid residues, namely L-tyrosine, L-proline, and L-tryptophan, forming a highly strained atrop-Tyr-Trp linkage with a cyclic peptide structure. The atropisomerism of micitide 982 (**1**) was determined through various techniques, including electronic circular dichroism (ECD) spectrum, NOESY spectrum, various NMR experiments, and computational chemistry. 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 atrop-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.[3] In this study, a new and convenient synthesis route for the highly strained atrop-Tyr-Trp linkage using ligand-enabled carboxylate-directed C-H activation and subsequent atroposelective Larock macrocyclization was developed. This modular synthesis approach enabled the first total synthesis of micitide 982 (**1**) and facilitated the straightforward large-scale synthesis of its analogs.

Figure 1A illustrates the synthesis strategy of micitide 982 (**1**). The most challenging aspect of the synthesis of micitide 982 (**1**) lies in the construction of the highly strained atrop-Tyr-Trp linkage composed of three amino acid residues. Recently, we reported the atroposelective total synthesis of cihunamide B.[4] In the total synthesis of cihunamide B, a biaryl linkage was established early in the synthesis, followed by the construction of the highly strained atrop-Trp-Trp linkage through atroposelective Larock macrocyclization

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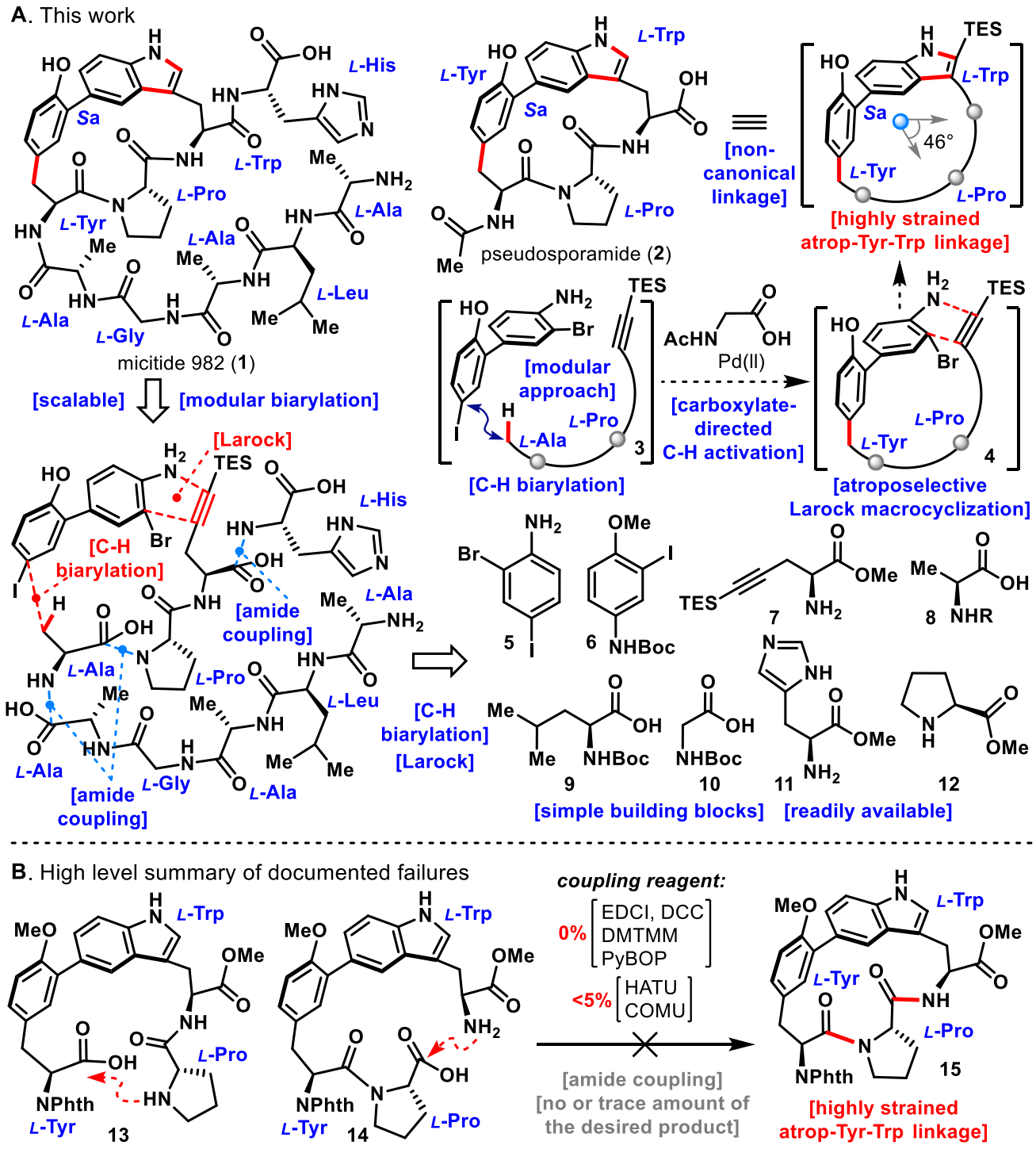


Figure 1. (A) A synthetic approach to micitide 982 (**1**). (B) High level summary of documented failures.

towards the end of the synthesis. We believed that this strategy of creating the biaryl linkage early in the synthesis could be applied to the synthesis of the highly strained atrop-Tyr-Trp linkage in micitide 982 (**1**).

Initially, we anticipated that the introduction of the biaryl moiety into the three amino acid residues could be achieved through modular C-H biarylation of L-Alanine. Subsequently, we planned the total synthesis of micitide 982 (**1**) through atroposelective Larock macrocyclization using Pd catalysts. Additionally, this modular synthesis approach was expected to allow the synthesis of micitide 982 (**1**) and analogs with various non-natural biaryl linkages.

One of the most common methods for the synthesis of cyclic peptides is macrocyclization through amide coupling.[5] Therefore, an attempt was made to construct the highly strained atrop-Tyr-Trp linkage in **15** through macrocyclization via amide coupling in the context of the total synthesis of micitide 982 (**1**) (Figure 1B). Compounds **13** and **14** were synthesized as precursors for cyclization, and various representative amide coupling reagents were screened. As a result,

compound **15** derived from **13** was not observed under the conditions employing EDCI, DCC, DMTMM, PyBOP, HATU, or COMU. Even when using compound **14**, compound **15** was not observed under the conditions employing EDCI, DCC, DMTMM, or PyBOP. Further screening revealed that while trace amounts of **15** were detected using compound **14** under the conditions employing HATU or COMU, the yield was significantly low (<5%). From these results, it became evident that the synthesis of atrop-Tyr-Trp linkage **15** through macrocyclization via amide coupling is challenging due to its significant strain.

RESULTS AND DISCUSSION

The synthesis route for the total synthesis of micitide 982 (**1**) begins with 2-bromo-4-iodoaniline (**5**) (Scheme 1). After protecting 2-bromo-4-iodoaniline (**5**) with an Ac group, boronic acid **16** was obtained on a decagram scale through Miyaura borylation followed by pinacol deprotection. Compound **16** was then subjected to a Suzuki coupling with compound **6** to synthesize biaryl **17**. The resulting biaryl **17** was adjusted on a decagram scale to obtain aryl iodide **18**, a precursor for C-H biarylation, through Boc deprotection and subsequent Sandmeyer reaction.

Subsequently, the C-H biarylation of *N*-phthaloyl-L-alanine (**19**) was attempted. With the recent advancements in C-H activation, numerous C-H arylation reactions utilizing Pd-catalyzed L-alanine derivatives and aryl iodides have been reported. [6-8] The most common approach in C-H arylation using L-alanine derivatives as substrates involves employing aminoquinoline as a directing group.[7] However, aminoquinoline often presents challenges due to its multi-step deprotection process, which is generally time-consuming and problematic for substrates sensitive to base and oxidation.[7c, 7e, 9] In our preliminary investigations, we attempted the C-H biarylation using an L-alanine derivative containing aminoquinoline as the directing group, along with aryl iodide **18**, following the reported conditions. [7] The desired C-H biarylation was observed to proceed; however, the deprotection of aminoquinoline required two steps (Boc protection and hydrolysis by $LiOH/H_2O_2$), resulting in a significantly low yield (21% for three steps from the C-H biarylation). Detailed investigation of the by-products revealed that the acetyl group on the biaryl moiety was deprotected during the Boc-aminoquinoline deprotection using $LiOH/H_2O_2$ conditions. Furthermore, the resulting aniline was oxidized by H_2O_2, leading to the formation of a complex mixture. Other conditions for aminoquinoline removal were also attempted but proved to be unsatisfactory in terms of both step count and yield.

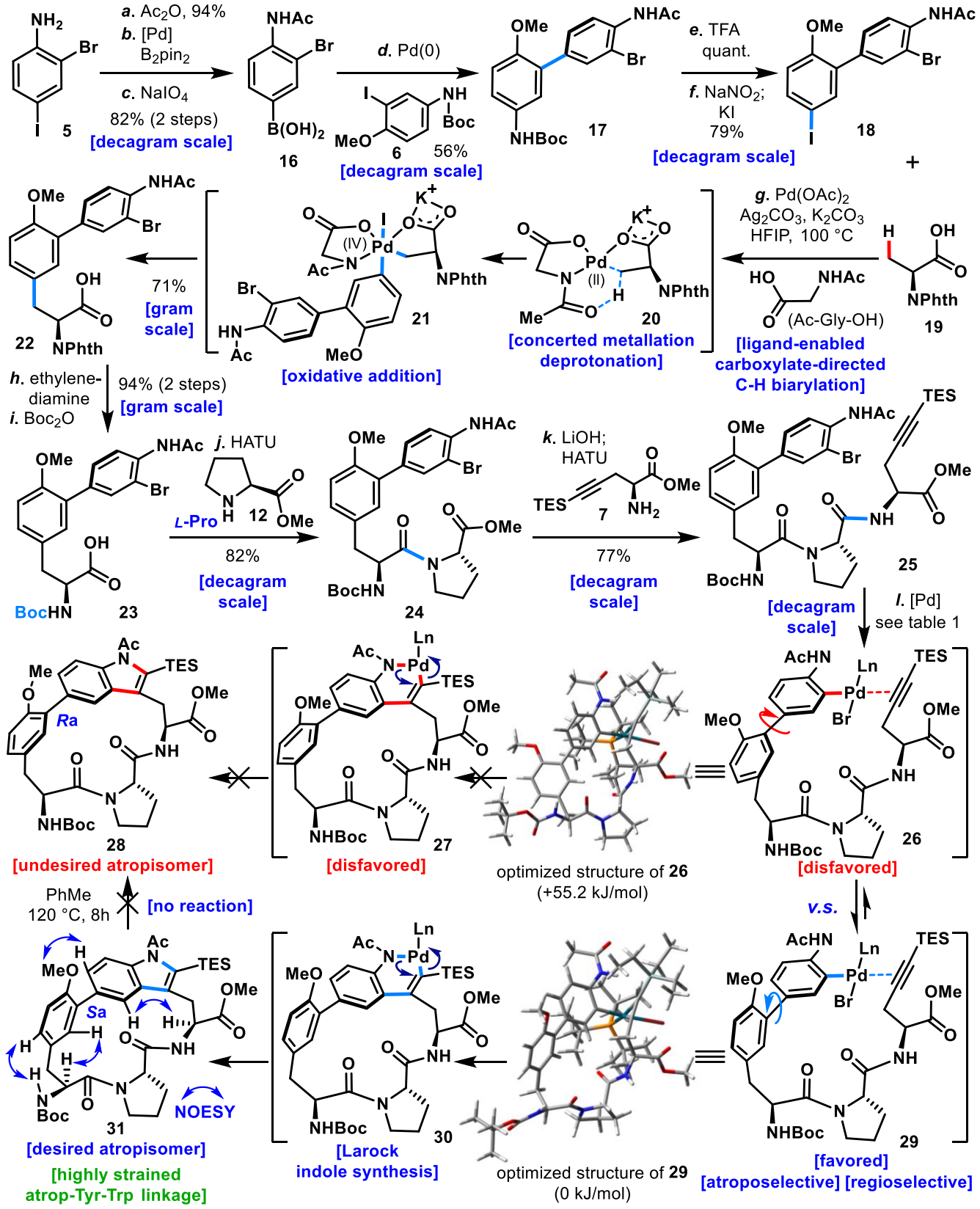
On the other hand, Zhao *et al.* and Yu *et al.* reported a direct C-H arylation using *N*-phthaloyl-L-alanine (**19**) without aminoquinoline in 2017. [6a, 6e] This reaction does not require aminoquinoline and is highly efficient and atom-economic, as it eliminates the need for aminoquinoline removal after C-H activation. Following Zhao's conditions, C-H biarylation was attempted using carboxylic acid **19** and aryl iodide **18**. Investigation of various conditions revealed that Ac-Gly-OH, as an amino acid ligand, effectively promoted concerted metallation deprotonation (CMD) and provided the desired compound **22** with an isolated yield of 71%. The reaction mechanism is proposed as follows: the carboxylate of *N*-phthaloyl-L-alanine (**19**), generated by Ac-Gly-OH and K_2CO_3, coordinates to Pd(II) to form intermediate **20** in the reaction system. This intermediate **20** is efficiently promoted by the acetyl group of Ac-Gly-OH, facilitating CMD and C-H metalation. Subsequently, oxidative addition of aryl iodide **18** leads to the formation of intermediate **21**. Finally, reductive elimination results in the conversion of intermediate **21** into the desired product **22**. [10] It is worth mentioning that when Boc-Gly-OH was used as a ligand, only trace amounts of the desired compound **22** were obtained. These experimental results clearly indicate the essential role of the acetyl group in this reaction. Further optimization of this C-H biarylation is described in Figure 2.

The obtained phthaloyl group of **22** was removed by ethylenediamine and converted to compound **23**, which was protected by the Boc group. There are two remaining amino acid residues necessary for the Larock macrocyclization key reaction. Carboxylic acid **23** was coupled with L-proline derivative **12** to induce the formation of amide **24**. After the hydrolysis of its Me ester, amide coupling with alkyne fragment **7** mediated by HATU led to the synthesis of compound **25**, the precursor for Larock macrocyclization.

The most challenging aspect in the total synthesis of micitide 982 (**1**) is the construction of the highly strained atrop-Tyr-Trp linkage. As mentioned earlier, obtaining the desired compound **15** was not possible under the conditions of intramolecular amide coupling due to excessive strain (Figure 1B). On the other hand, Larock macrocyclization is a bioorthogonal organic chemistry reaction that proceeds under mild conditions using Pd catalysts in the presence of an alkyne. It is known to be highly effective in the synthesis of macrocyclic peptides with significant strain. [4, 11, 12] Therefore, applying Larock macrocyclization to compound **15** was expected to enable the construction of the desired highly strained atrop-Tyr-Trp linkage.

To investigate the optimal conditions for Larock macrocyclization, several different phosphine ligands were tested under heating conditions at 110 °C in PhMe with $Pd(OAc)_2$ and DIPEA present (Scheme 2, Table 1). Interestingly, when PPh_3 was used, the desired compound **31**, containing the highly strained atrop-Tyr-Trp linkage, was obtained with a low yield of 22% (Table 1, entry 1). It is worth noting that this reaction exhibited complete atroposelectivity in the formation of compound **31**. Further exploration revealed that using the bulkier and electron-rich ligand PCy_3 improved the yield to 51% (entry 2). However, the electron-poor ligand $P(OMe)_3$ was not effective in this reaction (entry 3). Attempts were made to use bidentate ligands such as dppe and dppf, but they resulted in low yields (entries 4, 5). Since PCy_3 provided relatively good results, $Pd(t\text{Bu}_3P)_2$, which is a bulkier and electron-rich ligand, was used, but it was not very effective with a yield of 35% (entry 6). Interestingly, when $t\text{Bu}_3P{\cdot}HBF_4$ was used as a ligand, the yield improved to 59% (entry 7). This condition also proceeded well on an 18 g scale, and the desired compound **31** was synthesized with a yield of 45% (entry 8). Additionally, bases such as DBU, K_2CO_3, Cs_2CO_3, and NaOAc were investigated, but no results surpassing the best condition were obtained (entries 9-13). From this screening, it became clear that entry 7 is the best condition for this reaction.

Scheme 1. Atroposelective total synthesis of micitide 982 (**1**)[a]



[a]For detailed reagents and conditions, see the Supporting Information.

Scheme 2. Atroposelective total synthesis of micitide 982 (**1**)[a]

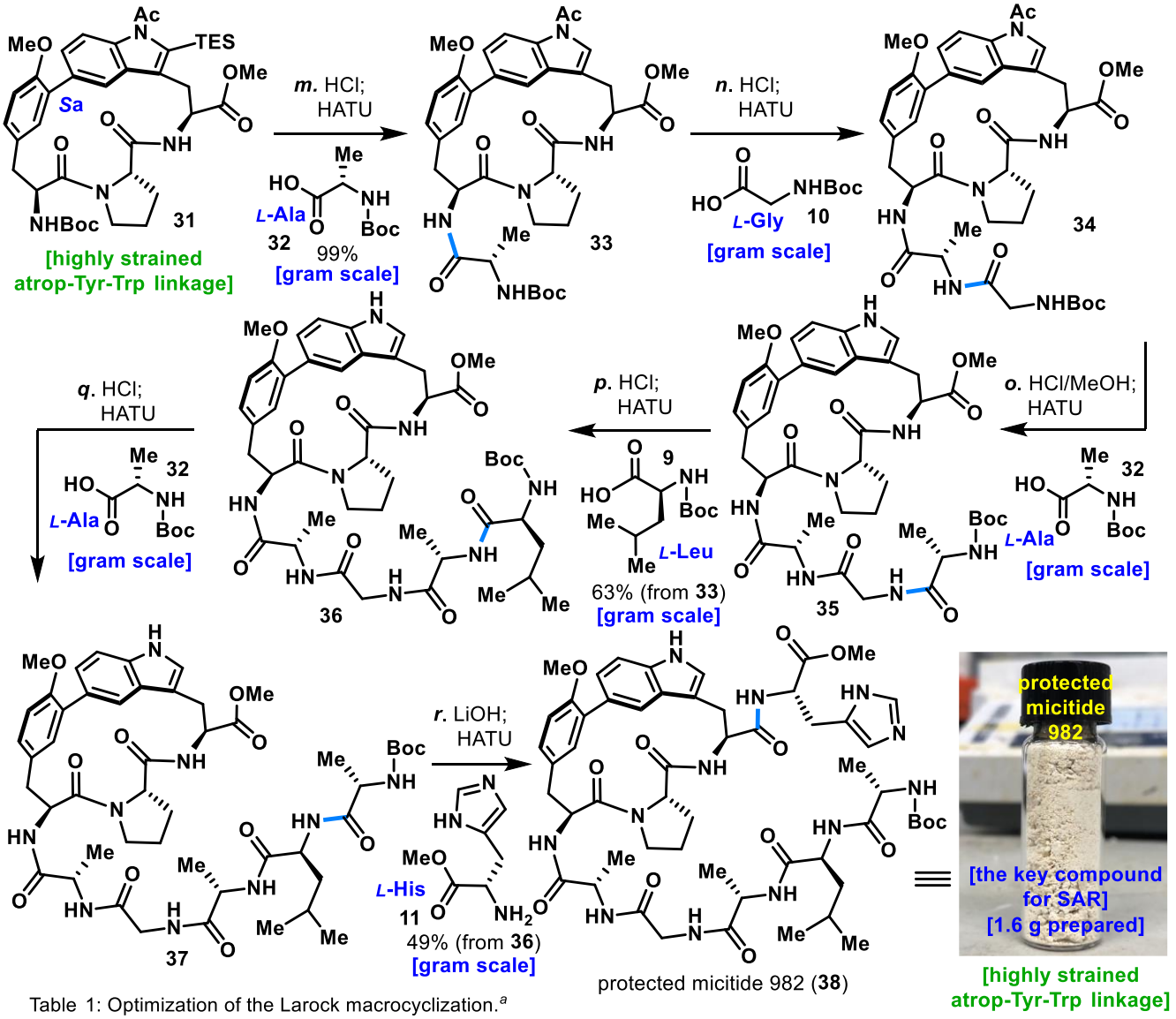


Table 1: Optimization of the Larock macrocyclization.[a]

entry	[Pd] 0.5 eq.	[ligand] 1.0 eq.	[base] 10 eq.	[solvent] 1 ml	yield[b]
1	$Pd(OAc)_2$	PPh_3	DIPEA	PhMe	22%
2	$Pd(OAc)_2$	PCy_3	DIPEA	PhMe	51%
3	$Pd(OAc)_2$	$P(OMe)_3$	DIPEA	PhMe	0%
4	$Pd(OAc)_2$	dppe (0.5)	DIPEA	PhMe	31%
5	$Pd(OAc)_2$	dppf (0.5)	DIPEA	PhMe	29%
6	$Pd(tBu_3P)_2$	—	DIPEA	PhMe	35%
7	$Pd(OAc)_2$	$tBu_3P{\cdot}HBF_4$	DIPEA	PhMe	59%
8[c]	$Pd(OAc)_2$	$tBu_3P{\cdot}HBF_4$	DIPEA	PhMe	45%
9	$Pd(OAc)_2$	$tBu_3P{\cdot}HBF_4$	Cy_2NMe	PhMe	50%
10	$Pd(OAc)_2$	$tBu_3P{\cdot}HBF_4$	DBU	PhMe	30%
11	$Pd(OAc)_2$	$tBu_3P{\cdot}HBF_4$	K_2CO_3	PhMe	42%
12	$Pd(OAc)_2$	$tBu_3P{\cdot}HBF_4$	Cs_2CO_3	PhMe	trace
13	$Pd(OAc)_2$	$tBu_3P{\cdot}HBF_4$	NaOAc	PhMe	36%

[a] The reactions were carried out on a 25 mg scale under conditions of 110 °C. [b] Isolated yields. [c] The reaction was performed on 18.2 g scale. PhMe (0.06 M) were used for this scale.

[a]For detailed reagents and conditions, see the Supporting Information.

The atropisomerism of compound **31** was determined to be in the *S*a conformation by its NOESY spectrum (see the Supporting Information).

The atroposelectivity of Larock cyclization is explained as follows: Initially, Pd(0) undergoes oxidative addition to the Ar-Br of the Larock Cyclization precursor **25**. Subsequently, Pd(II) undergoes migratory insertion into the internal akyne, leading to the formation of a six-membered palladacycle **27** or **30**. At this stage, the desired transition state **29**, which gives the desired atropisomer, is 55.2 kJ/mol more stable compared to the undesired transition state **26** (see supporting information for more details about the DFT calculation). Therefore, the reaction predominantly proceeds from transition state **29**, resulting in the atroposelective formation of the desired cyclized compound **31** as a single entity. To assess the thermal stability of the atrop-Tyr-Trp linkage formed by Larock cyclization, compound **31** was heated in toluene at 120 °C, confirming the absence of isomerization. Undesired atropisomer **28** was not observed at all. From these experimental results, it became evident that the atrop-Tyr-Trp linkage in compound **31** is thermodynamically stable in its preferred conformation.

The remaining challenges for the total synthesis of micitide 982 (**1**) are the introduction of side chain amino acid residues and the deprotection of protecting groups (Scheme 2). Compound **31**, possessing the highly strained atrop-Tyr-Trp linkage obtained via Larock macrocyclization, was converted to **33** by removing the Boc and TES groups with HCl, followed by condensation with Boc-L-alanine (**32**) mediated by HATU. Subsequently, using the same method, each amino acid residue (Boc-L-glycine (**10**), Boc-L-alanine (**32**), Boc-L-leucine (**9**), Boc-L-alanine (**32**) was sequentially condensed, leading to the conversion to compound **37** with a long side chain. The resulting **37** was subjected to hydrolysis followed by introduction of L-histidine methyl ester (**36**) to give protected micitide 982 (**38**) in good yield (49% from **36**) on a 1.6 g scale. The last remaining challenge for the total synthesis is deprotection. After removal of the Me-ether and Boc groups of protected micitide 982 (**38**) with BBr_3, the total synthesis of micitide 982 (**1**) was achieved after hydrolysis of the Me-ester with LiOH.

The optimization table for the C-H biarylation of *N*-phthaloyl-L-alanine (**19**) and aryl iodide **18** is shown (Figure 2A). Initially, following the work of Zhao *et al.*, the investigation of ligands was conducted in the presence of $Pd(OAc)_2$ catalyst, with the utilization of 1.0 equivalent of Ag_2CO_3 and 0.5 equivalents of K_2CO_3.[6a] As a result, when Ac-L-Phg-OH, Ac-L-Leu-OH, Ac-L-Ile-OH, Ac-L-Phe-OH, Ac-L-Ala-OH, and Ac-L-Val-OH were employed, the desired compound **22** was obtained with moderate yields ranging from 60% to 75% (Table 2, entries 1-6). Similarly, when Ac-D-Leu-OH and Ac-D-Phe-OH were employed, the C-H biarylation proceeded with moderate yields, although these two were in the moderate range (entries 7, 8). Further investigation of the ligands revealed that when Ac-Gly-OH was used, the desired compound **22** was obtained with the highest yield of 89% (entry 9). It is worth noting that this reaction also proceeded favorably on a gram scale with a yield of 71% (entry 10). Interestingly, when Boc-Gly-OH was used, as mentioned earlier, only traces of **22** were obtained. This indicates the essentiality of the Ac group in this reaction (entry 11). Regarding the Ag source, the reaction proceeded with a yield of 15% when $AgBF_4$ was employed, indicating a low yield (entry 12). Additionally, when AgOAc was used, the reaction proceeded with a moderate yield of 61% (entry 13). Finally, bases such as Na_2CO_3, Rb_2CO_3, KOAc, and NaOAc were investigated. The results showed that while each base provided the desired product **22**, the yields ranged from low to moderate (entries 14-17). From these results, it was evident that the best conditions for this C-H biarylation were observed in entries 9 and 10.

Subsequently, the substrate scope of this C-H biarylation was explored (Figure 2A, right). The results revealed that this C-H biarylation could be applied to various biaryl iodide derivatives. In order to synthesize non-natural derivatives of tyrosine, C-H biarylation was attempted using a substrate in which the OMe group was replaced by a methyl group. As a result, compound **39** was successfully obtained in 70% isolated yield. Furthermore, the reaction was applicable to the synthesis of compounds **40** and **41**, which are fluorine-substituted compounds playing an important role in the field of medicinal chemistry.

Furthermore, as an application, the synthesis of a non-natural fluoro-pseudosporamide (**42**) was attempted using the fluorine-substituted compound **40** (Figure 2B). L-Proline derivative **12** and alkyne fragment **7** were introduced to **40** using a similar method as the synthesis route of micitide 982 (**1**), resulting in the formation of a cyclization precursor. Subsequently, utilizing the best conditions of Larock macrocyclization mentioned earlier (Scheme 2, Table 1), the cyclization reaction was attempted, leading to the successful formation of the desired highly strained fluoro atrop-linkage in **42** with a yield of 30%. The atropisomerism of compound **42** was determined to be in the *S*a conformation by its NOESY spectrum and DFT calculations (see the Supporting Information). It is also worth noting that **42** was obtained as a single atropisomer. The synthesis method combining C-H biarylation and Larock macrocyclization demonstrated its remarkable effectiveness in the synthesis of strained cyclic peptides with any biaryl linkage. Moreover, its capability to easily synthesize non-natural biaryl linkages is noteworthy.

CONCLUSION

In summary, this work demonstrated the feasibility of synthesizing gram-scale strained biaryl linkages by combining C-H biarylation and subsequent atroposelective Larock macrocyclization. Furthermore, this modular approach enabled the first total synthesis of micitide 982 (**1**). Notably, the use of Ac-Gly-OH as a ligand in C-H biarylation proved to be highly effective in this reaction. Moreover, it became possible to introduce any biaryl group into *N*-phthaloyl-L-alanine (**19**) in a single step. This method has proven to be effective not only in various analog syntheses but also in the synthesis of fluoro-pseudosporamide (**42**) with a highly strained fluoro atrop-linkage, which possesses non-natural, fluorine-substituted characteristics. The combination of C-H biarylation and atroposelective Larock macrocyclization in this modular approach is expected to be further developed for the synthesis of natural products with diverse biological activities and strained biaryl linkages in RiPPs.

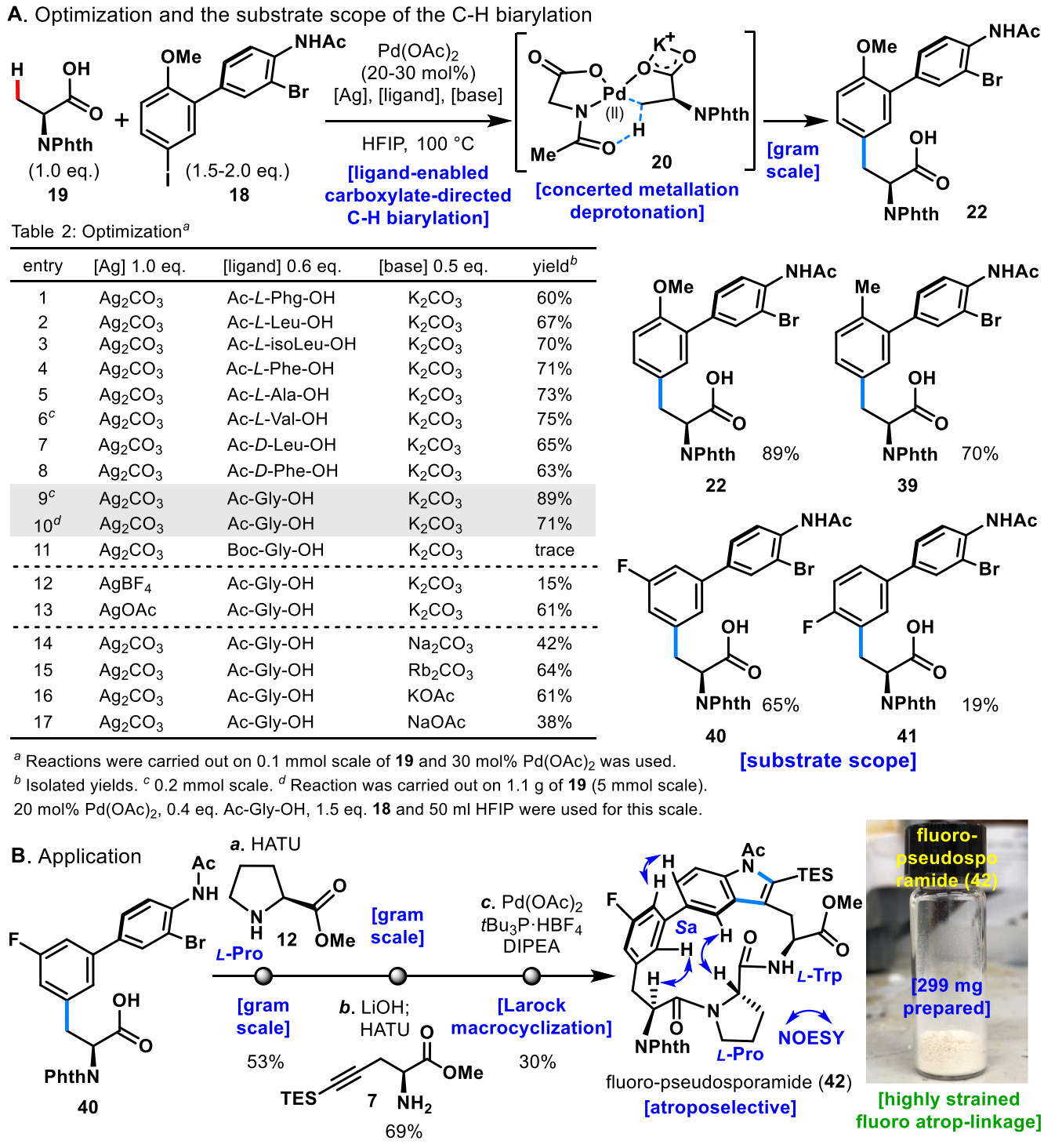


Figure 2[a]. (A) Optimization and the substrate scope of the C-H biarylation. (B) Application.

[a]For detailed reagents and conditions, see the Supporting Information.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data (^{1}H and ^{13}C NMR, MS) for all new compounds as well as optimization tables. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Author Contributions

§H.O. and L.Y. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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