Proposed Methods for the Synthesis of Ribosomally Synthesized and Post-Translationally Modified Peptides Containing C–C Cross-Links

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Background

- **Ribosomally synthesized and post-translationally modified peptides (RiPPs)** are peptide macrocycles that can target and modulate areas of proteins usually deemed "undruggable" (1).

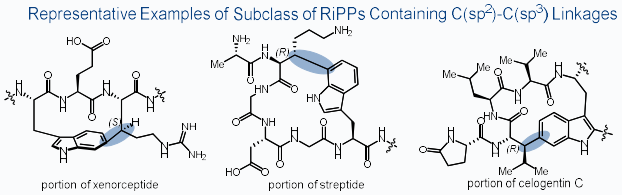


Figure 1: Examples of several RiPPs with useful biological activity.

- Current methods of synthesis focus on **linear, west-to-east methods**, forming an initial C-C cross-link (highlighted in Figure 1) between two amino acid residues before extending the peptide and cyclizing to form a ring (2).
  - Unnecessarily long and complex, tending lower yields and unnecessary manipulation

- Many RiPPS have yet to be successfully totally synthesized due to synthetic challenges like complex multimacrocyclic systems and a lack of functional handles

Aims

- Aim to simplify and optimize the full synthesis of RiPPs through more **convergent methods** while simultaneously exploring a new diastereoselective approach to metallaphotoredox reactions.

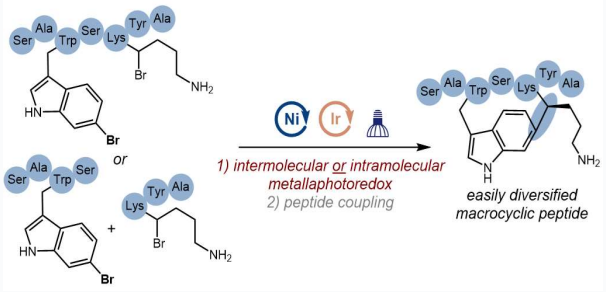


Figure 1. The overall proposed strategy for the convergent synthesis of the subclass of RiPPs containing C(sp2)-C(sp3) linkages.

- Optimize the synthesis of C(sp2)-C(sp3) crosslinks between a scope of various alkyl and aryl bromides containing amino acid derivatives.

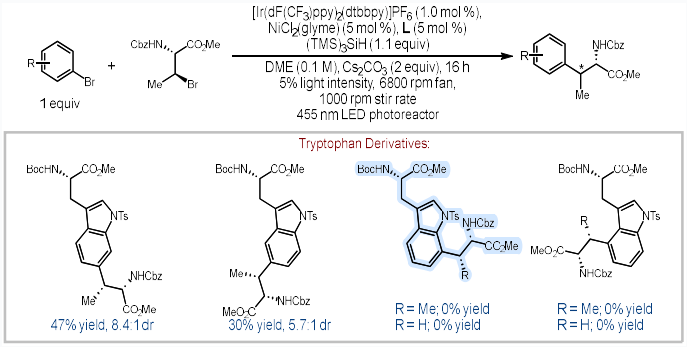
Applications

- An efficient, convergent synthesis of RiPPs will make these desirable natural products more **easily accessible** for use in research, advancing drug development.
- This research into the diastereoselective methods of metallaphotoredox reactions is the first of its kind, helping to advance the field and deepen understanding of how to better control these useful reactions.

Methodology

Scheme 1

- The proposed **diastereoselective metallaphotoredox reaction** shown in Scheme 1 has successfully been carried out in the Blakey Lab, forming crosslinks at high yields using aryl bromides containing Phenylalanine and Tyrosine derivatives.

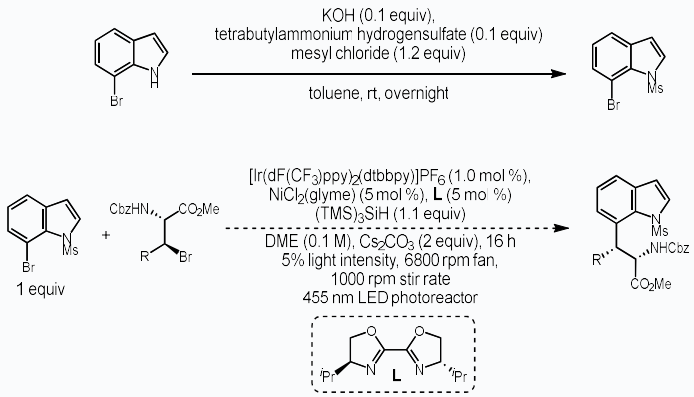


Scheme 1: The optimized conditions of the proposed diastereoselective metallaphotoredox cross-electrophile coupling reaction and the yield retained when this reaction was performed on several aryl bromide reagents containing Tryptophan derivatives.

- Low yield retained from the synthesis of the highlighted derivative in Scheme 1, likely due to the steric interaction caused by the bulky **tosyl** group.

Scheme 2

- Minimize the steric interactions by protecting the amine of the indole with a **mesyl** group.



Scheme 2: A proposed scheme to test the effect of a change in the protecting group on the yield of the tryptophan derivative of interest when synthesized using the reaction outlined in Scheme 1.

References

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2. David Laws III, Eleda V. Plouch, and Simon B. Blakey *Journal of Natural Products* **2022** *85* (10), 2519-2539 DOI: 10.1021/acs.jnatprod.2c00508

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