γ/α-Foldamers: Helical Constructs for asymmetric Catalysis

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1. Introduction

- Foldamers are designed peptides in which α-amino acids alternate with unnatural cyclic γ-amino acids residues. In solution, these backbones adopt defined helical architectures stabilized by noncovalent interactions.[1]
- Helical foldamers enable asymmetric catalysis by creating well-defined three-dimensional chiral environments that promote selective substrate recognition and enantioinduction.[2]
- Compared to small-molecule catalysts, the well-defined and repetitive structures of hybrid γ/α-peptide backbone offer superior modularity for the incorporation of functional groups.[3]

Aims and objectives

- To optimize the synthesis of γ-cyclic amino acid monomers.
- To synthesize the γ/α helix with potential catalytic property.
- To explore the application of a new and stable peptide helix.

Related techniques

- XRD (X-Ray Diffraction): characterization of foldamer crystals.
- NMR (NOESY, ROESY): validation of folding behavior.
- Chiral HPLC: *ee* test for asymmetric synthesis.
- CD (Circular dichroism), SPPS (Solid-phase peptide synthesis), etc.

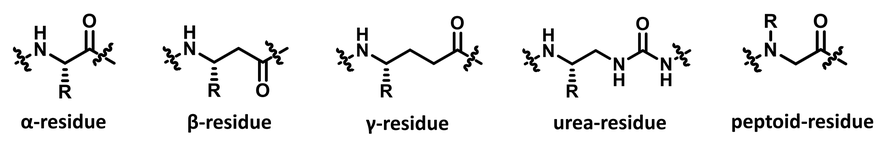
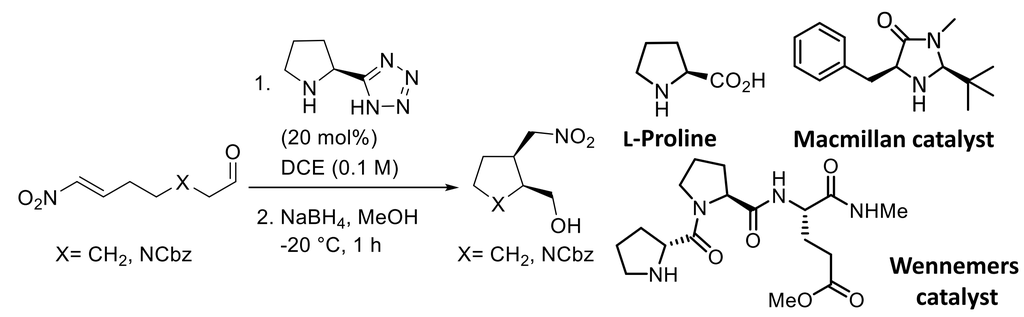


Figure 1 Selected natural and non-natural subunits found in foldamer backbones. R = generic side-chain group.[1]



Scheme 1 Asymmetric synthesis of γ-cyclic amino acid precursors.[2]

Figure 2 small-molecule catalysts.

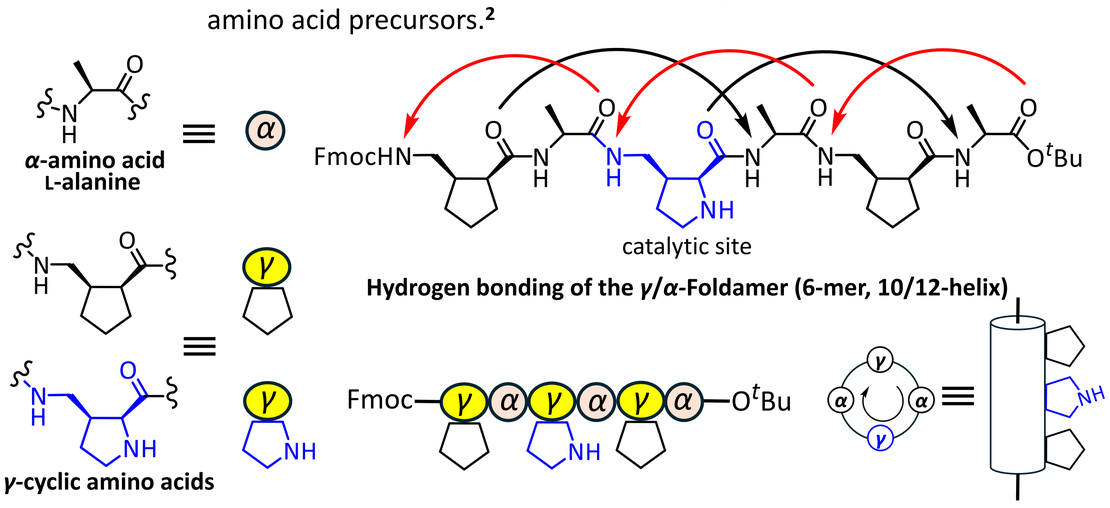
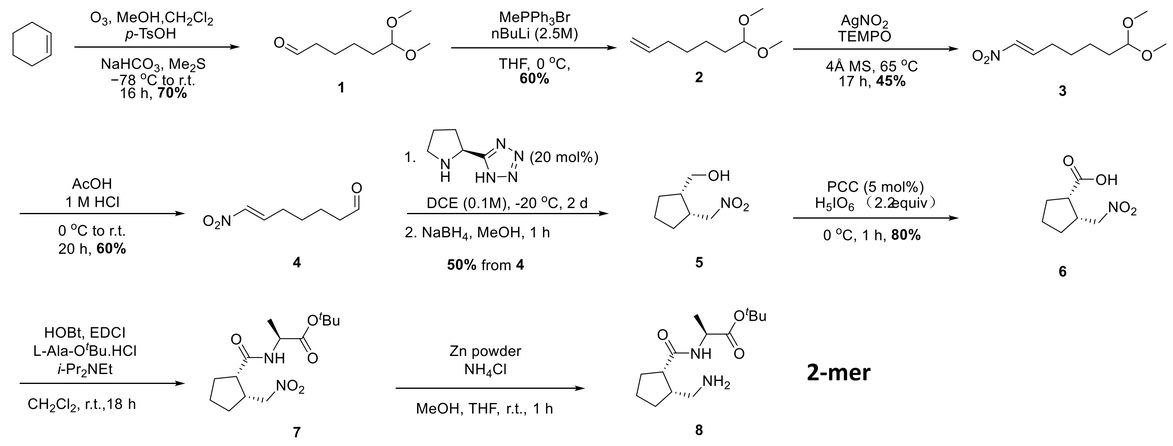
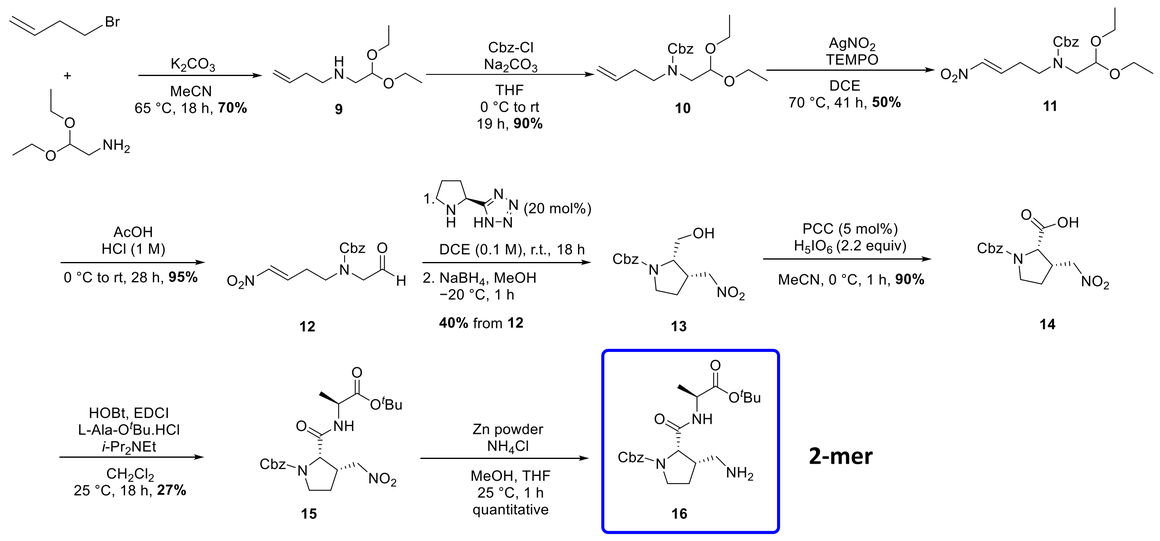


Figure 3 α- and γ-cyclic amino acid monomers and molecular design.

2. Synthesis of γ-cyclic amino acids

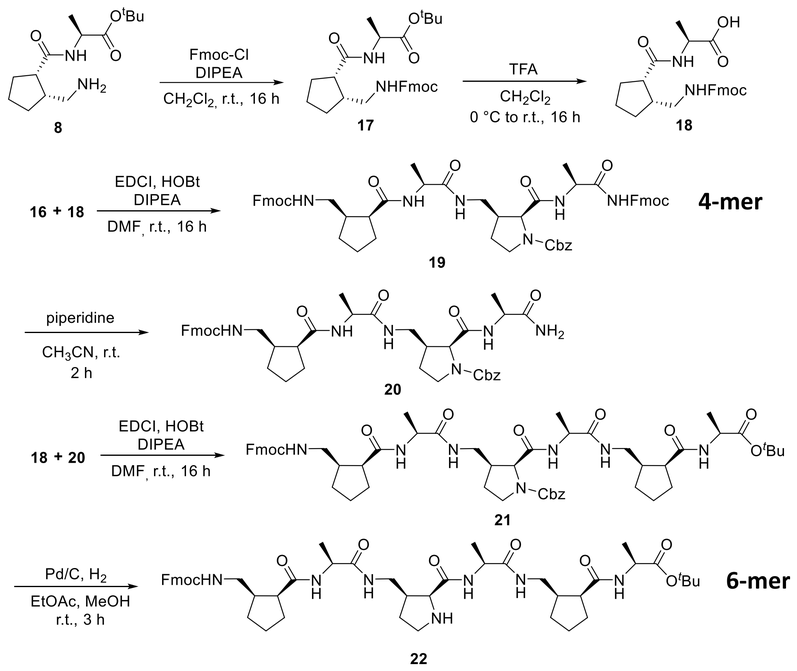


Scheme 2 The Synthesis of cyclopentane-based nitro olefin.



Scheme 3 The Synthesis of Cbz-protected pyrrolidine-based nitro olefin.

3. Amide coupling



Scheme 4 Peptide synthesis employing an orthogonal protecting group strategy.

- Single crystals of the foldamer will be grown and its structure elucidated by X-ray diffraction (XRD).
- The structural insights will enable a preliminary evaluation of the monofunctional model's catalytic potential and guide the future design of bifunctional systems.

4. Results

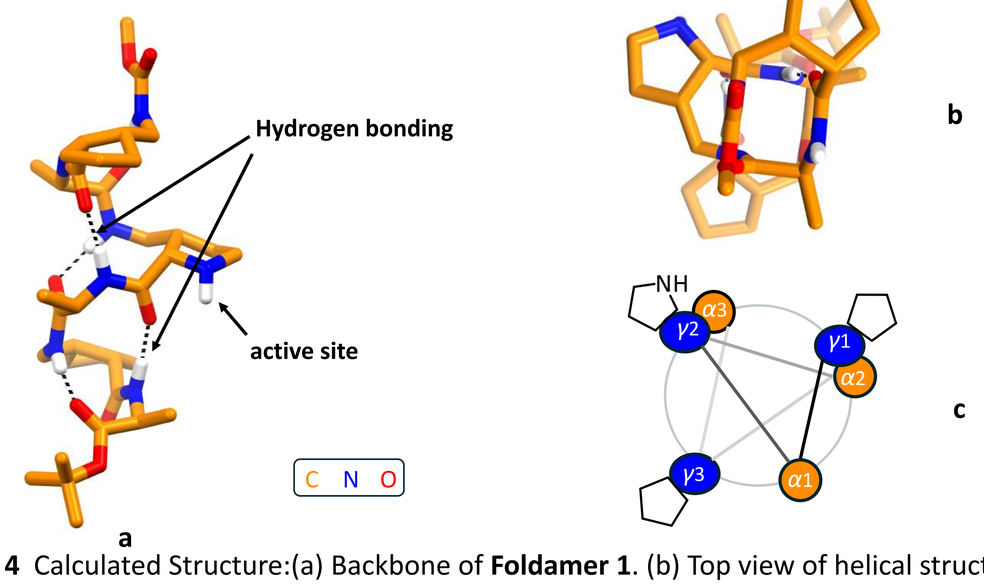


Fig 4 Calculated Structure:(a) Backbone of **Foldamer 1**. (b) Top view of helical structure (c) The corresponding wheel diagram of simplicity.

5. Future work

- Obtain single crystals of the foldamer and elucidate its solid-state structure by X-ray diffraction (XRD).
- Use the resolved structure to guide the design of suitable substrates and reaction types, enabling evaluation of the foldamer's catalytic activity.

6. Reference

1. Girvin, Z. C. & Gellman, S. H. Foldamer Catalysis. *J. Am. Chem. Soc.* **142**, 17211–17223 (2020).

2. Girvin, Z. C., Andrews, M. K., Liu, X. & Gellman, S. H. Foldamer-templated catalysis of macrocycle formation. Science 366, 1528–1531 (2019).

3. Fanelli, R. *et al.* Organocatalytic Access to a *cis* -Cyclopentyl-γ-amino Acid: An Intriguing Model of Selectivity and Formation of a Stable 10/12-Helix from the Corresponding γ/α-Peptide. *J. Am. Chem. Soc.* **142**, 1382–1393 (2020).

4. Lin, Q. et al. Crystal Structure and NMR of an α,δ-Peptide Foldamer Helix Shows Side-Chains are Well Placed for Bifunctional Catalysis: Application as a Minimalist Aldolase Mimic**. Angew. Chem. 135, e202305326 (2023).