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A reductive amination approach for the synthesis of catalytic peptide foldamers

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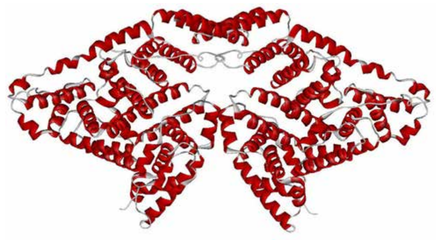
I look a lot like...

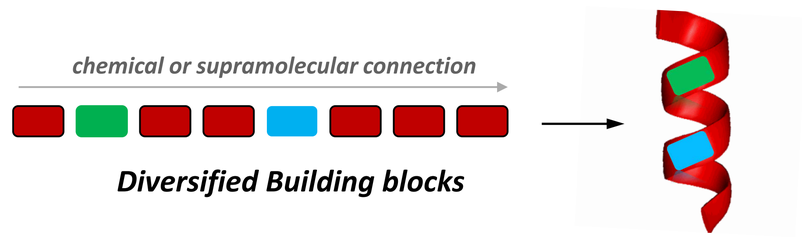
Intro

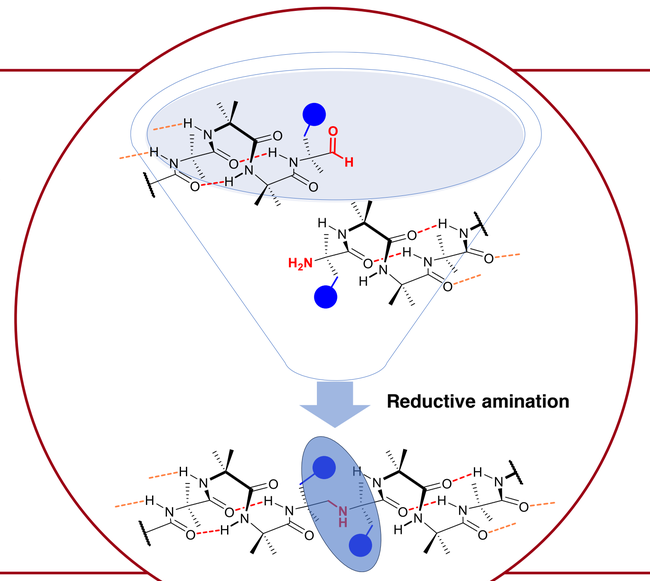
Enzymatic catalysis often depends on the proper spatial organization of two or more reactive groups within an active site.

Foldamers are synthetic, conformationally defined mimics of proteins and other biopolymers. The exploration of new moieties and new geometries for sets of reactive side chains is enabled by the modular nature of foldamers at the covalent level.

We report a reductive amination approach as a general synthetic strategy for the assembly of helical catalytic peptide foldamers.

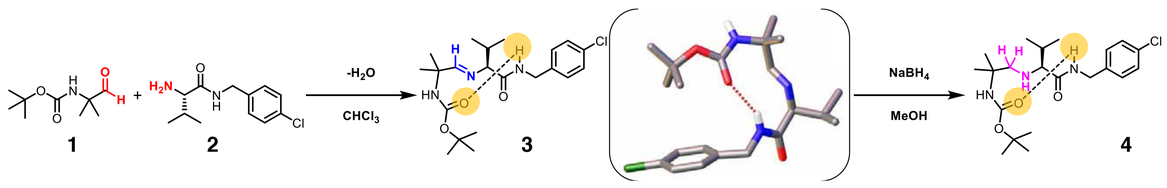






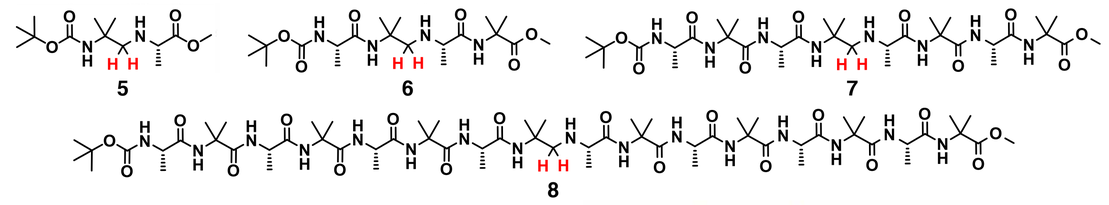
Secondary amine backbone modification

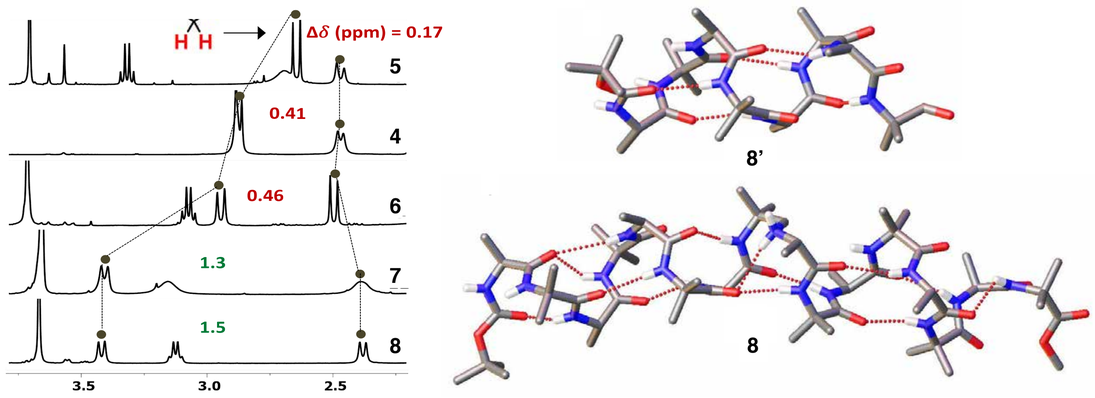
As a preliminary step, we explored the reductive amination reaction and conformational effects of the $\Psi[CH_2NH]$ backbone modification in a model compound.



- first crystallographic characterization of an imino surrogate for a peptide bond between two amino acids;
- β-turn conformation stabilized by an intramolecular N-H···O=C hydrogen bond;
- reduction of the imino group allows the formation of the $\Psi[CH_2NH]$ moiety.

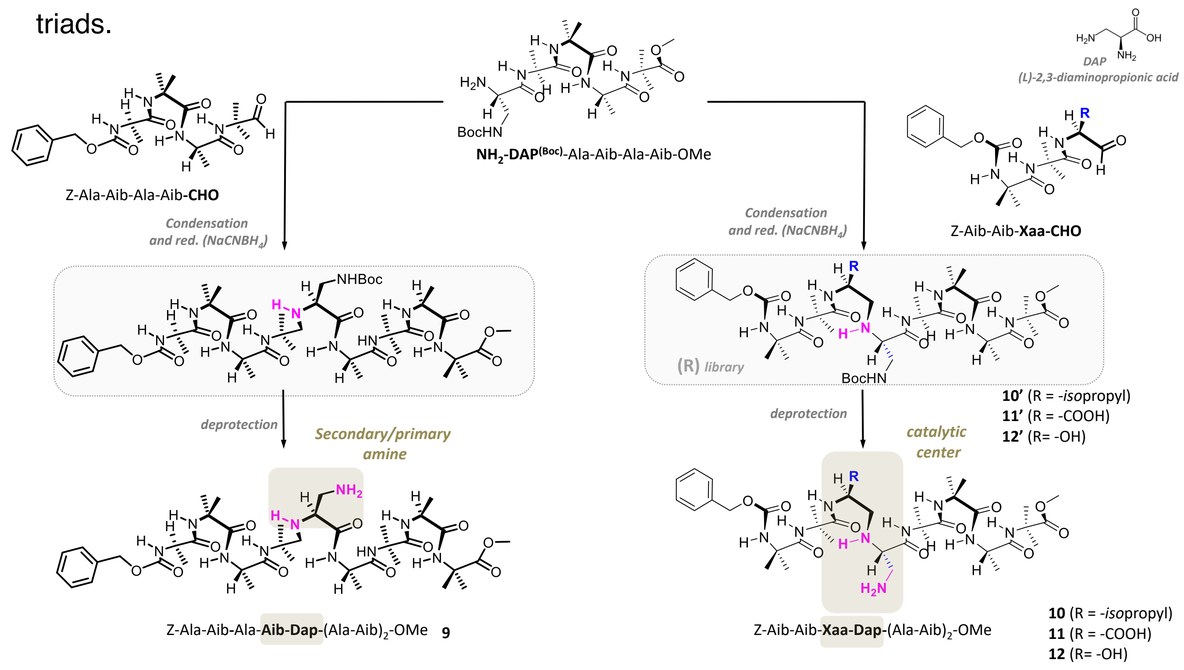
To explore the effect of the introduction of the secondary amine backbone modification in structured peptides, surrogate foldamers Boc-(L-Ala-Aib)$_n\Psi[CH_2NH]$-(L-Ala-Aib)$_n$-OMe were synthesized.



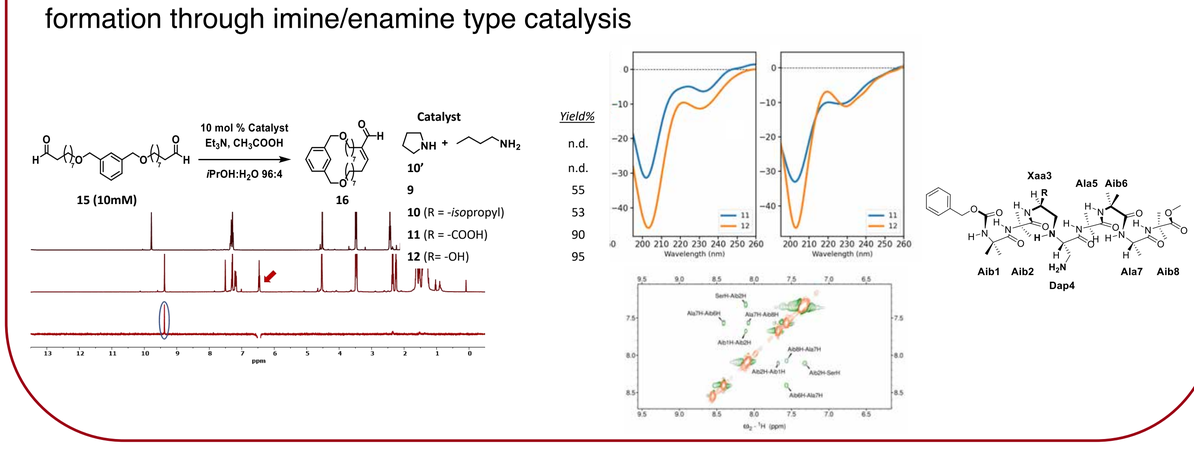


Helical foldamers with tri-dimensional catalytic centres

A set of helical peptide foldamers was synthesized with different reactive side chains in proximity of the newly-formed secondary amine for the creation of catalytic diads and triads.



We tested the catalytic performance of these foldamers to efficiently template C-C bond formation through imine/enamine type catalysis

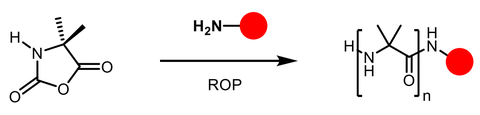


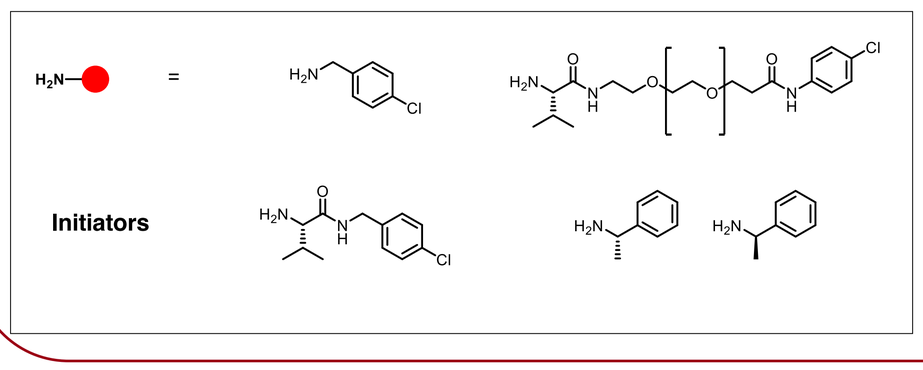
Synthesis and screening of screw-sense preferences of helical foldamers

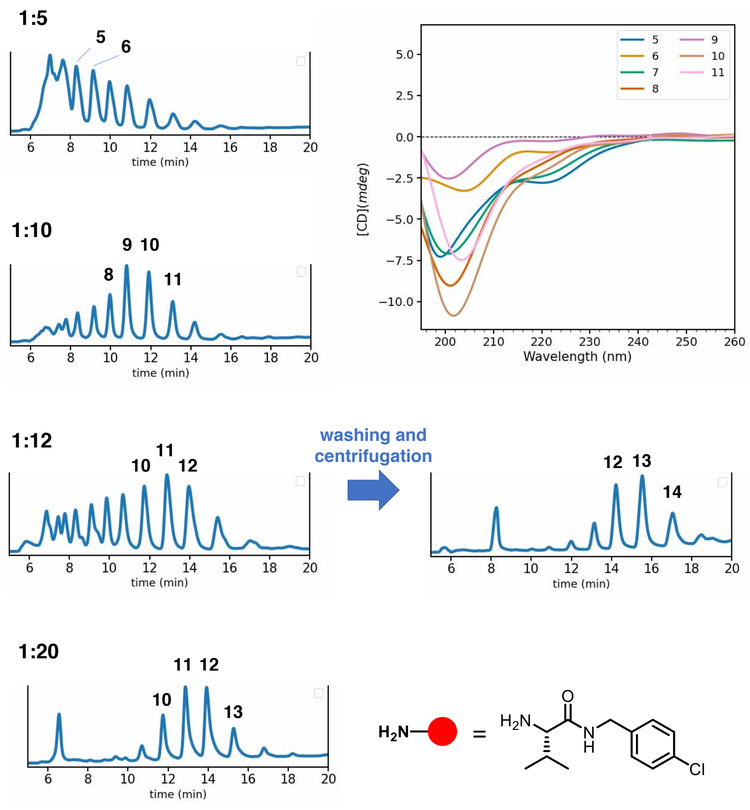
We applied the reductive amination approach for the functionalization of the N-termini of Aib oligomers synthesized by ROP of his NCA.

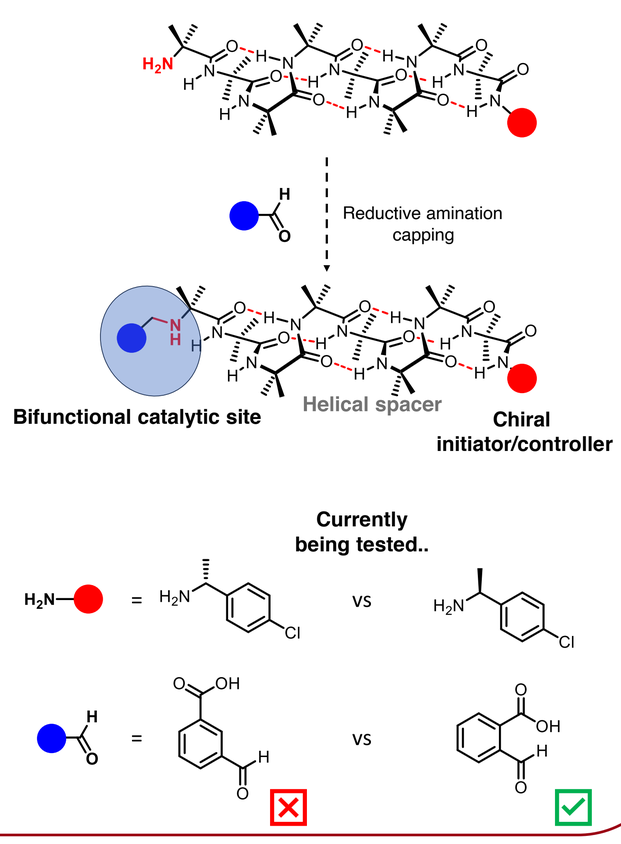
Firstly, we studied polymerization conditions and chromatographic methods.

Now, we are trying to develop catalysts for stereoselective enamine catalysis, where the N-terminal reactive site could be influenced by chiral residues located at the C terminus.









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