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Maastricht University

Diastereoselective Ugi Reactions via Biocatalytic Desymmetrization: A Modular Route to Collagen Mimetic peptides

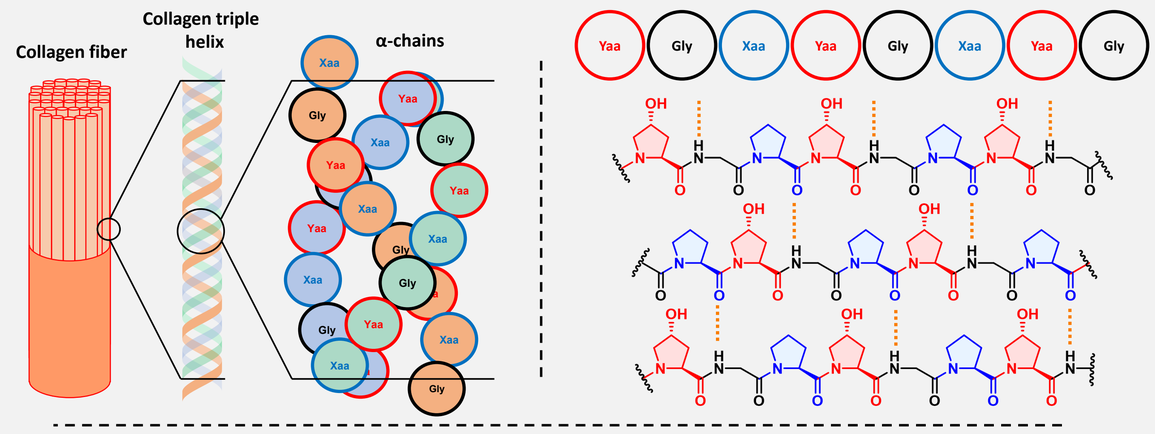
Felix M.J. Boerman[1], Jannes Wagemakers[1], Alessia Bubula[1], Daniele Castagnolo[2], Romano V.A. Orrù[1], Jordy M. Saya*[1]

[1]*Biobased Organic Chemistry, Aachen-Maastricht Institute for Biobased Materials, Maastricht University, Urmonderbaan 22, 6167RD Geleen, The Netherlands*

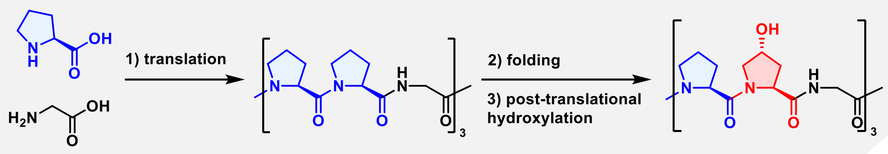
[2]*University College London, Gower St, London WC1E 6BT, United Kingdom.*

A Synthetic Approach to Collagen

Collagen's unique triple-helix structure makes it highly valuable for medical and material applications. However, relying on animal-derived sources introduces disease risks and inconsistent yields. Synthesizing collagen is difficult, but our research offers a novel solution. By combining biocatalytic desymmetrization with diastereoselective Ugi reactions, we efficiently construct collagen's core tripeptide units. Using solid-phase synthesis, we assemble these into collagen-mimetic peptides (CMPs) that accurately replicate natural structural features. This stereo-controlled, modular approach enables detailed studies of triple-helix folding and thermal stability, laying the essential groundwork for scalable, fully synthetic collagen.



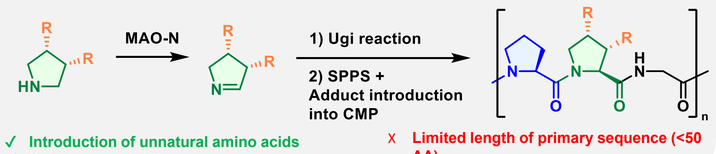
A) Recombinant synthesis of collagens



✓ Primary sequence 1000 amino acids
✓ Folding during translation

X Only natural amino acids
X Difficult Post-translational hydroxylation
X Expensive and difficult to scale up

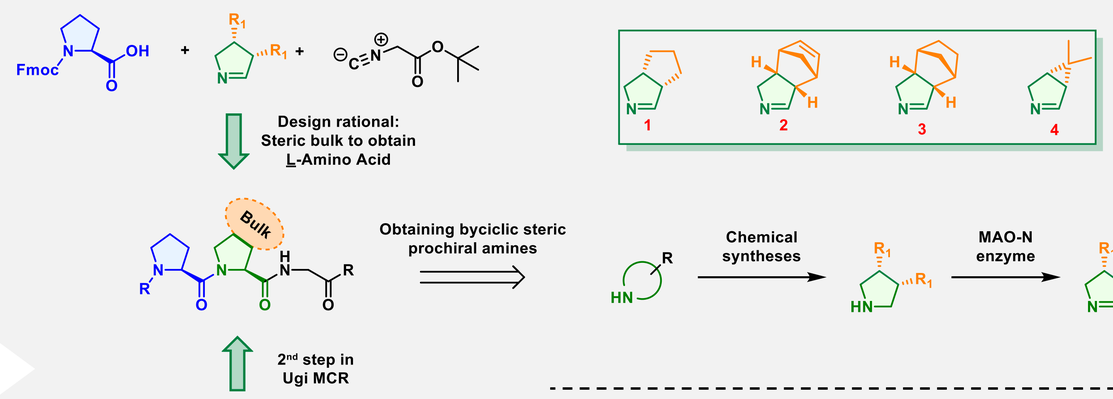
B) Diastereoselective Ugi reactions to synthesize proline-rich peptides



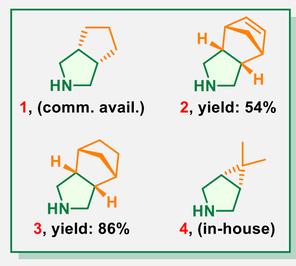
✓ Introduction of unnatural amino acids
✓ Spontaneous folding
✓ Foundation for scalable synthetic collagen
✓ Introducing tripeptide via single step

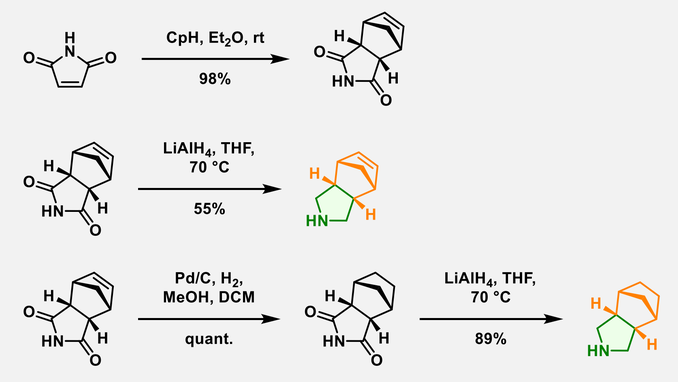
X Limited length of primary sequence (<50 AA)

Design & Synthesis of Prochiral Amines

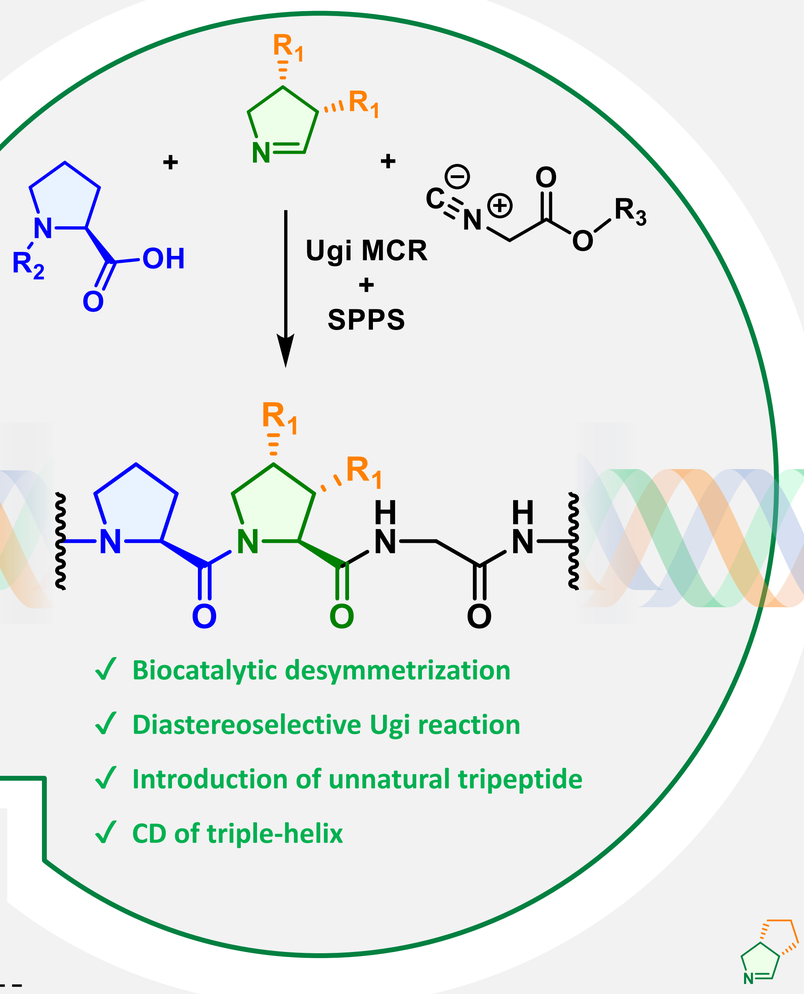


Prochiral Cyclic Amine syntheses



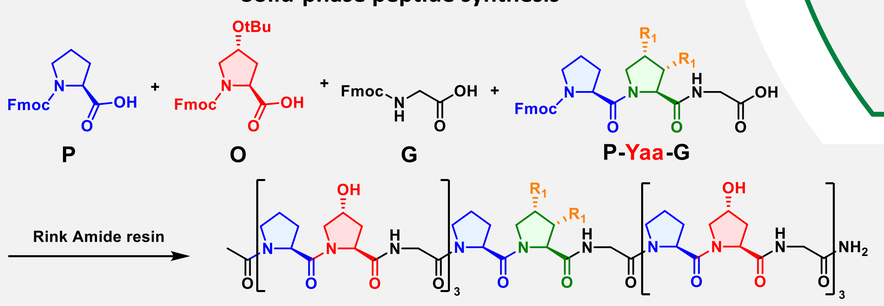


[1] CpH = Cyclopentadiene, THF = Tetrahydrofuran, DCM = Dichloromethane



CD Analysis Protocol: Assessing Triple Helix Stability

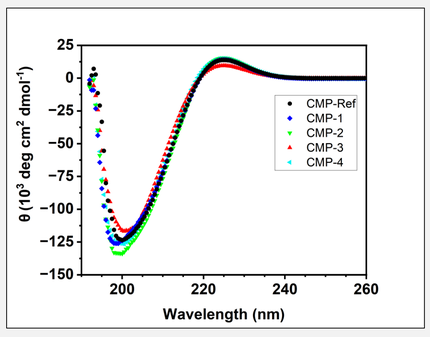
Solid-phase peptide synthesis



Circular Dichroism Analyses Results

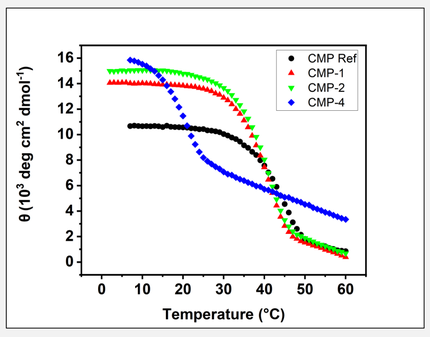
Waves scan:

Determining **secondary structure** and **folding quality** of CMPs in solution (200 µM in phosphate-buffered saline (PBS), pH 7.4)



Thermal denaturation study:

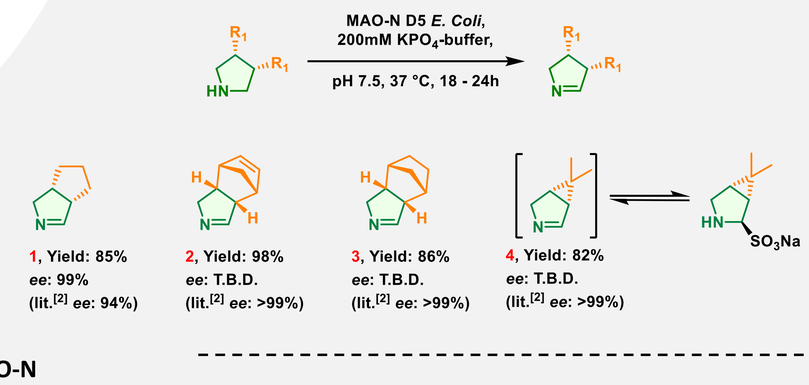
Determining when 50% of triple-helix's have **denatured** and **temperature stability** of CMPs in solution (200 µM in phosphate-buffered saline (PBS), pH 7.4).



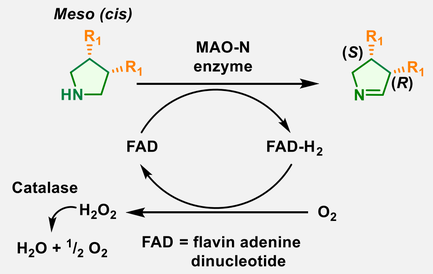
Entry	Imine	CMP	T_m (°C)	ΔT_m (°C)
Ref.	-	Ac-(POG)$_7$-NH$_2$	42.6	-
1		Ac-(POG)$_3$-P-1-G-(POG)$_3$-NH$_2$	39.3	- 3.3
2		Ac-(POG)$_3$-P-2-G-(POG)$_3$-NH$_2$	39.1	-3.5
3		Ac-(POG)$_3$-P-3-G-(POG)$_3$-NH$_2$	T.B.D.	-
4		Ac-(POG)$_3$-P-4-G-(POG)$_3$-NH$_2$	18.5	-24.1

Generating optically pure chiral imines as Ugi partners

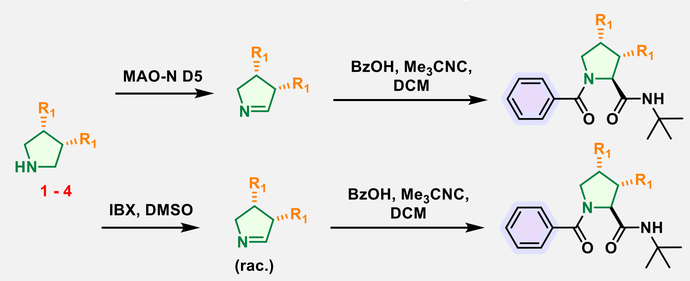
Biocatalytic Desymmetrization using MAO-N



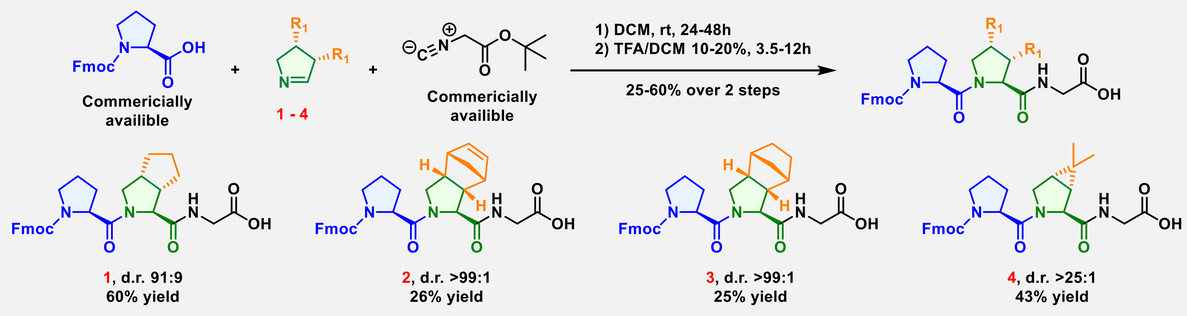
Biocatalytic Cycle of MAO-N



Derivatization for Enantioselectivity Determination



Diastereoselective Ugi MCR and Deprotection



Correspondence to:
Felix Boerman, Organic Chemistry

felix.boerman@maastrichtuniversity.nl T +31642570282

Biobased Organic Chemistry
biobasedorgchem.com

Maastricht University

Urmonderbaan 22, 6167RD,
Geleen, The Netherlands

[1] De Graaff, C., Bensch, L., Van Lint, M. J., Ruijter, E. and Orru. R. V. A. Org. Biomol. Chem., 2015, 13, 10108–10112 [2] Znabet, A., Raftery, J., Helliwell, M. and Turner, N. Angew. Chem. Int. Ed. 2010, 49, 2182 –2184. [3] Chen, W., Ma, L., Paul, A., D. Seidel. Nature Chem, 2018, 10, 165–169. [4] Liu, L., Wang, F., Tian, F., Peng, l., and Wang. L. Org. Process Res. Dev. 2016, 20, 320–324. [5] Fiala, T., Barros, E. P., Ebert, M. O., Ruijsenaars, E., Riniker, S. and Wennemers, H. J. Am. Chem. Soc. 2022, 144, 18642–18649.