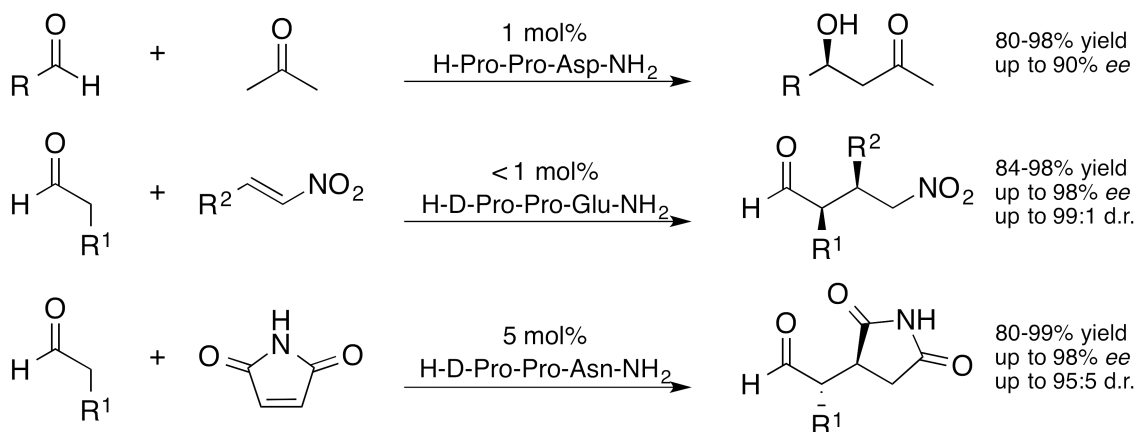


Conformational Investigation of Catalytically Active Peptides of the H-Pro-Pro-Xaa Type

T. Schnitzer¹, H. Wennemers^{1*}

¹ETH Zurich, Laboratory of Organic Chemistry, Zurich

Peptides of the type H-Pro-Pro-Xaa (Xaa = any amino acid) are highly reactive and stereoselective catalysts for organocatalytic C-C bond formations, such as aldol reactions (H-Pro-Pro-Asp-NH₂)^[1] as well as conjugate addition reactions of aldehydes to nitroolefins (H-D-Pro-Pro-Glu-NH₂)^[2] and unprotected maleimide (H-D-Pro-Pro-Asn-NH₂)^[3]. The peptide catalysts are so reactive that loadings of less than 1 mol% suffice to obtain the products in high yields, enantio- and diastereoselectivities and the peptides can be immobilized and used in flow chemistry.^[4] Mechanistic studies using ESI-MS, React-IR and NMR spectroscopy allowed to elucidate crucial intermediates and potential resting states as well as the role of the intramolecular carboxylic acid.^[5]



Recently, our interests focused on the structural features of H-Pro-Pro-Xaa type peptides and their consequences for reactivity and stereoselectivity of the catalyst.^[6] Towards this goal, we have investigated the conformational features of these peptides using NMR experiments. The obtained data allowed for an even deeper understanding of the reaction mechanism and guided us also to new peptide structures with superior reactivity and stereoselectivity.

[1] P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, 7, 6, 1101.

[2] a) M. Wiesner, M. Neuburger, H. Wennemers, *Chem. Eur. J.* **2009**, 15, 10103. b) J. Duschmalé, H. Wennemers, *Chem. Eur. J.* **2012**, 18, 1111. c) R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed.*, **2013**, 52, 7228.

[3] C. Grünenfelder, J. Kisunzu, H. Wennemers, *Angew. Chem. Int. Ed.* **2016**, 55, 8571.

[4] Y. Arakawa, H. Wennemers, *ChemSusChem*, **2013**, 6, 242.

[5] a) F. Bächle, J. Duschmale, C. Ebner, A. Pfalz, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, 25, 4511. b) J. Duschmalé, J. Wiest, M. Wiesner, H. Wennemers, *Chem. Sci.* **2013**, 4, 1312.

[6] a) C. E. Grünenfelder, J. K. Kisunzu, N. Trapp, R. Kastl, H. Wennemers, *Peptide Science* **2017**, asap. b) T. Schnitzer, M. Wiesner, H. Wennemers, *Org. Biomol. Chem.* **2017**, manuscript accepted.