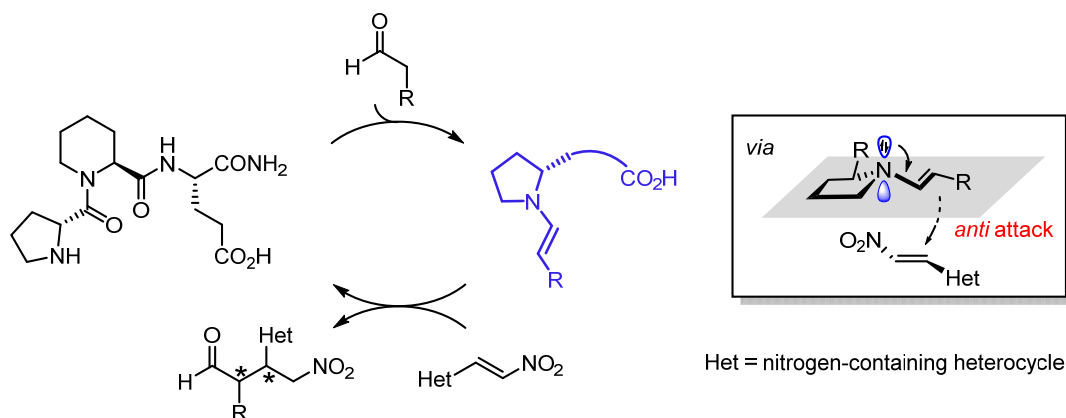


CONTROL OVER ENAMINE PYRAMIDALIZATION GIVES ACCESS TO N-HETEROCYCLIC SUBSTITUTED γ -NITROALDEHYDES

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Tripeptides of the type H-Pro-Pro-Xaa are highly reactive and stereoselective catalysts for C–C bond forming reactions such as aldol and conjugate addition reactions to maleimides, dicyanoolefins and nitroolefins.[1] For example, the reactivity of the catalyst H-Pro-DPip-DGlu-NH₂ is so high that 0.05 mol% of the peptide suffices to catalyze conjugate addition reactions of aldehydes to β -nitroolefins in excellent enantio- and diastereoselectivity.[2] Mechanistic studies revealed that the enamine intermediate is involved in the rate- and enantioselectivity determining step.[3] Herein, we show that the pyramidalization of the enamine-nitrogen[4] has a significant influence on the performance of the catalyst and how the system can be improved by defining the enamine conformation.[4] These insights led to the development of catalysts that allowed us to perform conjugate addition reactions with challenging substrates such as nitroolefins bearing nitrogen-containing heterocycles. The desired γ -nitroaldehydes were obtained with ≤ 1 mol% of catalyst loading in high yields and stereoselectivities.[5] This study provides general guidelines for the optimization of chiral 2° amines that catalyze reactions via an enamine-based mechanism.



[1] for examples, see: a) Krattiger, P.; Kovásy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, 7, 1101; b) Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem. Int. Ed.* **2008**, 47, 1871. c) Grünenfelder, C. E.; Kisunzu, J. K.; Wennemers, H. *Angew. Chem. Int. Ed.* **2016**, 55, 8571; d) Schnitzer, T.; Wennemers, H. *Synlett* **2017**, 28, 1282.

[2] Schnitzer, T.; Wennemers, H. *J. Am. Chem. Soc.* **2017**, 139, 15356.

[3] Bächle, F.; Duschmalé, J.; Ebner, C.; Pfaltz, A.; Wennemers, H. *Angew. Chem. Int. Ed.* **2013**, 52, 12619.

[4] Schnitzer, T.; Möhler, J. S. Wennemers, H. *submitted*.

[5] Möhler,* J. S.; Schnitzer,* T.; Budinska, A.; Wennemers, H. *manuscript in preparation*.