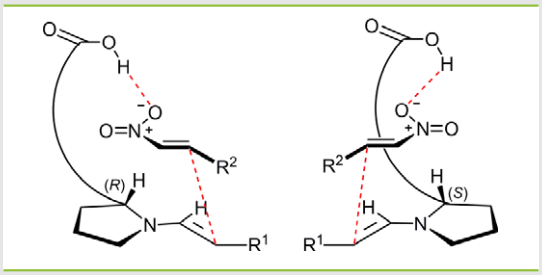
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2009/01

SYNSTORIES



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Thieme Chemistry

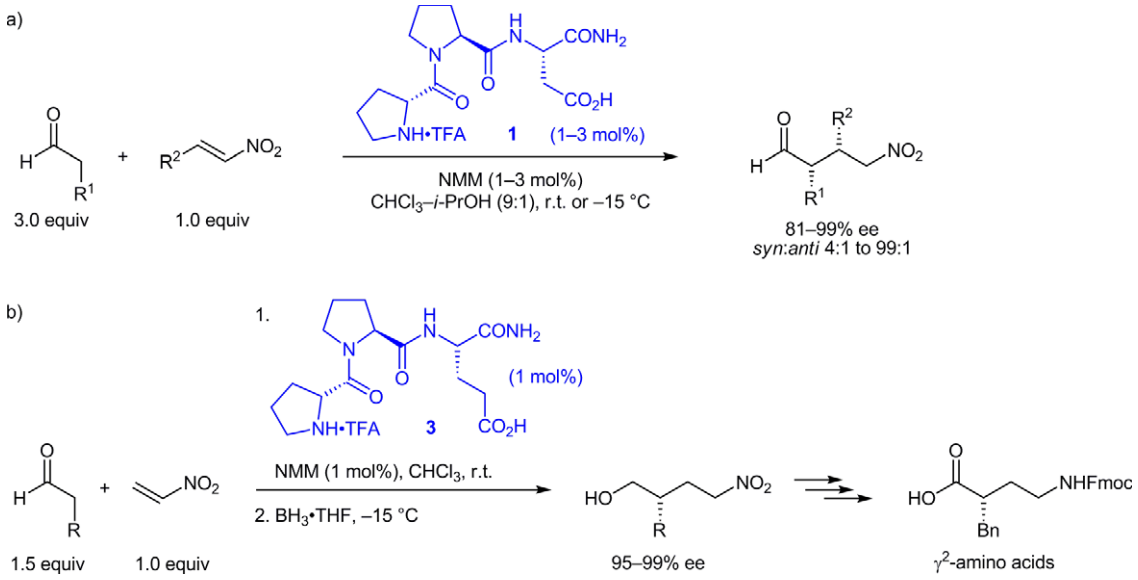
Peptides as Asymmetric Catalysts

Selected Presentation from the 2nd EuCheMS Chemistry Congress, Turin (Italy), *September 16–20*, **2008**

The conjugate addition reaction of aldehydes to nitroolefins has been a focus of research in recent years since it provides γ-nitroaldehydes as versatile building blocks to a plethora of other compound classes. The use of organocatalysts represents an efficient and straightforward route to perform this important process. Among the different types of organocatalysts, peptides are an attractive yet scarcely explored tool. "'It is impossible that short-chain peptides can function as catalysts' was typically heard in the last century from scientists reflecting on the possibility of applying peptides as catalysts," said Professor Helma Wennemers from the Department of Chemistry, University of Basel (Switzerland). This is not surprising since the flexibility of short-chain peptides is typically high. Thus, predicting the conformation of a peptide, and even more so its catalytic activity, is a significant challenge. Recent results from the group of Professor Wennemers, communicated at the EuCheMS congress, demonstrated that tripeptides such as H-Pro-Pro-Asp-NH_2 (**1**), H-D-Pro-Pro-Asp-NH_2 (**2**) and H-D-Pro-Pro-Glu-NH_2 (**3**) are highly effective asymmetric catalysts for aldol reactions and conjugate addition reactions of aldehydes to nitroolefins, respectively. Key to the discovery of the initial lead peptide H-Pro-Pro-Asp-NH_2 (**1**) was the use of the smart combinatorial screening technique "catalyst substrate co-immobilization" (see: *Angew. Chem. Int. Ed.* **2003**, *42*, 1722). Only small amounts of the peptide (1 mol%) are necessary to catalyze aldol reactions with good to excellent yields and stereoselectivities (see: *Org. Lett.* **2005**, *7*, 1101; *Adv. Synth. Catal.* **2008**, *350*, 1046; *Tetrahedron* **2007**, *63*, 8420; *Biopolymers (Pept. Sci.)* **2006**, *84*, 105). Conformational analysis studies then led to the development of H-D-Pro-Pro-Asp-NH_2 (**2**) as an excellent asymmetric catalyst for conjugate addition reactions of aldehydes to nitroolefins.

"The peptidic catalyst H-D-Pro-Pro-Asp-NH_2 (**2**) provided solutions to challenges encountered in this reaction," explained Professor Wennemers (see: *Angew. Chem. Int. Ed.* **2008**, *47*, 1871; *J. Am. Chem. Soc.* **2008**, *130*, 5610). "First of all, catalyst loadings of as low as 1 mol% suffice for effective catalysis. Secondly, only a small excess of the aldehyde (1.5–3.0 equiv) is necessary for effective catalysis. And last but not least, a broad substrate scope including functionalized aldehydes, aliphatic nitroolefins and nitroethylene is tolerated, and products are obtained in excellent yields and stereoselectivities."

Even the simplest of all nitroolefins, nitroethylene, known for its high tendency to polymerize, reacts readily with aldehydes in the presence of the peptidic catalysts. This reaction provides monosubstituted γ-nitroaldehydes that can be readily converted into the corresponding γ-amino acids. "γ-Amino acids are useful building blocks for the development of medi-



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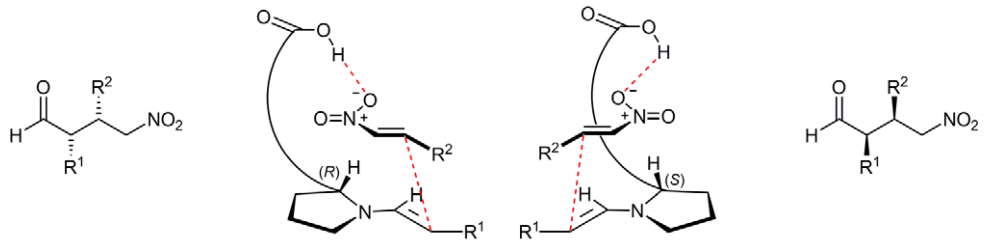

cinally relevant compounds and in foldamer research and have previously only been accessible using chiral auxiliaries," said Professor Wennemers. "Since a wide range of aldehydes react with nitroethylene, many different monosubstituted γ-amino acids are available using this protocol."

In a comment to this work, Professor Karl Gademann from the EPF Lausanne (Switzerland), who prepared monosubstituted γ-amino acids during his PhD thesis with Professor Dieter Seebach, said: "When I think about how much hard work went into the synthesis of these γ-amino acids, the peptidic catalyst provides a very elegant solution to facilitate their synthesis."

Organocatalysis is a highly competitive research field. The group of Professor Samuel Gellman (University of Madison, Wisconsin, USA) also worked on the idea of using conjugate addition reactions of aldehydes to nitroethylene to access monosubstituted γ-amino acids efficiently. The Gellman group took advantage of a prolinol derivative in combination with stoichiometric amounts of an acid cocatalyst to achieve this goal. "After the initial mutual shock when we found out about our common research interests, Sam and I were pleased that our research was published back to back," said Professor Wennemers (see: *J. Am. Chem. Soc.* **2008**, *130*, 5608 and *J. Am. Chem. Soc.* **2008**, *130*, 5610).

The peptidic catalysts are easy to use since no additives such as additional acids are necessary. "For practical reasons we typically use the TFA salts of the catalysts and add the equivalent amount of N-methylmorpholine to liberate the secondary amine," said Professor Wennemers. "However, the desalted peptide (the 'inner salt') has the same catalytic efficiency in the conjugate addition reactions. Another advantage of short-chain peptidic catalysts is their facile synthesis. A tripeptide can be prepared on a multigram scale within one day!"

An additional benefit of the peptidic catalysts is the facile tunability of their stereoselectivities; for example, the diastereomeric catalysts H-Pro-Pro-Asp-NH_2 (**1**) and H-D-Pro-Pro-Asp-NH_2 (**2**) exhibit opposite enantioselectivities. "Based on molecular modeling studies, this can be attributed to the fact that both peptides adopt turn-like conformations that are very similar apart from their N-terminal proline residues which point in opposite directions with respect to the turn," said Professor Wennemers. "Further conformational analyses suggest that the conformation of the peptides is not entirely rigid but allows for conformational freedom. It is intriguing to speculate that the 'right degree of flexibility' is the key to the effectiveness of the peptides as asymmetric catalysts."

Matteo Zanda

About the authors

Helma Wennemers studied chemistry at the Johann Wolfgang Goethe Universität in Frankfurt (Germany) and obtained her Ph.D. from Columbia University (New York, USA) under the direction of Professor W. Clark Still in 1996. Following postdoctoral studies at Nagoya University (Japan) with Professor Hisashi Yamamoto, she moved to the University of Basel where she is currently Associate Professor of organic chemistry. She was awarded Kekulé and Liebig fellowships from the "Fonds der Chemischen Industrie" and the Hammet Award for excellence in research from Columbia University. In 2004 she was the Goering Visiting Professor at the University of Wisconsin at Madison and she currently holds the Bachem endowed professorship at the University of Basel. Her research focuses on utilizing the large structural and functional diversity of peptides for the development of asymmetric catalysts and selective molecular receptors that find applications as building blocks of supramolecular assemblies.

Markus Wiesner studied chemistry at the University of Basel and is currently a Ph.D. student in the group of Professor Helma Wennemers. His research focuses on the development of peptides as asymmetric catalysts.

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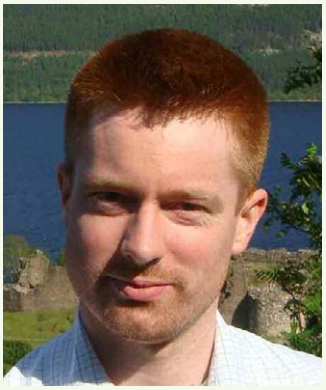
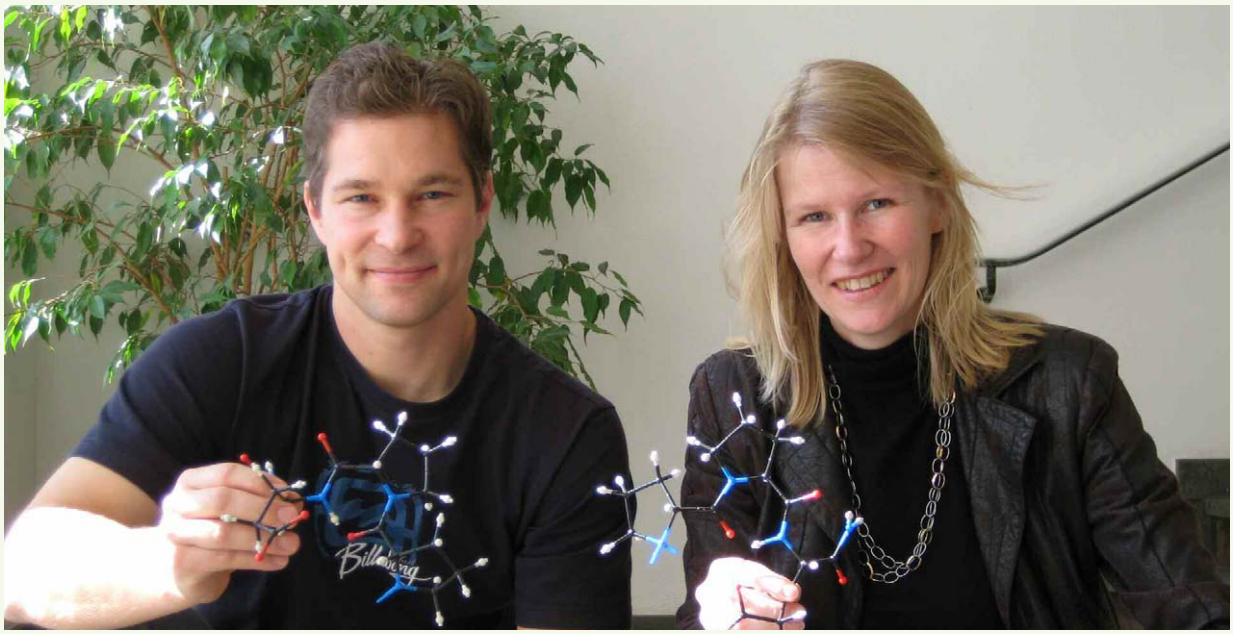
Jefferson D. Revell received his Ph.D. in 'Organic and Combinatorial Chemistry' in 2004 from the University of Southampton (UK) under the guidance of Dr. Arasu Ganesan. He then accepted a postdoctoral position investigating the 'Development of Peptides as Efficient Asymmetric Organocatalysts' at the University of Basel under the supervision of Professor Helma Wennemers. He is currently working on the development of peptides as therapeutics at Medimmune Ltd (Cambridge, UK).



Dr. J. D. Revell



From left: M. Wiesner, Prof. H. Wennemers

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