Peptidic Catalysts

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Tripeptides as Efficient Asymmetric Catalysts for 1,4-Addition Reactions of Aldehydes to Nitroolefins–A Rational Approach**

*Markus Wiesner, Jefferson D. Revell, and Helma Wennemers**

Peptides have become increasingly popular as asymmetric catalysts for a range of reactions.[1] Features such as facile synthesis, modularity, and often high selectivity and activity render peptidic catalysts attractive alternatives to metal-based catalysts and other organocatalysts. One of the largest challenges in the development of peptidic catalysts is the prediction and incorporation of desirable catalytic properties into a given peptide. This is already a challenge for small rigid organocatalysts, but even more so for short peptidic catalysts bearing many more degrees of rotational freedom. As a result, combinatorial chemistry has proven to be a valuable tool for the identification of peptidic catalysts.[2] In this study we used insight gained from conformational analysis to guide the development of tripeptides as efficient asymmetric catalysts for conjugate addition reactions of aldehydes to nitroolefins.

Recently, we introduced the peptide H-Pro-Pro-Asp-NH_2 (**1**) as a catalyst for direct asymmetric aldol reactions.[3] Studies of closely related peptides demonstrated that the secondary amine at the N terminus, the carboxylic acid in the side chain of the aspartic acid (Asp) residue, and a well-defined turn conformation are crucial for the high catalytic activity and selectivity of **1**.[4] These findings suggest a mechanism, similar to that proposed by the groups of List and Houk for proline catalysis,[5] involving enamine formation, subsequent reaction with the aldehyde, and proton transfer from the carboxylic acid (Figure 1b). However, in comparison to proline, the distance between the secondary amine and the carboxylic acid within peptide **1** is greater by approximately 3 Å as indicated by molecular modeling studies with MacroModel 8.0 (Figure 1a,c).[3a]

This led us to hypothesize that this extra distance of 3 Å might be spanned by two additional atoms in the structure of the electrophile, allowing catalysis of not only 1,2- but also 1,4-addition reactions. We chose the 1,4-addition reaction of aldehydes to nitroolefins as a test reaction to yield γ-nitroaldehydes as valuable synthetic intermediates.[6–10] Herein we present **1** and closely related peptides as highly effective and general catalysts for asymmetric conjugate addition reactions of aldehydes to nitroolefins. Furthermore, we demonstrate that the stereochemical outcome of the chiral

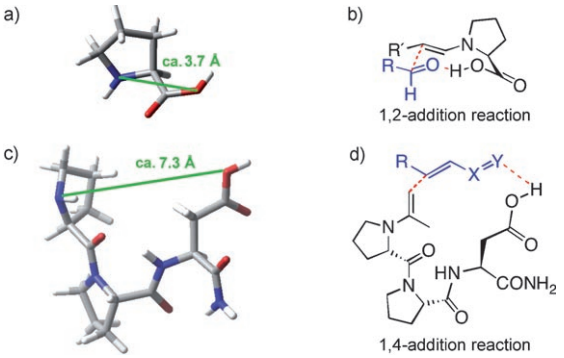
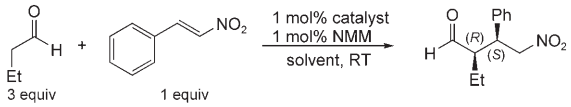


Figure 1. a) Lowest-energy conformation of proline as calculated by MacroModel 8.0. b) Transition state of aldol reactions catalyzed by proline as proposed by the groups of Houk and List.[5] c) Lowest-energy conformation of H-Pro-Pro-Asp-NH_2 (**1**),[3a] as calculated by MacroModel 8.0. d) Schematic of proposed conjugate addition reaction catalyzed by **1**. X and Y represent heteroatoms or carbon atoms.

Table 1: 1,4-addition reactions between *n*-butanal and nitrostyrene catalyzed by peptides **1**-**4**.[a]



H-Pro-Pro-Asp-NH_2 (**1**) H-Pro-D-Pro-Asp-NH_2 (**3**)
H-Pro-Pro-D-Asp-NH_2 (**2**) H-D-Pro-Pro-Asp-NH_2 (**4**)

Entry	Cat.	Solvent	*t* [h]	Conv. [%][b]	*syn*:*anti*[c]	*ee*[d] [%]	Abs. Conf.
1	**1**	EtOH	3	quant	10:1	71	(*R*,*S*)
2	**1**	*i*PrOH	3	quant	10:1	73	(*R*,*S*)
3	**1**	THF	24	≈90	12:1	73	(*R*,*S*)
4	**1**	DMSO	18	quant	6:1	57	(*R*,*S*)
5	**1**	EtOAc	24	>90	9:1	77	(*R*,*S*)
6	**1**	CH_3CN	1	quant	8:1	60	(*R*,*S*)
7	**1**	$CHCl_3$	24	>90	13:1	85	(*R*,*S*)
8	**1**	$CHCl_3$:*i*PrOH 9:1	6	96[e]	10:1	85	(*R*,*S*)
9	**2**	$CHCl_3$:*i*PrOH 9:1	10	84[e]	50:1	81	(*R*,*S*)
10	**3**	$CHCl_3$:*i*PrOH 9:1	20	92[e]	25:1	81	(*R*,*S*)
11	**4**	$CHCl_3$:*i*PrOH 9:1	12	93[e]	25:1	95	(*S*,*R*)
12	Pro[f]	$CHCl_3$:*i*PrOH 9:1	24	85[e]	8:1	39	(*R*,*S*)

[a] Reactions were performed by using the trifluoroacetic acid (TFA) salts of the peptidic catalysts and the equivalent amount of *N*-methylmorpholine (NMM). [b] Conversion estimated by TLC analysis. [c] Determined by ^{1}H NMR spectroscopy of the crude material. [d] Determined by chiral-phase HPLC analysis. [e] Yield of isolated product. [f] 10 mol%.

[*] M. Wiesner, Dr. J. D. Revell, Prof. Dr. H. Wennemers
Department of Chemistry
University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
Fax: (+41) 61-267-0976
E-mail: helma.wennemers@unibas.ch

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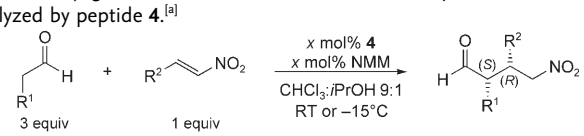
γ-nitroaldehydes can be switched by using diastereomeric peptides.

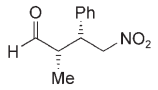
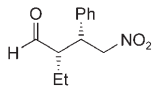
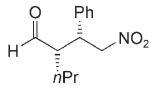
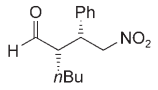
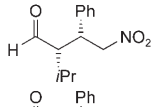
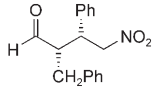
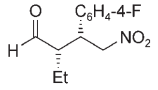
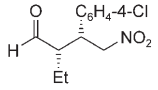
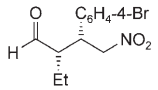
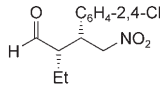
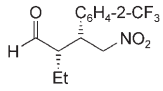
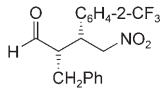
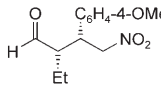
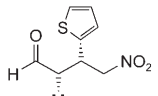
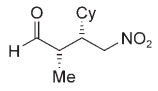
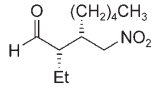
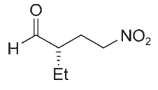
We used the reaction between *n*-butanal and nitrostyrene as a starting point and were delighted to find excellent conversion to the product and good selectivity when using only 1 mol% of H-Pro-Pro-Asp-NH_2 (**1**) in a range of solvents (Table 1). The best results were obtained in a 9:1 mixture of $CHCl_3$ and *i*PrOH (Table 1, entry 8). Still better selectivities were obtained with 1 mol% of the diastereomeric catalyst H-D-Pro-Pro-Asp-NH_2 (**4**), providing the 1,4-addition product in a yield of 93%, a *syn*:*anti* ratio of 25:1, and 95% *ee* (Table 1, entry 11). Proline, with the shorter distance between the secondary amine and the carboxylic acid in comparison to peptides **1** and **4**, is a poorer catalyst for this reaction (Table 1, entry 12 and reference [9]).[11] Notably, the diastereomeric peptides **1** and **4** both afforded the *syn* addition reaction products, but with opposite enantioselectivities (Table 1, entries 8 and 11). This result demonstrates that a switch in the stereoselectivity of peptidic catalysts can be easily achieved by seemingly small changes in their primary and thereby secondary structure.

To evaluate the scope of the peptidic catalysts, we investigated a range of aldehyde and nitroolefin combinations in the presence of 1 mol% of peptide **4**. High to excellent yields and stereoselectivities were obtained for a variety of aldehydes and nitroolefins reacting at room temperature for 12–24 hours (Table 2). Yet higher stereoselectivities were achieved when the reactions were performed at a lower temperature. These conditions required slightly greater amounts of catalyst (3–5 mol%) and longer reaction times, but provided diastereoselectivities of up to more than 99:1 and enantioselectivities of up to more than 99% *ee*. The best results were obtained using nitroolefins bearing electron-poor aromatic substituents (e.g. Table 2, entries 11 and 12). However, even with the poorest substrate combination (aliphatic nitroolefin and propanal, Table 2, entries 15 and 16) we obtained a diastereoselectivity of 4:1 and enantioselectivity of 94% *ee*. Aldehydes bearing branched substituents in the β-position are also tolerated (Table 2, entry 5), but require 3–5 mol% of catalyst to provide products in yields greater than 88%. Remarkably, peptide **4** is also a good catalyst for conjugate addition reactions of aldehydes to nitroethylene, yielding monosubstituted nitroaldehydes that can serve as precursors to γ^2-amino acids (Table 2, entry 17).[12]

These results demonstrate that peptide **4** is an excellent catalyst for conjugate addition reactions between aldehydes and nitroolefins. Other chiral amines that have been used to catalyze this reaction typically require the use of 10–20 mol% of catalyst and a large excess of aldehyde (10 equiv).[8–10,13] In addition, their substrate scope is often limited to aromatic nitroolefins, providing products of β-alkyl substituted nitroolefins in only moderate yields and stereoselectivities.[8–10,13] When using peptidic catalyst **4**, 1 mol% of catalyst and 3 equivalents of the aldehyde suffice to provide the addition products in high yields and stereoselectivities.[14]

Table 2: Conjugate addition reactions between aldehydes and nitroolefins catalyzed by peptide **4**.[a]



Entry	Product	mol% **4**	*T* [°C]	*t* [h]	Yield[b] [%]	*syn*:*anti*[c]	*ee*[d] [%]
1		1	RT	24	98	9:1	91
		5	−15	48	70	>99:1	97
2		1	RT	12	93	25:1	95
		3	−15	48	92	>99:1	97
3		1	RT	12	94	15:1	92
		3	−15	48	90	90:1	96
4		1	RT	12	quant	15:1	92
		5	−15	48	96	>99:1	96
5		3	RT	24	88	50:1	92
		5	−15	48	quant	>99:1	96
6		1	RT	12	89	15:1	95
		3	−15	48	95	80:1	98
7		1	RT	12	quant	25:1	95
		5	−15	48	quant	>99:1	97
8		1	RT	12	quant	30:1	95
		3	−15	48	97	>99:1	97
9		1	RT	12	quant	25:1	95
		5	−15	48	95	90:1	97
10		1	RT	12	90	20:1	95
		3	−15	48	97	50:1	97
11		1	RT	12	88	>99:1	98
		3	−15	48	95	>99:1	99
12		1	RT	12	93	60:1	98
		1	0	24	84	>99:1	>99
13		3	RT	12	quant	15:1	92
		5	−15	48	97	70:1	94
14		1	RT	12	84	6:1	88
		3	−15	48	94	30:1	95
15		3	RT	36	88	4:1	98
		5	−15	48	55	4:1	98
16		3	RT	12	82	15:1	93
		5	−15	48	80	20:1	94
17[e]		1	RT	48	65	–	81

[a] Reactions were performed using the TFA salts of the peptidic catalysts and the equivalent amount of NMM. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude material. [d] Determined by chiral-phase HPLC analysis. [e] Used 6 equiv of the aldehyde.

To understand the opposite enantioselectivities of the diastereomeric peptides **1** and **4**, their conformations were analyzed using molecular modelling by MacroModel 8.0.[15] In the lowest energy conformations, both peptides adopt turn-like conformations that are identical apart from the N-terminal proline (Pro) residue. These residues point in opposite directions with respect to the turn (Figure 1c and see the Supporting Information). Under the assumption that the *s-trans* enamines will form upon reaction of **1** and **4** with the aldehyde, the two transition states of the diastereomeric peptides will behave like pseudo enantiomers, providing *syn* products with opposite absolute configurations (Figure 2).[16]

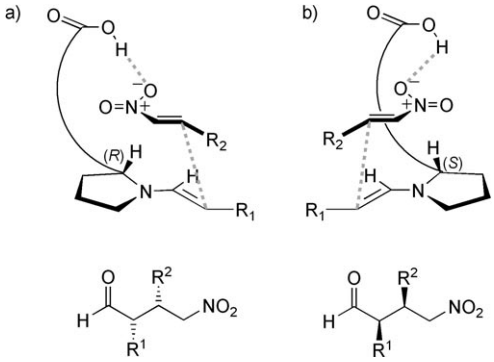


Figure 2. Proposed transition-state structures for a) **4** and b) **1** leading to enantiomeric *syn* products (bottom).

We have shown that peptide **4** is a highly effective catalyst for asymmetric conjugate addition reactions between aldehydes and nitroolefins. Synthetically useful chiral γ-nitroaldehydes were obtained in excellent yields and stereoselectivities under mild conditions using catalyst loadings of only 1 mol%. In this respect, **4** is among the most efficient asymmetric catalysts for the title reaction that has been developed to date.[17] Our findings illustrate: a) how insight into the conformation of a peptidic catalyst can guide the extension of its reaction scope, and b) how the modular nature of peptidic catalysts allows facile tuning of their catalytic performance. The results also suggest that the structure of peptidic catalysts can be sufficiently flexible to accommodate different transition state requirements, for example, those of 1,2- and 1,4-addition reactions.

Experimental Section

General procedure for 1,4-addition reactions of aldehydes to nitroolefins: The nitroolefin (0.45 mmol, 1.0 equiv) and the aldehyde (1.35 mmol, 3.0 equiv) were added to a solution of peptide **4**·TFA (2 mg, 4.5 μmol, 0.01 equiv) and *N*-methylmorpholine (4.5 μmol, 0.01 equiv) in a mixture of $CHCl_3$ and *i*PrOH (9:1, 1 mL). The reaction mixture was stirred for 6–48 h and then purified by column chromatography on silica gel using mixtures of pentanes and EtOAc as eluent.

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[17] While this manuscript was in press, an excellent article by Ma and co-workers appeared on the title reaction. See: S. Zhu, S. Yu, D. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 545 – 548.

