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Peptide Catalyzed Asymmetric Conjugate Addition Reactions of Aldehydes to Nitroethylene—A Convenient Entry into γ^2-Amino Acids

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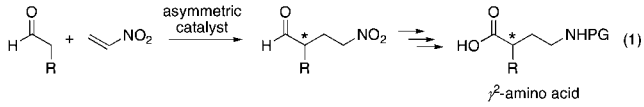
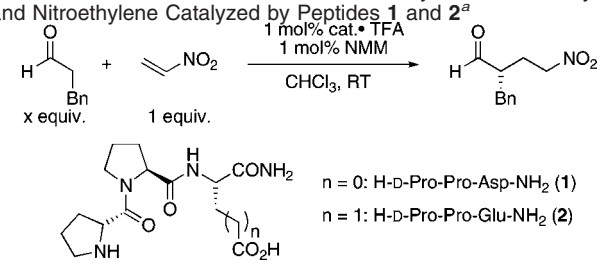
Asymmetric conjugate addition reactions of carbon-centered nucleophiles are among the most useful and challenging synthetic transformations.[1] Over recent years, impressive progress has been made on the development of asymmetric catalysts for conjugate addition reactions of aldehydes to nitroolefins, affording γ-nitroaldehydes as important synthetic intermediates.[2–4] The most commonly used Michael acceptors thus far are β-substituted nitroolefins, providing 2,3-disubstituted γ-nitroaldehydes. We became interested in employing nitroethylene as a Michael acceptor since this would afford access to monosubstituted γ-nitroaldehydes (eq 1). These would allow for conversion into monosubstituted γ^2-amino acids as important building blocks in the development of therapeutics or within foldamer research.[5,6] Common procedures for the synthesis of γ^2-amino acids rely on the use of chiral auxiliaries.[7] A direct more efficient route would thus facilitate their accessibility. Herein we present a highly effective tripeptidic catalyst for asymmetric conjugate addition reactions of aldehydes to nitroethylene. Only 1 mol % of the catalyst is sufficient to achieve high enantioselectivities and yields across a range of aliphatic and functionalized aldehydes. The γ-nitroaldehydes were readily converted into γ^2-amino acids.



(1)

Previously, we introduced the peptide H-D-Pro-Pro-Asp-NH_2 **1** as an efficient catalyst for conjugate addition reactions of aldehydes to β-substituted nitroolefins.[4,8] We therefore started our investigations by testing whether **1** would also catalyze asymmetric conjugate addition reactions of aldehydes to nitroethylene. The reaction between nitroethylene and dihydrocinnamaldehyde was used as a test reaction, and we were pleased to find that 1 mol % of **1** catalyzed the reaction with good conversion and enantioselectivity (Table 1, entry 1). Variations in the catalyst structure revealed that the homologous and more soluble catalyst H-D-Pro-Pro-Glu-NH_2 **2** bearing an additional methylene group is an even better catalyst (Table 1, entry 2). Notably, the product of a homoaldol reaction of the aldehyde that is often observed with other amine-based organocatalysts was not detected at all with catalytically active peptide **2**. This allowed for reducing the amount of aldehyde to as little as 1.5 equiv with respect to nitroethylene. Among the common reaction parameters, the concentration was particularly important. At a nitroethylene concentration of 0.1 M in chloroform, the product was obtained with significantly higher enantioselectivity compared to that of reactions performed at higher or lower concentration (Table 1, entry 5). Thus, the best results (95% conversion, >95% ee) were obtained with 1 mol % of **2**, a 1.5-fold excess of aldehyde at a concentration of 0.1 M in chloroform (Table 1, entry 5).[10]

Table 1. 1,4-Addition Reactions between Dihydrocinnamaldehyde and Nitroethylene Catalyzed by Peptides **1** and **2**[a]



entry	cat.	equiv of RCHO	conc[b] (M)	time (h)	conv[c] (%)	ee[d] (%)
1	**1**	3	0.5	30	70	85
2	**2**	3	0.5	10	90	90
3	**2**	3	0.25	10	95	95
4	**2**	1.5	0.25	15	90	>95
5	**2**	1.5	0.1	15	≥95	>95
6	**2**	1.5	0.05	15	80	90
7	**1**	1.5	0.1	50	85	90

[a] Reactions were performed using the TFA salts of the peptidic catalysts and the equivalent amount of *N*-methylmorpholine (NMM). [b] Concentration of nitroethylene in the $CHCl_3$ solution. [c] Conversion estimated by ^{1}H NMR spectroscopic analysis. [d] Determined by a ^{1}H NMR spectroscopic analysis using a chiral amine (ref 9; see Supporting Information).

With these reaction parameters defined, we reacted a range of different aldehydes with nitroethylene in the presence of 1 mol % of peptide **2** (Table 2). Since the resulting α-substituted γ-nitroaldehydes are prone to racemization upon purification by column chromatography, they were typically reduced to the corresponding alcohols before isolation. The conjugate addition reaction products were obtained in high yields and excellent enantioselectivities for a range of different aliphatic and functionalized aldehydes. Particularly notable is that, with slightly higher amounts of catalyst (3 mol %) and longer reaction times, not only isovaleraldehyde but even neopentylaldehyde with a *tert*-butyl group at the α-carbon is tolerated as a substrate (Table 2, entries 5 and 6). In addition, aldehydes bearing functional groups such as alkenes and esters also reacted readily with nitroethylene in the presence of only 1 mol % of peptide **2** (Table 2, entries 8–10).

We assume that the reactions proceed via enamine catalysis[2e] since methylation or acetylation of the N-terminal proline residue of **2** led to inactive catalysts. Interestingly, peptide H-D-Pro-Pro-Gln-NH_2 (**4**) with a carboxamide in place of the carboxylic acid is a poorer catalyst with respect to its reactivity but exhibited comparable selectivity. This result suggests that in

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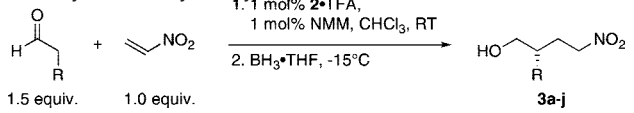
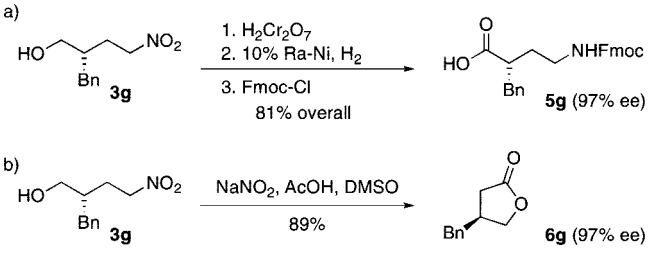
Table 2. 1,4-Addition Reactions between Aldehydes and Nitroethylene Catalyzed by Peptide **2**[a]



entry	R	time (h)	yield[b] (%)	ee[c] (%)
1	Me	20	84	95
2	Et	15	82	98
3	*n*-Pr	15	90	99
4	*n*-Bu	20	84	99
5	*i*-Pr	45	85	97[d]
6[e]	*t*-Bu	120	67	98
7	Bn	15	82	98
8[f]	$(CH_2)_5CH{=}CHCH_2CH_3$	25	86	98
9[f]	$CH_2CO_2CH_3$	70	78	95
10[f]	$CH_2CH_2CH_2CO_2CH_3$	25	80	96

[a] Reactions were performed using the TFA salt of **2** and the equivalent amount of *N*-methylmorpholine (NMM). [b] Isolated yield. [c] Determined by chiral phase HPLC or GC analysis. [d] The ee was determined by an ^{1}H NMR spectroscopic analysis of the aldehyde (ref 9; see Supporting Information). [e] 3 mol % of **2** and NMM was used. [f] Yield and ee were determined for the aldehyde (ref 11; see Supporting Information).

Scheme 1. Synthesis of γ^2-Amino Acids from γ-Nitroalcohols



contrast to direct aldol reactions, where an acidic functional group within the catalyst is a prerequisite for efficient catalysis,[12] conjugate addition reactions of aldehydes to nitroethylene require simply a coordinating functional group within the catalyst structure.[10]

Conversion of the conjugate addition products to γ^2-amino acids proved straightforward. As an illustration, nitroalcohol **3g** was oxidized to the carboxylic acid using Jones reagent followed by reduction of the nitro group with Raney-Ni and Fmoc protection of the resulting amino acid. The Fmoc-protected γ^2-amino acid **5g** was obtained in an overall yield of 81% with retention of optical purity as determined by reaction of **5g** with a chiral amine (Scheme 1a). In addition, **3g** was readily converted into the γ-lactone **6g** which was used to assign the absolute configuration (Scheme 1b).[3d,13] Such monosubstituted γ-lactones are also useful precursors to a multitude of biologically active compounds.[14]

In conclusion, peptide **2** is an excellent asymmetric catalyst for conjugate addition reactions of aldehydes to nitroethylene, affording monosubstituted γ-nitroaldehydes in high yields and enantioselectivities requiring only a small excess of the aldehyde and as little as 1 mol % of the catalyst. The products can be readily converted into monosubstituted γ^2-amino acids, which should thus facilitate research on the development of therapeutics and foldamers consisting of γ^2-amino acids.[15]

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Supporting Information Available: Experimental details on the syntheses and analyses of the presented compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Experiments with the inner salt of **2** in the absence of NMM proceeded with the same enantioselectivity but significantly slower. This could suggest that TFA influences the catalytic activity; however, the inner salt proved also not entirely soluble.

(11) The enantiomeric purity was determined by ^{1}H NMR spectroscopy after reacting the γ-amino aldehydes with a chiral amine to form diastereomeric imines (ref 9). Control experiments with substrates that allowed for the analysis of the ee both on the aldehyde and alcohol stage verified that this method is exact within an error of ±2% ee.

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