Asymmetric Catalysis

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Peptide-Catalyzed Stereoselective Conjugate Addition Reactions Generating All-Carbon Quaternary Stereogenic Centers**

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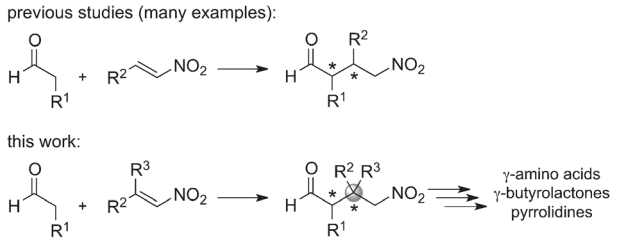
Dedicated to Professor Jack Dunitz on the occasion of his 90th birthday

Stereoselective conjugate addition reactions of carbon-based nucleophiles are among the most useful synthetic transformations.[1] Particularly challenging are C–C bond forming reactions that afford acyclic compounds with an all-carbon quaternary stereogenic center under mild organocatalytic conditions.[2–4] Among the few examples are mainly reactions in which the quaternary stereogenic center is derived from substituted 1,3-dicarbonyl compounds or α,α-disubstituted aldehydes that act as nucleophiles upon activation by a catalyst.[3] Reactions in which the quaternary stereogenic center is derived from the electrophile are even less common.[4,5] In the past decade, impressive progress has been made in the development of catalysts for stereoselective reactions between aldehydes and nitroolefins to provide synthetically valuable γ-nitroaldehydes.[6–13] The most commonly used Michael acceptors are β-monosubstituted nitroolefins (Scheme 1, top),[6–9] but also nitroethylene[10,11] and



Scheme 1. Conjugate addition reactions between aldehydes and nitroolefins.

α,β-disubstituted nitroolefins[12,13] have been reacted with aldehydes in the presence of chiral amine-based catalysts. In contrast, reactions with β,β-disubstituted nitroolefins to provide γ-nitroaldehydes with an all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter have so far not been realized (Scheme 1, bottom).

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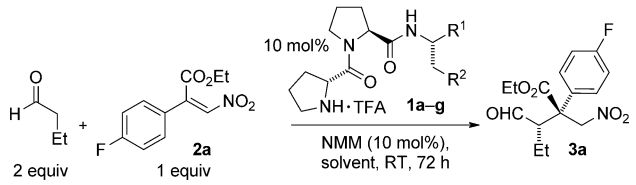
Herein we present a peptide as an effective stereoselective catalyst for asymmetric conjugate addition reactions of aldehydes to β,β-disubstituted nitroolefins. We also demonstrate that the resulting γ-nitroaldehydes can be readily converted into other valuable compounds with quaternary stereogenic centers such as chiral pyrrolidines, γ-amino acids, or γ-butyrolactones.

Previously our group introduced tripeptides of the type Pro-Pro-Xaa (Xaa = acidic amino acid) as highly reactive and stereoselective catalysts for aldol reactions and conjugate addition reactions of aldehydes to nitroolefins.[9,10,12,14] For example, H-D-Pro-Pro-Glu-NH_2 (**1a**) and H-Pro-Pro-D-Gln-OH catalyze conjugate addition reactions of aldehydes with β-monosubstituted nitroolefins and α,β-disubstituted nitroolefins, respectively.[9,12] Products resulting from homo-aldol reactions that are typical side products in such conjugate addition reactions form either not at all or only in minimal amounts despite the fact that the related peptide H-Pro-Pro-Asp-NH_2 is a very good catalyst for aldol reactions.[14] Thus, the modular nature of these peptidic catalysts allows for fine-tuning and optimizing their structural and functional properties to the desired reaction pathway and to accommodate the requirements of a given substrate combination. These features suggest that a member of the class of peptides Pro-Pro-Xaa might also fulfill the requirements for catalyzing stereoselective addition reactions between aldehydes and β,β-disubstituted nitroolefins.

We started our investigations by exploring the catalytic properties of peptides of the type Pro-Pro-Xaa in the reaction of butanal with (*Z*)-ethyl 2-(4-fluorophenyl)-3-nitroacrylate (**2a**). All reactions were performed with the trifluoroacetic acid (TFA) salts of the peptides, the equivalent amount of *N*-methylmorpholine (NMM) and 2 equivalents of the aldehyde with respect to the nitroolefin. Despite the electron-withdrawing and therefore activating substituents, β,β-disubstituted nitroolefin **2a** proved to be significantly less prone to form conjugate addition products with aldehydes than β-monosubstituted nitroolefins. Whereas β-nitroolefins react readily with aldehydes in the presence of as little as ≤ 1 mol% of H-D-Pro-Pro-Glu-NH_2 (**1a**) in a mixture of $CHCl_3$ and *i*PrOH,[9] only a small amount of the β,β-disubstituted nitroolefin **2a** (≤ 10%) was converted to the desired addition product **3a** in the presence of 10 mol% of **1a** within three days under the same reaction conditions (Table 1, entry 1). Instead, a significant amount of the homo-aldol reaction product formed. Reassuringly, the desired γ-nitroaldehyde **3a** was obtained in good stereoselectivity (d.r. 6.4:1, 86% *ee*, Table 1, entry 1). A higher conversion to the product was

Table 1: 1,4-Addition reactions between butanal and nitroolefin **2a** catalyzed by peptides of the type H-D-Pro-Pro-Xaa.



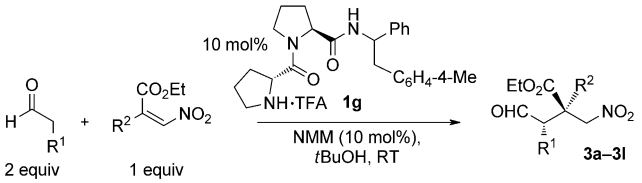
Entry	Catalyst	R^1	R^2	Solvent	Conv. [%][a]	d.r.[a]	*ee* [%][b]
1	**1a**	$CONH_2$	CH_2CO_2H	$CHCl_3$/*i*PrOH 9:1	<10	6.4:1	86
2	**1a**	$CONH_2$	CH_2CO_2H	*i*PrOH	50	4.0:1	75
3	**1b**	H	CH_2CO_2H	*i*PrOH	51	4.0:1	77
4	**1c**	H	CH_2CO_2Me	*i*PrOH	72	4.3:1	80
5	**1d**	H	$(CH_2)_2CO_2Me$	*i*PrOH	79	4.2:1	80
6	**1e**	CO_2Me	$(CH_2)_2CO_2Me$	*i*PrOH	86	3.6:1	80
7	**1f**	CO_2Me	Ph	*i*PrOH	86	4:7:1	85
8	**1g**[c]	Ph	4-Me-C_6H_4	*i*PrOH	78	4.6:1	90
9	**1g**[c]	Ph	4-Me-C_6H_4	MeOH	10	1.1:1	nd[d]
10	**1g**[c]	Ph	4-Me-C_6H_4	EtOH	33	3.0:1	81
11	**1g**[c]	Ph	4-Me-C_6H_4	$CHCl_3$	36	4:8:1	92
12	**1g**[c]	Ph	4-Me-C_6H_4	toluene	21	5.0:1	93
13	**1g**[c]	Ph	4-Me-C_6H_4	THF	27	6.1:1	89
14	**1g**[c]	Ph	4-Me-C_6H_4	*t*BuOH	96	6.0:1	94
15	**1g-R**[e]	Ph	4-Me-C_6H_4	*t*BuOH	98	5.6:1	95
16	**1g-S**[e]	Ph	4-Me-C_6H_4	*t*BuOH	86	6.0:1	93

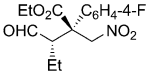
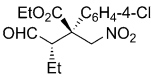
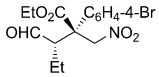
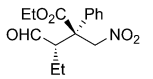
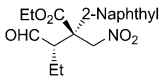
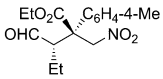
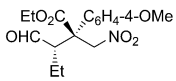
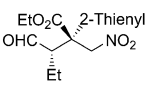
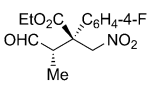
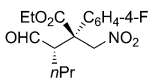
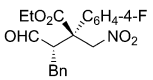
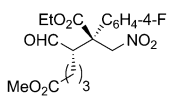
[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Determined by chiral-stationary-phase HPLC analysis. [c] Diastereoisomeric mixture with (*R*)- and (*S*)-configured C-terminal moiety. [d] Not determined. [e] Enantiomerically pure **1g** with either (*R*)- or (*S*)-configured C-terminal moieties.

observed when merely *i*PrOH was used as solvent although at the expense of the stereoselectivity (Table 1, entry 2). Variations in the catalyst structure revealed that the D-Pro-L-Pro motif is optimal for high stereoselectivities (see the Supporting Information for details). More importantly, the functional group at the C-terminal end was found to affect the reactivity and chemoselectivity (aldol versus conjugate addition reactions) of the peptidic catalysts significantly. The highest conversions to the conjugate addition product **3a** were achieved with peptides bearing a methylester and/or aromatic residues instead of a carboxylic acid at the C terminus (Table 1, entries 4–8). This is remarkable, since the presence of a carboxylic acid moiety within the peptidic catalyst had been found to provide highest reactivity and stereoselectivity in the previously examined peptide-catalyzed conjugate addition reactions.[9b,15] The best catalyst with respect to stereoselectivity and reactivity was found to be peptide H-D-Pro-Pro-NHCH(Ph)CH_2-4-Me-C_6H_4 (**1g**) with two aromatic residues at the C terminus (Table 1, entry 8). Further optimization of the reaction parameters showed that *t*BuOH is the best solvent (Table 1, entries 8–14). Under these optimized conditions nitroolefin **2a** reacted quantitatively to the conjugate addition product **3a**, which was obtained with a diastereoselectivity of 6:1 and an enantioselectivity of 94% *ee* (Table 1, entry 14).

Catalyst **1g** is a 1:1 mixture of the two diastereoisomers H-D-Pro-Pro-NH-(*R*)-CH(Ph)CH_2-4-Me-C_6H_4 (**1g-R**) and H-D-Pro-Pro-NH-(*S*)-CH(Ph)CH_2-4-Me-C_6H_4 (**1g-S**). Evaluation of the catalytic performance of the individual stereoisomers **1g-R** and **1g-S** showed that their reactivities and in particular stereoselectivities differ only slightly from those of the mixture (Table 1, entry 14–16). Since racemic 1-phenyl-2-(*p*-tolyl)ethylamine is more readily available than the enantiomerically pure amines needed for the synthesis of **1g-R** and **1g-S**, all further studies were performed with the mixture of the two diastereoisomers.

Table 2: Scope of 1,4-addition reactions between aldehydes and β,β-disubstituted nitroolefins.

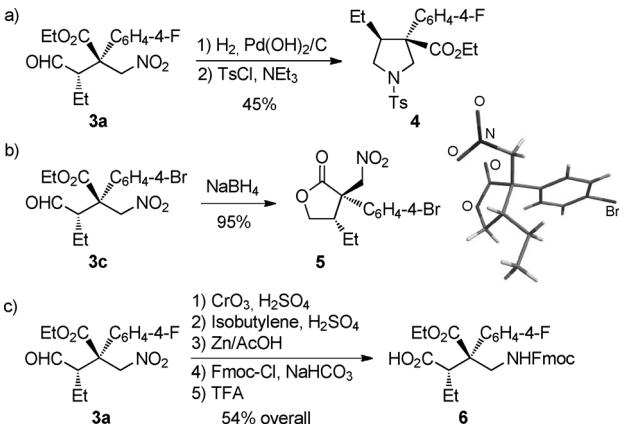


Entry	Product		Yield [%][a]	d.r.[b]	*ee* [%][c]
1		**3a**	82	6.0:1	94
2		**3b**	85	5.0:1	94
3		**3c**	84	5.5:1	94
4		**3d**	85	5.5:1	96
5		**3e**	83	6.5:1	91
6		**3f**	90	6.5:1	94
7		**3g**	72	6.0:1	94
8		**3h**	88	5.5:1	89
9		**3i**	83	3.0:1	95
10		**3j**	85	6.5:1	95
11		**3k**	87	10.0:1	97
12		**3l**	85	4.5:1	91

[a] Yields correspond to γ-nitroaldehydes isolated as a mixture of stereoisomers after 48–72 h. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral-stationary-phase HPLC analysis.

With the optimized reaction conditions defined we explored the scope of the peptide-catalyzed conjugate addition reactions and allowed a range of different aldehyde and β,β-disubstituted nitroolefin combinations to react with each other in the presence of 10 mol% of peptide **1g**. The desired γ-nitroaldehydes **3a**–**3l** bearing an all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter were obtained in good yields and stereoselectivities (Table 2). The best results with respect to the diastereoselectivity (10:1) and enantioselectivity (97% *ee*) were achieved when using electron-poor aromatic β,β-disubstituted nitroolefins (e.g. Table 2, entry 11); however, good product yields and stereoselectivities were also obtained with nitroacrylates bearing electron-rich aromatic substituents (e.g. Table 2, entries 7 and 8). Also aldehydes bearing functional groups such as esters reacted readily with the β,β-disubstituted nitroolefins (Table 2, entry 12). Current limitations are aliphatic nitroacrylates,[16] β,β-nitroolefins lacking an additional electron-withdrawing group, and α- or β-branched aldehydes that did not react or only in trace amounts to the desired γ-nitroaldehyde.

Next, we explored the synthetic versatility of the γ-nitroaldehydes for the preparation of γ-amino acids as well as heterocyclic compounds with all-carbon quaternary stereogenic centers that are valuable for the synthesis of therapeutically active compounds.[17] These studies also allowed for the unambiguous determination of the relative and absolute configuration of the major stereoisomer formed in the peptide-catalyzed addition reactions. For example, *N*-tosylated pyrrolidine **4** was obtained by reductive amination of γ-nitroaldehyde **3a** followed by tosylation (Scheme 2a). NMR-spectroscopic analysis including NOE spectroscopy of **4**



Scheme 2. Synthesis of pyrrolidine **4**, lactone **5**, γ-amino acid **6**, and the crystal structure of lactone **5**.[19]

supports, as expected from the related reactions with β- and α,β-substituted nitroolefins, the relative *syn* configuration of the ethyl group and the aromatic moiety within **3** (*anti* within **4**, see the Supporting Information for details). Reduction of the aldehyde moiety within γ-nitroaldehyde **3c** using $NaBH_4$ yielded after intramolecular cyclisation of the initially formed hydroxyester the crystalline γ-butyrolactone **5** in 95% yield (Scheme 2b). Crystals suitable for X-ray crystal structure analysis of lactone **5** were obtained from Et_2O/pentane. The crystal structure confirmed the relative configuration and allowed to determine the absolute configuration of both stereogenic centers within the parent γ-nitroaldehyde to be *S*. Aside from the pyrrolidines and lactones, also 2,3,3-trisubstituted γ-amino acid **6** was readily prepared (Scheme 2c). Towards this goal γ-nitroaldehyde **3a** was transformed to Fmoc-protected $\gamma^{2,3,3}$-amino acid **6** in five steps by following a previously established procedure.[12] Such amino acids with an all-carbon quaternary stereogenic center next to a tertiary stereocenter have to our knowledge not been prepared to date and might not only be interesting for the development of therapeutics but also for foldamer research.[17,18]

Previous studies on the mechanism of conjugate addition reactions between aldehydes and nitroolefins had shown that catalysts bearing an appropriately positioned proton donor do not require any additives for high reactivity and stereoselectivity, whereas an acidic cocatalyst is critical for catalysts lacking an intramolecular proton donor.[15,20] Thus, for the herein presented peptidic catalyst H-D-Pro-Pro-NHCH(Ph)CH_2-4-Me-C_6H_4 (**1g**) the presence of an additional acid was expected to be important. Studies in which the acidic cocatalyst was varied showed that this is indeed the case. Best results with respect to reactivity and stereoselectivity were obtained when the trifluoroacetic acid (TFA) salt of the peptide and an equivalent amount of *N*-methylmorpholine (NMM) were used.[21] Significantly lower reaction rates were observed when the peptide was used in the absence of any acidic additive.[21] The question why a peptidic catalyst lacking an intramolecular carboxylic acid moiety is better suited for the present reaction compared to peptides bearing a proton donor that had been found to be optimal for related reactions is not trivial. The findings suggest that steric shielding and/or interaction between the aromatic portion of catalyst **1g** and the β,β-disubstituted nitroolefin are critical for favoring the desired conjugate addition over the competing aldol reaction. Detailed NMR-spectroscopic and kinetic studies that will shed more light on the mechanism of the presented peptide-catalyzed reaction are currently ongoing and will be reported in due course.

In summary, we have shown that the peptide H-D-Pro-Pro-NHCH(Ph)CH_2-4-Me-C_6H_4 (**1g**) is a powerful catalyst for conjugate addition reactions of aldehydes to β,β-disubstituted nitroolefins to afford synthetically versatile γ-nitroaldehydes with an all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter in high yields and stereoselectivities. The γ-nitroaldehydes were obtained with high chemoselectivity over competing homo-aldol products and provide easy access to novel $\gamma^{2,3,3}$-amino acids, γ-butyrolactones, and chiral pyrrolidines bearing all-carbon quaternary stereogenic centers.

Experimental Section

General procedure for the conjugate addition reactions: The nitroolefin (0.42 mmol, 1 equiv) was added to a solution of the peptide (as the TFA salt, 42 μmol, 10 mol%), NMM (42 μmol, 10 mol%), and the aldehyde (0.84 mmol, 2 equiv) in *tert*-BuOH (1 mL). The reaction

mixture was agitated at room temperature for 48–72 h, and then all volatile components were removed at reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel by using a mixture of pentanes and EtOAc as eluent to afford γ-nitroaldehydes **3**.

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Keywords: 1,4-addition reactions · γ-amino acids · asymmetric catalysis · nitroolefins · peptides

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