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Adapting to Substrate Challenges: Peptides as Catalysts for Conjugate Addition Reactions of Aldehydes to α,β-Disubstituted Nitroolefins

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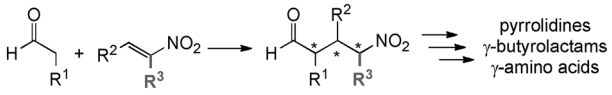
Abstract: Conjugate addition reactions of aldehydes to α,β-disubstituted nitroolefins are important because they provide synthetically useful γ-nitroaldehydes bearing three consecutive stereogenic centers. Such reactions are challenging due to the drastically lower reactivity of α,β-disubstituted nitroolefins compared to, for example, β-monosubstituted nitroolefins. The testing of a small collection of peptides of the type Pro-Pro-Xaa (Xaa = acidic amino acid) led to the identification of H-Pro-Pro-D-Gln-OH and H-Pro-Pro-Asn-OH as excellent stereoselective catalysts for this transformation. In the presence of 5 mol% of these peptides different combinations of aldehydes and α,β-disubstituted nitroolefins react readily with each other providing γ-nitroaldehydes in good yields and diastereoselectivities as well as excellent enantioselectivities. Chiral pyrrolidines as well as fully substituted γ-butyrolactams and γ-amino acids are easily accessible from the γ-nitroaldehydes. Mechanistic studies demonstrate that the configuration at all three stereogenic centers is induced by the peptidic catalysts. Only a minimal amount of products from homo-aldol reactions is observed demonstrating the high chemoselectivity of the peptidic catalysts.

Keywords: addition reactions · asymmetric catalysis · nitroolefins · peptides · proline

Introduction

Conjugate addition reactions of carbon-based nucleophiles to electron-deficient olefins are among the most useful C–C bond forming processes.[1] In particular, the conjugate addition of aldehydes to β-substituted nitroolefins is one of the most widely researched reactions, because the resulting γ-nitroaldehydes are versatile intermediates that can be readily transformed into a variety of useful building blocks including chiral γ-amino acids, γ-butyrolactams, and pyrrolidines.[2] Consequently, manifold chiral-amine-based catalysts have been explored that promote the conjugate addition reaction of aldehydes to β-substituted nitroolefins.[3–7] However, examples of addition reactions of carbonyl compounds to nitroolefins, which bear not only a substituent in the β- but also in the α-position, are rare.[8–12] The development of conjugate addition reactions of aldehydes to such α,β-disubstituted nitroolefins is highly desirable, as the resulting γ-nitroaldehydes bear three consecutive stereogenic centers and are therefore valuable intermediates for the synthesis of, for example, chiral pyrrolidines and fully substituted γ-amino acids or γ-butyrolactams (Scheme 1). Progress has likely been hampered by the lower reactivity of α,β-disubstituted nitroolefins compared to their β-monosubstituted counterparts as well as difficulties in controlling the absolute configuration at the carbon atom bearing the nitro group. In fact, the only α,β-disubstituted nitroolefins that have been explored in organocatalytic conjugate addition reactions with aldehydes are either cyclic[8,9] or profit from activation of the nitro group by an intramolecular hydrogen-bond donor.[10] A single example of the addition of an aldehyde to an acyclic non-activated disubstituted nitroolefin in the course of a total synthesis provided the product in low diastereoselectivity due to poor control of the stereogenic center at the carbon atom bearing the nitro group.[11]



Scheme 1. Conjugate addition reactions of aldehydes to α,β-disubstituted nitroolefins.

Our group has recently introduced peptides of the general type Pro-Pro-Xaa, where the turn inducing Pro-Pro-motive is combined with a C-terminal acidic amino acid (Xaa), as effective catalysts for enamine catalysis.[5–7,13] For example, the peptide H-D-Pro-Pro-Glu-NH_2 (**1a**) is an excellent catalyst for conjugate addition reactions of aldehydes to β-monosubstituted nitroolefins.[5–7] In the presence of as little as ≤1 mol% of **1a** a broad variety of aldehydes react readily with both aliphatic and aromatic nitroolefins to provide the corresponding γ-nitroaldehydes in very good yields and ste-

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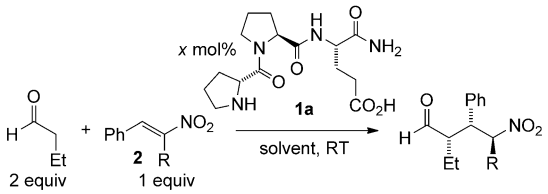
reoselectivities. In contrast to many other chiral secondary-amine-based catalysts, peptide **1a** strongly favors the conjugate addition reaction over competing homo-aldol reactions of the aldehyde.[6] This high chemoselectivity of the peptidic catalyst **1a** is remarkable, in particular because the closely related peptide H-Pro-Pro-Asp-NH_2 is a very good catalyst for aldol reactions.[13] It demonstrates that slight variations in the structure of peptides of the type Pro-Pro-Xaa allow for a fine tuning of their chemoselectivity. A high chemoselectivity for conjugate addition reactions over homo-aldol reactions becomes even more important when less reactive substrates, such as α,β-disubstituted nitroolefins, are employed. The unique catalytic performance combined with the modular nature of the Pro-Pro-Xaa motif, which allows for accessing a variety of structurally different catalysts easily by standard solid-phase peptide synthesis, suggested to us that this class of peptidic catalysts might contain members capable of catalyzing conjugate addition reactions between aldehydes and α,β-disubstituted nitroolefins. Here we present the peptides H-Pro-Pro-D-Gln-OH and H-Pro-Pro-Asn-OH as effective stereoselective catalysts for addition reactions between aldehydes and α,β-disubstituted nitroolefins. We also demonstrate that the resulting γ-nitroaldehydes can be further converted into chiral pyrrolidines as well as fully substituted γ-butyrolactams and γ-amino acids.

Results and Discussion

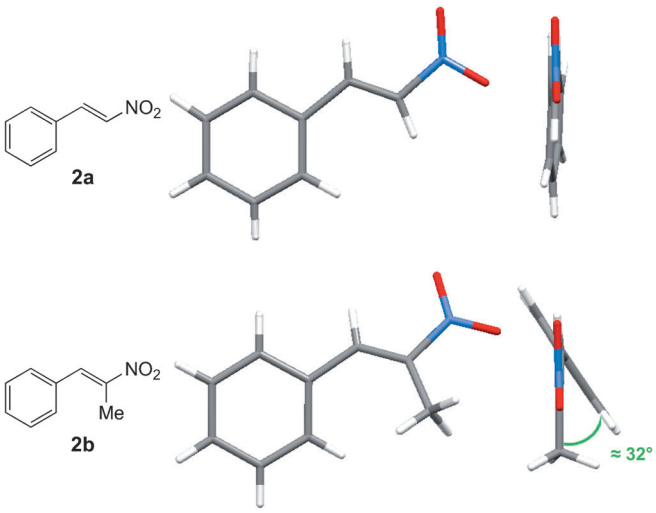
Reactivity of α,β-disubstituted nitroolefins: We started our investigations by testing peptide **1a** as a catalyst for the conjugate addition reaction of butanal to β-methyl-β-nitrostyrene (**2b**). This nitroolefin was chosen as a test substrate, because it is an acyclic α,β-disubstituted nitroolefin that is neither activated by an intramolecular hydrogen bond to the nitro group nor by an electron-withdrawing group on the phenyl ring. Nitroolefin **2b** should therefore represent a non-activated α,β-disubstituted nitroolefin and proved indeed to be significantly less reactive than β-monosubstituted nitroolefins such as β-nitrostyrene (**2a**) that react readily in the presence of 1 mol% of peptide **1a** (Table 1, entry 1). Nevertheless, in the presence of 5 mol% of the peptidic catalyst **1a**, 30% conversion to the desired addition product was observed also with nitroolefin **2b** within days by using conditions that had previously been optimized for the addition of aldehydes to β-monosubstituted nitroolefins (Table 1, entry 2).[6] Remarkably, the γ-nitroaldehyde was obtained in a good diastereomeric ratio of 86:8:3:3 and an excellent enantioselectivity of 99% *ee* of the major diastereoisomer. The reactivity of catalyst **1a** proved to be higher when aliphatic alcohols were used as the main solvent.[6,14] although at the expense of the stereoselectivity (Table 1, entry 3). To rationalize the reduced reactivity of β-methyl-β-nitrostyrene compared to β-nitrostyrene we had a closer look at the structure of **2b** and other α,β-disubstituted nitroolefins. Comparison of the X-ray crystal structures of **2a** and **2b** revealed a distinct difference (Scheme 2). Whereas **2a** is a

Table 1. 1,4-Addition reactions of butanal to β-nitrostyrene (**2a**) and the α,β-disubstituted nitroolefin **2b** catalyzed by the tripeptide H-D-Pro-Pro-Glu-NH_2 **1a**.[a]



	R	**1a** [mol%]	Solvent	*t* [h]	Conv [%][b]	d.r.[b]	*ee* [%][c]
1[d]	H	1	$CHCl_3$/*i*PrOH 9:1	12	100	42:1	97
2	Me	5	$CHCl_3$/*i*PrOH 9:1	150	30	86:8:3:3	99
3	Me	5	$CHCl_3$/*i*PrOH 1:9	150	40	67:15:10:8	98

[a] Reactions were typically carried out with the trifluoroacetic acid (TFA) salt of the peptide and the equivalent amount of *N*-methylmorpholine (NMM). The same results were obtained with the "desalted" peptide without NMM. [b] Diastereomeric ratio; determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Enantiomeric excess; determined by chiral-phase HPLC analysis. [d] Data from reference [6].



Scheme 2. X-ray crystal structures of *trans*-β-nitrostyrene (**2a**, top)[15] and *trans*-β-methyl-β-nitrostyrene (**2b**, bottom).

planar molecule, the phenyl ring in **2b** is twisted with respect to the plane of the nitroalkene. Such a twist is not only responsible for an increased steric demand of nitroolefin **2b**, but also hampers conjugation of the double bond with the aromatic ring and thereby renders the α,β-disubstituted nitroolefin less reactive compared to β-nitrostyrene. A similar deviation from a planar geometry is observed for most α,β-disubstituted *trans*-nitroolefins in the Cambridge Structural Database (see the Supporting Information for details). This distinct structural difference between β-mono- and α,β-disubstituted nitroolefins is also supported by ab initio calculations (MP2/cc-pVTZ) of nitroolefin **2b** (see the Supporting Information). These results show, that the drasti-

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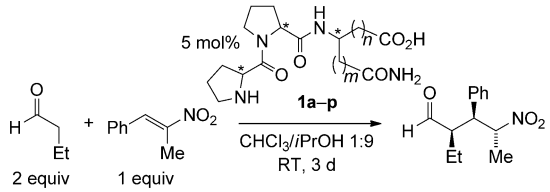
cally reduced reactivity of α,β-disubstituted nitroolefins is due to both, an increased steric demand of the additional α-substituent and a stereoelectronic effect.

Catalyst screening: The initial results demonstrated that despite the low reactivity of α,β-disubstituted nitroolefins the peptidic catalyst **1a** allows for conversion to the desired conjugate addition product with a very good control over the enantio- and diastereoselectivity of all three stereogenic centers including that at the carbon atom bearing the nitro group. In addition, the structural analysis of the nitroolefin **2b** showed that the geometry of α,β-disubstituted nitroolefins differs significantly from that of monosubstituted analogues. Based on these findings we hypothesized that a structurally related peptide of the type Pro-Pro-Xaa might be better suited to catalyze reactions of α,β-disubstituted nitroolefins compared to peptide **1a** that was optimized to accommodate β-monosubstituted nitroolefins. Thus, we synthesized and tested a small collection of fifteen different tripeptides of the type Pro-Pro-Xaa (**1b–p**, Table 2) as catalysts for the conjugate addition reaction of butanal with nitroolefin **2b**. Variations included 1) the stereochemistry of all three residues and thereby the geometry of the turn structure, 2) the position of the carboxylic acid either at the C terminus or in the side chain of the C-terminal amino acid, and 3) the length of the spacer to the carboxylic acid and amide moieties. This collection of peptides was prepared by using the 9-fluorenylmethoxycarbonyl/*tert*-butyl (Fmoc/*t*Bu) protocol for standard solid-phase peptide synthesis. Within a few days ≥50 mg of each peptide were prepared on a parallel peptide synthesizer demonstrating the ease of accessing a variety of peptides of the type Pro-Pro-Xaa. All of the fifteen different tripeptides proved to catalyze the conjugate addition reaction and provided the products in moderate to very good stereoselectivities (Table 2). Their catalytic reactivities and stereoselectivities differed, however, quite significantly depending on the stereochemistry of all three amino acids as well as the position of the carboxylic acid. The best catalysts with respect to both catalytic activity and stereoselectivity proved to be the peptides H-Pro-Pro-D-Gln-OH (**1i**) and H-Pro-Pro-Asn-OH (**1n**) (Table 2, entries 9 and 14). With both peptides the conjugate addition product was obtained in good diastereoselectivities (84:10:5:1 for **1i** and 82:12:4:2 for **1n**), excellent enantioselectivities of the major stereoisomer (99% *ee*), and full conversion is observed within 3 d.[16] Both peptides differ from the parent catalyst **1a** in the stereochemistry of the Pro–Pro motive (L–L versus D–L) and the position of the carboxylic acid, which is within **1i** and **1n** at the C terminus of the peptides and not in the side chain. Rationalizing the reason for the optimal performance of peptides **1i** and **1n** is not trivial because tripeptides have typically not only one preferred conformation. Whereas the Pro–Pro motive provides conformational rigidity,[17] the C-terminal part can be assumed to be rather flexible. It is likely that this combination of a certain degree of conformational flexibility and rigidity is key to the catalytic efficiency of peptides of the type Pro-Pro-Xaa in general. Studies with analogues of **1i** and **1n** in which the secondary amine and/or the carboxylic acid are replaced by other functional groups demonstrate that both functional groups are crucial for effective catalysis. In accord with previous studies, diastereomeric peptides bearing D-Pro versus L-Pro residues at the N terminus have opposite enantioselectivities (for example, peptides **1a** and **1b**, Table 2, entries 1 and 2). This is due to the opposite orientations of N-terminal D-Pro versus L-Pro residues relative to the rest of the peptide (for details see reference [5a]). An evaluation of the peptides **1i** and **1n** as catalysts for the conjugate addition between butanal and β-monosubstituted nitrostyrene demonstrated that both perform significantly poorer compared to peptide **1a**.[18] This shows that the different properties of β-monosubstituted versus α,β-disubstituted nitroolefins are optimally addressed by similar yet different peptidic catalysts. These results demonstrate that fifteen different peptides of the type Pro-Pro-Xaa were sufficient to identify two very good catalysts for conjugate addition reactions with α,β-disubstituted nitroolefins. It highlights the ease with which the catalytic activity, stereoselectivity, and chemoselectivity of peptides of the Pro-Pro-Xaa class can be fine-tuned by subtle structural modifications to accommodate the requirements of different substrate combinations.

Table 2. 1,4-Addition reactions of butanal to β-methyl-β-nitrostyrene (**2b**) catalyzed by different tripeptides of the type Pro-Pro-Xaa.[a]



	Catalyst	*t* [h]	Conv [%][b]	d.r.[b]	*ee* [%][c]
1	H-D-Pro-Pro-Glu-NH_2 (**1a**)	150	40	67:15:10:8	98[d]
2	H-Pro-Pro-Glu-NH_2 (**1b**)	150	100	67:16:10:7	96
3	H-Pro-D-Pro-Glu-NH_2 (**1c**)	150	40	48:23:19:10	91
4	H-Pro-Pro-D-Glu-NH_2 (**1d**)	150	85	55:21:15:9	96
5	H-Pro-Pro-Asp-NH_2 (**1e**)	72	100	71:18:6:5	97
6	H-Pro-Pro-D-Asp-NH_2 (**1f**)	150	100	65:17:10:8	96
7	H-Pro-Pro-β-homo-Asp-OH (**1g**)	84	100	75:15:6:4	97
8	H-D-Pro-D-Pro-β-homo-Asp-OH (**1h**)	150	90	70:13:9:8	98[d]
9	H-Pro-Pro-D-Gln-OH (**1i**)	54	100	84:10:5:1	99
10	H-Pro-Pro-Gln-OH (**1j**)	150	100	66:21:8:5	97
11	H-D-Pro-Pro-Gln-OH (**1k**)	150	30	42:27:19:12	84[d]
12	H-Pro-D-Pro-Gln-OH (**1l**)	150	40	48:20:17:15	86
13	H-Pro-Pro-D-Asn-OH (**1m**)	54	100	75:16:6:3	97
14	H-Pro-Pro-Asn-OH (**1n**)	54	100	82:12:4:2	99
15	H-D-Pro-Pro-Asn-OH (**1o**)	150	60	42:27:18:13	90[d]
16	H-Pro-Pro-cysteic acid-NH_2 (**1p**)	150	50	53:17:17:13	89

[a] Reactions were typically carried out with the TFA salt of the peptide and the equivalent amount of NMM. The same results were obtained with the "desalted" peptide without NMM. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral-phase HPLC analysis. [d] The opposite enantiomer of the major diastereoisomer was obtained.

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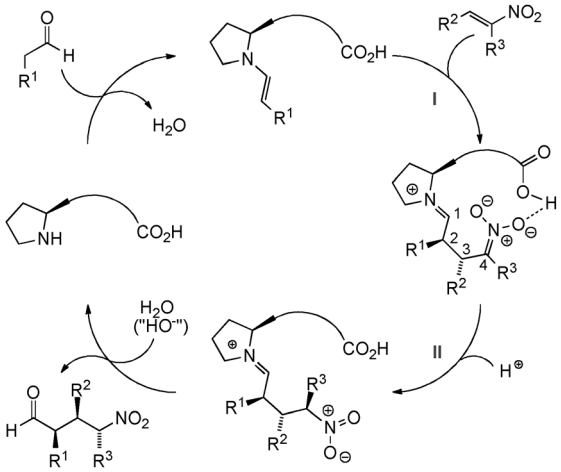
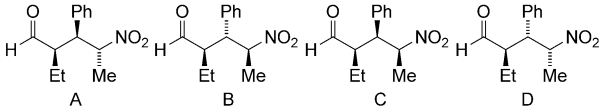
Do the peptides control the configuration at each stereogenic center? Determination of the relative configuration of compounds 3: Next, we sought to examine whether and the extent to which the catalysts control the configuration at all three stereogenic centers, formed in the conjugate addition reaction. Mechanistically, the stereochemistry at C(2) and C(3) is installed during the C–C bond formation step I, when the enamine, derived from the aldehyde and the catalyst, reacts with the nitroolefin (Scheme 3). The resulting nitronate, which is thought to be stabilized by coordination to the carboxylic acid moiety of the catalyst,[6,19] is then subsequently protonated (step II), which sets the absolute configuration of the third stereogenic center (C(4)). We expected that the geometry of the C–C bond formation step would be similar to that of our previously examined addition reactions between aldehydes and β-monosubstituted nitroolefins and therefore assumed a relative *syn* configuration at C(2) and C(3). The diastereoselectivity at C(4) is less obvious because it could either be controlled by the catalyst or the already formed stereogenic centers at C(2) and C(3). To analyze the extent to which the peptidic catalysts control the stereochemistry at each of the stereogenic centers, butanal and nitroolefin **2b** were also allowed to react in the presence of achiral pyrrolidine. In addition, proline was used as a catalyst to determine the effect of the additional two residues within the tripeptide. These experiments allowed for the formation of all four diastereoisomers, albeit a major side product or even the main product was in both cases the product of homo-aldol reactions.[20] In the presence of pyrrolidine the four diastereoisomers were formed in a ratio of 22:18:40:20, the ratio was 32:16:36:16 when proline was used. Thus, the distribution of the four diastereoisomers differs significantly from those observed with the tripeptides (Table 3). For example, the third most abundant diastereoisomer formed in the presence of the tripeptides is the major isomer formed in the presence of both proline and pyrrolidine. These results demonstrated immediately that the tripeptides control and overwrite the intrinsically preferred relative configuration of the γ-nitroaldehydes.[21] These reactions also allowed for isolating the four diastereoisomers in sufficient quantities to analyze their relative configurations by NMR spectroscopy. This was achieved after converting the diastereomeric γ-nitroaldehydes to the *N*-tosylated pyrrolidines **4** (Scheme 4). They were obtained in two steps by reductive amination by using palladium hydroxide on activated charcoal in a hydrogen atmosphere (4.5 bar) followed by tosylation of the resulting pyrrolidines. Analysis of the coupling constants and the NOEs observed in one- and two-dimensional NMR spectra allowed for the unambiguous determination of the relative configuration of the diastereoisomers of three of the four pyrrolidines **4** and thereby also those of the γ-nitroaldehydes (see the Supporting Information for details). The analysis revealed that the relative configuration of the major diastereoisomer **A** formed in the peptide-catalyzed reaction has the *rel*-(2*R*,3*S*,4*R*)-configuration (**A**, Table 3; for the determination of the absolute configuration see below).[22] Thus, as expected from the related reactions with β-monosubstituted nitro-



Scheme 3. Putative catalytic cycle of the peptide-catalyzed conjugate addition reaction of aldehydes to α,β-disubstituted nitroolefins. The two stereogenic centers at C(2) and C(3) are formed in the conjugate addition step I, whereas the center at C(4) is formed in a subsequent protonation of the intermediate nitronate (step II).

Table 3. Ratio of the diastereoisomers of γ-nitroaldehyde **3** formed in the presence of different secondary amines.

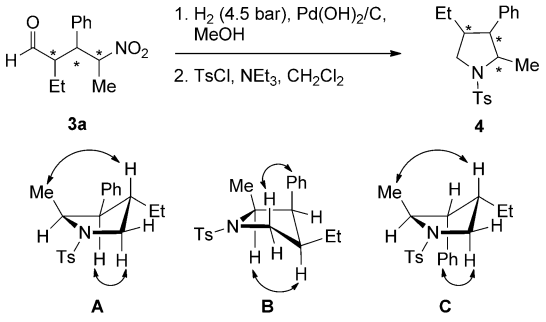


A B C D

rel-(2*R*,3*S*,4*R*) *rel*-(2*R*,3*R*,4*S*) *rel*-(2*R*,3*S*,4*S*) *rel*-(2*R*,3*R*,4*R*)

Entry	Catalyst	**A**[a]	**B**	**C**	**D**
1	pyrrolidine	22	18	40	20
2	proline	32	16	36	16
3	H-Pro-Pro-D-Gln-OH **(1i)**	84	10	5	1
4	H-Pro-Pro-Asn-OH **(1n)**	82	12	4	2

[a] Diastereoisomer A was obtained with 31% *ee* (proline) and 99% *ee* (peptidic catalysts **1i** and **1n**).



Scheme 4. Conversion of the isolated individual diastereoisomers of reaction product **3a** to the corresponding *N*-tosylated pyrrolidines **4** (top). Observed strong long range NOEs within the three analyzed diastereoisomers **A**–**C** (bottom).

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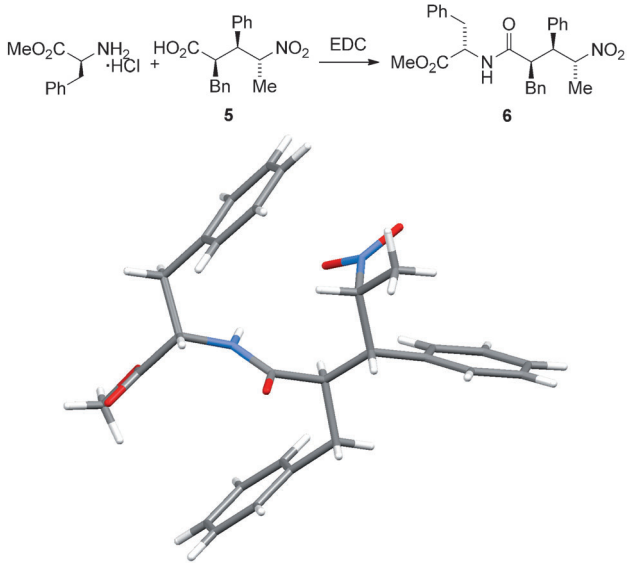
olefins, the major diastereoisomer has a *syn* relative configuration with respect to the stereogenic centers C(2) and C(3). The second most abundant diastereoisomer has the *rel*-(2*R*,3*R*,4*S*)-configuration (**B**), with an *anti* relative configuration at C(2) and C(3). The least abundant diastereoisomers **C** (*rel*-(2*R*,3*S*,4*S*)) and **D** (*rel*-(2*R*,3*R*,4*R*)) are the epimers of **A** and **B**, respectively, with opposite absolute configurations at C(4), the carbon atom bearing the nitro group that is installed in the protonation of the nitronate. These epimers form in significantly different ratios (**A**/**C** and **B**/**D**) in the peptide-catalyzed reactions, whereas they are either identical or have a reversed preference in the reactions performed in the presence of pyrrolidine and proline (Table 3). This demonstrates that the protonation step is controlled by the peptidic catalysts and not by the stereochemistry at C(2) and C(3). The higher abundance of **B** compared to **C** in the peptide-catalyzed reactions indicates that the protonation of the nitronate is even more stereoselective than the C–C bond formation.

Determination of the absolute configuration of the main conjugate addition product: To determine the absolute configuration of the major diastereoisomer formed in the peptide-catalyzed reaction, γ-nitrocarboxylic acid **5**, derived from oxidation of γ-nitroaldehyde **3b** (see below), was coupled to the methyl ester of L-phenylalanine (Scheme 5). The

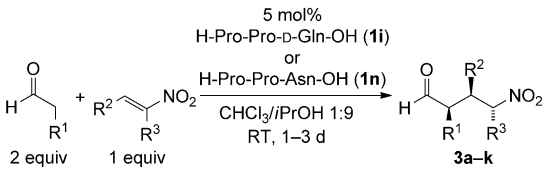


Scheme 5. Determination of the absolute configuration of the major isomer of the γ-nitroaldehyde by synthesis (top) and crystal structure analysis of dipeptide **6** (bottom).

resulting protected dipeptide **6** is a crystalline solid and crystals suitable for X-ray crystal structural analysis were obtained. The main stereoisomer of the γ-nitroaldehyde **3b** produced in the reaction between 3-phenylpropanal and β-methyl-β-nitrostyrene was thereby unambiguously assigned to be of the (2*R*,3*S*,4*R*) configuration. This is in agreement with the relative *syn*,*anti* configuration determined above for the major diastereoisomer. The stereochemical preference of the reaction is therefore analogous to that observed in the peptide-catalyzed conjugate addition reactions between aldehydes and β-monosubstituted nitroolefins demonstrating the similarity of the transition states.

Substrate scope: To probe the substrate scope of the peptide-catalyzed conjugate addition reactions different combinations of aldehydes and α,β-disubstituted nitroolefins were allowed to react in the presence of 5 mol% of the two optimal catalysts H-Pro-Pro-D-Gln-OH (**1i**) and H-Pro-Pro-Asn-OH (**1n**) (Table 4). To facilitate the isolation of diastereomerically pure samples and to prevent epimerization at

Table 4. Scope of 1,4-addition reactions of aldehydes to α,β-disubstituted nitroolefins.[a]



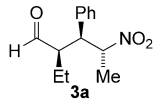
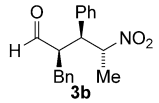
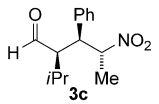
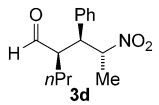
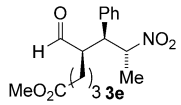
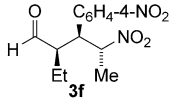
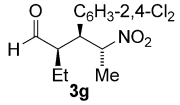
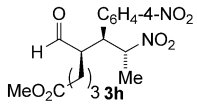
	Product	Catalyst	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	 **3a**	**1i**	81	84:10:5:1	99
		1n	88	82:12:4:2	99
2	 **3b**	**1i**	65	87:8:4:1	99
		1n	74	87:7:3:3	99
3[f]	 **3c**	**1i**	73	83:10:6:1	99
		1n	72	83:9:7:1	99
4[f]	 **3d**	**1i**	87	77:15:6:2	97
		1n	89	85:11:3:1	99
5	 **3e**	**1i**	98	74:18:6:2	98
		1n	90	72:19:6:3	99
6	 **3f**	**1i**	77	75:13:9:3	99
		1n	75	71:17:8:4	99
7	 **3g**	**1i**	81	86:7:6:1	99
		1n	73	86:7:5:2	98
8	 **3h**	**1i**	59	65:20:10:5	94
		1n	61	54:29:10:7	92

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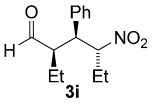
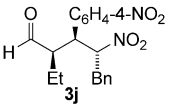
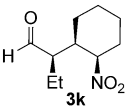
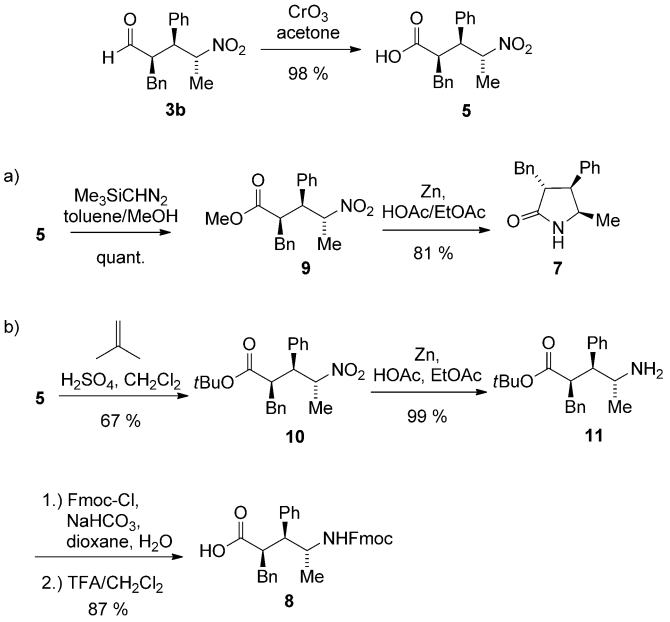
Table 4. (Continued)

	Product	Catalyst	Yield [%][b]	d.r.[c]	*ee* [%][d]
9[f]	 **3i**	**1i**	71	71:26(overlap):3	98
		1n	80	66:30(overlap):4	97
10	 **3j**	**1i**	66	61:29:7:3	98
		1n	66	58:31:7:4	98
11	 **3k**	**1i**	74	79:9:8:4	99
		1n	72	72:14:8:6	99

[a] Reactions were typically carried out with the TFA salt of the peptide and the equivalent amount of NMM. The same results were obtained with the "desalted" peptide without NMM. [b] Yields correspond to γ-nitroaldehydes isolated as a mixture of diastereoisomers. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis of the isolated major diastereoisomers of the corresponding δ-nitroalcohols obtained after $NaBH_4$ reduction. [e] The enantiomeric excess was determined at the level of the γ-nitroaldehyde. [f] Reaction times of 4–5 d were necessary.

C(2), the resulting γ-nitroaldehydes were isolated from the catalysis reaction and then reduced to the corresponding δ-nitroalcohols by using $NaBH_4$. In all cases diastereomerically pure samples of the major diastereoisomers were obtained by column chromatography or semi preparative HPLC. In general, both catalysts performed similarly well in all of the reactions examined. Variations in the aldehyde (Table 4, entries 1–5) as well as in the nitroolefin (Table 4, entries 6–11) are well tolerated. The products were obtained with at least one of the two catalysts in yields of generally >70%. The excess of the main diastereoisomer was typically >70% and the major stereoisomer was often obtained in perfect enantioselectivity. Aldehydes with sterically more demanding moieties in the β-position required longer reaction times but provided the addition products also in good yields and very good stereoselectivities (Table 4, entries 2–4). Also an aldehyde bearing an ester moiety reacted readily with the nitroolefins (Table 4, entries 5 and 8). Variations at both the α- and the β-position of aromatic nitroolefins are tolerated (Table 4, entries 6–10) and provided the products in very good stereoselectivities. Only α,β-disubstituted nitroolefins bearing aromatic substituents in both positions proved to be too unreactive to allow for product formation.[23] In addition, also the cyclic, aliphatic nitrocyclohexene was successfully converted to the conjugate addition product (Table 4, entry 11) in good yields and stereoselectivities. These results demonstrate that the peptides **1i** and **1n** are very good catalysts for conjugate addition reactions of a broad range of different aldehydes and α,β-disubstituted nitroolefins.

Synthesis of γ-butyrolactams and γ-amino acids: As demonstrated above, the obtained fully substituted γ-nitroaldehydes can be easily converted to chiral pyrrolidines with three consecutive stereogenic centers. Equally as versatile for medicinal chemistry as well as research on foldamers are chiral fully substituted γ-butyrolactams and γ-amino acids.[24–26] The syntheses of chiral γ-amino acids rely mostly on either chiral resolution or the use of chiral auxiliaries.[27] Direct catalytic enantioselective methods furnishing these building blocks are therefore highly desirable. γ-Nitroaldehyde **3b** was chosen as a model compound for the synthesis of γ-butyrolactams and γ-amino acids because it is a crystalline solid that was obtained in diastereomerically and enantiomerically pure form by a simple precipitation from pentane. The synthesis of the γ-butyrolactam **7** and the γ-amino acid **8** proved to be straightforward (Scheme 6). Jones oxidation of γ-nitroaldehyde **3b** provided the γ-nitrocarboxylic acid **5** in a yield of 98%. Carboxylic acid **5** served then as the common precursor en route to both, the fully substituted γ-butyrolactam **7** as well as the trisubstituted γ-amino acid **8**. Lactam **7** was easily prepared through methyl ester **9** followed by reduction of the nitro group by using zinc in an acidic environment. Under these conditions the intermediate γ-amino ester cyclizes spontaneously to form lactam **7**. Use of the bulkier *tert*-butyl ester **10** instead of the methyl ester prevents, upon reduction of the nitro group, spontaneous cyclization and the open-chain γ-amino ester **11** is isolated in nearly quantitative yield. The corresponding Fmoc-protected γ-amino acid building block **8** ready for standard solid-phase peptide synthesis is then obtained straightfor-



Scheme 6. Synthesis of the fully substituted lactam **7** and the Fmoc-protected γ-amino acid **8** from γ-nitroaldehyde **3b** (Ac = acyl).

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wardly through Fmoc protection and deprotection of the *tert*-butyl ester.

Conclusion

In conclusion, we have introduced the tripeptides H-Pro-Pro-D-Gln-OH (**1i**) and H-Pro-Pro-Asn-OH (**1n**) as effective catalysts for conjugate addition reactions of aldehydes to α,β-disubstituted nitroolefins. In the presence of 5 mol% of either **1i** or **1n** synthetically useful γ-nitroaldehydes bearing three consecutive stereogenic centers were obtained in good to excellent yields, diastereoselectivities, and enantiomeric excesses. Chiral pyrrolidines, γ-butyrolactams bearing three consecutive stereogenic centers, and fully substituted γ-amino acids are easily accessible in good yields from the γ-nitroaldehydes. The research also highlights the versatility of peptidic catalysts of the general type Pro-Pro-Xaa (Xaa = acidic amino acid) to accommodate different structural as well as electronic properties within the substrates. The distinctly different geometric and electronic properties of α,β-disubstituted nitroolefins compared to β-monosubstituted nitroolefins require a distinctly different catalyst to allow for efficient reactions of these significantly less reactive electrophiles. The modular nature of peptides of the type Pro-Pro-Xaa allowed to solve this challenge by the testing of a small collection of different yet closely related peptides that are synthetically easily accessible. The versatility of the peptidic catalysts is further highlighted by the high chemoselectivity of **1i** and **1n** for conjugate addition reactions over homoaldol reactions. Thus, peptides of the type Pro-Pro-Xaa are powerful tools for the fine-tuning of the catalyst structure to adapt to different substrate combinations and favor desired reaction pathways.

Experimental Section

General aspects and materials: Materials and reagents were of the highest commercially available grade and used without further purification. Reactions were monitored by thin layer chromatography by using Merck silica gel 60 F254 plates. Compounds were visualized by UV and $KMnO_4$. Flash chromatography was performed by using Merck silica gel 60, particle size 40–63 μm. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX 400 (400 MHz) or Bruker BZH NMR (250 MHz) spectrometers. Chemical shifts are reported in ppm by using TMS or the residual solvent peak as a reference. HPLC analyses were performed on an analytical HPLC with a diode array detector from Shimadzu. Bruker Esquire 3000 Plus was used for ESI mass spectrometry. For the synthesis of peptide catalysts **1** and non-commercially available α,β-disubstituted nitroolefins **2** see the Supporting Information.

General procedure for the conjugate addition reactions: To a solution of the peptide (as the TFA salt, 22.0 μmol, 5 mol%), NMM (22 μmol, 5 mol%), and the aldehyde (880 μmol, 2 equiv) in *i*PrOH and $CHCl_3$ (9:1, 1 mL) the nitroolefin (440 μmol, 1 equiv) was added. The resulting solution was agitated at room temperature. After consumption of the nitroolefin all volatile components were removed at reduced pressure and the resulting crude product was purified by flash column chromatography on silica gel by eluting with a mixture of pentanes and EtOAc to yield γ-nitroaldehydes **3**.

General procedure for the reduction of γ-nitroaldehydes 3: The isolated γ-nitroaldehyde (220 μmol, 1 equiv) was dissolved in MeOH (1 mL). The resulting solution was cooled to 0°C and $NaBH_4$ (220 μmol, 1 equiv) was added in one portion. The reaction mixture was stirred at 0°C. After consumption of the γ-nitroaldehyde the reaction was quenched by the addition of HOAc (220 μmol, 1 equiv). All volatiles were removed at reduced pressure and the resulting residue was purified by flash column chromatography on silica gel by eluting with a mixture of pentane and EtOAc. All δ-nitroalcohols were obtained in yields above 85%. Diastereomerically pure samples were either obtained after flash column chromatography on silica gel or by semi preparative HPLC by using a LichroCart 250-4 HPLC-Cartridge (LiChrospher Si 60 5 μm).

(2*R*,3*S*,4*R*)-2-Ethyl-4-nitro-3-phenylpentanal (3a): Colorless oil; ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 9.83$ (d, $J = 1.8$ Hz, 1H), 7.35–7.24 (m, 3H), 7.05–6.99 (m, 2H), 5.06–4.97 (m, 1H), 3.39 (dd, $J = 10.0$, 5.3 Hz, 1H), 3.15 (ddt, $J = 10.0$, 3.4, 1.8 Hz, 1H), 1.39 (d, $J = 6.6$ Hz, 3H), 1.58–1.47 (m, 1H), 1.46–1.25 (m, 1H), 0.75 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta = 203.9$, 134.9, 128.9, 128.7, 128.2, 83.5, 52.8, 48.3, 20.5, 17.4, 10.1 ppm; elemental analysis calcd (%) for $C_{13}H_{17}NO_3$: C 66.36, H 7.19, N 5.75; found: C 66.33, H 7.28, N 5.79; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 99:1, 25°C) at 0.5 mL min^{-1}, UV detection at $\lambda = 210$ nm: t_R(minor) = 25.0, (major) = 28.2 min.

(2*R*,3*S*,4*R*)-2-Benzyl-4-nitro-3-phenylpentanal (3b): Colorless solid; ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 9.81$ (d, $J = 1.5$ Hz, 1H), 7.38–7.29 (m, 3H), 7.24–7.14 (m, 3H), 7.11–7.07 (m, 2H), 6.96 (d, $J = 6.8$ Hz, 2H), 5.03 (dq, $J = 6.7$, 5.4 Hz, 1H), 3.54 (ddt, $J = 9.9$, 4.0, 1.5 Hz, 1H), 3.38 (dd, $J = 9.9$, 5.4 Hz, 1H), 2.73 (dd, $J = 14.1$, 4.0 Hz, 1H), 2.60 (dd, $J = 14.1$, 9.9 Hz, 1H), 1.38 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta = 204.4$, 137.1, 134.8, 129.0, 128.9, 128.9, 128.7, 128.4, 126.8, 83.0, 53.4, 49.5, 35.2, 17.3 ppm.

(2*R*,3*S*,4*R*)-2-Benzyl-4-nitro-3-phenylpentan-1-ol: Colorless solid; ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 7.36$–7.14 (m, 8H), 7.08–7.03 (m, 2H), 5.24 (dq, $J = 7.8$, 6.6 Hz, 1H), 3.75 (dd, $J = 11.0$, 3.7 Hz, 1H), 3.49 (dd, $J = 7.8$, 7.1 Hz, 1H), 3.35 (dd, $J = 11.0$, 6.6 Hz, 1H), 2.59 (dd, $J = 13.6$, 3.2 Hz, 1H), 2.43–2.35 (m, 1H), 2.26 (dd, $J = 13.6$, 11.0 Hz, 1H), 1.60 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta = 139.7$, 136.2, 129.2, 128.8, 128.6, 128.5, 127.8, 126.3, 84.1, 61.4, 50.4, 42.9, 34.0, 18.2 ppm; elemental analysis calcd (%) for $C_{18}H_{21}NO_3$: C 72.22, H 7.07, N 4.68; found: C 72.21, H 7.14, N 4.53; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 95:5, 25°C) at 0.5 mL min^{-1}, UV detection at $\lambda = 210$ nm: t_R(minor) = 40.2, (major) = 77.6 min.

(2*R*,3*S*,4*R*)-2-Isopropyl-4-nitro-3-phenylpentanal (3c): Colorless solid; ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 10.06$ (d, $J = 0.4$ Hz, 1H), 7.33–7.27 (m, 3H), 7.03–6.97 (m, 2H), 4.96–4.89 (m, 1H), 3.38–3.35 (m, 2H), 1.67–1.58 (m, 1H), 1.28 (d, $J = 6.6$ Hz, 3H), 1.11 (d, $J = 7.2$ Hz, 3H), 0.68 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta =$ 205.4, 134.7, 129.0, 128.7, 128.1, 83.0, 56.6, 47.6, 28.7, 21.8, 17.1, 16.2.

(2*R*,3*S*,4*R*)-2-Isopropyl-4-nitro-3-phenylpentan-1-ol: Colorless solid; ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 7.32$–7.26 (m, 3H), 7.10–7.02 (m, 2H), 5.35 (dq, $J = 6.7$, 4.5 Hz, 1H), 4.11 (dd, $J = 11.4$, 3.7 Hz, 1H), 3.82 (dd, $J = 11.4$, 4.9 Hz, 1H), 3.22 (dd, $J = 10.0$, 4.5 Hz, 1H), 2.15–2.08 (m, 1H), 1.50 (dsept, $J = 6.9$, 2.5 Hz, 1H), 1.44 (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.63 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta = 136.7$, 129.0, 128.5, 127.6, 83.4, 60.4, 51.0, 45.8, 27.5, 22.6, 18.0, 16.7 ppm; elemental analysis calcd (%) for $C_{14}H_{21}NO_3$: C 66.91, H 8.42, N 5.75; found: C 66.95, H 8.25, N 5.39; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 97.5:2.5, 25°C) at 0.5 mL min^{-1}, UV detection at $\lambda =$ 210 nm: t_R(minor) = 41.5, (major) = 52.7 min.

(2*R*,3*S*,4*R*)-4-Nitro-3-phenyl-2-propylpentanal (3d): Colorless oil; ^1H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 9.81$ (d, $J = 1.9$ Hz, 1H), 7.36–7.24 (m, 3H), 7.11–6.99 (m, 2H), 5.01 (quint, $J = 6.6$ Hz, 1H), 3.39 (dd, $J = 9.6$, 5.8 Hz, 1H), 3.16–3.08 (m, 1H), 1.40 (d, $J = 6.6$ Hz, 3H), 1.38–1.05 (m, 4H), 0.75 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta = 204.1$, 135.0, 128.8, 128.7, 128.2, 83.6, 51.7, 49.0, 29.9, 19.4, 17.4, 14.1 ppm.

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(2*R*,3*S*,4*R*)-4-Nitro-3-phenyl-2-propylpentan-1-ol: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.17 (m, 3H), 7.17–7.12 (m, 2H), 5.19 (dq, J = 9.2, 6.6 Hz, 1H), 3.79 (dd, J = 10.9, 3.7 Hz, 1H), 3.49–3.43 (m, 1H), 3.31 (dd, J = 10.9, 7.7 Hz, 1H), 2.08–1.99 (m, 1H), 1.58 (d, J = 6.6 Hz, 3H), 1.43–1.31 (m, 1H), 1.26–1.13 (m, 2H), 1.10–0.97 (m, 1H), 0.85 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 136.4, 129.1, 128.4, 127.6, 85.0, 62.5, 50.3, 40.6, 29.2, 20.9, 18.3, 14.3 ppm; elemental analysis calcd (%) for $C_{14}H_{21}NO_3$: C 66.91, H 8.42, N 5.75; found: C 66.64, H 8.22, N 5.66; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 97.5:2.5, 25 °C) at 0.5 mL min^{-1}, UV detection at λ = 210 nm: t_R(major) = 61.5, (minor) = 64.8 min.

(5*R*,6*S*,7*R*)-Methyl 5-formyl-7-nitro-6-phenyloctanoate (3e): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.84 (d, J = 1.8 Hz, 1H), 7.36–7.23 (m, 3H), 7.06–6.99 (m, 2H), 5.01 (dq, J = 6.7, 5.8 Hz, 1H), 3.57 (s, 3H), 3.42 (dd, J = 9.6, 5.8 Hz, 1H), 3.19–3.11 (m, 1H), 2.17–2.10 (m, 2H), 1.61–1.37 (m, 4H), 1.42 ppm (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.5, 173.2, 134.8, 128.9, 128.9, 128.4, 83.7, 51.7, 51.7, 48.9, 33.7, 26.9, 21.5, 17.5 ppm.

(5*R*,6*S*,7*R*)-Methyl 5-(hydroxymethyl)-7-nitro-6-phenyloctanoate: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.42–7.05 (m, 5H), 5.28–5.14 (m, 1H), 3.87 (dd, J = 11.1, 3.7 Hz, 1H), 3.64 (s, 3H), 3.48 (dd, J = 11.1, 6.7 Hz, 1H), 3.40 (t, J = 7.4 Hz, 1H), 2.29–2.21 (m, 2H), 2.16–2.00 (m, 1H), 1.78–1.62 (m, 1H), 1.56 (d, J = 6.6 Hz, 3H), 1.56–1.46 (m, 1H), 1.34–1.19 (m, 1H), 1.19–1.02 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.1, 136.4, 129.2, 128.5, 127.8, 84.5, 62.1, 51.7, 50.5, 40.8, 33.9, 27.0, 22.8, 18.3 ppm; elemental analysis calcd (%) for $C_{16}H_{23}NO_5$: C 62.12, H 7.49, N 4.53; found: C 61.88, H 7.79, N 4.66; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 92.5:7.5, 25 °C) at 0.5 mL min^{-1}, UV detection at λ = 210 nm: t_R(minor) = 45.6, (major) = 49.1 min.

(2*R*,3*S*,4*R*)-2-Ethyl-4-nitro-3-(4-nitrophenyl)pentanal (3f): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.86 (d, J = 1.4 Hz, 1H), 8.22–8.18 (m, 2H), 7.29–7.23 (m, 2H), 5.09 (dq, J = 6.7, 5.4 Hz, 1H), 3.56 (dd, J = 10.0, 5.4 Hz, 1H), 3.21 (dddd, J = 10.0, 8.5, 3.4, 1.4 Hz, 1H), 1.64–1.52 (m, 1H), 1.40–1.32 (m, 2H), 1.42 (d, J = 6.7 Hz, 3H), 0.78 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.8, 142.6, 130.2, 130.1, 124.0, 83.2, 52.5, 48.0, 20.6, 17.6, 10.1 ppm.

(2*R*,3*S*,4*R*)-2-Ethyl-4-nitro-3-(4-nitrophenyl)pentan-1-ol: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.16 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 5.23 (dq, J = 8.8, 6.6 Hz, 1H), 3.90 (dd, J = 10.8, 3.9 Hz, 1H), 3.67 (dd, J = 8.8, 6.0 Hz, 1H), 3.26 (dd, J = 10.8, 8.1 Hz, 1H), 2.08–1.96 (m, 1H), 1.62 (d, J = 6.6 Hz, 3H), 1.38–1.22 (m, 1H), 1.07–0.94 (m, 1H), 0.91 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 147.5, 144.5, 130.3, 123.6, 84.6, 61.5, 49.9, 42.8, 20.2, 18.5, 12.4 ppm; elemental analysis calcd (%) for $C_{13}H_{18}N_2O_5$: C 55.31, H 6.43, N 9.92; found: C 55.19, H 6.66, N 9.70; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 92.5:7.5, 25 °C) at 0.5 mL min^{-1}, UV detection at λ = 210 nm: t_R(minor) = 50.9, (major) = 52.9 min.

(2*R*,3*S*,4*R*)-3-(2,4-Dichlorophenyl)-2-ethyl-4-nitropentanal (3g): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.88 (d, J = 1.5 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 8.5, 2.2 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 5.15–5.04 (m, 1H), 4.15 (dd, J = 10.6, 4.8 Hz, 1H), 3.26–3.14 (m, 1H), 1.59–1.49 (m, 1H), 1.40 (d, J = 6.7 Hz, 3H), 1.38–1.30 (m, 1H), 0.76 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.9, 136.3, 134.7, 132.0, 130.0, 127.9, 83.3, 52.9, 42.2, 20.7, 16.7, 9.9 ppm.

(2*R*,3*S*,4*R*)-3-(2,4-Dichlorophenyl)-2-ethyl-4-nitropentan-1-ol: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.43 (d, J = 2.2 Hz, 1H), 7.21 (dd, J = 8.5, 2.2 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 5.20 (p, J = 6.7 Hz, 1H), 4.06–3.94 (m, 2H), 3.70 (dd, J = 11.5, 5.0 Hz, 1H), 1.98 (ddt, J = 12.7, 8.6, 4.3 Hz, 1H), 1.52 (d, J = 6.7 Hz, 3H), 1.22–1.09 (m, 2H), 0.86 ppm (t, J = 7.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 136.5, 134.0, 133.9, 129.8, 127.6, 84.0, 61.6, 45.4, 43.4, 21.3, 17.7, 12.0 ppm; elemental analysis calcd (%) for $C_{13}H_{17}NCl_2O_3$: C 51.00, H 5.60, N 4.57; found: C 51.04, H 5.79, N 4.55; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 97.5:2.5, 25 °C) at 0.5 mL min^{-1}, UV detection at λ = 210 nm: t_R(minor) = 32.0, (major) = 38.3 min.

(5*R*,6*S*,7*R*)-Methyl 5-formyl-7-nitro-6-(4-nitrophenyl)octanoate (3h): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.87 (d, J = 1.4 Hz, 1H), 8.22–8.17 (m, 2H), 7.28–7.23 (m, 2H), 5.12–5.04 (m, 1H), 3.69–3.64 (m, 1H), 3.58 (s, 3H), 3.25–3.17 (m, 1H), 2.20–2.13 (m, 2H), 1.59–1.32 (m, 4H), 1.44 ppm (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.4, 173.0, 147.9, 142.4, 130.1, 124.1, 83.3, 51.8, 51.4, 48.4, 33.5, 26.9, 21.3, 17.6 ppm.

(5*R*,6*S*,7*R*)-Methyl 5-(hydroxymethyl)-7-nitro-6-(4-nitrophenyl)octanoate: Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.19–8.12 (m, 2H), 7.38–7.31 (m, 2H), 5.22 (dq, J = 8.2, 6.6 Hz, 1H), 3.91 (dd, J = 11.0, 3.9 Hz, 1H), 3.64 (s, 1H), 3.61 (dd, J = 8.2, 6.6 Hz, 1H), 3.38 (dd, J = 11.0, 7.2 Hz, 1H), 2.29–2.22 (m, 2H), 2.17–2.07 (m, 1H), 1.75–1.62 (m, 1H), 1.59 (d, J = 6.6 Hz, 3H), 1.57–1.44 (m, 1H), 1.28–1.15 (m, 1H), 1.11–0.97 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.9, 147.6, 144.3, 130.3, 123.6, 84.2, 61.6, 51.8, 50.0, 40.8, 33.7, 27.0, 22.7, 18.4 ppm; elemental analysis calcd (%) for $C_{13}H_{17}NCl_2O_3$: C 55.73, H 6.05, N 7.65; found: C 56.00, H 6.32, N 7.30; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 90:10, 25 °C) at 0.5 mL min^{-1}, UV detection at λ = 210 nm: t_R-(minor) = 43.9, (major) = 52.9 min.

(2*R*,3*S*,4*R*)-2-Ethyl-4-nitro-3-phenylhexanal (3i): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.81 (d, J = 1.8 Hz, 1H), 7.35–7.27 (m, 3H), 7.07–7.00 (m, 2H), 4.83 (ddd, J = 10.1, 5.9, 4.3 Hz, 1H), 3.49 (dd, J = 9.7, 5.9 Hz, 1H), 3.08–2.98 (m, 1H), 1.84–1.74 (m, 1H), 1.74–1.64 (m, 1H), 1.58–1.47 (m, 1H), 1.47–1.34 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H), 0.76 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 203.8, 135.2, 129.0, 128.7, 128.2, 90.8, 53.0, 47.4, 25.1, 20.5, 10.6, 10.3 ppm.

(2*R*,3*S*,4*R*)-2-Ethyl-4-nitro-3-phenylhexan-1-ol: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.34–7.25 (m, 3H), 7.20–7.14 (m, 2H), 5.04 (td, J = 8.8, 5.5 Hz, 1H), 3.83 (dd, J = 10.9, 3.8 Hz, 1H), 3.55 (dd, J = 9.3, 5.8 Hz, 1H), 3.35 (dd, J = 10.9, 7.7 Hz, 1H), 2.01–1.88 (m, 3H), 1.37 (dqd, J = 14.9, 7.5, 2.9 Hz, 1H), 1.13–1.05 (m, 1H), 1.02 (t, J = 7.3 Hz, 3H), 0.91 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 136.5, 129.2, 128.3, 127.6, 91.8, 62.0, 49.2, 42.8, 25.4, 19.9, 12.4, 10.3 ppm; elemental analysis calcd (%) for $C_{14}H_{21}NO_2$: C 66.91, H 8.42, N 5.57; found: C 66.74, H 8.19, N 5.42; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 95:5, 25 °C) at 0.5 mL min^{-1}, UV detection at λ = 210 nm: t_R(minor) = 22.5, (major) = 26.3 min.

(2*R*,3*S*,4*R*)-2-Ethyl-4-nitro-3-(4-nitrophenyl)-5-phenylpentanal (3j): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.87 (d, J = 1.2 Hz, 1H), 8.26–8.20 (m, 2H), 7.35–7.21 (m, 5H), 7.15–7.09 (m, 2H), 5.31 (dt, J = 9.7, 5.0 Hz, 1H), 3.69 (dd, J = 10.4, 5.0 Hz, 1H), 3.26–3.18 (m, 1H), 3.00 (dd, J = 14.6, 9.7 Hz, 1H), 2.93 (dd, J = 14.6, 5.0 Hz, 1H), 1.60 (ddd, J = 14.7, 7.5, 3.4 Hz, 1H), 1.41–1.29 (m, 1H), 0.76 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.7, 148.1, 142.4, 135.0, 130.3, 129.1, 128.9, 127.7, 124.0, 89.1, 52.3, 46.7, 37.7, 20.7, 9.8 ppm.

(2*R*,3*S*,4*R*)-2-Ethyl-4-nitro-3-(4-nitrophenyl)-5-phenylpentan-1-ol: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.24–8.09 (m, 2H), 7.44–7.35 (m, 2H), 7.35–7.22 (m, 3H), 7.22–7.11 (m, 2H), 5.39 (ddd, J = 9.8, 8.2, 4.5 Hz, 1H), 3.97 (dd, J = 10.8, 3.8 Hz, 1H), 3.77 (dd, J = 8.2, 6.9 Hz, 1H), 3.35 (dd, J = 10.8, 7.3 Hz, 1H), 3.22 (dd, J = 14.5, 4.4 Hz, 1H), 3.14 (dd, J = 14.5, 9.9 Hz, 1H), 2.18–2.06 (m, 1H), 1.44–1.27 (m, 1H), 1.17–0.98 (m, 1H), 0.91 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 147.6, 144.2, 135.3, 130.4, 129.1, 128.9, 127.8, 123.6, 90.9, 61.4, 49.4, 42.9, 38.5, 20.6, 12.4 ppm; elemental analysis calcd (%) for $C_{19}H_{22}N_2O_5$: C 63.68, H 6.19, N 7.82; found: C 63.41, H 6.36, N 7.47; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 90:10, 25 °C) at 0.5 mL min^{-1}, UV detection at λ = 210 nm: t_R(minor) = 36.4, (major) = 40.3 min.

(*R*)-2-((1*R*,2*R*)-2-Nitrocyclohexyl)butanal (3k): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.68 (d, J = 1.6 Hz, 1H), 4.87 (q, J = 3.4 Hz, 1H), 2.50 (dddd, J = 9.7, 8.0, 3.7, 1.6 Hz, 1H), 2.32–2.23 (m, 1H), 2.17–2.06 (m, 1H), 1.92–1.52 (m, 7H), 1.44–1.16 (m, 2H), 0.84 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.6, 83.5, 53.1, 37.3, 29.6, 25.0, 23.2, 20.1, 19.3, 9.9 ppm.

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(*R*)-2-((1*R*,2*R*)-2-nitrocyclohexyl)butan-1-ol: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.00–4.92 (m, 1H), 3.68 (dd, J = 11.2, 3.8 Hz, 1H), 3.64 (dd, J = 11.2, 4.3 Hz, 1H), 2.35–2.25 (m, 1H), 1.93–1.00 (m, 11H), 0.87 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 84.4, 61.6, 43.0, 40.3, 31.0, 25.4, 23.5, 20.8, 20.3, 11.4 ppm; elemental analysis calcd (%) for $C_{10}H_{19}NO_3$: C 59.68, H 9.51, N 6.96; found: C 59.58, H 9.41, N 6.81; the enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 94:6, 25 °C) at 0.5 mL min^{-1}, UV detection at λ = 210 nm: t_R(minor) = 18.7, (major) = 20.8 min.

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[20] The ratios between the products of conjugate addition reactions and homo-aldol reactions are approximately 1:1 in the case of proline and 7:1 in the presence of peptides **1i** and **1n**.

[21] When a diastereomerically pure sample of (2*R*,3*S*,4*R*)-2-benzyl-4-nitro-3-phenylpentan-1-ol, the δ-nitroalcohol derived from conjugate addition product **3b**, was dissolved in $CDCl_3$ (66.8 mM) and stirred in the presence of 1.2 equivalents of NEt_3 epimerization at the carbon atom bearing the nitro group was observed. At equilibrium, a ratio of 1:2.4 in favor of the newly formed epimer was obtained, which is comparable to the ratio of the epimers formed in the presence of pyrrolidine.

[22] Interestingly, this is the same main stereoisomer that was obtained by Seebach and co-workers in the conjugate addition reaction between titanium enolates of chiral acyloxazolidinones and nitroolefin **2b** followed by diastereoselective protonation: M. Brenner, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 2365–2379.

[23] This low reactivity is presumably due to a close to 90° angle between the two aromatic moieties resulting in a significant steric hindrance and thereby preventing conversion of these substrates.

[24] For a review on γ-aminobutyric acid (GABA) analogues, see: K. Gajcy, S. Lochynski, T. Librowski, *Curr. Med. Chem.* **2010**, *17*, 2338–2347.

[25] For reviews, see: a) D. Seebach, D. F. Hook, A. Glättli, *Biopolymers* **2006**, *84*, 23–37; b) P. G. Vasudev, S. Chatterjee, N. Shamala, P. Balaram, *Chem. Rev.* **2011**, *111*, 657–687; c) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180.

[26] a) D. Seebach, M. Brenner, M. Rueping, B. Schweizer, B. Jaun, *Chem. Commun.* **2001**, 207–208; b) D. Seebach, M. Brenner, M. Rueping, B. Jaun, *Chem. Eur. J.* **2002**, *8*, 573–584.

[27] For an enantioselective catalytic method, see reference [8]; for a review on stereoselective syntheses of γ-amino acids see: M. Ordóñez, C. Cativiela, *Tetrahedron: Asymmetry* **2007**, *18*, 3–99.

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