DOI: 10.1002/chem.200901021

Tripeptides of the Type H-D-Pro-Pro-Xaa-NH_2 as Catalysts for Asymmetric 1,4-Addition Reactions: Structural Requirements for High Catalytic Efficiency

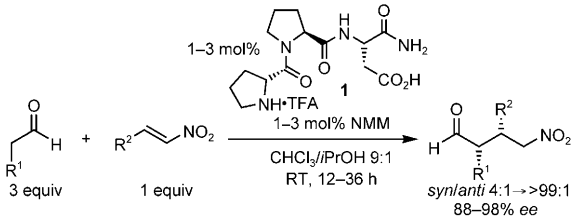
Markus Wiesner,[a] Markus Neuburger,[b] and Helma Wennemers*[a]

Abstract: Analysis of the structural and functional requirements within the asymmetric peptidic catalyst H-D-Pro-Pro-Asp-NH_2 led to the development of the closely related peptide H-D-Pro-Pro-Glu-NH_2 as an even more efficient catalyst for asymmetric conjugate addition reactions of aldehydes to nitroolefins. In the presence of as little as 1 mol% of H-D-Pro-Pro-Glu-NH_2, a broad range of aldehydes and nitroolefins react readily with each other. The resulting γ-nitroaldehydes were obtained in excellent yields and stereoselectivities at room temperature. Within the structure of the peptidic catalysts, the D-Pro-Pro motif is the major contributor to the high stereoselectivities. The C-terminal amide and the spacer to the carboxylic acid in the side-chain of the C-terminal amino acid are responsible for the fine-tuning of the stereoselectivity. The peptidic catalysts not only allow for highly effective asymmetric catalysis under mild conditions, but also function in the absence of additives.

Keywords: asymmetric catalysis · conformation analysis · conjugate addition reactions · peptides · proline

Introduction

Conjugate addition reactions between aldehydes and nitroolefins are among the most useful asymmetric C–C-bond forming reactions.[1] The resulting γ-nitroaldehydes are versatile building blocks for further transformations into, for example, chiral pyrrolidines, γ-butyrolactones, γ-amino acids, or tetrahydropyrans.[1–4] As a result, several research groups focused on the development of efficient catalysts for this asymmetric reaction and explored a range of different primary and secondary amine-based catalysts.[2–7] Recently, our group introduced the peptide H-D-Pro-Pro-Asp-NH_2, **1** as a highly effective catalyst for conjugate addition reactions of aldehydes to β-substituted nitroolefins.[7] In the presence of as little as 1 mol% of the peptidic catalyst **1** a broad range of different aldehydes and β-substituted nitroolefins react readily to provide the γ-nitroaldehydes in excellent yields and stereoselectivities (Scheme 1). In addition, only a small excess of the aldehyde (3 equiv) with respect to the nitroolefin is required. This is in contrast to many of the other amine-based catalysts that typically require the use of high catalyst loadings (10–20 mol%), high excess of the aldehyde (up to 10 equiv), and have often limited substrate scope.[3,5,8]



Scheme 1. Conjugate addition reactions of aldehydes to nitroolefins catalyzed by peptide **1**.

Additional attractive features of peptidic catalysts[9,10] in general are their modular nature; allowing for facile variations of their structural and functional properties as well as the ease of peptide synthesis by standard solid-phase synthesis. With this in mind we decided to investigate the structural and functional requirements necessary for effective catalysis with peptide **1** and at the same time seek an even better

[a] Dr. M. Wiesner, 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

[b] M. Neuburger
Department of Chemistry, University of Basel
Spitalstrasse 51, 4056 Basel (Switzerland)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901021.

catalyst for conjugate addition reactions of aldehydes to β-substituted nitroolefins.

Previous studies had revealed that the D-Pro-Pro motive as a turn-inducing element is important for high catalytic efficiency.[7] In addition, control experiments with N-terminally acetylated and methylated peptides showed the importance of the secondary amine for catalytic activity.[7,11] Inspired by a crystal structure of peptide **1**, we discuss within this manuscript the role of the functional group at the C terminus for effective catalysis. Furthermore, we evaluated the importance of the carboxylic acid as well as the spacer length between the peptidic backbone and the carboxylic acid. Finally we explored whether additives (acids or bases) that are known to affect the reactivity and stereoselectivity of many secondary amine-based catalysts[3,4b,5] also influence the catalytic performance of the peptidic catalysts. The research revealed that the closely related peptide H-D-Pro-Pro-Glu-NH_2, **2**, that had previously been identified as an effective catalyst for asymmetric addition reactions of aldehydes to nitroethylene,[4a] is also best suited for catalyzing conjugate addition reactions of aldehydes to a broad range of β-substituted nitroolefins. Both the catalytic reactivity and stereoselectivity of peptide **2** are even better compared to those of the parent peptide **1**. In addition, the work demonstrates that the peptidic catalysts do not require any additives for effective catalysis.

Results and Discussion

Crystal structure of H-D-Pro-Pro-Asp-NH_2 (1)—is a β-turn conformation important for effective catalysis? Crystal structures can provide important insight into the preferred conformation of catalysts. We were therefore pleased to obtain crystals of peptide **1** that were suitable for X-ray single-crystal structure analysis. In the solid state, peptide **1** adopts a β-turn structure as indicated by a hydrogen bond (H-bond) formed between the D-Pro-Pro amide bond and the C-terminal carboxamide (Figure 1).[12] This conformation is rather compact, suggesting that packing effects within the solid state could favor this β-turn structure.

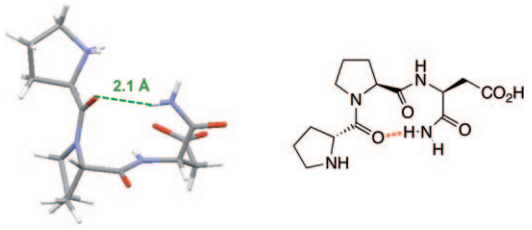


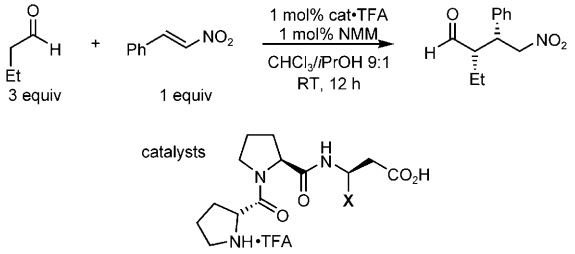
Figure 1. Crystal structure and schematic of H-D-Pro-Pro-Asp-NH_2 (**1**).

To evaluate the importance of the C-terminal amide for the catalytic efficiency of peptide **1** in the solution phase, we prepared closely related peptides that differ in the C-terminal functional groups. Within the structures of peptides H-D-Pro-Pro-β-Ala-OH, **3**, and H-D-Pro-Pro-Asp-OCH_3, **4**, the C-terminal carboxamide is replaced by functional groups (hydrogen and methyl ester, respectively) that are not able to function as H-bond donors (Table 1). Peptides H-D-Pro-Pro-Asp-OH, **5**, and H-D-Pro-Pro-Asp-NHPr (Pr = *n*-propyl), **6** bear carboxylic acid and secondary amide moieties, respectively, in place of the primary carboxamide, and in peptide H-D-Pro-Pro-β-Asp-NH_2, **7**, an additional methylene group is introduced as a spacer to the carboxamide (Table 1). To analyze the catalytic properties of peptides **3**–**7** the conjugate addition reaction between butanal and nitrostyrene served as a test reaction by using conditions that were previously found to be optimal for catalysis.[7] These involve the use of 1 mol% of the peptidic catalyst and 3 equivalents of butanal with respect to nitrostyrene in a mixture of $CHCl_3$/*i*PrOH 9:1.

With all of the peptidic catalysts good to very good conversions and stereoselectivities of the γ-nitroaldehyde (*syn*/*anti* ≥19:1, ≥85% *ee*) were observed (Table 1, entries 2–6). However, none of the peptides performed as well as the parent catalyst H-D-Pro-Pro-Asp-NH_2 (**1**) (*syn*/*anti* 25:1, 95% *ee*, Table 1, entry 1). This demonstrates that peptides that cannot be stabilized by an intramolecular H-bond to form a β turn and lack the stereogenic center of the C-terminal amino acid (as in **3**) are also reasonable asymmetric catalysts. At the same time, the results revealed that both the presence and the position of the C-terminal primary carboxamide are crucial for highly efficient asymmetric catalysis. Thus, the main contribution for the excellent asymmetric induction and catalytic activity of peptide **1** stems from the D-Pro-Pro portion, whereas the C-terminal amide is important for the fine-tuning of the stereoselectivity.

Abstract in German: *Die sorgfältige Analyse der strukturellen und funktionalen Erfordernisse des peptidischen Katalysators H-D-Pro-Pro-Asp-NH_2 führte zur Entwicklung des verwandten Peptids H-D-Pro-Pro-Glu-NH_2, das einen noch effizienteren Katalysator für asymmetrische konjugierte Additionsreaktionen von Aldehyden an Nitroolefine darstellt. In Gegenwart von nur 1 mol% von H-D-Pro-Pro-Glu-NH_2 reagiert eine große Auswahl verschiedenster Aldehyde und Nitroolefine unter milden Bedingungen bereitwillig miteinander. Die entstehenden γ-Nitroaldehyde bilden sich in exzellenten Ausbeuten und Stereoselektivitäten bei Raumtemperatur. Innerhalb der Struktur des peptidischen Katalysators trägt das D-Pro-Pro Motiv am meisten zu den hohen Stereoselektivitäten bei. Das C-terminale Amid und der Linker vom Peptidrückgrat zur Carbonsäure in der Seitenkette der C-terminalen Aminosäure sind für die Feineinstellung der Stereoselektivitäten verantwortlich. Die peptidischen Katalysatoren sind nicht nur höchst effiziente asymmetrische Katalysatoren sondern benötigen im Gegensatz zu vielen anderen chiralen Katalysatoren auch keine Additive für ihre katalytische Effizienz.*

Table 1. Conjugate addition reactions catalyzed by peptides **3–7** differing in the functional group at the C terminus.

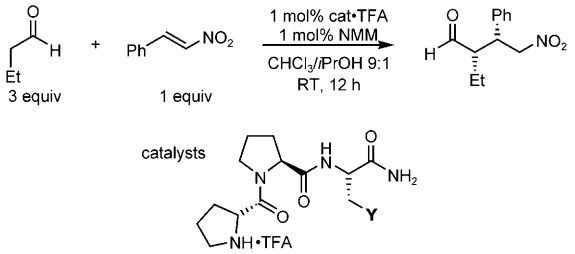


Entry	X	Catalyst	Conv. [%][a]	*syn*/*anti*[a]	*ee* [%][b]
1	$CONH_2$	**1**	95	25:1	95
2	H	**3**	80	26:1	88
3	CO_2CH_3	**4**	95	30:1	89
4	CO_2H	**5**	80	21:1	85
5	CONHPr	**6**	85	23:1	92
6	CH_2CONH_2	**7**	95	19:1	85

[a] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [b] Determined by chiral-phase HPLC analysis.

Importance of functional groups and the spacer length in the side-chain of the C-terminal amino acid: To evaluate the importance of the carboxylic acid within the structure of H-D-Pro-Pro-Asp-NH_2, **1** the analogues H-D-Pro-Pro-Asn-NH_2, **8** and H-D-Pro-Pro-Asp(O*t*Bu)-NH_2, **9** with amide and ester moieties, respectively, in place of the carboxylic acid were prepared. Both peptides proved to be significantly poorer catalysts compared to **1**, both with respect to their catalytic activities and stereoselectivities (Table 2, entries 1–3). Thus, not only the secondary amine but also the carboxylic acid is crucial for effective catalysis. This result suggests that the carboxylic acid plays a crucial role in coordinating and thereby orienting the nitroolefin into a position that allows for the excellent stereochemical induction that is observed for peptidic catalyst **1**.[13]

Table 2. Conjugate addition reactions catalyzed by peptides **1**, **2**, and **8–10** differing in the side-chain of the C-terminal amino acid.



Entry	Y	Catalyst	Conv. [%][a]	*syn*/*anti*[a]	*ee* [%][b]
1	CO_2H	**1**	95	25:1	95
2[c]	$CONH_2$	**8**	44	6:1	72
3[d]	CO_2tBu	**9**	30	8:1	64
4	CH_2CO_2H	**2**	quant.	50:1	97
5	$CH_2CH_2CO_2H$	**10**	quant.	30:1	94
6	$CH_2(CH_2)_2CO_2H$	**11**	95	27:1	92
7	$CH_2(CH_2)_3CO_2H$	**12**	85	24:1	86

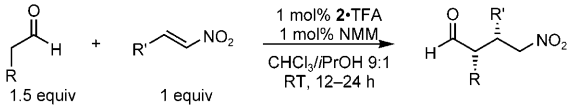
[a] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [b] Determined by chiral-phase HPLC analysis. [c] reaction time was 72 h. [d] reaction time was 36 h.

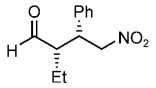
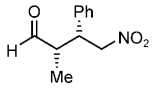
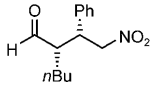
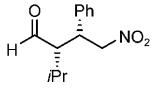
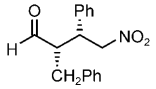
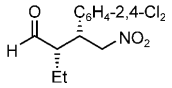
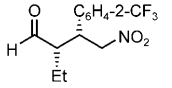
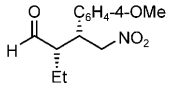
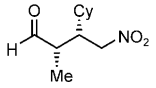
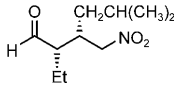
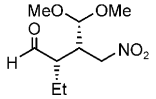
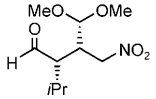
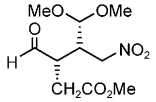
Next we tested the influence of the spacer from the peptidic backbone to the carboxylic acid in the side-chain of the C-terminal amino acid on the catalytic efficiency. Toward this goal we compared H-D-Pro-Pro-Asp-NH_2, **1** with the peptides H-D-Pro-Pro-Glu-NH_2, **2**, H-D-Pro-Pro-Aad-NH_2, **10** (Aad = α-amino adipic acid), H-D-Pro-Pro-Api-NH_2, **11** (Api = α-amino pimelic acid) and H-D-Pro-Pro-Asu-NH_2, **12** (Asu = α-amino suberic acid); these compounds bear up to four additional methylene groups as spacers between the backbone and the carboxylic acid. Remarkably, the glutamic acid analogue **2** with an additional methylene group in the side-chain proved to be an even better catalyst than **1**. The γ-nitroaldehyde was obtained in almost perfect diastereoselectivity (*syn*/*anti* 50:1) and excellent enantioselectivity of 97% ee (Table 2, entry 4). Peptide **10** with one more additional methylene group in the spacer is still a very good catalyst with an efficiency that is comparable to that of the parent peptide **1** (Table 2, entry 5). Even peptides **11** and **12** with more flexible spacers exhibit reasonable catalytic efficiencies (Table 2, entries 6 and 7). These findings demonstrate that a considerable degree of conformational flexibility is tolerated in the side-chain of the C-terminal amino acid. In addition, they further underline that the D-Pro-Pro motif is the major contributor to the high asymmetric induction of peptidic catalysts of the type H-D-Pro-Pro-Xaa-NH_2 in which Xaa is an amino acid with a carboxylic acid in the side-chain.

Substrate scope of peptidic catalyst H-D-Pro-Pro-Glu-NH_2 (2) in 1,4-addition reactions between aldehydes and nitroolefins: A careful comparison of the catalytic efficiencies of peptides **1** and **2** demonstrated that both the catalytic activity and stereoselectivity of peptide **2** are higher compared to those of **1**. Under the same conditions (3 equiv butanal, 1 equiv nitrostyrene), the conjugate addition reaction of butanal to nitrostyrene is complete within 8 h with **2**, whereas 12 h are required with **1**. This higher reactivity of **2** allowed us to further reduce the excess of aldehyde with respect to the nitroolefin, which is required for good reaction yields. By using as little as 1.5 equivalents of the aldehyde, the conjugate addition product was obtained in the same high enantioselectivity (97% ee) and only slightly lower diastereoselectivity (*syn*/*anti* 42:1) within a slightly longer reaction time under otherwise identical conditions (Table 3, entry 1). These improved conditions were used to evaluate the substrate scope of catalyst **2**.

In the presence of 1 mol% of **2** a range of aldehyde and nitroolefin combinations reacted readily with each other. The resulting γ-nitroaldehydes were obtained in excellent yields and stereoselectivities within 12–24 h at room temperature (Table 3). Aromatic nitroolefins bearing both electron-poor and electron-rich aromatic substituents (Table 3, entries 6–8) as well as aliphatic nitroolefins (Table 3, entries 9 and 10) react readily with aromatic as well as linear or β-branched aliphatic aldehydes (Table 3, entries 1–10). The best results were obtained with nitroolefins bearing electron-poor aromatic substituents (e.g. Table 3, entry 7), how-

Table 3. Substrate scope of conjugate addition reactions between aldehydes and nitroolefins catalyzed by peptide **2**.



Entry	Product		Yield[a] [%]	*syn*/*anti*[b]	*ee*[c] [%]
1		**13a**	96	42:1	97
2		**13b**	98	7:1	95
3		**13c**	98	27:1	96
4[d]		**13d**	93	61:1	96
5		**13e**	94	25:1	97
6		**13f**	97	36:1	96
7		**13g**	95	>99:1	98
8[d]		**13h**	quant.	21:1	95
9[d]		**13i**	84	6:1	98
10		**13j**	90	24:1	97
11[e]		**13k**	quant.	68:1	92
12[d,e]		**13l**	95	>99:1	95
13[e]		**13m**	95	16:1	90

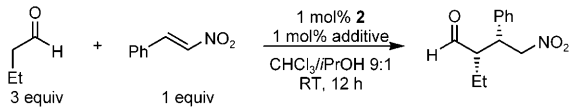
[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [c] Determined by chiral-phase HPLC analysis. [d] Use of 2 mol% of catalyst and NMM. [e] Reactions were performed in pure $CHCl_3$.

ever, even with the poorest substrate combination (aliphatic nitroolefin and propanal, entry 9) a diastereoselectivity of 6:1 and enantioselectivity of 98% ee was achieved. In comparison to **1** the improved catalyst **2** has generally an enantioselectivity that is greater by 2–4% ee at room temperature.[14]

We also tested the catalytic efficiency of **2** in conjugate addition reactions of different aldehydes with β-nitroacroleine dimethylacetal (Table 3, entries 11–13). This is a particularly interesting nitroolefin[3a,5m] because reactions with aldehydes bearing functional groups in their side-chains result in highly functionalized γ-nitroaldehydes that bear four different functional groups (Table 3, entry 13). Gratifyingly the highly functionalized products formed not only in yields of ≥95% but also with high diastereoselectivities (16:1 to >99:1) and enantioselectivities (90–95%). These results demonstrate that H-D-Pro-Pro-Glu-NH_2 **2** is an excellent catalyst not only for aromatic and aliphatic but also functionalized aldehydes and nitroolefins.

Effect of additives on the catalytic efficiency of peptide 2: The peptidic catalysts are easily prepared by solid-phase peptide synthesis on Rink amide resin by using the 9*H*-fluoren-9-ylmethoxycarbonyl (Fmoc)/*t*Bu protocol and removed from the acid-labile resin by using trifluoroacetic acid (TFA; see supporting information for details). The resulting TFA salts are isolated by simple precipitation from, for example, diethyl ether, and can be easily prepared on a multigram scale within a day. As a result, the addition of a base such as *N*-methylmorpholine (NMM)[15] is necessary to liberate the secondary amine and allow for catalysis. We were curious to test whether the presence of TFA and NMM affects the catalytic performance of the peptidic catalyst and investigated whether the high catalytic efficiency of peptide **2** is also achieved in the absence of TFA and NMM. Thus, the TFA of the peptide **2**·TFA salt was removed by ion exchange chromatography, and the resulting "desalted peptide **2**" was tested for its catalytic efficiency in the test reaction of butanal to nitrostyrene. In addition, we tested the effect of other additives such as HCl/NMM, AcOH/NMM, NMM and TFA on the catalytic activity of the "desalted peptidic catalyst" (Table 4).

Table 4. Effect of additives on the catalytic efficiency of peptide **2**.



Entry	Additive	Conv. [%][a]	*syn*/*anti*[a]	*ee* [%][b]
1	TFA·NMM	quant	50:1	97
2	none	quant	50:1	97
3	AcOH·NMM	quant	50:1	96
4	HCl·NMM	quant	52:1	96
5	NMM	98	50:1	97
6[c]	TFA	16	nd[d]	nd[d]

[a] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [b] Determined by chiral-phase HPLC analysis. [c] Reaction time of 72 h. [d] Not determined.

Remarkably, the "desalted peptide **2**" performed equally well as the TFA salt of **2** in the presence of NMM (Table 4, entry 2). Furthermore, also the addition of HCl·NMM, AcOH·NMM or NMM alone did not affect the excellent

catalytic efficiency of peptide **2** (entries 3–5). Only the addition of TFA to the desalted peptide reduced the catalytic activity dramatically, further underlining that the secondary amine is crucial for catalysis. These results demonstrate that no additives are necessary for the high catalytic efficiency of peptide **2**. This is in contrast to many of the other amine-based catalysts that require the addition of acids and/or bases.[3,4b,5]

Conclusions

Analysis of the structural and functional prerequisites for high catalytic efficiency within the asymmetric peptidic catalyst H-D-Pro-Pro-Asp-NH_2 (**1**) led to the establishment of the closely related peptide H-D-Pro-Pro-Glu-NH_2 (**2**) as an even more effective catalyst for conjugate addition reactions between aldehydes and nitroolefins. Peptide **2**, differing from **1** only by one additional methylene group, is a both more reactive and stereoselective catalyst. This allowed for a further improvement of the reaction conditions: in the presence of as little as 1 mol% of **2** and only 1.5 equivalents of the aldehyde, a broad range of different aldehydes and nitroolefins react readily at room temperature to provide synthetically useful γ-nitroaldehydes in excellent yields and stereoselectivities. Additional attractive features of the peptidic catalysts are their ease of synthesis and the fact that they do not require additives for their excellent catalytic performance but function equally as well in the presence of salts such as TFA·NMM.

The work also provided insight into the structural and functional features that render peptides of the type H-D-Pro-Pro-Xaa-NH_2 such efficient asymmetric catalysts: 1) Both the secondary amine and the carboxylic acid are crucial for effective catalysis, 2) whereas the D-Pro-Pro moiety is the basic contributor to high asymmetric induction, the C-terminal amide together with the distance of the carboxylic acid from the peptide backbone are responsible for the remarkably high stereoselectivities. Since the rational design of catalysts, and peptidic catalysts in particular, is still a tremendous challenge these insights provide important design concepts for new catalysts.

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 under UV light and with $KMnO_4$. Flash chromatography was performed by using Merck silica gel 60, particle size 40–63 mm. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are reported in ppm by using the residual solvent peak or tetramethylsilane as a reference. HPLC analyses were performed on an analytical instrument with a diode array detector from Shimadzu.

The peptidic catalysts were prepared by solid and solution-phase peptide synthesis by following the standard Fmoc/*t*Bu-protocol. For details on their syntheses and analytical data of peptides **3**–**12**, see the Supporting Information.

TFA·H-D-Pro-Pro-Glu-NH_2 (2): ^1H NMR (400 MHz, D_2O, 25 °C): δ = 4.51 (dd, J = 7.1, 8.8 Hz, 1H), 4.34 (dd, J = 3.6, 9.0 Hz, 1H), 4.23 (dd, J = 5.2, 9.5 Hz, 1H), 3.60 (m, 1H), 3.49 (m, 1H), 3.29 (m, 2H), 2.40 (m, 3H), 2.19 (m, 1H), 2.08–1.80 ppm (m, 8H); ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 177.4, 176.2, 174.5, 168.6, 61.2, 59.6, 53.2, 48.0, 47.0, 30.3, 29.8, 28.5, 26.4, 24.7, 24.3 ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{25}N_4O_5$ $[M+H]^+$ 341.1824; found, 341.1821.

General procedure for 1,4-addition reactions: *N*-Methylmorpholine (5.0 μL, 44 μmol, 0.1 equiv) was dissolved in a mixture of $CHCl_3$ and *i*PrOH 9:1 or neat $CHCl_3$ (10 mL). This solution (1 mL) was added to the catalyst (2.0 mg, 4.40 μmol, 0.01 equiv) and the mixture was stirred for 5 min. The nitroolefin (0.44 mmol, 1 equiv) and the aldehyde (0.66 mmol, 1.5 equiv) were added, and the reaction mixture (homogeneous solution) was stirred at RT. The reaction progress was followed by TLC. After consumption of the nitroolefin, the product was purified by flash column chromatography on silica gel by eluting with a mixture of pentanes and EtOAc. Collected fractions were concentrated in vacuo and the product was dried under high vacuum.

(2*S*,3*R*)-2-Ethyl-4-nitro-3-phenylbutanal (13a): The enantiomeric excess was determined by HPLC by using a Chiracel AD-H column (*n*-hexane/*i*PrOH 99.5:0.5, 25 °C) at 0.9 mL min^{-1}, UV detection at 254 nm: t_R (*syn*, minor) = 36.8 min, (*syn*, major) = 47.9 min; colorless oil; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.72 (d, J = 2.6 Hz, 1H), 7.32 (m, 3H), 7.18 (m, 2H), 4.72 (dd, J = 5.0, 12.7 Hz, 1H), 4.63 (dd, J = 9.7, 12.7 Hz, 1H), 3.79 (dt, J = 5.0, 9.8 Hz, 1H), 2.68 (dddd, J = 2.6, 5.0, 7.6, 10.1 Hz, 1H), 1.51 (m, 2H), 0.84 ppm (t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.1, 136.8, 129.1 (2), 128.1, 128.0 (2), 78.5, 55.0, 42.7, 20.4, 10.7 ppm (see also ref. [3g]); elemental analysis calcd (%) for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33; found: C 65.18, H 6.97, N 6.36.

(2*S*,3*R*)-2-Methyl-4-nitro-3-phenylbutanal (13b): The enantiomeric excess was determined by HPLC by using a Chiracel OD-H column (*n*-hexane/*i*PrOH 90:10, 25 °C) at 1 mL min^{-1}, UV detection at 254 nm: t_R (*syn*, major) = 23.5 min, (*syn*, minor) = 34.4 min; colorless oil; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.72 (d, J = 1.7 Hz, 1H), 7.32 (m, 3H), 7.17 (m, 2H), 4.80 (dd, J = 5.5, 12.7 Hz, 1H), 4.68 (dd, J = 9.31, 12.7 Hz, 1H), 3.81 (dt, J = 5.6, 9.2 Hz, 1H), 2.79 (m, 1H), 1.00 ppm (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.2, 136.5, 129.1 (2), 128.1, 128.0 (2), 78.1, 48.4, 44.0, 12.1 (see also ref. [3g]); elemental analysis calcd (%) for $C_{11}H_{13}NO_3$: C 63.76, H 6.32, N 6.76; found: C 63.75, H 6.35, N 6.64.

(2*S*,3*R*)-2-Butyl-4-nitro-3-phenylbutanal (13c): The enantiomeric excess was determined by HPLC by using a Chiracel OD-H column (*n*-hexane/*i*PrOH 80:20, 25 °C) at 1 mL min^{-1}, UV detection at 254 nm: t_R (*syn*, major) = 10.9 min, (*syn*, minor) = 13.7 min; colorless oil; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.70 (d, J = 2.8 Hz, 1H), 7.32 (m, 3H), 7.17 (m, 2H), 4.71 (dd, J = 9.5, 12.8 Hz, 1H), 4.64 (dd, J = 9.5, 12.8 Hz, 1H), 3.78 (dt, J = 5.3, 9.6 Hz, 1H), 2.60 (m, 1H), 1.54–1.09 (m, 6H), 0.78 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.2, 136.8, 129.1 (2), 128.1, 128.0 (2), 78.4, 53.9, 43.1, 28.5, 27.0, 22.5, 13.6 ppm (see also ref. [3g]); elemental analysis calcd (%) for $C_{14}H_{19}NO_3$: C 67.45, H 7.68, N 5.62, found: C 67.53, H 7.70, N 5.70.

(2*S*,3*R*)-2-Isopropyl-4-nitro-3-phenylbutanal (13d): The enantiomeric excess was determined by HPLC by using a Chiracel AD-H column (*n*-hexane/*i*PrOH 97:3, 25 °C) at 0.5 mL min^{-1}, UV detection at 254 nm: t_R (*syn*, minor) = 22.8 min, (*syn*, major) = 26.6 min; colorless oil; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.93 (d, J = 2.4 Hz, 1H), 7.32 (m, 3H), 7.19 (m, 2H), 4.67 (dd, J = 4.4, 12.5 Hz, 1H), 4.57 (dd, J = 10.0, 12.5 Hz, 1H), 3.90 (dt, J = 4.4, 10.3 Hz, 1H), 2.77 (ddd, J = 2.4, 4.1, 10.8 Hz, 1H), 1.72 (dsept., J = 4.2, 7.1 Hz, 1H), 1.10 (d, J = 7.2 Hz, 3H), 0.88 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 204.3, 137.0, 129.1 (2), 128.1, 127.9 (2), 79.0, 58.7, 41.9, 27.9, 21.6, 16.9 ppm (see also ref. [3g]); elemental analysis calcd (%) for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95; found: C 66.44, H 7.16, N 6.07.

(2*S*,3*R*)-2-Benzyl-4-nitro-3-phenylbutanal (13e): The enantiomeric excess was determined by HPLC by using a Chiracel AD-H column (*n*-hexane/*i*PrOH 97.5:2.5, 25 °C) at 1 mL min^{-1}, UV detection at 254 nm: t_R (*syn*,

minor) = 21.9 min, (*syn*, major) = 25.1 min; pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.64 (d, J = 2.3 Hz, 1H), 7.33–7.11 (m, 8H), 6.95 (m, 2H), 4.65 (m, 2H), 3.76 (dt, J = 6.1, 8.7 Hz, 1H), 3.04 (ddt, J = 2.3, 6.0, 8.6 Hz, 1H), 2.69 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.0, 137.1, 136.6, 129.3 (2), 128.8 (2), 128.7 (2), 128.3, 128.0 (2), 126.9, 78.0, 55.3, 43.5, 34.3 ppm; elemental analysis calcd (%) for $C_{17}H_{17}NO_3$: C 72.07, H 6.05, N 4.94; found: C 72.09, H 6.02, N 4.70.

(2*S*,3*R*)-3-(2,4-Dichlorophenyl)-2-ethyl-4-nitrobutyraldehyde (13f): The enantiomeric excess was determined by HPLC by using a Chiracel AD-H column (*n*-hexane/*i*PrOH 98.5:1.5, 25 °C) at 1 mL min^{-1}, UV detection at 254 nm: t_R (*syn*, minor) = 18.0 min, (*syn*, major) = 20.0 min; see also ref. [7]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.73 (d, J = 2.1 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.27 (m, 1H), 7.17 (d, J = 8.5 Hz, 1H), 4.85 (dd, J = 9.2, 13.0 Hz, 1H), 4.68 (dd, J = 4.5, 13.0 Hz, 1H), 4.30 (dt, J = 4.4, 9.5 Hz, 1H), 2.94 (m, 1H), 1.57 (m, 2H), 0.88 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.4, 135.0, 134.5, 133.1, 130.3, 127.8 (2), 76.5, 53.7, 38.7, 20.4, 10.6 ppm; elemental analysis calcd (%) for $C_{12}H_{13}Cl_2NO_3$: C 49.68, H 4.52, N 4.83; found: C 49.65, H 4.55, N 4.81.

(2*S*,3*R*)-2-Ethyl-4-nitro-3-(2-trifluoromethylphenyl)butanal (13g): The enantiomeric excess was determined by HPLC by using a Chiracel AD-H column (*n*-hexane/*i*PrOH 99:1, 25 °C) at 0.8 mL min^{-1}, UV detection at 254 nm: t_R (*syn*, minor) = 19.5 min, (*syn*, major) = 21.6 min; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.77 (dd, J = 1.7, 2.8 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 4.81 (ddd, J = 1.4, 7.2, 12.6 Hz, 1H), 4.63 (ddd, J = 1.5, 4.9, 12.6 Hz, 1H), 4.17 (m, 1H), 2.91 (m, 1H), 1.60 (m, 1H), 1.38 (m, 1H), 0.87 ppm (dt, J = 1.5, 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.0, 136.2, 132.6, 128.2 (2), 128.1, 126.9, 126.9, 77.9, 55.5, 38.2, 21.3, 11.3 ppm (see also ref. [3f]); elemental analysis calcd (%) for $C_{13}H_{14}F_3NO_3$: C 53.98, H 4.88, N 4.84; found: C 53.99, H 4.90, N 4.72.

(2*S*,3*R*)-2 Ethyl-4-nitro-3-(4-methoxyphenyl)butanal (13h): The enantiomeric excess was determined by HPLC by using a Chiral AM column (*n*-hexane/*i*PrOH 99.6:0.4, 25 °C) at 1.2 mL min^{-1}, UV detection at 254 nm: t_R (*syn*, minor) = 52.2 min, (*syn*, major) = 77.2 min; pale-yellow oil; ^{1}H NMR (400 MHz,$CDCl_3$, 25 °C): δ = 9.71 (d, J = 2.7 Hz, 1H), 7.09 (m, 2H), 6.87 (m, 2H), 4.69 (dd, J = 5.0, 12.5 Hz, 1H), 4.58 (dd, J = 9.8, 12.5 Hz, 1H), 3.79 (s, 3H), 3.47 (dt, J = 5.0, 9.9 Hz, 1H), 2.63 (m, 1H), 1.51 (m, 2H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.3, 159.2, 129.0 (2), 128.5, 114.5 (2), 78.8, 55.2, 55.2, 42.0, 20.3, 10.7 ppm (see also ref. [3f]); elemental analysis calcd (%) for $C_{13}H_{17}NO_4$: C 62.17, H 6.82, N 5.57; found: C 61.85, H 6.68, N 5.47.

(2*S*,3*S*)-3-Cylohexyl-2-methyl-4-nitrobutanal (13i): 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 210 nm: t_R = (*syn*, major) = 18.4 min, (*syn*, minor) = 19.6 min; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.69 (d, J = 0.8 Hz, 1H), 4.59 (dd, J = 5.4, 13.3 Hz, 1H), 4.39 (dd, J = 6.8, 13.3 Hz, 1H), 2.77–2.54 (m, 2H), 1.81–1.50 (m, 5H), 1.41 (m, 1H), 1.27–0.93 (m, 5H), 1.20 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.1, 75.8, 46.6, 43.5, 38.0, 31.6, 30.0, 26.4, 26.2, 26.0, 10.7 ppm (see also ref. [3f]); elemental analysis calcd (%) for $C_{11}H_{19}NO_3$: C 61.95, H 8.98, N 6.57; found: C 61.92, H 8.81, N 6.53.

(2*S*,3*S*)-2-Ethyl-5-methyl-3-(nitromethyl)hexanal (13j): The enantiomeric excess was determined by HPLC by using a Chiracel AD-H column (*n*-hexane/*i*PrOH 99.25:0.75, 25 °C) at 0.3 mL min^{-1}, UV detection at 210 nm: t_R = (*syn*, minor) = 29.5 min, (*syn*, major) = 33.0 min; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.72 (d, J = 1.3 Hz, 1H), 4.47 (dd, J = 6.4, 12.5 Hz, 1H), 4.42 (dd, J = 6.6, 12.5 Hz, 1H), 2.73 (m, 1H), 2.43 (dtd, J = 1.3, 4.7, 6.0 Hz, 1H), 1.80 (m, 1H), 1.61 (m, 1H), 1.50 (dqd, J = 4.9, 7.4, 14.8 Hz, 1H), 1.24 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H), 0.92 (d, J = 4.9, 3H), 0.90 ppm (d, J = 4.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.0, 77.1, 54.0, 38.3, 34.7, 25.2, 22.7, 22.0, 18.5, 12.2 ppm; elemental analysis calcd (%) for $C_{10}H_{19}NO_3$: C 59.68; H 9.51; N 6.96; found: C 59.83; H 9.26; N 6.80.

(2*S*,3*S*)-2-Ethyl-4,4-dimethoxy-3-(nitromethyl)butanal (13k): Reaction was performed in neat $CHCl_3$. 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 210 nm: t_R (*syn*, major) = 24.1 min, (*syn*, minor) = 26.4 min, colorless oil; ^{1}H NMR (400 MHz,$CDCl_3$, 25 °C): δ = 9.64 (d, J = 1.4 Hz, 1H), 4.61 (dd, J = 7.2, 13.7 Hz, 1H), 4.37 (m, 2H), 3.38 (s, 3H), 3.36 (s, 3H), 3.04 (m, 1H), 2.55 (s, 1H), 1.82 (m, 1H), 1.49 (m, 1H), 1.03 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.6, 104.4, 73.3, 55.3, 55.3, 51.3, 41.1, 19.5, 12.4 ppm (see also ref. [3k]); elemental analysis calcd (%) for $C_9H_{17}NO_5$: C 49.31, H 7.82, N 6.39; found: C 49.29, H 7.56, N 6.26.

(2*S*,3*S*)-2-Isopropyl-4,4-dimethoxy-3-(nitromethyl)butanal (13l): Reaction was performed in neat $CHCl_3$. The enantiomeric excess was determined by HPLC by using a Chiracel AS-H column (*n*-hexane/*i*PrOH 99:1, 25 °C) at 0.8 mL min^{-1}, UV detection at 210 nm: t_R (*syn*, major) = 19.1 min, (*syn*, minor) = 22.8 min; colorless oil; ^{1}H NMR (400 MHz,$CDCl_3$, 25 °C): δ = 9.75 (dd, J = 0.5, 2.5 Hz, 1H), 4.61 (dd, J = 8.9, 14.0 Hz, 1H), 4.42 (dd, J = 3.0, 14.0 Hz, 1H), 4.32 (d, J = 4.6 Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 3.04 (m, 1H), 2.61 (ddd, J = 2.6, 3.9, 9.0 Hz, 1H), 2.03 (sept d, J = 6.7, 8.7 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), 1.03 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 204.3, 105.3, 73.0, 56.0, 55.4 (2), 40.2, 27.2, 20.9, 20.8 ppm (see also ref. [3k]); elemental analysis calcd (%) for $C_{10}H_{19}NO_5$: C 51.49, H 8.21, N 6.00; found: C 51.52, H 8.10, N 6.00.

(3*S*,4*S*)-Methyl-3-formyl-5,5-dimethoxy-4-(nitromethyl)pentanoate (13m): Reaction was performed in neat $CHCl_3$. The enantiomeric excess was determined by HPLC by using a Chiracel AD-H column (*n*-hexane/*i*PrOH 97.5:2.5, 25 °C) at 0.5 mL min^{-1}, UV detection at 210 nm: t_R (*syn*, minor) = 57.2 min, (*syn*, major) = 75.4 min; colorless oil; ^{1}H NMR (400 MHz,$CDCl_3$, 25 °C): δ = 9.66 (s, 1H), 4.57 (dd, J = 6.7, 13.9 Hz, 1H), 4.41 (dd, J = 6.5, 13.9 Hz, 1H), 4.33 (d, J = 5.1 Hz, 1H), 3.71 (s, 3H), 3.39 (s, 3H), 3.38 (s, 3H), 3.23 (ddt, J = 3.3, 5.2, 6.6 Hz, 1H), 3.09 (m, 1H), 2.87 (dd, J = 8.20, 17.22 Hz, 1H), 2.48 ppm (dd, J = 5.21, 17.22 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 200.1, 172.0, 104.3, 73.4, 56.3, 55.4, 52.2, 45.7, 40.7, 30.5 ppm; elemental analysis calcd (%) for $C_{10}H_{17}NO_7$: C 45.63, H 6.51, N 5.32; found: C 45.90, H 6.40, N 5.40.

Acknowledgements

This work was supported by BACHEM and the Swiss National Science Foundation. We thank the EU for support by the Research Training Network REVCAT. H.W. is grateful to BACHEM for an endowed professorship.

[1] For reviews, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196.

[2] For recent reviews on 1,4-addition reactions catalyzed by organocatalysts, see: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; b) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123–3135; c) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065–2092; d) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.

[3] For selected examples of conjugate additions between aldehydes and nitroolefins catalyzed by organocatalysts followed by further derivatization, see a) N. Ruiz, E. Reyes, J. L. Vicario, D. Badia, L. Carrillo, U. Uria, *Chem. Eur. J.* **2008**, *14*, 9357–9367; b) S. Belot, A. Massaro, A. Tenti, A. Mordini, A. Alexakis, *Org. Lett.* **2008**, *10*, 4557–4560; c) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555–558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545–548; d) C. Palomo, S. Vera, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130–6133; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984–5987; e) J. Wang, J. Li, B. Lou, L. Zu, H. Guo, W. Wang, *Chem. Eur. J.* **2006**, *12*, 4321–4332; f) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147–1168; g) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740.

[4] a) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611. For another example of asymmet-

ric aldehyde to nitroethylene addition reactions, see: b) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608–5609.

[5] For selected examples of conjugate additions between aldehydes and nitroolefins catalyzed by organocatalysts, see: a) P. García-García, A. Ladépeche, R. Halder, B. List, *Angew. Chem.* **2008**, *120*, 4797–4799; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719–4721; b) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800–4802; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722–4724; c) Q. Tao, G. Tang, K. Lin, Y-F. Zhao, *Chirality* **2008**, *20*, 833–838; d) T. Mandal, C.-G. Zhao, *Angew. Chem.* **2008**, *120*, 7828–7831; *Angew. Chem. Int. Ed.* **2008**, *47*, 7714–7717; e) X.-j. Zhang, S.-P. Liu, X.-M. Li, M. Yan, A. S. C. Chan, *Chem. Commun.* **2009**, 833–835; f) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599–602; g) S. Sulzer-Mossé, M. Tissot, A. Alexakis, *Org. Lett.* **2007**, *9*, 3749–3752; h) M. T. Barros, A. M. Faísca Phillips, *Eur. J. Org. Chem.* **2007**, 178–185; i) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; j) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514–6518; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366–6370; k) Y. Li, X.-Y. Liu, G. Zhao, *Tetrahedron: Asymmetry* **2006**, *17*, 2034–2039; l) C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904; m) E. Reyes, J. L. Vicario, D. Badia, L. Carrillo, *Org. Lett.* **2006**, *8*, 6135–6138; n) S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559–2562; o) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; p) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079; q) L. Zu, H. Li, J. Wang, X. Yu, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 5131–5134; r) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165–3169; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097; s) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; t) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371; u) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; v) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527–2530; w) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611–3614; x) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740. For early examples of enamine catalysis involving nitroolefins, see: 5i D. Enders, A. Seki, *Synlett* **2002**, 0026–0028; y) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; z) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425.

[6] For selected examples of domino reactions, including conjugate addition reactions of aldehydes to nitroolefins, see: a) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649–7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539–7542; b) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267–279; c) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471–473; *Angew. Chem. Int. Ed.* **2007**, *46*, 467–469; d) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010–5013; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922–4925; e) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863.

[7] M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem.* **2008**, *120*, 1897–1900; *Angew. Chem. Int. Ed.* **2008**, *47*, 1871–1874.

[8] For examples of reactions requiring 5 mol% or less of the chiral amine catalyst see refs. [3c,d].

[9] For reviews on peptides as catalysts, see: a) E. A. Colby Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812; b) J. D. Revell, H. Wennemers, *Curr. Opin. Chem. Biol.* **2007**, *11*, 269–278; c) T. Darbre, J.-L. Reymond, *Acc. Chem. Res.* **2006**, *39*, 925–934; d) S. B. Tsogoeva, *Lett. Org. Chem.* **2005**, *2*, 208–213; e) S. J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601–610; f) A. Berkessel, *Curr. Opin. Chem. Biol.* **2003**, *7*, 409–419.

[10] For selected examples of peptides as asymmetric catalysts see: a) G. Peris, C. E. Jakobsche, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 8710–8711; b) C. A. Lewis, S. J. Miller, *Angew. Chem.* **2006**, *118*, 5744–5747; *Angew. Chem. Int. Ed.* **2006**, *45*, 5616–5619; c) C. A. Lewis, A. Chiu, M. Kubryk, J. Balsells, D. Pollard, C. K. Esser, J. Murry, R. Reamer, K. B. Hansen, S. J. Miller, *J. Am. Chem. Soc.* **2006**, *128*, 16454–16455; d) S. B. Tsogoeva, S. B. Jagtap, Z. A. Ardemasova, *Tetrahedron: Asymmetry* **2006**, *17*, 989–992; e) Y. Xu, W. Zou, H. Sundén, I. Ibrahem, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 418–424; f) P. Krattiger, R. Kovàsy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, *7*, 1101–1103; g) S. B. Tsogoeva, S. B. Jagtap, Z. A. Ardemasova, V. N. Kalikhevich, *Eur. J. Org. Chem.* **2004**, 4014–4019.

[11] For studies on related peptides that catalyze aldol reactions, see: a) J. D. Revell, H. Wennemers, *Adv. Synth. Catal.* **2008**, *350*, 1046–1052; b) J. D. Revell, H. Wennemers, *Tetrahedron* **2007**, *63*, 8420–8424.

[12] For turn structures observed for internal D-Pro-Pro motives within linear and cyclic peptides, see: a) R. Rai, S. Aravinda, K. Kanagarajadurai, S. Raghothama, N. Shamala, P. Balaram, *J. Am. Chem. Soc.* **2006**, *128*, 7916–7928; b) S. Hanessian, M. Angiolini, *Chem. Eur. J.* **2002**, *8*, 111–117; c) M. Favre, K. Moehle, L. Jiang, B. Pfeiffer, J. A. Robinson, *J. Am. Chem. Soc.* **1999**, *121*, 2679–2685; d) A. Aubry, B. Vitoux, M. Marraud, *Biopolymers* **1985**, *24*, 1089–1100.

[13] a) B. R. Linton, M. S. Goodman, A. D. Hamilton, *Chem. Eur. J.* **2000**, *6*, 2449–2455; b) T. R. Kelly, M. H. Kim, *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080. For a recent review on intermolecular interactions including the nitro group, see: R. Paulini, K. Müller, F. Diederich, *Angew. Chem.* **2005**, *117*, 1820–1839; *Angew. Chem. Int. Ed.* **2005**, *44*, 1788–1805.

[14] The stereoselectivities observed for peptide **2** at RT are comparable to those observed for peptide **1** at −15 °C.

[15] Use of other tertiary amines such as iPr$_2$EtN or NEt$_3$ provided comparable results.

Received: April 17, 2009
Published online: August 20, 2009

