

# Supporting Information

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

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#### 1. 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 using Merck silica gel 60  $F_{254}$  plates. Compounds were visualized by UV and KMnO<sub>4</sub>. Flash chromatography was performed using Merck silica gel 60, particle size 40 - 63 µm. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are reported in ppm 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. Specific rotations were measured on a Perkin Elmer Polarimeter 341. For automated peptide synthesis, a Syro I Peptide Synthesizer (MultiSynTech GmbH, Witten, Germany) was employed.

#### 2. Synthesis of peptidic catalysts

## a. General protocols for solid phase synthesis

Peptides were prepared on solid phase (Rink Amid resin) following the general protocol for Fmoc/<sup>t</sup>Bu peptide synthesis.

General procedure for peptide couplings:  ${}^{1}PrNEt_{2}$  (9eq as a 3M solution in N-methylpyrrolidone) was added to a solution of Fmoc-Xxx-OH (3 eq) and HCTU (3 eq) in DMF. The activated amino acid was added to the amino-functionalized resin, swollen in DMF ( $\approx$ 100 mM concentration) and the mixture was agitated for 1.5 h before washing with DMF (5x).

*General procedure for Fmoc-deprotections*: 40% piperidine in DMF was added to the resin (preswollen in DMF) and the reaction mixture was agitated for 3 min, drained and the piperidine treatment repeated for 10 min. Finally the resin was washed with DMF (7x).

General procedure for cleavage of peptides from the solid support: The solid supported peptides were cleaved from the Rink Amide resin by stirring in a mixture of TFA: $CH_2Cl_2$  2:1 for 1 h and a second time for 20 min. Pooling of filtrates and removal of all volatiles under reduced pressure followed by precipitation with Et<sub>2</sub>O afforded the peptides **1-4**.

#### b. Analytical data

**TFA·H-L-Pro-L-Pro-L-Asp-NH**<sub>2</sub> (1): Prepared according to the general protocols for solid phase synthesis. Spectroscopic data are in agreement with the published data.<sup>[1]</sup>

**TFA·H-L-Pro-L-Pro-D-Asp-NH**<sub>2</sub> (2): Prepared according to the general protocols for solid phase synthesis. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, 25°C)  $\delta$ = 4.77 (m, 1H), 4.64 (m, 1H), 4.51 (dd, J = 5.9 Hz, 8.5 Hz, 1H), 3.71 (m, 1H), 3.62 (m, 1H), 3.42 (m, 2H), 2.89 (dd, J = 5.1 Hz, 15.8 Hz, 1H), 2.80 (dd, J = 7.6 Hz, 15.7 Hz, 1H), 2.62 (m, 1H), 2.32 (m, 1H), 2.12-1.89 (m, 6H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O, 25°C)  $\delta$ = 175.3, 174.6, 173.9, 168.8, 61.2, 59.8, 50.1, 48.4, 47.3, 37.1, 30.2, 29.1, 25.2, 24.6; HRMS (ESI) *m/z*: calcd for C<sub>14</sub>H<sub>23</sub>N<sub>4</sub>O<sub>5</sub> 327.1668; found, 327.1668.

**TFA·H-L-Pro-D-Pro-L-Asp-NH**<sub>2</sub> (**3**): Prepared according to the general protocols for solid phase synthesis. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, 25°C)  $\delta$ = 4.75 (dd, *J* = 4.8 Hz, 8.4 Hz, 1H), 4.63 (m, 1H), 4.45 (dd, J = 4.9 Hz, 8.7 Hz, 1H), 3.73 (td, *J* = 6.5 Hz, 10.1 Hz, 1H), 3.62 (td, *J* = 7.0, 10.0, 1H), 3.42 (m, 2H), 2.97 (dd, J = 4.8 Hz, 17.0 Hz, 1H), 2.85 (dd, *J* = 8.4 Hz, 17.0 Hz, 1H), 2.56 (m, 1H), 2.30 (m, 1H), 2.12-1.93 (m, 6H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O, 25°C)  $\delta$ = 175.4, 174.6, 174.6, 168.5, 61.5, 59.7, 50.3, 48.2, 47.1, 35.9, 29.8, 28.6, 24.9, 24.4; HRMS (ESI) *m/z*: calcd for C<sub>14</sub>H<sub>23</sub>N<sub>4</sub>O<sub>5</sub> 327.1668; found, 327.1668.

**TFA·H-D-Pro-L-Pro-L-Asp-NH**<sub>2</sub> (**4**): Prepared according to the general protocols for solid phase synthesis. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, 25°C)  $\delta$ = 4.71 (dd, *J* = 5.3 Hz, 8.4 Hz, 1H), 4.64 (dd, J = 7.1 Hz, 8.7 Hz, 1H), 4.46 (dd, J = 3.7 Hz, 8.6 Hz, 1H), 3.73 (m, 1H), 3.60 (m, 1H), 3.42 (m, 1H), 2.97 (dd, J = 5.3 Hz, 16.9 Hz, 1H), 2.84 (dd, J = 8.4 Hz, 16.8 Hz, 1H), 2.55 (m, 1H), 2.31 (m, 1H), 2.11-1.97 (m, 6H); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O, 25°C)  $\delta$ = 175.2, 174.5, 174.3, 168.9, 61.4, 58.8, 50.4, 48.1, 47.1, 35.8, 29.9, 28.5, 24.7, 24.4; HRMS (ESI) *m/z*: calcd for C<sub>14</sub>H<sub>23</sub>N<sub>4</sub>O<sub>5</sub> 327.1668; found, 327.1661.

#### 3. General procedure of 1,4-addition reactions of aldehydes to nitroolefins

*N*-methylmorpholine (5.0  $\mu$ l, 0.045 mmol, 0.1 eq) was dissolved in the specified solvent (10 ml). 1 ml of this solution was added to the catalyst (2.0 mg, 4.54  $\mu$ mol. 0.01 eq) and the mixture was stirred for 5 min. The nitroolefin (1 eq) and the aldehyde (3 eq) were added and the reaction mixture was stirred at the specified temperature. The progress of the reaction was followed by TLC. After completion, the reaction mixture was directly separated by flash column chromatography on silica gel eluting with a mixture of pentanes and ethyl acetate.

#### 4. Characterisation of 1,4-addition products

Assignment of the stereoisomers was performed by comparison with literature and chromatographic data obtained using diastereomeric peptides **1** and **4** as catalysts for reactions performed under otherwise identical conditions. Peptides **1** and **4** have opposite enantioselectivity.

#### (2S,3R)-2-Methyl-4-nitro-3-phenylbutanal:



Prepared from *n*-propanal and *trans*- $\beta$ -nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Spectroscopic data are in agreement with the published data.<sup>[2]</sup> The enantiomeric excess was determined by HPLC using a Chiracel OD-H column (*n*-hexane/*i*-PrOH 90:10, 25°C) at 1 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, major) = 24.6 min, (*syn*, minor) = 37.0 min.

#### (2S,3R)-2-Ethyl-4-nitro-3-phenylbutanal:



Prepared from *n*-butanal and *trans*- $\beta$ -nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Spectroscopic data are in agreement with the published data.<sup>[2]</sup> The enantiomeric excess was determined by

HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 99.25:0.75, 25°C) at 0.8 ml/min, UV detection at 254 nm:  $t_R$  : (*syn*, minor) = 38.6 min, (*syn*, major) = 47.0 min.

#### (2S,3R)-2-Propyl-4-nitro-3-phenylbutanal:



Prepared from *n*-pentanal and *trans*- $\beta$ -nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 15:1). Spectroscopic data are in agreement with the published data.<sup>[3]</sup> The enantiomeric excess was determined by HPLC using a Chiracel OD-H column (*n*-hexane/*i*-PrOH 80:20, 25°C) at 1 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, major) = 11.7 min, (*syn*, minor) = 15.9 min.

#### (2S,3R)-2-Butyl-4-nitro-3-phenylbutanal:



Prepared from *n*-hexanal and *trans*- $\beta$ -nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Spectroscopic data are in agreement with the published data.<sup>[2]</sup> The enantiomeric excess was determined by HPLC using a Chiracel OD-H column (*n*-hexane/*i*-PrOH 80:20, 25°C) at 1 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, major) = 10.8 min, (*syn*, minor) = 13.9 min.

#### (2S,3R)-2-Isopropyl-4-nitro-3-phenylbutanal:



Prepared from isovaleraldehyde and *trans*- $\beta$ -nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Spectroscopic data are in agreement with the published data.<sup>[2]</sup> The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 97:3, 25°C) at 0.5 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, minor) = 24.1 min, (*syn*, major) = 28.4 min.

#### (2S,3R)-2-Benzyl-4-nitro-3-phenylbutanal:



Prepared from 3-phenylpropionaldehyde and *trans*- $\beta$ -nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Spectroscopic data are in agreement with the published data.<sup>[4]</sup> The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 97.5:2.5, 25°C) at 1 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, minor) = 24.9 min, (*syn*, major) = 28.5 min.

#### (2S,3R)-3-(4-Bromophenyl)-2-ethyl-4-nitrobutanal:



Prepared from *n*-butanal and *trans*-4-bromo-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Colourless oil; <sup>1</sup>H NMR (400 MHz,CDCl<sub>3</sub>, 25°C)  $\delta$ = 9.71 (d, *J* = 2.3 Hz, 1H; CHO), 7.48 (d, *J* = 8.4 Hz, 2H; Ph), 7.07 (d, *J* = 8.4 Hz, 2H; Ph), 4.72 (dd, *J* = 4.8 Hz, 12.8 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 4.60 (dd, *J* = 9.9 Hz, 12.8 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 3.77 (dt, *J* = 4.8 Hz, 9.9 Hz, 1H; CHPh), 2.67 (m, 1H; CHCHO), 1.58–1.43 (m, 2H; CH<sub>2</sub>CH<sub>3</sub>), 0.84 (t, *J* = 7.5 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$ = 202.6, 135.9, 132.3, 129.7, 122.1, 78.2, 54.7, 42.1, 20.3, 10.5; Anal. Calcd for C<sub>12</sub>H<sub>14</sub>BrNO<sub>3</sub>: C 48.02; H 4.70; N 4.67. Found: C 48.12; H 4.72; N 4.73; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, minor) = 30.4 min, (*syn*, major) = 42.9 min.

#### (2S,3R)-3-(4-Fluorophenyl)-2-ethyl-4-nitrobutanal:



Prepared from *n*-butanal and *trans*-4-fluoro-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Colourless oil; <sup>1</sup>H NMR (400 MHz,CDCl<sub>3</sub>, 25°C)  $\delta$ = 9.72 (d, *J* = 2.4 Hz, 1H; CHO), 7.17 (m, 2H; Ph), 7.04 (m, 2H; Ph), 4.72 (dd, *J* = 4.8 Hz, 12.7 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 4.59 (dd, *J* = 9.9 Hz, 12.7 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 3.80 (dt, *J* = 4.8 Hz, 10.0 Hz, 1H; CHPh), 2.67 (m, 1H; CHCHO), 1.58–1.43 (m, 2H; CH<sub>2</sub>CH<sub>3</sub>), 0.84 (t, *J* = 7.5 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$ = 202.8, 162.3 (d, *J*<sub>CF</sub> = 247.4 Hz), 132.5, 129.6, 116.1, 78.5, 54.9, 41.9, 20.3, 10.5; Anal. Calcd for C<sub>12</sub>H<sub>14</sub>FNO<sub>3</sub>: C 60.24; H 5.90; N 5.85. Found: C 60.39; H 5.96; N 5.72; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, minor) = 26.6 min, (*syn*, major) = 34.4 min.

#### (2S,3R)-3-(4-Chlorophenyl)-2-ethyl-4-nitrobutanal:



Prepared from *n*-butanal and *trans*-4-chloro-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Colourless oil; <sup>1</sup>H NMR (400 MHz,CDCl<sub>3</sub>, 25°C)  $\delta$ = 9.72 (d, *J* = 2.3 Hz, 1H; CHO), 7.33 (m, 1H; Ph), 7.13 (m, 1H; Ph), 4.72 (dd, *J* = 4.8 Hz, 12.8 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 4.60 (dd, *J* = 9.9 Hz, 12.8 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 3.79 (dt, *J* = 4.8 Hz, 10.0 Hz, 1H; CHPh), 2.67 (m, 1H; CHCHO), 1.50 (m, 2H; CH<sub>2</sub>CH<sub>3</sub>), 0.84 (t, *J* = 7.5 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$ = 202.7, 135.3, 134.0, 129.6, 129.3, 78.3, 54.68, 42.0, 20.3, 10.5; Anal. Calcd for C<sub>12</sub>H<sub>14</sub>ClNO<sub>3</sub>: C 56.37; H 5.52; N 5.48. Found: C 56.29; H 5.55; N 5.54; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-

PrOH 98.5:1.5, 25°C) at 1 ml/min, UV detection at 254 nm:  $t_R$  : (*syn*, minor) = 27.3 min, (*syn*, major) = 38.1 min.

## (2S, 3R)-3-(2,4-Dichlorophenyl)-2-ethyl-4-nitrobutyraldehyde:



Prepared from *n*-butanal and *trans*-2,4-dichloro-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1).Colourless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$ = 9.73 (d, *J* = 2.1 Hz, 1H; CHO), 7.44 (d, *J* = 2.1 Hz, 1H; Ph), 7.27 (m, 1H; Ph), 7.17 (d, *J* = 8.5 Hz, 1H; Ph), 4.85 (dd, *J* = 9.2 Hz, 13.0 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 4.68 (dd, *J* = 4.5 Hz, 13.0 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 4.30 (dt, *J* = 4.4 Hz, 9.5 Hz, 1H; CHPh), 2.94 (m, 1H; CHCHO), 1.57 (m, 2H; CH<sub>2</sub>CH<sub>3</sub>), 0.88 (t, *J* = 7.5 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$ = 202.4, 135.0, 134.5, 133.1, 130.3, 127.8, 76.5, 53.7, 38.7, 20.4, 10.6; Anal. Calcd for C<sub>12</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>3</sub>: C 49.68; H 4.52; N 4.83. Found: C 49.65; H 4.55; N 4.81; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, major) = 20.1 min, (*syn*, minor) = 22.6 min.

## (2S, 3R)-2Ethyl-4-nitro-3-(2-trifluoromethylphenyl)butanal:



Prepared from *n*-butanal and *trans*- $\beta$ -nitro-2-(trifluoromethyl)styrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Spectroscopic data are in agreement with the published data.<sup>[5]</sup> The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 99:1, 25°C) at 0.8 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, minor) = 20.2 min, (*syn*, major) = 22.0 min.

#### (2S, 3R)-2-Benzyl-4-nitro-3-(2-trifluoromethylphenyl)butanal:



Prepared from 3-phenylpropionaldehyde and *trans*-β-nitro-2-(trifluoromethyl)styrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1 to 5:1). Colourless oil; <sup>1</sup>H NMR (400 MHz,CDCl<sub>3</sub>, 25°C)  $\delta$ = 9.72 (d, *J* = 2.2 Hz, 1H; CHO), 7.75 (d, *J* = 7.9 Hz, 1H; Ph), 7.60 (t, *J* = 7.64, 1H; Ph), 7.45 (t, *J* = 8.4, 2H; Ph), 7.24 (m, 3H; Ph), 7.03 (d, *J* = 7.1 Hz, 1H; Ph), 4.86 (dd, *J* = 7.4 Hz, 12.7 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 4.69 (dd, *J* = 4.7 Hz, 12.7 Hz, 1H; CH<sub>2</sub>NO<sub>2</sub>), 4.22 (m, 1H; CHCH<sub>2</sub>NO<sub>2</sub>), 3.36 (m, 1H; CHCHO), 2.83 (dd, *J* = 10.9 Hz, 14.0 Hz, 1H; CH<sub>2</sub>Ph), 2.63 (dd, *J* = 4.4 Hz, 14.1 Hz, 1H; CH<sub>2</sub>Ph); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$ = 203.1, 137.0, 136.2, 132.7, 128.9, 128.8, 128.6, 128.3, 127.9, 127.0, 125.4, 122.7, 77.4, 55.5, 39.0, 35.4; Anal. Calcd for C<sub>18</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>3</sub>: C 61.54; H 4.59; N 3.99. Found: C 61.74; H 4.63; N 3.81; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, UV detection at 254 nm: t<sub>R</sub> : (*syn*, minor) = 20.7 min, (*syn*, major) = 27.5 min.

#### (2S, 3R)-2Ethyl-4-nitro-3-(4-methoxyphenyl)butanal:



Prepared from *n*-butanal and *trans*-4-methoxy-β-nitrostyrene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Spectroscopic data are in agreement with the published data.<sup>[5]</sup> The enantiomeric excess was determined by HPLC using a Chiracel AD column (*n*-hexane/*i*-PrOH 96:4, 25°C) at 0.8 ml/min, UV detection at 254 nm:  $t_R$  : (*syn*, minor) = 21.3 min, (*syn*, major) = 26.2 min.

#### (2S, 3R)-2-Methyl-4-nitro-3-(thien-2-yl)butanal:



Prepared from *n*-propanal and *trans*-2-(2-nitrovinyl)thiophene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 10:1). Spectroscopic data are in agreement with the published data.<sup>[6]</sup> The enantiomeric excess was determined by HPLC using a Chiracel AD column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, UV detection at 254 nm:  $t_R$  : (*syn*, minor) = 31.2 min, (*syn*, major) = 43.9 min.

#### (2S, 3S)-3-Cylohexyl-2-methyl-4-nitrobutanal:



Prepared from *n*-propanal and *trans*-1-nitro-1-cyclohexyl-ethene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 20:1). Spectroscopic data are in agreement with the published data.<sup>[6]</sup> The enantiomeric excess was determined by HPLC using a Chiracel AS-H column (*n*-hexane/*i*-PrOH 90:10, 25°C) at 0.5 ml/min, UV detection at 210 nm:  $t_R$  : (*syn*, major) = 18.8 min, (*syn*, minor) = 20.4 min.

#### (2S, 3S)-2-Ethyl-3-nitromethyloctanal:



Prepared from *n*-butanal and 1-nitro-1-heptene according to the general procedure. Purified by preparative chromatography on silica gel (pentanes/ethyl acetate 15:1). Colourless oil; <sup>1</sup>H NMR (400 MHz,CDCl<sub>3</sub>, 25°C)  $\delta$ = 9.71 (d, *J* = 1.5 Hz, 1H; CHO), 4.42 (m, 2H; CH<sub>2</sub>NO<sub>2</sub>), 2.65 (m, 1H; CHCH<sub>2</sub>NO<sub>2</sub>), 2.41 (dtd, *J* = 1.5 Hz, 4.82 Hz, 6.33 Hz, 1H; CHCHO), 1.59–1.23 (m, 10H; CH<sub>2</sub>), 1.00 (t, *J* = 7.4 Hz, 3H; CH<sub>3</sub>); 0.88 (t, *J* = 6.9 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$ = 203.1, 53.9, 37.3, 36.8, 31.6, 29.0, 26.4, 22.3, 18.6, 13.9, 12.1; Anal. Calcd for C<sub>11</sub>H<sub>21</sub>NO<sub>3</sub>: C 61.37; H 9.83; N 6.51. Found: C 61.5; H 9.85; N 6.38; The enantiomeric excess was determined by HPLC using a Chiracel AS-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 0.5 ml/min, UV detection at 210 nm: t<sub>R</sub> : (*syn*, major) = 21.1 min, (*syn*, minor) = 22.7 min.

## (+)-2-Ethyl-4-nitrobutanol:

HO \* NO<sub>2</sub>

Prepared from *n*-butanal and nitroethylene followed by *in-situ* reduction with NaBH<sub>4</sub> and work Purified bv preparative chromatography silica aqueous up. on gel (methanol/dichloromethane 3:97). Colourless oil;  $[\alpha]_D^{20} = +8$  (c = 0.1, CHCl<sub>3</sub>, 81%ee); <sup>1</sup>H NMR (400 MHz,CDCl<sub>3</sub>, 25°C)  $\delta$  = 4.51 (t, J = 7.4 Hz, 2H; CH<sub>2</sub>NO<sub>2</sub>), 3.68 (dd, J = 4.5 Hz, 10.7 Hz, 1H; CH<sub>2</sub>OH), 3.56 (dd, J = 6.3 Hz, 10.7 Hz, 1H; CH<sub>2</sub>OH), 2.10 (m, 2H;  $CH_2CH_2NO_2$ ), 1.54 (m, 1H;  $CHCH_2OH$ ), 1.47-1.31 (m, 2H;  $CH_2CH_3$ ), 0.94 (t, J = 7.2 Hz, 3H; CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C)  $\delta$  = 74.2, 64.7, 39.3, 29.2, 23.5, 11.1; MS (ESI, pos): m/z (%): 170.7 [M+Na]<sup>+</sup>; The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (n-hexane/i-PrOH 90:10, 25°C) at 0.5 ml/min, UV detection at 210 nm:  $t_R$ : (minor) = 16.1 min, (major) = 17.9 min.

## 5. Conformational analysis of peptides 2-4 using MacroModel 8.0:

The calculations used the OPLS-AA force field<sup>[7]</sup> and the GB/SA model for chloroform.<sup>[8]</sup> Searching was performed using the MCMM method in blocks of 20000 steps.

Lowest energy structures of peptides 1-4:









H-Pro-Pro-Asp-NH<sub>2</sub> (1)

 $H-Pro-Pro-D-Asp-NH_2(2)$ 

H-Pro-D-Pro-Asp-NH<sub>2</sub>(3)

H-D-Pro-Pro-Asp-NH<sub>2</sub>(4)

Overlay of the lowest energy structures of peptides H-Pro-Pro-Asp-NH<sub>2</sub> **1** and H-D-Pro-Pro-Asp-NH<sub>2</sub> **4**:



Peptide **1** in grey and peptide **4** in green illustrating that the two conformations are identical apart from the N-terminal proline (Pro) residues which point into opposite directions.

# 6. Catalytic Properties of Peptides with Protecting Groups on the Secondary Amine or Carboxylic Acid

To analyze the importance of the secondary amine and the carboxylic acid within the catalyst structure, the catalytic properties of Ac-D-Pro-Pro-Asp-NH<sub>2</sub> **5** and H-D-Pro-Pro-Asp(OtBu)-NH<sub>2</sub> **5** were examined as catalysts for the reaction between butanal and nitrostyrene. No product formation was observed when as much as 10 mol% of peptide **5** was employed, suggesting that enamine formation is crucial for catalysis. Peptide **6** is still catalytically active but has lower activity and selectivity (1 mol% of **6** provided the product in a yield of 20% within 24 hours with a selectivity of 73% ee). Similar results were obtained when the dipeptide H-Pro-Pro-OH was employed as a catalyst (52% yield, 68% ee).

## 7. NMR-spectra and HPLC-chromatograms

Only analytical data of new compounds are shown.

# TFA·H-D-Pro-L-Pro-L-Asp-NH<sub>2</sub>



100

150

ppm (f1)

50

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, 25°C)



0

## (2S,3R)-3-(4-Bromophenyl)-2-ethyl-4-nitrobutanal



Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, 254 nm (95% ee).



# (2S,3R)-3-(4-Fluorophenyl)-2-ethyl-4-nitrobutanal







# (2S,3R)-3-(4-Chlorophenyl)-2-ethyl-4-nitrobutanal



Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, 254 nm (95% ee).



# (2S, 3R)-3-(2,4-Dichlorophenyl)-2-ethyl-4-nitrobutyraldehyde



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C)

Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, 254 nm (95% ee).



# $(2S,\,3R)\mbox{-}2\mbox{-}Benzyl\mbox{-}4\mbox{-}nitro\mbox{-}3\mbox{-}(2\mbox{-}trifluoromethylphenyl) butanal$



Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1 ml/min, 254 nm (98% ee).



# (2S, 3S)-2-Ethyl-3-nitromethyloctanal



Chiracel AS-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 0.5 ml/min, 210 nm (93% ee).



# (+)-2-Ethyl-4-nitrobutanol





Chiracel AD-H column (*n*-hexane/*i*-PrOH 90:10, 25°C) at 0.5 ml/min, 210 nm (81% ee).



## 8. References

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