Electronic Supplementary Material (ESI) for Chemical Science.

Effects of Internal and External Carboxylic Acids on the Reaction Pathway of Organocatalytic 1,4-Addition Reactions between Aldehydes and Nitroolefins

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Supporting Information

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 F254 plates. Compounds were visualized by UV, $KMnO_4$ and ninhydrin. Flash chromatography was performed using Merck silica gel 60, particle size 40 – 63 μm. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400, a VARIAN Mercury 300 MHz or a Bruker Advance DRX 500 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. *In-situ* FT-IR spectroscopy was carried out on a ReactIR R4000 (SiComb probe) with a spectral range of 4000–650 cm^{-1}. All measurements were performed at room temperature, collecting spectra every minute (154 scans) or every 5 minutes (256 scans).

2. Synthesis of the catalysts

2.1. Peptides 1 and 1b – 1f

General protocols for solid phase peptide synthesis

Peptide **1** and **1b** – **1f** were prepared on solid phase using Rink Amide resin as the solid support. The general protocol for Fmoc/tBu peptide synthesis was followed according to the procedures described below.

General procedure for peptide couplings: $^{i}PrNEt_2$ (4.5 eq) was added to a solution of Fmoc-Xxx-OH (1.5 eq) and HCTU (1.5 eq) in DMF. The activated amino acid was added as a solution in DMF (≈500 mM concentration) to the amino-functionalized resin, swollen in DMF and the mixture was agitated for 1.5 h before washing with DMF (3x) and CH_2Cl_2 (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 10 min, drained and the piperidine treatment repeated for another 10 min. Finally the resin was washed with DMF (3x) and CH_2Cl_2 (5x).

General procedure for the cleavage of the peptide from the solid support: The solid supported peptide was cleaved from the Rink Amide resin by treatment with 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_2O afforded the peptide as its TFA salt. The TFA was removed by ion pair exchange using a VariPure^{TM} IPE cartouche (Varian, Inc.).

H-D-Pro-Pro-Glu-NH_2 (1): Spectroscopic data are in agreement with published data.[1,2]

H-D-Pro-Pro-Asp-NH_2 (1b): Spectroscopic data are in agreement with published data.[1]

H-D-Pro-Pro-Aad-NH_2 (1c): Spectroscopic data are in agreement with published data.[1]

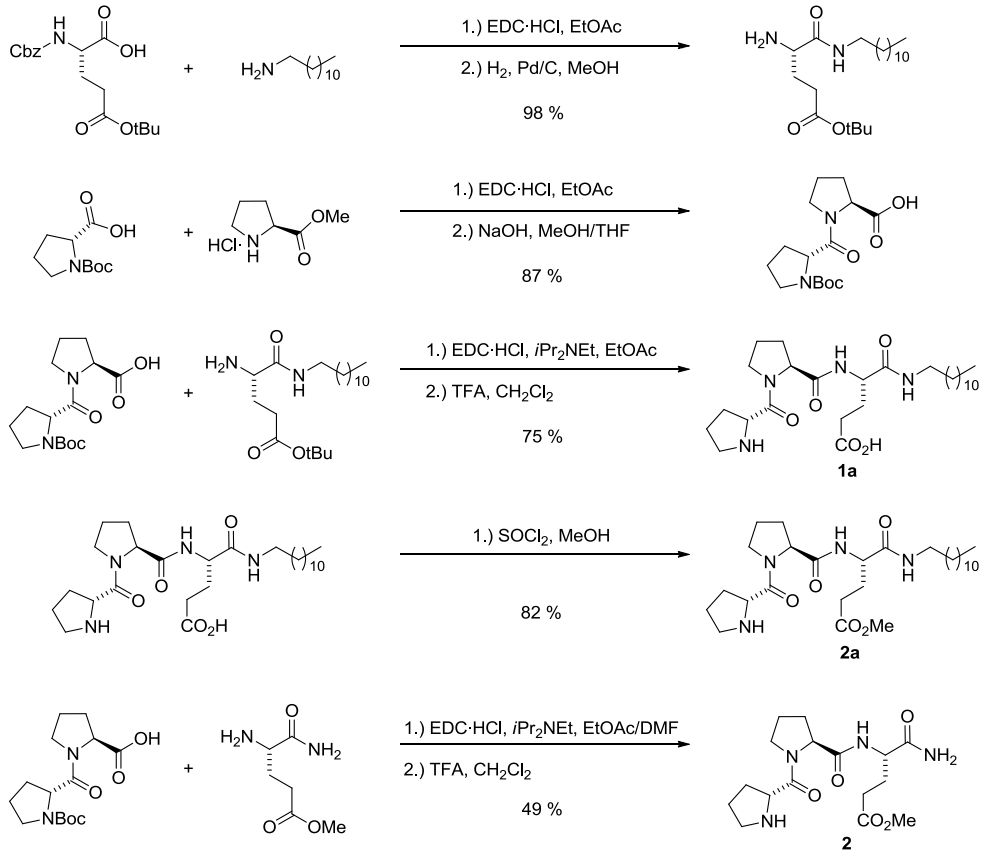
H-D-Pro-Pro-Api-NH_2 (1d): Spectroscopic data are in agreement with published data. [1]

H-D-Pro-Pro-Asu-NH_2 (1e): Spectroscopic data are in agreement with published data. [1]

H-D-Pro-Pro-Ada-NH_2 (1f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, *J* = 5.8 Hz, 1H), 4.55 (dd, *J* = 7.9, 2.5 Hz, 1H), 4.22 (t, *J* = 8.3 Hz, 1H), 3.87 – 3.77 (m, 1H), 3.41 (dd, *J* = 9.4, 7.8 Hz, 1H), 3.34 – 3.19 (m, 2H), 3.11 – 3.01 (m, 2H), 2.37 – 2.14 (m, 4H), 2.13 – 1.92 (m, 5H), 1.75 (dq, *J* = 12.5, 8.0 Hz, 1H), 1.64 – 1.51 (m, 2H), 1.51 – 1.39 (m, 2H), 1.34 – 1.19 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 170.4, 170.4, 61.2, 58.8, 46.7, 45.4, 39.8, 35.8, 29.6, 29.3, 29.0, 29.0, 28.9, 28.8, 28.8, 28.7, 26.7, 26.0, 25.4, 24.0. HRMS (ESI, $[M+H]^+$) Calcd for $C_{22}H_{40}N_3O_4$: 410.3013. Found: 410.3013.

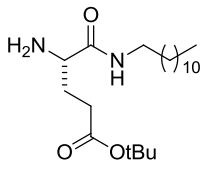
2.2. Peptides 1a, 2 and 2a

Peptides **1a**, **2**, and **2a** were synthesized in solution phase according to the route shown in Scheme S-1.



*Scheme S-1. Synthesis of Peptide Catalysts **1a**, **2** and **2a**.*

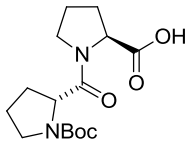
H-Glu(O*t*Bu)NH-$C_{12}H_{25}$



Z-Glu(OtBu)-OH (1.00 g, 2.97 mmol, 1.0 eq), dodecylamine (550 mg, 2.97 mmol, 1.0 eq) and EDC·HCl (680 mg, 3.55 mmol, 1.2 eq) were suspended in EtOAc (15 mL) and stirred at room temperature for 3 h. The mixture was diluted with EtOAc (70 mL) and washed with 0.1 M HCl (2 × 10 mL), 5 % Na_2CO_3 (2 × 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting colorless solid was dissolved in MeOH (15 mL). Pd/C (10 % w/w, 100 mg) was added and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 h. The reaction mixture was filtered over a pad of celite. The celite was washed with MeOH (3 × 5 mL). The solvent was removed under reduced pressure to give a colorless solid (1.08 g, 98 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, *J* = 5.9 Hz, 1H), 3.30 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.16 (td, *J* = 7.2, 5.9 Hz, 2H), 2.28 (t, *J* = 7.7 Hz, 1H), 2.27 (t, *J* = 7.2 Hz, 1H), 2.01 (ddt, J = 14.0, 7.2, 5.0 Hz, 1H), 1.73 (dtd, J = 14.0, 7.7, 7.5 Hz, 1H), 1.37 (s, 9H), 1.29 – 1.10 (m, 20H), 0.81 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 172.8, 80.5, 54.7, 39.1, 32.0, 31.9, 30.4, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 28.1, 27.0, 22.7, 14.1. MS (ESI, $[M+H]^+$) Calcd for $C_{21}H_{43}N_2O_3$: 371.3. Found: 371.3.

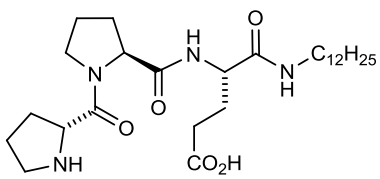
Boc-D-Pro-Pro-OH



Boc-D-Pro-OH (1.94 g, 9.00 mmol, 1.05 eq), HOBt·H_2O (1.65 g, 10.8 mmol, 1.2 eq) and EDC·HCl (2.07 g, 10.8 mmol, 1.2 eq) were dissolved in CH_2Cl_2 (24 mL) and cooled to 0°C. Then *i*Pr_2NEt (1.92 mL, 11.3 mmol, 1.3 eq) was added and the mixture was stirred for 10 min before H-Pro-OMe·HCl (1.42 g, 8.57 mmol, 1.0 eq) was added. The mixture was stirred at room temperature for 4 h. 0.1 M HCl (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 10 % $NaHCO_3$ (30 mL), H_2O (20 mL) and brine (30 mL), dried over Na_2SO_4 and filtered through a short plug of silica gel. The solvent was removed under reduced pressure. The resulting colorless solid was dissolved in THF/MeOH 1:1 (15 mL), 4 M NaOH (8 mL) was added slowly and the reaction mixture stirred at room temperature for 1 h. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL), acidified (pH ≈ 2) with concentrated HCl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded Boc-D-Pro-Pro-OH as a colorless solid (2.33 g, 87 %).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 10.21 (s br, 1 H), 4.54 (m, 1H), 4.39 (m, 1H), 3.95 – 3.28 (m, 4H), 2.45 – 1.68 (m, 8H), 1.37 and 1.33 (2 s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* = 175.6, 174.3, 172.0, 171.5, 154.9, 153.4, 143.7, 80.6, 80.4, 60.5, 57.9, 57.7, 47.5, 46.9, 46.6, 30.2, 29.1, 28.5, 28.4, 28.3, 28.1, 28.0, 27.0, 24.8, 24.7, 24.7, 23.7 (Mixture of two conformers in a ratio of approximately 2:1). MS (ESI, $[2M+Na]^+$) Calcd for $C_{30}H_{48}N_4NaO_{10}$: 647.3. Found: 647.3.

H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ (1a)

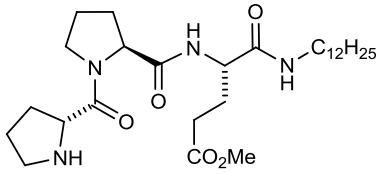


Boc-D-Pro-Pro-OH (1.00 g, 3.20 mmol, 1.0 eq) and EDC·HCl (736 mg, 3.84 mmol, 1.2 eq) were suspended in 20 mL EtOAc and *i*Pr_2NEt (660 μL, 1.2 eq) was added. After stirring for 10 min at room temperature

H-Glu(OtBu)NH-$C_{12}H_{25}$ (1.19 g, 3.2 mmol, 1.0 eq) was added and the suspension was stirred at room temperature for 3h. The reaction mixture was diluted with 40 mL of EtOAc, washed with 0.1 M HCl (2 x 10 mL), 5 % Na_2CO_3 (10 mL) and brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a colorless oil which was purified by flash column chromatography on silica gel eluting with 7 % MeOH in EtOAc. The protected peptide was dissolved in 5 mL of TFA/CH_2Cl_2 2:1 and stirred at room temperature for 30 min. All volatile components were removed under reduced pressure to afford peptide **1a** as the TFA salt (1.50 g, 75 %). The TFA was removed by ion exchange using a VariPure™ IPE cartouche (Varian, Inc.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 6.0 Hz, 1H), 6.85 (t, *J* = 5.5 Hz, 1H), 4.54 (t, *J* = 7.7 Hz, 1H), 4.44 (dd, *J* = 6.9, 5.3 Hz, 1H), 4.30 (td, *J* = 6.0, 3.0 Hz, 1H), 3.95 (dt, *J* = 9.9, 5.9 Hz, 1H), 3.51 (dt, *J* = 9.8, 7.8 Hz, 1H), 3.43 – 3.31 (m, 1H), 3.31 – 3.13 (m, 3H), 2.45 – 1.84 (m, 9H), 1.58 – 1.43 (m, 1H), 1.38 – 1.13 (m, 22H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.6, 170.7, 170.1, 169.4, 62.0, 59.3, 54.7, 47.5, 45.3, 39.7, 32.4, 32.1, 29.8, 29.8, 29.8, 29.5, 29.5, 29.5, 28.0, 27.1, 25.8, 25.0, 24.7, 22.8, 14.3. HRMS (ESI, $[M+H]^+$) Calcd for $C_{27}H_{49}N_4O_5$: 509.3697. Found: 509.3709.

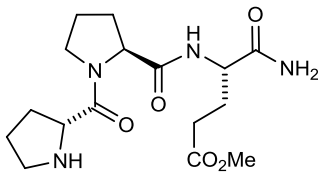
H-D-Pro-Pro-Glu(OMe)-NH-$C_{12}H_{25}$ (2a)



TFA·H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ (150 mg, 240 μmol, 1.0 eq) was dissolved in MeOH (4 mL) and cooled to -5°C with an ice/NaCl bath. Thionyl chloride (68.0 μL, 960 mmol, 4.0 eq) was added carefully and the solution was stirred for 90 min at -5 to 15 °C. The solution was added to 10 % $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (5x 10 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography on silica gel eluting with CH_2Cl_2:MeOH:NH_3(aq) 100:10:1 provided peptide **2a** as a colorless solid (82 %).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.70 (d, *J* = 7.8 Hz, 1H), 6.88 (t, *J* = 5.6 Hz, 1H), 4.45 – 4.30 (m, 2H), 3.95 (dd, *J* = 8.6, 5.8 Hz, 1H), 3.90 – 3.80 (m, 1H), 3.66 (s, 3H), 3.50 (dt, *J* = 9.9, 7.7 Hz, 1H), 3.29 – 3.03 (m, 4H), 2.84 (dt, *J* = 10.8, 6.7 Hz, 1H), 2.53 – 2.32 (m, 1H), 2.23 – 2.02 (m, 5H), 2.04 – 1.91 (m, 2H), 1.89 – 1.63 (m, 3H), 1.58 – 1.39 (m, 2H), 1.35 – 1.15 (m, 18H), 0.85 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 174.8, 171.5, 170.6, 61.5, 59.7, 53.2, 52.1, 47.6, 47.2, 39.8, 32.0, 30.5, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.2, 27.0, 26.5, 26.1, 24.9, 22.8, 14.2. HRMS (ESI, $[M+H]^+$) Calcd for $C_{28}H_{51}N_4O_5$: 523.3854. Found:523.3838.

H-D-Pro-Pro-Glu(OMe)-NH_2 (2)



Boc-D-Pro-Pro-OH (794 mg, 2.54 mmol, 1.0 eq) and EDC·HCl (584 mg, 3.05 mmol, 1.2 eq) were dissolved in EtOAc (12 mL) and DMF (1.2 mL). After adding *i*Pr_2NEt (508 µL, 3.05 mmol, 1.20 eq) the mixture was stirred at room temperature for 10 min. Then H-Glu(OMe)-NH_2 (500 mg, 2.54 mmol, 1.0 eq) was added and the resulting cloudy mixture was stirred at room temperature for 12 h. The mixture was diluted with EtOAc (20 mL) and washed with 0.1 M HCl (10 mL), H2O (10 mL), 10 % $NaHCO_3$ (10 mL) and brine (2 × 10 mL). The aqueous layer was re-extracted with CH_2Cl_2 (30 mL). The combined organic layers were dried over Na_2SO_4. After removing all volatiles under reduced pressure, the crude product was filtered through a plug of silica gel eluting with 10 % MeOH in EtOAc. The solvents were removed under reduced pressure and the product dissolved in a mixture of TFA/CH_2Cl_2 2:1 (5 mL). The mixture was stirred at room temperature for 2 hours. Then, the solvent was removed under reduced pressure and the peptide precipitated by the addition of Et_2O. The solvent was decanted and the resulting oil dried *in vacuo* to provide peptide **2** as the TFA salt (570 mg, 45 %). The TFA was removed by ion exchange using a VariPure^{TM} IPE cartouche (Varian, Inc.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 1H), 6.82 (s, 1H), 6.18 (s, 1H), 4.53 – 4.38 (m, 2H), 3.96 – 3.83 (m, 2H), 3.68 (s, 3H), 3.51 (dt, *J* = 10.8, 7.8 Hz, 1H), 3.22 – 3.07 (m, 1H), 2.81 (dt, *J* = 10.7, 7.0 Hz, 1H), 2.53 – 2.36 (m, 2H), 2.32 – 1.93 (m, 7H), 1.90 – 1.61 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 174.5, 173.8, 171.7, 61.6, 59.5, 52.4, 51.9, 47.2, 47.1, 30.6, 29.6, 29.3, 26.5, 25.8, 24.8. HRMS (ESI, $[M+Na]^+$) Calcd for $C_{16}H_{26}N_4NaO_5$: 377.1795. Found: 377.1807.

3. *In situ* FT-IR studies

3.1. General

All experiments were carried out at room temperature using *n*-butanal and *trans*-β-nitrostyrene. Toluene was purchased in crown-cap quality and used as such. Chloroform was filtered through a plug of basic alumina prior to use. Reaction progress was monitored by following the N-O-stretching mode of the product γ-nitroaldehyde at 1554 cm^{-1}. The N-O-stretching mode at 1554 cm^{-1} is an isolated band the intensity of which directly corresponds to the product concentration.[3] Spectra were collected every minute (154 scans) for the first three hours and thereafter every 5 minutes (256 scans) until completion of the reaction. Upon completion of the reaction an aliquot (100 μL) was withdrawn from the reaction mixture, diluted with $CDCl_3$ and subjected to ^{1}H-NMR spectroscopic analysis to determine the diastereoselectivity. The remaining reaction mixture was used to isolate the γ-nitroaldehyde and determine the enantioselectivity of the reaction.

3.2. Reaction setup

A volumetric flask (1 mL) was charged with the catalyst (22 μmol, 5 mol%) and *trans*-nitrostyrene (65.6 mg, 440 μmol, 1.0 eq). Solvent was added and the resulting mixture was sonicated until a homogeneous solution was obtained. Then *n*-butanal was added followed by the addition of the solvent until the total volume of 1 mL was reached. The clear solution was immediately transferred to a 3 mL round bottom flask containing the IR probe and a magnetic stirrer. The reaction mixture was gently stirred during the reaction.

3.3. Conversion-time curves

Catalysts 1 and 1a in $CHCl_3$:*i*PrOH 9:1

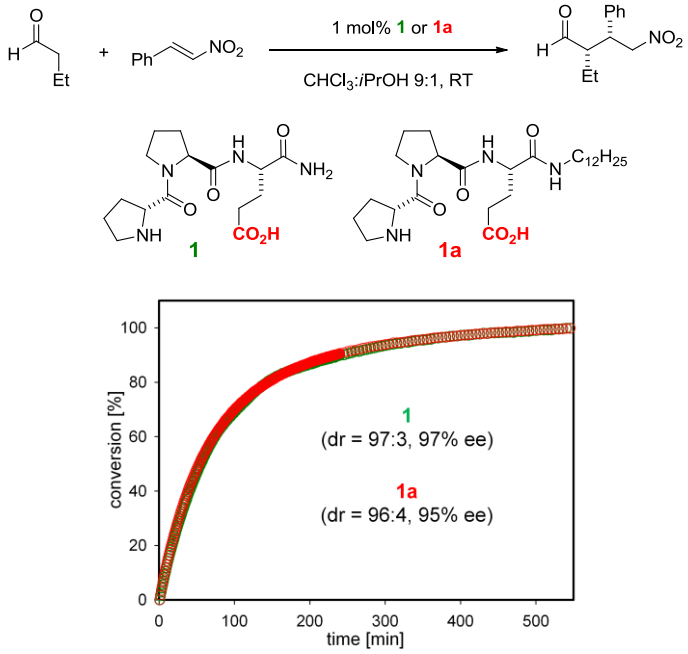


Figure S 1 *Conversion-time curves in the presence of catalysts **1** and **1a** in $CHCl_3$:iPrOH 9:1*

Catalysts 2 and 2a in $CHCl_3$:*i*PrOH 9:1

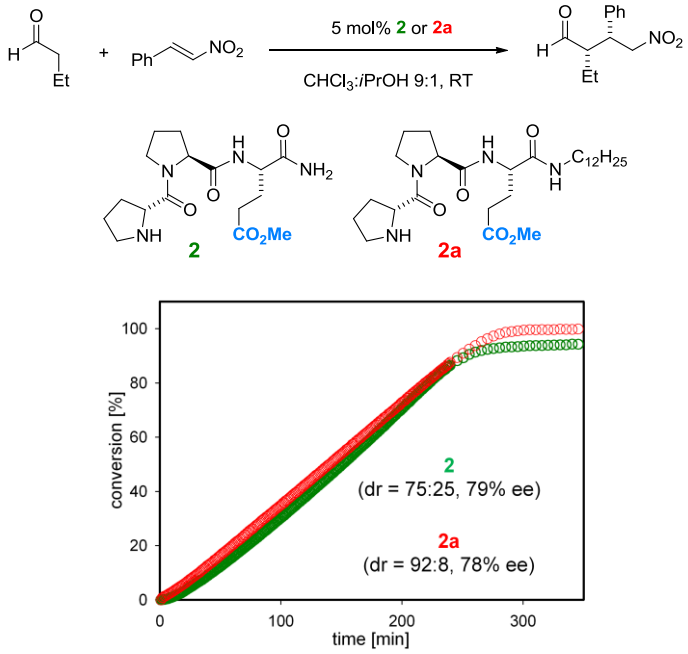


Figure S 2 *Conversion-time curves in the presence of catalysts **2** and **2a** in $CHCl_3$:iPrOH 9:1*

Catalysts 1 and 2 in $CHCl_3$:*i*PrOH 9:1

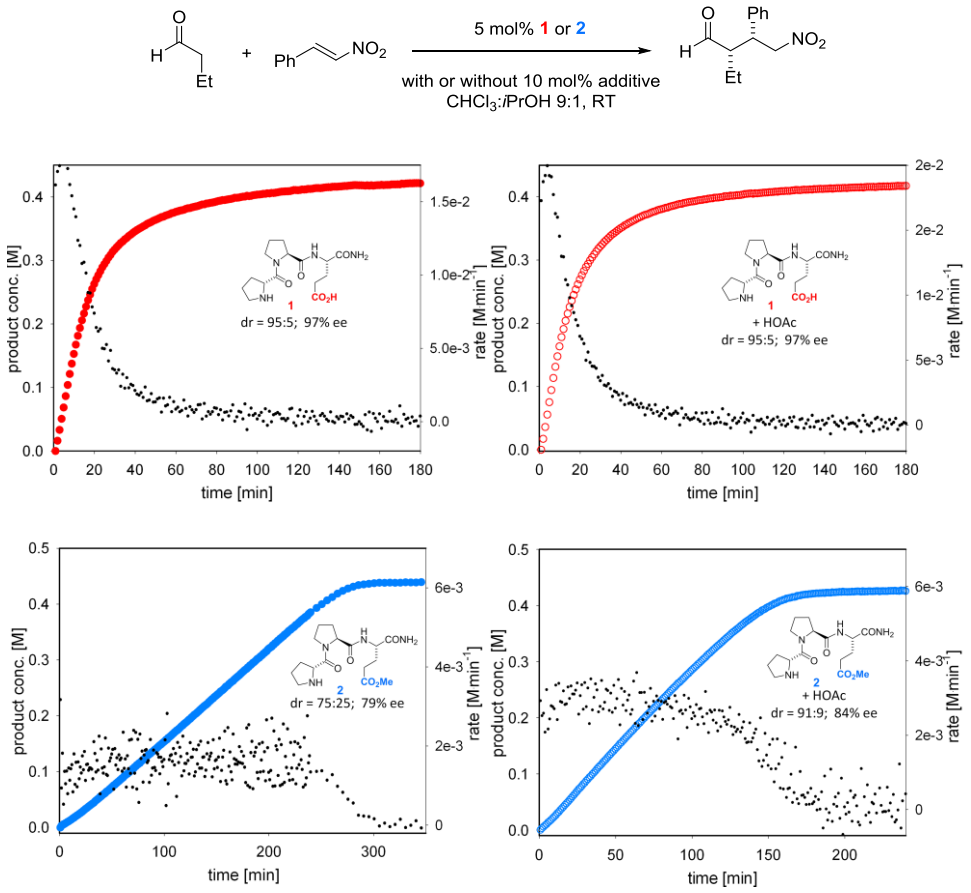
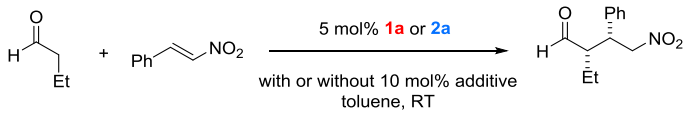


Figure S 3 *Conversion-time curves and their first derivatives in the presence of catalysts **1** and **2** in $CHCl_3$:iPrOH 9:1.*

Catalysts 1a and 2a in toluene



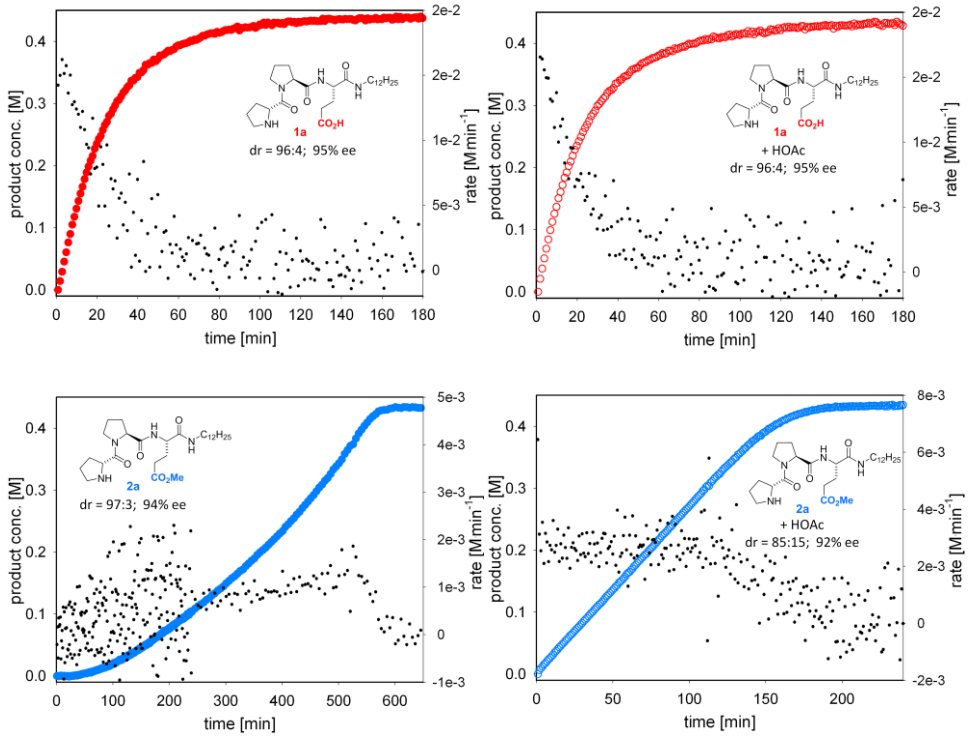


Figure S 4 *Conversion-time curves and their first derivatives in the presence of catalysts* ***1a*** *and* ***2a*** *in toluene*

Catalysts 1b – 1f in $CHCl_3$:*i*PrOH 9:1

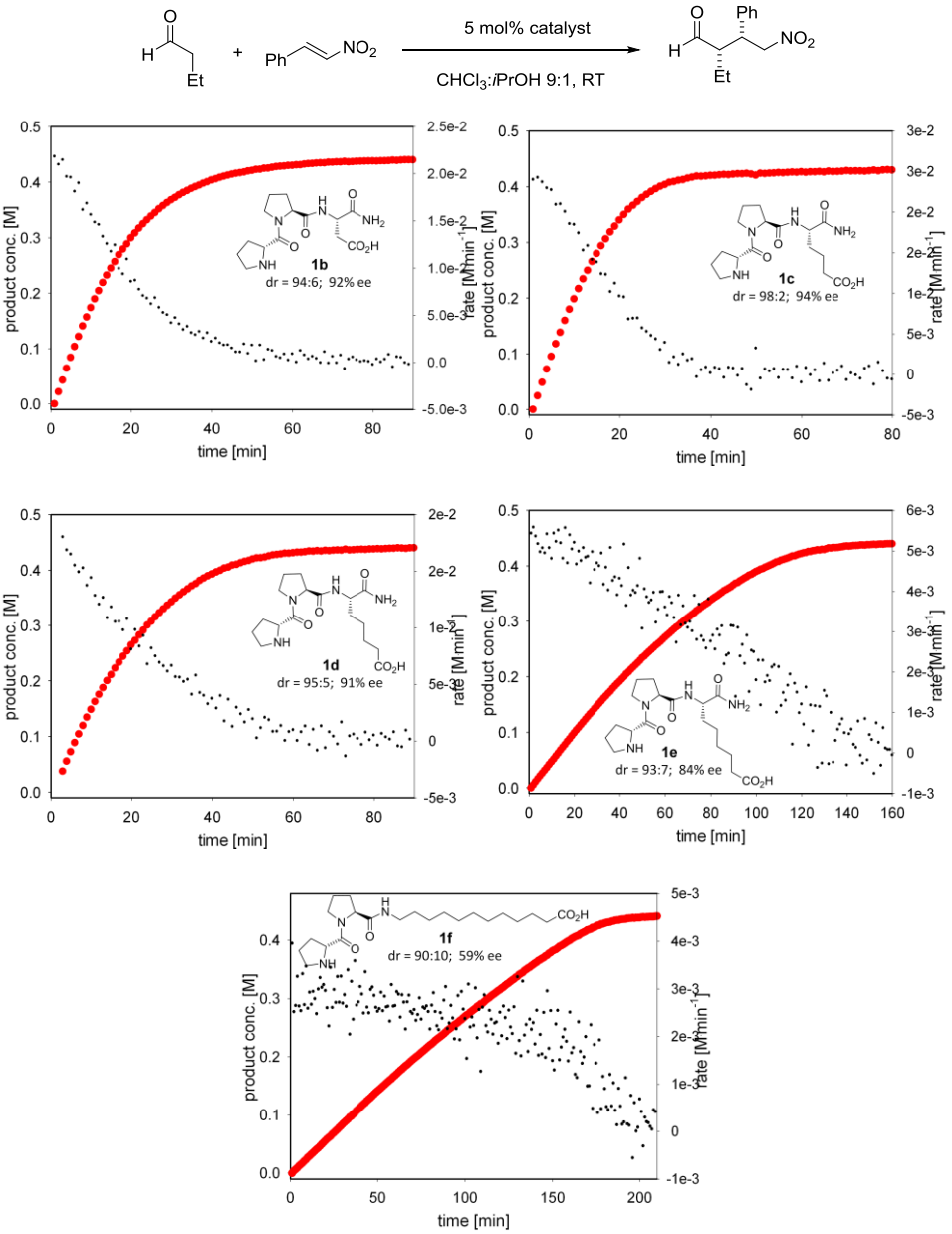
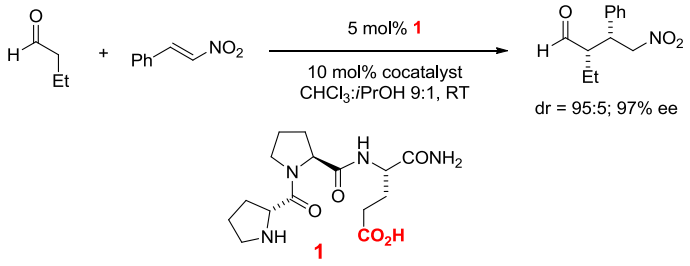


Figure S 5 *Conversion-time curves and their first derivatives in the presence of catalysts* ***1b*** *-* ***1f*** *in* $CHCl_3$*:iPrOH 9:1.*

Catalysts 1 in $CHCl_3$:*i*PrOH 9:1 in the presence of acidic additives with different pKa values



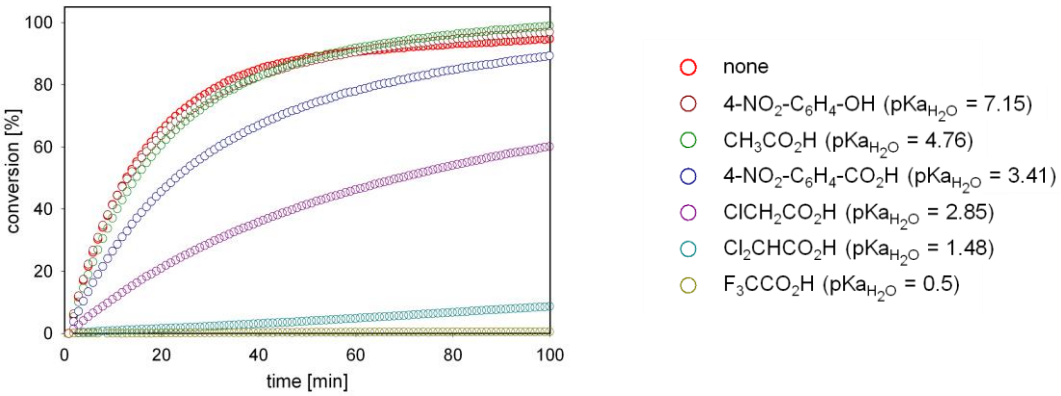
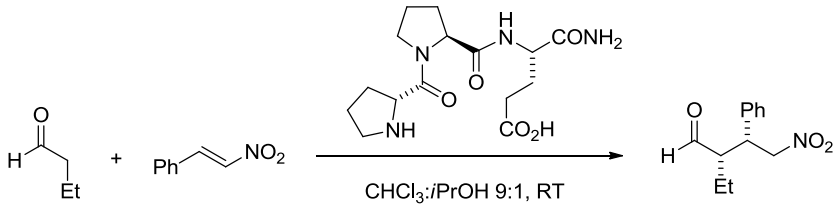


Figure S 6 *Conversion-time curves obtained in the presence of catalysts **1** in combination with acidic additives of different pK_a in $CHCl_3$:iPrOH 9:1*

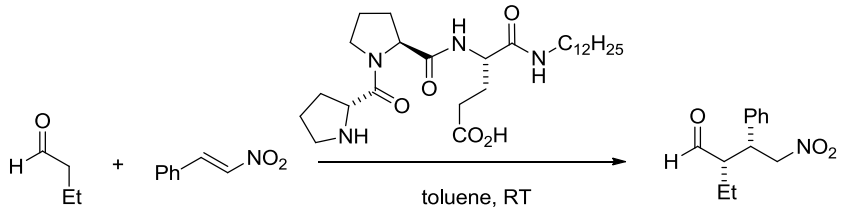
3.4. Determination of Reaction Orders

3.4.1. Reaction of n-butanal with nitrostyrene in the presence of H-D-Pro-Pro-Glu-NH_2 ***1*** *in $CHCl_3$:iPrOH 9:1.*



The reaction orders were determined previously.[1]

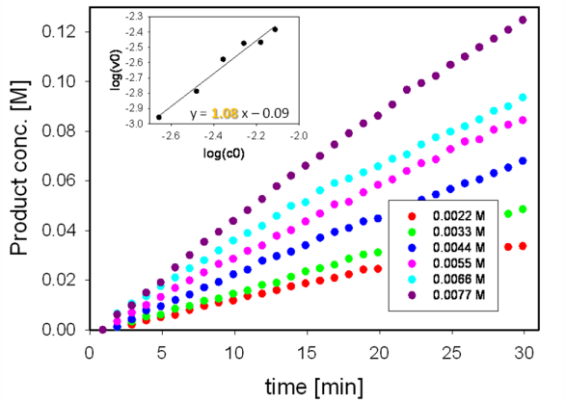
3.4.2. Reaction of n-butanal with nitrostyrene in the presence of H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ ***1a*** *in toluene.*



H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$

Experiments were carried out at constant initial concentrations of nitrostyrene (0.44 M) and *n*-butanal (0.44 M) varying the initial concentrations of H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ (2.2 mM, 4.4 mM, 6.6 mM, 8.8 mM, 11.0 mM, 12.1 mM). To obtain initial rates, the first derivative of the product concentration vs. time curve was calculated at t = 15 min.

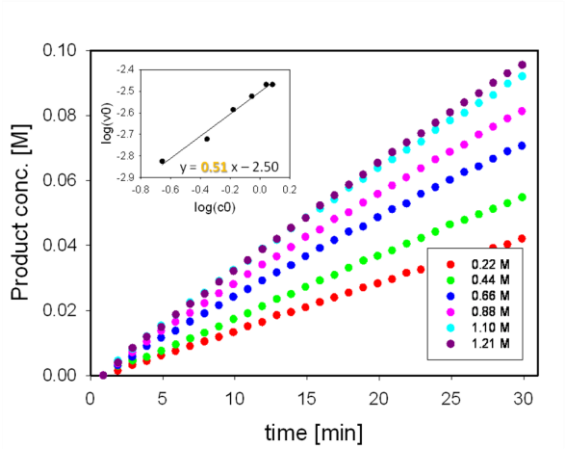
The product concentration vs. time curves, as well as the resulting log-log plot[4,5] are shown below: first order dependence on the catalyst concentration is observed.



Nitrostyrene

Experiments were carried out at constant initial concentrations of H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ **1a** (4.4 mM) and *n*-butanal (0.44 M) varying the initial concentrations of nitrostyrene (0.22 M, 0.44 M, 0.66 M, 0.88 M, 1.10 M, 1.21 M). To obtain initial rates, the first derivative of the product concentration vs. time curve was calculated at t = 15 min.

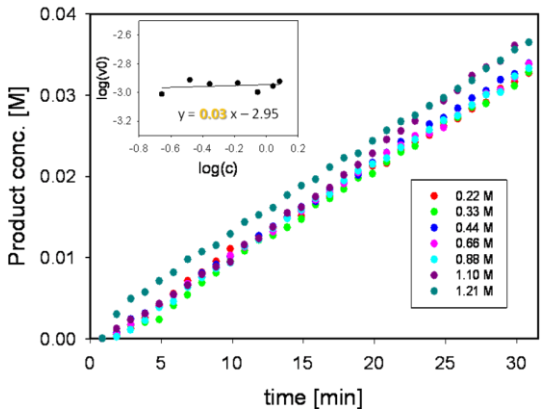
The product concentration vs. time curves, as well as the resulting log-log plot[4,5] are shown below: a reaction order of 0.5 is observed.



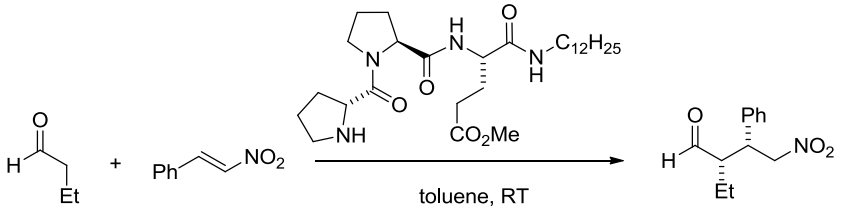
n-Butanal

Experiments were carried out at constant initial concentrations of H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ **1a** (4.4 mM) and nitrostyrene (0.44 M) varying the initial concentrations of butanal (0.22 M, 0.33 M 0.44 M, 0.66 M, 0.88 M, 1.10 M, 1.21 M). To obtain initial rates, the first derivative of the product concentration vs. time curve was calculated at t = 15 min.

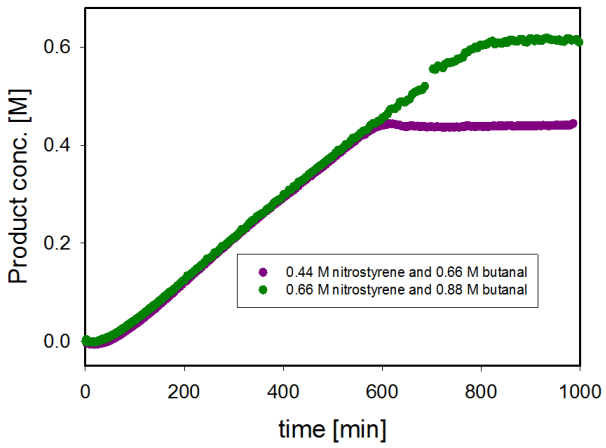
The product concentration vs. time curves, as well as the resulting log-log plot[4,5] are shown below: a zero order dependence on the aldehyde concentration is observed.



3.4.3. *Reaction of n-butanal with nitrostyrene in the presence of H-D-Pro-Pro-Glu(OMe)-NH-$C_{12}H_{25}$* ***2a*** *in toluene.*



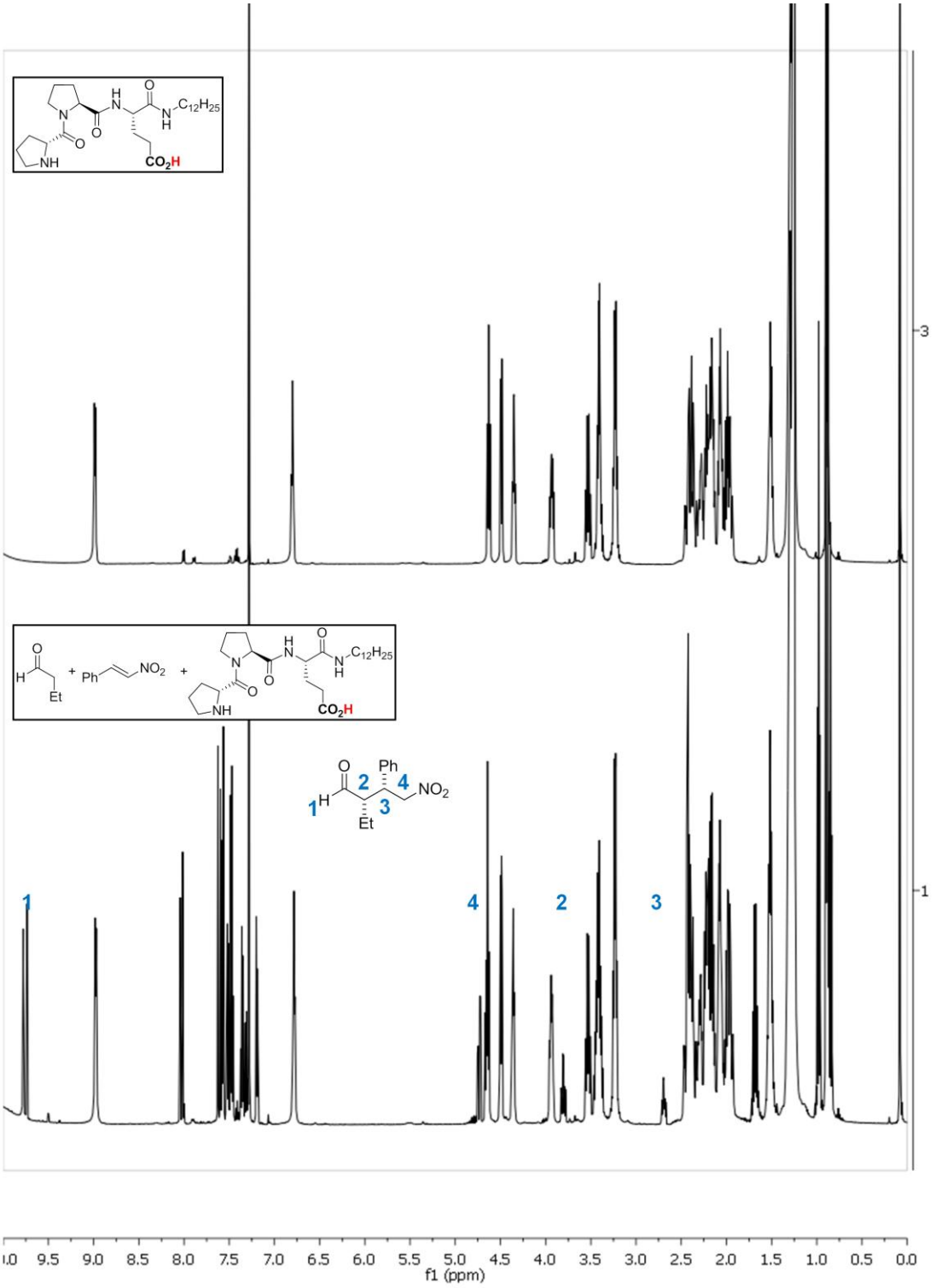
Two reactions using different initial concentrations of butanal (0.66 M and 0.88 M) and nitrostyrene (0.44 M and 0.66 M) at a constant catalyst concentration (22 mM) show identical reaction progress confirming a zero order dependence on both substrates.



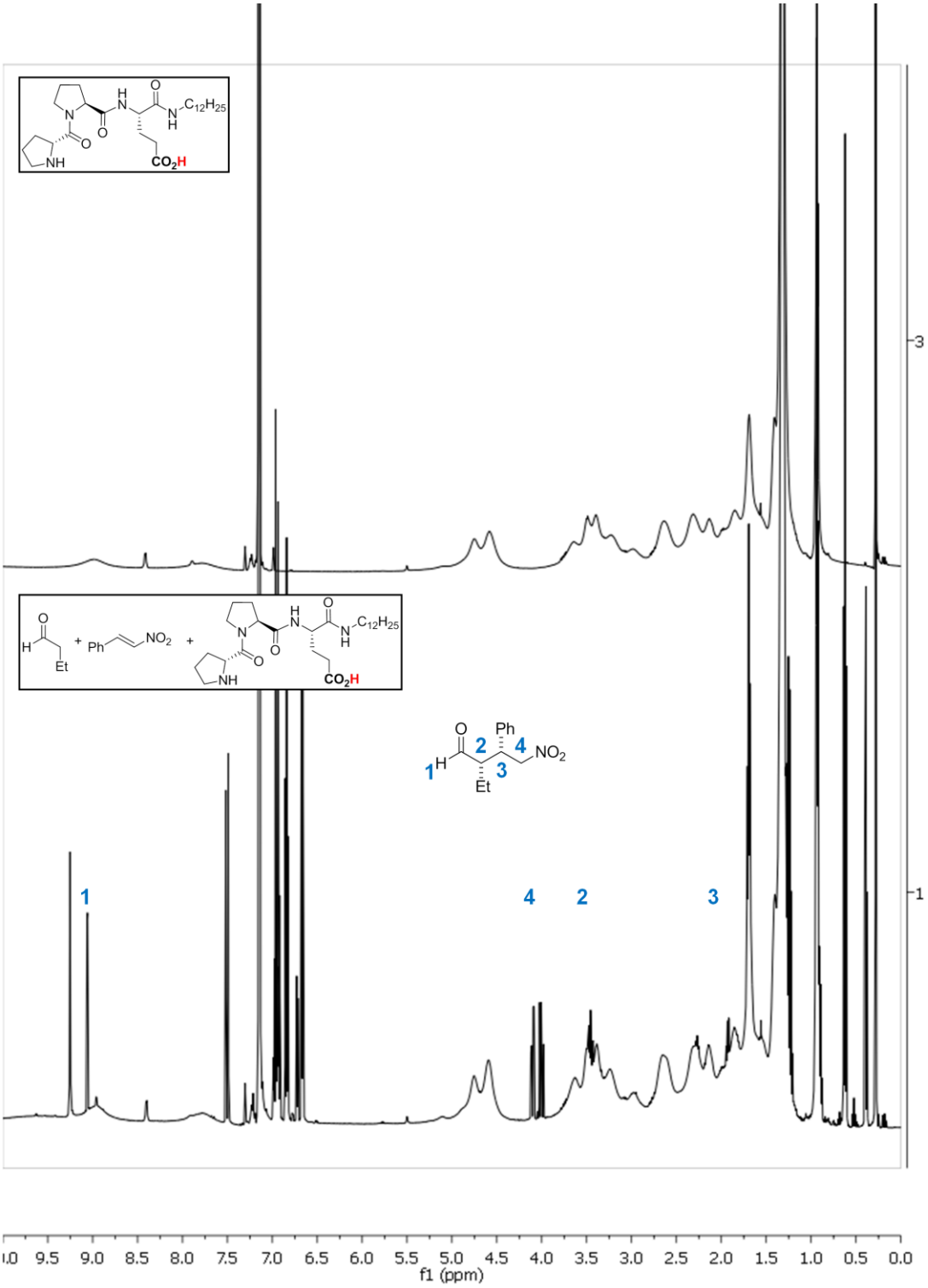
4. NMR-Experiments

Experimental setup: To a solution of the peptide (20 μmol, 2.0 eq) in the respective solvent (0.5 mL) was added a solution of butanal (0.90 μL, 10 μmol, 1.0 eq) in the respective solvent (0.1 mL). After 5 min a ^{1}H NMR spectrum was recorded. Then *trans*-nitrostyrene (1.49 mg, 10 μmol, 1.0 eq) was added as a solution in the respective solvent and again a ^{1}H NMR spectrum was collected after 5 min.

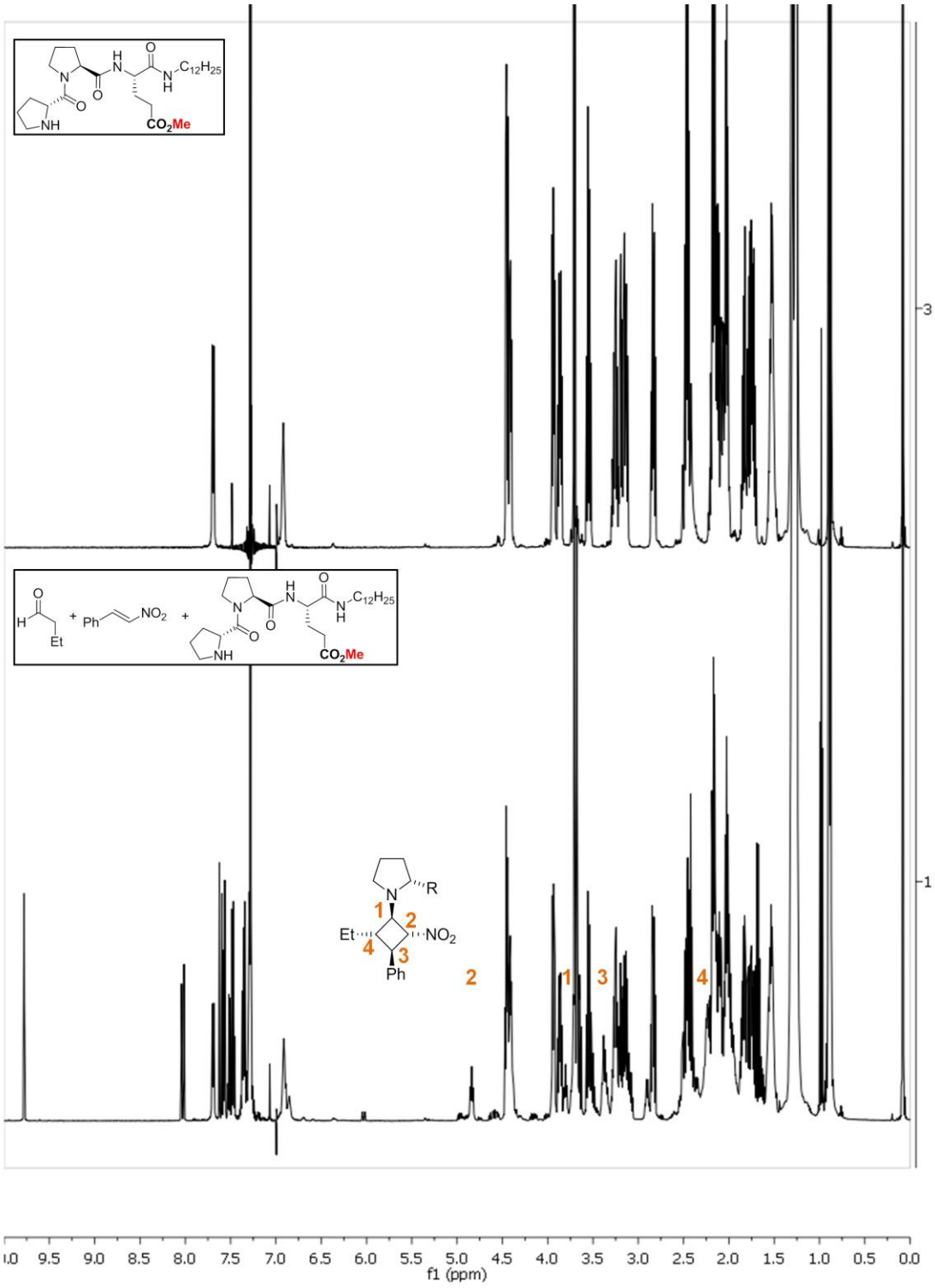
H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ (1a) in $CDCl_3$



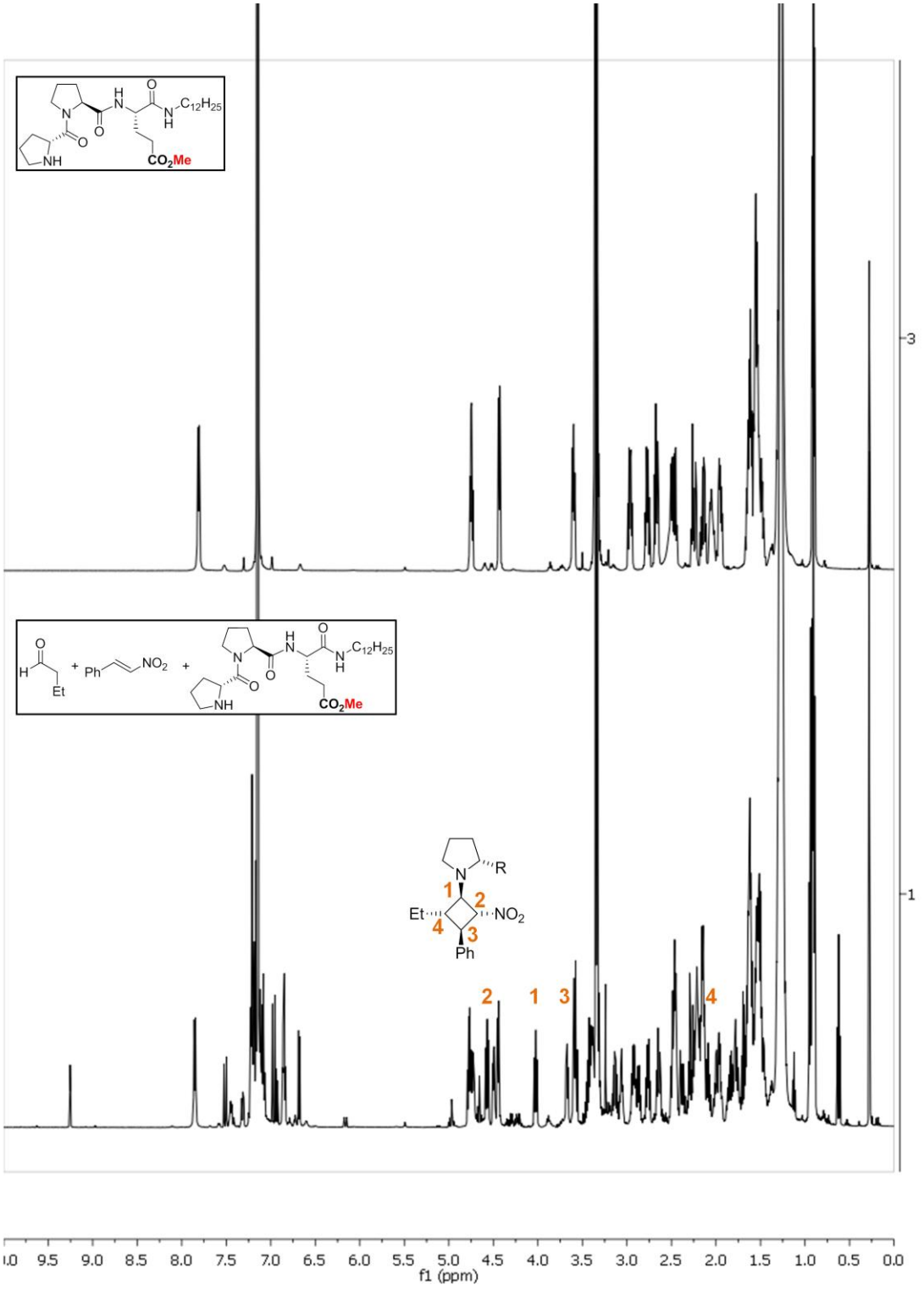
H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ (1a) in C_6D_6



H-D-Pro-Pro-Glu(OMe)-NH-$C_{12}H_{25}$ (2a) in $CDCl_3$



H-D-Pro-Pro-Glu(OMe)-NH-$C_{12}H_{25}$ (2a) in C_6D_6

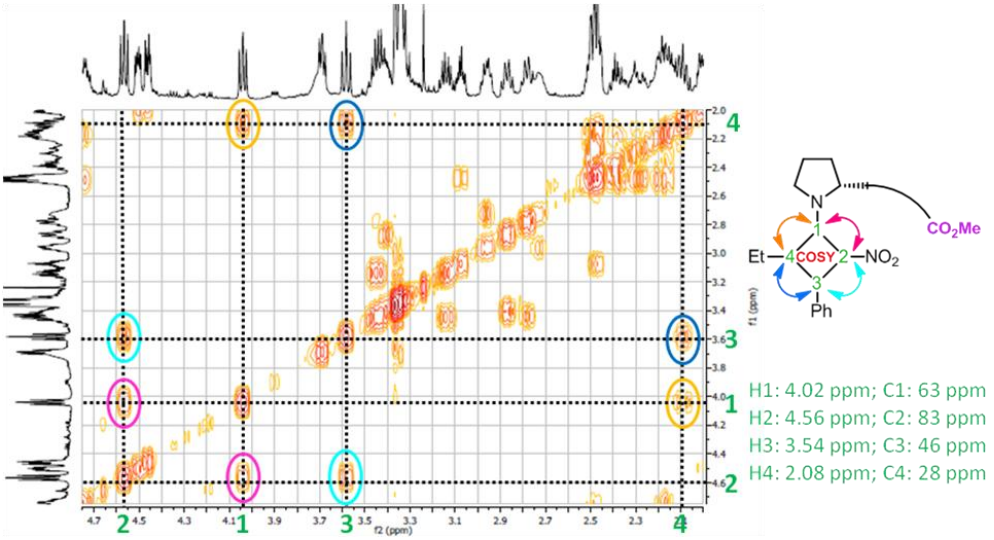


2D NMR spectroscopic analysis cyclobutane C derived from 2a

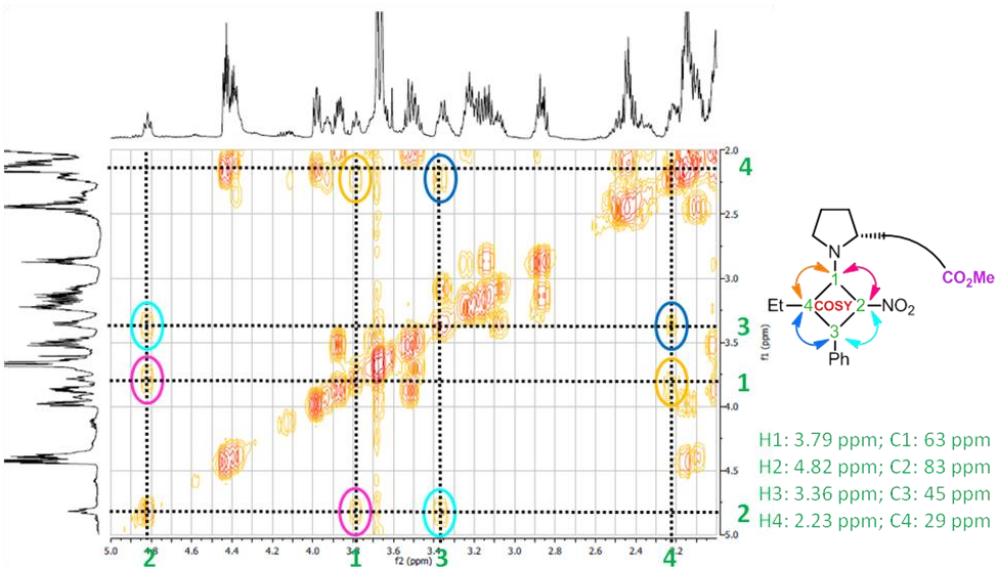
Conditions:

- 20 μmol of peptide **2a** (2.0 eq)
- Freshly activated 4Å molecular sieves
- 0.6 mL of solvent
- 10 μmol of butanal (1.0 eq)
- 10 μmol of nitrostyrene (1.0 eq)
- Room temperature, 5 min

Relevant excerpt in C_6D_6

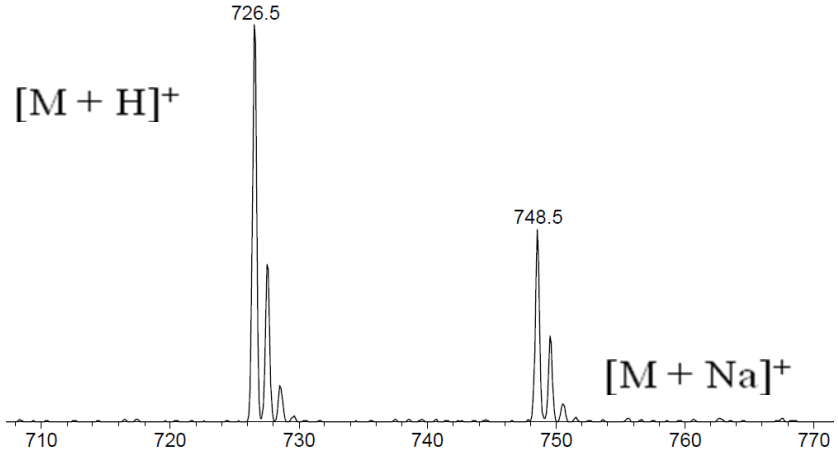


Relevant excerpt in $CDCl_3$



Electron spray mass spectrometric analysis of NMR sample

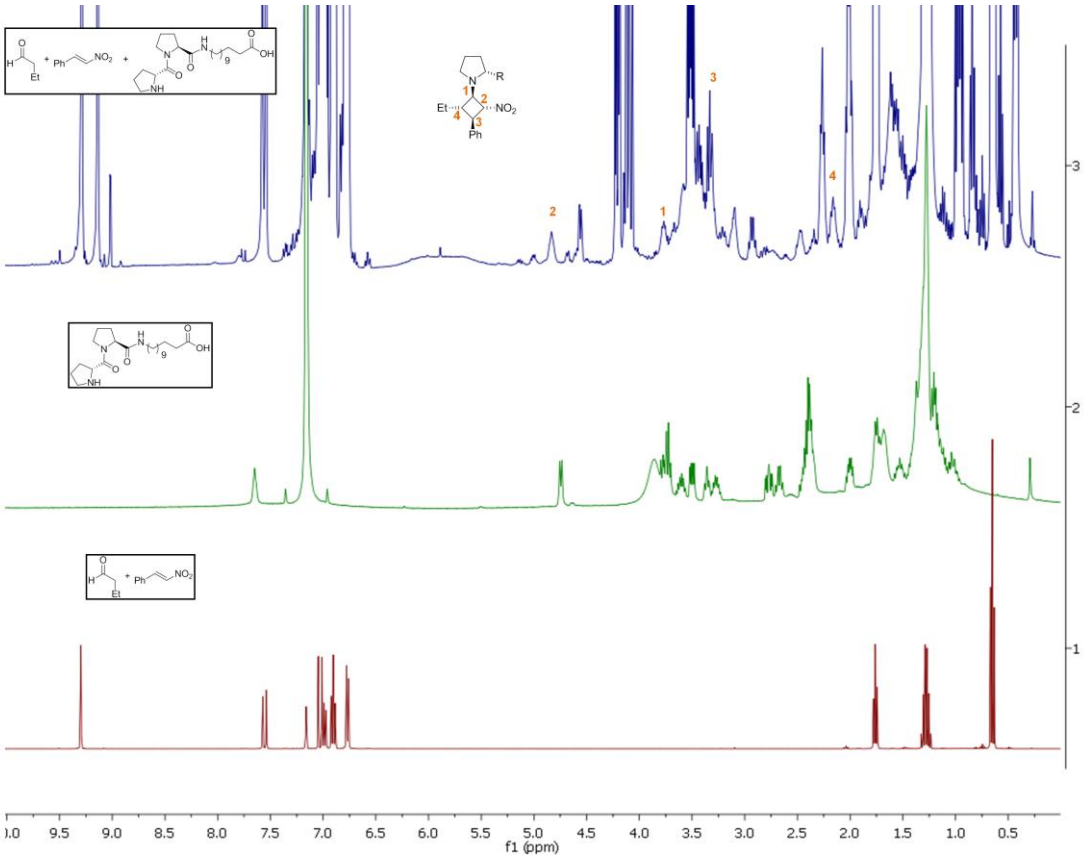
A small aliquot of the NMR sample in C_6D_6 was diluted with MeOH and injected into an ESI-MS spectrometer. In the resulting spectra the mass of a protonated cyclobutane intermediate as well as the corresponding sodium adduct are observed.

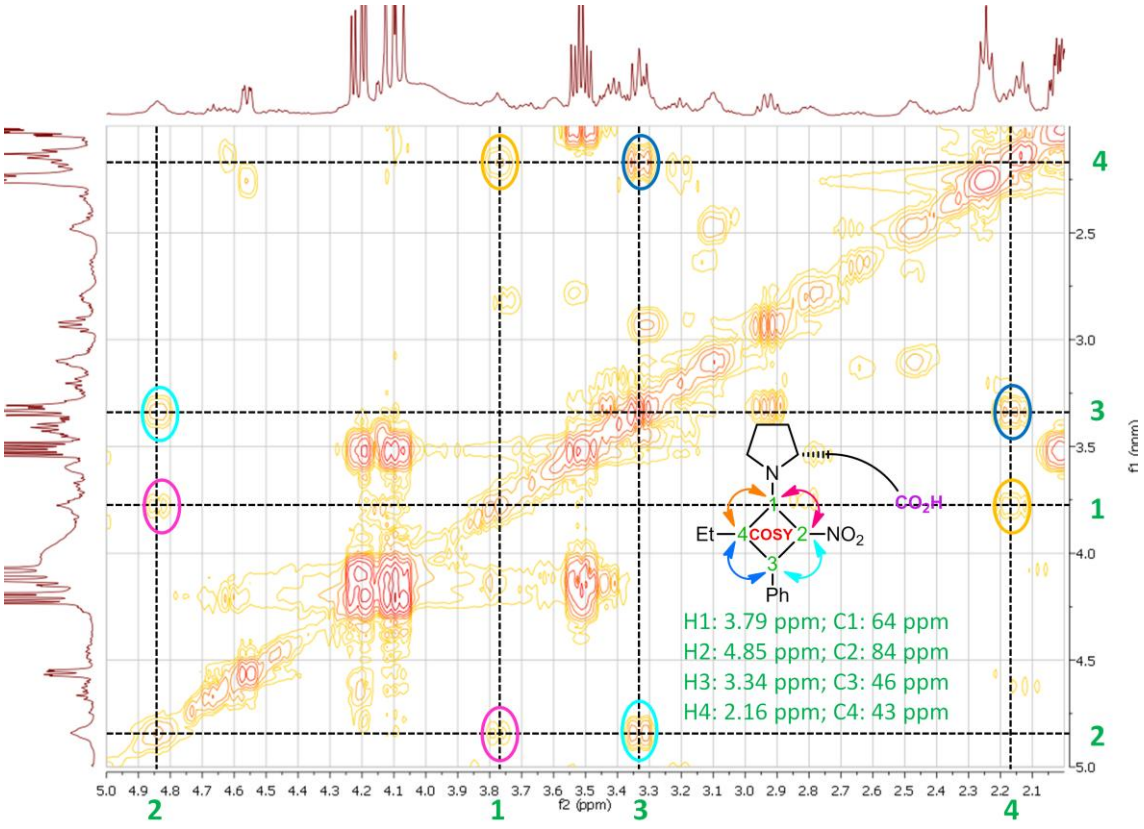


NMR spectroscopic analysis cyclobutane C derived from 1f

Conditions:

- 20 μmol of peptide **1f** (10 mol%)
- 0.6 mL of C_6D_6
- 200 μmol of butanal (1.0 eq)
- 200 μmol of nitrostyrene (1.0 eq)
- Room temperature, 60 min




H1: 3.79 ppm; C1: 64 ppm
H2: 4.85 ppm; C2: 84 ppm
H3: 3.34 ppm; C3: 46 ppm
H4: 2.16 ppm; C4: 43 ppm
COSY
f2 (ppm)
f1 (ppm)

5. References

1. M. Wiesner, M. Neuburger, and H. Wennemers, *Chem. Eur. J.*, 2009, **15**, 10103–10109.
2. M. Wiesner and H. Wennemers, *Synthesis*, 2010, 1568–1571.
3. M. Wiesner, G. Upert, G. Angelici, and H. Wennemers, *J. Am. Chem. Soc.*, 2010, **132**, 6–7.
4. J. P. Birk, *J. Chem. Educ.*, 1976, **53**, 195.
5. J. Casado, M. A. Lopez-Quintela, and F. M. Lorenzo-Barral, *J. Chem. Educ.*, 1986, **63**, 450.