Supporting Information

# Using Bifunctional Ureas to Increase the Rate of Proline-Catalyzed α-Aminoxylations

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## *1. Materials and Instrumentation*

All reagents were used without purification unless otherwise noted. Nitrosobenzene was recrystallized from ethanol prior to use. Ethyl phenyl urea was recrystallized from ethyl acetate prior to use. Propionaldehyde, hexanal, and octanal were vacuum distilled prior to use.

Reactions were rocked on a test tube rocker where indicated.

Gas chromatographic (GC) analyses were performed using a GC equipped with an autosampler, a flame ionization detector (FID), and a column (length = 30 m, inner diameter = 320 μm, and film thickness = 250 μm). The temperature program for GC analysis held the temperature constant at 80 $^{o}$C for 1 min, heated samples from 80 to 200 $^{o}$C at 25 $^{o}$C/min and held at 200 $^{o}$C for 1.5 min. Inlet and detector temperatures were set constant at 250 and 300 $^{o}$C, respectively. Mesitylene was used as an internal standard to calculate reaction conversion.

$^{1}$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ operating at 300.070 MHz and 75.452 MHz, respectively, using the residual solvent peak as reference. Data are reported as s = singlet, d = doublet, t = triplet, m = multiplet.

High performance liquid chromatography (HPLC) was performed using a chromatograph using a CHIRALPAK IA column (250 mm x 4.6 mm) and CHIRALPAK IA guard column (1 cm x 0.4 cm). Retention times for *R* and *S* isomers were determined by using (DL)-proline instead of (L)-proline in the general procedure. All chromatograms were obtained using a wavelength of 254 nm.

## *2. α-Aminoxylation of hexanal in the presence of additives*

### *2.1. Preparation of additives*

Ethyl phenyl urea (**2**) and N,N-dimethylethylamine (**3**) were purchased.

**1-(2-(dimethylamino)ethyl)-3-phenylurea (1).** Phenyl isocyanate (1.08 mL, 10 mmol, 1 eq) was added dropwise to a solution of *N*,*N*-dimethylethylenediamine (1.1 mL,10 mmol, 1 eq) in $CHCl_3$ (10 mL) at room temperature and the reaction was stirred for 30 min. The solvent was removed *in vacuo* and the product was recrystallized from EtOAc to afford white crystals (1.8 g, 87%). $^{1}$H NMR (300 Hz, $CDCl_3$) δ 7.35 (d, 2H), 7.22 (t, 2H), 6.97 (t, 1H), 6.36 (t, 1H), 3.30 (q, 2H), 2.42 (t, 2H), 2.12 (s, 3H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 157.8, 139.9, 129.2, 122.7, 120.0, 60.1, 45.5, 38.7. [4]

***N*-(2-(dimethylamino)ethyl)ethanamide (4).** Acetyl chloride (1.4 mL, 20 mmol, 2 eq) was added dropwise to a solution of *N*,*N*-dimethylethylenediamine (1.1 mL,10 mmol, 1 eq) in $CHCl_3$ (5 mL) at -78 $^{o}$C and the reaction was stirred for 2 h at -78 to 25 $^{o}$C. The solvent was removed *in vacuo* and the product was chromatographed (silica gel, 96:4 $CHCl_3$:MeOH) to afford a light yellow oil (1.2 g, 92%). $^{1}$H NMR (300 Hz, $CDCl_3$) δ 6.41 (br, 1H), 3.22 (m, 2H), 2.32 (t, 2H), 2.16 (s, 6H), 1.94 (s, 3H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 170.3, 57.9, 45.1, 36.9, 32.2.

### *2.2. General procedure*

A solution of additive (0.05 mmol, 0.05 eq) in 1 mL solvent was added to (L)-proline (5.8 mg, 0.05 mmol, 0.05 eq) in a 1 dram screw cap vial. The vial was sonicated for 1 min and held at 4 $^{o}$C for 15 min. 1 mL of a stock solution of nitrosobenzene (1 M), hexanal (3 M), and mesitylene (0.1 M) was added and the reaction was rocked at 4 $^{o}$C. Reaction conversion was monitored by withdrawing aliquots from the reaction, diluting into ethyl acetate, and analyzing by GC with reference to mesitylene. Yields at 40 minutes were determined using calibrated GC results.

*2.3. Examination of other ureas*

The α-aminoxylation of hexanal was performed in the presence of the following ureas using the general procedure described in section 2.2:

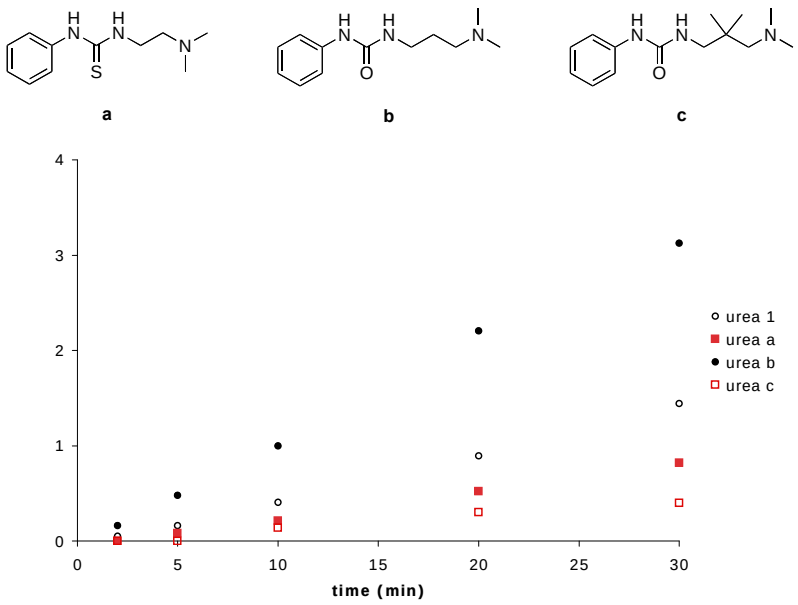



**Figure S1**. α-Aminoxylation of hexanal using ureas **a-c**.

*3. α-Aminoxylation of aldehydes*

General procedure: Nitrosobenzene (214 mg, 2.0 mmol, 1.0 eq), (L)-proline (11.6 mg, 0.1 mmol, 0.05 eq) and urea **1** (20.8 mg, 0.1 mmol, 0.05 eq) were added to a 2 dram screw cap vial equipped with a stir bar. Ethyl acetate (4 mL) was added to the vial, upon which the reaction mixture turned green. The reaction mixture was submerged in an ice bath and stirred for 15 min. The appropriate aldehyde (6.0 mmol, 3.0 eq) was added to the reaction mixture in one portion at 0 ˚C. The reaction mixture was continuously stirred at 0 ˚C until the reaction color changed from green to yellow and the reaction was determined to be complete by GC.

The reaction was transferred to a suspension of sodium borohydride (300 mg, 8.0 mmol, 4.0 eq) in ethanol (10 mL) at 0 ˚C. An additional 5 mL of ethanol was used to rinse the reaction vessel and added to the sodium borohydride suspension. After 20 min, the reaction mixture was poured into a separatory funnel containing 25 mL saturated aqueous $NaHCO_3$ and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried with $MgSO_4$, filtered, concentrated *in vacuo*, and dried under vacuum. The resulting residue was purified using column chromatography to afford the desired compounds. Enantioselectivities were determined using chiral HPLC analysis.

**(*R*)-2-(*N*-Phenyl-aminooxy)-hexan-1-ol (5a).** Prepared according to the general procedure using hexanal (750 µL, 6.0 mmol, 3.0 eq) for 2 h to afford the title compound

as a yellow oil (400 mg, 96 % yield, 99 % ee) after column chromatography (silica gel, 4:1 hexanes/EtOAc, $R_f$ = 0.18). $^1$H NMR (300 Hz, $CDCl_3$) δ 7.28 (m, 2H), 6.99 (m, 2H), 3.95 (m, 1H), 3.81 (m, 2H), 2.50 (bs, 1H), 1.68 (m, 1H), 1.40 (m, 6H), 0.93 (t, 3H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 148.7, 129.0, 122.1, 114.6, 84.0, 64.7, 29.7, 28.0, 22.9, 14.0. The enantiomeric ratio was determined by HPLC using a CHIRALPAK IA and IA guard column (5 % IPA/hexanes, 1 mL/min); (*S*) isomer $t_r$= 15.0 min and (*R*) isomer $t_r$= 17.6 min.

**(*R*)-2-(*N*-Phenyl-aminooxy)-propan-1-ol (5b).** Prepared according to the general procedure using propionaldehyde (437 μL, 6.0 mmol, 3.0 eq) for 3 h to afford the title compound as a yellow oil (300 mg, 90 % yield, 98 % ee) after column chromatography (silica gel, 4:1 hexanes/EtOAc, $R_f$ = 0.09). $^1$H NMR (300 Hz, $CDCl_3$) δ 7.28 (m, 2H), 7.00 (m, 3H), 4.13 (m, 1H), 3.76 (m, 2H), 1.26 (d, 3H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 148.8, 131.1, 129.1, 122.1, 80.2, 65.8, 15.5. The enantiomeric ratio was determined by HPLC using a CHIRALPAK IA and IA guard column (5 % IPA/hexanes, 1 mL/min); (*S*) isomer $t_r$= 20.2 min and (*R*) isomer $t_r$= 22.0 min.

**(*R*)-3-methyl-2-(*N*-Phenyl-aminooxy)-butan-1-ol (5c).** Prepared according to the general procedure using isovaleraldehyde (650 μL, 6.0 mmol, 3.0 eq) for 3.5 h to afford the title compound as a yellow oil (380 mg, 97 % yield, 99 % ee) after column chromatography (silica gel, 4:1 hexanes/EtOAc, $R_f$ = 0.18). $^1$H NMR (300 Hz, $CDCl_3$) δ 7.28 (m, 2H), 7.03 (bs, 1H), 7.01 (m, 3H), 3.88 (m, 2H), 3.75 (m, 1H), 2.84 (bs, 1H), 2.04 (m, 1H), 1.04 (dd, 6H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 148.6, 129.1, 122.5, 115.1, 88.7, 63.4, 28.8, 18.9, 18.7. The enantiomeric ratio was determined by HPLC using a CHIRALPAK IA and IA guard column (5 % IPA/hexanes, 1 mL/min); (*S*) isomer $t_r$= 13.4 min and (*R*) isomer $t_r$= 15.4 min.

**(*R*)-2-(*N*-Phenyl-aminooxy)-octan-1-ol (5d).** Prepared according to the general procedure using octanal (940 μL, 6.0 mmol, 3.0 eq) for 5 h to afford the title compound as a yellow oil (400 mg, 84 % yield, 99 % ee) after column chromatography (silica gel, 4:1 hexanes/EtOAc, $R_f$ = 0.14). $^1$H NMR (300 Hz, $CDCl_3$) δ 7.28 (m, 2H), 7.00 (m, 4H), 3.95 (m, 1H), 3.78 (m, 2H), 2.62 (bs, 1H), 1.48 (m, 10H), 0.91 (t, 3H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 148.7, 129.0, 122.2, 114.8, 84.1, 64.8, 31.8, 30.1, 29.3, 25.9, 22.7, 14.2. The enantiomeric ratio was determined by HPLC using a CHIRALPAK IA and IA guard column (5 % IPA/hexanes, 1 mL/min); (*S*) isomer $t_r$= 13.9 min and (*R*) isomer $t_r$= 16.0 min.

**(*R*)-3-phenyl-2-(*N*-Phenyl-aminooxy)-propan-1-ol (5e).** Prepared according to the general procedure using 3-phenylpropionaldehyde (793 μL, 6.0 mmol, 3.0 eq) for 3.5 h to afford the title compound as a yellow oil (410 mg, 84 % yield, >99 % ee) after column chromatography (silica gel, 4:1 hexanes/EtOAc, $R_f$ = 0.09). $^1$H NMR (300 Hz, $CDCl_3$) δ 7.18 (m, 7H), 6.97 (bs, 1H), 6.86 (t, 1H), 6.78 (d, 2H), 4.08 (m 1H), 3.78 (m, 1H), 3.66 (m, 1H), 3.02 (dd, 1H), 2.80 (dd, 1H), 2.38 (bs, 1H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 148.5, 138.0, 129.6, 1291, 128.6, 126.6, 122.3, 114.7, 85.2, 64.0, 36.6. The enantiomeric ratio was determined by HPLC using a CHIRALPAK IA and IA guard column (5 % IPA/hexanes, 1 mL/min); (*S*) isomer $t_r$= 25.8 min and (*R*) isomer $t_r$= 31.2 min.

**(*R*)-2-phenyl-2-(*N*-Phenyl-aminooxy)-ethan-1-ol (5f).** Prepared according to the general procedure using phenylacetaldehyde (766 μL, 6.0 mmol, 3.0 eq) for 2 h to afford the title compound as a yellow oil (250 mg, 55 % yield, 99 % ee) after column chromatography (silica gel, 4:1 hexanes/EtOAc, $R_f$= 0.20). $^1$H NMR (300 Hz, $CDCl_3$) δ 7.30 (m, 7H), 7.00 (m, 4H), 5.03 (dd, 1H), 3.98 (m, 1H), 3.86 (m, 1H), 2.58 (bs, 1H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 148.1, 138.0, 129.1, 128.7, 128.6, 127.2, 122.5, 115.0, 86.6, 66.1. The enantiomeric ratio was determined by HPLC using a CHIRALPAK IA and IA guard column (5 % IPA/hexanes, 1 mL/min); (*S*) isomer $t_r$= 25.9 min and (*R*) isomer $t_r$= 28.9 min.

**(*R*)-2-(*N*-Phenyl-aminooxy)-pent-4-en-1-ol (5g).** Prepared according to the general procedure using 4-pentenal (621 μL, 6.0 mmol, 3.0 eq) for 2.5 h to afford the title compound as a yellow oil (290 mg, 75 % yield, 99 % ee) after column chromatography (silica gel, 4:1 hexanes/EtOAc, $R_f$= 0.14). $^1$H NMR (300 Hz, $CDCl_3$) δ 7.28 (m, 2H), 7.05 (s, 1H), 7.00 (m, 3H), 5.89 (m, 1H), 5.14 (dt, 2H), 4.04 (m, 1H), 3.89 (m, 2H), 2.94 (m, 1H), 2.38 (m, 2H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 148.6, 134.2, 129.2, 122.6, 117.9, 114.9, 83.5, 64.6, 34.8. The enantiomeric ratio was determined by HPLC using a CHIRALPAK IA and IA guard column (5 % IPA/hexanes, 1 mL/min); (*S*) isomer $t_r$= 20.2 min and (*R*) isomer $t_r$= 23.1 min.

*4. Mannich reaction between benzaldehyde N-Boc imine and propionaldehyde*

Benzaldehyde *N*-Boc imine was prepared as reported in the literature.[1]

A solution of additive (0.05 mmol, 0.05 eq) in 1 mL solvent was added to (L)-proline (5.8 mg, 0.05 mmol, 0.05 eq) in a 1 dram screw cap vial. The vial was sonicated for 1 min and stirred at 0 °C for 15 min. 1 mL of a stock solution of benzaldehyde *N*-Boc imine (1.0 M) and mesitylene (0.1 M) was added, followed by propionaldehyde (72.2 μL, 4 mmol, 4 eq) and the reaction was stirred at 0 °C. Reaction conversion was monitored by withdrawing aliquots from the reaction, diluting into dichloromethane, and analyzing by GC with reference to mesitylene.

| additive | time (h) |
|---|---|
| none | 9 |
| urea **1** | 2.5 |
| ethyl phenyl urea **2** | 8 |
| N,N-dimethylethylamine **3** | 4 |
| **2** + **3** | 2.5 |

***tert*-butyl (2*S*)-2-methyl-3-oxo-1-phenylpropylcarbamate (6).** Prepared according to the procedure described above. After the reaction was complete, it was quenched into water and extracted with ether (3x). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. HPLC analysis was performed prior to

recrystallization from hexanes and ether. $^{1}$H NMR (300 Hz, $CDCl_3$) δ 9.71 (s, 1H), 7.38-7.23 (m, 5H), 5.09 (m, 2H), 2.91 (m, 1H), 1.42 (s, 9H), 1.05 (d, 3H); $^{13}$C NMR (75 Hz, $CDCl_3$) δ 203.2, 155.3, 129.0, 127.8, 126.8, 80.3, 54.9, 51.8, 28.5, 9.4. The enantiomeric ratio was determined by HPLC using a CHIRALPAK IA and IA guard column (10 % IPA/hexanes, 1 mL/min); $t_r$= 8.2 min and 9.8 min.

*5. $^{1}$H-NMR solubility studies*

To (L)-proline (17.3 mg, 0.15 mmol) and urea (31.1 mg, 0.15 mmol) in a 1 dram screw cap vial was added mesitylene (5 mM in $CDCl_3$). As a control a vial was prepared in the same way without urea. The vials were rocked at room temperature. After 2 h, the solution was filtered through a 0.45 μm PTFE membrane and assessed by $^{1}$H-NMR spectroscopy at 24 $^{o}$C using the following parameters:

| | |
|---|---|
| sfrq | 300.073 |
| tn | H1 |
| at | 1.666 |
| np | 16360 |
| sw | 4909.2 |
| fb | not used |
| pw | 10 |
| tpwr | 56 |
| d1 | 60.000 |
| tof | 685.1 |
| nt | 1 |
| gain | 28 |

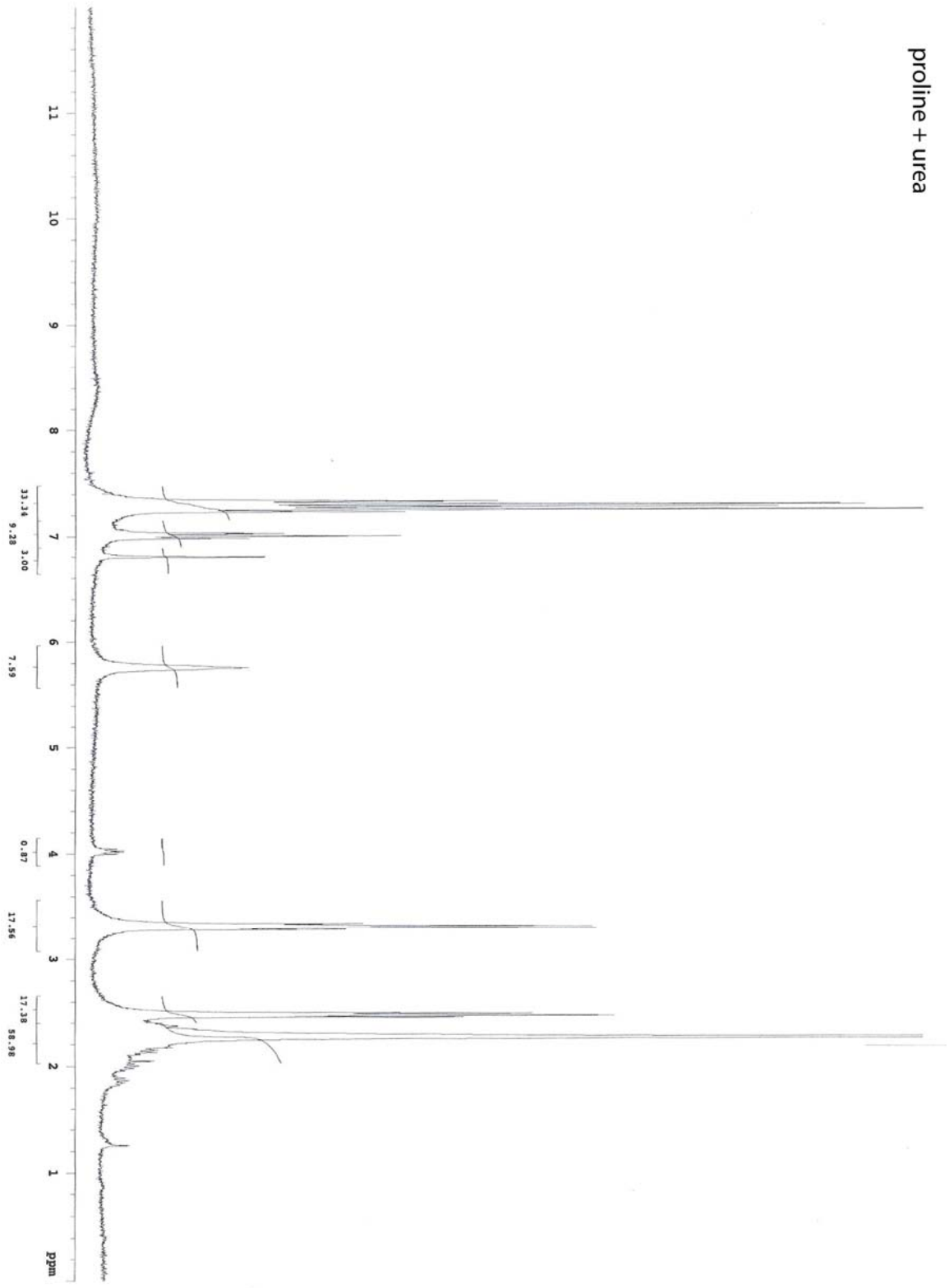



**Figure S2**. $^{1}$H-NMR spectrum of a 1:1 mixture of proline and urea **1**.

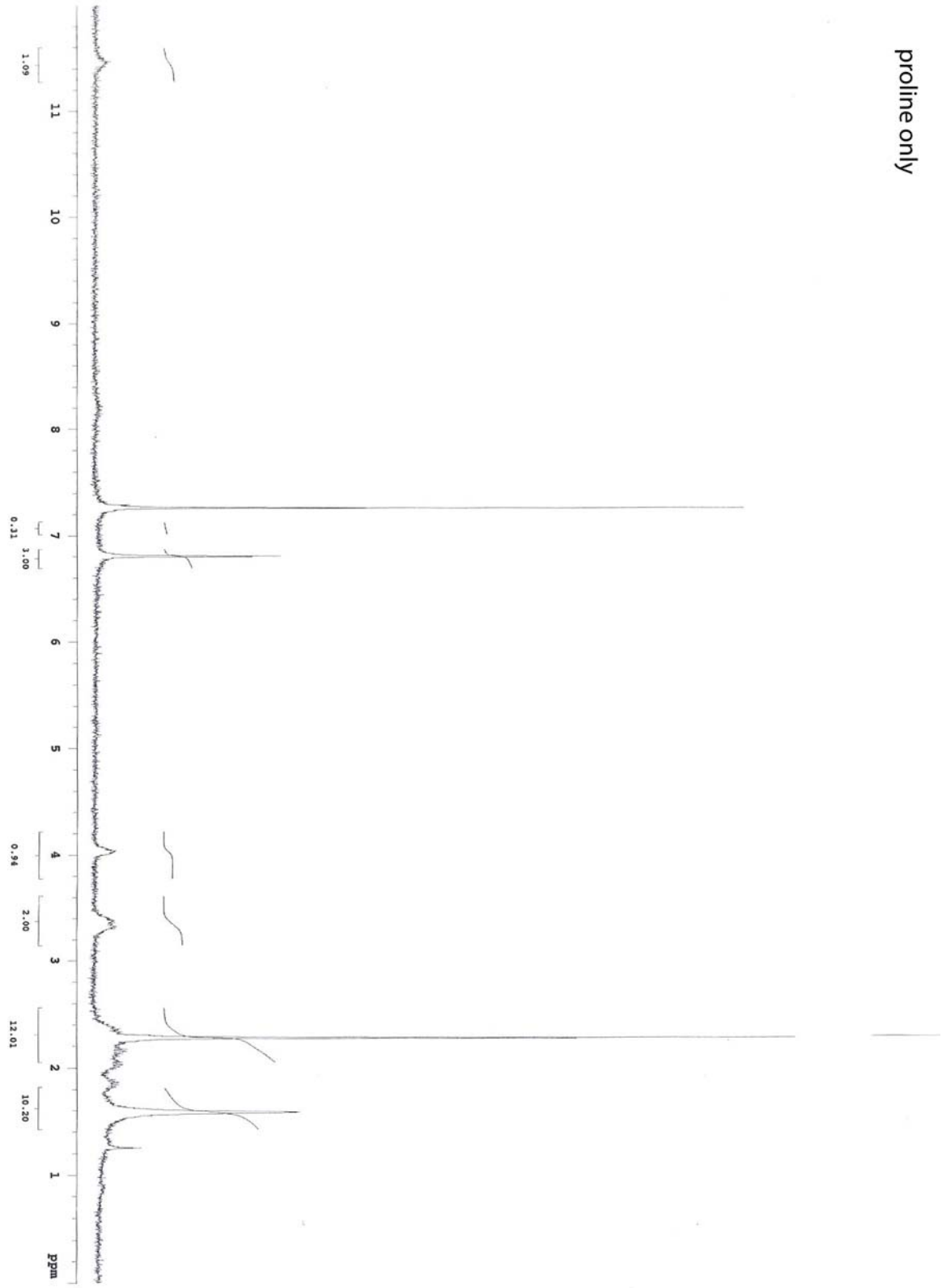



**Figure S3**. $^{1}$H-NMR spectrum of proline.

Comparison of the aromatic mesitylene proton shift (δ = 6.80) with the proline proton at δ = 4.02 indicates that there is no difference in the extent of dissolution in the two cases:

| | mesitylene : proline | proline concentration (M) |
|---|---|---|
| proline + 1 | 3.00 : 0.87 | 0.0044 |
| proline only | 3.00 : 0.94 | 0.0047 |

## *6. Oxazolidinone **7**-catalyzed α-aminoxylation of hexanal*

### *6.1. Formation of oxazolidinone **7***

Preparation of oxazolidinone **7** was modified from the literature.[2] Hexanal (123 μL, 1 mmol) and proline (115.2 mg, 1 mmol) and 4 Å molecular sieves (139 mg) were stirred in $CDCl_3$ (5 mL) under an environment of $N_2$ for 14 hours. Catalyst concentration was assessed by $^1H$ NMR using mesitylene as an internal standard. Typical concentrations were 0.02-0.05 M.

### *6.2. α-Aminoxylation of hexanal with oxazolidinone **7***

Urea **1** (10.4 mg, 0.05 mmol, 0.05 eq), $CHCl_3$ (volume varied depending on concentration of oxazolidinone **7**) and 4 Å molecular sieves (35 mg) were stirred at 0 $^oC$ for 10 min. Propionaldehyde (370 μL, 3 mmol, 3 eq) was added, followed by a stock solution (1 mL) of nitrosobenzene (1 M) and mesitylene (0.1 M) in $CHCl_3$. Oxazolidinone **7** in $CDCl_3$ (volume varied depending on concentration) was added, and reaction conversion was monitored by withdrawing aliquots from the reaction at different time intervals, diluting into ethyl acetate, and analyzing by GC with reference to mesitylene.

The control reaction was performed in the same way but without urea **1**.

## *7. Proline derivatives*

### *7.1. Pyrrolidine-tetrazole **8***

Pyrrolidine-tetrazole **8** (7.0 mg, 0.05 mmol), urea **1** (10.4 mg, 0.05 mmol) and EtOAc (1 mL) were sonicated in a 1 dram screw cap vial for 1 min. A stock solution (1 mL) of hexanal (3 M), nitrosobenzene (1 M), and mesitylene (0.1 M) in EtOAc was added and the reaction was rocked at 22 $^oC$. Reaction conversion was monitored by withdrawing aliquots from the reaction at different time intervals, diluting into ethyl acetate, and analyzing by GC with reference to mesitylene.

The control reaction was performed in the same way but without urea **1**.

### *7.2. Siloxyproline **9***

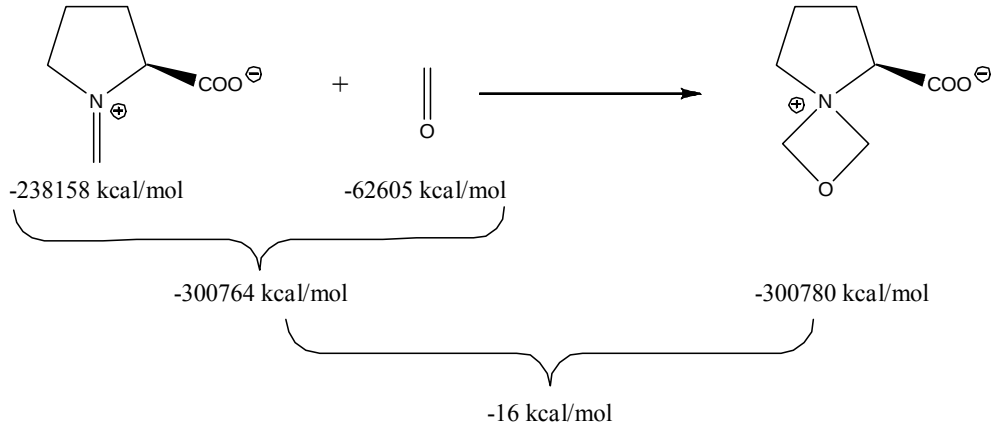
Siloxyproline **9** was prepared from *N*-Cbz-hydroxy-(L)-proline as reported in the literature.[3]

Siloxyproline **9** (12.3 mg, 0.05 mmol, 0.05 eq), urea **1** (10.4 mg, 0.05 mmol, 0.05 eq), and acetonitrile (1 mL) were placed in a 1 dram screw cap and stirred at 0 °C for 15 min. a stock solution (1 mL) of nitrosobenzene (1 M) and mesitylene (0.1 M) in acetonitrile was added, followed by hexanal (370 μL, 3 mmol, 3 eq) and the reaction was stirred at 0 °C. Reaction conversion was monitored by withdrawing aliquots from the reaction at different time intervals, diluting into ethyl acetate, and analyzing by GC with reference to mesitylene.

The control reaction was performed in the same way but without urea **1**.

*8. Calculations for iminium-enamine exchange*

The 2+2 cycloadduct proposed in Scheme 4 was investigated using the following isodesmic equation. The values provided were computed using the density functional B3LYP with a 3-21G basis set. Thought this is a low level of theory performed in the gas phase, we feel that the relatively similar energies of the sum of the starting materials and product indicate that formation of the intermediate is plausible.

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[3] a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435; b) Ohtake, H.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2737.

[4] Urea 1 has been reported Dovlatyan, V.V.; Ambartsumyan, E.N. Armyanskii Khimicheskii Zhurnal 1966, 19, 774-7. Written in Russian.