Novel catalysts for the enantioselective Henry reaction*

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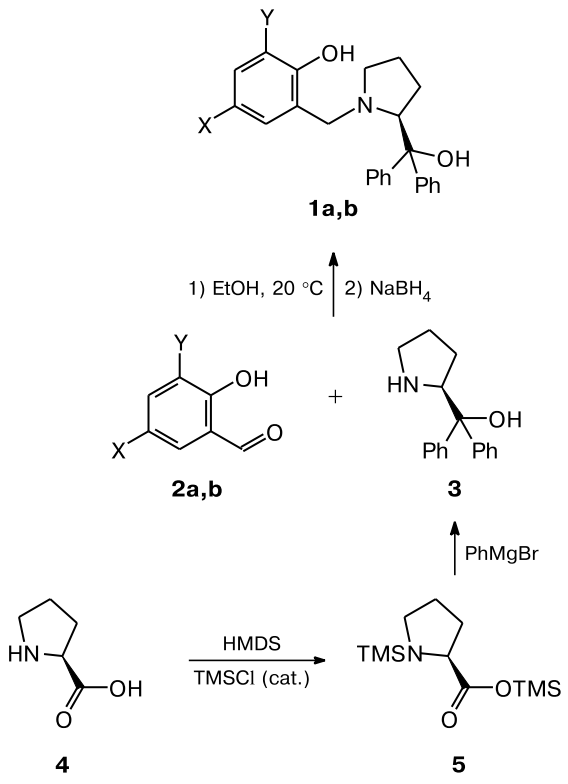
Two novel catalytic systems based on the Cu^{II} complexes with *N*-(3,5-dibromo-2-hydroxybenzyl)- and *N*-(2-hydroxy-3-nitrobenzyl)-(*S*)-α,α-diphenylprolinols were developed. These systems catalyze the condensation of 4-nitrobenzaldehyde with nitromethane to produce *S*-nitroaldol with maximum enantiomeric excess of >90% (99% yield). The reactions of nitromethane with aliphatic aldehydes give the corresponding products in the yields above 80% and *ee* > 90%.

Key words: enantioselective synthesis, nitroaldol condensation, Henry reaction, copper(II) complexes, (*S*)-diphenylprolinol.

Nitroaldol condensation (the Henry reaction) is one of the common methods for the C—C bond formation.[1] The Henry reaction yields valuable β-nitro alcohols, which can be further transformed into various functionalized derivatives, *e.g.*, nitroalkenes, amino alcohols, and amino acids.[1] In recent years, the special interest is paid to the development of different versions of the asymmetric Henry reaction,[2—6] some of which are already used as the key steps in the total syntheses of natural compounds (see, for example, Refs 4—6). The use of the organocatalysts for this purpose is described,[2,3] although an asymmetric metal complex catalysis is the most intensively developing field.[2,5] For instance, the reactions catalyzed by the Cu^{I} (see Ref. 7) and Cu^{II} (see Refs 6, 8—12) complexes with various chiral ligands are known. In the present work, we describe two novel chiral Cu^{II} complexes providing high enantioselectivity in the reactions of nitromethane with both aromatic and aliphatic aldehydes. L-Proline derivatives **1a**,**b** are used as the ligands for the Cu^{2+} ions. Ligands **1a**,**b** are synthesized by the reaction of available salicylaldehyde derivatives **2a**,**b** and (*S*)-diphenylprolinol **3** (Scheme 1). Amino alcohol **3** is synthesized in two steps involving transformation of the starting amino acid **4** into *N*,*O*-bis-trimethylsilyl intermediate **5**.

Reductive amination of aldehydes **2a**,**b** with diphenylprolinol **3** gives hitherto unknown compounds **1a** and **1b** in the yields of 68% and 70%, respectively. Catalytic performance of complexes of **1a**,**b** with the Cu^{II} salts is evaluated on the model asymmetric Henry reaction, *i.e.*, condensation of 4-nitrobenzaldehyde (**6**) with nitromethane.

Scheme 1



X = H, Y = NO_2 (**a**); X = Y = Br (**b**)

Thus, the reactions of aldehyde **6** (1 mmol) and 10-fold excess of nitromethane in the presence of ~0.1 mmol of compound **1a** (catalyst A) or **1b** (catalyst B) and ~0.11 mmol of $Cu(OAc)_2 \cdot 2H_2O$ in Pr^iOH afford in both cases non-racemic nitro alcohol **7** in good yields (Scheme 2).

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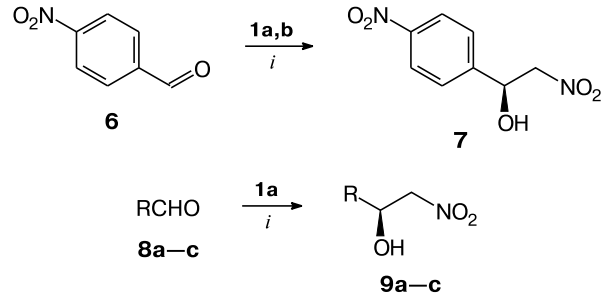
Enantiomeric excesses of (*S*)-**7** provided by ligand **1a** (20 h, 20 °C) and **1b** (28 h, 20 °C) are 94 and 81%, respectively (HPLC data).

Scheme 2



i. $Cu(OAc)_2 \cdot 2H_2O$, $MeNO_2$, Pr^iOH, 20 °C.

R = Bu^n (**a**), $CH_2{=}CH(CH_2)_2$ (**b**), $CH_2{=}CH(CH_2)_3$ (**c**)

Complete conversion of aliphatic aldehyde **8** in the presence of catalytic system A requires longer reaction time (30—40 h). Nitro alcohols **9** are obtained in good yields (>80%) and with high enantioselectivity (*ee* > 93%).

The structures of previously unknown compounds **1** are established by spectroscopy. The structures of nitro alcohols **7**[13] and **9a**,[13] **9b**[14] and **9c**[15] are confirmed by a comparison of their spectral data with that published for optically active and racemic compounds, respectively. The absolute configuration of hitherto unknown in an optically active form compound **9b** is assigned based on the results of its catalytic hydrogenation into the described enantiomer (*S*)-**9a**, and the absolute configuration of homolog **9c** is ascribed by analogy.

In summary, in the present work, two novel catalytic systems for highly enantioselective nitroaldol condensation are developed. It should be emphasized that under similar reaction conditions, the parent analog of compounds **1a**,**b** with X = Y = H provides the enantiomeric excess not exceeding 12% (see Ref. 16).

Experimental

Melting points were measured on a Kofler apparatus. IR spectra were recorded on a Bruker ALPHA-T instrument. ^{1}H NMR spectra were run on a Bruker AC-200 spectrometer at 298 K, the chemical shifts are given in the δ scale relative to the solvent residual signals (δ_H 7.27). High resolution electrospray ionization (ESI) mass spectra were recorded using a Bruker micrOTOF II mass spectrometer at capillary voltage of 4.5 kV using direct inlet (*via* syringe pump) with MeOH as a solvent (a flow rate of 3 μL min^{-1}) operating on a positive ion mode (the 500—3000 Da mass range), rate of the nebulizer gas (nitrogen) flow was 4 L min^{-1} (180 °C). Optical rotation was measured on a Jasco DIP polarimeter. Column chromatography was performed using Silica gel 60 (0.04—0.06 mm, Fluka); R_f values were measured using the precoated Silufol plates. For HPLC of compound **7** (UV detection at 250 nm, elution with 10 vol.% of Pr^iOH in hexane, flow rate of 1 mL min^{-1}) and compound **9** (UV detection at 210 nm, elution with 2 vol.% of Pr^iOH in hexane, flow rate of 1.5 mL min^{-1}), a chiral phase Kromasil 3 CelluCoat (column 4.6×150 mm) was used. Sonication was performed with an ultrasonic bath UZV-1/100-TN. The solvents were purified and dried following the standard procedures. Commercially available (Acros Organics) L-proline, nitromethane, 4-nitrobenzaldehyde, pentanal, and $Cu(OAc)_2 \cdot 2H_2O$ were used. 3-Nitrosalicylaldehyde **2a**,[17] 3,5-dibromosalicylaldehyde **2b**,[18] pent-4-enal **8b**,[19] and hex-5-enal **8c**[20] were synthesized by the known procedures.

Diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (3). A suspension of L-proline (2 g, 17.37 mmol), hexamethyldisilazane (4.4 g, 27.26 mmol), and TMSCl (0.05 mL) in MeCN (6 mL) was refluxed (~120 °C) for 3.5 h under Ar. Removal of the solvent and distillation of the residue afforded trimethylsilyl 1-(trimethylsilyl)-L-prolinate **5** in the yield of 3.78 g (84%), colorless liquid, b.p. 86—89 °C (1.5 Torr; *cf.* Ref. 21: 56—58 °C (1.6 Torr)). Compound **5** was used on the next step without further purification. To a solution of PhMgBr obtained from Mg (1.5 g, 63.78 mg atom) and PhBr (9.42 g, 60 mmol) in THF (50 mL) and cooled to 10 °C, a solution of compound **5** in THF (5 mL) was added dropwise over 5 min under Ar. Slight increase in the reaction temperature was observed. After 1 h stirring at 20 °C, the reaction mixture was carefully poured into Bu^tOMe—2 *M* HCl (100 mL, 1 : 1). The obtained two-phase mixture was concentrated *in vacuo*, the residue was triturated with Bu^tOMe (50 mL), and the precipitate was filtered and washed with water. The powder was suspended in a mixture of Bu^tOMe (50 mL) and 1 *M* NaOH (100 mL) and stirred for 1 h until complete dissolution. The organic layer was separated, washed with brine, dried with $NaSO_4$, and concentrated *in vacuo*. Compound **3** was obtained in the yield of 1.87 g (41% based on the starting L-proline (**4**)), colorless crystals, m.p. 76—78 °C (hexane; *cf.* Ref. 22: m.p. 79—79.5 °C). ^{1}H NMR spectrum of **3** is in good agreement with the published data.[22]

2-({(2*S*)-2-[Hydroxy(diphenyl)methyl]pyrrolidin-1-yl}methyl)-6-nitrophenol (1a). A solution of aldehyde **2a** (0.55 g, 2.17 mmol) and amino alcohol **3** (0.37 g, 2.21mmol) in a mixture of EtOH (15 mL) and $CHCl_3$ (15 mL) was stirred at 20 °C for 20 min. Then, $NaBH_4$ (84 mg, 2.21 mmol) was added in small portions. The reaction mixture was kept for 1 h and concentrated *in vacuo*. To the residue, 4% HCl and $CHCl_3$ were added. The aqueous layer was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined organics were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. Purification of the residue (~0.7 g) by column chromatography (SiO_2, gradient elution with Bu^tOMe—petroleum ether, up to 40% Bu^tOMe) afforded compound **1a** in the yield of 0.6 g (68%), orange crystals, m.p. 139—142 °C, $[\alpha]_D^{28}$ +54.1 (*c* 1.00, CH_2Cl_2). High resolution MS (ESI), *m/z*: found 387.1691, 405.1793; calculated for $C_{24}H_{24}N_2O_4$, *m/z*: 387.1703 $[M + H]^+$, 405.1809 $[M + Na]^+$. IR ($CHCl_3$), ν/cm^{-1}: 629, 707, 729, 791, 928, 1033, 1076, 1154, 1208, 1222, 1251, 1331, 1450, 1540, 1612, 2815, 3088, 3216, 3605, 3685. ^{1}H NMR ($CDCl_3$), δ: 1.54—2.14 (m, 4 H, C(3)H_2, C(4)H_2); 2.48 (dd, 1 H, C(5)H, *J* = 17.1 Hz, *J* = 8.5 Hz); 2.99 (m, 1 H, C(5)H′); 4.08 (m 1 H, C(2)H); 3.31, 3.46 (both d, 1 H each, CH_2N, *J* = 13.8 Hz); 6.78—8.09 (m, 13 H, HCAr).

4,6-Dibromo-2-({(2*S*)-2-[hydroxy(diphenyl)methyl]pyrrolidin-1-yl}methyl)phenol (1b) was synthesized similarly from aldehyde **2b** (0.59 g, 2.1 mmol) and amino alcohol **3** (0.5 g, 1.97 mmol) in the yield of 0.71 g (70%), light yellow amorphous powder, R_f 0.37 (AcOEt—petroleum ether, 1 : 5), $[\alpha]_D^{28}$ + 78.2 (*c* 1.00, CH_2Cl_2). High resolution MS (ESI), *m/z*: found 516.0164; calculated for $C_{24}H_{23}Br_2NO_2$, *m/z*: 516.0168 $[M + H]^+$. IR ($CHCl_3$), ν/cm^{-1}: 672, 726, 752, 767, 864, 1001, 1033, 1083, 1153, 1208, 1224, 1262, 1352, 1381, 1451, 1458, 1599, 2832—3063, 3113, 3603, 3683. ^{1}H NMR ($CDCl_3$), δ: 1.63—2.24 (m, 4 H, C(3)H_2, C(4)H_2); 2.42 (dd, 1 H, C(5)H, *J* = 17.4 Hz, *J* = 8.1 Hz); 3.03 (m, 1 H, C(5)H′); 3.27, 3.49 (both d, 1 H each, CH_2N, *J* = 15.1 Hz); 4.02 (dd, 1 H, C(2)H, *J* = 9.1 Hz, *J* = 4.9 Hz); 4.74 (br.s, 2 H, 2 OH); 6.84—7.71 (m, 12 H, HCAr).

(*S*)-1-(4-Nitrophenyl)-2-nitroethan-1-ol (7). ***A.*** A mixture of ligand **1a** (38.2 mg, 0.094 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (21.7 mg, 0.011 mmol), and anhydrous Pr^{i}OH (1.5 mL) was sonicated for 10 min, then 4-nitrobenzaldehyde **6** (151 mg, 1 mmol) and $MeNO_2$ (610 mg, 10 mmol) were added. The reaction mixture was kept for 20 h at 20 °C until complete consumption of the starting aldehyde (TLC monitoring) and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, elution with $CHCl_3$) afforded nitro alcohol **7** in the yield of 210 mg (99%), $[\alpha]_D^{28}$ + 37.8 (*c* 1.00, CH_2Cl_2) (~94% *ee*, HPLC data; *cf.* Ref. 13: $[\alpha]_D^{25}$ + 39.7 (*c* 1.0, CH_2Cl_2) for **7** with *ee* 98%). Retention times: 12.2 min for (*R*)-**7** and 15.3 min for (*S*)-**7**. M.p. 83—85 °C (*cf.* Ref. 13). ^{1}H NMR ($CDCl_3$), δ: 3.47 (br.s, 1 H, OH); 4.58—4.62 (m, 2 H, CH_2N); 5.61 (dd, 1 H, CHO, *J* = 7.4 Hz, *J* = 5.0 Hz); 7.62 (d, 2 H, 2 HAr, *J* = 8.7 Hz); 8.23 (d, 2 H, 2 HAr, *J* = 8.7 Hz) (*cf.* Ref. 13).

B. Nitro alcohol **7** was synthesized from aldehyde **6** (151 mg, 1 mmol), $MeNO_2$ (610 mg, 10 mmol), Pr^{i}OH (1.5 mL), and the catalyst obtained from ligand **1b** (52.2 mg, 0.101 mmol) and $Cu(OAc)_2 \cdot 2H_2O$ (20.9 mg, 0.105 mmol) following the procedure described above. Yield 198 mg (93%), $[\alpha]_D^{28}$ +33.5 (*c* 1.00, CH_2Cl_2; ~81% *ee*, HPLC data).

(*S*)-1-Nitrohexan-2-ol (9a). ***A.*** A mixture of ligand **1a** (40.1 mg, 0.10 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (20.0 mg, 0.11 mmol), and anhydrous Pr^{i}OH (1.5 mL) was sonicated for 10 min, then pentanal (**8a**) (100 mg, 1.02 mmol) and $MeNO_2$ (610 mg, 10 mmol) were added. The reaction mixture was kept for 44 h at 20 °C until complete consumption of the starting aldehyde (TLC monitoring) and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, elution with $CHCl_3$) afforded nitro alcohol **9a** in the yield of 130 mg (82%), oil, R_f 0.52 ($CHCl_3$—EtOAc, 4 : 1), $[\alpha]_D^{28}$ +9.6 (*c* 1.00, CH_2Cl_2; ~94% *ee*, HPLC data; *cf.* Ref. 13: $[\alpha]_D^{25}$ + 5.0 (*c* 2.5, CH_2Cl_2) for **9a** with *ee* 70%). Retention times: 9.1 min for (*R*)-**9a** and 10.3 min for (*S*)-**9a**. ^{1}H NMR ($CDCl_3$), δ: 0.92 (br.t, 3 H, Me, *J* = 6.9 Hz); 1.18—1.67 (m, 6 H, 3 CH_2); 3.48 (br.s, 1 H, OH); 4.21—4.53 (m, 3 H, CHO, CH_2N) (*cf.* Ref. 13).

B. To a suspension of 10% Pd/C (10 mg) in EtOH (0.5 mL) activated under H_2, a solution of unsaturated nitro alcohol **9b** (0.5 mL, 29 mg, 0.2 mmol, ~93% *ee* (HPLC data)) was slowly added over 20 min and the reaction mixture was stirred for 30 min until calculated amount of hydrogen was consumed (~4.8 mL). The catalyst was filtered off, washed with $CHCl_3$, and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, elution with $CHCl_3$ afforded compound **2** in the yield of 19 mg (64%), oil, R_f 0.52 ($CHCl_3$—EtOAc, 4 : 1), $[\alpha]_D^{24}$ +9.5 (*c* 1.3, CH_2Cl_2; ~94% *ee*, HPLC data).

(*S*)-1-Nitrohex-5-en-2-ol (9b). A mixture of ligand **1a** (39.0 mg, 0.096 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (20.0 mg, 0.11 mmol), and anhydrous Pr^{i}OH (1.5 mL) was sonicated for 10 min, then aldehyde **8b** (84 mg, 1.0 mmol) and $MeNO_2$ (610 mg, 10 mmol) were added. The reaction mixture was kept for 30 h at 20 °C until complete consumption of the starting aldehyde (TLC monitoring), and concentrated *in* vacuo. Purification of the residue by column chromatography (SiO_2, elution with $CHCl_3$) afforded nitro alcohol **9b** in the yield of 120 mg (83%), oil, R_f 0.26 ($CHCl_3$), $[\alpha]_D^{28}$ +8.3 (*c* 1.00, CH_2Cl_2; ~93% *ee*, HPLC data). Retention times: 9.6 min for (*R*)-**7** and 10.4 min for (*S*)-**7**. ^{1}H NMR ($CDCl_3$), δ: 1.63 (m, 2 H, C(3)H_2); 2.22 (m, 2 H, C(4)H_2); 2.54 (br.s, 1 H, OH); 4.27—4.52 (m, 3 H, CHO, CH_2N); 4.98—5.17 (m, 2 H, H_2C=); 5.81 (ddt, 1 H, —HC=, *J* = 16.7 Hz, *J* = 10.3 Hz, *J* = 6.4 Hz) (*cf.* for (±)-**9b**)[14].

(*S*)-1-Nitrohept-6-en-2-ol (9c). A mixture of ligand **1a** (40.1 mg, 0.10 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (21.3 mg, 0.11 mmol), and anhydrous Pr^{i}OH (1.5 mL) was sonicated for 10 min, then aldehyde **8c** (100 mg, 1.0 mmol) and $MeNO_2$ (610 mg, 10 mmol) were added. The reaction mixture was kept for 45 h at 20 °C until complete consumption of the starting alcohol (TLC monitoring) and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, elution with $CHCl_3$) afforded nitro alcohol **9c** in the yield of 130 mg (82%), oil, R_f 0.15 ($CHCl_3$), $[\alpha]_D^{28}$ +8.4 (*c* 1.00, CH_2Cl_2) (~94% *ee*, HPLC data). Retention time: 9.1 min for (*R*)-**9c** and 9.8 min for (*S*)-**9c**. ^{1}H NMR ($CDCl_3$), δ: 1.38—1.76 (m, 4 H, C(3)H_2, C(4)H_2); 2.12 (m, 2 H, C(5)H_2); 2.45 (br.s, 1 H, OH); 4.23—4.55 (m, 3 H, CHO, CH_2N); 4.93—5.14 (m, 2 H, H_2C=); 5.80 (ddt, 1 H, —HC=, *J* = 16.9 Hz, *J* = 10.1 Hz, *J* = 6.6 Hz) (*cf.* for (±)-**9c**).[15]

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