Novel C_2-symmetric bis-oxazoline ligands

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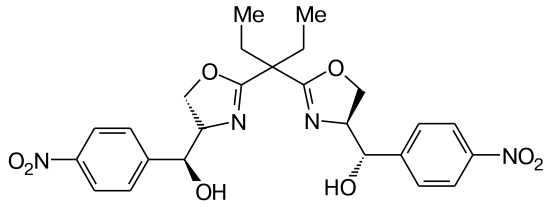
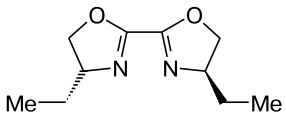
Two novel C_2-symmetric bis-oxazoline ligands were synthesized and their complexes with $Cu(OAc)_2$ were studied as catalysts in the enantioselective Henry reaction of 4-nitrobenzaldehyde with nitromethane giving high yield of nitro aldol with *ee* up to 40%.

Key word: C_2-symmetric bis-oxazoline ligands, copper complexes, enantioselective Henry reaction.

C_2-Symmetric chiral bis-oxazoline ligands are the components of known effective catalysts of many enantioselective processes,[1] including aldol and ene-carbonyl condensations, the Michael addition, carbo and hetero cycloaddition,[2] and nitro aldol Henry reaction.[3] At the same time, the search for new compounds of this series the most suitable for a particular reaction is still urgent (see, for example, Ref. 3b). Present work is devoted to the synthesis of two novel enantiomerically pure C_2-symmetric bis-oxazoline ligands **1** and **2** based on available starting compounds.



1



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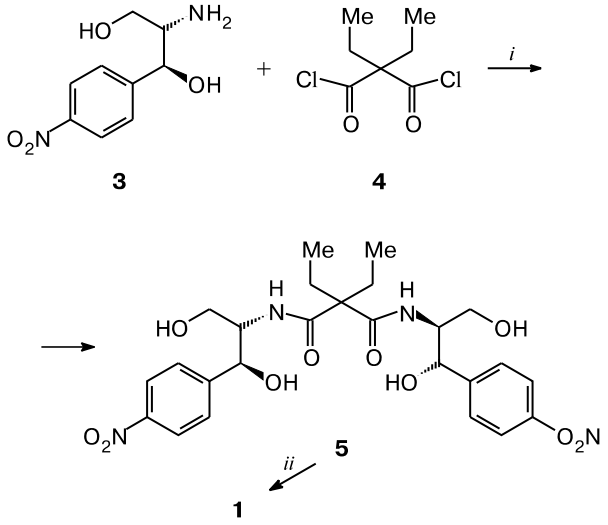
The starting compounds for the synthesis of bis-oxazoline **1** were amino diol **3**, the known intermediate in the synthesis of chloroamphenicol, and 2,2-diethylmalonyl chloride (**4**). Reaction between these compounds in the presence of a saturated aqueous NaOAc solution resulted in *N*-acylation product **5** in moderate yield (Scheme 1). Intramolecular ring closure of the latter under the Mitsunobu conditions proceeds with formation of two oxazoline cycles to give bis-oxazoline **1** in 76% yield.

Bis-oxazoline **2** was synthesized similarly to its optical antipode[4] from commercially available 2(*R*)-aminobutan-1-ol (**6**) and diethyl oxalate. The reaction of compound **6** and diethyl oxalate led to diamide **7** in moderate yield. Refluxing of diamide **7** with $SOCl_2$ afforded chloro-derivative **8** (Scheme 2). The latter underwent ring closure under heating with NaOH in MeOH giving target compound **2** in 82% yield.

Scheme 1



Reagents and conditions: *i*. NaOAc, H_2O, THF, 20 °C; *ii*. Ph_3P, $(NCO_2Et)_2$, THF, −5—20 °C.

Earlier unknown diamide **5** and bis-oxazoline **1** were characterized by combination of the spectroscopic methods. Structures of amide **7**, chloride **8**, and bis-oxazoline **2** were confirmed by ^1H NMR spectroscopy and by a comparison of their physicochemical properties with those of the corresponding optical antipodes.[4]

Catalytic performance of complexes of bis-oxazolines **1** and **2** with $Cu(OAc)_2$ were tested in a model reaction,

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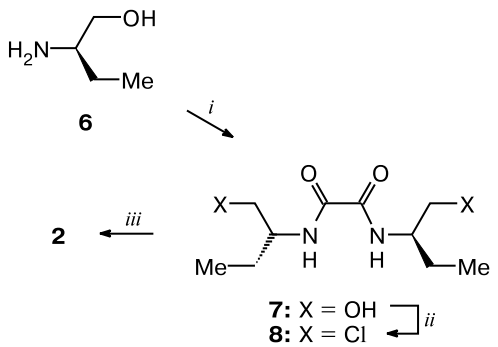
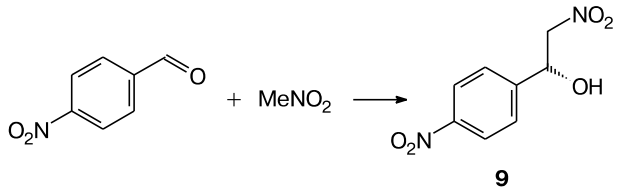
Scheme 2



Reagent and conditions: *i*. $(CO_2Et)_2$, PhMe, reflux, 2 h; *ii*. $SOCl_2$, PhMe, DMF (cat.), reflux, 3 h; *iii*. NaOH, MeOH, reflux, 2 h.

viz., nitro aldol condensation of nitromethane and 4-nitrobenzaldehyde (Scheme 3).

Scheme 3



Reagents and conditions: $Cu(OAc)_2$/**L** (10 mol.%, **L** = **1** or **2**), Pr^{i}OH.

In both cases, scalemic nitro alcohol **9** was obtained in high yield, however, enantiomeric excess of the reaction products was low (*ee* 18 and 40%, respectively, HPLC data), which is lower than the best *ee* value of 81% provided by the ligands of this type.[3b] Nevertheless, we continue the search for more promising ligands.

Experimental

Melting points were measured on a Koffler apparatus. IR spectra were recorded on a Bruker ALPHA-T instrument. ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer at 298 K, the chemical shifts are given in the δ scale relative to the residual solvent signals (δ 7.27). High resolution mass spectra (ESI) were recorded on a Bruker micrOTOF II 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 ions mode (the mass range 500—3000 Da), rate of the main nitrogen flow is 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 plates Silufol. For HPLC (UV detection at 254), a chiral phase Kromasil 3 CelluCoat (column 4.6×150 mm) was used, elution with 10 vol.% of Pr^{i}OH in hexane, flow rate of 1 mL min^{-1}. Retentions times are 22 and 29 min for (*R*)-**9** and (*S*)-**9**, respectively (*cf.* Ref. 3b). Sonication was performed with an ultrasonic bath UZV-1/100-TN. The solvents were purified and dried following the standard procedures. Commercially available amino alcohols **3**, **6**, NaOAc, Ph_3P, $(NCO_2Et)_2$, $SOCl_2$, $Cu(OAc)_2$ (Acros Organics), and diethylmalonic acid (Aldrich) were used. 2.2-Diethylmalonyl dichloride (**4**) was synthesized by a known procedure.[5]

(1*S*,1′*S*,2*S*,2′*S*)-*N*,*N*′-Bis[1,3-dihydroxy-1-(4-nitrophenyl)prop-2-yl)]diethylmalonamide (5). To a stirred solution of amine **3** (2.12 g, 10 mmol) in THF, saturated aqueous NaOAc (50 mL) was added at 20 °C following by additon of chloride **4** (1 g, 0.5 mmol). The reaction mixture was stirred for 1 h, the organic layer was separated, washed twice with brine, dried with $NaSO_4$, and concentrated *in vacuo*. Column chromatography (SiO_2 stabilized with EtOAc, gradient elution from EtOAc to EtOAc—10% MeOH) afforded 2 g of the product with R_f 0.28 (MeCN), recrystallization of which from MeCN gave diamide **5** in the yield of 1.2 g (44%), colorless crystals, m.p. 189.5—190.5 °C, $[\alpha]_D^{26}$ +26.6 (*c* 1.0, EtOH). MS (ESI), *m/z*: found 549.2187, 571.2005; calculated for $C_{25}H_{32}N_4O_{10}$, *m/z*: 549.2191 $[M + H]^+$, 571.2011 $[M + Na]^+$. IR (dispersion in Nujol), ν/cm^{-1}: 712, 720, 811, 820, 857, 868, 951, 1002, 1012, 1045, 1072, 1101, 1191, 1222, 1250, 1329, 1351, 1468, 1521, 1606, 1649, 2855, 2928, 3408. ^{1}H NMR ($CDCl_3$—CD_3OD), δ: 0.12 (t, 6 H, 2 Me, J = 7.2 Hz); 1.41 (dd, 2 H, CH_2, J = 13.0 Hz, J = 7.2 Hz); 1.51 (dd, 2 H, CH_2, J = 13.0 Hz, J = 7.2 Hz); 3.50 (dd, 2 H, CH_2OH, J = 10.8 Hz, J = 5.1 Hz); 3.58 (dd, 2 H, CH_2OH, J = 10.8 Hz, J = 6.4 Hz); 4.05 (m, 2 H, 2 CHN); 5.01 (d, 2 H, 2 CHO, J = 2.3 Hz); 7.43 (d, 4 H, 4 HC_{Ar}, J = 8.7 Hz); 8.00 (d, 4 H, 4 HC_{Ar}, J = 8.7 Hz).

2,2′-(Pentane-3,3-diyl)bis{4(*S*)-[1(*S*)-hydroxy-1(*S*)-(4-nitrophenyl)methyl]-4,5-dihydrooxazole} (1). To a stirred solution of diamine **5** (1.18 g, 2.15 mmol) and Ph_3P (1.35 g, 5.16 mmol) in THF (12 mL), a solution of diethyl azodicarboxylate (0.9 g, 0.8 mL, 5.16 mmol) in THF (5 mL) was added over 5 min at −5 °C under argon. The reaction mixture was stirred at 0 °C for 1 h and then kept at 20 °C for 15 h. The solvent was removed *in vacuo*, and the residue was dissolved in hot CH_2Cl_2. The precipitate (0.7 g) formed on cooling was filtered off and washed with CH_2Cl_2 (0.7 g). The filtrate was concentrated *in vacuo*. Column chromatography (SiO_2, gradient elution with CH_2Cl_2, CH_2Cl_2—EtOAc, EtOAc, EtOAc—5% MeOH) afforded bis-oxazoline **1** in the yield of 0.84 g (76%), m.p. 95—97 °C, $[\alpha]_D^{26}$ +94.5 (*c* 1.0, EtOH). MS (ESI), *m/z*: found 513.1974, 535.1790; calculated for $C_{25}H_{28}N_4O_8$, *m/z*: 513.1980 $[M + H]^+$, 535.1799 $[M + Na]^+$. IR (dispersion in Nujol), ν/cm^{-1}: 707, 751, 763, 849, 958, 982, 1023, 1043, 1081, 1110, 1128, 1142, 1227, 1248, 1346, 1364, 1465, 1524, 1607, 1642, 2669, 2855, 2924, 3004, 3160. ^{1}H NMR ($CDCl_3$—CD_3OD (4 : 1)), δ: 0.83 (t, 6 H, 2 Me, J = 7.5 Hz); 1.78—2.05 (m, 4 H, 2 CH_2); 4.06 (d, 2 H, 2 OH, J = 5.8 Hz); 4.28 (d, 4 H, 2 CH_2O, J = 8.2 Hz); 4.51 (ddd, 2 H, 2 CHN, J = 8.2 Hz, J = 8.2 Hz, J = 4.8 Hz); 4.74 (dd, 2 H, 2 CHO, J = 5.8 Hz, J = 4.8 Hz); 7.55 (d, 4 H, 4 HC_{Ar}, J = 8.8 Hz); 8.21 (d, 4 H, 4 HC_{Ar}, J = 8.8 Hz).

***N*,*N*′-Bis[(1*R*)-1-(hydroxymethyl)propyl]ethanediamide (7).** A solution of amino alcohol **6** (8.91 g, 100 mmol) and diethyl oxalate (7.31 g, 50 mmol) in toluene (50 mL) was refluxed for 2 h under argon and concentrated *in vacuo*. Recrystallization of the residue from EtOH afforded diamide **7** in the yield of 9.29 g (80%), m.p. 212—213.5 °C (MeOH), $[\alpha]_D^{25}$ +54.60 (*c* 0.5,

EtOH) (*cf.* Ref. 4 for (1*S*,1´*S*)-enantiomer: m.p. 211—213 °C, $[\alpha]_D^{24}$ –46 (*c* 0.5, EtOH)). ^{1}H NMR ($CDCl_3$—CD_3OD (4 : 1)), δ: 0.93 (t, 6 H, 2 Me, *J* = 7.4 Hz); 1.39—1.81 (m, 4 H, 2 CH_2); 3.58 (d, 4 H, 2 CH_2O, *J* = 5.2 Hz); 3.81 (m, 2 H, 2 CHN).

***N,N´*-Bis((2*R*)-1-chlorobut-2-yl)ethanediamide (8).** To a solution of diamide **7** (4.91 g, 21.14 mmol), $SOCl_2$ (25 g, 0.21 mol) and toluene (30 ml), DMF (0.1 mL) was added at 20 °C. The reaction mixture was refluxed for 3 h, cooled to room temperature, filtrated and the volatiles were removed *in vacuo*. Recrystallization of the residue from CH_2Cl_2 afforded chloride **8** in the yield of 3.17 g (56%), colorless crystals, m.p. 205—207.5 °C ($CHCl_3$), $[\alpha]_D^{25}$ +87.40 (*c* 0.5, $CHCl_3$) (*cf.* Ref. 4 for (1*S*,1´*S*)-enantiomer: m.p. 191—193 °C, $[\alpha]_D^{24}$ –47 (*c* 0.5, MeOH)). ^{1}H NMR ($CDCl_3$—CD_3OD), δ: 0.98 (t, 6 H, 2 Me, *J* = 7.4 Hz); 1.53—1.90 (m, 4 H, 2 CH_2); 3.67 (d, 4 H, 2 CH_2Cl, *J* = 4.1 Hz); 4.10 (m, 2 H, 2 CHN); 7.54 (br.s, 2 H, 2 HN, *J* = 7.7 Hz).

(4*R*,4´*R*)-4,4´-Diethyl-4,4´,5,5´-tetrahydro-2,2´-bi-1,3-oxazole (2). A suspension of chloride **8** (2.5 g, 9.29 mmol) and NaOH (0.88 g, 22.0 mmol) in MeOH (20 mL) was refluxed for 2 h. Then the reaction mixture was cooled, the precipitate was filtered off and washed with MeOH, the filtrate was concentrated *in vacuo*, and the residue was extracted with EtOAc (5×10 mL). Removal of the solvent *in vacuo* and vacuum distillation of the residue afforded bis-oxazoline **2** in the yield of 1.5 g (82%), viscous liquid, b.p 99—102 °C (0.08 Torr), $[\alpha]_D^{25}$ +167.20 (*c* 0.5, EtOH) (*cf.* Ref. 4 for (1*S*,1´*S*)-enantiomer: b.p. 121 °C (0.1 Torr), $[\alpha]_D^{24}$ –172 (without solvent)). ^{1}H NMR ($CDCl_3$—CD_3OD), δ: 0.97 (t, 6 H, 2 Me, *J* = 7.4 Hz); 1.45—1.85 (m, 4 H, 2 CH_2); 4.03 (dd, 2 H, 2 CHO, *J* = 8.5 Hz, *J* = 7.7 Hz); 4.22 (m, 2 H, 2 CHN); 4.49 (dd, 2 H, 2 CH´O, *J* = 9.4 Hz, *J* = 7.7 Hz).

(1*R*)-1-(4-Nitrophenyl)-2-nitroethan-1-ol (9). ***A.*** The reaction flask dried at 100 °C and cooled down to 20 °C under nitrogen stream was charged with bis-oxazoline **1** (51 mg, 0.1 mmol), $Cu(OAc)_2$ (16 mg, 0.09 mmol), and anhydrous Pr^iOH (1.5 mL). The mixture was sonicated for 10 min, then to a light blue solution formed, 4-nitrobenzaldehyde (151 mg, 1 mmol) and $MeNO_2$ (610 mg, 10 mmol) were added. The reaction mixture was kept for 20 h (TLC monitoring) and concentrated *in vacuo*. Column chromatography on SiO_2 (elution with $CHCl_3$) afforded scalemic nitro alcohol **9** in the yield of 203 mg (96%) (~18% *ee*, HPLC data). ^{1}H NMR ($CDCl_3$), δ: 3.47 (br.s, 1 H, OH); 4.58—4.62 (m, 2 H, CH_2O); 5.61 (dd, 1 H, CHO, *J* = 7.4 Hz, *J* = 5.0 Hz); 7.62 (d, 2 H, 2 H_{Ar}, *J* = 8.7 Hz); 8.23 (d, 2 H, 2 H_{Ar}, *J* = 8.7 Hz) (*cf.* Ref. 3b).

B. Similar reaction carried out with ligand **2** gave scalemic nitro alcohol **9** in 94% yield (~40% *ee*, HPLC data).

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References

1. E. Schulz, in *Topics in Organometallic Chemistry*, Eds M. Lemaire, P. Mangeney, Springer, Berlin—Heidelberg—New York, 2005, vol. **15**, p. 93.
2. J. Johnson, D. Evans, *Acc. Chem. Res.*, 2000, **33**, 325.
3. (a) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692; (b) S. K. Ginotra, V. K. Singh, *Org. Biomol. Chem.*, 2007, **5**, 3932.
4. I. Butula, G. Karlović, *Liebigs Ann. Chem.*, 1976, 1455.
5. J. Büchi, G. Enézian, H. Eichenberger, R. Lieberherr, *Helv. Chim. Acta*, 1952, **35**, 75.

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