Synthesis of new polydentate oxalamide-based ligands as chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde

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New polydentate oxalamide-based ligands have been studied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde

Keywords: aminoalcohols, diethylzinc, chiral catalysts, oxalamide

The catalytic enantioselective formation of C–C bonds is one of the most interesting and challenging areas in organic synthesis. Among current methods, the asymmetric addition of dialkylzinc compounds to aldehydes is very convenient for the synthesis of optically active secondary alcohols and naturally occurring products.[1] This reaction in the presence of chiral ligands has been widely explored since the first report by Noyori and co-workers[2] and, in particular, the reaction of diethylzinc with benzaldehyde has been used as a standard procedure for testing the efficiency of different molecules as chiral catalysts.

A variety of chiral catalysts[3] such as β-aminoalcohols, diamines, Ti-complexes has been developed for this reaction showing high enantioselectivity. However, the general applicability of these catalysts is limited because most of them are useful for certain types of aldehyde with only a few giving high enantioselectivity for a wide range of substrates.[4] Therefore, the search for new catalysts which are easy to prepare and exhibit high reactivity and enantioselectivity is a field of continued interest.

As an extension of our current research on stereoselective reactions,[5] we have designed new enantiopure polydentate ligands which are easily obtained from 1,2-diesters and chiral aminodiols. The catalytic efficiency of these ligands on the asymmetric addition of diethylzinc to benzaldehyde is reported herein.

Results and discussion

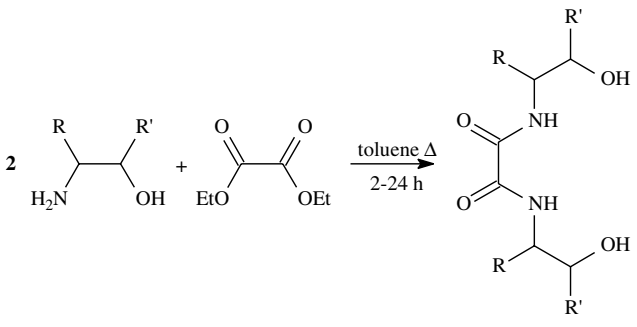
All ligands **1–6** were obtained by condensation of the appropriate aminodiol and diethyloxalate (molar ratio 2:1) in toluene by heating under reflux, according to the general synthetic route outlined in Scheme 1.

This procedure was accomplished in high yields (87–96%) and with an easy work-up procedure. For the synthesis of ligands **1–3**, we used commercially available (Aldrich) aminodiols (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol and its *para*-NO_2 or *para*-SCH_3 substituted derivatives. In the case of ligand **4**, a similar approach was employed, starting from the enantiopure aminodiol (2*R*,3*R*)-3-amino-3-phenyl-1,2-propanediol[6] prepared by ring opening with NH_4OH of (2*S*,3*S*)-3-phenyloxiran-2-yl-methanol arising from Sharpless epoxidation[7] of (*E*)-3-phenyl-2-propen-1-ol. Finally, we prepared compounds **5** and **6** by direct condensation of (*S*)-(+)-phenylglycinol or (*S*)-(-)-phenylalaninol, respectively, with diethyloxalate, so reducing the synthetic steps described in the literature.[8]

The appropriate stereochemistry of the obtained enantiopure oxalamide compounds **1–6** is shown in Fig. 1.

We compared all new ligands to compounds **5** and **6**, recently prepared[8] so as to verify the influence of an additional OH group in the studied reaction. As we can observe (Fig. 2), oxalamide **4** was designed to be positional isomer in C-1 and C-2 of ligand **1**; moreover, compounds **4** and **5** could be considered analogous simply replacing the CH_2OH group at C-2 with a hydrogen.

The catalytic activity of ligands **1–6** was tested in the enantioselective addition of diethylzinc to benzaldehyde. The influence of solvent, temperature and the ratio of diethylzinc and titanium isopropoxide (Ti(*i*-OPr)$_4$) in different reaction conditions was studied (see Table). In a first step, the asymmetric reactions were carried out in the presence of ligands **5** and **6** in a molar ratio benzaldehyde: ligand: Et_2Zn: Ti(*i*-OPr)$_4$ of 1: 0.25: 3: 1.4 (entries 1–8), changing solvent and temperature. In comparison to reported literature data[8] (entries 1 and 5), we found that the experiments carried out in toluene at –20 °C (entries 4 and 8) showed a better enantiomeric excess (ee) of (*S*)-1-phenyl-1-propanol. Under these reaction conditions, when compounds **1**, **3** and **4** (entries 9, 13 and 15) were used as asymmetric ligands, (*S*)-1-phenyl-1-propanol was obtained in good yields, but with moderate ees. However, when the reaction was performed with the oxalamide



1-6 (87-96 %)

1	R =PhCH(OH)	R' = H
2	R = *p*-$NO_2C_6H_4CH(OH)$	R' = H
3	R = *p*-$SCH_3C_6H_4CH(OH)$	R' = H
4	R = Ph	R' = CH_2OH
5	R = Ph	R' = H
6	R = Bn	R' = H

Scheme 1 Synthesis of ligands 1–6.

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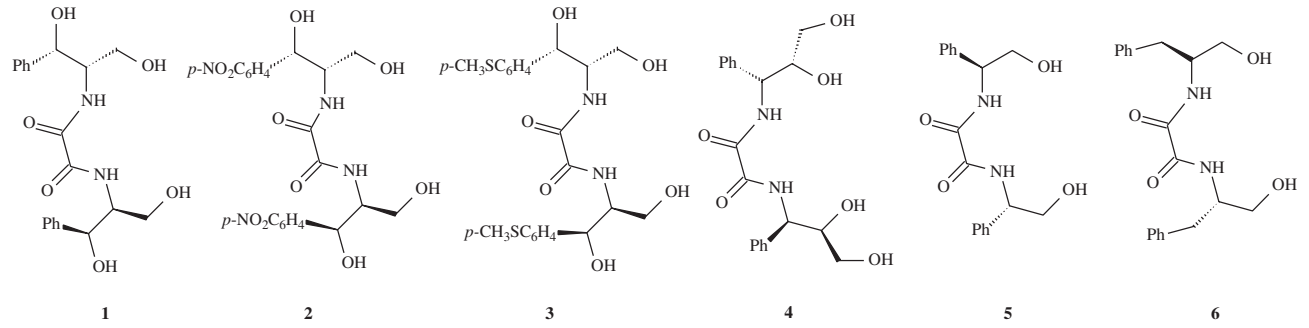

Fig. 1 *N,N′*-Bis[(1*S*,2*S*)-2-hydroxy-1-hydroxymethyl-2-phenylethyl]ethanediamide **1**. *N,N′*-Bis[(1*S*,2*S*)-2-hydroxy-1-hydroxymethyl-2-(4-nitrophenyl)ethyl]ethanediamide **2**. *N,N′*-Bis[(1*S*, 2*S*)-2-hydroxyl-1-hydroxymethyl-2-(4-methylsulfanylbenzene)ethyl] ethanediamide **3**. *N,N′*-Bis[(1*R*, 2*R*)-2,3-dihydroxy-1-phenylpropyl]ethanediamide **4**. *N,N′*-Bis[(1*S*)-2-hydroxy-1-phenylethyl] ethanediamide **5**. *N,N′*-Bis[(1*S*)-1-benzyl-2-hydroxyethyl]ethanediamide **6**.

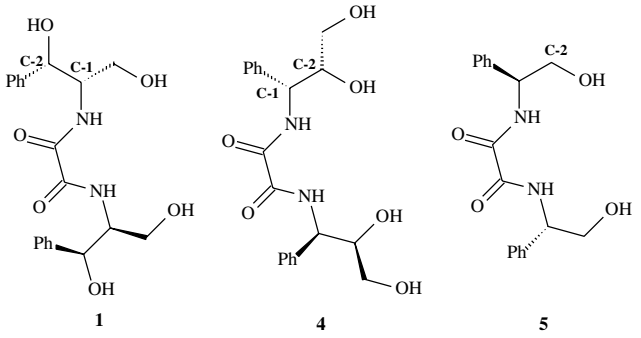

Fig. 2 *N,N′*-Bis[(1*S*, 2*S*)-2-hydroxy-1-hydroxymethyl-2-phenylethyl]ethanediamide **1**. *N,N′*-Bis[(1*R*, 2*R*)-2,3-dihydroxy-1-phenylpropyl]ethanediamide **4**. *N,N′*-Bis[(1*S*)-2-hydroxy-1-phenylethyl]ethanediamide **5**.

2, the opposite enantiomer was obtained, (*R*)-1-phenyl-1-propanol, with the best enantiomeric excess found (67% ee) (entry 11).

As it known, both chemical yield and extend of the enantioface discrimination depend on the catalyst and on the molar ratio of Et_2Zn/Ti(*i*-OPr)$_4$. In fact, when the molar ratio of Et_2Zn/Ti(*i*-OPr)$_4$ was changed in the experiments carried out in a molar ratio benzaldehyde: ligand: Et_2Zn: Ti(*i*-OPr)$_4$ of 1: 0.10: 3: 0.08 (entries 10, 12, 14 and 16), as suggested in the literature for some oxalamide catalysts,[9] we found lower ee. Under these reaction conditions, when *para*-substituted compounds (**2** and **3**) were used as ligands (entries 12 and 14) the resulting alcohol presented the inverted configuration at the stereogenic carbon in comparison with the alcohol obtained in the previous conditions (entries 11 and 13).

As a result of our work, we have obtained new polydentate oxalamide-based ligands in high yields (87–96%) in a very short synthetic sequence. All catalysts **1–6** were shown to induce enantioselectivity in a range of 5–67% ee. We have further demonstrated that both chemical yield and extent of the enantioface discrimination depend on the catalyst and on the molar ratio of Et_2Zn/Ti(*i*-OPr)$_4$. By using the best conditions found, ees reported in the literature were improved on and the highest ee was obtained when ligand **2** was used as catalyst affording (*R*)-1-phenyl-1-propanol with 67% ee. The results obtained in asymmetric catalysis by this new class of polydentate bis(aminodiol)oxalamide ligands appears of interest for further development.

Experimental

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. Solvents were distilled prior to use. TLC was performed on Merck PL60 F_{254} sheets. Preparative column chromatography was performed on Merck Kieselgel 60 (230–240 mesh) silica gel. Melting points were determined with a Sanyo-Gallenkamp capillary apparatus and are uncorrected. IR spectra were recorded on a Jasco FT-IR 5300 spectrometer. Optical rotations were measured at room temperature in a Perkin Elmer 241 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Avance DRX Bruker 300 MHz spectrometer, in DMSO-d_6 solutions. Chemical shifts were recorded in parts

Table 1 Asymmetric addition of Et_2Zn to benzaldehyde[a] in the presence of ligands **1–6**

Entry	Ligand (equiv)	Ti(*i*-OPr)$_4$ (equiv)	Solvent	T/°C	ee[b]/%	Yield/%	Configuration
1[c]	**5** (0.25)	1.4	CH_2Cl_2	0	39	80	*S*
2	**5** (0.25)	1.4	Toluene	0	48	75	*S*
3	**5** (0.25)	1.4	THF	0	10	68	*S*
4	**5** (0.25)	1.4	Toluene	–20	60	85	*S*
5 [c]	**6** (0.25)	1.4	CH_2Cl_2	0	12	83	*S*
6	**6** (0.25.)	1.4	Toluene	0	17	73	*S*
7	**6** (0.25)	1.4	THF	0	5	61	*S*
8	**6** (0.25)	1.4	Toluene	–20	23	82	*S*
9	**1** (0.25)	1.4	Toluene	–20	40	64	*S*
10	**1** (0.10)	0.08	Toluene	–20	36	55	*S*
11	**2** (0.25)	1.4	Toluene	–20	67	75	*R*
12	**2** (0.10)	0.08	Toluene	–20	18	73	*S*
13	**3** (0.25)	1.4	Toluene	–20	37	60	*S*
14	**3** (0.10)	0.08	Toluene	–20	15	57	*R*
15	**4** (0.25)	1.4	Toluene	–20	42	67	*S*
16	**4** (0.10)	0.08	Toluene	–20	24	70	*S*

[a]1 equiv of benzaldehyde was used

[b]Enantiomeric excess (ee) was determined by GC chiral column Supelco β-dex 120 30×0.25×0.25, temperature injector and detector 200 °C, temperature program: 40 °C for 1 min then 5 °C/min to 120 °C isomer (*S*) R_f = 34.5 min, (*R*) R_f = 36.1 min.

[c]Experiments reported in the literature[8]

per million (ppm), downfield from internal Me_4Si. The one-bond multiplicity of carbon atoms was determined by DEPT experiments. High-resolution mass spectroscopic data were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. The ionisation mode used in mass spectra was FAB. GC–MS analyses were performed on a GC–MS-QP5050A Shimadzu mass spectrometer with ionisation energy of 70 eV; enantiomeric excesses were determined with a chiral column Supelco β-dex 120 30×0.25×0.25.

General procedure for the synthesis of ligands **1–6**
Diethyloxalate (0.5 mmol) was added to a solution of the appropriate aminodiol (1 mmol) in toluene (4 ml). The mixture was stirred at reflux temperature until disappearance of the starting material (TLC monitoring) and, after cooling at room temperature, was filtered under reduced pressure. The isolated solid was identified as the corresponding oxalamide compound.

N, N'-Bis[(1S, 2S)-2-hydroxy-1-hydroxymethyl-2-phenylethyl] ethanediamide **1:** White solid (87%), m.p. 172–173 °C. $[\alpha]^{25}_D$ = +70.0 (*c* 1.0, CH_3OH). IR (KBr) ν_{max}: 3396; 3275; 1664; 1531 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.46 (m, 1H, C<u>H</u>$_2$–OH); 3.63 (m, 1H, C<u>H</u>$_2$–OH); 3.97 (m, 1H, CH–N); 4.98 (m, 1H, C<u>H</u>–OH); 5.03 (t, *J* = 5.6 Hz, 1H, exchangeable with D_2O, OH); 5.79 (d, *J* = 4.9 Hz, 1H, exchangeable with D_2O, OH); 7.30–7.40 (m, 5H, Ph); 7.93 (d, *J* = 9.4 Hz, 1H, exchangeable with D_2O, NH).^{13}C NMR (DMSO-d_6): δ 57.3 (d); 60.5 (t); 69.4 (d); 126.6 (d); 129.0 (d); 127.9 (d); 143.25 (s); 158.7 (s). HMRS (FAB) 389.17. Calcd for $C_{20}H_{25}N_2O_6$ 389.17.

N, N'-Bis[(1S, 2S)-2-hydroxy-1-hydroxymethyl-2-(4-nitrophenyl) ethyl]ethanediamide **2:** White solid (94%), m.p. 202–203 °C. $[\alpha]^{25}_D$ = + 73.9 (*c* 0.93, CH_3OH). IR (KBr) ν_{max}: 3404; 3329; 1691; 1529; 1516; 1354 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.45 (m, 1H, C<u>H</u>$_2$–OH); 3.60 (m, 1H, C<u>H</u>$_2$–OH); 4.00 (m, 1H, CH–N); 5.02 (t, *J* = 5.8 Hz, 1H, exchangeable with D_2O, OH); 5.05 (m, 1H, C<u>H</u>–OH); 6.01 (d, *J* = 5.5 Hz, 1H, exchangeable with D_2O, OH); 7.54 (d, *J* = 8.8 Hz, 2H, Ph); 7.90 (d, *J* = 9.6 Hz, 1H, exchangeable with D_2O, NH); 8.19 (d, *J* = 8.8 Hz, 2H, Ph). ^{13}C NMR (DMSO-d_6): δ 56.8 (d); 60.4 (t); 69.2 (d); 122.9 (d); 127.1 (d); 146.5 (s); 151.2 (s); 158.9 (s). HMRS (FAB): 479.15. Calcd for $C_{20}H_{23}N_4O_{10}$ 479.14.

N,N'-Bis[(1S,2S)-2-hydroxy-1-hydroxymethyl-2-(4-methylsulfanyl-benzene)ethyl] ethane diamide **3:** White solid (95%), m.p. 168–169 °C. $[\alpha]^{25}_D$ = + 67.0 (*c* 1.0, CH_3OH). IR (KBr) ν_{max}: 3356; 3290; 2920; 1658; 1525 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H, SCH_3); 3.32 (m, 1H, C<u>H</u>$_2$–OH); 3.47 (m, 1H, C<u>H</u>$_2$–OH); 3.82 (m, 1H, CH–N); 4.80 (t, *J* = 3.5 Hz, 1H, exchangeable with D_2O, OH); 4.88 (m, 1H, C<u>H</u>–OH); 5.64 (d, *J* = 4.7 Hz, 1H, exchangeable with D_2O, OH); 7.15 (s, 4H, Ph); 7.82 (d, *J* = 9.6 Hz, 1H, exchangeable with D_2O, NH). ^{13}C NMR (DMSO-d_6): δ 14.8 (q); 57.1 (d); 60.4 (t); 69.1 (d); 125.6 (d); 126.6 (d); 136.4 (s); 139.9 (s); 159.2 (s). HMRS (FAB): 481.14. Calcd for $C_{22}H_{29}N_2O_6S_2$ 481.15.

N,N'-Bis-[(1R, 2R)-2,3–dihydroxy–1-phenylpropyl]ethanediamide **4:** White solid (96%), m.p. 230–231 °C $[\alpha]^{25}_D$ = -66.0 (*c* 1.03, CH_3OH). IR (KBr) ν_{max}: 3574; 3414; 1655; 1516 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.27 (m, 1H, C<u>H</u>$_2$–OH); 3.44 (m, 1H, C<u>H</u>$_2$–OH); 3.84 (m, 1H, CH–N); 4.89 (s br, 1H, exchangeable with D_2O, OH); 4.94 (m, 1H, C<u>H</u>–OH); 5.16 (d, *J* = 3.8 Hz, 1H, exchangeable with D_2O, OH); 7.20–7.35 (m, 5H, Ph); 9.15 (d, *J* = 8.8 Hz, 1H, exchangeable with D_2O, NH). ^{13}C NMR (DMSO-d_6): δ 55.75 (d); 62.5 (t); 72.3 (d); 127.0 (d); 127.9 (d); 128.0 (d); 139.5 (s); 159.2 (s). HMRS (FAB): 389.17. Calcd for $C_{20}H_{25}N_2O_6$ 389.17.

Analytical and spectroscopic data for compounds **5** and **6** were coincident to those previously reported.[8]

N, N'-Bis-[(1S)-2–hydroxy–1-phenylethyl]ethanediamide **5:** White solid (92%), m.p. 262–263 °C [lit.[8] m.p. 263–265].

N, N'-Bis-[(1S)-1-benzyl-2–hydroxyethyl]ethanediamide **6:** White solid (90%), m.p. 252–253 °C [lit.[8] m.p. 253].

General procedure of the addition of diethylzinc to benzaldehyde
To a solution of titanium (IV) isopropoxide (1.4 mmol, 0.42 mg) and the chiral ligand (0.25 mmol) in dry toluene (5 ml) under N_2, benzaldehyde (1 mmol, 0.1 ml) was added dropwise. The mixture was stirred at room temperature for 1 h. The flask was cooled to –20 °C and diethylzinc (3 mmol, 3 ml, 1 M solution in hexane) was added dropwise. The mixture was stirred until disappearance of the starting material (TLC monitoring), quenched with 1M hydrochloric acid (20 ml) and filtered under reduced pressure. The filtrate was extracted with diethyl ether (3×15 ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography (on silica gel eluting with hexane:ethyl acetate 9:1) giving an oil which was analyzed by GC chiral column Supelco β-dex 120 30×0.25×0.25. Yields and ees are included in Table 1.

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