SHORT PAPER

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Syntheses of chiral C_2-symmetric bidentate ligands having different ring sizes of cyclic amines and their catalytic abilities on enantioselective cyclopropanation of styrene catalysed by copper(I) triflate†

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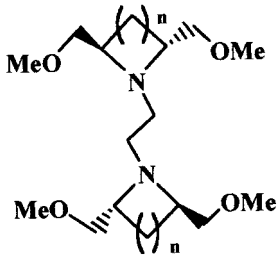
A series of chiral bidentate ligands having different ring sizes of cyclic amines have been synthesized. Their catalytic abilities on chiral inductions have been examined in the asymmetric cyclopropanation of styrene catalysed by copper(I) triflate.

Keywords: cyclopropanation, oxamides, reduction, diamines, bidentate ligands

High efficiencies of C_2-symmetric chiral reagents, including auxiliaries and catalyst ligands, in chiral induction have attracted much attention in asymmetric synthesis.[1] Previously, we reported chiral C_2-symmetric 2,4-disubstituted azetidine and C_2-symmetric 2,5-disubstituted pyrrolidine derivatives as chiral catalyst ligands in the reaction of diethylzinc with arylaldehydes.[2] Very high yields and very high enantioselectivities have been achieved in this asymmetric addition reaction by those novel chiral ligands.[3] The relatively rigid C_2-symmetric four- or five-membered ring structure has been considered as the determining factor for those ligands to be effective in this catalytic asymmetric addition reaction. Although the backbone structure of a chiral scaffold is important in chiral induction, little is known about the influence of different ring sizes of chiral C_2-symmetric cyclic amines on chiral induction in catalytic enantioselective reactions. In this paper, by synthesizing chiral C_2-symmetric bidentate ligands **1**–**4** having different ring sizes of cyclic amines and examining their catalytic abilities on enantioselective cyclopropanation of styrene catalyzed by copper(I) trifluoromethanesulfonate benzene complex $[(CuOTf)_2{\cdot}C_6H_6]$, we try to partially disclose the real effects of the backbone structure of a chiral scaffold on chiral induction (Fig. 1). We believe that, from those chiral ligands, we can easily draw a conclusion on the effects of backbone structures of chiral ligands on chiral induction. Furthermore, we selected them as chiral ligands because the key intermediates of these chiral ligands, namely chiral C_2-symmetric aziridine, azetidine, pyrrolidine, and piperidine, are easily available according to literature methods.[4]

The chiral C_2-symmetric (2*S*, 3*S*)-aziridine can be synthesised from *L*-tartaric acid which was used as a chiral pool according to the literature.[4b] The chiral C_2-symmetric (2*R*, 4*R*)-azetidine, (2*R*, 5*R*)-pyrrolidine and (2*R*, 6*R*)-piperidine were obtained by normal optical resolution using (*S*)-(-)-1-phenylethylamine as a chiral auxiliary. Chiral C_2-symmetric (2*R*, 4*R*)-azetidine and (2*R*, 5*R*)-pyrrolidine were available in their diethyl ester form through the column chromatographic separation (SiO_2) using ethyl acetate/hexane = 1/10 as eluent, but C_2-symmetric (2*R*, 6*R*)-piperidine was only available in diol form by the column chromatographic separation (SiO_2) using methanol/dichloromethane = 1/100 as eluent.[4] The optical purities of the obtained chiral C_2-symmetric aziridine, azetidine, pyrrolidine and piperidine were checked by comparison of their specific rotations with those of authentic samples reported previously.[4]



Ligand 1: n= 0; Ligand 2: n= 1;
Ligand 3: n= 2; Ligand 4: n= 3.

Fig. 1 The chiral bidentate ligands having different sizes.

Results and discussion

Chiral bidentate ligands **1**–**4** having different ring sizes of C_2-symmetric cyclic amines were synthesized by the coupling reaction of the corresponding two molecules of chiral C_2-symmetric cyclic amine with oxalyl chloride in the presence of triethylamine and then reduction of the obtained diamides **5**–**8** by $LiAlH_4$ in THF (Scheme 1). Unfortunately, in the preparation of diamide **5** from the C_2-symmetric aziridine, the ring opened products **9** and **10** became the major products. This is because the highly strained C_2-symmetric three-membered ring was very easily opened by nucleophilic attack of chloride ion (Cl^-), although it is a very weak nucleophile. The product with both rings opened was the amine **9** and the one with only one three-membered ring opened was the amide **10** (Scheme 1). The desired compound **5** was obtained in a very low yield. Although the compound **5** can be reduced by $LiAlH_4$ to give the desired chiral bidentate ligand **1**, only a few milligrams of **1** were obtained. Furthermore, it was very difficult to purify **5** by column chromatography. Therefore eventually we utilised **2**–**4** as the chiral bidentate ligands for Cu(I)-catalysed cyclopropanation of styrene to examine the chiral induction abilities of these chiral scaffolds having different ring sizes of C_2-symmetric cyclic amine (Scheme 2).[5]

We found that **2** and **3** are good chiral bidentate ligands for this reaction. High yields (70–80%) and moderate ee (34–50%) of cyclopropanation products could be obtained. However, the chiral bidentate ligand **4** having six-membered ring amines gave a moderate yield and very low ee of the cyclopropanation products in which the *cis*-cyclopropanation product was obtained as a major product (Scheme 2). We

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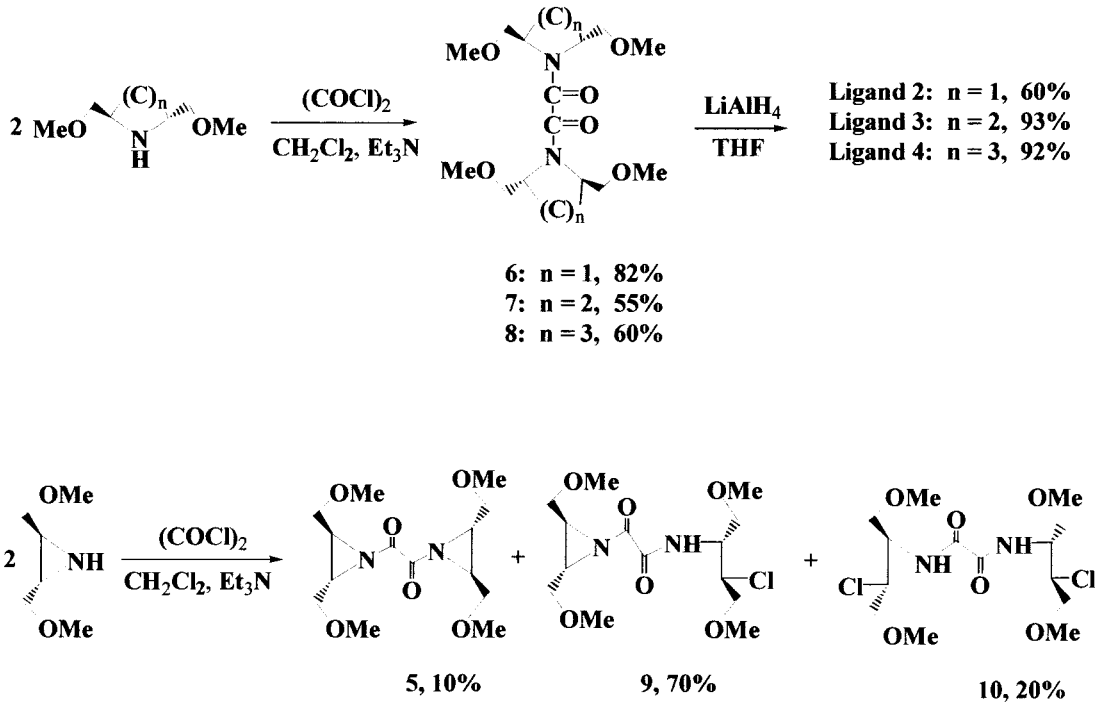
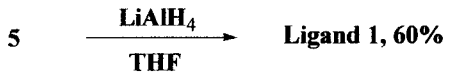
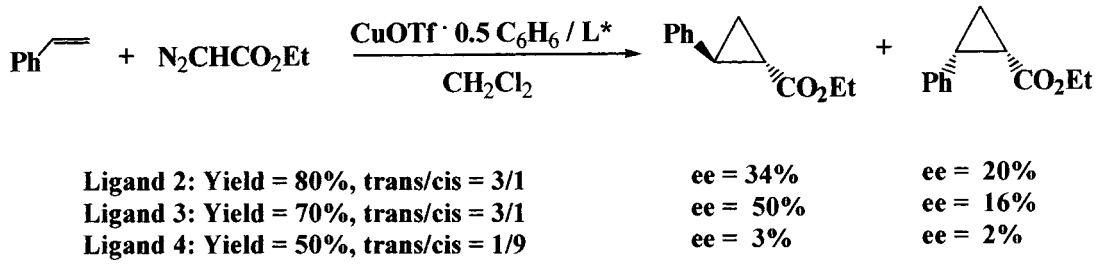
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.





Scheme 1



Scheme 2

believe this result is due to the ring structure of six-membered ring. For 1,3-*trans*-disubstituted six-membered ring, one substituent must be equatorial and one axial, and so the formal C_2-symmetry of the individual rings (of course, there is a second C_2 element in the structure) is not so apparent in the actual geometry of the structure. This point is particular to the six-membered rings, is far less apparent in the five-membered, and does not apply at all in the four-membered rings. Namely, the 1,3-*trans*-disubstituted six-membered ring do not have a pure and rigid C_2-symmetric ring structure. This is why the low ee has been achieved by chiral ligand **4**.

In conclusion, we have found that, in the preparation of chiral ligands from the chiral scaffold of cyclic amines, the four- and five-membered rings (azetidine and pyrrolidine) are excellent candidates, while the six-membered ring (piperidine) gives very low enantioselectivity owing to its ring backbone structure. The three-membered ring caused a lot of problems during the synthetic process because its backbone structure is too labile.

We plan to synthesise more chiral ligands of this type, having different ring sizes of cyclic amines, and utilize them as ligands for other catalytic asymmetric reactions in order to seek out more embedded information on the chiral induction. Undoubtedly these results can give helpful information on the design and synthesis of new chiral ligands. Work along this line is currently in progress.

Experimental

Melting points (m.p.s) were obtained with a Yanagimoto micro melting point apparatus. Optical rotations were determined in a solution of $CHCl_3$ at 20 °C by using a Perkin-Elmer-241 MC polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2/g. ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J* values are in Hz.

Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer.

All reactions were monitored by TLC with Huanghai $60F_{254}$ silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. The optical purities of cyclopropanes were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel OD and OJ; eluent, 100:0.5–2 hexane-propan-2-ol mixture; flow rate, 1.0 ml/min; detection, 254 nm light) and the absolute configurations of the major enantiomer were assigned according to the sign of the specific rotation.

Materials: Organic solvents used were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. Aldehyde and styrene were freshly distilled prior to use, ethyl diazoacetate, diethylzinc, copper(I) trifluoromethanesulfonate benzene complex $[(CuOTf)_2{\cdot}C_6H_6]$ and (*S*)-(-)-1-phenylethylamine were obtained from Aldrich (Milwaukee, WI). The optical purities of chiral C_2-symmetric aziridine, azetidine, pyrrolidine and piperidine were checked by specific rotation.

Chiral C_2-symmetric (2*S*, 3*S*)-aziridine: $[\alpha]_D^{20}$ +55.1 (c 10.0, Et_2O) [Lit: $[\alpha]_D^{20}$ +55.6 (c 10.0, Et_2O)].[4b] Chiral C_2-symmetric (2*R*, 4*R*)-azetidine: $[\alpha]_D^{20}$ –10.7 (c 1.3, $CHCl_3$) [Lit: $[\alpha]_D^{20}$ –11.0 (c 1.2, $CHCl_3$)].[4b] Chiral C_2-symmetric (2*R*, 5*R*)-pyrrolidine: $[\alpha]_D^{20}$ –7.8 (c 3.0, EtOH) [Lit: $[\alpha]_D^{20}$ –7.8 (c 3.0, EtOH)].[4a] Chiral C_2-symmetric (2*R*, 6*R*)-piperidine: $[\alpha]_D^{20}$ –7.8 (c 0.6, $CHCl_3$) [Lit: $[\alpha]_D^{20}$ –7.9 (c 0.6, $CHCl_3$)].[4d]

Diamide **8**: To a solution of chiral C_2-symmetric chiral piperidine (148 mg, 0.85 mmol) and triethylamine (104 mg, 0.14 ml, 1.03 mmol) in dichloromethane (10 ml) was added oxalyl chloride (63 mg, 0.044 ml, 0.50 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and diethyl ether (20 ml) was added into the residue. After filtration, the solvent was removed again under reduced pressure and the residue was purified by silica gel column chromatography to give the oxaldiamide **8** (102 mg, 60%) as a colourless soild (eluent: dichloromethane). m.p. 81–83 °C; $[\alpha]_D$ + 71.8 (c 0.90, CH_2Cl_2); $\delta_H(CDCl_3)$ 1.50–2.00 (12H, m, CH_2), 3.35 (4H, t, *J* = 6.1 Hz, CH_2), 3.38 (12H, s, OMe), 3.51 (4H, dd, *J* = 10.6, 5.1 Hz), 3.63 (4H, dd, *J* = 10.6, 3.8 Hz), 3.64-3.85 (4H, m); HRMS (EI) *m/z* 400.2575 (M^+), $C_{20}H_{36}N_2O_6$ requires 400.2573.

Diamide **5:** This compound was prepared in the same manner as that described above, along with the formation of amides **9** and **10**.

Physical data for **5**: A colourless oil; 14 mg, 10%; $[\alpha]_D$ –98.2 (c 0.89, $CHCl_3$); $\delta_H(CDCl_3)$ 2.95 (4H, dd, *J* = 5.8, 2.6 Hz), 3.33 (12H, s, OMe), 3.62 (4H, dd, *J* = 10.9, 3.6 Hz), 3.78 (4H, dd, *J* = 10.9, 2.6 Hz); HRMS (EI) *m/z* 317.1704 (M^++1), $C_{14}H_{25}N_2O_6$ requires 317.1713.

Physical data for amide **9**: A colourless oil; 105 mg, 70%; $[\alpha]_D$ –56.2 (c 0.81, $CHCl_3$); $\delta_H(CDCl_3)$ 2.98 (2H, t, *J* = 2.3 Hz), 3.33 (6H, s, OMe), 3.34 (3H, s, OMe), 3.36 (3H, s, OMe), 3.49 (2H, dd, *J* = 9.8, 5.8 Hz), 3.65 (2H, dd, *J* = 9.8, 5.8 Hz), 3.72 (4H, dd, *J* = 3.0, 2.6 Hz), 4.20–4.35 (1H, m), 4.35–4.51 (1H, m), 7.82 (1H, d, *J* = 8.7 Hz, NH); HRMS (EI) *m/z* 352.1398 (M^+), $C_{14}H_{25}ClN_2O_6$ requires 352.1401.

Physical data for amide **10**. A colourless oil; 33 mg, 20%; $[\alpha]_D$ –25.5 (c 0.65, $CHCl_3$); $\delta_H(CDCl_3)$ 3.35 (6H, s, OMe), 3.39 (6H, s, OMe), 3.49 (2H, dd, *J* = 9.8, 5.3 Hz), 3.60-3.73 (6H, m, CH_2), 4.23 (2H, q, 5.1 Hz), 4.35–4.51 (2H, m), 7.94 (2H, d, *J* = 9.1 Hz, NH); HRMS (EI) *m/z* 388.1175 (M^+), $C_{14}H_{26}Cl_2N_2O_6$ requires 388.1168.

Diamide **6**: This compound was prepared in the same manner as that described above. A colourless oil; 120 mg, 82%; $[\alpha]_D$ +264.5 (c 0.80, $CHCl_3$); $\delta_H(CDCl_3)$ 2.24–2.30 (2H, m), 2.33–2.40 (2H, m), 3.38 (12H, s, OMe), 3.45 (2H, dd, *J* = 10.4, 3.2 Hz), 3.58 (2H, dd, *J* = 10.2, 3.2 Hz), 3.67 (2H, dd, *J* = 10.4, 4.4 Hz), 3.81 (2H, dd, *J* = 10.0, 5.0 Hz), 4.46–4.50 (2H, m), 4.85–4.89 (2H, m); HRMS (EI) *m/z* 345.2032 (M^++1), $C_{16}H_{29}N_2O_6$ requires 345.2026.

Diamide **7**: This compound was prepared in the same manner as that described above. A colourless oil. 87 mg, 55%; $[\alpha]_D$ +189.6 (c 0.75, $CHCl_3$); $\delta_H(CDCl_3)$ 1.87–2.18 (8H, m), 3.25 (2H, dd, *J* = 14.2, 9.5 Hz), 3.32 (6H, s, OMe), 3.33 (6H, s, OMe), 3.35 (2H, dd, *J* = 9.5, 5.4 Hz), 3.50-3.58 (4H, m), 4.20-4.38 (2H, m), 4.38–4.45 (2H, m); HRMS (EI) *m/z* 372.2254 (M^+), $C_{18}H_{32}N_2O_6$ requires 372.2260.

Chiral bidentate ligand **4**: To a solution of $LiAlH_4$ (158 mg, 4.16 mmol) in THF (10 ml) was added **8** (140 mg, 0.35 mmol) in THF (5 ml) and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched by adding water (20 ml) and extracted with ethyl acetate (20 ml × 2). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the compound **4** (120 mg, 92%) as a colourless oil (eluent: ethanol/chloroform = 1/10). $[\alpha]_D$ + 5.6 (c 1.2, CH_2Cl_2); $\delta_H(CDCl_3)$ 1.20–2.0 (12H, m, CH_2), 2.75–3.20 (4H, m), 3.30 (12H, s, OMe), 3.37 (4H, dd, *J* = 10.6, 5.1 Hz), 3.51 (4H, dd, *J* = 10.6, 3.8 Hz), 3.34–3.50 (2H, m), 3.52–3.70 (2H, m); HRMS (EI) *m/z* 373.3063 (M^++1), $C_{20}H_{41}N_2O_4$ requires 373.3066.

Chiral bidentate ligand **1**: This compound was prepared in the same manner as that described above. A colourless oil. 63 mg, 60%; $[\alpha]_D$ +15.6 (c 0.94, $CHCl_3$); $\delta_H(CDCl_3)$ 1.80 (4H, t, *J* = 5.6 Hz), 3.34 (12H, s, OMe), 3.37 (4H, dd, *J* = 10.6, 5.1 Hz), 3.51 (4H, dd, *J* = 10.6, 3.8 Hz), 3.83 (4H, t, *J* = 5.6 Hz); HRMS (EI) *m/z* 288.2035 (M^+), $C_{14}H_{28}N_2O_4$ requires 288.2049.

Chiral bidentate ligand **2**: This compound was prepared in the same manner as that described above. A colourless oil. 67 mg, 60%; $[\alpha]_D$ +39.7 (c 1.10, $CHCl_3$); $\delta_H(CDCl_3)$ 2.03 (4H, t, *J* = 6.8 Hz, CH_2), 2.60 (2H, t, *J* = 7.0 Hz, CH_2), 2.80 (2H, t, *J* = 7.0 Hz, CH_2), 3.38 (12H, s, OMe), 3.45 (4H, dd, *J* = 10.1, 5.4 Hz), 3.53 (4H, dd, *J* = 10.1, 5.1 Hz), 3.64 (4H, quintet, *J* = 5.0 Hz); HRMS (EI) *m/z* 317.2433 (M^++1), $C_{16}H_{33}N_2O_4$ requires 317.2440.

Chiral bidentate ligand **3**: This compound was prepared in the same manner as that described above. A colourless oil. 112 mg, 93%; $[\alpha]_D$ +50.3 (c 1.42, $CHCl_3$); $\delta_H(CDCl_3)$ 1.44–1.47 (2H, m), 1.65-1.69 (2H, m), 1.87–2.05 (4H, m), 2.94–2.97 (2H, m), 3.12-3.20 (2H, m), 3.26 (4H, dd, *J* = 7.8, 1.3 Hz), 3.29 (4H, t, *J* = 5.8 Hz), 3.34 (6H, s, OMe), 3.35 (6H, s, OMe), 3.37–3.45 (4H, m); HRMS (EI) *m/z* 345.2742 (M^++1), $C_{18}H_{37}N_2O_4$ requires 345.2753.

Typical reaction procedure: cyclopropanation: To a solution of chiral ligand **3** (5.5 mg, 0.016 mmol) in dichloromethane (10 ml) was added CuOTf · 0.5 benzene (2 mg, 0.011 mmol) and the mixture was stirred for 1 h at room temperature under argon atmosphere. Styrene (104 mg, 1 mmol) was added into the solution and the resulting mixture was stirred for a further 5 min. Then ethyl diazoacetate (137 mg, 1.2 mmol) in dichloromethane (5 ml) was added and the reaction mixture was stirred for 16 h. The cyclopropanation products were isolated by preparative TLC plate (25 × 25 cm) (eluent ethyl acetate: petroleum ether = 1:10) to give the *trans*- and *cis*-cyclopropanes, respectively. The ee of the *trans*-cyclopropane and *cis*-cyclopropane was determined by chiral HPLC.

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