Tetrahedron: Asymmetry Vol. 4, No. 11, pp. 2389-2398, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00

Chiral Ligands Containing Heteroatoms. 11.[1] Optically Active 2-Hydroxymethyl Piperazines as Catalysts in the Enantioselective Addition of Diethylzinc to Benzaldehyde

Massimo Falorni,* Michele Satta, Sandra Conti and Giampaolo Giacomelli

Dipartimento di Chimica, Universita' di Sassari, via Vienna 2, I-07100 Sassari, Italy

(*Received in UK* 13 *September* 1993)

Key words: chiral piperazines; optically active alcohols; enantioselective additions

Abstract: Starting from enantiomerically pure serine, a series of (2*R*,5*S*) and (2*S*,5*S*)-2-hydroxymethyl-5-alkyl piperazines **1-5** were prepared in good yields without any racemization. The use of these compounds as chiral catalysts for the enantioselective addition of diethylzinc to aldehydes is described. This paper reports the first example of the use of piperazine methanols in asymmetric synthesis.

Catalytic enantioselective carbon-carbon bond forming is now recognised as one of the most important problems in organic synthesis.[2] It is known that enantioselective addition of organometallic reagents to aldehydes in the presence of amino alcohols affords optically active secondary alcohols.[3] Recently, in our laboratory, we found that amino pyridines also act as chiral catalysts in the enantioselective addition of diethylzinc to aldehydes.[1,4]

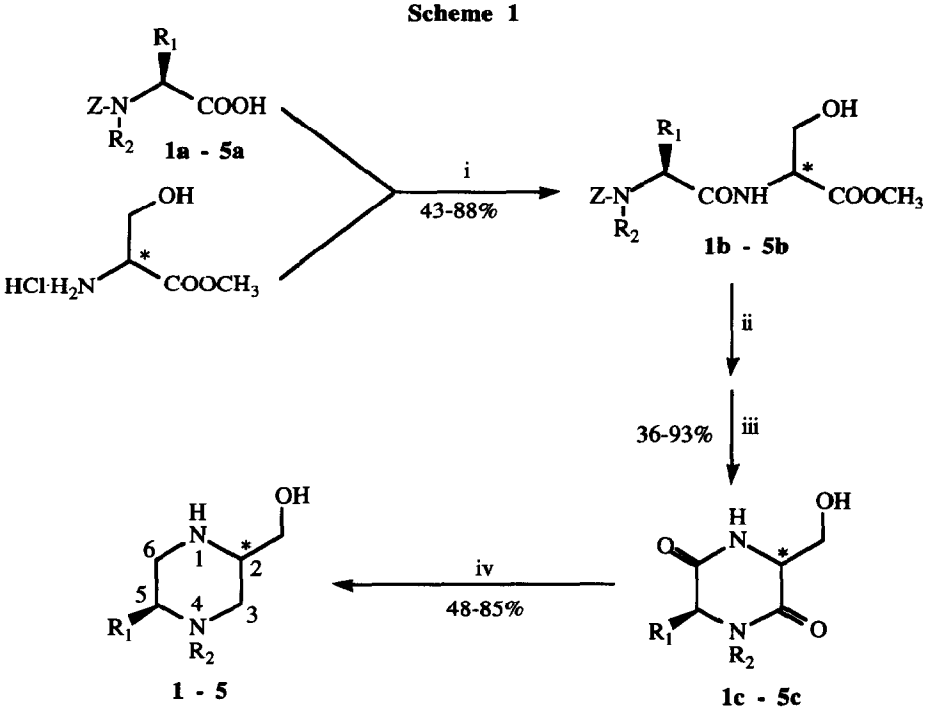
There are only a few examples reported, in which, optically active piperazines have been used as chiral modifiers in asymmetric reactions.[5] Although C_2-symmetric piperazines having an *o*-hydroxyphenyl substituent have been reported,[5c] this study represents the first example of the use of piperazine methanols in the enantioselective addition of diethylzinc to benzaldehyde.

We wish to report the synthesis of (2*R*,5*S*) and (2*S*,5*S*)-2-hydroxymethyl-5-alkyl piperazines **1-5** and a detailed study of the dialkylzinc-benzaldehyde addition carried out by using compounds **1-5** as chiral catalysts.

The piperazines **1-5** were prepared according Scheme I:[6] commercial amino acids were converted into the corresponding *N*-benzyloxycarbonyl derivatives **1a-5a** that were treated with (*S*) or (*R*) H-Ser-OMe·HCl to give dipeptides **1b-5b** using the mixed anhydride coupling method. Deblocking the benzyloxycarbonyl group was carried out by transfer hydrogenation (10% Pd/C, cyclohexene, MeOH, 65°C). After removal of any volatile product, the residues were suspended in dry methanol and, according to previously reported diketopiperazines

syntheses,[7] heating (65°C) was prolonged for 5 days to afford compounds **1c-5c**. The reduction of DKPs **1c-5c** to piperazines **1-5** was carried out by using an excess of LAH in refluxing THF:[8] the recovery of the products from the reaction mixtures was optimised carrying out the hydrolysis of LAH by triethanolamine.[9] Measurements of ^{1}H and ^{13}C NMR carried out at various temperatures (from 20° to 50°C) have indicated that compounds **1-5** have a diastereoisomeric purity ≥ 95% .

Scheme 1



a-c	R_1	R_2	Starting Serine Enantiomer
1	H	Me	(*S*)
2	$-CH_2-CH_2-CH_2-$		(*S*)
	$-CH_2-CH_2-CH_2-$		(*R*)
3	Pr^i	H	(*S*)
	Pr^i	H	(*R*)
4	Bu^i	H	(*S*)
5	(*S*)-Bu^s	H	(*S*)

1a = Z-Sar-OH
2a = Z-Pro-OH
3a = Z-Val-OH
4a = Z-Leu-OH
5a = Z-Ile-OH

Scheme Reagents: i, EtOCOCl, 4-methylmorpholine, EtOAc;
ii, 10% Pd/C, cyclohexene, MeOH;
iii, MeOH, 65°C, 110 h;
iv, $LiAlH_4$, 65°C, 72 h, THF.

Piperazine methanols **1-5** were obtained in 14% [compound (**2*R*,5*S*)-2**] to 60% (compound **1**) overall yields. Surprisingly, the cyclization of the dipeptide (**2*S*,5*S*)-2b** occurred in low yield (36%) whereas its diastereomer afforded the DKP (**2*R*,5*S*)-2c** in 93% yield. Several attempts to optimise this step failed.[8]

Enantioselective additions of diethylzinc to benzaldehyde in the presence of catalytic amounts (6 mol%) of **1-5** were carried out in several solvents at room temperature. The data obtained using chiral piperazines **1-5** are summarised in Tables 1 and 2. The ethyl phenyl carbinols were obtained in good chemical yields, within 14-20 h. Independently of the reaction temperature, 1-phenyl-propan-1-ol is the main product detected; benzyl alcohol is formed only in small amount (2-3%). The enantioselectivity ranges from low to moderate: it is noteworthy that the ligand (**2*R*,5*S*)-2** is the most efficient among those examined (entries 3-6). Also the diketopiperazines might act as catalyst in the alkylation of benzaldehyde (entry 1): in this case, however, the chemical yield and the enantioselectivity is lower than those of the reaction carried out with the corresponding piperazine (entry 3). Preliminary data obtained showed that, using ligand (**2*R*,5*S*)-2**, the cyclohexyl carboxyaldehyde and the 3-phenylpropionaldehyde were alkylated with a maximum of 20% enantioselectivity.

Table 1. Asymmetric Addition of Diethylzinc to Aldehydes Using Ligands 1-5[a]

					ethyl phenyl carbinol		
entry	ligand	Solvent	Temperature ℃	Time h	Conversion[b] %	$[\alpha]^{25}_D$ ($CHCl_3$)	e.e.%[c]
1	(**2*R*,5*S*)-2c**	CH_2Cl_2	20	18	28	-5.52	12(*S*)
2	**1**	Et_2O	25	14	90	-3.90	14(*S*)
3	(**2*R*,5*S*)-2**	CH_2Cl_2	27	15	92	-22.78	50(*S*)
4	(**2*R*,5*S*)-2**	CH_2Cl_2	-15	16	40	-27.83	61(*S*)
5	(**2*R*,5*S*)-2**	PhH	25	20	97	-20.33	45(*S*)
6	(**2*R*,5*S*)-2**	Et_2O	30	15	91	-17.15	38(*S*)
7	(**2*R*,5*S*)-2**	THF	30	20	75	-1.39	3(*S*)
8	(**2*S*,5*S*)-2**	CH_2Cl_2	19	18	67	+7.03	15(*R*)
9	(**2*S*,5*S*)-2**	PhH	20	20	93	+9.48	21(*R*)
10	(**2*S*,5*S*)-2**	Et_2O	22	20	93	+15.75	35(*R*)
11	(**2*S*,5*S*)-2**	THF	22	20	58	+13.34	29(*R*)
12	(**2*R*,5*S*)-3**	CH_2Cl_2	20	18	86	-6.75	15(*S*)
13	(**2*R*,5*S*)-3**	Et_2O	25	20	87	+0.71	1(*R*)
14	(**2*S*,5*S*)-3**	CH_2Cl_2	20	18	69	+4.30	9(*R*)
15	(**2*S*,5*S*)-3**	Et_2O	20	18	83	+4.81	11(*R*)
16	**4**	CH_2Cl_2	18	17	85	-2.45	5(*S*)
17	**4**	Et_2O	25	20	97	-1.72	6(*S*)
18	**5**	Et_2O	30	15	91	+0.84	2(*R*)

[a]) Reactions carried out with a molar ratio Et_2Zn/aldehyde/ligand = 2/1/0.06. [b]) GLC yields of the crude products.
[c]) Confirmed by GLC on chiral column.

It is noteworthy that this kind of 2-hydroxymethyl cyclic amine ligands give enantioselective additions, of the same order of magnitude of those recently observed with 2-hydroxymethyl oxazoline ligands,[10] while no asymmetric induction was observed with a structurally related ligand such as prolinol.[3]

As shown in Table 1, the solvent effect on the enantioselectivity of the process was examined: apolar solvents, such as CH_2Cl_2 and benzene, seem generally more suitable than donor solvents when ligands having absolute 2*R* configuration are involved. The ligand **(2*R*,5*S*)-2** is a good enantioselective catalyst in CH_2Cl_2, expecially at low temperature (entry 4), whereas it is actually inefficient in THF (entry 7). Surprisingly, working with catalysts having the 2*S* configuration, the effect of the solvent is quite opposite, the enantioselectivities being greater in polar solvents than in apolar ones (see for example entries 8 and 9). When using ligand **4** the influence of the solvent seems to be negligible (entries 16-17).

There is a direct relationship between the absolute configuration of the stereogenic center at the 2-position of the piperazine ligand and the absolute configuration of recovered carbinols: using (2*S*)-ligands, (*R*)-alcohols are recovered, while, when (2*R*)-catalysts are involved, (*S*)-alcohols are obtained. Only in entries 13 and 18, using (2*R*)-ligands, (*R*)-carbinols were recovered, even if with low ee. Moreover the stereochemical behaviours of a diastereomeric pair of ligands such as **(2*R*,5*S*)-2** and **(2*S*,5*S*)-2** are not specular: this fact should indicate that the catalyst molecule is entirely involved in the stereodifferentiating process confirming the important contribution of the stereogenic center in 5-position.

Some authors[5b, 11] have reported that lithiated ligands are more enantioselective catalysts then the parent compounds: therefore, we have also used the lithium salts of the piperazines **1-5**. The results are summarized in Table 2. Lithiation causes an increase of the ees only when the ligand **4** is involved (entries 16, 29-31). In the other cases the ees obtained are generally comparable with those related to the parent ligands. When **(2*S*,5*S*)-2·Li_2** and **4·Li_3** are used the ees are minor than those observed using the less lithiated ligands (entries 28 and 31). Moreover, when lithiated ligands are involved, the influence of the solvent is less significant: using Et_2O instead of CH_2Cl_2 only slight differences are observed (see for example entries 21 and 22).

As confirmed by our previous ^1H NMR studies reported,[1,4,11] this kind of process occurs through a six-membered cyclic transition state involving a stoichiometric diethylzinc/ligand complex, an aldehyde molecule and a further molecule of diethylzinc. It should be reasonable to suppose that, when piperazine methanols are involved, the zinc atom may be bonded to the alcoholic oxygen atom and coordinated at least by one of the two nitrogen atoms. Unfortunately, the nature of ^1H NMR spectra of the piperazine methanols **1-5** and of the related ligand/zinc complexes did not permit an accurate analysis of their structure to be obtained. Only the disappearance of the very broad signal due to the alcoholic proton in the ^1H NMR spectrum of the zinc complex comfirms the formation of an oxygen-zinc bond. Examination of molecular models and basic force-field calculations let us to exclude the existence of a complex in which the zinc atom simultaneously interacts with the three heteroatoms of the piperazine methanol.

According to that previously reported,[1,4,5b,11] it appears that a more constrained ligand should be essential as catalyst to achieve high enantioselectivity. From this point of view, the conformational rigidity of the fused pyrrolidine ring in **2** might slightly destabilize the congested transition state, in particular when **(2*R*,5*S*)-2** piperazine is used. In this case, the alkylation give better enantioselectivities.

Table 2. Asymmetric Addition of Diethylzinc to Aldehydes Using Ligands 1-5 and Their Lithium Salts[a]

					ethyl phenyl carbinol		
entry	ligand	Solvent	Temperature ℃	Time h	Conversion[b] %	$[\alpha]^{25}_D$ ($CHCl_3$)	e.e.%[c]
2	**1**	Et_2O	25	14	90	-3.90	14(*S*)
19	**1·Li**	Et_2O	20	18	96	-3.90	14(*S*)
20	**1·Li_2**	Et_2O	25	14	95	-3.89	13(*S*)
3	**(2*R*,5*S*)-2**	CH_2Cl_2	27	15	92	-22.78	50(*S*)
6	**(2*R*,5*S*)-2**	Et_2O	30	15	91	-17.15	38(*S*)
21	**(2*R*,5*S*)-2·Li**	CH_2Cl_2	27	14	92	-9.19	20(*S*)
22	**(2*R*,5*S*)-2·Li**	Et_2O	18	16	87	-9.27	20(*S*)
23	**(2*R*,5*S*)-2·Li_2**	CH_2Cl_2	30	14	94	-9.48	21(*S*)
24	**(2*R*,5*S*)-2·Li_2**	Et_2O	18	17	89	-16.35	36(*S*)
8	**(2*S*,5*S*)-2**	CH_2Cl_2	19	18	67	+7.03	15(*R*)
9	**(2*S*,5*S*)-2**	Et_2O	22	20	93	+15.75	35(*R*)
25	**(2*S*,5*S*)-2-Li**	CH_2Cl_2	20	20	94	+10.38	23(*R*)
26	**(2*S*,5*S*)-2·Li**	Et_2O	20	18	93	+14.44	32(*R*)
27	**(2*S*,5*S*)-2·Li_2**	CH_2Cl_2	19	18	87	+8.82	19(*R*)
28	**(2*S*,5*S*)-2·Li_2**	Et_2O	20	20	88	+3.30	7(*R*)
16	**4**	Et_2O	25	20	97	-1.72	6(*S*)
29	**4·Li**	Et_2O	30	15	91	-12.41	27(*S*)
30	**4·Li_2**	Et_2O	20	14	88	-11.73	26(*S*)
31	**4·Li_3**	Et_2O	30	18	89	-7.24	16(*S*)
18	**5**	Et_2O	30	15	91	+0.84	2(*R*)
32	**5·Li**	Et_2O	20	18	94	+1.72	6(*R*)

[a]) Reactions carried out with a molar ratio Et_2Zn/aldehyde/ligand = 2/1/0.06. [b]) GLC yields of the crude products. [c]) Verified by GLC on chiral column.

Experimental Section

Boiling points are uncorrected. Bulb to bulb distillations were carried out with a Büchi GRK-51 apparatus equipped with a vacuum controller Büchi B-168. Melting points were determined on a microscope Leitz LABORLUX S equipped with Leitz Microscope Heating Stage 350 and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 420 B analyser. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter in a 1 dm tube. GC analyses of the reaction products were carried out on a Perkin-Elmer 8600 gas chromatograph on fused silica megabore columns (15 m x 0.53 mm) DB-1, DB-5 (J&W), operating with an He flow rate of 9 mL/min, enantioseparations of ethyl phenyl carbinols were carried out on fused silica megabore column (30 m x 0.53 mm) BETA-DEX-120 (Supelchem). Optical purity of the carbinols was

determined also by direct comparison of optical rotations, which, when possible, was carefully done with the synthetic and authentic resolved matherials. The ^1H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) Fourier transform spectra were obtained with a Varian VXR-300 spectrometer on $CDCl_3$ solutions (unless otherwise specified) and with TMS as internal standard. All reactions were carried out at least in duplicate for all temperature conditions and under argon atmosphere: all reagents and solvents employed were reagent grade matherials purified by standard methods and distilled before use. As chiral starting materials (*S*)-proline, (*S*)-valine, (2*S*,3*S*)-isoleucine and (*S*)-leucine of "*BioChemica*" grade (chemical and enantiomeric purity >99%) purchased from Fluka Chemie AG were used; (*S*) and (*R*)-serine (enantiomeric purity >99%) purchased from Janssen were used. H-L-Ser-OMe·HCl {mp 162-165 °C, $[\alpha]_D^{25}$ -4.90 (c 1, MeOH)} and H-D-Ser-OMe·HCl {mp 164-166°C, $[\alpha]_D^{25}$ -4.97 (c 1, MeOH)} were prepared as previously reported for the *S* enantiomer.[12] L-α-*N*-(Benzyloxycarbonyl)amino acids were prepared according reported procedures; for the samples employed it was found: **1a**[13] mp 52-53°C; **2a**[14] mp 78-80°C, $[\alpha]_D^{25}$ -40.4 (c 1, EtOH); **3a**[15] mp 60-63 °C, $[\alpha]_D^{25}$ +1.5 (c 5, EtOH); **4a**[16] oil, $[\alpha]_D^{25}$ -16.0 (c 2, EtOH); **5a**[17] oil, $[\alpha]_D^{25}$ +4.52 (c 5, EtOH).

Products 1b-5b; General Procedure

Under vigorous stirring and at -15 °C, 4-methylmorpholine (32.9 mL, 30.3 g, 300 mmol) in EtOAc (30 mL) and ethylchloroformate (28.2 mL, 32.0 g, 295 mmol) in EtOAc (20 mL) were added to protected amino acids **1a-5a**, (295 mmol) in EtOAc (200 mL). The reaction mixtures were stirred at -15 °C for 15 min, then 4-methylmorpholine (32.9 mL, 30.3 g, 300 mmoli) and L- or R-H-Ser-OMe·HCl (44.2 g, 284 mmol, portionwise) were added; also EtOAc (250 mL) was added. The resulting mixtures were stirred at -15 °C for 1 h, then 12 h at r.t.. The reaction mixtures were treated with water (200 mL) and EtOAc (200 mL). The organic and aqueous layers were separated and the aqueous layers were extracted with EtOAc. The collected organic phases were washed with 10% aq $NaHCO_3$, sat. aq NaCl, 5% aq HCl and sat. aq NaCl (150 mL each) in that order, and dryed (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude products were recrystallized from the suitable solvents giving pure (TLC) protected dipeptides **1b-5b**.

(*S*)-*N*-[*N'*-(Benzyloxycarbonyl)sarcosyl]serine methylester (Z-Sar-Ser-OMe), 1b: recrystallized from EtOAc/hexane, 88% yield, mp 45-49 °C, $[\alpha]_D^{25}$ -16.20 (c 2, MeOH); ^1H NMR, δ: 7.45-7.3 (m, 5H), 7.0-6.8 (m, 1H), 5.17 (bs, 2H), 4.7-4.6 (m, 1H), 4.05-3.95 (d, 2H), 4.1-3.9 (m, 1H), 3.75 (bs, 3H), 3.05 (s, 3H), 1.3-1.2 ppm (m, 2H); ^{13}C NMR, δ: 172.1, 171.0, 169.4, 136.4, 128.6, 128.2, 128.0, 67.7, 62.6, 54.5, 52.6, 52.5, 35.7 ppm. Calculated for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.60; H, 6.10; N, 8.59.

***N*-[*N'*-(Benzyloxycarbonyl)-(*S*)-prolyl]-(*S*)-serine methylester (Z-Pro-Ser-OMe), (2*S*,2'*S*)-2b:** recrystallized from EtOAc/hexane, 72% yield mp 103-107 °C, $[\alpha]_D^{25}$ -28.95 (c 2, $CHCl_3$); ^1H NMR, δ: 7.43-7.23 (m, 6H), 5.22-4.75 (m, 2H), 4.65-4.48 (m, 1H), 4.37-4.20 (m, 1H), 3.80-3.40 (m, 5H), 3.58 (s, 3H), 2.24-1.78 ppm (m, 4H); ^{13}C NMR δ: 172.3, 170.7, 155.5, 136.4, 128.4, 128.0, 127.8, 67.3, 62.4, 60.7, 55.0, 52.5, 47.1, 29.3, 24.5 ppm. Calculated for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.43; H, 6.23; N, 8.08.

***N*-[*N'*-(Benzyloxycarbonyl)-(*S*)-prolyl]-(*R*)-serine methylester (Z-Pro-D-Ser-OMe), (2*R*,2'*S*)-2b:** 73% yield, recrystallized from EtOAc , mp 123-125 °C, $[\alpha]_D^{25}$ -100.72 (c 1.5, $CHCl_3$); ^1H NMR, δ: 7.40-7.27 (m, 5H), 7.23-7.17 (m, 0.6H), 6.96-6.90 (m, 0.4H), 5.26-5.00 (m, 2H), 4.64-4.56 (m, 1H), 4.40-4.32 (m, 1H), 3.99-3.85 (m, 2H), 3.74 (s, 3H), 3.65-3.43 (m, 2H), 3.23-3.17 (m, 0.6H), 2.72-

2.65 (m, 0.4H), 2.27-1.85 ppm (m, 4H); ^{13}C NMR δ: 172.7, 171.8, 170.6, 136.1, 128.5, 128.1, 127.9, 67.5, 62.5, 61.0, 54.7, 54.2, 52.6, 47.5, 47.1, 31.1, 29.2, 24.4, 23.5 ppm. Calculated for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.35; H, 6.34; N, 8.02.

***N*-[*N'*-(Benzyloxycarbonyl)-(*S*)-valyl]-(*S*)-serine methylester (Z-Val-Ser-OMe), (2*S*,2'*S*)-3b:** recrystallized from acetone, 66% yield, mp 160-163 °C, $[\alpha]_D^{25}$ +2.73 (c 2.8, $CHCl_3$); ^1H NMR, δ: 8.24 (d, 1H), 7.44-7.20 (d, 6H), 5.11-4.94 (m, 2H), 4.37-4.26 (m, 1H), 4.02-3.88 (m, 1H), 3.78-3.24 (m, 2H), 3.61 (s, 3H), 3.37-3.24 (m, 1H), 2.06-1.85 (m, 1H), 0.97-0.71 ppm (m, 6H); ^{13}C NMR δ: 171.2, 170.7, 156.0, 137.0, 128.2, 127.6, 127.5, 65.3, 61.1, 59.7 54.6, 51.6, 30.4, 18.9, 17.8 ppm. Calculated for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86; N, 7.95. Found: C, 57.87; H, 6.86; N, 8.00.

***N*-[*N'*-(Benzyloxycarbonyl)-(*S*)-valyl]-(*R*)serine methylester (Z-Val-D-Ser-OMe), (2*R*,2'*S*)-3b:** 53% yield, recrystallized from acetone , mp 161-163 °C, $[\alpha]_D^{25}$ -29.73 (c 2, $CHCl_3$); ^1H NMR, δ: 7.37-7.30 (m, 5H), 7.01-6.95 (m, 1H), 5.46-5.40 (m, 1H), 5.09 (s, 2H), 4.69-4.61 (m, 1H), 4.13-4.06, (m, 1H), 4.00-3.85 (m, 2H), 3.76 (s, 3H), 2.79-2.61 (m, 1H), 2.24-2.12 (m, 1H), 0.95 ppm (dd, 6H); ^{13}C NMR δ: 171.5, 170.7, 156.6, 136.0, 128.5, 128.3, 128.1, 67.3, 62.9, 60.5, 54.6, 52.8, 30.8, 19.2, 17.6 ppm. Calculated for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86; N, 7.95. Found: C, 57.80; H, 6.90; N, 7.99.

***N*-[*N'*-(Benzyloxycarbonyl)-(*S*)-leucyl]-(*S*)-serine methylester (Z-Leu-Ser-OMe), 4b:** 65% yield, mp 103-106 °C, $[\alpha]_D^{25}$ -3.73 (c 10, in $CHCl_3$); ^1H NMR, δ: 7.38-7.26 (m, 6H) 5.72 (bd, 1H) 5.12 (d, 1H) 5.0 (d, 1H) 4.70-4.61 (m, 1H) 4.38-4.27 (m, 1H) 3.97-3.82 (m, 3H) 3.75 (s, 3H) 1.77-1.48 (m, 3H) 0.98-0.85 ppm (m, 6H); ^{13}C NMR δ: 172.9, 170.7, 156.6, 136.0, 128.4, 128.1, 128.0, 67.1, 62.6, 54.6, 53.6, 52.6, 41.4, 24.6, 22.8, 21.9 ppm.Calculated for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.92; H, 7.17; N, 7.69.

***N*-[*N'*-(Benzyloxycarbonyl)-(2*S*,3*S*)-isoleucyl]-(*S*)-serine methylester (Z-Ile-Ser-OMe), 5b:** 43% yield, mp 175-177 °C, $[\alpha]_D^{25}$ +8.13 (c 2, in $CHCl_3$); ^1H NMR, δ: 7.38-7.28 (m, 6H), 5.81 (d, 1H), 5.12 (d, 1H), 4.98 (d, 1H), 4.71-4.65 (m, 1H), 4.19-4.12 (m, 1H), 3.98-3.81 (m, 3H), 3.75 (s, 3H), 1.90-1.78 (m, 1H), 1.63-1.48 (m, 1H), 1.23-1.07 (m, 1H), 1.01-0.84 ppm (m, 6H); ^{13}C NMR δ: 171.91, 170.7, 156.8, 136.0, 128.4, 128.1, 128.0, 127.9, 67.1, 62.6, 59.6, 54.5, 52.6, 37.5, 24.7, 15.3, 11.2 ppm.Calculated for $C_{18}H_{26}N_2O_6$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.14; H, 7.12; N, 7.64.

Products 1c-5c; General Procedure

Protected dipeptides **1b-5b** (266 mmol) were suspended in absolute MeOH (150 mL) with 10% Pd on active charcoal (2.5 g) and cyclohexene (120 mL). The reaction mixtures were refluxed for 5 h, then all the volatile products were eliminated under reduced pressure. The crude solids recovered were suspended in absolute MeOH (250 mL) and the resulting mixtures were heated at 62-65 °C for 110 h. The solvent was then eliminated under reduced pressure and the crude products were dryed in air and suspended in boiling dry acetone for 3 h. Filtration afforded pure (TLC) diketopiperazines **1c-5c.**

(*S*)-2-Hydroxymethyl-4-methyl-3,6-diketopiperazine (*cyclo*-Sar-Ser), 1c:[6] 82% yield, mp 227-230 °C (dec.), $[\alpha]_D^{25}$ +43.85 (c 0.6, DMF); ^1H NMR, (D_2O) δ: 4.2-4.05 (m, 2H), 4.0-3.85 (m, 2H), 3.75-3.65 (m, 1H), 2.9 ppm (s, 3H). Calculated for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71. Found: C, 45.48; H, 6.39; N, 17.73.

(2*S*,5*S*)-2-Hydroxymethyl-3,6-diketo-1,4-diaza[4.3.0]bicylononane (*cyclo*-Pro-Ser), (2*S*,5*S*)-2c:[6] 36% yield mp 134-136°C, $[\alpha]_D^{25}$ -114.8 (c 2, DMSO); ^1H NMR (DMSO d_6) δ: 7.83 (bs, 1H),

4.77-4.71 (m, 1H), 4.21-4.92 (m, 2H), 3.79-3.58 (m, 2H), 3.50-3.21 (m, 2H), 2.23-2.0 (m, 1H), 0.93-0.62 ppm (m, 3H); ^{13}C NMR (DMSO d_6) δ: 169.1, 164.4, 60.1, 58.4, 56.7, 44.6, 27.9, 22.0 ppm. Calculated for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.07; H, 6.61; N, 15.20.

(2*R*,5*S*)-2-Hydroxymethyl-3,6-diketo-1,4-diaza[4.3.0]bicylononane (*cyclo*-Pro-D-Ser), (2*R*,5*S*)-2c:[6] 93% yield, mp 248-250 °C (dec.), $[\alpha]_D^{25}$ -149.55 (c 0.7, DMSO); ^1H NMR (DMSO d_6) δ: 8.14-8.06 (m, 1H), 5.29-5.23 (m, 1H), 4.15-4.06 (m, 1H), 3.75-3.62 (m, 2H), 3.55-3.28 (m, 3H), 2.17-2.08 (m, 1H), 1.90-1.62 ppm (m, 3H); ^{13}C NMR (DMSO d_6) δ: 169.1, 164.7, 63.6, 59.6, 58.2, 44.9, 28.8, 21.6 ppm. Calculated for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.09; H, 6.63; N, 15.18.

(2*S*,5*S*)-2-Hydroxymethyl-5-*iso*-propyl-3,6-diketopiperazine (*cyclo*-Val-Ser), (2*S*,5*S*)-3c: 88% yield, mp 245-249 °C (dec.), $[\alpha]_D^{25}$ -85.52 (c 2, DMSO); ^1H NMR (DMSO d_6) δ: 8.07 (bs, 1H), 7.92 (bs, 1H), 4.99-4.92 (t, 1H), 3.79 (s, 1H) 3.70-3.52 (m, 3H), 2.25-2.48 (m, 1H), 0.94 (d, 3H), 0.84 ppm (d, 3H); ^{13}C NMR (DMSO d_6) δ: 166.6, 166.2, 62.4, 59.4, 56.8, 31.6, 18.8, 17.4 ppm. Calculated for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.71; H, 7.55; N, 15.00.

(2*R*,5*S*)-2-Hydroxymethyl-5-*iso*-propyl-3,6-diketopiperazine (*cyclo*-Val-D-Ser), (2*R*,5*S*)-3c: 89% yield, mp 230-232 (dec.)°C, $[\alpha]_D^{25}$ -23.88 (c 0.8, DMSO); ^1H NMR (DMSO d_6) δ: 8.01 (bs, 1H), 7.90 (bs, 1H), 5.04-4.97 (m, 1H), 3.79-3.70 (m, 2H), 3.64 (bs, 1H), 3.58-3.50 (m, 1H), 2.22-2.10 (m, 1H), 0.92 (d, 3H), 0.82 ppm (d, 3H); ^{13}C NMR (DMSO d_6) δ: 167.7, 167.4, 62.5, 59.4, 56.6, 31.5, 18.3, 16.7 ppm.Calculated for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.70; H, 7.59; N, 15.04.

(2*S*,5*S*)-2-Hydroxymethyl-5-*iso*-butyl-3,6-diketopiperazine (*cyclo*-Leu-Ser), 4c: 86% yield, mp 231-233 °C, (dec.) $[\alpha]_D^{25}$ -54.46 (c 0.6, DMF); ^1H NMR (DMSO d_6) δ: 8.22 (bs, 1H), 7.92 (bs, 1H), 5.15-5.06 (m, 1H), 3.75-3.62 (m, 3H), 3.54-3.43 (m, 1H), 1.90-1.74 (m, 1H), 1.69-1.51 (m, 2H), 0.95-0.75 ppm (t, 6H); ^{13}C NMR (DMSO d_6) δ: 168.1, 166.7, 62.3, 57.2, 52.7, 44.5, 23.3, 23.0, 21.6 ppm. Calculated for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99. Found: C, 54.08; H, 8.07; N, 13.92.

(2*S*,2'*S*,5*S*)-2-Hydroxymethyl-5-(2'-butyl)-3,6-diketopiperazine (*cyclo*-Ile-Ser), 5c: 79% yield, mp 235-237 °C (dec.), $[\alpha]_D^{25}$ -84.55 (c 1, DMF); ^1H NMR (DMSO d_6) δ: 8.50 (bs, 1H), 7.91 (bs, 1H), 5.0-4.09 (t, 1H), 3.92-3.52 (m, 4H), 1.93-1.78 (m, 1H), 1.56-1.40 (m, 1H), 1.26-1.06 (m, 1H) 0.96-0.72 ppm (m, 6H); ^{13}C NMR (DMSO d_6) δ: 166.6, 166.1, 62.4, 58.7, 56.8, 38.4, 24.3, 15.1, 11.8 ppm. Calculated for $C_9H_{16}N_2O_3$: C, 53.99; H, 8.05; N, 13.99. Found: C, 53.91; H, 8.07; N, 14.02.

Products 1-5; General Procedure

The diketopiperazines **1c-5c** (133 mmol) were added portionwise, during 30 min, under vigorous stirring, to LAH (20.0 g, 526 mmol) suspensions in THF (800 mL) at 0 °C. The reaction mixures were then heated at 65-68 °C for 72 h. The heating bath was then removed and triethanolamine (74 mL, 82 g, 550 mmol) was added cautiously over 45 min. After 1 h stirring, H_2O (20 mL, 20 g, 1.1 mmol) was added. After furter 12 h stirring, the reaction mixtures were filtered and the solvent was removed under vacuum. The residues were then distilled without fractionating and the oils obtained were dissolved in 10% aq HCl. The acid layers were washed with ether then aqueous solutions were made alkaline with solid KOH and extracted with CH_2Cl_2 several times. The collected organic phases were dryed (Na_2SO_4) and the solvent was eliminated under vacuum. The crude products were then distilled affording pure (GLC) piperazines **1-5**.

(*R*)-4-Methyl-2-hydroxymethylpiperazine, 1:[6] 85% yield, bp 95-100 °C/0.02 mBar, $[\alpha]_D^{25}$ -3.34 (c 0.9, EtOAc); ^1H NMR, δ: 3.65-3.55 (m, 1H) 3.55-3.35 (m, 2H), 3.0-2.9 (m, 2H), 2.9-2.75 (m, 2H), 2.7-2.6

(m, 2H), 2.2 (s, 3H), 2.05-1.9 (m, 1H), 1.8-1.,7 ppm (t, 1H); ^{13}C NMR δ: 63.9, 57.8, 56.2, 55.5, 46.3, 45.0 ppm. Calculated for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.52. Found: C, 55.27; H, 10.89; N, 21.51.

(2*R*,5*S*)-2-Hydroxymethyl-1,4-diaza[4.3.0]bicyclononane, (2*R*,5*S*)-2:[6] 52% yield bp 125-130 °C/0.5 mBar, $[\alpha]_D^{25}$ +7.77 (c 1.88, $CHCl_3$); ^1H NMR, δ: 3.95 (dd, 1H), 3.62 (dd, 1H), 3.05-2.89 (m, 5H), 2.8 (dd, 1H), 2.35 (dd, 1H), 2.12-1.99 (m, 1H), 1.97-1.58 (m, 5H), 1.44-1.29 ppm (m, 1H); ^{13}C NMR δ: 64.2, 63.7, 54.6, 54.4, 52.3, 46.3, 27.4, 20.4 ppm. Calculated for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93; . Found: C, 61.61; H, 10.22; N, 17.88.

(2*S*,5*S*)-2-Hydroxymethyl-1,4-diaza[4.3.0]bicyclononane, (2*S*,5*S*)-2:[6] 70% yield bp 112 °C/0.5 mBar, $[\alpha]_D^{25}$ +14.56 (c 1, $CHCl_3$); ^1H NMR, δ: 3.65-3.58 (dd, 1H), 3.50-3.43 (dd, 1H), 3.19-3.12 (dd, 1H), 3.09-2.88 (m, 4H), 2.58-2.49 (dd, 1H), 1.96-1.63 (m, 6H), 1.44-1.30 ppm (m, 1H); ^{13}C NMR δ: 63.8, 63.1, 55.9, 54.8, 53.6, 49.0, 27.1, 20.8 ppm. Calculated for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.60; H, 10.35; N, 17.89.

(2*R*,5*S*)-2-Hydroxymethyl-5-*iso*-propylpiperazine, (2*R*,5*S*)-3: 56% yield, bp 115-117 °C/0.025 mBar, $[\alpha]_D^{25}$ -12.78 (c 2.57, $CHCl_3$); ^1H NMR, δ: 3.94-3.85 (m, 1H), 3.66-3.58 (m, 1H), 2.98-2.92 (m, 2H), 2.90-2.75 (m, 4H), 2.38-2.28 (m, 2H), 1.75-1.61 (m, 1H), 0.99-0.86 ppm (m, 7H); ^{13}C NMR δ: 53.9, 52.5, 43.5, 38.2, 35.5, 20.8, 9.9, 9.7 ppm. Calculated for $C_8H_{18}N_2O$: C, 60.72; H, 11.47; N, 17.70. Found: C, 60.83; H, 11.41; N, 17.77.

(2*S*,5*S*)-2-Hydroxymethyl-5-*iso*-propylpiperazine, (2*S*,5*S*)-3: waxy solid purified by sublimation (80°C/30 Torr), yield 48%, $[\alpha]_D^{25}$ +5.61 (c 1, $CHCl_3$); ^1H NMR, δ: 3.60 (dd, 1H), 3.43 (dd, 1H), 3.09 (dd, 1H), 2.98 (dd, 1H), 2.82-2.73 (m, 1H), 2.57-2.42 (m, 2H), 2.37-2.29 (m, 1H), 2.10-1.80 (m, 1H), 1.61-1.48 (m, 1H), 0.98-0.89 (m, 6H); ^{13}C NMR δ: 64.3, 61.7, 57.0, 49.6, 49.1, 31.4, 19.0 ppm. Calculated for $C_8H_{18}N_2O$: C, 60.72; H, 11.47; N, 17.70. Found: C, 60.82; H, 11.45; N, 17.76.

(2*R*,5*S*)-2-Hydroxymethyl-5-*iso*-butylpiperazine, 4: 65% yield, bp 112-115 °C/0.15 mBar, $[\alpha]_D^{25}$ +4.9 (c 9, $CHCl_3$); ^1H NMR, δ: 3.84-3.73 (m, 1H), 3.62-3.52 (m, 1H), 3.21-2.5 (m, 9H), 1.71-1.54 (m, 1H), 1.4-1.15 (m, 2H), 1.0-0.81 ppm (m, 6H); ^{13}C NMR, δ: 62.1, 53.3, 52.8, 47.5, 46.3, 42.0, 24.1, 22.9, 22.3 ppm. Calculated for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26. Found: C, 62.63; H, 11.69; N, 16.31.

(2*R*,2'*S*, 5*S*)-2-Hydroxymethyl-5-(2'-butyl)piperazine, 5: 62% yield, bp 110-114 °C/0.15 mBar, $[\alpha]_D^{25}$ +20.47 (c 4, $CHCl_3$); ^1H NMR, δ: 3.98-3.90 (m, 1H), 3.66-3.59 (m, 1H), 2.97 (d, 2H), 2.90-2.70 (m, 3H), 2.52-2.42 (m, 1H), 2.26-1.84 (m, 3H), 1.57-1.37 (m, 2H), 1.27-1.06 (m, 1H), 0.97-0.8 ppm (m, 6H), ^{13}C NMR δ: 61.7, 59.2, 53.1, 46.5, 43.8, 35.9, 25.1, 14.9, 10.8 ppm. Calculated for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26. Found: C, 62.67; H, 11.72; N, 16.29.

Asymmetric Addition of Dialkylzinc to Benzaldehydes by Using Ligand 1-5 or Their Lithium Salts. General procedure - A solution of the ligand (0.37 mmol) in the suitable solvent (Et_2O, CH_2Cl_2, THF or benzene, 5 mL) was cooled at 0 °C and, if lithium salt is required, the suitable butyllithium amounts (0.25, 0.5 or 0.75 mL, 0.37, 0.74 or 1.11 mmol for mono- di- or tri-lithium salts respectively, 1.6 *M* in hexane) were added. After 5 min diethylzinc (1 M, 12.4 mL, 12.4 mmol) in hexane was added over a period of 5 min. The mixture was stirred at room temperature for 20 min, then thermostated at the suitable temperature and added with benzaldehyde (6.2 mL, 6.1 mmol). Stirring was prolonged for additional 14-20 h (sometimes the reaction course was followed by GLC). The reaction mixture was quenched with 10% H_2SO_4 (10 mL) then extracted with ether and the organic layer washed with 10% H_2SO_4, saturated $NaHCO_3$ and dried (Na_2SO_4). The crude

product was bulb to bulb distilled and purified by flash chromatography to afford pure (GLC) ethyl phenyl carbinol.

Acknowledgements. This work was financially supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and by the Consiglio Nazionale delle Ricerche (CNR), Rome.

References and notes

1) Part 10: Conti, S; Falorni, M.; Giacomelli, G.; Soccolini F. *Tetrahedron,* **1992**, *48*, 8993-9000.
2) See for recent representative examples of asymmetric catalytic processes: a) Oishi, T.; Hirama, M *Tetrahedron Lett.*, **1992**, *33*, 639-642; b) O'Connor, K.J.; Wey, S.-J.; Burrows, C.J. *Tetrahedron Lett.*, **1992**, *33*, 1001-1004; c) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron,* **1992**, *48*, 2143-2156; d) Brunel, J.-M.; Pardigon, O.; Faure, B.; Buono, G. *J. Chem. Soc., Chem. Commun.*, **1992**, 287-288; e) Allen, J.V.; Frost, C.G.; Williams, J.M.J. *Tetrahedron: Asymmetry*, **1993**, *4*, 649-650; f) Carreño, M.C.; Ruano, J.L.C.; Maestro, M.C.; Cabrejas, L.M.M. *Tetrahedron: Asymmetry*, **1993**, *4*, 727-734.
3) See for the more recent review on the argument: Soai, K.; Niwa, S. *Chem. Rev.*, **1992**, *92*, 833-856.
4) Chelucci, G.; Conti, S.; Falorni, M., Giacomelli, G. *Tetrahedron,* **1991**, *47*, 8251-8258.
5) For enantioselective addition of diethylzinc to aldehydes using chiral piperazines see: a) Soai, S.; Niwa, S.; Yamada, Y.; Inoue, H. *Tetrahedron Lett.*, **1987**, *28*, 4841; b) Niwa, S.; Soai, K. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2717-2720; c) Shono, T.; Kise, N; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.*, **1991**, *56*, 3063. For enantioselective reduction using chiral piperazines see: d) Falorni, M.; Lardicci, L.; Giacomelli, G.; Marchetti, M *Tetrahedron Lett.*, **1989**, *30*, 3551-3554; e) Falorni, M.; Lardicci, L.; Piroddi, A. M.; Giacomelli, G. *Gazz. Chim. Ital.*, **1989**, *119*, 511-512; f) Falorni, M.; Giacomelli, G.; Lardicci, L.*Gazz. Chim. Ital.*, **1990**, *120*, 765-769.
6) Although this is not in agreement with IUPAC nomenclature rules of compounds **1** and **2**, on account of a more simple reading of the data, for compounds **1-5** the system of numbering depicted in Scheme I is adopted.
7) Ueda, T.; Saito, M.; Kato, T.; Izumya, N., *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 568-572.
8) The inversion of the absolute configuration of 2-position carbon atom observed on passing from **1c-5c** to **1-5** is only due to the IUPAC nomenclature rules.
9) Powell, J.; James, N.; Smith, S.J., *Synthesis*, **1986**, 338-339.
10) Allen, J. V.; Frost, C. G.; Williams, J. M. J., *Tetrahedron: Asymmetry* , **1993**, *4*, 649-650
11) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron: Asymmetry* , **1990**, *1*, 843-894
12) Guttman, St.; Boissonnas, R.A. *Helv. Chim. Acta,* **1958**, *41*, 1852-1867.
13) Tipson, R.S.; Pawson, B.A.; *J. Org. Chem.*, **1961**, *26*, 4698-4701.
14) Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.*, **1978**, *51*, 1869-1873.
15) Schwarz, H.; Bumpus, F.M.; Page, I. H.; *J. Am. Chem. Soc.*, **1957**, *79*, 5697-5703.
16) Losse, G.; Demuth, H., *Chem. Ber.*, **1961**, *94*, 1762-1766.
17) Oki, K.; Suzuki, K.; Tuchida, S.; Saito, T.; Kotake, H. *Bull. Chem. Soc. Jpn.*, **1970**, *43*, 2554-2558.