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Chiral Ligands Containing Heteroatoms. 14.[1] 1,3-Oxazolidinyl Methanols as Chiral Catalysts in the Enantioselective Addition of Diethylzinc to Aldehydes

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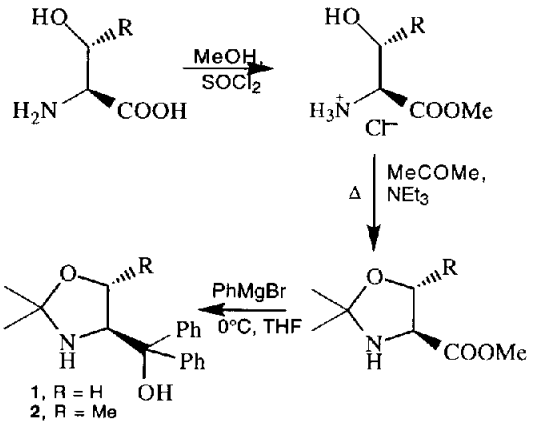
Abstract: Starting from L-serine and L-threonine, (S)-diphenyl-(2,2-dimethyl-1,3-oxazolidin-4-yl)-methanol and (4*S*,5*R*)-diphenyl-(2,2-dimethyl-5-methyl-1,3-oxazolidin-4-yl)-methanol were prepared in good yields. The use of these compounds as very efficient chiral catalysts for the enantioselective addition of diethylzinc to aldehydes is described. This paper reports the first example of the use of oxazolidine methanols in asymmetric synthesis.

Catalytic enantioselective carbon-carbon bond forming is known as one of the most important organic synthetic processes. In this field, considerable attention has been devoted to asymmetric addition of organometallic reagents to aldehydes in the presence of catalytic amounts of homochiral aminoalcohols,[2] and to ab initio molecular orbital studies.[3] We have found that homochiral amino pyridines also act as efficient catalysts in achieving high enantiocontrol in the addition of diethylzinc to aldehydes.[4] Recently, the use of chiral oxazolines tethered to alcohols has been reported as catalysts for the addition of organozinc reagents to aromatic aldehydes with moderate levels of enantioselectivity.[5]

We wish to report herein a new type of efficient chiral catalyst based on optically active oxazolidines systems, **1** and **2** (Scheme 1), obtained from natural occurring α-amino acids. We addressed our attention in particular toward compound **1**, as it resembles the chiral pyrrolidinylmethanols,[6] employed with high enantiocontrol in this kind of reactions. The effect of this analogy on the asymmetric trend of the reaction was the goal of this investigation.

The synthesis of (*S*)-diphenyl-(2,2-dimethyl-1,3-oxazolidin-4-yl)-methanol **1** and (4*S*,5*R*)-diphenyl-(2,2-dimethyl-5-methyl-1,3-oxazolidin-4-yl)-methanol **2** was carried out from L-serine and L-threonine, according the sequences of Scheme 1. Thus, H-Ser-OMe·HCl and H-Thr-OMe·HCl were treated with triethylamine and condensed with acetone to give the corresponding 2,2-dimethyl-1,3-oxazolidinyl derivatives, which were treated with excess phenylmagnesium bromide to afford **1** and **2** in 51 and 30% yields respectively. The enantiomeric and diastereisomeric (for **2**) purities of the ligands were determined (^{19}F NMR analysis) by means of the reaction of **1** and **2** with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPACl]. From the data obtained, it was shown that compound **1** was recovered from the Grignard addition procedure with a 70% ee, while compound **2** showed an 86% de: however, we could obtain enantiomerically pure ligands to use in asymmetric synthesis by enriching the ee% of both **1** and **2** by simple slow recrystallization from petroleum ether. The diastereoisomeric purity of **2** was further confirmed through the analysis of its ^{1}H NMR spectrum in which no signals due to a second diasteroisomer were detected.

Scheme 1



Enantioselective addition of diethylzinc to aldehydes in the presence of catalytic amounts (6 mol%) of **1** and **2** were carried out generally in diethyl ether at several temperatures. The data obtained are summarised in Table 1. The product carbinols were obtained in good chemical yields, within 18 h, the main product being detected independently of the reaction temperature; the reduction alcohol is formed only in small amount (2-3%). In the majority of the runs we have performed, the carbinols recovered exhibit *S* absolute configuration. The enantioselectivity ranges from very high to moderate, reaching the complete enantioselectivity in the ethylation of benzaldehyde, when carried out with ligand **1** in diethyl ether. Employing ligand **2** causes a slight decrease of ee, probably because of the influence of the substituent on the 5-position. All substituted benzaldehydes gave optically active carbinols with lower values of enantioselectivity, the effect of the *para*-substituent being significant in the case of *p*-chlorobenzaldehyde (run 4).

Contrary to what generally observed with other ligands, at least under the standard conditions and using diethyl ether as solvent, hexanal can be ethylated in very good enantioselectivity (> 75%) with both ligands **1** and **2** (runs 15, 16). To the best of our knowledge, such a degree of asymmetric induction has been achieved with only a few ligand systems.

Apparently, no significant change in the stereochemistry outcome of the reaction occurs on passing from ligand **1** to ligand **2** which possess another stereogenic center in the 5-position of the heterocyclic ring. However, the enantioselectivity of the reaction resulted depending upon the temperature: in the most of the cases investigated, a lowering of the temperature corresponded to an enhancement of ee: surprisingly, using ligand **2**, the ethylation of *p*-anisaldehyde occurs with a marked decrease of enantioselectivity when increasing the temperature, a reversal of stereochemical being observed at temperatures higher than 20°C.

Some authors have reported that lithiated ligands are more enantioselective promoters than the parent compounds. In this case, lithiation causes a considerable decrease of the ees (entries 17-19), along with a surprising reversed temperature effect.

There is a direct relationship between the absolute configuration of the stereogenic center in the 4-position of the ligand and that one of the recovered carbinols. The presence of another stereocenter in the 5-position, such as in ligand **2**, seems to have only a little influence on the stereochemical trend of the addition reaction, at least at temperature below 0°C.

Table 1. Asymmetric Addition of Diethylzinc to Aldehydes Using Ligands 1 and 2[a]

				optically active carbinol	
entry	ligand	aldehyde	T°C	Conv. (%)[b]	e.e.%[c]
1	**1**	benzaldehyde	-10	91	100(*S*)
2	**1**	benzaldehyde	20	99	100(*S*)
3	**1**	benzaldehyde[d]	20	95	87(*S*)
4	**1**	*p*-chlorobenzaldehyde	-15	64	40(*S*)
5	**1**	*p*-anisaldehyde	-10	91	78(*S*)
6	**1**	*p*-anisaldehyde	20	64	57(*S*)
7	**1**	*o*-tolualdehyde	-10	54	72(*S*)
8	**1**	*o*-tolualdehyde	20	40	55(*S*)
9	**1**	heptanal	20	94	79(*S*)
10	**2**	benzaldehyde	-10	76	98(*S*)
11	**2**	benzaldehyde	20	98	98(*S*)
12	**2**	*p*-anisaldehyde	-10	46	83(*S*)
13	**2**	*p*-anisaldehyde	20	95	1(*S*)
14	**2**	*p*-anisaldehyde	35	100	19(*R*)
15	**2**	heptanal	-10	71	84(*S*)
16	**2**	heptanal	20	100	81(*S*)
17	**Li-1**	benzaldehyde	-10	94	62(*S*)
18	**Li-1**	benzaldehyde	20	58	81(*S*)
19	**Li_2-1**	benzaldehyde	20	98	39(*S*)

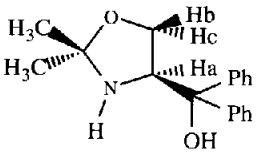
[a]) Reactions carried out in diethyl ether with a molar ratio Et_2Zn/aldehyde/ligand = 2/1/0.06. [b]) GLC yields of the crude products.[c]) Determined by optical rotations and confirmed by GLC on chiral column. [d]) Benzene as solvent.

However, the particular stereochemical behaviour of reaction between *p*-anisaldehyde and diethyl zinc with varying temperature (entries 5,6 and 12-14) should indicate that the catalyst molecule is entirely involved in the stereodifferentiating process pointing out the contribution of the stereogenic center in 5-position too.

Taking into account previous suggestions, the mechanism of the reaction involves the formation of a stoichioimetric complex between the dialkylzinc and the ligand, so providing an effective chiral environment for the reaction. It should be correct to suppose that, when oxazolidine methanols are involved as ligands, the zinc atom is bonded to the alcohol oxygen atom and co-ordinated by the nitrogen atom. This hypothesis is well supported by the ^1H NMR spectra of C_6D_6 solutions of the ligand **1** and a stoichioimetric amount of diethylzinc (Table 2). In fact, the examination of the data shows that, owing to internal hydrogen bonds, the resonance lines due to the N-H and O-H are very broaden and dispersed in the spectrum of the ligand: on adding of diethylzinc, a broad doublet appears at 3.93 ppm along with a shift of the double doublet, centered at 4.34 ppm, at 4.29 ppm which appears now to have a ddd structure. Moreover, the signals of the protons on the 5-position are shifted upfield. According to what previously noted, the adding of a stoichioimetric amount of benzaldehyde does not cause any occurrence of the reaction between the complex and the benzaldehyde: only slight shift of the

resonance of the carbonyl hydrogen of the benzaldehyde along with downfield shift of the resonances lines of the H-5 protons and of the aminic proton are observed upon the addition. Regarding the influence of the oxygen atom in the ring, examination of molecular models and basic force-field calculations allow us to exclude the existence of a complex in which the zinc atom may interact with the oxygen atom of the oxazolidine ring.

Table 2. ^{1}H NMR Chemical Shifts of 1, 1/ZnEt Complex and 1/ZnEt/PhCHO Adduct[a]



H	1 δ (ppm)	1/$ZnEt_2$ complex δ (ppm)	1/$ZnEt_2$/PhCHO adduct δ (ppm)
H_a	4.34 dd[b]	4.29 ddd[b,c]	4.29 ddd[b,c]
H_b	3.80 dd[b]	3.74 dd[b]	3.80 dd[b]
H_c	3.62 dd[b]	3.58 dd[b]	3.60 dd[b]
N-H	-	3.93 d[c]	4.18 d[c]
O-H	-	-	-
CH_3	1.20 s	1.20 s	1.20 s
	1.04 s	1.05 s	1.05 s
C_6H_5	7.48 m	7.49 m	7.49 m
	7.00 m	7.00 m	7.00 m
PhCHO	-	-	9.63 s

a) NMR spectra obtained in C6D6 using a 300 MHz spectrometer with a molar ratio Et_2Zn/ligand/aldehyde = 1/1/1. *b*) J_{ab} = 8.2 Hz, J_{ac} = 6.7 Hz, J_{bc} = 7.5 Hz. *c*) J_{aNH} = 8.2 Hz.

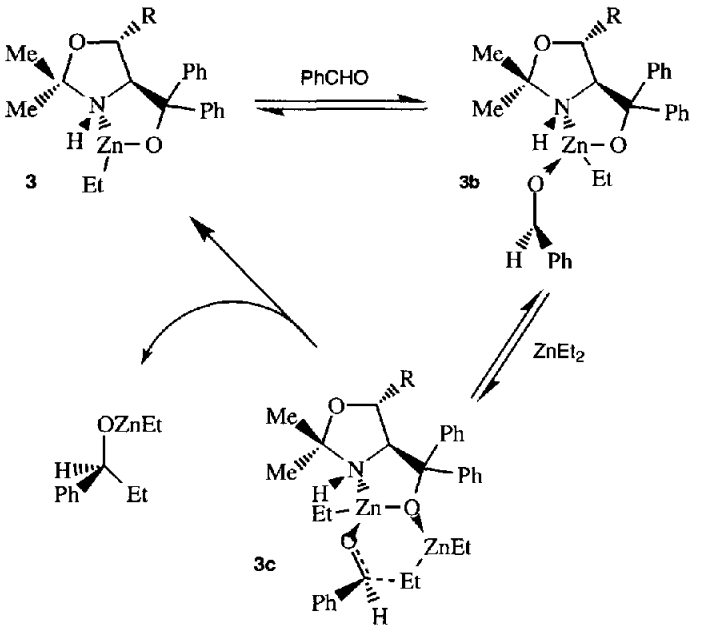
As confirmed by our previous ^{1}H NMR studies,[4] this kind of process occurs through a six-membered cyclic transition state involving a stoichioimetric diethylzinc/ligand complex, an aldehyde molecule and a further molecule of diethylzinc.

Taking into account the ^{1}H NMR and the stereochemical data, it is possible to suggest the catalytic cycle[9] shown in Scheme 2 for the enantioselective reaction. The starting step should be the co-ordination of the carbonyl oxygen atom to the zinc atom of the adduct **3** to form the adduct **3b** that does not ethylate benzaldehyde even if should form slowly benzyl alcohol.

Another $ZnEt_2$ molecule is required to afford the assembly **3c**, responsible of the alkylation reaction. The transfer of an ethyl group to the carbonyl carbon atom by way of a six-membered transition state should regenerates the catalytic chiral complex **3** through elimination of the optically active zinc alkoxide. It appears that the conversion of **3c** to **3** is the determining step.[4]

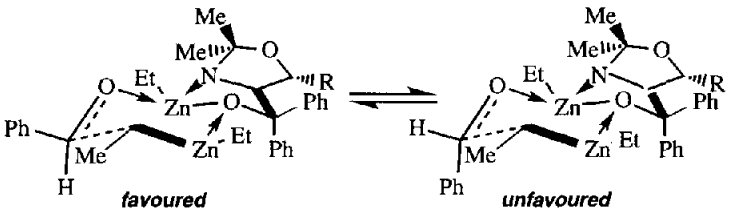
Some other considerations have to be made. Examination of molecular models and preliminary force-field calculation indicate that in the majority of the cases the aldehyde is to be co-ordinated in a manner that the transfer of the ethyl group in the assembly **3c** can occur to the *Si*-face leading to the (*S*) carbinol (Scheme 3).

Scheme 2



These models are purely speculative, but nevertheless consistent with the observed experimental outcome in terms of the sense of asymmetric inductions obtained.

Scheme 3



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), ^{19}F (282 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 asymmetric 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, L-serine and L-threonine of "*BioChemica*" grade (chemical and enantiomeric purity >99%) purchased from Fluka Chemie AG were used; L-serine {mp 222 °C, $[\alpha]_D^{25}$ +13.7 (c 10, HCl 1N)} and L-threonine {mp 256°C, $[\alpha]_D^{25}$ -27.4 (c 1, H_20)}.

L-serine methylester chloridrate: under vigorous stirring and at -10 °C, 260 mL of thionyl chloride was cautiously added dropwise to 1L of dry methanol, then L-serine (105 g, 1 mol, portionwise) was 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 mixture was turned slowly to room temperature and stirred for additional 24h.The mixture was concentrated under reduced pressure, treated with portions of anhydrous methanol. and then evaporated under reduced pressure to give (94% yield) pure (TLC) H-Ser-OMe·HCl as a crystalline solid (recrystallization solvent: methanol) which had mp 165-168°C (lit. 159-162°C). **L-threonine methylester chloridrate:** analogously, L-threonine (59.5 g, 0.5 mol) afforded 99% of H-Thr-OMe·HCl as a pale yellow liquid, highly hygroscopic.

(*S*)-2,2-Dimethyl-4-methoxycarbonyl-1,3-oxazolidine: a solution of H-Ser-OMe·HCl (15.7 g, 98.7 mmol) in anhydrous acetone (650 mL) and triethylamine (14.1 mL, 98.7 mmol) was placed in an 1 mL reaction vessel equipped with a Kumagawa extractor containing molecular sieves (4 Å) and the mixture was stirred for 2h. The solution was cooled to room temperature, filtered and evaporated under vacuum: the residue was then dissolved in ether, stirred for additional 4h and evaporated. The crude product was distilled (80°C/20 mBar) to give pure (GLC) (*S*)-2,2-dimethyl-4-methoxycarbonyl-1,3-oxazolidine (67 % yield); $[\alpha]_D^{25}$ -59 (c 4, $CHCl_3$); ^1H NMR, δ: 1.20 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 2.50-2.60 (bs, 1H, NH), 3.60 (t, 1H, CH), 3.67 (s, 3H, CH_3), 3.97 ppm (m, 2H, CH_2); ^{13}C NMR, δ: 25.7, 26.5, 52.3, 59.4, 67.4, 96.0, 172.7 ppm. Calculated for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.83; H, 8.21; N, 8.76. **(4*S*,5*R*)-2,2-Dimethyl-5-methyl-4-methoxycarbonyl-1,3-oxazolidine:** analogously, H-Thr-OMe·HCl (17.7 g, 104 mmol) yielded (67%) the title compound; b. p. 90°C/20 mBar, $[\alpha]_D^{25}$ -19.23 (c 4, $CHCl_3$); ^1H NMR, δ: 1.18 (s, 3H, CH_3), 1.19-1.22 (d, 3H, CH_3), 1.27 (s, 3H, CH_3), 2.50-3.00 (bs, 1H, NH), 3.38-3.42 (d, 1H, CH), 3.60 (s, 3H, CH_3), 3.65-3.76 ppm (m, 1H, CH); ^{13}C NMR, δ: 19.7, 28.3, 28.9, 52.0, 66.1, 76.1, 95.1, 171.5 ppm. Calculated for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.49; H, 8.71; N, 8.12.

(*S*)-Diphenyl-(2,2-dimethyl-1,3-oxazolidin-4-yl)-methanol, 1: a solution of (*S*)-2,2-dimethyl-4-methoxycarbonyl-1,3-oxazolidine (10.7 g, 37.9 mmol) in THF (20 mL) was added slowly at 0°C under stirring to phenylmagnesium bromide (189.5 mmol, 1 M in ether): the mixture was stirred (3 h), then hydrolyzed with saturated NH_4Cl, extracted (AcOEt) and dried (Na_2SO_4). The organic solution was evaporated and the residue recovered by filtration to give pure (TLC) **1** (51 % yield); m. p. 135-140°C, $[\alpha]_D^{25}$ -51.0 (c 0.3, $CHCl_3$); ^1H NMR, δ: 1.20 (s, 6H, CH_3), 1.80-2.20 (bs, 1H, OH), 3.35 (m, 2H, CH_2), 3.95-4.05 (bs, 1H, NH), 4.30 (dd, 1H, CH), 7.05-7.30 (m, 10H, Ph); ^{13}C NMR δ: 27.7, 28.2, 63.6, 66.4, 75.8, 94.2, 125.2, 125.9, 126.9, 128.2, 128.4, 144.3, 147.0 ppm. Calculated for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.47; N, 4.94. Found: C,

76.0; H, 7.47; N, 4.96. By slow crystallization from petroleum ether, a sample of **1** (11 % yield from the crude carbinol) was recovered having m. p. 135°C, $[\alpha]_D^{25}$ -72.8 (c 0.6, $CHCl_3$). **(4*S*,5*R*)-Diphenyl-(2,2-dimethyl-5-methyl-1,3-oxazolidin-4-yl)-methanol, 2:** analogously, (4*S*, 5*R*)-2,2-dimethyl-5-methyl-4-methoxycarbonyl-1,3-oxazolidine (6.92 g, 40 mmol) yielded (32%) pure (TLC) **2**; m. p. 90-92°C, $[\alpha]_D^{25}$ -138 (c 2, $CHCl_3$); ^1H NMR, δ (mixture of isomers in the ratio 93:7): 0.52 (d, 3H, CH_3, J = 4.96), 1.39 (s, 2.79H, CH_3), 1.45 (s, 2.79H, CH_3), 1.53 (s, 0.21H, CH_3), 1.60 (s, 0.21H, CH_3), 2.20-2.70 (bs, 1H, NH), 4.04 (d, 1H, CH, J = 7.84), 4.07 (qd, 1H, CH, J = 4.96, J = 7.84), 3.65-3.76 ppm (m, 1H, CH), 7.16-7.58 (m, 10H, Ph); ^{13}C NMR, δ: 20.0, 28.9, 29.4, 69.7, 73.4, 75.7, 91.7, 125.8, 126.4, 126.8, 127.0, 128.4, 143.2, 147.5 ppm. Calculated for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.75; H, 7.81; N, 4.70. By slow crystallization from petroleum ether, a sample of **2** (45% yield from the crude carbinol) was recovered having m. p. 92°C, $[\alpha]_D^{25}$ -160 (c 2, $CHCl_3$).

Asymmetric Addition of Dialkylzinc to Benzaldehydes by Using Ligand 1 and 2 or Their Lithium Salts. General procedure: a solution of the ligand (0.37 mmol) in ether (25 mL) was cooled at 0 °C and, if lithium salt is required, the suitable butyllithium amounts (0.25 or 0.5 mL, 0.37 or 0.74 mmol for mono- or di-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 the aldehyde (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, if necessary, purified by flash chromatography to afford pure (GLC) ethyl alkyl carbinol.

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References and notes

1) Part 13: Conti, S., Cossu, S., Giacomelli, G., Falorni, M. *Tetrahedron* **1994**, *50*, 13493-13500.
2) Reviews on the argument: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; (a) John Wiley & Sons: New York, 1994; Chapter 5. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833-856.
3) Yamakawa, M., Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327-6335.
4) Conti, S.; Falorni, M., Giacomelli, G., Soccolini, F. *Tetrahedron* **1992**, *48*, 8993-9000.
5) Allen, J. V., Williams, J. M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 277-282.
6) Soai, K.,Ookawa, A., Kaba, T, Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111-7115.

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