Tetrahedron Letters,Vol.30,No.27,pp 3551-3554,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

CHIRAL LIGANDS CONTAINING HETEROATOMS. III.[1] ENANTIOSELECTIVE KETONE REDUCTIONS USING TIN(II) ORGANOMETALLIC SYSTEMS FROM CHIRAL PIPERAZINES

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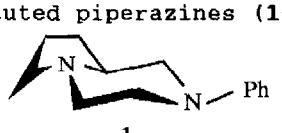
Summary: *Chiral reducing agents were prepared from stannous chloride, optically active piperazines as ligands and diisobutylaluminium hydride; these complexes were effectively employed in the asymmetric reduction of prochiral ketones.*

Asymmetric reduction of prochiral ketones by chiral reducing agents has been extensively studied and a number of methods have been reported.[2] Many of these works are based on the use of hydride reagents chirally modified with optically active ligands:[2c,d] in any case, chiral piperazines as auxiliary are not involved and, indeed, these cyclic diamines rarely have been prepared and utilized in asymmetric synthesis.[3] The use of easily recoverable chiral amines was also reported in connection with the development of an asymmetric reducing system obtained by treatment of a mixture of stannous chloride and a diamine with diisobutylaluminium hydride.[4]

In an earlier paper we have reported the synthesis of some chiral 1,2-diaminoethanes and their use in the preparation of modified lithium aluminium hydride reagents.[1] Now we have set up a simple procedure for the conversion of these diamines into the corresponding chiral *N,N'*-disubstituted piperazines (**1-3**).



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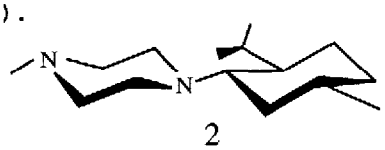

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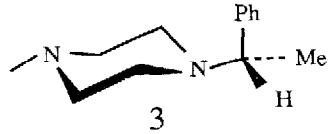

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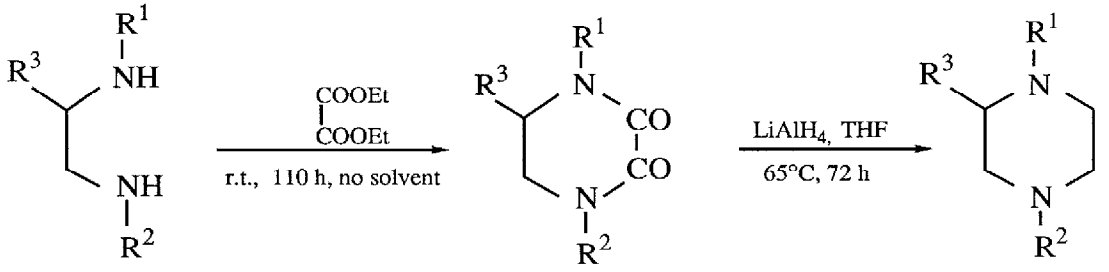
Here we wish to report the preliminary results obtained with the tin(II) hydride systems obtained from piperazines **1**, **2** and **3** in ketone reduction.

(*S*)-4-Phenyl-1,4-diaza[4.3.0]bicyclononane (**1**), 4-methyl-1-[(*R*)-menthyl]-piperazine (**2**), and 4-methyl-1-[(*S*)-1'-phenylethyl]piperazine (**3**) were prepared starting from (*S*)-2-(anilinomethyl)pyrrolidine (**1a**) (o.p. 98%)[5], *N*-methyl-*N*'-[(*R*)-menthyl]-1,2-diaminoethane (**2a**) (o.p. 95%)[1] and *N*-methyl-*N*'-[(*S*)-1'-phenylethyl]-1,2-diaminoethane (**3a**) (o.p. 93%)[1] respectively as shown in the scheme.

SCHEME



1 - 3

The treatment of diamines **1a-3a** with a molar amount of diethyl oxalate at room temperature without solvent for 110 h affords, in good yields (75-92%) the corresponding 1,2-diketopiperazines. The reductions of these amides to the corresponding piperazines **1-3** (60-65% yields) were carried out using an excess of $LiAlH_4$ in refluxing THF for 72 h; the reaction mixtures were hydrolyzed with $Na_2SO_4 \cdot 10\ H_2O$ and water. In a further preparation the recovered yields of $LiAlH_4$ reduction were improved (78-87%) carring out the hydrolysis with triethanolamine and water as previously reported.[6] For the products **1-3** was found: **1**: $[\alpha]_D^{25}$ -17.7 (*c* 1.5, ether), b.p. 110°C(0.05 Torr); **2**: $[\alpha]_D^{25}$ -67.6 (*c* 1.0, ether), b.p. 100°C(0.02 Torr); **3**: $[\alpha]_D^{25}$ -31.6 (*c* 2.0, ether), b.p. 96°C(0.1 Torr). The optical purity of the ligands **1-3** should be likely the same as the starting chiral materials **1a-3a**, since the procedures adopted for cyclization[7] (Scheme) do not involve the remote chiral centers. The piperazines obtained (**1-3**) have been used to prepare reducing systems by treatment with $SnCl_2$ and diisobutylaluminium hydride.

$$\mathbf{1} + SnCl_2 + AlBu^i_2H + Pr^iCOPh \xrightarrow[Et_2O]{-100°C} \xrightarrow[r.t.]{H_3O^+} Pr^iCHOHPh \quad \text{e.e. 85\% (S)}$$

A typical procedure is described: *Run 3* - Under an argon atmosphere piperazine **1** (2.02 g, 10 mmol) in dry CH_2Cl_2 (10 mL) was added to a stirred suspension of anhydrous $SnCl_2$ (1.90 g, 10 mmol) in CH_2Cl_2 (10 mL). After stirring for 3 h at room temperature the pale yellow solution was kept at -100°C and diisobutylaluminium hydride (1 *M* solution in hexane, 10 mL, 10

mmol) was added over 5 min. To the dark brown mixture obtained, *iso*-propyl phenyl ketone (1.00 g, 6.7 mmol) in CH_2Cl_2 (10 mL) was added (5 min). The reaction mixture was stirred at 100°C for 10 min, then the cool bath was removed. The mixture was treated, at room temperature, with aqueous (10%) H_2SO_4 and ether; organic layer, inorganic precipitate and aqueous layer was separated by centrifugation. Organic phase was washed with 10% H_2SO_4 and 5% $KHCO_3$, dried (Na_2SO_4) and concentrated. The crude product was purified by "flash chromatography" (80:20 light petroleum ether/ethyl acetate) affording pure (GLC) (-)-*iso*-propyl phenyl carbinol, (0.60 g, 60%) having $[\alpha]_D^{25}$ -37.2 (*c* 1.5, ether). The acid layer from the hydrolysis was made alkaline with KOH and extracted with ether. By the usual work up, piperazine 1 {(1.66 g, 82%), b.p. 110°C(0.05 Torr), $[\alpha]_D^{25}$ -17.8 (*c* 1.9, ether)}, was recovered.

Table. *Enantioselective reduction of prochiral ketones*[a]

Run	Substrate	Solvent	Ligand	Carbinol		
				%Conversion[b]	$[\alpha]_D^{25}$, deg	%ee
1	MeCOPh	CH_2Cl_2	**1**	100(69)	+28.42(neat)[c]	65(*R*)[d]
2	MeCOPh	Ether	**1**	100(72)	+33.68(neat)[c]	77(*R*)[d]
3	Pr^iCOPh	CH_2Cl_2	**1**	71(60)	-37.20(*c* 1, Et_2O)	78(*S*)[d]
4	Pr^iCOPh	Ether	**1**	100(85)	-40.42(*c* 1, Et_2O)	85(*S*)[d]
5	$Pr^iCOC{\equiv}CBu^n$	Ether	**1**	100(87)	-0.29(neat)[c]	3(*S*)[e]
6	Pr^iCOPh	Ether	**2**	78(65)	+1.10(neat)[c]	2(*R*)[d]
7	MeCOPh	CH_2Cl_2	**3**	92(62)	-7.01(neat)[c]	16(*S*)[d]
8	Pr^iCOPh	Ether	**3**	100(81)	-1.31(*c* 3, Et_2O)	3(*S*)[d]

[a]) Reaction carried out at -100°C for 10 min. [b]) GLC yields on the crude product. The number in parentheses refer to isolated yield. [c]) *l*=1. [d]) Determined by HPLC on chiral stationary phase.[8] [e]) Evaluated by ^{19}F NMR of MPTA ester.[9]

The preliminary data obtained using ligands **1**-**3** are reported in the table. In all the examined cases the GLC and isolated yields are good and the reduction carbinols are the only product detected. The values of ee are high when ligand **1** is involved (runs 1-4) and are low using ligands **2** and **3** (runs 6-8). The inspection of the table shows that, using ligand **1**:

i) the ee drops to 3% when 2-methyl-4-nonyn-3-one is employed as substrate (run 5).

ii) the optical yields are increased using ether as reaction medium (runs 2

and 4) instead of CH_2Cl_2 (runs 1 and 3).

iii) reduction carbinols of opposite configuration are recovered when acetophenone and *iso*-propyl phenyl ketone are involved.

This inversion of configuration resembles that observed using chirally modified $LiAlH_4$ with amines **2a**[1] and (*S*)-2-[(*R*)-menthylaminomethyl]pyrrolidine[1,7] as reducing agents.

Although the precise mechanism of these reductions is, at present, not clear, the reactions should proceed almost certainly through an intermediate tin(II) alkyl hydride, complexed with the diamine, in which the position of the chiral center on the piperazine ring seems to play an important role in order to obtain good optical yields. Work is in progress aimed at claryfing this point as well as at synthesizing new ligands having different stereoelectronic properties.

ACKNOWLEDGMENTS: We wish to thank the "Ministero della Pubblica Istruzione", Rome and "Regione Autonoma Sardegna" for supporting this research.

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(Received in UK 9 May 1989)