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CHIRAL LIGANDS CONTAINING HETEROATOMS.7.[1] AN INVESTIGATION ON THE STEREOCHEMISTRY OF THE KETONE REDUCTIONS BY CHIRAL DIAMINES/TIN HYDRIDE SYSTEMS.

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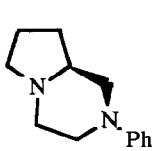
Summary - Reducing agents prepared from $SnCl_2$, chiral diamines and diisobutyl aluminum hydride have been applied to the enantioselective reduction of alkyl phenyl and α-alkynyl ketones. The extent of the ee observed was dependent on the hydrolysis temperature and the structure of the chiral diamine. Hypotheses on possible mechanistic pathways on the basis of stereochemical data and ^1H NMR studies were discussed too.

Asymmetric carbon-hydrogen bond forming reactions by means of organometallic complexes modified by chiral ligands are of great interest for the preparation of several types of optically active compounds.[2] Among these processes, an important position is occupied by the asymmetric reductions of carbonyl compounds, performed in the presence of chiral ligands, containing at least a nitrogen atom.[3] In this sense, these reactions are also to be considered as a simple test to check the enantiodifferentiating capability of new optically active ligands. In earlier papers,[4,5] we reported some preliminary data obtained in enantioselective reductions of ketones using tin(II) hydride systems complexed with chiral piperazines: the procedure was recently applied successfully to analogous organometallic systems involving magnesium(II) and zinc(II) species.[6] The results obtained showed that the enantioselectivity of the process was depending, apart from the ligand employed, on the hydrolysis temperature.[5] On these bases, taking also into account the lack of knowledge about the nature of these *in situ* generated organometallic species and about the possible mechanistic pathways involved in the reduction process, we have carried out a more deep investigation on the reduction of simple prochiral carbonyl compounds by chiral diamino tin(II) hydride complexes. For this purpose, several optically active 1,2-diaminoethanes (**1-7**) were prepared and used for complexing tin(II) hydride species generated by reaction of diisobutyl aluminum hydride with tin(II) chloride.



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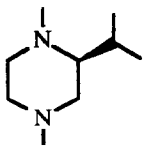

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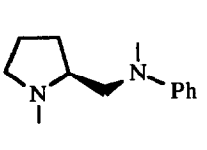

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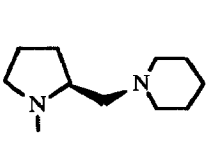

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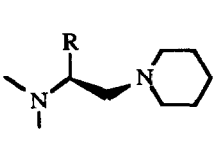
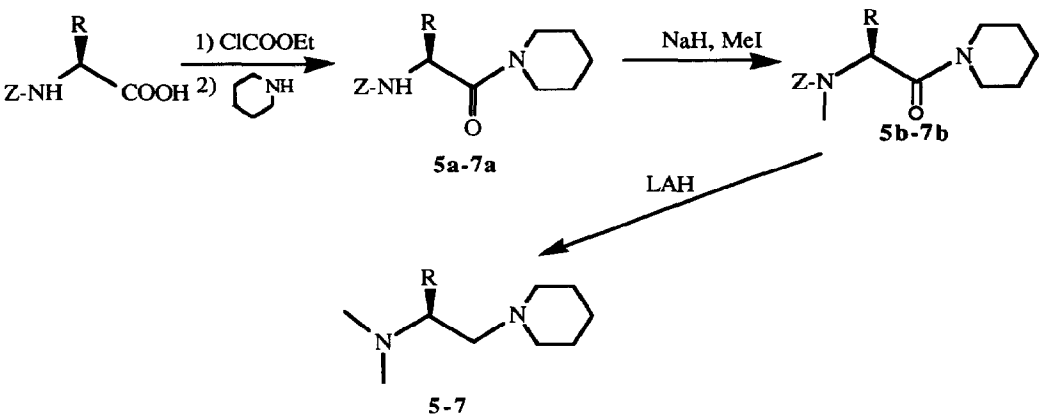


5 , R = Pr^i
6 , R = CH_2Ph
7 , R = Bu^s

All the diamines **1-7** were prepared from α-aminoacids, following procedures not involving the chiral center. In particular, while known procedures[4-7] were adopted for preparing diamines **1-4**, (*S*)-l-piperidyl-2-(*N*,*N*-dimethylamino)-3-alkyl-butanes (**5-7**) were synthetized according to the Scheme I from the corresponding Z-*N*-protected aminoacids in good yields.

Scheme I



Amides **5a-7a** were obtained from Z-Val-OH, Z-Phe-OH and Z-Ile-OH respectively by treatment with piperidine, using the mixed anhydrides coupling method. *N*-Methylation of **5a-7a** was carried out with NaH, in the presence of MeI, affording the derivatives **5b-7b**, which were then reduced to diamines **5-7**,by refluxing with LAH in THF for 72 h, carrying out the hydrolysis with triethanolamine.[8] The stereospecificity of the sequences adopted was checked by removing, from compounds **5b-7b**, the protective group with 10% PdC/tetralin transfer hydrogenolysis[9] and determining the enantiomeric purity of the l-piperidyl-2-(*N*-methylamino)-3-alkylbutanes obtained by analysis of the ^{19}F NMR spectra of the corresponding MPTA amides. The data collected indicated that no racemization takes place during the conversion of the α-aminoacids into the ligands **5-7**.

The enantioselective reductions of ketones have been carried out in dichloromethane solutions by following previously reported procedures.[4] Diisobutyl aluminum hydride and the ketone were sequentially added to a solution of tin(II) chloride and the diamine at -100°C, the reaction mixtures stirred for 10 min and then hydrolyzed with a phosphate buffer (pH 7), directly at the same temperature or at 20°C. Enantiomeric excesses of

the carbinols obtained as reduction products were evaluated by purifying the alcohols by flash chromatography[10] and measuring the rotatory power of each sample. However, most of the data were confirmed by direct HPLC analysis on chiral stationary phase.[11]

The systems studied are able to reduce alkyl phenyl ketones to the corresponding optically active carbinols in high yields and generally within short times (Table I): the conversions decrease noticeably when isopropyl phenyl ketone is used as substrate (e.g. run 24). At least in these cases, the enantiomeric excesses are moderate (up to 78%, run 4) and in some cases very low: when the reaction temperature is maintained at -100°C until the hydrolysis, the enantioselectivity of the process drops down using sterically hindered ketones such as ferrocenyl (run 14) and isopropyl phenyl ketone.

Table I

Reduction of alkyl phenyl ketones by chiral diamino tin(II) hydride systems.[a]

			optically active carbinol			
run	ligand	ketone	hydrolysis temp.°C	Conv.[b] %	$[\alpha]_D^{25}$,deg (c,solvent)	ee%[c]
1[d]	**1**	MeCOPh	-100	17	- 5.00 (neat)	12 (*S*)
2[d]		MeCOPh	20	100	+28.42 (neat)	65 (*S*)
3[d]		PriCOPh	-100	15	+ 6.66 (2, Et_2O)	14 (*S*)
4[d]		PriCOPh	20	71	-37.20 (1, Et_2O)	78 (*S*)
5[d]	**2**	MeCOPh	-100	13	- 0.03 (neat)	<1 (*R*)
6[d]		MeCOPh	20	95	-16.72 (neat)	38 (*S*)
7	**3**	MeCOPh	-100	74[e]	- 0.47 (neat)	1 (*S*)
8		EtCOPh	-100	67[e]	- 7.43 (neat)	26 (*S*)
9		PriCOPh	-100	27[f]	- 2.52 (2, Et_2O)	5 (*S*)
10	**4**	MeCOPh	-100	80	+34.80 (neat)	76 (*R*)
11		EtCOPh	-100	57	+20.60 (neat)	72 (*R*)
12		EtCOPh	20	48	- 0.02 (neat)	<1 (*S*)
13		PriCOPh	-100	91[g]	-12.75 (3, Et_2O)	27 (*S*)
14		$MeCO(Cp)_2Fe$	-100	100	- 1.85 (2, PhH)	6 (*R*)
15	**5**	MeCOPh	-100	100	+17.39 (neat)	40 (*R*)
16		MeCOPh	20	100	+19.15 (neat)	44 (*R*)
17		EtCOPh	-100	100	+ 6.60 (neat)	23 (*R*)
18		PriCOPh	-100	72[e]	+ 2.67 (4, Et_2O)	6 (*R*)
19	**6**	MeCOPh	-100	100	+15.94 (neat)	37 (*R*)
20		EtCOPh	-100	98	+ 2.51 (neat)	9 (*R*)
21		PriCOPh	-100	99	+ 3.61 (4, Et_2O)	8 (*R*)
22	**7**	MeCOPh	-100	99	+21.97 (neat)	50 (*R*)
23		EtCOPh	-100	31	+26.10 (3, $CHCl_3$)	57 (*R*)
24		PriCOPh	-100	22[f]	- 0.75 (2, Et_2O)	2 (*S*)

[a] Reactions carried out in CH_2Cl_2 for 10 min at -100°C. [b] GLC yields on the crude products. [c] Confirmed by HPLC on the csp. [d] From ref. 4 [e] Reaction time: 1.5h. [f] Reaction time: 2h. [g] Reaction time: 0.5h.

On the contrary, an excellent ee value in the reduction of this last ketone, in the presence of ligand **1** (run

4), is determined carrying out the hydrolysis after returning the reaction mixture at room temperature. This temperature effect was observed also in other cases to lead to an increase (runs 1-2, and 5-6) or to a decrease of the ee (runs 11-12) on passing from -100°C to 20°C.[5] Surprisingly, employing ligand **5**, no sensible variation in the ee of the reduction is noted changing the hydrolysis temperature (runs 15-16). A closer inspection of the data of Table I shows that everytime the reaction is not complete at -100°C, the change of the hydrolysis conditions from low to room temperature modifies the stereochemistry; in the case of the ligand **5**, the reduction is indeed quantitative even at low temperature.

Therefore, on the basis of these considerations, we have carried out some experiments to get a deeper insight into the question. Table II reports the data collected carrying out the reactions at various hydride/ketone ratios. It is interesting to note that the stereochemistry of the process is retained on passing from low to room temperature hydrolysis only when all ketone is transformed (runs 26, 15, 16), indicating the importance of the presence of residual ketone in the reaction mixture, heated at room temperature. Nevertheless this behaviour seems to depend upon the nature of the ligand used too, as revealed from data referring to the use of ligand **5**.

Table II

Reduction of alkyl phenyl ketones by chiral diamino tin(II) hydride systems at various hydride/ketone molar ratios.[a]

run	ligand	ketone	hydrolysis temp.°C	hydride/ketone ratio	optically active carbinol	
					Conv.[b]	ee%
11	**4**	EtCOPh	-100	1/0.7	57	72 (*R*)
12		EtCOPh	20	1/0.7	48	<1 (*S*)
25		EtCOPh	20	2.5/1	93	33 (*S*)
26		EtCOPh	20	4/1	100	77 (*R*)
15	**5**	MeCOPh	-100	1/0.7	100	40 (*R*)
16		MeCOPh	20	1/0.7	100	44 (*R*)
27		MeCOPh	20	1/1.6	63[c]	41 (*R*)

[a] *Reactions carried out in CH_2Cl_2 for 10 min at -100°C.* [b] *GLC yields on the crude products.*
[c] *Evaluated with respect to the employed ketone.*

In fact, in this case, no change of the stereochemistry is noted even in the presence of an excess of ketone (run 27). Taking into account that the raise of temperature up to 20°C causes a rapid decomposition of the complex metal hydride species, these results might be interpreted in terms of the intervention of chiral alkoxytin species formed in a requilibration process like a Meerwein-Pondorff-Verley reaction, which should play an important role in relation to the complexed ligand too and occur in an enantioselective fashion, as data of runs 2, 4 and 6 (Table I) seem to reveal.

The ligands we have prepared, in particular compounds **4-7**, are effective in the enantioselective reduction of α-acetylenic ketones too. Results are shown in Table III. With the exception of ligand **3**, the reactions of α-acetylenic ketones and the chiral diamino tin(II) systems afford the corresponding (*S*) carbinols in excellent yields and generally good enantioselectivities. Moreover, as the alcohol moiety became more bulky, the degree of asymmetric induction became higher: the reduction of 2-methyl-4-nonyn-3-one occurs with ee > 70 % (runs

31, 33, 35 and 37), of the same order of magnitude as reported for methods employing other complex metal hydrides.[12]

Table III

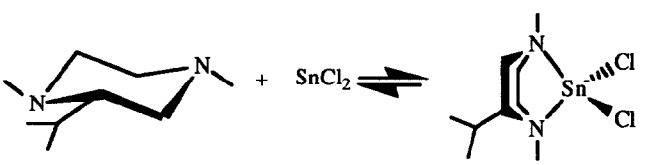
Reduction of α-acetylenic ketones RCOC≡CBu^n by chiral diamino tin(II) hydride systems.^{a}

run	ligand	ketone R	optically active carbinol Conv.^{b} %	optically active carbinol [a]$_D^{25}$,deg (c,solvent)	optically active carbinol ee%^{c}
28	**3**	Et	14	- 0.68 (2, hexane)	5 (*S*)
29		Pr^i	50	0.00	(*R*,*S*)
30	**4**	Et	99	-10.30 (2, hexane)	66 (*S*)
31		Pr^i	99	- 6.04 (neat)	74 (*S*)
32	**5**	Et	98	- 2.03 (3, hexane)	13 (*S*)
33		Pr^i	99	- 6.01 (neat)	73 (*S*)
34	**6**	Et	96	- 2.51 (2, hexane)	16 (*S*)
35		Pr^i	100	- 5.73 (neat)	70 (*S*)
36	**7**	Et	67	- 2.86 (2, hexane)	18 (*S*)
37		Pr^i	45	- 6.70 (neat)	82 (*S*)

^{a} Reactions carried out in CH_2Cl_2 for 10 min at -100°C: hydrolysis at the same temperature.
^{b} GLC yields on the crude products. ^{c} Confirmed by HPLC on the csp.

In the cases we have studied, the stereochemistry of the reduction seems to be satisfactorily rationalized in terms of a complex transition state assembly. Such a assumption is based on the formation of an initial complex by coordination of the diamino ligand and the metal chloride, such as in Scheme 2, which provides an effective chiral environment for the reaction.

Scheme II



2 **8**

This hypothesis is furtherly supported by the ^{1}H NMR spectra of $CDCl_3$ solutions of diamines **2** and **6** and tin(II) chloride at various molar ratios. The examination of the data (Table IV) shows that, on the adding of tin chloride, a significant downfield shifts of the resonance lines of the methyl groups bound to the nitrogen atoms occurs. No further shift is noted when the molar ratio $SnCl_2$/diamine is greater than 1.0.

Table IV

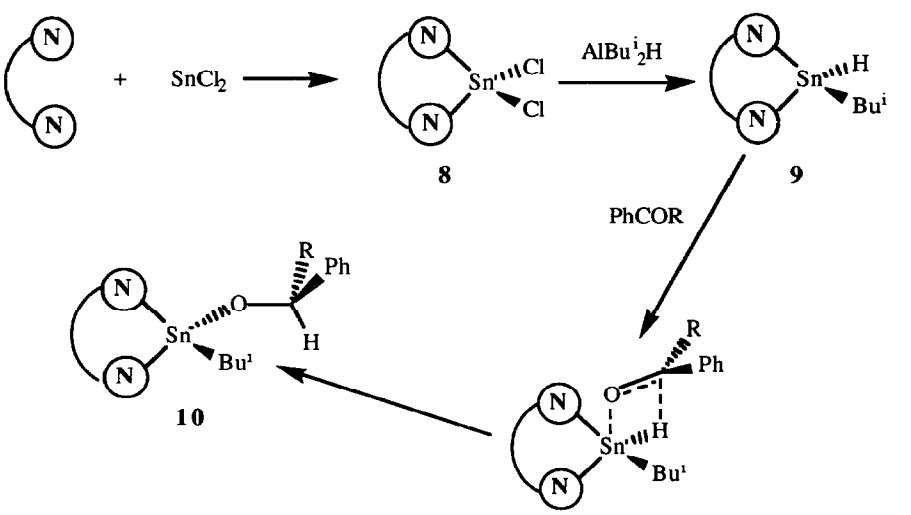
^1H NMR spectra of diamines and tin(II) chloride mixtures at various molar ratios.[a]

diamine	$SnCl_2$/diamine	CH_3 -N chemical shifts (δ)
2	-	2.25, 2.30
	0.3	2.33, 2.46
	0.6	2.40, 2.63
	1.0	2.50, 2.85
	1.6	2.50, 2.85
6	-	2.36
	0.5	2.60
	1.0	2.85
	1.3	2.85

[a] *Recorded in $CDCl_3$ at 20°C at 300 Mhz: all the shifts are relative to TMS as internal standard.*

These results are to be interpreted admitting that the metal halide and the diamine afford a stoichiometric complex like **8** whose formation is rapidly achieved and governed by a very large equilibrium constant. The data

Scheme III

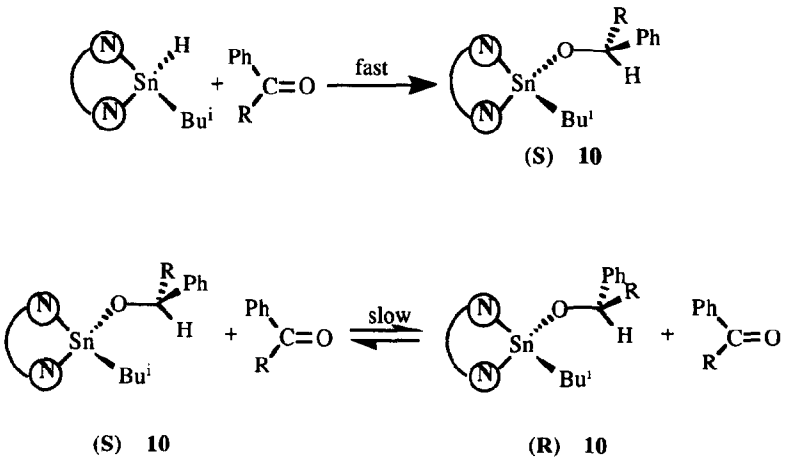


which refer to ligand **2** indicate also that the coordination to the metal atom involves both the nitrogen atoms of the ligand.

On these bases, we propose the mechanism shown in Scheme III. Complex **8** may be transmetalled by diisobutylaluminum hydride to form the tin hydride **9**, which should be stabilized through the coordination of

the diamine. The drawing presented is clearly oversimplifed and, in principle, the hypothesis of the formation of more complex mixed tin/aluminum/chiral diamine systems cannot be excluded. However, the reduction process should start with the complexation of the tin atom to the oxygen atom of the ketone, so activating the C=O group, followed by the hydride transfer, presumably through a four-membered transition state to form the complexed tin alcoholate **10**. At the raise of temperature above -100°C, the tin hemialkoxide formed might act as a new reducing agent in a MPV type reaction (Scheme IV).

Scheme IV



As a consequence of this competitive oxidation-reduction mechanism, the optical purity of the carbinols formed in the reduction of the ketones by the tin hydride system might change during the reaction time in relation to the stereochemistry of the MPV process too.

Experimental Section

Boiling and melting point are uncorrected. ^1H (300 MHz) and ^{13}C (75.4 MHz) NMR Fourier transform spectra were performed on $CDCl_3$ solutions (2% ca.) by a Varian VXR-300 spectrometer and with TMS as internal standard. Mass spectra were performed by VG Analytical Mod. 7070E spectrometer. The optical rotation were measured by a Perkin-Elmer 142 automatic polarimeter in a 1 dm tube. Gas chromatographic analyses were performed by a PerkinElmer 8600 chromatograph using N_2 as carrier gas and Silicon SE 30 or Carbowax 20M as stationary phase. Optical purity was determined in various ways: direct comparison of optical rotation, when possible, was carefully done with the synthetic and authentic resolved materials; chromatographic enantioseparation were carried out by a Jasco-Twinkle apparatus equipped with a Uvidec100 V, (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine as chiral stationary phase and hexane/PrⁱOH 99/1 as eluant.[11] All reactions involving air sensitive materials were carried out under argon atmosphere. All reagents and solvents employed were reagent

grade materials purified by standard methods and redistilled before use. Piperidine and 4-methylmorpholine were purified by distillation on KOH. Alkyl phenyl and ferrocenyl ketones were obtained by purification of commercial products. 4-Nonyn-3-one and 2-methyl-4-nonyn-3-one were prepared as previously reported.[13] As chiral starting materials were employed the following commercially available α-aminoacids without any purification: (*S*)-proline {Fluka, mp 228-233°C, $[\alpha]_D^{25}$ -84.0 (*c*, H_2O)}, (*S*)-valine {Aldrich, mp 300°C *(dec.)*, $[\alpha]_D^{25}$ +27.5 (*c* 8, HCl 6N)}, (*S*)-phenylalanine {Aldrich, mp 270-275°C *(dec.)*, $[\alpha]_D^{25}$ -35.2 (*c* 2, H_2O)}, (2*S*,3*S*)-isoleucine {Aldrich, mp 288°C *(dec.)*, $[\alpha]_D^{25}$ +41.0 (*c* 4, HCl 6N)}.

(*S*)-4-Phenyl-1,4-diaza[4.3.0]bicyclononane (1). The product **1** was prepared as previously reported.[4] For the sample employed was found: bp 118-125°C/0.07, $[\alpha]_D^{25}$ -17.7 (*c* 1.5, Et_2O), (pure at TLC, silica gel, EtOH/AcOH 7/3). MS, m/z(%): 202(M+, 100), 174(5), 120(8), 105(22), 97(77), 84(18), 69(35), 56(6), 42(12); ^1H NMR, δ: 7.35-7.25 (2H, t), 7.0-6.95 (2H, d), 6.9-6.8 (1H, t), 3.8-3.7 (1H, d), 3.7-3.6 (1H, d), 3.2-3.1 (2H, d), 3.0-2.9 (1H, dt), 2.6-2.5 (1H, t), 2.45-2.35 (1H, dt), 2.25-2.1 (2H, t), 1.8-1.7 (2H, m), 1.55-1.45 ppm (2H, m); ^{13}C NMR, δ: 151.3, 129.1, 119.4, 116.1, 62.6, 53.9, 53.6, 51.7, 48.6, 27.6, 21.3 ppm.

(*S*)-1,4-Dimethyl-2-isopropylpiperazine (2). The diamine **2** was prepared as previously reported starting from (*S*)-valine[6]. For the sample employed was found: bp 175-180°C, $[\alpha]_D^{25}$ +60.50 (*c* 1, Et_2O), (pure at TLC, silica gel, EtOH/AcOH 7/3). MS, m/z(%): 155(M++1, 10), 141(10), 127(10), 113(100), 98(21), 86(12), 70(61), 58(12), 42(43); ^1H NMR, δ: 2.8-2.7 (1H, m), 2,7-2.6 (2H, m), 2.35-2.25 (1H, dt), 2.22 (3H, s), 2.18 (3H, s), 2.15-2.0 (2H, m), 1.95-1.85 (1H, m), 1.8-1.7 (1H, t), 0.9-0.8 ppm (6H, dd); ^{13}C NMR, δ: 67.2, 56.5, 55.0, 54.0, 46.3, 42.0, 26.7, 19.7, 15.3 ppm. Anal. Calcd for $C_9H_{20}N_2$: C, 69.17; H, 12.90; N, 17.93. Found: C, 69.35; H, 12.75; N, 18.09.

(*S*)-*N*,*N*'-Di-(benzyloxycarbonyl)-2-(anilinomethyl)pyrrolidine (3a). A sample of (*S*)-2-(anilinomethyl) pyrrolidine[14] {17.6 g, 100 mmol, $[\alpha]_D^{25}$ +18.20 (*c* 2.0, EtOH)} in Et_2O (50 mL) was treated, at 0°C under vigorous stirring, with NaOH (10.0 g, 250 mmol) in H_2O (200 mL) and with benzylchloroformate (31.3 mL, 37.4 g, 220 mmol) in toluene (50 mL). The mixture was stirred for 1 h then was extracted with Et_2O. The organic layer was washed with 10% H_2SO_4 and with saturated NaCl, after drying (Na_2SO_4) and distillation of the crude product, the diamide **3a** was obtained (38.5 g, 87%), having bp 260°C/0.07, $[\alpha]_D^{25}$ +14.07 (*c* 1, Et_2O), (pure at TLC, silica gel, EtOH/H_2O 7/3); ^1H NMR, δ: 7.4-7.1 (15H, m), 5.2-4.9 (4H, m), 4.0-3.8 (3H, m), 3.4-3.2 (2H, m), 2.0-1.8 ppm (4H, m). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 72.95; H, 6.35; N, 6.30. Found: C, 73.12; H, 6.35; N, 6.17.

(*S*)-*N*,*N*'-Dimethyl-2-(anilinomethyl)pyrrolidine (3). A solution of **3a** (37.55 g, 85 mmol) in THF (50 mL) was added slowly to a suspension of LAH (30.0 g, 790 mmol) in THF (800 mL, 0°C). The resulting mixture was stirred for 72 h at 60-65°C, then triethanolamine (115 mL, 127 g, 850 mmol) and, after 1 h, H_2O (28.5 mL, 1.58 mol) was added. The resulting mixture was stirred for further 12 h then was filtered and the solvent was eliminated under reduced pressure. The oily residue was stirred with 10% H_2SO_4 (200 mL) and Et_2O (50 mL), then extracted with Et_2O and the organic layers were discarded. The acqueous layer was made alkaline (KOH) then extracted several times with Et_2O; the organic phase was then washed with saturated NaCl

and dried (Na_2SO_4). Distillation of the crude product afforded the diamine **3** (16.5 g, 95%) having bp 106-110°C/0.01, $[\alpha]_D^{25}$ -115.56 (*c* 2, Et_2O), (pure at TLC, silica gel, EtOH/AcOH 7/3). MS, m/z(%): 204(M^+, 204(77), 159(9), 144(17), 132(20), 120(5), 84(100), 42(11); ^1H NMR, δ: 7.3-7.2 (2H, m), 6.8-6.7 (3H, m), 3.7-3.6 (1H, m), 3.2-3.05 (2H, m), 3.0 (3H, s), 2.4 (3H, s), 2.25-2.15 (2H, m), 2.0-1.6 ppm (4H, m); ^{13}C NMR, δ: 149.5, 129.1, 116.0, 112.0, 63.9, 57.6, 57.3, 41.4, 39.4, 30.3, 22.4 ppm. Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.60; H, 9.69; N, 13.71.

(*S*)-1-Methyl-2-(piperidinomethyl)pyrrolidine (4). This product was prepared as previously reported starting from *(S)-N*-(benzyloxycarbonyl)proline and piperidine.[15] For the sample of **4** employed was found: bp 67°C/0.02, $[\alpha]_D^{25}$ -46.0 (*c* 2.0, EtOH); ^1H NMR, δ: 3.05-2.95 (1H, m), 2.5-2.4 (2H, m), 2.35 (3H, s), 2.42.05 (4H, m), 2.0-1.85 (2H, m), 1.8-1.6 (4H, m), 1.6-1.45 (4H,m), 1.4-1.3 ppm (2H, m); ^{13}C NMR, : 64.7, 62.9, 57.6, 55.3, 41.4, 31.2, 25.9, 24.4, 22.6 ppm.

(*S*)-*N*-(Benzyloxycarbonyl)valine (Z-Val-OH). Z-Val-OH was prepared as previously reported starting from (*S*)-valine.[16] For the sample employed was found: mp 58-60°C, $[\alpha]_D^{25}$ -3.06 (*c* 3, EtOH), (pure at TLC, silica gel, EtOH/NH_4OH 7/3).

(*S*)-*N*-(Benzyloxycarbonyl)valine piperidylamide (5a). Z-Val-OH, (50.2 g, 200 mmol) in EtOAc (400 mL) was added, slowly, under vigorous stirring at -15°C, with 4-methylmorpholine (22.0 mL, 20.2 g, 200 mmol) in EtOAc (25 mL) and ethylchloroformate (20.1 mL, 22.8 g, 210 mmol) in EtOAc (50 mL). The reaction mixture was stirred for 15 min at -15°C, then freshly distilled piperidine (20.8 mL, 17.9 g, 210 mmol) in EtOAc (25 mL) was added. After 1 h at -15°C, the reaction mixture was stirred for further 12 h at room temperature then water (200 mL) and EtOAc (200 mL) were added. The acqueous layer was separated from the organic one and was extracted with EtOAc. The organic solution was washed with 10% $NaHCO_3$, saturated NaCl, 2% HCl and saturated NaCl (150 mL each) in that order. After drying (Na_2SO_4), elimination of the solvent and distillation of the crude product, the amide **5a** was obtained (50.1 g, 79%), having bp 200-205°C/0.01, $[\alpha]_D^{25}$ +22.53 (*c* 3, $CHCl_3$), (pure at TLC, silica gel, EtOH/H_2O 7/3); ^1H NMR, δ: 7.45-7.3 (5H, m), 5.8-5.7 (1H, m), 5.1 (2H, s), 4.6-4.5 (1H, m), 3.6-3.4 (4H, m), 2.05-1.85 (1H, m), 1.7-1.5 (6H, m), 1.05-0.85 ppm (6H, dd). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.65; H, 8.25; N, 8.91.

(*S*)-*N*-Methyl-*N*-(benzyloxycarbonyl)valine piperidylamide (5b). A solution of amide **5a** (12.7 g, 40 mmol) and MeI (22.7 g, 160 mmol) in THF/DMF (10/1, 110 mL) was added, under stirring and cautiously, with NaH (1.8 g, 80% in oil, 60 mmol). The reaction mixture was stirred for 22 h at 80°C, then H_2O (200 mL) was added and the resulting mixture was extracted several times with Et_2O. The organic layer was washed with 5% $Na_2S_2O_3$ (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Distillation of the crude product afforded the amide **5b** (11.5 g, 87%) having bp 168-175°C/0.01, $[\alpha]_D^{25}$ -78.83 (*c* 2, $CHCl_3$), (pure at TLC, silica gel, EtOH/H_2O 7/3); ^1H NMR, δ: 7.45-7.3 (5H, m), 5.2 (2H, s), 4.7-4.65 (1H, m), 3.8-3.3 (4H, m), 2.9 (3H, s), 2.45-2.3 (1H, m), 1.7-1.4 (6H, m), 1.0-0.8 (6H, dd) ppm. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.43; N, 8.49. Found: C, 68.65; H, 8.57; N, 8.21.

(*S*)-1-Piperidyl-2-(*N*,*N*-dimethylamino)-3-methylbutane (5). A solution of **5b** (28.6 g, 89 mmol) in THF (50 mL) was slowly added to a suspension of LAH (20.0 g, 526 mmol) in THF (500 mL, 0°C). The reaction mixture was stirred for 72 h at 60-65°C, then, at room temperature was added with triethanolamine (74 mL, 82 g, 550 mmol) and, after 1 h, H_2O (20 mL, 1.11 mol) was added. The resulting mixture was stirred for further 12 h then was filtered and the solvent was eliminated under reduced pressure. The oily residue was stirred with 10% H_2SO_4 (200 mL) and Et_2O (50 mL), then extracted with Et_2O and organic layers were discarded. The acqueous layer was made alkaline (KOH) then extracted several times with Et_2O; the organic phase was then washed with saturated NaCl and dried (Na_2SO_4). After distillation of the crude product the diamine **5** was obtained (14.64 g, 83%) bp 60-65°C/0.01, $[\alpha]_D^{25}$ +19.27 (*c* 2, Et_2O), (pure at TLC, silica gel, EtOH/AcOH 7/3). MS, m/z(%): 198(M^+, 10), 197(57), 183(14), 154(84), 141(9), 114(100), 100(87), 86(41), 72(17), 55(18), 44(21); ^1H NMR, δ: 2.40-2.35 (3H, m), 2.3 (6H, s), 2.25-2.1 (4H, m), 1.8-1.7 (1H, m), 1.6-1.5 (4H, m), 1.45-1.35 (2H, m), 1.95-1.85 ppm (6H, dd); ^{13}C NMR, δ: 65.9, 57.7, 55.1, 41.9, 29.6, 26.2, 24.6, 21.2, 19.5 ppm. Anal. Calcd for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21; N, 14.12. Found: C, 72.60; H, 13.25; N, 14.18.

(*S*)-*N*-(Benzyloxycarbonyl)phenylalanine (Z-Phe-OH). Z-Phe-OH was prepared as previously reported starting from (*S*)-phenylalanine.[17] For the sample obtained was found: mp 87-88°C, $[\alpha]_D^{25}$ +5.15 (*c* 5, AcOH), (pure at TLC, silica gel, EtOH/NH_4OH 7/3).

(*S*)-*N*-(Benzyloxycarbonyl)phenylalanine piperidylamide (6a). The product **6a** was prepared as above described for **5a**: starting from Z-Phe-OH (59.8 g, 200 mmol) and from piperidine (17.9 g, 210 mmol), after crystallization from Et_2O amide **6a** was obtained (40.2 g, 54%), having mp 66-68°C, $[\alpha]_D^{25}$ +21.49 (*c* 2, $CHCl_3$), (pure at TLC, silica gel, EtOH/H_2O 7/3); ^1H NMR, δ: 7.47.2 (10H, m), 5.8-5.7 (1H, m), 5.1 (2H, s), 5.0-4.85 (1H, m), 3.55-3.45 (2H, m), 3.05-2.95 (4H, m), 1.9-1.8 (1H, m), 1.6-1.4 (4H, m), 1.1-0.9 ppm (2H, m). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.35; H, 7.13; N, 7.89.

(*S*)-1-Piperidyl-2-(*N*,*N*-dimethylamino)-3-phenylpropane (6). The amide **6a** (38.7 g, 106 mmol) and MeI (26.0 mL, 59.0 g, 416 mmol) in THF/DMF (10/1, 220 mL) were added, under stirring and cautiously, with NaH (4.2 g, 80% in oil, 140 mmol). The reaction mixture was stirred for 22 h at 80°C, then H_2O (400 mL) was added and the resulting mixture was extracted with Et_2O. The organic layer was washed with 5% $Na_2S_2O_3$ (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product obtained [41.8 g, ^1H NMR, δ: 7.6-7.2 (10H, m), 5.4-5.3 (1H, m), 5.05 (2H, s), 3.8-3.6 (2H, m), 3.35-3.2 (4H, m), 2.95 (3H, m), 1.6-1.4 (4H, m), 1.3-1.2 ppm (2H, m)] was employed without any further purification. Thus, a solution of this crude product (39.5 g) in THF (50 mL) was slowly added to a stirred suspension of LAH (23.0 g, 605 mmol) in THF (500 mL, 0°C). The reaction mixture was stirred for 72 h at 60-65°C then triethanolamine (87 mL, 96.4 g, 647 mmol) and, after 1 h, H_2O (22 mL, 1.22 mol) were added. The resulting mixture was stirred for further 12 h then was filtered and the solvent was eliminated under reduced pressure. The oily residue was stirred with 10% H_2SO_4 (200 mL) and Et_2O (50 mL), then extracted with Et_2O and organic layers were discarded. The acqueous layer was made alkaline (KOH) then extracted several times with Et_2O; the organic phase was then washed with saturated NaCl and dried (Na_2SO_4). After distillation of the crude

product diamine **6** was obtained (18.95 g, 73%) bp 105°C/0.01, $[\alpha]_D^{25}$ -18.69 (*c* 2, Et_2O), (pure at TLC, silica gel, EtOH/AcOH 7/3). MS, m/z(%): 246(M^+, 4), 245(6), 202(15), 162(39), 155(54), 148(100), 98(20); ^1H NMR, δ: 7.3-7.15 (5H, m), 3.0-2,75 (2H, m), 2.35 (6H, s), 2.55-2.0 (7H, m), 1.6-1.15 (4H, m), 1.4-1.5 ppm (2H, m); ^{13}C NMR, δ: 141.6, 129.3, 128.2, 125.7, 63.0, 59.5, 55.0, 40.7, 34.5, 25.8, 24.3 ppm. Anal. Calcd for $C_{16}H_{26}N_2$: C, 77.99; H, 10.64; N, 11.37. Found: C, 77.79; H, 10.72; N, 11.41.

(2*S*,3*S*)-*N*-(Benzyloxycarbonyl)isoleucine (Z-Ile-OH). Z-Ile-OH was prepared as previously reported starting from (2*S*,3*S*)-Isoleucine;[18] the sample employed was a colourless oil having $[\alpha]_D^{25}$ +4.52 (*c* 5, EtOH), (pure at TLC, silica gel, EtOH/NH_4OH 7/3).

(2*S*,3*S*)-*N*-(Benzyloxycarbonyl)isoleucine piperidylamide (7a). The product **7a** was prepared as above described for **5a**: starting from Z-Ile-OH (53.0 g, 200 mmol) and piperidine (17.9 g, 210 mmol), **7a** was obtained (40.5 g, 61%), having bp 220°C/0.05, 20 $[\alpha]_D^{25}$ +11.03 (*c* 2, $CHCl_3$), (pure at TLC, silica gel, EtOH/H_2O 7/3); ^1H NMR, δ: 7.45-7.25 (5H, m), 5.8-5.7 (1H, m), 5.1 (2H, s), 4.6-4.5 (1H, m), 3.6-3.4 (4H, m), 2.0-1.8 (1H, m), 1.7-1.4 (6H, m), 1.3-1.0 (2H, m), 1.0-0.8 ppm (6H, m). Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.79; H, 8.37; N, 8.39.

(2*S*,3*S*)-*N*-Methyl-*N*-(benzyloxycarbonyl)isoleucine piperidylamide (7b). The product **7b** was prepared as above described for **5b**: starting from amide **7a** (26.5 g, 80 mmol) **7b** was obtained (24.5 g, 87%), having bp 175°C/0.02, $[\alpha]_D^{25}$ -81.36 (*c* 3, $CHCl_3$), (pure at TLC, silica gel, EtOH/H_2O 7/3); ^1H NMR, δ: 7.4-7.3 (5H, m), 5.15 (2H, s), 4.8-4.7 (1H, m), 3.7-3.4 (4H, m), 2.85 (3H, s), 2.2-1.9 (1H, m), 1.7-0.8 ppm (14H, m). Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.30; H, 8.75; N, 7.91.

(2*S*,3*S*)-1-Piperidyl-2-(*N*,*N*-dimethylamino)-3-methylpentane (7). The product **7** was prepared as above described for **5**: starting from **7b** (22.5 g, 65 mmol) **7** was obtained (7.8 g, 57%), having bp 60-65°C/0.02, $[\alpha]_D^{25}$ -5.61 (*c* 1, Et_2O), (pure at TLC, silica gel, EtOH/AcOH 7/3); MS, m/z(%): 226(M^+, 5), 225(8), 182(17), 129(25), 114(51), 98(38), 85(46), 71(62), 57(100), 43(73); ^1H NMR, δ: 2.45-2.2 (7H, m), 2.35 (6H, s), 1.6-1.5 (4H, m), 1.45-1.35 (2H, m), 1.25-1.15, (1H, m), 0.95-0.85 ppm (6H, m); ^{13}C NMR, δ: 64.0, 57.9, 55.1, 42.0, 35.7, 27.5, 26.1, 24.5, 15.6, 11.5 ppm. Anal. Calcd for $C_{13}H_{28}N_2$: C, 73.52; H, 13.29; N, 13.19. Found: C, 73.65; H, 13.14; N, 13.23.

Asymmetric reduction of ketones. The following procedures are representative examples:

(A) Hydrolysis at -100°C. Run 15. A suspension of $SnCl_2$ (1.90 g, 10 mmol) in CH_2Cl_2 (10 mL) was added with a solution of the diamine **5** (1.98 g, 10 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 4 h, then cooled at -100°C and added with DIBAH (10 mL, 1 M solution in hexanes, 10 mmol) in 5-10 min. The reaction mixture was stirred for further 10 min at -100°C and was added with MeCOPh (0.74 g, 6.2 mmol) in CH_2Cl_2 (10 mL). After 10 min under stirring at -100°C phosphate buffer solution was rapidly added (40 mL, pH 7) and cooling bath was removed. The hydrolyzed mixture was treated with Et_2O and was centrifugated. The organic layer was separated, washed with acqueous H_2SO_4 (10%) and with

$NaHCO_3$ (5%), dried (Na_2SO_4) and concentrated under reduced pressure. After distillation and purification via flash chromatography (hexane/EtOAc = 80/20) pure (GLC) (+)(*R*)-methylphenylcarbinol (0.58 g, 69%) having $[\alpha]_D^{25}$ +17.39 (neat) was recovered.

(B) Hydrolysis at 20°C. Run 16. A suspension of $SnCl_2$ (1.90 g, 10 mmol) in CH_2Cl_2 (10 mL) was added with a solution of the diamine **5** (1.98 g, 10 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 4 h, then cooled at -100°C and added with DIBAH (10 mL, 1 M solution in hexanes, 10 mmol) in 5-10 min. The reaction mixture was stirred for further 10 min at -100°C and was added with MeCOPh (0.74 g, 6.2 mmol) in CH_2Cl_2 (10 mL). After 10 min under stirring at -100°C cooling bath was removed and the temperature was allowed to raise. After 3-4 h the reaction mixture was added with phosphate buffer solution (40 mL, pH 7) then was treated with Et_2O and centrifugated. The organic layer was separated, washed with acqueous H_2SO_4 (10%) and with $NaHCO_3$ (5%), dried (Na_2SO_4) and concentrated under reduced pressure. After distillation and purification via flash chromatography (hexane/EtOAc = 80/20) pure (GLC) (+)(*R*)-methylphenylcarbinol (0.60 g, 75%) having $[\alpha]_D^{25}$ +19.15 (neat) was recovered.

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