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Enantiomerically Pure Guanidine-Catalysed Asymmetric Nitroaldol Reaction

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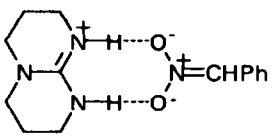
Abstract: Enantiomerically pure guanidines with and without C_2 symmetry have been prepared and used as catalysts in the addition of nitromethane to aldehydes (Henry reaction). The influence of the structure and amount of the guanidine, the solvent and the temperature in the enantioselectivity of the nitroaldol reaction has also been studied.

INTRODUCTION

The Henry (nitroaldol) reaction is one of the oldest carbon-carbon bond formation reactions in organic synthesis[1]. However, only recently the first efficient[2] asymmetric nitroaldol reaction catalysed by rare earth metal complexes has been reported[3]. Tetramethylguanidine (TMG) has been used as basic catalyst in Michael additions of nitroalkanes and in the Henry reaction of nitromethane with levoglucosenone[4]. Guanidines have been used for molecular recognition of carboxylate[5], phosphate[6] and nitrate[7] anions because of its ability to form strong hydrogen bonds between the guanidinium cation and the dioxoanion[8]. Moreover, the isolation of complex **1**[2,9] formed between the bicyclic guanidine 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and α-nitrotoluene suggested that these type of intermediates could be good models for an enantioselective guanidine-catalysed nitroaldol reaction[9,10]. All these antecedents prompted us to study the use of chiral guanidines of type **2**, derived from enantiomerically pure amines, as catalyst in the asymmetric Henry reaction.



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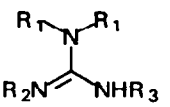

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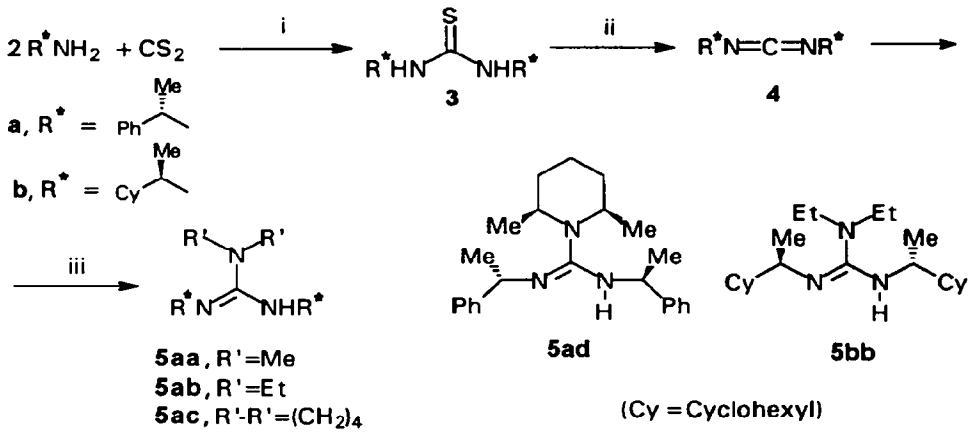
RESULTS AND DISCUSSION

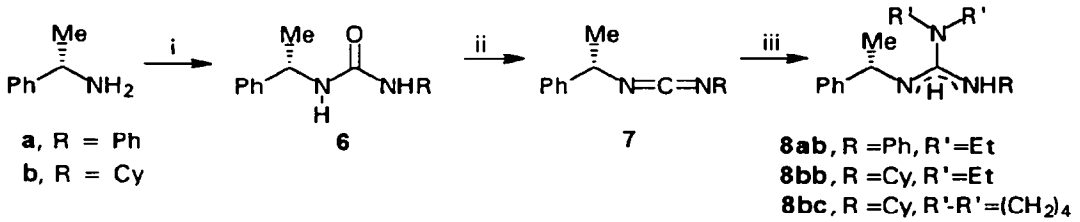
Guanidines **5** with C_2 symmetry were prepared starting from thioureas **3a** or **3b**, which were obtained by reaction of (*S*)-1-phenylethylamine or (*R*)-1-cyclohexylethylamine with carbon disulfide, respectively. Further desulfidryzation with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine[11] afforded homochiral

carbodiimides **4a** and **4b** which were transformed into guanidines **5aa-be** by treatment with different secondary amines (Scheme 1).



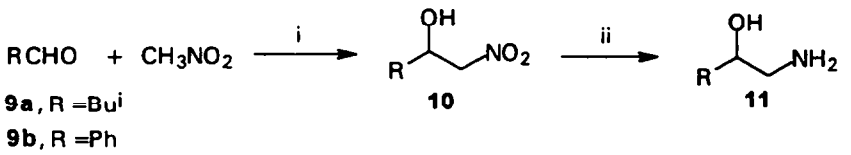
Scheme 1. *Reagents and conditions:* i, EtOH, reflux, 24 h; ii, DIAD, Ph_3P, THF, rt, 20 h; iii, Me_2NH, Et_2NH, pyrrolidine or *cis*-2,6-dimethylpiperidine, THF, rt, 24 h.

Homochiral guanidines **8** were obtained according to the synthetic sequence showed in Scheme 2. Reaction of (*S*)-1-phenylethylamine with phenyl or cyclohexyl isocyanate yielded the corresponding ureas **7**, which were dehydrated by treatment with bromotriphenylphosphonium bromide and triethylamine[12]. After reaction with diethylamine or pyrrolidine, guanidines **8ab-bc** were obtained. Guanidines **5** and **8** were purified by extractive work-up followed by vacuum distillation.



Scheme 2. *Reagents and conditions:* i, PhNCO or CyNCO, AcOEt, rt, 5 min; ii, Br_2·PPh_3, NEt_3, PhH, reflux, 90 min; iii, Et_2NH or pyrrolidine, THF, rt, 24 h.

The reaction of isopentanal (**9a**) or benzaldehyde (**9b**) with nitromethane in THF as solvent at room temperature in the presence of a catalytic amount of different chiral guanidines **5** or **8** (0.1 equiv) gave 1-nitro-4-methyl-2-pentanol (**10a**) or 2-nitro-1-phenyl-1-ethanol (**10b**) enantioselectively enriched (Scheme 3 and Table 1).



Scheme 3. *Reagents and conditions:* i, Guanidine **5** or **8**, THF; ii, H_2, 10% Pd-C, AcOEt, 24 h.

Table 1. Nitroaldol Reaction Catalysed by Homochiral Guanidines

					nitroalcohol			
entry	RCHO	guanidine	reaction time (h)	T(°C)	no.	yield(%)[a]	$[\alpha]_D^{25}$ [b]	e.e.(%)
1	**9a**	**5aa**	24	rt	**10a**	72	- 3.3	17[c]
2	**9a**	**5ab**	10	rt	**10a**	85	-5.8	26[c]
3	**9a**	**5ab**	7	-45	**10a**	40	-7.5	34[d]
4	**9a**	**5ab**	9	-65	**10a**	33	-11.9	54[d]
5	**9a**	**5ac**	16	rt	**10a**	77	-1.4	6[c]
6	**9a**	**5ad**	72	rt	**10a**	8	-	-
7	**9a**	**5bb**	15	rt	**10a**	75	-3.9	18[c]
8	**9a**	**8ab**	24	rt	**10a**	6	-	-
9	**9a**	**8bb**	24	rt	**10a**	60	-1.2	5[c]
10	**9a**	**8bc**	24	rt	**10a**	62	0	0
11	**9b**	**5ab**	9	rt	**10b**	31	+4.9	13[e]
12	**9b**	**5ab**	9	-65	**10b**	31	+11.1	33[e]
13	**9b**	**5ac**	24	rt	**10b**	27	+1.7	5[c]

[a] Isolated pure compound, based on starting aldehyde. [b] Ethanol. [c] Deduced from [α] value. [d] Deduced from 1-amino-4-methyl-2-pentanol (**10a**) (see text). [e] Deduced from lit.[13] [α] value for (*S*)-2-amino-1-phenyl-1-ethanol (**11b**) $[\alpha]_D^{18}$ +44.6 (EtOH).

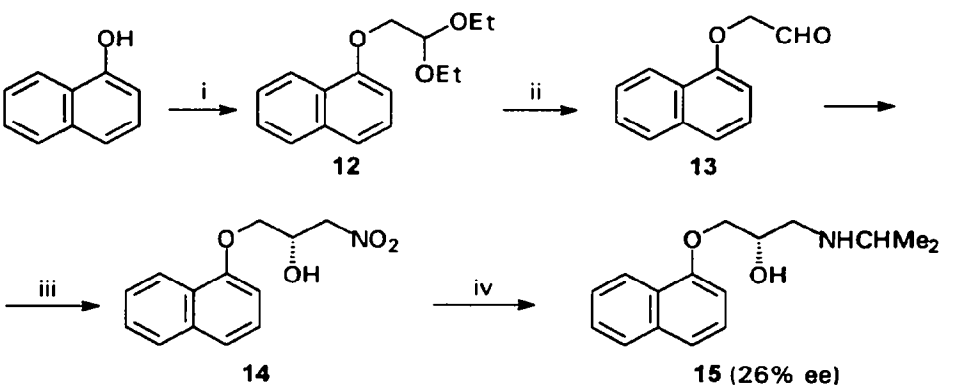
In general, the nitroaldol reaction took place with good chemical yields specially with isopentanal (**9a**). In the case of guanidines **5ad** and **8aa** (Table 1, entries 6 and 8) chemical yields were low, probably due to their lower basicity and steric hindrance respectively. The measured $[\alpha]_D$ value for nitroalcohols **10a** and **10b** showed that the best chiral discrimination was achieved with guanidines **5** with C_2 symmetry, specially when guanidine **5ab** was used.

The determination of the optical yield of nitroalcohols **10** could not be carried out by esterification with Mosher acid-DCC[14] or with its chloride, because they suffer dehydration to the corresponding nitroalkenes. In order to determine the corresponding e.e.'s they were quantitatively transformed into aminoalcohols **11** by catalytic hydrogenation with palladium on carbon in ethyl acetate at room temperature (see Scheme 3). In the

case of 2-amino-1-phenyl-1-ethanol (**11b**) optical yields were deduced from the $[\alpha]_D$ values in comparison with the literature[13] (see Table 1, footnote e). For 1-amino-4-methyl-2-pentanol (**11a**) the corresponding e.e.'s were deduced from ^1H NMR integral of the methine protons bonded to the OH group in the diastereomeric salts[15] formed between the aminoalcohol and the (*R*)-enantiomer of the *O*-(4-chloro-2-methylphenyl)lactic acid[17] in $CDCl_3$.

The influence of the amount of guanidine, the solvent and the temperature in the enantioselectivity of the Henry reaction was studied for the addition of nitromethane to isopentanal (**9a**) in the presence of guanidine **5ab**. When the amount of guanidine was reduced to 0.05 equiv the e.e. decreased to 22% and when 0.2 equiv were used the e.e. also decreased to 19%. The homochiral guanidine could be recuperated in all cases by extractive work-up and without any loss of activity. The reaction was carried out in different solvents such as: ethyl ether, hexane, toluene, dimethoxyethane, DMSO, nitromethane, and dioxane. In all cases chemical yields were rather similar (75-95%) except in dioxane where the reaction failed, whereas optical yields were in the range 18-29% for ethereal solvents and lower than 4% for the others. When the reaction was performed at low temperatures e.e.'s increased till 54% for compound **10a** and till 33% for compound **10b** (see Table 1, entries 3,4 and 12).

This asymmetric reaction was applied to the synthesis of enantiomerically enriched propanolol **15**[20] according with the synthetic sequence outlined in Scheme 4. Reaction of the sodium alcoxide of 1-naphtol with 2-bromoacetaldehyde diethyl acetal afforded acetal **12** which were hydrolyzed in acidic medium to aldehyde **13**. Further guanidine **5ab**-catalysed nitroaldol reaction of nitromethane with aldehyde **13** at low temperature yielded enantiomerically enriched nitroalcohol **14**. *R*-Propanolol was then obtained by catalytic hydrogenation of **14** in the presence of acetone (26 % e.e.).



Scheme 4. *Reagents and conditions:* i, $BrCH_2CH(OC_2H_5)_2$, NaOH, DMSO, 90° C, 72 h, 63%; ii, 2N HCl, THF, rt, 24 h, 68%; iii, CH_3NO_2, **5ab** (0.1 eq), THF, -40° C, 8 h, 21%; iv, a) H_2, 10% Pd-C, MeOH, rt, 18 h; b) CH_3COCH_3, H_2, 10% Pd-C, MeOH, 50° C, 72 h, 30%.

EXPERIMENTAL

General.- Melting points were obtained with a Reichert Thermovar apparatus and are uncorrected. Optical rotations were measured with an Optical Activity AA-100. IR spectra were obtained on a Pye Unicam SP3-200 spectrophotometer. NMR spectra were determined on a Bruker AC-300 (300 MHz for ^1H and 75 MHz for ^{13}C) using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated; chemical shifts are given in δ (ppm) and the coupling constants (*J*) are measured in Hz. Mass spectra (EI) were obtained on a Hewlett-Packard EM/GC HP-5988A spectrometer. Microanalyses were performed by the Microanalyses Service of the University of Alicante. High resolution mass spectra (EI) were determined by the corresponding Service of the University of Zaragoza.

Synthesis of Thioureas 3.-A solution of carbon disulfide (0.7 mL, 1.66 mmol) and the corresponding amine [(*S*)-1-phenylethylamine or (*R*)-1-cyclohexylethylamine] (3.32 mmol) in ethanol (6 mL) was refluxed during 20 h. The obtained precipitate was filtered off, washed with hexane and ether, and allowed to dry in air affording pure thioureas **3a** and **3b**

(S,S)-N,N'-*Bis(1-phenylethyl)thiourea* (**3a**): yield 79%, mp 202-203°C; $[\alpha]_D^{25}$ +105.4 (*c* 1.3; $CHCl_3$); ν_{max} (KBr) 3200 (NH), 1525, 1320 (C=S), 1065, 740 and 680 cm^{-1}; δ_H 1.45 (d, *J*=6.8, 6H, 2xCH_3), 5.07 (br s, 2H, 2xCH), 6.24 (br s, 2H, 2xNH) and 7.01-7.21 (m, 10H, ArH); δ_C 22.96, 53.97, 125.56, 127.43, 128.78, 142.17 and 179.87; *m/z* 284 (M^+, 47%), 120 (100), 105 (40), 103 (12), 79 (15), 77 (22) and 42 (14). Anal calcd for $C_{17}H_{20}N_2S$: C, 71.79; H, 7.09; N, 9.85; S, 11.27. Found: C, 71.84; H, 7.33; N, 9.93; S, 10.85.

(R,R)-N,N'-*Bis(1-cyclohexylethyl)thiourea* (**3b**): yield 63%; mp 182-183°C; $[\alpha]_D^{25}$ - 24.8 (*c* 2; $CHCl_3$); ν_{max} (KBr) 3180 (NH), 1540, 1430, 1325 (C=S), 1275 and 1135 cm^{-1}; δ_H 0.88-1.82 (m, 22H, Cy), 1.08 (d, *J*=6.7, 6H, 2xCH_3), 3.93 (br s, 2H, 2xCH) and 5.72 (br s, 2H, 2xNH); δ_C 17.39, 26.00, 26.08, 26.22, 28.70, 29.32, 43.06, 54.46 and 179 91; *m/z* 296 (M^+, 26%), 295 (15), 187 (100), 77 (61), 69 (39), 67 (16), 55 (54), 44 (44) and 41 (34). Anal calcd for $C_{17}H_{32}N_2S$: C, 68.86; H, 10.88; N, 9.45; S, 10.81. Found: C, 68.86; H, 11.50; N, 9.51; S, 9.83.

Synthesis of Carbodiimides 4.- A solution of triphenylphosphine (1.65 g, 6.27 mmol) in THF (5 mL) was added to a mixture of thiourea **3a** or **3b** (5.70 mmol) and diisopropyl azodicarboxylate (1.24 mL, 6.27 mmol) in THF (15 mL). The solution was stirred at room temperature for 15 h. The solvent was evaporated at reduced pressure (15 Torr) and the residue was extracted with hexane (3x20 mL). Filtration and evaporation of the hexane solution, and Kügelrohr distillation of the residue afforded carbodiimides **4a** or **4b.**

(S,S)-*Bis(1-phenylethyl)carbodiimide* (**4a**): yield 60%; bp 190°C/0.1 Torr, $[\alpha]_D^{23}$ +1.8 (*c* 1.6; CH_2Cl_2); ν_{max} (film) 3010, 2060 (NCN), 1570, 1530, 740 and 670 cm^{-1}; δ_H 1.46 (d, *J*=6.8, 6H, 2xCH_3), 4.55 (q, *J*=6.8, 2H, 2xCHN) and 7.21-7.34 (m, 10H, ArH); δ_C 24.52, 56.52, 125.83, 127.19, 128.35, 140.23 and 143.60; *m/z* 250 (M^+, 4%), 105 (100), 103 (11), 79 (14) and (77 (22). HRMS *m/z* calcd for $C_{17}H_{18}N_2$: 250.1470. Found: 250.1472.

(R,R)-*Bis(1-cyclohexylethyl)carbodiimide* (**4b**): yield 42%; bp 165°C/0.1 Torr; $[\alpha]_D^{23}$ +79.7 (*c* 1.9; CH_2Cl_2); ν_{max} (film) 2880, 2080 (NCN), 1430, 1240 and 1080 cm^{-1}; δ_H 0.95-1.83 (m, 28H, Cy and 2xCH_3) and 3.21 (q, *J*=6.5, 2H, 2xCH); δ_C 21.84, 26.14, 28.83, 29.29, 44.36, 58.26 and 139.70; *m/z* 247 (M^+-Me, 3%), 179 (17), 111 (64), 69 (100), 67 (14), 55 (71), 54 (11), 43 (11) and 41 (66). HRMS *m/z* calcd for $C_{16}H_{27}N_2$ (M^+-Me): 247.2174. Found: 247.2166.

Synthesis of Ureas 6.-A solution of phenyl or cyclohexyl isocyanate [(2.17 mL, 20 mmol) or (2.55 mL, 20 mmol)] and (*S*)-1-phenylethylamine (2.83 mL, 22 mmol) in ethyl acetate (20 mL) was stirred for 5 min at

room temperature. The precipitate was filtered off, washed with hexane and ether and allowed to dry in air affording pure ureas **6a** or **6b**.

(S)-N-*Phenyl*-N'-*(1-phenylethyl)urea* (**6a**): yield 85%; mp 152-153°C; $[\alpha]_D^{25}$ -25.2 (*c* 2.2; $CHCl_3$); ν_{max} (KBr) 3290 (NH), 3000, 1620 (C=O), 1580, 1535, 1220, 740, 720 and 680 cm^{-1}; δ_H 1.23 (d, *J*=6.9, 3H, CH_3), 4.82 (m, 1H, CH), 6.21 (d, *J*=7.5, 1H, (CH_3CHNH), 6.93 (m, 1H, ArH), 7.10-7.22 (m, 9H, ArH) and 7.83 (s, 1H, PhN*H*); δ_C 22.96, 49.61, 119.66, 122.65, 125.67, 126.90, 128.47, 128.84, 139.05, 144.31 and 155.96; *m/z* 240 (M^+, 17%), 105 (33), 104 (6), 103 (7), 94 (7), 93(100), 92 (6), 79 (10), 77 (23), 65 (9) and 51 (8). Anal calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.24; H, 6.74; N, 11.73.

(S)-N-*Cyclohexyl*-N'-*(1-phenylethyl)urea* (**6b**): yield 83%; mp 144-145°C; $[\alpha]_D^{25}$ -19.1 (*c* 2.2; $CHCl_3$); ν_{max} (KBr) 3300 (NH), 3040, 3010, 1615 (C=O), 1565, 1240, 740 and 690 cm^{-1}; δ_H 0.97-1.79 (m, 10H, Cy), 1.36 (d, *J*=6.9, 3H, CH_3), 3.48 (br s, 1H, NC*H*CH_2), 4.79 (m, 1H, CHN), 5.04 and 5.48 (2 br s, 2H, 2xNH) and 7.18-7.34 (m, 5H, ArH); δ_C 23.33, 24.73, 25.51, 33.63, 33.66, 48.52, 49.69, 125.82, 126.85, 128.45, 144.69 and 157.44; *m/z* 246 (M^+, 68%), 120 (68), 106 (100), 105 (89), 104 (25), 98 (46), 79 (39), 77 (43), 56 (76), 55 (26), 43 (23), 42 (21) and 41 (30). Anal calcd for $C_{15}H_{22}N_2O$· C, 73.13; H, 9.00; N, 11.37. Found: C, 73.00; H, 9.47; N, 11.30.

Synthesis of Carbodiimides 7.- To a solution of bromotriphenylphosphonium bromide (6.4 g, 5.2 mmol) prepared *in situ* mixing triphenylphosphine (3.99 g, 15.2 mmol) and bromine (0.78 mL, 15.2 mmol) in benzene (20 mL) was added triethylamine (4.3 mL, 30.8 mmol) at room temperature. To this suspension was added the corresponding urea **6** (12.2 mmol) in small portions for 15 min, and the resulting mixture was refluxed for 90 min and then cooled to 10°C. The solution was filtered off and the solvent was evaporated at reduced pressure (15 Torr). The residue was extracted with hexane (3x20 mL) and the combined organic layers were filtered and evaporated yielding the corresponding carbodiimides which were purified by vacuum distillation.

(S)-N-*Phenyl*-N'-*(1-phenylethyl)carbodiimide* (**7a**): yield 54%; bp 185°C/0.1 Torr; $[\alpha]_D^{23}$ +28.1 (*c* 1.6; CH_2Cl_2); ν_{max} (film) 3000, 2940, 2080 (NCN), 1570, 1240, 720 and 680 cm^{-1}; δ_H 1.64 (d, *J*=6.7, 3H, CH_3), 4.79 (q, *J*=6.7, 1H, CH) and 7.01-7.27 (m, 10H, ArH); δ_C 25.19, 57.40, 123.49, 124.75, 125.73, 127.58, 128.63, 129.28, 129.45, 138.37, 140.15 and 143.05; *m/z* 222 (M^+, 3%), 118 (50), 106 (11), 105 (100), 103 (18), 79 (18) and 77 (35). HRMS *m/z* calcd for $C_{15}H_{14}N_2$: 222.1157. Found: 222.1165.

(S)-N-*Cyclohexyl*-N'-*(1-phenylethyl)carbodiimide* (**7b**): yield 55%; bp 180°C/0.1 Torr; $[\alpha]_D^{23}$ -8.7 (*c* 1.7; CH_2Cl_2); ν_{max} (film) 3050, 3020, 2100 (NCN), 1670, 1550, 1440 y 695 cm^{-1}; δ_H 1.12-1.82 (m, 10H, Cy), 1.53 (d, *J*=6.7, 3H, CH_3), 3.16 (m, 1H, NC*H*CH_2), 4 58 (q, *J*=6 7, 1H, CHN) and 7.20-7.68 (m, 5H, ArH); δ_C 24.35, 24.56, 25.22, 34.61, 55.54, 56.46, 125.80, 127.07 128.26, 139.79 and 143.81; *m/z* 228 (M^+, 2%), 106 (13), 105 (199), 104 (15), 103 (12), 79 (15), 77 (39), 55 (28), 51 (12) and 41 (35). HRMS *m/z* calcd for $C_{15}H_{20}N_2$: 228.1626. Found: 228.1630.

Synthesis of Guanidines 5 and 8. General Procedure.- A solution of the corresponding carbodiimide (1 mmol) and amine (10 mmol) in THF (10 mL) was stirred at room temperature for 24 h. The solvent was evaporated at reduced pressure (15 Torr) and the remaining amine was removed under vacuum (0.1 Torr). The obtained crude guanidine was dissolved in ether (20 mL) and extracted with 2N HCl (3x10 mL). The combined aqueous layers were neutralised with NaOH and extracted with ether (3x15 mL) and the organic layers were dried over anhydrous sodium sulfate. Evaporation at reduced pressure (15 Torr) yielded guanidines **5aa-bb** and **8ab-bc** which were purified by Kügelrohr distillation.

(S,S)-N,N-*Dimethyl*-N',N''-*bis(1-phenylethyl)guanidine* (**5aa**): yield 60%; bp 160°C/0.1 Torr; $[\alpha]_D^{23}$ +52.1 (*c* 1; EtOH); ν_{max} (film) 3350, 3010, 2980, 2880, 1600, 735 and 675 cm^{-1}; δ_H (d_6-DMSO, 90°C) 1.36 (d, *J*=6.7,

6H, 2xCH_3CH), 2.62 (s, 6H, 2xCH_3N), 4.50 (q, *J*=6.7, 2H, 2xCHN) and 7.11-7.26 (m, 10H, ArH); δ_C (d_6-DMSO, 90°C) 24.21, 39.05, 53.37, 125.43, 125.49, 127.33, 146.42 and 154.37; *m/z* 295 (M^+, 10%), 175 (20), 120 (51), 106 (14), 105 (100), 104 (14), 103 (16), 79 (25), 78 (13), 77 (31), 71 (44), 44 (29) and 42 (18). HRMS *m/z* calcd for $C_{19}H_{25}N_3$: 295.2048. Found: 295.2042.

(S,S)-N,N-*Diethyl*-N',N''-*bis(1-phenylethyl)guanidine* (**5ab**): yield 62%; bp 170°C /0.1 Torr; $[\alpha]_D^{25}$ +50.3 (*c* 1; EtOH); ν_{max} (film) 3380 (NH), 3040, 3000, 1610, 1440, 1080, 750 y 690 cm^{-1}; δ_H (d_6-DMSO, 90°C) 0.93 (t, *J*=7.0, 6H, 2xCH_3CH_2), 1.35 (d, *J*=7.0, 6H, 2xCH_3CH), 3.01 (q, *J*=7.0, 4H, 2xCH_2N), 4.57 (q, *J*=7.0, 1H, CHN), and 7.11-7.26 (m, 10H, ArH); δ_C (d_6-DMSO, 90°C) 12.16, 24.16, 42.44, 53.37, 125.38, 125.49, 127.29, 146.65 and 152.72; *m/z* 323 (M^+, 10%), 218 (19), 203 (17), 120 (39), 106 (11), 104 (23), 103 (22), 99(17), 79 (30), 77 (29), 72 (28) and 43 (12); HRMS *m/z* calcd for $C_{21}H_{29}N_3$: 323.2361. Found: 323.2360.

(S,S)-N,N'-*Bis(1-phenylethyl)*-N'',N''-*tetramethyleneguanidine* (**5ac**): yield 56%; bp 170°C/0.1 Torr; $[\alpha]_D^{29}$ +15.8 (*c* 1; EtOH); ν_{max} (film) 3380 (NH), 3030, 3000, 1600, 1440, 1380, 750 and 690 cm^{-1}; δ_H 1.45 (d, *J*=6.6, 6H, 2xCH_3), 1.74 (m, 4H, 2xCH_2CH_2N), 3 24 (br s, 4H, 2xCH_2N), 4.40 (d, *J*=6.6, 2H, 2xCHN) and 7.14-7.24 (m, 11H, ArH and NH); δ_C 25.14, 25.50, 48.11, 55.00, 125.87, 126.39, 128.22, 146.00 and 154.00; *m/z* 321 (M^+, 2%), 217 (16), 202 (25), 120 (31), 107 (21), 105 (54), 103 (16), 79 (47), 78 (15), 77 (51), 70 (100), 55 (24), 51 (19) and 43 (28); HRMS *m/z* calcd for $C_{21}H_{27}N_3$: 321.2205. Found: 321.2207.

(S,S)-cis-N,N'-*Bis(1-phenylethyl)-2,6-dimethylpiperidylamidine* (**5ad**): yield 45%; bp 190°C/0.1 Torr; $[\alpha]_D^{23}$ +13.7 (*c* 1; EtOH); ν_{max} (film) 3220, 3010, 2980, 1620, 740 and 680 cm^{-1}, δ_H 0.43 (d, *J*=5.6, 3H, CH_3), 1.05 (d, *J*=5.9, 3H, CH_3), 1.23-1.66 (m, 6H, CH_2), 1.29 (d, *J*=6.7, 3H, CH_3), 1.50 (d, *J*=5.5, 3H, CH_3), 2.50 (m, 2H, 2xCH_2CHN), 5.05 (m, 1H, PhCHN), 5.22 (m, 1H, PhCHN) and 7.12-7.39 (m, 10H, ArH); δ_C 20.56, 21.00, 22.00, 24.62, 26.88, 34.54, 50.22, 54.56, 55.16, 55.70, 126.49, 127.45, 128.13, 145.73, 149.17 and 150.00; *m/z* 363 (M^+, 4%), 120 (23), 114 (15), 112 (199), 105 (88), 98 (22), 79 (27), 77 (27), 55 (28), 43 (19), 42 (25) and 41 (18). HRMS *m/z* calcd for $C_{24}H_{33}N_3$: 363.2674. Found: 363.2670.

(R,R)-N,N'-*Bis(1-cyclohexylethyl)*-N'',N''-*diethylguanidine* (**5bb**): yield 30%; bp 150°C/0.1 Torr; $[\alpha]_D^{29}$ -119.3 (*c* 1; EtOH); ν_{max} (film) 2960, 2910, 1620, 1440 and 1365 cm^{-1}; δ_H (d_6-DMSO, 90°C) 0.94-1.45 (m, 22H, Cy), 1.04 (t, *J*=7.3, 6H, 2xCH_3CH_2), 1.69 (m, 6H, 2xCH_3CH) and 2.90-3.25 (m, 6H, 2xCH_2CH_3 and 2xCH_3CHN) ; δ_C (d_6-DMSO, 90°C) 12.09, 25.38, 25.45, 25.64, 28.31, 28.73, 42.52, 43.57 and 154.78; *m/z* 335 (M^+, 3%), 127 (61), 99 (23), 83 (23), 72 (43), 71 (22), 69 (42), 55 (100), 43 (22) and 41 (54); HRMS *m/z* calcd for $C_{21}H_{41}N_3$: 335.3300. Found: 335.3310.

(S)-N,N-*Diethyl*-N'-*phenyl*-N''-*(1-phenylethyl)guanidine* (**8ab**): yield 30%; bp 155°C/0.1 Torr; $[\alpha]_D^{25}$ +116 (*c* 3; EtOH); ν_{max} (film) 3340 (NH), 3020, 3000, 1600, 1565, 1470, 735, 710 and 680 cm^{-1}; δ_H 1.09 (t, *J*= 7.1, 6H, 2xCH_3CH_2), 1.33 (d, *J*= 6.8, 3H, CH_3CH), 3.15-3.33 (m, 4H, 2xCH_2N), 4.47 (q, *J*= 6.8, 1H, CHN), 6.64 (d, *J*=8.2, 1H, ArH), 6.88 (m, 1H, ArH), 7.13-7.32 (m, 5H, ArH), 7.51 (m, 2H, ArH) and 7.66 (m, 1H, ArH); δ_C 12.96, 22.63, 42.75, 53.53, 121.21, 128.34, 128.38, 128.50, 128.89, 131.91, 144.03, 150.10 and 154.08; *m/z* 295 (M^+, 14%), 175 (22), 120 (35), 119 (32), 105 (100), 99 (25), 93 (29), 79 (31), 77 (80), 72 (63), 51 (28) and 44 (41); HRMS *m/z* calcd for $C_{19}H_{25}N_3$: 295.2048. Found: 295.2040.

(S)-N-*Cyclohexyl*-N',N'-*diethyl*-N''-*(1-phenylethyl)guanidine* (**8bb**): yield 78%; bp 160°C/0.1 Torr; $[\alpha]_D^{25}$ -3.6 (*c* 1; EtOH); ν_{max} (film) 3040, 3010, 1610, 1440, 750 and 695 cm^{-1}; δ_H (d_6-DMSO, 90°C) 0.99 (t, *J*=6.7, 6H, 2xCH_3CH_2), 1.07-1.21 (m, 6H, Cy), 1.30 (d, *J*=6.1, 3H, CH_3CH), 1.50-1.80 (m, 5H, Cy) 3.06 (q, *J*=6.7, 4H, 2xCH_3CH_2), 3.15 (br, s, 1H, NH), 4.50 (q, *J*=6.1, 1H, CH_3CH) and 7.13-7.36 (m, 5H, ArH); δ_C (d_6-DMSO, 90°C) 12.23, 24.33, 24.91, 33.33, 33.47, 42.25, 52.47, 54.09, 125.32, 125.64, 127.35, 147.24 and 152.98; *m/z* 301 (M^+, 7%), 105 (100), 99 (30), 79 (26), 77 (27), 72 (77), 55 (42), 44 (27), 43 (65) and 41 (39); HRMS *m/z* calcd for $C_{19}H_{31}N_3$. 301.2518. Found: 301.2515.

(S)-N-*Cyclohexyl*-N',N'-*tetramethylene*-N''-*(1-phenylethyl)guanidine* (**8bc**): yield 83%; bp 165°C/0.1 Torr; $[\alpha]_D^{29}$ +10.5 (*c* 1; EtOH); ν_{max} (film) 3070, 1645, 1600, 1440, 750 and 695 cm^{-1}; δ_H (d_6-DMSO, 90°C) 1.00-1.20 (m, 6H, Cy), 1.30 (d, *J*=6.7, 3H, CH_3), 1.55 (m, 5H, Cy), 1.74 (m, 4H, 2xCH_2CH_2N), 3.22 (m, 4H, 2xCH_2N), 3.30 (br s, 1H, NH), 4.46 (q, *J*=6.7, 1H, CH_3CH) and 7.10-7.36 (m, 5H, ArH) δ_C (d_6-DMSO, 90° C) 24.17, 24.31, 24.34, 33.60, 33.75, 47.29, 52.48, 54.12, 125.25, 125.66, 127.36, 147.73 and 152.26; *m/z* 299 (M^+, 5%), 105 (83), 98 (33), 91 (26), 79 (26), 77 (33), 70 (100), 55 (89), 43 (47), 42 (26) and 41 (63); HRMS *m/z* calcd for $C_{19}H_{29}N_3$: 299.2361. Found: 299.2357.

Enantioselective Nitroaldol Reaction. Synthesis of Nitroalcohols 10. General Procedure.- A solution of nitromethane (81 µl, 1.5 mmol), the corresponding aldehyde (1 mmol) and the guanidine **5** or **8** (0.1 mmol) in THF (3 mL) was stirred during the time and at the temperature shown in Table 1. The solvent was removed at reduced pressure (15 Torr) and the resulting residue was dissolved in ether (20 mL) and washed with 2N HCl (2x5 mL) and water (5 mL). The organic layer was dried (Na_2SO_4) and evaporated (15 Torr and 0.1 Torr in order to remove the remaining aldehyde), affording nitroalcohol **10**. The guanidine could be recuperated after neutralisation of the aqueous layer with NaOH and further extraction with ether.

1-Nitro-4-methyl-2-pentanol (**10a**). ν_{max} (film) 3380 (OH), 1530 (NO_2), 1450, 1350, 1190 and 1130 cm^{-1}; δ_H 0.95 (d, *J*=4.4, 3H, CH_3), 0.97 (d, *J*=4.4, 6H, 2xCH_3), 1.24 [m, 1H, $(CH_3)_2CH$], 1.50 (m, 1H, C*H*HCHOH), 1.81 (m, 1H, CH*H*CHOH), 2.78 (br s, 1H, OH) and 4.31-4.40 (m, 3H, C*H*OH and CH_2NO_2); δ_C 21.64, 23.04, 24.21, 42.39, 66.95 and 80.99; *m/z* 147 (M^+, 2%), 97 (33), 83 (20), 81 (20), 69 (26), 67 (21), 55 (100), 43 (60) and 41 (87).

2-Nitro-1-phenyl-1-ethanol (**10b**). ν_{max} (film) 3440 (OH), 3030, 3000, 1530 (NO_2), 1360, 1250, 1050, 720 and 680 cm^{-1}; δ_H 3.39 (br s, 1H, OH), 4.38-4.55 (m, 2H, CH_2NO_2), 5.35 (dd, *J*=3.3 and 9.4, 1H, C*H*OH) and 7.32 (s, 5H, ArH); δ_C 70.78, 81.00, 125.82, 128.70, 128.79 and 138.10; *m/z* 167 (M^+, 3%), 120 (100), 107 (42), 105 (60), 103 (52), 91 (36), 79 (51), 78 (43), 77 (97), 51 (43) and 43 (30).

Catalytic Hydrogenation of Nitroalcohols 10 to Aminoalcohols 11. General Procedure.- To a solution of the corresponding nitroalcohol **10** (2 mmol) in ethyl acetate (25 mL) was added 10% palladium on carbon (100 mg) and the resulting suspension was stirred under hydrogen atmosphere at normal pressure for 24 h. The mixture was filtered through celite and the solvent was evaporated (15 Torr) yielding quantitatively the aminoalcohols **11**.

1-Amino-4-methyl-2-pentanol (**11a**). ν_{max} (film) 3260 (OH and NH), 1635, 1350, 1130 and 1070 cm^{-1}; δ_H 0.92 (d, *J*=4.6, 3H, CH_3), 0.94 (d, *J*=4.6, 3H, CH_3), 1.16 [m, 1H, $(CH_3)_2CH$], 1.37 (m, 1H, C*H*HCHOH), 1.78 (m, 1H, CH*H*CHOH), 2.20 (br s, 3H, OH and NH_2), 2.50 (dd, *J*=8.3 and 12.7 Hz, 1H, C*H*HNH_2), 2.80 (dd, *J*=3.2 and 12.7 Hz, 1H, CH*H*NH_2) and 3.60 (m, 1H, C*H*OH); δ_C 21.95, 23.22, 24.30, 43.81, 47.84 and 69.81; *m/z* 117 (M^+, 1%), 74 (23), 73 (100), 60 (27), 59 (47), 45 (26), 43 (80) and 41 (47).

2-Amino-1-phenyl-1-ethanol (**11b**). ν_{max} (film) 3140 (OH and NH), 1465, 1350, 1225, 960 and 920 cm^{-1}; δ_H 2.50 (br s, 3H, OH and NH_2), 2.76 (dd, *J*=7.7 and 12.9, 1H, C*H*HNH_2), 2.87 (dd, *J*=4.1 and 12.9, 1H, CH*H*NH_2), 4.58 (dd, *J*=4.1 and 7.7, 1H, C*H*OH) and 7.22-7.35 (m, 5H, ArH); δ_C 49.19, 74.22, 125.81, 127.37, 128.28 and 142.69; *m/z* 137 (M^+, 2%), 107 (35), 105 (13), 91 (18), 79 (92), 78 (21), 77 (100), 51 (30) and 50 (16).

Synthesis of (1-naphthyloxy)acetaldehyde diethyl acetal (**12**). To a solution of 1-naphtol (0.97 g, 6.7 mmol) and sodium hydroxide (1.05 g, 26.2 mmol) in dimethylsulfoxide (20 mL) was added α-bromoacetaldehyde diethyl acetal (1.01 mL, 6.7 mmol). The resulting mixture was stirred at 90° C for 72 h

and the solvent was removed at reduced pressure (15 Torr). Water (15 mL) was added and the solution was extracted with ether (3x15 mL). The organic extracts were washed with water (2x10 mL), dried (Na_2SO_4) and evaporated (15 Torr) affording acetal **12** (1.1 g, 63%); ν_{max} (film) 3020, 1560, 1255, 1225, 1120, 1090, 1060, 780 and 760 cm^{-1}; δ_H 1.23 (t, *J*=7.1, 6H, 2xCH_3), 3.57-3.80 (m, 4H, 2xOCH_2CH_3), 4.13 (d, *J*=5.3, 2H, $ArOCH_2$), 4.92 [t, *J*=5.3, 1H, $CH(OC_2H_5)$], 6.75 (d, *J*=7.7, 1H, ArH), 7.26-7.46 (m, 4H, ArH), 7.73 (m, 1H, ArH) and 8.29 (m, 1H, ArH); δ_C 15.23, 62.50, 68.74, 100.51, 104.77, 120.41, 121.88, 125.00, 125.53, 125.65, 126.21, 127.27, 134.37 and 154.18; *m/z* 260 (M^+, 25%), 169 (21), 127 (25), 115 (64), 103 (100), 75 (59) and 47 (37).

Synthesis of (1-naphthyloxy)acetaldehyde (**13**). To a solution of (1-naphthyloxy)acetaldehyde diethyl acetal (**12**) (870 mg, 3.4 mmol) in THF (10 mL) was added 2N HCl (10 mL) and the mixture was stirred at room temperature for 24 h. Ether (25 mL) and water (25 mL) was added and the ethereal layer was separated. The aqueous layer was extracted with ether (3x10 mL) and all the combined organic layers were washed with water (2x10 mL) and dried over Na_2SO_4. Evaporation of the solvent (15 Torr) yielded pure aldehyde **13** (425 mg, 68%); ν_{max} (film) 3020, 1715 (CO), 1560, 1250, 1225, 1090, 780 and 755 cm^{-1}; δ_H 4.58 (s, 2H, $ArOCH_2$), 6.54 (d, *J*=7.7, 1H, ArH), 7.18-7.45 (m, 4H, ArH), 7.70 (m, 1H, ArH), 8.23 (m, 1H, ArH), and 9.83 (s, 1H, CHO); δ_C 72.66, 104.96, 121.59, 121.77, 125.33, 125.47, 125.63, 126.75, 127.52, 134.59, 153.29 and 199 43; *m/z* 186 (M^+, 65%), 157 (27), 144 (21), 143 (35), 129 (21), 128 (29), 127 (56), 115 (100) and 63 (14).

Synthesis of 1-(1-naphthyloxy)-3-nitro-2-propanol (**14**). A solution of 2-(1-naphthyloxy)acetaldehyde (**13**) (360 mg, 1.9 mmol) and nitromethane (309 µl, 5.7 mmol) in THF (8 mL) was cooled to -40° C and to this mixture was added a solution of guanidine **5ab** (62 mg, 0.2 mmol) in THF (2 mL). The resulting mixture was stirred at -40° C for 8 h and then water (2 mL) was added. The THF was evaporated at reduced pressure (15 Torr), ether was added (15 mL) and the organic layer was washed with 2N HCl (2x10 mL), water (10 mL) and dried (Na_2SO_4). After removal of the solvent *in vacuo* (15 Torr), flash chromatography (silica gel, CH_2Cl_2) gave the title compound (100 mg, 21%); $[\alpha]_D^{25}$ +4 (*c* 1; EtOH); ν_{max} (film) 3420 (OH), 3020, 1535 (NO_2), 1250, 1225, 1085, 1055, 780 and 760 cm^{-1}; δ_H 3.01 (br s, 1H, OH), 4.16 (m, 2H, $ArOCH_2$), 4.67-4.83 (m, 3H, $CHOH$ and CH_2NO_2), 6.74 (d, *J*=7.6, 1H, ArH), 7.32-7.52 (m, 4H, ArH), 7.79 (m, 1H, ArH) and 8.14 (m, 1H, ArH); δ_C 67.40, 68.57, 78.04, 105.02, 121.35, 121.38, 125.17, 125.61, 126.65, 127.63, 134.45 and 153.39; *m/z* 247 (M^+, 30%), 145 (11), 144 (100), 129 (12), 128 (12), 127 (33), 116 (21), 115 (76), 104 (24) and 60 (13).

Synthesis of 3-(isopropylamino)-1-(1-naphthyloxy)-2-propanol (propanolol) (**15**). To a solution of 1-(1-naphthyloxy)-3-nitro-2-propanol (**14**) (49 mg, 0.20 mmol) in methanol (8 mL) was added 10% palladium on carbon (30 mg) and the resulting suspension was stirred at room temperature under hydrogen atmosphere at normal pressure for 18 h. Acetone was then added (100 µl, 1.4 mmol) and the mixture was stirred for another 72 h at 50° C. The suspension was filtered through celite and the solvent evaporated (15 Torr) affording propanolol **15** which was purified by crystallization in hexane (15 mg, 30%); mp 88-89°C (lit[13]. mp 96° C racemic mixture; mp 73° C pure enantiomer); $[\alpha]_D^{25}$ +2.8 (*c* 0.8; EtOH) {lit[13]. $[\alpha]_D^{21}$ +10.6 (*c* 1.02; EtOH) *R* enantiomer}; ν_{max} (KBr) 3260 (OH and NH), 3030, 1570, 1445, 1260, 1230, 1090, 1060, 780 and 760 cm^{-1}; δ_H 1.09 (d, *J*=6.3, 6H, 2xCH_3), 2.83 (m, 1H, $CHHNH$), 2.97 (dd, *J*=3.1 and 12.1, 2H, $CHHNH$), 3.10 (br s, 2H, OH and NH), 4.03-4.21 (m, 3H, $CHOH$ and $ArOCH_2$) and 6.79 (d, *J*=7.5, 1H, ArH), 7.31-7.48 (m, 4H, ArH), 7.78 (m, 1H, ArH) and 8.24 (m, 1H, ArH); δ_C 22.89, 22.96, 48.90, 49.57, 68.47, 70.73, 104.87, 120.54, 121.79, 125.18, 125.51, 125.78, 126.36, 127.47, 134.45 and 154.30; *m/z* 259 (M^+, 5%), 144 (9), 127 (5), 116 (8), 115 (25), 72 (100), 57 (5), 56 (7), 43 (7) and 41 (5).

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