Synthesis and Investigation of a Hindered, Chiral, Bicyclic Guanidine
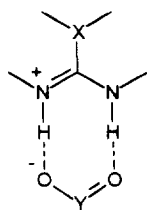
Anthony P. Davis[*] and Kevin J. Dempsey

Department of Chemistry, Trinity College, Dublin 2, Ireland

Abstract: Chiral amidines and guanidines have potential as enantioselective catalysts for reactions of nitroalkanes, through formation of hydrogen-bonded complexes with nitronate anions. With this in mind, the bicyclic guanidine **9** was synthesized from amino-alcohol **12**, employing pyrrole formation as a protection method for the amino-nitrogen. Low enantioselectivities were obtained when **9** was used as catalyst for conjugate additions of nitroalkanes. However, other applications are suggested by its hindered, chiral and strongly basic nature.
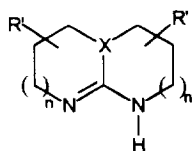
Introduction

Guanidium and amidinium units are much appreciated, by supramolecular chemists, for their ability to form hydrogen-bonded complexes **1** with a variety of oxoanions.[1,2] Bicyclic systems **2H$^+$** are especially useful in this context because of their preorganisation for binding with a single, unambiguous geometry.[1] A few years ago, we[3] and others[4] realised that these species might also have potential for synthetic chemists, especially those interested in enantioselective catalysis. Focussing on the similarity between carboxylates **3** and nitronate anions **4**, we hypothesised that the latter should also bind strongly to **2H$^+$** to give well-defined complexes **5**. Nitronate anions may be generated from nitroalkanes by deprotonation with moderately strong (organic) bases, and are intermediates in carbon-carbon bond-forming reactions such as the nitroaldol (Henry) reaction (eq. 1) and related conjugate additions (eq. 2). Catalysis of these reactions by amidines/guanidines **2** should proceed *via* **5**, and if a chiral variant of **2** were employed the involvement of such a tightly-bound and well-ordered intermediate should maximise the chance of asymmetric induction from catalyst to product. Nitro-compounds of general form **6** and **7** could be precursors for a variety of useful chiral products (notably the β-amino alcohols derivable by reduction of **6**), so that enantioselective catalysts for eqs. 1 and 2 could be of genuine practical importance.[5]

NMR experiments indicated that complexes **5** did indeed form in non-polar organic solvents,[3] and X-ray crystallography confirmed their existence in the solid state.[3,4] Encouraged by these results, we decided to synthesize a chiral variant of **2** for potential exploitation as an enantioselective catalyst. It seemed that the first requirement should be substituents which would impinge on the "binding region" of **2H$^+$**, such that electrophiles approaching the nucleophilic carbon in **5** would be placed in an asymmetric environment. The general structure **8** seemed appropriate, employing C$_2$ symmetry (in **8H$^+$**) to restrict the possible modes of interaction of an incoming electrophile with a bound nitronate. Although compounds **8** with R = CH$_2$OR' were already
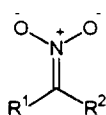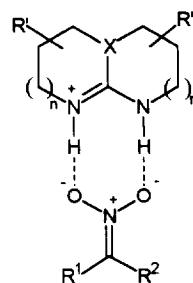
1   X = N or CR
        Y = C, P, S etc.

2   n = 0,1

3

4

5

$$R\diagdown NO_2 \;+\; R'\diagdown CHO \;\longrightarrow\; \begin{array}{c} OH \\ R\diagdown\diagup R' \\ NO_2 \end{array} \quad \mathbf{6}$$ (1)

$$R\diagdown NO_2 \;+\; R'\diagup\diagdown E \;\longrightarrow\; \begin{array}{c} R' \\ R\diagdown\diagup\diagdown E \\ NO_2 \end{array} \quad \mathbf{7}$$ (2)
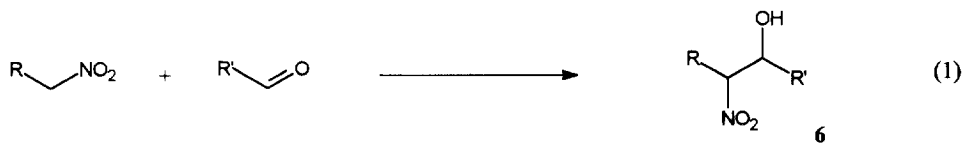
known,[1c-f] we felt that the flexibility of this class of side chains would be too great for our purposes. We therefore chose diphenylmethyl substituents for our target **9**. Molecular modelling on **9H**[+] established that a phenyl group from each substituent would be held roughly parallel to the N-H bonds, creating a hindered chiral environment for asymmetric recognition of substrates or transition states.[6]
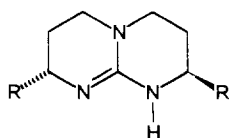
8
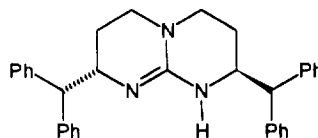
9

This paper describes the synthesis and characterisation of **9**,[6] as well as results from our investigations into its behaviour towards nitroalkanes. It should be said at this stage that these results were disappointing, providing modest reward for our preparative efforts. However, they do confirm the extremely hindered nature of this molecule, and considering its chiral, strongly basic and C_2-symmetric nature, we are hopeful that it will prove uniquely suitable for other applications in the areas of enantioselective recognition and synthesis.

Results and Discussion

As shown in Scheme 1, our synthetic strategy for **9** involved the bis-alkylation of an "NH_3-equivalent" with an N-protected chiral amine of general form **10**, followed by deprotection to a triamine and cyclisation onto a "CX_4-equivalent".

Although it raised a number of problems, this approach was readily conducted in parallel with a synthesis of the corresponding amidines **11**,[7] intended to have properties complementary to **9**. As described in the foregoing paper,[8] our starting material **12** could be prepared from (S)-methionine in acceptable yield and high enantiomeric purity. The key issue in the present work was the choice of protecting group P in **10**. Clearly it was necessary to suppress the nucleophilicity of the amino group so that it would be compatible with leaving group X. However, the most obvious protection strategies, acylation and carbamoylation, would leave the unit vulnerable to base-catalysed cyclisation. Indeed, while N-BOC-mesylate **13** reacted successfully with excess benzylamine (a suitable "NH_3-equivalent"[9]) to give amine **14** (see preceding paper),[8] attempts to bisalkylate the benzylamine with **13** led to oxazinone **15** (Scheme 2).[10] The N-acetyl-mesylate **16** behaved similarly, cyclising to oxazine **17** on treatment with a deficiency of benzylamine in the presence of sodium bicarbonate. Although phthalimido protection appeared to offer a solution to the problem, exposure of **18** to the same conditions yielded unidentified, polar side-products, probably resulting from breakdown of the phthalimido group.
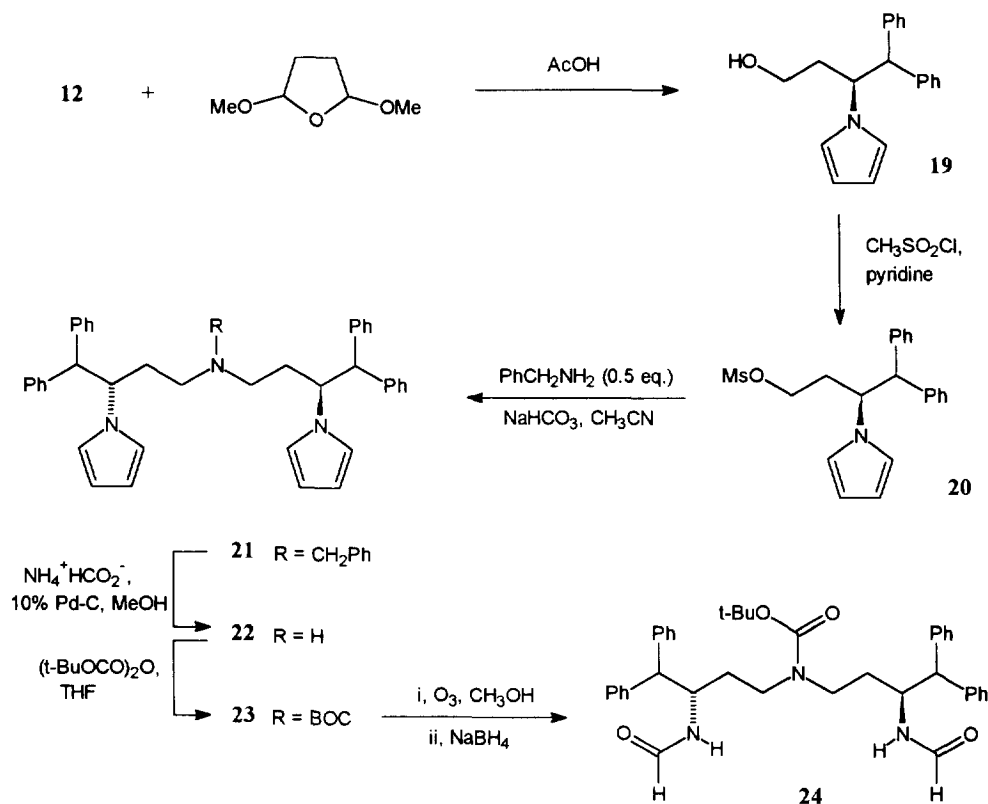

Scheme 1

11

12

PhCH₂NH₂
(as solvent)

14

13

PhCH₂NH₂ (0.5 eq.)
NaHCO₃, CH₃CN

15

Scheme 2

16

17

18
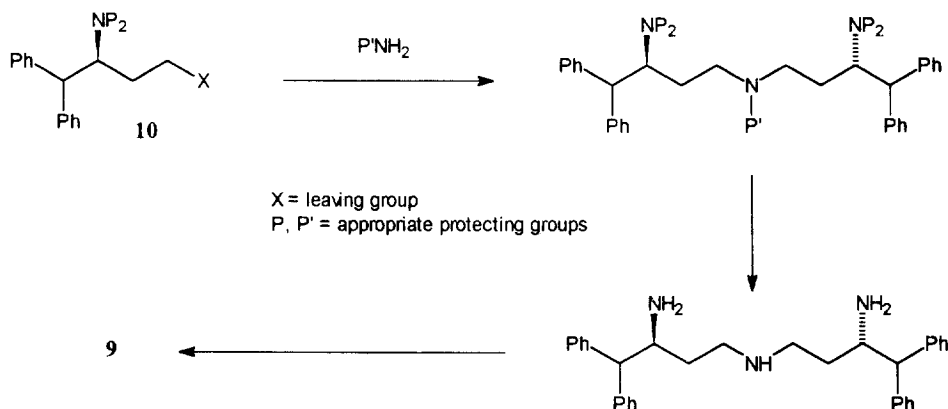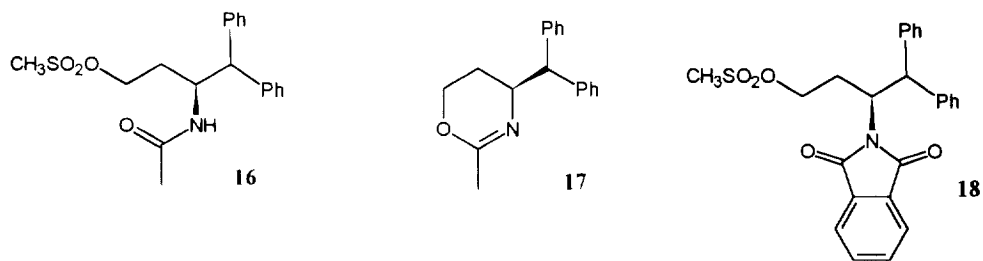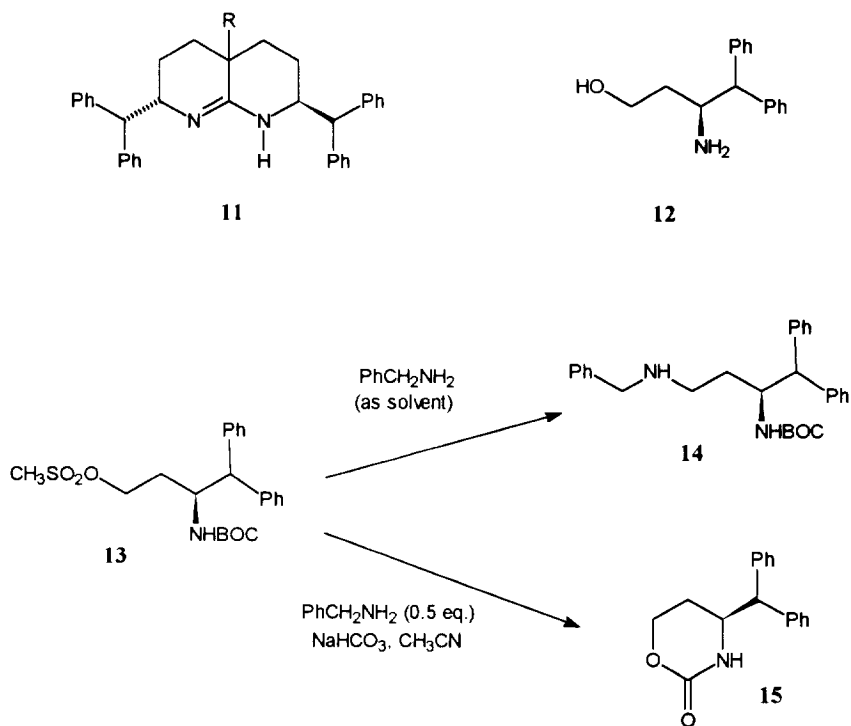
The above results highlighted a point which we had previously noted in another context, namely the dearth of N-protecting groups which suppress the nucleophilicity of the nitrogen atom while being essentially invulnerable to basic/nucleophilic conditions.[11] The solution adopted on that occasion was protection of the nitrogen atom as part of an unsubstituted pyrrole ring, originally introduced by Kashima *et al.* as a protection method for peptide synthesis.[12,13] We were pleased to find that this method could also be applied in the present case. As shown in Scheme 3, treatment of amino-alcohol **12** with 2,5-dimethoxytetrahydrofuran in acetic acid gave the N-protected derivative **19** in 70% yield. Mesylation proceeded successfully to give **20**, again in 70% yield. Prolonged treatment of **20** with benzylamine (0.5 equiv.) and a large excess of NaHCO₃ in acetonitrile gave the dialkylation product **21** in nearly quantitative yield. At this point it was possible to confirm the

enantiomeric purity of the material by ^{1}H NMR, as samples of **21** derived from optically impure **12**[8] showed additional peaks due to the R*S* diastereomer. The regeneration of "pyrrole-protected" amino groups may be accomplished by ozonolysis to formamides followed by hydrolysis. Ozonolysis of **21** was unsuccessful, possibly because of interference from the tertiary amino group. However, after debenzylation of **21** to **22**, and BOC-protection to give **23**, the ozonolysis proceeded smoothly to yield bis-formamide **24** (62% from **21**).


Scheme 3

The deprotection of **24** to give the hydrochloride salt of triamine **25** proceeded rapidly in methanolic HCl (Scheme 4). However, the triamine itself proved to be highly sensitive to the atmosphere (probably to CO_2), requiring that it be generated and handled under argon. Several methods were assessed for the final step of the synthesis, the conversion of **25** into **9**. Our experience paralleled that of Gleich and Schmidtchen[14] in their synthesis of **8** (R = CH$_2$OSiPh$_2$t-Bu), in that single-step methods [C(OR)$_4$/H$^+$, or (MeS)$_3$C$^+$ TfO$^-$] were less successful than the two-step procedure *via* thiourea **26** shown in Scheme 4. The product **9H$^+$**, presumably accompanied by I$^-$, was identified by NMR and high resolution MS. The free guanidine **9** could be obtained by shaking solutions of this salt in CH$_2$Cl$_2$ with 3 M aqueous sodium hydroxide, followed by evaporation. Dissolution of **9** in benzene and exposure to the atmosphere resulted in precipitation of white crystalline

material. After recrystallisation from acetonitrile-benzene, this compound analysed correctly for the hydrated hydrogen carbonate, $9H^+.HCO_3^-.2H_2O$.
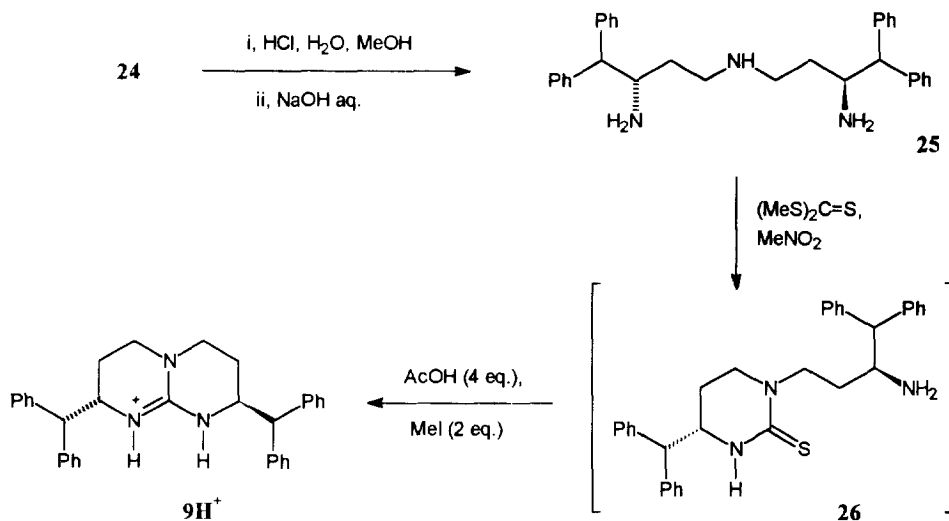
Scheme 4

As discussed previously,[6] cation $9H^+$ was found by NMR to form complexes with carboxylate anions, discriminating (in an analytical sense) between the enantiomers of Naproxenate **27**. Indeed, the observation of a single set of signals when $9H^+$ was combined with (S)-Naproxenate provided confirmation that the guanidine was enantiomerically pure. However, the behaviour of **9** with the nitroalkane/nitronate system did not conform to expectation. On the basis of our earlier work,[3] we anticipated that **9** should deprotonate nitroalkanes extensively in non-polar solvents, due to stabilisation of the nitronate anions by formation of complexes **28**. Unfortunately, when **9** was exposed to nitroethane or nitromethane in either C_6D_6 or CD_3CN, we observed no evidence of nitronate formation. This may be contrasted with the quantitative proton transfer observed between the unsubstituted guanidine **29** and nitroethane in either solvent.[3] We may presume that some proton transfer did take place with the chiral guanidine, as **9** was found to catalyse a number of additions of nitroalkanes to α,β-unsaturated ketones (e.g. eq. 3). However, the enantiomeric excesses for these reactions were of little interest, being in the range 9 - 12%.

[R, R' = (a) Me, H; (b) Et, H; (c) Me, CO₂Et]
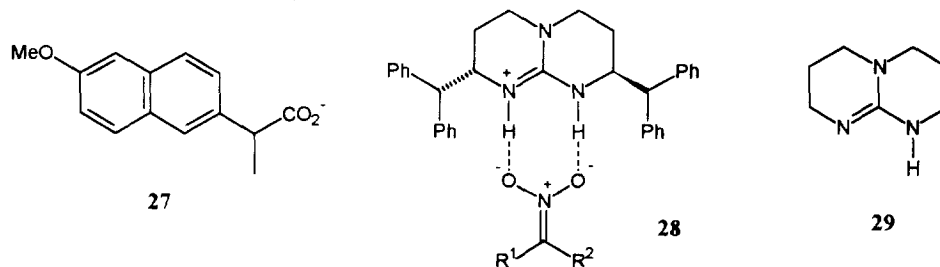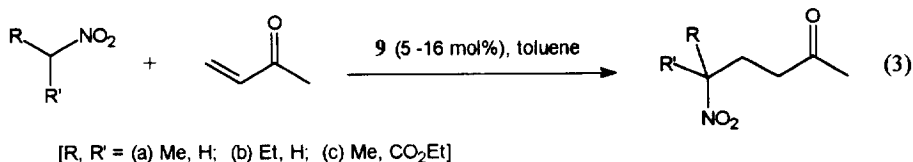
We suspect that this disappointing performance may be largely due to the hindered nature of **9**, revealed (for example) by its failure to react with methyl iodide, even on prolonged exposure.[6] In our determination to create a restricted, chiral environment around the binding functionality in **9H⁺**, we may have left insufficient room for formation of **28**, or, if **28** does form, for reaction to take place. However, this hindrance may well prove valuable in other contexts, and we are hopeful that a positive role may yet be found for **9** in asymmetric synthesis.

Experimental Section

General: All solvents were distilled before use. When reactions were carried out under dry conditions CH_2Cl_2 and acetonitrile were distilled from calcium hydride, nitroalkanes were distilled from calcium chloride and THF from sodium/benzophenone. The R_f values quoted are for thin-layer chromatography (tlc) on Merck DC-Fertigplatten Kieselgel F-254 plates. Flash column chromatography was performed on Merck Kieselgel 60 (particle size 0.040 - 0.063 mm). All melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter using the D line at 589 nm. All measurements were recorded in CH_2Cl_2 unless otherwise stated. ^1H NMR spectra were recorded in deuterated chloroform, unless otherwise stated, on a Bruker MSL-300 spectrometer (300.13 MHz) with tetramethylsilane as internal standard. Unless otherwise stated, ^{13}C NMR spectra were recorded in deuterated chloroform on the same instrument at 75.47 MHz using the central chloroform peak as reference (taken to be 77.00 p.p.m.). Signals were assigned with the assistance of the DEPT technique. IR spectra were recorded neat, unless otherwise stated, on a Perkin-Elmer 883 spectrometer. High Pressure Liquid Chromatography (HPLC) was performed using a Waters 994 instrument fitted with a photodiode array detector, using a Nucleosil C_{18} column (5 micron particle size, 15 cm x 4.6 mm) eluting with 100% methanol at a rate of 1 ml/minute. High resolution mass spectra (HRMS) were recorded in the Department of Pure and Applied Chemistry at the University of Strathclyde or at Glaxo Group Research laboratories, Ware.

(S)-1,1-Diphenyl-2-(1-pyrrolyl)-butan-4-ol **19**. To a solution of (S)-2-amino-1,1-diphenylbutan-4-ol (**12**) (105 mg, 0.44 mmol) in acetic acid (3 ml) was added 2,5-dimethoxytetrahydrofuran (57 µl, 0.44 mmol, 1 eq.). The mixture was stirred at 80 °C for 40 min. Water (10 ml) and CH_2Cl_2 (30 ml) were added to the dark reaction mixture which was then washed with saturated aqueous sodium carbonate (5 x 30 ml) and water (30 ml). The combined aqueous layers were then extracted with CH_2Cl_2 (2 x 10 ml) and the combined organic layers dried ($MgSO_4$). Evaporation followed by flash chromatography, eluting with hexane - ethyl acetate (2:1) yielded pyrrole **19** (89 mg, 70%), R_f 0.45. Recrystallisation from hexane - ethyl acetate gave colourless needles, m.p. 107 °C, $[\alpha]_D$ 15.4 (c = 4.23); v_{max}/cm^{-1} 3380, 1470, 1265, 730; δ_H 7.4 - 6.94 (10 H, m, arom H), 6.6 [2 H, t, J 2.08 Hz, N(CH=CH)₂], 5.97 [2 H, t, J 2.08 Hz, N(CH=CH)₂], 4.9 - 4.8 (1 H, ddd, NCH), 4.24 (1 H, d, J 11.3 Hz, CHPh₂), 3.5 - 3.43 (1 H, m, OCH_aH$_b$CH₂), 3.3 - 3.2 (1 H, m, OCH$_a$$H_b$CH₂), 2.06 - 1.95 (1 H, m, OCH₂CH$_c$H$_d$), 1.88 - 1.76 (1 H, m, CH₂CH$_c$$H_d$); δ_C 141.86, 141.59 (arom C-1'), 128.08, 128.01, 127.47, 126.84, 126.36, (arom CH), 119.35 [N(CH=CH)₂], 107.81 [N(CH=CH)₂], 60.14 (CHPh₂), 59.35 (OCH₂CH₂), 58.65 (NHCH) and 37.09 (OCH₂CH_2).

This compound developed an orange colour on exposure to the atmosphere over a period of hours, and was generally used in the following procedure immedietly after chromatography.

(S)-4-Methanesulphonyloxy-1,1-diphenyl-2-(1-pyrrolyl)-butane **20**. To a solution of pyrrolyl alcohol **19** (57 mg, 0.194 mmol) in anhydrous pyridine (157 µl, 1.94 mmol, 10 eq.) was added methanesulphonyl chloride (15 µl, 0.194 mmol, 1 eq.) dropwise under argon at 0 °C. Crystals of pyridinium hydrochloride appeared after *ca.* 20 min and the mixture was stirred at 0 °C for a further 2 h. Ice cold aqueous HCl was then used to acidify the mixture (litmus paper). The resulting oily suspension was extracted with cold CH_2Cl_2 (2 x 15 ml) and the combined organic layers were washed successively with ice cold HCl (10 ml), Na_2CO_3 (10 ml) and brine (10 ml). The extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the mesylate **20** (51 mg, 71%) as a clear oil which solidified on standing and was used without further purification. Crystals were obtained from hexane - ethyl acetate, m.p. 145-146 °C, $[\alpha]_D$ 19 (c = 0.68), R_f 0.45 (hexane - ethyl acetate, 2:1); v_{max}/cm^{-1} 1480, 1350, 1170, 730; δ_H 7.38 - 7.02 (10 H, m, arom *H*), 6.58 [2 H, t, *J* 2.03 Hz, N(C*H*=CH)$_2$], 5.98 [2 H, t, *J* 2.03 Hz, N(CH=C*H*)$_2$], 4.86 - 4.77 (1 H, ddd, NC*H*), 4.22 (1 H, d, *J* 11.3 Hz, C*H*Ph$_2$), 4.08 - 4.02 (1 H, m, OC*H$_a$*H$_b$CH$_2$), 3.7 - 3.63 (1 H, m, OCH$_a$*H$_b$*CH$_2$), 2.81 (3 H, s, OSO$_2$C*H$_3$*), 2.3 - 2.2 (1 H, m, OCH$_2$C*H$_c$*H$_d$), 2.04 - 1.92 (1 H, m, OCH$_2$CH$_c$*H$_d$*); δ_C 141.05 (arom C-1'), 129.03, 128.22, 128.02, 127.36, 127.11, 126.54 (arom *C*H), 119.18 [N(*C*H=CH)$_2$], 108.29 [N(CH=*C*H)$_2$], 66.97 (O*C*H$_2$), 59.44 (*C*HPh$_2$), 58.53 (N*C*H), 36.81 (OSO$_2$*C*H$_3$) and 34.13 (O*C*H$_2$CH$_2$).

N-Benzyl-N,N-bis[(S)-4,4-diphenyl-3-(1-pyrrolyl)-butyl]amine **21**. To a solution of mesylate **20** (87 mg, 0.24 mmol) in anhydrous acetonitrile (1 ml) was added solid sodium hydrogen carbonate (200 mg, 1.88 mmol, 8 eq.) and benzylamine (13 µl, 0.12 mmol, 0.5 eq.) under argon. The mixture was stirred at 70 °C for 48 h. CH_2Cl_2 (20 ml) was added and the solid sodium hydrogen carbonate was removed by filtration and washed until colourless with CH_2Cl_2. The combined filtrate was washed with water (2 x 30 ml), brine (20 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the title compound **21** (108 mg, 70%) isolated by flash chromatography, eluting with hexane - ethyl acetate (2:1), $[\alpha]_D$ 7.4 (c = 1.58), R_f 0.76 [HRMS; found 701.9173 (M$^+$), $C_{47}H_{47}N_3O$ requires 701.9169]; v_{max}/cm^{-1} 1490, 730; δ_H 7.39 - 7.0 (25 H, m arom *H*), 6.33 [4 H, t, *J* 2.1 Hz, N(C*H*=CH)$_2$], 5.89 [4 H, t, *J* 2.1 Hz, N(CH=C*H*)$_2$], 4.52 - 4.45 (2 H, ddd, NC*H*), 4.09 (2 H, d, *J* 11 Hz, C*H*Ph$_2$), 3.42, 3.03 (2 H, ABq, *J* 13.9 Hz, PhC*H$_2$*), 2.24 - 2.1 (2 H, m, NC*H$_2$*CH$_2$), 1.95 - 1.75 (4 H, m, NC*H$_2$*CH$_2$ and NCH$_2$C*H$_2$*), 1.7 - 1.55 (2 H, m, NCH$_2$C*H$_2$*); δ_C 142.04, 141.68, 139.41 (arom C-1'), 128.77, 128.61, 128.17, 128.05, 127.51, 126.76, 126.27 (arom *C*H), 119.27 [N(*C*H=CH)$_2$], 107.4 [N(CH=*C*H)$_2$], 61.51 (*C*HCHPh$_2$), 58.94 (*C*HPh$_2$), 58.2 (Ph*C*H$_2$), 50.43 (N*C*H$_2$CH$_2$), 31.9 (NCH$_2$*C*H$_2$). Unreacted mesylate **20** and the monoalkylation product (9 mg, 10%) were also recovered from the column.

In later experiments it was found that the reaction could be driven to completion by using an increased amount of $NaHCO_3$ (20 eq.), removing this material by filtration when the reaction stopped progressing, and adding a fresh sample. This modification removed the need for purification by chromatography.

N,N-Bis[(S)-4,4-diphenyl-3-(1-pyrrolyl)-butyl]amine **22**. A solution of the benzylamine **21** (71 mg, 0.109 mmol) in anhydrous methanol (1 ml) was added to a reaction vessel containing palladium on activated charcoal (10%, 110 mg) under anhydrous methanol (1.5 ml). Ammonium formate (126 mg, 2 mmol, ~18 eq.) was then added under argon and the mixture stirred and heated under reflux for 2.5 h. During the reflux white solid collected on the inner walls of the reflux condenser. Subsequent analysis indicated that this material was not derived from the starting material **21**. The catalyst was removed by filtering the reaction mixture through a plug of celite which was then washed through with methanol. The solvent was removed under reduced pressure to yield the title compound **22** as a white solid (43 mg, 70%); A sample was crystallised from a

methanol solution by adding CH₂Cl₂, m.p. 56-58 °C (Found C, 85.23; H, 7.48; N, 7.69. C₄₀H₄₁N₃ requires C, 85.17; H, 7.33; N, 7.45%); v_{max}/cm⁻¹ (KBr disc) 3428, 1490, 723; δ_H 7.41 - 6.95 (20 H, m, arom *H*), 6.63 [4 H, t, *J* 2.1 Hz, N(C*H*=CH)₂], 5.85 [4 H, t, *J* 2.1 Hz, N(CH=C*H*)₂], 4.74 - 4.65 (2 H, ddd, NC*H*), 4.26 (2 H, d, C*H*Ph₂), 2.26 - 2.18 [2 H, m, HN(C*H*ₐHᵦCH₂)₂], 2.1 - 2.01 [2 H, m, HN(CHₐ*H*ᵦCH₂)₂] and 1.8 - 1.7 [4 H, m, HN(CH₂C*H*₂)₂]; δ_C 143.65, 143.13 (arom C-1'), 129.76, 129.14, 128.9, 128.66, 127.79, 127.04 (arom C*H*), 120.24 [N(*C*H=CH)₂], 108.55 [N(CH=*C*H)₂], 62.45 (*C*HCHPh₂), 59.77 (*C*HPh₂), 47.19 (N*C*H₂CH₂), 34.71 (NCH₂*C*H₂).

N-tert-Butoxycarbonyl-N,N-bis[(S)-4,4-diphenyl-3-(1-pyrrolyl)-butyl]amine **23**. To a solution of amine **22** (125 mg, 0.23 mmol) in anhydrous THF (5 ml) was added di-*tert*-butyl dicarbonate (51 μl, 0.23 mmol) dropwise under argon at 0 °C. The mixture was stirred at 0 °C for 30 min and left stirring overnight. The solvent was removed under reduced pressure and the residue redissolved in ethyl acetate (10 ml). The solution was washed successively with HCl (20 ml), water (20 ml) and brine (20 ml), dried (Na₂SO₄) and evaporated to yield the title carbamate **23**, used without further purification, [α]_D 18.5 (c = 1.28), R_f 0.68 (hexane - ethyl acetate, 2:1); v_{max}/cm⁻¹ 1686, 1166, 730; δ_H 7.19 - 6.86 (20 H, m, arom C*H*), 6.3 [4 H, t, *J* 2.1 Hz, N(C*H*=CH)₂], 5.84 [4 H, t, *J* 2.1 Hz, N(CH=C*H*)₂], 4.6 - 4.18 (2 H, ddd, NC*H*), 4.07 (2 H, d, *J* 10 Hz, C*H*Ph₂), 3.00 - 2.77 [2 H, m, N(C*H*ₐHᵦCH₂)₂], 2.6 - 2.46 [2 H, m, N(CHₐ*H*ᵦCH₂)₂], 1.9 - 1.78 [2 H, m, N(CH₂C*H*ₐHᵈ)₂], 1.73 - 1.5 [2 H, m, N(CH₂CHₐ*H*ᵈ)₂], 1.27 (9 H, s, C*H*₃); δ_C 155.18 (*C*=O), 141.66, 141.41 (arom C-1'), 128.84, 128.12, 127.49, 126.83, 126.39 (arom C*H*), 119.14 [N(*C*H=CH)₂], 107.81 [N(CH=*C*H)₂], 61.59 (*C*HPh₂), 59.00 (*C*HCHPh₂), 44.73 (N*C*H₂CH₂), 32.98 (NCH₂*C*H₂), 27.41 (*C*H₃).

N-tert-Butoxycarbonyl-N,N-bis[(S)-4,4-diphenyl-3-formamidobutyl]amine **24**. To a solution of carbamate **23** (148 mg, 0.223 mmol) in a minimum quantity of CH₂Cl₂ (0.5 ml) was added anhydrous methanol (15 ml). The solution was cooled on an ethyl acetate/liquid nitrogen slush bath and ozone was passed through until a deep blue colour had been maintained for 5 min. The solution was purged, first with oxygen and then argon to yield a clear solution. Sodium borohydride (170 mg, 20 eq.) was added portionwise under argon at 0 °C (ice bath). The solvent was removed under reduced pressure and the residue was partitioned between water (35 ml) and ethyl acetate (35 ml). The aqueous layer was washed with ethyl acetate (2 x 20 ml) and the combined organic layers washed with water (20 ml) and brine (20 ml). The extract was dried (MgSO₄) and the solvent removed under reduced pressure to yield the title amide **24** (122 mg, 88.7%) as a colourless solid, m.p. 118-120 °C, [α]_D -26.9 (c = 1.35); v_{max}/cm⁻¹ 1679 (broad), 1454 , 1079; δ_H 7.9 (2 H, d, *J* 1.6 Hz, NHC*H*O), 7.3 - 7.15 (20 H, m, arom *H*), 6.13 (1 H, br s, N*H*), 5.24 (1 H, br s, N*H*), 4.86 - 4.68 (2 H, m, NC*H*), 1.27 (9 H, s, C*H*₃); δ_C 160.97 (N*C*OO), 155.5, 155.42 (NH*C*HO), 141.95, 141.86 (arom C-1'), 128.9, 128.81, 128.52, 128.39, 128.31, 128.02, 126.79, 126.70 (arom C*H*), 79.62 [O*C*(CH₃)₃], 60.33 (*C*HPh₂), 56.89 (*C*HCHPh₂), 44.62 (N*C*H₂CH₂), 32.96 (NCH₂*C*H₂), 28.23 (*C*H₃).

N,N-Bis[(S)-3-amino-4,4-diphenylbutyl]amine **25**. A solution of methanolic hydrochloric acid (3 ml, 3 M, from dilution of conc. HCl with methanol) was degassed by refluxing under argon for 1 hour. The solution was then cooled, bis-formamide **24** (38 mg, 0.06 mmol) was added and the mixture stirred under reflux for 3 h. The reaction mixture was allowed to cool to room temperature and the reflux condenser removed. The mixture was gently warmed and stirred vigorously under reduced pressure to remove the solvent yielding the hydrochloride salt of the triamine **25** as an off white solid, pure by HPLC (retention time = 1.12 min), [α]_D -12.6 (c = 2.62, MeOH); v_{max}/cm⁻¹ 3286, 1599, 1530; δ_H (CD₃OD) 7.5 - 7.22 (10 H, m, arom C*H*), 4.5 - 4.45 (2 H, m, NC*H*), 4.12 (2 H, d, *J* 11.3 Hz, C*H*Ph₂) 3.18 - 3.17 [2 H, m, N(C*H*ₐHᵦCH₂)₂], 3.03 - 2.9 [2 H, m, N(CHₐ*H*ᵦCH₂)₂], 2.1 - 2.0 [4 H, m, N(CH₂C*H*₂)₂]; δ_C 141.28, 140.41 (arom C-1'), 130.6, 130.39, 129.05, 128.71 (arom C*H*), 56.51 (*C*HPh₂), 52.92 (*C*HCHPh₂), 45.31 (N*C*H₂CH₂), 29.62 (NCH₂*C*H₂). Generation of

free triamine **25** was achieved by partitioning the above solid between degassed aq. 2 M NaOH and CH_2Cl_2 under argon. The organic layer was dried by passage into a two neck flask containing $MgSO_4$ fitted with a filter stick, followed by filtration through the sintered glass into an argon filled vessel. The solvent was removed under reduced pressure to yield the title compound as a white foam, pure by HPLC (retention time = 1.48 min). When the IR was recorded, peaks presumed to be associated with the uptake of atmospheric carbon dioxide were observed (1495 and 1453 cm^{-1}), increasing in intensity with time. Samples which had been exposed to the atmosphere gave multiple broad peaks on HPLC.

(4S,8S)-4,8-Bis(diphenylmethyl)-1,5,7-triazabicyclo[4.4.0]dec-5-ene hydroiodide **9.HI***. Bis-formamide **24** (50 mg, 0.08 mmol) was deprotected as above to yield triamine **25**. Anhydrous nitromethane (1.8 ml) was added to the triamine under argon, causing a cloudy suspension. Dimethyl trithiocarbonate (11.24 µl, 0.1 mmol, 1.25 eq.) was added as a solution in nitromethane (0.2 ml) dropwise over a period of 1 h. The mixture was refluxed for 2 h, then allowed to cool. Acetic acid (19 µl, 3.2 mmol, 4 eq.) and methyl iodide (10 µl, 2 eq.) were added. The reaction was refluxed for 3 h and then left stirring at room temperature overnight. The mixture was then evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 and water. Excess reagent was removed by passing a CH_2Cl_2 solution of the product through a plug of silica eluting with further CH_2Cl_2 and then recovering the desired **9.HI*** by elution with methanol - CH_2Cl_2 (1:4) as a foam (32 mg, 84.55%), HPLC retention time = 0.89 min [HRMS; found 472.2763 (MH^+), $C_{33}H_{34}N_3$ requires 472.2753]; δ_H 7.37 - 7.14 (20 H, m, arom H), 4.75 (br s, NH), 4.38 - 4.0 (2 H, m, NCH), 4.00 (2 H, m, J 10.2 Hz, CHPh$_2$), 3.44 - 3.23 [4 H, m, N(CH_2CH$_2$)$_2$], 1.91 - 1.80 [4 H, m, N(CH$_2$CH_2)$_2$]; δ_C 151.41 (guanidinium C), 140.70, 139.50 (arom C-1'), 129.02, 128.92, 128.39, 128.15, 128.01, 127.76, 127.19, 127.12 (arom CH), 56.32 (CHPh$_2$), 51.43 (CHCHPh$_2$), 45.89 (NCH$_2$CH$_2$), 25.14 (NCH$_2$$CH_2$).

*The anion was presumed to be I⁻ because of the absence of nmr signals for OAc⁻, the only reasonable alternative. However, it was not positively identified.

Generation of the free guanidine **9**. The procedure was conducted using degassed solvents under an atmosphere of argon. A sample of **9.HI** (12 mg, 0.024 mmol) was dissolved in CH_2Cl_2 (8 ml). The resulting solution was shaken with aq. NaOH (3 M, 8 ml). The organic layer was removed and washed with water (2 x 10 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure to yield the free guanidine as a white solid, HPLC retention time = 1.24 min; δ_H 7.3 - 7.0 (20 H, m, arom CH), 3.76 (4 H, m, CHPh$_2$ and NCH), 2.28 [4 H, m, N(CH_2CH$_2$)$_2$], 1.4 - 1.2 [4 H, m, N(CH$_2$CH_2)$_2$].

Formation and recrystallisation of the hydrogen carbonate of **9**. A solution of the hydrochloride salt of **9** (19 mg, *ca.* 0.037 mmol) in CH_2Cl_2 (5 ml) was shaken with aq. NaOH to liberate the free guanidine as above. The organic layer was removed and stirred with water for 3 h. After separation the organic phase was dried (MgSO$_4$), concentrated under reduced pressure and the residue redissolved in benzene (0.3 ml). On standing overnight crystals precipitated from the solution. Recrystallisation from acetonitrile - benzene (1:1) yielded the hydrogen carbonate of **9** (13 mg, *ca.* 60%), m.p. 196.5 - 197 °C (Found: C, 71.33; H, 6.61; N, 7.30. $C_{34}H_{35}N_3O_3.2H_2O$ requires C, 71.68; H, 6.9, N, 7.37%); δ_H (CD$_3$CN) 7.7 (2 H, br s, NH), 7.46 - 7.16 (20 H, m, arom H), 4.33 - 4.29 (2 H, m, NCH), 3.97 (2 H, d, J 10.5 Hz, CHPh$_2$), 3.36 - 3.20 [4 H, m, N(CH_2CH$_2$)$_2$], 1.95 - 1.92 [2 H, m, N(CH$_2$CH_aH$_b$)$_2$], 1.72 - 1.57 [2 H, m, N(CH$_2$CH$_a$$H_b$)$_2$].

References and Footnotes

1.   For bicyclic systems see e.g.: (a) Heinzer, F.; Soukup, M.; Eschenmoser, A. *Helv. Chim. Acta* **1978**, *61*, 2851. (b) Müller, G.; Riede, J; Schmidtchen, F.P. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1516. (c) Gleich, A.; Schmidtchen, F.P.; Mikulcik, P.; Müller G. *J. Chem. Soc., Chem. Commun.* **1990**, 55. (d) Schiessl, P.; Schmidtchen, F.P. *J. Org. Chem.* **1994**, *59*, 509. (e) Galán, A.; Andreu, D.; Echavarren, A.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511. (f) Deslongchamps, G.; Galán, A.; de Mendoza, J.; Rebek, J. Jr. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 61. (g) Chicharro, J.-L.; Prados, P.; de Mendoza, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1193. (h) Corey, E.J.; Ohtani, M. *Tetrahedron Lett.*, **1989** 30, 5227. (i) Convery, M.A.; Davis, A.P.; Dunne, C.J.; MacKinnon, J.W. *J. Chem. Soc., Chem. Commun.* **1994**, 2557.

2.   For other systems, see e.g.: (a) Dietrich, B.; Fyles, T.M.; Lehn, J.-M.; Pease, L.G.; Fyles, D.L. *J. Chem. Soc., Chem. Commun.* **1978**, 934; (b) Göbel, M.W.;. Bats, J.W; Dürner, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 207; (c) Terfort, A.; von Kiedrowski, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 654; (d) Smith, J.; Ariga, K.; Anslyn, E.V. *J. Am. Chem. Soc.* **1993**, *115*, 362; (e) Fan, E.; Van Arman, S.A.; Kincaid, S.; Hamilton, A.D. *J. Am. Chem. Soc.* **1993**, *115*, 369.

3.   Boyle, P.H.; Convery, M.A.; Davis, A.P.; Hosken, G.D.; Murray, B.A. *J. Chem. Soc., Chem. Commun.* **1992**, 239.

4.   (a) van Aken, E.; Wynberg, H; van Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1992**, 629. (b) van Aken, E., Ph.D. thesis, University of Groningen, **1992**.

5.   Since the inception of the present work, a highly effective enantioselective catalytic variant of the nitroaldol reaction, employing chiral lanthanide complexes, has been reported by Shibasaki and co-workers. This group has also demonstrated the value of such methodology in the synthesis of enantiomerically pure β-amino alcohols. See e.g.: (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, 114, 4418. (b) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, 34, 855. (c) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, 34, 2657. Simple chiral guanidines have been used recently by Nájera and co-workers to give moderate enantioselectivity in the nitro-aldol: (d) Chinchilla, C.; Nájera, C.; Sánchez-Agulló, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393. Various chiral amines have been employed, again with moderate success, for enantioselective catalysis of conjugate additions of nitroalkanes. See e.g. ref. 4b and: (e) Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc, Perkin Trans. 1* **1981**, 547. (f) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4*, 173. (g) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233.

6.   Preliminary communication: Boyle, P.H.; Davis, A.P.; Dempsey, K.J.; Hosken, G.D. *J. Chem. Soc., Chem. Commun.* **1994**, 1875.

7.   Convery, M.A.; Davis, A.P.; Dunne, C.J.; MacKinnon, J.W. *Tetrahedron Lett.* **1995**, *36*, 4279.

8.   Boyle, P.H.; Davis, A.P.; Dempsey, K.J.; Hosken, G.D., preceding paper in this Journal.

9.   Son, B.; Czech, B.; Bartsch, R.A. *Synthesis* **1984**, 776.

10.   For similar transformations, reported after completion of the present work, see: Curran, T.P.; Pollastri, M.P.; Abelleira, S.M.; Messier, R.J.; McCollum, T.A.; Rowe, C.G. *Tetrahedron Lett.* **1994**, *35*, 5409.

11.   Davis, A.P.; Egan, T.J. *Tetrahedron Lett.* **1992**, *33*, 8125.

12.   Kashima, C.; Maruyama, T.; Harada, K.; Hibi, S.; Omote, Y. *J. Chem. Res. (S)* **1988**, 62; *(M)* 0601.

13.   Protection as 2,5-dimethylpyrrole had been described previously by Meakins and co-workers. However, the deprotection conditions for this variant are somewhat vigorous. See: Bruekelman, S.P.; Leach, S.E.;Meakins, G.D.; Tirel, M.D. *J. Chem. Soc., Perkin Trans. 1* 1984, 2801.

14.   Gleich, A.; Schmidtchen, F.P. *Chem. Ber.* **1990**, *123*, 907.