Enantioselective Synthesis of α-Amino Nitriles from *N*-Benzhydryl Imines and HCN with a Chiral Bicyclic Guanidine as Catalyst

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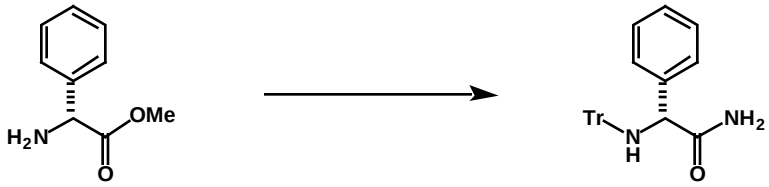
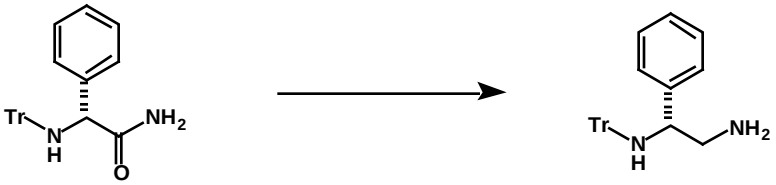
Supporting Information: Full experimental procedures for the synthesis and X-ray crystallographic analysis of **1**.

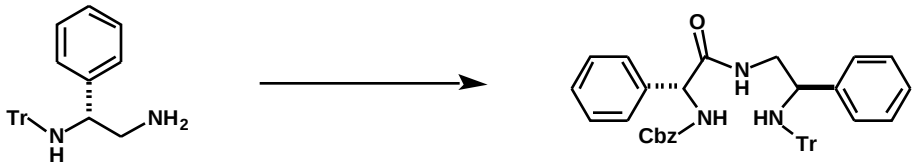


(*R*)-*N*$^{\alpha}$-Triphenylmethylphenylglycinamide: Into a 0 °C solution of methyl (*R*)-phenylglycinate (46.2 mmol) in methanol (50 mL) was bubbled ammonia for 30 min. The flask was sealed and stirred at 23 °C for 36 h. Concentration gave a clear oil that was dissolved in methylene chloride (100 mL) and treated with triethylamine (58 mmol) and triphenylmethyl chloride (56 mmol) with stirring at 23°C for 2 h. The mixture was diluted with 20% aqueous $NaHCO_3$ (150 mL) and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4, and concentrated to give a pale yellow solid which, when washed with ether and dried, gave a white solid (82% yield). mp 214-217 °C; $[\alpha]_D^{23}$ -94.3 (*c* 1.07 $CHCl_3$); FTIR (film) 3456, 3306, 3187, 3085, 3059, 3029, 1671, 1610, 1598, 1492, 1449, 1376, 1031, 906 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, 6H, *J* = 8.4 Hz), 7.28 (m, 4H), 7.23 (m, 10H), 5.98 (bs, 1H), 5.01 (bs, 1H), 4.22 (d, 1H, *J* = 4.7 Hz), 3.52 (d, 1H, *J* = 4.7 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 145.5, 141.2, 129.1, 128.8, 128.0, 127.8, 127.1, 126.9, 72.5, 62.4 ppm; FABMS 415 $[M+Na]^+$; HRMS calcd for $[C_{27}H_{24}N_2O+Na]^+$: 415.1786 , found: 415.1792.

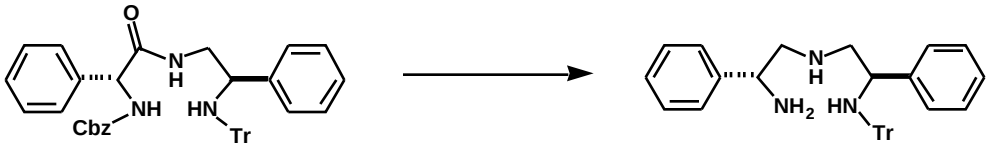


(1*R*)-*N*^{1}-Triphenylmethyl-1-phenyl-1,2-ethanediamine (6): (*R*)-*N*$^{\alpha}$-Triphenyl-methyl-phenylglycinamide was heated at reflux in ether (165 mL) with lithium aluminum hydride (6.75 g) for 48 h. The gray suspension was diluted with ether (500 mL), and slow addition of water (6.75 g), 15% aqueous NaOH (6.75 g), and then water (20.25 g) with vigorous stirring

over 2 h gave a white-gray suspension that was filtered and concentrated to yield a white foam (**6**, 80% yield). $[\alpha]_D^{25}$ -94.4 (*c* 0.1.08 $CHCl_3$); FTIR (film) 3390, 3297, 3058, 3027, 3002, 2957, 2856, 1865, 1613, 1595, 1490, 1448, 1055, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, 6H, *J* = 7.5 Hz), 7.23 (m, 14H), 3.61 (bs, 1H), 2.78 (bs, 1H), 2.39 (dd, 1H, *J* = 12.4, 3.7 Hz), 1.92 (dd, 1H, *J* = 12.4, 6.6 Hz), 0.60 (bs, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 144.9, 129.0, 128.1, 127.7, 127.3, 126.9, 126.3, 72.0, 59.0, 48.1 ppm; CIMS 379 $[M+H]^+$ 243; HRMS calcd for $[C_{27}H_{26}N_2+H]^+$: 379.2174 , found: 379.2156.

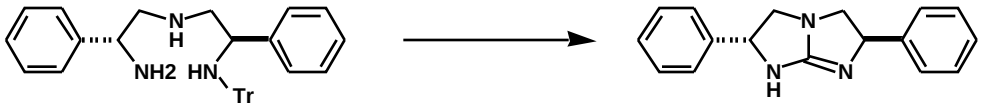


(1*R*,1'*R*)-*N*^{2}-(Carbobenzyloxyphenylglycyl)-*N*^{1}-triphenylmethyl-1-phenyl-1,2-ethanediamine (7): A THF solution (180 mL) of amine **6** (31.1 mmol) and (*R*)-*N*-Cbz-phenylglycine (31.1 mmol) was stirred at 0 °C with 1-hydroxybenzotriazole (31.1 mmol) and dicyclohexylcarbodiimide (31.1 mmol) for 1 h and then at 23 °C for 11 h. The white suspension was diluted with ether (50 mL) and filtered to remove urea. Concentration of the filtrate and silica gel chromatography (5 to 10% ethyl acetate-benzene on triethylamine-treated silica gel) gave a white foam (**7**, 78% yield). R_f 0.30 (50% ethyl acetate-hexanes). $[\alpha]_D^{25}$ -35.0 (*c* 0.8 $CHCl_3$); FTIR (film) 3405, 3384, 3085, 3060, 3031, 2937, 1713, 1666, 1596, 1586, 1493, 1348, 1329, 1265, 1233, 1214, 1155, 1077, 1040, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 6H), 7.33 (m, 8H), 7.19 (m, 12H), 7.07 (m, 4H), 6.76 (m, 2H), 6.16 (bs, 1H), 5.50 (m, 1H), 5.01 (m, 3H), 3.64 (bs, 1H), 3.25 (m, 1H), 2.85 (m, 1H), 2.47 (bs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 146.0, 142.9, 136.2, 129.0, 128.8, 128.45, 128.4, 128.3, 128.0, 127.8, 127.2, 126.6, 126.5, 71.7, 66.9, 58.8, 56.9, 45.9 ppm; FABMS 379 $[M+Na]^+$; HRMS calcd for $[C_{43}H_{39}N_3+Na]^+$: 668.2889, found: 668.2892.



(1*R*,5*R*)-*N*^{1}-Triphenylmethyl-1,5-diphenyl-1,5-(3-aza)-pentane-diamine (8): Carbamate **7** (23.2 mmol) in THF (125 mL) and methanol (125 mL) with 10% Pd/C (1.3 g) was stirred under an atmosphere of hydrogen gas for 4 h at 23 °C. Filtration of the suspension through Celite and concentration gave a white foam that was dissolved in benzene (250 mL) and treated with Red-Al (26.6 mL, 65% wt in toluene). The solution was heated at reflux for 2.5 h, diluted with ether (500 mL), and quenched by dropwise addition of water until precipitation of a white solid. The mixture was filtered through Celite, and silica gel chromatography of the residue from concentration of the filtrate (0.5% NH_4OH / 2.5 to 4.5% methanol / methylene chloride on triethylamine-treated silica gel) gave a clear syrup (**8**, 82% yield). R_f 0.20 (1% NH_4OH / 5% methanol / methylene chloride). $[\alpha]_D^{25}$ -73.8 (*c* 2.0 $CHCl_3$); FTIR (film): 3368, 3293, 3081, 3056, 3025, 2912, 2831, 1595, 1492, 1450, 1206, 1156, 1118, 1068, 1031, 906 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, 6H, *J* = 7.8 Hz), 7.28 (m, 5H), 7.17 (m, 14H), 3.72 (m, 2H),

2.89 (bs, 1H), 2.44 (dd, 1H, *J* = 11.7, 4.8 Hz), 2.28 (dd, 1H, *J* = 11.7, 4.2 Hz), 2.18 (dd, 1H, *J* = 11.7, 8.1 Hz), 1.69 (dd, 1H, *J* = 11.7, 6.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 145.2, 144.5, 128.9, 128.3, 128.0, 127.7, 127.1, 126.4, 126.2, 7.37, 72.0, 61.7, 57.5, 56.6 ppm; FABMS 520 $[M+Na]^+$; HRMS calcd for $[C_{35}H_{35}N_3+Na]^+$: 520.2729, found: 520.2740.



(3*R*,7*R*)-3,7-Diphenyl-1,4,6-triazabicyclo-[3.3.0]-oct-4-ene (1): Triamine **8** stirring (15.6 mmol) in methylene chloride (150 mL) with Na_2CO_3 (33.0 mmol) in water (150 mL) at 0 °C was treated with thiophosgene (16.0 mmol). After 15 min, quenching with NH_4OH (1 mL), extraction with ethyl acetate (2 x 300 mL), washing with brine, drying with Na_2SO_4, and concentration gave a pale yellow foam. This foam was stirred in methanol (150 mL) with iodomethane (31.2 mmol) at 55 °C for 45 min. Concentration of this orange-yellow solution gave a residue that was heated in DMF (100 mL) at 100 °C for 1.5 h. The mixture was concentrated to a dark orange syrup which was diluted with 15% NaOH (75 mL) and extracted with ethyl acetate (3 x 200 mL). Washing the combined extracts with brine (pH > 9), drying with Na_2SO_4, and concentration gave a residue that was purified by silica gel chromatography (1% NH_4OH / 7% MeOH / methylene chloride) to prove a white solid (**1**, 55 % yield). mp 159-160 °C. R_f 0.28 (1% NH_4OH, 10% MeOH/CH_2Cl_2); $[\alpha]_D^{25}$ +23.8 (*c* 0.58, $CHCl_3$); IR (film) 1452, 1492, 1674, 2829, 2926, 3027, 3058, 3106, 3156, 3205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, 4 H, *J* = 7.0 Hz), 7.32 (t, 4 H, *J* = 7.1 Hz), 7.25 (t, 2 H, *J* = 2.5 Hz), 6.37 (bs, 1 H), 5.17 (t, 2 H, *J* = 6.5 Hz), 3.50 (t, 2 H, *J* = 7.8 Hz), 3.03 (dd, 2 H, *J* = 6.3, 7.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 143.0, 128.5, 127.4, 126.4, 68.0, 57.2 ppm; CIMS 278 $[M+NH_4^+]$, 264 $[M+H^+]$; HRMS (EI) calcd for $[C_{17}H_{17}N_3]^+$: 263.1422, found: 263.1420.

Table 1. Crystal data and structure refinement for **1** • PhCOOH.

Empirical formula		$C_{24}H_{24}N_3O_2$
Formula weight		256.97
Temperature		213(2) K
Wavelength		0.71073 Å
Crystal system		Orthorhombic
Space group		P2(1)2(1)2(1)
Unit cell dimension		
a =	8.7909(3) Å	alpha = 90°
b =	10.4417(4) Å	beta = 90°
c =	22.3969(3) Å	gamma = 90°
Volume, Z		2055.85(11) $Å^3$, 6
Density (calculated)		1.245 mg/mm^3
Absorption coefficient		0.081 mm^{-1}
F(000)		816
Crystal size		0.10 x 0.10 x 0.25 mm
θ range for data collection		1.82 to 24.81°
Limiting indices		-10<h<9, -12<k<11, -26<l<18
Reflections collected		10865
Independent reflections		3511 (R_{int} = 0.0772)

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3511 / 0 / 356
Goodness-of-fit on F^2	0.707
Final R indices [I>2σ(I)]	R1 = 0.0416, wR2 = 0.0777
R indices (all data)	R1 = 0.1339, wR2 = 0.0924
Absolute structure parameter	4 0(2)
Extinction coefficient	0.0155(10)
Largest diff. peak and hole	0.136 and -0.160 $eÅ^{-3}$

Colorless prisms were grown by slow diffusion of hexanes into a hexanes-ethyl acetate solution of **1** • PhCOOH at 23 °C. Diffraction data were collected using a Bruker SMART CCD based diffractometer equipped with an LT-2 low-temperature apparatus operating at 213K. A suitable crystal was chosen and mounted on a glass fiber using grease. Data were measured using omega scans of 0.3\% per frame for 30 seconds, such that a hemisphere was collected. A total of 1271 frames were collected with a final resolution of 0.75\%A. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software which corrects for Lp and decay. No absorption corrections were applied. The structures are solved by the direct method using the SHELX-90 program and refined by least squares method on F2 SHELXL-97, incorporated in SHELXTL-PC V 5.10. The structure showed rotational twinning. Only the major contributions were included in the intesity data and integrated using the twinning package supplied by Bob Sparks, Bruker AX. The structure shows no racemic twinning, via refinement of the BASF parameter to 0.0001.