Supplementary Information

Ammonium-directed dihydroxylation of 3-aminocyclohex-1-enes: development of a metal-free dihydroxylation protocol

Caroline Aciro,[a] Timothy D. W. Claridge,[a] Stephen G. Davies,[a]* Paul M. Roberts,[a] Angela J. Russell[a,b] and James E. Thomson[a]

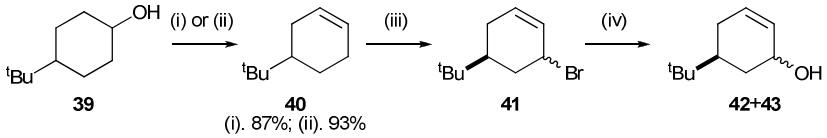
[a] *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK.*

[b] *Department of Pharmacology, University of Oxford, Mansfield Road, Oxford, OX1 3QT, UK.*

E-mail: steve.davies@chem.ox.ac.uk

Preparation of the diastereoisomers of 3-*N*,*N*-dibenzylamino-5-*tert*-butyl-cyclohex-1-ene

syn-**21** and *anti*-**22** were both prepared from 4-*tert*-butylcyclohexanol **39**, employing literature procedures reported by Ferrier,[1] Donohoe[2] and Aggarwal,[3] and other standard chemical transformations. 4-*tert*-Butylcyclohexene **40** was prepared *via* treatment of **39** with a solution of $POCl_3$ in pyridine in 87% yield. In an alternative and higher yielding synthesis, mesylation of **39** was achieved in 93% yield, with subsequent DBU mediated elimination giving **40** in quantitative yield. Allylic bromination of **40** gave **41** as a mixture of diastereoisomers, and treatment of this crude reaction mixture with Na_2CO_3 in H_2O/acetone gave 5-*tert*-butyl-3-hydroxycyclohexene as mixture of diastereoisomers **42** and **43**.

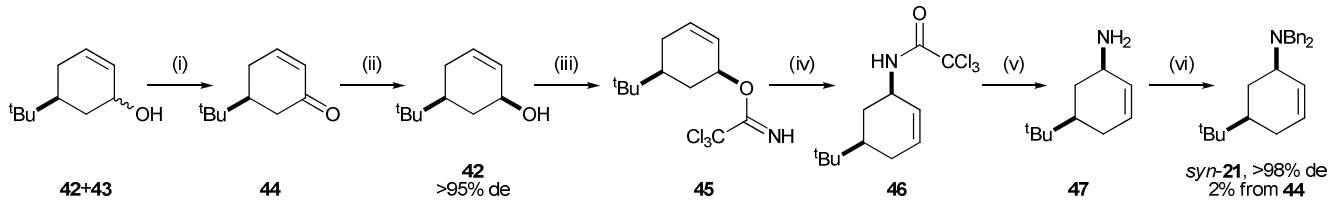


Reagents and conditions: (i) $POCl_3$, pyridine, 0 °C to rt, 24 h; (ii) MsCl, Et_3N, DMAP, DCM, 0 °C to rt, 16 h, then DBU, 100 °C, 24 h; (iii) NBS, benzoyl peroxide, CCl_4, Δ, 10 min; (iv) 27% aq acetone, Na_2CO_3, Δ, 40 min.

syn-**21** was accessed from the diastereomeric mixture of alcohols **42** and **43** *via* oxidation with IBX to give enone **44**, and stereoselective reduction with $LiAlH_4$ to give *syn*-**42** in 95% de. Formation of the corresponding trichloroacetimidate **45** was followed by Overman rearrangement to give trichloroacetamide **46**. Amide hydrolysis gave **47**, with subsequent exhaustive benzylation giving *syn*-**21** in >98% de and 2% overall yield from **44**.

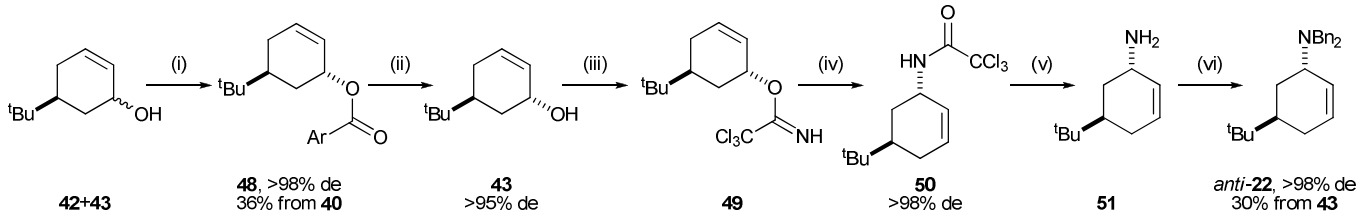
---

[1] R. J. Ferrier and N. Prasad, *J. Chem. Soc (C)*, **1967**, 1471.
[2] T. J. Donohoe, K. Blades, M. Halliwell, P. R. Moore and J. J. G. Winter, *J. Org. Chem.,* **1999**, *64*, 2980.
[3] V. K. Aggarwal and G. Y. Fang, *Chem. Commun.,* **2005**, 3448.



Reagents and conditions: (i) IBX, DMSO, 0 °C to rt, 10.5 h; (ii) $LiAlH_4$, THF, −78 °C, 4 h; (iii) Cl_3CCN, DBU, DCM, 0 °C, 75 h; (iv) K_2CO_3, *p*-xylene, Δ, 8.5 h; (v) NaOH (6 M, aq), EtOH, 0 °C, 24 h; (vi) BnBr, Hünig's base, DMAP, DCM, rt, 24 h.

anti-**22** was accessed from the diastereomeric mixture of alcohols **42** and **43** *via* acylation with *p*-nitrobenzoyl chloride to give a 69:31 *anti*:*syn* diastereoisomeric mixture, which was purified *via* recrystallisation from EtOH to give **48** in >98% de and 36% yield over 3 steps from **40**. Base catalysed hydrolysis of **48** gave **43** in >95% de. Manipulation of **43** to **50**, followed by hydrolysis, *N*,*N*-dibenzylation and column chromatography gave *anti*-**22** in >98% de and 30% yield from **43**.



Reagents and conditions: (i) *p*-nitrobenzoyl chloride, pyridine, DMAP, then recrystallisation (EtOH); (ii) NaOH, 66% MeOH (aq), Δ, 30 min; (iii) CCl_3CN, DBU, DCM, 0°C, 75 min; (iv) K_2CO_3, *p*-xylene, Δ, 8.5 h; (v) NaOH (6 M, aq), EtOH, 0 °C, 24 h; (vi) BnBr, $^iPr_2NEt$, DMAP, DCM, rt, 24 h. [Ar = *p*-$NO_2C_6H_4$].

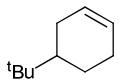
Experimental

General Experimental

Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column, or on a Biotage SP4 automated flash column chromatography platform.

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

(*RS*)-4-*tert*-Butylcyclohex-1-ene 40

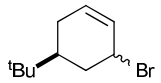


Method A: $POCl_3$ (31 mL, 332 mmol) was added to a stirred solution of 4-*tert*-butyl-cyclohexanol **39** (10.0 g, 64 mmol) in pyridine (77.6 mL) at 0 °C. The mixture was then allowed to warm to rt over 24 h before being cooled to 0 °C. The reaction mixture was then quenched by dropwise addition of H_2O (100 mL). The mixture was then extracted with Et_2O (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (eluent 30-40 °C petrol) to give **40** as a colourless oil (7.71 g, 87%); δ_H (400 MHz, $CDCl_3$) 0.87 (9H, s, C*Me*$_3$), 1.08-1.23 (1H, m, C(5)H_A), 1.24-1.35 (1H, m, C(4)*H*), 1.72-1.88 (2H, m, C(5)H_B, C(6)H_A), 1.94-2.16 (3H, m, C(3)H_2, C(6)H_B), 5.61-5.76 (2H, m, C(1)*H*, C(2)*H*).

Method B: MsCl (74.1 mL, 0.96 mol), Et_3N (892 mL, 3.2 mol) and DMAP (1.35 g, 53.0 mmol) were added sequentially to a stirred solution of 4-*tert*-butyl-cyclohexanol **39** (100 g, 0.64 mol) in DCM (1.2 L) at 0 °C. The mixture was stirred for 1 h at 0 °C before being allowed to warm to rt over 24 h. The reaction mixture was then quenched by dropwise addition of H_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 1.5 L). The combined organic extracts were washed sequentially with 1 M aq. HCl (1 L), sat. aq. $NaHCO_3$ (1 L), and brine (1 L), dried, and concentrated *in vacuo* to give 4-*tert*-butylcyclohexyl-methanesulfonate as an orange crystalline solid (162 g, 93%); mp 39-41 °C; δ_H (400 MHz, $CDCl_3$) 0.86 (9H, s, C*Me*$_3$), 1.01-2.21 (9H, m, C(2)H_2, C(3)H_2, C(4)*H*, C(5)H_2, C(6)H_2), 3.01 (3H, s, SO_2*Me*), 4.52-4.60 (1H, m, C(1)*H*).

4-*tert*-butylcyclohexyl-methanesulfonate (28.2 g, 120 mmol) was dissolved in DBU (54.1 mL, 362 mmol) and heated at 100 °C for 24 h. The mixture was then allowed to cool to rt before being further cooled to 0 °C. 1 M aq. HCl (100 mL) was then added and the mixture was extracted with 30-40 °C petrol (3 × 500 mL). The combined organic extracts were washed with 1 M aq. HCl (1 L), dried, and concentrated *in vacuo* to give **40** as a colourless oil (16.6 g, quant).

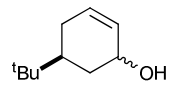
(3*RS*,5*RS*)- and (3*RS*,5*SR*)-3-Bromo-5-*tert*-butyl-cyclohex-1-ene 41



NBS (13.0 g, 73.1 mmol) and $(PhCO_2)_2$ (14.7 mg, 0.06 mmol) were added sequentially to a stirred solution of **40** (9.82 g, 71 mmol) in CCl_4 (45 mL) and the resultant suspension was heated to 80 °C for 10 min before being allowed to cool to rt. The suspension was then filtered through Celite® (eluent Et_2O) and concentrated *in vacuo* to give **41** as a mixture of diastereoisomers, as a brown oil (15.4 g, 71 mmol) that was used without

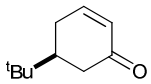
purification; δ_H (400 MHz, $CDCl_3$) [selected peaks for major diastereoisomer] 0.91 (9H, s, C*Me*$_3$), 4.95-5.00 (1H, m, C(3)*H*), 5.82-5.95 (2H, m, C(1)*H*, C(2)*H*).

(3*RS*,5*RS*)- and (3*RS*,5*SR*)-3-Hydroxy-5-*tert*-butyl-cyclohex-1-ene 42 and 43



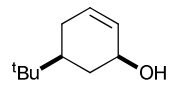
Na_2CO_3 (14.7 g, 138 mmol) was added to a stirred solution of **41** (15.4 g, 71 mmol) in 27% aq. acetone (250 mL) and the resultant suspension was heated to 90 °C for 40 min. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to a volume of approximately 100 mL. The mixture was then extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed with brine (2 × 100 mL), dried, and concentrated *in vacuo* to give a mixture of **42** and **43** as a yellow oil (11.0 g, quant) that was used without purification; δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.89 (9H, s, C*Me*$_3$), 4.19-4.33 (1H, m, C(3)*H*), 5.79-5.87 (1H, m, C(1)*H*), 5.88-5.97 (1H, m, C(2)*H*).

(*RS*)-5-*tert*-Butyl-cyclohex-2-ene-1-one 44



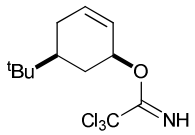
IBX (4.54 g, 16.2 mmol) was added to a stirred solution of a mixture of **42** and **43** (2.5 g, 16.2 mmol) in DMSO (35 mL) at 0 °C, and the resulting solution was stirred at rt for 10.5 h. The reaction mixture was then extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with H_2O (5 × 100 mL), dried and concentrated *in vacuo* to give **44** as a yellow oil (2.47 g, quant) that was used without purification; δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, C*Me*$_3$), 1.76-1.96 (1H, m, C*H*$_2$), 2.02 (2H, m C*H*$_2$), 2.32-2.62 (2H, m, C*H*$_2$), 5.98-6.10 (1H, m, C*H*=CH), 6.96-7.10 (1H, m, CH=C*H*).

(3*RS*,5*RS*)-3-Hydroxy-5-*tert*-butyl-cyclohex-1-ene 42



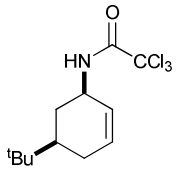
$LiAlH_4$ (1 M in THF, 17 mL, 17.4 mmol) was added to a stirred solution of **44** (2.65 g, 17.4 mmol) in THF (53 mL) at −78 °C and the resultant solution was stirred at −78 °C for 4 h. The reaction mixture was then allowed to warm to 0 °C and quenched by the slow addition of crushed ice. The mixture was then extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed sequentially with 10% aq. H_2SO_4 (20 mL) and sat. aq. $NaHCO_3$ (20 mL), dried, and concentrated *in vacuo* to give **42** as a brown oil (2.52 g, 94%, >95% de) that was used without purification; δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.87 (9H, s, C*Me*$_3$), 4.24-4.33 (1H, m, C(3)*H*), 5.61-5.68 (1H, m, C(2)*H*), 5.72-5.79 (1H, m, C(1)*H*).

(3*RS*,5*RS*)-5-*tert*-Butyl-cyclohex-1-en-3-yl trichloroacetimidate 45



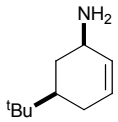
DBU (1.36 mL, 9.07 mmol) and Cl_3CCN (1.14 mL, 11.3 mmol) were added sequentially to a stirred solution of **42** (1.17 g, 7.56 mmol) in DCM (26 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with DCM (3 × 100 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **45** as a brown oil (771 mg, 35%, 95% de) that was used without purification; δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.91 (9H, s, C*Me*$_3$), 5.50-5.59 (1H, m, C(3)*H*), 5.70-5.79 (1H, m, C(2)*H*), 5.86-5.97 (1H, m, C(1)*H*), 8.29 (1H, br s, N*H*).

(3*RS*,5*RS*)-3-Trichloroacetamido-5-*tert*-butyl-cyclohex-1-ene 46



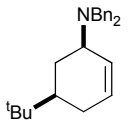
K_2CO_3 (79 mg) was added to a stirred solution of **45** in *p*-xylene (71 mL) and the resultant suspension was heated to 140 °C for 8.5 h before being allowed to cool to rt. The reaction mixture was then filtered through a pad of Celite (eluent PhMe) and the filtrate was concentrated *in vacuo* to give **46** as a brown oil (771 mg, 35%, >95% de); δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.98 (9H, s, C*Me*$_3$), 4.44-4.53 (1H, m, C(3)*H*), 5.48-5.55 (1H, m, C(2)*H*), 5.91-5.99 (1H, m, C(1)*H*), 6.42 (1H, br s, N*H*).

(3*RS*,5*RS*)-3-Amino-5-*tert*-butyl-cyclohex-1-ene 47



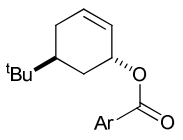
6 M aq. NaOH (2.28 mL) was added dropwise to a stirred solution of **46** (771 mg, 2.58 mmol) in EtOH (6.2 mL) at 0 °C and the reaction mixture was allowed to warm to rt over 24 h. The reaction mixture was then extracted with 30-40 °C petrol/Et_2O (v:v 4:1, 3 × 60 mL). The combined organic extracts were washed with H_2O (60 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give **47** as a brown oil (110 mg, 28%) that was used without purification; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, C*Me*$_3$), 1.39-1.45 (2H, m, C*H*$_2$), 1.68-1.79 (2H, m, C*H*$_2$), 2.00-2.12 (1H, m, C*H*$_2$), 3.41-3.48 (1H, m, C(3)*H*), 5.70-5.82 (2H, m, C(1)*H*, C(2)*H*).

(3*RS*,5*RS*)-3-*N*,*N*-dibenzylamino-5-*tert*-butyl-cyclohex-1-ene *syn*-21



BnBr (0.7 mL, 5.82 mmol), Hünig's base (1.0 mL, 5.82 mmol) and DMAP (10 mg) were added sequentially to a stirred solution of **47** (110 mg, 0.72 mmol) in DCM (12 mL) and the reaction mixture was stirred for 24 h at rt. 10% aq. $CuSO_4$ (10 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 40-60 °C petrol) gave *syn*-**21** as a yellow oil (30 mg, 13%, >98% de); ν_{max} (film) 3025, 2961, 2794 (C–H); δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, CMe_3), 1.12-1.21 (1H, m, C(4)H_A), 1.22-1.33 (1H, m, C(5)*H*), 1.73-1.84 (1H, m, C(6)H_A), 1.94-2.04 (2H, m, C(4)H_B, C(6)H_B), 3.33-3.41 (1H, m, C(3)*H*), 3.56 (2H, d, *J* 14.2, N(CH_AH$_B$Ph)$_2$), 3.73 (2H, d, *J* 14.2, N(CH$_A$$H_B$Ph)$_2$), 5.70-5.76 (1H, m, C(2)*H*), 5.78-5.85 (1H, m, C(1)*H*), 7.19-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.4 (*C*(4)), 27.2 (CMe_3), 27.3 (*C*(6)), 32.4 (*C*Me$_3$), 43.7 (*C*(5)), 53.8 (N(*C*H$_2$Ph)$_2$), 56.6 (*C*(3)), 126.6 (*p-Ph*), 128.1, 128.5 (*o*-, *m-Ph*), 129.8 (*C*(2)), 130.7 (*C*(1)), 140.9 (*i-Ph*); *m/z* (ESI$^+$) 334 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}N^+$ ([M+H]$^+$) requires 334.2529; found 334.2521. Further elution gave 3-*N*,*N*-dibenzylamino-6-*tert*-butyl-cyclohex-1-ene (4 mg);[4] ν_{max} (film) 3020, 2959 (C–H); δ_H (400 MHz, $CDCl_3$) 0.80 (9H, s, CMe_3), 1.50-1.59 (1H, m, C(5)H_A), 1.59-1.65 (1H, m, C(6)*H*), 1.69-1.77 (1H, m, C(5)H_B), 1.90-2.06 (2H, m, C(4)H_2), 3.26-3.32 (1H, m, C(3)*H*), 3.61 (2H, d, *J* 10.0, N(CH_AH$_B$Ph)$_2$), 3.70 (2H, d, *J* 10.0, N(CH$_A$$H_B$Ph)$_2$), 5.83-5.89 (1H, m, C(2)*H*), 6.01-6.07 (1H, m, C(1)*H*), 7.19-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.5 (*C*(5)), 24.3 (*C*(4)), 28.9 (CMe_3), 33.9 (*C*Me$_3$), 44.0 (*C*(6)), 54.1 (N(*C*H$_2$Ph)$_2$), 54.3 (*C*(3)), 126.6 (*C*(2)), 127.0 (*p-Ph*), 128.0, 129.1 (*o*-, *m-Ph*), 130.9 (*C*(1)), 140.5 (*i-Ph*); *m/z* (ESI$^+$) 334 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}N^+$ ([M+H]$^+$) requires 334.2529; found 334.2521.

(3*RS*,5*SR*)- 5-*tert*-butyl-cyclohex-1-en-3-yl *p*-nitrobenzoate 48

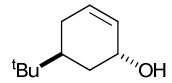


Pyridine (28.7 mL), *p*-nitrobenzoyl chloride (19.8 g, 107 mmol) and DMAP (500 mg) were added sequentially to a stirred solution of **42** and **43** (11.0 g, 71 mmol) in DCM (100 mL) and the resulting suspension was stirred at rt for 24 h. The reaction mixture was then poured over crushed ice and the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic extracts were washed sequentially with

[4] The isolation of 3-*N*,*N*-dibenzylamino-6-*tert*-butyl-cyclohex-1-ene from this reaction mixture presumably results from the generation of a minor regioisomer in the allylic bromination reaction of **40**.

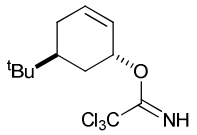
3 M aq. HCl (3 × 500 mL), H_2O (3 × 500 mL) and sat. aq. Na_2CO_3 (3 × 500 mL), dried, and concentrated *in vacuo* to give a 69:31 mixture of diastereoisomers. Recrystallisation from hot EtOH gave **48** as a yellow solid (7.75 g, 36%, >98% de); mp 99-100 °C (EtOH); δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, C*Me*$_3$), 1.46-1.56 (1H, m, C(4)*H*$_A$), 1.62-1.72 (1H, m, C(5)*H*), 1.80-1.91 (1H, m, C(6)*H*$_A$), 2.08-2.15 (1H, m, C(4)*H*$_B$), 2.18-2.28 (1H, m, C(6)*H*$_B$), 5.54-5.59 (1H, m, C(3)*H*), 5.89-5.96 (1H, m, C(2)*H*), 6.11-6.18 (1H, m, C(1)*H*), 8.18-8.23 (2H, d, *J* 8.3, *Ar*), 8.27-8.32 (2H, d, *J* 8.3, *Ar*).

(3*RS*,5*SR*)-3-Hydroxy-5-*tert*-butyl-cyclohex-1-ene 43



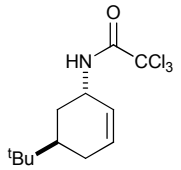
NaOH pellets (3.73 g, 93.3 mmol) were added to a stirred solution of **48** (6.71 g, 22.2 mmol) in 66% aq. MeOH (55.7 mL) and the resultant solution was heated to 90 °C for 30 min. The reaction mixture was allowed to cool to rt and concentrated *in vacuo*. H_2O (50 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **43** as a colourless oil (3.41 g, quant, >98% de); δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C*Me*$_3$), 1.28-1.38 (1H, m, C(4)*H*$_A$), 1.40-1.55 (2H, m, O*H*, C(5)*H*), 1.70-1.80 (1H, m, C(6)*H*$_A$), 1.90-1.97 (1H, m, C(4)*H*$_B$), 2.07-2.16 (1H, m, C(6)*H*$_B$), 4.21-4.27 (1H, m, C(3)*H*), 5.81-5.87 (1H, m, C(2)*H*), 5.91-5.97 (1H, m, C(1)*H*).

(3*RS*,5*SR*)-5-*tert*-Butyl-cyclohex-1-en-3-yl trichloroacetimidate 49



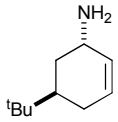
DBU (326 µL, 2.18 mmol) and Cl_3CCN (273 µL, 2.72 mmol) were added sequentially to a stirred solution of **43** (280 mg, 1.81 mmol) in DCM (2 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. Sat. aq. NH_4Cl (2 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **49** as a brown oil (540 mg, quant, >98% de) that was used without purification; δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, C*Me*$_3$), 1.32-1.44 (1H, m, C(4)*H*$_A$), 1.60-1.69 (1H, m, C(5)*H*), 1.75-1.87 (1H, m, C(6)*H*$_A$), 2.14-2.26 (2H, m, C(4)*H*$_B$, C(6)*H*$_B$), 5.42-5.48 (1H, m, C(3)*H*), 5.88-5.95 (1H, m, C(2)*H*), 6.12-6.18 (1H, m, C(1)*H*), 8.25 (1H, br s, N*H*).

(3*RS*,5*SR*)-3-Trichloroacetamido-5-*tert*-butyl-cyclohex-1-ene 50



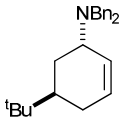
K_2CO_3 (19 mg) was added to a stirred solution of **49** in *p*-xylene (17 mL) and the resultant suspension was heated to 140 °C for 8.5 h before being allowed to cool to rt. The reaction mixture was then filtered through a pad of Celite (eluent PhMe) and the filtrate was concentrated *in vacuo* to give **50** as a brown oil (500 mg, 93%, >98% de); δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, C*Me*$_3$), 1.23-1.33 (1H, m, C(5)*H*), 1.35-1.46 (1H, m, C(4)H_A), 1.77-1.89 (1H, m, C(6)H_A), 1.99-2.07 (1H, m, C(6)H_B), 2.10-2.20 (1H, m, C(4)H_B), 4.45-4.54 (1H, br m, C(3)*H*), 5.70-5.78 (1H, br m, C(2)*H*), 6.03-6.12 (1H, m, C(1)*H*), 6.60 (1H, br s, N*H*).

(3*RS*,5*SR*)-3-Amino-5-*tert*-butyl-cyclohex-1-ene 51



6 M aq. NaOH (0.63 mL) was added dropwise to stirred solution of **50** (213 mg, 0.71 mmol) in EtOH (1.7 mL) at 0 °C and the reaction mixture was allowed to warm to rt over 24 h. The reaction mixture was then extracted with 30-40 °C petrol/Et_2O (v:v 4:1, 3 × 10 mL). The combined organic extracts were washed with H_2O (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give **51** as a brown oil (110 mg, 63%) that was used without purification; δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, C*Me*$_3$), 1.39-2.12 (5H, m, C(4)H_2, C(5)*H*, C(6)H_2), 3.41-3.48 (1H, m, C(3)*H*), 5.70-5.82 (2H, m, C(1)*H*, C(2)*H*).

(3*RS*,5*RS*)-3-*N,N*-Dibenzylamino-5-*tert*-butyl-cyclohex-1-ene *anti*-22



BnBr (0.21 mL, 1.78 mmol), Hünig's base (0.31 mL, 1.78 mmol) and DMAP (10 mg) were added sequentially to a stirred solution of **51** (110 mg, 0.72 mmol) in DCM (2 mL) and the reaction mixture was stirred for 24 h at rt. 10% aq. $CuSO_4$ (10 mL) was added and mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (gradient elution, 0%→100% EtOAc in 40-60 °C petrol) gave *anti*-**22** as a yellow oil (119 mg, 50%, >98% de); ν_{max} (film) 3085, 3062, 3025, 2961, 2833, 2791 (C–H); δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, C*Me*$_3$), 1.09-1.20 (1H, m, C(4)H_A), 1.48-1.61 (1H, m, C(5)*H*), 1.62-1.73 (1H, m, C(6)H_A), 2.08-2.18 (1H, m, C(6)H_B), 2.19-2.27 (1H, m, C(4)H_B), 3.36-3.43 (1H, br m, C(3)*H*), 3.55 (2H, d, *J* 13.9,

N($CH_AH_BPh)_2$), 3.91 (2H, d, *J* 13.9, N($CH_AH_BPh)_2$), 5.72-5.80 (1H, br m, C(2)*H*), 5.94-6.02 (1H, m, C(1)*H*), 7.21-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.4 (*C*(4)), 26.5 (*C*(6)), 27.4 (CMe_3), 32.6 (CMe_3), 40.1 (*C*(5)), 52.2 (*C*(3)), 54.7 (N($CH_2Ph)_2$), 126.6 (*p-Ph*), 128.2, 128.6 (*o*-, *m-Ph*), 128.7, 130.8 (*C*(1), *C*(2)), 140.9 (*i-Ph*); *m*/*z* (ESI^+) 334 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{32}N^+$ ($[M+H]^+$) requires 334.2529; found 334.2530.