'Towards Energetically Viable Asymmetric Deprotonations: Selectivity at More Elevated Temperatures with C_2-Symmetric Magnesium Bisamides'

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Supporting Information

1. General

1.1. Purification of Reagents

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[1]

Tetrahydrofuran and diethyl ether were dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen. Diethyl ether (for purification purposes) and petroleum ether 30-40 °C were used as obtained from suppliers without further purification.

Di-*n*-butylmagnesium, *n*-Bu_2Mg,[2] obtained as a 1 M solution in heptane, was standardised using salicaldehyde phenylhydrazone as indicator.[3]

Parent amines were dried by heating to 100 °C under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, before being purged with, and stored under N_2 over 4 Å molecular sieves.

1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) (DMPU) was dried by heating to reflux over calcium hydride and distilling under vacuum before being purged with, and stored under N_2 over 4 Å molecular sieves.

Chlorotrimethylsilane was distilled under N_2 and stored over 4 Å molecular sieves.

4-*t*-Butylcyclohexanone **1a** was recrystallised twice from dry hexane at 4 °C, purged with, and stored under N_2.

4-*n*-Propylcyclohexanone **1b**, 4-*i*-propylcyclohexanone **1c**, 4-methylcyclohexanone **1d**, and 4-(*tert*-butyldimethylsiloxy)cyclohexanone **1e**, were dried by heating to reflux over calcium chloride and distilled under vacuum before being purged with, and stored under N_2 over 4 Å molecular sieves.

1.2. Purification and Analysis of Products

Thin layer chromatography was carried out using Camlab silica plates coated with indicator UV_{254}. These were analysed using a Mineralight UVGL-25 lamp or developed using vanillin. Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

Gas chromatography was carried out using a Hewlett Packard 5890 Series 2 Gas Chromatograph and data was interpreted using Peaknet computer software:
Achiral G.C. analysis: (i) CP SIL-19CB column; (ii) carrier gas, H_2 (80 kPa): (i) injector/detector temperature, 200 °C; (ii) initial oven temperature, 45 °C; (iii) temperature gradient, 20 °C min^{-1}; (iv) final oven temperature, 190 °C; and (v) detection method, FID.
Chiral G.C. analysis: (i) CP Chirasil-DEX CB column; (ii) carrier gas, H_2 (80 kPa): (i) injector/detector temperature, 200 °C; (ii) initial oven temperature, 70 °C; (iii) temperature gradient, 1.5 °C min^{-1}; (iv) final oven temperature, 120 °C; and (v) detection method, FID.

FTIR spectra were obtained on a Perkin Elmer Spectrum One instrument.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise specified. Note: $CDCl_3$ referenced at δ 7.26 and 77.16 ppm.

Optical rotation measurements were recorded using a Rudolph Research Analytical Autopol V polarimeter, using a cell with a path length of 1 dm. Concentrations are expressed in g/100 cm^3.

High-resolution mass spectra were obtained on a Finnigan MAT900XLT instrument at the EPSRC National Mass Spectrometry Services Centre, University of Wales, Swansea, or on a JEOL JMS-700 instrument at the University of Glasgow, Glasgow, UK.

2. Experimental Procedures

All deprotonation reactions were air sensitive and, as such, were carried out using flame-dried Schlenk apparatus. Purging refers to an evacuation/nitrogen refilling procedure carried out 3 times.

2.1 Preparation of C_2-symmetric parent amine, (*R*,*R*)-(+)-bis(α-methylbenzyl)amine[4,5]

Following the procedure described by Alexakis:[4] A mixture of (*R*)-phenylethylamine (1.00 mL, 7.82 mmol), acetophenone (0.91 mL, 7.82 mmol) and Ti(O*i*-Pr)$_4$ (6.98 mL, 23.5 mmol) was stirred at room temperature for 20 min. To the mixture was added 10% palladium on carbon (36 mg, 0.5 mol %), and the mixture was hydrogenated under 3 atm of hydrogen with shaking. A small aliquot was removed after 24 h and analysed by ^{1}H NMR revealing complete consumption of starting materials. The reaction mixture was treated with NaOH aq. solution (1 M, 2 mL), followed by extraction with ethyl acetate (3 x 10 mL). The combined organics were filtered through Celite, dried (Na_2SO_4), filtered, and the solvent removed *in vacuo* to afford a pale yellow oil. ^{1}H NMR of the crude product allowed the diastereomeric ratio to be determined (7.5:1 (*R*,*R*):(*R*,*S*)). The crude product was dissolved in petroleum ether 30-40 ºC (50 mL) and treated with TFA (2 mL) to precipitate a white solid that was isolated by filtration. The mother liquor was treated with a further portion of TFA (2 mL) to precipitate more solid. This procedure was repeated until no more solid was precipitated. The combined solids were then dissolved in MeOH (50 mL) and recrystallised by slow evaporation of the MeOH solution. Each crop of the white, needle-like crystals was analysed by ^{1}H NMR to ensure the desired (*R*,*R*)-diastereomer was obtained with complete diastereomeric purity. The combined diastereomerically pure crystals were subsequently dissolved in CH_2Cl_2 (25 mL) and shaken with sat. $NaHCO_3$ aq. solution (25 mL). The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford (*R*,*R*)-(+)-bis(α-methylbenzyl)amine as a colourless oil (620 mg, 2.74 mmol, 35%). This was dried by heating to 100 °C under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, before being purged with, and stored under N_2 over 4 Å molecular sieves.

2.2 Preparation of C_2-symmetric magnesium amide complex (*R*,*R*)-**8**[6]

A flame-dried and purged Schlenk tube was charged with *n*-Bu_2Mg (1 M in heptane, 1 eq., 1 mmol, 1 mL) and the heptane removed *in vacuo* to produce a white solid. The solid was redissolved in THF (10 mL) and (*R*,*R*)-(+)-bis(α-methylbenzyl)amine (2 eq., 2 mmol, 450 mg) was added. This mixture was then refluxed for 1.5 h before cooling to room temperature where a quantitative formation of complex (*R*,*R*)-**8** was assumed.

2.3 Asymmetric deprotonation of prochiral ketones using complex (*R*,*R*)-**8**[6]

For example, using ketone **1a** at –78 °C: A solution of C_2-symmetric magnesium bisamide (*R*,*R*)-**8** (1 mmol) in THF (10 mL) (see procedure **2.2**) was cooled to –78 ºC using a dry-ice/acetone bath. The mixture was stirred at –78 ºC for 5 min before the addition of DMPU (1 eq., 1 mmol, 0.12 mL) and Me_3SiCl (1 eq., 1 mmol, 0.125 mL). The mixture was stirred for 10 min before the addition of 4-*tert*-butylcyclohexanone **1a** (0.8 eq., 0.8 mmol, 123 mg) as a solution in THF (2 mL) over 1 h *via* syringe pump. The mixture was then stirred for 15 h (overall reaction time 16 h) before quenching with sat. $NaHCO_3$ aq. solution (10 mL). The mixture was allowed to warm to room temperature before extracting with Et_2O (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and a

representative sample was analysed by achiral G.C. to obtain the product conversion (93%). The solution was then filtered and concentrated *in vacuo* to afford a residue that was purified by column chromatography (1% Et_2O/petroleum ether 30-40°) to afford 4-*tert*-butyl-1-trimethylsilyloxycyclohexene **2a** as a colourless oil (120 mg, 66%). Chiral G.C. analysis of this product determined the enantiomeric ratio to be 93:7 (*S*:*R*).

3. Application to substrates

Following procedure **2.3**. Results are presented in the following order:

(a) Ketone and quantity; (b) Product; (c) G.C. conversion; (d) G.C. enantiomeric ratio; (e) Yield; (f) Optical rotation.

Table 2: Use of Complex 8 at –78 °C.

Entry 1: (a) **1a** (0.8 eq., 0.8 mmol, 123 mg); (b) **2a**; (c) 93%; (d) 93:7 (*S*:*R*); (e) 119 mg, 66%; (f) $[\alpha]_D^{20}$: –66.3 (*c* 1.5, $CHCl_3$); Lit.:[6c] –54.2 (*c* 1.5, $CHCl_3$ (82:18 G.C. e.r. (*S*:*R*))).

Entry 2: (a) **1b** (0.8 eq., 0.8 mmol, 112 mg); (b) **2b**; (c) 92%; (d) 94:6 (*S*:*R*); (e) 110 mg, 65%; (f) $[\alpha]_D^{20}$: –41.8 (*c* 1.2, $CHCl_3$); Lit.:[6c] –35.2 (*c* 1.2, $CHCl_3$ (88:12 G.C. e.r. (*S*:*R*))).

Entry 3: (a) **1c** (0.8 eq., 0.8 mmol, 112 mg); (b) **2c**; (c) 96%; (d) 93:7 (*S*:*R*); (e) 114 mg, 67%; (f) $[\alpha]_D^{20}$: –48.2 (*c* 1.5, $CHCl_3$); Lit.:[6c] –49.0 (*c* 1.5, $CHCl_3$ (95:5 G.C. e.r. (*S*:*R*))).

Entry 4: (a) **1d** (0.8 eq., 0.8 mmol, 90 mg); (b) **2d**; (c) 96%; (d) 95:5 (*S*:*R*); (e) 101 mg, 69%; (f) $[\alpha]_D^{20}$: –62.1 (*c* 0.7, $CHCl_3$); Lit.:[6c] –17.0 (*c* 0.7, $CHCl_3$ (91:9 G.C. e.r. (*S*:*R*))).

Entry 5: (a) **1e** (0.8 eq., 0.8 mmol, 182 mg); (b) **2e**; (c) 91%; (d) -----; (e) 163 mg, 68%; (f) $[\alpha]_D^{20}$: –30.3 (*c* 0.3, $CHCl_3$), equating to an e.r. of 92:8 (*S*:*R*); Lit.:[7] –28.8 (*c* 0.3, $CHCl_3$ (90:10 G.C. e.r. (*S*:*R*))).

Table 2: Use of Complex 8 at –20 °C.

Entry 6: (a) **1a** (0.8 eq., 0.8 mmol, 123 mg); (b) **2a**; (c) 93%; (d) 88:12 (*S*:*R*); (e) 150 mg, 83%; (f) $[\alpha]_D^{20}$: –59.4 (*c* 1.5, $CHCl_3$); Lit.:[6c] –54.2 (*c* 1.5, $CHCl_3$ (82:18 G.C. e.r. (*S*:*R*))).

Entry 7: (a) **1b** (0.8 eq., 0.8 mmol, 112 mg); (b) **2b**; (c) 96%; (d) 89:11 (*S*:*R*); (e) 116 mg, 68%; (f) $[\alpha]_D^{20}$: –34.7 (*c* 1.2, $CHCl_3$); Lit.:[6c] –35.2 (*c* 1.2, $CHCl_3$ (88:12 G.C. e.r. (*S*:*R*))).

Entry 8: (a) **1c** (0.8 eq., 0.8 mmol, 112 mg); (b) **2c**; (c) 95%; (d) 87:13 (*S*:*R*); (e) 119 mg, 70%; (f) $[\alpha]_D^{20}$: –41.8 (*c* 1.5, $CHCl_3$); Lit.:[6c] –49.0 (*c* 1.5, $CHCl_3$ (95:5 G.C. e.r. (*S*:*R*))).

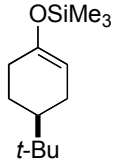
Entry 9: (a) **1d** (0.8 eq., 0.8 mmol, 90 mg); (b) **2d**; (c) 96%; (d) 90:10 (*S*:*R*); (e) 101 mg, 69%; (f) $[\alpha]_D^{20}$: –60.7 (*c* 0.7, $CHCl_3$); Lit.:[6c] –17.0 (*c* 0.7, $CHCl_3$ (91:9 G.C. e.r. (*S*:*R*))).

Entry 10: (a) **1e** (0.8 eq., 0.8 mmol, 182 mg); (b) **2e**; (c) 92%; (d) -----; (e) 168 mg, 70%; (f) $[\alpha]_D^{20}$: –26.5 (*c* 0.3, $CHCl_3$), equating to an e.r. of 87:13 (*S*:*R*); Lit.:[7] –28.8 (*c* 0.3, $CHCl_3$ (90:10 G.C. e.r. (*S*:*R*))).

4. Product Data

FTIR, ^{1}H NMR and ^{13}C NMR data are provided for each product.

2a: 4-*tert*-Butyl-1-trimethylsilyloxy-1-cyclohexene[6c,8-10]



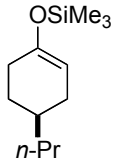
ν_{max} (KBr): 1674 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.19 (s, 9H, Si(CH_3)$_3$), 0.90 (s, 9H, C(CH_3)$_3$), 1.21-1.29 (m, 2H, CH_2), 1.78-1.85 (m, 2H, CH_2), 1.98-2.09 (m, 3H, C*H*+CH_2), 4.84-4.86 (m, 1H, C=C*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.13, 24.7, 26.9, 27.0, 30.7, 31.8, 43.8, 103.6, 149.9.

Achiral G.C. analysis: t_R (**1a**) = 5.27 min, t_R (**2a**) = 5.49 min.
Chiral G.C. analysis: t_R ((*S*)-**2a**) = 25.67 min, t_R ((*R*)-**2a**) = 25.95 min.

2b: 4-*n*-Propyl-1-trimethylsilyloxy-1-cyclohexene[6c]



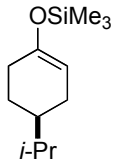
ν_{max} (KBr): 1671 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.19 (s, 9H, Si(CH_3)$_3$), 0.90 (t, 3H, CH_3, *J* = 7.1 Hz), 1.20-1.39 (m, 5H, 2xCH_2+C*H*), 1.40-1.51 (m, 1H, C*H*), 1.61-1.79 (m, 2H, CH_2), 1.92-2.00 (m, 1H, C*H*), 2.01-2.14 (m, 2H, CH_2), 4.81-4.85 (m, 1H, C=C*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.43, 14.5, 20.4, 29.4, 29.8, 30.5, 33.1, 38.4, 103.7, 150.3.

Achiral G.C. analysis: t_R (**1b**) = 4.75 min, t_R (**2b**) = 5.03 min.
Chiral G.C. analysis: t_R ((*S*)-**2b**) = 20.53 min, t_R ((*R*)-**2b**) = 20.85 min.

2c: 4-*iso*-Propyl-1-trimethylsilyloxy-1-cyclohexene[6c,8,11]



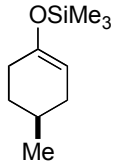
ν_{max} (KBr): 1672 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.18 (s, 9H, Si(CH_3)$_3$), 0.88 (d, 3H, CH_3, J = 6.8 Hz), 0.89 (d, 3H, CH_3, J = 6.8 Hz), 1.18-1.36 (m, 2H, CH_2), 1.43-1.55 (m, 1H, C*H*), 1.72-1.83 (m, 2H, CH_2), 1.94-2.15 (m, 3H, C*H*+CH_2), 4.83-4.87 (m, 1H, C=C*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.30, 20.2, 26.5, 27.4, 30.4, 32.1, 40.1, 103.9, 150.3.

Achiral G.C. analysis: t_R (**1c**) = 4.73 min, t_R (**2c**) = 5.02 min.
Chiral G.C. analysis: t_R ((*S*)-**2c**) = 20.83 min, t_R ((*R*)-**2c**) = 21.15 min.

2d: 4-Methyl-1-trimethylsilyloxy-1-cyclohexene[6c,8,11]



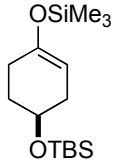
ν_{max} (CH_2Cl_2): 1668 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.18 (s, 9H, Si(CH_3)$_3$), 0.95 (d, 3H, CH_3, J = 6.3 Hz), 1.25-1.37 (m, 2H, CH_2), 1.57-1.73 (m, 3H, C*H*+CH_2), 1.92-2.15 (m, 2H, CH_2), 4.81-4.85 (m, 1H, C=C*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.40, 21.3, 28.4, 29.7, 31.4, 32.4, 103.7, 150.2.

Achiral G.C. analysis: t_R (**1d**) = 3.07 min, t_R (**2d**) = 3.57 min.
Chiral G.C. analysis: t_R ((*S*)-**2d**) = 9.23 min, t_R ((*R*)-**2d**) = 9.40 min.

2e: 4-(*tert*-Butyldimethylsiloxy)-1-trimethylsilyloxy-1-cyclohexene[8]



ν_{max} (CH_2Cl_2): 1668 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 3H, Si(C(CH_3)$_3$CH_3), 0.07 (s, 3H, Si(C(CH_3)$_3$)CH_3), 0.18 (s, 9H, Si(C(CH_3)$_3$), 0.89 (s, 9H, Si(CH_3)$_3$), 1.60-1.83 (m, 2H, CH_2), 1.97-2.16 (m, 3H, C*H*+CH_2), 2.17-1.27 (m, 1H, C*H*), 3.84-3.93 (m, 1H, C*H*), 4.66-4.73 (m, 1H, C=C*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.61, 0.37, 18.2, 26.0, 28.2, 31.8, 33.4, 67.4, 101.4, 149.8.

Achiral G.C. analysis: t_R (**1e**) = 6.70 min, t_R (**2e**) = 6.80 min.

5. References

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