‘Towards Energetically Viable Asymmetric Deprotonations: Selectivity at More Elevated Temperatures with C₂-Symmetric Magnesium Bisamides’

Linsey S. Bennie, William J. Kerr,* Michael Middleditch and Allan J. B Watson

Department of Pure and Applied Chemistry, WestCHEM, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, Scotland, UK.

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-Bu₂Mg,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 N₂ over 4 Å molecular sieves.

1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) (DMPU) was dried by heating to reflux over calcium hydride and distilling under vacuum before being purged with, and stored under N₂ over 4 Å molecular sieves.

Chlorotrimethylsilane was distilled under N₂ 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 N₂.

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 N₂ 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_{HH}$ interactions unless otherwise specified. Note: CDCl$_3$ referenced at $\delta$ 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, \((R,R)-(+)-\text{bis}(\alpha\text{-methylbenzyl})\)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(Oi-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\(_2\)SO\(_4\)), filtered, and the solvent removed \textit{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 °C (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\(_2\)Cl\(_2\) (25 mL) and shaken with sat. NaHCO\(_3\) aq. solution (2 mL) before being purified 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\(_2\)Mg (1 M in heptane, 1 eq., 1 mmol, 1 mL) and the heptane removed \textit{in vacuo} to produce a white solid. The solid was redissolved in THF (10 mL) (see procedure 2.2) and \((R,R)-\text{bis}(\alpha\text{-methylbenzyl})\)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 °C using a dry-ice/acetone bath. The mixture was stirred at –78 °C for 5 min before the addition of DMPU (1 eq., 1 mmol, 0.12 mL) and Me\(_3\)SiCl (1 eq., 1 mmol, 0.125 mL). The mixture was stirred for 10 min before the addition of 4-\textit{tert}-butylcyclohexanone \(1a\) (0.8 eq., 0.8 mmol, 123 mg) as a solution in THF (2 mL) over 1 h \textit{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\(_2\)O (3 x 25 mL). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and a...
representative sample was analysed by achiral G.C. to obtain the product conversion (93%). The solution was then filtered and concentrated \textit{in vacuo} to afford a residue that was purified by column chromatography (1\% Et\textsubscript{2}O/petroleum ether 30-40\°) to afford 4-\textit{tert}-butyl-1-trimethylsilyloxy-cyclohexene 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(a) Ketone</th>
<th>(b) Product</th>
<th>(c) G.C. conversion</th>
<th>(d) G.C. enantiomeric ratio</th>
<th>(e) Yield</th>
<th>(f) Optical rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a (0.8 eq., 0.8 mmol, 123 mg); 2a; (c) 93%; (d) 93:7 (S:R); (e) 119 mg, 66%; (f) $[\alpha]_D^{20} = -66.3$ (c 1.5, CHCl\textsubscript{3}); Lit.\textsuperscript{6c} –54.2 (c 1.5, CHCl\textsubscript{3}) (82:18 G.C. e.r. (S:R)).</td>
<td></td>
<td>93%</td>
<td>93:7 (S:R)</td>
<td>119 mg, 66%</td>
<td>$[\alpha]_D^{20} = -66.3$ (c 1.5, CHCl\textsubscript{3})</td>
</tr>
<tr>
<td>2</td>
<td>1b (0.8 eq., 0.8 mmol, 112 mg); 2b; (c) 92%; (d) 94:6 (S:R); (e) 110 mg, 65%; (f) $[\alpha]_D^{20} = -41.8$ (c 1.2, CHCl\textsubscript{3}); Lit.\textsuperscript{6c} –35.2 (c 1.2, CHCl\textsubscript{3}) (88:12 G.C. e.r. (S:R)).</td>
<td></td>
<td>92%</td>
<td>94:6 (S:R)</td>
<td>110 mg, 65%</td>
<td>$[\alpha]_D^{20} = -41.8$ (c 1.2, CHCl\textsubscript{3})</td>
</tr>
<tr>
<td>3</td>
<td>1c (0.8 eq., 0.8 mmol, 112 mg); 2c; (c) 96%; (d) 93:7 (S:R); (e) 114 mg, 67%; (f) $[\alpha]_D^{20} = -48.2$ (c 1.5, CHCl\textsubscript{3}); Lit.\textsuperscript{6c} –49.0 (c 1.5, CHCl\textsubscript{3}) (95:5 G.C. e.r. (S:R)).</td>
<td></td>
<td>96%</td>
<td>93:7 (S:R)</td>
<td>114 mg, 67%</td>
<td>$[\alpha]_D^{20} = -48.2$ (c 1.5, CHCl\textsubscript{3})</td>
</tr>
<tr>
<td>4</td>
<td>1d (0.8 eq., 0.8 mmol, 90 mg); 2d; (c) 96%; (d) 95:5 (S:R); (e) 101 mg, 69%; (f) $[\alpha]_D^{20} = -62.1$ (c 0.7, CHCl\textsubscript{3}); Lit.\textsuperscript{6c} –17.0 (c 0.7, CHCl\textsubscript{3}) (91:9 G.C. e.r. (S:R)).</td>
<td></td>
<td>96%</td>
<td>95:5 (S:R)</td>
<td>101 mg, 69%</td>
<td>$[\alpha]_D^{20} = -62.1$ (c 0.7, CHCl\textsubscript{3})</td>
</tr>
<tr>
<td>5</td>
<td>1e (0.8 eq., 0.8 mmol, 182 mg); 2e; (c) 91%; (d) -----; (e) 163 mg, 68%; (f) $[\alpha]_D^{20} = -30.3$ (c 0.3, CHCl\textsubscript{3}) (equating to an e.r. of 92:8 (S:R)); Lit.\textsuperscript{7} –28.8 (c 0.3, CHCl\textsubscript{3} (90:10 G.C. e.r. (S:R))).</td>
<td></td>
<td>91%</td>
<td>-----</td>
<td>163 mg, 68%</td>
<td>$[\alpha]_D^{20} = -30.3$ (c 0.3, CHCl\textsubscript{3})</td>
</tr>
</tbody>
</table>

Table 2: Use of Complex 8 at –20 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(a) Ketone</th>
<th>(b) Product</th>
<th>(c) G.C. conversion</th>
<th>(d) G.C. enantiomeric ratio</th>
<th>(e) Yield</th>
<th>(f) Optical rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1a (0.8 eq., 0.8 mmol, 123 mg); 2a; (c) 93%; (d) 88:12 (S:R); (e) 150 mg, 83%; (f) $[\alpha]_D^{20} = -59.4$ (c 1.5, CHCl\textsubscript{3}); Lit.\textsuperscript{6c} –54.2 (c 1.5, CHCl\textsubscript{3}) (82:18 G.C. e.r. (S:R)).</td>
<td></td>
<td>93%</td>
<td>88:12 (S:R)</td>
<td>150 mg, 83%</td>
<td>$[\alpha]_D^{20} = -59.4$ (c 1.5, CHCl\textsubscript{3})</td>
</tr>
<tr>
<td>7</td>
<td>1b (0.8 eq., 0.8 mmol, 112 mg); 2b; (c) 96%; (d) 89:11 (S:R); (e) 116 mg, 68%; (f) $[\alpha]_D^{20} = -34.7$ (c 1.2, CHCl\textsubscript{3}); Lit.\textsuperscript{6c} –35.2 (c 1.2, CHCl\textsubscript{3}) (88:12 G.C. e.r. (S:R)).</td>
<td></td>
<td>96%</td>
<td>89:11 (S:R)</td>
<td>116 mg, 68%</td>
<td>$[\alpha]_D^{20} = -34.7$ (c 1.2, CHCl\textsubscript{3})</td>
</tr>
<tr>
<td>8</td>
<td>1c (0.8 eq., 0.8 mmol, 112 mg); 2c; (c) 95%; (d) 87:13 (S:R); (e) 119 mg, 70%; (f) $[\alpha]_D^{20} = -41.8$ (c 1.5, CHCl\textsubscript{3}); Lit.\textsuperscript{6c} –49.0 (c 1.5, CHCl\textsubscript{3}) (95:5 G.C. e.r. (S:R)).</td>
<td></td>
<td>95%</td>
<td>87:13 (S:R)</td>
<td>119 mg, 70%</td>
<td>$[\alpha]_D^{20} = -41.8$ (c 1.5, CHCl\textsubscript{3})</td>
</tr>
<tr>
<td>9</td>
<td>1d (0.8 eq., 0.8 mmol, 90 mg); 2d; (c) 96%; (d) 90:10 (S:R); (e) 101 mg, 69%; (f) $[\alpha]_D^{20} = -60.7$ (c 0.7, CHCl\textsubscript{3}); Lit.\textsuperscript{6c} –17.0 (c 0.7, CHCl\textsubscript{3}) (91:9 G.C. e.r. (S:R)).</td>
<td></td>
<td>96%</td>
<td>90:10 (S:R)</td>
<td>101 mg, 69%</td>
<td>$[\alpha]_D^{20} = -60.7$ (c 0.7, CHCl\textsubscript{3})</td>
</tr>
<tr>
<td>10</td>
<td>1e (0.8 eq., 0.8 mmol, 182 mg); 2e; (c) 92%; (d) -----; (e) 168 mg, 70%; (f) $[\alpha]_D^{20} = -26.5$ (c 0.3, CHCl\textsubscript{3}) (equating to an e.r. of 87:13 (S:R)); Lit.\textsuperscript{7} –28.8 (c 0.3, CHCl\textsubscript{3} (90:10 G.C. e.r. (S:R))).</td>
<td></td>
<td>92%</td>
<td>-----</td>
<td>168 mg, 70%</td>
<td>$[\alpha]_D^{20} = -26.5$ (c 0.3, CHCl\textsubscript{3})</td>
</tr>
</tbody>
</table>
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$^{6c,8,10}$

$\nu_{max}$ (KBr): 1674 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 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, CH=C=H$_2$), 4.84-4.86 (m, 1H, C=C=H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 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$^6c$

$\nu_{max}$ (KBr): 1671 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.19 (s, 9H, Si(CH$_3$)$_3$), 0.90 (t, 3H, C(CH$_3$)$_3$, $J = 7.1$ Hz), 1.20-1.39 (m, 5H, 2xCH$_2$+CH), 1.40-1.51 (m, 1H, CH), 1.61-1.79 (m, 2H, CH$_2$), 1.92-2.00 (m, 1H, CH), 2.01-2.14 (m, 2H, CH$_2$), 4.81-4.85 (m, 1H, C=C=H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 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$^{6c,8,11}$

$\nu_{max}$ (KBr): 1672 cm$^{-1}$.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 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, CH), 1.72-1.83 (m, 2H, CH$_2$), 1.94-2.15 (m, 3H, CH+CH$_2$), 4.83-4.87 (m, 1H, C=CH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 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$^{6c,8,11}$

\[
\begin{array}{c}
\text{OSiMe}_3 \\
\text{Me} \\
\text{C}_6\text{H}_{12}
\end{array}
\]

$v_{\text{max}}$ (CH$_2$Cl$_2$): 1668 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 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, CH+CH$_2$), 1.92-2.15 (m, 2H, CH$_2$), 4.81-4.85 (m, 1H, C=CH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 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$^8$

\[
\begin{array}{c}
\text{OSiMe}_3 \\
\text{O}_{\text{TBS}} \\
\text{C}_6\text{H}_{12}
\end{array}
\]

$v_{\text{max}}$ (CH$_2$Cl$_2$): 1668 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 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$_3$)$_3$)Si(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, CH+CH$_2$), 2.17-1.27 (m, 1H, CH), 3.84-3.93 (m, 1H, CH), 4.66-4.73 (m, 1H, C=CH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: –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


2) Commercially available from the Aldrich Chemical Co., CAS# [1191-47-5], catalogue no. 345113.


5) (R,R)-(+-)Bis(α-methylbenzyl)amine is also commercially available from the Aldrich Chemical Co., CAS# [82398-30-9], catalogue no. 461520.


