Enantioselective Deprotonation of 2,6-Disubstituted Cyclohexanones with a Homochiral Magnesium Amide Base and the Observation of a Novel Kinetic Resolution Process

Kenneth W. Henderson,* William J. Kerr,* Jennifer H. Moir

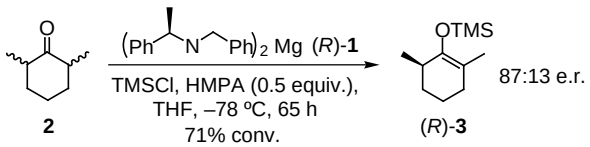
Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, G1 1XL, Scotland, UK
Fax +44 141 548 4246; E-mail: w.kerr@strath.ac.uk
Received 9 May 2001

Abstract: A recently developed homochiral magnesium amide base has been shown to be highly effective in the asymmetric deprotonation of *cis*-2,6-disubstituted cyclohexanones, affording excellent levels of both conversion and enantioselection (up to >99.5:0.5 e.r.). In addition, a novel kinetic resolution process has been realised with the corresponding *trans*-disubstituted substrates, allowing access to optically enriched enol ethers and chiral ketones.

Key words: asymmetric synthesis, enantioselective deprotonation, kinetic resolution, magnesium

In recent years considerable effort has been directed towards both the preparation of novel chiral base reagents and the subsequent scope of these species within asymmetric synthesis. Most notably, homochiral lithium amide bases have emerged as effective candidates for use in enantioselective transformations, allowing direct access to synthetically useful chiral synthons of good optical enrichment.[1] By comparison, the use of chiral magnesium species to mediate asymmetric processes has received little attention.[2] However, when considered it appears that magnesium amide reagents possess a series of key features which, in combination, are central to the development of a range of asymmetric transformations. Indeed, two of the most important aspects of magnesium amide chemistry are: (i) their solution aggregation is generally simple and predictable,[3] and (ii) they are highly reactive, yet selective, bases.[4] Such advantages over existing methodology have therefore led us to explore both the formation and utility of this important class of chiral reagent. In this respect, we have recently reported a convenient in situ preparation of novel, homochiral Mg-amide base (*R*)-**1** from the readily available and structurally very simple chiral amine, (*R*)-*N*-benzyl-α-methylbenzylamine. In turn, this Mg-amide reagent was found to be particularly effective in the desymmetrisation reaction of 4-substituted cyclohexanones and afforded the corresponding silyl enol ethers with high levels of both conversion and enantioselection (up to 95:5 e.r.).[5,6]

With a view to further probing the efficacy of our Mg-based deprotonation strategy, we have now extended the scope of our studies to encompass the enantioselective deprotonation of alternative prochiral ketonic substrates and more specifically, 2,6-disubstituted cyclohexanones. In particular and to initiate this investigation, 2,6-dimethylcyclohexanone **2** was available to us as an 82:18 mixture of *cis*-/*trans*-isomers. Upon optimisation of the reaction between (*R*)-**1** and **2**, we were pleased to observe a 71% conversion to silyl enol ether (*R*)-**3** which, on analysis, exhibited an appreciable enantiomeric ratio (e.r.) of 87:13 (Scheme 1). Moreover, as well as observing a good level of asymmetric induction, we were intrigued to note that the returned and initially racemic *trans*-ketone **2** now exhibited a 74:26 ratio of enantiomers, thus indicating that Mg-amide base (*R*)-**1** had also mediated a kinetic resolution process.

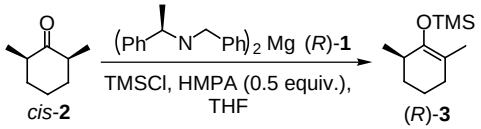


Scheme 1

Based upon these promising initial results, we then wished to further explore the potential of our system by reacting each of the *cis*- and *trans*-isomers of **2** in isolation with chiral Mg-amide base (*R*)-**1**. In this regard, when the *cis*-ketone **2** was utilised at −78 °C the resulting silyl enol ether (*R*)-**3** registered an excellent enantiomeric ratio of 97:3 (Table 1, Entry 1). This synthetic outcome is particularly noteworthy, in that, when *cis*-ketone **2** was reacted under similar conditions with the Li version of the same chiral amide, the deprotonation process delivered a significantly lower 64.5:35.5 e.r.[7] Returning to our Mg-amide base (*R*)-**1**, whilst a reduction in the reaction time from 65 h to 6 h resulted in a drop in conversion to 25%, pleasingly, increasing the reaction temperature to –60 °C, allowed enhanced levels of conversion to be noted (67%) with only a small drop off in enantioselection (94:6 e.r.). Upon raising the temperature still further, to –40 °C, we were delighted to note almost quantitative conversion (99%) of *cis*-**2** to (*R*)-**3** within 6 h. Additionally, this transformation was, again, complete without any considerable reduction in the enantioselectivity (93:7 e.r.).

Reaction of (*R*)-**1** with the *trans*-isomer of 2,6-dimethylcyclohexanone **2**, initially present as a racemic mixture, showed that our novel chiral Mg-amide base was indeed capable of mediating a kinetic resolution process. Following reaction at −78 °C and after 76% conversion, the op-

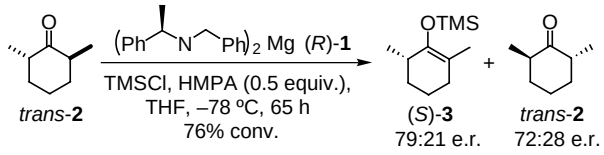
Table 1 Enantioselective Deprotonation Reactions of *cis*-**2** with Mg-amide (*R*)-**1**



Entry	Temp. (°C)	t (h)	Conversion (%)[a]	e.r. (*R*:*S*)[b]
1	-78	65	67	97:3
2	-78	6	25	97:3
3	-60	6	67	94:6
4	-40	6	99	93:7

[a]Conversions were determined by GC analysis.
[b]See ref. 8.

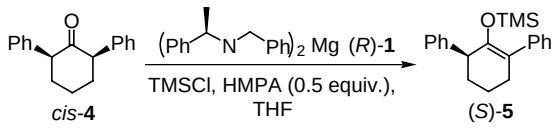
posite enol ether (*S*)-**3**, to that formed from the *cis*-isomer of **2**, was obtained in excess (Scheme 2).[10] Additionally, the unreacted ketone *trans*-**2** was returned displaying an enantiomeric ratio of 72:28. Based on the formation of the known (*S*)-isomer of **3**,[9] as well as literature data,[11] the predominant returned ketone was assigned as the (*R*,*R*)-enantiomer.



Scheme 2

With a practically convenient method for the desymmetrisation of 2,6-dimethylcyclohexanone in place, we then moved on to consider the enantioselective deprotonation of alternative substrates using chiral Mg-amide base (*R*)-**1**. Upon consideration of *cis*-2,6-diphenylcyclohexanone **4**,[12] reaction with (*R*)-**1** showed a temperature window within which acceptable yields of silyl enol ether (*S*)-**5** were achieved. Furthermore, good levels of enantioselection were observed in each case (Table 2).

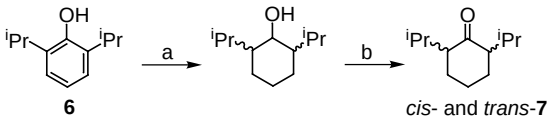
Table 2 Enantioselective Deprotonation Reactions of *cis*-**4** with Mg-amide (*R*)-**1**



Entry	Temp. (°C)	t (h)	Yield (%)	e.r. (*S*:*R*)[a]
1	-60	24	39	87:13
2	-40	8	86	82:18

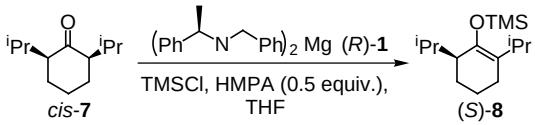
[a]See ref. 13.

Additional examples of 2,6-disubstituted cyclohexanones were required to be synthesised from the corresponding 2,6-disubstituted phenols, e.g. via Raney Nickel catalysed hydrogenation[14] and subsequent oxidation of the cyclohexanol intermediate with Dess-Martin reagent.[15] In particular, using the phenol **6** as starting material this route afforded quantities of both the *cis*- and *trans*-isomers of 2,6-di-*iso*-propylcyclohexanone **7** (Scheme 3) which were separated and reacted with the chiral Mg-amide base (*R*)-**1** in isolation. More specifically, reaction of *cis*-2,6-di-*iso*-propylcyclohexanone **7** with (*R*)-**1** produced silyl enol ether (*S*)-**8** in 54% conversion after 40 h reaction time at –78 °C. Remarkably, only one enantiomer of this product could be observed by chiral GC, thus, allowing us to register our highest enantiomeric ratio yet achieved of >99.5:0.5 (Table 3, Entry 1). Pleasingly, warming the reaction temperature sequentially to –40 °C allowed us to observe almost quantitative conversion of *cis*-**7** to silyl enol ether (*S*)-**8** which, only upon concentration of the GC sample, began to show a trace amount of the undesired second enantiomer (98.8:1.2 e.r.).[16] It is interesting and, indeed, practically relevant to note that when this deprotonation process with our chiral Mg-base (*R*)-**1** was performed at room temperature, high levels of enantioselection were still maintained (91:9 e.r.).[17,18]



Scheme 3 *Reagents and conditions:* (a) Raney Ni, H_2 (100 atm), 104 °C, 39 h, 97%; (b) Dess-Martin periodinane, CH_2Cl_2, r.t., 1 h, 98%.

Table 3 Enantioselective Deprotonation Reactions of *cis*-**7** with Mg-amide (*R*)-**1**

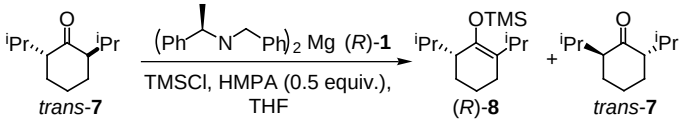


Entry	Temp. (°C)	t (h)	Conversion (%)	e.r. (*S*:*R*)[a]
1	-78	40	54	>99.5:0.5
2	-78	6	9	99.7:0.3[b]
3	-60	6	66	99.4:0.6[b]
4	-40	6	99	98.8:1.2[b]
5	r.t.	2	>99	91:9

[a]See ref. 8.
[b]See ref. 16.

In a drive to further explore the kinetic resolution potential of our base (*R*)-**1**, we subjected *trans*-2,6-di-*iso*-propylcyclohexanone **7** to our Mg-based deprotonation strategy (Table 4). We were delighted to note that, at

Table 4 Enantioselective Deprotonation Reactions of *trans*-**7** with Mg-amide (*R*)-**1**



trans-**7** (*R*)-**8** *trans*-**7**

Entry	Temp. (°C)	t	Conversion (%)	e.r. of 8 (*R*:*S*)	e.r. of *trans*-7
1	-40	67 h	66	81:19	94:6
2	0	100 min	59	76:24	80:20
3	0	19 h	99	53:47	99:1

–40 °C and after 66% conversion, silyl enol ether (*R*)-**8** was obtained in good enantiomeric ratio (81:19). Furthermore, the initially racemic *trans*-ketone **7** was returned displaying a substantially increased level of one enantiomer over the other (94:6 e.r.). This kinetic resolution could be further enhanced by simply performing the deprotonation reaction at 0 °C for 19 h. Based on similar reasoning to that used with *trans*-**2**, the predominant returned ketone was assigned as the (*S*,*S*)-enantiomer.

In conclusion, we have now succeeded in extending the scope of our enantioselective deprotonation strategy using the chiral Mg-amide base (*R*)-**1** to include 2,6-disubstituted cyclohexanones. More particularly, with these substrates excellent levels of asymmetric induction have been realised, up to >99.5:0.5 e.r. Indeed, this represents the highest degree of enantioselection attained within this specific area of chiral base chemistry.[19] Additionally, we have also observed a novel Mg-amide mediated kinetic resolution process during the reaction of both *trans*-2,6-dimethylcyclohexanone and *trans*-2,6-di-*iso*-propylcyclohexanone. Interestingly with respect to gaining access to the chiral synthon of choice, with both of these substrates the enantiomeric enol ether to that obtained from the corresponding *cis*-ketone is formed in excess. The returned ketones also display good to excellent enantiomeric ratios. Overall, we believe that the practical developments detailed here will be of general use to those concerned with the desymmetrisation of prochiral cyclic ketones. In addition, the further use of alternative Mg-bisamide systems and the development of related methodology is currently underway in our laboratories and will be reported in due course.

Acknowledgement

We thank The Carnegie Trust for the Universities of Scotland for a postgraduate studentship (J.H.M.) and The Royal Society for a University Research Fellowship (K.W.H.). We also thank Pfizer Global Research and Development, Sandwich for generous funding of our research endeavours and the EPSRC Mass Spectrometry Service, University of Wales, Swansea, for analyses.

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(6) It should be noted that, in contrast to our initially reported protocol which utilised hexane as solvent,[5] clean formation of (*R*)-**1** can now be achieved using THF; this removes the requirement for a solvent swap prior to any deprotonation processes (*vide infra*).

(7) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523. Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1986**, 88.

(8) Enantiomeric ratios for **3** and **8** were determined by GC analysis (see Representative experimental procedure). Additionally, the absolute configurations of the major and minor enantiomers for **3** were assigned by correlation of optical rotation measurements with those of Koga and co-workers;[9] for **8** the major and minor isomer configurations were tentatively assigned by comparison with **3**.

(9) Kim, H.; Shirai, R.; Kawasaki, H.; Nakajima, M.; Koga, K. *Heterocycles* **1990**, *30*, 307.

(10) It is worth noting that similar deprotonation of the same ketone *trans*-**2** with the equivalent chiral Li-base resulted in the formation of only completely racemic enol ether; see ref. 7.

(11) The returned ketone *trans*-**2** displayed a negative optical rotation completely equivalent to and in accord with previously reported data: Fauvre, A.; Renard, M. F.;

Veschambre, H. *J. Org. Chem.* **1987**, *52*, 4893. See also: Anziani, P.; Cornubert, R.; Lemoine, M. *C. R. Hebd. Seances Acad. Sci.* **1949**, *229*, 431.

(12) Commercially available 2,6-diphenylcyclohexanone **4** afforded <1% of the *trans*-ketone upon isomer separation using column chromatography. As such, deprotonation was performed on the *cis*-ketone only.

(13) Enantiomeric ratios for **5** were determined by HPLC analysis: Chirasil OD-H column; λ (254 nm); eluant: 0.5% ^{i}PrOH in heptane; 0.2 ml/min; t_R = 22.7 min [*(S)*-**5**], t_R = 25.0 min [*(R)*-**5**]. Additionally, the absolute configurations of the major and minor enantiomers for **5** were tentatively assigned by correlation with **3**.

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(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(16) It should be noted that GC analyses for Table 3, Entries 2, 3, and 4 were performed using a sample concentration of 10 mg/mL *c.f.* Table 3, Entry 1 where a more standard concentration of 1 mg/mL was adopted.

(17) **Representative experimental procedure**: To a Schlenk flask, under N_2, was added Bu_2Mg (0.79 M solution in heptane, 1.27 mL, 1 mmol). The heptane was then removed in vacuo and replaced with THF (10 mL), followed by addition of (*R*)-*N*-benzyl-α-methylbenzylamine (0.42 mL, 2 mmol). The resultant solution was heated to reflux for 90 min and then slowly cooled to –40 °C, whereupon TMSCl (0.5 mL, 4 mmol) and HMPA (0.09 mL, 0.5 mmol) were added. After stirring for 20 min at –40 °C, *cis*-2,6-di-*iso*-propylcyclohexanone **7** (146 mg, 0.8 mmol) was added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction was allowed to stir at –40 °C for a further 5 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). After warming to room temperature the reaction mixture was extracted with ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous phase was extracted with ether (2 × 20 mL), the combined organic phase was then dried (Na_2SO_4) and the solvent removed in vacuo. The reaction conversion was determined as 99% by GC analysis [CP SIL 19CB fused silica capillary column; carrier gas H_2 (80 kPa); 45-150 °C; temperature gradient: 5 °C/min; t_R = 11.9 min (*cis*-**7**); t_R = 12.2 min (**8**)]. Flash column chromatography (eluting with petrol/ether 19:1) afforded (6*S*)-2,6-di-*iso*-propyl-1-trimethylsiloxy-1-cyclohexene (*S*)-**8** (184 mg, 90%) as a clear oil which displayed an enantiomeric ratio of 98.8:1.2 {Chirasil-DEX CB capillary column; carrier gas H_2 (40 kPa); 75 °C (1 min)-115 °C; temperature gradient: 1.3°C/min; t_R = 27.4 min [(*S*)-**8**]; t_R = 27.8 [(*R*)-**8**]}. IR (film): 1664 cm^{-1} (s, C=C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.04 (1H, septet, *J* = 6.9 Hz, CH), 2.22-2.15 (1H, m, CH), 2.03-1.80 (3H, m, CH and CH_2), 1.70-1.60 (2H, m, CH_2), 1.36-1.27 (2H, m, CH_2), 0.90 (3H, d, *J* = 6.9 Hz, CH_3), 0.89 (6H, t, *J* = 7.3 Hz, 2 × CH_3), 0.74 (3H, d, *J* = 6.8 Hz, CH_3), 0.17 ppm (9H, s, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 123.8, 45.0, 28.2, 26.5, 23.4, 22.4, 22.25, 21.3, 20.9, 20.4, 16.9, 0.8. HRMS: $C_{15}H_{30}OSi$, M^+ requires 255.2144; found 255.2143. Analysis calculated for $C_{15}H_{30}OSi$: C, 70.80, H, 11.88; found: C, 70.80, H, 12.03. $[\alpha]_D^{20}$ -4.1°, c 1.4, $CHCl_3$. All other compounds gave satisfactory spectral and analytical data.

(18) It is worth noting that *cis*-2,6-di-*tert*-butylcyclohexanone was also prepared by Raney Ni catalysed hydrogenation of the corresponding phenol.[14] However, all attempts to deprotonate this substrate with a range of (achiral) bases proved unsuccessful.

(19) For a comparison with Li-base systems which employ appreciably more complex amides, see: Graf, C.-D.; Malan, C.; Harms, K.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 5581. Aoki, K.; Tomioka, K.; Noguchi, H.; Koga, K. *Tetrahedron* **1997**, *53*, 13641. See also ref. 9 and Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **2000**, *41*, 6941.

Article Identifier:
1437-2096,E;2001,0,08,1253,1256,ftx,en;D12201ST.pdf