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Enantioselective deprotonation reactions using a novel homochiral magnesium amide base

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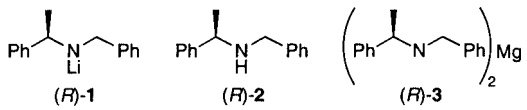
A novel homochiral magnesium bisamide base system has been prepared and reacted with a series of prochiral ketones in the presence of TMSCl to give efficient formation of the corresponding enol ethers in enantiomeric ratios of up to 95:5.

Optically pure lithium amide bases have proven to be versatile tools in modern asymmetric synthesis. Indeed, highly enantioselective deprotonation reactions have been accomplished for several sets of substrates, including conformationally locked ketones, epoxides, and tricarbonyl (η^6-arene)chromium complexes.[1] In turn, many of the more recent advances in this area have been accomplished by the development of new homochiral ligands and the tuning of reaction conditions to improve the selectivity of these lithium-mediated deprotonations.[2] In contrast to the Li-based strategies, magnesium reagents have received relatively little attention for use in asymmetric synthesis[3] and, in particular, as mediators of enantioselective deprotonation processes.

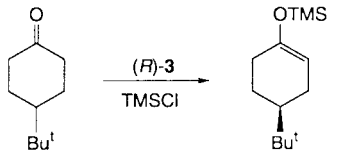
More recently, studies within our laboratories have shown how, in a racemic sense, magnesium amides can be employed as alternatives to their more widely used lithium counterparts in both enolisation and aldol addition reactions.[4] Indeed, advantages of the Mg-bases over the Li-analogues which have already been noted include their greater thermal stability (which, for example, allows aldol reactions between ketones to be promoted[4b]) and, in some instances, higher levels of more general reaction selectivity.[5] Consequently, with a view to developing asymmetric Mg-based protocols we considered that these observations, as well as the ability to formally bond two (chiral) ligands to the Mg centre, would allow good levels of stereoselectivity in organic transformations to be achieved. Herein, we report the first use of homochiral magnesium amide bases as reagents in the enantioselective deprotonation of conformationally locked ketones.

At the outset of this programme, and based on our recently reported structural study of the Li-amide (*R*)-**1**,[6] we chose to utilise readily available (*R*)-*N*-benzyl-α-methylbenzylamine, (*R*)-**2**. In due course, the Mg-amide base was readily prepared by the addition of dibutylmagnesium to 2 equiv. of the amine (*R*)-**2** in hexane solution, followed by heating to reflux for 90 min.† Analysis of the reaction mixture by ^{1}H NMR spectroscopy showed complete amination to the bisamide (*R*)-**3**.[7]



Subsequently, and based on extensive studies as reported in the chemical literature,[1] ketone **4a** was the substrate on which we chose to perform our initial deprotonation attempts. As shown in Table 1, a range of solvents, with and without HMPA as an additive,‡ were employed at −78 °C; from entries 1–5 it is clear that THF in the presence of 1 mol equiv. of HMPA provided good conversion to the silyl enol ether **5**.§ Furthermore and to our delight, even this simple Mg-amide base system displayed high levels of enantioselectivity for the (*S*)-silyl enol ether, (*S*)-**5a**.¶ Subsequent reaction optimisation (entries 5–8) showed that the use of only 0.5 mol equiv. of HMPA (entry 7) delivered a good reaction conversion and, at least as importantly, provided an enhanced level of enantioselection with a 91:9 enantiomeric ratio (82% ee) of (*S*)-**5a** over its optical isomer.‖ It should also be noted that reaction at −98 °C in THF, again with 0.5 mol equiv. of HMPA, gave a similar conversion (80%) and the same e.r. of 91:9, whereas reactions at more elevated temperatures with (*R*)-**3** led to a general reduction in enantioselectivity.

Table 1 Enantioselective deprotonations of **4a** and formation of silyl enol ether **5a**[a]



4a (*S*)-**5a**

Solvent	HMPA (mol equiv.)	Conversion (%)[b]	Enantiomeric ratio (e.r.)[b] (*S*):(*R*)
Et_2O	0	0	—
Et_2O	1	83	80:20
CH_2Cl_2	1	40	72:28
THF	0	33	90:10
THF	1	94	86:14
THF	2	26	84:16
THF	0.5	82	91:9
THF	0.1	53	91:9

[a] All reactions were performed at −78 °C for a period of 6 h. [b] Conversions and enantiomeric ratios were determined by separate GC analysis; see footnote ‖.

With these initial studies in hand and in order to investigate the wider applicability of this Mg-based strategy, a range of substituted cyclohexanones were subjected to our optimised reaction conditions. As can be seen from Table 2, using ketones **4a**–**e** the developed protocol with (*R*)-**3** was shown to consistently deliver the corresponding enol ethers **5a**–**e** with good efficiency and enantioselection, up to an excellent e.r. of 95:5 for **5d**.

To further extend our studies, as shown in Scheme 1, the less reactive 2,6-dimethyl ketone **4f** (82:18 *cis*:*trans* mixture; *trans*-ketone 50:50 e.r.) was also transformed with appreciable asymmetric induction (e.r. 90:10) to enol ether **5f** with the (*R*)-enantiomer in excess (55% conversion).** Notably, upon reaction completion the ratio of the returned ketone **4f** displayed a relatively unchanged 80:20 *cis*:*trans* ratio. However, the final enantiomeric ratio of the the *trans*-isomer of the starting ketone was 37:63. These latter observations and the elevated enantiomeric ratio for enol ether **5f** affirm that the Mg-amide base (*R*)-**3** had mediated a kinetic resolution process with the *trans*-ketone, as well as efficient asymmetric deprotonation with the *cis*-isomer.

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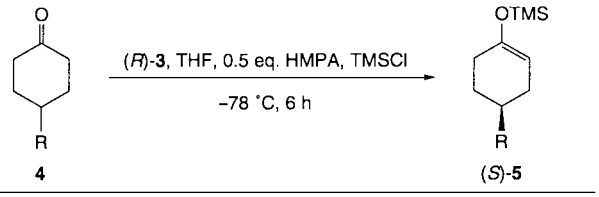
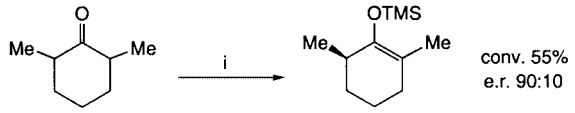
Table 2 Enantioselective deprotonations and silyl enol ether formation with Mg-amide (*R*)-**3**



4 (*S*)-**5**

R	Product	Conversion[a] (%)	Enantiomeric ratio (e.r.) (*S*):(*R*)[b]
Bu^t (**4a**)	**5a**	82	91:9
Ph (**4b**)	**5b**	79	87:13
Me (**4c**)	**5c**	81	91:9
Pr^i (**4d**)	**5d**	77	95:5
Pr^n (**4e**)	**5e**	88	88:12

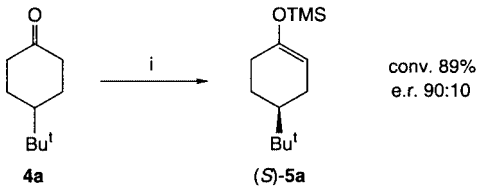
[a] Conversions were determined by GC analysis. [b] See footnote **.



4f (*R*)-**5f**

Scheme 1 *Reagents and conditions*: i, (*R*)-**3**, HMPA (0.5 equiv.), TMSCl (4 equiv.), THF, −78 °C, 65 h.

Finally, in attempts to find a more practically acceptable additive to replace HMPA, equivalent quantities of DMPU were introduced to reactions of **4a** with (*R*)-**3**. In THF solvent at −78 °C, when 0.5 mol equiv. of DMPU were used, pleasingly an enantiomeric ratio of 90:10 in favour of (*S*)-**5a** was achieved in 89% conversion (Scheme 2); use of 1 mol equiv. of DMPU led to comparable conversion (93%) and e.r. (86:14).



4a (*S*)-**5a**

Scheme 2 *Reagents and conditions*: i, (*R*)-**3**, DMPU (0.5 equiv.), TMSCl (4 equiv.), THF, −78 °C, 6 h.

In conclusion, having prepared a novel homochiral magnesium bisamide system, we have demonstrated, for the first time, that such bases can successfully mediate enantioselective deprotonation reactions. Indeed, significant levels of selection in these asymmetric processes have been realised, and to an extent that they are already approaching the optimum enantiomeric ratios achievable by more complex Li-base systems.[1] Furthermore, and more importantly for the widespread use of the Mg-based approach, this efficient enantioselection has been achieved using a reagent which is easily prepared from a simple, readily available, and inexpensive amine. The application of further Mg-bisamide systems and the development of related methodology is currently under investigation and will be reported in due course.

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Notes and references

† *Preparation* of Mg-amide base (*R*)-**3**: a Schlenk flask was charged with a solution of amine (*R*)-**2** (0.42 mL, 2 mmol) in dry hexane (8 mL) under N_2. To this stirred solution, dibutylmagnesium (0.85 mL of a 1.1 M solution in heptane, 1 mmol) was added dropwise and the mixture heated to reflux for 90 min. The reaction solution was then allowed to cool followed by removal of all solvent *in vacuo* and replacement by the solvent of choice for the subsequent deprotonation reaction. ^{1}H NMR spectroscopic analysis of the resultant yellow oil, after removal of the reaction solvent, is consistent with the formation of the bisamide (*R*)-**3**: (400 MHz, C_6D_6, 25 °C): δ 7.22–7.02 (m, 10H, Ph), 3.57–3.48 (m, 2H, 2 × CH), 3.40–3.35 (m, 1H, CH), 1.11 (d, *J* 6.6 Hz, 3H, CH_3).

‡ The beneficial use of HMPA as a co-solvent has been reported previously for various Li-mediated enantioselective reactions.[1a,c]

§ From the 94% conversion (by GC) shown as entry 5 in Table 1, following alumina column chromatography, an isolated yield of 64% was obtained for **5a** with a 90% recovery of the starting amine (*R*)-**2**.

¶ Formation of the (*S*)-silyl enol ether, (*S*)-**5a**, is consistent with the selectivity of the analogous Li-base (*R*)-**1**.[8] Additionally, GC analysis, by comparison with that of Knochel and co-workers[2b] allowed confirmation of the assignment of absolute stereochemistry for the enol ether **5a**.

‖ The typical procedure for the enantioselective deprotonation reactions is illustrated by a preparation of **5a**: a Schlenk flask containing base (*R*)-**3** (1 mmol) suspended in THF (10 mL) was cooled to −78 °C under N_2. The flask was then charged with TMSCl (0.5 mL, 4 mmol) and HMPA (0.09 mL, 0.5 mmol). After stirring for 20 min at −78 °C, 4-*tert*-butylcyclohexanone (123 mg, 1 mmol) was added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction was allowed to stir at −78 °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 diethyl ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The combined aqueous phase was extracted with diethyl ether (2 × 20 mL), the combined organic phase was then dried over Na_2SO_4, followed by removal of solvent *in vacuo*. The reaction conversion was determined as 82% by GC analysis [DB 179 fused silica capillary column, carrier gas H_2 (80 kPa), 60–190 °C; temperature gradient: 45 °C min^{-1}, t_r = 3.1 min (**4a**), t_R = 3.3 min (**5a**)]. The resultant yellow oil was then filtered through a silica plug and washed with a light petroleum–diethyl ether solution (9:1). This afforded **5a** as a colourless oil. The enantiomeric ratio was determined by GC analysis as 91:9 [Chirasil-DEX CB capillary column, carrier gas H_2 (30 kPa), 80 °C (1 min)–120 °C; temperature gradient: 1.5 °C min^{-1}, t_R = 32.2 min [(*S*)-**5a**], t_R = 32.8 min [(*R*)-**5a**)]].

** Enantiomeric ratios were determined by GC analysis. Additionally, the absolute configuration of the major and minor enantiomers for **5b**, **5c**, **5d** and **5f** were assigned by correlation of optical rotation measurements with those of Koga and coworkers;[9] for **5e** the major and minor isomer configurations were tentatively assigned by comparison with **5a–d**. Furthermore, all compounds exhibited satisfactory analytical and spectral data.

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