Novel Enantiomerically Pure Heteroleptic Magnesium Complexes for Use in Enantioselective Deprotonation Reactions

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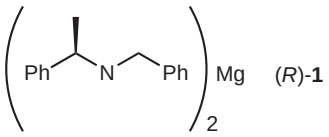
Abstract: Two classes of heteroleptic magnesium complexes, alkylmagnesium amides $RMgNR_2$ and aryloxymagnesium amides $ROMgNR_2$, have been prepared and subsequently shown to be efficient bases in the enantioselective deprotonation of substituted cyclic ketones. When compared with their magnesium bisamide counterparts, significantly different reactivity and selectivity profiles, including an unexpected reversal in enantioselectivity, has been observed with the new reagents.

Key words: asymmetric synthesis, chirality, magnesium amides, heteroleptic complexes

Enantiomerically pure magnesium bisamides $(R_2N)_2Mg$ have recently been shown to be excellent reagents for use in enantioselective deprotonation reactions,[2] providing a complementary system to their well-established lithium-counterparts.[3] Our previous studies have concentrated on the use of homoleptic magnesium complexes, where the metal binds to a pair of identical chiral amide anions. However, a key difference, and potential advantage of the magnesium reagents is the divalent nature of the metal, which permits covalent binding to two dissimilar anionic moieties, i.e. heteroleptic complexes.[4] In turn, this feature allows access to reagents where both a reactive anion and a spectator anion can be bound simultaneously to the metal centre. Hence, in addition to the reactive anion, the steric and electronic nature of the spectator may be varied in order to optimise the performance of the reagent. This possibility has led us to explore the formation and utility of two new classes of enantiopure heteroleptic complexes: alkylmagnesium amides, $RMgNR_2$, and aryloxymagnesium amides, $ROMgNR_2$. Very recently Eaton has utilised the alkylmagnesium amide $BuMgN\textit{i}\text{-}Pr_2$ as a highly effective base for the regioselective deprotonation and subsequent metallation of cyclopropylcarboxamides.[5] In addition, this type of complex has previously been used as a reducing reagent,[6] and also as a stereoselective alkylation reagent.[7] However, to date, there are no examples of the use of this type of complex as a base in asymmetric synthesis. Herein, we outline the application of such complexes as reagents in the enantioselective deprotonation of conformationally locked cyclic ketones.[8]

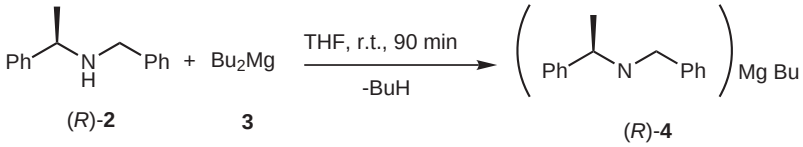
At the outset of this program, and based on our recently reported studies using magnesium bisamide (*R*)-**1** (Figure 1),[9] the structurally simple and commercially available (*R*)-*N*-benzyl-α-methylbenzylamine [(*R*)-**2**] was combined in equimolar amounts with dibutylmagnesium **3** in THF, to furnish the butylmagnesium amide (*R*)-**4** after stirring for 90 minutes at room temperature (Scheme 1).



(*R*)-**1**

Figure 1

Subsequently, initial deprotonation attempts were carried out with ketone **5a**, using conditions previously optimised for the bisamide (*R*)-**1**.[2] As can be seen from Table 1, a good 88% conversion to silyl enol ether (*S*)-**6a** was observed using 0.5 equivalents HMPA as an additive and, upon analysis, an enantiomeric ratio (e.r.) of 84:16 was displayed. These results are promising when compared to those obtained using the magnesium bisamide base (*R*)-**1**, which previously gave similar results (82% conversion, 91:9 e.r.), yet which required double the quantity of chiral ligand.[9,10]



(*R*)-**2** **3** (*R*)-**4**

Scheme 1

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Table 1 Enantioselective Deprotonations of **5a** with Various Additives Using Base (*R*)-**4**[12]

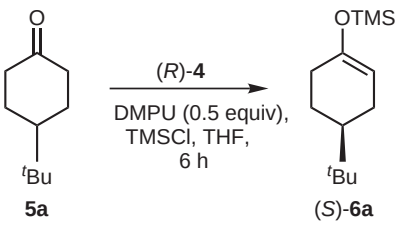
Additive (0.5 equiv)	Conversion (%)	Enantiomeric Ratio *S*:*R*
HMPA	88	84:16
DMPU	80	86:14
None	61	87:13

We were also pleased to note that the more environmentally benign additive DMPU could replace the known mutagen HMPA, in turn, furnishing a slight increase in selectivity (86:14 er).[11] Previously, the use of strong Lewis base additives in the magnesium-mediated enantioselective deprotonation reactions has been found to be necessary in order to affect good conversion to silyl enol ether.[2] However, in this instance significantly different reactivity is observed using the heteroleptic complex (*R*)-**4**, where reaction in the absence of any additive still gave a reasonable 61% conversion to silyl enol ether **6a**. It is also worth noting that the deprotonations using base (*R*)-**4** favoured the formation of (*S*)-**6a**, which is the same directional preference as that observed using bisamide (*R*)-**1**.[2,9]

Having established that base (*R*)-**4** was indeed capable of performing enantioselective deprotonation reactions, the effect of temperature on the selectivity of the base was then investigated. From Table 2 it can be seen that while lowering the temperature to –90 °C gave no improvement in e.r., reaction at the higher temperature of –40 °C still produced silyl enol ether **6a** with an appreciable enantioselectivity (81:19). Raising the temperature further to room temperature resulted in both a decrease in reaction conversion and in enantioselection.

With these initial studies complete, and in order to extend the utility of this novel heteroleptic base, a range of 4-substituted cyclohexanones was subjected to our optimised conditions, both with and without the additive, DMPU. As can be seen from Table 3, high conversions to the corresponding silyl enol ether were obtained when DMPU was present as an additive, and the selectivities found are comparable to those using the less readily accessible bisamide (*R*)-**1**.[2] For example, the reaction of (*R*)-**4** with ketone **5b** gives rise to an 85% conversion and 87:13 er, whereas the analogous reaction using bisamide base (*R*)-**1** produces an 83% conversion and an er of 88:12.[9] Even in the absence of any additive, good conversions to silyl enol ethers were again obtained over the range of ketones studied, with only a small reduction in selectivity (2–3%).

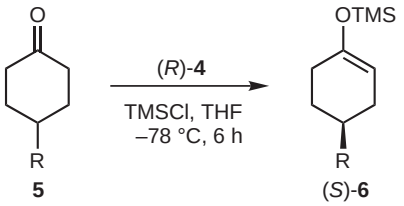
Table 2 Enantioselective Deprotonations of **5a** at Various Temperatures Using Base (*R*)-**4**



Temperature (°C)	Conversion (%)	Enantiomeric Ratio *S*:*R*
–90	71	85:15
–78	80	86:14
–40	87	81:19
r.t.	50	60:40

Next, to gain a more detailed understanding of the nature of the magnesium species in solution, a preliminary ^{1}H NMR spectroscopic study was carried out. Equimolar quantities of (*R*)-**2** and **3** were mixed in deuterated THF at room temperature and the spectra obtained after 15 min clearly showed the disappearance of the amine –NH at δ 1.9, and a reduction in the number of characteristic *n*- and *s*-butyl protons at δ –0.24 and δ –0.44, respectively. Integration of the alkyl protons and the benzylic amide protons indicated an approximately 1:1 ratio of amide to alkyl units. This, along with the presence of only one set of signals for the amide, supports the formation of the desired alkylmagnesium amide (*R*)-**4**. After this time, ketone **5a**

Table 3 Enantioselective Deprotonations Using Base (*R*)-**4** with a Range of 4-Substituted Cyclohexanones



R	Additive	Conversion (%)	Enantiomeric Ratio *S*:*R*
n-Pr (**5b**)	DMPU	85	87:13
	None	63	85:15
i-Pr (**5c**)	DMPU	84	86:14
	None	66	83:17
Me (**5d**)	DMPU	84	83:17
	None	70	80:20
Ph (**5e**)	DMPU	83	86:14
	None	47	84:16

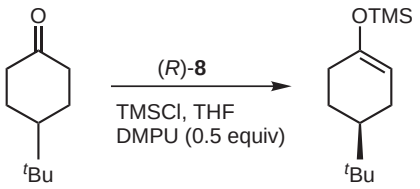
was added to the newly formed base at room temperature, and the resulting mixture examined after 50 min. The spectra now displayed the reappearance of the amine -NH with the retention of the butyl signals. Re-analysis of the mixture after 24 h showed no significant change, again with the amine proton and butyl peaks evident. These results are consistent with deprotonation of the ketone occurring via the amido unit of (*R*)-**4**. This mode of action for the base is also consistent with our findings that no alkylation or reduction products are found in these reactions.[13] In contrast, significant quantities of secondary and tertiary alcohols are formed on the direct reaction of **3** with **5a**. For example, adding ketone **5a** to a solution of **3** in THF at room temperature over one hour, followed by standard work-up, results in the formation of 44% of tertiary alcohols (alkylated product) and 13% of the alcohol (reduced product), with recovery of 43% of the starting ketone. These results clearly establish that the alkylmagnesum amide (*R*)-**4** is a far superior base in selective deprotonation reactions than the dialkylmagnesium compound **3**.[5]

To investigate further the scope and reactivity of heteroleptic magnesium complexes for use as selective bases, aryloxymagnesium amides were targeted as potential reagents. To initiate these studies, the readily available and inexpensive 2,6-di-*tert*-butylphenol (**7**) was used as a bulky achiral alcohol, along with our established chiral amine (*R*)-**2**. The new base (*R*)-**8** was readily prepared by combining **3** with 1 equiv of amine (*R*)-**2** in THF, followed by stirring at room temperature for 15 minutes before adding 1 equiv of alcohol **7** and heating to reflux for 1 hour, as illustrated in Scheme 2.

Once formed, base (*R*)-**8** was then reacted in situ with ketone **5a** over a range of temperatures to assess the effectiveness of this complex as an asymmetric induction reagent. As can be seen from Table 4, while base (*R*)-**8** gave good conversions to silyl enol ether, the selectivity achieved was only low across the temperature range studied (–78 °C to 40 °C).

Despite these results, we then moved on to a different ketonic substrate, in the form of the more hindered *cis*-2,6-dimethylcyclohexanone (**9**). This was subsequently reacted with base (*R*)-**8**, again over a range of different temperatures; the results of the reactions are displayed in Table 5. Firstly, the most striking aspect of this series of

Table 4 Enantioselective Deprotonations of **5a** at Various Temperatures Using Base (*R*)-**8**

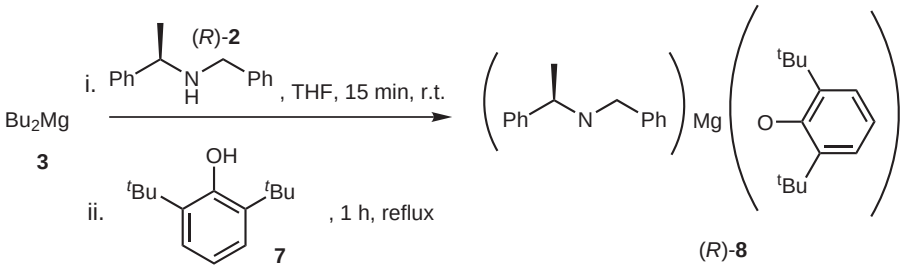


5a (*S*)-**6a**

Temperature (°C)	Time (h)	Conversion (%)	Enantiomeric Ratio *S*:*R*
–78	19	78	57:43
–40	19	54	57:43
–20	19	82	54:46
0	19	84	58:42
r.t.	19	83	55:45
40	1	64	57:43

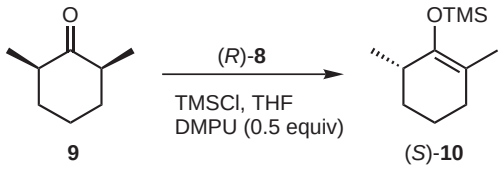
reactions is that the base gives rise to the opposite selectivity to that observed in the analogous reaction using bisamide (*R*)-**1**,[14] despite both reagents using the same chiral amide anion. Previously, selectivities of up to 97:3 in favour of (*R*)-**10** have been recorded using base (*R*)-**1**, making the reversal in selectivity observed using (*R*)-**8** all the more remarkable. These results suggest that the asymmetric induction in these reactions is controlled by the overall chiral environment created by the organometallic complex and not just by the local chirality of the attached amide anion. In fact, base (*R*)-**8** provides a complementary system to bisamide base (*R*)-**1**, allowing access to both enantiomers of silyl enol ether **10** from the same chiral amide source.

Again with regards the reactions of dimethylcyclohexanone **9** (Table 5), we were also intrigued to find that the enantioselectivity of the reactions increased on raising the reaction temperature. In fact, at –78 °C a low 46:54 er was recorded, whereas at 40 °C an er of 83:17 was obtained. Above this temperature the selectivity of the reactions again decreases. Since low temperatures are commonly required for efficient control within enantioselective



Scheme 2

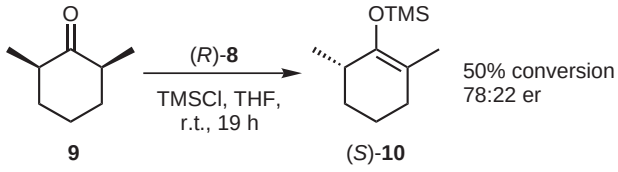
Table 5 Enantioselective Deprotonations of **9** at Various Temperatures Using Base (*R*)-**8**



Temperature (°C)	Time (h)	Conversion (%)	Enantiomeric Ratio *R*:*S*
–78	68	78	46:54
–40	68	54	76:24
r.t.	19	62	78:22
40	1	33	83:17
50	1	46	76:24
66	1	11	67:33

deprotonation reactions, this establishes an intriguing practical development. Additionally, this observation highlights the high thermal stability of these magnesium reagents.[15]

Finally, base (*R*)-**8** was reacted in the absence of DMPU, to ascertain whether this system required the presence of a strongly polar additive. To our delight, reaction at room temperature led to a retention of the previously observed selectivity, with only a small decrease in reaction conversion (Scheme 3).



Scheme 3

In conclusion, we have developed two new classes of enantiopure heteroleptic magnesium complexes for use in enantioselective deprotonation reactions. Alkylmagnesium amide (*R*)-**4** has been shown to be an effective base for a range of 4-substituted cyclohexanones, displaying enantioselectivities comparable to those of our bisamide (*R*)-**1**, but which requires only half the quantity of chiral ligand. Furthermore, our ^{1}H NMR spectroscopic studies indicate that the amide residue of the reagent is most likely to be responsible for the deprotonation process. If this is indeed the case, then the development of a sub-stoichiometric, catalytic, system should be possible and these studies are currently underway in our laboratories.[16] In addition, the aryloxymagnesium amide (*R*)-**8** has been found to be an efficient base for the enantioselective deprotonation of ketone **9**, and which interestingly displays the opposite selectivity to bisamide (*R*)-**1**. Also, the optimum selectivity for this system was unexpectedly observed at elevated temperatures (40 °C). This facet of chiral magnesium complexes, after further careful optimisation, should increase the applicability of these systems to a wider range of less reactive substrates, whilst also making them attractive for more widespread use. Moreover, it has also been shown that both (*R*)-**4** and (*R*)-**8** can be used in the absence of any Lewis basic additives to give good conversions, without any substantial deleterious effect on enantioselectivity. Finally, considering the critical effect of the 'spectator' aryloxy unit found in the reactions of (*R*)-**8**, we are now investigating the use of chiral alcohols in these systems to further improve upon the selectivities achieved thus far.

Acknowledgment

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(10) It is also worth noting that in order to access the bisamide species, heating to reflux in THF or hexane (with two equivalents of the chiral amine) is required.[2,9]
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(12) 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 the addition of (*R*)-*N*-benzyl-α-methylbenzylamine **2** (0.21 mL, 1 mmol). The resultant solution was stirred at room temperature for 90 min and then cooled to –78 °C, whereupon TMSCl (0.5 mL, 4 mmol) and DMPU (0.06 mL, 0.5 mmol) were added. After

stirring for 20 min at –78 °C, 4-*tert*-butylcyclohexanone **5a** (0.123 g, 0.8 mmol) was added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction was then quenched by the addition of saturated $NaHCO_3$ (5 mL). After warming to room temperature the reaction mixture was extracted with diethyl ether (30 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 dried (Na_2SO_4), and the solvent removed in vacuo. The reaction conversion was determined as 80% by G.C. analysis [CP SIL 19CB fused silica capillary column; carrier gas H_2 (80 kPa); 45 °C (1 min)–190 °C; temperature gradient: 45°C/min; t_R = 3.27 min (**5a**), t_R = 3.69 min (**6a**)]. Flash column chromatography (eluting with petroleum ether) afforded (*S*)-4-*tert*-butyl-1-trimethylsiloxy-1-cyclohexene (*S*)-**6a** (0.136 g, 60%) as a clear oil which displayed an enantiomeric ratio of 86:14 {Chirasil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70–130 °C; temperature gradient: 1.7 °C/min; t_R = 37.66 min [(*S*)-**6a**], t_R = 37.97 min [(*R*)-**6a**.]}.

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