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Application of polydentate chiral amines within magnesium-mediated asymmetric deprotonation reactions

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Abstract—A set of polydentate secondary amines, each containing two stereogenic centres, were prepared. These were subsequently utilised in magnesium-mediated asymmetric deprotonation reactions and excellent enantiomeric ratios were obtained (up to 94:6 er). Furthermore, these bases tend to be highly efficient in the absence of strong Lewis base additives, which demonstrates an additional practical advantage over existing protocols.

Chiral magnesium amides have been shown to be effective reagents in asymmetric synthesis both as homo-[1,2] and heteroleptic species.[3] Our recent studies into enantioselective deprotonations have, for the most part, been carried out using the structurally simple and commercially available (*R*)-*N*-benzyl-α-methylbenzylamine (*R*)-**1** as its respective magnesium bisamide (*R*)-**2** (Fig. 1). Having stated this and in a more general sense, the substantial literature on the lithium amide counterparts[4] has shown that many of the most selective systems utilise more complex ligands, which commonly incorporate side arms capable of chelating to the metal centre.[5] With this in mind, we decided to prepare a set of polydentate amines for use in our Mg-mediated enantioselective deprotonation processes.

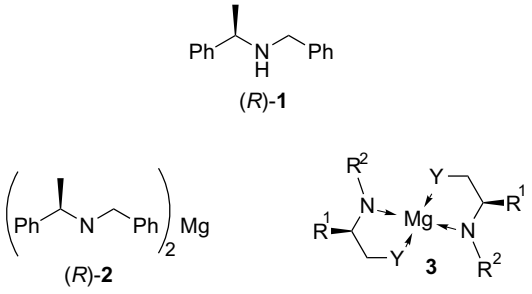

Figure 1.

There are three key points to our ligand design: (i) each ligand has the ability to form a stable five-membered chelate ring (chelation model **3** shown in Fig. 1); (ii) a subset of the amides contain yet another heteroatom as a potential donor site; and (iii) each amine features two stereocentres in order to investigate the effect of the second stereogenic centre upon the selectivity of their respective magnesium bisamides. In this regard we targeted the set of six amines shown in Figure 2.

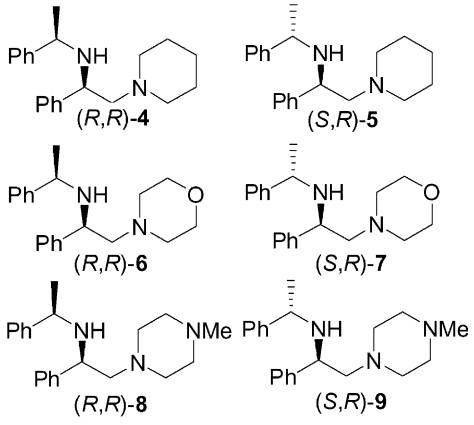

Figure 2.

Keywords: Asymmetric synthesis; Chiral amines; Enantioselective deprotonation; Magnesium amides.
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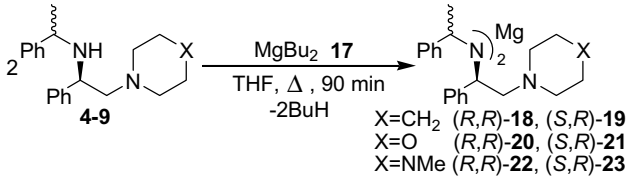
The original preparation, and hence application, of amines of this type has suffered from convoluted synthetic routes involving four or more steps from amino acid starting materials.[5a,6] However, alternatives to the initially published routes have appeared recently[7] and the 'one-step' synthesis from O'Brien and co-workers has been particularly notable.[7c] More specifically, this route starts from optically enriched styrene oxide **10**, which is commercially available, albeit around 1000-fold more expensive than in its racemic form. Alternatively, optically enriched styrene oxide may be obtained through the efficient catalytic hydrolytic kinetic resolution method of Jacobsen and co-workers.[8] Through the minor modification of doubling the catalyst loading (to 1.6%), in addition to increasing the quantity of the H_2O nucleophile (to 0.7 equiv), we found that (*R*)-**10** is consistently produced in excellent optical purity (>99% ee), without loss of catalyst activity.

With quantities of (*R*)-**10** in hand the synthesis of the first set of six amines was undertaken, following the route proposed by O'Brien and co-workers.[7c] Upon isolation and purification, pure amines **4**–**7** were obtained in 53–60% overall yield,[9] ready for application in Mg-mediated asymmetric processes. Somewhat disappointingly, using the same approach, the amine possessing the *N*-methylpiperazine unit (*R*,*R*)-**8** was isolated in a low 21% yield. Based on this, an alternative route to the remaining desired *N*-methylated amine (*S*,*R*)-**9** was attempted. More specifically, using an *N*-formyl unit (as a masked methyl group), (*R*)-**10** was treated with *N*-formylpiperazine **11**, giving the requisite aminoalcohols, and the aziridinium ion (*S*)-**12** upon mesylation. Trapping with the amine nucleophile (*S*)-**13** in a biphasic mixture, but this time using slightly different conditions, that is, with THF as co-solvent and an extended reaction time of 72 h, we obtained the *N*-formyl amine (*S*,*R*)-**14**. Subsequent reduction with $LiAlH_4$ gave the pure targeted amine (*S*,*R*)-**9** (74%; Scheme 1).

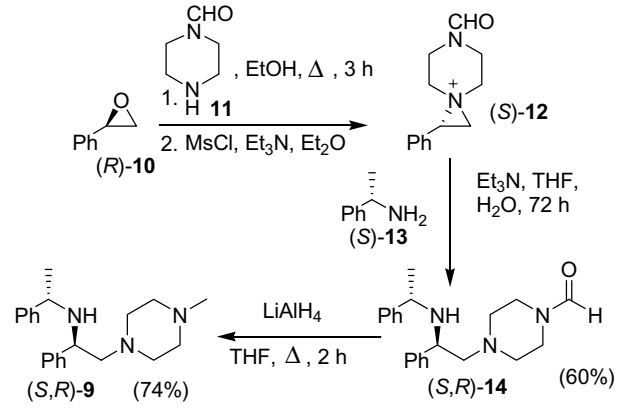
In order to test the generality of the latter set of conditions for amine formation, the syntheses of the piperidine-derived amines (*R*,*R*)-**4** and (*S*,*R*)-**5** were repeated employing THF as a co-solvent and a longer reaction time of 72 h. Using commercially available solvents and reagents, without additional purification, afforded 77% and 80% yields of (*R*,*R*)-**4** and (*S*,*R*)-**5**, respectively, showing a 20% improvement over the previous conditions.

With quantities of the desired set of amines in hand, initial tests using magnesium bisamide derivatives could be carried out. We chose the enantioselective deprotonation of the benchmark conformationally locked prochiral ketone 4-*tert*-butylcyclohexanone **15** to form optically enriched samples of trimethylsilyl enol ether **16**. Bisamide formation was carried out using our established method[1] of heating 2 equiv of the amine together with commercially available Bu_2Mg **17** in THF for 90 min (Scheme 2).

These bases were then used directly in deprotonation reactions, using the previously optimised conditions for our magnesium-mediated processes.[1] The reactions were carried out both in the absence and presence of the Lewis base additives HMPA and DMPU, since we have previously shown that these can have effects on both reactivity and selectivity.[10] Considering the magnesium bisamide derived from the piperidine substituted amine (*R*,*R*)-**18** we see good conversions and excellent ers of 93:7 observed for all reaction runs (Table 1, entries 1–3). These results are particularly encouraging in that they represent the highest levels of enantioselection achieved to date with this substrate within our magnesium-mediated systems.[1,10] Moreover, these enhanced levels of selectivity are achieved even in the absence of a donor additive. It is also interesting to note that the opposite

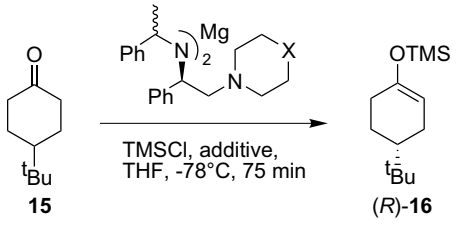


Scheme 2.



Scheme 1.

Table 1. Enantioselective deprotonation of **15** with Mg-bisamides **18/19**



Entry	Mg-amide	X	Additive (0.5 equiv)	Conv. (%)	er (*R*):(*S*)[1]
1	(*R*,*R*)-**18**	CH_2	HMPA	77	93:7
2	(*R*,*R*)-**18**	CH_2	DMPU	90	93:7
3	(*R*,*R*)-**18**	CH_2	None	58	93:7
4	(*S*,*R*)-**19**	CH_2	HMPA	66	87:13
5	(*S*,*R*)-**19**	CH_2	DMPU	88	88:12
6	(*S*,*R*)-**19**	CH_2	None	87	88:12

enantiomer of silyl enol ether (*R*)-**16** was formed preferentially here, compared with the (*S*)-enantiomer, which is accessed in excess from the use of the previously employed Mg-amide bases, for example, (*R*)-**2**.[1,10] The conversions obtained with the Mg-systems are also worthy of note; in the presence of additives a conversion of up to 90% was achieved (Table 1, entry 2)[11] and, importantly, in the absence of any additive the conversion of 58% was observed (cf. the 33% obtained previously with our more simple Mg-bisamide system (*R*)-**2** with no additive, over 6 h at −78 °C).[1] Additionally and overall, these results also compare favourably with those obtained using this substrate within the analogous chiral lithium amide base area.[4,5,12]

On examining the effect of changing to the (*S*,*R*)-diastereomer of this piperidine-derived base (*S*,*R*)-**19**, again, consistently high conversions were obtained and most notably 87% in the absence of donor additive (Table 1, entry 6). However, in each of these reactions a small reduction in enantioselectivity was observed. It is notable that the same (*R*)-enantiomer of product was formed preferentially,[1,10] indicating that this second chiral centre has only a minor effect on the selectivity of these bases.

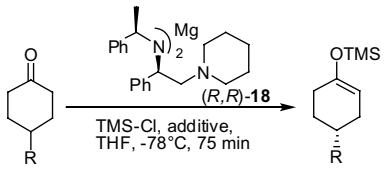
Next, we wished to test whether the presence of an additional heteroatom within the ligand would afford a more selective system. The first species investigated were the two *N*-methylpiperazine-derived Mg-amides, (*R*,*R*)-**22** and (*S*,*R*)-**23**. Good to excellent conversions were again achieved in all cases, most notably in the presence of 0.5 equiv of DMPU wherein up to 94% conversion was obtained after 75 min (Table 2, entry 2). For the most part, the ers obtained were comparable between the two stereoisomers (except that shown in entry 6, with no additive, wherein a lower er was observed). Overall with (*R*,*R*)-**22** and (*S*,*R*)-**23**, only slightly lower levels of selection were obtained than with (*R*,*R*)-**18**, with the optimum ers of 92:8 being obtained in the presence of DMPU with either diastereomer (Table 2, entries 2 and 5).

Moving to test the effect of changing to an oxygen heteroatom within our ligand, we observed comparable ers across the reactions attempted (Table 2, entries 7–12). Interestingly, the enantioselection observed with (*R*,*R*)-**20** increased in a stepwise fashion, from having HMPA to having no Lewis base additive (Table 2, entries 7–9). Relatively good conversions were also observed with, again, DMPU providing optimum efficiency (up to 96%; Table 2, entries 8 and 11). Indeed, this is in line with each of the bases studied (Tables 1 and 2). Therefore, it is clear that use of DMPU as additive (and even, in some cases, no additive at all) is preferred to the less acceptable HMPA.

Table 2. Enantioselective deprotonation of **15** with Mg-bisamides **20**–**23**

Entry	Mg-amide	X	Additive (0.5 equiv)	Conv. (%)	er (*R*):(*S*)[1]
1	(*R*,*R*)-**22**	NMe	HMPA	86	91:9
2	(*R*,*R*)-**22**	NMe	DMPU	94	92:8
3	(*R*,*R*)-**22**	NMe	None	88	91:9
4	(*S*,*R*)-**23**	NMe	HMPA	68	91:9
5	(*S*,*R*)-**23**	NMe	DMPU	92	92:8
6	(*S*,*R*)-**23**	NMe	None	59	87:13
7	(*R*,*R*)-**20**	O	HMPA	93	86:14
8	(*R*,*R*)-**20**	O	DMPU	96	88:12
9	(*R*,*R*)-**20**	O	None	89	90:10
10	(*S*,*R*)-**21**	O	HMPA	57	86:14
11	(*S*,*R*)-**21**	O	DMPU	83	89:11
12	(*S*,*R*)-**21**	O	None	55	89:11

Table 3. Enantioselective deprotonation of 4-substituted cyclohexanones **24**–**27** with Mg-bisamide (*R*,*R*)-**18**



24: R=Me
25: R=Ph
26: R=^{n}Pr
27: R=^{i}Pr

(*R*)-**28**
(*R*)-**29**
(*R*)-**30**
(*R*)-**31**

Entry	Ketone	Additive (0.5 equiv)	Conv. (%)	er (*R*):(*S*)[1]
1	**24**	DMPU	89	92:8
2	**24**	None	67	93:7
3	**25**	DMPU	91	94:6
4	**25**	None	60	94:6
5	**26**	DMPU	93	94:6
6	**26**	None	76	94:6
7	**27**	DMPU	97	94:6
8	**27**	None	78	94:6

In order to initially assess the wider utility of these chelating bases, the species found to give the highest levels of enantioselection, Mg-bisamide (*R*,*R*)-**18**, was tested on a series of 4-substituted cyclohexanones **24**–**27** (Table 3). This base was tested on each substrate both with no additive and in the presence of DMPU. In each case, excellent enantioselectivity was obtained. The ers of the products formed were comparable across each substrate and, pleasingly, there was, generally, a significant improvement in selectivity over our other Mg-amide bases.[1,10] Interestingly, the presence of DMPU as additive seems to have very little, if any, effect on selectivity, but affords a general increase in conversion of around 20%. These promising results have prompted further and ongoing investigations into the wider application of this, and other, Mg-amide bases.

As part of efforts towards rationalising the various effects of altering the ligand backbone, we carried out ab initio molecular calculations on model systems at the HF/6-31G* level of theory.[13] The simple bisamide complex **32** (Fig. 3), which contains a pair of *N*-methyl amino anions and two 5-membered chelate rings, geometry optimised to an energy minimum as shown. This demonstrates that it is, indeed, possible to form a chelate within such Mg-bisamide species, in the manner proposed.

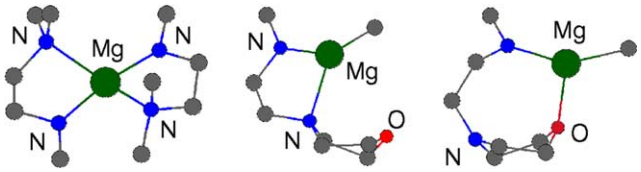


Figure 3.

Moving to examine the more complex system of a potentially tridentate ligand (e.g., as would be possible with the use of amines **6**–**9**), we chose to incorporate only one ligand onto the magnesium centre, to minimise any possible steric influences. Based on this, model complex **33** was constructed, which contains a morpholine-based side arm and a methyl group as the second anion on Mg (Fig. 3). Upon geometry optimisation of **33** it was found that the additional oxygen chelation is not possible, with the ligand preferring to undergo donation exclusively through the nitrogen atom. Finally, a comparative calculation was carried out using complex **34** to investigate the stability of the eight-membered ring chelate (Fig. 3). Comparing isomers **33** and **34** we see an increase in energy for the eight-membered chelate of +9.98 kcal/mol, indicating that the former would be significantly more stable.

In summary, a range of chiral amines with the potential for chelation were targeted and prepared. These were subsequently tested as their Mg-bisamides within asymmetric deprotonation reactions and found to be effective chiral bases that display the highest general selectivity yet found within these systems. Furthermore, even in the absence of donor additives, high reactivities and selectivities were retained. Computational studies on model compounds support the formation of the doubly chelated complexes containing a pair of five-membered chelate rings. However, these calculations indicate that tridentate chelation to a magnesium centre is precluded due to conformational constraints within the ligands and complexes studied.

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References and notes

1. Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Tetrahedron* **2002**, *58*, 4573.
2. Henderson, K. W.; Kerr, W. J. *Chem. Eur. J.* **2001**, *7*, 3430.
3. (a) Carswell, E. L.; Hayes, D.; Henderson, K. W.; Kerr, W. J.; Russell, C. J. *Synlett* **2003**, 1017; (b) Yong, K. H.; Taylor, N. J.; Chong, J. M. *Org. Lett.* **2002**, *4*, 3553; (c) Yong, K. H.; Chong, J. M. *Org. Lett.* **2002**, *4*, 4139.
4. (a) Simpkins, N. S. *Chem. Soc. Rev.* **1990**, *19*, 335; (b) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1; (c) Koga, K. *Pure Appl. Chem.* **1994**, *66*, 1487.
5. (a) Shiria, S.; Sato, D.; Aoki, K.; Tanaka, M.; Kawasaki, H.; Koga, K. *Tetrahedron* **1997**, *53*, 5963; (b) Aoki, K.; Tomioka, K.; Noguchi, H.; Koga, K. *Tetrahedron* **1997**, *53*, 13641.
6. Shirai, R.; Aoki, K.; Sato, D.; Kim, H.-D.; Murakata, M.; Yasukata, T.; Koga, K. *Chem. Pharm. Bull.* **1994**, *42*, 690.
7. (a) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 167; (b) de Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483; (c) Curthbertson, E.; O'Brien, P.; Towers, T. D. *Synthesis* **2001**, 693.
8. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
9. All amines prepared exhibited satisfactory analytical and spectral data.
10. Anderson, J. D.; García García, P.; Hayes, D.; Henderson, K. W.; Kerr, W. J.; Moir, J. H.; Fondekar, K. P. *Tetrahedron Lett.* **2001**, *42*, 7111.
11. Representative experimental procedure: To a Schlenk flask, under N_2, was added Bu_2Mg (0.97 M, 1.03 mL, 1.00 mmol, in heptanes) and the heptanes removed in vacuo. A solution of (1*R*)-*N*-[(1*R*)-1-phenylethyl]-1-phenyl-2-(piperidin-1-yl)ethanamine (*R*,*R*)-**4** (617 mg, 2.00 mmol) in THF (10 mL) was then added. The solution was heated to reflux for 90 min, under a nitrogen atmosphere, then cooled to −78 °C and then DMPU (60 μL, 0.5 mmol) and TMSCl (0.5 mL, 4 mmol) added. After stirring for 20 min, a solution of 4-*tert*-butylcyclohexanone **15** (123 mg, 0.8 mmol, in 2 mL THF) was added over 1 h, via a syringe pump. The resulting solution was allowed to stir for a further 15 min at −78 °C (overall reaction time 1.25 h) and was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). After warming to rt, the reaction was extracted with Et_2O (40 mL) and washed with saturated aqueous $NaHCO_3$ (2×20 mL). The combined aqueous phase was then extracted with Et_2O (2×20 mL) and the combined organics dried over Na_2SO_4 and the solvent removed in vacuo to yield the crude product. The reaction conversion was determined as 90% by GC 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 (**15**); $t_R = 3.68$ min (**16**)]. The crude product was then purified by flash silica column chromatography (eluting with petroleum ether) to afford the desired product (*R*)-**16** as a clear, colourless oil (130.6 mg, 72%).[1] The enantiomeric ratio was determined by chiral GC analysis to be 7:93 ((*S*):(*R*)) {Chirasil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70 °C (1 min)–130 °C; temperature gradient: 1.7 °C/min; $t_R = 39.20$ [(*S*)-**16**]; $t_R = 39.53$ min [(*R*)-**16**]}.
12. For a comparison with Li base systems, see: (a) Aoki, K.; Koga, K. *Chem. Pharm. Bull.* **2000**, *48*, 571; (b) Graf, C.-D.; Malan, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 3014; (c) Graf, C.-D.; Malan, C.; Harms, K.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 5581; (d) Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **2000**, *41*, 6941.
13. (a) The Gaussian 98 series of programs were used for the calculations: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G.

A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, **1998**; Frequency analysis was used to ensure that true minima were located. Absolute energies: **32**, −811.2193; **33**, −696.7553; **34**, −696.7393 (Hartrees); (b) Dill, J. D.; Pople, J. A. *J. Chem. Phys.* **1975**, *62*, 2921; (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213; (d) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.