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Effect of amine structure and reaction additives on enantioselective deprotonations mediated by homochiral magnesium amide bases

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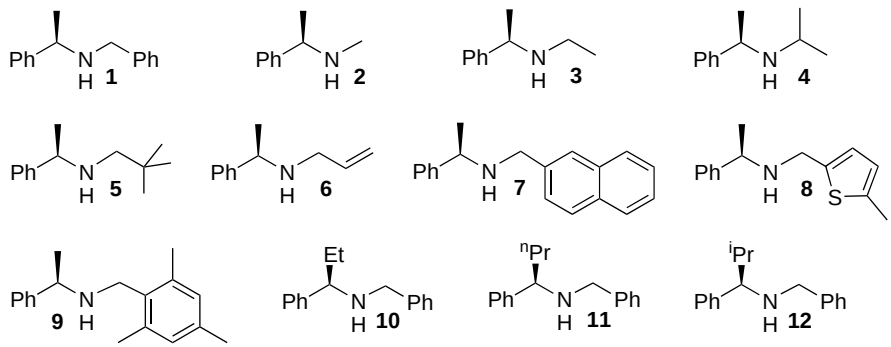
Abstract—A series of novel, optically pure, Mg-bisamides have been prepared and, in turn, used to mediate enantioselective deprotonations of conformationally locked ketones. The new bases exhibit a wide range of selectivities, from poor to excellent (up to 95:5 e.r.); trends between amine structure and the subsequent selectivity of the deprotonation system are detailed. In addition, the effects on the selectivity and the reactivity of the deprotonation process on replacing the Lewis base additive HMPA for DMPU have been investigated and found to be related to the reaction temperature.

Magnesium bisamides, $(R_2N)_2Mg$, have recently been highlighted as a class of reagent possessing distinctive stability, reactivity, and selectivity characteristics[1] when compared with more traditional metal base systems. In particular, Mg-bisamides have found good utility in the regio- and stereoselective formation[2] of synthetically useful enolate ions, as well as, more notably, in enantioselective deprotonation processes.[3] Indeed, this latter category of reaction has only very recently been developed and, to date, the sole chiral Mg-bisamide utilised within this class of asymmetric transformation has been that derived from the structurally simple amine (*R*)-*N*-benzyl-α-methylbenzylamine **1**. Use of this base system in the deprotonation of conformationally locked 4-substituted and 2,6-disubstituted cyclohexanones, followed by silyl enol ether formation, has resulted in good to excellent levels of enantioselection and reaction conversion.[3] Herein, we report the effects on enantioselectivity of systematically altering both the achiral and the chiral sidearms of **1**. In addition, the consequences of replac-



Scheme 1.

Keywords: additives; asymmetric synthesis; chiral amines; enantioselective deprotonation; magnesium.

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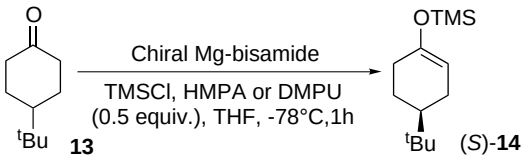
ing the reaction additive HMPA with DMPU are presented.

A series of chiral amines (**2**–**12**) were prepared (Scheme 1).[4] Initially, the chiral methylbenzyl sidearm was retained while the achiral portion of the amine was systematically varied (**2**–**9**). The results of the enantioselective deprotonation reactions involving the resulting Mg-bisamides in reaction with *tert*-butylcyclohexanone **13** are outlined in Table 1. Some clear trends are apparent. Firstly, for the alkyl substituted amines **2**–**5**, increasing the steric bulk of the achiral unit results in a progressive rise in the selectivity of the base (from 54:46 to 91:9 e.r.). In fact, the selectivity obtained using amine **5** is identical to the best results achieved using **1** (91:9 e.r.), although the conversion to silyl enol ether is significantly lower (18% with **5** and 80% with **1**).

Next, the effect of substituting the phenyl ring of the achiral sidearm in **1** by other unsaturated units was studied (**6**–**9**). The deprotonation reactions using the amines incorporating allyl, naphthyl, 5-methylthiophenyl, or mesityl units resulted in consistently good conversions and delivered a narrow range of efficient selectivities (between 81:19 and 87:13 e.r.). Having stated this, it should be noted that these amines do not provide any improvement over the selectivity of the reactions using **1**. In this respect, on consideration of the selectivities arising from all of the amines **1**–**9**, and in particular when comparing those from amines **1**, **5**, and the latter allyl/aryl-possessing amines **6**–**9**, it is likely that the preference for the benzyl unit (in **1**) arises from steric rather than electronic reasons.[5]

Table 1. Enantioselective deprotonations using Mg-bisamides derived from amines **2**–**9**



Entry	Amine	Additive	Conv. (%)	e.r. (*S*):(*R*)
1	**2**	HMPA	40	54:46
2	**2**	DMPU	42	55:45
3	**3**	HMPA	73	77:23
4	**3**	DMPU	73	75:25
5	**4**	HMPA	87	72:28
6	**4**	DMPU	87	80:20
7	**5**	HMPA	18	91:9
8	**5**	DMPU	17	88:12
9	**6**	HMPA	80	82:18
10	**6**	DMPU	87	81:19
11	**7**	HMPA	76	87:13
12	**7**	DMPU	87	87:13
13	**8**	HMPA	85	86:14
14	**8**	DMPU	83	87:13
15	**9**	HMPA	76	85:15
16	**9**	DMPU	97	84:16

Previously, we have shown that the use of the additive HMPA in these systems greatly improves the reaction rate and can also alter the selectivity of the deprotonation process.[3] From the results presented in Table 1, we were also pleased to note that, over a wide range of amine structures, HMPA (known to be a mutagen) could be replaced by the environmentally more acceptable substitute DMPU without any deleterious effects on either the conversions or the selectivities of the deprotonation reactions (with the single exception of amine **4**).[6]

Returning to our amine structure/selectivity studies and having established that the benzyl sidearm possesses the optimum steric properties to maximise selectivity with good reaction conversion, when used in combination with the α-methylbenzylamino unit, we next focused our attention on the chiral component of the amine. Thus, amine **10** was prepared,[4] using commercially available (*R*)-α-ethylbenzylamine, and subsequently incorporated as part of the deprotonation system (Table 2).[7,8]

Pleasingly, the deprotonation reactions with the ethyl-substituted amine **10** displayed a small but reproducible increase in selectivity compared to those with **1**. In fact, the 92:8 e.r. determined using **10** is the highest achieved thus far for this benchmark ketone **13** using our Mg-based strategy.[10] Encouraged by this result, amines **11** and **12** were targeted to determine if an incremental rise in selectivity would result from an increase in the steric component at the α-position of the ligand. Both **11** and **12** were first prepared as racemates, and the optically pure materials were isolated by fractional crystallisation of their salts formed with (*R*)-mandelic acid.[11] On reaction, both amines were found to give good conversions to silyl enol ether (*S*)-**14** but with lower selectivity than the reactions involving **10** (Table 2). In particular, the more highly substituted amine **12** showed an appreciable reduction in enantioselectivity. This indicates that branching at the α-position of the amine has a negative influence on the selectivity of the resultant base.

Throughout this study, again, HMPA and DMPU could be exchanged without any major effects for the reactions involving amines **10** and **11**. In contrast, the reactions using amine **12** displayed a 7% drop in selectivity on replacing HMPA by DMPU.

In order to determine if the choice of additive plays a role in the selectivity of the process at higher tempera-

Table 2. Enantioselective deprotonations of ketone **13** using Mg-bisamides derived from amines **10**–**12**

Entry	Amine	Additive	Conv. (%)	e.r. (*S*):(*R*)
1	**10**	HMPA	75	92:8
2	**10**	DMPU	70	92:8
3	**11**	HMPA	71	88:12
4	**11**	DMPU	88	88:12
5	**12**	HMPA	92	81:19
6	**12**	DMPU	93	74:26

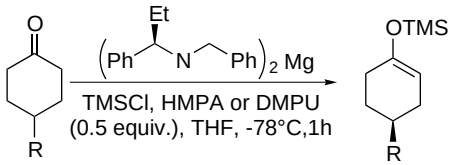
tures, a series of reactions were conducted at −40°C using amine **10** in conjunction with **13**, as well as with the more hindered ketone *cis*-2,6-dimethylcyclohexanone **15** (Table 3).

From Table 3 it is clear that there is indeed a relationship between the selectivity of the reaction and the additive used at −40°C.[8] However, any selectivity differences between the reactions appears to be temperature dependant, with very similar (or identical) results for each additive at −78°C. It should also be noted from Table 3 that increasing the reaction temperature from −78 to −40°C only reduces selectivity of the reactions by 2–3% when HMPA is present (entries 1, 3, 5 and 7), but by 9–12% for the DMPU reactions (entries 2, 4, 6 and 8). Therefore, although the exchange of HMPA for DMPU is clearly of benefit at −78°C, its utility at −40°C must be considered against a possible reduction in reaction selectivity.

Finally, to assess the wider utility of the base derived from **10**, a series of reactions were carried out on the 4-substituted cyclohexanones **17**–**19** (Table 4). Pleasingly, the selectivities obtained in these reactions are comparable with, or exceed those, found in the systems using **1**, confirming the general utility of **10** in the deprotonation process, and with either HMPA or DMPU.[3,8]

In summary, a range of chiral amines have been prepared based around the systematic modification of (*R*)-*N*-benzyl-α-methylbenzylamine and found, on conversion to their Mg-bisamide derivatives, to react with 4- and 2,6-substituted cyclohexanones with good to excellent enantioselectivities. It appears that the steric nature of the achiral sidearm of the amine is critically important in determining the selectivity of the base, with a benzyl unit achieving the optimum level of enantioselection while maintaining good reaction conversion. Substitution of the methyl group for an ethyl group on the chiral sidearm of the amine results in a small but consistent improvement in reaction selectivity. On the other hand, further increasing the size of the alkyl unit to either an ^{n}Pr group or an ^{i}Pr group leads to a drop in the selectivity of the resultant base. Furthermore, in almost all of the enantioselective deprotonation reactions studied at −78°C, the additive HMPA could be replaced by DMPU without any undue effect on either selectivity or conversion.

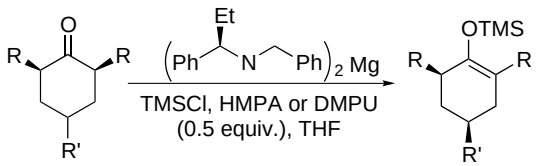
Table 4. Enantioselective deprotonation of 4-substituted cyclohexanones **17**–**19** using a Mg-bisamide derived from **10**



17: R = Me (*S*)-**20**
18: R = ^{n}Pr (*S*)-**21**
19: R = ^{i}Pr (*S*)-**22**

Entry	Ketone	Additive	Conv. (%)	e.r. (*S*):(*R*)
1	**17**	HMPA	65	91:9
2	**17**	DMPU	59	90:10
3	**18**	HMPA	68	92:8
4	**18**	DMPU	65	91:9
5	**19**	HMPA	58	95:5
6	**19**	DMPU	53	95:5

Table 3. Enantioselective deprotonation of ketones **13** and **15** using a Mg-bisamide derived from **10**



13: R = H, R' = ^{t}Bu (*S*)-**14**
15: R = Me, R' = H (*R*)-**16**

Entry	Ketone	Additive	Temp. (°C)	Conv. (%)[a]	e.r.[b]
1	**13**	HMPA	−78	75	92:8
2	**13**	DMPU	−78	70	92:8
3	**13**	HMPA	−40	74	89:11
4	**13**	DMPU	−40	70	80:20
5	**15**	HMPA	−78	36	94:6
6	**15**	DMPU	−78	57	96:4
7	**15**	HMPA	−40	75	92:8
8	**15**	DMPU	−40	44	87:13

[a] Reaction time 1 h for entries 1–4 and 7 and 8; 6 h for entries 5 and 6.
[b] (*S*):(*R*) for entries 1–4 and (*R*):(*S*) for entries 5–8.

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4. All amines were made by standard procedures and exhibited satisfactory analytical and spectral data.
5. For more information on the structures of Mg-bisamides, see: Clegg, W.; Craig, F. J.; Henderson, K. W.; Kennedy, A. R.; Mulvey, R. E.; O'Neil, P. A.; Reed, D. *Inorg. Chem.* **1997**, *36*, 6238.
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7. **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-ethylbenzylamine **10** (0.45 g, 2 mmol). The resultant solution was heated to reflux for 90 min and then slowly 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 **13** (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 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 70% by GC analysis [CP SIL 19CB fused silica capillary column; carrier gas H_2 (80 kPa); 45–190°C; temperature gradient: 45°C/min; $t_R = 4.23$ min (**14**); $t_R = 4.36$ min (**13**)]. Flash column chromatography (eluting with petrol/ether, 9:1) afforded (*S*)-4-*tert*-butyl-1-trimethylsiloxy-1-cyclohexene (*S*)-**14** (0.110 g, 61%) as a clear oil which displayed an enantiomeric ratio of 92:8 {Chirasil-DEX CB capillary column; carrier gas H_2 (80 kPa); 80°C (1 min)–120°C; temperature gradient: 1.8°C/min; $t_R = 19.49$ min [(*S*)-**14**]; $t_R = 19.73$ min [(*R*)-**14**]}.
8. The absolute configurations of the major and minor isomers of **14**, **16**, **20** and **22** were assigned by correlation of optical rotation measurements with those of Koga and co-workers;[9] for **21** the major and minor isomer configurations were tentatively assigned by comparison with the other enol ethers.
9. (a) Aoki, K.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 5105; (b) Kim, H.; Shirai, R.; Kawasaki, H.; Nakajima, M.; Koga, K. *Heterocycles* **1990**, *30*, 307.
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11. The absolute configurations of **11** and **12** were unambiguously assigned by single-crystal X-ray diffraction analyses of their (*R*)-mandelic acid salts.