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Development of chiral heteroleptic magnesium amides; asymmetric deprotonations mediated by six-membered metallocyclic amidomagnesium naphtholates

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In memory of Professor Sandy McKillop—an inspiring organic chemist and educator of international impact

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ABSTRACT

A series of enantioenriched six-membered metallocyclic amidomagnesium naphtholates were prepared and used to probe the structure–reactivity/selectivity relationships of heteroleptic magnesium base complexes within asymmetric deprotonation reactions. An effective complex was identified and applied within enantioselective enolisation processes, delivering good levels of enantioselectivity and also revealing key structural requirements for achieving such selectivity.

1. Introduction

Over recent years chiral magnesium amide complexes have been shown to be highly selective reagents for the asymmetric deprotonation of prochiral ketones.[1–3] In particular, homoleptic magnesium bisamides have demonstrated very good levels of asymmetric efficiency.[1a–e,g–i] Additionally, the divalency of magnesium enables the exploration of heteroleptic complexes within enantioselective enolisation processes.[1f] In this regard, some initial investigations have been conducted with two classes of chiral heteroleptic base. Alkylmagnesium amides,[1f] comprising a chiral amide and achiral alkyl ligand, demonstrated that good levels of asymmetric induction may be obtained while using only half the quantity of parent amine relative to that required by the homochiral bisamide system. Additionally, it was shown that the key deprotonation event was mediated by the amide and not by the alkyl ligand.[1f] In the second heteroleptic base approach, chiral amidomagnesium phenolate complexes,[1f] revealed that replacement of the achiral spectator ligand can generate an unusual reactivity/selectivity profile: in this case, both a reversal in the sense of enantioselectivity was observed and, further, the maximum levels of asymmetric induction were achieved at the unusually high reaction temperature of 40 °C (Fig. 1).[1f]

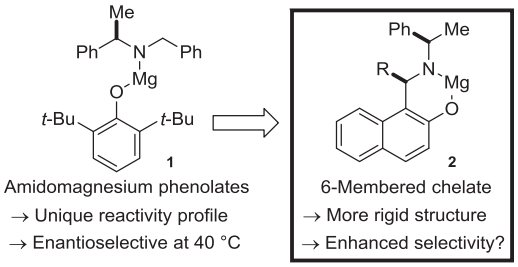

Fig. 1. Structural development of amidomagnesium phenolates.

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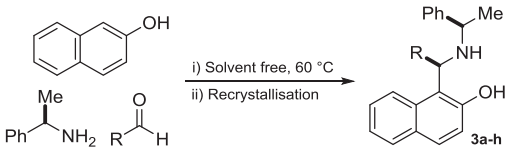
Inspired by the preliminary investigations with amidomagnesium alkoxides, we became intrigued by aminoalcohols, which when derivatised to the magnesium complex, would generate a conformationally rigid metallocycle that may deliver modified selectivity profiles and potentially enable effective asymmetric induction at more accessible reaction temperatures. Towards this end, we envisaged utilising a series of chiral aminonaphthols that could be expediently prepared following the diastereoselective Mannich processes detailed by the groups of Cimarelli and Gong.[4] We anticipated that exposure to *n*-Bu_2Mg[5] would result in the formation of a six-membered amidomagnesium naphtholate that could then be used to probe the effectiveness of such cyclic analogues (Fig. 1).

2. Results and discussion

Initially, we employed the synthetically flexible solvent-free procedure described by Cimarelli to prepare alkyl- and aryl-substituted aminonaphthols **3a**–**g**,[4a,b] and the convenient procedure of Gong to access the fluorinated derivative **3h**.[4c] Utilising (*R*)-1-phenylethylamine as the requisite chiral amine, alongside variation of the aldehyde component, provided a range of functionalised diastereomerically-enriched aminonaphthols after fractional recrystallisation (Table 1).

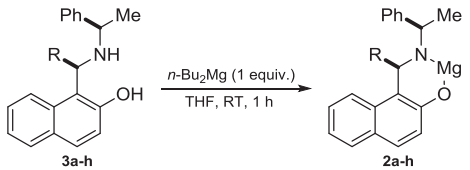
Table 1
Synthesis of aminonaphthols using the Cimarelli/Gong method[4]



Entry	R		Conv. (%)[a]	D.r. (*R*,*R*):(*S*,*R*)[a]	Yield (%)[b]
1	Ph	**3a**	91	99:1	73
2	4-Me-C_6H_4	**3b**	67	85:15	32
3	4-MeO-C_6H_4	**3c**	59	83:17	20
4	4-Cl-C_6H_4	**3d**	86	98:2	63
5	*c*-Hex	**3e**	69	99:1	59
6	*i*-Pr	**3f**	57	79:21	27
7	*n*-Pent	**3g**	61	75:25	12
8[c]	CF_3	**3h**	44[d]	26:74	18[e]

[a] Determined by ^{1}H NMR.
[b] Isolated yield of (*R*,*R*)-diastereomer.
[c] See Experimental section for full details.
[d] Yield of diastereomeric mixture.
[e] Isolated yield of (*S*,*R*)-diastereomer.

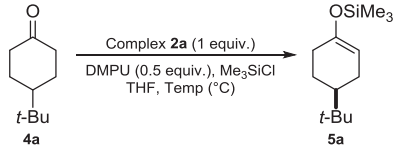
With these components in hand, we now required suitable conditions for the preparation of the corresponding amidomagnesium naphtholate complexes. Our previously disclosed system, **1**, required preparation at reflux in THF,[1f] however, ^{1}H NMR analysis confirmed that simply stirring equimolar quantities of *n*-Bu_2Mg and aminonaphthol at room temperature in THF was adequate to completely form the desired complex (Scheme 1).[6]



Scheme 1. Preparation of complexes **2a**–**h** from aminonaphthols **3a**–**h**.

With straightforward access to these novel complexes, we began to assess their ability to function as chiral base reagents. Utilising complex **2a** as a representative member of this class, we initially evaluated the impact of several Lewis basic additives, which revealed that DMPU was optimum for reactivity and selectivity at −78 °C, as had been observed with several preceding magnesium bases.[1a–d,f–i] Bearing in mind that base reagent **1** had demonstrated its greatest selectivity at the less conventional, and unexpected, reaction temperature of 40 °C,[1f] we next moved to establish the operating temperature for the new amidomagnesium naphtholate systems in benchmark asymmetric deprotonations of 4-*tert*-butylcyclohexanone **4a** (Table 2). From these results, it was apparent that this new base category did not display the unusual temperature/performance profile as shown by complex **1**. Indeed, **2a** exhibited reactivity that was much more analogous to magnesium bisamides and alkylmagnesium amides,[1a–i] where increasing the reaction temperature was generally detrimental to the levels of enantioselectivity observed within the asymmetric enolisation process (Entries 1–7). On the other hand, **2a** did display good levels of asymmetric induction at temperatures up to −20 °C, coupled with excellent reactivity between −60 and −20 °C (Entries 2–4). Accordingly, this establishes the first example of an amidomagnesium naphtholate displaying such enantioselectivity within an asymmetric deprotonation process, with an optimal efficiency balance conveniently achieved at the more accessible temperature of −40 °C (Entry 3).

Table 2
Temperature/performance profile of complex **2a**



Entry	Temp (°C)	Conv. (%)[a]	E.r. (*S*:*R*)[a]
1	−78	13	89:11
2	−60	77	85:15
3	−40	87	84:16
4	−20	89	81:19
5	0	69	71:29
6	20	45	68:32
7	40	23	56:44

[a] Determined by GC analysis.

Having developed reaction conditions that derive the best possible performance from complex **2a**, we focused our attention on appraising the remaining members of the set of amidomagnesium naphtholates, **2b**–**h**, within this benchmark reaction (Table 3). Based on that established to this stage, a reaction temperature of −40 °C was adopted throughout this extended base study.

In all cases, the overall performance of complexes **2a**–**h** were very similar, with selectivities at *c.a.* 84:16 (*S*:*R*) and reaction conversions generally above 80% (Entries 1–8). Since the range of R groups employed was diverse in stereoelectronic nature, these results seem to suggest that the stereocentre at this position has little effect on the overall reactivity and selectivity of the individual base species. In order to assess this hypothesis, we prepared the formaldehyde-derived aminonaphthol **3i** as well as the benzylamine-derived aminonaphthol **3j**, each lacking one of the stereocentres of **3a** (Fig. 2). Subsequent application of the corresponding amidomagnesium naphtholate derivatives, **2i** and **2j**, within the benchmark asymmetric deprotonation reaction conversely demonstrated that the stereogenic centre at *a* is crucial for