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Enantioselective deprotonation reactions using polymer-supported chiral magnesium amide bases†

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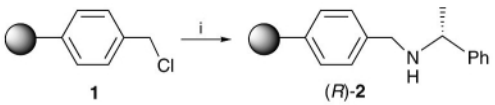
Novel and readily accessible polymer-supported chiral magnesium amide reagents have been prepared and shown to be effective in the asymmetric deprotonation of a series of prochiral cyclohexanones, affording good to excellent levels of both conversion and enantiomeric ratio (up to 93:7); the Merrifield-based chiral amine species has been shown to be readily recyclable.

The application of chiral lithium amide base reagents within asymmetric organic synthesis is widespread.[1] Additionally we have recently disclosed the preparation of a novel homochiral magnesium amide base and have shown it to be particularly effective in the desymmetrisation of both 4-substituted and 2,6-disubstituted cyclohexanones; the initially reported processes afforded the corresponding silyl enol ethers in up to 95:5 er.[2] Consequently, with a view to gaining the practical and economic advantages offered by solid phase chemistry,[3] we envisioned that tethering the chiral amine, and ultimately the Mg-amide, to a polymer support[4] would provide a convenient and potentially recyclable enantioselective reaction source. Furthermore and at least as importantly, based on our drive to alter the nature of the base itself, we believed that this approach would also allow the establishment of a library of supported chiral amines and, in turn, resin-bound Mg-amides, which would enable an effective assessment of the key structural requirements for the optimisation of such enantioselective reagents. Herein, we report our initial studies in this area and, more specifically, the first use of a polymer-supported chiral Mg-amide base to mediate enantioselective deprotonation processes.

At the outset of this programme, the simple and readily accessible Merrifield resin **1**[5] formed an attractive starting point for direct functionalisation with (*R*)-α-methylbenzylamine. The process shown in Scheme 1 cleanly afforded the supported chiral amine (*R*)-**2**.‡

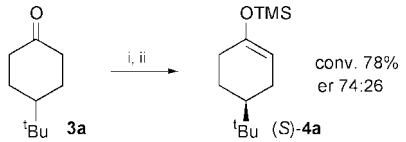
Having established a practically efficient approach to the preparation of (*R*)-**2**, its use as a Mg-amide derivative was then evaluated in the enantioselective deprotonation of **3a**. Optimum formation of the requisite Mg-amide species occurred following reflux of (*R*)-**2** with dibutylmagnesium for 90 min in THF.§ On cooling the resin-bound base to −78 °C, we were pleased to observe the first asymmetric deprotonations with our new supported reagent. As shown in Scheme 2, in the presence of 0.5 mol equiv. of DMPU and excess TMSCl, good levels of both conversion of **3a** to (*S*)-**4a** (78%) and enantiomeric ratio (74:26 er) were achieved.†

Based on this experimental protocol, we moved on to consider the desymmetrisation reaction of a series of alternative prochiral cyclohexanones **3** using our Merrifield-based chiral



Scheme 1 *Reagents and conditions*: i, (*R*)-α-methylbenzylamine (3 eq.), NaI (1 eq.), DMF, 48 h.

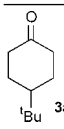
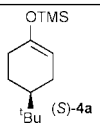
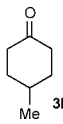
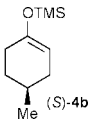
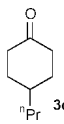
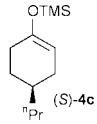
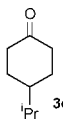
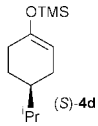
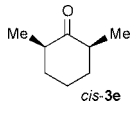
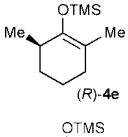
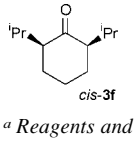
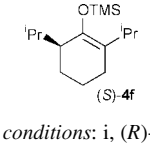
† Electronic supplementary information (ESI) available: representative experimental procedure. See http://www.rsc.org/suppdata/cc/b1/b104417f/



Scheme 2 *Reagents and conditions*: i, (*R*)-**2** (2 eq.), Bu_2Mg (1 eq.), THF, reflux, 90 min; ii, TMSCl (4 eq.), DMPU (0.5 eq.), THF, −78 °C, 4 h.

amine resin (*R*)-**2** (Table 1). At −78 °C the 4-substituted cyclohexanones **3a–d** all showed good levels of conversion and gave enol ethers (*S*)-**4a–d** with enantiomeric ratios of up to 75:25. With the 2,6-disubstituted substrates, higher temperatures were required to achieve acceptable levels of conversion. However, when all ketones (**3a–f**) employed here are considered, it should be noted that at room temperature higher conversions were achieved in almost every instance with, at worst, only small reductions in the recorded enantiomeric ratios. Indeed, the enantioselection observed upon reaction of *cis*-**3e** and *cis*-**3f** appears largely independent of temperature. Furthermore reaction of *cis*-diisopropylcyclohex-

Table 1 Enantioselective deprotonations using Merrifield-based amine (*R*)-**2**[a]

Ketone	Product	Temp.	*t*/h	Conversion (%)[b]	er[c]
		−78 °C	4	78	74:26
3a	(*S*)-4a	rt	2	91	65:35
		−78 °C	4	74	68:32
3b	(*S*)-4b	rt	2	94	64:36
		−78 °C	4	85	74:26
3c	(*S*)-4c	rt	2	91	68:32
		−78 °C	4	89	75:25
3d	(*S*)-4d	rt	2	88	69:31
		−78 °C	43	7	76:24
		−40 °C	24	86	73:27
cis-3e	(*R*)-4e	rt	2	98	75:25
		−78 °C	19	2	—
		−40 °C	68	69	91:9
cis-3f	(*S*)-4f	rt	2	97	93:7

[a] *Reagents and conditions*: i, (*R*)-**2** (2 eq), Bu_2Mg (1 eq.), THF, reflux, 90 min; ii, TMSCl (4 eq), DMPU (0.5 eq.), ketone (0.8 eq.), THF.† [b] Conversions were determined by GC analysis. [c] See footnote¶.

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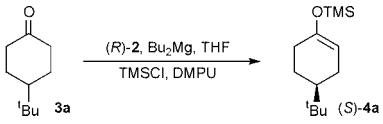
Table 2 Enantioselective deprotonation of **3a** using recycled amine (*R*)-**2**

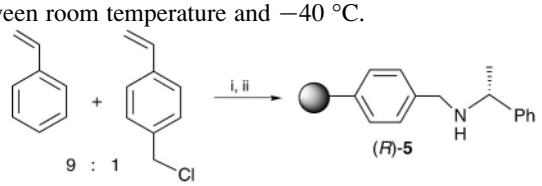


Cycle	Temp.	*t*/h	Conversion (%)	er (*S*):(*R*)
1	rt	2	91	65:35
2	rt	2	97	65:35
3	rt	2	86	65:35
4	rt	2	91	66:34
5	rt	2	92	66:34
6	−78 °C	4	71	73:27

anone *cis*-**3f** gives a 97% conversion and an outstanding er of 93:7 even at room temperature. As such, this method affords us a practically convenient method by which to generate high levels of asymmetric induction in the deprotonation of specific 2,6-disubstituted cyclohexanones.¶

In addition to establishing the initial deprotonation strategies using our Merrifield-based Mg-amide, we were also keen to develop an efficient recycling protocol. In this respect, following completion of reaction, the parent polymer-bound chiral amine (*R*)-**2** was readily regenerated by consecutively washing the resin with a 2:1 mixture of THF–HCl (1 M) and then, to liberate the amine from the HCl salt, with 10% $^{i}Pr_2NEt$ in DMF. This process opened up the possibility of re-using the supported chiral amine and, as such, we can now report that (*R*)-**2** can, indeed, be recycled up to and over 5 times. More specifically, in a series of deprotonations of **3a** to afford (*S*)-**4a**, no appreciable drop in conversion was noted and the enantiomeric ratio remained consistent throughout (Table 2). Furthermore, after 5 cycles at room temperature, the resin was also able to show a return to the enhanced levels of asymmetric induction observed at −78 °C (Cycle 6), thus demonstrating the durability of the tethered amine.‖

Having successfully optimised our deprotonation strategy using the accessible and readily recyclable Merrifield-based chiral amine resin (*R*)-**2**, we moved on to explore the effects of alternative polystyrene supports on the enantioselective potential of the resin-bound Mg-amide, In this respect, a soluble polystyrene resin[8] was prepared and, subsequently, functionalised with (*R*)-α-methylbenzylamine to afford the supported amine (*R*)-**5** (Scheme 3).‡ With this material in hand, we went on to assess the performance of (*R*)-**5**, as the Mg-amide, in the enantioselective deprotonation reaction of a selection of ketones. Pleasingly, as can be seen in Table 3, with **3a** and **3d** this new soluble resin-bound species provided excellent reaction conversions and, moreover, delivered enhanced levels of enantiomeric ratio at both room temperature and at −78 °C. One again, (*S*)-**4f** was formed in excellent er and with no appreciable difference in enantioselection being observed between room temperature and −40 °C.



Scheme 3 *Reagents and conditions*: i, AIBN, toluene, 70 °C, 40 h; ii, (*R*)-α-methylbenzylamine (3 eq.), NaI (1 eq.), DMF, 48 h.

In conclusion, we have successfully prepared two distinct polymeric species posessing chiral amino functionality and, in turn, chiral Mg-amide units and both of these have been shown to be effective in the enantioselective deprotonation reaction of a variety of 4-substituted and, more particularly, 2,6-disubstituted cyclohexanones. Moreover, moderate to high levels of asymmetric induction (up to 93:7 er) were observed, even during reactions performed at room temperature. In addition, the supported chiral amine derived from Merrifield resin was found to be efficiently recycled for further use within the deprotonation protocols. Indeed, it is envisaged that this facet of the supported Mg-amide chemistry disclosed here will be of considerable benefit when employing more precious chiral amines, which are either commercially unavailable or have required multi-step generation. The application of this methodology to the preparation of a library of chiral Mg-amide reagents and the use of other resins is underway and will be reported in due course.

Table 3 Enantioselective deprotonations using soluble supported amine (*R*)-**5**[a]

Ketone	Product	Temp.	*t*/h	Conversion (%)	er
3a	(*S*)-**4a**	−78 °C	4	91	83:17[b]
		rt	2	>99	70:30
3d	(*S*)-**4d**	−78 °C	4	82	80:20
		rt	2	96	71:29
cis-**3f**	(*S*)-**4f**	−40 °C	24	67	93:7
		rt	2	>99	93:7

[a] *Reagents and conditions*: i, (*R*)-**2** (2 eq.), Bu_2Mg (1 eq.), THF, reflux, 90 min; ii, TMSCl (4 eq.), DMPU (0.5 eq.), ketone (0.8 eq.), THF. [b] This result is comparable with that observed in our unsupported base studies (−78 °C, 6 h; 89% conv., 90:10 er); see ref. 2.

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Notes and references

‡ The amine loading level was established by derivatisation with FmocCl, followed by UV analysis of the subsequent cleavage reaction.[6] This routinely showed an amine loading of 1.30–1.40 mmol g^{-1} for (*R*)-**2** and 1.00 mmol g^{-1} for (*R*)-**5**.

§ It should be noted that whilst the production of a resin-bound Mg-bisamide reagent is supposed, the possible formation of some alkyl(Bu)-Mg-amide species must also be recognised. A control experiment performed between Bu_2Mg and **3a** gave no reaction, even at room temperature. Based on this observation, it is believed that the presence of such an alkyl–Mg intermediate would have no adverse affect on the deprotonation process.

¶ Enantiomeric ratios were determined by GC analysis. Additionally, the absolute configuration of the major and minor enantiomers for **4a**, **4b**, **4d**, and **4e** were assigned by correlation of optical rotation measurements with those of Koga and co-workers (ref. 7); for **4c** and **4f** the major and minor isomer configurations were tentatively assigned by comparison with **4a**, **b**, and **d**, and **4e**, respectively. All compounds also exhibited satisfactory analytical and spectral data.

‖ It should be noted that resin (*R*)-**2** was also effectively recycled following the initial reaction of *cis*-**3f** at room temperature, and afforded a >99% conversion and 93:7 er.

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5 Polymer Laboratories Ltd, Essex Road, Church Stretton, Shropshire, UK SY6 6AX; loading: 1.88 mmol g^{-1}; 1% cross-linking.
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8 M. Narita, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1477. For a review on soluble polymer-supported reagents in organic synthesis, see: P. H. Toy and K. D. Janda, *Acc. Chem. Res.*, 2000, **33**, 546.