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Magnesium amide base-mediated enantioselective deprotonation processes

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Abstract—A novel homochiral magnesium bisamide has been readily prepared and, following careful optimisation, this species has been shown to react efficiently with a series of prochiral 4-substituted cyclohexanones in the presence of TMSCl to give the corresponding silyl enol ethers in enantiomeric ratios of up to 95:5. Additionally, the same chiral base system has been shown to be highly effective in the desymmetrisation of *cis*-2,6-disubstituted cyclohexanones, providing excellent levels of both conversion and enantioselection (up to >99.5:0.5 er). Furthermore, the magnesium bisamide has also been shown to mediate a kinetic resolution process with the corresponding *trans*-disubstituted substrates, allowing access to enantioenriched enol ethers and ketones.

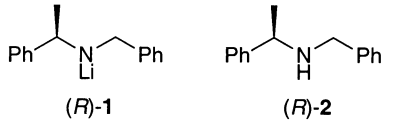
1. Introduction

Over recent years, the widespread and continued requirement for access to enantioenriched organic products and synthons has driven the explosion of interest in both the preparation of novel chiral base reagents and the subsequent application of such species in asymmetric synthesis. Notably, homochiral lithium amides have emerged as effective synthetic tools for use in a range of enantioselective transformations.[1] In comparison to their Li-counterparts, the use of chiral magnesium reagents within asymmetric organic synthesis and, in particular, as mediators of enantioselective deprotonation processes has received scant attention. Indeed, in a more general sense, only relatively rarely have Mg compounds, other than Grignard-type reagents,[2] been employed within asymmetric synthesis,[3] and even then they are most usually only present as the Lewis acid promoter in the presence of a chiral additive. However, when Mg-amide reagents are considered, it appears that they possess several key features which, in combination, are central to the development of a range of asymmetric transformations. In particular, and in contrast to the Li-systems, their solution aggregation state is generally simple and predictable.[4] Furthermore, Mg-amides are more thermally stable[5] and, in a racemic sense, it has already been noted that they are reactive yet selective bases.[5,6] Such advantages over existing methodology have therefore led us to explore the formation and utility of chiral reagents of this class. Herein, we report in full the development and first use of a homochiral magnesium amide base in the enantioselective deprotonation of prochiral ketones.[7]

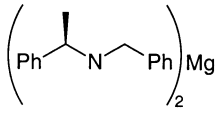
2. Results and discussion

2.1. Preparation of a homochiral magnesium amide base

Aided by the commercial availability of dibutylmagnesium, the synthesis and isolation of Mg-bisamides has now become a generally facile process. Indeed, heating a combination of a secondary amine (2 equiv.) and Bu_2Mg to reflux in hexane, heptane, or toluene often results in the formation of a crystalline bis(amido)Mg-product upon cooling.[4,5] To initiate this programme of study, and based on our structural study of the Li-amide (*R*)-**1**,[8] we chose to utilise the readily available, relatively inexpensive, and structurally simple amine, (*R*)-*N*-benzyl-α-methylbenzylamine (*R*)-**2**. As such, 2 equiv. of amine (*R*)-**2** were added to a solution of Bu_2Mg in hexane, followed by heating to reflux for 90 min. On removal of solvent, pleasingly, ^{1}H NMR spectroscopy showed clean formation of the novel chiral Mg-amide reagent (*R*)-**3**. Attempts to form (*R*)-**3** at room temperature led to incomplete reaction. It should also be noted that, to date and despite a series of attempts, we have yet to realise successful precipitation of our new Mg-bisamide.



(*R*)-**1** (*R*)-**2**



(*R*)-**3**

Keywords: asymmetric synthesis; chiral amines; enantioselective deprotonation; kinetic resolution; magnesium.

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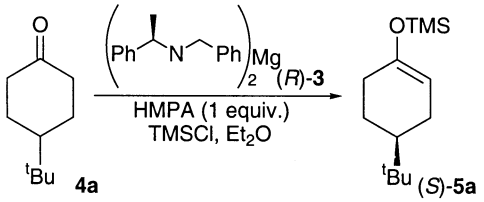


External quench	Internal quench
-78°C to r.t., 20 h;	r.t., 16 h;
53% yield, 58:42 e.r.	100% conv., 63:37 e.r.
-78°C, 7 h;	-78°C, 8 h;
12% yield, 60:40 e.r.	62% conv., 70:30 e.r.

[enantiomeric ratios were established using optical rotation[9]]

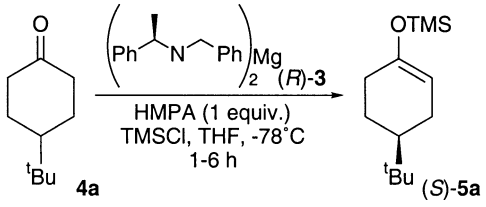
Scheme 1.

2.2. Development of an enantioselective deprotonation protocol with homochiral magnesium amide (*R*)-3 and 4-substituted cyclohexanones

Based on extensive studies as reported in the chemical literature,[1] ketone **4a** was the substrate on which we chose to perform our initial deprotonation attempts. At the outset, using an external quench protocol, ether was employed as the reaction solvent, both with and without the addition of 1 equiv. of HMPA. All reactants were added at −78°C, with the resultant mixtures then being allowed to warm to room temperature overnight in order to effect maximum conversion. The reaction carried out in the absence of HMPA afforded none of the desired silyl enol ether product **5a**. However, in the presence of 1 equiv. of HMPA, chiral Mg-amide base (*R*)-**3** was shown to deprotonate ketone **4a**, to afford silyl enol ether **5a**, in a moderate 53% yield and in an enantiomeric ratio of 58:42 in favour of the (*S*)-enantiomer.[9] In turn, using the same external quench technique and maintaining the reaction temperature at −78°C for 7 h delivered a similar 60:40 er and a significantly lower isolated yield of 12%.

In attempts to improve upon the poor levels of enantioselection observed thus far with ether as solvent, an internal quench protocol was examined.[10] Furthermore, a slow addition strategy for introducing the ketone to the base system was also adopted. These techniques proved somewhat beneficial in that an enantiomeric ratio of 63:37 for **5a** was observed at room temperature and at −78°C a further improved er of 70:30 was recorded (Scheme 1). Despite the relatively low levels of enantioselection, these initial results showed that this simple homochiral Mg-bisamide base system was, indeed, capable of mediating an enantioselective deprotonation process with the conformationally locked ketone **4a**.

Table 1. Enantioselective deprotonation reactions of ketone **4a** with Mg-bisamide (*R*)-**3** and varying levels of HMPA



Entry	HMPA (equiv.)	Conversion (%)	Enantiomeric ratio[a] (*S*)/(*R*)
1	1	96	75:25
2	2	38	57.5:42.5
3	0.5	81	82:18
4	0.1	72	76:24

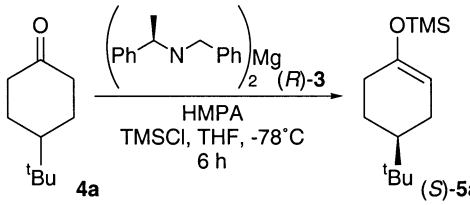
[a] Enantiomeric ratios were established using optical rotation.[9]

At this stage the choice of solvent was reconsidered and preliminary deprotonation studies in THF were performed. The first interesting observation on attempting the transformations in this alternative solvent was that it was possible to form silyl enol ether **5a** from ketone **4a** without the addition of HMPA. At room temperature, using chiral Mg-amide base (*R*)-**3** under external *or* internal quench conditions, conversions of 94–97% were achieved with the enol ether **5a** displaying enantiomeric ratios in the region of 58:42. On the other hand, upon lowering the reaction temperature to −78°C, no apparent change in the enantioselection was observed.

Despite being able to perform these deprotonations of prochiral ketone **4a** in the absence of HMPA, only low levels of asymmetric induction were recorded. Therefore, the introduction of HMPA to the THF-based processes was probed. Furthermore, in a similar approach to that taken with ether as solvent, an internal quench procedure was combined with the slow addition of the ketone at low temperature. In this respect, adding the ketone in THF over 1 h appeared to be optimal for this system. Indeed, as can be seen from Table 1 (entry 1), the use of 1 equiv. of HMPA gave a conversion of 96% and provided enol ether **5a** with an er of 75:25. Moreover, when the stoichiometry of HMPA was varied from 1 to 0.5 equiv. the enantiomeric ratio of **5a** was further enhanced to 82:18 (entry 3). In contrast, increasing the amount of HMPA is obviously deleterious to the asymmetric induction (entry 2), as is lowering the level to 0.1 equiv (entry 4). It should also be noted at this stage that small variations in the stoichiometry of the HMPA, above and below 0.5 equiv., led to no further enhancement in selectivity. The processes also appeared to be largely indifferent to any increases in reaction dilution.[11]

Having optimised the deprotonation system to this stage it is worth noting that the levels of selectivity being observed in reactions of **4a** with the enantiomerically pure Mg-amide base (*R*)-**3** (82:18 er) are already significantly higher than those achieved using the corresponding chiral Li-amide base (*R*)-**1** (75.5:24.5).[9a,b] On the other hand and, in particular, due to the ambiguities present in the chemical literature,[9] the use of optical rotation measurements to establish the enantiomeric ratios of the product enol ethers was of some concern. In this regard, during the course of this work, the disclosure of a series of results, including some careful chiral GC analysis, by Knochel and co-workers provided a rapid chromatographic technique for the accurate determination of the levels of enantioselection being attained in our asymmetric deprotonation processes. Furthermore, correlation with Knochel's results allowed confirmation of the assignment of the absolute stereochemistry for the enol ether **5a**.[12]

Table 2. Enantioselective deprotonation reactions of ketone **4a** with Mg-bisamide (*R*)-**3**



Entry	Solvent	HMPA (equiv.)	Conversion (%)	Enantiomeric ratio[a] (*S*)/(*R*)
1	Et_2O	1	83	80:20
2	CH_2Cl_2	1	40	72:28
3	THF	0	33	90:10
4	THF	1	94	86:14
5	THF	2	26	84:16
6	THF	0.5	82	91:9
7	THF	0.1	53	91:9

[a] Enantiomeric ratios were determined by GC analysis; see Section 4.

In due course and having established a chiral GC separation protocol, a series of key experiments were repeated (Table 2). Firstly, it should be noted that each of the reactions did show an enhanced level of enantioselection in comparison to the equivalent reactions which were analysed using polarimetry. Having stated this, it is clear that the overall trend remained consistent, with reaction in THF (entry 4) being superior with regards to both conversion (94%) and enantioselection (86:14 er) to the directly comparable reaction in ether (entry 1). Reaction in DCM (entry 2) also displayed lower overall efficiency.

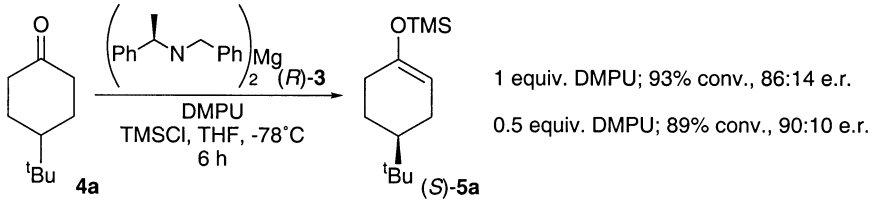
Upon further consideration of the results obtained using THF as the reaction solvent, once again, it became clear that an optimum level of the Lewis base additive HMPA was required in order to effect both high conversion and maximum enantioselection. In its absence (entry 3), reaction was slow, with only 33% conversion of **4a** to **5a** being observed after 6 h, although it should be noted that the enantiomeric discrimination (90:10 er) was comparable with the highest levels achieved thus far. As already mentioned, reaction in the presence of 1 equiv. of HMPA (entry 4) afforded high levels of both conversion and enantioselectivity, and, as expected, doubling the quantity of HMPA (entry 5) was detrimental to both enantioselection and, more significantly, to conversion. Once again, reducing the number of equivalents of HMPA from 1 to 0.5 (entry 6) afforded the optimum result with respect to enantioselection (91:9 er) whilst giving a good 82% conversion. Any further reduction in the quantity of HMPA (entry 7) had a negative effect on the reaction conversion.

Overall, it was concluded that our initial series of observations, on the factors which affect enantioselectivity in the deprotonation reaction of ketone **4a** by chiral Mg-amide base (*R*)-**3**, were indeed accurate. Additionally, it is now clear that the true level of selection being achieved in these Mg-based processes is appreciably higher than that originally recorded. It is also worth noting here that chiral amine (*R*)-**2** could be recovered from the reaction mixture with no loss in optical purity (in 90% yield following alumina column chromatography).

Ongoing efforts to further improve upon the results achieved to date prompted us to lower the deprotonation reaction temperature from −78 to −98°C. However, this afforded no appreciable change in either the conversion of **4a** (80%) or the enantiomeric ratio displayed by **5a** (91:9) after 6 h reaction time.

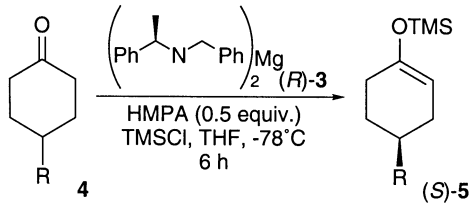
In addition to these studies, the requirement for the specific Lewis base additive HMPA was explored. Pleasingly, we found that this toxic co-solvent could be replaced by the more practically acceptable DMPU, without significant loss in either the reactivity or selectivity of chiral Mg-amide base (*R*)-**3**. As shown in Scheme 2, reaction of (*R*)-**3** with ketone **4a** in the presence of 1 equiv. of DMPU afforded silyl enol ether **5a** in 93% conversion and with an enantiomeric ratio of 86:14. In concordance with the HMPA reactions, halving the quantity of DMPU to 0.5 equiv. resulted in improved enantioselection (90:10 er), whilst a high level of conversion (89%) was maintained.

With these initial studies in hand and in order to investigate the wider applicability of our Mg-based strategy, a series of equivalent ketone substrates were then subjected to our



Scheme 2.

Table 3. Enantioselective deprotonation reactions of ketones **4a**–**e** with Mg-bisamide (*R*)-**3**



Entry	Ketone	R	Product	Conversion (%)	Enantiomeric ratio[a] (*S*)/(*R*)
1	**4a**	^{t}Bu	(*S*)-**5a**	82	91:9
2	**4b**	Me	(*S*)-**5b**	81	91:9
3	**4c**	^{n}Pr	(*S*)-**5c**	88	88:12
4	**4d**	Ph	(*S*)-**5d**	79	87:13
5	**4e**	^{i}Pr	(*S*)-**5e**	77	95:5

[a] Enantiomeric ratios were determined by GC analysis; see Section 4.

optimised reaction conditions with chiral Mg-amide (*R*)-**3**. As shown in Table 3, using ketones **4a**–**e** the developed protocol consistently delivered the corresponding enol ethers **5a**–**e** with good efficiency and enantioselection.[13] Indeed, the enantiomeric ratio displayed upon the desymmetrisation of 4-*iso*-propylcyclohexanone **4e** (95:5) is already approaching the optimum levels achievable for such transformations.

2.3. ^{1}H NMR spectroscopic study for probing Mg-enolate formation

As this study progressed it became increasingly important for us to attempt to ascertain the degree of Mg-enolate formation under a series of appropriate reaction conditions, with and without the co-solvent, HMPA, and the electrophilic trap, TMSCl. In order to achieve this goal, we chose to conduct a ^{1}H NMR spectroscopic study in THF-d_8. This allowed us to recreate our deprotonation reaction conditions, whilst also providing us with a suitable sample for direct analysis. In this regard, chiral Mg-amide base (*R*)-**3** was suspended in THF-d_8 at room temperature and ketone **4a** was added as a solution in THF-d_8. The resultant mixture was allowed to stir for 30 min before an aliquot was removed via cannula and the ^{1}H NMR spectrum obtained. The resulting spectral analysis indicated only a relatively small degree of enolate formation (22%). Furthermore, when the reaction was allowed to continue at room temperature for a total of 16 h this low level of enolate formation remained constant at 22%. In an effort to increase the extent of deprotonation of **4a**, 1 equiv. of HMPA was then added to the THF-d_8 reaction solution. However, ^{1}H NMR spectroscopy revealed no increase in the enolate concentration after 30 min. Indeed, this level remained unchanged over a 5-day period. It can be concluded, therefore, that deprotonation of ketone **4a** is minimal in the presence of Mg-base (*R*)-**3** alone. This study also suggests that the Lewis base additive, HMPA, plays no part in facilitating further enolate formation.

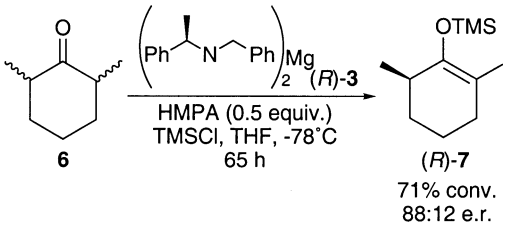
In an effort to further investigate the enolisation process and, more specifically, to establish the influence of TMSCl, a second ^{1}H NMR spectroscopic experiment was conducted. Initially, similar measurements were taken in THF-d_8, with enolate formation in the absence of both HMPA and TMSCl again being minimal (at 23%). As anticipated, the introduction of HMPA to the reaction solution had no effect upon enolate concentration. However, upon the addition of 4 equiv. of TMSCl a 58% conversion of ketone **4a** to **5a** was observed. This result indicates that the reaction of the formed Mg-enolate with TMSCl, to yield silyl enol ether, is clearly driving the reaction on and encouraging further Mg-enolate formation.

In summary, these NMR spectroscopic studies have allowed us to propose that HMPA has little influence over the reactivity of Mg-amide base (*R*)-**3** in the absence of TMSCl. On the other hand, with regards to the rate of the reaction overall, HMPA is believed to be influencing the reactivity of the Mg-enolate intermediate, with addition of HMPA being necessary in order to induce high conversion of **4a** to **5a** (as shown in Tables 1 and 2). It is also important to note that the presence of TMSCl is required from the outset of the reaction, in order to effect high levels of conversion of ketone to silyl enol ether. With respect to enantioselectivity, the presence of HMPA does not appear to significantly influence the asymmetric potential of our system, at least until higher equivalents of this Lewis base additive are employed.

2.4. Some practical improvements

Having further developed our understanding of the Mg-amide mediated deprotonation process, attempts were made to more closely monitor reaction progress and, indeed, establish the times required for formation of elevated quantities of silyl enol ether **5**. Interestingly, following a series of GC monitoring studies, using ketone **4a** as an exemplar, it was established that conversion to the silyl enol ether was consistently high (and in the region of 80%) immediately after addition of the ketone over 1 h. Importantly, we observed no significant change in the enantiomeric ratio of product **5a** after this 1 h reaction time.

With a view to increase the overall practical utility of our deprotonation strategy, we also attempted the synthesis of chiral Mg-amide base (*R*)-**3** directly in THF. This would allow the deprotonation process to be performed without the inconvenience of having to remove the hexane solvent in vacuo, followed by the re-suspension of (*R*)-**3** in THF. Pleasingly, following heating to reflux for 90 min, chiral



Scheme 3.

Mg-amide base (*R*)-**3** was cleanly synthesised in THF solution. Importantly, subsequent use of this base in deprotonation reactions allowed silyl enol ether formation with almost identical levels of conversion and enantioselection to those registered previously.

2.5. Enantioselective deprotonation reactions of 2,6-disubstituted cyclohexanones with homochiral magnesium amide (*R*)-3

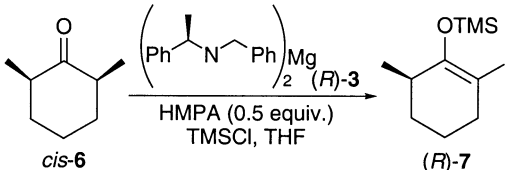
In an effort to further establish and, moreover, widen the scope of our novel Mg-amide mediated enantioselective deprotonation process, our attention was turned to consider the desymmetrisation reactions of alternative prochiral cyclic ketones and, more specifically, 2,6-disubstituted cyclohexanones. In particular and to initiate this investigation, 2,6-dimethylcyclohexanone **6** was available commercially as an 82:18 mixture of *cis*-/*trans*-isomers; the *trans*-ketone exhibited a 50:50 ratio of enantiomers. The *cis*/*trans* mixture of ketone **6** was subjected to reaction with chiral Mg-amide base (*R*)-**3** using our optimised deprotonation strategy. After 6 h reaction time, the corresponding silyl enol ether was obtained in a low 27% conversion. Upon consideration of the increased steric bulk around the site of deprotonation in ketone **6**, relative to that of the 4-substituted cyclohexanones **4**, it is perhaps not surprising that a lower conversion was noted for this transformation over a period of 6 h at −78°C. Therefore, in an effort to improve upon this, the reaction time was increased from 6 to 65 h. Pleasingly, this afforded (*R*)-**7** with an increased level of conversion (71%) and with an enantiomeric ratio of 88:12 (Scheme 3).[13] Moreover, as well as observing a good level of asymmetric induction, we were intrigued to note that the returned and initially racemic *trans*-ketone displayed an optical activity (74:26 er). This would suggest that as well as being particularly effective at performing an enantioselective deprotonation reaction of 2,6-dimethylcyclohexanone **6**, chiral Mg-amide base (*R*)-**3** is also capable of mediating a kinetic resolution process.

Based on these promising initial results and to further explore the potential of this reaction system, the *cis*- and *trans*-isomers of ketone **6** were then separated and reacted in isolation. More specifically, when *cis*-ketone **6** was subjected to the Mg-amide base (*R*)-**3** at −78°C for 40 h, 54% conversion was achieved and the resulting silyl enol ether registered an excellent enantiomeric ratio of 97:3 (Table 4, entry 1). This outcome is particularly noteworthy, in that, when *cis*-ketone **6** was reacted with the Li-version of the same chiral amide, the resulting enol ether was delivered with a significantly lower er of 64.5:35.5.[9a,14] Furthermore, this result is at least equivalent to those obtained for the desymmetrisation of ketone **6** using much more structurally complex Li-amide bases.[13b,14]

Returning to our Mg-amide base (*R*)-**3**, we remained unsatisfied at the length of time required to achieve an acceptable level of conversion of *cis*-**6** to **7**. In this regard, whilst a reduction in the reaction time to 6 h at −78°C resulted in a drop in conversion to 25% (Table 4, entry 2), we were pleased to find that increasing the reaction temperature to −60°C, afforded a significant rise in reaction conversion (67%) with only a small drop off in enantioselection (94:6 er; entry 3). Upon increasing the temperature yet further to −40°C (entry 4), we were delighted to observe almost quantitative conversion of *cis*-**6** within 6 h, with silyl enol ether (*R*)-**7** exhibiting a minimal reduction in enantioselectivity (to 93:7 er).

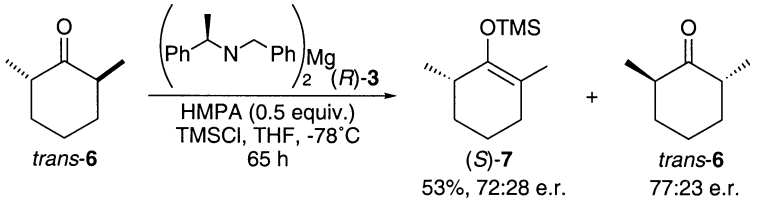
Moving on to consider reaction of *trans*-2,6-dimethylcyclohexanone, *trans*-**6**, initially present as a racemic mixture, at −78°C this isomer afforded a good 53% isolated yield of silyl enol ether **7** which displayed an enantiomeric ratio of 72:28 in favour of the (*S*)-enantiomer (Scheme 4). Interestingly, this is the enantiomeric silyl enol ether to that obtained in excess from reaction of *cis*-**6** with chiral Mg-amide base (*R*)-**3**, thereby providing us with a convenient route into either the (*R*)- or (*S*)-form of **7**. With regards to the unreacted *trans*-ketone, *trans*-**6** was returned displaying an enantiomeric ratio of 77:23, thus re-affirming our initial observation that a kinetic resolution reaction had, indeed, taken place. Based on the formation of the known (*S*)-isomer of **7**,[13b] as well as literature data,[15] the predominant

Table 4. Enantioselective deprotonation reactions of *cis*-**6** with Mg-bisamide (*R*)-**3**

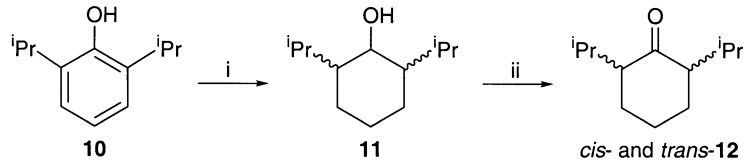


Entry	Temperature (°C)	Time (h)	Conversion (%)	Enantiomeric ratio[a] (*R*)/(*S*)
1	−78	40	54	97:3
2	−78	6	25	97:3
3	−60	6	67	94:6
4	−40	6	99	93:7

[a] Enantiomeric ratios were determined by GC analysis; see Section 4.



Scheme 4.



Scheme 5. *Reagents and conditions*: (i) Raney Ni, H_2 (96 atm), 104°C, 39 h, 97%; (ii) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 98%.

returned ketone was assigned as the (*R*,*R*)-enantiomer. Interestingly, and although chiral Li-amide bases have, indeed, been used to good effect in the kinetic resolution of certain racemic ketones,[16] when the equivalent Li-base to chiral Mg-amide base (*R*)-**3** was used in the desymmetrisation reaction of *trans*-**6**, completely racemic silyl enol ether **7** was observed.[9a]

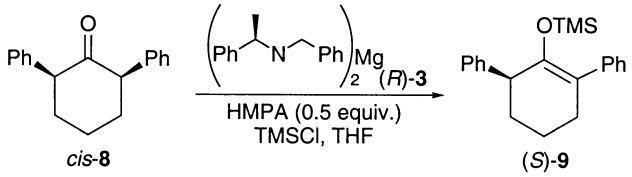
Following on from these encouraging results, we then decided to investigate the behaviour of chiral Mg-amide base (*R*)-**3** in the desymmetrisation reaction of alternative 2,6-disubstituted cyclohexanones. Upon consideration of 2,6-diphenylcyclohexanone **8**, the commercial sample afforded <1% of the *trans*-ketone upon isomer separation by column chromatography. As such, a deprotonation study was performed on the *cis*-ketone only.

With regards to the effect of temperature on the selectivity of the reaction to form enol ether **9** from *cis*-**8**, it was not surprising to view the lowest enantiomeric ratio at the highest reaction temperature of −20°C (Table 5, entry 1). Similar yields of silyl enol ether (*S*)-**9** were observed at both −20°C (entry 1) and −40°C (entry 2) with only a small increase in the enantioselectivity of the reaction being observed at the lower temperature. Further temperature reduction to −60°C afforded a drop in yield, even with an increased reaction time. On the other hand, the enol ether (*S*)-**9** obtained from this latter reaction did display the highest level of asymmetric induction observed during this study on the deprotonation of *cis*-2,6-diphenylcyclohexanone **8** with chiral Mg-amide base (*R*)-**3** (entry 3).[13]

Additional examples of 2,6-disubstituted cyclohexanones were required to be synthesised from the corresponding 2,6-disubstituted phenols. In particular, Raney Nickel catalysed hydrogenation of 2,6-di-*iso*-propylphenol **10** afforded the fully saturated ring product, cyclohexanol **11** (as a mixture of isomers), upon optimisation of the reaction conditions (Scheme 5).[17] In turn, a suitable method for the oxidation of alcohol **11** to afford *cis*- and *trans*-ketone **12** was required. As such, using the Dess–Martin periodinane reagent[18] we were delighted to observe complete reaction of the crude alcohol **11** to afford cyclohexanone **12** in 98% yield within 1 h. GC analysis allowed the ratio of *cis*/*trans*-isomers of **12** to be determined as 82:18 in favour of the *cis*-compound, with the *trans*-isomer exhibiting a 50:50 ratio of enantiomers. Subsequent silica column chromatography permitted the separation and isolation of the *cis*- and *trans*-isomers.

In due course, *cis*-ketone **12** was reacted with chiral Mg-amide base (*R*)-**3** to afford silyl enol ether (*S*)-**13** in 54% conversion after 39 h reaction time at −78°C. Remarkably, in this example, only one enantiomer of the product enol ether could be observed by chiral GC, allowing us to register our highest enantiomeric ratio yet achieved of >99.5:0.5

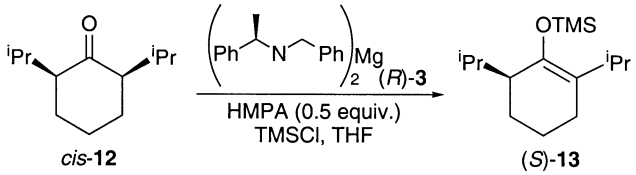
Table 5. Enantioselective deprotonation reactions of *cis*-**8** with Mg-bisamide (*R*)-**3**



Entry	Temperature (°C)	Time (h)	Yield (%)	Enantiomeric ratio[a] (*S*)/(*R*)
1	−20	8	83	79:21
2	−40	8	86	82:18
3	−60	24	39	87:13

[a] Enantiomeric ratios were determined by GC analysis; see Section 4.

Table 6. Enantioselective deprotonation reactions of *cis*-**12** with Mg-bisamide (*R*)-**3**



cis-**12** (*S*)-**13**

Entry	Temperature (°C)	Time (h)	Conversion (%)	Enantiomeric ratio[a] (*S*)/(*R*)
1	−78	39	54	>99.5:0.5
2	−78	6	9	99.7:0.3
3	−60	6	66	99.4:0.6
4	−40	6	99	98.8:1.2
5	rt	2	100	91:9

[a] Enantiomeric ratios were determined by GC analysis; see Section 4.

(entry 1, Table 6). Pleasingly, warming the reaction from −78°C through −60°C (entry 3), to −40°C (entry 4), allowed us to view almost quantitative conversion of *cis*-**12** to silyl enol ether (*S*)-**13** after only 6 h reaction time.[13] Furthermore, a trace of the undesired second enantiomer of the enol ether **13** only began to show upon a tenfold concentration of the GC sample. It is also encouraging, from a practical point of view, to note the high level of enantioselection observed when the desymmetrisation reaction is carried out at room temperature (entry 5).

Furthermore, in the anticipation that we would again observe a kinetic resolution process similar to that noted with *trans*-2,6-dimethylcyclohexanone **6**, we subjected *trans*-2,6-di-*iso*-propylcyclohexanone **12** to our Mg-based deprotonation strategy (Table 7). In turn, we were delighted to note that, at −40°C silyl enol ether (*R*)-**13** was afforded in a good enantiomeric ratio of 81:19 (entry 1). Furthermore, the initially racemic ketone **12** was returned displaying a substantially increased level of one enantiomer over the other (94:6 er). This kinetic resolution could be further enhanced by simply performing the deprotonation reaction at 0°C. Based on similar reasoning to that used previously with *trans*-**6**, the predominant returned ketone was assigned as the (*S*,*S*)-enantiomer.

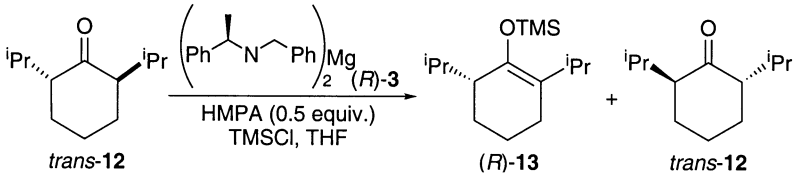
Finally, it is worth noting that the alternative 2,6-disubstitued ketone, 2,6-di-*tert*-butylcyclohexanone,[17] was also accessed with a view to exploring the reactivity of this even more hindered substrate within our enantioselective deprotonation study with homochiral Mg-amide base (*R*)-**3**. However, all attempts to deprotonate this material with a range of (achiral) bases proved unsuccessful.

3. Conclusions

In conclusion, we have been successful in developing a straightforward preparative route to a novel homochiral Mg-bisamide reagent, from a structurally simple, readily available, and relatively inexpensive chiral amine. Following this, we have gone on to demonstrate, for the first time, that such a species can successfully mediate enantioselective deprotonation reactions. Indeed, having explored a series of reaction conditions, a standard and optimum protocol has now been established. Importantly, these methods allow the desymmetrisation of a variety of 4-substituted cyclohexanones to be realised in high conversion and with good to excellent levels of asymmetric induction. Furthermore, we have also succeeded in extending the scope of our desymmetrisation strategy using chiral Mg-amide base (*R*)-**3** to encompass the enantioselective deprotonation reactions of 2,6-disubstituted cyclohexanones. More particularly, these substrates have afforded us excellent levels of asymmetric induction (up to >99.5:0.5 er). To date, these values represent the highest degree of enantioselection to have been attained within this specific area of chiral base chemistry.

In addition to these desymmetrisation studies, we have also

Table 7. Enantioselective deprotonation reactions of *trans*-**12** with Mg-bisamide (*R*)-**3**



trans-**12** (*R*)-**13** *trans*-**12**

Entry	Temperature (°C)	Time	Conversion (%)	Enantiomeric ratio of **13**[a] (*R*)/(*S*)	Enantiomeric ratio of *trans*-**12**[a] (*S*,*S*)/(*R*,*R*)
1	−40	67 h	66	81:19	94:6
2	0	100 min	59	76:24	80:20
3	0	19 h	99	53:47	99:1

[a] Enantiomeric ratios were determined by GC analysis; see Section 4.

established a novel Mg-amide mediated kinetic resolution process in the reactions of both *trans*-2,6-dimethyl- and *trans*-2,6-di-*iso*-propylcyclohexanone. Interestingly with respect to gaining access to the chiral synthon of choice, with both of these substrates the enantiomeric enol ether to that obtained from the corresponding *cis*-ketone is formed in excess. Additionally and importantly, the returned ketones also display good to excellent levels of optical enrichment.

With regards the more general utility of these methods, it is worth stressing that the practical developments and enantioselective processes detailed here have been realised by the application of a very simple and readily accessible amide base system. We believe that this feature, coupled with the relatively robust nature of Mg-amides in general, will impact positively on the more widespread use and adoption of these techniques. Furthermore, it is also envisaged that Mg-based reagents of this type have considerable scope for further development. In this respect, the application of alternative Mg-bisamide systems and the establishment of related methodology are currently underway in our laboratories and will be reported in due course.

4. Experimental

4.1. General

Diethyl ether, tetrahydrofuran, THF-d_8, and hexane were dried by heating to reflux over sodium wire, benzophenone ketyl being used as an indicator, and then distilled under N_2. Dichloromethane was distilled from calcium hydride under N_2. Light petroleum was distilled prior to use and refers to the fraction of bp 30–40°C.

n-Butyllithium, obtained as a 1.6 M solution in hexane, was standardised using diphenylacetic acid[19] or salicylaldehyde phenylhydrazone.[20] Dibutylmagnesium, obtained as a 1 M solution in heptane, was standardised using *sec*-butanol with phenanthroline being used as an indicator[21] or salicylaldehyde phenylhydrazone.[20]

(*R*)-(+)-*N*-Benzyl-α-methylbenzylamine (*R*)-**2**, HMPA, and DMPU were dried by heating to reflux over calcium hydride, distilled under vacuum, and stored over molecular sieves. Di-*iso*-propylamine was dried by heating to reflux over calcium hydride, distilled under N_2, and stored over molecular sieves.

4-Methylcyclohexanone **4b**, 4-*n*-propylcyclohexanone **4c**, 4-*iso*-propylcyclohexanone **4e**, 2,6-dimethylcyclohexanone **6**, and 2,6-di-*iso*-propylcyclohexanone **12** were dried by heating to reflux over fused $CaCl_2$, distilled under vacuum, and stored over molecular sieves. 4-*tert*-Butylcyclohexanone **4a**, 4-phenylcyclohexanone **4d**, *cis*-2,6-diphenylcyclohexanone **8**, and *cis*-2,6-di-*tert*-butylcyclohexanone, were recrystallised from dry hexane at 4°C. TMSCl was distilled under N_2 and stored over molecular sieves.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV_{254} or Merck aluminium oxide 60 (neutral) plates coated with fluorescent indicator F_{254}. These were analysed using a Mineralight UVGL-25 lamp or developed using potassium permanganate, vanillin, and/or Brady's reagent (2,4-DNP). Flash column chromatography was carried out using Prolabo silica gel (230–400 mesh). Gravity column chromatography was carried out using Merck aluminium oxide 90 (activity grade II–III, 70–230 mesh). This was neutralised by standing in ethyl acetate for 7 days, followed by filtration and washing with ethanol, water, and ethanol before drying at 120°C overnight. The alumina was deactivated to activity grade IV prior to use. This involved shaking with 10% (w/w) of water.

Gas chromatography was carried out using a Carlo Erba HRGC 5300 gas chromatograph fitted with: (i) a DB 179 column, (ii) a CP-SIL 19CB column, or (iii) a CP-Chirasil-DEX CB column. Detection was by flame ionisation and the chromatograph was interpreted using JCL 6000 computer software. HPLC was carried out on a Chirasil OD-H column using a Waters 501 HPLC pump, a Waters 484 tuneable absorbance detector (set at 254 nm unless otherwise specified), and processed using a Waters 746 data module.

IR spectra were obtained on a Nicolet Impact 400D FTIR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker DPX 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in hertz and refer to $^3J_{H-H}$ interactions unless otherwise specified. Where ^{13}C jmod NMR spectra have been recorded, up (u) indicates CH or CH_3 groups and down (d) indicates C or CH_2 groups.

High resolution mass spectra were obtained on a Finnigan MAT 900XLT double focussing mass spectrometer at the EPSRC National Mass Spectrometry Services Centre, University of Wales, Swansea, UK. Elemental analyses was obtained using a Carlo Erba 1106 CHN analyser. Polarimetry was carried out on a Perkin Elmer 341 polarimeter using a cell with a path length of 1 dm. Concentrations are expressed in g dm^{-3}.

Air-sensitive reactions were carried out using Schlenk apparatus. This was initially evacuated and flame dried, followed by purging with N_2 (×3).

4.2. Preparation of bis{(*R*)-*N*-benzyl-α-methylbenzylamido}magnesium (*R*)-3

4.2.1. Preparation in hexane. To a solution of Bu_2Mg (0.91 mL of a 1.1 M solution in heptane, 1 mmol) in hexane (8 mL), was added (*R*)-*N*-benzyl-α-methylbenzylamine (*R*)-**2** (0.42 mL, 2 mmol). The solution was heated to reflux under a N_2 atmosphere for 90 min, and allowed to cool to room temperature assuming quantitative formation of chiral Mg-amide (*R*)-**3** (1 mmol). If subsequent reactions were not to be performed in hexane, this was removed in vacuo, to afford a pale yellow oil, and replaced with the solvent of choice. δ_H (400 MHz, C_6D_6): 1.17 (d, J=6.6 Hz, 3H, CH_3), 3.35–3.40 (m, 1H, CH), 3.48–3.57 (m, 2H, CH_2), 7.02–7.22 ppm (m, 10H, ArH).

4.2.2. Preparation in THF. To a solution of Bu_2Mg (1 mmol; *NB* heptane was removed in vacuo prior to

the addition of THF) in THF (10 mL), was added (*R*)-*N*-benzyl-α-methylbenzylamine (*R*)-**2** (0.42 mL, 2 mmol). The solution was heated to reflux under a N_2 atmosphere for 90 min, and allowed to cool to room temperature assuming quantitative formation of chiral Mg-amide (*R*)-**3** (1 mmol).

4.3. Enantioselective deprotonation reactions of cyclohexanones using an external quench protocol

4.3.1. Typical procedure. A solution of chiral Mg-amide base (*R*)-**3** (1 mmol, see Section 4.2.1) in ether (10 mL) was cooled to −78°C under N_2. The Schlenk flask was then charged with 4-*tert*-butylcyclohexanone **4a** (123 mg, 0.8 mmol) as a solution in ether (2 mL) over 5 min. After stirring for 20 min at −78°C, TMSCl (0.5 mL, 4 mmol) was added, followed by HMPA (0.18 mL, 1 mmol). The resulting solution was allowed to warm to room temperature over a period of 20 h, and was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The reaction mixture was extracted with ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (2×20 mL). The combined aqueous phase was then extracted with ether (2×20 mL), the combined organic phase was dried over Na_2SO_4, followed by removal of the solvent in vacuo. Flash silica column chromatography (petrol/ether 9:1) afforded 4-*tert*-butyl-1-trimethylsiloxy-1-cyclohexene **5a**[9a,b] (96 mg, 53%) as a colourless oil. The enantiomeric ratio of **5a** was determined as 58:42 (*S*)/(*R*) using polarimetry; $[\alpha]_D=-12.2$ ($c=1.8$, $CHCl_3$). R_f (silica: petrol/ether 9:1): 0.90; R_f (alumina: petrol): 0.46; ν_{max} (film): 1677 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.18 (s, 9H, $Si(CH_3)_3$), 0.88 (s, 9H, $C(CH_3)_3$), 1.21–1.29 (m, 2H, CH_2), 1.79–1.84 (m, 2H, CH_2), 1.98–2.09 (m, 3H, $CHC(CH_3)_3$ and CH_2), 4.84–4.86 ppm (m, 1H, C=CH).

4.3.2. Preparation of (*S*)-4-*tert*-butyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-5a.[9a,b] The following experiments were carried out according to the typical procedure given in Section 4.3.1. Data are reported as: (a) chiral Mg-amide base, (b) deprotonation reaction solvent, (c) ketone **4a**, added as a solution in the reaction solvent (2 mL) over 5 min, (d) TMSCl, (e) HMPA, (f) temperature, (g) time, (h) conversion, (i) isolated yield, (j) $[\alpha]_D$, er (*S*)/(*R*).

(1) (a) (*R*)-**3**, 1 mmol, (b) ether (10 mL), (c) 123 mg, 0.8 mmol, (d) 0.5 mL, 4 mmol, (e) –, (f) −78°C to rt, (g) 20 h, (h) n/a, (i) 0%, (j) n/a.

(2) See the typical procedure given in Section 4.3.1.

(3) (a) (*R*)-**3**, 1 mmol, (b) ether (10 mL), (c) 123 mg, 0.8 mmol, (d) 0.5 mL, 4 mmol, (e) 0.18 mL, 1 mmol, (f) −78°C, (g) 7 h, (h) n/a, (i) 22 mg, 12%, (j) $[\alpha]_D=-15.6$ ($c=1.1$, $CHCl_3$), 60:40.

(4) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 123 mg, 0.8 mmol, (d) 0.5 mL, 4 mmol, (e) –, (f) rt, (g) 16 h, (h) reaction conversion was determined as 94% by GC analysis (see Section 4.4.1); purification was carried out by gravity column chromatography using neutral, deactivated (grade IV) alumina (petrol), (i) –, (j) $[\alpha]_D=-13.9$ ($c=1.5$, $CHCl_3$), 58:42.

(5) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 123 mg, 0.8 mmol, (d) 0.5 mL, 4 mmol, (e) –, (f) −78°C, (g) 24 h, (h) reaction conversion was determined as 31% by GC analysis (see Section 4.4.1); purification was carried out by gravity column chromatography using neutral, deactivated (grade IV) alumina (petrol), (i) –, (j) $[\alpha]_D=-11.6$ ($c=0.4$, $CHCl_3$), 57:43.

4.4. Enantioselective deprotonation reactions of cyclohexanones using an internal quench protocol

4.4.1. Typical procedure. A solution of chiral Mg-amide base (*R*)-**3** (1 mmol, see the procedure given in Section 4.2.1) in THF (10 mL) was cooled to −78°C under N_2. The Schlenk flask was then charged with TMSCl (0.5 mL, 4 mmol) and HMPA (90 μL, 0.5 mmol). After stirring for 20 min at −78°C, 4-*tert*-butylcyclohexanone **4a** (123 mg, 0.8 mmol) was added as a solution in THF (2 mL) over 1 h using a syringe pump. The resulting solution was allowed to stir at −78°C for a further 5 h (overall reaction time, 6 h), and 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 then extracted with ether (2×20 mL) and the combined organic phase was dried over Na_2SO_4. The reaction conversion was determined as 82% by GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 60–190°C; temperature gradient: 45°C/min; $t_R=3.1$ min (**4a**), 3.3 min (**5a**)). Following removal of the solvent in vacuo, the resultant yellow oil was then purified by gravity column chromatography on neutralised, deactivated alumina (petrol) to afford afforded 4-*tert*-butyl-1-trimethylsiloxy-1-cyclohexene **5a**[9a,b] (115 mg, 64%) as a colourless oil. The enantiomeric ratio of **5a** was determined as 91:9 (*S*)/(*R*) by GC analysis [Chirasil DEX CB capillary column; carrier gas H_2 (40 kPa); 80°C (1 min)–120°C; temperature gradient: 1.8°C/min; $t_R=25.4$ min [(*S*)-**5a**], 25.7 min [(*R*)-**5a**].

4.4.2. Preparation of (*S*)-4-*tert*-butyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-5a.[9a,b] The following experiments were carried out according to the typical procedure given in Section 4.4.1; in entries (1)–(7) polarimetry was used to determine the enantiomeric ratio of each sample. Data are reported as: (a) chiral Mg-amide base, (b) deprotonation reaction solvent, (c) TMSCl, (d) Lewis base additive, (e) ketone **4a**, (f) volume of addition solvent and addition time of **4a**, (g) temperature, (h) overall reaction time, (i) conversion, (j) isolated yield, (k) er (*S*)/(*R*).

(1) (a) (*R*)-**3**, 1 mmol, (b) ether (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 0.18 mL, 1 mmol, (e) 123 mg, 0.8 mmol, (f) 1 mL ether, 1 h, (g) rt, (h) 16 h, (i) 100%, (j) –, (k) $[\alpha]_D=-22.1$ ($c=1.5$, $CHCl_3$), 63:37.

(2) (a) (*R*)-**3**, 1 mmol, (b) ether (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 0.18 mL, 1 mmol, (e) 123 mg, 0.8 mmol, (f) 4 mL ether, 4 h, (g) −78°C, (h) 8 h, (i) 62%, (j) –, (k) $[\alpha]_D=-33.6$ ($c=1.1$, $CHCl_3$), 70:30.

(3) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) –, (e) 123 mg, 0.8 mmol, (f) 1 mL THF, 1 h,

(g) rt, (h) 16 h, (i) 97%, (j) $[\alpha]_D=-12.8$ ($c=1.5$, $CHCl_3$), 57.5:42.5.

(4) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 0.18 mL, 1 mmol, (e) 123 mg, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 96%, (j) –, (k) $[\alpha]_D=-42.4$ ($c=1.5$, $CHCl_3$), 75:25.

(5) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 0.36 mL, 2 mmol, (e) 123 mg, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 38%, (j) –, (k) $[\alpha]_D=-12.7$ ($c=1.2$, $CHCl_3$), 57.5:42.5.

(6) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 90 μL, 0.5 mmol, (e) 123 mg, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 81%, (j) –, (k) $[\alpha]_D=-54.2$ ($c=1.5$, $CHCl_3$), 82:18.

(7) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 18 μL, 0.1 mmol, (e) 123 mg, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 72%, (j) –, (k) $[\alpha]_D=-44.0$ ($c=1.4$, $CHCl_3$), 76:24.

(8) (a) (*R*)-**3**, 1 mmol, (b) ether (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 0.18 mL, 1 mmol, (e) 123 mg, 0.8 mmol, (f) 2 mL ether, 1 h, (g) −78°C, (h) 6 h, (i) 83%, (j) –, (k) 80:20.

(9) (a) (*R*)-**3**, 1 mmol, (b) CH_2Cl_2 (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 0.18 mL, 1 mmol, (e) 126 mg, 0.82 mmol, (f) 2 mL CH_2Cl_2, 1 h, (g) −78°C, (h) 6 h, (i) 40%, (j) –, (k) 72:28.

(10) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) –, (e) 122 mg, 0.79 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 33%, (j) –, (k) 90:10.

(11) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 0.18 mL, 1 mmol, (e) 123 mg, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 94%, (j) –, (k) 86:14; NB chiral amine (*R*)-**2** was recovered from the reaction mixture following alumina column chromatography (90% yield).

(12) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 0.36 mL, 2 mmol, (e) 125 mg, 0.81 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 26%, (j) –, (k) 84:16.

(13) See the typical procedure given in Section 4.4.1.

(14) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 18 μL, 0.1 mmol, (e) 122 mg, 0.79 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 53%, (j) –, (k) 91:9.

(15) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) HMPA, 90 μL, 0.5 mmol, (e) 123 mg, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −98°C, (h) 6 h, (i) 80%, (j) –, (k) 91:9.

(16) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) DMPU, 0.12 mL, 1 mmol, (e) 123 mg, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 93%, (j) –, (k) 86:14.

(17) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) DMPU, 60 μL, 0.5 mmol, (e) 124 mg, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 89%, (j) –, (k) 90:10.

(18) (a) (*R*)-**3**, 0.5 mmol, (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) HMPA, 45 μL, 0.5 mmol, (e) 61 mg, 0.4 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 1 h, (i) 81% (1 h); 80% (after quenching at 1 h), (j) 65 mg, 72%, (k) 88:12.

(19) (a) (*R*)-**3**, 0.5 mmol (prepared in THF according to the procedure given in Section 4.2.2), (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) HMPA, 45 μL, 0.25 mmol, (e) 62 mg, 0.4 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 1 h, (i) 81% (1 h); 75% (after quench at 1 h), (j) 57 mg, 63%, (k) 87:13.

4.4.3. Preparation of (*S*)-4-methyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-5b.[12,22] The following experiment was carried out according to the typical procedure given in Section 4.4.1 using chiral Mg-amide base (*R*)-**3** (1 mmol) in THF (10 mL), TMSCl (0.5 mL, 4 mmol), HMPA (90 μL, 0.5 mmol), and ketone **4b** (98 μL, 0.8 mmol) in THF (2 mL) added over 1 h. The reaction conversion was determined as 81% by GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 60–190°C; temperature gradient: 45°C/min; t_R=1.9 min (**4b**), 2.2 min (**5b**)). The resultant yellow oil was then purified by gravity column chromatography using neutral, deactivated alumina (petrol) to afford **5b** (100 mg, 68%) as a colourless oil. The enantiomeric ratio was determined as 91:9 by GC analysis {Chirasil-DEX CB capillary column; carrier gas H_2 (30 kPa); 60°C (1 min)–100°C; temperature gradient: 1.0°C/min; t_R=24.5 min [(*S*)-**5b**], 25.1 min [(*R*)-**5b**]}. R_f (silica: petrol/ether 9:1) 0.88; R_f (alumina: petrol) 0.45; ν_{max} (film): 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.19 (s, 9H, $Si(CH_3)_3$), 0.95 (d, J=6.3 Hz, 3H, CH_3), 1.10–2.10 (m, 7H, CH and 3×CH_2), 4.82–4.83 ppm (m, 1H, C=CH); $[\alpha]_D=-17.0$ ($c=0.7$, $CHCl_3$).

4.4.4. Preparation of (*S*)-4-*n*-propyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-5c. The following experiment was carried out according to the typical procedure given in Section 4.4.1 using chiral Mg-amide base (*R*)-**3** (1 mmol) in THF (10 mL), TMSCl (0.5 mL, 4 mmol), HMPA (90 μL, 0.5 mmol), and ketone **4c** (113 mg, 0.81 mmol) in THF (2 mL) added over 1 h. The reaction conversion was determined as 88% by GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 60–190°C; temperature gradient: 45°C/min; t_R=2.9 min (**4c**), 3.1 min (**5c**)). The resultant yellow oil was then purified by gravity column chromatography using neutral, deactivated alumina (petrol) to afford **5c** (98 mg, 58%) as a colourless oil. The enantiomeric ratio was determined as 88:12 by GC analysis {Chirasil-DEX CB capillary column; carrier gas H_2 (30 kPa); 80°C (1 min)–120°C; temperature gradient: 1.3°C/min; t_R=22.8 min [(*S*)-**5c**], 23.0 min [(*R*)-**5c**]}; NB: the major and minor isomer configurations for **5c** were tentatively assigned by comparison with **5a**-**b** and **5d**-**e**. R_f

(silica: petrol/ether 9:1) 0.90; R_f (alumina: petrol) 0.47; ν_{max} (film): 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.18 (s, 9H, $Si(CH_3)_3$), 0.89 (t, J=7.1, 3H, CH_3), 1.21–1.73 (m, 9H, CH and 4×CH_2), 1.99–2.11 (m, 2H, CH_2), 4.82–4.85 ppm (m, 1H, C=CH); δ_c (100 MHz, $CDCl_3$): 0.5, 14.6, 20.5, 29.5, 29.9, 30.6, 33.3, 38.5, 103.8, 150.5 ppm; HRMS (CH_2Cl_2) m/z calcd for $C_{12}H_{24}OSi$ (M^+): 212.1596. Found: 212.1604; $[\alpha]_D$=−35.2 (c=1.2, $CHCl_3$).

4.4.5. Preparation of (*S*)-4-phenyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-5d.[12,22] The following experiment was carried out according to the typical procedure given in Section 4.4.1 using chiral Mg-amide base (*R*)-**3** (1 mmol) in THF (10 mL), TMSCl (0.5 mL, 4 mmol), HMPA (90 μL, 0.5 mmol), and ketone **4d** (138 mg, 0.79 mmol) in THF (2 mL) added over 1 h. The reaction conversion was determined as 79% by GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 60–190°C; temperature gradient: 45°C/min; t_R=5.1 min (**4d**), 5.3 min (**5d**)). The resultant yellow oil was then purified by gravity column chromatography using neutral, deactivated alumina (petrol) to afford **5d** (94 mg, 48%) as a colourless oil. The enantiomeric ratio was determined as 87:13 by GC analysis {Chirasil-DEX CB capillary column; carrier gas H_2 (40 kPa); 110°C (1 min)–150°C; temperature gradient: 1.8°C/min; t_R=20.5 min [(*S*)-**5d**], 20.8 min [(*R*)-**5d**]}. R_f (silica: petrol/ether 9:1) 0.88; R_f (alumina: petrol) 0.44; ν_{max} (film): 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.25 (s, 9H, $Si(CH_3)_3$), 1.98–2.32 (m, 6H, 3×CH_2), 2.75–2.89 (m, 1H, PhCH), 4.98–5.00 (m, 1H, C=CH), 7.23–7.36 ppm (m, 5H, ArH); $[\alpha]_D$=−33.5 (c=2.3, $CHCl_3$).

4.4.6. Preparation of (*S*)-4-*iso*-propyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-5e.[12,22] The following experiment was carried out according to the typical procedure given in Section 4.4.1 using chiral Mg-amide base (*R*)-**3** (1 mmol) in THF (10 mL), TMSCl (0.5 mL, 4 mmol), HMPA (90 μL, 0.5 mmol), and ketone **4e** (113 mg, 0.81 mmol) in THF (2 mL) added over 1 h. The reaction conversion was determined as 77% by GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 60–190°C; temperature gradient: 45°C/min; t_R=2.9 min (**4e**), 3.1 min (**5e**)). The resultant yellow oil was then purified by gravity column chromatography using neutral, deactivated alumina (petrol) to afford **5e** (33 mg, 39%) as a colourless oil. The enantiomeric ratio was determined as 95:5 by GC analysis {Chirasil-DEX CB capillary column; carrier gas H_2 (40 kPa); 80°C (1 min)–120°C; temperature gradient: 1.3°C/min; t_R=24.3 min [(*S*)-**5e**], 24.8 min [(*R*)-**5e**]}. R_f (silica: petrol/ether 9:1) 0.90; R_f (alumina: petrol) 0.46; ν_{max} (film): 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.19 (s, 9H, $Si(CH_3)_3$), 0.88 (d, J=6.7 Hz, 3H, CH_3), 0.89 (d, J=6.7 Hz, 3H, CH_3), 1.20–1.34 (m, 4H, 2×CH_2), 1.47–1.52 (m, 1H, CH), 1.75–1.80 (m, 1H, CH), 2.00–2.08 (m, 2H, CH_2), 4.84–4.86 ppm (m, 1H, C=CH); $[\alpha]_D$=−49.0 (c=1.5, $CHCl_3$).

4.4.7. Preparation of (*R*)-2,6-dimethyl-1-trimethylsiloxy-1-cyclohexene, (*R*)-7.[9a,13b,14] The ratio of *cis*-**6**/*trans*-**6** was determined as 82:18 using GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 60–190°C; temperature gradient: 10°C/min; t_R=1.9 min (*cis*-**6**), 2.1 min (*trans*-**6**)); the enantiomeric ratio of *trans*-**6** was determined as 50:50 by GC analysis {Chirasil-DEX CB capillary column; carrier gas H_2 (40 kPa); 70°C (1 min)–110°C; temperature gradient: 1.3°C/min; t_R=14.8 and 15.0 min [(*S*,*S*)- and (*R*,*R*)-*trans*-**6**]}.

The *cis*- and *trans*-isomers of 2,6-dimethylcyclohexanone **6** were separated using flash silica column chromatography (petrol/ether 9:1). This afforded each isomer as a clear liquid. *cis*-**6**:[23] R_f 0.30; ν_{max} (film): 1715 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.99 (d, J=6.5 Hz, 6H, 2×CH_3), 1.28–1.39 (m, 2H, CH_2), 1.70–1.83 (m, 2H, CH_2), 2.06–2.12 (m, 2H, CH_2), 2.34–2.42 ppm (m, 2H, 2×CH); *trans*-**6**:[23] R_f 0.25; ν_{max} (film): 1715 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.06 (d, J=7.0 Hz, 6H, 2×CH_3), 1.49–1.58 (m, 2H, CH_2), 1.70–1.76 (m, 2H, CH_2), 1.87–1.95 (m, 2H, CH_2), 2.50–2.59 ppm (m, 2H, 2×CH).

The following experiments were carried out according to the typical procedure given in Section 4.4.1, with the exception that in some instances the base was prepared in THF by the procedure given in Section 4.2.2. Data are reported as: (a) chiral Mg-amide base (prepared by the procedure given in Section 4.2.1 or 4.2.2), (b) deprotonation reaction solvent, (c) TMSCl, (d) HMPA, (e) ketone **6**, (f) volume of addition solvent and addition time of **6**, (g) temperature, (h) overall reaction time, (i) conversion, (j) isolated yield following flash silica column chromatography (petrol/ether 9:1), (k) er (*R*):(*S*).

(1) (a) (*R*)-**3**, 1 mmol (Section 4.2.1), (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *cis*/*trans*-**6**, 0.11 mL, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) reaction conversion was determined as 27% by GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 60–190°C; temperature gradient: 10°C/min; t_R=1.9 min (*cis*-**6**), 2.1 min (*trans*-**6**), 2.4 min (**7**)); NB: unreacted ketone **6** showed a 78:22 *cis*/*trans* ratio, (j) –, (k) enantiomeric ratio was determined as 88:12 by GC analysis {Chirasil-DEX CB capillary column; carrier gas H_2 (40 kPa); 70°C (1 min)–110°C; temperature gradient: 1.3°C/min; t_R=13.1 min (*cis*-**6**), 14.8 min and 15.0 min [(*S*,*S*)- and (*R*,*R*)-*trans*-**6**], 17.3 min [(*R*)-**7**], 17.9 min [(*S*)-**7**]}; NB: unreacted *trans*-**6** exhibited a 57:43 er in favour of the (*R*,*R*)-isomer.[15] R_f (silica: petrol/ether 9:1) 0.91; R_f (alumina: petrol) 0.50; ν_{max} (film): 1683 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.18 (s, 9H, $Si(CH_3)_3$), 1.04 (d, J=6.9 Hz, 3H, $CHCH_3$), 1.33–1.49 (m, 3H, CH and CH_2), 1.56 (s, 3H, C=CCH_3), 1.59–1.64 (m, 1H, CH), 1.75–1.80 (m, 1H, CH), 1.93–1.96 (m, 1H, CH), 2.10–2.14 ppm (m, 1H, CH); $[\alpha]_D$=+14.3 (c=2.2, $CHCl_3$).

(2) (a) (*R*)-**3**, 1 mmol (Section 4.2.1), (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *cis*/*trans*-**6**, 0.11 mL, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 65 h, (i) 71%; NB: unreacted ketone **6** showed a 72:28 *cis*/*trans* ratio, (j) –, (k) 88:12; NB: unreacted *trans*-**6** exhibited a 74:26 er in favour of the (*R*,*R*)-isomer.[15]

(3) (a) (*R*)-**3** 1 mmol (Section 4.2.2), (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *cis*-**6**, 0.11 mL, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 40 h, (i) 54%, (j) 83 mg, 53%, (k) 97:3.

(4) (a) (*R*)-**3**, 1 mmol (Section 4.2.2), (b) THF (10 mL), (c)

0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *cis*-**6**, 0.11 mL, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 25%, (j) 41 mg, 25%, (k) 97:3.

(5) (a) (*R*)-**3**, 1 mmol (Section 4.2.2), (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *cis*-**6**, 0.11 mL, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −60°C, (h) 6 h, (i) 67%, (j) 85 mg, 54%, (k) 94:6.

(6) (a) (*R*)-**3**, 1 mmol (Section 4.2.2), (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *cis*-**6**, 0.11 mL, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −40°C, (h) 6 h, (i) 99%, (j) 147 mg, 92%, (k) 93:7.

4.4.8. Preparation of (*S*)-2,6-dimethyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-7.[9a,13b,14] The following experiment was carried out according to the typical procedure given in Section 4.4.1, with the exception that the base was prepared in THF by the procedure given in Section 4.2.2. Data are reported as: (a) chiral Mg-amide base, (b) deprotonation reaction solvent, (c) TMSCl, (d) HMPA, (e) ketone **6**, (f) volume of addition solvent and addition time of **6**, (g) temperature, (h) overall reaction time, (i) **7**, isolated yield, er (*S*)/(*R*), (j) recovered **6**, isolated yield, er (*R*,*R*)/(*S*,*S*); NB: isolated yields were obtained following flash silica column chromatography (petrol/ether 9:1); for GC conditions and analysis, see above.

(1) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *trans*-**6**, 88 mg, 0.7 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 65 h, (i) 74 mg, 53%; 72:28, $[\alpha]_D$=−9.7 (*c*=1.8, $CHCl_3$), (j) 5 mg, 6%; 77:23, $[\alpha]_D$=−59.2 (*c*=0.1, MeOH).[15]

4.4.9. Preparation of (*S*)-2,6-diphenyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-9.[24] 2,6-Diphenylcyclohexanone **8** was purified using flash silica column chromatography (petrol/ether 20:1). This afforded *cis*-**8** as a white solid which was further purified by recrystallisation using hexane. *Cis*-**8**:[25] R_f 0.34; ν_{max} (CH_2Cl_2): 1715 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.99–2.19 (m, 4H, 2×CH_2), 2.38–2.42 (m, 2H, CH_2), 3.78–3.82 (m, 2H, 2×CH), 7.15–7.33 ppm (m, 10H, ArH); δ_C (100 MHz, $CDCl_3$): 26.5 (d), 37.8 (d), 58.4 (u), 127.3 (u), 128.6 (u), 129.2 (u), 138.9 (d), 208.5 ppm (d): mp 121–122°C (lit. mp[25] 124°C).

The following experiments were carried out according to typical procedure in Section 4.4.1. Data are reported as: (a) chiral Mg-amide base, (b) deprotonation reaction solvent, (c) TMSCl, (d) HMPA, (e) *cis*-ketone **8**, (f) volume of addition solvent and addition time of *cis*-**8**, (g) temperature, (h) overall reaction time, (i) isolated yield following gravity column chromatography using neutral, deactivated alumina (petrol), (j) enantiomeric ratio, determined using HPLC and reported as (*S*)/(*R*) {Chirasil OD-H column; λ (254 nm); eluant: 0.5% *i*-PrOH in heptane; 0.2 mL/min; t_R=22.7 min [(*S*)-**9**], 25.0 min [(*R*)-**9**]}.[13]

(1) (a) (*R*)-**3**, 0.5 mmol, (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) 45 μl, 0.25 mmol, (e) recrystallised *cis*-**8**, 105 mg, 0.42 mmol, (f) 2 mL THF, 1 h, (g) −20°C, (h) 8 h, (i) 111 mg, 83%, (j) 79:21. R_f (silica: petrol/ether 9:1) 0.91; R_f (alumina: petrol) 0.41; ν_{max} ($CHCl_3$): 1645 cm^{-1}; δ_H (400 MHz, $CDCl_3$): −0.29 (s, 9H, $Si(CH_3)_3$), 1.59–1.65 (m, 1H, CH), 1.70–1.80 (m, 2H, CH_2), 2.07–2.14 (m, 1H, CH), 2.39–2.45 (m, 1H, CH), 2.51–2.57 (m, 1H, CH), 3.44–3.50 (m, 1H, PhCH), 7.17–7.44 ppm (m, 10H, ArH); $[\alpha]_D$=+5.1 (*c*=1.6, $CHCl_3$).

(2) (a) (*R*)-**3**, 0.5 mmol, (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) 45 μl, 0.25 mmol, (e) recrystallised *cis*-**8**, 98 mg, 0.39 mmol, (f) 2 mL THF, 1 h, (g) −40°C, (h) 8 h, (i) 108 mg, 86%, (j) 82:18.

(3) (a) (*R*)-**3**, 0.5 mmol, (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) 45 μl, 0.25 mmol, (e) recrystallised *cis*-**8**, 104 mg, 0.42 mmol, (f) 2 mL THF, 1 h, (g) −60°C, (h) 24 h, (i) 52 mg, 39%, (j) 87:13.

4.4.10. Preparation of (*S*)-2,6-di-*iso*-propyl-1-trimethylsiloxy-1-cyclohexene, (*S*)-13. The following experiments were carried out according to the typical procedure given in Section 4.4.1, with the exception that the base was prepared in THF by the procedure given in Section 4.2.2. Data are reported as: (a) chiral Mg-amide base, (b) deprotonation reaction solvent, (c) TMSCl, (d) HMPA, (e) ketone **12**, (f) volume of addition solvent and addition time of **12**, (g) temperature, (h) overall reaction time, (i) conversion, (j) isolated yield following flash silica column chromatography (petrol), (k) er (*S*)/(*R*).

(1) (a) (*R*)-**3**, 0.5 mmol, (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) 45 μl, 0.25 mmol, (e) *cis*-**12**, 85 μl, 0.4 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 39 h, (i) reaction conversion was determined as 54% by GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 45°C (1 min)–150°C; temperature gradient: 5°C/min; t_R=16.0 min (*cis*-**12**), 16.4 min (**13**)), (j) 35 mg, 34%, (k) enantiomeric ratio was determined as >99.5:0.5 by GC analysis (sample concentration 1 mg/mL) {Chirasil-DEX CB capillary column; carrier gas H_2 (40 kPa); 75°C (1 min)–115°C; temperature gradient: 1.3°C/min; t_R=26.4 min (*S*)-**13**, 26.9 min (*R*)-**13**}.[13] (Found: C, 70.80; H, 12.03%. $C_{15}H_{30}OSi$ requires C, 70.80; H, 11.88%) R_f (silica; petrol): 0.64; ν_{max} (film): 1664 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.17 (s, 9H, $Si(CH_3)_3$), 0.74 (d, *J*=6.8 Hz, 3H, C=CCH(CH_3)$_2$), 0.89 (t, *J*=7.3 Hz, 6H, CHCH(CH_3)$_2$), 0.90 (d, *J*=6.9 Hz, 3H, C=CCH(CH_3)$_2$), 1.27–1.36 (m, 2H, CH_2), 1.60–1.70 (m, 2H, CH_2), 1.80–2.02 (m, 3H, CH and CH_2), 2.15–2.22 (m, 1H, CH), 3.00–3.07 ppm (septet, *J*=6.9 Hz, 1H, C=CC*H*(CH_3)$_2$); δ_c (100 MHz, $CDCl_3$): 0.8 (u), 16.9 (u), 20.4 (u), 20.9 (u), 21.3 (u), 22.3 (d), 22.4 (d), 23.4 (d), 26.5 (u), 28.2 (u), 45.0 (u), 123.8 (d), 143.9 ppm (d); HRMS (CH_2Cl_2) *m*/*z* Calc. for $C_{15}H_{30}OSi$ (M^+): 255.2144. Found: 255.2143; $[\alpha]_D$=−4.1 (*c*=1.4, $CHCl_3$).

(2) (a) (*R*)-**3**, 0.5 mmol, (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) 45 μl, 0.25 mmol, (e) *cis*-**12**, 82 μl, 0.4 mmol, (f) 2 mL THF, 1 h, (g) −78°C, (h) 6 h, (i) 9%, (j) 5 mg, 5%, (k) 99.7:0.3 (sample concentration 10 mg/mL).

(3) (a) (*R*)-**3**, 0.5 mmol, (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) 45 μl, 0.25 mmol, (e) *cis*-**12**, 82 μl, 0.4 mmol, (f) 2 mL THF, 1 h, (g) −60°C, (h) 6 h, (i) 66%,

(j) 57 mg, 56%, (k) 99.4:0.6 (sample concentration 10 mg/mL).

(4) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.25 mmol, (e) *cis*-**12**, 164 μl, 0.8 mmol, (f) 2 mL THF, 1 h, (g) −40°C, (h) 6 h, (i) 99%, (j) 184 mg, 90%, (k) 98.8:1.2 (sample concentration 10 mg/mL).

(5) (a) (*R*)-**3**, 0.5 mmol, (b) THF (5 mL), (c) 0.25 mL, 2 mmol, (d) 45 μl, 0.25 mmol, (e) *cis*-**12**, 78 mg, 0.43 mmol, (f) 2 mL THF, 1 h, (g) rt, (h) 2 h, (i) 100%, (j) 104 mg, 95%, (k) 91:9 (sample concentration 1 mg/mL).

4.4.11. Preparation of (*R*)-2,6-di-*iso*-propyl-1-trimethylsiloxy-1-cyclohexene, (*R*)-13. The following experiments were carried out according to the typical procedure given in Section 4.4.1, with the exception that the base was prepared in THF by the procedure given in Section 4.2.2. Data are reported as (a) chiral Mg-amide base, (b) deprotonation reaction solvent, (c) TMSCl, (d) HMPA, (e) ketone **12**, (f) volume of addition solvent and addition time of **12**, (g) temperature, (h) overall reaction time, (i) conversion, (j) **13**, isolated yield, er (*R*)/(*S*),[13] (k) recovered **12**, isolated yield, er (*S*,*S*)/(*R*,*R*); NB: isolated yields were obtained following flash silica column chromatography (petrol).

(1) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *trans*-**12**, 134 mg, 0.74 mmol, (f) 2 mL THF, 1 h, (g) −40°C, (h) 67 h, (i) reaction conversion was determined as 66% by GC analysis (CP SIL 19CB fused silica capillary column; carrier gas H_2 (80 kPa); 45°C (1 min)–190°C; temperature gradient: 10°C/min; t_R=13.6 min (*trans*-**12**), 14.0 min (**13**)), (j) 93 mg, 49%, enantiomeric ratio was determined as 81:19 by GC analysis, $[\alpha]_D$=+1.8 (c=1.4, $CHCl_3$), (k) 43 mg, 32%, enantiomeric ratio was determined as 94:6 by GC analysis {Chirasil-DEX CB capillary column; carrier gas H_2 (40 kPa); 75°C (1 min)–115°C; temperature gradient: 1.3°C/min; t_R=26.6 min (*S*,*S*)-**12**, 27.7 min (*R*,*R*)-**12**}, $[\alpha]_D$=−73.3 (c=1.2, MeOH).

(2) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *trans*-**12**, 150 mg, 0.82 mmol, (f) 2 mL THF, 1 h, (g) 0°C, (h) 100 min, (i) 59%, (j) 100 mg, 48%, 76:24, (k) 58 mg, 39%, 80:20.

(3) (a) (*R*)-**3**, 1 mmol, (b) THF (10 mL), (c) 0.5 mL, 4 mmol, (d) 90 μl, 0.5 mmol, (e) *trans*-**12**, 146 mg, 0.80 mmol, (f) 2 mL THF, 1 h, (g) 0°C, (h) 19 h, (i) 98%, (j) 181 mg, 89%, 53:47, (k) 4 mg, 2%, 99:1.

4.5. ^{1}H NMR spectroscopic study

(i) To a solution of chiral Mg-amide base (*R*)-**3** (0.5 mmol, prepared by the procedure given in Section 4.2.1) in THF-d_8 (2 mL) at room temperature, was added 4-*tert*-butylcyclohexanone **4a** (62 mg, 0.4 mmol) as a solution in THF-d_8 (0.5 mL). An aliquot of the resultant mixture was then removed via cannula into a N_2 filled NMR spectroscopy tube, after both 30 min and 16 h. ^{1}H NMR spectroscopy indicated 22% formation of the intermediate Mg-enolate in both cases. Subsequently, HMPA (90 μl, 0.5 mmol) was added and an aliquot of the resultant solution again removed after both 30 min and 5 days. ^{1}H NMR spectroscopy revealed no increase in Mg-enolate formation (18 and 19%, respectively). δ_H (400 MHz, C_4D_8O): 0.92 (s, br, $C(CH_3)_3$ for Mg-enolate and **4a**), 4.82–4.87 ppm (m, C═CH for Mg-enolate).

(ii) To a solution of chiral Mg-amide base (*R*)-**3** (0.5 mmol, prepared by the procedure given in Section 4.2.1) in THF-d_8 (2 mL) at room temperature, was added 4-*tert*-butylcyclohexanone **4a** (62 mg, 0.4 mmol) as a solution in THF-d_8 (0.5 mL). An aliquot of the resultant mixture was then removed via cannula after 16 h, ^{1}H NMR spectroscopy indicating 23% formation of the Mg-enolate intermediate. HMPA (90 μl, 0.5 mmol) was then added, and an aliquot of the reactant solution again removed after 30 min. ^{1}H NMR spectroscopy revealed no increase in the Mg-enolate concentration (23%). TMSCl (0.25 mL, 2 mmol) was added and the resultant mixture was then stirred at room temperature for 16 h. ^{1}H NMR spectroscopy revealed a 58% conversion of ketone **6a** to silyl enol ether **7a**. δ_H (400 MHz, C_4D_8O): 0.83 (s, $C(CH_3)_3$), 4.74–4.75 ppm (m, C═CH).

4.6. Preparation of 2,6-di-*iso*-propylcyclohexanol, 11[17]

A 50 mL autoclave vessel was charged with aqueous Raney nickel (440 mg), followed by 2,6-di-*iso*-propylphenol **10** (3.7 mL, 20 mmol). The vessel was placed under H_2 pressure (96 atm), and heated to 104°C over a period of 4 h. During this time, the pressure inside the autoclave vessel was increased to 108 atm. Reaction was continued at 104°C and 108 atm for a total of 39 h, before the heat was discontinued. Once the vessel had cooled to room temperature the remaining H_2 gas was blown off and the vessel opened to allow filtration of the reactant mixture through a pad of kieselguhr (eluant: EtOH/EtOAc). The resulting solution was dried (Na_2SO_4) and the solvent was removed in vacuo to afford the desired product **11** (3.59 g, 97%) as a mixture of isomers. R_f (silica: petrol/ether 9:1) 0.41 and 0.32; ν_{max} (film): 3406 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.80–0.96 (m, 12H, 4×CH_3), 1.10–1.26 (m, 4H, 2×CH_2), 1.52–1.63 (m, 3H, CH and CH_2), 1.70–1.78 (m, 1H, CH), 2.18–2.22 (m, 1H, CH), 3.18–3.19 (m, 1H, CH), 3.67–3.72 (m, 1H, CH), 4.07–4.10 ppm (m, 1H, OH).

4.7. Preparation of Dess–Martin periodinane[26,27]

To a solution of Oxone® (353 g, 0.57 mol) in H_2O (1.3 L), was added 2-iodobenzoic acid (100 g, 0.40 mol). The reaction was warmed to 70°C over 50 min and then mechanically stirred at this temperature for 3 h, during which time the initially thick slurry became a finely dispersed suspension. This suspension was then cooled to 0°C for 2 h with *very* slow stirring. The resulting precipitate was filtered, washed with H_2O (5×200 mL), acetone (2×100 mL), and ether (2×100 mL) to afford a white, crystalline solid, 1-hydroxy-1,2-benziodoxol-3(*1H*)-one-1-oxide (IBX) (101 g, 89%). This solid was then suspended in acetic anhydride (400 mL), and *p*-toluenesulfonic acid (0.75 g, 4.8 mmol) was added. The flask was then equipped with a drying tube, and the reaction was stirred at 80°C for 2 h whereupon partial dissolution was observed. The resulting suspension was then cooled to 0°C for 4 h, filtered, and rinsed with

anhydrous ether (5×50 mL) to afford the Dess–Martin periodinane as a white crystalline solid which was dried under vacuum for 6 h (134 g, 88%). δ_H (400 MHz, $CDCl_3$): 1.91 (s, 9H, 3×CH_3), 7.82–7.86 (m, 1H, ArH), 8.00–8.04 (m, 2H, ArH), 8.13–8.16 ppm (m, 1H, ArH); mp 133°C (lit. mp[18] 124–126°C).

4.8. Preparation of 2,6-di-*iso*-propylcyclohexanone, 12

A solution of Dess–Martin periodinane (891 mg, 2.2 mmol) in CH_2Cl_2 (10 mL) was added to a solution of alcohol **11** (368 mg, 2 mmol) in CH_2Cl_2 (8 mL). The initially yellow solution turned cloudy upon stirring at room temperature for 1 h, after which time the reaction was diluted with ether (50 mL) and the resulting suspension hydrolysed with 1.3 M NaOH solution (20 mL). After stirring for 10 min, the ether layer was extracted with NaOH (20 mL), washed with H_2O (25 mL), and dried (Na_2SO_4), before the solvent was removed in vacuo. This afforded ketone **12** as a crude yellow oil (358 mg, 98%).

The ratio of *cis*-**12**/*trans*-**12** was determined as 82:18 using GC analysis (DB 179 fused silica capillary column; carrier gas H_2 (80 kPa); 45°C (1 min)–190°C; temperature gradient: 20°C/min; t_R=7.0 min (*cis*-**12**), 7.3 min (*trans*-**12**)); the enantiomeric ratio of *trans*-**12** was determined as 50:50 by GC analysis {Chirasil-DEX CB capillary column; carrier gas H_2 (40 kPa); 75°C (1 min)–115°C; temperature gradient: 1.3°C/min; t_R=26.6 min (*S*,*S*)-**12**, 27.7 min (*R*,*R*)-**12**}. Flash silica column chromatography (petrol/ether 20:1) afforded *cis*-2,6-di-*iso*-propylcyclohexanone, *cis*-**12**, and *trans*-2,6-di-*iso*-propylcyclohexanone, *trans*-**12**, as yellow oils.

cis-**12**: (Found: C, 78.88; H, 12.17%. $C_{12}H_{22}O$ requires C, 79.06; H, 12.16%) R_f 0.31; ν_{max} (film): 1715 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.83 (d, *J*=6.7 Hz, 6H, 2×CH_3), 0.87 (d, *J*=6.5 Hz, 3H, 2×CH_3), 1.26–1.36 (m, 2H, CH_2), 1.59–1.70 (m, 1H, CH), 1.88–1.94 (m, 1H, CH), 2.03–2.14 ppm (m, 6H, 2×CH and 2×CH_2); δ_c (100 MHz, $CDCl_3$): 19.4 (u), 22.0 (u), 26.3 (d), 26.7 (u), 31.7 (d), 58.5 (u), 214.4 ppm (d); HRMS (CH_2Cl_2) *m*/*z* Calc. for $C_{12}H_{22}O$ (M^+): 183.1749. Found: 183.1752.

trans-**12**: (Found: C, 78.86; H, 12.38%. $C_{12}H_{22}O$ requires C, 79.06; H, 12.16%) R_f (petrol/ether 20:1) 0.22; ν_{max} (film): 1715 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.85 (d, *J*=6.3 Hz, 6H, 2×CH_3), 0.90 (d, *J*=6.4 Hz, 6H, 2×CH_3), 1.66–1.72 (m, 4H, 2×CH_2), 1.83–1.90 (m, 2H, CH_2), 2.01–2.10 ppm (m, 4H, 4×CH); δ_c (100 MHz, $CDCl_3$): 19.9 (u), 21.2 (d), 21.3 (u), 27.1 (u), 30.7 (d), 56.9 (u), 216.7 ppm (d); HRMS (CH_2Cl_2) *m*/*z* Calc. for $C_{12}H_{22}O$ (M^+): 183.1749. Found: 183.1751.

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