The Development and Application of Magnesium Amide Bases in Asymmetric Synthesis

Thesis submitted to the University of Strathclyde in fulfilment of the requirements for the degree of Doctor of Philosophy

By

Linsey S. Bennie

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Department of Pure and Applied Chemistry
University of Strathclyde
Thomas Graham Building
295 Cathedral Street
Glasgow
G1 1XL

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Abstract

Using a structurally-simple and readily-available C_2-symmetric magnesium bisamide, superb conversions and selectivities were achieved for the asymmetric deprotonation of a range of prochiral ketones at both -78 ^{o}C (up to 95:5 er) and -20 ^{o}C (up to 90:10 er). The synthesis of a selection of optically-pure *pseudo*-C_2-symmetric amines from readily available starting materials was then undertaken, in order to allow the preparation of novel bisamides for use in asymmetric deprotonation processes involving 4-substituted cyclohexanones. Pleasingly, selectivities as high as 96:4 er could be achieved at -78 ^{o}C; these are some of the highest selectivities ever recorded for these substrates. Furthermore, at -20 ^{o}C, excellent selectivities and conversions were recorded for a number of our novel magnesium bisamide bases. It is important to note that this is in marked contrast to the typically low temperatures required by the equivalent lithium amide bases. A computational modelling study was also undertaken. Through our theoretical calculations, we have shown that the energy of the pathway which would lead to the (*S*)-enantiomer of the enol silane, the major product of our reactions using the (*R*,*R*)-configuration of the bisamide, is lower than the alternative pathway which would deliver the (*R*)-enantiomer. Furthermore, in general, the magnitude of the difference in activation energies between the (*R*)- and (*S*)-selective pathways correlates well with our experimental enantioselectivities.

A number of possible approaches towards an asymmetric deprotonation protocol, employing a sub-stoichiometric quantity of enantiopure amine, were explored. Initially, employing Hauser bases ((TMP)MgCl or (HMDS)MgCl) as the bulk organometallic reagent alongside a fluorinated amine delivered disappointing results. Attention was then focused on a recycling protocol employing di-*tert*-butylmagnesium as the bulk magnesium source. At first, attempts to develop a recycling transformation using a C_2-symmetric amine alongside di-*tert*-butylmagnesium at -78 ^{o}C resulted in no conversion to the silyl enol ether product. This was later shown to be due to poor reactivity between the C_2-symmetric amine and di-*tert*-butylmagnesium at -78 ^{o}C. Moreover, when the reaction temperature was increased, no enantioenrichment of the silyl enol ether product was observed. A more acidic fluorinated amine was then employed in an attempt to increase the reactivity of the system. However, low conversions were achieved after 16 h at -78 ^{o}C, and poor enantioselectivities were obtained at more elevated temperatures. Even when an extended reaction time of 48 hours was employed, the silyl enol ether product was obtained in similar yield to that achieved

previously. ^{1}H NMR studies were then employed to confirm that no alkylmagnesium amide formation occurred at -78 ^{o}C. Moreover, attempts to develop an efficient recycling procedure using an alternative electrophile (diphenylphosphoryl chloride) and a chiral aminoalcohol were unsuccessful.

A range of bridged bicyclic ketones were then prepared in order to probe their application in magnesium amide-mediated asymmetric deprotonation reactions. Initial studies were performed using a simple oxabicyclic substrate and our C_2-symmetric bisamide. Pleasingly, after a short period of optimisation, the enantioenriched silyl enol ether was obtained in unprecedented yield and enantioselectivity. Attention was then turned to the analogous thiabicyclic ketone substrate. When performing the asymmetric deprotonation of this novel substrate under the previously optimised conditions at -78 ^{o}C, an outstanding level of enantioselection was observed (99:1 er), and the silyl enol ether product was obtained in good yield. Having achieved such impressive results at -78 ^{o}C, the efficiency of the transformation at room temperature was probed. Pleasingly, the enantioenriched silyl enol ether was obtained in excellent enantioselectivity (94:6 er) and yield, without the requirement for sub-ambient temperatures. This is in marked contrast to the results achieved using the corresponding lithium amide, which delivered the silyl enol ether with a lower level of enantioselectivity (93:7) at -78 ^{o}C. Impressive results could also be achieved when the analogous alkylmagnesium amide was applied to the desymmetrisation of the thiabicyclic substrate.

Studies within the area of magnesium base chemistry have been extended to the enantioselective total synthesis of the bicyclic eicosanoid, (-)-mucosin. The synthetic strategy which has been devised involves a magnesium base-mediated enantioselective deprotonation as the key transformation. As such, the required *meso*-ketone substrate has been prepared efficiently using a series of simple synthetic transformations. With the *meso*-ketone in hand, conversion to the racemic enol silane has been achieved by utilising carbon-centred magnesium base chemistry. In addition, preparation of the required allylic bromide electrophile has been completed in a short number of synthetic steps using readily available starting materials, and the racemic enol silane and allylic bromide coupling partners were reacted to give the required α-substituted ketone in moderate yield. Efforts were then focused on the development of an asymmetric method for the preparation of the enol silane

intermediate, delivering the optically-enriched enol silane in high enantioselectivity using our C_2-symmetric magnesium bisamide (93:7 er) or the C_2-symmetric lithium amide (94:6 er) at -78 ^{o}C.

Acknowledgements

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Abbreviations

Bn	benzyl
BOM	benzyloxymethyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DG	directing group
DMA	dimethylacetamide
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalents
EQ	external quench
er	enantiomeric ratio
HMPA	hexamethylphosphoramide
IPA	*iso*-propanol
IQ	internal quench
IR	infrared
LDA	lithium di-*iso*-propylamide
Mes	mesityl
Ms	methane sulfonyl
NBO	natural bond orbital
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance

s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet

br	broad
brs	broad singlet
PDC	pyridinium dichromate
PE 30-40	petroleum ether (30-40 ^{o}C fraction)
PE 40-60	petroleum ether (40-60 ^{o}C fraction)
rt	room temperature
SP	soluble polymer
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	tetramethylpiperidine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	4-toluenesulfonyl
UV	ultraviolet
Z	benzyloxycarbonyl

Contents

Chapter 1

Novel C_2- and *pseudo*-C_2-symmetric magnesium bisamides

1. Introduction

One of the most difficult challenges facing today's chemists is the introduction of asymmetry within molecules. In this regard, a vast amount of research has been focused on the development of methods which allow expedient access to enantiopure compounds, and a number of distinct approaches have been taken.[1] Firstly, beginning with a naturally occurring chiral compound and employing achiral reagents to alter the functionality present is a well-established protocol. In addition, chiral auxiliaries have been used to create chirality in a substance, allowing subsequent manipulation by achiral reagents. More recently, the use of chiral reagents, in either stoichiometric or catalytic quantities, alongside achiral substrates has proven to be an attractive alternative to the established methods. This technique can involve less wastage and a lower number of synthetic steps. Moreover, the chiral reagents can, potentially, be recycled, providing an economic advantage.

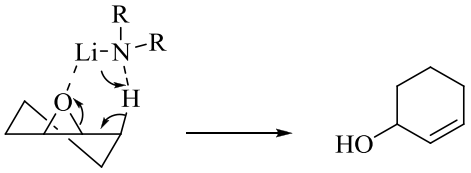
1.1 Chiral lithium amides

Over recent years, the requirement for access to enantioenriched organic synthons has resulted in considerable effort being focused on the development of chiral base reagents for enantioselective transformations. In this regard, optically pure lithium amide species have proven to be well-established reagents for asymmetric processes.[2] More specifically, the lithium amide can discriminate between two enantiotopic protons of a prochiral substrate. The use of lithium amide bases in this regard is well known for several classes of substrate, including epoxides, tricarbonyl (η^6-arene)chromium complexes, and conformationally locked ketones, and details of such transformations will be discussed herein.

1.1.1 Enantioselective rearrangement of epoxides

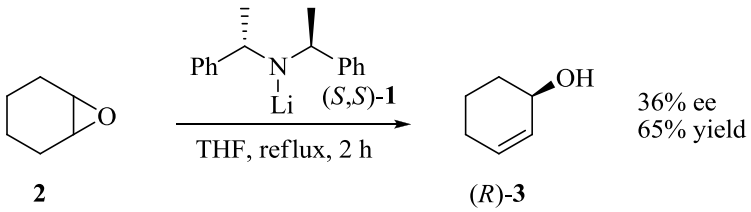
The lithium amide-mediated rearrangement of an epoxide to an allylic alcohol is thought to proceed *via* a cyclic *syn* β-elimination mechanism, assisted by coordination of the base to the epoxide (**Scheme 1.1**).[3] The *pseudo*-axial proton is preferentially abstracted and unfavourable steric interactions are avoided. When the epoxide

substrate is prochiral, the enantioselective rearrangement yields an optically active allylic alcohol.



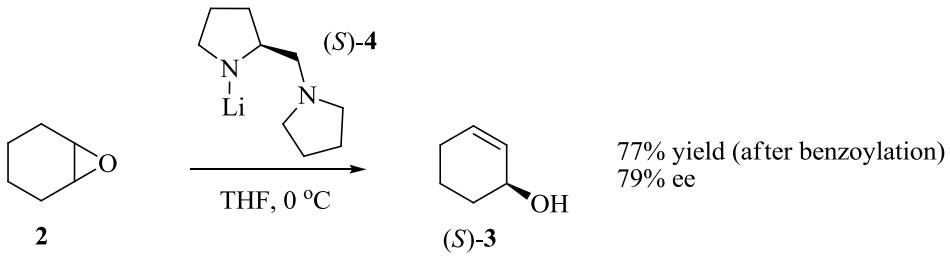
Scheme 1.1

The first enantioselective epoxide rearrangement protocol was realised by Whitesell in 1980.[4] A variety of mono- and dialkyl chiral lithium amides, the most notable of which being (*S*,*S*)-**1**, were investigated using cyclohexene oxide (**2**) as a substrate (**Scheme 1.2**). Although the selectivities and yields achieved were moderate, this seminal contribution is the first example of a chiral amide base being used in an asymmetric deprotonation process.



Scheme 1.2

Subsequent contributions from Asami (**Scheme 1.3**) demonstrated that the proline-derived lithium amide, (*S*)-**4**, possessing an internal chelation site, is capable of effecting greater selectivity than that achieved by Whitesell.[5] In contrast to the rearrangements which were carried out by Whitesell, in which the reaction mixture was heated to reflux, Asami demonstrated that a temperature of 0 ^{o}C was sufficient for the reaction to proceed efficiently.



Scheme 1.3

Asami rationalised the stereoselectivity observed using the proline-derived base by proposing that the chiral base can discriminate between the two conformations of cyclohexene oxide (**Figure 1.1**).[5] Deprotonation was suggested to occur through a transition state complex which contained minimal steric interactions between the substrate and the base. Hence, the allylic alcohol with (*S*)-configuration is formed preferentially.

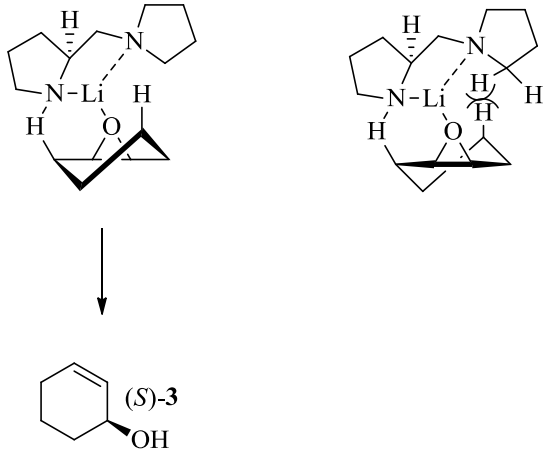
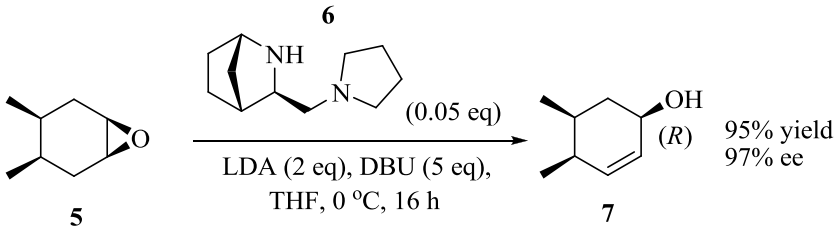


Figure 1.1

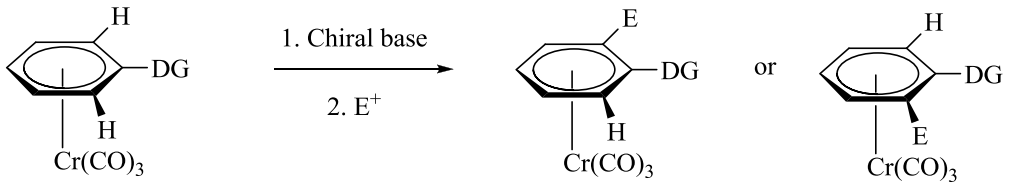
Further work in this area has involved the development of a variety of lithium amides, allowing access to either enantiomer of the required allylic alcohol in high enantiomeric excess.[6] In addition, several catalytic protocols have been realised,[7] including the highly enantioselective and non-substrate specific contribution from Andersson (**Scheme 1.4**).[8]



Scheme 1.4

1.1.2 Synthesis of chiral tricarbonyl (η^6-arene)chromium complexes

A significant amount of research has centred on the enantioselective deprotonation of tricarbonyl (η^6-arene)chromium complexes, which are activated towards deprotonation due to coordination of the aromatic ring to the strongly electron-withdrawing chromium tricarbonyl moiety.[2c,2d] This activation, combined with the presence of a directing group, allows an (arene)$Cr(CO)_3$ complex to be readily deprotonated with a lithium amide base. Asymmetric metallation can be achieved by employing a chiral lithium base which is able to differentiate between the two *ortho*-protons to give a non-racemic *ortho*-lithiated complex. This complex can be subsequently quenched by a range of electrophiles (**Scheme 1.5**). Furthermore, it is often possible to obtain enantiomerically-pure material by recrystallisation of the enantiomerically-enriched complex.

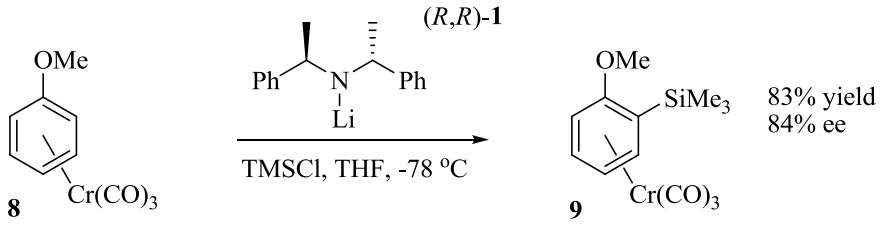


DG = OR, CH_2OR, $OCONi\text{-}Pr_2$, $CONi\text{-}Pr_2$, halide, $N(Me)COt\text{-}Bu$

E^+ = Me_3SiCl, PhCHO, MeO_2CCl, Me_2NCOCl, MeI, Me_2NCHO

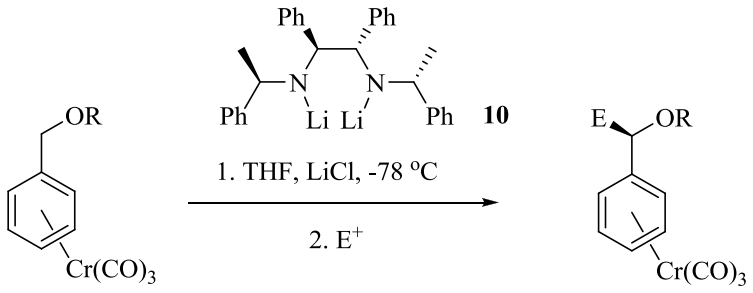
Scheme 1.5

The preparation of an enantiomerically-enriched chromium complex using a chiral lithium amide base was first accomplished by Simpkins in 1994 (**Scheme 1.6**).[9] More specifically, the chiral lithium base ((*R*,*R*)-**1**) was employed for the deprotonation of the chromium complex (**8**) in the presence of Me_3SiCl to afford the *ortho*-silylated complex (**9**) in 84% ee, which was then purified by recrystallisation to give an ee of >97%.



Scheme 1.6

The scope of this class of transformation also encompasses the benzylic functionalisation of tricarbonyl (η^6-arene)chromium complexes. Simpkins[10] and Gibson[11] independently realised the enantioselective deprotonation of benzylic tricarbonyl (η^6-arene)chromium complexes as a route into enantiomerically-enriched chromium complexes. Gibson has described extensive investigations of this class of transformation,[12] with impressive results being achieved utilising a dilithiated chiral base (**10**, **Scheme 1.7**). As can be seen from the selection of results presented in **Table 1.1**, excellent yields and ees were obtained with various combinations of alkoxy substituents and electrophiles.[11]



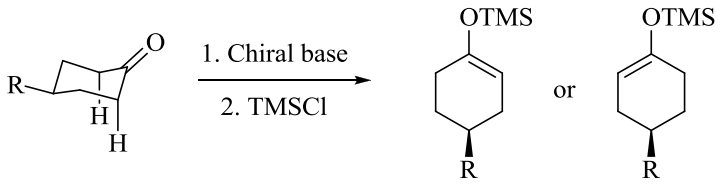
Scheme 1.7

R	E	Yield (%)	ee (%)
Me	SPh	86	97
Me	Me	96	97
Bn	SPh	95	99
Bn	Me	89	≥99

Table 1.1

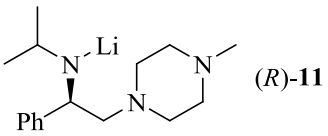
1.1.3 Deprotonation of prochiral ketones

The asymmetric deprotonation of conformationally-locked prochiral ketones is widespread in its application to organic synthesis.[2] In these processes, it is known that removal of the axial protons, over the equatorial protons, situated α to the carbonyl moiety is favoured stereoelectronically. The opportunity for desymmetrisation stems from the preference of the chiral base to selectively remove one of the axial protons, thus converting the prochiral ketone into an enantiomerically-enriched enolate. After chirality is generated in the deprotonation step, electrophilic trapping of the enolate, on carbon or oxygen, can be used to yield useful chiral products (**Scheme 1.8**).



Scheme 1.8

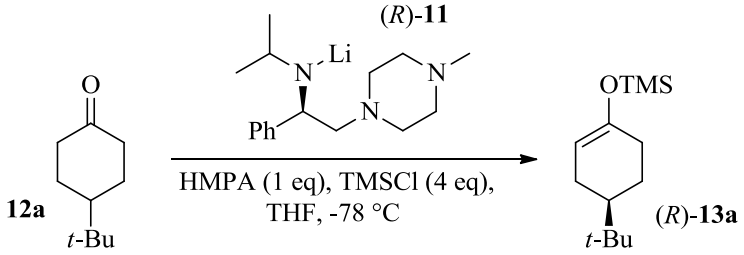
The preliminary findings in this area of asymmetric synthesis were published (independently) by Koga and Simpkins in 1986.[13] Koga employed lithium amides which were proposed to adopt a 5-membered chelate structure, with the isopropyl group being preferentially positioned *trans* to the bulky substituent on the stereogenic centre, as shown in **Figure 1.2**. Consequently, the orientation of the nitrogen lone pair was said to be fixed, resulting in effective induction of enantioselectivity during the deprotonation reaction.



(*R*)-**11**

Figure 1.2

Koga demonstrated the excellent enantioselectivity of these internally ligating bases in the deprotonation of 4-*tert*-butylcyclohexanone (**Scheme 1.9**, **Table 1.2**).[13a] These initial findings showed that the greatest selectivity could be achieved by employing bases containing an *N*-methylpiperazine moiety, and carrying out the reaction in a coordinating solvent in the presence of HMPA at low temperatures. Most notably, the enantioenriched silyl enol ether was obtained with an ee of 97% at -105 ^{o}C. Disappointingly, on performing the reaction at a more practically convenient temperature of -78 ^{o}C, the observed selectivity decreased to 84% ee. The desymmetrisation of this conformationally-locked ketone has become the benchmark reaction, with which the enantioselectivity of novel bases is often compared.



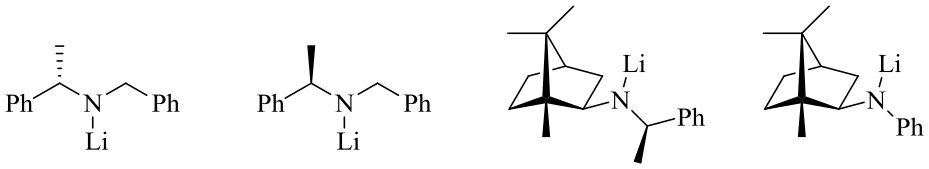
Scheme 1.9

Temperature (^{o}C)	Yield (%)	ee (%)
-78	87	84
-105	51	97

Table 1.2

The initial research carried out by Simpkins focused on the deprotonation of *cis*-2,6-dimethylcyclohexanone using bases of the form shown in **Figure 1.3**.[13b] These bases

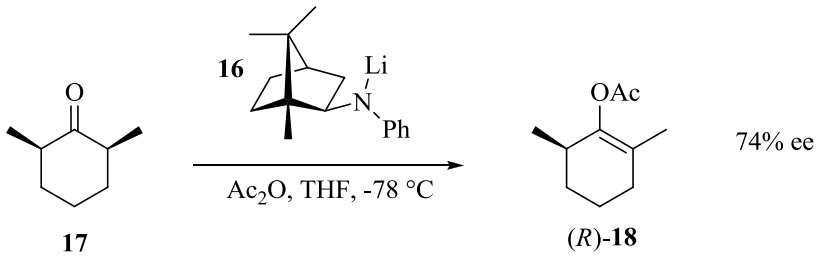
can be considered somewhat simpler than those employed by Koga, as they possess no additional chelating heteroatom groups.



(*S*)-**14** (*R*)-**14** **15** **16**

Figure 1.3

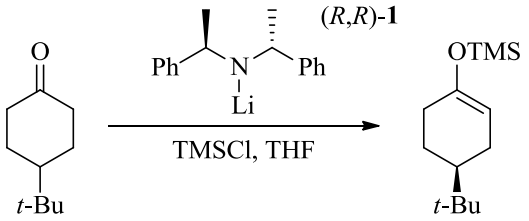
A variety of electrophiles, including allyl bromide, acetic anhydride, and TMSCl, was utilised by Simpkins for trapping the chiral lithium enolate. The most successful results were achieved by employing the camphor-derived base (**16**) in the deprotonation of *cis*-2,6-dimethylcyclohexanone (**17**) at -78 °C, followed by electrophilic quench using acetic anhydride (**Scheme 1.10**).



17 (*R*)-**18**

Scheme 1.10

Simpkins subsequently broadened the research scope to include the desymmetrisation of 4-*tert*-butylcyclohexanone,[14] employing the C_2-symmetric lithium amide base ((*R*,*R*)-**1**), originally used by Whitesell for the asymmetric rearrangement of epoxides to allylic alcohols.[4] By utilising this C_2-symmetric base in the presence of TMSCl at -90 °C, the enantioenriched silyl enol ether ((*S*)-**13a**) was obtained with a high ee of 88% and in a good 66% yield (**Scheme 1.11**, **Table 1.3**). Similar to the results achieved by Koga, the selectivity of the transformation decreases when the reaction is performed at -78 °C.



12a (*S*)-**13a**

Scheme 1.11

Temperature (^{o}C)	Yield (%)	ee (%)
-78	73	69
-90	66	88

Table 1.3

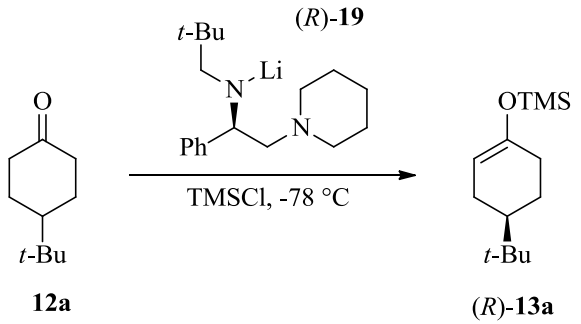
In the years following the initial publications from Koga and Simpkins, regarding the desymmetrisation of prochiral ketones, comprehensive studies were undertaken in order to enhance the efficiency of this asymmetric process. Accordingly, an overview of the key developments will be given herein.

Optimisation of reaction conditions

Additives

As described previously, the lithium amide-mediated desymmetrisation of prochiral ketones is typically performed in a coordinating solvent, such as THF, at low temperatures, in the presence of HMPA, and employing an excess of an electrophilic quench, commonly TMSCl. Koga investigated the role of Lewis basic additives on the efficiency of lithium amide bases and found that, when no Lewis basic additive was present, the enantioselectivities were highly dependent on the choice of solvent (**Scheme 1.12, Table 1.4**).[15] More specifically, when toluene was used as the reaction solvent for the deprotonation of 4-*tert*-butylcyclohexanone by the lithium amide base ((*R*)-**19**), the enantioselectivity and yield achieved was significantly lower than when THF was employed as solvent (**Table 1.4**). Contrastingly, when two equivalents of

HMPA were utilised, the solvent used had almost no effect on the yield and enantioselectivity of the reaction.



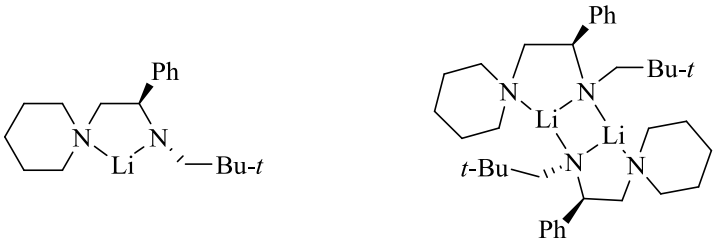
Scheme 1.12

Solvent	Additive	Yield (%)	ee (%)
THF	None	86	84
THF	HMPA	82	82
Toluene	None	12	58
Toluene	HMPA	87	82

Table 1.4

Koga proposed that the effect of the reaction solvent on the efficiency of the lithium amide base ((*R*)-**19**) could be attributed to the differing aggregation states of the lithium amide species in each solution (**Figure 1.4**). This hypothesis was supported by NMR studies which demonstrated that in THF (*R*)-**19** exists as a chelated monomer (**20**), whereas in toluene (*R*)-**19** forms a chelated dimer (**21**). Interestingly, in the presence of two equivalents of HMPA a chelated monomer is formed, regardless of the nature of the reaction solvent. These findings, when coupled with the results achieved for the benchmark deprotonation using different reaction solvents and additive conditions, imply that the chelated monomer (**20**) is more reactive and is capable of imparting greater selectivity in the desymmetrisation reaction than the corresponding dimer (**21**). In addition to Koga's extensive studies regarding the effect of HMPA on the efficiency of base (*R*)-**19**, HMPA has also been shown to

induce elevated levels of selectivity for a range of structurally similar lithium amides.[16]



20 **21**

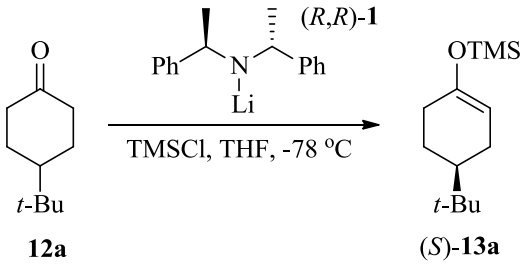
Figure 1.4

Internal quench vs. external quench

When preparing enantioenriched silyl enol ethers by the lithium amide-mediated deprotonation of conformationally-locked ketones, Koga[13a] and Simpkins[14] both adopted the internal quench (IQ) procedure, established by Corey.[17] More specifically, this protocol involves adding a solution of the substrate to a preformed solution of the lithium amide and TMSCl. Hence, as the reaction proceeds, there would be a concomitant accumulation of LiCl in the reaction mixture. Formation of LiCl is proposed to occur *via* reaction of the TMSCl electrophile with a lithium amide to form an *N*-silylated amine, or by electrophilic trapping of a lithium enolate with TMSCl to form a silyl enol ether. Alternatively, the complementary external quench (EQ) procedure involves addition of the electrophile to a solution of the lithium enolate. In general, the enantioselectivities achieved for the desymmetrisation of prochiral ketones were found to be greater under internal quench conditions than when an external quench procedure was employed. As such, the effect of the LiCl salt on the course of the reaction of 4-*tert*-butylcyclohexanone with the C_2-symmetric base (*R*,*R*)-**1** was explored by both Koga[13a,16a] and Simpkins.[18,19]

The results presented by Simpkins for the preparation of silyl enol ether **13a** illustrate that the IQ technique gives significantly greater enantioselectivity when compared to the EQ protocol (**Scheme 1.13**, **Table 1.5**). Having stated this, the selectivity achieved using the EQ protocol can be considerably increased (from 23% to 83% ee)

by the addition of LiCl to the reaction mixture. Simpkins also found that LiCl could be used, under EQ conditions, to increase the selectivity for the desymmetrisation of several prochiral ketones using a variety of lithium amide bases.[18,19]

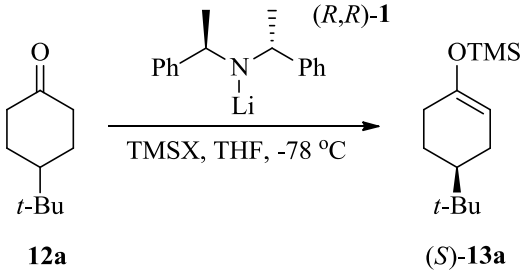


Scheme 1.13

Quench Protocol	Equivalents of LiCl	ee (%)
IQ	-	69
EQ	-	23
EQ	0.5	83

Table 1.5

Given that, when using an IQ protocol, a lithium halide is formed as the silylation proceeds, studies into the effect of the nature of the halide in the TMS source were conducted by Koga (**Scheme 1.14**, **Table 1.6**).[20] From this investigation, some clear trends are apparent. Firstly, on changing the nature of the halide from Cl to Br to I, the yield increases significantly. However, this increase in yield is accompanied by a decrease in enantioselectivity, with the best results being achieved using TMSCl.

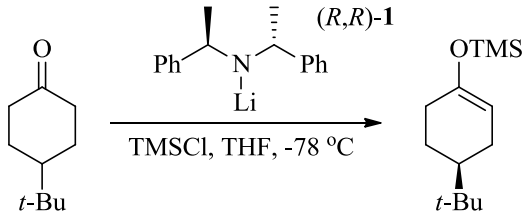


Scheme 1.14

X	Yield	ee (%)
Cl	71	90
Br	86	65
I	97	31

Table 1.6

Subsequently, the effect of the added lithium halide, under EQ conditions, was examined (**Scheme 1.15**, **Table 1.7**).[20] As expected, and in fair agreement with the results obtained by Simpkins,[18,19] in the absence of a lithium salt, the observed enantioselectivity was relatively low. Furthermore, the enantioselectivity decreased when the lithium salt was changed from LiCl to LiBr to LiI. This finding supports the theory that it is the LiCl formed during the silylation reaction which leads to greater selectivity being achieved when using TMSCl, compared to TMSBr or TMSI.



12a (*S*)-**13a**

Scheme 1.15

LiX (1.2 eq)	Yield	ee (%)
-	84	44
LiCl	97	88
LiBr	89	63
LiI	85	44

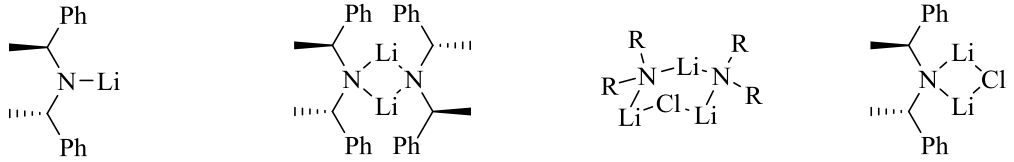
Table 1.7

Accordingly, the equivalents of LiCl were increased using the external quench method, as it was envisaged that this could lead to greater levels of enantioselectivity

of the deprotonation reaction. However, no change in ee was observed on increasing the excess of LiCl from 1.2 to 3.6 equivalents.[20]

NMR studies

Since the varied enantioselectivity was thought to be due to different lithium amide species existing in solution, Koga carried out detailed ^{6}Li and ^{15}N NMR analysis of the solution structures of [^{6}Li,^{15}N]-(*S*,*S*)-**1** in THF-d_8, both in the presence and absence of ^{6}LiCl.[20] Four different species were detected in solution (**Figure 1.5**). When no lithium salt was present, (*S*,*S*)-**1** was found to exist, almost exclusively, as the homo dimer (**22**). On the inclusion of ^{6}LiCl, two new mixed aggregates were recognised (**23** and **24**), with **24** being the predominant solution species. Thus, it was inferred that **24** is likely to be the reacting species which imparts high selectivity in the asymmetric transformation.



(*S*,*S*)-**1** **22** **23** **24**

Figure 1.5

The mixed dimer (analogous to **24**) is also observed in the presence of ^{6}LiBr. However, it is not the predominant solution species.[20] Koga determined that the homo dimer (**22**) was still present in a significant concentration, even when three equivalents of ^{6}LiBr were employed. Thus, it was proposed that the enantioselectivity observed in the asymmetric deprotonation using the C_2-symmetric base ((*R*,*R*)-**1**) in the presence of LiBr is lower than in the presence of LiCl because the more selective mixed dimer species is not prevalent. Similarly, the addition of ^{6}LiI does not vary the aggregation state of the lithium amide, which remains as the homo dimer (**22**).[20]

In addition to the solution structures which were elucidated by Koga for the C_2-symmetric lithium amide ((*S*,*S*)-**1**), studies were also carried out to determine the

major solution species of the chelating lithium amides (**Figure 1.6**).[21] In THF, without ^{6}LiCl, base **19** is known to exist as a chelated monomer. In the presence of ^{6}LiCl, the mixed dimer (**25**) was formed, and was considered to be the reactive species in the asymmetric deprotonation reaction.

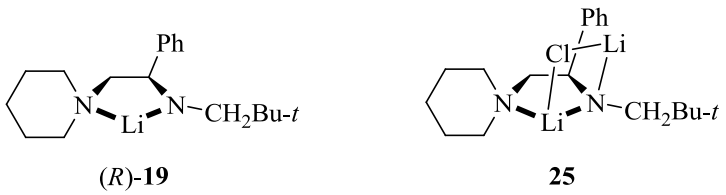
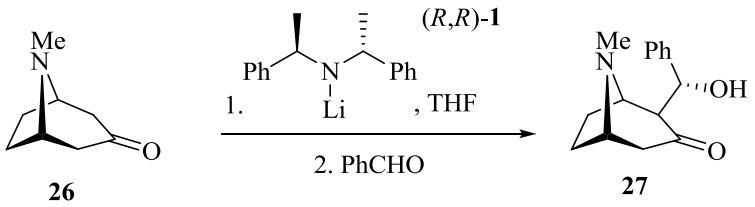


Figure 1.6

Encouraged by the advantages of utilising LiCl as an additive in lithium amide-mediated asymmetric deprotonations, Simpkins then investigated the effects of alternative salt additives on the asymmetric aldol reaction of tropinone (**26**), utilising an EQ protocol (**Scheme 1.16**, **Table 1.8**).[18] In addition to the lithium salts which have already been discussed, the effects of other inorganic salts (LiF, KCl, NaCl, NaBr, and $MgBr_2$) were probed. Unfortunately, none of these additives yielded any improvement over the established procedure. Strongly Lewis acidic additives, such as $SnCl_4$ and $TiCl_4$, were also investigated. However, none of the desired product was obtained using these additives. Of the additives screened by Simpkins, $ZnCl_2$ exhibited the most notable enhancement in enantioselectivity, affording the enantioenriched aldol product (**27**) in an 85% ee. Simpkins proposed that the improved results achieved with $ZnCl_2$ could, in fact, be due to the formation of LiCl during the reaction. On the other hand, it is possible that the $ZnCl_2$ forms a more selective aggregate with the lithium amide.



Scheme 1.16

Additive (0.5 eq)	ee (%)
-	24
LiCl	78
$ZnCl_2$	85

Table 1.8

In summary, a vast body of work has been undertaken, chiefly by the groups of Koga and Simpkins, in order to improve and to rationalise the processes involved in the deprotonation of prochiral ketones using lithium amide bases. In general, the optimal conditions require an internal quench protocol, or an external quench protocol in the presence of LiCl or $ZnCl_2$, at low temperatures (typically -78 ^oC) in a coordinating solvent. Detailed NMR studies have led to a greater understanding of the solution species which are responsible for high selectivity in this asymmetric transformation.

Structural development of bases

Since the initial publications from both Koga and Simpkins in 1986,[13] the scope of the lithium amide-mediated asymmetric deprotonation protocol has been explored extensively. A wide structural variety of bases have been synthesised and applied to the desymmetrisation of a range of prochiral substrates. The key developments will now be discussed in turn.

Perhaps the most successful class of lithium amide bases, in terms of both reactivity and enantioselectivity, is the Koga-type chelating base, of the general form illustrated in **Figure 1.7**. These bases consist of two bulky groups around nitrogen, one of which possesses a heteroatom which is capable of internally chelating to lithium. Thus, it can be envisaged that a stable, 5-membered chelate is formed between the lithium unit and the heteroatom present. Additionally, the amide nitrogen is rendered stereogenic by the propensity of the R^1 substituent on nitrogen to orient itself *trans* to the substituent, R^2, on the chiral carbon. Koga proposed that these chelating bases would form aggregates in solution, the aggregation state of which could be tuned by employing coordinating solvents and Lewis basic additives, such as HMPA.[13a]

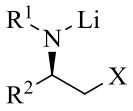
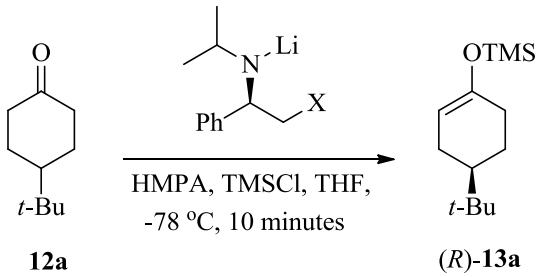


Figure 1.7

A range of bases were designed on the basis of the structure shown in **Figure 1.7**, and were applied to the benchmark deprotonation of 4-*tert*-butylcyclohexanone. Firstly, the nature of the chelating group was altered by employing either ether or tertiary amine substituents (**Scheme 1.17**, **Table 1.9**)[13a] In general, nitrogen-containing chelating groups exhibited the greatest selectivity, perhaps due to the greater availability of the lone pair on nitrogen for chelation to lithium, thus greating a more rigid and selective structure.



Scheme 1.17

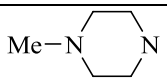
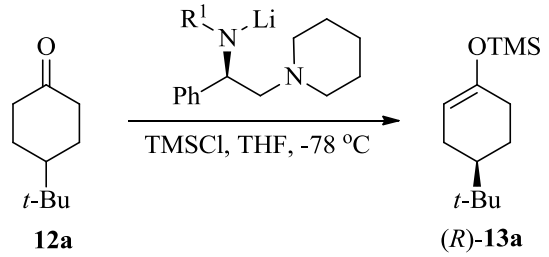
X	Yield (%)	ee (%)
	87	84
Me−O	90	47

Table 1.9

Additionally, the steric bulk and electronic nature of the R^1 substituent on the amide nitrogen was altered (**Scheme 1.18**, **Table 1.10**).[22] From these data, some clear trends can be observed. Firstly, on increasing the steric bulk of the *N*-alkyl group, the selectivity of the base increases. It is also apparent that fluorine-containing chains generally exhibit greater selectivities than their alkyl equivalents. These differences

in selectivity were proposed to be attributable to a more rigid, and hence more selective, base structure being formed in the fluorine-containing species. Koga explained this added rigidity by suggesting that an electrostatic interaction was present between the electronegative fluorine atoms and the electropositive lithium, locking the conformation of the monomeric form.[22]



Scheme 1.18

R^1	Yield (%)	ee (%)
CH_2CH_3	86	52
$CH_2CH(CH_3)_2$	92	81
$CH_2C(CH_3)_3$	93	86
CH_2CF_3	88	84
$CH_2CF_2CF_3$	79	85

Table 1.10

The structure of the Koga-type bases was then varied further by altering the R^2 substituent (**Figure 1.8**).[21] The chelating bases described thus far possess a phenyl group as the R^2 substituent. In an attempt to design more selective bases, Koga proposed that substituents on the stereogenic carbon which exhibited greater steric hindrance could impart superior selectivity in deprotonation reactions. Accordingly, bases containing either α-naphthyl (**28**), β-naphthyl (**29**), 3,5-dimethylphenyl (**30**), or 3,5-di-*tert*-butylphenyl (**31**) were prepared and applied to the deprotonation of 4-*tert*-butylcyclohexanone (**12a**) in the presence of TMSCl.

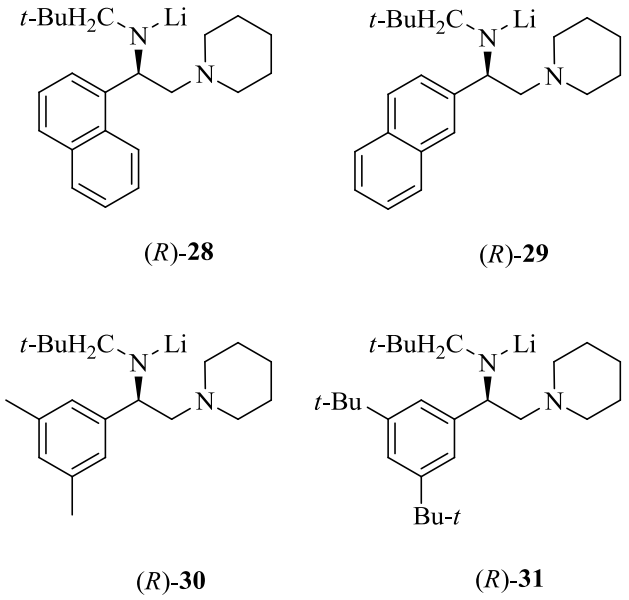
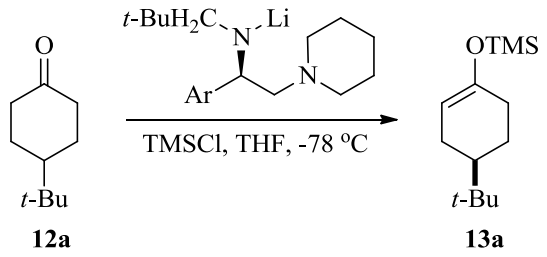


Figure 1.8

The results show that a slight improvement in selectivity over that using base (*R*)-**19** was achieved when base (*R*,*R*)-**28** was employed (**Scheme 1.19**, **Table 1.11**). However, this increase in selectivity was accompanied by a significant lowering of the reaction yield. It was also observed that the enantioselectivity of the reaction decreased on changing the aryl substituent from α-naphthyl ((*R*,*R*)-**28**) to β-naphthyl ((*R*,*R*)-**29**), and decreased further using 3,5-dimethylphenyl ((*R*,*R*)-**30**), or 3,5-di-*tert*-butylphenyl ((*R*,*R*)-**31**).



Scheme 1.19

Base	Yield (%)	ee (%)	Configuration of 13a
(*R*)-**19**	95	84	*R*
(*R*)-**28**	84	86	*R*
(*R*)-**29**	93	72	*R*
(*R*)-**30**	99	41	*R*
(*R*)-**31**	76	24	*S*

Table 1.11

Koga suggested an explanation for this observation using an 8-membered transition state model for the interaction between the ketone and the lithium chloride mixed dimer (**Figure 1.9**).[21] As the asymmetric deprotonation proceeds, a steric interaction is proposed to develop between the aryl group of the base and the substituent at the 4-position of the cyclohexanone. This interaction must be significantly small, in order for the reaction to proceed through the favoured 8-membered transition state, to give the highly enantioenriched silyl enol ether. Therefore, the diminished selectivity observed using bulkier aryl groups is thought to be a result of increasing unfavourable interactions in the transition state.

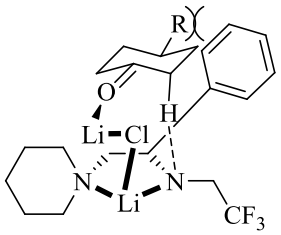
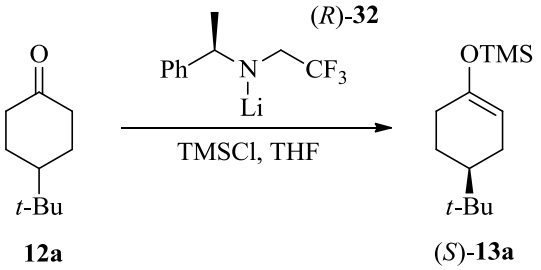


Figure 1.9

Koga also explored the efficiency of more structurally simple lithium amides, such as (*R*)-**32**, containing an α-phenethylamine motif and a fluoro-alkyl group.[23] On applying base (*R*)-**32** to the deprotonation of 4-*tert*-butylcyclohexanone (**12a**) in the presence of TMSCl, excellent selectivities and reactivities for the formation of the enantioenriched silyl enol ether were achieved (**Scheme 1.20**, **Table 1.12**). A clear advantage of this base is that these results were realised in the absence of the known carcinogen, HMPA.

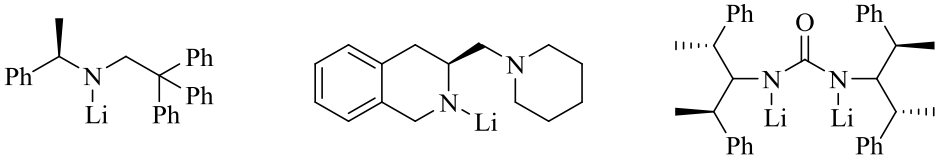


Scheme 1.20

Temperature (^{o}C)	Yield (%)	ee (%)
-78	98	89
-100	86	92

Table 1.12

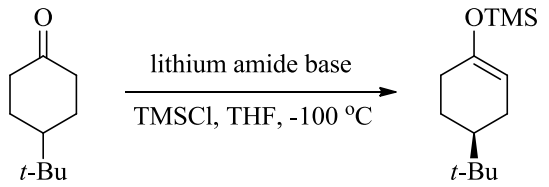
In addition to the research carried out by Koga and Simpkins into the development of lithium amide bases, there have been several significant contributions from Corey ((*R*)-**33**),[24] Aggarwal ((*R*)-**34**),[25] and Knochel ((*R*,*R*,*R*,*R*)-**35**, **Figure 1.10**),[26] the most noteworthy of which are shown.



(*R*)-**33** (*S*)-**34** (*R*,*R*,*R*,*R*)-**35**

Figure 1.10

The results achieved when these bases were applied to the benchmark deprotonation reaction using 4-*tert*-butylcyclohexanone (**12a**) are shown below (**Scheme 1.21**, **Table 1.13**). Although these bases were found to be efficient in the asymmetric transformation, no real advantage over the traditional bases was apparent. Indeed, it should be noted that a practically and economically less viable temperature of -100 ^{o}C was required for optimal results.



12a (*S*)-**13a**

Scheme 1.21

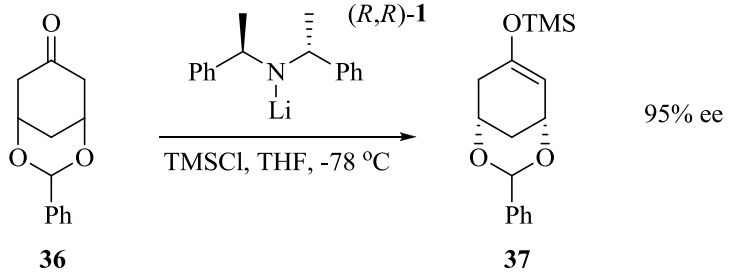
Base	Yield (%)	ee (%)	Additive
(*R*)-**33**	89	91	LiBr
(*R*)-**34**	89	81	HMPA
(*R*,*R*,*R*,*R*)-**35**	85	87	-

Table 1.13

Substrates

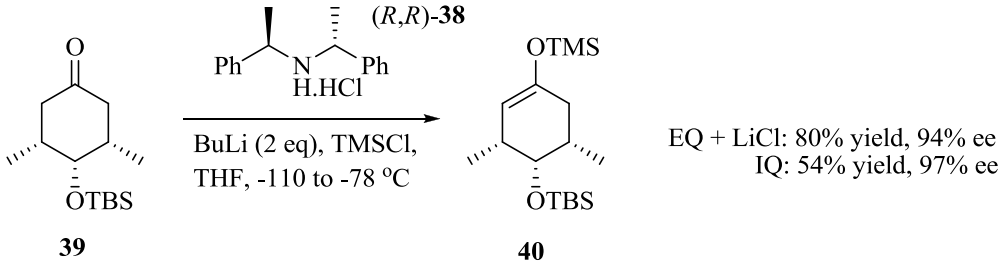
In the years following the preliminary publications regarding lithium amide-mediated transformations of conformationally-locked ketones, the substrate scope has been widened to encompass a wide range of ketones, in addition to the benchmark substrate, 4-*tert*-butylcyclohexanone (**12a**). There are numerous examples of the application of lithium bases in the synthesis of valuable natural products, a selection of which will be discussed herein.

Honda has described a novel route to enantiomerically-enriched 5-hydroxycyclohex-2-enone, which is often employed as a precursor in the synthesis of a variety of natural products.[27] A key step in the preparation of this chiral synthon involves the enantioselective deprotonation of a conformationally rigid bicyclic ketone (**36**) with the C_2-symmetric lithium amide ((*R*,*R*)-**1**), under internal quench conditions with TMSCl, to furnish the required silyl enol ether (**37**) in an exceptional 95% ee (**Scheme 1.22**).



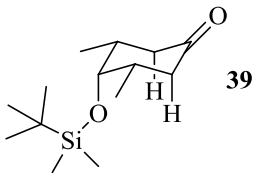
Scheme 1.22

Furthermore, the use of 3,4,5-trisubstituted cyclohexanones as substrates for lithium amide bases was explored by Prunet and Férézou for the synthesis of a fragment of bafilomycin A_1.[28] The crucial desymmetrisation step in the synthesis employed the amine hydrochloride salt (**38**), either under external quench conditions with added LiCl, or using the internal quench protocol, with both procedures giving the highly enantioenriched silyl enol ether (**40**, **Scheme 1.23**).



Scheme 1.23

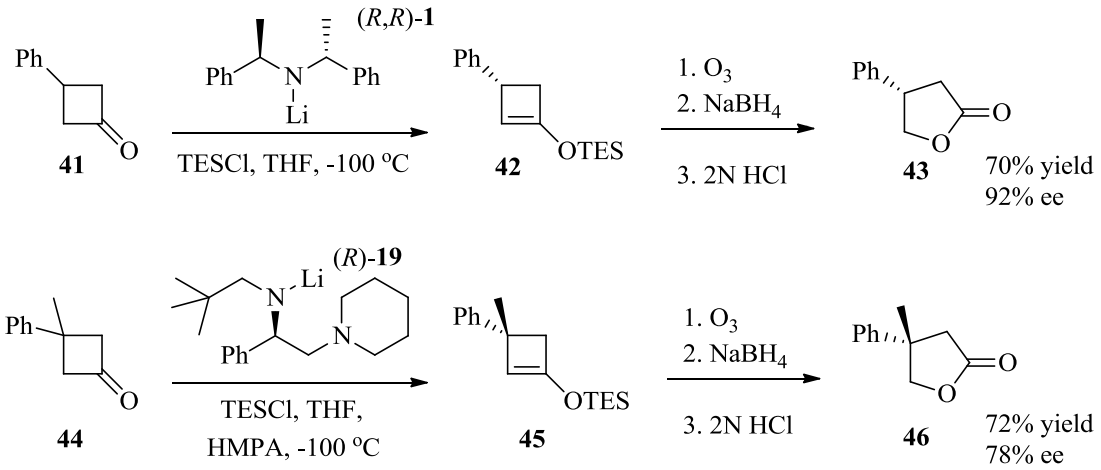
The remarkably high enantioselectivity of this transformation was proposed to be as a result of the close proximity of the methyl groups of the silyl group, which adopts an axial position, to the acidic axial protons in the ketone (**39**), as illustrated in **Figure 1.11**. It can be envisaged that such interactions would create a more hindered environment around the acidic protons and allow better discrimination by the base.



39

Figure 1.11

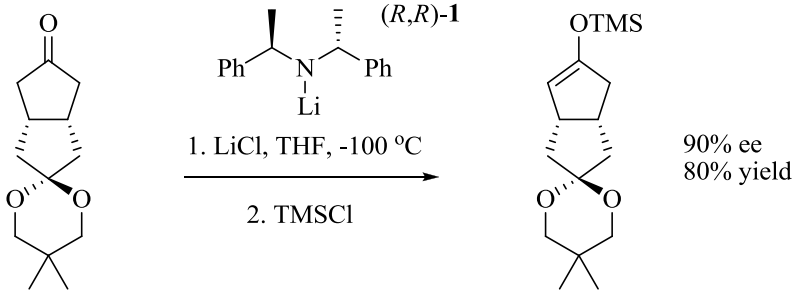
In addition to the increase in substrate scope of cyclohexanones, the asymmetric deprotonation conditions have been applied to ketones of other ring sizes. For instance, Honda examined the efficiency of both C_2-symmetric and chelating bases toward the enantioselective transformation of cyclobutanone derivatives into 3-substituted and 3,3-disubstituted γ-butyrolactones (**Scheme 1.24**).[29,30] In the case of the 3-substituted cyclobutane (**41**), the C_2-symmetric base ((*R*,*R*)-**1**) proved to be the most efficient for the preparation of the enantioenriched silyl enol ether (**42**). On the other hand, the chelating base ((*R*)-**19**) was required to convert the 3,3-disubstituted cyclobutane (**44**) to the corresponding silyl enol ether in high enantiomeric excess. With the intermediate silyl enol ethers in hand, the corresponding γ-butyrolactones could then be delivered in good yield and enantioselectivity.



Scheme 1.24

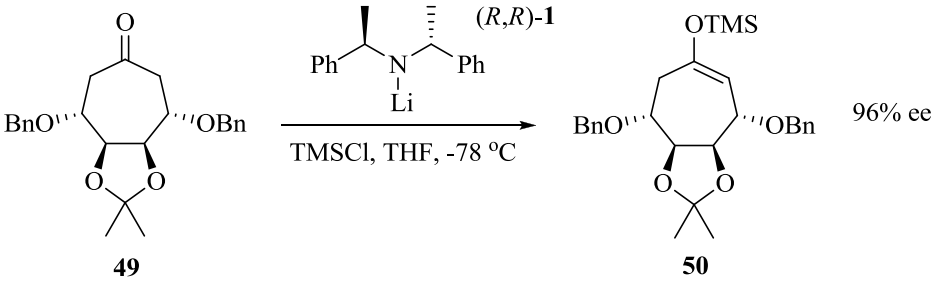
The use of bicyclic ketones containing a cyclopentanone unit has been illustrated by Gais in the enantioselective synthesis of carba-prostacyclin analogues.[31] More specifically, asymmetric deprotonation of the bicyclic ketone (**47**) with the C_2-

symmetric base ((*R*,*R*)-**1**), followed by trapping of the resultant lithium enolate with TMSCl gave the desired silyl enol ether (**48**) in a high yield and excellent ee (**Scheme 1.25**). This key transformation allowed facile access to the highly enantioenriched silyl enol ether, further demonstrating the synthetic value of the asymmetric deprotonation chemistry.



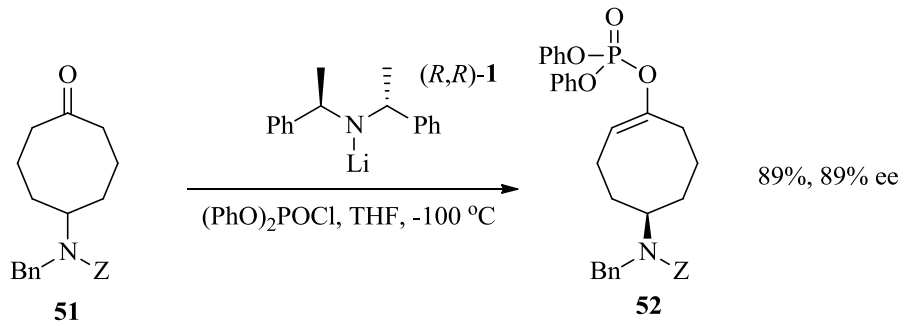
Scheme 1.25

Although the enantioselective deprotonation strategy has frequently been utilised for the desymmetrisation of 5- and 6-membered cyclic ketones, its application to cycloheptanones is less well-documented. The first example of an enantioselective deprotonation of a simple *meso*-cycloheptanone was illustrated by Honda in the synthesis of pseudomonic acid B.[32] The cycloheptanone (**49**) was transformed using the C_2-symmetric base ((*R*,*R*)-**1**) to the enantioenriched lithium enolate, in the presence of TMSCl, furnishing the required silyl enol ether (**50**) in an excellent 96% ee (**Scheme 1.26**). The high enantioselectivity of this reaction is remarkable, considering the numerous conformations that could be possible for such a relatively large cycle.



Scheme 1.26

Similar to the work by Honda, Aggarwal has also made contributions to the enantioselective deprotonation strategy for ketones of larger ring sizes, applying the C_2-symmetric base ((*R*,*R*)-**1**) towards desymmetrisation of a cyclooctanone (**51**) in the total synthesis of anatoxin-a (**Scheme 1.27**).[33] In contrast to much of the work done previously in this field using a chlorosilane to quench a lithium enolate, Aggarwal used diphenyl phosphoryl chloride as the electrophile to furnish an enol phosphate (**52**) in high yield and ee.



Scheme 1.27

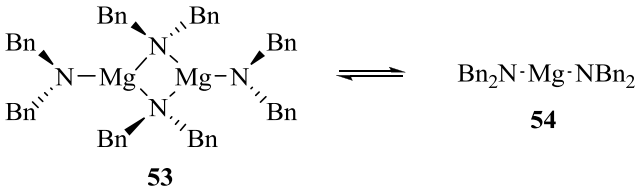
1.2 Chiral magnesium bases

1.2.1 Introduction

Since the first report of an optically pure lithium amide species being employed for an asymmetric process in 1980 by Whitesell,[4] this class of reagent has become a versatile tool for asymmetric synthesis. As discussed in the previous sections, the use of lithium amide bases is well-documented for the asymmetric transformation of several classes of substrate, including epoxides, tricarbonyl (η^6-arene)chromium complexes, and conformationally-locked ketones. There are, however, a number of weaknesses associated with lithium amides that can hinder their wider application in asymmetric synthesis. These include their requirement for low reaction temperatures,[13,14,23-26,29-31,33] their often complex solution behaviour,[15,20] and the structural complexity of the amines required for the highest selectivity.[13a,21,22,24-26] Therefore, in recent years, the use of chiral magnesium amide bases has been explored, since these reagents have properties similar to the lithium amides but with several possible advantages.

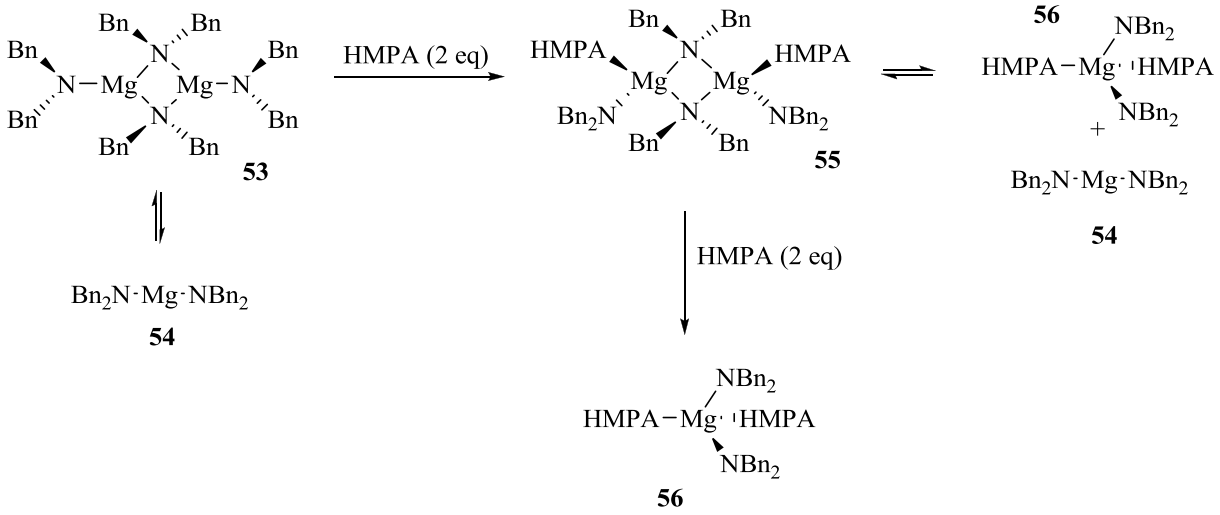
Solution aggregation

In general, in non-coordinating solvents, lithium amide species are present as a variety of different oligomeric complexes. These aggregates can be broken down to more simple monomers and dimers by using donating solvents. Additionally, strongly Lewis basic additives, such as HMPA, are often essential. Koga has illustrated that a specific aggregation state is often required for a given asymmetric transformation, in order to achieve high enantioselectivity.[15,20] This can lead to difficulties when attempting to develop robust and reproducible conditions using lithium amides. On the other hand, magnesium amides have been shown to exist mainly as monomers and dimers in solution. Indeed, examination of a toluene solution of bis(dibenzylamido)magnesium has shown that this bisamide exists solely in equilibrium between its dimer (**53**) and monomer (**54**, **Scheme 1.28**).[34]



Scheme 1.28

The solution structure of such magnesium amide species can be simplified further by inclusion of HMPA (**Scheme 1.29**). More specifically, addition of two equivalents of HMPA gives the bis-solvated dimer (**55**) which is in equilibrium with the solvated and non-solvated monomers (**56** and **54**, respectively). Addition of a further two equivalents of HMPA leads to deaggregation of the solvated dimer (**55**) to the solvated monomer (**56**).[34] This elegant control of the solution structure of magnesium amides illustrates the possibility of predictable solution environments, which can, in turn, lead to consistent and reproducible results in the reactions of these compounds.



Scheme 1.29

Thermal stability

As detailed previously, lithium amides require low reaction temperatures, typically between -78 °C and -100 °C, due to their poor thermal stability, coupled with their highly reactive nature. In contrast, magnesium amides are more thermally stable and

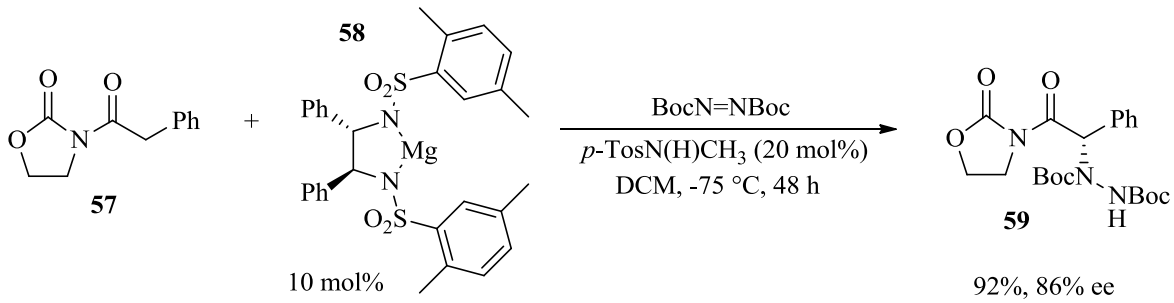
less reactive than their lithium counterparts.[35] Since most asymmetric deprotonations are governed by kinetic control, this decreased reactivity can often be beneficial, leading to greater selectivity being achieved using magnesium amides.[36] Another consequence of the lesser reactivity of magnesium amides is that it could be possible to achieve high enantioselectivity with these reagents at temperatures above -78 ^{o}C, making them more economically attractive and more compatible with less reactive substrates.

Divalency of magnesium

Due to the divalent nature of magnesium, both homo- and heteroleptic complexes can be employed. Thus, the design of magnesium complexes containing both a reactive ligand and a spectator ligand can be envisaged. This allows the possibility of employing a chiral ligand to carry out the asymmetric deprotonation reaction to give an optically-enriched magnesium enolate, possessing a chiral spectator ligand which could influence subsequent chemistry. In comparison, monovalent lithium has no means by which to control this type of process.

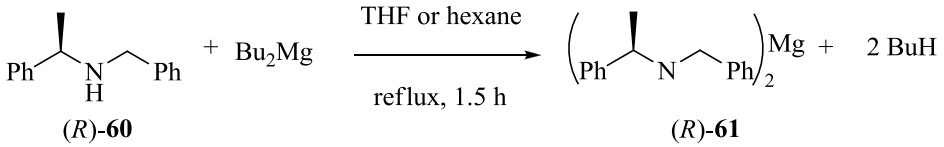
1.2.2 Magnesium bisamides

In contrast to lithium amides, magnesium bases have received relatively little attention in asymmetric synthesis. The first example of the use of magnesium bisamides in an asymmetric transformation was reported by Evans and Nelson in 1997.[37] A chiral magnesium bis(sulfonamide) (**58**) was employed catalytically in an enantioselective amination reaction (**Scheme 1.30**) to yield the desired product (**59**) in a highly enantioenriched form.



Scheme 1.30

After this initial contribution to chiral magnesium bisamide chemistry, magnesium bisamides received little attention until 2000, when Kerr and Henderson reported a novel magnesium bisamide base for the enantioselective deprotonation of prochiral ketones ((*R*)-**61**, **Scheme 1.31**).[38] This simple base can be readily prepared by treating two equivalents of the commercially available and inexpensive amine ((*R*)-**60**) with dibutylmagnesium and refluxing in THF or hexane.



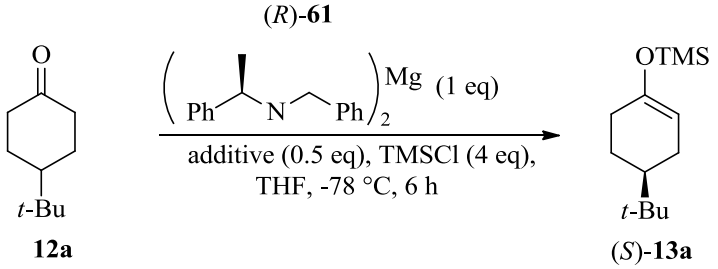
Scheme 1.31

Substrate scope

4-Substituted cyclohexanones

On application of the magnesium bisamide ((*R*)-**61**) to the benchmark deprotonation reaction of 4-*tert*-butylcyclohexanone (**12a**), the corresponding silyl enol ether (**13a**) was obtained with excellent conversion and selectivity, especially considering the simple nature of the chiral amide unit (**Scheme 1.32**, **Table 1.14**).[38] The optimised reaction conditions for this transformation involve internal quench conditions, where a THF solution of 4-*tert*-butylcyclohexanone is added to a solution of the chiral bisamide, HMPA, and TMSCl in THF at -78 ^{o}C. This preliminary result clearly illustrates that homochiral magnesium bisamides are capable of effectively mediating

an enantioselective deprotonation reaction. Pleasingly, it was subsequently shown that the toxic HMPA additive could be replaced with a more acceptable Lewis base, DMPU, without any deleterious effect on the reactivity or enantioselectivity.[38]

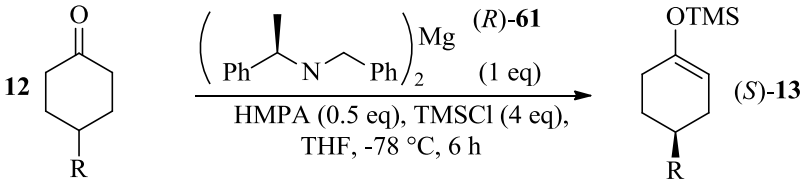


Scheme 1.32

Additive	Conversion (%)	(*S*):(*R*)
HMPA	82	91:9
DMPU	89	90:10

Table 1.14

With this promising result in hand, the magnesium bisamide ((*R*)-**61**) was employed for the enantioselective deprotonation of a range of 4-substituted cyclohexanones, with a view to increasing the scope of this novel transformation (**Scheme 1.33**, **Table 1.15**). The results outlined in **Table 1.15** demonstrate the exceptional reactivity and selectivity which was revealed for the magnesium bisamide ((*R*)-**61**). Of most note is the excellent er achieved for the desymmetrisation of 4-*iso*-propylcyclohexanone (**13b**, 95:5).



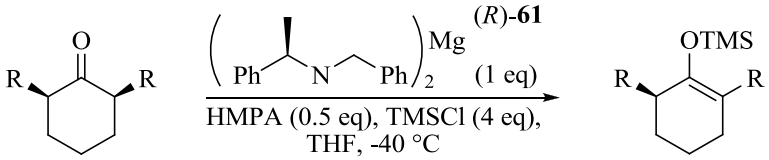
Scheme 1.33

Enol Silane	Conversion (%)	Yield (%)	(*S*):(*R*)
R = *t*-Bu (**13a**)	82	64	91:9
R = *i*-Pr (**13b**)	77	39	95:5
R = *n*-Pr (**13c**)	88	58	88:12
R =Me (**13d**)	81	68	91:9
R = Ph (**13e**)	79	48	87:13

Table 1.15

2,6-Substituted cyclohexanones

The deprotonation strategy was then extended to the conversion of 2,6-disubstituted cyclohexanones, affording outstanding levels of conversion and enantioselectivity for a variety of substrates (**Scheme 1.34**, **Table 1.16**).[39] It should be noted that these reactions were carried out at a relatively high temperature of -40 ^{o}C, which is in stark contrast to the low temperatures required when using lithium amide bases.



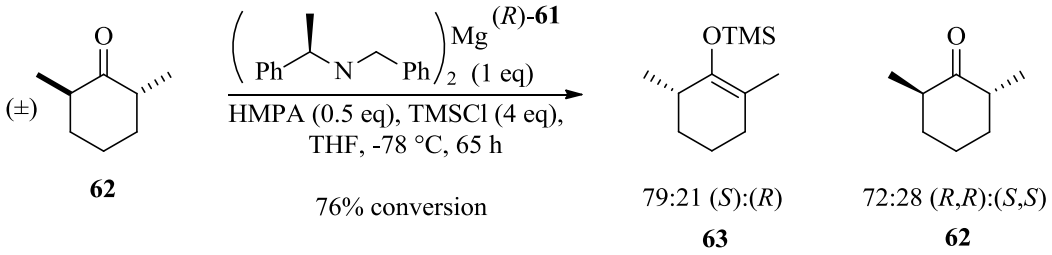
Scheme 1.34

R	Time (h)	Conversion (%)	Yield (%)	er
Me	6	99	92%	93:7 (*R*):(*S*)
i-Pr	6	99	90%	98.8:1.2 (*S*):(*R*)
Ph	8	-	86%	82:18 (*S*):(*R*)

Table 1.16

In addition to the high stereoinduction observed for the magnesium bisamide ((*R*)-**61**) in the asymmetric deprotonation of *cis*-2,6-disubstituted cyclohexanones, a kinetic

resolution process was exposed for the *trans*-isomer of 2,6-dimethylcyclohexanone (**62**, **Scheme 1.35**).[39] More specifically, reaction of the racemic ketonic mixture at -78 ^{o}C furnished the silyl enol ether (**63**) in 79:21 er, while returning the initially racemic starting material (**62**) in an enantioenriched form (72:28 er).



Scheme 1.35

Structural development of magnesium bisamides

Altering the achiral sidearm

Having demonstrated the utility of the magnesium bisamide ((*R*)-**61**) in the enantioselective deprotonation of various prochiral ketones, a series of alternative magnesium bisamides was synthesised in order for their efficiency to be tested against the benchmark deprotonation reaction.[40] Firstly, preserving the chiral phenylethylamine motif, the achiral substituent was first altered using a range of alkyl and aryl groups (**Figure 1.12**).

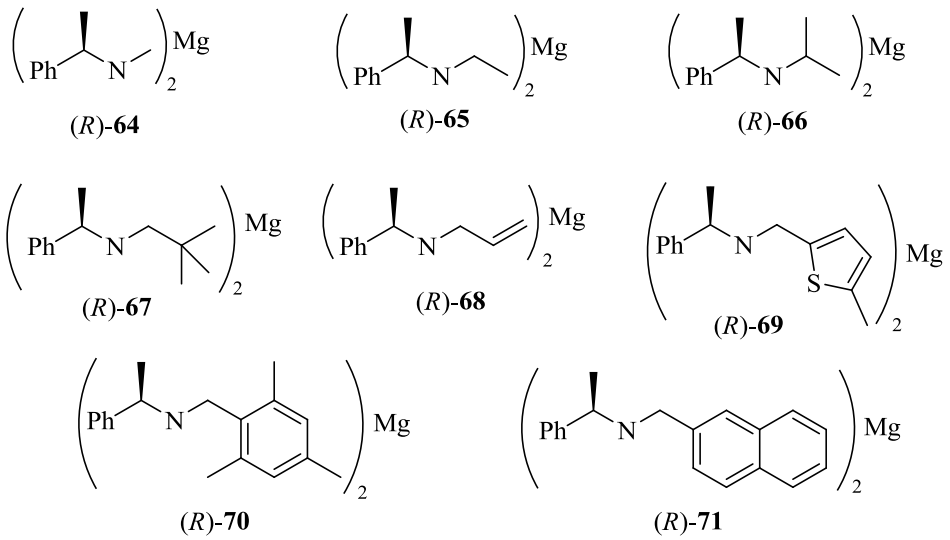
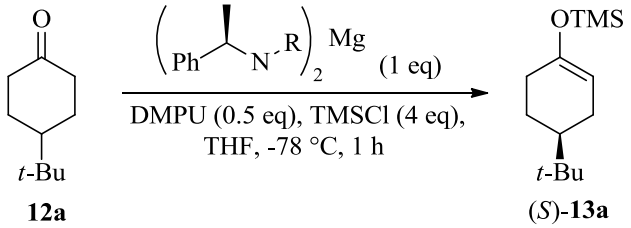


Figure 1.12

Upon inspection of the results achieved using these novel magnesium bisamides for the deprotonation of 4-*tert*-butylcyclohexanone, some clear trends are apparent (**Scheme 1.36**, **Table 1.17**). Firstly, in relation to the alkyl-substituted amides, increasing the steric bulk of the achiral unit results in a progressive rise in the selectivity of the base ((*R*)-**64** to (*R*)-**67**). Indeed, the selectivity obtained using the *tert*-butyl amide ((*R*)-**67**) approaches the best results achieved using the original magnesium bisamide ((*R*)-**61**), although the conversion is significantly lower. Furthermore, on increasing the steric bulk of the alkyl group from methyl to ethyl to isopropyl, the conversion steadily increases. However, on moving to the more bulky tertiary butyl substituent, the reactivity decreases significantly. The use of alternative unsaturated units also gave good conversion and selectivity ((*R*)-**68** to (*R*)-**71**). However, none of these novel magnesium bisamides offered an improvement over the original magnesium bisamide complex.



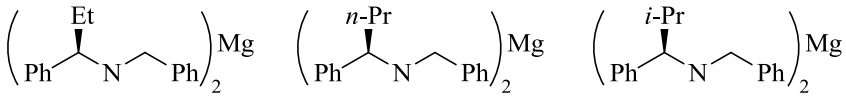
Scheme 1.36

Base	Conversion (%)	er (*S*):(*R*)
(*R*)-**64**	42	55:45
(*R*)-**65**	73	75:25
(*R*)-**66**	87	80:20
(*R*)-**67**	17	88:12
(*R*)-**68**	87	81:19
(*R*)-**69**	83	87:13
(*R*)-**70**	97	84:16
(*R*)-**71**	87	87:13

Table 1.17

Altering the stereogenic sidearm

Having established that the benzyl substitiuent was the most effective of the achiral sidearms employed thus far, altering the structure of the stereogenic component was then investigated by increasing the size of the alkyl substituent.[40] Thus, the bases shown in **Figure 1.13** were prepared and applied to the desymmetrisation of 4-*tert*-butylcyclohexanone.

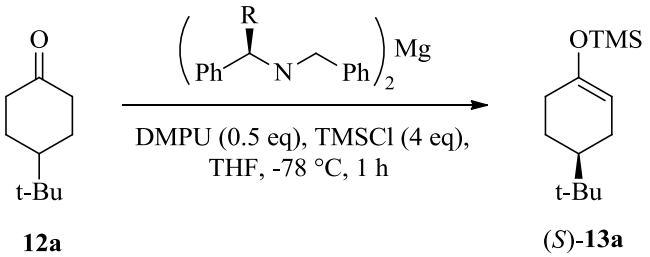


(*R*)-**72** (*R*)-**73** (*R*)-**74**

Figure 1.13

Pleasingly, an increase in enantioselectivity was achieved by employing an ethyl-substituted amine ((*R*)-**72**); however, this was accompanied by a decrease in reaction conversion (**Scheme 1.37**, **Table 1.18**). Additionally, on increasing the steric bulk of the alkyl group further, from *n*-propyl ((*R*)-**73**) to *iso*-propyl ((*R*)-**74**) the selectivity decreased and an incremental rise in conversion resulted. Although the asymmetric induction obtained using the ethyl-substituted bisamide ((*R*)-**72**) was the highest

observed thus far in the magnesium bisamide-mediated deprotonation of 4-*tert*-butylcyclohexanone, at this juncture, the original bisamide remained the most successful in terms of both reactivity and selectivity.



Scheme 1.37

Base	Conversion (%)	er (*S*):(*R*)
(*R*)-**72**	70	92:8
(*R*)-**73**	88	88:12
(*R*)-**74**	93	74:26

Table 1.18

Chelating amines

In order to further develop the range of chiral magnesium bisamides, chelating diamines, capable of forming a stable 5-membered chelate ring with magnesium, were prepared (**Figure 1.14**).[41] Furthermore, the effect of employing an additional donor atom was investigated in the morpholine- and piperazine-derived bases (**77**-**80**, **Figure 1.14**).

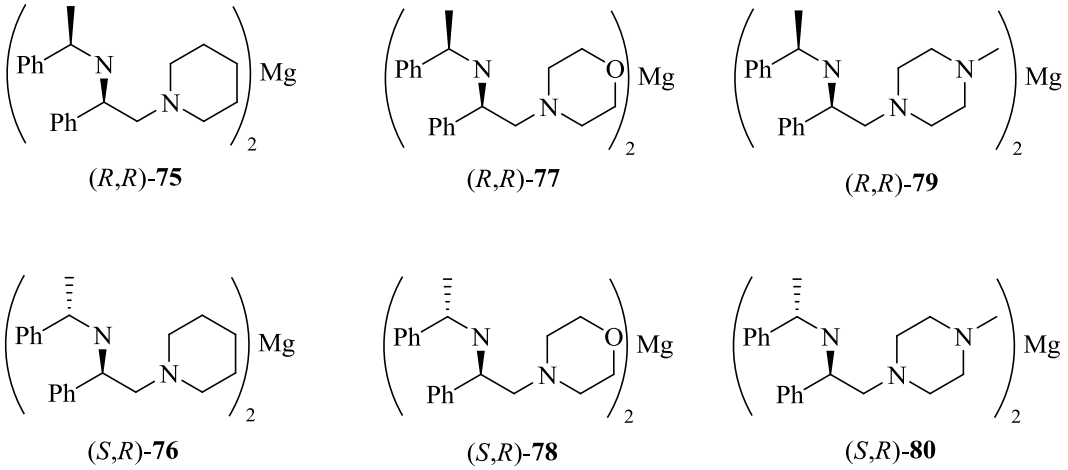
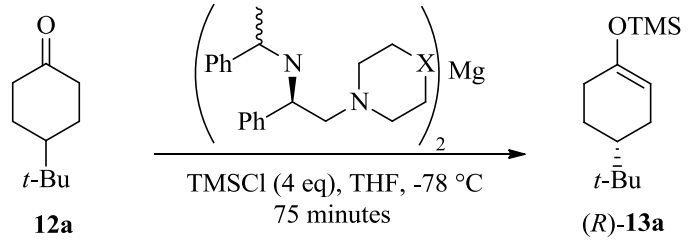


Figure 1.14

The results obtained in the benchmark deprotonation reaction are illustrated (**Scheme 1.38**, **Table 1.19**). In all cases, excellent enantioselectivity was achieved, whilst the observed conversions were variable. A clear advantage that these chelating bases have over existing protocols is the high selectivity displayed in the absence of strongly Lewis basic additives. Moreover, inversion of one of the stereocentres on moving from the (*R*,*R*)-isomer to the (*S*,*R*)-isomer had only a small effect on the selectivity of the reaction, indicating that the selectivity-controlling stereocentre was that closest to the chelating moiety.



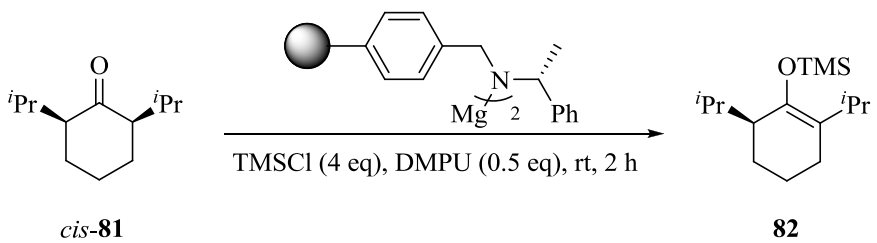
Scheme 1.38

Base	Conversion (%)	Yield (%)	(*R*):(*S*)
(*R*,*R*)-**75**	58	45	93:7
(*S*,*R*)-**76**	87	45	88:12
(*R*,*R*)-**77**	89	57	90:10
(*S*,*R*)-**78**	55	34	89:11
(*R*,*R*)-**79**	88	42	91:9
(*S*,*R*)-**80**	59	36	87:13

Table 1.19

Polymer-supported magnesium bisamides

With regard to extending the synthetic utility of the magnesium bisamides, it was envisaged that tethering the chiral amine, and hence the magnesium amide, to a polymer support would provide a practically convenient and recyclable reagent. To this end, polymer-supported magnesium amides of (*R*)-*N*-benzyl-α-methylbenzylamine (**60**) were prepared, using either a Merrifield resin or a soluble polystyrene resin.[42] The supported reagents were applied to the asymmetric deprotonation of a range of 4-substituted and 2,6-disubstituted cyclohexanones, with the most impressive results being achieved in the transformation of *cis*-di-*iso*-propylcyclohexanone (**81**) at room temperature (**Scheme 1.39**, **Table 1.20**). Furthermore, when the Merrifield resin was employed for the deprotonation of 4-*tert*-butylcyclohexanone, the supported amine could be recovered and recycled up to 5 times, achieving consistent selectivities and no appreciable drop in conversion.[42]



cis-**81** **82**

Scheme 1.39

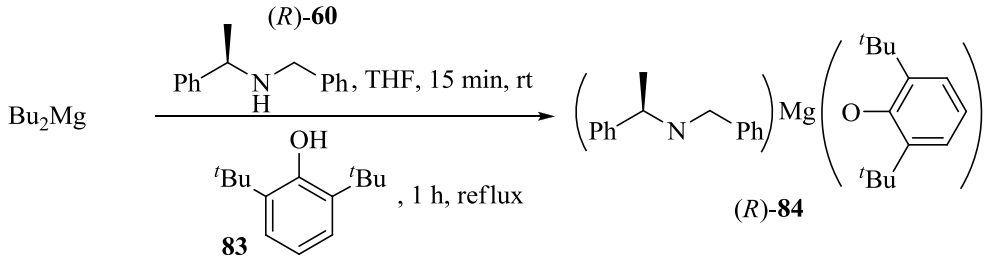
Resin	Conversion (%)	Yield (%)	(*R*):(*S*)
Merrifield	97	95	93:7
Soluble polystyrene	>99	96	93:7

Table 1.20

1.2.3 Heteroleptic magnesium amides

Aryloxymagnesium amides

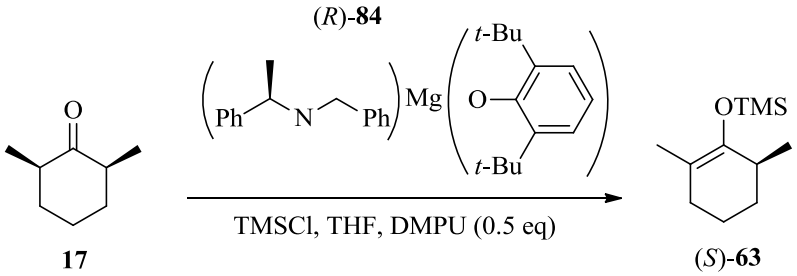
The magnesium bases described thus far have been homoleptic complexes, possessing two identical amide ligands. However, a potential advantage of magnesium reagents is the divalent nature of the metal, which allows access to heteroleptic complexes possessing a reactive anion and a spectator anion, requiring only half the quantity of chiral amine. In order to explore the potential advantages of such heteroleptic magnesium complexes, aryloxymagnesium amides were prepared as reagents for the enantioselective deprotonation of prochiral ketones (**Scheme 1.40**).[43] More specifically, the readily available achiral phenol (**83**) was employed alongside the established chiral amine ((*R*)-**60**) in the relatively sterically encumbered aryloxymagnesium amide ((*R*)-**84**), which was subsequently applied to the transformation of various conformationally-locked ketones.



Scheme 1.40

Although the enantioselectivity achieved for the benchmark deprotonation of 4-*tert*-butylcyclohexanone (**12a**) was somewhat disappointing, the heteroleptic base complex proved to be far more selective for the asymmetric deprotonation of *cis*-2,6-

dimethylcyclohexanone (**Scheme 1.41**, **Table 1.21**). Intriguingly, the highest selectivities were observed at elevated temperatures. Furthermore, the selectivity achieved is the opposite of that delivered by the analogous magnesium bisamide, allowing access to either enantiomer of the silyl enol ether (**63**) using the same enantiomer of chiral amine ((*R*)-**60**). These observations infer that the sense of stereochemical induction imparted by a particular magnesium base complex is not purely controlled by the local stereogenicity of the amide ligand, but is, in fact, directed by the overall chiral environment within the magnesium base complex.



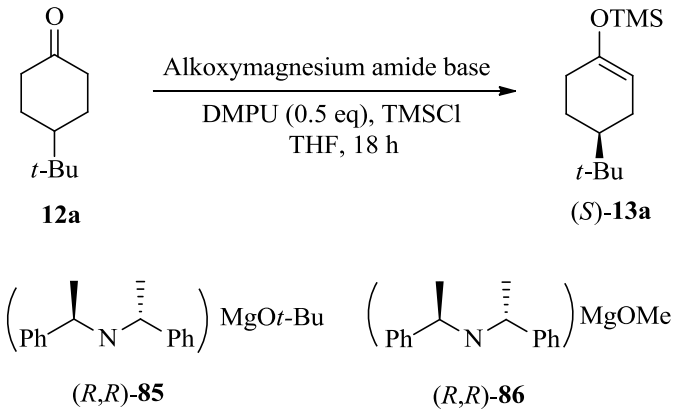
Scheme 1.41

Temp. (°C)	Time (h)	Conversion (%)	(*S*):(*R*)
-78	68	78	46:54
-40	68	54	76:24
r.t.	19	62	78:22
40	1	33	83:17
50	1	46	76:24
66	1	11	67:33

Table 1.21

Alkoxymagnesium amides

In addition to the magnesium bisamides containing the 2,6-di-*tert*-butylphenoxide moiety, a series of more simple alkoxymagnesium amides was also synthesised.[44] In particular, the C_2-symmetric alkoxymagnesium amides (**85** and **86**, **Scheme 1.42**) displayed high reactivity and enantioselectivity in the deprotonation of 4-*tert*-butylcyclohexanone (**Table 1.22**). These bases provide a valuable alternative to the previously described aryloxymagnesium amide ((*R*)-**84**), which exhibited poor selectivity in the transformation of 4-substituted cyclohexanones.



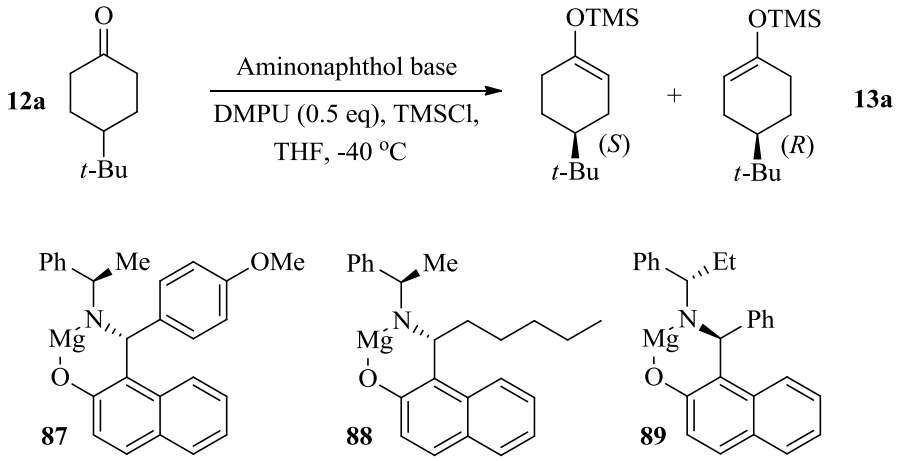
Scheme 1.42

Base	Temperature (°C)	Conversion (%)	Yield (%)	(*S*):(*R*)
(*R*,*R*)-**85**	-78	56	53	95:5
(*R*,*R*)-**86**	-78	87	83	75:25
(*R*,*R*)-**86**	rt	90	87	78:22

Table 1.22

Aminonaphthols

The study of heteroleptic magnesium bases then progressed to the assessment of chiral amino alcohols, which are capable of forming a 6-membered cyclic complex when treated with dibutylmagnesium (**87**, **88**, and **89**, **Scheme 1.43**).[45,46] When employed for the benchmark deprotonation of 4-*tert*-butylcyclohexanone, these bases proved to be capable of high levels of stereoinduction and reactivity (**Table 1.23**). A clear benefit of such complexes is their ability to impart high enantioselectivity at a relatively elevated temperature of -40 °C. Despite the apparent advantages of the heteroleptic magnesium bases discussed to this stage, it should be noted that the magnesium bisamides are still the most efficient in the asymmetric transformation of prochiral ketones.



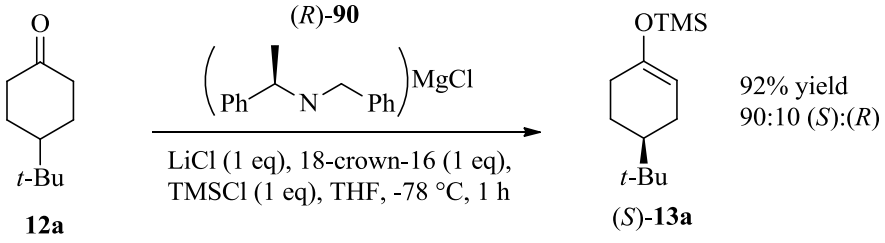
Scheme 1.43

Base	Conversion (%)	Yield (%)	(*S*):(*R*)
87	84	69	85:15
88	74	64	86:14
89	91	83	15:85

Table 1.23

Hauser bases

Initial investigations into the efficacy of Hauser bases, which had never been shown to be capable of mediating an asymmetric deprotonation process, had shown that these species imparted poor (almost racemic) selectivity in the transformation of prochiral ketones.[47] However, a reassessment of these bases proved that high selectivities were achievable under novel additive conditions.[44] More specifically, by employing LiCl and 18-c-6 as additives, selectivities as high as 90:10 er and yields of up to 92% were attainable when the homochiral Hauser base ((*R*)-**90**) was utilised for the benchmark deprotonation reaction (**Scheme 1.44**).



Scheme 1.44

The use of LiCl and 18-c-6 as additives for magnesium amide complexes is novel and, consequently, no elucidations regarding the solution structures have been published. The addition of LiCl to solutions of lithium amides is, however, well-documented. As described previously, a new species forms in solution, incorporating the lithium chloride into the aggregation state of the amide base to form a more selective mixed dimer (**24**, **Figure 1.15**).[20] Thus, it can be envisaged that magnesium amides form similar activated structures with lithium chloride (**91**).

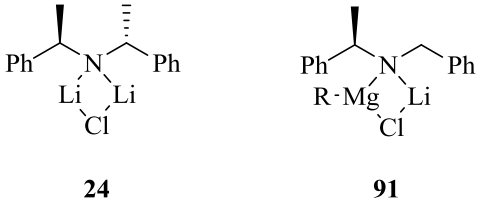
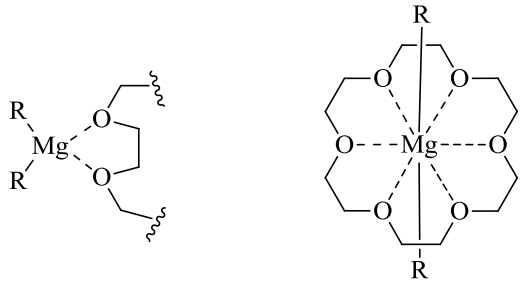


Figure 1.15

The role of crown ethers has, in contrast, been documented in relation to their structures with dialkylmagnesium compounds, which interact with the crown ether in either an edge-on fashion (**92**) or *via* formation of a threaded complex (**93**), where the crown ether is equatorial and the R groups adopt the remaining axial positions (**Figure 1.16**).[48] If similar structures are, indeed, formed on addition of 18-c-6 to magnesium bases, a more hindered and hence more selective complex could potentially result.

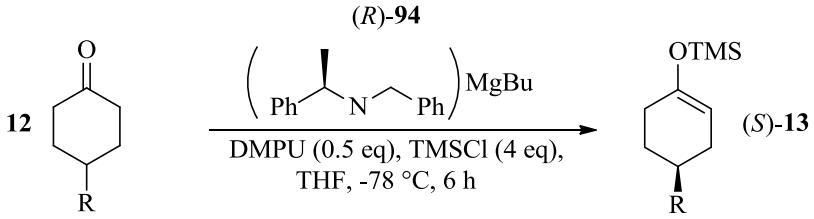


92 **93**

Figure 1.16

Alkylmagnesium amides

In order to extend the application of enantiopure heteroleptic magnesium complexes further, alkylmagnesium amides were prepared and applied to the enantioselective deprotonation of a selection of conformationally-locked ketones (**Scheme 1.45**, **Table 1.24**).[43] As can be seen from the results shown, excellent conversions and good enantioselectivities were achieved for the preparation of a variety of enantioenriched silyl enol ethers. Indeed, the consistently high selectivities are approaching those obtained using the original bisamide ((*R*)-**61**), while requiring only half the quantity of chiral ligand.



Scheme 1.45

Enol Silane	Conversion (%)	(*S*):(*R*)
R = ^{t}Bu (**13a**)	80	86:14
R = ^{i}Pr (**13b**)	84	86:14
R = ^{n}Pr (**13c**)	85	87:13
R = Me (**13d**)	84	83:17
R = Ph (**13e**)	83	86:14

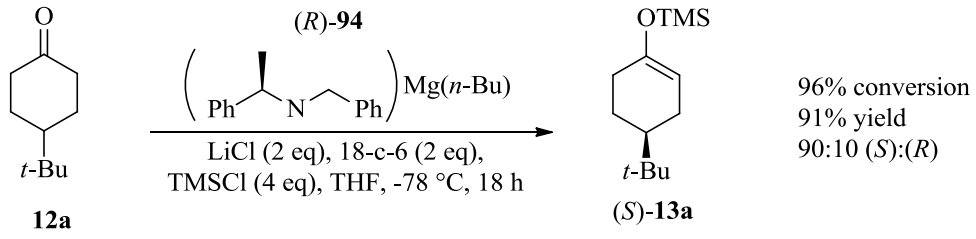
Table 1.24

NMR studies

In order to understand the reactivity of the alkylmagnesium amide ((*R*)-**94**) in more detail, ^{1}H NMR analysis was employed to monitor its preparation from dibutylmagnesium and (*R*)-*N*-benzyl-α-methylbenzylamine, and its reaction with 4-*tert*-butylcyclohexanone.[43] Formation of the alkylmagnesium amide was complete within 15 minutes, after which time the substrate was added. Subsequent examination of the reaction mixture after 50 minutes revealed that the amine NH signal had reappeared, with retention of the signals corresponding to the butyl ligand. Hence, it was elucidated that deprotonation of the ketone occurs via the amide unit of the alkylmagnesium amide, while the butyl group acts as a spectator anion.

Improved additive conditions

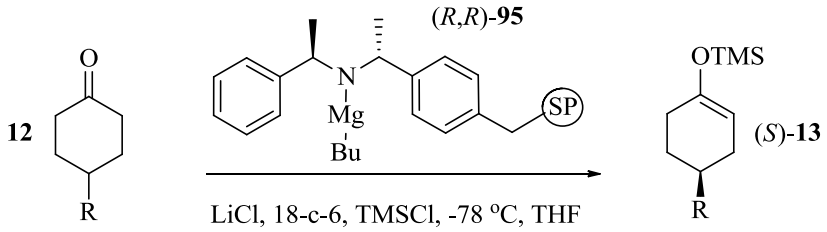
The efficiency with which the alkyl magnesium amide ((*R*)-**94**) mediates the deprotonation of prochiral ketones was improved by employing LiCl and 18-crown-6, in the same fashion as for the analogous Hauser base. Indeed, the selectivity achieved under these novel conditions was shown to equal that obtained with the original bisamide, alongside DMPU, in the deprotonation of 4-tert-butylcyclohexanone (**Scheme 1.46**).[44] Overall, this simple alkylmagnesium amide is able to effect outstanding reactivity and selectivity in the benchmark deprotonation reaction, using only half the quantity of chiral amine, compared to the analogous bisamide ((*R*)-**61**).



Scheme 1.46

Polymer-supported alkylmagnesium amides

The applicability of this asymmetric deprotonation protocol towards polymer-supported synthesis was then probed by preparing a soluble polymer-supported alkylmagnesium amide ((*R*,*R*)-**95**) and applying this reagent to the deprotonation of various 4-substituted cyclohexanones (**Scheme 1.46**, **Table 1.25**).[46] Pleasingly, all chosen substrates showed superb levels of enantioselectivity for the asymmetric deprotonation reaction at -78 ^{o}C. Moreover, almost quantitative conversions were displayed in these reactions, and the silyl enol ethers were isolated in excellent 88-92% yields, illustrating the robustness of this polymer-supported technique. Furthermore, the supported reagent can be recycled up to four times with no appreciable drop in conversion or selectivity.



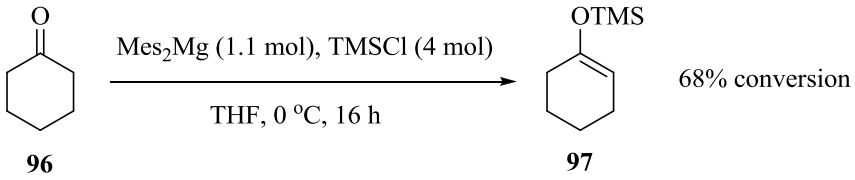
Scheme 1.47

Enol Silane	Conversion (%)	Yield (%)	(*S*):(*R*)
R = ^{t}Bu (**13a**)	96	91	92:8
R = ^{i}Pr (**13b**)	97	88	93:7
R = ^{n}Pr (**13c**)	97	90	93:7
R = Me (**13d**)	98	92	94:6
R = Ph (**13e**)	98	89	93:7
R = OTBS (**13f**)	98	90	92:8

Table 1.25

1.2.4 Carbon-centred magnesium bases

Within programmes aimed at the development of an amine-recycling protocol (for further details, see Chapter 2 - Introduction), in order to avoid alkylation and reduction of the ketone substrate, bismesitylmagnesium was investigated as a possible stoichiometric source of magnesium due to its non-nucleophilic reactivity, and lack of β-hydrogens.[44] After performing a control reaction to ascertain whether bismesitylmagnesium was, itself, able to carry out the deprotonation of a cyclohexanone, it became apparent that this diarylmagnesium species was, indeed, capable of mediating such a process (**Scheme 1.48**).[49]



Scheme 1.48

Following up on this surprising discovery, a detailed programme of optimisation was initiated, so as to probe the wider application of the emerging system.[49] The optimal conditions from this study were found to require the use of 0.5 mol of preformed Mes_2Mg, 2 mol LiCl, and 1 mol TMSCl at 0 °C. With these optimised conditions in hand, their efficiency towards a range of enolisable ketones was probed (**Figure 1.17**). Of most note is the excellent yield achieved in the reaction of 4-chlorobutyrophenone, on consideration that the analogous reaction employing LDA led only to elimination products.

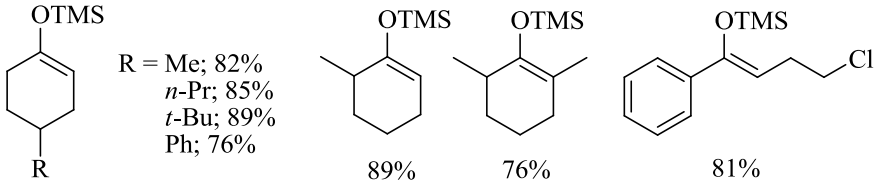


Figure 1.17

In addition to the initial findings in the area of carbon-centred magnesium bases, a practically more convenient one-pot procedure has been developed, which allows the *in situ* preparation of the dialkylmagnesium reagent.[50] Furthermore, this procedure has proved to be more efficient than the previously described method. In addition to the development of bismesitylmagnesium as a carbon-centred base, di-*tert*-butylmagnesium has also been demonstrated to be a more atom-economical alternative, and has displayed superior reactivity at lower temperatures.[51] Research towards the use of these bases in established reactions, such as the Shapiro reaction[46,52] and the Wittig reaction[50,53] is currently underway within our laboratories.

2. Proposed Work

At this stage, a wide variety of magnesium bisamides have been prepared within our laboratories and have been shown to be effective bases for the desymmetrisation of prochiral ketones.[38-41] Perhaps the most attractive of these bases, in terms of both efficacy and accessibility of the chiral amine precursor, are those which contain a dibenzylamine motif. Thus, we were interested in preparing a series of structurally similar magnesium bisamides, possessing variations of the original magnesium bisamide ((*R*)-**61**), with a view to obtaining more selective bases than those developed to date. With this in mind, and as described previously, the C_2-symmetric lithium amide ((*R*,*R*)-**1**) has illustrated high reactivity and selectivity in the asymmetric deprotonation of prochiral ketones.[14,19,20] There are, however, a number of limitations associated with the use of this lithium amide, including the complex solution behavior of (*R*,*R*)-**1**,[20] and the necessity to perform reactions at low temperatures of -78 ^{o}C and below to obtain high enantioselectivity.[14,29,30,31,33] Considering the potential advantages of simple solution aggregation and higher thermal stability of the corresponding magnesium amide, the C_2-symmetric bisamide ((*R*,*R*)-**98**), as well as the more sterically encumbered analogue ((*S*,*S*)-**99**), will be assessed in the asymmetric deprotonation reactions of prochiral ketones (**Figure 1.18**).

(*R*,*R*)-**98** (*S*,*S*)-**99**

Figure 1.18

Once these simple C_2-symmetric bisamides have been applied to the benchmark deprotonation reaction, the efficiency of this class of base will be probed further by employing a range of structurally similar bisamides with subtly different steric properties ((*R*,*R*)-**100** to (*R*,*R*)-**121**, **Figure 1.19**). When employing bases (*R*,*R*)-**100** to (*S*,*R*)-**102**, the effect of increasing the steric bulk at one of the stereogenic centres will be explored. In addition, bases (*R*,*R*)-**103** to (*R*,*R*)-**105** will be applied to the benchmark deprotonation reaction in order to determine any changes in enantioselectivity that occur when a greater degree of saturation is introduced to the bisamide structure. Also, the effect of employing

various substitution patterns on one of the aromatic rings, including the addition of groups possessing differing electronic properties, will be determined ((*R*,*R*)-**106** to (*R*,*R*)-**111**). The effect of employing biphenyl- and naphthyl-containing bisamides ((*R*,*R*)-**112** to (*R*,*R*)-**118**), which could have greater ability for π-π and π-Mg interactions, will also be explored. Furthermore, the preparation and application of alternative *pseudo*-C_2-symmetric bisamides, having one of the substituents of a stereogenic centre tethered to the adjacent aromatic ring, thus restricting rotation, will be embarked upon ((*R*,*R*)-**119** to (*R*,*R*)-**121**).

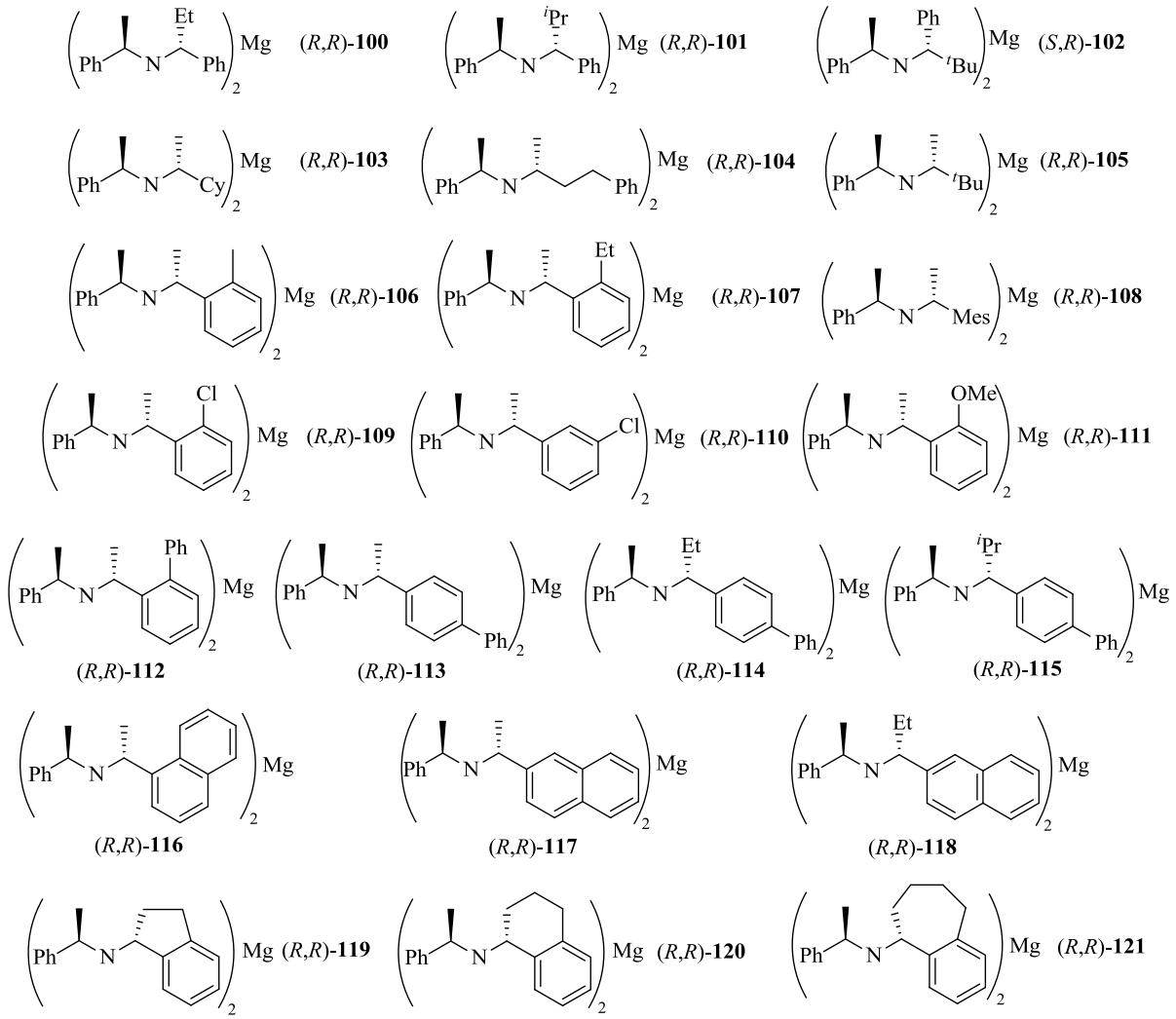
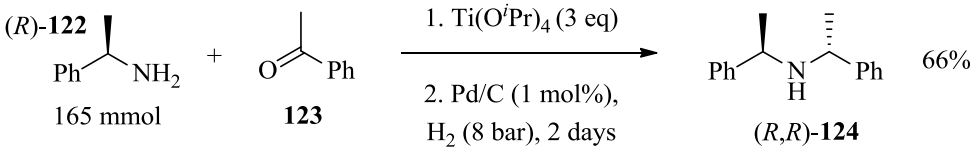


Figure 1.19

3. Results and Discussion

3.1 Asymmetric deprotonations employing C_2-symmetric bases ((*R*,*R*)-98 and (*R*,*R*)-125)

In order to allow the evaluation of the C_2-symmetric magnesium bisamide ((*R*,*R*)-**98**) as an enantioselective base for the deprotonation of prochiral ketone substrates, the required parent amine was prepared. The C_2-symmetric amine ((*R*,*R*)-**124**) was synthesised from (*R*)-phenylethylamine ((*R*)-**122**) and acetophenone (**123**) by the reductive amination method developed by Alexakis, using titanium tetra-*iso*-propoxide to mediate imine formation followed by reduction to the amine *in situ* by palladium on charcoal and hydrogen gas (**Scheme 1.49**).[54] This procedure has become the method of choice within our laboratory for the synthesis of this class of amine and routinely delivers the required amines on appreciable scale with high diastereoselectivity. The enantioenriched amines are then isolated after recrystallisation of their HCl or TFA salts. Using this method, the required amine was obtained in good yield, providing sufficient quantities for the optimisation of the proposed asymmetric deprotonations. The (*R*,*R*) stereochemistry was confirmed by comparison with literature ^{1}H NMR data,[55] and by X-ray analysis of the HCl salt (**Figure 1.20**).



Scheme 1.49

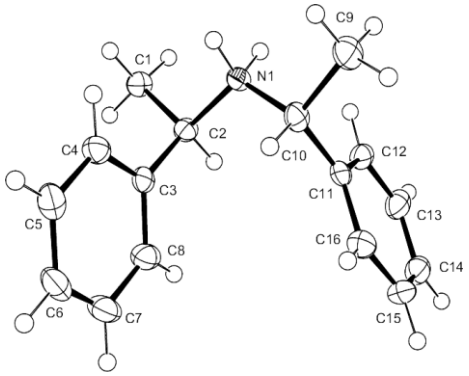
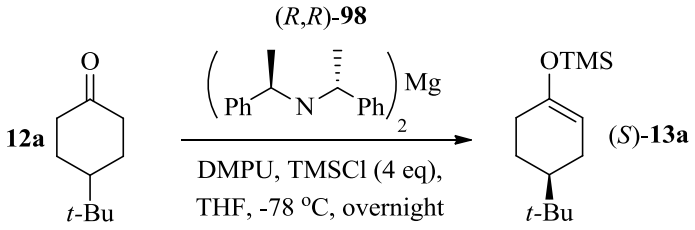


Figure 1.20

With a successful route to (*R*,*R*)-**124** to hand, we next wanted to initiate an optimisation study using the magnesium bisamide ((*R*,*R*)-**98**). As has now become standard procedure in our laboratory, DMPU was employed as a Lewis basic additive alongside the benchmark substrate, 4-*tert*-butylcyclohexanone, and an excess of TMSCl electrophile, using Corey's internal quench procedure[17] at a reaction temperature of –78 °C (**Scheme 1.50**, **Table 1.26**). To our delight, this initial optimisation study delivered both superb conversions and selectivities for the enantioselective deprotonation of the benchmark substrate (**12a**), compared to results achieved previously. As expected,[38] when the Lewis basic additive, DMPU, was omitted from the reaction, conversion to the desired enol ether ((*S*)-**13a**) was moderate. With DMPU present in the reaction, conversions increased by >20% (**Table 1.26**, entries 2-4), while selectivites reached a high of 94:6 er (**Table 1.26**, entry 3). In addition, we were also pleased to find that the starting C_2-symmetric amine (*R*,*R*)-**124** could be recovered from each reaction in around 85% yield after column chromatography.



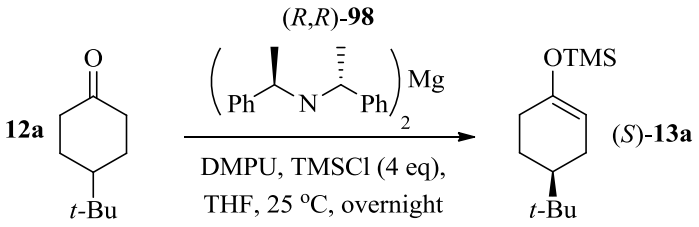
Scheme 1.50

Entry	DMPU (eq)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	0	72	48	90:10
2	0.5	93	73	93:7
3	1	97	88	94:6
4	2.5	96	76	92:8

Table 1.26

Excited by the excellent initial results using DMPU, we next wanted carry out the reactions at a more elevated temperature. As a starting point, it was decided to perform the reactions at room temperature (**Scheme 1.51**, **Table 1.27**). Somewhat disappointingly, moderate

selectivities were achieved under these conditions. However, we were encouraged by the fact that enantioinduction was still possible at this much more accessible temperature.

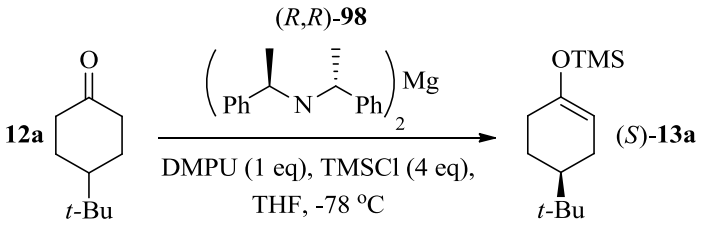


Scheme 1.51

Entry	DMPU (eq)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	0	75	58	69:31
2	0.5	78	59	73:27
3	1	89	66	75:25
4	2.5	94	72	75:25

Table 1.27

Following the results obtained from the initial DMPU study, it was decided to use one equivalent of DMPU in further optimisation studies employing (*R*,*R*)-**98**. Subsequently, a time study was initiated, the results of which are shown in **Scheme 1.52** and **Table 1.28**. The results from the time study indicate that the enantioselective deprotonation of 4-*tert*-butylcyclohexanone was essentially complete within 6 h, shown by a conversion of 93%, and a selectivity of 92:8 er (**Table 1.28**, entry 4). These results compared favourably to those obtained previously in which the reaction was quenched after 16 h, resulting in a 97% conversion and a comparable selectivity of 94:6 er (**Table 1.26**, entry 3). While we were delighted to establish that the reaction was essentially complete after just 6 h, subsequent optimisation studies were still performed over 16 h, since this had a practical advantage over performing reactions over 6 h.

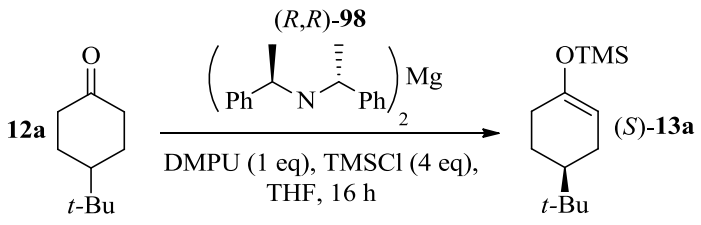


Scheme 1.52

Entry	Reaction time (h)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	1	80	53	92:8
2	2	83	61	93:7
3	4	80	58	91:9
4	6	93	77	92:8

Table 1.28

The next optimisation study was a more in-depth temperature study (**Scheme 1.53**, **Table 1.29**, previous results obtained at –78 °C and 25 °C are also shown for comparison). Overall, the results obtained employing magnesium bisamide base (*R*,*R*)-**98** for the enantioselective deprotonation of 4-*tert*-butylcyclohexanone across a wide range of temperatures were outstanding.[56] The conversions remained very high across the temperature range, while selectivities remained as high as 88:12 er at temperatures of up to –20 °C (**Table 1.29**, entry 4). These results compared extremely favourably with the equivalent lithium amide base ((*R*,*R*)-**1**). Indeed it is notable that the selectivity obtained at 0 °C (86:14 er, **Table 1.29**, entry 5) was still higher than the selectivity previously reported under similar conditions for the same transformation at –78 °C with the lithium amide base ((*R*,*R*)-**1**, 85:15 er).[14]

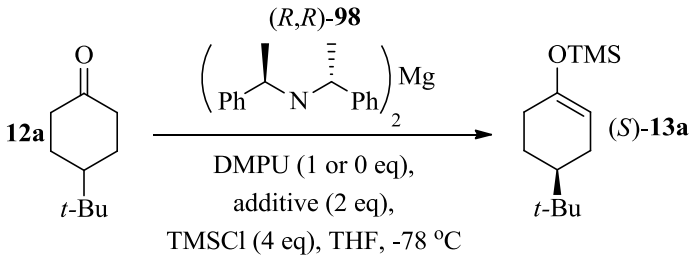


Scheme 1.53

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	97	88	94:6
2	-60	93	69	92:8
3	-40	95	74	90:10
4	-20	97	78	88:12
5	0	93	66	86:14
6	25	89	66	75:25

Table 1.29

An additional study was then performed to assess any possible advantage in employing alternative additives alongside DMPU. More specifically, a series of alternative additives were added to the benchmark reaction, with the anticipation that conversions and/or selectivities could be further increased (**Scheme 1.54**, **Table 1.30**). As shown, interesting results were obtained when a further additive was added to the benchmark reaction. In all cases, conversions were lower than those results obtained with only DMPU present as an additive (*cf.* **Table 1.29**, entry 1). Surprisingly, when LiCl additive was present, a poor conversion (54%) was obtained (**Table 1.30**, entry 1). This was unexpected as LiCl had been shown to increase conversions in certain cases for both magnesium and lithium amide bases.[18,19,44] However, more interesting was the slight increase in selectivities shown in several cases. For example, a high of 95:5 er was recorded when two equivalents of DABCO were added (**Table 1.30**, entry 2). In order to probe this result further, this reaction was repeated using no DMPU additive (**Table 1.30**, entry 7). In this case, although a high selectivity was also obtained (93:7 er), the conversion dropped to a disappointing level (61%).

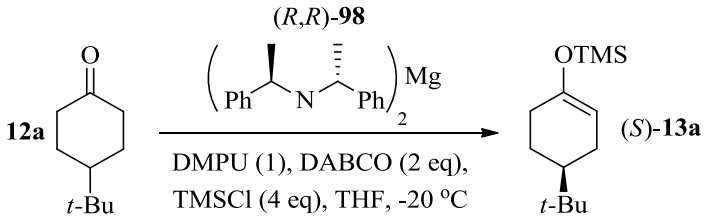


Scheme 1.54

Entry	DMPU (eq)	Additive	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	1	LiCl	54	30	91:9
2	1	DABCO	69	47	95:5
3	1	TMEDA	75	55	94:6
4	1	PMDTA	88	68	91:9
5	1	15-c-5	83	58	93:7
6	1	18-c-6	62	46	91:9
7	0	DABCO	61	34	93:7

Table 1.30

With these interesting results to hand, and in an attempt to increase the reaction conversion, the benchmark deprotonation was performed using DABCO at the more elevated temperature of -20 ^{o}C (**Scheme 1.55**, **Table 1.31**). In this instance, the conversion increased to a high of 95%, while the selectivity remained at a reasonable level (87:13 er) and was in line with that obtained previously at this elevated temperature (*cf.* **Table 1.29**, entry 4). However, in light of the poor conversions achieved at -78 ^{o}C and the only slight increase in selectivity recorded at both -78 ^{o}C and -20 ^{o}C, it was decided not to use additional additives in future studies employing C_2- or *pseudo*-C_2-symmetric magnesium amide bases.

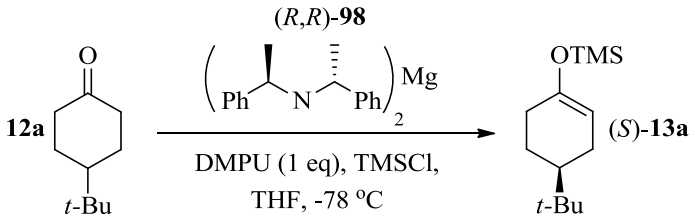


Scheme 1.55

Conversion (%)	Yield (%)	er (*S*):(*R*)
95	83	87:13

Table 1.31

Prior to the application of our optimised conditions to a series of substrates, a final study was performed to investigate the number of equivalents of TMSCl electrophile required for the reaction (**Scheme 1.56**, **Table 1.32**).[56] We were delighted to find that the number of equivalents of TMSCl could be reduced to just one (**Table 1.32**, entry 4), without any notable deterioration in the observed conversion or selectivity. This is an additional advantage of our magnesium amide bases over the corresponding lithium amides which are known to require an excess of TMSCl electrophile, typically four equivalents.[13,14,17]

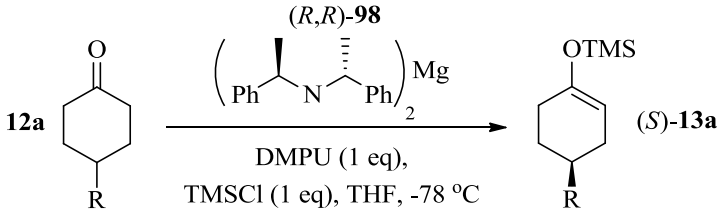


Scheme 1.56

Entry	TMSCl (eq)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	4	97	88	94:6
2	3	90	63	92:8
3	2	92	64	92:8
4	1	93	66	93:7

Table 1.32

Finally, a substrate study was initiated, employing the now optimised conditions for the magnesium bisamide ((*R*,*R*)-**98**). The substrate study was first performed at –78 °C (**Scheme 1.57** and **Table 1.33**). We were delighted to find that the now optimised conditions for magnesium bisamide (*R*,*R*)-**98** could be transferred to a range of 4-substituted cyclohexanone substrates.[56] Indeed, a high selectivity of 95:5 er was achieved for the enantioselective deprotonation of 4-methylcyclohexanone (**Table 1.33**, entry 4).



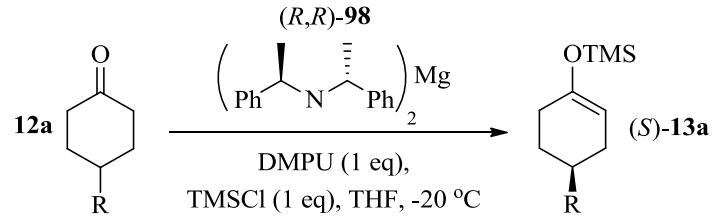
Scheme 1.57

Entry	Enol Silane	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	R = ^{t}Bu (**13a**)	93	66	93:7
2	R = ^{i}Pr (**13b**)	96	67	93:7
3	R = ^{n}Pr (**13c**)	92	65	94:6
4	R = Me (**13d**)	96	69	95:5
5	R = OTBS (**13f**)	91	68	92:8*

* Determined by specific rotation.

Table 1.33

Encouraged by these results, the deprotonation of the same range of substrates was then performed at the more elevated temperature of -20 °C (**Scheme 1.58**, **Table 1.34**).[56] We were delighted to find that excellent selectivities could, indeed, be achieved across a range of substrates at this temperature. This was highlighted by the superb 96% conversion and 90:10 er achieved for the enantioselective deprotonation of 4-methylcyclohexanone (**Table 1.34**, entry 4).



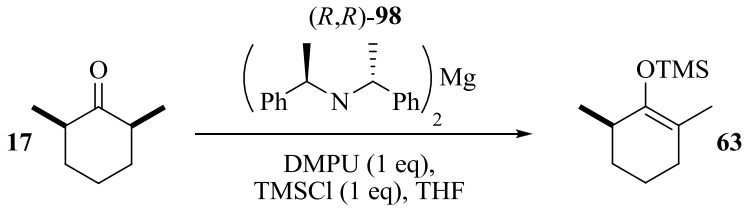
Scheme 1.58

Entry	R	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	R = ^{t}Bu (**13a**)	93	83	88:12
2	R = ^{i}Pr (**13b**)	95	70	87:13
3	R = ^{n}Pr (**13c**)	96	68	89:11
4	R = Me (**13d**)	96	69	90:10
5	R = OTBS (**13f**)	92	70	87:13*

* Determined by specific rotation.

Table 1.34

We then moved on to consider the asymmetric deprotonation of an alternative, 2,6-di-substituted cyclohexanone substrate (**17**) under the optimised conditions (**Scheme 1.59**, **Table 1.35**). Perhaps unsurprisingly, at -78 ^{o}C no conversion was recorded for the deprotonation of this sterically encumbered 2,6-dimethylcyclohexanone (**Table 1.35**, entry 1). However, on moving to a more elevated temperature of –40 ^{o}C, a conversion of 55% was recorded, alongside a pleasing selectivity of 86:14 er (**Table 1.35**, entry 2). Finally, on increasing the reaction temperature to -20 ^{o}C near quantitative conversion to the desired enol silane was recorded, alongside a moderate 85:15 selectivity (**Table 1.35**, entry 3).

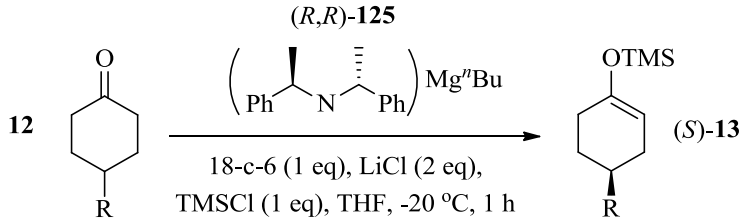


Scheme 1.59

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*R*):(*S*)
1	-78	0	-	-
2	-40	55	47	86:14
3	-20	99	51	85:15

Table 1.35

Recent work within our laboratory has shown that alkylmagnesium amides derived from the C_2-symmetric amine ((*R*,*R*)-**124**) can be employed in the deprotonation of 4-substituted cyclohexanones to give excellent results (er of up to 98:2) under alternative additive conditions, employing 18-crown-6 and LiCl, at -78 °C.[44] With this in mind, and considering the efficiency of the novel C_2-symmetric bisamide at more elevated temperatures, the desymmetrisation of a range of 4-substituted cyclohexanones was performed at -20 °C (**Scheme 1.60**, **Table 1.36**). Although the enantioselectivites achieved under these novel conditions were slightly lower than those achieved using the corresponding magnesium bisamide at -20 °C, it should be noted that only one equivalent of chiral amine is required, giving a clear practical advantage, over short one hour reaction times.



Scheme 1.60

Entry	Enol Silane	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	R = ^{t}Bu (**13a**)	95	83	82:18
2	R = ^{i}Pr (**13b**)	95	81	81:19
3	R = ^{n}Pr (**13c**)	93	75	83:17
4	R = Me (**13d**)	93	80	85:15
5	R = Ph (**13e**)	-*	82	90:10

* Not determined due to overlapping signals in the GC trace.

Table 1.36

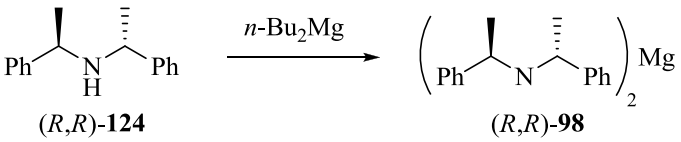
3.2 Crystallisation studies

Having demonstrated that the C_2-symmetric magnesium bisamide ((*R*,*R*)-**98**) is a highly selective base for the desymmetrisation of prochiral ketones, we wished to further broaden our knowledge of this species by elucidating the crystal structure using X-ray crystallography. Accordingly, crystallisation of (*R*,*R*)-**98** was attempted (**Scheme 1.61**,

Table 1.37). Firstly, the magnesium bisamide was prepared from the parent amine and *n*-Bu_2Mg in the normal manner, by initial removal of the heptane solvent from *n*-Bu_2Mg followed by addition of THF and the chiral amine ((*R*,*R*)-**124**), and refluxing for 1.5 hours to give a 0.5 M solution of the magnesium bisamide. Slow cooling of the solution from 65 ^oC to room temperature followed by storage at -20 ^oC for 3 days did not result in any crystallisation. In a further attempt to initiate crystallisation, 4 mL of hexane was added slowly to the solution. However, this resulted in the precipitation of a powdery solid and did not deliver any crystalline material (**Table 1.37**, entry 1).

In an alternative attempt to induce crystallisation of the magnesium bisamide ((*R*,*R*)-**98**), hexane was employed as the solvent for base formation (**Table 1.37**, entry 2). The resulting 0.5 M solution of (*R*,*R*)-**98** was allowed to cool slowly to room temperature before being stored at -20 ^oC for 24 hours. This resulted in the precipitation of a significant quantity of amorphous solid. Accordingly, more hexane was added and the mixture was heated gently until all of the solid dissolved. The resulting solution was, once more, allowed to cool slowly and was then stored at -20 ^oC for 24 hours. Unfortunately, an amorphous solid was, yet again, obtained and no crystalline material was formed using this method.

Finally, similar to the procedure followed by Henderson and Mulvey for the crystallisation of the magnesium bisamide derived from dibenzylamine,[34] toluene was employed in the attempted crystallisation of (*R*,*R*)-**98** (**Table 1.37**, entry 3). Using toluene as the solvent for base formation, followed by slow cooling and storage at -20 ^oC for 24 hours, delivered a precipitate which appeared to be crystalline. However, analysis of the material by single crystal X-ray diffraction was unsuccessful, possibly indicating that the material was not crystalline, or that co-crystallisation had occurred. At this stage in our research programme, due to the difficulties encountered, the crystallisation of the magnesium bisamide ((*R*,*R*)-**98**) remains to be realised.



(*R*,*R*)-**124** (*R*,*R*)-**98**

Scheme 1.61

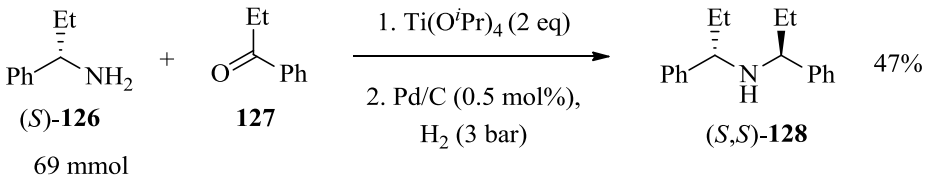
Entry	Crystallisation solvent	Result
1	THF/hexane	Powdery solid obtained
2	Hexane	Powdery solid obtained
3	Toluene	Resulting solid appeared to be crystalline but X-ray analysis failed

Table 1.37

3.3 Alternative C_2- and *pseudo*-C_2-symmetric magnesium bisamides

3.3.1 Preparation of alternative C_2- and pseudo-C_2-symmetric amines

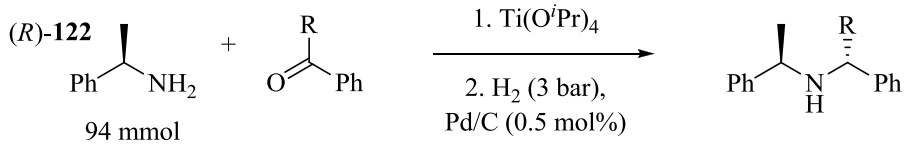
The exceptional results achieved using the very simple C_2-symmetric magnesium bisamide ((*R*,*R*)-**98**) encouraged us to expand upon the synthesis of alternative C_2- and *pseudo*-C_2-symmetric amines, with the anticipation of achieving even higher selectivities. We therefore initially decided to synthesise a slightly more sterically encumbered C_2-symmetric amine ((*S*,*S*)-**128**), incorporating ethyl substituents, *via* the Alexakis one-pot method (**Scheme 1.62**).[54] This amine was of interest to us as it would provide a good comparison with amine (*R*,*R*)-**98** in terms of sterics, and both starting materials ((*S*)-phenylpropylamine (**126**) and propiophenone (**127**)) were commercially available. The crude C_2-symmetric amine ((*S*,*S*)-**128**) was isolated as an 8:1 (*S*,*S*)/(*S*,*R*) mixture of diastereoisomers. Salting from HCl, recrystallisation from MeOH, and extraction with $NaHCO_3$/DCM resulted in isolation of the desired secondary amine ((*S*,*S*)-**128**) in 47% overall yield.



Scheme 1.62

The preparation of a range of *pseudo*-C_2-symmetric bisamides was also a major goal for this project. In relation to this, the one-pot preparation of a wide range of *pseudo*-C_2-symmetric

amines has also been described by Alexakis.[57] Taking advantage of this and the ready availability of (*R*)-phenylethylamine (**122**), the synthesis of a variety of *pseudo*-C_2-symmetric amines was embarked upon. To start, we looked to increase the steric bulk at the alkyl portion of one of the stereocentres by employing either an ethyl or *iso*-propyl substituent (**Scheme 1.63** and **Table 1.38**). It was envisaged that this would ultimately result in an increase in the enantioselectivity of the corresponding magnesium bisamide bases. Employing the Alexakis method, the *pseudo*-C_2-symmetric amine ((*R*,*R*)-**129**) was isolated in 41% yield, after salting of the crude product mixture of diastereoisomers (5:1 (*R*,*R*)/(*R*,*S*)) with TFA, and recrystallisation from MeOH (**Scheme 1.63** and **Table 1.38**, entry 1). We then moved on to increase the steric bulk around one of the stereocentres further by employing an *iso*-propyl substituent. Again, the commercially available chiral amine, (*R*)-phenylethylamine (**122**), was employed during the synthesis of this *pseudo*-C_2-symmetric amine using the one-pot Alexakis route (**Scheme 1.63** and **Table 1.38**, entry 2). In this instance, however, difficulties were found during isolation of the pure diastereomer. Unfortunately, ^{1}H NMR analysis of the TFA salt of the amine revealed a 1:1 mixture of diastereomers. This was most unexpected, considering that the Alexakis route typically delivers amines of this class in between 5:1 to 10:1 dr, in favour of the desired *trans*-diastereoisomer.[54,57] However, recrystallisation from methanol by slow evaporation of the solvent resulted in isolation of the desired *trans*-diastereoisomeric salt of (*R*,*R*)-**130**. Subsequent extraction of the TFA salt with $NaHCO_3$/DCM, delivered the desired secondary amine ((*R*,*R*)-**130**), albeit in a disappointing 6% yield. Nevertheless, this small amount of pure amine would allow for the synthesis of the appropriate magnesium bisamide. Isolation of the desired diastereoisomer was confirmed by single crystal X-ray crystallography of the TFA salt (**Figure 1.21**).



Scheme 1.63

Entry	R	dr of crude product ((*R*,*R*):(*R*,*S*))	Yield (%) of enriched (*R*,*R*)-amine
1	Et ((*R*,*R*)-**129**)	5:1	41
2	^{i}Pr ((*R*,*R*)-**130**)	1:1	6

Table 1.38

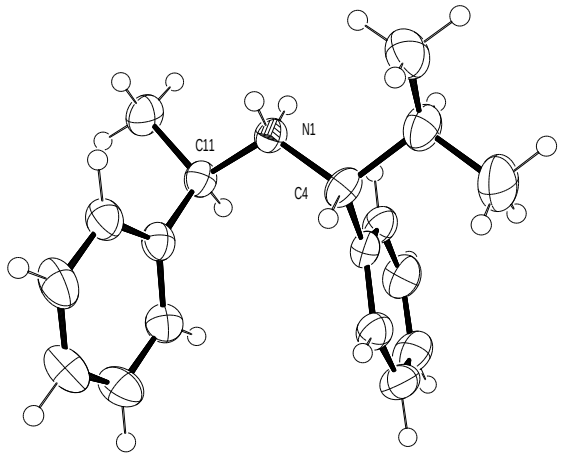
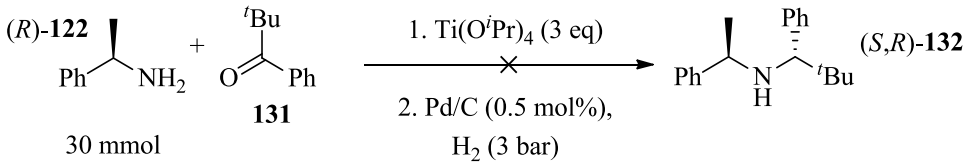


Figure 1.21

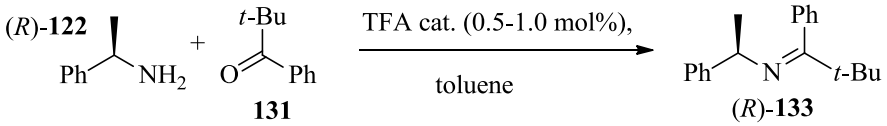
Further elaboration of the alkyl chain by preparation of the *tert*-butyl-substituted amine ((*S*,*R*)-**132**, **Scheme 1.64**) was attempted under the conditions developed by Alexakis. Unfortunately, under these conditions, no conversion of the starting materials was achieved, probably due to the large steric bulk of the *tert*-butyl group.



Scheme 1.64

In a further effort to synthesise the desired amine ((*S*,*R*)-**132**), the required amine ((*R*)-**122**) and ketone (**131**) were refluxed in toluene with a catalytic quantity of trifluoroacetic acid

using a Dean-Stark trap for water removal (**Scheme 1.65**, **Table 1.39**). Using this alternative method, the imine ((*R*)-**133**) was isolated in a moderate 49% yield (entry 1). The reaction was then repeated on a larger scale (entry 2) to obtain additional quantities of the imine.

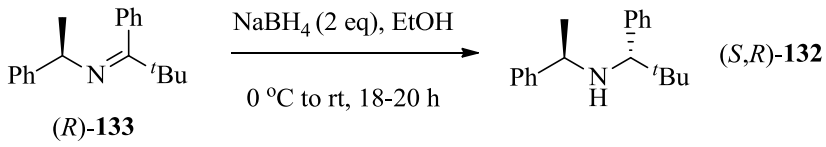


Scheme 1.65

Entry	Scale (mmol)	Yield (%)
1	20	49
2	30	49

Table 1.39

With the required imine in hand, sodium borohydride-mediated reduction was employed to deliver the desired amine ((*S*,*R*)-**132**) in good yield and, furthermore, forming the (*S*,*R*)-diastereomer exclusively (**Scheme 1.66**, **Table 1.40**). The configuration of the introduced stereocentre was elucidated by single crystal X-ray crystallography (**Figure 1.22**).



Scheme 1.66

Entry	Scale (mmol)	Yield (%)
1	4	79
2	20	56

Table 1.40

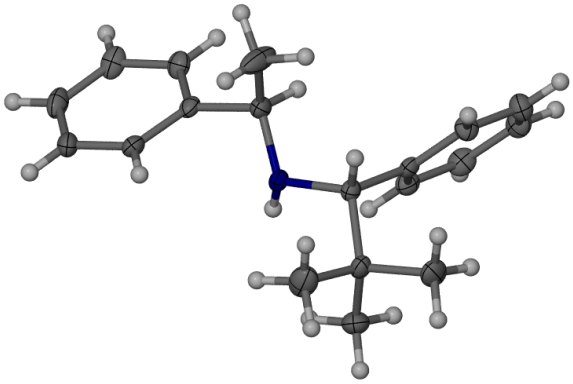
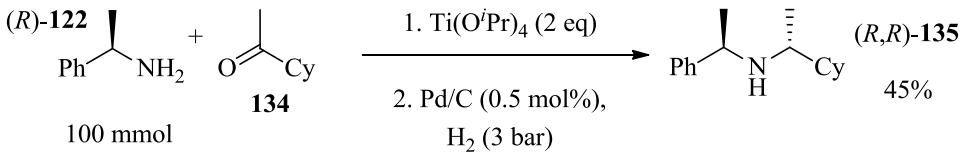


Figure 1.22

Next, we decided to change tack by introducing greater saturation in the amine structure, replacing one of the phenyl substituents with a cyclohexyl substituent. It was envisaged that the slight increase in steric bulk of the cyclohexyl group, compared to that of the phenyl group, could result in an increase in enantioselectivity of the magnesium bisamide. Furthermore, the effect of decreasing the ability of the amide to interact with the magnesium centre through the aromatic ring could be evaluated. Therefore, the appropriate *pseudo*-C_2-symmetric secondary amine ((*R*,*R*)-**135**) was synthesised by reaction of (*R*)-phenylethylamine ((*R*)-**122**) with cyclohexyl methyl ketone (**134**, **Scheme 1.67**). The crude mixture of diastereoisomers was isolated in a 2.5:1 ratio ((*R*,*R*)/(*R*,*S*)). The crude amine was therefore salted with HCl, and recrystallised from MeOH, allowing isolation of the diastereomerically pure salt of (*R*,*R*)-**135**, the configuration of which was confirmed by single crystal X-ray analysis (**Figure 1.23**). Extraction with $NaHCO_3$/DCM then revealed the desired secondary amine ((*R*,*R*)-**135**) in a moderate 45% yield.



Scheme 1.67

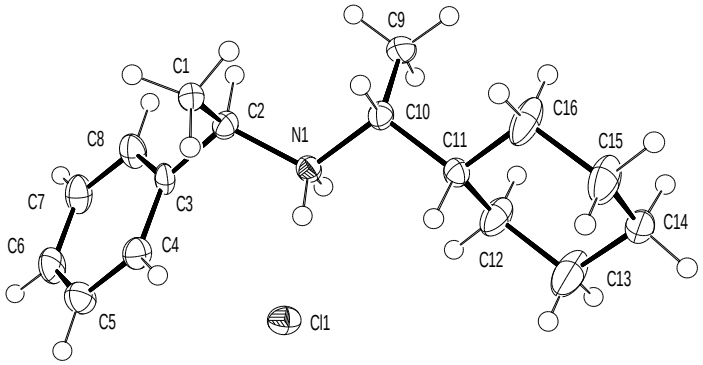
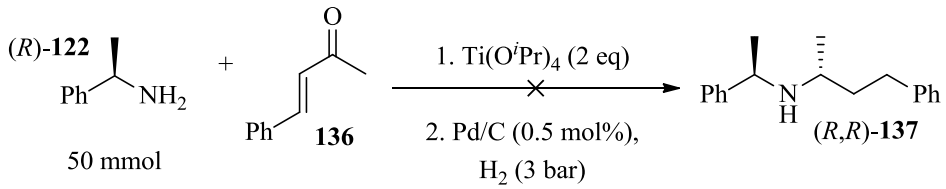


Figure 1.23

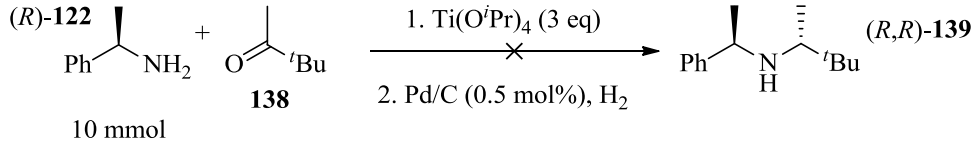
Again moving away from the dibenzyl amine core which has been employed previously, the synthesis of a *bis*-homologated version of the simple C_2-symmetric amine ((*R*,*R*)-**124**) was attempted, employing (*R*)-phenylethylamine ((*R*)-**122**) and the commercially available 4-phenyl-3-butene-2-one (**136**, **Scheme 1.68**). It was anticipated that imine formation would be followed by hydrogenation of both the imine and olefinic double bond to deliver the desired amine ((*R*,*R*)-**137**) as a mixture of diastereoisomers. Indeed, crude ^{1}H NMR analysis revealed conversion to the desired secondary amine in a 2.5:1 (*R*,*R*)/(*R*,*S*) diastereomeric ratio, but along with a number of other unidentifiable by-products. Unfortunately, purification by salt formation could not be achieved, despite repeated attempts to isolate both the TFA and HCl salts of the amine; both salts remained as viscous oils despite repeated crystallisation attempts. Also, amine (*R*,*R*)-**137** could not be isolated by column chromatography. The synthesis of the desired amine ((*R*,*R*)-**137**) was, therefore, halted.



Scheme 1.68

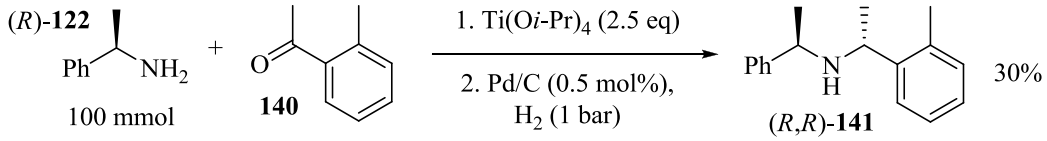
It was also of interest to synthesise a *pseudo*-C_2-symmetric amine containing a bulky *tert*-butyl substituent in place of one of the phenyl substituents ((*R*,*R*)-**139**). Unfortunately, we could not synthesise amine ((*R*,*R*)-**139**) *via* the normal Alexakis method from reaction of (*R*)-**122** with *tert*-butyl methyl ketone (**138**, **Scheme 1.69**). ^{1}H NMR analysis of the crude

reaction mixture revealed only starting materials, even after high pressure hydrogenation (3 bar) for 24 h. This was presumably due to the increased steric bulk of the *tert*-butyl substituent, either preventing imine formation or subsequent hydrogenation. Due to the difficulties encountered, the attempted synthesis of the amine ((*R*,*R*)-**139**) was halted.



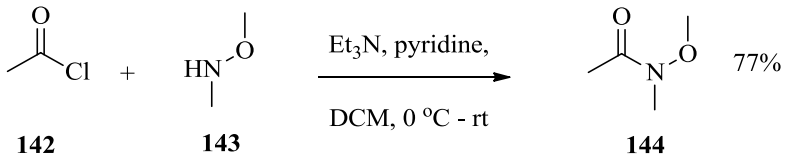
Scheme 1.69

Moving on to the preparation of a range of *pseudo*-C_2-symmetric amines with different substitution patterns on one of the aromatic rings, the synthesis of the tolyl-containing amine ((*R*,*R*)-**141**) was embarked upon. Pleasingly, when the Alexakis reductive amination method was utilised, the desired product was isolated in moderate yield after recrystallisation of the TFA salt of the crude amine, which was initially formed with a 6:1 dr ((*R*,*R*):(*R*,*S*)). Thus, ample quantities of the *pseudo*-C_2-symmetric amine ((*R*,*R*)-**141**) were available for preparation of the corresponding magnesium bisamide.



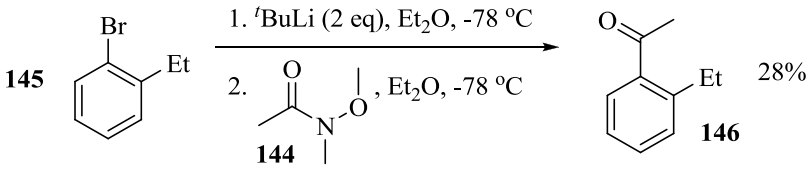
Scheme 1.70

We were also interested to ascertain if a further extension to the aromatic alkyl chain, from a methyl group to an ethyl group, would increase the enantioselectivity observed with the magnesium bisamide. Therefore, the synthesis of the appropriate ketone (**146**) from the corresponding Weinreb amide (**144**) was embarked upon. Firstly, synthesis of the Weinreb amide (**144**) was required (**Scheme 1.71**). Reaction of acetyl chloride (**142**) with *N*,*O*-dimethylhydroxylamine (**143**) resulted in isolation of the desired Weinreb amide (**144**) in a respectable 77% yield.



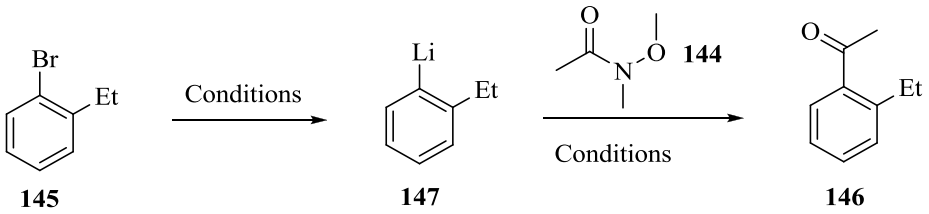
Scheme 1.71

The Weinreb amide (**144**) was then reacted with the freshly prepared lithiated species, formed by reaction of the aryl bromide (**145**) with *t*-butyllithium, to afford the desired ketone in a 28% overall yield from **145** (**Scheme 1.72**).



Scheme 1.72

In an attempt to improve on the modest yield obtained for the synthesis of **146**, the reaction was repeated using the less sterically encumbered *n*-butyllithium under a variety of conditions (**Scheme 1.73**, **Table 1.41**). Unfortunately, despite the various alterations in reaction conditions, outlined in **Table 1.41**, the highest yield obtained was 35% (entry 3). The poor yield of this reaction could perhaps be attributed to the steric bulk of the aryl ethyl substituent, either hindering the lithium-halogen exchange reaction or subsequent addition of the lithiated intermediate (**147**) into the Weinreb amide (**144**). Fortunately, the combined reactions produced a sufficient quantity of the desired ketone (**146**) for the attempted synthesis of the *pseudo*-C_2-symmetric amine (*R*,*R*)-**148**.

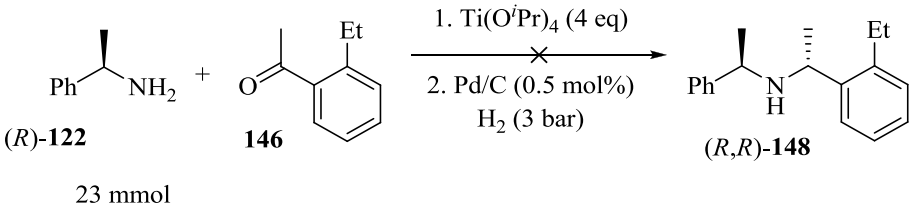


Scheme 1.73

Entry	Conditions	Yield of 146 (%)
1	Added ^{n}BuLi to **145** in Et_2O at -78 ^{o}C. Warmed to rt then cooled to -78 ^{o}C after 2 h at rt. Weinreb amide (**144**) added at -78 ^{o}C. Quenched at -78 ^{o}C.	16
2	^{n}BuLi cooled to -20 ^{o}C before addition of **145**. Warmed to 5 ^{o}C over 45 min. Cooled to -78 ^{o}C before addition of Weinreb amide (**144**). Allowed to warm to rt before quench.	24
3	As in entry 1, but (i) stirred for 18 h at rt before re-cooling to -78 ^{o}C; and (ii) allowed to warm to rt before quench.	35

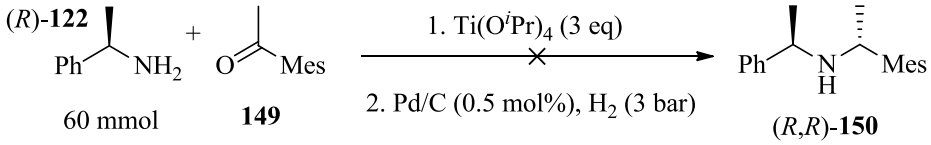
Table 1.41

Subsequently, when the Alexakis method was employed for the preparation of the *pseudo*-C_2-symmetric amine ((*R*,*R*)-**148**), analysis of the crude reaction mixture revealed a complex mixture of products (**Scheme 1.74**). Unfortunately, attempted salting of the crude product with both HCl and TFA failed to precipitate any solid salt. Therefore, after repeated attempts to isolate a salt of amine (*R*,*R*)-**148**, its synthesis was halted.



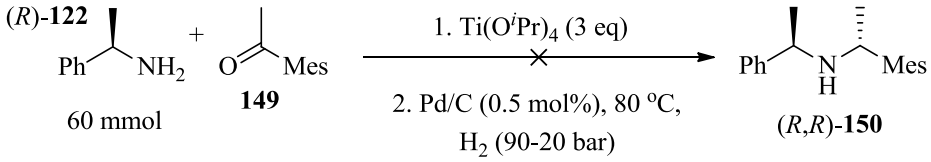
Scheme 1.74

Investigations involving the synthesis of novel bisamides then progressed to the mesityl-substituted amine ((*R*,*R*)-**150**). At first, the standard Alexakis conditions were employed in an attempt to prepare the desired amine (**Scheme 1.75**). However, no conversion of the starting material was achieved using this method.



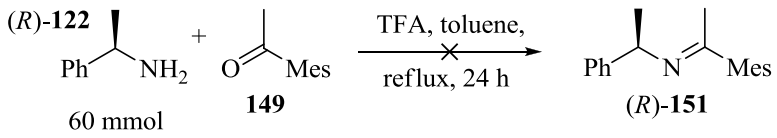
Scheme 1.75

Due to the lack of reactivity observed at room temperature and a hydrogen pressure of 3 bar, more forcing conditions were utilised in order to drive the reaction forward (**Scheme 1.76**). More specifically, the reaction temperature was increased to 80 ^{o}C and a hydrogen pressure of 90 bar was employed. Unfortunately, under these relatively severe conditions, decomposition was observed.



Scheme 1.76

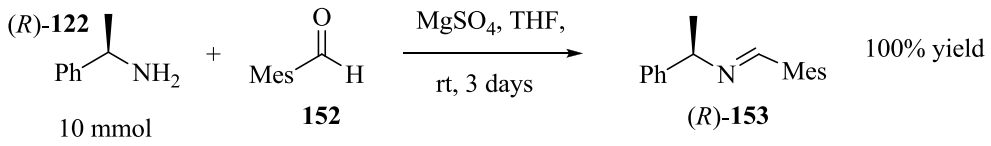
The use of an alternative procedure was then explored. Thus, (*R*)-phenylethylamine ((*R*)-**122**) and the mesityl-substituted ketone (**149**) were refluxed in toluene using a catalytic amount of trifluoroacetic acid and a Dean-Stark trap for water removal (**Scheme 1.77**). Disappointingly, no conversion of the starting materials was observed under these conditions.



Scheme 1.77

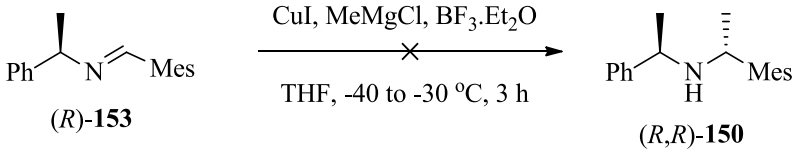
A change in strategy was then required, owing to the poor reactivity of the ketone substrate (**149**) towards imine formation, which was probably due to the steric encumbrance around the carbonyl functionality. Indeed, there is literature precedent for the difficulty in forming imines from the mesityl-substituted ketone (**149**).[57] As such, an alternative route was

devised, whereby (*R*)-phenylethylamine (**122**) was reacted with mesitaldehyde (**152**) to obtain the corresponding imine ((*R*)-**153**, **Scheme 1.78**). It was envisaged that subsequent reaction with methyllithium or a Grignard species could deliver the desired *pseudo*-C_2-symmetric amine diastereoselectively. In order to initiate this alternative route, the required imine ((*R*)-**153**) was prepared in quantitative yield and was distilled before any subsequent reactions (**Scheme 1.78**).



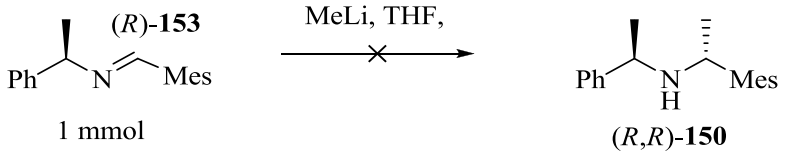
Scheme 1.78

Research by Savoia has shown that *pseudo*-C_2-symmetric amines, similar in structure to (*R*,*R*)-**150**, can be prepared in a highly diastereoselective fashion by employing the reaction of dimethylcuprate-boron trifluoride reagents with imines derived from (*R*)-phenylethylamine (**122**).[58] Encouraged by these findings, the dimethylcuprate-boron trifluoride reagent was applied to the synthesis of the amine ((*R*,*R*)-**150**) from the imine ((*R*)-**153**). Unfortunately, no conversion of the starting material was achieved using this reagent system (**Scheme 1.79**).



Scheme 1.79

Given the lack of conversion which was observed using the cuprate reagent, the use of methyllithium was probed as an alternative (**Scheme 1.80**, **Table 1.42**). When methyllithium was employed, no conversion of the starting material was achieved after a reaction time of one hour at -78 °C (entry 1). Accordingly, the reaction was performed over three hours, starting at a temperature of -70 °C and slowly warming to -30 °C, in an attempt to increase the reactivity (entry 2). Unfortunately, no improvement was gained under these reaction conditions.

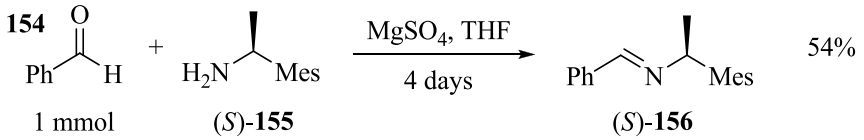


Scheme 1.80

Entry	Time (h)	Temperature (^{o}C)
1	1	-78
2	3	-70 to -30

Table 1.42

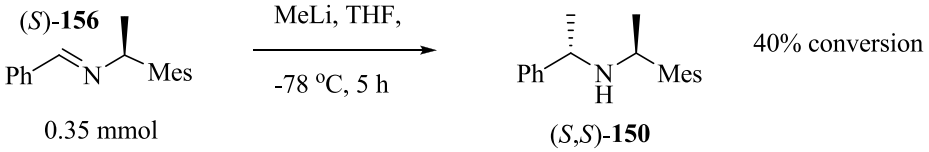
The poor reactivity of the imine ((*R*)-**153**) towards addition of the dimethylcuprate or methyllithium was proposed to be attributable to the steric encumbrance imparted by the nearby mesityl substituent. Consequently, it was envisaged that using the mesityl-substituted amine ((*S*)-**155**, **Scheme 1.81**) alongside benzaldehyde (**154**) would deliver a more reactive imine ((*S*)-**156**), allowing the organometallic reagent to attack into a less-hindered electrophilic group. Although the required amine ((*S*)-**155**) is not commercially available, a small quantity was kindly donated by BASF, allowing for the preparation of the desired imine ((*S*)-**156**) in moderate yield.



Scheme 1.81

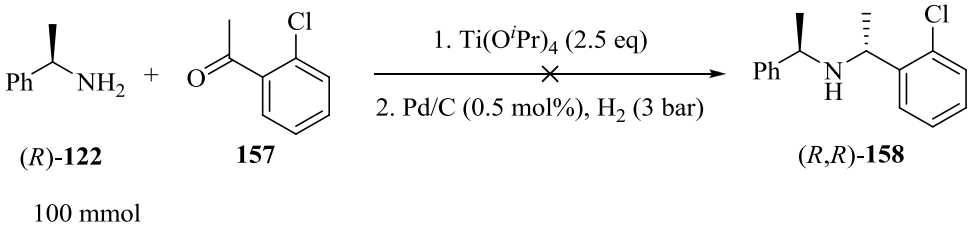
With the required imine ((*S*)-**156**) available, reaction with methyllithium was attempted (**Scheme 1.82**). Under these conditions, 40% conversion (^{1}H NMR) of the less sterically-hindered imine ((*S*)-**156**) to the desired product ((*S,S*)-**150**) was observed. However, analysis by ^{1}H NMR spectroscopy indicated that a complex mixture had been formed, from which none of the pure amine ((*S,S*)-**150**) could be isolated by column chromatography. At this

stage, the preparation of the mesityl-substituted amine ((*S*,*S*)-**150**) on a larger scale, in order to allow the use of the corresponding magnesium bisamide, remains to be realised.



Scheme 1.82

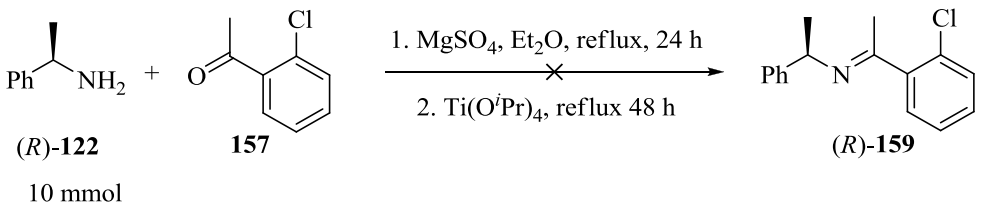
In addition to the preparation of a range of magnesium amides with differing steric properties, we also aimed to investigate the effects of altering the electronic nature of the amide species. To this end, the synthesis of *pseudo*-C_2-symmetric amines containing a chloro substituent on the aromatic ring was initiated. It was anticipated that the introduction of chloro groups could generate a more rigid solution aggregate, by coordination with the magnesium centre, leading to enhanced selectivities. First, the synthesis of an *ortho*-chloro substituted amine ((*R*,*R*)-**158**) was attempted by reaction of (*R*)-phenylethylamine (**122**) and 2-chloroacetophenone (**157**) under the conditions developed by Alexakis (**Scheme 1.83**). Unfortunately, the desired *pseudo*-C_2-symmetric amine ((*R*,*R*)-**158**) could not be isolated. Instead, ^{1}H NMR analysis of the crude reaction mixture revealed a complex mixture of products, which included substantial quantities of both the amine and ketone starting materials.



Scheme 1.83

An alternative approach, involving isolation of the corresponding imine prior to hydrogenation, was then utilised. More specifically, the primary amine ((*R*)-**122**) and the ketone (**157**) were refluxed in ether in the presence of $MgSO_4$ over 24 h (**Scheme 1.84**). Unfortunately, TLC analysis after this time revealed that no conversion to the desired product

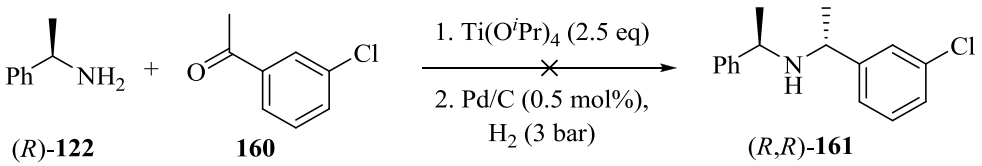
had occurred. Furthermore, no conversion could be achieved by the addition of $Ti(O^iPr)_4$ and refluxing for a further 48 h. The attempted preparation of the *ortho*-substituted amine ((*R*,*R*)-**158**) was, therefore, halted and attention was turned to the synthesis of the less sterically encumbered *meta*-substituted amine ((*R*,*R*)-**161**).



(*R*)-**122** 10 mmol — **157** — (*R*)-**159**

Scheme 1.84

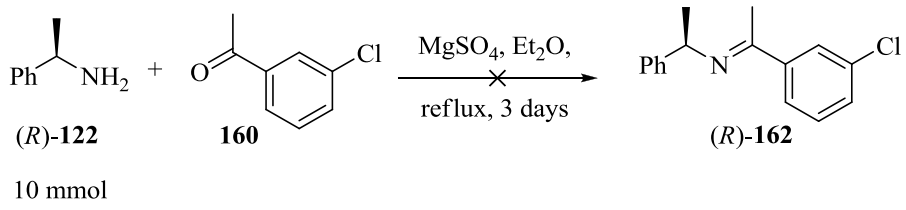
The Alexakis method was, again, employed in the attempted preparation of the *meta*-chloro-substituted *pseudo*-C_2-symmetric amine ((*R*,*R*)-**161**, **Scheme 1.85**). Unfortunately, similar to the attempted preparation of the analogous amine ((*R*,*R*)-**158**), the desired secondary amine ((*R*,*R*)-**161**) could not be isolated when these conditions were employed. Interestingly, the ^1H NMR of the crude product was relatively clean and the spectra suggested a symmetrical structure, with just one quartet (corresponding to two benzylic protons) and one doublet (corresponding to the protons of two methyl groups). This seemed to infer that the Cl group had been cleaved during the reaction to leave the C_2-symmetric amine ((*R*,*R*)-**124**), presumably during the Pd/C hydrogenation stage of the reaction.



(*R*)-**122** 34 mmol — **160** — (*R*,*R*)-**161**

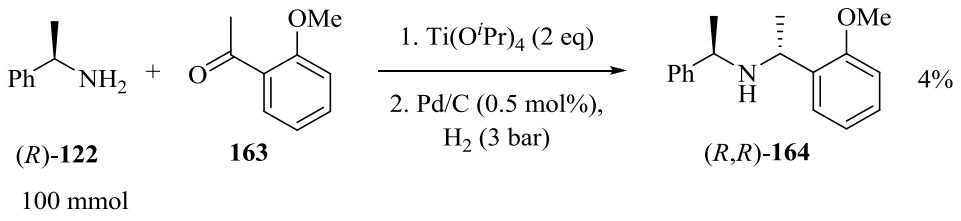
Scheme 1.85

Subsequently, isolation of the intermediate imine was attempted ((*R*)-**162**, **Scheme 1.86**). Unfortunately, however, TLC and ^1H NMR analysis after 2 days at reflux revealed that no imine formation had taken place. It was therefore decided to halt the attempted synthesis of ((*R*,*R*)-**161**) at this stage.



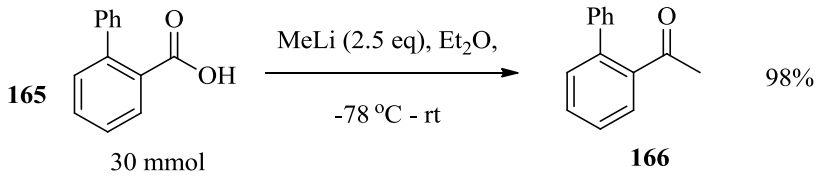
Scheme 1.86

In a further attempt to prepare a *pseudo*-C_2-symmetric amine containing an electronically influencing substituent, the synthesis of the *ortho*-methoxy-substituted amine was initiated ((*R*,*R*)-**164**, **Scheme 1.87**). Commercially available 2-methoxyacetophenone (**163**) was reacted with (*R*)-phenylethylamine ((*R*)-**122**) *via* the Alexakis method to deliver the crude amine ((*R*,*R*)-**164**) as a 6:1 ((*R*,*R*)/(*R*,*S*)) mixture of diastereoisomers. Subsequent salting with HCl and recrystallistion from MeOH afforded a small amount of the desired pure *trans*-diastereomeric salt of (*R*,*R*)-**164**. Extraction with $NaHCO_3$/DCM was then employed to afford (*R*,*R*)-**164** in a poor 4% yield, giving sufficient quantities of the desired amine for use in asymmetric deprotonation reactions.



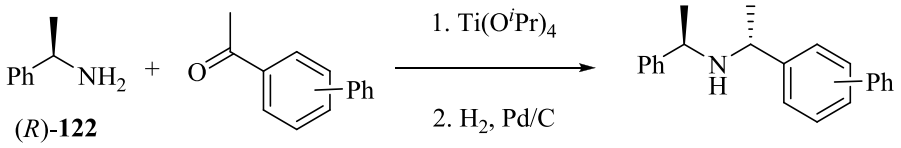
Scheme 1.87

The preparation of a range of biphenyl-substituted *pseudo*-C_2-symmetric amines was then embarked upon. To allow the preparation of the *ortho*-phenyl-substituted amine ((*R*,*R*)-**167**), the starting ketone (**166**) needed to be synthesised (**Scheme 1.88**). Addition of 2.5 equivalents of MeLi to the commercially available 2-phenylbenzoic acid (**165**) resulted in isolation of the desired ketone (**166**) in an excellent 98% yield.



Scheme 1.88

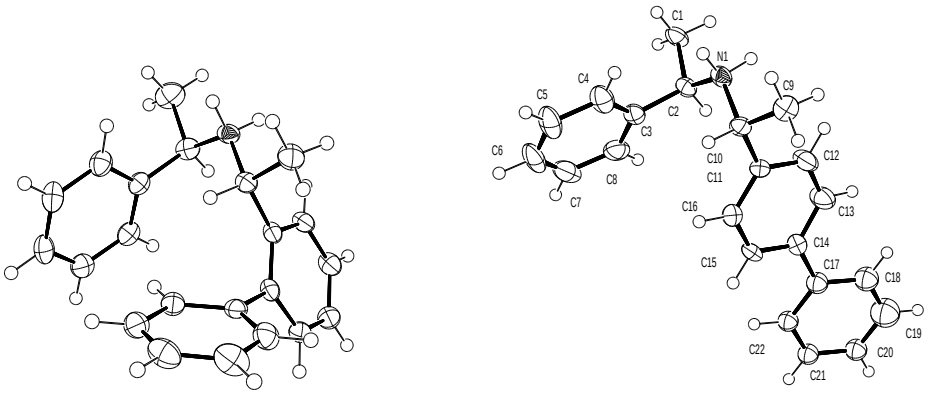
The preparation of both the *ortho*- and *para*-phenyl-substituted *pseudo*-C_2-symmetric amines was then carried out according to the Alexakis method (**Scheme 1.89**, **Table 1.43**). The crude amines were salted from HCl and recrystallised from MeOH to deliver their pure HCl salts. Subsequent extraction from $NaHCO_3$/DCM revealed the desired biphenyl-substituted amines. Formation of the desired (*R*,*R*)-diastereomers of **167** and **168** was confirmed by X-ray crystallography of the respective HCl salts (**Figure 1.24**).



Scheme 1.89

Entry	Substituent position	Amine	Scale (mmol)	dr of crude product ((*R*,*R*):(*R*,*S*))	Yield (%)
1	*ortho*	(*R*,*R*)-**167**	40	20.5:1	45
2	*para*	(*R*,*R*)-**168**	100	8:1	11

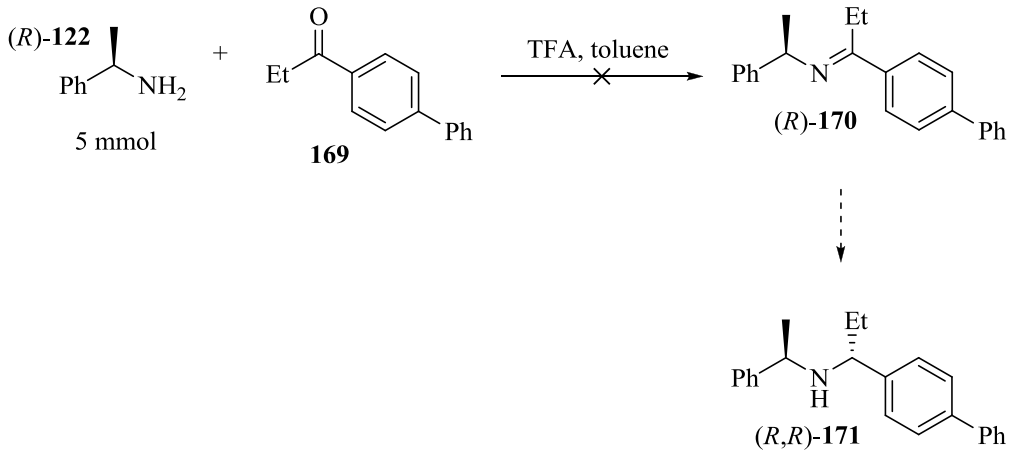
Table 1.43



(*R*,*R*)-**167**.HCl (*R*,*R*)-**168**.HCl

Figure 1.24

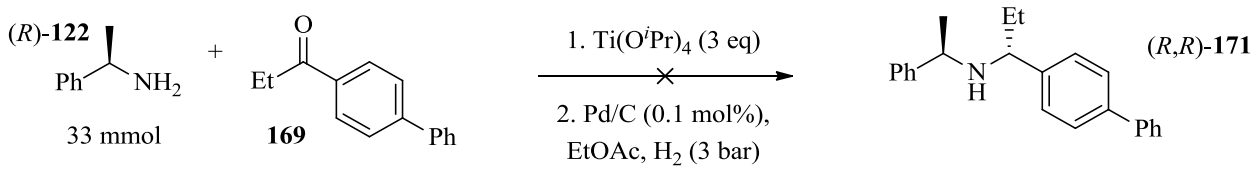
Attention was then turned to the synthesis of the analogous ethyl-substituted amine *via* the corresponding imine ((*R*)-**170**, **Scheme 1.90**). Taking the required amine ((*R*)-**122**) and ketone (**169**) precursors and refluxing in toluene with catalytic trifluoroacetic acid under Dean-Stark conditions yielded none of the desired imine ((*R*)-**170**). In fact, analysis of the reaction mixture after 16 h reflux showed that a significant amount of the starting materials was present, in addition to several unwanted by-products.



Scheme 1.90

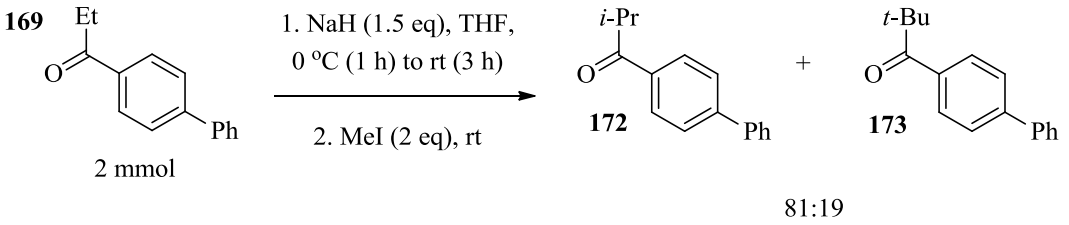
The synthesis of the amine ((*R*,*R*)-**171**) using Alexakis conditions was then investigated (**Scheme 1.91**). Pleasingly, these conditions allowed access to the desired amine in a good

51% crude yield. In order to separate the mixture of diastereomers by fractional recrystallisation, preparation of the appropriate crystalline salt was required. Disappointingly, numerous attempts to crystallise either the hydrochloric or trifluoroacetic acid salt, which formed as a gum, using a variety of solvent conditions proved unsuccessful. In addition, it was not possible to separate the diastereomers by column chromatography. As a result, the use of this amine as its magnesium bisamide was not pursued.



Scheme 1.91

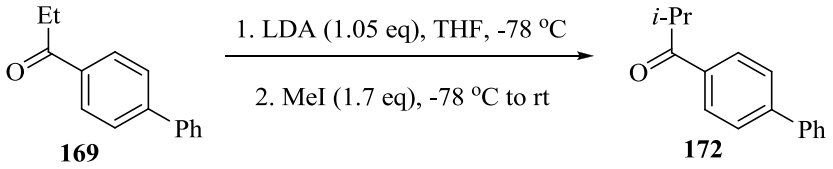
Subsequently, preparation of the analogous *iso*-propyl-substituted amine was commenced. Because the required ketone (**172**, **Scheme 1.92**) is not commercially available, its synthesis was required. Accordingly, deprotonation of the corresponding ethyl-substituted ketone (**169**) using sodium hydride, followed by quenching of the resultant enolate with methyl iodide, was carried out. Employing these conditions, a mixture of the desired ketone (**172**) and the *tert*-butyl-substituted analogue (**173**) was produced. The composition of the mixture was determined as 81:19 (**172**:**173**) using ^{1}H NMR analysis.



Scheme 1.92

It was suspected that the impurity (**173**) was formed as a result of the excess sodium hydride reacting with the *iso*-propyl-substituted ketone (**172**) to generate an enolate which was quenched by methyl iodide. Hence, the use of an alternative base, the excess of which could be quenched by methyl iodide, was investigated. Accordingly, a slight excess of LDA was used to convert the ketone (**169**) to the corresponding enolate, which was then quenched with

methyl iodide (**Scheme 1.93**, **Table 1.44**). By using this alternative method, the desired ketone (**172**) was formed exclusively and in quantitative yield.

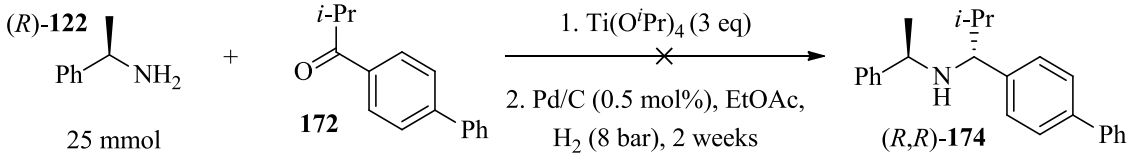


Scheme 1.93

Entry	Scale (mmol)	Yield (%)
1	2.4	100
2	24	100

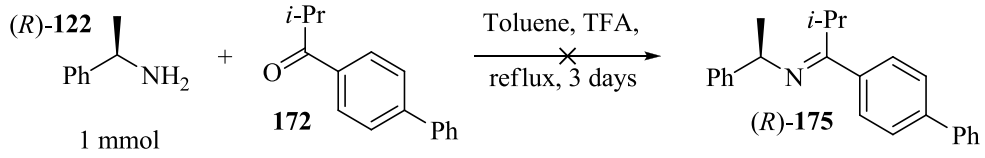
Table 1.44

Having prepared the required ketone (**172**), synthesis of the desired amine ((*R*,*R*)-**174**) was initiated by employing the conditions developed by Alexakis (**Scheme 1.94**). Unfortunately, under these conditions, no conversion of the starting material was achieved.



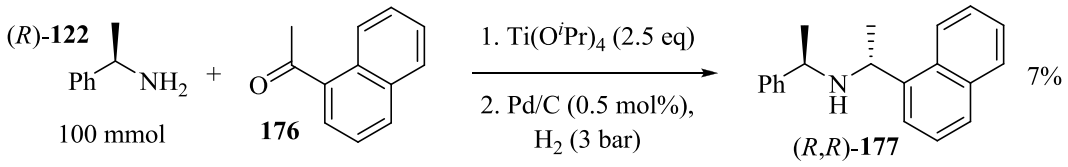
Scheme 1.94

Subsequently, an alternative method involving isolation of the corresponding imine ((*R*)-**175**, **Scheme 1.95**) *via* acid-catalysed condensation under Dean-Stark conditions, followed by diastereoselective reduction, was investigated. Disappointingly, synthesis of the imine using these fairly forceful conditions was unsuccessful. Consequently, due to the difficulties encountered, the synthesis of the *iso*-propyl-substituted amine ((*R*,*R*)-**174**) was not taken any further.



Scheme 1.95

Investigations then progressed to the preparation of a range of naphthyl-substituted *pseudo*-C_2-symmetric amines. At first, it was noted that 1-acetylnaphthalene (**176**) was commercially available, allowing the synthesis of the *pseudo*-C_2-symmetric amine ((*R*,*R*)-**177**) by reaction with (*R*)-phenylethylamine (**122**) to be attempted using the conditions developed by Alexakis (**Scheme 1.96**). The synthesis of ((*R*,*R*)-**177**) proved to be straightforward, furnishing the crude amine with high diastereoselectivity (>20:1 (*R*,*R*)/(*R*,*S*)). Salt formation using TFA, recrystallisation from MeOH, and extraction from $NaHCO_3$/DCM delivered (*R*,*R*)-**177** in 7% yield. Formation of the desired (*R*,*R*)-diastereoisomer was confirmed by single crystal X-ray crystallography (**Figure 1.25**).



Scheme 1.96

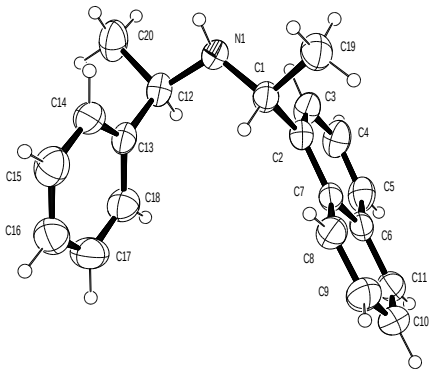
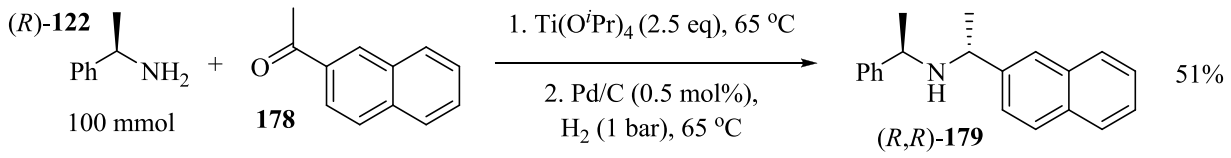


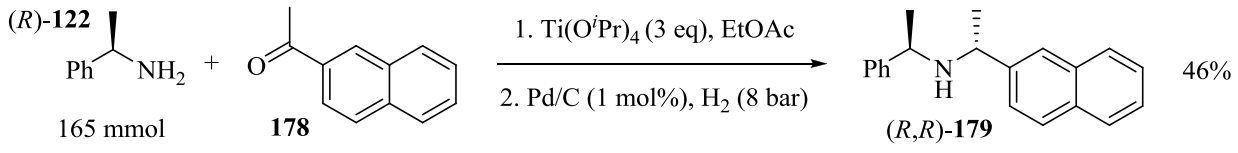
Figure 1.25

Extending the range of naphthyl-substituted amines available, the synthesis of the *pseudo*-C_2-symmetric amine (*R*,*R*)-**179**, from the reaction of commercially available 2-acetylnaphthalene (**178**) and (*R*)-phenylethylamine (**122**), was carried out (**Scheme 1.97**). The synthesis of (*R*,*R*)-**179** was initially complicated by the fact that 2-acetylnaphthalene is a solid at room temperature. This resulted in very little starting material dissolving and ultimately reacting in the $Ti(O^iPr)_4$ solvent. In order to increase the solubility of the reactants in the $Ti(O^iPr)_4$, the reaction mixture was heated at 65 ^oC throughout the course of the reaction. Pleasingly, under these conditions, the desired product was formed, displaying excellent selectivity for the desired (*R*,*R*)-diastereoisomer (12.5:1 (*R*,*R*)/(*R*,*S*)). The amine was then salted from a mixture of HCl, MeOH, and EtOAc. The salt was subsequently treated with $NaHCO_3$/DCM to reveal the pure secondary amine ((*R*,*R*)-**179**) in a good 51% yield.



Scheme 1.97

On further syntheses of this amine ((*R*,*R*)-**179**), it was demonstrated that EtOAc could be employed as a co-solvent, in order to solubilise the starting ketone, obviating the need for heating of the reaction mixture (**Scheme 1.98**). Furthermore, this method delivered a superior diastereoselectivity, with only the desired (*R*,*R*)-diastereomer being detected by ^1H NMR analysis. Isolation of the desired (*R*,*R*)-diastereoisomer was confirmed by single crystal X-ray crystallography of the HCl salt (**Figure 1.26**).



Scheme 1.98

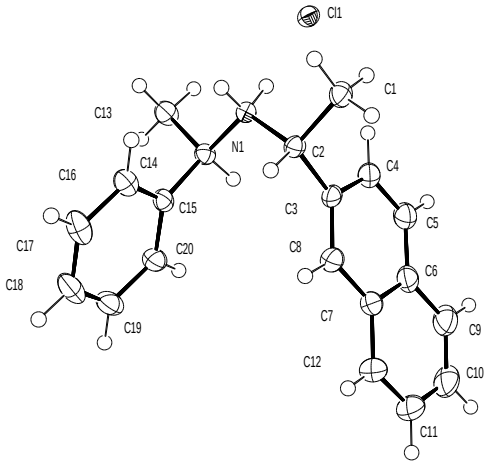
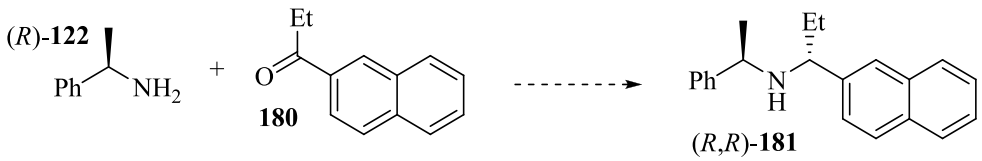


Figure 1.26

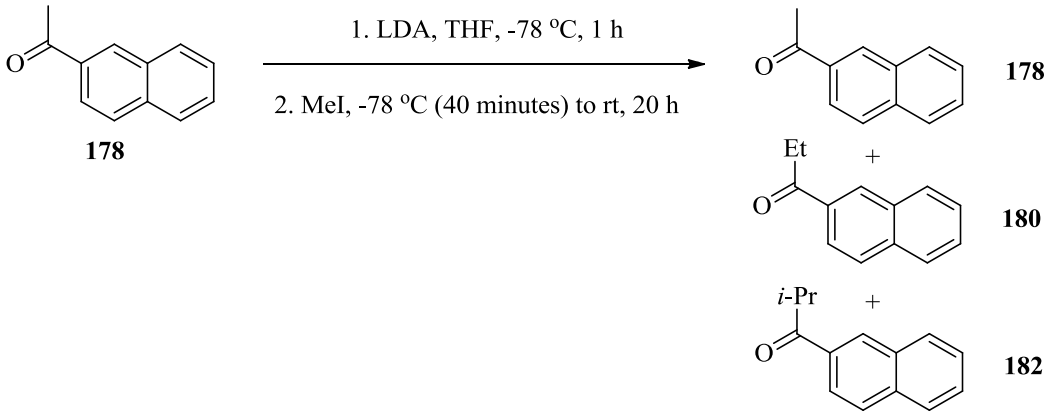
Attention was then focused on the preparation of a further extension to this amine class, the ethyl-substituted amine ((*R*,*R*)-**181**). It was envisaged that this amine could be synthesised diastereoselectively by reductive amination of the requisite amine ((*R*)-**122**) and ketone (**180**, **Scheme 1.99**). Additionally, because the ketone (**180**) is not commercially available, its synthesis was required.



Scheme 1.99

In view of the success achieved in the synthesis of the *iso*-propyl-substituted ketone (**172**) by deprotonation of the corresponding ethyl-substituted ketone (**169**) and subsequent alkylation, a similar strategy was employed for preparation of **180** (**Scheme 1.100**, **Table 1.45**). The initial attempt in this strategy involved addition of the ketone (**178**) in THF to a solution of LDA in THF, generating the corresponding enolate species, which was then quenched by addition of methyl iodide to the reaction mixture. Unfortunately, under these conditions, a mixture of the starting material (**178**), the desired product (**180**), and the *iso*-propyl-substituted ketone (**182**) resulted (**Table 1.45**, entry 1). It was proposed that the starting material (**178**) could persist in the reaction mixture as a result of protonation of the

corresponding enolate species, or due to incomplete conversion. In addition, it was envisaged that formation of the *iso*-propyl-substituted ketone (**182**) could occur through deprotonation and alkylation of the desired product (**180**). In order to circumvent the formation of such a mixture, the order of addition was reversed (entry 2). More specifically, the enolate species in THF was added to a solution of methyl iodide in order to immediately quench the enolate and any remaining LDA. However, no real improvement was gained over the previous method. In a final attempt to prepare the desired ketone by this route, the number of equivalents of LDA was increased, in order to ensure complete conversion of the starting material, while also increasing the number of equivalents of methyl iodide, to ensure rapid quenching of the enolate species and excess LDA (entry 3). Although a significant increase in the selectivity for the desired ketone (**180**) was gained by employing these modified conditions, a more efficient method was sought.



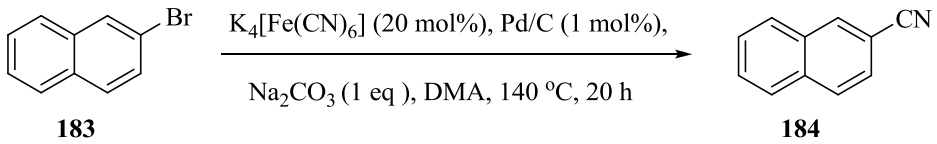
Scheme 1.100

Entry	Scale (mmol)	Eq of LDA	Eq of MeI	Order of addition	Ratio 178:180:182
1	29	1.05	1.7	MeI to enolate	31:45:24
2	2.9	1.05	1.7	Enolate to MeI	30:48:22
3	2.9	1.2	6.0	Enolate to MeI	15:73:12

Table 1.45

It was anticipated that Pd-catalysed cyanation chemistry[59] could be employed to yield the 2-cyanonaphthalene compound (**184**, **Scheme 1.101**), which could then be treated with an ethyl

Grignard reagent and then hydrolysed to the required ketone (**180**). Accordingly, cyanation of 2-bromonaphthalene (**183**) was performed using catalytic palladium on charcoal, employing potassium hexacyanoferrate as the cyanide source. Pleasingly, this method[59b,c] allowed access to significant quantities of the nitrile compound (**184**) in good yield (**Scheme 1.101**, **Table 1.46**).



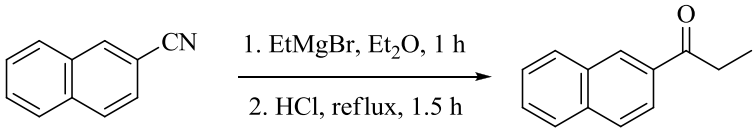
183 **184**

Scheme 1.101

Entry	Scale (mmol)	Yield (%)
1	3	67
2	90	77

Table 1.46

With the required nitrile intermediate (**184**) in hand, the ketone (**180**) was delivered in excellent yield *via* Grignard addition using ethylmagnesium bromide followed by refluxing in aqueous hydrochloric acid (**Scheme 1.102**, **Table 1.47**). Thus, ample quantities of the ethyl ketone (**180**) were isolated to allow the synthesis of the desired amine ((*R*,*R*)-**181**) to be attempted.



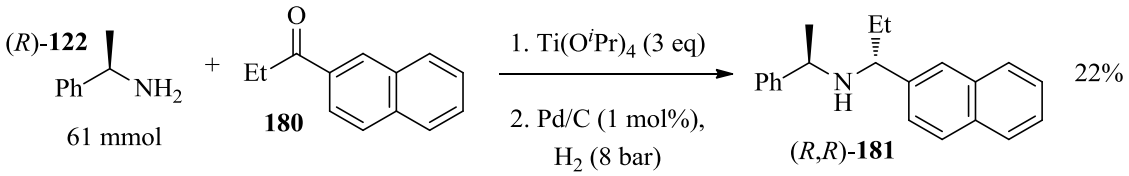
184 **180**

Scheme 1.102

Entry	Scale (mmol)	Yield (%)
1	1	80
2	68	90

Table 1.47

Pleasingly, employing the Alexakis conditions allowed access to the *pseudo*-C_2-symmetric amine ((*R*,*R*)-**181**, **Scheme 1.103**). The desired diastereomer was then isolated after salting with hydrochloric acid to give a solid material which was recrystallised several times. The (*R*,*R*)-configuration was confirmed by X-ray crystallography of the hydrochloride salt (**Figure 1.27**). Although a poor yield of 22% was achieved, sufficient quantities of the amine were obtained in order to allow preparation of the corresponding magnesium bisamide.



Scheme 1.103

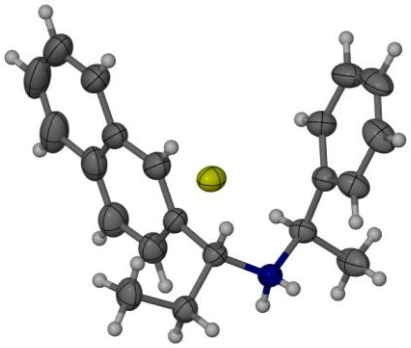
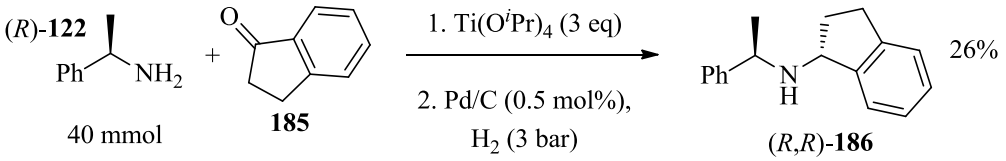


Figure 1.27

Synthesis of alternative *pseudo*-C_2-symmetric amines, having one of the substituents of a stereogenic centre tethered to the adjacent aromatic ring, was then embarked upon. First of all, the preparation of the amine ((*R*,*R*)-**186**) derived from (*R*)-phenylethylamine (**122**) and indanone (**185**) was attempted (**Scheme 1.104**). By employing the conditions developed by

Alexakis, the desired amine was obtained with high diastereoselectivity (88:12, (*R*,*R*):(*R*,*S*)). The (*R*,*R*)-isomer was isolated after forming the hydrochloride salt and recrystallising from isopropanol. The free amine was then generated by treatment of the hydrochloride salt with dilute aqueous sodium hydroxide and extracting with ethyl acetate to give the pure product in 26% yield.



Scheme 1.104

The (*R*,*R*) configuration was confirmed using X-ray crystallography of the HCl salt (**Figure 1.28**) and comparison of the measured specific rotation of the free amine to that reported in the literature.[60] Although it should be noted that, in this instance, the quality of the crystals used for X-ray analysis was fairly poor, the data obtained is reliable enough to allow elucidation of the absolute stereochemistry of the molecule.

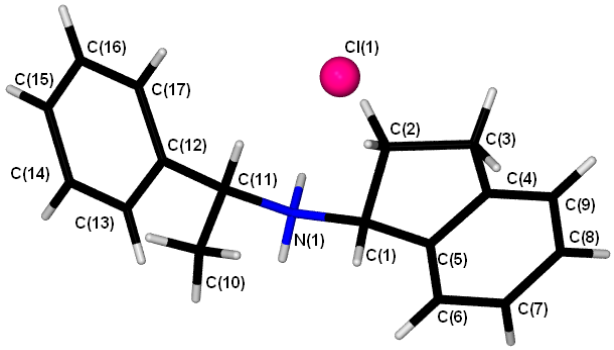
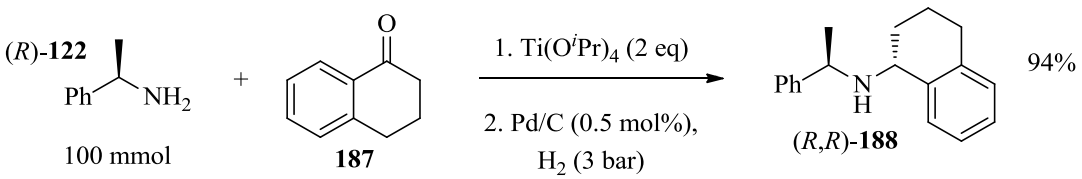


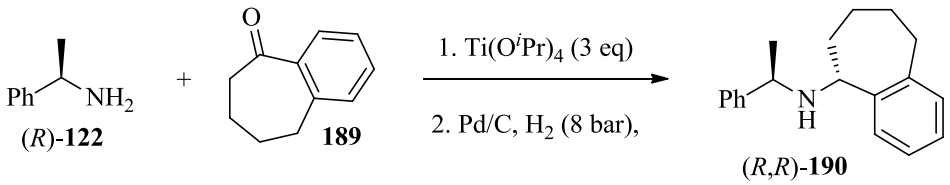
Figure 1.28

The preparation of the related amine in this series, having one chiral centre tethered in a 6-membered ring ((*R*,*R*)-**188**), was initiated using the Alexakis reductive amination method (**Scheme 1.105**). Pleasingly, under these conditions the desired (*R*,*R*)-diastereomer was formed exclusively, and the product was isolated in an excellent 94% yield.



Scheme 1.105

Attention was then turned to the synthesis of the analogous *pseudo*-C_2-symmetric amine, containing a seven-membered ring ((*R*,*R*)-**190**, **Scheme 1.106**). Employment of the Alexakis conditions allowed access to the desired amine with high diastereoselectivity (78:22, (*R*,*R*):(*R*,*S*)) (**Table 1.48**, entry 1). Preparation of the appropriate crystalline salt was then attempted, in order to separate the mixture of diastereomers by fractional recrystallisation. Unfortunately, several attempts to crystallise either the hydrochloric or trifluoroacetic acid salts, using a variety of solvent conditions, proved difficult. However, small quantities of crystalline salt were isolated by triturating the hydrochloride salt, which formed as a gum, in acetone. In order to obtain sufficient quantities of the salt to allow recrystallisation and isolation of the required amine, the synthesis was repeated on a larger scale (entry 2). Although the diastereomerically pure amine ((*R*,*R*)-**190**) was isolated in a poor 7% yield after trituration and recrystallisation of the hydrochloride salt using acetone, sufficient quantities were available for the preparation of the analogous magnesium bisamide.



Scheme 1.106

Entry	Scale (mmol)	Yield (%)
1	30	-
2	60	7

Table 1.48

In summary, the synthesis of a selection of *pseudo*-C_2-symmetric amines was undertaken, in order to allow the preparation of novel magnesium bisamides for use in asymmetric deprotonation processes. The amines which were successfully prepared are illustrated below (**Figure 1.29**). With these amines in hand, the efficacy of their corresponding magnesium bisamides was then explored.

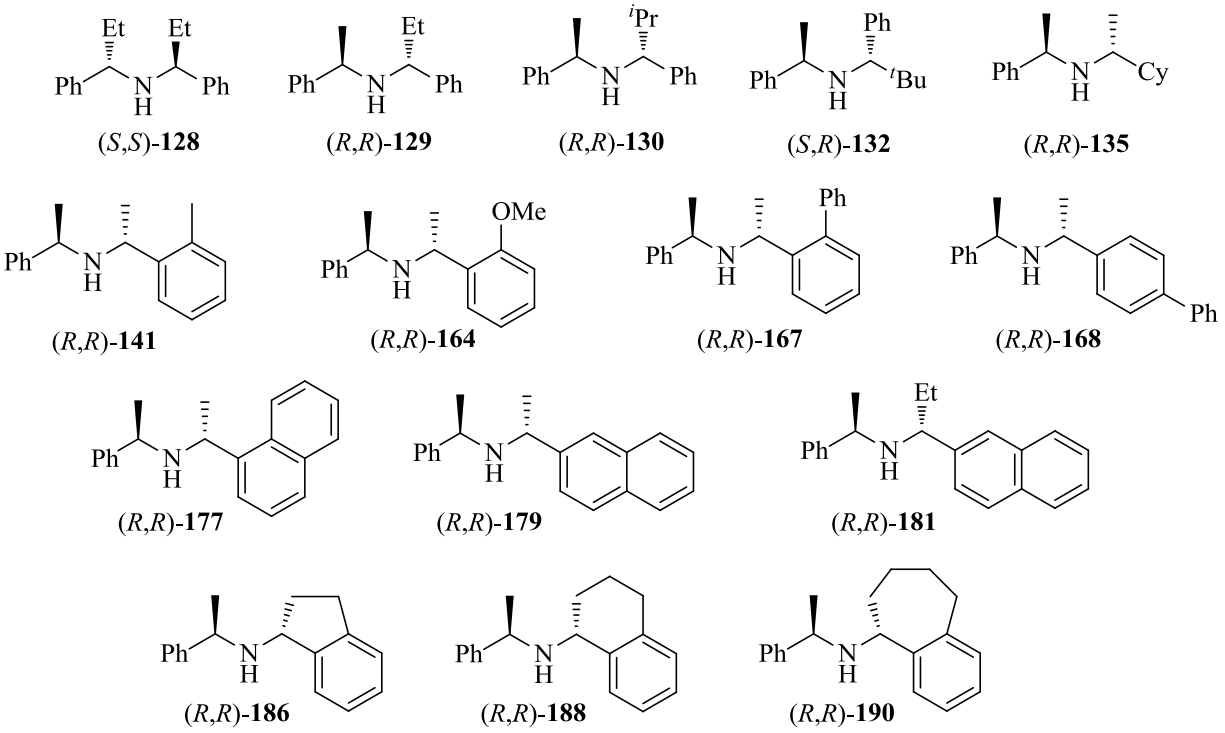
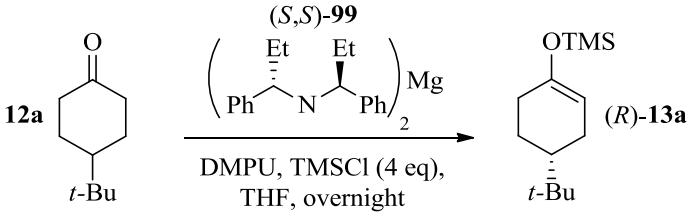


Figure 1.29

3.3.2 Application of novel C_2- and *pseudo*-C_2-symmetric bisamides to asymmetric deprotonations

Having prepared a wide range of C_2- and *pseudo*-C_2-symmetric amines, the application of the corresponding magnesium bisamides to the asymmetric deprotonation of prochiral ketones was investigated. To begin with, the C_2-symmetric bisamide ((*S*,*S*)-**99**), having slightly bulkier ethyl substituents in the benzylic position, relative to the simple bisamide ((*R*,*R*)-**98**), was employed in the benchmark deprotonation of 4-*tert*-butylcyclohexanone. Initial studies involved the optimisation of the quantity of DMPU employed in the reaction at both -78 °C and room temperature (**Scheme 1.107**, **Table 1.49**). Overall, this novel magnesium bisamide ((*S*,*S*)-**99**) achieved encouraging results at both temperatures. However, these results are slightly disappointing when compared to the original C_2-symmetric magnesium bisamide ((*R*,*R*)-**98**). At -78 °C, the highest conversion recorded was 88% (**Table 1.49**, entry 2), while the enantioselectivity remained constant (88:12 er), irrespective of the quantity of DMPU (**Table 1.49**, entries 1-4). At the outset, it had been hoped that the increase in steric bulk surrounding the magnesium bisamide would push selectivities beyond the 94:6 er recorded for the simpler bisamide ((*R*,*R*)-**98**) at -78 °C. On moving to room temperature, the observed selectivities were consistently around 25:75 er, in line with the results observed using (*R*,*R*)-**98** at room temperature. Pleasingly, conversions reached a high of 98% employing 2.5 eq. of DMPU additive at room temperature (**Table 1.49**, entry 8).

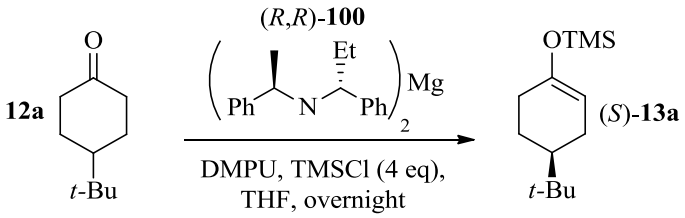


Scheme 1.107

Entry	Temperature (^{o}C)	DMPU (eq)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	0	77	60	12:88
2	-78	0.5	88	71	12:88
3	-78	1	81	56	12:88
4	-78	2.5	84	68	12:88
5	25	0	83	76	28:72
6	25	0.5	86	80	26:74
7	25	1	94	87	24:76
8	25	2.5	98	82	25:75

Table 1.49

Having discovered that the more sterically encumbered base ((*S*,*S*)-**99**) did not give any gain in enantioselectivity, relative to the simple C_2-symmetric bisamide (*R*,*R*)-**98**, the *pseudo*-C_2-symmetric bisamide ((*R*,*R*)-**100**), possessing intermediate steric properties, was assessed in the asymmetric deprotonation of the benchmark ketone (**12a**, **Scheme 1.108**, **Table 1.50**). To our delight, employment of this *pseudo*-C_2-symmetric magnesium bisamide ((*R*,*R*)-**100**) resulted in increased enantioselectivities to a new high for this study, reaching a superb 95:5 er (**Table 1.50**, entries 2 and 4). Indeed, selectivities remained very high at -78 ^{o}C across all additive quantities of DMPU. Further, an encouragingly high selectivity of 76:24 er was achieved at room temperature (**Table 1.50**, entries 6 and 7).

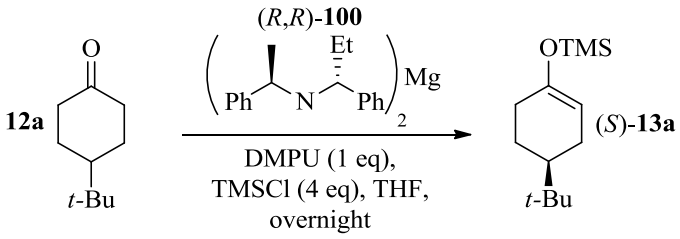


Scheme 1.108

Entry	Temperature (^{o}C)	DMPU (eq)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	0	60	41	94:6
2	-78	0.5	67	48	95:5
3	-78	1	88	71	94:6
4	-78	2.5	84	59	95:5
5	25	0	66	51	71:29
6	25	0.5	87	58	76:24
7	25	1	94	67	76:24
8	25	2.5	73	58	75:25

Table 1.50

With these excellent initial results employing (*R*,*R*)-**100** in hand, a temperature study was initiated to allow comparison with (*R*,*R*)-**98** (**Scheme 1.109**, **Table 1.51**). Pleasingly, it was found that excellent selectivities could be retained at elevated temperatures, including a superb 90:10 er at as high a temperature as -40 ^{o}C (**Table 1.51**, **entry 3**). These results were in line with those obtained using the C_2-symmetric bisamide ((*R*,*R*)-**98**) and, once more, proved the stability and potential for the use of magnesium bisamide bases at elevated temperatures.

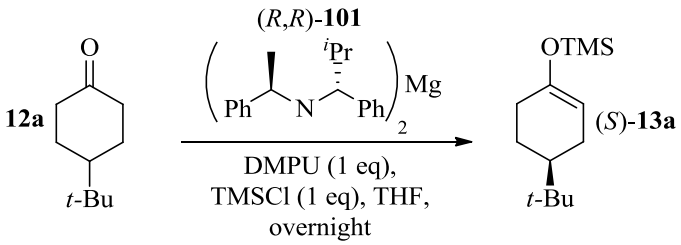


Scheme 1.109

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	88	71	94:6
2	-60	92	66	90:10
3	-40	94	67	90:10
4	-20	89	56	87:13
5	0	93	59	87:13
6	25	94	67	76:24

Table 1.51

Having achieved greater enantioselectivity by employing a bulkier substituent in the benzylic position of ((*R*,*R*)-**100**), we probed the effect of increasing the steric bulk in this position further. More specifically, the *iso*-propyl-substituted bisamide ((*R*,*R*)-**101**) was utilised in the asymmetric deprotonation of 4-*tert*-butylcyclohexanone, employing the now optimised conditions of one equivalent of DMPU and one equivalent of TMSCl (**Scheme 1.110**, **Table 1.52**). Unfortunately, the expected increase in selectivity employing magnesium bisamide (*R*,*R*)-**101** did not result. A moderate 87:13 er was achieved at -78 ^{o}C (**Table 1.52**, entry 1), and this was accompanied by a very poor conversion of just 30%. The reaction conversion could not be increased significantly on a repeated attempt (**Table 1.52**, entry 2). Furthermore, at the more elevated temperature of -20 ^{o}C, the conversion was increased to a respectable 87%, yet the selectivity was reduced to a relatively poor 70:30 er (**Table 1.52**, entry 3).

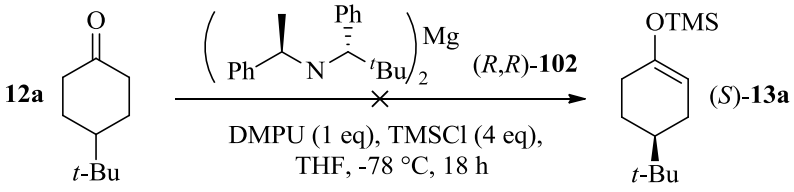


Scheme 1.110

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	30	14	87:13
2	-78	36	21	86:14
3	-20	87	68	70:30

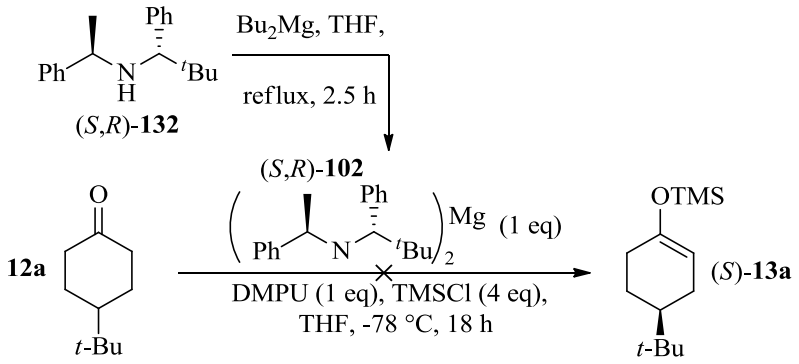
Table 1.52

From these results, it was clear that a delicate balance was required in terms of the steric bulk of the alkyl substituent α- to the nitrogen atom of the secondary amine. While introduction of an ethyl substituent in (*R*,*R*)-**100** had led to an increase in selectivity over that of (*R*,*R*)-**98**, a further slight increase in steric bulk, by introduction of an *iso*-propyl substituent in (*R*,*R*)-**101**, had led to a decrease in selectivity. To be sure of the reliability of this apparent trend, the *tert*-butyl-substituted bisamide ((*S*,*R*)-**102**) was applied to the benchmark deprotonation reaction (**Scheme 1.111**). Firstly, the *tert*-butyl-substituted bisamide was prepared in the usual manner, by refluxing two equivalents of the corresponding amine with one equivalent of di-*n*-butylmagnesium in THF over 1.5 h. The ketone was then added to the reaction mixture at -78 ^{o}C in the presence of DMPU and TMSCl. Unfortunately, using these standard conditions, a complex mixture of products was formed, and none of the starting material or silyl enol ether ((*S*)-**13a**) could be detected.



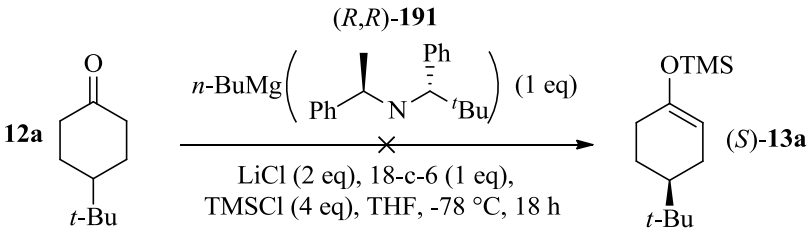
Scheme 1.111

Since none of the desired product ((*S*)-**13a**) had been formed, it was thought that the active base species ((*S*,*R*)-**102**) may not be forming under the reaction conditions, due to the increased steric bulk around the nitrogen centre of the amine. Accordingly, a longer reflux period of 2.5 h was employed in an attempt to force the desired base to form (**Scheme 1.112**). However, no improvement over the results achieved previously was obtained.



Scheme 1.112

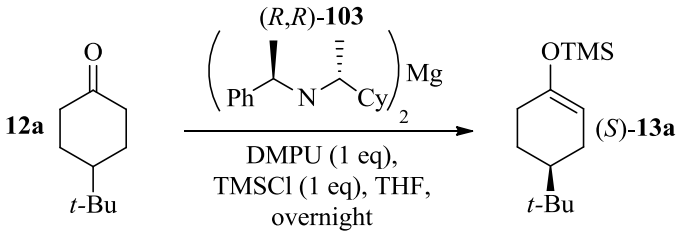
In light of the lack of success achieved using the *pseudo*-C_2-symmetric amine ((*S*,*R*)-**102**) as its magnesium bisamide ((*S*,*R*)-**102**), alternative conditions were sought. In particular, the novel additive conditions, using LiCl and 18-c-6, which were developed for the alkylmagnesium amide-mediated deprotonation reactions, were investigated (**Scheme 1.113**).[44] Disappointingly, under these conditions, no conversion to the desired silyl enol ether was observed. As a result, investigations into the use of this novel magnesium base in the deprotonation of 4-*tert*-butylcyclohexanone were discontinued.



Scheme 1.113

Next, we moved on to evaluate the effect of introducing greater saturation in the magnesium bisamide structure. In particular, the results obtained when employing the cyclohexyl-substituted bisamide ((*R*,*R*)-**103**) in the enantioselective deprotonation of 4-*tert*-butylcyclohexanone are illustrated (**Scheme 1.114**, **Table 1.53**). Overall, the conversion and enantioselectivity achieved under the optimised conditions were rather disappointing. At -78 ^{o}C, a reasonable 67% conversion was recorded, along with a relatively poor 85:15 er (**Table 1.53**, entry 1). On moving to a more elevated temperature of -20 ^{o}C, the conversion increased to an excellent 93%, but this was accompanied by a poor 70:30 er (**Table 1.53**, entry 2). It

was reasoned that the poor selectivity could be due to a reduction in the magnesium-π stacking that is possibly occurring in solution when the aromatic group is present, as in the C_2-symmetric magnesium amide base ((*R*,*R*)-**98**). The potential for magnesium-π stacking in magnesium amide base (*R*,*R*)-**103** is, of course, reduced compared to that of the magnesium amide base ((*R*,*R*)-**98**), possibly resulting in a dramatic change in the solution structure of the magnesium bisamide and altering the chiral environment around the reaction site.

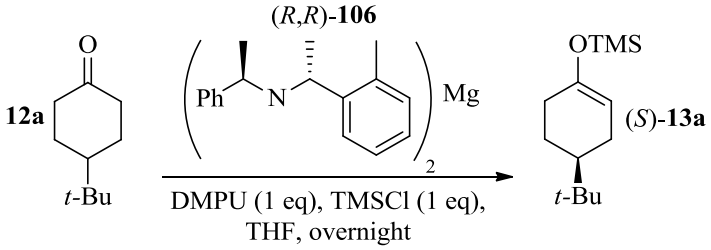


Scheme 1.114

Entry	Temperature (^oC)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	67	47	85:15
2	-20	93	76	70:30

Table 1.53

We next aimed to employ *pseudo*-C_2-symmetric magnesium bisamides with differing functionality on one of the aromatic rings. Firstly, the *ortho*-methyl-substituted magnesium bisamide ((*R*,*R*)-**106**) was applied to the asymmetric deprotonation of 4-*tert*-butylcyclohexanone (**Scheme 1.115** and **Table 1.54**). To our delight, an impressive enantioselectivity of 95:5 er was achieved when employing this bisamide at -78 ^oC (entry 1). However, the reaction conversion was moderate at this temperature. In an attempt to improve on the conversion and evaluate the efficacy of the magnesium bisamide ((*R*,*R*)-**106**) at more elevated temperatures, the reaction was repeated at -20 ^oC. Pleasingly, in this instance, the selectivity remained at a high level (90:10 er), while the conversion to the desired product increased significantly to 92% (entry 2).

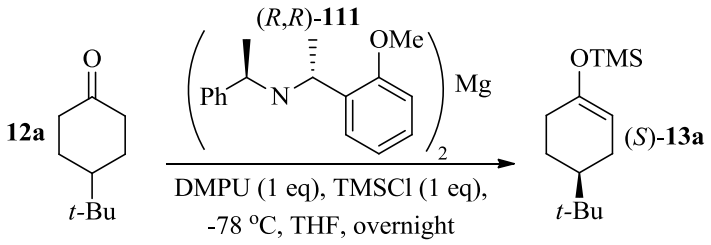


Scheme 1.115

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	55	42	95:5
2	-20	92	79	90:10

Table 1.54

The benchmark deprotonation reaction was then performed using the *ortho*-methoxy-substituted magnesium bisamide ((*R*,*R*)-**111**). When the optimised conditions were employed at -78 ^{o}C, the result was very disappointing (**Scheme 1.116**, **Table 1.55**). Although a moderate conversion of 65% was obtained for the desymmetrisation of 4-*tert*-butylcyclohexanone, the enantioenrichment of the product was negligible (**Table 1.55**). It became clear that the methoxy substituent was playing a crucial role in the overall process, unfortunately, to the detriment of the selectivity obtained. The result suggested that the methoxy substituent was, perhaps, forming a chelating structure with the magnesium metal, in turn producing a solution aggregate that resulted in very poor enantioselectivity.

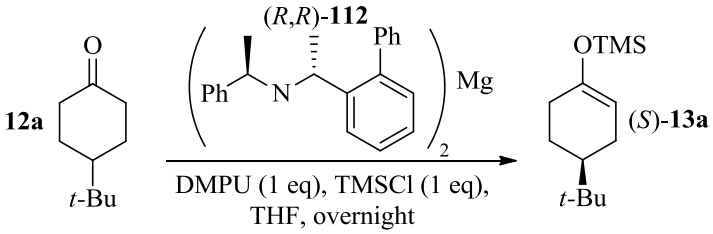


Scheme 1.116

Conversion (%)	Yield (%)	er (*S*):(*R*)
65	45	48:52

Table 1.55

Investigations then moved on to the application of magnesium amides containing a biphenyl substituent. Firstly, the *ortho*-substituted bisamide ((*R*,*R*)-**112**) was applied to the asymmetric deprotonation of 4-*tert*-butylcyclohexanone at both -78 and -20 ^{o}C (**Scheme 1.117**, **Table 1.56**). To our delight, employment of the magnesium bisamide ((*R*,*R*)-**112**) at -78 ^{o}C resulted in the highest selectivity that this programme of study had achieved (**Table 1.56**, entry 1). Moreover, at the elevated temperature of –20 ^{o}C, a very pleasing conversion was recorded (98%), alongside a high 87:13 er (entry 2).



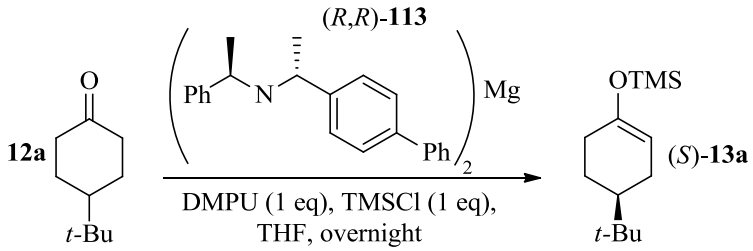
Scheme 1.117

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	84	68	96:4
2	-20	98	78	87:13

Table 1.56

With these encouraging results in hand, the alternative *para*-substituted magnesium bisamide ((*R*,*R*)-**113**) was then applied to the desymmetrisation of 4-*tert*-butylcyclohexanone (**Scheme 1.118**, **Table 1.57**). Yet again, employment of a biphenyl substituent delivered excellent results in the benchmark reaction at both -78 and -20 ^{o}C. More specifically, a high selectivity of 94:6 er was achieved at -78 ^{o}C (entry 1), while a very good 87:13 er was recorded at the more elevated temperature of -20 ^{o}C (entry 2). In comparison with the *ortho*-substituted

magnesium bisamide ((*R*,*R*)-**112**), however, the reaction conversion at -78 °C was significantly lower.

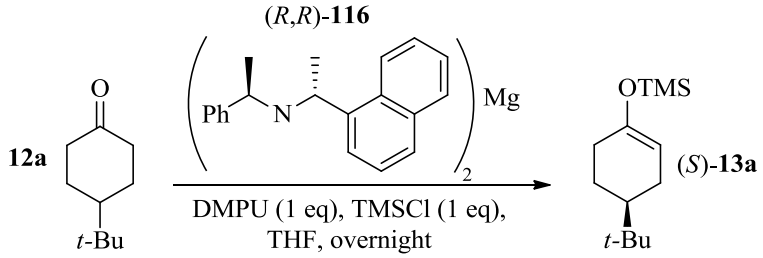


Scheme 1.118

Entry	Temperature (°C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	62	48	94:6
2	-20	97	83	87:13

Table 1.57

Subsequently, focus was turned to the utilisation of magnesium bisamides possessing a naphthyl substituent. Initially, the bisamide with substitution at the 1-position ((*R*,*R*)-**116**) was employed in the benchmark desymmetrisation at both -20 and -78 °C (**Scheme 1.119**, **Table 1.58**). Pleasingly, the results obtained using this magnesium bisamide ((*R*,*R*)-**116**) were very good, delivering a high selectivity of 94:6 er for the desymmetrisation of 4-*tert*-butylcyclohexanone at -78 °C, although the observed conversion was somewhat disappointing (**Table 1.58**, entry 1). In addition, at the more elevated temperature of -20 °C, a good selectivity of 84:16 er was achieved alongside a high reaction conversion (entry 2). Overall, although this novel bisamide delivered high conversions and selectivities, the results displayed are not as outstanding as those achieved using other novel bisamides from this study.

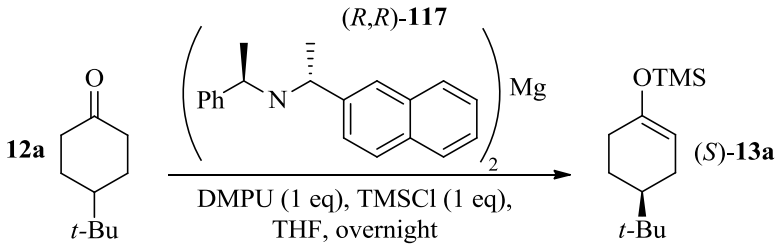


Scheme 1.119

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	68	58	94:6
2	-20	92	72	84:16

Table 1.58

Attention was then turned to the analogous naphthyl-substituted bisamide ((*R*,*R*)-**117**, **Scheme 1.120**, **Table 1.59**). We were delighted to find that an excellent selectivity of 96:4 er could be achieved for the asymmetric deprotonation of 4-*tert*-butylcyclohexanone when employing this magnesium bisamide at -78 ^{o}C (**Table 1.59**, entry 1). Furthermore, on moving to the more elevated temperature of -20 ^{o}C, an excellent 89:11 er was recorded along with an increased reaction conversion (**Table 1.59**, entry 2). It should be noted that these are the best results achieved so far, in terms of both yield and enantioselectivity, in this base screening study.

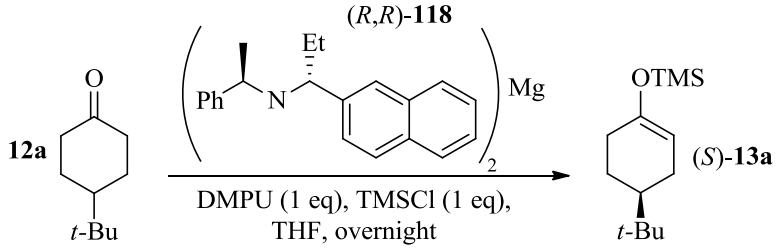


Scheme 1.120

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	85	72	96:4
2	-20	90	78	89:11

Table 1.59

The next naphthyl-containing magnesium bisamide to be investigated for its use in the asymmetric deprotonation protocol was (*R*,*R*)-**118**, which possesses a slightly bulkier ethyl substituent in the benzylic position (**Scheme 1.121**). The initial reaction employing this novel bisamide was carried out under the standard conditions at -78 ^{o}C (**Table 1.60**, entry 1). Under these conditions, almost quantitative conversion was achieved, along with an excellent 80% isolated yield. However, this bisamide exhibited a relatively poor enantioselectivity (82:18 er). Similarly, when the effect of performing the reaction at an elevated temperature of -20 ^{o}C was explored, disappointing enantioselectivity was observed (entry 2). Although high conversion and yield were obtained in this reaction, the enantioselectivity decreased significantly to 69:31 er.



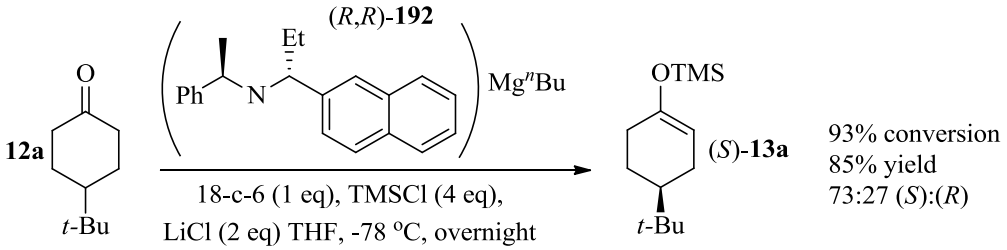
Scheme 1.121

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	98	80	82:18
2	-20	90	75	69:31

Table 1.60

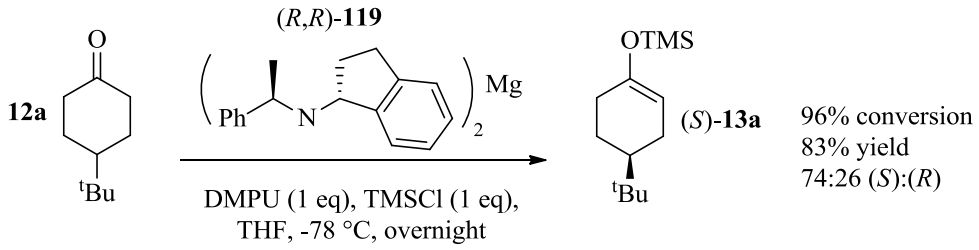
With the aim of improving the selectivity achieved at -78 ^{o}C, the novel additive conditions were employed for the reaction of the alkylmagnesium amide ((*R*,*R*)-**192**) with 4-*tert*-

butylcyclohexanone (**Scheme 1.122**). Using this novel alkylmagnesium amide, an excellent 93% conversion to the silyl enol ether (**13a**) was observed and the product was isolated in an 85% yield. However, this novel bisamide delivered the silyl enol ether with moderate stereocontrol, exhibiting an enantiomeric ratio of 73:27 (*S*):(*R*).



Scheme 1.122

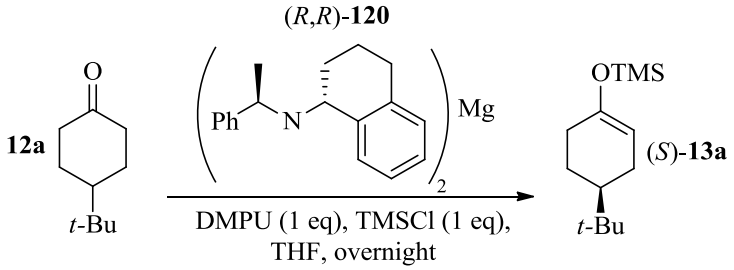
Attention was then focused on the employment of a range of *pseudo*-C_2-symmetric bisamides which have one of the chiral centres tethered to an aromatic ring, beginning with the bisamide containing a five-membered ring ((*R*,*R*)-**119**). Pleasingly, when this bisamide was applied to the deprotonation of 4-*tert*-butylcyclohexanone, almost complete conversion to the silyl enol ether was achieved (**Scheme 1.123**). Although, somewhat disappointingly, the enantioselectivity achieved was moderate (74:26 er).



Scheme 1.123

Increasing the length of the chain in the tether, the magnesium bisamide ((*R*,*R*)-**120**) was also employed for the asymmetric deprotonation of 4-*tert*-butylcyclohexanone, at both -78 °C and -20 °C (**Scheme 1.124** and **Table 1.61**). Pleasingly, this base delivered an improvement in enantioselectivity, compared to (*R*,*R*)-**119**, when the benchmark deprotonation reaction was performed at -78 °C (**Table 1.61**, entry 1). Moreoever, the enantioinduction imparted by (*R*,*R*)-**120** at -20 °C (entry 2) is in line with that observed using (*R*,*R*)-**119** at the much less

practicable temperature of -78 °C. However, overall, the results achieved using (*R*,*R*)-**120** are relatively poor, compared with other novel bisamides in this study.

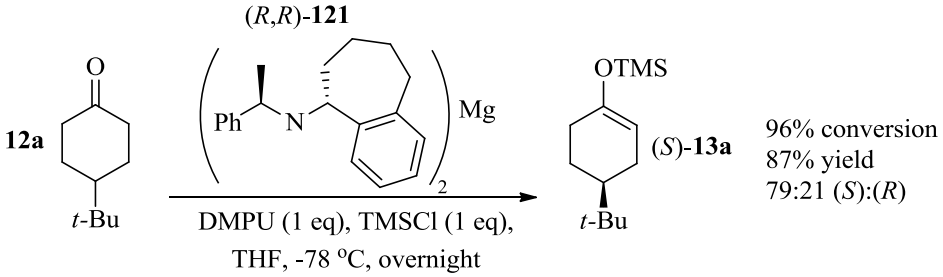


Scheme 1.124

Entry	Temperature (°C)	Conversion (%)	Yield (%)	er (*S*):(*R*)
1	-78	83	62	82:18
2	-20	96	73	74:26

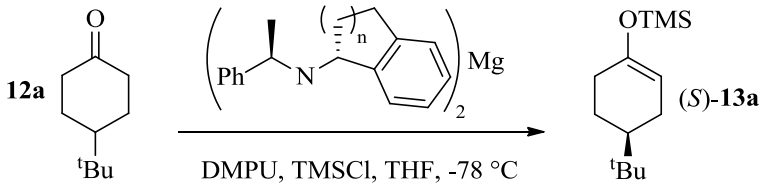
Table 1.61

In an attempt to increase selectivities further, the analogous *pseudo*-C_2-symmetric bisamide ((*R*,*R*)-**121**), containing a seven-membered ring, was then applied to the benchmark deprotonation of 4-*tert*-butylcyclohexanone (**Scheme 1.125**). Using this novel bisamide, an excellent 96% conversion to the silyl enol ether (**13a**) was observed and the product was isolated in an 87% yield. However, this novel bisamide delivered the silyl enol ether with only moderate enantioselectivity (79:21 er).



Scheme 1.125

Overall, the results achieved for the homologous series of magnesium bisamides, having one of the substituents of a stereogenic centre tethered to the adjacent aromatic ring, are outlined below (**Scheme 1.126**, **Table 1.162**). As can be seen from these findings, no improvement in enantioselectivity has been gained over the simple C_2-symmetric bisamide ((*R*,*R*)-**98**). Also, it would appear that the optimum results with this class of *pseudo*-C_2-symmetric base are achieved using the bisamide containing a six-membered ring.



Scheme 1.126

Base	n	Conversion (%)	Yield (%)	(*S*):(*R*)
(*R*,*R*)-**119**	1	96	83	74:26
(*R*,*R*)-**120**	2	83	62	82:18
(*R*,*R*)-**121**	3	96	87	79:21

Table 1.62

In summary, a wide array of novel C_2- and *pseudo*-C_2-symmetric bases has been applied to the desymmetrisation of the benchmark substrate, 4-*tert*-butylcyclohexanone (**12a**). Although, overall, these novel bases have delivered a range of reactivities and enantioselectivities, some of the results achieved in this study are among the best recorded for the asymmetric deprotonation of prochiral ketones. Additionally and at least as importantly, this class of base has exhibited high enantioselectivity at more elevated temperatures. Furthermore, it is envisaged that the wide breadth of results achieved will allow a greater knowledge of the relationship between base structure and efficacy to be developed. To this end, a computational modelling study was initiated, in collaboration with Dr Tell Tuttle at the University of Strathclyde, using a selection of the novel C_2- and *pseudo*-C_2-symmetric bisamides; details of this research will be described in the following section.

3.4 Computational modelling studies

3.4.1 Introduction

Having obtained a range of results, in terms of both reactivity and enantioselectivity, for the desymmetrisation of 4-*tert*-butylcyclohexanone using our C_2- and *pseudo*-C_2-symmetric magnesium bisamides, we decided to investigate (i) the structure of the chiral magnesium bisamide bases, and (ii) the reaction energetics for the enantioselective reaction of the bases with 4-*tert*-butylcyclohexanone, using computational modelling techniques.

Relevant mechanistic studies have been carried out by a number of research groups.[61] In deprotonation reactions which lead to enantiomeric or diastereomeric enolates, the precise nature of the factors which control the relative rates of deprotonation is unknown. However, various aspects of ketone deprotonation have been studied quantitatively. The groups of Williard[61(d),(e)] and, particularly, Collum[61(a)] have characterised the aggregates involved and have explored their role in the reaction. In terms of magnesium bases, Henderson has studied deprotonations,[61(b),(c)] paying particular attention to the stereochemical integrity of magnesium enolates.

Altogether, we have studied fifteen chiral magnesium bisamide bases (**Figure 1.30**), two of which are C_2-symmetric and the rest are *pseudo*-C_2-symmetric. In order to study the optimised structure of our bases, we performed geometry optimisation followed by a Natural Bond Orbital (NBO) analysis on the optimised geometries to deliver a clear representation of the electronic structure and interactions between neighbouring groups. The main goal in the modelling of electronic interactions within the base species was to build a correlation between the strength of the interaction between the amide ligands and the magnesium centre (and hence, the availability of the magnesium centre for interaction and complexation with the ketone substrate), and the reactivity of the base.

With regards to modelling of the reaction energetics, we proposed that the reaction between 4-*tert*-butylcyclohexanone and our magnesium bisamides occurs *via* initial complexation of the magnesium centre to the carbonyl oxygen of the substrate to form a base-ketone complex. The initial complexation process is, therefore, considered to be of fundamental importance in any modelling of the reaction energetics. Accordingly, the energetics for initial association

of the base to the ketone and internal H abstraction have been studied computationally for a selection of our magnesium bisamides ((*R*,*R*)-**98**, (*R*,*R*)-**103**, (*R*,*R*)-**117**, and (*R*,*R*)-**118**). These bases were chosen as they cover a range of efficacies in the benchmark deprotonation reaction. In addition, the reaction energetics for the C_2-symmetric lithium amide ((*R*,*R*)-**1**) have been studied for comparison. In order to reduce the complexity of our computational study of the reaction energetics, we have made a number of simplifications to the system at this stage; we have chosen a monomeric base and have not included interactions with the solvent, Lewis basic additives, or the electrophile (TMSCl).

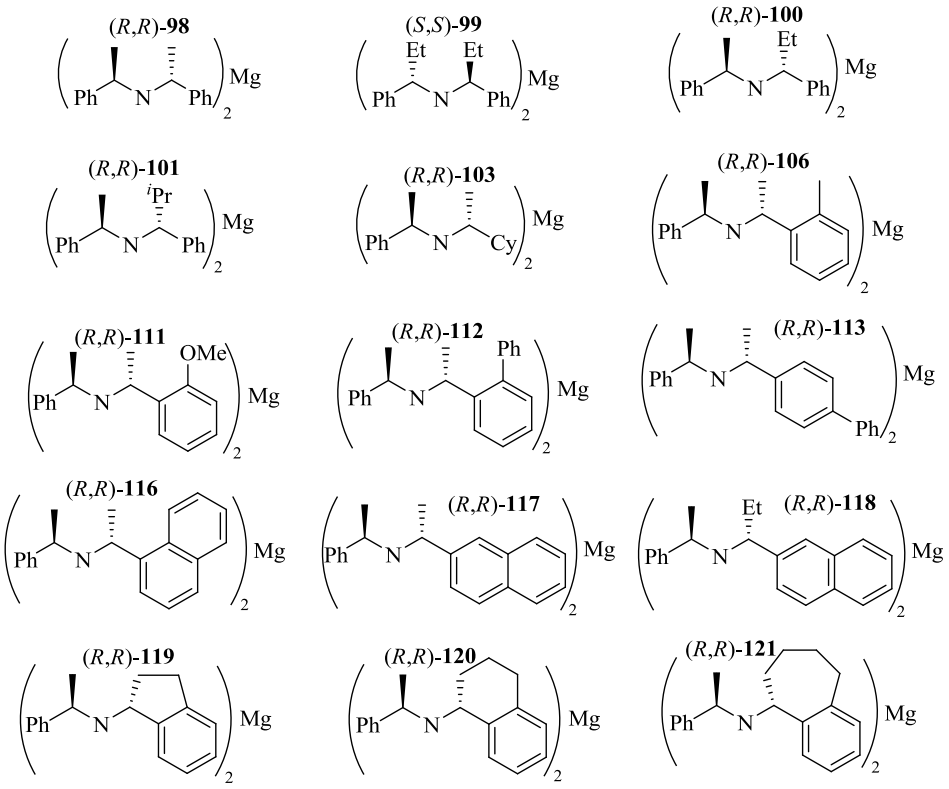


Figure 1.30: Magnesium bisamides subjected to this study

3.4.2 Computational details

The structures of all of the magnesium bisamides shown (**Figure 1.30**) have been optimised using Density Functional Theory (DFT)[62] with BP86 functional in conjunction with the def2-SVP basis set as implemented in the TURBOMOLE program.[63] Furthermore, the resolution-of-the-identity (RI) approach[64] was employed with DFT in order to take advantage of the low computational cost. It should be noted that further refinement of the structures and proper

reaction energetics would require a better density functional. We have chosen the M06 functional[65] in conjunction with the 6-31+G(d) basis set to perform the electronic structure calculations using Gaussian 09. The M06 is a hybrid meta functional; this functional is known to display good accuracy across-the-board for transition metals, main group thermochemistry, medium-range correlation energy, and barrier heights.[66] The NBO analysis[67] has been performed with M06 optimised structures using the Linux-based NBO 5.0 program. For this purpose, the NBO 5.0 input file, which is an information file containing the wave function information of the molecular system, was generated using the Gaussian 09 program suite. The NBO molecular orbital plots were generated using the UNIX-based NBOView 1.0 Orbital Graphics program. The NBO analysis was performed with (*R*,*R*)-**98**, (*R*,*R*)-**100**, (*R*,*R*)-**101**, (*R*,*R*)-**111**, and (*R*,*R*)-**116**-**118**. Bases (*R*,*R*)-**98**, (*R*,*R*)-**100**, and (*R*,*R*)-**101** were chosen to determine the effect of the differing size of the alkyl substitution around the magnesium centre. Base (*R*,*R*)-**111** was chosen in order to study the energetics of the postulated O-Mg interaction. Finally, the effects of differing napthyl substitution, as well as alkyl size, was examined using bases (*R*,*R*)-**116**-**118**. All of the bases have been subjected to optimisation at the M06/6-31+G(d) level of theory without symmetry constrain, which optimises to C_1-symmetry. Symmetry constrain (C_2) is imposed during optimisation of (*R*,*R*)-**98**. The change in energy with and without symmetry constrain was found to be 0.0002 a.u. (<1 kcal mol^{-1}). No imaginary frequency due to symmetry constrain was found, which was tested with a simplified model chiral base, analogous to (*R*,*R*)-**98** but containing ethyl substituents in place of the phenyl groups. It should be noted that for two of the bases, (*S*,*S*)-**99** and (*R*,*R*)-**106**, optimisation failed at the M06/6-31+G(d) level.

3.4.3 Results and discussion

3.4.3.1 Optimised structure of the bases

From the M06 optimised geometries, it can be shown that all of the bases, except the methoxy-substituted base ((*R*,*R*)-**111**, discussed in the following section), have structures analogous to that shown for the simple C_2-symmetric base ((*R*,*R*)-**98**, **Figure 1.31**).

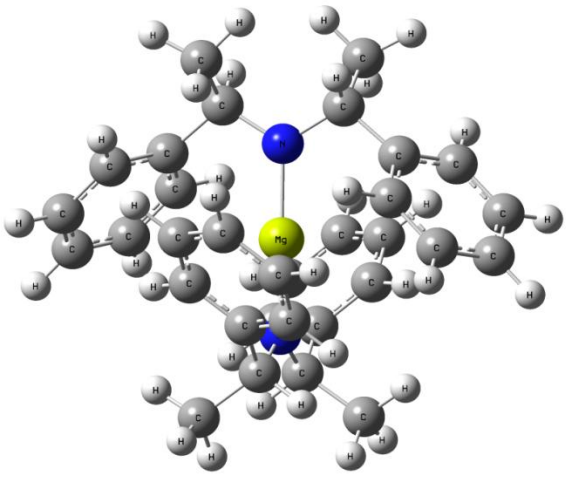


Figure 1.31: Optimised structure of (*R*,*R*)-**98** at the M06/6-31+G(d) level of theory

For all of the bases, the central N-Mg-N moiety is of particular interest because of its postulated key role in the reaction mechanism and its interactions with neighbouring groups within the amide structure. Accordingly, the N-Mg-N bond angle and the Mg-N bond distances of the optimised bases were examined (**Table 1.63**). Interactions of the N-Mg-N moiety with neighbouring groups are clearly reflected in the N-Mg-N angle which is not equal to 180.0º for most of the bases. However, the N-Mg bond distances remain approximately equal for every base structure, indicating that only the central magnesium atom is participating in interactions with the neighbouring groups. Although one might expect the bond distances, Mg-N(1) and Mg-N(2), to be equal, the electronic structure is dynamic and so, at any one point, the bond distances could be different; the most stable scenario will be optimised, possibly leading to unequal bond distances.

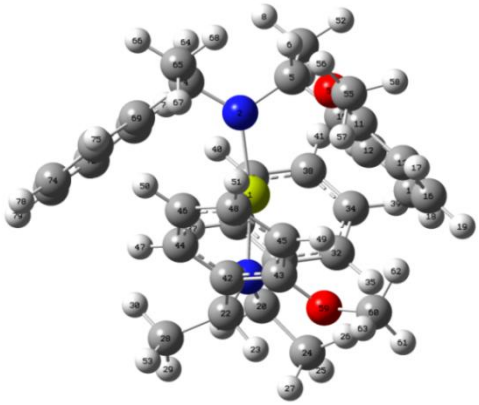
Base	N-Mg-N (°)	Mg-N(1) (Å)	Mg-N(2) (Å)
(*R*,*R*)-**98**	178.8	1.95	-
(*S*,*S*)-**99**	163.1	1.95	-
(*R*,*R*)-**100**	174.7	1.95	-
(*R*,*R*)-**101**	169.0	1.95	-
(*R*,*R*)-**103**	162.0	1.96	1.95
(*R*,*R*)-**106**	174.4	1.95	-
(*R*,*R*)-**112**	161.4	1.96	-
(*R*,*R*)-**113**	161.4	1.95	1.96
(*R*,*R*)-**116**	162.3	1.95	-
(*R*,*R*)-**117**	173.7	1.95	-
(*R*,*R*)-**118**	171.9	1.96	-
(*R*,*R*)-**119**	176.5	1.95	-
(*R*,*R*)-**120**	164.9	1.95	1.94
(*R*,*R*)-**121**	160.7	1.96	1.94

Table 1.63: Central unit parameters at the M06/6-31+G(d) level. For equal Mg-N(1) and Mg-N(2) distances, the Mg-N(2) cells are left blank.

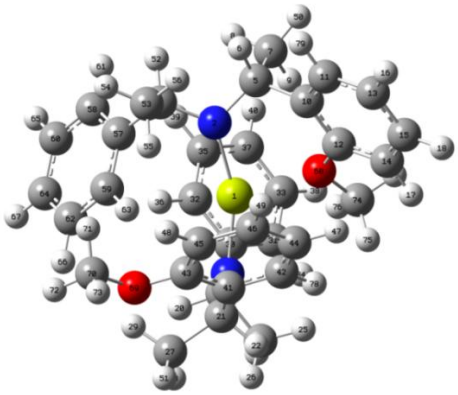
An anomaly: The methoxy-substituted base ((*R*,*R*)-111)

We have located three different structures for (*R*,*R*)-**111**, a novel bisamide which proved to be completely non-selective in our optimisation studies, based on the direct interaction of the methoxy group with the central magnesium atom (**Figure 1.32**, **Table 1.64**). The first structure ((*R*,*R*)-**111a**) shows no direct interaction of the methoxy moiety with the magnesium centre, and has a similar optimised structure to that shown in **Figure 1.31**. In comparison, alternative structures have been optimised which contain a direct interaction of the methoxy group with the magnesium centre. More specifically, an interaction involving one of the methoxy substituents of the bisamide has been found in (*R*,*R*)-**111b**, whereas simultaneous interactions of both methoxy substituents are present in (*R*,*R*)-**111c**. It should be noted that the C_2-symmetry of the nitrogen centres has been lost completely in (*R*,*R*)-**111c**. In terms of the relative stability of the three optimised structures, (*R*,*R*)-**111c** has the lowest calculated energy, followed by (*R*,*R*)-**111b** and with (*R*,*R*)-**111a** being the least stable; the

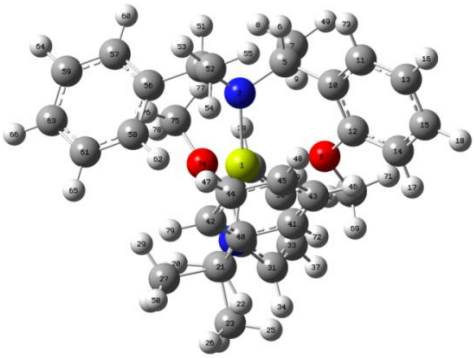
M06/6-31+G(d) calculated stability order of the three different bases is (*R*,*R*)-**111c** (0.00) > (*R*,*R*)-**111b** (3.36) > (*R*,*R*)-**111a** (8.29) in kcal mol^{-1}. The vast difference between the most stable structure located for (*R*,*R*)-**111** and the general structure of the other bases (**Figure 1.31**) could help to explain the surprising lack of enantioselectivity observed with this base.



(*R*,*R*)-**111a**



(*R*,*R*)-**111b**



(*R*,*R*)-**111c**

Figure 1.32: Optimised structures of (*R*,*R*)-**111** at M06/6-31+G(d) Level of Theory.

Base	N-Mg-N (°)	Mg-N(1) (Å)	Mg-N(2) (Å)
(*R*,*R*)-**111a**	170.8	1.95	1.48
(*R*,*R*)-**111b**	159.2	1.96	-
(*R*,*R*)-**111c**	162.7	1.99	2.00

Table 1.64: Central unit parameters at the M06/6-31+G(d) level. For equal Mg-N(1) and Mg-N(2) distances, the Mg-N(2) cells are left blank.

NBO Analysis

The reported values in **Table 1.63** for the central unit parameters of the bases show that the two N-Mg distances for each base are almost constant, irrespective of the substitution around the amide nitrogen. In contrast, the N-Mg-N bond angles deviate from linearity over a wide range, indicating various interactions of the central magnesium atom with the neighbouring groups. Based on the different types of substitution around the nitrogen centres, the significant interactions can be assumed to be π(C-C) to Mg and agostic σ(C-H) to Mg (**Figure 1.33**). To quantify these interactions, we have performed a Natural Bond Orbital (NBO) analysis on the equilibrated structures, concentrating on the appropriate fragments (the central magnesium, the neighbouring C-H, and adjacent aromatic C-C).

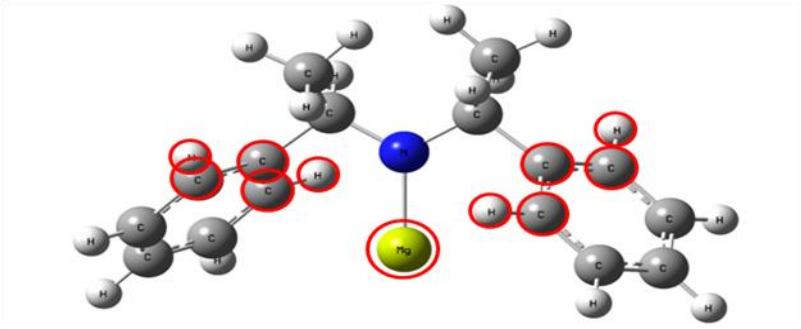


Figure 1.33: Significant interactions of the central Mg atom.

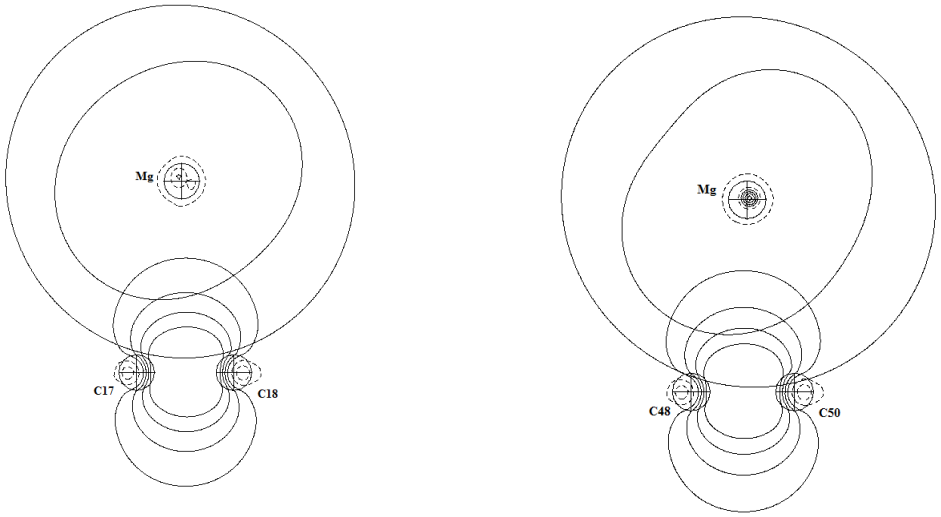
The NBO analysis transfers the delocalised molecular orbitals into the localised molecular orbitals that are closely tied to chemical bond concepts. Filled NBOs describe the hypothetical, strictly localised Lewis structure. The interaction between filled orbitals, including lone pairs, and antibonding orbitals represents the deviation of the molecule from

the Lewis structure and can be used as a measure of delocalisation due to π(C-C) to Mg and agostic σ(C-H) to Mg interactions. Since the occupancies of filled NBOs are highly condensed, the delocalising interactions can be further treated by the second-perturbation energies, E(2). The asymmetric nature of the interactions, which is responsible for the bending of the N-Mg-N moiety, can also be described using the E(2) values, as reported in **Table 1.65** for the *pseudo*-C_2-symmetric base ((*R*,*R*)-**101**). We have presented the values as a sum of the value for each of the four units surrounding the central magnesium atom. The results obtained for this particular base have been exemplified in order to illustrate the large differences that can occur between the summed E(2) values for each of the four units. In comparison, in the case of the simple C_2-symmetric base ((*R*,*R*)-**98**), the summed E(2) values are almost identical, leading to a N-Mg-N angle close to 180° (178.8°, not shown).

From NR_2(1) to Mg			**From NR_2(2) to Mg**		
Donor NBO	**Acceptor NBO**	**E(2) (kcal mol^{-1})**	**Donor NBO**	**Acceptor NBO**	**E(2) (kcal mol^{-1})**
π(C-C)	n*(Mg)	3.72	π(C-C)	n*(Mg)	2.27
π(C-C)	n*(Mg)	2.12	π(C-C)	n*(Mg)	4.23
σ(C-H)	n*(Mg)	3.07	σ(C-H)	n*(Mg)	0.61
σ(C-H)	n*(Mg)	0.54	σ(C-H)	n*(Mg)	3.87
		Σ = 9.45			Σ = 10.98
π(C-C)	n*(Mg)	1.01	π(C-C)	n*(Mg)	0.77
π(C-C)	n*(Mg)	2.49	π(C-C)	n*(Mg)	1.68
σ(C-H)	n*(Mg)	0.16	σ(C-H)	n*(Mg)	0.15
σ(C-H)	n*(Mg)	3.55	σ(C-H)	n*(Mg)	1.78
		Σ = 7.21			Σ = 4.38

Table 1.65: Second order perturbation energies for the key interactions in (*R*,*R*)-**101** (having a calculated N-Mg-N angle of 169.0°).

The interactions can also be visualised using the two dimensional plot of the interacting orbitals. **Figure 1.34** shows a 2D plot of the major interactions of the two amide ligands in (*R*,*R*)-**101**. For both amide ligands, the major interactions are between the π(C-C) orbital and the one-centre lone-pair antibonding orbital (n*) on the central magnesium atom.



π(C-C)→n*(Mg) in NR_2(1) (3.72 kcal/mol) π(C-C)→n*(Mg) in NR_2(2) (4.23 kcal/mol)

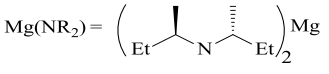
Figure 1.34: Two dimensional plot of the donor→acceptor NBOs of the major interactions for (*R*,*R*)-**101**

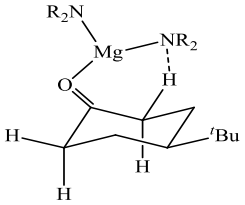
To summarise the findings from the modelling of the electronic structure of the bases, for some bases the π(C-C) interactions were found to be the strongest, whereas for the others the agostic σ(C-H) interactions were the most significant. Only in the case of the optimised structures of the methoxy-substituted amide ((*R*,*R*)-**111b** and (*R*,*R*)-**111c**), the interaction of the methoxy substituent with the magnesium centre surpasses all of the π(C-C) and σ(C-H) interactions. It is possible that this anomaly could be attributed to the distinct lack of enantioselectivity imparted by this base. We initially postulated that the strength of the interactions between the magnesium centre and its neighbouring groups could be linked to the availability of the central magnesium atom to coordinate with the ketone substrate. However, no direct correlation was found between the reaction conversion and the summed E(2) values.

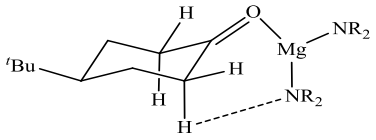
3.4.3.2 Reaction mechanism and energetics

When considering the mechanism involved in our asymmetric deprotonation reactions, at the most basic level, enolisation is expected to proceed through formation of a base-ketone complex followed by intramolecular transfer of the enantiotopic proton from the α-carbon of the bound ketone to the nitrogen of the magnesium bisamide, releasing one of the amide ligands from the complex.

To allow us to build a computational model of this process, we started with a more structurally simple C_2-symmetric base and have modelled the initial base-ketone complexation (**Figure 1.35**). Two possible conformations of the base-ketone complex of 4-*tert*-butylcyclohexanone and the model magnesium bisamide were located. The two conformers were found to differ from each other with respect to the alignment of the protons α to the carbonyl group with the lone pair on nitrogen; conformer I has a nitrogen lone pair in close proximity to one of the equatorial hydrogens α to the carbonyl moiety, whereas conformer II has a nitrogen lone pair aligned with an axial hydrogen.







Conformer I:
Amide close to equatorial H

Conformer II:
Amide close to axial H

Figure 1.35: Two possible conformations of the coordinated complex with a model base

Among these two conformers (conformer I and conformer II), the first is stable over the second (ΔH = 2.51 kcal/mol) and a rotational barrier around O-Mg bond is expected to separate them energetically. Indeed, conformer I was found to be kinetically trapped due to a high rotational barrier around the O-Mg bond which involves large steric interactions between the amide and ketone moieties. Due to these findings, and the fact that removal of the axial hydrogen is favoured stereoelectronically, we have included only conformer II in the potential energy surface (PES) calculations. Among the two properly aligned axial protons in conformer II, one should lead to the (*R*)-enolate and the other to (*S*)-enolate. Based on this we have modelled the reaction path with the two different enantiotopic axial hydrogens.

Table 1.65 presents the energetics data for the reaction of 4-*tert*-butylcyclohexanone with the simplest chiral model base (as in **Figure 1.35**). The internal axial H-abstraction transition

state was located on the potential energy surface with an activation barrier of 2.18 kcal/mol towards the (*S*)-selective pathway. In contrast, the activation barrier towards the (*R*)-selective pathway was found to be higher at 3.43 kcal/mol. Therefore, the calculated energetics data are in good agreement with the observed experimental (*S*)-selectivity using real magnesium bisamides. In addition, the overall intramolecular hydrogen transfer process was computed to be highly exothermic in nature (~14 kcal/mol) for both of the enantiotopic axial hydrogens.

Species	**ΔE_{corr} (kcal/mol)**	**ΔH (kcal/mol)**	**ΔG (kcal/mol)**
(*S*)-base-ketone complex	0.00	0.00	0.00
(*S*)-TS	2.97	2.18	6.12
(*S*)-enolate	-14.38	-14.67	-13.44
(*R*)-base-ketone complex	-0.30	-0.90	2.58
(*R*)-TS	3.03	2.53	5.31
(*R*)-enolate	-13.82	-14.21	-11.80

Table 1.65: Energetics for the reaction of the model chiral magnesium bisamide

Our calculations were then extended to the study of the C_2-symmetric magnesium bisamide (*R*,*R*)-**98**. Focusing on conformer II of the base-ketone complex, the reaction pathways towards both the (*S*)- and (*R*)-products were modelled. **Table 1.66** presents the reaction energetics for the enolisation reaction of 4-*tert*-butylcyclohexanone, mediated by the selected magnesium bisamide ((*R*,*R*)-**98**). The reaction pathway for this transformation is also depicted in **Figure 1.36**. The energetics data demonstrate that the (*S*)-selective deprotonation reaction is kinetically, as well as thermodynamically, more favourable.

Species	ΔE_{corr} (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)
98 (*S*)-base-ketone complex	0.00	0.00	0.00
98 (*S*)-TS	7.54	7.00	9.51
98 (*S*)-enolate	-6.91	-6.98	-6.87
98 (*R*)-base-ketone complex	-1.77	-1.85	-1.31
98 (*R*)-TS	9.28	8.79	11.34
98 (*R*)-enolate	-5.17	-5.27	-4.56

Table 1.66: Energetics for the reaction of (*R*,*R*)-**98**

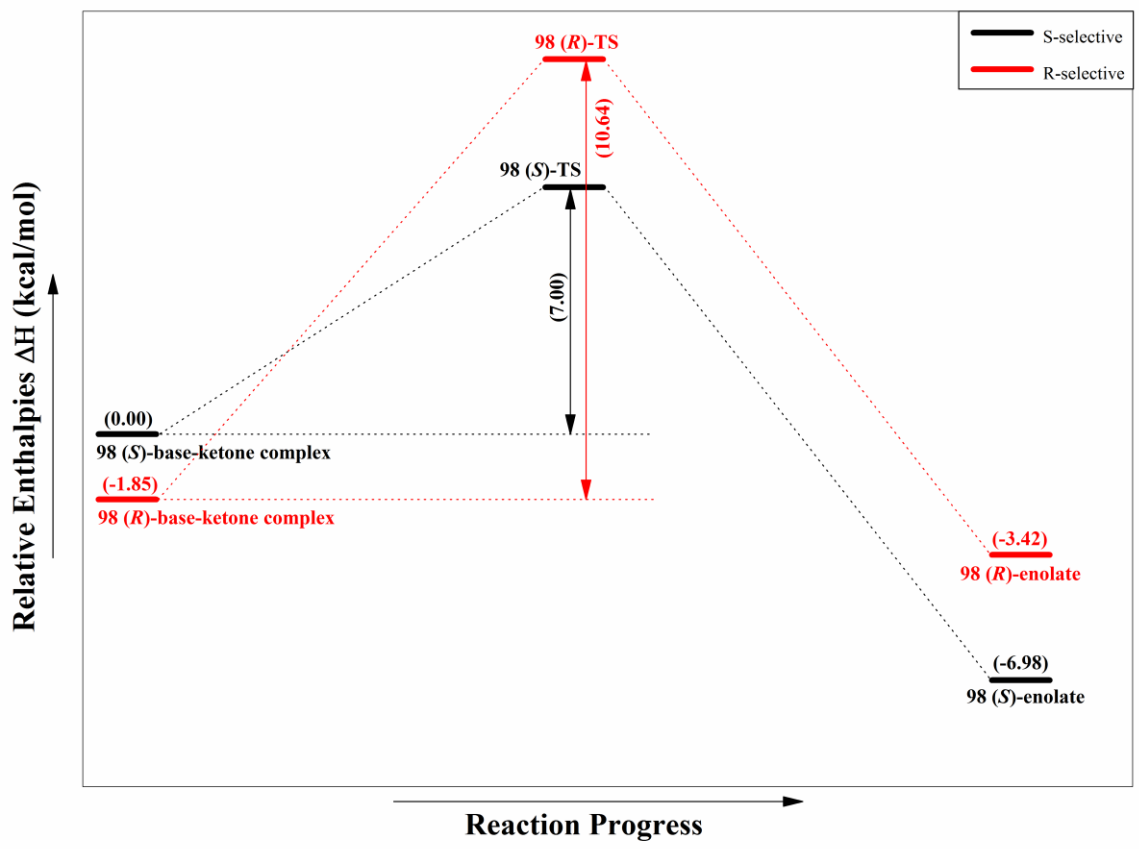
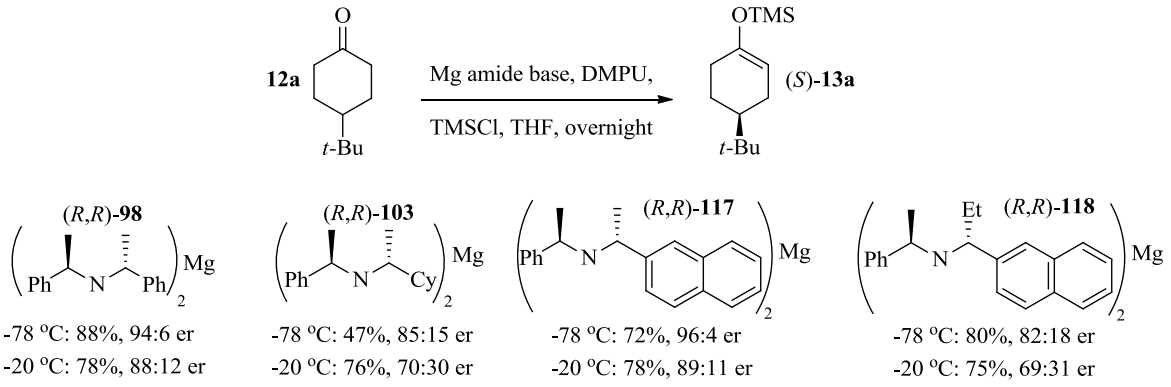


Figure 1.36: Potential energy surface for the key step of the deprotonation reaction

We then broadened our model reaction energetics calculation to include a total of four of the synthesised magnesium bases, (*R*,*R*)-**98**, (*R*,*R*)-**103**, (*R*,*R*)-**117**, and (*R*,*R*)-**118**. In particular, these four bases were chosen for comparison due to their varying steric and electronic nature,

and the relatively wide range of experimental (*S*):(*R*) selectivities in the deprotonation of 4-*tert*-butylcyclohexanone (**Scheme 1.127**).



Scheme 1.127: Observed enantioselectivities for the selected bases

Again, focusing on conformer II of the base-ketone complex, the reaction pathways towards both the (*S*)- and (*R*)-products were modelled. **Table 1.67** presents the reaction energetics for the enolisation reaction of 4-*tert*-butylcyclohexanone, mediated by the selected magnesium bisamides.

Species	ΔE_{corr} (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)
103 (*S*)-base-ketone complex	0.00	0.00	0.00
103 (*S*)-TS	5.36	4.65	7.51
103 (*S*)-enolate	-11.37	-12.01	-8.97
103 (*R*)-base-ketone complex	-1.31	-1.37	-0.28
103 (*R*)-TS	5.51	4.72	8.75
103 (*R*)-enolate	-15.09	-14.99	-14.84
117 (*S*)-base-ketone complex	0.00	0.00	0.00
117 (*S*)-TS	8.38	8.06	8.84
117 (*S*)-enolate	-7.46	-7.44	-7.88
117 (*R*)-base-ketone complex	-6.89	-6.91	-5.99
117 (*R*)-TS	7.16	6.56	8.79
117 (*R*)-enolate	-8.66	-9.03	-8.49
118 (*S*)-base-ketone complex	0.00	0.00	0.00
118 (*S*)-TS	10.00	9.57	11.04
118 (*S*)-enolate	-6.11	-6.16	-6.19
118 (*R*)-base-ketone complex	-6.51	-6.80	-5.23
118 (*R*)-TS	7.35	6.74	9.82
118 (*R*)-enolate	-7.04	-7.14	-6.36

Table 1.67: Energetics for the reaction of selected bisamides

These results can be used to correlate the difference in activation enthalpies of the (*R*)- and (*S*)-selective pathways with the observed experimental enantioselectivities for the range of bases (**Table 1.68**). Firstly, on replacing one of the phenyl substituents of the C_2-symmetric bisamide ((*R*,*R*)-**98**, entry 1) with a cyclohexyl substituent, the difference between the activation enthalpies for the (*R*)- and (*S*)-selective pathways decreases (entry 2). This is mirrored by a reduced experimental enantioselectivity for the silyl enol ether formation using (*R*,*R*)-**103**. The calculated activation enthalpies for the asymmetric deprotonation using the naphthyl-substituted bisamide ((*R*,*R*)-**117**) are also in good agreement with the experimental results; a relative increase in the activation enthalpy of the (*R*)-selective pathway is accompanied by increased selectivity for the (*S*)-enol silane (entry 3). Curiously, the calculated activation enthalpies for the reaction mediated by (*R*,*R*)-**118** do not compare so

well with the experimental data (entry 4). More specifically, the calculated data would support the hypothesis that (*R*,*R*)-**118** should have intermediate enantioselectivity compared to (*R*,*R*)-**98** and (*R*,*R*)-**117**. However, the experimental data shows that (*R*,*R*)-**118** is less selective than both (*R*,*R*)-**98** and (*R*,*R*)-**117**.

Entry	Bisamide	$(\Delta H^{\ddagger}$ (*R*)) – $(\Delta H^{\ddagger}$ (*S*)), kcal/mol	Experimental (*S*):(*R*) at -78 °C
1	(*R*,*R*)-**98**	3.64	94:6
2	(*R*,*R*)-**103**	1.44	85:15
3	(*R*,*R*)-**117**	5.41	96:4
4	(*R*,*R*)-**118**	3.97	82:18

Table 1.68: Difference in calculated activation enthalpies alongside experimental data

If we consider the activation enthalpies obtained for the model ethyl-substituted base against the known bases ((*R*,*R*)-**98**, (*R*,*R*)-**103**, (*R*,*R*)-**117**, and (*R*,*R*)-**118**) the activation barrier is always higher in the case of the real bases. This could be due to the fact that in the case of the real bases, the interactions of the central magnesium with the more sterically-encumbered amide ligands make the magnesium centre less available for interaction with the carbonyl group of the substrate, leading to higher activation enthalpies.

In addition to modelling of the reaction energetics, key interatomic distances in the postulated base-ketone complex were calculated (**Figure 1.37**). For the (*S*)-selective reaction of (*R*,*R*)-**98**, the axial hydrogen in the α-position of 4-*tert*-butylcyclohexanone is 2.75 Å away from the amide nitrogen. In contrast, the pro-(*R*) axial hydrogen is less accessible at 3.00 Å. Similarly, in the (*S*)-selective reaction of (*R*,*R*)-**103**, the distance between the acidic hydrogen of the ketone and the nitrogen of the amide was measured at 2.24Å. In the less favourable (*R*)-selective pathway, the axial hydrogen is 2.50Å away from the nitrogen of the base-ketone complex.

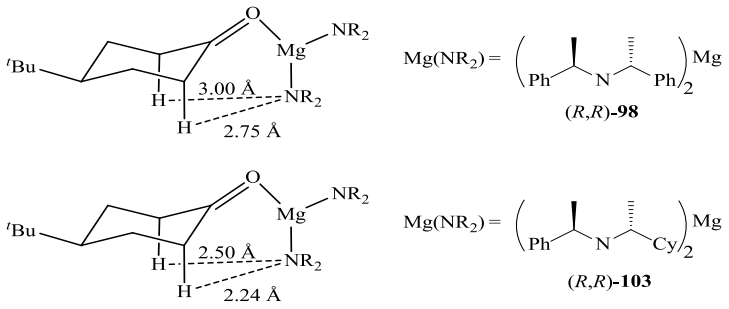


Figure 1.37: Interatomic distances in the base-ketone complexes

Comparison with a chiral Li-amide base

We have also performed calculations using (*R*,*R*)-**1** at the M06/6-31+G(*d*) DFT level of theory (**Table 1.69**). Calculation of the reaction energetics of the simple C_2-symmetric lithium amide base ((*R*,*R*)-**1**) indicates that the overall reaction pathway is analogous to that of the magnesium bisamides, with structurally-similar optimised intermediates.

Species	ΔE_{corr} (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)
(*S*)-base-ketone complex	0.00	0.00	0.00
(*S*)-TS	5.23	4.53	6.85
(*S*)-enolate	-7.27	-7.82	-5.34
(*R*)-base-ketone complex	-0.14	-0.21	0.61
(*R*)-TS	5.64	4.96	8.34
(*R*)-enolate	-8.75	-9.1	-6.8

Table 1.69: Energetics for the reaction of (*R*,*R*)-**1**

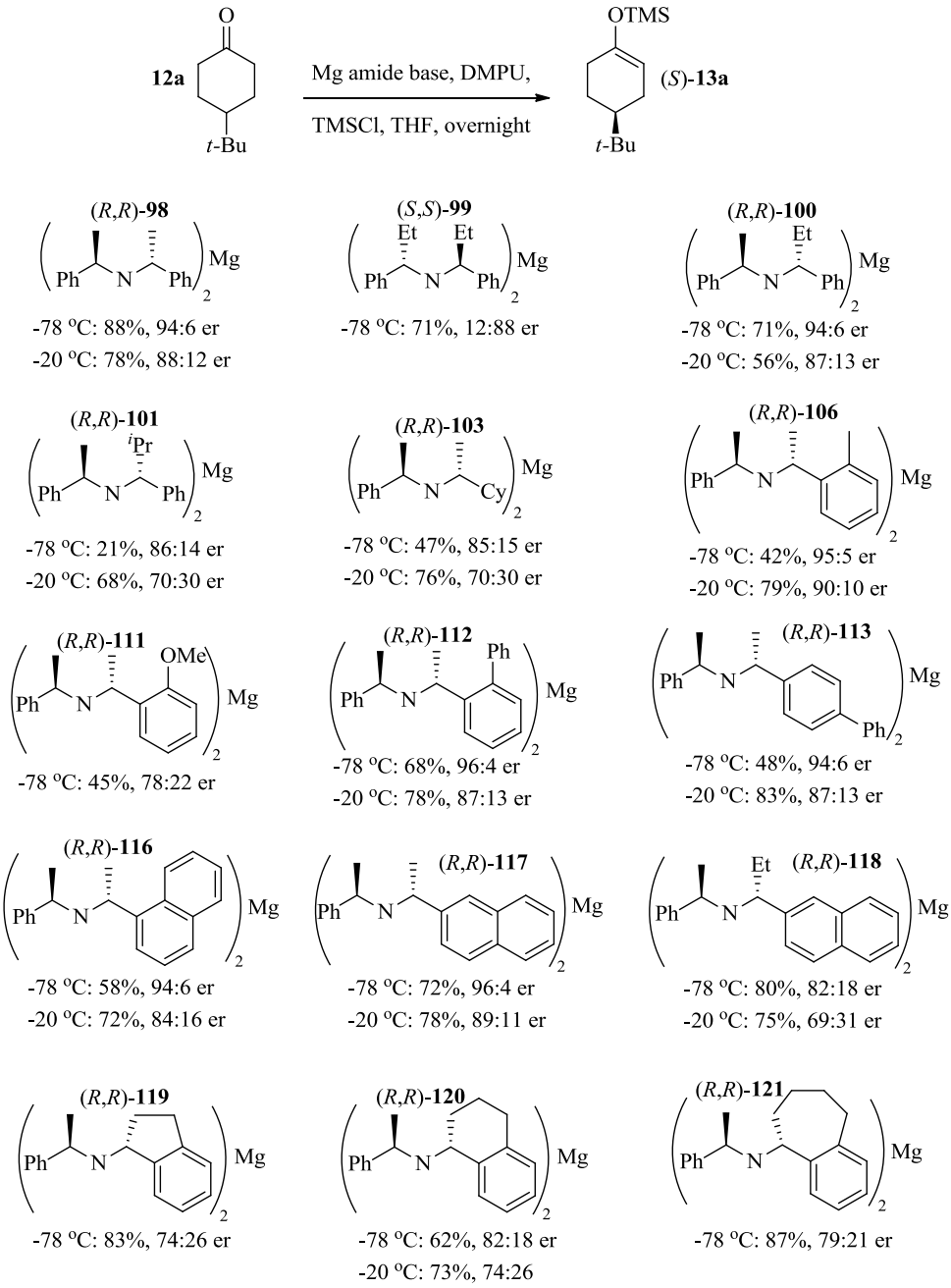
However, when considering the energetic bias towards the (*S*)-selective pathway using the lithium amide, there is a relatively small difference between the (*R*)- and (*S*)-transition states, correlating with poorer discrimination between the (*R*)- and (*S*)-products (**Table 1.70**).

Species	($\Delta H^{‡}$ (*R*)) – ($\Delta H^{‡}$ (*S*)), kcal/mol	Experimental (*S*):(*R*) at -78 °C
Model Mg amide	1.25	-
(*R*,*R*)-**98**	3.64	91:9
(*R*,*R*)-**103**	1.44	85:15
(*R*,*R*)-**117**	5.41	96:4
(*R*,*R*)-**1**	0.64	85:15

Table 1.70: Difference in calculated activation enthalpies alongside experimental data

3.5 Summary

Based on previous results employing the simple magnesium bisamide base ((*R*)-**61**), possessing only one stereogenic centre, investigations involving the evaluation of a slightly more sterically hindered, C_2-symmetric magnesium bisamide ((*R*,*R*)-**98**) were embarked upon. Pleasingly, after a short period of optimisation, superb conversions and selectivities could be achieved for the asymmetric deprotonation of a range of prochiral ketones at both -78 ^{o}C (up to 95:5 er) and -20 ^{o}C (up to 90:10 er). The synthesis of a selection of enantioenriched *pseudo*-C_2-symmetric amines from readily available starting materials was then undertaken, in order to allow the preparation of novel bisamides for use in asymmetric deprotonation processes involving 4-*tert*-butylcyclohexanone. Pleasingly, selectivities as high as 96:4 er could be achieved at -78 ^{o}C; these are some of the highest selectivities ever recorded for this substrate (**Scheme 1.128**). Furthermore, at -20 ^{o}C, excellent selectivities and conversions were recorded for a number of novel magnesium bisamide bases. While, in a more general sense, the success of the novel bisamides that have been investigated in this programme of study has been variable, a series of highly selective bases which exhibit excellent reactivity and selectivity over a range of temperatures has emerged. In addition, the findings from this line of research have allowed greater understanding to be gained with regards to the optimum structure of our *pseudo*-C_2-symmetric magnesium bisamides.

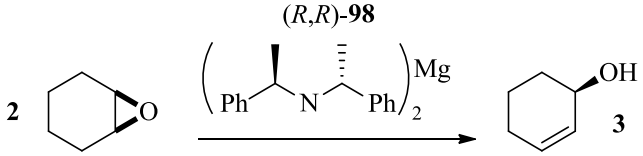


Scheme 1.128

With a varied set of C_2- and *pseudo*-C_2-symmetric magnesium bisamides at our disposal, a computational modelling study was initiated. It was envisaged that, by modelling the interactions which were present between our amide ligands and the magnesium centre, a correlation between base structure and enantioselectivity could be devised. Unfortunately, this was not the case, and no clear trend became apparent when a range of our novel bases was examined. However, interesting results from studies involving the modelling of a

simplified transition state are beginning to emerge. More specifically, theoretical calculations have shown that the activation energy of the pathway which would lead to the (*S*)-enantiomer of the enol silane, the major product of our reactions using the (*R*,*R*)-configuration of the bisamide, is lower than the alternative pathway which would deliver the (*R*)-enantiomer. Furthermore, in general, the magnitude of the difference in activation energies between the (*R*)- and (*S*)-selective pathways correlates well with our experimental findings. Now that a computational model is in place which allows us to calculate the difference in energy between the transition states involved in the removal of each of the axial enantiotopic protons, this should be used to evaluate a wider range of proposed C_2- and *pseudo*-C_2-symmetric magnesium bisamides, before the eventual application of these novel bisamides to the desymmetrisation of prochiral ketones.

Having stated this, at this stage in the development of enantioselective magnesium amide bases, and based on the outcomes of this specific programme, an array of efficient reagents is available for use in asymmetric synthesis. On the other hand, the substrate scope of magnesium bases remains to be fully explored. As such, future work in this area should focus on increasing the applicability of our magnesium bases to include a wider range of substrates. For example, it is envisaged that magnesium bisamide reagents could be capable of mediating the enantioselective rearrangement of epoxides to allylic alcohols (**Scheme 1.129**). Accordingly, the applicability of our optically pure magnesium bisamides to this transformation should be probed. In addition, the utilisation of alternative electrophilic quench reagents, other than chlorotrimethylsilane, to give useful chiral organic synthons should be investigated. Indeed, initial studies within our laboratories employing diphenylphosphoryl chloride as the electrophile in the desymmetrisation of 4-*tert*-butylcyclohexanone have delivered impressive results. This, as well as other electrophiles, should be explored more fully in order to increase the wider applicability of our desymmetrisation stategy.



Scheme 1.129

4. Experimental

4.1 General experimental procedures

All reagents were obtained from commercial suppliers (Aldrich, TCI, Alfa Aesar or Acros) and used without further purification, unless otherwise stated. Purification was carried out according to standard laboratory methods.[68]

- Dichloromethane, diethyl ether, hexane and toluene were obtained from an Innovative Technology, Pure Solv, SPS-400-5 solvent purification system.
- Tetrahydofuran was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen.
- DMA was distilled from CaH_2 at 86 ^oC, 75 mbar.
- TMSCl was distilled from CaH_2 under argon and was stored over 4Å molecular sieves under argon.
- DMPU was distilled from CaH_2 (0.03 mbar, 88 ^oC) and was stored over 4Å molecular sieves under argon.
- 15-Crown-6 and 18-crown-6 were dried by heating to 125 ^oC under high vacuum (0.005 mbar) using Kugelrohr apparatus for two hours, then were stored under argon over 4 Å molecular sieves.
- *N*,*N*,*N*',*N*'-Tetramethylethylenediamide (TMEDA) and *N*,*N*,*N*',*N*',*N*''-pentamethyldiethylenetriamine (PMDETA) were dried by distillation over sodium under reduced pressure, then purged with and stored under argon over 4 Å molecular sieves.
- 1,4-Diazabicyclo[2.2.0]octane (DABCO) was recrystallised from ethanol at 4^oC then placed under high vacuum for a minimum of 6 hours, then purged with and stored under nitrogen.
- $^nBu_2Mg$ was standardised using salicylaldehyde phenylhydrazone.[69]
- 4-*tert*-Butylcyclohexanone and 4-phenylcyclohexanone were purified by recrystallisation from hexane at 4 ^oC and dried by storing under vacuum (0.005 mbar) for 16 h.
- 4-*iso*-Propylcyclohexanone, 4-*n*-propylcyclohexanone, 4-methylcyclohexanone, 4-(*tert*-butyldimethylsiloxy)cyclohexanone and *cis*-2,6-dimethylcyclohexanone

were dried by distillation from calcium chloride, and were stored under argon over 4 Å molecular sieves.

Thin layer chromatography was carried out using Camlab silica plates, coated with fluorescent indicator UV_{254}, and analysed using a Mineralight UVGL-25 lamp.

Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

IR spectra were obtained on a Perkin Elmer Spectrum 1 machine.

^{1}H and ^{13}C spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise specified.

General procedure A – preparation of magnesium bisamides

$^{n}Bu_2Mg$ in heptane was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by the required amine, and the solution was heated at reflux, assuming quantitative formation of the magnesium bisamide.

General procedure B – preparation of alkylmagnesium amides

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under argon, was added LiCl (85 mg, 2 mmol). The Schlenk tube was then flame-dried under vacuum (0.005 mbar), taking care not to melt the LiCl, and allowed to cool to room temperature under argon. $^{n}Bu_2Mg$ in heptane was transferred to the Schlenk flask and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by the required amine, and the solution was stirred at room temperature for 1.5 h, assuming quantitative formation of the alkylmagnesium amide.

General procedure C – asymmetric deprotonation reactions using Mg bases

A solution of magnesium base in THF, prepared *via* General Procedure A or B, was cooled under argon to the appropriate temperature. The Schlenk flask was then charged with the required additives, followed by TMSCl, and the reaction mixture was stirred for 10 minutes at the temperature stated. The substrate was then added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction mixture was stirred at the temperature stated for the appropriate time before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (2 x 25 mL) gave a solution of the crude product which was analysed by GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave the crude product which was purified by column chromatography on silica gel using 1% Et_2O in PE 30-40 to give the product as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

4.2 Asymmetric deprotonations employing C_2-symmetric bases ((*R*,*R*)-98 and (*R*,*R*)-125)

4.2.1 Preparation of (*R*)-bis((*R*)-1-phenylethyl)amine ((*R*,*R*)-124)[55]

Scheme 1.49

(*R*)-1-Phenylethylamine (20.0 g, 165 mmol), acetophenone (19.8 g, 165 mmol) and titanium tetra-*iso*-propoxide (141.0 g, 500 mmol) were stirred for 30 minutes before addition of palladium (720 mg, 10% on carbon). The reaction mixture was then hydrogenated under H_2 (8 bar) with stirring for 48 h before being partitioned between H_2O (500 mL) and EtOAc (500 mL), and filtered through celite. The aqueous layer was extracted with EtOAc (3 x 300 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give an orange oil. The dr was determined as 87:13 by ^1H NMR analysis. The crude product was converted to its HCl salt and purified by recrystallisation from IPA. The diastereomerically pure free amine was then generated by dissolving the salt in 2M NaOH (500 mL), extracting with EtOAc (3 x 300 mL), drying over Na_2SO_4, and concentrating *in vacuo* to give 24.5 g (66%) of colourless oil. The amine was heated at 50 °C over CaH_2 *in vacuo* (0.4 mbar) for 4 h before being distilled *in vacuo* (98 °C, 0.4 mbar).

$[\alpha]_D^{20}$ = +171.6° (*c* = 6.71, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -171.6° ((*S*,*S*), *c* = 6.71, $CHCl_3$).[55]

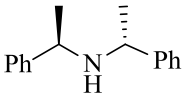
$\nu_{max}(CDCl_3)$: 2962 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.23 (m, 10H, ArH), 3.56 (q, J = 6.7 Hz, 2H, $N(CH)_2$), 1.33 (d, J = 6.7 Hz, 6H, $N(CHCH_3)_2$).

Peaks used to deduce dr of crude amine from ^1H NMR (400 MHz, $CDCl_3$):
δ 3.56 ((*R*,*R*), q, 1H, CH).
δ 3.82 ((*R*,*S*), q, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 128.5, 126.8, 126.7, 55.2, 25.1.

See appendix for X-ray crystallographic details of HCl salt.



(*R*,*R*)-**124**

4.2.2 Application of C_2-symmetric magnesium bisamide (*R*,*R*)-98

Scheme 1.50, Table 1.26

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^nBu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 °C, (c) none, (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 72%, (i) 87 mg, 48%, and (j) 90:10.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)- **124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (60 μL, 0.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 93%, (i) 132 mg, 73%, and (j) 93:7.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)- **124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 97%, (i) 159 mg, 88%, and (j) 94:6.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)- **124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (300 μL, 2.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 96%, (i) 137 mg, 76%, and (j) 92:8.

Scheme 1.51, Table 1.27

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) rt, (c) none, (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 75%, (i) 105 mg, 58%, and (j) 69:31.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) rt, (c) DMPU (60 μL, 0.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 78%, (i) 107 mg, 59%, and (j) 73:27.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) rt, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 89%, (i) 119 mg, 66%, and (j) 75:25.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) rt, (c) DMPU (300 μL, 2.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 94%, (i) 130 mg, 72%, and (j) 75:25.

Scheme 1.52, Table 1.28

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 1 h, (h) 80%, (i) 96 mg, 53%, and (j) 92:8.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 2 h, (h) 83%, (i) 110 mg, 61%, and (j) 93:7.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 4 h, (h) 80%, (i) 105 mg, 58%, and (j) 91:9.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 6 h, (h) 93%, (i) 139 mg, 77%, and (j) 92:8.

Scheme 1.53, Table 1.29

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 97%, (i) 159 mg, 88%, and (j) 94:6.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -60 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 93%, (i) 125 mg, 69%, and (j) 92:8.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -40 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 95%, (i) 134 mg, 74%, and (j) 90:10.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -20 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 97%, (i) 141 mg, 78%, and (j) 88:12.

Entry 5: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) 0 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 93%, (i) 119 mg, 66%, and (j) 86:14.

Entry 6: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) rt, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 89%, (i) 119 mg, 66%, and (j) 75:25.

Scheme 1.54, Table 1.30

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol) and LiCl (85 mg, 2 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 54%, (i) 54 mg, 30%, and (j) 91:9.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol) and DABCO (224 mg, 2 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 69%, (i) 85 mg, 47%, and (j) 95:5.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol) and TMEDA (301 μL, 2 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-

butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 75%, (i) 99 mg, 55%, and (j) 94:6.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol) and PMDTA (418 μL, 2 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 88%, (i) 123 mg, 68%, and (j) 91:9.

Entry 5: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol) and 15-crown-5 (397 μL, 2 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 83%, (i) 105 mg, 58%, and (j) 93:7.

Entry 6: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol) and 18-crown-6 (529 mg, 2 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 62%, (i) 83 mg, 46%, and (j) 91:9.

Entry 7: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DABCO (224 mg, 2 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 61%, (i) 61 mg, 34%, and (j) 93:7.

Scheme 1.55, Table 1.31

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -20 ^{o}C, (c) DMPU (120 μL, 1 mmol) and DABCO (224 mg, 2 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 95%, (i) 150 mg, 83%, and (j) 87:13.

Scheme 1.56, Table 1.32

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 97%, (i) 160 mg, 88%, and (j) 94:6.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.38 mL, 3 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 90%, (i) 114 mg, 63%, and (j) 92:8.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.26 mL, 2 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 92%, (i) 116 mg, 64%, and (j) 92:8.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 93%, (i) 119 mg, 66%, and (j) 93:7.

Scheme 1.57, Table 1.33

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 93%, (i) 119 mg, 66%, and (j) 93:7.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*iso*-propylcyclohexanone, (f) 123 μL, 0.8 mmol, (g) 16 h, (h) 96%, (i) 114 mg, 67%, and (j) 93:7.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*n*-propylcyclohexanone, (f) 123 μL, 0.8 mmol, (g) 16 h, (h) 92%, (i) 110 mg, 65%, and (j) 94:6.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-methylcyclohexanone, (f) 98 μL, 0.8 mmol, (g) 16 h, (h) 96%, (i) 102 mg, 69%, and (j) 95:5.

Entry 5: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**98**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**124**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-(*tert*-butyldimethylsilyloxy)cyclohexanone, (f) 183 μL, 0.8 mmol, (g) 16 h, (h) 91%, (i) 164 mg, 68%, and (j) 92:8 ($[\alpha]_D^{20}$ = –30.3 ^{o} (c = 0.3, $CHCl_3$); Lit: $[\alpha]_D^{25}$ = –28.8 ^{o} (er = 90:10 (*S*):(*R*), c = 0.3, $CHCl_3$)).[70]

Scheme 1.58, Table 1.34

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -20 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 93%, (i) 150 mg, 83%, and (j) 88:12.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -20 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*iso*-propylcyclohexanone, (f) 123 μL, 0.8 mmol, (g) 16 h, (h) 95%, (i) 119 mg, 70%, and (j) 87:13.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -20 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*n*-propylcyclohexanone, (f) 123 μL, 0.8 mmol, (g) 16 h, (h) 96%, (i) 116 mg, 68%, and (j) 89:11.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -20 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-methylcyclohexanone, (f) 98 μL, 0.8 mmol, (g) 16 h, (h) 96%, (i) 102 mg, 69%, and (j) 90:10.

Entry 5: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -20 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-(*tert*-butyldimethylsilyloxy)cyclohexanone, (f) 183 μL, 0.8 mmol, (g) 16 h, (h) 92%, (i) 168 mg, 70%, and (j) 87:13 ($[\alpha]_D^{20}$ = –26.5 ^{o} (c = 0.3, $CHCl_3$) ; Lit: $[\alpha]_D^{25}$ = –28.8 ^{o} (er = 90:10 (*S*):(*R*), c = 0.3, $CHCl_3$)).[70]

Scheme 1.59, Table 1.35

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**98**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 2,6-dimethylcyclohexanone, (f) 109 μL, 0.8 mmol, (g) 16 h, (h) 0%, (i) 0%, and (j) not applicable.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -40 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 2,6-dimethylcyclohexanone, (f) 109 μL, 0.8 mmol, (g) 16 h, (h) 55%, (i) 76 mg, 47%, and (j) 14:86.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.44 mL, 2 mmol. General procedure C: (a) (*R*,*R*)-**98**, (b) -20 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 2,6-dimethylcyclohexanone, (f) 109 μL, 0.8 mmol, (g) 16 h, (h) 99%, (i) 81 mg, 51%, and (j) 15:85.

4.2.3 Application of C_2-symmetric alkylmagnesium amide (*R*,*R*)-125

Scheme 1.60, Table 1.36

Following general procedure B for the preparation of magnesium base (*R*,*R*)-**125**, data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure B: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.22 mL, 1 mmol. General procedure C: (a) (*R*,*R*)-**125**, (b) -20 ^{o}C, (c) 18-c-6 (264 mg, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 1 h, (h) 95%, (i) 150 mg, 83%, and (j) 82:18.

Entry 2: General procedure B: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.22 mL, 1 mmol. General procedure C: (a) (*R*,*R*)-**125**, (b) -20 ^{o}C, (c) 18-c-6 (264 mg, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*iso*-propylcyclohexanone, (f) 123 μL, 0.8 mmol, (g) 1 h, (h) 95%, (i) 137 mg, 81%, and (j) 81:19.

Entry 3: General procedure B: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.22 mL, 1 mmol. General procedure C: (a) (*R*,*R*)-**125**, (b) -20 ^{o}C, (c) 18-c-6 (264 mg, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*n*-propylcyclohexanone, (f) 123 μL, 0.8 mmol, (g) 1 h, (h) 93%, (i) 127 mg, 75%, and (j) 83:17.

Entry 4: General procedure B: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.22 mL, 1 mmol. General procedure C: (a) (*R*,*R*)-**125**, (b) -20 ^{o}C, (c) 18-c-6 (264 mg, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-methylcyclohexanone, (f) 98 μL, 0.8 mmol, (g) 1 h, (h) 93%, (i) 118 mg, 80%, and (j) 85:15.

Entry 5: General procedure B: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**124**, and (c) 0.22 mL, 1 mmol. General procedure C: (a) (*R*,*R*)-**125**, (b) -20 ^{o}C, (c) 18-c-6 (264 mg, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-phenylcyclohexanone, (f) 139 mg, 0.8 mmol, (g) 1 h, (h) not available, (i) 161 mg, 82%, and (j) 90:10.

4.2.4 Crystallisation attempts

Scheme 1.61, Table 1.37

Entry 1

To a Schlenk flask, which had previously been flame-dried under vacuum and allowed to cool under argon, was added *n*-Bu_2Mg (1 M, 1 mL, 1 mmol). The heptane solvent was then removed under vacuum, and THF (2 mL) and the chiral amine ((*R*,*R*)-**124**, 0.44 mL, 2 mmol) were added. The reaction mixture was then refluxed for 1.5 h, after which time the oil bath was turned off and the solution was allowed to cool slowly to room temperature overnight. After this time, no crystals had formed so the Schlenk flask was stored at -20 ^{o}C for 3 days. Since no crystal formation had occurred after this time, 4 mL of hexane was added dropwise. However, this resulted in the precipitation of a powdery solid and did not deliver any crystalline material.

Entry 2

To a Schlenk flask, which had previously been flame-dried under vacuum and allowed to cool under argon, was added *n*-Bu_2Mg (1 M, 1 mL, 1 mmol). The heptane solvent was then removed under vacuum, and hexane (2 mL) and the chiral amine ((*R*,*R*)-**124**, 0.44 mL, 2 mmol) were added. The reaction mixture was then refluxed for 1.5 h, after which time the oil bath was turned off and the solution was allowed to cool slowly to room temperature overnight. After this time, no crystals had formed so the Schlenk flask was stored at -20 ^{o}C for 24 h. This resulted in the precipitation of a significant quantity of amorphous solid. More hexane (2 mL) was added and the mixture was heated gently until all of the solid dissolved. The resulting solution was allowed to cool slowly to room temperature and was then stored at -20 ^{o}C for 24 hours. An amorphous solid was obtained and no crystalline material was formed using this method.

Entry 3

To a Schlenk flask, which had previously been flame-dried under vacuum and allowed to cool under argon, was added *n*-Bu_2Mg (1 M, 1 mL, 1 mmol). The heptane solvent was then removed under vacuum, and toluene (2 mL) and the chiral amine ((*R*,*R*)-**124**, 0.44 mL, 2 mmol) were added. The reaction mixture was then refluxed

for 1.5 h, after which time the oil bath was turned off and the solution was allowed to cool slowly to room temperature overnight. After this time, no crystals had formed so the Schlenk flask was stored at -20 ^{o}C for 24 h, resulting in precipitation of a solid with a crystalline appearance. However, the crystal structure could not be obtained using single crystal X-ray diffraction.

4.3 Synthesis of alternative C_2- and *pseudo*-C_2-symmetric amines

Preparation of (*S*,*S*)-bis(1-phenylpropyl)amine ((*S*,*S*)-128)[54]

Scheme 1.62

A mixture of (*S*)-phenylpropylamine (10.0 mL, 68.8 mmol), propiophenone (**127**, 9.15 mL, 68.8 mmol) and titanium (IV) isopropoxide (40.9 mL, 137 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (313 mg, 0.3 mmol), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing complete conversion by ^{1}H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (100 mL), followed by extraction with ethyl acetate (3 x 200 mL). The combined organics were filtered through celite, dried (Na_2SO_4), and concentrated *in vacuo* to leave a pale yellow oil. From the crude ^{1}H NMR, the (*S*,*S*)/(*S*,*R*) ratio was deduced to be 8:1. The oil was dissolved in Et_2O (100 mL) and concentrated HCl (10 mL) was added. Removal of the solvent *in vacuo* revealed a white solid which was isolated by filtration and washed with cold Et_2O (10 mL). To the filtrate was added more concentrated HCl to yield more solid. This procedure was repeated until no more solid precipitated from the diethyl ether solution. The combined solids were recrystallised from MeOH, ensuring isolation of the desired diastereoisomer. The diastereomerically pure salt was subsequently dissolved in DCM (300 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organics were dried (Na_2SO_4), and the solvent was removed *in vacuo* to give the product as a colourless oil (8.19 g, 47%). The product was dried by heating to 100 ^{o}C under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, and stored over 4Å molecular sieves under a nitrogen atmosphere.

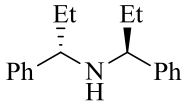
$[\alpha]_D^{20}$ = +160.5 ^{o} (c = 13.5, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = +159.0 ^{o} (c = 13.5, $CHCl_3$).[54]

ν_{max}(DCM): 2981 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.24 (m, 10H, ArH), 3.26 (t, *J* = 7.0 Hz, 2H, CH), 1.80-1.53 (m, 5H, CH_2 and NH), 0.83 (t, *J* = 7.4 Hz, 6H, CH_3).

Peaks used to deduce dr of crude amine from ^{1}H NMR (400 MHz, $CDCl_3$):
δ 3.26 ((*S*,*S*), t, 2H, CH).
δ 3.82 ((*S*,*R*), t, 2H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 128.3, 127.5, 126.8, 61.5, 31.6, 11.0.



(*S*,*S*)-**128**

Preparation of (*R*)-1-phenyl-*N*-((*R*)-1-phenylethyl)propan-1-amine ((*R*,*R*)-129)[72]

Scheme 1.63, Table 1.38, entry 1

A mixture of (*R*)-1-phenylethylamine (12.0 mL, 93.9 mmol), propiophenone (12.5 mL, 93.9 mmol) and titanium (IV) isopropoxide (55.9 mL, 188 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (427 mg, 0.4 mmol), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing complete conversion by ^{1}H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (2 x 300 mL). The combined organics were filtered through celite, dried (Na_2SO_4), and concentrated *in vacuo* to leave a pale yellow oil. From the crude ^{1}H NMR, the (*R*,*R*)/(*R*,*S*) ratio was deduced to be 5:1. The oil was dissolved in Et_2O (100 mL) and TFA (16 g) was added. Removal of the solvent *in vacuo* revealed a white solid which was isolated by filtration and washed with cold diethyl ether (10 mL). To the filtrate was added more TFA (5 g) to yield more solid. This procedure was repeated until no more solid precipitated from the diethyl ether solution. The combined solids were recrystallised from MeOH to give the desired (*R*,*R*)-diastereoisomer only. The

diastereomerically pure salt was subsequently dissolved in DCM (400 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to leave the desired product as a colourless oil (9.21 g, 41%). The product was dried by heating to 100 ^oC under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, and stored over 4Å molecular sieves under a nitrogen atmosphere.

$[\alpha]_D^{20}$ = +300.9 ^{o} (c = 1.5, $CHCl_3$). No literature data are available for comparison.

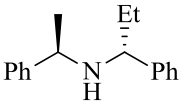
ν_{max}(DCM): 2982 cm^{-1}.

HRMS (ESI) m/z calculated for $C_{17}H_{22}N[M+H]$: 240.1747. Found: 240.1746.

^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.21 (m, 10H, ArH), 3.54 (q, *J* = 6.7 Hz, 1H, C*H*CH_3), 3.26 (t, *J* = 7.0 Hz, 1H, C*H*CH_2), 1.74-1.56 (m, 3H, C*H*$_2CH_3$ and NH), 1.30 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 0.80 (t, *J* = 7.4 Hz, 3H, CH_2C*H*$_3$).

Peaks used to deduce dr of crude amine from ^1H NMR (400 MHz, $CDCl_3$):
δ 1.30 ((*R*,*R*), d, 3H, CH_3).
δ 1.38 ((*R*,*S*), d, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 144.6, 128.4, 128.3, 127.4, 126.8, 61.8, 55.0, 31.5, 25.2, 11.0.



(*R*,*R*)-**129**

Preparation of (*R*)-2-methyl-1-phenyl-*N*-((*R*)-1-phenylethyl)propan-1-amine ((*R*,*R*)-130)

Scheme 1.63, Table 1.38, entry 2

A mixture of (*R*)-1-phenylethylamine (12.0 mL, 93.9 mmol), isobutyrophenone (14.1 mL, 93.9 mmol) and titanium (IV) isopropoxide (27.9 mL, 93.9 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (427 mg, 0.4 mmol), and the mixture hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing complete conversion by ^{1}H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (2 x 300 mL). The combined organics were filtered through celite, dried (Na_2SO_4), and concentrated *in vacuo* to leave a pale yellow oil. From the crude ^{1}H NMR, the (*R*,*R*)/(*R*,*S*) ratio was deduced to be 1:1. The oil was dissolved in MeOH, TFA (16 g) was added and the resulting salt was crystallised by cooling of the solution to 5 ^{o}C for 3 days, giving the desired (*R*,*R*) diastereoisomer. The combined diastereomerically pure salts were subsequently dissolved in DCM (400 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to leave the desired product as a colourless oil (1.48 g, 6%). The product was dried by heating to 100 ^{o}C under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, and stored over 4Å molecular sieves under a nitrogen atmosphere.

$[\alpha]_D^{20}$ = +175.4 ^{o} (c = 1.5, $CHCl_3$). No literature data are available for comparison.

ν_{max}(DCM): 2962 cm^{-1}.

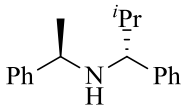
HRMS (ESI) m/z calculated for $C_{18}H_{24}N$: 254.1903. Found: 254.1904.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.13 (m, 10H, ArH), 3.44 (q, *J* = 6.7 Hz, 1H, C*H*CH_3), 2.98 (d, *J* = 7.6 Hz, 1H, C*H*$CH(CH_3)_2$) 1.79 (octet, *J* = 6.8 Hz, 1H, C*H*$(CH_3)_2$), 1.63 (brs, 1H, NH), 1.26 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 0.98 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3)_2$), 0.65 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3)_2$).

Peaks used to deduce dr of crude HCl salt from ^{1}H NMR (400 MHz, $CDCl_3$):
δ 1.68 ((*R*,*R*), d, 3H, CH_3).
δ 1.62 ((*R*,*S*), d, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 143.7, 128.4, 128.1, 127.9, 126.9, 126.7, 126.7, 66.3, 55.0, 34.6, 25.4, 19.9, 19.7.

See appendix for X-ray crystallographic details of the trifluoroacetate salt.



(*R*,*R*)-**130**

Attempted preparation of (*S*)-2,2-dimethyl-1-phenyl-*N*-((*R*)-1-phenylethyl)propan-1-amine ((*S*,*R*)-132)

Scheme 1.64

A mixture of (*R*)-1-phenylethylamine (3.7 g, 30 mmol), 2,2,2-trimethylacetophenone (5.0 g, 30 mmol), and titanium tetra-*iso*-propoxide (26.3 g, 90 mmol) was stirred for 20 minutes at rt before the addition of 10% Pd/C (133 mg, 0.12 mmol). The reaction mixture was then placed under 3 bar of hydrogen and was stirred at room temperature for 3 days. After this time, a sample was taken and was treated with aqueous NaOH (2 M, 50 mL) to cause a precipitate to form. After filtration, the filter cake was washed with EtOAc (300 mL) until no more product could be extracted. The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated. ^{1}H NMR analysis showed only the starting materials and minor impurities.

Preparation of (*R*)-*N*-(2,2-dimethyl-1-phenylpropylidene)-1-phenylethanamine ((*R*)-133)

Scheme 1.65, Table 1.39

Entry 1

(*R*)-1-Phenylethylamine (2.4 g, 20 mmol), 2,2,2-trimethylacetophenone (3.3 g, 20 mmol) and TFA (12 mg, 0.1 mmol) were refluxed in toluene (25 mL) using a Dean-Stark trap for removal of H_2O. After 48 h, the reaction mixture was washed with H_2O (20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a clear oil, which was purified by column chromatography on silica gel (2-5% Et_2O in PE (30-40 °C)) to afford the desired product as a colourless oil (2.6 g, 49%).

Entry 2

(*R*)-1-Phenylethylamine (3.7 g, 30 mmol), 2,2,2-trimethylacetophenone (5.0 g, 30 mmol) and TFA (36 mg, 0.3 mmol) were refluxed in toluene (40 mL) using a Dean-Stark trap for removal of H_2O. After 48 h, the reaction mixture was washed with H_2O (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a clear oil, which was purified by column chromatography on silica gel (2-5% Et_2O in PE (30-40 °C)) to afford the desired product as a colourless oil (4.0 g, 49%).

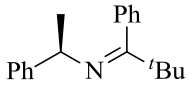
$[\alpha]_D^{20}$ = +93.7 ° (c = 1, $CHCl_3$). No literature data are available for comparison.

$\nu_{max}(CDCl_3)$: 1674 cm^{-1}.

HRMS (ESI) m/z calculated for $C_{19}H_{24}N[M+H]$: 266.1903. Found: 266.1900.

^1H NMR (400 MHz, $CDCl_3$): δ 7.46-7.10 (m, 8H, ArH), 7.09 (m, 1H ArH), 6.84 (m, 1H, ArH), 4.14 (q, *J* = 6.5 Hz, 1H, C*H*CH_3), 1.32 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$), 1.21 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 146.8, 138.7, 137.9, 137.8, 130.8, 128.2, 128.1, 127.9, 127.9, 127.3, 126.6, 126.3, 60.5, 40.0, 28.6, 25.2.



(*R*)-**133**

Preparation of (*S*)-2,2-dimethyl-1-phenyl-*N*-((*R*)-1-phenylethyl)propan-1-amine ((*S*,*R*)-132)

Scheme 1.66, Table 1.40

Entry 1

A solution of (*R*)-*N*-(2,2-dimethyl-1-phenylpropylidene)-1-phenylethanamine (1.0 g, 3.8 mmol) and $NaBH_4$ (140 mg, 3.8 mmol) in EtOH (10 mL) was stirred for 3 h at 0 °C. More $NaBH_4$ (140 mg, 3.8 mmol) was added and the reaction mixture was stirred at 0 ^oC for 1 h before being allowed to warm to room temperature, stirred for 16 h, and partitioned between EtOAc (10 mL) and H_2O (10 mL). The aqueous was extracted with EtOAc (3 x 10 mL), and the extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* before being purified by column chromatography on silica gel (10% Et_2O in PE (30-40 °C)) to give the product as a white powder (800 mg, 79%). Analysis by ^1H NMR showed that only one diastereomer had been formed.

Entry 2

A solution of (*R*)-*N*-(2,2-dimethyl-1-phenylpropylidene)-1-phenylethanamine (5.0 g, 20 mmol) and $NaBH_4$ (1.4 g, 40 mmol) in EtOH (50 mL) was stirred for 2 h at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 16 h before being partitioned between EtOAc (50 mL) and H_2O (50 mL). The aqueous was extracted with EtOAc (3 x 50 mL), and the extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* before being purified by column chromatography on silica gel (10% Et_2O in PE (30-40 °C)) to give the product as a white powder (2.8 g, 56%). Analysis by ^1H NMR showed that only one diastereomer had been formed. The amine was dried in vacuo (0.005 mbar) overnight before being used in asymmetric deprotonation reactions.

$[\alpha]_D$ = +40.4 ° (c = 1, $CHCl_3$). No literature data are available for comparison.

Melting point = 57-59 °C. No literature data are available for comparison.

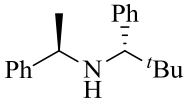
$\nu_{max}(CDCl_3)$: 2967 cm^{-1}.

HRMS (ESI) m/z calculated for $C_{19}H_{26}N[M+H]$: 268.2060. Found: 268.2056.

^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 10H, ArH), 3.59-3.54 (m, 2H, $(CH)_2NH$), 1.34 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 0.99 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 140.7, 127.9, 127.1, 126.4, 125.64, 125.56, 125.5, 68.2, 53.4, 33.9, 26.2, 20.4.

See appendix for X-ray crystallographic details.



(*S*,*R*)-**132**

Preparation of (*R*)-1-cyclohexyl-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-135)[73]

Scheme 1.67

A mixture of (*R*)-1-phenylethylamine (12.5 mL, 100 mmol), cyclohexyl methyl ketone (13.8 mL, 100 mmol) and titanium (IV) isopropoxide (59.8 mL, 200 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (455 mg, 0.4 mmol), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing complete conversion by ^1H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (3 x 300 mL). The combined organics were filtered through celite, dried over Na_2SO_4, and the solvent was removed *in vacuo* to leave a yellow oil. The oil was dissolved in a 1:1 mixture of MeOH: ethyl acetate, and concentrated HCl (14 mL) was added. Slow evaporation of the solvent revealed a white solid. The crude

solid was isolated by filtration and washed with cold Et_2O (10 mL). From the crude ^1H NMR of the HCl salt, the (*R*,*R*)/(*R*,*S*) ratio was deduced to be 2.5:1. The solvent was removed from the filtrate *in vacuo* to reveal a yellow oil which was subjected to salt formation as before. This procedure was repeated until no more solid precipitated from the MeOH/ethyl acetate solution. The combined solids were recrystallised from MeOH to give the desired (*R*,*R*)-diastereoisomer. The diastereomerically pure salt was subsequently dissolved in DCM (400 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (400 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organics were dried (Na_2SO_4), and the solvent was removed *in vacuo* to leave the desired product as a colourless oil (0.44g, 45%). The product was dried by heating to 100 ^oC under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, and stored over 4Å molecular sieves under a nitrogen atmosphere.

$[\alpha]_D^{20}$ = +167.2 ^{o} (c = 1.5, $CHCl_3$). No literature data are available for comparison.

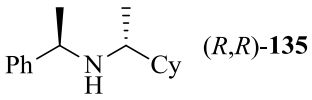
ν_{max}(KBr disc): 2924 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 4H, ArH), 7.26-7.21 (m, 1H, ArH), 3.87 (q, *J* = 6.6 Hz, 1H, C*H*CH_3), 2.41 (pentet, *J* = 6.5 Hz, 1H, C*H*Cy), 1.83-1.65 (m, 4H, aliphatic ring protons and NH), 1.64-1.51 (m, 1H, aliphatic ring protons), 1.45-1.34 (m, 1H, aliphatic ring protons), 1.31 (d, *J* = 6.6 Hz, 3H, CH_3), 1.30-1.12 (m, 3H, aliphatic ring protons), 1.11-0.93 (m, 3H, aliphatic ring protons), 0.89 (d, *J* = 6.6 Hz, 3H, CH_3),

Peaks used to deduce dr of crude HCl salt from ^1H NMR (400 MHz, $CDCl_3$):
δ 3.94 ((*R*,*R*), q, 1H, CH).
δ 4.02 ((*R*,*S*), q, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 128.3, 126.6, 126.6, 55.5, 54.8, 42.9, 30.3, 27.4, 26.9, 26.8, 26.7, 24.6, 17.6.

See appendix for X-ray crystallographic details of the HCl salt.



(*R*,*R*)-**135**

Attempted preparation of (*R*)-4-phenyl-*N*-((*R*)-1-phenylethyl)butan-2-amine ((*R*,*R*)-137)

Scheme 1.68

A mixture of (*R*)-1-phenylethylamine (6.39 mL, 50 mmol), 4-phenyl-3-butene-2-one (7.31 mL, 50 mmol) and titanium (IV) isopropoxide (30.3 mL, 100 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (455 mg, 0.4 mmol), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 48 h, revealing complete conversion of the starting materials by ^{1}H NMR analysis. The reaction mixture was then treated with an aqueous solution of 1 M sodium hydroxide (100 mL), followed by extraction with ethyl acetate (3 x 200 mL). The combined organics were filtered through celite, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to leave a yellow oil. Analysis by ^{1}H NMR revealed a complex mixture of products, although from the crude ^{1}H NMR of the HCl salt, the (*R*,*R*)/(*R*,*S*) ratio could be deduced to be 2.5:1. Attempted formation of the crystalline TFA or HCl salts failed under a variety of conditions. Additionally, purification of the free amine was attempted by column chromatography without success. Accordingly, this preparative procedure was halted.

Attempted preparation of (*R*)-3,3-dimethyl-*N*-((*R*)-1-phenylethyl)butan-2-amine ((*R*,*R*)-139)

Scheme 1.69

A mixture of (*R*)-1-phenylethylamine (1.27 mL, 10 mmol), 3,3-dimethylbutan-2-one (1.25 mL, 10 mmol) and titanium (IV) isopropoxide (8.88 mL, 30 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (53 mg, 0.05 mmol), and the mixture was hydrogenated under 3 bar of

hydrogen with shaking. A small aliquot was removed after 24 h, revealing that no conversion of the starting materials had occurred.

Preparation of (*R*)-1-phenyl-*N*-((*R*)-1-*o*-tolylethyl)ethanamine (*R*,*R*)-141[74]

Scheme 1.70

A mixture of (*R*)-1-phenylethylamine (12.5 mL, 100 mmol), 2-methylacetophenone (13.2 mL, 100 mmol) and titanium (IV) isopropoxide (74.4 mL, 250 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (455 mg, 0.4 mmol), and the mixture was hydrogenated under 1 bar of hydrogen with stirring. After 14 days, the reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (3 x 300 mL). The combined organics were filtered through celite, dried over Na_2SO_4, and the solvent removed *in vacuo* to leave a yellow oil. From the crude ^{1}H NMR, the (*R*,*R*)/(*R*,*S*) ratio was deduced to be 6:1. The oil was dissolved in 30-40 PE (10 mL), and TFA (17 g) was added, resulting in the precipitation of a white solid. The crude solid was isolated by filtration and was recrystallised from MeOH to give the desired (*R*,*R*)-diastereoisomer. The diastereomerically pure salt was subsequently dissolved in DCM (300 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organics were dried (Na_2SO_4), and the solvent was removed *in vacuo* to leave the desired product as a colourless oil (7.72 g, 30%). The product was dried by heating to 100 ^{o}C under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, and stored over 4Å molecular sieves under a nitrogen atmosphere.

$[\alpha]_D^{20}$ = +141.4 ^{o} (c = 1.24, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -129.1 ^{o} (*S*,*S*) (c = 1.24, $CHCl_3$).[74]

ν_{max}(KBr disc): 2962 cm^{-1}.

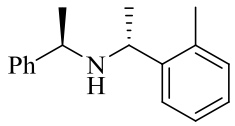
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 7.0 Hz, 1H, ArH), 7.34-7.21 (m, 4H, ArH), 7.19-7.14 (m, 4H, ArH), 3.78 (q, *J* = 6.6 Hz, 1H, C*H*CH_3), 3.51 (q, *J* = 6.6 Hz, 1H, C*H*CH_3), 1.97 (s, 3H, ArCH_3), 1.61 (s, 1H, NH), 1.31 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 1.21 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$).

Peaks used to deduce dr of crude amine from ^{1}H NMR (400 MHz, $CDCl_3$):

δ 3.51 ((*R*,*R*), q, 1H, CH).

δ 4.02 ((*R*,*S*), q, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 143.7, 135.6, 130.4, 126.8, 126.7, 126.8, 126.4, 126.3, 125.1, 55.2, 50.4, 24.9, 24.1, 18.9.



(*R*,*R*)-**141**

Preparation of *N*-methyoxy-*N*-methylacetamide (144)[75]

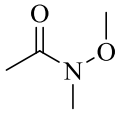
Scheme 1.71

To a solution of acetyl chloride (21.3 mL, 300 mmol) in DCM (200 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (32.2 g, 330 mmol). The solution was left to stir at 0 ^{o}C for 20 minutes before addition of Et_3N (41.8 mL, 300 mmol) dropwise over 10 minutes. A further 200 mL of DCM was added, before addition of pyridine (24.3 mL, 300 mmol) dropwise over 5 minutes. The suspension was left to warm to room temperature with stirring. After 18 h, the suspension was filtered, the filtrate was cooled to 0 ^{o}C, and an aqueous solution of 1M HCl (200 mL) was added slowly. The solution was extracted with DCM (3 x 100 mL), washed with H_2O (100 mL), dried over Na_2SO_4, and filtered to leave a yellow oil. The crude product was then purified by column chromatography (1:1 PE 30-40:Et_2O), followed by Kugelrohr distillation (60 ^{o}C, 30 mbar) to yield the product as a colourless liquid (23.8 g, 77%).

ν_{max} (KBr disc): 1668 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 3H, OCH_3), 3.18 (s, 3H, NCH_3), 2.13 (s, 3H, $COCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 61.0, 31.9, 19.8.



144

Preparation of 2-ethylacetophenone (146)[76]

Scheme 1.72

To a solution of 2-ethylbromobenzene (3.19 mL, 18.9 mmol) in dry Et_2O at -78 ^oC was added *t*-butyllithium (1.7 M, 22.2 mL, 37.8 mmol) over 10 minutes. The solution was stirred at -78 ^oC for 30 minutes before addition of *N*-methyoxy-*N*-methylacetamide (2.38 g, 23.1 mmol). The reaction mixture was left to stir at -78 ^oC for a further hour. A saturated aqueous solution of NH_4Cl (100 mL) was added, the solution was extracted with Et_2O (3 x 30 mL), and the combined organics were dried over Na_2SO_4. The organic layer was filtered, and the solvent removed *in vacuo* to leave a yellow oil. The crude product was then purified by column chromatography (4:1 PE 30-40:Et_2O) to yield the product as a colourless liquid (0.78 g, 28%).

Scheme 1.73, Table 1.41

Entry 1

To a solution of 2-ethylbromobenzene (3.19 mL, 18.9 mmol) in dry Et_2O at -78 ^oC was added *n*-butyllithium (2.5 M, 8.3 mL, 20.79 mmol) over 10 minutes. The solution was allowed to warm slowly to rt, and left to stir for 2 h. The reaction mixture was recooled to -78 ^oC, *N*-methyoxy-*N*-methylacetamide (2.38 g, 23.1 mmol) was added and the solution was left to stir at -78 ^oC for a further 4 h. A saturated aqueous solution of NH_4Cl (100 mL) was added, the solution was extracted with Et_2O (3 x 30 mL), and the combined organics were dried over Na_2SO_4. The organic layer was filtered, and the solvent removed *in vacuo* to leave a yellow oil. The crude product was then purified by column chromatography (4:1 PE 30-40:Et_2O) to yield the product as a colourless liquid (0.55 g, 16%).

Entry 2

To a solution of *n*-butyllithium (2.5 M, 4.56 mL, 11.4 mmol) in dry Et_2O (40 mL) cooled to -20 ^oC was added 2-ethylbromobenzene (1.50 mL, 10.8 mmol) slowly over

10 minutes. The solution was allowed to stir and warm to 5 ^{o}C over 45 minutes. The solution was recooled to -78 ^{o}C and *N*-methyoxy-*N*-methylacetamide (1.12 g, 10.8 mmol) was added over 5 minutes. The solution was allowed to stir and warm to rt over 4 h. The solution was cooled to 0 ^{o}C and a saturated aqueous solution of NH_4Cl (70 mL) was added. The solution was extracted with Et_2O (3 x 30 mL), and the combined organics were dried over Na_2SO_4. The organic layer was filtered and the solvent was removed *in vacuo* to leave a yellow oil. The crude product was then purified by column chromatography (4:1 PE 30-40/Et_2O) to yield the product as a colourless liquid (0.38 g, 24%).

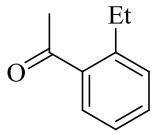
Entry 3

To a solution of 2-ethylbromobenzene (4.50 mL, 32.5 mmol) in dry Et_2O cooled to -78 ^{o}C was added *n*-butyllithium (2.5 M, 14.3 mL, 35.8 mmol) over 10 minutes. The solution was allowed to warm slowly to rt and was left to stir for 18 h. The solution was recooled to -78 ^{o}C and *N*-methyoxy-*N*-methylacetamide (5.03 g, 48.8 mmol) was added. The solution was again allowed to warm slowly rt and was left to stir for a further 4 h. The reaction mixture was cooled to 0 ^{o}C and a saturated aqueous solution of NH_4Cl (100 mL) was added. The mixture was extracted with Et_2O (3 x 30 mL), and the combined organics were dried over Na_2SO_4. The organic layer was filtered and the solvent was removed *in vacuo* to leave a yellow oil. The crude product was then purified by column chromatography (4:1 PE 30-40/Et_2O) to yield the product as a colourless liquid (1.68 g, 35%).

ν_{max}(KBr disc): 1687 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 7.7 and 1.2 Hz, 1H, ArH), 7.41 (td, *J* = 7.6 and 1.4 Hz, 1H, ArH), 7.31-7.24 (m, 2H, ArH), 2.88 (q, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_3$), 2.59 (s, 3H, CH_3), 1.23 (t, *J* = 7.5 Hz, 3H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 144.3, 138.0, 131.5, 130.5, 129.0, 125.7, 30.0, 27.1, 16.0.



146

Attempted preparation of (*R*)-1-(2-ethylphenyl)-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-148)

Scheme 1.74

A mixture of (*R*)-1-phenylethylamine (2.97 mL, 23.3 mmol), 2-ethylacetophenone (3.45 g, 23.3 mmol) and titanium (IV) isopropoxide (30.3 mL, 100 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (106 mg, 0.1 mmol), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing incomplete conversion by ^{1}H NMR analysis. The reaction was therefore placed under 3 bar of hydrogen for a further 48 h. The reaction mixture was then treated with an aqueous solution of 1 M sodium hydroxide (~20 mL), followed by extraction with ethyl acetate (3 x 100 mL). The combined organics were filtered through celite, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to leave a yellow oil. Analysis by ^{1}H NMR revealed a complex mixture of products, which included both the amine and ketone starting materials. Attempted salting of the crude oil with both TFA and concentrated HCl failed under various conditions. An orange oil, rather than the desired solid salt, was obtained on each occasion so these preparative attempts were halted.

Attempted preparation of (*R*)-1-mesityl-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-150)

Scheme 1.75

A mixture of (*R*)-1-phenylethylamine (7.1 g, 59 mmol), 2',4',6'-trimethylacetophenone (9.5 g, 59 mmol), and titanium tetra-*iso*-propoxide (49.9 g, 176 mmol) was stirred for 20 minutes at rt before the addition of 10% Pd/C (256 mg, 0.2 mmol). The reaction mixture was then placed under 3 bar of hydrogen and was

stirred at room temperature for 2 days. ^{1}H NMR analysis showed that no reaction had occurred.

Scheme 1.76

A mixture of (*R*)-1-phenylethylamine (7.1 g, 59 mmol), 2',4',6'-trimethylacetophenone (9.5 g, 59 mmol), titanium tetra-*iso*-propoxide (49.9 g, 176 mmol), and 10% Pd/C (256 mg, 0.2 mmol) was placed under 90 bar of hydrogen and was stirred at 80 ^{o}C for 24 h (after this time, the pressure in the reactor had dropped to 20 bar). ^{1}H NMR analysis showed that decomposition of the reaction mixture had occurred.

Attempted preparation of (*R*,*E*)-*N*-(1-mesitylethylidene)-1-phenylethanamine ((*R*)-151)

Scheme 1.77

A solution of (*R*)-1-phenylethylamine (7.27 g, 60 mmol), 2',4',6'-trimethylacetophenone (9.75 g, 60 mmol), and TFA (50 mg, 0.4 mmol) in toluene (100 mL) was refluxed using a Dean-Stark trap for 24 h. Analysis by TLC showed that no reaction had occurred.

Preparation of (*R*,*E*)-1-phenyl-*N*-(2,4,6-trimethylbenzylidene)ethanamine ((*R*)-153)

Scheme 1.78

A solution of (*R*)-1-phenylethylamine (1.21 g, 10 mmol), mesitaldehyde (1.48 g, 10 mmol), and $MgSO_4$ (2.04 g, 17 mmol) in THF was stirred at rt for 3 days. After this time, the reaction mixture was filtered and concentrated *in vacuo* to give the product as a colourless oil (2.51 g, 100%).

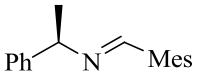
$[\alpha]_D^{20}$ = -18.7 ° (c =1, $CHCl_3$). No literature data are available for comparison.

$\nu_{max}(CDCl_3)$: 1638 cm^{-1}.

HRMS (ESI) m/z calculated for $C_{18}H_{22}N[M+H]$: 252.1747. Found: 252.1743.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H, HC=N), 7.53 (d, *J* = 7.3 Hz, 2H, ArH), 7.41 (t, *J* = 7.4, 2H, ArH), 7.34-7.29 (m, 1H, ArH), 6.92 (s, 2H, ArH), 4.57 (q, *J* = 6.6 Hz, 1H, NC*H*CH_3), 2.46 (s, 6H, $ArCH_3$), 2.34 (s, 3H, $ArCH_3$), 1.67 (d, *J* = 6.6 Hz, 3H, NCHC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 145.6, 138.7, 137.5, 131.3, 129.4, 128.5, 126.8, 126.7, 71.5, 25.8, 21.2, 20.7.



(*R*)-**153**

Attempted preparation of (*R*)-1-mesityl-*N*-((*R*)-1-phenylethyl)ethanamine ((*R,R*)-150)

Scheme 1.79

A solution of CuI (381 mg, 2 mmol) in THF (8 mL) was cooled to -40 ^{o}C. MeMgCl (3 M, 1.3 mL, 4 mmol) in THF (3 mL) was added dropwise and the reaction mixture was stirred at -40 ^{o}C for 20 minutes before being cooled to -78 ^{o}C. $BF_3.Et_2O$ (284 mg, 2 mmol) was then added and the mixture was stirred at -78 ^{o}C for 5 minutes before addition of (*R,E*)-1-phenyl-*N*-(2,4,6-trimethylbenzylidene)ethanamine (251 mg, 1 mmol) in THF (0.8 mL). The temperature was then raised to -40 ^{o}C and the reaction mixture was stirred for 3 h, slowly warming to -30 ^{o}C. After this time, a mixture of NH_4Cl/NH_4OH (1:1, 10 mL) was added. The reaction mixture was then extracted with Et_2O (2 x 10 mL), and the Et_2O extracts were washed with brine, dried over $NaSO_4$, and concentrated *in vacuo* to give 240 mg of colourless oil. ^{1}H NMR showed starting material only.

Attempted preparation of (*R*)-1-mesityl-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-150)

Scheme 1.80, Table 1.42

Entry 1

To a solution of MeLi (1.6 M, 0.81 mL, 1.3 mmol) in THF (0.75 mL) at -78 ^{o}C was added (*R*,*E*)-1-phenyl-*N*-(2,4,6-trimethylbenzylidene)ethanamine (251 mg, 1 mmol) in THF (0.75 mL). The reaction mixture was stirred at -78 ^{o}C for 1 h before being quenched with water (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL), and the Et_2O extracts were dried over $NaSO_4$, and concentrated *in vacuo* to give 284 mg of colourless oil. ^{1}H NMR showed starting material only.

Entry 2

To a solution of MeLi (1.6 M, 0.81 mL, 1.3 mmol) in THF (0.75 mL) at -70 ^{o}C was added (*R*,*E*)-1-phenyl-*N*-(2,4,6-trimethylbenzylidene)ethanamine (251 mg, 1 mmol) in THF (0.75 mL). The reaction mixture was allowed to warm slowly to -30 ^{o}C over 3 h before being quenched with water (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL), and the Et_2O extracts were dried over $NaSO_4$, and concentrated *in vacuo* to give 284 mg of colourless oil. ^{1}H NMR showed starting material only.

Preparation of (*S*,*E*)-*N*-benzylidene-1-mesitylethanamine ((*S*)-156)

Scheme 1.81

A solution of (*S*)-1-mesitylethanamine (163 mg, 1 mmol), benzaldehyde (106 mg, 1 mmol), and $MgSO_4$ (480 mg, 4 mmol) in THF (5 mL) was stirred at rt for 4 days. After this time, the reaction mixture was filtered, the residue was washed with Et_2O (10 mL), and the filtrate was concentrated *in vacuo* to give 298 mg of yellow oil. Purification using silica gel chromatography, eluting with 0-5% Et_2O in PE 40-60, gave the product as a colourless oil (136 mg, 54%).

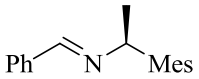
$[\alpha]_D$ = -132.7 ° (c =1.05, $CHCl_3$). No literature data are available for comparison.

ν_{max}($CDCl_3$): 1641 cm^{-1}.

HRMS (ESI) m/z calculated for $C_{18}H_{22}N[M+H]$: 252.1747. Found: 252.1744.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 0.7 Hz, 1H, N=CH), 7.78-7.76 (m, 2H, ArH), 7.42-7.41 (m, 3H, ArH), 6.88 (s, 2H, ArH), 5.08 (qd, *J* = 7.0, 0.6 Hz, 1H, NC*H*CH_3), 2.52 (s, 6H, $ArCH_3$), 2.28 (s, 3H, $ArCH_3$), 1.68 (d, *J* = 7.0 Hz, 3H, NC*H*CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 138.4, 136.8, 136.0, 135.9, 130.4, 130.1, 128.5, 128.2, 64.7, 21.7, 21.6, 20.7.



(*S*)-**156**

Attempted preparation of (*S*)-1-mesityl-*N*-((*S*)-1-phenylethyl)ethanamine ((*S*,*S*)-150)

Scheme 1.82

To a solution of MeLi (1.7 M, 0.27 mL, 0.45 mmol) in THF (0.5 mL) at -78 ^oC was added (*S*,*E*)-*N*-benzylidene-1-mesitylethanamine (87 mg, 0.35 mmol) in THF (0.5 mL). The reaction mixture was stirred at -78 ^oC for 5 h before being quenched with water (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL), and the Et_2O extracts were dried over $NaSO_4$, and concentrated *in vacuo* to give 77 mg of colourless oil. Analysis by ^{1}H NMR revealed that 40% of the starting material had been converted to the desired product. Attempted purification using silica gel chromatography, eluting with 10% Et_2O in PE 40-60 to remove less polar impurities, and then with MeOH, was unsuccessful.

Attempted preparation of (*R*)-1-(2-chlorophenyl)-*N*-((*R*)-1-phenylethyl)ethanamine (*R*,*R*)-158

Scheme 1.83

A mixture of (*R*)-1-phenylethylamine (12.8 mL, 100 mmol), 2-chloroacetophenone (11.7 mL, 100 mmol) and titanium (IV) isopropoxide (74.4 mL, 250 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium

on carbon (455 mg, 0.4 mmol), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing incomplete conversion by ^{1}H NMR analysis. The reaction was therefore placed under 3 bar of hydrogen for a further 24 h. The reaction mixture was then treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (3 x 300 mL). The combined organics were filtered through celite, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to leave a yellow oil. Analysis by ^{1}H NMR revealed a complex mixture of products, which included substantial quantities of both the amine and ketone starting materials. Attempted salting of the crude oil with both TFA and concentrated HCl, in an attempt to isolate a salt of the desired product, failed under various conditions. A yellow oil, rather than the desired solid salt, was obtained on each occasion so these preparative attempts were halted.

Attempted preparation of (*R*,*E*)-*N*-(1-(2-chlorophenyl)ethylidene)-1-phenylethanamine ((*R*)-159)

Scheme 1.84

A mixture of (*R*)-1-phenylethylamine (1.28 mL, 10 mmol) and 2-chloroacetophenone (1.17 mL, 10 mmol) were dissolved in dry Et_2O, and $MgSO_4$ (5 g) was added. The mixture was heated to reflux and stirred for 24 h. After 24 h the reaction was analysed by TLC (4:1 PE 30-40:Et_2O), revealing that no conversion had occurred. Therefore, $Ti(O^iPr)_4$ (3 drops) was added, and the reaction was left to reflux for a further 48 h. Again, TLC analysis after this time revealed that no conversion had occurred so the reaction was halted.

Attempted preparation of (*R*)-1-(3-chlorophenyl)-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-161)

Scheme 1.85

A mixture of (*R*)-1-phenylethylamine (4.38 mL, 34.3 mmol), 3-chloroacetophenone (4.00 mL, 34.3 mmol) and titanium (IV) isopropoxide (25.3 mL, 85.0 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (156 mg, 0.1 mmol), and the mixture was hydrogenated under 3 bar of

hydrogen with shaking. A small aliquot was removed after 48 h, revealing complete conversion of the starting materials to give the secondary amine product of Cl cleavage ((*R*,*R*)-**124**).

Attempted preparation of (*R*,*E*)-*N*-(1-(3-chlorophenyl)ethylidene)-1-phenylethanamine ((*R*)-162)

Scheme 1.86

A mixture of (*R*)-1-phenylethylamine (1.28 mL, 10 mmol) and 3-chloroacetophenone (1.17 mL, 10 mmol) were dissolved in dry Et_2O (50 mL), and $MgSO_4$ (5 g, 42 mmol) was added. The mixture was heated to reflux and stirred for 24 h. After 24 h, the reaction was analysed by TLC (4:1 PE 30-40:Et_2O), revealing that no conversion of the starting materials had occurred. The reaction was heated to reflux for a further 48 h. Again, TLC analysis revealed that no conversion had occurred so these preparative attempts were halted.

Preparation of (*R*)-1-(2-methoxyphenyl)-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-164)[58,74]

Scheme 1.87

A mixture of (*R*)-1-phenylethylamine (12.8 mL, 100 mmol), 2-methoxyacetophenone (13.8 mL, 100 mmol) and titanium (IV) isopropoxide (59.8 mL, 200 mmol) was stirred at rt for 20 minutes. To the mixture was added 10% palladium on carbon (455 mg, 0.4 mol %), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing complete conversion by ^{1}H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (3 x 300 mL). The combined organics were filtered through celite, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to leave a pale yellow oil. The oil was dissolved in MeOH (50 mL) and concentrated HCl (14 mL) was added. Removal of the solvent *in vacuo* revealed a white solid. The crude solid was isolated by filtration and washed with cold Et_2O (20 mL). From the crude ^{1}H NMR of the HCl salt, the (*R*,*R*)/(*R*,*S*) ratio was deduced to be 6:1. The solvent was removed from the filtrate *in vacuo* to reveal a yellow oil which was salted as described. This procedure was repeated until

no more solid precipitated from the MeOH solution. The combined solids were recrystallised from MeOH to give the desired (*R*,*R*)-diastereoisomer. The combined salts were subsequently dissolved in DCM (300 mL) and shaken with an aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 100 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to leave the desired product as a colourless oil (0.97 g, 4%). The product was dried by heating to 100 ^oC under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, and stored over 4Å molecular sieves under a nitrogen atmosphere.

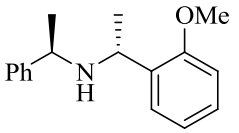
$[\alpha]_D^{20}$ = +146.3 ^{o} (c = 1.08, $CHCl_3$). Lit $[\alpha]_D^{20}$ = -119.2 ^{o} (c = 1.08, $CHCl_3$).[74]

ν_{max}(DCM): 2965 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.21 (m, 6H, ArH), 7.16 (dd, *J* = 7.5 and 1.7 Hz, 1H, ArH), 6.94 (td, *J* = 7.4 and 1.0 Hz, 1H, ArH), 6.87 (d, *J* = 8.2 Hz, 1H, ArH), 3.81-3.72 (m, 4H, OCH_3 and ArCH), 3.52 (q, *J* = 6.6 Hz, 1H, PhCH), 1.99 (brs, 1H, NH), 1.31 (d, *J* = 6.8 Hz, 3H, ArCHC*H*$_3$), 1.28 (d, 3H, *J* = 6.6 Hz, PhCHC*H*$_3$).

Peaks used to deduce dr of crude HCl salt from ^1H NMR (400 MHz, $CDCl_3$):
δ 3.65 ((*R*,*R*), s, 3H, OCH_3).
δ 3.84 ((*R*,*S*), s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 146.2, 133.5, 128.2, 128.1, 127.6, 126.9, 126.7, 120.7, 110.8, 55.4, 55.2, 51.7, 25.3, 22.9.



(*R*,*R*)-**164**

Preparation of 2-phenylacetophenone (166)[76]

Scheme 1.88

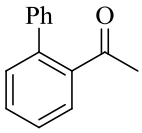
A dry Et_2O (50 mL) solution of 2-phenylbenzoic acid (5.89 g, 29.7 mmol) was cooled to -78 ^oC. Methyllithium (1.6 M, 46.4 mL, 74.3 mmol) was slowly added to the

stirred solution, and the mixture was allowed to slowly warm to rt and stir for 18 h. The solution was then recooled to -78 ^{o}C and quenched with a saturated aqueous solution of NH_4Cl (50 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to reveal 2-phenylacetophenone as a colourless oil (5.93 g, 98%).

ν_{max}(KBr disc): 1685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.54 (m, 1H, ArH), 7.52 (dd, *J* = 7.5 and 1.5 Hz, 1H, ArH), 7.47-7.38 (m, 5H, ArH), 7.38-7.34 (m, 2H, ArH), 2.02 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1, 141.0, 140.8, 140.6, 130.8, 130.0, 129.0, 128.8, 128.0, 128.0, 127.5, 30.5.



166

Preparation of (*R*)-1-(biphenyl-2-yl)-*N*-((*R*)-1-phenylethyl)ethanamine ((*R,R*)-167)

Scheme 1.89, Table 1.43

Entry 1

A mixture of (*R*)-1-phenylethylamine (5.19 mL, 40.6 mmol), 2-phenylacetophenone (7.97 g, 40 mmol) and titanium (IV) isopropoxide (27.1 mL, 102 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (185 mg, 0.2 mmol), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing complete conversion by ^{1}H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (50 mL), followed by extraction with ethyl acetate (3 x 100 mL). The combined organics were filtered through celite, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to leave a pale yellow oil. The oil was dissolved in a 1:1 mixture of MeOH:ethyl acetate (10 mL), and concentrated HCl (6 mL) was added. Removal of the solvent *in vacuo* revealed a white solid. The

crude solid was isolated by filtration and washed with cold Et_2O (10 mL). From the crude ^1H NMR of the HCl salt, the (*R*,*R*)/(*R*,*S*) ratio was deduced to be 20.5:1. The solvent was removed from the filtrate *in vacuo* to reveal a yellow solid. The combined solids were recrystallised from MeOH to give the desired (*R*,*R*)-diastereoisomer. The diastereomerically pure salt was subsequently dissolved in DCM (100 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with DCM (3 x 50 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to give the desired product as a white solid (10.4 g, 45%). The product was dried by placing under high vacuum (0.1 mbar) for 5 h, and was stored under a nitrogen atmosphere.

$[\alpha]_D^{20} = +73.3^{o}$ (c = 1.5, $CHCl_3$). No literature data are available for comparison.

Melting point = 52-54 ^{o}C. No literature data are available for comparison.

ν_{max}(DCM Soln): 2982 cm^{-1}.

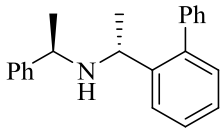
HRMS (ESI) m/z calculated for $C_{22}H_{24}N$[M+H]: 302.1903. Found: 302.1903.

^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H, ArH), 7.44 (td, *J* = 7.5 and 1.3 Hz, 1H, ArH), 7.32-7.15 (m, 8H, ArH), 7.14-7.08 (m, 2H, ArH), 6.95 (d, *J* = 6.6 Hz, 2H, ArH), 3.80 (q, *J* = 6.6 Hz, 1H, CH), 3.58 (q, *J* = 6.6 Hz, 1H, CH), 1.58 (brs, 1H, NH), 1.26 (d, *J* = 6.7 Hz, 3H, CH_3), 1.17 (d, *J* = 6.6 Hz, 3H, CH_3).

Peaks used to deduce dr of crude HCl salt from ^1H NMR (400 MHz, $CDCl_3$):
δ 1.85 ((*R*,*R*), d, 3H, CH_3).
δ 2.01 ((*R*,*S*), d, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 143.3, 141.8, 141.1, 130.1, 129.2, 128.4, 127.9, 127.8, 126.6, 126.6, 126.2, 125.6, 55.2, 50.7, 25.4, 25.2.

See appendix for X-ray crystallographic data of the HCl salt.



(*R*,*R*)-**167**

Preparation of (*R*)-1-(biphenyl-4-yl)-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-168)

Scheme 1.89, Table 1.43

Entry 2

A mixture of (*R*)-1-phenylethylamine (12.8 mL, 100 mmol), 4-phenylacetophenone (19.6 g, 100 mmol) and titanium (IV) isopropoxide (74.7 mL, 250 mmol) was stirred at 65 ^{o}C for 20 minutes. To the mixture was added 10% palladium on carbon (455 mg, 0.4 mmol), and the mixture was hydrogenated under 1 bar of hydrogen with stirring. A small aliquot was removed after 5 days, revealing complete conversion by ^{1}H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (3 x 300 mL). The combined organics were filtered through celite, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to leave a yellow oil. The oil was dissolved in a 1:1 mixture of MeOH:ethyl acetate (30 mL), and concentrated HCl (14 mL) was added. Removal of the solvent *in vacuo* revealed a white solid. The crude solid was isolated by filtration and was washed with cold Et_2O (10 mL). From the crude ^{1}H NMR of the HCl salt, the (*R*,*R*)/(*R*,*S*) ratio was deduced to be 8:1. The solvent was removed from the filtrate *in vacuo* to reveal a yellow oil which was salted as described. This procedure was repeated until no more solid precipitated from the MeOH/ethyl acetate solution. The combined solids were recrystallised from MeOH to deliver the desired (*R*,*R*)-diastereoisomer. The combined diastereomerically pure salts were subsequently dissolved in DCM (300 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 100 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to give the desired product as a colourless oil (3.59 g, 11%). The product was dried by heating to 100 ^{o}C under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, and stored over 4Å molecular sieves under a nitrogen atmosphere.

$[\alpha]_D^{20}$ = +277.2 ^{o} (c = 1.5, $CHCl_3$). No literature data are available for comparison.

ν_{max}(KBr disc): 2961 cm^{-1}.

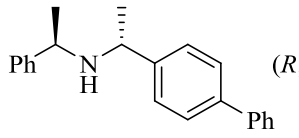
HRMS (ESI) m/z calculated for $C_{22}H_{24}N$[M+H]: 302.1903. Found: 302.1901.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.61 (m, 2H, ArH), 7.60-7.56 (m, 2H, ArH), 7.49-7.43 (m, 2H, ArH), 7.39-7.34 (m, 3H, ArH), 7.33-7.25 (m, 5H, ArH), 3.57 (qd, *J* = 6.7 and 2.3 Hz, 2H, CH), 1.60 (brs, 1H, NH), 1.32 (d, *J* = 6.7 Hz, 3H, CH_3), 1.31 (d, *J* = 6.7 Hz, 3H, CH_3).

Peaks used to deduce dr of crude HCl salt from ^{1}H NMR (400 MHz, $CDCl_3$):
δ 3.93 ((*R*,*R*), m, 2H, CH + CH).
δ 4.33 ((*R*,*S*), m, 1H, CH) and 4.24 ((*R*,*S*), m, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 145.0, 141.1, 139.8, 128.8, 128.5, 127.2, 127.1, 127.1, 126.9, 126.8, 55.2, 54.8, 25.1, 25.1.

See appendix for X-ray crystallographic data of the HCl salt.



(*R*,*R*)-**168**

Attempted preparation of (*R*,*E*)-*N*-(1-(biphenyl-4-yl)propylidene)-1-phenylethanamine ((*R*)-170)

Scheme 1.90

A solution of (*R*)-1-phenylethylamine (580 mg, 4.8 mmol), 1-(biphenyl-4-yl)propan-1-one (1.0 g, 4.8 mmol), and trifluoroacetic acid (6 mg, 0.05 mmol) in toluene (10 mL) was refluxed using a Dean-Stark trap for 16 h. ^{1}H NMR analysis of the reaction mixture after 16 h reflux showed that a significant amount of the starting materials was present, in addition to several unwanted by-products.

Attempted preparation of (*R*)-1-(biphenyl-4-yl)-*N*-((*R*)-1-phenylethyl)propan-1-amine ((*R*,*R*)-171)

Scheme 1.91

A mixture of (*R*)-1-phenylethylamine (4.04 g, 33 mmol), 1-(biphenyl-4-yl)propan-1-one (7.0 g, 33 mmol), and titanium tetra-*iso*-propoxide (28.5 g, 100 mmol) was stirred for 20 minutes at rt before the addition of 10% Pd/C (110 mg, 0.1 mmol) and EtOAc (200 mL). The reaction mixture was then placed under 3 bar of hydrogen and was stirred at room temperature for 6 days. The reaction mixture was then treated with saturated NaOH solution (100 mL) to cause a precipitate to form. The reaction mixture was filtered and the filter cake washed with EtOAc (500 mL) until no more product could be extracted. The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give 7.517 g of yellow oil (51% crude yield). Due to the presence of various impurities, the dr could not be determined using ^{1}H NMR analysis. Purification by silica gel chromatography gave 5.37 g of yellow oil which was treated with concentrated HCl or TFA to form a gum which could not be crystallised from a variety of solvents. Additionally, separation of the diastereomers by column chromatography was unsuccessful.

Preparation of 1-(biphenyl-4-yl)-2-methylpropan-1-one (172)[77]

Scheme 1.92

A solution of NaH (90 mg, 3.6 mmol) in THF (10 mL) was cooled to 0 ^{o}C and 1-(biphenyl-4-yl)propan-1-one (500 mg, 2.4 mmol) was added as a solution in THF (5 mL) over 5 minutes. The reaction mixture was stirred at 0 ^{o}C for 1 h before being warmed to rt and stirred for 3 h. After this time, the reaction mixture was quenched with MeI (680 mg, 4.8 mmol), diluted with EtOAc (10 mL), and washed with water (2 x 10 mL). The aqueous was extracted with EtOAc (2 x 10 mL), the EtOAc extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give 495 mg of yellow solid. ^{1}H NMR analysis showed a mixture of 1-(biphenyl-4-yl)-2-methylpropan-1-one and 1-(biphenyl-4-yl)-2,2-dimethylpropan-1-one (81:19, respectively). Attempted separation of the mixture by silica gel chromatography (0-10% Et_2O in PE 30-40) and recrystallisation from MeOH was unsuccessful.

Peaks used to deduce the composition of the mixture (^{1}H NMR, 400 MHz, $CDCl_3$):

δ 1.26 (**172**, d, J = 6.8 Hz, 6H, $CH(CH_3)_2$),

δ 1.41 (**173**, s, 9H, $C(CH_3)_3$).

Scheme 1.93, Table 1.44

Entry 1

To a flask, which had been previously flame-dried and allowed to cool, was added di-*iso*-propylamine (290 mg, 2.9 mmol) and THF (10 mL). The solution was cooled to 0 ^oC before dropwise addition of *n*-BuLi (2.52 M, 1.1 mL, 2.5 mmol). After stirring for 10 minutes at 0 ^oC, the reaction mixture was cooled to -78 ^oC and 1-(biphenyl-4-yl)propan-1-one (500 mg, 2.4 mmol) was added as a solution in THF (10 mL). The reaction mixture was then stirred at -78 ^oC for 1 h before the addition of MeI (580 mg, 4.1 mmol). After stirring at -78 ^oC for 40 minutes, the reaction mixture was allowed to reach rt and stirred for 20 h. The reaction mixture was then diluted with EtOAc (10 mL), and washed with water (2 x 10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the EtOAc extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give the product as an orange crystalline solid (531 mg, 100%).

Entry 2

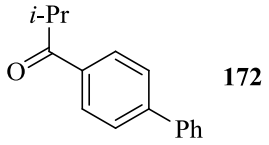
To a flask, which had been previously flame-dried and allowed to cool, was added di-*iso*-propylamine (2.9 g, 29 mmol) and THF (100 mL). The solution was cooled to 0 ^oC before dropwise addition of *n*-BuLi (2.52 M, 10 mL, 25 mmol). After stirring for 10 minutes at 0 ^oC, the reaction mixture was cooled to -78 ^oC and 1-(biphenyl-4-yl)propan-1-one (4.74 g, 24 mmol) was added as a solution in THF (100 mL). The reaction mixture was then stirred at -78 ^oC for 1 h before the addition of MeI (5.78 g, 41 mmol). After stirring at -78 ^oC for 40 minutes, the reaction mixture was allowed to reach rt and stirred for 20 h. The reaction mixture was then diluted with EtOAc (100 mL), and washed with water (2 x 100 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL), and the EtOAc extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give the product as an orange crystalline solid (5.06 g, 100%).

Melting point = 61-63 °C. Lit: 62 °C.[77]

$\nu_{max}(CDCl_3)$: 1682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.5 Hz, 2H, ArH), 7.70 (d, *J* = 8.6 Hz, 2H, ArH), 7.64 (d, *J* = 7.1 Hz, 2H, ArH), 7.50-7.39 (m, 3H, ArH), 3.61 (septet, *J* = 6.8 Hz, 1H, C*H*$(CH_3)_2$), 1.26 (d, *J* = 6.8 Hz, 6H, CH(C*H*$_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 145.5, 140.0, 134.9, 128.9, 128.2, 127.3, 35.4, 19.2.



172

Attempted preparation of (*R*)-1-(biphenyl-4-yl)-2-methyl-*N*-((*R*)-1-phenylethyl)propan-1-amine ((*R*,*R*)-174)

Scheme 1.94

A mixture of (*R*)-1-phenylethylamine (2.98 g, 25 mmol), 1-(biphenyl-4-yl)-2-methylpropan-1-one (5.5 g, 25 mmol), and titanium tetra-*iso*-propoxide (21.0 g, 74 mmol) was stirred for 20 minutes at rt before the addition of 10% Pd/C (110 mg, 0.1 mmol) and EtOAc (200 mL). The reaction mixture was then placed under 8 bar of hydrogen and was stirred at room temperature for 2 weeks. The reaction mixture was then treated with saturated NaOH solution (200 mL) to cause a precipitate to form. The reaction mixture was filtered and the filter cake washed with EtOAc (300 mL) until no more product could be extracted. The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give 4.2 g of orange crystalline solid. ^1H NMR analysis showed mostly starting material, plus minor impurities.

Attempted preparation of (*R*,*E*)-*N*-(1-(biphenyl-4-yl)-2-methylpropylidene)-1-phenylethanamine ((*R*)-175)

Scheme 1.95

A solution of (*R*)-1-phenylethylamine (121 mg, 1 mmol), 1-(biphenyl-4-yl)-2-methylpropan-1-one (223 mg, 1 mmol), and TFA (1 drop) in toluene (5 mL) was refluxed for 3 days using a Dean-Stark trap. ^{1}H NMR analysis showed a complex mixture from which no product could be isolated.

Preparation of (*R*)-1-(naphthalen-1-yl)-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-177)[78]

Scheme 1.96

A mixture of (*R*)-1-phenylethylamine (12.78 mL, 100 mmol), 1-acetylnaphthalene (15.2 g, 100 mmol) and titanium (IV) isopropoxide (74.7 mL, 250 mmol) was stirred at room temperature for 20 minutes. To the mixture was added 10% palladium on carbon (455 mg, 0.4 mmol), and the mixture was hydrogenated under 3 bar of hydrogen with shaking. A small aliquot was removed after 24 h, revealing complete conversion by ^{1}H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (3 x 300 mL). The combined organics were filtered through celite, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to leave a pale yellow oil. From the crude ^{1}H NMR of the HCl salt the (*R*,*R*)/(*R*,*S*) ratio was deduced to be >20:1. The oil was dissolved in a 1:1 mixture of MeOH: ethyl acetate (20 mL), and TFA (17 g) was added. Removal of the solvent *in vacuo* revealed a white solid. The crude solid was isolated by filtration and washed with cold Et_2O (10 mL). The solvent was removed from the filtrate *in vacuo* to reveal a yellow oil which was salted as described. This procedure was repeated until no more solid precipitated from the MeOH/ethyl acetate solution. The combined solids were recrystallised from MeOH to give the desired (*R*,*R*)-diastereoisomer. The combined diastereomerically pure salts were subsequently dissolved in DCM (300 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 200 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to give the product as a crystalline white solid (1.98 g, 7%). The

product was dried by placing under high vacuum (0.1 mbar) for 5 h, and stored under a nitrogen atmosphere.

Melting point = 90-92 ^{o}C. Lit: 95.5-96 ^{o}C.[78]

$[\alpha]_D^{20}$ = +101.3 ^{o} (c = 0.98, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = +89.3 ^{o} (c = 0.98, $CHCl_3$).[78]

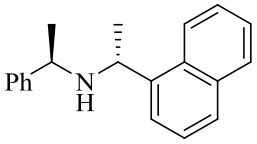
ν_{max}(DCM): 2982 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.88 (m, 2H, ArH), 7.81 (d, *J* = 8.1 Hz, 1H, ArH), 7.74 (d, *J* = 6.9 Hz, 1H, ArH), 7.57 (t, *J* = 7.3 Hz, 1H, ArH), 7.48 (td, *J* = 6.8 and 1.0 Hz, 1H, ArH), 7.43 (td, *J* = 8.6 and 1.4 Hz, 1H, ArH), 7.38-7.25 (m, 3H, ArH), 7.24-7.18 (m, 2H, ArH), 4.46 (q, *J* = 6.6 Hz, 1H, CH_3CH), 3.65 (q, *J* = 6.6 Hz, 1H, CH_3CH), 0.85 (brs, 1H, NH), 1.44 (d, *J* = 6.7 Hz, 3H, CH_3), 1.39 (d, *J* = 6.7 Hz, 3H, CH_3).

Peaks used to deduce dr of crude HCl salt from ^{1}H NMR (400 MHz, $CDCl_3$):
δ 1.75 ((*R*,*R*), d, 3H, CH_3).
δ 1.89 ((*R*,*S*), d, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 128.9, 128.4, 127.1, 126.9, 126.7, 125.8, 125.6, 125.3, 123.2, 122.8, 55.4, 50.8, 24.8, 24.7.

See appendix for X-ray crystallographic details.



(*R*,*R*)-**177**

Preparation of (*R*)-1-(naphthalen-2-yl)-*N*-((*R*)-1-phenylethyl)ethanamine ((*R*,*R*)-179)[79]

Scheme 1.97

A mixture of (*R*)-1-phenylethylamine (12.8 mL, 100 mmol), 2-acetylnaphthalene (17.0 g, 100 mmol) and titanium (IV) isopropoxide (74.7 mL, 250 mmol) was stirred at 65 ^{o}C for 20 minutes. To the mixture was added 10% palladium on carbon (455 mg, 0.4 mmol), and the mixture was hydrogenated under 1 bar of hydrogen with stirring at 65 ^{o}C. A small aliquot was removed after 5 days, revealing complete conversion by ^{1}H NMR analysis. The reaction mixture was treated with an aqueous solution of 1 M sodium hydroxide (150 mL), followed by extraction with ethyl acetate (3 x 300 mL). The combined organics were filtered through celite, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to leave a pale yellow oil. From the crude ^{1}H NMR of the HCl salt, the (*R*,*R*)/(*R*,*S*) ratio was deduced to be 12.5:1. The oil was dissolved in a 1:1 mixture of MeOH: ethyl acetate (20 mL), and concentrated HCl (14 mL) was added. Removal of the solvent *in vacuo* revealed a white solid. The crude solid was isolated by filtration and washed with cold Et_2O (10 mL). The solvent was removed from the filtrate *in vacuo* to reveal a yellow oil which was salted as before. This procedure was repeated until no more solid precipitated from the MeOH/ethyl acetate solution. The combined solids were recrystallised from MeOH to deliver the desired (*R*,*R*)-diastereoisomer. The combined diastereomerically pure salts were subsequently dissolved in DCM (300 mL) and shaken with a saturated aqueous solution of $NaHCO_3$ (300 mL). The aqueous layer was extracted with DCM (3 x 200 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the product as a colourless oil (14.0 g, 51%). The product was dried by heating to 100 ^{o}C under vacuum (0.1 mbar) using a Kugelrohr apparatus for 2 h, and stored over 4Å molecular sieves under a nitrogen atmosphere.

Scheme 1.98

(*R*)-1-Phenylethylamine (20.0 g, 165 mmol), 2-acetylnaphthylene (28.1 g, 165 mmol) and titanium tetra-*iso*-propoxide (140.8 g, 496 mmol) in EtOAc (300 mL) were stirred at room temperature for 10 minutes before the addition of 10% palladium on charcoal (1.5 g, 1.5 mmol). The reaction mixture was placed under an atmosphere of hydrogen

at 8 bar and was shaken for 2 days before being treated with a saturated solution of NaOH (500 mL), causing a grey precipitate to form. The mixture was filtered to remove the precipitate, and the aqueous filtrate was extracted with EtOAc (3 x 200 mL). The precipitate was washed repeatedly with 200 mL portions of EtOAc until no more product could be detected in the washings by TLC, and the organics were combined, washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a colourless oil. None of the undesired diastereomer could be detected by ^{1}H NMR analysis. The crude amine was purified by formation of the HCl salt (using 24 mL HCl) and recrystallisation from *iso*-propanol. The salt was then treated with a saturated solution of $NaHCO_3$ (500 mL), extracted with DCM (2 x 300 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the title compound as a colourless oil (20.9 g, 46%). The product was dried by distillation from CaH_2 at 141 ^{o}C and 0.001 mbar before use.

$[\alpha]_D^{20}$ = +255.3 ^{o} (c = 1.5, $CHCl_3$). No literature data is available for comparison.

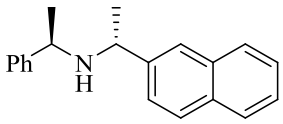
ν_{max}($CDCl_3$): 2962 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.86-7.81 (m, 3H, ArH), 7.61 (s, 1H, ArH), 7.51-7.44 (m, 3H, ArH), 7.38-7.34 (m, 2H, ArH), 7.30-7.26 (m, 1H, ArH), 7.25-7.23 (m, 2H, ArH), 3.70 (q, *J* = 6.6 Hz, 1H, C*H*CH_3), 3.55 (q, *J* = 6.6 Hz, 1H, C*H*CH_3), 1.67 (brs, 1H, NH), 1.37 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.31 (d, *J*= 6.6 Hz, 3H, CHC*H*$_3$).

Peaks used to deduce dr of crude HCl salt from ^{1}H NMR (400 MHz, $CDCl_3$):
δ 3.70 ((*R*,*R*), q, 1H, CH).
δ 3.81 ((*R*,*S*), q, 1H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ144.8, 142.2, 132.4, 131.8, 127.4, 127.2, 126.7, 126.6, 125.8, 125.6, 124.9, 124.4, 124.3, 123.8, 54.2, 54.1, 24.0, 23.9.

See appendix for X-ray crystallographic details of the HCl salt.



(*R*,*R*)-**179**

Attempted preparation of 1-(naphthalen-2-yl)propan-1-one (180)

Scheme 1.100, Table 1.45

Entry 1

To a flask, which had been previously flame-dried and allowed to cool, was added di-*iso*-propylamine (3.56 g, 35 mmol) and THF (100 mL). The solution was cooled to 0 ^{o}C before dropwise addition of *n*-BuLi (2.52 M, 12.3 mL, 31 mmol). After stirring for 10 minutes at 0 ^{o}C, the reaction mixture was cooled to -78 ^{o}C and 1-(naphthalen-2-yl)ethanone (5.0 g, 29 mmol) was added as a solution in THF (100 mL). The reaction mixture was then stirred at -78 ^{o}C for 1 h before the addition of MeI (7.1 g, 50 mmol). After stirring at -78 ^{o}C for 40 minutes, the reaction mixture was allowed to reach rt and stirred for 20 h. The reaction mixture was then diluted with EtOAc (100 mL), and washed with water (2 x 100 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL), and the EtOAc extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis showed a mixture of 1-(naphthalen-2-yl)ethanone (**178**), 1-(naphthalen-2-yl)propan-1-one (**180**), and, 2-methyl-1-(naphthalen-2-yl)propan-1-one (**182**); 31:45:24, respectively.

Peaks used to deduce the composition of the mixture (^{1}H NMR, 400 MHz, $CDCl_3$):

δ 2.72 (**178**, s, 3H, CH_3),

δ 3.12 (**180**, q, J = 7.3 Hz, 2H, CH_2CH$_3$),

δ 3.72 (**182**, m, 1H, CH(CH$_3$)$_2$).

Entry 2

To a flask, which had been previously flame-dried and allowed to cool, was added di-*iso*-propylamine (360 mg, 3.5 mmol) and THF (10 mL). The solution was cooled to 0 ^{o}C before dropwise addition of *n*-BuLi (2.52 M, 1.2 mL, 3.1 mmol). After stirring for 10 minutes at 0 ^{o}C, the reaction mixture was cooled to -78 ^{o}C and 1-(naphthalen-2-yl)ethanone (500 mg, 2.9 mmol) was added as a solution in THF (10 mL). The

reaction mixture was then stirred at -78 ^{o}C for 1 h before being added to a solution of MeI (710 mg, 5.0 mmol) in THF (5 mL). After stirring at -78 ^{o}C for 40 minutes, the reaction mixture was allowed to reach rt and stirred for 20 h. The reaction mixture was then diluted with EtOAc (10 mL), and washed with water (2 x 10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the EtOAc extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis showed a mixture of 1-(naphthalen-2-yl)ethanone (**178**), 1-(naphthalen-2-yl)propan-1-one (**180**), and, 2-methyl-1-(naphthalen-2-yl)propan-1-one (**182**); 30:48:22, respectively.

Entry 3

To a flask, which had been previously flame-dried and allowed to cool, was added di-*iso*-propylamine (390 mg, 3.8 mmol) and THF (10 mL). The solution was cooled to 0 ^{o}C before dropwise addition of *n*-BuLi (2.50 M, 1.4 mL, 3.5 mmol). After stirring for 10 minutes at 0 ^{o}C, the reaction mixture was cooled to -78 ^{o}C and 1-(naphthalen-2-yl)ethanone (500 mg, 2.9 mmol) was added as a solution in THF (10 mL). The reaction mixture was then stirred at -78 ^{o}C for 1 h before being added to a solution of MeI (2.5 g, 17.6 mmol) in THF (5 mL). After stirring at -78 ^{o}C for 40 minutes, the reaction mixture was allowed to reach rt and stirred for 20 h. The reaction mixture was then diluted with EtOAc (10 mL), and washed with water (2 x 10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the EtOAc extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis showed a mixture of 1-(naphthalen-2-yl)ethanone (**178**), 1-(naphthalen-2-yl)propan-1-one (**180**), and, 2-methyl-1-(naphthalen-2-yl)propan-1-one (**182**); 15:73:12, respectively.

Preparation of 2-cyanonaphthalene (184)[80]

Scheme 1.101, Table 1.46

Entry 1

A solution of 2-bromonaphthalene (621 mg, 3 mmol), potassium hexacyanoferrate (253 mg, 0.6 mmol), 10% Pd/C (32 mg, 0.03 mmol), and Na_2CO_3 (318 mg, 3 mmol) in DMA (5 mL) was heated at 140 ^{o}C for 20 h. After this time, the reaction mixture was diluted with EtOAc (10 mL), filtered, and washed with H_2O (2 x 10 mL). The EtOAc layer was dried over Na_2SO_4, and concentrated *in vacuo* before being purified

using silica gel chromatography, eluting with 1-10% Et_2O in PE 40-60, to give the product as a white solid (309 mg, 67%).

Entry 2

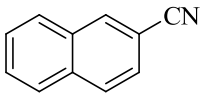
A solution of 2-bromonaphthalene (18.6 g, 90 mmol), potassium hexacyanoferrate (7.6 g, 18 mmol), 10% Pd/C (960 mg, 0.9 mmol), and Na_2CO_3 (9.54 g, 90 mmol) in DMA (150 mL) was heated at 140 ^oC for 20 h. After this time, the reaction mixture was diluted with EtOAc (300 mL), filtered, and washed with H_2O (2 x 300 mL). The EtOAc layer was dried over Na_2SO_4, and concentrated *in vacuo* before being purified using silica gel chromatography, eluting with 1-10% Et_2O in PE 40-60, to give the product as a white solid (10.63 g, 77%).

Melting point = 67-69 ^oC. Lit: = 68-70^oC.[80]

$\nu_{max}(CDCl_3)$: 2253 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H, ArH), 7.95-7.90 (m, 3H, ArH), and 7.68-7.60 (m, 3H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 134.2, 132.3, 129.2, 129.1, 128.4, 128.1, 127.7, 126.4, 119.3, 109.4.



184

Preparation of 1-(naphthalen-2-yl)propan-1-one (180)[81]

Scheme 1.102, Table 1.47

Entry 1

A solution of 2-cyanonaphthalene (153 mg, 1 mmol) in Et_2O (1 mL) was added dropwise to an Et_2O solution of EtMgBr (3 M, 1.3 mL, 4 mmol). The reaction mixture was stirred for 1 h then left to stand overnight. After this time, the reaction mixture was added to a mixture of ice (2 g) and concentrated HCl (1.2 mL). The

aqueous layer was taken and refluxed for 1.5 h before being allowed to cool to rt and extracted with Et_2O (2 x 10 mL). The organic extracts were dried over $NaSO_4$ and concentrated *in vacuo* to give the product as a yellow solid (147 mg, 80%).

Entry 2

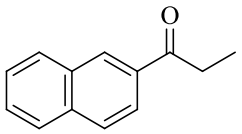
A solution of 2-cyanonaphthalene (10.44 g, 68 mmol) in Et_2O (70 mL) was added dropwise to an Et_2O solution of EtMgBr (3 M, 91 mL, 270 mmol). The reaction mixture was stirred for 1 h then left to stand overnight. After this time, the reaction mixture was added to a mixture of ice (140 g) and concentrated HCl (82 mL). The aqueous layer was taken and refluxed for 1.5 h before being allowed to cool to rt and extracted with Et_2O (2 x 100 mL). The organic extracts were dried over $NaSO_4$ and concentrated *in vacuo* to give the product as a yellow solid (11.26 g, 90%).

Melting point = 63-64 ^oC. Lit: 62-64 ^oC.[81]

$\nu_{max}(CDCl_3)$: 1676 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H, ArH), 8.05 (dd, *J* = 8.6, 1.7 Hz, 1H, ArH), 7.97 (d, *J* = 8.0 Hz, 1H, ArH), 7.90 (t, *J* = 8.4 Hz, 2H, ArH), m (7.63-7.54, 2H, ArH), 3.15 (q, *J* = 7.3 Hz, 2H, CH_2CH_3), 1.30 (t, *J* = 7.3 Hz, 3H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 134.4, 133.1, 131.4, 128.4, 128.4, 127.2, 127.2, 126.6, 125.5, 122.7, 30.7, 7.3.



180

Preparation of (*R*)-1-(naphthalen-2-yl)-*N*-((*R*)-1-phenylethyl)propan-1-amine ((*R*,*R*)-181)

Scheme 1.103

A mixture of (*R*)-1-phenylethylamine (7.4 g, 61 mmol), 1-(naphthalen-2-yl)propan-1-one (11.26 g, 61 mmol), and titanium tetra-*iso*-propoxide (52.1 g, 183 mmol) was stirred for 20 minutes at rt before the addition of 10% Pd/C (541 mg, 0.5 mmol) and EtOAc (200 mL). The reaction mixture was then placed under 8 bar of hydrogen and was stirred at room temperature for 2 days. The reaction mixture was then treated with saturated NaOH solution (300 mL) to cause a precipitate to form. The reaction mixture was filtered and the filter cake washed with EtOAc (3 x 300 mL) until no more product could be extracted. The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to 18.6 g of yellow oil. Due to the presence of various impurities, it was not possible to determine the dr of the product by ^{1}H NMR analysis. Attempts to prepare the HCl or TFA salts were unsuccessful so the oil was purified by silica gel chromatography, eluting with 10-50% Et_2O in PE 40-60, to give 11.9 g of yellow oil. Salting with HCl (5 mL) produced a gum which was crystallised from acetone/hexane to give 7.59 g of white solid. The diastereomerically pure product was isolated by recrystallisation of the HCl salt from EtOH, followed by treatment with NaOH (2 M, 200 mL) and extraction with EtOAc (3 x 100 mL). Drying of the organic extracts over Na_2SO_4 and concentrating *in vacuo* gave the product as a colourless oil (3.88 g, 22%). The product was dried by distillation from CaH_2 at 0.001 mbar, 172 ^oC.

$[\alpha]_D$ = +229 ° (c = 1.2, $CHCl_3$). No literature data are available for comparison.

$\nu_{max}(CDCl_3)$: 2962 cm^{-1}.

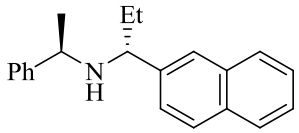
HRMS (ESI) m/z calculated for $C_{21}H_{24}N$[M+H]: 290.1903. Found: 290.1898.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.82 (m, 3H, ArH), 7.57 (s, 1H, ArH), 7.50-7.47 (m, 3H, ArH), 7.43 (dd, *J* = 8.4, 1.6 Hz, 2H, ArH), 7.39-7.35 (m, 1H, ArH), 7.31-7.23 (m, 2H, ArH), 3.53 (q, *J* = 6.7 Hz, 1H, NHC*H*CH_3), 3.41 (t, *J* = 7.1 Hz, 1H,

NHC*H*CH_2CH_3), 1.78-1.67 (m, 3H, NH and CHC*H*$_2CH_3$), 1.29 (d, *J* = 6.7 Hz, 3H, NHCHC*H*$_3$), 0.80 (t, *J* = 7.4 Hz, 3H, NHCHCH_2C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 141.8, 133.4, 132.9, 128.2, 127.8, 127.7, 126.8, 126.8, 126.4, 125.9, 125.4, 125.2, 61.9, 55.0, 31.3, 25.1, 11.0.

See appendix for X-ray crystallographic details of the HCl salt.



(*R*,*R*)-**181**

Preparation of (*R*)-*N*-((*R*)-1-phenylethyl)-2,3-dihydro-1*H*-inden-1-amine ((*R*,*R*)-186)[60]

Scheme 1.104

(*R*)-1-Phenylethylamine (4.6 g, 40 mmol), indanone (5.0 g, 40 mmol) and titanium tetra-*iso*-propoxide (32.2 g, 110 mol) were stirred for 30 minutes before addition of 10% Pd/C (163 mg, 0.2 mmol). The reaction mixture was then hydrogenated under H_2 (3 bar) with shaking for 4 days before being partitioned between H_2O (200 mL) and EtOAc (200 mL), and filtered through celite. The aqueous layer was extracted with EtOAc (2 x 200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a brown oil. The dr was determined as 88:12 (*R*:*R*):(*R*:*S*) by ^{1}H NMR analysis. The crude product was purified by column chromatography on silica gel (10% Et_2O in PE (30-40 °C)) before being converted to its HCl salt (using 6 mL conc. HCl) and purified further by recrystallisation from IPA. The diastereomerically pure free amine was then generated by dissolving the salt in 2M NaOH (200 mL), extracting with EtOAc (2 x 200 mL), drying over Na_2SO_4, and concentrating *in vacuo* to give 2.3 g (26%) of colourless oil. The amine was dried by heating at 50 °C over CaH_2 *in vacuo* (0.005 mbar) for 4 h before being distilled *in vacuo* (119 °C, 0.005 mbar).

$[\alpha]_D^{20}$ = +90.8° (c = 0.9, MeOH). Lit: $[\alpha]_D^{20}$ = +91° (c = 0.9, MeOH).[60]

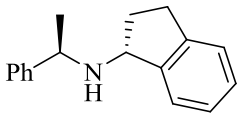
ν_{max}($CDCl_3$): 2962 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.23 (m, 9H, ArH), 4.19 (t, J = 6.6 Hz, 1H, NC*H*CH_2), 4.16 (q, J = 6.6 Hz, 1H, NC*H*CH_3), 3.04-2.96 (m, 1H, CH), 2.81-2.73 (m, 1H, CH), 2.31-2.26 (m, 1H, CH), 1.79-1.74 (m, 1H, CH), 1.54 (brs, 1H, NH), 1.44 (d, J = 6.5 Hz, 3H, CH_3).

Peaks used to deduce dr of crude amine from ^{1}H NMR (400 MHz, $CDCl_3$):
δ 4.19 ((*R*,*R*), t, 1H, NC*H*CH_2) and 4.16 ((*R*,*R*), q, 1H, NC*H*CH_3).
δ 4.13-4.04 ((*R*,*S*), m, 2H, $N(CH)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 145.2, 142.5, 127.4, 126.2, 125.9, 125.8, 125.1, 123.8, 123.0, 60.0, 55.6, 34.0, 29.3, 23.6.

See appendix for X-ray crystallographic details of the HCl salt.



(*R*,*R*)-**186**

Preparation of (*R*)-*N*-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (*R*,*R*)-188[60]

Scheme 1.105

(*R*)-1-Phenylethylamine (12.4 mL, 100 mmol), tetralone (13.3 mL, 100 mmol) and titanium tetra-*iso*-propoxide (60 mL, 200 mol) were stirred for 30 minutes before addition of 10% Pd/C (450 mg, 0.4 mmol). The reaction mixture was then hydrogenated under H_2 (3 bar) with shaking for 24 h before being partitioned between NaOH (1 M, 500 mL) and EtOAc (500 mL), and filtered through celite. The aqueous layer was extracted with EtOAc (3 x 200 mL), and the organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give a colourless oil. Analysis of the product using ^{1}H NMR revealed that the desired (*R*,*R*)-diastereomer had been formed exclusively. The HCl salt was formed by addition of concentrated HCl (14 mL) to the crude product. Recrystallisation from EtOH followed by treatment with saturated $NaHCO_3$ (300 mL), and extraction using DCM (2 x 300 mL)

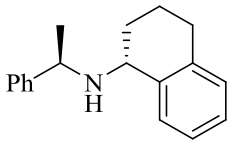
delivered the pure product as a colourless oil (23.8 g, 94%). The amine was dried by heating at 100 °C using a Kugelrohr apparatus at 0.01 mbar for 2 h.

$[\alpha]_D^{20}$ = 92.0 ° (c = 1.09, MeOH). Lit: $[\alpha]_D^{20}$ = 94.0 ° (c = 1.09, MeOH).[60]

ν_{max}(DCM): 2929 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.33 (m, 2H, ArH), 7.31-7.21 (m, 3H, ArH), 7.20-7.13 (m, 1H, ArH), 7.12-7.03 (m, 2H, ArH), 7.02-6.94 (m, 1H, ArH), 4.06 (q, *J* = 6.5 Hz, 1H, NC*H*CH_3), 3.89 (t, *J* = 4.4 Hz, 1H, NC*H*CH_2), 2.77-2.58 (m, 2H), 1.92-1.55 (m, 4H), 1.29 (d, *J* = 6.5 Hz, 3H, NCHC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 140.0, 137.2, 129.2, 128.9, 128.4, 126.9, 126.8, 126.7, 125.6, 56.2, 53.2, 29.6, 29.1, 24.8, 18.7.



(*R*,*R*)-**188**

Preparation of (*R*)-*N*-((*R*)-1-phenylethyl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-amine ((*R*,*R*)-190)[60]

Entry 1

(*R*)-1-Phenylethylamine (3.63 g, 30 mmol), benzosuberone (4.8 g, 30 mmol) and titanium tetra-*iso*-propoxide (25.6 g, 90 mmol) were stirred for 30 minutes before addition of 10% Pd/C (265 mg, 0.25 mmol). The reaction mixture was then hydrogenated under H_2 (8 bar) with stirring for 4 days before being treated with a saturated solution of NaOH (125 mL) and filtered to remove the resultant precipitate, which was washed with EtOAc (3 x 200 mL). The EtOAc extracts were washed with H_2O (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The dr was determined as 78:22 (*R*:*R*):(*R*:*S*) by ^{1}H NMR analysis. The crude product was purified by column chromatography on silica gel (0-50% Et_2O in PE 30-40) before attempted crystallisation of the HCl and TFA salts. Using a variety of solvents and conditions, the TFA salt could not be crystallised. However, it was noted that

trituration of the HCl salt in acetone gave some precipitation so the reaction was performed on a larger scale to allow isolation of the HCl salt.

Entry 2

(*R*)-1-Phenylethylamine (7.6 g, 60 mmol), benzosuberone (10.0 g, 60 mmol) and titanium tetra-*iso*-propoxide (53.2 g, 190 mmol) were stirred for 30 minutes before addition of 10% Pd/C (552 mg, 0.5 mmol). The reaction mixture was then hydrogenated under H_2 (8 bar) with stirring for 4 days before being treated with a saturated solution of NaOH (250 mL) and filtered to remove the resultant precipitate, which was washed with EtOAc (3 x 400 mL). The EtOAc extracts were washed with H_2O (400 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The dr was determined as 78:22 (*R*:*R*):(*R*:*S*) by ^{1}H NMR analysis. The crude product was purified by column chromatography on silica gel (0-50% Et_2O in PE 30-40) before being converted to its HCl salt (using 10 mL HCl and crystallising by trituration in acetone) and purified further by recrystallisation from acetone. The diastereomerically pure free amine was then generated by dissolving the salt in 2M NaOH (200 mL), extracting with EtOAc (2 x 200 mL), drying over Na_2SO_4, and concentrating *in vacuo* to give 1.2 g (7%) of colourless oil. The amine was heated at 50 °C over CaH_2 *in vacuo* (0.4 mbar) for 4 h before being distilled *in vacuo* (140°C, 0.001 mbar).

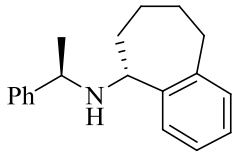
$[\alpha]_D^{20}$ = +121.2 ° (c = 0.94, MeOH). Lit: $[\alpha]_D^{20}$ = +120 ° (c = 0.94, MeOH).[60]

$\nu_{max}(CDCl_3)$: 2929 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H, ArH), 7.17-7.09 (m, 4H, ArH), 3.67-3.63 (m, 2H, $(CH)_2NH$)), 3.06-3.00 (m, 1H, CH), 2.70 (dd, *J* = 14.0, 8.5 Hz, 1H, CH), 1.95-1.76 (m, 1H, CH), 1.74-1.55 (m, 5H, aliphatic ring protons), 1.34 (d, *J* = 6.6 Hz, 3H, CH_3).

Peaks used to deduce dr of crude amine from ^{1}H NMR (400 MHz, $CDCl_3$):
δ 1.34 ((*R*,*R*), d, 3H, CH_3).
δ 1.44 ((*R*,*S*), d, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 142.1, 141.3, 128.8, 127.4, 125.7, 125.6, 125.5, 124.7, 58.3, 54.1, 34.6, 33.8, 26.9, 26.1, 24.0.



(*R*,*R*)-**190**

4.4 Asymmetric deprotonations employing alternative C_2- and *pseudo*-C_2-symmetric magnesium bisamides

Application of C_2-symmetric magnesium bisamide (*S*,*S*)-99

Scheme 1.107, Table 1.49

Following general procedure A for the preparation of magnesium base (*S*,*S*)-**99**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*S*)-**128**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*S*,*S*)-**99**, (b) -78 ^{o}C, (c) none, (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 77%, (i) 108 mg, 60%, and (j) 12:88.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*S*)-**128**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*S*,*S*)-**99**, (b) -78 ^{o}C, (c) DMPU (60 μL, 0.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 88%, (i) 128 mg, 71%, and (j) 12:88.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*S*)-**128**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*S*,*S*)-**99**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1

mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 81%, (i) 101 mg, 56%, and (j) 12:88.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*S*)-**128**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*S*,*S*)-**99**, (b) -78 ^{o}C, (c) DMPU (300 μL, 2.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 84%, (i) 123 mg, 68%, and (j) 12:88.

Entry 5: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*S*)-**128**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*S*,*S*)-**99**, (b) rt, (c) none, (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 83%, (i) 137 mg, 76%, and (j) 28:72.

Entry 6: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*S*)-**128**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*S*,*S*)-**99**, (b) rt, (c) DMPU (60 μL, 0.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 86%, (i) 145 mg, 80%, and (j) 26:74.

Entry 7: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*S*)-**128**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*S*,*S*)-**99**, (b) rt, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 94%, (i) 157 mg, 87%, and (j) 24:76.

Entry 8: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*S*)-**128**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*S*,*S*)-**99**, (b) rt, (c) DMPU (300 μL, 2.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 98%, (i) 148 mg, 82%, and (j) 25:75.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-100

Scheme 1.108, Table 1.50

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**100**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine.

Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) -78 ^{o}C, (c) none, (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 60%, (i) 74 mg, 41%, and (j) 94:6.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) -78 ^{o}C, (c) DMPU (60 μL, 0.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 67%, (i) 87 mg, 48%, and (j) 95:5.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) -78 ^{o}C, (c) DMPU (120 μL, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 88%, (i) 128 mg, 71%, and (j) 94:6.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) -78 ^{o}C, (c) DMPU (300 μL, 2.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 84%, (i) 107 mg, 59%, and (j) 95:5.

Entry 5: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) rt, (c) none, (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 66%, (i) 92 mg, 51%, and (j) 71:29.

Entry 6: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) rt, (c) DMPU (60 μl, 0.5

mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 87%, (i) 105 mg, 58%, and (j) 76:24.

Entry 7: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) rt, (c) DMPU (120 μl, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 94%, (i) 121 mg, 67%, and (j) 76:24.

Entry 8: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) rt, (c) DMPU (300 μl, 2.5 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 73%, (i) 105 mg, 58%, and (j) 75:25.

Scheme 1.109, Table 1.51

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**100**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 88%, (i) 128 mg, 71%, and (j) 94:6.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) -60 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 92%, (i) 119 mg, 66%, and (j) 90:10.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) -40 ^{o}C, (c) DMPU (120 μl,

1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 94%, (i) 121 mg, 67%, and (j) 90:10.

Entry 4: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 89%, (i) 101 mg, 56%, and (j) 87:13.

Entry 5: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) 0 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 93%, (i) 107 mg, 59%, and (j) 87:13.

Entry 6: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**129**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**100**, (b) rt, (c) DMPU (120 μl, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 94%, (i) 121 mg, 67%, and (j) 76:24.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-101

Scheme 1.110, Table 1.152

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**101**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**130**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**101**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 30%, (i) 25 mg, 14%, and (j) 87:13.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**130**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**101**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 36%, (i) 38 mg, 21%, and (j) 86:14.

Entry 3: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**130**, and (c) 506 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**101**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 87%, (i) 123 mg, 68%, and (j) 70:30.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*S*,*R*)-102

Scheme 1.111

Following general procedure A for the preparation of magnesium base (*S*,*R*)-**102**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*R*)-**132**, and (c) 0.55 mL, 2 mmol. General procedure C: (a) (*S*,*R*)-**102**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 0%, (i) 0%, and (j) not applicable.

Scheme 1.112

Bu_2Mg (1.00 M, 1.00 mL, 1 mmol) in heptane was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by the amine ((*S*,*R*)-**132**, 0.55 mL, 2 mmol), and the solution was heated at reflux for 2.5 h. The reaction mixture was then cooled under argon to -78 ^{o}C. The Schlenk flask was then charged with DMPU (120 μL, 1 mmol) and TMSCl (0.5 mL, 4 mmol), and the reaction mixture was stirred for 10 minutes at -78 ^{o}C. 4-*tert*-Butylcyclohexanone

(123 mg, 0.8 mmol) was then added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction mixture was stirred at -78 ^{o}C for 18 h before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (2 x 25 mL) gave a solution of the crude product which was analysed by GC to determine the reaction conversion (0%).

Application of *pseudo*-C_2-symmetric alkylmagnesium amide (*S*,*R*)-191

Scheme 1.113

Following general procedure B for the preparation of magnesium base (*S*,*R*)-**191**, data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure B: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*S*,*R*)-**132**, and (c) 0.28 mL, 1 mmol. General procedure C: (a) (*S*,*R*)-**191**, (b) -78 ^{o}C, (c) 18-c-6 (264 mg, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 0%, (i) 0%, and (j) not applicable.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-103

Scheme 1.114, Table 1.53

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**103**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**135**, and (c) 462 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**103**, (b) -78 ^{o}C, (c) DMPU (120 μl,

1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 67%, (i) 85 mg, 47%, and (j) 85:15.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**135**, and (c) 462 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**103**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 93%, (i) 137 mg, 76%, and (j) 70:30.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-106

Scheme 1.115, Table 1.54

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**106**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**141**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**106**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 55%, (i) 76 mg, 42%, and (j) 95:5.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**141**, and (c) 478 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**106**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 92%, (i) 143 mg, 79%, and (j) 90:10.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-111

Scheme 1.116, Table 1.55

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**111**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine.

Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**164**, and (c) 510 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**111**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 65%, (i) 81 mg, 45%, and (j) 48:52.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-112

Scheme 1.117, Table 1.56

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**112**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**167**, and (c) 602 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**112**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 84%, (i) 123 mg, 68%, and (j) 96:4.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**167**, and (c) 602 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**112**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 98%, (i) 141 mg, 78%, and (j) 87:13.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-113

Scheme 118, Table 1.57

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**113**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**168**, and (c) 602 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**113**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 62%, (i) 87 mg, 48%, and (j) 94:6.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**168**, and (c) 602 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**113**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 97%, (i) 150 mg, 83%, and (j) 87:13.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-116

Scheme 1.119, Table 1.58

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**116**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**177**, and (c) 550 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**116**, (b) -78 ^{o}C, (c) DMPU (120 μl,

1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 68%, (i) 105 mg, 58%, and (j) 94:6.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**177**, and (c) 550 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**116**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 92%, (i) 130 mg, 72%, and (j) 84:16.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-117

Scheme 1.120, Table 1.59

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**117**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**179**, and (c) 550 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**117**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 85%, (i) 130 mg, 72%, and (j) 96:4.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**179**, and (c) 550 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**117**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 90%, (i) 141 mg, 78%, and (j) 89:11.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-118

Scheme 1.121, Table 1.60

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**118**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine.

Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**181**, and (c) 578 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**118**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 98%, (i) 145 mg, 80%, and (j) 82:18.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**181**, and (c) 578 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**118**, (b) -20 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 90%, (i) 136 mg, 75%, and (j) 69:31.

Application of *pseudo*-C_2-symmetric alkylmagnesium amide (*R*,*R*)-192

Scheme 1.122

Following general procedure B for the preparation of magnesium base (*R*,*R*)-**192**, data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

General procedure B: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**181**, and (c) 289 mg, 1 mmol. General procedure C: (a) (*R*,*R*)-**192**, (b) -78 ^{o}C, (c) 18-c-6 (264 mg, 1 mmol), (d) 0.5 mL, 4 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 93%, (i) 154 mg, 85%, and (j) 73:27.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-119

Scheme 1.123

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**119**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**186**, and (c) 474 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**119**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 96%, (i) 150 mg, 83%, and (j) 74:26.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-120

Scheme 1.124, Table 1.61

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**120**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**188**, and (c) 502 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**120**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 83%, (i) 112 mg, 62%, and (j) 82:18.

Entry 2: General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**188**, and (c) 502 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**120**, (b) -20 ^{o}C, (c) DMPU (120 μl,

1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 96%, (i) 132 mg, 73%, and (j) 74:26.

Application of *pseudo*-C_2-symmetric magnesium bisamide (*R*,*R*)-121

Scheme 1.125

Following general procedure A for the preparation of magnesium base (*R*,*R*)-**121**, data are presented as (a) amount of $^{n}Bu_2Mg$, (b) amine used, and (c) amount of amine. Following general procedure C for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amounts of additives, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to enol silane, (i) yield, and (j) (*S*):(*R*).

General procedure A: (a) 1.00 M, 1.00 mL, 1 mmol, (b) (*R*,*R*)-**190**, and (c) 530 mg, 2 mmol. General procedure C: (a) (*R*,*R*)-**121**, (b) -78 ^{o}C, (c) DMPU (120 μl, 1 mmol), (d) 0.13 mL, 1 mmol, (e) 4-*tert*-butylcyclohexanone, (f) 123 mg, 0.8 mmol, (g) 16 h, (h) 96%, (i) 157 mg, 87%, and (j) 79:21.

4.5 Enol silane data

(*S*)-(4-*tert*-Butylcyclohex-1-enyloxy)trimethylsilane (13a)[71]

Achiral GC analysis: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 ^{o}C (1 min)-190 ^{o}C; temperature gradient; 20 ^{o}C min^{-1}; t_R = 5.27 minutes (**12a**), t_R = 5.49 minutes (**13a**).

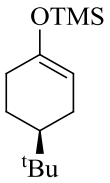
Chiral GC analysis: Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-130 ^{o}C; temperature gradient; 1.5 ^{o}C min^{-1}; t_R = 25.67 minutes ((*S*)-**13a**), t_R = 25.95 min ((*R*)-**13a**)

$[\alpha]_D^{20}$ = -62.9 ° (95:5 (*S*):(*R*), c = 1.5, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -54.2 ° (82:18 (*S*):(*R*), c = 1.5, $CHCl_3$).[71]

ν_{max}(KBr disc): 1674 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86-4.84 (m, 1H, C=CH), 2.13-1.97 (m, 3H), 1.85-1.77 (m, 2H), 1.32-1.24 (m, 2H), 0.88 (s, 9H, $C(CH_3)_3$), 0.19 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 103.6, 43.7, 31.8, 30.7, 27.0, 24.8, 24.1, 0.0.



(*S*)-**13a**

(*S*)-(4-*iso*-Propylcyclohex-1-enyloxy)trimethylsilane (13b)[71]

Achiral GC analysis: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 ^{o}C (1 min)-190 ^{o}C; temperature gradient; 20 ^{o}C min^{-1}; t_R = 4.73 minutes (**12b**), t_R = 5.02 minutes (**13b**).

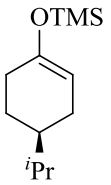
Chiral GC analysis: Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-130 ^{o}C; temperature gradient; 1.5 ^{o}C min^{-1}; t_R = 20.83 minutes ((*S*)-**13b**), t_R = 21.15 minutes ((*R*)-**13b**).

$[\alpha]_D^{20}$ = -48.2 ° (93:7 (*S*):(*R*), c = 1.5, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -49.0 ° (95:5 (*S*):(*R*), c = 1.5, $CHCl_3$).[71]

ν_{max}(KBr disc): 1672 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87-4.83 (m, 1H, C=CH), 2.15-1.94 (m, 3H), 1.83-1.72 (m, 2H), 1.43-1.55 (m, 1H), 1.36-1.18 (m, 2H), 0.89 (d, *J* = 6.8 Hz, 3H, CH_3), 0.88 (d, *J* = 6.8 Hz, 3H, CH_3), 0.18 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 103.9, 40.1, 32.1, 30.4, 27.4, 26.5, 20.2, 0.3.



(*S*)-**13b**

(*S*)-(4-*n*-Propylcyclohex-1-enyloxy)trimethylsilane (13c)[71]

Achiral GC analysis: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 ^oC (1 min)-190 ^oC; temperature gradient; 20 ^oC min^{-1}; t_R = 4.75 minutes (**12c**), t_R = 5.03 minutes (**13c**).

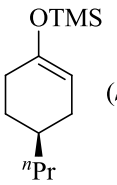
Chiral GC analysis: Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-130 ^oC; temperature gradient; 1.5 ^oC min^{-1}; t_R = 20.53 minutes ((*S*)-**13c**), t_R = 20.85 minutes ((*R*)-**13c**).

$[\alpha]_D^{20}$ = -41.8 ° (94:6 (*S*):(*R*), c = 1.2, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -35.2 ° (88:12 (*S*):(*R*), c = 1.2, $CHCl_3$).[71]

ν_{max}(KBr disc): 1671 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85-4.81 (m, 1H, C=CH), 2.14-2.01 (m, 2H), 2.00-1.92 (m, 1H), 1.79-1.61 (m, 2H), 1.51-1.40 (m, 1H), 1.39-1.20 (m, 5H), 0.90 (t, *J* = 7.1 Hz, 3H, CH_3), 0.19 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 103.7, 38.4, 33.1, 30.5, 29.8, 29.4, 20.4, 14.5, 0.43.



(*S*)-**13c**

(*S*)-(4-Methylcyclohex-1-enyloxy)trimethylsilane (13d)[71]

Achiral GC analysis: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 ^oC (1 min)-190 ^oC; temperature gradient; 20 ^oC min^{-1}; t_R = 3.07 minutes (**12d**), t_R = 3.57 minutes (**13d**).

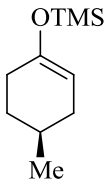
Chiral GC analysis: Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-130 ^oC; temperature gradient; 1.5 ^oC min^{-1}; t_R = 9.23 minutes ((*S*)-**13d**), t_R = 9.40 minutes ((*R*)-**13d**).

$[\alpha]_D^{20}$ = -62.1 ° (95:5 (*S*):(*R*), c = 0.7, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -17.0 ° (91:9 (*S*):(*R*), c = 0.7, $CHCl_3$).[71]

ν_{max}(DCM): 1668 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85-4.81 (m, 1H, C=CH), 2.15-1.92 (m, 2H), 1.73-1.57 (m, 3H), 1.37-1.25 (m, 2H), 0.95 (d, *J* = 6.3 Hz, 3H, CH_3), 0.18 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 103.7, 32.4, 31.4, 29.7, 28.4, 21.3, 0.4.



(*S*)-**13d**

(*S*)-(4-Phenylcyclohex-1-enyloxy)trimethylsilane (13e)[71]

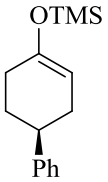
Chiral GC analysis: Chiralsil-DEX CB capillary column; carrier gas H_2 (40 kPa); 110 (1 minute)-150 ^oC; temperature gradient; 1.8 ^oC min^{-1}; t_R = 20.5 minutes ((*S*)-**13e**), t_R = 20.8 minutes ((*R*)-**13e**).

$[\alpha]_D^{20}$ = -36.0 ° (90:10 (*S*):(*R*), c = 2.3, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -33.5 ° (87:13 (*S*):(*R*), c = 2.3, $CHCl_3$).[71]

ν_{max}(DCM): 1670 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.19 (m, 5H, ArH), 4.97-4.96 (m, 1H, C=CH), 2.77-2.75 (m, 1H), 2.30-2.21 (m, 3H), 2.10-2.05 (m, 1H), 1.97-1.86 (m, 2H), 0.23 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 146.6, 128.3, 126.9, 125.0, 103.7, 39.9, 31.9, 30.2, 30.1, 0.4.



(*S*)-**13e**

(*S*)-4-(*tert*-Butyldimethylsilanyloxy)-1-trimethylsiloxy-1-cyclohexene (13f)[70]

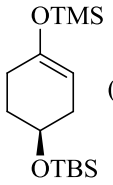
Achiral GC analysis: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 ^{o}C (1 min)-190 ^{o}C; temperature gradient; 20 ^{o}C min^{-1}; t_R = 6.70 minutes (**12f**), t_R = 6.80 minutes (**13f**).

$[\alpha]_D^{20}$ = -30.3 ° (92:8 (*S*):(*R*), c = 0.3, $CHCl_3$). Lit: $[\alpha]_D^{25}$ = -28.8 ° (90:10 (*S*):(*R*), c = 0.3, $CHCl_3$).[70]

ν_{max}(DCM): 1668 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72-4.70 (m, 1H, C=CH), 3.91-3.85 (m, 1H, TBSOCH), 2.23-1.99 (m, 4H), 1.78-1.67 (m, 2H), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 9H, $Si(CH_3)_3$), 0.07 (s, 3H, $Si(C(CH_3)_3)CH_3$), 0.06 (s, 3H, $Si(C(CH_3)_3)CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 101.4, 67.4, 33.4, 31.8, 28.2, 26.0, 18.2, 0.37, -4.61.



(*S*)-**13f**

(*R*)-2,6-Dimethyl-1-trimethylsiloxy-1-cyclohexene, (*R*)-63[71]

Achiral GC analysis: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 ^{o}C (1 min)-190 ^{o}C; temperature gradient; 45 ^{o}C min^{-1}; t_R = 4.20 minutes (**17**), t_R = 4.82 minutes (**63**).

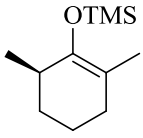
Chiral GC analysis: Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-130 ^{o}C; temperature gradient; 1.7 ^{o}C min^{-1}; t_R = 10.98 minutes ((*R*)-**63**), t_R = 11.28 minutes ((*S*)-**63**).

$[\alpha]_D^{20}$ = +78.4 ° (86:14 (*R*):(*S*), c = 0.1, MeOH). Lit: $[\alpha]_D^{20}$ = -59.2 ° (77:23 (*S*):(*R*), c = 0.1, MeOH).[71]

ν_{max}(DCM): 1679 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15-2.11 (m, 1H), 1.96-1.93 (m, 2H), 1.82-1.74 (m, 1H), 1.66-1.59 (m, 1H), 1.56-1.55 (m, 3H), 1.51-1.42 (m, 1H), 1.41-1.33 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H, CH_3), 0.18 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 112.1, 34.1, 32.3, 30.8, 20.5, 19.0, 16.9, 0.7.



(*R*)-**63**

5. References

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6. Appendix:

X-ray Crystallography Data

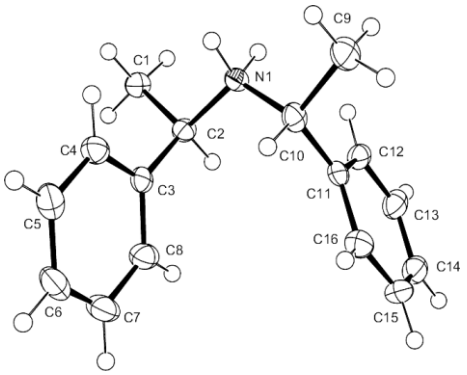


Figure 1.20

Identification code	kerr0603	
Empirical formula	C16 H20 Cl N	
Formula weight	261.78	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	P32	
Unit cell dimensions	a = 22.6779(2) Å	α= 90°.
	b = 22.6779(2) Å	β= 90°.
	c = 7.51450(10) Å	γ = 120°.
Volume	3346.85(6) $Å^3$	
Z	9	
Density (calculated)	1.169 Mg/m^3	
Absorption coefficient	0.240 mm^{-1}	
F(000)	1260	
Crystal size	0.35 x 0.20 x 0.16 mm^3	
Theta range for data collection	3.11 to 26.99°.	
Index ranges	-28<=h<=28, -28<=k<=28, -9<=l<=9	
Reflections collected	45705	
Independent reflections	9731 [R(int) = 0.0327]	
Completeness to theta = 26.99°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.94524	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9731 / 1 / 517	
Goodness-of-fit on F^2	1.027	

Final R indices [I>2sigma(I)]	R1 = 0.0311, wR2 = 0.0685
R indices (all data)	R1 = 0.0364, wR2 = 0.0709
Absolute structure parameter	-0.02(3)
Largest diff. peak and hole	0.502 and -0.179 e.Å^{-3}

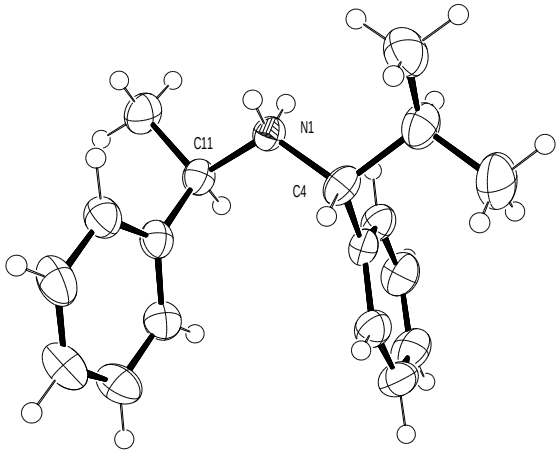


Figure 1.21

Identification code	kerr0906	
Empirical formula	C20 H24 F3 N O2	
Formula weight	367.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Trigonal	
Space group	P32	
Unit cell dimensions	a = 13.1330(3) Å	α= 90°.
	b = 13.1330(3) Å	β= 90°.
	c = 9.7897(3) Å	γ = 120°.
Volume	1462.27(7) Å^3	
Z	3	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	582	
Crystal size	0.35 x 0.33 x 0.28 mm^3	
Theta range for data collection	2.75 to 27.45°.	

Index ranges	-17<=h<=17, -14<=k<=14, -12<=l<=12
Reflections collected	17122
Independent reflections	2213 [R(int) = 0.031]
Completeness to theta = 27.45°	99.2 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2213 / 1 / 246
Goodness-of-fit on F^2	1.081
Final R indices [I>2sigma(I)]	R1 = 0.0558, wR2 = 0.1541
R indices (all data)	R1 = 0.0618, wR2 = 0.1609
Largest diff. peak and hole	0.547 and -0.272 e.Å^{-3}

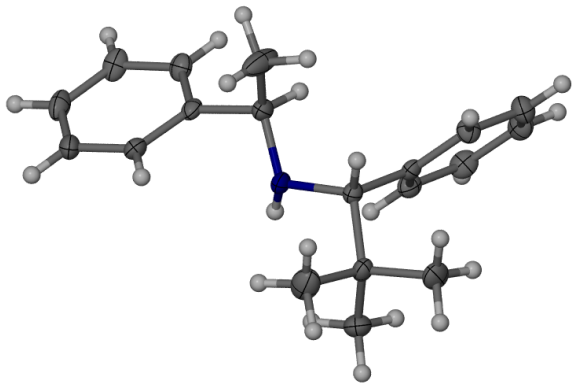


Figure 1.22

Identification code	kerr0603b	
Empirical formula	C19 H25 N	
Formula weight	267.40	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 9.4339(3) Å	α= 90°.
	b = 11.9384(3) Å	β= 90°.
	c = 14.6081(4) Å	γ = 90°.
Volume	1645.25(8) Å^3	
Z	4	

Density (calculated)	1.080 Mg/m^3
Absorption coefficient	0.062 mm^{-1}
F(000)	584
Crystal size	0.45 x 0.22 x 0.20 mm^3
Theta range for data collection	3.09 to 30.05°.
Index ranges	-12<=h<=13, -16<=k<=16, -19<=l<=19
Reflections collected	12590
Independent reflections	4420 [R(int) = 0.0286]
Completeness to theta = 27.00°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.86942
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4420 / 0 / 190
Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0432, wR2 = 0.0830
R indices (all data)	R1 = 0.0568, wR2 = 0.0907
Absolute structure parameter	-1(3)
Extinction coefficient	0.0138(14)
Largest diff. peak and hole	0.203 and -0.164 $e.Å^{-3}$

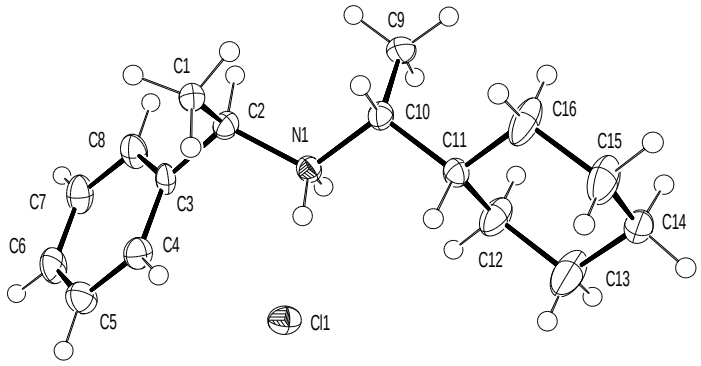
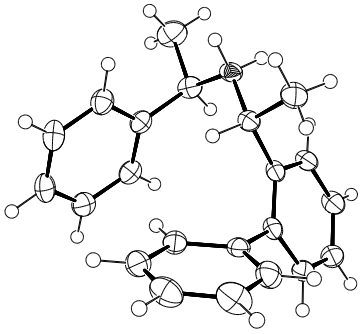


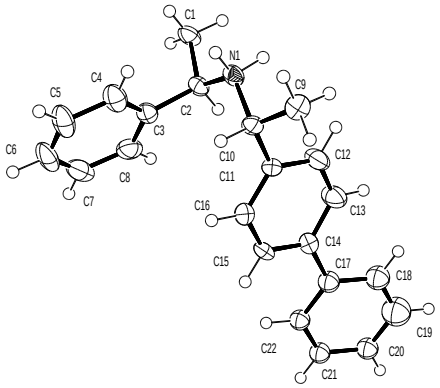
Figure 1.23

Identification code	ker0307b
Empirical formula	C16 H26 Cl N
Formula weight	267.83
Temperature	123(2) K
Wavelength	0.71070 Å

Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.6186(3) Å	α= 90°.
	b = 11.3735(8) Å	β= 90°.
	c = 23.5273(17) Å	γ = 90°.
Volume	1503.47(17) $Å^3$	
Z	4	
Density (calculated)	1.183 Mg/m^3	
Absorption coefficient	0.239 mm^{-1}	
F(000)	584	
Crystal size	0.30 x 0.10 x 0.04 mm^3	
Theta range for data collection	4.46 to 24.98°.	
Index ranges	-5<=h<=6, -13<=k<=13, -27<=l<=27	
Reflections collected	6452	
Independent reflections	2417 [R(int) = 0.079]	
Completeness to theta = 24.98°	95.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2417 / 0 / 165	
Goodness-of-fit on F^2	1.113	
Final R indices [I>2sigma(I)]	R1 = 0.0644, wR2 = 0.0929	
R indices (all data)	R1 = 0.0853, wR2 = 0.0995	
Absolute structure parameter	-0.01(11)	
Largest diff. peak and hole	0.293 and -0.211 $e.Å^{-3}$	



(*R*,*R*)-**167**.HCl



(*R*,*R*)-**168**.HCl

Figure 1.24

(*R*,*R*)-**167**.HCl:

Identification code	ker0507a	
Empirical formula	C22 H24 Cl N	
Formula weight	337.87	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.9884(2) Å	α= 90°.
	b = 11.3959(3) Å	β= 90°.
	c = 18.5925(5) Å	γ = 90°.
Volume	1904.45(8) $Å^3$	
Z	4	
Density (calculated)	1.178 Mg/m^3	
Absorption coefficient	0.203 mm^{-1}	
F(000)	720	
Crystal size	0.35 x 0.15 x 0.10 mm^3	
Theta range for data collection	2.10 to 27.49°.	
Index ranges	-11<=h<=11, -14<=k<=14, -23<=l<=24	
Reflections collected	24148	
Independent reflections	4364 [R(int) = 0.045]	
Completeness to theta = 27.49°	99.8 %	
Absorption correction	None	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4364 / 0 / 228
Goodness-of-fit on F^2	1.077
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.0788
R indices (all data)	R1 = 0.0614, wR2 = 0.0870
Absolute structure parameter	0.00(6)
Largest diff. peak and hole	0.362 and -0.472 e.Å^{-3}

(*R*,*R*)-**168**.HCl:

Identification code	ker0507a	
Empirical formula	C22 H24 Cl N	
Formula weight	337.87	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.9884(2) Å	α= 90°.
	b = 11.3959(3) Å	β= 90°.
	c = 18.5925(5) Å	γ = 90°.
Volume	1904.45(8) Å^3	
Z	4	
Density (calculated)	1.178 Mg/m^3	
Absorption coefficient	0.203 mm^{-1}	
F(000)	720	
Crystal size	0.35 x 0.15 x 0.10 mm^3	
Theta range for data collection	2.10 to 27.49°.	
Index ranges	-11<=h<=11, -14<=k<=14, -23<=l<=24	
Reflections collected	24148	
Independent reflections	4364 [R(int) = 0.045]	
Completeness to theta = 27.49°	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4364 / 0 / 228	
Goodness-of-fit on F^2	1.077	
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.0788	
R indices (all data)	R1 = 0.0614, wR2 = 0.0870	

Absolute structure parameter	0.00(6)
Largest diff. peak and hole	0.362 and -0.472 e.Å^{-3}

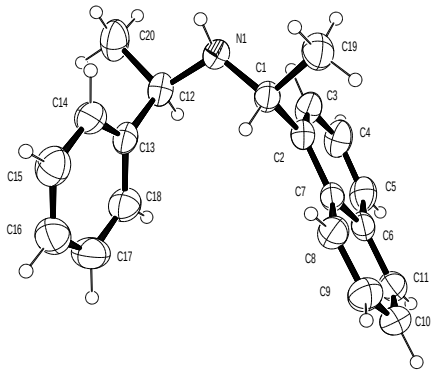


Figure 1.25

Identification code	ark3	
Empirical formula	C20 H21 N	
Formula weight	275.38	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 9.611(5) Å	α= 90°.
	b = 11.799(7) Å	β= 90°.
	c = 14.320(10) Å	γ = 90°.
Volume	1623.9(17) Å^3	
Z	4	
Density (calculated)	1.126 Mg/m^3	
Absorption coefficient	0.065 mm^{-1}	
F(000)	592	
Crystal size	0.35 x 0.30 x 0.20 mm^3	
Theta range for data collection	3.08 to 27.47°.	
Index ranges	-12<=h<=12, -14<=k<=15, -18<=l<=15	
Reflections collected	10239	
Independent reflections	2107 [R(int) = 0.0588]	
Completeness to theta = 27.47°	99.0 %	
Absorption correction	None	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2107 / 0 / 197
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0422, wR2 = 0.0929
R indices (all data)	R1 = 0.0646, wR2 = 0.1036
Absolute structure parameter	6(5)
Extinction coefficient	0.037(5)
Largest diff. peak and hole	0.144 and -0.116 e.Å^{-3}

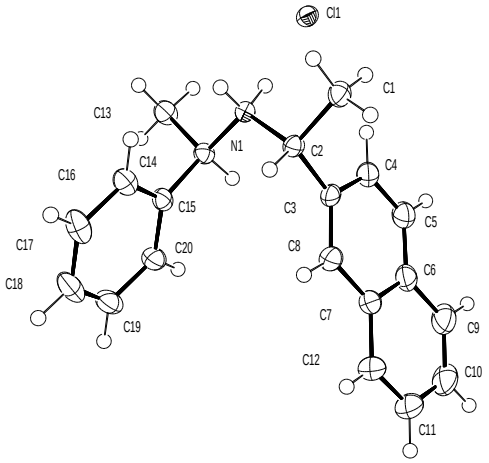


Figure 1.26

Identification code	kerr0407	
Empirical formula	C20 H22 Cl N	
Formula weight	311.84	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.4582(1) Å	α= 90°.
	b = 14.6338(2) Å	β= 90°.
	c = 15.9580(2) Å	γ = 90°.
Volume	1741.69(4) Å^3	
Z	4	
Density (calculated)	1.189 Mg/m^3	
Absorption coefficient	0.216 mm^{-1}	

F(000)	664
Crystal size	0.24 x 0.22 x 0.10 mm^3
Theta range for data collection	2.91 to 27.67°.
Index ranges	-9<=h<=9, -18<=k<=19, -20<=l<=20
Reflections collected	31485
Independent reflections	4015 [R(int) = 0.0374]
Completeness to theta = 27.67°	98.6 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4015 / 0 / 210
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0345, wR2 = 0.0921
R indices (all data)	R1 = 0.0353, wR2 = 0.0931
Absolute structure parameter	0.04(5)
Largest diff. peak and hole	0.470 and -0.207 e.$Å^{-3}$

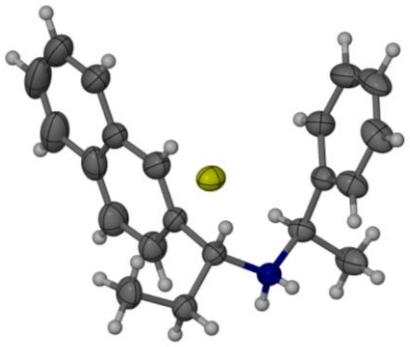


Figure 1.27

Identification code	kerrbena	
Empirical formula	C21 H24 Cl N	
Formula weight	325.86	
Temperature	233(2) K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.6966(2) Å	α= 90°.
	b = 14.6179(3) Å	β= 90°.

	c = 16.2421(4) Å γ = 90°.
Volume	1827.37(8) $Å^3$
Z	4
Density (calculated)	1.184 Mg/m^3
Absorption coefficient	1.820 mm^{-1}
F(000)	696
Crystal size	0.40 x 0.20 x 0.16 mm^3
Theta range for data collection	4.07 to 73.01°.
Index ranges	-9<=h<=6, -17<=k<=18, -18<=l<=20
Reflections collected	6632
Independent reflections	3560 [R(int) = 0.0264]
Completeness to theta = 70.00°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.27120
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3560 / 0 / 219
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0485, wR2 = 0.1351
R indices (all data)	R1 = 0.0505, wR2 = 0.1384
Absolute structure parameter	0.005(18)
Largest diff. peak and hole	0.444 and -0.204 $e.Å^{-3}$

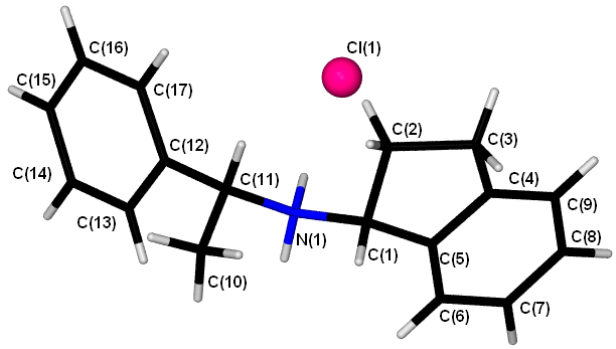


Figure 1.28

Identification code	kerr0409
Empirical formula	C17 H20 Cl N
Formula weight	273.79

Temperature	123(2) K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 5.6368(7) Å	α= 90°.
	b = 11.2383(13) Å	β= 90°.
	c = 23.058(5) Å	γ = 90°.
Volume	1460.7(4) $Å^3$	
Z	4	
Density (calculated)	1.245 Mg/m^3	
Absorption coefficient	2.178 mm^{-1}	
F(000)	584	
Crystal size	0.55 x 0.18 x 0.01 mm^3	
Theta range for data collection	3.83 to 59.98°.	
Index ranges	-4<=h<=6, -12<=k<=12, -25<=l<=25	
Reflections collected	4477	
Independent reflections	1291 [R(int) = 0.0695]	
Completeness to theta = 59.98°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.14663	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1291 / 1 / 187	
Goodness-of-fit on F^2	1.283	
Final R indices [I>2sigma(I)]	R1 = 0.1009, wR2 = 0.2867	
R indices (all data)	R1 = 0.1096, wR2 = 0.2918	
Absolute structure parameter	0.53(8)	
Largest diff. peak and hole	1.272 and -0.435 $e.Å^{-3}$	

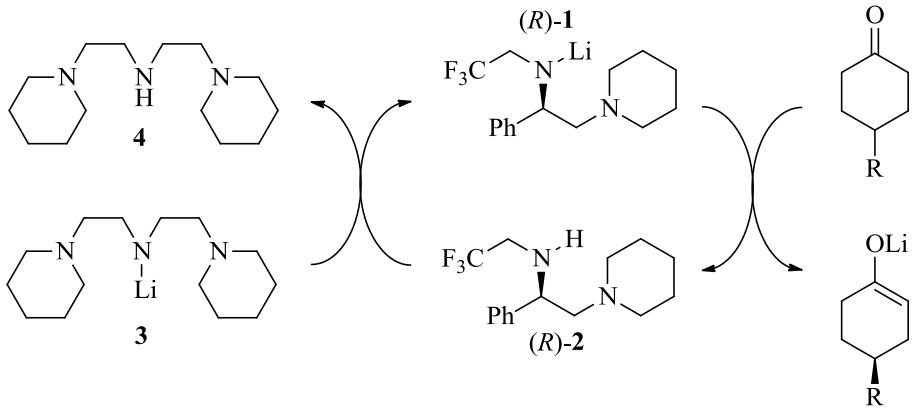
Chapter 2

The development of a recycling protocol

1. Introduction

1.1 Lithium amide-mediated recycling protocols

The asymmetric deprotonation of prochiral ketones using a stoichiometric quantity of a chiral lithium amide base is now a robust tool in organic chemistry, allowing access to an array of synthetically useful chiral compounds.[1] There is, however, a continuous demand among the scientific community for efficient recycling processes which require merely a substoichiometric quantity of chiral reagent. In this regard, Koga conducted the initial investigations towards a recycling protocol for the lithium amide-mediated asymmetric deprotonation.[2] The proposed reaction cycle for such a process is outlined in **Scheme 2.1**.

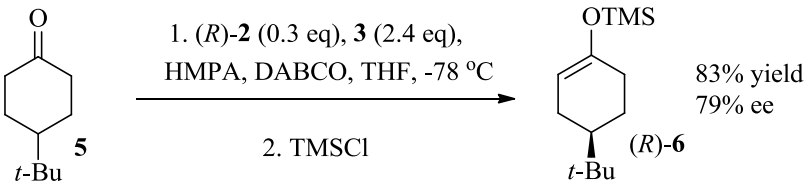


Scheme 2.1

Koga suggested that after the chiral lithium amide ((*R*)-**1**) had deprotonated the prochiral ketone, liberating free chiral amine ((*R*)-**2**) in solution, the chiral base could be regenerated by employing a stoichiometric quantity of an achiral lithium amide, such as **3** (**Scheme 2.1**). Tridentate lithium amides were chosen since they had been shown to be less reactive towards ketone deprotonation than those derived from diamines.[2] Furthermore, by employing an electron-withdrawing trifluoromethyl group on the chiral

amine ((*R*)-**2**), it was envisaged that lithium-hydrogen exchange with the achiral lithium base (**3**) would occur rapidly to form the chiral lithium amide ((*R*)-**1**) preferentially.

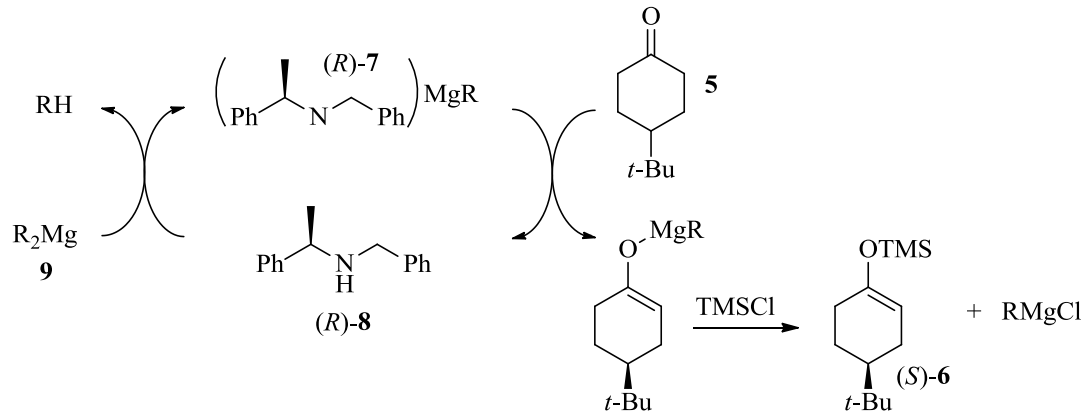
Accordingly, the chelating amine ((*R*)-**2**) was employed in a sub-stoichiometric quantity of 0.3 equivalents, along with 2.4 equivalents of the achiral base (**3**), for the deprotonation of the benchmark substrate, 4-*tert*-butylcyclohexanone (**5**, **Scheme 2.2**). Trapping of the resultant lithium enolate using TMSCl under external quench conditions yielded 83% of the silyl enol ether ((*R*)-**6**) in a good 79% ee.



Scheme 2.2

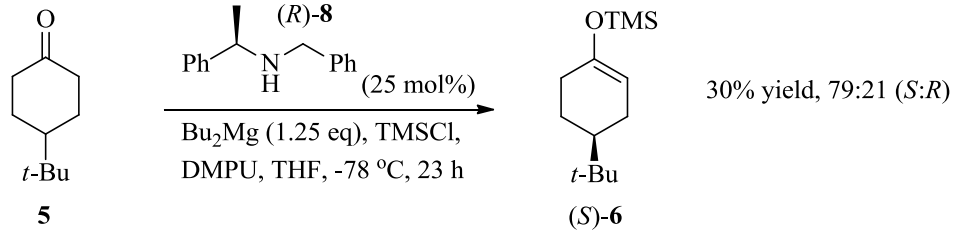
1.2 Magnesium amide-mediated recycling protocols

Having established the asymmetric deprotonation of conformationally-locked cyclic ketones using a stoichiometric quantity of a chiral magnesium amide base, the development of an efficient recycling protocol, which would operate using only a sub-stoichiometric quantity of chiral reagent became a key goal within our research group. It was envisaged that after a chiral alkylmagnesium amide ((*R*)-**7**) had deprotonated the substrate, liberating the free chiral amine ((*R*)-**8**) in solution, the chiral base ((*R*)-**7**) could be regenerated by reaction of the chiral amine with a stoichiometric quantity of dialkylmagnesium (**9**). The reaction cycle which was proposed for such a process is outlined in **Scheme 2.3**.[3]



Scheme 2.3

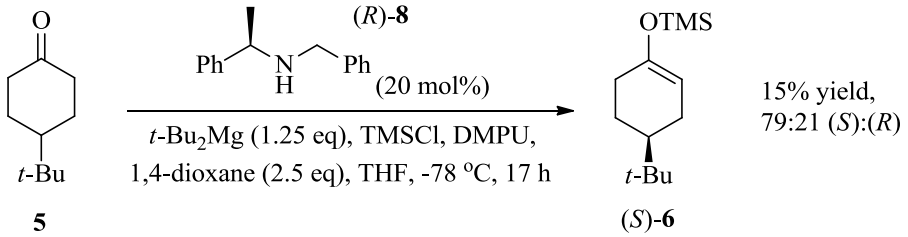
Initial attempts to perform a recycling reaction centred on the use of di-butylmagnesium (as a mixture of *n*- and *s*-isomers) as the bulk organometallic reagent. More specifically, 1.25 equivalents of dibutylmagnesium were employed alongside 25 mol% of the chiral amine ((*R*)-**8**), furnishing the enantioenriched silyl enol ether ((*S*)-**6**) in a 30% yield and 79:21 er (**Scheme 2.4**).[3]



Scheme 2.4

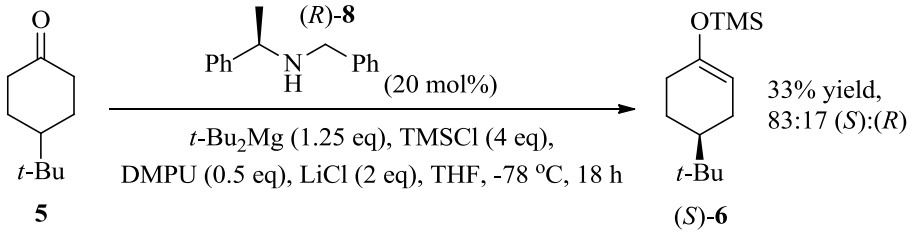
Despite these relatively promising results, further analysis of the reaction products revealed that significant amounts of unwanted side-products were being formed, namely the products of alkylation and reduction of the ketone. With the aim of suppressing such unwanted side reactions, the more sterically hindered and less nucleophilic organomagnesium source, di-*tert*-butylmagnesium (prepared *via* the reaction of *t*-BuLi with *t*-BuMgCl followed by filtration to remove LiCl),[4] was employed.[3] Additionally,

since it was apparent that a potentially less selective Hauser base species could be formed during the reaction, 1,4-dioxane was employed in order to induce disproportionation of the Hauser base to its corresponding magnesium bisamide.[5] It was envisaged that these changes in the reaction conditions could result in a more selective recycling system. However, as illustrated in **Scheme 2.5**, the selectivity remained the same as before and a lower reaction yield was achieved.[3] In addition, during the course of this study, it was suspected that variable quantities of residual LiCl, formed during the preparation of *t*-Bu_2Mg, could be present in the reaction mixture, and were responsible for inconsistent and irreproducible results.



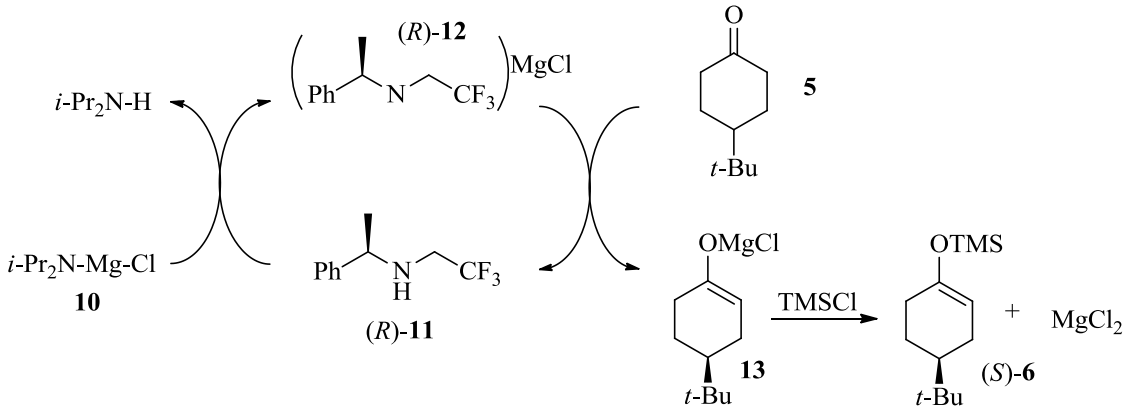
Scheme 2.5

With these initial results in hand, an exhaustive assessment of all reaction variables, including addition of salts and donor species, as well as variation of the chiral amine, was carried out.[6] In addition, in order to access *t*-Bu_2Mg without the concomitant formation of LiCl, disproportionation of the parent Grignard species was employed, mediated by 1,4-dioxane.[5] Unfortunately, after these extensive studies and despite appreciable enantioselectivities, the reaction conversion remained poor at -78 °C, with the optimum results being achieved under the conditions shown in **Scheme 2.6**. Attempting to increase the reaction conversion by performing the reaction at an elevated temperature of -40 °C led to a competing achiral deprotonation, mediated by *t*-Bu_2Mg.[6] Based on this precedent, it was evident that an alternative approach was needed.



Scheme 2.6

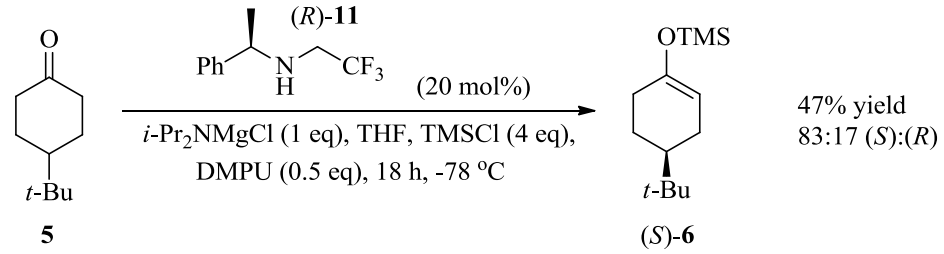
A perceived problem associated with the recycling approaches explored thus far was the slow rate of alkylmagnesium amide regeneration at the low temperatures required to deliver appreciable enantioselectivities. Thus, an alternative method, relying upon an amide transfer procedure was explored (**Scheme 2.7**).[6] This method involved the use of a preformed achiral Hauser base species (**10**), which was used with a sub-stoichiometric quantity of a more acidic trifluoromethyl-substituted chiral amine ((*R*)-**11**), allowing magnesium-hydrogen exchange with the achiral magnesium base to occur rapidly to form the chiral magnesium amide ((*R*)-**12**) preferentially.



Scheme 2.7

The results achieved when applying the amide transfer protocol to the benchmark deprotonation reaction are outlined below (**Scheme 2.8**).[6] By employing this alternative procedure, improvements were gained over the original approach in both the reaction yield and enantioselectivity. To date, the amide transfer protocol has proved to be the

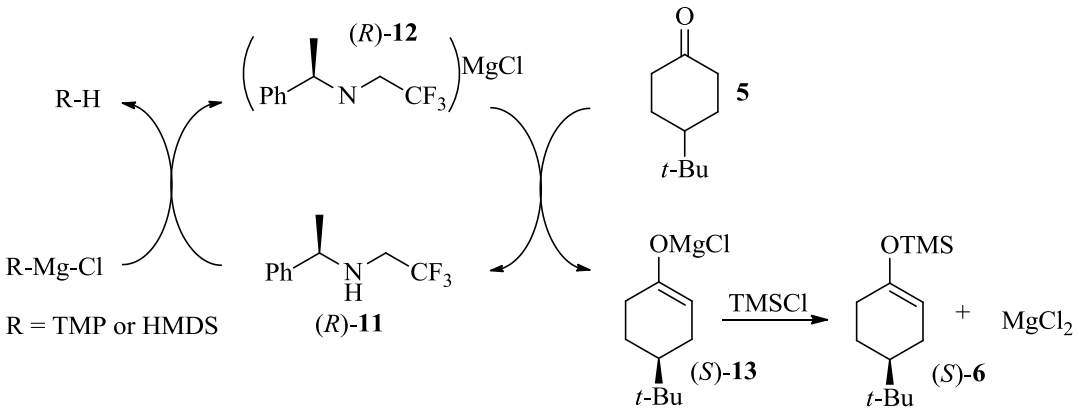
most promising for the development of a recycling protocol for magnesium amide-mediated asymmetric deprotonations.



Scheme 2.8

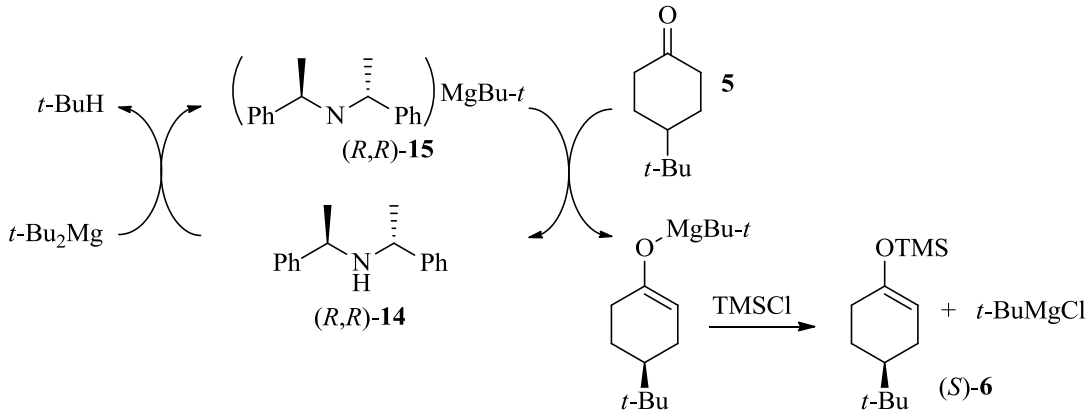
2. Proposed work

Due to encouraging results being achieved previously in our recycling protocol utilising an amide transfer approach, further investigations will be carried out using this method. More specifically, (TMP)MgCl and (HMDS)MgCl will be employed as alternative Hauser bases to the previously studied *i*-Pr_2NMgCl, under the optimised conditions for the amide transfer protocol, to evaluate what effect these more sterically-encumbered species impart on the asymmetric transformation (**Scheme 2.9**). It is envisaged that the rate of any non-selective deprotonation of 4-*tert*-butylcyclohexanone by the achiral Hauser base species could be minimised by employing these bulkier Hauser bases.



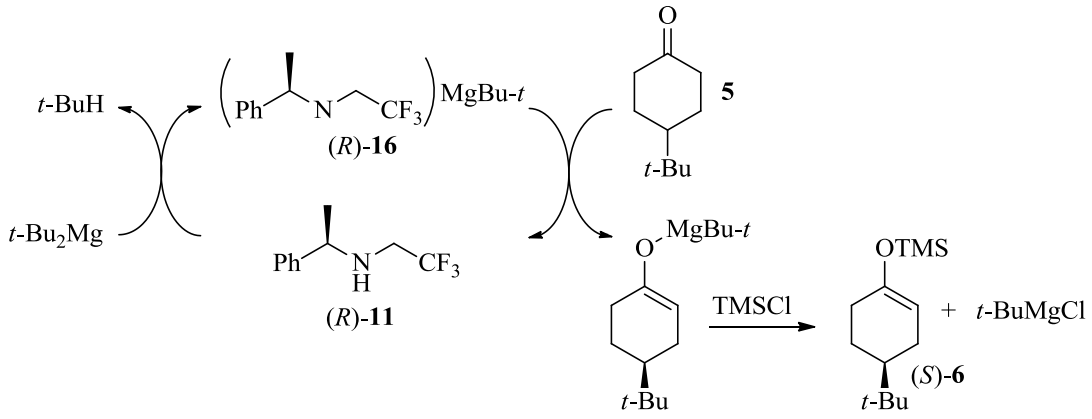
Scheme 2.9

Previous investigations have illustrated that magnesium amide species derived from the C_2-symmetric amine ((*R*,*R*)-**14**) are highly enantioselective bases over a range of temperatures above -78 ^{o}C.[7] Indeed, the magnesium bisamides and Hauser bases[6] of amine (*R*,*R*)-**14** have proven to be some of the most selective and efficient magnesium bases developed to date. However, the use of this enantiopure amine in the development of a recycling protocol has not been fully explored.[6] With the object of increasing the efficiency of our dialkylmagnesium-mediated recycling protocol, the C_2-symmetric chiral amine ((*R*,*R*)-**14**) will be employed in optimisation studies using di-*tert*-butylmagnesium as the bulk organometallic reagent (**Scheme 2.10**).



Scheme 2.10

In addition, attention will be focused on the use of an alternative, more acidic, chiral amine (**11**, **Scheme 2.11**). Extensive studies employing this amine in the amide transfer protocol have previously been carried out.[6] However, the efficiency of reactions employing this amine and di-*tert*-butylmagnesium as the stock magnesium source has not been fully explored. It is envisaged that by using the more acidic, fluorinated amine (**11**), formation of the selective base species will occur more readily than in earlier investigations employing chiral dibenzylamines at low temperatures.[3,6]

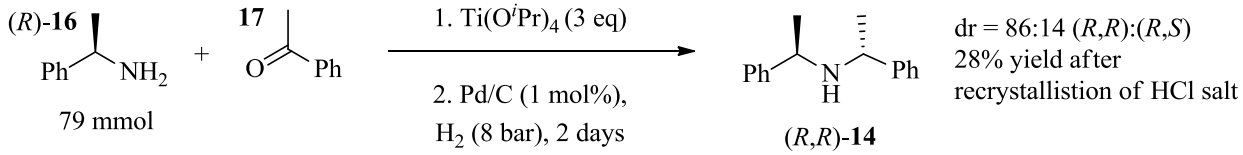


Scheme 2.11

3. Results and discussion

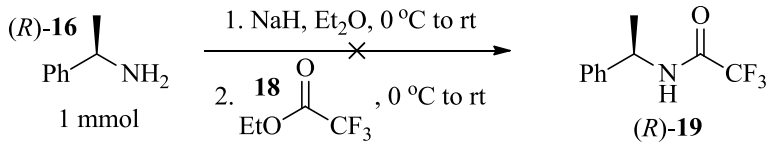
3.1 Synthesis of reagents

As described in the previous section, attempts to establish a recycling protocol for the magnesium amide-mediated asymmetric deprotonation of the benchmark prochiral ketone, 4-*tert*-butylcyclohexanone, have delivered somewhat disappointing results.[3,6] Thus, it remains a major goal within our research group to develop an efficient recycling process. Therefore, a number of possible alternative approaches were devised, and, during a two month placement at the University of Notre Dame, Indiana, in the laboratory of Professor Kenneth Henderson, initial investigations were performed. In order to allow evaluation of the proposed alternative approaches, the preparation of the appropriate optically-pure amine ligands was required. To begin, the C_2-symmetric amine ((*R*,*R*)-**14**) was prepared, employing conditions developed by Alexakis[8] to deliver the product with good diastereoselectivity (86:14, (*R*,*R*):(*R*,*S*)) and sufficient yield of optically-pure amine after recrystallisation of the hydrochloride salt (**Scheme 2.12**).



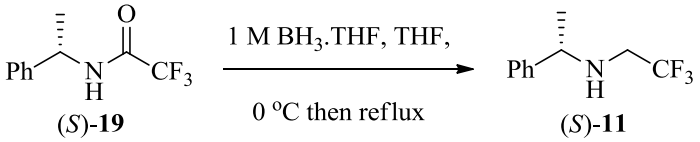
Scheme 2.12

Subsequently, synthesis of the more acidic, trifluoromethyl-substituted, chiral amine ((*R*)-**11**) was attempted *via* the corresponding amide ((*R*)-**19**, **Scheme 2.13**). Surprisingly, deprotonation of (*R*)-phenylethylamine (**16**) using sodium hydride, followed by treatment of the reaction mixture with ethyl trifluoromethylacetate (**18**), led to none of the desired product being isolated.



Scheme 2.13

Consequently, the commercially-available (*S*)-enantiomer of **19** was obtained and was reduced to the desired amine *via* a borane-mediated reduction (**Scheme 2.14**, **Table 2.1**). Using this method, the trifluoromethyl-substituted amine ((*S*)-**11**) was obtained in high yield on a multi-gram scale.

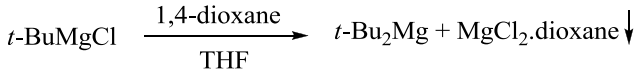


Scheme 2.14

Entry	Scale (mmol)	Yield (%)
1	1	75
2	46	72

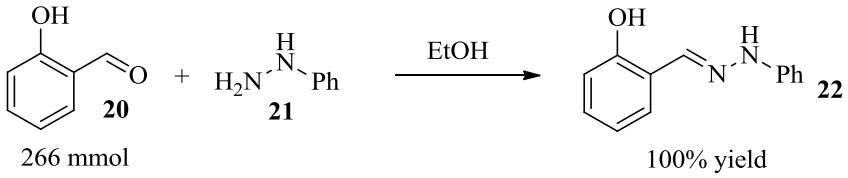
Table 2.1

With the required chiral amines in hand, preparation of di-*tert*-butylmagnesium was carried out, using the standard procedure adopted within our research group (**Scheme 2.15**).[5] This involved the treatment of *tert*-butylmagnesium chloride in THF with 1,4-dioxane, inducing disproportionation of the Grignard species to the corresponding dialkylmagnesium. This was accompanied by precipitation of the polymeric complex formed between magnesium chloride and 1,4-dioxane, allowing the removal of the supernatant di-*tert*-butylmagnesium as a solution in THF.



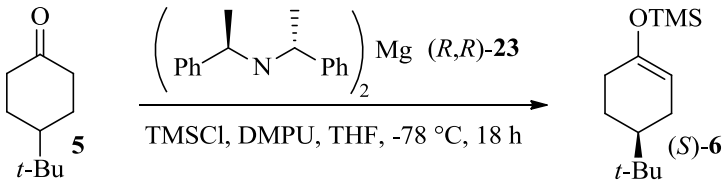
Scheme 2.15

To allow the determination of the concentration of the resulting THF solution, salicylaldehyde phenylhydrazone (**22**, **Scheme 2.16**) was then prepared. This compound is commonly used in the standardisation of solutions of organometallic reagents, which is possible due to the colour change observed on its deprotonation.[9] Pleasingly, large quantities of salicylaldehyde phenylhydrazone were obtained cleanly and in quantitative yield by simply stirring salicylaldehyde (**20**) together with phenylhydrazine (**21**) in ethanol and filtering the resulting suspension.



Scheme 2.16

Having prepared the required organometallic reagents and chiral amines, a test reaction was performed in order to ensure the transferability of our magnesium amide-mediated deprotonation to an alternative research lab (**Scheme 2.17**, **Table 2.2**). Gratifyingly, employing the standard conditions developed for our C_2-symmetric magnesium amide, reproducible high yields and enantioselectivities were achieved. Moreover, the observed yields and enantioselectivities were consistent with those obtained in our laboratory at Strathclyde.[7] With these results in hand, asymmetric deprotonation reactions under novel recycling conditions could be attempted.



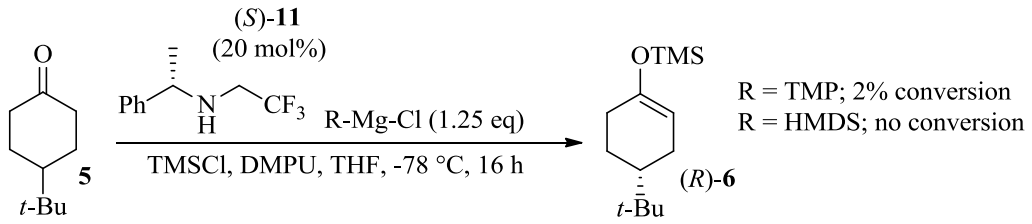
Scheme 2.17

Entry	Conversion (%)	Yield (%)	(*S*):(*R*)
1	95	83	93:7
2	97	86	93:7
3	96	87	92:8
4	94	82	93:7

Table 2.2

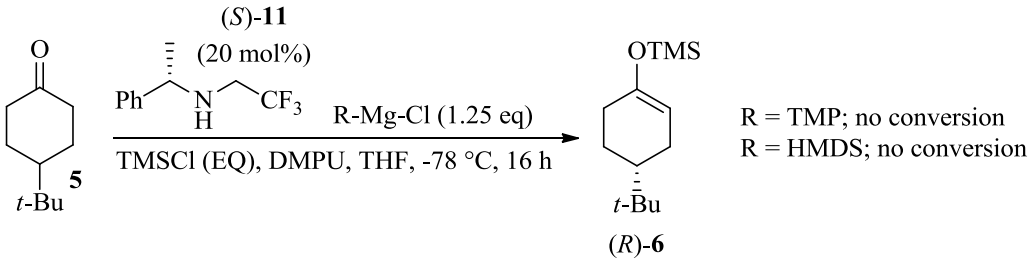
3.2 Recycling reactions employing Hauser bases

At first, alternative Hauser bases to the previously studied *i*-Pr_2NMgCl were employed under the optimised conditions for the amide transfer protocol.[6] It was envisaged that, by utilising more sterically encumbered Hauser bases, the rate of any non-selective deprotonation of 4-*tert*-butylcyclohexanone by the achiral Hauser base species could be minimised. Thus, (HMDS)MgCl and (TMP)MgCl were chosen as possible alternatives. Disappointingly, however, employing 1.25 equivalents of these alternative Hauser bases at -78 ^{o}C alongside chiral amine (*S*)-**11**, TMSCl and DMPU in THF, no significant formation of the silyl enol ether product was observed (**Scheme 2.18**).



Scheme 2.18

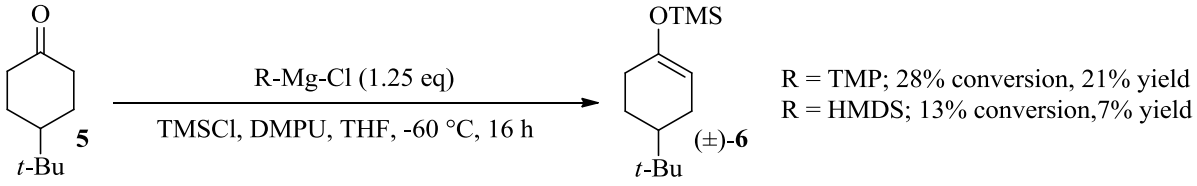
In the development of an asymmetric deprotonation procedure mediated by a substoichiometric quantity of chiral lithium amide, Koga employed an external quench protocol to avoid *N*-silylation of the chiral amine (**2**) by TMSCl.[2] Thus, external quench conditions were then applied to the desymmetrisation of **5**, in an attempt to increase the reaction conversion using the alternative Hauser bases (**Scheme 2.19**). However, utilising an external quench protocol in our amide transfer approach resulted in no conversion to the desired product.



Scheme 2.19

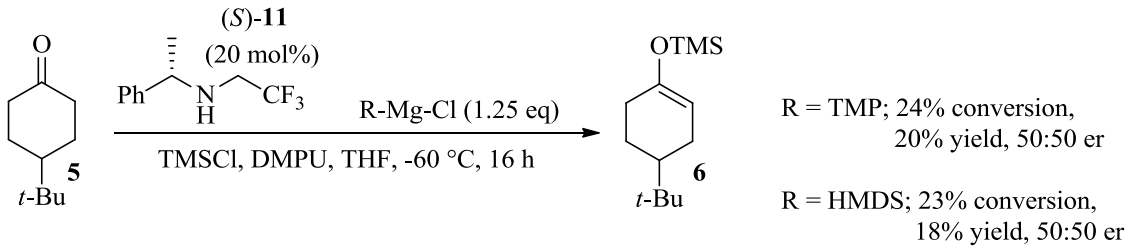
When examining the results achieved thus far, it was apparent that the main problem in this approach is the lack of formation of the selective magnesium amide species at -78 ^{o}C. Encouraging, however, was the fact that the achiral Hauser base species did not show any reactivity towards the ketone substrate at this temperature. It was envisaged that the overall reactivity of the system could be increased by employing a more elevated reaction temperature. However, before attempting asymmetric deprotonations at elevated temperatures, control reactions were required to evaluate the reactivity of the achiral

Hauser base species towards **5**. Hence, control reactions at -60 °C in the presence of no chiral amine ((*S*)-**11**) were performed (**Scheme 2.20**). Under these conditions, low levels of conversion to the silyl enol ether were achieved.



Scheme 2.20

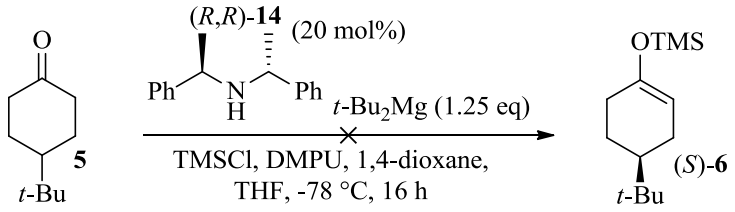
Although conversion of the ketone substrate (**5**) to the corresponding silyl enol ether was observed in reactions using both (HMDS)MgCl and (TMP)MgCl at -60 °C, the conversions were deemed sufficiently low to merit evaluation of the asymmetric variants at the same temperature. It was envisaged that this would allow determination of the ability of the chiral Hauser base, formed from chiral amine ((*S*)-**11**), to compete with the achiral magnesium amide source in the deprotonation of 4-*tert*-butylcyclohexanone (**5**) at elevated temperatures. Disappointingly, however, no enantioenrichment in the silyl enol ether product (**6**) was achieved under the conditions shown (**Scheme 2.21**). Due to the lack of success achieved using (TMP)MgCl and (HMDS)MgCl in the amide transfer protocol, an alternative recycling method was explored.



Scheme 2.21

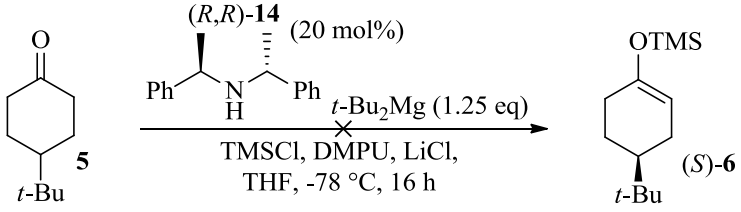
3.3 Recycling reactions employing *t*-Bu_2Mg

Previous investigations in our research group have illustrated that magnesium amide species derived from the C_2-symmetric amine ((*R*,*R*)-**14**) are highly enantioselective bases over a range of temperatures above -78 °C.[6,7] However, the use of this optically-pure amine in the development of a recycling protocol has not been fully explored.[6] With the object of increasing the efficiency of our dialkylmagnesium-mediated recycling protocol, the C_2-symmetric chiral amine ((*R*,*R*)-**14**) was employed in optimisation studies. To start, amine (*R*,*R*)-**14** was utilised in place of (*R*)-**8**, which has been employed in most of the recycling studies to date,[3,6] under the originally developed recycling conditions with 1,4-dioxane and DMPU as additives (**Scheme 2.22**).[3] Surprisingly, no conversion to the silyl enol ether (**6**) was achieved.



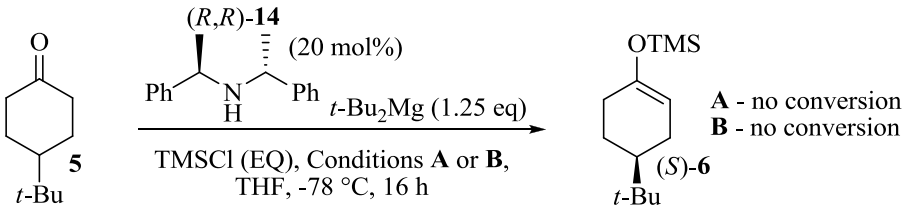
Scheme 2.22

Subsequently, alternative conditions, which have previously delivered high enantioselectivity (although with moderate conversion) with (*R*)-**8** alongside LiCl and DMPU as additives,[6] were employed (**Scheme 2.23**). However, once more, no conversion of the starting material was obtained under these alternative conditions.



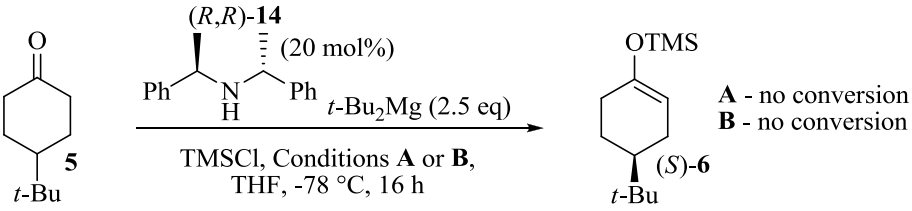
Scheme 2.23

As mentioned previously, Koga discovered that it was necessary to follow an external quench procedure when developing a lithium amide-mediated asymmetric deprotonation protocol, due to *N*-silylation of the chiral amine (**2**).[2] Accordingly, subsequent asymmetric deprotonations were attempted under external quench conditions, utilising either LiCl and DMPU (conditions **A**)[6] or 1,4-dioxane and DMPU (conditions **B**)[3] as additives, in an attempt to increase the reactivity of the system (**Scheme 2.24**). Disappointingly, employing an external quench procedure under both sets of conditions resulted in no conversion to the silyl enol ether product (**6**).



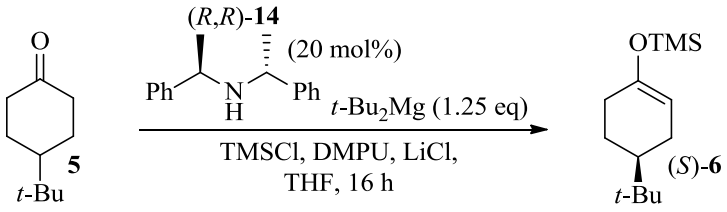
Scheme 2.24

Subsequently, the effect of increasing the quantity of the magnesium source was investigated. More specifically, the number of equivalents of di-*tert*-butylmagnesium was increased from 1.25 to 2.5 in an attempt to affect conversion of the starting material (**Scheme 2.25**). Unfortunately, employing DMPU and either LiCl (Conditions **A**) or 1,4-dioxane (Conditions **B**) as additives, no conversion to the silyl enol ether (**6**) was achieved.



Scheme 2.25

In a further attempt to increase the reactivity of the system, the recycling reactions were attempted over a range of elevated temperatures (**Scheme 2.26**, **Table 2.3**). As described previously, magnesium amide bases derived from the C_2-symmetric amine ((*R*,*R*)-**14**) have proven to be highly enantioselective bases over a range of temperatures above -78 ^{o}C.[7] In addition, since results from parallel optimisation studies (detailed in the following section), employing the more acidic trifluoromethyl-substituted amine ((*S*)-**11**), had revealed the most promising results when employing LiCl and DMPU as additives, these conditions were applied to the temperature study using the C_2-symmetric amine ((*R*,*R*)-**14**). Initially, employing a reaction temperature of -60 ^{o}C, no conversion of the ketone starting material was achieved (**Table 2.3**, entry 1). Accordingly, a higher temperature of -40 ^{o}C was employed under the same conditions (**Table 2.3**, entry 2). At this relatively high temperature, an excellent reaction conversion was achieved. However, no enantioselection had occurred in the reaction. This is, most likely, due to a non-selective deprotonation, mediated by di-*tert*-butylmagnesium, at this temperature. Indeed, carbon-centred bases, such as di-*tert*-butylmagnesium, have been shown to be highly efficient bases for the formation of a range of silyl enol ethers from enolisable ketones at more elevated temperatures.[10] Thus, an intermediate temperature of -50 ^{o}C was chosen in an attempt to maintain the high conversion obtained at -40 ^{o}C, while imparting greater enantioselectivity. At this temperature, however, a lower reaction conversion was achieved, and no enantioselectivity was observed (**Table 2.3**, entry 3).

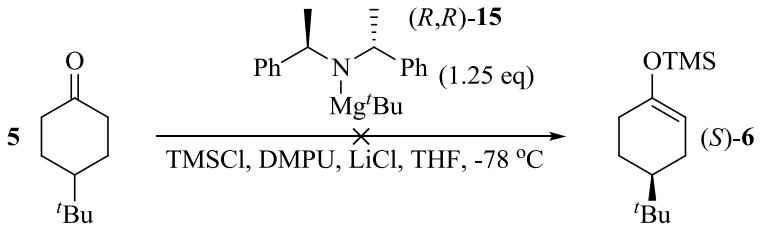


Scheme 2.26

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	(*S*):(*R*)
1	-60	0	-	-
2	-40	96	87	50:50
3	-50	59	50	50:50

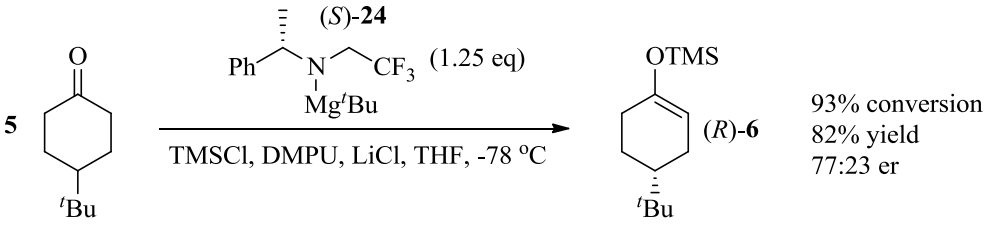
Table 2.3

Upon further consideration of the results that had been achieved using the C_2-symmetric amine ((*R*,*R*)-**14**) alongside di-*t*-butylmagnesium, we were puzzled by the fact that no conversion is observed at -78 ^{o}C. The practical method involves addition of 20 mol% of the chiral amine ((*R*,*R*)-**14**) to a solution of di-*t*-butylmagnesium and LiCl in THF, followed by stirring at room temperature for 1.5 hours before being cooled to -78 ^{o}C for reaction with the ketone substrate (**5**). Under these conditions, it was assumed that at least 20 mol% of the chiral alkylmagnesium amide ((*R*,*R*)-**15**) would form, and would subsequently react with the substrate to deliver the enol silane product (**6**). Indeed, it has been shown that alkylmagnesium amide reagents can be prepared at room temperature using one equivalent of di-*n*-butylmagnesium alongside one equivalent of the appropriate amine.[6,11] Therefore, a test reaction employing a stoichiometric quantity (one equivalent) of chiral amine was performed, to ascertain whether any conversion to the enol silane product could be achieved (**Scheme 2.27**). Surprisingly, no conversion to the desired product was observed. This led us to deduce that, most likely, the alkylmagnesium amide ((*R*,*R*)-**15**) does not form when di-*t*-butylmagnesium is employed at room temperature or, indeed, at -78 ^{o}C. Consequently, at this stage in the development of a recycling protocol, attention was turned to the potentially more acidic, fluorinated amine ((*S*)-**11**).



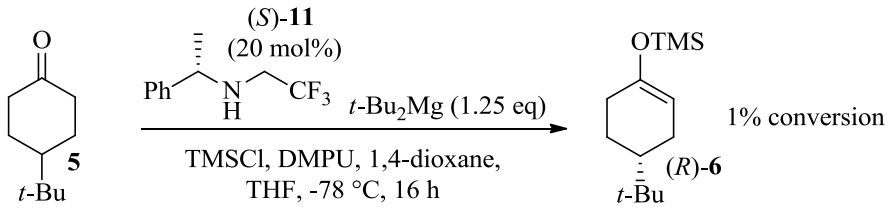
Scheme 2.27

Extensive studies employing the fluorinated amine ((*R*)-**11**) in the amide transfer protocol have previously been carried out.[6] However, the efficiency of reactions employing this amine and di-*tert*-butylmagnesium as the stock magnesium source has not been fully explored. In light of the problems encountered when employing the C_2-symmetric amine ((*R*,*R*)-**14**), a reaction employing a stoichiometric quantity of the alkylmagnesium amide ((*R*)-**24**) was attempted (**Scheme 2.28**). Pleasingly, we found that high yields could be achieved under these conditions, alongside moderate enantioselectivity.



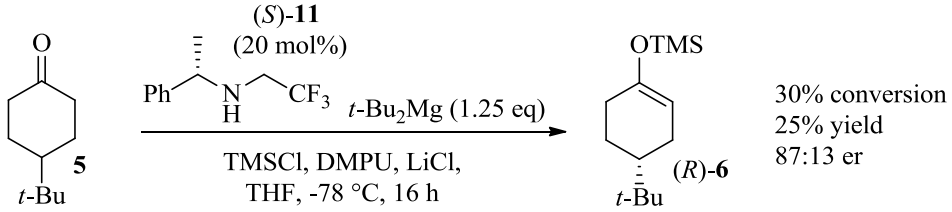
Scheme 2.28

Initial investigations into the development of a recycling protocol employing (*S*)-**11** were performed utilising DMPU and either LiCl or 1,4-dioxane as additives with 20 mol% of the fluorinated amine ((*S*)-**11**), 1.25 equivalents of di-*tert*-butylmagnesium, and TMSCl to trap the magnesium enolate at -78 °C. When employing DMPU and 1,4-dioxane as additives, no appreciable conversion to the silyl enol ether product (**6**) was observed (**Scheme 2.29**).



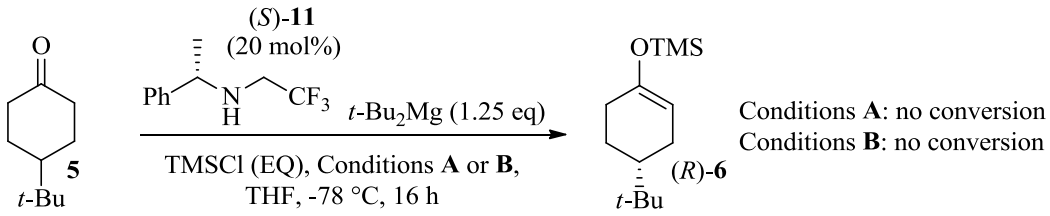
Scheme 2.29

In contrast to the above, when DMPU and LiCl were utilised, the silyl enol ether (**6**) was isolated in 25% yield and with a relatively high enantiomeric ratio of 87:13 (**Scheme 2.30**). Since the conversion for the reaction was shown by GC analysis to be greater than the maximum possible conversion using only 20 mol% of the chiral amine, it was apparent that a recycling process was, indeed, taking place.



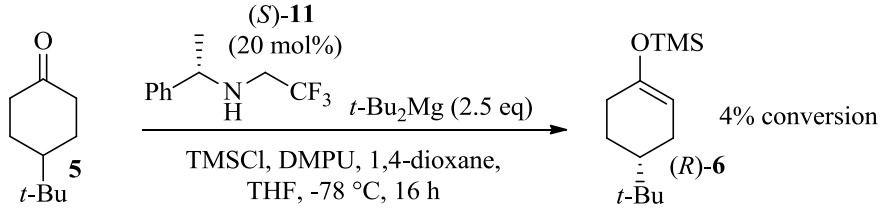
Scheme 2.30

As mentioned previously, Koga discovered that it was necessary to avoid *N*-silylation of the chiral amine (**2**) by following an external quench procedure when developing a lithium amide-mediated asymmetric deprotonation protocol.[2] For that reason, subsequently attempted recycling reactions were conducted under external quench conditions, utilising either LiCl and DMPU (conditions **A**) or 1,4-dioxane and DMPU (conditions **B**) as additives, in an attempt to increase the reactivity of the system (**Scheme 2.31**). Disappointingly, no conversion to the silyl enol ether product (**6**) was achieved using either set of conditions.



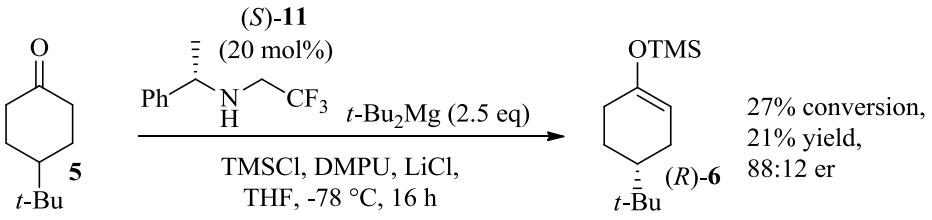
Scheme 2.31

In a further attempt to furnish higher conversions in our recycling reactions, a greater quantity of di-*tert*-butylmagnesium was employed, using DMPU and either 1,4-dioxane or LiCl as additives. Unfortunately, employing double the standard amount of di-*tert*-butylmagnesium with DMPU and 1,4-dioxane as additives, a poor reaction conversion of only 4% was achieved (**Scheme 2.32**).



Scheme 2.32

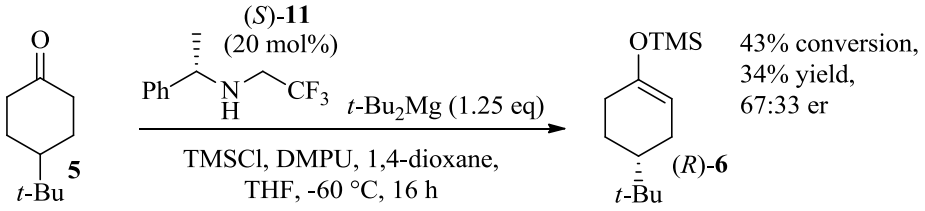
Contrastingly, when DMPU and LiCl were employed as additives alongside 2.5 equivalents of di-*tert*-butylmagnesium, the silyl enol ether was isolated in 21% yield and high enantioselectivity (88:12, **Scheme 2.33**). We were pleased to note that the observed enantioselectivity was comparable with that obtained when half the amount of di-*tert*-butylmagnesium was employed, indicating that using a larger excess of di-*tert*-butylmagnesium does not result in an increase in the amount of non-selective deprotonation.



Scheme 2.33

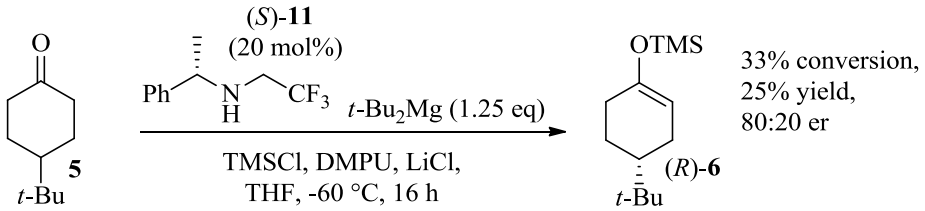
Subsequently, a more elevated temperature of -60 ^{o}C was employed in an attempt to increase the conversion to the silyl enol ether product ((*R*)-**6**). When employing DMPU

and 1,4-dioxane as additives, the reaction conversion was, indeed, increased to 43% (**Scheme 2.34**). However, the observed enantioselectivity was moderate (67:33 er).



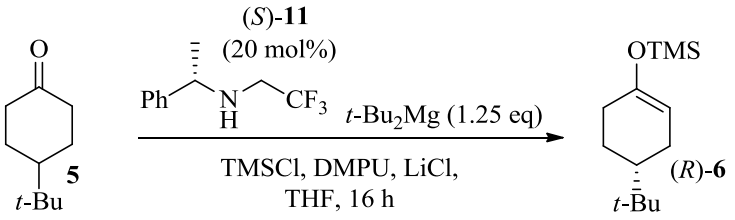
Scheme 2.34

Alternatively, when DMPU and LiCl were employed at -60 ^{o}C, the reaction conversion remained in line with that obtained at -78 ^{o}C, while the enantioselectivity dropped slightly to 80:20 er (**Scheme 2.35**). Since the most promising results so far were achieved using DMPU and LiCl as additives, these conditions were employed in subsequent optimisation studies.



Scheme 2.35

In order to fully evaluate the efficiency and enantioselectivity achieved when DMPU and LiCl were employed at more elevated temperatures, a temperature study was carried out (**Scheme 2.36**, **Table 2.4**). While the reaction conversion increased significantly on increasing the reaction temperature from -60 ^{o}C to -50 ^{o}C and -40 ^{o}C, the enantioselectivity of the reaction decreased considerably, and remained at a comparable level at both -50 ^{o}C and -40 ^{o}C.

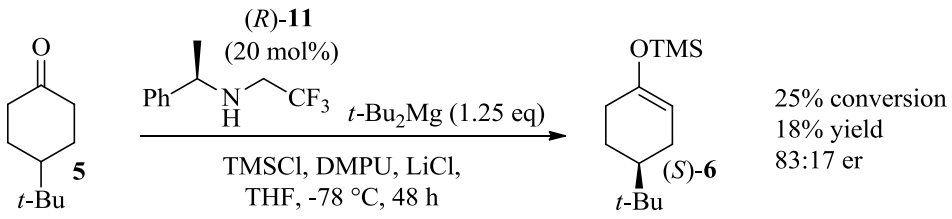


Scheme 2.36

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	(*R*):(*S*)
1	-40	94	83	67:33
2	-50	66	58	66:34

Table 2.4

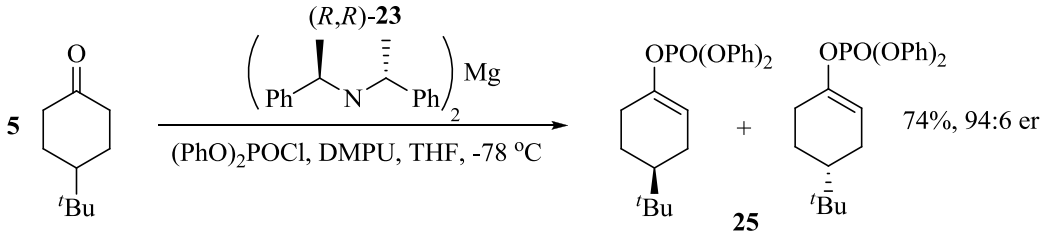
Since the poor conversions achieved so far could not be improved by increasing the reaction temperature, as a concomitant decrease in the enantioselectivity was observed, on returning from Notre Dame, an attempt was made to increase the conversion to the desired product (**6**) by employing an extended reaction time. More specifically, the conditions which had delivered the greatest selectivity and conversion during this short period of optimisation were applied to the desymmetrisation of **5** over a reaction time of 48 hours (**Scheme 2.37**). The (*R*)-enantiomer of the chiral amine (**11**) was employed due to its availability in our lab. Disappointingly, under these conditions, the silyl enol ether product ((*S*)-**6**) was obtained in similar yield and enantioselectivity to that achieved previously.



Scheme 2.37

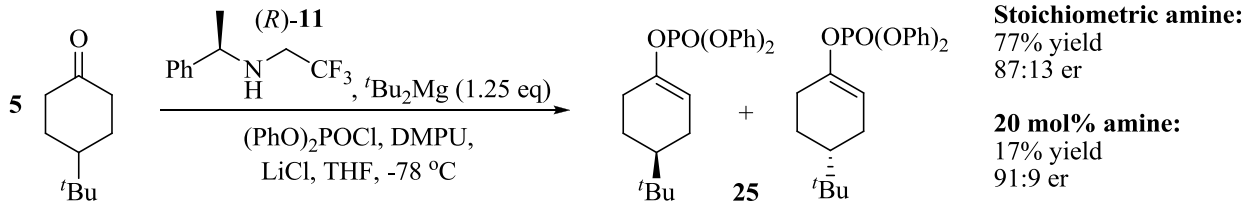
3.4 Investigations into an alternative electrophile

Attention was then turned to the use of diphenylphosphoryl chloride as an alternative, and possibly more activating electrophile. Initially, the performance of this electrophile in the benchmark stoichiometric asymmetric deprotonation reaction was assessed (**Scheme 2.38**). To our delight, this alternative electrophile, which can provide access to useful enol phosphate compounds,[12] was applied to the desymmetrisation of 4-*tert*-butylcyclohexanone to deliver the enantioenriched enol phosphate (**25**) in high yield and excellent enantioselectivity. It should also be noted that the enol phosphate product (**25**) is significantly more stable than the corresponding enol silane (**6**), surviving acidic aqueous work-up and relatively slow column chromatography.



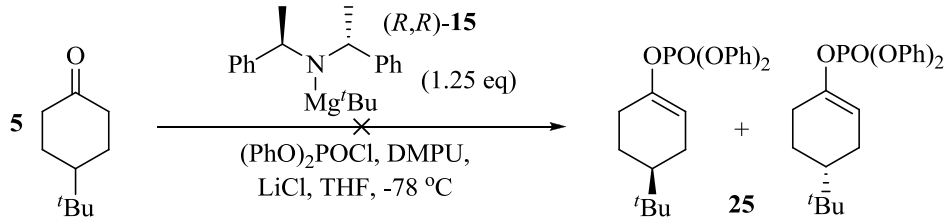
Scheme 2.38

Diphenylphosphoryl chloride was then employed in the asymmetric deprotonation reactions employing (*R*)-**11** as the chiral amine (**Scheme 2.39**). At first, this electrophile was employed alongside a stoichiometric quantity of (*R*)-**11**. Pleasingly, under the conditions shown, the desired enol phosphate (**25**) was obtained in high yield (77%) and good selectivity (87:13 er). With this result in hand, the reaction was attempted using a substoichiometric quantity of the chiral amine ((*R*)-**11**). Unfortunately, and despite the very good enantioselectivity observed, no significant increase in yield, compared to that achieved using TMSCl as the electrophilic quench, was delivered.



Scheme 2.39

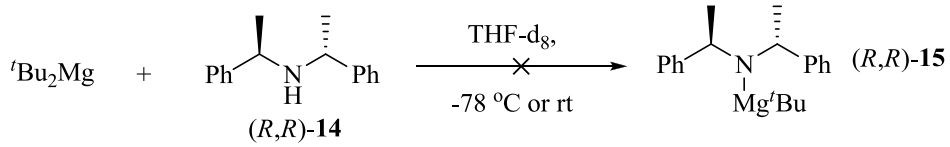
Subsequently, a stoichiometric quantity of the C_2-symmetric amine ((*R*,*R*)-**14**) was employed alongside di-*t*-butylmagnesium and diphenylphosphoryl chloride in the attempted desymmetrisation of the prochiral ketone (**5**, **Scheme 2.40**). Previous attempts to develop a recycling protocol for the preparation of enol silane **6** using the C_2-symmetric amine ((*R*,*R*)-**14**) and di-*t*-butylmagnesium had failed to deliver any conversion at -78 °C. It was proposed that the alkylmagnesium amide ((*R*,*R*)-**15**) did not form, at room temperature or -78 °C, when the C_2-symmetric amine ((*R*,*R*)-**14**) was treated with di-*t*-butylmagnesium. Therefore, perhaps unsurprisingly, when diphenylphosphoryl chloride was employed in place of chlorotrimethylsilane, no conversion to the desired enol phosphate was achieved (**Scheme 2.40**).



Scheme 2.40

3.5 NMR studies

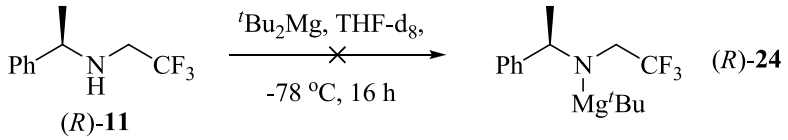
At this stage in the attempted development of a recycling protocol for our asymmetric deprotonations, the key limitation was believed to be the lack of base formation at the low temperatures required for high enantioselectivity, in particular, when using the C_2-symmetric amine ((*R*,*R*)-**14**). Therefore, the base formation step was followed by ^{1}H NMR analysis to determine whether this was, indeed, an issue (**Scheme 2.41**). When the amine ((*R*,*R*)-**14**) was added to di-*t*-butylmagnesium in THF-d_8 in an NMR tube at -78 ^{o}C, and was maintained at -78 ^{o}C overnight, no conversion to the alkylmagnesium amide ((*R*,*R*)-**15**) could be detected using ^{1}H NMR analysis. Instead, the parent amine ((*R*,*R*)-**14**) and di-*t*-butylmagnesium were persistent in the reaction mixture. Accordingly, to ascertain if the alkylmagnesium amide ((*R*,*R*)-**15**) would form at more elevated temperatures, the NMR study was repeated after 1.5 hours at room temperature. As expected, no formation of the alkylmagnesium amide ((*R*,*R*)-**15**) could be detected. This is consistent with the disappointing results achieved so far when the C_2-symmetric amine ((*R*,*R*)-**14**) has been applied to the desymmetrisation of 4-*tert*-butylcyclohexanone alongside di-*t*-butylmagnesium.



Scheme 2.41

Subsequently, NMR studies were employed to deduce whether the fluorinated amine ((*R*)-**11**) would react with di-*t*-butylmagnesium at -78 ^{o}C (**Scheme 2.42**). More specifically, the amine ((*R*)-**11**) was added to di-*t*-butylmagnesium in THF-d_8 at -78 ^{o}C, and the resulting solution was kept at -78 ^{o}C in an NMR tube overnight. Subsequently, the ^{1}H NMR spectrum was acquired and was compared with that which was obtained for the alkylmagnesium amide preparation at room temperature. As envisaged, no formation of the alkylmagnesium amide ((*R*)-**24**) could be detected at -78 ^{o}C. Alternatively, the ^{1}H

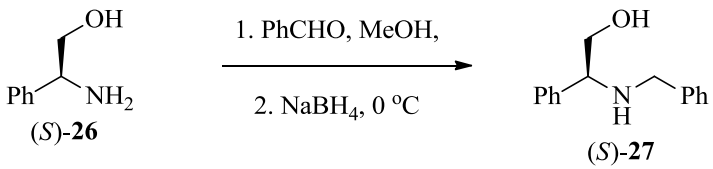
NMR spectrum of the reaction mixture displayed the signals corresponding to the secondary amine ((*R*)-**11**) in addition to a signal at around 0.85 ppm for the $^{t}Bu_2Mg$. With the knowledge that the alkylmagnesium amide ((*R*)-**24**) did not form from the parent amine ((*R*)-**11**) and di-*t*-butylmagnesium at -78 °C, attention was turned to an alternative, potentially more reactive amine.



Scheme 2.42

3.6 The use of a chiral aminoalcohol

In relation to the application of a potentially more reactive chiral amine in our recycling protocol, it was proposed that di-*t*-butylmagnesium would rapidly react with the aminoalcohol ((*S*)-**27**) to deliver the corresponding alkylmagnesium alkoxide through deprotonation of the alcohol moiety. Subsquently, it was envisaged that deprotonation of the amine portion, in an intramolecular fashion, would occur readily. In order to test this hypothesis, the aminoalcohol ((*S*)-**27**) was prepared by reductive amination using the commercially available chiral amine ((*S*)-**26**) and benzaldehyde (**Scheme 2.43**, **Table 2.5**). Pleasingly, the desired aminoalcohol ((*S*)-**27**) could be accessed in good yield on an appreciable scale.

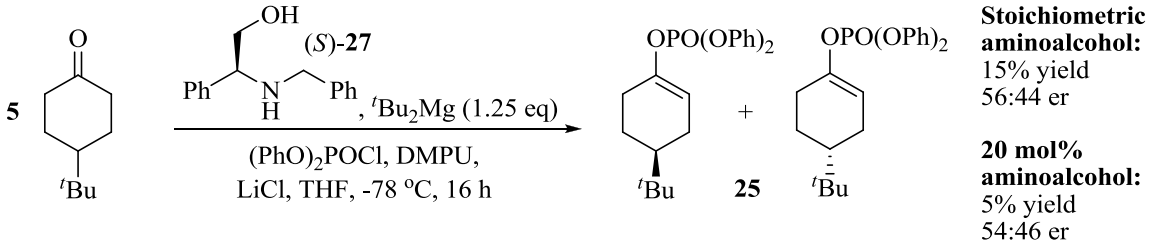


Scheme 2.43

Entry	Scale (mmol)	Yield (%)
1	1	85
2	37	53

Table 2.5

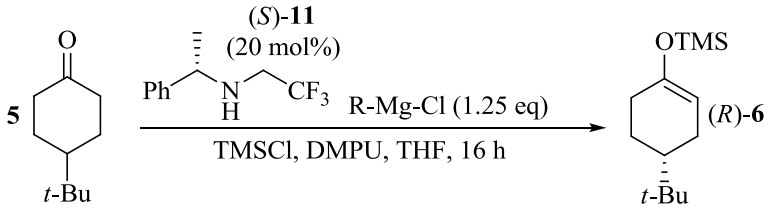
With the required aminoalcohol in hand, the preparation of the enol phosphate (**25**) using a stoichiometric quantity of the alkoxymagnesium amide was attempted at -78 ^{o}C (**Scheme 2.44**). Disappointingly, a very low yield of 15% was achieved, alongside an insignificant enantioinduction (56:44 er). Similarly, poor results were delivered when a sub-stoichiometric quantity of the aminoalcohol was employed (5% yield, 54:46 er). Thus, it would appear that a non-selective base species, which is either formed in insufficient quantities or is unreactive towards deprotonation of **5**, results when the chiral aminoalcohol ((*S*)-**27**) is treated with di-*tert*-butylmagnesium. Unfortunately, at this stage in our research, the development of an amine recycling protocol for the desymmetrisation of 4-*tert*-butylcyclohexanone (**5**) remains to be realised.



Scheme 2.44

3.7 Summary

A number of possible approaches towards an asymmetric deprotonation protocol, employing a sub-stoichiometric quantity of optically-pure amine, were devised and, during a two month placement at the University of Notre Dame, Indiana, preliminary investigations were performed. Initially, employing Hauser bases ((TMP)MgCl or (HMDS)MgCl) as the bulk organometallic reagent alongside the fluorinated amine ((*S*)-**11**) delivered disappointing results. More specifically, poor conversions were achieved when the reactions were performed at -78 ^{o}C, and poor enantioselectivities were observed at more elevated temperatures (**Scheme 2.45**). As such, alternative approaches were investigated.

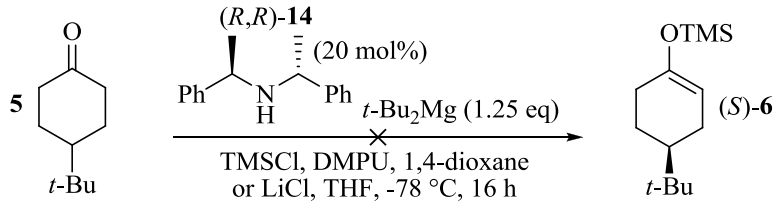


-78 ^{o}C
R = TMP; 2% conversion
R = HMDS; no conversion

-60 ^{o}C
R = TMP; 24% conversion, 20% yield, 50:50 er
R = HMDS; 23% conversion, 18% yield, 50:50 er

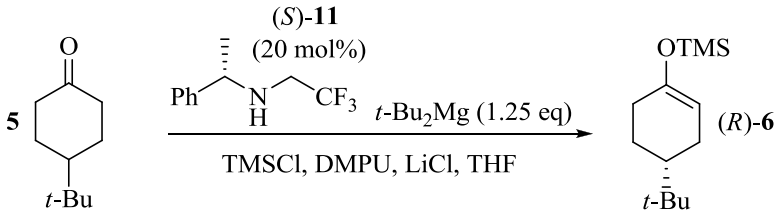
Scheme 2.45

Attention was then focused on a recycling protocol employing di-*tert*-butylmagnesium as the bulk magnesium source. At first, attempts to develop a recycling transformation using the C_2-symmetric amine ((*R*,*R*)-**14**) alongside di-*tert*-butylmagnesium at -78 ^{o}C resulted in no conversion to the silyl enol product (**Scheme 2.46**). This was later shown to be due to poor reactivity between the C_2-symmetric amine ((*R*,*R*)-**14**) and di-*tert*-butylmagnesium at -78 ^{o}C. Moreover, when the reaction temperature was increased, no enantioenrichment of the silyl enol ether product (**6**) was observed.



Scheme 2.46

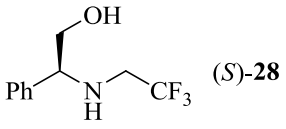
As it was envisaged that the poor conversions achieved at -78 °C using the C_2-symmetric amine ((*R*,*R*)-**14**) may be attributable to a lack of reactivity between ((*R*,*R*)-**14**) and di-*tert*-butylmagnesium, the more acidic fluorinated amine ((*S*)-**11**) was employed in an attempt to increase the reactivity of the system (**Scheme 2.47**). However, low conversions were achieved after 16 h at -78 °C, and poor enantioselectivities were obtained at more elevated temperatures. Even when an extended reaction time of 48 hours was employed, the silyl enol ether product (**6**) was obtained in similar yield to that achieved previously. ^{1}H NMR studies were then employed to confirm that no alkylmagnesium amide formation occurred at -78 °C. Moreover, attempts to develop an efficient recycling procedure using an alternative electrophile (diphenylphosphoryl chloride) and a chiral aminoalcohol ((*S*)-**27**) were unsuccessful.



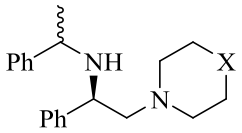
-78 °C, 16 h	**-50 °C, 16 h**	**-78 °C, 48 h**
30% conversion	66% conversion	25% conversion
25% yield	58% yield	18% yield
87:13 (*R*):(*S*)	66:34 (*R*):(*S*)	83:17 (*S*):(*R*) (using (*R*)-**11**)

Scheme 2.47

Future work should centre on increasing the overall reactivity of our developing method, by focusing on increasing the rate of base formation at -78 ^{o}C. Although the use of the chiral aminoalcohol ((*S*)-**27**) did not deliver beneficial results in our studies, an even more acidic aminoalcohol ((*S*)-**28**, **Figure 2.1**) could be trialled in the asymmetric deprotonation of 4-*tert*-butylcyclohexanone. Having stated this, a fine balance needs to be reached between the acidity of the chiral amine, to increase the rate of alkylmagnesium amide formation, and the basicity of the resulting alkylmagnesium amide, to allow deprotonation of the ketone substrate. Alternatively, a chiral amine which possesses a heterocyclic ring with the potential for additional chelation (**29**) could be assessed. Indeed, the magnesium amides derived from this class of amine have proven to be highly selective bases for the desymmetrisation of prochiral ketones.[13] Perhaps the heterocyclic ring could act as a directing group, to assist in the deprotonation of the chiral amine by the achiral source of magnesium ($^{t}Bu_2Mg$), leading to more facile alkylmagnesium amide formation at low temperatures.



(*S*)-**28**



29

Figure 2.1

4. Experimental

4.1 General experimental procedures

All reagents were obtained from commercial suppliers (Aldrich, TCI, Alfa Aesar or Acros) and used without further purification, unless otherwise stated. Purification was carried out according to standard laboratory methods.[14]

- Dichloromethane, diethyl ether, hexane and toluene were obtained from an Innovative Technology, Pure Solv, SPS-400-5 solvent purification system.
- Tetrahydofuran, tetrahydrofuran-d_8 and 1,4-dioxane were dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under argon.
- TMSCl was distilled from CaH_2 under argon and was stored over 4Å molecular sieves under argon.
- DMPU and diphenylphosphoryl chloride were distilled from CaH_2 under high vacuum and were stored over 4Å molecular sieves under argon.
- Organometallic reagents were standardised using salicylaldehyde phenylhydrazone.[9]
- 4-*tert*-Butylcyclohexanone was purified by recrystallisation from hexane at 4 ^oC and was dried by storing under vacuum (0.005 mbar) for 16 h.

Thin layer chromatography was carried out using Camlab silica plates, coated with fluorescent indicator UV_{254}, and analysed using a Mineralight UVGL-25 lamp.

Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

IR spectra were obtained on a Perkin Elmer Spectrum 1 machine.

^1H, ^{13}C and ^{31}P spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz, 100 MHz, and 162 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^3J_{H\text{-}H}$ interactions unless otherwise specified.

General procedure A – preparation of magnesium bisamides

$^{n}Bu_2Mg$ in heptane was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of nitrogen, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by the required amine, and the solution was heated at reflux for 1.5 h, assuming quantitative formation of the magnesium bisamide.

General procedure B – asymmetric deprotonation reactions using Mg bases

A solution of magnesium base in THF, prepared *via* General Procedure A, was cooled under nitrogen to the appropriate temperature. The Schlenk flask was then charged with DMPU, followed by TMSCl, and the reaction mixture was stirred for 10 minutes at the temperature stated. 4-*tert*-Butylcyclohexanone was then added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction mixture was stirred at the temperature stated for the required time before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-2% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

General procedure C – deprotonations employing a Hauser base as the Mg source under internal quench conditions

To a Schlenk tube, which had previously been flame-dried under vacuum and allowed to cool to room temperature under nitrogen, was added THF, *t*-BuMgCl, and the appropriate achiral amine before stirring at room temperature for 1 h. The reaction mixture was then treated with the appropriate chiral amine before stirring at room temperature for 30 minutes and then cooling to the required temperature. DMPU and TMSCl were then

added and the reaction mixture was stirred for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at a constant temperature, using a dry ice/acetone bath for reactions performed at -78 ^{o}C or cryogenic cooling equipment for temperatures up to 0 ^{o}C, and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-2% Et_2O in petroleum ether (30-40 °C) to give (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

General procedure D – deprotonations employing a Hauser base as the Mg source under external quench conditions

To a Schlenk tube, which had previously been flame-dried under vacuum and allowed to cool to room temperature under nitrogen, was added THF, *t*-BuMgCl and the appropriate achiral amine before stirring at room temperature for 1 h. The reaction mixture was then treated with the appropriate chiral amine before stirring at room temperature for 30 minutes and then cooling to the required temperature. DMPU was then added and the reaction mixture was stirred for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at a constant temperature, using a dry ice/acetone bath for reactions performed at -78 ^{o}C or cryogenic cooling equipment for temperatures up to 0 ^{o}C, and was subsequently treated with TMSCl before stirring for 30 minutes. After this time, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-2% Et_2O in petroleum ether

(30-40 °C) to give (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

General Procedure E – deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under internal quench conditions

To a Schlenk tube, which had previously been flame-dried under vacuum and allowed to cool to room temperature under nitrogen, was added THF, *t*-Bu_2Mg (prepared as detailed in section **4.2**), and the appropriate chiral amine before stirring at room temperature for 1.5 h. The reaction mixture was then cooled to the required temperature and DMPU, 1,4-dioxane and TMSCl were added. The reaction mixture was stirred at this temperature for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at a constant temperature, using a dry ice/acetone bath for reactions performed at -78 ^{o}C or cryogenic cooling equipment for temperatures up to 0 ^{o}C, and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-2% Et_2O in petroleum ether (30-40 °C) to give (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

General Procedure F – deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under nitrogen, was added LiCl. The Schlenk tube was then flame-dried under vacuum, taking care not to melt the LiCl, and allowed to cool to room temperature under nitrogen. THF and *t*-Bu_2Mg (prepared as detailed in section **4.2**) were then added and the mixture was stirred for 15 minutes at room temperature before

addition of the appropriate chiral amine and stirring at room temperature for 1.5 h. The reaction mixture was then cooled to the required temperature and DMPU and TMSCl were added. The reaction mixture was stirred at this temperature for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at a constant temperature, using a dry ice/acetone bath for reactions performed at -78 ^{o}C or cryogenic cooling equipment for temperatures up to 0 ^{o}C, and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-2% Et_2O in petroleum ether (30-40 °C) to give (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

General Procedure G – Deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under external quench conditions

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under nitrogen, was added LiCl. The Schlenk tube was then flame-dried under vacuum, taking care not to melt the LiCl, and allowed to cool to room temperature under nitrogen. THF and *t*-Bu_2Mg (prepared as detailed in section **4.2**) were then added and the mixture was stirred for 15 minutes at room temperature before addition of the appropriate chiral amine and stirring at room temperature for 1.5 h. The reaction mixture was then cooled to the required temperature and DMPU was added. The reaction mixture was stirred at this temperature for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at a constant temperature, using a dry ice/acetone bath for reactions performed at -78 ^{o}C or cryogenic cooling equipment for temperatures up to 0 ^{o}C, and was subsequently treated with TMSCl before stirring for 30 minutes. After this time, the reaction mixture was quenched with a saturated aqueous

solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-2% Et_2O in petroleum ether (30-40 °C) to give (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

General Procedure H – Deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under external quench conditions

To a Schlenk tube, which had previously been flame-dried under vacuum and allowed to cool to room temperature under nitrogen, was added THF, *t*-Bu_2Mg (prepared as detailed in section **4.2**), and the appropriate chiral amine before stirring at room temperature for 1.5 h. The reaction mixture was then cooled to the required temperature and DMPU and 1,4-dioxane were added. The reaction mixture was stirred at this temperature for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at a constant temperature, using a dry ice/acetone bath for reactions performed at -78 ^oC or cryogenic cooling equipment for temperatures up to 0 ^oC, and was subsequently treated with TMSCl before stirring for 30 minutes. After this time, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-2% Et_2O in petroleum ether (30-40 °C) to give (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

4.2 Synthesis of reagents

Preparation of bis((*R*)-1-phenylethyl)amine ((*R*,*R*)-14)[15]

Scheme 2.12

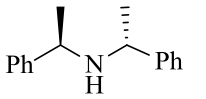
(*R*)-Phenylethylamine (9.52 g, 79 mmol), acetophenone (9.40 g, 79 mmol) and titanium tetra-*iso*-propoxide (67.0 g, 236 mmol) were stirred at room temperature for 10 minutes before the addition of 10% palladium on charcoal (1.0 g, 1.0 mmol). The reaction mixture was placed under an atmosphere of hydrogen (8 bar) and was shaken for 2 days before being treated with a saturated solution of NaOH (500 mL), causing a grey precipitate to form. The mixture was filtered to remove the precipitate, and the aqueous filtrate was extracted with EtOAc (3 x 200 mL). The precipitate was washed repeatedly with EtOAc until no more product could be detected in the washings by TLC, and the organics were combined, washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a colourless oil (dr 86:14 (*R*,*R*):(*R*,*S*)). Formation of the HCl salt (using 12 mL conc. HCl) and recrystallisation from *iso*-propanol delivered the diastereomerically pure salt which was then treated with a saturated solution of $NaHCO_3$ (500 mL), extracted with DCM (2 x 300 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 4.90 g (28%) of bis((*R*)-1-phenylethyl)amine as a colourless oil. The product was dried by distillation from CaH_2 at 98 ^oC and 0.4 mbar before use.

$[\alpha]_D^{20}$ = +171.6° (*c* = 6.71, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -171.6° (*S*,*S*) (c = 6.71, $CHCl_3$).[15]

$\nu_{max}(CDCl_3)$: 2962 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.23 (m, 10H, ArH), 3.56 (q, *J* = 6.7 Hz, 2H, $N(CH)_2$), 1.33 (d, *J* = 6.7 Hz, 6H, $N(CHCH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 128.5, 126.8, 126.7, 55.2, 25.1.



(*R*,*R*)-**14**

Attempted preparation of (*R*)-2,2,2-trifluoro-*N*-(1-phenylethyl)acetamide ((*R*)-19)

Scheme 2.13

To a round-bottomed flask, which had previously been flame-dried under vacuum and allowed to cool under nitrogen, was added anhydrous Et_2O (3 mL) and NaH (60% dispersion in mineral oil, 44 mg, 1.1 mmol). The suspension was cooled to 0 ^oC and (*R*)-phenylethylamine (121 mg, 1 mmol) was added over 10 minutes. The reaction mixture was stirred at 0 ^oC for 1 h and was then allowed to warm to room temperature and stirred for 2 h. After this time, the reaction mixture was cooled to 0 ^oC and ethyl trifluoroacetate (170 mg, 1.2 mmol) was added dropwise. The reaction temperature was then allowed to warm to room temperature slowly over 16 h. After this time, none of the desired product could be detected by ^1H NMR.

Preparation of (*S*)-2,2,2-trifluoro-*N*-(1-phenylethyl)ethanamine ((*S*)-11)[16]

Scheme 2.14, Table 2.1

Entry 1

To a round-bottomed flask which had previously been flame-dried under vacuum and allowed to cool under nitrogen was added (*S*)-2,2,2-trifluoro-*N*-(1-phenylethyl)acetamide (217 mg, 1 mmol) and THF (2 mL). The solution was cooled to 0 ^oC before the dropwise addition of BH_3.THF (1 M, 2 mL, 2 mmol). The reaction mixture was then allowed to warm to room temperature before refluxing under nitrogen for 22 h. After this time, the reaction mixture was quenched by careful addition of aqueous HCl (2 M, 4 mL) at room temperature before being neutralised by addition of KOH. Extraction with Et_2O (3 x 10 mL), drying of the organic extracts (Na_2SO_4), and concentration *in vacuo* then gave the title compound as a colourless oil (152 mg, 75%).

Entry 2

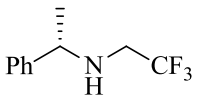
To a round-bottomed flask which had previously been flame-dried under vacuum and allowed to cool under nitrogen was added (*R*)-2,2,2-trifluoro-*N*-(1-phenylethyl)acetamide (9.92 g, 46 mmol) and THF (100 mL). The solution was cooled to 0 ^{o}C before the dropwise addition of BH_3.THF (1 M, 92 mL, 92 mmol). The reaction mixture was then allowed to warm to room temperature before refluxing under nitrogen for 19 h. After this time, the reaction mixture was quenched by careful addition of aqueous HCl (2 M, 50 mL) at room temperature before being neutralised by addition of KOH. Extraction with Et_2O (3 x 200 mL), drying of the organic extracts (Na_2SO_4), and concentration *in vacuo* then gave the title compound as a colourless oil. The HCl salt was then formed and recrystallised from IPA to give 7.71 g of white crystalline solid, which was then treated with a saturated aqueous solution of $NaHCO_3$ (400 mL), extracted with DCM (3 x 200 mL), dried using Na_2SO_4, and concentrated *in vacuo* to give the title compound as a colourless oil (6.70 g, 72%). The product was dried by distillation from CaH_2 at 78 ^{o}C and 16 mbar.

$[\alpha]_D^{20}$ = -55.6 ^{o} (c = 0.98, MeOH); Lit (*R*): +54.9 ^{o} (c = 0.98, MeOH).[16b]

ν_{max} (DCM): 2969 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.26-7.38 (m, 5H, ArH), 3.91 (q, *J* = 6.6 Hz, 1H, CH), 3.01 (q, $^3J_{FH}$ = 9.5 Hz, 2H, CH_2), 1.59 (brs, 1H, NH), 1.38 (d, *J* = 6.6 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ144.1, 128.7, 127.0, 126.6, 124.3 (q, $^1J_{CF}$ = 278.9 Hz), 57.3, 48.2 (q, $^2J_{CF}$ = 31.1 Hz), 24.4.



(*S*)-**11**

Preparation of di-*tert*-butylmagnesium

Scheme 2.15

To a Schlenk tube which had previously been flame-dried under vacuum and cooled under nitrogen was added *t*-BuMgCl (1 M in THF, 100 mL, 100 mmol) *via* cannula. 1,4-Dioxane (8.95 mL, 105 mmol) was then added dropwise with vigorous stirring, causing the formation of a white precipitate. The reaction mixture was stirred for 3 h at room temperature before the precipitate was allowed to settle to the bottom of the flask to allow transferral of di-*tert*-butylmagnesium, *via* canula, to a dry round-bottomed flask. The brown solution of di-*tert*-butylmagnesium in THF was standardised using salicylaldehyde phenylhydrazone before use.[9]

Preparation of salicylaldehyde phenylhydrazone (22)[9]

Scheme 2.16

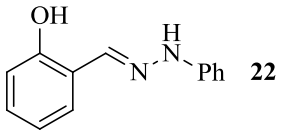
To a warmed solution of phenylhydrazine (29.95 g, 277 mmol) in EtOH (120 mL) was added salicylaldehyde (32.5 g, 266 mmol), dropwise, using vigorous stirring. An exotherm was observed on addition, and the formation of the product as a precipitate was evident towards the end of the 30 minute addition period. The reaction mixture was allowed to cool to room temperature before being cooled further to 0 ^{o}C and stirred for 30 minutes. After this time, the solid was collected by filtration, was washed with EtOH (100 mL), and dried *in vacuo* to give the product as a pale yellow solid (56.36 g, 100%).

Melting point = 141-142 °C. Lit: 142 ^{o}C.[17]

ν_{max} ($CHCl_3$): 1621 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ10.89 (s, 1H, OH), 7.83 (s, 1H, CH), 7.49 (brs, 1H, NH), 7.34-7.14 (m, 4H, ArH), 7.04-6.89 (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ157.1, 143.4, 141.2, 130.1, 129.6, 129.4, 120.9, 119.5, 118.6, 116.6, 112.7.



22

Scheme 2.17, Table 2.2

Following general procedure A for the preparation of magnesium bisamide ((*R*,*R*)-**23**), data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure B for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amount of DMPU, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to **6**, (i) yield of **6**, and (j) (*S*):(*R*).

Entry 1: General procedure A: (a) 1.02 M, 0.98 mL, 1 mmol, (b) (*R*,*R*)-**14**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) (*R*,*R*)-**23**, (b) -78 ^{o}C, (c) 0.06 mL, 0.5 mmol, (d) 0.50 mL, 4 mmol, (e) **5**, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 95%, (i) 150 mg, 83%, and (j) 93:7.

Entry 2: General procedure A: (a) 1.02 M, 0.98 mL, 1 mmol, (b) (*R*,*R*)-**14**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) (*R*,*R*)-**23**, (b) -78 ^{o}C, (c) 0.06 mL, 0.5 mmol, (d) 0.50 mL, 4 mmol, (e) **5**, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 97%, (i) 155 mg, 86%, and (j) 93:7.

Entry 3: General procedure A: (a) 1.02 M, 0.98 mL, 1 mmol, (b) (*R*,*R*)-**14**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) (*R*,*R*)-**23**, (b) -78 ^{o}C, (c) 0.06 mL, 0.5 mmol, (d) 0.50 mL, 4 mmol, (e) **5**, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 96%, (i) 157 mg, 87%, and (j) 92:8.

Entry 4: General procedure A: (a) 1.02 M, 0.98 mL, 1 mmol, (b) (*R*,*R*)-**14**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) (*R*,*R*)-**23**, (b) -78 ^{o}C, (c) 0.06 mL, 0.5 mmol, (d) 0.50 mL, 4 mmol, (e) **5**, (f) 123 mg, 0.8 mmol, (g) 18 h, (h) 94%, (i) 148 mg, 82%, and (j) 93:7.

(*S*)-(4-*tert*-Butylcyclohex-1-enyloxy)trimethylsilane (6)[18]

Achiral GC conditions: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 ^{o}C (1 min)-190 ^{o}C; temperature gradient; 20 ^{o}C min^{-1}; t_R = 5.85 min (**5**), t_R = 6.01 min (**6**).

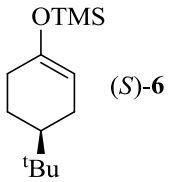
Chiral GC conditions: Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-130 ^{o}C; temperature gradient; 1.7 ^{o}C min^{-1}; t_R = 27.52 min ((*S*)-**6**), t_R = 27.83 min ((*R*)-**6**).

$[\alpha]_D^{20}$: –66.3 ° (93:7 er, c = 1.5, $CHCl_3$). Lit: –54.2 ° (82:18 er, c = 1.5, $CHCl_3$).[19]

$\nu_{max}(CDCl_3)$: 1674 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86-4.84 (m, 1H, C=CH), 2.13-1.97 (m, 3H, C*H*C$(CH_3)_3$ and CH_2), 1.85-1.77 (m, 2H, CH_2), 1.32-1.24 (m, 2H, CH_2), 0.88 (s, 9H, C$(CH_3)_3$), 0.19 (s, 9H, Si$(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 103.6, 43.7, 31.8, 30.7, 27.0, 24.8, 24.1, 0.0.



(*S*)-**6**

4.3 Recycling reactions employing Hauser bases

Scheme 2.18

Following general procedure C for deprotonations employing a Hauser base as the Mg source under internal quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-BuMgCl, (c) achiral amine, (d) amount of achiral amine, (e) chiral amine, (f) amount of chiral amine, (g) reaction temperature, (h) amount of DMPU, (i) amount of TMSCl, (j) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (k) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (l) (*S*):(*R*).

R* = *TMP: (a) 9 mL, (b) 1.00 M, 1 mL, 1 mmol, (c) 2,2,6,6-tetramethylpiperidine, (d) 0.17 mL, 1 mmol, (e) (*S*)-**11**, (f) 30 μL, 0.16 mmol (g) -78 ^{o}C (h) 60 μL, 0.5 mmol, (i) 0.5 mL, 4 mmol, (j) 2%, (k) 0%, and (l) not applicable.

R* = *HMDS: (a) 9 mL, (b) 1.00 M, 1 mL, 1 mmol, (c) hexamethyldisilazide, (d) 0.21 mL, 1 mmol (e) (*S*)-**11**, (f) 30 μL, 0.16 mmol, (g) -78 ^{o}C, (h) 60 μL, 0.5 mmol, (i) 0.5 mL, 4 mmol, (j) trace, (k) 0%, and (l) not applicable.

Scheme 2.19

Following general procedure D for deprotonations employing a Hauser base as the Mg source under external quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-BuMgCl, (c) achiral amine, (d) amount of achiral amine, (e) chiral amine, (f) amount of chiral amine, (g) reaction temperature, (h) amount of DMPU, (i) amount of TMSCl, (j) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (k) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (l) (*S*):(*R*).

R* = *TMP: (a) 9 mL, (b) 1.00 M, 1 mL, 1 mmol, (c) 2,2,6,6-tetramethylpiperidine, (d) 0.17 mL, 1 mmol, (e) (*S*)-**11**, (f) 30 μL, 0.16 mmol, (g) -78 ^{o}C, (h) 60 μL, 0.5 mmol, (i) 0.5 mL, 4 mmol, (j) 0%, (k) 0%, and (l) not applicable.

R* = *HMDS: (a) 9 mL, (b) 1.00 M, 1 mL, 1 mmol, (c) hexamethyldisilazane, (d) 0.21 mL, 1 mmol, (e) (*S*)-**11**, (f) 30 μL, 0.16 mmol, (g) -78 ^{o}C, (h) 60 μL, 0.5 mmol, (i) 0.5 mL, 4 mmol, (j) 0%, (k) 0%, and (l) not applicable.

Scheme 2.20

Following general procedure C for deprotonations employing a Hauser base as the Mg source under internal quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-BuMgCl, (c) achiral amine, (d) amount of achiral amine, (e) chiral amine, (f) amount of chiral amine, (g) reaction temperature, (h) amount of DMPU, (i) amount of TMSCl, (j) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (k) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (l) (*S*):(*R*).

R* = *TMP: (a) 9 mL, (b) 1.00 M, 1 mL, 1 mmol, (c) 2,2,6,6-tetramethylpiperidine, (d) 0.17 mL, 1 mmol, (e) not applicable, (f) not applicable, (g) -60 ^{o}C, (h) 60 μL, 0.5 mmol, (i) 0.5 mL, 4 mmol, (j) 28%, (k) 38 mg, 21%, and (l) not applicable.

R* = *HMDS: (a) 9 mL, (b) 1.00 M, 1 mL, 1 mmol, (c) hexamethyldisilazide, (d) 0.21 mL, 1 mmol, (e) not applicable, (f) not applicable, (g) -60 ^{o}C, (h) 60 μL, 0.5 mmol, (i) 0.5 mL, 4 mmol, (j) 13%, (k) 13 mg, 7%, and (l) not applicable.

Scheme 2.21

Following general procedure C for deprotonations employing a Hauser base as the Mg source under internal quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-BuMgCl, (c) achiral amine, (d) amount of achiral amine, (e) chiral amine, (f) amount of chiral amine, (g) reaction temperature, (h) amount of DMPU, (i) amount of TMSCl, (j) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (k) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (l) (*S*):(*R*).

R* = *TMP: (a) 9 mL, (b) 1.00 M, 1 mL, 1 mmol, (c) 2,2,6,6-tetramethylpiperidine, (d) 0.17 mL, 1 mmol, (e) (*S*)-**11**, (f) 30 μL, 0.16 mmol, (g) -60 ^{o}C, (h) 60 μL, 0.5 mmol, (i) 0.5 mL, 4 mmol, (j) 24%, (k) 36 mg, 20%, and (l) 50:50.

R* = *HMDS: (a) 9 mL, (b) 1.00 M, 1 mL, 1 mmol, (c) hexamethyldisilazide, (d) 0.21 mL, 1 mmol (e) (*S*)-**11**, (f) 30 μL, 0.16 mmol, (g) -60 ^{o}C, (h) 60 μL, 0.5 mmol, (i) 0.5 mL, 4 mmol, (j) 23%, (k) 33 mg, 18%, and (l) 50:50.

4.4 Recycling reactions employing *t*-Bu_2Mg

Scheme 2.22

Following general procedure E for deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under internal quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-Bu_2Mg, (c) chiral amine, (d) amount of chiral amine, (e) reaction temperature, (f) amount of DMPU, (g) amount of 1,4-dioxane, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)tri-methylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 8.3 mL, (b) 0.60 M, 1.67 mL, 1 mmol, (c) (*R*,*R*)-**14**, (d) 37 μL, 0.16 mmol, (e) -78 ^{o}C, (f) 60 μL, 0.5 mmol, (g) 85 μL, 1 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Scheme 2.23

Following general procedure F for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 8.3 mL, (c) 0.60 M, 1.67 mL, 1 mmol, (d) (*R*,*R*)-**14**, (e) 37 μL, 0.16 mmol, (f) -78 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Scheme 2.24

Conditions A

Following general procedure G for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under external quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 8.4 mL, (c) 0.61 M, 1.64 mL, 1 mmol, (d) (*R*,*R*)-**14**, (e) 37 μL, 0.16 mmol (f) -78 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Conditions B

Following general procedure H for deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under external quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-Bu_2Mg, (c) chiral amine, (d) amount of chiral amine, (e) reaction temperature, (f) amount of DMPU, (g) amount of 1,4-dioxane, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)tri-methylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 8.4 mL, (b) 0.61 M, 1.64 mL, 1 mmol, (c) (*R*,*R*)-**14**, (d) 37 μL, 0.16 mmol, (e) -78 ^{o}C, (f) 60 μL, 0.5 mmol, (g) 85 μL, 1 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Scheme 2.25

Conditions A

Following general procedure G for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under external quench conditions, data are presented as (a) amount of LiCl, (b)

volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 6.7 mL, (c) 0.61 M, 3.28 mL, 2 mmol, (d) (*R*,*R*)-**14**, (e) 37 μL, 0.16 mmol, (f) -78 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Conditions B

Following general procedure H for deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under external quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-Bu_2Mg, (c) chiral amine, (d) amount of chiral amine, (e) reaction temperature, (f) amount of DMPU, (g) amount of 1,4-dioxane, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)tri-methylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 6.7 mL, (b) 0.61 M, 3.28 mL, 2 mmol, (c) (*R*,*R*)-**14**, (d) 37 μL, 0.16 mmol, (e) -78 ^{o}C, (f) 60 μL, 0.5 mmol, (g) 85 μL, 1 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Scheme 2.26, Table 2.3

Following general procedure G for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

Entry 1

(a) 85 mg, 2 mmol, (b) 8.4 mL, (c) 0.61 M, 1.64 mL, 1 mmol, (d) (*R,R*)-**14**, (e) 37 μL, 0.16 mmol (f) -60 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Entry 2

(a) 85 mg, 2 mmol, (b) 8.4 mL, (c) 0.61 M, 1.64 mL, 1 mmol, (d) (*R,R*)-**14**, (e) 37 μL, 0.16 mmol (f) -40 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 96%, (j) 157 mg, 87%, and (k) 50:50.

Entry 3

(a) 85 mg, 2 mmol, (b) 8.4 mL, (c) 0.61 M, 1.64 mL, 1 mmol, (d) (*R,R*)-**14**, (e) 37 μL, 0.16 mmol (f) -50 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 59%, (j) 90 mg, 50%, and (k) 50:50.

Scheme 2.27

Following general procedure F for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 8.3 mL, (c) 0.60 M, 1.67 mL, 1 mmol, (d) (*R,R*)-**14**, (e) 0.22 mL, 1 mmol, (f) -78 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Scheme 2.28

Following general procedure F for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f)

reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 8.3 mL, (c) 0.60 M, 1.67 mL, 1 mmol, (d) (*S*)-**11**, (e) 0.18 mL, 1 mmol, (f) -78 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 93%, (j) 148 mg, 82%, and (k) 23:77.

Scheme 2.29

Following general procedure E for deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under internal quench conditions, data are presented as data are presented as (a) volume of THF, (b) amount of *t*-Bu_2Mg, (c) chiral amine, (d) amount of chiral amine, (e) reaction temperature, (f) amount of DMPU, (g) amount of 1,4-dioxane, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)tri-methylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 8.3 mL, (b) 0.60 M, 1.67 mL, 1 mmol, (c) (*S*)-**11** (d) 30 μL, 0.16 mmol, (e) -78 ^{o}C, (f) 60 μL, 0.5 mmol, (g) 85 μL, 1 mmol, (h) 0.5 mL, 4 mmol, (i) 1%, (j) 0%, and (k) not applicable.

Scheme 2.30

Following general procedure F for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 8.3 mL, (c) 0.60 M, 1.67 mL, 1 mmol, (d) (*S*)-**11**, (e) 30 μL, 0.16 mmol, (f) -78 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 30%, (j) 43 mg, 25%, and (k) 13:87.

Scheme 2.31

Conditions A

Following general procedure G for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under external quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 8.4 mL, (c) 0.61 M, 1.64 mL, 1 mmol, (d) (*S*)-**11**, (e) 30 μL, 0.16 mmol (f) -78 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Conditions B

Following general procedure H for deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under external quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-Bu_2Mg, (c) chiral amine, (d) amount of chiral amine, (e) reaction temperature, (f) amount of DMPU, (g) amount of 1,4-dioxane, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)tri-methylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 8.4 mL, (b) 0.61 M, 1.64 mL, 1 mmol, (c) (*S*)-**11**, (d) 30 μL, 0.16 mmol, (e) -78 ^{o}C, (f) 60 μL, 0.5 mmol, (g) 85 μL, 1 mmol, (h) 0.5 mL, 4 mmol, (i) 0%, (j) 0%, and (k) not applicable.

Scheme 2.32

Following general procedure E for deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under internal quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-Bu_2Mg, (c) chiral amine, (d) amount of chiral amine, (e) reaction temperature, (f) amount of DMPU, (g) amount of 1,4-dioxane, (h) amount of TMSCl, (i)

conversion to (4-*tert*-butylcyclohex-1-enyloxy)tri-methylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 6.7 mL, (b) 0.61 M, 3.28 mL, 2 mmol, (c) (*S*)-**11**, (d) 30 μL, 0.16 mmol, (e) -78 ^{o}C, (f) 60 μL, 0.5 mmol, (g) 85 μL, 1 mmol, (h) 0.5 mL, 4 mmol, (i) 4%, (j) 0%, and (k) not applicable.

Scheme 2.33

Following general procedure F for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 6.7 mL, (c) 0.61 M, 3.28 mL, 2 mmol, (d) (*S*)-**11**, (e) 30 μL, 0.16 mmol, (f) -78 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 27%, (j) 38 mg, 21%, and (k) 12:88.

Scheme 2.34

Following general procedure E for deprotonations employing *t*-Bu_2Mg as the Mg source without LiCl under internal quench conditions, data are presented as (a) volume of THF, (b) amount of *t*-Bu_2Mg, (c) chiral amine, (d) amount of chiral amine, (e) reaction temperature, (f) amount of DMPU, (g) amount of 1,4-dioxane, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)tri-methylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 8.4 mL, (b) 0.61 M, 1.64 mL, 1 mmol, (c) (*S*)-**11**, (d) 30 μL, 0.16 mmol, (e) -60 ^{o}C, (f) 60 μL, 0.5 mmol, (g) 85 μL, 1 mmol, (h) 0.5 mL, 4 mmol, (i) 43%, (j) 78 mg, 34%, and (k) 33:67.

Scheme 2.35

Following general procedure F for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

(a) 85 mg, 2 mmol, (b) 8.4 mL, (c) 0.61 M, 1.64 mL, 1 mmol, (d) (*S*)-**11**, (e) 30 μL, 0.16 mmol, (f) -60 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 33%, (j) 45 mg, 25%, and (k) 20:80.

Scheme 2.36, Table 2.4

Following general procedure F for deprotonations employing *t*-Bu_2Mg as the Mg source with LiCl under internal quench conditions, data are presented as (a) amount of LiCl, (b) volume of THF, (c) amount of *t*-Bu_2Mg, (d) chiral amine, (e) amount of chiral amine, (f) reaction temperature, (g) amount of DMPU, (h) amount of TMSCl, (i) conversion to (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, (j) yield of (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane, and (k) (*S*):(*R*).

Entry 1: (a) 85 mg, 2 mmol, (b) 8.4 mL, (c) 0.61 M, 1.64 mL, 1 mmol, (d) (*S*)-**11**, (e) 30 μL, 0.16 mmol, (f) -40 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 94%, (j) 150 mg, 83%, and (k) 33:67.

Entry 2: (a) 85 mg, 2 mmol, (b) 8.4 mL, (c) 0.61 M, 1.64 mL, 1 mmol, (d) (*S*)-**11**, (e) 30 μL, 0.16 mmol, (f) -50 ^{o}C, (g) 60 μL, 0.5 mmol, (h) 0.5 mL, 4 mmol, (i) 66%, (j) 105 mg, 58%, and (k) 34:66.

Scheme 2.37

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under nitrogen, was added LiCl (85 mg, 2 mmol). The Schlenk tube

was then flame-dried under vacuum, taking care not to melt the LiCl, and allowed to cool to room temperature under nitrogen. THF (8.4 mL) and *t*-Bu_2Mg (0.61 M, 1.64 mL, 1 mmol, prepared as detailed in section **4.2**) were then added and the mixture was stirred for 15 minutes at room temperature before addition of the chiral amine ((*R*)-**11**, 30 μL, 0.16 mmol) and stirring at room temperature for 1.5 h. The reaction mixture was then cooled to -78 ^{o}C, and DMPU (60 μL, 0.5 mmol) and TMSCl (0.5 mL, 4 mmol) were added. The reaction mixture was stirred at this temperature for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 48 h at -78 ^{o}C, and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion (25%). Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-2% Et_2O in petroleum ether (30-40 °C) to give (4-*tert*-butylcyclohex-1-enyloxy)trimethylsilane as a colourless oil (33 mg, 18%). The enantiomeric ratio of the product was determined by analysis using chiral GC (83:17 (*S*):(*R*)).

4.5 Investigations into an alternative electrophile

Preparation of *O,O*-diphenyl 4-*tert*-butylcyclohex-1-enylphosphonate[20]

Scheme 2.38

$^{n}Bu_2Mg$ in heptane (1 mL, 1 M, 1 mmol) was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by (*R*,*R*)-**14** (0.44 mL, 2 mmol), and the solution was heated at reflux for 1.5 h, assuming quantitative formation of the magnesium bisamide. The solution of magnesium base in THF was then cooled under argon to -78 ^{o}C. The Schlenk flask was then charged with DMPU (60 μL, 0.5 mmol), followed by diphenylphosphoryl chloride (0.83 mL, 4 mmol), and the reaction mixture

was stirred for 10 minutes at -78 °C. 4-*tert*-Butylcyclohexanone (123 mg, 0.8 mmol) was then added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction mixture was stirred at -78 °C for 16 h before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was washed with 1 M HCl (3 x 25 mL) to remove (*R*,*R*)-**14**, and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel using 0-20% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (228 mg, 74%). The enantiomeric ratio of the product was determined by analysis using chiral HPLC (94:6, (-):(+)).

Chiral HPLC analysis: Chiracel OD-H column, 0.5% IPA in *n*-hexane, 1.5 mL/minute flow rate, 254 nm detector, t_R (+) = 31.65 minutes and t_R (-) = 33.67 minutes.

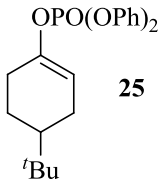
$[\alpha]_D^{20}$ = -34.6 ° (94:6 er, c = 1, $CHCl_3$). No literature data are available for comparison.

$\nu_{max}(CDCl_3)$: 1690, 1191, 963 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (m, 4H, ArH), 7.26-7.18 (m, 6H, ArH), 5.57-5.55 (m, 1H, C=CH), 2.29-2.25 (m, 2H), 2.09-2.08 (m, 1H), 1.89-1.85 (m, 2H), 1.37-1.29 (m, 2H), 0.88 (s, 9H, $C(CH_3)_3$).

^{31}P NMR (400 MHz, $CDCl_3$): δ 17.4

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 147.3, 129.2, 124.8, 119.6, 111.3, 42.7, 31.6, 28.2, 26.8, 24.5, 23.5.



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Scheme 2.39

Stoichiometric amine

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under argon, was added LiCl (85 mg, 2 mmol). The Schlenk tube was then flame-dried under vacuum, taking care not to melt the LiCl, and allowed to cool to room temperature under argon. THF (8.4 mL) and *t*-Bu_2Mg (0.61 M, 1.64 mL, 1 mmol, prepared as detailed in section **4.2**) were then added and the mixture was stirred for 15 minutes at room temperature before addition of the chiral amine ((*R*)-**11**, 0.18 mL, 1 mmol) and stirring at room temperature for 1.5 h. The reaction mixture was then cooled to -78 ^{o}C and DMPU (60 μL, 0.5 mmol) and diphenylphosphoryl chloride (0.83 mL, 4 mmol) were added. The reaction mixture was stirred at -78 ^{o}C for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at -78 ^{o}C and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was washed with 1 M HCl (3 x 25 mL) to remove (*R*,*R*)-**11**, and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel using 0-20% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (237 mg, 77%). The enantiomeric ratio of the product was determined by analysis using chiral HPLC (87:13, (-):(+)).

20 mol% amine

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under argon, was added LiCl (85 mg, 2 mmol). The Schlenk tube was then flame-dried under vacuum, taking care not to melt the LiCl, and allowed to cool to room temperature under argon. THF (8.4 mL) and *t*-Bu_2Mg (0.61 M, 1.64 mL, 1 mmol, prepared as detailed in section **4.2**) were then added and the mixture was stirred for 15 minutes at room temperature before addition of the chiral amine ((*R*)-**11**, 30 μL, 0.16 mmol) and stirring at room temperature for 1.5 h. The reaction mixture was then cooled to -78 ^{o}C and DMPU (60 μL, 0.5 mmol) and diphenylphosphoryl chloride (0.83

mL, 4 mmol) were added. The reaction mixture was stirred at -78 ^{o}C for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at -78 ^{o}C and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was washed with 1 M HCl (3 x 25 mL) to remove (*R*,*R*)-**11**, and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel using 0-20% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (52 mg, 17%). The enantiomeric ratio of the product was determined by analysis using chiral HPLC (91:9, (-):(+)).

Scheme 2.40

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under argon, was added LiCl (85 mg, 2 mmol). The Schlenk tube was then flame-dried under vacuum, taking care not to melt the LiCl, and allowed to cool to room temperature under argon. THF (8.4 mL) and *t*-Bu_2Mg (0.61 M, 1.64 mL, 1 mmol, prepared as detailed in section **4.2**) were then added and the mixture was stirred for 15 minutes at room temperature before addition of the chiral amine ((*R*)-**14**, 0.22 mL, 1 mmol) and stirring at room temperature for 1.5 h. The reaction mixture was then cooled to -78 ^{o}C and DMPU (60 μL, 0.5 mmol) and diphenylphosphoryl chloride (0.83 mL, 4 mmol) were added. The reaction mixture was stirred at -78 ^{o}C for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at -78 ^{o}C and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was washed with 1 M HCl (3 x 25 mL) to remove (*R*,*R*)-**14**, and concentrated *in vacuo* to give an oil which was analysed using ^{1}H NMR to reveal that no conversion to the desired product had occurred.

4.6 NMR Studies

Scheme 2.41

To an NMR tube which had been oven dried (200 ^{o}C) and cooled under vacuum (0.005 mbar) was added $^{t}Bu_2Mg$ (0.17 mL, 0.58 M, 0.1 mmol). The THF solvent was removed under vacuum (0.005 mbar) before the addition of THF-d_8 (0.6 mL). The solution was then cooled to -78 ^{o}C and the amine ((*R*,*R*)-**14**, 20 μL, 0.1 mmol) was added. The temperature of the reaction mixture was then maintained at -78 ^{o}C for 16 h. ^{1}H NMR analysis after this time revealed that no conversion had occurred. The reaction mixture was then allowed to warm to room temperature. After 1.5 h at this temperature, ^{1}H NMR analysis revealed that no conversion had occurred.

Scheme 2.42

To an NMR tube which had been oven dried (200 ^{o}C) and cooled under vacuum (0.005 mbar) was added $^{t}Bu_2Mg$ (0.17 mL, 0.58 M, 0.1 mmol). The THF solvent was removed under vacuum (0.005 mbar) before the addition of THF-d_8 (0.6 mL). The solution was then cooled to -78 ^{o}C and the amine ((*R*,*R*)-**11**, 20 μL, 0.1 mmol) was added. The temperature of the reaction mixture was then maintained at -78 ^{o}C for 16 h. ^{1}H NMR analysis after this time revealed that no conversion had occurred.

4.7 The use of a chiral aminoalcohol

Preparation of (*S*)-2-(benzylamino)-2-phenylethanol[21]

Scheme 2.43, Table 2.5

Entry 1: To a solution of (*S*)-2-amino-2-phenylethanol (137 mg, 1 mmol) in MeOH (1.3 mL) was added benzaldehyde (106 mg, 1 mmol). After stirring for 1.5 h at room temperature, the reaction mixture was cooled to 0 ^{o}C and $NaBH_4$ (53 mg, 1.4 mmol)) was added portionwise. The reaction was allowed to warm to room temperature before being quenched with a saturated solution of $NaHCO_3$ (5 mL) and extracted with DCM (3 x 5

mL). The organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to give the title compound as a white solid (194 mg, 85%).

Entry 2: To a solution of (*S*)-2-amino-2-phenylethanol (5.02 g, 37 mmol) in MeOH (50 mL) was added benzaldehyde (3.9 g, 37 mmol). After stirring for 1.5 h at room temperature, the reaction mixture was cooled to 0 ^oC and $NaBH_4$ (1.9 g, 51 mmol)) was added portionwise. The reaction was allowed to warm to room temperature before being quenched with a saturated solution of $NaHCO_3$ (100 mL) and extracted with DCM (3 x 100 mL). The organic extracts were dried (Na_2SO_4), and concentrated *in vacuo* to give the title compound as a white solid (4.4 g, 53%).

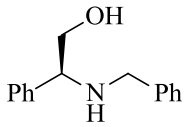
Melting point = 72-73 ^oC. Lit: 70-71 ^oC.[21]

$[\alpha]_D^{20}$ = -82.5 ° (c = 1.6, EtOH). Lit: $[\alpha]_D^{20}$ = -83.2 ° (c = 1.6, EtOH).[22]

$\nu_{max}(CDCl_3)$: 3434, 3011 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ7.41-7.25 (m, 10H, ArH), 3.87-3.68 (m, 3H, C*H*NCH_2), 3.65-3.54 (m, 2H, CH_2OH), 2.71 (brs, 1H, OH), 1.88 (brs, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.0, 139.6, 128.2, 128.0, 127.7, 127.2, 126.8, 126.6, 66.3, 63.3, 50.7.



Preparation of *O,O*-diphenyl 4-*tert*-butylcyclohex-1-enylphosphonate[20]

Scheme 2.44

Stoichiometric aminoalcohol

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under argon, was added LiCl (85 mg, 2 mmol). The Schlenk tube was then flame-dried under vacuum, taking care not to melt the LiCl, and allowed to cool to room temperature under argon. *t*-Bu_2Mg (0.61 M, 1.64 mL, 1 mmol, prepared as detailed in section **4.2**) was then added, followed by a solution of the chiral aminoalcohol ((*S*)-**27**, 227 mg, 1 mmol) in THF (8.4 mL) and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was then cooled to -78 ^{o}C and DMPU (60 μL, 0.5 mmol) and diphenylphosphoryl chloride (0.83 mL, 4 mmol) were added. The reaction mixture was stirred at -78 ^{o}C for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at -78 ^{o}C and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was washed with 1 M HCl (3 x 25 mL) to remove (*S*)-**27**, and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel using 0-20% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (46 mg, 15%). The enantiomeric ratio of the product was determined by analysis using chiral HPLC (56:44, (-):(+)).

20 mol% aminoalcohol

To a Schlenk tube, which had previously been oven-dried at 180 ^{o}C and allowed to cool to room temperature under argon, was added LiCl (85 mg, 2 mmol). The Schlenk tube was then flame-dried under vacuum, taking care not to melt the LiCl, and allowed to cool to room temperature under argon. *t*-Bu_2Mg (0.61 M, 1.64 mL, 1 mmol, prepared as detailed in section **4.2**) was then added, followed by a solution of the chiral aminoalcohol ((*S*)-**27**, 36 mg, 0.16 mmol) in THF (8.4 mL) and the reaction mixture was stirred at room

temperature for 1.5 h. The reaction mixture was then cooled to -78 ^{o}C and DMPU (60 μL, 0.5 mmol) and diphenylphosphoryl chloride (0.83 mL, 4 mmol) were added. The reaction mixture was stirred at -78 ^{o}C for 5 minutes before addition of 4-*tert*-butylcyclohexanone (123 mg, 0.8 mmol) in THF (2 mL) over 1 h *via* syringe pump. After this time, the reaction mixture was stirred for 16 h at -78 ^{o}C and was subsequently quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and allowed to reach room temperature. Extraction with Et_2O (50, 25, and 25 mL) gave a solution of the crude product which was washed with 1 M HCl (3 x 25 mL) to remove (*S*)-**27**, and concentrated *in vacuo* to give an oil which was purified by column chromatography on silica gel using 0-20% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (15 mg, 5%). The enantiomeric ratio of the product was determined by analysis using chiral HPLC (54:46, (-):(+)).

Chiral HPLC analysis: Chiracel OD-H column, 0.5% IPA in *n*-hexane, 1.5 mL/minute flow rate, 254 nm detector, t_R (+) = 31.65 minutes and t_R (-) = 33.67 minutes.

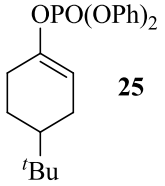
$[\alpha]_D^{20}$ = -34.6 ° (94:6 er, c = 1, $CHCl_3$). No literature data are available for comparison.

ν_{max}($CDCl_3$): 1690, 1191, 963 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (m, 4H, ArH), 7.26-7.18 (m, 6H, ArH), 5.57-5.55 (m, 1H, C=CH), 2.29-2.25 (m, 2H), 2.09-2.08 (m, 1H), 1.89-1.85 (m, 2H), 1.37-1.29 (m, 2H), 0.88 (s, 9H, $C(CH_3)_3$).

^{31}P NMR (400 MHz, $CDCl_3$): δ 17.4

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 147.3, 129.2, 124.8, 119.6, 111.3, 42.7, 31.6, 28.2, 26.8, 24.5, 23.5.



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Chapter 3

Asymmetric deprotonation of bridged bicyclic substrates

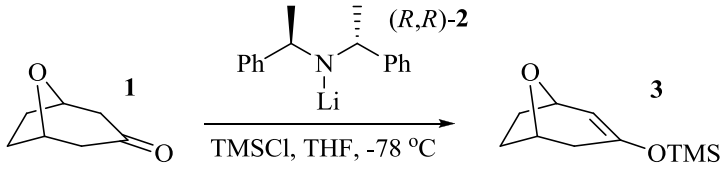
1. Introduction

As described in the previous sections, optically-pure lithium amide species have proven to be well-established reagents for asymmetric processes. The use of lithium amide bases in asymmetric deprotonation reactions is well known for several classes of prochiral substrate, including epoxides, tricarbonyl (η^6-arene)chromium complexes, and conformationally-locked ketones.[1] Of particular relevance to the current programme of research is the asymmetric deprotonation of bridged bicyclic ketones, and details of such transformations will be discussed herein.

1.1 Enantioselective deprotonation of bridged bicyclic ketones

1.1.1 Oxabicyclo[3.2.1]ketone substrates

Simpkins has carried out detailed investigations on the desymmetrisation of bridged bicyclic substrates. In particular, the effect of LiCl on the asymmetric deprotonation of the oxabicyclic ketone (**1**) has been explored, comparing the results obtained using the C_2-symmetric lithium amide ((*R*,*R*)-**2**) under both internal quench (IQ) conditions, where the TMSCl electrophile is present in the reaction mixture throughout the course of the reaction, and external quench (EQ) conditions, in which the electrophilic quench is added after the ketone has been fully converted to its lithium enolate (**Scheme 3.1**, **Table 3.1**).[2] Initial findings from the desymmetrisation of **1** in the absence of LiCl indicated that superior enantioselectivites could be afforded when IQ conditions were employed (**Table 3.1**, entries 1 and 2). However, a dramatic enhancement in ee was achieved when an EQ procedure was employed using only 0.1 equivalents of LiCl (**Table 3.1**, entry 4). Interestingly, when the quantity of LiCl was increased, no alteration in the enantioselectivity was observed (**Table 3.1**, entries 5-7), and the ee of the product remained comparable to that obtained using the IQ protocol with no added LiCl.

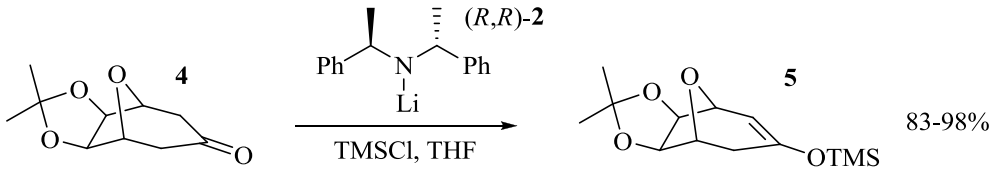


Scheme 3.1

Entry	Quench Protocol	LiCl (equivalents)	ee (%)
1	IQ	0	82
2	EQ	0	33
3	EQ	0.05	63
4	EQ	0.10	84
5	EQ	0.40	82
6	EQ	0.70	83
7	EQ	1.50	84

Table 3.1

The methodology which was developed for the asymmetric deprotonation of **1** was then applied to the more complex oxabicyclic ketone **4** (**Scheme 3.2**, **Table 3.2**), with a similar trend being apparent.[2] However, the optimal ee achieved for this substrate was considerably lower at a reaction temperature of -78 °C than those observed previously (**Table 3.2**, entry 1),[3] and the enhancement of enantioselectivity imparted by inclusion of LiCl in the EQ protocol was also less significant (**Table 3.2**, entries 2 and 3). However, when the reaction was performed at the lower temperature of -94 °C the enantioselectivity increased to a more acceptable level (**Table 3.2**, entry 4). In relation to this and more generally, it should be noted that the requirement for temperatures below -78 °C for the delivery of high enantioselectivities is a common constraint in lithium amide-mediated asymmetric deprotonation reactions.[4]

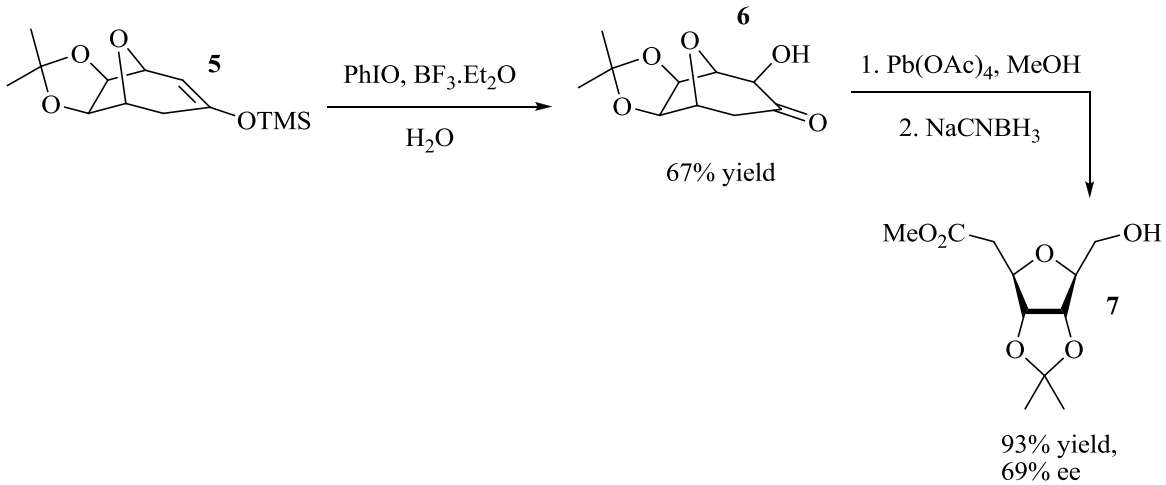


Scheme 3.2

Entry	Temperature (°C)	Quench Protocol	LiCl (equivalents)	ee (%)
1	-78	IQ	0	70
2	-78	EQ	0	27
3	-78	EQ	0.5	58
4	-94	IQ	0	85

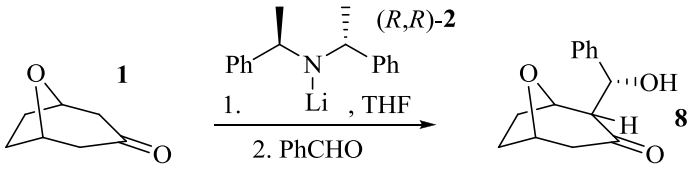
Table 3.2

Illustrating the synthetic utility of optically-enriched silyl enol ethers of this class, **5** was applied to the total synthesis of a known key intermediate in *C*-nucleoside synthesis (**7**, **Scheme 3.3**) to give the target compound in high yield and good enantioselectivity.[3]



Scheme 3.3

In addition to the preparation of optically-enriched bicyclic silyl enol ethers using the asymmetric deprotonation methodology, Simpkins has also applied chiral lithium amides to enantioselective aldol reactions (**Scheme 3.4**, **Table 3.3**).[5] More specifically, the oxabicyclic ketone (**1**) was converted to its lithium enolate, using the optically pure lithium amide ((*R*,*R*)-**2**) in the presence of $ZnCl_2$, and was subsequently trapped with benzaldehyde to give the corresponding aldol product (**8**) in acceptable ee. $ZnCl_2$ was found to have a positive effect on the enantioselectivity, with the optimum quantity lying between 0.1 and 0.5 equivalents. Although evidence for the origin of this effect was not available, Simpkins speculated that the observed increase in enantioselectivity could not be simply attributed to the generation of LiCl in the reaction mixture, which could lead to the formation of a more selective aggregated species, since the trends in enantioselectivity observed for the reactions using either $ZnCl_2$ or LiCl were not identical.[5]

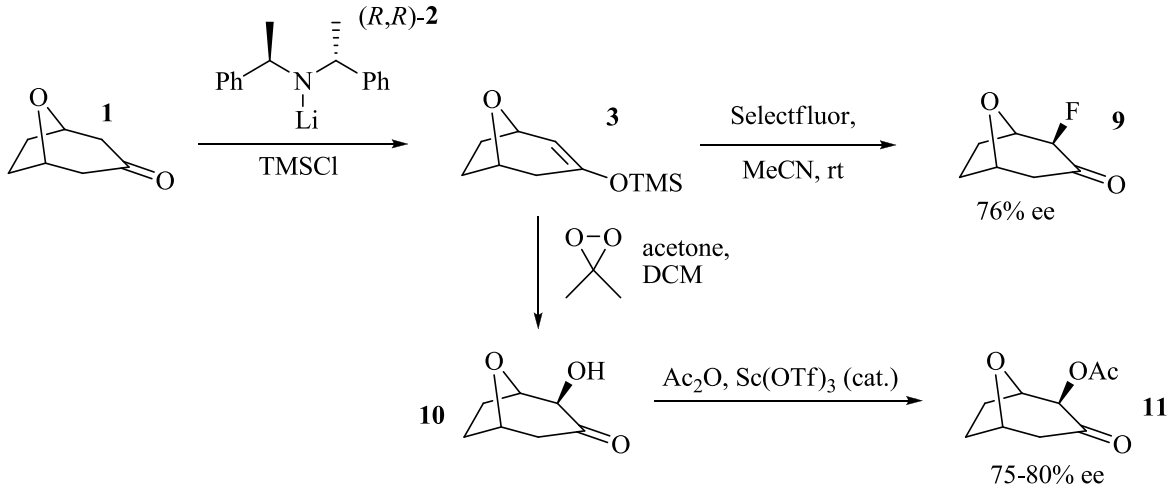


Scheme 3.4

Entry	$ZnCl_2$ (equivalents)	ee (%)
1	0	34
2	0.1	74
3	0.2	72
4	0.4	70
5	0.5	74

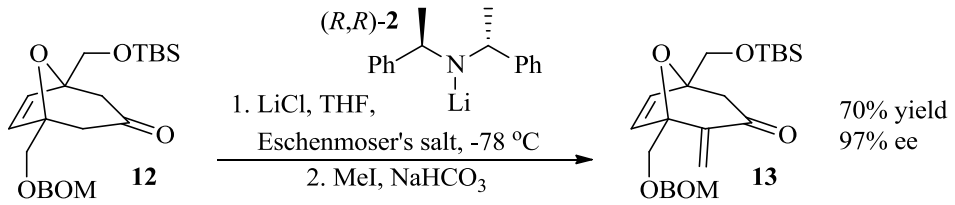
Table 3.3

The asymmetric deprotonation approach to enantioenriched silyl enol ethers has been employed by Armstrong in the synthesis of α-substituted ketones for use as enantioselective epoxidation catalysts.[6] Unfortunately, using the chiral base ((*R*,*R*)-**2**) for the preparation of the silyl enol ether (**3**), the α-substituted ketones (**9** and **11**) were delivered with modest optical purity (75-80% ee, **Scheme 3.5**).[6b] Since optically pure catalysts were not available, to allow evaluation of catalyst activity in epoxidation processes, a linear relationship between catalyst ee and (epoxidised) product ee was assumed. This relationship was used to calculate an ee_{max} value for the epoxide product, which is, essentially, the expected enantiomeric excess afforded with enantiomerically-pure catalyst. Overall, this demonstrates the requirement for silyl enol ethers of this class with more elevated levels of optical enrichment to allow the subsequent asymmetric processes to become more practicable.



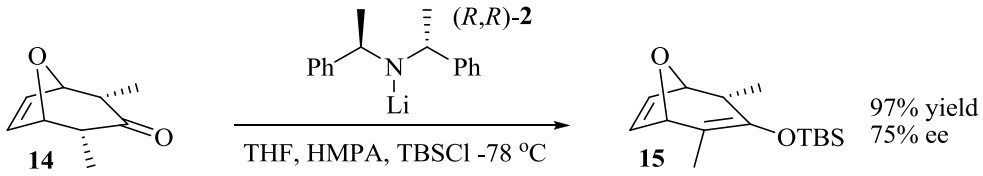
Scheme 3.5

Demonstrating the asymmetric deprotonation of bridged bicyclic ketones in the preparation of natural products, Cha reported the formal total synthesis of (+)-phorbol using the desymmetrisation of **12** as a key step (**Scheme 3.6**).[7] More specifically, the C_2-symmetric lithium amide base ((*R*,*R*)-**2**) was used to prepare the required enone (**13**) in a regio- and stereoselective manner by deprotonation of the *pseudo*-symmetric ketone (**12**), followed by Mannich condensation and elimination, giving **13** in 97% ee.



Scheme 3.6

Expanding the oxabicyclic substrate scope further, Grieco illustrated the asymmetric deprotonation of an α,α-disubstituted oxabicyclic ketone (**14**) in the synthesis of chiral fragments of scytophycin C (**Scheme 3.7**).[8] The C_2-symmetric lithium amide base ((*R*,*R*)-**2**) was employed for the desymmetrisation of the prochiral ketone (**14**) in the presence of TBSCl and HMPA. It was noted that the exclusion of LiCl was crucial for high yield and enantioselectivity in this instance, with the best results being achieved when HMPA was used as an additive. Having stated all of this, the ee of the product remains moderate when using the lithium amide ((*R*,*R*)-**2**).

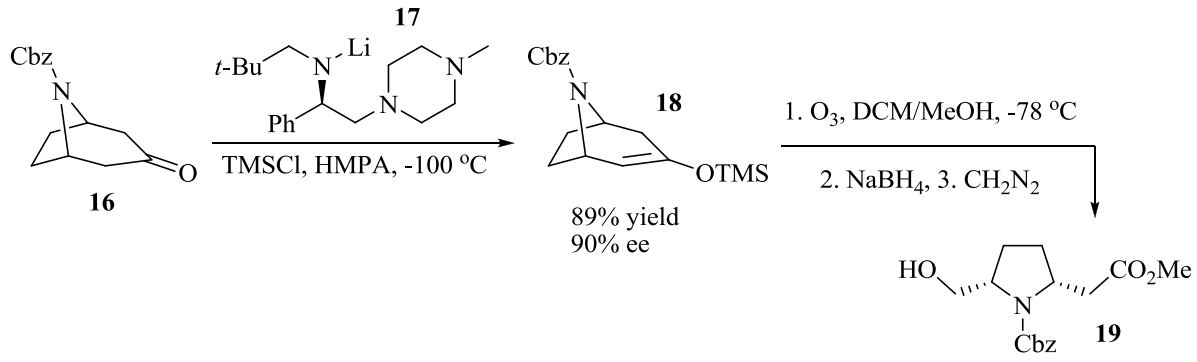


Scheme 3.7

1.1.2 Azabicyclo[3.2.1]ketone substrates

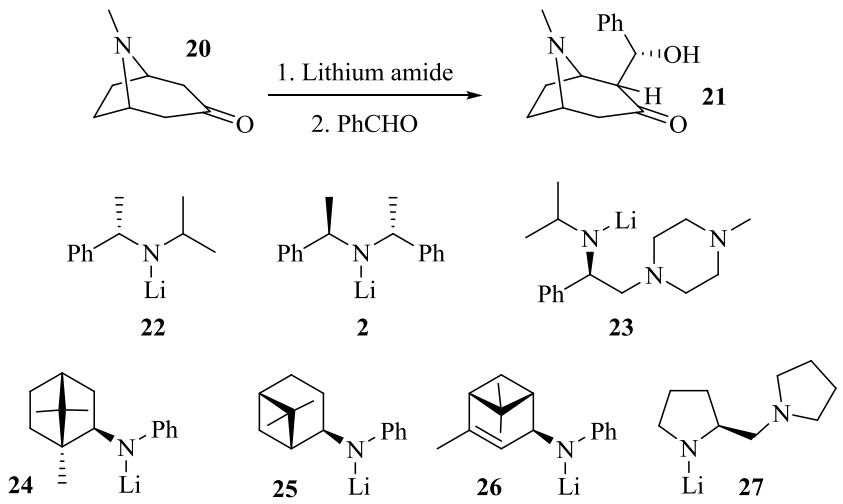
The first example of the asymmetric deprotonation of a tropinone-type substrate was reported by Momose in 1990 as a key step in the total synthesis of (+)-monomorine I (**Scheme 3.8**).[9] Koga's chelated lithium amide (**17**) was employed for the deprotonation of the *N*-protected azabicycle (**16**) in the presence of TMSCl and HMPA at -100 °C to give the corresponding silyl enol ether (**18**) in high yield and ee. This intermediate was

then subject to ozonolysis, sodium borohydride reduction, and esterification with diazomethane to yield *cis*-2,5-disubstituted pyrrolidine (**19**) as the crucial chiral building block in the synthetic pathway.



Scheme 3.8

Majewski then illustrated that tropinone itself could be subject to enantioselective deprotonation conditions with good results (**Scheme 3.9**, **Table 3.4**).[10] A variety of chiral lithium amide bases were applied to the asymmetric aldol reaction between tropinone (**20**) and benzaldehyde, giving a wide range of selectivities. While all of the selected bases afforded high yields for the transformation, the observed enantioselectivies were modest, with Koga's chelated lithium amide (**23**) being the most enantioselective, giving the chiral alcohol (**21**) in 60% ee. The enantioenriched aldol product was then used in the synthesis of a variety of tropane alkaloids.[11]



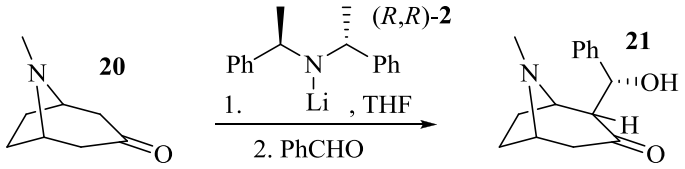
Scheme 3.9

Base	Yield (%)	ee (%)
22	88	34
2	84	40
23	64	60
24	75	40
25	70	26
26	97	16
27	85	8

Table 3.4

As described previously, Simpkins has investigated the effect of the addition of LiCl on the asymmetric deprotonation of bridged oxabicyclic substrates.[2] This methodology has also been extended to the desymmetrisation of tropinone under external quench conditions.[2] More specifically, optically pure lithium amide ((*R*,*R*)-**2**) was applied to the enolisation of tropinone (**20**), and benzaldehyde was used to quench the resultant enolate, giving the chiral alcohol product with variable enantioselectivity, depending on the quantity of LiCl employed (**Scheme 3.10**, **Table 3.5**). It was discovered that the enantioselectivity for this transformation increased sharply when relatively small

quantities of LiCl were added to the reaction mixture, with the optimal selectivity being achieved using 0.5 equivalents of this additive.

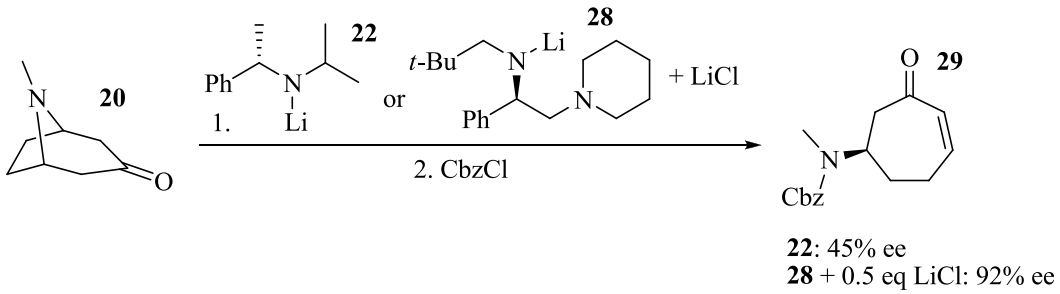


Scheme 3.10

Entry	LiCl (equivalents)	ee (%)
1	0	24
2	0.01	35
3	0.03	42
4	0.05	59
5	0.07	62
6	0.09	66
7	0.5	78

Table 3.5

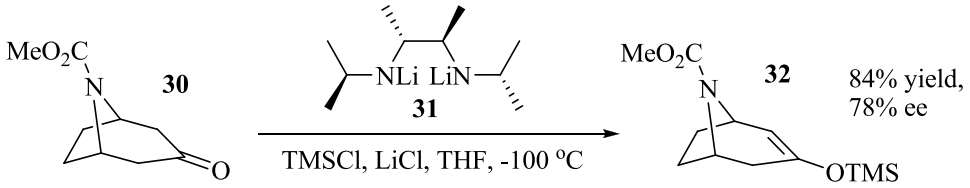
Similarly, Majewski investigated the beneficial effect of LiCl on a novel ring-opening reaction of tropinone,[12] which was found to occur when the tropinone enolate, generated using chiral base **22**, was quenched with benzylchloroformate (**Scheme 3.11**).[10b] The product of the reaction was found to be the cycloheptenone (**29**) which was formed in 45% optical purity when no LiCl was employed. The enantiomeric excess of the product could be increased significantly, to 92%, by employing lithium amide (**28**) together with only 0.5 equivalents of LiCl.[12]



Scheme 3.11

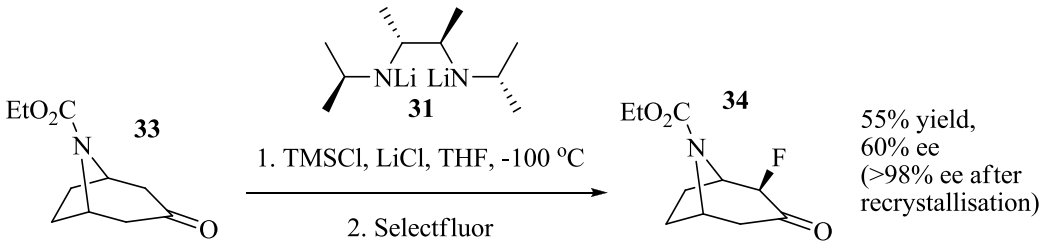
The practical expediency of the LiCl-enhanced reactions was then improved by Majewski. More specifically, an alternative method for the generation of the C_2-symmetric lithium amide, by treating the corresponding amine hydrochloride salt with two equivalents of *n*-BuLi, was developed.[11] The required LiCl was generated *in situ* and the procedure proved to be much more convenient than employing the free amine, which readily absorbs moisture and CO_2 from the air. Furthermore, the hydrochloride salts are crystalline and are readily purified by recrystallisation.

The azabicyclic substrate (**30**), possessing a carbamate moiety in the bridge, has been employed by Simpkins in the asymmetric synthesis of (-)-anatoxin-a (**Scheme 3.12**).[13] The asymmetric deprotonation of **30**, mediated by the dilithiated amide base (**31**), represented a key step in this total synthesis project. Although the more commonly used C_2-symmetric lithium amide ((*R*,*R*)-**2**) delivered poor enantioselectivity (15-20% ee) for the transformation, the more structurally elaborate dilithiated species proved to be highly efficient for the formation of silyl enol ether **32**, delivering the enantioenriched product in high yield and reasonable enantioselectivity. It should be noted, however, that a low temperature of -100 ^{o}C was required in order to induce this more satisfactory selectivity.



Scheme 3.12

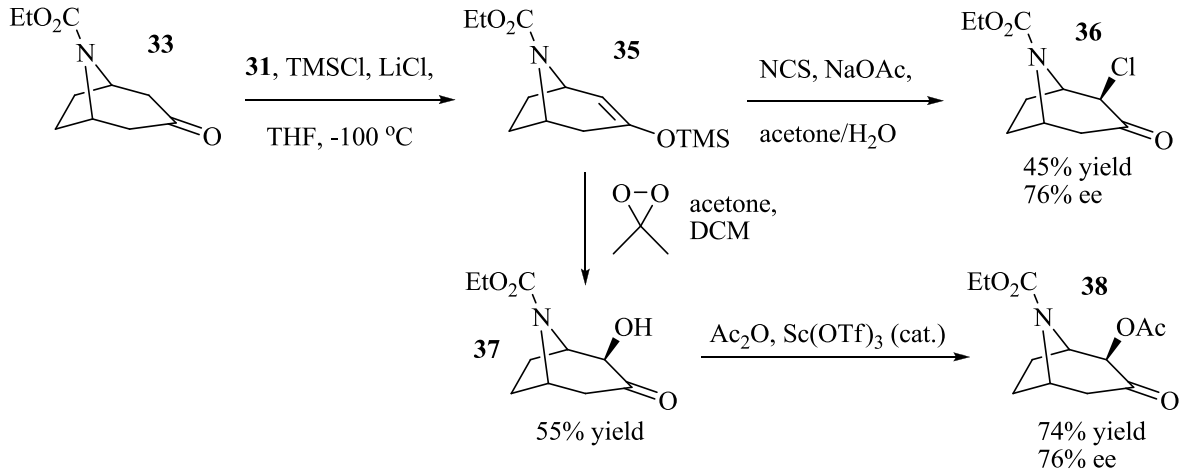
Illustrating the valuable synthetic utility of the products of desymmetrisation of tropinone-type substrates, Armstrong has employed enantioenriched silyl enol ethers, prepared from *N*-carbethoxytropinone (**33**), in the synthesis of enantioselective epoxidation catalysts.[6] Similar to the approach described in the previous section for the preparation of α-substituted oxabicyclic ketones, the azabicyclic silyl enol ether was prepared *via* an enantioselective deprotonation reaction, using the lithium amide (**31**) in the presence of TMSCl and LiCl at -100 °C, and the crude product was reacted with Selectfluor to give the α-substituted ketone (**34**) in moderate yield and enantioselectivity (**Scheme 3.13**).[6a] The enantiopurity of the product (**34**) could be increased to >98% by recrystallisation, delivering the required enantiopurity to allow use of this fluorinated species as an enantioselective epoxidation catalyst.



Scheme 3.13

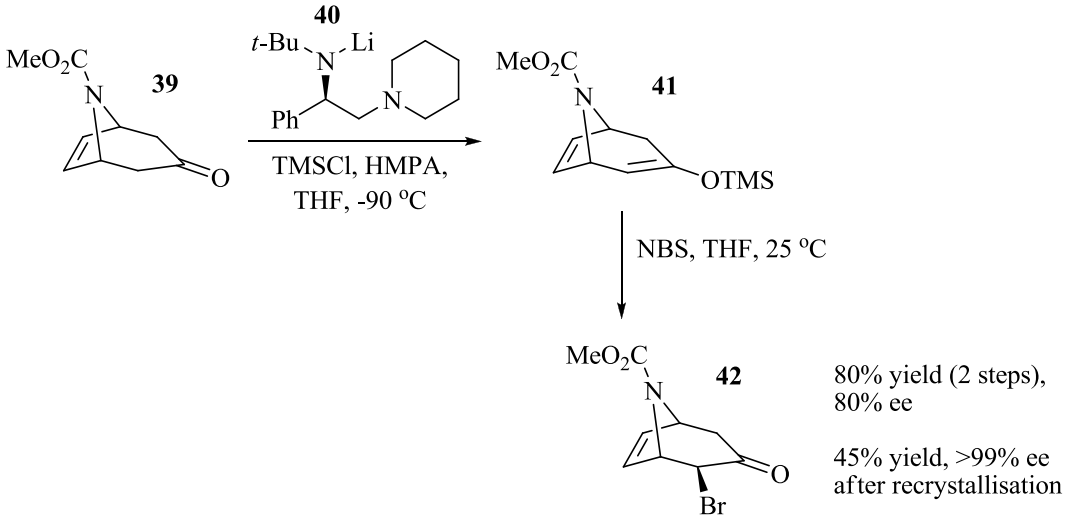
The strategy which was employed for the synthesis of the α-fluoroketone (**34**) was then applied to the preparation of alternative α-substituted ketones, to allow their use as asymmetric epoxidation catalysts (**Scheme 3.14**).[6c] The α-acetoxy (**38**) and α-chloro (**36**) ketones were prepared from the enantioenriched silyl enol ether (**35**). However,

unlike the α-fluoroketone (**34**), the enantiopurity could not be increased by recrystallisation methods, and samples of approximately 76% ee were used in the asymmetric epoxidation of olefins. Since optically pure catalysts were not available, an ee_{max} value for the epoxide product was calculated to allow evaluation of catalyst activity.



Scheme 3.14

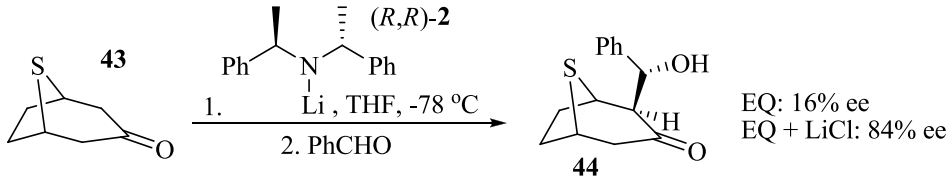
In addition to the research that has been carried out for the chiral lithium amide-mediated deprotonation of tropinone-type substrates, enantioselective deprotonation of an unsaturated analogue (**39**) has also been achieved and applied to a natural product synthesis by Hodgson (**Scheme 3.15**).[14] Employing a relatively low reaction temperature of -90 °C for the desymmetrisation of **39**, mediated by the chelated lithium amide (**40**), the α-bromoketone (**42**) was delivered with modest enantioselectivity. Fortunately, the ee of the α-bromoketone product could be increased to give optically pure material on recrystallisation.



Scheme 3.15

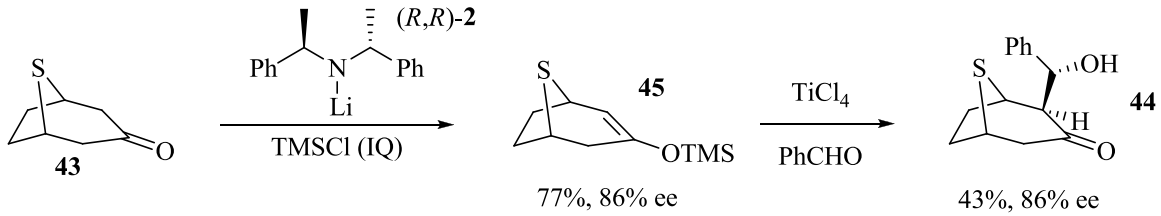
1.1.3 Thiabicyclo[3.2.1]ketone substrates

While performing investigations involving the effect of added salts on the asymmetric deprotonation of oxabicyclic ketones, Simpkins also explored the possible beneficial effects of LiCl and $ZnCl_2$ on the desymmetrisation of the sulfur-bridged ketone (**43**) by the C_2-symmetric lithium amide (**2**, **Scheme 3.16**).[5] Initial studies, in the absence of added salts, had demonstrated that the aldol reaction between the lithium enolate of **43** and benzaldehyde proceeded with a poor enantioselectivity of 16% ee under external quench conditions. However, the enantioselectivity was increased dramatically when LiCl was employed.



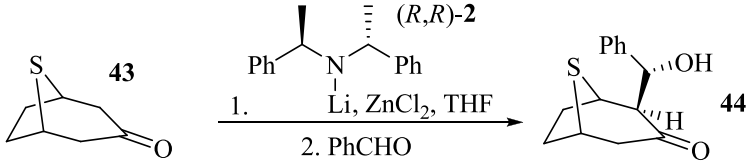
Scheme 3.16

Simpkins has also demonstrated that the enantioenriched silyl enol ether (**45**) could be employed as an intermediate in the synthesis of the aldol product (**44**) with similar results (**Scheme 3.17**).[5] It should be noted that, in this example, use of IQ conditions delivered the desired enol ether (**45**) in good ee.



Scheme 3.17

After also probing the effect of LiCl on the enantioselectivity of the transformation, $ZnCl_2$ was utilised as an additive under external quench conditions (**Scheme 3.18**, **Table 3.6**).[5] The degree of enhancement of the enantioselectivity was found to be greatly dependent on the quantity of $ZnCl_2$ employed. More specifically, when up to 0.4 equivalents of $ZnCl_2$ were employed, the enantioselectivity increased up to 86% ee. However, if greater quantities of $ZnCl_2$ were added to the reaction, the enantioselectivity reached a level comparable to that achieved when no salts were added.

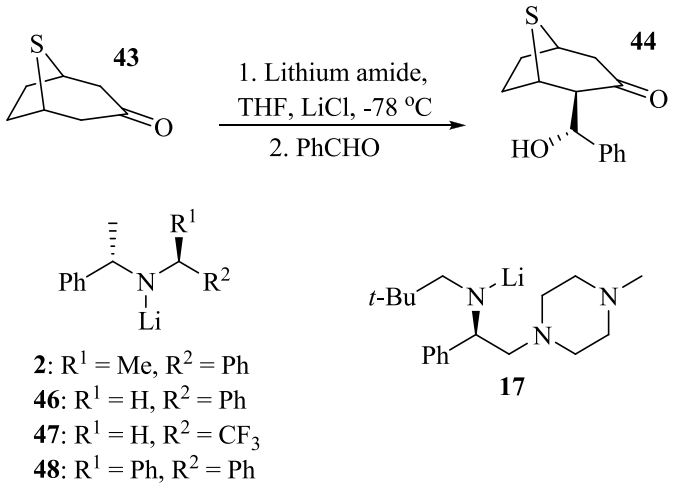


Scheme 3.18

$ZnCl_2$ equivalents	0	0.05	0.10	0.20	0.40	0.60	0.70	0.80	0.90	1.00
ee(%)	15	75	76	86	86	74	63	68	45	21

Table 3.6

Further developing the methodology reported by Simpkins, Majewski applied a variety of lithium amide bases to the asymmetric aldol reaction between the thiabicyclic ketone (**43**) and benzaldehyde, under external quench conditions (**Scheme 3.19**, **Table 3.7**).[15] Curiously, the enantioselectivity achieved by Simpkins[5] using the C_2-symmetric base (**2**) could not be replicated by Majewski. However, high enantioselectivity was achieved using alternative bases, including the related lithium amide (**48**).



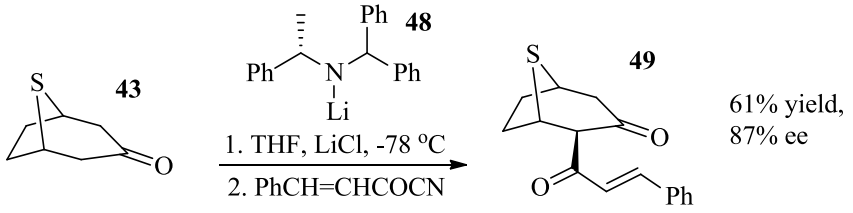
Scheme 3.19

Base	Yield (%)	ee (%)
2	58	80
46	45	78
47	70	72
48	95	82
17	74	75

Table 3.7

The application of a range of alternative electrophiles was then investigated (**Scheme 3.20**).[15] Although the reaction of a variety of typical alkylating agents (benzyl bromide, alkyl halides, and sulfonates) proved unsuccessful, several acyl cyanide reagents were

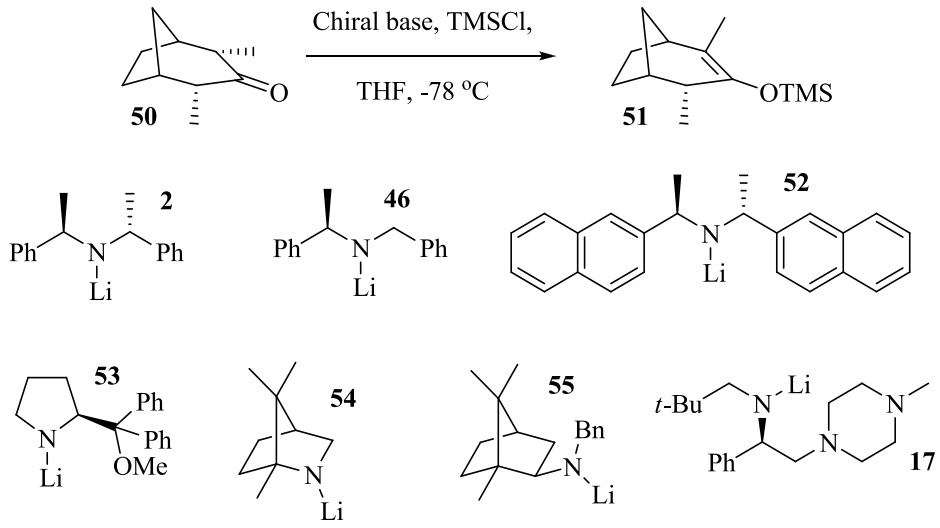
employed to give the acylated products in high yields and selectivities. For example, deprotonation of the thiabicyclic ketone (**43**) using the lithium amide (**48**), followed by treatment of the resulting enolate with cinnamoyl cyanide, afforded the levorotatory isomer of the α-substituted ketone (**49**) in good yield and high enantioselectivity.



Scheme 3.20

1.1.4 Carbobicyclo[3.2.1]ketone substrates

Although most of the research which has been carried out on the asymmetric deprotonation of bridged bicyclic ketones by lithium amide bases has involved heterocyclic substrates, more simple carbocyclic substrates, possessing a methylene unit in the bridge, have also been employed.[16] MaGee has performed detailed investigations into the optimal base structure for this class of substrate (**Scheme 3.21**, **Table 3.8**). More specifically, a wide variety of optically pure lithium amides was applied to the desymmetrisation of 2,4-dimethylbicyclo[3.2.1]octan-3-one (**50**), using either an internal quench or external quench procedure, to give enantioselectivities ranging from 5% for the camphor- and proline-derived amides (**53** and **54**) to 85% using Koga's chelating amide (**17**). In all instances, the enantioselectivity achieved under internal quench conditions was either equal or superior to that achieved using an external quench.[16]



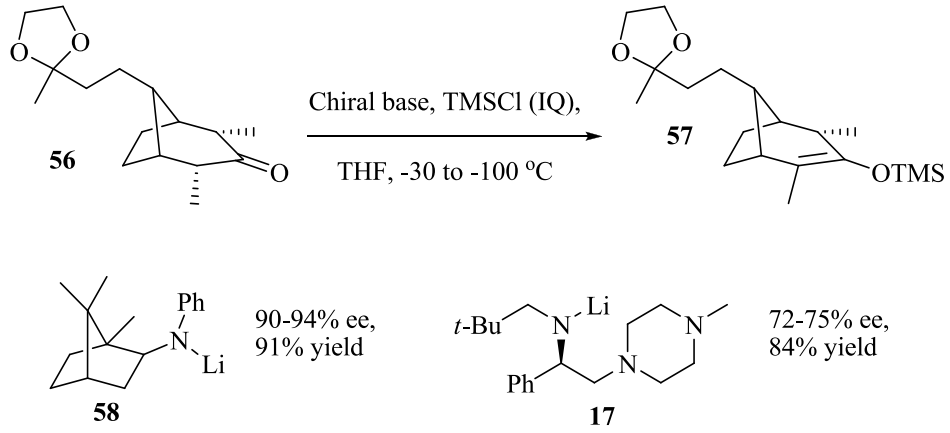
Scheme 3.21

Base	Yield (%)	ee (%, IQ)	ee (%, EQ)
2	96	23	15
46	89	10	10
52	95	45	30
53	80	5	-
54	95	5	5
55	75	76	46
17	62	85	-

Table 3.8

Having established conditions for the enantioselective deprotonation of the bridged carbocyclic substrate (**50**), MaGee applied the developed methodology towards a more complex related substrate (**56**) in the synthesis of reiswigin A (**Scheme 3.22**).[17] Chiral lithium amides **58** and **17**, developed by Simpkins and Koga, respectively, were employed for the asymmetric deprotonation of **56** in the presence of TMSCl, with **58** affording the greatest enantioselectivity for the transformation. Furthermore, this

reaction represents the first successful enantioselective deprotonation of a fully substituted *meso*-cyclohexanone.



Scheme 3.22

2. Proposed work

Although it has been demonstrated that optically pure lithium amide bases are capable of mediating asymmetric deprotonation reactions of bridged bicyclic ketone substrates, there are a number of weaknesses associated with lithium amides that can hinder their wider application in asymmetric synthesis. These include their requirement for low reaction temperatures,[4] their often complex solution behaviour,[18] and the structural complexity of the amines required for the highest selectivity.[4] It should be noted that, in a number of instances, the available lithium amide bases cannot deliver preparatively useful levels of enantioselectivity, as detailed in the previous section. Due to the greater thermal stability[19] and simpler solution aggregation[20] exhibited by magnesium amides, this class of reagent has proven to be a beneficial alternative to the commonly used lithium bases.[21] Hence, it was envisaged that superior results could be achieved using the magnesium amide bases which have been developed within our laboratory for the asymmetric deprotonation reactions of bridged bicyclic substrates. As detailed in the previous section, the optically-enriched products of these desymmetrisation reactions have a number of useful applications in asymmetric synthesis and represent an attractive class of substrate for the application of our magnesium amide-mediated desymmetrisations. Thus, the bridged bicyclic ketones shown were chosen as substrates for the magnesium amide-mediated asymmetric deprotonation reaction (**Figure 3.1**). In relation to this, the synthesis of these non-commercially available substrates would be required in order to allow their application in asymmetric deprotonation reactions.

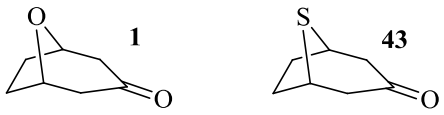
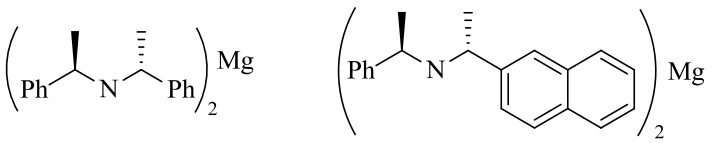


Figure 3.1

Having previously demonstrated outstanding efficiency and enantioselectivity in the deprotonation of 4-substituted cyclohexanones, the C_2- and *pseudo*-C_2-symmetric

bisamides (**59** and **60**) will be applied to the preliminary investigations involving the desymmetrisation of the selected bridged bicyclic substrates (**Figure 3.2**).



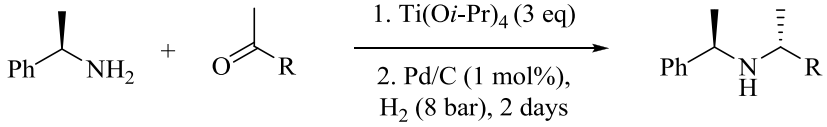
59 **60**

Figure 3.2

3. Results and discussion

3.1 Synthesis of chiral amines

In order to allow the evaluation of our magnesium bisamides (**59** and **60**) as enantioselective bases for the deprotonation of bridged bicyclic substrates, the required parent amines were prepared. Accordingly, the C_2- (**61**) and *pseudo*-C_2-symmetric (**62**) amines were synthesised from (*R*)-phenylethylamine and the appropriate ketone by the reductive amination method developed by Alexakis, using titanium tetra-*iso*-propoxide to mediate imine formation, followed by reduction to the amine *in situ* by palladium on charcoal and hydrogen gas (**Scheme 3.23**, **Table 3.9**).[22] This procedure has become the method of choice within our laboratory for the synthesis of this class of amine and routinely delivers the required amines on appreciable scale with high diastereoselectivity. The optically pure amines are then isolated after recrystallisation of their HCl salts. Using this method, the required amines were obtained in moderate yield, providing sufficient quantities for the optimisation of the proposed asymmetric deprotonations.



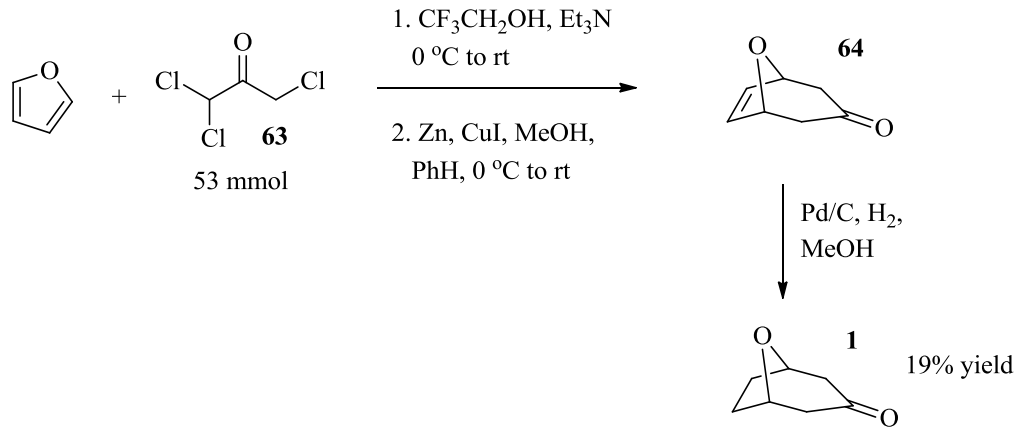
Scheme 3.23

Entry	R	Scale (mmol)	dr ((*R*,*R*):(*R*,*S*)) of crude product	Yield of purified material (%)
1	Ph (**61**)	165	91:9	52
2	Ph (**61**)	165	90:10	45
3	2-Naphthyl (**62**)	165	≥95:5	46

Table 3.9

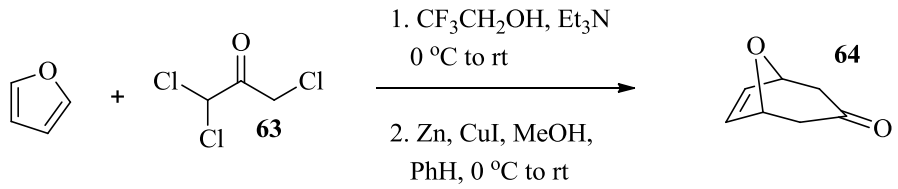
3.2 Synthesis of bridged bicyclic substrates

Having synthesised the amines required for the preparation of the corresponding magnesium bisamides, the preparation of selected bridged bicyclic ketones was then embarked upon. Initial efforts focused on the preparation of the oxabicyclic ketone (**1**, **Scheme 3.24**). Following the conditions developed by Föhlisch and co-workers[23] delivered the unsaturated analogue (**64**) which was then hydrogenated, without previous purification, using palladium on charcoal under a balloon pressure of hydrogen gas. Unfortunately, using this method, the oxabicyclic ketone (**1**) was isolated in a poor yield of 19% after column chromatography. Moreover, the level of purity of the product was inadequate.



Scheme 3.24

In an attempt to improve on these somewhat disappointing results, the intermediate unsaturated ketone (**64**) was purified by column chromatography and trituration using diethyl ether before being taken on to the subsequent hydrogenation step. Pleasingly, performing these additional purification processes delivered the unsaturated ketone (**64**) as a highly crystalline solid which could be analysed by X-ray crystallography (**Scheme 3.25**, **Table 3.10**, **Figure 3.3**). Although the yields obtained were low, it was envisaged that the hydrogenation step would proceed in high yield.



Scheme 3.25

Entry	Scale (mmol)	Yield (%)
1	131	33
2	284	26
3	284	34

Table 3.10

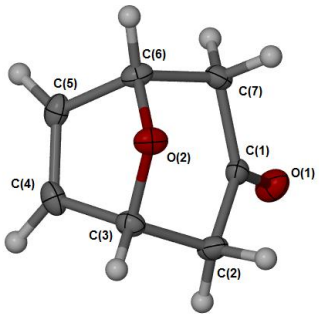
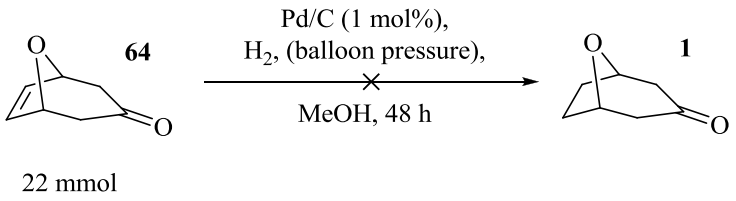


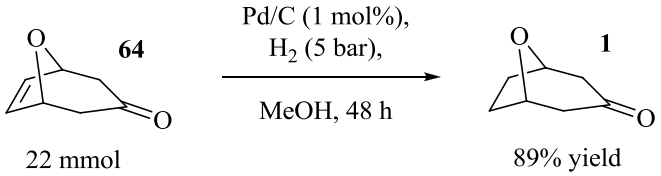
Figure 3.3

The hydrogenation of this substrate (**64**) was then attempted using palladium on charcoal under an atmospheric pressure of hydrogen gas, as employed previously for the crude material. Surprisingly, after 48 h of stirring under these conditions, very little conversion to the saturated product (**1**) was observed (**Scheme 3.26**).



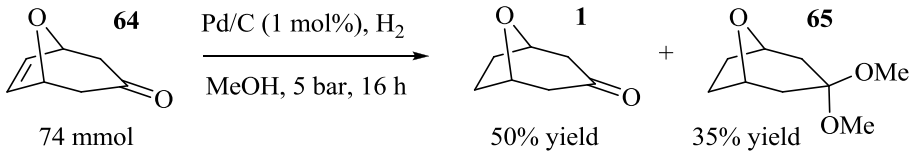
Scheme 3.26

Consequently, the reaction mixture was subjected to a higher pressure of hydrogen gas in an attempt to accelerate the hydrogenation (**Scheme 3.27**). Pleasingly, after stirring under 5 bar of hydrogen for 2 days, complete conversion was achieved, and the product was isolated in an excellent 89% yield after column chromatography.



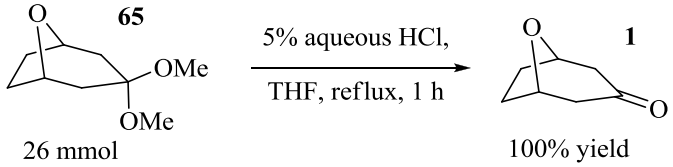
Scheme 3.27

Having established suitable conditions for the preparation of the oxabicyclic ketone (**1**), its synthesis was attempted on a larger scale. As before, the unsaturated analogue was stirred under 5 bar of hydrogen gas for 16 hours in methanol (**Scheme 3.28**). After this time, complete conversion of the starting material was achieved. However, a major impurity was identified by ^{1}H NMR as the dimethyl acetal (**65**), and a significant amount (35% yield) of this by-product was isolated by column chromatography, along with 50% yield of the desired ketone (**1**). Most probably, the batch of methanol which was used as solvent contained acidic impurities which catalysed the acetal formation.



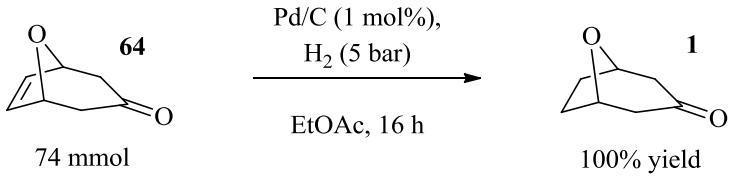
Scheme 3.28

In order to deliver the required oxabicyclic ketone (**1**), hydrolysis of **65** was carried out using dilute aqueous hydrochloric acid in THF (**Scheme 3.29**). Pleasingly, the hydrolysis proceeded smoothly and the ketone (**1**) was isolated in quantitative yield after column chromatography.



Scheme 3.29

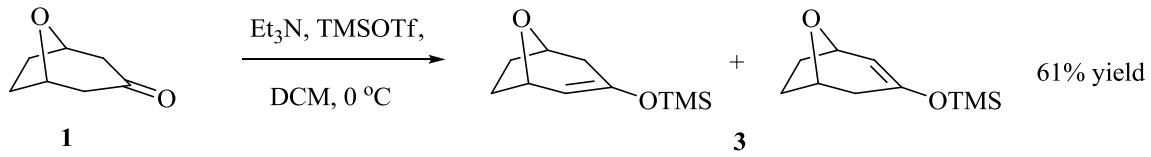
In subsequent hydrogenations of the unsaturated bridged bicycle (**64**), to avoid the formation of unwanted by-products, the reaction was performed using ethyl acetate as solvent to efficiently deliver the desired oxabicyclic ketone (**1**) in quantitative yield (**Scheme 3.30**).



Scheme 3.30

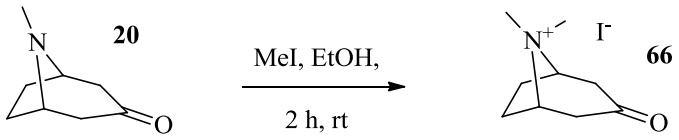
Having established a reliable method for the synthesis of **1**, the preparation of the corresponding racemic silyl enol ether (**3**) was carried out in order to allow identification

of each enantiomer by chiral GC analysis (**Scheme 3.31**). Pleasingly, after the racemate was formed in good yield using triethylamine and trimethylsilyl triflate, the enantiomers were readily separated using chiral GC methods.



Scheme 3.31

An additional bridged bicyclic ketone which has been chosen as a substrate for magnesium amide-mediated asymmetric deprotonation reactions is the thiabicycle (**43**). This bicycle is readily prepared from tropinone (**20**), *via* the quaternary ammonium salt (**66**), which is generated by treatment of tropinone with methyl iodide in EtOH (**Scheme 3.32**, **Table 3.11**). This procedure has proven to be a reliable and scalable process for the synthesis of the intermediate (**66**), delivering the desired product in good yield.



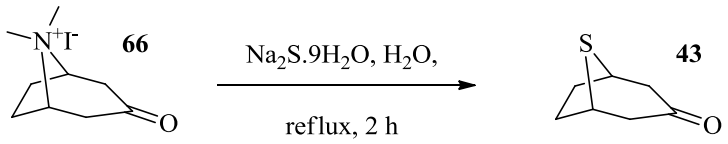
Scheme 3.32

Entry	Scale (mmol)	Yield (%)
1	1	46
2	67	75

Table 3.11

Subsequently, the thiabicycle (**43**) was prepared by displacement of dimethylamine from the quaternary ammonium species (**66**) using aqueous sodium sulfide (**Scheme 3.33**,

Table 3.12). Significant quantities of the thiabicyclic ketone, which was easily purified by column chromatography followed by trituration in low-boiling petroleum ether, were delivered using this method.

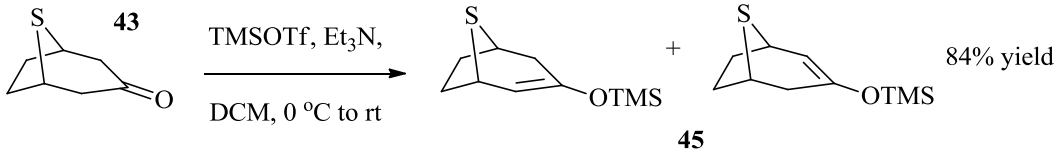


Scheme 3.33

Entry	Scale (mmol)	Yield (%)
1	0.2	43
2	51	90

Table 3.12

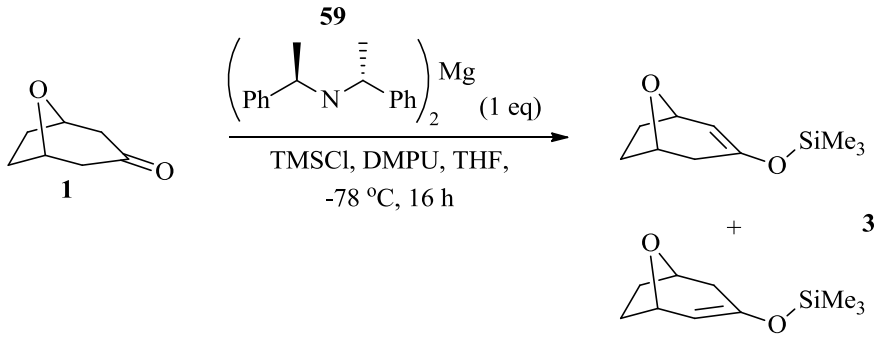
Pleasingly, the corresponding racemic silyl enol ether (**45**) was then obtained in high yield using triethylamine and trimethylsilyl triflate, and the peaks for each enantiomer were clearly resolved using chiral GC methods (**Scheme 3.34**).



Scheme 3.34

3.3 Asymmetric deprotonation of bridged bicyclic substrates

Having prepared the oxabicyclic (**1**) and thiabicyclic (**43**) ketones, and successfully separated their enantiomers using chiral GC techniques, the application of these substrates in magnesium amide-mediated deprotonation reactions was investigated. At the outset, the C_2-symmetric bisamide (**59**) was chosen for the desymmetrisation of **1**, having demonstrated outstanding efficiency in the deprotonation of the benchmark 4-substituted cyclohexanone substrates.[24] Using DMPU as a Lewis basic additive, and TMSCl to trap the resulting magnesium enolate as the corresponding silyl enol ether (**3**), initial deprotonation attempts focused on the optimisation of the quantities of each of these reagents in the deprotonation of the oxabicycle (**1**) at -78 ^{o}C in THF (**Scheme 3.35**, **Table 3.13**). Pleasingly, performing the desymmetrisation of **1** using a variety of combinations in the quantities of DMPU and TMSCl gave very pleasing results. Of particular note is the fact that this magnesium amide-mediated desymmetrisation method does not require a great excess of TMSCl to effect high yields and enantioselectivities. Indeed, the requirement of super-stoichiometric quantities (around four equivalents) of TMSCl is a common feature in the deprotonations of prochiral ketones using lithium amide bases.[1a,b] After performing this initial set of optimisation reactions, the best results were achieved using two equivalents of TMSCl and one equivalent of DMPU (**Table 3.13**, entry 3) to deliver the enantioenriched silyl enol ether (**3**) in excellent yield and enantioselectivity. These results compare favourably with the corresponding lithium amide which delivers the silyl enol ether in 91:9 er at -78 ^{o}C (**Scheme 3.1**).[2]

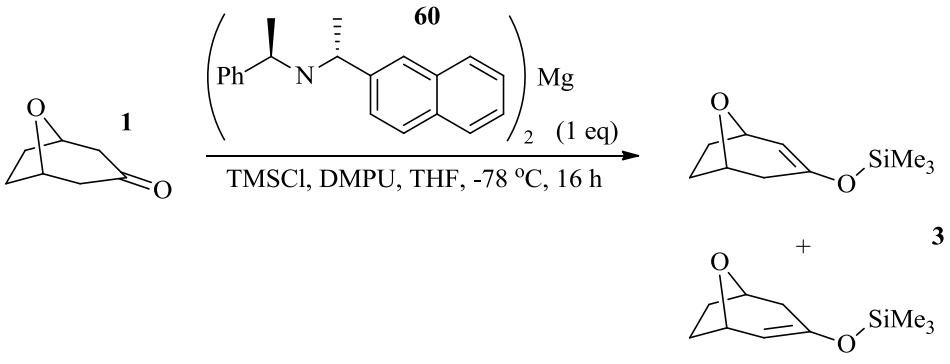


Scheme 3.35

Entry	TMSCl (eq)	DMPU (eq)	Conversion (%)	Yield (%)	er
1	1	1	94	67	93:7
2	1	0.5	80	73	92:8
3	2	1	97	95	96:4
4	2	0.5	79	68	89:11

Table 3.13

The evaluation of an alternative, *pseudo*-C_2-symmetric, magnesium bisamide (**60**), which has also proven to be a very efficient base for the asymmetric deprotonation of 4-substituted cyclohexanones (see Chapter 1), was then carried out to establish if superior results could be achieved (**Scheme 3.36**, **Table 3.14**). In a similar fashion to the optimisation studies using magnesium bisamide (**59**), the desymmetrisation of the oxabicyclic substrate (**1**) was performed over a range of quantites of DMPU and TMSCl. Again, excellent yields and enantioselectivities were obtained for the asymmetric deprotonation reaction under a variety of conditions, with the most favourable results, in terms of both yield and selectivity, being achieved when employing two equivalents of TMSCl alongside one equivalent of DMPU (**Table 3.14**, entry 3). Since the *pseudo*-C_2-symmetric magnesium bisamide (**60**) exhibited similar efficiency and enantioselectivity to the C_2-symmetric bisamide (**59**) in the studies conducted so far, and thus offered no apparent advantage at this stage, the more structurally simple and inexpensive C_2-symmetric bisamide (**59**) was employed in subsequent optimisation studies.

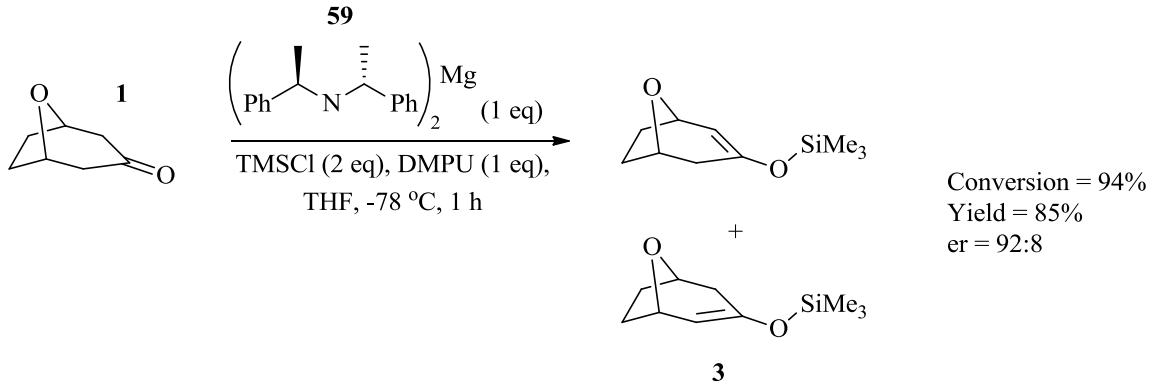


Scheme 3.36

Entry	TMSCl (eq)	DMPU (eq)	Conversion (%)	Yield (%)	er
1	1	1	92	78	96:4
2	1	0.5	90	61	93:7
3	2	1	97	92	95:5
4	2	0.5	81	70	91:9
5	4	1	98	85	97:3

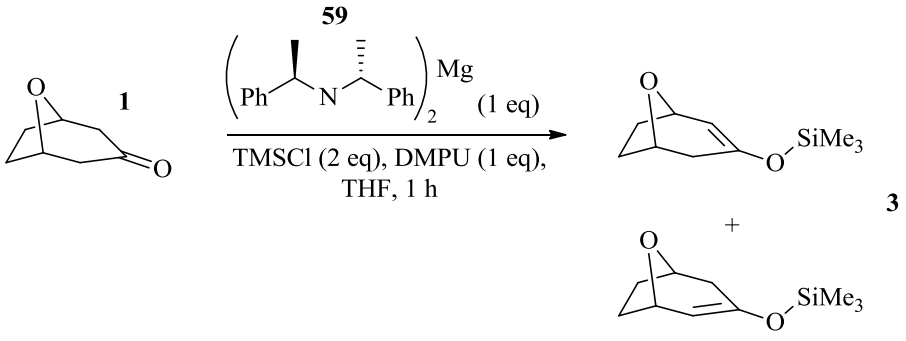
Table 3.14

Having established the optimal conditions in terms of the quantities of both TMSCl and DMPU, the optimisation of alternative variables in the asymmetric deprotonation of oxabicycle (**1**) was explored. In particular, the effect of shortening the reaction time was probed in order to improve the overall efficiency of the process (**Scheme 3.37**). Pleasingly, when the reaction was quenched immediately after the solution of the ketone had been added to the reaction mixture (over one hour), comparable results to those achieved after a significantly longer time period of 16 hours were achieved. Thus, reactions in further optimisation studies were quenched immediately after the ketone addition was complete.



Scheme 3.37

An impressive feature of the magnesium bisamide (**59**) is that it has previously displayed consistently high enantioselectivites when applied to asymmetric deprotonation reactions at elevated reaction temperatures.[24] Thus, it was envisaged that the desymmetrisation of the oxabicyclic substrate (**1**) could proceed efficiently using this magnesium bisamide at temperatures above -78 °C. Indeed, when the desymmetrisation reactions were performed at temperatures up to 0 °C, the observed enantioselectivity remained at an impressively high level, with the er fluctuating only very slightly on increasing the reaction temperature from -60 °C to 0 °C (**Scheme 3.38**, **Table 3.15**). However, disappointing reaction conversions were obtained in some cases (**Table 3.15**, entries 2-4).

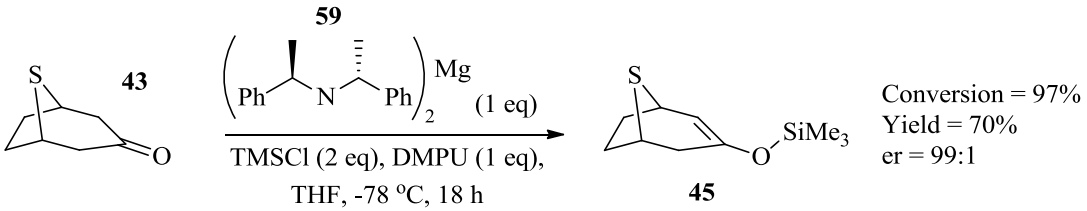


Scheme 3.38

Entry	Temperature (^{o}C)	Conversion (%)	Yield (%)	er
1	-78	94	85	92:8
2	-60	78	60	87:13
3	-40	55	54	82:18
4	-20	80	63	84:16
5	0	97	84	83:17

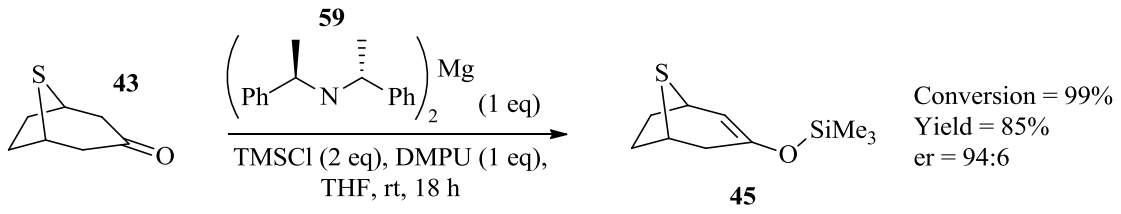
Table 3.15

Attention was then focused on the asymmetric deprotonation of the thiabicyclic substrate (**43**) using the *C_2*-symmetric magnesium bisamide (**59**, **Scheme 3.39**). Remarkably, after a reaction time of 18 hours at -78 ^{o}C, an outstanding level of enantioselectivity (99:1 er) was achieved in the preparation of the silyl enol ether (**45**). This is a real improvement on the lithium amide-mediated preparation of **45**, which was shown by Simpkins to proceed with a lower enantioselectivity of 93:7 at -78 ^{o}C.[5]



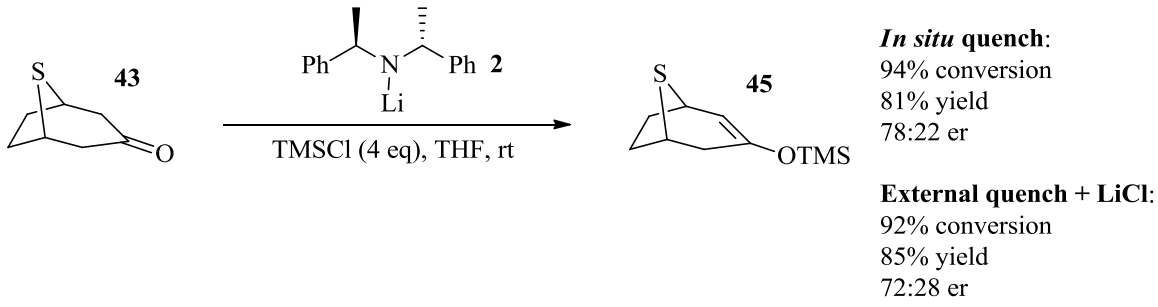
Scheme 3.39

Having obtained the enantioenriched silyl enol ether (**45**) in outstanding enantiomeric excess at -78 ^{o}C, the desymmetrisation was then performed at room temperature (**Scheme 3.40**). Astonishingly, under these conditions, the enantioselectivity for the transformation remained at an excellent level (94:6 er), and the optically-enriched silyl enol ether (**45**) was obtained in high yield.



Scheme 3.40

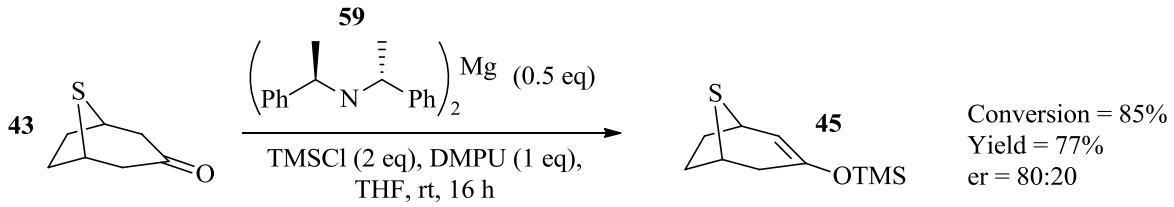
In order to allow a direct comparison to be drawn with the performance of the analogous lithium base, the efficacy of the lithium amide (**2**) was tested at room temperature under both internal and external quench conditions (**Scheme 3.41**). As envisaged, although the desired enol silane was obtained in high yield, the enantioinduction was moderate. This result clearly demonstrates the advantage in the use of the more robust and thermally-stable magnesium amides, over their lithium counterparts, allowing more energy-efficient processes to be performed without the requirement of cooling.



Scheme 3.41

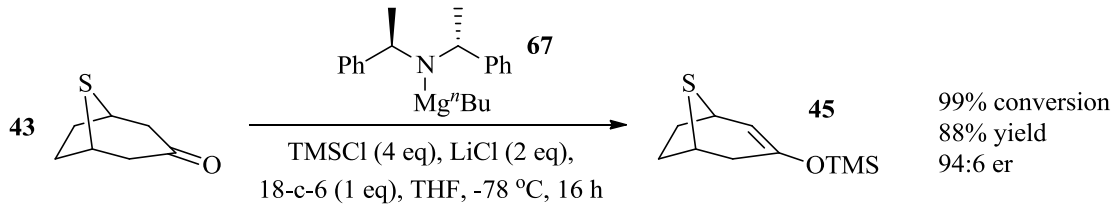
Encouraged by the outstanding results that had been achieved when our magnesium bisamide (**59**) was applied to the desymmetrisation of **43**, we looked to improve the efficiency of the transformation further by reducing the number of equivalents of chiral amine. At first, the desymmetrisation of **43** was attempted using just 0.5 equivalents of the magnesium bisamide (**59**, **Scheme 3.42**). Pleasingly, under the conditions shown it was possible to utilise both amide ligands in the transformation, although the reaction did

not reach completion. Moreover, the enantioselectivity decreased significantly to 80:20 er.



Scheme 3.42

Alternatively, alkylmagnesium amides, employing half the quantity of chiral amine (**61**) compared to the corresponding magnesium bisamide (**59**), have proven to be excellent enantioselective bases for the desymmetrisation of 4-substituted cyclohexanones using novel additive conditions.[25] With this in mind, we sought to apply the C_2-symmetric alkylmagnesium amide (**67**) to the asymmetric deprotonation of **43** (**Scheme 3.43**). To our delight, comparable yield and enantioselectivity to that achieved using the magnesium bisamide (**59**) was observed at -78 ^{o}C.



Scheme 3.43

3.4 Summary

The bridged bicyclic ketones shown (**Figure 3.4**) were prepared in order to probe their application in magnesium amide-mediated asymmetric deprotonation reactions.

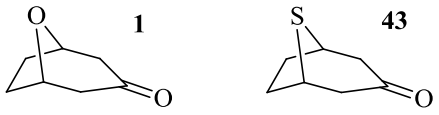
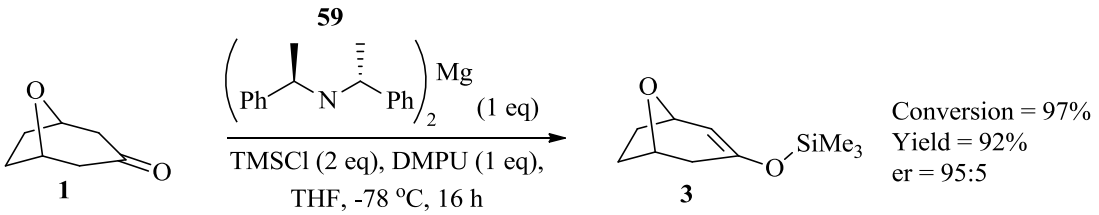


Figure 3.4

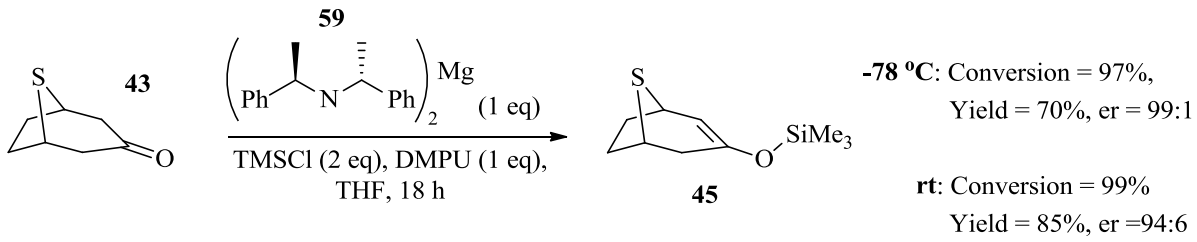
With the bridged bicyclic substrates in hand, initial studies were performed using the oxabicyclic substrate (**1**). Pleasingly, after a short period of optimisation, outstanding results were achieved using only two equivalents of TMSCl and one equivalent of DMPU to deliver the enantioenriched silyl enol ether (**3**) in unprecedented yield and enantioselectivity (**Scheme 3.44**).



Scheme 3.44

With these initial results in hand, attention was turned to the analogous thiabicyclic ketone substrate (**43**, **Scheme 3.45**). When performing the asymmetric deprotonation of this novel substrate under the previously optimised conditions, an outstanding level of enantioselection was observed (99:1 er), and the silyl enol ether product (**45**) was obtained in good yield. Having achieved such impressive results at -78 °C, the efficiency of the transformation at room temperature was probed (**Scheme 3.45**). Pleasingly, the enantioenriched silyl enol ether (**45**) was obtained in excellent enantioselectivity (94:6 er)

and yield, without the requirement for sub-ambient temperatures. This is in marked contrast to the results achieved using the corresponding lithium amide (**2**), which delivered silyl enol ether **45** with a lower level of enantioselectivity (93:7) at -78 ^{o}C. Impressive results could also be achieved when the analogous alkylmagnesium amide, containing just one chiral amide unit, was applied to the desymmetrisation of **43**.



Scheme 3.45

As mentioned in the introductory chapter, the asymmetric deprotonation approach to enantioenriched bridged bicyclic silyl enol ethers has been employed by Armstrong in the synthesis of α-substituted ketones for use as enantioselective epoxidation catalysts (**Figure 3.5**).[6] Unfortunately, using optically-pure lithium amide bases for the preparation of the required silyl enol ethers, the α-substituted ketones were delivered with modest optical purity (60-80% ee), resulting in lower than optimal enantioselectivities being achieved for the asymmetric epoxidation.[6b] In order to demonstrate the synthetic utility of our magnesium amide-mediated deprotonations, the α-substituted ketones (**Figure 3.5**) should be prepared *via* the corresponding enantioenriched silyl enol ethers, and their efficiency in the asymmetric epoxidation of alkenes should be evaluated.

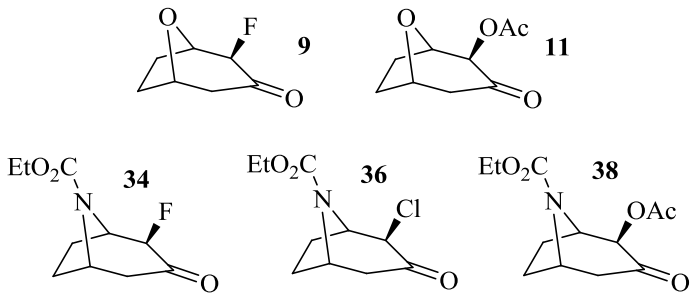


Figure 3.5

4. Experimental

4.1 General

All reagents were obtained from commercial suppliers (Aldrich, TCI, Alfa Aesar or Acros) and used without further purification, unless otherwise stated. Purification was carried out according to standard laboratory methods.[26]

- Dichloromethane was obtained from an Innovative Technology, Pure Solv, SPS-400-5 solvent purification system.
- Tetrahydofuran was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen.
- 18-Crown-6 was dried by heating to 125 ^{o}C under high vacuum (0.005 mbar) using Kugelrohr apparatus for two hours, then were stored under argon over 4 Å molecular sieves.
- Organometallic reagents were standardised using salicylaldehyde phenylhydrazone.[27]

Thin layer chromatography was carried out using Camlab silica plates, coated with fluorescent indicator UV_{254}, and analysed using a Mineralight UVGL-25 lamp.

Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

IR spectra were obtained on a Perkin Elmer Spectrum 1 machine.

^{1}H and ^{13}C spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{\text{H-H}}$ interactions unless otherwise specified.

4.2 Preparation of substrates and reagents

Preparation of bis((*R*)-1-phenylethyl)amine (61)[28]

Scheme 3.23, Table 3.9, Entry 1

(*R*)-Phenylethylamine (20.0 g, 165 mmol), acetophenone (19.8 g, 165 mmol) and titanium tetra-*iso*-propoxide (140.8 g, 496 mmol) were stirred at room temperature for 10 minutes before the addition of 10% palladium on charcoal (1.5 g, 1.5 mmol). The reaction mixture was placed under an atmosphere of hydrogen at 8 bar and was shaken for 2 days before being treated with a saturated solution of NaOH (500 mL), causing a grey precipitate to form. The mixture was filtered to remove the precipitate, and the aqueous filtrate was extracted with EtOAc (3 x 200 mL). The precipitate was washed repeatedly with 200 mL portions of EtOAc until no more product could be detected in the washings by TLC, and the organics were combined, washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a colourless oil. The dr of the crude product was determined as 91:9 using ^{1}H NMR analysis. Formation of the HCl salt and recrystallisation from *iso*-propanol delivered the diastereomerically pure salt which was then treated with a saturated solution of $NaHCO_3$ (500 mL), extracted with DCM (2 x 300 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 19.7 g (52%) of bis((*R*)-1-phenylethyl)amine as a colourless oil. The product was dried by distillation from CaH_2 at 98 ^{o}C and 0.4 mbar before use.

Scheme 3.23, Table 3.9, Entry 2

(*R*)-Phenylethylamine (20.0 g, 165 mmol), acetophenone (19.8 g, 165 mmol) and titanium tetra-*iso*-propoxide (140.8 g, 496 mmol) were stirred at room temperature for 10 minutes before the addition of 10% palladium on charcoal (1.5 g, 1.5 mmol). The reaction mixture was placed under an atmosphere of hydrogen at 8 bar and was shaken for 2 days before being treated with a saturated solution of NaOH (500 mL), causing a grey precipitate to form. The mixture was filtered to remove the precipitate, and the aqueous filtrate was extracted with EtOAc (3 x 200 mL). The precipitate was washed repeatedly with 200 mL portions of EtOAc until no more product could be detected in the

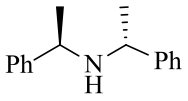
washings by TLC, and the organics were combined, washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a colourless oil. The dr of the crude product was determined as 90:10 using ^1H NMR analysis. Formation of the HCl salt and recrystallisation from *iso*-propanol delivered the diastereomerically pure salt which was then treated with a saturated solution of $NaHCO_3$ (500 mL), extracted with DCM (2 x 300 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford 17.1 g (45%) of (*R*)-bis((*R*)-1-phenylethyl)amine as a colourless oil. The product was dried by distillation from CaH_2 at 98 ^oC and 0.4 mbar before use.

$[\alpha]_D^{20}$ = +171.6° (*c* = 6.71, $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -171.6° (*S*,*S*) (c = 6.71, $CHCl_3$).[28]

$\nu_{max}(CDCl_3)$: 2962 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.23 (m, 10H, ArH), 3.56 (q, J = 6.7 Hz, 2H, $N(CH)_2$), 1.33 (d, J = 6.7 Hz, 6H, $N(CHC\mathit{H}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 128.5, 126.8, 126.7, 55.2, 25.1.



61

Preparation of (*R*)-1-(naphthalen-2-yl)-*N*-((*R*)-1-phenylethyl)ethanamine (62)[29]

Scheme 3.23*, *Table 3.9, Entry 3

(*R*)-Phenylethylamine (20.0 g, 165 mmol), 2-acetylnaphthalene (28.1 g, 165 mmol) and titanium tetra-*iso*-propoxide (140.8 g, 496 mmol) in EtOAc (300 mL) were stirred at room temperature for 10 minutes before the addition of 10% palladium on charcoal (1.5 g, 1.5 mmol). The reaction mixture was placed under an atmosphere of hydrogen at 8 bar and was shaken for 2 days before being treated with a saturated solution of NaOH (500 mL), causing a grey precipitate to form. The mixture was filtered to remove the precipitate, and the aqueous filtrate was extracted with EtOAc (3 x 200 mL). The

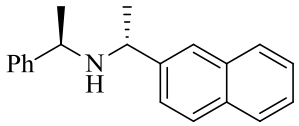
precipitate was washed repeatedly with 200 mL portions of EtOAc until no more product could be detected in the washings by TLC, and the organics were combined, washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a colourless oil. None of the undesired diastereomer could be detected by H^1 NMR analysis. The crude amine was purified by formation of the HCl salt and recrystallisation from *iso*-propanol. The salt was then treated with a saturated solution of $NaHCO_3$ (500 mL), extracted with DCM (2 x 300 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford (*R*)-1-(naphthalen-2-yl)-*N*-((*R*)-1-phenylethyl)ethanamine as a colourless oil. The product was dried by distillation from CaH_2 at 141 ^oC and 0.001 mbar before use.

$[\alpha]_D^{20}$ = +255.3^o (c = 1.5, $CHCl_3$). No literature rotation is available for comparison.

$\nu_{max}(CDCl_3)$: 2962 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ7.86-7.81 (m, 3H, ArH), 7.61 (s, 1H, ArH), 7.51-7.44 (m, 3H, ArH), 7.38-7.34 (m, 2H, ArH), 7.30-7.26 (m, 1H, ArH), 7.25-7.23 (m, 2H, ArH), 3.70 (q, *J* = 6.6 Hz, 1H, C*H*CH_3), 3.55 (q, *J* = 6.6 Hz, 1H, C*H*CH_3), 1.67 (brs, 1H, NH), 1.37 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.31 (d, *J*= 6.6 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ144.8, 142.2, 132.4, 131.8, 127.4, 127.2, 126.7, 126.6, 125.8, 125.6, 124.9, 124.4, 124.3, 123.8, 54.2, 54.1, 24.0, 23.9.



62

Preparation of 8-oxabicyclo[3.2.1]oct-6-en-3-one (64)[30]

Scheme 3.24

To a solution of furan (21.6 g, 318 mmol) in trifluoroethanol (20 mL) was added 1,1,3-trichloroacetone (8.6 g, 53 mmol) at 0 ^oC. After stirring for 5 minutes, triethylamine

(10.7 g, 106 mmol) was added dropwise. The reaction mixture was then allowed to warm to room temperature before stirring for 72 h. After this time, the reaction mixture was transferred *via* cannula to a round-bottomed flask containing a Zn/Cu couple (prepared as below) at 0 ^{o}C. The reaction mixture was then stirred at rt for 24 h before being filtered through celite to remove any Zn and Cu residues which were washed with MeOH until no more product could be detected in the washings by TLC. The washings were concentrated *in vacuo* and then dissolved in DCM (200 mL) before being washed with a saturated solution of Na_2EDTA (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give 5.68 g of brown oil.

Zn/Cu couple preparation:[23] To a round-bottomed flask containing Zn dust (41.1 g, 627 mmol) and CuI (39.8 g, 209 mmol) was added MeOH (56 mL). On addition of MeOH, an exotherm was observed which caused the reaction mixture to reflux. Benzene (56 mL) was added slowly and the reaction mixture was stirred until reflux ceased. The mixture was then cooled to 0 ^{o}C before addition of the substrate.

Preparation of 8-oxabicyclo[3.2.1]octan-3-one (1)[31]

Scheme 3.24

The previously prepared crude 8-oxabicyclo[3.2.1]oct-6-en-3-one (2.84 g, 23 mmol) and 10% palladium on charcoal (245 mg, 0.23 mmol) were stirred at room temperature in MeOH (70 mL) under a balloon pressure of hydrogen for 24 h. The reaction mixture was then filtered through celite and concentrated *in vacuo* to give the crude product as a brown oil. Flash chromatography on silica gel (10-50% Et_2O in 40-60 ^{o}C petroleum ether) delivered the impure product as a yellow oil (535 mg, 19%). The product was subsequently dried by distillation from CaH_2 at 35 ^{o}C and 0.001 mbar.

Preparation of 8-oxabicyclo[3.2.1]oct-6-en-3-one (64)[30]

Scheme 3.25, Table 3.10, Entry 1

To a solution of furan (53.6 g, 788 mmol) in trifluoroethanol (50 mL) was added 1,1,3-trichloroacetone (24.9 g, 131 mmol) at 0 ^{o}C. After stirring for 5 minutes, triethylamine (26.5 g, 263 mmol) was added dropwise. The reaction mixture was then allowed to warm to room temperature before stirring for 24 h. After this time, the reaction mixture was transferred *via* cannula to a round-bottomed flask containing a Zn/Cu couple (prepared as below) at 0 ^{o}C. The reaction mixture was then stirred at rt for 48 h before being filtered through celite to remove any Zn and Cu residues, which were washed with MeOH until no more product could be detected in the washings by TLC. The washings were concentrated *in vacuo* and then dissolved in DCM (400 mL) before being washed with a saturated solution of Na_2EDTA (500 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a brown oil. Purification by flash chromatography on silica gel (0-50% Et_2O in 40-60 ^{o}C petroleum ether), and trituration using Et_2O delivered the product as a white solid (5.3 g, 33%).

Zn/Cu couple preparation:[23] To a round-bottomed flask containing Zn dust (101.3 g, 1.55 mol) and CuI (100.0 g, 525 mmol) was added MeOH (140 mL). On addition of MeOH, an exotherm was observed which caused the reaction mixture to reflux. Benzene (140 mL) was added slowly and the reaction mixture was stirred until reflux ceased. The mixture was then cooled to 0 ^{o}C before addition of the substrate.

Scheme 3.25, Table 3.10, Entry 2

To a solution of furan (96.6 g, 1.42 mol) in trifluoroethanol (300 mL) was added 1,1,3-trichloroacetone (45.8 g, 284 mmol) at 0 ^{o}C. After stirring for 5 minutes, triethylamine (57.4 g, 568 mmol) was added dropwise. The reaction mixture was then allowed to warm to room temperature before stirring for 48 h. After this time, the reaction mixture was transferred *via* cannula to a round-bottomed flask containing a Zn/Cu couple (prepared as below) at 0 ^{o}C. The reaction mixture was then stirred at rt for 48 h before being filtered through celite to remove any Zn and Cu residues which were washed with MeOH until

no more product could be detected in the washings by TLC. The washings were concentrated *in vacuo* and then dissolved in DCM (400 mL) before being washed with a saturated solution of Na_2EDTA (2 x 500 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a brown oil. Purification by flash chromatography on silica gel (0-50% Et_2O in 40-60 ^oC petroleum ether), and trituration using Et_2O delivered the product as a white solid (9.1 g, 26%).

Zn/Cu couple preparation:[23] To a round-bottomed flask containing Zn dust (185.7 g, 2.84 mol) and CuI (180.3 g, 947 mmol) was added MeOH (300 mL). On addition of MeOH, an exotherm was observed which caused the reaction mixture to reflux. Benzene (300 mL) was added slowly and the reaction mixture was stirred until reflux ceased. The mixture was then cooled to 0 ^oC before addition of the substrate.

Scheme 3.25, Table 3.10, Entry 3

To a solution of furan (96.6 g, 1.42 mol) in trifluoroethanol (300 mL) was added 1,1,3-trichloroacetone (45.8 g, 284 mmol) at 0 ^oC. After stirring for 5 minutes, triethylamine (57.4 g, 568 mmol) was added dropwise. The reaction mixture was then allowed to warm to room temperature before stirring for 24 h. After this time, the reaction mixture was transferred *via* cannula to a round-bottomed flask containing a Zn/Cu couple (prepared as below) at 0 ^oC. The reaction mixture was then stirred at rt for 24 h before being filtered through celite to remove any Zn and Cu residues which were washed with MeOH until no more product could be detected in the washings by TLC. The washings were concentrated *in vacuo* and then dissolved in DCM (400 mL) before being washed with a saturated solution of Na_2EDTA (2 x 500 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a brown oil. Purification by flash chromatography on silica gel (0-50% Et_2O in 40-60 ^oC petroleum ether), and trituration using Et_2O delivered the product as a white solid (11.9 g, 34%).

Zn/Cu couple preparation:[23] To a round-bottomed flask containing Zn dust (185.7 g, 2.84 mol) and CuI (180.3 g, 947 mmol) was added MeOH (300 mL). On addition of MeOH, an exotherm was observed which caused the reaction mixture to reflux. Benzene (300

mL) was added slowly and the reaction mixture was stirred until reflux ceased. The mixture was then cooled to 0 ^{o}C before addition of the substrate.

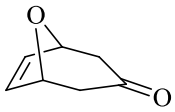
Melting point = 37-38 ^{o}C. Lit: 37-38 ^{o}C.[23]

$\nu_{max}(CDCl_3)$: 2967 and 1709 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.27 (s, 2H, CH=CH), 5.04 (d, *J* = 5.3 Hz, 2H, CH-O-CH), 2.76 (dd, *J* = 17.0 and 5.2 Hz, 2H, (C=O)CH_{ax}), 2.31-2.35 (m, 2H, (C=O)CH_{eq}).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.3, 133.3, 77.1, 46.6.

See appendix for X-ray crystallographic details.



64

Preparation of 8-oxabicyclo[3.2.1]octan-3-one (1)[31]

Scheme 3.26

8-Oxabicyclo[3.2.1]oct-6-en-3-one (2.67 g, 22 mmol) and 10% palladium on charcoal (230 mg, 0.22 mmol) were stirred at room temperature in MeOH (65 mL) under a balloon pressure of hydrogen for 48 h. After this time, very little conversion to the saturated product was observed by ^{1}H NMR spectroscopy.

Scheme 3.27

The reaction mixture from the previous hydrogenation attempt was transferred to a high pressure reaction vessel and was stirred at room temperature under hydrogen (5 bar) for 48 h. The reaction mixture was then filtered through celite and concentrated *in vacuo* to give the crude product as a brown oil. Purification by flash chromatography on silica gel

(10-50% Et_2O in 40-60 ^oC petroleum ether) delivered the product as a yellow oil (2.42 g, 89%). The product was dried by distillation from CaH_2 at 35 ^oC and 0.001 mbar.

Scheme 3.28

8-Oxabicyclo[3.2.1]oct-6-en-3-one (9.12 g, 74 mmol) and 10% palladium on charcoal (782 mg, 0.74 mmol) in MeOH (225 mL) were stirred at room temperature under hydrogen (5 bar) for 16 h. The reaction mixture was then filtered through celite and concentrated *in vacuo* to give the crude product as a brown oil. Analysis of the crude product using ^1H NMR spectroscopy revealed that, alongside the desired product, a significant amount of the corresponding dimethyl acetal had been formed. Purification by flash chromatography on silica gel (0-20% Et_2O in 40-60 ^oC petroleum ether) delivered the desired product as a yellow oil (4.61 g, 50%). In addition, the dimethyl acetal (**65**) was isolated as a colourless oil (4.39 g, 35% yield).

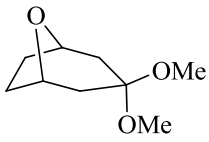
3,3-Dimethoxy-8-oxabicyclo[3.2.1]octane (**65**):

$\nu_{max}(CDCl_3)$: 2830 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 4.41-4.39 (m, 2H, CH-O-CH), 3.18 (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 1.96-1.92 (m, 4H), 1.84-1.79 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 98.2, 73.8, 48.3, 47.0, 38.6, 28.0.

Due to instability, no further analysis could be obtained for this novel compound.



65

Scheme 3.29

To a solution of 3,3-dimethoxy-8-oxabicyclo[3.2.1]octane (4.39 g, 26 mmol) in THF (75 mL) was added HCl (37 mL, 37% aqueous solution). The reaction mixture was then heated at reflux for 1 h. After this time, the reaction mixture was cooled to room temperature, neutralised with a saturated solution of $NaHCO_3$, extracted with DCM (3 x 100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil (3.22 g, 100%). The product was dried by distillation from CaH_2 at 35 ^oC and 0.001 mbar.

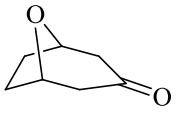
Scheme 3.30

8-Oxabicyclo[3.2.1]oct-6-en-3-one (9.12 g, 74 mmol) and 10% palladium on charcoal (782 mg, 0.74 mmol) in EtOAc (100 mL) were stirred at room temperature under hydrogen (5 bar) for 16 h. The reaction mixture was then filtered through celite and concentrated *in vacuo* to give the crude product as a brown oil. Purification by flash chromatography on silica gel (0-20% Et_2O in 40-60 ^oC petroleum ether) delivered the desired product as a yellow oil (9.27 g, 100%).

$\nu_{max}(CDCl_3)$: 1715 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 4.74-4.71 (m, 2H, CH-O-CH), 2.70 (dd, *J* = 15.9 and 5.5 Hz, 2H, $(C=O)CH_{ax}$), 2.31-2.27 (m, 2H, $(C=O)CH_{eq}$), 2.08-2.04 (m, 2H, CH_2CH-O-CHCH_2), 1.78-1.73 (m, 2H, CH_2CH-O-CHCH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 73.8, 48.7, 28.5.



1

Preparation of (8-oxabicyclo[3.2.1]oct-2-en-3-yloxy)trimethylsilane (3)[2a]

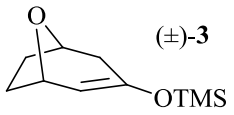
Scheme 3.31

To a round-bottomed flask which had been previously flame-dried under vacuum and allowed to cool under argon was added 8-oxabicyclo[3.2.1]octan-3-one (109 mg, 0.8 mmol), triethylamine (242 mg, 2.4 mmol), and DCM (12 mL). The reaction mixture was then cooled to 0 ^{o}C before addition of trimethylsilyl triflate (196 mg, 0.9 mmol) and stirring for 1 h at 0 ^{o}C. The reaction mixture was then quenched with a saturated solution of $NaHCO_3$ (10 mL) and extracted with DCM (3 x 10 mL). The extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* before being purified by flash chromatography on silica gel (0-10% Et_2O in 30-40 ^{o}C petroleum ether) to deliver the title compound as a colourless oil (96 mg, 61% yield).

$\nu_{max}(CDCl_3)$: 1657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (d, *J* = 4.9 Hz, 1H, CH=C), 4.58-4.55 (m, 1H, O-C*H*-CH=C), 4.50 (t, *J* = 5.1 Hz, 1H, C*H*-O-CH-CH=C), 2.69 (dd, *J* = 16.6 and 5.1 Hz, 1H, CH=C(OTMS)CH_2), 2.14-2.06 (m, 1H), 2.01-1.87 (m, 2H), 1.75-1.68 (m, 2H), 0.20 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 108.1, 73.1, 72.1, 39.4, 35.8, 29.3, 0.0.



(±)-**3**

Preparation of tropinone methiodide (66)[32]

Scheme 3.32*, *Table 3.11

Entry 1

MeI (0.08 mL, 1.3 mmol) was added dropwise to a solution of tropinone (139 mg, 1 mmol) in EtOH (1 mL). The reaction mixture was stirred at room temperature for 2 h and then filtered to collect the precipitate which was washed with Et_2O to afford the product as a white powder (130 mg, 46%).

Entry 2

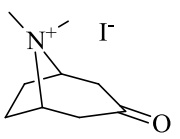
MeI (5.5 mL, 88 mmol) was added dropwise to a solution of tropinone (9.4 g, 67 mmol) in EtOH (70 mL). The reaction mixture was stirred at room temperature for 2 h and then filtered to collect the precipitate which was washed with Et_2O to afford the product as a white powder (14.2 g, 75%).

Melting point = 268-270 ^oC. Lit: 276-279 ^oC.[32]

$\nu_{max}(CDCl_3)$: 1724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 4.16 (brs, 2H, C*H*N(Me)$_2$C*H*), 3.42 (s, 3H, CH_3), 3.24-3.20 (m, 5H, (C=O)CH_{ax} and CH_3), 2.62 (d, *J* = 19.2 Hz, 2H, (C=O)CH_{eq}), 2.56-2.53 (m, 2H, CH_2), 2.09 (d, *J* = 10.1 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.9, 68.4, 50.5, 44.2, 43.6, 25.6.



66

Preparation of 8-thiabicyclo[3.2.1]octan-3-one (43)[32]

Scheme 3.33*, *Table 3.12

Entry 1

Tropinone methiodide (50 mg, 0.2 mmol) and sodium sulfide nonahydrate (51 mg, 0.2 mmol) were refluxed in water (5 mL) for 2 h before being allowed to cool to room temperature. The reaction mixture was then extracted with Et_2O (2 x 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a colourless oily solid (10 mg, 43%).

Entry 2

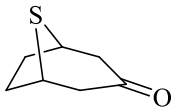
Tropinone methiodide (14.2 g, 51 mmol) and sodium sulfide nonahydrate (14.6 g, 61 mmol) were refluxed in water (1 L) for 2 h before being allowed to cool to room temperature. The reaction mixture was then extracted with Et_2O (2 x 300 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give 7.2 g of yellow oily solid. Purification using flash chromatography on silica gel (0-10% EtOAc in 40-60 ^oC petroleum ether) gave a pale yellow oily solid which was purified further by trituration in 30-40 ^oC petroleum ether to afford a beige powder (5.9 g, 90%).

Melting point = 156-157 ^oC. Lit: 155-157 ^oC.[32]

$\nu_{max}(CDCl_3)$: 1704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 3.84-3.82 (m, 2H, CH-S-CH), 2.81-2.65 (m, 4H, $(CH_2)_2C=O$), 2.19-2.00 (m, 4H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.2, 52.9, 45.5, 34.3.



43

Preparation of (8-thiabicyclo[3.2.1]oct-2-en-3-yloxy)trimethylsilane (45)[15b]

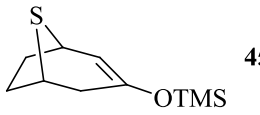
Scheme 3.34

To a round-bottomed flask, which had previously been flame dried *in vacuo* and allowed to cool under argon, was added 8-thiabicyclo[3.2.1]octan-3-one (104 mg, 0.8 mmol), DCM (10 mL), and triethylamine (0.33 mL, 2.4 mmol). The reaction mixture was cooled to 0 ^{o}C before addition of trimethylsilyl triflate (0.16 mL, 0.9 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for 4 h before quenching with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with DCM (2 x 10 mL), and the organics were pooled, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification using flash chromoatography on silica gel (0-5% Et_2O in 30-40 ^{o}C petroleum ether) delivered the desired product as a colourless oil (144 mg, 84% yield).

$\nu_{max}(CDCl_3)$: 1703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ5.38 (dt, *J* = 7.5 and 1.3 Hz, 1H, CH=C), 3.89-3.86 (m, 1H, SC*H*CH=C), 3.69-3.66 (m, 1H, SCH), 2.67-2.62 (m, 1H), 2.38-1.94 (m, 5H), 0.13 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ149.8, 111.3, 45.4, 43.4, 43.0, 41.4, 34.2, 0.0.



45

4.3 Asymmetric deprotonation of bridged bicyclic substrates

4.3.1 General experimental procedures

General procedure A – preparation of magnesium bisamides

$^{n}Bu_2Mg$ in heptane was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by the required amine, and the solution was heated at reflux for 1.5 h, assuming quantitative formation of the magnesium bisamide.

General procedure B – asymmetric deprotonation reactions using Mg bases

A solution of magnesium base in THF, prepared *via* General Procedure A, was cooled under argon to the appropriate temperature. The Schlenk flask was then charged with DMPU, followed by TMSCl, and the reaction mixture was stirred for 10 minutes at the temperature stated. The relevant ketone was then added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction mixture was stirred at the temperature stated for the required time before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion. Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral GC.

4.3.2 Asymmetric deprotonation of 8-oxabicyclo[3.2.1]octan-3-one (1)

Scheme 3.35*, *Table 3.13

Following general procedure A for the preparation of magnesium bisamide (**59**), data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure B for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amount of DMPU, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to **3**, (i) yield of **3**, and (i) (+):(-).

Entry 1: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.13 mL, 1 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 94%, (i) 106 mg, 67%, and (i) 7:93.

Entry 2: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -78 ^{o}C, (c) 0.06 mL, 0.5 mmol, (d) 0.13 mL, 1 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 80%, (i) 116 mg, 73%, and (i) 8:92.

Entry 3: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 97%, (i) 150 mg, 95%, and (i) 4:96.

Entry 4: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -78 ^{o}C, (c) 0.06 mL, 0.5 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 79%, (i) 108 mg, 68%, and (i) 11:89.

Scheme 3.36*, *Table 3.14

Following general procedure A for the preparation of magnesium bisamide (**60**), data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure B for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amount of DMPU, (d) amount of TMSCl, (e)

ketone, (f) amount of ketone, (g) reaction time, (h) conversion to **3**, (i) yield of **3**, and (i) (+):(-).

Entry 1: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **62**, and (c) 0.52 mL, 2 mmol; General procedure B: (a) **60**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.13 mL, 1 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 92%, (i) 124 mg, 78%, and (i) 4:96.

Entry 2: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **62**, and (c) 0.52 mL, 2 mmol; General procedure B: (a) **60**, (b) -78 ^{o}C, (c) 0.06 mL, 0.5 mmol, (d) 0.13 mL, 1 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 90%, (i) 97 mg, 61%, and (i) 7:93.

Entry 3: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **62**, and (c) 0.52 mL, 2 mmol; General procedure B: (a) **60**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 97%, (i) 146 mg, 92%, and (i) 5:95.

Entry 4: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **62**, and (c) 0.52 mL, 2 mmol; General procedure B: (a) **60**, (b) -78 ^{o}C, (c) 0.06 mL, 0.5 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 81%, (i) 111 mg, 70%, and (i) 9:91.

Entry 5: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **62**, and (c) 0.52 mL, 2 mmol; General procedure B: (a) **60**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.50 mL, 4 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 16 h, (h) 98%, (i) 135 mg, 85%, and (i) 3:97.

Scheme 3.37

Following general procedure A for the preparation of magnesium bisamide (**59**), data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure B for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amount of DMPU, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to **3**, (i) yield of **3**, and (i) (+):(-).

General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 1 h, (h) 94%, (i) 135 mg, 85%, and (i) 8:92.

Scheme 3.38, ***Table 3.15***

Following general procedure A for the preparation of magnesium bisamide (**59**), data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure B for the asymmetric deprotonation reaction, data are presented as (a) Mg base, (b) reaction temperature, (c) amount of DMPU, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to **3**, (i) yield of **3**, and (i) (+):(-).

Entry 1: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 1 h, (h) 94%, (i) 135 mg, 85%, and (i) 8:92.

Entry 2: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -60 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 1 h, (h) 78%, (i) 95 mg, 60%, and (i) 13:87.

Entry 3: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -40 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 1 h, (h) 55%, (i) 86 mg, 54%, and (i) 18:82.

Entry 4: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -20 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 1 h, (h) 80%, (i) 100 mg, 63%, and (i) 16:84.

Entry 5: General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) 0 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **1**, (f) 0.09 mL, 0.8 mmol, (g) 1 h, (h) 97%, (i) 133 mg, 84%, and (i) 17:83.

((1*R*,5*S*)-8-oxabicyclo[3.2.1]oct-2-en-3-yloxy)trimethylsilane (3)[2a]

$[\alpha]_D^{20}$ = -19.2° (c = 1.27, EtOAc, sample with 97:3 er by chiral GC analysis). Lit: $[\alpha]_D^{24}$ = -14.9° (c = 1.27, EtOAc, sample with 94:6 er by chiral GC analysis).[2a]

The absolute stereochemistry of the major enantiomer was assigned as (1*R*,5*S*) by comparison with results obtained using the analogous lithium amide.

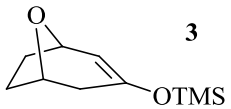
$\nu_{max}(CDCl_3)$: 1657 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (d, *J* = 4.9 Hz, 1H, CH=C), 4.58-4.55 (m, 1H, O-C*H*-CH=C), 4.50 (t, *J* = 5.1 Hz, 1H, C*H*-O-CH-CH=C), 2.69 (dd, *J* = 16.6 and 5.1 Hz, 1H, CH=C(OTMS)CH_2), 2.14-2.06 (m, 1H), 2.01-1.87 (m, 2H), 1.75-1.68 (m, 2H), 0.20 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 108.1, 73.1, 72.1, 39.4, 35.8, 29.3, 0.0.

Achiral GC: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 ^oC (1 min)-190 ^oC; temperature gradient; 45 ^oC min^{-1}; t_R = 4.21 min (**1**), t_R = 5.14 min (**3**).

Chiral GC: Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-120 ^oC; temperature gradient; 5.0 ^oC min^{-1}; t_R = 20.8 min ((1*R*,5*S*)-**3**), t_R = 21.2 min ((1*S*,5*R*)-**3**).



3

4.3.3 Asymmetric deprotonation of 8-thiabicyclo[3.2.1]octan-3-one (43)

Following general procedure A for the preparation of magnesium bisamide (**59**), data are presented as (a) amount of Bu_2Mg, (b) amine used, and (c) amount of amine. Following general procedure B for the asymmetric deprotonation reaction, data are presented as (a)

Mg base, (b) reaction temperature, (c) amount of DMPU, (d) amount of TMSCl, (e) ketone, (f) amount of ketone, (g) reaction time, (h) conversion to **45**, (i) yield of **45**, and (i) (+):(-).

Scheme 3.39

General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **43**, (f) 104 mg, 0.8 mmol, (g) 18 h, (h) 97%, (i) 120 mg, 70%, and (i) 1:99.

Scheme 3.40

General procedure A: (a) 1 M, 1 mL, 1 mmol, (b) **61**, and (c) 0.44 mL, 2 mmol; General procedure B: (a) **59**, (b) rt, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **43**, (f) 104 mg, 0.8 mmol, (g) 18 h, (h) 99%, (i) 146 mg, 85%, and (i) 6:94.

Scheme 3.41

In situ quench

To a Schlenk flask which had previously been flame-dried under vacuum and allowed to cool under argon was added the amine **61** (0.26 mL, 1.2 mmol) and THF (9.4 mL). The solution was then cooled to -78 ^{o}C before addition of *n*-BuLi (0.48 mL, 2.5 M, 1.2 mmol). The reaction mixture was stirred at -78 ^{o}C for 5 minutes before being allowed to warm to room temperature. TMSCl (0.5 mL, 4 mmol) was added, followed by dropwise addition of the ketone (**43**, 104 mg, 0.8 mmol) in THF (0.8 mL). The reaction mixture was stirred for 45 minutes at room temperature before being quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion (94%). Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (139 mg, 81%). The enantiomeric ratio of the product was determined by analysis using chiral GC (78:22, (-):(+)).

External quench + LiCl

A Schlenk flask containing LiCl (17 mg, 0.4 mmol) was flame-dried under vacuum and was then allowed to cool to room temperature under argon. THF (8.4 mL) and the amine **61** (0.26 mL, 1.2 mmol) were added before the reaction mixture was cooled to -78 ^{o}C. *n*-BuLi (0.48 mL, 2.5 M, 1.2 mmol) was added and the reaction mixture was stirred at -78 ^{o}C for 5 minutes before being allowed to warm to room temperature. The ketone (**43**, 104 mg, 0.8 mmol) was added dropwise as a solution in THF (0.8 mL) and the mixture was stirred for 15 minutes before the addition of TMSCl (0.5 mL, 4 mmol). After a further 30 minutes at room temperature, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion (92%). Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (146 mg, 85%). The enantiomeric ratio of the product was determined by analysis using chiral GC (72:28, (-):(+)).

Scheme 3.42

General procedure A: (a) 1 M, 0.5 mL, 0.5 mmol, (b) **61**, and (c) 0.22 mL, 1 mmol; General procedure B: (a) **59**, (b) -78 ^{o}C, (c) 0.12 mL, 1 mmol, (d) 0.26 mL, 2 mmol, (e) **43**, (f) 104 mg, 0.8 mmol, (g) 16 h, (h) 85%, (i) 132 mg, 77%, and (i) 20:80.

Scheme 3.43

A Schlenk flask containing LiCl (85 mg, 2 mmol) was flame-dried under vacuum and allowed to cool to room temperature under argon. $^{n}Bu_2Mg$ in heptane (1 mL, 1 M, 1 mmol) was transferred to the Schlenk flask and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by the required amine (**61**, 0.22 mL, 1 mmol), and the solution was stirred at room temperature for 1.5 h, assuming quantitative formation of the alkylmagnesium amide. The reaction mixture was then charged with 18-crown-6 (264 mg, 1 mmol) before being cooled to -78 ^{o}C. TMSCl (0.5 mL, 4 mmol) was then added and the reaction mixture was stirred for 10 minutes at -78 ^{o}C. The ketone (**43**, 104 mg, 0.8 mmol) was added as a solution in THF (2

mL) over 1 h using a syringe pump. The reaction mixture was stirred at -78 °C for 16 h before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was analysed by achiral GC to determine the reaction conversion (99%). Removal of the solvent *in vacuo* gave an oil which was purified by column chromatography on silica gel using 0-5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (151 mg, 88%). The enantiomeric ratio of the product was determined by analysis using chiral GC (94:6, (-):(+)).

((1*R*,5*S*)-8-thiabicyclo[3.2.1]oct-2-en-3-yloxy)trimethylsilane (45)[15b]

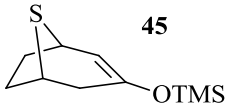
$[\alpha]_D^{20}$ = -36.0 ° (c = 1.0, $CHCl_3$, sample with 99:1 er by chiral GC analysis). No literature rotation is available for comparison. The absolute stereochemistry was tentatively assigned as (1*R*,5*S*) by comparison with results obtained using the analogous lithium amide.

$\nu_{max}(CDCl_3)$: 1703 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ5.38 (dt, *J* = 7.5 and 1.3 Hz, 1H, CH=C), 3.89-3.86 (m, 1H, SC*H*CH=C), 3.69-3.66 (m, 1H, SCH), 2.67-2.62 (m, 1H), 2.38-1.94 (m, 5H), 0.13 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ149.8, 111.3, 45.4, 43.4, 43.0, 41.4, 34.2, 0.0.

Achiral GC: CP SIL-19 CB capillary column; carrier gas H_2 (80 kPa); 45 °C (1 min)-190 °C; temperature gradient; 45 °C min^{-1}; t_R = 5.50 min (**43**), t_R = 6.15 min (**45**). Chiral GC: Chiralsil-DEX CB capillary column; carrier gas H_2 (80 kPa); 70-120 °C; temperature gradient; 5.0 °C min^{-1}; t_R = 39.4 min ((1*R*,5*S*)-**45**), t_R = 40.9 min ((1*S*,5*R*)-**45**).



45

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6. Appendix:

X-ray Crystallography Data

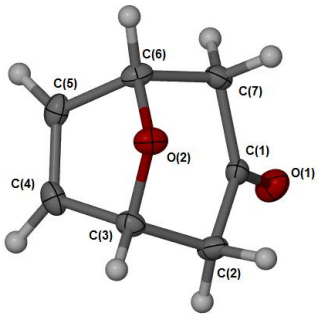


Figure 3.3

Identification code	kerr0603a	
Empirical formula	C7 H8 O2	
Formula weight	124.13	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.2717(3) Å	α= 90°.
	b = 6.4638(2) Å	β= 109.551(4)°.
	c = 10.6882(4) Å	γ = 90°.
Volume	603.62(4) $Å^3$	
Z	4	
Density (calculated)	1.366 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	264	
Crystal size	0.4 x 0.3 x 0.25 mm^3	
Theta range for data collection	3.75 to 30.10°.	
Index ranges	-12<=h<=13, -8<=k<=9, -14<=l<=13	
Reflections collected	8797	
Independent reflections	1670 [R(int) = 0.0180]	
Completeness to theta = 27.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.81726	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1670 / 0 / 115	

Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0357, wR2 = 0.0904
R indices (all data)	R1 = 0.0400, wR2 = 0.0945
Extinction coefficient	0.088(8)
Largest diff. peak and hole	0.360 and -0.188 e.$Å^{-3}$

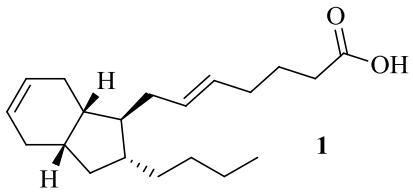
Chapter 4

Towards the total synthesis of mucosin

1. Introduction

In addition to the methodological studies concerning the development of our novel magnesium bases, broadening the synthetic application of these reagents is also a significant goal within our group. Hence, it was envisaged that applying the novel magnesium bases to the synthesis of a challenging natural product would illustrate their value to the wider synthetic community. To further this goal, the fused bicyclic eicosanoid, (-)-mucosin (**1**, **Figure 4.1**), was chosen as an attractive synthetic target.

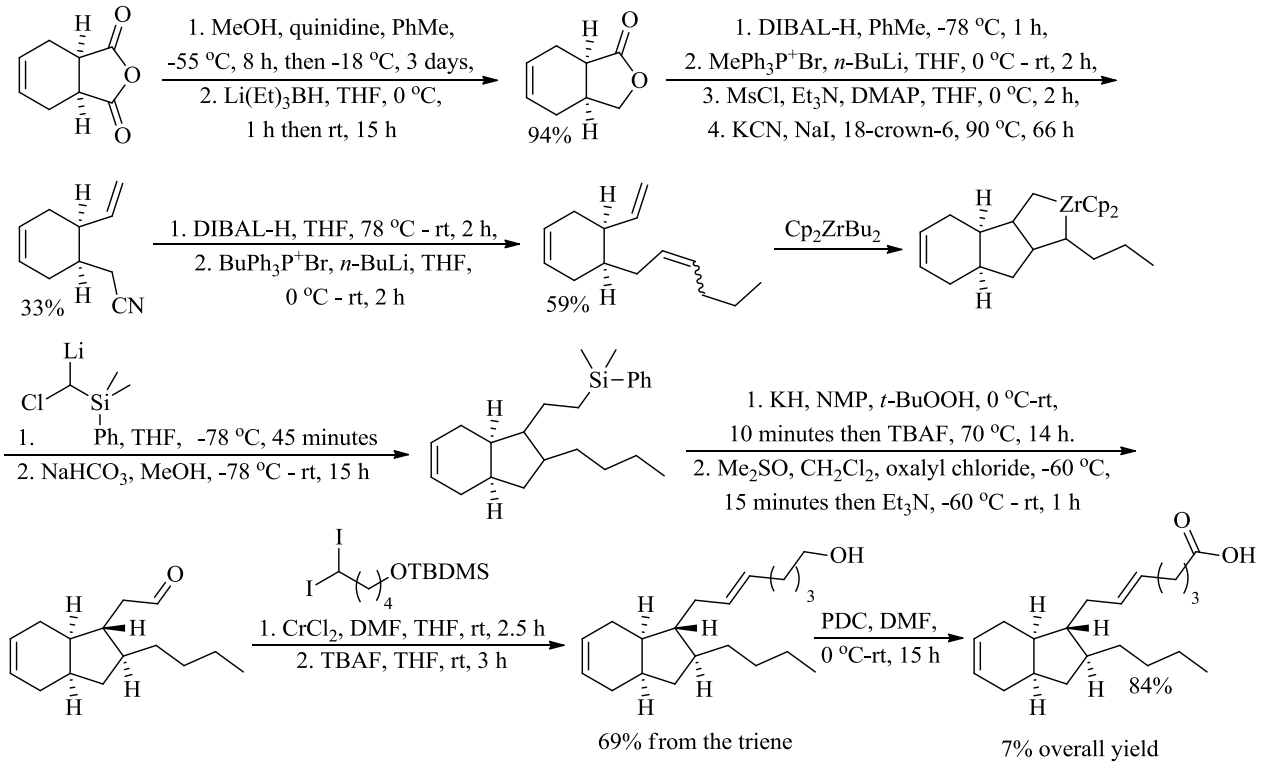
Mucosin is a bicyclic eicosanoid, possessing a [4.3.0]nonane skeleton, which was isolated from the Mediterranean marine sponge *Reniera Mucosa* in 1997.[1] Eicosanoids are key to the equilibrium processes in the normal physiology of mammalian systems.[2] However, the biochemical and ecological role of mucosin is still unknown. Thus, the opportunity to apply our established chiral magnesium base methodology to the development of an asymmetric route into this natural product would allow any possible medicinal properties to be evaluated. Structural features of this natural product which make it an appealing synthetic target include the two stereocentres of the *cis* ring junction of the bicyclic core, and the additional stereogenic centres at the branching alkyl chains. Furthermore, the requirement for *E*-stereochemistry of the double bond makes mucosin an interesting and challenging target.



1

Figure 4.1

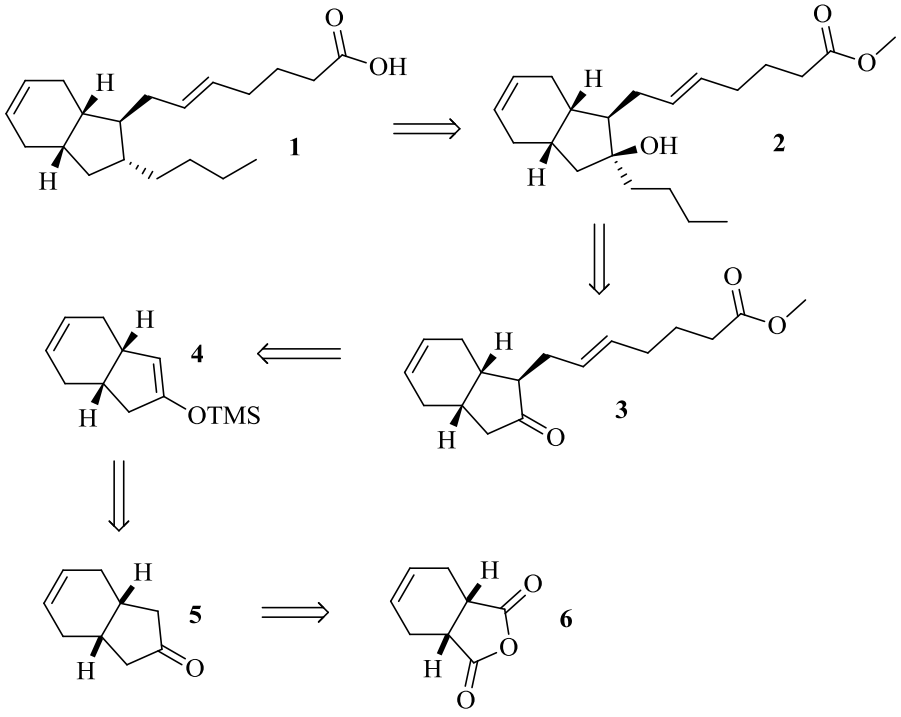
The total synthesis of the unnatural enantiomer of mucosin was reported in 2012 by Whitby (**Scheme 4.1**).[3] (+)-Mucosin was prepared using an alkaloid-catalysed asymmetric ring-opening and a zirconium-induced co-cyclisation as the key steps to install the correct relative stereochemistry of the four contiguous stereocentres. Using this strategy, the (+)-enantiomer was obtained in 7% overall yield.



Scheme 4.1

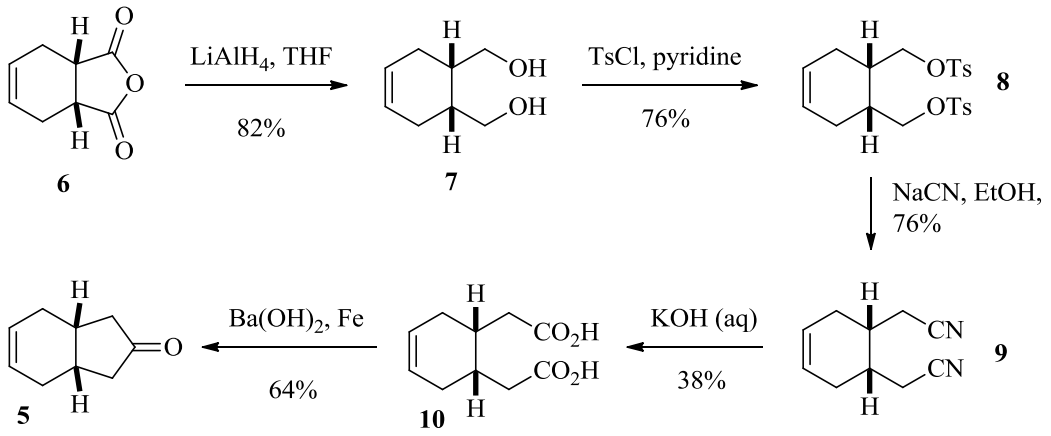
Our envisaged synthetic pathway to mucosin involves a magnesium base-mediated enantioselective deprotonation as the key step for introducing the required stereochemistry within the target molecule. The initial retrosynthetic step from mucosin involves conversion to the alcohol intermediate (**2**, **Scheme 4.2**). In addition, by utilising **2** as the corresponding ester, it is anticipated that any potential practical difficulties associated with employing an acidic function throughout the synthesis can be avoided. It is envisaged that this alcohol-ester intermediate could be obtained from nucleophilic addition of an *n*-butyl group into the parent ketone (**3**), which could, in turn, be prepared from the reaction of the enantioenriched silyl enol ether (**4**) with the required allyl bromide. Magnesium base-mediated deprotonation of the *meso*-ketone (**5**) will be employed to gain access to the necessary enantiomer of the silyl enol ether (**4**). Crucially, it is expected that the stereochemistry installed in the bicyclic silyl enol ether will be exploited in subsequent steps, in order to direct the overall diastereoselectivity. Finally, the bicyclic ketone (**5**) is readily available *via* a series of straightforward manipulations of the commercially available *cis*-1,2,3,6-

tetrahydrophthalic anhydride (**6**),[4] which is inexpensive and available on a kilogram scale.



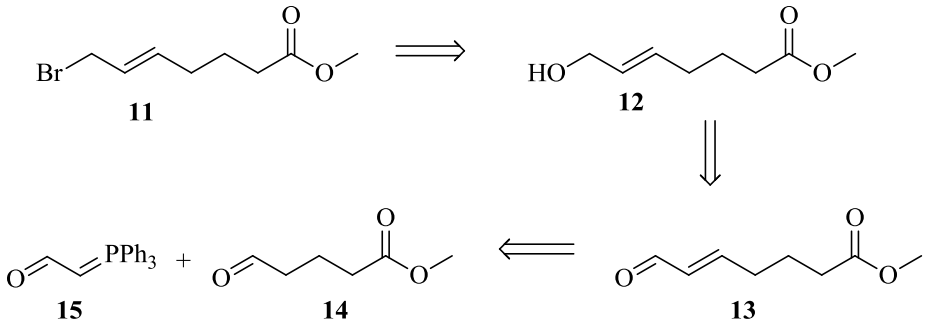
Scheme 4.2

The required *meso*-ketone (**5**) is a known compound and has been previously synthesised by Mundy, using a series of straightforward transformations (**Scheme 4.3**).[4] In particular, $LiAlH_4$-mediated reduction of the anhydride (**6**) delivered the diol (**7**), which was then converted to the corresponding ditosylate (**8**), in order to install an efficient leaving group, which could subsequently be displaced using the appropriate cyanide reagent. The resulting dinitrile (**9**) was then hydrolysed to the analogous diacid (**10**) which was, in turn, cyclised to the *meso*-ketone (**5**) under classical conditions using barium hydroxide.[4] Overall, these steps deliver the required ketone in 12% yield. It is envisaged that significant improvements can be made to develop a more efficient route to this key intermediate in the total synthesis programme.



Scheme 4.3

In addition to the stepwise transformations from the commercially available anhydride in the route to mucosin, synthesis of the allyl bromide (**11**, **Scheme 4.4**) will also be required for the electrophilic quench of the enantioenriched silyl enol ether (**4**). Access to this allyl bromide is proposed to be achieved *via* conversion of the corresponding allylic alcohol (**12**), which could be made by selective reduction of the α,β-unsaturated aldehyde (**13**). It can then be envisaged that the Wittig reaction could be employed for the synthesis of **13**, allowing access to the required *E*-isomer.

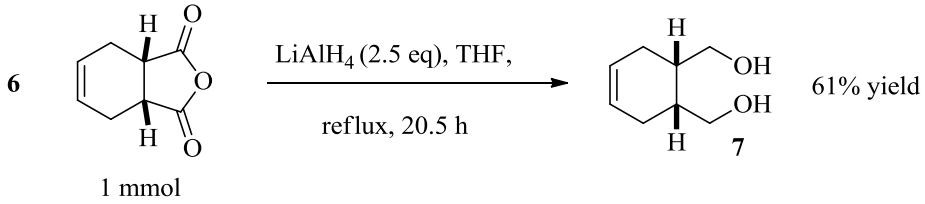


Scheme 4.4

2. Results and discussion

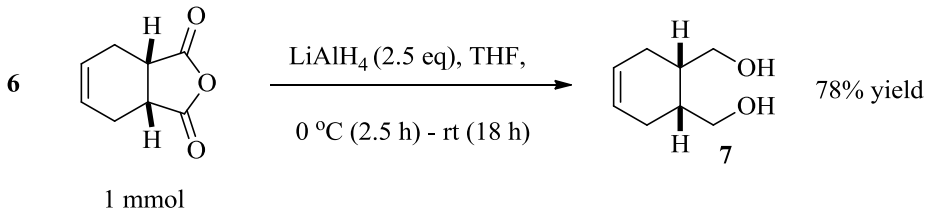
2.1 Preparation of *cis*-bicyclo[4.3.0]non-3-en-8-one (5)

As described in the preceding section, the initial step in the route to the required *meso*-ketone (**5**) is the $LiAlH_4$-mediated reduction of the commercially available *cis*-1,2,3,6-tetrahydrophalic anhydride (**6**, **Scheme 4.5**). Following the procedure reported by Mundy,[4] the anhydride was refluxed in THF, employing 2.5 equivalents of $LiAlH_4$. A surprisingly low yield of 61% was obtained under these conditions, compared to the high 82% documented in the literature. Further examination of the reaction products revealed that a significant quantity of aromatic by-products was formed during the reaction. It is proposed that such aromatic impurities could result from the hydroxyl groups of the desired product being activated as leaving groups by residual aluminium species present in the reaction, to give an unconjugated triene which could subsequently aromatise to *o*-xylene.



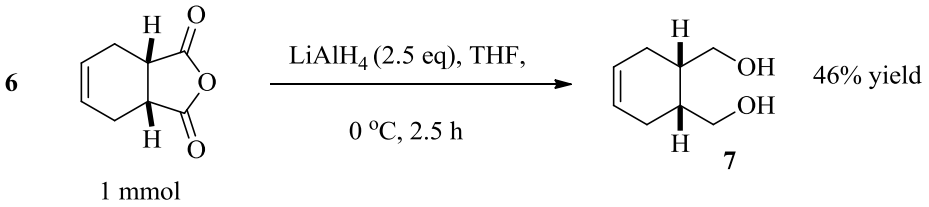
Scheme 4.5

In order to avoid the formation of any aromatic by-products, an alternative set of milder conditions were employed, whereby the reaction temperature was initially held at 0 ^{o}C and then warmed to room temperature overnight (**Scheme 4.6**). Pleasingly, under these conditions, the yield was increased significantly to 78%. However, aromatic by-products were, again, detected, and so, further improvements were sought.



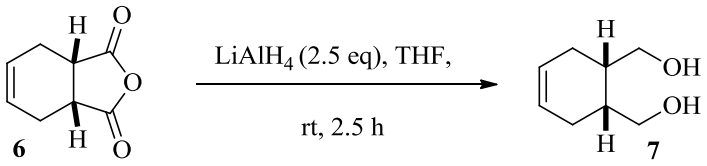
Scheme 4.6

It was predicted that shortening the reaction time, while maintaining a low temperature, would furnish the desired diol (**7**) without leading to the formation of any aromatics. Accordingly, the reaction was performed over only 2.5 hours at 0 °C (**Scheme 4.7**). Indeed, by employing these altered reaction conditions, no aromatic by-products were observed. However, a disappointingly low yield of 46% was achieved.



Scheme 4.7

Encouraged by the results obtained by quenching the reaction after a relatively short time of 2.5 hours, the reaction was repeated in a similar fashion. More specifically, with the object of increasing the yield of the diol (**7**), the reaction temperature was elevated slightly to room temperature, while maintaining a 2.5 hour reaction time (**Scheme 4.8**, **Table 4.1**). This procedure has now been employed several times for the synthesis of the diol intermediate (**7**) and has proved to be a robust and scalable method.

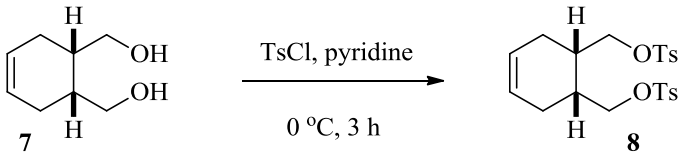


Scheme 4.8

Entry	Scale (mmol)	Yield (%)
1	1	100
2	10	97
3	100	90
4	100	94
5	200	91

Table 4.1

Having developed reliable conditions for the preparation of the required diol, attention was turned to the synthesis of the ditosylate compound (**8**, **Scheme 4.9**). Following Mundy's established conditions which were reported to furnish the ditosylate (**8**) in a high 76% yield, the diol (**7**) was treated with tosyl chloride in pyridine over 3 hours at 0 ^{o}C. Using this procedure, the desired ditosylate was obtained in good yield and in a highly pure form after simply triturating the solid product in methanol (**Scheme 4.9**, **Table 4.2**).

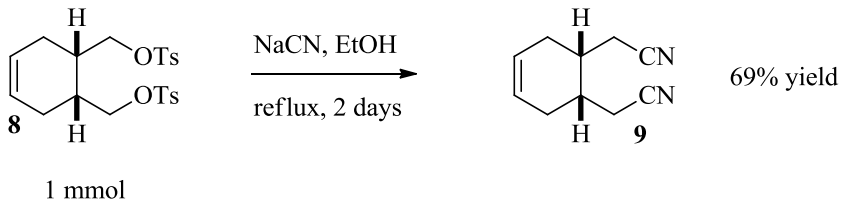


Scheme 4.9

Entry	Scale (mmol)	Yield (%)
1	1	75
2	9.7	67

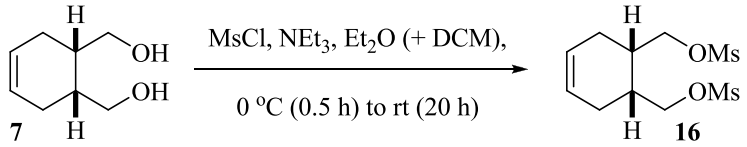
Table 4.2

After successfully preparing the ditosylate compound (**8**), sodium cyanide was employed to furnish the dinitrile species (**9**) in a good 69% yield, although a relatively lengthy reaction time of two days at reflux was required (**Scheme 4.10**).



Scheme 4.10

Despite the fact that access to the ditosylate compound (**8**) and subsequent transformation into the dinitrile (**9**) proceeded with no difficulties, a more atom-economical and efficient route was desired. Consequently, the possibility of installing an alternative leaving group, such as a mesylate, was investigated. Conversion of the diol (**7**) to the dimesylate (**16**) was undertaken using mesyl chloride and triethylamine in Et_2O, and proved to be highly efficient and amenable to larger scale synthesis (**Scheme 4.11**, **Table 4.3**). It should be noted that on increasing the scale of the reaction, DCM was required as a cosolvent to aid in the deaggregation and stirring of the resulting triethylamine hydrochloride salt precipitate (**Table 4.3**, entries 2-4).

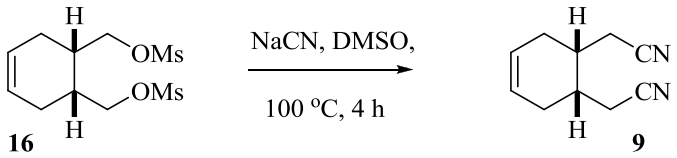


Scheme 4.11

Entry	Scale (mmol)	Yield (%)
1	10	75
2	90	72
3	90	76
4	181	78

Table 4.3

With the dimesylate (**16**) in hand, the synthesis advanced to delivery of the dinitrile intermediate (**9**, **Scheme 4.12**). An initial, small-scale attempt using sodium cyanide in DMSO at 100 ^{o}C afforded the desired product in a high 84% yield, after employing column chromatography to remove the residual DMSO (**Table 4.4**, entry 1). In subsequent scale-up attempts, the need for column chromatography was eliminated by simply washing any residual DMSO out of the product using water, while maintaining high yields for the reaction (**Table 4.4**, entries 2-5).



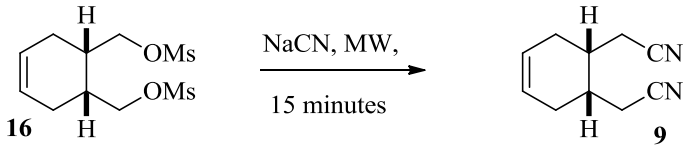
Scheme 4.12

Entry	Scale (mmol)	Yield (%)
1	1	84
2	6	93
3	65	74
4	61	100
5	142	87

Table 4.4

In addition to the thermally-promoted cyanation of the dimesylate (**16**), applicability of the reaction to microwave-controlled conditions was explored using a variety of

polar aprotic solvents (**Scheme 4.13**, **Table 4.5**). Pleasingly, although no reaction occurred using MeCN, and DMF gave complex mixtures (**Table 4.5**, entries 1 and 2), when DMSO was employed as the reaction solvent, an excellent 80% yield was obtained (entry 3). Disappointingly, on attempting to increase the scale of the microwave-promoted reaction, a complex mixture of products resulted (entry 4). As a consequence, the development of a microwave-promoted route to the dinitrile compound (**9**) was not pursued further.

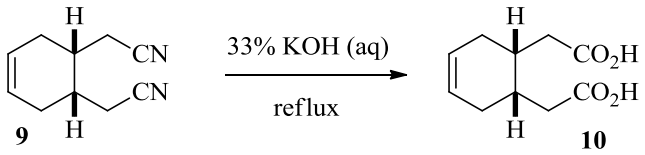


Scheme 4.13

Entry	Scale (mmol)	Temperature (^{o}C)	Solvent	Yield (%)
1	0.3	100	MeCN	-
2	0.3	100	DMF	-
3	0.3	189	DMSO	80%
4	10	189	DMSO	-

Table 4.5

Preparation of the diacid (**10**) was subsequently achieved *via* hydrolysis of the dinitrile (**9**) using an aqueous solution of potassium hydroxide (**Scheme 4.14**). The initial, small-scale attempt to hydrolyse **9** resulted in a high 74% isolated yield, and no problems were encountered when the reaction was scaled-up (**Table 4.6**). Also, it should be noted that a significant improvement in yield was achieved, compared to the 38% yield reported by Mundy.[4]

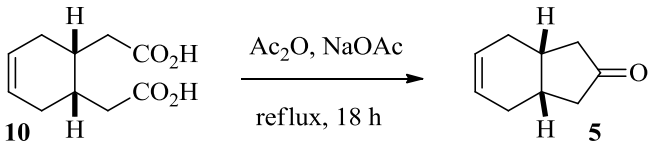


Scheme 4.14

Entry	Scale (mmol)	Time (h)	Yield (%)
1	6	17	74
2	48	12	66
3	61	14	90
4	123	16	74

Table 4.6

With the required diacid (**10**) in hand, the final step in the synthesis of the *meso*-ketone (**5**) could be embarked upon. The literature procedure for the cyclisation of **10** involves a solvent-free reaction employing barium hydroxide and iron powder, using an open flame to heat the solid reaction mixture, to afford the product as an oil by distillation in 64% yield.[4] Despite the good yield which is reported using this method, it was anticipated that a more expedient procedure could be devised. To this end, an alternative cyclisation method, employing acetic anhydride and sodium acetate at reflux, was attempted (**Scheme 4.15**).[5] When the reaction was performed on a small scale, a moderate yield of 52% was achieved (**Table 4.7**, entry 1). However, when the reaction was attempted on a larger scale, a significant improvement in yield was attained (entries 2-4).



Scheme 4.15

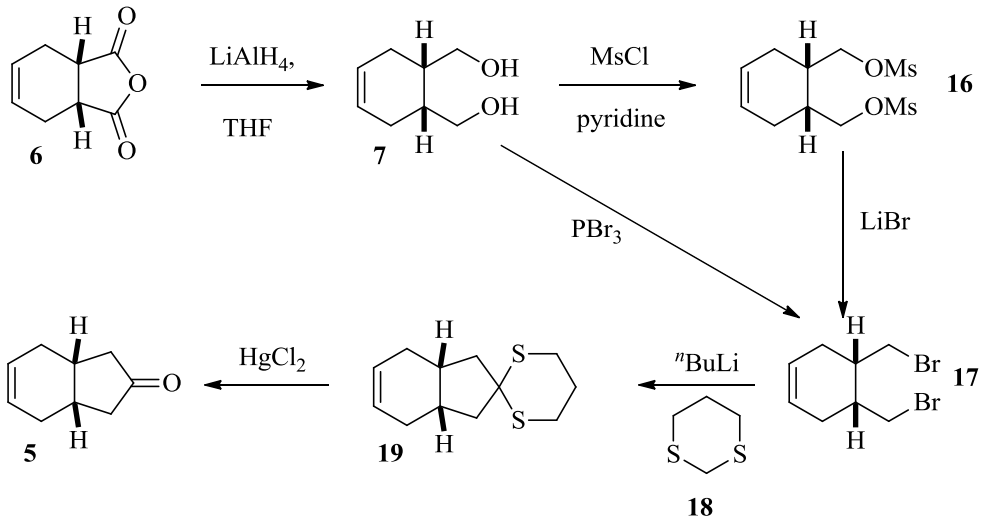
Entry	Scale (mmol)	Yield (%)
1	1	52
2	22	73
3	54	78
4	90	69

Table 4.7

To summarise, the requisite *meso*-ketone (**5**) has been prepared efficiently using a series of simple synthetic transformations. Moreover, further practical development of the literature route has been sought, in order to improve the efficiency of the whole process. As a consequence, an overall yield of 55% was achieved for the synthesis of the ketone (**5**), which is a significant improvement on the 12% literature yield.[4]

2.1.1 Attempted development of an alternative route to *cis*-bicyclo[4.3.0]non-3-en-8-one (5)

In order to reduce the number of steps required for the synthesis of the *meso*-ketone (**5**), an alternative route, centred around the chemistry of 1,3-dithiane (**18**), was devised. The proposed route is outlined in **Scheme 4.16**, with the initial steps being adopted from the original route. Ideally, the dibromide (**17**) could be accessed *via* direct conversion of the corresponding diol (**7**), although there is no literature precedent for a comparable substrate. The dimesylate (**16**) is, however, known to react with lithium bromide to furnish the dibromide (**17**).[6] Subsequently, it is envisaged that double nucleophilic attack by lithiated 1,3-dithiane would give the dithiane compound (**19**) which could be treated with an appropriate Hg(II) salt to yield the desired ketone (**5**).

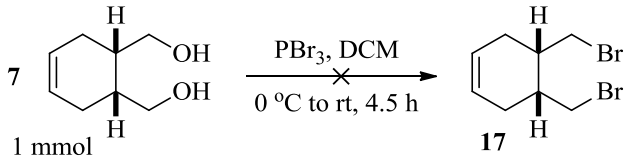


Scheme 4.16

Preliminary investigations into this novel route began with the synthesis of the dibromide (**17**). Since multigram quantities of the ditosylate (**8**) were available, this compound was used in the synthesis of the dibromide (**17**). Accordingly, treatment of the ditosylate compound (**8**) with LiBr in DMF at 100 ^{o}C resulted in formation of the desired product in 68% yield (**Scheme 4.17**).

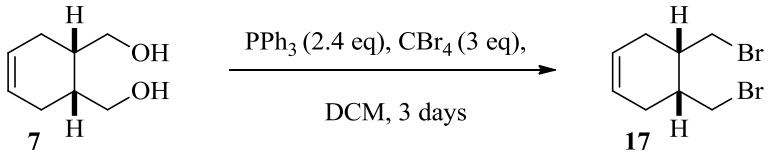
Scheme 4.17

Although this method allowed access to the dibromide (**17**) in good yield, the real goal of this alternative route was to deliver **17** directly from the diol (**7**). Consequently, attempted bromination using phosphorus tribromide was undertaken (**Scheme 4.18**). Unfortunately, analysis of the reaction mixture revealed a complex mixture, containing a significant amount of aromatic by-products. Indeed, complications associated with aromatisation, in a similar fashion to that observed during the reduction of the anhydride (**6**), had been anticipated.



Scheme 4.18

It was envisaged that by employing milder bromination conditions, the formation of such aromatic impurities could be avoided. Accordingly, the use of carbon tetrabromide and triphenylphosphine as an alternative method was explored (**Scheme 4.19**). Pleasingly, under these milder reaction conditions, no aromatics were detected and the desired dibromo compound was isolated in a high 73% yield (**Table 4.8**, entry 1). Problems were, however, encountered on increasing the scale of the reaction, with an increase in the severity of the exotherm observed (entry 2). In addition, a gum formed when triturating the crude product with Et_2O in an attempt to remove the triphenylphosphine oxide by-product. Thus, the larger scale reaction was repeated and care was taken to avoid the problems associated with the previous attempt. More specifically, the reaction mixture was cooled in an ice bath until addition of triphenylphosphine to a solution of the diol (**7**) and carbon tetrabromide was complete. Furthermore, instead of removing the triphenylphosphine oxide by-product with an Et_2O trituration, the crude reaction product was applied directly to a silica gel column for subsequent purification. Gratifyingly, by employing these modified procedures, the yield achieved was quantitative (entry 3).

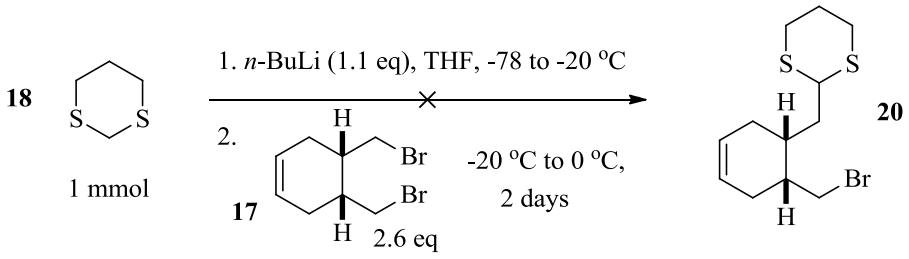


Scheme 4.19

Entry	Scale (mmol)	Yield (%)
1	1	73
2	20	35
3	20	100

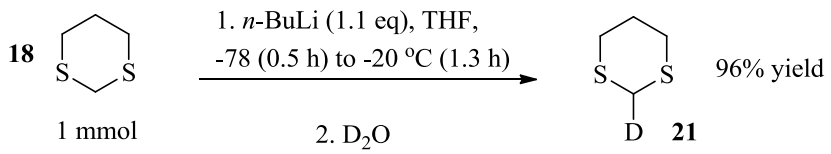
Table 4.8

With the required dibromide (**17**) in hand, preliminary investigations involved the attempted monosubstitution with lithiated dithiane, using a literature procedure for a similar substrate as a guide.[7] Lithiated dithiane was prepared, accordingly, and was then treated with the dibromide (**17**) at -20 ^{o}C (**Scheme 4.20**). The reaction mixture was then stirred at this temperature for 24 hours before being warmed to 0 ^{o}C and stirred for a further 24 hours. After this relatively long reaction time, however, no conversion of the starting material was achieved.



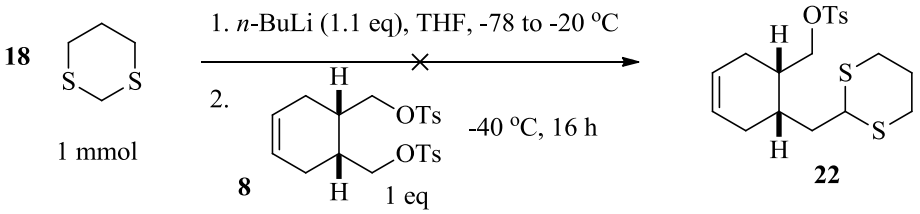
Scheme 4.20

In order to ascertain whether lithiated 1,3-dithiane was, in fact, generated under the reaction conditions, the reaction was repeated using deuterated water as the electrophilic quench (**Scheme 4.21**). When employing this alternative electrophile, it was found that 1,3-dithiane was completely converted to the deuterated product (**21**), illustrating that the problem with the previous reaction is likely to be a lack of reactivity of lithiated dithiane towards the dibromide (**17**).



Scheme 4.21

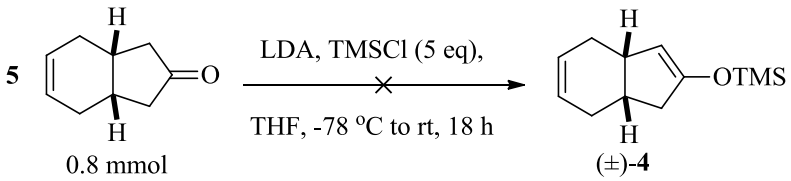
The employment of an alternative leaving group was then explored. In particular, the ditosylate compound (**8**) was chosen because of the literature precedent for the displacement of tosylate groups using lithiated dithiane.[8] However, when lithiated 1,3-dithiane was treated with this substrate, no conversion to the substituted product (**22**) was observed (**Scheme 4.22**). Considering the lack of success achieved at this stage, the development of an alternative route to the prochiral ketone (**5**) was halted.



Scheme 4.22

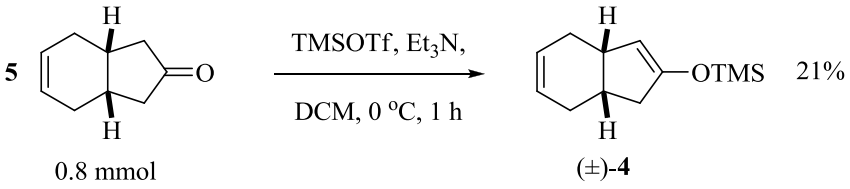
2.2 Preparation of the enol silane intermediate (4)

Attention was then focused on the synthesis of the novel enol silane intermediate (**4**), initially in a non-enantioselective fashion. Preliminary attempts employed freshly prepared LDA alongside TMSCl to trap the resulting enolate under internal quench conditions at -78 °C (**Scheme 4.23**). Surprisingly, under these conditions, no conversion of the parent ketone (**5**) was detected.



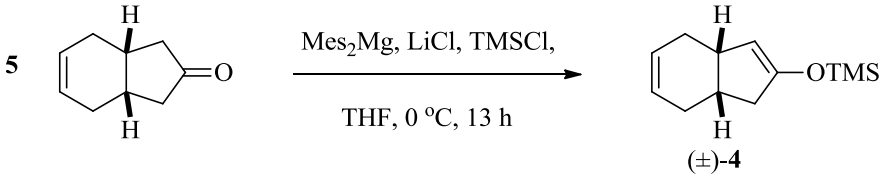
Scheme 4.23

Alternatively, the ketone substrate (**5**) was treated with triethylamine and TMSOTf in DCM at 0 ^{o}C. Pleasingly, these conditions delivered the novel intermediate (**4**), albeit in a low 21% yield.



Scheme 4.24

In an attempt to improve on the isolated yield of the enol silane (**4**), an alternative method, utilising a novel deprotonation procedure developed in our laboratories,[10] was adopted (**Scheme 4.25**). More specifically, bismesitylmagnesium, which has been established as a non-nucleophilic carbon-centred base for the preparation of silyl enol ethers, was employed in the presence of LiCl and TMSCl. To our delight, an initial small scale reaction furnished the desired product (**4**) in high yield (**Table 4.9**, entry 1). Furthermore, when the reaction was repeated on an appreciable 8 mmol scale, the enol silane (**4**) was isolated in 70% yield after distillation to remove the mesitylene by-product (**Table 4.9**, entry 2).



Scheme 4.25

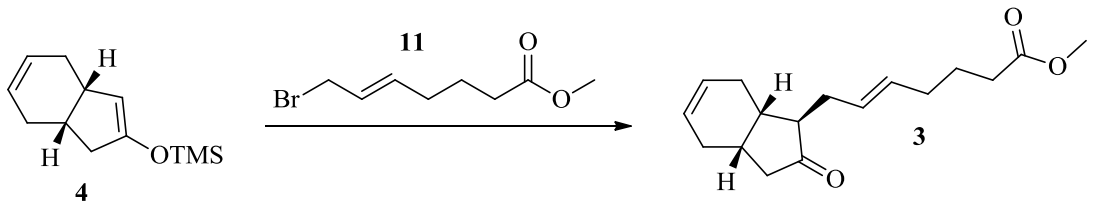
Entry	Scale (mmol)	Yield (%)
1	1	76*
2	8	70

*^{1}H NMR yield

Table 4.9

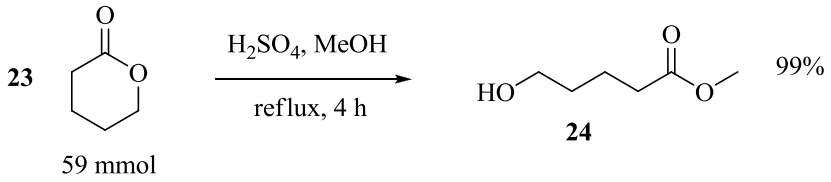
2.3 Preparation of the allyl bromide

The next challenge in the total synthesis programme was the preparation of the allyl bromide (**11**), which is required for eventual reaction with the silyl enol ether intermediate (**4**) to install the appropriate side chain (**Scheme 4.26**).



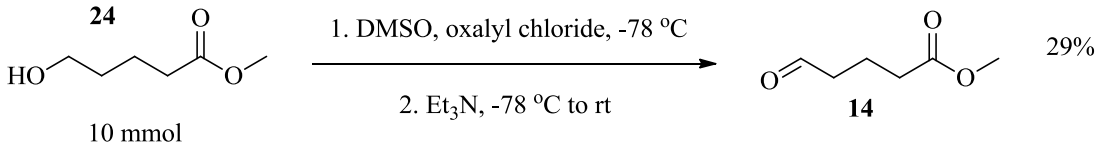
Scheme 4.26

The proposed synthesis of the allyl bromide (**11**) employs ring opening of δ-valerolactone (**23**) as the first step, followed by oxidation of the resulting alcohol (**24**). Pleasingly, the initial step in this process afforded the alcohol in an excellent 99% yield (**Scheme 4.27**).



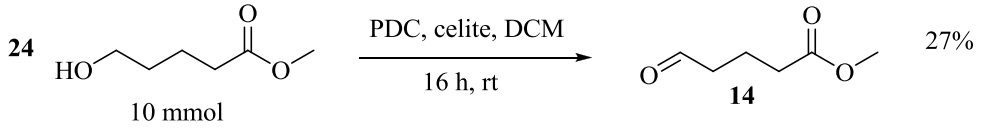
Scheme 4.27

A Swern oxidation was subsequently employed for the preparation of the required aldehyde (**14**, **Scheme 4.28**). Disappointingly, this reaction did not proceed efficiently and a poor yield of 29% was achieved after column chromatography. It was suspected this poor yield could, in part, be attributed to the incompatibility of the aldehyde product to silica gel chromatography.



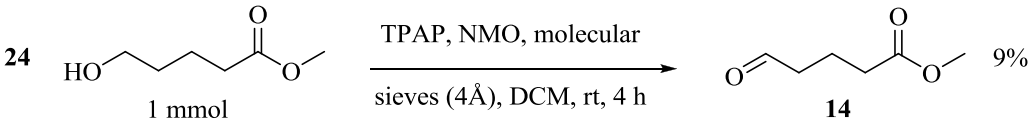
Scheme 4.28

In an attempt to improve upon the yield achieved previously, an alternative oxidation method was explored. More specifically, PDC was employed as the oxidising agent for the conversion of the alcohol (**24**) into the corresponding aldehyde (**14**, **Scheme 4.29**). Although the reaction appeared to cleanly afford the desired product, significant decomposition was observed on purification by distillation, resulting in a poor 27% yield.



Scheme 4.29

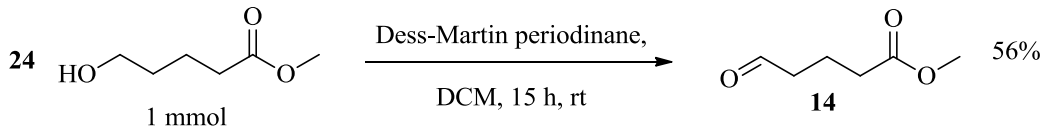
Next, the oxidation was attempted using the Ley-Griffith reagent alongside NMO (**Scheme 4.30**). It was envisaged that any reaction by-products could be easily removed by filtration through a short plug of silica to deliver the desired product. However, disappointingly, the product was isolated in a poor 9% yield after stirring at room temperature for 4 hours. It was proposed that the lack of success in this method was due to the instability of the aldehyde product on silica gel.



Scheme 4.30

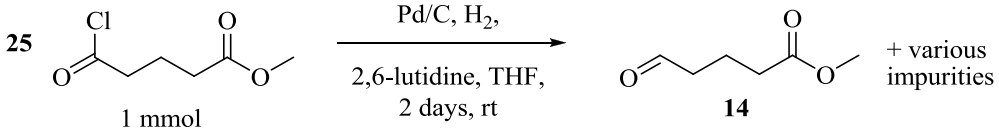
Subsequently, attention was focused on methods which could deliver the desired aldehyde cleanly, without the need for purification by chromatography or distillation.

Accordingly, the Dess-Martin reagent was employed in a further attempt to improve on the yield of the desired aldehyde (**14**, **Scheme 4.31**). Although this alternative method resulted in an apparent increase in the reaction yield, it should be noted that the product contained significant quantities of the iodo-compound by-product after attempted removal by repeated washing of the crude product with saturated $Na_2S_2O_3$.



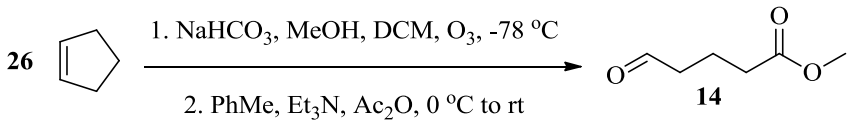
Scheme 4.31

Next, the Rosenmund reduction of the commercially-available acid chloride (**25**) was utilised as it was envisaged that the aldehyde product could simply be filtered through celite to remove the palladium catalyst and leave the desired product. However, along with the desired aldehyde product, a variety of impurities was also detected (**Scheme 4.32**).



Scheme 4.32

A change in strategy was then required in order to circumvent the problems which had been encountered in the preparation of **14**. Accordingly, an alternative synthesis of the aldehyde (**14**), involving a Schreiber ozonolysis of cyclopentene,[11] was invoked. To our delight, using this method, the desired aldehyde could be delivered in high yields on a significant scale (**Scheme 4.33**, **Table 4.10**). Although the reaction product contained residual quantities of toluene and acetic anhydride, it was envisaged that these impurities would not pose a problem in the subsequent Wittig reaction of the aldehyde (**14**).



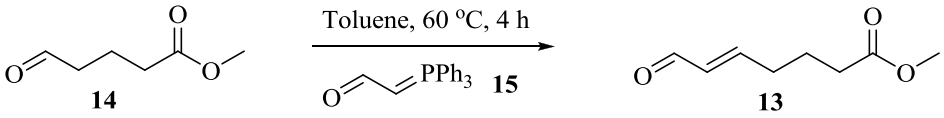
Scheme 4.33

Entry	Scale (mmol)	Ozonolysis Time (h)	^{1}H NMR Yield (%)*
1	23	2	52
2	172	7	72

*The product contained residual toluene and Ac_2O.

Table 4.10

Efforts were then focused on the Wittig reaction of the aldehyde (**14**) with (triphenylphosphoranylidene)acetaldehyde (**15**, **Scheme 4.34**, **Table 4.11**). To our delight, the required enal intermediate (**13**) could be isolated in good yield on scales of up to 30 mmol after heating in toluene at 60 °C for 4 hours. Moreover, the quantity of the phosphorane reagent (**15**) could be reduced to just 1.1 equivalents with no appreciable decrease in yield, compared to the literature protocol.[12]

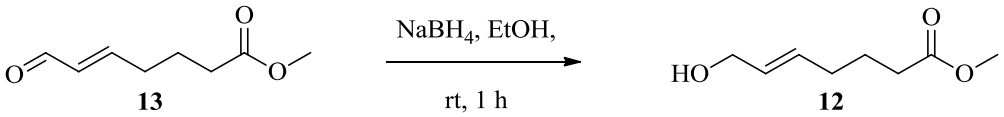


Scheme 4.34

Entry	Scale (mmol)	15 (eq)	Yield (%)
1	2	2.4	70
2	14	1	60
3	30	1.1	68

Table 4.11

Sodium borohydride-mediated reduction was then utilised for the selective reduction of the enal (**13**) to the allylic alcohol intermediate (**12**, **Scheme 4.35**). Pleasingly, the desired allylic alcohol was isolated in good yield after treatment with sodium borohydride over one hour at room temperature, delivering sufficient quantites for subsequent conversion to the required allylic bromide (**11**).

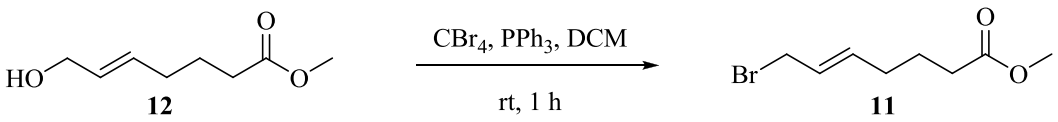


Scheme 4.35

Entry	Scale (mmol)	Yield (%)
1	2	53
2	9	61
3	20	51

Table 4.12

With the allylic alcohol (**12**) in hand, synthesis of the corresponding allylic bromide (**11**) was realised utilising carbon tetrabromide and triphenylphosphine in DCM (**Scheme 4.36**, **Table 4.13**). After subjecting the allylic alcohol to these reagents over one hour at room temperature, the key allylic bromide compound (**11**) was delivered in good yield, allowing subsequent coupling of **11** with the enol silane intermediate (**4**) to be attempted.

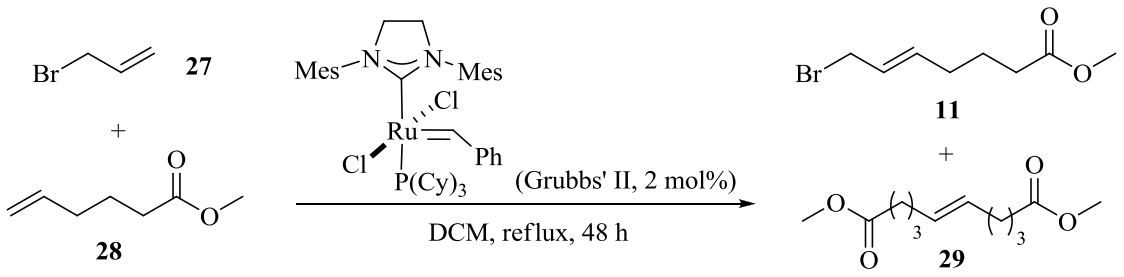


Scheme 4.36

Entry	Scale (mmol)	Yield (%)
1	1	55
2	5	61
3	10	51

Table 4.13

Considering the number of steps involved in the described synthesis of the allylic bromide intermediate (**11**), a more expedient route was tested. More specifically, the cross metathesis of allyl bromide (**27**) and methyl hex-5-enoate (**28**) using Grubbs' second generation catalyst was employed for the preparation of **11** (**Scheme 4.37**, **Table 4.14**). Initial attempts utilised an excess of the ester metathesis partner (**28**, **Table 4.14**, entry 1). In this case, the allylic bromide (**11**) was obtained in high yield. However, **11** was formed as a mixture of *E*:*Z* isomers (6:1). Moreoever, a significant quantity of the homocoupled ester product (**29**) was also isolated. With a view to limiting the formation of the homocoupled ester (**29**), allyl bromide (**27**) and methyl hex-5-enoate (**28**) were employed in a 1:1 ratio (**Table 4.14**, entry 2). Pleasingly, under these conditions, formation of the diester (**29**) was significantly reduced, and the allylic bromide (**11**) was delivered in high yield. However, a mixture of *E*- and *Z*-isomers (7:1) was, once more, obtained. Consequently, the preparation of the allylic bromide intermediate (**11**) using cross metathesis was not pursued further.



Scheme 4.37

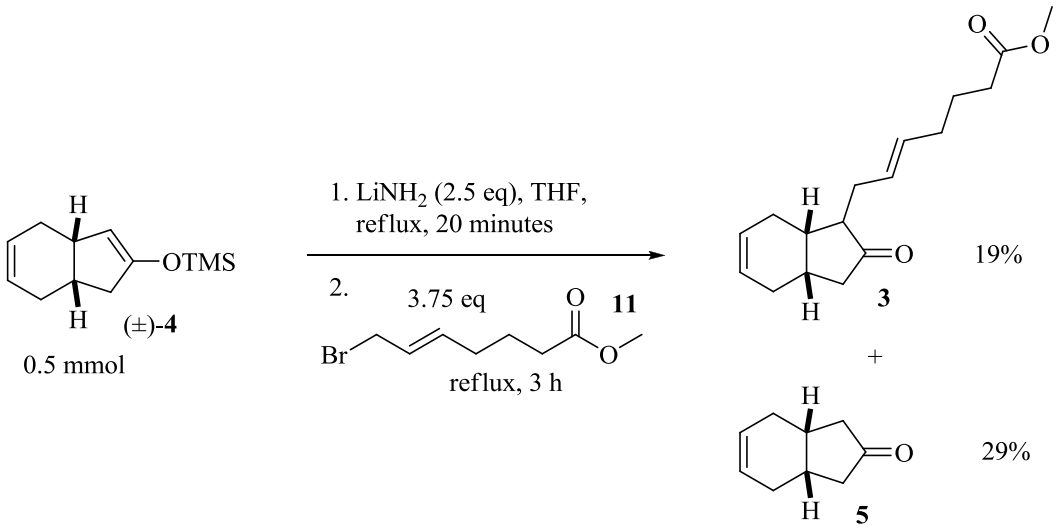
Entry	28 (eq)	Yield of 11 (%)[a]	Yield of 29 (%)[b]	*E*:*Z* (11)
1	4	77	55	6:1
2	1	88	11	7:1

[a]Based on **27**. [b]Based on **28**.

Table 4.14

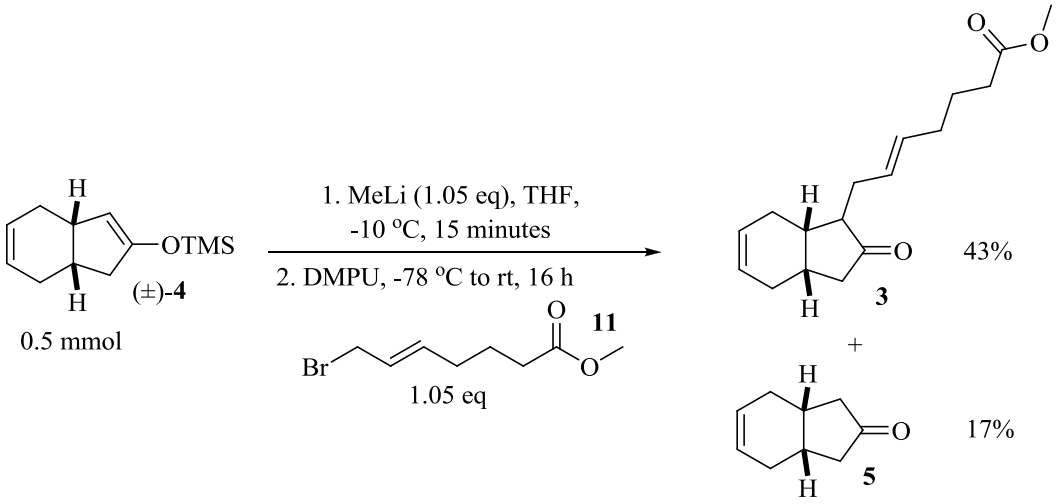
2.4 Coupling of the enol silane and allylic bromide

Reaction of the racemic enol silane (**4**) with the allylic bromide electrophile (**11**) to give the novel α-substituted ketone (**3**) was then embarked upon (**Scheme 4.38**). Our preliminary attempt employed lithium amide for generation of the lithium enolate of (**4**), followed by trapping of the resulting lithium enolate with the allylic bromide (**11**, **Scheme 4.38**), using a literature procedure for a similar reaction as a guide.[13] Employing this method, the desired intermediate (**3**) was isolated in a modest 19% yield, alongside 29% of the parent ketone (**5**). Analysis of the desired product (**3**) using ^{1}H NMR appeared to reveal a single diastereomer, although the relative stereochemistry could not be deduced using 2D ^{1}H NMR (COSY and ROESY) due to the large amount of overlapping signals in the aliphatic region. In comparison, the ^{13}C NMR revealed a mixture of two compounds, possibly the diastereomers of **3**, the signals for which did not coalesce when the ^{13}C NMR experiment was repeated at 50 ^{o}C.



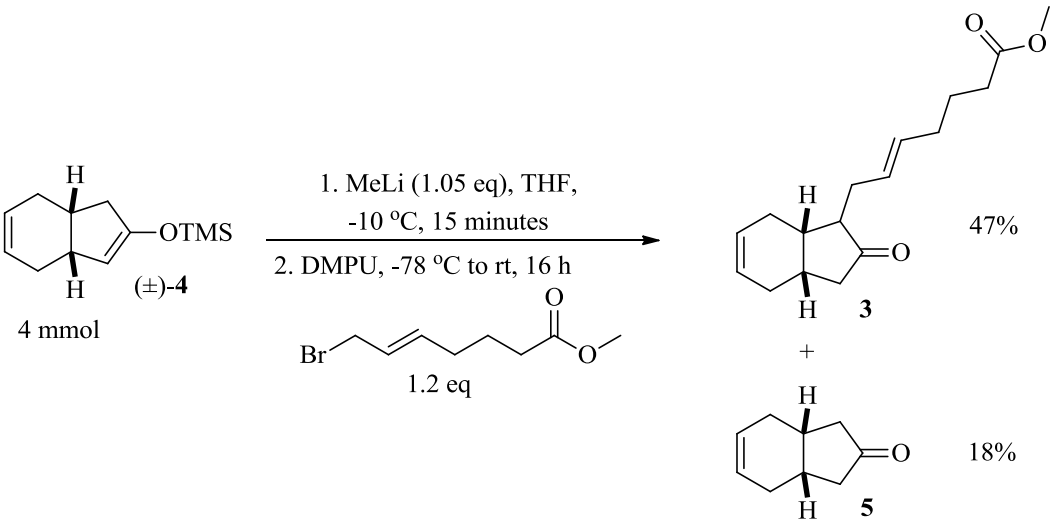
Scheme 4.38

Subsequently, alternative conditions were explored for the formation of **3** from the racemic enol silane (**4**) and the allylic bromide (**11**, **Scheme 4.39**). Following the literature procedure for a similar reaction,[14] the enol silane (**4**) was treated with methyllithium at -10 ^{o}C before being cooled to -78 ^{o}C for the addition of the allylic bromide (**11**). After warming to room temperature over 16 hours, the desired product (**3**) was delivered in good yield (43%), alongside 17% of the parent ketone (**5**). However, as before, analysis of the ^{13}C NMR indicated that the product had been formed as a mixture of diastereomers.



Scheme 4.39

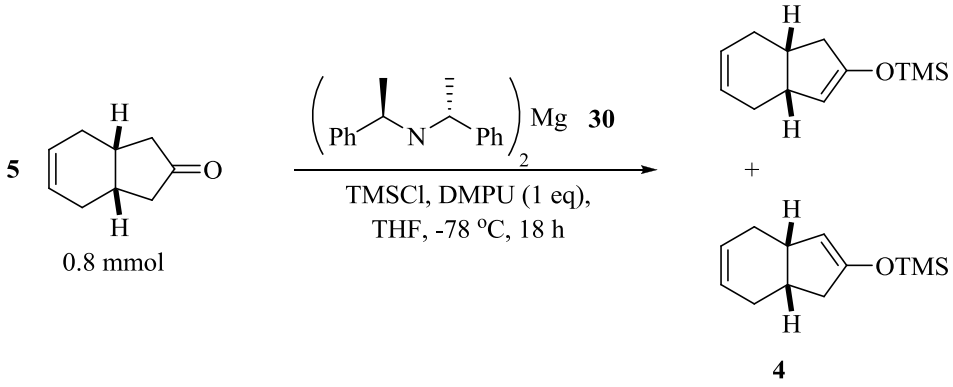
In an attempt to increase the yield of the desired product (**3**), while minimising the formation of the parent ketone (**5**), which is, presumably, formed from the unreacted lithium enolate upon aqueous work-up, a greater excess of the allylic bromide electrophile (**11**) was employed (**Scheme 4.40**). Under these conditions, a slight increase in the yield of the coupled product (**3**) was gained. However, the parent ketone (**5**) was returned in comparable yields to those observed previously. Once more, examination of the ^{13}C spectrum of the coupled product (**3**) appeared to imply that the compound was present as a mixture of diastereomers. Nevertheless, having demonstrated that the coupling of the racemic enol silane (**4**) with the allylic bromide (**11**) was possible, efforts were then focused on the development of an asymmetric method for the preparation of the required enantiomer of **4**.



Scheme 4.40

2.5 Asymmetric deprotonation of cis-bicyclo[4.3.0]non-3-en-8-one

Initial efforts towards the desymmetrisation of the prochiral ketone (**4**) centred on the use of the C_2-symmetric magnesium bisamide (**30**), which has proven to be a highly effective enantioselective base for the deprotonation of a range of prochiral ketones (**Scheme 4.41**).[15] Employing four equivalents of TMSCl, to trap the resulting magnesium enolate under internal quench conditions, alongside one equivalent of DMPU at -78 °C in THF delivered the enantioenriched enol silane (**4**) in moderate yield (46%) and good enantioselectivity (90:10 er, **Table 4.15**, entry 1). Alternatively, the quantity of TMSCl could be reduced to just one equivalent while imparting an increased enantioselectivity and yield (**Table 4.15**, entry 2).



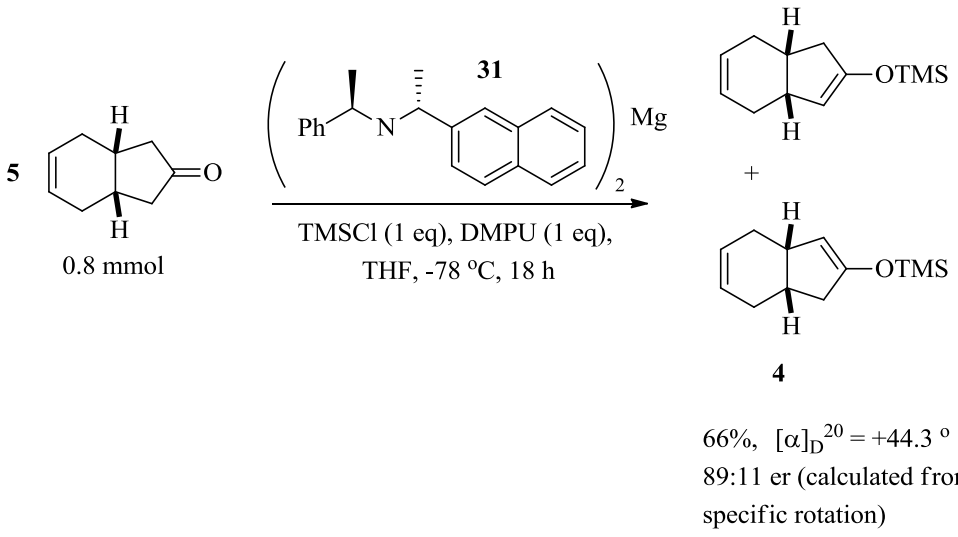
Scheme 4.41

Entry	TMSCl (eq)	Yield (%)	$[\alpha]_D^{20}$	er ((+):(-))
1	4	46	+45.8 ^{o}	90:10
2	1	61	+49.1 ^{o}	93:7*

*Calculated from specific rotation.

Table 4.15

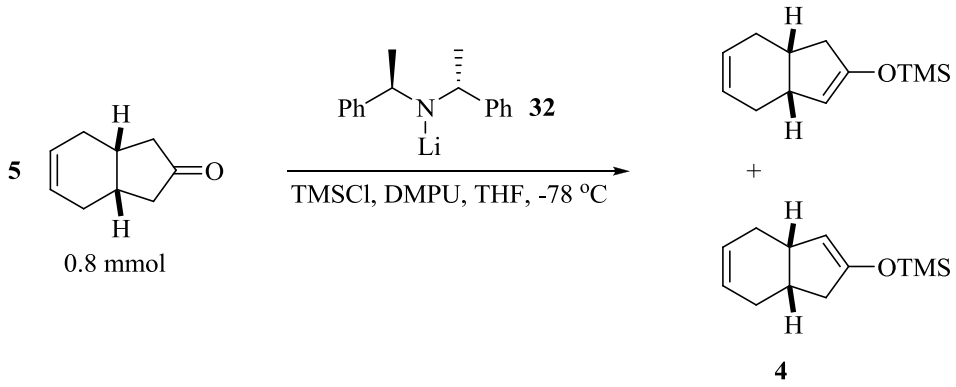
Subsequently, an analogous *pseudo*-C_2-symmetric magnesium bisamide (**31**), which has also been demonstrated as a highly selective base for the desymmetrisation of prochiral ketones (Chapters 1 and 3), was applied to the enantioselective synthesis of the enol silane (**4**, **Scheme 4.42**). Unfortunately, no increase in the enantioselectivity of the transformation was achieved when employing this alternative magnesium bisamide.



Scheme 4.42

In order to allow a direct comparison to be drawn with the corresponding lithium amide, the C_2-symmetric lithium amide (**32**) was applied to the desymmetrisation of the prochiral ketone (**5**) under both internal and external quench conditions (**Scheme 4.43, Table 4.16**). Under internal quench conditions, the highest enantioselectivity in this short study was recorded (**Table 4.16**, entry 1). In comparison, and rather surprisingly, the enantioinduction and yield deteriorated significantly when an

external quench protocol was employed (**Table 4.16**, entry 2). Nonetheless, after a short period of optimisation, it has been shown that the optically-enriched enol silane intermediate (**4**) can be delivered with high enantioselectivity using an asymmetric deprotonation strategy.



Scheme 4.43

Entry	Quench conditions	Yield (%)	$[\alpha]_D^{20}$	er ((+):(-))*
1	Internal	66	+50.0 ^{o}	94:6
2	External	26	+32.4 ^{o}	78:22

*Calculated from specific rotation.

Table 4.16

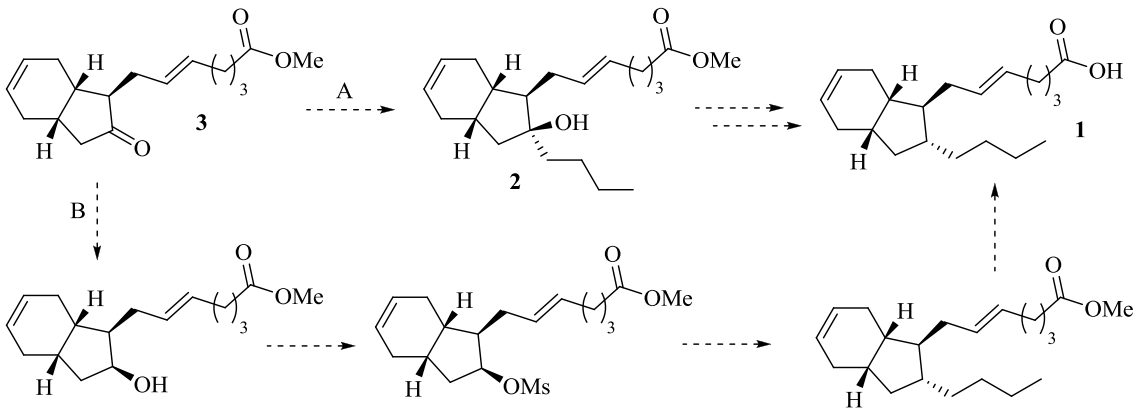
2.6 Summary

Studies within the area of magnesium base chemistry have been extended to the enantioselective total synthesis of the bicyclic eicosanoid, mucosin. The synthetic strategy which has been devised involves a magnesium base-mediated enantioselective deprotonation as the key transformation. As such, the *meso*-ketone substrate (**5**) has been prepared efficiently using a series of simple synthetic transformations, while further practical improvements over the literature route have been realised. Overall, a yield of 55% was achieved for the synthesis of the ketone, which is a vast improvement on the 12% literature yield.[4] In addition to the initial route which was developed for the preparation of the *meso*-ketone substrate (**5**) in the synthesis of mucosin, an alternative strategy, centred around the chemistry of 1,3-dithiane, was devised. At this stage in the total synthesis programme, limited success has been achieved using our alternative route.

With the *meso*-ketone (**5**) in hand, conversion to the racemic enol silane (**4**) has been achieved by utilising carbon-centred magnesium base chemistry. In addition, preparation of the required allylic bromide electrophile (**11**) has been completed in a short number of synthetic steps using readily available starting materials. The enol silane (**4**) and allylic bromide (**11**) coupling partners were then reacted to give the required α-substituted ketone (**3**) in moderate yield. Future work should focus on the optimisation of this key step in the total synthesis programme in order to improve on the yield and dr of the desired α-substituted ketone intermediate (**3**).

Having demonstrated that the coupling of the racemic enol silane (**4**) with the allylic bromide (**11**) was possible, efforts were then focused on the development of an asymmetric method for the preparation of the enol silane (**4**). After a short period of optimisation, it has been shown that the optically-enriched enol silane intermediate (**4**) can be delivered with high enantioselectivity using either the C_2-symmetric magnesium bisamide (**30**, 93:7 er) or the C_2-symmetric lithium amide (**32**, 94:6 er) at -78 ^{o}C. Future work in this area should probe the enantioselectivity that can be achieved when using our C_2-symmetric magnesium bisamides at more accessible temperatures.

In addition to the further optimisation of the established steps in the total synthesis of mucosin, research should be progressed to the final stages of the synthesis (**Scheme 4.44**). It is envisaged that the alcohol-ester intermediate (**2**) could be obtained from nucleophilic addition of an *n*-butyl group into the parent ketone (**3**), followed by dehydroxylation to give the target compound (Path A). Alternatively, reduction of the α-substituted ketone (**3**) to the corresponding alcohol, followed by conversion to a labile moiety and nucleophilic displacement by the appropriate organometallic reagent could be employed (Path B). Finally, conversion of the ester moiety to the carboxylic acid should be pursued to furnish the target compound, mucosin (**1**).



Scheme 4.44

3. Experimental

3.1 General

All reagents were obtained from commercial suppliers (Aldrich, TCI, Alfa Aesar or Acros) and used without further purification, unless otherwise stated. Purification was carried out according to standard laboratory methods.[16]

- DCM, Et_2O and toluene were obtained from an Innovative Technology, Pure Solv, SPS-400-5 solvent purification system.
- THF was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen.
- Carbon tetrabromide and triphenylphosphine were purified by recrystallisation from EtOH.
- MsCl, TMSCl, DMPU, DMF and DMSO were distilled from calcium hydride and stored over 4Å molecular sieves under argon.
- Organometallic reagents were standardised using salicylaldehyde phenylhydrazone.[17]

Thin layer chromatography was carried out using Camlab silica plates, coated with fluorescent indicator UV_{254}, and analysed using a Mineralight UVGL-25 lamp.

Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

IR spectra were obtained on a Perkin Elmer Spectrum 1 machine.

^{1}H and ^{13}C spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise specified.

3.2 Preparation of *cis*-bicyclo[4.3.0]non-3-en-8-one (5)

Preparation of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (7)[4]

Scheme 4.5

$LiAlH_4$ (44 mg, 2.5 mmol) was added to a round-bottomed flask which had previously been flame-dried and allowed to cool under argon. THF (1.25 mL) was then added, followed by a solution of *cis*-1,2,3,6-tetrahydrophthalic anhydride (152 mg, 1 mmol) in THF (1 mL). The reaction mixture was refluxed under argon for 20.5 h before being quenched with MeOH (1 mL) and poured into a saturated solution of Na_2SO_4 (10 mL). The mixture was filtered to remove the resulting white solid, which was washed with EtOAc (2 x 10 mL). The aqueous filtrate was extracted with EtOAc (2 x 10 mL) and the organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give the product, which was contaminated with aromatic by-products (detected by ^{1}H NMR), as a colourless oil (87 mg, 61%).

Scheme 4.6

$LiAlH_4$ (95 mg, 2.5 mmol) was added to a round-bottomed flask which had previously been flame-dried and allowed to cool under argon. THF (4 mL) was then added and the reaction mixture was cooled to 0 ^oC. A solution of *cis*-1,2,3,6-tetrahydrophthalic anhydride (152 mg, 1 mmol) in THF (1 mL) was then added dropwise. The reaction mixture was stirred at 0 ^oC under argon for 2.5 h before warming to rt and stirring for a further 18 h. After this time, the reaction mixture was quenched with MeOH (2 mL) and poured into a saturated solution of Na_2SO_4 (10 mL). The mixture was filtered to remove the resulting white solid, which was washed with EtOAc (2 x 10 mL). The aqueous filtrate was extracted with EtOAc (2 x 10 mL) and the organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give the product, which was contaminated with aromatic by-products (detected by ^{1}H NMR), as a colourless oil (111 mg, 78%).

Scheme 4.7

$LiAlH_4$ (95 mg, 2.5 mmol) was added to a round-bottomed flask which had previously been flame-dried and allowed to cool under argon. THF (4 mL) was then added and the reaction mixture was cooled to 0 ^oC. A solution of *cis*-1,2,3,6-

tetrahydrophthalic anhydride (152 mg, 1 mmol) in THF (1 mL) was then added dropwise. The reaction mixture was stirred at 0 ^{o}C under argon for 2.5 h before being quenched with MeOH (2 mL) and poured into a saturated solution of Na_2SO_4 (10 mL). The mixture was filtered to remove the resulting white solid, which was washed with EtOAc (2 x 10 mL). The aqueous filtrate was extracted with EtOAc (2 x 10 mL) and the organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil (65 mg, 46%).

Scheme 4.8, Table 4.1

General Procedure

$LiAlH_4$ was added to a round-bottomed flask which had previously been flame-dried and allowed to cool under argon. THF was then added and the reaction mixture was cooled to 0 ^{o}C. A solution of *cis*-1,2,3,6-tetrahydrophthalic anhydride in THF was then added dropwise. The reaction mixture was warmed to rt then stirred under argon for 2.5 h before being quenched with MeOH and poured into a saturated solution of Na_2SO_4. The mixture was filtered to remove the resulting white solid, which was washed with EtOAc. The aqueous filtrate was extracted with EtOAc and the organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil.

Data are reported as (a) amount of $LiAlH_4$, (b) volume of THF for $LiAlH_4$, (c) amount of *cis*-1,2,3,6-tetrahydrophthalic anhydride, (d) volume of THF for *cis*-1,2,3,6-tetrahydrophthalic anhydride, (e) volume of MeOH quench, (f) volume of saturated Na_2SO_4, (g) volume of EtOAc for washings, (h) volume of EtOAc for extractions, and (i) yield.

Entry 1

(a) 95 mg, 2.5 mmol, (b) 4 mL, (c) 152 mg, 1 mmol, (d) 1 mL, (e) 2 mL, (f) 10 mL, (g) 2 x 10 mL, (h) 2 x 10 mL, and (i) 142 mg, 100%.

Entry 2

(a) 950 mg, 25 mmol, (b) 25 mL, (c) 1.52 g, 10 mmol, (d) 10 mL, (e) 20 mL, (f) 100 mL, (g) 2 x 100 mL, (h) 2 x 100 mL, and (i) 1.38 g, 97%.

Entry 3

(a) 9.5 g, 250 mmol, (b) 250 mL, (c) 15.2 g, 100 mmol, (d) 100 mL, (e) 200 mL, (f) 500 mL, (g) 2 x 500 mL, (h) 2 x 500 mL, and (i) 12.78 g, 90%.

Entry 4

(a) 9.5 g, 250 mmol, (b) 250 mL, (c) 15.2 g, 100 mmol, (d) 100 mL, (e) 200 mL, (f) 500 mL, (g) 2 x 500 mL, (h) 2 x 500 mL, and (i) 13.35 g, 94%.

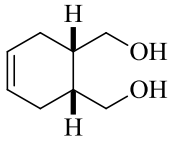
Entry 5

(a) 19 g, 500 mmol, (b) 500 mL, (c) 30.4 g, 200 mmol, (d) 200 mL, (e) 400 mL, (f) 1 L, (g) 3 x 500 mL, (h) 3 x 500 mL, and (i) 25.8 g, 91%.

$\nu_{max}(CDCl_3)$: 1029, 1438, 1652, 3313 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 5.57 (s, 2H, CH=CH), 4.46 (s, 2H, OH), 3.63 (dd, *J* = 14.3, 7.1 Hz, 2H, C*H*$_2$OH), 3.49 (dd, *J* = 11, 3.6 Hz, 2H, C*H*$_2$OH), 2.09-1.94 (m, 6H, aliphatic ring protons).

^{13}C NMR (100 MHz, $CDCl_3$): δ 125.5, 63.5, 37.8, 26.9.



7

Preparation of *cis*-1,2,3,6-tetrahydrophthalyl alcohol di-*p*-toluenesulfonate (8)[4]

Scheme 4.9, Table 4.2

Entry 1

A solution of tosyl chloride (572 mg, 3 mmol) in pyridine (2 mL) was cooled to 0 ^{o}C before *cis*-1,2,3,6-tetrahydrophthalyl alcohol (142 mg, 1 mmol) was added as a solution in pyridine (1 mL). The reaction mixture was stirred at 0 ^{o}C for 3 h before being diluted with EtOAc (5 mL) and washed with water (2 x 10 mL) to remove pyridine. The EtOAc layer was dried over Na_2SO_4 and then concentrated *in vacuo* to give the product as a white solid (339 mg, 75%).

Entry 2

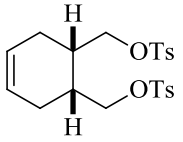
A solution of tosyl chloride (5.56 g, 29.2 mmol) in pyridine (20 mL) was cooled to 0 ^{o}C before *cis*-1,2,3,6-tetrahydrophthalyl alcohol (1.38 g, 9.7 mmol) was added as a solution in pyridine (10 mL). The reaction mixture was stirred at 0 ^{o}C for 3 h before being diluted with EtOAc (50 mL) and washed with water (2 x 100 mL). The EtOAc layer was dried over Na_2SO_4 and then concentrated *in vacuo* to give a brown oil which was triturated with heptane (5 mL) and filtered to give the product as a white solid (2.91 g, 67%).

Melting point = 92-93 ^{o}C. Lit: 91.5-92.5 ^{o}C.[18]

$\nu_{max}(CDCl_3)$: 1174, 1358, 1596 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 4H, SO_2CCH), 7.36 (d, *J* = 8.3 Hz, 4H, CH_3CCH), 5.51 (t, *J* = 1.4 Hz, 2H, CH=CH), 3.97-3.89 (m, 4H, CH_2OTs), 2.47 (s, 6H, $ArCH_3$), 2.24-2.21 (m, 2H, aliphatic ring protons), 2.13-2.08 (m, 2H, aliphatic ring protons), 1.79-1.77 (m, 2H, aliphatic ring protons).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 132.8, 129.9, 127.9, 124.7, 70.5, 34.0, 26.0, 21.7.



8

Preparation of cyclohexene-4-*cis*-1,2-diacetonitrile (9)[4]

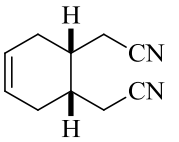
Scheme 4.10

cis-1,2,3,6-Tetrahydrophthalyl alcohol di-*p*-toluenesulfonate (418 mg, 1 mmol) and NaCN (147 mg, 3 mmol) were refluxed in EtOH (3 mL) for 48 h before the addition of water (1 mL). EtOH was removed *in vacuo* and the remaining aqueous was extracted with DCM (2 x 2 mL). The DCM extracts were dried over Na_2SO_4 and concentrated *in vacuo* to an orange oil (110 mg, 69%).

$\nu_{max}(CDCl_3)$: 1649, 2253 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (s, 2H, CH=CH), 2.31-2.28 (m, 8H, aliphatic ring protons and CH_2CN), 1.99-1.94 (m, 2H, aliphatic ring protons).

^{13}C NMR (100 MHz, $CDCl_3$): δ 124.4, 118.6, 33.0, 28.5, 18.4.



9

Preparation of *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (16)[7]

Scheme 4.11, Table 4.3

Entry 1

A solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (1.42 g, 10 mmol) in Et_2O (75 mL) was cooled to 0 ^oC before addition of triethylamine (3.03 g, 48 mmol). Mesyl chloride (5.36 g, 48 mmol) was then added dropwise, causing a white precipitate to form. The reaction mixture was stirred at 0 ^oC for 30 minutes before being stirred at rt for 20 h. After this time, the reaction mixture was concentrated *in vacuo*,

partitioned between DCM (50 mL) and water (50 mL), and the aqueous layer was extracted with DCM (2 x 50 mL). The DCM extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a brown solid which was triturated in MeOH (5 mL) to give the product as a white solid (2.23 g, 75%).

Entry 2

A solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (12.79 g, 90 mmol) in Et_2O (675 mL) was cooled to 0 ^oC before addition of triethylamine (27.28 g, 270 mmol). Mesyl chloride (24.12 g, 216 mmol) was then added dropwise, causing a white precipitate to form. The precipitate formed a gum so DCM (200 mL) was added to allow efficient stirring of the mixture. The reaction mixture was stirred at 0 ^oC for 30 minutes before being stirred at rt for 20 h. After this time, the reaction mixture was concentrated *in vacuo*, partitioned between DCM (300 mL) and water (300 mL), and the aqueous layer was extracted with DCM (2 x 300 mL). The DCM extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a brown solid which was triturated in MeOH (10 mL) to give the product as a white solid (19.35 g, 72%).

Entry 3

A solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (12.79 g, 90 mmol) in Et_2O (675 mL) was cooled to 0 ^oC before addition of triethylamine (27.28 g, 270 mmol). Mesyl chloride (24.12 g, 216 mmol) was then added dropwise, causing a white precipitate to form. The precipitate formed a gum so DCM (200 mL) was added to allow efficient stirring of the mixture. The reaction mixture was stirred at 0 ^oC for 30 minutes before being stirred at rt for 20 h. After this time, the reaction mixture was concentrated *in vacuo*, partitioned between DCM (300 mL) and water (300 mL), and the aqueous layer was extracted with DCM (2 x 300 mL). The DCM extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a brown solid which was triturated in MeOH (10 mL) to give the product as a white solid (20.38 g, 76%).

Entry 4

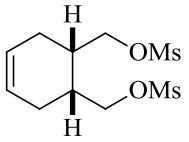
A solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (25.7 g, 181 mmol) in Et_2O (725 mL) and DCM (180 mL) was cooled to 0 ^oC before addition of triethylamine (76 mL,

543 mmol). Mesyl chloride (33 mL, 435 mmol) was then added dropwise, causing a white precipitate to form. The reaction mixture was stirred at 0 ^{o}C for 30 minutes before being stirred at rt for 20 h. After this time, the reaction mixture was concentrated *in vacuo*, partitioned between DCM (500 mL) and water (500 mL), and the aqueous layer was extracted with DCM (3 x 500 mL). The DCM extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a brown solid which was triturated in MeOH (20 mL) to give the product as a white solid (42.3 g, 78%).

$\nu_{max}(CDCl_3)$: 1174, 1358 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68 (s, 2H, CH=CH), 4.29 (dd, *J* = 10.0, 7.4 Hz, 2H, CH_2OMs), 4.17 (dd, *J* = 9.9, 6.9 Hz, 2H, CH_2OMs), 3.05 (s, 6H, SO_2CH_3), 2.45-2.43 (m, 2H, aliphatic ring protons), 2.28-2.23 (m, 2H, aliphatic ring protons), 2.02-1.98 (m, 2H, aliphatic ring protons).

^{13}C NMR (100 MHz, $CDCl_3$): δ 124.8, 70.0, 37.4, 34.0, 26.0.



16

Preparation of cyclohexene-4-*cis*-1,2-diacetonitrile (9)[4]

Scheme 4.12, Table 4.4

Entry 1

To a round-bottomed flask, which had previously been flame-dried and allowed to cool, was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (298 mg, 1 mmol), NaCN (186 mg, 3.8 mmol), and DMSO (5 mL). A condenser was fitted and the vessel was evacuated/argon-purged 3 times before heating to 100 ^{o}C for 4 h. After this time, water (5 mL) was added to the reaction mixture and the aqueous phase was extracted with DCM (2 x 5 mL). The DCM extracts were dried over Na_2SO_4, and concentrated *in vacuo* to give a colourless oil. Purification using silica gel

chromoatography, eluting with 20-50% EtOAc in hexane, gave the product as a colourless oil (134 mg, 84%).

Entry 2

To a round-bottomed flask, which had previously been flame-dried and allowed to cool, was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (1.84 g, 6 mmol), NaCN (1.15 g, 23 mmol), and DMSO (30 mL). A condenser was fitted and the vessel was evacuated/argon-purged 3 times before heating to 100 ^{o}C for 4 h. After this time, water (30 mL) was added to the reaction mixture and the aqueous phase was extracted with DCM (2 x 30 mL). The DCM extracts were concentrated *in vacuo*, dissolved in EtOAc (50 mL), washed with water (3 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil (920 mg, 93%).

Entry 3

To a round-bottomed flask, which had previously been flame-dried and allowed to cool, was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (19.35 g, 65 mmol), NaCN (12.08 g, 247 mmol), and DMSO (300 mL). A condenser was fitted and the vessel was evacuated/argon-purged 3 times before heating to 100 ^{o}C for 4 h. After this time, water (100 mL) was added to the reaction mixture and the aqueous phase was extracted with DCM (3 x 50 mL). The DCM extracts were concentrated, dissolved in EtOAc (100 mL), washed with water (3 x 200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil (7.68 g, 74%).

Entry 4

To a round-bottomed flask, which had previously been flame-dried and allowed to cool, was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (18.16 g, 61 mmol), NaCN (11.3 g, 232 mmol), and DMSO (250 mL). A condenser was fitted and the vessel was evacuated/argon-purged 3 times before heating to 100 ^{o}C for 4 h. After this time, water (100 mL) was added to the reaction mixture and the aqueous phase was extracted with DCM (3 x 50 mL). The DCM extracts were concentrated, dissolved in EtOAc (100 mL), washed with water (3 x 200 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil (9.73 g, 100%).

Entry 5

To a round-bottomed flask, which had previously been flame-dried and allowed to cool, was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (42.3 g, 142 mmol), NaCN (24.7 g, 503 mmol), and DMSO (500 mL). A condenser was fitted and the vessel was evacuated/argon-purged 3 times before heating to 100 ^{o}C for 4 h. After this time, water (200 mL) was added to the reaction mixture and the aqueous phase was extracted with DCM (3 x 100 mL). The DCM extracts were concentrated, dissolved in EtOAc (200 mL), washed with water (3 x 400 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil (19.7 g, 87%).

Microwave reactions

Scheme 4.13, Table 4.5

Entry 1

To a microwave vial was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (100 mg, 0.3 mmol), NaCN (60 mg, 1.27 mmol), and MeCN (3 mL). The reaction mixture was then heated under microwave irradiation at 100 ^{o}C for 15 minutes. TLC analysis showed that no reaction had taken place.

Entry 2

To a microwave vial was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (100 mg, 0.3 mmol), NaCN (60 mg, 1.27 mmol), and DMF (3 mL). The reaction mixture was then heated under microwave irradiation at 100 ^{o}C for 15 minutes. Analysis of the reaction mixture using ^{1}H NMR showed a complex mixture of products, containing no cyclohexene-4-*cis*-1,2-diacetonitrile.

Entry 3

To a microwave vial was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (100 mg, 0.3 mmol), NaCN (60 mg, 1.27 mmol), and DMSO (3 mL). The reaction mixture was then heated under microwave irradiation at 189 ^{o}C for 15 minutes. After this time, the reaction mixture was diluted with DCM (25 mL), washed with water (5 x 5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil (38 mg, 80%).

Entry 4

To a microwave vial was added *cis*-1,2,3,6-tetrahydrophthalyl alcohol dimethanesulfonate (2.98 g, 10 mmol), NaCN (2.07 g, 42 mmol), and DMSO (20 mL). The reaction mixture was then heated under microwave irradiation at 189 ^{o}C for 15 minutes. After this time, the reaction mixture was diluted with DCM (100 mL), washed with water (5 x 25 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Analysis using ^{1}H NMR showed that a complex mixture had been formed.

Data for **9** was quoted previously (see experimental section for **Scheme 4.10**).

Preparation of cyclohexene-4-*cis*-1,2-diacetic acid (10)[4]

Scheme 4.14, Table 4.6

Entry 1

Cyclohexene-4-*cis*-1,2-diacetonitrile (920 mg, 6 mmol) was refluxed in aqueous KOH (33%, 6.5 mL) for 17 h. The reaction mixture was then extracted with Et_2O (5 mL), and the aqueous was acidified with 3 mL of concentrated HCl, causing a precipitate to form. The precipitate was filtered and washed with water (5 mL). Residual water was azeotroped using toluene to give the product as a beige solid (843 mg, 74%).

Entry 2

Cyclohexene-4-*cis*-1,2-diacetonitrile (7.68 g, 48 mmol) was refluxed in aqueous KOH (33%, 50 mL) for 12 h. The reaction mixture was then extracted with Et_2O (40 mL), and the aqueous was acidified with 25 mL of concentrated HCl, causing a precipitate to form. The precipitate was filtered and washed with water (40 mL). Residual water was azeotroped using toluene to give the product as a beige solid (6.29 g, 66%).

Entry 3

Cyclohexene-4-*cis*-1,2-diacetonitrile (9.7 g, 61 mmol) was refluxed in aqueous KOH (33%, 45 mL) for 14 h. The reaction mixture was then extracted with Et_2O (50 mL), and the aqueous was acidified with 35 mL of concentrated HCl, causing a precipitate

to form. The precipitate was filtered and washed with water (50 mL). Residual water was azeotroped using toluene to give the product as a beige solid (10.7 g, 90%).

Entry 4

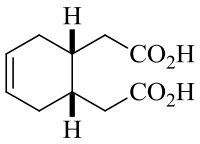
Cyclohexene-4-*cis*-1,2-diacetonitrile (19.7 g, 123 mmol) was refluxed in aqueous KOH (33%, 135 mL) for 16 h. The reaction mixture was then extracted with Et_2O (100 mL), and the aqueous was acidified with 70 mL of concentrated HCl, causing a precipitate to form. The precipitate was filtered and washed with water (100 mL). Residual water was azeotroped using toluene to give the product as a beige solid (18 g, 74%).

Melting point = 157-158 ^{o}C. Lit: 157-158 ^{o}C.[19]

$\nu_{max}(CDCl_3)$: 1693, 2885 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.05 (s, 2H, CO_2H), 5.58 (s, 2H, CH=CH), 2.21-2.03 (m, 8H, aliphatic ring protons and C*H*$_2CO_2H$), 1.76-1.73 (m, 2H, aliphatic ring protons).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 125.2, 34.7, 32.1, 28.8.



10

Preparation of *cis*-bicyclo[4.3.0]non-3-en-8-one (5)[4]

Scheme 4.15, Table 4.7

Entry 1

Cyclohexene-4-*cis*-1,2-diacetic acid (198 mg, 1 mmol) in acetic anhydride (2.16 g, 21 mmol) was refluxed for 2.5 h before addition of sodium acetate (279 mg, 3.4 mmol). The reaction mixture was refluxed for a further 15.5 h before being diluted with Et_2O

(5 mL) and washed with saturated $NaHCO_3$ (2 x 5 mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to a brown oil which was purified by silica gel chromatography, eluting with 0-10% Et_2O in PE 30-40. The product was isolated as a colourless oil (71 mg, 52%).

Entry 2

Cyclohexene-4-*cis*-1,2-diacetic acid (4.28 g, 22 mmol) in acetic anhydride (46.3 g, 454 mmol) was refluxed for 2.5 h before addition of sodium acetate (6.02 g, 73.4 mmol). The reaction mixture was refluxed for a further 15.5 h before being diluted with Et_2O (50 mL) and washed with saturated $NaHCO_3$ (2 x 50 mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to a brown oil which was purified by silica gel chromatography, eluting with 0-10% Et_2O in PE 30-40. The product was isolated as a colourless oil (2.13 g, 73%).

Entry 3

Cyclohexene-4-*cis*-1,2-diacetic acid (10.8 g, 54 mmol) in acetic anhydride (116.5 g, 1.1 mol) was refluxed for 2.5 h before addition of sodium acetate (15.2 g, 185 mmol). The reaction mixture was refluxed for a further 15.5 h before being diluted with Et_2O (100 mL) and washed with saturated $NaHCO_3$ (2 x 100 mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to a brown oil which was purified by silica gel chromatography, eluting with 0-10% Et_2O in PE 30-40. The product was isolated as a colourless oil (5.8 g, 78%).

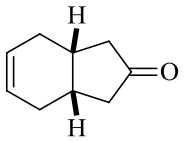
Entry 4

Cyclohexene-4-*cis*-1,2-diacetic acid (18 g, 90 mmol) in acetic anhydride (180 mL, 1.9 mol) was refluxed for 2.5 h before addition of sodium acetate (25.3 g, 309 mmol). The reaction mixture was refluxed for a further 15.5 h before being diluted with Et_2O (200 mL) and washed with saturated $NaHCO_3$ (2 x 200 mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to a brown oil which was purified by silica gel chromatography, eluting with 0-10% Et_2O in PE 30-40. The product was isolated as a colourless oil (8.6 g, 69%).

$\nu_{max}(CDCl_3)$: 1734 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70-5.64 (m, 2H, CH=CH), 2.41-2.31 (m, 2H, aliphatic ring protons), 2.29-2.23 (m, 4H, aliphatic ring protons), 2.07-2.01 (m, 2H, aliphatic ring protons), 1.86-1.81 (m, 2H, aliphatic ring protons).

^{13}C NMR (100 MHz, $CDCl_3$): δ 218.5, 123.6, 43.6, 31.3, 25.3.



5

3.2.1 Attempted development of an alternative route to *cis*-bicyclo[4.3.0]non-3-en-8-one (5)

Preparation of *cis*-4,5-bis(bromomethyl)cyclohexene (17)[7]

Scheme 4.17

LiBr (261 mg, 3 mmol) was added to a solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol di-*p*-toluenesulfonate (418 mg, 1 mmol) in DMF (2.5 mL). The flask was evacuated/argon-purged 3 times before being heated at 100 ^{o}C for 4 h. After this time, the reaction mixture was partitioned between Et_2O (5 mL) and water (5 mL). The aqueous phase was extracted with Et_2O (2 x 5 mL), and the extracts were dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a colourless oil (181 mg, 68%).

Scheme 4.18

A solution of phosphorus tribromide (2.71 g, 10 mmol) in DCM (10 mL) was added to a solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (142 mg, 1 mmol) in DCM (10 mL) at 0 ^{o}C. The reaction mixture was warmed to rt and stirred for 4.5 h before being poured into water (10 mL). The aqueous was extracted with DCM (2 x 5 mL), and the extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give an orange oil which was contaminated with aromatic by-products (detected by ^{1}H NMR). None of the desired product was detected by ^{1}H NMR.

Scheme 4.19, Table 4.8

Entry 1

To a solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (142 mg, 1 mmol) and CBr_4 (995 mg, 3 mmol) in DCM (4.5 mL) was added PPh_3 (629 mg, 2.4 mmol) in DCM (1 mL) over 40 minutes *via* syringe pump. After 3 days, the reaction mixture was concentrated *in vacuo* to a brown oil, triturated with Et_2O (10 mL), filtered and concentrated *in vacuo*. Purification using silica gel chromatography, eluting with 10% Et_2O in PE 30-40, gave the product as a colourless oil (195 mg, 73%).

Entry 2

To a solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (2.84 g, 20 mmol) and CBr_4 (19.9 g, 60 mmol) in DCM (90 mL) was added PPh_3 (12.6 g, 48 mmol) in DCM (20 mL) dropwise over 20 minutes. An exotherm and the formation of a white precipitate were observed on addition. After 3 days, the reaction mixture was concentrated *in vacuo* to a brown oil, triturated with Et_2O (100 mL) to give a gummy precipitate, filtered and concentrated *in vacuo*. Purification using silica gel chromatography, eluting with 10% Et_2O in PE 30-40, gave the product as a colourless oil (1.85 g, 35%).

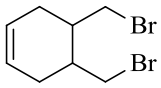
Entry 3

To a solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol (2.84 g, 20 mmol) and CBr_4 (19.9 g, 60 mmol) in DCM (90 mL) was added PPh_3 (12.6 g, 48 mmol) in DCM (20 mL) dropwise over 20 minutes at 0 ^oC. An exotherm and the formation of a white precipitate were observed on addition. During the addition, care was taken to maintain the reaction temperature at around 0 ^oC. The reaction mixture was then warmed to room temperature. After 3 days, the reaction mixture was concentrated *in vacuo* to a brown oil and purified using silica gel chromatography, eluting with 10% Et_2O in PE 30-40, to give the product as a colourless oil (5.36 g, 100%).

$\nu_{max}(CDCl_3)$: 1671, 713 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (s, 2H, CH=CH), 3.40 (dd, *J* = 10.0, 5.4 Hz, 2H, CH_2Br), 3.32 (t, *J* = 9.0 Hz, 2H, CH_2Br), 2.39-2.33 (m, 2H, aliphatic ring protons), 2.26-2.21 (m, 2H, aliphatic ring protons), 2.09-2.03 (m, 2H, aliphatic ring protons).

^{13}C NMR (100 MHz, $CDCl_3$): δ 123.9, 37.9, 33.0, 27.3.



17

Attempted preparation of 2-((6-(bromomethyl)cyclohex-3-enyl)methyl)-1,3-dithiane (20)

Scheme 4.20

n-BuLi (2.54 M in hexanes, 0.43 mL, 1.1 mmol) was added to a solution of 1,3-dithiane (120 mg, 1 mmol) in THF (5 mL) at -78 ^oC. The reaction mixture was stirred at -78 ^oC for 30 minutes then -20 ^oC for 1.3 h. *cis*-4,5-Bis(bromomethyl)cyclohexene (697 mg, 2.6 mmol) was added neat and the reaction mixture was stirred at -20 ^oC for 24 h. After stirring for a further 24 h at 0 ^oC, the reaction mixture was quenched with water (5 ml), and extracted with Et_2O (2 x 10 mL). The Et_2O extracts were dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. ^1H NMR showed that no reaction had taken place.

Preparation of 2-deuterio-1,3-dithiane (21)[20]

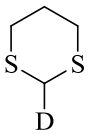
Scheme 4.21

A solution of 1,3-dithiane (120 mg, 1 mmol) in THF (5 mL) was cooled to -78 ^oC. To this solution was added *n*-BuLi (2.50 M in hexanes, 0.44 mL, 1.1 mmol), and the mixture was stirred at -78 ^oC for 30 minutes then at -20 ^oC for 1.3 h. After this time, the reaction mixture was quenched with D_2O (1 mL) and the aqueous phase was extracted with Et_2O (2 x 5 mL). The Et_2O extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the product as a colourless oil (116 mg, 96%).

$\nu_{max}(CDCl_3)$: 713 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 3.76 (t, *J* = 2.0 Hz, 1H, CH(D)), 2.84-2.81 (m, 4H, SCH_2), 2.10-2.04 (m, 2H, SCH_2CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 30.7 (t), 28.9, 25.6.



21

Attempted preparation of (6-((1,3-dithian-2-yl)methyl)cyclohex-3-enyl)methyl 4-methylbenzenesulfonate (22)

Scheme 4.22

A solution of 1,3-dithiane (120 mg, 1 mmol) in THF (5 mL) was cooled to -78 ^oC. To this solution was added *n*-BuLi (2.50 M in hexanes, 0.44 mL, 1.1 mmol), and the mixture was stirred at -78 ^oC for 30 minutes then at -20 ^oC for 1.3 h. After this time, the reaction mixture was transferred *via* canula to a solution of *cis*-1,2,3,6-tetrahydrophthalyl alcohol di-*p*-toluenesulfonate (418 mg, 1 mmol) in THF (5 mL) at -40 ^oC. After 16 h at this temperature, the reaction mixture was quenched with saturated NH_4Cl (5 mL) and extracted with EtOAc (2 x 5 mL). The extracts were dried over Na_2SO_4 and concentrated *in vacuo* to a yellow oil. ^1H NMR showed that no reaction had taken place.

3.2 Preparation of the enol silane intermediate (4)

Scheme 4.23

To a round-bottomed flask, which had previously been flame-dried and allowed to cool under argon, was added di-*iso*-propylamine (101 mg, 1 mmol) and THF (10 mL). *n*-BuLi in hexanes (2.5 M, 0.4 mL, 1 mmol) was then added at -78 ^{o}C and the reaction mixture was stirred at -78 ^{o}C for 10 minutes before allowing to warm to room temperature and stirring for 15 minutes. After cooling the reaction once more to -78 ^{o}C, TMSCl (0.5 mL, 4 mmol) was added, followed by *cis*-bicyclo[4.3.0]non-3-en-8-one (109 mg, 0.8 mmol) in THF (2 mL). The reaction mixture was then allowed to warm to room temperature over 18 h before quenching with a saturated solution of $NaHCO_3$ (10 mL) and extracting with Et_2O (2 x 25 mL). The organic extracts were then dried over Na_2SO_4 and concentrated *in vacuo*. Analysis of the crude product using ^{1}H NMR spectroscopy revealed that no conversion of the starting material had occurred.

Scheme 4.24

To a round-bottomed flask, which had been flame-dried and allowed to cool under argon, was added *cis*-bicyclo[4.3.0]non-3-en-8-one (109 mg, 0.8 mmol), triethylamine (0.33 mL, 2.4 mmol), and DCM (12 mL). The reaction mixture was cooled on an ice bath before the dropwise addition of TMSOTf (0.16 mL, 0.9 mmol). The reaction mixture was stirred for 1 h at 0 ^{o}C before quenching with a saturated solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with DCM (2 x 10 mL) and the extracts were dried (Na_2SO_4) and concentrated to give the product as a colourless oil (35 mg, 21%).

Scheme 4.25, Table 4.9

Entry 1

A Schlenk tube was charged with LiCl (85 mg, 2 mmol) and flame-dried under vacuum. The tube was then purged three times with argon before allowing to cool to room temperature and charging with Mes_2Mg in THF (0.51 M, 0.5 mmol, 0.98 mL) and THF (9 mL). The mixture was stirred for 15 minutes at room temperature before cooling to 0 ^{o}C. TMSCl (0.13 mL, 1 mmol) was added and the mixture was stirred

for 5 minutes before addition of the ketone (**5**, 136 mg, 1 mmol) as a solution in THF (2 mL) over 1 h *via* syringe pump. The reaction mixture was stirred at 0 ^{o}C under argon for 13 h before quenching with a saturated solution of $NaHCO_3$ (10 mL). The mixture was allowed to warm to room temperature before extracting with Et_2O (40, 25, 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification using silica gel chromatography, eluting with 100% petroleum ether (30-40 °C), gave the product as a colourless oil (413 mg). Analysis of the product using ^{1}H NMR spectroscopy revealed that the mesitylene by-product had co-eluted with the desired product. Therefore, the yield of trimethyl((3a,4,7,7a-tetrahydro-1*H*-inden-2-yloxy)silane was calculated from the ^{1}H NMR spectrum as 76%.

Entry 2

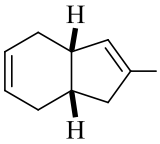
A Schlenk tube was charged with LiCl (652 mg, 15 mmol) and flame-dried under vacuum. The tube was then purged three times with argon before allowing to cool to room temperature and charging with Mes_2Mg in THF (0.51 M, 4 mmol, 7.5 mL) and THF (70 mL). The mixture was stirred for 15 minutes at room temperature before cooling to 0 ^{o}C. TMSCl (0.97 mL, 8 mmol) was added and the mixture was stirred for 5 minutes before addition of the ketone (**5**, 1.05 g, 8 mmol) as a solution in THF (15 mL) over 1 h *via* syringe pump. The reaction mixture was stirred at 0 ^{o}C under argon for 13 h before quenching with a saturated solution of $NaHCO_3$ (80 mL). The mixture was allowed to warm to room temperature before extracting with Et_2O (200, 100, 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give 2.87 g of yellow oil. Purification by distillation (8 mbar, 91 ^{o}C) gave the product as a colourless oil (1.16 g, 70%).

$\nu_{max}(CDCl_3)$: 1646 cm^{-1}.

HRMS (ESI) m/z calculated for $C_{12}H_{20}OSi$[M]: 208.1278. Found: 208.1278.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92-5.82 (m, 2H, CH=CH), 4.58-4.57 (m, 1H, CH=COTMS), 2.80-2.73 (m, 1H), 2.51-2.37 (m, 2H), 2.24-2.14 (m, 2H), 2.00-1.94 (m, 1H), 1.92-1.85 (m, 1H), 1.83-1.77 (m, 1H), 0.21 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 128.7, 128.0, 108.1, 41.2, 39.4, 33.2, 29.0, 28.8, 1.0.



4

3.3 Preparation of the allyl bromide (11)

Preparation of methyl 5-hydroxypentanoate (24)[21]

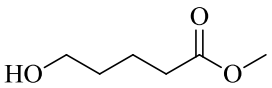
Scheme 4.27

A solution of δ-valerolactone (5.90 g, 59 mmol) and concentrated H_2SO_4 (6 drops) in MeOH (120 mL) was refluxed for 4 h before being cooled to 0 ^{o}C and treated with $NaHCO_3$ (600 mg, 7 mmol). The mixture was stirred for 10 minutes and then filtered. The filtrate was concentrated *in vacuo* to give the product as a colourless oil (7.73 g, 99%).

ν_{max}($CDCl_3$): 1728, 3461 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H, CO_2CH_3), 3.58-3.56 (m, 2H, C*H*$_2$OH), 2.31 (t, *J* = 7.2 Hz, 2H, C*H*$_2$CO$_2$CH$_3$), 1.70-1.63 (m, 2H, C*H*$_2$CH$_2$CO$_2$CH$_3$), 1.57-1.50 (m, 2H, C*H*$_2$CH$_2$OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 61.9, 51.5, 33.6, 31.9, 21.1.



24

Preparation of methyl 5-oxopentanoate (14)[21]

Scheme 4.28

DMSO (1.79 g, 23 mmol) was added to a solution of oxalyl chloride (1.65 g, 13 mmol) in DCM (20 mL) at -78 ^{o}C. The reaction mixture was stirred at -78 ^{o}C for 10

minutes before addition of methyl 5-hydroxypentanoate (1.32 g, 10 mmol) in DCM (5 mL). The reaction mixture was stirred for a further 30 minutes before addition of Et_3N (5.05 g, 50 mmol). After warming to rt, the reaction mixture was stirred for 15 h and then quenched with a saturated solution of NH_4Cl (10 mL). The mixture was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to an orange oily solid. Purification by silica gel chromatography (0-50% Et_2O in PE 30-40) gave the product as a yellow oil (372 mg, 29%).

Scheme 4.29

Methyl 5-hydroxypentanoate (1.32 g, 10 mmol) in DCM (3 mL) was added to a mixture of PDC (5.64 g, 15 mmol) and celite (2 g) in DCM (16 mL). On addition, the reaction mixture changed colour from orange to brown. After stirring at rt overnight, the reaction mixture was filtered and the residue was washed with Et_2O (10 mL). The cloudy filtrate was filtered through celite and concentrated *in vacuo* to give 1.29 g of orange oil. This oil was distilled at 5 mbar and 75 ^oC to give the product as a colurless oil (347 mg, 27%).

Scheme 4.30

TPAP (18 mg, 0.05 mmol) was added in one portion to a solution of methyl 5-hydroxypentanoate (132 mg, 1 mmol), NMO (176 mg, 1.5 mmol), and powdered 4Å molecular sieves (500 mg) in DCM (2 mL) at room temperature under argon. The reaction mixture was stirred for 4 h before being filtered through a short plug of silica which was washed with EtOAc (5 mL). The filtrate was concentrated to give the product as a colourless oil (12 mg, 9%).

Scheme 4.31

DMP (424 mg, 1 mmol) was added in one portion to a solution of methyl 5-hydroxypentanoate (132 mg, 1 mmol) in DCM (10 mL) under argon. The reaction mixture was stirred at room temperature for 15 h before being diluted with EtOAc (20 mL) and washed saturated $NaHCO_3$ (10 mL) and saturated $Na_2S_2O_3$ (3 x 10 mL). The organic layer was then dried (Na_2SO_4) and concentrated to 73 mg (56%) of colourless oil. Analysis using ^1H NMR spectroscopy revealed that the crude product contained significant amounts of DMP by-product.

Scheme 4.32

A round-bottomed flask containing Pd/C (16 mg, 0.015 mmol) was flushed with H_2 before being charged with THF (5 mL), 2,6-lutidine (117 mg, 1.1 mmol), and methyl 5-chloro-5-oxopentanoate (165 mg, 1 mmol). The reaction mixture was stirred at room temperature under a balloon pressure of H_2 for 2 days. ^{1}H NMR analysis after this time showed that complete conversion of the starting material had occurred, although the aldehyde product was contaminated with a mixture of impurities.

Scheme 4.33, Table 4.10

Entry 1

A mixture of cyclopentene (2 mL, 23 mmol) and $NaHCO_3$ (300 mg, 3.6 mmol) in MeOH (6 mL mL) and DCM (30 mL) was cooled to -78 ^{o}C. Ozone was bubbled through the reaction mixture for 2 h (until the solution remained blue). Oxygen was then bubbled through the solution for 5 minutes. After diluting with toluene (150 mL) and concentrating slightly *in vacuo* to remove MeOH, the reaction mixture was cooled to 0 ^{o}C and was treated with Et_3N (6.4 mL, 46 mmol) and Ac_2O (4.3 mL, 46 mmol). The reaction mixture was then stirred and allowed to reach room temperature overnight. The reaction mixture was diluted with DCM (200 mL) and washed with a saturated solution of $NaHCO_3$ (3 x 100 mL) before being dried over Na_2SO_4 and concentrated *in vacuo*. The yield of the desired product was calculated as 52% by ^{1}H NMR analysis and the crude product (containing residual toluene and acetic anhydride) was taken on to the next step without purification.

Entry 2

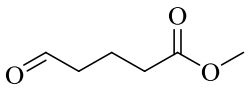
A mixture of cyclopentene (15.2 mL, 172 mmol) and $NaHCO_3$ (52 g, 619 mmol) in MeOH (45 mL mL) and DCM (230 mL) was cooled to -78 ^{o}C. Ozone was bubbled through the reaction mixture until the trap containing saturated KI turned dark brown (this was used as an indication that the reaction had reached completion because the reaction mixture did not turn blue after a prolonged reaction time of 7 h, possibly due to the relatively low concentration of ozone present in solution on this scale). Oxygen was then bubbled through the solution for 5 minutes. After diluting with toluene (500 mL) and concentrating slightly *in vacuo* to remove MeOH, the reaction mixture was cooled to 0 ^{o}C and was treated with Et_3N (48 mL, 344 mmol) and Ac_2O (65 mL, 688

mmol). The reaction mixture was then stirred and allowed to reach room temperature overnight. The reaction mixture was diluted with DCM (500 mL) and washed with a saturated solution of $NaHCO_3$ (3 x 300 mL) before being dried over Na_2SO_4 and concentrated *in vacuo*. The yield of the desired product was calculated as 72% by ^1H NMR analysis and the crude product (containing residual toluene and acetic anhydride) was taken on to the next step without purification.

$\nu_{max}(CDCl_3)$: 1728, 2951 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 9.94 (t, *J* = 1.3 Hz, 1H, CHO), 3.64 (s, 3H, CO_2CH_3), 2.50 (td, *J* = 7.2 and 1.3 Hz, 2H, CHOCH_2), 2.35 (t, *J* = 7.3 Hz, 2H, C$H_2CO_2CH_3$), 1.92 (quintet, *J* = 7.2 Hz, 2H, C$H_2CH_2CO_2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 173.3, 51.6, 42.9, 32.9, 17.3.



14

Preparation of (*E*)-methyl 7-oxohept-5-enoate (13)[12]

Scheme 4.34, Table 4.11

Entry 1

A mixture of methyl 5-oxopentanoate (299 mg, 2 mmol) and (triphenylphosphoranylidene)acetaldehyde (1.47 g, 4.8 mmol) in toluene (15 mL) was heated at 60 ^oC for 4 h under argon. After this time, the reaction mixture was treated with PE 30-40 (5 mL) and then filtered. The filtrate was concentrated to give an orange oil which was purified by column chromatography on SiO_2, eluting with 0-30% EtOAc in *n*-hexane, to give the product as a yellow oil (251 mg, 70%).

Entry 2

A mixture of methyl 5-oxopentanoate (1.85 g (in 6.5 g of a mixture containing Ac_2O and toluene), 14 mmol) and (triphenylphosphoranylidene)acetaldehyde (9.07 g, 14 mmol) in toluene (100 mL) was heated at 60 ^oC for 4 h under argon. After this time,

the reaction mixture was concentrated to give an orange oil which was purified by column chromatography on SiO_2, eluting with 0-30% EtOAc in *n*-hexane, to give the product as a yellow oil (1.34 g, 60%).

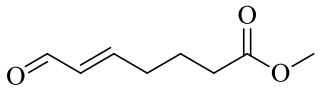
Entry 3

A mixture of methyl 5-oxopentanoate (3.9 g (in 14.2 g of a mixture containing Ac_2O and toluene), 30 mmol) and (triphenylphosphoranylidene)acetaldehyde (10 g, 33 mmol) in toluene (200 mL) was heated at 60 ^oC for 4 h under argon. After this time, the reaction mixture was concentrated to give an orange oil which was purified by column chromatography on SiO_2, eluting with 0-30% EtOAc in *n*-hexane, to give the product as a yellow oil (3.18 g, 68%).

$\nu_{max}(CDCl_3)$: 1731, 1687, 1634 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 9.51 (d, *J* = 7.9 Hz, 1H, CHO), 6.82 (dt, *J* = 15.6 and 6.8 Hz, 1H, OHCCH=C*H*), 6.14 (ddt, *J* = 15.8, 8.0 and 1.5 Hz, 1H, OHCC*H*=CH), 3.68 (s, 3H, CO_2CH_3), 2.43-2.34 (m, 4H, $CH_2CH_2CH_2$), 1.87 (quintet, *J* = 7.4 Hz, 2H, $CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 173.4, 157.0, 133.5, 51.7, 33.1, 31.9, 23.0.



13

Preparation of (*E*)-methyl 7-hydroxyhept-5-enoate (12)

Scheme 4.35, Table 4.12

Entry 1

A mixture of $NaBH_4$ (61 mg, 1.6 mmol) in EtOH (5 mL) was cooled to 0 ^oC under argon. (*E*)-Methyl 7-oxohept-5-enoate (251 mg, 2 mmol) was then added dropwise and the reaction mixture was stirred at 0 ^oC for 10 minutes before being allowed to warm to room temperature and stirring for 1 h. The reaction mixture was then

quenched with H_2O (2 mL), extracted with DCM (2 x 5 mL), dried (Na_2SO_4), and concentrated to 134 mg of yellow oil (53%).

Entry 2

A mixture of $NaBH_4$ (325 mg, 9 mmol) in EtOH (30 mL) was cooled to 0 ^oC under argon. (*E*)-Methyl 7-oxohept-5-enoate (1.34 g, 9 mmol) was then added dropwise and the reaction mixture was stirred at 0 ^oC for 10 minutes before being allowed to warm to room temperature and stirring for 1 h. The reaction mixture was then quenched with H_2O (10 mL), extracted with DCM (2 x 25 mL), dried (Na_2SO_4), and concentrated to 826 mg of yellow oil (61%).

Entry 3

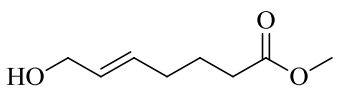
A mixture of $NaBH_4$ (771 mg, 20 mmol) in EtOH (60 mL) was cooled to 0 ^oC under argon. (*E*)-Methyl 7-oxohept-5-enoate (3.18 g, 20 mmol) was then added dropwise and the reaction mixture was stirred at 0 ^oC for 10 minutes before being allowed to warm to room temperature and stirring for 1 h. The reaction mixture was then quenched with H_2O (20 mL), extracted with DCM (2 x 50 mL), dried (Na_2SO_4), and concentrated to 1.63 g of yellow oil (51%).

$\nu_{max}(CDCl_3)$: 3599 and 1728 cm^{-1}.

HRMS (ESI) m/z calculated for $C_8H_{14}O_3[M+NH_4]$: 176.1281. Found: 176.1277.

^1H NMR (400 MHz, $CDCl_3$): δ 5.67-5.66 (m, 2H, CH=CH), 4.09 (s, 2H, HOC*H*$_2$CH=CH), 3.67 (m, 4H, CH_3 and OH), 2.32 (t, *J* = 7.4 Hz, 2H, C*H*$_2CO_2CH_3$), 2.12-2.08 (m, 2H, $CH=CHCH_2$), 1.73 (quintet, *J* = 6.8 Hz, 2H, $CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 130.7, 129.0, 62.6, 50.5, 32.3, 30.5, 23.2.



12

Preparation of (*E*)-methyl 7-bromohept-5-enoate (11)

Scheme 4.36, Table 4.13

Entry 1

To a solution of (*E*)-methyl 7-hydroxyhept-5-enoate (123 mg, 1 mmol) and carbon tetrabromide (284 mg, 1 mmol) in DCM (5 mL) was added triphenylphosphine (224 mg, 1 mmol) portionwise. The reaction mixture was stirred at room temperature for 1 h before being concentrated and then purified by column chromatography on SiO_2, eluting with 0-10% EtOAc in *n*-hexane, to give the product as a yellow oil (97 mg, 55%).

Entry 2

To a solution of (*E*)-methyl 7-hydroxyhept-5-enoate (826 mg, 5 mmol) and carbon tetrabromide (1.91 g, 6 mmol) in DCM (30 mL) was added triphenylphosphine (1.51 g, 6 mmol) portionwise. The reaction mixture was stirred at room temperature for 1 h before being concentrated and then purified by column chromatography on SiO_2, eluting with 0-10% EtOAc in *n*-hexane, to give the product as a yellow oil (700 mg, 61%).

Entry 3

To a solution of (*E*)-methyl 7-hydroxyhept-5-enoate (1.63 g, 10 mmol) and carbon tetrabromide (6.82 g, 20 mmol) in DCM (60 mL) was added triphenylphosphine (5.39 g, 20 mmol) portionwise. The reaction mixture was stirred at room temperature for 1 h before being concentrated and then purified by column chromatography on SiO_2, eluting with 0-10% EtOAc in *n*-hexane, to give the product as a yellow oil (1.16 g, 51%).

Scheme 4.37, Table 4.14

Entry 1

A solution of allyl bromide (121 mg, 1 mmol), methyl hex-5-enoate (512 mg, 4 mmol) and Grubbs' second generation catalyst (17 mg, 0.02 mmol) in DCM (20 mL) was refluxed for 2 days. The reaction mixture was then concentrated and purified by

column chromatography on SiO_2, eluting with 0-10% EtOAc in *n*-hexane, to give the product (**11**) as a yellow oil (170 mg, 77% (based on allyl bromide)). ^{1}H NMR analysis of the product showed a 6:1 mixture of *E*:*Z* isomers. The *Z*-isomer was identified by comparison with literature ^{1}H NMR data,[22] and the signals at δ 5.61-5.54 (m, 1H, *Z*-isomer) and 5.78-5.69 (m, 2H, *E*-isomer) were used to calculate the *E*:*Z* ratio. Dimethyl dec-5-enedioate (**29**) was also isolated as a colourless oil (250 mg, 55% (based on methyl hex-5-enoate)).

Entry 2

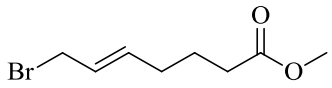
A solution of allyl bromide (121 mg, 1 mmol), methyl hex-5-enoate (128 mg, 1 mmol) and Grubbs' second generation catalyst (17 mg, 0.02 mmol) in DCM (20 mL) was refluxed for 2 days. The reaction mixture was then concentrated and purified by column chromatography on SiO_2, eluting with 0-10% EtOAc in *n*-hexane, to give the product (**11**) as a yellow oil (194 mg, 88%). ^{1}H NMR analysis of the product showed a 7:1 mixture of *E*:*Z* isomers. The *Z*-isomer was identified by comparison with literature ^{1}H NMR data,[22] and the signals at δ 5.61-5.54 (m, 1H, *Z*-isomer) and 5.78-5.69 (m, 2H, *E*-isomer) were used to calculate the *E*:*Z* ratio. Dimethyl dec-5-enedioate (**29**) was also isolated as a colourless oil (13 mg, 11% (based on methyl hex-5-enoate)).

$\nu_{max}(CDCl_3)$: 1728 cm^{-1}.

HRMS (ESI) m/z calculated for $C_8H_{17}NO_2Br[M+NH_4]$: 238.0437. Found: 238.0437.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78-5.69 (m, 2H, CH=CH), 3.94 (d, *J* = 6.3 Hz, 2H, $BrCH_2$), 3.68 (s, 3H, CH_3), 2.32 (t, *J* = 6.3 Hz, 2H, $CH_2CO_2CH_3$), 2.14-2.10 (m, 2H, $BrCH_2CH{=}CHCH_2$), 1.74 (quintet, *J* = 7.6 Hz, 2H, $CH_2CH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 135.1, 127.4, 51.5, 33.2, 33.1, 31.3, 24.0.



11

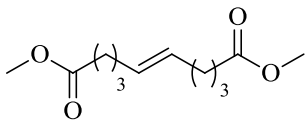
Dimethyl dec-5-enedioate

$\nu_{max}(CDCl_3)$: 1728 cm^{-1}.

HRMS (ESI) m/z calculated for $C_{12}H_{21}O_4[M+H]$: 229.1434. Found: 229.1434.

^1H NMR (400 MHz, $CDCl_3$): δ 5.40-5.37 (m, 2H, CH=CH), 3.66 (s, 6H, CH_3), 2.29 (t, *J* = 7.5 Hz, 4H, CH=CHC*H*$_2$), 2.04-1.99 (m, 4H, C*H*$_2$CO$_2$CH$_3$), 1.68 (quintet, *J* = 7.3 Hz, 4H, CH$_2$C*H*$_2$CH$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 130.1, 51.4, 33.3, 31.8, 24.6.



29

3.4 Coupling of the enol silane and allylic bromide

Scheme 4.38

Trimethyl(3a,4,7,7a-tetrahydro-1*H*-inden-2-yloxy)silane (104 mg, 0.5 mmol) in THF (1 mL) was added to lithium amide (29 mg, 1.25 mmol) in THF (3 mL). The reaction mixture was refluxed for 20 minutes before cooling to room temperature. (*E*)-Methyl 7-bromohept-5-enoate (414 mg, 1.9 mmol) in THF (0.5 mL) was then added and the reaction mixture was refluxed for 3 h before being quenched with a saturated aqueous solution of NH_4Cl (5 mL), extracted with DCM (2 x 5 mL), dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography on SiO_2, eluting with 0-5% EtOAc in *n*-hexane, to give the ketone precursor (**5**, 20 mg, 29%), the desired product (**3**, 26 mg, 19%), and (*E*)-methyl 7-bromohept-5-enoate (**11**, 168 mg, 41%).

Scheme 4.39

A solution of trimethyl(3a,4,7,7a-tetrahydro-1*H*-inden-2-yloxy)silane (104 mg, 0.5 mmol) in THF (3 mL) was cooled to -10 ^oC. Methyllithium (0.33 mL, 1.6 M, 0.53 mmol) was then added and the reaction mixture was stirred at -10 ^oC for 15 minutes.

After this time, DMPU (0.24 mL, 2 mmol) was added and the reaction mixture was cooled to -78 ^{o}C. (*E*)-Methyl 7-bromohept-5-enoate (116 mg, 0.53 mmol) was then added and the reaction mixture was allowed to warm from -78 ^{o}C to room temperature over 16 h before being quenched with a saturated aqueous solution of NH_4Cl (5 mL), extracted with DCM (2 x 5 mL), dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography on SiO_2, eluting with 0-5% EtOAc in *n*-hexane, to give the ketone precursor (**5**, 16 mg, 17%) and the desired product (**3**, 60 mg, 43%).

Scheme 4.40

A solution of trimethyl(3a,4,7,7a-tetrahydro-1*H*-inden-2-yloxy)silane (799 mg, 4 mmol) in THF (23 mL) was cooled to -10 ^{o}C. Methyllithium (2.52 mL, 1.6 M, 4 mmol) was then added and the reaction mixture was stirred at -10 ^{o}C for 15 minutes. After this time, DMPU (1.84 mL, 15 mmol) was added and the reaction mixture was cooled to -78 ^{o}C. (*E*)-Methyl 7-bromohept-5-enoate (1.02 g, 4.6 mmol) was then added and the reaction mixture was allowed to warm from -78 ^{o}C to room temperature over 16 h before being quenched with a saturated aqueous solution of NH_4Cl (40 mL), extracted with DCM (2 x 40 mL), dried (Na_2SO_4) and concentrated. The crude product was purified using column chromatography on SiO_2, eluting with 0-5% EtOAc in *n*-hexane, to give the ketone precursor (**5**, 95 mg, 18%) and the desired product (**3**, 496 mg, 47%).

(*E*)-Methyl 7-(2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)hept-5-enoate (3)

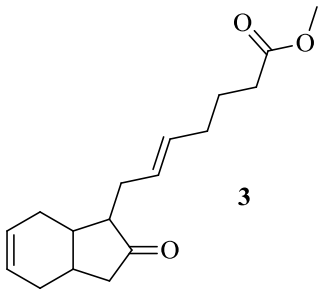
$\nu_{max}(CDCl_3)$: 1731 cm^{-1}.

HRMS (ESI) m/z calculated for $C_{17}H_{25}O_3$[M+H]: 277.1798. Found: 277.1798.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74-5.64 (m, 2H, ring CH=CH), 5.48-5.31 (m, 2H, chain CH=CH), 3.67 (s, 3H, CH_3), 2.51-1.87 (m, 14H), 1.75-1.62 (m, 3H).

For the major component: ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.9, 173.5, 131.2, 127.3, 124.5, 124.0, 50.9, 50.3, 45.7, 36.4, 32.8, 31.3, 30.4, 29.4, 26.6, 24.8, 24.0.

The distinct peaks for the minor component: ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.5, 173.1, 130.0, 128.4, 124.1, 124.0, 57.1, 40.4, 33.3, 32.8, 27.0, 25.6, 21.6.



3

3.5 Asymmetric deprotonation of *cis*-bicyclo[4.3.0]non-3-en-8-one

Scheme 4.41, Table 4.15

Entry 1

$^{n}Bu_2Mg$ in heptane (1 mL, 1 M, 1 mmol) was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by (*R*)-bis((*R*)-1-phenylethyl)amine (0.44 mL, 2 mmol), and the solution was heated at reflux for 1.5 h, assuming quantitative formation of the magnesium bisamide. The reaction mixture was then cooled to -78 ^{o}C before being charged with DMPU (0.12 mL, 1 mmol), followed by TMSCl (0.5 mL, 4 mmol), and the reaction mixture was stirred for 10 minutes at -78 ^{o}C. *Cis*-bicyclo[4.3.0]non-3-en-8-one (0.1 mL, 0.8 mmol) was then added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction mixture was stirred at -78 ^{o}C for 18 h before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was concentrated and then purified by column chromatography on silica gel using 0-2.5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (77 mg, 46%). The optical rotation was then measured ($[\alpha]_D^{20}$ = +45.8 ^{o} (c = 1, $CHCl_3$)) and the er was established as 90:10 using chiral HPLC (4.6mmid x 25cm Chiralpak AS column, 1:1

heptane: EtOH, 1.0 mL/minute flow rate, 210 nm detector, t_R (+) = 13 minutes and t_R (-) = 8.5 minutes).

Entry 2

$^{n}Bu_2Mg$ in heptane (1 mL, 1 M, 1 mmol) was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by (*R*)-bis((*R*)-1-phenylethyl)amine (0.44 mL, 2 mmol), and the solution was heated at reflux for 1.5 h, assuming quantitative formation of the magnesium bisamide. The reaction mixture was then cooled to -78 ^{o}C before being charged with DMPU (0.12 mL, 1 mmol), followed by TMSCl (0.13 mL, 1 mmol), and the reaction mixture was stirred for 10 minutes at -78 ^{o}C. *Cis*-bicyclo[4.3.0]non-3-en-8-one (0.1 mL, 0.8 mmol) was then added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction mixture was stirred at -78 ^{o}C for 18 h before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was concentrated and then purified by column chromatography on silica gel using 0-2.5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (102 mg, 61%). The optical rotation was then measured ($[\alpha]_D^{20}$ = +49.1 ^{o} (c = 1, $CHCl_3$)) and was used to calculate the er (93:7).

Scheme 4.42

$^{n}Bu_2Mg$ in heptane (1 mL, 1 M, 1 mmol) was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by (*R*)-1-(naphthalen-2-yl)-*N*-((*R*)-1-phenylethyl)ethanamine (0.52 mL, 2 mmol), and the solution was heated at reflux for 1.5 h, assuming quantitative formation of the magnesium bisamide. The reaction mixture was then cooled to -78 ^{o}C before being charged with DMPU (0.12 mL, 1 mmol), followed by TMSCl (0.13 mL, 1 mmol), and the reaction mixture was stirred for 10 minutes at -78 ^{o}C. *Cis*-bicyclo[4.3.0]non-3-en-8-one (0.1 mL, 0.8 mmol) was then added as a solution in THF (2 mL) over 1 h using

a syringe pump. The reaction mixture was stirred at -78 ^{o}C for 18 h before being quenched with a saturated solution of $NaHCO_3$ (10 mL) and allowed to warm to room temperature. Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was concentrated and then purified by column chromatography on silica gel using 0-2.5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (110 mg, 66%). The optical rotation was then measured ($[\alpha]_D^{20}$ = +44.3 ^{o} (c = 1, $CHCl_3$)) and was used to calculate the er (89:11).

Scheme 4.43, Table 4.16

Entry 1

To a Schlenk flask which had previously been flame-dried under vacuum and allowed to cool under argon was added (*R*)-bis((*R*)-1-phenylethyl)amine (0.22 mL, 1 mmol) and THF (10 mL). The solution was then cooled to -78 ^{o}C before addition of *n*-BuLi (0.41 mL, 2.46 M, 1 mmol). The reaction mixture was stirred at -78 ^{o}C for 5 minutes before being allowed to warm to room temperature and then re-cooled to -78 ^{o}C. TMSCl (0.13 mL, 1 mmol) and DMPU (0.12 mL, 1 mmol) were added, followed by dropwise addition of the ketone (**5**, 0.1 mL, 0.8 mmol) in THF (2 mL). The reaction mixture was stirred for 15 minutes at -78 ^{o}C before being quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was concentrated and then purified by column chromatography on silica gel using 0-2.5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (110 mg, 66%). The optical rotation was then measured ($[\alpha]_D^{20}$ = +50.0 ^{o} (c = 1, $CHCl_3$)) and was used to calculate the er (94:6).

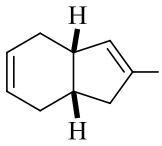
Entry 2

A Schlenk flask containing LiCl (25 mg, 0.6 mmol) was flame-dried under vacuum and was then allowed to cool to room temperature under argon. THF (10 mL) and (*R*)-bis((*R*)-1-phenylethyl)amine (0.26 mL, 1.2 mmol) were added before the reaction mixture was cooled to -78 ^{o}C. *n*-BuLi (0.49 mL, 2.46 M, 1.2 mmol) was added and the reaction mixture was stirred at -78 ^{o}C for 5 minutes before being allowed to warm to room temperature and then re-cooled to -78 ^{o}C. The ketone (**5**, 0.1 mL, 0.8 mmol) was added dropwise as a solution in THF (2 mL) and the mixture was stirred for 15 minutes before the addition of TMSCl (0.5 mL, 4 mmol). After a further 30 minutes

at -78 ^{o}C, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). Extraction with Et_2O (50, 25, 25 mL) gave a solution of the crude product which was concentrated and then purified by column chromatography on silica gel using 0-2.5% Et_2O in petroleum ether (30-40 °C) to give the desired product as a colourless oil (43 mg, 26%). The optical rotation was then measured ($[\alpha]_D^{20}$ = +32.4 ^{o} (c = 1, $CHCl_3$)) and was used to calculate the er (78:22).

Chiral HPLC analysis: 4.6mmid x 25cm Chiralpak AS column, 1:1 heptane: EtOH, 1.0 mL/minute flow rate, 210 nm detector, t_R (+) = 13 minutes and t_R (-) = 8.5 minutes.

Data for **4** was quoted previously (see experimental section for **Scheme 4.25**).



4

4. References

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